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The formation of bicyclo[*n*.2.0]alkan-1-ols from the reaction of the lithium enolates of simple ketones and phenyl vinyl sulfoxide †

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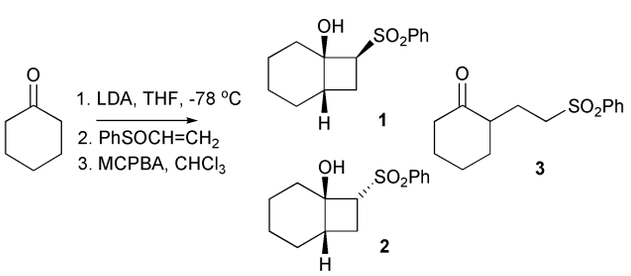
The enolates generated from cyclopentanone, cycloheptanone or cyclooctanone and LDA at −78 °C in THF react with (±)-phenyl vinyl sulfoxide under controlled conditions of temperature, reaction time, and concentration. Upon oxidation with MCPBA of the product mixtures, the novel sulfonylbicyclo[3.2.0]heptan-1-ols **10**–**12**, sulfonylbicyclo[5.2.0]-nonan-1-ols **16**–**18**, and sulfonylbicyclo[6.2.0]decan-1-ols **21** and **22** in conjunction with alkylated ketones **8**, **9**, **15**, **19** and **20** were obtained from the respective ketones. The enolate generated from cyclobutanone and LDA at −78 °C in THF reacts with (±)-phenyl vinyl sulfoxide and upon oxidation with MCPBA, the cyclohexanone **4** and monoalkylated cyclobutanone **5** were obtained. The ratio of bicyclo[*n*.2.0]alkan-1-ol to alkylated products varied with the ketone enolate, conversion of phenyl vinyl sulfoxide, time, temperature and concentration of reaction and the stability and steric strain of the final bicyclo[*n*.2.0]alkan-1-ol product.

Introduction

During the course of investigations towards the synthesis of fused-ring natural products we sought to access a fused six and four member carbocyclic ring bearing a bridgehead hydroxyl group. Recently in concurrent studies we have shown that provided accurate control of temperature, concentration, and reaction time was maintained, the reaction of the enolate generated from cyclohexanone and LDA at −78 °C in THF with (±)-phenyl vinyl sulfoxide gave novel sulfinylbicyclo[4.2.0]-octan-1-ols and monoalkylated sulfinylcyclohexanone in a 95 : 5 ratio. These compounds were oxidised with MCPBA to the sulfonylbicyclo[4.2.0]octan-1-ols **1** and **2** and the mono-alkylated sulfone **3** (Scheme 1).[1] The relative stereochemistries of the bicyclooctanols **1**–**2** were established by X-ray structural determination.[2]



Scheme 1

In the current study we sought to explore the potential scope of this cyclisation reaction, by exploring the ring size of the starting ketone. One previous example with the use of a functionalised ketone has been reported.[3] The construction of bicyclo[3.2.0]heptan-1-ols, bicyclo[5.2.0]nonan-1-ols and bicyclo[6.2.0]decan-1-ols bearing a bridgehead hydroxyl occurs typically within polycyclic compounds, although such unfunctionalised bicyclo[*n*.2.0]alkan-1-ols have been observed in limited mechanism and solvolysis studies.[4] Access to bicyclo[*n*.2.0]alkan-1-ols includes addition processes such as intramolecular [2+2] photochemical cycloaddition,[5] [2 + 2] photoaddition of a cyclic enone with a silyl enol ether,[6] photocycloaddition of bicyclo[3.3.1]nonanediones to allene,[7] photochemical cyclisation of aliphatic 4-oxoacetals,[8] cycloaddition of a silylenol ether with propynoates,[9] arynic condensation of ketone enolates,[10] condensation of dehydro dihydropyrans with ketone enolates,[11] and Norrish type-II cyclization.[12] Rearrangements are also observed and include rearrangement of tricyclo[3.1.1.0^{3,6}]heptyl and tricyclo[3.2.1.0^{3,6}]octyl systems,[13] cationic rearrangement of α-aryl pentacyclooctanes,[14] and solvolysis of substituted cyclopropyl carbinylic systems to include ring enlargement to form substituted cyclobutanols.[15] Other transformations include Clemmensen reduction of strained diketones,[16] intramolecular reductive ring closure with samarium iodide of alkene chloroketones,[17] samarium diiodide-mediated pinacolization of diketones,[18] and reduction of α-acetoxy ketones.[19] Facile access to bicyclo[3.2.0]heptan-1-ols, bicyclo[5.2.0]nonan-1-ols and bicyclo[6.2.0]decan-1-ols bearing a bridgehead hydroxyl in simple systems using the one methodology is unreported. Described herein are our investigations into the reaction of the lithium enolates of simple ketones with (±)-phenyl vinyl sulfoxide and the controlled formation of bicyclo[*n*.2.0]alkan-1-ols.

Results and discussion

Synthesis of the bicycloalkanols

The current investigation sought to explore the potential scope of the cyclisation (Scheme 1) with respect to the ring size of the starting ketone and thus the formation of bicyclo[*n*.2.0]alkan-1-ols. Four representative ketones were reacted with (±)-phenyl vinyl sulfoxide under the initial cyclisation conditions that had generated bicyclo[4.2.0]alkan-1-ols from cyclohexanone and phenyl vinyl sulfoxide. The lithium enolate of cyclobutanone, cyclopentanone, cycloheptanone or cyclooctanone was reacted at 0.155 M with (±)-phenyl vinyl sulfoxide in THF under a nitrogen atmosphere for 45 minutes (Method A, Table 1). Direct oxidation of the crude sulfoxide mixture using MCPBA was followed by analysis of the crude sulfone product mixture by ^{1}H NMR (400 MHz) spectroscopy. The product ratios are reported in Table 1. All yields are calculated on conversion of phenyl vinyl sulfoxide, as the starting ketones were generally volatile.

Cyclobutanone was reacted with phenyl vinyl sulfoxide using method A and upon oxidation gave the cyclohexanone **4**[20] and

† Electronic supplementary information (ESI) available: full experimental details. See http://www.rsc.org/suppdata/ob/b2/b208365e/

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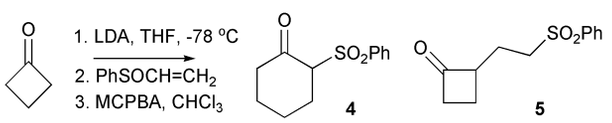
Table 1 Product yields for the reaction of cyclobutanone, cyclopentanone, cycloheptanone or cyclooctanone and phenyl vinyl sulfoxide from methods A–D

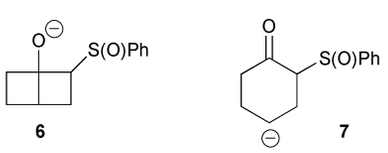
		Reaction method[a]			
Ketone	Product	A (% yield)	B	C	D
Cyclobutanone	**4**	5.5	6	—	—
	5	38.5	18	—	—
	PVS[b]	0	0.5	—	—
Cyclopentanone	**10**	3	18.5	26.5	22.5
	11	2.5	0.5	1	1
	8	55.5	19.5	22	25.5
	9	2.5	0.5	0	0
	12	1.5	0.5	0.5	1
	PVS[b]	0	6	26.5	6.5
Cycloheptanone	**16**	26	61.5	42	43.5
	17	8	8.5	5	12
	18	0	1	0	0
	15	41	3	6	9
	PVS[b]	0	5	13.5	12
Cyclooctanone	**21**	2	19	6	23
	22	0	3.5	0	6
	19	65	49.5	44	47
	20	14.5	9	2	7
	PVS[b]	0	0	21	0.5

[a] Method A (0.155 M, 45 min, −30 °C to 0 °C, laboratory light); Method B (0.155 M, 5 min, −30 °C, dark); Method C (0.01 M, 5 min, −30 °C, dark); Method D (0.31 M, 5 min, −30 °C, dark). [b] Combined recovery of phenyl vinyl sulfoxide and/or yield of phenyl vinyl sulfone.

