Synthesis and structure determination of 8- and 9-iodocamphorquinone bis(ethylene ketal)

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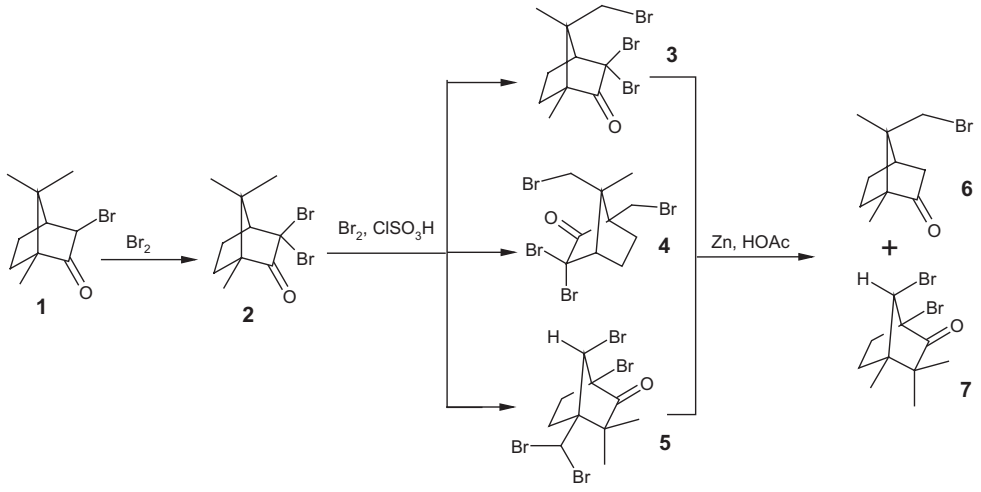
The structures of 8- and 9-iodocamphorquinone bis(ethylene ketal) have been confirmed by spectroscopic and single crystal X-ray analysis. The unexpected formation of the latter isomer is attributed to intramolecular rearrangement of the camphor skeleton, the mechanistic details of which have been explored using coset analysis.

Keywords: camphor, skeletal rearrangement, 8- and 9-iodocamphorquinone bis(ethylene ketal)

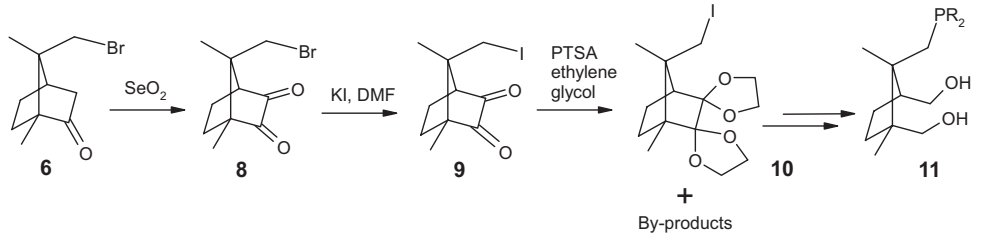
Various camphor derivatives have been targeted in our research on the development of multidentate ligands.[1,2] Such systems readily undergo acid-catalysed intramolecular rearrangement,[3] often resulting in complete reorganisation of the camphor skeleton. Selective bromination of camphor at C-8 requires pre-functionalisation at C-3 to prevent intramolecular rearrangements that lead to undesirable by-products.[4] Thus, following Money's procedure,[4] 3-bromocamphor **1** was treated with neat bromine to afford 3,3-dibromocamphor **2**. Selective C-8 bromination and Zn-catalysed debromination then gave 8-bromocamphor **6** in 38% yield, together with 3,3,4-trimethyl-1,7-dibromonorbornan-2-one **7** (*ca* 6%) (Scheme 1). Prior to the debromination step, a sample was chromatographed and fractions were subjected to NMR analysis. This revealed the presence of 3,3,8-tribromocamphor **3**, 3,3,8,10-tetrabromocamphor **4** and 1,7-dibromo-4-dibromomethyl-3,3-dimethylnorbornan-2-one **5** in a 7:1:5 ratio. While all of these camphor derivatives have been previously isolated and characterised by Money and co-workers,[4] our particular interest lay in the conversion of 8-bromocamphor **6** to the previously unreported 8-iodocamphorquinone **9**, which was expected to provide access, *via* the diketal **10**, to chiral, tridentate ligands, such as compound **11** (Scheme 2).

