Stereocontrolled intermolecular radical additions to methylidenepiperazine-2,5-diones

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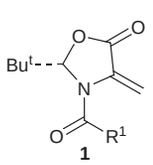
The use of latent amino acid functionalities for the syntheses of methylidenepiperazine-2,5-diones is reported. These piperazinediones are potential chiral templates in the synthesis of functionalised piperazinediones and amino acids. Carbon–carbon bond formation utilising radical addition reactions between the methylidenepiperazinediones and a number of alkyl radicals resulted in good yields of the addition adduct. Moderate to high diastereoselectivities were observed and factors controlling the chiral induction are discussed here.

Introduction

The potential applications of dehydroamino acids and derivatives as versatile intermediates in asymmetric synthesis have long been recognised.[1] The reactivity of the double bond is unique due to the captodative nature[2] of the adjacent substituents and this accounts for the range of reactions that can take place.[3] In addition, these alkenes are prochiral synthons and highly regio- and stereoselective functionalisation of the double bond, particularly in new carbon–carbon bond formation, have been exploited in the synthesis of chiral molecules. One such type of reaction utilises radical additions to the alkene moiety.[4–6] These reactions have been shown to be efficient and with cyclic derivatives, new carbon–carbon bond formation occurs with moderate to high diastereoselectivities. An elegant application of this has been demonstrated by Beckwith and co-workers where new optically active α-amino acids were synthesised *via* radical addition reactions with methylideneoxazolidinones (**1**).[5,6] The reactions occur with high stereocontrol, directed by



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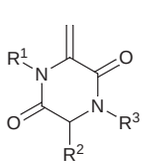


2 **a** R^1=Ac, R^2=H or Me, R^3=Ac
b R^1=Ac, R^2=H or Me, R^3=Me
c R^1=Me, R^2=H or Me, R^3=Ac
d R^1=Me, R^2=H or Me, R^3=Me

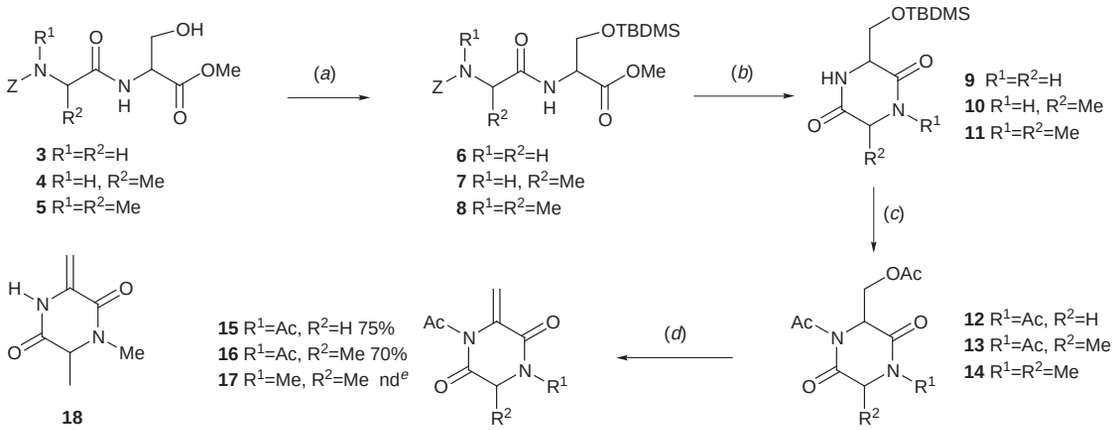
the substituents present in the ring system. α-Amino acids were subsequently isolated following hydrolysis of the oxazolidinones. In a similar manner, dehydropiperazine-2,5-diones (cyclic dehydrodipeptides) (**2**) can also be utilised to direct the stereochemical outcome of reactions.[7,8] For example, dehydropiperazine-2,5-diones have been employed as chiral templates in the synthesis of optically active α-amino acids and derivatives *via* catalytic asymmetric hydrogenation reactions.[9] However, to date there are only few reports of new carbon–carbon bond forming reactions involving dehydropiperazine-2,5-diones.[7,10] A number of naturally occurring piperazine-2,5-diones have complex structures and the syntheses of such natural products are often difficult; complicated by sensitive functionalities present as well as, in numerous cases, the number of stereogenic centres. In view of this, mild, regio- and stereoselective routes for building the carbon framework of piperazinediones are highly coveted. As radical chemistry has been successfully applied to the difficult syntheses of some natural products,[11] it was envisaged that such chemistry may be utilised in the synthesis of complex piperazinediones. Hence our efforts, directed at investigating the scope and limitations of alkyl radical additions will employ methylidenepiperazine-2,5-diones as the key precursors for regio- and stereocontrolled carbon functionalisation. Some preliminary results from this work have been published in communication form.[7]

Results

Synthesis of methylidenepiperazine-2,5-diones

Dehydroamino acids and derivatives can be readily obtained from a number of suitably derived α-amino acid precursors such as *O*-tosylserine, β-chloroalanine and sulfoxides and sulfones derived from cysteine.[12] In contrast, dehydropiperazine-2,5-diones such as the alkylidenes and arylidenes are commonly synthesised *via* condensation procedures.[13] In spite of this, efficient routes to the synthesis of methylidenepiperazine-2,5-diones (**2**) are not well established and our targets, methylidenepiperazinediones of types **2a**–**d**, were chosen to represent piperazine-2,5-dione precursors with varying *N*-substitution patterns. In our strategies to these compounds, the latent functionalities of the amino acids alanine, serine and glycine are exploited for the introduction of the double bond. Unfortunately there is no one universal method for the synthesis of methylidenepiperazinediones **2a**–**d**, as the method of choice depends on the *N*-substitution pattern on the piperazinedione ring. Thus the three routes presented here nicely complement each other.

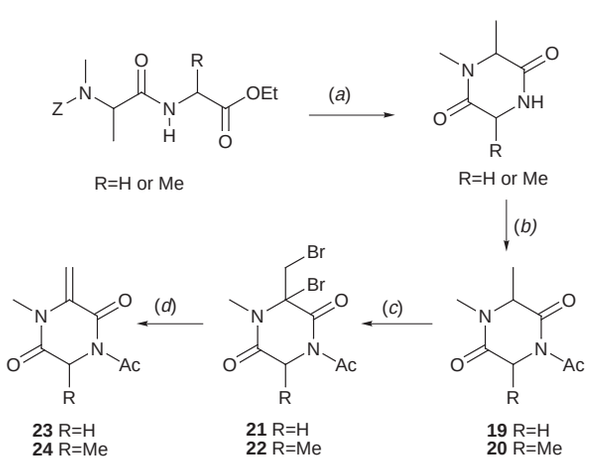
From serine. Methylidenepiperazine-2,5-diones of types **2a** and **2b** can be readily prepared from the corresponding serinyl dipeptide esters (**3**–**5**) following the route shown in Scheme 1. Protection of the free hydroxy group as the TBDMS ether, followed by hydrogenolysis of the benzyloxycarbonyl (Z) group gave the free dipeptide, which cyclised *in situ* to the piperazinedione. However, for the *N*-benzyloxycarbonyl-*N*-Me derivative (**8**), cyclisation of the deprotected dipeptide did not occur readily and in order to effect piperazinedione formation, heating the dipeptide in toluene in the presence of base was



Scheme 1 *Reagents and conditions*: (*a*) TBDMSCl, imidazole, DMF (79–94%); (*b*) i, H_2, MeOH, 10% Pd/C (95%) ii, for **8** Δ, toluene, NEt_3; (*c*) i, Ac_2O, Δ. ii, Ac_2O, $FeCl_3$ (75–86%); (*d*) NEt_3, CH_2Cl_2; (*e*) yield not determined.

necessary. The free nitrogen atom(s) of the piperazinediones was then acetylated and conversion of the protected serine moiety to the α,β-unsaturated moiety was achieved *via* the acetoxy derivatives. Unexpectedly, the preparation of methylidenepiperazinedione **17** from the corresponding acetoxy derivative proved to be problematic. Under typical conditions, where triethylamine was employed as the base, only starting material was recovered. Various attempts to effect the elimination with different bases repeatedly failed to give the desired methylidenepiperazinedione. The 'best' conditions for elimination utilised *t*-BuOK (2 equiv.) and the sole product isolated was identified as 1,6-dimethyl-3-methylidenepiperazine-2,5-dione **18** (70%). This presumably arises from hydrolysis of the acetoxy moiety to the alkoxide followed by intramolecular (N→O) acyl transfer. Elimination of the intermediate acetoxy compound then gives methylidenepiperazinedione **18**.

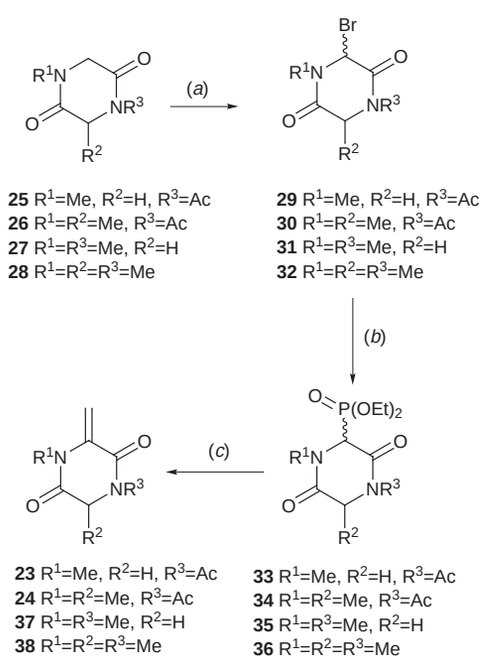
From alanine. Our previous studies have shown that radical bromination of piperazine-2,5-diones can occur in a highly regioselective fashion depending on the nature of the substituents present.[14–16] For example, bromination can be directed to an alanyl in preference to a glycyl centre when the *N*-substituent adjacent to the glycyl center is deactivating (*e.g.* *N*-Ac) as compared to the *N*-substituent adjacent to the alanyl centre (*e.g.* *N*-Me). Thus, in the synthesis of methylidenepiperazinediones of type **2c** (Scheme 2), bromination of piperazinediones



Scheme 2 *Reagents and conditions*: (*a*) i, H_2 MeOH, 10% Pd/C, ii, Δ, toluene, NEt_3 (80–100%); (*b*) Ac_2O, Δ (77–84%); (*c*) NBS, AIBN, CCl_4, Δ (80–100%); (*d*) NaI, CH_3CN (79–87%).

19 and **20** with NBS (two equivalents) gave the dibromopiperazinediones **21** and **22** respectively, consistent with previous observations.[15,17] Debromination to yield the desired methylidenepiperazine-2,5-diones (**23**,**24**) was then achieved with an excess of sodium iodide. It is important to note that this synthetic route is only applicable to methylidenepiperazinediones of type **2c**. Bromination of piperazinedione precursors **26** and **28** will result in preferential bromination of the glycyl center.