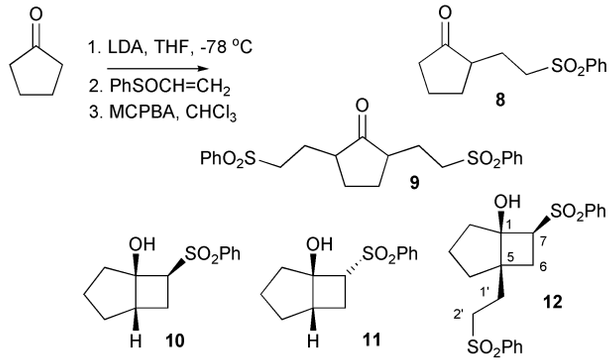


Scheme 2

monoalkylated cyclobutanone **5** (Scheme 2). Apparent polymerisation of the phenyl vinyl sulfoxide to some extent was evidenced by polymeric material in the workup. No bicyclo[2.2.0]hexan-1-ols in the crude product mixture were evident in the ^{1}H NMR spectrum or by HPLC analysis. However the presence of a bicyclohexanolide intermediate **6** in the formation of the cyclohexanone **4** is plausible. Ring opening of the intermediate **6** to break the strained bridgehead bond could give rise to an anion **7** in equilibrium with enolate anions that upon quenching and oxidation would give the cyclohexanone **4**.

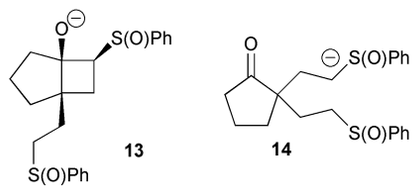


Next, cyclopentanone was reacted with phenyl vinyl sulfoxide using method A and upon oxidation gave monoalkylated cyclopentanone **8** as the major product, in conjunction with minor amounts of dialkylated cyclopentanone **9**, bicyclo[3.2.0]heptan-1-ols **10** and **11** and the unexpected bicyclo[3.2.0]heptan-1-ol **12** (Scheme 3). The predominance of monoalkylated cyclopentanone **8** was consistent with the longer reaction time of 45 minutes, where a similar trend was observed with cyclohexanone.[1] Polyalkylations of non-symmetrical ketone enolates in which only alkyl groups are present are generally not regioselective and are dependent on the nature of the substrate, the base, the cation and the solvent.[21] Thus, equilibration of the monoalkylated enolate must occur at two sites to give the substitution patterns observed in dialkylated cyclopentanone **9** and substituted bicyclo[3.2.0]heptan-1-ol **12**. The formation of the corresponding sulfinylbicyclo[3.2.0]heptan-1-olide intermediate **13** presumably arises from cyclisation of the 2,2-dialkylated

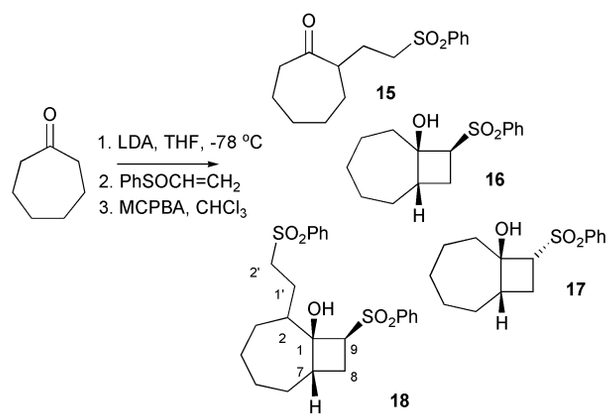


Scheme 3

intermediate **14**. This is perhaps promoted by conformational effects arising from the presence of two alkyl side chains at position two.



Next, cycloheptanone was reacted with phenyl vinyl sulfoxide using method A and upon oxidation gave monoalkylated cycloheptanone **15**[22] as the major product, in conjunction with the bicyclo[5.2.0]nonan-1-ols **16** and **17** (Scheme 4). In the final example, cyclooctanone was reacted with phenyl vinyl sulfoxide using method A and upon oxidation gave monoalkylated cyclooctanone **19**[22] as the major product in conjunction with the dialkylated cyclooctanone **20** and bicyclo[6.2.0]decan-1-ol **21** (Scheme 5). Compared to the previous results for cyclopentanone and cycloheptanone, in the cyclooctanone example an increase in the dialkylated product **20** was observed. This was attributed to a difference in reactivity of the cyclooctanone enolate and a monoalkylated cyclooctanone enolate with phenyl vinyl sulfoxide. The structural identity of the novel bicyclo[*n*.2.0]alkan-1-ols was unambiguously determined prior to further synthetic investigations.



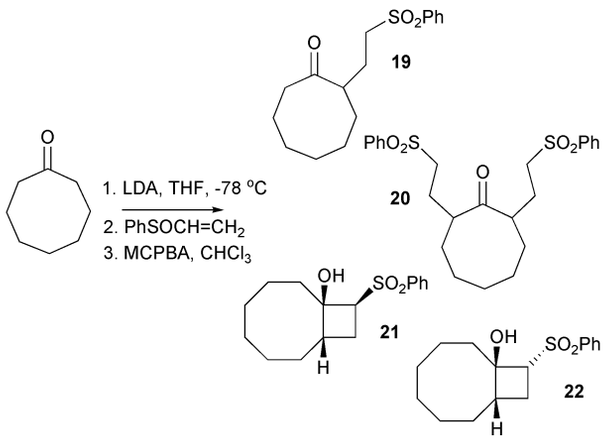
Scheme 4

Structure of the bicycloalkanols

Analytical samples of the sulfone derivatives were obtained by preparative HPLC for structural determination and characterisation. From these studies eight novel sulfonylbicyclo[*n*.2.0]alkan-1-ols were obtained, bicyclo[3.2.0]heptan-1-ols **10**–**12**, bicyclo[5.2.0]nonan-1-ols **16**–**18**, and bicyclo[6.2.0]decan-1-ols **21** and **22** (Schemes 3, 4 and 5). The characterisation data for bicyclo[*n*.2.0]alkan-1-ols **10**, **16** and **21** have been reported in a recent separate structural study.[2] The sulfonylbicyclo[*n*.2.0]-

Table 2 Key assignments and δ values (ppm) from the ^{1}H and ^{13}C NMR spectra of bicyclo[3.2.0]heptan-1-ols **10**–**12**, bicyclo[5.2.0]nonan-1-ols **16**–**18** and bicyclo[6.2.0]decan-1-ols **21** and **22**

	δ (ppm)						
	Ca	Cb	Cc	Hb	Hc	Hc^1	Hd
10	83.6	64.2	46.3	3.62 (ddd, 9.5, 5.5, < 1 Hz)	2.62–2.72	1.46–1.60	2.62–2.72
11	85.3	65.3	44.6	3.79 (ddd, 10, 10, 1 Hz)	2.04–2.22	1.68–1.95	2.45–2.54
12	83.4	62.2	49.2	3.5 (dd, 10, 7 Hz)	2.20	1.60–1.74	
16	78.9	64.1	48.7	3.530 (ddd, 9.5, 5.5, 1 Hz)	2.48–2.66	1.54–1.80	2.48–2.66
17	81.8	66.0	45.0	3.600 (dd, 10, 9 Hz)	1.90–2.07	1.65–1.78	2.17–2.30
18	81.7	62.7	49.6	3.74 (dd, 10.5, 4 Hz)	2.47–2.62	1.27–1.46	2.47–2.62
21	78.3	65.3	48.1	3.44 (ddd, 10, 6, 1 Hz)	2.61	1.39–1.60	2.30–2.39
22	81.4	67.3	44.6	3.58 (dd, 10.5, 9 Hz)	1.86–1.95	1.62–1.77	1.96–2.05



Scheme 5

alkan-1-ols **10**–**12**, **16**–**18**, **21** and **22** were characterized by interpretation of spectral data from ^{1}H and ^{13}C one-dimensional and gCOSY, HMQC, HSQC and HMBC two-dimensional NMR spectroscopy studies. Key assignments and δ values are reported in Table 2. Using non-IUPAC labels (Fig. 1) to aid comparison, the connectivity of the cyclobutyl ring system typically was established as follows. The connectivity of the cyclobutyl ring was apparent from correlations between the signals due to Hb (δ = 3.44–3.79 ppm) and Hc (δ = 1.86–2.72 ppm) and Hc^1 (δ = 1.27–1.95 ppm) in the gCOSY. In the HSQC, CH signals were observed for Cb–Hb and Cd–Hd with the carbon signals for Cb and Cd occurring typically at around δ 65 and δ 46 ppm respectively. The quaternary carbon for Ca (about δ 80 ppm) was identified by its absence in the HSQC. In the HMBC, ^2J and ^3J correlations were observed between Ca and Hb, Hc/Hc^1 and Hd.