Before attempting to introduce an intrinsically nucleophilic phosphine donor into the 8-iodo diketone **9**, the carbonyl groups were protected by acid-catalysed ketalisation following a procedure described by Komarov and co-workers.[5] Spectroscopic analysis of the crude material recovered after the reaction indicated the presence of a mixture of compounds, chromatographic separation of which afforded five different ketal products, *viz*., the 8-iodo monoketals **12** and **13**, the known diketal **14**[6] and a pair of isomers. Both isomers exhibited spectroscopic properties consistent with the desired 8-iodocamphorquinone bis(ethylene ketal) **10**.

Single crystal X-ray analysis (Fig. 1) permitted assignment of structure **10** to the major product (24%). Interestingly, the X-ray crystal structure reveals a particular orientation of the 8-methylene hydrogens relative to the ketal groups such



Scheme 1



Scheme 2

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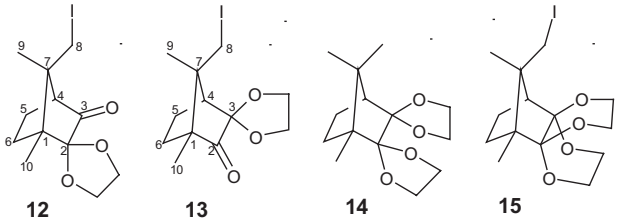


that one of these atoms participates in strong, bifurcated hydrogen bonds C10–HA···O12 and C10–HA···O16 (H···O and C···O distances ~2.2 and 2.9 Å respectively). If a similar conformation is favoured in $CDCl_3$, this could account for the significant ^{1}H NMR chemical shift difference (*ca* 1.2 ppm) observed for these protons. Thus, the hydrogen-bonded atom (HA) would be deshielded by the electronegative oxygens while the other (HB) would be shielded by the 9- and 10-methyl groups. In the molecule of **10**, the C–I bond length is 2.167(3) Å and the torsion angle C9–C8–C10–I11 is –67.5(3)°. One of the ketal rings adopts an envelope conformation (flap at C14) while the other is a twist form (twisted around the bond O16–C17).

The only significant differences between the ^{1}H NMR spectra of compound **10**, and the isomeric diketal lay in the chemical shifts of the diastereotopic 8-methylene protons. In the diketal **10**, these protons resonate as doublets at 3.13 and 4.33 ppm, while the corresponding protons in the isomer resonate at 3.42 and 3.92 ppm. The isomeric diketal was initially thought to be structure **15**, the rationale being that either diketal could, in principle, be formed from 8-iodocamphorquinone **9**. However, single crystal X-ray analysis revealed the isomeric diketal to be 9-iodocamphorquinone bis(ethylene ketal) **16** (Fig. 2).

The crystallographic asymmetric unit of **16** comprises three molecules (A, B, C) of which the representative molecule A is shown in Fig. 2. Molecules A, B and C adopt slightly different conformations, the C9–C8–C10–I11 torsion angle values spanning the narrow range 70.1(4)–73.6(4)°, suggesting that the common C–I bond orientation observed is energetically favoured. In contrast to **10**, in the crystal of **16**, the methylene hydrogen atoms on the respective atoms C10A–C10C do not engage in significant intra- or intermolecular interactions. C–I distances are in the narrow range 2.159(5)–2.166(5) Å.

In order to explore the possibility that the 9-iodomethyl diketal **16** might be formed as a minor product during the ketalisation of 8-iodocamphorquinone **9**, the latter compound was thoroughly purified by semi-preparative HPLC and then reacted with ethylene glycol in the presence of *p*-toluenesulfonic acid. Surprisingly, ^{1}H NMR analysis of the crude material collected after the repeated reaction revealed that *both* diketal isomers **10** and **16** were again present.

