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The synthesis of water soluble decalin-based thiols and *S*-nitrosothiols—model systems for studying the reactions of nitric oxide with protein thiols

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The syntheses of three decalin-based *tert*-thiols displaying varying degrees of solubility in aqueous milieu are described. The *S*-nitroso derivatives of these compounds have also been prepared and the structures of two of these determined by single crystal X-ray diffraction. These compounds have been designed for studying the interaction of nitric oxide (NO) with thiols under physiological conditions.

Introduction

Nitric oxide (NO) is an important redox messenger in many cellular signal transduction pathways and has been shown to be intimately involved in a host of regulatory roles including control of vasodilation, platelet aggregation, neurotransmission and in the immune system.[1,2] Signalling is achieved primarily by three types of post-translational protein modifications: nitrosylation of metal centres (*e.g.* Fe in the heam unit of guanylate cyclase),[3] nitrosation/nitration of aromatic rings of aromatic amino acids (*e.g.* Tyr-385 in prostaglandin-H_2 (PGH_2) synthase)[4] and nitrosation/oxidation of the sulfur atom of cysteine residues (*e.g.* Cys-34 in human serum albumin (HSA)).[5] Interactions with cysteine residues are particularly interesting because a wide range of oxidised products, including *S*-nitrosothiol (RSNO), disulfide (RSSR'), sulfenic acid (RSOH), sulfinic acid (RSO_2H) and sulfonic acid (RSO_3H) derivatives, are formed following nitrosative stress.[6] These modifications can dynamically mediate a diverse array of perturbations of protein structure and function.[7] However, despite intensive research efforts, the molecular mechanisms by which these modifications are effected remain contentious[8] and a concensus has yet to emerge as to the relative importance of various putative NO-derived oxidising/nitrosating species *in vivo* (and their mode of formation and transport).[9–11] A significant factor confounding progress in this area is that the primary derivatives, RSNOs[12] and RSOHs,[13] are both highly susceptible towards further transformations (*e.g.* to give disulfides) and do not have strong spectroscopic fingerprints, making them difficult to identify and monitor in proteins.[14–16] We have initiated a program to develop small molecule model systems on which to study the formation and reactivity of these important derivatives under physiologically compatible conditions in order to gain insight into the factors that control specificity and reactivity in particular cellular microenvironments. Here we describe the synthesis of a class of aqueous soluble *tert*-decalin thiols for which the *S*-NO derivatives display sufficient kinetic stability to allow isolation and full characterisation and for which the scaffold offers opportunities for introducing proximal functionality (*e.g.* pendent peptides) to study further transformations.

Results and discussion

Although *S*-nitrosothiols and sulfenic acids are generally very labile, kinetic stability can be imparted to both species by steric shielding of the sulfur centre. This is apparent from the few examples of *S*-nitrosothiols (**1–7**)[17–24] and sulfenic acids (**8–11**)[25–29] in the Cambridge crystallographic database (CCDC), most of which contain these functional groups in highly hindered environments (Fig. 1).

We therefore sought to design a thiol located within a molecular scaffold that would provide an appropriately hindered environment to allow formation of stable *S*-nitrosothiol and sulfenic acid derivatives that would be soluble in physiologically compatible aqueous milieu and that would also be amenable to the introduction of pendent peptidic chains, to allow study of the reactions of the derivatives with side chain functional groups. To this end we were particularly interested in the synthesis by Yoshimura *et al.* of *trans*-decalin sulfenic acid **12**, which was reported to be a stable crystalline solid (although no X-ray crystal structure was obtained).[30,31] We envisaged that the rigid *trans*-decalin ring system could provide a useful framework for incorporation of both water solubilising substituents and peptide chains in a spatially well-defined manner relative to the hindered thiol group. Consequently, we identified molecules based on functionalised decalin **I** as our target model thiol. Based on the work of Kelly *et al.*[32] we envisaged employing oxyacetate groups to impart aqueous solubility, although it was unclear at the outset how many of these groups would need to be incorporated (Fig. 2).

Our initial approach to the synthesis of this type of molecule is shown in Scheme 1. Epoxy *bis*-alkene **13** was prepared from naphthalene by Birch reduction ($Na–NH_3$; 74%) then epoxidation (CH_3CO_3H; 87%).[33,34] Ring-opening of this epoxide with benzylthiol in ethylene glycol[35] afforded thioether *bis*-alkene **14a** (78%). The plan was to chemo- and stereoselectively oxidise this thioether *bis*-alkene to the corresponding *bis*-epoxide using the axial *tert*-alcohol at C10 to direct epoxidation onto the α-face.[36] However, in the event we were unable to delineate conditions to achieve this *bis*-epoxidation without prior/concomitant oxidation of the benzyl thioether group. Oxidation of the thioether *bis*-alkene **14a** with $VO(acac)_2$-*tert*-butyl hydroperoxide (TBHP, 2 eq.)[37] in CH_2Cl_2 at various temperatures resulted in complex reaction mixtures that by ^1H NMR did not look promising for further investigation. The use of $Mo(CO)_6$–TBHP (2 eq.)[38] in CH_2Cl_2 at 0 °C, or excess DMD[39] in acetone–benzene at 0 °C, or *m*-CPBA (1.5 eq.)[40] in CH_2Cl_2 at rt gave mixtures of sulfoxide *bis*-alkene **15a** and sulfone *bis*-alkene **15b**. Reaction with *m*-CPBA (3 eq.) in CH_2Cl_2 at rt gave the sulfone mono-epoxide **16** as the major product (89%) and

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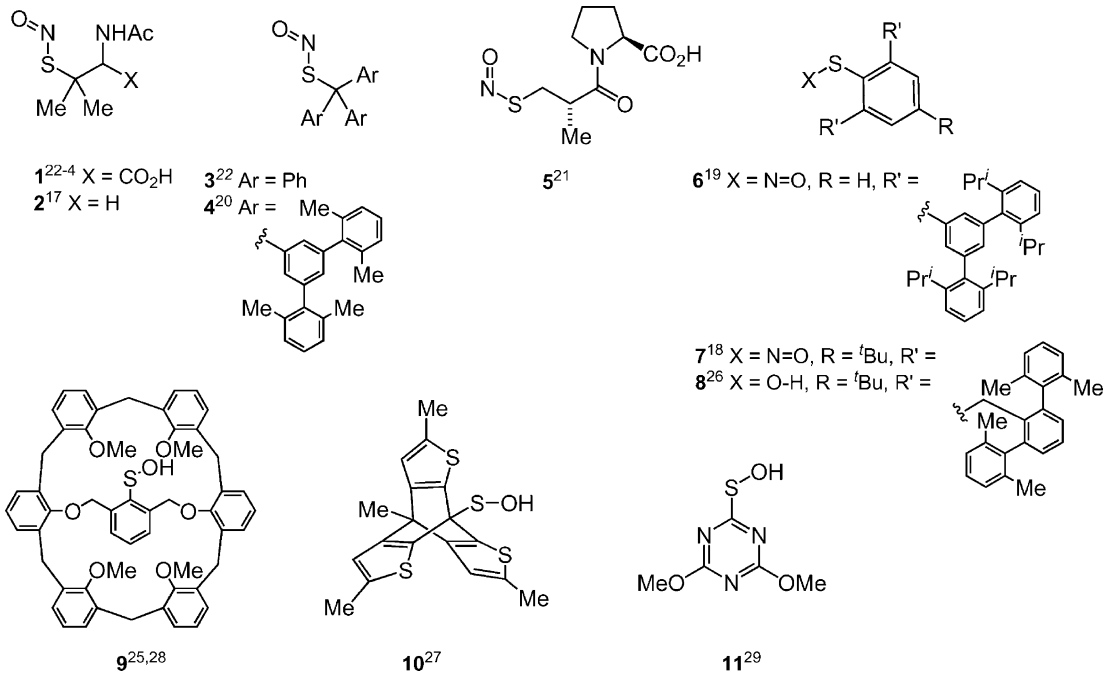


Fig. 1 Structures of all reported *S*-nitrosothiol and sulfenic acid containing compounds characterised by single crystal X-ray diffraction.

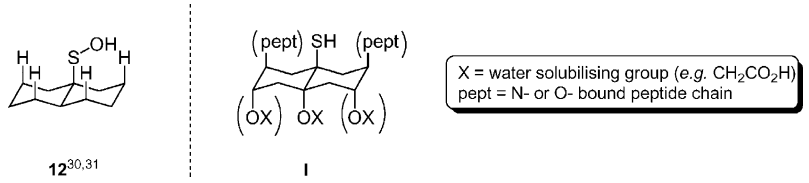
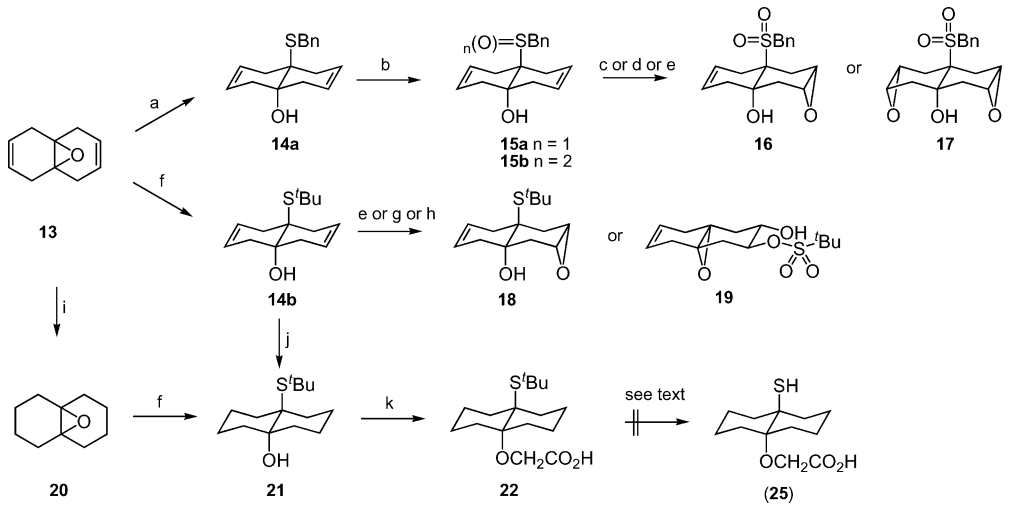


Fig. 2 Yoshimura's *trans*-decalin-9-sulfenic acid **12** and proposed target thiol **I**.

use of excess *m*-CPBA in CH_2Cl_2 at rt gave sulfone *bis*-epoxide **17** as the major product (56%). The sulfone *bis*-epoxide **17** could also be obtained by oxidation of sulfone *bis*-alkene **15b** with $VO(acac)_2$–TBHP (2 eq.) in CH_2Cl_2 at rt (79%, Scheme 1).

