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Studies towards complex bridged alkaloids: regio- and stereocontrolled enolate chemistry of 2,5-diketopiperazines

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Abstract

The substitution of symmetrical *N*-protected diketopiperazines (DKPs) via enolate intermediates has been studied. The enolate reactions were highly diastereocontrolled, leading to enantiopure DKP products if chiral amino acid precursors were employed, and giving racemic products, starting with centrosymmetric DKPs, even when a chiral lithium amide base was used to generate the lithium enolate. With unsymmetrical DKPs derived from proline and either alanine, phenylalanine or valine, the enolate substitution occurred with high regio- and stereoselectivity on the proline residue. This enabled the synthesis of substituted DKPs that could be cyclised via cationic processes to give the bicyclo[2.2.2]diazaoctane core structure present in paraherquamide and stephacidin natural products.
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Keywords: Diketopiperazine; Cationic cyclisation; Stephacidin; Paraherquamide

1. Introduction

The 2,5-diketopiperazine (DKP) motif has emerged as an important core structure in natural product chemistry, medicinal chemistry and crystal engineering.[1] Natural products that incorporate DKPs range in complexity from cyclodipeptides like brevianamide F (**1**), through members of the trypostatin family, such as spirotryprostatin B (**2**), to the immensely complex alkaloid stephacidin B (**3**).[2–4]

The more complex members of these families pose significant synthetic challenges, and many research groups have been interested in the development of new synthetic methods and strategies to enable access to such compounds. In many cases these efforts have been driven by the interesting biological activities of the natural products, for example, the very potent and selective, antitumour activities associated with the stephacidins.

In parallel to these activities, the medicinal chemistry community has identified the DKP motif as a privileged structure for drug development, including diversity-orientated synthesis, and resin-bound and combinatorial library approaches.[5] This chemistry has already unearthed diverse bioactive DKPs, for example, as oxytocin antagonists, ligands for G-protein-coupled receptors and as potential inhibitors of calpain.[6] The role of small peptides, including DKPs, may be particularly significant in the latter area as these compounds have been identified as important in bacterial quorum sensing and cross talk.[7]

Finally, the DKP motif is proving to be versatile as a probe for crystal engineering, for example, the propensity of DKPs to form extended macromolecular arrays in the solid state enables the predictable formation of planar or non-planar 'tape' structures.[8]

With this background it is clear that the development of methods for the formation and selective manipulation of DKPs is an important topic of considerable current interest. We became interested in two closely related areas of DKP chemistry that rely upon substitution of preformed DKPs using metal enolates. In the first project we wanted to explore the chemistry of simple, symmetrical *trans*-disubstituted DKPs

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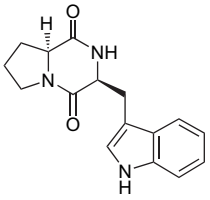
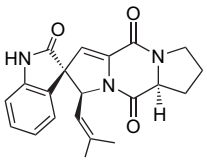
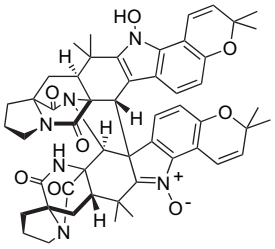


1 brevianamide F

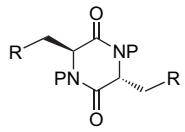


2 spirotryprostatin B

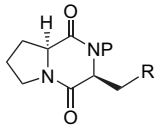


3 stephacidin B

of general structure **4**. These compounds are centrosymmetric and so are potential substrates for asymmetric synthesis by enantiotopic group differentiation, for example, enantioselective enolisation using a chiral lithium amide base.[9] In the event, we also explored analogous enolate chemistry using the enantiopure *cis*-disubstituted DKP series.



4 P = protection



5 P = protection

In the second project we were interested in probing the regio- and stereochemical outcome of enolisation–substitution of unsymmetrical DKPs incorporating proline, i.e., **5**. The objective of this project was to make available intermediates that could be further transformed towards complex natural product targets (and analogues), such as the aforementioned stephacidins.

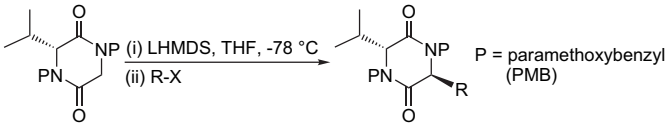
Herein we describe the results of these studies, which have uncovered some useful results that should find significant future application in the synthesis of highly substituted DKPs.

2. Result and discussion

2.1. Synthesis and substitution of symmetrically substituted DKPs

For the synthesis of symmetrical *trans*-disubstituted DKPs **4** we first considered access by cyclisation of a stereodefined dipeptide or via equilibration of the, much better known, *cis*-substituted DKPs. Neither of these approaches appeared attractive, due to either the longwinded nature of the synthesis or the difficulties of separating mixtures of cis and trans isomers. Instead, we chose to prepare the desired compounds by alkylation of the parent cyclo[Gly–Gly] in appropriately N-protected form. This part of our work was influenced by the findings of Davies and co-workers, who had shown that the cyclo[Val–Gly] derivative **6** underwent highly trans-selective enolate substitution reactions to give **7**, Scheme 1.[10]

The high levels of diastereocontrol achieved were shown to be due to a relay effect that depended on the use of bulky benzyl type protection (especially *N*-PMB) on the ring nitrogen atoms. We expected that analogous chemistry would be possible, starting from a doubly protected cyclo[Gly–Gly]



6 **7** >90% de

Scheme 1. Davies' method for stereoselective alkylation of DKPs.

and introducing substituents in a stepwise manner. Commercially available glycine anhydride **8** was doubly protected to give bis-PMB derivative **9**, Scheme 2. Alkylation of this compound to give **10** proved straightforward, although a subsequent second allylation provided only moderate yields of the desired product **11a**. A simple solution was to treat **9** with 2 equiv of base, followed by excess alkylating agent, which immediately provided *trans*-diallylated DKP **11a** in very good yield, accompanied by only small quantities of tris- and tetra-alkylated product, Scheme 2.

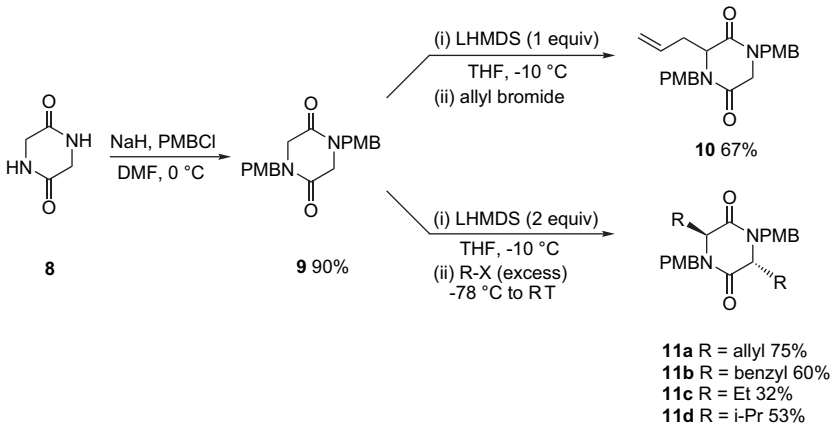
This proved to be a rather convenient method to access these compounds and three other members of the family were also prepared by this one-pot procedure. This process must involve sequential enolisation–substitution steps, since a bis-enolate would have anti-aromatic character.

As expected from the precedent set by the Davies work,[10] we obtained only the trans-disubstituted products, despite the less encumbered nature of the intermediates in the case of **11a–c**, compared to the established ^{i}Pr substituted system.

Although the stereochemistry of **11a–d** was expected to be as shown, we secured these assignments by comparison of ^{1}H NMR data with the much better known cis-isomers (vide infra), and also obtained an X-ray structure determination for bis-allyl DKP **11a**, Figure 1.

The structure confirms our assignment and also shows the highly symmetrical pattern of nitrogen and carbon substituents that occupy positions alternately above and below the planarised DKP ring.

With a selection of *trans*-substituted DKPs available we then set about testing them in enolate alkylation chemistry. In contemporaneous studies with the corresponding *cis*-DKPs (vide infra), we established that the usual lithium bases, including LDA and LHMDS, were ineffectual for this type of enolisation. In all cases, quenching with a range of electrophiles, including attempted deuterium incorporation using D_2O, MeOD or AcOD, gave only recovered starting material. In fact, for **11d**, which has a bulky ^{i}Pr group (and also a PMB substituent) on *each* face of the DKP ring, we were unable to find conditions for effective enolate formation, even using very



Scheme 2. A convenient access to symmetrical *trans*-disubstituted DKPs.

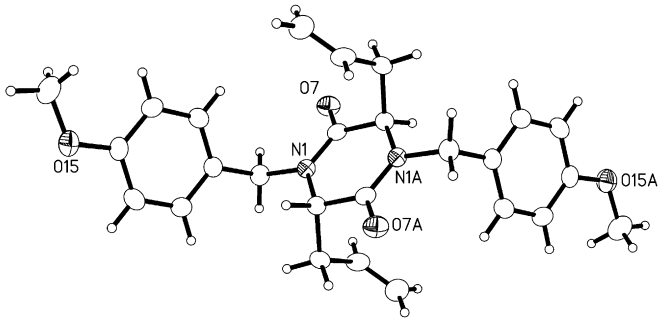
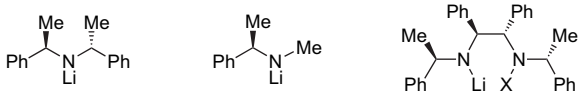


Figure 1. X-ray structure of DKP **11a**. Atoms bearing the suffix A are related to their unsuffixed equivalents by the symmetry operation (1−*x*, 1−*y*, 1−*z*).

strong bases such as NaH or *n*-BuLi. We then discovered that the simple bis-lithium amide base **12** enabled reasonably efficient substitution of **11a**–**c**, Table 1.

These studies were not fully optimised, since our objective was to effect an asymmetric variant of this type of reaction by means of a chiral base. The origins of the unique effectiveness of the bis-lithium amide base in these reactions (and in many others, vide infra), compared to ordinary lithium amides, are not entirely clear. Davies also recently reported difficulties with the use of lithium bases for substitutions of disubstituted DKPs but this was ascribed to poor reactivity of the hindered lithium enolate.[10b] This problem was solved by swapping to the corresponding potassium enolates. In our case it appears that enolate *formation* is the problematic step and that the use of a bis-lithium amide, which is probably less aggregated (and so more reactive) than a normal lithium amide, is uniquely effective. In each case only a single diastereomer was isolated, the assignments initially being based mainly on the precedent shown in Scheme 1, although further evidence was garnered later on (vide infra).

The alkylation of DKPs **11a**–**c** was then attempted using a number of chiral bases, including **14**–**17**, and also by use of the *s*-BuLi–sparteine combination.

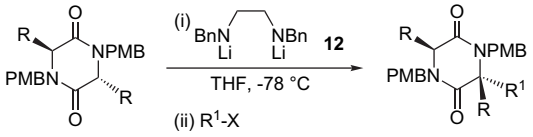


As found using achiral bases, no effective substitution could be achieved with simple (mono) lithium amides **14**–**16**. In contrast, the bis-lithium amide base **17** delivered high yields of alkylation product, for example, benzylation of **11a** gave **13a** in 90% yield, but the enantiomeric excess of this product was shown to be only 8%. The antipode of base **17** gave the same level of induction but in the opposite sense.

This was a great disappointment to us and it did not prove possible to achieve higher levels of induction using any of the DKPs **11a**–**c**, or by using additives (like LiCl)[11] or by in situ trapping procedures with carbon or silicon electrophiles (Me_3SiCl trapping did not give a stable product). Similarly, the *s*-BuLi–sparteine reagent gave only racemic material from attempted desymmetrisations of DKPs.

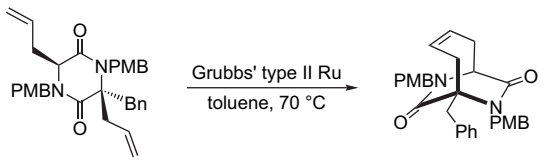
At this point we had to abandon our efforts to effect a novel asymmetric synthesis using chiral bases. However, we had demonstrated highly diastereoselective access to DKPs with structures **13a**–**g** and it became clear that some of these types of compound were potentially of further interest, and that some could undergo additional useful transformation, for

Table 1
Alkylation of DKPs **11** to give **13** as racemates



Starting DKP	R	R^1–X	Product DKP	Yield (%)
11a	Allyl	BnBr	**13a**	76
11a	Allyl	EtI	**13b**	41
11a	Allyl	PhSSPh	**13c**	49
11b	Bn	Allyl Br	**13d**	69
11b	Bn	EtI	**13e**	37
11b	Bn	PhSSPh	**13f**	61
11c	Et	BnBr	**13g**	72

example, ring-closing metathesis of **13a** gave bridged DKP **18** in good yield, Scheme 3.[12]



rac-**13a** **18** 92%

Scheme 3. Metathesis route to a bridged DKP.

At this stage it appeared worthwhile to establish access to compounds of generic formula **13** by the chiral pool approach, starting from readily available amino acid precursors. Starting from the proteinogenic amino acids, this approach places obvious limitations on the starting substituents R in **13** but should furnish useful DKP building blocks.

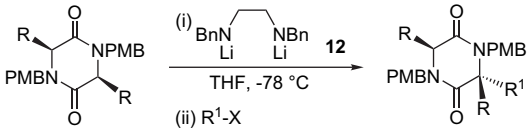
We probed this idea in a limited way, starting from enantiomerically pure DKPs prepared in a conventional fashion, Scheme 4.[13]

Both the intermediates *N*-Boc dipeptides **21** and the *N*–H DKPs corresponding to **22** (not shown) are well known for these series of compunds, and the final protected DKPs **22** were quite distinct from the *trans*-substituted counterparts **11** prepared previously.[14] The final protection was best carried out by slow addition of a suspension NaH in DMF to a mixture of *N*–H DKP and 4-methoxybenzyl chloride. In our hands, this method proved more effective than the published protocol for avoiding DKP epimerisation to give the trans-compounds.[15] In the case of **22b** we also checked for any sign of racemisation during N-protection by deprotecting using ceric ammonium nitrate, which furnished a sample of *N*–H DKP with the identical specific rotation as seen initially.

In subsequent enolisation chemistry we found that the valine derived DKP **22b**, rather like the *trans*-isomer **11d**, would not undergo effective deprotonation–substitution using a number of bases, including LDA, LHMDS, LiH, MeLi, *n*-BuLi and base **12**. We focused instead on the alanine and phenylalanine derived systems and found that either *n*-BuLi or base **12** gave the expected products. Alkylation–substitution chemistry was then carried out using these two DKPs and a range of electrophiles, Table 2.

Enolate reactions of the phenylalanine derived DKP **22a** were optimised compared to the rather preliminary studies of the corresponding *trans*-DKP **11b**, which is reflected in the excellent yields seen for alkylation, sulfenylation, aldol and acylation for this compound. As before, we observed formation of only a single diastereomer in each case, which is to be expected since both series of reactions proceed via the same enolate (albeit racemic for Table 1 and enantiomerically pure for Table 2).

Table 2
Alkylation of DKPs **22a** and **22b** to give **13** in enantiomerically pure form



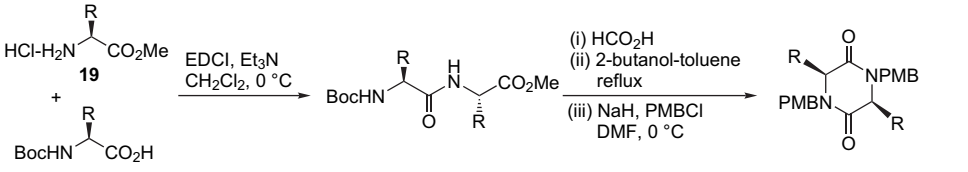
22 **13**

Starting DKP	R	R^1–X	Product DKP	Yield (%)
22a	Bn	Allyl Br	**13d**	91
22a	Bn	EtI	**13e**	91
22a	Bn	PhSSPh	**13f**	99
22a	Bn	PhCHO	**13h**	96[a]
22a	Bn	$NCCO_2Et$	**13i**	98
22c	Me	Allyl Br	**13j**	84
22c	Me	EtI	**13k**	47
22c	Me	PhSSPh	**13l**	81
22c	Me	$NCCO_2Et$	**13m**	91
22c	Me	MeI	**13n**	76
22c	Me	BnBr	**13o**	91

[a] Product formed as 1:1 mixture of diastereomers at new carbinol centre.

Initially, reactions of the alanine derived DKP **22c** proved problematic due to the formation of over-alkylated DKP by-products, along with starting DKP. At first sight this outcome might appear as a consequence of using a bis-lithium amide (and thus excess base), but the use of less base simply resulted in the recovery of larger quantities of starting DKP. We proposed that the problem was due to intermolecular proton exchange between first alkylated DKP and the enolate of the starting DKP (perhaps within an aggregate). The more highly substituted DKP enolate would be expected to be less aggregated than the parent, and so more reactive in alkylations. This problem was alleviated by running the reactions with **22c** substantially more dilute (with respect to DKP) than the other systems, and increasing the equivalents of available alkylating agent.

Chiral ylidenepiperazine diones are intermediates of established synthetic utility, since they undergo a range of stereocontrolled addition reactions to give DKPs.[16] Since we had prepared two sulfur substituted DKPs, **13f** and **13l**, we chose

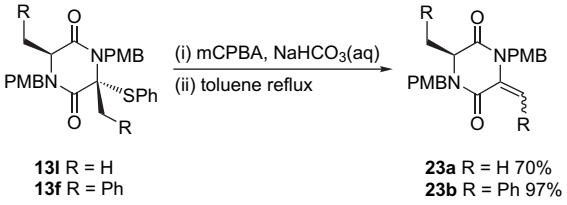


21a R = Bn (86%)
21b R = *i*-Pr (81%)
21c R = Me (88%)

22a R = Bn (42%)
22b R = *i*-Pr (37%)
22c R = Me (46%)

Scheme 4. Synthesis of enantiopure DKPs.

to convert these into the corresponding ylidene systems via sulfoxide *syn*-elimination, Scheme 5.



Scheme 5. Synthesis of enantiopure ylidenepiperazine diones.

The phenylalanine derived system **23b** was formed as a mixture of geometric isomers, slightly favouring the *E*-isomer (1.4:1), in which the alkene substituent (Ph) is orientated away from the bulky *N*-PMB substituent. Although probably of limited use in this particular context, we were to revisit this type of sulfoxide elimination chemistry in our studies aimed at stephacidin synthesis.

2.2. Synthesis and substitution of unsymmetrical proline derived DKPs

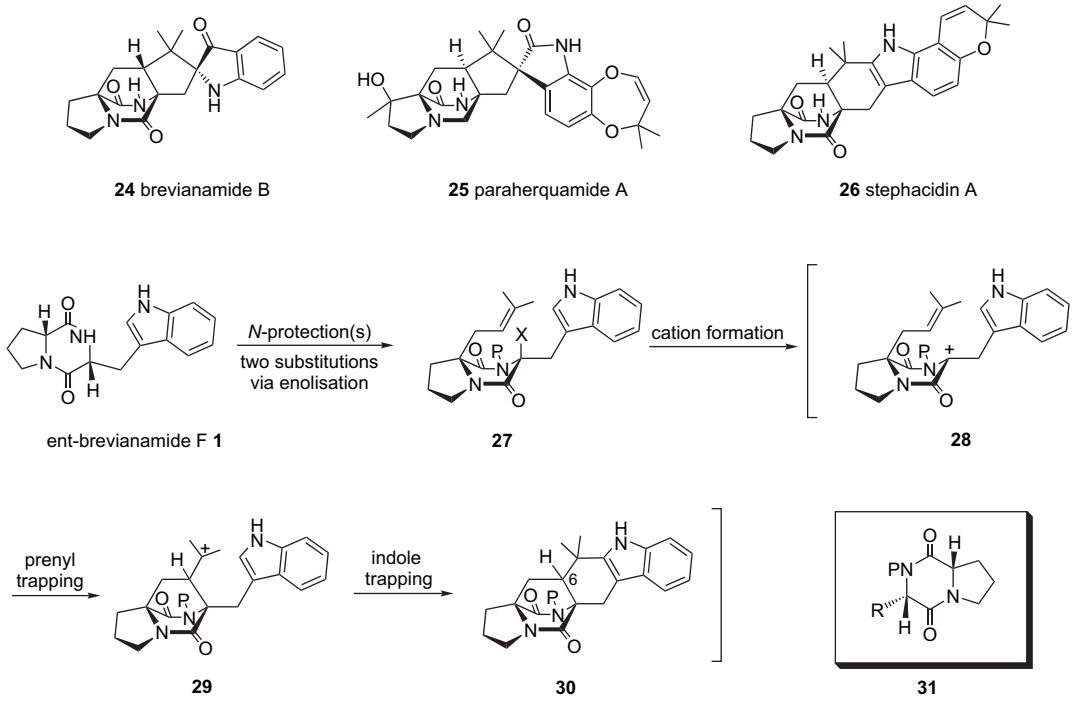
As mentioned above, proline derived DKPs, or modifications thereof, appear as structural motifs in a range of important natural products, including **1**–**3**. Of particular significance are members of several families of fungal metabolites, possessed of a bicyclo[2.2.2]diazaoctane core structure, which includes the brevianamides, e.g., brevianamide B (**24**) and paraherquamides, e.g., paraherquamide A (**25**).[17]

These compounds combine synthetically challenging structures, intriguing biosynthetic origins and, in many cases, potent biological activities (especially anthelmintic and antinematodal properties). These aspects have been probed over many years, most notably by the Williams group, who have achieved several total syntheses of the natural products and have also provided much detailed evidence for the biosynthesis.[18]

Recent additions to these families of compounds are the aforementioned stephacidin B (**3**) and stephacidin A (**26**), potent antitumour compounds produced by Aspergillus ochraceus WC76466.[4] Total syntheses of stephacidins have been described by the groups of Baran, Meyers and Williams, and stephacidin A (**26**) has been demonstrated to be a viable precursor for the aforementioned stephacidin B (**3**) via the related compound, avrainvillamide.[19–21] Only following this synthetic work, the absolute configuration of the stephacidins was assigned with certainty, the naturally occurring compounds having the structures shown herein.

