Recoverable chiral sulfoxides for asymmetric synthesis: application to stereoselective carbonyl reduction and the asymmetric synthesis of allylic alcohols

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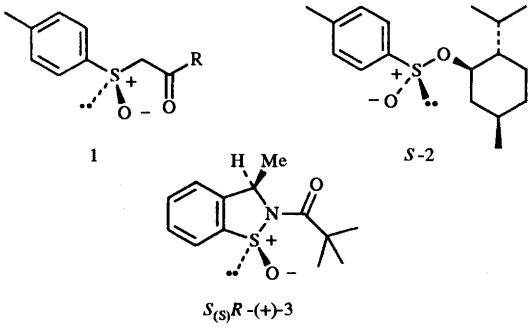
The enantiomerically pure cyclic sulfinamide $S_{(S)}R$-(+)-3 reacts with the sodium enolates of ketones to give the corresponding homochiral sulfoxides. Reduction of the carbonyl group in these products may be achieved using a variety of reducing agents the best of which were DIBAL-H or DIBAL-H/$ZnBr_2$, which give complementary products of high diastereoisomeric excess. Reduction of the hydroxy sulfoxides with Raney nickel proceeds in low yield and causes partial racemisation of the products. However the combined use of a directed reduction followed by a facile sulfenic acid elimination provides a synthesis of allylic alcohols in high enantiomeric excess.

Introduction

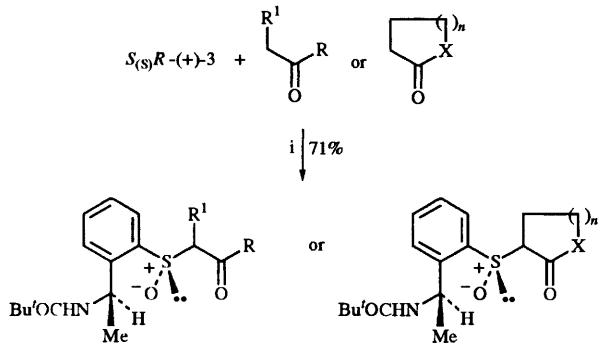
Chiral sulfoxides are known to provide excellent control of the stereoselective reduction of a proximal ketone group in, for example, compound **1**.[1] The reaction of methylmagnesium bromide with (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-toluene-*p*-sulfinate **2**[2] followed by acylation of the resulting methyl sulfoxide has been widely employed for the synthesis of the appropriate reagents of general structure **1**.[1] However, a more convenient approach to compounds such as **1** would be by direct reaction of (*S*)-**2** with the enolate of a methyl ketone. A major drawback of this approach is that the use of sodium and lithium enolates has been shown to cause epimerisation [3] of **2** whilst the use of a magnesium enolate requires forcing reaction conditions.[4] We



have recently reported the synthesis and applications to asymmetric synthesis of cyclic sulfinamide $S_{(S)}R$-(+)-**3**, a compound which provides a convenient source of chiral sulfoxide.[5,6] Sulfinamide $S_{(S)}R$-(+)-**3** possesses a number of practical advantages over (*S*)-**2**, the most significant of which is that it may be recycled after use.[5] In this paper we describe the application of $S_{(S)}R$-(+)-**3** to the synthesis of β-keto sulfoxides and subsequently enantiomerically pure alcohols *via* diastereoselective reduction of the carbonyl group.

Preparation of β-keto sulfoxides

Treatment of $S_{(S)}R$-(+)-**3** at −78 °C with the sodium enolates of a number of methyl ketones resulted in formation of sulfoxides **4a–d** as single diastereoisomers in good yields (Scheme 1). On the basis of our previous studies on $S_{(S)}R$-(+)-**3**



4a R = Ph, R^1 = H (71%)
4b R = *p*-$MeOC_6H_4$, R^1 = H (100%)
4c R = *o*-MeC_6H_4, R^1 = H (73%)
4d R = Bu^t, R^1 = H (70%)
4e R = Ph, R^1 = Me (75%; 3:2)

4f *n* = 1, X = CH_2 (45%; 10:1)
4g *n* = 2, X = CH_2 (78%; 6:1)
4h *n* = 3, X = CH_2 (98%; 3:2)
4i *n* = 6, X = CH_2 (88%; 3:2)
4j *n* = 11, X = CH_2 (82%; 3:2)
4k *n* = 1, X = O (76%; 10:1)

Scheme 1 *Reagents:* i, $NaN(TMS)_2$, toluene, −78 °C

the stereochemistry of products **4a–d** was assigned as that of inversion of configuration at sulfur during ring opening.[5–7] Toluene proved to be a superior solvent to diethyl ether or tetrahydrofuran (THF) for these reactions, and the use of a sodium enolate [generated using sodium bis(trimethylsilyl-amide] gave better results than a magnesium or lithium reagent (generated from *tert*-butylmagnesium bromide or lithium diisopropylamide, respectively).

Keto sulfoxide **4a** could also be prepared by the reaction of methyl sulfoxide **5** [prepared from $S_{(S)}R$-(+)-**3** in 89% yield] [5d] with lithium diisopropylamide and ethyl benzoate (94% yield). This procedure represents a convenient, although longer, alternative route to the reduction precursors **4a–d**.

The reaction of α-substituted or cyclic ketones with $S_{(S)}R$-(+)-**3** also gave products of ring opening **4e–j** in high yield (Scheme 1). However, assuming that substitution once again takes place with inversion of configuration at sulfur, the stereoselectivity at the newly formed chiral centre adjacent to the sulfoxide is low. Reaction of $S_{(S)}R$-(+)-**3** with the sodium

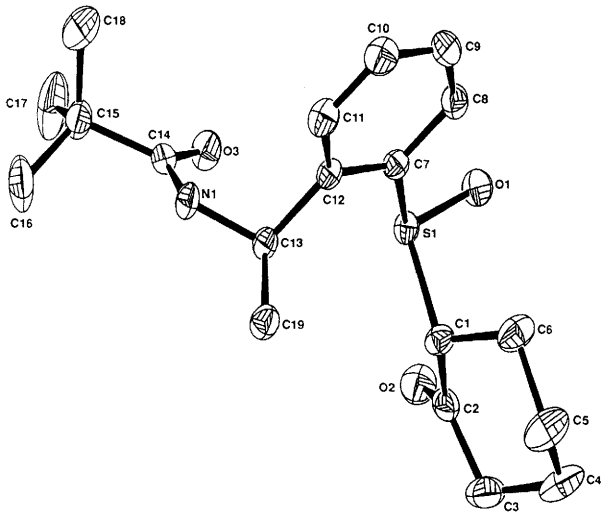
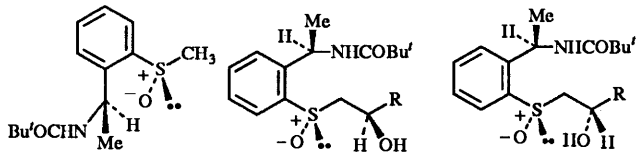
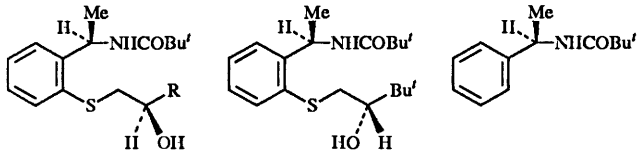


Fig. 1 ORTEP plot of adduct **4g**. Thermal ellipsoids are illustrated at the 30% probability level.



5 **6a** R = Ph, R^1 = H; **6b** R = *p*-$MeOC_6H_4$, R^1 = H; **6c** R = *o*-MeC_6H_4, R^1 = H; **6d** R = Bu^t, R^1 = H; **7a** R = Ph, R^1 = H; **7b** R = *p*-$MeOC_6H_4$, R^1 = H; **7c** R = *o*-MeC_6H_4, R^1 = H; **7d** R = Bu^t, R^1 = H



8a R = Ph; **8b** R = Bu^t **9** **10**

enolate of cyclohexanone resulted in the formation of a 6:1 mixture of adducts **4g** in 78% yield. The major isomer from this reaction was purified by recrystallisation from dichloromethane and its structure elucidated by X-ray crystallographic analysis (Figs. 1 and 2). The X-ray structure confirms that inversion of configuration at sulfur had indeed taken place. Large-ring ketones worked well in this process—reaction of the sodium enolate of cyclopentadecanone with $S_{(S)}R$-(+)-**3** gave the sulfoxide **4j** as a mixture of diastereoisomers in 82% yield. The reaction of lactones also appears favourable (product **4k**), but 1-methylpyrrolidin-2-one gave no addition product in the reaction.

Stereoselective reductions

The reduction of **4a**, the adduct of acetophenone, with a series of reducing agents was studied (Table 1). As expected,[1] the use of DIBAL-H and DIBAL-H/$ZnBr_2$ gave complementary major diastereoisomers of β-hydroxy sulfoxides with high diastereoselectivity (**6a** and **7a**, respectively). The diastereoisomeric ratio was measured by integration of the signal from the proton adjacent to the hydroxy group, which was distinct in each isomer. The stereochemistry of the product was assigned on the basis of the reported reduction selectivities towards related

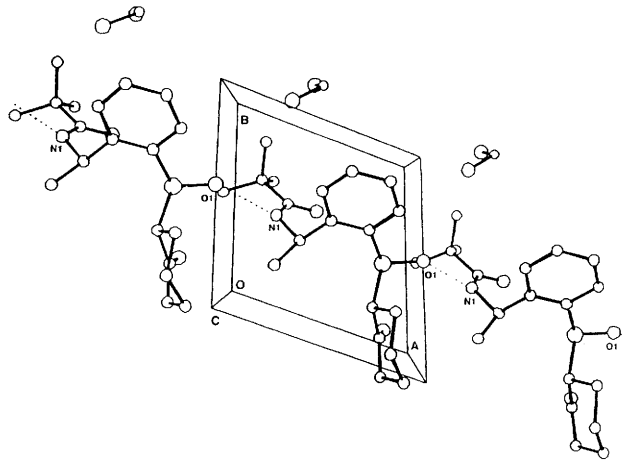


Fig. 2 Packing diagram of **4g** viewed along the *c* axis to show intermolecular hydrogen-bonding distances

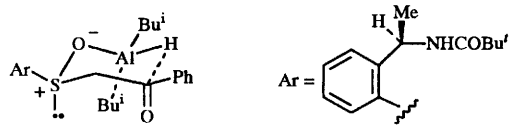


Fig. 3 Reduction of keto sulfoxides by DIBAL-H

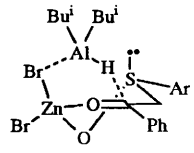


Fig. 4 Reduction of keto sulfoxides by DIBAL-H–$ZnBr_2$

substrates for these reducing agents.[1] In the absence of zinc(II) the reaction is believed to take place *via* the intermediate illustrated in Fig. 3 in which sulfoxide and reducing agent describe a chair conformation. Both the aryl group on the sulfoxide and the group adjacent to the ketone adopt equatorial positions, which lead to the formation of **6a**. When zinc dibromide is present, a complex is formed in which the carbonyl and sulfoxide groups are chelated (Fig. 4). Addition of hydride to the upper face (as illustrated) is favoured due to the immediate formation of a 'chair' conformation reduction product and thus **7a** after work-up. Reducing agents other than DIBAL-H were not as selective, presumably because less conformationally-rigid transition states are involved.

