Synthesis of conformationally constrained amino acid and peptide derivatives

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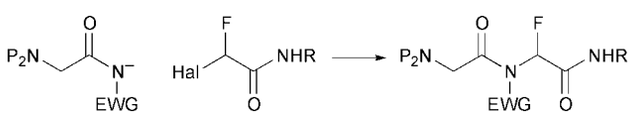
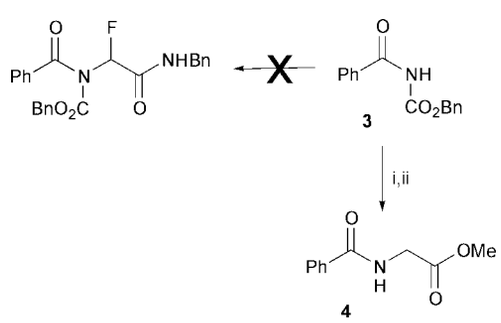
6-Benzylpiperazine-2,3,5-trione **5**, a cyclic phenylalanine derivative, can be selectively and sequentially alkylated at N^4, C^6 and N^1 to provide a range of conformationally constrained phenylalanine mimetics. Alkylation at C^6, the α-carbon of the phenylalanine moiety is achieved under mild conditions and gives rise to Phe derivatives posessing a dialkylated α-carbon. Alkylation of piperazine **5** using methyl bromoacetate and ethyl bromopropionate gives access to peptoids **7** and **21** which are conformationally contrained Phe-Gly and Phe-Ala analogues respectively. The X-ray crystal structure of triallylated derivative **17** is also reported.

Introduction

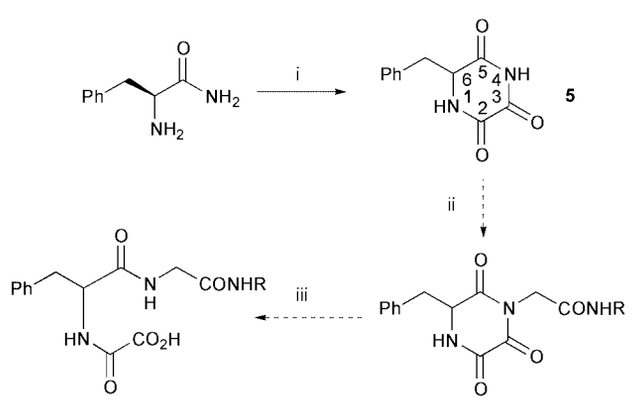
During the course of a programme on the synthesis of α-fluoroglycine derivatives, we were searching for a suitably activated amino acid amide derivative **1**. Our interest was in constructing peptides through O=CN⟶CHR bond formation, as opposed to the normal acylation at nitrogen O=C⟵NCHR, allowing access to peptides in which the free amino acid was considered to be too unstable to use conventional coupling methods.[1] With the derivatives **1** we wanted selectively to alkylate at the amidic nitrogen with an α-fluoro-α-halocarboxamide, as a route to access fluorodipeptides of the general structure **2** (Scheme 1). Our initial studies[1] had shown how simple nitrogen nucleophiles, such as succinimide and glutarimide, could be successfully used to displace iodide from α-fluoro-α-iodocarboxamides. So we then started to look for suitable substrates (*cf.* **1**) that would ultimately give us access compounds such as **2** with a true dipeptide skeleton. After some unsuccessful attempts to utilise acyclic compounds as 'amide anion equivalents' (*e.g.* **3**, Scheme 2) our focus turned to piperazine-2,3,6-trione **5**. This compound is a closer analogue of glutarimide, with which successful reaction had already been achieved, and which can be readily made from phenylalaninamide and diethyl oxalate.[2,3] Unlike the hydantoins used by Takeuchi *et al.* for essentially the same purpose,[4] this class of compound seemed an ideal candidate for further modification. Some initial results[5] indicated that the $O{=}C^3{-}N^4$ bond in **5** can be selectively cleaved at a later date to give something which resembles more closely a dipeptide (Scheme 3). Indeed Person and Le Corre[3] have shown the 3-oxo group in **5** is sufficiently reactive to undergo selective methylenation with Wittig reagents. Before progressing with our work on α-fluoroglycine derivatives, trial alkylation reactions of the piperazinetrione **5** were investigated.



Scheme 1



Scheme 2 *Reagents and conditions*: i, K_2CO_3, $BrCH_2CO_2Me$; ii, Pd–C/H_2.



Scheme 3 *Reagents and conditions*: i, $(CO_2Et)_2$, NaOEt–EtOH then 1 M HCl (aq) (63%); ii, alkylate; iii, H_3O^+ or OH^-.

N-Methylation of **5** was achieved using sodium hydride (1 equiv.) and methyl iodide to give **6** (76%), but to our surprise when the alkylating agent employed was methyl bromoacetate (1.05 equiv.) we isolated the dialkylated species **8** (22%) as well as the expected product **7** (60%). If potassium carbonate was used as base trione **8**, in which the α-carbon of the phenylalanine residue has been alkylated, was the only product obtained, with yields depending on the amount of electrophile added (Scheme 4). Derivatives **7** and **8** are interesting as they represent novel conformationally constrained Phe-Gly dipeptide analogues. Modified amino acids, such as those

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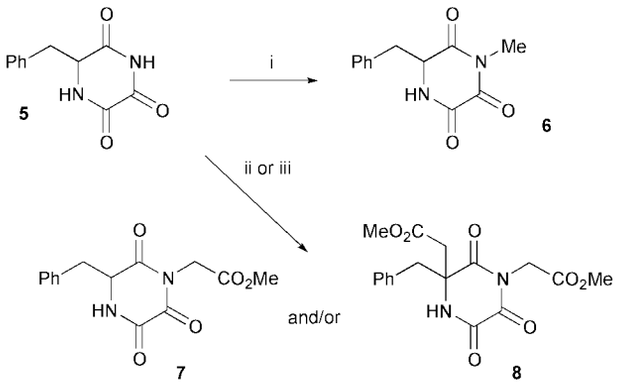


Scheme 4 *Reagents and conditions*: i, NaH, DMF then MeI (76%); ii, NaH, DMF then 1.05 mol equiv. $BrCH_2CO_2Me$ (60% **7**, 22% **8**); iii, K_2CO_3, DMF, 2.2 mol equiv. $BrCH_2CO_2Me$ (61% **8**).

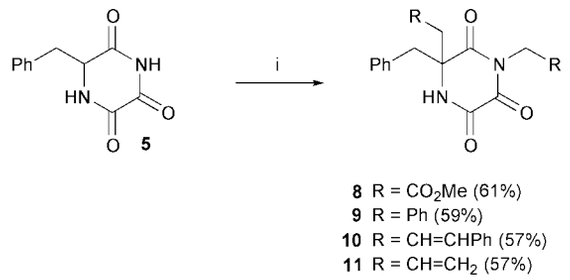
containing dialkylated α-carbon atoms,[6] and those that are conformationally constrained by incorporation of the amino acid into a ring,[7] are currently receiving attention as synthetic targets. Their use in the synthesis of peptides or other natural products as replacements of a proteinogenic amino acid, can not only result in marked changes in preferred molecular conformation, but can also affect a compound's susceptibility to enzymatic hydrolysis. The synthesis and incorporation of α-dialkylated α-amino acids into peptides is therefore an important goal for the medicinal chemist. In the light of our early results[5] we considered that alkylation of piperazinetriones should give access to a wide range of conformationally constrained phenylalanine derivatives.

