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The synthetic versatility of alkoxycarbonyl- and hydroxymethyl-piperazine-2,5-diones

Christina L.L. Chai,* John A. Elix and Paul B. Huleatt

Department of Chemistry, The Faculties, Australian National University, Canberra, ACT 0200, Australia

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Abstract—Alkoxycarbonylpiperazine-2,5-diones are versatile precursors for the α-functionalisation of piperazine-2,5-diones. The alkoxycarbonyl group activates the α-carbon position to alkylation reactions and this provides a mild and selective method for the extension of the carbon framework of piperazine-2,5-diones. In addition, the alkoxycarbonyl group can be converted to the carboxy group, which in turn can be 'deleted' or manipulated for the installation of carbon and/or heteroatom substituents where desired, the latter via *N*-acyliminium chemistry. We also demonstrate that hydroxymethylpiperazine-2,5-diones complement carboxypiperazinediones as precursors for the generation of *N*-acyliminium ions.

1. Introduction

The ubiquity of the piperazine-2,5-dione motif in a number of biologically active natural products[1] has encouraged research into the development of methods for the selective functionalisation of piperazine-2,5-diones. Although piperazine-2,5-diones are cyclic dipeptides and can formally be synthesized from the condensation of the requisite α-amino acids,[2] in practice complex piperazine-2,5-diones are accessed by the functionalisation of readily available piperazine-2,5-dione precursors.[3] This approach has the advantage of enabling the assembly of the carbon and heteroatom framework of piperazine-2,5-diones without the need to develop individual strategies for the synthesis of the requisite α-amino acids.

The existing methods for *C*-functionalisation are limited in scope due to the necessity of using strong bases in cases where the generation of the enolate of the piperazinedione is required.[4] Regioselectivity is also a problem with unsymmetrical piperazine-2,5-diones. Other methods for *C*-functionalisation of piperazinediones include using radical addition chemistry[5] and Diels–Alder reactions.[6] The former relies on the ability to synthesise suitable radical precursors and/or substrates and is sensitive to polar and steric effects while the latter is more suitable for the synthesis of bicyclic frameworks. Due to the limitations of the aforementioned methodologies, we sought to develop complementary synthetic routes for the *C*-functionalisation of piperazinediones. In addition we also recognized the need to be able to install heteroatom functionalities on the α-carbon positions of the piperazine-2,5-dione ring as this substitution is present in numerous bioactive piperazine-2,5-diones. These heteroatom functionalised piperazine-2,5-diones can also serve as radical or cationic precursors in subsequent chemical transformations.

Our plan involved the use of an alkoxycarbonyl group as a 'traceless' substituent on the piperazine-2,5-dione ring. The choice of the alkoxycarbonyl group was expected to enhance the reactivity of the α-carbon center of the piperazine-2,5-dione ring towards alkylation reactions. In addition, we envisage that the alkoxycarbonyl group can be converted to the carboxy group, which in turn can be 'deleted' or manipulated for the installation of carbon and/or heteroatom substituents where desired.

Following on from our previous communication,[7] the studies reported herein detail the synthetic utility of alkoxycarbonyl piperazine-2,5-diones in the functionalisation of the piperazine-2,5-dione nucleus. In the course of our studies we also discovered that the readily accessible hydroxymethylpiperazine-2,5-diones complement the chemistry of alkoxycarbonyl derivatives.

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* Corresponding author at present address: Institute of Chemical and Engineering Sciences, 1 Pesek Road, Jurong Island, Singapore 627833. Tel.: +65 6796 3902; fax: +65 6316 6184;
e-mail: christina_chai@ices.a-star.edu.sg

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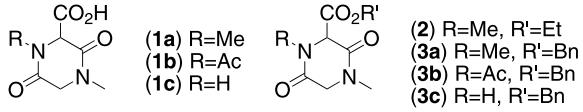
2. Results and discussion

2.1. Synthesis of alkoxycarbonyl- and carboxy-piperazine-2,5-diones

In order to examine the effects of various substitution patterns on the chemistry of carboxy piperazine-2,5-diones, the acids **1a**–**c** derived from the esters of types **2** and **3**, were targeted.



Our initial work was directed towards the synthesis of the target, acid **1a**. A three step synthesis of diethyl *N*-methylaminomalonate (**6**) was carried out using modification of literature procedures.[8–10] Diethyl malonate was readily converted to diethyl α-bromomalonate **4** in 70% yield using bromine in carbon tetrachloride.[8] However, when the bromide **4** was treated with *N*-methylbenzylamine using conditions reported in the literature,[9,10] only diethyl malonate was recovered. After much experimentation, the synthesis of the desired diethyl *N*-methylbenzylaminomalonate (**5**) was achieved by treatment of the bromide **4** with *N*-methylbenzylamine in chloroform at reflux. Hydrogenolytic cleavage of the benzyl group from amine **5** then cleanly afforded diethyl *N*-methylaminomalonate (**6**) in 95% yield. With the aminomalonate **6** in hand, DCC mediated coupling of the amine with CBZ-sarcosine afforded the dipeptide **7** in good yield. Hydrogenolytic cleavage of the CBZ protecting group from the dipeptide **7**, followed by thermally promoted cyclisation of the deprotected dipeptide afforded the α-ethoxycarbonyl piperazinedione **2** (see Scheme 1).

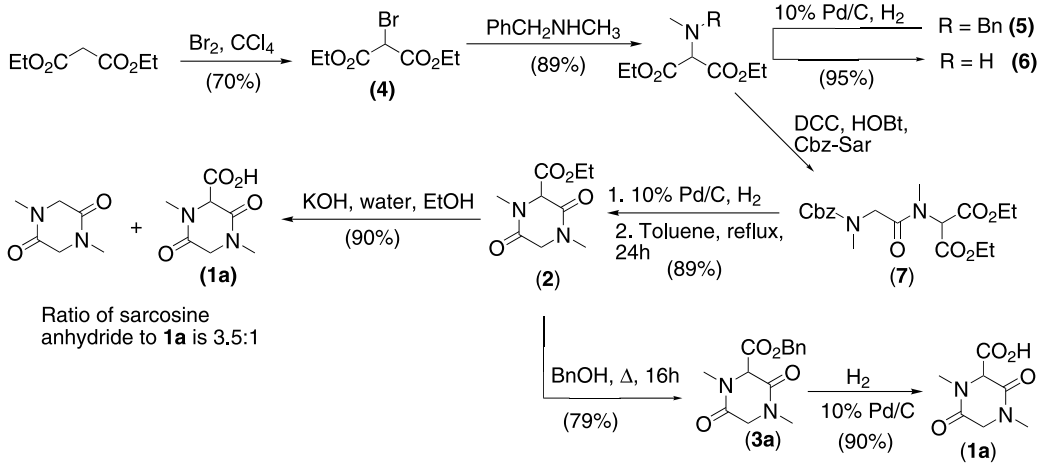
With the α-ethoxycarbonyl piperazinedione **2** in hand, saponification of the ethyl ester moiety using potassium hydroxide in aqueous ethanol was carried out as reported in the literature.[11] Disappointingly, we were unable to achieve the smooth conversion of the ester **2** to the acid **1a**. Approximately 70% of the material recovered from the reaction was identified as sarcosine anhydride, clearly resulting from the premature decarboxylation of the acid **1a**. Our attempts to minimise the premature decarboxylation of acid **1a** by numerous modifications to the work-up procedure were unsuccessful and sufficient quantities of the acid **1a** could not be obtained. Consequently, a milder method of generating the acid **1a** was desired. We envisaged that the acid **1a** may be attainable via hydrogenolysis of the benzyl ester **3a**. Thus, ester **2** was successfully transesterified with benzyl alcohol and the desired benzyl ester **3a** was obtained in good yield.

Subsequent hydrogenolysis of the ester **3a** using 10% palladium on carbon under a hydrogen atmosphere proceeded smoothly and the desired acid **1a** was obtained in excellent yield. Premature decarboxylation of the acid **1a** was suppressed and sarcosine anhydride was only observed as a minor byproduct.

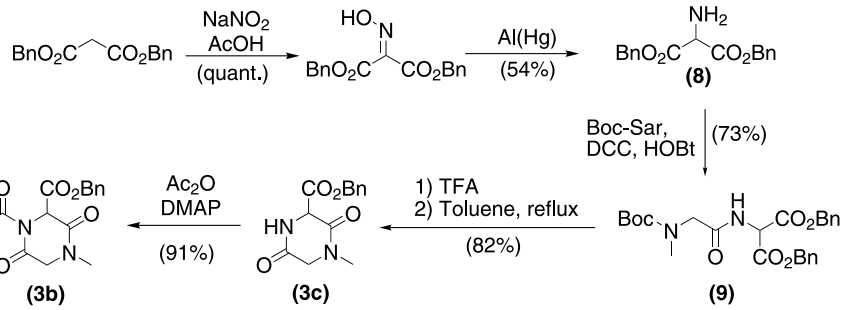
From the studies above it is evident that the benzyloxycarbonyl piperazine-2,5-diones of type **3** are suitable precursors to the corresponding acids. With this in mind, a synthetic route to the esters was undertaken. The synthesis of dibenzyl aminomalonate (**8**) was carried out following literature procedures[12] starting from dibenzyl malonate. Peptide coupling of dibenzyl aminomalonate (**8**) with BOC-sarcosine, deprotection of the resultant dipeptide **9** and subsequent cyclisation gave the piperazinedione **3c** in good yields. *N*-acetylation of piperazinedione **3c** using acetic anhydride and DMAP under standard conditions gave the corresponding ester **3b** (see Scheme 2).

With the two esters **3b** and **3c** in hand, the target acids **1b** and **1c** were accessed via hydrogenolysis. When the *N*-acetyl ester **3b** was treated with hydrogen and 10% palladium on carbon, as described above, a 2:1 mixture of the desired acid **1b** and 1-acetyl-4-methylpiperazine-2,5-dione was formed (Scheme 3). Unfortunately, this mixture could not be separated because of the instability of the acid **1b** and in subsequent experiments this mixture of compounds was utilised without purification.

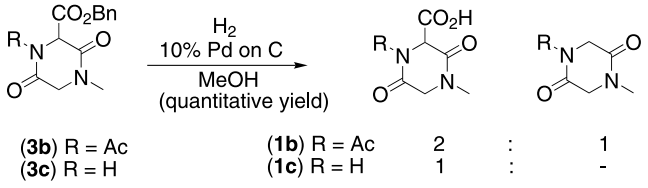
When the free amido ester **3c** was reacted under similar conditions only the desired acid **1c** was obtained. The greater stability of the acid **1c** as compared with the acid **1b** maybe due to the relief of steric strain upon decarboxylation of acid **1b**. Since analogous steric effects are not present in



Scheme 1.



Scheme 2.



Scheme 3.

1c, the latter is relatively stable. Whilst the acid **1c** showed greater stability than **1b**, it was highly insoluble in organic solvents including dichloromethane and chloroform and only showed appreciable solubility in more polar solvents such as methanol and DMSO.

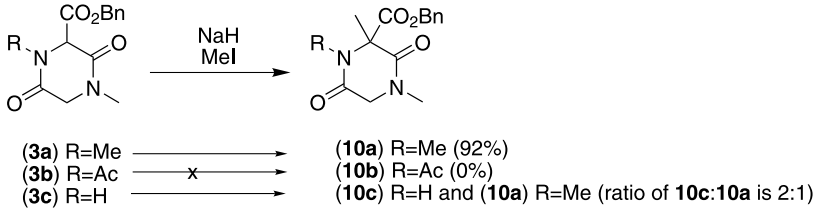
2.2. Extension of the carbon framework of alkoxycarbonyl piperazine-2,5-diones

The α-alkylation reactions of piperazine-2,5-diones are usually accomplished using strong bases such as *n*-butyl lithium or sodamide.[4] In our studies, the α-methylation of piperazinedione **3a** was effected in excellent yields using NaH and MeI. This is due to the presence of the activating alkoxycarbonyl group at the α-carbon center of the piperazine-2,5-dione ring. When the *N*-acetyl ester **3b** was reacted with NaH and MeI under similar conditions, only unreacted starting material was recovered. The failure of this system to undergo α-alkylation is surprising and may be related to subtle conformational effects associated with the substitution pattern of the piperazinedione ring.

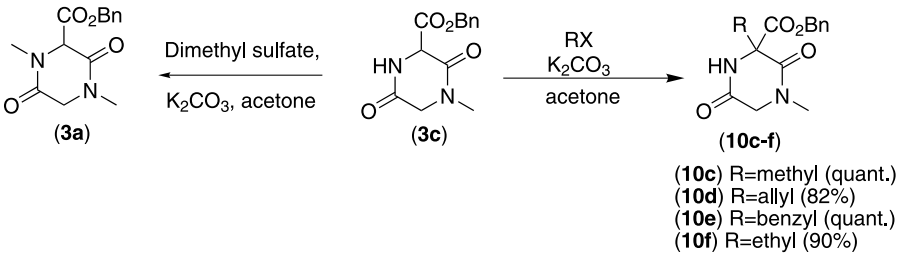
Alkylation of piperazinedione **3c** with one equivalent of NaH yielded a mixture of products comprising the α-methylated ester **10c** as the major component and equal amounts of the trimethyl compound **10a** and the starting material **3c** (Scheme 4). Thus the use of NaH as base does not discriminate between *C*- and *N*-alkylation. With excess NaH and MeI, complete conversion of piperazine-2,5-dione **3c** and **10c** to the trimethyl compound **10a** was observed.

When the ester **3c** was reacted with one equivalent of potassium carbonate and excess methyl iodide, α-methyl piperazinedione **10c** was formed exclusively and in excellent yields. The excellent regioselectivity observed in the alkylation of piperazinedione **3c** is general for a number of alkyl halides studied. Scheme 5 summarises the range of alkyl substituents that can be selectively installed at the α-carbon position of piperazinedione **3c** under these mild alkylation conditions.

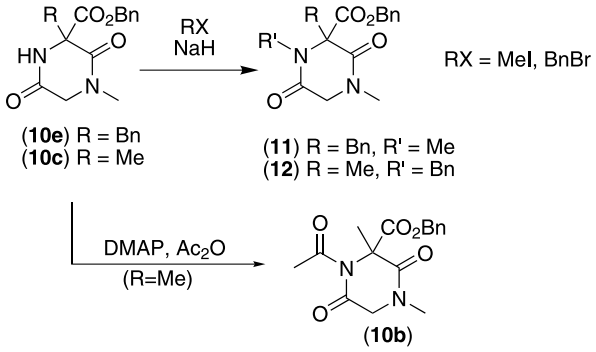
Surprisingly when dimethyl sulfate was used as the alkylating agent instead of MeI, only ester **3a** was obtained (Scheme 5). Thus the choice of alkylating agents provides complementary routes to the α-methylated derivative **10c** as well as to the *N*-methylated piperazine-2,5-dione **3a**.



Scheme 4.



Scheme 5.



Scheme 6.

The potential of this selective alkylation methodology is highlighted when sequential *C*- and *N*-functionalisation steps are carried out. For example, ester **3c** can be selectively *C*-benzylated to give piperazinedione **10e**. This compound is then readily *N*-methylated with methyl iodide and sodium hydride in DMF to yield the *N*-methylated, *C*-benzylated piperazinedione **11** in 85% yield. Alternatively, by simply changing the sequence of addition of the alkylating agents, the ester **3c** can be *C*-methylated and subsequently *N*-benzylated to afford piperazinedione **12** (Scheme 6).

The methodology to selectively install *C*-alkyl functionality onto the piperazinedione ring can also be used for the synthesis of piperazinedione **10b**. As previously outlined in Scheme 4, the synthesis of piperazinedione **10b** could not be achieved via α-methylation of the *N*-acetyl piperazinedione **3b**. However, with the *C*-methylated piperazinedione **10c** in hand, *N*-acetylation was readily achieved using acetic anhydride and DMAP to afford piperazinedione **10b** (Scheme 6).