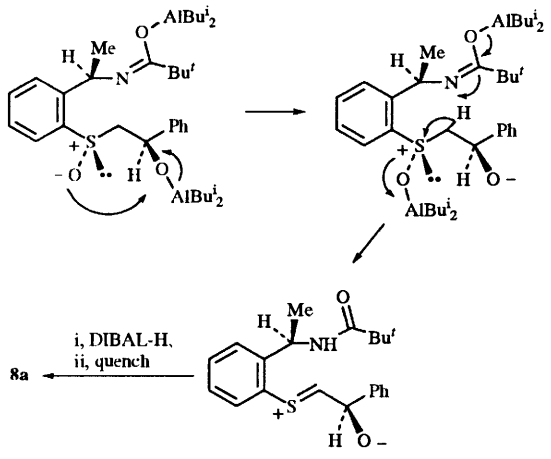
The use of DIBAL-H alone (exactly 1 equiv.) also gave a small quantity (*ca.* 5%) of the corresponding β-hydroxy sulphide **8a** resulting from sulfoxide reduction. A sample of authentic **8a** was prepared for comparison by reduction of **6a** with triphenylphosphine–iodine. Product **8a** may be formed *via* a Pummerer-type rearrangement[1m-o,q] involving aluminium(III)-promoted sulfur deoxygenation followed by reduction of the intermediate iminium salt. It is likely that the amide side chain in **4** participates in this process by promoting the elimination in the mechanism as depicted in Scheme 2. Presumably this mechanism is suppressed when zinc(II) is added, since sulfides are not then observed. Evidence that the sulfoxide reduction occurs after the carbonyl reduction was provided by treatment of a pure sample of **6a** with 4 equiv. of DIBAL-H in THF for 2 h at −78 °C. This resulted in formation of **8a** in 30% yield, the remaining mass balance being accounted for by unchanged starting material.

Highly diastereoselective reductions of keto sulfoxides **4b–d** were also achieved using combinations of DIBAL-H with or without added zinc(II) bromide, the ratio of products mirroring that observed with **4a** (Table 1). In the case of DIBAL-H reduction of **4d** in the absence of zinc(II) bromide, however, the major product was the hydroxy sulfide **8b**, together with its

Table 1 Diastereoselective reductions of β-keto sulfoxides **4a–d**

Substrate	Reducing agent	Yield (%)	**6**:**7**
4a	DIBAL-H	73	94:6
4a	NBu_4BH_4	Quant.	62:38
4a	$NaBH_4$	Quant.	60:40
4a	$NaBH_4$–$CeCl_3$	Quant.	57:43
4a	$NaB(OAc)_3H$	Quant.	40:60
4a	$LiAlH_4$	87	25:75
4a	DIBAL-H–$ZnBr_2$	80	<2: >98
4b	DIBAL-H	90[a]	91:9
4b	DIBAL-H–$ZnBr_2$	Quant.	<2: >98
4c	DIBAL-H	90	91:9
4c	DIBAL-H–$ZnBr_2$	90	<2: >98
4d	DIBAL-H	10[b]	94:6
4d	DIBAL-H–$ZnBr_2$	90	<2: >98

[a] Starting material (10%) recovered. [b] 55% of product was **8b** and **9** in ratio of 94:6.

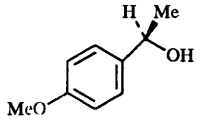


Scheme 2 Proposed sulfoxide reduction mechanism

diastereoisomer **9**. The proposal above that the sulfoxide reduction is the later step was further supported by the observation that the ratio of **8b** to **9** matched that of **6d** to **7d**. Although it is most extreme for **4d**, it has been a general observation that the over-reduction of non-aromatic keto sulfoxides to the sulfides appears to be more significant than the corresponding process in aromatic substrates.

Attempts at formation of chiral alcohols

Attempted reductive cleavage of recrystallised **7a** using Raney nickel[1h,j,k,o,p] or nickel boride[8] gave a mixture of amide **10**, a trace of racemic 1-phenylethanol and ethylbenzene. The loss of chirality was confirmed by conversion of the alcohol into the (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA) derivative and analysis by ^1H NMR spectroscopy. Raney nickel has been reported to be capable of oxidising benzylic alcohols



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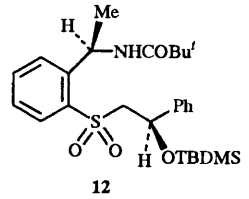

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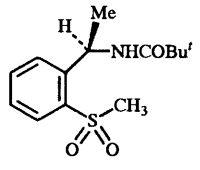

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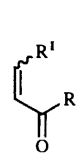
in a disproportionation reaction.[9] Subsequent reduction of this ketone would account for the epimerisation of the cleaved alcohol. The Raney nickel reduction of diastereoisomerically pure **7b** gave an equimolar mixture of **10** and alcohol *R*-**11**. The alcohol was shown by conversion into its (*R*)-MTPA derivative to be of 81% ee, corresponding to a significant drop in enantiomeric purity upon reduction. In the case of reduction of pure **7d** the isolated alcohol was of only 63% ee. Whilst it has been demonstrated that direct reduction of hydroxy sulfoxides **6** and **7** is not a viable synthetic process, the results served to confirm the sense of the diastereoselective reductions of compounds **4a–d**. Although direct reduction of hydroxy sulfoxides has proved successful for others,[1h,k,o,p] we chose not to continue this line of research.

In view of these disappointing results, we sought an alternative approach which would permit the formation of non-racemic products without compromising the ability to recycle $S_{(S)}R$-(+)-**3**. An attractive approach to this appeared to be conversion of the sulfoxide in **6** or **7** into a leaving group, for example by conversion into the sulfone. Treatment with a base would then be expected to lead to epoxide formation. A similar approach to epoxides has been described in which the sulfoxide is first reduced and then methylated;[1a] however, we discounted this approach because it leads to formation of a methyl sulfoxide. Hydroxy sulfoxide **6a** was first protected as the *tert*-butyldimethylsilyl ether (TBDMSCl, imidazole, DMF) and oxidised with a combination of ruthenium(III) chloride and sodium periodate to give **12** (58% yield for two steps). However, desilylation with TBAF resulted in formation of the methyl sulfone **13** in 89% yield, presumably accompanied by formation of the corresponding aldehyde, although this was not isolated. Indeed it proved impossible to prevent this 'retro-aldol' type fragmentation from taking place under any conditions and this approach was not studied further.

Asymmetric synthesis of allylic alcohols

We have found that adducts of $S_{(S)}R$-(+)-**3** with ketones undergo a very facile sulfenic acid elimination to give enones.[10] Our preliminary studies suggest that the elimination appears to



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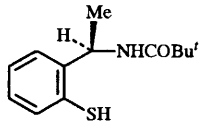

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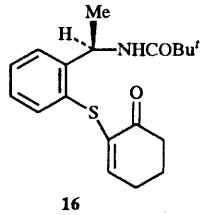

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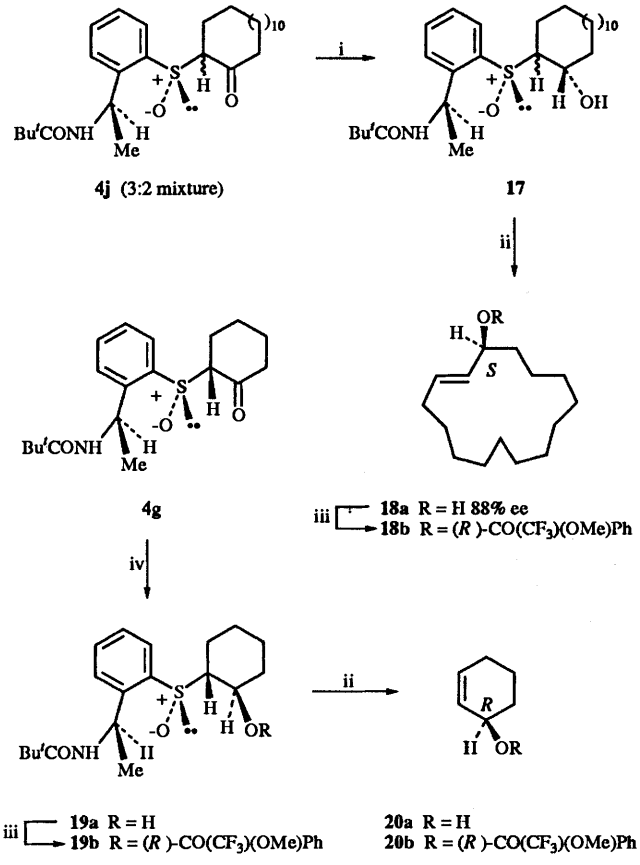
be marginally preferable to the corresponding reaction of substrates which lack the amide side chain. In the latter cases slightly higher reaction temperatures and longer reaction times are required. Typically, solutions of **4e** and **4g–j** when heated for 2–3 h at 60 °C in toluene containing a small amount of sodium hydrogen carbonate[10g] gave the corresponding enones **14a–e** in yields of 60–98% (Table 2).[11] Furthermore, several detailed studies have concluded that the reduction of β-keto sulfoxides bearing α-substituents is controlled essentially completely by the configuration of the sulfoxide group.[1c,g,h] It therefore appeared to us that the combination of a stereoselective reduction followed by thermal elimination[4b] would provide an attractive approach to chiral allylic alcohols. A further advantage of this approach is that the side-products from the sulfoxide component (sulfenic acids and derivatives) may be recycled by treatment of the crude combined residues with triphenylphosphine and iodine[12] to give the thiol **15**, which we have already shown to be a precursor to **3**.[5d]

An interesting observation that is worthy of note at this point, was the formation of cyclohexanone vinyl sulfide **16**

Table 2 Synthesis of enones **14** by thermal elimination

Substrate	R	R^1	Product	Yield (%)	*cis/trans*
4e	Ph	H	**14a**	60	—
4g	$(CH_2)_3$		**14b**	84	*cis*
4h	$(CH_2)_4$		**14c**	80	*cis*
4i	$(CH_2)_7$		**14d**	98	96:4
4j	$(CH_2)_{12}$		**14e**	72	*trans*



Scheme 3 *Reagents:* i, DIBAL-H–$ZnBr_2$, THF, −78 °C; ii, toluene, 60 °C, 5 h; iii, (*R*)-$HO_2CC(OMe)(CF_3)Ph$, DCC, DMAP; iv, DIBAL-H, THF, −78 °C

when trifluoroacetic acid was used in an attempt to promote the elimination. Pummerer reaction products have been isolated in similar reactions, although the anhydride is usually used.[13]

To demonstrate the proposed methodology we selected representative examples of cyclic keto sulfoxides. Firstly, reduction of **4j** with DIBAL–H/$ZnBr_2$ at −78 °C followed by heating of the crude reduction mixture **17** at 60 °C in toluene for 5 h gave the allylic alcohol **18a** in 82% overall yield along with a number of sulfenic acid derived side-products (Scheme 3). The enantiomeric excess of **18a** was shown to be 88% in favour of the *S*-enantiomer based on the assigned reduction selectivity and by integration of the methoxy signals from the (*R*)-MTPA ester derivatives **18b**[11] by comparison with a sample from racemic modification (270 MHz ^{1}H NMR). Allylic alcohol **18a** has been employed as a key intermediate in a recent synthesis of enantiomerically pure muscone.[14] A quantity (12%) of enone **14e** was also isolated from the elimination, presumably from unchanged keto sulfoxide **4j**. The use of DIBAL-H alone for the reduction of **4j** followed by the same sequence resulted in the formation of **18a** (44% yield) of only 12% enantiomeric excess in favour of the *R*-enantiomer, together with 20% of **14e**. This sequence confirms that with the use of DIBAL-H–$ZnBr_2$ the sulfoxide chirality overrides any control by the configuration at the α-centre, although this is not the case with DIBAL-H alone.