The biosynthetic origin of many of these compounds appears to involve modification of brevianamide F **1** by indole reverse-prenylation, and a subsequent intramolecular Diels–Alder cycloaddition of the pendant prenyl group onto an aza-diene generated by oxidation of the core diketopiperazine (DKP). Some aspects of the proposed biosynthesis have been realised by Williams and co-workers in their synthetic endeavours.[18d,e] We became interested in an alternative access to this type of bridged structure, which would also originate from a simple DKP starting material, which is outlined in Scheme 6.

Following the aforementioned clarification of absolute stereochemistry for the stephacidins, our proposed synthesis would require D-proline, or some derived DKP, such as *ent*-brevianamide F, as starting material.[22] According to this plan, regioselective enolate formation and substitution would be employed to convert **1** (in suitably protected form) into **27**, where X is a heteroatom group appropriate for the formation of an *N*-acyliminium-type of cationic reactive



Scheme 6. Planned cationic cascade route to complex bridged DKPs.

intermediate.[23] Triggering of cation formation from **27** would enable a cascade process in which sequential trapping of cation intermediate **28** by the pendant prenyl group, and then **29** by the indole, would give the desired polycyclic product **30**. This process appeared to promise an extremely concise access to natural products, including **1**–**3**, and we could be assured of the second 'indole trapping' step, since Williams and co-workers had previously demonstrated the viability of such a cyclisation.[24]

Surprisingly, given the ubiquity of DKPs and their derived systems (such as Schöllkopf lactim ethers) in stereocontrolled processes,[25] we could find only a single report relating to the transformation of proline derived *unsymmetrical* DKPs such as **1** into products with *quaternary* centres.[26] Thus an exploration of the regio- and stereocontrol in the enolate reactions of DKPs such as **1** appeared a pre-requisite to any total synthesis adventure. Similarly, the choice of the group 'X', the practicalities of generating the unusual type of cationic intermediate **28**[27] and the crucial stereochemical outcome at C-6 (stephacidin numbering) could not be taken for granted.

Herein, we describe our preliminary results towards realising this approach, in which we use model L-proline derived DKP systems **31** (R=Me, Bn or ^{i}Pr; P=PMB) to address the key aspects described above.

In initial preparations of appropriate DKPs for this study, starting from cheap amino acid precursors, we observed that N-protection of the ring N–H in **31** (P=H) led to significant epimerisation at the proline residue. Therefore, we adopted a route that combined commercially available proline methylester with alanine, phenylalanine or valine derived partners, already incorporating the required PMB protection, Scheme 7.

Initial reductive amination was followed by double nitrogen protection, amide coupling, *N*-Boc removal and thermally induced cyclisation to give the desired DKPs **36a**–**c**.[28]

We were delighted to find that a range of electrophilic substitution reactions could be conducted with these systems, in a highly regio- and stereoselective fashion, through the intermediacy of lithium enolates, generated using LiHMDS, Table 3.

This brief survey demonstrated that effective alkylation, acylation, aldol and sulfenylation reactions are viable in good yields. In all cases we observed completely regioselective reaction at the proline α-centre, which is in accord with the single result reported previously for a cyclo[Val–Pro] derivative similar to **36c**.[26a] This is likely both the kinetic and thermodynamic outcome.

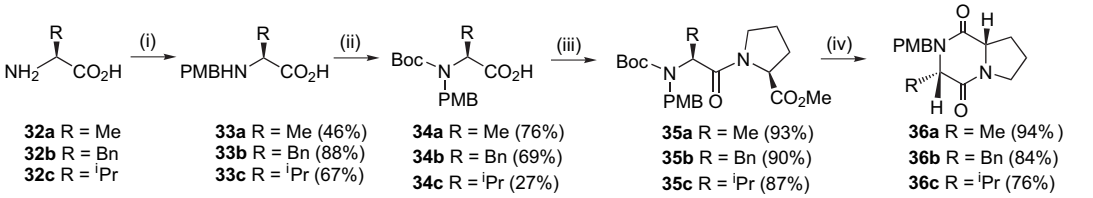
With the exception of sulfides **42a**–**c** all of the products were isolated as single diastereomers, the reaction occurring with overall retention at the proline α-centre. The result is in accord with the aforementioned results of Davies, involving alkylation of a valine derived DKP, where the stereochemical result was explained via enolate conformation **A**, Figure 2.[10a]

The conformation shown was proposed to be favoured because torsional strain between the isopropyl substituent at C-3 and the N-4 group destabilises an alternative conformation where both of these groups are pseudo-equatorial. The pseudo-axial isopropyl group conveys a high level of facial selectivity on the subsequent axial mode of enolate alkylation. For our proline derived systems an analogous situation may explain the results, as represented by conformation B. However, this argument is less convincing when considering relatively small groups (R), particularly the alanine derived DKP where R=Me. In this case, the steric shielding afforded by a methyl substituent in a 1,4-arrangement does not seem adequate to explain the high selectivities generally observed. Also, in the case of R=Me, the argument for enforcing conformation B due to 1,2-torsional strain also seems weaker, and the alternative conformation C appears reasonable. In this case there is a strong argument for top face alkylation based on a well-established tendancy for various lactam enolates to react anti to the pyramidilised nitrogen lone pair (shown).[29,30] This apparent stereoelectronic effect can result in very high facial selectivity when only rather small ring substituents are present as conformational anchors.

For the sulfenylation reactions stereoselectivity was poor, with ratios obtained being 1:1 in the case of **36a**, 2:1 for **36b** and 3.3:1 in the case of **36c**, the selectivity apparently depending on the size of the side chain of the acyclic amino acid DKP component. We ascribe the loss of complete selectivity in the sulfenylations, compared to all of the other reactions carried out, to a longer *forming* bond (i.e., C–S vs C–C) in the transition state.

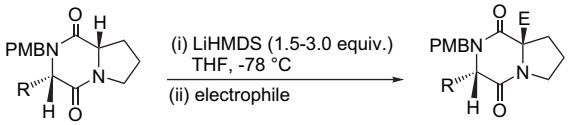
Our initial assignment of relative stereochemistry of the products **37**–**43** rested on the aforementioned single precedent for alkylation of an enolate related to **36c**.[26] Fortunately, we were able to confirm this assignment by X-ray crystallography in the case of the key prenylated compound **38b**, required for our cyclisation work, Figure 3.

In the case of the two benzaldehyde aldol products **43a** and **43b** we were initially a little surprised that single diastereomers were formed. Unfortunately we were unable to determine the stereochemistry of these compounds at the newly formed off-template secondary alcohol centre using NOE experiments, and the compounds were not crystalline. We tentatively propose the stereochemistry shown below for these



Scheme 7. Preparation of unsymmetrical DKPs. Reagents and conditions: (i) *p*-methoxybenzaldehyde, $NaBH_3CN$, MeOH; (ii) $(Boc)_2O$, $^{i}Pr_2NEt$, 1,4-dioxan–H_2O (1:1); (iii) L-proline methylester–HCl salt, EDCI, HOBT, Et_3N, CH_2Cl_2; (iv) HCO_2H then reflux in 2-butanol–toluene (xylene used for **36c**).

Table 3
Alkylation of DKPs **36a–c**



36 **37 - 43**

DKP	Electrophile[a]						
	Allyl bromide	Prenyl bromide	$PhCH_2Br$	EtI	$NCCO_2Et$	PhSSPh[b]	PhCHO
36a	**37a** (51)	**38a** (60)	**39a** (62)	—	**41a** (83)	**42a** (52)	**43a** (63)
36b	**37b** (71)	**38b** (82)	**39b** (58)	**40b** (56)	**41b** (69)	**42b** (60)	**43b** (57)
36c	**37c** (73)	—	**39c** (83)	**40c** (61)	**41c** (55)	**42c** (64)	—

[a] Values in brackets are isolated yields (%) of pure DKP product.
[b] These products isolated as mixtures of diastereoisomers (see text).

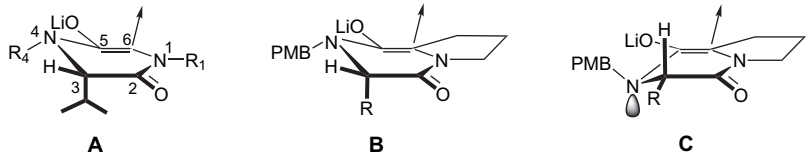


Figure 2. Rationalisation of DKP enolate selectivity.

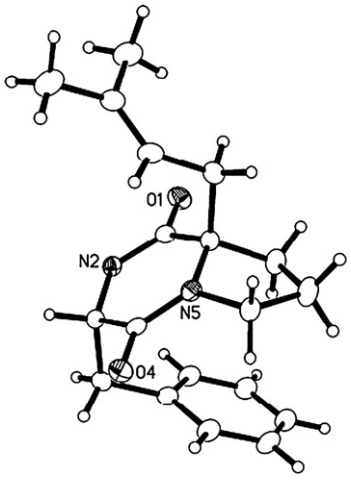


Figure 3. X-ray structure of **38b** (*N*-PMB group has been omitted for clarity).

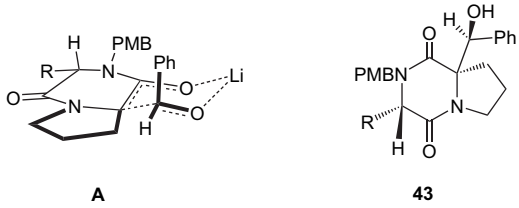


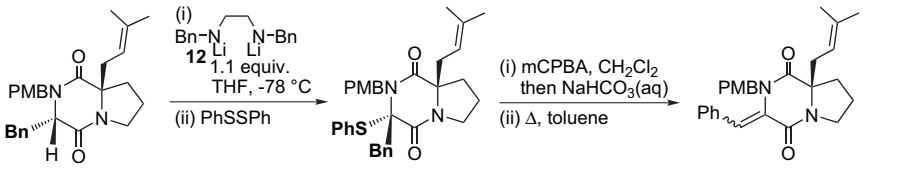
Figure 4. Tentative assignment of stereochemistry for **43a** and **43b**.

compounds, which we expect to arise via transition state A, in which interactions between the proline ring and the phenyl ring on the aldehyde are minimised in the usual type of Zimmerman–Traxler arrangement, Figure 4.

With a model DKP system, equipped with a suitable prenyl appendage, we required to explore the installation of a second group X, as indicated earlier in Scheme 6, which would allow cation formation–cyclisation. Initially, we chose to carry out sulfenylation of **38b** (i.e., X=SPh) to give **44**, since this also enabled subsequent sulfoxide *syn*-elimination to give *exo*-benzylidene product **45**, Scheme 8.

As seen in some of our earlier enolisation studies, the enolisation of DKP **38b** was unsuccessful using conventional bases such as LDA, LiHMDS, KHMDS or *n*-BuLi, and we achieved acceptable results only by employing the bis-lithiated base **12**. Deprotonation using this base, followed by addition of diphenyl disulfide gave a single diastereomeric product **44** in reasonable yield. The formation of a single diastereomer in this reaction was unexpected (especially bearing in mind the mixtures of products generated in our other sulfenylations), since reaction on the more exposed convex face of the system appeared to be hindered by the prenyl substituent. We subsequently secured the stereochemical assignment shown in Scheme 8 by X-ray crystallography, Figure 5.

The structure shows clearly that installation of the new SPh substituent has occurred anti to the prenyl group and on the



38b **44** (64%) **45** (94%) *E*:*Z* = 1:1

Scheme 8. Sulfenylation and sulfoxide elimination sequence, starting from **38b**.

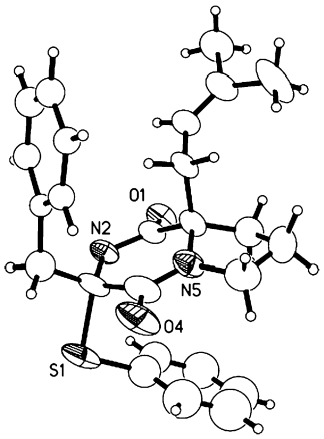
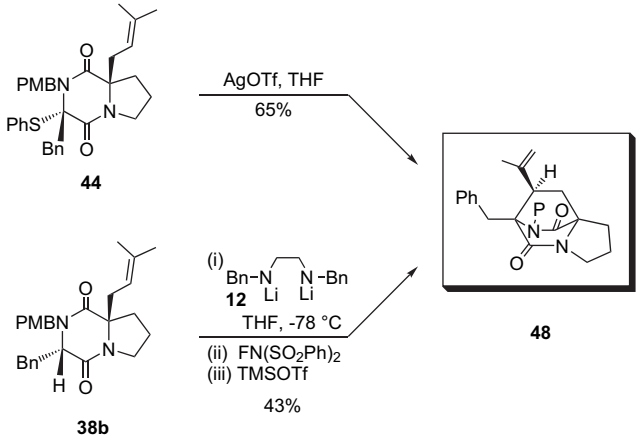


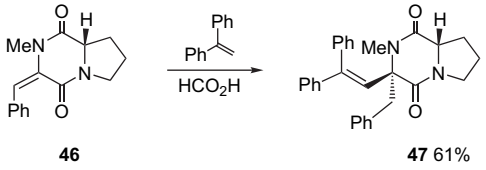
Figure 5. X-ray structure of **44** (*N*-PMB group has been omitted for clarity).



Scheme 10. Stereoselective cyclisations of DKPs **44** and **38b**.

more concave face of the bicyclic system. Subsequent sulfoxide elimination proved very efficient, providing **45** as a mixture of geometrical isomers.

Ylidenepiperazine-2,5-diones, such as **45**, have been demonstrated to undergo intermolecular alkene trapping reactions, analogous to the cyclisation that we planned, under acidic conditions, for example, conversion of starting DKP **46** into product **47** on heating with 1,1-diphenylethene and formic acid, Scheme 9.[27b]



Scheme 9. A known cationic trapping result on a DKP framework.

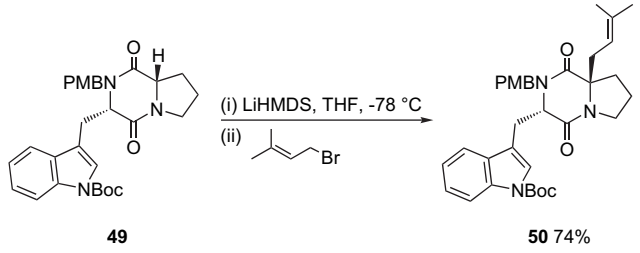
Unfortunately, treatment of our related DKP **45** with a number of acidic reagents, including formic acid, TFA and mineral acids, led only to destruction of the starting material.

We turned instead to previous reports in which substitution of thioether groups on a DKP scaffold had been accomplished using AgOTf.[31] Reaction of **44** under these conditions gave rise to a single cyclised product to which we assigned structure **48** by comparison of NMR data with those published previously by Williams and co-workers, Scheme 10.[32]

Pleasingly, the relative configuration of this product at C-6 is correct for the synthesis of paraherquamide and stephacidin natural products; the absolute stereochemistry being opposite to that of our prime targets, the stephacidins, following the aforementioned revision.

As shown, we also developed a novel one-pot transformation of **38b**, to give the same tricyclic DKP product **48**, by sequential treatment with base **12**, electrophilic fluorinating agent $FN(SO_2Ph)_2$ and then trimethylsilyltriflate. This procedure was based on another report from the Davies group, in which halo-diketopiperazines were employed as chiral glycine cation equivalents.[27a] Initial DKP fluorination was used as an access to the 2-chloro derivatives via transhalogenation. In our hands, in situ fluorination followed by Lewis acid activation, using TMSOTf provided a direct and reliable protocol, compared to the AgOTf method, although the yield of **48** was only moderate. The success of this strategy makes available bridged DKP **48** in *only six steps* from the starting commercial phenylalanine **10b**.

Finally, we attempted to apply this approach to a brevianamide F derivative (i.e., a variant of structure **27**) capable of undergoing double cyclisation to form a polycyclic fused indole represented by **30**. Preparation of the suitably protected DKP **49** was straightforward,[33] following the procedure outlined before, and we were pleased to find that prenylation was highly regio- and stereoselective, as before, to give **50**, Scheme 11.



Scheme 11. Synthesis of DKP substrate **50** for attempted double cyclisation.

Unfortunately, we were then unable, under any of the conditions employed before, to further substitute DKP **50** in order to install the appropriate 'trigger' for cationic double cyclisation. This failure is most likely due to the extremely crowded nature of this DKP system due to the presence of the Boc-protected indole. We have not persisted with this approach, since we have subsequently established an alternative approach that enables much more concise access to the desired intermediates **27**. This new chemistry, which has enabled us to realise the desired double cyclisation as outlined in Scheme 6 will be described elsewhere in due course.

3. Experimental part

*3.1. Preparation of 3-allyl-1,4-bis-(4-methoxybenzyl)-3-piperazine-2,5-dione **10***

To a solution of HMDS (0.65 mL, 3.10 mmol) in THF (3 mL), cooled to −78 °C, was added *n*-BuLi (1.8 mL of

a 1.6 M solution in hexanes, 2.8 mmol) and the solution was warmed to rt for 15 min. The reaction mixture was added, via cannula, to a suspension of 1,4-bis-(4-methoxybenzyl)-piperazine-2,5-dione **9** (1.0 g, 2.8 mmol) in THF (10 mL) at −10 °C. After stirring the reaction mixture for 1 h, it was cooled to −78 °C and allyl bromide (0.24 mL, 2.80 mmol) was added. The mixture was allowed to warm to rt over 2 h and then the reaction mixture was quenched by the cautious addition of a saturated aqueous solution of ammonium chloride (10 mL). The mixture was separated and the aqueous phase was extracted with $CHCl_3$ (2×10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 2:1) to yield allyl DKP **10** as a colourless solid (0.75 g, 67%), mp 80–82 °C. ν_{max} ($CHCl_3$)/cm^{-1} 2936, 2838, 1663, 1613, 1463, 1321, 1304, 1036; δ_H (400 MHz, $CDCl_3$) 2.57 (1H, ddd, *J* 14.5, 7.5, 5.2, C*H*HCH=CH_2), 2.66 (1H, ddd, *J* 14.2, 7.5, 4.2, C*H*HCH=CH_2), 3.76 (1H, d, *J* 17.5, NC*H*HCO), 3.80 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.92 (1H, d, *J* 17.5, NC*H*HCO), 3.98 (1H, d, *J* 14.5, NC*H*HAr), 3.99 (1H, dd, *J* 5.2, 4.2, NC*H*CO), 4.18 (1H, d, *J* 14.5, NC*H*HAr), 4.82 (1H, d, *J* 14.5, NC*H*HAr), 5.07 (1H, dd, *J* 10.1, 1.6, H*H*C=$CHCH_2$), 5.10 (1H, dd, *J* 17.1, 1.6, H*H*C=$CHCH_2$), 5.19 (1H, d, *J* 14.5, NC*H*HAr), 5.60 (1H, dddd, *J* 17.1, 10.1, 7.5, 7.5, CH_2=C*H*CH_2), 6.86 (4H, d, *J* 8.6, Ar, C*H*), 7.18 (4H, d, *J* 8.6, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 36.1 (CH_2), 46.2 (CH_2), 49.0 (CH_2), 49.2 (CH_2), 55.4 (2×OCH_3), 58.9 (CH), 114.3 (Ar, CH), 114.4 (Ar, CH), 120.9 (H_2C=CH), 127.3 (C, Ar), 127.5 (C, Ar), 129.9 (Ar, CH), 130.0 (Ar, CH), 130.8 (*C*H=CH_2), 159.5 (2×C, Ar), 164.3 (C=O), 165.9 (C=O); *m/z* (EI) $C_{23}H_{26}N_2O_4$ requires: 394.1893, found M^+: 394.1894.

*3.2. Typical procedure for double alkylation of **9** to give trans-DKPs **11***

3.2.1. (3R,6S*)-3,6-Diallyl-1,4-bis-(4-methoxybenzyl)-piperazine-2,5-dione **11a***

To a solution of HMDS (3.9 mL, 19 mmol) in THF (15 mL), cooled to −78 °C, was added *n*-BuLi (11.3 mL of a 1.6 M solution in hexanes, 18 mmol) and the solution was warmed to rt for 15 min. The basic solution was added, via cannula to a suspension of 1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **9** (3.0 g, 8.5 mmol) in THF (30 mL) at −10 °C. After stirring the reaction mixture for 1 h, it was cooled to −78 °C and allyl bromide (1.83 mL, 21.2 mmol) was added. The mixture was allowed to warm to rt over 2 h and then the reaction was quenched by the cautious addition of a saturated aqueous solution of ammonium chloride (30 mL). The mixture was separated and the aqueous phase was extracted with $CHCl_3$ (2×25 mL). The combined organic extracts were washed with water (25 mL), brine (25 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/CH_3COCH_3, 99:1), then recrystallised (EtOAc) to yield the title compound **11a** as a colourless crystalline solid (2.75 g, 75%), mp 168–170 °C. Found: C, 71.85; H, 6.94; N, 6.35. $C_{26}H_{30}N_2O_4$ requires: C, 71.87; H, 6.96; N, 6.45. ν_{max} ($CHCl_3$)/cm^{-1} 2937, 2838, 1651, 1613, 1457, 1318, 1304, 1036; δ_H (400 MHz, $CDCl_3$) 2.71 (2H, ddd, *J* 14.7, 7.1, 4.5, C*H*HCH=CH_2), 2.88 (2H, dddd, *J* 14.7, 7.1, 2.8, 1.4, C*H*HCH=CH_2), 3.79 (2H, d, *J* 14.7, NCH*H*Ar), 3.81 (6H, s, OCH_3), 3.99 (2H, dd, *J* 4.5, 2.8, COC*H*N), 5.13 (2H, dd, *J* 10.2, 1.6, H*H*C=$CHCH_2$), 5.18 (2H, dd, *J* 17.1, 1.6, H*H*C=$CHCH_2$), 5.51 (2H, d, *J* 14.7, NC*H*HAr), 5.57 (2H, dddd, *J* 17.1, 10.2, 7.1, 7.1, CH_2C*H*=CH_2), 6.86 (4H, d, *J* 8.5, Ar, C*H*), 7.20 (4H, d, *J* 8.5, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 35.1 (CH_2), 45.6 (CH_2), 55.4 (OCH_3), 57.0 (CH), 114.3 (Ar, CH), 120.5 (H_2C=CH), 127.1 (Ar, C), 130.0 (Ar, CH), 130.8 (H_2C=*C*H), 159.5 (Ar, C), 166.2 (C=O); *m/z* (EI) $C_{26}H_{30}N_2O_4$ requires: 434.2206, found M^+: 434.2192. A sample for X-ray crystal structure determination was prepared from DKP **11a** (50 mg) via recrystallisation from petrol (2 mL) and EtOAc (0.2 mL) over a period of 5 days.