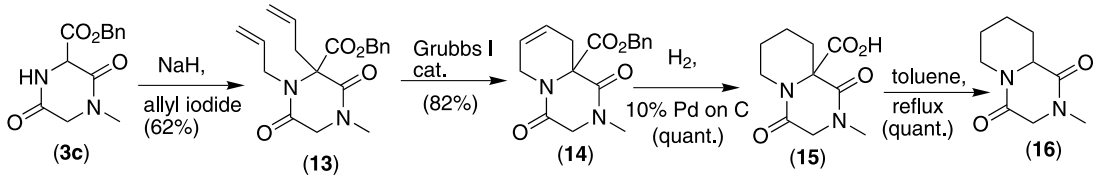
2.3. Applications to the synthesis of ring fused piperazinediones

The methodology described above can be applied to the synthesis of conformationally constrained α-amino acid derivatives such as that derived from pipecolic acid and baikiain.[13] Two approaches are possible for the synthesis of these fused ring systems, both of which involve a sequence of *N*- and *C*-alkylation reactions. In the first approach (Scheme 7), allylation of **3c** afforded the 3,4-diallyl piperazinedione **13** in moderate yield. The fused six-membered ring of the baikiain derivative **14** was then formed efficiently via a ring closing metathesis reaction using either Grubb's type I or type II catalysts. Hydrogenolysis of the benzylic ester **14** is accompanied by the concomitant reduction of the alkene to give the carboxylic acid **15**. Finally, the known pipecolic acid derivative **16**[14] was prepared via the quantitative thermal decarboxylation of the acid **15**.

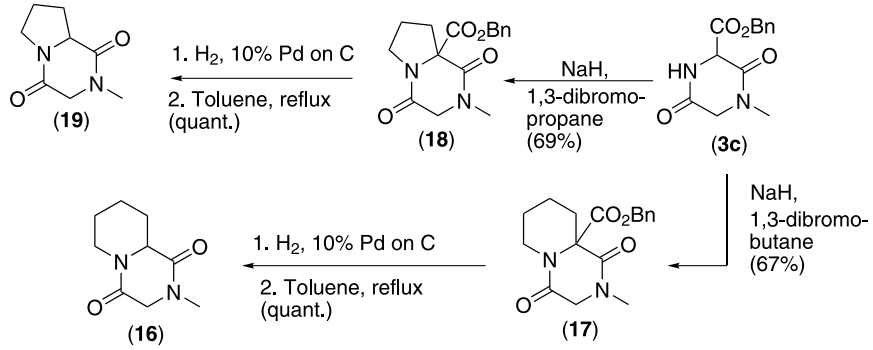
The second approach, outlined in Scheme 8, to the pipecolic acid derivative **16** is more direct. When the key precursor **3c** was treated with 2 equiv of sodium hydride and 1 equiv of 1,4-dibromobutane the desired ester **17** was obtained in moderate yield. The identity of the ester **17** was confirmed by quantitative conversion to piperazinedione **16** using the standard decarboxylation conditions.

Similarly the five membered ring analogue of **16** was also be synthesized in this manner using 1,3-dibromopropane as the alkylating agent (Scheme 8). The piperazine-2,5-dione formed was subsequently converted to the known derivative **19**[14] via ester cleavage and decarboxylation.

This study into the functionalisation of ester **3c** resulted in the development of a versatile synthetic route to piperazinediones with varying *N*- and α-substitution patterns. Our subsequent studies focussed on sequential decarboxylation oxidation nucleophilic addition (DONA) reactions of carboxy piperazine-2,5-diones. We envisaged that in conjunction with the mild, efficient and selective alkylation procedures described above, the DONA protocol could lead to piperazinediones with greater functional diversity.



Scheme 7.



Scheme 8.

2.4. Decarboxylation oxidation nucleophilic addition reactions (DONA) of carboxy piperazine-2,5-diones

In 1999, Suarez et al. reported the synthesis of α-functionalised pyrrolidines from proline derivatives, in the presence of iodine and diacetoxyiodobenzene (DIB).[15] The transformation is believed to occur via the intermediacy of the *N*-acyliminium ion. Although the synthetic potential of acyl iminium ion chemistry has long been recognized,[16] the study by Suarez provides a mild and efficient method for the generation and trapping of *N*-acyl iminium ion species.

This methodology offered an attractive means for preparing α-functionalised piperazinediones from the corresponding acids. Thus treatment of acid **1a** with 1 equiv of diacetoxyiodobenzene (DIB) and 0.5 equiv iodine gave the α-acetoxy derivative **22a**. The mechanism, as outlined in Scheme 9, is likely to proceed through the intermediacy of the carboxy radical which then undergoes rapid decarboxylation to the α-carbon centred radical **20**. DIB mediated one electron oxidation of this radical species would give the *N*-acyliminium ion intermediate **21a**. In the absence of an added nucleophile, the acetate ions (or acetic acid) would add to the *N*-acyliminium ion **21a** to yield the α-acetoxy piperazinedione **22a**. The simplicity and versatility of this sequence is demonstrated when the acid **1a** was treated with DIB and iodine in the manner described above and methanol was added as an external nucleophile. This resulted in the efficient conversion of the acid **1a** into the corresponding α-methoxy product **22b**, a compound which displayed spectroscopic data identical to that reported in the literature.[17]

The successful use of the acid **1a** as a substrate for such DONA reactions prompted us to assess the relative reactivity of the acids **1b** and **1c**. In view of the proposed mechanism of the reaction, it is evident that the ease of generation as well as the stability of the *N*-acyliminium ion may be strongly influenced by electronic and/or steric effects. For example, the generation of the *N*-acyliminium ion **21b** may be more difficult than **21a** and **21c** as the radical intermediate derived from acid **1b** would be expected to be more difficult to oxidise to the highly electron deficient species **21b**. If formed, the *N*-acyliminium ion **21b** will also be destabilised by electronic effects and would be expected to be more reactive with nucleophiles.

In contrast to the *N*-methyl carboxylic acid **1a**, which showed poor solubility in dichloromethane, the *N*-acetyl acid **1b** was very soluble in chlorinated solvents. Thus, when the acid **1b** was treated with DIB and I_2 in the absence and in the presence of methanol, respectively, the α-acetoxy piperazinedione **22c** and the α-methoxy piperazinedione **22d** were obtained in excellent yields.

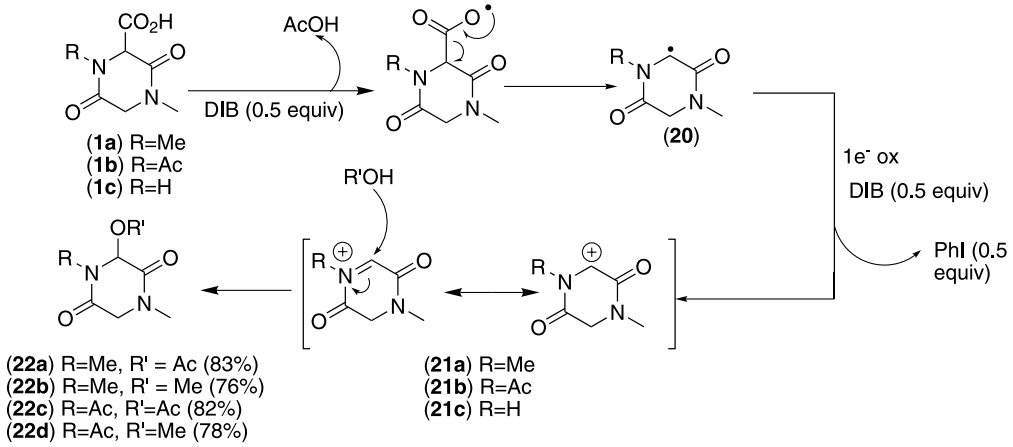
These experiments indicate that under these conditions, the acid **1b** appears to have similar reactivity to the acid **1a** despite the expected disparity in the ease of generation and stability of the reactive *N*-acyliminium ion intermediates, **21a** and **21b**. This result is noteworthy as *N*-acyliminium ions such as **21b** have not been available for synthetic purposes prior to this work.[16]

In contrast to the *N*-acetyl acid **1b**, the free amido acid **1c** was sparingly soluble in solvents suitable for use in the DONA reaction, namely dichloromethane and acetonitrile. As a result, when the acid **1c** was subjected to the DONA protocol outlined previously no reaction was observed and in all cases the starting material was recovered quantitatively.

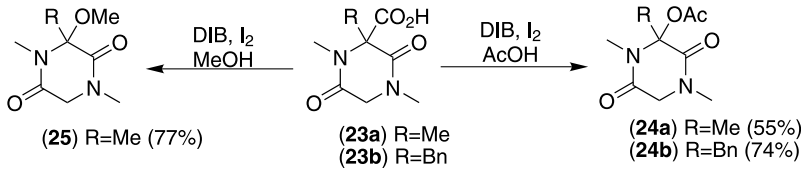
2.5. DONA reactions of α,α-disubstituted piperazine-2,5-diones

The effect of an α-substituent on the formation and reactivity of the *N*-acyliminium ion intermediates generated using the DONA strategy was examined using the α-methyl acid **23a** obtained from the hydrogenolysis of the corresponding ester **10a**. It is interesting to note that in contrast to the acid **1a**, no premature decarboxylation of the acid **23a** was detected. This suggests that the α-substituted acid **23a** is more stable than the unsubstituted acid, **1a**, presumably because the presence of the α-methyl substituent hinders the ability of the acid **23a** to adopt the planar six-membered ring transition state required for the decarboxylation to occur.

Treatment of the α-methyl carboxylic acid **23a** with DIB and iodine in the presence of either acetic acid or methanol



Scheme 9.



Scheme 10.

gave rise to the α-acetoxy (**24a**) and the α-methoxy (**25**) piperazinediones, respectively in yields comparable to those obtained for acids **1a** and **1b**. Similarly, conversion of the acid **23b** (which was obtained from the ester **11**) to the corresponding α-acetoxy compound **24b** was also achieved (Scheme 10).

The synthetic sequence described above led to piperazinedione derivatives which cannot be readily accessed using other synthetic methods. Studies carried out within our group have established that selective heteroatom α-functionalisation of piperazinediones can be difficult in some cases.[18] For example, the α-methoxy compound **25** cannot be prepared by the established protocols for the α-functionalisation of piperazinediones. 3-Bromo-1,3,4-trimethylpiperazine-2,5-dione cannot be accessed through established methods as radical bromination of 1,3,4-trimethylpiperazine-2,5-dione with NBS leads to exclusive formation of the regioisomer, 6-bromo-1,3,4-trimethylpiperazine-2,5-dione.[18b] This in turn means that the formation of the α-methoxy compound **25**, via nucleophilic displacement of the bromide, cannot be obtained by this route.

2.6. Carbon–carbon bond forming reactions via *N*-acyliminium ions derived from piperazine-2,5-diones

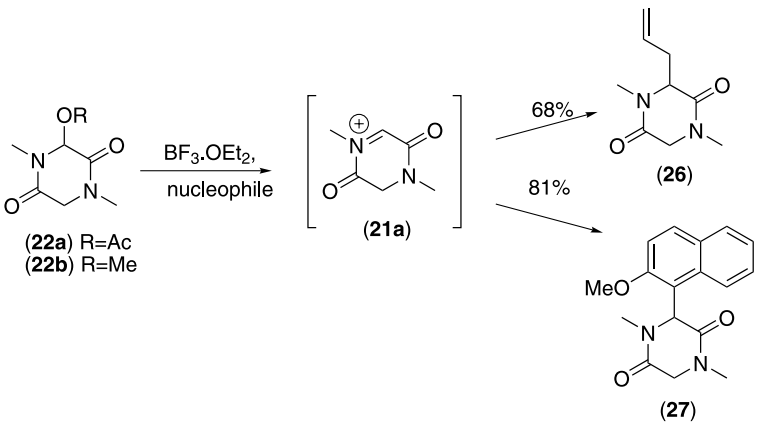
In order to increase the repertoire of synthetic transformations that can be achieved with *N*-acyliminium ions generated from piperazinedione precursors, carbon–carbon bond forming reactions were investigated. The use of such *N*-acyliminium ions as glycine cation equivalents in carbon chain extension reactions has been reported.[19] Our initial studies focussed on the use of 3-methoxy-1,4-dimethylpiperazine-2,5-dione (**22b**) as an *N*-acyliminium ion precursor. Thus, treatment of piperazinedione **22b** with boron trifluoride diethyl etherate in the presence of allyltrimethylsilane afforded the desired 3-allyl-1,4-dimethylpiperazine-2,5-dione (**26**) in 68% yield (Scheme 11).

Similarly when 2-methoxynaphthalene was used as the carbon nucleophile in the presence of boron trifluoride diethyl etherate, Friedel–Crafts alkylation of the intermediate **21a** occurred to yield the α-aryl piperazinedione **27** in 81% yield (Scheme 11).

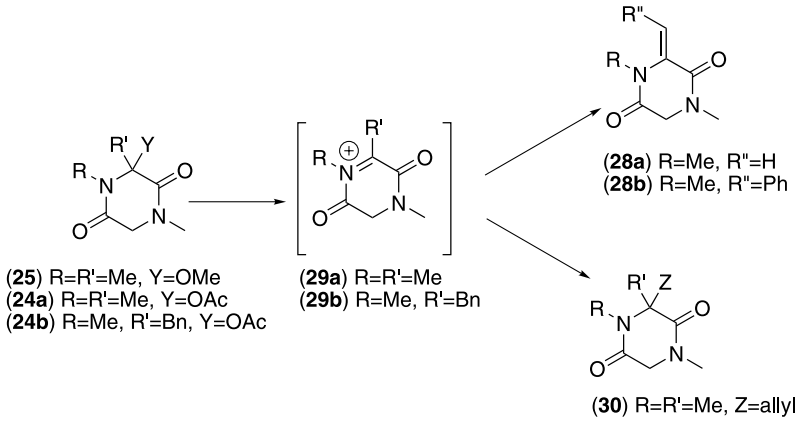
In contrast to the stability of the α-acetoxy and α-methoxy compounds, **22a** and **22b**, respectively, the C-methyl piperazinediones **24a** and **25**, were unstable. Upon standing, these piperazinediones are converted to the methylidene piperazinedione **28a**. Although Schmidt et al. have reported the synthesis of methylidene piperazinediones from α-methyl-α-hydroxypiperazinediones under acidic conditions,[20] there is no literature precedence for a conversion of this type under neutral conditions. This elimination process probably proceeds through the intermediacy of an α-carbocation/*N*-acyliminium ion intermediate **29a** as outlined in Scheme 12.

Due to the competing elimination process, efficient *C*-allylation of the *N*-acyliminium ion **29a** (generated from α-methoxy piperazinedione **25**) was difficult to achieve. Treatment of the piperazinedione **25** with boron trifluoride diethyl etherate and allyltrimethylsilane gave a 1:1 mixture of the desired product **30** and the methylidene piperazinedione **28a**. The formation of the desired product **30** was favoured when 10 equiv of allyltrimethylsilane was used. Using these optimised conditions, the conversion of the α-methoxy piperazinedione **25** to the α-allyl piperazinedione **30** was achieved in 66% yield.

The conversion of the *N*-acyliminium ion **29a** to the methylidene piperazinedione **28a** can be exploited for the synthesis of a variety of alkylidene piperazinediones



Scheme 11.

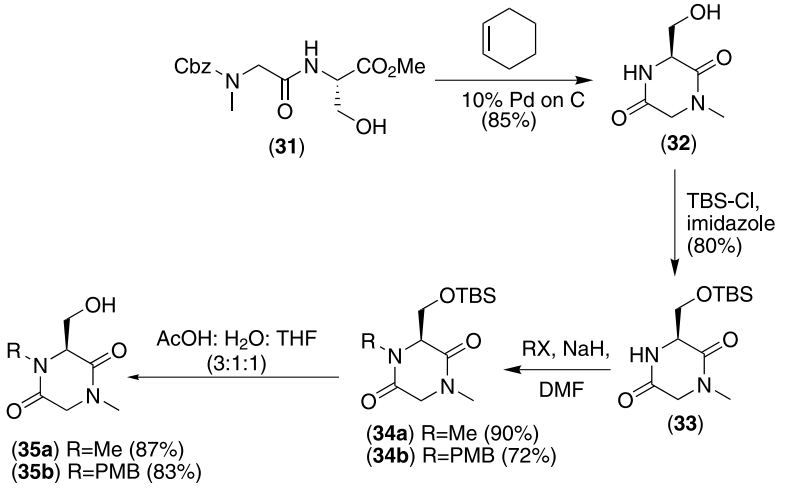


Scheme 12.