The sulfone *bis*-epoxide **17** did not prove to be a productive intermediate for preparation of the target structures as we were unable to convert it into the corresponding sulfone triol using hydride reducing agents (*e.g.* $LiAlH_4$ or DIBAL-H) or the corresponding thiol triol using Birch reduction (Li/NH_3–THF). Reasoning that if we employed a more bulky thiol in place of benzyl thiol in the original ring-opening reaction the resulting thioether would be less susceptible to oxidation at sulfur, we prepared *bis*-alkenyl thioether **14b** by ring-opening of epoxide **13** with *tert*-butylthiol in ethylene glycol (85%). Although treatment of *bis*-alkenyl thioether **14b** with *m*-CPBA (2 eq.) or MMPP (2 eq.)[41] in CH_2Cl_2 at rt again resulted in preferential oxidation at sulfur, oxidation with $VO(acac)_2$–trityl hydroperoxide (THP, 4 eq.) in CH_2Cl_2 at rt gave thioether mono-epoxide **18** cleanly (80%). However, if the temperature was raised to 80 °C (in benzene) to try to induce *bis*-epoxide formation the only isolated



Scheme 1 *Reagents and conditions:* a) BnSH, NaOH, $HOCH_2CH_2OH$, 100 °C [78%]; b) DMD, acetone–benzene [**15a** 67% + **15b** 33%]; c) *m*-CPBA (3 eq.), CH_2Cl_2 [**16** 89% from **15a**]; d) *m*-CPBA (5 eq.), CH_2Cl_2 [**17** 56% from **15a**]; e) $VO(acac)_2$, TBHP, CH_2Cl_2 [**17** 79% from **15b**; **19** 77%]; f) ^{t}BuSH, NaOH, $HOCH_2CH_2OH$, 100 °C [**14b** 85%; **21** 80%]; g) $VO(acac)_2$, THP, CH_2Cl_2 [**18** 80%]; h) $VO(acac)_2$, THP, benzene [**19** 69%]; i) PtO_2, H_2, Et_2O [90%]; j) PtO_2, H_2, EtOAc [83%]; k) NaH, $ClCH_2CO_2H$, THF, 70 °C [65%].

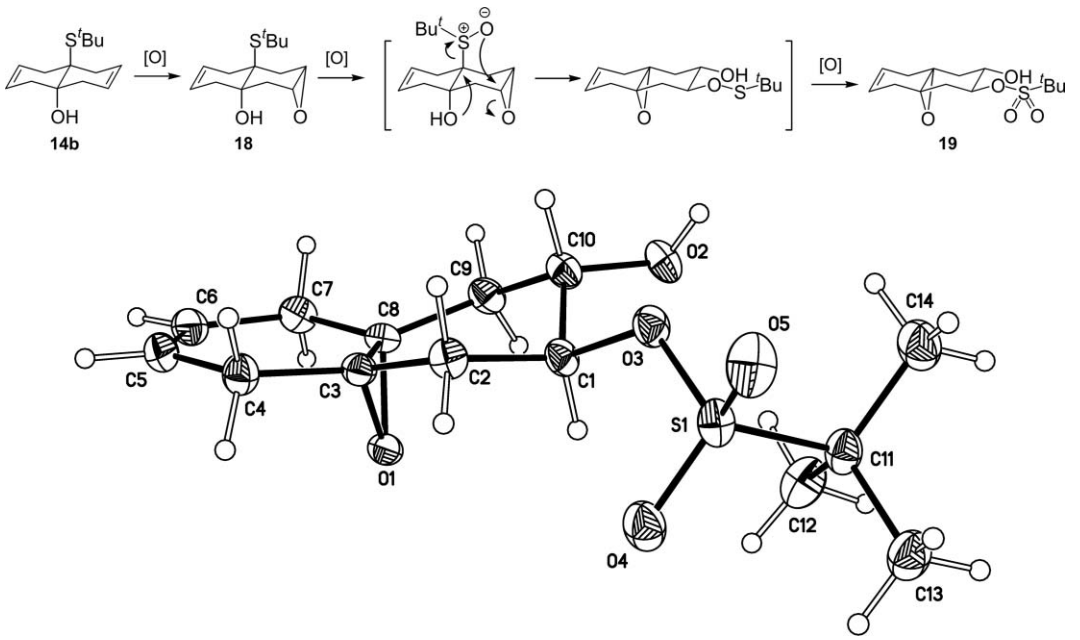


Fig. 3 ORTEP diagram of sulfate ester **19** and a proposed pathway for its formation.

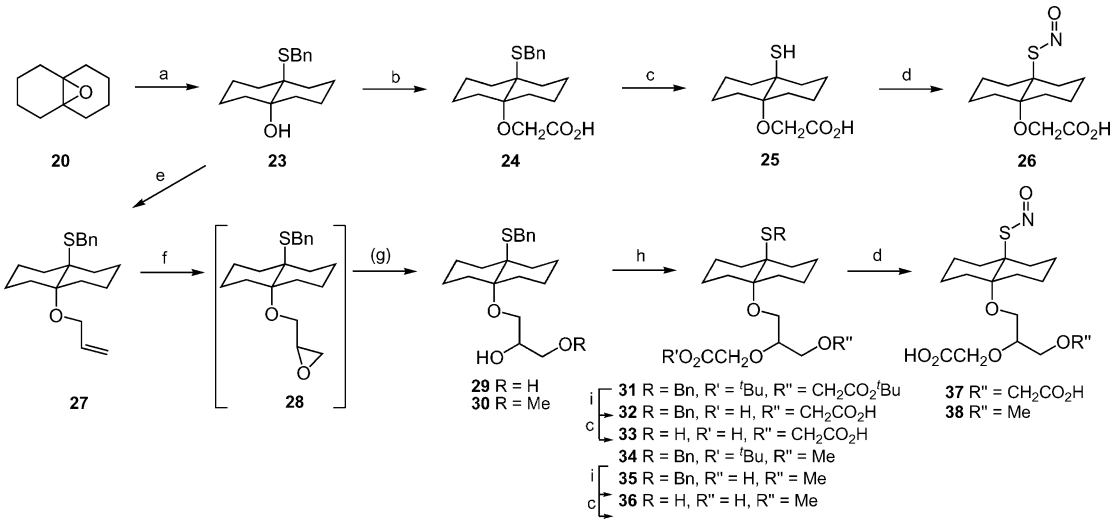
product was sulfate ester **19** (69%). This compound was also the exclusive product (77%) when employing $VO(acac)_2$–TBHP (4 eq.) in CH_2Cl_2 at rt. The identity of the unexpected sulfate ester **19** was secured by single crystal X-ray diffraction; its structure and a possible pathway for the formation of this product are shown in Fig. 3.

It appears that following initial α-face alkene epoxidation to give thioether mono-epoxide **18** further oxidation occurs at sulfur rather that at the other alkene. The resulting sulfoxide (or sulfone) then undergoes a rearrangement in which the C10 *tert*-alcohol displaces the sulfoxide (or sulfone) to form a C9–C10 tetrasubstituted α-epoxide and the sulfoxide (sulfone) oxygen ring-opens the C2–C3 disubstituted α-epoxide at C3 to give a sulfenate (or sulfinate) intermediate, which is then further oxidised to the sulfate ester **20**. That ring-opening of the epoxide occurs to give the di-equatorial product suggests that the intermeduate epoxy sulfoxide (sulfone) occupies a non-chair conformation.

Several attempts were made to effect conversion of the isolated thioether *mono*-epoxide **18** to the desired diepoxide using *m*-CPBA, MMPP and oxone® but to no avail; complex mixtures of uncharacterised products were formed. Consequently, we decided to direct our effort towards the preparation of a less highly functionalised target structure lacking functionality on the decalin rings. To access this framework, the two alkenes in thioether *bis*-alkene **14b** were hydrogenated (PtO_2–H_2) to give decalin thioether **21** (83%). This compound could also be obtained by hydrogenation of epoxy *bis*-alkene **13** (PtO_2–H_2), to give volatile epoxide **20** (90%), then ring opening with *tert*-butyl thiol (80%). The *tert*-alcohol function in thioether **21** was smoothly converted to the oxyacetate function (→ **22**) by treatment with chloroacetic acid and excess sodium hydride (65%) but, unfortunately, deprotection of the *tert*-butyl group to give the free thiol proved problematic. The use of mercuric acetate–TFA–anisole according to the method of Nishimura and coworkers[42] appeared to be successful as the crude ^1H NMR showed complete disappearance of the *tert*-butyl signal at δ 1.40 and no signals in the alkene region, but we were unable to isolate any of the desired thiol following work-up. Notwithstanding the possibility to access the sulfenic acid by a thermolysis reaction on the sulfoxide derivative[43] of thioether **22**, we decided to revert to the use of a benzyl protected thiol so as to allow final deprotection to give the free thiol by hydrogenolysis. This chemistry proved very efficient: thus, ring-opening of epoxide **20** with benzylthiol in ethylene glycol gave decalin benzyl thioether **23** (72%), which was converted to oxyacetate **24** using chloroacetic acid–sodium hydride (52%) and the benzyl group removed under Birch reductive conditions to give the desired thiol **25** (95%, Scheme 2).

Pleasingly, treatment of thiol **25** with a slight excess of *tert*-butyl nitrite in CH_2Cl_2 at rt resulted in a clean and rapid conversion into the *S*-nitroso derivative **26**, which crystallised as small pale green plates and proved suitable for a single crystal X-ray structure determination (see later, Fig. 4). Although this compound exhibited good stability both in solution and in the solid-state, as expected from the work of Yoshimura *et al.*,[30,31] the aqueous solubility of parent thiol **25** was not as high as we had hoped (see Table 1). Consequently, we decided to prepare a closely related analogue containing two oxyacetate solubilising groups; compound **33**. The synthesis of this derivative was achieved by allylation of alcohol **23** using ^{n}BuLi–allyl bromide in THF at 50 °C to give thioether allyl ether **27** (75%). Selective oxidation of the terminal double bond in the presence of the benzyl ether was achieved using an epoxidation protocol employed by Anderson *et al.*[44] for a similar purpose, involving conversion to the bromohydrin using NBS and ring-closure to the thioether terminal epoxide **28** with K_2CO_3 in MeOH (55% overall). Subsequent $BF_3{\cdot}Et_2O$ promoted ring-opening with water gave the thioether diol **29**. Conversion of this diol directly to the corresponding thioether *bis*-oxyacetate **32** was achieved on one occasion using chloroacetic acid–sodium hydride (79%); however, this method proved capricious on a larger scale and so a two step method was developed involving reaction with *tert*-butyl bromoacetate under phase transfer conditions (50% aqueous NaOH, CH_2Cl_2, $^n Bu_4NBr$, 29%),[45] then saponification of the resulting *bis*-*tert*-butyloxyacetate **31** (LiOH, THF–MeOH)[46] to give thioether *bis*-oxyacetate **32** (100%). As before, the benzyl group was cleanly removed under Birch reductive conditions to give the desired thiol **33** (100%). A related thiol, compound **36**, having a methyl ether in place of the primary oxyacetate group (*cf.* thiol **33**) was also prepared using an analogous sequence following ring-opening of (unisolated) epoxide **28** by methanol (**27** → **30** → **34** → **35** → **36**, Scheme 2).

As with thiol **25**, treatment of thiols **33** and **36** with an excess of *tert*-butyl nitrite in CH_2Cl_2 at rt resulted in a rapid conversion to the corresponding *S*-nitroso derivatives **37**



Scheme 2 *Reagents and conditions:* a) BnSH, NaOH, $HOCH_2CH_2OH$, 100 °C [72%]; b) NaH, $ClCH_2CO_2H$, THF, 70 °C [52%]; c) Na, NH_3–THF, −33 °C [**25** 95%; **33** 100%; **36** 50%]; d) ^{t}BuONO, CH_2Cl_2 [**26** 57%; **37** 56% from **33**; **38** 69% from **36**]; e) ^{n}BuLi, $^n Bu_4NI$, $CH_2{=}CHCH_2Br$, THF [75%]; f) (i) NBS, THF–H_2O, (ii) K_2CO_3, MeOH [**28** 55%; **30** 83%]; g) $BF_3{\cdot}Et_2O$, THF–H_2O [**29** 92%]; h) NaOH, $^n Bu_4NBr$, $BrCH_2CO_2{}^t Bu$, CH_2Cl_2–H_2O [**31** 29% from **29**; **34** 64% from **30**]; i) LiOH, MeOH–THF [**32** 100%; **35** 100%].