From glycine. As discussed above, radical bromination reactions can also be used in the α-functionalisation of glycine-derived piperazinediones. The corresponding bromides can then be utilised as precursors to phosphonate esters, which in turn can be used in Wittig–Horner chemistry for the installation of the double bond. Using this methodology (Scheme 3),



Scheme 3 *Reagents and conditions*: (*a*) NBS, AIBN, CCl_4, Δ; (*b*) $P(OEt)_3$, CH_2Cl_2; (*c*) NaH, CH_2O, CH_2Cl_2.

the synthesis of methylidenepiperazinediones **23**, **24**, **37** and **38** were achieved in moderate to good yields as was previously reported by us.[18]

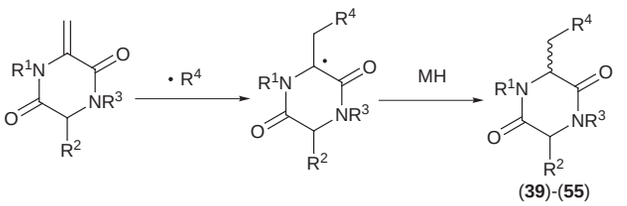
Intermolecular radical additions to methylidenepiperazine-2,5-diones

With the methylidenepiperazinediones in hand, the synthetic utility of these derivatives in radical carbon–carbon bond forming reactions was systematically investigated (Scheme 4).

The regioselectivities of radical addition were initially investigated using methylidenepiperazinediones **15** and **23**

Table 1 Radical addition to methylidenepiperazinediones **15** and **23**

Entry	Methylidene piperazinedione	Radical	Product	Yield (%)
1	**15**	Pr^i	**39**	48
2	**15**	*c*-Hex	**40**	46
3	**23**	Pr^i	**41**	32
4	**23**	*c*-Hex	**42**	57



Scheme 4

(Table 1) using the alkylmercury method. In all of the cases examined, only one regioisomer, that resulting from β-addition to the double bond was observed.

Effect of different alkyl radicals on the stereoselectivity of addition. In cases where there is a C-6 substituent in the 3-methylidenepiperazinediones, a mixture of stereoisomers can result. Thus the diastereoselectivities of the addition reactions were determined using a combination of methods. Careful ^1H NMR integration of appropriate resonances of the stereoisomers and/or quantitative gas chromatographic analysis of the crude reaction mixtures gave the tabulated ratios of the stereoisomers (Table 2).

For each of the methylidenepiperazinediones, it is apparent that increasing the size of the adding radical causes a marked improvement in the diastereoselectivity of addition. For example, addition of a methyl radical to methylidenepiperazinedione **16** gives rise to a diastereoselectivity of 4:1 whereas addition of an isopropyl radical only yields one stereoisomer. Similar trends are also observed with the other methylidenepiperazinediones.

The major isomer in each of the addition reactions above was determined to be *cis*. The assignment of the relative stereochemistry of the addition products was carried out in most cases using NOE experiments. In the case of the addition adducts **45** and **51**, further confirmation of the stereochemical assignment was obtained through the independent synthesis of piperazinediones **45** and **51** starting from suitably protected dipeptide esters of L-leucyl-L-alanine.

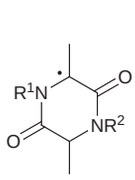
Effect of *N*-substituents on the stereoselectivity of addition. It is apparent from entries 2, 11, 12 and 18 in Table 2 that the stereochemical outcome for radical addition is in part dependent on the structure of the methylidenepiperazinediones. For example, the *cis*:*trans* ratio for ethyl radical addition increases in the order of 1,4-dimethyl < 1-acetyl-4-methyl < 1,4-diacetyl derivatives of methylidenepiperazinediones (1.5:1 to 4:1 to 5:1). Similar trends were also observed in the addition of methyl and isopropyl radicals.

Method of radical addition. Both tin mediated as well as alkylmercury mediated methods to effect radical additions were examined. In general, both methods of addition are efficient in the synthesis of new carbon–carbon bonds of the piperazinediones. Both methods can be conducted under mild reaction conditions and gave good to moderate yields of the addition product in our studies. Whereas the alkylmercury method is limited by the ready availability of alkylmercurys, the tin methods are more versatile in that commercially available alkyl iodides are utilised. For the latter, tin mediated radical addition was carried out under either infinite dilution conditions or *via* the catalytic tin method. The catalytic tin method boasts easier purification procedures (due to smaller amounts of tin by-products) but cannot be utilised in certain systems. For example, our studies show that when radical additions to piperazinedione **16** were carried out using the catalytic tin method (Method 2), *cis*-1,4-diacetyl-3,6-dimethylpiperazine-2,5-dione (*cis*-1,4-diacetylated alanine anhydride) was the only product isolated (Table 2, entries 3, 5). This reduced compound presumably arises from direct borohydride reduction of the double bond, as has been observed previously with enamines.[19] It is interesting to note that analogous direct reduction of the double bond was not observed for piperazinedione **24** under similar catalytic tin conditions. The different chemical outcome is apparently dependent on the *N*-substitution pattern of the piperazinedione ring and this in turn may be related to the relative reactivities of the double bonds. The use of highly reactive alkyl halides, *e.g. tert*-butyl iodide, in our reactions were also incompatible with the catalytic tin method as alanine anhydride derivatives as well as tarry reaction mixtures result.[20]

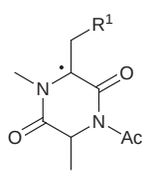
We also note that the choice of either a tin mediated or an alkylmercury method for radical addition has little or no effect on the diastereoselectivity of the addition despite the increase in reaction temperatures when the catalytic tin method is used.

Discussion

Despite much interest in recent literature on the stereocontrolled formation of new carbon–carbon bonds of piperazinediones,[21,22] the utilisation of methylidenepiperazinediones as chiral templates has not been fully exploited.[10] Our studies above show that high diastereoselectivity in radical carbon–carbon bond formation can be achieved by a combination of judicious choice of *N*-substituents on the piperazinedione ring as well as the nature of the alkyl radicals added. The addition reaction proceeds in all cases in a regioselective fashion to yield the captodatively stabilised, α-carbon centred piperazinedione radical. In all the cases studied above, the major *cis*-isomer results from quenching of the intermediate piperazinedione radical from the opposite face to the remote α-carbon substituent. This is presumably due to the more hindered approach of the reducing agent (tributyltin hydride or alkylmercury hydride) to one face of the planar or the nearly planar radical intermediate (Scheme 4). This is nicely supported by AM1 calculations of the piperazinedione radical **56**. It is evident that the remote



56 $R^1=R^2=Ac$
57 $R^1=Me$, $R^2=Ac$
58 $R^1=R^2=Me$



59 $R^1=Me$
60 $R^1=Pr^i$
61 $R^1=Bu^t$

α-methyl group adopts a pseudoaxial position, consistent with other conformational studies on piperazinediones and that this renders the β-face less accessible to the approach of the reducing agent. Previous workers have shown that the conformation of piperazinediones is dramatically affected by the substituents present on the piperazinedione ring.[23] The sensitivity of the ring conformation to such changes is also illustrated by AM1 calculations of piperazinedione radicals **57** and **58**. A measure of the degree of folding of the piperazinedione ring is the Hooker parameter (β).[24] In 1,4-diacetylated piperazinedione radical **56**, the β-value is 26.0° as compared to that for the 1-acetyl-4-methyl piperazinedione radical **57** and 1,4-dimethylated piperazinedione radical **58** with values of 20.5 and

Table 2 Radical addition to methylidenepiperazinediones **16**, **24** and **38**

Entry	Methylidene piperazinedione	Radical	Method[a]	Product	*cis*:*trans*[b]	Yield (%)
1	**16**	Me	1	**43**	4:1	52
2	**16**	Et	1	**44**	5:1	55
3	**16**	Et	2	Reduced[c]	—	nd[d]
4	**16**	Pr^i	3	**45**	1:0	66
5	**16**	Pr^i	2	Reduced[c]	—	nd[d]
6	**16**	*c*-Hex	3	**46**	1:0	49
7	**16**	Bu^t	1	**47**	1:0	65
8	**16**	CH_2Ph	1	**48**	1:0	63
9	**24**	Me	1	**49**	2:1	56
10	**24**	Me	2	**49**	2:1	nd[d]
11	**24**	Et	1	**50**	4:1	54
12	**24**	Et	2	**50**	4:1	65
13	**24**	Pr^i	2	**51**	6:1	53
14	**24**	Pr^i	3	**51**	6:1	45
15	**24**	*c*-Hex	3	**52**	1:0	37
16	**24**	Bu^t	1	**53**	1:0	77
17	**24**	CH_2Ph	1	**54**	1:0	38
18	**38**	Et	2	**55**	1.5:1	73

[a] Method 1: Bu_3SnH, RI, AIBN. Method 2: Bu_3SnCl, $NaCNBH_3$, RI, AIBN. Method 3: RHgCl, $NaBH_4$. For details, see Experimental. [b] Determined by NMR and/or gas chromatography. [c] *cis*-1,4-Diacetylated alanine anhydride was obtained. [d] nd: yield not determined.

18.3° respectively (Fig. 1). Thus, it is suggestive that the increase in the β-value translates to an increase in steric crowding on the β-face. This in turn leads to better observed diastereoselectivities for methylidenepiperazinedione **16** > **24** > **38**, for the same adding radical. Similar trends were also observed in the AM1 geometry minimisation of the intermediate radicals **59**, **60** and **61**, each of which results from the addition of an ethyl, isopropyl and *tert*-butyl radical to methylidenepiperazinedione **24**. The general trend shows that there is an increase in β-values (21.5, 22.4 and 26.7° respectively for radicals **59**, **60** and **61**), consistent with the improvement in diastereoselectivities with the size of the incoming alkyl radical.

The dehydropiperazinedione ring system evidently exerts stereochemical control through steric effects amplified by particular ring conformations. Although similar steric effects must also operate for other cyclic dehydroalanine systems *e.g.* the dehydrooxazolidinones, the precise stereochemical outcome cannot be easily predicted and is highly sensitive to a number of factors. In the methylideneoxazolidinones, the stereochemical preference can even be reversed by changing the *N*-substituents on the oxazolidinone ring.[5] In radical addition reactions, the greater sensitivity of the oxazolidinones to the influence of the *N*-substituents as compared to that of the methylidenepiperazinediones must be intimately linked to the more compact five-membered ring system in the former.

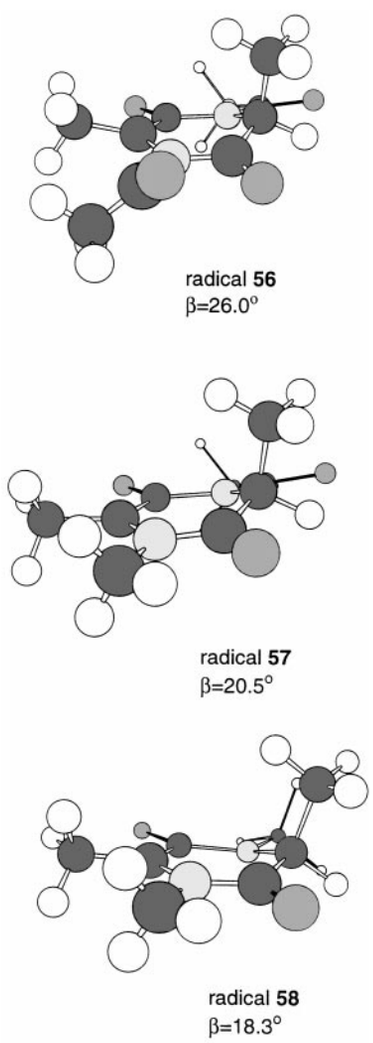


Fig. 1 AM1 geometry optimisation of radical structures **56**–**58**.