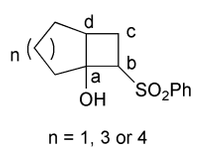


Fig. 1 Correlation of IUPAC numbering and generalised label for bicyclo[*n*.2.0]alkan-1-ols.

The relative stereochemistries of the sulfonylbicyclo[*n*.2.0]-alkan-1-ols **10**–**12**, **16**–**18**, **21** and **22** were established through a combination of X-ray crystallography and NMR spectroscopy. Using X-ray crystallography, the relative stereochemistry of bicyclo[*n*.2.0]alkan-1-ols **10**, **16** and **21** was established as reported elsewhere.[2] Thus it was determined that bicyclo-[3.2.0]heptan-1-ol **10** was the (1*RS*,5*SR*,7*SR*)-isomer, bicyclo-[5.2.0]nonan-1-ol **16** was the (1*RS*,7*SR*,9*SR*)-isomer and bicyclo[6.2.0]decan-1-ol **21** was the (1*RS*,8*SR*,10*SR*)-isomer as shown (Schemes 3–5). In previous work [1,2] we noted that the ^{1}H NMR spectrum displayed characteristic couplings and shifts for Hb, dependent on the epimer observed at Cb. These trends were correlated by X-ray crystallography of selected examples (bicyclo[*n*.2.0]alkan-1-ols **1**, **2**, **10**, **16**, **21**). By analogy, the relative stereochemistry of the bicyclo[*n*.2.0]alkan-1-ols **11**, **17** and **22** was inferred from the shift (δ ppm) and the coupling constants of Hb in the ^{1}H NMR as the relative stereochemistry was not established by 2D NMR spectroscopy methods.

An upfield δ value of Hb was indicative of a *cis* relationship between the hydroxyl and sulfonyl groups. For bicyclo[*n*.2.0]-alkan-1-ols **10**, **16** and **21**, couplings of 9.5–10 Hz and 5.5–6 Hz to Hc and Hc^1 and a long range coupling of 1 Hz, typical of cyclobutyl ring systems,[23] to Hd was observed for Hb. The long range coupling between Hb and Hd was correlated with a *trans* relationship of Hb and Hd in bicyclo[*n*.2.0]alkan-1-ols **10**, **16** and **21**. For bicyclo[*n*.2.0]alkan-1-ols **11**, **17**, and **22** couplings of 9–10 Hz, and 10–10.5 Hz to Hc and Hc^1 were observed for Hb. The absence of the 1 Hz coupling between Hb and Hd was correlated with a *cis* relationship of Hb and Hd and thus a *trans* relationship between the hydroxyl and sulfonyl groups in bicyclo[*n*.2.0]alkan-1-ols **11**, **17** and **22**. The additional 1 Hz coupling observed for Hb of bicyclo[3.2.0]heptan-1-ol **11** was assigned to a W-coupling between Hb and the hydrogen alpha to Ca in the cyclopentyl ring. Thus, it was established that bicyclo[3.2.0]heptan-1-ol **11** was the (1*RS*,5*SR*,7*RS*)-isomer, bicyclo[5.2.0]nonan-1-ol **17** was the (1*RS*,7*SR*,9*RS*)-isomer and bicyclo[6.2.0]decan-1-ol **22** was the (1*RS*,8*SR*,10*RS*)-isomer as shown (Schemes 3–5).

A further two bicyclo[*n*.2.0]alkan-1-ols were isolated and determined using gCOSY, HSQC and HMBC two-dimensional NMR spectroscopy studies to be the substituted bicyclo[*n*.2.0]-alkan-1-ols **12** and **18**. The relative stereochemistry at C5 in **12** and C2 in **18** was not established by 2D NMR spectroscopy methods. However upon comparison of shifts and coupling constants, as discussed above, for key signals in the ^{1}H NMR spectra, it was inferred that bicyclo[3.2.0]heptan-1-ol **12** was the (1*RS*,5*RS*,7*SR*)-isomer as shown (Scheme 3) and bicyclo-[5.2.0]nonan-1-ol **18** was the (1*RS*,2*RS*,7*SR*,9*SR*)-isomer as shown (Scheme 4).

The FTIR spectra of bicyclo[*n*.2.0]alkan-1-ols **10**–**12**, **16**–**18**, **21** and **22** displayed sharp absorption bands with maximums in the range 3448–3536 cm^{-1} in combination with weak to strong broad bands at about 3400 cm^{-1}. The sharp hydroxyl stretching bands at about 3500 cm^{-1} were attributed to the 'free' hydroxyl group of the alcohol and the broad absorption bands at about 3400 cm^{-1} to intermolecular hydrogen bonding. The appearance of both types of hydroxyl stretches is consistent with intermolecular hydrogen bonding increasing as the concentration of the KBr disc increases.

Synthesis variations

With the structure of the novel bicyclo[*n*.2.0]alkan-1-ols established, we now sought to improve the ratio of bicyclo[*n*.2.0]-alkan-1-ols to alkylated products observed. Guided by our concurrent studies on cyclohexanone we altered the reaction

Table 3 Product ratios for the reaction of cyclopentanone, cycloheptanone or cyclooctanone and phenyl vinyl sulfoxide from methods B–D

		Reaction method[a]		
Ketone	Products	C (product ratio)	B	D
Cyclopentanone	**10** + **11** : **8** + **9**	56 : 44	49 : 51	48 : 52
Cycloheptanone	**16** + **17** : **15**	89 : 11	96 : 4	86 : 14
Cyclooctanone	**21** + **22** : **19** + **20**	12 : 88	28 : 72	35 : 65

[a] Method B (0.155 M, 5 min, −30 °C, dark); Method C (0.01 M, 5 min, −30 °C, dark); Method D (0.31 M, 5 min, −30 °C, dark).

conditions. We carried out ensuing reactions in the dark, to exclude potential competing pathways that may be promoted by light.[24] Phenyl vinyl sulfoxide was added rapidly to decrease the time for potential equilibration of intermediates and the reaction time was decreased to 5 minutes. Short reaction times of less than 15 minutes had favoured bicyclo[4.2.0]octan-1-ol formation over monoalkylation in the cyclohexanone case.[1] The lithium enolate of cyclobutanone, cyclopentanone, cycloheptanone or cyclooctanone was reacted rapidly with phenyl vinyl sulfoxide in THF under a nitrogen atmosphere at −30 °C for 5 minutes in the dark (Method B, Table 1). Upon oxidation of the crude sulfoxide mixtures with MCPBA, sulfone products were identified. The yields are presented in Table 1.

