

Chiral glycine cation equivalents: *N*-acyliminium species derived from diketopiperazines



Steven D. Bull, Stephen G. Davies,* A. Christopher Garner, Michael D. O'Shea, Edward D. Savory and Emma J. Snow

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY. E-mail: steve.davies@chemistry.ox.ac.uk

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Studies towards a *N,N'*-bis(*p*-methoxybenzyl)diketopiperazine asymmetric glycine cation equivalent for the synthesis of homochiral α -amino acids are described. The oxidation of enolate **3** with molecular oxygen provides either a mixture of hydroxylated diketopiperazines **7** and **8** or trione **10** depending upon the reaction conditions. The nucleophilic reduction of trione **10** and the reaction of acetoxy *N*-acyliminium ion precursors **5** and **6**, derived from **7** and **8**, with allyltrimethylsilane and boron trifluoride etherate is examined and a model for the stereoselectivity observed in these additions is presented.

Introduction

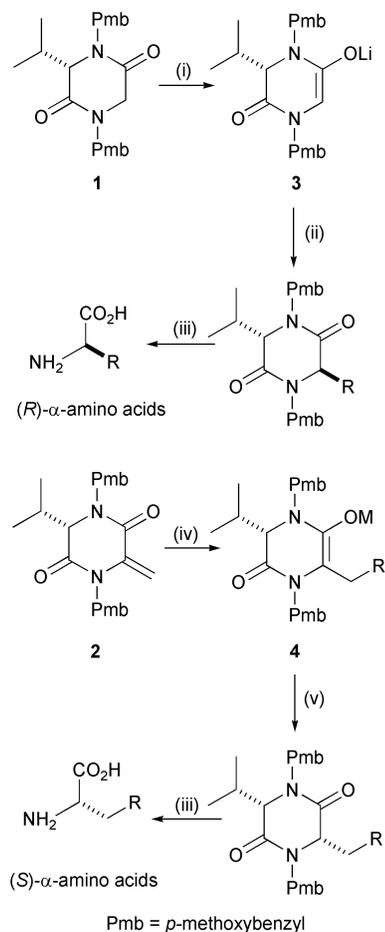
There are many auxiliary based asymmetric syntheses of α -amino acids that employ chiral glycine anion equivalents.¹ Auxiliaries acting as chiral glycine cation equivalents are less common,² although a number of cyclic chiral auxiliaries of this type have been described.³ We have recently reported two new diketopiperazine derived chiral auxiliaries **1** and **2** for the asymmetric synthesis of homochiral α -amino acids based upon the alkylation of chiral glycine anion equivalent **1**,⁴ and conjugate addition and protonation of chiral dehydroalanine acceptor **2** (Scheme 1).⁵ The high diastereoselectivities obtained for *trans*-alkylation of the enolate **3** with electrophiles to afford (*R*)- α -amino acids, and the selectivity in protonation of intermediate enolate **4** derived from **2** to afford (*S*)- α -amino acids, have been proposed to arise from a novel chiral relay effect operating to control and enhance facial selectivity.⁴⁻⁶

We report herein studies on a glycine cation substitution strategy for the asymmetric synthesis of α -amino acids based on additions of allyltrimethylsilane to *N*-acyliminium species derived from a diketopiperazine chiral auxiliary.

Results and discussion

N-Acyl-*O*-acetyl-*N,O*-aminals have found extensive application as precursors for the generation of *N*-acyliminium species under Lewis acidic conditions.⁷ Therefore it was envisaged that acetoxy substituted diketopiperazines **5** or **6** should provide access to *N*-acyliminium species under similar conditions.^{8,9} Initial synthetic efforts were directed towards the preparation of alcohols **7** and **8** via the addition of oxygen (O₂) to a THF solution of the lithium enolate **3** to afford a separable 2 : 1 mixture of (3*R*,6*S*)-**7** and (3*S*,6*S*)-**8** in moderate yields (36% and 25% respectively) (Scheme 2).¹⁰ Acetylation of **7** or **8** with acetic anhydride and DMAP in pyridine then provided (3*R*,6*S*)-acetate **5** and the corresponding (3*S*,6*S*)-acetate **6** respectively in good yields (88% and 83% respectively).

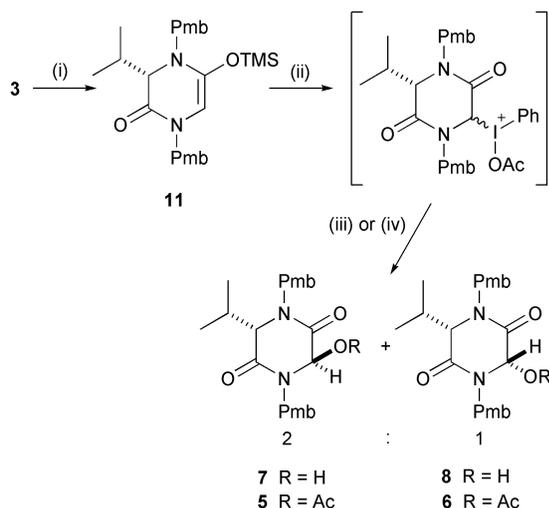
The relative configurations within diastereoisomeric alcohols **7** and **8** were determined from inspection of the ¹H NMR spectroscopic data. Examination of ¹H NMR data for simple alkyl substituted diketopiperazines^{4,5} reveals that the difference in chemical shift between the two diastereotopic C-3 isopropyl methyl groups is diagnostic for the relative (*cis* or *trans*) con-



Scheme 1 Reagents and conditions: (i) LHMDs, THF, -78°C ; (ii) alkyl halide, THF, -78°C ; (iii) CAN (6 equivalents), H₂O, CH₃CN; 6 M HCl, 100°C ; (iv) 2 \times RMgX or 2 \times RLi, CuCN, BF₃·OEt₂, THF, -78°C ; (v) NH₄Cl (aq).

