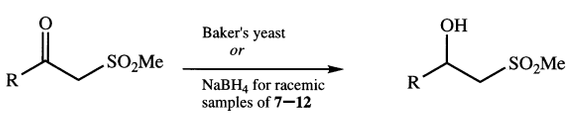
Asymmetric reduction of 1-methylsulfonylalkan-2-ones with baker's yeast

Anita R. Maguire* and Declan G. Lowney

Department of Chemistry, University College Cork, Ireland

Baker's yeast mediated enantioselective reduction of 1-methylsulfonylalkan-2-ones, forming the corresponding alcohols with up to 87% ee, is described.

Enantioselective synthesis of organic compounds has attracted enormous attention in recent years principally due to the recognition that the two enantiomers of a compound may display significantly different biological activity. One of the techniques which offers considerable potential in this regard is the use of biotransformations, thereby exploiting the intrinsic enantioselectivity of enzymes as biocatalysts in synthetic organic chemistry. Asymmetric reduction of ketones with baker's yeast (*Saccharomyces cerevisiae*) as reducing agent has attracted considerable attention in this regard,[1] largely due to the ready availability and versatility of this microorganism, and the ease with which this microbial reduction can be undertaken. While there has been some success in the enantioselective yeast reduction of ketones bearing α-phenylsulfonyl, α-tolylsulfonyl and α-benzylsulfonyl groups[2] (*e.g.* 1-phenylsulfonylpropan-2-one is reduced to the *S*-alcohol in 98% yield and 95% ee), the outcome of the yeast reduction in terms of yield and enantioselectivity decreases considerably as the alkyl chain on the sulfonyl ketone lengthens.[3] We report our investigations of the baker's yeast reductions of 1-methylsulfonylalkan-2-ones[4] (see Scheme 1



R	
1	C_4H_9
2	C_5H_{11}
3	C_6H_{13}
4	C_7H_{15}
5	$Ph(CH_2)_3$
6	$Ph(CH_2)_4$

R	
7	C_4H_9
8	C_5H_{11}
9	C_6H_{13}
10	C_7H_{15}
11	$Ph(CH_2)_3$
12	$Ph(CH_2)_4$

Scheme 1

and Table 1). Samples of racemic 1-methylsulfonylalkan-2-ols [prepared by sodium borohydride reduction (88–95% yield) of the ketones] were used for comparison of their ^{1}H NMR spectra in the presence of $Eu(hfc)_3$ with those of the scalemic samples obtained from the yeast reductions.

Two sets of conditions (methods A and B) were employed for the reduction, the second method consisting of a much more concentrated yeast and sugar mixture than the first (Table 1). In this way the influence of the concentration of the yeast mixture on the outcome of the reduction could be explored.

Enantioselective reduction of the β-keto sulfones **1**–**6** was achieved as shown in Table 1. It was found that the yeast reductions are very sensitive; changes in either the reaction conditions or the substrate structure dramatically alter the outcome of the microbial reduction.[1–3] The reductions conducted using method B are much more satisfactory than those using method A, in terms of yield, conversion, enantioselectivity and reproducibility. The low recovery from the yeast reductions may be due to enzymatic degradation of the compounds in the yeast medium or due to difficulty in extracting them from the yeast mixture after reduction. Interestingly the recoveries of the more hydrophobic derivatives **11** and **12** were more satisfactory than those of the less hydrophobic compounds **7**–**10**. The sensitivity of the process to the reaction conditions indicates that further modification of the latter, for example by immobilisation of the yeast or use of additives, may enhance the yield and stereoselectivity of the transformation.

Reduction efficiency

In general, the reductions are more efficient under the more concentrated conditions associated with method B than under the more dilute conditions of method A. The percentage conversion, based on isolated yields of recovered β-keto sulfones and the reduction products, β-hydroxy sulfones, appears to increase as the length of the hydrophobic alkyl chain increases and is highest for the compounds, *e.g.* **5** and **6**, containing an aromatic substituent at the end of the chain. However, the conversion is particularly low for the octanone derivative **3**: the analogous phenylsulfonyloctanone is reported to be unreactive towards the baker's yeast.[3] In general, the reduction of the methylsulfonylalkanones is more efficient than that of the analogous phenylsulfonyl derivatives, especially for the longer chain analogues *e.g.* the phenylsulfonyl analogue of **2** was reduced to the corresponding alcohol in only 10% yield (10% ee).

