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A biocatalytic route to enantioenriched, sulfanyl aldol products

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Abstract—The aldol products derived from sulfur- or selenium containing acceptors were prepared by kinetic resolution in the presence of antibody 84G3 with enantiomeric excesses ranging from 56 to 70%. Much higher level of enantioselectivity was obtained (enantiomeric excesses all superior to 96%) for sulfanyl aldol products derived from thiomethoxyacetone with three different acceptors.

1. Introduction

The development of strategies for the preparation of enantiomerically pure heterocycles remains a very important area of research. Recently, Warren and House have reviewed the effectiveness of using the sulfanyl group as a tool for the construction of various heterocyclic compounds with in most cases total control over the product stereochemistry.[1] The sulfanyl migration of several enantiopure 1,3-diols has been studied and allowed the preparation of various heterocycles, including heavily substituted tetrahydrofurans with excellent level of diastereo- and enantiocontrol.[2] In addition, sulfanyl 1,3-diols have been transformed into the corresponding β,γ-epoxy alcohols upon methylation of the sulfide functionality followed by cyclization under basic conditions.[3] Therefore, numerous strategies are reported in the literature for the synthesis of sulfanyl-based cyclization precursors, including organometallic addition to aldehydes, Sharpless asymmetric dihydroxylation or asymmetric aldol reaction.[4] In this contribution, we report the first abzymatic route to various enantioenriched sulfanyl aldols that are direct precursors of sulfanyl 1,3-diols and the corresponding heterocyclic targets. We recently described aldolase antibody 84G3 as a highly efficient catalyst for the regio- and enantioselective aldol reaction of various unsymmetrical methyl ketones with *para*-nitrobenzaldehyde.[5,6] This study revealed that in the presence of this antibody, the catalysed reaction of thiomethoxyacetone with *para*-nitrobenzaldehyde was highly regioselective with the preferential formation of the otherwise disfavoured linear regioisomer resulting from an addition at the less substituted carbon. Both linear aldol enantiomers could be accessed through aldol or retro-adol reactions using the same antibody. Herein, we report that antibody 84G3 has also the ability to catalyse aldol reactions involving sulfur containing acceptors and the corresponding retroaldolisation processes. In addition, we have investigated the sense and level of regioselectivity for the antibody-mediated aldol reactions of thiomethoxyacetone with two acceptors other than *para*-nitrobenzaldehyde and the corresponding retroaldolisations. We have also determined the enantioselectivity for the forward and reverse aldol reactions allowing the preparation of various sulfanyl aldols and the assignment of their absolute configurations. Finally, we are reporting the kinetic parameters for selected reactions.

2. Results and discussion

2.1. Antibody-catalysed forward aldol reactions of acetone, 2-pentanone and 3-pentanone with various sulfur and selenium containing aldehydes and antibody-mediated retroaldolisation of the corresponding racemic aldols

First, we set out to study the ability of ab84G3 to catalyse the forward aldol reactions of three representative donors with sulfur- and selenium containing acceptors, and for the unsymmetrical donor 2-pentanone, the degree of regiocontrol that antibody 84G3 could exercise on the aldol process (Table 1).

For all experiments, the product assignment and the product distribution were proven unambiguously by comparison of the retention times with independently chemically synthesized standards using high performance liquid chromatography (HPLC).[7] To screen for catalytic activity,

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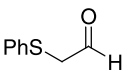
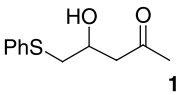
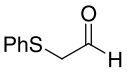
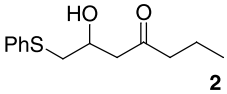
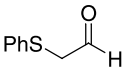
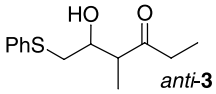
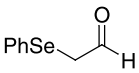
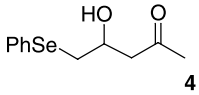
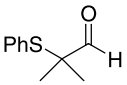
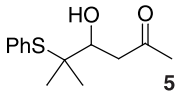
Table 1. Aldol reactions of S- and Se-containing acceptors with acetone, 2-pentanone and 3-pentanone

Entry	Acceptor and donor		Conditions[a]	Conversion (%)	Product
1 2		+acetone	PBS, 20 h Ab84G3, 20 h	0 24	 **1**
3 4		+2-pentanone	PBS, 3 h Ab84G3, 3 h	0 48	 **2**
5 6		+3-pentanone	PBS, 20 h Ab84G3, 20 h	0 3	 *anti*-**3**
7 8		+acetone	PBS, 20 h Ab84G3, 20 h	0 27	 **4**
9 10		+acetone	PBS, 18 h Ab84G3, 18 h	0 0	 **5**

[a] All reactions at pH=7.4, rt.

we performed the reactions under the following defined conditions: 90 mM of donor, 130 μM of acceptor and 9 mol% antibody in PBS (pH=7.4) at room temperature. Control experiments revealed that, in the absence of antibody, no reactions take place under these conditions (entries 1, 3, 5, 7, 9). For the antibody-mediated reactions, we found that all the reactions were taking place in the presence of ab84G3 with the exception of the reaction of acetone with 2-phenylthiobutyraldehyde[8] (entry 10). Indeed, this latter reaction did not produce any detectable amount of aldol product after 18 h in the presence of up to 9 mol% ab84G3 suggesting that 2-phenylthiobutyraldehyde is not a suitable donor for this antibody. The data collected in Table 1 revealed that the best-catalysed antibody transformation is the aldol reaction of phenylthioacetaldehyde[9] with 2-pentanone (entry 4). For this reaction, only the linear regioisomer was formed with no trace of the branched regioisomer detectable by HPLC. The reaction of phenylthioacetaldehyde with acetone was less efficient with 24% of the desired aldol product formed after 20 h at room temperature (entry 2). The aldol reaction of phenylselenoacetaldehyde[10] was also successfully catalysed by antibody 84G3 but the use of the selenoaldehyde did not present any significant advantage in comparison with the 'thioanalogue' (entry 8). Finally, we have found that only 3% of the branched *anti* regioisomer was detected by HPLC for the antibody-mediated aldol reaction involving 3-pentanone, suggesting that this antibody-mediated transformation has no synthetic utility. For all the antibody-catalysed reactions (entries 2, 4, 6, 8), another compound was detected by HPLC in addition to the desired aldol product. The structure of this side product is unclear but we hypothesised that this compound is arising from a self-condensation aldol reaction of the S- or Se-containing aldehyde, which are both prone to enolisation. This hypothesis is supported by the observation that the retention time (HPLC analysis) of this side-product was the same for all aldol reactions involving phenylthioacetaldehyde independent of the structure of the donors examined herein. In addition, a control experiment revealed that this same product was formed upon incubation of phenylthioacetaldehyde as the sole substrate in the presence of ab84G3.[11]

In addition to these experiments, we also assessed the ability of ab84G3 to catalyse the retroaldolisation of racemic sulfanyl aldols **1**-**5** all prepared according to standard literature procedures (Table 2).[7] The racemic aldols (228 μM) were treated with ab84G3 (10 mol%) in aqueous buffer (PBS, pH=7.4, at room temperature). Analysis by high-performance liquid chromatography (HPLC) indicated that no reaction takes place in the absence of the antibody. In contrast, the antibody-mediated retro-aldolisation reactions of compounds **1**, **2** and **4** halted at approximately 50% conversion, auguring an efficient kinetic resolution for these substrates. As expected from our results on the corresponding forward aldol reactions, the antibody-catalysed retroaldolisation of the *anti*-**3** was slow with 26% conversion of the starting material after 90 h and no reaction was observed for the *syn*-**3** stereoisomer. No retroaldolisation was observed with compound **5** suggesting that the binding pocket of 84G3 does not tolerate the presence of the quaternary carbon.

Table 2. Retro-aldolisation of compounds **1**-**4** in the presence of antibody 84G3

Entry	Substrate	Conditions	Conversion
1	(±)-**1**	PBS, rt, 20 h	0
2	(±)-**1**	10 % ab84G3, rt, 20 h	49
3	(±)-**2**	PBS, rt, 3.5 h	0
4	(±)-**2**	10 % ab84G3, rt, 3.5 h	45
5	(±)-*anti*-**3**	PBS, rt, 90 h	0
6	(±)-*anti*-**3**	10 % ab84G3, rt, 90 h	26
7	(±)-*syn*-**3**	PBS, rt, 90 h	0
8	(±)-*syn*-**3**	10 % ab84G3, rt, 90 h	0
9	(±)-**4**	PBS, rt, 20 h	0
10	(±)-**4**	10 % ab84G3, rt, 20 h	47

2.2. Antibody-catalysed forward aldol reactions of thiomethoxyacetone with benzaldehyde and *para*-methoxycinnamaldehyde and the antibody-mediated retro-aldolisations of the corresponding racemic aldols

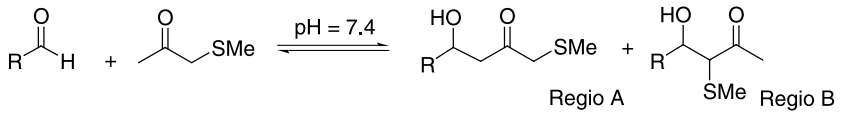
Previous work from our laboratory has shown that the reaction of thiomethoxyacetone with *para*-nitrobenzaldehyde **6** catalysed by ab84G3 is highly regioselective with the preferential formation of the linear regioisomer **9** resulting from an addition at the less substituted carbon (entry 2) (Table 3).[5,6] We have now further investigated the scope of this reaction and we have found that, in the presence of antibody 84G3, thiomethoxyacetone also undergoes the aldol condensation with benzaldehyde to afford predominantly the linear regioisomer **10** with a conversion of 12% after 3 h at room temperature (entry 4). The sense and level of regioselectivity of these antibody-mediated transformations suggest that in the presence of the donor thiomethoxyacetone, ab84G3 catalyses predominantly the formation of the linear regioisomers independent of the structure of the acceptors. We have also found that no reaction was observed with the less reactive acceptor *para*-methoxycinnamaldehyde **8** (entry 6). In contrast to the forward aldol reactions, the corresponding antibody-mediated retroaldolisations were much more efficient with a rapid reaction taking place with the three racemic linear aldol products **9**-**11** (entries 8, 10, 12). The reactions were halting at approximately 50% as expected for a kinetic resolution. The retroaldolisation of compounds **10** and **11** derived from the less reactive acceptors were the best-catalysed transformations as reflected by the shorter reaction time required to reach 50% conversion.

2.3. Enantioselectivity of the aldol and retro-aldol products and assignment of absolute configurations

To probe further the synthetic scope of these antibodies, we studied the enantioselectivity of selected forward aldol and retroaldol reactions. The enantiomeric excesses of the products were determined by HPLC using chiral stationary phases and are collected in Table 4.