Reduction of the purified major diastereoisomer of **4g** with DIBAL-H gave a single diastereoisomer of alcohol **19a** in low yield (31%) although unchanged **4g** was recovered (65%). Thermally-promoted sulfenic acid elimination was attempted on **19a**, but very little alcohol **20a** was formed (< 5%). In the belief that this lack of reactivity was due to stabilisation by an intramolecular hydrogen bond, this alcohol was first converted into its (*R*)-MTPA ester derivative **19b** in quantitative yield. Sulfenic acid elimination then proceeded smoothly to furnish the protected alcohol **20b** in quantitative yield, as a single diastereoisomer (Scheme 3). Authentic samples of (*R*)-MTPA derivatives of racemic **20a** were independently prepared to confirm this result. The same sequence of reactions from **4g** to **20b** using DIBAL–H–$ZnBr_2$ gave a product in 54% overall yield which was a 1 : 1 mixture of diastereoisomers. This result is in contrast to the expected result based on the observations on the reduction of the larger ring compound **4j** and shows that the factors controlling the relative contributions to the stereochemical control from the sulfoxide and the configuration at the α-centre are complex.

In conclusion we have demonstrated that the cyclic sulfinamide $S_{(S)}R$-(+)-**3** may be used as an auxiliary for the diastereoselective reductions of β-keto groups and for the enantioselective synthesis of allylic alcohols. Since we have shown that $S_{(S)}R$-(+)-**3** may be recycled from the sulfenic acid elimination side-products,[5d] it is effectively recoverable in this application.

Experimental

General details

All mp measurements were carried out on a Gallenkamp hot-stage apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1310 grating Spectrometer. ^{1}H NMR were recorded on either a JEOL GX270 FT at 270 MHz or a JEOL EX400 instrument operating at 400 MHz. The observed spectra were for solutions in deuteriochloroform unless otherwise stated. The chemical shifts were recorded relative to tetramethylsilane as an internal standard; all coupling constants, *J*, are reported in Hz. ^{13}C NMR spectra were recorded on a Jeol GX270 FT instrument operating at 67.8 MHz or a JEOL EX400 instrument operating at 100 MHz. The spectra were recorded for solutions in deuteriochloroform unless otherwise stated. The chemical shifts were recorded relative to deuteriochloroform as internal standard in a broad band decoupled mode; the multiplicities were obtained by using 135 and 90 DEPT experiments to aid in assignments (q = methyl, t = methylene, d = methine, s = quaternary).

Mass spectra were recorded on a VG analytical 7070E instrument with VG2000 data system using electron ionisation (E.I., 70 eV), chemical ionisation (CI isobutane) and fast atom bombardment (FAB) techniques. High-resolution MS was carried out by the E.P.S.R.C. regional service at the University College of Swansea. Microanalytic data were obtained on a Carlo Erba 1106 Elemental Analyser. Optical rotations, carried out using a Perkin Elmer 141 polarimeter, are recorded as 10^{-1} deg cm^2 g^{-1}. Flash chromatography was performed on Merck silica gel 60 and the solvents ethyl acetate, acetone and light petroleum (boiling range 60–80 °C) were distilled before use. All reactions were monitored by TLC on aluminium or plastic sheets precoated with 250 μm silica gel which were visualised by UV light and then by potassium permanganate solution, phosphomolybdic acid solution or anisaldehyde solution.

Tetrahydrofuran and diethyl ether were dried over sodium benzophenone ketyl under nitrogen and distilled prior to use. Toluene was dried over sodium and distilled before use. Dichloromethane was distilled from phosphorus pentoxide. 4-Dimethylaminopyridine (DMAP) was provided in the form of a

gift from Reilly chemicals (USA) or purchased from the Aldrich Chemical Company. Butyllithium and *tert*-butyllithium were provided as solutions in hexane of 1.6 and 1.7 mol dm^{-3}, respectively. Methyllithium was provided as a 1.4 mol dm^{-3} solution in diethyl ether. Diisobutylaluminium hydride and sodium bis(trimethylsilyl)amide were provided as 1.0 mol dm^{-3} solutions in hexanes and tetrahydrofuran, respectively. All reactions, unless otherwise stated, were carried out in Schlenk glassware under a positive pressure of dry nitrogen in a vacuum flame-dried apparatus.

Synthesis of β-keto sulfoxide 4a by acylation of 5

To a stirred solution of diisopropylamine (0.23 cm^3, 1.63 mmol) in tetrahydrofuran (0.60 cm^3) at 0 °C was added dropwise a solution of *tert*-butyllithium in pentane (0.87 cm^3, 1.48 mmol). The resulting solution was stirred at 0 °C for 0.5 h and then cooled to −60 °C and treated with a solution of $S_{(S)}R$-(−)-**3** (0.10 g, 0.37 mmol) in tetrahydrofuran (0.95 cm^3), added dropwise. The reaction mixture was allowed to warm up to 0 °C over a period of 0.5 h and then stirred for 1.0 h at this temperature. A 10% solution (v/v) of ethyl benzoate in tetrahydrofuran (0.50 cm^3, 0.37 mmol) was added to the reaction mixture which was then stirred at 0 °C for 1.0 h, before being quenched with saturated aqueous ammonium chloride (2 cm^3). The organic phase was removed and the aqueous phase extracted with dichloromethane (3 × 5 cm^3). The combined organic phase and extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The product, $S_{(S)}R$-(−)-**4a** was isolated after column chromatography (50% ethyl acetate–light petroleum) (0.13 g, 94%), mp 133–134 °C (light petroleum–dichloromethane); $[\alpha]_D^{25}$ −142.5 (*c*0.59, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3321, 1681, 1645 and 1056; δ_H($CDCl_3$, 270 MHz) 1.20 (9 H, s, CMe_3), 1.55 (3 H, d, *J* 6.75, CH*Me*), 4.55 (1 H, d, *J* 13.5, CH_{AB}), 4.95 (1 H, d, *J* 13.5, CH_{AB}), 5.54 (1 H, quintet, *J* 6.75, C*H*Me), 6.05 (1 H, br d, *J* 6.75, NH), 7.62–7.35 (5 H, m, ArH), 7.80 (1 H, d, *J* 4.5, ArH) and 8.00 (2 H, d, *J* 4.5, ArH); δ_C($CDCl_3$) 22.20 (q), 27.42 (q), 38.45 (s), 45.85 (d), 63.62 (t), 125.6 (d), 126.7 (d), 128.2 (d), 128.7 (d, 2 C), 129.0 (d, 2 C), 131.9 (d), 134.0 (s), 136.2 (s), 140.7 (s), 143.3 (s), 177.8 (s) and 191.9 (s); *m/z* (FAB) 372 (MH^+, 100), 319 (6) and 305 (7) (Found: C, 67.7; H, 6.75; N 3.84. $C_{13}H_{19}NO_3S$ requires C, 67.9; H, 6.74; N, 3.77%).

Synthesis of β-keto sulfoxides 4 by addition of ketone enolates to $S_{(S)}R$-(+)-*cis*-3

A typical procedure is as follows. To a stirred solution of sodium bis(trimethylsilylamide) (1.0 mol dm^{-3} in tetrahydrofuran; 1.00 cm^3, 1.00 mmol) at −78 °C was added dropwise a solution of the ketone (1.00 mmol) in toluene (1 cm^3). The resultant solution was stirred at −78 °C for 1 h after which a solution of $S_{(S)}R$-(+)-*cis*-**3** (0.10 g, 0.40 mmol) in toluene (1 cm^3) was then added dropwise to it and stirring continued at −78 °C for 1 h. The reaction mixture was allowed to warm to ambient temperature after which it was stirred until examination by TLC showed all $S_{(S)}R$-(+)-*cis*-**3** had been consumed. The reaction was quenched by addition of saturated aqueous ammonium chloride (5 cm^3) to the mixture which was then diluted with water (5 cm^3). The organic phase was removed and the aqueous phase extracted with ethyl acetate (3 × 5 cm^3). The combined organic phase and extracts were washed with brine (15 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure and the residue was column chromotographed on silica (50–100% ethyl acetate in light petroleum) to give the required adducts.

Acetophenone adduct 4a. The product $S_{(S)}R$-(−)-**4a** was isolated as a colourless solid (71%)—see previous synthesis for spectroscopic details.

***p*-Methoxyphenyl methylketone adduct 4b.** Product $S_{(S)}R$-(−)-**4b** was isolated as a colourless solid (quantitative), mp 75 °C (ethyl acetate light petroleum) $[\alpha]_D^{25}$ −198.7 (*c* 0.15, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3459, 1710, 1663 and 1032; δ_H($CDCl_3$) 1.18 (9 H, s, CMe_3), 1.54 (3 H, d, *J* 7.0, $CHCH_3$), 3.87 (3 H, s, OMe), 4.46 (1 H, d, *J* 14.3, CH), 4.86 (1 H, d, *J* 14.3, CH), 5.51 (1 H, quintet, *J* 7.0, C*H*Me), 6.01 (1 H, br d, *J* 7.0, NH), 6.89–6.92 (2 H, d, *J* 7.0, ArH), 7.34–7.47 (3 H, m, ArH), 7.75–7.78 (1 H, m, ArH) and 7.95–7.97 (2 H, d, *J* 7.0, ArH); δ_C($CDCl_3$) 22.06 (q), 27.34 (q), 38.37 (s), 45.37 (d), 55.43 (q), 63.44 (t), 113.8 (2C, d), 125.4 (d), 126.7 (d), 128.1 (d), 129.3 (s), 131.5 (2C, d), 131.8 (d), 140.7 (s), 143.2 (s), 164.2 (s), 177.7 (s) and 190.0 (s); *m/z* (FAB) 402 (MH^+, 81), 384 (2), 251 (5) and 150 (100) (Found: C, 64.1; H, 6.88; N, 3.39. $C_{22}H_{27}NO_4S$·0.5 H_2O requires C, 64.4; H, 6.83; N, 6.41%).

Methyl *p*-tolyl ketone adduct 4c. Product $S_{(S)}R$-(−)-**4c** was isolated as a colourless solid (73%), mp 78 °C (ethyl acetate–light petroleum); $[\alpha]_D^{25}$ −151.4 (*c* 0.62, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3459, 1730, 1665 and 1034; δ_H($CDCl_3$) 1.17 (9 H, s, CMe_3), 1.54 (3 H, d, *J* 6.7, $CHCH_3$), 2.46 (3 H, s, Me), 4.49 (1 H, d, *J* 15.0, CH), 4.85 (1 H, d, *J* 15.0, CH), 5.46 (1 H, quintet, *J* 6.7, C*H*Me), 6.02 (1 H, br d, *J* 6.7, NH), 7.25 (2 H, m, ArH), 7.40 (4 H, m, ArH) and 7.81 (2 H, br t, *J* 6.7, ArH); δ_C($CDCl_3$) 21.57 (q), 22.05 (q), 27.37 (q), 38.41 (s), 46.06 (d), 65.88 (t), 125.6 (d), 125.9 (d), 126.7 (d), 128.3 (d), 130.5 (d), 131.8 (d), 132.1 (d), 132.5 (d), 135.7 (s), 139.8 (s), 140.9 (s), 143.0 (s), 177.6 (s) and 194.3 (s); *m/z* (FAB) 386 (MH^+, 100), 368 (5), 285 (10) and 253 (10) (Found: C, 67.0; H, 7.3; N, 3.3. $C_{22}H_{27}NO_3S$·0.5 H_2O requires C, 67.0; H, 7.15; N, 3.55%).

