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The cleavage of *meso*-epoxides with homochiral thiols: synthesis of (+)- and (−)-*trans*-1-mercaptocyclohexan-2-ol

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Abstract

The synthesis of (+)- and (−)-*trans*-1-mercaptocyclohexan-2-ol is described. Ring opening of cyclohexene oxide with (−)-4-methoxybenzylnopan-3(*R*)-thiol **1a** followed by oxidation gives two readily separable diastereomeric sulfoxides. These sulfoxides display very different thermal stability but both undergo regio-specific *syn*-elimination to give cyclohexan-1-ol-2-sulfenic acid that can be reacted in situ with 3,5-dimethylthiophenol to give a mixed disulfide. Reduction of these disulfides with lithium aluminium hydride gives the title compounds in enantiomerically pure form.

1. Introduction

The cleavage of *meso*-epoxides with homochiral nucleophiles and bases has proven to be a versatile means of synthesising enantio-enriched compounds. The challenge of discriminating between identical enantiotopic groups, attached to centres of opposite configuration, has led to ingenious chemical methods for the synthesis of compounds such as β-azido alcohols,[1] allylic alcohols,[2] hydroxy sulfides[3] and halohydrins.[4] This success prompted our own investigations into the cleavage of cyclohexene oxide with the homochiral thio-nucleophiles **1a** and **1b**.

Cleavage of cyclohexene oxide **2** with a chiral thiol can give rise to two possible diastereomeric hydroxy sulfides **3**, oxidation of which can lead to four possible hydroxy sulfoxides **4** (Scheme 1). Providing these diastereomeric sulfoxides were separable then their thermolysis should lead to either homochiral allylic alcohols or hydroxy sulfenic acids.

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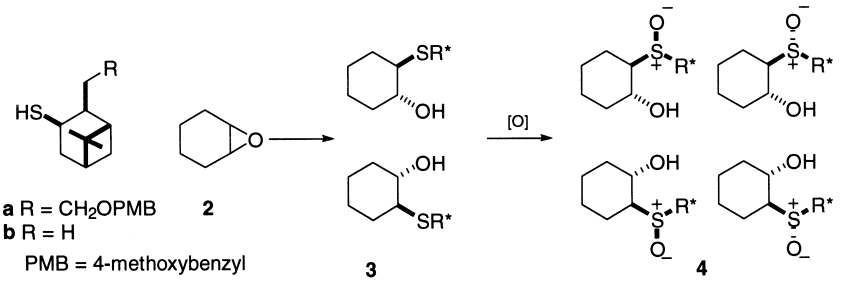
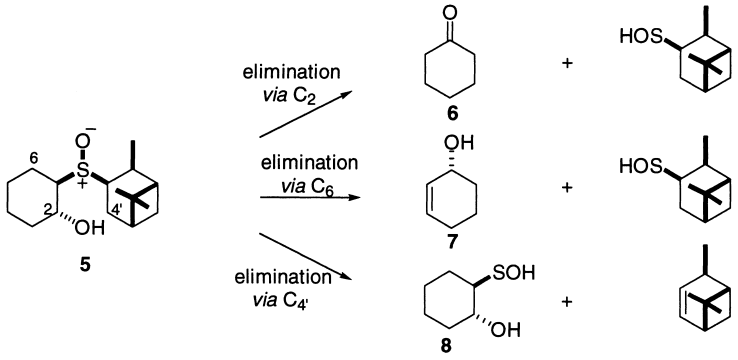


Scheme 1.

It is well established that sulfoxides bearing a β-hydrogen can thermolyse via a *syn*-elimination to give an alkene and the corresponding sulfenic acid.[5] Sulfoxide **5** is one of the four possible diastereomeric sulfoxides formed from the cleavage of cyclohexene oxide with pinane thiol **1b**, followed by oxidation. This compound has three available *syn* β-hydrogens, two on the cyclohexane ring and one on the bicyclic moiety. Elimination into the cyclohexane ring could lead to either cyclohexanone **6**, formed by tautomerisation of the corresponding enol, or the allylic alcohol **7**. Elimination into the pinane ring system would generate the hydroxysulfenic acid **8** (Scheme 2). By analogy with β-selenoxides,[6] it would be expected that the sulfoxide **5** would eliminate away from the hydroxy group, thus from the thermolysis of **5** we would expect to produce homochiral allylic alcohols **7** and/or hydroxysulfenic acids **8**. Herein we report a short synthetic route to the homochiral thiols **1a** and **1b** starting from inexpensive and readily available (−)-nopol and (−)-α-pinene, the regio and stereochemical course of the thermolysis of hydroxy sulfoxides of the general type **5**, and the synthesis of (+)- and (−)-*trans*-1-mercaptocyclohexan-2-ol.

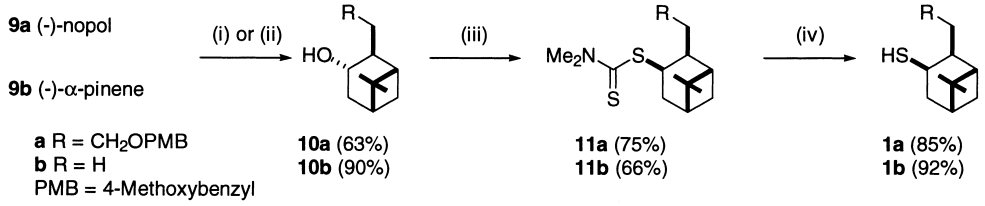


Scheme 2.

2. Results and discussion

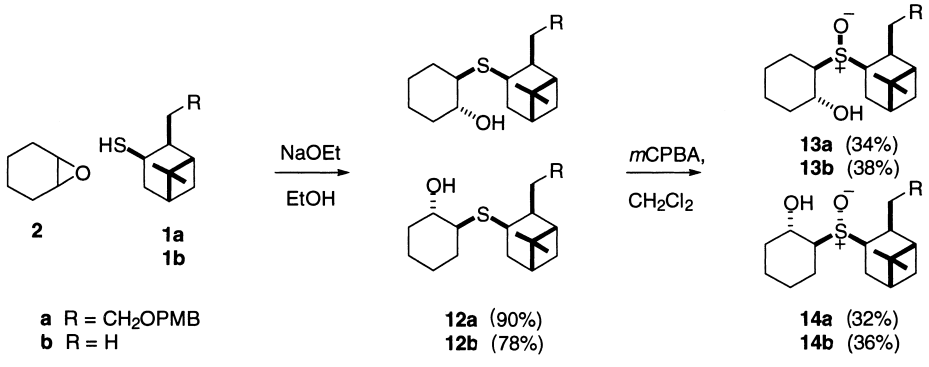
(−)-Nopol **9a** was converted to its 4-methoxybenzyl ether under standard conditions,[7] followed by hydroboration with borane–dimethyl sulfide complex to give the alcohol **10a** as a single diastereoisomer (Scheme 3).[8] Attempts to introduce sulfur functionality to **10a** via the corresponding sulfonate ester were complicated by loss of enantiomeric purity, elimination and rearrangement of the pinane skeleton. Success was achieved, however, via a modified Misunobu procedure as reported by Rollin.[9] Treatment of the alcohol **10a** with zinc *N*,*N*-dimethyldithiocarbamic acid in the presence of triphenylphosphine and diethylazodicarboxylate (DEAD) proceeded with inversion of configuration at C_3 to give the dithiocarbamate **11a** in 75% yield after chromatography. Reduction of **11a** with lithium aluminium

hydride gave (−)-4-methoxybenzyl-nopan-3(*R*)-thiol **1a** as a colourless oil (Scheme 3). Similarly, (−)-pinan-3(*R*)-thiol **1b** was obtained in three steps from (−)-α-pinene **10b** in 55% overall yield as a colourless oil.[10]



