Recoverable Chiral Sulfoxides for Asymmetric Synthesis[1]: Preparation, Regeneration and Application to the Asymmetric Aldol Reaction

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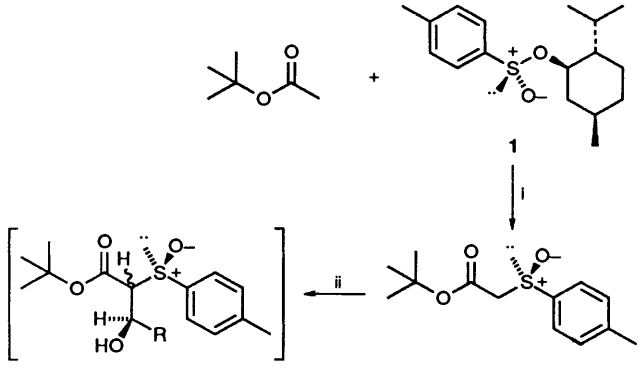
The synthesis of a novel source of chiral sulfoxide and its application to the control of asymmetric aldol reactions is described. The sulfoxide precursor $S_{(S)}R$-(+)-*cis*-**4** may be recycled and thus affords a considerable advantage over currently available methodology. Studies of the origin of the stereochemical outcome of the aldol reactions of the derived enolate $S_{(S)}R$-(−)-**10b** reveal that it is the result of thermodynamic, not kinetic, control.

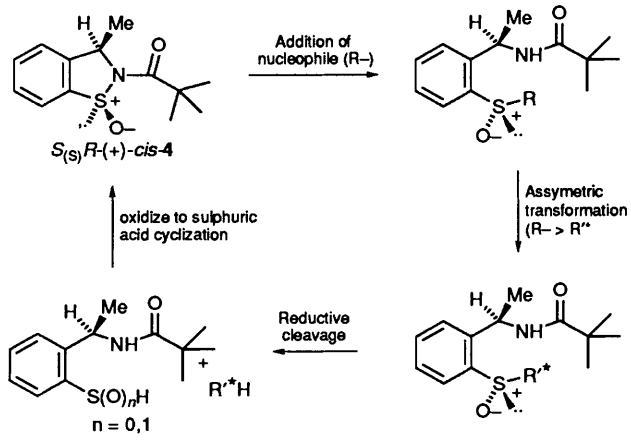
Homochiral sulfoxides have been used for the control of numerous asymmetric reactions[2] including aldol condensations,[3] Michael additions[4] and carbonyl reductions.[5] Although several new methods for the synthesis of sulfoxides have recently been described,[6a,b] the majority of current chiral sulfoxide methodology is centred around the use of (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-toluene-*p*-sulfinate **1** which is prepared in enantiomerically pure form by recrystallisation of an epimeric mixture from acidic acetone.[6c,d,e] Nucleophilic displacement of the menthyloxy group with the magnesium enolate of *tert*-butyl acetate takes place with inversion of configuration at sulfur to furnish sulfinyl acetate **2**.[3b,c,7] Aldol reactions between the anion derived from **2** and aldehydes proceed in good yield and high selectivity and removal of the sulfoxide moiety completes an efficient synthesis of α-unsubstituted β-hydroxy esters **3** (Scheme 1).[6]Other sulfoxide-mediated reactions involve similar reagent preparation and sulfoxide cleavage processes.



R	yield (%)	e.e. (%)
Ph	85	91
C_7H_{15}	80	86
C_6H_{11}	88	95

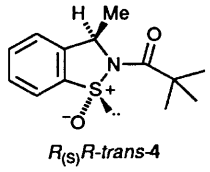
Scheme 1 *Reagents and conditions:* i, Pr^i_2NMgBr, Et_2O, THF, −40 °C; ii, Bu^tMgBr, RCHO, THF, −78 °C; iii, Na/Hg, THF/H_2O

Although excellent enantiomeric excesses are obtained in the reaction described above, the methodology is less than ideal because; (1) the preparation of **1** requires several crystallisation/epimerisation steps for purification to a quality suitable for asymmetric reactions[3b,c] (2) The reductive cleavage[8] at the end of the synthetic sequence necessitates destruction of the chiral sulfoxide group, which cannot therefore be recovered and reused; and (3) **1** is prone to (slow) epimerisation at sulfur during reactions as well as during storage.[9] In a programme directed at the development of improved sulfoxide auxiliaries which provide solutions to the problems outlined above we envisaged the use of a cyclic form of **1** in which the leaving group from nucleophilic attack would remain on the same molecule. Subsequent elaboration of the new side-chain under the influence of the sulfoxide could then be followed by reductive cleavage to the required product and a reduced form of our chiral sulfoxide source, which could be regenerated by reoxidation and cyclisation (Scheme 2). The cyclic system is



Scheme 2

important in the design since the sulfoxide configuration is controlled by diastereoselective cyclisation with respect to an existing chiral centre.[6a,b,10] In designing a reagent for this application it is essential that the side chain from the leaving group does not influence the reaction unfavourably and that the reagent can be readily cyclised to the sulfoxide precursor. In practice, we have found that the cyclic sulfinamide $S_{(S)}R$-(+)-*cis*-**4** is a suitable reagent for the sequence described above, and the full results of our preliminary studies[1] are given below.



$R_{(S)}R$-*trans*-**4**

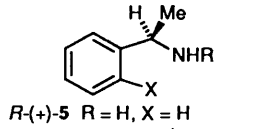
Table 1 Aldol reactions of $S_{(S)}R$-(−)-**10b**

Product **11**	R	Yield(%)*a*	d.e.(%)14*b*
a	Ph	75	> 92
b	*p*-$MeOC_6H_4$	70	> 92
c	*m*-$MeOC_6H_4$	80	> 92
d	*o*-$MeOC_6H_4$	90	33
e	*p*-$NO_2C_6H_4$	70	> 92
f	*o*-$NO_2C_6H_4$	80	> 92
g	Bu^t	90	> 92
h	Pr^i	75	75
i	Me	60	50

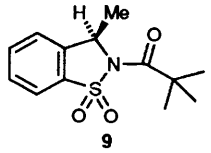
[a] Yield of recrystallised compounds in case of **4a,b,c,e,f,g**. [b] d.e. > 92% = single diastereoisomer in 270 MHz ^1H NMR spectrum of *crude* product.

Results and Discussion

Acylation of readily available inexpensive amine (*R*)-(+)-**5** with pivaloyl chloride and triethylamine to give crystalline (*R*)-(+)-**6** was followed by *ortho*-lithiation with 2.2 equiv. of *tert*-butyllithium and treatment with sulfur dioxide to yield the sulfinic acid (*R*)-(−)-**7**.* The next step in the synthetic sequence outlined above is stereoselective cyclisation of (*R*)-(−)-**7** to cyclic sulfinamide ($S_{(S)}R$-(+)-**4** with the generation of a



R-(+)-**5** R = H, X = H
R-(+)-**6** R = $COBu^t$, X = H
R-(−)-**7** R = $COBu^t$, X = SO_2H
8 R = $COBu^t$, X = SO_2Me



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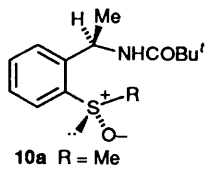
new chiral centre at the sulfur atom. This was achieved with the use of thionyl chloride and dimethylaminopyridine (DMAP) at 0 °C, under which conditions the *cis*-isomer '$S_{(S)}R$-(+)-**4**' was the exclusive product.[11] The use of alternative bases such as triethylamine or pyridine results in contamination of the product with 15–40% of the *trans*-isomer.[1a] $R_{(S)}R$-(+)-**4** may be purified by careful flash chromatography and is a crystalline solid. However, treatment with strong acid (aqueous HCl) or base (lithium methoxide) results in opening of the heterocyclic ring *via* nucleophilic attack on the sulfur atom to give acid *R*-(−)-**7** or methyl sulfinate ester **8**, respectively. Compound *trans*-**4** is rather less stable than *cis*-**4**, is consumed faster in the above reactions and is also more rapidly oxidised to the sultam **9** when subjected to a ruthenium-catalysed periodate oxidation. The latter process serves as a useful method for the purification of $S_{(S)}R$-(+)-**4** if it is contaminated by a small amount of the *trans*-isomer, since **9** is readily separable by flash chromatography.

When we initiated this work no sulfinamides bearing acylated nitrogen atoms had been employed for the synthesis of sulfoxides. Since then, however, the use of *N*-sulfinyloxazolidinones to resolve sulfinamides which are subsequently converted into chiral sulfoxides has been reported by Evans.[12] The superiority of the reagents reported in this report over sulfinate ester reagents in terms of practical applicability mirrors our findings.

The second stage in the application of $S_{(S)}R$-(+)-**4** in

* Although both enantiomers of **5** are readily available, that of *R* configuration is used throughout the work described in this paper.