For the cyclobutanone example, no bicyclo[2.2.0]hexan-1-ol was observed, rather lower yields of the cyclohexanone **4** and monoalkylated cyclobutanone **5** were observed in conjunction with the decreased reaction time. For the cyclopentanone example, an increase in the major bicyclo[3.2.0]heptan-1-ol **10** from 3% to 18.5% was observed with a concomitant decrease in the yield of monoalkylated cyclopentanone **8** from 55.5% to 19.5%, and with a slight decrease (6% recovery) in the overall conversion of phenyl vinyl sulfoxide. This trend was also observed for cycloheptanone and cyclooctanone with an increase in yields of bicyclo[*n*.2.0]alkan-1-ol products **16** and **21** and a decrease in yields of monoalkylated ketones **15** and **19**. Compared to Method A, two further bicyclo[*n*.2.0]alkan-1-ols **18** and **22** were observed from the Method B results using the ketones cycloheptanone and cyclooctanone respectively. The substituted bicyclo[5.2.0]nonan-1-ol **18** was observed in 1% yield from cycloheptanone (Method B). Its formation must occur by a process similar to that for bicyclo[3.2.0]heptan-1-ol **12**, the difference in regiochemistry a consequence of pK_a and conformational effects in the enolate intermediates.

Having obtained a generally improved product ratio of bicyclo[*n*.2.0]alkan-1-ols to monoalkylated product for cyclopentanone, cycloheptanone and cyclooctanone we sought to explore the effects of total concentration of the reaction mixture on the product outcome. A dilute set of reaction conditions of 0.01 M (Method C, Table 1) and a more concentrated set of reaction conditions of 0.31 M (Method D, Table 1) were employed for cyclopentanone, cycloheptanone and cyclooctanone. Notably, there was decreased conversion for the dilute conditions (Method C, Table 1) where 13.5–26.5% of phenyl vinyl sulfoxide was unreacted. A comparison of the results for the three concentrations (Methods C, B and D) for cyclopentanone, cycloheptanone and cyclooctanone is displayed in Table 3.

When comparing the concentrations of 0.01, 0.155 and 0.310 M for each ring size of the starting ketone, there was a notable change in trends for product distribution. For the three concentrations, cyclopentanone gave an approximate 50 : 50 ratio of bicyclo[3.2.0]heptan-1-ols **10** and **11** to alkylated cyclopentanones **8** and **9** (Table 3) with the bicyclo[3.2.0]heptan-1-ol **10** being the major bicyclo[*n*.2.0]alkan-1-ol isomer. For the three concentrations, cycloheptanone gave the bicyclo[5.2.0]-nonan-1-ol **16** as the major product in significant preference to the alkylated cycloheptanone **15** (Table 3). Interestingly, at the intermediate concentration (0.155 M) the notably best ratio of 96 : 4 for bicyclo[5.2.0]nonan-1-ols **16** and **17** to alkylated cycloheptanone **15** was obtained. Cyclooctanone gave yet a different product ratio. For all concentrations, the monoalkylated cyclooctanone **19** is obtained as the major product (Table 3). The ratio changes to increase the preference towards bicyclo-[6.2.0]decan-1-ols **21** and **22** as the concentration increases. Thus, at the higher concentration (0.31 M) a ratio of 35 : 65 for bicyclo[6.2.0]decan-1-ols **21** and **22** to alkylated cyclooctanones **19** and **20** was obtained. However, the apparent trends in Table 3 of the changes in ratio of bicyclo[*n*.2.0]alkan-1-ol to alkylated ketones as reaction concentration was varied from 0.01 M to 0.155 M to 0.31 M may be distorted by the reduction of conversion of phenyl vinyl sulfoxide at 0.01 M.

Comparison of the yields of bicyclo[*n*.2.0]alkan-1-ols to alkylated ketones for each ketone at a concentration of 0.01, 0.155 or 0.31 M displayed a distinct trend. Fig. 2 shows the trend for the 0.31 M series and is illustrative of the trend observed at the other concentrations of 0.01 M and 0.155 M. For the ketones which gave bicyclo[*n*.2.0]alkan-1-ols as products, the smallest ring ketone, cyclopentanone, gave the lowest conversion of phenyl vinyl sulfoxide with combined yields of bicyclo[*n*.2.0]alkan-1-ol and alkylated ketones of 39–49% compared to cycloheptanone (53–73%) and cyclooctanone (52–80%). The slightly improved conversions of cyclooctanone were in favour of alkylation not bicyclo[6.2.0]decan-1-ol formation as previously discussed. Cycloheptanone consistently gave the highest yields of bicycloalkan-1-ols.

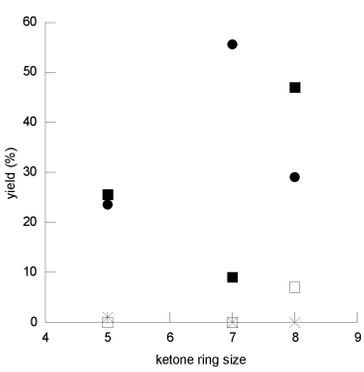


Fig. 2 Ketone ring size *vs.* % composition of product in total reaction products using Method D (0.31 M) for the products, monoalkylated ketone (■), dialkylated ketone (□), bicyclo[*n*.2.0]alkan-1-ols (●), and substituted bicyclo[*n*.2.0]alkan-1-ol (X).

Here, we account for the product preference in terms of the stability and steric interactions observed in the final bicyclo-[*n*.2.0]alkan-1-ol compound. Elsewhere, we have reported the X-ray structures for bicyclo[*n*.2.0]alkan-1-ols **10**, **16** and **21**.[2] Notably, it was seen that in the solid state structures, the torsion angles at the ring junction varied between the bicyclo[*n*.2.0]-alkan-1-ols **10**, **16** and **21** and the overall steric strain is of the order bicyclo[5.2.0]nonan-1-ol **16** < bicyclo[3.2.0]heptan-1-ol **10** ≅ bicyclo[6.2.0]decan-1-ol **21**. Correspondingly, the yields of bicyclo[*n*.2.0]alkan-1-ol products observed were in the order bicyclo[3.2.0]heptan-1-ol **10** ≅ bicyclo[6.2.0]decan-1-ol **21** < bicyclo[5.2.0]nonan-1-ol **16** for the higher concentrations (0.155 M and 0.31 M) employed and bicyclo[6.2.0]decan-1-ol **21** < bicyclo[3.2.0]heptan-1-ol **10** < bicyclo[5.2.0]nonan-1-ol **16** at the lower concentration (0.01 M) (Table 1). Generally, as the strain of the bicyclo[*n*.2.0]alkan-1-ol product decreases, an increase in product distribution towards the bicyclo[*n*.2.0]-alkan-1-ol in conjunction with increased yield of bicyclo-[*n*.2.0]alkan-1-ol is observed. This also was thought to account for the preference of bicyclo[3.2.0]heptan-1-ol **10** over **11**,

bicyclo[5.2.0]nonan-1-ol **16** over **17** and bicyclo[6.2.0]decan-1-ol **21** over **22** for cyclopentanone, cycloheptanone and cyclooctanone respectively, where the *trans* relationship of the hydroxyl group and sulfonyl group must alter the ring strain and hydrogen bonding in the bicyclo[*n*.2.0]alkan-1-ols **11**, **17** and **22**. In addition, as changes in the reaction concentration affect the bicyclo[*n*.2.0]alkan-1-ol to alkylated product ratio obtained from an individual ketone, this may be linked to stabilization of the transition states or intermediates leading to the final bicyclo[*n*.2.0]alkan-1-ol products by the reaction solvent (THF) and the basicity of the carbonyl group of cyclopentanone (pK_a −7.5),[25] cycloheptanone (pK_a −6.6)[25] and cyclooctanone (pK_a −6.2)[25] and thus preference for formation of the final bicyclo[*n*.2.0]alkan-1-ol product.

Taking into consideration conversion of phenyl vinyl sulfoxide and overall yield of bicyclo[*n*.2.0]alkan-1-ol, in this study, the optimal reaction concentration for formation of bicyclo[*n*.2.0]alkan-1-ols from cyclopentanone was 0.01 M, from cycloheptanone was 0.155 M and from cyclooctanone was 0.31 M, the latter giving a slightly better result (about 5%) than method B at 0.155 M. However, these results and the variances observed at each reaction concentration also suggest that the prediction of whether increasing or decreasing the reaction concentration will favour formation of bicyclo[*n*.2.0]alkanols from a ketone enolate is not singularly reflective of the product outcome.