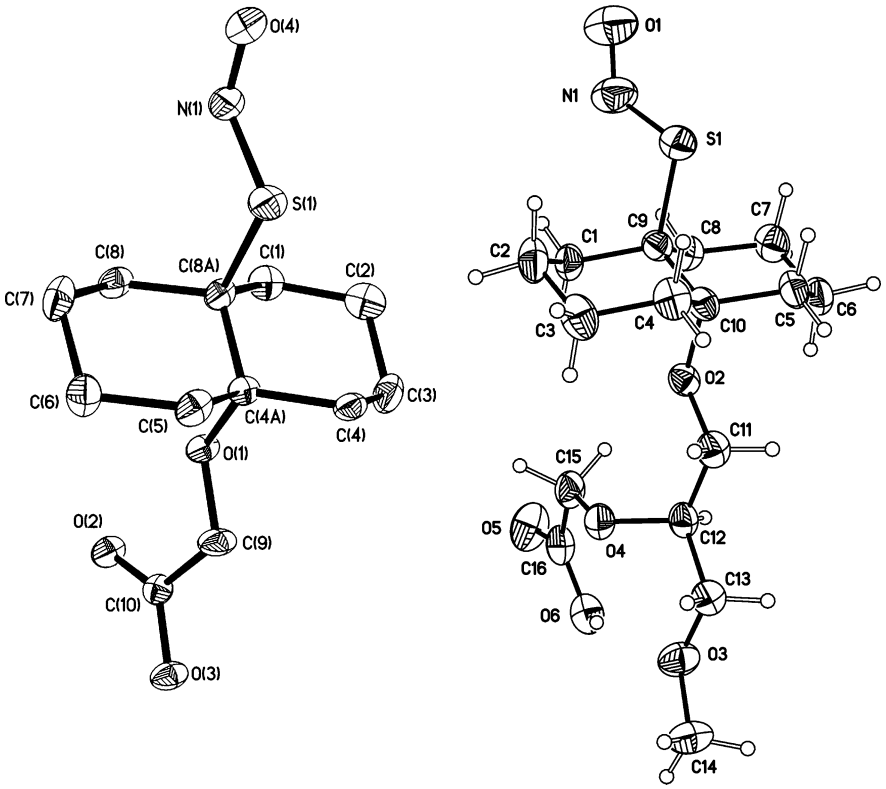


Fig. 4 ORTEP diagrams of *S*-nitrosothiols **26** and **38**.

and **38**, respectively, both of which were crystalline. Crystals suitable for single crystal X-ray structure determination could be obtained for *S*-nitrosothiol **38** but not *S*-nitrosothiol **37** (Fig. 4).

The structures of the *S*-nitrosothiol groups in compounds **26** and **38** are closely similar: both occupy an s-*trans* conformation about the S–N bond, which is aligned parallel to the C8-C9 bond (the decalin ring fusion). Comparison of these structures with those of the five previous aliphatic *S*-nitrosothiols in the CCDC (structures **1–5**, Fig. 1) reveals that this *anti*-conformation is also found in all four previously reported *tert*-thiol derived *S*-nitrosothiols (structures **1–4**), whereas an s-*cis*-conformation is adopted by the primary thiol derived *S*-nitrosocaptopril **5** (Table 2).

These conformational preferences are in accord with hybrid DFT calculations by Houk *et al.*[21] who showed that for primary and secondary *S*-nitrosothiols the s-*cis* conformation is electronically preferred due to an $n_S \rightarrow \sigma^*_{NO}$ anomeric interaction (*cf.* in alkyl esters)[47], whereas competing steric effects cause tertiary *S*-nitrosothiols to prefer an s-*trans* conformation. *S*-Nitrosothiols display significant barriers to rotation about the S–N bond (46–50 kJ mol^{-1})[21] as the result of strong $n_S \rightarrow \pi^*_{NO}$ delocalisation, which imparts π-bond character to the S–N bond. The overall weakness of the S–N bond is believed to result from a strong $n_O \rightarrow \sigma^*_{SN}$ anomeric effect.[48]

As expected,[49] the solubility of thiol *bis*-oxyacetate **33** in aqueous solution was significantly higher than either of the thiol *mono*-oxyacetates **25** or **36**, being soluble in phosphate buffered

Table 1 Measured solubility of thiols **25**, **33** and **36**

Buffer	Concentration/mM	Soluble?		
		25	**33**	**36**
PBS[a]	4	yes	yes	yes
	20	no	yes	no
KRB[b]	4	partially	yes	yes
	20	no	yes[c]	no
H_2O	4	yes	yes	yes
	20	no	yes	no

[a] Buffer was made up using ($\times 10^{-2}$ mol dm^{-3}): phosphate buffer 1.0, NaCl 1.37 and KCl 0.27 in water. [b] Buffer was made up using ($\times 10^{-3}$ mol dm^{-3}): NaCl 118.9, $CaCl_2$ 1.2, $NaHCO_3$ 20.4, K_2HPO_4 2.4, KH_2PO_4 0.6, $MgCl_2$ 1.2 and glucose 10 in water adjusted to pH 7.4 by bubbling a gaseous mixture of 95% O_2 and 5% CO_2 through the solution for 5 min. [c] Brief sonication required to achieve complete dissolution.

saline (PBS), Krebs–Ringer bicarbonate buffer (KBS) and water in concentrations up to 20 mM (Table 1).

Conclusions

The preparation of *tert*-thiol **33** has been achieved in nine steps and ~5% overall yield from naphthalene. This compound has been shown to have significant solubility in water and buffered aqueous solutions at pH 7.4 and to form a relatively stable *S*-nitroso derivative **37**, analogues of which (*i.e.* *S*-nitrosothiols **26** and **38**) have been characterised by X-ray crystallography. It is anticipated that these features will make this compound a useful model for studying the *S*-nitrosation and related oxidation processes under aqueous conditions. Experiments to prepare and characterise the sulfenic acid derivative of this thiol and to probe the reactivity of this thiol towards NO and putative NO-donors under physiologically compatible conditions are currently underway and will be reported in due course.

Experimental

General directions

All reactions were performed under anhydrous conditions and an inert atmosphere of nitrogen in the oven-dried glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials, unless otherwise indicated. Reagents were used as obtained from commercial sources or purified according to known procedures.[50] Flash chromatography was carried out using Merck Kiesegel 60 F_{254} (230–400 mesh) silica gel. Only distilled solvents were used as eluents. Thin layer chromatography (TLC) was performed on Merck DC-Alufolien or glass plates precoated with silica gel 60 F_{254} which were visualised either by quenching of ultraviolet fluorescence (λ_{max} = 254 nm) or by charring with 5% w/v phosphomolybdic acid in 95% EtOH, 10% w/v ammonium molybdate in 1M H_2SO_4, or 10% $KMnO_4$ in 1M H_2SO_4. Observed retention factors (R_f) are quoted to the nearest 0.05. All reaction solvents were distilled before use and stored over activated 4 Å molecular sieves, unless otherwise indicated. Anhydrous CH_2Cl_2 was obtained by refluxing over CaH_2. Anhydrous THF and Et_2O were obtained by distillation, immediately before use, from sodium–benzophenone ketyl under an inert atmosphere of nitrogen. Anhydrous DMF was obtained by distillation from CaH_2 under a reduced pressure. Ethylene glycol was distilled immediately prior to use. Petrol refers to the fraction of light petroleum boiling between 40–60 °C. NMR *J* values are given in Hz. High Resolution Mass Spectrometry (HRMS) measurements are valid to ±5 ppm.

9β-Benzylthio-10α-hydroxy-1,4,5,8,9,10-hexahydronaphthalene 14a. To a suspension of epoxy *bis*-alkene **13** (100 mg, 0.676 mmol) and powdered NaOH (270 mg, 6.76 mmol) in ethylene glycol (10 cm^3) was added benzyl thiol (790 cm^3, 6.76 mmol, **CAUTION** stench) and the resulting mixture heated at 100 °C for 2 h. An aqueous solution of saturated Na_2SO_4 (5 cm^3) was then added dropwise and the phases separated. The aqueous phase was extracted further with EtOAc (2 × 15 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give a cloudy oil. Purification by flash chromatography (petrol–EtOAc, 9 : 1) gave thioether **14a** as a clear oil (143 mg, 78%). R_f (petrol–EtOAc, 4 : 1) 0.40; ν_{max}/cm^{-1} ($CHCl_3$) 3483 (OH), 3026, 2897, 1653, 1494, 1241, 869; δ_H (250 MHz, $CDCl_3$) 2.08–2.20 (2H, CH_2′s), 2.10 (1H, bs, OH), 2.38–2.42 (4H, 2 × CH_2), 2.47–2.61 (2H, CH_2), 3.75 (2H, s, CH_2Ph), 5.67 (4H, m, 2 × CH_2), 7.18–7.35 (5H, Ph); δ_C (63 MHz, $CDCl_3$) 33.5 (2 × t), 34.8 (2 × t), 36.9 (t), 49.7 (s), 71.0 (s), 124.4 (2 × d), 124.6 (2 × d), 126.9 (s), 128.4 (2 × d), 129.1 (2 × d), 137.9 (s); *m*/*z* (EI$^+$) 272 (M$^+$, 19%), 181 (100), 148 (27), 94 (80); found: *m*/*z* (EI$^+$) M$^+$ 272.1227, $C_{17}H_{20}OS$ requires 272.1235 (Δ = −2.9 ppm).

9β-Benzylsulfinyl-10α-hydroxy-1,4,5,8,9,10-hexahydronaphthalene 15a and 9β-benzylsulfonyl-10α-hydroxy-1,4,5,8,9,10-hexahydronaphthalene 15b. To a solution of thioether *bis*-alkene **14a** (100 mg, 0.37 mmol) in benzene (5 cm^3) at 0 °C was added a solution of dimethyldioxirane[51] in acetone (~0.1 M, 7.4 cm^3, ~0.74 mmol) dropwise. After 30 min the volatiles were removed *in vacuo* and the residue purified by flash chromatography (EtOAc–petrol, 2 : 3 → 4 : 1) to give:

Sulfoxide **15a** as a white crystalline solid (71 mg, 67%). Mp 45–51 °C (EtOAc); R_f (EtOAc–petrol, 2 : 1) 0.15; ν_{max}/cm^{-1} ($CHCl_3$) 3014, 1496, 1454; δ_H (250 MHz, $CDCl_3$) 2.20–2.35 (2H, CH_2), 2.40–2.45 (2H, CH_2), 2.50–2.65 (5H, 2 × CH_2 + OH), 2.77–2.9 (2H, CH_2), 3.94 and 3.77 (2H, AB_q J_{AB} 11.9, CH_2Ph), 5.60–5.75 (4H, 4 × =CH), 7.27–7.40 (5H, Ph); δ_c (63 MHz, $CDCl_3$) 29.4 (t), 30.0 (t), 37.2 (t), 37.3 (t), 54.8 (s), 63.0 (s), 69.0 (s), 124.2 (d), 125.2 (d), 125.6 (d), 125.7 (d), 128.2 (s), 128.8 (2 × s), 130.5 (2 × s), 131.7 (s); *m*/*z* (CI$^+$) 289 (MH$^+$, 34%), 263 (9), 231 (13), 158 (27); found: *m*/*z* (CI$^+$) MH$^+$ 289.1268, $C_{17}H_{21}O_2S$ requires 289.1262 (Δ = +2.1 ppm).