10a R = Me
10b R = $CH_2CO_2Bu^t$

asymmetric synthesis requires stereoselective opening of the heterocyclic ring to generate a chiral sulfoxide. Sulfinate esters such as **1** react with Grignard reagents and certain alkyllithium reagents with inversion of configuration at sulfur.[3-5] However, in some cases, particularly the use of ketone enolates, epimerisation at sulfur is observed, which may be the result of pseudorotation of the trigonal bipyramidal intermediate prior to departure of the leaving group.[9a,b] In the case of $S_{(S)}R$-(+)-**4**

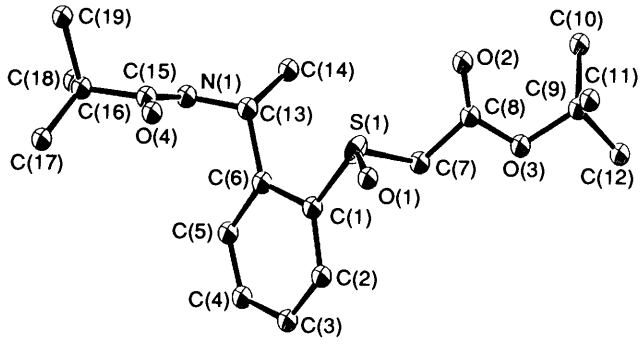


Fig. 1 X-Ray crystal structure of $S_{(S)}R$-(−)-**10b**

ring opening with methyllithium, methylmagnesium iodide and the magnesium enolate of *tert*-butyl acetate all gave good yields of sulfoxide products. In all cases, a single diastereoisomer was formed which was assumed to be that resulting from inversion of configuration at sulfur. That this was the case for the example $S_{(S)}R$-(−)-**10b** was confirmed by an X-ray crystallographic study (Fig. 1). When aged methyllithium or methylmagnesium iodide was used in this reaction the alternative diastereoisomer was formed to a small extent. In the latter case this may be due to heterocyclic ring-opening and epimerisation by iodide anion.

To demonstrate the synthetic utility of the new source of chiral sulfoxide, we chose to study aldol reactions of the ester $S_{(S)}R$-(−)-**10b** (Scheme 3). Previous studies of this reaction on related materials required the use of the magnesium enolate, since the lithium enolate undergoes retro-aldolisation.[3a] Aldol reactions of $S_{(S)}R$-(−)-**10b** were carried out using *tert*-butylmagnesium bromide as the base in tetrahydrofuran solution. The aldehyde was added at low temperature (−78 °C) and the reaction mixture was subsequently allowed to reach room temperature over 2–3 h. Analysis of the crude product (after flash chromatography) from all but one of the aromatic examples by ^1H NMR spectroscopy showed that a single diastereoisomer of the aldol product **11** had been formed (the assignment of the relative configurations is dealt with below). We could measure ratios of up to 25:1 using ^1H NMR spectroscopy, hence the arbitary assignment of > 92% diastereoisomeric excess (de) when only one diastereoisomer was observed. Purification by a single recrystallisation was sufficient to furnish analytically pure samples, yields of which

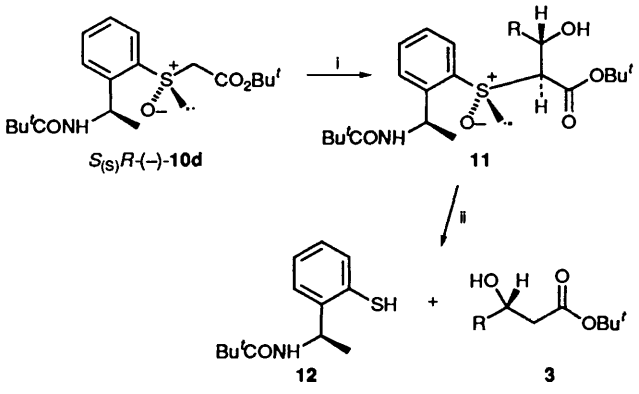
Table 2 Reductive cleavage reactions of the aldol adducts **11**

11	Yield of 3 (%)	E.e. % of 3	Yield of 12 (%)
a (recrystallised)	85	> 92 (*R*)	80
f (recrystallised)	65[a]	> 92 (*R*)	—
d (2:1 mixture)	68	33 (*R*)	—
h (7:1 mixture)	75	75 (*R*)	73

[a] Nitro group was reduced to an amine.

are given in Table 1. The use of aliphatic aldehydes gave products of rather lower diastereoisomeric purity, which decreased markedly with the size of the alkyl group. In the cases where the crude de was low it was possible to obtain single diastereoisomers by recrystallisation, but only at the cost of low yields. The selectivities in this reaction compare with those obtained using the sulfoxide **2** which lacks the side chain on the aromatic ring.[3b,c] It, therefore, appears that this group does not interfere unfavourably with the aldol reaction.

In order to determine the relative configurations in products **11** we attempted to obtain an X-ray crystal structure of one of the adducts; however, in all cases the crystals decomposed in the X-ray beam. A representative number of aldol adducts **11** were, therefore, treated with aluminium amalgam, resulting in reductive cleavage of the S–C_{alkyl} bond and formation of the β-hydroxy esters **3** together with the thiol *R*-(+)-**12** (Scheme 3,



Scheme 3 *Reagents and conditions:* i, 5 equiv. Bu^{t}MgBr, 3.0 equiv. RCHO, THF, − 78 °C, 6 h, then room temp. 6 h; ii, Al/Hg amalgam, THF/H_2O, room temp

Table 2). Although, initially, we believed that the corresponding disulfide had been formed in this process, it transpired that this is the result of aerial oxidation of the thiol, which results from exposure of the crude reaction mixture to air. The structure of the thiol *R*-(+)-**12** was confirmed by comparison with a sample prepared by reduction of the sulfinic acid *R*-(−)-**7** using triphenylphosphine and iodine.[13] In the case of the adduct **11a** (from benzaldehyde) the β-hydroxy ester **3a** had an optical rotation ($[\alpha]_D^{20}$) of +13 (*c* 0.15, ethanol) which indicates that the configuration at the hydroxy centre is *R* [reported[3c] for *S*-**3a**; $[\alpha]_D^{20}$ −16.6 (*c* 5.45, ethanol)]. Although our rotation was rather lower than that reported for the enantiomeric molecule, in view of the low values and unreliability of optical rotation as a definitive measure of enantiomeric purity we checked the purity of all of the β-hydroxy esters with the use of the ^{1}H NMR chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) derivative **13** (Aldrich). Addition of *ca.* 0.2 equiv. of **13** to a [2 H]chloroform solution of racemic **3a** (prepared from the reaction between lithium *tert*-butyl acetate and the aldehyde) resulted in splitting of the *tert*-butyl signals due to each enantiomer. The same experiment on a solution of enantiomerically pure *R*-(+)-**3a** isolated from **11a** resulted in observation of only one singlet. Since baseline resolution was possible the enantiomeric excess was assumed to be >92%. The same procedure demonstrated that the corresponding β-hydroxy ester from **11f** was also a single enantiomer. In the case of R = *o*-methoxyphenyl or isopropyl, the ee of the β-hydroxy ester was determined by integration of the *tert*-butyl signals, which matched the de's of the precursors **11d** and **11h**, respectively, therefore confirming that the epimeric position in these compounds was the β centre. It should be noted that the minor diastereoisomer could have been an epimer at both the α *and* β centres, however this would require a dramatic difference in the transition state requirements for the formation of each product and is, therefore, unlikely. In accord with related published studies we predict that the major diastereoisomer in each case is that illustrated in Scheme 3 above, probably formed *via* the stabilised chelated intermediate illustrated in Fig. 2.[3c]

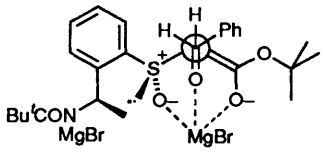
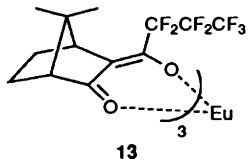


Fig. 2 Transition state for aldol reactions

In seeking an explanation for the selectivities observed, we examined whether they were the result of kinetic or thermodynamic selectivity. Deprotonation of $S_{(S)}R$-(−)-**10b** at low temperature was followed by addition of benzaldehyde at −78 °C and reaction at this temperature for 30 min and then quenching with saturated aqueous ammonium chloride. The product of this reaction consisted of a 1:1 mixture of two diastereoisomers of the aldol adduct **11a**. Reductive cleavage of the carbon–sulfur bond as described above resulted in formation of the racemic β-hydroxy ester **3a**, therefore confirming that the epimeric position in the aldol adduct was adjacent to the hydroxy group. In a second experiment, the adduct **11c** (a single diastereoisomer) was treated with an excess of *tert*-butylmagnesium bromide and benzaldehyde at room temperature for 1 h. At the end of this time the solution was quenched and worked up to give a stoicheiometric equilibrium mixture of **11a** and unchanged **11c**. Both of the above experiments confirm that the major product is formed by a thermodynamic equilibration process which only occurs significantly at elevated temperatures (0 °C or above). By way of contrast, quenching of the aldol reaction between the magnesium enolate of **2** and benzaldehyde after 2 h at −78 °C gave an aldol adduct of high diastereoisomeric excess.[14] It is, therefore, possible that the deprotonated amide side chain in the dianion derived from $S_{(S)}R$-(−)-**10b** is weakening the reactive aldol complex illustrated in Fig. 2. This will reduce the strength of the binding in the initial transition state (hence the lower kinetic selectivity), and promote reversal of the reaction and formation of the thermodynamic product. Although the pK_a of $S_{(S)}R$-(−)-**10b** has not been determined, Professor F. Bordwell (Northwestern University)[15] has estimated, by comparison with related reagents, a value of 20 for the proton adjacent to the sulfoxide and 25 for the proton on the amide. Both should, therefore, be deprotonated if an excess of *tert*-butylmagnesium bromide is used.

