Diastereoselective Sulfur Oxidation of 2-Thio-3-Chloroacrylamides

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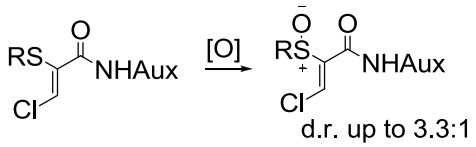
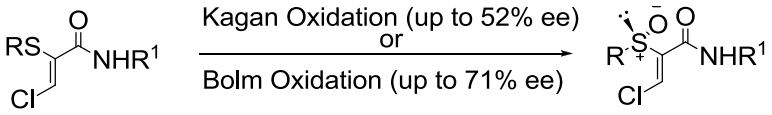


Abstract:

Diastereoselective sulfur oxidation in 2-thio-3-chloroacrylamides is described. A range of chiral amine auxiliaries were incorporated in the β-chloroacrylamide, and the efficiency with which the stereochemistry was relayed to the sulfur centre during sulfoxidation was investigated. Diastereomeric ratios of up to 3.3:1 were achieved.

Introduction

The asymmetric synthesis of sulfoxides has received particular attention in recent years as the sulfoxide moiety has been shown to provide excellent stereochemical control as a chiral auxiliary.[1-5] Furthermore, many enantiopure sulfoxides are known to have significant biological activity.[6-8] Several methods are currently available for the preparation of optically active sulfoxides.[9-16] We have recently described the enantioselective sulfur oxidation of the β-chloroacrylamides, with enantioselectivities of up to 52% ee achieved using the Kagan oxidation and up to 71% ee when the Bolm oxidation is employed (Scheme 1).[17]



Scheme 1

The diastereoselective oxidation of chiral sulfides using achiral oxidants has also been described by several research groups.[18-25] The basic principle of diastereoselective oxidation is to exploit the proximity of a defined chiral centre to relay stereochemistry to the newly formed sulfoxide. Steric interactions or neighbouring group participation accounts for the diastereoselectivity achieved.[26]

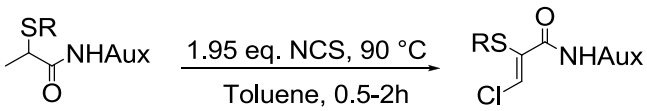
As the Kagan and Bolm methods led to limited success in the asymmetric sulfur oxidation of the β-chloroacrylamides,[17] the diastereoselective sulfur oxidation of the β-chloroacrylamides was investigated in detail during the current study. A range of chiral amine auxiliaries were incorporated in the β-chloroacrylamide, and the efficiency with which the stereochemistry was relayed to the sulfur centre during sulfoxidation was investigated. While the diastereomeric ratios achieved are modest, the resulting sulfoxides have significant synthetic potential, for example as Michael acceptors, dienophiles or dipolarophiles.[27,28]

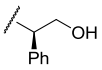
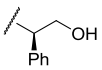
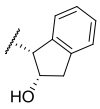
Results and Discussion

Preparation of the sulfides

Treatment of a series of α-thioamides with *N*-chlorosuccinimide resulting in the efficient stereoselective transformation to the analogous α-thio-β-chloroacrylamides has been described.[29-31] A variety of α-thioamides bearing chiral amide auxiliaries were similarly transformed to the analogous β-chloroacrylamides by reaction with NCS (typically 1.95 equivalents at 90 °C), with yields following chromatographic purification ranging from 29-76%; Table 1 summarises the results.

Table 1 Synthesis of β-chloroacrylamides bearing chiral amide auxiliaries



Sulfide	R	Aux	*Z*/*E*	β-Cl	% efficiency[a]	% yield[b]	$[\alpha]_{20}^{D}$ [c]
1[d]	Bn		*Z*	**(*R*)-11**	70	61	66.5
2[d]	Bn		*Z*	**(*R*)-12**	40	32	–54.2
3[d]	Bn		*Z*	**(*S*)-13**	35	51	–30.0
4[d]	Bn		*Z*	**(*S*)-14**	36	29	106.0
5[e]	Ph		*Z*	**(*R*)-15**	56	47	6.4
6[d]	Ph		*Z*	**(*R*)-16**	41	41	64.5
7[d]	Ph		*Z*	**17**	26	47	60.1
8[d]	Ph		*Z*	**(*S*)-18**	20	34	84.3
9[f]	Ph		*Z*	**(*S*)-19**	28	44	–67.7

10[d]	Ph		*Z*	**(*R*)-20**	96	76	92.9

a) Estimated by integration of the β-H signal in the ^{1}H NMR of the crude product. The remaining material is a complex mixture of unidentified material.
b) Yield after chromatography on silica gel.
c) For details, see experimental. An interesting effect was observed for the optical rotation values; for the auxiliaries bearing a hydroxyl group on the amide, the sign of the optical rotation measurement was opposite for the benzylthio- and phenylthio derivatives.
d) Equimolar mixture of diastereomers.
e) 1 : 1.40 mixture of diastereomers.
f) 1 : 1.22 mixture of diastereomers.

The β-chloroacrylamides **11**−**20** were synthesised in toluene by reacting the corresponding α-thioamide with 1.95 equivalents of NCS at 90 °C. The presence of a hydroxyl group on the amide appears to have a significant impact on the efficiency of the transformation, with poor efficiency observed on transformation of the α-thioamides **2**, **4,** and **7**−**9** relative to analogous derivatives without hydroxyl groups. On removal of the hydroxyl group a substantial increase in the efficiency was observed; for example, sulfides **9** and **10** differ only in the presence of a primary hydroxyl group, and on reaction with NCS under identical conditions there is a dramatic difference in the efficiency of the transformation to the β-chloroacrylamides (28% with **9** and 96% with **10).** The reaction mixtures from the amides bearing the hydroxyl groups were complex; no other significant identifiable product was isolated, but all of the starting material had been consumed.

Information on the conformation of the hydroxylated β-chloroacrylamides, and in particular, the hydrogen bonding patterns, was of interest as this may aid in explaining the preferred approach of the oxidant in subsequent diastereoselective oxidations. The conformation of **16** in the solid state was determined by single crystal X-ray diffraction after recrystallisation from dichloromethane/pentane (Figure 1).

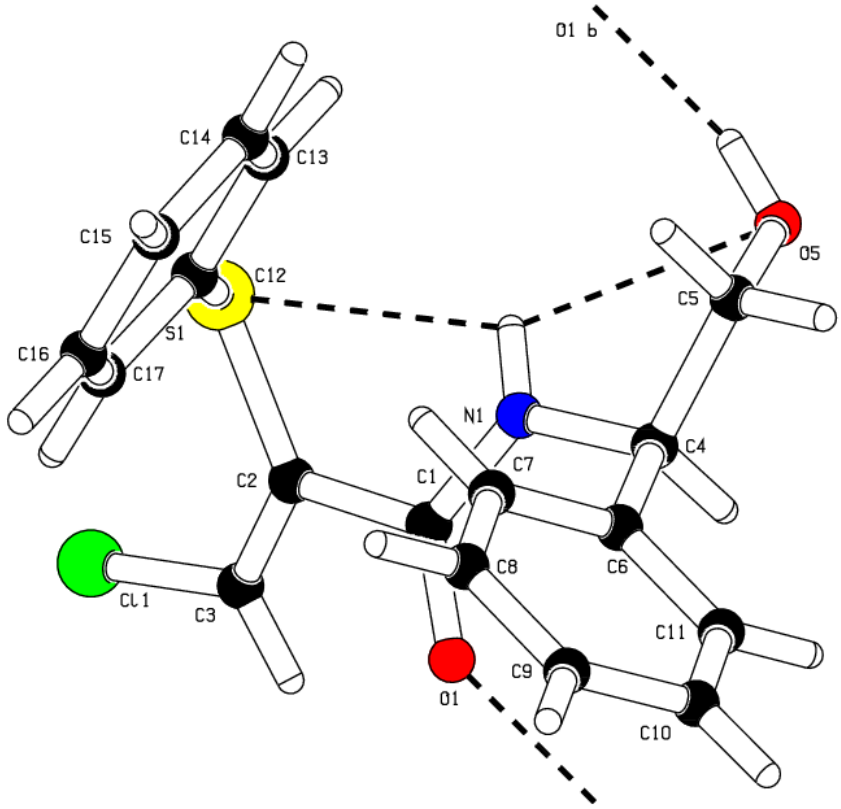


Figure 1 X-Ray Structure of ***16***

Examination of the resulting structure revealed some very interesting features. Firstly, the structure confirms the *Z*-stereochemistry of the hydroxylated β-chloroacrylamide **16**. Notably, an unexpected intramolecular attractive edge-to-face CH-π aromatic interaction was also evident, leading to a crowded conformation with the benzene rings in a T-shaped orientation. The angle between the benzene ring planes is 87.4°. The edge hydrogen atom on the benzene ring of the phenylglycinol moiety (labelled H7) is projected into the face of the phenylthio ring at a close-contact perpendicular distance of 2.69 Å, with a H7-to-centroid distance of 2.70 Å and offset by 0.18 Å from the benzene ring centre. These values are within the range of those normally observed for edge-to-face interactions.[32]

Edge-to-face interactions between aromatic rings were first reported in 1958 by Cox *et al.* in single crystals of benzene.[33] Influential work by Burley and Petsko established the importance of edge-to-face interactions between aromatic rings in determining the tertiary and quaternary crystalline structure of peptides and proteins.[34,35] Edge-to-face interactions have since been cited as a structure-determining factor in many examples of molecular recognition.[36-39] Jennings *et al.* were the first to identify an intramolecular edge-to-face

interaction in a simple synthetic acyclic organic molecule in both solution and the solid state.[32]

The hydrogen bonding network present in the solid state of **16** is depicted in Figure 1; intramolecular hydrogen bonds exist between the amide proton and the oxygen of the hydroxyl group (with a bond length of 2.56 Å) and between the amide proton and the sulfur atom (with a bond length of 2.74 Å). An intermolecular hydrogen bond between the hydroxyl proton and the carbonyl group is also evident, with a bond length of 1.91 Å.

Based on this structural analysis, a similar intramolecular hydrogen bond between the amide proton and the oxygen of the hydroxyl group can be envisaged in the related hydroxylated β-chloroacrylamides (Figure 2), thereby locating the 2′- *t*-butyl, phenyl or benzyl substituent over one face of the vinyl sulfide and thus impacting on the diastereofacial approach of the subsequent oxidation.

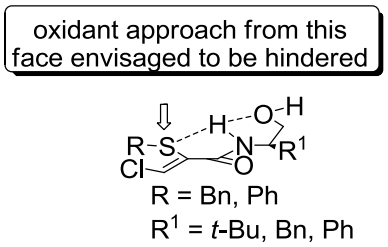
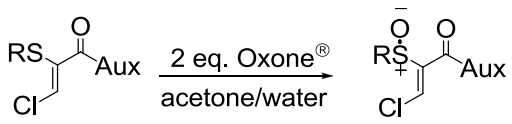


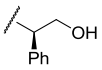
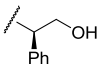
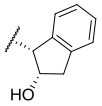
Figure 2 Oxidant Approach to β-Chloroacrylamides

Diastereoselective Oxidation

The diastereoselective sulfur oxidation of a range of β-chloroacrylamides containing some simple chiral amide auxiliaries was next investigated, with the results summarised in Table 2. All oxidations were conducted using 2 equivalents of Oxone® in acetone and water at room temperature.

Table 2 Diastereoselective Oxidation of the β-Chloroacrylamides



entry	β-Cl	R	Aux	sulfoxide	d.r.[a]	%de[a]	% yield[b]	$[\alpha]_{20}^{D}$ [c]
1	**11**	Bn		**21**	1.3 : 1	13	78[d]	–179.0[f] & 323.3[g]
2	**12**	Bn		**22**	1.8 : 1	29	74[d]	–67.5[f] & 122.6[g]
3	**16**	Ph		**23**	2.2 : 1	38	50[d]	–139.5[h] & –65.0[i]
4	**13**	Bn		**24**	1.1 : 1	5	85[e]	–1.4[j]
5	**18**	Ph		**25**	1.1 : 1	5	95[e]	–30.7[j]
6	**17**	Ph		**26**	1.6 : 1	23	89[d]	–66.4[j] & 99.3[i]
7	**14**	Bn		**27**	3.3 : 1	53	85[d]	193.7[f] & –123.5[g]
8	**19**	Ph		**28**	2.8 : 1	47	30[d]	127.2[h] & –109.3[i]
9	**20**	Ph		**29**	1.1 : 1	5	85[e]	–52.1[j]

a) Determined by integration of the ^{1}H NMR spectrum of the crude product.
b) Combined yield after chromatography unless otherwise stated.
c) For details, see experimental.
d) The sulfoxide diastereomers were separable by chromatography on silica gel.
e) As the ^{1}H NMR spectrum of the crude product was very clean, no further purification was necessary.
f) Less polar, major diastereomer.
g) More polar, minor diastereomer.
h) Less polar, minor diastereomer.

i) More polar, major diastereomer.
j) Mixture of diastereomers.

Oxidation of the α-methylbenzylamide derived β-chloroacrylamide **11** led to a sulfoxide **21** with diastereomeric ratio of 1.3:1, indicating that simple steric effects do not lead to high diastereoselection. The introduction of a hydroxyl group in the phenylglycinol derived β-chloroacrylamides **12** and **16** allows the potential for conformational control through hydrogen bonding to the nitrogen or carbonyl group, and moderate diastereoselection was achieved; one of the faces of the β-chloroacrylamide is sterically protected due to the position of the phenyl group on the auxiliary. When the phenyl group is moved further away from the stereogenic centre in the phenylalaninol derivatives **13** and **18**, the diastereoselection dramatically decreases as the introduction of the extra CH_2 group introduces more conformational flexibility into the structure and the phenyl group has less impact on the reaction site. Employment of the aminoindanol substituted β-chloroacrylamide **17**, a conformationally constrained analogue of phenylglycinol, resulted in a slight decrease in the selectivity to afford a diastereomeric ratio of **26** of 1.6:1, but incorporation of the more sterically demanding *t*-leucinol as a chiral auxiliary in **14** and **19** led to a significant increase, with a diastereomeric ratio of 3.3:1 achieved for the *S*-benzyl derived sulfoxide **27**. To confirm that the hydroxy group is critical, the diastereoselection in the oxidation of **20**, in which the *t*-butyl group was maintained and the hydroxy group was removed, was studied and the stereoselectivity decreased dramatically to just 5% de (Figure 3). Interestingly, the diastereoselection in the *S*-benzyl and *S*-phenyl series is very similar; comparing entries 2 & 3 and entries 7 & 8 in Table 2, slightly higher diastereocontrol is observed in the phenylalaninol series with the *S*-phenyl substituent, while in the *t*-leucinol series the *S*-benzyl derivative results in slightly higher diastereocontrol.