Scheme 3. *Reagents*: (i) (a) NaH, PMBCl, THF, Δ; (b) $BH_3 \cdot Me_2S$, THF, then H_2O_2, NaOH, EtOH, Δ; (ii) $BH_3 \cdot Me_2S$, THF, then H_2O_2, NaOH, EtOH, Δ; (iii) PPh_3, DEAD, $Zn(CS_2NMe_2)_2$, PhMe; (iv) $LiAlH_4$, Et_2O, Δ

The pinane thiolate anion, generated by treatment of **1b** with one equivalent of sodium ethoxide in ethanol, cleaved cyclohexene oxide to give two diastereomeric hydroxy sulfides **12** in the ratio of 1:1. These sulfides were chromatographically identical, and the ratio of the diastereoisomers was established by interpretation of the ^{1}H NMR spectrum of the mixture. The hydroxy directed oxidation of this mixture with one equivalent of *meta*-chloroperoxybenzoic acid (*m*CPBA) at 0°C gave a mixture of hydroxy sulfoxides (1*R*,2*R*,*S*s)-2-pinanylsulfinylcyclohexanol **13b** and the (1*S*,2*S*,*R*s) isomer **14b** which were readily separable by virtue of their relative chromatographic mobilities on silica. Similarly, the thiol **1a** was converted into the sulfoxides **13a** and **14a** (Scheme 4). Independent oxidation of the sulfoxides **13a** and **14a** to their corresponding sulfones with one equivalent of *m*CPBA gave two diastereomeric sulfones. These sulfones had different specific rotations and ^{1}H NMR characteristics, indicating that the sulfoxides have opposite absolute configurations at the cyclohexyl hydroxyl group.



Scheme 4.

The absolute configuration assigned to the sulfoxides **13a**, **13b**, **14a** and **14b** was confirmed by X-ray crystallography and ^{1}H NMR spectroscopy. The single crystal X-ray crystal structure of the sulfoxide **13b** is shown in Fig. 1, where the absolute configuration at sulfur is (*S*s). Thus, the absolute configuration at sulfur in the hydroxy sulfoxide **14b** was assigned as (*R*s), on the basis of the X-ray structure of **13b** and the known directing power of hydroxy groups in the *m*CPBA oxidation of sulfides.[11] Comparison of the ^{1}H NMR resonance of the C_3 proton in the pinane ring system enabled us to assign the absolute configuration of **13a** and **14a** to that shown in Scheme 4 (Table 1).

The thermolysis of sulfoxide **13a** in refluxing xylenes was complete after 1.5 h. The alkene **15** was isolated in 83% yield, which indicated that *syn*-elimination had occurred into the bicyclic moiety rather than the cyclohexane ring and therefore the hydroxysulfenic acid **16** must have been formed. However,

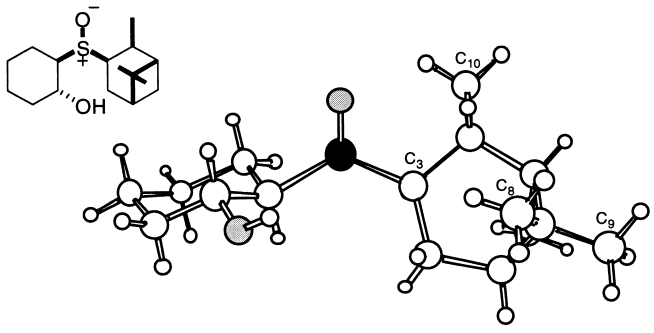
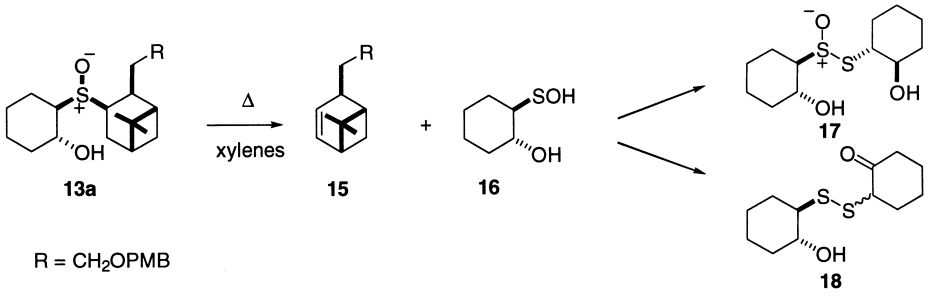


Figure 1. Chem. 3D representation of the X-ray crystal structure of sulfoxide **13b**

Table 1
Salient ^{1}H NMR ($CDCl_3$, 250 MHz) resonances of the sulfoxides **13a**, **13b**, **14** and **14b**

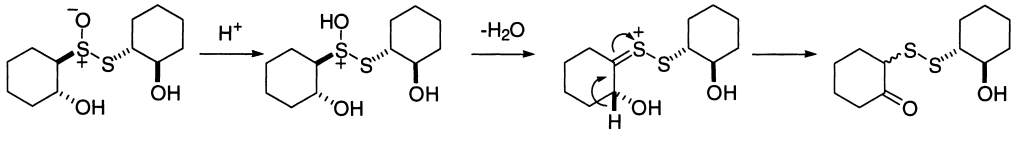
Sulfoxide	H_3	H_8	H_9	H_{10}
13a	3.21	1.17	1.01	-
14a	3.82	1.20	0.97	-
13b	3.21	1.20	0.96	1.42
14b	3.83	1.22	0.99	1.47

the expected dihydroxythiosulfinate **17** was not detected, instead the disulfide **18** was isolated in 32% yield (Scheme 5).



Scheme 5.