Conclusion

The three methods developed for the synthesis of methylidenepiperazine-2,5-diones allow for efficient access to this important class of prochiral synthetic precursors. The methodologies developed here utilise readily available piperazinediones, synthesised from simple amino acid derivatives and the routes lead to the desired methylidenepiperazinediones in moderate to excellent yields. These methylidenepiperazinediones have been shown to be excellent precursors in asymmetric carbon skeleton extension and hence have applications in the stereoselective synthesis of new α-amino acids as well as functionalised piperazine-2,5-diones. There are a number of factors which influence the stereoselectivity of intermolecular radical addition to methylidenepiperazinediones. These parameters, such as the nature of the *N*-substituents as well as the adding alkyl radical, indirectly affect the degree of 1,4-inductive effects of the remote α-methyl substituent of the piperazinedione ring. Substituent effects similar to this have also been observed in suitably substituted piperazinediones where certain combinations of *N*- and *C*-substituents enhance the diastereoselectivities of alkylation reactions *via* a chiral relay network.[21] Our study on methylidenepiperazinediones is another example where stereocontrol is affected through the combination of substituents present.

Experimental

General

Melting points (mp) were determined on a Reichert hot-stage apparatus and are uncorrected. Infrared spectra were recorded as KBr discs (solids) or as a thin film on KBr or NaCl plates (oils) on a Perkin-Elmer spectrometer. NMR spectra were recorded on a Varian Gemini BB 300 or Gemini 1 300 at 300 MHz for proton NMR and at 75 MHz for carbon NMR. For ^{1}H NMR spectra, chemical shifts are reported by using the following as references: in $CDCl_3$, by referencing either the residual solvent ($CHCl_3$) at 7.26 ppm or relative to tetramethylsilane (TMS) at 0.0 ppm; in CD_3OD, by referencing the residual solvent (CHD_2OD) at 3.4 ppm; in D_2O, by referencing the residual solvent (HOD) at 4.7 ppm. *J* Values are given in Hz. For ^{13}C NMR spectra recorded in $CDCl_3$, the centre line of the triplet due to $CDCl_3$ was referenced to 77.0 ppm. Nuclear Overhauser experiments were carried out on an Innova 500 instrument at 500 MHz with solvent used as a reference in all cases. Diastereoselectivities were determined by accurate peak integration of the ^{1}H NMR spectra of the crude reaction products or by GC. Gas chromatography was performed on a Varian 3400 Gas Chromatograph employing a Supelco SPB-2 (30 m × 0.25 mm, 0.25 μm film) column. Low resolution mass spectra (*m*/*z*) were recorded on a VG Micromass 7070F mass spectrometer or a Hewlett Packard HP-5995C instrument at 70 eV. Microanalyses were performed by the Analytical Facility of the Australian National University. Column chromatography employed Merck Kieselgel 60 (230–400 mesh ASTM). Solvents used were of AR grade, with benzene being dried over sodium and deoxygenated prior to use. Light petroleum refers to fractions with bp 60–80 °C. Methylidenepiperazine-2,5-diones **23** and **38** were prepared as reported previously[15] as was piperazine-2,5-dione **20**.[25] Dipeptides were prepared by standard methods (DCC, HOBt).[26]

Molecular modelling calculations were carried out with Spartan SG1 Ver. 5.0.1 © Wavefunction Inc., using AM1 parameters.

Methyl *N*-(*N*-benzyloxycarbonylglycyl)-*O*-*tert*-butyldimethylsilyl-L-serinate 6

This was prepared following the procedure of Corey.[27] To a stirred solution of methyl Z-glycyl-L-serinate (1 g, 3.23 mmol) in DMF (4 cm^3) was added *tert*-butyldimethylsilyl chloride (0.58 g, 3.88 mmol) and imidazole (0.55 g, 3.88 mmol). The reaction mixture was stirred at room temperature for a further 16 hours following which the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate (20 cm^3) and washed with water (10 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The protected dipeptide ester was purified by column chromatography (7 : 3 light petroleum–ethyl acetate, R_f 0.3) to give the desired product as a colourless oil (1.1 g, 79%) (Found: C, 56.6; H, 7.9; N, 6.6. Calc. for $C_{20}H_{32}N_2O_6Si$: C, 56.6; H, 7.6; N, 6.6%); ν_{max}(film)/cm^{-1} 3330, 2957, 2926, 1756, 1709, 1529, 1264, 1102, 1054; δ_H (300 MHz; $CDCl_3$) 0.077 (3H, s, Si(CH_3)CH$_3$), 0.083 (3H, s, Si(CH$_3$)CH_3), 0.91 (9H, s, SiC(CH_3)$_3$), 3.79 (3H, s, OCH_3), 3.8–4.2 (4H, m, CH_2 and CHCH_2), 4.73 (1H, m, CHCH$_2$), 5.63 (1H, br s, NH), 5.19 (2H, s, CH_2Ph), 6.89 (1H, br s, NH), 7.41 (5H, s, Ph); *m*/*z* (EI) 424 (M$^{+\bullet}$, 2%), 367 (43), 91 (100).

Methyl *N*-(*N*-benzyloxycarbonyl-L-alanyl)-*O*-*tert*-butyldimethylsilyl-L-serinate 7

To a stirred solution of methyl L-Z-alanyl-L-serinate (3.85 g, 11.8 mmol) in DMF (20 cm^3) was added *tert*-butyldimethylsilyl chloride (2.15 g, 14.3 mmol) and imidazole (2.02 g, 29.7 mmol). The reaction mixture was stirred at room temperature for a further 16 hours following which the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate (60 cm^3) and washed with water (30 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The protected dipeptide ester was purified by column chromatography (1 : 1 light petroleum–ethyl acetate, R_f 0.6) to give the desired product as a white solid (4.85 g, 94%). mp 50–52 °C (ethyl acetate–light petroleum) (Found: C, 57.2; H, 8.1; N, 6.3. Calc. for $C_{21}H_{34}N_2O_6Si$: C, 57.5; H, 7.8; N, 6.4%); ν_{max}(KBr)/cm^{-1} 3301, 1748, 1685, 1647, 1534, 1264, 1055, 780; δ_H (300 MHz; $CDCl_3$) 0.02 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 1.43 (3H, d, *J* 7, CHCH_3), 3.74 (3H, s, OCH_3), 3.81 (1H, dd, *J* 3 and 10, CHCH_AH$_B$), 4.07 (1H, dd, *J* 3 and 10, CHCH$_A$$H_B$), 4.31 (1H, m, C$HCH_3$), 4.64 (1H, dt, *J* 3 and 8, CHCH$_2$), 5.12 (2H, m, CH_2Ph), 5.37 (1H, br d, NH), 6.63 (1H, br d, *J* 8, NH), 7.36 (5H, s, Ph); *m*/*z* (EI) 438 (M$^{+\bullet}$, 1%), 381 (33), 91 (100).

Methyl *N*-(*N*-benzyloxycarbonyl-*N*-methyl-L-alanyl)-*O*-*tert*-butyldimethylsilyl-L-serinate 8

To a stirred solution of methyl *N*-(*N*-benzyloxycarbonyl-*N*-methyl-L-alanyl)-L-serinate (2.87 g, 8.5 mmol) in DMF (12 cm^3) was added *tert*-butyldimethylsilyl chloride (1.53 g, 10.2 mmol) and imidazole (0.69 g, 10.2 mmol). The reaction mixture was stirred at room temperature for a further 16 hours, following which the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate (30 cm^3) and washed with water (15 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo*. The protected dipeptide ester was purified by flash chromatography (7 : 3 light petroleum–ethyl acetate, R_f 0.4) to give the product as a yellow oil (85%) (Found: C, 58.2, H, 7.8, N, 6.3. Calc. for $C_{22}H_{36}N_2O_6Si$: C, 58.4, H, 8.0, N, 6.2%); ν_{max}(film)/cm^{-1} 2954, 2931, 2857, 1750, 1693, 1511, 1399, 1309, 1255, 1157, 1111, 836, 779; δ_H (300 MHz; $CDCl_3$) 0.01 (6H, s, Si(CH_3)$_2$), 0.84 (9H, s, C(CH_3)$_3$), 1.38 (3H, d, *J* 7, CHCH_3), 2.87 (3H, s, NCH_3), 3.74 (3H, s, OCH_3), 3.78 (1H, dd, *J* 3 and 10, CHCH_AH$_B$), 4.04 (1H, dd, *J* 3 and 10, CHCH$_A$$H_B$), 4.62 (1H, dt, *J* 3 and 8, CHCH$_2$), 4.9 (1H, br m, CHCH$_3$), 5.17 (2H, br s, PhCH_2), 7.36 (5H, s, Ph); *m*/*z* (EI) 452 (M$^{+\bullet}$, 0.2%), 437 (2), 421 (1.5), 395 (57), 192 (35), 148 (58), 91 (100).

General procedure for the conversion of benzyloxycarbonyl dipeptide esters to piperazine-2,5-diones

To a solution of the Z-dipeptide ester (typically 2 g) in methanol (25 cm^3 g^{-1}) was added a catalytic amount of 10% Pd/C and two drops of triethylamine. The reaction flask was evacuated and charged with H_2 (3×) and then left to stir for a further 16 hours at room temperature under a hydrogen atmosphere. The reaction mixture was filtered over Whatman glass microfibre filters and the filtrate evaporated under reduced pressure.

(3*S*)-3-(*tert*-Butyldimethylsilyloxymethyl)piperazine-2,5-dione 9. The protected dipeptide ester **6** was converted to the corresponding piperazine-2,5-dione **9** following the general procedure above. The product was obtained as a white solid (90%), mp 233–234 °C (decomp.) (methanol) (Found: C, 50.9; H, 8.8; N, 10.6. Calc. for $C_{11}H_{22}N_2O_3Si$: C, 51.1; H, 8.6; N, 10.8%); ν_{max}(KBr)/cm^{-1} 3202, 3086, 2929, 2857, 1695, 1677, 1463, 1334, 1114, 837, 779; δ_H (300 MHz; D_2O) 0.02 (6H, s, Si(CH_3)$_2$), 0.78 (9H, s, SiC(CH_3)$_3$), 3.45 (2H, m, CH_2), 3.8–3.6 (2H, m, CHCH_2), 4.56 (1H, t, CHCH$_2$); *m*/*z* (EI) 258 (M$^{+\bullet}$, 1%), 201 (100), 73 (50).

(3*S*,6*S*)-3-*tert*-Butyldimethylsilyloxymethyl-6-methylpiperazine-2,5-dione 10. The protected dipeptide ester **7** was converted to the corresponding piperazine-2,5-dione **10** following the general procedure above. The product was obtained as a white solid (63%), mp 136–138 °C (decomp.) (methanol) (Found: C, 52.9; H, 8.9; N, 10.6. Calc. for $C_{12}H_{24}N_2O_3Si$: C, 52.6; H, 8.7; N, 10.3%); ν_{max}(KBr)/cm^{-1} 3218, 2955, 1685, 1465, 1107, 833, 777; δ_H (300 MHz; CD_3OD) 0.19 (6H, s, Si(CH_3)$_2$),

1.00 (9H, s, SiC(CH_3)$_3$), 1.57 (3H, d, *J* 7, CHCH_3), 3.86 (1H, dd, *J* 1 and 11, CHCH_AH$_B$), 4.09 (2H, m, C*H*CH$_3$ and C*H*CH$_A$H$_B$), 4.18 (1H, dd, *J* 1 and 11, CHCH$_A$$H_B$); *m*/*z* (EI) 272 (M$^{+\bullet}$, 2%), 215 (100), 73 (48) (Found: 272.1553. Calc. for $C_{12}H_{24}N_2O_3Si$ 272.155).

