PERKIN 2

Investigations into the reaction of the lithium enolate of cyclohexanone and phenyl vinyl sulfoxide: A simple synthesis of a bicyclo[4.2.0]octan-1-ol

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Received (in Cambridge, UK) 28th August 2001, Accepted 20th November 2001

The enolate generated from cyclohexanone and LDA at −78 °C in THF reacts with (±)-phenyl vinyl sulfoxide to give the novel sulfinylbicyclo[4.2.0]octanols **1**–**3** and monoalkylated sulfoxide **4**. The effects of changes in temperature, concentration, and reaction time were studied. By accurate control of temperature, concentration, and reaction time the ratio of bicyclooctanols **1**–**3** to monoalkylated sulfoxide **4** obtained was 95 : 5. The bicyclooctanols **1**–**3** were characterised as the sulfones **5** and **6**. The relative stereochemistries of the bicyclooctanols **1**–**3** were established by X-ray structural determination.

Introduction

During the course of investigations towards the synthesis of fused-ring natural products we sought to access a fused six- and four-membered carbocyclic ring bearing a bridgehead hydroxy group. A review of the literature showed that simple and polycyclic fused six- and four-membered carbocyclic rings bearing a bridgehead hydroxy group can be accessed using [2 + 2] cycloaddition processes,[1,2] samarium diiodide mediated pinacol coupling[3] and tandem intramolecular Michael–aldol reaction of α,β-unsaturated esters using TBDMSOTf.[4] The construction of a substituted cyclobutanol using Diels–Alder methodology and cycloaddition processes with ethylene[5] was also reported in the synthesis of a sterpurene. Such routes are reliant on internal directing groups, controlling reagents and often display non-stereoselectivity. In the present work we examined whether fused six-four membered ring systems bearing a bridgehead hydroxy group could be accessed in systems not possessing additional directing groups or in the absence of additives and thus under mild conditions. We chose cyclohexanone and phenyl vinyl sulfoxide as our case study reactants. Described herein are our investigations into the reaction of the lithium enolate of cyclohexanone and (±)-phenyl vinyl sulfoxide and the exploration of conditions that lead to the controlled formation of 8-phenylsulfinylbicyclo[4.2.0]octan-1-ol as the major product.

Results and discussion

The enolate generated from cyclohexanone and LDA at −78 °C reacts with (±)-phenyl vinyl sulfoxide to give the novel sulfinylbicyclo[4.2.0]octanols **1**–**3** with the relative configurations shown, and the monoalkylated sulfoxide **4** as mixture of diastereoisomers (Scheme 1). The bicyclooctanols **1**–**3** were characterised as the sulfones **5** and **6** using MCPBA or Oxone® as the oxidant.† The bicyclooctanols **2** and **3** independently oxidised to the sulfone **6** confirming that they are epimeric at sulfur. The sulfones **5** and **6** were characterized by interpretation of spectral data from ^{1}H and ^{13}C 1D NMR and gCOSY, HMQC or HSQC and HMBC 2D NMR studies. The connectivity of the cyclobutyl ring was apparent from correlations between the signals due to H8 (δ = 3.43 or 3.52 ppm) and H7 (δ = 1.76–1.88 or 1.78–1.88 ppm), and H7 (δ = 1.96 or 2.32 ppm), and H6 to H7 and H7 (δ = 2.14–2.25 or 2.82–2.92 ppm) in the COSY, for the sulfones **5** and **6** respectively. From the HSQC, signals due to a CH were observed between C6 (δ = 38.9 or 43.1 ppm) and H6, and C8 (δ = 67.1 or 67.1 ppm) and H8 and the signal for a quaternary carbon due to C1 (δ = 76.4 or 73.8 ppm) was identified in the ^{13}C NMR spectrum, for sulfones **5** and **6** respectively. In the HMBC, ^2J and ^3J correlations were observed between C1 and H7, H7, H8 for sulfone **5** and C1 and H6, H7, H7, H8 for sulfone **6**. For sulfone **5**, couplings of (J = 9 and 3.5 Hz) to H7 and a long range coupling (J = 1 Hz) to H6 was observed for H8. The latter was confirmed by homonuclear ^{1}H decouplings of H8 and H6. Thus the relative stereochemistry of the carbon ring of bicyclooctanols **1**, **2** and **3** was confirmed by correlation of the ^{1}H NMR's of **1**, **2** and **3** with those of sulfones **5** and **6**.

The complete relative configuration of bicyclooctanols **1**–**3** was subsequently established by X-ray structural determination to be the $(1RS_{\mathrm{C}},6SR_{\mathrm{C}},8RS_{\mathrm{C}},RS_{\mathrm{S}})$-isomer, $(1RS_{\mathrm{C}},6SR_{\mathrm{C}},8SR_{\mathrm{C}},SR_{\mathrm{S}})$ and $(1RS_{\mathrm{C}},6SR_{\mathrm{C}},8SR_{\mathrm{C}},RS_{\mathrm{S}})$-isomer respectively. ORTEP diagrams of the molecular structures of these compounds are displayed in Fig. 1. These diagrams each clearly show the *cis* ring junction with the six-membered ring in a chair conformation fused to the puckered four-membered ring with the torsion angle C1–C8–C7–C6 ranging between 17 and 23°. In each structure the molecules pack across a crystallographic

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† Initially, oxidation of the crude sulfoxide product mixture was carried out with Oxone® (1.0 equivalent) in water–methanol (1 : 1) at room temperature for 16 hours. One of the compounds isolated after extraction with ethyl acetate and by column chromatography (ethyl acetate–hexane 20 : 80 increasing to 50 : 50 in 5% increments) was the ester arising from over oxidation of the monoalkylated sulfone *via* a Baeyer–Villiger type process to give a seven-membered lactone which was subsequently transesterified with methanol under the conditions of Oxone® oxidation. *6-Hydroxy-8-phenylsulfonyloctanoic acid, methyl ester* was obtained as a colourless oil (Found: C, 57.25; H, 7.08. $C_{15}H_{22}O_5S$ requires C 57.30; H, 7.05); ν_{max}(KBr)/cm^{-1} 3510 (m), 1734 (s), 1305 (m), 1148 (m); δ_{H}(400 MHz) 1.22–1.32 (1H, m, H4), 1.32–1.44 (2H, m, H4, H5), 1.46–1.62 (2H, m, 2 × H3), 1.64–1.75 (1H, m, H7), 1.81–1.92 (1H, m, H7), 2.25 (2H, dd, $J_{2,3}$ 8, $J_{2,3}$ 8, 2 × H2), 2.60 (1H, br s, $W_{h/2}$ 28, OH), 3.10–3.20 (1H, m, H8), 3.22–3.33 (1H, m, H8), 3.60 (4H, m, –OCH$_3$, H6), 7.50–7.60 (3H, m, SO$_2$Ph), 7.80–7.90 (2H, m, SO$_2$Ph); δ_{C}(50 MHz) 24.6 (C3), 25.0 (C4), 30.0 (C7), 33.8 (C2), 37.0 (C5), 51.6 (C6), 53.1 (C8), 69.5 (–OCH$_3$), 127.7, 128.0 (o-C$_6$H$_5$), 129.4 (m-C$_6$H$_5$), 133.8 (p-C$_6$H$_5$), 139.1 (i-C$_6$H$_5$), 174.2 (C=O); (ESMS+) 337 (MNa$^+$, 100%).