Direction of enantioselection

Based on literature precedent the yeast reduction was expected to form preferentially the *S*-enantiomer of the β-hydroxy sulfones. This was found to be the case for most of the substrates studied, in agreement with the results reported for the phenylsulfonyl derivatives[2] and other related compounds.[1] Interestingly the major enantiomer of the alcohol isolated changes from *S*, when the alkyl chain is relatively short, to *R*, with the longer aliphatic and aromatic chains, for reductions conducted using method A.[7] Method B is more satisfactory in this regard as the principal enantiomer isolated in each case is *S*, irrespective of the structure of the β-keto sulfone employed.

For compounds **4** and **5**, the direction of the enantioselection was found to be very sensitive to slight variations in reaction conditions under the more dilute conditions associated with method A; minor changes in concentration for example resulted in a switch in the direction of enantioselection, albeit in all cases with a low degree of enantioselection.

Degree of enantioselection

Moderate to good enantioselections (71–87% ee) are obtained using method B while those from method A are in general lower (10–36% ee); increasing the concentration of yeast improves the enantioselection of the reduction.[8] The degree of enantioselec-

Table 1 Enantioselective reduction of 1-methylsulfonylalkan-2-ones with baker's yeast

Substrate	R	Method[a]	Ketone (%)[b]	Alcohol (%)[c]	%Ee[d]	$[\alpha]_D^{20}$[a]	Major enantiomer[f]
1	C_4H_9	A	43	8	36	+17.3	*S*
		B	28	12	71	+36.2	*S*
2	C_5H_{11}	A	52	12	23	+11.3	*S*
		B	22	26	87	+46.0	*S*
3	C_6H_{13}	A	45	8	33	—	*S*
		B	35	14	76	+44.3	*S*
4	C_7H_{15}	A	42	10	35	−25.8	*R*
		B	24	16	83	+61.1	*S*
5	$Ph(CH_2)_3$	A	30	15	10	−3.6	*R*
		B	28	36	74 (76)	+13.3	*S*
6	$Ph(CH_2)_4$	A	22	19	28	−14.1	*R*
		B	26	30	84	+48.6	*S*

[a] Method A [ref. 5(*a*)]: 0.20 g β-keto sulfone, 2 ml DMSO, 3 g sucrose, 0.40 g baker's yeast (Type II, Sigma), 138 ml tap water, 4 d, 28 °C. Method B [ref. 5(*b*)]: 0.20 g β-keto sulfone, 2 ml DMSO, 30 g sucrose, 20 g baker's yeast (Type II, Sigma), 124 ml tap water, 4 d, 28 °C. [b] Yield of recovered β-keto sulfone. [c] Yield of β-hydroxy sulfone isolated. [d] The % enantiomeric excess was measured by ^{1}H NMR spectroscopy in $CDCl_3$ in the presence of Eu(hfc)$_3$. In the case of ketone **5**, the enantiomeric purity of the alcohol **11** obtained was also measured by chiral HPLC (value in parentheses) on a Chiralcel OD-H column using hexane–propan-2-ol (88:12) as eluent, 1 ml min^{-1}, UV detection (220 nm), and found to agree closely with the % ee determined by ^{1}H NMR spectroscopy. [e] Units of specific rotation 10^{-1} deg cm^2 g^{-1}, *c* 1, $CHCl_3$. [f] The absolute configuration of alcohol **8**, derived from **2**, was assigned as *S* on the basis of the ^{1}H NMR spectrum with Eu(hfc)$_3$ and the sign of its optical rotation (ref. 6, footnote †). The absolute configuration of the other compounds was assigned on the basis of similar behaviour in their ^{1}H NMR spectra.

tion obtained is in general superior to that reported with the analogous phenylsulfonyl derivatives[2,3] *e.g.* the phenylsulfonyl analogue of **2** (R = C_5H_{11}) was reduced to the alcohol with only 10% ee. Thus, yeast reduction of longer chain compounds is more successful with methylsulfonyl analogues than with phenylsulfonyl derivatives.

