Stereoselective synthesis of 2,3-difunctionalised thioesters using nucleophilic epoxidation of 1-arylthio-1-nitroalkenes†

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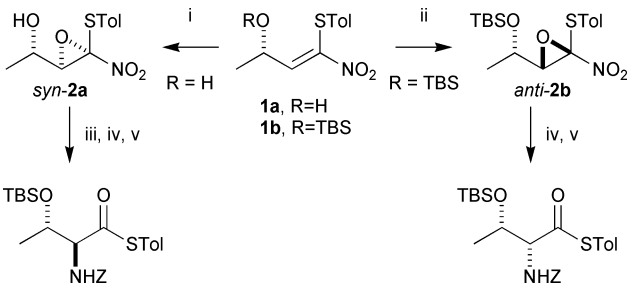
Stereoselective nucleophilic epoxidation of protected 3-amino and 3-hydroxy-substituted 1-arylthio-1-nitroalkenes, followed by intramolecular capture involving the amino and hydroxyl protecting groups, has led to the formation of isomeric oxazolidinones **5** and **7**, and a cyclic carbonate **11**. Together with the oxazolidinone precursor *anti*-α-bromo thioester **15a**, the absolute and relative stereochemistry of these compounds has been determined by X-ray crystallography.

Introduction

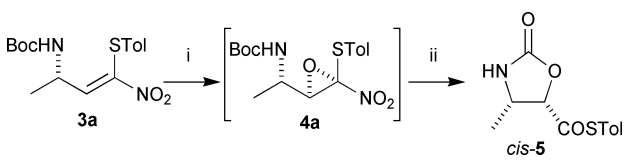
The synthesis of enantiomerically pure α-hydroxy-β-amino acids is of great interest as this structure is present in a variety of drugs and natural products that exhibit potent biological activities.[1–6] α-Hydroxy-β-amino acid derivatives often display potent protease inhibition as this structural unit is an efficient transition-state mimic of peptide hydrolysis.[4] Selected examples include the KMI- and KNI- series of compounds that contain a 3-amino-2-hydroxy-4-phenylbutyric acid derivative as an isostere.[7] The KMI compounds are highly potent β-secretase (BACE1) inhibitors[8] and have therapeutic potential for Alzheimer's disease.[9] Kynostatins KNI-227, -272[10,11] and -279[12] are highly active HIV-1 protease inhibitors and (−)-bestatin[13] is a specific inhibitor of aminopeptidase B. The side-chain of taxol (paclitaxel), a potent antitumour compound, also contains an α-hydroxy-β-amino acid derivative.[14]

Isomeric β-hydroxy-α-amino acids are present in many biologically active compounds such as the ustiloxins,[15,16] a family of cyclic peptides that are potent antimitotic agents that display growth inhibition of various tumour cell lines, and numerous glycopeptide antibiotics,[17] including vancomycin.[18] We have shown that 1-arylthio-1-nitroalkenes with an allylic hydroxyl substituent **1** can undergo stereoselective nucleophilic epoxidation and subsequent ring-opening with ammonia to give enantiomerically pure β-hydroxy-α-amino acid derivatives. The stereochemical outcome of the epoxidation reaction can be controlled by the combined influence of the presence, or absence, of a protecting group on the allylic hydroxyl substituent, and by the choice of nucleophilic oxidant. The combination of lithium *tert*-butylperoxide and an unprotected hydroxyl group gives *syn*-epoxides, while potassium tritylperoxide gives *anti*-epoxides (Scheme 1).[19]



Scheme 1 *Reagents and conditions*: (i) ^{t}BuOOLi, THF, −78 °C; (ii) Ph_3COOK, THF, −78 °C; (iii) ^{t}BuMe$_2$SiOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (iv) aq. NH_3 (*d* 0.880), CH_2Cl_2, rt; (v) $PhCH_2OCOCl$.[19]

Epoxidation of 1-arylthio-1-nitroalkenes **3** possessing an allylic nitrogen substituent, gives access to protected α-hydroxy-β-amino acid derivatives (Scheme 2).[20] In contrast to the analogous oxygen substituted systems,[19] it was found that epoxidation using either lithium *tert*-butylperoxide or potassium tritylperoxide gives the *cis*-oxazolidinone **5** in a highly stereoselective fashion after work-up, presumably *via* the same *syn*-epoxide intermediate **4a**.[20]



Scheme 2 *Reagents and conditions*: (i) ^{t}BuOOLi, THF, −78 °C or Ph_3COOK, THF, −78 °C; (ii) work-up.[20]

We now report that introduction of a carbamate protecting group on the epoxide *syn*-**2a** allows the stereocontrolled synthesis of a β-hydroxy-α-amino derivative **7** that is isomeric to *cis*-**5**, and that analogous use of a carbonate protecting group allows the synthesis of a cyclic carbonate **11**. A modified strategy also permits the synthesis of a *syn*-α-hydroxy-β-amino acid derivative, masked as the *trans*-oxazolidinone **5**, previously inaccessible using this approach.

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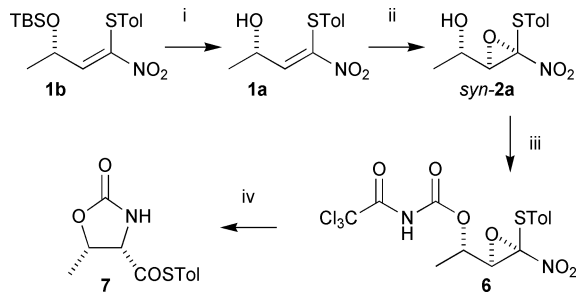
Results and discussion

The key starting material, alkene **1b**, was prepared by the previously reported method.[19] Although deprotection of the *tert*-butyldimethylsilyl (TBS) protecting group of compound **1b** using $BF_3{\cdot}OEt_2$ in dichloromethane[21] had previously worked satisfactorily,[19] the process subsequently proved to be somewhat capricious. A related observation by Yoshida prompted a change of solvent to acetonitrile,[22] which allowed deprotection of the silyl ether **1b** to give the allylic alcohol **1a** in a consistent yield of 80% (Scheme 3). As previously reported,[19] treatment of the allylic alcohol **1a** with ^{t}BuOOLi (prepared from ^{n}BuLi and ^{t}BuOOH) gave the epoxide *syn*-**2a** as a single diastereoisomer, as judged by ^{1}H NMR. The stereoselectivity exhibited in this reaction is believed to originate from coordination of the Li to the allylic alcohol, delivering the nucleophilic oxygen *syn* to the hydroxyl substituent.[19]



Scheme 3 *Reagents and conditions*: (i) $BF_3{\cdot}OEt_2$, MeCN, 0 °C, 80%; (ii) ^{t}BuOOLi, THF, −78 °C, 86%; (iii) CCl_3CONCO, $CHCl_3$, 86%; (iv) SiO_2, $CHCl_3$, 46% (over 2 steps).