Since the ketalisation is acid-catalysed, protonation of the substrate, 8-iodocamphorquinone **9**, can be expected to afford the resonance-stabilised cation **17** (Scheme 3). Such bicyclic cations readily undergo skeletal rearrangement,[4]

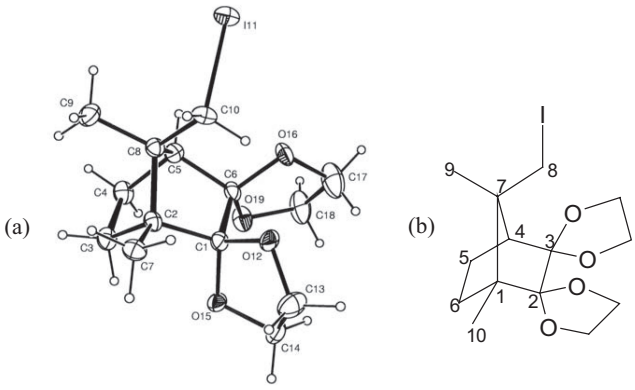


Fig. 1 (a) X-ray crystal structure of 8-iodocamphorquinone bis(ethylene ketal) **10**, showing the crystallographic numbering and thermal ellipsoids at the 50% probability level, and (b) the corresponding wire-frame structure showing the systematic numbering.

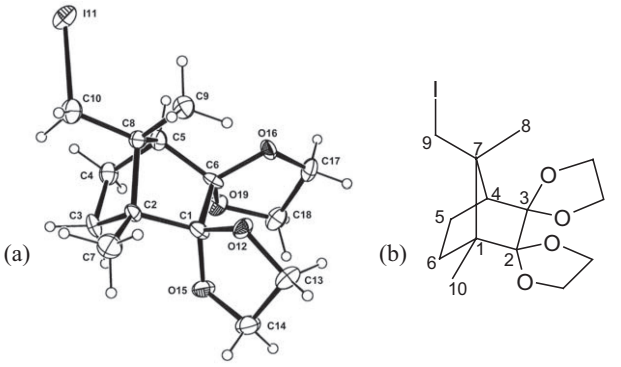
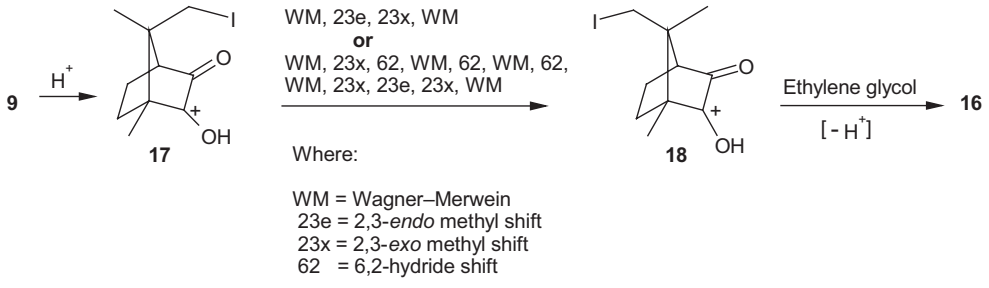
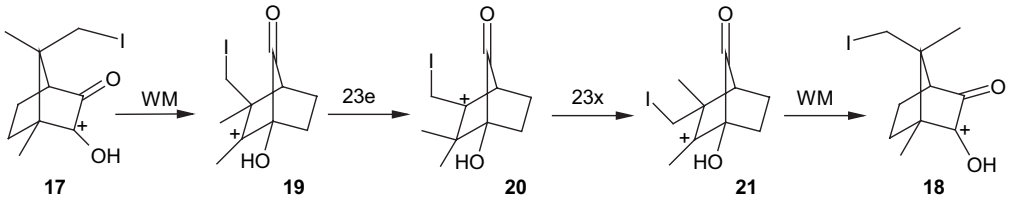