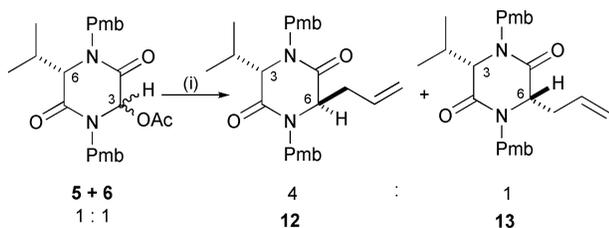
figuration of the C-3 and C-6 ring substituents. For *cis* substituted diketopiperazines, derived from conjugate addition methodology, the chemical shift differences lie in the range 0.01–0.13 ppm⁵ while the corresponding differences in chemical shift for the *trans*-alkylation products lie in the range of 0.20–

which diastereoisomerically pure samples of **5** and **6** could be obtained by column chromatography (Scheme 5).



Scheme 5 Reagents and conditions: (i) TMSCl, 30 min, THF, -78°C ; (ii) PhI(OAc)₂, THF, -78°C ; (iii) H₂O, room temperature; (iv) NaOAc, room temperature.

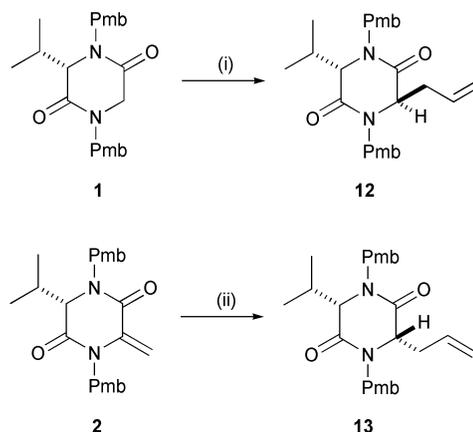
The suitability of acetates **5** and **6** to act as glycine cation equivalents was next examined. Treatment of a 1 : 1 mixture of *trans*-acetate **5** and *cis*-acetate **6** with allyltrimethylsilane and BF₃·OEt₂ in CH₂Cl₂ at -78°C afforded a clean mixture of (3*S*,6*R*)-**12** and (3*S*,6*S*)-**13**, in a 4 : 1 ratio, that were separated in good yield *via* chromatography (64% and 8% respectively) (Scheme 6).



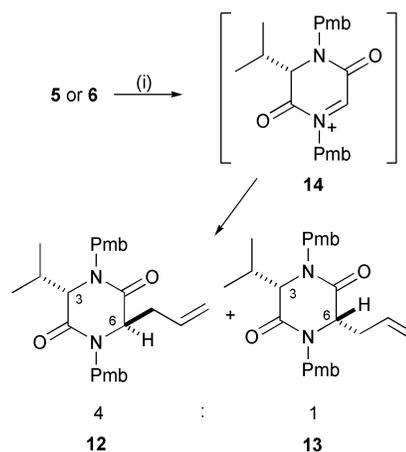
Scheme 6 Reagents and conditions: (i) CH₂=CHCH₂SiMe₃, BF₃·OEt₂, CH₂Cl₂, -78°C .

The relative configurations within *trans*-(3*S*,6*R*)-**12** and *cis*-(3*S*,6*S*)-**13** were evident from ¹H NMR spectroscopic data with both compounds exhibiting diagnostic isopropyl methyl group chemical shift differences (*trans*-(3*S*,6*R*)-**12** $\Delta\delta_{\text{Me}} = 0.26$ ppm; *cis*-(3*S*,6*S*)-**13** $\Delta\delta_{\text{Me}} = 0.08$ ppm). The major isomer (3*S*,6*R*)-**12** was confirmed unambiguously as *trans* by comparison with an authentic sample prepared from the stereoselective alkylation of the enolate of **1** with allyl bromide.⁴ The identity of the minor diastereoisomer (3*S*,6*S*)-**13** was confirmed unambiguously *via* comparison with the product obtained from vinyl cuprate addition to α,β -unsaturated acceptor **2**, a procedure which exclusively provides *cis* configured diketopiperazines (Scheme 7).⁵

In order to establish whether an *N*-acyliminium species was an intermediate in this transformation, diastereoisomerically pure *trans*-acetate **5** was treated with allyltrimethylsilane and BF₃·OEt₂ to afford a clean 4 : 1 mixture of (3*S*,6*R*)-**12** and (3*S*,6*S*)-**13**. Similar treatment of diastereoisomerically pure *cis*-acetate **6**, also afforded a 4 : 1 mixture of (3*S*,6*R*)-**12** and (3*S*,6*S*)-**13** (Scheme 8). The formation of the same ratio of **12** and **13** from either **5** or **6** or a 1 : 1 mixture thereof in these reactions is consistent with the initial formation of an *N*-acyliminium ion **14**. This species then reacts with allyltrimethylsilane by preferential addition to the *Re* face of *N*-acyliminium species **14**, *anti* to the C-3 isopropyl group.



