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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Received 14th March 2005, Accepted 5th April 2005 First published as an Advance Article on the web 19th April 2005

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-H₂ (PGH₂) 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 Snitrosothiol (RSNO), disulfide (RSSR'), sulfenic acid (RSOH), sulfinic acid (RSO₂H) and sulfonic acid (RSO₃H) 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 contentious⁸ and a concensus has yet to emerge as to the relative importance of various putative NOderived 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, RSNOs¹² 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

DOI: 10.1039/b503758

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-NH₃; 74%) then epoxidation (CH₃CO₃H; 87%).^{33,34} Ring-opening of this epoxide with benzylthiol in ethylene glycol³⁵ afforded thioether bisalkene 14a (78%). The plan was to chemo- and stereoselectively oxidise this thioether bis-alkene to the corresponding bisepoxide 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-tertbutyl hydroperoxide (TBHP, 2 eq.)³⁷ in CH₂Cl₂ 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 CH₂Cl₂ at 0 °C, or excess DMD³⁹ in acetone–benzene at 0 °C, or *m*-CPBA (1.5 eq.)⁴⁰ in CH₂Cl₂ at rt gave mixtures of sulfoxide bis-alkene 15a and sulfone bisalkene 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



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.* LiAlH₄ or DIBAL-H) or the corresponding thiol triol using Birch reduction (Li/NH₃-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 CH₂Cl₂ at rt again resulted in preferential oxidation at sulfur, oxidation with VO(acac)₂-trityl hydroperoxide (THP, 4 eq.) in CH₂Cl₂ 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, HOCH₂CH₂OH, 100 °C [78%]; b) DMD, acetone–benzene [**15a** 67% + **15b** 33%]; c) *m*-CPBA (3 eq.), CH₂Cl₂ [**16** 89% from **15a**]; d) *m*-CPBA (5 eq.), CH₂Cl₂ [**17** 56% from **15a**]; e) VO(acac)₂, TBHP, CH₂Cl₂ [**17** 79% from **15b**; **19** 77%]; f) 'BuSH, NaOH, HOCH₂CH₂OH, 100 °C [**14b** 85%; **21** 80%]; g) VO(acac)₂, THP, CH₂Cl₂ [**18** 80%]; h) VO(acac)₂, THP, benzene [**19** 69%]; i) PtO₂, H₂, Et₂O [90%]; j) PtO₂, H₂, EtOAc [83%]; k) NaH, ClCH₂CO₂H, 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 CH₂Cl₂ 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 (PtO₂- 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 (\rightarrow 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 coworkers⁴² 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 derivative43 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 tertbutyl nitrite in CH₂Cl₂ 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 "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 ringclosure to the thioether terminal epoxide 28 with K_2CO_3 in MeOH (55% overall). Subsequent BF₃·Et₂O promoted ringopening 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, CH₂Cl₂, "Bu₄NBr, 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 $(27 \rightarrow 30 \rightarrow 34 \rightarrow 35 \rightarrow 36$, 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, HOCH₂CH₂OH, 100 °C [72%]; b) NaH, ClCH₂CO₂H, THF, 70 °C [52%]; c) Na, NH₃–THF, -33 °C [25 95%; 33 100%; 36 50%]; d) 'BuONO, CH₂Cl₂ [26 57%; 37 56% from 33; 38 69% from 36]; e) "BuLi, "Bu₄NI, CH₂=CHCH₂Br, THF [75%]; f) (i) NBS, THF–H₂O, (ii) K₂CO₃, MeOH [28 55%; 30 83%]; g) BF₃·Et₂O, THF–H₂O [29 92%]; h) NaOH, "Bu₄NBr, BrCH₂CO₂'Bu, CH₂Cl₂–H₂O [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 $n_{\rm S} \rightarrow \sigma^*_{\rm NO}$ 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 $n_{\rm S} \rightarrow \pi^*_{\rm NO}$ 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 $n_{\rm O} \rightarrow \sigma^*_{\rm SN}$ 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

		Soluble?		
Buffer	Concentration/mM	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 (× 10^{-2} mol dm⁻³): phosphate buffer 1.0, NaCl 1.37 and KCl 0.27 in water. ^{*b*} Buffer was made up using (× 10^{-3} mol dm⁻³): NaCl 118.9, CaCl₂ 1.2, NaHCO₃ 20.4, K₂HPO₄ 2.4, KH₂PO₄ 0.6, MgCl₂ 1.2 and glucose 10 in water adjusted to pH 7.4 by bubbling a gaseous mixture of 95% O₂ and 5% CO₂ 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 $\sim 5\%$ 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 (¹H 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 F₂₅₄ (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 F₂₅₄ which were visualised either by quenching of ultraviolet fluorescence ($\lambda_{max} =$ 254 nm) or by charring with 5% w/v phosphomolybdic acid in 95% EtOH, 10% w/v ammonium molybdate in 1M H₂SO₄, or 10% KMnO₄ in 1M H₂SO₄. 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.