3,3-Dimethylbutan-2-one adduct 4d

Product $S_{(S)}R$-(−)-**4d** was isolated as a colourless solid (70%), mp 124 °C (ethyl acetate–light petroleum); $[\alpha]_D^{25}$ −160.8 (*c* 0.365, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3460, 1705, 1660 and 1034; δ_H($CDCl_3$) 1.11 (9 H, s, CMe_3), 1.17 (9 H, s, CMe_3), 1.53 (3 H, d, *J* 7.0, $CHCH_3$), 4.07 (1 H, d, *J* 15.6, CH), 4.55 (1 H, d, *J* 15.6, CH), 5.50 (1 H, quintet, *J* 7.0, C*H*Me), 6.01 (1 H, bd, *J* 7.0, NH), 7.40–7.49 (3 H, m, ArH) and 7.83 (1 H, d, *J* 7.7, ArH); δ_C($CDCl_3$) 22.35 (q), 25.43 (q), 27.31 (q), 38.31 (s), 44.53 (s), 45.93 (d), 62.96 (t), 125.6 (d), 126.9 (d), 128.1 (d), 131.8 (d), 141.0 (s), 143.7 (s), 177.6 (s) and 207.6 (s); *m/z* (FAB) 352 (MH^+, 100) 334 (8) and 251 (10) (Found: C, 65.1; H, 8.35; N, 3.9. $C_{19}H_{29}NO_3S$ requires C, 65.0; H, 8.26; N, 3.99%).

Propiophenone adduct 4e. Product $S_{(S)}R$-(−)-**4e** was isolated as a white foam (75%) as a 3:2 mixture of diastereoisomers; ν_{max}(Nujol)/cm^{-1} 3460, 1705, 1660 and 1034; δ_H($CDCl_3$), major isomer 1.19 (9 H, s, CMe_3), 1.50 (3 H, d, *J* 7.1, $CHCH_3$), 1.76 (3 H, d, *J* 7.0, $CHCH_3$), 5.42 (1 H, q, *J* 7.1, C*H*CH_3), 5.71 (1 H, quintet, *J* 7.0, C*H*CH_3), 5.98 (1 H, br d, *J* 7.0, NH), 7.12–7.68 (7 H, m, ArH) and 8.02 (2 H, d, *J* 7.5, ArH); minor isomer 1.21 (9 H, s, CMe_3), 1.34 (3 H, d, *J* 7.1, $CHCH_3$), 1.44 (3 H, d, *J* 7.0, $CHCH_3$), 5.58 (1 H, q, *J* 7.1, C*H*CH_3), 5.84 (1 H, quintet, *J* 7.0, C*H*CH_3), 5.92 (1 H, br d, *J* 7.0, NH), 7.12–7.68 (7 H, m, ArH) and 7.78 (2 H, d, *J* 7.5, ArH); δ_C($CDCl_3$) 13.07 (q, 0.5 C), 13.14 (q, 0.5 C), 21.97 (d, 0.5 C), 22.23 (d, 0.5 C), 27.33 (q, 3 C), 38.28 (s, 1 C), 44.67 (d, 0.5 C), 45.14 (d, 0.5 C), 63.07 (t, 0.5 C), 66.12 (t, 0.5 C), 126.2 (d, 0.5 C), 126.4 (d, 1 C), 127.2 (d, 0.5 C), 127.3 (d, 0.5 C), 127.5 (d, 0.5 C), 128.3 (d, 1 C), 128.4 (d, 2 C), 128.5 (d, 1 C), 128.8 (d, 1 C), 131.6 (d, 0.5 C), 132.0 (d, 0.5 C), 133.4 (d, 1 C), 135.5 (s, 0.5 C), 136.4 (s, 0.5 C), 138.2 (s, 0.5 C), 139.7 (s, 0.5 C), 144.0 (s, 0.5 C), 144.7 (s, 0.5 C), 177.3 (s, 0.5 C), 177.6 (s, 0.5 C), 196.4 (s, 0.5 C) and 196.7 (s, 0.5 C); *m/z* (FAB) 386 (MH^+, 100), 275 (12) and 252 (13) (Found: *m/z* 386.1772. $C_{22}H_{27}NO_3S$ requires MH^+, 386.1790).

Cyclopentanone adduct 4f. Product $S_{(S)}R$-(−)-**4f** was isolated as a mixture of diastereoisomers in a 10:1 ratio (45%) and

purified by further column chromatography to furnish a single diastereoisomer as a white foam; ν_{max}(Nujol)/cm^{-1} 3460, 1705, 1660 and 1034; δ_H($CDCl_3$) 1.14 (9 H, s, CMe_3), 1.49 (3 H, d, *J* 6.8, $CHCH_3$), 1.60–1.90 (2 H, m, CH), 2.00–2.45 (3 H, m, CH), 2.45–2.60 (1 H, m, CH), 3.45 (1 H, t, *J* 8.6, CH), 5.05 (1 H, quintet, *J* 6.8, C*H*Me), 6.01 (1 H, d, *J* 6.8, NH), 7.38–7.50 (3 H, m, ArH) and 7.83 (1 H, m, ArH); δ_C($CDCl_3$) 20.08 (t), 20.37 (t), 21.41 (q), 27.28 (q), 38.47 (s), 38.89 (t), 45.93 (d), 69.35 (d), 125.3 (d), 126.7 (d), 128.1 (d), 131.5 (d), 140.2 (s), 141.1 (s), 177.7 (s) and 211.6 (s); *m/z* (FAB) 336 (MH^+, 100) [Found: *m/z* 336.1633. $C_{18}H_{25}NO_3S$ requires (MH^+), 336.1619].

Cyclohexanone adduct 4g. Product $S_{(S)}R$-(−)-**4g** was isolated as a 6:1 mixture of diastereoisomers (78%) which was recrystallised from dichloromethane for analytical purposes. Data for major diastereoisomer: mp 133 °C (dichloromethane); $[\alpha]_D^{25}$ −153.9 (*c* 0.395, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3240, 1707, 1642 and 1023; δ_H($CDCl_3$) 1.17 (9 H, s, CMe_3), 1.51 (3 H, d, *J* 6.8, $CHCH_3$), 1.62–2.62 (8 H, m, CH_2), 4.08 (1 H, t, *J* 7.5, CH), 5.40 (1 H, quintet, *J* 6.8, C*H*Me), 5.90 (1 H, br d, *J* 6.8, NH), 7.40–7.50 (3 H, m, ArH) and 7.90 (1 H, m, ArH); δ_C($CDCl_3$) 21.37 (q), 23.26 (t), 26.43 (t), 26.66 (t), 27.47 (q), 38.01 (s), 42.36 (t), 45.51 (d), 72.62 (d), 126.4 (d), 126.7 (d), 128.3 (d), 131.7 (d), 141.3 (2, s), 177.5 (s) and 205.7 (s); *m/z* (FAB) 350 (MH^+, 100), 332 (5) and 253 (15) [Found: *m/z* 350.1782. $C_{19}H_{27}NO_3S$ requires (MH^+), 350.1790].

X-Ray crystal data for **4g** (*major diastereoisomer*).—A crystal of approximate dimensions 0.2 × 0.2 × 0.2 mm was used for data collection.

Crystal data.—$C_{20}H_{29}Cl_2NO_3S$, *M* = 434.4, triclinic, *a* = 8.106(1), *b* = 8.801(2), *c* = 9.611(2) Å α = 112.39(2), β = 102.71(2), γ = 103.49(2)°, *U* = 578.9 Å^3, space group *P*1, *Z* = 1, D_c = 1.24 g cm^{-3}, μ(Mo-Kα) = 3.41 cm^{-1}, *F*(000) = 230. Data were measured at room temperature on a CAD4 four-cycle diffractometer in the range 2 ⩽ θ ⩽ 26°. 2432 Reflections were collected of which 2118 were unique with $I \geqslant 3\sigma(I)$. Data were corrected for Lorentz and polarisation effects but not for absorption. The structure was solved by direct methods and refined using the SHELX suite of programs.[15] The lattice was seen to contain one molecule of recrystallisation solvent (CH_2Cl_2) per asymmetric unit. In the final least-squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions except in the case of N-1, where the hydrogen was located in an advanced Fourier and refined at a fixed distance (0.96 Å) from the parent atom. Examination of the overall packing arrangement revealed that molecules are linked in a 1-dimensional array along *x*, by intermolecular hydrogen bonds between N-1 and O-1, and O-1 and N-1 of molecules generated by the operators *x* − 1, *y*, *z* and *x* + 1, *y*, *z* respectively. Final residuals after 12 cycles of least squares were $R = R_w = 0.0493$, for unit weights. Unit weights were used because in this structure final shift/esd values were smaller that those for a weighted refinement. Max. final shift/esd was 0.005. The max. and min. residual densities were 0.20 and −0.15 e Å^{-3}, respectively. A copy of the full structural data and structure factors has been deposited at the Cambridge Crystallographic Database.

Cycloheptanone adduct 4h. Compound **4h** was isolated as a mixture of diastereoisomers (3:2); ν_{max}(Nujol)/cm^{-1} 3460, 1705, 1660 and 1034; δ_H($CDCl_3$), major isomer 1.16 (9 H, s, CMe_3), 1.54 (3 H, d, *J* 6.8, $CHCH_3$), 1.60–2.50 (10 H, m, CH_2), 4.20 (1 H, dd, *J* 11.3, 4.5, CH), 5.40 (1 H, quintet, *J* 6.8, C*H*Me), 5.97 (1 H, br d, *J* 6.8, NH), 7.38–7.52 (3 H, m, ArH) and 7.83 (1 H, d, *J* 7.7, ArH); minor isomer 1.16 (9 H, s, CMe_3), 1.56 (3 H, d, *J* 6.8, $CHCH_3$), 1.60–2.50 (10 H, m, CH_2), 3.80 (1 H, dd, *J* 12.0, 6.0, CH), 5.20 (1 H, quintet, *J* 6.8, C*H*Me), 5.82 (1 H, br d, *J* 6.8, NH), 7.38–7.52 (3 H, m, ArH) and 7.78 (1 H, d, *J* 7.7, ArH); δ_C($CDCl_3$), major isomer 21.34 (q), 23.77 (t), 25.46 (t), 27.15 (q), 27.57 (t), 29.58 (t), 38.18 (s), 44.14 (t), 45.08 (d), 74.92 (d), 125.0 (d), 126.1 (d), 127.7 (d), 131.5 (d), 141.5 (s), 142.9 (s), 177.2 (s) and 209.4 (s); minor isomer 20.95 (q), 23.61 (t), 24.94 (t), 27.15 (q), 27.63 (t), 28.83 (t), 38.18 (s), 43.43 (t), 44.24 (d), 72.56 (d), 125.9 (d), 126.3 (d), 127.9 (d), 131.5 (d), 139.0 (s), 140.3 (s), 177.2 (s) and 207.3 (s); *m/z* (FAB) 364 (MH^+, 100) [Found: *m/z* 364.1943. $C_{20}H_{29}NO_3S$ requires (MH^+), 364.1946].