Results and discussion

The simple preparation of piperazinetriones from a range of amino amides has been reported by Safir *et al.*,[2] though we found that the reported propensity towards rapid hydrolysis of the intermediate N^4-salts† meant that yields were often variable (20–65%). Thus, during the reaction work-up the salt must be isolated and protonation carried out promptly to avoid excessive hydrolysis back to the acyclic oxamic acid. Also, the natural inclination to use ethanol–sodium ethoxide for a reaction using the diethyl ester of oxalic acid is, in this case, definitely not as good as the methanol–methoxide system employed by Person and Le Corre.[3] The intermediate salt precipitates much more cleanly and in greater yield from methanol in this particular case, though serious 'bumping' during the latter period of heating is a problem. Even though our synthesis of the trione **7** used enantiomerically pure phenylalaninamide, the reaction was conducted under basic conditions. Checking the specific rotation of **7** we found an $[\alpha]_D$ of only +2.1 ($c = 0.1$, DMSO). Even though this value was slightly variable and the analysis hampered by poor solubility, the near-zero value seems to concur with the reports of Person and Le Corre that total racemization occurs in the synthesis of piperazinetriones using this method.

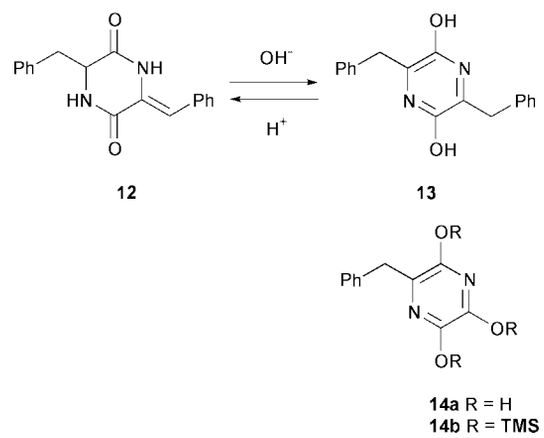
In addition to the early results mentioned above we also observed by TLC that in a 'blank run' with potassium carbonate–DMF only (no electrophile added) the trione was consumed quickly to give just 'baseline material'. Again the hydrolysis of the anion of **5** is undoubtedly the competing reaction in this system due to the difficulty of complete removal of water from the DMF and the carbonate base. However, in the presence of 2.2 equivalents of an activated electrophile

† The parent piperazine **5** is named as a piperazine-2,3,5-trione using the Chemical Abstracts system, but additional substituents can in certain cases alter the numbering pattern. For clarity, reference to the locants N^1, N^4 and C^6 in the discussion are based on the parent piperazine **5**. The correct numbering however is used in the Experimental section.



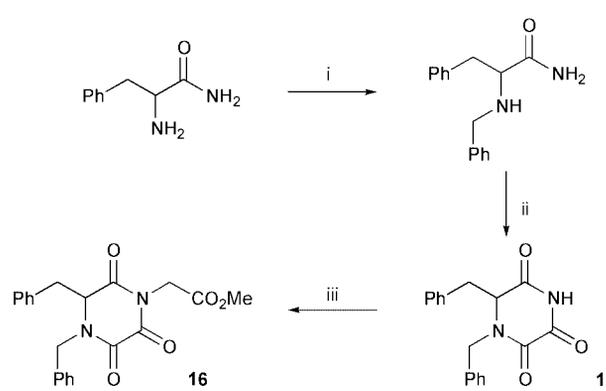
Scheme 5 *Reagents and conditions*: i, K_2CO_3, DMF, 2.2 mol equiv. RCH_2Br.

(Scheme 5) reactions took place, giving moderate yields of the dialkylated amino acid derivatives **8**–**11**. In the cases of methyl iodide and unactivated alkyl halides, however, no alkylation products were isolated or identified. Sammes and co-workers have previously found[8] that α,β-unsaturated diketopiperazines can be isolated as their aromatic 'iminol' tautomer from basic conditions **13** or their amide tautomer **12** from acidic conditions (Scheme 6).



Scheme 6

Undoubtedly the facile C^6-alkylation observed was due to the increased acidity of C^6-H due to the presence of the aromatic tautomer **14a** under the basic reaction conditions. We made an attempt to isolate the TMS derivative **14b** by heating **5** in hexamethydisilazane, however the experiment was unsuccessful. To investigate this matter further, the N^1-blocked trione **15** was synthesised from *N*-benzylphenylalaninamide (Scheme 7)

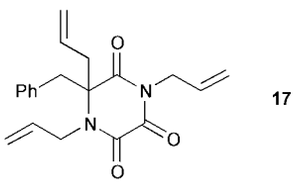


Scheme 7 *Reagents and conditions*: i, (a) PhCHO, azeotrope, cat. *p*-TsOH; (b) $NaBH_4$, MeOH, (73%, 2 steps); ii, $(CO_2Et)_2$, NaOEt–EtOH, Δ, then AcOH (43%); iii, 3 equiv. K_2CO_3, DMF, 1.5 equiv. $BrCH_2CO_2Me$ (83%).

and this compound underwent clean, rapid alkylation only at N^4 giving **16** (83%); no C^6-alkylation was observed. The N^1-benzyl group prevents **15** from forming a stable conjugated

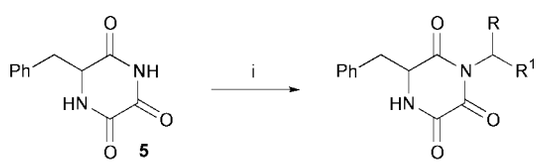
tautomer and therefore presumably causes a significant drop in the acidity of the C^6-H.

In the case of alkylation of piperazinetrione **5** with allyl bromide we noticed that alkylation at N^1 could also be achieved if left for longer times with sufficient electrophile present. The rate of alkylation at N^1 could be accelerated using the phase transfer catalyst (PTC) tetra-*n*-butylammonium bromide. Thus we were able to isolate and analyse the crystalline triallylated product **17** using X-ray diffraction.[5] However, if the PTC was present from the beginning of the reaction and less than 3 equivalents of alkyl halide were present, then it was difficult to isolate a single product in anything but modest yield.



17

Knowing that we could alkylate at C^6 using potassium carbonate and DMF, and then promote further N^1-alkylation using a PTC, we speculated that with the right choice of conditions and reaction time, we should be able to alkylate the piperazinetrione selectively with up to three different groups. We therefore next investigated a way of selectively alkylating at N^4 without concomitant reaction at C^6, as had been observed with sodium hydride and potassium carbonate. Use of the non-nucleophilic DBU in both DMF and MeCN was unsuccessful, and with stoichiometric amounts of triethylamine and alkyl halide, competitive quaternization of the tertiary amine reduced isolated yields of the desired product. However if the substrate ratio was 1.0 equiv. trione, 1.2 equiv. base and 1.5 equiv. alkyl halide, moderate to good yields of the N^4 alkylated products were produced if the reaction was conducted at room temperature or with warming (Scheme 8). Due to its

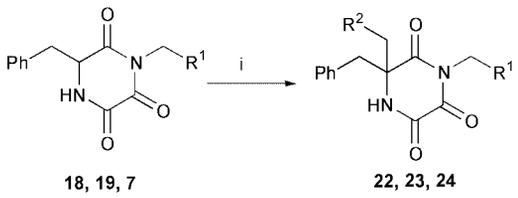


18 R^1 = $CH{=}CH_2$, R = H
19 R^1 = $(4\text{-}BrC_6H_4)$, R = H
20 R^1 = $(CH_2)_2CH{=}CH_2$, R = H
21 R^1 = CO_2Et, R = CH_3

Scheme 8 *Reagents and conditions*: i, 1.1 equiv. Et_3N, MeCN–DMF, 1.5 equiv. R^1RCHBr (65–75%, except 16% for **21**).

lower boiling point, acetonitrile proved easier to handle than DMF, but the solubility of the trione in HPLC-grade or other rigorously dried solvent was severely limited and hampered progress of the reaction. So in certain cases some DMF was added to the reaction mixture to aid solubility. In this way a range of N^4-derivatised piperazinetriones **18**–**21** were made, and under these conditions no reaction at C^6 was observed. Alkylation with an unactivated alkyl bromide was even possible under these conditions with heating (giving **20**), and reaction with ethyl 2-bromopropionate gave the Phe-Ala peptidomimetic **21** as a 1 : 1 mixture of diastereoisomers. However, in this last case, even with extensive efforts at optimisation of the reaction conditions, we could not get the yields of **21** above 15–20%. This is presumably because the reaction involves a more hindered secondary bromide.

