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Synthesis towards complex bridged alkaloids derived from diketopiperazines: a cationic cascade approach to stephacidins, paraherquamides and related systems

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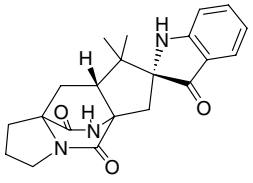
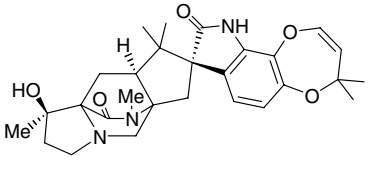
Abstract—Regioselective enolate formation, followed by stereoselective electrophilic quenching of unsymmetrical proline-derived diketopiperazines (DKPs), enabled the synthesis of variously substituted DKPs, including one substrate which could be further substituted and cyclised to give the bicyclo[2.2.2]diazaoctane core structure present in paraherquamide and stephacidin natural products.

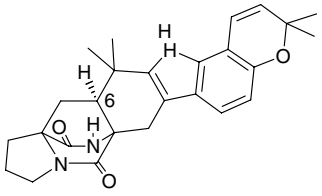
Brevianamide B (**1**) and paraherquamide A (**2**) are representative members of a significant family of fungal metabolites, possessed of an unusual bicyclo-[2.2.2]diazaoctane core structure, which includes the asperparalines, marcfortines and aspergamides.[1] These compounds combine synthetically challenging 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.[2]



1 brevianamide B



2 paraherquamide A



3 stephacidin A

A recent addition to this family of compounds is stephacidin A (**3**), a potent antitumour compound produced by *Aspergillus ochraceus* WC76466.[3] The research group of Baran has recently achieved the total synthesis of stephacidin A and congeners, which led to a revision of the absolute stereochemistry (to that shown above for **3**).[4,5]

The biosynthetic origin of these compounds involves the modification of brevianamide F (see **4** below), 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).[1,2,6] Some aspects of the proposed biosynthesis have been realised by Williams and co-workers in their synthetic endeavours.[2a] 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 1.

According to this plan, regioselective enolate formation and substitution would be employed to convert **4** (in suitably protected form) into **5**, where X is a heteroatom group appropriate for the formation of an *N*-acyliminium-type of cationic reactive intermediate. Triggering of cation formation from **5** would enable a cascade

Keywords: Diketopiperazine; Cationic cyclisation; Stephacidin; Paraherquamide.
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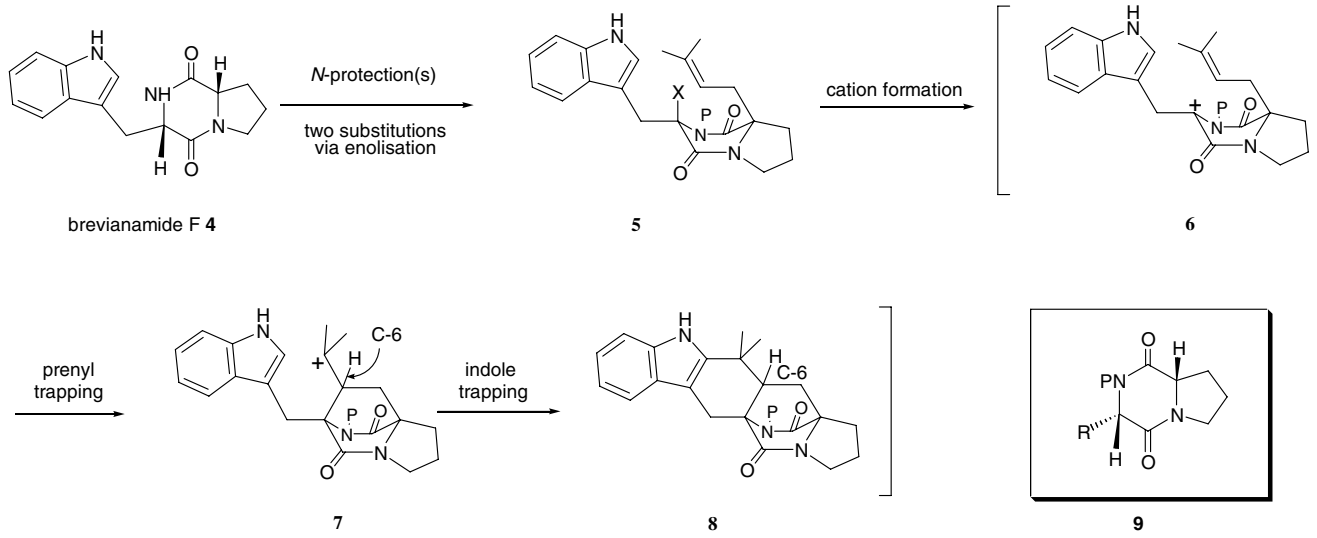