DOI: 10.1039/b107705h

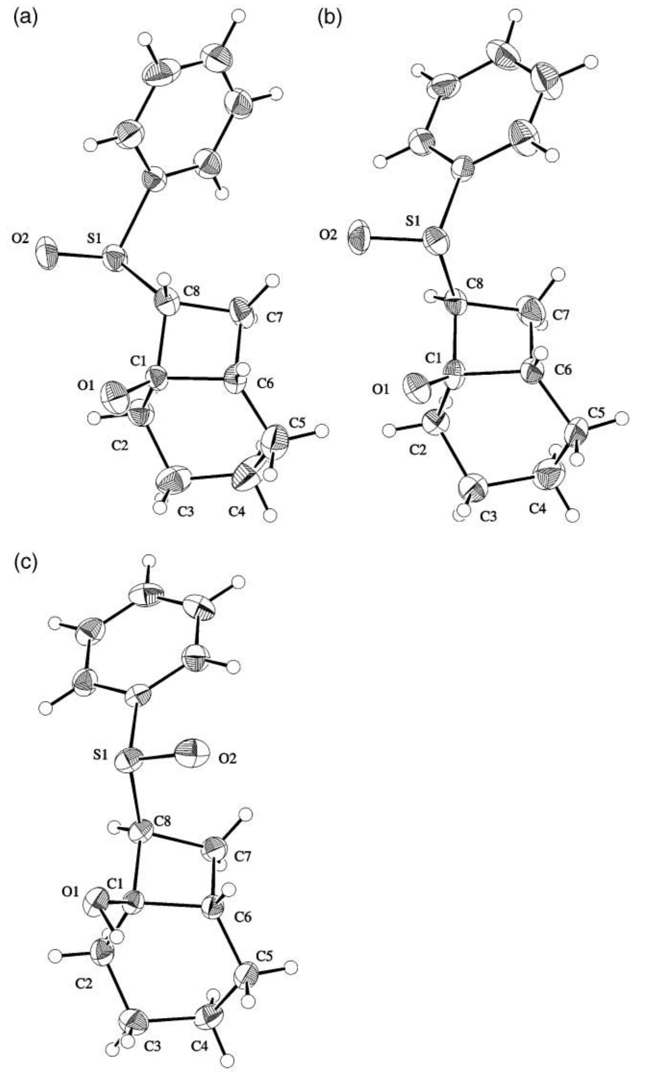


Fig. 1 Molecular structure of (a) bicyclooctanol **1**, (b) bicyclooctanol **2** and (c) bicyclooctanol **3**. Displacement ellipsoids are drawn at 30% probability level.

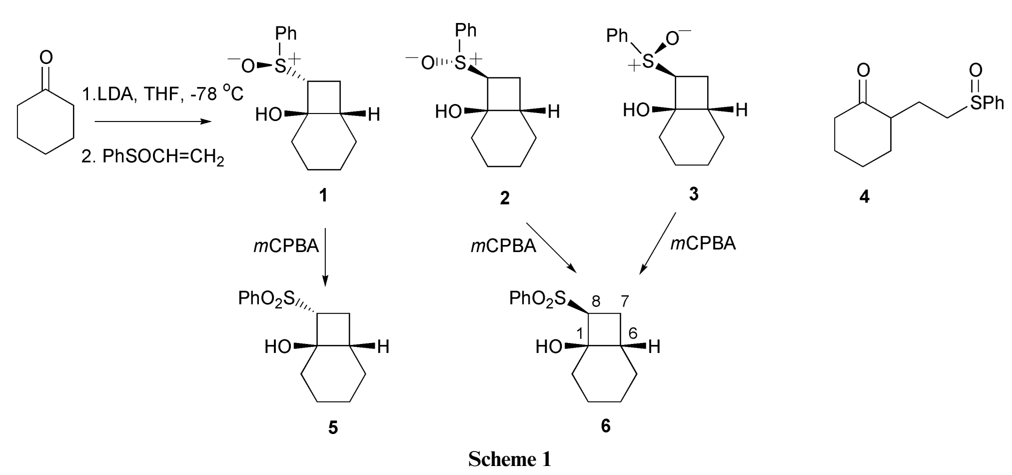
inversion centre as H-bonded dimers with O1 ··· O2 distances of the order of 2.7–2.8 Å. The existence of all three structures as dimers was interesting in that it could be accomodated whatever the initial conformational structure of the S=O and C–OH bonds.

Initially, the lithium enolate of cyclohexanone was reacted with phenyl vinyl sulfoxide in THF under a nitrogen atmosphere at −30 °C for 45 minutes. In the crude mixture, bicyclooctanols **1** (13%), **2** (32%), **3** (5%) and monoalkylated sulfoxide **4** (24%) were present. The alkylation of various enolates with vinyl sulfoxides to produce ketosulfoxides has been described.[6] Cyclobutanol formation has been observed in one instance with a functionalised ketone.[7] In the above reaction, the formation of bicyclobutanols **1**–**3** in a combined unoptimized yield of 48% compared to 24% yield of the monoalkylated sulfoxide **4** from simple substrates under mild conditions prompted us to examine improving the yield of bicyclobutanols **1**–**3**. Due to the presence of monoalkylated sulfoxide **4** the above reaction was repeated with an immediate quench using ammonium chloride. Unreacted phenyl vinyl sulfoxide was recovered and less than 5% of other products were observed. We now studied the effects of reaction time, temperature and concentration on the product distribution.