Sulfone **15b** as a white solid (36 mg, 33%). Mp 176–178 °C (EtOAc); R_f (EtOAc–petrol, 2 : 1) 0.60; ν_{max}/cm^{-1} ($CHCl_3$) 3019, 1494, 1434; δ_H (250 MHz, $CDCl_3$) 2.20–2.55 (5H, CH_2′s + OH), 2.72–2.81 (2H, CH_2), 2.84–2.87 (2H, CH_2), 4.22 (2H, s, CH_2Ph),

Table 2 Comparison of X-ray crystal data of *S*-nitrosothiols **26** and **38** and previously reported *S*-nitrosothiols

Structure	Conformation C–S–N=O	Torsion Angle C–S–N=O/°	Bond Lengths		
			C–S/Å	S–N/Å	N=O/Å
26 (tertiary)	s-*trans*	179.3	1.875	1.744	1.307
38 (tertiary)	s-*trans*	175.0	1.815	1.703	1.231
1[22–24] (tertiary)	s-*trans*	176.3	1.841	1.771	1.214
2[17] (tertiary)	s-*trans*	178.6	1.828	1.755	1.207
3[22] (tertiary)	s-*trans*	175.7	1.867	1.792	1.177
4[20] (tertiary)	s-*trans* : s-*cis* (7 : 3)	179.6[a]	1.841[a]	1.781[a]	1.205[a]
5[21] (primary)	s-*cis*	0.68	1.800	1.766	1.206

[a] Data for the s-*trans* isomer.

5.65–5.78 (4H, 4 × =CH), 7.25–7.35 (5H, Ph); δ_c (63 MHz, $CDCl_3$) 32.1 (2 × t), 36.9 (2 × t), 57.3 (t), 67.5 (s), 68.8 (s), 124.0 (2 × d), 125.3 (2 × d), 126.7 (s), 128.4 (2 × s), 128.7 (s), 131.5 (2 × s); *m/z* (EI^+) 304 (M^+, 7%), 157 (10), 149 (48), 131 (48); found: *m/z* (EI^+) M^+ 304.1134, $C_{17}H_{20}O_3S$ requires 304.1133 ($\Delta = +0.3$ ppm).

9β-Benzylsulfonyl-(2α,3α)-oxido-10α-hydroxy-1,2,3,4,5,8,9,10-octahydronaphthalene 16. To a solution of thioether *bis*-alkene **14a** (100 mg, 0.37 mmol) in CH_2Cl_2 (5 cm^3) was added *m*-CPBA (420 mg, 1.11 mmol) and the resulting mixture stirred for 15 min. The reaction was then quenched by addition of a saturated aqueous solution of $Na_2S_2O_5$ (5 cm^3) and the resulting reaction mixture extracted with CH_2Cl_2 (3 × 10 cm^3). The organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash chromatography (EtOAc–petrol, 3 : 7) to give sulfone mono-epoxide **16** as a white solid (106 mg, 89%). Mp 119–125 °C (EtOAc); R_f (EtOAc–petrol, 1 : 1) 0.30; ν_{max}/cm^{-1} ($CHCl_3$) 3372, 2921, 1439, 1260, 1061, 746; δ_H (250 MHz, $CDCl_3$) 2.17–2.40 (3H, CH_2's), 2.52–2.65 (3H, CH_2's), 2.65–2.87 (2H, CH_2), 3.40–3.52 (2H, 2 × CHO), 4.21 and 4.31 (2H, AB_q J_{AB} 12.5, CH_2Ph), 4.45 (1H, s, OH), 5.65–5.75 (2H, 2 × =CH), 7.36–7.44 (5H, Ar); δ_c (63 MHz, $CDCl_3$) 31.4 (t), 32.2 (t), 33.5 (t), 38.0 (t), 51.9 (d), 55.5 (d), 56.8 (t), 66.6 (s), 70.0 (s), 121.6 (2 × d), 126.3 (2 × d), 128.7 (2 × s), 129.1 (s), 131.6 (2 × s); *m/z* (CI^+) 321 MH^+, 6%), 231 (7), 165 (69), 147 (40); found: *m/z* (CI^+) MH^+ 321.1154, $C_{17}H_{21}O_4S$ requires 321.1161 ($\Delta = -2.2$ ppm).

9β-Benzylsulfonyl-(2α,3α),(6α,7α)-dioxido-10α-hydroxy-1,2,3,4,5,6,7,8,9,10-decahydronaphthalene 17. To a solution of thioether *bis*-alkene **14a** (100 mg, 0.37 mmol) in CH_2Cl_2 was added *m*-CPBA (560 mg, 1.85 mmol) and the resulting mixture stirred stirred for 2 h. The reaction was then quenched by addition of a saturated aqueous solution of $Na_2S_2O_5$ (10 cm^3) and the resulting reaction mixture extracted with CH_2Cl_2 (3 × 10 cm^3). The organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (10 cm^3), dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash chromatography (EtOAc–petrol, 1 : 1 → 2 : 1) to give sulfone bis-epoxide **17** as a white solid (70 mg, 56%). Mp 184–186 °C (EtOAc); R_f (EtOAc–petrol, 1 : 1) 0.10; ν_{max}/cm^{-1} (nujol) 3398, 1459, 1376, 1120; δ_H (250 MHz, $CDCl_3$) 2.23–2.34 (4H, 2 × CH_2), 2.38–2.53 (4H, 2 × CH_2), 3.27 (2H, m, 2 × CHO), 3.38 (2H, m, 2 × CHO), 4.24 (1H, s, OH), 4.35 (2H, s, CH_2Ph), 7.38–7.47 (5H, Ph); δ_c (63 MHz, $CDCl_3$) 31.3 (2 × t), 35.2 (2 × t), 49.9 (2 × d), 54.0 (2 × d), 56.7 (t), 64.9 (s), 71.4 (s), 126.4 (s), 129.0 (2 × s), 129.4 (s), 131.3 (2 × s); *m/z* (EI^+) 336 (M^+, 6%), 245 (14), 216 (5), 181 (29); found: *m/z* (EI^+) M^+ 326.1032, $C_{17}H_{20}O_5S$ requires 326.1031 ($\Delta = +0.3$ ppm).

9β-*tert*-Butylthio-10α-hydroxy-1,4,5,8,9,10-hexahydronaphthalene 14b. To a suspension of epoxy *bis*-alkene 13 (100 mg, 0.68 mmol) and powdered NaOH (270 mg, 6.8 mmol, 10 eq) in ethylene glycol (10 cm^3) was added *tert*-butyl thiol (380 mm^3, 3.4 mmol, 5 eq., **CAUTION** stench) and the resulting mixture heated at 100 °C for 16 h. Excess *tert*-butyl thiol was removed *in vacuo* and the remaining reaction mixture partitioned between EtOAc (10 cm^3) and H_2O (10 cm^3). The aqueous phase was extracted with EtOAc (4 × 10 cm^3) and the combined organic extracts washed with saturated brine (10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol–EtOAc, 9 : 1) to give thioether *bis*-alkene **14b** as off-white needles (137 mg, 85%). Mp 56.5–58.5 °C (EtOAc); R_f (petrol–EtOAc, 4 : 1) 0.45; ν_{max}/cm^{-1} (CH_2Cl_2) 3578, 3030, 2970, 2902, 1460, 1425, 1366, 1270; δ_H (250 MHz, $CDCl_3$) 1.42 [9H, s, $C(CH_3)_3$], 1.98–2.11 (2H, CH_2), 2.09 (1H, bs, OH), 2.33–2.48 (2H, CH_2), 2.49–2.61 (2H, CH_2), 2.62–2.75 (2H, CH_2), 5.63–5.75 (4H, 4 × =CH); δ_C (63 MHz, $CDCl_3$) 33.2 (3 × q), 35.2 (2 × t), 36.6 (2 × t), 45.8 (s), 50.9 (s), 70.8 (s), 123.9 (2 × d), 124.9 (2 × d); *m/z* (EI^+) 238 (M^+, 39%), 181 ($M^+ - {}^t$Bu, 91), 148 (100), 131 (88); found: *m/z* (EI^+) M^+ 238.1395, $C_{14}H_{22}OS$ requires 238.1391 ($\Delta = +1.7$ ppm).

9β-*tert*-Butylthio-(2α,3α)-oxido-10α-hydroxy-1,2,3,4,5,8,9,10-octahydronaphthalene 18. To a solution of thioether *bis*-alkene **14b** (50 mg, 0.21 mmol) and vanadyl bis(acetylacetonate) (3 mg, 0.011 mmol, 0.05 eq.) in CH_2Cl_2 (3 cm^3) was added trityl hydroperoxide (230 mg, 0.84 mmol, 4 eq.) and the resulting mixture stirred at rt for 14 h. A saturated aqueous solution of $Na_2S_2O_5$ (5 cm^3) was added, the organic phase separated and the aqueous phase extracted with $CHCl_3$ (3 × 10 cm^3). The combined organic extracts were washed with a saturated aqueous solution of $Na_2S_2O_5$ (10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol–EtOAc, 4 : 1 → 2 : 1) to give thioether mono-epoxide **18** as white needles (45 mg, 80%). Mp 92–95 °C (EtOAc); R_f (petrol–EtOAc, 1 : 1) 0.80; ν_{max}/cm^{-1} (CH_2Cl_2) 3594, 3482, 2964, 2907, 1461, 1425, 1366, 1158, 1074, 1020; δ_H (250 MHz, $CDCl_3$) 1.41 [9H, s, $C(CH_3)_3$], 1.95–2.10 (2H, CH_2), 2.13–2.28 (2H, CH_2 + OH), 2.30–2.38 (2H, CH_2), 2.40–2.60 (2H, CH_2), 2.70–2.80 (1H, CH_2), 3.39–3.45 (2H, 2 × CHO), 5.55–5.63 (2H, 2 × =CH); δ_C (63 MHz, $CDCl_3$) 32.9 (2 × q), 33.0 (t), 34.8 (t), 35.1 (t), 36.9 (t), 46.1 (s), 50.5 (s), 51.9 (d), 54.3 (d), 71.3 (s), 123.6 (d), 123.8 (d); *m/z* (EI^+) 254 (M^+, 14%), 197 (37), 181 (4), 165 (15); found: *m/z* (EI^+) M^+, 254.1338, $C_{14}H_{22}O_2S$ requires 254.1341 ($\Delta = -1.2$ ppm).

2α-Hydroxy-3β-*O*-*tert*-butylsulfonyl-(9α,10α)-oxido-1,2,3,4,5,8,9,10-octahydronaphthalene 19. To a solution of thioether *bis*-alkene **14b** (100 mg, 0.42 mmol) and vanadyl bis(acetylacetonate) (6 mg, 0.022 mmol, 0.05 eq.) in CH_2Cl_2 (5 cm^3) was added a solution of TBHP in toluene (550 mm^3, 3.05 M, 1.68 mmol, 4 eq.) dropwise and the resulting solution was stirred at rt for 15 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (petrol–EtOAc, 3 : 2) to give the sulfonate ester **19** as off-white needles (98 mg, 77%). Mp 178.5–181 °C (EtOAc); R_f (petrol–EtOAc, 1 : 1) 0.40; ν_{max}/cm^{-1} (CH_2Cl_2) 3589, 3488, 2929, 1427, 1321, 1270, 1145; δ_H (250 MHz, $CDCl_3$) 1.44 [9H, s, $C(CH_3)_3$], 2.08–2.35 (4H, 2 × CH_2), 2.36–2.73 (4H, 2 × CH_2), 3.30 (1H, m, CHOH), 3.91 (1H, s, CHOH), 4.85 (1H, dd, *J* 9.4 and 4.4, CHOSO$_2$Bu^t), 5.43–5.49 (2H, 2 × =CH); δ_C (63 MHz, $CDCl_3$) 24.5 (3 × q), 30.7 (t), 31.3 (t), 32.8 (t), 33.3 (t), 59.3 (s), 60.7 (s), 62.0 (d), 67.3 (d), 76.9 (d), 121.9 (d), 122.0 (d); *m/z* (EI^+) 164 ($M^+ - {}^t$BuSO$_3$H, 38%), 146 (26), 120 (36), 108 (93).