3.2.2. (3R,6S*)-3,6-Dibenzyl-1,4-bis-(4-methoxybenzyl)-piperazine-2,5-dione **11b***

The above procedure was followed using HMDS (1.5 mL, 7.1 mmol), *n*-BuLi (3.9 mL of a 1.6 M solution in hexanes, 6.2 mmol), 1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **9** (2.00 g, 5.64 mmol), benzyl bromide (1.7 mL, 14 mmol) and THF (45 mL). The crude product was purified by flash column chromatography on silica gel (CH_2Cl_2/$(CH_3)_2CO$, 99:1), then recrystallised (EtOAc) to yield the dibenzyl DKP **11b** as a colourless crystalline solid (0.89 g, 60%), mp 204–206 °C. ν_{max} ($CHCl_3$)/cm^{-1} 2937, 2838, 1645, 1613, 1454, 1303, 1035; δ_H (400 MHz, $CDCl_3$) 3.18 (4H, d, *J* 3.8, C*H*HPh), 3.75 (2H, t, *J* 3.8, COC*H*N), 3.82 (6H, s, OCH_3), 3.88 (2H, d, *J* 14.8, NC*H*HAr), 5.44 (2H, d, *J* 14.8, NC*H*HAr), 6.68 (4H, d, *J* 8.6, Ar–OMe, C*H*), 6.75 (4H, d, *J* 8.6, Ar–OMe, C*H*), 7.04 (2H, d, *J* 6.1, Ar, C*H*), 7.04 (2H, d, *J* 8.5, Ar, C*H*), 7.21 (2H, ddd, *J* 6.1, 6.1, 1.2, Ar, C*H*), 7.21 (2H, ddd, *J* 8.5, 8.5, 1.2, Ar, C*H*), 7.28 (2H, dddd, *J* 8.5, 6.1, 1.4, 1.2, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 35.5 (CH_2), 45.8 (CH_2), 55.4 (OCH_3), 57.6 (CH), 114.2 (Ar, CH), 126.3 (Ar, C), 127.1 (Ar, CH), 128.8 (Ar, CH), 129.9 (Ar, CH), 135.1 (Ar, CH), 159.3 (Ar, C), 165.6 (C=O); *m/z* (EI) $C_{34}H_{34}N_2O_4$ requires: 534.2518, found M^+: 534.2538.

3.2.3. (3R,6S*)-3,6-Diethyl-1,4-bis-(4-methoxybenzyl)-piperazine-2,5-dione **11c***

The above procedure was followed using HMDS (0.97 mL, 4.6 mmol), *n*-BuLi (2.9 mL of a 1.6 M solution in hexanes, 4.7 mmol), 1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **9** (0.75 g, 2.1 mmol), iodoethane (0.85 mL, 11 mmol) and THF (12 mL). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 2:1), then recrystallised (EtOAc) to yield the diethyl DKP **11c** as a colourless crystalline solid (0.28 g, 32%), mp 168–170 °C. Found: C, 69.92; H, 7.31; N, 6.80%. $C_{24}H_{30}N_2O_4$ requires: C, 70.22; H, 7.37; N, 6.82%. ν_{max} ($CHCl_3$)/cm^{-1} 2971, 2838, 1650, 1613, 1461, 1319, 1303, 1036; δ_H (400 MHz, $CDCl_3$) 0.77

(6H, dd, *J* 7.4, 7.4, C*H*$_3$CH$_2$), 2.01 (2H, dqd, *J* 14.6, 7.4, 4.9, CH$_3$C*H*H), 2.19 (2H, dqd, *J* 14.6, 7.4, 2.5, CH$_3$C*H*H), 3.71 (2H, d, *J* 14.6, NC*H*HAr), 3.80 (6H, s, OC*H*$_3$), 3.98 (2H, dd, *J* 4.9, 2.5, COC*H*N), 5.53 (2H, d, *J* 14.6, NC*H*HAr), 6.86 (4H, d, *J* 8.7, Ar, C*H*), 7.20 (4H, d, *J* 8.6, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 7.2 (CH_3), 24.1 (CH_2), 45.4 (CH_2), 55.4 (OCH_3), 57.6 (CH), 114.3 (Ar, CH), 127.5 (Ar, C), 129.9 (Ar, CH), 159.4 (Ar, C), 166.7 (C=O); *m/z* (EI) $C_{24}H_{30}N_2O_4$ requires: 410.2206, found M^+: 410.2207.

3.2.4. (3R*,6S*)-3,6-Diisopropyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **11d**

The above general procedure was followed using HMDS (2.62 mL, 12.4 mmol), *n*-BuLi (8.0 mL of a 1.6 M solution in hexanes, 12 mmol), 1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **9** (2.00 g, 5.64 mmol), 2-iodopropane (1.4 mL, 14 mmol) and THF (60 mL). The crude product was purified by recrystallisation (EtOAc) to yield the diisopropyl DKP **11d** as a colourless crystalline solid (1.32 g, 53%), mp 192–193 °C (lit. mp 180 °C).[15] Found: C, 68.40; H, 7.10; N, 3.61%. $C_{26}H_{34}N_2O_4$ requires: C, 68.55; H, 7.06; N, 3.61%. ν_{max} ($CHCl_3$)/cm^{-1} 2963, 2838, 1650, 1614, 1463, 1303, 1036; δ_H (500 MHz, $CDCl_3$) 0.80 (6H, d, *J* 6.9, CH(C*H*$_3$)$_2$), 1.12 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 2.34–2.37 (2H, m, C*H*(CH$_3$)$_2$), 3.77 (2H, d, *J* 2.7, C=OC*H*N), 3.81 (6H, s, OC*H*$_3$), 3.89 (2H, d, *J* 14.7, NC*H*HAr), 5.31 (2H, d, *J* 14.7, NC*H*HAr), 6.86 (4H, d, *J* 8.6, Ar, C*H*), 7.18 (4H, d, *J* 8.6, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 15.9 (CH_3), 20.0 (CH_3), 30.8 (CH), 46.3 (CH_2), 55.3 (OCH_3), 62.6 (CH), 114.0 (Ar, CH), 127.5 (Ar, C), 130.0 (Ar, CH), 159.3 (Ar, C), 165.7 (C=O); *m/z* (EI) $C_{26}H_{34}N_2O_4$ requires: 438.2519, found M^+: 438.2520.

3.3. Typical procedure for substitution of trans-DKPs **11** to give products **13** (Table 1)

3.3.1. (3R*,6S*)-3,6-Diallyl-3-benzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione rac-**13a**

N,*N*′-Dibenzylethylene diamine (59 μL, 0.25 mmol) was dissolved in THF (2 mL), cooled to −78 °C and *n*-BuLi (0.32 mL of a 1.6 M solution in hexanes, 0.50 mmol) added. The solution was warmed to rt for 10 min before being recooled to −78 °C. The mixture was then added via cannula, over a period of 5 min, to a solution of (3*R**,6*S**)-3,6-diallyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **11a** (100 mg, 0.230 mmol) in THF (15 mL) at −78 °C. After stirring the solution for 1 h, benzyl bromide (0.14 mL, 1.2 mmol) was added and the solution was stirred for a further 2 h. The reaction mixture was quenched by the careful addition of a saturated aqueous solution of ammonium chloride (10 mL). After warming to rt the phases were separated and the organic phase was washed with brine (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2×10 mL), then the combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **13a** as a colourless solid (92 mg, 76%), mp 100–102 °C. ν_{max} ($CHCl_3$)/cm^{-1} 2937, 2838, 1650, 1613, 1456, 1304, 1036; δ_H (400 MHz, $CDCl_3$) 2.50 (1H, dddd, *J* 14.9, 7.0, 5.6, 1.2, C*H*HCH=CH$_2$), 2.66 (1H, dd, *J* 14.3, 5.8, C*H*HCH=CH$_2$), 2.74 (1H, dddd, *J* 14.9, 7.3, 2.9, 1.4, C*H*HCH=CH$_2$), 2.96 (1H, dd, *J* 14.3, 8.2, C*H*HCH=CH$_2$), 3.25 (1H, d, *J* 14.0, C*H*HPh), 3.25 (1H, dd, *J* 5.6, 2.9, NC*H*CO), 3.25 (1H, d, *J* 14.0, C*H*HPh), 3.80 (6H, s, OC*H*$_3$), 3.99 (1H, d, *J* 14.6, NC*H*HAr), 4.19 (1H, d, *J* 14.9, NC*H*HAr), 4.82 (1H, dd, *J* 16.9, 2.0, CH$_2$CH=C*H*H), 4.87 (1H, d, *J* 10.2, 2.0, CH$_2$CH=C*H*H), 4.92 (1H, d, *J* 14.9, NC*HH*Ar), 5.00 (1H, dd, *J* 10.0, 1.7, CH$_2$CH=C*H*H), 5.03 (1H, dd, *J* 16.7, 1.7, CH$_2$CH=C*H*H), 5.19 (1H, dddd, *J* 16.9, 10.2, 8.2, 8.2, CH$_2$C*H*=CH$_2$), 5.43 (1H, d, *J* 14.6, NC*H*HAr), 5.50 (1H, dddd, *J* 16.9, 10.2, 7.0, 7.0, CH$_2$C*H*=CH$_2$), 6.74 (2H, d, *J* 8.8, Ar–OMe, C*H*), 6.82 (4H, d, *J* 8.8, Ar, C*H*), 7.00–7.04 (2H, m, Ar, C*H*), 7.12–7.18 (2H, m, Ar, C*H*), 7.22 (1H, m, Ar, C*H*), 7.39 (2H, d, *J* 8.8, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 36.0 (CH_2), 42.4 (CH_2), 43.7 (CH_2), 46.2 (CH_2), 46.5 (CH_2), 55.3 (2×OCH_3), 56.9 (CH), 77.1 (*C*-3), 113.7 (Ar, CH), 113.9 (Ar, CH), 119.3 (H$_2$*C*=CH), 119.7 (*C*H$_2$*C*=CH), 127.0 (Ar, C), 127.3 (Ar, CH), 128.6 (Ar, CH), 130.1 (Ar, CH), 130.2 (Ar, C), 130.5 (2×*C*H=CH$_2$), 131.9 (Ar, CH), 132.0 (Ar, CH), 135.0 (Ar, C), 159.0 (Ar, C), 159.1 (Ar, C), 166.5 (C=O), 167.4 (C=O); *m/z* (ESI) $C_{33}H_{36}N_2NaO_4$ requires: 547.2567, found $[MNa]^+$: 547.2534.

3.3.2. (3S*,6S*)-3,6-Diallyl-3-ethyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5 dione rac-**13b**

The above general procedure was followed using *N*,*N*′-dibenzylethylene diamine (59 μL, 0.25 mmol), *n*-BuLi (0.32 mL of a 1.6 M solution in hexane, 0.50 mmol), (3*R**,6*S**)-3,6-diallyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **11a** (100 mg, 0.230 mmol) and iodoethane (92 μL, 1.2 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **13b** as a colourless solid (44 mg, 41%), mp 82–83 °C. ν_{max} ($CHCl_3$)/cm^{-1} 2936, 2838, 1652, 1614, 1457, 1354, 1318, 1304, 1036; δ_H (500 MHz, $CDCl_3$) 0.51 (3H, dd, *J* 7.3, 7.3, C*H*$_3$CH$_2$), 1.84 (1H, dq, *J* 14.4, 7.3, C*H*HCH$_3$), 2.18 (1H, dq, *J* 14.4, 7.3, C*H*HCH$_3$), 2.48 (1H, dd, *J* 14.4, 7.0, C*H*HCH=CH$_2$), 2.73 (1H, ddd, *J* 14.6, 7.3, 5.8, C*H*HCH=CH$_2$), 2.77 (1H, dd, *J* 14.4, 7.6, C*H*HCH=CH$_2$), 2.88 (1H, ddd, *J* 14.6, 7.3, 3.5, C*H*HCH=CH$_2$), 3.79 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 3.88 (1H, *J* 14.6, NC*H*HAr), 4.03 (1H, dd, *J* 5.8, 3.5, NC*H*CO), 4.32 (1H, d, *J* 15.0, NC*H*HAr), 4.82 (1H, d, *J* 15.0, NC*H*HAr), 4.87 (1H, dd, *J* 17.1, 1.7, H*H*C=CH), 4.97 (1H, dd, *J* 10.2, 1.7, H*H*C=CH), 5.13 (1H, dd, *J* 17.1, 1.5, H*H*C=CH), 5.18 (1H, dd, *J* 10.2, 1.5, H*H*C=CH), 5.43 (1H, dddd, *J* 17.3, 10.2, 7.3, 7.3, CH$_2$C*H*=CH$_2$), 5.49 (1H, d, *J* 14.6, NC*H*HAr), 5.75 (1H, dddd, *J* 17.3, 10.2, 7.3, 7.3, CH$_2$C*H*=CH$_2$), 6.80 (2H, d, *J* 6.7, Ar, C*H*), 6.86 (2H, d, *J* 6.7, Ar, C*H*), 7.21 (2H, d, *J* 8.6, Ar, C*H*), 7.32 (2H, d, *J* 8.6, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 8.1 (CH_3), 32.2 (CH_2), 37.0 (CH_2), 42.5 (CH_2), 45.2 (CH_2), 46.1 (CH_2), 55.3 (OCH_3), 55.4 (OCH_3), 57.0 (CH), 70.4 (*C*-3), 113.7 (Ar, CH), 114.2 (Ar, CH), 119.1 (H$_2$*C*=CH), 119.5 (H$_2$*C*=CH), 126.7 (Ar, C), 127.5 (Ar, C), 130.2 (*C*H=CH$_2$), 130.2 (*C*H=CH$_2$), 132.6 (Ar,

CH), 132.8 (Ar, CH), 158.9 (Ar, C), 159.4 (Ar, C), 167.2 (C=O), 167.4 (C=O); *m/z* (EI) $C_{28}H_{34}N_2O_5$ requires: 462.2519, found M^+: 462.2502.

3.3.3. (3R*,6S*)-3,6-Diallyl-1,4-bis-(4-methoxybenzyl)-3-phenylsulfanylpiperazine-2,5-dione rac-**13c**

The above general procedure was followed using *N*,*N*′-dibenzylethylene diamine (59 μL, 0.25 mmol), *n*-BuLi (0.32 mL of a 1.6 M solution in hexane, 0.50 mmol), (3*R**,6*S**)-3,6-diallyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **11a** (100 mg, 0.230 mmol) and diphenyl disulfide (0.25 g, 1.2 mmol), as a solution in THF (1.5 mL). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **13c** as a colourless solid (61 mg, 49%), mp 206–208 °C. ν_{max} ($CHCl_3$)/cm^{-1} 2998, 1657, 1613, 1403, 1303, 1036; δ_H (400 MHz, $CDCl_3$) 2.55 (1H, m, C*H*HCH=CH_2), 2.72 (1H, dddd, *J* 14.8, 7.4, 2.7, 1.4, C*H*HCH=CH_2), 2.77 (1H, dd, *J* 14.0, 5.6, C*H*HCH=CH_2), 3.15 (1H, dd, *J* 14.0, 8.0, C*H*HCH=CH_2), 3.19 (1H, dd, *J* 5.6, 2.9, NC*H*CO), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.14 (1H, d, *J* 14.7, NC*H*HAr), 4.64 (1H, d, *J* 15.1, NC*H*HAr), 4.71 (1H, d, *J* 14.7, NC*H*HAr), 4.77 (1H, dd, *J* 16.9, 1.9, H*H*C=$CHCH_2$), 4.84 (1H, dd, *J* 10.4, 1.9, H*H*C=$CHCH_2$), 4.96 (1H, dd, *J* 10.4, 1.9, H*H*C=$CHCH_2$), 5.00 (1H, dd, *J* 17.1, 1.9, H*H*C=$CHCH_2$), 5.05 (1H, m, H_2C=C*H*CH_2), 5.39 (1H, dddd, *J* 17.1, 10.4, 7.4, 7.4, H_2C=C*H*CH_2), 5.48 (1H, d, *J* 15.1, NC*H*HAr), 6.81 (2H, d, *J* 6.7, Ar–OMe, C*H*), 6.82 (2H, d, *J* 8.7, Ar–OMe, C*H*), 7.08 (2H, d, *J* 8.7, Ar–OMe, C*H*), 7.15 (2H, dd, *J* 8.2, 7.3, SAr, C*H*), 7.30 (2H, dd, *J* 8.2, 1.2, SAr, C*H*), 7.34 (2H, d, *J* 8.7, Ar–OMe, C*H*), 7.37 (1H, m, SAr, C*H*); δ_C (100 MHz, $CDCl_3$) 36.4 (CH_2), 40.1 (CH_2), 47.0 (CH_2), 47.5 (CH_2), 55.3 (OCH_3), 55.4 (OCH_3), 57.7 (CH), 80.0 (*C*-3), 113.8 (Ar, CH), 114.0 (Ar, CH), 119.8 (H_2C=CH), 120.8 (H_2C=CH), 127.6 (Ar, C), 129.2 (Ar, CH), 129.5 (Ar, C), 130.0 (Ar, C), 130.2 (Ar, CH), 130.4 (Ar, CH), 130.6 (*C*H=CH_2), 130.7 (*C*H=CH_2), 131.1 (Ar, CH), 137.0 (Ar, CH), 159.4 (2×Ar, C), 164.1 (C=O), 167.3 (C=O); *m/z* (CI) $C_{32}H_{35}N_2O_4S$ requires: 543.2318 found $[MH]^+$: 543.2318.

3.3.4. (3S*,6S*)-3-Allyl-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione rac-**13d**

The above general procedure was followed using *N*,*N*′-dibenzylethylene diamine (48 μL, 0.21 mmol), *n*-BuLi (0.32 mL of a 1.6 M solution in hexane, 0.50 mmol), (3*R**,6*S**)-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **11b** (100 mg, 0.187 mmol), allyl bromide (81 μL, 0.94 mmol) and THF (15 mL). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 4:1) to yield the title DKP **13d** as a colourless solid (74 mg, 69%), mp 58–60 °C. ν_{max} ($CHCl_3$)/cm^{-1} 2938, 2838, 1645, 1613, 1456, 1309, 1036; δ_H (400 MHz, $CDCl_3$) 1.31 (1H, dd, *J*, 14.6, 7.0, C*H*HPh), 2.27 (1H, dd, *J* 14.6, 4.4, C*H*HPh), 2.75 (1H, dd, *J* 14.3, 5.6, C*H*HCH=CH_2), 3.06 (1H, dd, *J* 14.3, 8.2, C*H*HCH=CH_2), 3.10 (1H, d, *J* 13.8, CC*H*HPh), 3.27 (1H, d, *J* 14.6, NC*H*HAr), 3.29 (1H, d, *J* 13.8, CC*H*HPh), 3.76 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.96 (1H, dd, *J* 7.0, 4.4, NC*H*CO), 4.54 (1H, d, *J* 14.6, NC*H*HAr), 4.86 (1H, dd, *J* 10.2, 2.0, H*H*C=$CHCH_2$), 4.91 (1H, dd, *J* 17.2, 2.0, H*H*C=$CHCH_2$), 5.09 (1H, d, *J* 14.6, NC*H*HAr), 5.10 (1H, m, H_2C=C*H*CH_2), 5.33 (1H, d, *J* 14.6, NC*H*HPMB), 6.69 (4H, br s, Ar–OMe, C*H*), 6.84 (2H, d, *J* 8.8, Ar, C*H*), 6.97 (2H, d, *J* 6.8, Ar, C*H*), 7.09 (2H, d, *J* 6.8, Ar, CH), 7.17–7.37 (6H, m, Ar, CH), 7.42 (2H, d, *J* 8.8, Ar, CH); δ_C (100 MHz, $CDCl_3$) 41.0 (CH_2), 43.0 (CH_2), 43.2 (CH_2), 46.3 (CH_2), 46.5 (CH_2), 55.3 (OCH_3), 55.4 (OCH_3), 59.3 (CH), 71.7 (*C*-3), 113.8 (Ar, CH), 113.9 (Ar, CH), 120.2 (H_2C=CH), 126.7 (Ar, CH), 127.0 (Ar, C), 127.7 (Ar, CH), 128.6 (Ar, CH), 128.9 (Ar, CH), 129.1 (Ar, CH), 130.2 (Ar, CH), 130.4 (Ar, C), 130.8 (Ar, CH), 131.0 (Ar, CH), 131.2 (CH_2=*C*H), 135.8 (Ar, C), 139.1 (Ar, C), 159.1 (2×Ar, C), 166.2 (C=O), 168.0 (C=O); *m/z* (EI) $C_{37}H_{38}N_2O_4$ requires: 574.2831, found M^+: 574.2841.