Since previous work had shown that epoxidation of 1-arylthio-1-nitroalkenes bearing an allylic nitrogen, protected as a carbamate, resulted in the protecting group ring-opening the epoxide intermediate generating an oxazolidinone,[20] the feasibility of an isomeric carbamate derived from the *syn*-epoxide **2a** undergoing a similar process was explored.

Following the strategy reported by Ichikawa *et al.*,[23] treatment of the *syn*-epoxide **2a** with trichloroacetyl isocyanate gave the trichloroacetyl carbamate **6** (86%). Although basic hydrolysis of the trichloroacetyl carbamate would have revealed the unsubstituted carbamate, we were concerned that the basic conditions reported by Ichikawa were incompatible with the functionalised epoxide. Unfortunately, use of a milder deprotection method involving neutral alumina[24] resulted in extensive decomposition. However, treatment of the trichloroacetyl carbamate **6** with silica gel, which had previously been used to induce cyclisation of a dimethylcarbamate group,[25] gave the substituted *cis*-oxazolidinone **7** (isomeric to the *cis*-oxazolidinone **5** previously reported)[20] in an overall 46% yield from the *syn*-epoxide **2a**. Nucleophilic attack through the carbonyl oxygen, which would ultimately have led to the *cis*-cyclic carbonate **11** after hydrolysis, was not observed.

A crystal structure of the *cis*-oxazolidinone **7** (Fig. 1) confirmed the relative and absolute stereochemistry, which results from intramolecular nucleophilic attack with inversion at C-3 of the epoxide. The crystal structure also revealed an unusually strong hydrogen bonding interaction between the carbonyl oxygen (O3)

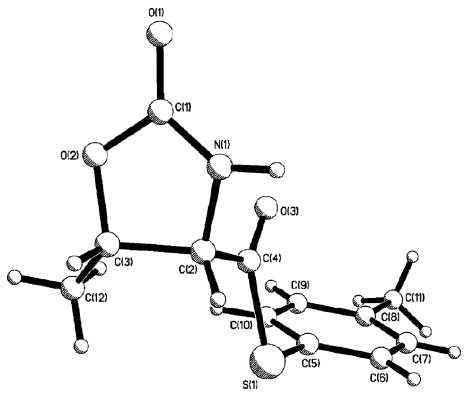
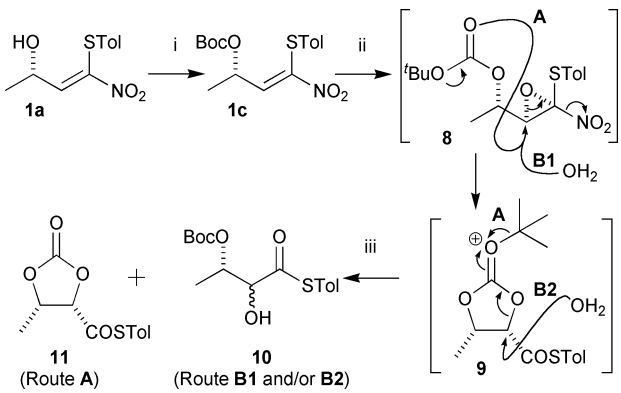


Fig. 1 *cis*-Oxazolidinone **7**.

and the *meta*-hydrogen of the aromatic ring of another molecule (2.587 Å, not shown).

Since it had already been established that intramolecular attack at C3 of a 2-arylthio-2-nitrooxirane by the carbonyl group of a carbamate could occur,[20] the possibility that the carbonyl group of a carbonate might also participate was explored. Thus, treatment of the allylic alcohol **1a** with di-*tert*-butyl dicarbonate in the presence of *N*-methylimidazole,[26] which reduces the formation of the symmetrical carbonate by-product, gave the Boc-protected alcohol **1c** in 70% yield. Epoxidation of the alkene **1c** with ^{t}BuOOLi gave the *cis*-cyclic carbonate **11** (47%) (Route A), as well as an epimeric mixture (10 : 3) of the α-hydroxy thioesters **10** (35%). The α-hydroxy thioesters **10** may result from hydrolysis of either the presumed epoxide intermediate **8** (Route B1) and/or the intermediate **9** (Route B2, Scheme 4).



Scheme 4 *Reagents and conditions*: (i) Boc_2O, *N*-methylimidazole, toluene, 70%; (ii) ^{t}BuOOLi, THF, −78 °C; (iii) SiO_2; **10** (35% over 2 steps) and **11** (47% over 2 steps).

The stereochemistry of the *cis*-cyclic carbonate **11** was determined by X-ray crystallography, shown in Fig. 2. ^{1}H NMR showed an ABX_3 system, from which the ^3J coupling between the two protons on the oxazolidinone ring was determined to be 8.5 Hz, typical for a *syn*-relationship in similar systems.[27] The formation of the *cis*-carbonate **11** suggests that the *syn*-epoxide **8** was preferentially formed in the epoxidation step. This implies that, during nucleophilic epoxidation with ^{t}BuOOLi, the Boc-protected allylic oxygen substituent was effective at coordinating lithium, so delivering the nucleophilic oxidant *syn* to the carbonate substituent.

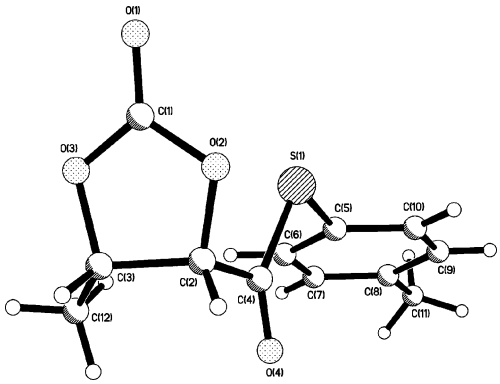
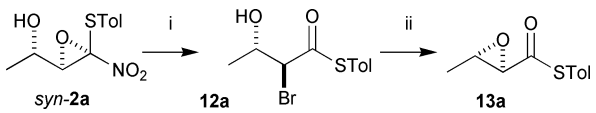


Fig. 2 *cis*-Cyclic carbonate **11**.