Table 1 Time course study over 24 hours: % composition of bicyclooctanols **1**, **2** and **3** or monoalkylated sulfoxide **4** in total reaction product mixture

	Product composition (%)					
Time/h	Phenyl vinyl sulfoxide	**1**	**2**	**3**	**4**	**1**, **2** and **3**
0.25	8	33	43	8	8	84
1.25	2	33	43	5	17	81
5.25	0	20	31	2	47	53
24.0	0	0	0	0	100	0

A time course experiment was carried out to determine an appropriate reaction time for bicyclooctanol formation. Thus the lithium enolate of cyclohexanone was reacted with phenyl vinyl sulfoxide in THF under a nitrogen atmosphere at −10 °C in the dark using a cryogenic unit for temperature control. Over a 24 hour period, aliquots of the reaction mixture were analyzed. We carried out this and ensuing reactions in the dark to exclude competing pathways which may be promoted by light.[8] The results are presented in Table 1. A clear trend can be seen over 24 h. Bicyclooctanol formation was favoured with short reaction times, of less than 15 minutes. After 24 hours only monoalkylated sulfoxide **4** was observed. The presumed ring opening of the bicyclooctanol intermediate to form the monoalkylated sulfoxide **4** upon quenching was observed to be relatively slow as the ratio of combined bicyclooctanols **1**–**3** to monoalkylated sulfoxide **4** at 5.25 hrs was 55 : 45 respectively. The exact time of complete conversion to monoalkylated sulfoxide **4** was not established. A further experiment at the temperature of −30 °C, combined with rapid addition of phenyl vinyl sulfoxide, after 5 minutes reaction time gave bicyclooctanols **1** (10%), **2** (26%), **3** (5%), monoalkylated sulfoxide **4** (3%) and unreacted phenyl vinyl sulfoxide (27%). The decreased reaction time of 5 minutes resulted in decreased conversion of phenyl vinyl sulfoxide and thus a reaction time of 10 minutes was chosen for the remaining studies. A smaller scale of reactants and thus a lower concentration (0.085 M) of enolate was used.



Scheme 1

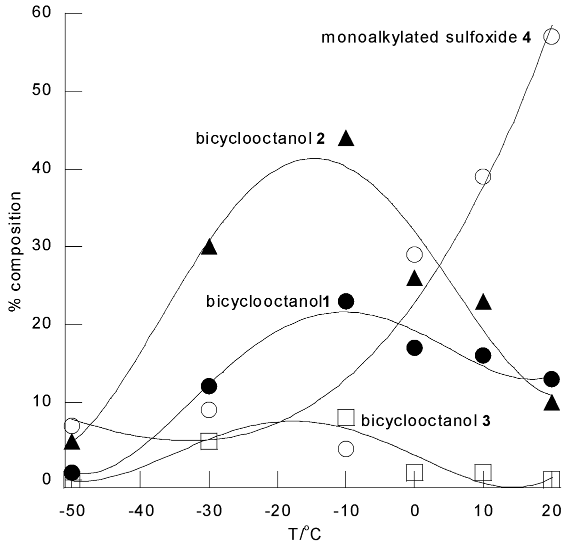


Fig. 2 Reaction temperature *vs.* % composition of product in total reaction products with 0.085 M of cyclohexanone enolate for the products, bicyclooctanol **1** (●), bicyclooctanol **2** (▲), bicyclooctanol **3** (□) and monoalkylated sulfoxide **4** (○).

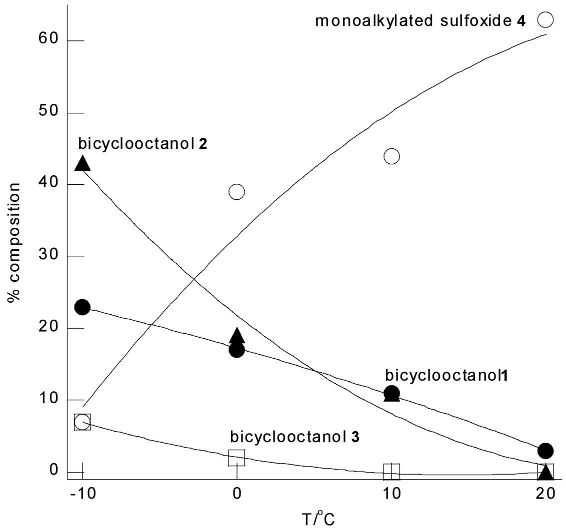


Fig. 3 Reaction temperature *vs.* % composition of product in total reaction products with 0.17 M of cyclohexanone enolate for the products, bicyclooctanol **1** (●), bicyclooctanol **2** (▲), bicyclooctanol **3** (□) and monoalkylated sulfoxide **4** (○).

Next, the effects of temperature were explored. Six enolate trapping experiments were carried out at the discreet temperatures of −50 °C, −30 °C, −10 °C, 0 °C, 10 °C and 20 °C. The results are summarised in Fig. 2. At −30 °C bicyclooctanol formation decreased as a result of incomplete conversion of phenyl vinyl sulfoxide and at −50 °C bicyclooctanol formation was less than 6%. Similarly, alkylation of the cyclohexanone enolate to form monoalkylated sulfoxide **4** at the lower temperatures was also reduced. Bicyclooctanol **2** was observed to be the major bicyclooctanol product between −30 °C and 10 °C. At these temperatures bicyclooctanols **1** and **3** are also observed. At 20 °C bicyclooctanols **1** and **2** are present in similar yield and bicyclooctanol **3** was not observed. Monoalkylated sulfoxide **4** was also formed. The ratio of combined bicyclooctanol **1**–**3** to monoalkylated sulfoxide **4** changes from a 95 : 5 ratio at −10 °C to a 29 : 71 ratio at 20 °C.

Next, the effect of concentration was examined. Four enolate trapping experiments were carried out at the discreet temperatures of −10 °C, 0 °C, 10 °C and 20 °C. This series was conducted at twice the concentration of the enolate (0.17 M) compared with the above experiments which were carried at a 0.085 M concentration of the enolate. The results are summarised in Fig. 3.

At 0.17 M bicyclooctanol **2** was observed to be the major bicyclooctanol product at 0 °C and −10 °C. At these temperatures bicyclooctanols **1** and **3** are also observed. At 10 °C bicyclooctanols **1** and **2** are present in similar yield and bicyclooctanol **3** was not observed. At 20 °C the only bicyclooctanol observed was **1** in 3% yield. Monoalkylated sulfoxide **4** was also formed. The ratio of combined bicyclooctanols **1**–**3** to monoalkylated sulfoxide **4** changes from a 91 : 9 ratio at −10 °C to 5 : 95 ratio at room temperature. At −10 °C the ratio of the combined bicyclooctanols **1**–**3** and monoalkylated sulfoxide **4** was comparable between 0.085 M and 0.17 M. However, the point at which bicyclooctanol **2** was the major bicyclooctanol product changed from 10 °C at 0.085 M to 0 °C at 0.17 M. Monoalkylated sulfoxide **4** was observed in increased yield of 63% at 0.17 M as compared to a yield of 57% at 0.085 M. A further experiment conducted at the concentration of 0.017 M with respect to the enolate was carried out −10 °C, the temperature at which bicyclooctanol formation was observed to predominate. At this concentration, bicyclooctanols **1** (11 %), **2** (31%), **3** (3%) and monoalkylated sulfoxide **4** (10%) were observed in decreased yields in addition to an increase in unreacted phenyl vinyl sulfoxide (18%).