Scheme 1. Planned cationic cascade route to complex bridged DKPs.

process in which sequential trapping of cation intermediate **6** by the pendent prenyl group, and then **7** by the indole, would give the desired polycyclic product **8**. 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.[2i,j]

Surprisingly, given the ubiquity of DKPs and their derived systems (such as Schöllkopf lactim ethers) in stereocontrolled processes,[7] we could find only a single report relating to the transformation of proline-derived *unsymmetrical* DKPs such as **4**, into products with *quaternary* centres.[8] Thus an exploration of the regio- and stereo-control in the enolate reactions of DKPs such as **4** 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 **6**, and the crucial stereochemical outcome at C-6 (stephacidin numbering) could not be taken for granted.

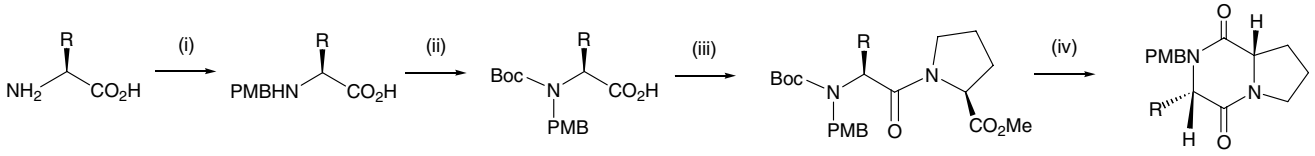
Herein, we describe our preliminary results towards realising this approach, in which we use model L-proline derived DKP systems **9** (R = Me, Bn or ^{i}Pr; P = PMB) to address the key aspects described above.

In initial preparations of appropriate DKPs **9** for this study, starting from cheap amino acid precursors, we observed that *N*-protection of the ring N–H in **9** (P = H) led to significant epimerisation at the proline residue. Therefore, we adopted a route that combined the commercially available proline methyl ester with alanine, phenylalanine or valine-derived partners, already incorporating the required PMB protection, Scheme 2.

Initial reductive amination was followed by nitrogen protection, amide coupling, N-Boc removal, and thermally induced cyclisation to give the desired DKPs **9a**–**c**.[9]

We were delighted to find that a range of electrophilic substitution reactions could be conducted with these systems, in a highly regio- and stereo-selective fashion, through the intermediacy of lithium enolates, generated using LiHMDS, Table 1.[10]

This brief survey demonstrated that effective alkylation, acylation, aldol and sulfenylation reactions are viable in good yields. In all cases, we observed a completely regioselective reaction at the proline α-centre and, with the exception of sulfenylation (compounds **19a**–**c**), all of the products were isolated as single diastereomers.[11]



10a R = Me
10b R = Bn
10c R = ^{i}Pr

11a R = Me (46%)
11b R = Bn (88%)
11c R = ^{i}Pr (67%)

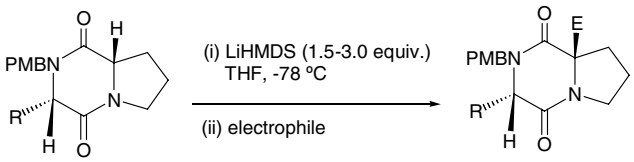
12a R = Me (76%)
12b R = Bn (69%)
12c R = ^{i}Pr (27%)

13a R = Me (93%)
13b R = Bn (90%)
13c R = ^{i}Pr (87%)

9a R = Me (94%)
9b R = Bn (84%)
9c R = ^{i}Pr (76%)

Scheme 2. Preparation of unsymmetrical DKPs. Reagents and conditions: (i) *p*-methoxybenzaldehyde, $NaBH_3CN$, MeOH; (ii) $(Boc)_2O$, $^{i}Pr_2NEt$, 1,4-dioxane–H_2O (1:1); (iii) L-proline methyl ester–HCl salt, EDCI, HOBT, Et_3N, CH_2Cl_2; (iv) HCO_2H then reflux in 2-butanol–toluene (xylene used for **9c**).

Table 1. Alkylation of DKPs **9a–9c**



9 **14 - 20**

DKP	Electrophile[a]						
	Allyl bromide	Prenyl bromide	$PhCH_2Br$	EtI	$NCCO_2Et$	PhSSPh[b]	PhCHO
9a	**14a** (51)	**15a** (60)	**16a** (62)	—	**18a** (83)	**19a** (52)	**20a** (63)
9b	**14b** (71)	**15b** (82)	**16b** (62)	**17b** (56)	**18b** (69)	**19b** (60)	**20b** (57)
9c	**14c** (73)	—	**16c** (83)	**17c** (61)	**18c** (55)	**19c** (64)	—

[a] Values in brackets are % isolated yields of pure DKP product.
[b] Products were isolated as mixtures of diastereoisomers.