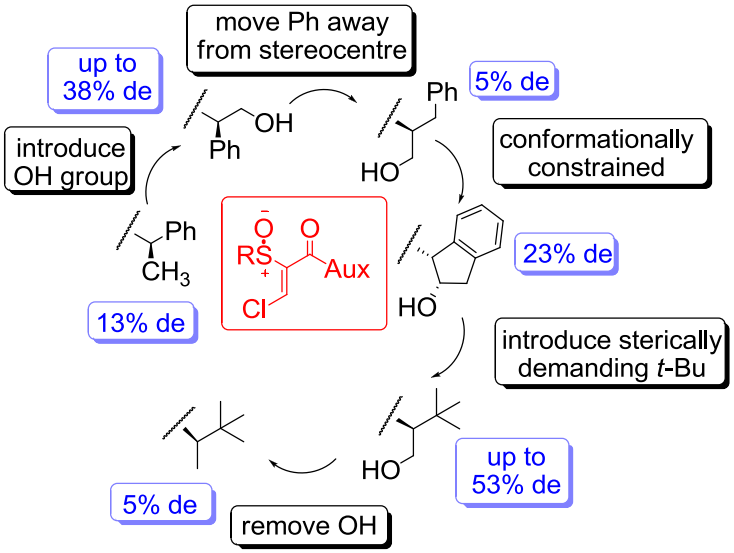


Figure 3 Effect of Amide Auxiliary on Diastereoselective Sulfur Oxidation

While there is no structural data confirming the relative stereochemistry in the hydroxylated derivatives, an X-ray crystal structure has been determined of one of the compounds bearing the α-methylbenzylamide auxiliary. Thus, the diastereomers **21a** & **21b** were readily separated by chromatography and the minor diastereomer **21b** (diastereomerically pure by ^{1}H NMR spectroscopy) led to a crystal suitable for diffraction studies after recrystallisation from ethanol. The resulting crystal structure confirms the *Z*–stereochemistry of the β-chloroacrylamide and established the configuration at the sulfur centre as (*R*) (Figure 4). Also, an intramolecular hydrogen-bond exists from the amide proton to the oxygen atom of the sulfoxide to form a six-membered ring, with a bond length of 2.06 Å.

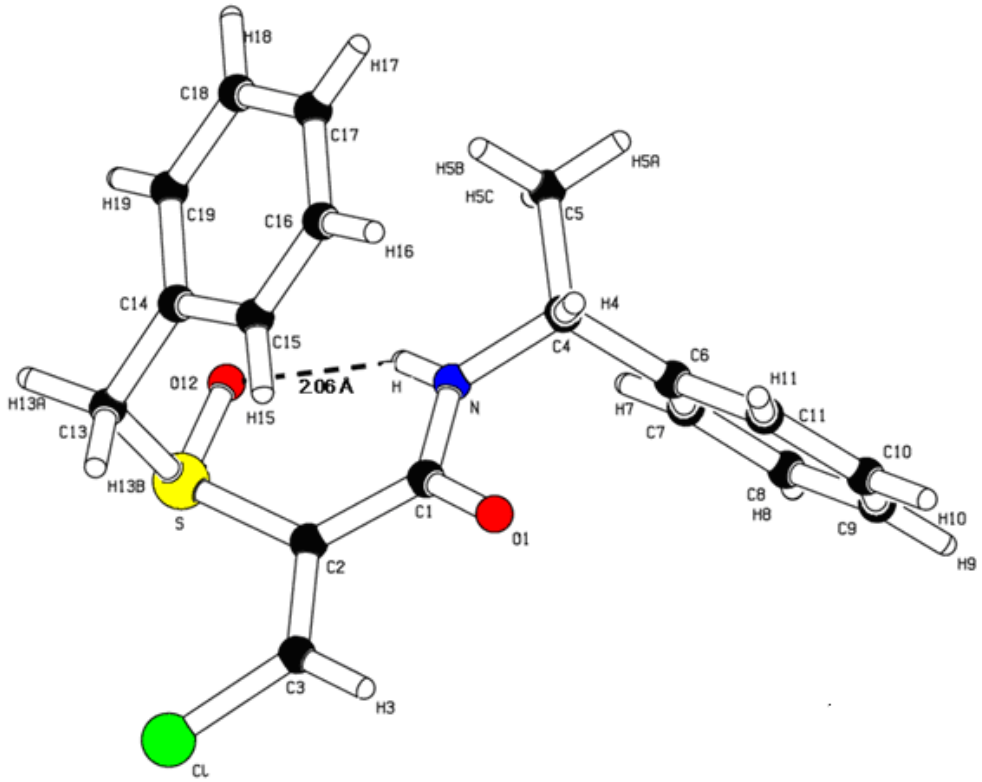


Figure 4 X-Ray Structure of Minor Diastereomer ***21b***

For the β-chloroacrylamides **12**−**14** and **16**−**19** with hydroxyl groups incorporated, as illustrated by the X-ray structure of **16** (Figure 1), the hydroxyl group participates in hydrogen bonding to the amide nitrogen thus holding the β-chloroacrylamide in a particular conformation, thereby enhancing the diastereocontrol as sterically there is preferential attack of the oxidising agent on one of the two diastereotopic lone pairs of the sulfur atom (Figure 2). Changing the steric requirements of the auxiliary has a large impact on the diastereoselection, with the diastereoselectivity increasing on going from R^1 = benzyl to phenyl to *t*-butyl group on the auxiliary. As the direction of diastereocontrol in the presence of the hydroxylated chiral auxiliaries has not been confirmed, it is not possible to state conclusively that the direction of approach is controlled by the steric effect of the R^1 substituent, although the evidence suggests this.

An alternative explanation is due to neighbouring group participation by the hydroxyl group. As mentioned earlier, it has been reported that suitably positioned hydroxyl substitutents have been used as to direct the diastereoselective oxidation of sulfides;[40-42] when a percarboxylic acid such as *m*CPBA is employed as the oxidant, incipient hydrogen bonding between the

substrate hydroxyl group and the percarboxylic acid results in the preferential attack of the oxidant on the same side of the substrate as the hydroxyl group. Investigation of the diastereoselective oxidation with *m*CPBA is underway to explore in greater detail the impact of the hydroxylated chiral auxiliary. Investigation of the synthetic potential of the enantioenriched vinyl sulfoxides will be reported in due course, including efficient cleavage of the amide chiral auxiliary.

Conclusion

Sulfur oxidation of enantiomerically pure α-thio-β-chloroacrylamides affords sulfoxides with reasonable levels of diastereocontrol; diastereomeric ratios of up to 3.3:1 were achieved, with the highest levels of diastereoselection observed in systems constrained by intramolecular hydrogen-bonding The conformational freedom of the sulfide precursors is constrained by hydrogen bonding and attractive edge to face interactions, as seen in the solid state. The corresponding enantioselective sulfur oxidation of the β-chloroacrylamides using the Kagan and Bolm methods of oxidation had previously led to enantioselectivities of up to 52% ee and up to 71% ee respectively.[17]

Experimental

All solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorous pentoxide and ethyl acetate was distilled from potassium carbonate, ethanol and methanol were distilled from magnesium in the presence of iodine. Organic phases were dried using anhydrous magnesium sulphate. All commercial reagents, including *N*-chlorosuccinimide, were used without further purification.

^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker (300 MHz) NMR spectrometer. ^{1}H (400 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. All spectra were recorded at room temperature (~20 °C) in deuterated chloroform ($CDCl_3$) unless otherwise stated using tetramethylsilane (TMS) as an

internal standard. Chemical shifts were expressed in parts per million (ppm) and coupling constants in Hertz (Hz).

Elemental analyses were performed by the Microanalysis Laboratory, National University of Ireland, Cork, using a Perkin-Elmer 240 elemental analyzer. Melting points were carried out on a uni-melt Thomas Hoover Capillary melting point apparatus. Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer in electrospray ionization (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier Time of Flight spectrometer in electrospray ionization (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile. Infrared spectra were recorded as potassium bromide (KBr) discs for solids or thin films on sodium chloride plates for oils on a Perkin-Elmer Paragon 1000 FT-IR spectrometer.

Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF_{254}). Column chromatography was performed using Merck silica gel 60. Visualisation was achieved by UV (254nm) light detection, iodine staining, vanillin staining and ceric sulfate staining. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at 589 nm in a 10 cm cell; concentrations (*c*) are expressed in g/100 mL. $[\alpha]_D^T$ is the specific rotation of a compound and is expressed in units of 10^{-1} deg cm^2 g^{-1}.

Single crystal X-ray analysis was conducted using a Nonius Mach 3 diffractometer and a Bruker Apex II Duo Diffractometer with graphite monochromatised Mo-Kα radiation (λ = 0.71069 Å). Calculations for **16** were made using the APEX2 software,[43,44] and for **21b** using PLATON,[45] SHELXS and SHELXL.[44] Diagrams were prepared using PLATON.[42] Full structural data has been deposited at the Cambridge Crystallographic Data Centre. CCDC reference numbers 768983 and 768984.

2-(Benzylthio)-*N*-[(*R*)-1-phenylethyl]propanamide 1

Sodium hydride (2.84 g of a 60% dispersion in mineral oil, 71.1 mmol) was placed in a three-necked round bottom flask under a flow of nitrogen. Following washing with hexane (3 × 40 mL), dry *N*,*N*-dimethylformamide (130 mL) was added and the resulting suspension was

stirred for 10 min. The reaction mixture was cooled to 0 °C and benzyl mercaptan (8.43 mL, 71.1 mmol) was added slowly *via* syringe. After stirring for 20 min, a solution of 2-chloro-*N*-[(*R*)-1-phenylethyl)propanamide (10.02 g, 47.4 mmol) in dry *N*,*N*-dimethylformamide (20 mL) was added. On completion of the addition, the ice bath was removed and the reaction mixture stirred at room temperature for 4 h. The reaction was quenched by the addition of water (150 mL) and dichloromethane (150 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 150 mL), and the combined organic layers were washed with sodium hydroxide (1 M, 150 mL), water (2 × 150 mL), hydrochloric acid (2 M, 2 × 150 mL) and brine (150 mL), dried, filtered and concentrated at reduced pressure to give the crude sulfide **1** as a brown oil. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 10-40% ethyl acetate), the pure *sulfide* **1** (10.45 g, 74%)* was isolated as a white solid and an equimolar mixture of diastereomers, mp 75-77 °C; $[\alpha]_D^{20}$ 43.15 (*c* 0.1, $CHCl_3$); (Found C, 72.43; H, 7.02; N, 4.79; S, 11.16. $C_{18}H_{21}NOS$ requires C, 72.20; H, 7.07; N, 4.68; S, 10.71%); ν_{max}/cm^{-1} (KBr) 3360 (NH), 3314 (NH), 3029 (CH), 2973 (CH), 1646 (CO), 1526 (NH bend), 1494, 1371 (CN stretch); δ_H (300 MHz, $CDCl_3$) 1.41-1.50 [6H, 3 × overlapping d, *J* 7.5, 7.5, 6.9, C(3)H_3 & CH(CH_3) of 2 diastereomers], 3.25-3.35 [1H, 2 × overlapping q, *J* 7.5, 7.5, C(2)*H* of 2 diastereomers], 3.61 (1H, s, SCH_2 of 1 diastereomer), 3.66 (0.5H, A of AB system, J_{AB} 13.2, one of SCH_2 of 1 diastereomer), 3.72 (0.5H, B of AB system, J_{AB} 13.2, one of SCH_2 of 1 diastereomer), 5.00-5.17 (1H, m, NHC*H* of 2 diastereomers), 6.81 (0.5H, br d, *J* 7.8, N*H* of 1 diastereomer), 6.88 (0.5H, br d, *J* 7.8, N*H* of 1 diastereomer), 7.11-7.41 (10H, m, Ar*H* of 2 diastereomers); δ_C (75.5 MHz, $CDCl_3$) 18.4 [CH_3, *C*(3)H_3 of 2 diastereomers, 1 signal for 2 carbons], 21.6, 21.9 [2 × CH_3, CH(*C*H_3) of 2 diastereomers], 36.1, 36.2 (2 × CH_2, S*C*H_2 of 2 diastereomers), 44.1, 44.3, 48.8, 48.9 [4 × CH, *C*(2)H of 2 diastereomers & *C*HNH of 2 diastereomers], 126.0, 126.2, 127.32, 127.35, 127.4, 127.5, 128.65, 128.71, 128.72, 128.77, 128.87, 128.88 (12 × CH, aromatic *C*H of 2 diastereomers), 137.1, 137.3, 143.1, 143.2 (4 × C, aromatic *C* of 2 diastereomers), 171.2, 171.3 (2 × C, *C*O of 2 diastereomers); HRMS (ES+): Exact mass calculated for $C_{18}H_{22}NOS$ $[M+H]^+$, 300.1422. Found 300.1416; m/z (ES+) 300.1 {$[(C_{18}H_{21}NOS)+H]^+$, 100%}, 104.9 (4%).

*A yield of 91% was obtained for a batch that was synthesised later.

2-(Benzylthio)-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]propanamide 2

The title compound was synthesised according to the procedure described for **1** using 2-chloro-*N*-[(*R*)-2-hydroxy-1-phenylethyl)propanamide (0.76 g, 3.4 mmol), benzyl mercaptan (0.60 mL, 5.0 mmol), and sodium hydride (0.20 g of 60% dispersion in mineral oil, 5.0 mmol) in dry *N*,*N*-dimethylformamide (15 mL) to give the crude sulfide **2** as a clear oil. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 40-80% ethyl acetate), the pure *sulfide* **2** (0.80 g, 76%) was isolated as a white solid and an equimolar mixture of diastereomers, mp 95-96 °C; $[\alpha]_D^{20}$ –49.49 (*c* 0.3 in EtOH); (Found C, 68.40; H, 6.79; N, 4.65; S, 9.93. $C_{18}H_{21}NO_2S$ requires C, 68.54; H, 6.71; N, 4.44; S, 10.17%); ν_{max}/cm^{-1} (KBr) 3396 (OH), 3307 (NH), 3060 (CH), 2929 (CH), 1645 (CO), 1542 (NH bend), 1495; δ_H (400 MHz, $CDCl_3$) 1.46 [1.5H, d, *J* 7.6, C(3)*H*$_3$ of 1 diastereomer], 1.50 [1.5H, d, *J* 7.2, C(3)*H*$_3$ of 1 diastereomer], 2.39 (0.5H, t, *J* 6.0, O*H* of 1 diastereomer), 2.50 (0.5H, t, *J* 6.0, O*H* of 1 diastereomer), 3.31-3.41 [2H, 2 × overlapping q, *J* 7.6, 7.2, C(2)*H* of 2 diastereomers], 3.69 (1H, SC*H*$_2$ of 1 diastereomer), 3.77 (1H, s, SC*H*$_2$ of 1 diastereomer), 3.84 (1H, overlapping dd, A of ABM, J_{AB} 5.6, J_{AM} 5.2, one of C*H*$_2$OH of 2 diastereomers), 3.86 (1H, overlapping dd, B of ABM, J_{AB} 5.6, J_{BM} 5.2, one of C*H*$_2$OH of 2 diastereomers), 4.96-5.07 (1H, m, NHC*H* of 2 diastereomers), 7.16-7.43 (11H, m, N*H* & Ar*H* of 2 diastereomers); δ_C (75.5 MHz, $CDCl_3$) 18.4, 18.5 [2 × CH_3, *C*(3)H_3 of 2 diastereomers], 36.2, 36.3 (2 × CH_2, SC*H*$_2$ of 2 diastereomers), 44.2, 44.3 [2 × CH, *C*(2)H of 2 diastereomers], 56.0, 56.1 (2 × CH, NH*C*H of 2 diastereomers), 66.6, 66.7 (2 × CH_2, *C*H_2OH of 2 diastereomers), 126.6, 126.7, 127.4, 127.97, 128.03, 128.68, 128.71, 128.9, 129.0 (9 × CH, aromatic *C*H of 2 diastereomers, 9 signals for 12 carbons), 137.2, 137.3, 138.7, 138.9 (4 × C, aromatic *C* of 2 diastereomers), 172.8, 173.0 (2 × C, *C*O of 2 diastereomers); HRMS (ES+): Exact mass calculated for $C_{18}H_{22}NO_2S$ $[M+H]^+$, 316.1371. Found 316.1378; m/z (ES+) 316.1 {$[(C_{18}H_{21}NO_2S)+H]^+$, 100%}.