Single crystals of sulfonate ester **19** suitable for X-ray diffraction were obtained by re-crystallisation (CH_2Cl_2–hexane), mounted in inert oil and transferred to the cold gas stream of the diffractometer. *Crystal data*: $C_{14}H_{22}O_5S_1$, $M = 302.38$, triclinic, $a = 6.8076(9)$, $b = 9.3008(12)$, $c = 12.2010(18)$ Å, $\alpha = 96.400(8)$, $\beta = 105.284(9)$, $\gamma = 92.286(9)°$, $U = 738.62(17)$ Å^3, $T = 123$ K, space group $P\bar{1}$, (C_i^1, no. 2), $Z = 2$, Mo-K_α radiation ($\tilde{\lambda} = 0.71073$ Å), μ(Mo–K_α) = 0.235 mm^{-1}, 6317 reflections measured, 2987 unique, ($R_{int} = 0.0182$). Refinement converged, (Δ/σ, max, mean = 0.000, 0.000 respectively), with final $wR(F^2) = 0.1012$, (all data), $R_1 = 0.0368$, $S = 1.008$ for 2426 reflections with $I > 2\sigma(I)$ and 188 parameters.†

(9α,10α)-Oxido-1,2,3,4,5,6,7,8,9,10-decahydronaphthalene 20[52]. To a solution of epoxy *bis*-alkene **13** (5.10 g, 34.4 mmol) in Et_2O (30 cm^3) was added PtO_2 (Adams' catalyst, 600 mg, 2.64 mmol, 0.08 eq.) and the resulting suspension stirred vigorously under an atmosphere of hydrogen for 14 h. The reaction mixture was filtered through a pad of celite® and the solvent removed by careful distillation at atmospheric pressure

† CCDC reference numbers 266148, 266149 and 266150. See http://www.rsc.org/suppdata/ob/b5/b503758a/ for crystallographic data in CIF or other electronic format.

to leave epoxide **20** as a colourless oil (4.71 g, 90%) which was used directly without further purification. R_f (EtOAc–petrol, 1 : 19) 0.70; ν_{max}/cm^{-1} (neat) 2934, 2857, 1449; δ_H (250 MHz, $CDCl_3$) 1.13–1.27 (4H, 2 × CH_2), 1.32–1.48 (4H, 2 × CH_2), 1.49–1.62 (4H, 2 × CH_2), 1.74–1.87 (4H, 2 × CH_2); δ_C (63 MHz, $CDCl_3$) 20.5 (4 × t), 31.0 (4 × t), 62.2 (2 × s); *m/z* (EI^+) 152 (M^+, 50%), 111 (100), 62 (95); found: *m/z* (EI^+) M^+ 152.1203, $C_{10}H_{16}O$ requires 152.1201 ($\Delta = +1.3$ ppm).

9β-*tert*-Butylthio-10α-hydroxy-1,2,3,4,5,6,7,8,9,10-decahydronaphthalene 21.

Method 1. To a solution of saturated epoxide **20** (1.52 g, 10.0 mmol) and powdered NaOH (4.0 g, 100.0 mmol, 10 eq.) in ethylene glycol (25.0 cm^3) was added *tert*-butyl thiol (5.60 cm^3, 50 mmol, 5 eq., **CAUTION** stench) and the resulting mixture heated at 100 °C for 48 h. The reaction mixture was partitioned between H_2O (30 cm^3) and Et_2O (30 cm^3) and the phases separated. The organic phase was washed with H_2O (20 cm^3) and the combined aqueous phases re-extracted with Et_2O (2 × 20 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol → EtOAc–petrol, 1 : 4) to give decalin thioether **21** as colourless needles (1.94 g, 80%). Mp 64–65 °C (EtOAc); R_f (EtOAc–petrol, 1 : 9) 0.50; ν_{max}/cm^{-1} ($CHCl_3$) 3687, 3614, 2946, 2861, 1461, 1364, 1256, 1153; δ_H (250 MHz, $CDCl_3$) 1.06–1.18 (2H, CH_2), 1.38 [9H, s, $C(CH_3)_3$], 1.45 (1H, s, OH), 1.52–1.67 (6H, 3 × CH_2), 1.71–1.82 (4H, 2 × CH_2), 2.03 (2H, td, *J* 13.0 and 6.0, CH_2), 2.16–2.37 (2H, CH_2); δ_C (100 MHz, $CDCl_3$) 21.0 (2 × t), 21.1 (2 × t), 32.2 (2 × t), 33.4 (3 × q), 34.2 (2 × t), 46.9 (s), 59.0 (s), 73.1 (s); *m/z* (EI^+) 242 (M^+, 81%), 153 [$M^+ - SC(CH_3)_3$, 93], 135 (100); found: *m/z* (EI^+) M^+ 242.1697, $C_{14}H_{26}OS$ requires 242.1704 ($\Delta = -2.9$ ppm).

Method 2. To a solution of thioether *bis*-alkene **14b** (59 mg, 247 μmol) in EtOAc (3 cm^3) was added PtO_2 (Adams' catalyst, 6 mg, 26 μmol, 0.1 eq.) and the resulting suspension stirred vigorously under an atmosphere of hydrogen for 14 h. The reaction mixture filtered through a pad of celite® and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography (petrol–EtOAc, 16 : 1) to give thioether alcohol **21** as white needles (50 mg, 83%). Spectroscopic data as above.

(9β-*tert*-Butylthio-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-acetic acid 22. To a suspension of sodium hydride (39 mg, 1.547 mmol) in THF (3 cm^3) was added a solution of thioether alcohol **21** (150 mg, 0.619 mmol) in THF (3 cm^3) and the resulting mixture heated to reflux for 1 h. A solution of chloroacetic acid (55 mg, 0.582 mmol, 0.94 eq.) in THF (3 cm^3) was then added and the reaction mixture stirred at reflux for a further 12 h. The reaction mixture was then allowed to cool to rt, H_2O (5 cm^3) added dropwise and the resulting solution concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ (10 cm^3) and an aqueous solution of citric acid (10 cm^3, 1 M), the phases separated and the the aqueous phase extracted with $CHCl_3$ (2 × 10 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated to give a white solid which was dissolved in CH_2Cl_2 (10 cm^3) and extracted with an aqueous solution of NaOH (3 × 10 cm^3, 1 M). The aqueous extracts were acidified to pH 1 with an aqueous solution of HCl (1 M) and extracted with $CHCl_3$ (3 × 10 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give thioether oxyacetate **22** as white needles (120 mg, 65%). Mp 178–180 °C (EtOAc); R_f (CH_2Cl_2–HCO_2H, 50 : 1) 0.60; ν_{max}/cm^{-1} ($CHCl_3$) 3686, 3523, 3395, 2944, 2863, 1785, 1459, 1365, 1159, 1087; δ_H (250 MHz, $CDCl_3$) 1.24–1.36 (4H, 2 × CH_2), 1.40 [9H, s, $C(CH_3)_3$], 1.45–1.58 (4H, 2 × CH_2), 1.68–1.80 (2H, CH_2), 1.81–2.00 (4H, 2 × CH_2), 2.14–2.36 (2H, CH_2), 3.85 (2H, s, OCH_2CO_2H), CO_2H absent; δ_C (63 MHz, $CDCl_3$) 20.9 (2 × t), 21.0 (2 × t), 27.9 (2 × t), 32.1 (2 × t), 33.4 (3 × q), 47.1 (s), 57.6 (t), 59.1 (s), 79.4 (s), 173.4 (s); *m/z* (EI^+) 300 (M^+, 20%), 238 (11), 211 ($M^+ - SC(CH_3)_3$, 22), 135 (100); found: *m/z* (EI^+) M^+ 300.1747, $C_{16}H_{28}O_3S$ requires 300.1759 ($\Delta = -4.0$ ppm).

9β-Benzylthio-10α-hydroxy-1,2,3,4,5,6,7,8,9,10-decahydronaphthalene 23. To a suspension of saturated epoxide **20** (1.49 g, 10.0 mmol) and powdered NaOH (4.0 g, 100 mmol, 10.0 eq.) in ethylene glycol (25 cm^3) was added benzyl thiol (12.4 cm^3, 100 mmol, 10.0 eq., **CAUTION** stench) and the resulting mixture heated at 100 °C for 15 h. A deep orange colour developed. The reaction mixture was partitioned between H_2O (60 cm^3) and Et_2O (40 cm^3), the phases separated and the organic phase washed with H_2O (3 × 40 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography (EtOAc–petrol, 1 : 19 → 1 : 9 → EtOAc) gave decalin thioether **23** as a pale yellow amorphous powder (1.99 g, 72%). Mp 69.4–70.6 °C (pentane); R_f (EtOAc–petrol, 1 : 19) 0.15; ν_{max}/cm^{-1} ($CHCl_3$) 3616 (OH), 2940, 1602, 1495; δ_H ($CDCl_3$, 250 MHz) 1.14–1.33 (4H, 2 × CH_2), 1.41–1.82 (8H, 4 × CH_2), 1.87–2.02 (2H, CH_2), 2.06–2.25 (2H, CH_2), 3.48 (2H, s, SCH_2Ph), 7.17–7.36 (5H, Ph), OH absent; δ_C ($CDCl_3$, 63 MHz) 20.8 (2 × t), 20.9 (2 × t), 30.9 (2 × t), 32.2 (t), 34.5 (2 × t), 56.5 (s), 72.6 (s), 126.9 (d), 128.5 (2 × d), 129.2 (2 × d), 138.0 (s); *m/z* (EI^+) 276 (M^+, 46%), 153 ($M^+ - SCH_2Ph$, 89), 135 (100) 111 (89); found: *m/z* (EI^+) M^+ 276.1544, $C_{17}H_{24}SO$ requires M+, 276.1548 ($\Delta = -1.4$ ppm).

