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

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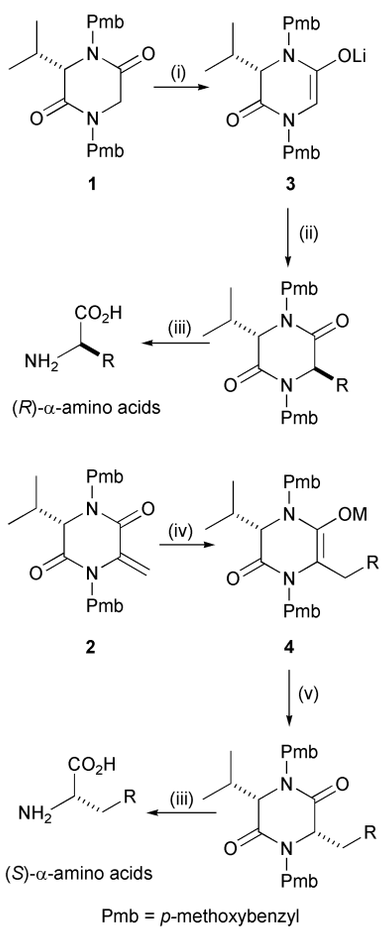
Studies towards a *N*,*N*′-bis(*p*-methoxybenzyl)diketopiperazine asymmetric glycine cation equivalent for the synthesis of homochiral α-amino acids are described. The oxidation of enolate **3** with molecular oxygen provides either a mixture of hydroxylated diketopiperazines **7** and **8** or trione **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.



Scheme 1 *Reagents and conditions*: (i) LHMDS, THF, −78 °C; (ii) alkyl halide, THF, −78 °C; (iii) CAN (6 equivalents), H_2O, CH_3CN; 6 M HCl, 100 °C; (iv) 2 × RMgX or 2 × RLi, CuCN, $BF_3{\cdot}OEt_2$; THF, −78 °C; (v) NH_4Cl (aq).

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 (O_2) 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 ^{1}H NMR spectroscopic data. Examination of ^{1}H 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*) configuration 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 ppm[5] while the corresponding differences in chemical shift for the *trans*-alkylation products lie in the range of 0.20–

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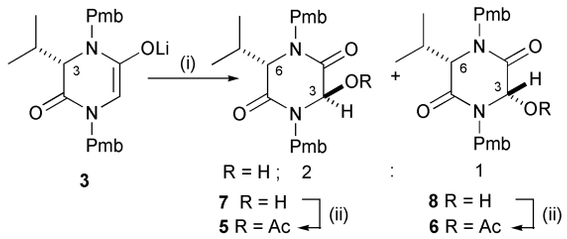


Scheme 2 *Reagents and conditions*: (i) O_2, −78 °C, THF; (ii) Ac_2O, pyridine, DMAP.

0.31 ppm.[4] This chemical shift difference probably arises from a preferred conformation of the *trans* compounds in which one diastereotopic isopropyl methyl group lies beneath the diketopiperazine ring, minimising steric interaction with the adjacent N^4-*p*-methoxybenzyl group, a conformation that is disfavoured for the *cis* configured compounds. This conformation for the *trans* diastereoisomers has consistently been observed in the solid state[11] and is also supported in solution by a generally small 3-*H*–C*H*$(CH_3)_2$ coupling ($J_{3\text{-}H}$ 2.5–4.5 Hz) for *trans* configured compounds suggesting a conformation in which C*H*$(CH_3)_2$ lies orthogonal to 3-*H*. In contrast 3-*H* of *cis* configured compounds shows larger couplings to C*H*$(CH_3)_2$ (in the range $J_{3\text{-}H}$ 7.2–8.9 Hz) consistent with the isopropyl proton occupying a position beneath the ring. In accordance with these observations the minor diastereoisomer (3*S*,6*S*)-**8** exhibits an isopropyl chemical shift difference typical of a *cis* configured diketopiperazine ($\Delta\delta_{Me}$ 0.11 ppm) while the ^{1}H NMR spectrum of (3*R*,6*S*)-alcohol **7** was consistent with a *trans* configuration ($\Delta\delta_{Me}$ 0.24 ppm). Acetates **5** and **6** also exhibited typical diagnostic ^{1}H NMR isopropyl chemical shifts {*trans*-(3*R*,6*S*)-**5**, $\Delta\delta_{Me}$ = 0.32 ppm; *cis*-(3*S*,6*S*)-**6**, $\Delta\delta_{Me}$ = 0.11 ppm}. Finally, the spectroscopic model employed for the assignment of the relative stereochemistry of these compounds was unambiguously verified by X-ray crystallographic analysis of *trans*-(3*R*,6*S*)-**5** (Fig. 1).