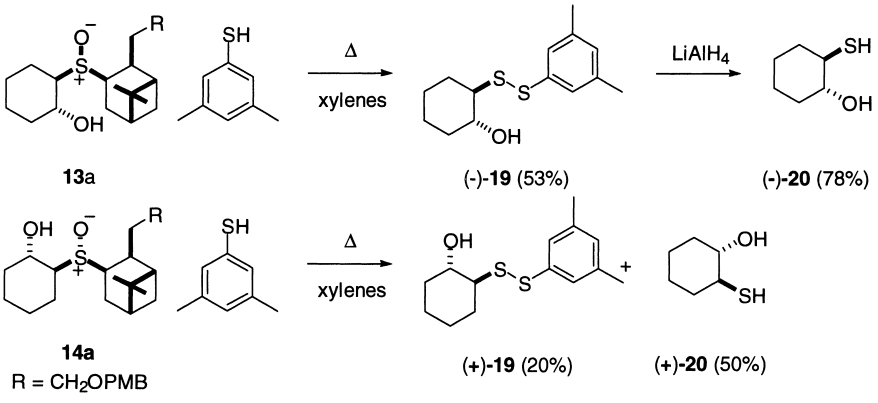
This initially surprising result may be rationalised in terms of an unforeseen Pummerer type rearrangement of the initially formed dihydroxythiosulfinate **17** under the acidic conditions of the thermolysis (Scheme 6).[12]



Scheme 6.

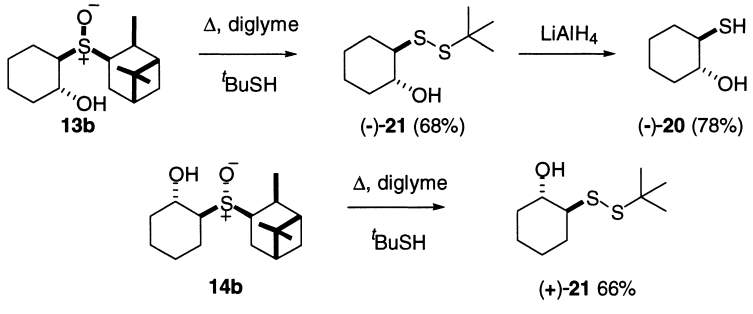
This problem was circumvented by the use of the sulfenic acid trapping agent 3,5-dimethylthiophenol.[13] Thermolysis of **13a** in the presence of 5 equivalents of 3,5-dimethylthiophenol

in xylenes for 1.5 h gave the mixed disulfide (−)-**19** in 53% isolated yield. Reduction of this disulfide (−)-**19** with lithium aluminium hydride in diethyl ether gave (−)-*trans*-1-mercaptocyclohexan-2-ol (−)-**20** (Scheme 7). The sulfoxide **14a** proved to be a lot more thermally stable than **13a**; however, thermolysis in refluxing xylenes for 18 h gave the mixed disulfide (+)-**19**, along with (+)-*trans*-1-mercaptocyclohexan-2-ol (+)-**20**. We attribute the direct formation of the hydroxythiol (+)-**20** to the reaction of excess 3,5-dimethylthiophenol with the expected mixed disulfide (+)-**19** under the reaction conditions.



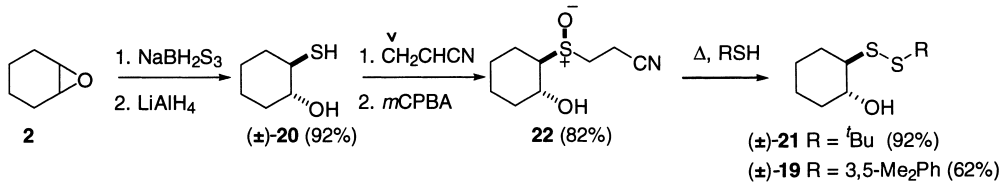
Scheme 7.

The thermolysis of the pinane thiol derived sulfoxides **13b** and **14b** proved to be more troublesome. After considerable experimentation, consistent results were realised with the use of *tert*-butylthiol as a sulfenic acid trapping agent. Treatment of sulfoxide **13b** with a boiling diglyme/*tert*-butylthiol mixture for 2 h gave the disulfide (−)-**21** in 68% yield, which was reduced with lithium aluminium hydride to give (−)-*trans*-1-mercaptocyclohexan-2-ol (−)-**20** (Scheme 8). Thermolysis of the sulfoxide **14b** in a boiling diglyme/*tert*-butylthiol mixture for 48 h gave the mixed disulfide (+)-**21**; no *trans*-1-mercaptocyclohexan-2-ol (+)-**20** was detected under these conditions.



Scheme 8.

In order to determine the enantiomeric excess of the hydroxythiols (−)- and (+)-**20** and their disulfide precursors racemic modifications of the compounds were prepared. Treatment of cyclohexene oxide **2** with sulfurated sodium borohydride, prepared in situ from sodium borohydride and sulfur, gave a pungent crude disulfide, which on reduction with lithium aluminium hydride provided racemic *trans*-1-mercaptocyclohexan-2-ol (±)-**20** in 92% yield.[14] Base catalysed conjugate addition of (±)-**20** to acrylonitrile in the presence of trimethylbenzylammonium hydroxide gave a sulfide, which was oxidised to the sulfoxide **22** by treatment with *m*CPBA. Thermolysis of **22** in the presence of either *tert*-butylthiol or 3,5-dimethylthiophenol gave the disulfides (±)-**21** and (±)-**19** in good yield (Scheme 9).



Scheme 9.

Table 2
Enantiomeric excesses for the disulfides **19** and **21**

Disulfide	$[\alpha]_D$	e.e. %
(±)-**19**	0	0
(-)-**19**	-53	>95
(+)-**19**	+52	>95
(±)-**21**	0	0
(-)-**21**	-37	>95
(+)-**21**	+7	18

Spectroscopic examination of the disulfides (−)- and (+)-**19** and (−)- and (+)-**21** by ^{1}H NMR techniques in conjunction with the chiral shift reagent *tris*-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III) ($Eu(hfc)_3$), examining the proton adjacent to sulfur on the cyclohexane ring, revealed the enantiomeric excesses for the disulfides as shown in Table 2. The disulfides (−)- and (+)-**19** and (−)-**21** had an enantiomeric excess >95% which was not compromised in the reduction with lithium aluminium hydride.[15] The low and somewhat disappointing enantiomeric excess for the disulfide (+)-**21** suggests that the optical purity is diminished under the harsh conditions of thermolysis, which involved long reaction times (48 h) and high temperatures (140°C).

3. Conclusions

In summary, we have found a short and valuable route to both enantiomers of *trans*-1-mercaptocyclohexan-2-ol. This involves the base catalysed opening of cyclohexene oxide with the homochiral thiol **1a**, oxidation with *m*CPBA, thermolysis of the sulfoxides in the presence of 3,5-dimethylthiophenol and reduction of the resulting disulfides to give enantiomerically pure (+)- and (−)-*trans*-1-mercaptocyclohexan-2-ol. This route is not viable for pinane thiol **1b** which only gives one enantiomer of **20** in enantiomerically pure form.