9B-Benzylthio-10a-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 cm³) was added benzyl thiol (790 cm³, 6.76 mmol, CAUTION stench) and the resulting mixture heated at 100 °C for 2 h. An aqueous solution of saturated Na₂SO₄ (5 cm³) was then added dropwise and the phases separated. The aqueous phase was extracted further with EtOAc $(2 \times 15 \text{ cm}^3)$, dried (MgSO₄) 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; $v_{\text{max}}/\text{cm}^{-1}$ (CHCl₃) 3483 (OH), 3026, 2897, 1653, 1494, 1241, 869; δ_H (250 MHz, CDCl₃) 2.08–2.20 (2H, CH₂'s), 2.10 (1H, bs, OH), 2.38–2.42 (4H, $2 \times CH_2$), 2.47–2.61 (2H, CH₂), 3.75 (2H, s, CH_2Ph), 5.67 (4H, m, 2 × CH_2), 7.18–7.35 (5H, Ph); $\delta_{\rm C}$ (63 MHz, CDCl₃) 33.5 (2 × t), 34.8 (2 × t), 36.9 (t), 49.7 (s), 71.0 (s), 124.4 (2 \times d), 124.6 (2 \times d), 126.9 (s), 128.4 (2 \times 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, C₁₇H₂₀OS requires 272.1235 ($\Delta = -2.9$ 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 cm³) at 0 °C was added a solution of dimethyldioxirane⁵¹ in acetone (~0.1 M, 7.4 cm³, ~0.74 mmol) dropwise. After 30 min the volatiles were removed *in vacuo* and the residue purified by flash chromatography (EtOAc-petrol, 2 : 3 \rightarrow 4 : 1) to give:

Sulfoxide **15a** as a white crystalline solid (71 mg, 67%). Mp 45– 51 °C (EtOAc); $R_{\rm f}$ (EtOAc–petrol, 2 : 1) 0.15; $\nu_{\rm max}$ /cm⁻¹ (CHCl₃) 3014, 1496, 1454; $\delta_{\rm H}$ (250 MHz, CDCl₃) 2.20–2.35 (2H, CH₂), 2.40–2.45 (2H, CH₂), 2.50–2.65 (5H, 2 × CH₂ + OH), 2.77–2.9 (2H, CH₂), 3.94 and 3.77 (2H, AB_q $J_{\rm AB}$ 11.9, CH₂Ph), 5.60–5.75 (4H, 4 × =CH), 7.27–7.40 (5H, Ph); $\delta_{\rm c}$ (63 MHz, CDCl₃) 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, C₁₇H₂₁O₂S requires 289.1262 (Δ = +2.1 ppm).

Sulfone **15b** as a white solid (36 mg, 33%). Mp 176–178 °C (EtOAc); $R_{\rm f}$ (EtOAc–petrol, 2 : 1) 0.60; $v_{\rm max}$ /cm⁻¹ (CHCl₃) 3019, 1494, 1434; $\delta_{\rm H}$ (250 MHz, CDCl₃) 2.20–2.55 (5H, CH₂'s + OH), 2.72–2.81 (2H, CH₂), 2.84–2.87 (2H, CH₂), 4.22 (2H, s, *CH*₂Ph),

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

			Bond Lengths		
Structure	Conformation C–S–N=O	Torsion Angle C–S–N=O/°	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- <i>trans</i>	175.7	1.867	1.792	1.177
4 ²⁰ (tertiary)	s-trans : s -cis (7 : 3)	179.6 ^a	1.841^{a}	1.781a	1.205ª
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, CDCl₃) 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, C₁₇H₂₀O₃S requires 304.1133 ($\Delta = +0.3$ ppm).