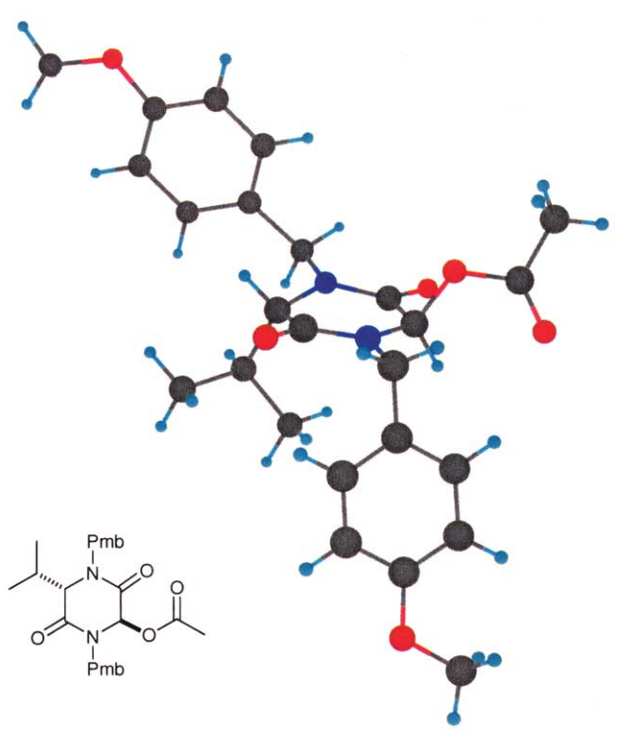
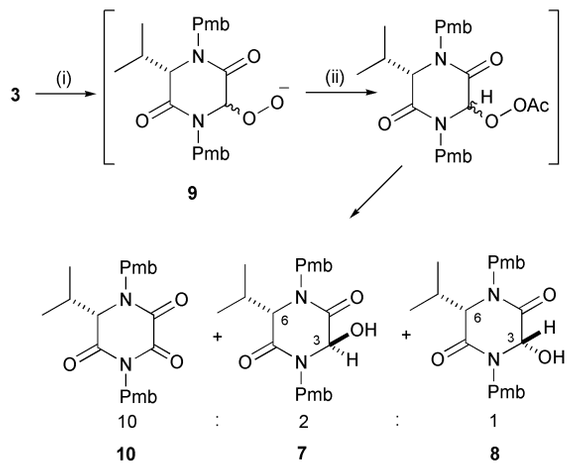


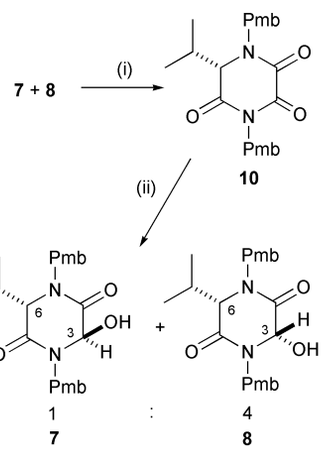
Fig. 1 Chem3D representation of X-ray crystal structure of (3*R*,6*S*)-acetate **5**.