The data showed that the enantiomeric excesses of all aldol products derived from sulfur- and selenium containing acceptors ranged from 56% to 70%. As expected the ee values of the forward aldol reaction correlate well with the ee values of the corresponding retroaldolisations. Gratifyingly, the catalyst was highly enantioselective and allowed the recovery of the unreacted aldols **9**-**11** with ee values typically greater than 96% for the retroaldolisation of the racemic aldol products **9**-**11** derived from the reactions of *para*-benzaldehyde, benzaldehyde or *para*-methoxycinnamaldehyde with thiomethoxyacetone. These results suggest that for antibody 84G3, the highest enantioselectivities (>96%) were observed for aldol reactions where conjugated aldehydes served as acceptors. Lower enantioselectivities were obtained when aldol acceptors containing an sp^3 center in the α-position are selected as reaction partners. All the enantioenriched aldol products formed via an antibody-mediated forward aldol reactions possess the (*R*)-configuration and the recovered aldols resulting from a retroaldolisation process possess the (*S*)-configuration. To assign the absolute configurations unambiguously, products **1**, **2**, **9** and **10** were prepared independently by asymmetric synthesis or catalysis. The absolute configurations of all other aldol products were

Table 3. Aldolisation of thiomethoxyacetone with various acceptors and retro aldolisations



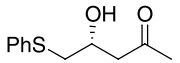
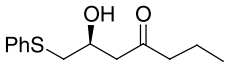
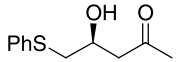
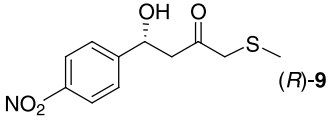
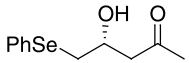
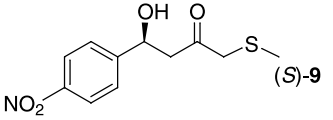
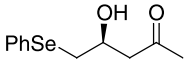
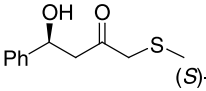
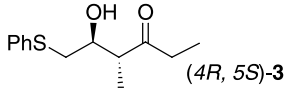
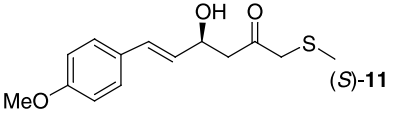
6 R = *para*-NO_2Ph
7 R = Ph
8 R = *para*-MeOPhCH=CH-

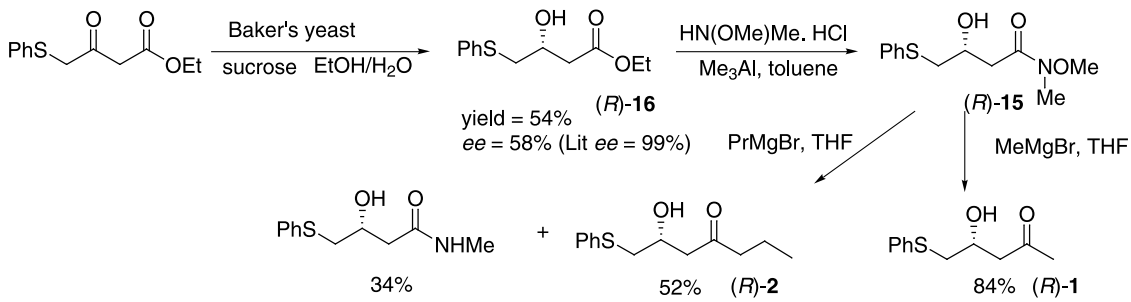
9 R = *para*-NO_2Ph
10 R = Ph
11 R = *para*-MeOPhCH=CH-

12 R = *para*-NO_2Ph
13 R = Ph
14 R = *para*-MeOPhCH=CH-

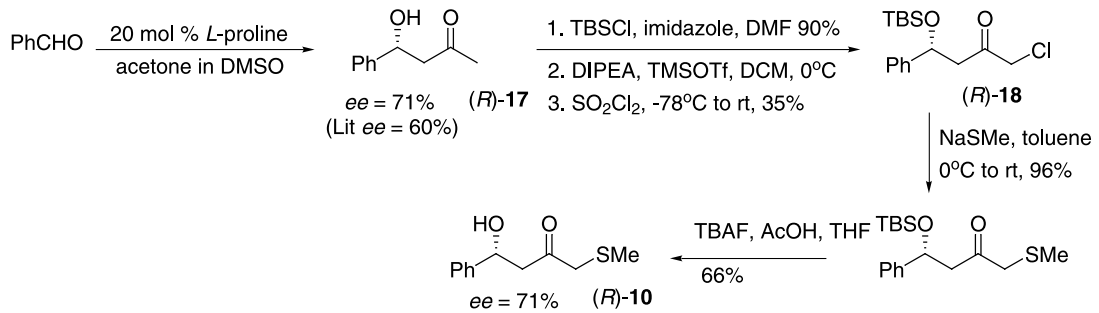
Entry	Acceptor and donor	Conditions[a]	Conversion (%)	Ratio A/B
Aldolisation				
1	**6**	PBS, 0 °C, 1 h 40	9	10:90
2	**6**	25% ab84G3, 0 °C, 1 h 40	56	98:2
3	**7**	PBS, rt, 3 h	1	0:100
4	**7**	9% ab84G3, rt, 3 h	12	92:8
5	**8**	PBS, 40 h	0	—
6	**8**	9% ab84G3, rt, 24 h	0	—
Retroaldolisation				
Entry	Substrate	Conditions	Conversion (%)	
7	(±)-**9**	PBS, rt, 2 h	0	
8	(±)-**9**	10 % ab84G3, rt, 2 h	51	
9	(±)-**10**	PBS, rt, 1 h	0	
10	(±)-**10**	10 % ab84G3, rt, 1 h	50	
11	(±)-**11**	PBS, rt, 1 h	0	
12	(±)-**11**	10 % ab84G3, rt, 1 h	50	

Table 4. ee Values for antibody-catalysed aldol and retro-aldol reactions

Entry	Product	Method conversion (%)	ee (%)	Entry	Product	Method conversion (%)	ee (%)
1	 (*R*)-**1**	Aldol (30%)	60	6	 (*S*)-**2**	Retro-aldol (50%)	60
2	 (*S*)-**1**	Retro-aldol (50%)	56	7	 (*R*)-**9**	Aldol (10%)	97
3	 (*R*)-**4**	Aldol (65%)	64	8	 (*S*)-**9**	Retro-aldol (50%)	96
4	 (*S*)-**4**	Retro-aldol (54%)	66	9	 (*S*)-**10**	Retro-aldol (50%)	98
5	 (*4R, 5S*)-**3**	Retro-aldol (37%)	70	10	 (*S*)-**11**	Retro-aldol (50%)	99



Scheme 1. Independent asymmetric syntheses of enantioenriched aldols **1** and **2**.



Scheme 2. Independent asymmetric syntheses of enantioenriched aldol **10**.

assigned by analogy. It was anticipated that compounds **1** and **2** could be prepared in enantiomerically pure form from a common precursor, the Weinreb amide **15** by functional group manipulation of the methoxy-N-methylamide group (Scheme 1).

The absolute configuration of the Weinreb amide **15** could be easily secured through Bakers' yeast reduction of the corresponding ketoester according to a procedure described in the literature.[12] Although the Bakers' yeast reduction of the ethyl 4-phenylthio-3-oxobutanoate is reported to produce the corresponding (*R*)-hydroxy ester **16** in 99% ee, in our hands, this reaction gave the desired product with a lower enantiomeric excess of 58% as determined by chiral HPLC. Transamination of this enantioenriched compound to give the N-methoxy-N-methylamide **15**, followed by addition of the Grignard reagent afforded the desired enantioenriched compounds **1** and **2** with respective yields of 84% and 52%. For the addition of *n*-PrMgBr on compound **15**, a side product resulting from elimination of formaldehyde was observed and isolated with a chemical yield of 34%.[13] This side reaction was not observed when compound **15** was treated with MeMgBr. Analysis of these compounds by chiral HPLC revealed that no epimerisation has occurred converting the Weinreb amide into the desired ketones as these two compounds were obtained with an ee of 58%. Comparison of the retention times of these enantioenriched independently synthesised reference compounds with the antibody-products established the (*R*) configuration of the stereogenic center of the enantioenriched antibody aldol products, which is consistent with preferential addition of the ketone to the Si face of the aldehyde. For the retro-aldol reactions, HPLC analysis confirmed that at approximately 50% conversion, the major enantiomer for the recovered enantioenriched aldol products **1** and **2** possess the (*S*)-configuration. For the aldol compounds derived from thiomethoxyacetone, the absolute configuration of compound **9** was already established correlating the absolute configuration of the antibody-product with the enantiopure sample prepared according to the Evans's asymmetric aldol methodology.[14] Herein, we suggest an alternative route for the preparation of enantioenriched **10** using *L*-proline as the organocatalyst (Scheme 2).[15] The (*R*)-aldol product **17** (ee=71%) derived from acetone and benzaldehyde was prepared in DMSO, in the presence of 20 mol% *L*-proline at room temperature. Chlorination of the corresponding protected terminal silyl enol ether followed by nucleophilic substitution of the chlorine group of **18** with sodium thiomethoxide in toluene at 0 °C proceeded smoothly to afford, after deprotection, the enantioenriched compound **10** in 96% yield and with an ee of 71%. HPLC analysis revealed that the retention time of the minor (*S*)-enantiomer of this sample is identical to the retention time of the antibody-product resulting from the retro-aldolisation process, confirming that the antibody-product possess the (*S*)-configuration.