The scope of the current study on the reaction of the lithium enolate of cyclohexanone with phenyl vinyl sulfoxide was restricted to reactions carried out in the dark. Under these conditions we found that the length of reaction time, the temperature and the concentration of the enolate were all critical to the formation of bicyclooctanol in preference to the monoalkylated sulfoxide **4**. The bicyclooctanol intermediates are relatively stable under the reaction conditions for periods of hours (<5 hours) but eventually ring open to form the monoalkylated sulfoxide **4** upon quenching of the reaction at 24 hours. It was established that a short reaction time of 10 minutes favoured the yield of bicyclooctanols **1**–**3** in conjunction with excellent conversion of phenyl vinyl sulfoxide.

From the temperature and concentration studies, the ratio of bicyclooctanols **1**–**3** to monoalkylated sulfoxide **4** and total conversion of phenyl vinyl sulfoxide varied significantly. The general effect of lower temperature was to decrease conversion of phenyl vinyl sulfoxide and that of higher temperature to increase formation of monoalkylated sulfoxide **4** in preference to bicyclooctanols **1**–**3**. At −10 °C, the general effect of concentration was at dilute concentration (0.017 M), conversion of phenyl vinyl sulfoxide was decreased with concominant decrease in bicyclooctanol formation. However, at the other concentrations studied (0.085 M and 0.17 M) the ratio of bicyclooctanols **1**–**3** to monoalkylated sulfoxide **4** varied slightly from 95 : 5 to 91 : 9 respectively. This ratio varied significantly over the temperature range −10 °C to room temperature and between the enolate concentration of 0.17 M and 0.085 M (Fig. 4). At higher enolate concentration, of 0.17 M compared to 0.085 M, and higher temperature of above −10 °C, bicyclooctanol formation was decreased. Thus the point at which bicyclooctanols **1**–**3** was preferred over monoalkylated sulfoxide **4** formation was dependent on both the temperature and concentration used. It was established that a critical temperature of −10 °C and an enolate concentration of 0.085 M was required for formation of bicyclooctanols **1**–**3**. By accurate control of the temperature and concentration, and reaction time the bicyclooctanols **1**–**3** were obtained in a yield of 75% and in a ratio of 95 : 5 to monoalkylated sulfoxide **4**. The dramatic change in product ratios obtained from the above studies are suggestive of an ionic process.

The ratio of bicyclooctanols **1** : **2** : **3** also was shown to be dependent on the temperature and concentration used. Noteworthy is the order of formation of the bicyclooctanols **1**–**3**. Under higher temperature and concentration only bicyclooctanol **1** was observed, albeit in low yield. Bicyclooctanol **3**

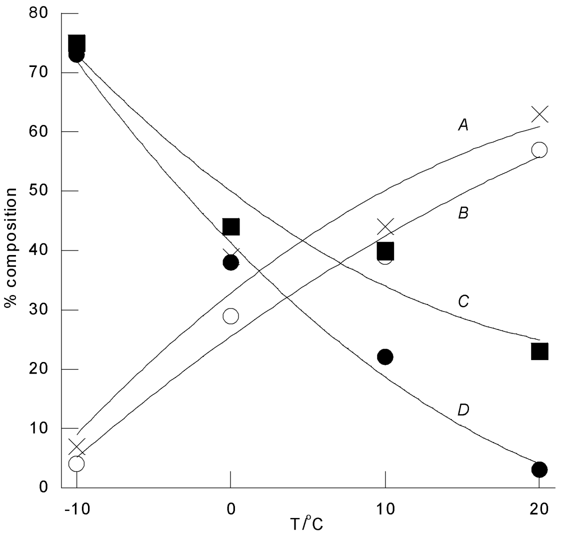


Fig. 4 Effects of concentration and reaction temperature on the % composition of bicyclooctanols **1**, **2** and **3** or monoalkylated sulfoxide **4** in total reaction products for cyclohexanone enolate of 0.085 or 0.17 M: monoalkylated sulfoxide **4** at 0.17 M (*A*), monoalkylated sulfoxide **4** at 0.085 M (*B*), bicyclooctanols **1**, **2** and **3** at 0.085 M (*C*), and bicyclooctanols **1**, **2** and **3** at 0.17 M (*D*).

was the minor isomer and initially formed at lower temperatures compared to bicyclooctanols **1** and **2**. Formation of bicyclooctanols **2** as the major isomer was favoured by lower temperature and lower concentration. Factors such as thermodynamic stability of the products, and steric interactions in the intermediates leading to the bicyclooctanols **1**–**3** presumably influence the ratio of **1** : **2** : **3** observed. The position of the oxygens, phenyl ring and the bicyclooctanol ring in the X-ray structures of **1**–**3** are supportive of this.

Bicyclooctanols **2** and **3** were established to be epimeric at sulfur. The sulfur epimer of bicyclooctanol **1** was not observed. The absence of this epimer may be due to unfavourable steric interactions between the phenyl ring and the six-membered ring derived form the cyclohexanone.

In conclusion, we have established that with control of the reaction time, temperature, and concentration, the reaction of the lithium enolate of cyclohexanone with phenyl vinyl sulfoxide gave bicyclooctanols **1**–**3** as the major product(s) in 75% yield and containing <5% of the monoalkylated sulfoxide **4**. This is the first example of the controlled *in situ* alkylation of a lithium enolate and subsequent ring closure to form a fused six and four-membered ring system bearing a bridgehead hydroxy group. This occurs to give exclusively the *cis* ring junction in all bicyclooctanol products suggesting a selective process for the C1–C8 bond formation. Noteworthy is that the reaction occurs in the absence of any additives and can be controlled to give synthetically useful yields of bicycloaddition adduct in preference to the monoalkylated adduct. The formation of bicyclooctanols **1**–**3** in the absence of light indicates their formation is likely to occur *via* an ionic process or alternatively a thermally allowed SET process. Competeing pathways may be involved in the formation of bicyclooctanols **1**–**3** and monoalkylated sulfoxide **4**. Although more complex ring systems[9] have been generated using Michael type processes, the direct formation of a fused six-four membered ring system using simple synthons under the partially optimised conditions established here indicates that the reaction may have potential for synthetic applications. From both preparative and mechanistic viewpoints the reaction is important and further investigations are in progress.

Experimental

^{1}H NMR and ^{13}C NMR spectra were assigned through use of COSY, HMBC and HMQC experiments. All NMR spectra were recorded on Varian Gemini 200 or Varian Unity 400 spectrometers, with samples dissolved in $CDCl_3$, and referenced to the solvent peak. Infrared spectra were recorded on a Perkin–Elmer FTIR 1725X spectrophotometer as KBr discs. Mass Spectra were recorded on a Fisons VG-Platform II, using electrospray as the ionization technique, and using Mass Lynx Version I (IBM) to acquire and process data. Melting points were recorded on a Gallenkamp Variable Temperature Apparatus, and are uncorrected. All chromatographic separations were carried out by flash chromatography with Merck silica gel 60 (70–230 mesh, ATM). Analytical thin-layer chromatography (tlc) was carried out with Merck precoated tlc plastic sheets coated with silica gel 60 F254 (0.2 mm). Lithium diisopropyl amine was standardized by titration against 2,5-dimethoxybenzyl alcohol prior to use.[10] Solvents and commercially available reagents were purified in the standard manner.