Cyclodecanone adduct 4i. Product $S_{(S)}R$-(−)-**4i** was isolated as a mixture of diastereoisomers (3:2) (88%); ν_{max}(Nujol)/cm^{-1} 3460, 1705, 1660 and 1034; δ_H($CDCl_3$), major isomer 1.16 (9 H, s, CMe_3), 1.50 (3 H, d, *J* 6.7, $CHCH_3$), 1.10–1.90 (14 H, m, CH_2), 2.20–2.60 (2 H, m, CH_2), 4.45 (1 H, m, CH), 5.35 (1 H, quintet, *J* 6.7, C*H*Me), 5.80 (1 H, br d, *J* 6.7, NH), 7.40–7.55 (3 H, m, ArH) and 7.83 (1 H, m, ArH); minor isomer 1.17 (9 H, s, CMe_3), 1.57 (3 H, d, *J* 6.7, $CHCH_3$), 1.10–1.90 (14 H, m, CH_2), 2.20–2.60 (2 H, m, CH_2), 4.66 (1 H, m, CH), 5.47 (1 H, quintet, *J* 6.7, C*H*Me), 6.00 (1 H, br d, *J* 6.7, NH), 7.40–7.55 (3 H, m, ArH) and 7.83 (1 H, m, ArH); δ_C($CDCl_3$), major isomer 22.07 (q), 22.83–26.27 (11 t), 26.82 (q), 37.85 (s), 44.17 (d), 44.37 (t), 76.06 (d), 125.4 (d), 125.9 (d), 127.4 (d), 131.5 (d), 139.0 (s), 143.9 (s), 176.9 (s) and 209.0 (s); minor isomer 21.05 (q), 22.83–26.27 (11 t), 26.82 (q), 37.75 (s), 42.85 (t) 43.98 (d), 71.91 (d), 125.9 (d), 127.6 (d), 127.6 (d), 131.8 (d), 138.8 (s), 142.3 (s), 176.7 (s) and 207.0 (s); *m/z* (FAB) 406 (MH^+, 100) and 253 (15) [Found: *m/z* 406.2412. $C_{23}H_{35}NO_3S$ requires (MH^+), 406.2416].

Cyclopentadecanone adduct 4j. Product $S_{(S)}R$-(−)-**4j** was isolated as a mixture of diastereoisomers (3:2) (82%); ν_{max}(Nujol)/cm^{-1} 3463, 1710, 1668 and 1037; δ_H($CDCl_3$) 1.16 (9 H, s, CMe_3), 1.50 (3 H, d, *J* 7.1, CH*Me*), 1.60–1.80 (22 H, m, CH_2), 2.00–2.50 (4 H, m, CH_2), 4.06 (0.67 H, dd, *J* 12.2, 2.9, CH), 4.53 (0.33 H, m, CH), 5.30 (0.67 H, quintet, *J* 7.1, C*H*Me), 5.53 (0.33 H, quintet, *J* 7.1, C*H*Me), 5.83 (0.67 H, br d, *J* 7.1, NH), 5.91 (0.33 H, br d, *J* 7.1, NH), 7.31–7.52 (3 H, m, ArH) and 7.66–7.76 (1 H, m, ArH); δ_C, major 21.47 (q), 25.66 (t), 25.79 (t), 26.01 (t), 26.14 (t, 2 C), 26.24 (t), 26.37 (t), 26.76 (t), 26.82 (t), 26.99 (t), 27.12 (t), 27.28 (q, 3 C), 27.57 (t), 38.30 (s), 43.95 (t), 44.50 (d), 72.67 (d), 125.5 (d), 126.3 (d), 128.0 (d), 131.9 (d), 139.1 (s), 142.6 (s), 177.3 (s) and 207.5 (s); minor 21.76 (q), 25.66 (t), 25.79 (t), 26.01 (t), 26.14 (t, 2 C), 26.24 (t), 26.37 (t), 26.76 (t), 26.82 (t), 26.99 (t), 27.12 (t), 27.28 (q, 3 C), 27.57 (t), 38.21 (s), 43.62 (t), 44.63 (d), 75.48 (d), 126.1 (d), 126.5 (d), 127.8 (d), 132.0 (s), 139.7 (s), 144.3 (s), 177.2 (s) and 207.5 (s); *m/z* (FAB) 476 (M + H^+, 100) [Found: *m/z* 476.3171. $C_{28}H_{45}NO_3S$ requires (MH^+), 476.3198].

Butyrolactone adduct 4k. Product $S_{(S)}R$-(+)-*cis*-**4k** was isolated as a mixture of diastereoisomers in a 10:1 ratio (76%) and was recrystallised for characterisation purposes. Data for major isomer: mp 108–109 °C (ethyl acetate–light petroleum); $[\alpha]_D^{25}$ −165.6 (*c* 0.16, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3305, 1760, 1638, 1068 and 1015; δ_H($CDCl_3$) 1.19 (9 H, s, CMe_3), 1.56 (3 H, d, *J* 7.0, $CHCH_3$), 2.30 (1 H, m, CH), 3.00 (1 H, m, CH), 4.05 (1 H, dd, *J* 9.5, 7.5, CH), 4.35 (1 H, m, CH), 4.50 (1 H, td, *J* 9.0, 5.3, CH), 5.25 (1 H, quintet, *J* 7.0, C*H*Me), 5.96 (1 H, br d, *J* 7.0, NH), 7.42–7.59 (3 H, m, ArH) and 7.89 (1 H, d, *J* 7.5, ArH); δ_C($CDCl_3$) 19.00 (t), 21.41 (q), 27.05 (q), 38.14 (s), 44.92 (d), 61.50 (d), 67.17 (t), 124.4 (d), 126.5 (d), 127.9 (d), 131.9 (d), 139.0 (s), 142.0 (s), 171.7 (s) and 177.7 (s); *m/z* (FAB) 338 (MH^+, 100), 254 (19) and 237 (10) [Found: *m/z* 338.1457. $C_{17}H_{23}NO_4S$ requires (MH^+), 338.1426].

Reduction of keto sulfoxides with diisobutylaluminium hydride

To a stirred solution of the β-keto sulfoxide (0.093 g, 0.25 mmol) in tetrahydrofuran 1.2 cm^3) was added dropwise at −78 °C a solution of diisobutylaluminium hydride (0.50 cm^3, 0.50 mmol) in hexanes. The resulting reaction mixture was stirred at this

temperature for 1.0 h and then quenched with saturated aqueous ammonium chloride (2 cm^3). The resulting mixture was treated with a few drops of aqueous hydrochloric acid (2 mol dm^{-3}) after which the organic phase was removed and the aqueous phase extracted with dichloromethane (3 × 5 cm^3). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The title compound was isolated after column chromatography (50% ethyl acetate–light petroleum) for evaluation by ^1H NMR spectroscopy.

Reduction of keto sulfoxides with sodium boranuide

To a stirred suspension of sodium boranuide (0.01 g, 0.27 mmol) in tetrahydrofuran–water (3:0.5 cm^3) at −78 °C was added dropwise a solution of the ketone (0.099 g, 0.27 mmol) in tetrahydrofuran (3 cm^3). The resultant reaction mixture was stirred at −78 °C for 2 h and then treated with saturated aqueous ammonium chloride (6 cm^3). The organic phase was removed and the resultant aqueous phase extracted with ethyl acetate (3 × 10 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to yield the crude compound for evaluation by ^1H NMR spectroscopy.

Reduction of keto sulfoxide with tetrabutylammonium boranuide

To a suspension of tetrabutylammonium boranuide (0.068 g, 0.26 mmol) in tetrahydrofuran (3 cm^3) at 0 °C was added a solution of the ketone (0.102 g, 0.27 mmol) in tetrahydrofuran (3 cm^3). The reaction mixture was stirred at ambient temperature for 48 h after which it was treated with hydrogen peroxide solution (3%; 10 cm^3) and aqueous sodium hydroxide (2 mol dm^{-3}; 5 cm^3). After being stirred for 0.25 h, the mixture was extracted with dichloromethane (3 × 15 cm^3) and the combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to yield the crude compound for evaluation by ^1H NMR spectroscopy.

Reduction of keto esters with sodium boranuide–cerium(III) chloride

To a stirred suspension of cerium(III) chloride heptahydrate (0.201 g, 0.52 mmol) and the ketone (0.097 g, 0.26 mmol) in methanol (3 cm^3) at 0 °C was added in one portion sodium boranuide (0.066 g, 1.69 mmol). The resultant reaction mixture was stirred at ambient temperature for 2.5 h and then treated with saturated aqueous ammonium chloride (6 cm^3). The organic phase was removed and the resultant aqueous extracted with ethyl acetate (3 × 10 cm^3). The combined organic phases and extracts were dried (Na_2SO_4) and evaporated under reduced pressure to yield the crude compound for evaluation by ^1H NMR spectroscopy.

Reduction of keto sulfoxides with sodium triacetoxyboranuide

To a stirred suspension of sodium triacetoxyboranuide (0.229 g, 1.08 mmol) in tetrahydrofuran (3 cm^3) at 0 °C was added a solution of the ketone (0.106 g, 0.29 mmol) in tetrahydrofuran (3 cm^3). The reaction mixture was stirred at ambient temperature for 48 h after which it was diluted with water (10 cm^3) and extracted with ethyl acetate (3 × 10 cm^3). The combined organic phases dried (Na_2SO_4) and evaporated under reduced pressure to yield the crude compound for evaluation by ^1H NMR spectroscopy.

Reduction of keto sulfoxides with lithium aluminium hydride

To a stirred suspension of lithium aluminium hydride (0.012 g, 0.32 mmol) in tetrahydrofuran (3 cm^3) at −78 °C was added dropwise a solution of the ketone (0.099 g, 0.27 mmol) in tetrahydrofuran (3 cm^3). The resultant reaction mixture was stirred at −78 °C for 2.5 h and then treated with saturated aqueous ammonium chloride (6 cm^3). The organic phase was removed and the resultant aqueous extracted with ethyl acetate (3 × 10 cm^3). The combined organic phases and extracts were dried (Na_2SO_4) and evaporated under reduced pressure to yield the crude compound for evaluation by ^1H NMR spectroscopy.

Reduction of keto sulfoxides with diisobutylaluminium hydride–zinc bromide

To a stirred solution of the ketone (0.40 mmol) in tetrahydrofuran (1 cm^3) at ambient temperature was added a solution of zinc bromide (1.00 mol dm^{-3} in tetrahydrofuran; 1.00 cm^3, 1.00 mmol). The mixture was then stirred at ambient temperature for 1 h and then cooled to −78 °C at which temperature a solution of diisobutylaluminium hydride (1.00 mol dm^{-3} in tetrahydrofuran; 1.00 cm^3, 1.00 mmol) was added to it and stirring continued for 1 h. After the mixture had been quenched sequentially with methanol (1 cm^3) and saturated aqueous sodium tartrate (1 cm^3) it was allowed to warm to ambient temperature when aqueous hydrochloric acid (2 mol dm^3) was added to it sufficient to dissolve the white precipitate. The resultant aqueous phase was then extracted with ethyl acetate (3 × 10 cm^3) and the combined organics were washed with brine (15 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was column chromatography on silica (50–100% ethyl acetate–light petroleum) to give the title compounds.