Fig. 2 (a) X-ray crystal structure of 9-iodocamphorquinone bis(ethylene ketal) **16**, showing one of the three molecules in the asymmetric unit with thermal ellipsoids drawn at the 50% probability level, and the crystallographic numbering, and (b) the corresponding wire-frame structure showing the systematic numbering.

and possible intramolecular rearrangement pathways to the 9-iodocamphorquinone cation **18** were explored using a fine-tuned version[7] of Johnson and Collins' computer-assisted coset analysis.[8] This analysis permits the identification of all possible pathways between a given substituted bicyclo[2.2.1]heptyl cation and a designated isomeric norbornyl cation *via* common intramolecular rearrangements (the "generator permutations"). Intermediate cations are mapped on coset graphs, which permit assessment of alternative pathways to the designated norbornyl cation. Rearrangement sequences were limited to a maximum of 13 steps, and two pathways were generated involving the following "permutation operators":- Wagner–Meerwein rearrangements (WM), 2,3-*exo*-methyl



Scheme 3



Scheme 4

(23x), 2,3-*endo*-methyl (23e) and 6,2-hydride (62) shifts. These pathways for achieving the transformation **17→18** are summarised in Scheme 3, while the shorter, 4-step pathway is detailed in Scheme 4.

The shorter pathway (Scheme 4) involves rearrangements common to norbornane systems, whereas the longer pathway requires the unusual 6,2-hydride shifts. Moreover, coset analysis of the analogous C-3 carbocation failed to afford a feasible rearrangement pathway. Consequently, we tentatively attribute formation of the 9-iodo diketal **16** to acid-catalysed, skeletal rearrangement of 8-iodocamphorquinone during the ketalisation process *via* the shorter mechanistic sequence detailed in Scheme 4.

Experimental

NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer at 303 K in $CDCl_3$, and calibrated using solvent signals. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum 2000 spectrometer. Low-resolution (EI) mass spectra were obtained on a Finnigan-Mat GCQ mass spectrometer and high-resolution (EI) mass spectra on a VG70-SEQ double-focusing magnetic sector spectrometer (Department of Chemistry, University of the Witwatersrand). Optical rotations were measured on a Perkin Elmer 141 polarimeter using a 1 dm cell, with concentrations cited in g/100 ml. Optically pure compounds were derived from commercially available, homochiral, (1*R*)-(+)-camphor.

*(1*R*,4*S*,7*S*)-(–)-8-Iodocamphorquinone* **9**

A solution of 8-bromocamphorquinone **6**[4] (4.00 g, 16.3 mmol) and KI (13.5 g) in DMF (50 ml) was stirred under argon at 110°C overnight. The mixture was then cooled to room temperature, diluted with water (200 ml) and extracted with diethyl ether (2 × 100 ml). The organic extracts were combined, washed with water (3 × 100 ml), dried (anhydrous Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed [flash chromatography on silica; elution with hexane–ethyl acetate (3:1)] to afford *(1*R*,4*S*,7*S*)-8-iodocamphorquinone* **9,** as yellow crystals (1.50 g, 27.3%), m.p. 78–85°C (Found $\mathbf{M}^+$: 291.99603. $C_{10}H_{13}O_2I$ requires *M*, 291.99603); $[\alpha]_D^{22}$ = –76.5° (*c* 1.1, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1754 (C=O); δ_H 1.13 (3H, s, 10-CH_3), 1.23 (3H, d, *J* = 1.0 Hz, 9-CH_3), 1.66 (1H, m, 5-H_a), 1.87 (1H, m, 6-H_a), 2.10 (2H, m, 5-H_b and 6-H_b), 2.76 (1H, dd, *J* = 11.1 and 1.0 Hz, 8-H_a), 2.89 (1H, d, *J* = 5.1 Hz, 4-H), 3.14 (1H, d, *J* = 11.1 Hz, 8-H_b); δ_C 9.02, 11.9, 16.3, 21.5, 32.7, 46.8, 58.3, 58.6, 201.2 and 203.3 (C=O); *m/z* 292 (100%).