When a yeast reduction (method B) of compound **2** was continued for 6 days instead of the usual 4 days, 12% of unchanged β-keto sulfone **2** was recovered and 11% of the alcohol **8** was isolated with 42% ee, major enantiomer *S*. Therefore the longer reaction time was detrimental in terms of yield and enantiomeric purity of the product, possibly due to enzymatic degradation of the sulfone derivatives in the yeast medium.

The sensitivity of the degree and direction of the enantioselection, and reduction efficiency, of the yeast reductions to the reaction conditions employed and the substrate structure, is probably due to the presence of a number of reducing enzymes in the microbe,[9] some of which selectively produce the *R*-enantiomer and others the *S*-enantiomer of the sulfonyl alcohols. Under different reaction conditions, the relative activities of the various enzymes appear to change: clearly under the more concentrated conditions associated with method B, the *S* selective enzymes predominate. Furthermore, as the hydrophobic chain length increases, it is possible that the reduction is carried out by different enzymes. Modification of the conditions of the yeast reduction, for example by immobilisation or use of additives, may alter the relative activities of the enzymes present in the yeast cells and thereby enhance the enantioselectivity of the reduction.

In conclusion, baker's yeast reductions of 1-methylsulfonylalkan-2-ones proceed with moderate to good enantioselectivities (up to 87% ee). The results obtained are dependent on reduction conditions and substrate structure, and in several cases are superior to those reported for the analogous phenylsulfonyl derivatives, especially the longer chain analogues. The enantiomerically enriched β-hydroxy sulfones **7**–**12** may prove useful as chiral synthons as both the hydroxy and sulfonyl groups are synthetically versatile.

† The absolute configuration of the related (*R*)-β-hydroxysulfone R = C_8H_{17} was assigned by conversion to decan-2-ol (ref. 6). By comparison of data the authors assigned the alcohol **8** as *R* when the specific rotation is negative, $[\alpha]_D^{20}$ −13.7 (*c* 5, EtOH), 69% ee. A sample of **8** from a yeast reduction (74% ee by ^{1}H NMR studies) has a specific rotation $[\alpha]_D^{20}$ +12.1° (*c* 1, EtOH); the stereochemistry of the major enantiomer was therefore assigned as *S*. This paper (ref. 6) also reports similar ^{1}H NMR results with Eu(hfc)$_3$.

Experimental

All solvents were dried and distilled before use. Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 F_{254}); preparative thin layer chromatography was conducted using Merck silica gel 60 PF_{254}; column chromatography was conducted using Merck silica gel 60. *Saccharomyces cerevisiae* (baker's yeast) Sigma Type II was used for the reductions.

Elemental analyses were performed in the Microanalysis Laboratory at University College Cork on a Perkin-Elmer 240 elemental analyser. Optical rotations were measured on a Perkin-Elmer 141 Polarimeter at 589 nm in a 10 cm cell; concentrations are expressed in g 100 ml^{-1}. Melting points were determined on a Uni-melt Thomas Hoover Capillary melting point apparatus and are uncorrected.

^{1}H (270 MHz) and ^{13}C (67.8 MHz) NMR spectra were recorded on a JEOL GSX 270 NMR spectrometer in $CDCl_3$, unless otherwise specified, using tetramethylsilane (TMS) as internal standard. Chemical shifts are expressed in parts per million (ppm) and coupling constants in Hertz (Hz). Infrared spectra were recorded as KBr discs (solids) or thin films on NaCl plates (oils) on a Perkin-Elmer Paragon 1000 FT-IR spectrometer or a Mattson Polaris FT-IR spectrometer.