Recycling of the sulfinamide required a means for the oxidation of *R*-(+)-**12** to the sulfinic acid oxidation level, and preferably to *R*-(−)-**7** itself.[16–18] The use of *m*-chloroperbenzoic acid[16a] proved to be impractical owing to the difficulty of removing the carboxylic acid from the sulfinic acid products. In our investigations into a convenient alternative procedure, we found that treatment of *p*-thiocresol with sodium periodate in methanol–water (9:1) at room temperature together with a



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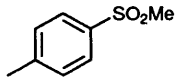

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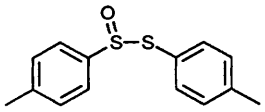

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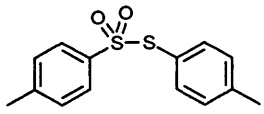

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catalytic quantity of iodine[17] resulted in the clean formation of methylsulfinate esters **14** in good yields. Presumably, the thiol is initially converted into a disulfide and then oxidised to a monoxide before iodide-catalysed methanolysis of the sulfur–sulfur bond occurs. The proposed intermediacy of the monoxide **15** is supported by the observation that *ca.* 5% of the dioxide **16**, from competitive oxidation of **15**, is also formed, and that this rises to 10–15% of the product when iodine is not added. In the *absence* of iodine the proportion of the disulfide dioxide has been reported to increase further with the bulk of the alcohol used.[17a,b] Treatment of thiol *R*-(+)-**12** with sodium periodate and a catalytic quantity of iodine in 10% aqueous methanol at *reflux* for 16 h gave a 1:1 mixture of epimeric methyl sulfinate ester **8** (68%) together with a 15:2 (*trans:cis*) diastereoisomeric mixture of the sulfinamide **4** (32%). Treatment of the crude reaction mixture with 2 mol dm^{-3} sodium hydroxide in THF furnished the sulfinic acid *R*-(−)-**7** in 82% overall yield from **12**. This sequence, therefore, represents a convenient method for recycling the chiral sulfoxide auxiliary in high yield. The thiol **12** could also be converted into *R*-(−)-**7** using *N*-bromosuccinimide and potassium carbonate[18] followed by aqueous sodium hydroxide in 80% overall yield.

In conclusion, we have demonstrated that $S_{(S)}R$-(+)-**4** represents a recoverable source of chiral sulfoxide, the utility of which has been demonstrated with reference to the control of asymmetric induction in the aldol reaction. Further work is currently in progress to define other applications of this new reagent, and these will be reported in further communications.

Experimental

General Details—All m.p.s were carried out on a Gallenkamp hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1310 grating Spectrometer. ^{1}H NMR spectra were recorded on either a JEOL GX270 FT machine at 270 MHz or a JEOL GX400 instrument operating at 400 MHz. The spectra were recorded 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. The spectra were recorded for solutions in deuteriochloroform unless otherwise stated. The chemical shifts were recorded relative to tetramethylsilane as an 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 and s = quaternary).

Mass spectra were recorded on a VG analytical 7070E instrument with VG2000 data system using electron ionisation (E.I., 70eV), chemical ionisation (C.I. isobutane) and fast atom bombardment (FAB) techniques. High resolution MS was carried out by the SERC regional service at the University College of Swansea. Microanalytic data were obtained on a Carlo Erba 1106 Elemental Analyser. Optical rotations were carried out using a Perkin–Elmer 141 polarimeter; $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}.

Flash chromatography[19] was performed on Merck silica gel 60 and the solvents ethyl acetate and light petroleum (b.p. 60–80 °C) were distilled before use. All reactions were monitored by TLC on aluminium sheets precoated with 250 μm silica gel which were visualised by UV light and then by aqueous potassium permanganate or aqueous phosphomolybdic acid.

Tetrahydrofuran and diethyl ether were dried over sodium benzophenone ketyl under nitrogen and distilled prior to 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 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. All reactions, unless otherwise stated, were carried out under a positive pressure of dry nitrogen in a vacuum-flame-dried apparatus.

(R)-(+)*N*-(α-*Methylbenzyl*)*pivalamide* **6**.—Pivaloyl chloride (43.0 cm^3, 350 mmol) was added dropwise to a cooled (0 °C), mechanically stirred, solution of (*R*)-(+)-*N*-α-methylbenzylamine **5** (37.8g, 40.0 cm^3, 315 mmol) and triethylamine (48.5 cm^3, 350 mmol) in dichloromethane (750 cm^3). The resulting white suspension was stirred at ambient temperature for 16 h before dilution with water (250 cm^3) which gave two layers. The aqueous portion was separated and extracted with dichloromethane (2 × 50 cm^3). The combined organic layer and extracts were washed with dilute hydrochloric acid (2 mol dm^{-3}; 200 cm^3), dried (Na_2So_4) and evaporated under reduced pressure to yield a white solid from which *R*-(+)-**6** was isolated by recrystallisation from dichloromethane hexane (51.5 g, 80%), m.p. 125 °C; $[\alpha]_D^{20}$ + 102.4 (*c* 0.63, chloroform); $\nu_{max.}$(Nujol)/cm^{-1}; 3337 at 1637; δ_H 1.19 (9 H, s, CMe_3), 1.46 (3 H, d, *J* 7.0, $CHCH_3$), 5.10 (1 H, quintet, *J* 7.0, CH), 5.92 (1 H, br d, *J* 7.0, NH) and 7.24–7.35 (4 H, m, ArH); δ_C 21.63 (q), 27.41 (q), 38.18 (s), 48.33 (d), 125.5 (d, 2C), 127.7 (d), 128.2 (d, 2C), 143.6 (s) and 177.3 (s); *m/z* 206 (M + 1$^+$), 105 (95) [Found: C, 76.5; H 9.1; N, 7.1. $C_{13}H_{19}NO$ requires C, 76.09; H, 9.27; N, 6.83 %].

R-(−)-o-(1-*Pivalolylaminoethyl*)*benzene sulfinic Acid* **7**.—To a mechanically stirred solution of the pivalamide **6** (2.50 g, 12.25 mmol) in diethyl ether at −78 °C was added rapidly a solution of *tert*-butyllithium (7.20 cm^3, 12.25 mmol). After the resultant white suspension had been stirred at −78 °C for 0.5 h a further portion of *tert*-butyllithium (8.65 cm^3, 14.70 mmol) was added over 0.5 h. The solution was stirred at −78 °C for 0.5 h and then allowed to warm to 0 °C at which temperature it was stirred for 0.5 h. The resulting thick red suspension was recooled to −78 °C when a stream of sulfur dioxide gas was passed over its surface until all the red colouration had faded, to be replaced by a white suspension. The suspension was allowed to reach ambient temperature when it was quenched by the addition of water (20 cm^3). Solid sodium hydroxide was added until the pH of the solution exceeded 12 and the resulting layers were separated. The organic layer was extracted with further aqueous sodium hydroxide (2 mol dm^{-3}; 50 cm^3). The basic aqueous extracts were combined and treated with concentrated hydrochloric acid until the pH was < 1, at which point a white suspension had formed. The suspension was extracted with

dichloromethane (5 × 50 cm^3) and, the combined extracts were dried (Na_2SO_4) and evaporated at low pressure to give the sulfinic acid *R*-(−)-**7** (3.12 g, 11.6 mmol, 95%), m. p. 66 °C; $[\alpha]_D^{20}$ −70 (*c* 0.43, chloroform); ν_{max} (Nujol)/cm^{-1} 3316, 2485, 1660, 1102 and 805; δ_H 1.16 (9 H, s, CMe_3), 1.55 (3 H, d, *J* 6.8, $CHCH_3$), 6.10 (1 H, quintet, *J* 6.8, CH), 6.53 (1 H, br d, *J* 6.8, NH), 7.49 (3 H, m, ArH) and 7.61 (1 H,d,*J* 6.4, ArH); δ_C 22.21 (q), 27.37 (q), 37.95 (s), 43.98 (d), 122.3 (d), 126.0 (d), 127.2 (d), 131.7 (d), 141.1 (s), 145.2 (s) and 176.9 (s); *m*/*z* 270 (10, M^+ 1^+ 100), 252 (7), 205 (21) and 150 (93) [*m*/*z*, 270.1160. $C_{13}H_{19}NO_3S$ requires ($M + 1^+$) 270.1164].