*(1*R*,4*S*,7*S*)-(+)-8-Iodocamphorquinone bis(ethylene ketal)* **10**, *(1*R*,4*S*,7*R*)-(+)-9-iodocamphorquinone bis(ethylene ketal)* **16**, *(1*R*,4*S*,7*S*)-(–)-2,2-(ethylenedioxy)-8-iodocamphorquinone* **12**, *(1*R*,4*S*,7*S*)-(+)-3,3-(ethylenedioxy)-8-iodocamphorquinone* **13** *and camphorquinone bis(ethylene ketal)* **14**

A mixture of 8-iodocamphorquinone **9** (1.30 g, 4.44 mmol), ethylene glycol (13.4 ml), *p*-toluene-sulfonic acid (1.40 g, 6.83 mmol) and benzene (42 ml) was boiled under reflux under nitrogen in a flask fitted with a Dean-Stark trap containing 5Å molecular sieves. After 5 days, the mixture was cooled to room temperature, diluted with diethyl ether (100 ml), washed sequentially with brine (100 ml) and water (3 × 100 ml), and dried (anhydrous Na_2SO_4). The solvent was removed *in vacuo*, and the crude product was chromatographed [flash chromatography on silica; elution with hexane–ethyl acetate (3:1)] to afford (1R,4S,7S)-(+)-8-iodocamphorquinone bis(ethylene ketal) **10** (400 mg, 24%) as white crystals. An analytical sample was prepared by further chromatography [HPLC on Partsil 10; elution with hexane–ethyl acetate 4:1] to give *(1*R*,4*S*,7*S*)-(+)-8-iodocamphorquinone bis(ethylene ketal)* **10,** m.p. 98–104°C (Found $\mathbf{M}^+$– I: 253.14204. $C_{14}H_{21}O_4$ - I requires M, 253.14398); $[\alpha]_D^{22}$ = +15.8° (c 1.00, $CHCl_3$); δ_H 0.82 (3H, s, 10-CH_3), 1.10 (3H, d, *J* = 1.1 Hz, 9-CH_3), 1.56 (2H, m, 5-H_a and 6-H_a), 1.78 (1H, m, 6-H_b), 1.98 (1H, d, *J* = 4.2 Hz, 4-H), 2.20 (1H, m, 5-H_b), 3.13 (1H, d, *J* = 9.7 Hz, 8-H_a), 3.92 (8H, m, 2xOCH_2CH_2O) and 4.33 (1H, dd, *J* = 9.7 and 1.2 Hz, 8-H_b); δ_C 9.9, 19.5, 19.8, 20.7, 31.9, 48.5, 51.9, 53.2, 64.2, 64.6, 65.2, 66.1, 113.0 and 113.5; m/z 380 (M^+, 9.2%) and 253 (100);

The residual material from flash chromatography was chromatographed further [HPLC on Partsil 10; elution hexane–EtOAc (4:1)] to afford four fractions.

(i) *(1*R*,4*S*,7*R*)-(+)-9-Iodocamphorquinone bis(ethylene ketal)* **16** as white crystals (102 mg, 6%), m.p. 57–60°C; $[\alpha]_D^{22}$ = + 6.4° (*c* 1.00, $CHCl_3$); δ_H 0.83 (3H, s, 10-CH_3), 1.34 (3H, s, 8-CH_3), 1.46 (2H, m, 5-H_a and 6-H_a), 1.83 (1H, m, 6-H_b), 1.87 (1H, d, *J* = 4.0 Hz, 4-H), 2.06 (1H, m, 5-H_b), 2.96 (1H, d, *J* = 9.7 Hz, 9-H_a), 3.42 (1H, dd, *J* = 9.7 and 1.3 Hz, 9-H_b) and 3.92 (8H, m, 2xOCH_2CH_2O); δ_C 10.1, 18.5, 18.8, 20.6, 29.1, 48.5, 52.6, 53.7, 64.4, 64.6, 65.0, 66.0, 113.0 and 115.6; *m/z* 380 (M^+, 17.6%) and 253 (100).