4. Experimental

Proton magnetic resonance spectra were recorded on a Bruker ACF-250 and on a Bruker WH-400 spectrometer supported by an Aspect 2000 data system. Mass spectra were obtained on a Kratos MS 25 instrument operating in E.I., C.I. mode and on a Kratos MS 80 in +ve FAB mode. Melting points were determined on a Kofler Hot Stage Micro Melting Point Apparatus and are uncorrected. Elemental microanalyses were carried out using a Perkin–Elmer 2400 Elemental Analyser CHN. Sulfur content was

determined by oxygen combustion followed by wet titration. Infrared spectra were recorded in the range 4000–600 cm^{-1} using a Perkin–Elmer 157G Grating Infrared Spectrophotometer. Optical rotations were measured on an Optical Activity AA-1000 polarimeter at room temperature. Thin layer chromatography (TLC) was performed on Merck 5554 60F silica gel coated aluminium plates and detection was effected with a solution of 10% ceric sulfate in 10% sulfuric acid, followed by heating the plates. Purification of compounds was achieved by medium pressure chromatography using Merck 9385 60 silica gel.

4.1. *(4-Methoxybenzyl)-nop-2-ene*

Sodium hydride (7.0 g, 50%, 146 mmol) was added to a stirred solution of (−)-nopol (22 g, 132 mmol) in dry THF (200 mL) under nitrogen and the resulting solution was stirred for 10 min. A solution of 4-methoxybenzyl chloride (19.5 g, 124 mmol) in dry THF (20 mL) was added dropwise under nitrogen and the solution was stirred for 20 min and then refluxed for 1.5 h. The solvent was removed under reduced pressure and the residue was dissolved in ether (350 mL), washed with water (3×150 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was chromatographed on silica eluting with ether/light petroleum (10%) to give the product (31.5 g, 88%) as a yellow oil; $[\alpha]_D$ −23 (*c* 5.2, $CHCl_3$); ν_{max} cm^{-1} ($CHCl_3$) 3030 (C=C), 2920 (OCH_3), 1620 (aromatic), 1070 (OCH_2Ar); ^1H NMR (250 MHz, $CDCl_3$) δ 7.28 (2H, d, *J*=9 Hz, Ar), 6.84 (2H, d, *J*=9 Hz, Ar), 5.26 (1H, m, CH), 4.42 (2H, s, C*H*$_2$Ar), 3.80 (3H, s, OC*H*$_3$), 3.45 (2H, t, *J*=7 Hz, C-11 protons), 2.38–1.97 (7H, m, aliphatic), 1.24 (3H, s, C*H*$_3$), 0.81 (3H, s, C*H*$_3$); (found: C, 79.5; H, 9.2; *m/z* 286. $C_{19}H_{26}O_2$ requires: C, 79.7; H, 9.2; M^+ 286).

4.2. *(3*S*)-(4-Methoxybenzyl)-nopan-3-ol* ***10a***

A solution of (4-methoxybenzyl)-nop-2-ene (31.1 g, 0.11 mol) in light petroleum (55 mL) was cooled to 0°C under nitrogen and treated cautiously with borane–dimethyl sulfide (35 mL, 2 M in THF), the solution was allowed to warm to room temperature and stirring was continued overnight. The reaction mixture was cooled to 0°C and ethanol (75 mL) was added dropwise followed by sodium hydroxide solution (35 mL, 2 M) and aqueous hydrogen peroxide (18 mL, 30% w/v). After addition was complete the reaction mixture was refluxed for 1 h and cooled to room temperature. The organic phase was separated and the aqueous layer was extracted with ether (2×150 mL). The combined organics were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified on silica eluting with ether/light petroleum (40%) to give **10a** (21.9 g, 71%) as a yellow oil; $[\alpha]_D$ 0 (*c* 5.25, $CHCl_3$); ν_{max} cm^{-1} (liquid film) 3420 (OH), 2920 (OCH_3), 1620 (aromatic), 1070 (CH_2OCH_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.26 (2H, d, *J*=9 Hz, Ar), 6.82 (2H, d, *J*=9 Hz, Ar), 4.44 (2H, *J*=11 Hz, CH_2Ar), 4.14 (1H, br s, C*H*OH), 3.78 (3H, s, OC*H*$_3$), 3.60 (2H, m, C11 protons), 3.39 (1H, d, *J*=3 Hz, CHO*H*), 1.98–1.50 (6H, m, aliphatic), 1.18 (3H, s, C*H*$_3$), 0.88 (3H, s, C*H*$_3$); (found: C, 74.9; H, 9.4; *m/z* 305. $C_{19}H_{28}O_3$ requires: C, 75.0; H, 9.3; M^+ 305).

4.3. *(3*R*)-(4-Methoxybenzyl)-nopan-3-*N,N*-dimethyldithiocarbamate* ***11a***

Zinc *N*,*N*-dimethyldithiocarbamate (7.24 g, 23.7 mmol) was added to a stirred solution of triphenylphosphine (33.0 g, 126 mmol) and the alcohol **10a** (12.0 g, 39.5 mmol) in dry toluene (50 mL). The reaction flask was protected from light and cooled to 0°C under nitrogen. Diethylazodicarboxylate (19 mL, 126 mmol) was carefully added and the suspension dissolved to give a light brown solution which was stirred overnight and loaded directly onto a silica gel column eluting with first light petroleum (500

mL) followed by ethyl acetate/light petroleum (10%) to give the crude product **11a** as a pink oil (12.1 g, 75%). A sample was re-chromatographed on silica eluting with ether/light petroleum (5–20%) for characterisation; $[\alpha]_D$ +52 (*c* 1.00, $CHCl_3$); ν_{max} cm^{-1} ($CHCl_3$) 1612 (aromatic), 1140, 1090 (C=S); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, d, *J*=9 Hz, Ar), 6.84 (2H, d, *J*=9 Hz, Ar), 4.73 (1H, dt, *J*=10 and 10 Hz, C*H*S), 4.39 (2H, *J*=11 Hz, CH_2Ar), 3.56 (3H, s, OCH_3), 3.50 (3H, s, NCH_3), 3.38 (2H, m, OCH_2CH), 3.36 (3H, s, NCH_3), 2.76–1.49 (9H, m, aliphatic), 1.17 (3H, s, CH_3), 0.97 (3H, s, CH_3); (found: C, 64.8; H, 8.3; N, 3.5; S, 15.6; *m/z* 408. $C_{22}H_{33}O_2S_2N$ requires: C, 64.8; H, 8.2; N, 3.4, S; 15.7; M^+ 408).

*4.4. (3*R*)-(4-Methoxybenzyl)-nopan-3-thiol **1a***

Lithium aluminium hydride (6 g, 0.16 mol) was carefully added to a stirred solution of the dithiocarbamate **11a** (12 g, 29 mmol) in dry ether (250 mL) and the resulting solution was heated at reflux overnight under nitrogen. The solution was cooled to 0°C and lithium aluminium hydride was quenched with careful addition of wet ether followed by dropwise addition of water. The reaction mixture was filtered through Celite and the filtrate was dried over $MgSO_4$. Removal of solvent under reduced pressure gave the crude product which was chromatographed on silica eluting with ethyl acetate/light petroleum (5%) to give the product **1a** as a pungent colourless oil (8.06 g, 85%); $[\alpha]_D$ −11 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, d, *J*=9 Hz, Ar), 6.84 (2H, d, *J*=9 Hz, Ar), 4.42 (2H, s, CH_2Ar), 3.80 (3H, s, OCH_3), 3.45 (2H, m, OCH_2CH), 2.45–1.41 (9H, m, aliphatics), 1.17 (3H, s, CH_3), 0.95 (3H, s, CH_3); (found C, 71.2; H, 8.7; S, 10.2; *m/z* 320. $C_{19}H_{28}O_2S$ requires: C, 71.2; H, 8.8; S, 10.0; M^+ 320).