Preparation of β-keto sulfones[4]

1-Methylsulfonylhexan-2-one 1. Sodium hydride (0.92 g, 60% in mineral oil, 0.023 mol) was washed with hexane (4 × 10 ml) under nitrogen. A solution of dimethyl sulfone (2.12 g, 0.023 mol) in dry DMSO (10 ml) was added slowly while stirring under nitrogen. The reaction mixture was heated to 70–75 °C until all of the sodium hydride had dissolved and hydrogen evolution had ceased (~30 min) giving a cloudy yellow solution. The reaction mixture was cooled to room temperature, dry THF (15 ml) was added, then cooled to 0 °C and a solution of ethyl pentanoate (1.48 g, 0.011 mol) in THF (10 ml) was added dropwise over 10 min. Stirring was continued for 2 h while the reaction mixture slowly returned to room temperature, then the reaction mixture was poured onto ice–water (30 ml), acidified to pH 1 with dilute aqueous hydrochloric acid, extracted with dichloromethane (3 × 25 ml), dried ($MgSO_4$) and evaporated at reduced pressure. Purification by chromatography on silica gel using gradient ethyl acetate–hexane as eluent gave 1-methylsulfonylhexan-2-one **1** (1.08 g, 54%) as a clear colourless oil (Found: C, 47.23; H, 7.75; S, 18.55. $C_7H_{14}O_3S$ requires C, 47.17; H, 7.92; S, 17.99%); ν_{max}(film)/cm^{-1} 1715, 1305 and 1147; δ_H($CDCl_3$) 0.70–1.80 (7 H, m,

$CH_3CH_2CH_2$), 2.61–2.78 (2 H, t, *J* 7, CH_2CO), 3.07 (3 H, s, CH_3SO_2) and 4.08 (2 H, s, CH_2SO_2); $\delta_C(CDCl_3)$ 13.77 (CH_3), 21.96 (CH_2), 25.01 (CH_2), 41.58 (CH_3SO_2), 44.51 (CH_2), 64.39 (CH_2SO_2) and 199.92 (CO).

1-Methylsulfonylheptan-2-one 2. This was prepared following the procedure described for **1** from sodium hydride (2.83 g, 60% in mineral oil, 0.07 mol) and dimethyl sulfone (6.60 g, 0.07 mol) in DMSO (20 ml), THF (30 ml) and ethyl hexanoate (5.01 g, 0.035 mol) in THF (10 ml). Purification by chromatography on silica gel using gradient ethyl acetate–hexane as eluent gave 1-methylsulfonylheptan-2-one **2** (3.36 g, 50%) as a white crystalline solid; mp 41–42 °C (lit.,[10] 42 °C, lit.,[11] 28–30 °C) (Found: C, 50.0; H, 8.2; S, 16.9. $C_8H_{16}O_3S$ requires C, 49.97; H, 8.39; S, 16.67%); ν_{max}(KBr)/cm^{-1} 1717, 1312 and 1143; $\delta_H(CDCl_3)$ 0.83–1.73 [9 H, m, $CH_3(CH_2)_3$], 2.65–2.74 (2 H, t, *J* 7, CH_2CO), 3.06 (3 H, s, CH_3SO_2) and 4.08 (2 H, s, CH_2SO_2); $\delta_C(CDCl_3)$ 14.01 (CH_3), 22.42, 28.46, 31.42 (3 × CH_2), 41.55 (CH_3SO_2), 44.85 (CH_2), 64.38 (CH_2SO_2) and 199.91 (CO).

1-Methylsulfonyloctan-2-one 3. This was prepared following the procedure described for **1** from sodium hydride (1.60 g, 60% in mineral oil, 0.04 mol) and dimethyl sulfone (3.78 g, 0.04 mol) in DMSO (20 ml), THF (30 ml) and ethyl heptanoate (3.16 g, 0.02 mol) in THF (20 ml). Recrystallisation from diethyl ether gave 1-methylsulfonyloctan-2-one **3** (2.10 g, 51%) as a white crystalline solid; mp 46–47 °C (Found: C, 52.6; H, 8.9; S, 15.8. $C_9H_{18}O_3S$ requires C, 52.40; H, 8.79; S, 15.54%); ν_{max}(KBr)/cm^{-1} 1720, 1320 and 1140; $\delta_H(CDCl_3)$ 0.85–0.95 (3 H, m, CH_3), 1.20–1.40 [6 H, m, $CH_3(CH_2)_3$], 1.52–1.70 (2 H, m, CH_2CH_2CO), 2.65–2.75 (2 H, t, *J* 7, CH_2CO), 3.10 (3 H, s, CH_3SO_2) and 4.07 (2 H, s, CH_2SO_2); $\delta_C(CDCl_3)$ 14.12 (CH_3), 22.17, 22.72, 27.14, 29.70 (4 × CH_2), 41.26 (CH_3SO_2), 44.62 (CH_2), 64.56 (CH_2SO_2) and 199.81 (CO).