3.3.5. (3S*,6S*)-3,6-Dibenzyl-3-ethyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione rac-**13e**

The above general procedure was followed using *N*,*N*′-dibenzylethylene diamine (48 μL, 0.21 mmol), *n*-BuLi (0.26 mL of a 1.6 M solution in hexane, 0.41 mmol), (3*R**,6*S**)-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **11b** (100 mg, 0.187 mmol) and iodoethane (75 μL, 0.94 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 4:1) to yield the title DKP **13e** as a colourless solid (39 mg, 37%), mp 85–87 °C. ν_{max} ($CHCl_3$)/cm^{-1} 2938, 2838, 1644, 1613, 1455, 1035; δ_H (400 MHz, $CDCl_3$) 0.36 (3H, t, *J* 7.1, CH_3CH_2), 1.25 (1H, dd, *J* 14.6, 7.0, C*H*HPh), 1.94 (1H, dq, *J* 14.2, 7.1, C*H*HCH_3), 2.24 (1H, dd, *J* 14.6, 4.3, C*H*HPh), 2.32 (1H, dq, *J* 14.2, 7.1, C*H*HCH_3), 3.11 (1H, d, *J* 13.8, C*H*HPh), 3.27 (1H, d, *J* 13.8, C*H*HPh), 3.27 (1H, d, *J* 14.6, NC*H*HAr), 3.75 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.02 (1H, dd, *J* 7.0, 4.3, NC*H*CO), 4.36 (1H, d, *J* 14.8, NC*H*HAr), 5.18 (1H, d, *J* 14.6, NC*H*HAr), 5.34 (1H, d, *J* 14.8, NC*H*HAr), 6.68 (4H, br s, Ar–OMe, C*H*), 6.84 (2H, d, *J* 8.7, Ar, C*H*), 6.96 (2H, d, *J* 7.0, Ar, C*H*), 7.10 (2H, d, *J*, 7.0, Ar, C*H*), 7.17–7.31 (4H, m, Ar, C*H*), 7.35 (2H, app. t, *J* 7.5, Ar, C*H*), 7.42 (2H, d, *J* 8.7, Ar, CH); δ_C (100 MHz, $CDCl_3$) 8.1 (CH_3), 32.2 (CH_2), 41.0 (CH_2), 43.5 (CH_2), 46.3 (CH_2), 46.5 (CH_2), 55.3 (CH), 59.6 (2×OCH_3), 72.3 (*C*-3), 113.8 (Ar, CH), 114.0 (Ar, CH), 126.7 (Ar, CH), 127.3 (Ar, C), 127.7 (Ar, CH), 12.7 (Ar, CH), 128.9 (Ar, CH), 129.1 (Ar, CH), 130.0 (Ar, CH), 130.6 (Ar, C), 130.7 (Ar, CH), 130.9 (Ar, CH), 136.1 (Ar, C), 139.3 (Ar, C), 159.0 (Ar, C), 159.2 (Ar, C), 168.3 (C=O), 166.8 (C=O); *m/z* (EI) $C_{36}H_{38}N_2O_4$ requires: 562.2831, found M^+: 562.2820.

3.3.6. (3R*,6S*)-3,6-Dibenzyl-1,4-bis-(4-methoxybenzyl)-3-phenylsulfanylpiperazine-2,5-dione rac-**13f**

The above general procedure was followed using *N*,*N*′-dibenzylethylene diamine (48 μL, 0.21 mmol), *n*-BuLi (0.26 mL of a 1.6 M solution in hexane, 0.41 mmol), (3*R**,6*S**)-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **11b** (100 mg, 0.187 mmol) and diphenyl disulfide (204 mg, 0.94 mmol) as a solution in THF (1.5 mL). The

crude product was purified by flash column chromatography (petrol/EtOAc, 4:1) to yield the title DKP **13f** as a colourless solid (73 mg, 61%), mp 140–142 °C. ν_{max} ($CHCl_3$)/cm^{-1} 2936, 2838, 1657, 1613, 1455, 1402, 1351, 1310, 1036; δ_H (400 MHz, $CDCl_3$) 1.71 (1H, dd, *J* 14.6, 6.4, C*H*HPh), 2.08 (1H, dd, *J* 14.6, 5.8, C*H*HPh), 3.36 (1H, d, *J* 13.7, C*H*HPh), 3.43 (1H, d, *J* 14.7, NC*H*HAr), 3.60 (1H, dd, *J* 6.4, 5.8, COC*H*N), 3.71 (1H, d, *J* 13.7, C*H*HPh), 3.77 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.00 (1H, d, *J* 14.7, NC*H*HAr), 5.15 (1H, d, *J* 14.7, NC*H*HAr), 5.32 (1H, d, *J* 14.7, NC*H*HAr), 6.31 (2H, d, *J* 8.8, Ar–OMe, C*H*), 6.62 (2H, d, *J* 8.8, Ar–OMe, C*H*), 6.70–6.75 (4H, m, Ar, C*H*), 6.89 (2H, d, *J* 8.8, Ar–OMe, C*H*), 7.13–7.21 (8H, m, Ar, C*H*), 7.29 (2H, dd, *J* 8.7, 1.3, Ar, C*H*), 7.36 (1H, dddd, *J* 8.7, 6.2, 1.3, 1.3, Ar, C*H*), 7.48 (2H, d, *J* 8.8, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 41.1 (CH_2), 42.7 (CH_2), 47.1 (CH_2), 48.1 (CH_2), 55.3 (OCH_3), 55.4 (OCH_3), 59.0 (CH), 82.5 (*C*-3), 113.9 (Ar, CH), 113.9 (Ar, CH), 126.3 (Ar, C), 126.7 (Ar, CH), 127.6 (Ar, CH), 128.4 (Ar, CH), 128.5 (Ar, CH), 129.1 (Ar, CH), 129.3 (Ar, CH), 129.7 (Ar, CH), 130.0 (Ar, C), 130.1 (Ar, CH), 130.7 (Ar, C), 131.4 (Ar, CH), 131.7 (Ar, CH), 134.5 (Ar, C), 136.0 (Ar, CH), 137.7 (Ar, C), 159.1 (Ar, C), 159.3 (Ar, C), 163.8 (C=O), 167.3 (C=O); *m/z* (EI) $C_{40}H_{39}N_2O_4S$ requires: 643.2606, found $[MH]^+$: 643.2594.

3.3.7. (3R,6S*)-3-Benzyl-3,6-diethyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione* ***13g***

The above general procedure was followed using *N*,*N*′-dibenzylethylene diamine (32 μL, 0.14 mmol), *n*-BuLi (0.17 mL of a 1.6 M solution in hexane, 0.27 mmol), (3*R**,6*S**)-3,6-diethyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **11c** (50 mg, 0.12 mmol) and benzyl bromide (80 μL, 0.60 mmol). The crude product was purified by flash column chromatography (petrol/EtOAc, 4:1) to yield the title DKP **13g** as a colourless solid (44 mg, 72%), mp 138–141 °C. ν_{max} ($CHCl_3$)/cm^{-1} 2938, 2838, 1648, 1612, 1456, 1353, 1304, 1035; δ_H (400 MHz, $CDCl_3$) 0.46 (3H, dd, *J* 7.3, 7.3, CCH_2CH_3), 0.61 (3H, dd, *J* 7.3, 7.3, $CHCH_2CH_3$), 1.76 (1H, dqd, *J* 14.7, 7.3, 2.6, $CHCHHCH_3$), 1.92 (1H, dq, *J* 14.0, 7.3, $CCHHCH_3$), 2.10 (1H, dqd, *J* 14.7, 7.3, 2.6, $CHCHHCH_3$), 2.35 (1H, dq, *J* 14.7, 7.3, $CCHHCH_3$), 3.09 (1H, dd, *J* 2.6, 2.6, COC*H*N), 3.19 (1H, d, *J* 13.7, C*H*HPh), 3.27 (1H, d, *J* 13.7, C*H*HPh), 3.80 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.05 (1H, d, *J* 14.6, NC*H*HAr), 4.07 (1H, d, *J* 14.6, NC*H*HAr), 4.76 (1H, d, *J* 14.6, NC*H*HAr), 5.48 (1H, d, *J* 14.6, NC*H*HAr), 6.77 (2H, d, *J* 8.7, Ar–OMe, C*H*), 6.83 (2H, d, *J* 8.7, Ar–OMe, C*H*), 6.95 (2H, d, *J* 8.7, Ar–OMe, C*H*), 6.98 (2H, d, *J* 6.6, Ar, C*H*), 7.12 (2H, dd, *J* 8.6, 6.6, Ar, C*H*), 7.21 (1H, dddd, *J* 8.2, 6.6, 1.2, 1.2, Ar, C*H*), 7.43 (2H, d, *J* 8.7, C Ar–OMe, C*H*); δ_C (100 MHz, $CDCl_3$) 7.5 (CH_3), 8.8 (CH_3), 24.2 (CH_2), 31.5 (CH_2), 44.2 (CH_2), 45.9 (CH_2), 46.7 (CH_2), 55.3 (OCH_3), 55.3 (OCH_3), 58.0 (CH), 71.9 (*C*-3), 113.8 (Ar, CH), 113.9 (Ar, CH), 127.7 (Ar, C), 128.5 (Ar, CH), 291.1 (Ar, C), 130.1 (Ar, CH), 130.2 (Ar, CH), 130.4 (Ar, CH), 130.7 (Ar, CH), 135.2 (Ar, C), 158.9 (Ar, C), 159.0 (Ar, C), 167.8 (C=O), 168.2 (C=O); *m/z* (EI) $C_{31}H_{36}N_2O_4$ requires: 500.2675, found M^+: 500.2661.

3.3.8. Ring-closing metathesis to give (Z)-1-benzyl-7,9-bis-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2]dec-3-ene-8,10-dione ***18***

To a solution of (3*R**,6*S**)-3,6-diallyl-3-benzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione (*rac*-**13a**) (38 mg, 0.072 mmol) in toluene (5 mL) was added Grubb's 2nd generation catalyst (6.0 mg 0.01 mmol) and the mixture was heated at 70 °C for 16 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (petrol/EtOAc, 7:3) to yield the bicyclic DKP **18** as a colourless solid (33 mg, 92%), mp 176–179 °C. ν_{max} ($CHCl_3$)/cm^{-1} 2975, 2935, 2838, 1660, 1613, 1455, 1353, 1319, 1304, 1036; δ_H (400 MHz, $CDCl_3$) 2.18 (1H, app. dq, *J* 18.8, 2.1, C*H*HCH=CH), 2.64 (1H, m, C*H*HCH=CH), 2.92–2.96 (2H, m, C*H*HCH=CH), 3.20 (1H, d, *J* 16.8, C*H*HPh), 3.73 (1H, d, *J* 15.4, NC*H*HAr), 3.80 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.90 (1H, d, *J* 14.6, NC*H*HAr), 3.95 (1H, d, *J* 16.8, C*H*HPh), 4.18 (1H, app t, *J* 3.8, NC*H*CO), 4.95 (1H, m, C*H*=CH), 5.24 (1H, m, C*H*=CH), 5.28 (1H, d, *J* 14.6, NC*H*HAr), 5.46 (1H, d, *J* 15.4, NC*H*HAr), 6.70 (2H, d, *J* 8.7, Ar–OMe, C*H*), 6.88 (2H, d, *J* 8.7, Ar–OMe, C*H*), 7.14–7.28 (9H, m, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 35.9 (CH_2), 40.9 (CH_2), 45.3 (CH_2), 46.2 (CH_2), 47.2 (CH_2), 55.3 (OCH_3), 55.4 (OCH_3), 57.2 (NCHCO), 65.6 (N*C*CO), 113.8 (Ar, CH), 114.3 (Ar, CH), 122.1 (HC=CH), 124.0 (HC=CH), 126.5 (CH), 127.8 (Ar, C), 128.1 (Ar, CH), 128.7 (Ar, CH), 129.4 (Ar, CH), 130.0 (Ar, CH), 130.1 (Ar, C), 136.6 (Ar, C), 159.1 (Ar, C), 159.5 (Ar, C), 168.8 (C=O), 169.3 (C=O); *m/z* (ESI) $C_{31}H_{32}N_2NaO_4$ requires: 519.2254, found $[MNa]^+$: 519.2252.

3.4. Typical procedure for substitution of cis-DKP ***22a*** *to give products* ***13*** *(Table 2)*

In the case of DKP **22a** the same procedure was followed as for the centrosymmetric *trans*-DKPs **11** (see typical procedure for product **13a**).

3.4.1. (3S,6S)-3-Allyl-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione ***13d***

The general procedure was followed, using *N*,*N*′-dibenzylethylene diamine (48 μL, 0.21 mmol), *n*-BuLi (0.26 mL of a 1.6 M solution in hexanes, 0.41 mmol), (3*S*,6*S*)-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **22a** (100 mg, 0.187 mmol), THF (13 mL) and allyl bromide (80 μL, 0.94 mmol).

The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield DKP (−)-**13d** as a colourless solid (98 mg, 91%), mp 59–61 °C. $[\alpha]_D^{18}$ −98.7 (*c* 0.51, $CHCl_3$); spectroscopic data were identical to those for the racemic material.

3.4.2. (3S,6S)-3,6-Dibenzyl-3-ethyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione ***13e***

The general procedure was followed using *N*,*N*′-dibenzylethylene diamine (48 μL, 0.21 mmol), *n*-BuLi (0.26 mL of a 1.6 M solution in hexanes, 0.41 mmol), (3*S*,6*S*)-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **22a**

(100 mg, 0.187 mmol), THF (15 mL) and iodoethane (70 μL, 0.94 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield DKP (−)-**13e** as a colourless solid (98 mg, 91%), mp 91–93 °C. $[\alpha]_D^{18}$ −94.4 (*c* 0.62, $CHCl_3$); spectroscopic data were identical to those for the racemic material.

3.4.3. (3*R*,6*S*)-3,6-Dibenzyl-1,4-bis-(4-methoxybenzyl)-3-phenylsulfanylpiperazine-2,5-dione **13f**

The general procedure was followed using *N*,*N*′-dibenzylethylene diamine (48 μL, 0.21 mmol), *n*-BuLi (0.26 mL of a 1.6 M solution in hexanes, 0.41 mmol), (3*S*,6*S*)-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **22a** (100 mg, 0.187 mmol), THF (15 mL) and diphenyl disulfide (200 mg, 0.94 mmol) as a solution in THF (1 mL). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP (+)-**13f** as a colourless solid (120 mg, 99%), mp 146–149 °C. $[\alpha]_D^{18}$ +22.3 (*c* 0.67, $CHCl_3$); spectroscopic data were identical to those for the racemic material.

3.4.4. (3*S*,6*S*)-1,4-Bis-(4-methoxybenzyl)-3,6-dibenzyl-3-(hydroxyl(phenyl)methyl)piperazine-2,5-dione **13h**

The general procedure was followed using *N*,*N*′-dibenzylethylene diamine (48 μL, 0.21 mmol), *n*-BuLi (0.26 mL of a 1.6 M solution in hexanes, 0.41 mmol), (3*S*,6*S*)-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **22a** (100 mg, 0.187 mmol), THF (15 mL) and benzaldehyde (0.10 mL, 0.94 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **13h**, as a 1:1 mixture of diastereoisomers, as a colourless solid (109 mg, 96%). An analytical sample was prepared by preparative TLC (petrol/EtOAc, 4:1), mp 70–72 °C. ν_{max} ($CHCl_3$)/cm^{-1} 3603, 2936, 2838, 1650, 1612, 1444, 1357, 1304, 1036; δ_H (400 MHz, $CDCl_3$) 1.52 (1H, dd, *J* 14.6, 6.1, CHC*H*HPh), 2.14 (1H, dd, *J* 14.6, 5.0, CHC*H*HPh), 3.41 (1H, d, *J* 14.6, NC*H*HAr), 3.44 (1H, d, *J* 14.3, CC*H*HPh), 3.60 (1H, dd, *J* 6.1, 5.0, C*H*CH_2Ph), 3.75 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.13 (1H, d, *J* 14.3, CC*H*HPh), 4.84 (1H, d, *J* 14.6, NC*H*HAr), 5.00 (1H, d, *J* 14.6, NC*H*HAr), 5.06 (1H, d, *J* 14.6, NC*H*HAr), 5.31 (1H, d, *J* 11.1, C*H*OH), 5.88 (1H, d, *J* 11.1, CHO*H*), 6.10 (2H, d, *J* 8.8, Ar, C*H*), 6.54 (2H, d, *J* 8.5, Ar, C*H*), 6.77 (2H, dd, *J* 7.3, 3.5, Ar, C*H*), 6.82 (2H, d, *J* 8.8, Ar, C*H*), 6.88–6.92 (2H, m, Ar, C*H*), 7.04 (2H, d, *J* 7.3, Ar, C*H*), 7.10 (2H, dd, *J* 7.3, 7.3, Ar, C*H*), 7.16–7.22 (7H, m, Ar, C*H*), 7.43 (2H, d, *J* 8.8, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 39.6 (CH_2), 40.6 (CH_2), 46.1 (CH_2), 47.2 (CH_2), 55.3 (OCH_3), 55.4 (OCH_3), 58.6 (CH), 72.8 (*C*-3), 75.8 (CH), 113.9 (Ar, CH), 114.1 (Ar, CH), 125.4 (Ar, C), 126.7 (Ar, CH), 127.0 (Ar, CH), 127.5 (Ar, CH), 127.7 (Ar, CH), 128.3 (Ar, CH), 128.5 (Ar, CH), 128.7 (Ar, CH), 129.0 (Ar, CH), 129.9 (Ar, C), 130.0 (Ar, CH), 131.3 (Ar, CH), 131.7 (Ar, CH), 135.5 (Ar, C), 138.4 (Ar, C), 139.5 (Ar, C), 159.1 (Ar, C), 159.4 (Ar, C), 167.3 (C=O), 167.7 (C=O); *m*/*z* (ESI) $C_{41}H_{40}N_2NaO_5$ requires: 663.2829, found $[MNa]^+$: 663.2803.

Second isomer δ_H (400 MHz, $CDCl_3$) 1.66 (1H, dd, *J* 14.7, 6.4, CHC*H*HPh), 2.35 (1H, dd, *J* 14.7, 4.7, CHC*H*HPh), 3.41 (1H, d, *J* 14.0, CC*H*HAr), 3.44 (1H, d, *J* 14.9, NC*H*HAr), 3.45 (1H, br s, O*H*), 3.77 (1H, d, *J* 14.0, CC*H*HPh), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.86 (1H, dd, *J* 6.4, 4.7, C*H*CH_2Ph), 4.86 (1H, d, *J* 14.9, NC*H*HAr), 5.19 (1H, d, *J* 14.9, NC*H*HAr), 5.35 (1H, d, *J* 14.9, NC*H*HAr), 5.51 (1H, br s, C*H*OH), 6.71 (4H, br s, Ar, C*H*), 6.84 (2H, d, *J* 8.8, Ar, C*H*), 6.88 (4H, m, Ar, C*H*), 7.19–7.29 (11H, m, Ar, C*H*), 7.39 (2H, d, *J* 8.8, Ar, C*H*).

3.4.5. (3*S*,6*S*)-3-Carboethoxy-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **13i**

The general procedure was followed using *N*,*N*′-dibenzylethylene diamine (48 μL, 0.21 mmol), *n*-BuLi (0.26 mL of a 1.6 M solution in hexanes, 0.41 mmol) (3*S*,6*S*)-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **22a** (100 mg, 0.187 mmol), THF (15 mL) and ethyl cyanoformate (90 μL, 0.94 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP (−)-**13i** as a colourless oil (111 mg, 98%), $[\alpha]_D^{18}$ −14.8 (*c* 0.97, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2838, 1746, 1657, 1613, 1455, 1356, 1304, 1039; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, dd, *J* 7.2, 7.2, C$H_3$$CH_2$), 1.00 (1H, dd, *J* 14.5, 6.4, C*H*HPh), 2.32 (1H, dd, *J* 14.5, 4.0, C*H*HPh), 3.06 (1H, d, *J* 14.8, NC*H*HAr), 3.24 (1H, dq, *J* 10.7, 7.2, C*H*HCH_3), 3.60 (1H, d, *J* 14.3, C*H*HPh), 3.74 (1H, d, *J* 14.3, C*H*HPh), 3.76 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.96 (1H, dq, *J* 10.7, 7.2, C*H*HCH_3), 3.97 (1H, dd, *J* 6.4, 4.0, NC*H*CO), 4.32 (1H, d, *J* 14.9, NC*H*HAr), 5.13 (1H, d, *J* 14.9, NC*H*HAr), 5.33 (1H, d, *J* 14.8, NC*H*HAr), 6.68 (4H, br s, Ar–OMe, C*H*), 6.84 (2H, d, *J* 8.6, Ar–OMe, C*H*), 6.93 (2H, d, *J* 6.8, Ar, CH), 7.14 (2H, d, *J* 7.2, Ar, CH), 7.21–7.35 (6H, m, Ar, CH), 7.41 (2H, app t, *J* 7.5, Ar, CH); δ_C (125 MHz, $CDCl_3$) 13.5 (CH_3), 38.2 (CH_2), 41.1 (CH_2), 46.3 (CH_2), 46.8 (CH_2), 55.3 (OCH_3), 55.4 (OCH_3), 59.2 (CH), 62.4 (CH_2), 72.7 (*C*-3), 113.6 (Ar, CH), 113.9 (Ar, CH), 126.8 (Ar, C), 126.9 (Ar, CH), 128.0 (Ar, CH), 128.5 (Ar, C), 128.7 (Ar, CH), 129.0 (Ar, CH), 129.2 (Ar, CH), 129.6 (Ar, CH), 130.6 (Ar, CH), 131.2 (Ar, CH), 134.7 (Ar, C), 138.9 (Ar, C), 159.2 (Ar, C), 159.2 (Ar, C), 163.4 (C=O), 167.0 (C=O), 167.8 (C=O); *m*/*z* (EI) $C_{37}H_{38}N_2O_6$ requires: 606.2730, found M^+: 606.2738.