^{1}H NMR product analysis and determination of percentage composition

The crude product mixtures were dried under high vacuum, freeze dried, and the mass of the crude product determined. The ^{1}H NMRs were obtained using $CDCl_3$ as solvent. A D_2O exchange was performed on all samples and the ^{1}H 400 (MHz) spectrum obtained. Integration of the baseline resolved peaks at δ 3.20, 3.14, 3.05, 2.95 and 6.18 ppm, for bicyclooctanols **1**, **2**, **3**, monoalkylated sulfoxide **4** and unreacted phenyl vinyl sulfoxide respectively, was used to calculate the percentage composition of these components from the integral of the total crude mixture. The crude product mixtures from experiments −30 °C, 45 minutes, −10 °C 24 hour timecourse and −30 °C, 5 minutes were not freeze dried prior to analysis. Crude yields greater than the theoretical 100% yield were found to include water and this was included in calculations.

Enolate trapping

Lithium enolate of cyclohexanone. The lithium enolate of cyclohexanone was generated using LDA (~1.5 M, 5.60 mmol, 3.70 ml) and cyclohexanone (0.50 g, 0.53 ml, 5.10 mmol) in THF (30 ml) at −78 °C (0.17 M) or by using LDA (~1.7 M, 2.80 mmol, 1.65 ml) and cyclohexanone (0.25 g, 0.26 ml, 2.55 mmol) in THF (30 ml) at −78 °C (0.085 M) or by using LDA (~1.6 M, 2.80 mmol, 1.75 ml) and cyclohexanone (0.25 g, 0.26 ml, 2.55 mmol) in THF (150 ml) at −78 °C (0.017 M).

−30 °C, 45 minutes. The lithium enolate of cyclohexanone (5.10 mmol) was allowed to warm to −30 °C. Phenyl vinyl sulfoxide (0.78 g, 0.68 ml, 5.10 mmol) added dropwise over 5 minutes at a rate such that the temperature remained at −30 °C. The reaction stirred for 45 minutes at −30 ± 5 °C. The reaction was quenched with NH_4Cl (saturated aqueous) and extracted with ethyl acetate (3 × 50 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$), filtered and evaporated to give the crude product mixture as an amber oil (1.47 g). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (24%); bicyclooctanol **1** (13%); bicyclooctanol **2** (32 %); bicyclooctanol **3** (5%).

−10 °C, 24 hour timecourse. The lithium enolate of cyclohexanone was generated using LDA (~1.3 M, 17.2 ml, 22.41 mmol) and cyclohexanone (2.1 ml, 2.0 g, 20.38 mmol) in THF (125 ml) at −78 °C. After warming to −12 °C, the reaction was placed in the dark ‡ and phenyl vinyl sulfoxide (2.7 ml, 3.1 g, 20.38 mmol)

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‡ Reactions done in the dark were carried out with the reaction vessel thoroughly covered in aluminium foil. Dark conditions were applied before electrophile addition and were maintained until after the reaction was quenched.

was added over 15 minutes at a rate such that the temperature remained at −10 °C. The reaction stirred for 24 hours at −10 ± 5 °C Aliquots (15 ml) were removed at the end of sulfoxide addition (0.25 hours), 1.25, and 5.25 hours. Each aliquot was quenched and worked up as described above. The crude product mixture was obtained as a yellow oil. After 24 hours, the remaining reaction mixture was quenched and extracted in the same manner as the aliquots to give the crude product as an amber oil. The crude products from each aliquot were analysed by ^{1}H NMR (400 MHz) (Table 1).

−30 °C, 5 minutes. The lithium enolate of cyclohexanone (5.10 mmol) was allowed to warm to −30 °C and phenyl vinyl sulfoxide (0.78 g, 0.68 ml, 5.10 mmol) added as a bolus. The reaction was stirred for 5 minutes. The temperature was maintained at −30 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber oil (1.34 g). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (3%); bicyclooctanol **1** (11%); bicyclooctanol **2** (26%); bicyclooctanol **3** (5%); phenyl vinyl sulfoxide (27 %).

20 °C and 0.085 M. The lithium enolate of cyclohexanone (2.55 mmol) was allowed to warm to 20 °C, placed in the dark and phenyl vinyl sulfoxide (0.39 g, 0.34 ml, 2.55 mmol) was added as a bolus and the reaction mixture stirred for 10 minutes. The temperature was maintained at 20 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber oil (587 mg). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (57%); bicyclooctanol **1** (13%); bicyclooctanol **2** (10 %).

10 °C and 0.085 M. The lithium enolate of cyclohexanone (2.55 mmol) was allowed to warm to 10 °C, placed in the dark and phenyl vinyl sulfoxide (0.39 g, 0.34 mL, 2.55 mmol) was added as a bolus and the reaction mixture stirred for 10 minutes. The temperature was maintained at 10 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber oil, which later solidified (610 mg). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (39%); bicyclooctanol **1** (16%); bicyclooctanol **2** (23%); bicyclooctanol **3** (1 %).

0 °C and 0.085 M. The lithium enolate of cyclohexanone (2.55 mmol) was allowed to warm to 0 °C, placed in the dark and phenyl vinyl sulfoxide (0.39 g, 0.34 mL, 2.55 mmol) was added as a bolus and the reaction mixture stirred for 10 minutes. The temperature was maintained at 0 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as a dark amber solid (584 mg). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (29%); bicyclooctanol **1** (17%); bicyclooctanol **2** (26 %); bicyclooctanol **3** (1 %).

−10 °C and 0.085 M. The lithium enolate of cyclohexanone (2.55 mmol) was allowed to warm to −10 °C, placed in the dark and phenyl vinyl sulfoxide (0.39 g, 0.34 mL, 2.55 mmol) was added as a bolus and the reaction mixture stirred for 10 minutes. The temperature was maintained at −10 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber solid (577 mg). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (4 %); bicyclooctanol **1** (23%); bicyclooctanol **2** (44%); bicyclooctanol **3** (8%).

−30 °C and 0.085 M. The lithium enolate of cyclohexanone (2.55 mmol) was allowed to warm to −30 °C, placed in the dark and phenyl vinyl sulfoxide (0.39 g, 0.34 mL, 2.55 mmol) was added as a bolus and the reaction mixture stirred for 10 minutes. The temperature was maintained at −30 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber oil (528 mg). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (9%); bicyclooctanol **1** (12%); bicyclooctanol **2**(30 %); bicyclooctanol **3** (5%); phenyl vinyl sulfoxide (19%).