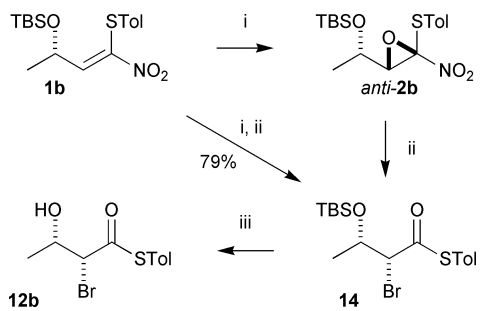
Synthesis of epoxythioesters

We have previously demonstrated that 2-arylthio-2-nitrooxiranes undergo regioselective ring-opening with inversion of configuration in the presence of $MgBr_2{\cdot}Et_2O$ to afford the corresponding α-bromo thioesters.[28–30] Analogous reaction of the epoxide *syn*-**2a** with $MgBr_2{\cdot}Et_2O$ gave the *anti*-α-bromo-β-hydroxy thioester **12a** (77%), as a single diastereoisomer. Subsequent treatment of the alcohol **12a** with NaH gave the *trans*-epoxy thioester **13a** (47%) (Scheme 5).



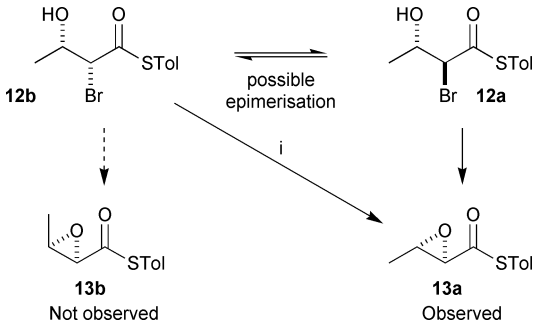
Scheme 5 *Reagents and conditions*: (i) $MgBr_2{\cdot}OEt_2$, THF, 77%; (ii) NaH, THF, 47%.

With the aim of preparing the isomeric *cis*-epoxy thioester **13b**, epoxidation of the silyl-protected allylic alcohol **1b** with Ph_3COOK (prepared from Ph_3COOH and KH) gave the *anti*-epoxide **2b** with high diastereoselectivity.[19] Stereospecific ring-opening with $MgBr_2{\cdot}Et_2O$ gave the *syn*-α-bromo thioester **14** (87%). A one-pot procedure was also investigated in which the silyl-protected allylic alcohol **1b** was initially treated with Ph_3COOK, followed by the addition of solid $MgBr_2{\cdot}Et_2O$, to give the *syn*-α-bromo thioester **14** (79% over two steps). Deprotection of the silyl group using $BF_3{\cdot}OEt_2$ in acetonitrile[22] gave the *syn*-α-bromo-β-hydroxy thioester **12b** (80%) (Scheme 6).



Scheme 6 *Reagents and conditions*: (i) Ph_3COOK, THF, 74% (15 : 1 *anti* : *syn*);[19] (ii) $MgBr_2{\cdot}OEt_2$, Et_2O, 87%; (iii) $BF_3{\cdot}OEt_2$, MeCN, 0 °C, 80%.

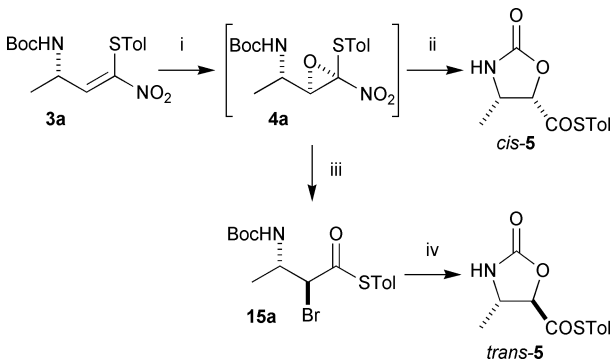
Attempts to convert the *syn*-α-bromo-β-hydroxy thioester **12b** into the *cis*-epoxy thioester **13b** under a variety of conditions failed, although there was ^{1}H NMR evidence for the formation of the *trans*-epoxide **13a** in the crude reaction mixture. The transition state for the cyclisation leading to the *cis*-epoxide is expected to be more crowded than that for formation of the *trans*-epoxide **13a**, and it is therefore likely that epimerisation of **12b** to give **12a**, followed by cyclisation, occurs preferentially (Scheme 7). Epimerisation of thioesters is known to be facile.[31]



Scheme 7 *Reagents and conditions*: (i) NaH, THF.

Preparation of protected α-hydroxy-β-amino acid *trans*-5

Stereoselective nucleophilic epoxidation of 1-arylthio-1-nitroalkenes had been previously developed as a route for the synthesis of *anti*-α-hydroxy-β-amino acid derivatives, masked as oxazolidinones (Scheme 2).[20] It was anticipated that the unstable intermediate epoxide might be amenable to trapping by an external nucleophile that could then act as a leaving group, thereby leading to the previously inaccessible oxazolidinone *trans*-**5**. Addition of $MgBr_2{\cdot}Et_2O$ to the reaction mixture containing the *syn*-epoxide **4a**, followed by silica gel chromatography, gave a mixture of the *anti*-α-bromo thioester **15a** as a single diastereoisomer (15%), the desired cyclised product oxazolidinone *trans*-**5** (36%) and the isomeric oxazolidinone *cis*-**5** (14%) (Scheme 8). The relative and absolute stereochemistry of the *anti*-α-bromo thioester **15a** was determined by X-ray crystallography (Fig. 3).



Scheme 8 *Reagents and conditions*: (i) ^{t}BuOOLi, THF, −78 °C; (ii) SiO_2, 72%;[20] (iii) $MgBr_2{\cdot}OEt_2$(s); (iv) SiO_2; **15a** (15%), *trans*-**5** (36%), *cis*-**5** (14%) (from **3a**).

