CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Selective ß-oxidation of α-sulfanyl amides
Authors	Kissane, Marie;Murphy, Maureen;Bateman, Lorraine M.;McCarthy, Daniel G.;Maguire, Anita R.
Publication date	2011-07-29
Original Citation	KISSANE, M., MURPHY, M., BATEMAN, L. M., MCCARTHY, D. G. & MAGUIRE, A. R. 2011. Selective ß-oxidation of α-sulfanyl amides. Tetrahedron, 67, 5494-5499. doi: 10.1016/j.tet.2011.05.041
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1016/j.tet.2011.05.041
Rights	© 2011 Elsevier Ltd. All rights reserved. NOTICE: this is the author's version of a work that was accepted for publication in Tetrahedron. Changes resulting from the publishing process, such as peer review, editing, corrections, structural formatting, and other quality control mechanisms may not be reflected in this document. Changes may have been made to this work since it was submitted for publication. A definitive version was subsequently published in Tetrahedron, [67, 30, (14/05/2011)] DOI 10.1016/j.tet.2011.05.041 - https://creativecommons.org/licenses/by-nc-nd/4.0/
Download date	2026-11-03 23:53:56
Item downloaded from	https://hdl.handle.net/10468/591

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

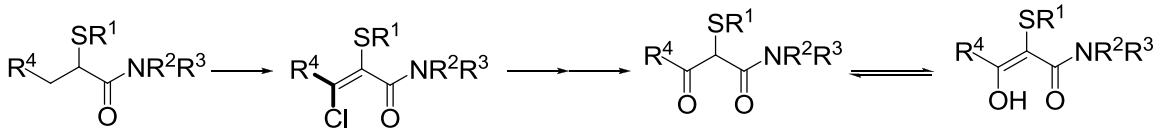
Selective β-Oxidation of α-Sulfanyl Amides

Marie Kissane,[a] Maureen Murphy,[a] Lorraine M. Bateman,[a] Daniel G. McCarthy[a] and Anita R. Maguire[b]*

[a]*Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Ireland*

[b]*Department of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Ireland*

email: a.maguire@ucc.ie



Abstract: A selective β-oxidation of a series of α-sulfanyl amides to the corresponding β-oxo-α-sulfanyl amides is described. This selective efficient oxidation of an unfunctionalised methyl or methylene group occurs under mild conditions, involving three sequential transformations conducted without isolation of the intermediates. Critically neither the sulfur nor the reactive α-CH bond are affected in the overall process.

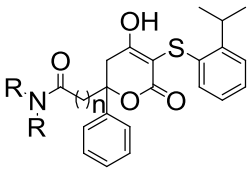
Keywords: oxidation, organosulfur chemistry, stereoselective synthesis

Introduction

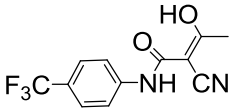
The selective oxygenation of unactivated C-H bonds is challenging and has attracted much attention. Alkane oxidation is normally achieved using oxidants such as hydrogen peroxide or molecular oxygen in the presence of a transition metal catalyst.[1-4] For substrates which contain a sulfide, selective oxidation at carbon over the sulfur centre is extremely difficult to achieve.

β-Oxo esters and amides are very useful compounds having widespread biological applications. For example, 5,6-dihydro-2H-pyran-2-ones **1**, which contain the β-keto-α-

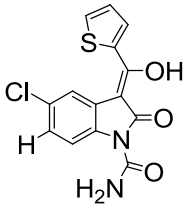
sulfanyl ester functionality, have been investigated as inhibitors of HIV protease, which is essential for viral replication.[5,6] Westwood *et al.* reported the activity of α-cyano-β-oxoamide **2** and its derivatives as an inhibitor of an enzyme that is involved in the *de novo* pyrimidine biosynthesis.[7] Antirheumatic oxindoles contain a β-ketoamide functionality in which the acidic enolic OH group is essential for cyclooxygenase inhibitory activity;[8] Tenidap **3** is one of the most potent oxindoles in the treatment of rheumatoid and osteoarthritis.



1



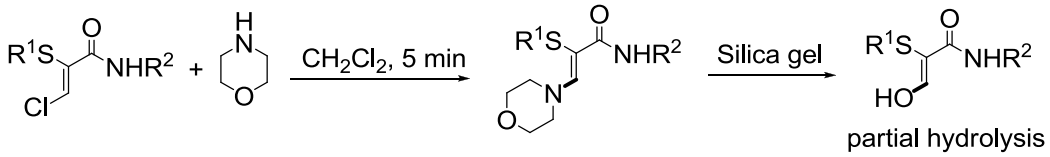
2



3

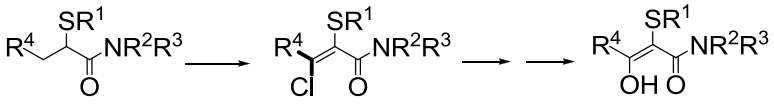
The preparation of β-oxo esters/amides does not usually involve direct oxidation at the β-carbon. Oxidation of a nonactivated methyl or methylene group is challenging,[9] and almost invariably involves attack by free radicals, resulting in regiocontrol and selectivity problems. β-Keto amides and esters may be prepared by various methods where the β-carbon is already at the same level of oxidation as a carbonyl carbon.[10,11]

We recently reported a highly efficient and stereoselective transformation of α-sulfanyl amides to the corresponding α-sulfanyl-β-chloroacrylamide derivatives on treatment with NCS.[12] Chemoselective and stereoselective oxidations of the β-chloroacrylamides to the sulfoxide and sulfone levels of oxidation has extended the scope of this methodology,[13,14] and the dipolarophilic and dienophilic behaviour of the β-chloroacrylamides has also been described.[15-17] The synthetic potential of the β-chloroacrylamides as Michael acceptors in nucleophilic addition/substitution reactions has also been investigated, including addition of morpholine to yield β-enaminoamides.[18] In early experiments, partial hydrolysis was seen on purification of the morpholine adducts by chromatography on silica gel, hence showing that the β-enaminoamides could be hydrolysed (Scheme 1).



Scheme 1

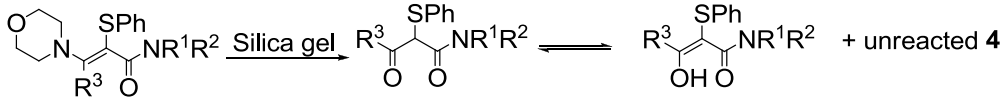
Herein, the optimisation of the hydrolysis of the β-enaminoamides to the corresponding β-hydroxyacrylamides is described. Having established that the β-enaminoamides could be efficiently hydrolysed, a 'one-pot' oxidation from the α- sulfanyl amides to the β-hydroxyacrylamides was subsequently developed (Scheme 2).