In conclusion, this study has demonstrated that a range of simple ketones of varying ring sizes (five to eight members) can react with phenyl vinyl sulfoxide to give bicyclo[3.2.0]heptan-1-ols **10** and **11**, bicyclo[5.2.0]nonan-1-ols **16** and **17** and bicyclo[6.2.0]decan-1-ols **21** and **22** under controlled conditions of time, temperature and concentration of reaction in partially optimised yields of 27.5–70%. It is noteworthy that the bicyclo[*n*.2.0]alkan-1-ol (n = 3, 5, 6) ring system is generated in a convergent approach from readily available synthons, a cyclic ketone and phenyl vinyl sulfoxide, and that the ring junction is generated with apparent selectivity. Bicyclo[2.2.0]hexan-1-ols could not be obtained under the current variations of reaction conditions. The ratio of bicyclo[*n*.2.0]alkan-1-ols to alkylated ketones was reflective of the balance of the variables of enolate reactivity, conversion of phenyl vinyl sulfoxide, time, temperature and concentration of reaction, and stability and steric strain observed in the final bicyclo[*n*.2.0.]alkan-1-ol product. This study, in conjunction with our previous work,[1,2] has demonstrated that this novel cyclisation methodology has potential scope for the construction of complex fused ring systems. From both a preparative and mechanistic viewpoint the reaction is important and further investigations are in progress.

Experimental

The general experimental conditions and instrumentation have been described elswhere.[1] Solvents and commercially available reagents were purified in the standard manner. A full description of all experiments is given in the Electronic Supplementary Information. †

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

The crude product mixtures from oxidation were dried under high vacuum, and the mass of the crude product determined. The ^{1}H-NMR (400 MHz) spectra were obtained using $CDCl_3$ as solvent. Integration of the baseline resolved key peaks (to ± 1%) in the region δ 2.80–3.80 ppm, for bicyclo[*n*.2.0]alkan-1-ol and monoalkylated and dialkylated products, and in the region δ 5.80–6.80 ppm, for unreacted phenyl vinyl sulfoxide as phenyl vinyl sulfoxide and/or phenyl vinyl sulfone, was used to calculate the percentage composition of these components if present from the integral of the total crude mixture. Crude yields greater than theoretical 100% were found to include water and this was included in the calculations.

General procedures for synthesis of bicyclo[*n*.2.0]alkan-1-ol sulfoxides

Method A: 45 min, laboratory light, 0.155 M. Lithium diisopropylamide (1 equivalent, 1.4–1.95 M) was added to THF (19.5–39.5 ml) under an atmosphere of nitrogen at −10 °C and the solution cooled to −75–78 °C. The ketone (1 equivalent) was added over 5 minutes and the temperature maintained between −70–78 °C. The system was allowed to warm to −30 °C and phenyl vinyl sulfoxide (1 equivalent) was added over 5 minutes. The reaction mixture was warmed to 0 °C, stirred for 45 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was extracted with ethyl acetate (3 × 40 ml) and the combined organic layers were washed with water (2 × 50 ml), brine (50 ml) and dried ($MgSO_4$, anhydrous). The solvent was removed under reduced pressure to afford the crude sulfoxide mixture.

Method B: 5 min, dark, 0.155 M. The lithium enolate of the ketone was generated according to method A using lithium diisopropylamide (1 equivalent, 1.27–1.95 M), THF (12.5–39.5 ml) and ketone (1 equivalent). The system was shielded from light and allowed to warm to −30 °C. Phenyl vinyl sulfoxide (1 equivalent) was added rapidly as a neat solution. The reaction mixture was maintained at −30 °C, stirred for 5 minutes and quenched with ammonium chloride (40 ml). The mixture was worked up according to method A.

Method C: 5 min, dark, 0.01 M. The lithium enolate of the ketone was generated according to method B using lithium diisopropylamide (1 equivalent, 1.70 M), THF (76–113 ml), ketone (1 equivalent) and phenyl vinyl sulfoxide (1 equivalent). The reaction was quenched with ammonium chloride (40 ml) and worked up according to method A.

Method D: 5 min, dark, 0.31 M. The lithium enolate of the ketone was generated according to method B using lithium diisopropylamide (1 equivalent, 1.95 M), THF (7.3–14.2 ml), ketone (1 equivalent) and phenyl vinyl sulfoxide (1 equivalent). The reaction was quenched with ammonium chloride (40 ml) and worked up according to method A.

Oxidation of bicyclo[*n*.2.0]alkan-1-ol sulfoxide mixtures

The crude sulfoxide mixture (1 mole, based on crude yield inclusive of ethyl acetate in some instances and assumed conversion to monoalkylated product) dissolved in chloroform (10–20 ml) was added to a vigorously stirred solution of MCPBA (1.0–1.1 mole, 57–77%) and chloroform (10–30 ml) at 0 °C, over 20 minutes. The mixture was stirred at room temperature for 16 hours and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 ml), washed with aqueous sodium hydrogen carbonate (3 × 40 ml), brine (40 ml) and dried ($MgSO_4$, anhydrous). The solvent was removed under reduced pressure and dried under high vacuum to afford the crude sulfone mixture, the ^{1}H NMR spectrum of which displayed no signals due to sulfoxide products (bicyclo[*n*.2.0]alkan-1-ols or alkylated products).

Reaction of cyclobutanone

From **Method A** using cyclobutanone (0.53 ml, 7.134 mmole) the crude sulfoxide mixture (1.408 g, 6.334 mmole) was oxidised according to the general procedure to give the crude sulfone mixture (0.877 g). Column chromatography (hexane–ethyl acetate, 60 : 40) and semi preparative HPLC (hexane–ethyl acetate; **4**, 70 : 30; **5**, 50 : 50) were performed.

2-(Phenylsulfonyl)cyclohexanone **4** was isolated as a white solid, mp 65.7–66.6 °C (ethyl acetate–hexane) (lit.[20] 87 °C from

CCl_4) (Rt 13.0 min, 3 ml min^{-1}) (Found: C, 60.53; H, 6.11. Calc. for $C_{12}H_{14}SO_3$: C, 60.48; H, 5.92%); ν_{max}(KBr)/cm^{-1} 1710, (CO), 1309, (SO_2), 1149, (SO_2); δ_H (400 MHz, $CDCl_3$) 7.85–7.90 (2 H, m, *o*-C_6H_5), 7.61–7.67 (1 H, m, *p*-C_6H_5), 7.51–7.57 (2 H, m, *m*-C_6H_5), 3.82 (1 H, ddd, $J_{2,3}$ 5.5, $J_{2,3}$ 5.5, $J_{2,4\ or\ 6}$ 1.5, 2-H), 2.80 (1 H, ddd, $J_{6,6}$ 15, $J_{6,5}$ 9.5, $J_{6,5}$ 5, 6-H), 2.47–2.60 (1 H, m, 3-H), 2.37–2.45 (1 H, m, 6-H), 2.13–2.28 (2 H, m, 3-H, 4-H), 1.93–2.05 (1 H, m, 5-H), 1.67–1.87 (2 H, m, 4-H, 5-H); δ_C (50 MHz, $CDCl_3$) 202.3 C-1; 138.4 *i*-C_6H_5; 134.2 *p*-C_6H_5; 129.3 *m*-C_6H_5; 129.1 *o*-C_6H_5; 72.9 C-2; 41.9 C-6; 27.8 C-3; 26.7 C-5; 22.3 C-4; (ESMS+) 245 (MLi^+, 24%), 261 (MNa^+, 100%).