Scheme 7 Reagents and conditions: (i) LHMDs, THF, -78°C ; CH₂=CHCH₂Br; (ii) 2 × CH₂=CHMgCl, CuCN, BF₃·OEt₂, THF, -78°C ; NH₄Cl (aq).



Scheme 8 Reagents and conditions: (i) CH₂=CHCH₂SiMe₃, BF₃·OEt₂, CH₂Cl₂, -78°C .

The facial selectivity of this addition is markedly lower (60% de) than that observed for alkylation of enolate **3** with allylbromide (94% de) and for the protonation of conjugate addition intermediates (>95% de). In these systems a chiral relay mechanism, resulting from the conformational preference of the *N*-*p*-methoxybenzyl protecting groups, is operating⁴⁻⁶ and molecular modelling suggests a similar conformation and chiral relay for *N*-acyliminium intermediate **14** and trione **10**.¹⁵ If the reaction of **14**, **3** and **10** occurs on a trajectory perpendicular to the plane of the diketopiperazine ring then similar selectivities in the reaction of each of the species would be expected. However, the steric interactions encountered on the *Re* and *Si* faces of the auxiliary will vary considerably if the reaction of species **14**, **3** and **10** occur *via* trajectories close to the Bürgi–Dunitz angle.¹⁶ The observed variation in selectivity may then derive from the different directions of reagent approach due to the inherent structural differences between *N*-acyliminium ion **14**, enolate **3** and trione **10** (Fig. 2).

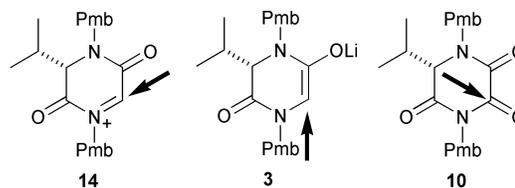


Fig. 2 Directions of reagent approach to reactive species **14**, **3** and **10**.

Thus, the reaction of the *N*-acyliminium ion **14** with allyltrimethylsilane preferentially occurs on the *Re* face of the auxiliary (60% de), as seen for the alkylation of enolate **3**

(94% de). However, the required direction of approach of allyltrimethylsilane to *N*-acyliminium species **14** results in less effective blocking of the *Si* face by the *N*¹-*p*-methoxybenzyl and C-3 isopropyl groups (Fig. 3, A) in comparison to the

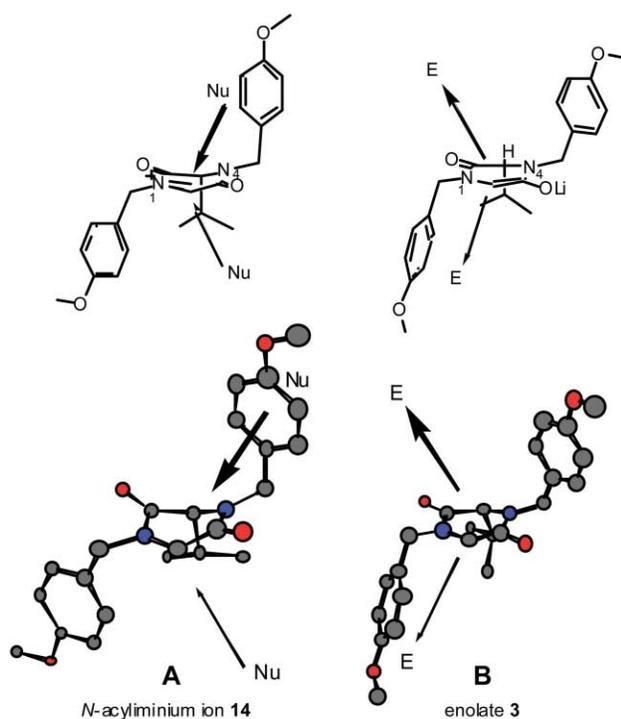


Fig. 3 Trajectories of approach to minimised molecular models: A; **14** and B; **3**.¹⁵

approach of an electrophile to the *Si* face of enolate **3** from the alternative direction, resulting in lower diastereoselectivity (Fig. 3, B). Alternatively, it cannot be discounted that the *N*-acyliminium–allyltrimethylsilane system may also be inherently more reactive than the corresponding enolate alkylation reaction and hence exhibit poorer selectivity.

Similarly, the reduction of trione **10** with diisobutylaluminum hydride proceeds with *Re* face selectivity to afford a 1 : 4 mixture of alcohols *trans*-**7** and *cis*-**8**. In this system the direction of approach to the carbonyl group, over the diketopiperazine ring, leads to preferred addition to the *Re* face due to hindrance of the *Si*-face by the isopropyl group. The moderate levels of diastereoselectivity observed in this system may reflect a competing steric interaction with the *N*⁴-protecting group on the *Re* face (Fig. 4, C).