1-Methylsulfonylnonan-2-one 4. This was prepared following the procedure described for **1** from sodium hydride (0.83 g, 60% in mineral oil, 0.02 mol) and dimethyl sulfone (1.90 g, 0.02 mol) in DMSO (15 ml), THF (20 ml) and ethyl octanoate (1.72 g, 0.01 mol) in THF (10 ml). Recrystallisation from diethyl ether gave 1-methylsulfonylnonan-2-one **4** (1.51 g, 69%) as a white crystalline solid; mp 43–45 °C (lit.,[10] 56 °C) (Found: C, 54.41; H, 9.37. $C_{10}H_{20}O_3S$ requires C, 54.51; H, 9.15%); ν_{max}(KBr)/cm^{-1} 1705, 1309 and 1139; $\delta_H(CDCl_3)$ 0.77–0.98 (3 H, t, *J* 7, CH_3), 1.15–1.43 [8 H, m, $CH_3(CH_2)_4$], 1.56–1.72 (2 H, m, CH_2CH_2CO), 2.64–2.76 (2 H, t, *J* 7, CH_2CO), 3.07 (3 H, s, CH_3SO_2) and 4.06 (2 H, s, CH_2SO_2); $\delta_C(CDCl_3)$ 14.45 (CH_3), 22.97, 23.36, 29.14, 29.36, 31.99 (5 × CH_2), 41.88 (CH_3SO_2), 45.30 (CH_2), 64.87 (CH_2SO_2) and 200.19 (CO).

1-Methylsulfonyl-5-phenylpentan-2-one 5. This was prepared following the procedure described for **1** from sodium hydride (0.83 g, 60% in mineral oil, 0.02 mol) and dimethyl sulfone (1.90 g, 0.02 mol) in DMSO (15 ml), THF (20 ml) and ethyl 4-phenylbutanoate (1.92 g, 0.01 mol) in THF (20 ml). Recrystallisation from diethyl ether gave 1 methylsulfonyl-5-phenylpentan-2-one **5** (1.47 g, 61%) as a white crystalline solid; mp 45–46 °C (Found: C, 59.74; H, 7.03; S, 13.84. $C_{12}H_{16}O_3S$ requires C, 59.98; H, 6.71; S, 13.34%); ν_{max}(KBr)/cm^{-1} 1702, 1305 and 1138; $\delta_H(CDCl_3)$ 1.84–2.00 (2 H, m, CH_2), 2.56–2.78 (4 H, m, $PhCH_2$ and CH_2CO), 3.03 (3 H, s, CH_3SO_2) 3.99 (2 H, s, CH_2SO_2) and 7.12–7.38 (5 H, m, aromatic *H*); $\delta_C(CDCl_3)$ 24.47 (CH_2), 34.97 (CH_2), 41.47 (CH_3SO_2), 44.06 (CH_2), 64.49 (CH_2SO_2), 126.16, 128.48 (aromatic CH), 141.02 (aromatic C) and 199.38 (CO).