9β-Benzylsulfonyl-(2α,3α)-oxido-10α-hydroxy-1,2,3,4,5,8,9,10octahydronaphthalene 16. To a solution of thioether bis-alkene 14a (100 mg, 0.37 mmol) in CH₂Cl₂ (5 cm³) 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 cm³) and the resulting reaction mixture extracted with CH_2Cl_2 (3 × 10 cm³). The organic extracts were dried (MgSO₄), 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; $v_{\text{max}}/\text{cm}^{-1}$ (CHCl₃) 3372, 2921, 1439, 1260, 1061, 746; $\delta_{\rm H}$ (250 MHz, CDCl₃) 2.17–2.40 (3H, CH₂'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, CH₂Ph), 4.45 (1H, s, OH), 5.65–5.75 (2H, 2 × =CH), 7.36–7.44 (5H, Ar); δ_c (63 MHz, CDCl₃) 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 \times d), 126.3 (2 \times d), 128.7 (2 \times 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, C₁₇H₂₁O₄S 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 Na₂S₂O₅ (10 cm^3) and the resulting reaction mixture extracted with CH_2Cl_2 (3 × 10 cm³). The organic extracts were washed with a saturated aqueous solution of NaHCO₃ (10 cm³), dried $(MgSO_4)$, concentrated *in vacuo* and the residue purified by flash chromatography (EtOAc-petrol, $1: 1 \rightarrow 2: 1$) to give sulfone bis-epoxide 17 as a white solid (70 mg, 56%). Mp 184–186 °C (EtOAc); $R_{\rm f}$ (EtOAc–petrol, 1 : 1) 0.10; $v_{\rm max}/{\rm cm^{-1}}$ (nujol) 3398, 1459, 1376, 1120; $\delta_{\rm H}$ (250 MHz, CDCl₃) 2.23–2.34 (4H, 2 \times CH₂), 2.38–2.53 (4H, 2 \times CH₂), 3.27 (2H, m, 2 \times 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, CDCl₃) 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 cm³) was added *tert*-butyl thiol (380 mm³, 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 cm³) and H₂O (10 cm³). The aqueous phase was extracted with EtOAc (4×10 cm³) and the combined organic extracts washed with saturated brine (10 cm³), dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (petrol-EtOAc, 9:1) to give thioether bisalkene 14b as off-white needles (137 mg, 85%). Mp 56.5-58.5 °C (EtOAc); $R_{\rm f}$ (petrol-EtOAc, 4 : 1) 0.45; $v_{\rm max}/{\rm cm}^{-1}$ (CH₂Cl₂) 3578, 3030, 2970, 2902, 1460, 1425, 1366, 1270; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.42 [9H, s, C(CH₃)₃], 1.98-2.11 (2H, CH₂), 2.09 (1H, bs, OH), 2.33–2.48 (2H, CH₂), 2.49–2.61 (2H, CH₂), 2.62–2.75 (2H, CH₂), 5.63–5.75 (4H, 4 × =CH); $\delta_{\rm C}$ (63 MHz, CDCl₃) $33.2 (3 \times q), 35.2 (2 \times t), 36.6 (2 \times t), 45.8 (s), 50.9 (s), 70.8$ (s), 123.9 (2 × d), 124.9 (2 × d); m/z (EI⁺) 238 (M⁺, 39%), 181 (M⁺ – '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-1,2,3,4,5,8,9,10octahydronaphthalene 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 cm³) 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 cm³) was added, the organic phase separated and the aqueous phase extracted with $CHCl_3$ (3 × 10 cm³). The combined organic extracts were washed with a saturated aqueous solution of $Na_2S_2O_5$ (10 cm³), dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (petrol-EtOAc, $4: 1 \rightarrow 2: 1$) to give thioether mono-epoxide 18 as white needles (45 mg, 80%). Mp 92-95 °C (EtOAc); $R_{\rm f}$ (petrol-EtOAc, 1 : 1) 0.80; $v_{\rm max}/{\rm cm}^{-1}$ (CH₂Cl₂) 3594, 3482, 2964, 2907, 1461, 1425, 1366, 1158, 1074, 1020; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.41 [9H, s, C(CH₃)₃], 1.95-2.10 (2H, CH₂), 2.13-2.28 (2H, CH₂ + OH), 2.30-2.38 (2H, CH₂), 2.40-2.60(2H, CH₂), 2.70–2.80 (1H, CH₂), 3.39–3.45 (2H, 2 × CHO), 5.55–5.63 (2H, 2 × =CH); $\delta_{\rm C}$ (63 MHz, CDCl₃) 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).

2a-Hydroxy-3β-O-tert-butylsulfonyl-(9a,10a)-oxido-1,2,3,4,5, 8,9,10-octahydronaphthalene 19. To a solution of thioether bisalkene 14b (100 mg, 0.42 mmol) and vanadyl bis(acetylacetonate) (6 mg, 0.022 mmol, 0.05 eq.) in CH₂Cl₂ (5 cm³) was added a solution of TBHP in toluene (550 mm³, 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; v_{max}/cm^{-1} (CH₂Cl₂) 3589, 3488, 2929, 1427, 1321, 1270, 1145; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.44 [9H, s, C(CH₃)₃], 2.08-2.35 (4H, 2 × CH₂), 2.36-2.73 (4H, 2 × CH₂), 3.30 (1H, m, CHOH), 3.91 (1H, s, CHOH), 4.85 (1H, dd, J 9.4 and 4.4, CHOSO₂Bu^{*i*}), 5.43–5.49 (2H, 2 × =CH); $\delta_{\rm C}$ (63 MHz, CDCl₃) 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 $(M^+ - {}^tBuSO_3H, 38\%), 146 (26), 120 (36), 108 (93).$

Single crystals of sulfonate ester **19** suitable for X-ray diffraction were obtained by re-crystallisation (CH₂Cl₂-hexane), mounted in inert oil and transferred to the cold gas stream of the diffractometer. *Crystal data*: C₁₄H₂₂O₅S₁, M = 302.38, triclinic, a = 6.8076(9), b = 9.3008(12), c = 12.2010(18) Å, $\alpha = 96.400(8)$, $\beta = 105.284(9)$, $\gamma = 92.286(9)^{\circ}$, U = 738.62(17) Å³, T = 123 K, space group *P*Ī, (C¹₁, no. 2), Z = 2, Mo- K_a radiation ($\tilde{\lambda} = 0.71073$ Å), μ (Mo- K_a) = 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.[†]

(9a,10a)-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 Et₂O (30 cm³) was added PtO₂ (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. $R_{\rm f}$ (EtOAc–petrol, 1 : 19) 0.70; $\nu_{\rm max}/\rm cm^{-1}$ (neat) 2934, 2857, 1449; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.13–1.27 (4H, 2 × CH₂), 1.32–1.48 (4H, 2 × CH₂), 1.49–1.62 (4H, 2 × CH₂), 1.74–1.87 (4H, 2 × CH₂); $\delta_{\rm C}$ (63 MHz, CDCl₃) 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, C₁₀H₁₆O requires 152.1201 (Δ = +1.3 ppm).