Conclusion

We have exploited the ready oxidation of the enolate of diketopiperazine **1** in the preparation of *N*-acyliminium ion precursors **5** and **6**. The addition of allyltrimethylsilane, under Lewis acidic conditions, to **5** and **6** proceeds with *Re* facial selectivity, consistent with the intermediacy of an *N*-acyliminium species.

Experimental

General experimental

All reactions involving organometallic or moisture sensitive reagents were performed under an atmosphere of nitrogen *via* standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. In all cases, the reaction diastereoselectivity was assessed by peak integration in the ¹H NMR spectrum of the crude reaction mixture. Tetrahydrofuran

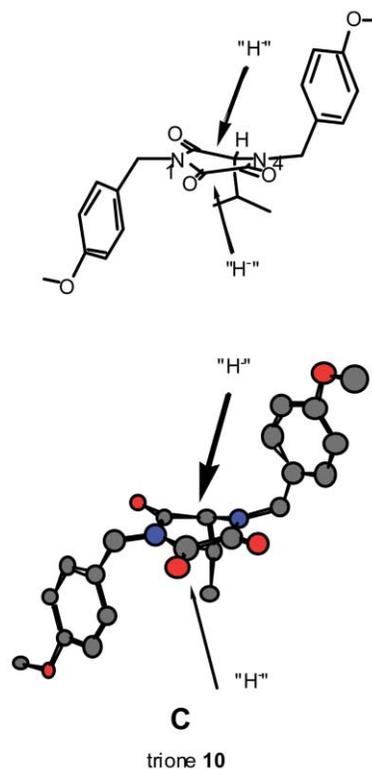


Fig. 4 Trajectories of approach to minimised molecular model: C; trione **10**.¹⁵

was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. Thin layer chromatography was performed on aluminium sheets coated with 60 F₂₅₄ silica. Sheets were visualised using 10% phosphomolybdic acid in ethanol. Flash chromatography was performed on Kieselgel 60 silica. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC 200 (¹H: 200 MHz and ¹³C: 50.3 MHz), Bruker DPX 400 (¹H: 400 MHz and ¹³C: 100.6 MHz) or Bruker AMX 500 (¹H: 500 MHz and ¹³C: 125 MHz) spectrometer in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (*J*) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. ¹³C multiplicities were assigned using a DEPT sequence. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted in cm⁻¹. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm; [α]_D values are given in units of 10⁻¹ deg cm² g⁻¹. Concentrations are quoted in g/100 ml. Low resolution mass spectra were obtained upon a VG micromass ZAB IF, a VG MassLab 20–250, a VG Bio Q or an APCI Platform spectrometer with only molecular ions, fragments from molecular ions and major peaks being reported. High resolution mass spectroscopic data was obtained upon Micromass AutoSpec or Micromass ToFSpec spectrometers. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford.

Note. CAUTION: Explosion Hazard. Reactions involving molecular oxygen in THF were performed with glassware and magnetic stirrers that had been sequentially rinsed with concentrated HCl, distilled water and acetone, then oven dried and cooled under vacuum. Reactions were performed behind a blast shield.

(3*S*,6*S*)- and (3*S*,6*R*)-*N,N'*-Bis(*p*-methoxybenzyl)-6-hydroxy-3-isopropylpiperazine-2,5-dione **7 and **8****

CAUTION: Explosion Hazard: see Note in General experimental section.

To a solution of (3*S*)-*N,N'*-bis(*p*-methoxybenzyl)-3-isopropylpiperazine-2,5-dione **1** (1.00 g, 2.52 mmol) in dry THF (40 ml) at $-78\text{ }^{\circ}\text{C}$ was added lithium hexamethyldisilazide (3.0 ml, 1 M solution in THF, 3.0 mmol). After stirring (1 h at $-78\text{ }^{\circ}\text{C}$) the mixture was purged with a stream of oxygen for 15 min at $-78\text{ }^{\circ}\text{C}$ and then stirred for a further 30 min. Saturated aqueous sodium metabisulfite (3 ml) was added followed by saturated NH_4Cl (10 ml) then the THF was removed *in vacuo* and the residue partitioned between water and ether. The aqueous phase was extracted with ether and the combined organic layers were dried (MgSO_4) and the solvent removed to afford a 2 : 1 mixture of **7** and **8** respectively. Chromatography (silica, 1 : 1 ether–hexane) gave *trans*-alcohol **7** (383 mg, 37%). Mp $112\text{--}114\text{ }^{\circ}\text{C}$ (ether) (Found: C, 66.9; H, 7.0; N, 6.6. $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_5$ requires C, 67.0; H, 6.8; N, 6.8%); $[\alpha]_{\text{D}}^{23} +9.6$ (c 0.35, CHCl_3); ν_{max} (film)/ cm^{-1} 3281 (OH), 1659 (NC=O), 1635; δ_{H} (500 MHz, CDCl_3) 0.80 (3H, d, J 6.9, CH_3CHCH_3), 1.04 (3H, d, J 6.9, CH_3CHCH_3), 2.14 (1H, dsept, J 6.9, 5.2, CH_3CHCH_3), 3.75 (1H, d, J 5.2, 3-*H*), 3.80 (6H, s, $2 \times \text{OMe}$), 3.93 (1H, d, J 14.7, ArCH_2), 4.27 (1H, d, J 13.9, ArCH_2), 4.55 (1H, br s, OH), 5.06 (1H, s, CHOH), 5.18 (1H, d, J 13.9, ArCH_2), 5.33 (1H, d, J 14.7, ArCH_2), 6.84–6.87 (4H, m, *ortho-H* ArOMe), 7.14 (2H, m, aromatic *H*), 7.37 (2H, m, aromatic *H*); δ_{C} (125 MHz, CDCl_3) 18.0, 19.8, 32.1, 43.9, 48.5, 55.2, 55.3, 64.9, 74.0, 113.8, 114.4, 126.8, 128.2, 129.5, 130.7, 159.1, 159.5, 164.6, 167.0; m/z (APCI⁺) 413 (MH^+ , 2%), 395 ($\text{MH}^+ - \text{H}_2\text{O}$, 12), 121 (100).