*4.5. (1*R*,2*R*,1′*R*,2′*S*,3′*R*)*-trans-*2-Pinanylthiocyclohexanol and (1*S*,2*S*,1′*R*,2′*S*,3′*R*)*-trans-*2-pinanylthiocyclohexanol **12b***

Pinane thiol (12 g, 70.6 mmol) was added to a stirred solution of sodium (1.62 g, 70.5 mmol) in absolute ethanol (400 mL) under argon, and stirring was continued for 10 min. Cyclohexene oxide (7.14 mL, 70.6 mmol) was added and the solution was stirred at room temperature overnight (18 h). The reaction mixture was diluted with ether (10 mL) and washed with water (3×50 mL). The organic layer was separated and dried ($MgSO_4$). Removal of solvent under reduced pressure gave the crude product which was chromatographed on silica eluting with ether/light petroleum (5%) to give the products **12b** as a mixture of diastereoisomers (14.66 g, 78%); ν_{max} cm^{-1} (thin film) 3456 (OH), 2981 (C-H); ^1H NMR (250 MHz, $CDCl_3$) δ 3.66 (1H, dt, *J*=10 and 10 Hz, C*H*S), 3.63 (1H, dt, *J*=10 and 10 Hz, C*H′*S), 3.30 (2H, m, C*H*OH and C*H′*OH), 2.63–1.26 (16H, m, aliphatics), 1.21 (3H, d, *J*=8 Hz, CHCH_3), 1.18 (6H, s, CH_3 and CH'_3), 1.18 (3H, d, *J*=8 Hz, CHCH'_3), 1.10 (3H, s, CH_3), 1.09 (3H, s, CH'_3) (H and H′ denote different isomers); (found: C, 71.8; H, 10.5; S, 12.1; *m/z* 268. $C_{16}H_{28}O_1S_1$ requires: C, 71.6; H, 10.5; S, 11.9; M^+ 268).

*4.6. (−)-(1*R*,2*R*,*S*s,1′*R*,2′*S*,3′*R*)*-trans-*2-Pinanylsulfinylcyclohexanol **13b** and (+)-(1*S*,2*S*,*R*s,1′*R*,2′*S*,3′*R*)*-trans-*2-pinanylsulfinylcyclohexanol **14b***

meta-Chloroperoxybenzoic acid (10.23 g, 58 mmol) was added to a stirred solution of hydroxy sulfides **12b** (14.4 g, 53.7 mmol) in dry dichloromethane (200 mL) at 0°C. The solution was stirred for 30 min and TLC showed the reaction was complete. Anhydrous potassium fluoride (9.52 g, 3 equiv.) was added followed by Celite (5 g). The solution was filtered and reduced to give the crude product which was chromatographed on silica eluting with ethyl acetate/light petroleum first (30%), followed by (50%) to

give the product **13b** as a white crystalline solid (5.87 g, 40%); mp 96°C (ethyl acetate/light petroleum); $[\alpha]_D$ −100 (*c* 0.87, $CHCl_3$); ν_{max} cm^{-1} (thin film) 3380 (OH), 1065 (S=O); ^1H NMR (250 MHz, $CDCl_3$) δ 4.10 (1H, ddd, *J*=10, 10 and 4 Hz, C*H*OH), 3.81 (1H, dt, *J*=10 and 10 Hz, C*H*SO), 2.84 (1H, m, SOC*H*), 2.74 (1H, ddq, *J*=10, 8 and 4 Hz, C*H*CH_3), 1.48 (3H, d, *J*=8 Hz, CHC*H*$_3$), 1.20 (3H, s, C*H*$_3$), 1.00 (3H, s, C*H*$_3$); (found: C, 67.5; H, 9.8; S, 11.5; *m/z* 285. $C_{16}H_{28}O_2S_1$ requires: C, 67.6; H, 9.9; S, 11.3; M^+ 285). Followed by the product **14b** as a white crystalline solid (5.34 g, 36%); mp 166°C (ethyl acetate/light petroleum); $[\alpha]_D$ +29 (*c* 0.84, $CHCl_3$); ν_{max} cm^{-1} (thin film) 3380 (OH), 1065 (S=O); ^1H NMR (250 MHz, $CDCl_3$) δ 4.08 (1H, ddd, *J*=10, 10 and 4 Hz, C*H*OH), 3.22 (1H, dt, *J*=9 and 9 Hz, C*H*SO), 2.85 (1H, ddd, *J*=12, 9 and 4 Hz, C*H*SO), 2.74 (1H, m, C*H*CH_3), 2.33–1.54 (11H, m, ring protons), 1.47 (3H, d, *J*=8 Hz, CHC*H*$_3$), 1.22 (3H, s, C*H*$_3$), 0.99 (3H, s, C*H*$_3$); (found: C, 67.7; H, 9.8; S, 11.4; *m/z* 285. $C_{16}H_{28}O_2S_1$ requires: C, 67.6; H, 9.9; S, 11.3; M^+ 285).

*4.7. (1*R,*2*R,*1′*R,*2′*S,*3′*R*)*-*trans*-*2-(4-Methoxybenzyl)-nopylthiocyclohexanol and (1*S,*2*S,*1′*R,*2′*S,*3′*R*)*-*trans*-*2-4-methoxybenzyl)-nopylthiocyclohexanol **12a***