It is likely that the conversion of **15a** into oxazolidinone *trans*-**5**, the structure of which was confirmed by X-ray crystallography (Fig. 4), occurs through silica gel promoted nucleophilic attack of

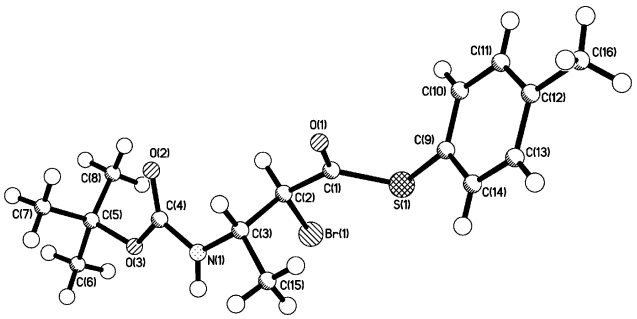


Fig. 3 *anti*-α-Bromo thioester **15a**.

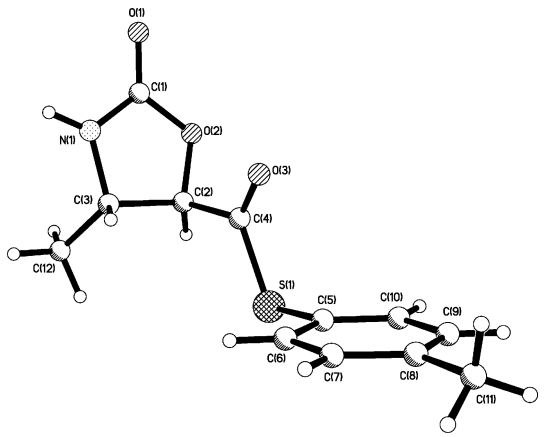
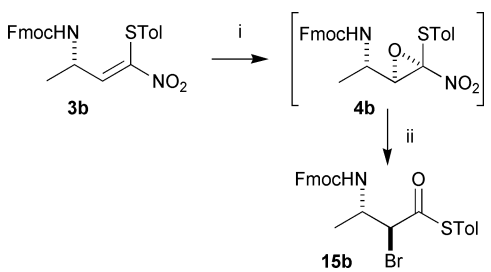


Fig. 4 Oxazolidinone *trans*-**5**.

the carbonyl group of the Boc-protected amino oxygen on the *anti*-α-bromo thioester. A related transformation was reported by Righi in similar vinylogous substrates.[32] Formation of the oxazolidinone *cis*-**5** presumably arises from direct attack of the Boc group on the intermediate epoxide **4a**, as already shown in Scheme 2. This process competes with attack by the external bromide nucleophile.

Previous work had shown that the Fmoc protecting group is less prone to participate in cyclisation processes than the Boc group, an observation that has been used in the synthesis of *anti*-α,β-diamino acid derivatives.[20,33] Therefore, in a preliminary study, stereoselective epoxidation of the Fmoc-protected allylic amine **3b**[20] and treatment of the intermediate epoxide **4b** with $MgBr_2{\cdot}Et_2O$ gave the α-bromo thioester **15b**, a potentially useful synthetic intermediate, in an unoptimised 35% yield over 2 steps (Scheme 9).



Scheme 9 *Reagents and conditions*: (i) ^{t}BuOOLi, THF, −78 °C; (ii) $MgBr_2{\cdot}OEt_2$(s), 35% (2 steps).

Conclusions

Intramolecular capture of 2-arylthio-2-nitrooxirane intermediates has been successfully carried out using carbamate and carbonate protecting groups, generating the β-hydroxy-α-amino acid derivative, oxazolidinone **7**, and the α,β-dihydroxy acid derivative, cyclic carbonate **11**, respectively. The preparation of the previously inaccessible *syn*-α-hydroxy-β-amino acid derivative (masked as the oxazolidinone *trans*-**5**) was achieved by a combination of intermolecular ring-opening of the epoxide followed by intramolecular nucleophilic attack. Extension of this ring-opening/ring-closing strategy has also allowed the synthesis of *trans*-epoxy thioester **13a** and α-bromo thioester **15b** which are both potentially useful synthetic intermediates.

Experimental

All reagents used were purchased from commercial sources or prepared and purified according to literature procedures. All moisture/air sensitive reactions were conducted under a positive pressure of nitrogen in flame dried or oven dried glassware. Petroleum ether refers to the fraction with a boiling point between 40–60 °C.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-250, Bruker AMX2-400 or Bruker DRX-500 NMR spectrometer at room temperature. Chemical shifts were measured relative to residual solvent and are expressed in parts per million (δ). Coupling constants (J) are given in Hertz and the measured values are rounded to the nearest 0.5 Hertz. High-resolution mass spectra were recorded using a MicroMass LCT operating in electrospray (ES) mode. Chemical analyses were performed using a Perkin Elmer 2400 CHN elemental analyser. Optical rotations were measured on a Perkin Elmer 241 automatic polarimeter at λ 589 nm (Na, D-line) with a path length of 1 dm at the stated temperature and concentrations. The concentration is given in g per 100 cm^3 and the optical rotations are quoted in 10^{-1} deg cm^2 g^{-1}. Infra-red spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer (ν_{max} in cm^{-1}) as thin films using NaCl plates. Melting points were determined using a Linkam HFS91 heating stage, used in conjunction with a TC92 controller and are uncorrected.

Thin layer chromatography (TLC) was performed on precoated plates (Merck aluminium sheets silica 60 F_{254}, art. no. 5554). Column chromatography was performed using silica gel 60 (Merck 9385).

(2,2,2-Trichloroacetyl)-carbamic acid (*S*)-1-[(2*R*,3*R*)-3-nitro-*p*-tolylsulfanyl-oxiranyl]-ethyl ester 6

Trichloroacetyl isocyanate (12 µl, 0.1 mmol, 1.05 eq.) was added in one portion to a stirred solution of the epoxide *syn*-**2a** (prepared according to the procedure previously reported,[19] 24.4 mg, 0.0956 mmol) in chloroform (2 cm^3) under a nitrogen atmosphere at room temperature. After 1.5 h, the solution was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford the carbamate **6** (36.3 mg, 86%) as a colourless waxy solid. $[\alpha]_D^{22}$ −44.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3479, 3351, 3290, 2987, 1799, 1725, 1569, 1494 and 824; δ_H (250 MHz; $CDCl_3$) 1.47 (3H, d, J 6.5 Hz, CH_3CH), 2.29 (3H, s, ArCH_3),

3.77 (1H, d, *J* 8.0 Hz, COCH), 5.19 (1H, dq, *J* 8.0 and 6.5 Hz, CH_3CHO), 7.18 (2H, d, *J* 8.5 Hz, Ar), 7.45–7.49 (2H, m, Ar) and 8.47 (1H, s, br, NH); δ_C (62.5 MHz; $CDCl_3$) 16.8, 21.3, 65.1, 72.4, 81.1, 94.9, 121.1, 130.6, 135.2, 141.3, 148.6 and 157.8.