Having now developed a route to N^4-derivatised piperazinetriones, further reaction with a different alkyl halide was possible. Using potassium carbonate in DMF, derivatives **7**, **18**, and **19** could be further alkylated selectively at C^6 giving derivatives **22**–**24**. However, the yields of these reactions were quite variable 40–78% (Scheme 9). Whereas the solubility of



18, 19, 7 **22, 23, 24**

22 R^1 = $CH{=}CH_2$, R^2 = $(4\text{-}BrC_6H_4)$
23 R^1 = $(4\text{-}BrC_6H_4)$, R^2 = $CH{=}CH_2$
24 R^1 = CO_2Me, R^2 = Ph

Scheme 9 *Reagents and conditions*: i, 3 equiv. K_2CO_3, DMF, 1.2 equiv. R^2CH_2Br, (40–80%).

trione **5** is quite low, the derivatives **7** and **18**–**21** are much more soluble in DMF and so competing alkylation at N^1 causes a drop in the yield of the N^4,C-dialkylated derivatives.

Given that all the piperazinetriones made so far can be considered as conformationally constrained phenylalanine analogues we thought that a modelling study may reveal some trends in the preferred low-energy conformation of these derivatives. Simple molecular modelling studies[9] of the dipeptide analogues **7**, **8**, **16** and **21** and the triallylated derivative **17** were therefore undertaken. In the cases of **7**, **8**, **16** and **17**, which all bear an N^4-CH_2R group, the plane containing the N^4–C–C atoms was found to be near to perpendicular relative to the approximate plane of the piperazine ring (Fig. 1). This

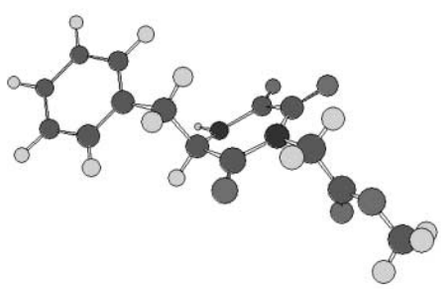


Fig. 1 Chem-3D® representation of the Phe-Gly dipeptide analogue **7**.

was also seen in the single crystal X-ray structure[10] of triallylated derivative **17** (Fig. 2). From conformational analysis of rotation about the N^4–CH_2 bond there seemed to be a distinct preference for such conformations but with no great difference in energy when the bulk of the N^4 group was either *syn* or *anti* to the C^6 benzyl group.

In conclusion, we have reported a mild and versatile route to conformationally constrained phenylalanine derivatives. This method has allowed the preparation of a range of cyclic piperazine derivatives containing a phenylalanine core, some (**9**–**11**, **17**, **22**, **23**) with and some (**6**, **15**, **18**–**20**) without an alkylated α-carbon. In addition, conformationally constrained analogues of the dipeptides Phe-Gly (**7**, **8**, **16**, **24**) and Phe-Ala (**21**) have been prepared (derivative **8** can also be considered as an Asp-Gly analogue). Given that triketopiperazines from a range of amino acids have been prepared, this methodology should allow the preparation of larger numbers of novel conformationally constrained amino acid and dipeptide derivatives.

Experimental

Anhydrous *N*,*N*-dimethylformamide was stored over 4 Å molecular sieves; methanol was dried by distillation from and stored over calcium hydride. Triethylamine was dried and

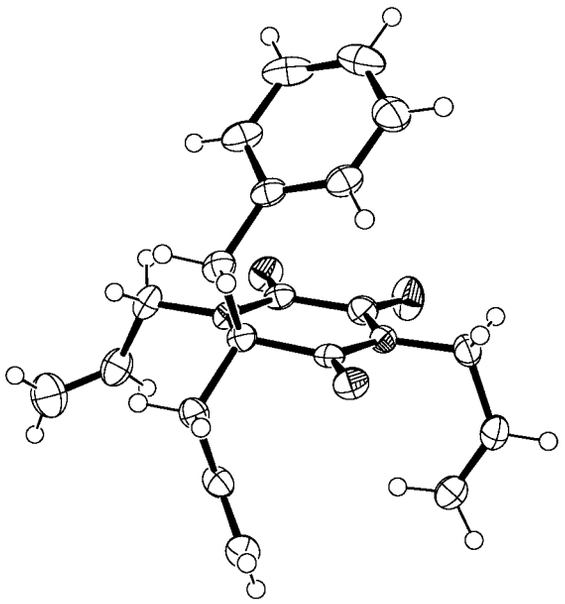


Fig. 2 X-Ray crystal structure of derivative **17**.

stored over potassium hydroxide. HPLC grade acetonitrile and all other reagents were used as purchased. In reporting ^{1}H NMR data for AB and ABX systems the chemical shift of the centre of the pattern is quoted, followed by a Δ value (Hz) giving the spread of the outermost lines of the pattern. The coupling constants for ABX systems are given with the coupling constant J_{Ha-Hb} first, then J_{Ha-X} for the downfield proton and lastly the J_{Hb-X} for the upfield proton. In the cases where $\Delta > 80$ Hz (0.2 ppm at 400 MHz), the data are simply quoted as being two separate doublets (or doublet of doublets).

N-(Benzyloxycarbonyl)benzamide, 3

Finely ground benzamide (3.0 g, 25 mmol) was suspended in dry dichloromethane (40 cm^3) under an argon atmosphere. Next, to the vigorously stirred mixture at 0 °C, oxalyl chloride (3.28 cm^3, 38 mmol) in dichloromethane (20 cm^3) was added dropwise over a period of 45 minutes. The mixture was then allowed to slowly warm to room temperature over 1.5 h and heated at reflux for 22 h. After re-cooling to 0 °C benzyl alcohol (12.9 cm^3, 125 mmol) in dichloromethane (75 mmol) was added dropwise to the solution over a period of 2.5 h. After stirring at ambient temperature overnight, the solvent was removed *in vacuo*, and the resulting sludge was washed thoroughly with hexane. Recrystallization of the crude solid (CH_2Cl_2–hexane) gave 6.04 g (95%) of the *title compound* as colourless plates. R_f 0.21 (CH_2Cl_2); Mp 112–114 °C (CH_2Cl_2–hexane); δ_H(90 MHz, $CDCl_3$) 7.90–7.70 and 7.50–7.30 (10 H, m, ArH), 8.57 (1 H, bs, NH), 5.15 (2 H, s, CH_2); δ_C(22.5 MHz, $CDCl_3$) 165.1 (s), 151.0 (s), 135.0 (s), 132.8 (d), 128.7 (d), 128.5 (d), 127.8 (d), 67.7 (t); ν_{max}($CHCl_3$)/cm^{-1} 3430, 1780, 1715; *m*/*z* 256 FAB-MS (NOBA) (MH^+, 60), 105 (19), 91 (100), 77 (9).