The reaction of enolate **3** with molecular oxygen may proceed *via* an intermediate peroxide anion **9**,[12] which furnishes alcohols **7** and **8** upon aqueous work up. In support of this mechanism, the addition of acetic anhydride to the solution of oxygenated enolate at −78 °C gave a 10 : 2 : 1 mixture of trione **10** and alcohols **7** and **8**. Isolation of **10** from this mixture was hampered by the co-elution of *trans*-alcohol **7** and trione **10** upon chromatography (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) O_2, THF, −78 °C; (ii) Ac_2O, −78 °C–room temperature.

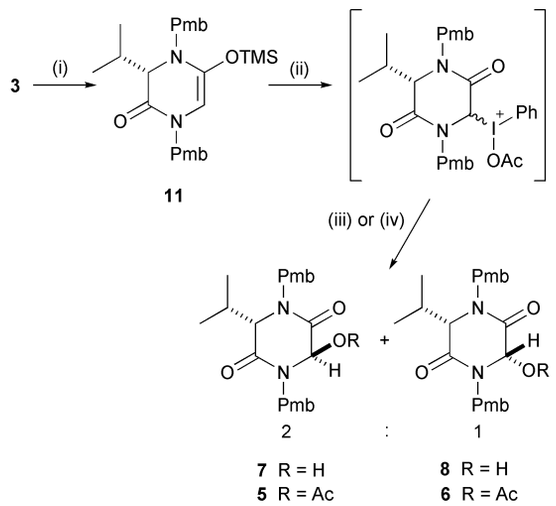
A pure sample of trione **10** was obtained, however, from the oxidation of a mixture of **7** and **8** with *o*-iodoxybenzoic acid (IBX) in DMSO, which provided **10** in 80% isolated yield after chromatography. Examination of the course of the reaction indicated that the *trans*-alcohol **7** was oxidised more rapidly than the *cis*-alcohol **8**. Considering the established mechanism of IBX oxidation, this result is consistent with a faster rate determining decomposition of the hypervalent iodine complex derived from the *trans*-alcohol **7**, which must be thermodynamically less stable than the corresponding *cis* complex derived from **8**.[13] The stereo- and regioselective reduction of trione **10** with diisobutylaluminium hydride provided a 1 : 4 mixture of alcohols *trans*-**7** and *cis*-**8**, from which **8** was isolated in 69% yield *via* chromatography (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) IBX (3 equivalents), DMSO; (ii) diisobutylaluminium hydride, THF, −78 °C.

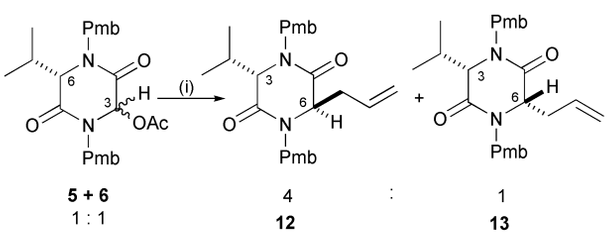
Due to the potential hazards associated with oxygen saturated THF, larger scale oxidation of enolate **3** was achieved *via* treatment with a hypervalent iodine reagent.[14] Although treatment of lithium enolate **3** with (diacetoxyiodo)benzene was not successful, the addition of (diacetoxy)iodobenzene to the trimethylsilyl enol ether **11**, prepared *in situ* from **3**, followed by aqueous work up provided a 2 : 1 mixture of alcohols **7** and **8**. Furthermore, a 2 : 1 mixture of acetates **5** and **6** could most efficiently be accessed in good combined yield (74%) by the addition of sodium acetate prior to aqueous work up, from

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) H_2O, room temperature; (iv) NaOAc, room temperature.