($S_{(S)}$R)-(+)-3-*Methyl*-2-*pivaloyl*-2,3-*dihydroisothiazole* 1-*Oxide* **4**.—Thionyl chloride (2.50 cm^3, 34.27 mmol) was added dropwise with stirring to a cooled (0 °C) solution of (*R*)-(−)-**7** (5.00 g, 18.59 mmol) and DMAP (2.43 g, 19.92 mmol) in THF (50 cm^3) under nitrogen. The mixture was stirred at room temperature for 16 h after which further DMAP (5.00 g, 40.98 mmol) was added portionwise; the mixture was then stirred at room temperature for a further 2 h. After this time, the reaction was quenched by the addition of saturated aqueous ammonium chloride (50 cm^3) and the organic phase was separated; the aqueous solution was then extracted with ethyl acetate (3 × 50 cm^3). The combined organic phases were washed with brine (50 cm^3), dried (Na_2SO_4) and evaporated to give a yellow oil which solidified with time. $S_{(S)}$*R*-(+)-*cis*-**4** was isolated by flash chromatography [light petroleum (b.p. 60–80 °C) /EtOAc 9:1] as a white solid which was recrystallised from dichloromethane–hexane (3.13 g, 12.5 mmol, 67 %), m.p. 115–117 °C; $[\alpha]_D^{20}$ +9.00 (*c* 0.8, ethanol); ν_{max}(Nujol)/cm^{-1} 1661, 1278, 1137 and 1096; δ_H 1.19 (9 H, s, CMe_3), 1.74 (3 H, d, *J* 6.8, $CHCH_3$), 5.64 (1 H, q, *J* 6.6, CH), 7.44–7.62 (3 H, m, ArH) and 7.77 (1 H, d, *J* 6.7 ArH); δ_C 23.94 (q), 28.48 (q), 41.03 (s), 63.96 (d), 123.6 (d), 124.8 (d), 128.8 (d), 132.4 (d), 143.0 (s, 2C) and 177.0 (s); *m*/*z* 149 (23), 91 (26) and 57 (100) (Found: C, 59.3; H, 6.5; N 5.3. $C_{13}H_{17}NO_2S$ requires C, 59.6; H, 6.5; N, 5.3%). The aqueous extract from the above reaction was acidified with concentrated HCl until the pH was < 1 when it was extracted with dichloromethane (3 × 50 cm^3); this afforded a quantity of unchanged *R*-(−)-**7** which was retained for use in subsequent reactions. Formation of a quantity of the $R_{(S)}$*R*-(*trans*)-**4** was observed when triethylamine or pyridine was used as a base in place of DMAP; $R_{(S)}$*R*-(*trans*)-**4**, δ_H 1.50 (9 H,s, $COCMe_3$) 1.56 (3 H,d, *J* 6.8, $CHCH_3$) and 5.80 (1 H, q, *J* 6.8, $CHCH_3$).

Reaction of $S_{(S)}$R-(+)-**4** *with Sodium Methoxide; Formation of the Sulfinate Ester* **8**.— Butyllithium (1.50 cm^3 2.40 mmol) was added dropwise to cooled (0 °C) methanol (1.00 cm^3 24.7 mmol) under a nitrogen atmosphere. After the mixture had been stirred for 1 h a solution of $S_{(S)}$*R*-(+)-**4** (249 mg, 1.00 mmol) in THF (1 cm^3) was added dropwise to it. Examination by TLC showed full consumption of starting material within 1 h. The reaction was then quenched with saturated aqueous ammonium chloride (5 cm^3) and the mixture extracted with ethyl acetate (3 × 5 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated to give the sulfinate ester **8** as a 2:1 mixture of diastereoisomers (180 mg, 64%); ν_{max}(Nujol)/cm^{-1} 3352 (NH), 1649 (C=O) and 1112 (SO_2Me); δ_H 1.18 (6 H,s, CMe_3, major isomer), 1.22 (3 H, s,. CMe_3, minor isomer), 1.48 (2 H, d, *J* 7.0, CH_3, major isomer), 1.51 (1 H, d, *J* 7.0, CH_3, minor isomer), 3.55 (2 H, s, OCH_3 major isomer), 3.57 (1 H, s, OCH_3 minor isomer), 5.38 (0.66 H, quintet, *J* 7.0, CH major isomer), 5.46 (0.33 H, d, *J* 7.0, CH minor isomer), 5.92 (0.33 H, br d, *J* 7.0, NH, minor isomer), 6.02 (0.66 H, br d, *J* 7.0, NH, major isomer), 7.26–7.57 (3 H, m, ArH, both isomers), 7.97 (1 H, d, *J* 1.65 , ArH, minor isomer) and 8.00 (1 H, d, *J* 1.65, ArH, major isomer); δ_C (major isomer) 21.48 (q), 27.15 (q), 38.15 (q), 44.28 (s), 49.95 (d), 124.1 (d), 125.8 (d), 127.1 (d), 132.4 (d), 140.4 (s), 143.3 (s), 177.4 (s); δ_C(minor isomer) 22.45 (q), 27.25 (q), 38.28 (q), 44.09 (s), 50.44 (d), 124.7 (d), 125.4 (d), 127.3 (d), 132.5 (d), 139.9 (s), 143.0 (s) and 177.2 (s); *m*/*z* (CI) 284 (100, $M + 1^+$), 252 (14), 204 (17) and 150 (60).

Oxidation of a Mixture of $S_{(S)}$R-(cis)-(+)-**4** *and* $R_{(S)}$R-(trans)-**4** *to* R-(+)-3-*Methyl*-2,3-*dihydroisothiazole* 1,1-*Dioxide* **9** *with Sodium Periodate and Ruthenium Trichloride*.— To a mixture of *cis*- and *trans*-**4** (5:1 mixture of diastereoisomers; 1.54 g, 6.1 mmol) in carbon tetrachloride (6 cm^3), acetonitrile (6 cm^3) and water (0.9 cm^3) was added, with rapid stirring, solid sodium periodate (2.6 g, 7.5 mmol), followed by ruthenium trichloride hydrate (1 mg). The mixture was stirred for 1 h to give a green solution, TLC analysis of which revealed that a new product had formed. At this stage the mixture was diluted with diethyl ether (44 cm^3) and stirring continued for 5 min. The two layers were separated and the aqueous layer extracted with diethyl ether (2 × 10 cm^3). The combined organic layer and extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a white solid. The products were isolated by flash chromatography as white crystalline solids. The dioxide **9** was eluted first (577 mg, 37%); m.p. 66 °C; $[\alpha]_{365}^{20}$ +20.5° (*c* ethanol); ν_{max}(Nujol)/cm^{-1} 1690 (C=O), 1500, 1330, 1250, 1150 and 750; δ_H 1.48 (9 H, s, CMe_3), 1.6 (3 H, d, *J* 6.5, $CHCH_3$), 5.68 (1 H, q, *J* 6.5, CH), 7.41 (1 H, d, *J* 7.9, ArH), 7.56 (1 H, t, *J* 7.9, ArH), 7.67 (1 H, dt, *J* 1.3, 7.9, ArH) and 7.77 (1 H, d, *J* 7.9, ArH). (Found: C, 59.7; H, 6.6, N 5.2. $C_{13}H_{17}NO_3S$ requires C, 58.4; H, 6.37; N, 5.24%). Removal of solvent from the second fraction from the column yielded diastereoisomerically pure $S_{(S)}$*R*-(*cis*)-(+)-**4**(399 mg, 26 %) which was identified by comparison with an authentic sample.

Reaction of $S_{(S)}$R-(+)-**4** *with Methyllithium; Synthesis of the Sulfoxide* **10a**.—Methyllithium (0.30 cm^3, 0.42 mmol) was added dropwise to a solution of $S_{(S)}$*R*-(+)-**4** (0.10 g, 0.40 mmol) in diethyl ether (7 cm^3) at −78 °C. The reaction mixture was stirred at this temperature for 1 h and then quenched by the addition of saturated aqueous ammonium chloride (7 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 10 cm^3). The combined organic layer and extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to yield an oil from which **10a** was isolated by flash chromatography (light petroleum ether–ethyl acetate, 1:1) and recrystallisation from light petroleum–ethyl acetate (96 mg, 89%), m.p. 118 °C; $[\alpha]_D^{25}$ −100 (*c* 0.75, chloroform); ν_{max}(Nujol)/cm^{-1} 3410, 1640 and 1060; δ_H 1.11 (9 H, s, CMe_3), 1.43 (3 H, d, *J* 7.0, $CHCH_3$), 2.70 (3 H, s, $SOCH_3$), 5.23 (1 H, quintet, *J* 7.0, CH), 6.20 (1 H, br d, *J* 7.0, NH), 7.38–7.43 (3 H, m, ArH) and 7.85 (1 H, m, ArH); δ_C 21.7 (q), 27.2 (q), 38.3 (s), 43.0 (q), 45.0 (d), 123.9 (d), 126.2 (d), 128.5 (d), 131.3 (d), 141 (s), 143 (s) and 177 (s); *m*/*z* 268 (M^+ 1, 100), 234 (10) and 204 (16) (Found: C, 62.4; H, 8.1; N 5.25. $C_{13}H_{19}NO_3S$ requires C, 62.4; H, 7.94; N, 5.24%).