2-(Benzylthio)-*N*-[(*S*-1-hydroxy-3-phenylpropan-2-yl]propanamide 3

The title compound was synthesised according to the procedure described for **1** using 2-chloro-*N*-[(*S*)-1-hydroxy-3-phenylpropan-2-yl]-propanamide (0.73 g, 3.0 mmol), benzyl mercaptan (0.53 mL, 4.5 mmol), and sodium hydride (0.18 g of 60% dispersion in mineral oil, 4.5 mmol) in dry *N*,*N*-dimethylformamide (15 mL) to give the crude sulfide **3** as a clear

oil. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 20-80% ethyl acetate), the pure *sulfide* **3** (0.59 g, 61%) was isolated as a white solid and an equimolar mixture of diasteromers, mp 80-81 °C; $[\alpha]_D^{20}$ –17.89 (*c* 0.4 in EtOH); (Found C, 68.84; H, 6.83; N, 4.27; S, 9.95. $C_{19}H_{23}NO_2S$ requires C, 69.27; H, 7.04; N, 4.25; S, 9.73%); ν_{max}/cm^{-1} (KBr) 3341 (OH), 3274 (NH), 3062 (CH), 2925 (CH), 1650 (CO), 1634, 1529 (NH bend), 1495; δ_H (400 MHz, $CDCl_3$) 1.29 [1.5H, d, *J* 7.6, C(3)*H*$_3$ of 1 diastereomer], 1.38 [1.5H, d, *J* 7.2, C(3)*H*$_3$ of 1 diastereomer], 2.37 (0.5H, br t, *J* 5.2, O*H* of 1 diastereomer), 2.67 (0.5H, br t, *J* 5.2, O*H* of 1 diastereomer), 2.74-3.01 (2H, m, C*H*$_2$Ph of 2 diastereomers), 3.17 [0.5H, q, *J* 7.2, C(2)*H* of 1 diastereomer], 3.21-3.28 [1H, m, contains A of AB system at 3.25, J_{AB} 13.2, one of SC*H*$_2$ of 1 diastereomer & C(2)*H* of 1 diastereomer], 3.45 (0.5H, B of AB system, J_{AB} 13.2, one of SC*H*$_2$ of 1 diastereomer), 3.51-3.76 (3H, m, SC*H*$_2$ of 1 diastereomer & C*H*$_2$OH of 2 diastereomers; SC*H*$_2$ could be distinguished as a singlet at 3.64 ppm), 4.11-4.24 (1H, m, NHC*H* of 2 diastereomers), 6.80-6.94 (1H, m, N*H* of 2 diastereomers), 7.08-7.40 (10H, m, Ar*H* of 2 diastereomers); δ_C (75.5 MHz, $CDCl_3$) 18.4, 18.6 [2 × CH_3, *C*(3)H_3 of 2 diastereomers], 35.9, 36.3, 36.9, 37.0 (4 × CH_2, S*C*H_2 & *C*H_2Ph of 2 diastereomers), 44.1, 44.4 [2 × CH, *C*(2)H of 2 diastereomers], 52.8, 53.2 (2 × CH, NH*C*H of 2 diastereomers), 64.5, 64.8 (2 × CH_2, *C*H_2OH of 2 diastereomers), 126.75, 126.84, 127.29, 127.32, 128.63, 128.65, 128.76, 128.85, 128.90, 129.17, 129.23 (11 × CH, aromatic *C*H of 2 diastereomers, 11 signals for 12 carbons), 137.2, 137.4, 137.5 (3 × C, aromatic *C* of 2 diastereomers), 173.0, 173.2 (2 × C, *C*O of 2 diastereomers); HRMS (ES+): Exact mass calculated for $C_{19}H_{24}NO_2S$ $[M+H]^+$ 330.1528. Found 330.1516; 330.1 {$[(C_{19}H_{23}NO_2S)+H]^+$, 100%}, 147.0 (88%).

2-(Benzylthio)-*N*-[(*S*-1-hydroxy-3,3-dimethylbutan-2-yl]propanamide 4

Benzyl mercaptan (1.08 mL, 9.1 mmol) was added to a solution of freshly prepared sodium ethoxide [prepared from sodium (0.21 g, 9.1 mmol) in dry ethanol (30 mL) at 0 °C] while stirring under nitrogen. After stirring for 20 min under nitrogen, a solution of 2-chloro-*N*-[(*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]-propanamide (1.58 g, 7.6 mmol) in ethanol (20 mL) was added gradually over 15 min to the reaction mixture. Following stirring for 16 h at room temperature, the reaction was quenched by addition of water (40 mL) and dichloromethane (30 mL). The phases were separated and the aqueous layer was extracted with

dichloromethane (2 × 30 mL). The combined organic layers were washed with aqueous sodium hydroxide (1 M, 2 × 30 mL), water (30 mL) and brine (30 mL), dried and concentrated under reduced pressure to give the crude sulfide **4** as a clear oil. Following purification by column chromatography on silica gel using hexane-ethyl acetate (40:60) as eluent, the pure *sulfide* **4** (1.77 g, 79%) was isolated as a white solid and an equimolar mixture of diastereomers, mp 54-55 °C; $[\alpha]_D^{20}$ 6.00 (*c* 0.5 in $CHCl_3$); (Found C, 64.36; H, 8.36; N, 4.79. $C_{16}H_{25}NO_2S$ requires C, 65.05; H, 8.53; N, 4.74%); ν_{max}/cm^{-1} (KBr) 3249 (NH), 3085 (CH), 2963 (CH), 1646 (CO), 1567 (NH bend), 1495, 1370 (CN stretch); δ_H (400 MHz, $CDCl_3$) 0.97 [4.5H, s, C(C*H*$_3$)$_3$ of 1 diastereomer], 0.98 [4.5H, s, C(C*H*$_3$)$_3$ of 1 diastereomer], 1.46 [1.5H, d, *J* 7.6, C(3)*H*$_3$ of 1 diastereomer], 1.48 [1.5H, d, *J* 7.2, C(3)*H*$_3$ of 1 diastereomer], 2.32 (0.5H, br t, *J* 5.6, O*H* of 1 diastereomer), 2.49 (0.5H, br t, *J* 5.6, O*H* of 1 diastereomer), 3.35 [0.5H, q, *J* 7.2, C(2)*H* of 1 diastereomer], 3.37 [0.5H, q, *J* 7.6, C(2)*H* of 1 diastereomer], 3.49 (0.5H, ddd, *J* 11.0, 8.4, 5.6, NHC*H* of 1 diastereomer), 3.54 (0.5H, ddd, *J* 11.0, 8.0, 5.2, NHC*H* of 1 diastereomer), 3.71-3.94 (4H, m, SC*H*$_2$ & C*H*$_2$OH of 2 diastereomers), 6.86 (0.5H, br d, *J* 8.4, N*H* of 1 diastereomer), 6.99 (0.5H, br d, *J* 8.8, N*H* of 1 diastereomer), 7.21-7.37 (5H, m, Ar*H*); δ_C (75.5 MHz, $CDCl_3$) 18.7, 18.8 [2 × CH_3, *C*(3)H$_3$ of 2 diastereomers], 26.9, 27.0 [2 × CH_3, C(*C*H$_3$)$_3$ of 2 diastereomers], 33.45, 33.54 [2 × C, *C*(CH$_3$)$_3$ of 2 diastereomers], 36.1, 36.4 (2 × CH_2, S*C*H$_2$ of 2 diastereomers), 44.3, 44.8 [2 × CH, *C*(2)H of 2 diastereomers], 59.8, 60.1 (2 × CH, NH*C*H of 2 diastereomers), 63.2, 63.4 (2 × CH_2, *C*H$_2$OH of 2 diastereomers), 127.39, 127.44, 128.7, 128.8, 128.92, 128.93 (6 × CH, aromatic *C*H of 2 diastereomers), 137.1, 137.3 (2 × C, aromatic *C* of 2 diastereomers), 173.7, 173.8 (2 × C, *C*O of 2 diastereomers); HRMS (ES+): Exact mass calculated for $C_{16}H_{26}NO_2S$ $[M+H]^+$ 296.1684. Found 296.1685; m/z (ES+) 296.1 {[($C_{16}H_{25}NO_2S$)+H]$^+$, 100%}, 79.8 (6%).

_N_-[(_R_)-1-Phenylethyl]-2-(phenylthio)propanamide 5

The title compound was synthesised according to the procedure described for **1** using 2-chloro-*N*-[(*R*)-1-phenylethyl)propanamide (2.45 g, 11.6 mmol), benzenethiol (1.83 mL, 17.4 mmol), and sodium hydride (0.69 g of 60% dispersion in mineral oil, 17.4 mmol) in dry *N*,*N*-dimethylformamide (70 mL) to give the crude sulfide **5** as pale yellow oil. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent

(gradient elution 10-20% ethyl acetate), the pure *sulfide* **5** (2.35 g, 71%) was isolated as a white solid (as a 1:1.37 mixture of diastereomers), mp 98-99 °C; $[\alpha]_D^{20}$ 58.05 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3267 (NH), 3059 (CH), 2973 (CH), 1660 (CO), 1553 (NH bend), 1494, 1374 (CN stretch); δ_H (400 MHz, $CDCl_3$) 1.32 [1.2H, d, *J* 7.2, CH(C*H*$_3$) of 1 diastereomer], 1.43 [1.8H, d, *J* 6.8, CH(C*H*$_3$) of 1 diastereomer], 1.54 [1.2H, d, *J* 7.6, C(3)*H*$_3$ of 1 diastereomer], 1.58 [1.8H, d, *J* 7.2, C(3)*H*$_3$ of 1 diastereomer], 3.84 [0.6H, q, *J* 7.6, C(2)*H* of 1 diastereomer], 3.85 [0.4H, q, *J* 7.2, C(2)*H* of 1 diastereomer], 4.98-5.08 (1H, m, NHC*H* of 2 diastereomers), 6.77-6.89 (1H, br d, N*H* of 2 diastereomers), 7.00-7.07 (1H, m, Ar*H* of 2 diastereomers), 7.17-7.37 (8H, m, Ar*H* of 2 diastereomers).

_N_-[(1_R_)-2-Hydroxy-1-phenylethyl]-2-(phenylthio)propanamide 6

The title compound was synthesised according to the procedure described for **1** using 2-chloro-*N*-[(*R*)-2-hydroxy-1-phenylethyl)propanamide (0.76 g, 3.4 mmol), benzenethiol (0.53 mL, 5.0 mmol), and sodium hydride (0.20 g of 60% dispersion in mineral oil, 5.0 mmol) in dry *N*,*N*-dimethylformamide (15 mL) to give the crude sulfide **6** as a clear oil. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 40-80% ethyl acetate), the pure *sulfide* **6** (0.80 g, 76%) was isolated as a white solid and an equimolar mixture of diastereomers, mp 69-70 °C; $[\alpha]_D^{20}$ –49.91 (*c* 0.1 in EtOH); (Found C, 68.25; H, 6.65; N, 4.36; S, 10.51. $C_{17}H_{19}NO_2S$ requires C, 67.74; H, 6.35; N, 4.65; S, 10.51%); ν_{max}/cm^{-1} (KBr) 3385 (OH), 3284 (NH), 3060 (CH), 2927 (CH), 1647 (CO), 1541 (NH bend); δ_H (400 MHz, $CDCl_3$) 1.57 [1.5H, d, *J* 7.6, C(3)*H*$_3$ of 1 diastereomer], 1.61 [1.5H, d, *J* 7.2, C(3)*H*$_3$ of 1 diastereomer], 2.07-2.19 (1H, m, O*H* of 2 diastereomers), 3.66-3.86 (2H, m, C*H*$_2$OH of 2 diastereomers), 3.87-3.96 [1H, 2 × overlapping q, *J* 7.6, 7.2, C(2)*H* of 2 diastereomers], 4.94-5.02 (1H, m, NHC*H* of 2 diastereomers), 6.96-7.03 (1H, m, N*H* of 2 diastereomers), 7.15-7.40 (10H, m, Ar*H* of 2 diastereomers); δ_C (75.5 MHz, $CDCl_3$) 18.1, 18.2 [2 × CH_3, *C*(3)H_3 of 2 diastereomers], 47.0, 47.1 [2 × CH, *C*(2)H of 2 diastereomers], 55.8, 55.9 (2 × CH, NH*C*H of 2 diastereomers), 66.34, 66.36 (2 × CH_2, *C*H_2OH of 2 diastereomers), 126.55, 126.61, 127.4, 127.5, 127.8, 127.9, 128.8, 128.9, 129.3, 130.5, 130.6 (11 × CH, aromatic *C*H of 2 diastereomers, 11 signals for 12 carbons), 133.80, 133.83, 138.5, 138.6 (4 × C, aromatic *C* of 2 diastereomers), 172.1, 172.3 (2 × C, *C*O of 2 diastereomers); HRMS (ES+): Exact mass calculated for

$C_{17}H_{20}NO_2S$ $[M+H]^+$, 302.1215. Found 302.1221; m/z (ES+) 302.1 {$[(C_{17}H_{19}NO_2S)+H]^+$, 100%}.

_N_-[(1_R_,2_S_)-2,3-Dihydro-2-hydroxy-1_H_-inden-1-yl]-2-(phenylthio)propanamide 7

The title compound was synthesised according to the procedure described for **4** using 2-chloro-*N*-[(1*R*,2*S*)-2,3-dihydro-2-hydroxy-1*H*-inden-1-yl]propanamide (0.69 g, 2.9 mmol), benzenethiol (0.36 mL, 3.5 mmol), and sodium (0.08 g, 3.5 mmol) in dry ethanol (20 mL) to give the crude sulfide **7** as a white solid. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 40-60% ethyl acetate), the pure *sulfide* **7** (0.65 g, 73%) was isolated as a white solid and an equimolar mixture of diasteromers, mp 138-140 °C; $[\alpha]_D^{20}$ 19.13 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3429 (OH), 3320 (NH), 3071 (CH), 2954 (CH), 1642 (CO), 1541 (NH bend), 1477, 1368 (CN stretch); δ_H (400 MHz, $CDCl_3$) 1.65 [1.5H, d, *J* 7.2, C(3)H_3 of 1 diastereomer], 1.68 [1.5H, d, *J* 7.2, C(3)H_3 of 1 diastereomer], 2.83-2.95, 3.08-3.18 (2 × 1H, 2 × m, ArCH_2 of 2 diastereomers), 3.97-4.05 [1H, 2 overlapping q, *J* 7.2, 7.2, C(2)*H* of 2 diastereomers], 4.44-4.48 (0.5H, ddd, *J* 5.0, 4.8, 1.6, C*H*OH of 1 diastereomer), 4.54-4.59 (0.5H, ddd, *J* 5.0, 4.8, 2.0, C*H*OH of 1 diastereomer), 5.28-5.34 (1H, m, NHC*H* of 2 diastereomers), 7.00-7.42 (10H, m, N*H* & Ar*H* of 2 diastereomers); δ_C (75.5 MHz, $CDCl_3$) 18.3, 18.4 [2 × CH_3, *C*(3)H_3 of 2 diastereomers], 39.6, 39.7 (2 × CH_2, Ar*C*H_2 of 2 diastereomers), 47.0, 47.1 [2 × CH, *C*(2)H of 2 diastereomers], 57.66, 57.70 (2 × CH, NH*C*H of 2 diastereomers), 73.6, 73.7 (2 × CH, *C*HOH of 2 diastereomers), 124.3, 124.4, 125.3, 125.4, 127.1, 127.2, 127.35, 127.39, 128.2, 128.3, 129.28, 129.32, 130.2, 130.7 (14 × CH, aromatic *C*H of 2 diastereomers), 134.1, 134.2, 139.8, 140.0, 140.1, 140.2 (6 × C, aromatic *C* of 2 diastereomers), 172.50, 172.53 (2 × C, *C*O of 2 diastereomers); HRMS (ES+): Exact mass calculated for $C_{18}H_{20}NO_2S$ $[M+H]^+$ 314.1215. Found 314.1223; m/z (ES+) 314.0 {$[(C_{18}H_{19}NO_2S)+H]^+$, 100%}.