(3*S*,6*S*)-3-*tert*-Butyldimethylsilyloxymethyl-1,6-dimethylpiperazine-2,5-dione 11. The dipeptide ester **8** was deprotected following the general procedure above. As cyclisation did not occur *in situ*, the deprotected dipeptide ester was refluxed in toluene in the presence of base (NEt_3) for several days. The desired piperazine-2,5-dione **11** was isolated as a white solid following column chromatography (9:1 ethyl acetate–methanol, R_f 0.5) (92%), mp 92–95 °C (ethyl acetate) (Found: C, 54.1; H, 8.9; N, 9.7. Calc. for $C_{13}H_{26}N_2O_3Si$: C, 54.5; H, 9.15; N, 9.8%); ν_{max}(KBr)/cm^{-1} 2930, 1688, 1671, 1649, 1463, 1337, 1252, 1105, 834, 782; δ_H (300 MHz; $CDCl_3$) 0.03 (6H, s, Si(CH_3)$_2$), 0.84 (9H, s, SiC(CH_3)$_3$), 1.53 (3H, d, *J* 7, CHCH_3), 2.91 (3H, s, NCH_3), 3.83 (2H, m, C*H*CH$_3$ and CHCH_ACH$_B$), 3.94 (1H, d, *J* 10, CHCH$_A$$H_B$), 4.02 (1H, m, C*H*CH$_AH_B$); δ_C (75 MHz; $CDCl_3$) −5.58 (Si*C*H$_3$), −5.51 (Si*C*H$_3$), 17.63 (CH*C*H$_3$), 18.07 (Si*C*(CH$_3$)$_3$), 25.71 (SiC(*C*H$_3$)$_3$), 31.91 (N*C*H$_3$), 54.94 (*C*HCH$_3$), 58.10 (*C*HCH$_2$), 63.99 (CH*C*H$_2$), 164.17 (*C*O), 168.54 (*C*O); *m*/*z* (EI) 286 (5%, M$^{+\bullet}$), 271 (29), 256 (23), 229 (100), 158 (49), 116 (31), 89 (31).

(3*S*)-1,4-Diacetyl-3-acetoxymethylpiperazine-2,5-dione 12

Piperazine-2,5-dione **9** (1.5 g) was refluxed in acetic anhydride (10 equiv. by weight) for 4 hours. Upon completion of the reaction, excess acetic anhydride was removed by repeated co-evaporation with toluene. The residue was then purified by flash chromatography (1:1 light petroleum–ethyl acetate, R_f 0.7) to give (3*S*)-1,4-diacetyl-3-(*tert*-butyldimethylsilyloxymethyl)-piperazine-2,5-dione as a clear oil (74%) (Found: C, 52.4; H, 7.95; N, 8.4. Calc. for $C_{15}H_{26}N_2O_5Si$: C, 52.6; H, 7.65; N, 8.2%); ν_{max}(film)/cm^{-1} 2654, 2929, 2859, 1716, 1369, 1308, 1220, 1106, 839; δ_H (300 MHz; $CDCl_3$) 0.02 (6H, s, Si(CH_3)$_2$), 0.85 (9H, s, SiC(CH_3)$_3$), 2.58 (3H, s, N*Ac*), 2.59 (3H, s, N*Ac*), 3.95 (1H, dd, *J* 3 and 10, CHCH_AH$_B$), 4.22 (1H, dd, *J* 3 and 10, CHCH$_A$$H_B$), 4.27 (1H, d, *J* 18, CH_CH$_D$), 4.85 (1H, d, *J* 18, CH$_C$$H_D$), 5.13 (1H, m, C*H*CH$_AH_B$); *m*/*z* (EI) 342 (M$^{+\bullet}$, 6%), 300 (9), 285 (100), 243 (96), 201 (94), 158 (69), 116 (59), 73 (62).

To a solution of the piperazine-2,5-dione above (0.22 g, 0.64 mmol) in acetic anhydride (0.4 cm^3, 3.84 mmol) at 0 °C was added iron trichloride (52 mg, 0.32 mmol). The reaction mixture was stirred at ambient temperature and the reaction was monitored by TLC for the disappearance of the starting piperazinedione. Upon complete consumption of the starting piperazinedione, light petroleum (5 cm^3) was added to the reaction mixture and the organic layer washed with water. The aqueous phase was extracted with ethyl acetate (3 × 5 cm^3) and the combined organic layers dried (Na_2SO_4). The solvent was removed *in vacuo* and was co-evaporated several times with toluene. The residue was purified by flash chromatography (1:1 light petroleum–ethyl acetate, R_f 0.27) to give **12** as a yellow oil (63%) (Found: C, 49.3; H, 5.4; N, 10.3. Calc. for $C_{11}H_{14}N_2O_6$: C, 48.9; H, 5.2; N, 10.4%); ν_{max}(film)/cm^{-1} 3012, 2943, 1749, 1715, 1371, 1309, 1220, 1140, 1046, 975, 941; δ_H (300 MHz; $CDCl_3$) 2.06 (3H, s, O*Ac*), 2.58 (3H, s, N*Ac*), 2.59 (3H, s, N*Ac*), 4.21 (1H, d, *J* 18, CH_CH$_D$), 4.47 (1H, dd, *J* 4 and 14, CHCH_AH$_B$), 4.55 (1H, dd, *J* 4 and 14, CHCH$_A$$H_B$), 4.98 (1H, d, *J* 18, CH$_C$$H_D$), 5.35 (1H, m, C*H*CH$_AH_B$); *m*/*z* (EI) 270 (M$^{+\bullet}$, 4%), 240 (15), 228 (69), 198 (77), 186 (29), 168 (35), 156 (100), 126 (37), 114 (71).

(3*S*,6*S*)-1,4-Diacetyl-3-acetoxymethyl-6-methylpiperazine-2,5-dione 13

Piperazine-2,5-dione **10** (1.5 g) was refluxed in acetic anhydride (10 equiv. by weight) for 4 hours. Upon completion of the reaction, excess acetic anhydride was removed by co-evaporating several times with toluene. The crude residue was purified by column chromatography (8:2 light petroleum–ethyl acetate, R_f 0.55) to give (3*S*,6*S*)-1,4-diacetyl-3-*tert*-butyldimethylsilyl-oxymethyl-6-methylpiperazine-2,5-dione as a clear oil (86%) (Found: C, 54.2; H, 8.2; N, 7.8. Calc. for $C_{16}H_{28}N_2O_5Si$: C, 53.9; H, 7.9; N, 7.9%); ν_{max}(film)/cm^{-1} 2955, 2933, 2858, 2359, 1706, 1372, 1237, 1100, 838; δ_H (300 MHz; $CDCl_3$) 0.004 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3), 0.84 (9H, s, SiC(CH_3)$_3$), 1.63 (3H, d, *J* 7, CHCH_3), 2.52 (3H, s, N*Ac*), 2.53 (3H, s, N*Ac*), 3.98 (1H, dd, *J* 3 and 11, CHCH_AH$_B$), 4.22 (1H, dd, *J* 2 and 11, CHCH$_A$$H_B$), 5.11 (2H, m, C*H*CH$_3$ and C*H*CH$_A$H$_B$); *m*/*z* (EI) 357 (MH$^{+\bullet}$, 1%), 299 (72), 257 (89), 215 (100), 158 (83), 73 (82).

To a solution of the piperazine-2,5-dione above (1.31 g, 3.68 mmol) in acetic anhydride (2 cm^3, 22.1 mmol) at 0 °C was added iron trichloride (0.30 g, 1.85 mmol). The reaction mixture was stirred at ambient temperature and monitored by TLC for the disappearance of the starting piperazinedione. Upon complete consumption of the starting materials, light petroleum (10 cm^3) was added to the reaction mixture and the organic layer washed with water. The aqueous phase was extracted with ethyl acetate (3 × 10 cm^3) and the combined organic layers dried (Na_2SO_4). The solvent was removed *in vacuo* and was co-evaporated several times with toluene. The residue was purified by flash chromatography (7:3 light petroleum–ethyl acetate, R_f 0.4) to give the desired product **13** as a clear oil (0.66 g, 80%) (Found: C, 50.7; H, 5.75; N, 9.6. Calc. for $C_{12}H_{16}N_2O_6$: C, 50.7; H, 5.7; N, 9.85%); ν_{max}(film)/cm^{-1} 2917, 1753, 1709, 1373, 1226, 447; δ_H (300 MHz; $CDCl_3$) 1.69 (3H, d, *J* 7, CHCH_3), 2.04 (3H, s, O*Ac*), 2.54 (6H, s, N*Ac*), 4.43 (1H, dd, *J* 3 and 12, CHCH_AH$_B$), 4.62 (1H, dd, *J* 4 and 12, CHCH$_A$$H_B$), 5.18 (1H, q, *J* 7, C*H*CH$_3$), 5.33 (1H, m, C*H*CH$_A$H$_B$); *m*/*z* (EI) 284 (M$^{+\bullet}$, 4%), 254 (31), 242 (19), 212 (90), 182 (36), 170 (100), 157 (38), 140 (40), 128 (81), 111 (30), 82 (42).

(3*S*,6*S*)-1-Acetyl-6-acetoxymethyl-3,4-dimethylpiperazine-2,5-dione 14

Piperazine-2,5-dione **11** (1.26 g, 4.4 mmol) was refluxed in acetic anhydride (10 equiv. by weight) for 4 hours. Upon completion of the reaction, excess acetic anhydride was removed by repeated co-evaporation with toluene. The crude residue was purified by column chromatography (1:1 light petroleum–ethyl acetate, R_f 0.4) and recrystallisation (ethyl acetate–light petroleum) to give 1-acetyl-6-*tert*-butyldimethylsilyloxymethyl-3,4-dimethylpiperazine-2,5-dione as white crystals (84%), mp 56–58 °C (Found: C, 54.7; H, 8.4; N, 8.4. Calc. for $C_{15}H_{28}N_2O_4Si$: C, 54.9; H, 8.6; N, 8.5%); ν_{max}(KBr)/cm^{-1} 2960, 2850, 1722, 1698, 1665, 1650, 1390, 1254, 1104; δ_H (300 MHz; $CDCl_3$) 0.01 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3), 0.83 (9H, s, SiC(CH_3)$_3$), 1.62 (3H, d, *J* 7, CHCH_3), 2.53 (3H, s, N*Ac*), 2.95 (3H, s, NCH_3), 3.94 (1H, dd, *J* 3 and 11, CHCH_AH$_B$), 4.10 (2H, m, C*H*CH$_3$ and CHCH$_A$$H_B$), 4.91 (1H, m, C*H*CH$_AH_B$); *m*/*z* (EI) 328 (M$^{+\bullet}$, 0.6%), 313 (4), 298 (2.5), 285 (1.5), 271 (10), 243 (25), 229 (100), 158 (32), 116 (26), 73 (44).