2-[2′-(Phenylsulfonyl)ethyl]cyclobutanone **5** was isolated as a white solid, mp 40.5–41.8 °C (ethyl acetate–hexane) (Rt 9.4 min, 3 ml min^{-1}) (Found: C, 60.31; H, 6.05; S, 13.30. Calc. for $C_{12}H_{14}SO_3$: C, 60.48; H, 5.92; S, 13.45%); ν_{max}(KBr)/cm^{-1} 1776, (CO), 1294, (SO_2), 1144, (SO_2); δ_H (400 MHz, $CDCl_3$) 7.86–7.91 (2 H, m, *o*-C_6H_5), 7.63–7.69 (1 H, m, *p*-C_6H_5), 7.51–7.60 (2 H, m, *m*-C_6H_5), 3.36 (1 H, dddddd, $J_{2,3}$ 10.5, $J_{2,3}$ 7.5, $J_{2,1'}$ 7.5, $J_{2,1'}$ 7.5, $J_{2,4}$ 2.5, $J_{2,4}$ 2.5, 2-H), 3.26 (1 H, ddd, $J_{2',2'}$ 14, $J_{2',1'}$ 10, $J_{2',1'}$ 6, 2′-H), 3.12 (1 H, ddd, $J_{2',2'}$ 14, $J_{2',1'}$ 10, $J_{2',1'}$ 6, 2′-H), 3.05 (1 H, dddd, $J_{4,4}$ 18.5, $J_{4,3}$ 10, $J_{4,3}$ 7.5, $J_{4,2}$ 2.5, 4-H), 2.90 (1 H, dddd, $J_{4,4}$ 18, $J_{4,3}$ 9.5, $J_{4,3}$ 5, $J_{4,2}$ 3, 4-H), 2.22 (1 H, dddd, $J_{3,3}$ 10.5, $J_{3,4}$ 10.5, $J_{3,2}$ 10.5, $J_{3,4}$ 5, 3-H), 1.90–2.08 (2 H, m, 2 × 1′-H), 1.62 (1 H, dddd, $J_{3,3}$ 11, $J_{3,4}$ 9.5, $J_{3,4}$ 8, $J_{3,2}$ 8, 3-H); δ_C (50 MHz, $CDCl_3$) 209.3 C-1; 139.9 *i*-C_6H_5; 133.8 *p*-C_6H_5; 129.3 *m*-C_6H_5; 128.0 *o*-C_6H_5; 57.9 C-2; 53.7 C-2′; 44.8 C-4; 22.8 C-1′; 16.9 C-3; (ESMS+) 245 (MLi^+, 40%), 261 (MNa^+, 100%).

Reaction of cyclopentanone

From **Method A** using cyclopentanone (0.55 ml, 6.220 mmole), the crude sulfoxide mixture (1.365 g, 5.775 mmole) was oxidised according to the general procedure to give the crude sulfone mixture (1.139 g). Column chromatography (hexane–ethyl acetate, 60 : 40) and semi preparative HPLC (hexane–ethyl acetate; **11**, 70 : 30; **8**, **9**, **10**, **12**, 50 : 50) were performed.

2-[2′-(Phenylsulfonyl)ethyl]cyclopentanone **8** was isolated as a white solid, mp 75.2–76.0 °C (ethyl acetate–hexane) (Rt 10.7 min, 4 ml min^{-1}) (Found: C, 61.98; H, 6.43. Calc. for $C_{13}H_{16}SO_3$: C, 61.87; H, 6.39%); ν_{max}(KBr)/cm^{-1} 1733, (CO), 1299, (SO_2), 1143, (SO_2); δ_H (400 MHz, $CDCl_3$) 7.85–7.93 (2 H, m, *o*-C_6H_5), 7.60–7.68 (1 H, m, *p*-C_6H_5), 7.50–7.60 (2 H, m, *m*-C_6H_5), 3.31 (1 H, ddd, $J_{2',2'}$ 7, $J_{2',1'}$ 5.5, $J_{2',1'}$ 3, 2′-H), 3.16 (1 H, ddd, $J_{2',2'}$ 7, $J_{2',1'}$ 5.5, $J_{2',1'}$ 3, 2′-H), 2.00–2.15 (4 H, m, 2-H, 3-H, 2 × 5-H), 1.93–2.00 (2 H, m, 4-H, 1′-H), 1.67–1.83 (2 H, m, 4-H, 1′-H), 1.42–1.52 (1 H, m, 3-H); δ_C (50 MHz, $CDCl_3$) 219.7 C-1; 139.3 *i*-C_6H_5; 133.7 *p*-C_6H_5; 129.7 *m*-C_6H_5; 128.3 *o*-C_6H_5; 54.0 C-2′; 47.5 C-2; 37.4 C-5; 29.3 C-3; 22.8 C-1′; 20.5 C-4; (ESMS+) 259 (MLi^+, 94%), 275 (MNa^+, 100%). HRMS (Found: 253.08884. $C_{13}H_{17}SO_3$ requires 253.0898).

2,5-Bis[2′-(Phenylsulfonyl)ethyl]cyclopentanone **9** was isolated as a tacky solid. (Rt 15.7 min, 4 ml min^{-1}) (Found: C, 59.67; H, 5.96. Calc. for $C_{21}H_{24}S_2O_5$: C, 59.96; H, 5.75%). ν_{max}(KBr)/cm^{-1} 1738, (CO), 1305, (SO_2), 1150, (SO_2); δ_H (400 MHz, $CDCl_3$) 7.80–7.94 (4 H, m, *o*-C_6H_5), 7.63–7.73 (2 H, m, *p*-C_6H_5), 7.53–7.63 (4 H, m, *m*-C_6H_5), 2.80–3.12 (4 H, m, 2 × 2′-H, 2 × 2″-H), 2.17–2.30 (2 H, m, 2-H, 5-H), 1.67–2.00 (8 H, m, 2 × 3-H, 2 × 4-H, 2 × 1′-H, 2 × 1″-H); δ_C (50 MHz, $CDCl_3$) 219.3 C-1; 138.8 *i*-C_6H_5; 134.0 *p*-C_6H_5; 129.5 *m*-C_6H_5; 128.0 *o*-C_6H_5; 51.1 C-2′, C-2″; 37.5 C-2, C5; 25.7 C-1′, C-1″; 18.4 C-3, C-4; (ESMS+) 427 (MLi^+, 100%), 443 (MNa^+, 100%); (ESMS−) 419 (M − H 54%).

(1*RS*,5*SR*,7*SR*)-7-(Phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol **10**[2] was isolated as a white solid, mp 89.1–92.6 °C (ethyl acetate–hexane) (Rt 8.9 min, 3 ml min^{-1}).

(1RS,5SR,7RS)-7-(Phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol **11** was isolated as a white solid, mp 94.9–95.8 °C (ethyl acetate–hexane) (Rt 28.7 min, 3 ml min^{-1}) (Found: C, 61.84; H, 6.45; S, 12.35. Calc. for $C_{13}H_{16}SO_3$: C, 61.87; H, 6.39; S, 12.72%); ν_{max}(KBr)/cm^{-1} 3457, (OH), 1295, (SO_2), 1147, (SO_2); δ_H (400 MHz, $CDCl_3$) 7.82–7.92 (2 H, m, *o*-C_6H_5), 7.58–7.68 (1 H, m, *p*-C_6H_5), 7.48–7.58 (2 H, m, *m*-C_6H_5), 3.79 (1 H, ddd, $J_{7,6}$ 10, $J_{7,6}$ 10, $J_{7,4}$ 1, 7-H), 2.90 (1 H, ddd, $J_{2,2}$ 14, $J_{2,3}$ 7, $J_{2,3}$ 4, 2-H), 2.45–2.54 (1 H, m, 5-H), 2.04–2.22 (2 H, m, 3-H, 6-H), 1.68–1.95 (3 H, m, 3-H, 4-H, 6-H), 1.53–1.68 (2 H, m, 2-H, 4-H), OH not observed; δ_C (50 MHz, $CDCl_3$) 140.2 *i*-C_6H_5; 133.4 *p*-C_6H_5; 129.2 *m*-C_6H_5; 127.6 *o*-C_6H_5; 85.3 C-1; 65.3 C-7; 44.6 C-5; 36.8 C-2; 31.3 C-4; 25.6 C-3; 20.8 C-6; (ESMS+) 275 (MNa^+, 100%).