2.4. Kinetic studies

The results of the kinetic studies of several retro-aldol reactions are provided in Table 5. The kinetic parameters are reported per antibody active site assuming that both active sites of the antibody function independently. All the

Table 5. Kinetic parameters for selected retro-aldol reaction

Entry	Substrates	k_{cat} (min^{-1})	K_M (μM)	k_{cat}/k_{uncat}	$(k_{cat}/K_M)/k_{uncat}$ (M^{-1})
1	(±)-**1**	0.031	474	—	—
2	(±)-**2**	0.604	148	—	—
3	(±)-*anti*-**3**	0.006	390	—	—
4	(±)-**4**	0.053	584	—	—
5	(±)-**9**	0.81	69	4.3×10^5	6.2×10^9
6	(±)-**10**	3.17	56	1.9×10^6	3.3×10^{10}

retro-aldol reactions followed typical Michaelis–Menten kinetics. The determination of k_{cat}/k_{uncat} was not determined for compounds **1**-**4** as no product resulting from a retro-aldolisation process was observed to be formed for the uncatalysed reaction under our essay conditions, even after prolonged reaction times. For compounds **1**-**4**, the kinetic data suggest that the linear aldol product **2** derived from 2-pentanone was processed by the antibody more efficiently (k_{cat}=0.6 min^{-1}) than the aldol products **1** or **4** derived from acetone. A similar trend was reported in the literature as it was found that the retroaldolisation of a linear aldol product derived from butanone was processed approximately 20 times more efficiently by antibody 84G3 than the corresponding aldol product derived from acetone.[16] We have also found that the presence of the additional methyl group of the branched aldol product *anti*-**3** slowed down considerably the antibody-mediated retroaldolisation of this racemic substrate as reflected by the much lower rate constant (k_{cat}=0.006 min^{-1}). The data also revealed that the antibody-mediated retro-aldolisation of the aldol product derived from the less reactive acceptor (benzaldehyde) is significantly more efficient than the catalysed retroaldolisation of compounds derived from the more electron deficient acceptor (*para*-nitrobenzaldehyde). The high catalytic proficiencies of ab84G3 for both the retro-aldolisation of aldols (±)-**9** and (±)-**10** suggest that these reactions are synthetically valuable processes as the recovered aldol products resulting from these kinetic resolutions were formed with enantiomeric excesses superior to 98%.

3. Conclusion

Two major issues were under consideration. First was the critical issue as to whether aldolase antibody 84G3 could catalyse aldol reactions of all carbon donors with sulfur or selenium-containing acceptors. Second, the possibility of controlling simultaneously the regio- and enantioselectivity of aldol reactions of thiomethoxyacetone with three electronically and structurally different acceptors had to be determined as well as the ability of ab84G3 to catalyse the corresponding retro-aldolisations. It was found that the antibody-aldol products derived from sulfur- or selenium containing acceptors were obtained with enantiomeric excesses ranging from 56 to 70%. In contrast, various enantiopure (ee >96%) sulfanyl aldol products derived from thiomethoxyacetone with three different acceptors were obtained using antibody-catalysed aldolisation and retro-aldolisations. The retro-aldolisations are synthetically superior as reflected by the catalytic proficiency of ab84G3 for these reactions. Further exploration of ab84G3 to produced enantioenriched precursors of various heterocyclic systems is in progress in our laboratory.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF) was obtained by distillation over sodium and benzophenone, dry methylene chloride (CH_2Cl_2) was obtained by distillation over calcium hydride. Yields refer to chromatography and spectroscopically (^{1}H NMR) homogeneous materials. Commercially available reagents were used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck aluminum foil backed sheets precoated with Kieselgel 60 F-254 using UV light as visualizing agent and an ethanolic solution of potassium permanganate and heat as developing agent. Merck Silica gel C60 (40–60 μM) was used for flash column chromatography. NMR spectra were recorded on a Bruker DPX-400 or Bruker AMX-500 spectrometer and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain multiciplicities: s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, b=broad. The coupling constants *J* are given in hertz. IR spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer. Mass spectra (*m*/*z*) and HRMS were recorded on Micromass GCT using Chemical Ionisation (NH_3, CI), Electronic Impact (EI+) or Field Ionization (FI). Microanalyses were performed by 'Elemental Microanalysis Limited', Devon. Melting points were determined in a capillary and are uncorrected.

HPLC information. Analytical HPLC and semi-preparative HPLC were performed on a Waters HPLC system (626 Pump, 600 S Controller, 996 Photodiode Array Detector, Millenium^{32} Software). Reactions were followed by analytical RP-HPLC: Nova-pak Waters column, C-18, 60 Å pore size, 4 μm particle size, 3.9×150 mm, flow rate 1.0 ml/min. Enantiomeric excesses (ee) were determined by chiral normal phase HPLC: Daicel Chiralpak AD or Daicel Chiracel OJ, OD or OJ-H columns (4.6×250 mm), flow rate 1.0 ml/min. The solvent systems used for the retention times provided for the donors, acceptors and aldol products studied are defined as: solvent A: hexane; solvent B: *i*PrOH; solvent C: EtOH.

4.2. Antibody assays

All antibody-catalysed reactions were performed in phosphate buffered saline (10 mM phosphate, 16 mM NaCl, pH 7.4). All antibody-catalysed reactions and background reactions were monitored by high-pressure liquid chromatography (HPLC; Waters HPLC system (626 Pump, 600 S Controller, 996 Photodiode Array Detector, Millenium^{32} Software) using a Nova-pak Waters column (C-18, 60 Å pore size, 4 micrometer particle micrometer size, 3.9×150 mm) and acetonitrile/water or methanol/water mixtures (containing 0.1% trifluoroacetic acid) as eluents at a flow rate of 1.0 ml/min.

4.3. Michaelis–Menten kinetics

Product formation or percent conversion of antibody-catalysed reaction mixtures was monitored by HPLC. The points were determined experimentally and the best fit value of V_{max} and K_m were obtained by fitting the v_i versus $[S]_0$ data to hyperbolic saturation curves by weighted non-linear regression. All data are reported per antibody active site. An IgG antibody possesses 2 active sites per MW of ~150,000 g/mol.

4.4. Determination of enantiomeric excesses: forward aldol reaction

Antibody (64 nmol) was added to a stock solution containing the aldehyde (10 ml of 66 mM in 10% acetonitrile, 90% PBS, 660 nmol), the ketone (100 ml of 65 mM in PBS, 6.5 mmol) and PBS (amount required to make the final volume up to 2.11 ml). The reactions were monitored by RP-HPLC using a Nova-pak Waters column. After reaching a suitable conversion, the unreacted aldol was isolated by semi-preparative reversed-phase HPLC, Hypersil ODS column, 5 micrometer particle size, 7×250 mm, flow rate 2.0 ml min^{-1} or Phenomenex Luna C18 column, 8.8 micrometer particle size, 15×250 mm, flow rate 8.0 ml min^{-1}. The fractions were freeze-dried, the residue was redissolved in 200 ml of dichloromethane/hexane (50:50) and the ee was determined by chiral normal-phase HPLC.

Retro-aldol reactions. Antibody (32 nmol) was added to racemic stock solution of aldol (10 ml of 80 mM in acetonitrile, 800 nmol). The reactions were monitored by RP-HPLC using using a Waters Nova-pak column. After reaching 50% conversion, the unreacted aldol was isolated by semi-preparative reversed-phase HPLC, Hypersil ODS column, 5 micrometer particle size, 7×250 mm, flow rate 2.0 ml min^{-1} or Phenomenex Luna C18 column, 8.8 micrometer particle size, 15×250 mm, flow rate 8.0 ml min^{-1}. The fractions were freeze-dried, the residue was redissolved in 200 ml of dichloromethane/hexane (50:50) and the ee was determined by normal-phase HPLC.

4.5. General procedure 1: aldol reactions

To a solution of LDA [prepared by dropwise addition of *n*-butyllithium (11.2 mmol, 2 M) to a solution of diisopropylamine (11.3 mmol) in dry THF (15 ml) at 0 °C] at −78 °C was added the donor ketone (11.3 mmol) in dry THF (7.5 ml) via cannula. The reaction was allowed to stir at −78 °C for 30 min. The aldehyde acceptor (7.5 mmol) in dry THF (7.5 ml) was then added via cannula, and the mixture allowed to stir at −78 °C for 15 min. The reaction was then quenched with saturated NH_4Cl and allowed to warm to room temperature. The aqueous layer was extracted with EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo.

4.6. General procedure 2: formation of Weinreb amide from the corresponding ester

To N,O-dimethylhydroxylamine hydrochloride (43 mmol) in dry toluene (50 ml) at 0 °C was added $AlMe_3$ (39 mmol, 2 M in hexanes) dropwise. The mixture was allowed to warm to room temperature and stirred for 30 min before being cooled to 0 °C and ester (10.4 mmol) in dry toluene (35 ml) added dropwise via cannula. The mixture was allowed to warm to room temperature and stir for 2 h, then poured in to aqueous tartaric acid and allowed to stir for a further 1.5 h. The mixture was extracted with DCM. The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent removed in vacuo.

4.7. General procedure 3: formation of Weinreb amide from the corresponding ester

To N,O-dimethylhydroxylamine hydrochloride (4 mmol) in THF (13 ml) at 0 °C was added $AlMe_3$ (2 M in DCM, 4 mmol). The mixture was stirred at 0 °C for 30 min and room temperature for 20 min. The reaction mixture was then cooled to −15 °C and ester (1.3 mmol) in THF (10 ml) was added dropwise. The mixture was warmed to 0 °C and stirred for a further 4 h. The reaction was then quenched with 0.5 M HCl and the mixture extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$ and concentrated in vacuo.

4.8. General procedure 4: Grignard addition to the Weinreb amide

The Grignard reagent (8.5 mmol) was added to a solution of Weinreb amide (1.6 mmol) in THF (15 ml) at −40 °C. The mixture was allowed to warm to 0 °C over 30 min and stirred for a further 3–48 h. Sat. NH_4Cl was added, and the mixture allowed to warm to room temperature. The mixture was extracted with DCM, dried over $MgSO_4$ and the solvent removed in vacuo.

4.9. General procedure 5: TBS protection

To the aldol product (20 mmol) in DMF (80 ml) at 0 °C was added imidazole (98 mmol) and TBSCl (48 mmol). The mixture was allowed to warm to room temperature and stir for 18 h. The reaction was quenched with water. The mixture was extracted with DCM, the combined organic fractions dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo.

4.10. General procedure 6: TBS-deprotection of aldol product

A stock solution was prepared by the addition of AcOH (0.3 ml) to a solution of TBAF (5 ml, 1 M in THF). TBS protected aldol (0.37 mmol) in THF (3.7 ml) was treated with a portion of this stock solution (4 ml) and allowed to stir at room temperature for 15 h. The reaction was then quenched by addition of sat. $NaHCO_3$ (10 ml). The mixture was extracted with EtOAc, the combined organic fractions dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo.

4.11. General procedure 7: substitution of chloride with sodium thiomethoxide

To the chlorinated aldol (1.6 mmol) in toluene (35 ml) at 0 °C was added sodium thiomethoxide (3.2 mmol). The mixture was allowed to slowly warm to room temperature, stirred for 18 h and then quenched with saturated NH_4Cl. The mixture was extracted with DCM, the combined organic fractions dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo.