9β -*tert*-Butylthio-10 α -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 cm³) was added tert-butyl thiol (5.60 cm³, 50 mmol, 5 eq., CAUTION stench) and the resulting mixture heated at 100 °C for 48 h. The reaction mixture was partitioned between H₂O (30 cm³) and Et₂O (30 cm³) and the phases separated. The organic phase was washed with H_2O (20 cm³) and the combined aqueous phases re-extracted with Et₂O (2 \times 20 cm³). The combined organic phases were dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (petrol \rightarrow EtOAc-petrol, 1 : 4) to give decalin thioether **21** as colourless needles (1.94 g, 80%). Mp 64–65 °C (EtOAc); $R_{\rm f}$ (EtOAc-petrol, 1:9) 0.50; $v_{\rm max}$ /cm⁻¹ (CHCl₃) 3687, 3614, 2946, 2861, 1461, 1364, 1256, 1153; *δ*_H (250 MHz, CDCl₃) 1.06-1.18 (2H, CH₂), 1.38 [9H, s, C(CH₃)₃], 1.45 (1H, s, OH), 1.52-1.67 (6H, $3 \times CH_2$), 1.71-1.82 (4H, $2 \times CH_2$), 2.03 (2H, td, J 13.0 and 6.0, CH₂), 2.16–2.37 (2H, CH₂); $\delta_{\rm C}$ (100 MHz, CDCl₃) 21.0 (2 × t), 21.1 (2 × t), 32.2 (2 × t), 33.4 (3 × q), 34.2 $(2 \times t)$, 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 μ mol) in EtOAc (3 cm³) was added PtO₂ (Adams' catalyst, 6 mg, 26 μ mol, 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 cm³) was added a solution of thioether alcohol 21 (150 mg, 0.619 mmol) in THF (3 cm³) 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 cm³) 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, H₂O (5 cm³) added dropwise and the resulting solution concentrated in vacuo. The residue was partitioned between CHCl₃ (10 cm³) and an aqueous solution of citric acid (10 cm³, 1 M), the phases separated and the the aqueous phase extracted with CHCl₃ (2 \times 10 cm³). The combined organic extracts were dried (Na₂SO₄) and evaporated to give a white solid which was dissolved in CH₂Cl₂ (10 cm³) and extracted with an aqueous solution of NaOH (3 \times 10 cm³, 1 M). The aqueous extracts were acidified to pH 1 with an aqueous solution of HCl (1 M) and extracted with CHCl₃ (3 \times 10 cm³). The organic extracts were dried (MgSO₄) and concentrated in vacuo to give thioether oxyacetate 22 as white needles (120 mg, 65%). Mp 178-180 °C (EtOAc); $R_{\rm f}$ (CH₂Cl₂-HCO₂H, 50 : 1) 0.60; $v_{\rm max}$ /cm⁻¹ (CHCl₃) 3686, 3523, 3395, 2944, 2863, 1785, 1459, 1365, 1159, 1087; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.24–1.36 (4H, 2 × CH₂), 1.40 [9H, s, $C(CH_3)_3$], 1.45–1.58 (4H, 2 × CH₂), 1.68–1.80 (2H, CH₂), 1.81-2.00 (4H, 2 × CH₂), 2.14–2.36 (2H, CH₂), 3.85 (2H, s, OCH_2CO_2H), CO_2H absent; δ_C (63 MHz, $CDCl_3$) 20.9 (2 × t), $21.0 (2 \times t), 27.9 (2 \times t), 32.1 (2 \times t), 33.4 (3 \times q), 47.1 (s), 57.6$ (t), 59.1 (s), 79.4 (s), 173.4 (s); m/z (EI⁺) 300 (M⁺, 20%), 238 (11), 211 (M^+ – SC(CH₃)₃, 22), 135 (100); found: m/z (EI⁺) M^+ 300.1747, $C_{16}H_{28}O_3S$ requires 300.1759 ($\Delta = -4.0$ ppm).

9B-Benzylthio-10a-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 cm³) was added benzyl thiol (12.4 cm³, 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 H₂O (60 cm³) and Et_2O (40 cm³), the phases separated and the organic phase washed with H_2O (3 × 40 cm³). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo to give a yellow oil. Purification by flash chromatography (EtOAc-petrol, 1 : 19 \rightarrow 1 : 9 \rightarrow 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; $v_{\rm max}/{\rm cm}^{-1}$ (CHCl₃) 3616 (OH), 2940, 1602, 1495; $\delta_{\rm H}$ (CDCl₃, 250 MHz) 1.14–1.33 (4H, 2 \times CH₂), 1.41–1.82 (8H, 4 \times CH₂), 1.87–2.02 (2H, CH₂), 2.06–2.25 (2H, CH₂), 3.48 (2H, s, SCH₂Ph), 7.17–7.36 (5H, Ph), OH absent; $\delta_{\rm C}$ (CDCl₃, 63 MHz) 20.8 (2 \times t), 20.9 (2 \times t), 30.9 (2 \times t), 32.2 (t), 34.5 (2 \times t), 56.5 (s), 72.6 (s), 126.9 (d), 128.5 (2 \times d), 129.2 (2 \times d), 138.0 (s); m/z (EI^+) 276 (M⁺, 46%), 153 (M⁺ - SCH₂Ph, 89), 135 (100) 111 (89); found: m/z (EI⁺) M⁺ 276.1544, C₁₇H₂₄SO requires M+, 276.1548 ($\Delta = -1.4$ ppm).