1-Methylsulfonyl-6-phenylhexan-2-one 6. This was prepared following the procedure described for **1** from sodium hydride (0.83 g, 60% in mineral oil, 0.02 mol) and dimethyl sulfone (1.90 g, 0.02 mol) in DMSO (15 ml), THF (20 ml) and ethyl 4-phenylpentanoate (2.06 g, 0.01 mol) in THF (20 ml). Recrystallisation from diethyl ether gave 1-methylsulfonyl-6-phenylhexan-2-one **6** (1.38 g, 54%) as a white crystalline solid; mp 48–50 °C (Found: C, 61.16; H, 7.19; S, 12.74. $C_{13}H_{18}O_3S$ requires C, 61.39; H, 7.13; S, 12.60%); ν_{max}(KBr)/cm^{-1} 1703, 1301 and 1141; $\delta_H(CDCl_3)$ 1.52–1.73 (4 H, m, 2 × CH_2), 2.54–2.81 (4 H, m, $PhCH_2$ and CH_2CO), 3.04 (3 H, s, CH_3SO_2), 4.02 (2 H, s, CH_2SO_2) and 7.14–7.36 (5 H, m, aromatic *H*); $\delta_C(CDCl_3)$ 22.53, 30.44, 35.56 (3 × CH_2), 41.44 (CH_3SO_2), 44.67 (CH_2), 64.49 (CH_2SO_2), 125.85, 128.37 (aromatic CH), 141.86 (aromatic C) and 199.47 (CO).

Sodium borohydride reduction of β-keto sulfones

1-Methylsulfonylhexan-2-ol 7. 1-Methylsulfonylhexan-2-one **1** (0.10 g, 0.56 mmol) in ethanol (10 ml) was added dropwise over 5 min to sodium borohydride (0.025 g, 0.66 mmol) in ethanol (15 ml) while stirring at 0 °C under nitrogen. Stirring was continued for 20 min then water (10 ml) was added and the reaction mixture was concentrated at reduced pressure. The residue was partitioned between diethyl ether (40 ml) and water (10 ml) and the layers were separated. The aqueous layer was washed with diethyl ether (3 × 20 ml) and the combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated at reduced pressure. Purification by passage through a short column of silica gel using dichloromethane as eluent gave 1-methylsulfonylhexan-2-ol **7** (0.092 g, 91%) as a white crystalline solid; mp 44–46 °C (Found: C, 46.84; H, 9.01; S, 17.58. $C_7H_{16}O_3S$ requires C, 46.64; H, 8.95; S, 17.79%); ν_{max}(KBr)/cm^{-1} 3420 (br), 1290 and 1124; $\delta_H(CDCl_3)$ 0.73–0.92 (3 H, t, *J* 7, CH_3), 1.13–1.63 [6 H, m, $CH_3(CH_2)_3$], 2.12 (1 H, s, O*H*), 2.91–3.19 (5 H, m, $CH_3SO_2CH_2$, contains s for CH_3SO_2 at 2.94) and 4.13–4.30 (1 H, m, CHOH); $\delta_C(CDCl_3)$ 13.47 (CH_3), 21.92, 26.72, 36.02 (3 × CH_2), 42.12 (CH_3SO_2), 60.32 (CH_2SO_2) and 66.12 (CHOH).

1-Methylsulfonylheptan-2-ol 8. Reduction was conducted as described for **1** using 1-methylsulfonylheptan-2-one **2** (0.10 g, 0.52 mmol) in ethanol (10 ml) and sodium borohydride (0.02 g, 0.53 mmol) in ethanol (15 ml) to give 1-methylsulfonylheptan-2-ol **8** (0.093 g, 92%) as a white crystalline solid; mp 52–54 °C (Found: C, 49.6; H, 9.4; S, 16.4. $C_8H_{18}O_3S$ requires C, 49.46; H, 9.34; S, 16.50%); ν_{max}(KBr)/cm^{-1} 3430 (br), 1305 and 1140; $\delta_H(CDCl_3)$ 0.76–0.89 (3 H, t, *J* 7, CH_3), 1.17–1.64 [8 H, m, $CH_3(CH_2)_4$], 2.81–2.89 (1 H, d, *J* 10, O*H*), 2.94–3.19 (5 H, m, $CH_3SO_2CH_2$, contains s for CH_3SO_2 at 2.96) and 4.14–4.28 (1 H, m, CHOH); $\delta_C(CDCl_3)$ 13.96 (CH_3), 22.51, 24.74, 31.46, 36.82 (4 × CH_2), 42.62 (CH_3SO_2), 60.84 (CH_2SO_2) and 66.59 (CHOH).