4.11.1. 4-Hydroxy-5-phenylsulfanyl-pentan-2-one (±)-1. Synthesised from (phenylthio)-acetaldehyde (2 g, 13 mmol) and dry acetone (1 ml, 14.5 mmol) using general procedure 1. Purification by column chromatography (1:1 hexane/

EtOAc) afforded **1** (1.9 g, 70%) as an oil. R_F (1:1 hexane/EtOAc): 0.25; δ ^{1}H NMR (400 MHz): 2.12 (3H, s, CH_3), 2.67 (1H, dd, J=8.0, 17.5 Hz, CH_AH$_B$CHO), 2.75 (1H, dd, J=4.0, 17.5 Hz, CH$_A$$H_B$CHO), 3.04 (1H, dd, J=6.5, 14.0 Hz, CH_AH$_B$S), 3.05 (1H, dd, J=6.0, 14.0 Hz, CH$_A$$H_B$S), 3.40 (1H, br s, O$H$), 4.10–4.18 (1H, m, C$H$), 7.1.5–7.38 (5H, m, Ar); δ ^{13}C NMR (100 MHz): 30.7 (*C*H$_3$), 40.0 (*C*H$_2$S), 48.4 (*C*H$_2$CO), 66.2 (*C*H), 126.4 (Ar–*C*), 129.1 (Ar–*C*, 2C), 129.5 (Ar–*C*, 2C), 135.3 (Ar–*C*, quarternary), 208.7 (*C*=O); ν_{max} (neat): 3418.0 (br, O–H), 1710.9 (s, C=O); *m/z* (autospec, CI$^+$): 207 ([M−OH]$^+$, 100%), 225 ([M+H]$^+$, 51%), 242 ([M+NH$_4$]$^+$, 26%); (HRMS, autospec CI$^+$): found 211.0800 ([M+H]$^+$), $C_{11}H_{15}SO_2$ requires 211.0793.

4.12. Synthesis of the two aldol regioisomers derived from 2-pentanone and phenylthioacetaldehyde

4.12.1. (±)-3-Hydroxy-4-phenylsulfanyl-butyric acid ethyl ester. Synthesised from (phenylthio)acetaldehyde (4.365 g, 28.7 mmol) and ethyl acetate (4.17 ml, 43 mmol) using general procedure 1. Purification by column chromatography (4:1 hexane/EtOAc) afforded the desired compound (5.6 g, 82%) as an oil. R_f (4:1 hexane/EtOAc): 0.50; δ ^{1}H NMR (500 MHz): 1.27 (3H, t, J=7.2 Hz, CH_3), 2.58 (1H, dd, J=16.4, 8.1 Hz, CH_AH$_B$CHO), 2.67 (1H, dd, J=16.4, 4.1 Hz, CH$_A$$H_B$CHO), 3.07 (1H, dd, J=13.8, 7.0 Hz, CH_AH$_B$S), 3.11 (1H, dd, J=13.8, 5.7 Hz), 3.21 (1H, d, J=3.9 Hz, OH), 4.11–4.17 (1H, m, CHOH), 4.17 (2H, q, J=7.0 Hz, CH_2CH$_3$), 7.19–7.24 (1H, m, Ar), 7.28–7.33 (2H, m, Ar), 7.37–7.42 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 14.0 (*C*H$_3$), 39.8 (*C*H$_2$CHO), 40.1 (*C*H$_2$S), 60.8 (*C*H$_2$CH$_3$), 66.5 (*C*HOH), 126.5 (Ar–*C*), 129.0 (Ar–*C*, 2C), 129.7 (Ar–*C*, 2C), 135.1 (Ar–*C*, quarternary), 172.0 (*C*=O); ν_{max} (neat): 3458.4 (br, O–H), 1729.5 (s, C=O); *m/z* (autospec, CI$^+$): 223 ([M−OH]$^+$, 100%), 241 ([M+H]$^+$, 21%), 258 ([M+NH$_4$]$^+$, 34%); (HRMS, GCT, FI): found 240.0821 ([M·]), $C_{12}H_{16}SO_3$ requires 240.0820.

4.12.2. (±)-3-Hydroxy-N-methoxy-N-methyl-4-phenylsulfanyl-butyramide. Synthesised from 3-hydroxy-4-phenylsulfanyl-butyric acid ethyl ester (2.5 g, 10.4 mmol) using general procedure 2. Purification by column chromatography (1:1 hexane/EtOAc) afforded the desired compound (2.1 g, 78%) as a white solid. R_f (1:1 hexane/EtOAc): 0.16; δ ^{1}H NMR (500 MHz): 2.65 (1H, dd, J=16.8, 8.5 Hz, CH_AH$_B$CHO), 2.86 (1H, dd, J=16.8, 2.2 Hz CH$_A$$H_B$CHO), 3.09 (1H, dd, J=13.4, 6.7 Hz, CH_AH$_B$S), 3.17 (1H, dd, J=13.4, 5.0 Hz), 3.19 (3H, s, CH_3N), 3.67 (3H, s, CH_3O), 3.97 (1H, d, J=3.0 Hz, OH), 4.14–4.22 (1H, m, CHOH), 7.18–7.22 (1H, m, Ar), 7.27–7.32 (2H, m, Ar), 7.39–7.42 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 31.7 (*C*H$_3$N), 36.6 (*C*H$_2$CO), 39.6 (*C*H$_2$S), 61.2 (*C*H$_3$O), 66.9 (*C*HOH), 126.2 (Ar–*C*), 128.9 (Ar–*C*, 2C), 129.3 (Ar–*C*, 2C), 135.5 (Ar–*C*, quarternary), 172.9 (*C*=O); ν_{max} (neat): 3430.1 (br, O–H), 1643.7 (s, C=O); *m/z* (autospec, CI$^+$): 238 ([M−OH]$^+$, 52%), 256 ([M+H]$^+$, 100%); (HRMS, GCT, CI$^+$): found 256.1018 ([M+H]$^+$), $C_{12}H_{18}SO_3N$ requires 256.1007. Analysis for $C_{12}H_{17}SO_3N$: calculated C: 56.45, H: 6.71, N: 5.49; found C: 56.61, H: 6.87, N: 5.53.

4.12.3. 2-Hydroxy-1-phenylsulfanyl-heptan-4-one (±)-2. Magnesium turnings (1.75 g, 72 mmol) were stirred vigorously in a round-bottomed flask overnight under argon. Dry THF (12 ml) was added. A single crystal of iodine was added and a solution of propyl bromide (2.2 ml, 2.95 g, 24 mmol) in dry THF (12 ml) was added dropwise. The mixture was allowed to stir until it cooled to room temperature. The mixture was then added to a solution of Weinreb amide (1.02 g, 4 mmol) in dry THF (8 ml) at −40 °C via cannula. The mixture was allowed to warm to 0 °C over 30 min and allowed to stir for a further 1.5 h. Saturated ammonium chloride solution (25 ml) was added and the mixture extracted with DCM. The organic fractions were combined, dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo. Purification by column chromatography (5:1 hexane/EtOAc) afforded **2** (520 mg, 55%) as an oil. R_f (1:1 hexane/EtOAc): 0.16; δ ^{1}H NMR (400 MHz): 0.91 (3H, t, J=7.6 Hz, CH_3), 1.59 (2H, tq, J=7.6, 7.6 Hz, CH_2CH$_3$), 2.39 (2H, t, J=7.6 Hz, CH_2CH$_2$CH$_3$), 2.67 (1H, dd, J=17.4, 7.9 Hz, CH_AH$_B$CHO), 2.76 (1H, dd, J=17.4, 3.9 Hz, CH$_A$$H_B$CHO), 3.05 (1H, dd, J=13.9, 6.4 Hz, CH_AH$_B$S), 3.06 (1H, dd, J=13.9, 6.4 Hz, CH$_A$$H_B$S), 3.28 (1H, d, J=2.2 Hz, OH), 4.11–4.20 (1H, m, CHOH), 7.18–7.24 (1H, m, Ar), 7.27–7.33 (2H, m, Ar), 7.36–7.41 (2H, m, Ar); δ ^{13}C NMR (100 MHz): 13.6 (*C*H$_3$), 17.0 (*C*H$_2$CH$_3$), 40.0 (C*H*$_2$S), 45.5 (*C*H$_2$CH$_2$CH$_3$), 47.3 (CH(OH)*C*H$_2$CHO), 66.4 (*C*HOH), 126.5 (Ar–*C*), 129.1 (2C, Ar–*C*), 129.6 (2C, Ar–*C*), 135.3 (Ar–*C*, quarternary), 211.2 (*C*=O); ν_{max} (neat): 3445.5 (br, O–H), 1706.7 (s, C=O); *m/z* (autospec, CI$^+$): 221 ([M−OH]$^+$, 100%), 239 ([M+H]$^+$, 87%), 256 ([M+NH$_4$]$^+$, 45%); (HRMS, GCT, FI): found 238.1026 ([M·]), $C_{13}H_{18}SO_2$ requires 238.1028.

4.12.4. (±)-2-Ethyl-3-hydroxy-4-phenylsulfanyl-butyric acid ethyl ester. Synthesised from (phenylthio)acetaldehyde (88 mg, 6.5 mmol) and ethyl butanoate (1.2 ml, 9.8 mmol) using general procedure 1. Purification by column chromatography afforded the desired compound (1.1 g of a mixture of diastereomers, 64% yield, 44% de) as an oil. Major diastereomer (isomer 1): δ ^{1}H NMR (500 MHz): 0.92 (3H, t, J=7.7 Hz, CH_3CH$_2$CH), 1.27 (3H, t, J=7.2 Hz, CH_3CH$_2$O), 1.69–1.80 (2H, m, CHCH_2CH$_3$), 2.40 (1H, ddd, J=5.1, 6.8, 9.0 Hz, CHEt), 2.87 (1H, br s, OH), 2.95 (1H, dd, J=13.8, 8.5 Hz, CH_AH$_B$S), 3.18 (1H, dd, J=13.8, 3.4 Hz, CH$_A$$H_B$S), 3.87–3.91 (1H, m, C$H$OH), 4.12–4.24 (2H, m, OCH_2CH$_3$), 7.19–7.24 (1H, m, Ar), 7.27–7.33 (2H, m, Ar), 7.37–7.41 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 11.6 (*C*H$_3$CH$_2$CH), 14.1 (*C*H$_3$CH$_2$O), 21.1 (CH*C*H$_2$CH$_3$), 39.1 (*C*H$_2$S), 51.7 (*C*HEt), 60.5 (*C*H$_2$O), 69.5 (*C*HOH), 126.5 (Ar–*C*), 128.9 (Ar–*C*, 2C), 129.6 (Ar–*C*, 2C), 134.9 (Ar–*C*, quarternary), 174.2 (CO); minor diastereomer: δ ^{1}H NMR (500 MHz): 0.92 (3H, t, J=7.7 Hz, CH_3CH$_2$CH), 1.28 (3H, t, J=7.3 Hz, CH_3CH$_2$O), 1.60–1.69 (2H, CHCH_2CH$_3$), 2.60 (1H, ddd, J=5.4, 5.4, 8.9 Hz, CHEt), 2.87 (1H, br s, OH), 3.05 (1H, dd, J=13.7, 7.7 Hz, CH_AH$_B$S), 3.12 (1H, dd, J=13.7, 5.0 Hz, CH$_A$$H_B$S), 3.82–3.86 (1H, m, C$H$OH), 4.12–4.24 (2H, OC$H_2CH_3$), 7.19–7.24 (1H, m, Ar), 7.27–7.33 (2H, m, Ar), 7.37–7.41 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 11.6 (*C*H$_3$CH$_2$CH), 14.1 (*C*H$_3$CH$_2$O), 22.3 (CH*C*H$_2$CH$_3$), 39.6 (*C*H$_2$S), 50.9 (*C*HEt), 60.5 (*C*H$_2$O), 70.4 (*C*HOH), 126.5 (Ar–*C*), 128.9 (Ar–*C*, 2C), 129.9 (Ar–*C*, 2C), 135.2 (Ar–*C*, quarternary), 174.6 (CO); ν_{max} (neat): 3468.3 (br, O–H), 1725.7 (s, C=O); *m/z* (HRMS, GCT, FI): found 268.1146 ([M·]), $C_{14}H_{20}O_3S$ requires 268.1133.