To a solution of the piperazinedione above (1.01 g, 3.1 mmol) in acetic anhydride (2 cm^3) at 0 °C was added iron trichloride (0.25 g, 1.5 mmol). The reaction mixture was stirred at ambient temperature and monitored by TLC for the disappearance of the starting piperazinedione. Upon complete consumption of the starting material, light petroleum (10 cm^3) was added to the reaction mixture and the organic layer washed with water. The aqueous phase was extracted with ethyl acetate (3 × 10 cm^3) and the combined organic layers dried (Na_2SO_4). The solvent was removed *in vacuo* and was co-evaporated several times with toluene. The residue was purified by flash chromatography (ethyl acetate, R_f 0.4) to give the product **14** as a clear oil (84%) (Found: C, 51.6; H, 6.2; N, 10.9. Calc. for $C_{11}H_{16}N_2O_5$: C, 51.6;

H, 6.3; N, 10.9%); ν_{max}(film)/cm^{-1} 1749, 1709, 1670, 1381, 1232, 1046; δ_H (300 MHz; $CDCl_3$) 1.67 (3H, d, *J* 7, CHCH_3), 2.03 (3H, s, O*Ac*), 2.54 (3H, s, N*Ac*), 2.99 (3H, s, NCH_3), 4.16 (1H, q, *J* 7, C*H*CH$_3$), 4.38 (1H, dd, *J* 3 and 12, CHCH_AH$_B$), 4.56 (1H, dd, *J* 3 and 12, CHCH$_A$$H_B$), 5.14 (1H, m, C*H*CH$_AH_B$); *m*/*z* (EI) 256 ($M^{+\bullet}$, 1.3%), 241 (0.5), 226 (9), 214 (20), 196 (35), 184 (56), 154 (24), 142 (100), 127 (36), 113 (25), 84 (10), 58 (45).

1,4-Diacetyl-3-methylidenepiperazine-2,5-dione 15

To a solution of acetoxypiperazine-2,5-dione **12** (55 mg, 0.2 mmol) in dichloromethane (2 cm^3) was added triethylamine (28 μL, 0.2 mmol). The reaction mixture was monitored by TLC (1 : 1 light petroleum–ethyl acetate) for the disappearance of the starting piperazinedione. Upon completion of the reaction, the reaction mixture was washed with water and the organic layer dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a white solid **15** (31 mg, 75%). The methylidenepiperazinedione was purified by either column chromatography (1 : 1 light petroleum–ethyl acetate, R_f 0.65) or recrystallisation (ethyl acetate–hexane), mp 105–106 °C (Found: C, 51.2; H, 5.0; N, 13.2. Calc. for $C_9H_{10}N_2O_4$: C, 51.4; H, 4.8; N, 13.3%); ν_{max}(KBr)/cm^{-1} 3442, 3007, 2931, 1717, 1699, 1629, 1368, 1313, 1202, 1117, 1037, 1012, 961, 941; δ_H (300 MHz; $CDCl_3$) 2.59 (3H, s, N*Ac*), 2.62 (3H, s, N*Ac*), 4.55 (2H, s, CH_2), 6.07 (1H, s, C=CH_AH$_B$), 6.52 (1H, s, C=CH$_A$$H_B$); *m*/*z* (EI) 210 ($M^{+\bullet}$, 8%), 168 (75), 126 (56), 111 (100), 98 (43) (Found: 210.0641. Calc. for $C_9H_{10}N_2O_4$ 201.0641).

(6*S*)-1,4-Diacetyl-6-methyl-3-methylidenepiperazine-2,5-dione 16

To a solution of piperazinedione **13** (110 mg, 0.4 mmol) in dichloromethane (4 cm^3) was added triethylamine (56 μL, 0.4 mmol). The reaction mixture was monitored by TLC (7 : 3 light petroleum–ethyl acetate) for the disappearance of the starting piperazinedione. Upon completion of the reaction, the reaction mixture was washed with water and the organic layer dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a white solid which was recrystallised from dichloromethane–hexane (70%), mp 121–124 °C (Found: C, 53.3; H, 5.15; N, 12.4. Calc. for $C_{10}H_{12}N_2O_4$: C, 53.6; H, 5.4; N, 12.5%); ν_{max}(KBr)/cm^{-1} 3020, 2943, 1727, 1630, 1455, 1399, 1369, 1301, 1240, 1203, 1137, 1039; δ_H (300 MHz; $CDCl_3$) 1.49 (3H, d, *J* 7, CHCH_3), 2.58 (3H, s, N*Ac*), 2.62 (3H, s, N*Ac*), 2.59 (1H, q, *J* 7, C*H*CH$_3$), 6.10 (1H, d, *J* 1, C=CH_AH$_B$), 6.53 (1H, d, *J* 1, C=CH$_A$$H_B$); δ_C (75 MHz; $CDCl_3$) 18.2 (CH*C*H$_3$), 26.6 (NCO*C*H$_3$), 27.8 (NCO*C*H$_3$), 53.3 (*C*HCH$_3$), 122.1 (C=*C*H$_2$), 131.8 (*C*=CH$_2$), 161.8 (*C*O), 168.1 (*C*O), 170.3 (*C*O), 171.1 (*C*O); *m*/*z* (EI) 224 ($M^{+\bullet}$, 14%), 182 (64), 154 (70), 140 (80), 111 (100), 97 (58).

(6*S*)-1,6-Dimethyl-3-methylidenepiperazine-2,5-dione 18

To a solution of piperazinedione **14** (109 mg, 0.4 mmol) in *t*-BuOH (2.2 cm^3) and ether (7.6 cm^3) at 0 °C was added *t*-BuOK (101 mg, 0.85 mmol). The reaction was monitored by TLC (ethyl acetate) and upon complete consumption of the starting material (typically 1 hour), the reaction mixture was diluted with water and extracted repeatedly with ethyl acetate to yield the product as a white solid (69%). Due to the unstable nature of the compound, the methylidenepiperazinedione was used without further purification; δ_H (300 MHz; $CDCl_3$)[28] 1.54 (3H, d, *J* 7, CHCH_3), 3.03 (3H, s, NCH_3), 4.00 (1H, q, *J* 7, C*H*CH$_3$), 4.90 (1H, s, CH_AH$_B$), 5.61 (1H, s, CH$_A$$H_B$); *m*/*z* (EI) 154 ($M^{+\bullet}$, 88%), 139 (24), 111 (100), 58 (23).

(3*R*,6*S*)- or (3*S*,6*S*)-1-Acetyl-3-bromo-3-bromomethyl-4,6-dimethylpiperazine-2,5-dione 22

To a solution of 1-acetyl-3,4,6-trimethylpiperazine-2,5-dione (**20**) (49.5 mg, 0.27 mmol) in refluxing CCl_4 (5 cm^3) under N_2 was added *N*-bromosuccinimide (95.7 mg, 0.54 mmol) and catalytic amounts of AIBN. The reaction mixture was stirred at reflux (80 °C) for a further two hours or until no more succinimide was generated. The reaction mixture was then cooled to room temperature, the succinimide filtered off and the filtrate concentrated under reduced pressure to give the dibromopiperazine-2,5-dione **22** as a yellow oil (95%). Due to the instability of this compound, it was used without further purification; δ_H (300 MHz; $CDCl_3$) 1.67 (3H, d, *J* 7, CHCH_3), 2.63 (3H, s, N*Ac*), 3.12 (3H, s, NCH_3), 4.09 (1H, d, *J* 11, CH_AH$_B$), 4.75 (1H, d, *J* 11, CH$_A$$H_B$), 5.15 (1H, q, *J* 7, C*H*CH$_3$); *m*/*z* (EI) 355 [$(M - H)^{+\bullet}$, 1%], 275 (50), 169 (62), 157 (100), 111 (77), 55 (49) (Found: 277.0010. Calc. for $C_9H_{12}N_2O_3{}^{81}Br$ 277.0011).

(6*S*)-1-Acetyl-4,6-dimethyl-3-methylidenepiperazine-2,5-dione 24

To a solution of the dibromopiperazinedione **22** (110 mg, 0.3 mmol) in acetonitrile (5 cm^3) was added NaI (446 mg, 3 mmol). The clear yellow solution was observed to become opaque brick red in colour. The reaction was monitored by TLC for the disappearance of starting materials. When the reaction was complete, the mixture was filtered and the filtrate concentrated under reduced pressure. The dark red residue was taken up in chloroform (10 cm^3) and washed with 10% sodium thiosulfate solution (2 × 10 cm^3) and water (5 cm^3). The organic layer was dried (Na_2SO_4) and the solvent evaporated to give a clear oil (79%). The data for this compound is consistent with that reported previously; δ_H (300 MHz; $CDCl_3$) 1.45 (3H, d, *J* 7, CHCH_3), 2.57 (3H, s, N*Ac*), 3.23 (3H, s, NCH_3), 5.12 (2H, m, CH_AH$_B$ and C*H*CH$_3$), 5.13 (1H, d, *J* 1.5, CH$_A$$H_B$).

General procedures for radical addition reactions

Method 1. To a degassed solution of the methylidenepiperazine-2,5-dione (typically 100 mg) in benzene (5 cm^3 per 250 mg substrate) was added the alkyl iodide (10 equiv.). The mixture was irradiated with a UV lamp at room temperature while a solution of tributyltin hydride (1.2 equiv.) and AIBN (catalytic) in benzene (either a 0.06 mol L^{-1} or 0.12 mol L^{-1} solution) was added slowly with a syringe pump at a rate of 5 cm^3 h^{-1}. The reaction was monitored by TLC and upon completion of the reaction, the solvent was removed under reduced pressure. The diastereoselectivities of the reaction were determined by ^{1}H NMR spectroscopy and/or GC analysis. The crude product was redissolved in acetonitrile and the acetonitrile solution was washed several times with hexane. The acetonitrile layer was then concentrated *in vacuo* and the residue purified by flash chromatography.

Method 2. A solution of the methylidenepiperazine-2,5-dione (typically 100 mg) and the alkyl iodide (20 equiv.) in *t*-BuOH (1 cm^3 per 10 mg substrate) was heated to reflux (80 °C). Tributyltin chloride (0.1 mol equiv.), AIBN (catalytic) and $NaCNBH_3$ (2 equiv.) were added to the reaction mixture and this was refluxed under N_2. The reaction was monitored by TLC and when completed, the reaction mixture was cooled and the solvent removed under reduced pressure. The diastereoselectivities of the reaction were determined by ^{1}H NMR spectroscopy and/or GC analysis. The resulting residue was subsequently purified by flash chromatography.

Method 3. To a vigorously stirred solution of the methylidenepiperazine-2,5-dione (typically 50 mg) and the alkylmercury chloride (2.4 equiv.) in dichloromethane (1 cm^3 per 0.04 mmol of substrate) was added rapidly dropwise a solution of $NaBH_4$ (10 equiv.) in water (1 cm^3 per 0.4 mmol of substrate). The reaction mixture immediately turned dark grey and

with time, the reaction mixture clarified to give a colourless solution with droplets of mercury. The reaction was monitored by TLC for the disappearance of starting materials and when the reaction was completed, the mixture was filtered over Celite and the filtrate dried over Na_2SO_4. Evaporation of the solvent gave a residue and the diastereoselectivities of the reaction were determined by ^{1}H NMR spectroscopy and/or GC analysis. The crude residue was subsequently purified by flash chromatography.