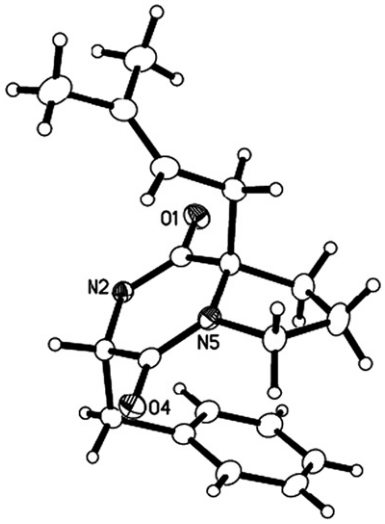


Figure 1. X-ray structure of **15b** (NPMB group has been omitted for clarity).

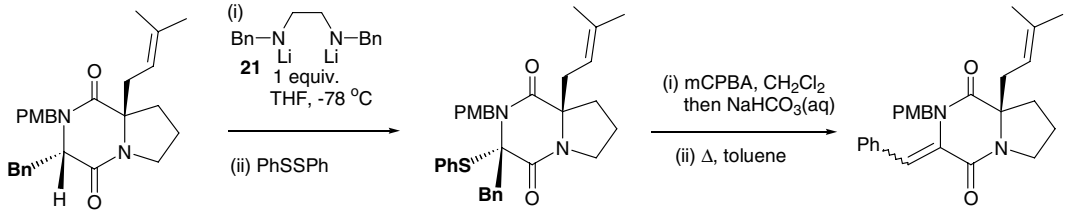
Our initial assignment of relative stereochemistry of the products **14–20** rested on the aforementioned single precedent for alkylation of an enolate related to **9c**.[8a] Fortunately, we were able to confirm this assignment by X-ray crystallography in the case of the key prenylated compound **15b**, required for our cyclisation work, Figure 1.[12]

With a model DKP system, equipped with a suitable prenyl appendage we next explored the installation of a second group X, as indicated earlier in Scheme 1, which would allow cation formation—cyclisation. Initially, we chose to carry out sulfenylation of **15b** (i.e. X = SPh) to give **22**, since this also enabled subsequent sulfoxide *syn*-elimination to give *exo*-benzylidene product **23**, Scheme 3.

Surprisingly, the enolisation–prenylation 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 **21**.[13] Product **22** was obtained in good yield as a single diastereomer, the stereochemical assignment being secured by X-ray crystallography.[14] Sulfoxide elimination proved very efficient, providing **23** as a mixture of geometrical isomers.

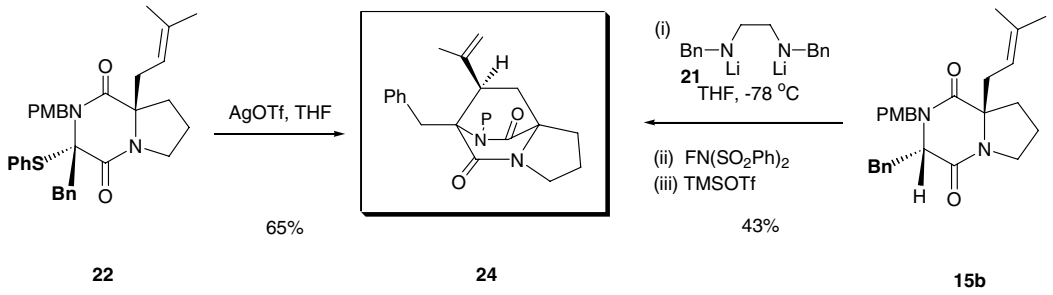
Ylidenepiperazine-2,5-diones, such as **23**, have been demonstrated to undergo intermolecular alkene trapping reactions, analogous to the cyclisation that we planned, under acidic conditions (e.g., with styrenes on heating with formic acid).[15] Unfortunately, treatment of **23** with a number of acidic reagents, including formic acid, TFA and mineral acids, led only to the destruction of the starting material.

We turned instead to the previous reports in which the substitution of thioether groups on a DKP scaffold had been accomplished using AgOTf.[16] The reaction of **22** under these conditions gave rise to a single cyclised product to which we assigned structure **24** by comparison of NMR data with those published previously by Williams and co-workers, Scheme 4.[2i,17]



15b **22** (64%) **23** (94%) *E*:*Z* = 1:1

Scheme 3. Sulfenylation and sulfoxide elimination sequence, starting from **15b**.



Scheme 4. Stereoselective cyclisations of DKPs **22** and **15b**.