(1RS,5RS,7SR)-7-(Phenylsulfonyl)-5-[2-(phenylsulfonyl)-ethyl]bicyclo[3.2.0]heptan-1-ol **12** was isolated after extensive drying as a hygroscopic gum. (Rt 16.2 min, 4 ml min^{-1}) (Found: C, 58.84; H, 5.67. Calc. for $C_{21}H_{24}S_2O_5 \cdot ½H_2O$: C, 58.72; H, 5.87%). ν_{max}(KBr)/cm^{-1} 3451, (OH), 1305, (SO_2), 1147, (SO_2); δ_H (400 MHz, $CDCl_3$) 7.84–7.96 (4 H, m, *o*-C_6H_5), 7.50–7.70 (6 H, m, *p*-C_6H_5, *m*-C_6H_5), 4.27 (1 H, br s, $W_{h/2}$ 1.5, OH), 3.01–3.15 (2 H, m, 2 × 2′-H), 3.50 (1 H, dd, $J_{7,6}$ 10, $J_{7,6}$ 7, 7-H), 2.20 (1 H, dd, $J_{6,6}$ 14, $J_{6,7}$ 7, 6-H), 2.11 (1 H, ddd, $J_{1',1'}$ 13.5, $J_{1',2'}$ 11, $J_{1',2'}$ 6, 1′-H), 1.88 (1 H, ddd, $J_{1',1'}$ 13.5, $J_{1',2'}$ 11, $J_{1',2'}$ 5.5, 1′-H), 1.75–1.82 (1 H, m, 3-H), 1.60–1.74 (2 H, m, 2-H, 6-H), 1.36–1.59 (4 H, m, 2-H, 3-H, 2 × 4-H); δ_C (100 MHz, $CDCl_3$) 139.7, 138.7 *i*-C_6H_5; 133.9, 133.8 *p*-C_6H_5; 129.4, 129.3 *m*-C_6H_5; 128.2, 127.9 *o*-C_6H_5; 83.4, C-1; 62.2, C-7; 52.3, C-2′; 49.2 C-5; 40.1 C-2; 35.9 C-4; 26.7 C-1′; 26.6 C-6; 21.8 C-3; (ESMS+) 427 (MLi^+, 100%), 443 (MNa^+, 100%).

Reaction of cycloheptanone

From **Method A** using cycloheptanone (0.5 ml, 4.239 mmole), the crude sulfoxide mixture (1.074 g, 4.063 mmole) was oxidised according to the general procedure to give the crude sulfone mixture (0.890 g). Column chromatography (hexane–ethyl acetate, 60 : 40) and semi preparative HPLC (hexane–ethyl acetate; **16**, 70 : 30; **15**, **17**, 50 : 50) were performed.

2-[2′-(Phenylsulfonyl)ethyl]cycloheptanone **15**[22] was isolated as an oil (Rt 10.0 min, 3 ml min^{-1}); ν_{max} (KBr)/cm^{-1}: 1702, (CO), 1306, (SO_2), 1148, (SO_2); δ_H (200 MHz, $CDCl_3$) 7.80–7.92 (2 H, m, *o*-C_6H_5), 7.47–7.70 (3 H, m, *m*-C_6H_5, *p*-C_6H_5), 2.95–3.23 (2 H, m, 2 × 2′-H), 2.62–2.80 (1 H, m, 2-H), 2.30–2.55 (2 H, m, 2 × 7-H), 1.07–2.10 (10 H, m, 2 × 3-H, 2 × 4-H, 2 × 5-H, 2 × 6-H, 2 × 1′-H); δ_C (50 MHz, $CDCl_3$) 214.3 C-1; 139.1 *i*-C_6H_5; 133.6 *p*-C_6H_5; 129.2 *m*-C_6H_5; 127.9 *o*-C_6H_5; 54.0 C-2′; 49.8 C-2; 43.2 C-7; 31.8, 29.1, 28.8, 25.0, 23.8 C-3, C-4, C-5, C-6, C-1′; (ESMS+) 287 (MLi^+, 44%), 303 (MNa^+, 100%).

(1*RS*,7*SR*,9*SR*)-9-(Phenylsulfonyl)bicyclo[5.2.0]nonan-1-ol **16**[2] was isolated as a white solid, mp 99.3–101.1 °C (ethyl acetate–hexane) (Rt 8.8 min, 3 ml min^{-1}).

(1RS,7SR,9RS)-9-(Phenylsulfonyl)bicyclo[5.2.0]nonan-1-ol **17** was isolated as a tacky solid (Rt 11.4 min, 3 ml min^{-1}) (Found: C, 64.29; H, 7.22; S, 11.55. Calc. for $C_{15}H_{20}SO_3$: C, 64.25; H, 7.19; S, 11.43%); ν_{max}(KBr)/cm^{-1} 3452, (OH), 1300, (SO_2), 1143, (SO_2); δ_H (400 MHz, $CDCl_3$) 7.78–7.85 (2 H, m, *o*-C_6H_5), 7.56–7.62 (1 H, m, *p*-C_6H_5), 7.45–7.56 (2 H, m, *m*-C_6H_5), 3.60 (1 H, dd, $J_{9,8}$ 10, $J_{9,8}$ 9, 9-H), 2.31–2.41 (1 H, m, 2-H), 2.17–2.30 (2 H, m, 2-H, 7-H), 1.90–2.07 (2 H, m, 6-H, 8-H), 1.78–1.86 (1 H, m, 4-H), 1.65–1.78 (4 H, m, 2 × 3-H, 5-H, 8-H), 1.11–1.36 (3 H, m, 4-H, 5-H, 6-H), OH not observed; δ_C (50 MHz, $CDCl_3$) 140.2 i-C_6H_5; 133.3 *p*-C_6H_5; 129.1 *m*-C_6H_5; 127.6 *o*-C_6H_5; 81.8 C-1; 66.0 C-9; 45.0 C-7; 34.3 C-6; 32.1 C-2; 31.8 C-4; 26.7 C-5; 23.7, 23.4 C-3, C-8; (ESMS+) 287 (MLi^+, 8%), 303 (MNa^+, 100%).

From **Method B** using cycloheptanone (0.530 ml, 4.458 mmole), the crude sulfoxide mixture (1.063 g, 4.021 mmole) was oxidised according to the general procedure to give the crude sulfone mixture (1.043 g). Column chromatography (hexane–ethyl acetate, 60 : 40) and semi preparative HPLC (hexane–ethyl acetate; **18**, 70 : 30) were performed.

(1RS,2RS,7SR,9SR)-9-(Phenylsulfonyl)-2-[2-(phenyl-sulfonyl)ethyl]bicyclo[5.2.0]nonan-1-ol **18** was isolated as a

cream solid, mp 123.3–126.1 °C (ethyl acetate–hexane). Minor inseparable impurities (< 5%) were present. (Rt 20.4 min, 3 ml min^{-1}); ν_{max}(KBr)/cm^{-1} 3536, (OH), 1302, (SO_2), 1149, (SO_2); δ_H (400 MHz, $CDCl_3$) 7.80–7.86 (4 H, m, *o*-C_6H_5), 7.60–7.63 (2 H, m, *p*-C_6H_5), 7.44–7.60 (4 H, m, *m*-C_6H_5), 3.74 (1 H, dd, $J_{9,8}$ 10.5, $J_{9,8}$ 4, 9-H), 3.09 (1 H, ddd, $J_{2',2'}$ 14, $J_{2',1}$ 8, $J_{2',1'}$ 6, 2′-H), 2.97 (1 H, ddd, $J_{2',2'}$ 14.5, $J_{2',1'}$ 8, $J_{2',1'}$ 7, 2′-H), 2.47–2.62 (2 H, m, 7-H, 8-H), 1.46–1.91 (6 H, m, 2-H, 3-H, 4-H, 5-H, 6-H, 1′-H), 1.27–1.46 (2 H, m, 8-H, 1′-H), 1.06–1.27 (4 H, m, 3-H, 4-H, 5-H, 6-H), OH not observed; δ_C (50 MHz, $CDCl_3$) 138.9 *i*-C_6H_5; 133.7, 133.5 *p*-C_6H_5; 129.2 *m*-C_6H_5; 128.2, 127.8 *o*-C_6H_5; 81.7 C-1; 62.7 C-9; 54.3 C-2′; 49.6 C-7; 43.6 C-2; 33.8 C-6; 30.4 C-3; 28.3 C-4; 27.0 C-5; 23.7 C-1′; 22.0 C-8; (ESMS+) 455 (MLi^+, 100%), 471 (MNa^+, 100%). HRMS (Found: 449.14396. $C_{23}H_{28}S_2O_5$ requires 449.14564).