Scheme 2

Results and Discussion

The nucleophilic addition of morpholine to a range of β-chloroacrylamides has been described.[18] The resulting β-morpholinoacrylamides contain an enamine functionality, and during chromatographic purification with a number of these β-morpholinoacrylamides, partial or complete hydrolysis of the acid labile enamine group was observed (Scheme 3). For example, partial hydrolysis of the β-morpholinoacrylamide **4a** on silica gel led to a 3:1 mixture of the keto and enol tautomers of **5a**, while hydrolysis of **4b** and **4c** led to the enol tautomers **5b** and **5c** exclusively.



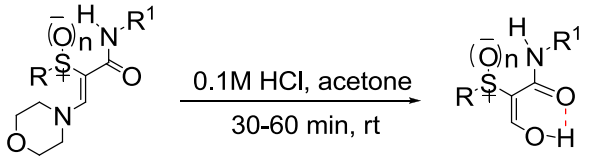
R^1=Me, R^2=Me, R^3=H	**4a**	**5a-keto**	**5a-***keto ; enol* 3:1	**5a-enol**	60%	40%
R^1=H, R^2=$CH(CH_3)Ph$, R^3=Et	**4b**		**5b**, **5c** *enol only*	**5b**	30%	70%
R^1=H, R^2=*p*-Tol, R^3=Me	**4c**			**5c**	complete	-

Extent of hydrolysis *recovered **4***

Scheme 3

As formation of β-oxygenated acrylamides by hydrolysis was an interesting and potentially useful transformation, the conditions were optimised using the β-morpholinoacrylamide **4d**. Use of silica gel in 1:1 ethanol-water or 0.1 M hydrochloric acid in hexane, water or toluene led to partial hydrolysis on stirring at room temperature for 16 hours. However, the use of 0.1 M hydrochloric acid in acetone at room temperature resulted in complete hydrolysis of **4d** within 30 minutes. Hydrolysis of the β-morpholinosulfinylacrylamide **6a** and a number of β-morpholinosulfonylacrylamides (**8a**–**8c**) was also achieved under these conditions (Table 1), highlighting that the transformation can be achieved equally efficiently at the sulfide, sulfoxide and sulfone levels of oxidation. Notably, exposure of the α–sulfanyl-β–chloroacrylamides to aqueous HCl does not result in hydrolysis to form the enol under the same reaction conditions; therefore the sequential morpholine addition followed by enamine hydrolysis is necessary.

Table 1 Hydrolysis of β-Morpholinoacrylamides



Starting Material	R	R^1	n	Product	% Yield
4d	Ph	*p*-Tol	0	**5d**	86[a]
6a	Bn	4-F-C_6H_4	1	**7a**	71[a]
8a	Bn	Bn	2	**9a**	95[a]
8b	Bn	4-F-C_6H_4	2	**9b**	72[a]
8c	Bn	*p*-Tol	2	**9c**	54[b]

a) Crude yield, further purification was not required.
b) Isolated yield after recrystallisation from dichloromethane/hexane.

The β-hydroxyacrylamides **5d**, **7a**, **9a**–**9c** were isolated following extraction into dichloromethane and concentration as single stereoisomers (tentatively assigned as *E*), while a second set of minor signals (~7%) which were present in the ^{1}H NMR spectrum of **9c**, and which persisted on recrystallisation, were tentatively assigned as the other

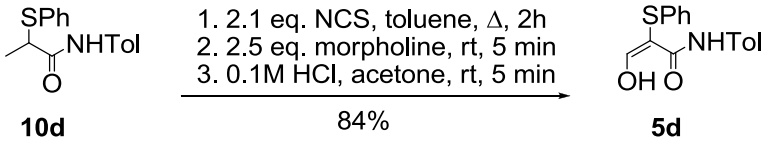
stereoisomer. The β-hydroxyacrylamides **5d**, **7a**, **9a**−**9b** were clean by ^{1}H and ^{13}C NMR spectroscopy, and further purification was not required.

The β-hydroxyacrylamides may exist as the *E*- or *Z*-isomers. It is likely that the *E*-isomer is favoured due to a stabilising intramolecular hydrogen-bond between the enol OH and the amide carbonyl; however, at this stage there is no definitive structural evidence for the stereochemistry. The enol form predominates in most instances as indicated by the signal for the β-hydrogen at 7.10−7.99 ppm and the signal for the OH group at 13.52−15.70 ppm in the ^{1}H NMR spectra.

In the room temperature ^{1}H NMR spectra of **9a**−**9c**, the signals for the β-hydrogens were evident as broad singlets. To establish if the broadening of the β-hydrogen signal arises from the interconversion of the *E*- and *Z*-isomers on the NMR timescale or if coupling to the adjacent hydroxyl group is responsible, the ^{1}H NMR spectrum of **9a** was recorded at 220K on a 500 MHz NMR spectrometer in $CDCl_3$; both signals for the β-hydrogen and the hydroxyl proton split into clearly resolved doublets with a coupling constant of 11.0 Hz. Thus, the broadening of the signal for the β-hydrogen when the ^{1}H NMR spectrum is recorded at room temperature is attributed to coupling to the exchanging hydroxyl proton, and is not due to rapid *E*-*Z* interconversion.

Since the chlorination, nucleophilic substitution and hydrolysis conditions are intrinsically compatible, we decided to explore the possibility of a 'one pot' oxidation sequence. To that end, the conditions for the transformation of the α- sulfanyl amide **10d** to the corresponding β-hydroxyacrylamide **5d** without isolation of the intermediates were subsequently developed; treatment of the sulfide **10d** with 2.1 equivalents of NCS in toluene under reflux for 2 hours gave quantitative transformation to the β-chloroacrylamide **11d**. The oil bath was removed and the reaction mixture was allowed to cool to room temperature before 2.5 equivalents morpholine was added to the stirring solution. The morpholine substitution reaction was complete within 5 minutes by TLC analysis and the product was cooled to 0 °C enabling most of the succinimide and morpholine hydrochloride by-products to be removed by filtration prior to evaporation of the toluene. The sample was subsequently redissolved in acetone and one equivalent of 0.1 M hydrochloric acid was added. Following stirring at room temperature for 5 minutes

and extraction into dichloromethane, the β-hydroxyacrylamide **5d** was isolated. This simple, rapid procedure involving only filtration, evaporation and extraction gave a very clean product within a total reaction time of 2.5 hours in 84% yield over three steps (Scheme 4). When the transformations were conducted in a stepwise manner, the yields of the oxidative β-chlorination, morpholine enamide formation and enamine hydrolysis are 80%, 67% and 86% respectively, leading to an overall yield of 46%, highlighting the advantage of the telescoped process.