_N_-[(_S_-1-Hydroxy-3-phenylpropan-2-yl]-2-(phenylthio)propanamide 8

The title compound was synthesised according to the procedure described for **1** using 2-chloro-*N*-[(*S*)-1-hydroxy-3-phenylpropan-2-yl]-propanamide (0.73 g, 3.0 mmol), benzenethiol (0.47 mL, 4.5 mmol), and sodium hydride (0.18 g of a 60% dispersion in

mineral oil, 4.5 mmol) in dry *N*,*N*-dimethylformamide (15 mL) to give the crude sulfide **8** as a pale yellow oil. Following purification by column chromatography on silica gel using hexane-ethyl acetate 60:40 as eluent, the pure *sulfide* **8** (0.43 g, 45%) was isolated as a white solid and as an equimolar mixture of diasteromers, mp 90-92 °C; $[\alpha]_D^{20}$ 26.95 (*c* 0.1 in EtOH); (Found C, 68.51; H, 6.65; N, 4.67; S, 10.50. $C_{18}H_{21}NO_2S$ requires C, 68.54; H, 6.71; N, 4.44; S, 10.17%); ν_{max}/cm^{-1} (KBr) 3379 (OH), 3282 (NH), 3060 (CH), 2927 (CH), 1655 (CO), 1638 (CO), 1536 (NH bend); δ_H (400 MHz, $CDCl_3$) 1.42 [1.5H, d, *J* 7.2, C(3)*H*$_3$ of 1 diastereomer], 1.53 [1.5H, d, *J* 7.6, C(3)*H*$_3$ of 1 diastereomer], 1.90 (0.5H, br s, O*H* of 1 diastereomer), 2.38 (0.5H, br s, O*H* of 1 diastereomer), 2.67-2.91 (2H, m, C*H*$_2$Ph of 2 diastereomers), 3.37-3.65 (2H, m, C*H*$_2$OH of 2 diastereomers), 3.73-3.85 [1H, 2 × q, *J* 7.6, 7.2, C(2)*H* of 2 diastereomers], 4.02-4.18 (1H, m, NHC*H* of 2 diastereomers), 6.72-6.87 (1H, br d, N*H* of 2 diastereomers), 7.05-7.13 (1H, m, Ar*H*), 7.14-7.36 (9H, m, Ar*H*); δ_C (75.5 MHz, $CDCl_3$) 18.0, 18.4 [2 × CH_3, *C*(3)H_3 of 2 diastereomers], 36.8, 36.9 (2 × CH_2, *C*H_2Ph of 2 diastereomers), 47.1, 47.2 [2 × CH, *C*(2)H of 2 diastereomers], 52.7, 53.2 (2 × CH, NH*C*H of 2 diastereomers), 64.0, 64.1 (2 × CH_2, *C*H_2OH of 2 diastereomers), 126.68, 126.71, 127.28, 127.34, 128.6, 129.15, 129.22, 130.2, 130.3 (9 × CH, aromatic *C*H of 2 diastereomers, 9 signals for 12 carbons), 134.0, 137.3, 137.4 (3 × C, aromatic *C* of 2 diastereomers, 3 signals for 4 carbons), 172.1, 172.6 (2 × C, *C*O of 2 diastereomers); HRMS (ES+): Exact mass calculated for $C_{18}H_{22}NO_2S$ $[M+H]^+$ 316.1371. Found 316.1374; m/z (ES+) 316.1 {$[(C_{18}H_{21}NO_2S)+H]^+$, 100%}.

N-[(*S*-1-Hydroxy-3,3-dimethylbutan-2-yl]-2-(phenylthio)propanamide 9

The title compound was synthesised according to the procedure described for **4** using 2-chloro-*N*-[(*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]-propanamide (1.94 g, 9.4 mmol), benzenethiol (1.18 mL, 11.2 mmol), and sodium (0.26 g, 11.2 mmol) in dry ethanol (60 mL) to give the crude sulfide **9** as a clear oil. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 40-80%), the pure *sulfide* **9** (1.98 g, 75%) was isolated as a white solid and a 1:1.22 mixture of diasteromers (material contained ~14% starting material), mp 64-66 °C; $[\alpha]_D^{20}$ 1.80 (*c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3369 (OH), 3280 (NH), 3082 (CH), 2961 (CH), 1654 (CO), 1642 (CO), 1547 (NH bend), 1470, 1370 (CN stretch); δ_H (400 MHz, $CDCl_3$) 0.76 [4.95H, s, C(C*H*$_3$)$_3$ of 1

diastereomer], 0.91 [4.05H, s, C(C*H*$_3$)$_3$ of 1 diastereomer], 1.60 [1.35H, d, *J* 7.2, C(3)*H*$_3$ of 1 diastereomer], 1.61 [1.65H, *J* 7.6, C(3)*H*$_3$ of 1 diastereomer], 1.77 (0.45H, t, *J* 5.6, O*H* of 1 diastereomer), 2.20 (0.55H, bt, *J* 5.6, O*H* of 1 diastereomer), 3.31-3.40 (0.45H, m, NHC*H* of 1 diastereomer), 3.50 (0.55H, ddd, *J* 13.2, 8.0, 5.2, NHC*H* of 1 diastereomer), 3.64-3.85 (2H, m, C*H*$_2$OH of 2 diastereomers), 3.97 [0.55H, q, *J* 7.6, C(2)*H* of 1 diastereomer], 3.99 [0.45H, q, *J* 7.2, C(2)*H* of 1 diastereomer], 6.85 (0.55H, br d, N*H* of 1 diastereomer), 6.88 (0.45H, br d, N*H* of 1 diastereomer), 7.18-7.39 (5H, m, Ar*H* of 2 diastereomers); δ_C (75.5 MHz, $CDCl_3$) 18.4*, 18.5 [2 × CH_3, *C*(3)H$_3$ of 2 diastereomers], 26.7*, 26.8 [2 × CH_3, C(*C*H$_3$)$_3$ of 2 diastereomers], 33.3*, 33.6 [2 × C, *C*(CH$_3$)$_3$ of 2 diastereomers], 46.6, 47.2* [2 × CH, *C*(2)H of 2 diastereomers], 59.9, 60.0* (2 × CH, NH*C*H of 2 diastereomers), 63.0, 63.4 (2 × CH_2, *C*H$_2$OH of 2 diastereomers), 127.0*, 127.2, 129.1*, 129.3*, 129.36, 129.40 (6 × CH, aromatic *C*H), 134.1*, 134.3 (2 × C, aromatic *C*), 172.7, 173.2* (2 × C, *C*O); HRMS (ES+): Exact mass calculated for $C_{15}H_{24}NO_2S$ $[M+H]^+$ 282.1528. Found 282.1527; m/z (ES+) 282.1 {$[(C_{15}H_{23}NO_2S)+H]^+$, 100%}, 208.1 (4%), 172.1 (2%), 118.0 (2%).

*Major diastereomer

_N_-[(_R_)-3,3-Dimethylbutan-2-yl]-2-(phenylthio)propanamide 10

The title compound was synthesised according to the procedure described for **1** using 2-chloro-*N*-[(*S*)-3,3-dimethylbutan-2-yl]propanamide (2.02 g, 10.5 mmol), benzenethiol (1.17 mL, 11.1 mmol), and sodium hydride (0.44 g of 60% dispersion in mineral oil, 11.1 mmol) in dry *N*,*N*-dimethylformamide (50 mL) to give the crude sulfide **10** as a yellow oil. Following purification by column chromatography on silica gel using hexane-ethyl acetate as eluent (gradient elution 10-40%), the pure *sulfide* **10** (2.19 g, 79%) was isolated as a white solid and an equimolar mixture of diastereomers, mp 109-110 °C; $[\alpha]_D^{20}$ 20.35 (*c* 0.14 in $CHCl_3$); (Found C, 68.03; H, 8.70; N, 5.35; S, 12.22. $C_{15}H_{23}NOS$ requires C, 67.88; H, 8.73; N, 5.28; S, 12.08%); ν_{max}/cm^{-1} (KBr) 3286 (NH), 3059 (CH), 2970 (CH), 1638 (CO), 1553 (NH bend), 1446, 1374 (CN stretch); δ_H (400 MHz, $CDCl_3$) 0.67 [4.5H, s, C(C*H*$_3$)$_3$ of 1 diastereomer], 0.83 (1.5H, d, *J* 6.8, NHCHC*H*$_3$ of 1 diastereomer), 0.86 [4.5H, s, C(C*H*$_3$)$_3$ of 1 diastereomer], 1.00 (1.5H, d, *J* 6.8, NHCHC*H*$_3$ of 1 diastereomer), 1.56 [1.5H, d, *J* 7.2, C(3)*H*$_3$], 1.58 [1.5H, d, *J* 7.6, C(3)*H*$_3$], 3.70-3.79 (1H, m, NHC*H* of 2 diastereomers), 3.89 [0.5H, q, *J* 7.6, C(2)*H* of 1 diastereomer], 3.93 [0.5H, q, *J* 7.2, C(2)*H* of 1 diastereomer],

6.52-6.67 (1H, 2 overlapping br d, N*H* of 2 diastereomers), 7.16-7.36 (5H, m, Ar*H*); δ_C (75.5 MHz, $CDCl_3$) 15.6, 16.0 (2 × CH_3, NHCH*C*H_3 of 2 diastereomers), 18.3, 18.6 [2 × CH_3, *C*(3)H_3 of 2 diastereomers], 33.9, 34.1 [2 × C, *C*$(CH_3)_3$ of 2 diastereomers], 46.5, 47.4, 52.9, 53.1 [4 × CH, *C*(2)H & NH*C*H of 2 diastereomers], 126.8, 127.0, 129.1, 129.2, 129.5 (5 × CH, aromatic *C*H of 2 diastereomers, 5 signals for 6 carbons), 134.3 (C, aromatic *C* of 2 diastereomers, 1 signal for 2 carbons), 170.77, 170.83 (2 × C, *C*O of 2 diastereomers); HRMS (ES+): Exact mass calculated for $C_{15}H_{24}NOS$ $[M+H]^+$ 266.1579. Found 266.1580; m/z (ES+) 266.1 {$[(C_{15}H_{23}NOS)+H]^+$, 100%}, 104.9 (6%).

(*Z*)-2-(Benzylthio)-3-chloro-*N*-[(*R*)-1-phenylethyl)acrylamide 11

Unrecrystallised NCS (2.80 g, 20.6 mmol) was added in one portion to a solution of the sulfide 2-(benzylthio) in toluene (60 mL). The flask was immediately immersed in an oil bath and heated at 90 °C for 2 h. Following filtration and evaporation of the solvent at reduced pressure, the crude product was obtained as a yellow oil, containing 70% β-chloroacrylamide by ^{1}H NMR spectroscopy. This was purified by column chromatography on silica gel using hexane-ethyl acetate 95:5 as eluent to give the pure product **11** (2.14 g, 61%) as a white solid, mp 77-78 °C; $[\alpha]_D^{20}$ 66.50 (*c* 0.5 in $CHCl_3$); (Found C, 65.50; H, 5.30; Cl, 10.30; N, 4.16; S, 9.90. $C_{18}H_{18}ClNOS$ requires C, 65.15; H, 5.47; Cl, 10.68; N, 4.22; S, 9.66%); ν_{max}/cm^{-1} (KBr) 3309 (NH), 2977 (CH), 1630 (CO), 1529 (NH bend), 1451 (CN stretch); δ_H (400 MHz, $CDCl_3$) 1.34 [3H, d, *J* 6.8, CH(C*H*$_3$)], 3.90 (2H, s, SC*H*$_2$), 4.95 (1H, overlapping dq, *J* 7.2, 6.8, NHC*H*), 7.07-7.39 (11H, m, N*H* & Ar*H*), 7.83 [1H, s, Cl*H*C(3)=]; δ_C (75.5 MHz, $CDCl_3$) 21.7 [CH_3, CH(C*H*$_3$)], 38.2 (CH_2, S*C*H$_2$), 49.6 (CH, NH*C*H), 126.0, 127.5, 127.69, 128.74, 128.77, 128.80 (6 × CH, 6 × aromatic *C*H), 130.9, 137.2 [2 × C, aromatic *C* or *C*(2)S], 139.4 [C, ClH*C*(3)=], 142.6 [C, aromatic *C* or *C*(2)S], 161.9 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{18}H_{19}NOS^{35}Cl$ $[M+H]^+$ 332.0876. Found 332.0891; m/z (ES+) 334.0 {$[(C_{18}H_{18}NOS^{37}Cl)+H^+]$, 44%}, 332.0 {$[(C_{18}H_{18}NOS^{35}Cl)+H^+]$, 100%}.

(*Z*)-2-(Benzylthio)-3-chloro-*N*-[(*R*)-2-hydroxy-1-phenylethyl]acrylamide 12

This was prepared following the procedure described above for **11** using 2-(benzylthio)-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]propanamide **2** (2.46 g, 7.8 mmol), *N*-chlorosuccinimide (2.08 g, 15.2 mmol) and toluene (50 mL). The reaction mixture was heated at 90 °C for 2 h.

Following filtration and evaporation of the solvent at reduced pressure, the crude product was obtained as a brown oil, containing 40% β-chloroacrylamide by ^{1}H NMR spectroscopy. This was purified by column chromatography on silica gel using hexane-ethyl acetate (gradient elution 10-40% ethyl acetate) as eluent to give the pure product **12** (0.86 g, 32%) as a pale brown solid, mp 95-96 °C; $[\alpha]_D^{20}$ –54.16 (*c* 0.1 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3379 (OH), 3304 (NH), 3029 (CH), 2928 (CH), 1625 (CO), 1524 (NH bend), 1453 (CN stretch); δ_H (400 MHz, $CDCl_3$) 2.14 (1H, dd, *J* 6.8, 5.6, O*H*), 3.70-3.75 (2H, m, C*H*$_2$OH), 3.95 (2H, s, SC*H*$_2$), 4.87-4.94 (2H, overlapping ddd, *J* 7.2, 5.2, 5.0, NHC*H*), 7.10-7.15 (2H, m, Ar*H*), 7.18-7.39 (8H, m, Ar*H*), 7.54 (1H, br d, *J* 6.8, N*H*), 7.89 [1H, s, Cl*H*C(3)=]; δ_C (75.5 MHz, $CDCl_3$) 38.2 (CH_2, S*C*H$_2$), 56.5 (CH, NH*C*H), 66.5 (CH_2, *C*H$_2$OH), 126.6, 127.7, 128.0, 128.78, 128.86, 128.93 (6 × CH, 6 × aromatic *C*H), 130.7, 137.2, 138.3 [3 × C, 2 × aromatic *C* & *C*(2)S], 140.0 [CH, ClH*C*(3)=], 163.3 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{18}H_{19}NO_2S^{35}Cl$ $[M+H]^+$ 348.0825. Found 348.0834; m/z (ES+) 349.9 {[($C_{18}H_{18}NO_2S^{37}Cl$)+H^+], 44%}, 348.0 {[($C_{18}H_{18}NO_2S^{35}Cl$)+H^+], 100%}.