N-Benzoyl-*N*-(benzyloxycarbonyl)glycine methyl ester

The protected benzamide **3** (150 mg, 0.59 mmol) and anhydrous potassium carbonate (406 mg, 5 equiv.) were mixed with DMF (5 cm^3) under argon. Next methyl bromoacetate (56 µl, 0.59 mmol) in DMF (3 cm^3) was added and the mixture left stirring at ambient temperature for 5 h. After this time the DMF was removed *in vacuo* and the residue thoroughly triturated chloroform. The chloroform washings were combined, the solvent evaporated and the resulting residue purified using silica flash chromatography (CH_2Cl_2) to yield the *title compound* (170 mg, 67%) as a colourless oil. R_f 0.52 (CH_2Cl_2); δ_H(90 MHz, $CDCl_3$) 7.70–6.90 (10 H, m, ArH), 5.01 (2 H, s, $PhCH_2$), 4.59 (2 H, s, CH_2), 3.72 (3 H, s, CO_2Me); δ_C(22.5 MHz, $CDCl_3$) 172.3 (s), 169.1 (s), 154.1 (s), 136.0 (s), 134.2 (s), 131.5 (d), 128.3 (d), 128.1 (d), 127.9 (d), 68.9 (t), 52.3 (q), 46.5 (t); ν_{max}($CHCl_3$)/cm^{-1} 1740, 1680; *m*/*z* FAB-MS 328 (MH^+, 48%), 105 (29), 77 (100).

N-Benzoylglycine methyl ester, 4

The protected glycine derivative (113 mg, 0.35 mmol) was dissolved in methanol (10 cm^3), and in this solution was suspended a 10% palladium-on-charcoal catalyst (16 mg). The mixture was then stirred under a hydrogen atmosphere for 16 h after which the solution was diluted, filtered and then evaporated to dryness. The resulting residue was purified by 'filtration' through a small pad of flash silica (eluent dichloromethane), yielding 41 mg (61%) of the *title compound*. R_f 0.25 (CH_2Cl_2); mp 72–82 °C (without further purification) (lit.[11] 85 °C); δ_H(90 MHz, $CDCl_3$) 7.87–7.30 (5 H, m, ArH), 6.90 (1 H, broad s, NH), 4.22 (2 H, d, *J* 5.0, $NHCH_2$), 3.77 (3 H, s, CO_2Me); δ_C(22.5 MHz, $CDCl_3$) 169.5 (s), 166.6 (s), 132.6 (s), 130.7 (d), 127.5 (d), 126.1 (d), 51.4 (q), 40.7 (t); ν_{max}($CHCl_3$)/cm^{-1} 3440, 1745, 1660; *m*/*z* 193 (M^+, 11%), 161 (6), 134 (20), 105 (100), 77 (45).

6-Benzylpiperazine-2,3,5-trione, 5[3]

(L)-Phenylalaninamide (1.0 g, 6.1 mmol) and diethyl oxalate were dissolved in methanol (15 cm^3), and heated at reflux for 0.25 h. Then, whilst refluxing was continued, 1.1 equivalents of sodium methoxide in methanol were added dropwise over a period of 0.25 h (353 mg of sodium was dissolved in 4.5ml of methanol, and then 2 cm^3 of this solution used). After addition of the last portion of the sodium methoxide, refluxing was continued for 0.3 h. Next the mixture was cooled in an ice bath, before removal of the resulting precipitate by filtration. The salt collected was added with stirring to 1 M hydrochloric acid (6 cm^3) to liberate the free trione. The suspension was filtered immediately, and the solid dried under vacuum to yield 842 mg (63%) of 5-benzylpiperazine-2,3,6-trione **5** as a white solid, mp 230–240 °C (without further purification) [lit.[4] 264 °C (H_2O)]. R_f 0.11 [(1 : 1) chloroform–ethyl acetate]; δ_H(400 MHz, d_6-DMSO) 11.75 (1H, s, NH), 9.23 (1 H, broad s, NH), 7.29–7.20 (3 H, m, Ph), 7.10–7.09 (2 H, m, Ph), 4.61 (1 H, t, *J* 3.5, CH), 3.10 (2 H, ABX, Δ = 41.5 Hz, *J* 13.8, 4.3 and 5.2, $PhCH_2$); δ_C(22.5MHz, d_6-DMSO) 174.8 (s), 162.2 (s), 158.2 (s), 139.0 (s), 133.9 (d), 132.2 (d), 131.0 (d), 61.2 (d), 43.1 (t); ν_{max}(Nujol)/cm^{-1} 3230, 1755, 1720–1680; *m*/*z* 218 (M^+, 2%), 91 (100).

6-Benzyl-4-methylpiperazine-2,3,5-trione, 6

The piperazinetrione **5** (55 mg, 0.25 mmol) was dissolved in DMF (1 cm^3), and then added to a stirred suspension of sodium hydride (7.5 mg, 0.25 mmol) in DMF (2 cm^3) under an argon atmosphere. After the solution had been stirred for 10 minutes, methyl iodide (25 µl, 1.5 equiv.) in DMF (2 cm^3) was added to the reaction vessel. After 8 h the DMF was removed *in vacuo* to leave a residue, which was thoroughly triturated with ethyl acetate (5 cm^3). The fine white precipitate that formed was collected by filtration, yielding 44 mg (76%) of the methylated product **6**. R_f 0.54 [(2 : 1 : 17) methanol–acetic acid–chloroform); δ_H(d_4-MeOH; 90 MHz) 7.40–7.20 (6 H, m, Ph + NH), 4.73 (1 H, t, *J* 4.6, CH), 3.25 (2 H, m, $PhCH_2$), 2.98 (3 H, s, Me); δ_C(22.5 MHz, d_6-DMSO) 169.0 (s), 156.9 (s), 152.6 (s), 134.5 (s), 129.6 (d), 128.1 (d), 127.1 (d), 56.6 (d), 39.9 (t), 26.1 (t); *m*/*z* 230 (M^+, 3%), 165 (10), 91 (100).

(3-Benzyl-2,5,6-trioxopiperazin-1-yl)acetic acid methyl ester 7 and (3-benzyl-3-methoxycarbonylmethyl-2,5,6-trioxopiperazin-1-yl)acetic acid methyl ester, 8

Sodium hydride (13.8 mg, 0.46 mmol) was suspended in DMF (2 cm^3) under an argon atmosphere. Then trione **5**