Diisobutylaluminium hydride reduction product 6a. Product **6a** (73%), mp 94–96 °C (dichloromethane–hexane); $[\alpha]_D^{25}$ −151.5 (*c* 0.13, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3451, 3354, 1661, 1496 and 1029; δ_H($CDCl_3$, 270 MHz) 1.19 (9 H, s, CMe_3), 1.53 (3 H, d, *J* 7.0, CH*Me*), 2.98–3.05 (1 H, dd, *J* 13.5, 1.5, CH_{AB}), 3.26–3.36 (1 H, dd, *J* 13.5, 12.0, CH_{AB}), 5.28–5.33 (2 H, m, C*H*Me and C*H*OH), 5.93 (1 H, br d, *J* 7.0, NH), 7.26–7.57 (8 H, m, ArH) and 8.04–8.07 (1 H, m, ArH); δ_C 22.18 (q), 27.34 (q, 3C), 38.53 (s), 45.31 (d), 64.35 (t), 68.53 (d), 124.9 (d), 125.6 (d, 2C), 126.6 (d), 127.8 (d), 128.5 (d, 2C), 128.7 (d), 131.4 (d), 140.6 (s), 141.4 (s), 142.2 (s) and 177.9 (s); *m/z* (CI) 374 ($M + 1^+$, 100), 340 (40), 238 (50) and 204 (80) (Found: C, 66.0; H, 7.44; N, 3.55. $C_{21}H_{27}NO_3S·0.5H_2O$ requires C, 66.0; H, 7.32; N, 3.66%). β-Hydroxy sulfide (*R,R*)-**8a** (5%), δ_H($CDCl_3$, 270 MHz) 1.20 (9 H, s, CMe_3), 1.45 (3 H, d, *J* 7.0, CH*Me*), 2.20 (1 H, exchangeable, OH), 2.95–3.00 (1 H, dd, *J* 13.5, 10.5, CH_{AB}), 3.29–3.35 (1 H, dd, *J* 13.5, 3.0, CH_{AB}), 4.40–4.45 (1 H, dd, *J* 10.5, 3.0, C*H*OH), 5.85 (1 H, quintet, *J* 7.0, C*H*Me), 6.11 (1 H, d, *J* 7.0, NH), 7.21–7.55 (8 H, m, ArH) and 7.92–7.98 (1 H, m, ArH); *m/z* (FAB) 356 ($M - H^+$, 15), 340 (40) and 204 (50).

Diisobutylaluminium hydride reduction product 6b. Product **6b**, mp 90 °C (dichloromethane–hexane); $[\alpha]_D^{25}$ −177.4 (*c* 0.42, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3332, 1641, 1513 and 1026; δ_H($CDCl_3$, 400 MHz) 1.02 (9 H, s, CMe_3), 1.37 (3 H, d, *J* 6.8, CH*Me*), 2.81–2.85 (1 H, dd, *J* 13.7, 2.0, CH_{AB}), 3.03–3.09 (1 H, dd, *J* 13.7, 10.7, CH_{AB}), 3.60 (3 H, s, OMe), 4.50 (1 H, br s, OH), 5.09–5.18 (2 H, m, C*H*OH and C*H*Me), 6.00 (1 H, br d, *J* 6.8, NH), 6.67 (2 H, d, *J* 8.8, ArH), 7.12 (2 H, d, *J* 8.8, ArH), 7.26–7.34 (3 H, m, ArH) and 7.84–7.85 (1 H, m, ArH); δ_C 21.50 (q), 27.31 (q, 3 C), 38.49 (s), 45.42 (d), 55.18 (s), 64.53 (s), 68.09 (s), 113.9 (d, 2 C), 124.1 (d), 126.6 (d), 126.9 (d, 2 C), 127.1 (d), 131.4 (d), 134.5 (s), 140.8 (s), 141.5 (s), 159.1 (s) and 177.8 (s); *m/z* (FAB) 404 (MH^+, 35), 386 (75) and 253 (30).

Diisobutylaluminium hydride reduction product 6c. Product **6c**, mp 96–98 °C (dichloromethane–hexane); $[\alpha]_D^{25}$ −133.0 (*c*

0.115, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3334, 1638, 1522 and 1020; δ_H($CDCl_3$) 1.19 (9 H, s, CMe_3), 1.52 (3 H, d, *J* 7.0, CH*Me*), 2.05 (3 H, s, Me), 2.82–2.86 (1 H, dd, *J* 13.7, 1.5, CH_{AB}), 3.22–3.28 (1 H, dd, *J* 13.7, 10.1, CH_{AB}), 4.22 (1 H, d, *J* 3.4, OH), 5.25 (1 H, quintet, *J* 7.0, C*H*Me), 5.50 (1 H, br d, *J* 11.3, C*H*OH), 5.91 (1 H, br d, *J* 7.0, NH), 7.05 (1 H, d, *J* 7.3, ArH), 7.14 (H, td, *J* 7.4, 1.6, ArH), 7.23 (1 H, t, *J* 7.3, ArH), 7.44–7.59 (4 H, m, ArH) and 8.10 (1 H, m, ArH); δ_C 18.41 (q), 21.26 (q), 27.40 (q, 3 C), 38.60 (s), 45.01 (d), 61.75 (s), 65.41 (s), 125.0 (d), 125.5 (d), 126.5 (d), 126.7 (d), 127.6 (d), 128.6 (d), 130.4 (d), 131.5 (d), 133.6 (s), 140.0 (s), 140.2 (s), 141.4 (s) and 177.8 (s); *m/z* (FAB) 388 (MH^+, 100), 370 (30) and 253 (30) (Found: C, 66.0; H, 7.7; N, 3.3. $C_{22}H_{29}NO_3S$·0.75H_2O requires C, 65.9; H, 7.62; N, 3.50%).

Diisobutylaluminium hydride reduction product sulfide 8b. Product **8b** (55%), mp 134–136 °C (CH_2Cl_2–hexane); $[\alpha]_D^{25}$ −57.8 (*c* 0.735, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3346 and 1635; δ_H($CDCl_3$) 0.86 (9 H, s, CMe_3), 1.19 (9 H, s, CMe_3), 1.38 (3 H, d, *J* 6.8, CH*Me*), 2.63–2.72 (1 H, dd, *J* 13.4, 10.8, CH_{AB}), 2.96–3.01 (1 H, dd, *J* 10.8, 1.7, CH_{AB}), 3.23–3.28 (1 H, dd, *J* 13.4, 1.7, C*H*OH), 5.75 (1 H, quintet, *J* 6.8, C*H*Me), 6.05 (1 H, br d, *J* 6.8, NH), 7.15–7.30 (3 H, m, ArH) and 7.40–7.50 (1 H, m, ArH); δ_C 22.67 (q), 25.69 (q, 3 C), 27.34 (q, 3 C), 37.74 (s), 38.50 (s), 39.05 (t), 46.61 (d), 74.73 (d), 124.6 (d), 127.3 (d), 127.5 (d), 128.6 (d), 132.8 (s), 146.7 (s) and 177.4 (s); *m/z* (FAB) 338 (M + H^+, 40), 320 (5), 280 (18) and 204 (45) (Found C, 67.6; H, 9.38, N, 3.54. $C_{19}H_{31}NO_2S$ requires C, 67.7; H, 9.20; N, 4.15%).

***Reduction of the* β-hydroxy sulfoxide 6a to the β-hydroxy sulfide *R,R*-8a**

To a stirred yellow slurry of triphenylphosphine (0.247 g, 0.94 mmol) and iodine (0.244 g, 0.96 mmol) in acetonitrile (6 cm^3) was added in a single portion sulfoxide $S_{(S)}R,S$-(−)-**6a** (0.300 g, 0.80 mmol). Stirring was continued for 5 min after which solid sodium iodide (0.234 g, 1.56 mmol) was added to the suspension and the resultant black mixture stirred at ambient temperature for 2 h; it was then diluted with ethyl acetate (15 cm^3). The organic phase was separated, washed sequentially with saturated aqueous sodium thiosulphate (15 cm^3) and water (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified using flash column chromatography on silica (0–50% ethyl acetate–light petroleum as eluent) to give the product a white foam. Spectral details were identical with those observed in the DIBAL-H reduction.

Diisobutylaluminium hydride–zinc(II) bromide reduction product 7a. Product **7a** (80%), mp 54 °C (dichloromethane–hexane); $[\alpha]_D^{25}$ −94.5 (*c* 0.22, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3453, 3355, 1662 and 1029; δ_H($CDCl_3$) 1.19 (9 H, s, CMe_3), 1.49 (3 H, d, *J* 7.0, CHCH_3), 3.05–3.11 (1 H, dd, *J* 2.0, 13.2, CH), 3.36–3.45 (1 H, dd, *J* 13.2, 10.1, CH), 4.57 (1 H, br s, OH), 5.30 (1 H, quintet, *J* 7.0, C*H*Me), 5.46 (1 H, dd, *J* 10.5, 1.5, CH), 5.91 (1 H, br d, *J* 7.0, NH), 7.26–7.53 (8 H, m, ArH) and 8.00 (1 H, m, ArH); δ_C($CDCl_3$) 21.70 (q), 27.44 (q), 38.53 (s), 44.99 (d), 62.24 (t), 71.49 (d), 124.9 (d), 125.8 (2 C, d), 126.2 (d), 128.1 (d), 128.6 (2 C, s, d), 129.0 (d), 131.8 (d), 141.1 (s), 141.9 (s), 142.0 (s) and 177.6 (s); *m/z* (FAB) 374 (MH^+, 100) and 150 (65) (Found: C, 64.7; H, 7.21; N, 3.33. $C_{21}H_{27}NO_3S$·H_2O requires C, 64.5; H, 7.42; N, 3.53%).

Diisobutylaluminium hydride–zinc(II) bromide reduction product 7b. Product **7b** (quantitative), mp 50 °C (dichloromethane–hexane); $[\alpha]_D^{25}$ −81.7 (*c* 0.235, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3334, 1640, 1513 and 1026; δ_H($CDCl_3$) 1.18 (9 H, s, CMe_3), 1.46 (3 H, d, *J* 7.0, CHCH_3), 2.99–3.05 (1 H, dd, *J* 2.4, 13.0, CH), 3.32–3.41 (1 H, dd, *J* 13.0, 9.7, CH), 4.65 (1 H, br s, OH), 5.25–5.40 (2 H, m, C*H*Me, C*H*OH), 6.04 (1 H, br d, *J* 7.0, NH), 6.86 (2 H, d, *J* 8.6, ArH), 7.32 (2 H, d, *J* 8.6, ArH), 7.40–45 (1 H, m, ArH), 7.45–7.55 (2 H, m, ArH) and 8.00 (1 H, m, ArH); δ_C($CDCl_3$) 21.62 (q), 27.37 (q), 38.45 (s), 44.94 (d), 55.20 (q), 62.63 (t), 70.84 (d), 113.9 (2 C, d), 124.8 (d), 126.2 (d), 127.1 (2 C, d), 128.8 (d), 131.7 (s), 134.3 (d), 141.3 (s), 141.9 (s), 159.3 (s) and 177.5 (s); *m/z* (FAB) 404 (MH^+, 47), 386 (100) and 253 (60) (Found: C, 63.0; H, 7.2; N, 3.3. $C_{22}H_{29}NO_4S$·H_2O requires C, 62.7; H, 7.36; N, 3.29).