4.12.5. (±)-2-Ethyl-3-hydroxy-N-methoxy-N-methyl-4-phenylsulfanyl-butyramide. To N,O-dimethylhydroxylamine hydrochloride (840 mg, 8.6 mmol) in dry toluene (10 ml) at 0 °C was added trimethylaluminium (3.9 ml, 7.8 mmol, 2 M in hexanes) dropwise. The mixture was allowed to warm to room temperature and stirred for 30 min. The mixture was then cooled to 0 °C and 2-ethyl-3-hydroxy-4-phenylsulfanyl-butyric acid ethyl ester (500 mg of mixture of diastereomers, 2.1 mmol) in dry toluene (7 ml) was added dropwise via cannula. The mixture was heated to reflux for 2.5 h. The mixture was then allowed to cool, and poured into aqueous tartaric acid (250 ml, 1 M) and allowed to stir for 1.5 h. The mixture was extracted with Et_2O. The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent removed in vacuo. Purification by column chromatography (4:1 hexane/EtOAc) afforded *anti*-isomer (254 mg, 43%) and *syn*-isomer (96 mg, 16%) as oils (46% de). Analysis *syn*-isomer: R_f (1:1 hexane/EtOAc): 0.32; δ ^{1}H NMR (400 MHz): 0.88 (3H, t, J=7.6 Hz, CH_3CH$_2$), 1.62–1.85 (2H, m, CH_2CH$_3$), 3.07 (1H, dd, J=13.8, 7.5 Hz, CH_AH$_B$S), 3.13 (1H, dd, J=13.8, 5.8 Hz, CH$_A$$H_B$S), 3.15–3.24 (1H, m, C$H$Et), 3.21 (3H, s, C$H_3$N), 3.49 (1H, br s, O$H$), 3.68 (3H, s, C$H_3$O), 3.88–3.95 (1H, m, C$H$OH), 7.16–7.21 (1H, m, Ar), 7.26–7.31 (2H, m, Ar), 7.35–7.39 (2H, m, Ar); δ ^{13}C NMR (100 MHz): 11.9 (CH_3CH$_2$), 20.1 (CH_2CH$_3$), 31.9 (CH_3N), 37.8 (CH_2S), 45.1 (CHEt), 61.5 (*C*H$_3$O), 70.5 (CHOH), 126.3 (Ar–*C*), 129.0 (2C, Ar–*C*), 129.3 (2C, Ar–*C*), 135.3 (Ar–*C*, quaternary), 176.1 (CO); ν_{max} (neat): 3426.5 (br, O–H), 1643.6 (s, C=O); *m/z* (autospec, ESI$^+$): 589 ([2M+Na]$^+$, 78%), 306 ([M+Na]$^+$, 100%);*m/z* (HRMS, autospec, ESI$^+$): found 306.1131 ([M+Na]$^+$): $C_{14}H_{21}NO_3SNa$ requires 306.1140. Analysis for *anti*-isomer: (1:1 hexane/EtOAc): 0.28; δ ^{1}H NMR (400 MHz): 0.91 (3H, t, J=7.6 Hz, CH_3CH$_2$),1.68–1.82 (2H, m, CH_2CH$_3$),2.99–3.26 (3H, m, CH_2S and OH), 3.22 (3H, s, CH_3N), 3.76 (3H, s, CH_3O), 3.80–3.90 (1H, m, CHOH), 4.11–4.17 (1H, m, CHEt), 7.17–7.22 (1H, m, Ar), 7.27–7.31 (2H, m, Ar), 7.35–7.39 (2H, m, Ar); δ ^{13}C NMR (100 MHz):11.9 (CH_3CH$_2$), 22.7 (CH_2CH$_3$), 31.8 (CH_3N), 39.3 (CH_2S), 44.3 (CHEt), 61.6 (*C*H$_3$O), 70.8 (CHOH), 126.4 (Ar–*C*), 129.0 (2C, Ar–*C*), 129.5 (2C, Ar–*C*), 135.5 (Ar–*C*, quaternary), 176.4 (CO); ν_{max} (neat): 3415.8 (br, O–H), 1635.2 (s, C=O); *m/z* (autospec, ESI$^+$): 589 ([2M+Na]$^+$, 42%), 306 ([M+Na]$^+$, 100%); *m/z* (HRMS, autospec, ESI$^+$): found 306.1131 ([M+Na]$^+$): $C_{14}H_{21}NO_3$-SNa requires 306.1140.

4.12.6. (±)-3-Ethyl-4-hydroxy-5-phenylsulfanyl-pentan-2-one. *syn*-Isomer synthesised from the corresponding 2-ethyl-3-hydroxy-N-methoxy-N-methyl-4-phenylsulfanyl-butyramide (120 mg, 0.42 mmol) using general procedure 4 and a reaction time of 1.5 h. Purification by column chromatography afforded the product (69 mg, 69%) as an oil. R_f (1:1 hexane/EtOAc): 0.46; δ ^{1}H NMR (400 MHz): 0.87 (3H, t, J=7.6 Hz, CH_3CH$_2$), 1.59–1.69 (1H, m, CH_AH$_B$Me), 1.71–1.84 (1H, m, CH$_A$$H_B$Me), 2.17 (3H, s, C$H_3$CO), 2.76–2.81 (1H, m, C$H$Et), 2.89 (1H, dd, J=11.1, 2.4 Hz, CH_AH$_B$S), 2.90 (1H, br s, OH), 3.14 (1H, dd, J=11.1, 3.9 Hz, CH$_A$$H_B$S), 3.87–3.92 (1H, m, C$H$OH), 7.17–7.22 (1H, m, Ar), 7.26–7.31 (2H, m, Ar), 7.35–7.40 (2H, m, Ar); δ ^{13}C NMR (100 MHz): 11.7 (CH_3CH$_2$), 22.6 (CH_2CH$_3$), 31.6 (CH_3CO), 39.1 (CH_2S), 57.5 (CHEt), 69.1 (CHOH), 126.7 (Ar–*C*), 129.1 (2C, Ar–*C*), 129.8 (2C, Ar–*C*), 134.8 (Ar–*C*, quaternary), 212.1 (CO); ν_{max} (neat): 3437.5 (br, O–H), 1784.3 (s, C=O); *m/z* (HRMS, GCT, FI): found 238.1038 ([M·]), $C_{13}H_{18}O_2S$ requires 238.1028; *anti*-isomer synthesised from the corresponding 2-ethyl-3-hydroxy-N-methoxy-N-methyl-4-phenylsulfanyl-butyramide (30 mg, 0.1 mmol) using general procedure 4 with a reaction time of 6 h. Purification by column chromatography (4:1 hexane/EtOAc) afforded the product (10 mg, 42%) as an oil. R_f (1:1 hexane/EtOAc): 0.44; δ ^{1}H NMR (500 MHz): 0.91 (3H, t, J=7.7 Hz, CH_3CH$_2$), 1.57–1.73 (2H, m, CH_2Me), 2.18 (3H, s, CH_3CO), 2.71–2.77 (1H, m, CHEt), 3.01 (1H, dd, J=13.7, 7.7 Hz, CH_AH$_B$S), 3.13 (1H, dd, J=13.7, 5.1 Hz, CH$_A$$H_B$S), 3.15 (1H, br s, O$H$), 3.78–3.85 (1H, m, C$H$OH), 7.21–7.25 (1H, m, Ar), 7.28–7.33 (2H, m, Ar), 7.37–7.41 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 11.7 (CH_3CH$_2$), 21.8 (CH_2CH$_3$), 31.3 (CH_3CO), 39.8 (CH_2S), 56.9 (CHEt), 70.4 (CHOH), 126.6 (Ar–*C*), 129.0 (2C, Ar–*C*), 130.0 (2C, Ar–*C*), 134.9 (Ar–*C*, quaternary), 213.2 (CO); ν_{max} (neat): 3413.9 (br, O–H), 1704.7 (s, C=O); *m/z* (GCT, FI): 238 ([M·], 100%); *m/z* (HRMS, autospec, CI$^+$): found 239.1106 ([M+H]$^+$), $C_{13}H_{19}SO_2$ requires 239.1106.