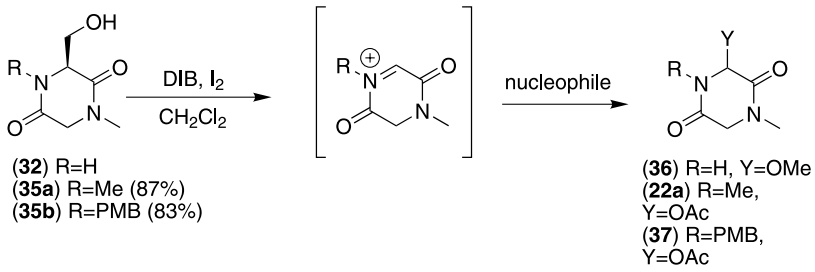
including natural products. For example, dehydrophenylahistin contains a *Z*-benzylidene piperazinedione moiety.[21] Thus, to demonstrate the generality of the elimination process, a conversion of the piperazinedione **24b** to the benzylidene piperazinedione **28b** was attempted. Treatment of the α-acetoxypiperazinedione **24b** with boron trifluoride diethyl etherate afforded the benzylidene piperazinedione **28b** as a single stereoisomer in 76% yield. The stereochemistry of the product was assigned as (*Z*) by comparison of the ^{1}H NMR data observed for piperazinedione **28b** with data reported in the literature.[22] It is likely that formation of the *E*-isomer is disfavoured due to steric interaction between the phenyl ring and the carbonyl group of the piperazinedione ring.

2.7. Alternative piperazine-2,5-dione precursors for modified DONA type reactions: the use of hydroxymethylpiperazinediones

In order to extend the utility of the DONA methodology, we sought to examine alternative substrates for the DONA type reactions. The work of Suarez et al. on the synthesis of α-aryl amino acids from serine derivatives provided the impetus for our studies.[23] In that study Suarez et al. demonstrated that the hydroxylmethyl moiety can act as a latent functionality for the *N*-acyliminium ion via a sequence of radical deformylation and oxidation steps. We envisaged that such a modified DONA protocol could be applied to serine derived piperazinediones in which the α-hydroxymethyl moiety could be employed as a latent functionality for the *N*-acyliminium ion in the same manner as the carboxylic acid group in the previous study. This is an attractive alternative as the serine based piperazinediones are readily accessible using peptide coupling procedures. For example as outlined in Scheme 13, the dipeptide **31** can be readily converted to piperazinedione **32** using the standard two step hydrogenolysis/thermal cyclisation protocol. More efficient conversion was achieved using catalytic transfer hydrogenolysis conditions. Using 10% palladium on carbon and cyclohexene in methanol at reflux, cleavage of the CBZ protecting group was followed by the in situ cyclisation of the free amine to afford the piperazinedione **32** in 85% yield.[24] The piperazinedione **32** was only sparingly soluble in most organic solvents, however, protection of the hydroxy functionality as a silyl ether afforded the readily soluble piperazinedione **33**. Piperazinedione **33** is a key synthetic intermediate that can be selectively *N*-alkylated with a wide variety of alkyl halides in a combinatorial fashion. In this study, the *N*-methyl **34a** and *N*-*p*-methoxybenzyl **34b** derivatives were targeted. Treatment of piperazinedione **33** with sodium hydride and either methyl iodide or *p*-methoxybenzyl chloride afforded piperazinediones **34a** and **34b**, respectively. Acidic cleavage of the *t*-butyldimethylsilyl group



Scheme 13.



Scheme 14.

then yielded the piperazinediones **35a** and **35b** in excellent yield.

Our initial work in the study focussed on the DONA reactions of piperazinedione **32**. A suspension of the hydroxymethyl piperazinedione **32** in dichloromethane was treated with iodine and DIB, followed by addition of excess methanol to give the desired α-methoxy piperazinedione **36** in a moderate yield of 44%.

In contrast to the solubility and stability complications encountered with the carboxylic acid **1a**, the *N*-methylated serine derived piperazinedione **35a** was stable and readily soluble in dichloromethane. Furthermore, using the standard DONA reaction conditions, complete conversion of the alcohol **35a** to the α-acetoxy compound **22a** was achieved (Scheme 14). Similarly, the *N*-*p*-methoxybenzyl compound **35b** underwent the modified DONA reaction to give the α-acetoxy compound **37** in excellent yield.

3. Conclusion

Our studies have demonstrated that carboxy- and hydroxymethyl-piperazinediones are complementary precursors for the generation of *N*-acyliminium ions. The carboxy piperazinediones potentially suffer from problems with premature decarboxylation and lack of solubility in the solvents typically used in these reactions. On the other hand, the carboxy piperazinediones (with the exception of the *N*-acetylated systems) allow for mild *C*-alkylation reactions by activating the α-carbon positions of the piperazine-2,5-dione. By contrast the hydroxymethyl piperazinediones are readily accessible from commercially available serine and derivatives, have a much better solubility profile in organic solvents but cannot be *C*-functionalised under mild conditions.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini II NMR spectrometer at 300 and 75.4 MHz, respectively. $CDCl_3$ was used as the solvent unless otherwise indicated. The chemical shifts (δ) are reported as the shift in ppm from tetramethylsilane (TMS, 0.00 ppm). ^{1}H spectra were appropriately referenced to either the $CHCl_3$ singlet (7.26 ppm), CHD_2OD quintet (3.31 ppm), $CHD_2S(O)CD_3$ quintet (2.50 ppm), $CHD_2(CD_3)NC(O)D$ quintet (2.90 ppm) or to TMS. ^{13}C spectra were appropriately referenced to either $CDCl_3$ (77.0 ppm), CD_3OD (49.0 ppm), $(CD_3)_2SO$ (39.5 ppm). Infrared spectra were recorded on a Perkin Elmer 1800 or a Shimadzu FTIR-8400 Fourier Transform Infrared Spectrometer. Samples were analysed as KBr discs (for solids) or as thin liquid films (for oils and liquids) on NaCl plates. Low and high resolution mass spectra were recorded on a VG Micromas 7070F double focussing mass spectrometer using positive ion electron impact techniques. Melting points are uncorrected and were recorded on a Leica Galen III microscope. Flash chromatography utilised Merck silica gel 60 (200–400 mesh ASTM) and analytical reagent (AR) grade solvents as indicated. Unless stated otherwise, reagents were purchased from Aldrich, Merck, Fluka, AJAX or BDH Chemicals. All solvents were of AR grade, purified by literature procedures[25] and where appropriate, stored over molecular sieves. All reactions were carried out under an atmosphere of dry, oxygen-free nitrogen unless otherwise specified. Reactions which involved moisture sensitive compounds were carried out using oven-dried or flame-dried apparatus with dry solvents.

4.2. Syntheses of alkoxycarbonyl- and carboxy-piperazine-2,5-diones

4.2.1. Ethyl *N*-[*N*-benzyloxycarbonylsarcosyl]-2-ethoxycarbonylsarcosinate (7). To a stirred solution of CBZ-sarcosine (5.58 g, 25.0 mmol) in DMF (60 mL) at 0 °C was added DCC (5.21 g, 25.0 mmol) and HOBt (3.38 g, 25.0 mmol). The resultant reaction mixture was stirred at 0 °C for 2 h and filtered to remove the DCU byproduct. To the filtrate was added a solution of diethyl (*N*-methylamino)malonate (**6**)[8–10] (4.73 g, 25.0 mmol) in DMF (20 mL). The reaction mixture was allowed to warm to room temperature and stirred for a further 16 h. After this time, the reaction mixture was filtered and the solvent was removed in vacuo. The residue was taken up in ethyl acetate (100 mL) and washed successively with saturated sodium carbonate solution (50 mL) and water (50 mL). The organic phase was separated, dried over magnesium sulfate and the solvent was removed in vacuo to give the crude product. Purification via flash column chromatography (7:3, ethyl acetate–petroleum spirit, R_f: 0.58) afforded the title compound **7** as a thick, clear oil (8.06 g, 81%). ν_{max} film/cm^{-1} 2981 m, 2938 m, 1740 vs, 1709 vs, 1675 vs, 1478 m, 1456 m, 1399 m, 1368 m, 1308 s, 1233 s, 1180 s, 1154 s, 1113 m, 1034 m. δ_H (300 MHz, $CDCl_3$) 1.30 (m, 6H, 2× $CO_2CH_2CH_3$), 2.99 (s, 3H, NCH_3), 3.04, 3.09 (rotamers 2× s, 3H, NCH_3), 4.14–4.25 (m, 6H, 2×$CO_2CH_2CH_3$ and $CH_2C(O)NCH_3$), 5.11, 5.14 (rotamers 2×s, 2H, CH_2Ar), 5.92 (s, 1H, $CH(CO_2Et)_2$), 7.30–7.36 (m, 5H, C_6H_5). δ_C

(75 MHz, $CDCl_3$) 13.7 ($2\times CO_2CH_2CH_3$), 32.3 (NCH_3), 35.0, 35.7 (rotamers CBZ-NCH_3), 50.0, 50.2 (rotamers $CH_2C(O)NCH_3$), 59.9, 59.9 (rotamers $CH(CO_2Et)_2$), 61.8 ($2\times CO_2CH_2CH_3$), 66.9, 67.1 (rotamers CH_2Ar), 127.3, 127.4, 127.5, 127.6, 128.1, 128.1 (rotamers aromatic *C*H), 136.3 (2×quaternary aromatic *C*), 155.9, 156.5 (rotamers *C*(O)), 165.9 (*C*(O)), 168.9 (*C*(O)). *m/z* (EI) 394.1741 ($M^{+\cdot}$. $C_{19}H_{26}N_2O_7$ requires 394.1740), 349 ($[M-OEt]^+$, 5%), 259 ($[M-Cbz]^+$, 10%), 188 (15%), 116 (33%), 91 ($[C_7H_7]^+$, 100%).

4.2.2. 3-Ethoxycarbonyl-1,4-dimethylpiperazine-2,5-dione (2). A solution of ethyl *N*-[*N*-benzyloxycarbonylsarcosyl]-2-ethoxycarbonylsarcosinate (**7**) (4.14 g, 10.4 mmol) in degassed methanol (100 mL) was stirred in the presence of 10% palladium on carbon (450 mg) under an atmosphere of hydrogen for 16 h. The reaction mixture was filtered through celite and the solvent evaporated under reduced pressure. The oily residue was taken up in toluene (50 mL) and the resultant solution was heated at reflux for 48 h. After this time the solvent was removed in vacuo and the crude product was recrystallised from ethyl acetate/petroleum spirit affording 3-ethoxycarbonyl-1,4-dimethylpiperazine-2,5-dione (**2**) as colourless crystals (1.99 g, 89%). The product may also be purified by column chromatography (5:1, ethyl acetate–methanol, R_f: 0.48). Mp 66–68 °C. ν_{max} KBr/cm^{-1} 2980 m, 2941 m, 1738 vs, 1678 vs, 1479 s, 1404 s, 1323 m, 1229 s, 1196 s, 1045 s, 746 w, 648 w. δ_H (300 MHz, $CDCl_3$) 1.31 (t, 3H, $J=6$ Hz, $CO_2CH_2CH_3$), 2.94 (s, 3H, NCH_3), 2.98 (s, 3H, NCH_3), 3.84 (d, 1H, $J_{AB}=17$ Hz, ring CH_aH_b), 4.18 (d, 1H, $J_{AB}=17$ Hz, ring CH_aH_b), 4.28 (m, 2H, $CO_2CH_2CH_3$), 4.55 (s, 1H, $CHCO_2Et$). δ_C (75 MHz, $CDCl_3$) 13.9 ($CO_2CH_2CH_3$), 32.7 (NCH_3), 33.7 (NCH_3), 51.5 (ring CH_2), 62.9 ($CO_2CH_2CH_3$), 65.9 ($CHCO_2Et$), 160.0 (*C*(O)), 164.5 (*C*(O)), 166.3 (*C*(O)). *m/z* (EI) 214.0953 ($M^{+\cdot}$. $C_9H_{14}N_2O_4$ requires 214.0954), 171 (12%), 141 ($[M-CO_2Et]^+$, 67%), 113 (100%).

4.2.3. 3-Benzyloxycarbonyl-1,4-dimethylpiperazine-2,5-dione (3a). *Method A*. A stirred solution of 3-ethoxycarbonyl-1,4-dimethylpiperazine-2,5-dione (**2**) (203 mg, 0.95 mmol) in benzyl alcohol (2 mL) was heated at 180 °C for 16 h. The solvent was then removed by distillation and the residue purified by column chromatography (ethyl acetate, R_f: 0.45) to afford 3-benzyloxycarbonyl-1,4-dimethylpiperazine-2,5-dione (**3a**) as a colourless solid (207 mg, 79%).

Method B. To a stirred solution of 3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (**3c**) (978 mg, 3.7 mmol) in acetone (20 mL) was added anhydrous K_2CO_3 (1.031 g, 7.46 mmol) and dimethyl sulfate (1.4 mL, 14.9 mmol). The reaction mixture was heated at reflux under nitrogen for 48 h. After this time the inorganic salts were filtered off and the filtrate was concentrated under reduced pressure. Trituration with ether (10 mL) followed by filtration afforded 3-benzyloxycarbonyl-1,4-dimethylpiperazine-2,5-dione (**3a**) as a colourless solid (909 mg, 89%). If necessary the product may be purified by column chromatography (ethyl acetate, R_f: −0.45). Mp 110–112 °C. (Found: C 60.6; H, 6.0; N, 10.1. $C_{14}H_{16}N_2O_4$ requires C, 60.9; H, 5.8; N, 10.1%); ν_{max} KBr/cm^{-1} 3449 w, 3039 w, 2969 w, 1740 vs, 1700 vs, 1696 vs, 1405 s, 1278 s, 1189 s, 1035 m, 739 m. δ_H (300 MHz, $CDCl_3$) 2.91 (s, 3H, NCH_3), 2.97 (s, 3H, NCH_3), 3.82 (d, 1H, $J_{AB}=17$ Hz, ring CH_aH_b), 4.13 (d, 1H, $J_{AB}=17$ Hz, ring CH_aH_b), 4.60 (s, 1H, ring C*H*), 5.12 (d, 1H, $J_{AB}=12$ Hz, benzyl CH_aH_b), 5.29 (d, 1H, $J_{AB}=12$ Hz, benzyl CH_aH_b), 7.35 (m, 5H, aromatic C_6H_5). δ_C (75 MHz, $CDCl_3$) 32.7 (NCH_3), 33.6 (NCH_3), 51.5 (ring CH_2), 65.8 (ring *C*H), 68.2 (benzyl CH_2), 128.0 (2×aromatic *C*H), 128.5 (3×aromatic *C*H), 134.4 (quaternary aromatic *C*), 159.8 (*C*(O)), 164.4 (*C*(O)), 166.2 (*C*(O)). *m/z* (EI) 276.1105 ($M^{+\cdot}$. $C_{14}H_{16}N_2O_4$ requires 276.1110), 232 (17%), 185 ($[M-C_7H_7]^+$, 6%), 141 ($[M-CO_2Bn]^+$, 95%), 113 (80%), 91 ($[C_7H_7]^+$, 100%).

4.2.4. 3-Carboxyl-1,4-dimethylpiperazine-2,5-dione (1a). To a solution of 3-benzyloxycarbonyl-1,4-dimethylpiperazine-2,5-dione (**3a**) (920 mg, 3.33 mmol) in degassed methanol (20 mL) was added 10% palladium on carbon (80 mg). The reaction mixture was then stirred under a hydrogen atmosphere for 1 h after which time it was filtered through a bed of celite. The filtrate was reduced in vacuo and following co-evaporation with chloroform (3×5 mL), the acid (**1a**) was obtained as an unstable colourless solid (552 mg, ~90%) which was contaminated with a small amount of sarcosine anhydride. δ_H (300 MHz, CD_3OD) 2.97 (s, 3H, NCH_3), 3.00 (s, 3H, NCH_3), 3.97 (d, 1H, $J=18$ Hz, ring CH_aH_b), 4.20 (d, 1H, $J=18$ Hz, ring CH_aH_b), 4.73 (s, 1H, ring C*H*).