4-Methoxybenzylnopan-3(*R*)-thiol (1 g; 3.12 mmol) was added to a stirred solution of sodium ethoxide (67 mg, in 20 mL of absolute ethanol), and stirring was continued for 15 min. Cyclohexene oxide (0.32 mL, 3.12 mmol) was added and the reaction mixture was stirred for 2.5 h and refluxed for 0.5 h. The solution was diluted with ether (20 mL), washed with water (3×10 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude product which was chromatographed on silica eluting with ether/light petroleum (15%) to give a mixture of two diastereoisomeric hydroxy sulfides **12a** as a colourless oil (1.19 g, 91%). High performance liquid chromatography on a small sample gave a 90% separation of the diastereoisomers; first diastereoisomer: ν_{max} cm^{-1} (liquid film) 3456 and 2981 (OH), 2860 (OMe), 1610 (aromatic); ^1H NMR (250 MHz, $CDCl_3$) δ 7.28 (2H, d, *J*=9 Hz, Ar), 6.84 (2H, d, *J*=9 Hz, Ar), 4,42 (2H, s, C*H*$_2$Ar), 3.90 (3H, s, OC*H*$_3$), 3.64 (1H, dt, *J*=10 and 10 Hz, H-3), 3.43 (2H, t, *J*=7 Hz, OC*H*$_2$), 3.28 (1H, dt, *J*=9.5 and 4 Hz, C*H*S), 3.03 (1H, br s, C*H*OH), 2.52–1.21 (17H, m, aliphatic), 1.17 (3H, s, C*H*$_3$), 0.95 (3H, s, C*H*$_3$); *m/z* 418 (M^+); second diastereoisomer: ν_{max} cm^{-1} 3456 and 2981 (OH), 2860 (OMe), 1610 (aromatic); ^1H NMR (250 MHz, $CDCl_3$) δ 7.29 (2H, d, *J*=9 Hz, Ar), 6.85 (2H, d, *J*=9 Hz, Ar), 4.42 (2H, s, C*H*$_2$Ar), 3.81 (3H, s, OC*H*$_3$), 3.63 (1H, dt, *J*=10 and 10 Hz), 3.45 (2H, m, OC*H*$_2$), 3.25 (1H, br s, O*H*), 3.03 (1H, ddd, *J*=11, 9 and 4 Hz, C*H*S), 2.49–1.23 (17H, m, aliphatic), 1.21 (3H, s, C*H*$_3$), 0.94 (3H, s, C*H*$_3$); *m/z* 418 (M^+).

*4.8. (−)-(1*R,*2*R,S*s,1′*R,*2′*S,*3′*R*)*-*trans*-*2-(4-Methoxybenzyl)-nopylsulfinylcyclohexanol **13a** and (+)-(1*S,*2*S,R*s,1′*R,*2′*S,*3′*R*)*-*trans*-*2-(4-methoxybenzyl)-nopylsulfinylcyclohexanol **14a***

meta-Chloroperoxybenzoic acid (451 mg, 2.62 mmol) was added to a stirred solution of sulfides **12a** (1.093 g, 2.62 mmol) in dichloromethane (20 mL) at 0°C. The solution was stirred for 20 min after which time the reaction was complete. Na_2SO_3 solution was added, and the organic layer was separated and washed with saturated $NaHCO_3$ solution (3×30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was chromatographed on silica eluting with ethyl acetate/light petroleum (40%) to give the product **13a** as a colourless viscous oil (388 mg, 34%); $[\alpha]_D$ −95 (*c* 0.104, $CHCl_3$); ν_{max} cm^{-1} (liquid film) 3645, 3450 (OH), 1607 (aromatic), 1060 (S=O); ^1H NMR (250 MHz, $CDCl_3$) δ 7.32 (2H, d, *J*=9 Hz, Ar), 6.88 (2H, d, *J*=9 Hz, Ar), 5.39 (1H, br s, O*H*), 4.42 (2H, s, C*H*$_2$Ar), 4.05 (1H, m, C*H*OH), 3.81 (1H, s, OC*H*$_3$), 3.50 (2H, m, OC*H*$_2$), 3.21 (1H, dt, *J*=9 and 9 Hz, H-3), 1.17 (3H, s, C*H*$_3$), 1.01 (3H, s, C*H*$_3$); (found: C, 67.8; H, 8.7; S, 7.2; *m/z* 424. $C_{25}H_{38}SO_4 \cdot 0.5H_2O$ requires: C, 67.7; H, 8.9; S, 7.2; M^+ 424). Further elution with ethyl acetate/light petroleum (70%) gave

product **14a** as a white crystalline solid (364 mg, 32%); $[\alpha]_D$ +15 (*c* 0.100, $CHCl_3$); ν_{max} cm^{-1} ($CHCl_3$) 3645, 3450 (OH), 1608 (aromatic), 1050 (S=O); ^1H NMR (250 mHz, $CDCl_3$) δ 7.29 (2H, d, *J*=9 Hz, Ar), 6.85 (2H, d, Ar), 4.42 (2H, s, C*H*$_2$Ar), 4.09 (1H, m, C*H*OH), 3.82 (1H, dt, 9.5 and 9.5 Hz, H-3), 3.80 (3H, s, OC*H*$_3$), 3.52 (2H, m, OC*H*$_2$), 2.88 (1H, ddd, *J*=13, 9 and 4 Hz, cyclohexyl SOC*H*), 2.75–1.24 (17H, m, aliphatics), 1.19 (3H, s, C*H*$_3$), 0.97 (3H, s, C*H*$_3$); (found: C, 68.7; H, 8.9; S, 7.4; *m/z* 424. $C_{25}H_{38}SO_4$ requires: C, 69.1; H, 8.8; S, 7.4; M^+ 424).

*4.9. (−)-(1*R,*2*R,*1′*R,*2′*S,*3′*R*)*-*trans*-*2-(4-Methoxybenzyl)-nopylsulfonylcyclohexanol*

meta-Chloroperbenzoic acid (32 mg, 0.18 mmol) was added to a stirred solution of the hydroxy sulfoxide **10a** (74 mg, 0.17 mmol) in dichloromethane (2 mL) at 0°C. After 5 min the reaction mixture was washed with $NaHCO_3$ solution (3×10 mL), and the organic layer was separated and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude product which was purified on silica eluting with ethyl acetate/light petroleum (30%) to give the product (67 mg, 83%); $[\alpha]_D$ −20 (*c* 0.88; $CHCl_3$); ν_{max} cm^{-1} 3614 and 3512 (OH), 2871 (OMe), 1614 (aromatic), 1126, 1317 (SO_2); ^1H NMR ($CDCl_3$) (250 mHz, $CDCl_3$) δ 7.29 (2H, d, *J*=9 Hz, aromatic), 6.85 (2H, d, *J*=9 Hz, aromatic), 4.42 (2H, *J*=12 Hz, C*H*$_2$Ar), 4.05 (1H, m, C*H*OH), 3.94 (1H, dt, *J*=9.5 and 9.5 Hz, H-3), 3.81 (3H, s, OC*H*$_3$), 3.71 (1H, d, *J*=3 Hz, O*H*), 3.47 (2H, m, OC*H*$_2$), 3.11 (1H, ddd, *J*=12, 9 and 4 Hz, SO_2C*H*), 1.19 (3H, s, C*H*$_3$), 1.07 (3H, s, C*H*$_3$); *m/z* 450 (MH^+).