***(Z)*-2-(Benzylthio)-3-chloro-*N*-[(*S*)-1-hydroxy-3-phenylpropan-2-yl]acrylamide 13**

This was prepared following the procedure described above for **11** using 2-(benzylthio)-*N*-[(*S*-1-hydroxy-3-phenylpropan-2-yl]propanamide **3** (1.76 g, 5.4 mmol), *N*-chlorosuccinimide (1.42 g, 10.5 mmol) and toluene (50 mL). The reaction mixture was heated at 90 °C for 1 h. Following filtration and evaporation of the solvent at reduced pressure, the crude product was obtained as a brown oil, containing 35% β-chloroacrylamide by ^{1}H NMR spectroscopy. This was purified by column chromatography on silica gel using hexane-ethyl acetate (gradient elution 20-40% ethyl acetate) as eluent to give the pure product **13** (1.00 g, 51%) as a pale brown solid, mp 77-78 °C; $[\alpha]_D^{20}$ –30.00 (*c* 0.1 in $CHCl_3$); (Found C, 62.72; H, 5.73; Cl, 10.00; N, 4.01; S, 9.09. $C_{19}H_{20}ClNO_2S$ requires C, 63.06; H, 5.57; Cl, 9.80; N, 3.87; S, 8.86%); ν_{max}/cm^{-1} (KBr) 3363 (NH), 3062 (CH), 2929 (CH), 1644 (CO), 1515 (NH bend), 1454 (CN stretch); δ_H (400 MHz, $CDCl_3$) 2.20 (1H, dd, *J* 5.6, 5.6, O*H*), 2.72 (1H, dd, A of ABX, J_{AX} 13.8, J_{AB} 7.2, one of C*H*$_2$Ph), 2.83 (1H, dd, B of ABX, J_{BX} 14.0, J_{AB} 7.2, one of C*H*$_2$Ph), 3.41-3.48 (1H, m, one of C*H*$_2$OH), 3.51-3.57 (1H, m, one of C*H*$_2$OH), 3.74 (2H, s, SC*H*$_2$), 4.03-4.14 (1H, m, NHC*H*), 7.04-7.39 (11H, m, N*H* & Ar*H*), 7.80 [1H, s, Cl*H*C(3)=]; δ_C (75.5 MHz, $CDCl_3$) 36.7, 38.1 (2 × CH_2, S*C*H$_2$ & *C*H$_2$Ph), 53.4 (CH, NH*C*H), 64.1 (CH_2,

CH_2OH), 126.9, 127.6, 128.7, 128.8, 128.9, 129.2 (6 × CH, 6 × aromatic *C*H), 130.8, 137.1, 137.2 [3 × C, 2 × aromatic *C* & *C*(2)S], 139.9 [CH, ClH*C*(3)=], 163.3 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{19}H_{21}NO_2S^{35}Cl$ $[M+H]^+$ 362.0982. Found 362.0968; m/z (ES+) 364.0 {[($C_{19}H_{20}NO_2S^{37}Cl$)+H^+], 42%}, 362.0 {[($C_{19}H_{20}NO_2S^{35}Cl$)+H^+], 100%}.

(*Z*)-2-(Benzylthio)-3-chloro-*N*-[(*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]acrylamide 14

This was prepared following the procedure described above for **11** using 2-(benzylthio)-*N*-[(*S*-1-hydroxy-3,3-dimethylbutan-2-yl]propanamide **4** (1.66 g, 5.6 mmol), *N*-chlorosuccinimide (1.50 g, 11.0 mmol) and toluene (50 mL). The reaction mixture was heated at 90 °C for 1 h. Following filtration and evaporation of the solvent at reduced pressure, the crude product was obtained as a brown oil, containing 36% β-chloroacrylamide by ^{1}H NMR spectroscopy. This was purified by column chromatography on silica gel using hexane-ethyl acetate (gradient elution 20-40% ethyl acetate) as eluent to give the pure product **14** (0.54 g, 29%) as an orange oil; $[\alpha]_D^{20}$ 106.00 (*c* 0.1 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3440 (OH), 3367 (NH), 3062 (CH), 2963 (CH), 1645 (CO), 1515 (NH bend), 1455 (CN stretch); δ_H (400 MHz, $CDCl_3$) 0.88 [9H, s, C(C*H*$_3$)$_3$], 1.97 (1H, br s, O*H*), 3.33 (1H, br dd, *J* 7.9, 7.0, NHC*H*), 3.64-3.76 (2H, m, C*H*$_2$OH), 3.95 (1H, A of AB system, J_{AB} 12.9, one of SC*H*$_2$), 4.00 (1H, B of AB system, J_{AB} 12.9, one of SC*H*$_2$), 7.12 (1H, br d, *J* 7.0, N*H*), 7.18-7.40 (5H, m, Ar*H*), 7.90 [1H, s, Cl*H*C(3)=]; δ_c (75.5 MHz, $CDCl_3$) 26.8 [CH_3, C(*C*H$_3$)$_3$], 33.5 [C, *C*(CH$_3$)$_3$], 38.1 (CH_2, S*C*H$_2$), 60.6 (CH, NH*C*H), 63.1 (CH_2, *C*H$_2$OH), 127.8, 129.1 (signal for 2 × CH) (2 × CH, 2 × aromatic *C*H), 130.8, 137.4 [2 × C, aromatic *C* & *C*(2)S], 140.0 [CH, ClH*C*(3)=], 164.0 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{16}H_{23}NO_2S^{35}Cl$ $[M+H]^+$ 328.1138. Found 328.1148; m/z (ES+) 330.0 {[($C_{16}H_{22}NO_2S^{37}Cl$)+H^+], 44%}, 328.0 {[($C_{16}H_{22}NO_2S^{35}Cl$)+H^+], 100%}.

(*Z*)-2-(Phenylthio)-3-chloro-*N*-[(*R*)-1-phenylethyl)acrylamide 15

This was prepared following the procedure described above for **11** using *N*-[(*R*)-1-phenylethyl]-2-(phenylthio)propanamide **5** (2.51 g, 8.8 mmol), *N*-chlorosuccinimide (2.33 g, 17.1 mmol) and toluene (60 mL). The reaction mixture was heated at 90 °C for 2 h. Following filtration and evaporation of the solvent at reduced pressure, the crude product was

obtained as a yellow oil, containing 56% β-chloroacrylamide by ^{1}H NMR spectroscopy. This was purified by column chromatography on silica gel using hexane-ethyl acetate 95:5 as eluent to give the pure product **11** (1.30 g, 47%) as a white solid, mp 51-53 °C; $[\alpha]_D^{20}$ 6.40 (*c* 0.5 in EtOH); ν_{max}/cm^{-1} (KBr) 3302 (NH), 2918 (CH), 1643 (CO), 1514 (NH bend); δ_H (400 MHz, $CDCl_3$) 1.30 [3H, d, *J* 6.8, CH(C*H*$_3$)], 4.99 (1H, overlapping dq, *J* 7.6, 6.8, NHC*H*), 6.89-7.05 (3H, m, Ar*H* & N*H*), 7.17-7.38 (8H, m, Ar*H*), 7.87 [1H, s, Cl*H*C(3)=].

(*Z*)-3-Chloro-*N*-[(*R*)-2-hydroxy-1-phenylethyl]-2-(phenylthio)acrylamide 16

This was prepared following the procedure described above for **11** using *N*-[(1*R*)-2-hydroxy-1-phenylethyl]-2-(phenylthio)propanamide **6** (2.04 g, 6.8 mmol), *N*-chlorosuccinimide (1.80 g, 13.2 mmol) and toluene (40 mL). The reaction mixture was heated at 90 °C for 2 h. Following filtration and evaporation of the solvent at reduced pressure, the crude product was obtained as a yellow oil, containing 41% β-chloroacrylamide by ^{1}H NMR spectroscopy. This was purified by column chromatography on silica gel using hexane-ethyl acetate (gradient elution 20-40% ethyl acetate) as eluent to give the pure product **16** (0.92 g, 41%) as a white solid, mp 102-103 °C; $[\alpha]_D^{20}$ 64.50 (*c* 0.5 in $CHCl_3$); (Found C, 61.16; H, 4.83; Cl, 10.62; N, 4.20; S, 9.61. $C_{17}H_{16}ClNO_2S$ requires C, 61.07; H, 4.92; Cl, 10.95; N, 4.22; S, 9.60%); ν_{max}/cm^{-1} (KBr) 3400 (OH), 3361 (NH), 3047 (CH), 2929 (CH), 1643 (CO), 1518 (NH bend), 1452 (CN stretch); δ_H (400 MHz, $CDCl_3$) 1.82 (1H, dd, *J* 7.2, 5.2, O*H*), 3.66-3.78 (2H, m, C*H*$_2$OH), 4.94-4.98 (2H, overlapping ddd, *J* 7.2, 4.8, 4.4, NHC*H*), 6.88-6.96 (2H, m, Ar*H*), 7.18-7.37 (8H, m, Ar*H*), 7.46 (1H, br d, *J* 6.8, N*H*), 7.89 [1H, s, Cl*H*C(3)=]; δ_C (75.5 MHz, $CDCl_3$) 56.0 (CH, NH*C*H), 66.1 (CH_2, *C*H_2OH), 126.4, 127.4, 127.8, 128.7, 128.8, 129.7 (6 × CH, 6 × aromatic *C*H), 130.7, 133.0, 138.2 [3 × C, 2 × aromatic *C* & *C*(2)S], 139.2 [CH, ClH*C*(3)=], 162.4 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{17}H_{17}NO_2S^{35}Cl$ $[M+H]^+$ 334.0669. Found 334.0672; m/z (ES+) 336.0 {[($C_{17}H_{16}NO_2S^{37}Cl$)+H^+], 40%}, 334.0 {[($C_{17}H_{16}NO_2S^{35}Cl$)+H^+], 100%}.

The structure of **16** was determined by single crystal X-ray diffraction on a crystalline sample of **16** recrystallised from dichloromethane/pentane. Crystals of **16** are monoclinic, space group *C* 121, formula $C_{17}H_{16}ClNO_2S$, M = 333.82, a = 21.1484(15) Å, b = 6.0525(4) Å, c = 15.0786(11) Å, α = 90.00 °, β = 121.914(3) °, γ = 90.00 °, U = 1638.3(2) Å^3, F(000) = 696, μ(Mo-Kα) = 0.366 mm^{-1}, R(F_o) = 0.0282, for 2862 observed reflections with I>2σ(I),

$wR_2(F^2)$ = 0.0596 for all 3105 unique reflections. Data in the θ range 1.59-26.02 ° were collected at 100 K on a Bruker Apex II Duo diffractometer using Mo-Kα radiation, λ = 0.71073 Å, and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

(*Z*)-3-Chloro-*N*-[(1*R*,2*S*)-2,3-dihydro-2-hydroxy-1*H*-inden-1-yl]-2-(phenylthio)acrylamide 17

This was prepared following the procedure described above for **11** using *N*-[(1*R*,2*S*)-2,3-dihydro-2-hydroxy-1*H*-inden-1-yl]-2-(phenylthio)propanamide **7** (0.63 g, 2.0 mmol), *N*-chlorosuccinimide (0.53 g, 3.9 mmol) and toluene (20 mL). The reaction mixture was heated at 90 °C for 30 min. Following filtration and evaporation of the solvent at reduced pressure, the crude product was obtained as a brown oil, containing 26% β-chloroacrylamide by ^{1}H NMR spectroscopy. This was purified by column chromatography on silica gel using hexane-ethyl acetate (gradient elution 10-20% ethyl acetate) as eluent to give the pure product **17** as a white solid (0.33 g, 47%), mp 124-125 °C; $[\alpha]_D^{20}$ 60.10 (*c* 0.5 in $CHCl_3$); (Found C, 62.15; H, 4.46; Cl, 10.69; N, 4.09; S, 8.96. $C_{18}H_{16}ClNO_2S$ requires C, 62.51; H, 4.66; Cl, 10.25; N, 4.05; S, 9.27%); ν_{max}/cm^{-1} (KBr) 3388 (OH), 3290 (NH), 3036 (CH), 2916 (CH), 1630 (CO), 1514 (NH bend), 1457 (CN stretch); δ_H (400 MHz, $CDCl_3$) 2.86 (1H, dd, A of ABX, J_{AB} 16.6, J_{AX} 1.6, one of ArCH_2), 3.10 (1H, B of ABX, J_{AB} 16.6, J_{AX} 4.8, one of ArCH_2), 4.43-4.50 (1H, m, C*H*OH), 5.29-5.35 (1H, m, NHC*H*), 6.69 (1H, d, *J* 7.2, Ar*H*), 7.05-7.13 (1H, m, Ar*H*), 7.25-7.36 (8H, m, N*H* & Ar*H*), 7.96 [1H, s, Cl*H*C(3)=]; δ_C (75.5 MHz, $CDCl_3$) 39.6 (CH_2, Ar*C*H_2), 58.2 (CH, NH*C*H), 73.6 (CH, *C*HOH), 124.2, 125.3, 127.2, 127.3, 128.3, 128.6, 129.6 (7 × CH, 7 × aromatic *C*H), 131.0, 133.2 [2 × C, *C*(2)S or aromatic *C*], 139.0 [CH, ClH*C*(3)=], 139.78, 139.82 [2 × C, *C*(2)S or aromatic *C*], 162.9 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{18}H_{17}NO_2S^{35}Cl$ $[M+H]^+$ 346.0669. Found 346.0681; m/z (ES+) 348.0 {[($C_{18}H_{17}NO_2S^{37}Cl$)+H^+], 38%}, 345.9 {[($C_{18}H_{17}NO_2S^{35}Cl$)+H^+], 100%}.

***(Z)*-3-Chloro-*N*-[(S)-1-hydroxy-3-phenylpropan-2-yl]-2-(phenylthio)acrylamide 18**

This was prepared following the procedure described above for **11** using *N*-[(*S*-1-hydroxy-3-phenylpropan-2-yl]-2-(phenylthio)propanamide **8** (1.78 g, 5.6 mmol), *N*-chlorosuccinimide (1.50 g, 11.0 mmol) and toluene (50 mL). The reaction mixture was heated at 90 °C for 1 h. Following filtration and evaporation of the solvent at reduced pressure, the crude product was obtained as a yellow oil, containing 20% β-chloroacrylamide by ^{1}H NMR spectroscopy. This was purified by column chromatography on silica gel using hexane-ethyl acetate (gradient elution 20-40% ethyl acetate) as eluent to give the pure product **18** (0.67 g, 34%) as a white solid, mp 80-81 °C; $[\alpha]_D^{20}$ 84.33 (*c* 0.1 in EtOH); (Found C, 61.83; H, 5.21; Cl, 10.40; N, 4.08; S, 8.90. $C_{18}H_{18}ClNO_2S$ requires C, 62.15; H, 5.22; Cl, 10.19; N, 4.03; S, 9.22%); ν_{max}/cm^{-1} (KBr) 3423 (OH), 3368 (NH), 3061 (CH), 2928 (CH), 1640 (CO), 1518 (NH bend), 1439 (CN stretch); δ_H (400 MHz, $CDCl_3$) 1.81 (1H, br t, *J* 5.0, O*H*), 2.68 (1H, dd, A of ABX, J_{AB} 13.9, J_{AX} 7.4, one of C*H*$_2$Ph), 2.74 (1H, dd, B of ABX, J_{AB} 13.9, J_{BX} 7.4, one of C*H*$_2$Ph), 3.38-3.48 (2H, m, C*H*$_2$OH), 4.07-4.13 (1H, sym m, NHC*H*), 6.97-7.11 [3H, m, N*H* (br d) & Ar*H*], 7.14-7.34 (8H, m, Ar*H*), 7.86 [1H, s, Cl*H*C(3)=]; δ_c (75.5 MHz, $CDCl_3$) 36.7 (CH_2, *C*H$_2$Ph), 53.2 (CH, NH*C*H), 63.6 (CH_2, *C*H$_2$OH), 126.8, 127.3, 128.4, 128.7, 129.2, 129.5 (6 × CH, 6 × aromatic *C*H), 130.8, 133.0, 137.1 [3 × C, 2 × aromatic *C* & *C*(2)S], 139.2 [CH, ClH*C*(3)=], 162.6 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{18}H_{19}NO_2S^{35}Cl$ $[M+H]^+$ 348.0825. Found 348.0831; m/z (ES+) 350.0 {[($C_{18}H_{18}NO_2S^{37}Cl$)+H^+], 40%}, 348.0 {[($C_{18}H_{18}NO_2S^{35}Cl$)+H^+], 100%}.