4.2.5. Benzyl *N*-[*N*-*t*-butoxycarbonylsarcosyl]-2-benzyloxycarbonylglycinate (9). To a solution of *N*-*t*-butoxycarbonylsarcosine (227 mg, 1.20 mmol) in DMF (10 mL) at 0 °C was added DCC (248 mg, 1.20 mmol) and HOBt (163 mg, 1.21 mmol). The resultant reaction mixture was stirred at 0 °C for 2 h and filtered to remove the DCU byproduct. To the filtrate was added a solution of dibenzyl aminomalonate (**8**) (360 mg, 1.20 mmol) in DMF (5 mL). The reaction mixture was warmed to room temperature and stirred for a further 16 h. After this time, the reaction mixture was filtered and the solvent was removed in vacuo to give a viscous, pale yellow oil. The residue was taken up in chloroform (20 mL) and washed with saturated sodium carbonate solution (10 mL) and water (10 mL). The organic phase was separated, dried over magnesium sulfate and the solvent was removed in vacuo to give the crude product as a clear oil. Purification via flash column chromatography (4:1, ethyl acetate–petroleum spirit, R_f: 0.55) afforded the title compound **9** as a clear and colourless oil which solidified upon prolonged standing (547 mg, 97%). Mp 82–84 °C. (Found: C, 63.9; H, 6.7; N, 5.7. $C_{25}H_{30}N_2O_7$ requires C, 63.8; H, 6.4; N, 5.95%); ν_{max} KBr/cm^{-1} 3239 s, 3054 w, 2976 m, 1765 vs, 1743 vs, 1708 vs, 1678 vs, 1550 s, 1456 s, 1396 s, 1329 s, 1217 s, 1143, 743 s, 698 s. δ_H (300 MHz, $CDCl_3$) 1.46 (s, 9H, $(CH_3)_3C$), 2.91 (s, 3H, NCH_3), 3.93 (bs, 2H, $NCH_2C(O)$), 5.15 (d, 2H, $J_{AB}=12$ Hz, $2\times CH_aH_bPh$), 5.21 (d, 2H, $J_{AB}=12$ Hz, $2\times CH_aH_bPh$), 5.29 (d, 1H, $J=7$ Hz, NHC*H*C(O)), 7.24–7.33 (m, 11H, N*H* and $2\times C_6H_5$). δ_C (75 MHz, $CDCl_3$) 28.0 ($3\times(CH_3)_3C$), 35.4 (NCH_3), 52–53 (rotamers $CH_2C(O)NH$), 56.0 ($CH(CO_2Bn)_2$), 68.0 ($2\times CH_2Ph$), 80.6 ($C(CH_3)_3$), 128.0 (4×aromatic *C*H), 128.4 (6×aromatic *C*H), 134.4 (2×quaternary aromatic *C*), 165.6 (3×*C*(O)), 169.2 (carbamate *C*(O)). *m/z* (EI) 470.2050 ($M^{+\cdot}$. $C_{25}H_{30}N_2O_7$ requires 470.2053), 414 ($MH-C(CH_3)_3]^+$,

16%), 371 ([M−Boc+2]$^+$, 17%), 279 ([M−Boc–C_7H_7]$^+$, 21%), 91 ([C_7H_7]$^+$, 100%).

4.2.6. 3-Benzyloxycarbonyl-1-methylpiperazine-2,5-dione (3c). To a solution of benzyl *N*-[*N*-*t*-butoxycarbonylsarcosyl]-2-benzyloxycarbonylglycinate (**9**) (8.24 g, 17.5 mmol) in chloroform (125 mL) at 0 °C was added TFA (10 mL). The resultant solution was stirred for 16 h at room temperature. After this time the solvent and excess TFA were removed in vacuo. The resulting residue was taken up in chloroform (100 mL) and washed with saturated sodium bicarbonate solution (50 mL). The separated organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was then taken up in toluene (125 mL) and heated at reflux for 24 h. The product crystallised from solution upon cooling and was collected by filtration. The filtrate was evaporated and further product was obtained from the residue via chromatographic purification (5:1, ethyl acetate–methanol, R_f: 0.58). Using a combination of these purification methods, the title compound was obtained as a colourless crystalline solid (4.59 g, 82%). Mp 119–120 °C. (Found C, 59.6; H, 5.4; N, 10.6. $C_{13}H_{14}N_2O_4$ requires C, 59.5; H, 5.4; N, 10.7%). ν_{max} KBr/cm^{-1} 3338 s, 3069 w, 3016 w, 1742 vs, 1702 vs, 1670 vs, 1457 s, 1248 s, 1180 s, 1040 m, 945 m, 718 m, 700 s. δ_H (300 MHz, $CDCl_3$) 2.97 (s, 3H, NCH_3), 3.80 (d, 1H, J_{AB}=18 Hz, ring CH_aH$_b$), 4.12 (d, 1H, J_{AB}=18 Hz, ring CH$_a$$H_b$), 4.70 (d, 1H, J=4 Hz, NHCHC(O)), 5.19 (d, 1H, J_{AB}=12 Hz, benzyl CH_aH$_b$), 5.27 (d, 1H, J_{AB}=12 Hz, benzyl CH$_a$$H_b$), 6.80 (bs, 1H, N$H$), 7.35 (s, 5H, Aromatic C$_6$$H_5$). δ_C (75 MHz, $CDCl_3$) 34.1 (NCH_3), 51.4 (ring CH_2), 59.2 (NHCHC(O)), 68.3 (CH_2Ph), 128.2 (2×aromatic CH), 128.6 (3×aromatic CH), 134.6 (quaternary aromatic CH), 160.2 (C(O)), 166.6 (C(O)), 167.1 (C(O)). *m/z* (EI) 262.0953 (M$^+$. $C_{13}H_{14}N_2O_4$ requires 262.0954), 218 (21%), 171 ([M−C_7H_7]$^+$, 18%), 143 (19%), 127 ([M−CO_2Bn]$^+$, 23%), 99 (26%), 91 ($C_7H_7^+$, 100%).

4.2.7. 4-Acetyl-3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (3b). To a stirred solution of 3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (**3c**) (646 mg, 2.46 mmol) in dichloromethane (10 mL) was added DMAP (331 mg, 2.71 mmol) and acetic anhydride (0.26 mL, 2.76 mmol). The resultant solution was stirred under nitrogen until TLC analysis of the reaction mixture showed complete consumption of starting material (typically 2 h). After this time the solvent was removed in vacuo and the residue was purified via column chromatography (4:1, ethyl acetate–petroleum spirit, R_f: 0.49). The title compound was obtained as a colourless oil (682 mg, 91%) which solidified upon standing. Mp 100–101 °C. (Found C, 59.2; H, 5.4; N, 9.1. $C_{15}H_{16}N_2O_5$ requires C, 59.2; H, 5.3; N, 9.2%). ν_{max} KBr/cm^{-1} 3439 w, 2996 w, 1730 vs, 1711 vs, 1676 vs, 1383 s, 1232 s, 1189 s, 998 m, 761 m. δ_H (300 MHz, $CDCl_3$) 2.59 (s, 3H, NC(O)CH_3), 2.98 (s, 3H, NCH_3), 3.86 (d, 1H, J_{AB}=18 Hz, ring CH_aH$_b$), 4.23 (d, 1H, J_{AB}=18 Hz, ring CH$_a$$H_b$), 5.22 (d, 1H, J_{AB}=12 Hz, benzyl CH_aH$_b$), 5.29 (d, 1H, J_{AB}=12 Hz, benzyl CH$_a$$H_b$), 5.68 (s, 1H, C$HCO_2$Bn), 7.34 (m, 5H, aromatic C$_6$$H_5$). δ_C (75 MHz, $CDCl_3$) 26.6 (NC(O)CH_3), 33.8 (NCH_3), 53.2 (ring CH_2), 59.8 (CHCO$_2$Bn), 68.4 (benzyl CH_2), 127.8 (2×aromatic CH), 128.5 (aromatic CH), 128.6 (2×aromatic CH), 134.6 (quaternary aromatic C), 159.8 (C(O)), 165.7 (C(O)), 165.9 (C(O)), 171.3 (ester C(O)). *m/z* (EI) 304.1059 (M$^{+\cdot}$. $C_{15}H_{16}N_2O_5$ requires 304.1059), 262 ([MH−Ac]$^+$, 15%), 213 ([M−C_7H_7]$^+$, 25%), 170 ([MH−CO_2Bn]$^+$, 20%), 127 ([MH−CO_2Bn-Ac]$^+$, 42%), 91 ($C_7H_7^+$, 100%).

4.2.8. 4-Acetyl-3-carboxyl-1-methylpiperazine-2,5-dione (1b). To a solution of 4-acetyl-3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (**3b**) (241 mg, 0.79 mmol) in degassed methanol (20 mL) was added 10% palladium on carbon (20 mg). The reaction mixture was then stirred under a hydrogen atmosphere for 1 h after which time it was filtered through a bed of celite. The filtrate was reduced in vacuo and following co-evaporation with chloroform (3×5 mL), the acid (**1b**) (~112 mg, 66%) was obtained as an unstable colourless oil which also contained 1-acetyl-4-methylpiperazine-2,5-dione (~45 mg, 33%).

δ_H (300 MHz, $CDCl_3$) 2.54 (s, 3H, NC(O)CH_3), 2.97 (s, 3H, NCH_3), 3.89 (d, 1H, J_{AB}=18 Hz, ring CH_aH$_b$), 4.36 (d, 1H, J_{AB}=18 Hz, ring CH$_a$$H_b$), 5.58 (s, 1H, ring C$H$).

4.3. 3-Carboxyl-1-methylpiperazine-2,5-dione (1c)

To a solution of 3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (**3c**) (710 mg, 2.71 mmol) in degassed methanol (30 mL) was added 10% palladium on carbon (100 mg). The reaction mixture was then stirred under a hydrogen atmosphere for 1 h after which time it was filtered through a bed of celite. The filtrate was reduced in vacuo and following co-evaporation with chloroform (5×10 mL), the acid (**1c**) was obtained as a colourless gum (468 mg, 100%). δ_H (300 MHz, CD_3OD) 3.01 (s, 3H, NCH_3), 3.94 (d, 1H, J_{AB}=18 Hz, ring CH_aH$_b$), 4.21 (d, 1H, J_{AB}=18 Hz, ring CH$_a$$H_b$), 4.62 (s, 1H, C$HCO_2$H). δ_C (75 MHz, CD_3OD) 34.3 (NCH_3), 52.3 (CH_2), 60.2 (CHCO$_2$H), 163.1 (C(O)), 168.9 (C(O)), 170.0 (C(O)).

4.4. Syntheses of N- and/or C-functionalised piperazine-2,5-diones from alkoxycarbonyl piperazinedione precursors

4.4.1. 3-Benzyloxycarbonyl-1,3,4-trimethylpiperazine-2,5-dione (10a). *Method A*. To a solution of 3-benzyloxycarbonyl-1,4-dimethylpiperazine-2,5-dione (**3a**) (552 mg, 2.00 mmol) in DMF (10 mL) at 0 °C under nitrogen was added sodium hydride (160 mg, 4.00 mmol, 60% in paraffin) and methyl iodide (2 mL, excess). The resultant solution was stirred under a nitrogen atmosphere for 24 h and after this time the solvent was removed under reduced pressure. The residue was taken up in chloroform (20 mL) and washed with water (5 mL), brine (5 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was purified by column chromatography (ethyl acetate, R_f: 0.47) giving (**10a**) as a clear and colourless oil which solidified upon prolonged standing (533 mg, 92%).

Method B. The title compound was prepared, as described in *Method A*, from 3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (**3c**) (820 mg, 3.13 mmol) in DMF (10 mL), with sodium hydride (276 mg, 6.89 mmol, 60% in paraffin) and methyl iodide (2 mL, excess). The title compound was

obtained as a clear and colourless oil which solidified upon prolonged standing (754 mg, 83%).

Mp 86–88 °C. (Found C, 61.7; H, 6.3; N, 9.5. $C_{15}H_{18}N_2O_4$ requires C, 62.1; H, 6.3; N, 9.7%). ν_{max} KBr/cm^{-1} 3451 w, 3000 w, 2943 w, 1746 vs, 1664 vs, 1458 m, 1403 m, 1262 s, 1128 m, 769 m, 710 m. δ_H (300 MHz, $CDCl_3$) 1.79 (s, 3H, C–CH_3), 2.81 (s, 3H, NCH_3), 2.96 (s, 3H, NCH_3), 3.93 (d, 1H, J_{AB}=18 Hz, ring CH_aH$_b$), 4.00 (d, 1H, J_{AB}=18 Hz, ring CH$_a$$H_b$), 5.16 (d, 1H, J_{AB}=12 Hz, benzyl CH_aH$_b$), 5.24 (d, 1H, J_{AB}=12 Hz, benzyl CH$_a$$H_b$), 7.28–7.35 (m, 5H, aromatic C_6H_5). δ_C (75 MHz, $CDCl_3$) 20.1 (α-CH$_3$), 29.1 (NCH$_3$), 33.6 (NCH$_3$), 50.9 (ring CH$_2$), 67.6 (quaternary C–CH$_3$), 67.7 (benzyl CH$_2$), 127.7 (2×aromatic CH), 128.1 (aromatic CH), 128.2 (2×aromatic CH), 134.5 (quaternary aromatic C), 163.0 (C(O)), 163.6 (C(O)), 167.6 (C(O)). *m/z* (EI) 290.1264 ($M^{+\cdot}$. $C_{15}H_{18}N_2O_4$ requires 290.1267), 155 ([M−CO_2Bn]$^+$, 100%), 127 (82%), 91 ([C_7H_7]$^+$, 60%).

4.4.2. 4-Acetyl-3-benzyloxycarbonyl-1,3-dimethylpiperazine-2,5-dione (10b). To a stirred solution of 3-benzyloxycarbonyl-1,3-methylpiperazine-2,5-dione (**10c**) (140 mg, 0.51 mmol) in dichloromethane (10 mL) was added DMAP (63 mg, 0.52 mmol) and acetic anhydride (0.05 mL, 0.530 mmol). The resultant solution was stirred under nitrogen until TLC analysis of the reaction mixture showed complete consumption of starting material (typically 2 h). After this time the solvent was removed in vacuo and the residue was purified via column chromatography (4:1, ethyl acetate–petroleum spirit, R_f: 0.44). The title compound was obtained as a colourless oil (140 mg, 87%). δ_H (300 MHz, $CDCl_3$) 1.82 (s, 3H, C–CH_3), 2.47 (s, 3H, NC(O)CH_3), 3.00 (s, 3H, NCH_3), 4.05 (d, 1H, J_{AB}=18 Hz, ring CH_aH$_b$), 4.18 (d, 1H, J_{AB}=18 Hz, ring CH$_a$$H_b$), 5.12 (d, 1H, J_{AB}=12 Hz, OCH_aH$_b$Ph), 5.16 (d, 1H, J_{AB}=12 Hz, OCH$_a$$H_b$Ph), 7.33 (m, 5H, aromatic H). δ_C (75 MHz, $CDCl_3$) 21.4 (C–CH$_3$), 27.8 (NC(O)CH$_3$), 33.8 (NCH$_3$), 52.1 (ring CH$_2$), 67.1 (quaternary ring C), 67.9 (OCH$_2$Ph), 128.3 (2×aromatic CH), 128.3 (aromatic CH), 128.4 (2×aromatic CH), 135.1 (quaternary aromatic C), 164.3 (C(O)), 165.2 (C(O)), 166.9 (C(O)), 173.4 (C(O)). *m/z* (EI) 318.1207 ($M^{+\cdot}$. $C_{16}H_{18}N_2O_5$ requires 318.1216), 276 ([M−Ac+1]$^+$, 12%), 211 (25%), 141 ([M−Ac–CO_2Bn+1]$^+$, 91%), 91 ([C_7H_7]$^+$, 100%).

4.5. General procedure for the selective α-alkylation of piperazinedione 3c to 10c–10f

To a stirred solution of 3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (**3c**) (1 mol equiv, typical scales 0.5–2 mmol) in acetone (ca. 10 mL per mmol of **3c**) was added anhydrous K_2CO_3 (1 mol equiv). For the synthesis of **10c**, **10d** and **10f**, this was followed by the addition of the appropriate alkyl halide in excess (5 mol equiv) and the reaction mixture was heated under reflux in a sealed tube. For the synthesis of **10e**, 1 mol equiv of the appropriate alkyl halide was utilized and the reaction mixture was heated at reflux under nitrogen.

After 24 h of reflux, the reaction mixture was cooled and filtered to remove the inorganic salts. The filtrate was then concentrated under reduced pressure.

For **10c** and **10e**, the resulting solid was triturated with ether and the solid was further purified (if necessary) via recrystallisation from the mixed solvent of ethyl acetate/petroleum spirits. For **10d** and **10f**, the residue obtained was purified by column chromatography.