*4.10. (+)-(1*S,*2*S,*1′*R,*2′*S,*3′*R*)*-*trans*-*2-(4-Methoxybenzyl)-nopylsulfonylcyclohexanol*

meta-Chloroperbenzoic acid (32 mg, 0.18 mmol) was added to a stirred solution of hydroxy sulfoxide **13a** (71 mg, 0.164 mmol) in dichloromethane (2 mL) at 0°C. The solution was stirred for 5 min and diluted with diethyl ether (20 mL). The reaction mixture was washed with $NaHCO_3$ solution (3×10 mL), and the organic layer was separated and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude product which was purified on silica eluting with ethyl acetate/light petroleum (30%) to give the product (35 mg, 46%); $[\alpha]_D$ +19 (*c* 0.151, $CHCl_3$); ν_{max} cm^{-1} 3615 (OH), 2871 (OMe), 1614 (aromatic), 1328, 1143 and 1126 (SO_2); ^1H NMR (250 mHz, $CDCl_3$) δ 7.25 (2H, d, *J*=10 Hz, aromatic), 6.81 (2H, d, *J*=10 Hz, aromatic), 4.38 (2H, *J*=12 Hz, C*H*$_2$Ar), 4.01 (1H, m, C*H*OH), 3.89 (1H, dt, *J*=10 and 10 Hz, H-3), 3.85 (3H, s, OC*H*$_3$), 3.45 (2H, m, OC*H*$_2$), 3.06 (1H, ddd, 14, 10 and 4 Hz, SO_2C*H*), 1.14 (3H, s, C*H*$_3$), 1.02 (3H, s, C*H*$_3$); *m/z* 450 (MH^+).

*4.11. (−)-(1*R,*2*R)-trans-*2-(3,5-Dimethylphenyl)-dithiocyclohexanol **19***

3,5-Dimethylthiophenol (831 mg, 6.01 mmol) was added to a stirred solution of the hydroxy sulfoxide **13a** (522 mg, 1.20 mmol) in dry xylenes (5 mL). The resulting solution was heated at 140–150°C for 2 h and then allowed to cool to ambient temperature. The solvent was removed under reduced pressure and the crude product was purified on silica eluting with ether/light petroleum (20%) to give the product (−)-**19** (167 mg, 53%); $[\alpha]_D$ −53 (*c* 0.415; $CHCl_3$). All other spectral properties as for racemic modification.

*4.12. (1*R,*2*R)-*(−)*-trans-*1-Mercaptocyclohexan-2-ol **20***

Lithium aluminium hydride (65 mg, 1.71 mmol) was added to a stirred solution of disulfide (−)-**19** (154 mg, 0.58 mmol) in dry ether (5 mL). The solution was stirred at room temperature for 1 h. Excess lithium aluminium hydride was quenched with first 'wet' ether followed by careful dropwise addition of

water. 2 M HCl (3 mL) was added and the ethereal layer was decanted off and dried ($MgSO_4$). The crude product was chromatographed on silica eluting with light petroleum followed by ether/light petroleum (40%) to give the product (−)-**20** (38 mg, 50%); $[\alpha]_D$ −42 (*c* 0.68, $CHCl_3$). All other spectral properties as for racemic modification.

*4.13. (1*S*,2*S*)-(+)*-trans-*2-(3,5-Dimethylphenyl)-dithiocyclohexanol **19** and (1*S*,2*S*)-(+)*-trans-*1-mercaptocyclohexan-2-ol **20***

A solution of the sulfoxide **14b** (1.18 g, 2.73 mmol) and 3,5-dimethylthiophenol (1.89 g, 13.6 mmol) in xylenes (20 mL) was heated at reflux overnight under nitrogen. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure to give the crude product which was purified on silica eluting with first ether/light petroleum (10%) followed by ether/light petroleum (20%) to give product (+)-**19** (151 mg, 21%); $[\alpha]_D$ +52 (*c* 1.67, $CHCl_3$). All other spectral properties as for racemic modification. Followed by the product (+)-**20** (179 mg, 50%); $[\alpha]_D$ +39 (*c* 1.43, $CHCl_3$). All other spectral properties as for racemic modification.

*4.14. (−)-(1*R*,2*R*)-*trans-*2-*tert-*Butyldithiocyclohexanol **21***

To a boiling mixture of diglyme:*tert*-butylthiol (4:1, v/v) (10 mL) under argon was added the sulfoxide **13b** (200 mg, 0.73 mmol). The solution was refluxed for 12 h and TLC showed no starting sulfoxide to be present. The reaction mixture was diluted with ether (20 mL) and washed with aqueous sodium hydroxide solution (3×15 mL, 2 M) and water (2×15 mL). The organic layer was dried ($MgSO_4$) and reduced under reduced pressure to give the crude product which was chromatographed on silica eluting with ether/light petroleum (20%) to give the product (−)-**21** (109 mg, 68%) as a white solid; mp 30–32°C (ether); $[\alpha]_D$ −37 (*c* 0.82, $CHCl_3$). All other spectral properties as for racemic modification.

*4.15. (1*R*,2*R*)-(−)*-trans-*1-Mercaptocyclohexan-2-ol **20***

Lithium aluminium hydride (51 mg, 1.36 mmol) was added to a stirred solution of disulfide **23** (100 mg, 0.45 mmol) in dry ether (5 mL). The solution was stirred at room temperature for 3 h. Excess lithium aluminium hydride was destroyed with first wet ether followed by careful dropwise addition of water. Dilute hydrochloric acid (3 mL, 2 M) was added, followed by vigorous stirring, and the ether layer was decanted off and dried ($MgSO_4$). The crude product was chromatographed on silica eluting with ether/light petroleum (20%) to give the product (−)-**20** (38 mg, 63%), as a colourless oil; $[\alpha]_D$ −40 (*c* 0.56, $CHCl_3$). All other spectral properties as for racemic modification.

*4.16. (1*S*,2*S*)-(+)*-trans-*2-*tert-*Butyldithiocyclohexanol **21***

To a boiling mixture of diglyme:*tert*-butylthiol (4:1, v/v) (10 mL) under argon was added the sulfoxide **11b** (200 mg, 0.73 mmol). The solution was refluxed for 48 h and TLC showed no starting sulfoxide to be present. The reaction mixture was diluted with ether (20 mL) and washed with aqueous sodium hydroxide solution (3×15 mL, 2 M) and water (2×15 mL). The organic layer was dried ($MgSO_4$) and reduced to give the crude product which was chromatographed on silica eluting with ether/light petroleum to give the product **24** (106 mg, 66%) as a white solid; mp 31–32°C (ether/light petroleum); $[\alpha]_D$ +7 (*c* 0.97, $CHCl_3$). All other spectral properties as for racemic modification.

4.17. (±)-trans-1-Mercaptocyclohexan-2-ol **20**

Dry tetrahydrofuran (300 mL) was added rapidly to an ice cooled mixture of sulfur (35.52 g, 1.11 mmol) and sodium borohydride (14.06 g, 0.38 mmol) under argon. After evolution of hydrogen had ceased (ca. 30 min), cyclohexene oxide (18.5 g, 0.19 mmol) was added and the mixture was heated at reflux for 14 h, after which no epoxide was detected by TLC. The solvent was removed under reduced pressure, and the residue separated between NaOH (200 mL, 2 M) and dichloromethane (200 mL). Re-extraction of the aqueous phase with dichloromethane (3×150 mL), followed by drying of the combined organics ($MgSO_4$) and removal of the solvent, gave a very pungent crude disulfide (25.6 g) as a white solid.