3.5. Typical procedure for substitution of cis-DKP **22c** to give products **13j–o** (Table 2)

3.5.1. (3*R*,6*S*)-3-Allyl-1,4-bis-(4-methoxybenzyl)-3,6-dimethylpiperazine-2,5-dione **13j**

To a solution of *N*,*N*′-dibenzylethylene diamine (67 μL, 0.29 mmol) in THF (3 mL) at −78 °C was added *n*-BuLi (0.36 mL of a 1.6 M solution in hexane, 0.57 mmol). The solution was warmed to rt for 10 min, before being recooled to −78 °C. The basic solution was added via cannula to a solution of (3*S*,6*S*)-3,6-dimethyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **22c** (100 mg, 0.261 mmol) in THF (30 mL) at −78 °C. After 60 min, allyl bromide (0.23 mL, 2.6 mmol) was added and the solution was stirred for a further 75 min. The

reaction mixture was quenched by the careful addition of a saturated solution of ammonium chloride (10 mL). After warming to rt the mixture was separated and the organic phase was washed with brine (10 mL). The aqueous phase was extracted with CH_2Cl_2 (25 mL), the combined organic extracts dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 2:1) to yield the DKP (+)-**13j** as a colourless oil (92 mg, 84%), mp 93–94 °C. $[\alpha]_D^{24}$ +4.2 (*c* 1.4, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2838, 1657, 1650, 1614, 1461, 1304, 1038; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, s, CC*H*$_3$), 1.56 (3H, d, *J* 6.9, CHC*H*$_3$), 2.62 (1H, dd, *J* 14.7, 7.0, C*H*HCH=CH_2), 3.00 (1H, dd, *J* 14.7, 7.1, C*H*HCH=CH_2), 3.78 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 3.89 (1H, d, *J* 14.7, NC*H*HAr), 3.96 (1H, q, *J* 6.9, NC*H*CO), 4.17 (1H, d, *J* 15.4, NC*H*HAr), 5.05 (1H, dd, *J* 10.3, 1.5, H*H*C=CH), 5.11 (1H, d, *J* 15.4, NC*H*HAr), 5.11 (1H, dd, *J* 17.2, 1.5, H*H*C=CH), 5.37 (1H, d, *J* 14.7, NC*H*HAr), 5.45 (1H, dddd, *J* 17.2, 10.3, 7.1, 7.0, CH_2C*H*=CH_2), 6.83 (2H, d, *J* 6.8, Ar, C*H*), 6.86 (2H, d, *J* 6.8, Ar, C*H*), 7.20 (4H, app. t, *J* 9.0, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 19.8 (CH_3), 27.0 (CH_3), 42.5 (CH_2), 44.9 (CH_2), 46.4 (CH_2), 53.7 (CH), 55.3 (OCH_3), 55.3 (OCH_3), 65.6 (*C*-3), 114.0 (Ar, CH), 114.2 (Ar, CH), 120.2 (*C*H_2=CH), 127.6 (Ar, C), 128.8 (Ar, CH), 129.9 (Ar, CH), 130.4 (Ar, C), 131.6 (*C*H=CH_2), 158.8 (Ar, C), 159.4 (Ar, C), 167.9 (C=O), 168.3 (C=O); *m/z* (EI) $C_{25}H_{30}N_2O_4$ requires: 442.2206, found M^+: 442.2200.

3.5.2. (3R,6S)-3-Ethyl-1,4-bis-(4-methoxybenzyl)-3,6-dimethylpiperazine-2,5-dione ***13k***

The general procedure was followed using *N*,*N*′-dibenzylethylene diamine (67 μL, 0.29 mmol), *n*-BuLi (0.36 mL of a 1.6 M solution in hexane, 0.57 mmol), (3*S*,6*S*)-3,6-dimethyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **22c** (100 mg, 0.261 mmol) and iodoethane (0.21 mL, 2.6 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the DKP (+)-**13k** as a colourless solid (50 mg, 47%), 100–102 °C. $[\alpha]_D^{24}$ +12.0 (*c* 0.97, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2936, 2838, 1650, 1613, 1462, 1354.8, 1304, 1037; δ_H (500 MHz, $CDCl_3$) 0.65 (3H, dd, *J* 7.3, 7.3, CH_2C*H*$_3$), 1.38 (3H, s, C*H*$_3$), 1.57 (3H, d, *J* 6.9, CHC*H*$_3$), 1.87 (1H, dq, *J* 14.5, 7.3, C*H*HCH$_3$), 2.29 (1H, dq, *J* 14.5, 7.3, C*H*HCH$_3$), 3.79 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 3.87 (1H, d, *J* 14.7, NC*H*HAr), 4.00 (1H, q, *J* 6.9, NC*H*CO), 4.21 (1H, d, *J* 15.3, NC*H*HAr), 4.99 (1H, d, *J* 15.3, NC*H*HAr), 5.41 (1H, d, *J* 14.7, NC*H*HAr), 6.83 (2H, d, *J* 8.8, CH_3OCC*H*), 6.86 (2H, d, *J* 8.7, Ar, C*H*), 7.19 (2H, d, *J* 8.7, Ar, C*H*), 7.23 (2H, d, *J* 8.8, CH_3OCCHC*H*); δ_C (125 MHz, $CDCl_3$) 8.6 (CH_3), 19.8 (CH_3), 27.4 (CH_3), 31.5 (CH_2), 44.7 (CH_2), 46.5 (CH_2), 53.8 (CH), 55.4 (2×OCH_3), 66.2 (*C*-3), 114.0 (Ar, CH), 114.3 (Ar, CH), 127.7 (Ar, C), 129.0 (Ar, CH), 129.8 (Ar, CH), 130.6 (Ar, C), 158.8 (Ar, C), 159.4 (Ar, C), 168.4 (C=O), 168.6 (C=O); *m/z* (EI) $C_{24}H_{30}N_2O_4$ requires: 410.2206, found M^+: 410.2198.

3.5.3. (3R,6S)-1,4-Bis-(4-methoxybenzyl)-3,6-dimethyl-3-phenylsulfanylpiperazine-2,5-dione ***13l***

The general procedure was followed using *N*,*N*′-dibenzylethylene diamine (67 μL, 0.29 mmol), *n*-BuLi (0.36 mL of a 1.6 M solution in hexane, 0.57 mmol), (3*S*,6*S*)-3,6-dimethyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **22c** (100 mg, 0.261 mmol), THF (30 mL) and diphenyl disulfide (1.1 g, 5.2 mmol) as a solution in THF (10 mL). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the DKP (−)-**13l** as a colourless solid (104 mg, 81%), mp 124–126 °C. $[\alpha]_D^{24}$ −6.2 (*c* 1.1, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2936, 2838, 1658, 1613, 1455, 1304, 1036; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.9, CHC*H*$_3$), 1.72 (3H, s, CC*H*$_3$), 3.05 (1H, q, *J* 6.9, NC*H*CO), 3.79 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 4.23 (1H, d, *J* 14.8, NC*H*HAr), 4.58 (1H, d, *J* 15.7, NC*H*HAr), 4.69 (1H, d, *J* 14.9, NC*H*HAr), 5.44 (1H, d, *J* 15.7, NC*H*HAr), 6.82–6.88 (4H, m, Ar, C*H*), 7.05 (2H, d, *J* 9.0, Ar, C*H*), 7.16–7.21 (4H, m, Ar, C*H*), 7.34 (1H, dd, *J* 8.3, 1.4, Ar, C*H*), 7.40 (1H, m, Ar, C*H*), 7.51 (1H, d, *J* 8.1, 1.4, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 20.5 (CH_3), 26.2 (CH_3), 46.1 (CH_2), 47.6 (CH_2), 54.2 (CH), 55.3 (OCH_3), 55.4 (OCH_3), 75.5 (*C*-3), 114.0 (Ar, CH), 114.1 (Ar, CH), 127.8 (Ar, C), 128.3 (Ar, CH), 129.2 (Ar, CH), 129.8 (Ar, C), 130.0 (Ar, CH), 130.0 (Ar, C), 130.4 (Ar, CH), 137.1 (Ar, CH), 158.7 (Ar, C), 159.2 (Ar, C), 165.2 (C=O), 168.2 (C=O); *m/z* (CI) $C_{28}H_{31}N_2O_4S$ requires: 491.2005, found $[MH]^+$: 491.2003.

3.5.4. (3S,6S)-3-Carboethoxy-1,4-bis-(4-methoxybenzyl)-3,6-dimethylpiperazine-2,5-dione ***13m***

The general procedure was followed using *N*,*N*′-dibenzylethylene diamine (67 μL, 0.29 mmol), *n*-BuLi (0.36 mL of a 1.6 M solution in hexane, 0.57 mmol), (3*S*,6*S*)-3,6-dimethyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **22c** (100 mg, 0.261 mmol), THF (30 mL) and ethyl cyanoformate (0.52 mL, 5.2 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the DKP (−)-**13m** as a colourless oil (108 mg, 91%). $[\alpha]_D^{26}$ −86.9 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2939, 1749, 1660, 1456, 1303, 1114, 1036; δ_H (400 MHz, $CDCl_3$) 1.11 (3H, dd, *J* 7.2, 7.2, CH_2C*H*$_3$), 1.57 (3H, d, *J* 7.0, CHC*H*$_3$), 1.71 (3H, s, CC*H*$_3$), 3.73 (1H, dq, *J* 10.7, 7.2, OC*H*HCH$_3$), 3.78 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 3.86 (1H, d, *J* 14.9, NC*H*HAr), 4.00 (1H, q, *J* 7.0, NC*H*CO), 4.11 (1H, dq, *J* 10.7, 7.2, OC*H*HCH$_3$), 4.33 (1H, d, *J* 15.3, NC*H*HAr), 4.59 (1H, d, *J* 15.3, NC*H*HAr), 5.40 (1H, d, *J* 14.9, NC*H*HAr), 6.81 (2H, d, *J* 8.7, Ar, C*H*), 6.85 (2H, d, *J* 8.7, Ar, C*H*), 7.17 (4H, app. t, *J* 10.4, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 13.7 (CH_3), 19.4 (CH_3), 22.3 (CH_3), 46.3 (CH_2), 46.8 (CH_2), 53.8 (CH), 55.3 (OCH_3), 55.3 (OCH_3), 62.5 (CH_2), 68.4 (*C*-3), 113.8 (Ar, CH), 114.3 (Ar, CH), 127.3 (Ar, C), 129.0 (Ar, C), 129.4 (Ar, CH), 129.6 (Ar, CH), 159.0 (Ar, C), 159.4 (Ar, C), 164.9 (C=O), 167.4 (C=O), 168.0 (C=O); *m/z* (EI) $C_{25}H_{30}N_2O_6$ requires: 454.2104, found M^+: 454.2112.

3.5.5. (S)-1,4-Bis-(4-methoxybenzyl)-3,3,6-trimethylpiperazine-2,5-dione ***13n***

The general procedure was followed using *N*,*N*′-dibenzylethylene diamine (67 μL, 0.29 mmol), *n*-BuLi (0.36 mL of a 1.6 M solution in hexane, 0.57 mmol), (3*S*,6*S*)-3,6-dimethyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **22c**

(100 mg, 0.261 mmol), THF (30 mL) and methyl iodide (0.80 μL, 1.3 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 2:1) to yield DKP (−)-**13n** as a colourless oil (79 mg, 76%). $[\alpha]_D^{25}$ −51.2 (*c* 1.15, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2935, 2838, 1650, 1454, 1355, 1304, 1036; δ_H (500 MHz, $CDCl_3$) 1.45 (3H, s, C*H*$_3$), 1.54 (3H, d, *J* 7.0, CHC*H*$_3$), 1.58 (3H, s, C*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 3.99 (1H, d, *J* 14.7, NC*H*HAr), 4.03 (1H, q, *J* 7.0, NC*H*CO), 4.58 (1H, d, *J* 15.4, NC*H*HAr), 4.70 (1H, d, *J* 15.4, NC*H*HAr), 5.23 (1H, d, *J* 14.7, NC*H*HAr), 6.83 (2H, d, *J* 8.6, Ar, C*H*), 6.87 (2H, d, *J* 8.6, Ar, C*H*), 7.17 (4H, d, *J* 8.6, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 19.0 (CH_3), 26.3 (CH_3), 27.7 (CH_3), 45.3 (CH_2), 46.8 (CH_2), 54.3 (CH), 55.3 (OCH_3), 55.4 (OCH_3), 61.8 (*C*-3), 114.0 (Ar, CH), 114.3 (Ar, CH), 127.9 (Ar, C), 127.9 (Ar, C), 128.5 (Ar, CH), 129.5 (Ar, CH), 158.7 (Ar, C), 159.4 (Ar, C), 168.2 (C=O), 169.3 (C=O); *m*/*z* (ESI) $C_{23}H_{30}N_2O_4$ requires: 397.2122, found $[MH]^+$: 397.2127.

*3.5.6. (3R,6S)-3-Benzyl-1,4-bis-(4-methoxybenzyl)-3,6-dimethylpiperazine-2,5-dione **13o***

The general procedure was followed using *N*,*N*′-dibenzylethylene diamine (67 μL, 0.29 mmol), *n*-BuLi (0.36 mL of a 1.6 M solution in hexane, 0.57 mmol), (3*S*,6*S*)-3,6-dimethyl-1,4-bis-(4-methoxybenzyl)piperazine-2,5-dione **22c** (100 mg, 0.261 mmol), THF (30 mL) and benzyl bromide (0.31 mL, 2.6 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the DKP (+)-**13o** as a colourless solid (112 mg, 91%), mp 191−193 °C. $[\alpha]_D^{26}$ +2.3 (*c* 0.32, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2939, 2838, 1643, 1614, 1461, 1405, 1304, 1038; δ_H (400 MHz, $CDCl_3$) 1.44 (3H, d, *J* 6.8, CHC*H*$_3$), 1.62 (3H, s, CC*H*$_3$), 3.19 (1H, d, *J* 14.0, C*H*HPh), 3.22 (1H, q, *J* 6.8, COC*H*N), 3.38 (1H, d, *J* 14.0, C*H*HPh), 3.80 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 4.08 (1H, d, *J* 14.8, NC*H*HAr), 4.18 (1H, d, *J* 15.4, NC*H*HAr), 4.92 (1H, d, *J* 14.8, NC*H*HAr), 5.43 (1H, d, *J* 15.4, NC*H*HAr), 6.78 (2H, d, *J* 8.7, Ar−OMe, C*H*), 6.87 (4H, d, *J* 8.8, Ar, C*H*), 7.06 (2H, dd, *J* 8.5, 1.5, Ar, C*H*), 7.19−7.30 (5H, m, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 20.0 (CH_3), 27.2 (CH_3), 44.0 (CH_2), 45.4 (CH_2), 46.7 (CH_2), 53.6 (OCH_3), 53.7 (OCH_3), 55.3 (CH), 66.7 (*C*-3), 114.0 (Ar, CH), 114.1 (Ar, CH), 127.2 (CH Ar), 127.4 (Ar, C), 128.3 (Ar, CH), 128.6 (Ar, CH), 129.6 (Ar, CH), 129.9 (Ar, CH), 130.0 (Ar, C), 135.4 (Ar, C), 158.6 (Ar, C), 159.0 (Ar, C), 167.8 (C=O), 168.1 (C=O); *m*/*z* (EI) $C_{29}H_{32}N_2O_4$ requires: 472.2362, found M^+: 472.2355.

*3.5.7. Sulfoxide syn-elimination to give (S)-1,4-bis-(4-methoxybenzyl)-3-methyl-6-methylenepiperazine-2,5-dione **23a***

To a solution of (3*R*,6*S*)-1,4-bis-(4-methoxybenzyl)-3,6-dimethyl-3-phenylsulfanylpiperazine-2,5-dione **13l** (50 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (68 mg, 0.22 mmol) and the reaction mixture was stirred at rt for 16 h. A saturated solution of sodium hydrogencarbonate (10 mL) was added and the mixture was stirred for a further 30 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Toluene (15 mL) was added to the resultant red oil and the solution heated at reflux for 2 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 4:1) to yield the title DKP (−)-**23a** as a colourless solid (27 mg, 70%), mp 70−72 °C. $[\alpha]_D^{24}$ −95.2 (*c* 0.60, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2936, 2838, 1682, 1614, 1352, 1305, 1037; δ_H (500 MHz, $CDCl_3$) 1.51 (3H, d, *J* 7.0, CHC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 4.08 (1H, d, *J* 14.6, NC*H*HAr), 4.09 (1H, q, *J* 7.0, NC*H*CO), 4.57 (1H, d, *J* 15.5, NC*H*HAr), 4.99 (1H, d, *J* 1.2, C=C*H*H), 5.18 (1H, d, *J* 15.5, NC*H*HAr), 5.23 (1H, d, *J* 14.6, NC*H*HAr), 5.83 (1H, d, *J* 1.2, C=C*H*H), 6.87 (4H, app. t, *J* 8.4, Ar, C*H*), 7.11 (2H, d, *J* 8.6, Ar, C*H*), 7.22 (2H, d, *J* 8.6, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 19.6 (CH_3), 46.6 (CH_2), 47.1 (CH_2), 55.2 (OCH_3), 55.3 (OCH_3), 55.4 (CH), 104.9 (C=*C*H$_2$), 114.3 (Ar, CH), 114.4 (Ar, CH), 127.6 (Ar, C), 128.0 (Ar, CH), 129.9 (Ar, CH), 129.9 (Ar, *C*), 136.4 (CH_2=*C*), 158.8 (Ar, C), 159.0 (Ar, C), 159.5 (C=O), 166.6 (C=O); *m*/*z* (ESI) $C_{22}H_{24}N_2NaO_4$ requires: 403.1628, found $[MNa]^+$: 403.1618.

*3.5.8. Sulfoxide syn-elimination to give (S)-1,4-bis-(4-methoxybenzyl)-3-benzyl-6-benzylidenepiperazine-2,5-dione (**23b**) as an E/Z mixture*

To a solution of (3*R*,6*S*)-3,6-dibenzyl-1,4-bis-(4-methoxybenzyl)-3-phenylsulfanylpiperazine-2,5-dione **13f** (100 mg, 0.192 mmol) in CH_2Cl_2 (20 mL) was added *m*-CPBA (57 mg, 0.19 mmol) and the reaction mixture was stirred at rt for 4 h. A saturated solution of $NaHCO_3$ (15 mL) was added and the mixture stirred for a further 30 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Toluene (15 mL) was added to the resultant red oil and the solution heated at reflux for 2 h. The solvent was then evaporated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petrol/EtOAc, 4:1) to yield **23b** as a colourless solid, and as a 1.4:1 mixture of stereoisomers (80 mg, 97%).

Data for mixture of ***Z*-23b** and ***E*-23b***: mp 75−78 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2935, 2838, 1681, 1626, 1456, 1386, 1353, 1304, 1036; δ_H (500 MHz, $CDCl_3$) 3.10 (1H, dd, *J* 13.6, 8.1, C*H*HPh), 3.20 (1H, dd, *J* 13.6, 6.6, C*H*HPh*), 3.24 (1H, d, *J* 14.9, NC*H*HAr), 3.25 (1H, dd, *J* 13.6, 5.1, C*H*HPh), 3.28 (1H, dd, *J* 13.6, 4.7, C*H*HPh*), 3.48 (1H, d, *J* 14.9, NC*H*HAr*), 3.76 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$*), 3.81 (3H, s, OC*H*$_3$*), 3.87 (1H, d, *J* 14.9, NC*H*HAr), 4.16 (1H, dd, *J* 8.1, 5.1, C*H*CH$_2$Ph), 4.31 (1H, dd, *J* 6.6, 4.7, C*H*CH$_2$Ph*), 4.90 (2H, br s, NC*H*$_2$Ar*), 5.17 (1H, d, *J* 14.9, NC*H*HAr), 5.23 (1H, d, *J* 14.9, NC*H*HAr), 5.29 (1H, *J* 14.9, NC*H*HAr*), 6.35 (1H, s, C=C*H*Ph*), 6.72 (2H, d, *J* 8.9, Ar−OMe, C*H*), 6.77 (2H, d, *J* 8.5, Ar−OMe, C*H*), 6.80 (2H, d, *J* 9.0, Ar−OMe, C*H*), 7.10 (2H, d, *J* 8.5, Ar−OMe, C*H*), 7.11 (1H, s, C=C*H*Ph), 7.14 (2H, d, *J* 9.0, Ar−OMe, C*H*), 7.18 (2H, d, *J* 8.7, Ar−OMe, C*H*),

7.18–7.28 (15H, m, Ar, C*H*), 7.30 (2H, d, *J* 7.3, Ar, C*H*), 7.31 (2H, d, *J* 7.3, Ar, C*H*), 7.38 (1H, d, *J* 7.3, Ar, C*H**), 7.42 (1H, dd, *J* 7.3, 7.3, Ar, C*H*), 7.44 (1H, d, *J* 7.3, Ar, C*H**); δ_C (125 MHz, $CDCl_3$) 38.4 (CH_2*), 38.7 (CH_2), 47.2 (CH_2*), 47.4 (2×CH_2), 47.7 (CH_2*), 55.2 (OCH_3), 55.3 (OCH_3), 60.8 (CH*), 61.8 (CH), 113.8 (Ar, CH), 114.2 (Ar, CH), 114.2 (Ar, CH), 114.3 (Ar, CH), 122.9 (C=*C*H), 123.9 (C=*C*H*), 127.6 (Ar, CH), 127.7 (Ar, CH), 127.7 (Ar, CH), 127.7 (Ar, CH), 127.8 (Ar, CH), 128.5, 128.6 (Ar, C), 128.6 (Ar, CH), 128.9 (Ar, CH), 129.1 (Ar, CH), 129.1 (Ar, CH), 129.2 (Ar, C), 129.3 (Ar, CH), 129.4 (Ar, CH), 129.5 (Ar, CH), 129.7 (Ar, CH), 129.8 (Ar, CH), 129.9 (Ar, CH), 133.5 (Ar, C), 134.3 (Ar, C), 135.2 (*C*=CH), 135.5 (*C*=CH), 159.0 (Ar, C), 159.1 (Ar, C), 159.2 (Ar, C), 159.4 (Ar, C), 159.8 (C=O), 163.0 (C=O), 166.3 (C=O), 167.6 (C=O); *m/z* (ESI) $C_{34}H_{32}N_2NaO_4$ requires: 555.2254, found $[MNa]^+$: 555.2257.