tert-*Butyl* o-[1-(tert-*Butylcarbonylamino*)*ethyl*]*phenylsulfinylacetate* $S_{(S)}$R-**10b**—Bromoethane (3.56 cm, 47.7 mmol) was added dropwise to a stirred suspension of magnesium (1.15 g, 42.48 mmol) in diethyl ether (70 cm^3) and the mixture was stirred at ambient temperature until all the magnesium had been consumed. Diisopropylamine (5.53 cm^3, 39.46 mmol) was added dropwise to the reaction mixture which was then heated at reflux for 1 h to give a red suspension. This was cooled to −40 °C and diluted with tetrahydrofuran (5 cm^3). A solution of *tert*-butyl acetate (4.22 cm^3, 40.15 mmol) and $S_{(S)}$*R*-(+)-**4** (3.22g, 12.81 mmol) in tetrahydrofuran (5 cm^3) and diethyl ether (40 cm^3) was added dropwise over 1 h to the mixture which was then stirred for 4 h at −40 °C before saturated aqueous ammonium chloride (50 cm^3) was added and the

organic phase separated. The aqueous phase was extracted with ethyl acetate (3 × 50 cm^3) and the combined organic extracts were washed with brine (25 cm^3) and dried (Na_2SO_4). Removal of the solvent followed by flash chromatography (50/50 ethyl acetate–light petroleum) gave $S_{(S)}R$-**10b** as a white solid which was recrystallised from dichloromethane–hexane (3.85 g, 84%), m.p. 118–119 °C $[\alpha]_D^{20}$ −114.2 (*c* 0.33, chloroform); ν_{max}(Nujol)/cm^{-1} 3350 (CO), 3000, 1730 (CO_2), 1650 (CON) and 1040 (SO); δ_H 1.18 (9 H, s, CMe_3), 1.39 (9 H, s, CMe_3), 1.53 (3 H, d, *J* 7.0, CH_3), 3.74 (1 H, J_{AB} 13.6, CH_2), 3.90 (1 H, d, *J* 13.6, CH_2), 5.34 (1 H, quintet, *J* 7.0, C*H*Me), 6.25 (1 H, br d, *J* 7.0, NH), 7.50–7.47 (3 H, m, ArH) and 7.93 (1 H, d, *J* 5.9, ArH); δ_C 21.57 (q), 27.24 (q), 27.67 (q), 38.27 (s), 45.60 (d), 60.65 (t), 82.84 (s), 125.2 (d), 126.5 (d), 128.2 (d), 131.8 (d), 141.0 (s), 142.0 (s), 163.8 (s) and 177.0 (s); *m/z* (EI) 368 (9, M + 1^+) and 312 (100) (Found: C, 61.9; H, 8.0; N 3.8. $C_{19}H_{29}NO_4S$ requires C, 62.10; H, 7.96; N, 3.76%).

Reaction of the Enolate derived from **10b** *with Aldehydes; General Procedure.*—*tert*-Butyl bromide (1.54g, 7.92 mmol) was added dropwise to a cooled (0 °C) stirred suspension of magnesium (19 mg, 7.92 mmol) in diethyl ether (3 cm^3). The mixture was stirred until all the magnesium had been consumed at which point the resultant grey-brown solution was added dropwise to a stirred solution of the sulfinyl ester **10b** (139 mg, 0.38 mmol) in THF (20 cm^3) at −78 °C. The white suspension was stirred for 1.5 h at −78 °C before a solution of the aldehyde (1.14 mmol) in THF (5 cm^3) was added dropwise to the solution. The mixture was stirred at −78 °C for 4 h and then allowed to reach ambient temperature over a period of *ca.* 16 h (left in a solid CO_2 bath overnight). Saturated aqueous ammonium chloride (25 cm^3) was then added to the mixture and the organic phase removed. The aqueous phase was extracted with ethyl acetate (3 × 25 cm^3) and the combined organic layer and extracts were combined, washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue furnished the aldol products **11a–i**.

Adduct with benzaldehyde **11a**. The product was isolated as a white foam which was recrystallised from dichloromethane–hexane to yield **11a** as a colourless crystalline solid (77 %), m.p. 184 °C; $[\alpha]_D^{25}$ −158.7 (*c* 0.126, chloroform); ν_{max}(Nujol)/cm^{-1} 3320, 1720, 162 and 1040; δ_H 1.13 (9 H, s, $OCMe_3$), 1.14 (9 H, s, CMe_3), 1.51 (d, *J* 6.8, CH_3), 4.21 (1 H, d, *J* 5.1, SOCH), 5.18 (1 H, bd, PhC*H*), 5.24 (1 H, quintet, *J* 6.8, C*H*Me), 5.89 (1 H, br d, *J* 6.8, NH) and 7.24–8.00 (9 H, m, ArH); δ_C 21.18 (q), 27.37 (q), 27.57 (q), 38.37 (s), 44.70 (d), 72.10 (d), 72.36 (d), 83.10 (s), 126.0 (s), 126.2 (d, 2C), 126.4 (d), 128.0 (d), 128.3 (d), 128.4 (d, 2C), 131.8 (d), 139.5 (s), 139.7 (s), 142.3 (s) 165.5 (s) and 177.3 (s); *m/z* (FAB) 474 (32, M + 1^+), 418 (M-Bu^{t+} 74) and 312 (M-Bu^t-PhCHO$^+$, 10) (Found: C, 65.6; H, 7.45; N 2.9. $C_{26}H_{35}NO_5S$ requires C, 65.96; H, 7.40; N, 2.96%).

Adduct with 4-*methoxybenzaldehyde* **11b**. The product was initially isolated as a white foam which was recrystallised from ether to yield **11b** as a colourless crystalline solid (70%), m.p. 112–114 °C; $[\alpha]_D^{25}$ −125 (*c* 0.088, chloroform); ν_{max}(Nujol)/cm^{-1} 3400, 3200, 1730, 1660 and 1040; δ_H 1.06 (9 H, s, $OCMe_3$), 1.08 (9 H, s, CMe_3), 1.44 (d, *J* 6.8, CH_3), 3.80 (3 H, s, OCH_3), 4.07 (1 H, d, *J* 5.5, CHCO), 5.16 (1 H, br d, C*H*OH), 5.16 (1 H, quintet, *J* 6.8, C*H*Me), 5.76 (1 H , br d, *J* 6.8, NH), 6.81 (2 H, d *J* 8.6, ArH), 7.20–7.43 (4 H, m, ArH) and 7.89 (2 H, m, ArH); δ_C 21.15 (q), 27.41 (q), 27.63 (q), 38.40 (s), 44.73 (d), 55.24 (q), 72.00 (d), 72.14 (d), 83.00 (s), 113.9 (d), 125.9 (d), 126.5 (d), 127.7 (d, 2C), 128.3 (d), 131.7 (d), 139.0 (s), 140.0 (s), 142.0 (s) 159.0 (s), 165.4 (s) and 177.3 (s); *m/z* (FAB) 504 (89, M + 1^+), 448 (M-Bu^{t+}, 57), 312 [M-Bu^t-(MeO)$C_6H_4CHO^+$ 50] (Found: C, 64.0; H, 7.4; N 2.8; $C_{26}H_{35}NO_6S$ requires C, 64.39; H, 7.40; N, 2.78%).

Adduct with 3-*methoxybenzaldehyde* **11c**. The product was initially isolated as a yellow foam which was recrystallised from ether to yield **11c** as a colourless crystalline solid (80%), m.p. 66–68 °C: $[\alpha]_D^{25}$ −169 (*c* 0.14, chloroform); ν_{max}(Nujol)/cm^{-1} 3400, 3200, 1730, 1660 and 1040; δ_H 1.11 (9 H,s, $OCMe_3$), 1.15 (9 H,s, CMe_3), 1.49 (d, *J* 6.8, CH_3), 3.77 (3 H,s, OCH_3), 4.30 (1 H,d, *J* 7.50, SOCH), 5.12 (1 H, br d, *J* 6.8, C*H*OH), 5.25 (1 H, quintet, *J* 6.8, C*H*Me), 5.94 (1 H, br d, *J* 6.8, NH) and 6.78–7.90 (8 H, m, ArH); δ_C 21.34 (q), 27.34 (q), 27.60 (q), 38.40 (s), 44.76 (d), 55.20 (q), 72.14 (d), 72.23 (d), 83.10 (s), 111.2 (d), 114.2 (d), 118.4 (d), 125.9 (d), 126.6 (d), 128.1 (d), 129.4 (d), 131.8 (d), 139.0 (s), 141.3 (s), 142.6 (s), 159.6 (s), 165.6 (s) and 177.3 (s); *m/z* (FAB) 504 (36, M + 1^+), 448 (M-Bu^{t+} 88), 312 (M-Bu^t-$MeOC_6H_4CHO^+$ 50) and 253 (50) (Found: C, 64.5; H, 7.8; N 2.7. $C_{26}H_{35}NO_6S$ requires C, 64.41; H, 7.40; N, 2.78%).