(9β-Benzylthio-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10αyloxy)-acetic acid 24. To a suspension of sodium hydride (319 mg, 13.3 mmol, 4 eq.) in THF (6 cm³) was added a solution of thioether alcohol 23 (915 mg, 3.32 mmol) in THF (5 cm³) 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 N2 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 cm³), H₂O (2 cm³) added dropwise and the resulting solution concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (20 cm³) and an aqueous solution of sodium hydroxide (10 cm³, 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 cm³). The organic extracts were dried (MgSO₄) and concentrated in vacuo to give thioether oxyacetate 24 as a white amorphous powder (578 mg, 52%). Mp 154–156 °C (pentane); v_{max}/cm^{-1} $(CHCl_3)$ 2800 (OH), 2936, 1729 (C=O), 1602, 1495; δ_H (CDCl₃, 250 MHz) 1.32–1.60 (10H, 5 \times CH₂), 1.74–1.94 (4H, 2 \times CH₂), 2.05–2.26 (2H, CH₂), 3.51 (2H, s, SCH₂Ph), 3.90 (2H, s, OCH_2CO_2H), 7.19–7.35 (5H, Ph), OH absent; δ_C (CDCl₃, 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 \times 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-10αyloxy)-acetic acid 25. To a solution of thioether oxyacetate 24 (257 mg, 0.75 mmol) in THF (1 cm³) in a two-necked flask fitted with a cold-finger condenser was condensed NH₃ (10 cm³). 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 NH₃ allowed to evaporate. The residue was concentrated in vacuo and then partitioned between $CHCl_3$ (10 cm³) and an aqueous solution citric acid (10 cm³, of 1 M). The phases were separated and the organic phase dried (MgSO₄) and concentrated *in vacuo* to give thiol oxyacetate 25 as an off-white amorphous powder (176 mg, 95%). Mp 152–154 °C (CHCl₃); v_{max}/cm^{-1} (CHCl₃) 3200 (OH), 2895, 2578, 1729 (C=O); $\delta_{\rm H}$ (CDCl₃, 250 MHz) 1.21–1.67 (10H, 5 × CH₂), 1.75–1.92 (4H, 2 × CH₂), 2.01–2.16 (2H, CH₂), 3.89 (2H, s, OCH₂CO₂H), SH and OH absent; $\delta_{\rm C}$ (CDCl₃, 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, C₁₂H₂₀O₃S 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 CH₂Cl₂ (3.0 cm³) was added *tert*-butyl nitrite (27 mm³, 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 (CH₂Cl₂–hexane, 1 : 4); v_{max} /cm⁻¹ (CHCl₃) 3421, 2941, 2866, 1781, 1624, 1521; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.17–2.66 (16H, 8 × CH₂), 3.92 (1H, s, OH), 4.04 (2H, s, OCH₂CO₂H); $\delta_{\rm C}$ (100 MHz, CDCl₃) 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, C₁₂H₁₈O₄SN requires 272.0957 (Δ = +1.1 ppm).

Single crystals of S-nitrosothiol oxyacetate 26 suitable for X-ray diffraction were obtained by recrystallisation (CH₂Cl₂hexane). Crystal data: $C_{12}H_{18}NO_4S$; M = 273.33, monoclinic, $a = 10.927(8), b = 8.372(2), c = 14.620(10) \text{ Å}, \beta = 96.444(14)^{\circ},$ $U = 1329.1(16) \text{ Å}^3$, T = 150 K, space group P2₁ (C_2^2 No.4), Mo– K_a radiation ($\tilde{\lambda} = 0.71073$ Å), μ (Mo– K_a) = 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 symmetryequivalent 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, $(\Delta/\sigma, \max,$ 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 cm³) at 0 °C was added a solution of "BuLi (4.10 cm3, 2.5 M in hexanes, 10.0 mmol) and the solution stirred for 30 min at this temperature before adding ^{*n*}Bu₄NI (342 mg, 0.94 mmol) and then allyl bromide (2.40 cm³, 28.1 mmol) dropwise. The reaction mixture was heated at 50 °C for 48 h, H_2O (10 $\mbox{cm}^3)$ was added and the resulting solution extracted with CH_2Cl_2 (3 × 30 cm³). The combined organic phases were washed with H₂O (20 cm³), dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (petrol \rightarrow 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; v_{max}/cm^{-1} (CHCl₃) 3009, 2934, 2860, 1723, 1644, 1602, 1494, 1453; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.34–1.62 (10H, 5 × CH₂), 1.66–1.85 (2H, CH₂), 1.96–2.27 (4H, $2 \times CH_2$), 3.53 (2H, s, SCH₂Ph), 3.69–3.77 (2H, OCH₂CH=CH₂), 5.15 (1H, app dq, J 10.4 and 2.0, OCH₂CH=CHH), 5.39 (1H, app dq, J 17.1 and 2.0, OCH₂CH=CHH), 6.00 (1H, ddt, J 17.1, 10.4 and 7.0, $OCH_2CH=CH_2$), 7.20–7.40 (5H, Ph); δ_C (100 MHz, CDCl₃) 20.9 (2 \times t), 21.1 (2 \times t), 28.2 (2 \times t), 30.5 (2 \times t), 32.0 (t), 57.7 (s), 59.9 (s), 76.3 (t), 114.5 (t), 126.8 (d), 128.4 ($2 \times d$), 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 cm³) and H₂O (7.0 cm³) 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 cm³) and Et₂O (25 cm³). The phases were separated and the aqueous phase extracted with further Et₂O (3 × 25 cm³). The combined organic extracts were washed with a saturated aqueous solution of NaHCO₃ (30 cm³) and brine (10 cm³), dried (MgSO₄), 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 cm³) and K₂CO₃ (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 cm³) and EtOAc-petrol (50 : 50, 25 cm³). The phases were separated and the aqueous phase extracted with further EtOAc-petrol (50 : 50, 25 cm³). The combined organic extracts were then dried (MgSO₄), 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. $R_{\rm f}$ (EtOAc-petrol, 1 : 19) 0.30; v_{max}/cm^{-1} (CHCl₃) 3007, 2934, 2860, 1495, 1456; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.32–1.59 (10H, 5 \times CH₂), 1.59–1.80 (2H, CH₂), 1.87–2.22 (4H, $2 \times CH_2$) 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, OCH2CHOC), 3.20 and 3.48 (2H, AB_q, J_{AB} 7.2, OCH₂CHOC), 3.50 (2H, s, SCH₂Ph), 7.19–7.39 (5H, Ph); $\delta_{\rm C}$ (100 MHz, CDCl₃) 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 \times d), 129.2 (2 \times 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, C₂₀H₂₈O₂S requires $332.1810 (\Delta = +4.2 \text{ ppm}).$