(9β-Benzylthio-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-acetic acid 24. To a suspension of sodium hydride (319 mg, 13.3 mmol, 4 eq.) in THF (6 cm^3) was added a solution of thioether alcohol **23** (915 mg, 3.32 mmol) in THF (5 cm^3) and chloroacetic acid (345 mg, 3.6 mmol, 1.1 eq.). The resulting mixture was heated to reflux for 1.5 h before removing the solvent under a stream of N_2 and heating the residual solid at 85 °C for a further 48 h. The residue was allowed to cool to rt, resuspended in THF (20 cm^3), H_2O (2 cm^3) added dropwise and the resulting solution concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 cm^3) and an aqueous solution of sodium hydroxide (10 cm^3, 1 M), the phases separated, the aqueous phase acidified to pH 1 with an aqueous solution of hydrochloric acid (1 M) and extracted with $CHCl_3$ (3 × 10 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give thioether oxyacetate **24** as a white amorphous powder (578 mg, 52%). Mp 154–156 °C (pentane); ν_{max}/cm^{-1} ($CHCl_3$) 2800 (OH), 2936, 1729 (C=O), 1602, 1495; δ_H ($CDCl_3$, 250 MHz) 1.32–1.60 (10H, 5 × CH_2), 1.74–1.94 (4H, 2 × CH_2), 2.05–2.26 (2H, CH_2), 3.51 (2H, s, SCH_2Ph), 3.90 (2H, s, OCH_2CO_2H), 7.19–7.35 (5H, Ph), OH absent; δ_C ($CDCl_3$, 63 MHz) 20.7 (2 × t), 20.8 (2 × t), 28.2 (2 × t), 30.7 (2 × t), 32.0 (t), 56.7 (s), 57.9 (t), 79.1 (s), 127.1 (d), 128.5 (2 × d), 129.2 (2 × d), 137.5 (s), 172.4 (s); *m/z* (EI^+) 334 (M^+, 26%), 135 (100), 91 ($M^+ - C_{12}H_{19}SO_3$, 76); found: *m/z* (EI^+)M^+ 334.1587, $C_{19}H_{26}SO_3$ requires M^+, 334.1603 ($\Delta = -4.8$ ppm).

(9β-Mercapto-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-acetic acid 25. To a solution of thioether oxyacetate **24** (257 mg, 0.75 mmol) in THF (1 cm^3) in a two-necked flask fitted with a cold-finger condenser was condensed NH_3 (10 cm^3). Sodium metal (220 mg, 10 mmol, 13 eq.) was then added and the resulting deep blue solution stirred for 4 h at −33 °C. Solid ammonium chloride was then added until the solution went clear and the NH_3 allowed to evaporate. The residue was concentrated *in vacuo* and then partitioned between $CHCl_3$ (10 cm^3) and an aqueous solution citric acid (10 cm^3, of 1 M). The phases were separated and the organic phase dried ($MgSO_4$) and concentrated *in vacuo* to give thiol oxyacetate **25** as an off-white amorphous powder (176 mg, 95%). Mp 152–154 °C ($CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3200 (OH), 2895, 2578, 1729 (C=O); δ_H ($CDCl_3$, 250 MHz) 1.21–1.67 (10H, 5 × CH_2), 1.75–1.92 (4H, 2 × CH_2), 2.01–2.16 (2H, CH_2), 3.89 (2H, s, OCH_2CO_2H), SH and OH absent; δ_C ($CDCl_3$, 63 MHz) 20.5 (2 × t), 21.1 (2 × t), 28.2 (2 × t), 36.7 (2 × t), 54.0 (s), 58.6 (t), 79.8 (s), 171.7 (s); *m/z* (EI^+) 244 (M^+, 10%), 212 (20),

168 (100); found: m/z (EI$^+$) M$^+$ 244.1121, $C_{12}H_{20}O_3S$ requires 244.1133 ($\Delta = -4.9$ ppm).

***S*-Nitroso-(9β-mercapto-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-acetic acid 26.** To a solution of thiol oxyacetate **25** (50 mg, 0.20 mmol) in CH_2Cl_2 (3.0 cm^3) was added *tert*-butyl nitrite (27 mm^3, 0.23 mmol). After 20 min the reaction was concentrated *in vacuo* to give the *S*-nitrosothiol oxyacetate **26** as pale green plates (32 mg, 57%). Mp 144–146 °C (CH_2Cl_2–hexane, 1 : 4); ν_{max}/cm^{-1} ($CHCl_3$) 3421, 2941, 2866, 1781, 1624, 1521; δ_H (250 MHz, $CDCl_3$) 1.17–2.66 (16H, 8 × CH_2), 3.92 (1H, s, OH), 4.04 (2H, s, OCH_2CO$_2$H); δ_C (100 MHz, $CDCl_3$) 20.4 (2 × t), 20.5 (2 × t), 29.4 (2 × t), 33.6 (2 × t), 57.2 (s), 57.9 (t), 67.6 (s) 173.2 (s); m/z (ES$^+$) 296 (MNa$^+$, 23%), 260 (29), 257 (39), 219 (45), 193 (100); Found: m/z (ES$^-$) M − H$^-$ 272.0960, $C_{12}H_{18}O_4SN$ requires 272.0957 ($\Delta = +1.1$ ppm).

Single crystals of *S*-nitrosothiol oxyacetate **26** suitable for X-ray diffraction were obtained by recrystallisation (CH_2Cl_2–hexane). *Crystal data*: $C_{12}H_{18}NO_4S$; M = 273.33, monoclinic, a = 10.927(8), b = 8.372(2), c = 14.620(10) Å, β = 96.444(14)°, U = 1329.1(16) Å^3, T = 150 K, space group P2$_1$ (C_2^2 No.4), Mo–K_α radiation ($\tilde{\lambda}$ = 0.71073 Å), μ(Mo–K_α) = 0.250 mm^{-1}, 7349 reflections measured, 2394 unique, (R_{int} = 0.1197) all of which were corrected for Lorentz and polarisation effects and for absorption by semi empirical methods based on symmetry-equivalent and repeated reflections (minimum and maximum transmission coefficients 0.9001 and 0.9925) 3499 independent reflections exceeded the significance level $|F|/\sigma(|F|) > 4.0$. N1A and O4A where found to be disordered and refined to an occupancy of 67% to 33%. Refinement converged, (Δ/σ, max, mean = 0.000, 0.000 respectively), with final $wR(F^2) = 0.2352$, (all data), $R_1 = 0.0842$, $S = 0.927$ for 2394 reflections with $I > 2\sigma(I)$ and 345 parameters Flack parameter value 0.0(2).†

9β-Benzylthio-10α-allyloxy-1,2,3,4,5,6,7,8,9,10-decahydronaphthalene 27. To a solution of thioether alcohol **23** (2.56 g, 9.40 mmol) in THF (25.0 cm^3) at 0 °C was added a solution of ^{n}BuLi (4.10 cm^3, 2.5 M in hexanes, 10.0 mmol) and the solution stirred for 30 min at this temperature before adding ^{n}Bu$_4$NI (342 mg, 0.94 mmol) and then allyl bromide (2.40 cm^3, 28.1 mmol) dropwise. The reaction mixture was heated at 50 °C for 48 h, H_2O (10 cm^3) was added and the resulting solution extracted with CH_2Cl_2 (3 × 30 cm^3). The combined organic phases were washed with H_2O (20 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol → EtOAc–petrol, 1 : 4) to give allyl ether **27** as a yellow oil (2.23 g, 75%). R_f (EtOAc–petrol, 1 : 19) 0.80; ν_{max}/cm^{-1} ($CHCl_3$) 3009, 2934, 2860, 1723, 1644, 1602, 1494, 1453; δ_H (250 MHz, $CDCl_3$) 1.34–1.62 (10H, 5 × CH_2), 1.66–1.85 (2H, CH_2), 1.96–2.27 (4H, 2 × CH_2), 3.53 (2H, s, SCH_2Ph), 3.69–3.77 (2H, OCH_2CH=CH$_2$), 5.15 (1H, app dq, J 10.4 and 2.0, OCH$_2$CH=CHH), 5.39 (1H, app dq, J 17.1 and 2.0, OCH$_2$CH=CHH), 6.00 (1H, ddt, J 17.1, 10.4 and 7.0, OCH$_2$CH=CH$_2$), 7.20–7.40 (5H, Ph); δ_C (100 MHz, $CDCl_3$) 20.9 (2 × t), 21.1 (2 × t), 28.2 (2 × t), 30.5 (2 × t), 32.0 (t), 57.7 (s), 59.9 (s), 76.3 (t), 114.5 (t), 126.8 (d), 128.4 (2 × d), 129.2 (2 × d), 135.9 (t),138.1 (s); m/z (EI$^+$) 316 (M$^+$, 52%), 259 (77), 136 (100), 135 (53), 91(85), 67 (32); found: m/z (EI$^+$) M$^+$ 316.1854, $C_{20}H_{28}OS$ requires 316.1861 ($\Delta = -2.2$ ppm).

2-(9β-Benzylthio-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-oxirane 28. To a solution of allyl ether **27** (1.79 g, 5.64 mmol) in THF (21.0 cm^3) and H_2O (7.0 cm^3) at 0 °C was added *N*-bromosuccinimide (1.50 g, 8.46 mmol) portionwise and the reaction mixture stirred at 0 °C for 3 h. The reaction mixture was then concentrated *in vacuo* and the residue partitioned between brine (15 cm^3) and Et_2O (25 cm^3). The phases were separated and the aqueous phase extracted with further Et_2O (3 × 25 cm^3). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (30 cm^3) and brine (10 cm^3), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude bromohydrin [R_f (EtOAc–petrol, 1 : 19) 0.20] which was directly dissolved in dry MeOH (26.0 cm^3) and K_2CO_3 (3.12 g, 22.6 mmol) added. After stirring at rt for 1 h, the resulting suspension was filtered under suction and the filtrate concentrated *in vacuo* and the residue partitioned between brine (15 cm^3) and EtOAc–petrol (50 : 50, 25 cm^3). The phases were separated and the aqueous phase extracted with further EtOAc–petrol (50 : 50, 25 cm^3). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give thioether epoxide **28** as a yellow oil (1.0 g, 55%) which was used directly without further purification. R_f (EtOAc–petrol, 1 : 19) 0.30; ν_{max}/cm^{-1} ($CHCl_3$) 3007, 2934, 2860, 1495, 1456; δ_H (250 MHz, $CDCl_3$) 1.32–1.59 (10H, 5 × CH_2), 1.59–1.80 (2H, CH_2), 1.87–2.22 (4H, 2 × CH_2) 2.69 (1H, dd, J 5.2 and 2.4, CCOHH), 2.83 (1H, dd, J 5.2 and 3.2, CCOHH), 3.13–3.19 (1H, OCH$_2$CHOC), 3.20 and 3.48 (2H, AB$_q$, J_{AB} 7.2, OCH_2CHOC), 3.50 (2H, s, SCH_2Ph), 7.19–7.39 (5H, Ph); δ_C (100 MHz, $CDCl_3$) 20.7 (2 × t), 21.0 (2 × t), 27.9 (t), 28.2 (t), 30.4 (2 × t), 31.9 (t), 44.6 (t), 51.4 (d), 57.5 (s), 60.1 (s), 76.5 (t), 126.9 (d), 128.4 (2 × d), 129.2 (2 × d), 138.0 (s); m/z (EI$^+$) 332 (M$^+$, 50%), 209 (55), 136 (84), 135 (100), 91(67), 57 (33); found: m/z (EI$^+$) M$^+$ 332.1824, $C_{20}H_{28}O_2S$ requires 332.1810 ($\Delta = +4.2$ ppm).