3.6. Typical procedure for substitution of proline derived DKPs **36** to give products **37–43** (Table 3)

3.6.1. (3*S*,8a*R*)-8a-Allyl-2-(4-methoxybenzyl)-3-methyl-octahydropyrrolo[1,2a]pyrazine-1,4-dione **37a**

To a solution of (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-methyl-octahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36a** (100 mg, 0.347 mmol) in THF (30 mL), cooled to −78 °C was added LiHMDS (0.49 mL of a 1.06 M solution in THF, 0.52 mmol). After stirring the solution for 1 h, allyl bromide (0.15 mL, 1.7 mmol) was added. The solution was stirred for a further 3 h, after which time, the reaction mixture was quenched by the careful addition of a saturated solution of ammonium chloride (15 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (2×10 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 2:1) to yield the title compound **37a** as a colourless foam (58 mg, 51%). $[\alpha]_D^{18}$ −42.9 (*c* 0.34, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2957, 1652, 1456, 1404, 1304, 1036; δ_H (400 MHz, $CDCl_3$) 1.54 (3H, d, *J* 7.0, CHC*H*$_3$), 1.94–2.20 (2H, m, CH_2C*H*HCH_2), 2.17–2.32 (2H, m, CC*H*HCH_2), 2.44 (1H, dd, *J* 13.7, 7.6, C*H*HCH=CH_2), 2.61 (1H, dd, *J* 13.7, 7.8, C*H*HCH=CH_2), 3.50 (1H, m, NC*H*HCH_2), 3.81 (3H, s, OC*H*$_3$), 3.87 (1H, ddd, *J* 12.3, 8.3, 8.2, NC*H*HCH_2), 4.04 (1H, q, *J* 7.0, NC*H*CO), 4.08 (1H, d, *J* 15.2, NC*H*HAr), 5.10 (1H, dd, *J* 11.1. 0.9, HC=C*H*H), 5.14 (1H, dd, *J* 17.2, 0.9, HC=C*H*H), 5.34 (1H, d, *J* 15.2, NC*H*HAr), 5.68 (1H, dddd, *J* 17.2, 11.1, 7.8, 7.6, H_2C=C*H*), 6.86 (2H, d, *J* 8.5, Ar, C*H*), 7.21 (2H, d, *J* 8.5, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 16.4 (CH_3), 20.0 (CH_2), 35.1 (CH_2), 41.8 (CH_2), 45.2 (CH_2), 45.4 (CH_2), 54.3 (CH), 55.3 (OCH_3), 67.3 (*C*-8a), 114.1 (Ar, CH), 120.6 (CH=*C*H_2), 128.4 (Ar, C), 129.2 (Ar, CH), 131.3 (H_2C=*C*H), 159.1 (Ar, C), 165.7 (C=O), 170.2 (C=O); *m/z* (ESI) $C_{19}H_{24}N_2O_3$ requires: 328.1787, found $[MH]^+$: 328.1789.

All reactions of **36a** were carried out in a similar way, using 1.5 equiv of LHMDS with respect to the starting DKP. For DKPs **36b** and **36c**, the procedure was the same, except that more base was employed—2 equiv for **36b** and 3 equiv for **36c**.

3.6.2. (3*S*,8a*R*)-8a-Allyl-3-benzyl-2-(4-methoxybenzyl-octahydropyrrolo[1,2a]pyrazine-1,4-dione **37b**

The general procedure was followed using (3*S*,8a*S*)-3-benzyl-2-(4-methoxybenzyl)octahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36b** (100 mg, 0.274 mmol), THF (5 mL), LiHMDS (0.54 mL of a 1.06 M solution in THF, 0.58 mmol) and allyl bromide (0.11 mL, 1.4 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **37b** as a colourless wax (79 mg, 71%). $[\alpha]_D^{21}$ −37.7 (*c* 0.70, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2957, 2838, 1651, 1614, 1454, 1304, 1036; δ_H (500 MHz, $CDCl_3$) 0.51 (1H, m, CC*H*HCH_2), 1.41 (1H, m, CH_2C*H*HCH_2), 1.66–1.69 (2H, m, CC*H*HCH_2, CH_2C*H*HCH_2), 2.16 (1H, dd, *J* 13.8, 7.2, C*H*HCH=CH_2), 2.49 (1H, dd, *J* 13.8, 7.8, C*H*HCH=CH_2), 3.13–3.18 (1H, m, NC*H*HCH_2), 3.22 (1H, dd, *J* 13.9, 4.2, C*H*HPh), 3.29 (1H, dd, *J* 13.9, 3.0, C*H*HPh), 3.75 (1H, m, NC*H*HCH_2), 3.82 (3H, s, OC*H*$_3$), 3.97 (1H, d, *J* 14.6, NC*H*HAr), 4.17 (1H, app. t, *J* 3.6, C*H*CH_2Ph), 4.98–5.02 (2H, m, C*H*$_2$=CH), 5.40 (1H, m, C*H*=CH_2), 5.63 (1H, d, *J* 14.6, NC*H*HAr), 6.88 (2H, d, *J* 7.7, Ar–OMe, C*H*), 7.08 (2H, d, *J* 7.7, Ar–OMe, C*H*), 7.21–7.29 (5H, m, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 19.2 (CH_2), 34.0 (CH_2), 36.1 (CH_2), 41.8 (CH_2), 43.2 (CH_2), 45.8 (CH_2), 53.4 (CH_3), 59.5 (CH), 67.2 (*C*-8a), 114.2 (Ar, CH), 120.3 (HC=*C*H_2), 127.0 (Ar, C), 127.3 (Ar, CH), 128.5 (H_2C=*C*H), 130.0 (Ar, CH), 130.5 (Ar, CH), 131.3 (Ar, CH), 134.9 (Ar, C), 159.5 (Ar, C), 163.9 (C=O), 167.9 (C=O); *m/z* (ESI) $C_{25}H_{28}N_2O_3$ requires: 427.1992, found $[MNa]^+$: 427.1997.

3.6.3. (3*S*,8a*R*)-8a-Allyl-3-isopropyl-2-(4-methoxybenzyl)-octahydropyrrolo[1,2a]pyrazine-1,4-dione **37c**

The general procedure was followed using (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-isopropylpyrrolooctahydro[1,2*a*]pyrazine-1,4-dione **36c** (50 mg, 0.16 mmol), THF (10 mL), LiHMDS (0.45 mL of a 1.06 M solution in THF, 0.47 mmol) and allyl bromide (68 μL, 0.79 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **37c** as a colourless foam (41 mg, 73%). $[\alpha]_D^{15}$ −80 (*c* 0.19, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2963, 1647, 1454, 1342, 1303, 1036; δ_H (500 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.9, C*H*$_3$), 1.13 (3H, d, *J* 7.0, C*H*$_3$), 1.96–2.10 (3H, m, CC*H*HCH_2, CH_2C*H*$_2$CH$_2$), 2.22 (1H, ddd, *J* 9.4, 6.8, 3.3, CC*H*HCH_2), 2.32 (1H, app. qd, *J* 6.9, 2.4, C*H*(CH_3)$_2$), 2.37 (1H, dd, *J* 13.7, 7.4, C*H*HCH=CH_2), 2.61 (1H, dd, *J* 13.7, 7.4, C*H*HCH=CH_2), 3.38 (1H, ddd, *J* 12.5, 8.7, 5.8, NC*H*HCH_2), 3.75 (1H, d, *J* 2.4, NC*H*CO), 3.81 (3H, s, OC*H*$_3$), 3.90 (1H, ddd, *J* 12.5, 5.5, 3.6, NC*H*HCH_2), 3.92 (1H, d, *J* 14.5, NC*H*HAr), 5.02 (1H, dd, *J* 10.3, 1.5, CH_2CH=C*H*H), 5.08 (1H, dd, *J* 17.2, 1.5, CH_2CH=C*H*H), 5.34 (1H, d, *J* 14.5, NC*H*HAr), 5.50 (1H, dddd, *J* 17.2, 10.3, 7.4, 7.4, CH_2C*H*=CH_2), 6.86 (2H, d, *J* 8.6, Ar, C*H*), 7.20 (2H, d, *J* 8.6, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 15.4 (CH_3), 19.7 (CH_2), 20.0 (CH_3), 30.2 (CH), 35.2 (CH_2), 42.2 (CH_2), 43.3 (CH_2), 46.4 (CH_2), 55.4 (OCH_3), 63.7 (CH), 67.1

(*C*-8a), 114.1 (Ar, CH), 120.6 (HC=*C*H_2), 127.3 (Ar, C), 130.4 (Ar, CH), 131.3 (H*C*=CH_2), 159.3 (Ar, C), 163.9 (C=O), 168.5 (C=O); *m/z* (ESI) $C_{21}H_{28}N_2NaO_3$ requires: 379.1992, found $[MNa]^+$: 379.1981.

3.6.4. (3*S*,8a*R*)-2-(4-Methoxybenzyl)-3-methyl-8a-(3-methylbut-2-enyl)octahydropyrrolo[1,2a]-pyrazine-1,4-dione **38a**

The general procedure was followed using (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-methyloctahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36a** (100 mg, 0.347 mmol), THF (30 mL), LiHMDS (0.49 mL of a 1.06 M solution in THF, 0.52 mmol) and 1-bromo-3-methylbut-2-ene (20 μL, 1.7 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 2:1) to yield the title DKP **38a** as a colourless foam (76 mg, 60%). $[\alpha]_D^{14}$ −52 (*c* 0.58, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2935, 2838, 1650, 1614, 1455, 1304, 1036; δ_H (500 MHz, $CDCl_3$) 1.54 (3H, d, *J* 7.0, CHC*H*$_3$), 1.56 (6H, br s, C(C*H*$_3$)$_2$), 1.92–2.04 (2H, m, CH_2C*HH*CH_2), 2.16–2.28 (2H, m, CC*HH*CH_2), 2.41 (1H, dd, *J* 14.0, 8.0, C*H*HCH=C(CH$_3$)$_2$), 2.56 (1H, dd, *J* 14.0, 7.7, C*H*HCH=C(CH$_3$)$_2$), 3.48 (1H, ddd, *J* 12.6, 9.1, 4.4, NC*H*HCH_2), 3.79 (3H, s, OC*H*$_3$), 3.84 (1H, ddd, *J* 12.6, 8.4, 8.4, NC*H*HCH_2), 3.94 (1H, q, *J* 7.0, NC*H*CO), 4.04 (1H, d, *J* 15.0, NC*H*HAr), 4.96 (1H, app. tt, *J* 7.7, 1.2, C*H*=C(CH$_3$)$_2$), 5.35 (1H, d, *J* 15.0, NC*H*HAr), 6.86 (2H, d, *J* 8.6, Ar, C*H*), 7.20 (2H, d, *J* 8.6, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 16.9 (CH_3), 17.9 (CH_3), 20.2 (CH_2), 25.9 (CH_3), 35.6 (CH_2), 36.5 (CH_2), 45.2 (CH_2), 45.4 (CH_2), 54.5 (CH), 55.3 (OCH_3), 67.8 (*C*-8a), 113.9 (Ar, CH), 117.3 (C=*C*H), 128.4 (Ar, C), 129.4 (Ar, CH), 137.4 (*C*=CH), 159.1 (Ar, C), 165.6 (C=O), 170.5 (C=O); *m/z* (ESI) $C_{21}H_{28}N_2NaO_3$ requires: 379.1992, found $[MNa]^+$: 379.1971.

3.6.5. (3*S*,8a*R*)-3-Benzyl-2-(4-methoxybenzyl)-8a-(3-methylbut-2-enyl)octahydropyrrolo[1,2a]pyrazine-1,4-dione **38b**

The general procedure was followed using (3*S*,8a*S*)-3-benzyl-2-(4-methoxybenzyl)octahydropyrrolo[1,2*a*]pyrazine-1,4-dione (500 mg, 1.37 mmol), THF (25 mL), LiHMDS (2.65 mL of a 1.06 M solution in THF, 2.81 mmol) and 1-bromo-3-methylbut-2-ene (0.80 mL, 6.9 mmol). The crude product was purified by flash column chromatography on silica gel (light petroleum/EtOAc, 3:1), to yield the title DKP **38b** as a colourless solid (467 mg, 82%), mp 90–91 °C. $[\alpha]_D^{25}$ −60.0 (*c* 0.97, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2934, 2839, 1732, 1651, 1614, 1454, 1303, 1109, 1036; δ_H (500 MHz, $CDCl_3$) 0.63 (1H, m, CC*H*HCH_2), 1.40 (1H, ddd, *J* 20.0, 9.9, 4.7, CH_2C*H*HCH_2), 1.49 (3H, d, *J* 0.6, C*H*$_3$), 1.52 (3H, d, *J* 0.6, C*H*$_3$), 1.66–1.74 (2H, m, CC*H*HCH_2, CH_2C*H*HCH_2), 2.17 (1H, dd, *J* 14.2, 7.7, C*H*HCH=C(CH$_3$)$_2$), 2.43 (1H, dd, *J* 14.2, 7.5, C*H*HCH=C(CH$_3$)$_2$), 3.17 (1H, ddd, *J* 12.3, 9.1, 4.7, NC*H*HCH_2), 3.23 (1H, dd, *J* 14.0, 4.2, C*H*HPh), 3.29 (1H, dd, *J* 14.0, 3.0, C*H*HPh), 3.65 (1H, ddd, *J* 12.3, 9.9, 5.8, NC*H*HCH_2), 3.81 (3H, s, OC*H*$_3$), 3.94 (1H, d, *J* 14.5, NC*H*HAr), 4.13 (1H, app. t, *J* 3.6, C*H*CH_2Ph), 4.75 (1H, app. tt, *J* 7.6, 1.2, C*H*=C(CH$_3$)$_2$), 5.68 (1H, d, *J* 14.5, NC*H*HAr), 6.88 (2H, d, *J* 8.7, Ar–OMe, C*H*), 7.08 (2H, d, *J* 8.7, Ar–OMe, C*H*), 7.21–7.28 (5H, m, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 18.0 (CH_3), 19.4 (CH_2), 25.9 (CH_3), 34.3 (CH_2), 36.0 (CH_2), 36.5 (CH_2), 43.6 (CH_2), 45.5 (CH_2), 55.4 (OCH_3), 59.2 (CH), 67.5 (*C*-8a), 114.3 (Ar, CH), 117.2 (C=*C*H), 127.2 (Ar, CH), 127.3 (Ar, C), 128.4 (Ar, CH), 129.9 (Ar, CH), 130.4 (Ar, CH), 135.0 (Ar, C), 137.1 (CH=*C*), 159.5 (Ar, C), 163.8 (C=O), 168.4 (C=O); *m/z* (ESI) $C_{27}H_{33}N_2O_3$ requires: 433.2491, found $[MH]^+$: 433.2486. A sample for X-ray crystal structure determination was prepared from DKP **38b** (25 mg) via vapour diffusion from EtOAc (0.5 mL) and petrol (5 mL) over a period of 3 days.

3.6.6. (3*S*,8a*R*)-8a-Benzyl-2-(4-methoxybenzyl)-3-methyl-octahydropyrrolo[1,2a]pyrazine-1,4-dione **39a**

The general procedure was followed using (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-methyloctahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36a** (100 mg, 0.347 mmol), THF (30 mL), LiHMDS (0.49 mL of a 1.06 M solution in THF, 0.52 mmol) and benzyl bromide (0.21 mL, 1.7 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 2:1) to yield the title DKP **39a** as a colourless foam (82 mg, 62%). $[\alpha]_D^{28}$ +10 (*c* 0.18, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2957, 1650, 1454, 1374, 1303, 1039; δ_H (500 MHz, $CDCl_3$) 1.26 (3H, d, *J* 7.0, C*H*$_3$), 1.96–2.04 (2H, m, CH_2C*HH*CH_2), 2.27 (1H, ddd, *J* 12.8, 11.1, 9.2, CC*H*HCH_2), 2.39 (1H, ddd, *J* 12.8, 7.2, 2.4, CC*H*HCH_2), 2.63 (1H, q, *J* 7.0, C*H*CH_3), 2.93 (1H, d, *J* 13.4, C*H*HPh), 3.20 (1H, d, *J* 13.4, C*H*HPh), 3.68 (1H, ddd, *J* 12.6, 9.3, 4.6, NC*H*HCH_2), 3.80 (3H, s, OC*H*$_3$), 3.95 (1H, ddd, *J* 12.6, 8.5, 8.5, NC*H*HCH_2), 4.40 (1H, d, *J* 15.1, NC*H*HAr), 4.47 (1H, d, *J* 15.1, NC*H*HAr), 6.82 (2H, d, *J* 8.6, Ar, C*H*), 7.03 (2H, d, *J* 8.6, Ar, C*H*), 7.06 (2H, d, *J* 7.3, Ar, C*H*), 7.18 (2H, d, *J* 8.2, Ar, C*H*), 7.25 (1H, m, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 17.1 (CH_3), 19.8 (CH_2), 36.6 (CH_2), 43.2 (CH_2), 45.0 (CH_2), 46.7 (CH_2), 55.2 (CH), 55.3 (OCH_3), 68.7 (*C*-7a), 113.9 (Ar, CH), 127.5 (Ar, CH), 128.6 (Ar, CH), 129.0 (Ar, C), 129.2 (Ar, CH), 130.2 (Ar, CH), 135.2 (Ar, C), 158.9 (Ar, C), 165.8 (C=O), 170.3 (C=O); *m/z* (ESI) $C_{23}H_{27}N_2O_3$ requires: 379.2016, found $[MH]^+$: 379.2026.

3.6.7. (3*S*,8a*R*)-3-Benzyl-8a-benzyl-2-(4-methoxybenzyl)-octahydropyrrolo[1,2a]pyrazine-1,4-dione **39b**

The general procedure was followed using (3*S*,8a*S*)-3-benzyl-2-(4-methoxybenzyl)octahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36b** (100 mg, 0.274 mmol) THF (5 mL), LiHMDS (0.54 mL of a 1.06 M solution in THF, 0.58 mmol) and benzyl bromide (0.16 mL, 1.4 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **39b** as a colourless solid (71 mg, 58%), mp 127–129 °C. $[\alpha]_D^{21}$ −17.5 (*c* 0.99, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2937, 2838, 1650, 1614, 1454, 1304, 1036; δ_H (400 MHz, $CDCl_3$) 0.55–0.64 (1H, ddd, *J* 19.8, 9.3, 6.5, CC*H*HCH_2), 1.49 (1H, m, CH_2C*H*HCH_2), 1.74–1.86 (2H, m, CC*H*HCH_2, CH_2C*H*HCH_2), 2.79 (1H, d, *J* 13.4, CC*H*HPh), 2.98 (1H, dd, *J* 14.0, 4.2, CHC*H*HPh), 3.01 (1H, d, *J* 13.4, CC*H*HPh), 3.07 (1H, dd, *J* 14.0, 3.1, CHC*H*HPh), 3.39 (1H, ddd, *J* 12.1, 9.5, 4.6, NC*H*HCH_2), 3.56 (1H, app. t, *J* 3.6,

C*H*CH_2Ph), 3.80 (3H, s, OCH_3), 3.90 (1H, ddd, *J* 12.1, 9.5, 5.6, NC*H*HCH_2), 3.91 (1H, d, *J* 14.8, NC*H*HAr), 5.32 (1H, d, *J* 14.8, NC*H*HAr), 6.57 (2H, d, *J* 8.6, Ar–OMe, C*H*), 6.71 (2H, d, *J* 8.6, Ar–OMe, C*H*), 6.99–7.05 (4H, m, Ar, C*H*), 7.20–7.31 (6H, m, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 19.4 (CH_2), 35.2 (CH_2), 35.8 (CH_2), 42.6 (CH_2), 43.5 (CH_2), 45.9 (CH_2), 55.3 (CH_3), 58.8 (CH), 68.6 (*C*-8a), 114.1 (Ar, CH), 126.2 (Ar, C), 127.0 (Ar, CH), 127.2 (Ar, CH), 128.5 (Ar, CH), 128.7 (Ar, CH), 129.9 (Ar, CH), 130.1 (Ar, CH), 130.1 (Ar, CH), 135.0 (Ar, C), 135.6 (Ar, C), 159.2 (Ar, C), 164.3 (C=O), 167.5 (C=O); *m/z* (ESI) $C_{29}H_{31}N_2O_3$ requires: 455.2329, found $[MH]^+$: 455.2320.

3.6.8. (3S,8aR)-8a-Benzyl-3-isopropyl-2-(4-methoxybenzyl)-octahydropyrrolo[1,2a]pyrazine-1,4-dione ***39c***

The general procedure was followed using (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-isopropylpyrrolooctahydro[1,2*a*]pyrazine-1,4-dione **36c** (50 mg, 0.16 mmol), THF (10 mL), LiHMDS (0.45 mL of a 1.06 M solution in THF, 0.47 mmol) and benzyl bromide (94 μL, 0.79 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **39c** as a colourless foam (53 mg, 83%). $[\alpha]_D^{15}$ −23.9 (*c* 1.74, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2933, 2895, 1651, 1456, 1345, 1303, 1037; δ_H (500 MHz, $CDCl_3$) 0.62 (3H, d, *J* 7.0, CH_3), 0.91 (3H, d, *J* 7.0, CH_3), 2.00 (1H, qd, *J* 7.0, 2.2, C*H*$(CH_3)_2$), 2.02–2.14 (2H, m, $CH_2CH_2CH_2$), 2.17 (1H, ddd, *J* 12.2, 9.5, 9.5, CC*H*HCH_2), 2.38 (1H, ddd, *J* 12.2, 9.8, 8.0, CC*H*HCH_2), 2.89 (1H, d, *J* 2.2, NC*H*CO), 2.97 (1H, d, *J* 13.3, C*H*HPh), 3.14 (1H, d, *J* 13.3, C*H*HPh), 3.58 (1H, ddd, *J* 12.6, 9.8, 4.7, NC*H*HCH_2), 3.77 (3H, s, OCH_3), 4.03 (1H, ddd, *J* 12.6, 9.5, 6.2, NC*H*HCH_2), 4.04 (1H, d, *J* 15.0, NC*H*HAr), 4.66 (1H, d, *J* 15.0, NC*H*HAr), 6.62 (2H, d, *J* 8.4, Ar–OMe, C*H*), 6.70 (2H, d, *J* 8.8, Ar, C*H*), 7.07 (2H, d, *J* 8.4, Ar–OMe, C*H*), 7.28 (2H, dd, *J* 8.8, 7.3, Ar, C*H*), 7.32 (1H, d, *J* 7.3, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 15.1 (CH_3), 19.9 (CH_3), 19.9 (CH_2), 29.9 (CH), 36.5 (CH_2), 43.2 (CH_2), 43.6 (CH_2), 47.2 (CH_2), 55.3 (OCH_3), 63.7 (CH), 68.5 (*C*-8a), 113.8 (Ar, CH), 127.1 (Ar, C), 127.2 (Ar, CH), 128.7 (Ar, CH), 129.8 (Ar, CH), 130.2 (Ar, CH), 135.5 (Ar, C), 158.9 (Ar, C), 164.2 (C=O), 168.4 (C=O); *m/z* (ESI) $C_{25}H_{30}N_2NaO_3$ requires: 429.2149, found $[MNa]^+$: 429.2141.