Adduct with 2-*methoxybenzaldehyde* **11d**. The product was isolated and characterised as a yellow foam (90%) which consisted of a 2:1 mixture of diastereoisomers; ν_{max}(Nujol)/cm^{-1} 3400 (OH), 3200, 1730, 1660 and 1040; δ_H 1.11 (9 H, s, $OCMe_3$), 1.15 (9 H, s, CMe_3), 1.55 (3 H, d, *J* 6.8, CH_3), 3.85 (2 H, s, OCH_3 major isomer), 3.95 (1 H, s, OCH_3 minor isomer), 4.16 (0.66 H, d, *J* 9.0, SOCH major isomer), 4.35 (0.33 H, d, *J* 9.0, SOCH minor isomer), 5.10–5.25 (1 H, 2 × quintet, *J* 6.8, C*H*Me), 5.31 (0.66 H, d, *J* 10.5, C*H*OH, major isomer), 5.45 (0.33 H, d, *J* 10.5, C*H*OH minor isomer), 5.90 (1 H, br d, *J* 6.8, NH, both diastereoisomers), 6.85–7.00 (2 H, m, ArH), 7.20–7.35 (1 H, m, ArH), 7.40–7.58 (4 H,m, ArH) and 8.00–8.10 (1 H, m, ArH); δ_C(major diastereoisomer) 20.66 (q), 26.95 (q), 27.08 (q), 38.05 (s), 44.21 (d), 54.94 (q), 69.22 (d), 69.83 (d), 82.45 (s), 110.0 (d), 120.3 (d), 125.2 (d), 125.6 (d), 127.2 (d), 127.9 (d), 128.9 (d), 131.6 (d), 139.4 (s), 139 (s), 140.4 (s), 141.9 (s), 155.6 (s), 165.0 (s) and 177.4 (s); *m/z* (FAB) 504 (24 M + 1^+), 448 (M-Bu^{t+} 31), 312 (M-Bu^t-$MeOC_6H_4CHO^+$ 10) and 253 (30) (Found: *m/z* 504.2393; C, 63.3; H, 7.5; N 2.7%, $C_{26}H_{35}NO_6S$ 0.16 H_2O requires *m/z* 504.2419, C, 64.2; H, 7.46; N, 2.73%).

Adduct with 4-*nitrobenzaldehyde* **11e** The product was isolated as a brown foam (70%); $[\alpha]_D^{25}$ −91 (*c* 0.35, chloroform); ν_{max}(Nujol)/cm^{-1} 3580–3020, 1720, 1660, 1480, 1340 and 1040; δ_H 1.17 (9 H, s, CMe_3), 1.32 (9 H, s, CMe_3), 1.52 (d, *J* 6.78, CH_3), 4.45 (1 H, d, *J* 5.13, SOCH), 5.18 (1 H, br d, *J* 5.1, C*H*OH), 5.42 (1 H, quintet, *J* 6.8, C*H*Me), 5.88 (1 H, br d, *J* 6.8, NH), 7.26–7.94 (6 H,m, ArH) and 8.22 (2 H, d, *J* 9.0, ArH); δ_C 21.96 (q), 27.76 (q), 28.02 (q), 38.78 (s), 45.12 (d), 71.26 (d), 72.04 (d), 83.10 (s), 123.9 (d), 126.5 (d), 127.5 (d), 127.9 (d), 128.5 (d), 132.6 (d), 139.0 (s), 141.0 (s), 143.0 (s), 147.9 (s), 165.0 (s) and 177.0 (s); *m/z* (FAB) 519 (6. M + 1^+), 463 (M-Bu^{t+}, 75) and 253 (50) (Found: MH^+, 519.2145. $C_{26}H_{35}N_2O_7S$ requires 519.2165).

Adduct with 2-*nitrobenzaldehyde* **11f**. The product was isolated as a brown foam (80%); $[\alpha]_D^{25}$ −147 (*c* 1.15, chloroform); ν_{max}(Nujol)/cm^{-1} 3580–3020, 1720, 1660, 1480, 1340 and 1040; δ_H 1.10 (9 H, s, CMe_3), 1.15 (9 H, s, CMe_3), 1.52 (d, *J* 6.8, CH_3), 4.45 (1 H,d, *J* 4.5, SOCH), 5.29 (1 H, quintet, *J* 6.8, C*H*Me), 5.82 (1 H, d, *J* 4.5, C*H*OH), 5.96 (1 H, br d, *J* 6.8, NH) and 7.42–8.07 (8 H, m, ArH); δ_C 20.95 (q), 27.31 (q), 27.50 (q), 38.31 (s), 44.37 (d), 69.15 (d), 69.74 (d), 83.39 (s), 124.9 (d), 125.7 (d), 125.8 (d), 128.4 (d), 129.0 (d), 129.4 (d), 132.1 (d), 133.7 (d), 135.6 (d), 139.0 (s), 142.2 (s), 147.0 (s), 164.8 (s) and 177.4 (s); *m/z* (FAB) 519 (16, M + 1^+), 463 (M-Bu^{t+}, 100) (Found: MH^+, 519.2143, $C_{26}H_{35}N_2O_7S$ requires 519.2165).

Adduct with trimethylacetaldehyde **11g**. The product was isolated as a colourless oil (90%), $[\alpha]_D^{25}$ −125 (*c* 48, chloroform); ν_{max}(Nujol)/cm^{-1} 3410–3380, 1700, 1640 and 1060; δ_H 0.91 (9 H, s, CMe_3), 1.15 (9 H,s,CMe_3), 1.27 (9 H,s, CMe_3), 1.54 (d, *J* 6.8, CH_3), 3.69 (1 H, dd, *J* 6.0, 1.5, C*H*OH), 3.83 (1 H, d, *J* 1.5, OH), 4.36 (1 H, d, *J* 6.2, CHSO), 5.25 (1 H, quintet, *J* 6.8, C*H*Me), 5.90 (1 H, br d, *J* 6.8, NH), 7.42–7.56 (3 H, m, ArH) and 7.97 (1 H, dd, *J* 6.0, 3.0, ArH); δ_C 20.98 (q), 26.01 (q), 27.73 (q), 27.63 (q), 36.46 (q), 38.30 (s), 44.57 (d),

66.62 (d), 78.78 (d), 83.0 (s), 125.9 (d), 128.4 (d), 131.9 (d), 139.0 (s), 142.0 (s), 166 (s) and 177.0 (s); *m/z* (FAB) 454 (24, M + 1$^+$), 398 (M-Bu^t$^+$, 100) and 253 (50) (Found: M$^+$ 454.2630. $C_{24}H_{38}NO_5S$ requires 454.2627)

Adduct with 2-methylpropanal **11h**. The product was isolated as a white solid as a 7:1 mixture of two diastereoisomers (75%). Recrystallisation furnished the pure major diastereoisomer: $[\alpha]_D^{25}$ −111 (*c* 55, chloroform); ν_{max}(Nujol)/cm^{-1} 3410–3380, 1700, 1640 and 1060; δ_H 0.94 (3 H, d, *J* 6.6, CHC*H*$_3$), 1.01 (3 H, d, *J* 6.6, CHC*H*$_3$), 1.16 (9 H, s, CMe$_3$), 1.29 (9 H, s, CMe$_3$), 1.54 (d, *J* 6.6, NCHC*H*$_3$), 3.70 (2 H, m, OH and C*H*OH), 3.83 (1 H, d, *J* 4.4, CHSO), 5.25 (1 H, quintet, *J* 6.6, C*H*Me), 5.89 (1 H, br d, *J* 6.6, NH), 7.42–7.56 (3 H, m, ArH) and 7.96–8.02 (1 H, m, ArH); δ_C 17.74 (q), 19.10 (q), 21.11 (q), 27.37 (q), 27.76 (q), 32.56 (d), 38.00 (s), 44.57 (d), 69.57 (d), 75.48 (d), 83.16 (s), 125.9 (d), 128.4 (d), 131.8 (d), 139.8 (s), 142.0 (s), 166.0 (s) and 177.3 (s); *m/z* (FAB) 440 (31, M + 1$^+$), 384 (M-Bu^t$^+$ 100) and 312 (M-Bu^t-2-methylpropanal, 8) (Found: C, 62.5; H, 8.7; N, 3.1. $C_{23}H_{37}NO_5S$ requires C, 62.80; H, 8.48; N, 31.19%).

Adduct with acetaldehyde **11i**. The product (a 3:1 mixture of diastereoisomers) was isolated as a white solid (60%); ν_{max}(Nujol)/cm^{-1} 3410–3380, 1700, 1640 and 1090; δ_H 0.94 [2.25 H, d, *J* 6.6, CH(OH)C*H*$_3$], 1.01; [0.75 H, d, *J* 6.6, CH(OH)CH$_3$], 1.16 (9 H, s, CMe$_3$), 1.29 (9 H, s, CMe$_3$), 1.50 (2.25 H, d, *J* 6.6 CHC*H*$_3$), 1.51 (0.75 H, d, *J* 6.6, CHC*H*$_3$), 3.68–3.84 (2 H, m, C*H*OH and OH, both isomers), 4.50 (0.75 H, m, CHSO), 4.70 (0.25 H, m, CHSO), 5.25 (0.75 H, quintet, *J* 6.6 CH), 5.47 (0.25 H, quintet, *J* 6.6, CH), 5.89–5.95 (1 H, 2 × br d, *J* 6.6, NH), 7.42–7.56 (3 H, m, ArH) and 7.96–8.02 (1 H, m, ArH); δ_C 20.92 (q), 20.98 (q), 27.34 (q), 27.80 (q), 32.60 (d), 38.50 (s), 44.86 (d), 68.15 (d), 75.41 (d), 83.00 (s), 125.8 (d), 126.3 (d), 128.3 (d), 131.7 (d), 139.8 (s), 141.3 (s), 165.2 (s) and 177.5 (s); *m/z* (FAB) 412 (44, M + 1$^+$), 356 (M-Bu^t$^+$ 100) (Found: M + 1$^+$, 412.2189, $C_{21}H_{32}NO_5S$ requires 412.2158).