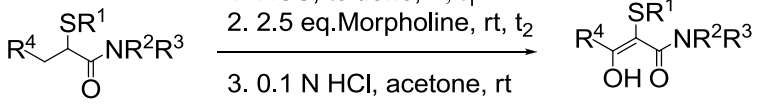


10d **5d**

Scheme 4

Investigation of the efficiency of the sequential oxidation sequence with a range of thio, amide and β-alkyl substituent was undertaken to establish the scope of this synthetic method. Table 2 summarises the results of these experiments.

Table 2 β-Oxidation of α-Sulfanyl Amides – Telescoped Process without Isolation of Intermediates



Sulfide	**R^1**	**R^2**	**R^3**	**R^4**	**t_1[a] (h)**	**t_2[b] (h)**	**Product**	**% yield[c]**
10d	Ph	Tol	H	H	2	0.1	**5d**	84[d]
10e	Ph	*i*-Pr	H	H	2	0.1	**5e**	88
10f	*n*-Bu	Tol	H	H	1.5	2	**5f**	60[e]
10g	Ph	H	H	H	1.5	0.1	**5g**	81
10a	Ph	Me	Me	H	2	16	**5a**	41[f]
10b	Ph	(*S*)-$CH(CH_3)Ph$	H	Et	2	23	**5b**	67
10h	Ph	Tol	H	Ph	2	60[g]	**5h**	<17
10i	*n*-Bu	Bn	H	H	1.5	0.1	**5i**	83
11j[h]	$(CH_2)_2OH$	Ph	H	Me	-[h]	22	**5j**	24[e]

a) Reaction with NCS was complete within this time.
b) Reaction with morpholine was complete within this time.
c) Yield of β-hydroxyacrylamide based on starting sulfide.
d) Isolated yield following trituration using water and hexane.
e) Isolated yield following chromatographic purification.
f) Isolated as a mixture of the enol and keto tautomers.
g) Heating at reflux was required for reaction completion.
h) **5j** was prepared from the β-chloroacrylamide **11j** and not the sulfide. Dichloromethane was used as the solvent in the reaction with morpholine.

As is evident from Table 2, the limiting step in the reaction sequence is the nucleophilic substitution of the chloride with morpholine, with the reaction time for this step varying from 5 minutes for **10d** to 60 hours for **10h**. In most instances, the β-hydroxyacrylamides were isolated in good yields as clean products, although purification by trituration or chromatography was necessary for **5d**, **5f** and **5j**. The reactivity of the β-chloroacrylamide is dependant on the electrophilicity of the β-carbon, with the rate of morpholine substitution and yield of β-hydroxyacrylamide highest for the primary and secondary β-chloroacrylamides. The reduced yield observed for the β-hydroxyacrylamide **5a** derived from tertiary propanamide is presumably due to conformational effects,[12,19] while steric effects account for the lower yields of the extended chain acrylamides **5b** and **5h**.

Furthermore, the rate of the nucleophilic addition is dependent on the stereochemistry. Thus, treatment of the tertiary propanamide **10a** with NCS led to a mixture of the *E* and *Z* isomers of the β-chloroacrylamide **11a**. Upon addition of morpholine, both the *E* and *Z* isomers reacted to give the corresponding β-morpholinoacrylamide **4a**, and subsequent hydrolysis yielded the β-hydroxyacrylamide **5a**. Reaction of the extended chain α-thioamides **10b** and **10h** with NCS also led to a mixture of the *E* and *Z* β-chloroacrylamides **11b** and **11h**. In both instances, the *Z* isomers **11b**-*Z* and **11h**-*Z* were found to react much more rapidly with morpholine than the corresponding *E* isomers **11b**-*E* and **11h**-*E*. For the α-sulfanyl amides **10d**−**10g**, **10i**, treatment with NCS led to the exclusive formation of the *Z* β-chloroacrylamides **11d**−**11g**, **11i**.

The β-hydroxyacrylamides **5b**, **5d**−**5j** were isolated exclusively as the enol tautomer, while the *N*,*N*-dimethyl-β-oxopropanamide **5a** was isolated as a 3:1 mixture of the keto and enol tautomers; this was the only instance that there was evidence for the existence of the keto tautomer. β-Keto esters and amides normally adopt the conformation that allows

stabilising hydrogen bond formation between the β-OH and the carbonyl oxygen. The hydrogen bond between the amide NH and sulfur holds the primary and secondary propanamides in a rigid *s-cis* conformation favouring hydrogen bonding between the β-OH and the carbonyl oxygen in these β-hydroxyacrylamides. In the tertiary amides, there is no NH-S hydrogen bond thereby allowing the β-chloroacrylamide to adopt either the *s-cis* or *s-trans* conformation.[12] In the *s-trans* conformation, hydrogen bonding between the carbonyl oxygen and the OH is not possible and therefore this compound would exist in the keto form. However, in the *s-cis* conformation the tertiary β-hydroxyacrylamide **5a** could exist in the enol form (Figure 1). Apparently, **5a** exists in both *s-cis* and *s-trans* conformations (possibly in equilibrium) as both the keto and enol forms were observed.

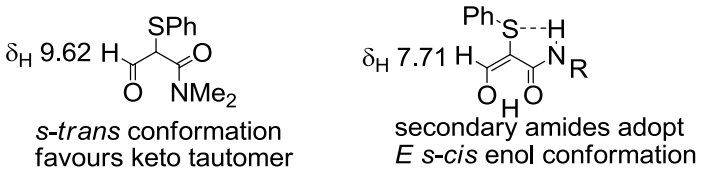


Figure 1

Conclusion

The transformation of secondary propanamides into the corresponding β-hydroxypropenamides in a telescoped process without isolation of the intermediates proceeds under mild conditions, without the use of metal catalysis, in good yields of 60-88% and in a very short time (~2.5 hours) for the overall three step process. In effect, this transformation oxidises the unactivated β-methyl group of the α- sulfanyl amide to the aldehyde level, while the products exist predominantly as the enol tautomer. In most instances, product purification is not required. This 'one-pot' oxidation is also possible for primary, tertiary and extended chain amides, albeit in lower yields than those obtained for the secondary propanamides. The synthetically powerful oxidative functionalisation of the β-carbon without affecting the sulfur centre provides scope for further reaction at this carbon, including olefination or asymmetric 1,2-addition.