3.6.9. (3S,8aS)-3-Benzyl-8a-ethyl-2-(4-methoxybenzyl)-octahydropyrrolo[1,2a]pyrazine-1,4-dione ***40b***

The general procedure was followed using (3*S*,8a*S*)-3-benzyl-2-(4-methoxybenzyl)octahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36b** (100 mg, 0.274 mmol), THF (5 mL), LiHMDS (0.54 mL of a 1.06 M solution in THF, 0.58 mmol) and iodoethane (0.11 mL, 1.4 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **40b** as a colourless wax (60 mg, 56%). $[\alpha]_D^{21}$ −72.2 (*c* 0.68, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2971, 2838, 1645, 1614, 1456, 1304, 1035; δ_H (400 MHz, $CDCl_3$) 0.45 (1H, ddd, *J* 14.8, 4.5, 1.4, CC*H*HCH_2), 0.61 (3H, t, *J* 7.4, CH_2CH_3), 1.34 (1H, m, CH_2CHHCH_2), 1.44 (1H, dq, *J* 14.6, 7.4, C*H*HCH_3), 1.58–1.67 (2H, m, CC*H*HCH_2, CH_2CHHCH_2), 1.80 (1H, dq, *J* 14.6, 7.4, C*H*HCH_3), 3.07 (1H, ddd, *J* 12.1, 10.1, 5.3, NC*H*HCH_2), 3.24 (1H, dd, *J* 13.9, 4.2, C*H*HPh), 3.31 (1H, dd, *J* 13.9, 3.0, C*H*HPh), 3.72 (1H, ddd, *J* 10.1, 7.3, 5.1, NC*H*HCH_2), 3.80 (3H, s, OCH_3), 3.97 (1H, d, *J* 14.4, NC*H*HAr), 4.22 (1H, app. t, *J* 3.6, C*H*CH_2Ph), 5.67 (1H, d, *J* 14.4, NC*H*HAr), 6.88 (2H, d, *J* 8.7, Ar–OMe, C*H*), 7.08 (2H, d, *J* 8.7, Ar–OMe, C*H*), 7.21–7.29 (5H, m, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 8.1 (CH_3), 19.3 (CH_2), 30.7 (CH_2), 34.1 (CH_2), 36.1 (CH_2), 43.1 (CH_2), 45.8 (CH_2), 55.3 (CH_3), 59.4 (CH), 67.7 (*C*-8a), 114.3 (Ar, CH), 127.2 (Ar, C), 127.3 (Ar, CH), 129.1 (Ar, CH), 130.6 (Ar, CH), 130.7 (Ar, CH), 134.9 (Ar, C), 159.5 (Ar, C), 164.1 (C=O), 168.3 (C=O); *m/z* (ESI) $C_{24}H_{29}N_2O_3$ requires: 393.2173, found $[MH]^+$: 393.2184.

3.6.10. (3S,8aR)-8a-Ethyl-3-isopropyl-2-(4-methoxybenzyl)-octahydropyrrolo[1,2a]pyrazine-1,4-dione ***40c***

The general procedure was followed using (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-isopropylpyrrolooctahydro[1,2*a*]pyrazine-1,4-dione **36c** (50 mg, 0.16 mmol), THF (10 mL), LiHMDS (0.45 mL of a 1.06 M solution in THF, 0.47 mmol) and iodoethane (64 μL, 0.79 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **40c** as a colourless foam (33 mg, 61%). $[\alpha]_D^{15}$ −70 (*c* 0.06, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2959, 1731, 1644, 1462, 1374, 1046; δ_H (500 MHz, $CDCl_3$) 0.72 (3H, t, *J* 7.5, CH_2CH_3), 0.79 (3H, d, *J* 6.6, CH_3), 1.16 (3H, d, *J* 7.0, CH_3), 1.65 (1H, m, CH_2CHHCH_2), 1.94 (2H, q, *J* 7.5, CH_2CH_3), 1.94 (1H, m, CH_2CHHCH_2), 2.06 (1H, ddd, *J* 12.4, 11.0, 9.5, CC*H*HCH_2), 2.19 (1H, ddd, *J* 12.4, 7.0, 3.3, CC*H*HCH_2), 2.38 (1H, qd, *J* 7.0, 2.2, C*H*$(CH_3)_2$), 3.31 (1H, ddd, *J* 12.4, 8.8, 5.9, NC*H*HCH_2), 3.80 (1H, d, *J* 2.2, NC*H*CO), 3.81 (3H, s, OCH_3), 3.91 (1H, m, NC*H*HCH_2), 3.93 (1H, d, *J* 14.4, NC*H*HAr), 5.40 (1H, d, *J* 14.4, NC*H*HAr), 6.87 (2H, d, *J* 8.8, Ar, C*H*), 7.21 (2H, d, *J* 8.8, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 8.2 (CH_3), 15.5 (CH_3), 19.9 (CH_2), 20.1 (CH_3), 30.3 (CH), 31.2 (CH_2), 35.3 (CH_2), 43.3 (CH_2), 46.4 (CH_2), 55.3 (OCH_3), 63.6 (CH), 67.6 (*C*-8a), 114.2 (Ar, CH), 127.5 (Ar, C), 130.3 (Ar, CH), 159.4 (Ar, C), 164.0 (C=O), 168.7 (C=O); *m/z* (ESI) $C_{20}H_{28}N_2NaO_3$ requires: 367.1992, found $[MNa]^+$: 367.1961.

3.6.11. (3S,8aS)-8a-Carboethoxy-2-(4-methoxybenzyl)-3-methyloctahydropyrrolo[1,2a]pyrazine-1,4-dione ***41a***

The general procedure was followed using (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-methyloctahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36a** (100 mg, 0.347 mmol), THF (30 mL), LiHMDS (0.49 mL of a 1.06 M solution in THF, 0.52 mmol) and ethyl cyanoformate (0.17 mL, 1.7 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 2:1) to yield the title DKP **41a** as a colourless foam (103 mg, 83%). $[\alpha]_D^{24}$ −99 (*c* 0.41, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2838, 1738, 1668, 1614, 1458, 1402, 1304, 1037; δ_H (500 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1, CH_2CH_3), 1.52 (3H, d, *J* 7.0, CHCH_3), 1.96–2.03 (2H, m, CH_2CHHCH_2), 2.46 (1H, ddd, *J* 13.2, 10.2, 8.4, CC*H*HCH_2), 2.73 (1H, ddd, *J* 13.2, 6.2, 4.0, CC*H*HCH_2), 3.62 (1H, ddd, *J* 12.1, 7.7, 5.1, NC*H*HCH_2), 3.73 (1H, ddd, *J* 12.1, 8.0, 7.3,

NC*H*HCH$_2$), 3.79 (3H, s, OC*H*$_3$), 4.01 (1H, d, *J* 15.4, NC*H*HAr), 4.06 (1H, q, *J* 7.0, NC*H*CO), 4.24 (2H, app. qd, *J* 7.1, 1.0, C*H*$_2$CH$_3$), 5.42 (1H, d, *J* 15.4, NC*H*HAr), 6.84 (2H, d, *J* 8.6, Ar, C*H*), 7.14 (2H, d, *J* 8.6, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 14.2 (CH_3), 14.8 (CH_3), 21.3 (CH_2), 34.0 (CH_2), 45.3 (CH_2), 46.0 (CH_2), 54.4 (CH), 55.3 (OCH_3), 63.0 (CH_2), 71.2 (*C*-8a), 114.1 (Ar, CH), 128.4 (Ar, C), 128.7 (Ar, CH), 159.1 (Ar, C), 166.1 (C=O), 166.4 (C=O), 168.7 (C=O); *m*/*z* (ESI) $C_{19}H_{25}N_2O_5$ requires: 361.1763, found $[MH]^+$: 361.1728.

3.6.12. (3*S*,8a*R*)-3-Benzyl-8a-carboethoxy-2-(4-methoxybenzyl)octahydropyrrolo[1,2a]pyrazine-1,4-dione **41b**

The general procedure was followed using (3*S*,8a*S*)-3-benzyl-2-(4-methoxybenzyl)octahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36b** (100 mg, 0.274 mmol), THF (5 mL), LiHMDS (0.54 mL of a 1.06 M solution in THF, 0.58 mmol) and ethyl cyanoformate (0.14 mL, 1.4 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **41b** as a colourless solid (83 mg, 69%), mp 118–120 °C. $[\alpha]_D^{21}$ −83.3 (*c* 0.76, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2838, 1738, 1667, 1613, 1454, 1303, 1111, 1036; δ_H (500 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.98–2.02 (2H, m, CH$_2$C*H*$_2$CH$_2$), 2.44 (1H, ddd, *J* 13.3, 11.0, 9.5, CC*H*HCH$_2$), 2.66 (1H, ddd, *J* 13.3, 5.5, 3.7, CC*H*HCH$_2$), 2.85 (1H, dd, *J* 13.9, 9.9, C*H*HPh), 3.02 (1H, d, *J* 15.0, NC*H*HAr), 3.20 (1H, dd, *J* 13.9, 5.5, C*H*HPh), 3.65 (1H, ddd, *J* 12.1, 7.0, 5.5, NC*H*HCH$_2$), 3.76 (3H, s, OC*H*$_3$), 3.80 (1H, ddd, *J* 12.1, 8.8, 5.9, NC*H*HCH$_2$), 4.05 (1H, dd, *J* 9.9, 5.5, C*H*CH$_2$Ph), 4.38 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 5.04 (1H, d, *J* 15.0, NC*H*HAr), 6.76 (2H, d, *J* 8.6, Ar–OMe, C*H*), 6.86 (2H, d, *J* 8.6, Ar–OMe, C*H*), 7.20 (2H, d, *J* 7.0, Ar, C*H*), 7.30 (1H, app. t, *J* 7.7, Ar, C*H*), 7.35 (2H, dd, *J* 7.5, 7.0, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 14.3 (CH_3), 20.7 (CH_2), 35.8 (CH_2), 45.9 (CH_2), 46.4 (CH_2), 48.1 (CH_2), 55.3 (OCH_3), 62.9 (CH), 63.1 (CH_2), 70.6 (*C*-8a), 114.3 (Ar, CH), 127.3 (Ar, CH), 127.6 (Ar, C), 128.8 (Ar, CH), 129.2 (Ar, CH), 129.7 (Ar, CH), 136.8 (Ar, C), 159.3 (Ar, C), 164.3 (C=O), 165.3 (C=O), 169.8 (C=O); *m*/*z* (EI) $C_{25}H_{29}N_2O_5$ requires: 437.2071, found $[MH]^+$: 437.2079.

3.6.13. (3*S*,8a*S*)-8a-Carboethoxy-3-isopropyl-2-(4-methoxybenzyl)octahydropyrrolo[1,2a]pyrazine-1,4-dione **41c**

The general procedure was followed using (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-isopropylpyrrolooctahydro[1,2*a*]pyrazine-1,4-dione **36c** (50 mg, 0.16 mmol), THF (10 mL), LiHMDS (0.45 mL of a 1.06 M solution in THF, 0.47 mmol) and ethyl cyanoformate (78 μL, 0.79 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **41c** as a colourless foam (34 mg, 55%). $[\alpha]_D^{15}$ −71.8 (*c* 0.51, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2965, 2934, 1744, 1658, 1456, 1303, 1037; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.9, C*H*$_3$), 1.18 (3H, d, *J* 7.3, C*H*$_3$), 1.22 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.92–2.00 (2H, m, CH$_2$C*H*$_2$CH$_2$), 2.16 (1H, ddd, *J* 13.0, 10.8, 9.3, CC*H*HCH$_2$), 2.40 (1H, app. dp, *J* 7.0, 2.3, C*H*(CH$_3$)$_2$), 2.90 (1H, ddd, *J* 13.0, 6.6, 3.7, CC*H*HCH$_2$), 3.38 (1H, ddd, *J* 12.2, 8.7, 6.0, NC*H*HCH$_2$), 3.78 (1H, ddd, *J* 12.2, 8.7, 7.7, NC*H*HCH$_2$), 3.80 (3H, s, OC*H*$_3$), 3.84 (1H, d, *J* 2.3, NC*H*CO), 3.91 (1H, d, *J* 15.0, NC*H*HAr), 4.19 (1H, q, *J* 7.1, OC*H*HCH$_3$), 4.20 (1H, q, *J* 7.1, OC*H*HCH$_3$) 5.52 (1H, d, *J* 15.0, NC*H*HAr), 6.85 (2H, d, *J* 8.6, Ar, C*H*), 7.14 (2H, d, *J* 8.6, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 14.0 (CH_3), 15.6 (CH_3), 20.1 (CH_2), 20.4 (CH_3), 29.6 (CH), 33.1 (CH_2), 44.4 (CH_2), 46.0 (CH_2), 55.3 (OCH_3), 63.0 (CH_2), 63.4 (CH), 71.0 (*C*-8a), 114.1 (Ar, CH), 127.5 (Ar, C), 129.5 (Ar, CH), 159.3 (Ar, C), 164.6 (C=O), 164.8 (C=O), 168.5 (C=O); *m*/*z* (ESI) $C_{21}H_{28}N_2NaO_5$ requires: 411.1890, found $[MNa]^+$: 411.1870.

3.6.14. Preparation of (3*S*)-2-(4-methoxybenzyl)-3-methyl-8a-(phenylthio)octahydropyrrolo[1,2a]-pyrazine-1,4-dione **42a**

The general procedure was followed using (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-methyloctahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36a** (100 mg, 0.347 mmol), THF (30 mL), LiHMDS (0.49 mL of a 1.06 M solution in THF, 0.52 mmol) and diphenyl disulfide (20 mg, 1.7 mmol) as a solution in THF (1 mL). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 2:1) to yield the title DKP **42a** as a 1:1 mixture of diastereoisomers, and in the form of a colourless foam (71 mg, 52%). Data for diastereomeric mixture: ν_{max} ($CHCl_3$)/cm^{-1} 2935, 2838, 1660, 1614, 1456, 1349, 1304, 1110, 1037; δ_H (500 MHz, $CDCl_3$) 1.34 (6H, br d, *J* 7.3, C*H*$_3$), 1.94–2.08 (2H, m, C*H*$_2$), 2.14–2.34 (3H, m, C*H*$_2$), 2.36–2.50 (3H, m, C*H*$_2$), 3.09 (1H, q, *J* 7.0, NC*H*CO), 3.67–3.84 (4H, m, NC*H*$_2$CH$_2$), 3.79 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 3.88 (1H, q, *J* 7.3, NC*H*CO), 3.98 (1H, d, *J* 14.5, NC*H*HAr), 4.29 (1H, d, *J* 15.1, NC*H*HAr), 4.81 (1H, d, *J* 15.1, NC*H*HAr), 5.14 (1H, d, *J* 14.5, NC*H*HAr), 6.84 (2H, d, *J* 8.8, Ar, C*H*), 6.88 (2H, d, *J* 8.8, Ar, C*H*), 7.19–7.24 (2H, m, SAr, C*H*), 7.20 (2H, d, *J* 8.8, Ar, C*H*), 7.24 (2H, d, *J* 8.8, Ar, C*H*), 7.33–7.39 (5H, m, SAr, C*H*), 7.42 (1H, app. tt, *J* 7.3, 1.3, SAr, C*H*), 7.55 (2H, dd, *J* 8.0, 1.3, SAr, C*H*); δ_C (125 MHz, $CDCl_3$) 16.8 (CH_3), 17.8 (CH_3), 19.7 (CH_2), 20.0 (CH_2), 36.0 (CH_2), 36.8 (CH_2), 45.6 (CH_2), 45.8 (CH_2), 46.3 (CH_2), 46.6 (CH_2), 55.1 (CH), 55.3 (OCH_3), 55.4 (OCH_3), 56.6 (CH), 74.2 (*C*-8a), 75.1 (*C*-8a), 114.1 (Ar, CH), 114.2 (Ar, CH), 128.0 (Ar, C), 128.4 (Ar, CH), 129.1 (Ar, CH), 129.2 (Ar, CH), 129.3 (Ar, CH), 129.8 (C, Ar), 130.0 (Ar, CH), 130.2 (Ar, CH), 130.3 (Ar, C), 130.7 (Ar, C), 136.9 (Ar, CH), 137.4 (Ar, CH), 159.1 (Ar, C), 159.4 (Ar, C), 165.3 (C=O), 166.3 (C=O), 166.8 (C=O), 166.9 (C=O); *m*/*z* (CI) $C_{22}H_{25}N_2O_3S$ requires: 397.1586, found $[MH]^+$: 397.1574.

3.6.15. (3*S*)-3-Benzyl-2-(4-methoxybenzyl)-8a-(phenylsulfanyl)octahydropyrrolo[1,2a]pyrazine-1,4-dione **42b**

The general procedure was followed using (3*S*,8a*S*)-3-benzyl-2-(4-methoxybenzyl)octahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36b** (100 mg, 0.274 mmol), THF (5 mL), LiHMDS (0.54 mL of a 1.06 M solution in THF, 0.58 mmol) and diphenyl disulfide (0.30 g, 1.4 mmol). The crude product was purified by flash column chromatography on silica gel

(petrol/EtOAc, 3:1) to yield the title compound **42b** as a 2:1 mixture of diastereoisomers, and in the form of a colourless solid (78 mg, 60%). Data for a diastereomeric mixture (*=minor isomer): ν_{max} ($CHCl_3$)/cm^{-1} 2957, 2934, 2838, 1660, 1613, 1454, 1305, 1036; δ_H (400 MHz, $CDCl_3$) 1.13 (1H, m, CH_2CHHCH_2*), 1.55 (1H, m, CH_2CHHCH_2*), 1.98 (1H, m, CH_2CHHCH_2), 2.04–2.11 (2H, m, $CCHHCH_2$*), 2.12 (1H, m, $CCHHCH_2$), 2.23 (1H, m, CH_2CHHCH_2), 2.40 (1H, ddd, *J* 13.1, 7.0, 6.4, CH_2CHHCH_2), 3.04 (1H, d, *J* 14.6, NC*H*HAr), 3.09 (1H, dd, *J* 14.1, 3.2, C*H*HPh*), 3.16 (1H, dd, *J* 14.1, 4.1, C*H*HPh*), 3.31 (1H, dd, *J* 14.0, 5.5, C*H*HPh), 3.36 (1H, dd, *J* 14.0, 9.0, C*H*HPh), 3.51–3.62 (2H, m, $NCHHCH_2$*), 3.64 (1H, app. t, *J* 3.6, $CHCH_2Ph$*), 3.70 (1H, ddd, *J* 12.2, 9.6, 2.6, $NCHHCH_2$), 3.77 (3H, s, OCH_3), 3.78 (1H, ddd, *J* 12.2, 8.5, 3.2, $NCHHCH_2$), 3.85 (3H, s, OCH_3*), 4.04 (1H, d, *J* 14.6, NC*H*HAr*), 4.12 (1H, dd, *J* 9.0, 5.5, $CHCH_2Ph$), 5.15 (1H, d, *J* 14.6, NC*H*HAr), 5.32 (1H, d, *J* 14.6, NC*H*HAr*), 6.76 (2H, d, *J* 8.8, Ar, C*H*), 6.86 (2H, d, *J* 8.8, Ar, C*H*), 6.88 (2H, d, *J* 8.8, Ar, C*H*), 6.99 (2H, dd, *J* 7.9, 1.5, Ar, C*H*), 7.11 (2H, d, *J* 8.5, Ar, C*H*), 7.16 (1H, d, *J* 7.0, Ar, C*H*), 7.21 (2H, dd, *J* 8.2, 1.5, Ar, C*H*), 7.23–7.27 (2H, m, Ar, C*H*), 7.32–7.53 (5*H*+6*H**, m, Ar, C*H*), 7.67 (2H, dd, *J* 7.6, 1.5, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 19.3 (CH_2), 19.7 (CH_2), 35.7 (CH_2), 35.9 (CH_2), 36.4 (CH_2), 40.3 (CH_2), 44.5 (CH_2), 45.8 (CH_2), 46.7 (CH_2), 47.3 (CH_2), 55.3 (OCH_3), 55.4 (OCH_3), 59.9 (CH), 62.5 (CH), 73.8 (*C*-8a), 75.8 (*C*-8a), 114.1 (Ar, CH), 114.2 (Ar, CH), 127.1 (Ar, C), 127.2 (Ar, C), 127.3 (Ar, CH), 127.5 (Ar, CH), 127.9 (Ar, C), 128.4 (Ar, CH), 129.0 (Ar, CH), 129.1 (Ar, CH), 129.2 (Ar, CH), 129.4 (Ar, CH), 129.7 (Ar, CH), 129.8 (Ar, CH), 129.9 (Ar, CH), 130.1 (Ar, C), 130.2 (Ar, CH), 130.8 (Ar, CH), 130.9 (Ar, C), 134.6 (Ar, C), 136.8 (Ar, CH), 136.9 (Ar, CH), 159.3 (Ar, C), 159.5 (Ar, C), 163.8 (C=O), 165.6 (C=O), 166.1 (2×C=O); *m/z* (CI) $C_{28}H_{29}N_2O_3S$ requires: 473.1899, found $[MH]^+$: 473.1890.