Further elution provided *cis*-alcohol **8** as a colourless solid (256 mg, 25%). Mp $126\text{--}127\text{ }^{\circ}\text{C}$ (ether); $[\alpha]_{\text{D}}^{23} -172.3$ (c 0.30, CHCl_3); ν_{max} (film)/ cm^{-1} 3204 (OH), 1658 (NC=O), 1636; δ_{H} (500 MHz, CDCl_3) 1.04 (3H, d, J 6.9, CH_3CHCH_3), 1.15 (3H, d, J 6.9, CH_3CHCH_3), 2.34 (1H, dsept, J 6.9, 5.1, CH_3CHCH_3), 3.74 (1H, d, J 5.1, 3-*H*), 3.79 (3H, s, *OMe*), 3.81 (3H, s, *OMe*), 3.91 (1H, d, J 14.8, ArCH_2), 4.29 (1H, d, J 14.5, ArCH_2), 4.61 (1H, d, J 4.4, OH), 4.98 (1H, d, J 14.5, ArCH_2), 5.12 (1H, d, J 4.4, CHOH), 5.30 (1H, d, J 14.8, ArCH_2), 6.82–6.86 (4H, m, *ortho-H* ArOMe), 7.12–7.21 (4H, m, aromatic *H*); δ_{C} (125 MHz, CDCl_3) 18.1, 20.3, 31.9, 46.2, 48.0, 55.2, 55.3, 64.5, 77.5, 114.1, 114.3, 127.0, 127.8, 129.6, 130.1, 159.3, 159.4, 165.6, 166.0; m/z (APCI⁺) 413 (MH^+ , 1%), 395 ($\text{MH}^+ - \text{H}_2\text{O}$, 12), 121 (100) [HRMS (Cl^+) Found: 413.2076. $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_5^+$ requires 413.2076].

(6*S*,3*R*)-*N,N'*-Bis(*p*-methoxybenzyl)-3-acetoxy-6-isopropylpiperazine-2,5-dione **5**

To alcohol **7** (100 mg, 0.24 mmol) in pyridine (3 ml) was added DMAP (10 mg, 0.08 mmol) then acetic anhydride (2 ml). The mixture was stirred for 12 h then partitioned between ether and saturated aqueous CuSO_4 and the organic layer washed with saturated aqueous CuSO_4 , dried (MgSO_4), and the solvent removed *in vacuo*. Chromatography (silica, 1 : 1 ether–hexane) gave **5** as a colourless solid (97 mg, 88%). Mp $148\text{ }^{\circ}\text{C}$ (ether) (Found: C, 66.1; H, 6.7; N, 6.1. $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_4$ requires C, 66.1; H, 6.7; N, 6.2%); $[\alpha]_{\text{D}}^{23} -125.5$ (c 1.00, CHCl_3); ν_{max} (KBr)/ cm^{-1} 2962, 2834, 1750 ($\text{CH}_3\text{C}=\text{O}$), 1678 (NC=O), 1615; δ_{H} (400 MHz, C_6D_6) 0.62 (3H, d, J 6.9, CH_3CHCH_3), 1.14 (3H, d, J 7.0, CH_3CHCH_3), 1.75 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.04 (1H, m, CH_3CHCH_3), 3.34 (6H, s, $2 \times \text{OMe}$), 3.80 (1H, d, J 14.9, ArCH_2), 3.99 (1H, d, J 3.4, 3-*H*), 4.14 (1H, d, J 14.4, ArCH_2), 5.06 (1H, d, J 14.4, ArCH_2), 5.32 (1H, d, J 14.9, ArCH_2), 6.51 (1H, s, CHOAc), 6.75–6.83 (4H, m, *ortho-H* ArOMe), 7.17–7.21 (2H, m, aromatic *H*), 7.41–7.45 (2H, m, aromatic *H*); δ_{C} (50 MHz, CDCl_3) 16.2, 19.5, 20.7, 31.4, 45.8, 46.7, 55.2, 55.3, 63.0, 76.2, 113.9, 114.3, 126.7, 127.4, 129.7, 130.3, 159.3, 159.4,

161.7, 164.9, 169.5; m/z (APCI⁺) 455 (MH^+ , 0.2%), 395 ($\text{M}^+ - \text{OAc}$, 70), 121 (100).