−50 °C and 0.085 M. The lithium enolate of cyclohexanone (2.55 mmol) was allowed to warm to −50 °C, placed in the dark and phenyl vinyl sulfoxide (0.39 g, 0.34 mL, 2.55 mmol) was added as a bolus and the reaction mixture stirred for 10 minutes. The temperature increased to −40 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber oil (286 mg). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (7%); bicyclooctanol **1** (1%); bicyclooctanol **2** (5%); phenyl vinyl sulfoxide (39%).

20 °C and 0.17 M. The lithium enolate of cyclohexanone (5.10 mmol) was allowed to warm to 20 °C, placed in the dark and phenyl vinyl sulfoxide (0.78 g, 0.68 mL, 5.10 mmol) was added as a bolus and the reaction mixture stirred for 10 minutes. The temperature was maintained at 20 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber oil (1.28 g). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (63%); bicyclooctanol **1** (3%).

10 °C and 0.17 M. The lithium enolate of cyclohexanone (5.10 mmol) was allowed to warm to 10 °C, placed in the dark and phenyl vinyl sulfoxide (0.78 g, 0.68 ml, 5.10 mmol) was added as a bolus and the reaction mixture stirred for 10 minutes. The temperature was maintained at 10 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber oil (1.28 g). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (44%); bicyclooctanol **1** (11 %); bicyclooctanol **2** (11 %).

0 °C and 0.17 M. The lithium enolate of cyclohexanone (5.10 mmol) was allowed to warm to 0 °C, placed in the dark and phenyl vinyl sulfoxide (0.78 g, 0.68 mL, 5.10 mmol) was added as a bolus and the reaction mixture stirred for 10 minutes. The temperature was maintained at 0 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber oil (1.26 g). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (39%); bicyclooctanol **1** (17%); bicyclooctanol **2** (19%); bicyclooctanol **3** (2%).

−10 °C and 0.17 M. The lithium enolate of cyclohexanone (5.10 mmol) was allowed to warm to −10 °C, placed in the dark and phenyl vinyl sulfoxide (0.78 g, 0.68 mL, 5.10 mmol) was added as a bolus and the reaction mixture stirred for 10 minutes. The temperature was maintained at −10 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as a dark amber solid (1.24 g). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (7%); bicyclooctanol **1** (23%); bicyclooctanol **2** (43%); bicyclooctanol **3** (7%).

−10 °C and 0.017 M. The lithium enolate of cyclohexanone (2.55 mmol) was allowed to warm to −10 °C, placed in the dark and phenyl vinyl sulfoxide (0.39 g, 0.34 ml, 2.55 mmol) was added as a bolus and the reaction mixture stirred for 10 minutes. The temperature was maintained at −10 °C during this time. The reaction was quenched and worked up as described above. The crude product mixture was obtained as an amber oil (512 mg). The percentage composition of the major products, as determined by ^{1}H NMR (400 MHz) analysis of the crude product mixture, was: monoalkylated sulfoxide **4**, as a mixture of diastereomers (10%); bicyclooctanol **1** (11 %); bicyclooctanol **2** (31 %); bicyclooctanol **3** (3%); phenyl vinyl sulfoxide (18%).

Isolation of bicyclooctanols 1–3

Bicyclooctanols 1, 2 and monoalkylated sulfoxide 4. The crude product mixture from the reaction between the lithium enolate of cyclohexanone and phenyl vinyl sulfoxide at 20 °C in the dark (2.55 mmol scale) was separated by silica column chromatography (4% isopropanol in DCM) and three major fractions were obtained.

Fraction 1 (303 mg, 47%) contained a 1 : 1 diastereomeric mixture of 2-[2′-(phenylsulfinyl)ethyl]cyclohexanone **4** as a pale yellow solid, mp 88–89 °C§ (ether), (lit.,[7] 83–84 °C), ν_{max}(KBr)/cm^{-1} 1699 (s), 1032 (m); δ_H(400 MHz) (* denotes second isomer) 1.32–1.48 (1H, m, H3), 1.50–1.80 (3H, m, H1′, H4, H5), 1.80–2.20 (4H, m, H1′, H3, H4, H5), 2.20–2.42 (3H, m, H2, 2 × H6), 2.46–2.58 (1H, m, H2), 2.70* (1H, ddd, $J_{2',1'}$ 5, $J_{2',1'}$ 10, $J_{2',2'}$ 13, H2′), 2.84–2.91 (2H, m, 2 × H2′), 2.95* (1H, ddd, $J_{2',1'}$ 5, $J_{2',1'}$ 10, $J_{2',2'}$ 13, H2′), 7.40–7.65 (5H, m, C_6H_5); δ_C(100 MHz) (* denotes second isomer) 22.0, 23.0* (C1′), 25.0 (C4), 27.9 (C5), 34.3 or 34.4 (C3), 42.1 (C6), 49.2 or 49.8 (C2), 54.3, 55.1* (C2′), 123.9 or 124.0 (*o*-C_6H_5), 129.1 (*m*-C_6H_5), 130.8 (*p*-C_6H_5), 143.5 or 144.0 (*i*-C_6H_5 ipso), 212.1 (C1); (ESMS+) 251 (MH$^+$, 100%); (LSIMS) (Found: 251. 11161. $C_{14}H_{19}O_2S$ requires 251.11058).

Fraction 2 (64 mg, 10%) contained (*1RS*$_C$,6SR$_C$,8SR$_C$,SR$_S$)-8-phenylsulfinylbicyclo[4.2.0]octan-1-ol **2**, as a white solid, mp 121–123 °C (ether) (Found: C, 67.30; H, 7.35; S, 13.06. $C_{14}H_{18}O_2S$ requires C, 67.16; H, 7.25; S, 12.81); ν_{max}(KBr)/cm^{-1} 3338 (s), 2930 (s) 2912 (s), 1031 (s); δ_H(400 MHz) 1.20–1.38 (2H, m, H4, H5), 1.38–1.52 (3H, m, H4, H3), 1.52–1.61 (1H, m, H2), 1.66–1.80 (3H, m, H2, H5, H7), 2.00 (1H, ddd, $J_{7,8\alpha}$ 4, $J_{7,6\beta}$ 10, $J_{7,7}$ 13, H7), 2.69–2.79 (1H, m, H6β), 3.14 (1H, ddd, $J_{8\alpha,6\beta}$ 1, $J_{8\alpha,7}$ 4, $J_{8\alpha,7}$ 8, H8α), 4.15 (1H, s, OH), 7.42–7.52 (3H, m, *m*- and *p*-C_6H_5), 7.63–7.70 (2H, m, *o*-C_6H_5); δ_C(100 MHz) 20.8 (C3), 21.1 (C4), 21.4 (C7), 25.0 (C5), 36.5 (C2), 40.9 (C6), 67.0 (C8), 75.8 (C1), 125.0 (*o*-C_6H_5), 129.0 (*m*-C_6H_5),130.9 (*p*-C_6H_5), 142.7 (*i*-C_6H_5); (ESMS+) 257 (MLi$^+$, 100%); (LSIMS) (Found: 251.11134. $C_{14}H_{19}O_2S$ requires 251.11058).