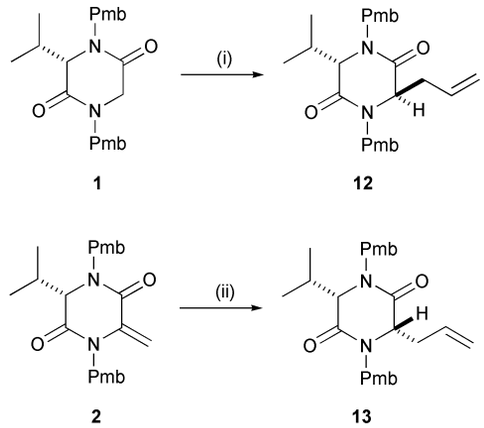
The suitability of acetates **5** and **6** to act as glycine cation equivalents was next examined. Treatment of a 1 : 1 mixture of *trans*-acetate **5** and *cis*-acetate **6** with allyltrimethylsilane and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C afforded a clean mixture of (3*S*,6*R*)-**12** and (3*S*,6*S*)-**13**, in a 4 : 1 ratio, that were separated in good yield *via* chromatography (64% and 8% respectively) (Scheme 6).



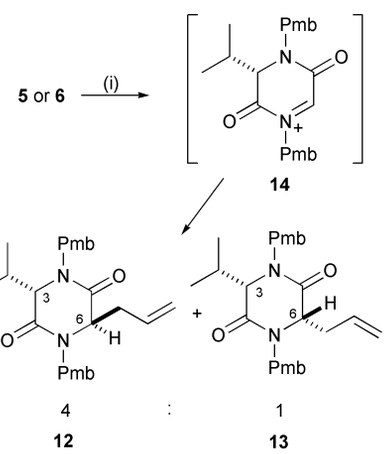
Scheme 6 *Reagents and conditions*: (i) $CH_2{=}CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C.

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** $\Delta\delta_{Me}$ = 0.26 ppm; *cis*-(3*S*,6*S*)-**13** $\Delta\delta_{Me}$ = 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 $BF_3{\cdot}OEt_2$ 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; $CH_2{=}CHCH_2Br$; (ii) 2 × $CH_2{=}CHMgCl$, CuCN, $BF_3{\cdot}OEt_2$, THF, −78 °C; NH_4Cl (aq).



Scheme 8 *Reagents and conditions*: (i) $CH_2{=}CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −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 operating[4–6] 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).

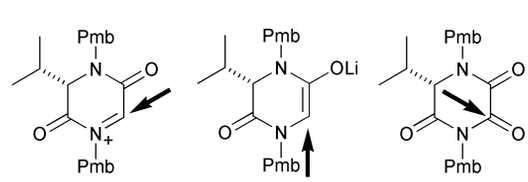


Fig. 2 Directions of reagent approach to reactive species **14**, **3** and **10**.

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

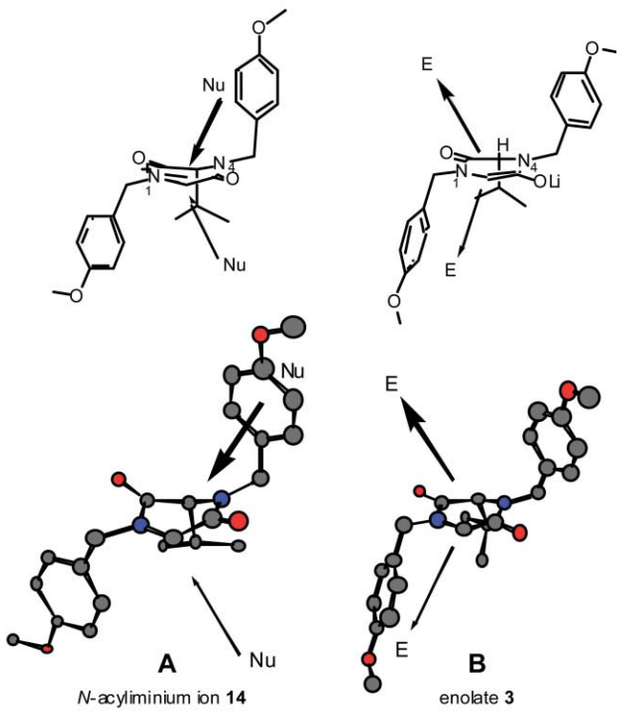


Fig. 3 Trajectories of approach to minimised molecular models: A; **14** and B; **3**.[15]