(3*R*)- and (3*S*)-1,4-Diacetyl-3-(2-methylpropyl)piperazine-2,5-dione 39

This was prepared from methylidenepiperazine-2,5-dione **15** following Method 3 using isopropylmercury chloride and purified by flash chromatography (7:3 light petroleum–ethyl acetate, R_f 0.6) to give the product as a white solid (48%) mp 86–89 °C (ethyl acetate–hexane) (Found: C, 56.6; H, 7.35; N, 10.8. Calc. for $C_{12}H_{18}N_2O_4$: C, 56.7; H, 7.1; N, 11.0%); ν_{max}(KBr)/cm^{-1} 2961, 1709, 1455, 1415, 1368, 1205, 979, 565; δ_H (300 MHz; $CDCl_3$) 0.98 (3H, d, *J* 6, $CH(CH_3)_2$), 1.05 (3H, d, *J* 6, $CH(CH_3)_2$), 1.55 (1H, m, $CH(CH_3)_2$, 1.70 (2H, m, $CHCH_2$), 2.56 (3H, s, N*Ac*), 2.59 (3H, s, N*Ac*), 4.09 (1H, d, *J* 18, CH_AH_B), 5.15 (1H, d, *J* 18, CH_AH_B), 5.30 (1H, q, $CHCH_2$); *m*/*z* (EI) 255 ($MH^{+\bullet}$, 27%), 212 (32), 198 (54), 169 (48), 156 (100), 127 (58), 114 (48), 100 (39), 85 (56), 72 (39).

(3*R*)- and (3*S*)-1,4-Diacetyl-3-(cyclohexylmethyl)piperazine-2,5-dione 40

This was prepared from methylidenepiperazine-2,5-dione **15** following Method 3 using cyclohexylmercury chloride and purified by flash chromatography (7:3 light petroleum–ethyl acetate, R_f 0.5) to give the product as a clear oil (46%) (Found: C, 60.9; H, 7.5; N, 9.8. Calc. for $C_{15}H_{22}N_2O_4$: C, 61.2; H, 7.5; N, 9.5%); ν_{max}(film)/cm^{-1} 2919, 2848, 1707, 1369, 1212, 1138, 1041, 963; δ_H (300 MHz; $CDCl_3$) 0.98–1.78 (13H, m, $CH_2C_6H_{11}$), 2.56 (3H, s, N*Ac*), 2.59 (3H, s, N*Ac*), 4.06 (1H, d, *J* 19, CH_AH_B), 5.13 (1H, d, *J* 19, CH_AH_B), 5.33 (1H, m, $CHCH_2$); *m*/*z* (EI) 294 ($M^{+\bullet}$, 11%), 198 (54), 156 (100), 114 (48) (Found: 294.1580. Calc. for $C_{15}H_{22}N_2O_4$ 294.1580).

(3*R*)- and (3*S*)-1-Acetyl-4-methyl-3-(2-methylpropyl)piperazine-2,5-dione 41

This was prepared from methylidenepiperazine-2,5-dione **23** following Method 3 using isopropylmercury chloride and purified by flash chromatography (1:1 light petroleum–ethyl acetate, R_f 0.3) to give the product as a white solid (32%), mp 69–71 °C (ethyl acetate–hexane) (Found: C, 58.2; H, 7.9; N, 12.0. Calc. for $C_{11}H_{18}N_2O_3$: C, 58.4; H, 8.0; N, 12.4%); ν_{max}(film)/cm^{-1} 2963, 2936, 1708, 1676, 1499, 1449, 1367, 1261, 1211, 1169, 1123, 565; δ_H (300 MHz; $CDCl_3$) 1.01 (7H, m, $CH(CH_3)_2$ and $CH(CH_3)_2$), 1.68 (2H, m, $CHCH_2$), 2.58 (3H, s, N*Ac*), 3.01 (3H, s, NCH_3), 3.93 (1H, d, *J* 18, CH_AH_B), 3.95 (1H, m, $CHCH_2$), 4.86 (1H, d, *J* 18, CH_AH_B); *m*/*z* (EI) 227 ($MH^{+\bullet}$, 55%), 170 (73), 141 (86), 127 (65), 99 (100), 84 (39), 57 (86).

(3*R*)- and (3*S*)-1-Acetyl-3-cyclohexylmethyl-4-methylpiperazine-2,5-dione 42

This was prepared from methylidenepiperazine-2,5-dione **23** following Method 3 using cyclohexylmercury chloride and purified by flash chromatography (1:1 light petroleum–ethyl acetate, R_f 0.4) to give the product as a clear oil (57%) (Found: C, 63.45; H, 8.0; N, 10.6. Calc. for $C_{14}H_{22}N_2O_3$: C, 63.14; H, 8.3; N, 10.5%); ν_{max}(film)/cm^{-1} 2992, 2850, 1712, 1682, 1449, 1367, 1262, 1215; δ_H (300 MHz; $CDCl_3$) 1.24-1.68 (11H, m, cyclohexyl protons), 1.85 (2H, m, $CH_2C_6H_{11}$), 2.58 (3H, s, N*Ac*), 3.01 (3H, s, NCH_3), 3.96 (1H, d, *J* 18, CH_AH_B), 3.99 (1H, t, $CHCH_2$), 4.86 (1H, d, *J* 18, CH_AH_B); *m*/*z* (EI) 267 ($MH^{+\bullet}$, 23%), 170 (100), 141 (41), 128 (66), 99 (72), 57 (82) (Found: 266.1630. Calc for $C_{14}H_{22}N_2O_3$ 266.1631).

(3*S*,6*S*)- and (3*R*,6*S*)-1,4-Diacetyl-3-ethyl-6-methylpiperazine-2,5-dione 43

This was prepared from methylidenepiperazine-2,5-dione **16** following Method 1 with methyl iodide (20 equiv. rather than 10 equiv.) and the addition of a 0.06 M solution of tributyltin hydride in benzene to give the products as a 4:1 mixture of diastereomers (NMR). The residue was purified by flash chromatography (7:3 light petroleum–ethyl acetate, R_f 0.5) to give the product as a clear oil (52%). Data for major (3*S*,6*S*)-isomer (Found: C, 54.8; H, 6.9; N, 11.8. Calc. for $C_{11}H_{16}N_2O_4$: C, 55.0; H, 6.7; N, 11.7%); ν_{max}(film)/cm^{-1} 1710, 1586, 1370, 1230; δ_H (300 MHz; $CDCl_3$) 1.08 (3H, t, *J* 7, CH_2CH_3), 1.61 (3H, d, *J* 7, $CHCH_3$), 1.87 (2H, m, $CHCH_2$), 2.53 (3H, s, *N*Ac), 2.55 (3H, s, *N*Ac), 5.05 (1H, t, *J* 7, $CHCH_2$), 5.17 (1H, q, *J* 7, $CHCH_3$); δ_C (75 MHz; $CDCl_3$) 10.5 (CH_2CH_3), 19.6 ($CHCH_3$), 26.3 ($CHCH_2$), 26.9 ($COCH_3$), 28.0 ($COCH_3$), 53.5 ($CHCH_3$), 58.0 ($CHCH_2$), 167.9 (*C*O), 169.7 (*C*O), 170.8 (*C*O), 171.1 (*C*O); *m*/*z* (EI) 240 ($M^{+\bullet}$, 21%), 212 (56), 198 (100), 155 (69), 113 (89), 86 (64), 58 (79).

(3*S*,6*S*)- and (3*S*,6*R*)-1,4-Diacetyl-3-methyl-6-propylpiperazine-2,5-dione 44

This was prepared from methylidenepiperazine-2,5-dione **16** following Method 1 with ethyl iodide and a 0.06 M solution of tributyltin hydride in benzene to give the addition product as a 5:1 mixture of diastereomers (NMR). The residue was purified by flash chromatography (7:3 light petroleum–ethyl acetate, R_f 0.45) to give the products as a clear oil (55%). Data for the major (3*S*,6*S*) isomer (Found: C, 56.7; H, 7.45; N, 10.7. Calc. for $C_{12}H_{18}N_2O_4$: C, 56.7; H, 7.13; N, 11.0%); ν_{max}(film)/cm^{-1} 1711, 1385, 1370, 1231; δ_H (300 MHz; $CDCl_3$) 0.97 (3H, t, *J* 7, CH_2CH_3), 1.51 (2H, m, CH_2CH_3), 1.62 (3H, d, *J* 7, $CHCH_3$), 1.80 (2H, m, CH_2CH_2), 2.54 (3H, s, N*Ac*), 2.56 (3H, s, N*Ac*), 5.17 (2H, m, $CHCH_3$ and $CHCH_2$); δ_C (75 MHz; $CDCl_3$) 13.5 (CH_2CH_3), 19.7 (CH_2CH_2), 20.1 ($CHCH_3$), 26.8 ($COCH_3$), 27.4 ($COCH_3$), 37.3 ($CHCH_2$), 54.0 ($CHCH_3$), 57.1 ($CHCH_2$), 168.5 (*C*O), 170.3 (*C*O), 171.2 (*C*O), 171.5 (*C*O); *m*/*z* (EI) 255 ($MH^{+\bullet}$, 30%), 212 (100), 170 (82), 141 (34), 127 (53), 115 (24), 99 (37), 86 (35).

(3*S*,6*S*)-1,4-Diacetyl-6-methyl-3-(2-methylpropyl)piperazine-2,5-dione 45

This was prepared from methylidenepiperazine-2,5-dione **16** following Method 3 using isopropylmercury chloride to give the addition product as a single diastereomer (NMR). The residue was purified by flash chromatography (7:3 light petroleum–ethyl acetate, R_f 0.6) to give the product as a clear oil (66%) (Found: C, 58.1; H, 7.4; N, 10.7. Calc. for $C_{13}H_{20}N_2O_4$: C, 58.2; H, 7.5; N, 10.4%); ν_{max}(film)/cm^{-1} 2954, 1713, 1371, 1227, 1085, 1024, 729; δ_H (300 MHz; $CDCl_3$) 0.99 (3H, d, *J* 6, $(CH_3)_2CH$), 1.06 (3H, d, *J* 6, $(CH_3)_2CH$), 1.63 (3H, d, *J* 7, $CHCH_3$), 1.77 (3H, m, $CHCH_2CH$ and $CHCH_2CH$), 2.54 (3H, s, N*Ac*), 2.57 (3H, s, N*Ac*), 5.19 (1H, q, $CHCH_3$), 5.25 (1H, m, $CHCH_2$); *m*/*z* (EI) 269 ($MH^{+\bullet}$, 3%), 226 (8), 112 (52), 183 (24), 170 (100), 128 (66), 141 (34), 113 (23), 86 (57), 70 (36).