Fraction 3 (70 mg, 11%) contained *(1RS$_C$,6SR$_C$,8RS$_C$,RS$_S$)-8-phenylsulfinylbicyclo[4.2.0]octan-1-ol* **1**, as an off-white solid, mp 146–147 °C (ether) (Found: C, 67.00; H, 7.24; S, 12.78. $C_{14}H_{18}O_2S$ requires C, 67.16; H, 7.25; S, 12.81); ν_{max}(KBr)/cm^{-1} 3420 (s), 2916 (m), 1010 (m); δ_H(400 MHz) 1.21–1.70, 2.04–2.32 (11H, m, 2 × H2, 2 × H3, 2 × H4, 2 × H5, H6β, 2 × H7), 3.20 (1H, s, OH), 3.29 (1H, dd, $J_{8\beta,7}$ 8, $J_{8\beta,7}$ 10, H8β), 7.44–7.51 (3H, m, *m*- and *p*-$C_6H_5C_6H_5$), 7.57–7.62 (2H, m, *o*-C_6H_5); δ_C(100 MHz) 18.7, 20.1, 21.2, 23.2 (C3, C4, C5 & C7), 31.6 (C2), 38.6 (C6), 69.3 (C8), 74.5 (C1), 124.2 (*o*-C_6H_5), 129.2 (*m*-C_6H_5), 131.1 (*p*-C_6H_5), 142.2 (*i*-C_6H_5); (ESMS+) 257 (MLi$^+$, 100%); (LSIMS) (Found: 251.10956. $C_{14}H_{19}O_2S$ requires 251.11058).

Bicyclooctanol 3. The crude reaction mixture from the reaction between the lithium enolate of cyclohexanone and phenyl vinyl sulfoxide at −10 °C in the dark (5.10 mmol scale) was separated be silica column chromatography (100% ether) and two major fractions were obtained.

Fraction 1 (74 mg, 6%) contained *(1RS$_C$,6SR$_C$,8SR$_C$,RS$_S$)-8-phenylsulfinyl bicyclo[4.2.0]octan-1-ol* **3** as a white solid, mp 134–135 °C (ether) (Found: C, 67.49; H, 7.34; S, 12.73. $C_{14}H_{18}O_2S$ requires C, 67.16; H, 7.25; S, 12.81); ν_{max}(KBr)/cm^{-1} 3318 (s), 2934 (s), 1017 (s);); δ_H(400 MHz) 1.20–1.70 (8H, m, H2, 2 × H3, 2 × H4, 2 × H5, H7), 1.86–1.98 (1H, m, H2), 2.21 (1H, ddd, $J_{7,8\alpha}$ 3.5, $J_{7,6\beta}$ 10, $J_{7,7}$ 12.5, H7), 2.58–2.69 (1H, m, H6β); 3.05 (1H, ddd, $J_{8\alpha,6\beta}$ 1, $J_{8\alpha,7}$ 3.5, $J_{8\alpha,7}$ 8, H8α), 3.36 (1H, s, OH), 7.41–7.50 (3H, m, *m*- and *p*-C_6H_5), 7.52–7.56 (2H, m, *o*-C_6H_5); δ_C(100 MHz) 17.4 (C7), 20.7 (C3 & C4), 24.5 (C5), 35.6 (C2), 43.3 (C6), 67.4 (C8), 74.6 (C1), 124.2 (*o*-C_6H_5), 129.0 (*m*-C_6H_5), 130.5 (*p*-C_6H_5), 141.4 (*i*-C_6H_5); (ESMS+) 257 (MLi$^+$, 100%).

Fraction 2 (851 mg, 66%) contained monoalkylated sulfoxide, **4** as a mixture of diastereomers, bicyclooctanol **1** and **2**.

Oxidation of 8-phenylsulfinylbicyclo[4.2.0]octanol 1

(1*RS*$_C$,6*SR*$_C$,8*RS*$_C$,*RS*$_S$)-8-Phenylsulfinylbicyclo[4.2.0]octan-1-ol **1** (28 mg, 0.11 mmol) in methanol (1 ml) and Oxone® (138 mg, 0.22 mmol) in water (1 ml) were stirred at room temperature for 24 hours. The reaction mixture was extracted with ethyl acetate (3 × 20 ml), the combined organic layers were washed with brine (20 ml), dried ($MgSO_4$), filtered and evaporated. Recrsytallisation of the solid residue yielded *(1RS, 6SR, 8RS)-8-phenylsulfonyl bicyclo[4.2.0]octan-1-ol* **5** (26mg, 89%) as a white solid, mp 132–134 °C (ether) (Found: C, 63.07, H, 6.79. $C_{14}H_{18}O_3S$ requires C, 63.13, H, 6.81); ν_{max}(KBr)/cm^{-1} 3494 (s), 1304 (s), 1148 (s); δ_H(400 MHz) 1.16–1.40 (2H, m, H3, H4), 1.41–1.50 (1 H, m, H5), 1.50–1.65 (3H, m, H3, H4, H5),1.76–1.88 (2H, m, H2, H7), 1.96 (1H, ddd, $J_{7,8\beta}$ 10.5, $J_{7,6\beta}$ 11, $J_{7,7}$ 11, H7), 2.14–2.25 (1H m, H6β), 2.52–2.64 (2H, m, H2, OH), 3.43 (1H, dd, $J_{8\beta,7}$ 10.5 and 11, H8β), 7.48–7.55 (2H, m, *m*-C_6H_5, 7.57–7.64 (1H, m, *p*-C_6H_5), 7.81–7.86 (*o*-C_6H_5); δ_C(100 MHz) 19.9 (C3/C4), 20.3 (C7), 21.1 (C3/C4), 23.1 (C5), 30.7 (C2), 38.9 (C6), 67.1 (C8), 76.4 (C1), 127.5(*o*-C_6H_5), 129.1 (*m*-C_6H_5),133.4 (*p*-C_6H_5),140.5 (*i*-C_6H_5); (ESMS+) 289 (MNa$^+$, 100%).