X-Ray crystal structure data for **5.** Data were collected using a Nonius Kappa CCD diffractometer with graphite monochromated Mo- $\text{K}\alpha$ radiation using standard procedures at 190 K. The structure was solved by direct methods (Sir92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.¹⁷

Crystal data for **5** [$\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_4$], colourless block, $M = 454.52$, orthorhombic, space group $P2_12_12_1$, $a = 7.4482(1)\text{ \AA}$, $b = 10.8159(2)\text{ \AA}$, $c = 29.5153(4)\text{ \AA}$, $U = 2377.7\text{ \AA}^3$, $Z = 4$, $\mu = 0.091$, crystal dimensions $0.4 \times 0.4 \times 0.4\text{ mm}$. A total of 3044 unique reflections were measured for $4.55 < \theta < 27.50$ and 2646 reflections were used in the refinement. The final parameters were $wR_2 = 0.0201$ and $R_1 = 0.0325$ [$I > 3\sigma(I)$].

CCDC reference number 187479. See <http://www.rsc.org/suppdata/p1/b2/b207457p/> for crystallographic files in .cif or other electronic format.

(6*S*,3*S*)-*N,N'*-Bis(*p*-methoxybenzyl)-3-acetoxy-6-isopropylpiperazine-2,5-dione **6**

To alcohol **8** (100 mg, 0.24 mmol) in pyridine (3 ml) was added DMAP (10 mg, 0.08 mmol) followed by acetic anhydride (2 ml). The mixture was stirred for 12 h at room temperature then partitioned between ether saturated aqueous CuSO_4 and the organic layer washed with saturated aqueous CuSO_4 , dried (MgSO_4), and the solvent removed *in vacuo*. Chromatography (silica, 1 : 1 ether–hexane) gave **6** as a colourless oil (91 mg, 83%). $[\alpha]_{\text{D}}^{23} -139.4$ (c 1.20, CHCl_3); ν_{max} (film)/ cm^{-1} 2964, 2837, 1757 ($\text{CH}_3\text{C}=\text{O}$), 1681 (NC=O), 1612, 1585, 1248, 1216; δ_{H} (400 MHz, CDCl_3) 1.06 (3H, d, J 6.8, CH_3CHCH_3), 1.17 (3H, d, J 6.9, CH_3CHCH_3), 2.00 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.33 (1H, m, CH_3CHCH_3), 3.72 (1H, d, J 6.2, 3-*H*), 3.80 (3H, s, *OMe*), 3.81 (3H, s, *OMe*), 3.83 (1H, d, J 14.8, ArCH_2), 4.30 (1H, d, J 14.5, ArCH_2), 4.77 (1H, d, J 14.5, ArCH_2), 5.34 (1H, d, J 14.8, ArCH_2), 6.46 (1H, s, CHOAc), 6.81–6.86 (4H, m, *ortho-H* ArOMe), 7.06–7.21 (4H, m, aromatic *H*); δ_{C} (50 MHz, CDCl_3) 18.6, 20.4, 20.7, 32.4, 47.4, 48.3, 55.2 ($\times 2$), 64.6, 76.9, 114.0, 114.3, 126.9, 128.0, 129.5, 129.8, 159.3, 159.4, 161.4, 167.1, 169.6; m/z (APCI⁺) 455 (MH^+ , 0.3%), 395 ($\text{M}^+ - \text{OAc}$, 85), 121 (100) [HRMS (TOF FI) Found: M^+ , 454.2115. $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_6$ requires 454.2104].

Oxidation of **1 with (diacetoxyiodo)benzene**

To a solution of **1** (5.0 g, 12.6 mmol) in dry THF (100 ml) was added lithium hexamethyldisilazide (13.9 ml, 1 M solution in THF, 13.9 mmol) at $-78\text{ }^{\circ}\text{C}$. After stirring (1 h at $-78\text{ }^{\circ}\text{C}$) this mixture was treated with chlorotrimethylsilane (1.75 ml, 13.9 mmol) and the mixture stirred for 30 min at $-78\text{ }^{\circ}\text{C}$ before (diacetoxyiodo)benzene (4.47 g, 13.9 mmol) was added. This mixture was stirred (2 h, $-78\text{ }^{\circ}\text{C}$) then sodium acetate (2.0 g, 33.4 mmol) was added and the mixture stirred (3 h, $-78\text{ }^{\circ}\text{C}$) then warmed to room temperature over 12 h. Saturated NH_4Cl (50 ml) and water (500 ml) was added and the mixture extracted with ether, the organic layer was dried (MgSO_4) and the solvent removed to afford a 2 : 1 mixture of *trans*- and *cis*- acetates **5** and **6** respectively. Chromatography (silica, ether–hexane 1 : 1) gave *cis*- acetate **6** as a colourless oil (0.96 g, 17%). Further elution provided mixed fractions of **5** and **6** (2.85 g, 50%) followed by *trans*-acetate **5** as a colourless solid (0.51 g, 9%). Spectroscopic properties were identical to those described above.