(3*S*,6*S*)-1,4-Diacetyl-3-cyclohexylmethyl-6-methylpiperazine-2,5-dione 46

This was prepared from methylidenepiperazine-2,5-dione **16** by Method 3 using cyclohexylmercury chloride and only a single diastereomer (NMR) was detected. The residue was purified by flash chromatography (7:3 light petroleum–ethyl acetate) to give the product as a clear oil (49%) (Found: C, 62.4; H, 8.1; N, 9.0. Calc. for $C_{16}H_{24}N_2O_4$: C, 62.3; H, 7.8; N, 9.1%); ν_{max}(film)/cm^{-1} 2923, 2850, 1716, 1698, 1385, 1226; δ_H (300 MHz; $CDCl_3$)

0.96 (2H, m, cyclohexyl), 1.26 (5H, m, cyclohexyl), 1.63 (3H, d, *J* 6, CHCH_3), 1.70 (6H, m, CHCH_2 and cyclohexyl), 2.54 (3H, s, N*Ac*), 2.57 (3H, s, N*Ac*), 5.19 (1H, q, C*H*CH$_3$), 5.29 (1H, m, C*H*CH$_2$); *m*/*z* (EI) 309 ($MH^{+\bullet}$, 74%), 267 (23), 212 (48), 170 (100), 128 (51), 99 (25), 86 (33), 55 (23).

(3*S*,6*S*)-1,4-Diacetyl-3-(2,2-dimethylpropyl)-6-methylpiperazine-2,5-dione 47

This was prepared from methylidenepiperazine-2,5-dione **16** following Method 1 with *tert*-butyl iodide and a 0.12 M solution of tributyltin hydride in benzene to give the product as a single diastereomer (NMR). The product was purified by flash chromatography (8:2 light petroleum–ethyl acetate, R_f 0.7) to give the product as a clear oil (65%) (Found: C, 59.7; H, 8.2; N, 10.1. Calc. for $C_{14}H_{22}N_2O_4$: C, 59.6; H, 7.9; N, 9.9%); ν_{max}(film)/cm^{-1} 3408, 1711, 1383, 1230; δ_H (300 MHz; $CDCl_3$) 1.01 (9H, s, C(CH_3)$_3$), 1.62 (1H, m, CHCH_AH$_B$), 1.65 (3H, d, *J* 7, CHCH_3), 1.82 (1H, m, CHCH$_A$$H_B$), 2.46 (3H, s, N*Ac*), 2.53 (3H, s, N*Ac*), 5.18 (1H, q, *J* 7, C*H*CH$_3$), 5.34 (1H, m, C*H*CH$_A$H$_B$); δ_C (75 MHz; $CDCl_3$) 19.8 (C(*C*H$_3$)$_3$), 26.5 (CO*C*H$_3$), 27.9 (CO*C*H$_3$), 29.3 (CH*C*H$_3$), 31.0 (CH*C*H$_2$), 49.6 (*C*(CH$_3$)$_3$), 54.3 (*C*HCH$_3$), 54.6 (*C*HCH$_2$), 169.5 (*C*O), 170.4 (*C*O), 171.1 (*C*O), 171.7 (*C*O); *m*/*z* (EI) 282 ($M^{+\bullet}$, 61%), 267 (83), 240 (61), 225 (85), 183 (96), 169 (53), 155 (64), 141 (87), 127 (60), 113 (58), 99 (79), 86 (94), 71 (60), 57 (100).

(3*S*,6*S*)-1,4-Diacetyl-3-methyl-6-phenethylpiperazine-2,5-dione 48

This was prepared from methylidenepiperazine-2,5-dione **16** following Method 1 with benzyl iodide and a 0.06 M solution of tributyltin hydride in benzene to give the product as a single diastereomer (NMR). The product was purified by flash chromatography (7:3 light petroleum–ethyl acetate, R_f 0.5) to give the product as a clear oil (63%); ν_{max}(film)/cm^{-1} 1709, 1385, 1369, 1229; δ_H (300 MHz; $CDCl_3$) 1.62 (3H, d, *J* 7, CHCH_3), 2.12 (2H, m, CHCH_2), 2.54 (3H, s, N*Ac*), 2.58 (3H, s, N*Ac*), 2.84 (2H, m, PhCH_2), 5.19 (2H, m, C*H*CH$_2$ and C*H*CH$_3$), 7.2 (5H, m, aromatic); δ_C (75 MHz; $CDCl_3$) 20.2 (CH*C*H$_3$), 26.8 (CO*C*H$_3$), 27.4 (CO*C*H$_3$), 32.6 (*C*H$_2$Ph), 36.9 (CH*C*H$_2$), 54.0 (*C*HCH$_3$), 57.1 (*C*HCH$_2$), 126.4 (Ph), 128.4 (Ph), 128.6 (Ph), 139.9 (Ph), 168.3 (CO), 170.0 (CO), 171.3 (CO), 171.5 (CO); *m*/*z* (EI) 317 ($MH^{+\bullet}$, 28%), 275 (12), 224 (14), 212 (99), 182 (21), 170 (100), 140 (21), 128 (88), 91 (49) (Found: ($MH^{+\bullet}$) 317.1498. Calc. for $C_{17}H_{21}N_2O_4$ 317.1501).

(3*S*,6*S*)- and (3*R*,6*S*)-1-Acetyl-3-ethyl-4,6-dimethylpiperazine-2,5-dione 49

This was prepared from methylidenepiperazine-2,5-dione **24** following Method 1 with methyl iodide and a 0.12 M solution of tributyltin hydride in benzene to give the desired addition adducts as a 2:1 mixture of diastereomers. The products were purified by flash chromatography (1:1 light petroleum–ethyl acetate, R_f 0.2 (major), 0.3 (minor)) to give the isomers as clear oils (56%). Data for major (3*S*,6*S*)-isomer; ν_{max}(film)/cm^{-1} 2973, 2941, 1709, 1668, 1390, 1236; δ_H (300 MHz; $CDCl_3$) 1.10 (3H, t, *J* 7, CH$_2$CH_3), 1.54 (3H, d, *J* 7, CHCH_3), 1.95 (1H, m, CHCH_AH$_B$), 2.05 (1H, m, CHCH$_A$$H_B$), 2.56 (3H, s, N*Ac*), 3.01 (3H, s, NCH_3), 3.92 (1H, m, C*H*CH$_A$H$_B$), 4.97 (1H, q, *J* 7, C*H*CH$_3$); δ_C (75 MHz; $CDCl_3$) 10.8 (CH$_2$*C*H$_3$), 20.4 (CH*C*H$_3$), 26.5 (CO*C*H$_3$), 27.7 (*C*H$_2$CH$_3$), 32.8 (N*C*H$_3$), 52.9 (*C*HCH$_3$), 65.2 (*C*HCH$_2$), 167.3 (*C*O), 168.6 (*C*O), 171.8 (*C*O); *m*/*z* (EI) 212 ($M^{+\bullet}$, 44%), 199 (11), 183 (33), 157 (32), 141 (41), 127 (94), 113 (100), 99 (39), 70 (62) (Found: 212.1163. Calc. for $C_{10}H_{16}N_2O_3$ 212.1161). Data for minor (3*R*,6*S*)-isomer; δ_H (300 MHz; $CDCl_3$) 0.86 (3H, t, *J* 7, CH$_2$CH_3), 1.47 (3H, d, *J* 7, CHCH_3), 2.28 (2H, m, CH_2CH$_3$), 2.50 (3H, s, N*Ac*), 2.98 (3H, s, NCH_3), 4.10 (1H, dd, *J* 3 and 5, C*H*CH$_2$), 4.96 (1H, q, *J* 7, C*H*CH$_3$).

(3*S*,6*S*)- and (3*R*,6*S*)-1-Acetyl-4,6-dimethyl-3-propylpiperazine-2,5-dione 50

This was prepared from methylidenepiperazine-2,5-dione **24** following Method 2 using ethyl iodide to give the products as a 4:1 mixture of diastereomers. The products were purified by flash chromatography (1:1 light petroleum–ethyl acetate, R_f 0.26 (major), 0.3 (minor)) to give a clear oil (65%). This was also prepared following Method 1 which also gave the products as a 4:1 mixture of diastereomers (54%). Data for the major (3*S*,6*S*) isomer (Found: C, 58.2; H, 8.0; N, 12.4. Calc. for $C_{11}H_{18}N_2O_3$: C, 58.4; H, 8.0; N, 12.4%); ν_{max}(film)/cm^{-1} 2963, 1709, 1669, 1390, 1369, 1238, 1155, 1031, 980, 573; δ_H (300 MHz; $CDCl_3$) 1.01 (3H, t, *J* 7, CH$_2$CH_3), 1.54 (2H, m, CH_2CH$_3$), 1.54 (3H, d, *J* 7, CHCH_3), 1.90 (2H, m, CHCH_2), 2.56 (3H, s, N*Ac*), 3.00 (3H, s, NCH_3), 3.98 (1H, m, C*H*CH$_2$), 4.96 (1H, q, *J* 7, C*H*CH$_3$); δ_C (75 MHz; $CDCl_3$) 13.5 (CH$_2$*C*H$_3$), 19.4 (*C*H$_2$CH$_3$), 19.9 (CH*C*H$_3$), 27.4 (CO*C*H$_3$), 32.5 (N*C*H$_3$), 35.3 (*C*H$_2$CH$_2$), 52.6 (*C*HCH$_3$), 63.4 (*C*HCH$_2$), 166.9 (CO), 168.4 (CO), 171.5 (CO); *m*/*z* (EI) 226 ($M^{+\bullet}$, 6%), 184 (37), 155 (21), 141 (72), 127 (13), 113 (100), 98 (16), 86 (49), 70 (32), 57 (43). Data for the minor (3*R*,6*S*)-isomer: δ_H (300 MHz; $CDCl_3$) 0.95 (3H, t, *J* 7, CH$_2$CH_3), 1.1–1.4 (2H, m, CH_2CH$_3$), 1.44 (3H, d, *J* 7, CHCH_3), 1.97 (1H, m, CHCH_AH$_B$), 2.20 (1H, m, CHCH$_A$$H_B$), 2.48 (3H, s, COC$H_3$), 2.96 (3H, s, NC$H_3$), 4.08 (1H, dd, *J* 3 and 5, C*H*CH$_2$), 4.93 (1H, q, *J* 7, C*H*CH$_3$); δ_C (75 MHz; $CDCl_3$) 13.8 (CH$_2$*C*H$_3$), 16.5 (*C*H$_2$CH$_3$), 20.2 (CH*C*H$_3$), 28.9 (CO*C*H$_3$), 30.9 (N*C*H$_3$), 33.3 (*C*H$_2$CH$_2$), 52.5 (*C*HCH$_3$), 61.3 (*C*HCH$_2$), 169.0 (*C*O), 169.6 (*C*O), 171.2 (*C*O); *m*/*z* (EI) 226 ($M^{+\bullet}$, 7%), 184 (40), 155 (22), 141 (85), 127 (11), 113 (100), 98 (17), 86 (47), 70 (29), 57 (41).