***(Z)*-3-Chloro-*N*-[(*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]-2-(phenylthio)acrylamide 19**

This was prepared following the procedure described above for **11** using 2-(phenylthio)-*N*-[(*S*-1-hydroxy-3,3-dimethylbutan-2-yl]propanamide **9** (1.93 g, 6.9 mmol), *N*-chlorosuccinimide (1.83 g, 13.4 mmol) and toluene (50 mL). The reaction mixture was heated at 90 °C for 1 h. Following filtration and evaporation of the solvent at reduced pressure, the crude product was obtained as a pale yellow oil, containing 28% β-chloroacrylamide by ^{1}H NMR spectroscopy. This was purified by column chromatography on silica gel using hexane-ethyl acetate (gradient elution 20-40% ethyl acetate) as eluent to give the pure product **19** (0.95 g, 44%) as pale yellow solid, mp 37-39 °C; $[\alpha]_D^{20}$ –67.70 (*c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3401 (OH), 3264 (NH), 3062 (CH), 2964 (CH), 1657 (CO), 1635, 1526 (NH bend), 1476 (CN stretch); δ_H (400 MHz, $CDCl_3$) 0.74 [9H, s, C(C*H*$_3$)$_3$], 1.82 (1H,

br s, O*H*), 3.39 (1H, dd, *J* 7.9, 7.4, NHC*H*), 3.64-3.76 (2H, m, CH_2OH), 7.00 (1H, br d, *J* 8.0, N*H*), 7.20-7.36 (5H, m, Ar*H*), 7.97 [1H, s, Cl*H*C(3)=]; δ_C (75.5 MHz, $CDCl_3$) 26.6 [CH_3, C(*C*H_3)$_3$], 33.4 [C, *C*(CH_3)$_3$], 60.4 (CH, NH*C*H), 63.0 (CH_2, *C*H_2OH), 127.3, 128.0, 129.6 (3 × CH, 3 × aromatic *C*H), 130.5, 133.1 [2 × C, aromatic *C* & *C*(2)S], 140.0 [CH, ClH*C*(3)=], 163.2 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{15}H_{21}NO_2S^{35}Cl$ $[M+H]^+$ 314.0982. Found 314.0979; m/z (ES+) 316.0 {[($C_{15}H_{20}NO_2S^{37}Cl$)+H^+], 46%}, 314.0 {[($C_{15}H_{20}NO_2S^{35}Cl$)+H^+], 100%}.

***(Z)*-3-Chloro-*N*-[(*R*)-3,3-dimethylbutan-2-yl]-2-(phenylthio)acrylamide 20**

This was prepared following the procedure described above for **11** using *N*-[(*R*)-3,3-dimethylbutan-2-yl]-2-(phenylthio)propanamide **10** (1.10 g, 4.1 mmol), *N*-chlorosuccinimide (1.10 g, 8.1 mmol) and toluene (40 mL). The reaction mixture was heated at 90 °C for 1 h. Following filtration and evaporation of the solvent at reduced pressure, the crude product was obtained as an off-white solid, containing 96% β-chloroacrylamide by ^{1}H NMR spectroscopy. This was purified by column chromatography on silica gel using hexane-ethyl acetate 95:5 as eluent to give the pure product **20** (0.94 g, 76%) as a white solid, mp 85-86 °C; $[\alpha]_D^{20}$ 92.94 (*c* 0.1 in $CHCl_3$); (Found C, 60.41; H, 6.70; N, 4.66; S, 11.17; Cl, 11.99. $C_{15}H_{20}ClNOS$ requires C, 60.49; H, 6.77; N, 4.70; S, 10.77; Cl, 11.90%); ν_{max}/cm^{-1} (KBr) 3276 (NH), 3064 (CH), 2965 (CH), 1636 (CO), 1533 (NH bend), 1475 (CN stretch); δ_H (400 MHz, $CDCl_3$) 0.68 [9H, s, C(CH_3)$_3$], 0.86 (3H, d, *J* 6.8, CHCH_3), 3.71-3.78 (1H, dq, *J* 9.6, 6.8, NHC*H*), 6.69 (1H, br d, *J* 9.6, N*H*), 7.19-7.33 (5H, m, Ar*H*), 7.93 [1H, s, Cl*H*C(3)=]; δ_C (75.5 MHz, $CDCl_3$) 15.6 (CH_3, CH*C*H_3), 25.9 [CH_3, C(*C*H_3)$_3$], 33.9 [C, *C*(CH_3)$_3$], 53.7 (CH, NH*C*H), 127.1, 128.1, 129.6 (3 × CH, 3 × aromatic *C*H), 130.8, 133.1 [2 × C, aromatic *C* & *C*(2)S], 139.2 [CH, ClH*C*(3)=], 161.4 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{15}H_{21}NOS^{35}Cl$ $[M+H]^+$ 298.1032. Found 298.1038; m/z (ES+) 300.0 {[($C_{15}H_{20}NOS^{37}Cl$)+H^+], 44%}, 298.0 {[($C_{15}H_{20}NOS^{35}Cl$)+H^+], 100%}.

(*Z*)-2-(*S*s)-(Benzylsulfinyl)-3-chloro-*N*-[(*R*)-1-phenylethyl)acrylamide 21a and (*Z*)-2-(*R*s)-(benzylsulfinyl)-3-chloro-*N*-[(*R*)-1-phenylethyl)acrylamide 21b

A solution of Oxone® (3.93 g, 6.4 mmol) in water (20 mL) was added to a stirring solution of (*Z*)-2-(benzylthio)-3-chloro-*N*-[(*R*)-1-phenylethyl)acrylamide **11** (1.06 g, 3.2 mmol) in acetone (60 mL) at room temperature. A colourless precipitate formed immediately. The reaction mixture was stirred for 2 h. Water (80 mL) was added and the aqueous solution was extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with water (2 × 50 mL) and brine (50 mL), dried, filtered and concentrated at reduced pressure to give the crude sulfoxides **21a** and **21b** as a white solid and a 1.3:1 mixture of diastereomers. The ^{1}H NMR spectrum of the crude product was very clean, with no evidence of sulfone formation. Following purification by column chromatography using hexane-ethyl acetate (gradient elution 5-20% ethyl acetate) as eluent, the less polar and major diastereomer **21a** was isolated as a clear oil (0.31 g, 28%); $[\alpha]_D^{20}$ –179.0 (*c* 0.4 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3237 (NH), 3071 (CH), 2925 (CH), 1667 (CO), 1571, 1455 (CN stretch), 1030 (SO); δ_H (400 MHz, $CDCl_3$) 1.48 [3H, d, *J* 6.8, CH(C*H*$_3$)], 4.05 (1H, d, A of AB system, J_{AB} 12.4, one of SC*H*$_2$), 4.23 (1H, d, B of AB system, J_{AB} 12.8, one of SC*H*$_2$), 5.09 (1H, overlapping dq, *J* 7.2, 6.8, NHC*H*), 7.05-7.15 (2H, m, Ar*H*), 7.17-7.46 (8H, m, Ar*H*), 7.67 [1H, s, Cl*H*C(3)=], 8.86 (1H, br d, *J* 6.8, N*H*); δ_C (75.5 MHz, $CDCl_3$) 22.4 [CH_3, CH(*C*H$_3$)], 49.5 (CH, NH*C*H), 58.6 (CH_2, S*C*H$_2$), 126.3, 127.4 (2 × CH, 2 × aromatic *C*H), 128.2 (C, aromatic *C*), 128.75, 128.83, 128.9, 130.4 (4 × CH, 4 × aromatic *C*H), 135.5 [C, aromatic *C* or *C*(2)S], 136.6 [C, ClH*C*(3)=], 143.0 [C, aromatic *C* or *C*(2)S], 159.8 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{18}H_{19}NO_2S^{35}Cl$ $[M+H]^+$ 348.0825. Found 348.0822; m/z (ES+) 350.0 {[($C_{18}H_{18}NO_2S^{37}Cl$)+H^+], 42%}, 348.0 {[($C_{18}H_{18}NO_2S^{35}Cl$)+H^+], 100%}.

The more polar minor diastereomer **21b** was isolated as a white solid (0.22 g, 19%), mp 137-138 °C; $[\alpha]_D^{20}$ 323.3 (*c* 0.5 in $CHCl_3$); (Found C, 61.90; H, 4.96; N, 3.98; S, 8.79; Cl, 10.27. $C_{18}H_{18}ClNO_2S$ requires C, 62.15; H, 5.22; N, 4.03; S, 9.22; Cl, 10.19%); ν_{max}/cm^{-1} (KBr) 3247 (NH), 3030 (CH), 2973 (CH), 1655 (CO), 1572, 1454 (CN stretch), 1035 (SO); δ_H (400 MHz, $CDCl_3$) 1.27 [3H, d, *J* 6.8, CH(C*H*$_3$)], 4.24 (1H, d, A of AB system, J_{AB} 12.8, one of SC*H*$_2$), 4.29 (1H, d, B of AB system, J_{AB} 13.2, one of SC*H*$_2$), 4.91 (1H, overlapping dq, *J* 7.2, 7.2, NHC*H*), 7.16-7.35 (7H, m, Ar*H*), 7.37-7.46 (3H, m, Ar*H*), 7.67 [1H, s, Cl*H*C(3)=], 8.64 (1H, br d, *J* 7.2, N*H*); δ_C (75.5 MHz, $CDCl_3$) 22.6 [CH_3, CH(*C*H$_3$)], 49.3 (CH, NH*C*H), 58.2 (CH_2, S*C*H$_2$), 125.9, 127.3 (2 × CH, 2 × aromatic *C*H), 128.2 (C, aromatic *C*), 128.7, 128.9, 129.0, 130.8 (4 × CH, 4 × aromatic *C*H), 135.4 [C, aromatic *C* or *C*(2)S], 136.0 [C, ClH*C*(3)=], 142.9 [C, aromatic *C* or *C*(2)S], 159.6 (C, *C*O); HRMS (ES+): Exact mass

calculated for $C_{18}H_{19}NO_2S^{35}Cl$ $[M+H]^+$ 348.0825. Found 348.0814; m/z (ES+) 350.0 {[($C_{18}H_{18}NO_2S^{37}Cl$)+H^+], 42%}, 348.0 {[($C_{18}H_{18}NO_2S^{35}Cl$)+H^+], 100%}.

The stereochemistry was determined by single crystal X-ray diffraction on a crystalline sample of **21b** recrystallised from ethanol.

Crystals of **21b** are monoclinic, space group *P* 2_1, formula $C_{18}H_{18}ClNO_2S$, M = 347.84, a = 5.8018(6) Å, b = 18.291(3) Å, c = 8.1019(13) Å, α = 90.00 °, β = 93.218(11) °, γ = 90.00 °, U = 858.4(2) $Å^3$, F(000) = 364, μ(Mo-Kα) = 0.352 mm^{-1}, $R(F_o)$ = 0.0611, for 1827 observed reflections with I>2σ(I), $wR_2(F^2)$ = 0.1539 for all 3195 unique reflections. Data in the θ range 2.23-25.51 ° were collected at 293 K on a Nonius MACH3 diffractometer using Mo-Kα graphite monochromated radiation, λ = 0.7107 Å, and corrected for Lorentz and polarization effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

A fraction containing a mixture of the 2 diastereomers **21a** and **21b** in a ratio of 1:2.8 was also isolated from the column as a white solid (0.34 g, 31%).

(*Z*)-2-(*S*s/*R*s)-(Benzylsulfinyl)-3-chloro-*N*-[(*R*)-2-hydroxy-1-phenylethyl]acrylamide 22

This was prepared following the procedure described above for **21** by addition of (*Z*)-2-(benzylthio)-3-chloro-*N*-[(*R*)-2-hydroxy-1-phenylethyl]acrylamide **12** (0.16 g, 0.5 mmol) in acetone (15 mL) to Oxone® (0.57 g, 0.9 mmol) in water (5 mL). Following stirring at room temperature for 16 h, the crude sulfoxides **22a** and **22b** and a 1.8:1 mixture of diastereomers. Following purification using hexane-ethyl acetate (gradient elution 10-40% ethyl acetate) as eluent, the less polar major diastereomer **22a** was isolated as a clear oil (0.09 g, 50%); $[\alpha]_D^{20}$ –67.47 (*c* 0.1 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3396 (OH), 3247 (NH), 2926 (CH), 1656 (CO), 1534 (NH bend), 1454 (CN stretch), 1028 (SO); δ_H (400 MHz, $CDCl_3$) 2.08 (1H, t, *J* 6.0, O*H*), 3.56-3.71 (2H, m, CH_2OH), 4.31 (1H, d, A of AB system, J_{AB} 13.2, one of SCH_2), 4.38 (1H, d, B of AB system, J_{AB} 13.2, one of SCH_2), 4.87-4.94 (1H, overlapping dt, *J* 6.8, 7.2, NHC*H*), 7.18-7.47 (10H, m, Ar*H*), 7.68 [1H, s, Cl*H*C(3)=], 8.98 (1H, br d, *J* 7.2, N*H*); δ_C (75.5 MHz, $CDCl_3$) 56.1 (CH, NH*C*H), 58.1 (CH_2, S*C*H_2), 66.7 (CH_2, *C*H_2OH), 126.7, 127.9 (2 × CH, 2 × aromatic *C*H), 128.3 (C, aromatic *C*), 128.89, 128.92, 129.1, 130.9 (4 × CH, 4 × aromatic *C*H), 135.6 [C, *C*(2)S or aromatic *C*], 136.6 [CH, ClH*C*(3)=], 138.1 [C, *C*(2)S or

aromatic *C*], 161.0 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{18}H_{19}NO_3S^{35}Cl$ $[M+H]^+$ 364.0774. Found 364.0770; m/z (ES+) 366.0 {[($C_{18}H_{18}NO_3S^{37}Cl$)+H^+], 42%}, 364.0 {[($C_{18}H_{18}NO_3S^{35}Cl$)+H^+], 100%}.