1-Methylsulfonyloctan-2-ol 9. Reduction was conducted as described for **1** using 1-methylsulfonyloctan-2-one **3** (0.10 g, 0.48 mmol) in ethanol (10 ml) and sodium borohydride (0.02 g, 0.53 mmol) in ethanol (15 ml) to give 1-methylsulfonylheptan-2-ol **9** (0.088 g, 88%) as a white crystalline solid; mp 57–60 °C (Found: C, 52.26; H, 9.36; S, 15.83. $C_9H_{20}O_3S$ requires C, 51.89; H, 9.68; S, 15.39%); ν_{max}(KBr)/cm^{-1} 3500 (br), 1291 and 1130; $\delta_H(CDCl_3)$ 0.80–0.97 (3 H, t, *J* 7, CH_3), 1.20–1.71 [10 H, m, $CH_3(CH_2)_5$], 2.80–2.91 (1 H, br s, O*H*), 2.97–3.26 (5 H, m, $CH_3SO_2CH_2$, contains s for CH_3SO_2 at 3.04) and 4.23–4.40 (1 H, m, CHOH); $\delta_C(CDCl_3)$ 14.01 (CH_3), 22.54, 25.05, 28.99, 31.61, 36.89 (5 × CH_2), 42.65 (CH_3SO_2), 60.98 (CH_2SO_2) and 66.67 (CHOH).

1-Methylsulfonylnonan-2-ol 10. Reduction was conducted as described for **1** using 1-methylsulfonylnonan-2-one **4** (0.10 g, 0.45 mmol) in ethanol (10 ml) and sodium borohydride (0.023 g, 0.60 mmol) in ethanol (15 ml) to give 1-methylsulfonylheptan-2-ol **10** (0.095 g, 95%) as a white crystalline solid; mp 62–64 °C (Found: C, 54.36; H, 9.81; S, 14.36. $C_{10}H_{22}O_3S$ requires C, 54.02; H, 9.97; S, 14.42%); ν_{max}(KBr)/cm^{-1} 3480 (br), 1290 and 1126; $\delta_H(CDCl_3)$ 0.76–0.83 (3 H, t, *J* 7, CH_3), 1.10–1.62 [12 H, m, $CH_3(CH_2)_6$], 2.63–2.74 (1 H, br d, *J* 5, O*H*), 2.94–3.16 (5 H, m, $CH_3SO_2CH_2$, contains s for CH_3SO_2 at 3.02) and 4.12–4.30 (1 H, m, CHOH); $\delta_C(CDCl_3)$ 14.04 (CH_3), 22.61, 25.08, 29.14, 29.30, 31.74, 36.91 (6 × CH_2), 42.65 (CH_3SO_2), 60.97 (CH_2SO_2) and 66.65 (CHOH).

1-Methylsulfonyl-5-phenylpentan-2-ol 11. Reduction was conducted as described for **1** using 1-methylsulfonyl-5-

phenylpentan-2-one **5** (0.10 g, 0.42 mmol) in ethanol (10 ml) and sodium borohydride (0.017 g, 0.45 mmol) in ethanol (15 ml) to give 1-methylsulfonyl-5-phenylpentan-2-ol **11** (0.09 g, 88%) as a white crystalline solid; mp 92–94 °C (Found: C, 59.28; H, 7.27; S, 13.07. $C_{12}H_{18}O_3S$ requires C, 59.48; H, 7.49; S, 13.23%; ν_{max}(KBr)/cm^{-1} 3482 (br), 1261 and 1124; δ_H($CDCl_3$) 1.42–1.97 (4 H, m, CH_2CH_2), 2.25–2.34 (2 H, t, *J* 7, PhCH_2), 2.93–3.34 (5 H, m, CH_3SO$_2$CH_2, contains s for CH_3SO$_2$ at 2.98), 4.13–4.29 (1 H, m, C*H*OH) and 7.06–7.28 (5 H, m, aromatic *H*); δ_C($CDCl_3$) 26.74, 35.35, 36.16 (3 × CH_2), 42.50 (CH_3SO_2), 60.68 (CH_2SO_2), 66.32 (CHOH), 125.94, 128.33, 128.39 (aromatic CH) and 141.58 (aromatic C).