(3*S*,6*S*)- and (3*R*,6*S*)-1-Acetyl-4,6-dimethyl-3-(2-methylpropyl)-piperazine-2,5-dione 51

This was prepared from methylidenepiperazine-2,5-dione **24** following Method 3 using isopropylmercury chloride to give the product as a 6:1 mixture of diastereomers (NMR, GC). The crude residue was purified by flash chromatography (1:1 light petroleum–ethyl acetate, R_f 0.3 (major), 0.4 (minor)) to give the products as clear oils (45%). This compound was also prepared following Method 2, which gave the products as a 6:1 mixture of diastereomers (53%). Data for the major (3*S*,6*S*)-isomer (Found: C, 60.2; H, 8.1; N, 11.9. Calc. for $C_{12}H_{20}N_2O_3$: C, 60.0; H, 8.4; N, 11.7%); ν_{max}(film)/cm^{-1} 3391, 2361, 2344, 1707, 1653, 1395, 1237; δ_H (300 MHz; $CDCl_3$) 1.01 (3H, d, *J* 7, CH(CH$_3$)CH_3), 1.04 (3H, d, *J* 7, CH(CH_3)CH$_3$), 1.54 (3H, d, *J* 7, CHCH_3), 1.65 (1H, m, CHCH_AH$_B$), 1.7 (1H, m, CHCH$_A$$H_B$), 2.56 (3H, s, N*Ac*), 2.99 (3H, s, NCH_3), 3.97 (1H, m, C*H*CH$_A$H$_B$), 4.98 (1H, q, *J* 7, C*H*CH$_3$); δ_C (75 MHz; $CDCl_3$) 20.1 (CH(*C*H$_3$)CH$_3$), 21.8 (CH(CH$_3$)*C*H$_3$), 22.8 (*C*H(CH$_3$)$_3$), 25.3 (CH*C*H$_3$), 27.7 (CO*C*H$_3$), 32.6 (N*C*H$_3$), 43.3 (CH*C*H$_2$), 52.9 (*C*HCH$_3$), 62.0 (*C*HCH$_2$), 167.4 (*C*O), 168.9 (*C*O), 171.8 (*C*O); *m*/*z* (EI): 241 ($MH^{+\bullet}$, 3%), 197 (6), 184 (84), 155 (73), 142 (39), 127 (36), 113 (100), 100 (43), 84 (39), 57 (61). Data for the minor (3*R*,6*S*)-isomer; δ_H (300 MHz; $CDCl_3$) 0.93 (3H, d, *J* 7, CH(CH_3)CH$_3$), 0.97 (3H, d, *J* 7, CH(CH$_3$)CH_3), 1.49 (3H, d, *J* 7, CHCH_3), 1.74 (1H, m, C*H*(CH$_3$)$_2$), 1.94 (2H, m, CHCH_2), 2.48 (3H, s, N*Ac*), 2.99 (3H, s, NCH_3), 4.03 (1H, dd, *J* 4 and 6, C*H*CH$_2$), 4.93 (1H, q, *J* 7, C*H*CH$_3$); δ_C (75 MHz; $CDCl_3$) 20.4 (CH(*C*H$_3$)CH$_3$), 22.2 (CH(CH$_3$)*C*H$_3$), 23.3 (*C*H(CH$_3$)$_3$), 24.7 (CH*C*H$_3$), 26.7 (CO*C*H$_3$), 31.6 (N*C*H$_3$), 40.4 (CH*C*H$_2$), 52.9 (*C*HCH$_3$), 62.7 (*C*HCH$_2$), 167.6 (*C*O), 169.7 (*C*O), 171.4 (*C*O); *m*/*z* (EI) 240 ($M^{+\bullet}$, 100%), 197 (41), 184 (47), 155 (74), 142 (42), 127 (38), 113 (71), 84 (53), 57 (77).

(3*S*,6*S*)-1-Acetyl-3-cyclohexylmethyl-4,6-dimethylpiperazine-2,5-dione 52

This was prepared from methylidenepiperazine-2,5-dione **24** following Method 3 using cyclohexylmercury chloride to give

the product as a single diastereomer (NMR). The residue was purified by flash chromatography (ethyl acetate, R_f 0.5) to give the product as a clear oil (37%) (Found: C, 64.3, H, 8.8, N, 9.7. Calculated for $C_{15}H_{24}N_2O_3$: C, 64.3; H, 8.6; N, 10.0%); ν_{max}(film)/cm^{-1} 2924, 2361, 1716, 1673, 1393, 1234; δ_H (300 MHz; $CDCl_3$) 1.26–1.73 (11H, m, cyclohexyl protons), 1.52 (3H, d, *J* 7, CHCH_3), 1.91 (2H, m, CHCH_2), 2.56 (3H, s, N*Ac*), 2.98 (3H, s, NCH_3), 4.01 (1H, m, C*H*CH$_2$), 4.98 (1H, q, C*H*CH$_3$); *m*/*z* (EI) 280 (M$^{+\bullet}$, 5%), 238 (42), 184 (100), 142 (60), 113 (65), 57 (53) (Found: 280.1795. Calc. for $C_{15}H_{24}N_2O_3$ 280.1787).

(3*S*,6*S*)-1-Acetyl-3-(2,2-dimethylpropyl)-4,6-dimethylpiperazine-2,5-dione 53

This was prepared from methylidenepiperazine-2,5-dione **24** following Method 1 with *tert*-butyl iodide and a 0.12 M solution of tributyltin hydride in benzene to give the product as a single diastereomer (NMR). The product was purified by flash chromatography (1:1 light petroleum–ethyl acetate, R_f 0.44) to give the product as a clear oil (77%) (Found C, 61.2; H, 8.9; N, 10.95. Calc. for $C_{13}H_{22}N_2O_3$ C, 61.4; H, 8.7; N, 11.0%); ν_{max}(film)/cm^{-1} 2957, 1711, 1674, 1388, 1370, 1238; δ_H (300 MHz; $CDCl_3$) 1.04 (9H, s, C(CH_3)$_3$), 1.52 (3H, d, *J* 7, CHCH_3), 1.58 (1H, m, CHCH_AH$_B$), 1.97 (1H, m, CHCH$_A$$H_B$), 2.53 (3H, s, N*Ac*), 2.96 (3H, s, NCH_3), 3.92 (1H, dd, *J* 2.5 and 8, C*H*CH$_A$H$_B$), 4.99 (1H, q, *J* 7, C*H*CH$_3$); δ_C (75 MHz; $CDCl_3$) 19.9 (C(*C*H$_3$)$_3$), 27.7 (CH*C*H$_3$), 29.5 (CO*C*H$_3$), 30.8 (CH*C*H$_2$), 32.4 (N*C*H$_3$), 49.3 (*C*(CH$_3$)$_3$), 52.9 (*C*HCH$_3$), 60.8 (*C*HCH$_2$), 167.8 (*C*O), 169.8 (*C*O), 171.8 (*C*O); *m*/*z* (EI) 254 (M$^{+\bullet}$, 26%), 197 (30), 183 (45), 169 (99), 155 (44), 141 (46), 113 (100), 84 (52), 57 (80).

(3*S*,6*S*)-1-Acetyl-4,6-dimethyl-3-phenethylpiperazine-2,5-dione 54

This was prepared from methylidenepiperazine-2,5-dione **24** following Method 1 with benzyl iodide and a 0.06 M solution of tributyltin hydride in benzene to give the product as a single diastereomer (NMR). The product was purified by flash chromatography (1:1 light petroleum–ethyl acetate, R_f 0.52) to give the product as a clear oil (38%); ν_{max}(film)/cm^{-1} 3320, 1706, 1669, 1391, 1234, 1040; δ_H (300 MHz; $CDCl_3$) 1.56 (3H, d, *J* 7, CHCH_3), 2.22 (2H, m, CHCH_2), 2.58 (3H, s, N*Ac*), 2.84 (2H, m, PhCH_2), 2.88 (3H, s, NCH_3), 3.94 (1H, m, C*H*CH$_2$), 4.99 (1H, q, *J* 7, C*H*CH$_3$), 7.23–7.36 (5H, m, aromatic); δ_C (75 MHz; $CDCl_3$) 20.4 (CH*C*H$_3$), 27.7 (CO*C*H$_3$), 32.2 (CH$_2$*C*H$_2$), 32.4 (N*C*H$_3$), 35.1 (CH*C*H$_2$), 52.9 (*C*HCH$_3$), 62.6 (*C*HCH$_2$), 126.6 (Ph), 128.5 (Ph), 128.7 (Ph), 139.6 (Ph), 167.25 (*C*O), 168.6 (*C*O), 171.7 (*C*O); *m*/*z* (EI) 288 (M$^{+\bullet}$, 7%), 184 (100), 155 (19), 142 (100), 127 (20), 113 (33), 91 (51) (Found: 288.1471. Calc. for $C_{16}H_{20}N_2O_3$ 288.1474).

(3*S*,6*S*)- and (3*S*,6*R*)-1,3,4-Trimethyl-6-propylpiperazine-2,5-dione 55

This was prepared from methylidenepiperazine-2,5-dione **38** following Method 2 using ethyl iodide to give the product as a 1.5:1 mixture of diastereomers (NMR and GC). The products were purified by flash chromatography (18:3 chloroform–methanol) to give a clear oil (73%). Major (3*S*,6*S*)-isomer; ν_{max}(film)/cm^{-1} 2961, 1663, 1466, 1402, 1336, 1251; δ_H (300 MHz; $CDCl_3$) 0.96 (3H, t, *J* 7, CH$_2$CH_3), 1.4 (2H, m, CH_2CH$_3$), 1.53 (3H, d, *J* 7, CHCH_3), 1.78 (1H, m, CHCH_AH$_B$), 1.91 (1H, m, CHCH$_A$$H_B$), 2.97 (6H, s, NC$H_3$), 3.90 (2H, m, C*H*CH$_3$ and C*H*CH$_A$H$_B$); δ_C (75 MHz; $CDCl_3$) 13.82 (CH$_2$*C*H$_3$), 18.63 (CH$_2$*C*H$_2$CH$_3$), 19.12 (CH*C*H$_3$), 31.93 (N*C*H$_3$), 32.60 (N*C*H$_3$), 34.94 (CH*C*H$_2$), 57.90 (*C*HCH$_3$), 62.21 (*C*HCH$_2$), 165.68 (*C*O), 166.88 (*C*O); *m*/*z* (EI) 198 (M$^{+\bullet}$, 18%), 169 (90), 156 (100), 141 (18), 127 (73), 113 (16), 99 (19), 86 (27), 58 (58). Data for the minor (3*S*,6*R*)-isomer (Found: C, 60.9; H, 9.0; N, 14.1. Calc. for $C_{10}H_{18}N_2O_2$: C, 60.6; H, 9.15; N, 14.1%); ν_{max}(film)/cm^{-1} 2960, 1660, 1460, 1399, 1335, 1247; δ_H (300 MHz; $CDCl_3$) 0.92 (3H, t, *J* 7, CH$_2$CH_3), 1.2 (2H, m, CH_2CH$_3$), 1.57 (3H, d, *J* 7, CHCH_3), 1.85 (1H, m, CHCH_AH$_B$), 2.05 (1H, m, CHCH$_A$$H_B$), 2.96 (3H, s, NC$H_3$), 2.98 (3H, s, NC$H_3$), 3.99 (2H, m, C*H*CH$_3$ and C*H*CH$_A$H$_B$); δ_C (75 MHz; $CDCl_3$) 13.7 (CH$_2$*C*H$_3$), 16.6 (CH$_2$*C*H$_2$CH$_3$), 18.7 (CH*C*H$_3$), 31.6 (N*C*H$_3$), 32.2 (N*C*H$_3$), 33.4 (CH*C*H$_2$), 56.5 (*C*HCH$_3$), 61.3 (*C*HCH$_2$), 165.9 (*C*O), 166.9 (*C*O); *m*/*z* (EI) 197 [(M − H)$^{+\bullet}$, 100%], 169 (35), 142 (8), 128 (3), 84 (32) (Found: 197.1291. Calc. for $C_{10}H_{17}N_2O_2$: 197.1290).

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