The more polar minor diastereomer **22b** was isolated as a clear oil, containing ~18% of the major diastereomer **22a** (0.04 g, 24%); $[\alpha]_D^{20}$ 122.60 (*c* 0.08 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3401 (OH), 3203 (NH), 2923 (CH), 1651 (CO), 1529 (NH bend), 1455 (CN stretch), 1029 (SO); δ_H (400 MHz, $CDCl_3$) 2.49 (1H, t, *J* 6.0, O*H*), 3.78 (2H, overlapping dd, *J* 6.0, 5.6, CH_2OH), 4.12 (1H, d, A of AB system, J_{AB} 13.2, one of SCH_2), 4.23 (1H, d, B of AB system, J_{AB} 13.2, one of SCH_2), 4.97 (1H, overlapping dt, *J* 7.2, 5.6, NHC*H*), 7.08-7.50 (10H, m, Ar*H*), 7.73 [1H, s, Cl*H*C(3)=], 9.04 (1H, br d, *J* 7.2, N*H*); δ_C (75.5 MHz, $CDCl_3$) 56.6 (CH, NH*C*H), 58.2 (CH_2, S*C*H_2), 67.1 (CH_2, *C*H_2OH), 127.0 (CH, aromatic *C*H), 127.9 (C, aromatic *C*), 128.0, 128.79, 128.89, 128.93, 130.5 (5 × CH, 5 × aromatic *C*H), 135.1 [C, *C*(2)S or aromatic *C*], 137.0 [CH, ClH*C*(3)=], 138.1 [C, *C*(2)S or aromatic *C*], 161.2 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{18}H_{19}NO_3S^{35}Cl$ $[M+H]^+$ 364.0774. Found 364.0774; m/z (ES+) 366.0 {[($C_{18}H_{18}NO_3S^{37}Cl$)+H^+], 44%}, 364.0 {[($C_{18}H_{18}NO_3S^{35}Cl$)+H^+], 100%}.

(*Z*)-3-Chloro-*N*-[(*R*)-2-hydroxy-1-phenylethyl]-2-(*S*s/*R*s)-(benzenesulfinyl)acrylamide 23

This was prepared following the procedure described above for **21** by addition of (*Z*)-3-chloro-*N*-[(*R*)-2-hydroxy-1-phenylethyl]-2-(phenylthio)acrylamide **16** (0.10 g, 0.3 mmol) in acetone (10 mL) to Oxone® (0.35 g, 0.6 mmol) in water (5 mL). Following stirring at room temperature for 16 h, the crude sulfoxides **23a** and **23b** were obtained as a clear oil and 2.2:1 mixture of diastereomers. The ^{1}H NMR spectrum of the crude product was very broad. The crude product was purified by column chromatography on silica gel using hexane-ethyl acetate 60:40 as eluent to give the less polar minor diastereomer **23b** as a clear oil (0.01 g, 14%), containing ~4% of **23a**; $[\alpha]_D^{20}$ –139.5 (*c* 0.1 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3391 (OH), 3253 (NH), 3055 (CH), 2923 (CH), 1656 (CO), 1536 (NH bend), 1446 (CN stretch), 1026 (SO); δ_H (400 MHz, $CDCl_3$) 1.87 (1H, overlapping dd, *J* 7.2, 6.0, O*H*), 3.65-3.77 (2H, m, CH_2OH), 4.96 (1H, overlapping dt, *J* 7.6, 5.2, NHC*H*), 7.23-7.43 (5H, m, Ar*H*), 7.53-7.63 (3H, m, Ar*H*), 7.72 [1H, s, Cl*H*C(3)=], 7.74-7.81 (2H, m, Ar*H*), 9.17 (1H, br d, *J* 7.6, N*H*); δ_C (75.5 MHz, $CDCl_3$) 55.7 (CH, NH*C*H), 66.3 (CH_2, *C*H_2OH), 124.2, 126.7, 128.0, 128.9, 129.7, 131.9 (6 × CH, 6 × aromatic *C*H), 137.7 [CH, ClH*C*(3)=], 138.1, 138.6, 141.0 [3 × C,

C(2)S & 2 × aromatic *C*], 160.4 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{17}H_{17}NO_3S^{35}Cl$ $[M+H]^+$ 350.0618. Found 350.0611; m/z (ES+) 352.0 {[($C_{17}H_{16}NO_3S^{37}Cl$)+H^+], 40%}, 350.0 {[($C_{17}H_{16}NO_3S^{35}Cl$)+H^+], 100%}.

The more polar major diastereomer **23a** was isolated as a white solid (0.04 g, 36%) and contained ~4% of **23b**, mp 105-107 °C; $[\alpha]_D^{20}$ –65.00 (*c* 0.1 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3401 (OH), 3293 (NH), 3042 (CH), 2919 (CH), 1629 (CO), 1538 (NH bend), 1444 (CN stretch), 1056 (SO); δ_H (400 MHz, $CDCl_3$) 2.35 (1H, t, *J* 6.0, O*H*), 3.81-3.98 (2H, m, CH_2OH), 5.02 (1H, overlapping dt, *J* 6.4, 6.0, NHC*H*), 6.99-7.13 (2H, m, Ar*H*), 7.24-7.60 (8H, m, Ar*H*), 7.79 [1H, s, Cl*H*C(3)=], 9.03 (1H, br d, *J* 6.8, N*H*); δ_C (75.5 MHz, $CDCl_3$) 56.1 (CH, NH*C*H), 66.2 (CH_2, *C*H_2OH), 124.1, 126.8, 127.8, 128.7, 128.9, 129.6 (6 × CH, 6 × aromatic *C*H), 138.1 [C, aromatic *C* or *C*(2)S], 138.2 [CH, ClH*C*(3)=], 138.4, 140.7 [2 × C, *C*(2)S or aromatic *C*], 160.6 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{17}H_{17}NO_3S^{35}Cl$ $[M+H]^+$ 350.0618. Found 350.0617; m/z (ES+) 352.0 {[($C_{17}H_{16}NO_3S^{37}Cl$)+H^+], 52%}, 350.0 {[($C_{17}H_{16}NO_3S^{35}Cl$)+H^+], 100%}.

(*Z*)-3-Chloro-*N*-[(1*R*,2*S*)-2,3-dihydro-2-hydroxy-1*H*-inden-1-yl]-2-(*S*s/*R*s)-(benzenesulfinyl)acrylamide 26

This was prepared following the procedure described above for **21** by addition of (*Z*)-3-chloro-*N*-[(1*R*,2*S*)-2,3-dihydro-2-hydroxy-1*H*-inden-1-yl]-2-(phenylthio)acrylamide **17** (0.07 g, 0.2 mmol) in acetone (8 mL) to Oxone® (0.26 g, 0.4 mmol) in water (4 mL). Following stirring at room temperature for 16 h, the crude sulfoxides **26a** and **26b** were obtained as a clear oil and a 1.6:1 mixture of diastereomers. This was purified by column chromatography on silica gel using hexane-ethyl acetate 60:40 as eluent to give a 1.1:1 mixture of the 2 diastereomers **26a** and **26b** as a clear oil (0.04 g, 46%); $[\alpha]_D^{20}$ –66.39 (*c* 0.2 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3436 (OH), 3231 (NH), 3055 (CH), 2924 (CH), 1650 (CO), 1534 (NH bend), 1474 (CN stretch), 1033 (SO); δ_H (300 MHz, $CDCl_3$) 1.83 (1H, br s, O*H* of **26a** and **26b**), 2.93 (0.52H, dd, A of ABX, J_{AB} 16.5, J_{AX} 1.8, one of ArCH_2 of **26b**), 2.96 (0.48H, dd, A of ABX, J_{AB} 16.5, J_{AX} 2.1, one of ArCH_2 of **26a**), 3.06-3.23 (1H, m, one of ArCH_2 of **26a** and **26b**), 4.49 (0.52H, dt, *J* 8.1, 1.8, C*H*OH of **26b**), 4.63 (0.48H, dt, *J* 7.8, 2.1, C*H*OH of **26a**), 5.26-5.47 (1H, m, NHC*H* of **26a** and **26b**), 6.59 (0.48H, d, *J* 7.5, Ar*H* of **26a**), 7.02-7.77 (10H, m, Ar*H* of **26a** and **26b**), 7.81 [0.52H, s, Cl*H*C(3)= of **26b**], 7.82 [0.48H, s,

Cl*H*C(3)= of **26a**], 8.78-9.06 (1H, br m, N*H* of **26a** and **26b**); δ_C (75.5 MHz, $CDCl_3$) 39.7, 39.8* (2 × CH_2, Ar*C*H_2 of 2 diastereomers), 57.6*, 58.3 (2 × CH, NH*C*H of 2 diastereomers), 73.6*, 73.7 (2 × CH, *C*HOH of 2 diastereomers), 124.2*, 124.3, 124.5*, 124.6, 125.3*, 125.4, 126.9*, 127.4, 128.2*, 128.4, 129.67*, 129.70, 131.6*, 131.8 (14 × CH, aromatic *C*H of 2 diastereomers), 137.5, 138.0* [2 × CH, ClH*C*(3)= of 2 diastereomers], 139.0*, 139.7, 139.8, 139.9*, 140.9*, 141.1 [6 × C, *C*(2)S & aromatic *C* of 2 diastereomers], 160.9*, 161.0 (2 × C, *C*O of 2 diastereomers); HRMS (ES+): Exact mass calculated for $C_{18}H_{17}NO_3S^{35}Cl$ $[M+H]^+$ 362.0618. Found 362.0609; m/z (ES+) 364.0 {[($C_{18}H_{17}NO_3S^{37}Cl$)+H^+], 40%}, 362.0 {[($C_{18}H_{17}NO_3S^{35}Cl$)+H^+], 100%}.

*Signals for **26a**

A second fraction containing the more polar major diastereomer **26a** was also isolated (0.03 g, 43%) and contained ~4% of **26b**; $[\alpha]_D^{20}$ 99.28 (*c* 0.1 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3414 (OH), 3247 (NH), 3051 (CH), 2922 (CH), 1654 (CO), 1527 (NH bend), 1475 (CN stretch), 1034 (SO); δ_H (300 MHz, $CDCl_3$) 2.24 (1H, d, *J* 5.4, O*H*), 2.97 (1H, dd, A of ABX, J_{AB} 16.5, J_{AX} 2.1, one of ArCH_2), 3.06-3.23 (1H, dd, B of ABX, J_{AB} 16.5, J_{AX} 5.1, one of ArCH_2), 4.65 (1H, ddd, *J* 10.2, 5.1, 2.1, C*H*OH), 5.36 (1H, dd, *J* 8.1, 5,1, NHC*H*), 6.59 (1H, d, *J* 7.5, Ar*H*), 7.03-7.34 (4H, m, Ar*H*), 7.43-7.63 (5H, m, Ar*H*), 7.83 [1H, s, Cl*H*C(3)=], 8.90 (1H, br d, *J* 8.1, N*H*); δ_C (75.5 MHz, $CDCl_3$) 39.8 (CH_2, Ar*C*H_2), 57.6 (CH, NH*C*H), 73.6 (CH, *C*HOH), 124.2, 124.5, 125.3, 126.9, 128.2, 129.7, 131.6 (7 × CH, 7 × aromatic *C*H), 138.1 [CH, ClH*C*(3)=], 138.9, 139.9, 140.9 [3 × C, *C*(2)S & aromatic *C*], 160.9 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{18}H_{17}NO_3S^{35}Cl$ $[M+H]^+$ 362.0618. Found 362.0605; m/z (ES+) 364.0 {[($C_{18}H_{17}NO_3S^{37}Cl$)+H^+], 40%}, 362.0 {[($C_{18}H_{17}NO_3S^{35}Cl$)+H^+], 100%}.

(Z)-2-(*S*s/*R*s)-(Benzylsulfinyl)-3-chloro-*N*-[(*S*)-1-hydroxy-3-phenylpropan-2-yl]acrylamide 24

This was prepared following the procedure described above for **21** by addition of (*Z*)-2-(benzylthio)-3-chloro-*N*-[(S)-1-hydroxy-3-phenylpropan-2-yl]acrylamide **13** (0.13 g, 0.4 mmol) in acetone (8 mL) to Oxone® (0.44 g, 0.7 mmol) in water (5 mL). Following stirring at room temperature for 16 h, the crude sulfoxides **24a** and **24b** were obtained as a clear oil (0.11 g, 85%) and a 1.1 : 1 mixture of diastereomers. As the ^1H NMR spectrum of the crude

product was very clean, no purification was necessary; $[\alpha]_D^{20}$ –1.40 (*c* 0.3 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3412 (OH), 3253 (NH), 3061 (CH), 2926 (CH), 1655 (CO), 1571, 1455 (CN stretch), 1031; δ_H (300 MHz, $CDCl_3$) 2.44 (1H, br s, O*H* of **24a** and **24b**), 2.73 (0.48H, dd, A of ABX, J_{AX} 14.1, J_{AB} 9.3, one of CH_2Ph of **24b**), 2.82 (1.04H, d, *J* 7.2, CH_2Ph of **24a**) 2.96 (0.48H, dd, B of ABX, J_{AX} 14.1, J_{AB} 9.3, one of CH_2Ph of **24b**), 3.43 (0.48H, dd, A of ABX, J_{BX} 11.4, J_{AB} 5.7, one of CH_2OH of **24b**), 3.52 (0.48H, dd, B of ABX, J_{BX} 11.4, J_{AB} 3.9, one of CH_2OH of **24b**), 3.62 (0.52H, dd, A of ABX, J_{BX} 11.1, J_{AB} 5.4, one of CH_2OH of **24a**), 3.66 (0.48H, d, A of AB system, J_{AB} 12.9, one of SCH_2 of **24b**), 3.72 (0.52H, dd, B of ABX, J_{BX} 11.1, J_{AB} 3.9, one of CH_2OH of **24a**), 3.99 (0.48H, d, B of AB system, J_{AB} 12.9, one of SCH_2 of **24b**), 4.07-4.16 (0.48H, m, NHC*H* of **24b**), 4.18 (0.52H, d, A of AB system, J_{AB} 12.9, one of SCH_2 of **24a**), 4.26 (0.52H, d, B of AB system, J_{AB} 12.9, one of SCH_2 of **24a**), 4.32-4.46 (0.52H, m, NHC*H* of **24a**), 6.99-7.46 (10H, m, Ar*H* of **24a** and **24b**), 7.58 [0.52H, s, Cl*H*C(3)= of **24a**], 7.60 [0.48H, s, Cl*H*C(3)= of **24b**], 8.47 (0.48H, br d, *J* 7.5, N*H* of **24b**), 8.61 (0.52H, br d, *J* 7.5, N*H* of **24a**); δ_C (75.5 MHz, $CDCl_3$) 36.8, 37.0* (2 × CH_2, *C*H_2Ph of 2 diastereomers), 53.1*, 53.7 (2 × CH, NH*C*H of 2 diastereomers), 58.1, 58.5* (2 × CH_2, S*C*H_2 of 2 diastereomers), 63.9, 64.6 (2 × CH_2, *C*H_2OH of 2 diastereomers), 126.7*, 126.8 (2 × CH, aromatic *C*H), 128.1, 128.3 (2 × C, aromatic *C*), 128.6, 128.7, 128.8, 128.9, 129.0, 129.3, 130.5, 130.8 (8 × CH, aromatic *C*H), 134.8, 135.3 [2 × C, aromatic *C* or *C*(2)S], 136.5 (CH, aromatic *C*H), 137.5 (C, aromatic *C*), 137.79*, 137.81 [2 × CH, ClH*C*(3)= of 2 diastereomers], 161.1, 161.3* (2 × C, *C*O of 2 diastereomers) - all of the aromatic signals were not resolved; HRMS (ES+): Exact mass calculated for $C_{19}H_{21}NO_3S^{35}Cl$ $[M+H]^+$ 378.0931. Found 378.0917; m/z (ES+) 380.0 {[($C_{19}H_{20}NO_3S^{37}Cl$)+H^+], 42%}, 378.0 {[($C_{19}H_{20}NO_3S^{35}Cl$)+H^+], 100%}.

*Signals for **24a** (major).