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 diisobutylaluminium 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 ^{1}H NMR spectrum of the crude reaction mixture. Tetrahydrofuran

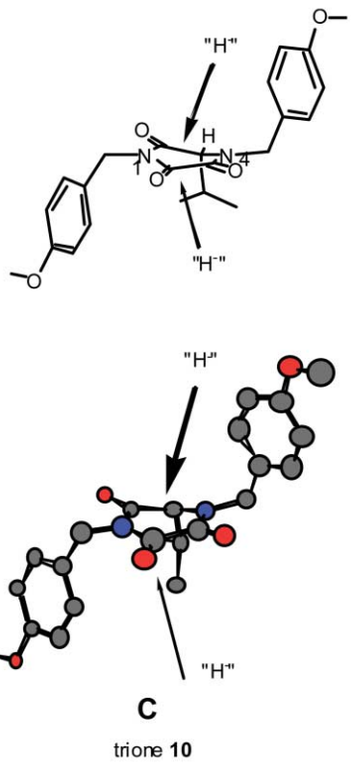


Fig. 4 Trajectories of approach to minimised molecular model: C; trione **10**.[15]

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 F_{254} 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 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz), Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) or Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 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. ^{13}C 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; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 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 °C was added lithium hexamethyldisilazide (3.0 ml, 1 M solution in THF, 3.0 mmol). After stirring (1 h at −78 °C) the mixture was purged with a stream of oxygen for 15 min at −78 °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 112–114 °C (ether) (Found: C, 66.9; H, 7.0; N, 6.6. $C_{23}H_{28}N_2O_5$ requires C, 67.0; H, 6.8; N, 6.8%); $[\alpha]_D^{23}$ +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, C*H*$_3$CHCH$_3$), 1.04 (3H, d, *J* 6.9, CH$_3$CHC*H*$_3$), 2.14 (1H, dsept, *J* 6.9, 5.2, CH$_3$C*H*CH$_3$), 3.75 (1H, d, *J* 5.2, 3-*H*), 3.80 (6H, s, 2 × O*Me*), 3.93 (1H, d, *J* 14.7, ArC*H*$_2$), 4.27 (1H, d, *J* 13.9, ArC*H*$_2$), 4.55 (1H, br s, O*H*), 5.06 (1H, s, C*H*OH), 5.18 (1H, d, *J* 13.9, ArC*H*$_2$), 5.33 (1H, d, *J* 14.7, ArC*H*$_2$), 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 (MH$^+$ − H_2O, 12), 121 (100).

Further elution provided *cis*-alcohol **8** as a colourless solid (256 mg, 25%). Mp 126–127 °C (ether); $[\alpha]_D^{23}$ −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, C*H*$_3$CHCH$_3$), 1.15 (3H, d, *J* 6.9, CH$_3$CHC*H*$_3$), 2.34 (1H, dsept, *J* 6.9, 5.1, CH$_3$C*H*CH$_3$), 3.74 (1H, d, *J* 5.1, 3-*H*), 3.79 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 3.91 (1H, d, *J* 14.8, ArC*H*$_2$), 4.29 (1H, d, *J* 14.5, ArC*H*$_2$), 4.61 (1H, d, *J* 4.4, O*H*), 4.98 (1H, d, *J* 14.5, ArC*H*$_2$), 5.12 (1H, d, *J* 4.4, C*H*OH), 5.30 (1H, d, *J* 14.8, ArC*H*$_2$), 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 (MH$^+$ − H_2O, 12), 121 (100) [HRMS (CI$^+$) Found: 413.2076. $C_{23}H_{29}N_2O_5^+$ 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 °C (ether) (Found: C, 66.1; H, 6.7; N, 6.1. $C_{25}H_{30}N_2O_4$ requires C, 66.1; H, 6.7; N, 6.2%); $[\alpha]_D^{23}$ −125.5 (*c* 1.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2962, 2834, 1750 (CH$_3$C=O), 1678 (NC=O), 1615; δ_H(400 MHz, C_6D_6) 0.62 (3H, d, *J* 6.9, C*H*$_3$CHCH$_3$), 1.14 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 1.75 (3H, s, C*H*$_3$C=O), 2.04 (1H, m, CH$_3$C*H*CH$_3$), 3.34 (6H, s, 2 × O*Me*), 3.80 (1H, d, *J* 14.9, ArC*H*$_2$), 3.99 (1H, d, *J* 3.4, 3-*H*), 4.14 (1H, d, *J* 14.4, ArC*H*$_2$), 5.06 (1H, d, *J* 14.4, ArC*H*$_2$), 5.32 (1H, d, *J* 14.9, ArC*H*$_2$), 6.51 (1H, s, C*H*OAc), 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 (M$^+$ − OAc, 70), 121 (100).