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 cm³) and H_2O (16.0 cm³) was added BF₃·Et₂O (3.20 cm³, 10% vol.) dropwise and the solution stirred for 1 h at rt. A saturated aqueous solution of NaHCO₃ (10 cm³) was added and the resulting reaction mixture extracted with Et₂O (4 \times 25 cm³), the combined organic extracts dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (EtOAc-petrol, $1: 4 \rightarrow 2: 3$) gave diol **29** as a colourless oil (970 mg, 92%). $R_{\rm f}$ (EtOAc-petrol, 1 : 1) 0.30; $v_{\rm max}/{\rm cm}^{-1}$ (CHCl₃) 3580, 3009, 2936, 2862, 1454, 1186; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.36–1.57 (10H, $5 \times CH_2$), 1.65–1.92 (4H, 2 × CH₂), 2.05–2.22 (2H, CH₂), 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, SCH₂Ph), 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, OCH2CH(OH)], 7.19-7.34 (5H, Ph), 2 × OH absent; $\delta_{\rm C}$ (100 MHz, CDCl₃) 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 $(2 \times d)$, 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-(9B-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 "Bu4NBr (140 mg, 4.20 mmol) in CH2Cl2 (3.37 cm³) at 0 °C was added a 50% w/v aqueous solution of NaOH (3.37 cm³) and then *tert*-butyl bromoacetate (0.87 cm³, 5.90 mmol) dropwise. The reaction mixture was stirred at 0 °C for 3 h, partitioned between H_2O (15.0 cm³) and petrol (25.0 cm³) and the phases separated. The aqueous layer was extracted further with petrol $(2 \times 25 \text{ cm}^3)$ and then the combined organic phases washed with saturated brine (10 cm^3) , dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (petrol \rightarrow EtOAc-petrol, 1 : 4) gave diester **31** as a clear oil (472 mg, 29%). $R_{\rm f}$ (EtOAc-petrol, 1 : 9) 0.40; *v*_{max}/cm⁻¹ (CHCl₃) 3008, 2982, 2934, 2861, 1742 (C=O), 1369; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.29–2.18 (16H, 8 × CH₂), 1.47 [18H, s, $2 \times C(CH_3)_3$, 3.24–3.42 (2H, OCH₂CH), 3.47 (2H, s, SCH₂Ph), 3.63-3.88 (3H, CHCH₂O), 4.02, 4.08 (2H, AB_q J_{AB} 17.5, OCH2CO'Bu), 4.24, 4.26 (2H, ABq JAB 17.5, OCH2CO'Bu), 7.16–7.35 (5H, Ph); $\delta_{\rm C}$ (100 MHz, CDCl₃) 20.6 (t), 20.7 (t), 20.9 $(2 \times t)$, 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 cm³) was added a solution of diol 29 (32 mg, 0.09 mmol) in THF (5 cm³) 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 cm³) added dropwise and the resulting solution concentrated *in vacuo*. The residue was partitioned between CH₂Cl₂ (5 cm³) and an aqueous solution of NaOH (5 cm³, 1 M), the phases separated and the aqueous phase washed with CH_2Cl_2 (2 × 5 cm³) and acidified to pH 1 with an aqueous solution of hydrochloric acid (1 M). The resulting solution was extracted with CHCl₃ (3×5 cm³), the organic extracts dried (MgSO₄) and concentrated in vacuo to give bis-oxyacetate 32 as a clear oil (33 mg, 79%). $v_{\rm max}/{\rm cm^{-1}}$ (CHCl₃) 3690, 2936, 2861, 1766 (C=O), 1732 (C=O), 1454; $\delta_{\rm H}$ $(250 \text{ MHz}, \text{CDCl}_3)$ 1.29–1.54 (10H, 5 × CH₂), 1.63–1.90 (4H, $2 \times CH_2$), 1.99–2.19 (2H, CH₂), 3.20–3.37 (2H, OCH₂CH), 3.48 (2H, s, SCH₂Ph), 3.67 (1H, CHCHHO), 3.83 (2H, CHCHHO), 4.17, 4.19 (2H, $AB_q J_{AB}$ 16.5, $OCH_2CO'Bu$), 4.31, 4.44 (2H, AB_a J_{AB} 17.5, OCH₂CO'Bu), 7.16–7.35 (5H, Ph), 8.39 (2H, bs, $2 \times CO_2H$); δ_C (63 MHz, CDCl₃) 20.7 (t), 20.8 (t), 20.9 (2 × t), 27.8 (t), 27.9 (t), 30.6 (2 \times 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 $(2 \times d)$, $129.2 (2 \times d), 137.8 (s), 174.0 (s), 174.4 (s); m/z (ES⁺) 490 (9%),$ 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 cm³) and MeOH (4 cm³) was added an aqueous solution of LiOH (4 cm³, 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 ($3 \times 10 \text{ cm}^3$). The combined organic extracts were washed with brine (10 cm^3), dried (MgSO₄) 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 cm³) in a two-necked flask fitted with a cold-finger condenser was condensed NH₃ (10 cm³). 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 NH₃ allowed to evaporate. The residue was concentrated in vacuo and then partitioned between CH2Cl2 (10 cm3) and an aqueous solution of NaOH (10 cm³, 1 M). The phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 10 cm³) before being acidified to pH 1 with a saturated aqueous solution of citric acid. The aqueous phase was then extracted with CHCl₃ $(3 \times 10 \text{ cm}^3)$ and the combined organic extracts dried (MgSO₄) and concentrated *in vacuo* to give thiol bis-oxyacetate 33 as a thick clear oil (227 mg, 100%). ν_{max}/cm^{-1} (CHCl₃) 3690, 3026, 3016, 2936, 1767 (C=O), 1602; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.26–1.60 $(10H, 5 \times CH_2), 1.64-1.94 (4H, 2 \times CH_2), 2.04 (2H, app tt, J)$ 13.4 and 3.7, CH₂), 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, OCH₂COH), 4.28, 4.43 (2H, AB_q J_{AB} 17.4, OCH₂COH), 9.37 (2H, bs, $2 \times CO_2H$), SH absent; δ_C (100 MHz, CDCl₃) 20.5 (2 \times t), 21.3 (2 \times 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, C₁₇H₂₈O₇NaS 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 CH₂Cl₂ (2.0 cm³) was added *tert*-butyl nitrite (49 mm³, 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%). v_{max}/cm^{-1} (CH₂Cl₂), 2934, 2863, 1735 (C=O), 1496, 1452; $\delta_{\rm H}$ (270 MHz, CDCl₃) 1.24–1.75 (12 C 6 × CH₂), 2.38–2.49 (4H, 2 × CH₂), 3.30–3.40 (2H, OCH₂CH), 3.75–4.00 (3H, OCH₂CH), 4.20–4.55 (4H, 2 × O CH₂COOH); $\delta_{\rm C}$ (270 MHz, CDCl₃) 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 cm³) and K₂CO₃ (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; v_{max}/cm^{-1} (CHCl₃) 3500, 2948, 2910, 2862, 1458, 1192; δ_{H} $(250 \text{ MHz}, \text{CDCl}_3) 1.32 - 1.52 (10\text{H}, 5 \times \text{CH}_2), 1.63 - 1.91 (4\text{H}, 1.63 - 1.91)$ $2 \times CH_2$), 2.04–2.18 (2H, CH₂), 2.31 (1H, bs, OH), 3.24 (2H, d, J 6.5, CH₂OMe), 3.39 (3H, s, OMe), 3.47 [1H, dd, J 11.5 and 4.5, OCHHCH(OH)], 3.50 (2H, s, SCH₂Ph), 3.52 [1H, dd, J 11.5 and 4.5, OCHHCH(OH)], 3.95 [1H, app quintet, J 7.0, OCH₂CH(OH)], 7.17–7.36 (5H, Ph); $\delta_{\rm C}$ (100 MHz, CDCl₃) 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 $(2 \times d)$, 129.3 $(2 \times d)$, 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-(9ß-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*}Bu₄NBr (1.99 g, 5.98 mmol) in CH₂Cl₂ (5 cm³) at 0 $^{\circ}$ C was added a 50% w/v aqueous solution of NaOH (5 cm³) and then tert-butyl bromoacetate (0.88 cm³, 5.90 mmol) dropwise. The reaction mixture was stirred at 0 °C for 5 h, partitioned between $H_2O(21.0 \text{ cm}^3)$ and petrol (35.0 cm³) and the phases separated. The aqueous layer was extracted further with petrol (4 \times 30 cm³) and then the combined organic phases washed with saturated brine (50 cm³), dried (Na₂SO₄), and concentrated *in* vacuo. Purification by flash chromatography (EtOAc-petrol, 1: 9) gave ester 34 as a clear oil (1.83 g, 64%). $R_{\rm f}$ (EtOAc-petrol, 1 : 4) 0.80; $v_{\text{max}}/\text{cm}^{-1}$ (CHCl₃) 2930, 2860, 1748 (C=O), 1454, 1136; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.32–1.51 (10H, 5 × CH₂), 1.46 [9H, s, C(CH₃)₃], 1.58–1.72 (2H, CH₂), 1.77–1.93 (2H, CH₂), 2.00–2.15 (2H, CH₂), 3.23-3.40 (2H, CH₂OMe), 3.37 (3H, s, OMe), 3.45 (2H, s, SCH₂Ph), 3.52–3.66 (2H, CHCH₂O), 3.68–3.75 (1H, CHCH₂O), 4.18, 4.22 (2H, AB_q J_{AB} 17.5, OCH₂CO'Bu), 7.18–7.33 (5H, Ph); $\delta_{\rm C}$ (63 MHz, CDCl₃) 20.7 (t), 20.8 (t), 21.0 $(2 \times t)$, 27.9 $(2 \times t)$, 28.2 $(3 \times q)$, 30.6 $(2 \times t)$, 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 (MNH₄⁺, 15%), 355 (15), 259 (100); found: m/z (CI⁺) MNH₄⁺ 496.3100, C₂₇H₄₆O₅SN requires 496.3097 ($\Delta =$ +0.6 ppm).