3-(9β-Benzylthio-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-propane-1,2-diol 29. To a solution of thioether epoxide **28** (1.0 g, 3.0 mmol) in THF (16.0 cm^3) and H_2O (16.0 cm^3) was added $BF_3{\cdot}Et_2O$ (3.20 cm^3, 10% vol.) dropwise and the solution stirred for 1 h at rt. A saturated aqueous solution of $NaHCO_3$ (10 cm^3) was added and the resulting reaction mixture extracted with Et_2O (4 × 25 cm^3), the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (EtOAc–petrol, 1 : 4 → 2 : 3) gave diol **29** as a colourless oil (970 mg, 92%). R_f (EtOAc–petrol, 1 : 1) 0.30; ν_{max}/cm^{-1} ($CHCl_3$) 3580, 3009, 2936, 2862, 1454, 1186; δ_H (250 MHz, $CDCl_3$) 1.36–1.57 (10H, 5 × CH_2), 1.65–1.92 (4H, 2 × CH_2), 2.05–2.22 (2H, CH_2), 3.22 (1H, dd, J 6.1 and 4.5, CHHOH), 3.26 (1H, dd, J 6.1 and 4.5, CHHOH), 3.50 (2H, s, SCH_2Ph), 3.64 [1H, dd, J 11.5 and 4.5, OCHHCH(OH)], 3.71 [1H, dd, J 11.5 and 4.5, OCHHCH(OH)], 3.87–3.96 [1H, OCH$_2$CH(OH)], 7.19–7.34 (5H, Ph), 2 × OH absent; δ_C (100 MHz, $CDCl_3$) 20.7 (2 × t), 20.7 (2 × t), 27.9 (t), 27.9 (t), 30.6 (t), 30.7 (t), 31.9 (t), 57.2 (s), 60.6 (s), 64.5 (t), 71.1 (d), 76.8 (t), 126.9 (d), 128.5 (2 × d), 129.2 (2 × d), 138.1 (s); m/z (EI$^+$) 350 (M$^+$, 22%), 227 (25), 153 (24), 136 (100), 135 (79), 91 (49); found: m/z (EI$^+$) M$^+$ 350.1909, $C_{20}H_{30}O_3S$ requires 350.1916 ($\Delta = -2.0$ ppm).

[2-(9β-Benzylthio-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-1-*tert*-butoxycarbonylmethoxymethylethoxy]-acetic acid *tert*-butyl ester 31. To a solution of diol **29** (982 mg, 2.80 mmol) and ^{n}Bu$_4$NBr (140 mg, 4.20 mmol) in CH_2Cl_2 (3.37 cm^3) at 0 °C was added a 50% w/v aqueous solution of NaOH (3.37 cm^3) and then *tert*-butyl bromoacetate (0.87 cm^3, 5.90 mmol) dropwise. The reaction mixture was stirred at 0 °C for 3 h, partitioned between H_2O (15.0 cm^3) and petrol (25.0 cm^3) and the phases separated. The aqueous layer was extracted further with petrol (2 × 25 cm^3) and then the combined organic phases washed with saturated brine (10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (petrol → EtOAc–petrol, 1 : 4) gave diester **31** as a clear oil (472 mg, 29%). R_f (EtOAc–petrol, 1 : 9) 0.40; ν_{max}/cm^{-1} ($CHCl_3$) 3008, 2982, 2934, 2861, 1742 (C=O), 1369; δ_H (250 MHz, $CDCl_3$) 1.29–2.18 (16H, 8 × CH_2), 1.47 [18H, s, 2 × C(CH$_3$)$_3$], 3.24–3.42 (2H, OCH_2CH), 3.47 (2H, s, SCH_2Ph), 3.63–3.88 (3H, CHCH_2O), 4.02, 4.08 (2H, AB$_q$ J_{AB} 17.5, OCH_2CO^{t}Bu), 4.24, 4.26 (2H, AB$_q$ J_{AB} 17.5, OCH_2CO^{t}Bu), 7.16–7.35 (5H, Ph); δ_C (100 MHz, $CDCl_3$) 20.6 (t), 20.7 (t), 20.9 (2 × t), 27.8 (t), 27.9 (t), 28.1 (6 × q), 30.5 (2 × t), 31.9 (t), 57.4 (s), 59.4 (s), 68.7 (t), 69.4 (t), 72.6 (t), 76.5 (t), 78.9 (d), 81.3 (s), 81.5 (s), 126.8 (d), 128.4 (2 × d), 129.2 (2 × d), 137.9 (s), 169.5

(s), 167.0 (s); *m/z* (EI$^+$) 579 (2%), 578 (M$^+$, 5), 321 (35), 265 (42), 259 (88), 209 (100), 136 (73),135 (63); found: *m/z* (EI$^+$) M$^+$ 578.3276, $C_{32}H_{50}O_7S$ requires 578.3277 ($\Delta = -0.2$ ppm).

[2-(9β-Benzylthio-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-1-carboxymethoxymethylethoxy]-acetic acid 32.

Method 1. To a suspension of sodium hydride (30 mg, 1.1 mmol) in THF (1 cm^3) was added a solution of diol **29** (32 mg, 0.09 mmol) in THF (5 cm^3) and the resulting reaction mixture heated at 60 °C for 1 h. The reaction mixture was then cooled to 0 °C and chloroacetic acid (20 mg, 2.0 mmol) was added portionwise. The reaction mixture was then heated to reflux for 24 h, the solution allowed to cool to rt, H_2O (2 cm^3) added dropwise and the resulting solution concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 cm^3) and an aqueous solution of NaOH (5 cm^3, 1 M), the phases separated and the aqueous phase washed with CH_2Cl_2 (2 × 5 cm^3) and acidified to pH 1 with an aqueous solution of hydrochloric acid (1 M). The resulting solution was extracted with $CHCl_3$ (3 × 5 cm^3), the organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to give bis-oxyacetate **32** as a clear oil (33 mg, 79%). ν_{max}/cm^{-1} ($CHCl_3$) 3690, 2936, 2861, 1766 (C=O), 1732 (C=O), 1454; δ_H (250 MHz, $CDCl_3$) 1.29–1.54 (10H, 5 × CH_2), 1.63–1.90 (4H, 2 × CH_2), 1.99–2.19 (2H, CH_2), 3.20–3.37 (2H, OCH_2CH), 3.48 (2H, s, SCH_2Ph), 3.67 (1H, CHCHHO), 3.83 (2H, CHCHHO), 4.17, 4.19 (2H, AB$_q$ J_{AB} 16.5, OCH_2CO^{t}Bu), 4.31, 4.44 (2H, AB$_q$ J_{AB} 17.5, OCH_2CO^{t}Bu), 7.16–7.35 (5H, Ph), 8.39 (2H, bs, 2 × CO_2H); δ_C (63 MHz, $CDCl_3$) 20.7 (t), 20.8 (t), 20.9 (2 × t), 27.8 (t), 27.9 (t), 30.6 (2 × t), 32.0 (t), 57.2 (s), 59.1 (s), 68.3 (t), 68.4 (t), 72.5 (t), 77.2 (t), 80.5 (d), 126.9 (d), 128.5 (2 × d), 129.2 (2 × d), 137.8 (s), 174.0 (s), 174.4 (s); *m/z* (ES$^+$) 490 (9%), 489 (MNa$^+$, 100), 260 (3), 259 (68); found: *m/z* (ES$^+$) MNa$^+$ 489.1918, $C_{24}H_{34}O_7NaS$ requires 489.1923 ($\Delta = -1.0$ ppm).

Method 2. To a solution of diester **31** (445 mg, 0.77 mmol) in THF (4 cm^3) and MeOH (4 cm^3) was added an aqueous solution of LiOH (4 cm^3, 2 M). The reaction mixture was stirred at rt for 48 h, acidified to pH 1 with aqueous hydrochloric acid (1 M) and extracted with EtOAc (3 × 10 cm^3). The combined organic extracts were washed with brine (10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give bis-oxyacetate **32** as a clear oil (359 mg, 100%). Spectroscopic data as above.

[1-Carboxymethoxymethyl-2-(9β-mercapto-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-ethoxy]-acetic acid 33. To a solution of bis-oxyacetate **32** (310 mg, 0.66 mmol) in THF (5 cm^3) in a two-necked flask fitted with a cold-finger condenser was condensed NH_3 (10 cm^3). Sodium metal (199 mg, 8.64 mmol) was then added and the resulting deep blue solution stirred for 4 h at −33 °C. Solid ammonium chloride was then added until the solution went clear and the NH_3 allowed to evaporate. The residue was concentrated *in vacuo* and then partitioned between CH_2Cl_2 (10 cm^3) and an aqueous solution of NaOH (10 cm^3, 1 M). The phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 10 cm^3) before being acidified to pH 1 with a saturated aqueous solution of citric acid. The aqueous phase was then extracted with $CHCl_3$ (3 × 10 cm^3) and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to give thiol bis-oxyacetate **33** as a thick clear oil (227 mg, 100%). ν_{max}/cm^{-1} ($CHCl_3$) 3690, 3026, 3016, 2936, 1767 (C=O), 1602; δ_H (250 MHz, $CDCl_3$) 1.26–1.60 (10H, 5 × CH_2), 1.64–1.94 (4H, 2 × CH_2), 2.04 (2H, app tt, *J* 13.4 and 3.7, CH_2), 3.22 (1H, dd, *J* 11.8 and 5.8, OCHHCH), 3.26 (1H, dd, *J* 11.8 and 5.8, OCHHCH), 3.66 (1H, dd, *J* 9.4 and 7.6, CHCHHO), 3.75–3.86 (2H, CHCHHO), 4.16, 4.24 (2H, AB$_q$ J_{AB} 16.8, OCH_2COH), 4.28, 4.43 (2H, AB$_q$ J_{AB} 17.4, OCH_2COH), 9.37 (2H, bs, 2 × CO_2H), SH absent; δ_C (100 MHz, $CDCl_3$) 20.5 (2 × t), 21.3 (2 × t), 27.8 (t), 27.9 (t), 36.5 (t), 36.6 (t), 54.6 (s), 59.8 (s), 68.2 (2 × t), 72.3 (t), 77.6 (t), 80.4 (d), 174.3 (s), 174.6 (s); *m/z* (ES$^+$) 400 (6%), 399 (MNa$^+$, 100), 367 (4); found: *m/z* (ES$^+$) MNa$^+$ 399.1459, $C_{17}H_{28}O_7NaS$ requires 399.1453 ($\Delta = +1.5$ ppm).

***S*-Nitroso-[1-carboxymethoxymethyl-2-(9β-mercapto-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-ethoxy]-acetic acid 37.** To a solution of thiol bis-oxyacetate **33** (50 mg, 0.13 mmol) in CH_2Cl_2 (2.0 cm^3) was added *tert*-butyl nitrite (49 mm^3, 0.41 mmol). After 40 min the reaction was concentrated *in vacuo* to give the *S*-nitrosothiol oxyacetate **37** as a pale green oil (30 mg, 56%). ν_{max}/cm^{-1} (CH_2Cl_2), 2934, 2863, 1735 (C=O), 1496, 1452; δ_H (270 MHz, $CDCl_3$) 1.24–1.75 (12 C 6 × CH_2), 2.38–2.49 (4H, 2 × CH_2), 3.30–3.40 (2H, OCH_2CH), 3.75–4.00 (3H, OCH_2CH), 4.20–4.55 (4H, 2 × O CH_2COOH); δ_C (270 MHz, $CDCl_3$) 20.4 (2 × t), 21.2 (2 × t), 29.1 (t), 29.2 (t), 33.6 (t), 33.7 (t), 59.2 (s), 68.0 (s), 68.4 (t), 68.5 (t), 72.5 (t), 75.9 (t), 80.4 (d), 174.5 (s), 174.7 (s); *m/z* (ES$^-$) 404 (M − H, 20%), 374 (50), 341 (55%), 75 (100).