(4*S*,5*S*)-4-(*p*-Tolylthiocarbonyl)-5-methyloxazolidin-2-one 7

Trichloroacetyl isocyanate (17.4 µl, 0.146 mmol, 1.05 eq.) was added in one portion to a stirred solution of the epoxide *syn*-**2a** (prepared according to the procedure previously reported,[19] 35.5 mg, 0.139 mmol) in chloroform (2 cm^3) under a nitrogen atmosphere at room temperature. After 1.5 h, silica gel (355 mg, 10× w/w) was added in one portion and the mixture was stirred for a further 1 h at 65 °C. The slurry was filtered, washed with EtOAc (2 × 5 cm^3) and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography (20% EtOAc–petroleum ether) to afford the *cis*-oxazolidinone **7** (16 mg, 46%) as a pale yellow solid. Recrystallisation by slow evaporation from petroleum ether–Et_2O gave colourless needles which were analysed by X-ray crystallography. Mp 94–96 °C; $[\alpha]_D^{22}$ −76.9 (*c* 0.33 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3283 (br), 1756 and 1699; δ_H (250 MHz; $CDCl_3$) 1.41 (3H, d, *J* 6.5 Hz, CH_3CH), 2.31 (3H, s, $ArCH_3$), 4.46 (1H, d, *J* 9.0 Hz, NHC*H*), 4.94 (1H, dq, *J* 9.0 and 6.5 Hz, CH_3CH), 6.28 (1H, br s, NH) and 7.18–7.20 (4H, m, Ar); δ_C (125 MHz; $CDCl_3$) 16.0, 21.4, 64.0, 75.6, 122.2, 130.4, 134.4, 140.5, 158.6 and 197.5; *m*/*z* (ES) 525 (M_2Na^+, 14%), 503 (M_2H^+, 12), 274 (MNa^+, 30) and 252 (MH^+, 100); found (MH^+) 252.0704, $C_{12}H_{14}NO_3S$ requires 252.0694.

(*Z*)-(3*S*)-3-(*tert*-Butoxycarbonyloxy)-1-nitro-1-*p*-tolylthio-but-1-ene 1c

N-Methylimidazole (76 µl, 0.95 mmol, 1 eq.) was added dropwise to a stirred cooled solution (~5 °C) of the allylic alcohol **1a** (227 mg, 0.95 mmol, 1 eq.), prepared according to the procedure previously reported,[19] and di-*tert*-butyl dicarbonate (208 mg, 0.95 mmol, 1 eq.) in toluene (14 cm^3) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and was stirred for 40 min. The crude reaction mixture was filtered through a short plug of silica gel and the solvent was evaporated to give the Boc-protected allylic alcohol **1c** (226 mg, 70%) as an oil. $[\alpha]_D^{22}$ −44.3 (*c* 0.84 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2983, 2931, 1744, 1537 and 1277; δ_H (250 MHz; $CDCl_3$) 1.40 (3H, d, *J* 6.5 Hz, CH_3CH), 1.44 (9H, s, ^{t}Bu), 2.25 (3H, s, $ArCH_3$), 5.68 (1H, dq, *J* 8.0 and 6.5 Hz, CH_3CH), 7.03–7.11 (2H, m, Ar), 7.24–7.36 (2H, m, Ar) and 7.39 (1H, d, *J* 8.0 Hz, CHC); δ_C (125 MHz; $CDCl_3$) 19.8, 21.0, 27.7, 71.1, 83.2, 128.5, 130.3, 130.9, 138.7, 143.6, 148.3 and 152.5; *m*/*z* (ES) 362 (MNa^+, 70%), 335 (100), 306 (7) and 279 (18); found (MNa^+) 362.1044, $C_{16}H_{21}NO_5NaS$ requires 362.1038.

(4*S*,5*S*)-4-(*p*-Tolylthiocarbonyl)-5-methyl-[1,3]-dioxolan-2-one 11 and *S*-(*p*-tolyl) (2*RS*,3*S*)-3-(*tert*-butoxycarbonyloxy)-2-hydroxybutanethioate 10

^{n}BuLi (2.5 M in hexanes, 320 µl, 0.80 mmol, 1.2 eq.) was added dropwise to a stirred solution of *tert*-butyl hydroperoxide (3.8 M in toluene, 260 µl, 1.0 mmol, 1.5 eq.) in THF (10 cm^3) at −78 °C under a nitrogen atmosphere. A solution of the Boc-protected allylic alcohol **1c** (227 mg, 0.67 mmol, 1 eq.) in THF (7 cm^3) was added dropwise to the stirred solution at −78 °C and after 30 min the reaction was quenched at that temperature by the addition of silica gel (2.3 g, 10× w/w). The mixture was allowed to warm to room temperature, filtered and washed with EtOAc (20 cm^3). The solvent was removed under reduced pressure and the brown residue (171 mg) was dissolved in $CHCl_3$ (50 cm^3) and silica gel (1.71 g, 10× w/w) was added in one portion. The reaction mixture was stirred at room temperature for 3 h, filtered and washed with EtOAc (20 cm^3) and the solvent was removed under reduced pressure. Purification by column chromatography (10% EtOAc–petroleum ether) gave the *cis*-cyclic carbonate **11** (79 mg, 47%) as an oil. Crystallisation by slow evaporation from petroleum ether–Et_2O gave colourless cubes which were analysed by X-ray crystallography. Mp 119–120 °C; $[\alpha]_D^{22}$ −80.0 (*c* 0.13 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2916, 2854, 1808 and 1695; δ_H (500 MHz; $CDCl_3$) 1.48 (3H, d, *J* 6.5 Hz, $CHCHCH_3$, ABX_3), 2.39 (3H, s, $ArCH_3$), 5.07 (1H, dq, *J* 8.5 and 6.5 Hz, $CHCHCH_3$, ABX_3), 5.13 (1H, d, *J* 8.5 Hz, $CHCHCH_3$, ABX_3) and 7.25–7.27 (4H, m, Ar); δ_C (125 MHz; $CDCl_3$) 15.6, 21.4, 75.6, 81.0, 121.1, 130.5, 134.5, 140.8, 155.2 and 194.7. *m*/*z* (ES) 275 (MNa^+, 100%); found (MNa^+) 275.0364, $C_{12}H_{12}O_4NaS$ requires 275.0354. An inseparable 10 : 3 epimeric mixture of α-hydroxy thioesters **10** (79 mg, 35%) was also isolated by column chromatography as an oil; ν_{max} (film)/cm^{-1} 3482 (br), 2981, 2937, 1742, 1701 and 1280; δ_H (500 MHz; $CDCl_3$) (3 : 10 mixture, A : B) 1.36 (3H (A), d, *J* 6.5 Hz, CH_3CH), 1.43 (3H (B), d, *J* 6.5 Hz, CH_3CH), 1.47 (9H (B), s, ^{t}Bu), 1.50 (9H (A), s, ^{t}Bu), 2.35 (3H (A), s, $ArCH_3$), 2.37 (3H (B), s, $ArCH_3$), 4.26 (1H (B), d, *J* 3.0 Hz, CHOH), 4.55 (1H (A), d, *J* 2.5 Hz, CHOH), 5.06 (1H (A), dq, *J* 6.5 and 2.5 Hz, CH_3CH), 5.15 (1H (B), dq, *J* 6.5 and 3.0 Hz, CH_3CH), 7.20–7.28 (4H (A + B), Ar); δ_C (125 MHz $CDCl_3$) 14.5 (A), 16.5 (B), 21.3 (A + B), 27.7 (A + B), 73.8 (B), 75.3 (A), 79.4 (A), 79.8 (B), 82.8 (B), 83.1 (A), 123.0 (A + B), 130.1 (A + B), 134.6 (A + B), 140.0 (A + B), 152.7 (B), 153.5 (A), 199.4 (A), 199.7 (B); *m*/*z* (ES) 349 (MNa^+, 100%) and 293 (40); found (MNa^+) 349.1077, $C_{16}H_{22}O_5NaS$ requires 349.1086.