(100 mg, 0.46 mmol) was added, and the solution stirred for 10 minutes, after which effervescence had ceased and the solution cleared. Methyl bromoacetate (46 μl, 0.48 mmol, 1.05 equiv.) in DMF (1 cm^3) was added to the reaction flask, and the mixture stirred for 6 h at room temperature. The DMF was then removed *in vacuo* and the products separated and purified using silica flash chromatography [(4 : 1) chloroform–ethyl acetate] yielding 80 mg (60%) of **7**; R_f 0.25 [(1 : 1) chloroform–ethyl acetate]; found: MH^+ 291.0979. $C_{14}H_{15}N_2O_5$ requires *M*, 291.0981; δ_H(300 MHz, $CDCl_3$) 8.30 (1 H, broad s, NH), 7.34–7.25 and 7.15–7.12 (5 H, m, Ph), 4.77 (1 H, m, CH), 4.46 (2 H, m, CH_2N), 3.75 (3 H, s, CO_2Me), 3.30 (2 H, ABX, Δ = 46.1 Hz, *J* 13.8, 4.5 and 6.3, $PhCH_2$); δ_C(75 MHz, $CDCl_3$) 167.7 (s), 166.9 (s), 155.9 (s), 153.6 (s), 133.3 (s), 129.8 (d), 129.0 (d), 128.1 (d), 57.7 (d), 52.8 (q), 41.3 (t), 41.2 (t); ν_{max}($CHCl_3$)/cm^{-1} 3380, 3230 (two broad, weak absorptions), 1750, 1710; *m*/*z* 291 (MH^+, 100%). Also isolated was **8** (36 mg, 22%), mp 155–158 °C (chloroform–hexane); found: M^+ 363.1200. $C_{17}H_{19}N_2O_7$ requires *M*, 363.1192; R_f 0.35 [(1 : 1) chloroform–ethyl acetate]; δ_H(300 MHz, $CDCl_3$) 8.57 (1 H, broad s, NH), 7.31–7.26 and 7.10–7.07 (5 H, m, Ph), 4.39 (2 H, AB, Δ = 40.8 Hz, *J* 16.7, NCH_2O_2), 3.72 (3 H, s, CO_2Me), 3.68 (3 H, s, CO_2Me), 3.54 (1 H, d, *J* 17.4, one proton from $PhCH_2$), 3.01 (1 H, d, *J* 17.4, other proton from $PhCH_2$), 3.23 (2 H, AB, Δ = 53.4 Hz, *J* 13.4, MeO_2CCH_2C); δ_C(75 MHz, $CDCl_3$) 170.0 (s), 169.6 (s), 166.7 (s), 155.7 (s), 153.9 (s), 132.3 (s), 130.4 (d), 128.8 (d), 128.3 (d), 63.4 (s), 52.6 (q), 52.5 (q), 46.9 (t), 43.0 (t), 41.3 (t); ν_{max}($CHCl_3$)/cm^{-1} 3370, 3230, 3100 (three broad, weak absorptions), 1745–1710; *m*/*z* 363 (MH^+, 100%).

General procedure for the dialkylation of 6-benzylpiperazine-2,3,5-trione 5 using potassium carbonate

The alkyl halide (2.1 to 2.4 equiv.) was added to a stirred suspension of the piperazinetrione **5** (1 equiv.) in dry DMF [~2 cm^3 $mmol^{-1}$ of **5**] and anhydrous potassium carbonate (5 equiv.). Stirring was continued for 2–3 h after which time TLC indicated the disappearance of starting material. After dilution with ethyl acetate and filtration to remove the inorganic salts, the DMF was removed *in vacuo* and the resulting oil purified using silica gel column chromatography (CH_2Cl_2 or chloroform–ethyl acetate).

(3-Benzyl-3-methoxycarbonylmethyl-2,5,6-trioxopiperazin-1-yl)acetic acid methyl ester, 8

The piperazinetrione **5** (50 mg, 0.23 mmol), caesium carbonate (374 mg, 5 equiv.), DMF (4 cm^3) and methyl bromoacetate (46 μl, 2.1 equiv.) gave 51 mg (61%) of the *title compound* **8** after chromatographic purification [(2 : 1) chloroform–ethyl acetate]. The ^1H, and ^{13}C NMR, IR and mass spectra of this compound were identical to those for the minor product isolated from the previous reaction.

4,6,6-Tribenzylpiperazine-2,3,5-trione, 9

The piperazinetrione **5** (218 mg, 1 mmol), potassium carbonate (690 mg, 5 equiv.), DMF (2 cm^3) and benzyl bromide (0.26 cm^3, 2.2 equiv.) gave 234 mg (59%) of the dialkylated product **9** after chromatographic purification [(6 : 1) chloroform–ethyl acetate]. Mp 253–254 °C (decomp.) ($CHCl_3$–hexane); R_f 0.52 [(4 : 1) chloroform–ethyl acetate]; found: C, 74.89; H, 5.54; N, 6.99%. $C_{25}H_{22}N_2O_3$ requires C, 75.36; H, 5.56; N, 7.03%; δ_H(400 MHz, d_6-DMSO) 9.86 (1 H, s, NH), 7.25–7.14 (9 H, m, aromatics), 7.07–7.05 (4 H, m, aromatics), 6.72–6.69 (2 H, m, aromatics), 4.53 (2 H, s, NCH_2), 3.48 (2 H, d, *J* 13.2, 2 × PhC*H*H), 3.08 (2 H, dd, *J* 13.2, 2 × PhCH*H*); δ_C(100 MHz, d_6-DMSO) 170.1, 155.8, 152.2, 134.9, 134.3, 130.1, 128.3, 128.2, 127.2(9), 127.2(5), 127.2(0), 67.3, 46.1, 42.7; *m*/*z* 398 (M^+, 15%), 307 (45), 91 (100).

6-Benzyl-4,6-bis[(*E*)-3-phenylallyl]piperazine-2,3,5-trione, 10

The piperazinetrione **5** (218 mg, 1 mmol), potassium carbonate (690 mg, 5 equiv.), DMF (2 cm^3) and (*E*)-cinnamyl bromide (473 mg, 2.4 equiv.) gave after chromatographic purification [(4 : 1) chloroform–ethyl acetate] the *title compound* (258 mg, 57%). Mp 239–240 °C (decomp.); R_f 0.55 [(4 : 1) chloroform–ethyl acetate]; found: M^+ 450.2040. $C_{29}H_{26}N_2O_3$ requires M^+, 450.1943; δ_H(400 MHz, d_6-DMSO) 9.66 (1 H, s, NH), 7.31–7.15 (13 H, m, aromatics), 7.06–7.04 (2 H, m, aromatics), 6.51 (1 H, d, *J* 15.7, PhC*H*=), 6.37 (1 H, d, *J* 16.1, PhC*H*=), 6.15 (1 H, dt, *J* 15.7 and 7.8, CH=C*H*–CH_2), 5.88 (1 H, dt, *J* 16.1 and 7.5, CH=C*H*–CH_2), 4.31–4.21 (2 H, m, NCH_2), 3.30 (1 H, d, *J* 13.2, PhC*H*H), 3.06 (1 H, dd, *J* 13.7 and 7.7, C–C*H*H–C=), 2.98 (1 H, d, *J* 13.2, PhCH*H*), 2.74 (1 H, dd, *J* 13.7 and 7.7, C–CH*H*–C=); δ_C(100 MHz, d_6-DMSO) 170.1, 156.2, 152.8, 136.3, 135.8, 135.0, 134.2, 132.9, 130.1, 128.5(2), 128.4(9), 128.2, 127.8, 127.6, 127.3, 126.1(9), 126.1(6), 122.4, 122.2, 65.9, 46.0, 43.5, 41.5; *m*/*z* 450 (M^+, 0.2%), 306 (8), 191 (10), 117 (22), 91 (20), 28 (100).