3-(9β-Benzylthio-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-1-*O*-methyl-propane-1,2-diol 30. Obtained using the same method as described above for the preparation of thioether epoxide **28** employing allyl ether **27** (2.53 g, 8.0 mmol), *N*-bromosuccinimide (2.13 g, 12 mmol), MeOH (30 cm^3) and K_2CO_3 (4.42 g, 32 mmol) but employing a reaction time of 12 h (*cf.* 1 h) for the second step. Purification by flash chromatography (EtOAc–petrol, 1 : 4) gave methyl ether **30** as a yellow oil (2.41 g, 83%). R_f (EtOAc–petrol, 1 : 9) 0.20; ν_{max}/cm^{-1} ($CHCl_3$) 3500, 2948, 2910, 2862, 1458, 1192; δ_H (250 MHz, $CDCl_3$) 1.32–1.52 (10H, 5 × CH_2), 1.63–1.91 (4H, 2 × CH_2), 2.04–2.18 (2H, CH_2), 2.31 (1H, bs, OH), 3.24 (2H, d, *J* 6.5, CH_2OMe), 3.39 (3H, s, OMe), 3.47 [1H, dd, *J* 11.5 and 4.5, OCHHCH(OH)], 3.50 (2H, s, SCH_2Ph), 3.52 [1H, dd, *J* 11.5 and 4.5, OCHHCH(OH)], 3.95 [1H, app quintet, *J* 7.0, OCH$_2$CH(OH)], 7.17–7.36 (5H, Ph); δ_C (100 MHz, $CDCl_3$) 20.7 (2 × t), 21.0 (2 × t), 28.0 (2 × t), 30.6 (2 × t), 32.0 (t), 57.4 (s), 59.3 (s), 60.0 (t), 70.0 (d), 74.2 (q), 76.4 (t), 127.0 (d), 128.5 (2 × d), 129.3 (2 × d), 137.9 (s); *m/z* (CI$^+$) 365 (4%), 364 (M$^+$, 5), 259 (100), 241 (55), 135 (55); found: *m/z* (CI$^+$) M$^+$ 364.2073, $C_{21}H_{32}O_3S$ requires 364.2072 ($\Delta = +0.3$ ppm).

[2-(9β-Benzylthio-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-1-methoxymethylethoxy]-acetic acid *tert*-butyl ester 34. To a solution of methyl ether **30** (1.98 g, 5.43 mmol) and ^{n}Bu$_4$NBr (1.99 g, 5.98 mmol) in CH_2Cl_2 (5 cm^3) at 0 °C was added a 50% w/v aqueous solution of NaOH (5 cm^3) and then *tert*-butyl bromoacetate (0.88 cm^3, 5.90 mmol) dropwise. The reaction mixture was stirred at 0 °C for 5 h, partitioned between H_2O (21.0 cm^3) and petrol (35.0 cm^3) and the phases separated. The aqueous layer was extracted further with petrol (4 × 30 cm^3) and then the combined organic phases washed with saturated brine (50 cm^3), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by flash chromatography (EtOAc–petrol, 1 : 9) gave ester **34** as a clear oil (1.83 g, 64%). R_f (EtOAc–petrol, 1 : 4) 0.80; ν_{max}/cm^{-1} ($CHCl_3$) 2930, 2860, 1748 (C=O), 1454, 1136; δ_H (250 MHz, $CDCl_3$) 1.32–1.51 (10H, 5 × CH_2), 1.46 [9H, s, C(CH_3)$_3$], 1.58–1.72 (2H, CH_2), 1.77–1.93 (2H, CH_2), 2.00–2.15 (2H, CH_2), 3.23–3.40 (2H, CH_2OMe), 3.37 (3H, s, OMe), 3.45 (2H, s, SCH_2Ph), 3.52–3.66 (2H, CHCH_2O), 3.68–3.75 (1H, CHCH$_2$O), 4.18, 4.22 (2H, AB$_q$ J_{AB} 17.5, OCH_2CO^{t}Bu), 7.18–7.33 (5H, Ph); δ_C (63 MHz, $CDCl_3$) 20.7 (t), 20.8 (t), 21.0 (2 × t), 27.9 (2 × t), 28.2 (3 × q), 30.6 (2 × t), 32.0 (t), 57.4 (s), 59.3 (s), 59.3 (t), 68.5 (d), 73.6 (q), 76.6 (t), 78.7 (t), 81.4 (s), 126.9 (d), 128.5 (2 × d), 129.2 (2 × d), 138.0 (s), 170.0 (s); *m/z* (CI$^+$) 496 (MNH$_4^+$, 15%), 355 (15), 259 (100); found: *m/z* (CI$^+$) MNH$_4^+$ 496.3100, $C_{27}H_{46}O_5SN$ requires 496.3097 ($\Delta = +0.6$ ppm).

[2-(9β-Benzylthio-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-1-methoxymethylethoxy]-acetic acid 35. To a solution of ester **34** (1.75 g, 3.66 mmol) in THF (15 cm^3) and MeOH (15 cm^3) was added an aqueous solution of LiOH (15 cm^3, 2 M). The reaction mixture was stirred at rt for 14 h, acidified to pH 1 with aqueous hydrochloric acid (1 M) and extracted with EtOAc (3 × 40 cm^3). The combined organic

extracts were washed with brine (40 cm^3), dried (Na_2SO_4) and concentrated *in vacuo* to give oxyacetate **35** as a thick, clear oil (1.54 g, 100%). ν_{max}/cm^{-1} ($CHCl_3$) 3260, 2930, 2861, 1762 (C=O), 1454, 1188; δ_H (250 MHz, $CDCl_3$) 1.32–1.54 (10H, 5 × CH_2), 1.65–1.88 (4H, 2 × CH_2), 2.02–2.17 (2H, CH_2), 3.15–3.26 (2H, CH_2OMe), 3.48 (3H, s, OMe), 3.49 (2H, s, SCH_2Ph), 3.50–3.60 (2H, CHCH_2O), 3.68–3.77 (1H, CHCH_2O), 4.22, 4.41 (2H, AB_q J_{AB} 17.5, OCH_2CO_2H), 7.18–7.33 (5H, Ph), CO_2H absent; δ_C (63 MHz, $CDCl_3$) 20.7 (t), 20.8 (t), 20.9 (2 × t), 27.8 (t), 27.9 (t), 30.5 (t), 30.6 (t), 32.0 (t), 57.3 (s), 59.4 (s), 59.4 (t), 69.3 (d), 72.8 (q), 77.2 (t), 81.2 (t), 127.0 (d), 128.6 (2 × d), 129.3 (2 × d), 137.7 (s), 172.0 (s); *m/z* (CI^+) 440 (MNH_4^+, 3%), 423 (MH^+, 1), 259 (100), 182 (76); found: *m/z* (CI^+) MNH_4^+ 440.2471, $C_{23}H_{38}O_5SN$ requires 440.2471 (Δ = 0.0 ppm).

[2-(9β-Mercapto-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-1-methoxymethylethoxy]-acetic acid 36. To a solution of oxyacetate **35** (1.45 g, 3.43 mmol) in THF (20 cm^3) in a two-necked flask fitted with a cold-finger condenser was condensed NH_3 (150 cm^3). Sodium metal (1.03 g, 44.6 mmol) was then added and the resulting deep blue solution stirred for 4 h at −33 °C. Solid ammonium chloride was then added until the solution went clear and the NH_3 allowed to evaporate. The residue was concentrated *in vacuo* and then partitioned between CH_2Cl_2 (50 cm^3) and an aqueous solution of NaOH (50 cm^3, 1 M). The phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 40 cm^3) before being acidified to pH 1 with a saturated aqueous solution of citric acid. The aqueous phase was then extracted with $CHCl_3$ (4 × 50 cm^3) and the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo* to give thiol oxyacetate **36** as a thick clear oil (640 mg, 50%). ν_{max}/cm^{-1} ($CHCl_3$) 3200, 2934, 1860, 1763 (C=O), 1452, 1188; δ_H (250 MHz, $CDCl_3$) 1.26–1.57 (10H, 5 × CH_2), 1.63–1.89 (4H, 2 × CH_2), 2.02 (2H, app td, *J* 13.5 and 3.6, CH_2), 3.17 (1H, dd, *J* 11.6 and 3.9, OC*H*HCH), 3.22 (1H, dd, *J* 11.6 and 3.9, OCH*H*CH), 3.42 (3H, s, OMe), 3.46–3.57 (2H, CHCH_2O), 3.64–3.72 (1H, CHCH_2O), 4.20, 4.38 (2H, AB_q J_{AB} 16.5, OCH_2CO_2H), CO_2H and SH absent; δ_C (63 MHz, $CDCl_3$) 20.5 (2 × t), 21.4 (2 × t), 27.8 (t), 27.9 (t), 36.6 (t), 36.7 (t), 54.7 (s), 59.3 (s), 60.2 (q), 69.0 (t), 72.9 (t), 77.6 (t), 80.8 (d), 172.6 (s); *m/z* (CI^+) 350 (MNH_4^+, 20%), 294 (100), 278 (32); found: *m/z* (CI^+) MNH_4^+ 350.1989, $C_{16}H_{32}O_5SN$ requires 350.2001 (Δ = −3.4 ppm).

***S*-Nitroso-[2-(9β-mercapto-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10α-yloxy)-1-methoxymethylethoxy]-acetic acid 38.** To a solution of thiol oxyacetate **36** (60 mg, 0.18 mmol) in CH_2Cl_2 (3.0 cm^3) was added *tert*-butyl nitrite (170 mm^3, 1.43 mmol). After 20 min the reaction was concentrated *in vacuo* to give the *S*-nitrosothiol oxyacetate **38** as a pale green oil (45 mg, 69%). ν_{max}/cm^{-1} (CH_2Cl_2.) 3427, 2933, 2862, 1731 (C=O), 1503 (N=O), 1453; δ_H (250 MHz, $CDCl_3$) 1.37–1.72 (12H, 6 × CH_2), 2.38–2.49 (4H, 2 × CH_2), 3.30–3.40 (2H, OCH_2CH), 3.44 (3H, s, OMe), 3.52–3.66 (2H, CHCH_2O), 3.76–3.87 (1H, CHCH_2O), 4.28, 4.41 (2H, AB_q J_{AB} 16.0, OCH_2CO_2H), 8.96 (1H, bs, CO_2H); δ_C (270 MHz, $CDCl_3$) 20.4 (2 × t), 21.2 (2 × t), 29.1 (t), 29.2 (t), 33.6 (t), 33.7 (t), 59.4 (q), 68.0 (s), 69.2 (t), 72.8 (t), 75.9 (s), 77.6 (t), 80.9 (d), 172.2 (s); *m/z* (ES^-) 360 (M − H, 20%), 330 (50), 297 (100%).

Single crystals of sulfonate ester **37** suitable for X-ray diffraction were obtained by recrystallisation (CH_2Cl_2–hexane), mounted in inert oil and transferred to the cold gas stream of the diffractometer. *Crystal data*: $C_{16}H_{27}N_1O_6S_1$, M = 361.45, monoclinic, a = 15.095(1), b = 10.338 (6), c = 11.718 (5) Å, β = 97.582(4)°, U = 1812.7(18) $Å^3$, T = 120 K, space group $P2_1/c$, (C_{2k}^5, No. 14), Z = 4, Mo-K_α radiation ($\tilde{\lambda}$ = 0.71073 Å), μ(Mo–K_α) = 0.209 mm^{-1}, 22 881 reflections measured, 3744 unique, (R_{int} = 0.1151). Structure was discovered in the latter stages of refinement to be a non-merohedral twin with a dominant domain. Refinement on this single domain converged, (Δ/σ, max, mean = 0.005, 0.001 respectively), with final $wR(F^2)$ = 0.2950, (all data), R_1 = 0.0943, S = 1.010 for 2778 reflections with $I > 2\sigma(I)$ and 223 parameters.†

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