Similar treatment of **1** (200 mg) with lithium hexamethyldisilazide (0.60 ml, 1 M solution in THF), chlorotrimethylsilane (0.10 ml), (diacetoxyiodo)benzene (177 mg) omitting the addition of sodium acetate afforded a 2 : 1 mixture of *trans*- and *cis*-alcohols **7** and **8** respectively (166 mg, 83%).

(5S)-N,N'-Bis(*p*-methoxybenzyl)-5-isopropylpiperazine-2,3,6-trione **10**

Alcohols **7** and **8** (1 : 4 mixture of **7** and **8**, 200 mg, 0.48 mmol) and *o*-iodoxybenzoic acid (630 mg, 2.25 mmol)¹⁸ were stirred in DMSO (3 ml) for 48 h at room temperature. The mixture was then partitioned between ether (50 ml) and water (50 ml) and the aqueous phase extracted with ether. The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to yield the crude product. Purification by flash column chromatography (silica, 1 : 1 ether–hexane) yielded trione **10** as a colourless solid (165 mg, 83%). Mp 116 °C; [α]_D²³ –108.9 (*c* 0.63, CHCl₃); ν_{\max} (KBr)/cm⁻¹ 2969, 1735 (CH₃C=O), 1675 (NC=O), 1514, 1241; δ_{H} (400 MHz, CDCl₃) 0.60 (3H, d, *J* 7.0, CH₃CHCH₃), 0.96 (3H, d, *J* 7.0, CH₃CHCH₃), 2.22 (1H, m, CH₃CHCH₃), 3.78 (3H, s, *OMe*), 3.80 (3H, s, *OMe*), 3.97 (1H, d, *J* 3.6, 3-*H*), 3.99 (1H, d, *J* 13.5, ArCH₂), 4.87 (1H, d, *J* 13.5, ArCH₂), 4.92 (1H, d, *J* 13.5, ArCH₂), 5.35 (1H, d, *J* 14.7, ArCH₂), 6.79–7.41 (8H, m, aromatic *H*); δ_{C} (100 MHz, CDCl₃) 15.9, 18.6, 31.9, 43.6, 47.9, 55.2, 55.3, 64.5, 113.7, 114.5, 126.2, 127.4, 130.1, 131.3, 153.5, 157.2, 159.4, 159.7, 166.8; *m/z* (APCI+) 411 (MH⁺, 10%), 121 (ArCH₂⁺, 100%) [HRMS (CI⁺) Found: MH⁺, 411.1908. C₂₃H₂₇N₂O₅⁺ requires 411.1920].

Preparation of trione **10** via O₂ oxidation of **1**

CAUTION: Explosion Hazard: see Note in General experimental section.

Lithium hexamethyldisilazide (0.55 ml, 1 M in THF, 0.55 mmol) was added to **1** (200 mg, 0.50 mmol) in dry THF (10 ml) at –78 °C. After stirring for 1 h at –78 °C the solution was placed under an atmosphere of oxygen and stirred (2 h, –78 °C) before addition of acetic anhydride (0.20 ml, 1.81 mmol). The mixture was left to warm to room temperature overnight, before addition of sodium metabisulfite (500 mg) in water (5 ml). The mixture was partitioned between ether (50 ml) and water (50 ml) and the aqueous phase extracted with ether. The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to yield a mixture containing **10**, **7** and **8** in a ratio of 10 : 2 : 1 respectively (212 mg). Chromatography (silica, 4 : 1 ether–hexane) provided **10** contaminated with **7** (*ca.* 20%, 118 mg).

DIBAL-H reduction of trione **10**

DIBAL-H (0.27 ml, 1 M solution in THF, 0.27 mmol) was added to trione **10** (100 mg, 0.24 mmol) in THF at –78 °C. The mixture was stirred for 4 h at –78 °C and then allowed to warm to room temperature over 12 h. Saturated aqueous NH₄Cl (1 ml) and water (50 ml) were added and the mixture extracted with ether. The organic layer was dried (MgSO₄) and the solvent removed to afford a mixture containing *cis*- and *trans*-alcohols **7** and **8** in a ratio of 4 : 1. Chromatography (silica, 1 : 1 ether–hexane) gave *cis*-alcohol **6** as a colourless oil (69 mg, 69%). Spectroscopic properties were identical to those described above.

(3S,6S)- and (3S,6R)-N,N'-Bis(*p*-methoxybenzyl)-6-allyl-3-isopropylpiperazine-2,5-dione **12** and **13**

To a mixture of *cis*- and *trans*-acetates **5** and **6** (1 : 1, 1.0 g, 2.20 mmol) and allylsilane (0.38 ml, 2.4 mmol) in dichloromethane was added boron trifluoride–diethyl ether (0.30 ml, 2.4 mmol) and the mixture stirred for 4 h at –78 °C. Saturated aqueous NH₄Cl was added and the mixture extracted with ether, the organic phase dried (MgSO₄) and the solvent removed to provide a gum. ¹H NMR spectra of the crude material indicated a 4 : 1 mixture of *trans* to *cis* allyl products **12** and **13** (60% de). Chromatography (silica, 1 : 1 ether–hexane) gave *trans*-allyl isomer **12** as a colourless solid (613 mg, 64%). [α]_D²³ +23.6 (*c* 1.00, CHCl₃) (lit.⁴ [α]_D²³ +25.8 (*c* 0.99, CHCl₃)); δ_{H} (400 MHz, CDCl₃) 0.84 (3H, d, *J* 7.0, CH₃CHCH₃), 1.10 (3H, d, *J* 7.0,