4.12.7. (±)-5-Hydroxy-4-methyl-6-phenylsulfanyl-hexan-3-one 3. Formed from (phenylthio)-acetaldehyde (447.5 mg, 2.9 mmol) and 3-pentanone (0.45 ml, 376 mg, 4.4 mmol) using general procedure 1. Purification by column chromatography (2:1 40–60 petrol/Et_2O) afforded the two diastereomers: *anti*-**3**: oil, (70 mg, 10.1%); R_f (2:1 40–60 petrol/Et_2O): 0.27; δ ^{1}H NMR (500 MHz): 1.04 (3H, t, J=7.2 Hz, CH_3CH$_2$), 1.15 (3H, d, J=7.3 Hz, CH_3CH), 2.38–2.47 (1H, m, CH_AH$_B$CH$_3$), 2.50–2.59 (1H, m, CH$_A$$H_BCH_3$), 2.88 (1H, dq, J=7.0, 7.2 Hz, CHMe), 2.98 (1H, dd, J=13.9, 8.5 Hz, CH_AH$_B$CHOH), 3.17 (1H, dd, J=13.9, 5.0 Hz, CH$_A$$H_B$CHOH), 3.18 (1H, d, J=5.5 Hz, OH), 3.76–3.83 (1H, m, CHOH), 7.20–7.54 (1H, m, Ar), 7.26–7.33 (2H, m, Ar), 7.37–7.41 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 7.3 (*C*H$_3$CH$_2$), 13.8 (*C*H$_3$CH), 35.9 (CH$_3$*C*H$_2$), 39.3 (*C*H$_2$S), 48.8 (CH$_3$*C*H), 71.9 (*C*HOH), 126.6 (Ar–*C*), 129.0 (2C, Ar–*C*), 129.8 (2C, Ar–*C*), 135.0 (Ar–*C*, quaternary), 215.6 (*C*=O); ν_{max} (KBr disk): 3339.6 (br, O–H), 1708.4 (s, C=O); *m/z* (autospec, CI$^+$): 221 ([M−OH]$^+$, 100%), 239 ([M+H]$^+$, 48%), 256 ([M+NH$_4$]$^+$, 15%); (HRMS, autospec, CI$^+$): found 239.1104 ([M+H]$^+$), $C_{13}H_{19}SO_2$ requires 239.1106; HPLC OD: 80% solvent A/20% solvent B: 7.4 min (5*R*, 4*S*), 8.4 min (5*S*, 4*R*); *syn*-**3**: oil, 375 mg, 54.3%); R_f (2:1 40–60 petrol/Et_2O): 0.23; δ ^{1}H NMR (500 MHz): 1.04 (3H, t, J=7.3 Hz, CH_3CH$_2$), 1.17 (3H, d, J=7.0 Hz, CH_3CH), 2.40–2.50 (1H, m, CH_AH$_B$CH$_3$), 2.52–2.61 (1H, m, CH$_A$$H_BCH_3$), 2.84 (1H, dq, J=4.5, 7.0 Hz, CHCH$_3$), 2.98 (1H, dd, J=13.9, 7.5 Hz, CH_AH$_B$CH$_3$S), 3.04 (1H, dd, J=13.9, 5.5 Hz), 3.00 (1H, d, J=3.0 Hz, OH), 3.98–4.02 (1H, m, CHOH), 7.20–7.25 (1H, m, Ar), 7.25–7.33 (2H, m, Ar), 7.37–7.40 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 8.0 (*C*H$_3$CH$_2$), 11.4 (*C*H$_3$CH), 35.7 (CH$_3$*C*H$_2$), 38.5 (*C*H$_2$S), 49.2 (CH$_3$*C*H), 70.0 (*C*HOH), 127.0 (Ar–*C*), 129.6 (2C, Ar–*C*), 130.1 (2C, Ar–*C*), 135.5 (Ar–*C*, quaternary), 215.8 (*C*=O); ν_{max} (neat): 3437.4 (br, O–H), 1704.0 (s, C=O); *m/z* (autospec, CI$^+$): 221 ([M−OH]$^+$, 100%), 239 ([M+H]$^+$, 60%); (HRMS, autospec, CI$^+$): found 239.1110, ([M+H]$^+$), $C_{13}H_{19}SO_2$ requires 239.1106.

4.12.8. 4-Hydroxy-5-phenylselenyl-pentan-2-one (±)-4. Formed from (phenylselenyl)-acetaldehyde (100 mg,

0.53 mmol) and acetone (0.06 ml, 0.80 mmol) using general procedure 1. Purification by column chromatography (1:1 hexane/EtOAc) afforded **4** (95 mg, 70%) as an oil. R_f (1:1 hexane/EtOAc): 0.30; δ ^{1}H NMR (400 MHz): 2.14 (3H, s, CH_3), 2.71 (1H, dd, J=17.5, 7.9 Hz, CH_AH$_B$CHO), 2.77 (1H, dd, J=17.5, 4.0 Hz, CH$_A$$H_B$CHO), 3.02 (1H, dd, J=12.7, 6.8 Hz, CH_AH$_B$Se), 3.06 (1H, dd, J=12.7, 5.9 Hz, CH$_A$$H_B$Se), 3.25 (1H, br s, O$H$), 4.12–4.21 (1H, m, C$H$) 7.25–7.30 (3H, m, Ar) 7.50–7.55 (2H, m, Ar); δ ^{13}C NMR (100 MHz): 30.7 (*C*H$_3$), 34.5 (*C*H$_2$Se), 48.8 (*C*H$_2$CO), 66.8 (*C*H), 127.3 (Ar–*C*, quaternary), 127.3 (Ar–*C*), 129.2 (2C, Ar–*C*), 132.7 (2C, Ar–*C*), 208.7 (*C*=O); ν_{max} (neat): 3422.8 (br, O–H), 1710.7 (s, C=O); *m*/*z* (HRMS, autospec, ESI$^+$) found 281.0061 ([M+Na]$^+$), $C_{11}H_{14}O_2SeNa$ requires 281.0057; HPLC OJ–H: 93% solvent A/7% solvent C: 24.2 min (*S*), 23.2 min (*R*).

4.12.9. 4-Hydroxy-5-methyl-5-phenylsulfanyl-hexan-2-one (±)-5. 2-Methyl-2-phenylsulfanyl-propionaldehyde (200 mg, 1.1 mmol) and acetone (0.22 ml, 3.2 mmol) using general procedure 1. Purification by column chromatography (2:1 hexane/EtOAc) afforded **5** (250 mg, 95%) as an oil. R_f (1:1 hexane/EtOAc): 0.34; δ ^{1}H NMR (400 MHz): 1.21 (3H, s, CH_3CMe) 1.26 (3H, s, CH_3CMe), 2.23 (3H, s, CH_3CO), 2.65 (1H, dd, J=16.5, 10.1 Hz, CH_AH$_B$CHO), 2.80 (1H, dd, J=16.5, 1.9 Hz, CH$_A$$H_B$CHO), 3.19 (1H, d, O$H$), 3.91 (1H, ddd, J=2.4, 2.4, 10.1 Hz, CHOH), 7.30–7.40 (3H, m, Ar), 7.50–7.55 (2H, m, Ar); δ ^{13}C NMR (100 MHz): 23.9 (*C*H$_3$CMe), 24.7 (*C*H$_3$CMe), 31.0 (*C*H$_3$CO), 44.9 (*C*H$_2$CO), 53.1 (*C*H$_2$S), 72.1 (*C*H), 128.8 (2C, Ar–*C*), 129.2 (Ar–*C*), 130.4 (Ar–*C*, quaternary), 137.5 (2C, Ar–*C*), 185.8 (*C*O); ν_{max} (neat): 3418.0 (br, O–H), 1710.9 (s, C=O); *m*/*z* (autospec, CI$^+$): 239 ([M+H]$^+$, 12%), 221 ([M−OH]$^+$, 100%); *m*/*z* (HRMS, autospec, CI$^+$): found 239.1109 ([M+H]$^+$) $C_{13}H_{19}SO_2$ requires 239.1106.

4.12.10. 4-Hydroxy-1-methylsulfanyl-4-phenyl-butan-2-one (±)-10. Formed from benzaldehyde (1 ml, 10 mmol) and methylthioacetone (1.5 ml, 15 mmol) using general procedure 1. The product was formed as a mixture (linear regioisomer **10**/branched-*syn* **13**/branched-*anti* **13** 15:15:14). Purification by column chromatography (4:1 hexane/EtOAc) afforded **10** (622 mg of 1:1 mix with *anti* regioisomer **13**, 15%) as an oil; linear isomer:R_f (1:1 hexane/EtOAc): 0.43; δ ^{1}H NMR (400 MHz): 2.04 (3H, s, SCH_3), 3.00 (1H, dd, J=17.2, 3.4 Hz, CH_AH$_B$CH), 3.09 (1H, dd, J=17.2, 9.0 Hz, CH$_A$$H_B$CH), 3.16 (2H, s, C$H_2$S), 3.19 (1H, br s, O$H$), 5.18 (1H, dd, J=3.4, 9.0 Hz, CHOH), 7.24–7.41 (5H, m, Ar); δ ^{13}C NMR (100 MHz): 15.6 (S*C*H$_3$), 43.6 (*C*H$_2$S), 48.6 (*C*H$_2$CH), 70.3 (*C*H), 125.7 (2C, Ar–*C*), 127.8 (Ar–*C*), 128.6 (2C, Ar–*C*), 142.7 (Ar–*C*, quaternary), 205.3 (*C*O); ν_{max} (neat): 3430.0 (br, O–H), 1700.5 (s, C=O); *m*/*z* (GCT, FI): found 209.0640 ([M·]), $C_{11}H_{13}O_2S$ requires 209.0636.

4.12.11. 4-Hydroxy-3-methylsulfanyl-4-phenyl-butan-2-one (±)-13. Formed from benzaldehyde (1 ml, 10 mmol) and methylthioacetone (1.5 ml, 15 mmol) using general procedure 1. The product was formed as a mixture (linear/*syn*/*anti* 15:15:14). Purification by column chromatography (4:1 hexane/EtOAc) afforded *anti*-**13** (622 mg of 1:1 mix with linear regioisomer **10**, 15%) as an oil and *syn*-**13** (301 mg, 14%) as an oil. *anti*-**13** (from mixture with linear regioisomer): R_f (1:1 hexane/EtOAc): 0.43; δ ^{1}H NMR (400 MHz): 1.82 (3H, CH_3S), 2.34 (3H, s, CH_3CO), 3.43 (1H, d, J=9.7 Hz, CHS), 3.46 (1H, br s, OH), 4.91 (1H, d, J=9.7 Hz, CHOH), 7.24–7.38 (5H, m, Ar); δ ^{13}C NMR (100 MHz): 13.3 (*C*H$_3$S), 28.0 (*C*H$_3$CO), 59.6 (*C*HS), 73.2 (*C*HOH), 126.9 (2C, Ar–*C*), 128.3 (Ar–*C*), 128.4 (2C, Ar–*C*), 140.8 (Ar–*C*, quaternary), 204.7 (CO); ν_{max} (neat): 3436.1 (br, O–H), 1700.2 (s, C=O); *m*/*z* (GCT, FI): found 209.0640 ([M·]), $C_{11}H_{13}O_2S$ requires 209.0636; *syn*-**13**: R_f (1:1 hexane/EtOAc): 0.46; δ ^{1}H NMR (400 MHz): 2.06 (3H, CH_3S), 2.13 (3H, s, CH_3CO), 3.28 (1H, br s, OH), 3.51 (1H, d, J=8.6 Hz, CHS), 4.97 (1H, d, J=8.6 Hz, CHOH), 7.25–7.40 (5H, m, Ar); δ ^{13}C NMR (100 MHz): 12.3 (*C*H$_3$S), 29.1 (*C*H$_3$CO), 60.5 (*C*HS), 69.8 (*C*HOH), 126.9 (2C, Ar–*C*), 128.2 (Ar–*C*), 128.4 (2C, Ar–*C*), 140.4 (Ar–*C*, quaternary), 202.7 (CO); ν_{max} (neat): 3448.3 (br, O–H), 1700.4 (s, C=O); *m*/*z* (GCT, FI): found 209.0634 ([M·]), $C_{11}H_{13}O_2S$ requires 209.0636.