X-Ray crystal structure data for 5. Data were collected using a Nonius Kappa CCD diffractometer with graphite monochromated Mo-Kα 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** [$C_{25}H_{30}N_2O_6$], colourless block, M = 454.52, orthorhombic, space group $P2_12_12_1$, a = 7.4482(1) Å, b = 10.8159(2) Å, c = 29.5153(4) Å, U = 2377.7 Å^3, Z = 4, μ = 0.091, crystal dimensions 0.4 × 0.4 × 0.4 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%). $[\alpha]_D^{23}$ −139.4 (*c* 1.20, $CHCl_3$); ν_{max}(film)/cm^{-1} 2964, 2837, 1757 (CH$_3$C=O), 1681(NC=O), 1612, 1585, 1248, 1216; δ_H(400 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.17 (3H, d, *J* 6.9, CH$_3$CHC*H*$_3$), 2.00 (3H, s, C*H*$_3$C=O), 2.33 (1H, m, CH$_3$C*H*CH$_3$), 3.72 (1H, d, *J* 6.2, 3-*H*), 3.80 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 3.83 (1H, d, *J* 14.8, ArC*H*$_2$), 4.30 (1H, d, *J* 14.5, ArC*H*$_2$), 4.77 (1H, d, *J* 14.5, ArC*H*$_2$), 5.34 (1H, d, *J* 14.8, ArC*H*$_2$), 6.46 (1H, s, C*H*OAc), 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 (× 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 (M$^+$ − OAc, 85), 121 (100) [HRMS (TOF FI) Found: M$^+$, 454.2115. $C_{25}H_{30}N_2O_6$ 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 °C. After stirring (1 h at −78 °C) this mixture was treated with chlorotrimethylsilane (1.75 ml, 13.9 mmol) and the mixture stirred for 30 min at −78 °C before (diacetoxyiodo)benzene (4.47 g, 13.9 mmol) was added. This mixture was stirred (2 h, −78 °C) then sodium acetate (2.0 g, 33.4 mmol) was added and the mixture stirred (3 h, −78 °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%).

(5*S*)-*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 ($MgSO_4$), 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; $[\alpha]_D^{23}$ −108.9 (*c* 0.63, CHCl3); ν_{max}(KBr)/cm^{-1} 2969, 1735 (CH_3C=O), 1675 (NC=O), 1514, 1241; δ_H(400 MHz, $CDCl_3$) 0.60 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.96 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.22 (1H, m, CH$_3$C*H*CH$_3$), 3.78 (3H, s, O*Me*), 3.80 (3H, s, O*Me*), 3.97 (1H, d, *J* 3.6, 3-*H*), 3.99 (1H, d, *J* 13.5, ArC*H*$_2$), 4.87 (1H, d, *J* 13.5, ArC*H*$_2$), 4.92 (1H, d, *J* 13.5, ArC*H*$_2$), 5.35 (1H, d, *J* 14.7, ArC*H*$_2$), 6.79–7.41 (8H, m, aromatic *H*); δ_C(100 MHz, $CDCl_3$) 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 ($ArCH_2^+$, 100%) [HRMS (CI^+) Found: MH^+, 411.1908. $C_{23}H_{27}N_2O_5^+$ requires 411.1920].