[2-(9 β -Benzylthio-1,2,3,4,5,6,7,8,9,10-decahydronaphthalen-10 α -yloxy)-1-methoxymethylethoxy]-acetic acid 35. To a solution of ester 34 (1.75 g, 3.66 mmol) in THF (15 cm³) and MeOH (15 cm³) was added an aqueous solution of LiOH (15 cm³, 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 cm³). The combined organic extracts were washed with brine (40 cm³), dried (Na₂SO₄) and concentrated *in vacuo* to give oxyacetate **35** as a thick, clear oil (1.54 g, 100%). v_{max}/cm^{-1} (CHCl₃) 3260, 2930, 2861, 1762 (C=O), 1454, 1188; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.32–1.54 (10H, 5 × CH₂), 1.65–1.88 (4H, 2 × CH₂), 2.02–2.17 (2H, CH₂), 3.15–3.26 (2H, CH₂OMe), 3.48 (3H, s, OMe), 3.49 (2H, s, SCH₂Ph), 3.50–3.60 (2H, CHCH₂O), 3.68–3.77 (1H, CHCH₂O), 4.22, 4.41 (2H, AB_q J_{AB} 17.5, OCH₂CO₂H), 7.18–7.33 (5H, Ph), CO₂H absent; $\delta_{\rm C}$ (63 MHz, CDCl₃) 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 (MNH₄⁺, 3%), 423 (MH⁺, 1), 259 (100), 182 (76); found: m/z (CI⁺) MNH₄⁺ 440.2471, C₂₃H₃₈O₅SN requires 440.2471 (Δ = 0.0 ppm).