4.12.12. 4-Hydroxy-6-(4-methoxy-phenyl)-1-methylsulfanyl-hex-5-en-2-one (±)-11. Formed from 4-methoxycinnamaldehyde (1.62 g, 10 mmol) and methylthioacetone (1.5 ml, 15 mmol) using general procedure 1. The product was formed as a mixture (**11**/*syn*-**14**/*anti*-**14** 69:8:23). Purification by column chromatography afforded **11** (1.1 g of mix with *anti* product, 37%) as an oil; R_f (1:1 hexane/EtOAc): 0.38; δ ^{1}H NMR (400 MHz): 2.06 (3H, s, CH_3S), 2.89 (1H, dd, J=15.2, 4.8 Hz, CH_AH$_B$CH), 2.93 (1H, dd, J=15.2, 7.3 Hz, CH$_A$$H_B$CH), 3.20 (2H, s, C$H_2$S), 3.79 (3H, s, C$H_3$O), 4.71–4.76 (1H, m, C$H$OH), 6.07 (1H, dd, J=6.3, 15.9 Hz, CH=CHAr), 6.57 (1H, d, J=15.9 Hz, CHAr), 6.80 (2H, d, J=8.7 Hz, Ar), 7.26 (2H, d, J=8.8 Hz, Ar); δ ^{13}C NMR (100 MHz): 15.6 (*C*H$_3$S), 43.7 (*C*H$_2$S), 46.9 (*C*H$_2$CH), 55.2 (*C*H$_3$O), 69.0 (*C*H), 114.0 (2C, Ar–*C*), 127.7 (2C, Ar–*C*), 127.9 (*C*H=CHAr), 129.2 (Ar–*C*, quaternary), 129.9 (*C*HAr), 159.3 (Ar–*C*, quaternary), 204.9 (*C*O); ν_{max} (neat):1700.4 (s, C=O), 1606.3 (s, C=C); *m*/*z* (GCT, FI): 266.0987 ([M·]), $C_{14}H_{18}O_3S$ requires 266.0977; HPLC OD: 85% solvent A/15% solvent C: 17.3 min (*S*), 19.1 min (*R*).

4.12.13. 4-Hydroxy-6-(4-methoxy-phenyl)-3-methylsulfanyl-hex-5-en-2-one (±)-14. Formed from 4-methoxycinnamaldehyde (1.62 g, 10 mmol) and methylthioacetone (1.5 ml, 15 mmol) using general procedure 1. The product was formed as a mixture (**11**/*syn*-**14**/*anti*-**14** 69:8:23). Purification by column chromatography afforded *anti*-**14** (1.1 g of mix with linear regioisomer, 4%) as an oil and *syn*-**14** (213 mg, 8%) as an oil; *anti*-**14**; R_f (1:1 hexane/EtOAc): 0.38; δ ^{1}H NMR (400 MHz): 1.99 (3H, s, CH_3S), 2.36 (3H, s, CH_3CO), 3.29 (1H, d, J=9.1 Hz, CHS), 3.79 (3H, s, CH_3O), 4.61 (1H, app t, J=7.9 Hz, CHOH), 6.20 (1H, dd, J=6.8, 15.8 Hz, CHCHAr), 6.63 (1H, d, J=15.9 Hz, CHAr), 6.84 (2H, d, J=8.7 Hz, Ar), 7.33 (2H, d, J=8.7 Hz, Ar); δ ^{13}C NMR (100 MHz): 12.9 (*C*H$_3$S), 28.0 (*C*H$_3$C), 55.3 (*C*H$_3$O), 58.1 (*C*HS), 71.3 (*C*HOH), 114.0 (2C, Ar–*C*), 125.9 (*C*H=CHAr), 128.0 (2C, Ar–*C*), 129.2 (Ar–*C*, quaternary), 131.8 (*C*HAr), 159.4 (Ar–*C*, quaternary), 204.5 (*C*O); ν_{max} (neat):1700.1 (s, C=O), 1606.8 (s, C=C); *m*/*z* (GCT, FI): 266.0965 ([M·]), $C_{14}H_{18}O_3S$ requires 266.0977; *syn*-**14**: R_f (1:1 hexane/EtOAc): 0.40; δ ^{1}H NMR (400 MHz): 2.06 (3H, s, CH_3S), 2.32 (3H, s, CH_3C),

3.34 (1H, d, J=8.3 Hz, C*H*S), 3.79 (3H, s, CH_3O), 4.58 (1H, app t, J=6.8 Hz, C*H*OH), 6.04 (1H, dd, J=6.6, 15.9 Hz, C*H*=CHAr),6.65 (1H, d, J=15.8 Hz, C*H*Ar), 6.84 (2H, d, J=8.8 Hz, Ar), 7.31 (2H, d, J=8.7 Hz, Ar); δ ^{13}C NMR (100 MHz): 12.4 (*C*H_3S), 29.0 (*C*H_3C), 55.3 (*C*H_3O), 59.4 (*C*HS), 68.8 (*C*HOH), 113.9 (2C, Ar–*C*), 125.1 (*C*H=CHAr), 127.8 (2C, Ar–*C*), 129.1 (Ar–*C*, quarternary), 132.3 (*C*HAr), 159.5 (Ar–*C*, quarternary), 203.0 (*C*O); ν_{max} (neat):1699.7 (s, C=O), 1606.7 (s, C=C); *m/z* (HRMS, autospec, ESI$^-$): 265.0894 ([M−H]$^-$), $C_{14}H_{17}O_3S$ requires 265.0898.

4.12.14. (*R*)-3-Hydroxy-4-phenylsulfanyl-butyric acid ethyl ester 16. To baker's yeast (42 g) in distilled water (420 ml) was added sucrose (50.4 g). The mixture was allowed to stir for 30 min and then 3-oxo-4-phenylsulfanyl-butyric acid ethyl ester (2 g, 8.3 mmol) in EtOH (42 ml) added. The mixture was allowed to stir for 18 h and then the mixture was filtered through celite. The celite was washed with EtOAc (100 ml) and the layers separated. The aqueous layer was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-**16** (1.08 g, 54%) as an oil. R_f (4:1 hexane/EtOAc): 0.50; δ ^{1}H NMR (500 MHz): 1.27 (3H, t, J=7.2 Hz, CH_3), 2.58 (1H, dd, J=16.4, 8.1 Hz, CH_AH$_B$CHO), 2.67 (1H, dd, J=16.4, 4.1 Hz, CH$_A$$H_B$CHO), 3.07 (1H, dd, J=13.8, 7.0 Hz, CH_AH$_B$S), 3.11 (1H, dd, J=13.8, 5.7 Hz), 3.21 (1H, d, J=3.9 Hz, O*H*), 4.11–4.17 (1H, m, C*H*OH), 4.17 (2H, q, J=7.0 Hz, CH_2CH$_3$), 7.19–7.24 (1H, m, Ar), 7.28–7.33 (2H, m, Ar), 7.37–7.42 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 14.0 (*C*H$_3$), 39.8 (*C*H$_2$CHO), 40.1 (*C*H$_2$S), 60.8 (*C*H$_2$CH$_3$), 66.5 (*C*HOH), 126.5 (Ar–*C*), 129.0 (Ar–*C*, 2C), 129.7 (Ar–*C*, 2C), 135.1 (Ar–*C*, quarternary), 172.0 (*C*HO); ν_{max} (neat): 3458.4 (br, O–H), 1729.5 (s, C=O); *m/z* (autospec, CI$^+$): 223 ([M−OH]$^+$, 100%), 241 ([M+H]$^+$, 21%), 258 ([M+NH$_4$]$^+$, 34%); (HRMS, GCT, FI): found 240.0821 ([M·]), $C_{12}H_{16}SO_3$ requires 240.0820; $[\alpha]_D$=+5.8 (c=10, CHCl$_3$); ee=58%.

4.12.15. 3-Hydroxy-N-methoxy-N-methyl-4-phenyl-sulfanyl-butyramide (*R*)-15. Synthesised from 3-hydroxy-4-phenylsulfanyl-butyric acid ethyl ester **16** (1 g, 4.16 mmol) using general procedure 2. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-**15** (863 mg, 81%) as an oil. R_f (1:1hexane/EtOAc): 0.16; δ ^{1}H NMR (500 MHz): 2.65 (1H, dd, J=16.8, 8.5 Hz, CH_AH$_B$CHO), 2.86 (1H, dd, J=16.8, 2.2 Hz CH$_A$$H_B$CHO), 3.09 (1H, dd, J=13.4, 6.7 Hz, CH_AH$_B$S), 3.17 (1H, dd, J=13.4, 5.0 Hz), 3.19 (3H, s, CH_3N), 3.67 (3H, s, CH_3O), 3.97 (1H, d, J=3.0 Hz, O*H*), 4.14–4.22 (1H, m, C*H*OH), 7.18–7.22 (1H, m, Ar), 7.27–7.32 (2H, m, Ar), 7.39–7.42 (2H, m, Ar); δ ^{13}C NMR (125 MHz): 31.7 (*C*H$_3$N), 36.6 (*C*H$_2$CO), 39.6 (*C*H$_2$S), 61.2 (*C*H$_3$O), 66.9 (*C*HOH), 126.2 (Ar–*C*), 128.9 (Ar–*C*, 2C), 129.3 (Ar–*C*, 2C), 135.5 (Ar–*C*, quarternary), 172.9 (*C*=O); ν_{max} (neat): 3430.1 (br, O–H), 1643.7 (s, C=O); *m/z* (autospec, CI$^+$): 238 ([M−OH]$^+$, 52%), 256 ([M+H]$^+$, 100%); (HRMS, GCT, CI$^+$): found 256.1018 ([M+H]$^+$), $C_{12}H_{18}SO_3N$ requires 256.1007. Analysis for $C_{12}H_{17}SO_3N$: calculated C: 56.45, H: 6.71, N: 5.49; found C: 56.61, H: 6.87, N: 5.53; $[\alpha]_D$=+39.3 (c=10, CHCl$_3$). ee=58%.