S-(*p*-Tolyl) (2*S*,3*S*)-2-bromo-3-hydroxybutanethioate 12a

Magnesium bromide ethyl etherate (296 mg, 1.15 mmol, 1.5 eq.) was added to a stirred solution of the epoxide *syn*-**2a** (prepared according to the procedure previously reported,[19] 196 mg, 0.77 mmol, 1 eq.) in THF (4 cm^3) under a nitrogen atmosphere. The mixture was stirred for 2.5 h at room temperature and quenched with water (3 cm^3). The aqueous layer was extracted with EtOAc (2 × 5 cm^3) and the combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (20% EtOAc–petroleum ether) to give the α-bromo-β-hydroxy thioester **12a** (170 mg, 77%) as a yellow oil. $[\alpha]_D^{22}$ +57 (*c* 1.0 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3435 (br), 2925 and 1685; δ_H (400 MHz; $CDCl_3$) 1.45 (3H, d, *J* 6.5 Hz, CH_3CH), 2.42 (3H, s, $ArCH_3$), 2.53 (1H, br s, OH), 4.30–4.33 (1H, m, CH_3CH), 4.48 (1H, d, *J* 6.5 Hz, CHBr), 7.27 (2H, d, *J* 8.5 Hz, Ar) and 7.36 (2H, d, *J* 8.5 Hz, Ar); δ_C (100 MHz; $CDCl_3$) 20.1, 21.4, 57.2, 69.1, 123.0, 130.3, 134.4, 140.4 and 195.0; *m*/*z* (ES) 291 and 289 (MH^+, 100%), 245 and 243 (30); found (MH^+) 288.9910. $C_{11}H_{14}BrO_2S$ requires 288.9898.

S-(*p*-Tolyl) (2*R*,3*S*)-3-methyloxirane-2-carbothioate 13a

Sodium hydride (60% w/w dispersion in oil, 32 mg, 0.8 mmol, 1 eq.) was added in one portion to a stirred cooled (0 °C) solution of the thioester **12a** (230 mg, 0.8 mmol, 1 eq.) in THF (10 cm^3) under a nitrogen atmosphere. The reaction was monitored by TLC [eluent, petroleum ether–EtOAc (8 : 2)] and quenched after 15 min with saturated aqueous ammonium chloride solution (10 cm^3). EtOAc (10 cm^3) was added, the organic phase was separated, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography (10% EtOAc–petroleum ether) to afford the epoxide **13a** (78 mg, 47%) as a colourless oil. $[\alpha]_D^{22}$ +97.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2924 and 1693; δ_H (250 MHz; $CDCl_3$) 1.44 (3H, d, *J* 5.0 Hz, C*H*$_3$CH), 2.37 (3H, s, ArC*H*$_3$), 3.35 (1H, qd, *J* 5.0 and 2.0 Hz, CH$_3$C*H*), 3.42 (1H, d, *J* 2.0 Hz, CHC) and 7.12–7.24 (4H, m, Ar); δ_C (125 MHz; $CDCl_3$) 17.2, 21.2, 56.4, 60.8, 122.4, 130.1, 134.5, 139.8 and 196.7; *m*/*z* (ES) 231 (MNa^+, 100%); found (MNa^+) 231.0447, $C_{11}H_{12}O_2NaS$ requires 231.0456.

S-(*p*-Tolyl) (2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-bromobutanethioate 14

Magnesium bromide diethyl etherate (145 mg, 0.560 mmol, 1.5 eq.) was added to a stirred solution of the epoxide *anti*-**2b** (prepared according to the procedure previously reported,[19] 138 mg, 0.373 mmol, 1 eq.) in Et_2O (1.5 cm^3) under a nitrogen atmosphere. The mixture was stirred overnight at room temperature and quenched with water (10 cm^3). The aqueous layer was extracted with EtOAc (2 × 5 cm^3) and the combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (20% EtOAc–petroleum ether) to give the *syn*-α-bromo-β-silyloxy thioester **14** (132 mg, 87%) as an oil. $[\alpha]_D^{22}$ −58.3 (*c* 0.64 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2929, 2856, 1712, 1257 and 1137; δ_H (400 MHz; $CDCl_3$) 0.08 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.91 (9H, s, ^{t}Bu), 1.30 (3H, d, *J* 6.0 Hz, C*H*$_3$CH), 2.37 (3H, s, ArC*H*$_3$), 4.27 (1H, qd, *J* 6.0 and 5.5 Hz, CH$_3$C*H*), 4.39 (1H, d, *J* 5.5 Hz, CHBr) and 7.20–7.30 (4H, m, Ar); δ_C (100 MHz; $CDCl_3$) −4.8, −4.4, 18.1, 21.4, 21.5, 25.7, 60.5, 69.5, 123.8, 130.2, 134.3, 140.1 and 193.9; *m*/*z* (ES) 427 and 425 (MNa^+, 30%), 405 and 403 (MH^+, 100); found (MH^+) 403.0762, $C_{17}H_{28}BrO_2SSi$ requires 403.0763.