A solution of the disulfide (25.6 g) in tetrahydrofuran (200 mL) was added dropwise with stirring to lithium aluminium hydride (6.22 g, 86 mmol) in dry ether (200 mL). The reaction was stirred at room temperature for 3 h and the excess lithium aluminium hydride was quenched with wet ether followed by careful dropwise addition of water. The ether was decanted off and the white precipitate was dissolved in dilute hydrochloric acid (250 mL, 2 M). Extraction of the aqueous phase with ether (4×200 mL) and drying of the combined organics afforded the product (±)-**20** (24.25 g) as a colourless oil which was purified by vacuum distillation at 56–60°C, 0.3 mmHg (22.3 g, 90%); ν_{max} cm^{-1} (thin film) 3480 (OH); ^1H NMR (250 mHz, $CDCl_3$) δ 3.21 (1H, dddd, *J*=10, 10, 4 and 2 Hz, C*H*OH), 2.76 (1H, bd, *J*=2 Hz, O*H*), 2.52 (1H, dddd, *J*=12, 10, 7 and 4 Hz, C*H*SH), 1.43 (1H, d, *J*=10 Hz, S*H*); (found: C, 54.6; H, 9.1; S, 24.3; *m/z* 132. $C_6H_{12}O_1S_1$ requires: C, 54.5; H, 9.1; S, 24.2; M^+ 132).

4.18. (±)-trans-2-(2-Cyanoethylthio)cyclohexanol

Trimethylbenzyl ammonium hydroxide B (0.14 mL, 40% solution in methanol) was added to a stirred solution of racemic hydroxythiol (±)-**20** (500 mg, 3.82 mmol) in dry tetrahydrofuran (10 mL) at −78°C. The solution was stirred for 15 min and acrylonitrile (0.28 mL, 4.2 mmol) was added. After 20 min the reaction was allowed to warm up to room temperature over 45 min. The solvent was removed under reduced pressure leaving a yellow oil which was separated between ether (20 mL) and water (20 mL). The ether layer was washed with a further 20 mL of water before being dried ($MgSO_4$) and reduced. Purification by chromatography on silica eluting with ethyl acetate/light petroleum (30%) gave the product (629 mg, 87%) as a colourless oil which was crystallised from ethyl acetate/light petroleum; mp 51–52°C (ethyl acetate/light petroleum); ν_{max} cm^{-1} (thin film) 3540 (OH), 2250 (CN); ^1H NMR (250 mHz, $CDCl_3$) δ 3.35 (1H, m, C*H*OH), 2.90 (2H, m, SCH_2), 2.69 (1H, br d, *J*=7 Hz, CHO*H*), 2.66 (2H, dd, *J*=9 and 7 Hz, CH_2CN, 2.47 (1H, m, C*H*S); (found: C, 58.0; H, 8.1; N, 7.5; S, 17.1; *m/z* 185. $C_9H_{15}O_1N_1S_1$ requires: C, 58.3; H, 8.2; N, 7.6; S, 17.3; M^+ 185).

4.19. (±)-trans-2-(2-Cyanoethylsulfinyl)cyclohexanol **22**

meta-Chloroperbenzoic acid (0.511 g, 1.1 equiv.) was added to a stirred solution of the sulfide prepared above (0.5 g, 2.7 mmol) in dry dichloromethane (10 mL) at 0°C. The solution was stirred for a further 2 h. The reaction mixture was diluted with dichloromethane (15 mL) and potassium fluoride (173 mg) and stirring was continued for 1.5 h to allow precipitation of 3-chlorobenzoic acid. The reaction mixture was filtered through Celite and the solvent removed under reduced pressure. The crude product was chromatographed on silica eluting with methanol/dichloromethane (5%) to give the product **22** (443 mg, 82%) as a white solid which was recrystallised from ethyl acetate/light petroleum; mp 88–90°C; ν_{max} cm^{-1} (thin film) 3430 (OH), 2250 (CN), 1070 (S=O); ^1H NMR (250 mHz, $CDCl_3$) δ 4.10 (1H, ddd,

J=10, 10 and 5 Hz, C*H*OH), 3.52 (1H, br s, O*H*), 3.14 (2H, dt, *J*=7 and 2 Hz, SOCH_2), 2.92 (2H, dt, *J*=7 and 2 Hz, CH_2CN), 2.78 (1H, ddd, *J*=12, 10 and 4 Hz, C*H*SO), 2.16–1.15 (8H, m, aliphatics); (found: C, 53.7; H, 7.5; N, 6.9; S, 16.1; *m/z* 201. $C_9H_{15}N_1O_2S_1$ requires: C, 53.7; H, 7.5; S, 16.1; M^+ 201).

4.20. (±)-trans-2-tert-Butyldithiocyclohexanol **21**

To a boiling mixture of diglyme:*tert*-butylthiol (4:1, v/v) (10 mL) was added the cyanosulfoxide **22** (200 mg, 1 mmol), and the mixture was refluxed for 45 min. After cooling to room temperature the reaction mixture was diluted with ether (50 mL). The organic phase was washed with sodium hydroxide solution (3×50 mL, 2 M), water (2×50 mL), dried ($MgSO_4$) and reduced to give the crude product which was purified by column chromatography on silica, eluting with ether/light petroleum (20%) to afford the product (±)-**21** (202 mg, 92%) as a white solid, which was recrystallised from ether; mp 29–31°C; ν_{max} cm^{-1} ($CHCl_3$) 3480 (OH); ^{1}H NMR (250 mHz, $CDCl_3$) δ 3.45 (1H, ddd, *J*=10, 10 and 5 Hz, C*H*OH), 3.52 (1H, bs, O*H*), 2.5 (1H, ddd, *J*=12, 10 and 4 Hz, C*H*S), 1.3 (9H, s, ^{t}Bu), 1.98–1.05 (8H, m, ring protons); (found: C, 54.6; H, 9.3; S, 28.3; *m/z* 220. $C_{10}H_{20}O_1S_2$ requires: C, 54.5; H, 9.2; S, 29.1; M^+ 220).

4.21. (±)-trans-3,5-Dimethylphenyldithiocyclohexanol **19**

3,5-Dimethylthiophenol (1.16 g, 8.41 mmol) was added to a stirred solution of cyanosulfoxide **22** (338 mg, 1.68 mmol) in dry xylenes (10 mL), and the reaction mixture was heated at 110°C for 0.5 h under nitrogen. The reaction mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure to give the crude disulfide which was purified on silica eluting with ether/light petroleum (30%) to give the product (±)-**19** (281 mg, 62%); ^{1}H NMR (250 mHz, $CDCl_3$) δ 7.19 (2H, s, aromatic), 6.85 (1H, s, aromatic), 3.48 (1H, m, C*H*OH), 2.59 (1H, ddd, *J*=12, 9 and 4 Hz, C*H*S), 2.43 (1H, d, *J*=2 Hz, O*H*), 2.31 (6H, s, ArCH_3); (found: C, 62.9; H, 7.6; S, 23.6; *m/z* 268. $C_{14}H_{20}S_2O$ requires: C, 62.6; H, 7.5; S, 23.9; M^+ 268).

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