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. Acetone was distilled from potassium permanganate and toluene was distilled from sodium and stored over 4Å molecular sieves. Dimethylformamide was stored overnight over calcium hydride, then distilled and stored over 4 Å molecular sieves. Organic phases were dried using anhydrous magnesium sulphate.

^{1}H (500 MHz) and ^{13}C (125.8 MHz) NMR spectra were recorded on a Bruker (500 MHz) NMR spectrometer. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker (AV300) NMR spectrometer. ^{1}H (270 MHz) and ^{13}C (67.8 MHz) NMR spectra were recorded on a Jeol GSX (270 MHz) NMR spectrometer. ^{1}H (60 MHz) NMR spectra were recorded on a Jeol PMX-60SI spectrometer. All spectra were recorded at room temperature (~20^{o}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. Mass spectra were recorded on a Kratos Profile HV-4 double focusing high resolution mass spectrometer (EI), a Waters/Micromass LCT Premier Time of Flight spectrometer (ESI) and a Waters/Micromass Quattro Micro triple quadrupole spectrometer (ESI). 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.

_Z_-3-Hydroxy-_N_-(4-methylphenyl)-2-(phenylsulfanyl)propenamide 5d

a) Hydrolysis of β-morpholinopropenamide

Aqueous HCl (3.1 mL, 0.1 M, 0.31 mmol) was added to a stirred solution of *N*-(4-methylphenyl)-3-morpholino-2-(phenylsulfanyl)propenamide **4d** (0.10 g, 0.28 mmol) in acetone (4 mL). Further acetone (2-3 mL) was added to redissolve the propenamide **4d** if it came out of solution. After stirring at room temperature for 5 min, the reaction was complete (by TLC analysis). CH_2Cl_2 (10 mL) was added, the phases were separated and the organic layer was washed with brine (2 × 5 mL), dried and evaporated to give **17** (76 mg, 86 %) as a light pink, crystalline solid which was essentially pure by ^{1}H NMR spectroscopy; mp 61-63 °C; Found C, 67.47; H, 5.28; N, 5.01; S, 11.20. $C_{16}H_{18}NO_2S$ requires C, 67.34; H, 5.30; N, 4.91; S, 11.24; UV λ_{max} 274, 245, 207/nm ε/dm^{-3} mol^{-1} cm^{-1} 16180, 17470, 25,770; ν_{max}/cm^{-1} (KBr) 3355 (br NH, OH), 1628, 1594 (CO α,β-unsaturated amide); δ_H 2.29 (3 H, s, ArC*H*$_3$), 7.09-7.32 (9 H, m, Ar*H*), 7.74 (1 H, d, *J* 11 C*H*OH=), 8.30 (1 H, br s, N*H*), 14.21 (1 H, d, *J* 11, =CHO*H*); δ_C 20.8 (Ar*C*H$_3$) 96.4 (S*C*=), 120.2, 125.4, 125.8, 129.3, 129.8 (aromatic *C*H), 133.9, 134.8, 136.5 (aromatic *C*), 169.0 (*C*O amide), 172.0 (*C*HOH=); MS *m/z* 285 (M$^+$, 32 %), 196 (89), 107 (100), 91 (100).

b) One pot synthesis

NCS (0.31 g, 2.3 mmol) was added in one portion to a solution of **10d** (0.30 g, 1.11 mmol) in toluene (6 mL) and the reaction flask was submerged rapidly in an oil-bath preheated to 130 °C. After 2 h the reaction was complete (by TLC analysis) and the reaction mixture was removed from the oil bath and cooled to room temperature. Morpholine (243 μL, 2.78 mmol) was added generating fumes (probably hydrogen chloride gas). TLC analysis after 5 min showed complete reaction. Filtration to remove the by-products (succinimide and morpholine hydrochloride) followed by evaporation of the toluene gave the β-morpholinopropenamide **4d** (436 mg, quant.) which was dissolved in acetone (3 mL). HCl (0.1 M, 11 mL, 1.11 mmol) was added followed by acetone (3 mL) to redissolve the reactants. After stirring for 10 min at room temperature the reaction was complete (by TLC analysis) and CH_2Cl_2 (10 mL) was added. The aqueous layer was washed with CH_2Cl_2 (2 × 5 mL) and the combined organic layers were washed with brine

(2 × 10 mL), dried and evaporated to give **5d** (0.30 mg, 94%) as a dark pink, crystalline solid. The compound was essentially pure by ^{1}H NMR spectroscopy at this stage, however trituration with water-hexane (99:1) gave **5d** (0.27 g, 84%) as a light pink, crystalline solid. The spectroscopic details were identical to those outlined above.

***N*-(4-Fluorophenyl)-3-hydroxy-2-(benzylsulfinyl)propenamide 7a**

Aqueous hydrochloric acid (8.0 mL, 0.1 M, 0.80 mmol) was added to a solution of **6a** (0.16 g, 0.40 mmol) in acetone (5 mL). Following stirring at room temperature for 15 min, TLC analysis indicated that the reaction was complete. CH_2Cl_2 (10 mL) was added to the reaction mixture, the phases were separated and the organic layer was washed with brine (2 × 5 mL), dried, filtered and concentrated at reduced pressure to give the product **7a** (0.09 g, 71%) as a sticky yellow solid, as a single isomer; ν_{max}/cm^{-1} (KBr) 3368 (br, OH & NH), 2924 (CH), 1620 (CO), 1572, 1508, 1371 (CN stretch), 1013 (SO); δ_H (300 MHz, $CDCl_3$) 4.30 (2H, s, SC*H*$_2$), 6.99-7.07 (2H, m, Ar*H*), 7.10 [1H, s, C(3)*H*=], 7.16-7.39 (5H, m, Ar*H*), 7.42-7.49 (2H, m, Ar*H*), 10.14 (1H, br s, N*H*), 13.52 (1H, br s, O*H*); δ_c (75.5 MHz, $CDCl_3$) 60.9 (CH_2, S*C*H$_2$), 104.8 [C, *C*(2)S], 115.7 [CH, d, $^{2}J_{CF}$ 23, aromatic *C*(3′)H], 122.5 [CH, d, $^{3}J_{CF}$ 8, aromatic *C*(2′)H], 128.88, 128.93, 129.1 (3 × CH, 3 × aromatic *C*H), 132.5, 132.6 (2 × C, 2 × aromatic *C*), 159.8 [C, d, $^{1}J_{CF}$ 245, aromatic *C*(4′)], 165.7 [CH, *C*(3)H=], 167.0 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{16}H_{15}NO_3SF$ $[M+H]^+$ 320.0757. Found 320.0764; m/z (ES-) 318.0 {[($C_{16}H_{14}NO_3SF$) – H^-], 100%}.