CH₃CHCH₃), 2.31 (1H, m, CH₃CHCH₃), 2.78 (1H, dt, *J* 12.5, 6.0, CH₂CH=CH₂), 2.97 (1H, ddt, *J* 15.0, 7.0 and 1.0, CH₂CH=CH₂), 3.78 (1H, d, *J* 4.0, 3-*H*), 3.80 (1H, d, *J* 15.5, ArCH₂), 3.81 (3H, s, *OMe*), 3.81 (3H, s, *OMe*), 3.81 (1H, d, *J* 14.5, ArCH₂), 3.99 (1H, dd, *J* 5.0, 2.5, 6-*H*), 5.12 (1H, d, *J* 10.5, CH₂CH=CH₂), 5.19 (1H, dd, *J* 17, 1.5, CH₂CH=CH₂), 5.41 (1H, d, *J* 14.5, ArCH₂), 5.53 (1H, d, *J* 15.0, ArCH₂), 5.54 (1H, m, CH₂CH=CH₂), 6.85 (2H, m, aromatic *H*), 6.87 (2H, m, aromatic *H*), 7.16 (2H, m, aromatic *H*), 7.23 (2H, m, aromatic *H*). Spectroscopic data identical to that of an authentic sample.⁴

Further elution provided *cis*-allyl isomer **13** as a clear oil (82 mg, 8%). [α]_D²³ –137.8 (*c* 1.00, CHCl₃); ν_{\max} (KBr)/cm⁻¹ 1660 (NC=O), 1513, 1248; δ_{H} (500 MHz, CDCl₃) 1.09 (3H, d, *J* 6.8, CH₃CHCH₃), 1.17 (3H, d, *J* 6.9, CH₃CHCH₃), 2.19 (1H, dsept, *J* 6.9, 6.9, CH₃CHCH₃), 2.56–2.65 (1H, m, CH₂CH=CH₂), 2.70–2.78 (1H, m, CH₂CH=CH₂), 3.67 (1H, d, *J* 7.0, 3-*H*), 3.79 (3H, s, *OMe*), 3.79 (3H, s, *OMe*), 3.83 (1H, d, *J* 14.8, ArCH₂), 3.93 (1H, d, *J* 14.8, ArCH₂), 3.96 (1H, t, *J* 6.6, 6-*H*), 5.15 (1H, br t, *J* 1.2, CH₂CH=CH₂), 5.13–5.20 (1H, m, CH₂CH=CH₂), 5.22 (1H, d, 14.8, ArCH₂), 5.35 (1H, d, *J* 14.8, ArCH₂), 5.87–5.97 (1H, m, CH₂CH=CH₂), 6.80–6.85 (4H, m, *ortho*-H ArOMe), 7.03–7.10 (4H, m, aromatic *H*); δ_{C} (125 MHz, CDCl₃) 19.2, 20.4, 32.8, 38.5, 46.8, 48.5, 54.9 (× 2), 58.9, 64.7, 113.9, 118.0, 127.5, 127.6, 128.9, 129.1, 133.8, 158.9, 165.5, 166.4; *m/z* (CI) 437 (MH⁺, 100%) [HRMS (CI⁺) Found: MH⁺, 437.2443. C₂₆H₃₃N₂O₄ requires 437.2440].

Treatment of either pure *trans*-acetate **5** or pure *cis*-acetate **6** under the same conditions gave similar crude mixtures with ¹H NMR spectra showing a 4 : 1 ratio of *trans* to *cis* allyl products **12** and **13** (60% de).

Preparation of **13** via cuprate addition

To a flame dried Schlenk tube charged with anhydrous copper(I) cyanide (267 mg, 2.94 mmol) and anhydrous THF (20 mL) at –78 °C under a nitrogen atmosphere was added vinylmagnesium bromide (5.88 ml, 1 M in THF). The suspension was allowed to stir at –78 °C for 5 min prior to the removal of the cooling bath and the mixture was allowed to slowly warm to *ca.* –20 °C by which time it had become homogeneous. This mixture was then recooled to –78 °C and BF₃·OEt₂ (0.24 ml, 2.45 mmol) was added and the reaction stirred for 10 minutes at –78 °C. Acceptor **2**⁵ (1.00 g, 2.45 mmol) in THF (2 ml) was added, the reaction stirred for 2 h at –78 °C then allowed to warm to room temperature over 4 h. Saturated aqueous NH₄Cl was added and the mixture partitioned between water and ether, the aqueous phase extracted with ethyl acetate and the combined organic phases were washed with water, dried (MgSO₄), and the solvents removed *in vacuo*. Analysis of the ¹H NMR spectrum of the crude reaction mixture indicated a de > 95%. Chromatography (silica, 1 : 5 ethyl acetate–hexane) afforded *cis*-allyl isomer **13** as an oil (929 mg, 87%). Spectroscopic properties were identical to those described above.

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