4.12.16. 4-Hydroxy-5-phenylsulfanyl-pentan-2-one (*R*)-1. Synthesised from 3-hydroxy-N-methoxy-N-methyl-4-phenylsulfanyl-butyramide (*R*)-**15** (255 mg, 1 mmol) using general procedure 4. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-**1** (176 mg, 84%) as an oil. Analysis as described above for the racemic compound. $[\alpha]_D$=+8.6 (c=10, CHCl$_3$). ee=58%; HPLC OD: 93% solvent A/7% solvent B: 15.5 min (*S*), 16.7 min (*R*).

4.12.17. 2-Hydroxy-1-phenylsulfanyl-heptan-4-one (*R*)-2. Magnesium turnings (438 mg, 18 mmol) were stirred vigorously overnight. Dry THF (3 ml) was added. Iodine (a single crystal) was added and a solution of propyl bromide (0.55 ml, 6 mmol) in dry THF (3 ml) was added dropwise. The mixture was allowed to stir until it cooled to room temperature. The mixture was then added to a solution of amide (**22**) (255 mg, 1 mmol) in dry THF (2 ml) at −40 °C via cannula. The mixture was allowed to warm to 0 °C over 30 min and allowed to stir for a further 1.5 h. Saturated ammonium chloride solution (15 ml) was added and the mixture extracted with DCM. The organic fractions were combined, dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-(**c4**) (123 mg, 52%) as an oil. Analysis as described above for the racemic compound. $[\alpha]_D$=+14.4 (c=10, CHCl$_3$). ee=58%; HPLC OD: 85% solvent A/15% solvent B: 12.2 min (*S*), 10.2 min (*R*).

4.12.18. 4-Hydroxy-4-phenyl-butan-2-one (*R*)-17. To benzaldehyde (2 ml, 20 mmol) in DMSO (160 ml) and acetone (40 ml) was added (*L*)-proline (690 mg, 6 mmol). The mixture was allowed to stir for 3 h. Water (100 ml) was added and the mixture extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-**17** (920 mg, 28%) as an oil; R_f (1:1 hexane/EtOAc): 0.38; δ ^{1}H NMR (400 MHz): 2.20 (3H, s, CH_3), 2.83 (1H, dd, J=17.3, 3.3 Hz, CH_AH$_B$), 2.89 (1H, dd, J=17.3, 9.1 Hz, CH$_A$$H_B$), 3.33 (1H, br s, O*H*), 5.16 (1H, dd, J=3.3, 9.1 Hz, C*H*), 7.26–7.37 (5H, m, Ar); δ ^{13}C NMR (100 MHz): 30.8 (*C*H$_3$), 52.0 (*C*H$_2$), 69.8 (*C*H), 125.6 (2C, Ar–*C*), 127.7 (Ar–*C*), 128.6 (2C, Ar–*C*), 142.7 (Ar–*C*, quarternary), 209.1 (*C*O); ν_{max} (neat): 3448.9 (br, O–H), 1708.1 (s, C=O); *m/z* (HRMS, GCT, FI): found: 164.0833 ([M·]), $C_{10}H_{12}O_2$ requires 164.0837; $[\alpha]_D$=+45.1 (c=10, CHCl$_3$). ee=71%.

4.12.19. (*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-4-phenyl-butan-2-one. Synthesised from 4-hydroxy-4-phenyl-butan-2-one (850 mg, 5.2 mmol) using general procedure 5. Purification by column chromatography (4:1 hexane/DCM) afforded the desired compound (1.29g, 90%) as an oil. R_f (1:1 hexane/Et$_2$O): 0.70; δ ^{1}H NMR (400 MHz): −0.18 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3), 0.85 (9H, s, C(CH_3)$_3$), 2.55 (1H, dd, J=14.9, 4.0 Hz, CH_AH$_B$), 2.95 (1H, dd, J=14.9, 8.9 Hz, CH$_A$$H_B$), 5.16 (1H, dd, J=4.0, 8.8 Hz, C*H*), 7.22–7.36 (5H, m, Ar); δ ^{13}C NMR (100 MHz): −5.3 (Si*C*H$_3$), −4.7 (Si*C*H$_3$), 18.1 (Si*C*(CH$_3$)$_3$), 25.7 (3C, C(*C*H$_3$)$_3$), 31.8 (*C*H$_3$CO), 54.4 (CH_2), 71.9 (*C*H), 125.8 (2C, Ar–*C*), 127.4 (Ar–*C*), 128.3 (2C, Ar–*C*), 144.4

(Ar–*C*, quarternary), 207.3 (CO); ν_{max} (neat): 1720.6 (s, C=O); *m/z* (GCT, CI$^+$): 279 ([M+H]$^+$, 7%), 221 ([M−C_4H_9]$^+$, 15%), 164 ([M−OTBS+NH_3]$^+$, 33%), 147 ([M−OTBS]$^+$, 100%); $[\alpha]_D$=+65.9 (*c*=10, $CHCl_3$).

4.12.20. 4-(*tert*-Butyl-dimethyl-silanyloxy)-1-chloro-4-phenyl-butan-2-one (*R*)-18. To 4-(*tert*-butyl-dimethyl-silanyloxy)-4-phenyl-butan-2-one (556 mg, 2 mmol) in dry DCM (30 ml) at 0 °C was added DIPEA (1.7 ml, 12 mmol). To this was added TMSOTf (1.5 ml, 4 mmol) dropwise. The mixture was allowed to stir at 0 °C for 1.5 h. The reaction was then cautiously quenched with sat. NH_4Cl (50 ml). The mixture was extracted with hexane, the organic fractions combined, dried over Na_2SO_4, filtered under suction and the solvent removed in vacuo. The residue was taken up in dry DCM (2 ml) and added dropwise to a solution of SO_2Cl_2 (0.19 ml, 2.4 mmol) in DCM (10 ml) at −78 °C. The mixture was allowed to warm to room temperature over 30 min and allowed to stir at room temperature for 30 min. The reaction was then quenched with ice-cold water (15 ml). The mixture was extracted with DCM, the organic layers combined, dried over $MgSO_4$, filtered under suction and the solvent removed in vacuo. Purification by column chromatography (4:1 hexane/DCM) afforded (*R*)-**18** (221 mg, 35%) as an oil. R_f (1:1 hexane/DCM): 0.32; δ ^{1}H NMR (400 MHz): −0.18 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3), 0.85 (9H, s, SiC(CH_3)$_3$), 2.65 (1H, dd, *J*=14.6, 3.8 Hz, CH_AH$_B$CH), 3.05 (1H, dd, *J*=14.6, 9.2 Hz, CH$_A$-H_BCH), 4.10 (1H, dd, *J*=16.0 Hz, CH_AH$_B$Cl), 4.19 (1H, dd, *J*=16.0 Hz, CH$_A$$H_B$Cl), 5.17 (1H, dd, *J*=3.8, 9.1 Hz, C*H*), 7.24–7.37 (5H, m, Ar); δ ^{13}C NMR (100 MHz): −5.3 (Si*C*H$_3$), −4.8 (Si*C*H$_3$), 18.0 (Si*C*(CH$_3$)$_3$), 25.7 (3C, SiC(*C*H$_3$)$_3$), 50.0 (*C*H$_2$Cl), 50.7 (*C*H$_2$CH), 72.2 (*C*H), 125.7 (2C, Ar–*C*), 127.7 (Ar–*C*), 128.4 (2C, Ar–*C*), 143.7 (Ar–*C*, quarternary), 200.3 (CO); ν_{max} (neat):1736.5 (s, C=O); *m/z* (autospec, CI$^+$): 315 ([M+H]$^+$ ^{37}Cl, 1%) 313 ([M+H]$^+$ ^{35}Cl, 2.5%), 257 ([M−C(CH$_3$)$_3$]$^+$ ^{37}Cl, 18%), 255 ([M−C(CH$_3$)$_3$]$^+$ ^{35}Cl, 49%), 183 ([M−OTBS]$^+$ ^{37}Cl, 35%), 181 ([M−OTBS]$^+$ ^{35}Cl, 100%); *m/z* (autospec, CI$^+$): 313.1389 ([M+H]$^+$(^{35}Cl)), $C_{16}H_{26}O_2SiCl$ requires 313.1391; $[\alpha]_D$=+78.7 (*c*=10, $CHCl_3$).

4.12.21. (*R*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-1-methylsulfanyl-4-phenyl-butan-2-one. Synthesised from 4-(*tert*-butyl-dimethyl-silanyloxy)-1-chloro-4-phenyl-butan-2-one (130 mg, 0.44 mmol) using general procedure 7. Purification by column chromatography (4:1 hexane/DCM) afforded the desired compound (137 mg, 96%) as an oil. R_f (1:1 hexane/DCM): 0.25; δ ^{1}H NMR (400 MHz): −0.18 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3), 0.85 (9H, s, SiC(CH_3)$_3$), 2.00 (3H, s, CH_3S), 2.73 (1H, dd, *J*=15.0, 4.2 Hz, CH_AH$_B$CH), 3.13 (1H, dd, *J*=15.0, 8.8 Hz, CH$_A$-H_BCH), 3.14 (1H, d, *J*=13.9 Hz, CH_AH$_B$S), 3.21 (1H, d, *J*=13.9 Hz, CH$_A$$H_B$S), 5.18 (1H, dd, *J*=4.2, 8.8 Hz, C*H*), 7.21–7.40 (5H, m, Ar); δ ^{13}C NMR (100 MHz): −5.2 (Si*C*H$_3$), −4.7 (Si*C*H$_3$), 15.4 (S*C*H$_3$), 18.0 (*C*(CH$_3$)$_3$), 25.7 (3C, C(*C*H$_3$)$_3$), 44.5 (*C*H$_3$SMe), 51.1 (*C*H$_2$CH), 72.1 (*C*H), 125.8 (2C, Ar–*C*), 127.5 (Ar–*C*), 128.4 (2C, Ar–*C*), 144.2 (Ar–*C*, quarternary), 203.4 (*C*O); ν_{max} (neat):1708.7 (s, C=O); *m/z* (GCT, FI): 324.1592 ([M·]), $C_{17}H_{28}O_2SiS$ requires 324.1579; $[\alpha]_D$=+77.5 (*c*=10, $CHCl_3$).

4.12.22. 4-Hydroxy-1-methylsulfanyl-4-phenyl-butan-2-one (*R*)-10. Synthesised from 4-(*tert*-butyl-dimethyl-silanyloxy)-1-methylsulfanyl-4-phenyl-butan-2-one (130 mg, 0.37 mmol) using general procedure 6. Purification by column chromatography (4:1 hexane/EtOAc) afforded (*R*)-**10** (40 mg, 66%) as an oil. Analysis as described above for the racemic compound. $[\alpha]_D$=+43.7 (*c*=10, $CHCl_3$); HPLC OD: 90% solvent A/10% solvent B: 15.6 min (*S*), 16.7 min (*R*).

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