1-Methylsulfonyl-6-phenylhexan-2-ol 12. Reduction was conducted as described for **1** using 1-methylsulfonyl-6-phenylhexan-2-one **6** (0.10 g, 0.39 mmol) in ethanol (10 ml) and sodium borohydride (0.019 g, 0.50 mmol) in ethanol (15 ml) to give 1-methylsulfonyl-6-phenylhexan-2-ol **12** (0.092 g, 91%) as a white crystalline solid; mp 108–109 °C (Found: C, 61.10; H, 7.66; S, 12.31. $C_{13}H_{20}O_3S$ requires C, 60.91; H, 7.86; S, 12.51%); ν_{max}(KBr)/cm^{-1} 3380 (br), 1305 and 1130; δ_H($CDCl_3$) 1.19–1.66 [6 H, m, (CH_2)$_3$], 2.45–2.60 (2 H, t, *J* 7, PhCH_2), 2.91–3.18 (5 H, m, CH_3SO$_2$CH_2, contains s for CH_3SO$_2$ at 2.99), 4.11–4.27 (1 H, m, C*H*OH) and 7.06–7.30 (5 H, m, aromatic *H*); δ_C($CDCl_3$) 24.60, 31.07, 35.67, 36.62 (4 × CH_2), 42.53 (CH_3SO_2), 60.74 (CH_2SO_2), 66.43 (CHOH), 125.78, 128.32 (aromatic CH) and 142.08 (aromatic C).

Baker's yeast reduction of β-keto sulfones

General procedure: method A.[5a] A suspension of baker's yeast (Sigma, Type II, 0.20 g) and sucrose (1.5 g) in tap water (80 ml) was stirred at 28 °C for 1 h. The substrate (0.10 g) in DMSO (1 ml) and water (4 ml) was added dropwise and the mixture was stirred for 24 h. Sucrose (1.0 g) in water (50 ml) was added and stirring continued for 1 h. A further addition of the substrate (0.10 g) in DMSO (1 ml) and water (4 ml) was made and stirring continued for a further 20 h. To assist further reduction, sucrose (0.50 g) and yeast (0.20 g) were added and stirring continued for 48 h. Filtration through Celite, which was then washed with water (50 ml), saturation of the aqueous solution with sodium chloride, extraction with ethyl acetate (4 × 75 ml), drying ($MgSO_4$) and evaporation gave the crude product which was then separated by chromatography on silica with gradient ethyl acetate–hexane as eluent.

General procedure: method B.[5b] A suspension of baker's yeast (Sigma, Type II, 20 g) and sucrose (20 g) in tap water (120 ml) was stirred gently at room temperature for 30 min. The substrate (0.20 g) in DMSO (2 ml) and water (4 ml) was added and the mixture was stirred at 28 °C for 24 h. Sucrose (10 g) was added and stirring continued for 72 h. The product was isolated as described in method A.

The results of the yeast reductions are shown in Table 1. In each case the spectral characteristics of the recovered β-keto sulfone and the β-hydroxy sulfone were identical to those described above. The enantiomeric purity of each of the β-hydroxy sulfones was determined by ^{1}H NMR spectroscopy in $CDCl_3$ in the presence of Eu(hfc)$_3$ as chiral shift reagent: the signal corresponding to the SO_2CH_3 group in the *S*-enantiomer appears at lower field than that of the *R*-enantiomer, typically by ~16 Hz when 0.08 equiv. of Eu(hfc)$_3$ is present. In the case of β-hydroxy sulfone **11**, the enantiomeric purities of a number of the samples obtained were measured by chiral HPLC on a Chiralcel OD-H column using hexane–propan-2-ol (88:12) as eluent, 1 ml min^{-1}, UV detection (220 nm) and found to agree closely with the % ee determined by ^{1}H NMR spectroscopy.

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