General Procedure for the Synthesis of Authentic Racemic Samples of β-Hydroxy Esters **3**—To a stirred solution of diisopropylamine (19.7 mmol) in tetrahydrofuran (10 cm^3) at 0 °C was added a solution of butyllithium (19.7 mmol) in hexane. After being stirred for 0.2 h the solution was cooled to −78 °C and a solution of *tert*-butyl acetate (19.68 mmol) in tetrahydrofuran (2 cm^3) was added dropwise to it. Stirring was continued for 0.5 h after which a solution of the aldehyde (19.7 mmol) in tetrahydrofuran (10 cm^3) was added dropwise to the reaction mixture. After 0.2 h, the reaction was quenched with aqueous hydrochloric acid (10 cm^3). The organic layer was removed and the aqueous phase was extracted with dichloromethane (3 × 50 cm^3). The combined organic layer and extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The product hydroxy esters were isolated by flash chromatography (10% ethyl acetate–light petroleum).

tert-*Butyl* 3-*hydroxy*-3-*phenylpropanoate* **3a**. The product was isolated as a colourless oil (73%); ν_{max}(neat)/cm^{-1} 3410 and 1700; δ_H(CDCl$_3$, 270 MHz) 1.20 (9 H, s,C-Me$_3$), 2.55 (2 H, CH$_2$), 3.49 (1 H, d, OH), 4.96 (1 H, quintet, *J* 8.3, C*H*OH) and 7.10 (5 H, m, ArH); δ_C (CDCl$_3$) 27.89 (q), 44.21 (t), 70.22 (d), 81.20 (s), 125.6 (d), 127.5 (d), 128.2 (d), 142.7 (s) and 171.6 (s); *m/z* (CI) 223 (M$^+$ + 1, 20), 167 (M$^+$ − Bu^t, 60) and 149 (M$^+$ − Bu^t-H$_2$O, 100) (Found: C, 70.0; H, 8.2 $C_{13}H_{18}O_3$ requires C, 70.2; H, 8.16%).

tert-*Butyl* 3-*hydroxy*-3-(2-*methoxyphenyl*)*propanoate* **3d**. The product was isolated as a white solid (60%); ν_{max}/cm^{-1} 3450, 2850 and 1659; δ_H(CDCl$_3$, 270 MHz) 1.38 (9 H, s, CMe$_3$) 2.75–2.49 (2 H, ABX, *J* 16, 9, 4.5, CH$_2$), 3.51 (1 H, d, *J*, 5.1, OH), 3.80 (3 H,s, OMe), 5.25 (1 H, quintet, *J* 4.5, C*H*OH), 6.80 (1 H, d, *J* 8.3, ArH), 6.90 (1 H, dt, *J* 7.5, 1.0, ArH), 7.20 (1 H, dt, *J* 7.5, 2.0, ArH) and 7.35 (1 H, dd, *J* 7.51, 2.0, ArH); δ_C (CDCl$_3$) 28.02 (q), 42.59 (t), 55.17 (q), 66.46 (d), 81.05 (s), 110.1 (d), 120.6 (d), 126.6 (d), 128.4 (d), 130.6 (s), 155.9 (s) and 172.0 (s); *m/z* (EI) 252 (M$^+$ + 1, 2), 196 (M$^+$ − Bu^t, 15), 137 (M$^+$ − methoxy-benzaldehyde + 1, 100) (Found: C, 66.4; H, 8.0. $C_{14}H_{20}O_3$ requires C, 66.6; H, 7.99%).

tert-*Butyl* 3-*hydroxy*-4-*methylpentanoate* **3h**. The product was isolated as a colourless oil (75%); ν_{max}/cm^{-1} 3500 and 1730; δ_H (CDCl$_3$, 270 MHz) 0.92 (3 H, d, *J* 6.8, CH*Me*), 0.94 (3 H, d, *J* 6.8, CH*Me*), 1.47 (9 H, s, CMe$_3$), 1.70 (1 H, br hextet, *J* 7.5, C*H*Me$_2$), 2.64–2.45 (2 H, *AB*X, *J* 15.9, 9.1, 3.4, CH$_2$), 3.33 (1 H, d, *J* 4.0, OH) and 3.73 (1 H, br sextet, *J* 6.00, C*H*OH); δ_C (CDCl$_3$) 17.41 (q) 18.10 (q), 27.80 (q), 39.34 (t), 72.43 (d), 80.60 (s) and 172.5 (s); *m/z* (CI) 189 (M$^+$ + 1, 2), 133 (M$^+$ − Bu^t, 70) and 115 (M$^+$ − Bu^t-H$_2$O, 100) (Found: C, 63.5; H, 10.9. $C_{10}H_{20}O_3$ requires C, 63.8; H, 10.7%).

tert-*Butyl* 3-*hydroxy*-3-(2-*nitrophenyl*)*propanoate* **3f**. The product was isolated as a yellow solid (49%); ν_{max}/cm^{-1} 3475, 1695 and 1340; δ_H(CDCl$_3$, 270 MHz) 1.46 (9 H, s, CMe$_3$), 2.92–2.53 (2 H, *AB*X, *J* 16.7, 9.2, 2.7, CH$_2$), 3.91 (1 H, br s, OH), 5.61 (1 H, dd, *J* 9.2, 2.7, C*H*OH), 7.43 (1 H, dt, *J* 7.5, 1.5, ArH), 7.67 (1 H, dt, *J* 7.5, 1.5, ArH), 7.89 (1 H, dd, *J* 7.5, 1.5, ArH), 7.93 (1 H, dd, *J* 7.5, 1.5, ArH); δ_C(CDCl$_3$) 27.99 (q), 43.14 (t), 66.55 (d), 81.83 (s), 124.4 (d), 128.2 (d), 128.3 (d), 133.6 (d), 138.1 (s), 147.3 (s) and 171.7 (s); *m/z* 212 (80), 197 (70), 164 (60) and 146 (100) (Found: C, 58.5; H, 6.5, N, 5.3 $C_{13}H_{17}NO_5$ requires C, 58.4; H, 6.49; N, 5.24%).

tert-*Butyl* 3-*hydroxy*-3-(2-*aminophenyl*)*propanoate*. To a stirred solution of *tert*-butyl 3-hydroxy-3-(2-nitrophenyl)-propanoate (0.10 g, 0.38 mmol) in 10% aqueous tetrahydrofuran (22 cm^3) was added portionwise aluminium amalgam (generated by dipping commercial baking foil in 2% aqueous mercuric chloride and washing it in ethanol and diethyl ether) (1.35 g, 56 mmol). The resulting suspension was stirred at ambient temperature for 16 h and then diluted with dichloromethane (50 cm^3) and filtered through glass wool. The resulting residue was washed with dichloromethane (50 cm^3) and the combined filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure. The product was isolated by column chromatography as a yellow solid (0.068g, 77%); ν_{max}/cm^{-1} 3475, 400 and 1700; δ_H(CDCl$_3$, 270 MHz) 1.48 (9 H, s, C-Me$_3$), 2.60–3.12 (2 H, *AB*X, *J* 16.7, 9.2, 2.7, CH$_2$), 3.86 (3 H, br s, OH/NH$_2$), 5.12 (1 H, dd, *J* 9.2, 2.7, C*H*OH), 6.65 (1 H, dt, *J* 7.5, 1.5, ArH), 6.80 (1 H, dt, *J* 7.5, 1.5, ArH), 7.02 (1 H, dd, *J* 7.5, 1.5, ArH) and 7.10 (1 H, dd, *J* 7.50, 1.50, ArH); δ_C(CDCl$_3$) 28.09 (q), 28.09 (q), 40.10 (t), 70.35 (d), 81.57 (s), 116.8 (d), 118.2 (d), 125.6 (s), 127.2 (d), 128.8 (d), 145.3 (s) and 172.7 (s); m/z 237 (M$^+$ 10), 181 (15), 146 (15) and 122 (35) [Found (EI): M$^+$, 237.1370, $C_{21}H_{32}NO_5S$ requires 237.1365].

(*R*)-(+)-o-(1-*Pivaloylaminoethyl*)*thiophenol* **12**.—To a stirred solution of sulfinic acid **7** (6.43 g, 23.9mmol) in toluene (75 cm^3) and chloroform (75 cm^3) was added, at ambient temperature, triphenylphosphine (37.6 g, 143 mmol) and iodine (6.17 g, 24.3 mmol). The mixture was vigorously stirred for 4.0 h and then poured into ethyl acetate (200 cm^3) and the mixture washed with water (2 × 200 cm^3). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure and the product *R*-(+)-**12** was isolated after column chromatography (10–30% ethyl acetate–light petroleum) as a white solid (5.10 g, 90%), m.p 144 °C (ethyl acetate–hexane); $[\alpha]_D^{25}$ +24.4 (*c* 0.5, chloroform); ν_{max}/cm^{-1} 3326 and 1638; δ_H(DMSO, 270 MHz) 1.11 (9 H, s, CMe$_3$) 1.31 (3 H, d, *J* 6.7, Me) 5.05 (1 H, q, *J* 6.7, CH), 5.14 (1 H, s, SH), 7.15–7.02 (2 H, m, aromatic H), 7.32 (2 H, dd, *J* 6.1, 3.3, ArH), 7.76 (1 H, br d, *J* 6.7, NH); δ_C(DMSO) 21.27 (q) 27.37 (q), 40.22 (s), 46.21 (d), 125.5 (d), 127.0 (d), 130.3 (d), 133.6 (d), 142.9 (s), 144.3 (s) and 176.5 (s); *m/z* (CI) 238(M$^+$ + 1) and 204 (-H$_2$S) (Found: C, 64.6; H, 8.1; N, 5.8 $C_{13}H_{19}NOS$·0.25 H_2O requires C, 64.6; H, 8.1; N, 5.8%).