One-pot procedure

Trityl hydroperoxide (295 mg, 1.07 mmol, 1.5 eq.) was added to a stirred solution of KH (35% dispersed in mineral oil, 106 mg, 0.93 mmol, 1.3 eq.) in THF (8 cm^3) under a nitrogen atmosphere at −78 °C. A solution of the silyl-protected allylic alcohol **1b** (prepared according to the procedure previously reported,[19] 251 mg, 0.71 mmol) in THF (8 cm^3) was added dropwise to the reaction mixture at −78 °C, followed by the addition of magnesium bromide diethyl etherate (275 mg, 1.07 mmol, 1.5 eq.) in one portion. The reaction mixture was allowed to warm to room temperature overnight and was quenched with the addition of water (10 cm^3). The aqueous layer was extracted with EtOAc (8 cm^3) and the combined organic extracts were dried over $MgSO_4$, filtered and solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography (20% EtOAc–petroleum ether) to give the *syn*-α-bromo-β-silyloxy thioester **14** (226 mg, 79%) as an oil, which was identical to the compound prepared previously.

S-(*p*-Tolyl) (2*R*,3*S*)-2-bromo-3-hydroxybutanethioate 12b

Boron trifluoride diethyl etherate (39 µl, 0.31 mmol, 2 eq.) was added to a stirred cooled (0 °C) solution of the *syn*-α-bromo-β-silyloxy thioester **14** (61.5 mg, 0.153 mmol) in dry acetonitrile (7 cm^3) under a nitrogen atmosphere. The clear solution immediately turned yellow and was stirred at 0 °C for a further 15 min before being quenched with pH 7 phosphate buffer (7 cm^3). The solution changed from yellow to colourless. EtOAc (5 cm^3) was added and the organic layer was separated, dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography (20% EtOAc–petroleum ether) to afford the α-bromo-β-hydroxy thioester **12b** (35 mg, 80%) as a colourless oil. $[\alpha]_D^{22}$ −33 (*c* 1.12 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3445, 2978, 2926, 1684 and 800; δ_H (500 MHz; $CDCl_3$) 1.34 (3H, d, *J* 6.5 Hz, C*H*$_3$CH), 2.38 (3H, s, ArC*H*$_3$), 2.67 (1H, br s, OH), 4.19 (1H, qd, *J* 6.5 and 4.5 Hz, CH$_3$C*H*), 4.46 (1H, d, *J* 4.5 Hz, CHBr) and 7.20–7.35 (4H, m, Ar); δ_C (125 MHz; $CDCl_3$) 20.2, 21.4, 60.0, 68.0, 123.0, 130.3, 134.4, 140.5 and 194.9; *m*/*z* (ES) 313 and 311 (MNa^+, 100%); found (MNa^+) 310.9708, $C_{11}H_{13}O_2NaSBr$ requires 310.9717.

S-(*p*-Tolyl) (2*S*,3*S*)-3-(*tert*-butoxycarbonylamino)-2-bromobutanethioate 15a, (4*S*,5*R*)-4-methyl-5-(*p*-tolylthiocarbonyl)oxazolidin-2-one *trans*-5 and (4*S*,5*S*)-4-methyl-5-(*p*-tolylthiocarbonyl)oxazolidin-2-one *cis*-5

^{n}BuLi (2.5 M in hexanes, 145 µl, 0.363 mmol, 1.2 eq.) was added dropwise to a stirred solution of *tert*-butyl hydroperoxide (3.8 M in toluene, 118 µl, 0.454 mmol, 1.5 eq.) in THF (6 cm^3) at −78 °C under a nitrogen atmosphere. A solution of the Boc-protected allylic amine **3a** (prepared according to the procedure previously reported,[20] 102.2 mg, 0.302 mmol) in THF (3 cm^3) was added dropwise to the stirred solution at −78 °C. After 10 min solid magnesium bromide ethyl etherate (780 mg, 3.0 mmol, 10 eq.) was added and the reaction was allowed to warm to room temperature and stirred overnight. EtOAc (6 cm^3) was added and the organic fraction was separated, washed with water (3 × 15 cm^3), brine (15 cm^3), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (10% EtOAc–petroleum ether) gave the *anti*-α-bromo thioester **15a** (17.4 mg, 15%) as a white solid. Crystallisation by vapour diffusion techniques using petroleum ether–Et_2O gave colourless plates which were analysed by X-ray crystallography. Mp 93–94 °C; $[\alpha]_D^{22}$ −65 (*c* 1.0 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3310 (br), 2977, 2926, 1768, 1702, 1163 and 809; δ_H (500 MHz; $CDCl_3$) 1.27 (3H, d, *J* 7.0 Hz, C*H*$_3$CH), 1.45 (9H, s, ^{t}Bu), 2.38 (3H, s, ArC*H*$_3$), 4.20–4.29 (1H, br m, C*H*NH), 4.90 (1H, d, *J* 3.0 Hz, CHBr), 4.93 (1H, d, *J* 7.0 Hz, CHN*H*) and 7.21–7.33 (4H, m, Ar); δ_C (125 MHz; $CDCl_3$) 17.3, 21.4, 28.4, 48.8, 58.8, 80.1, 123.3, 130.3, 134.5, 140.4, 154.8 and 193.8; *m*/*z* (ES) 412 and 410 (MNa^+, 35%) and 274 ($M^+ - {}^t$Bu − Br, 100); found (MNa^+) 410.0417, $C_{16}H_{22}NO_3NaSBr$ requires 410.0401. The oxazolidinone *trans*-**5** (27 mg, 36%) was isolated as a white solid. Crystallisation by vapour diffusion techniques from petroleum ether–Et_2O gave

colourless plates which were analysed by X-ray crystallography. Mp 108–109 °C; found: C 57.1%, H 4.9%, N 5.8%, $C_{12}H_{13}NO_3S$ requires C 57.35%, H 5.2%, N 5.6%); $[\alpha]_D^{22}$ −45 (*c* 0.23 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3290 (br), 2916, 1767 and 1698; δ_H (500 MHz; $CDCl_3$) 1.43 (3H, d, *J* 6.0 Hz, C*H*$_3$CH), 2.38 (3H, s, ArC*H*$_3$), 4.02 (1H, qd, *J* 6.0 and 4.5 Hz, CH$_3$C*H*), 4.63 (1H, d, *J* 4.5 Hz, CHO), 5.32 (1H, br s, NH) and 7.22–7.30 (4H, m, Ar); δ_C (125 MHz; $CDCl_3$) 21.4, 21.7, 52.3, 85.0, 121.8, 130.3, 134.5, 140.4, 156.7 and 197.9. *m*/*z* (ES) 274 (MNa^+, 60%) and 252 (MH^+, 100); found (MNa^+) 274.0522, $C_{12}H_{13}NO_3NaS$ requires 274.0514.