***N*-Benzyl-*Z*-3-hydroxy-2-(benzylsulfonyl)propenamide 9a**

The title compound was prepared as described for **7a** using **8a** (0.14 g, 0.36 mmol) in acetone (10 mL) and hydrochloric acid (7.1 mL, 0.1 M, 0.71 mmol). Following stirring at room temperature for 60 min, TLC analysis indicated that the reaction had gone to completion. Dichloromethane (15 mL) was added to the reaction mixture, the phases were separated and the organic layer was washed with brine (2 × 10 mL), dried, filtered and concentrated at reduced pressure to give **9a** (0.11 g, 95%) as an off-white solid, mp 113-114 °C; ν_{max}/cm^{-1} (KBr) 3434 (OH), 3350 (NH), 2923 (CH), 1619 (CO), 1552 (NH

bend), 1453 (CN stretch), 1360 (asymmetric SO_2 stretch), 1148 (symmetric SO_2 stretch); δ_H (400 MHz, $CDCl_3$) 4.24 (2H, s, SC*H*$_2$), 4.28 (2H, d, *J* 6.0, NHC*H*$_2$), 7.14-7.20 (2H, m, Ar*H*), 7.23-7.41 (8H, m, Ar*H*), 7.55 (1H, br s, N*H*), 7.88 [1H, br s, C(3)*H*=], 15.70 (1H, br s, O*H*); δ_H (500 MHz, $CDCl_3$, 220K) 4.23 (2H, d, *J* 4.7, SC*H*$_2$), 4.32 (2H, s, NHC*H*$_2$), 7.19 (2H, d , *J* 7.2, Ar*H*), 7.30-7.52 (9H, m, N*H* & Ar*H*), 7.93 [1H, d, *J* 11.0, C(3)*H*=], 15.88 (1H, d, *J* 11.0, O*H*); δ_c (75.5 MHz, $CDCl_3$) 43.2 (CH_2, NH*C*H$_2$), 63.9 (CH_2, S*C*H$_2$), 105.1 [C, *C*(2)S], 127.6, 127.9 (2 × CH, 2 × aromatic *C*H), 128.0 (C, aromatic *C*), 128.9, 129.0, 129.3, 130.9 (4 × CH, 4 × aromatic *C*H), 136.5 (C, aromatic *C*), 167.2 (C, *C*O), 176.1 [CH, *C*(3)H=]; HRMS (ES+): Exact mass calculated for $C_{17}H_{18}NO_4S$ $[M+H]^+$ 332.0957. Found 332.0947; m/z (ES+) 332.0 {[($C_{17}H_{18}NO_3S$)+H^+], 48%}.

***N*-(4-Fluorophenyl)-3-hydroxy-2-(benzylsulfonyl)propenamide 9b**

This was synthesised as outlined for **7a** using **8b** (0.10 g, 0.3 mmol) in acetone (5 mL) and hydrochloric acid (10.0 mL, 0.1 M, 10.0 mmol). TLC analysis showed the reaction to be complete after 40 min and following the work-up, **9b** (0.06 g, 72%) was obtained as a white solid and as a single isomer, mp 113-114 °C; ν_{max}/cm^{-1} (KBr) 3429 (OH), 3320 (NH), 2923 (CH), 1618 (CO), 1567 (NH bend), 1507, 1367 (asymmetric SO_2 stretch), 1143 (symmetric SO_2 stretch); δ_H (400 MHz, $CDCl_3$) 4.34 (2H, s, SC*H*$_2$), 6.95-7.03 (2H, m, Ar*H*), 7.18-7.36 (7H, m, Ar*H*), 7.99 [1H, br s, C(3)*H*=], 8.91 (1H, br s, N*H*), 15.16 (1H, br s, O*H*); δ_c (75.5 MHz, $CDCl_3$) 64.4 (CH_2, S*C*H$_2$), 106.1 [C, *C*(2)S], 115.7 [CH, d, $^2J_{CF}$ 23, aromatic *C*(3′)H], 122.9 [CH, d, $^3J_{CF}$ 8, aromatic *C*(2′)H], 127.8 (C, aromatic *C*), 129.1, 129.5, 130.9 (3 × CH, 3 × aromatic *C*H), 131.6 (C, aromatic *C*), 160.1 [C, d, $^1J_{CF}$ 245, aromatic *C*(4′)], 165.3 (C, *C*O), 175.9 [CH, *C*(3)H=]; HRMS (ES–): Exact mass calculated for $C_{16}H_{13}NO_4SF$ $[M–H]^-$ 334.0549. Found 334.0560; m/z (ES–) 334.0 {[($C_{16}H_{13}NO_4SF$) – H^-], 100%}.