Diisobutylaluminium hydride–zinc(II) bromide reduction product 7c. Product **7c** (90%), mp 52 °C (CH_2Cl_2–hexane); $[\alpha]_D^{25}$ −72.1 (*c* 0.52, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3333, 1639 and 1021; δ_H($CDCl_3$) 1.19 (9 H, s, CMe_3), 1.47 (3 H, d, *J* 6.8, CHCH_3), 2.36 (3 H, s, Me), 3.00–3.40 (2 H, 2 × dd, *J* 1.8, 9.9, 13.4, CH_{AB}) 4.51 (1 H, br s, OH), 5.31 (1 H, quintet, *J* 6.8, C*H*Me), 5.31 (1 H, br d, *J* 9.9, CH), 5.89 (1 H, br d, *J* 6.8, NH), 7.15 (3 H, m, ArH), 7.42 (1 H, m, ArH), 7.55 (3 H, m, ArH) and 8.00 (1 H, m, ArH); δ_C($CDCl_3$) 18.83 (q), 21.49 (q), 27.32 (q), 38.40 (s), 44.55 (d), 61.69 (t), 67.53 (d), 124.6 (d), 125.6 (d), 126.0 (d), 126.4 (d), 127.6 (2C, s, d), 128.8 (d), 130.4 (d), 131.7 (d), 134.0 (s), 140.0 (s), 141.2 (s), 141.9 (s) and 177.5 (s); *m/z* (FAB) 388 (MH^+, 95), 370 (60) and 353 (5) (Found: C, 65.1; H, 7.5; N, 3.3. $C_{22}H_{29}NO_3S$·H_2O requires C, 65.2; H, 7.65; N, 3.45%).

Diisobutylaluminium hydride–zinc(II) bromide reduction product 7d. Product **7d** (90%), mp 65–66 °C (CH_2Cl_2–hexane); $[\alpha]_D^{25}$ −112° (*c* 0.25, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3320, 1645 and 1020; δ_H($CDCl_3$) 0.91 (9 H, s, CMe_3), 1.17 (9 H, s, CMe_3), 1.50 (3 H, d, *J* 6.8, CHCH_3), 2.91–3.06 (2 H, qd, *J* 23.2, 9.8, 1.5, CH_{ABX}), 3.95 (1 H, dd, *J* 9.8, 1.5, C*H*OH), 4.05 (1 H, br s, OH), 5.29 (1 H, quintet, *J* 6.8, C*H*Me), 5.95 (1 H, br d, *J* 6.8, NH), 7.40–7.55 (3 H, m, ArH) and 8.00 (1 H, d, *J* 7.70, ArH); δ_C($CDCl_3$) 21.64 (q), 25.41 (q), 27.35 (q), 35.27 (s), 38.43 (s), 44.83 (d), 56.99 (t), 76.25 (d), 124.9 (d), 126.0 (d), 128.8 (d), 131.6 (d), 141.2 (s), 142.1 (s), 177.4 (s); *m/z* (FAB) 354 (MH^+, 100) and 340 (18) (Found: C, 63.0; H, 8.9; N, 3.7. $C_{19}H_{31}NO_3S$·0.5H_2O requires C, 63.0; H, 8.84; N, 3.87%).

Methyl sulfone *R*-13. To a stirred solution of the alcohol **6a** (0.379 g, 1.02 mmol) and imidazole (0.297 g, 4.60 mmol) in DMF (5 cm^3) was added in a single portion *tert*-butyldimethylsilyl chloride (0.337 g, 2.30 mmol). The mixture was stirred at ambient temperature for 16 h and then poured into saturated aqueous ammonium chloride (25 cm^3). The mixture was extracted with ethyl acetate (3 × 15 cm^3) and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product (0.444 g, 89%) which was used directly in the next step; δ_H($CDCl_3$) −0.05 (3 H, s, SiMe), 0.01 (3 H, s, SiMe), 0.16 (9 H, s, $SiCMe_3$), 1.20 (9 H, s, CMe_3), 1.56 (3 H, d, *J* 7.0, CH*Me*), 2.87–2.95 (1 H, dd, *J* 12.8, 10.5, CH_{AB}), 3.02–3.08 (1 H, dd, *J* 12.8, 2.4, CH_{AB}), 5.26–5.36 (2 H, m, C*H*Me and CHOSi), 5.92 (1 H, br d, *J* 7.0, NH), 7.23–7.50 (8 H, m, ArH) and 7.90–7.94 (1 H, m, ArH). To a stirred solution of the crude sulfoxide (0.444 g, 0.91 mmol) and sodium periodate (0.332 g, 1.55 mol) in acetonitrile (1 cm^3) and water (1.5 cm^3) was added ruthenium(III) chloride heptahydrate (0.003 g). The resultant black solution was stirred at ambient temperature for 4 h and then added to water (15 cm^3). The aqueous phase was extracted with ethyl acetate (3 × 15 cm^3) and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give **12** (0.300 g, 58% from alcohol) as a white foam; δ_H($CDCl_3$) −0.19 (3 H, s, SiMe), 0.12 (3 H, s, SiMe), 0.82 (9 H, s, $SiCMe_3$), 1.17 (9 H, s, CMe_3), 1.49 (3 H, d, *J* 7.0, CHMe), 3.90–3.99 (1 H, dd, *J* 14.5, 9.0, CH_{AB}), 4.12–4.18 (1 H, dd, *J* 14.5, 2.9, CH_{AB}), 5.49–5.56 (2 H, m, C*H*Me and C*H*OSi), 6.09 (1 H, br d, *J* 7.0, NH), 7.21–7.55 (8 H, m, ArH) and 7.98–8.02 (1 H, m, ArH); *m/z* (FAB) 503 (MH^+, 10), 446 (55) and 372 (100). To an ice-cooled solution of **12** (0.097 g, 0.19 mmol) in tetrahydrofuran (2.3 cm^3) was added dropwise a solution of tetrabutylammonium fluoride (1.0 mol dm^{-3} in tetrahydrofuran; 0.95 cm^3, 0.95 mmol). The mixture was stirred at ambient temperature for 16 h and then diluted with ethyl

acetate (10 cm^3). The organic phase was separated, washed with water (10 cm^3) and saturated brine (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure. The residue afforded the methyl sulphone **R-13** (0.048 g, 89%) by flash column chromatography; $\delta_H(CDCl_3)$ 1.20 (9 H, s, CMe_3), 1.49 (3 H, d, *J* 6.8, CH*Me*), 3.48 (3 H, s, SO_2Me), 5.57 (1 H, quintet, *J* 6.8, C*H*Me), 6.30 (1 H, br d, *J* 6.8, NH), 7.36–7.50 (2 H, m, ArH), 7.61 (1 H, td, *J* 13.5, 1.5, ArH) and 8.02 (1 H, dd, *J* 7.5, 1.5, ArH); *m/z* (CI) 284 (MH^+, 100) and 204 (**21**).

General method for the removal of the sulfinyl unit coupled with determination of enantiomeric excess: Raney™ reduction and (*R*)-(+)-MTPA ester preparation[16]

To a stirred suspension of Raney™ nickel (ex Aldrich; 0.250 g) was added a solution of the β-hydroxy sulfoxide (0.025 g, 0.07 mmol) in tetrahydrofuran (0.6 cm^3). The stirring was continued until the starting material had been consumed (as determined by TLC) after which the suspension was filtered through a plug of silica and the residue washed with chloroform (5 cm^3). The combined filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure to give a crude mixture containing the alcohol and amide (*R*)-(+)-**10** (as determined by ^1H NMR spectroscopy). To a stirred chloroform (1 cm^3) solution of the crude reaction mixture was added sequentially 4-dimethylaminopyridine (trace), dicyclohexylcarbodiimide (0.027 g, 0.12 mmol) and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.025 g, 0.10 mmol) and the stirring continued for 16 h. The reaction mixture was filtered through a plug of Celite and the residue washed with further chloroform (5 cm^3). The combined filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure. Examination of the ^1H NMR (Table) spectra of the crude reaction mixture furnished the required enantiomeric excesses. The derivatives of 1-phenylethanol have been reported,[16] whilst the other products gave the following resolved peaks. 1-(4-Methoxyphenyl)ethanol: methyl at δ 1.55* and 1.61, methoxy at δ 3.45* and 3.55; 3,3-dimethylbutan-2-ol: methyl at δ 1.19* and 1.29, methoxy at δ 3.51* and 3.56. The peaks marked * in each sample correspond to the major isomer isolated in each case, the ratio is given in the main text. The authenticity of these peaks was confirmed by derivatisation of samples of racemic alcohol formed by sodium boranuide reduction of the corresponding ketones.

Thermal elimination to form enones 14a–e

A typical procedure is as follows. A sample of the ketone–sulfinamide adduct (1 mmol) was dissolved in toluene (10 cm^3) containing sodium hydrogen carbonate (5 mg) and heated to 60 °C. After 3 h at this temperature the solvent was removed and the product was isolated by flash chromatography. Cyclohexenone was identified by comparison with an authentic sample, whilst other compounds were identified by comparison of their physical data with those of literature values. Selected data: 1-phenylprop-2-enone **14a** (60%), δ_H 7.96–7.93 (2 H, m, CH ArH), 7.62–7.46 (3 H, m, CH ArH), 7.22–7.11 (1 H, dd, *J* 17.2, 10.6, COCH), 6.48–6.41 (1 H, dd, *J* 17.2, 1.8 C=CH_2) and 5.97–5.92 (1 H, dd, *J* 10.6, 1.8, C=CH_2).[11d] Cycloheptenone **14c** (80%), δ_H 6.63–6.54 (1 H, dt, *J* 12.1, 5.5, COCH=C*H*), 6.04–5.99 (1 H, d, *J* 12.1, COCH=), 2.64–2.59 (2 H, m, CH_2CO), 2.47–2.43 (2 H, m) and 1.88–1.80 (4 H, m).[11a] Cyclodecenone **14d** (98%), ratio of *cis*:*trans*:96:4, δ_H, *cis* isomer: 6.32–6.29 (1 H, d, *J* 11.7, COCH=), 5.78–5.71 (1 h, dt, *J* 12, 8.5, COCH=C*H*); *trans* isomer: 6.63–6.59 (1 H, dt, *J* 16.1, 7.8, COCH=C*H*), 6.25 (1 H, d, *J* 16.1, COCH).[11b] Cyclopentadecenone **14e** (72%), δ_H 6.88–6.76 (1 H, dt, *J* 15.7, 7.3, COCH=C*H*), 6.22–6.16 (1 H, d, *J* = 15.7, COCH), 2.52–2.48 (2 H, dd, *J* 6.4, 6.8, CH_2CO), 2.30–2.23 (2 H, qd, *J* 6.23, 60.5, 5.9, β′ to CH_2CH=CHCO) and 1.7–1.44 (20 H, m).[11c]

Cyclohexanone vinyl sulfide 16

Cyclohexanone adduct **4g** (770 mg 2.21 mmol) was dissolved in trifluoroacetic acid (24 cm^3) and the solution stirred at room temperature for 22 h. It was then diluted with ethyl acetate and poured onto a slurry of sodium hydrogen carbonate in water and stirred vigorously. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (3 × 10 cm^3). The combined organic layer and extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure and the crude product was purified by flash chromatography using 0–100% ethyl acetate–light petroleum gradient elution to yield **16** (678 mg, 93%) as a yellow oil. This was then crystallised from diethyl ether–light petroleum to give fine white crystals (358 mg); ν_{max}/cm^{-1} 3313 (NH), 1681 (C=O ketone), 1632 (C=O amide) and 1594 (vinyl); $\delta_H([^2H_6]$-DMSO) 7.78–7.76 (1 H, d, *J* 7.51, NH), 7.48–7.19 (4 H, m, ArH), 6.46–6.43 (1 H, t, *J* 4.4, =CH), 5.20–5.15 (1 H, p, *J* 7.14, CH), 2.50–1.92 (6 H, m, cyclohexyl H), 1.32–1.29 (3 H, d, *J* 6.96, Me) and 1.10 (9 H, s, Bu^t); $\delta_C([^2H_6]$-DMSO) 194.83 (C=O ketone), 176.38 (C=O amide), 148.48, 146.83 (*ipso* ArC), 146.83 (*ipso* vinyl), 134.39, 134.7, 129.05, 127.66, 125.9 (Ar and vinyl C), 46.44 (CH–Me), 40.5 (C Bu^t), 38.66 (CH_2 α to C=O), 27.40 (3Me Bu^t), 26.72 (Me side chain) and 22.4 and 22.18 (2 CH_2 cyclohexyl); *m/z* (low eV) 331 (M^+), 246, 230, 204 and 174 (Found: C, 68.8; H, 7.9; N, 4.0. $C_{19}H_{25}NO_2S$ requires C, 68.88; H, 7.55; N, 4.23%).