(ii) *(1*R*,4*S*,7*S*)-(+)-2,2-(Ethylenedioxy)-8-iodocamphorquinone* **12** as a yellow oil (19.4 mg, 1.4%), (Found $\mathbf{M}^+$– CH_2O: 307.02175. $C_{11}H_{16}O_2I$ – CH_2O requires *M*, 307.01951); ν_{max}(thin film)/cm^{-1} 1749 (C=O); $[\alpha]_D^{22}$ = + 137° (*c* 1.9, $CHCl_3$); δ_H 0.92 (3H, s, 10-CH_3), 1.16 (3H, d, *J* = 1.0 Hz, 9-CH_3), 1.90 (4H, m, 5-CH_2 and 6-CH_2), 2.23 (1H, d, *J* = 3.9 Hz, 4-H), 3.07 (1H, d, *J* = 9.9 Hz, 8-H_a), 3.43 (1H, dd, *J* = 9.9 and 1.1 Hz, 8-H_b) and 4.16 (4H, m, OCH_2CH_2O); δ_C 9.2, 16.5, 18.2, 20.3, 33.7, 47.8, 50.9, 58.2, 64.7, 66.3, 106.4 and 215.9.

(iii) *(1*R*,4*S*,7*S*)-(–)-3,3-(Ethylenedioxy)-8-iodocamphorquinone* **13** (trace amount) as a pale yellow oil; ν_{max} (thin film)/cm^{-1} 1757 (C=O); $[\alpha]_D^{22}$ = –16.0 (*c* 0.12 $CHCl_3$); δ_H 1.07 (3H, s, 10-CH_3), 1.08 (3H, s, 9-CH_3), 1.76–2.06 (5H, series of overlapping multiplets, 4-H, 5-CH_2 and 6-CH_2), 3.05 (1H, d, *J* = 10.5 Hz, 8-H_a), 3.25 (1H, d, *J* = 10.5 Hz, 8-H_b), 4.17 (4H, m, OCH_2CH_2O); δ_C 11.4 (C-8), 18.7 (C-10), 19.4 (C-9) 20.0 (C-6), 31.5 (C-5), 45.1 (C-7), 52.7 (C-4), 59.7 (C-1), 64.5 and 66.3 (OCH_2CH_2O), 106.4 (C-2) and 213.3 (C=O).

(iv) Camphorquinone bis(ethylene ketal) **14**, as colourless crystals (trace amount), m.p. 59–63°C (lit.[6] 58–59°C); δ_H 0.80, 0.87 and 1.18 (9H, 3xs, 8-, 9- and 10-CH_3), 1.31–2.00 (4H, series of multiplets, 5- and 6-CH_2), 1.68 (1H, d, *J* = 4.6, 4-H), 3.74–4.00 (8H, m, 2xOCH_2CH_2O); δ_C 9.9, 20.7, 21.0, 21.1, 29.3, 44.5, 52.7, 53.3, 64.2, 64.5, 65.0, 65.9, 113.5 and 114.7.

*X-ray analysis of (1*R*,4*S*,7*S*)-(+)-8-iodocamphorquinone bis(ethylene ketal)* **10** *and (1*R*,4*S*,7*R*)-(+)-9-iodocamphorquinone bis(ethylene ketal)* **16**

Crystal data **10**: $C_{14}H_{21}IO_4$, M_r = 380.21, monoclinic, C2, *a* = 16.3127(4), *b* = 7.1753(2), *c* = 12.5202(4) Å, β = 97.618(1)°, *V* = 1452.54(7) Å^3, D_x = 1.739 g cm^{-3}, *Z* = 4, μ = 2.212 mm^{-1}, *T* = 113K. The final refinement was based on 2643 reflections and 174 variable parameters and converged at R_1 = 0.0204 (2586 reflections with $I > 2\sigma(I)$), wR_2 = 0.0503 and *S* = 1.112. The final maximum difference electron density peak (1.27 eÅ^{-3}, not modelled) was attributed to an alternative, minor site for atom C17, the two disordered components giving rise to two slightly different ring conformations. The correct assignment of absolute structure was indicated by the Flack parameter value of –0.02(2). Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre (CCDC 639803).