3-Hydroxy-*N*-(4-methylphenyl)-2-(benzylsulfonyl)propenamide 9c

The title compound was prepared as described for **7a** using **8c** (0.09 g, 0.2 mmol) in acetone (5 mL) and hydrochloric acid (9.0 mL, 0.1 M, 0.9 mmol). Following stirring for 30 min, TLC analysis indicated that the reaction had gone to completion and the crude

product **9c** was obtained as an off-white solid after the work-up. After recrystallation from dichloromethane-hexane, **9c** was isolated as a white solid (0.04 g, 54%), mp 126-127 °C; ν_{max}/cm^{-1} (KBr) 3439 (OH), 3314 (NH), 2984 (CH), 1630 (CO), 1607, 1558 (NH bend), 1509, 1408 (CN stretch), 1324 (asymmetric SO_2 stretch), 1125 (symmetric SO_2 stretch); δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, ArC*H*$_3$), 4.33 (2H, s, SC*H*$_2$), 7.11 (2H, d, *J* 8.4, Ar*H*), 7.16 (2H, d, *J* 8.4, Ar*H*), 7.22-7.40 (5H, m, Ar*H*), 7.94 [1H, s, C(3)*H*=], 8.92 (1H, br s, N*H*), 15.36 (1H, br s, O*H*); δ_c (75.5 MHz, $CDCl_3$) 20.9 (CH_3, Ar*C*H_3), 64.2 (CH_2, S*C*H_2), 105.9 [C, *C*(2)S], 121.2 (CH, aromatic *C*H), 127.8 (C, aromatic *C*), 129.1, 129.5 (signal for 2 × CH), 130.9 (3 × CH, 3 × aromatic *C*H), 133.0, 135.5 (2 × C, 2 × aromatic *C*), 165.3 (C, *C*O), 176.0 [CH, *C*(3)H=]; HRMS (ES+): Exact mass calculated for $C_{17}H_{18}NO_4S$ $[M+H]^+$ 332.0957. Found 332.0962; m/z (ES–) 330.1 {[($C_{17}H_{17}NO_3S$)+H^+], 100%}.

A second set of signals (~ 7%) was also present in the ^{1}H NMR spectrum and were tentatively assigned to the stereoisomer: δ_H (400 MHz, $CDCl_3$) 4.37 (2H, s), 7.88 (1H, br d), 9.45 (1H, br s).

3-Hydroxy-*N*-*i*-propyl-2-(phenylsulfanyl)propenamide 5e

This was prepared following the procedure described for **5d** using **10e** (0.30 g, 1.35 mmol), NCS (0.38 g, 2.83 mmol) and toluene (6 mL) with a reaction time of 1.5 h, followed by morpholine (0.29 mL, 3.36 mmol) with a reaction time of 5 min. Hydrolysis using acetone (4 mL) and HCl (14 mL, 0.1 M, 1.4 mmol) gave **5e** (0.19 g, 60 %) as a pink oil. The propenamide was judged to be analytically pure; ν_{max}/cm^{-1} (film) 3380 (br NH, OH), 1613 (CO α,β-unsaturated amide); δ_H 1.06 (6 H, d, *J* 7, NHCH(C*H*$_3$)$_2$), 4.07 (1 H, symm m, *J* 7, NC*H*), 6.31-6.41 (1 H, br m, N*H*), 7.13-7.31 (5 H, m, Ar*H*), 7.65 (1 H, d, *J* 7, C*H*OH=), 14.52 (1 H, br d, CHO*H*=); δ_C 22.9 [NHCH(*C*H$_3$)$_2$], 41.8 (NC*H*), 96.4 (S*C*=), 125.7, 126.4, 129.3 (aromatic *C*H), 137.6 (quaternary aromatic *C*), 170.2, 171.6 (*C*O amide and *C*HOH=); MS *m/z* 237 (M^+, 78 %), 208 (30, M^+-CHO), 178 (68), 120 (100), 105 (49) ; Found (HRMS, EI) M^+ 237.08249 $C_{12}H_{15}NO_2S$ requires *m/z* 237.08235.

3-Hydroxy-*N*-(4-methylphenyl)-2-(*n*-butylsulfanyl)propenamide 5f

This was prepared following the procedure described for **5d** using **10f** (0.25 g, 1.0 mmol), NCS (0.28 mg, 2.09 mmol) and toluene (5 mL) with a reaction time of 2 h, followed by morpholine (0.22 mL, 2.49 mmol) with a reaction time of 2 h. Hydrolysis using acetone (5 mL) and HCl (0.1 M, 10 mL, 1 mmol) gave crude 3-hydroxypropenamide **5f** (0.22 mg, 82 %) as a yellow oil. Purification by chromatography using ethyl acetate-hexane (4:96) as eluent gave **27** (0.16 g, 60 %) as a light pink oil; Found C, 63.42; H, 7.31; N, 5.42; S, 12.17. $C_{14}H_{19}NO_2S$ requires C, 63.37; H, 7.22; N, 5.28; S, 12.09; ν_{max}/cm^{-1} (filmt) 3330 (br NH, OH), 1625, 1595 (CO amide); δ_H 0.91 [3 H, t, *J* 7, C(4′)H_3], 1.34-1.45 [2 H, m, C(3′)H_2], 1.47-1.62 [2 H, m, C(2′)H_2], 2.33 (3 H, s, ArCH_3), 2.52 (2 H, t, *J* 7, SCH_2), 7.15-7.45 (4 H, ABq, *J* 8, Ar*H*), 7.60 (1 H, d, *J* 12 C*H*OH=), 8.70 (1 H, br s, N*H*), 13.81 (1 H, d, *J* 12, CHO*H*=); δ_C 13.6 [*C*(4′)H_3], 20.9 (Ar*C*H_3), 21.7 [*C*(3′)H_2], 31.1 [*C*(2′)H_2], 36.9 [*C*(1′)H_2], 98.7 (S*C*=), 120.4, 129.6 (aromatic *C*H), 134.3, 134.7 (aromatic *C*), 169.5 (*C*O amide), 170.1 (*C*HOH=); MS *m/z* 265 (M^+, 18 %), 107 (100), 91 (8, $[Tol]^+$).

***Z*-3-Hydroxy-2-(phenylsulfanyl)propenamide 5g**

This was prepared following the procedure described for **5d** using **10g** (0.30 g, 1.66 mmol), NCS (0.47 g, 3.5 mmol) and toluene (6 mL) with a reaction time of 2 h, followed by morpholine (0.36 mL, 4.15 mmol) with a reaction time of 10 min. Hydrolysis using acetone (4 and 4 mL) and HCl (1 M, 2 mL, 2 mmol) gave **5g** (0.21 g, 81 %) as a light pink, crystalline solid; mp 58-60 °C; Found C 55.65; H, 4.84; N, 7.33; S, 16.08. $C_9H_9NO_2S$ requires C, 55.37; H, 4.65; N, 7.17; S, 16.42; ν_{max}/cm^{-1} (KBr) 3421 (br NH, OH), 1654, 1604 (CO α,β-unsaturated amide); δ_H 6.11 (1 H, br s, N*H*), 6.48 (1 H, br s, N*H*), 7.14-7.48 (5 H, m, Ar*H*), 7.70 (1 H, br s, C*H*=), (1 H, br d, CO*H*=); δ_C 95.2 (S*C*=), 124.7, 125.7, 129.4 (aromatic *C*H), 136.7 (aromatic *C*), 172.6 (aromatic *C*H), 173.7 (*C*O); MS *m/z* 195 (M^+ , 80 %), 178 (71, M^+-OH), 121 (100, $[PhS{=}C]^+$).