4.5.1. 3-Benzyloxycarbonyl-1,3-dimethylpiperazine-2,5-dione (10c). The title compound **10c** was synthesised from **3c** following the general procedure above. Compound **10c** is a colourless solid which was obtained in quantitative yield. Mp 142–143 °C. (Found C, 60.6; H, 5.9; N, 10.0. $C_{14}H_{16}N_2O_4$ requires C, 60.9; H, 5.8; N, 10.1%). ν_{max} KBr/cm^{-1} 3179 w, 3100 w, 2950 w, 1719 vs, 1675 vs, 1448 m, 1414 m, 1239 vs, 1120 m, 920 w, 761 m, 704 m. δ_H (300 MHz, $CDCl_3$) 1.73 (s, 3H, C–CH_3), 2.95 (s, 3H, NCH_3), 3.78 (d, 1H, J_{AB}=18 Hz, ring CH_aH$_b$), 4.02 (d, 1H, J_{AB}=18 Hz, ring CH$_a$$H_b$), 5.19 (m, 2H, benzyl C$H_2$), 6.97 (bs, 1H, N$H$), 7.32 (m, 5H, aromatic C_6H_5). δ_C (75 MHz, $CDCl_3$) 21.3 (C–CH$_3$), 34.3 (NCH$_3$), 52.1 (ring CH$_2$), 62.6 (quaternary ring C), 68.0 (benzyl CH$_2$), 127.7 (2×aromatic CH), 128.4 (aromatic CH), 128.5 (2×aromatic CH), 134.7 (quaternary aromatic C), 163.7 (C(O)), 167.1 (C(O)), 169.0 (C(O)). *m/z* (EI) 276.1109 ($M^{+\cdot}$. $C_{14}H_{16}N_2O_4$ requires 276.1110), 232 (3%), 185 ([M−C_7H_7]$^+$, 5%), 141 ([M−CO_2Bn]$^+$, 100%), 113 (58%), 91 ([C_7H_7]$^+$, 87%).

4.5.2. 3-Allyl-3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (10d). The title compound **10d** was synthesized from **3c** following the general procedure outlined. Compound **10d** is a colourless oil which was obtained in 82% yield after column chromatography (ethyl acetate, R_f: −0.55). ν_{max} film/cm^{-1} 3237 m, 3089 w, 2932 w, 1746 s, 1696 vs, 1667 vs, 1499 w, 1455 m, 1435 m, 1406 m, 1219 s, 751 m, 698 m. δ_H (300 MHz, $CDCl_3$) 2.78 (m, 1H, C–CH_aH$_b$CH=CH$_2$), 2.95 (s, 3H, NCH_3), 3.06 (m, 1H, C–CH$_a$$H_b$CH=CH$_2$), 3.79 (d, 1H, J_{AB}=18 Hz, ring CH_aH$_b$), 4.01 (d, 1H, J_{AB}=18 Hz, ring CH$_a$$H_b$), 5.23 (m, 4H, OC$H_2$Ph and C–CH$_2$CH=C$H_2$), 5.60 (m, 1H, C–CH$_2CH$=CH$_2$), 6.32 (bs, 1H, N$H$), 7.34 (m, 5H, aromatic C_6H_5). δ_C (75 MHz, $CDCl_3$) 34.3 (NCH$_3$), 38.8 (C–CH$_2$CH=CH$_2$), 51.9 (ring CH$_2$), 65.2 (quaternary ring C), 68.2 (OCH$_2$Ph), 121.7 (C–CH$_2$CH=CH$_2$), 127.8 (2×aromatic CH), 128.4 (aromatic CH), 128.5 (2×aromatic CH), 130.3 (C–CH$_2$$C$H=CH$_2$), 134.7 (quaternary aromatic C), 162.3 (C(O)), 166.5 (C(O)), 168.1 (C(O)). *m/z* (EI) 302.1266 ($M^{+\cdot}$. $C_{16}H_{18}N_2O_4$ requires 302.1267), 167 ([M−CO_2Bn]$^+$, 100%), 139 (35%), 91 ([C_7H_7]$^+$, 95%).

4.5.3. 3-Benzyl-3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (10e). The title compound **10e** was synthesized from **3c** following the general procedure outlined. Compound **10e** is a colourless solid which was obtained in quantitative yield. Mp 153–154 °C. (Found C, 68.1; H, 5.9; N, 7.8. $C_{20}H_{20}N_2O_4$ requires C, 68.2; H, 5.7; N, 7.95%). ν_{max} KBr/cm^{-1} 3209 w, 1751 vs, 1696 s, 1661 vs, 1457 m, 1224 s, 735 m, 701 m. δ_H (300 MHz, $CDCl_3$) 2.85 (s, 3H, NCH_3), 3.17 (d, 1H, J_{AB}=18 Hz, ring CH_aH$_b$), 3.44 (d, 1H, J_{AB}=14 Hz, C–CH_aH$_b$Ph), 3.50 (d, 1H, J_{AB}=14 Hz, C–CH$_a$$H_b$Ph), 3.71 (d, 1H, J_{AB}=18 Hz, ring CH$_a$$H_b$), 5.23 (d, 1H, J_{AB}=12 Hz, OCH_aH$_b$Ph), 5.30 (d, 1H, J_{AB}=12 Hz, OCH$_a$$H_b$Ph), 6.32 (bs, 1H, N$H$), 7.10 (m, 2H, aromatic H), 7.25 (m, 3H, aromatic H), 7.36 (s, 5H, aromatic H). δ (75 MHz, $CDCl_3$) 34.1 (NCH$_3$), 41.6

(C–CH_2Ph), 51.3 (ring CH_2), 66.9 (quaternary ring *C*), 68.4 (OCH_2Ph), 127.8 (aromatic *C*H), 128.2 (2×aromatic *C*H), 128.6 (2×aromatic *C*H), 128.7 (3×aromatic *C*H), 130.5 (2×aromatic *C*H), 133.5 (quaternary aromatic *C*), 134.8 (quaternary aromatic *C*), 162.4 (*C*(O)), 165.8 (*C*(O)), 168.0 (*C*(O)). *m/z* (EI) 352.1423 ($M^{+\cdot}$. $C_{20}H_{20}N_2O_4$ requires 352.1423), 217 ($[M-CO_2Bn]^+$, 86%), 189 (27%), 132 (18%), 91 ($[C_7H_7]^+$, 100%).

4.5.4. 3-Benzyloxycarbonyl-3-ethyl-1-methylpiperazine-2,5-dione (10f). The title compound **10f** was synthesized from **3c** following the general procedure outlined. Compound **10f** is a colourless solid which was obtained in 90% yield after purification by flash column chromatography (ethyl acetate, R_f: 0.53). Mp 122–123 °C. ν_{max} KBr/cm^{-1} 3209 m, 3101 m, 2978 w, 1730 vs, 1686 vs, 1670 vs, 1415 s, 1217 s, 1188 s, 1179 s, 917 m, 757 m, 748 m, 699 m. δ_H (300 MHz, $CDCl_3$) 0.91 (t, 3H, $J=7$ Hz, C–CH_2CH_3), 1.96 (m, 1H, C–$CH_aH_bCH_3$), 2.42 (m, 1H, C–$CH_aH_bCH_3$), 2.95 (s, 3H, NCH_3), 3.81 (d, 1H, $J_{AB}=18$ Hz, ring CH_aH_b), 3.99 (d, 1H, $J_{AB}=18$ Hz, ring CH_aH_b), 5.16 (d, 1H, $J_{AB}=12$ Hz, benzyl CH_aH_b), 5.22 (d, 1H, $J_{AB}=12$ Hz, benzyl CH_aH_b), 7.03 (bs, 1H, N*H*), 7.33 (m, 5H, aromatic C_6H_5). δ_C (75 MHz, $CDCl_3$) 7.8 (α-CCH_2CH_3), 27.7 (α-CCH_2CH_3), 34.3 (NCH_3), 52.0 (ring CH_2), 66.8 (quaternary ring *C*), 68.1 (benzyl CH_2), 127.9 (2×aromatic *C*H), 128.5 (aromatic *C*H), 128.6 (2×aromatic *C*H), 134.8 (quaternary aromatic *C*), 162.7 (*C*(O)), 167.1 (*C*(O)), 168.8 (*C*(O)). *m/z* (EI) 290.1270 ($M^{+\cdot}$. $C_{15}H_{18}N_2O_4$ requires 290.1267), 155 ($[M-CO_2Bn]^+$, 100%), 127 ($[MH-Et\text{-}CO_2Bn]^+$, 44%), 91 ($[C_7H_7]^+$, 70%).

4.5.5. 3-Benzyl-3-benzyloxycarbonyl-1,4-dimethylpiperazine-2,5-dione (11). To a stirred solution of 3-benzyl-3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (**10e**) (449 mg, 1.27 mmol) in DMF (15 mL) at 0 °C under nitrogen was added sodium hydride (51 mg, 1.275 mmol, 60% in paraffin) and methyl iodide (0.8 mL, 12.74 mmol). The reaction mixture was stirred under a nitrogen atmosphere for 24 h and after this time the solvent was removed under reduced pressure. The residue was taken up in chloroform (25 mL) and washed with water (10 mL), brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was purified by column chromatography (3:2, ethyl acetate–petroleum spirit, R_f: 0.49) giving **11** as a clear and colourless oil which solidified upon standing (398 mg, 85%). Mp 96–97 °C. (Found C, 68.5; H, 6.2; N, 7.5. $C_{21}H_{22}N_2O_4$ requires C, 68.8; H, 6.1; N, 7.7%). ν_{max} KBr/cm^{-1} 3037 w, 2945 w, 1755 s, 1672 s, 1399 m, 1224 m, 1043 m, 745 m. δ_H (300 MHz, $CDCl_3$) 2.27 (d, 1H, $J_{AB}=17$ Hz, ring CH_aH_b), 2.70 (s, 3H, NCH_3), 2.82 (s, 3H, NCH_3), 3.24 (d, 1H, $J_{AB}=14$ Hz, C–CH_aH_bPh), 3.40 (d, 1H, $J_{AB}=17$ Hz, ring CH_aH_b), 3.62 (d, 1H, $J_{AB}=14$ Hz, C–CH_aH_bPh), 5.15 (d, 1H, $J_{AB}=12$ Hz, OCH_aH_bPh), 5.39 (d, 1H, $J_{AB}=12$ Hz, OCH_aH_bPh), 7.03 (m, 2H, aromatic *H*), 7.27 (m, 4H, aromatic *H*), 7.36 (m, 4H, aromatic *H*). δ_C (75 MHz, $CDCl_3$) 30.0 (NCH_3), 33.2 (NCH_3), 38.9 (C–CH_2Ph), 50.2 (ring CH_2), 68.3 (OCH_2Ph), 72.9 (quaternary ring *C*), 127.9 (aromatic *C*H), 128.5 (2×aromatic *C*H), 128.6 (2×aromatic *C*H), 128.7 (3×aromatic *C*H), 129.9 (2×aromatic *C*H), 133.7 (quaternary aromatic *C*), 134.7 (quaternary aromatic *C*), 163.0 (*C*(O)), 163.4 (*C*(O)), 167.2 (*C*(O)). *m/z* (EI) 366.1577 ($M^{+\cdot}$. $C_{21}H_{22}N_2O_4$ requires 366.1580), 275 ($[M-C_7H_7]^+$, 33%), 231 ($[M-CO_2Bn]^+$, 93%), 203 (26%), 132 (35%), 91 ($[C_7H_7]^+$, 100%).

4.5.6. 4-Benzyl-3-benzyloxycarbonyl-1,3-dimethylpiperazine-2,5-dione (12). To a stirred solution of 3-benzyloxycarbonyl-1,3-dimethylpiperazine 2,5-dione (**10c**) (174 mg, 0.63 mmol) in DMF (10 mL) at 0 °C under nitrogen was added sodium hydride (27 mg, 0.68 mmol, 60% in paraffin) and benzyl bromide (0.1 mL, 0.84 mmol). The reaction mixture was stirred under a nitrogen atmosphere for 24 h and after this time the solvent was removed under reduced pressure. The residue was taken up in chloroform (15 mL) and washed with water (5 mL), brine (5 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was purified by column chromatography (3:2, ethyl acetate–petroleum spirit, R_f: 0.45) giving **12** as a clear and colourless oil (155 mg, 67%). δ_H (300 MHz, $CDCl_3$) 1.76 (s, 3H, CCH_3), 2.98 (s, 3H, NCH_3), 4.01 (d, 1H, $J_{AB}=18$ Hz, ring CH_aH_b), 4.12 (d, 1H, $J_{AB}=18$ Hz, ring CH_aH_b), 4.47 (d, 1H, $J_{AB}=16$ Hz, NCH_aH_bPh), 4.74 (d, 1H, $J_{AB}=16$ Hz, NCH_aH_bPh), 4.82 (d, 1H, $J_{AB}=12$ Hz, OCH_aH_bPh), 5.02 (d, 1H, $J_{AB}=12$ Hz, OCH_aH_bPh), 7.18–7.37 (m, 10H, Aromatic *H*). *m/z* (EI) 366.1581 ($M^{+\cdot}$. $C_{21}H_{22}N_2O_4$ requires 366.1580), 304 (15%), 231 ($[M-CO_2Bn]^+$, 52%), 91 ($[C_7H_7]^+$, 100%).

4.6. General procedure for the α,α-dialkylation of 3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (3c): conversion of 3c to piperazinediones 13, 17, 18.

To a solution of 3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (**3c**) (1 mol equiv, typical scale ca. 1 mmol) in DMF (15 mL/mmol) at 0 °C under nitrogen was added sodium hydride (2 mol equiv, 60% in paraffin) and the appropriate alkyl halide. For the synthesis of piperazinedione **13**, excess allyl iodide was added (5 mol equiv) while for the synthesis of piperazinediones **17** and **18**, 1 mol equiv of the appropriate dibromoalkane was utilized. The resultant solution was stirred under a nitrogen atmosphere for 24 h and after this time the solvent was removed under reduced pressure. The residue was taken up in chloroform and washed with water, brine and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was purified by column chromatography.

4.6.1. 3,4-Diallyl-3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (13). The title compound **13** was obtained as a clear and colourless oil in 66% yield after purification by column chromatography (4:1, ethyl acetate–petroleum spirit, R_f: 0.51). ν_{max} film/cm^{-1} 3089 w, 2934 w, 1751 vs, 1667 vs, 1455 s, 1407 s, 1340 m, 1275 s, 1224 s, 929 m, 755 m, 699 m. δ_H (300 MHz, $CDCl_3$) 2.88 (dd, 1H, $^2J=15$ Hz, $^3J=7$ Hz, C–$CH_aH_bCH{=}CH_2$), 2.95 (s, 3H, NCH_3), 3.21 (dd, 1H, $^2J=15$ Hz, $^3J=7$ Hz, C–$CH_aH_bCH{=}CH_2$), 3.74 (dd, 1H, $^2J=15$ Hz, $^3J=7$ Hz, $NCH_aH_bCH{=}CH_2$), 3.97–4.05 (m, 3H, ring CH_2 & $NCH_aH_bCH{=}CH_2$), 5.05–5.25 (m, 6H, benzyl CH_2, C–$CH_2CH{=}CH_2$ & $NCH_2CH{=}CH_2$), 5.55 (m, 1H, C–$CH_2CH{=}CH_2$), 5.76 (m, 1H, $NCH_2CH{=}CH_2$), 7.33 (m, 5H, Aromatic C_6H_5). δ_C (75 MHz, $CDCl_3$) 33.4 (NCH_3), 37.0 (C–$CH_2CH{=}CH_2$), 46.5 ($NCH_2CH{=}CH_2$), 50.9 (ring CH_2), 67.7 (quaternary ring *C*), 71.0 (OCH_2Ph), 118.1 (allyl $CH_2CH{=}CH_2$), 121.0 (allyl $CH_2CH{=}CH_2$),

127.9 (2×aromatic *C*H), 128.3 (3×aromatic *C*H), 129.7 (allyl $CH_2CH{=}CH_2$), 131.9 (allyl $CH_2CH{=}CH_2$), 134.4 (quaternary aromatic *C*), 162.5 (*C*(O)), 163.3 (*C*(O)), 167.3 (*C*(O)). *m/z* (EI) 342.1583 ($M^{+\cdot}$. $C_{19}H_{22}N_2O_4$ requires 342.1580), 292 (28%), 251 ($[M-C_7H_7]^+$, 40%), 207 ($[M-CO_2Bn]^+$, 100%), 91 ($[C_7H_7]^+$, 42%).

