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.

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 (3R,6S)-7 and (3S,6S)-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 (3R,6S)-acetate 5 and the corresponding (3S,6S)-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 diketopiperazines4 reveals that the difference in chemical shift between the two diastereotopic C-3 isopropyl methyl groups is diagnostic for the relative (cis or trans) configurational 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 ppm3 whereas the corresponding differences in chemical shift for the trans-alkylation products lie in the range of 0.20–
isopropyl 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 1\(^{a}\)-\(3\)-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-\(\text{H}\)–CH\((\text{CH}_3)_2\) coupling (\(J_{3H\Delta}=2.5–4.5\) Hz) for trans configured compounds suggesting a conformation in which CH\((\text{CH}_3)_2\) lies orthogonal to 3-\(\text{H}\). In contrast 3-\(\text{H}\) of cis configured compounds shows larger couplings to CH\((\text{CH}_3)_2\) (in the range \(J_{3H\Delta}=7.2–8.9\) Hz) consistent with the isopropyl proton occupying a position beneath the ring. In accordance with these observations the minor diastereoisomer (3S,6S)-8 exhibits an isopropyl chemical shift difference typical of a cis configured diketopiperazine (\(\Delta\delta_{\Delta}=0.11\) ppm) while the \(\text{H}\) NMR spectrum of (3R,6S)-alcohol 7 was consistent with a trans configuration (\(\Delta\delta_{\Delta}=0.24\) ppm). Acetates 5 and 6 also exhibited typical diagnostic \(\text{H}\) NMR isopropyl chemical shifts (\(\text{trans}(3R,6S)-5, \Delta\delta_{\Delta}=0.32\) ppm; \(\text{cis}(3S,6S)-6, \Delta\delta_{\Delta}=0.11\) 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 \(\text{trans}(3R,6S)-5\) (Fig. 1).

![Diagram](image)

**Scheme 2** Reagents and conditions: (i) O\(_2\), −78 °C, THF; (ii) Ac\(_2\)O, 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\(^{a}\)-\(3\)-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-\(\text{H}\)–CH\((\text{CH}_3)_2\) coupling (\(J_{3H\Delta}=2.5–4.5\) Hz) for trans configured compounds suggesting a conformation in which CH\((\text{CH}_3)_2\) lies orthogonal to 3-\(\text{H}\). In contrast 3-\(\text{H}\) of cis configured compounds shows larger couplings to CH\((\text{CH}_3)_2\) (in the range \(J_{3H\Delta}=7.2–8.9\) Hz) consistent with the isopropyl proton occupying a position beneath the ring. In accordance with these observations the minor diastereoisomer (3S,6S)-8 exhibits an isopropyl chemical shift difference typical of a cis configured diketopiperazine (\(\Delta\delta_{\Delta}=0.11\) ppm) while the \(\text{H}\) NMR spectrum of (3R,6S)-alcohol 7 was consistent with a trans configuration (\(\Delta\delta_{\Delta}=0.24\) ppm). Acetates 5 and 6 also exhibited typical diagnostic \(\text{H}\) NMR isopropyl chemical shifts (\(\text{trans}(3R,6S)-5, \Delta\delta_{\Delta}=0.32\) ppm; \(\text{cis}(3S,6S)-6, \Delta\delta_{\Delta}=0.11\) 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 \(\text{trans}(3R,6S)-5\) (Fig. 1).

![Diagram](image)

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

![Diagram](image)

**Scheme 3** Reagents and conditions: (i) O\(_2\), THF, −78 °C; (ii) Ac\(_2\)O, −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 disobutylaluminium 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).