***N*,*N*-Dimethyl-3-oxo-2-(phenylsulfanyl)propanamide 5a**

Note: This compound is judged to be a mixture of keto and enol tautomers

This was prepared following the procedure described for **5d** using **10a** (0.20 g, 1.0 mmol), NCS (0.28 mg, 2.06 mmol) and toluene (4 mL) with a reaction time of 2 h, followed by morpholine (0.22 mL, 2.5 mmol) with a reaction time of 16 h. Hydrolysis

using acetone (6 mL) and HCl (10 mL, 0.1 M, 1 mmol) gave a mixture of products. Purification by chromatography using ethyl acetate-hexane (25:75) as eluent gave *N*,*N*-dimethyl-3-oxo-2-(phenylthio)propanamide **5a** (0.90 g, 41 %) as a colourless oil which is unstable at room temperature. The estimated ratio of keto to enol tautomeric forms is 3:1; ν_{max}/cm^{-1} (film) 3272 (br NH), 1721 (CO aldehyde), 1645 (CO amide); δ_H 3.00 (ArCH_3), 3.13, 3.18 [6 H, 3 × s, N(CH_3)$_2$ enol/keto forms], 4.33 (< 1 H, d, *J* 5, C*H*S keto form), 7.13-7.57 (5 H, m, Ar*H*), 7.71 (< 1 H, s, C*H*OH= enol form), 9.62 (< 1 H, d, *J* 5, C*H*O keto form); δ_C 35.8, 37.2, 38.2 [N(*C*H$_3$)$_2$], 57.6 (*C*HS), 129.2, 129.3, 133.3 (aromatic *C*H), 136.0 (aromatic *C*), 165.2, 175.7, 192.2 (*C*O amide, *C*-3 enol/keto forms); MS *m/z* 223 (M^+, 5 %), 194 (8, M^+-CHO), 72 (100, $[CON(CH_3)_2]^+$).

_Z_-3-Hydroxy-(1′S)-_N_-1′-phenylethyl-2-(phenylsulfanyl)-2-pentenamide 5b

This was prepared following the procedure described for **5d** using **10b** (0.20 g, 0.64 mmol), NCS (0.18 g, 1.34 mmol) and toluene (4 mL) with a reaction time of 2 h, followed by morpholine (0.14 mL, 1.6 mmol) with a reaction time of 23 h. Acetone (6 mL) and HCl (0.1 M, 6.5 mL, 0.65 mmol) were used for hydrolysis giving a crude reacton mixture (190 mg). Purification by chromatography using ethyl acetate-hexane (10:90) as eluent gave **5b** (95 mg, 67 %) (Rf 0.6 using ethyl acetate-hexane (25:75) as eluent) as a colourless oil; $[\alpha]_D^{20}$ 13.48 (*c* 7 in ethanol); ν_{max}/cm^{-1} (film) 3380 (br NH, OH), 1581, 1518 (CO α,β-unsaturated amide), δ_H 1.09 [3 H, t, *J* 8, C(5)*H*$_3$], 1.35 [3 H, d, *J* 8, C(2′)*H*$_3$], 2.64 [1 H, q, *J* 8, C(4)*H*$_2$], 5.00-5.13 [1 H, dq, *J* 8, 8, C(1′)*H*], 7.09-7.30 (11 H, m, Ar*H*, N*H*), enolic OH seen at δ > 10 ppm; δ_C 11.0 [*C*(5)H$_3$], 22.2 [*C*(2′)H$_3$], 27.2 [*C*(4)H$_2$], 48.9 [*C*(1′)H], 90.0 (S*C*=), 125.3, 125.8, 126.1, 127.2, 128.6, 129.2 (aromatic *C*H), 137.2, 143.1 (aromatic *C*), 171.3 (*C*O amide), 187.5 (*C*OH=); MS *m/z* 327 (M^+, 100 %), 271 (5), 120 (15, $[NHCHCH_3Ph]^+$), 105 (28, $[CHCH_3Ph]^+$); Found (HRMS, EI) M^+ 327.13609 $C_{19}H_{21}NO_2S$ requires *m/z* 327.12930.

3-Hydroxy-_N_-(4-methylphenyl)-3-phenyl-2-(phenylsulfanyl)propenamide 5h

This was prepared following the procedure described for **5d** using **10h** (0.30 g, 0.86 mmol), NCS (0.24 g, 1.76 mmol) and toluene (6 mL) with a reaction time of 2 h,

followed by morpholine (0.19 mL, 2.15 mmol) with a reaction time of 60 h (by TLC analysis), including heating at reflux for 1 h. Hydrolysis using acetone (7 mL) and HCl (0.1 M, 9 mL, 0.9 mmol) in a reaction time of 24 h gave a crude reaction mixture (198 mg) as an oil. Purification by chromatography using ethyl acetate-hexane (5:95) as eluent gave **5h** ν_{max}/cm^{-1} (film) 3339 (br NH, OH), 1678 (CO α,β-unsaturated amide), δ_H 2.31 (3 H, s, ArC*H*$_3$), 7.09-7.62 (14 H, m, Ar*H*), 8.85 (1 H, br s, N*H*), the signal for the enolic proton was seen at δ_H >11.