4.6.2. 9a-Benzyloxycarbonyl-2-methyl-1,4-dioxo-octahydropyrido[1,2-*a*]pyrazine (17). The title compound **17** was obtained as a solid in 67% yield after purification by column chromatography (ethyl acetate, R_f: 0.51), followed by trituration with ether. Mp 107–109 °C. (Found C, 64.5; H, 6.5; N, 8.7. $C_{17}H_{20}N_2O_4$ requires C, 64.5; H, 6.4; N, 8.9%). ν_{max} KBr/cm^{-1} 2949 w, 2856 w, 1751 s, 1665 s, 1427 m, 1209 m, 1122 m, 761 m, 706 w. δ_H (300 MHz, $CDCl_3$) 1.30–1.55 (m, 2H, 7-CH_aH$_b$ and 8-CH_aH$_b$), 1.60–1.70 (m, 2H, 9-CH_aH$_b$ and 7-CH$_a$$H_b$), 1.79–1.83 (m, 1H, 8-CH$_a$$H_b$), 2.35–2.46 (m, 1H, 6-C$H_aH_b$), 2.91–2.97 (m, 1H, 9-CH$_a$$H_b$), 2.92 (s, 3H, NC$H_3$), 3.84 (d, 1H, J_{AB}=17 Hz, 3-CH_aH$_b$), 3.98 (d, 1H, J_{AB}=17 Hz, 3-CH$_a$$H_b$), 4.48 (dm, 1H, ^2J=12 Hz, 6-CH$_a$$H_b$), 5.16 (d, 1H, J_{AB}=12 Hz, OCH_aH$_b$Ph), 5.27 (d, 1H, J_{AB}=12 Hz, OCH$_a$$H_b$Ph), 7.26–7.39 (m, 5H, 5×aromatic C*H*). δ_C (75 MHz, $CDCl_3$) 20.4 (8-*C*H$_2$), 22.8 (7-*C*H$_2$), 31.0 (9-*C*H$_2$), 33.5 (N*C*H$_3$), 40.2 (6-*C*H$_2$), 50.8 (3-*C*H$_2$), 67.1 (9a-*C*), 67.7 (O*C*H$_2$Ph), 127.5 (2×aromatic *C*H), 128.1 (aromatic *C*H), 128.2 (2×aromatic *C*H), 134.5 (quaternary aromatic *C*), 162.1 (*C*(O)), 164.7 (*C*(O)), 167.2 (*C*(O)). *m/z* (EI) 316.1425 ($M^{+\cdot}$. $C_{17}H_{20}N_2O_4$ requires 316.1423), 181 ($[M-CO_2Bn]^+$, 100%), 153 (43%), 91 ($[C_7H_7]^+$, 23%).

4.6.3. 8a-Benzyloxycarbonyl-2-methyl-1,4-dioxo-hexahydropyrrolo[1,2-*a*]pyrazine (18). The title compound **18** was obtained as a colourless oil in 69% yield after purification by column chromatography (ethyl acetate). ν_{max} film/cm^{-1} 2955 w, 1740 s, 1682 vs, 1445 m, 1213 m, 700 w. δ_H (300 MHz, $CDCl_3$) 1.70–2.00 (m, 2H, 7-CH_2), 2.25–2.37 (m, 1H, 8-CH_aH$_b$), 2.67–2.75 (m, 1H, 8-CH$_a$$H_b$), 2.92 (s, 3H, NC$H_3$), 3.50–3.70 (m, 2H, 6-C$H_2$), 3.69 (d, 1H, J_{AB}=17 Hz, 3-CH_aH$_b$), 4.07 (d, 1H, J_{AB}=17 Hz, 3-CH$_a$$H_b$), 5.16 (d, 1H, J_{AB}=12 Hz, OCH_aH$_b$Ph), 5.23 (d, 1H, J_{AB}=12 Hz, OCH$_a$$H_b$Ph), 7.26–7.33 (m, 5H, 5×aromatic C*H*). δ_C (75 MHz, $CDCl_3$) 20.8 (7-*C*H$_2$), 32.7 (8-*C*H$_2$), 33.6 (N*C*H$_3$), 44.9 (6-*C*H$_2$), 53.1 (3-*C*H$_2$), 67.7 (O*C*H$_2$Ph), 70.7 (8a-*C*), 127.4 (2×aromatic *C*H), 128.1 (1×aromatic *C*H), 128.2 (2×aromatic *C*H), 134.4 (quaternary aromatic *C*), 163.1 (*C*(O)), 163.4 (*C*(O)). *m/z* (EI) 302.1270 ($M^{+\cdot}$. $C_{16}H_{18}N_2O_4$ requires 302.1267), 226 (20%), 167 ($[M-CO_2Bn]^+$, 100%), 139 (72%), 108 (65%), 91 ($[C_7H_7]^+$, 43%), 79 (65%).

4.6.4. 9a-Benzyloxycarbonyl-2-methyl-1,4-dioxo-1,2,3,4,6,9-hexahydropyrido[1,2-*a*]pyrazine (14). To a solution of 3,4-diallyl-3-benzyloxycarbonyl-1-methylpiperazine-2,5-dione (**13**) (81 mg, 0.24 mmol) in dichloromethane (3 mL) was added benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium (8 mg, ~10% w/w). The reaction mixture was stirred under nitrogen for 16 h following which the solvent was removed in vacuo. The residue was purified via column chromatography (4:1, ethyl acetate–petroleum spirit) to give the title compound **14** (61 mg, 82%) as a clear and colourless oil. ν_{max} cm^{-1} 3034 w, 2938 w, 1754 vs, 1732 s, 1673 vs, 1499 m, 1428 s, 1330 m, 1247 s, 1195 s, 754 m, 699 m. δ_H (300 MHz, $CDCl_3$) 2.48 (dm, 1H, ^2J=18 Hz, 9-CH_aH$_b$), 2.96 (s, 3H, NCH_3), 3.40 (dd, 1H, ^2J=18 Hz, ^3J=6 Hz, 9-CH$_a$$H_b$), 3.56 (dm, 1H, ^2J=19 Hz, 6-CH_aH$_b$), 3.92 (d, 1H, J_{AB}=18 Hz, 3-CH_aH$_b$), 4.05 (d, 1H, J_{AB}=18 Hz, 3-CH$_a$$H_b$), 4.37 (dm, 1H, ^2J=19 Hz, ^3J=4 Hz, 6-CH$_a$$H_b$), 5.15 (d, 1H, J_{AB}=12 Hz, OCH_aH$_b$Ph), 5.22 (d, 1H, J_{AB}=12 Hz, OCH$_a$$H_b$Ph), 5.62–5.58 (m, 1H, 7 or 8-C*H*), 5.81–5.88 (m, 1H, 7 or 8-C*H*), 7.25–7.35 (m, 5H, C_6H_5). δ_C (75 MHz, $CDCl_3$) 31.4 (9-*C*H$_2$), 33.4 (N*C*H$_3$), 41.9 (6-*C*H$_2$), 51.1 (3-*C*H$_2$), 65.9 (9a-*C*), 68.3 (O*C*H$_2$Ph), 121.9 (7 or 8-*C*H), 122.6 (7 or 8-*C*H), 127.8 (2×aromatic *C*H), 128.4 (aromatic *C*H), 128.5 (2×aromatic *C*H), 134.7 (quaternary aromatic *C*); 162.1 (*C*(O)), 164.5 (*C*(O)), 167.4 (*C*(O)). *m/z* (EI) 315.1351 ($[MH]^+$), $C_{17}H_{19}N_2O_4$ ($[MH]^+$) requires 315.1345), 223 ($[M-Bn]^+$, 19%), 195 (18%), 179 ($[M-CO_2Bn]^+$, 100%), 151 (41%), 91 ($[C_7H_7]^+$, 59%).

4.6.5. 2-Methyl-hexahydropyrido[1,2-*a*]pyrazine-1,4-dione (16). To a solution of 9a-benzyloxycarbonyl-2-methyl-1,4-dioxo-1,2,3,4,6,9-hexahydropyrido[1,2-*a*]pyrazine (**14**) (43 mg, 0.14 mmol) or 9a-benzyloxycarbonyl-2-methyl-1,4-dioxo-octahydropyrido [1,2-a]pyrazine (**17**) in degassed methanol (10 mL) was added 10% palladium on carbon (5 mg). The reaction mixture was then stirred under a hydrogen atmosphere for 1 h after which time it was filtered through a bed of celite. The filtrate was concentrated in vacuo and suspended in toluene (25 mL). The reaction mixture was then heated at reflux for 24 h, following which the solvent was removed in vacuo to give the title compound **16** (25 mg, 100%) as a colourless oil which solidified upon standing. The physical data for **16** is consistent with that previously reported, although the NMR data has not been reported previously.[14] Mp 85–86 (lit.: 84–86 °C).[14] δ_H (300 MHz, $CDCl_3$) 1.35–1.80 (m, 4H, 7-CH_2, 8-CH_2), 1.97 (m, 1H, 9-CH_aH$_b$), 2.34 (m, 1H, 9-CH$_a$$H_b$), 2.49 (dt, 1H, 6-C$H_aH_b$), 2.94 (s, 3H, NC$H_3$), 3.80 (dm, 1H, 9a-C*H*), 3.91 (d, 1H, J_{AB}=18 Hz, 3-CH_aH$_b$), 3.99 (d, 1H, J_{AB}=18 Hz, 3-CH$_a$$H_b$), 4.64 (dm, 1H, J=13 Hz, 6-CH$_a$$H_b$). δ_C (75 MHz, $CDCl_3$) 24.3 (8-*C*H$_2$), 24.5 (7-*C*H$_2$), 31.3 (9-*C*H$_2$), 33.3 (N*C*H$_3$), 42.4 (6-*C*H), 51.2 (3-*C*H$_2$), 59.1 (9a-*C*H), 161.3 (*C*(O), 165.4 (*C*(O). *m/z* (EI) 182.1056 ($M^{+\cdot}$. $C_9H_{14}N_2O_2$ requires 182.1055), 153 (40%), 125 (38%), 97 (70%), 151 (41%), 83 (100%).

4.6.6. 2-Methyl-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (19). To a stirred solution of 8a-benzyloxycarbonyl-2-methyl-1,4-dioxo-hexahydropyrrolo[1,2-*a*]pyrazine (**18**) (197 mg, 1.17 mmol) in degassed methanol (10 mL) was added 10% palladium on carbon (5 mg). The reaction mixture was then stirred under a hydrogen atmosphere for 1 h after which time it was filtered through a bed of celite. The filtrate was reduced in vacuo and suspended in toluene (25 mL). The reaction mixture was then heated at reflux for 24 h. After this time the solvent was removed in vacuo giving the title compound **19** (197 mg, 100%) as a colourless oil. The NMR data has not been reported previously.[14] δ_H (300 MHz, $CDCl_3$) 1.81–2.05 (m, 3H, 7-CH_2 and 8-CH_aH$_b$), 2.31–2.43 (m, 1H, 8-CH$_a$$H_b$), 2.97(s, 3H, NC$H_3$), 3.51–3.63 (m, 2H, 6-C$H_2$), 3.78 (d, 1H, J_{AB}=17 Hz, 3-CH_aH$_b$), 4.06 (bt, 1H, J=7 Hz, 8a-C*H*), 4.16 (d, 1H, J_{AB}=17 Hz, 3-CH$_a$$H_b$). δ_C (75 MHz, $CDCl_3$) 19.6 (7-*C*H$_2$), 28.4 (8-*C*H$_2$), 33.0 (N*C*H$_3$), 44.8 (6-*C*H$_2$), 53.0

(3-*C*H_2), 58.4 (8a-*C*), 162.2 (*C*(O)), 166.8 (*C*(O)). *m/z* (EI) 168.0897 ($M^{+\cdot}$. $C_8H_{12}N_2O_2$ requires 168.0899), 83 (71%), 42 (100%).

4.7. DONA reactions of carboxypiperazine-2,5-diones

General procedure for the DONA reactions of carboxypiperazine-2,5-diones. To a stirred solution of the appropriate carboxy piperazine-2,5-dione (1 mol equiv) in dichloromethane (ca. 7.5 mL/mmol of carboxypiperazinedione) was added iodine (0.5 mol equiv) and diacetoxyiodobenzene (1 mol equiv). In reactions where external nucleophiles were added, the reaction mixture was stirred for 1 min (for **22a** and **22b**) or 10 min (for **22d**, **24a**, **25**) before the addition of the appropriate additive. For the acetoxy compounds, excess glacial acetic acid (typically 0.4 mL/mmol of carboxypiperazinedione) is added while for methoxy derivatives, excess methanol (typically 2.2 mL/mmol of carboxypiperazinedione) is added.

Stirring under a nitrogen atmosphere was continued for 16 h following which time the reaction mixture was washed with a saturated solution of sodium thiosulfate, dried ($MgSO_4$) and the solvent removed under reduced pressure.

4.7.1. 3-Acetoxy-1,4-dimethylpiperazine-2,5-dione (22a). The title compound **22a** was synthesized from 3-carboxy-1,4-dimethylpiperazine-2,5-dione (**1a**) with acetic acid as additive, using the general procedure outlined above for the DONA reactions. 3-Acetoxy-1,4-dimethylpiperazine-2,5-dione (**22a**) was purified by column chromatography (5:1, ethyl acetate–methanol, R_f: −0.42) and was isolated as a colourless oil which crystallised upon standing (83%). The title compound has also been prepared from (*S*)-hydroxymethyl-1,4-dimethylpiperazine-2,5-dione (**35a**) using the procedure described above (86% yield). Mp 92–94 °C. ν_{max} KBr/cm^{-1} 3429 w, 2981 w, 2935 w, 1757 vs, 1692 vs, 1487 m, 1399 s, 1331 m, 1205 s, 1011 s, 946 s, 750 w. δ_H (300 MHz, $CDCl_3$) 2.11 (s, 3H, OC(O)CH_3), 2.99 (s, 3H, NCH_3), 3.01 (s, 3H, NCH_3), 3.89 (d, 1H, J_{AB}=18 Hz, ring C$H_a$$H_b$), 4.21 (d, 1H, J_{AB}=18 Hz, ring C$H_a$$H_b$), 6.03 (s, 1H, C*H*OAc). δ_C (75 MHz, $CDCl_3$) 20.2 (OC(O)*C*H_3), 31.7 (N*C*H_3), 33.0 (N*C*H_3), 51.0 (ring *C*H_2), 79.4 (*C*HOAc), 160.5 (*C*(O)), 165.1 (*C*(O)), 169.4 (*C*(O)). *m/z* (EI) 201.0874 ($[MH]^+$. $C_8H_{13}N_2O_4$ requires 201.0875), 157 (36%), 142 ($[MH-OAc]^+$, 100%), 113 (65%).

4.7.2. 3-Methoxy-1,4-dimethylpiperazine-2,5-dione (22b). The title compound **22b** was synthesized from 3-carboxy-1,4-dimethylpiperazine-2,5-dione (**1a**) with methanol as additive, using the general procedure outlined above for the DONA reactions. Purification by column chromatography (5:1, ethyl acetate–methanol, R_f: 0.33) gave 3-methoxy-1,4-dimethylpiperazine-2,5-dione (**22b**) as a colourless oil (76%) with physical and spectral properties consistent with data reported previously.[15] δ_H (300 MHz, $CDCl_3$) 2.94 (s, 3H, NCH_3), 3.00 (s, 3H, NCH_3), 3.44 (s, 3H, OCH_3), 3.79 (d, 1H, J_{AB}=18 Hz, ring C$H_a$$H_b$), 4.12 (d, 1H, J_{AB}=18 Hz, ring C$H_a$$H_b$), 4.67 (s, 1H, C*H*OMe).

4.7.3. 3-Acetoxy-4-Acetyl-1-methylpiperazine-2,5-dione (22c). The title compound **22c** was synthesised from 4-acetyl-3-carboxyl-1-methylpiperazine-2,5-dione (**1b**) using the general procedure outlined above for the DONA reactions. No external nucleophile was added. The residue obtained was purified by column chromatography (ethyl acetate, R_f: 0.45) to afford 3-acetoxy-4-acetyl-1-methylpiperazine-2,5-dione (**22c**) as a colourless solid (98 mg, 82%). Mp 156–157 °C. δ_H (300 MHz, $CDCl_3$) 2.08 (s, 3H, OC(O)CH_3), 2.54 (s, 3H, NC(O)CH_3), 2.99 (s, 3H, NCH_3), 4.00 (d, 1H, J_{AB}=18 Hz, ring C$H_a$$H_b$), 4.42 (d, 1H, J_{AB}=18 Hz, ring C$H_a$$H_b$), 6.89 (s, 1H, C*H*OAc). δ_C (75 MHz, $CDCl_3$) 20.6 (OC(O)*C*H_3), 26.7 (NC(O)*C*H_3), 33.3 (N*C*H_3), 53.1 (ring *C*H_2), 73.6 (*C*HOAc), 161.4 (*C*(O)), 166.4 (*C*(O)), 168.6 (*C*(O)), 170.4 (*C*(O)). *m/z* (EI) 229.0825 ($[MH]^+$, $C_9H_{13}N_2O_5$ requires 229.0824), 168 ($[MH-AcOH]^+$, 33%), 126 ($[M-Ac-AcOH]^+$, 100%), 115 (36%), 99 (34%).