4,6-Diallyl-6-benzylpiperazine-2,3,5-trione, 11

The piperazinetrione **5** (436 mg, 2 mmol), potassium carbonate (1380 mg, 5 equiv.), DMF (4 cm^3) and allyl bromide (400 μl, 2.2 equiv.) gave 340 mg (57%) of the *title compound* after chromatographic purification [(6 : 1) chloroform–ethyl acetate]. Mp 156.5–158.5 °C (CCl_4–hexane); R_f 0.40 [(4 : 1) chloroform–ethyl acetate]; found: C, 68.04; H, 6.11; N, 9.25%. $C_{17}H_{18}N_2O_3$ requires C, 68.44; H, 6.08; N, 9.39%; found: M^+ 298.1318. $C_{17}H_{18}N_2O_3$ requires M^+, 298.1317; δ_H(400 MHz, $CDCl_3$) 9.31 (1 H, s, NH), 7.27–7.21 (3 H, m, aromatics), 7.08–7.06 (2 H, m, aromatics), 5.71–5.53 (2 H, m, 2 × C–CH=C), 5.24–5.09 (4 H, m, 2 × C=CH_2), 4.26 (2 H, dd, *J* 5.9 and 1.4, NCH_2), 3.41 (1 H, d, *J* 13.4, PhC*H*H), 3.05 (1 H, dd, *J* 13.4, PhCH*H*), 3.03 (1 H, dd, *J* 13.9 and 7.3, C–C*H*H–C=), 2.65 (1 H, dd, *J* 13.9 and 7.6, C–CH*H*–C=); δ_C(100 MHz, $CDCl_3$) 169.9, 155.9, 155.0, 133.4, 130.3, 129.9 (2 × CH), 128.6, 127.9, 122.2, 119.2, 66.6, 47.0, 44.7, 42.8; *m*/*z* 298 (M^+, 40%), 257 (25), 207 (35), 91 (100), 50 (100). Also isolated in yields of around 10% was compound **17**.

1,4,6-Triallyl-6-benzylpiperazine-2,3,5-trione, 17. Mp 100–102 °C (chloroform–hexane); R_f 0.79 [(4 : 1) chloroform–ethyl acetate]; found: C, 70.81; H, 6.60; N, 8.31%. $C_{20}H_{22}N_2O_3$ requires C, 70.99; H, 6.55; N, 8.28%; δ_H(400 MHz, $CDCl_3$) 7.23–7.21 (3 H, m, aromatics), 6.96–6.94 (2 H, m, aromatics), 6.09 (1 H, dddd, *J* 17.3, 10.0, 7.3 and 5.4, CH_2–C*H*=CH_2), 5.62–5.47 (2 H, m, 2 × CH_2–C*H*=CH_2), 5.41 (1 H, d, *J* 17.3, CH=C*H*H), 5.32 (1 H, d, *J* 10.0, CH=CH*H*), 5.20–5.08 (4 H, m, 2 × C=CH_2), 4.59 (1 H, dd, *J* 14.8 and 5.5, NCH*H*), 4.21–4.19 (2 H, m, NCH_2), 4.03 (1 H, dd, *J* 14.8 and 7.6, NC*H*H), 3.26 (2 H, Δ = 55.7 Hz, *J* 13.9, $PhCH_2$), 3.05 (1 H, dd, *J* 14.4 and 8.3, C–C*H*H–C=), 2.83 (1 H, dd, *J* 14.9 and 5.9, C–CH*H*–C=); δ_C(100 MHz, $CDCl_3$) 169.4, 154.8, 153.7, 133.1, 129.9, 129.6, 129.5, 129.4, 128.9, 128.1, 121.7, 119.5, 119.3, 72.8, 47.2, 44.4, 42.8, 41.9.

1,6-Dibenzylpiperazine-2,3,5-trione, 15

Phenylalaninamide (0.50 g, 3.05 mmol) and benzaldehyde (310 μl, 3.05 mmol) were dissolved in sodium-dried benzene (20 cm^3) and refluxed for 1.5 h in a flask fitted with a Dean–Stark trap and condenser. After cooling, the benzene was removed *in vacuo*, and the resulting crude imine taken up in methanol (20 cm^3). Next sodium borohydride (58 mg, 1.5 mmol) was added portionwise to the solution, which was subsequently left stirring for 1 h. After removal of the methanol, the residue was partitioned between ethyl acetate (10 cm^3) and water (10 cm^3), then the organic layer dried over magnesium sulfate. Removal of the solvent yielded 564 mg (73%) of *N*-benzylphenylalaninamide. A 490 mg (1.93 mmol)

sample of the protected amino acid amide was cyclised in an identical fashion to that described for **5**, except for the following modified work-up procedure: After the final period of refluxing, the mixture was cooled in an ice–salt bath. No precipitate formed, so 1 M acetic acid (2 cm^3) was added directly to the methanolic solution with stirring. The methanol was removed *in vacuo* leaving a slurry, which was partitioned between ethyl acetate (20 cm^3) and water (20 cm^3). The ethyl acetate was separated, dried over magnesium sulfate, then evaporated to dryness. The crude product was dissolved in a minimum of ethyl acetate, then precipitated out with diethyl ether–hexane to yield 271 mg (43%) of the 1,6-dibenzyl derivative **15** as a white solid, mp 150–152 °C (ethyl acetate–hexane). R_f 0.49 [(1 : 1) chloroform–ethyl acetate]; found: M^+ 309.1237. $C_{18}H_{17}N_2O_3$ requires M^+, 309.1239; δ_H(300 MHz, d_6-DMSO) 11.88 (1 H, broad s, NH), 7.46–7.25 (8 H, m, Ph), 7.02–6.97 (2 H, m, *ortho* protons from $PhCH_2N$), 5.17 (1 H, d, *J* 14.9, one proton from $PhCH_2N$), 4.48 (1 H, d, *J* 14.9, other proton from $PhCH_2N$), 4.50 (1 H, dd, *J* 5.1 and 3.2, $PhCH_2CH$), 3.43 (1 H, dd, *J* 14.0 and 5.1, one proton from $PhCH_2CH$), 3.10 (1 H, dd, *J* 14.0 and 3.2, other proton from $PhCH_2CH$); δ_C(75 MHz, d_6-DMSO) 168.9 (s), 155.9 (s), 153.4 (s), 135.5 (s), 133.7 (s), 129.7 (d), 128.5 (d), 128.4 (d), 128.3 (d), 127.6 (d), 127.4 (d), 61.4 (d), 47.2 (t), 37.4 (t); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490, 3360, 1675; *m*/*z* 309 (MH^+, 70%), 107 (32), 91 (57).

(3,4-Dibenzyl-2,5,6-trioxopiperazin-1-yl)acetic acid methyl ester, 16

To anhydrous potassium carbonate (112 mg, 5 equiv.) and trione **15** (50 mg, 0.16 mmol) in DMF (2 cm^3) was added methyl bromoacetate (16 µl, 1.05 equiv.) in DMF (1 cm^3). The mixture was stirred at ambient temperature for 3 h, the solvent was removed *in vacuo*, and then the product purified using silica flash chromatography [(1 : 1) chloroform–ethyl acetate] yielding the title compound as a colourless oil (51 mg, 83%). R_f 0.63 [(1 : 1) chloroform–ethyl acetate]; found: M^+ 381.1470. $C_{21}H_{21}N_2O_5$ requires M^+ 381.1450; δ_H(90 MHz, $CDCl_3$) 7.45–7.15 (1 H, broad s, NH), 7.05–6.85 (2 H, m, *ortho* protons from $PhCH_2N$), 5.51 (1 H, d, *J* 14.9, one proton from $PhCH_2N$), 4.07 (1 H, d, *J* 14.9, other proton from $PhCH_2N$), 4.51 (1 H, t, *J* 4.3, $PhCH_2CH$), 4.29 (2 H, s, CH_2CO_2Me), 3.70 (3 H, s, CO_2Me), 3.26 (2 H, m, $PhCH_2CH$); δ_C(22.5 MHz, $CDCl_3$) 167.6 (s), 166.7 (s), 155.4 (s), 152.9 (s), 134.0 (s), 132.9 (s), 129.4 (d), 129.3 (d), 129.1 (d), 128.8 (d), 128.3 (d), 60.9 (d), 52.7 (q), 48.3 (t), 41.0 (t), 39.2 (t); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1740, 1690; *m*/*z* 381.2 (MH^+, 100%).