![Diagram](image)

**Scheme 4** Reagents and conditions: (i) IBX (3 equivalents), DMSO; (ii) disobutylaluminium 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 (diacetoxyiodobenzene 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), THF, −78 °C; (iii) H2O, room temperature; (iv) NaOAc, room temperature.](image)

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 allylttrimethylsilane and BF3·OEt2 in CH2Cl2 at −78 °C afforded a clean mixture of (3S,6R)-12 and (3S,6S)-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) CH3-CHCH2SiMe3, BF3·OEt2, CH2Cl2, −78 °C.](image)

The relative configurations within trans-(3S,6R)-12 and cis-(3S,6S)-13 were evident from 1H NMR spectroscopic data with both compounds exhibiting diagnostic isopropyl methyl group chemical shift differences (trans-(3S,6R)-12 ΔδMe = 0.26 ppm; cis-(3S,6S)-13 ΔδMe = 0.08 ppm). The major isomer (3S,6R)-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. The identity of the minor diastereoisomer (3S,6S)-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).

In order to establish whether an N-acyliminium species was an intermediate in this transformation, diastereoisomerically pure trans-acetate 5 was treated with allylttrimethylsilane and BF3·OEt2 to afford a clean 4 : 1 mixture of (3S,6R)-12 and (3S,6S)-13. Similar treatment of diastereoisomerically pure cis-acetate 6, also afforded a 4 : 1 mixture of (3S,6R)-12 and (3S,6S)-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 allylttrimethylsilane by preferential addition to the Re face of N-acyliminium species 14, anti to the C-3 isopropyl group.

The facial selectivity of this addition is markedly lower (60% de) than that observed for alkylation of enolate 3 with allyl bromide (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-β-methoxybenzyl protecting groups, is operating and molecular modelling suggests a similar conformation and chiral relay for N-acyliminium intermediate 14 and trione 10. 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. 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).

![Scheme 7 Reagents and conditions: (i) LHMDS, THF, −78 °C; CH2=CHCH2Br; (ii) 2 × CH2=CHMgCl, CuCN, BF3·OEt2, THF, −78 °C; NH4Cl (aq.).](image)

![Scheme 8 Reagents and conditions: (i) CH3-CHCH2SiMe3, BF3·OEt2, CH2Cl2, −78 °C.](image)

![Fig. 2 Directions of reagent approach to reactive species 14, 3 and 10.](image)

Thus, the reaction of the N-acyliminium ion 14 with allylttrimethylsilane preferentially occurs on the Re face of the auxiliary (60% de), as seen for the alkylation of enolate 3
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 diketo-piperazine 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 N1-protecting group on the Re face (Fig. 4, C).

**Conclusion**

We have exploited the ready oxidation of the enolate of diketo-piperazine 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 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.
CAUTION: Explosion Hazard: see Note in General experimental section.

To a solution of (3S)-N,N'-bis(3-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 (5.9 mmol, 6.0 ml in THF at 30 °C). 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 NH₄Cl (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 (MgSO₄) 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. C₂₄H₂₇N₂O₂ requires C, 66.0; H, 6.6 N (4%).

Further elution provided cis-alcohol 8 as a colourless oil (256 mg, 25%). Mp 126–127 °C (ether); [α]D ≡ −172.3 (c 0.30, CHCl₃); νmax (film/cm⁻¹) 3281 (OH), 1659 (N=C=O), 1635; δmax (500 MHz, CDCl₃) 0.80 (3H, d, J 6.9, CH₃CH₂CH₂), 1.04 (3H, d, J 6.9, CH₃CH₂CH₃), 2.14 (1H, d, J 6.9, 9.5, C₂H₂CH₂), 3.75 (1H, d, J 5.2, 3-H), 3.80 (4H, s, 2 × OMe), 3.93 (1H, d, J 14.7, ArCH₂), 4.27 (1H, d, J 13.9, ArCH₂), 4.55 (1H, br s, OH), 5.06 (1H, s, CHO₂), 5.18 (1H, d, J 13.9, ArCH₂), 5.33 (1H, d, J 14.7, ArCH₂), 6.84–6.87 (4H, m, ortho-H ArOMe), 7.14 (2H, m, aromatic H₇), 7.37 (2H, m, aromatic H₈), δ₁₂5 (125 MHz, CDCl₃) 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, 170.0; m/z (APCI) 413 (MH⁺, 2%), 395 (MH⁺ – H₂O, 12), 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 [C₂₃H₂₄N₂O₄] colourless block, M = 454.52, orthorhombic, space group P₂₁2₁2₁, a = 7.4482(1) Å, b = 10.8159(2) Å, c = 29.5153(4) Å, U = 2377.7 Å³; Z = 4, μ = 0.081, crystal dimensions 0.4 × 0.4 × 0.4 mm. A total of 3044 unique reflections were measured for 4.55 < θ < 27.50 and 2646 reflections were used in the refinement. The final parameters were wR₂ = 0.0201 and R₁ = 0.0325 [I > 3σ(I)].