***N*-Benzyl-3-hydroxy-2-*(n*-butylsulfanyl)propenamide 5i**

This was prepared following the procedure described for **5d** using **10i** (0.28 g, 1.12 mmol), NCS (0.31 g, 2.34 mmol) and toluene (6 mL) with a reaction time of 1.5 h, followed by morpholine (0.25 mL, 2.8 mmol), with a reaction time of 5 min. Hydrolysis using acetone (6 mL) and HCl (0.1 M, 11 mL, 1.1 mmol) gave **5i** (0.21 g, 83 %), as a pink oil; ν_{max}/cm^{-1} (film) 3369 (br NH, OH), 1618 (CO α,β-unsaturated amide); δ_H 0.86 [3 H, t, *J* 7, C(4′)*H*$_3$], 1.27-1.38 [2 H, m, C(3′)*H*$_2$],1.39-1.65 [2 H, m, C(2′)*H*$_2$], 2.39-2.45 [2 H, m, C(1′)*H*$_2$], 4.51 (2 H, d, *J* 6, C*H*$_2$Ph), 7.25-7.35 (5 H, m, Ar*H*), 7.52 (1 H, d, *J* 10, C*H*=), 11.30 (1 H, d, *J* 11, CO*H*=); δ_C 14.0 [*C*(4′)H$_3$], 22.0 [*C*(3′)H$_2$], 31.6 [*C*(2′)H$_2$], 36.9 [*C*(1′)H$_2$], 44.2 (*C*H$_2$Ph), 98.6 (S*C*=), 128.1, 128.8 (aromatic *C*H, 2 signals for 3 carbons), 138.1 (aromatic *C*), 169.8 (*C*H=), 171.5 (*C*O); MS *m/z* 265 (M^+, 20 %), 237 (22, M^+-CO), 208 (12), 178 (18); Found (HRMS, EI), M^+ 265.11326 $C_{14}H_{19}NO_2S$ requires *m/z* 265.11365.

***N*-Phenyl-2-[2′-(hydroxyethyl)sulfanyl]-3-hydroxy-2-butenamide 5j**

This was prepared following the procedure described for **5d** using **11j-*Z*** (85 mg, 0.31 mmol), morpholine (68 μl, 0.78 mmol) and CH_2Cl_2 (2 mL) with a reaction time of 22 h. Acetone (4 mL) and HCl (0.1 M, 3 mL, 3 mmol) were used for the hydrolysis giving a crude mixture (50 mg). Purification by preparative thin layer chromatography using ethyl acetate-DCM-hexane (25:5:70) gave **5j** (16 mg, 24 %) as a red oil; ν_{max}/cm^{-1} (film) 3314 (br NH, OH), 1682, 1597 (CO α,β-unsaturated amide); δ_H 2.39 [3 H, s, C(4)*H*$_3$], 2.74 (2 H, dd, *J* 6, 6, C*H*$_2$S), 3.80 (2 H, dd, *J* 6, 6, C*H*$_2$O), 7.13-7.59 (5 H, m, Ar*H*), 9.35 (1 H, br

s, N*H*). The enolic OH could be seen in one sample at > 10 ppm; MS *m/z* 253 (M^+, 17 %), 209 (9), 107(48), 93 (100, $[NH_2Ph]^+$).

Acknowledgements

IRCSET, Forbairt and University College Cork are gratefully acknowledged for funding of this work.

References

Reference List

1. *Oxidations in organic chemistry*; Hudlicky, Milos American Chemical Society: Washington DC, 1990.
2. Thomas, J. M.; Raja, R.; Sankar, G.; Bell, R. G. *Acc. Chem. Res.*, **2001**, *34*, 191-200.
3. Mizuno, N.; Nozaki, C.; Kiyoto, I.; Misono, M. *J. Am. Chem. Soc.*, **1998**, *120*, 9267-9272.
4. Hayashi, T.; Kishida, A.; Mizuno, N. *Chem. Commun.*, **2000**, 381-382.
5. Hahn, H. G.; Nam, K. D.; Mah, H.; Lee, J. J. *J. Org. Chem.*, **1996**, *61*, 3894-3896.
6. Hamilton, H. W.; Tait, B. D.; Gajda, C.; Hagen, S. E.; Ferguson, D.; Lunney, E. A.; Pavlovsky, A.; Tummino, P. J. *Bioorg. Med. Chem. Lett.*, **1996**, *6*, 719-724.
7. Kuo, E. A.; Hambleton, P. T.; Kay, D. P.; Evans, P. L.; Matharu, S. S.; Little, E.; McDowall, N.; Jones, C. B.; Hedgecock, C. J.; Yea, C. M.; Chan, A. W.; Hairsine, P. W.; Ager, I. R.; Tully, W. R.; Williamson, R. A.; Westwood, R. *J. Med. Chem.*, **1996**, *39*, 4608-4621.
8. Robinson, R. P.; Reiter, L. A.; Barth, W. E.; Campeta, A. M.; Cooper, K.; Cronin, B. J.; Destito, R.; Donahue, K. M.; Falkner, F. C.; Fiese, E. F.; Johnson, D. L.; Kuperman, A., V; Liston, T. E.; Malloy, D.; Martin, J. J.; Mitchell, D. Y.; Rusek, F. W.; Shamblin, S. L.; Wright, C. F. *J. Med. Chem.*, **1996**, *39*, 10-18.
9. *Methods for the Oxidation of Organic Compounds*; Haines, A. H. Academic Press: London, 1985.
10. Kanner, C. B.; Pandit, U. K. *Tetrahedron*, **1982**, *38*, 3597-3604.

11. Abram, T. S.; Boeshagen, H.; Butler, J. E.; Cuthbert, N. J.; Francis, H. P.; Gardiner, P. J.; Hartwig, W.; Kluender, H. C.; Meier, H. *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 1517-1522.

12. Murphy, M.; Lynch, D.; Schaeffer, M.; Kissane, M.; Chopra, J.; O'Brien, E.; Ford, A.; Ferguson, G.; Maguire, A. R. *Organic & Biomolecular Chemistry*, **2007**, *5*, 1228-1241.

13. Kissane, M.; Lynch, D.; Chopra, J.; Lawrence, S. E.; Maguire, A. R. *Tetrahedron: Asymmetry*, **2008**, *19*, 1256-1273.

14. Kissane, M.; Lawrence, S. E.; Maguire, A. R. *Tetrahedron Asymmetry*, **2010**, *21*, 871-884.

15. Kissane, M.; Lawrence, S. E.; Maguire, A. R. *Org. Biomol. Chem.*, **2010**, *8*, 2735-2748.

16. Kissane, M.; Lawrence, S. E.; Maguire, A. R. *Tetrahedron*, **2010**, *66*, 4564-4572.

17. Kissane, M.; Lynch, D.; Chopra, J.; Lawrence, S. E.; Maguire, A. R. *Org. Biomol. Chem.*, **2010**, *8*, 5602-5613.

18. Kissane, M., Murphy, M., O'Brien, E., Chopra, J., Murphy, L., Collins, S.G., Lawrence, S.E., Maguire, A.R., *Org. Biomol. Chem*., 2010, DOI: 10.1039/c0ob00805b.

19. Kissane, M.; Murphy, M.; Lynch, D.; Ford, A.; Maguire, A. R. *Tetrahedron*, **2008**, *64*, 7639-7649.