[2-(9ß-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 cm³) in a two-necked flask fitted with a cold-finger condenser was condensed NH₃ (150 cm³). 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 NH₃ allowed to evaporate. The residue was concentrated in vacuo and then partitioned between CH₂Cl₂ (50 cm³) and an aqueous solution of NaOH (50 cm³, 1 M). The phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 × 40 cm³) before being acidified to pH 1 with a saturated aqueous solution of citric acid. The aqueous phase was then extracted with $CHCl_3$ (4 \times 50 cm³) and the combined organic extracts dried (Na₂SO₄) and concentrated in vacuo to give thiol oxyacetate 36 as a thick clear oil (640 mg, 50%). v_{max}/cm⁻¹ (CHCl₃) 3200, 2934, 1860, 1763 (C=O), 1452, 1188; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.26–1.57 (10H, 5 \times CH₂), 1.63–1.89 (4H, $2 \times$ CH₂), 2.02 (2H, app td, J 13.5 and 3.6, CH₂), 3.17 (1H, dd, J 11.6 and 3.9, OCHHCH), 3.22 (1H, dd, J 11.6 and 3.9, OCHHCH), 3.42 (3H, s, OMe), 3.46-3.57 (2H, CHCH₂O), 3.64-3.72 (1H, CHCH₂O), 4.20, 4.38 (2H, AB_q J_{AB} 16.5, OC H_2 CO₂H), CO₂H and SH absent; δ_C (63 MHz, CDCl₃) 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 (MNH₄⁺, 20%), 294 (100), 278 (32); found: m/z (CI⁺) MNH₄⁺ 350.1989, C₁₆H₃₂O₅SN requires $350.2001 \ (\Delta = -3.4 \text{ ppm}).$

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 CH₂Cl₂ (3.0 cm³) was added *tert*-butyl nitrite (170 mm³, 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%). v_{max} /cm⁻¹ (CH₂Cl₂.) 3427, 2933, 2862, 1731 (C=O), 1503 (N=O), 1453; $\delta_{\rm H}$ (250 MHz, CDCl₃) 1.37–1.72 (12H, 6 × CH₂), 2.38–2.49 (4H, 2 × CH₂), 3.30–3.40 (2H, OCH₂CH), 3.44 (3H, s, OMe), 3.52–3.66 (2H, CHCH₂O), 3.76–3.87 (1H, CHCH₂O), 4.28, 4.41 (2H, AB_q *J*_{AB} 16.0, OCH₂CO₂H), 8.96 (1H, bs, CO₂H); $\delta_{\rm C}$ (270 MHz, CDCl₃) 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 (CH₂Cl₂-hexane), mounted in inert oil and transferred to the cold gas stream of the diffractometer. *Crystal data*: C₁₆H₂₇N₁O₆S₁, M = 361.45, monoclinic, a = 15.095(1), b = 10.338 (6), c = 11.718 (5) Å, $\beta = 97.582(4)^{\circ}$, U = 1812.7(18) Å³, T = 120 K, space group $P2_1/c$, (C_{2k}° , No. 14), Z = 4, Mo- K_a radiation ($\lambda = 0.71073$ Å), μ (Mo- K_a) = 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.[†]

Acknowledgements

Grateful acknowledgement is made to the ESPRC for a Quota studentship (J. C.) and Pfizer Ltd for a Summer Scholarship (K. I. C.). Merck Sharp & Dohme Ltd and Pfizer Ltd are also thanked for unrestricted research funds.

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