Crystal data **16**: $C_{14}H_{21}IO_4$, M_r = 380.21, monoclinic, $P2_1$, *a* = 7.227(1), *b* = 22.840(5), *c* = 13.149(3) Å, β = 92.18(3)°, *V* = 2168.9(8) Å^3, D_x = 1.747 g cm^{-3}, *Z* = 6, μ = 2.223 mm^{-1}, *T* = 113K. Final refinement was based on 7847 reflections and 520 variables and converged at R_1 = 0.0343 (6459 reflections with $I > 2\sigma(I)$), wR_2 = 0.0566 and *S* = 0.973. The final difference electron density was 0.59 eÅ^{-3}. The Flack parameter value –0.04(1) indicated the correct assignment of absolute structure. Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre (CCDC 639804).

Intensity data were collected from crystal specimens cooled in a stream of nitrogen vapour (Cryostream cooler, Oxford Cryosystems) using a Nonius Kappa CCD diffractometer and Mo-Kα radiation ($\lambda = 0.71073$ Å). No phase changes occurred on cooling the specimens from ambient temperature. Cell refinement and data reduction were performed with DENZO-SMN.[9] Data reduction included Lorentz-polarisation corrections and empirical absorption corrections with program SADABS.[10] The structures were solved using SHELXS-86[11] and refined on F^2 with SHELXL-97.[12] All H atoms were identified in difference electron density maps but were added in idealised positions in a riding model with isotropic displacement parameters 1.2–1.5 times those of their parent atoms. All non-hydrogen atoms were treated anisotropically.

The authors thank Sasol Technology Ltd. for a bursary (N.M.) and Sasol Technology Ltd., the Technology and Human Resources for Industry Programme (THRIP; Project no. 2642), Rhodes University and the University of Cape Town for generous financial support. M.R.C also acknowledges research funding from the NRF (Pretoria).

Received 26 March 2007; accepted 23 April 2007
Paper 07/4560 doi: 10.3184/030823407X209714

References

1 I.T. Sabbagh and P.T.Kaye, *J. Molec. Structure: THEOCHEM,* (submitted).
2 I.T Sabbagh, PhD thesis, Rhodes University, 2006.
3 R. Antkowiak and W.Z. Antkowiak, *Pol. J. Chem.,* 1994, **68**, 2297; T. Money, *Nat. Prod. Rep.*, 1985, **2**, 253
4 P. Cachia, N. Darby, C.R. Eck and T. Money, *J. Chem. Soc., Perkin I*, 1976, 359.
5 I.V. Komarov, A. Monsees, A. Spannenberg, W. Baumann, U. Schmidt, C. Fischer and A. Börner, *Eur. J. Org. Chem.*, 2003, 138.
6 R. Klein, MSc thesis, Rhodes University, 1999.
7 K.A. Lobb, unpublished work.
8 C.J. Collins and C.K. Johnson, *J. Am. Chem. Soc.*, 1973, **95**, 4766; C.J. Collins and C.K. Johnson, *J. Am. Chem. Soc.*, 1974, **96**, 2514.
9 Z. Otwinowski and W.Minor, in *Methods in Enzymology*, C.W. Carter and R.M. Sweet (eds.), Academic Press, New York, 1997, pp.307-326.
10 G.M. Sheldrick, *SADABS*, *Program for Empirical Absorption Correction of Area Detector Data;* University of Göttingen, Germany, 1996.
11 *SHELXS-86*: G.M. Sheldrick, in *Crystallographic Computing 3,* G. M. Kruger and R. Goddard (eds.), Oxford University Press, Oxford, UK, 1985, pp.175-178.
12 G.M. Sheldrick, *SHELXL-97, Program for refinement of crystal structures,* University of Göttingen, Germany, 1997.