4.7.4. 4-Acetyl-1-methyl-3-methoxypiperazine-2,5-dione (22d). The title compound **22d** was synthesized from 4-acetyl-3-carboxyl-1-methylpiperazine-2,5-dione (**1b**) with methanol as additive, using the general procedure outlined above for the DONA reactions. The residue was purified by column chromatography (ethyl acetate, R_f: 0.57) to give 4-acetyl-1-methyl-3-methoxypiperazine-2,5-dione (**22d**) as a colourless solid (74 mg, 78%). Mp 89–91 °C. δ_H (300 MHz, $CDCl_3$) 2.57 (s, 3H, NC(O)CH_3), 3.01 (s, 3H, NCH_3), 3.50 (s, 3H, OCH_3), 3.84 (d, 1H, J_{AB}=18 Hz, ring C$H_a$$H_b$), 4.44 (d, 1H, J_{AB}=18 Hz, ring C$H_a$$H_b$), 5.80 (s, 1H, C*H*OCH$_3$). δ_C (75 MHz, $CDCl_3$) 26.6 (NC(O)*C*H_3), 33.1 (N*C*H_3), 52.9 (*C*H_2), 57.9 (O*C*H_3), 81.5 (*C*HOCH$_3$), 163.0 (*C*(O)), 167.2 (*C*(O)), 171.6 (*C*(O)). *m/z* (EI) 201.0876 ($[MH]^+$. $C_8H_{13}N_2O_4$ requires 201.0875), 145 ($[MH-OMe]^+$, 46%), 128 (31%), 55 (86%).

4.7.5. 3-Carboxyl-1,3,4-trimethylpiperazine-2,5-dione (23a). To a solution of 3-benzyloxycarbonyl-1,3,4-trimethylpiperazine-2,5-dione (**10a**) (503 mg, 1.73 mmol) in degassed methanol (10 mL) was added 10% palladium on carbon (40 mg). The reaction mixture was stirred under a hydrogen atmosphere for 1 h. The reaction mixture was then filtered through a bed of celite. The filtrate was reduced in vacuo and following co-evaporation with chloroform (3× 5 mL), the acid (**23a**) was obtained as a colourless solid (346 mg, 100%). The acid is unstable and was used without purification. δ_H (300 MHz, CD_3OD) 1.74 (s, 3H, α-CH_3), 2.91 (s, 3H, NCH_3), 2.98 (s, 3H, NCH_3), 4.11 (s, 2H, ring CH_2). δ_C (75 MHz, CD_3OD) 20.6 (α-*C*H_3), 30.1 (N*C*H_3), 34.3 (N*C*H_3), 52.0 (ring *C*H_2), 69.3 (quaternary α-*C*CH_3), 165.8 (*C*(O)), 166.5 (*C*(O)), 170.7 (*C*O_2H). *m/z* (EI) 200.0799 ($M^{+\cdot}$. $C_8H_{12}N_2O_4$ requires 200.0797), 156 ($[M-CO_2]^+$, 100%), 141 ($[M-CH_3-CO_2]^+$, 30%), 127 (47%), 113 (85%).

4.7.6. 3-Acetoxy-1,3,4-trimethylpiperazine-2,5-dione (24a). The title compound **24a** was synthesized from 3-carboxyl-1,3,4-trimethylpiperazine-2,5-dione (**23a**) with glacial acetic acid as additive, using the general procedure outlined above for the DONA reactions. However, in this case, stirring after addition of all reaction components was continued for only 6 h before work-up commenced. The residue obtained from the reaction was purified by column chromatography (5:1, ethyl acetate–methanol, R_f: 0.53) to give the title compound **24a** as a thick colourless oil (56 mg, 55%). The compound is unstable and eliminates acetic acid

to give the known 1,4-dimethyl-3-methylidenepiperazine-dione[26] (**28a**) when stored. δ_H (300 MHz, $CDCl_3$) 1.75 (s, 3H, α-CH_3), 2.03 (s, 3H, C(O)CH_3), 2.91 (s, 6H, 2×NCH_3), 3.93 (d, 1H, $J=18$ Hz, ring CH_aH_b), 4.07 (d, 1H, $J=18$ Hz, ring CH_aH_b). δ_C (75 MHz, $CDCl_3$) 20.6 (α-CH$_3$), 24.4 (NCH$_3$), 27.2 (NCH$_3$), 33.7 (C(O)CH$_3$), 51.8 (ring CH$_2$), 86.0 (α-COAc), 163.8 (NC(O)), 164.1 (NC(O)), 169.7 (C(O)CH$_3$).

4.7.7. 3-Acetoxy-3-benzyl-1,4-dimethylpiperazine-2,5-dione (24b). To a solution of 3-benzyl-3-benzyloxycarbonyl-1,4-dimethylpiperazine-2,5-dione (**11**) (265 mg, 0.72 mmol) in degassed methanol (20 mL) was added 10% palladium on carbon (20 mg). The reaction mixture was stirred under a hydrogen atmosphere for 1 h after which time the reaction mixture was filtered through a bed of celite. The filtrate was reduced in vacuo and taken up in dichloromethane (10 mL). DIB (233 mg, 0.72 mmol) and iodine (92 mg, 0.36 mmol) were added and the reaction mixture was stirred under nitrogen for 6 h. After this time, the reaction mixture was washed with saturated sodium thiosulfate solution (5 mL). The organic phase was separated, dried and concentrated in vacuo. The oily residue was purified via column chromatography (ethyl acetate, R_f: 0.61) to give the title compound **24b** as a colourless oil (155 mg, 74%). ν_{max} film/cm^{-1} 3476 w, 3027 w, 2943 w, 1751 s, 1676 vs, 1399 m, 1222 s, 1016 m, 745 m, 703 m. δ_H (300 MHz, $CDCl_3$) 2.15 (s, 3H, OC(O)CH_3), 2.71 (s, 3H, NCH_3), 2.88 (d, 1H, $J_{AB}=18$ Hz, ring CH_aH_b), 3.05 (s, 3H, NCH_3), 3.24 (d, 1H, $J_{AB}=13$ Hz, α-CCH_aH_bPh), 3.45 (d, 1H, $J_{AB}=13$ Hz, α-CCH_aH_bPh), 3.67 (d, 1H, $J_{AB}=18$ Hz, ring CH_aH_b), 7.07 (m, 2H, aromatic H), 7.27 (m, 3H, aromatic H). δ_C (75 MHz, $CDCl_3$) 20.6 (OC(O)CH$_3$), 27.4 (NCH$_3$), 33.0 (NCH$_3$), 41.3 (α-CCH$_2$Ph), 50.7 (ring CH$_2$), 88.5 (quaternary ring C), 127.9 (2×aromatic CH), 128.4 (aromatic CH), 129.9 (2×aromatic CH), 131.8 (quaternary aromatic C), 162.3 (C(O)), 163.3 (C(O)), 168.9 (C(O)). m/z (EI) 290.1273 ($M^{+\cdot}$. $C_{15}H_{18}N_2O_4$ requires 290.1267), 231 ([M−OAc]$^+$, 26%), 199 ([M−C$_7$H$_7$]$^+$, 39%), 157 (100%), 91 ([C$_7$H$_7$]$^+$, 35%).

4.7.8. 3-Methoxy-1,3,4-trimethylpiperazine-2,5-dione (25). The title compound **24a** was synthesized from 3-carboxyl-1,3,4-trimethylpiperazine-2,5-dione (**23a**) with methanol as additive, using the general procedure outlined above for the DONA reactions. However, in this case, stirring after addition of all reaction components was continued for only 6 h before work-up commenced. The residue obtained after work-up was purified by column chromatography (5:1, ethyl acetate–methanol, R_f: −0.35) to give the title compound **25** as a thick colourless oil (79 mg, 77%). The compound is unstable and eliminates acetic acid to give the known 1,4-dimethyl-3-methylidenepiperazine-dione[26] (**28a**) when stored. Data for **25**: δ_H (300 MHz, $CDCl_3$) 1.60 (s, 3H, α-CH_3); 2.93 (s, 3H, NCH_3), 3.00 (s, 3H, NCH_3), 3.09 (s, 3H, OMe), 4.01 (s, 2H, ring CH_2). δ_C (75 MHz, $CDCl_3$) 24.1 (α-CH$_3$), 26.6 (NCH$_3$), 33.6 (NCH$_3$), 51.2 (ring CH$_2$), 51.2 (OCH$_3$), 88.0 (quaternary α-CCH$_3$), 163.5 (C(O)), 164.0 (C(O)). m/z (EI) 187 ([M+1]$^+$, 3%); 186.1001 ($M^{+\cdot}$. $C_8H_{14}N_2O_3$ requires 186.1004), 171 ([M−CH$_3$]$^+$, 20%), 156 ([M−OCH$_3$+1]$^+$, 80%), 127 (100%), 114 (50%), 101 (35%), 87 (30%), 72 (50%).

4.8. Reactions of *N*-acyliminium ions derived from piperazine-2,5-diones

4.8.1. 3-Allyl-1,4-dimethylpiperazine-2,5-dione (26). To a stirred solution of 3-methoxy-1,4-dimethylpiperazine-2,5-dione (**22b**) (587 mg, 3.41 mmol) in dichloromethane (10 mL) at 0 °C was added allyltrimethylsilane (5.5 mL, 35.3 mmol) and boron trifluoride diethyl etherate (0.9 mL, 7.06 mmol). The cooling bath was removed, the reaction mixture was warmed to room temperature and stirring was continued for a further 24 h. After this time the reaction mixture was washed with brine (5 mL), the organic phase was separated, dried and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (5:1, ethyl acetate–methanol, R_f: 0.31) to give the title compound **26** as a colourless oil which crystallized upon prolonged standing (422 mg, 68%). Mp 60–62 °C. ν_{max} KBr/cm^{-1} 3447 m, 2923 m, 1651 vs, 1492 s, 1400 s, 1347 s, 1256 m, 1039 m, 946 m. δ_H (300 MHz, $CDCl_3$) 2.61 (m, 1H, allyl CHCH_aH_bCH=CH$_2$), 2.72 (m, 1H, allyl CHCH_aH_bCH=CH$_2$), 2.96 (s, 3H, NCH_3), 2.98 (s, 3H, NCH_3), 3.81 (d, 1H, $J_{AB}=18$ Hz, ring CH_aH_b), 3.98 (m, 1H, ring CHCH$_2$), 4.04 (d, 1H, $J_{AB}=18$ Hz, ring CH_aH_b), 5.15 (bs, 1H, allyl CHCH$_2$CH=CH_aH_b), 5.20 (d, 1H, $J=9$ Hz, allyl CHCH$_2$CH=CH_aH_b), 5.68 (m, 1H, allyl CHCH$_2$CH=CH$_2$). δ_C (75 MHz, $CDCl_3$) 32.2 (NCH$_3$), 33.4 (NCH$_3$), 36.0 (allyl CHCH$_2$CH=CH$_2$), 51.6 (ring CH$_2$), 62.2 (ring CH), 121.0 (allyl CHCH$_2$CH=CH$_2$), 130.7 (allyl CHCH$_2$$C$H=CH$_2$), 163.8 ($C$(O)), 165.6 ($C$(O)). m/z (EI) 182.1055 ($M^{+\cdot}$. $C_9H_{14}N_2O_2$ requires 182.1055), 141 ([M−allyl]$^+$, 100%), 113 (90%).

4.8.2. 3-(2-Methoxynaphthalen-1-yl)-1,4-dimethylpiperazine-2,5-dione (27). To a stirred solution of 3-acetoxy-1,4-dimethylpiperazine-2,5-dione (**22a**) (181 mg, 0.90 mmol) in dichloromethane (10 mL) was added 2-methoxynaphthalene (286 mg, 1.81 mmol) and boron trifluoride diethyl etherate (0.23 mL, 1.81 mmol). The resultant reaction mixture was stirred under nitrogen for 16 h. After this time, the reaction mixture was washed with brine (5 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified via column chromatography (5:1, ethyl acetate–methanol, R_f: 0.42) to afford the title compound **27** (218 mg, 81%). Mp 174–175 °C. ν_{max} KBr/cm^{-1} 2939 w, 1655 vs, 1518 m, 1485 m, 1271 s, 1122 m, 1094 m, 1001 m, 806 m, 750 m, 741 m. δ_H (300 MHz, $CDCl_3$) 2.67 (s, 3H, NCH_3), 3.03 (s, 3H, NCH_3), 3.92 (s, 3H, OCH_3), 4.08 (d, 1H, $J_{AB}=18$ Hz, ring CH_aH_b), 4.19 (d, 1H, $J_{AB}=18$ Hz, ring CH_aH_b), 5.95 (bs, 1H, ring CH), 7.27 (d, 1H, $J=8$ Hz, aromatic CH), 7.38 (t, 1H, $J=7$ Hz, aromatic CH), 7.56 (t, 1H, $J=7$ Hz, aromatic CH), 7.82 (d, 1H, $J=8$ Hz, aromatic CH), 7.88 (d, 1H, $J=9$ Hz, aromatic CH), 8.08 (bd, 1H, $J=8$ Hz, aromatic CH). δ_C (75 MHz, $CDCl_3$) 31.0 (NCH$_3$), 33.2 (NCH$_3$), 51.9 (ring CH$_2$), 56.5 (OCH$_3$), 57.0 (ring CH), 112.7 (aromatic CH), 116.8 (quaternary aromatic C), 121.3 (aromatic CH), 123.5 (aromatic CH), 127.6 (aromatic CH), 128.7 (aromatic CH), 128.9 (quaternary aromatic C), 131.0 (aromatic CH), 133.3 (quaternary aromatic C); 155.0 (quaternary aromatic COCH$_3$), 163.6 (C(O)), 165.0 (C(O)). m/z (EI) 298.1318 ($M^{+\cdot}$. $C_{17}H_{18}N_2O_3$ requires 298.1317); 210 (38%); 198 (63%); 183 (30%); 169 (39%); 113 (48%).

4.8.3. (*Z*)-3-Benzylidene-1,4-dimethylpiperazine-2,5-dione (28b). To a stirred solution of 3-acetoxy-3-benzyl-1,4-dimethylpiperazine-2,5-dione (**24b**) (55 mg, 0.19 mmol) in dichloromethane (5 mL) at 0 °C was added boron trifluoride diethyl etherate (0.03 mL, 0.21 mmol). The reaction mixture was warmed to room temperature and stirring was continued for a further 16 h. After this time the reaction mixture was washed with brine (1 mL), dried and filtered. The solvent was removed in vacuo to give the crude product as a yellow oil. The oil was purified via column chromatography (ethyl acetate, R_f: 0.5) to afford the title compound (33 mg, 76%) as a colourless oil with spectroscopic properties consistent with the *Z*-isomer reported previously.[22]

4.8.4. 3-Allyl-1,3,4-trimethylpiperazine-2,5-dione (30). To a solution of 3-methoxy-1,3,4-trimethylpiperazine-2,5-dione (**25**) (30 mg, 0.16 mmol) in dichloromethane (1 mL) at 0 °C was added allyltrimethylsilane (0.26 mL, 1.61 mmol) and boron trifluoride diethyl etherate (0.04 mL, 0.32 mmol). The cooling bath was removed and the reaction mixture was warmed slowly to room temperature. Stirring was continued for a further 4 h following which time the reaction mixture was washed with brine (1 mL), the organic phase was separated, dried and concentrated in vacuo. The residue was purified by column chromatography (5:1, ethyl acetate–methanol, R_f: 0.46) to give the title compound **30** as a colourless oil (21 mg, 66%). δ_H (300 MHz, $CDCl_3$) 1.56 (s, 3H, α-CH_3), 2.43 (dd, 1H, J=14 Hz, 8 Hz, allyl α-CCH_aH$_b$CH), 2.76 (dd, 1H, J=14 Hz, 7 Hz, allyl α-CCH$_a$$H_b$CH), 2.96 (s, 6H, 2×NC$H_3$), 3.95 (m, 2H, ring C$H_2$), 5.09 (m, 1H, allyl α-CCH$_2$CHCH_aH$_b$), 5.13 (m, 1H, allyl α-CCH$_2$CHCH$_a$$H_b$), 5.55 (m, 1H, allyl α -CCH$_2$CH). δ_C (75 MHz, $CDCl_3$) 24.6 (α-CH$_3$), 27.8 (NCH$_3$), 33.8 (NCH$_3$), 42.0 (allyl CCH$_2$CH), 51.4 (ring CH$_2$), 64.5 (quaternary ring carbon), 120.2 (allyl CCH$_2$CHCH$_2$), 131.4 (allyl CCH$_2$$C$H), 163.5 ($C$(O)), 167.7 ($C$(O)). The by-product 1,4-dimethyl-3-methylidenepiperazine-2,5-dione[26] (**28a**) (~33%) had spectral properties consistent with those reported previously.