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

Finally, we also developed a novel one-pot transformation of **15b**, to give the same tricyclic DKP product **24**, by sequential treatment with base **21**, electrophilic fluorinating agent $FN(SO_2Ph)_2$, and then trimethylsilyltriflate.[18]

The success of this strategy makes available bridged DKP **24** in *only six steps* from the starting commercial phenylalanine **10b**, and has the potential to deliver the indole analogue **8** in a similarly concise fashion. We anticipate applying this strategy to the synthesis of members of the important paraherquamide and stephacidin natural product families, and their analogues, and we are actively pursuing these objectives.

Acknowledgements

We thank the Engineering and Physical Sciences Research Council (EPSRC) and the University of Nottingham for financial support.

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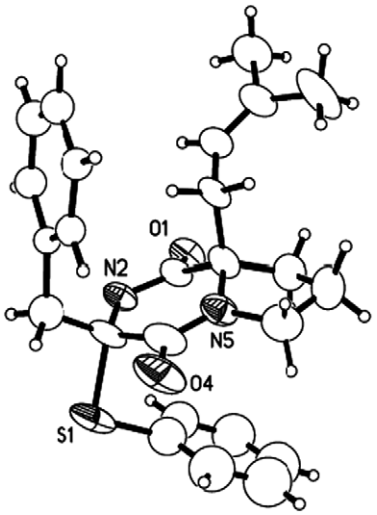
10. *Alkylation of DKP* **9** *to give DKP* **15b**: To a solution of (3*S*,8a*S*)-2-(4-methoxybenzyl)-3-benzylhexahydropyrrolo-[1,2a]pyrazine-1,4-dione **9** (500 mg, 1.37 mmol) in THF, cooled to −78 °C, was added LiHMDS (2.65 mL of a 1.06 M solution in THF, 2.81 mmol) and the solution was stirred at this temperature for 1 h before the addition of prenyl bromide (0.80 mL, 6.9 mmol). 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 (10 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 (light petroleum–EtOAc, 3:1), to yield DKP **15b** 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 and 1036; δ_H (500 MHz, $CDCl_3$) 0.60–0.67 (1H, m, CC*H*HCH$_2$), 1.40 (1H, ddd, *J* 20.0, 9.9, 4.7, CH$_2$C*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$_2$C*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, OCH_3), 3.94 (1H, d, *J* 14.5, NC*H*HAr), 4.13 (1H, app. t, *J* 3.6, C*H*CH$_2$Ph), 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*) and 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. We observed that effective substitution required ca.1.5 equiv of base for **9a**; ca. 2 equiv for **9b**; and ca. 3 equiv for **9c**.

11. The diastereomeric mixtures obtained for **19a** (1:1), **19b** (2:1) and **19c** (3.3:1) seem to reflect poor control in a looser transition state than the other reactions—presumably a result of a relatively long C–S bond, although we have not ruled out epimerisation as yet. Benzaldehyde aldols **20a** and **20b** are single diastereomers, but we have not yet unequivocally assigned the configuration at the new carbinol centre in these adducts.
12. The figure shows one of the two crystallographically independent molecules. Displacement ellipsoids are drawn at 30% probability level. The structure has been deposited at the Cambridge Crystallographic Data Centre, deposition number CCDC 617970.
13. The reasons for the effectiveness of base **21** are not clear at this time.
14. Characterisation data along with the X-ray structure for this product (CCDC deposition number 617971) are shown below (in the structure displacement ellipsoids are drawn at 30% probability level, the PMB protecting group bound to N–2 and a second disorder component of the benzyl ring are omitted for clarity).



Data for **22**: mp 61–63 °C; $[\alpha]_D^{20}$ −22.8 (*c*, 0.560, $CHCl_3$); 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, CH_3), 1.50 (1H, m, CH$_2$C*H*HCH$_2$), 1.58 (3H, s, CH_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, OCH_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 (MH^+, 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 **22** (25 mg) via vapour diffusion from EtOAc (0.5 mL) and petrol (5 mL) over a period of seven days.

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17. The reaction of DKP **22** with AgOTf to give **24**: To a solution of (3*S*,8a*R*)-2-(4-methoxybenzyl)-3-benzyl-hexahydro-8a-(3-methylbut-2-enyl)-3-(phenylthio)pyrrolo-[1,2a]pyrazine-1,4-dione **22** (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 cyclised compound **24** 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.
18. This procedure was based on related *N*-acyliminium chemistry of DKPs, reported by Davies and co-workers, see for example: Bull, S. D.; Davies, S. G.; Garner, A. C.; Savory, E. D.; Snow, E. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2004**, *15*, 3989; For related work, see: Bull, S. D.; Davies, S. G.; Garner, A. C.; O'Shea, M. D.; Savory, E. D.; Snow, E. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2442.