General procedure for the mono N^4-alkylation of the 5-benzylpiperazine-2,3,6-trione 5 using triethylamine

The piperazinetrione and acetonitrile were mixed, then triethylamine followed by the halogenoalkane were added. The solution, with some DMF to aid dissolution if necessary, was stirred whilst heating at reflux until TLC showed consumption of starting material (2 to 3 h). After removal of the solvent the crude mixture was purified by column chromatography [CH_2Cl_2 or chloroform–ethyl acetate] to give the product.

4-Allyl-6-benzylpiperazine-2,3,5-trione, 18

The piperazinetrione **5** (218 mg, 1 mmol), triethylamine (0.7 cm^3, 5 equiv.), MeCN (6 cm^3) and allyl bromide (0.2 cm^3, 2.2 equiv.) gave 198 mg (77%) of the *title compound* after chromatographic purification [(5 : 1) chloroform–ethyl acetate]. Mp 105–110 °C (CH_2Cl_2–hexane); R_f 0.20 [(4 : 1) chloroform–ethyl acetate]; found: M^+ 258.1013. $C_{14}H_{14}N_2O_5$ requires M^+, 258.1004; δ_H(400 MHz, d_6-DMSO) 9.40 (1 H, s, NH), 7.30–7.15 (3 H, m, aromatics), 7.10–7.00 (2 H, m, aromatics), 5.17 (1 H, ddt, *J* 17.1, 10.5 and 5.3, CH_2–C*H*=CH_2), 4.99 (1 H, d, *J* 10.5, C=C*H*H), 4.85 (1 H, d, *J* 17.1, C=CH*H*), 4.73 (1H, m, CH), 4.10 (2 H, ABX, Δ = 51.4 Hz, *J* 15.0, 5.6 and 5.1, NCH_2CH=), 3.24 (1 H, dd, *J* 13.6 and 3.9, PhC*H*H), 3.03 (1 H, dd, *J* 13.6 and 4.8, PhCH*H*), δ_C(67.8 MHz, $CDCl_3$) 167.9, 156.2, 154.3, 133.2, 130.1, 130.0, 128.9, 128.0, 119.5, 57.5, 42.9, 41.1; *m*/*z* 258 (M^+, 8%), 130 (18), 117 (20), 91 (100), 77 (22), 65 (30).

6-Benzyl-4-(4-bromobenzyl)piperazine-2,3,5-trione, 19

5-Benzylpiperazine-2,3,6-trione **5** (201 mg, 0.923 mmol), acetonitrile (6 cm^3), triethylamine (0.103 g, 0.14 cm^3, 1.1 equiv.) and *p*-bromobenzyl bromide (346 mg, 1.384 mmol, 1.5 equiv.) gave the *title compound* as a white solid (231 mg, 65% yield). Mp 188–190 °C; R_f 0.20 [(2 : 1) chloroform–ethyl acetate]; found: C, 55.68; H, 3.99; N, 7.16%. $C_{18}H_{15}BrN_2O_3$ requires C, 55.83; H, 3.90; N, 7.23%; δ_H(400 MHz, d_6-DMSO) 9.44 (1 H, s, NH), 7.43 (2 H, d, *J* 9.1, ArH × 2), 7.28–7.11 (4 H, m, aromatic), 6.98–6.95 (4H, m, aromatic), 4.77 (1 H, m, CH), 4.66 (2 H, AB, Δ = 44.4 Hz, *J* 14.6, NCH_2), 3.23 (1 H, dd, *J* 13.9 and 3.8, PhC*H*H), 3.03 (1 H, dd, *J* 13.9 and 4.9, PhCH*H*); δ_C(67.8 MHz, $CDCl_3$) 162.0, 150.2, 147.0, 127.7, 126.8, 124.7, 123.4, 122.1, 121.7, 50.7, 36.6, 34.3; *m*/*z* 388 (M^+, Br^{81} 4%), 386 (M^+, Br^{79}, 4%), 360 (2), 358 (2), 162 (25), 91 (100).

6-Benzyl-4-(pent-4-enyl)piperazine-2,3,5-trione, 20

5-Benzylpiperazine-2,3,6-trione **5** (218 g, 1.0 mmol), triethylamine (0.15 cm^3, 1.1 equiv.), 5-bromopent-1-ene (0.20 cm^3, 1.7 equiv.) in acetonitrile (6 cm^3) after chromatographic purification [(4 : 1) chloroform–ethyl acetate] gave the *title compound* as a colourless oil which solidifed on standing (186 mg, 65% yield). Mp 82–83 °C; R_f 0.38 [(1 : 1) chloroform–ethyl acetate]; δ_H(400 MHz, $CDCl_3$) 9.03 (1 H, s, NH), 7.26–7.21 (3 H, m, aromatic), 7.11–7.09 (2 H, m, aromatic), 5.77 (1 H, ddt, *J* 17.1, 10.5 and 6.6, CH_2–C*H*=CH_2), 5.03 (1 H, br d, *J* ~16, C=CH*H*), 5.03 (1 H, br d, *J* ~12, C=C*H*H), 4.79 (1 H, br q, *J* 2.4, HN–C*H*–CH_2), 3.71–3.59 (2 H, m, NCH_2), 3.29 (2 H, ABX, Δ = 64.9 Hz, *J* 13.9, 4.4 and 4.4, $PhCH_2$), 2.04–1.95 (2 H, m, CH_2), 1.58–1.40 (2 H, m, CH_2); δ_C(67.8 MHz, $CDCl_3$) 168.2, 156.5, 154.4, 137.0, 133.2, 130.0, 128.8, 127.9, 115.3, 57.4, 41.2, 40.5, 30.8, 26.1; *m*/*z* 286 (M^+, 5%), 91 (100), 43 (40); ν_{max}(Nujol)/cm^{-1} 3550, 1686.

2-(3-Benzyl-2,5,6-trioxopiperazin-1-yl)propionic acid ethyl ester, 21

5-Benzylpiperazine-2,3,6-trione **5** (1.0 g, 4.58 mmol), acetonitrile (20 cm^3), triethylamine (0.75 cm^3, 1.2 equiv.) and ethyl 2-bromopropionate (1.0 cm^3, 1.7 equiv.) gave a 1 : 1 mixture of diastereoisomers of the *title compound* (226 mg, 16% yield) as a colourless oil after chromatographic purification [(3 : 1) chloroform–ethyl acetate]. δ_H (270 MHz, $CDCl_3$) δ first isomer [δ second isomer if resolved] 8.55 [8.45] (1 H, s, NH), 7.31–7.26 (3 H, m, ArH), 7.12–7.17 (2 H, m, ArH), 5.24 [5.13] (1 H, q, *J* 7, C*H*CH_2), 4.75 (1 H, m, C*H*CH_3), 4.17 (2 H, q, *J* 7, CH_2CH_3), 3.31 (2 H, m, CH_2Ph), 1.41 [1.34] (3 H, d, *J* 7, $CHCH_3$), 1.23 (3 H, t, *J* 7, CH_2CH_3); δ_C(67.8 MHz, $CDCl_3$) δ first isomer (δ second isomer) 168.6, 167.5 (167.3), 155.8 (155.6), 153.9 (153.8), 133.3 (133.2), 130.1 (130.0), 129.1 (129.0), 128.1 (128.0), 61.9 (61.8), 57.6 (57.4), 50.2 (50.0), 41.3 (41.0), 14.1, 14.0 (13.9); *m*/*z* 318 (M^+, 4%), 275 (12), 201 (7), 146 (12), 120 (15), 91 (100).