Allylic alcohol 18a

To an ice-cooled solution of the cyclopentadecanone adduct **4j** (0.090 g, 0.19 mmol) in tetrahydrofuran (4 cm^3) was added in a single portion sodium boranuide (0.023 g, 0.61 mmol). The resultant mixture was stirred at ambient temperature for 1 h after which it was treated with saturated aqueous ammonium chloride (10 cm^3) and extracted with ethyl acetate (3 × 10 cm^3). The combined extracts were dried and evaporated to give the crude alcohol. The alcohol and sodium hydrogen carbonate (0.010 g) were heated at 60 °C in toluene (4 cm^3) for 16 h after which the mixture was evaporated and the resultant crude solid adsorbed onto silica. Allylic alcohol **18a** (0.031 g, 77%) was isolated by flash column chromatography; δ_H 0.86–0.99 (2 H, m, CH_2), 0.99–1.73 (20 H, m, CH_2), 1.88–2.08 (3 H, m, CH_2), 4.06 (1 H, m, C*H*OH), 5.39–5.45 (1 H, dd, *J* 15.3, 7.65, CH) and 5.50–5.62 (1 H, m, CH); δ_C 24.08 (t), 25.72 (t), 26.76 (t), 26.80 (t), 26.85 (t), 26.98 (t, 2C), 27.09 (t), 27.46 (t), 28.15 (t), 31.28 (t), 36.88 (t), 73.54 (d) and 133.7 (d, 2C); *m/z* (FAB) 223 ($M - 1^+$, 75) and 207 (100) (Found: *m/z* 223.2055. $C_{15}H_{28}O$ requires *M* − 1, 223.2062). Conversion into the corresponding (*R*)-(+)-MTPA ester **18b** followed by examination of the ^1H NMR spectroscopic data revealed two distinct resonances for the methoxy group at 5.57 and 5.54 ppm in a *ca.* 1:1 ratio, showing that the sodium boranuide reduction had been unselective.

Diisobutylaluminium hydride–zinc(II) bromide approach to enantiomerically enriched allylic alcohol *S*-18a

To a stirred solution of the cyclopentadecanone adduct **4j** (0.441 g, 0.93 mmol) in tetrahydrofuran (10 cm^3) at ambient temperature was added a solution of zinc bromide (0.98 mol dm^{-3} in tetrahydrofuran; 1.10 cm^3, 0.98 mmol). The mixture was stirred at ambient temperature for 1 h and then cooled to −78 °C, when it was treated with a solution of diisobutylaluminium hydride (1.00 mol dm^{-3} in tetrahydrofuran; 2.40 cm^3, 2.40 mmol). The resultant mixture was stirred at −78 °C for 1 h after which it was quenched sequentially with methanol (1 cm^3) and saturated aqueous ammonium chloride (15 cm^3) and allowed to warm to ambient temperature. Aqueous hydrochloric acid (2 mol dm^{-3}) was added to the mixture sufficient to dissolve the white precipitate. The organic layer was separated and the aqueous phase was then extracted with ethyl acetate

(3 × 15 cm^3). The combined organic phase and extracts were washed with brine (30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to furnish the crude alcohol. The crude alcohol (0.256 g, 0.54 mmol) and sodium hydrogen carbonate (0.045 g, 0.54 mmol) in toluene (12 cm^3) were heated at 60 °C for 16 h after which the solvent was removed and the resultant crude solid adsorbed onto silica. Allylic alcohol *S*-**18a** (0.099 g, 82%) was isolated by flash column chromatography. For spectral characteristics see the racemic synthesis; $[\alpha]_D^{25}$ −20.9 (*c* 4.85, $CHCl_3$). Conversion into the (*R*)-(+)-MTPA ester[16] showed a diastereoisomeric excess of 88% with the signal at 5.54 ppm corresponding to the major diastereoisomer.

Diisobutyl aluminium hydride approach to enantiomerically enriched allylic alcohol *R*-18a

To a stirred solution of the cyclopentadecanone adduct **4j** (0.100 g, 0.21 mmol) in tetrahydrofuran (1.5 cm^3) was added dropwise at −78 °C a solution of diisobutyl aluminium hydride (1.00 mol dm^{-3} in hexanes; 0.53 cm^3, 0.53 mmol). The resulting reaction mixture was stirred at this temperature for 2 h and then quenched with saturated aqueous ammonium chloride (5 cm^3). The resulting mixture was treated with a few drops of aqueous hydrochloric acid (2 mol dm^{-3}) after which the organic phase was removed. The aqueous phase was extracted with dichloromethane (3 × 5 cm^3) and the combined organic phase and extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to furnish the crude alcohol. The crude alcohol (0.100 g, 0.21 mmol) and sodium hydrogen carbonate (0.010 g, 0.21 mmol) in toluene (5 cm^3) was heated at 60 °C for 16 h after which it was evaporated and the resultant crude solid adsorbed onto silica. Allylic alcohol *R*-**18a** (0.020 g, 44%) and enone **14e** (0.010 g, 20%) were isolated by flash column chromatography. For spectral characteristics see the racemic synthesis. $[\alpha]_D^{25}$ +2.80 (*c* 1.05, $CHCl_3$). Conversion into the (*R*)-(+)-MTPA ester[16] showed a diastereoisomeric excess of 12% with the signal at 5.57 ppm corresponding to the major diastereoisomer.

Allylic alcohol 20a and MTPA derivative[16] 20b

To an ice-cooled stirred solution of **14b** (1.00 cm^3, 10.34 mmol) and cerium(III) chloride heptahydrate (4.69 g, 12.6 mmol) in methanol (50 cm^3) was added portionwise sodium boranuide (0.435 g, 11.76 mmol). The mixture was stirred at ambient temperature for 15 min and then added to saturated aqueous ammonium chloride (50 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to yield a crude product which was assumed to be essentially racemic. Allylic alcohol (±)-**20a** was isolated as a colourless oil (0.912 g, 90%); $\delta_H(CDCl_3)$ 1.51–2.05 (6 H, m, CH_2), 4.17 (1 H, m, C*H*OH), 5.71–5.75 (1 H, m, CH) and 5.78–5.83 (1 H, m, CH). To a stirred solution of (±)-**20a** (0.038 g, 0.39 mmol) in chloroform (0.6 cm^3) was added sequentially 4-dimethylaminopyridine (trace), dicyclohexylcarbodiimide (0.129 g, 0.63 mmol) and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.110 g, 0.48 mmol).[16] The resultant mixture was stirred at ambient temperature for 4 h and then filtered and the residue washed with chloroform. The combined filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure to yield crude MTPA ester **20b**. The ^1H NMR spectrum of the racemate showed distinct resonances at 3.22 and 3.24 ppm corresponding to the methoxy signal, and at 5.69–5.75 and 5.77–5.84 ppm corresponding to one of the vinyl protons of each of the diastereoisomers.

Diisobutyl aluminium hydride approach to the (*R*)-MTPA derivative[16] of enantiomerically enriched allylic alcohol *R*-20a

To a stirred solution of the cyclohexanone adduct $S_{(S)}R$-(−)-**4g** (0.213 g, 0.61 mmol) in tetrahydrofuran (4.5 cm^3) was added dropwise at −78 °C a solution of diisobutylaluminium hydride (1.00 mol dm^{-3} in hexanes; 1.50 cm^3, 1.50 mmol). The resulting reaction mixture was stirred at −78 °C for 2 h and then quenched with saturated aqueous ammonium chloride (10 cm^3). The resulting mixture was treated with a few drops of aqueous hydrochloric acid (2 mol dm^{-3}) after which the organic layer was separated. The aqueous phase was extracted with dichloromethane (3 × 15 cm^3) and the combined organic phase and extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. Unchanged $S_{(S)}R$-(−)-**4g** was removed by flash column chromatography to yield **19a** (0.067 g, 31%). To a stirred solution of **19a** (0.067 g, 0.19 mmol) in chloroform (1 cm^3) was added sequentially 4-dimethylaminopyridine (trace), dicyclohexylcarbodiimide (0.078 g, 0.38 mmol) and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.079 g, 0.34 mmol).[16] The resultant mixture was stirred at ambient temperature for 4 h and then filtered and the residue washed with chloroform. The combined filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure to yield crude Mosher ester **19b** (0.081 g, 75%). Crude ester **19b** (0.057 g, 0.10 mmol) and sodium hydrogen carbonate (0.005 g, 0.10 mmol) in toluene (2 cm^3) were heated at reflux for 16 h after which the mixture was evaporated and the resultant crude solid adsorbed onto silica. The required allylic ester (0.036 g, quantitative) **20b** was isolated by flash column chromatography. Examination of the ^1H NMR spectrum of the ester revealed only the single signal corresponding to the vinyl proton at 5.77–5.84 ppm. Hence a diastereoisomeric ratio of >25:1 can be assigned.

Diisobutyl aluminium hydride–zinc(II) bromide approach to the (*R*)-MTPA derivative[16] of enantiomerically enriched allylic alcohol 20a

To a stirred solution of the cyclohexanone adduct $S_{(S)}R$-(−)-**4g** (0.213 g, 0.61 mmol) in tetrahydrofuran (4 cm^3) and zinc(II) bromide (0.89 mol dm^{-3} in tetrahydrofuran; 0.90 cm^3, 0.88 mmol), previously stirred at ambient temperature for 1 h, was added dropwise at −78 °C a solution of diisobutyl aluminium hydride (1.00 mol dm^{-3} in hexanes; 0.90 cm^3, 0.90 mmol). The resulting reaction mixture was stirred at −78 °C for 2 h and then quenched with saturated aqueous ammonium chloride (10 cm^3). The resulting mixture was treated with a few drops of aqueous hydrochloric acid (2 mol dm^{-3}) after which the organic phase was separated and the aqueous phase extracted with dichloromethane (3 × 15 cm^3). The combined organic phase and extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The unchanged $S_{(S)}R$-(−)-**4g** was removed by flash column chromatography to yield **19a** (0.103 g, 82%). To a stirred solution of **19a** (0.103 g, 0.29 mmol) in chloroform (3 cm^3) was added sequentially 4-dimethylaminopyridine (trace), dicyclohexylcarbodiimide (0.122 g, 0.59 mmol) and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (0.106 g, 0.45 mmol). The resultant mixture was stirred at ambient temperature for 16 h and then filtered and the residue washed with chloroform. The combined filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure to yield crude Mosher ester **19b** (0.083 g, 50%). The crude ester (0.083 g, 0.15 mmol) **19b** and sodium hydrogen carbonate (0.008 g, 0.15 mmol) in toluene (3 cm^3) were heated at reflux for 16 h and then evaporated. The resultant crude solid was adsorbed onto silica and the required allylic ester **20b** (0.025 g, 54%) isolated by flash column chromatography. Examination of the ^1H NMR spectrum of the ester revealed signals of equal intensity at 5.69–5.75 and 5.77–5.84 ppm. Hence the allylic ester was assigned as essentially racemic.

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