Oxazolidinone *cis*-**5** was also isolated (11 mg, 14%) as a white solid, mp 100–102 °C (lit. mp 102–103 °C[20]). The Boc-protected allylic amine **3a** starting material was also recovered (9.1 mg, 9%).

S-(*p*-Tolyl) (2*S*,3*S*)-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2-bromobutanethioate 15b

^{n}BuLi (2.5 M in hexanes, 70 μl, 0.175 mmol, 1.2 eq.) was added dropwise to a stirred solution of *tert*-butyl hydroperoxide (3.8 M in toluene, 57 μl, 0.218 mmol, 1.5 eq.) in THF (4 cm^3) at −78 °C under a nitrogen atmosphere. A solution of the Fmoc-protected allylic amine **3b** (prepared according to the procedure previously reported,[20] 67 mg, 0.145 mmol) in THF (2 cm^3) was added dropwise to the stirred solution at −78 °C. After 10 min solid magnesium bromide ethyl etherate (380 mg, 1.45 mmol, 10 eq.) was added and the reaction was allowed to warm to room temperature and stirred overnight. EtOAc (5 cm^3) was added and the organic fraction was separated, washed with water (3 × 10 cm^3), brine (15 cm^3), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (20% Et_2O–petroleum ether) gave the *anti*-α-bromo thioester **15b** (26.1 mg, 35%) as a yellow oil. $[\alpha]_D^{22}$ −36.7 (*c* 0.3 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3328, 2947, 1702, 1509, 1244 and 741; δ_H (250 MHz; $CDCl_3$) 1.25 (3H, d, *J* 7.0 Hz, C*H*$_3$CH), 2.31 (3H, s, ArC*H*$_3$), 4.10–4.45 (4H, m, CHC*H*$_2$O and CH$_3$C*H*), 4.77 (1H, d, *J* 3.0 Hz, CHBr), 5.21 (1H, br d, *J* 8.5 Hz, NH), 7.14–7.38 (8H, m, Ar), 7.51 (2H, d, *J* 8.5 Hz, Ar) and 7.69 (2H, d, *J* 8.5 Hz, Ar); δ_C (125 MHz; $CDCl_3$) 17.5, 21.4, 47.2, 49.4, 57.6, 66.9, 120.0, 123.1, 125.0, 127.1, 127.8, 130.3, 134.4, 140.5, 141.3, 143.8, 155.4 and 193.9; *m*/*z* (ES) 534 and 532 (MNa^+, 100%); found (MNa^+) 532.0554, $C_{26}H_{24}NO_3NaSBr$ requires 532.0558.

X-Ray crystallography

Crystallographic data were collected and measured on a Bruker Smart CCD area detector with an Oxford Cryosystems low temperature system at $T = 150(2)$ K.

Crystal data for **7**: $C_{12}H_{13}NO_3S$, $M = 251.29$, monoclinic, $a = 9.243(5)$, $b = 5.497(3)$, $c = 12.258(7)$ Å, $U = 620.4(6)$ Å^3, space group $P2_1$ (C^2_2, no. 4), $Z = 2$, μ (Mo-Kα) = 0.256 mm^{-1}, 5727 reflections collected, 2147 independent ($R_{int} = 0.0954$). Final *R* indices [$I > 2\sigma(I)$] $R_1 = 0.0664$, w$R_2 = 0.1539$. *R* indices (all data) $R_1 = 0.1055$, w$R_2 = 0.1731$. Absolute structure parameter 0.14(19).

Crystal data for **11**: $C_{12}H_{12}O_4S$, $M = 252.28$, orthorhombic, $a = 7.5636(11)$, $b = 10.4554(16)$, $c = 15.375(2)$ Å, $U = 1215.9(3)$ Å^3, space group $P2_12_12_1$ (D^4_2, no. 19), $Z = 4$, μ (Mo-Kα) = 0.266 mm^{-1}, 13372 reflections collected, 2758 independent ($R_{int} = 0.0424$). Final *R* indices [$I > 2\sigma(I)$] $R_1 = 0.0315$, w$R_2 = 0.0770$. *R* indices (all data) $R_1 = 0.0398$, w$R_2 = 0.0803$. Absolute structure parameter 0.01(7).

Crystal data for **15a**: $C_{16}H_{22}BrNO_3S$, $M = 388.32$, monoclinic, $a = 8.587(3)$, $b = 5.2659(18)$, $c = 19.647(7)$ Å, $U = 884.2(5)$ Å^3, space group $P2_1$ (C^2_2, no. 4), $Z = 2$, μ (Mo-Kα) = 2.454 mm^{-1}, 6409 reflections collected, 3063 independent ($R_{int} = 0.0504$). Final *R* indices [$I > 2\sigma(I)$] $R_1 = 0.0433$, w$R_2 = 0.0914$. *R* indices (all data) $R_1 = 0.0577$, w$R_2 = 0.0971$. Absolute structure parameter 0.037(12).

Crystal data for *trans*-**5**: $C_{12}H_{13}NO_3S$, $M = 251.29$, monoclinic, $a = 5.249(3)$, $b = 5.794(3)$, $c = 20.357(12)$ Å, $U = 617.4(6)$ Å^3, space group $P2_1$ (C^2_2, no. 4), $Z = 2$, μ (Mo-Kα) = 0.258 mm^{-1}, 6821 reflections collected, 2777 independent ($R_{int} = 0.0599$). Final *R* indices [$I > 2\sigma(I)$] $R_1 = 0.0568$, w$R_2 = 0.1300$. *R* indices (all data) $R_1 = 0.0750$, w$R_2 = 0.1356$. Absolute structure parameter 0.05(13).

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