3.6.16. (3S)-3-Isopropyl-2-(4-methoxybenzyl)-8a-(phenylsulfanyl)octahydropyrrolo[1,2a]pyrazine-1,4-dione ***42c***

The general procedure was followed using (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-isopropylpyrrolooctahydro[1,2*a*]pyrazine-1,4-dione **36c** (50 mg, 0.16 mmol), THF (10 mL), LiHMDS (0.45 mL of a 1.06 M solution in THF, 0.47 mmol) and diphenyl disulfide (0.17 g, 0.79 mmol) as a solution in THF (1 mL). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title compound **42c** as a 1.6:1 mixture of diastereomers, and in the form of a colourless foam (43 mg, 64%). Data for a diastereomeric mixture (*=minor isomer): ν_{max} ($CHCl_3$)/cm^{-1} 2932, 1658, 1461, 1304, 1038; δ_H (500 MHz, $CDCl_3$) 0.60 (3H, d, *J* 7.0, CH_3*), 0.96 (3H, d, *J* 7.0, CH_3*), 1.16 (3H, d, *J* 7.0, CH_3), 1.27 (3H, d, *J* 7.0, CH_3), 1.90 (1H, m, CH_2CHHCH_2), 1.99 (1H, ddd, *J* 13.2, 11.7, 7.7, $CCHHCH_2$), 2.06 (1H, m, CH_2CHHCH_2*), 2.09 (1H, ddd, *J* 13.1, 11.7. 7.7, $CCHHCH_2$*), 2.19–2.21 (2H, m, 2×CH_2CHHCH_2), 2.28–2.32 (2H, m, 2×$CH(CH_3)_2$), 2.34–2.41 (2H, m, 2×$CCHHCH_2$), 2.50 (1H, ddd, *J* 13.6, 9.9, 8.0, $NCHHCH_2$*), 2.74 (1H, ddd, *J* 13.5, 8.5, 6.5, $NCHHCH_2$), 2.92 (1H, d, *J* 2.6, NC*H*CO*), 3.75 (1H, m, $NCHHCH_2$), 3.76 (1H, d, *J* 2.6, NC*H*CO), 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3*), 3.86 (1H, m, $NCHHCH_2$*), 3.89 (1H, d, *J* 14.6, NC*H*HAr), 4.22 (1H, d, *J* 15.0, NC*H*HAr*), 4.65 (1H, d, *J* 15.0, NC*H*HAr*), 5.44 (1H, *J* 14.6, NC*H*HAr), 6.82 (2H, *J* 8.5, Ar–OMe, C*H*), 6.83 (2H, d, *J* 8.5, Ar–OMe, C*H**), 7.04 (2H, d, *J* 8.5, Ar–OMe, C*H**), 7.13 (2H, d, *J* 8.5, Ar–OMe, C*H*), 7.35 (2H, dd, *J* 8.1, 1.4, SAr, C*H*), 7.38 (2H, dd, *J* 7.3, 1.5, SAr, C*H*), 7.40–7.45 (2H, m, 2×SAr, C*H*), 7.62 (1H, d, *J* 8.0, SAr, C*H**), 7.63 (1H, d, *J* 8.0, SAr, C*H*); δ_C (125 MHz, $CDCl_3$) 15.0 (CH_2), 19.7 (CH_2), 19.8 (CH_2), 19.9 (CH_2), 20.1 (CH_3), 21.1 (CH_3), 30.1 (CH), 33.0 (CH), 36.0 (CH_2), 36.9 (CH_2), 44.6 (CH_2), 45.9 (CH_2), 47.9 (CH_2), 49.5 (CH_2), 55.3 (OCH_3), 55.4 (OCH_3), 64.8 (CH), 67.3 (CH), 73.4 (*C*-8a), 76.1 (*C*-8a), 113.9 (Ar, CH), 114.3 (Ar, CH), 127.9 (Ar, C), 128.2 (Ar, C), 129.0 (Ar, CH), 129.1 (Ar, CH), 129.5 (Ar, CH), 129.9 (Ar, CH), 130.0 (Ar, CH), 130.2 (Ar, CH), 130.3 (Ar, C), 131.2 (Ar, C), 136.6 (Ar, CH), 137.3 (Ar, CH), 159.1 (Ar, C), 159.3 (Ar, C), 166.2 (C=O), 166.3 (C=O), 166.8 (C=O), 167.2 (C=O); *m/z* (ESI) $C_{24}H_{29}N_2O_3S$ requires: 425.1899, found $[MH]^+$: 425.1890.

3.6.17. (3S,8aR)-8a-(S)-Hydroxy(phenyl)methyl-2-(4-methoxybenzyl)-3-methyloctahydropyrrolo-[1,2a]pyrazine-1,4-dione ***43a***

The general procedure was followed using (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-methyloctahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36a** (100 mg, 0.347 mmol), THF (30 mL), LiHMDS (0.49 mL of a 1.06 M solution in THF, 0.52 mmol) and benzaldehyde (0.18 μL, 1.7 mmol). The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 2:1) to yield the title DKP **43a** as a colourless foam (82 mg, 63%). $[\alpha]_D^{28}$ −11 (*c* 0.11, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2934, 1650, 1455, 1305, 1037; δ_H (500 MHz, $CDCl_3$) 1.40 (3H, d, *J* 7.0, CH_3), 1.67 (1H, m, CH_2CHHCH_2), 1.77 (1H, m, CH_2CHHCH_2), 2.28 (1H, ddd, *J* 13.5, 10.2, 10.2, $CCHHCH_2$), 2.65 (1H, ddd, *J* 13.5, 8.8, 2.9, $CCHHCH_2$), 3.27 (1H, ddd, *J* 11.5, 9.9, 4.8, $NCHHCH_2$), 3.31 (1H, q, *J* 7.0, $CHCH_3$), 3.80 (3H, s, OCH_3), 3.82 (1H, ddd, *J* 11.5, 9.5, 6.2, $NCHHCH_2$), 4.29 (1H, d, *J* 15.2, NC*H*HAr), 4.83 (1H, d, *J* 15.2, NC*H*HAr), 5.02 (1H, br s, C*H*OH), 6.85 (2H, d, *J* 8.8, Ar, C*H*), 7.15 (2H, d, *J* 8.8, Ar, C*H*), 7.28 (2H, d, *J* 8.8, Ar, C*H*), 7.29 (2H, d, *J* 8.8, Ar, C*H*), 7.33 (1H, m, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 16.5 (CH_3), 20.8 (CH_2), 32.5 (CH_2), 46.5 (CH_2), 47.3 (CH_2), 54.9 (CH), 55.3 (OCH_3), 71.4 (*C*-8a), 78.1 (CH), 114.2 (Ar, CH), 127.3 (Ar, CH), 128.4 (Ar, CH), 128.5 (Ar, C), 128.8 (Ar, CH), 129.0 (Ar, CH), 138.5 (Ar, C), 159.0 (Ar, C), 166.0 (C=O), 170.3 (C=O); *m/z* (ESI) $C_{23}H_{26}N_2NaO_4$ requires: 417.1785, found $[MNa]^+$: 417.1786.

3.6.18. (3S,8aR)-3-Benzyl-8a-(S)-hydroxy(phenyl)methyl)-2-(4-methoxybenzyl)octahydropyrrolo[1,2a]pyrazine-1,4-dione ***43b***

The general procedure was followed using (3*S*,8a*S*)-3-benzyl-2-(4-methoxybenzyl)octahydropyrrolo[1,2*a*]pyrazine-1,4-dione **36b** (100 mg, 0.274 mmol), THF (5 mL), LiHMDS (0.54 mL of a 1.06 M solution in THF, 0.58 mmol) and benzaldehyde (0.14 mL, 1.4 mmol). The crude product was

purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1) to yield the title DKP **43b** as a colourless oil (74 mg, 57%). $[\alpha]_D^{28}$ −0.50 (*c* 1.2, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3401, 2930, 1652, 1624, 1455, 1305, 1088, 1063; δ_H (400 MHz, $CDCl_3$) 0.41 (1H, ddd, *J* 12.4, 10.5, 10.2, CC*H*HCH$_2$), 1.51 (1H, m, CH$_2$C*H*HCH$_2$), 1.82 (1H, m, CH$_2$C*H*HCH$_2$), 2.51 (1H, ddd, *J* 12.4, 8.5, 1.2, CC*H*HCH$_2$), 2.98 (1H, dd, *J* 14.0, 4.1, C*H*HPh), 3.12 (1H, dd, *J* 14.0, 3.2, C*H*HPh), 3.39 (1H, ddd, *J* 12.3, 10.5, 4.5, NC*H*HCH$_2$), 3.60 (1H, app. t, *J* 3.5, C*H*CH$_2$Ph), 3.83 (3H, s, OC*H*$_3$), 3.89 (1H, ddd, *J* 12.3, 9.9, 6.1, NC*H*HCH$_2$), 3.95 (1H, d, *J* 14.6, NC*H*HAr), 4.54 (1H, d, *J* 9.9, C*H*OH), 4.98 (1H, d, *J* 9.9, O*H*), 5.28 (1H, d, *J* 14.6, NC*H*HAr), 6.64 (2H, d, *J* 8.5, Ar, C*H*), 6.76 (2H, *J* 8.8, Ar, C*H*), 7.03 (2H, dd, *J* 7.6, 1.8, Ar, C*H*), 7.17 (2H, dd, *J* 8.5, 1.7, Ar, C*H*), 7.26–7.34 (6H, m, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 19.4 (CH$_2$), 31.7 (CH$_2$), 35.9 (CH$_2$), 44.3 (CH$_2$), 46.0 (CH$_2$), 55.4 (OCH$_3$), 58.8 (CH), 69.8 (*C*-8a), 73.4 (CH), 114.2 (Ar, CH), 125.4 (Ar, C), 126.6 (Ar, CH), 127.6 (Ar, CH), 127.8 (Ar, CH), 128.5 (Ar, CH), 128.7 (Ar, CH), 129.9 (Ar, CH), 130.3 (Ar, CH), 134.8 (Ar, C), 139.1 (Ar, C), 159.5 (Ar, C), 164.6 (C=O), 168.0 (C=O); *m/z* (ESI) $C_{29}H_{30}N_2NaO_4$ requires: 493.2098, found $[MNa]^+$: 493.2083.

*3.6.19. (3S,8aR)-3-Benzyl-2-(4-methoxybenzyl)-8a-(3-methylbut-2-enyl)-3-(phenylthio)octahydropyrrolo-[1,2a]pyrazine-1,4-dione **44***

To a solution of *N*,*N*′-dibenzylethylene diamine (62 μL, 2.6 mmol) in THF (2 mL) cooled to −78 °C, was added *n*-BuLi (0.31 mL of a 1.6 M solution in hexanes, 4.9 mmol). The solution was allowed to warm to rt for 10 min, then re-cooled to −78 °C. The basic solution was added via cannula to a solution of (3*S*,8a*R*)-3-benzyl-2-(4-methoxybenzyl)-8a-(3-methylbut-2-enyl)octahydropyrrolo[1,2*a*]pyrazine-1,4-dione **38b** (100 mg, 0.231 mmol), in THF (12 mL), cooled to −78 °C. The solution was stirred for 60 min, after which time, a solution of diphenyl disulfide (0.26 g, 1.2 mmol) in THF (2 mL) was added. After stirring for a further 70 min, the reaction mixture was quenched by the careful addition of a saturated solution of ammonium chloride (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1), to yield the title DKP **44** as a colourless crystalline solid (80 mg, 64%), mp 61–63 °C. $[\alpha]_D^{20}$ −22.8 (*c* 0.56, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2934, 1710, 1656, 1612, 1454, 1392, 1108, 1036; δ_H (500 MHz, $CDCl_3$) 0.62 (1H, app. dd, *J* 23.0, 10.4, CC*H*HCH$_2$), 1.26–1.36 (2H, m, CC*H*HCH$_2$, CH$_2$C*H*HCH$_2$), 1.32 (3H, s, C*H*$_3$), 1.50 (1H, m, CH$_2$C*H*HCH$_2$), 1.58 (3H, s, C*H*$_3$), 1.63 (1H, dd, *J* 15.1, 7.4, C*H*HCH=C(CH$_3$)$_2$), 1.73 (1H, dd, *J* 15.1, 7.0, C*H*HCH=C(CH$_3$)$_2$), 3.21 (1H, ddd, *J* 12.5, 10.5, 4.2, NC*H*HCH$_2$), 3.23 (1H, d, *J* 14.0, C*H*HPh), 3.55 (1H, ddd, *J* 12.5, 9.6, 7.0, NC*H*HCH$_2$), 3.78 (1H, d, *J* 14.0, C*H*HPh), 3.83 (3H, s, OC*H*$_3$), 4.88 (1H, app. t, *J* 7.2, C*H*=C(CH$_3$)$_2$), 4.98 (1H, d, *J* 15.2, NC*H*HAr), 5.54 (1H, d, *J* 15.2, NC*H*HAr), 6.63 (2H, d, *J* 7.3, Ar, C*H*), 6.85 (2H, d, *J* 8.6, Ar–OMe, C*H*), 6.98 (2H, app. t, *J* 7.6, Ar, C*H*), 7.06 (1H, app. t, *J* 7.3, Ar, C*H*), 7.30 (2H, d, *J* 8.6, Ar–OMe, C*H*), 7.34 (2H, d, *J* 7.7, Ar, C*H*), 7.36–7.41 (1H, m, Ar, C*H*), 7.46 (2H, d, *J* 6.9, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 18.0 (CH$_3$), 18.8 (CH$_2$), 25.9 (CH$_3$), 31.9 (CH$_2$), 38.2 (CH$_2$), 41.6 (CH$_2$), 44.8 (CH$_2$), 47.6 (CH$_2$), 55.4 (OCH$_3$), 66.5 (*C*-8a), 85.1 (*C*-3), 114.0 (Ar, CH), 118.0 (C=*C*H), 127.2 (Ar, CH), 128.0 (Ar, CH), 129.1 (Ar, CH), 129.7 (Ar, C), 130.2 (Ar, CH), 130.5 (Ar, CH), 130.7 (Ar, C), 131.1 (Ar, CH), 134.5 (Ar, C), 134.7 (*C*=CH), 137.3 (Ar, CH), 159.1 (Ar, C), 162.0 (C=O), 170.1 (C=O); *m/z* (CI) 541 (M^+, 9%), 448 (M^+−Bn, 3%), 433 (M^+−SPh, 69%), 121 ($CH_3OC_6H_4CH_2^+$, 100%), 110 (PhS^+, 10%). A sample for X-ray crystal structure determination was prepared from DKP **44** (25 mg) via vapour diffusion from EtOAc (0.5 mL) and petrol (5 mL) over a period of 7 days.

*3.6.20. (1R,7R,10R)-1-Benzyl-2,8-diketo-9-(4-methoxybenzyl)-10-(1-methylethenyl)-3,9-diazatricyclo-[4.4.3.0]undecane **45***

To a solution of (3*S*,8a*R*)-3-benzyl-2-(4-methoxybenzyl)-8a-(3-methylbut-2-enyl)-3-(phenylthio)octahydropyrrolo[1,2*a*]-pyrazine-1,4-dione **44** (50 mg, 0.095 mmol) in CH_2Cl_2 (10 mL), cooled to 0 °C, was added *m*-CPBA as a solution in CH_2Cl_2 (1 mL). After stirring the solution for 16 h, a saturated solution of sodium hydrogencarbonate (10 mL) was added and the mixture was stirred for a further 45 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Toluene (10 mL) was added to the residue and the mixture was heated at reflux for 45 min. The reaction mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 4:1), to yield the title DKP as a 1:1 mixture of *E*/*Z* isomers, and in the form of a colourless oil (37 mg, 94%). ν_{max} ($CHCl_3$)/cm^{-1} 2936, 1675, 1625, 1454, 1383, 1304, 1037; δ_H (400 MHz, $CDCl_3$) 0.80 (1H, m, CH_2), 1.15 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.83–1.95 (4H, m, CH_2), 2.08–2.21 (4H, m, CH_2), 2.29 (1H, ddd, *J* 13.1, 10.2, 8.7, CC*H*HCH$_2$), 2.48 (1H, ddd, *J* 12.3, 7.6, 5.3, CC*H*HCH$_2$), 2.52 (1H, m, CH_2), 2.95 (1H, m, CH_2), 3.12 (1H, m, CH_2), 3.49 (1H, ddd, *J* 12.6, 8.2, 4.0, NC*H*HCH$_2$), 3.65 (3H, s, OCH_3), 3.67 (1H, m, NC*H*HCH$_2$), 3.72 (3H, s, OCH_3), 3.97 (1H, d, *J* 14.6, NC*H*HAr), 4.52 (1H, m, *H*C=C(CH$_3$)$_2$), 4.66 (1H, d, *J* 15.5, NC*H*HAr), 5.05 (1H, m, *H*C=C(CH$_3$)$_2$), 5.10 (1H, d, *J* 15.5, NC*H*HAr), 5.11 (1H, d, *J* 14.6, NC*H*HAr), 6.45 (1H, s, C=C*H*Ph), 6.61 (2H, d, *J* 8.8, Ar, C*H*), 6.72 (2H, d, *J* 8.8, Ar, C*H*), 6.78 (2H, d, *J* 8.8, Ar, C*H*), 7.00 (1H, s, C=C*H*Ph), 7.12–7.15 (4H, m, Ar, C*H*), 7.17–7.20 (4H, m, Ar, C*H*), 7.26–7.29 (3H, m, Ar, C*H*), 7.32 (1H, d, *J* 6.1, Ar, C*H*); δ_C (100 MHz, $CDCl_3$) 8.4 (CH$_3$), 18.0 (CH$_3$), 21.0 (CH$_2$), 26.2 (CH$_3$), 28.4 (CH$_3$), 34.0 (CH$_2$), 34.5 (CH$_2$), 36.5 (CH$_2$), 37.3 (CH$_2$), 38.1 (CH$_2$), 45.2

(CH_2), 46.0 (CH_2), 47.3 (CH_2), 48.0 (CH_2), 55.2 (OCH_3), 55.3 (OCH_3), 68.2 (*C*-8a), 68.5 (*C*-8a), 113.8 (Ar, CH), 114.3 (Ar, CH), 117.0 (C=*C*H), 117.2 (C=*C*H), 120.5 (*C*=CH), 122.6 (*C*=CH), 126.7 (Ar, CH), 127.8 (Ar, CH), 128.2 (Ar, CH), 128.3 (Ar, CH), 128.6 (Ar, CH), 128.7 (Ar, C), 128.8 (Ar, CH), 128.9 (Ar, C), 129.4 (Ar, CH), 129.6 (Ar, CH), 132.1 (Ar, C), 133.9 (Ar, C), 136.8 (*C*=CH), 137.2 (*C*=CH), 155.3 (2×*C*=CH), 158.8 (Ar, CH), 158.9 (Ar, CH), 159.2 (C=O), 161.5 (C=O), 169.6 (C=O), 170.7 (C=O); *m/z* (ESI) $C_{27}H_{31}N_2O_3$ requires: 431.2329, found $[MH]^+$: 431.2325.

3.6.21. (1R,7R,10R)-1-Benzyl-2,8-diketo-9-(4-methoxybenzyl)-10-(1-methylethenyl)-3,9-diazatricyclo[4.4.3.0]undecane ***48***

3.6.21.1. Using the AgOTf method. To a solution of (3*S*,8a*R*)-3-benzyl-2-(4-methoxybenzyl)-8a-(3-methylbut-2-enyl)-3-(phenylthio)octahydropyrrolo[1,2*a*]pyrazine-1,4-dione **44** (50 mg, 0.095 mmol) in THF (2 mL) at −10 °C, was added silver triflate (37 mg, 0.14 mmol). After stirring the solution for 1 h, a 1 M solution of sodium hydroxide (5 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1), to yield the title bridged DKP **48** as a colourless solid (27 mg, 65%), mp 165–167 °C. $[\alpha]_D^{21}$ −4.0 (*c* 0.65, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2965, 1682, 1454, 1393, 1304, 1036; δ_H (500 MHz, $CDCl_3$) 1.53 (3H, s, CH_3), 1.79 (1H, dd, *J* 13.5, 5.5, CC*H*HCHC), 1.94 (1H, ddd, *J* 13.3, 7.0, 7.0, CC*H*HCH$_2$), 2.04–2.12 (2H, m, CH$_2$C*HH*CH$_2$), 2.16 (1H, dd, *J* 13.5, 10.2, CC*H*HCHC), 2.74 (1H, dd, *J* 10.2, 5.5, CC*H*CH$_2$C), 2.92 (1H, ddd, *J* 13.3, 7.3, 7.3, CCH_2CH$_2$), 3.17 (1H, d, *J* 18.0, C*H*HPh), 3.60 (1H, d, *J* 18.0, C*H*HPh), 3.57–3.65 (2H, m, NC*HH*CH$_2$), 3.79 (3H, s, OCH_3), 4.16 (1H, d, *J* 15.5, NC*H*HAr), 4.42 (1H, br s, *H*HC=C), 4.72 (1H, app. t, *J* 1.5, *H*HC=C), 4.89 (1H, d, *J* 15.5, NC*H*HAr), 6.79 (2H, d, *J* 8.7, Ar–OMe, C*H*), 7.05 (2H, d, *J* 8.7, Ar–OMe, C*H*), 7.19–7.30 (5H, m, Ar, C*H*); δ_C (125 MHz, $CDCl_3$) 19.0 (CH_3), 24.2 (CH_2), 29.9 (CH_2), 34.4 (CH_2), 36.2 (CH_2), 44.5 (CH_2), 45.7 (CH_2), 52.4 (CH), 55.3 (OCH_3), 66.1 (C), 68.6 (C), 114.0 (Ar, CH), 116.3 (C=*C*H$_2$), 126.1 (Ar, CH), 128.4 (Ar, CH), 128.9 (Ar, CH), 129.2 (Ar, CH), 130.5 (Ar, C), 136.7 (Ar, C), 142.8 (H_2C=*C*), 159.0 (Ar, C), 167.2 (C=O), 173.7 (C=O); *m/z* (EI) $C_{27}H_{31}N_2O_3$ requires: 431.2335, found $[MH]^+$: 431.2302.

3.6.21.2. Using the in situ fluorination–TMSOTf method. To a solution of *N*,*N*′-dibenzylethylene diamine (19 μL, 0.079 mmol) in THF (1 mL) at −78 °C was added *n*-BuLi (0.98 μL of a 1.6 M solution in hexanes, 0.16 mmol). The solution was allowed to warm to rt for 10 min and then recooled to −78 °C. The basic solution was added via cannula to a solution of (3*S*,8a*R*)-3-benzyl-2-(4-methoxybenzyl)-8a-(3-methylbut-2-enyl)-3-(phenylthio)octahydropyrrolo[1,2*a*]-pyrazine-1,4-dione **38b** (22 mg, 0.053 mmol), cooled to −78 °C. After stirring the solution for 60 min, a solution of *N*-fluoro-benzenesulfonimide (33 mg, 1.1 mmol) in THF (1 mL) cooled to −78 °C was added via cannula. After a further 70 min, trimethylsilyl triflate (95 μL, 0.53 mol) was added and the solution allowed to warm to rt over 60 min. The reaction mixture was quenched by the careful addition of a saturated solution of ammonium chloride (10 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petrol/EtOAc, 3:1), to yield DKP **48** as a colourless solid (10 mg, 43%). ^1H, ^{13}C NMR spectra, mp and optical rotation were identical to the sample prepared via above method.

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Supplementary data

General experimental conditions and detailed procedures and compound data for compounds **9**, **22a–c** and **36a–c**. Tabulated crystal data for compounds **11a**, **38b** and **44**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.020.

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