4-Allyl-6-benzyl-6-(4-bromobenzyl)piperazine-2,3,5-trione, 22

To potassium carbonate (0.481 g, 3 equiv.) and 4-allyl-6-benzylpiperazine-2,3,5-trione **18** (0.300 g, 1.163 mmol) in DMF–acetonitrile (1 + 4 cm^3) was added 4-bromobenzyl bromide (0.436 g, 1.5 equiv.). After stirring for several hours at room temperature TLC indicated the consumption of starting material. The mixture was then filtered and the solvent removed *in vacuo*. The resulting residue was purified using silica flash chromatography [(2 : 1) chloroform–ethyl acetate] to

yield the *title compound* (248 mg, 50%). Mp 241–245 °C (dichloromethane–hexane); R_f 0.6 [(1 : 1) dichloromethane–ethyl acetate]; found: C, 59.37; H, 4.61; N, 6.26%. $C_{21}H_{19}BrN_2O_3$ requires C, 59.03; H, 4.48; N, 6.56%; δ_H(400 MHz, $CDCl_3$) 7.59 (1 H, br s, NH), 7.41 (2 H, br d, *J* 8.4, ArH), 7.30–7.29 (3 H, m, ArH), 7.11–7.09 (2 H, m, ArH), 6.99 (2 H, br d, *J* 8.4, ArH), 5.46 (1 H, ddt, *J* 17.1, 10.2 and 6.1, CH_2–C*H*=CH_2), 5.10 (1 H, ddt, *J* 10.2, 1.2 and 1.0, CH_2–CH=CH_{cis}H), 4.97 (1 H, dtd, *J* 17.1, 1.4 and 1.2, CH_2–CH=CHH_{trans}), 4.62 (2 H, ddd, *J* 6.1, 1.4 and 1.0, NCH_2), 3.55 (1 H, d, *J* 13.6, PhCH*H*), 3.52 (1 H, d, *J* 13.7, ArC*H*H), 3.07 (1 H, d, *J* 13.7, PhC*H*H), 3.01 (1 H, d, *J* 13.6, ArCH*H*); δ_C(100 MHz, $CDCl_3$) 169.3, 155.3, 154.8, 133.1, 132.6, 132.0, 131.9, 130.3, 129.6, 128.8, 128.2, 122.2, 119.3, 67.6, 47.4, 45.9, 42.8; ν_{max}(KBr)/cm^{-1} 1695; *m*/*z* 428 (M^+, Br^{81} 1%), 426 (M^+, Br^{79}, 1), 257 (8), 171 (10), 91 (100).

6-Allyl-6-benzyl-4-(4-bromobenzyl)piperazine-2,3,5-trione, 23

Following the method described above, potassium carbonate (0.320 g, 3 equiv.), 1-(4-bromobenzyl)-6-benzylpiperazine-2,3,5-trione **19** (0.300 g, 0.775 mmol), DMF–acetonitrile (1 + 4 cm^3) and allyl bromide (0.10 cm^3, 1.5 equiv.) gave the *title compound* (132 mg, 40%). Mp 197–199 °C (CH_2Cl_2–hexane); R_f 0.57 (ethyl acetate); found: C, 58.74; H, 4.60; N, 6.21%. $C_{21}H_{19}BrN_2O_3$ requires C, 59.03; H, 4.48; N, 6.56%; δ_H(400 MHz, d_6-DMSO) 9.61 (1 H, s, NH), 7.28 (2 H, br d, *J* 8.3, ArH × 2), 7.07 (1 H, br t, *J* 7.1, ArH), 6.98 (2 H, br t, *J* 7.3, ArH × 2), 6.93 (2 H, br d, *J* 8.3, ArH × 2), 6.87 (2 H, br d, *J* 7.3, ArH × 2), 5.57–5.46 (1 H, m, C–CH=C), 5.08–5.02 (2 H, m, C=CH_2), 4.62 (2 H, AB, Δ = 45.9 Hz, *J* 14.0, NCH_2), 3.19 (2 H, d, *J* 13.4, PhCH*H*), 2.88 (2 H, d, *J* 13.4, PhC*H*H), 2.83 (2 H, dd, *J* 13.7 and 6.1, C*H*H–C=C), 2.51 (2 H, dd, *J* 13.7 and 7.3, CH*H*–C=C); δ_C(68.7 MHz, $CDCl_3$) 170.0, 156.3, 154.9, 133.9, 133.1, 131.6, 131.3, 130.1, 129.7, 128.7, 127.9, 122.4, 122.2, 66.5, 47.0, 44.9, 43.5; *m*/*z* 428 (M^+, Br^{81} 1%), 426 (M^+, Br^{79}, 1), 91 (100).

(3,3-Dibenzyl-2,5,6-trioxopiperazin-1-yl)acetic acid methyl ester, 24

Anhydrous potassium carbonate (50 mg, 2 equiv.) and trione **7** (49 mg, 0.16 mmol) were dissolved in DMF (4 cm^3) with stirring, then benzyl bromide (32 μl, 0.27 mmol) was added. After 0.25 h the solvent was removed *in vacuo*, and the solid obtained was triturated thoroughly with chloroform (2 × 5 ml). After combination of the organic fractions and removal of the solvent the residue was purified using silica flash chromatography [eluent (4 : 1) chloroform–ethyl acetate] to yield 50 mg (78%) of the dibenzyl derivative **24**. Mp 196–199 °C (chloroform-hexane); R_f 0.53 [(1 : 1) chloroform-ethyl acetate]; Found: MH^+ 381.1460. $C_{21}H_{21}N_2O_5$ requires MH^+, 381.1450; δ_H(300 MHz, $CDCl_3$) 9.15 (1 H, broad s, NH), 7.32–7.26 and 7.15–7.12 (10 H, m, Ph), 4.24 (2 H, s, NCH_2), 3.65 (3 H, s, CO_2Me), 3.59 [2 H, d, *J* 13.6, two protons from $(PhCH_2)_2C$], 3.10 [1 H, dd, *J* 14.0 and 3.2, other two protons from $(PhCH_2)_2C$]; δ_C(22.5 MHz, $CDCl_3$) 169.7 (s), 166.3 (s), 155.3 (s), 154.3 (s), 133.4 (s), 130.3 (d), 128.7 (d), 128.0 (d), 67.9 (s), 52.5 (q), 46.8 (t), 41.1 (t); ν_{max}($CHCl_3$)/cm^{-1} 3680, 1750, 1710; *m*/*z* 381 (MH^+).

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9 The PC software used for molecular modelling was CS Chem3D Pro v 5.0, from CambridgeSoft Corporation, and Nemesis for Windows v 2.0, from Oxford Molecular.

10 Crystal data for **17**: colourless crystal (0.80 × 0.52 × 0.16 mm) from ethyl acetate–hexane, coated with Nujol and mounted on a glass fibre, $C_{20}H_{22}N_2O_3$, M = 338.40, monoclinic, space group $P2_1/c$, a = 8.813(8), b = 11.418(12), c = 18.102(17) Å, β = 103.540(7)°, V = 1770.9(4) Å^3, Z = 4, D_c = 1.269 g cm^{-3}, μ = 0.086 mm^{-1}. $R1$ = 0.0372, for 2579 unique observed [$I > 2\sigma(I)$] data; $R1$ = 0.0476 $wR2$ = 0.1010 and goodness of fit 1.022 for all 3115 data and 226 parameters. Full data have been deposited with the Cambridge Crystallographic Data Centre. CCDC reference number 135218. See http://www.rsc.org/suppdata/p1/b1/b108872f/ for crystallographic files in .cif or other electronic format.

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