4.9. Hydroxymethylpiperazinediones as precursors in modified DONA reactions

4.9.1. (*S*)-3-(*t*-Butyldimethylsilanyloxymethyl)-1-methylpiperazine-2,5-dione (33). To a stirred solution of (*S*)-3-hydroxymethyl-1-methylpiperazine-2,5-dione (**32**)[24] (851 mg, 5.38 mmol) in DMF (15 mL) was added *t*-butyldimethylsilylchloride (983 mg, 6.52 mmol) and imidazole (888 mg, 13.0 mmol). The reaction mixture was stirred for 1 h and the solvent was then removed in vacuo. The residue was taken up in ethyl acetate (20 mL) and washed with water (10 mL). The organic phase was dried ($MgSO_4$) and the solvent removed to afford the title compound **33** as a colourless solid (1.17 g, 80%). Mp 115–117 °C. ν_{max} KBr/cm^{-1} 3213 w, 2932 w, 1670 s, 1443 m, 1335 m, 1250 m, 1096 m, 837 m, 779 m. δ_H (300 MHz, $CDCl_3$) 0.01 (s, 6H, Si(CH_3)$_2$), 0.83 (s, 9H, C(CH_3)$_3$), 2.94 (s, 3H, NCH_3), 3.82 (d, 1H, J=17 Hz, 6-CH_aH$_b$), 3.83–3.87 (m, 1H, CH_aH$_b$OSi), 3.86 (bs, 1H, 3-CH), 3.93–4.00 (m, 1H, CH$_a$$H_b$OSi), 4.02 (d, 1H, J=17 Hz, 6-CH$_a$$H_b$). δ_C (75 MHz, $CDCl_3$) −5.8 (2×Si(CH$_3$)$_2$), 17.9 (C(CH$_3$)$_3$), 25.5 (3×C(CH$_3$)$_3$), 33.4 (NCH$_3$), 51.4 (6-CH$_2$), 57.3 (3-CH), 65.7 (CH$_2$O), 164.9 (C(O)), 166.6 (C(O)). *m/z* (EI) 272.1533 ($M^{+\cdot}$. $C_{12}H_{24}N_2O_3Si$ requires 272.1556), 215 ([M−C(CH$_3$)$_3$]$^+$, 100%), 158 ([M−Si(CH$_3$)$_2$C(CH$_3$)$_3$]$^+$, 30%), 73 (33%).

4.9.2. (*S*)-3-(*t*-Butyldimethylsilanyloxymethyl)-1,4-dimethylpiperazine-2,5-dione (34a). To a stirred solution of (*S*)-3-(*t*-butyldimethylsilanyloxymethyl)-1-methylpiperazine-2,5-dione (**33**) (1.24 g, 4.56 mmol) in DMF (10 mL) at 0 °C under nitrogen was added sodium hydride (182 mg, 4.60 mmol, 60% in paraffin) and methyl iodide (5 mL, excess). The resultant solution was stirred under a nitrogen atmosphere for 24 h and after this time the solvent was removed under reduced pressure. The residue was taken up in chloroform (30 mL) and washed with water (10 mL), brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was purified by column chromatography (ethyl acetate, R_f: 0.49) giving **34a** as a colourless solid (1.17 g, 90%). Mp 147–149 °C. ν_{max} KBr/cm^{-1} 2932 w, 2858 m, 1666 s, 1474 m, 1408 m, 1335 m, 1258 m, 1111 m, 837 m, 783 m. δ_H (300 MHz, $CDCl_3$) 0.01 (s, 3H, SiCH_3), 0.02 (s, 3H, SiCH_3), 0.83 (s, 9H, C(CH_3)$_3$), 2.94 (s, 3H, NCH_3), 2.95 (s, 3H, NCH_3), 3.77 (d, 1H, J=17 Hz, 6-CH_aH$_b$), 3.84 (bs, 1H, 3-CH), 3.90 (dd, 1H, ^2J=10 Hz, ^3J=2 Hz, CH_aH$_b$O), 4.04 (dd, 1H, ^2J=10 Hz, ^3J=2 Hz, CH$_a$$H_b$O), 3.82 (d, 1H, J=17 Hz, 6-CH$_a$$H_b$). δ_C (75 MHz, $CDCl_3$) −5.8 (2×Si(CH$_3$)$_2$), 18.0 (C(CH$_3$)$_3$), 25.5 (3×C(CH$_3$)$_3$), 31.6 (NCH$_3$), 33.2 (NCH$_3$), 51.8 (6-CH$_2$), 62.3 (CH$_2$O), 64.5 (3-CH), 164.7 (C(O)), 165.4 (C(O)). *m/z* (EI) 286.1710 ($M^{+\cdot}$. $C_{13}H_{26}N_2O_3Si$ requires 286.1713); 229 ([M−C(CH$_3$)$_3$]$^+$, 100%); 158 ([M−Si(CH$_3$)$_2$C(CH$_3$)$_3$]$^+$, 30%); 73 (37%).

4.9.3. (*S*)-3-(*t*-Butyldimethylsilanyloxymethyl)-4-(*p*-methoxybenzyl)-1-methylpiperazine-2,5-dione (34b). The title compound was prepared from (*S*)-3-(*t*-butyldimethylsilanyloxymethyl)-1-methylpiperazine-2,5-dione (**33**) (2.18 g, 8.00 mmol) as outlined for **34a**. In this case *p*-methoxybenzyl chloride was used instead of methyl iodide. The compound was purifed via column chromatography (ethyl acetate, R_f: 0.53). Piperazinedione **34b** was obtained as a colourless solid (2.26 g, 72%). Mp 94–97 °C. ν_{max} KBr/cm^{-1} 2932 m, 1666 s, 1647 s, 1512 m, 1466 m, 1331 m, 1246 s, 1115 m. δ_H (300 MHz, $CDCl_3$) 0.00 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3), 0.85 (s, 9H, C(CH_3)$_3$), 2.94 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 3.75–3.85 (m, 3H, CH_aH$_b$O & 6-CH_aH$_b$ & 3-CH), 3.95–3.98 (m, 1H, CH$_a$$H_b$O), 4.00 (d, 1H, J_{AB}=15 Hz, NCH_aH$_b$Ph), 4.21 (d, 1H, J_{AB}=17 Hz, 6-CH$_a$$H_b$), 5.15 (d, 1H, J_{AB}=15 Hz, NCH$_a$$H_b$Ph), 6.83 (d, 2H, J=9 Hz, 2×aromatic CH), 7.17 (d, 2H, J=9 Hz, 2×aromatic CH). δ_C (75 MHz, $CDCl_3$) −5.6 (2×Si(CH$_3$)$_2$), 18.1 (C(CH$_3$)$_3$), 25.7 (3×C(CH$_3$)$_3$), 33.4 (NCH$_3$), 46.4 (NCH$_2$Ph), 52.2 (ring CH$_2$), 55.3 (OCH$_3$), 61.4 (ring CH), 62.8 (CH$_2$OSi), 114.3 (2×aromatic CH), 127.5 (quaternary aromatic), 129.7 (2×aromatic CH), 159.3 (quaternary aromatic), 164.9 (C(O)), 166.0 (C(O)). *m/z* (EI) 393 ([MH]$^+$, 1%), 392.2130 ($M^{+\cdot}$. $C_{20}H_{32}N_2O_4Si$ requires 392.2131), 335 ([M−C(CH$_3$)$_3$]$^+$, 63%), 121 (57%), 61 (100%).

4.9.4. 3-Hydroxymethyl-1,4-dimethylpiperazine-2,5-dione (35a). 3-(*t*-Butyldimethylsilanyloxymethyl)-1,4-dimethylpiperazine-2,5-dione (**34a**) (620 mg, 2.41 mmol) was dissolved in acetic acid (6 mL), THF (2 mL) and water

(2 mL). The resultant solution was heated at reflux for 24 h, following which the solvent was removed in vacuo. The residue was purified via column chromatography (9:1, chloroform–ethyl acetate, R_f: 0.29) to give 3-hydroxymethyl-1,4-dimethylpiperazine-2,5-dione (**35a**) as a colourless solid (361 mg, 87%). Mp 127–129 °C. (Found C, 48.9; H, 7.3; N, 16.5. $C_7H_{12}N_2O_3$ requires C, 48.8; H, 7.0; N, 16.3%). ν_{max} KBr/cm^{-1} 3379 s, 2992 w, 2816 w, 1672 vs, 1647 vs, 1493 s, 1410 s, 1340 s, 1259 s, 1070 m, 1056 m, 1032 m, 833 w. δ_H (300 MHz, $CDCl_3$) 2.97 (s, 3H, NCH_3), 3.00 (s, 3H, NCH_3), 3.17 (bs, 1H, OH), 3.78 (d, 1H, $J_{AB}=17$ Hz, 6-CH_aH$_b$), 3.85 (bs, 1H, 3-CH), 3.96 (dd, 1H, $^2J_{AB}=12$ Hz, $^3J=3$ Hz, CH_aH$_b$OH), 4.05 (dd, 1H, $^2J_{AB}=12$ Hz, $^3J=3$ Hz, CH$_a$$H_b$OH), 4.16 (d, 1H, $J_{AB}=17$ Hz, 6-CH$_a$$H_b$). δ_C (75 MHz, $CDCl_3$) 31.7 (NCH_3), 33.3 (NCH_3), 51.6 (6-CH_2), 61.2 (CH_2OH), 64.5 (3-CH), 165.2 (C(O)), 165.7 (C(O)). *m/z* (EI) 173.0923 ([MH]$^+$. $C_7H_{13}N_2O_3$ requires173.0926), 142 ([MH−CH_2OH]$^+$, 100%), 113 (72%), 71 (32%).

4.9.5. 3-Hydroxymethyl-4-(*p*-methoxybenzyl)-1-methylpiperazine-2,5-dione (35b). The title compound was prepared from (*S*)-3-(*t*-butyldimethylsilanyloxymethyl)-4-(*p*-methoxybenzyl)-1-methylpiperazine-2,5-dione (**34b**) (1.01 g, 2.57 mmol) as outlined for the conversion of **34a** to **35a**. The compound was purifed via column chromatography (5:1, ethyl acetate–methanol, R_f: 0.39). Piperazinedione **35b** was obtained as a colourless solid (594 mg, 83%). Mp 94–97 °C. ν_{max} KBr/cm^{-1} 3368 w, 2936 w, 1666 s, 1647 m, 1512 m, 1246 m. δ_H (300 MHz, $CDCl_3$) 2.97 (s, 3H, NCH_3), 3.79 (s, 3H, OCH_3), 3.82–3.90 (m, 3H, 6-CH_aH$_b$, 3-CH, CH_aH$_b$O), 4.00 (dd, 1H, $^2J=12$ Hz, $^3J=3$ Hz, CH$_a$$H_b$O), 4.07 (d, 1H, $J=15$ Hz, NCH_aH$_b$), 4.27 (d, 1H, $J=17$ Hz, 6-CH$_a$$H_b$), 5.16 (d, 1H, $J=15$ Hz, NCH$_a$$H_b$), 6.85 (d, 2H, $J=9$ Hz, 2×aromatic H), 7.19 (d, 2H, $J=9$ Hz, 2×aromatic H). δ_C (75 MHz, $CDCl_3$) 33.5 (NCH_3), 46.4 (NCH_2), 52.1 (6-CH_2), 55.4 (OCH_3), 61.8 (CH_2OH), 114.4 (2×aromatic CH), 127.2 (quaternary aromatic C), 129.8 (2×aromatic CH), 159.5 (quaternary aromatic C), 165.4 (C(O)), 166.2 (C(O)). *m/z* (EI) 278.1266 (M$^{+\cdot}$. $C_{14}H_{18}N_2O_4$ requires 278.1267), 248 (26%), 121 (100%).

4.9.6. 3-Methoxy-1-methylpiperazine-2,5-dione (36). To a solution of 3-hydroxymethyl-1-methylpiperazine-2,5-dione (**32**) (225 mg, 1.42 mmol) in dichloromethane (10 mL) was added iodine (718 mg, 2.84 mmol) and DIB (462 mg, 1.43 mmol). The reaction mixture was then stirred under a nitrogen atmosphere for 16 h. After this time, methanol (10 mL) was added and the reaction mixture was stirred for a further 24 h. Then reaction mixture was then washed with a saturated solution of sodium thiosulfate (2 mL). The aqueous phase was extracted with dichloromethane (5×5 mL). The organic washings were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography (5:1, ethyl acetate–methanol, R_f: 0.35) to afford the title compound **36** as a colourless solid (99 mg, 44%). Mp 118–120 °C. ν_{max} KBr/cm^{-1} 3267 w, 1682 s, 1655 s, 1477 m, 1327 m, 1072 s, 1018 m. δ_H (300 MHz, $CDCl_3$) 2.99 (s, 3H, NCH_3), 3.45 (s, 3H, OCH_3), 3.78 (d, 1H, $J_{AB}=18$ Hz, ring CH_aH$_b$), 4.23 (d, 1H, $J_{AB}=18$ Hz, ring CH$_a$$H_b$), 4.74 (d, 1H, $J=4$ Hz, ring CH), 7.84 (bs, 1H, NH). δ_C (75 MHz, $CDCl_3$) 33.7 (NCH_3), 51.3 (ring CH_2), 55.9 (OCH_3), 82.3 (ring CH), 162.4 (C(O)), 167.9 (C(O)). *m/z* (EI) 159.0767 ([MH]$^+$. $C_6H_{11}N_2O_3$ requires 159.0767), 128 ([M−OCH_3+1]$^+$, 71%), 101 (100%), 73 (32%).

4.9.7. 3-Acetoxy-4-(*p*-methoxybenzyl)-1-methylpiperazine-2,5-dione (37). To a solution of **35b** (106 mg, 0.38 mmol) in dichloromethane (10 mL) was added iodine (48 mg, 0.19 mmol) and DIB (125 mg, 0.39 mmol). The reaction mixture was then stirred under a nitrogen atmosphere for 16 h. After this time, the reaction mixture was washed with a saturated solution of sodium thiosulfate (1 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was triturated with diethyl ether and collection of the solid afforded the title compound **37** as a colourless solid (110 mg, 94%). Mp 118–120 °C. δ_H (300 MHz, $CDCl_3$) 1.98 (s, 3H, OC(O)CH_3), 2.96 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 3.93 (d, 1H, $J_{AB}=18$ Hz, 6-CH_aH$_b$), 4.18 (d, 1H, $J_{AB}=18$ Hz, NCH_aH$_b$), 4.28 (d, 1H, $J_{AB}=18$ Hz, 6-CH$_a$$H_b$), 4.94 (d, 1H, $J_{AB}=18$ Hz, NCH$_a$$H_b$), 5.98 (s, 1H, 3-C$H$), 6.84 (d, 2H, $J=9$ Hz, 2×aromatic H), 7.23 (d, 2H, $J=9$ Hz, 2×aromatic H). δ_C (75 MHz, $CDCl_3$) 20.5 (OC(O))CH_3), 33.5 (NCH_3), 46.9 (NCH_2), 51.7 (6-CH_2), 55.2 (OCH_3), 77.7 (3-CH), 114.1 (2×aromatic CH), 127.2 (quaternary aromatic C), 130.1 (2×aromatic CH), 159.4 (quaternary aromatic), 161.1 (C(O)), 165.2 (C(O)), 169.7 (C(O)). *m/z* (EI) 306.1219 (M$^{+\cdot}$. $C_{15}H_{18}N_2O_5$ requires 306.1216), 246 ([M−OAc−1]$^+$, 56%), 147 (39%), 136 (29%), 121 (100%).

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