(Z)-3-Chloro-*N*-[(S)-1-hydroxy-3-phenylpropan-2-yl]-2-(*S*s/*R*s)-(benzenesulfinyl)acrylamide 25

This was prepared following the procedure described above for **21** by addition of (*Z*)-3-chloro-*N*-[(S)-1-hydroxy-3-phenylpropan-2-yl]-2-(phenylthio)acrylamide **18** (0.22 g, 0.6 mmol) in acetone (15 mL) to Oxone® (0.78 g, 1.3 mmol) in water (5 mL). Following stirring at room temperature for 16 h, the crude sulfoxides **25a** and **25b** were obtained as a white

solid (0.22 g, 95%) and a 1.1 : 1 mixture of diastereomers. As the ^{1}H NMR spectrum of the crude product was very clean, purification was not required; $[\alpha]_D^{20}$ –30.74 (*c* 0.1 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3401 (OH), 3231 (NH), 3045 (CH), 2922 (CH), 1643 (CO), 1541 (NH bend), 1444 (CN stretch), 1032 (SO); δ_H (300 MHz, $CDCl_3$) 1.74 (0.52H, br s, O*H* of **25a**), 2.45 (0.48H, br s, O*H* of **25b**), 2.69 (0.48H, dd, A of ABX, J_{AB} 14.1, J_{AX} 8.1, one of CH_2Ph of **25b**), 2.82-2.94 (1.52H, m, CH_2Ph of **25a** and one of CH_2Ph of **25b**), 3.42 (0.48H, dd, A of ABX, J_{AB} 11.1, J_{AX} 4.8, one of CH_2OH of **25b**), 3.47 (0.48H, dd, B of ABX, J_{AB} 11.1, J_{BX} 4.8, one of CH_2OH of **25b**), 3.62 (0.52H, dd, A of ABX, J_{AB} 11.1, J_{AX} 4.8, one of CH_2OH of **25a**), 3.70 (0.52H, dd, A of ABX, J_{AB} 11.1, J_{AX} 3.6, one of CH_2OH of **25a**), 4.09-4.31 (1H, m, NHC*H* of **25a** and **25b**), 7.11-7.56 (9H, m, Ar*H* of **25a** and **25b**), 7.59-7.66 (1H, m, Ar*H* of **25a** and **25b**), 7.68 [0.48H, s, Cl*H*C(3)= of **25b**], 7.71 [0.52H, s, Cl*H*C(3)= of **25a**], 8.58 (0.48H, br d, *J* 7.2, N*H* of **25b**), 8.73 (0.52H, br d, *J* 7.8, N*H* of **25a**); δ_C (75.5 MHz, $CDCl_3$) 36.9, 37.0* (2 × CH_2, *C*H_2Ph of 2 diastereomers), 53.2*, 53.5 (2 × CH, NH*C*H of 2 diastereomers), 63.5, 64.3* (2 × CH_2, *C*H_2OH of 2 diastereomers), 124.2, 124.3*, 126.65*, 126.71, 128.60, 128.62, 129.1, 129.3, 129.7, 131.76, 131.80 [11 × CH (11 signals for 12 carbons), aromatic *C*H of 2 diastereomers], 137.32 [C, aromatic *C* or *C*(2)S of 1 diastereomer], 137.3*, 137.4 [2 × CH, ClH*C*(3)= of 2 diastereomers], 137.5, 138.3*, 138.7, 140.9*, 141.1 [5 × C, *C*(2)S & aromatic *C* of 2 diastereomers], 160.6, 161.0* (2 × C, *C*O of 2 diastereomers); HRMS (ES+): Exact mass calculated for $C_{18}H_{19}NO_3S^{35}Cl$ $[M+H]^+$ 364.0774. Found 364.0757; m/z (ES+) 366.0 {[($C_{18}H_{18}NO_3S^{37}Cl$)+H^+], 38%}, 364.0 {[($C_{18}H_{18}NO_3S^{35}Cl$)+H^+], 100%}.

*Signals for **25a** (major).

(Z)-2-(*S*s/*R*s)-(Benzylsulfinyl)-3-chloro-*N*-[(*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]acrylamide 27

This was prepared following the procedure described above for **21** by addition of (*Z*)-2-(benzylthio)-3-chloro-*N*-[(*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]acrylamide **14** (0.12 g, 0.4 mmol) in acetone (10 mL) to Oxone® (0.44 g, 0.7 mmol) in water (5 mL). Following stirring at room temperature for 16 h, the crude sulfoxides **27a** and **27b** were obtained as a clear oil and a 3.3 : 1 mixture of diastereomers. Following purification by column chromatography on silica gel using hexane-ethyl acetate 60:40 as eluent, the less polar major diastereomer **27a**

was isolated as a clear oil (0.08 g, 64%), containing ~6% of **27b**; $[\alpha]_D^{20}$ 193.70 (*c* 0.2 in $CHCl_3$); ν_{max}/cm^{-1} (film) 3429 (OH), 3247 (NH), 3064 (CH), 2924 (CH), 1668 (CO), 1650, 1580, 1456 (CN stretch), 1021 (SO); δ_H (400 MHz, $CDCl_3$) 0.92 [9H, s, C(C*H*$_3$)$_3$], 2.24 (1H, t, *J* 6.0, O*H*), 3.23-3.35 (1H, m, NHC*H*), 3.73-3.92 (2H, m, C*H*$_2$OH), 4.32 (1H, d, A of AB system, J_{AB} 12.8, one of SC*H*$_2$), 4.39 (1H, d, B of AB system, J_{AB} 12.8, one of SC*H*$_2$), 7.21-7.50 (5H, m, Ar*H*), 7.68 [1H, s, Cl*H*C(3)=], 8.49 (1H, br d, *J* 8.0, N*H*); δ_C (75.5 MHz, $CDCl_3$) 26.9 [CH_3, C(*C*H$_3$)$_3$], 33.3 [C, *C*(CH$_3$)$_3$], 58.0 (CH_2, S*C*H$_2$), 61.0 (CH, NH*C*H), 63.4 (CH_2, *C*H$_2$OH), 128.4 [C, *C*(2)S or aromatic *C*], 128.9, 129.0, 130.8 (3 × CH, 3 × aromatic *C*H), 135.3 [C, *C*(2)S or aromatic *C*], 136.4 [CH, ClH*C*(3)=], 162.2 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{16}H_{23}NO_3S^{35}Cl$ $[M+H]^+$ 344.1087. Found 344.1088; m/z (ES+) 346.0 {[($C_{16}H_{22}NO_3S^{37}Cl$)+H^+], 48%}, 344.0 {[($C_{16}H_{22}NO_3S^{35}Cl$)+H^+], 100%}.

The more polar minor diastereomer **27b** was isolated as a white solid (0.03 g, 21%), containing ~21% of **27a**; $[\alpha]_D^{20}$ –123.50 (*c* 0.12 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3434 (OH), 3271 (NH), 3060 (CH), 2966 (CH), 1665 (CO), 1574, 1445 (CN stretch), 1032 (SO); δ_H (400 MHz, $CDCl_3$) 0.99 [9H, s, C(C*H*$_3$)$_3$], 2.75 (1H, br t, O*H*), 3.51-3.65 (1H, m, NHC*H*), 3.84-3.98 (2H, m, C*H*$_2$OH), 4.21 (1H, d, A of AB system, J_{AB} 12.4, one of SC*H*$_2$), 4.39 (1H, d, B of AB system, J_{AB} 12.8, one of SC*H*$_2$), 7.22-7.47 (5H, m, Ar*H*), 7.72 [1H, s, Cl*H*C(3)=], 8.78 (1H, br d, *J* 7.6, N*H*); δ_C (75.5 MHz, $CDCl_3$) 27.1 [CH_3, C(*C*H$_3$)$_3$], 33.5 [C, *C*(CH$_3$)$_3$], 59.1 (CH_2, S*C*H$_2$), 61.4 (CH, NH*C*H), 63.7 (CH_2, *C*H$_2$OH), 129.1, 130.5 [2 × CH (2 signals for 3 × CH), 2 × aromatic *C*H], 135.3, 136.4 [2 × C, *C*(2)S & aromatic *C*], 137.2 [CH, ClH*C*(3)=], 162.4 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{16}H_{23}NO_3S^{35}Cl$ $[M+H]^+$ 344.1087. Found 344.1071; m/z (ES+) 346.0 {[($C_{16}H_{22}NO_3S^{37}Cl$)+H^+], 44%}, 344.0 {[($C_{16}H_{22}NO_3S^{35}Cl$)+H^+], 100%}.

(Z)-3-Chloro-*N*-[(*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]-2-(*S*s/*R*s)-(benzenesulfinyl)acrylamide 28

This was prepared following the procedure described above for **21** by addition of (*Z*)-3-chloro-*N*-[(*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]-2-(phenylthio)acrylamide **19** (0.25 g, 0.8 mmol) in acetone (20 mL) to Oxone® (0.96 g, 1.6 mmol) in water (5 mL). Following stirring at room temperature for 16 h, the crude sulfoxides **28a** and **28b** were obtained as a clear oil and a 2.8:1 mixture of diastereomers. This was purified by column chromatography on silica

gel using hexane-ethyl acetate 60:40 as eluent to give the less polar minor diastereomer **28b** as a clear oil (0.02 g, 10%); $[\alpha]_D^{20}$ 127.20 (*c* 0.1 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3428 (OH), 3264 (NH), 3060 (CH), 2963 (CH), 1667 (CO), 1573, 1547 (NH bend), 1476 (CN stretch), 1032 (SO); δ_H (400 MHz, $CDCl_3$) 0.98 [9H, s, C(C*H*$_3$)$_3$], 1.66 (1H, dd, *J* 7.2, 4.8, O*H*), 3.36 (1H, ddd, *J* 11.4, 8.4, 4.8, NHC*H*), 3.68-3.84 (2H, m, C*H*$_2$OH), 7.48-7.60 (3H, m, Ar*H*), 7.67-7.74 (2H, m, Ar*H*), 7.78 [1H, s, Cl*H*C(3)=], 8.58 (1H, br d, *J* 8.4, N*H*); δ_C (75.5 MHz, $CDCl_3$) 26.9 [C(*C*H$_3$)$_3$], 33.5 [*C*(CH$_3$)$_3$], 60.8 (NH*C*H), 63.3 (*C*H$_2$OH), 124.5, 129.8, 131.9 (3 × aromatic *C*H), 137.5 [ClH*C*(3)=], 138.6, 141.3 [*C*(2)S & aromatic *C*], 161.6 (*C*O); HRMS (ES+): Exact mass calculated for $C_{15}H_{21}NO_3S^{35}Cl$ $[M+H]^+$ 330.0931. Found 330.0935; m/z (ES+) 332.0 {[($C_{15}H_{20}NO_3S^{37}Cl$)+H^+], 46%}, 330.0 {[($C_{15}H_{20}NO_3S^{35}Cl$)+H^+], 100%}.

The more polar major diastereomer **28a** was isolated as a clear oil (0.05 g, 20%); $[\alpha]_D^{20}$ –109.30 (*c* 0.2 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3412 (OH), 3277 (NH), 3060 (CH), 2962 (CH), 1663 (CO), 1545 (NH bend), 1476 (CN stretch), 1052 (SO); δ_H (400 MHz, $CDCl_3$) 0.75 [9H, s, C(C*H*$_3$)$_3$], 2.49 (1H, t, *J* 4.8, O*H*), 3.51-3.62 (1H, m, NHC*H*), 3.78-3.89 (2H, m, C*H*$_2$OH), 7.47-7.60 (3H, m, Ar*H*), 7.62-7.75 (2H, m, Ar*H*), 7.90 [1H, s, Cl*H*C(3)=], 8.39 (1H, br d, *J* 8.4, N*H*); δ_C (75.5 MHz, $CDCl_3$) 26.7 [CH_3, C(*C*H$_3$)$_3$], 33.4 [C, *C*(CH$_3$)$_3$], 60.4 (CH, NH*C*H), 62.9 (CH_2, *C*H$_2$OH), 124.4, 129.7, 131.6 (3 × CH, 3 × aromatic *C*H), 138.3 [C, *C*(2)S or aromatic *C*], 138.7 [CH, ClH*C*(3)=], 141.0 [C, *C*(2)S or aromatic *C*], 161.8 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{15}H_{21}NO_3S^{35}Cl$ $[M+H]^+$ 330.0931. Found 330.0935; m/z (ES+) 332.0 {[($C_{15}H_{20}NO_3S^{37}Cl$)+H^+], 62%}, 330.0 {[($C_{15}H_{20}NO_3S^{35}Cl$)+H^+], 100%}.

(Z)-3-Chloro-*N*-[(*R*)-3,3-dimethylbutan-2-yl]-2-(*S*s/*R*s)-(benzenesulfinyl)acrylamide 29

This was prepared following the procedure described above for **21** by addition of (*Z*)-3-chloro-*N*-[(*R*)-3,3-dimethylbutan-2-yl]-2-(phenylthio)acrylamide **20** (0.18 g, 0.6 mmol) in acetone (10 mL) to Oxone® (0.75 g, 1.2 mmol) in water (5 mL). Following stirring at room temperature for 16 h, the crude sulfoxides **29a** and **29b** were obtained as a clear oil (0.16 g, 85%) and a 1.1 : 1 mixture of diastereomers. As the ^{1}H NMR spectrum of the crude product was very clean, no purification was necessary; $[\alpha]_D^{20}$ –52.10 (*c* 0.1 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3269 (NH), 3060 (CH), 2966 (CH), 1669 (CO), 1549 (NH bend), 1476 (CN stretch), 1032 (SO); δ_H (400 MHz, $CDCl_3$) 0.68 [4.68H, s, C(C*H*$_3$)$_3$ of **29a**], 0.86 (1.56H, d, *J* 6.8,

CHC*H*$_3$ of **29b**), 0.93 [5.32H, s, C(C*H*$_3$)$_3$ of **29b**], 1.07 (1.44H, d, *J* 6.8, CHC*H*$_3$ of **29a**), 3.73-3.88 (1H, m, NHC*H* of **29a** and **29b**), 7.46-7.58 (3H, m, Ar*H* of **29a** and **29b**), 7.60-7.68 (2H, m, Ar*H* of **29a** and **29b**), 7.73 [0.48H, s, Cl*H*C(3)= of **29b**], 7.86 [0.52H, s, Cl*H*C(3)= of **29a**], 8.15 (0.52H, br d, *J* 9.6, N*H* of **29a**), 8.37 (0.48H, br d, *J* 9.2, N*H* of **29b**); δ_C (75.5 MHz, $CDCl_3$) 15.67, 15.71 (2 × CH_3, CH*C*H$_3$ of 2 diastereomers), 26.0*, 26.2 [2 × CH_3, C(*C*H$_3$)$_3$ of 2 diastereomers], 34.0*, 34.1 [2 × C, *C*(CH$_3$)$_3$ of 2 diastereomers], 53.4*, 53.6 (2 × CH, NH*C*H of 2 diastereomers), 124.1*, 124.3, 129.5, 129.6*, 131.4*, 131.6 (6 × CH, aromatic *C*H of 2 diastereomers), 137.0, 138.0* [2 × CH, ClH*C*(3)= of 2 diastereomers], 138.6*, 138.9, 141.1, 141.2* [4 × C, *C*(2)S & aromatic *C* of 2 diastereomers], 159.8, 160.0* (2 × C, *C*O of 2 diastereomers); HRMS (ES+): Exact mass calculated for $C_{15}H_{21}NO_2S^{35}Cl$ $[M+H]^+$ 314.0982. Found 314.0974; m/z (ES+) 316.0 {[($C_{15}H_{20}NO_2S^{37}Cl$)+H^+], 66%}, 314.0 {[($C_{15}H_{20}NO_2S^{35}Cl$)+H^+], 100%}.

*Signals for **29a** (major).

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