Reaction of cyclooctanone

From **Method A** using cyclooctanone (0.5 ml, 3.796 mmole), the crude sulfoxide mixture (1.128 g, 4.051 mmole) was oxidised according to the general procedure to give the crude sulfone mixture (1.021 g). Column chromatography (hexane–ethyl acetate, 60 : 40) and semi preparative HPLC (hexane–ethyl acetate; **20**, 70 : 30; **21**, **19** 50 : 50) were performed.

2-[2′-(Phenylsulfonyl)ethyl]cyclooctanone **19**[22] was isolated as an oil. (Rt 9.5 min, 3 ml min^{-1}); ν_{max}(KBr)/cm^{-1} 1698, (CO), 1306, (SO_2), 1151, (SO_2); δ_H (400 MHz, $CDCl_3$) 7.80–7.91 (2 H, m, *o*-C_6H_5), 7.57–7.80 (1 H, m, *p*-C_6H_5), 7.48–7.57 (2 H, m, *m*-C_6H_5), 2.93–3.09 (2 H, m, 2 × 2′-H), 2.72–2.81 (1 H, m, 2-H), 2.23–2.42 (2 H, m, 2 × 8-H), 0.90–2.06 (10 H, m, 2 × 4-H, 2 × 5-H, 2 × 6-H, 2 × 7-H, 2 × 1′-H), 1.82–1.86 (1 H, m, 3-H), 1.42–1.64 (1 H, m, 3-H); δ_C (50 MHz, $CDCl_3$) 218.4 C-1; 139.0 *i*-C_6H_5; 133.6 *p*-C_6H_5; 129.2 *m*-C_6H_5; 127.9 *o*-C_6H_5; 54.1 C-2′; 48.2 C-2; 42.5 C-8; 33.0 C-3; 27.4, 25.0, 24.8, 24.6 C-4, C-5, C-6, C-7, C-1′; (ESMS+) 301 (MLi^+, 27%), 317 (MNa^+, 100%).

2,8-Bis[2′-(phenylsulfonyl)ethyl]cyclooctanone **20** was isolated as a white solid, mp 122.8–124.1 °C (ethyl acetate–hexane) (Rt 25.8 min, 3 ml min^{-1}) (Found: C, 62.44; H, 6.59; S, 13.72. Calc. for $C_{24}H_{30}S_2O_5$: C, 62.31; H, 6.54; S, 13.86%); ν_{max}(KBr)/cm^{-1} 1690, (CO), 1305, (SO_2), 1144, (SO_2); δ_H (400 MHz, $CDCl_3$) 7.80–7.89 (4 H, m, *o*-C_6H_5), 7.45–7.70 (6 H, m, *m*-C_6H_5, *p*-C_6H_5), 3.05 (2 H, ddd, $J_{2'/2'',2'/2''}$ 14, $J_{2'/2'',1'/1''}$ 9, $J_{2'/2'',1'/1''}$ 6.5, 2′-H, 2″-H), 2.91 (2 H, ddd, $J_{2'/2'',2'/2''}$ 14, $J_{2'/2'',1'/1''}$ 9.5, $J_{2'/2'',1'/1''}$ 6.5, 2′-H, 2″-H), 2.53–2.66 (2 H, m, 2-H, 8-H), 1.72–1.95 (4 H, m, 2 × 1′-H, 2 × 1″-H), 1.43–1.72 (6 H, m, 2 × 3-H, 2 × 4-H or 2 × 6-H, 2 × 7-H), 1.10–1.43 (4 H, m, 2 × 5-H, 2 × 4-H or 2 × 6-H); δ_C (50 MHz, $CDCl_3$) 218.9 C-1; 138.8 *i*-C_6H_5; 133.8 *p*-C_6H_5; 129.4 *m*-C_6H_5; 128.0 *o*-C_6H_5; 53.8 C-2′, C-2″; 48.4 C-2, C-8; 32.5 C-3, C-7; 26.1 C-4, C-6; 25.7 C-1′, C-1″; 24.5 C-5; (ESMS+) 469 (MLi^+, 100%), 485 (MNa^+, 100%).

(1*RS*,8*SR*,10*SR*)-10-(Phenylsulfonyl)bicyclo[6.2.0]decan-1-ol **21**[2] was isolated as a white solid, mp 98.1–100.2 °C (ethyl acetate–hexane) (Rt 7.70 min, 3 ml min^{-1}).

From **Method B** using cyclooctanone (0.5 ml, 3.796 mmole), the crude sulfoxide mixture (1.033 g, 3.710 mmole) was oxidised according to the general procedure to give the crude sulfone mixture (0.933 g). Column chromatography (hexane–ethyl acetate, 60 : 40) and semi preparative HPLC (hexane–ethyl acetate; **22**, 75 : 25) were performed.

(1RS,8SR,10RS)-10-(Phenylsulfonyl)bicyclo[6.2.0]decan-1-ol **22** was isolated as a white solid, mp 132.6–134.5 °C (ethyl acetate–hexane (Rt 19.7 min, 3 ml min^{-1}) (Found: C, 65.12; H, 7.54; S, 10.60. Calc. for $C_{16}H_{22}SO_3$: C, 65.26; H, 7.53; S, 10.90%); ν_{max}(KBr)/cm^{-1}: 3448, (OH), 1284, (SO_2), 1143, (SO_2); δ_H (400 MHz, $CDCl_3$) 7.77–7.84 (2 H, m, *o*-C_6H_5), 7.57–7.64 (1 H, m, *p*-C_6H_5), 7.49–7.55 (2 H, m, *m*-C_6H_5), 3.58 (1 H, dd, $J_{10,9}$ 10.5, $J_{10,9}$ 9, 10-H), 2.45 (1 H, br s, $W_{h/2}$ = 2.5 Hz, OH), 2.40 (1 H, ddd, $J_{2,2}$ 15.5, $J_{2,3}$ 4.5, $J_{2,3}$ 3.5, 2-H), 2.24 (1 H, ddd, $J_{2,2}$ 15.5, $J_{2,3}$ 13, $J_{2,3}$ 3, 2-H) 1.96–2.05 (1 H, m, 8-H), 1.86–1.95 (1 H, m, 9-H), 1.62–1.77 (6 H, m, 3-H, 4-H, 6-H, 2 × 7-H, 9-H), 1.45–1.58 (2 H, m, 3-H, 6-H), 1.28–1.40 (2 H, m, 2 × 5-H), 1.07–1.18 (1 H, m, 4-H); δ_C (50 MHz, $CDCl_3$) 139.9, *i*-C_6H_5; 133.4, *p*-C_6H_5; 129.2, *m*-C_6H_5; 127.7, *o*-C_6H_5; 81.4, C-1; 67.3, C-10; 44.6, C-8; 29.7, C-2; 28.5, C-6; 27.1, C-5; 24.7, C-4; 24.4, C-7; 24.2, C-3; 22.6, C-9; (ESMS+) 301 (MLi^+ 100%), 317 (MNa^+ 100%).

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