Preparation of trione 10 *via* O_2 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 ($MgSO_4$), 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 NH_4Cl (1 ml) and water (50 ml) were added and the mixture extracted with ether. The organic layer was dried ($MgSO_4$) 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.

(3*S*,6*S*)- and (3*S*,6*R*)-*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 NH_4Cl was added and the mixture extracted with ether, the organic phase dried ($MgSO_4$) and the solvent removed to provide a gum. ^{1}H 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%). $[\alpha]_D^{23}$ +23.6 (*c* 1.00, $CHCl_3$) (lit.[4] $[\alpha]_D^{23}$ +25.8 (*c* 0.99, $CHCl_3$)); δ_H(400 MHz, $CDCl_3$) 0.84 (3H, d, *J* 7.0, C*H*$_3$CHCH$_3$), 1.10 (3H, d, *J* 7.0, CH$_3$CHC*H*$_3$), 2.31 (1H, m, CH$_3$C*H*CH$_3$), 2.78 (1H, dt, *J* 12.5, 6.0, C*H*$_2$CH=CH$_2$), 2.97 (1H, ddt, *J* 15.0, 7.0 and 1.0, C*H*$_2$CH=CH$_2$), 3.78 (1H, d, *J* 4.0, 3-*H*), 3.80 (1H, d, *J* 15.5, ArC*H*$_2$), 3.81 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 3.81 (1H, d, *J* 14.5, ArC*H*$_2$), 3.99 (1H, dd, *J* 5.0, 2.5, 6-*H*), 5.12 (1H, d, *J* 10.5, CH$_2$CH=C*H*$_2$), 5.19 (1H, dd, *J* 17, 1.5, CH$_2$CH=C*H*$_2$), 5.41 (1H, d, *J* 14.5, ArC*H*$_2$), 5.53 (1H, d, *J* 15.0, ArC*H*$_2$), 5.54 (1H, m, CH$_2$C*H*=CH$_2$), 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%). $[\alpha]_D^{23}$ −137.8 (*c* 1.00, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1660 (NC=O), 1513, 1248; δ_H(500 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.8, C*H*$_3$CHCH$_3$), 1.17 (3H, d, *J* 6.9, CH$_3$CHC*H*$_3$), 2.19 (1H, dsept, *J* 6.9, 6.9, CH$_3$C*H*CH$_3$), 2.56–2.65 (1H, m, C*H*$_2$CH=CH$_2$), 2.70–2.78 (1H, m, C*H*$_2$CH=CH$_2$), 3.67 (1H, d, *J* 7.0, 3-*H*), 3.79 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 3.83 (1H, d, *J* 14.8, ArC*H*$_2$), 3.93 (1H, d, *J* 14.8, ArC*H*$_2$), 3.96 (1H, t, *J* 6.6, 6-*H*), 5.15 (1H, br t, *J* 1.2, CH$_2$CH=C*H*$_2$), 5.13–5.20 (1H, m, CH$_2$CH=C*H*$_2$), 5.22 (1H, d, 14.8, ArC*H*$_2$), 5.35 (1H, d, *J* 14.8, ArC*H*$_2$), 5.87–5.97 (1H, m, CH$_2$C*H*C=CH$_2$), 6.80–6.85 (4H, m, *ortho*-H ArOMe), 7.03–7.10 (4H, m, aromatic *H*); δ_C(125MHz, $CDCl_3$) 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. $C_{26}H_{33}N_2O_4$ requires 437.2440].

Treatment of either pure *trans*-acetate **5** or pure *cis*-acetate **6** under the same conditions gave similar crude mixtures with ^{1}H 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 $BF_3{\cdot}OEt_2$ (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 NH_4Cl 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 ($MgSO_4$), and the solvents removed *in vacuo*. Analysis of the ^{1}H 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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