Reductive Cleavage of Aldol Alducts **11**; *General Procedure.*—To a stirred solution of the aldol adduct (0.2 mmol) in 10% aqueous tetrahydrofuran (16.5 cm^3) was added portionwise aluminium amalgam (generated by dipping commerical baking foil in 2% aqueous mercuric chloride and washing it in ethanol and diethyl ether) (32.2 mmol). The resulting suspension was stirred at ambient temperature for 16 h and then diluted with dichloromethane (50 cm^3) and filtered through glass wool. The resulting residue was washed with dichloromethane (50 cm^3) and the combined organic filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure. The title compounds were recovered by column chromatography; the yields are given in Table 3. In all cases the β-hydroxy esters **3** and the thiol **12** were identified by comparison of their ^1H NMR spectra with those of authentic materials described above.

Reduction of adduct **11a**. (*R*)-(+) Compound **3a** was isolated as a colourless oil (85%); $[\alpha]_D^{25}$ +32 (*c* 0.20, $CHCl_3$); $[\alpha]_D^{25}$ +13 (*c* 0.15, EtOH). Compound **12** was isolated as a white solid (80%).

Reduction of adduct **11f**. Compound **3f** was isolated as a yellow solid (65%); $[\alpha]_D^{25}$ +9.7 (*c* 0.53, $CHCl_3$).

Reduction of adduct **11d**. Compound **3d** was isolated as a white solid (68%).

Reduction of adduct **11h**. Compound **3h** was isolated as a colourless oil (75%). Compound **12** was isolated as a white solid (73%).

Proof of Enantiomeric Purity of β-Hydroxy Esters with Shift Reagent **13**.—Compound **3a**. Addition of 0.15 equiv. of shift reagent to racemic material shifted the OBu^t resonances to δ 1.77 and 1.71. Addition of the same quantity of **13** to the enantiomerically enriched material gave only a single peak at δ 1.70 (270 MHz NMR).

Compound **3f**. Addition of 0.15 equiv. of shift reagent to racemic material shifted the OBu^t resonances to δ 1.66 and 1.63. Addition of the same quantity of **13** to the enantiomerically enriched material gave only a single peak at δ 1.66 (270 MHz NMR).

Compound **3d**. Addition of 0.28 equiv. of shift reagent to racemic material shifted the OBu^t resonances to δ 1.84 and 1.77. The OMe peaks also shifted to δ 3.98 and 3.87. Addition of the same quantity of **13** to the enantiomerically enriched material resulted in the same peak splitting in a 1:3 ratio (270 MHz NMR).

Compound **3h**. Addition of 0.15 equiv. of shift reagent to racemic material shifted the OBu^t resonances to δ 1.85 and 1.77. Addition of the same quantity of **13** to the enantiomerically enriched material resulted in the same peak splitting in a 7:1 ratio (270 MHz NMR).

Study of Aldol Reaction of **10b** *with Benzaldehyde at Low Temperature.*—*tert*-Butyl bromide (2.0 cm^3, 17.4 mmol) was added dropwise to a cooled (0 °C) stirred suspension of magnesium (375 mg, 15.6 mmol) in diethyl ether (6 cm^3). The mixture was stirred until all the magnesium had been consumed at which point the resultant grey–brown solution was added dropwise to a stirred solution of the sulfinyl ester **10b** (280 mg, 0.78 mmol) in THF (40 cm^3) at −78 °C. The white suspension was stirred for 1.5 h at −78 °C before a solution of benzaldehyde (710 mm^3, 7.0 mmol) in THF (10 cm^3) was added dropwise to it; it was then stirred at −78 °C for 0.5 h. Saturated aqueous ammonium chloride (50 cm^3) was added at low temperature to the mixture and the organic phase removed. The aqueous phase was extracted with ethyl acetate (3 × 25 cm^3) and the combined extracts were combined, washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue furnished **11a** (392 mg, 92%) which by ^1H NMR spectroscopy was shown to consist of a 1:1 mixture of two diastereoisomers. The peaks from one of the isomers matched those previously described for **11a**. The other diastereoisomer was responsible for the following peaks: δ_H 0.82 (9 H, s, $OCMe_3$), 1.20 (9 H, s, CMe_3), 1.56 (d, *J* 6.8, CH_3), 4.18 (1 H, d, *J* 10, SOCH), 5.38 (1 H, br d, *J* 10, PhC*H*), 5.24 (1 H, quintet, *J* 6.8, C*H*Me), 5.94 (1 H , br d, *J* 6.8, NH) and 7.24–8.00 (9 H, m, aromatic H). A sample of this mixture was cleaved using sodium amalgam to give a β-hydroxy ester **3a** (80%) which was shown by a chiral shift NMR experiment (as described above) to be racemic.

Crossover Experiment to prove Reversibility of Aldol Reaction.—*tert*-Butyl bromide (0.080 cm^3, 0.65 mmol) was added dropwise to a cooled (0 °C) stirred suspension of magnesium (17 mg, 0.65 mmol) in diethyl ether (1 cm^3). The mixture was stirred until all the magnesium had been consumed at which point the resultant grey–brown solution was added dropwise at −78 °C to a stirred solution of **11c** (100 mg, 0.20 mmol) in THF (10 cm^3). The mixture was stirred at −78 °C for 1.5 h after which benzaldehyde (0.050 cm^3, 0.50 mmol) was added to it and stirring continued at room temperature for 16 h. At the end of this time the reaction was quenched by the addition of saturated aqueous ammonium chloride (10 cm^3) and extracted with ethyl acetate (3 × 10 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated. Purification by flash chromatography was used to remove the excess of aldehyde and for the isolation of the reaction products which were identified by comparison of their ^1H NMR spectra with those described above as **11a** (56 mg, 58%, a single diastereoisomer) and **10b** (30 mg, 20%).

Oxidation of **12** *with Sodium Periodate to give* R-(−)-**7**.—To a solution of compound **12** (0.25 g, 1.05 mmol) in 10% aqueous methanol (8.0 cm^3) was added in one portion sodium periodate (0.45 g, 2.10 mmol). The resultant brown suspension was heated at reflux for 16 h after which it was poured into ethyl acetate (10 cm^3) and the mixture washed with water (2 × 10 cm^3) and saturated aqueous sodium thiosulfate (10 cm^3). The organic phase was separated, dried (Na_2SO_4) and evaporated under reduced pressure. The resultant oil was dissolved in tetrahydrofuran (5 cm^3) and stirred vigorously with aqueous sodium hydroxide (1.0 mol dm^{-3}; 5 cm^3) for 1.0 h. The organic solvent was removed under reduced pressure and the resulting aqueous suspension treated with concentrated hydrochloric acid until it reached pH 1. The aqueous fraction was extracted with dichloromethane (3 × 5 cm^3) and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give *R*-(−)-**7** (232 mg, 82%) as a white solid with spectral characteristics identical with those of known material.

Oxidation of **12** *with* N-*Bromosuccinamide to give* R-(−)-**7**.—To a solution of compound **12** (102 mg, 0.43 mmol) in methanol (2 cm^3) at 0 °C was added *N*-bromosuccinimide (226 mg, 1.29 mmol). The solution was stirred for 2 h at room temp. and then diluted with ethyl acetate (10 cm^3) and washed with aqueous sodium hydrogen carbonate (2 × 10 cm^3) and water (10 cm^3). The organic phase was dried (Na_2SO_4) and evaporated to give a white solid (122 mg). This material was treated directly with aqueous sodium hydroxide (2.0 mol dm^{-3}; 1 cm^3, 2 mmol) in THF (1 cm^3) for 1 h at room temp. This was then acidified with 6 mol dm^{-3} HCl until it reached pH 1 and extracted with dichloromethane (3 × 5 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated to give *R*-(−)-**7** as a white solid (90 mg, 80% from thiol).

X-*Ray Details for Compound* $S_{(S)}$R-(−)-**10b**; $C_{19}H_{28}NO_4S$, M = 366.5, orthorhombic, *a* = 10.168(4), *b* = 11.497(3), *c* = 18.294(5), *U* = 2138.2 A^3, space group $P2_12_12_1$, *Z* = 4, D_c =

1.14 g cm $^{-3}$, μ(Mo-Kα) = 1.53 cm^{-1}, F(000) = 788. Data were measured at room temperature on a Hilger and Watts Y290 four circle diffractometer in the range $2 < \theta < 22°$. 1545 Reflections were collected of which 541 were unique with $I > 3\sigma(I)$. Data were corrected for Lorentz and polarisation effects but not for absorption. The structure was solved by direct methods and refined using the SHELX[20] suite of programs. In the final least-squares cycles the sulfur was allowed to vibrate anisotropically. All other atoms were treated isotropically. Hydrogen atoms were included at calculated positions where appropriate. Final residuals after 10 cycles of least squares were $R = Rw = 0.0904$, for unit weights. Max. final shift/esd was 0.005. The max. and min. residual densities were 0.11 and -0.12 eA^{-3} respectively. Full details have been deposited with the Cambridge Crystallographic Data Centre.

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