Oxidation of 8-phenylsulfinylbicyclo[4.2.0]octanol 2

3-Chloroperoxybenzoic acid (77%, 50 mg, 0.22 mmol) was added to a solution of (1*RS*$_C$,6*SR*$_C$,8*SR*$_C$,*SR*$_S$)-8-phenylsulfinyl bicyclo[4.2.0]octan-1-ol **2** (49 mg, 0.20 mmol) in chloroform (2 ml). The solution was stirred at room temperature for 21 hours. The chloroform was removed *in vacuo* and the residue taken up in ethyl acetate (25 ml). The ethyl acetate was washed with $NaHCO_3$ (saturated aqueous) (3 × 50 ml), brine (50 ml), dried ($MgSO_4$), filtered and evaporated to give a colourless oil (33 mg, 62%). Recrystallisation yielded *(1RS,6SR,8SR)-8-phenylsulfonylbicyclo[4.2.0]octan-1-ol* **6** as a white solid, mp 90–92 °C (ether) (Found: C, 63.30; H, 6.65. $C_{14}H_{18}O_3S$ requires C, 63.13, H, 6.81); ν_{max}(KBr)/cm^{-1} 3475 (s), 2934 (m), 1304 (s), 1138 (s); δ_H(400 MHz) 1.21–1.34 (1H, m, H4), 1.34–1.56 (5H, m, H2, H3, H3, H4, H5), 1.59–1.73 (1H, m, H5), 1.78–1.88 (2H, m, H2, H7), 2.32 (1H, ddd, $J_{7,8\alpha}$ 3.5, $J_{7,6\beta}$ 10, $J_{7,7}$ 13, H7), 2.82–2.92 (1H, m, H6β), 3.52 (1H, ddd, $J_{8\alpha,6\beta}$ 1, $J_{8\alpha,7}$ 3.5, $J_{8\alpha,7}$ 9,

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§ It was assumed that the difference in melting point was due to a different diastereomeric ratio in the product.

H8α), 7.49–7.56 (2H, m, *m*-C_6H_5), 7.58–7.64 (1H, m, *p*-C_6H_5), 7.89–7.94 (2H, m, *o*-C_6H_5); δ_C(100 MHz) 19.8 (C7), 20.6 & 20.7 (C3 & C4), 24.1 (C5), 35.5 (C2), 43.1 (C6), 67.1 (C8), 73.8 (C1), 127.9 (*o*-C_6H_5), 129.1 (*m*-C_6H_5), 133.5 (*p*-C_6H_5), 139.9 (*i*-C_6H_5); (ESMS+) 289 (MNa^+, 100%).

Oxidation of 8-phenylsulfinylbicyclo[4.2.0]octanol 3

3-Chloroperoxybenzoic acid (57%, 7 mg, 0.023 mmol) was added to a solution of (1RS_C,6SR_C,8SR_C,RS_S)-8-phenylsulfinylbicyclo[4.2.0]octan-1-ol **3** (6 mg, 0.024 mmol) in chloroform (1 ml). The solution was stirred at room temperature for 16 hours. The chloroform was removed *in vacuo* and the residue taken up in ethyl acetate (20 ml). The ethyl acetate was washed with $NaHCO_3$ (saturated aqueous) (3 × 50 ml), brine (50 ml), dried ($MgSO_4$), filtered and evaporated to give (1*RS*,6*SR*,8*SR*)-8-phenylsulfonylbicyclo[4.2.0] octan-1-ol **6** as a white solid (6 mg, 94%) with identical ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data as the sulfone obtained from the oxidation of bicyclooctanol **2**.

Crystal structure determination of 8-phenylsulfinylbicyclo-[4.2.0]octanols 1–3

Data collection, structure solution and refinement.¶ Unique data sets were measured at 295 K within $2\theta_{max} = 50°$ using a Rigaku AFC7R four circle diffractometer (ω-2 θ scan mode, monochromated Mo-Kα radiation $\lambda = 0.71069$ Å) yielding N independent reflections, N_o with $I > 2\sigma(I)$ being considered 'observed'. The structures were solved by direct methods and refined by full matrix least squares refinement on $|F|$. Anisotropic thermal parameters were refined for non-hydrogen atoms; (x, y, z, U_{iso})H were located by difference methods and constrained at estimated values with the exception of the hydroxyl protons on **1** and **2** which were not located. Weights derivative of $w = 1/[\sigma^2(F)]$ were employed. Conventional residuals R, R_w on $|F|$ at convergence are quoted; statistical weights were employed. Neutral atom complex scattering factors were employed, computation used the teXsan crystallographic software package, version 1.8 of the Molecular Structure Corporation.[11]

Crystal data for (1RS_C,6SR_C,8RS_C,RS_S)-8-phenylsulfinylbicyclo[4.2.0]octan-1-ol ***1***. Recrystallized from ether. $C_{14}H_{18}O_2S_1$ $M = 250.4$, orthorhombic, space group *Pbca* (D_{2h}^{15} No.61), $a = 11.296(3)$, $b = 22.296(3)$, $c = 10.547(4)$ Å, $U = 2656$ Å^3, $Z = 8$, $D_c = 1.37$ g cm^{-3}, μ (Mo-Kα) = 2.38 cm^{-1}, Crystal size: 0.60 × 0.15 × 0.05 mm, $N = 2699$, N_o $[I > 2\sigma(I)] = 1015$; $R = 0.052$, $R_w = 0.038$.

(1RS_C,6SR_C,8SR_C,SR_S)-8-Phenylsulfinylbicyclo[4.2.0]octan-1-ol ***2***. Recrystallized from ether. $C_{14}H_{18}O_2S_1$ $M = 250.4$, monoclinic, space group $P2_1$/a (C_{2h}^5 No. 14 variant), $a = 12.719(6)$, $b = 19.14(1)$, $c = 11.106(7)$ Å, β = 102.55(5)°, $U = 2639$ Å^3, $Z = 8$, $D_c = 1.26$g cm^{-3}, $F(000) = 1072$, μ (Mo-Kα) = 2.33 cm^{-1}, Crystal size: 0.25 × 0.20 × 0.15 mm, $N = 4807$, N_o $[I > 2\sigma(I)] = 1474$; $R = 0.072$, $R_w = 0.073$.

(1RS_C,6SR_C,8SR_C,RS_S)-8-Phenylsulfinylbicyclo[4.2.0]octan-1-ol ***3***. Recrystallized from ether. $C_{14}H_{18}O_2S_1$ $M = 250.4$, monoclinic, space group $P2_1$/a, $a = 12.774(2)$, $b = 9.135(2)$, $c = 11.388(2)$ Å, $\beta = 104.79(1)°$, $U = 1285$ Å^3, $Z = 4$, $D_c = 1.29$ g cm^{-3}, μ(Mo-Kα) = 2.39 cm^{-1}, Crystal size: 0.40 × 0.30 × 0.25 mm, $N = 2430$, N_o $[I > 2\sigma(I)] = 1726$; $R = 0.046$, $R_w = 0.055$.

Acknowledgements

We gratefully acknowledge support for this work from the Australian Research Council and Griffith University and the award of an APAWS to C. Rowen.

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¶ Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre (CCDC reference numbers 170562–170564). See http://www.rsc.org/suppdata/p2/b1/b107705h/ for crystallographic files in cif or other electronic format.