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

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 (4.7 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 NH₄Cl (50 ml) and water (500 ml) was added and the mixture extracted with ether, the organic layer was dried (MgSO₄) and the solvent removed to afford a 2:1 mixture of trans- and cis-acetates 5 and 6 respectively. Chromatography (silica, 1:1 ether–hexane) 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%).

(35,65S)- and (35,65R)-N,N'-Bis(3-p-methoxybenzyl)-6-hydroxy-3-isopropylpiperazine-2,5-dione 7 and 8

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 CuSO₄ and the organic layer washed with saturated aqueous CuSO₄, dried (MgSO₄), and the solvent removed in vacuo. Chromatography (silica, 1:1 ether–hexane) gave 6 as a colourless oil (91 mg, 83%). [α]D ≡ −139.4 (c 1.20, CHCl₃); νmax (film/cm⁻¹) 2964, 2837, 1757 (CH₂=O), 1681 (N=C=O), 1612, 1585, 1248, 1216; δ₂₉₀₀ (400 MHz, CDCl₃) 1.06 (3H, d, J 6.8, CH₃CH₂), 1.17 (3H, d, J 6.9, CH₃CH₂), 2.00 (3H, s, CH₃O), 2.33 (1H, m, CH₂CH₂), 3.72 (1H, d, J 6.2, 3-H), 3.80 (1H, s, OMe), 3.81 (1H, d, J 14.8, ArCH₂), 4.30 (1H, d, J 14.5, ArCH₂), 4.77 (1H, d, J 14.5, ArCH₂), 5.34 (1H, d, J 14.8, ArCH₂), 6.46 (1H, s, CHOAc), 6.81–6.84 (4H, m, ortho-H ArOMe), 7.06–7.12 (4H, m, aromatic H₇); δ₂₀₀ (50 MHz, CDCl₃) 18.6, 20.4, 20.7, 24.0, 44.7, 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 Fl) Found: M⁺, 454.2115. C₂₃H₂₄N₂O₄ requires 454.2104].
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) \(\text{Br}^+\) 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; \[\text{C}_{18}\text{H}_{21}\text{O}_3\text{Si} (276.3) \text{calcd} 276.2 \text{found} 276.5 \text{m/z} \text{(M}^+)\text{.} \]

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 metabisulphite (300 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\(_4\)Cl (1 ml) and water (50 ml) were added and the mixture extracted. 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.

Notes and References

For a recent review of $\alpha$-amino acid cation equivalents, see:


11 One diastereoisotopic isopropyl methyl group consistently lies beneath the diketopiperazine ring in X-ray crystal structures of trans configured $N,N'$-bis[p-methoxybenzyl]diketopiperazines while in the X-ray crystal structures of cis configured compounds both methyl groups lie outside the ring. See X-ray crystal structure of acetate 5, references 4b, 4c and unpublished data.


15 Modelling was performed using the Macromodel suite of programs. 1000 starting conformations of N-acyliminium ion 14 were generated using a Monte Carlo simulation and minimised using an MM2 force field.

