Synthesis, Separation and Absolute Configuration Assignment to Enantiomers of 1,3-Benzodithiole 1-Oxide and 2-Alkyl-1,3-Benzodithiole 1-Oxides

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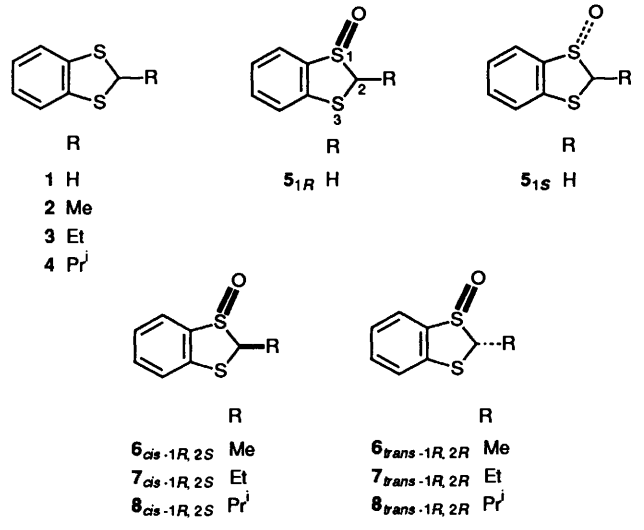
1,3-Benzodithiole 1-oxide, **5**, has been resolved into enantiomers using chiral stationary phase high performance liquid chromatography. Alkylation of an excess (25%) of the late eluting (+)-(1*R*) enantiomer of the sulfoxide **5** under basic conditions yielded both *cis* and trans isomers of 2-methyl ($\mathbf{6}_{cis\text{-}1R,2S}$, $\mathbf{6}_{trans\text{-}1R,2R}$), 2-ethyl ($\mathbf{7}_{cis\text{-}1R,2S}$, $\mathbf{7}_{trans\text{-}1R,2R}$) and 2-isopropyl ($\mathbf{8}_{cis\text{-}1R,2S}$, $\mathbf{8}_{trans\text{-}1R,2R}$)-benzodithiole 1-oxide (25% e.e.) and allowed a stereochemical correlation of absolute configuration between the sulfoxides **5**–**8**.

Treatment of racemic 1,3-benzodithiole 1-oxide ($\mathbf{5}_{1S}/\mathbf{5}_{1R}$) with potassium bis(trimethylsilyl)amide and (S)-(+)-1-iodo-2-methylbutane yielded four diastereoisomers of 2-(2′-methylbutyl)-1,3-benzodithiole 1-oxide ($\mathbf{9}_{cis\text{-}1R,2S,2'S}$, $\mathbf{9}_{cis\text{-}1S,2R,2'S}$, $\mathbf{9}_{trans\text{-}1S,2S,2'S}$, $\mathbf{9}_{trans\text{-}1R,2R,2'S}$) which were separated by chiral stationary phase HPLC (CSP-HPLC). The most strongly retained diastereoisomer was analysed by X-ray crystallography and was assigned the (1*S*:2*S*:2′*S*) absolute configuration. Further alkylation of $\mathbf{9}_{trans\text{-}1S,2S,2'S}$ under similar conditions yielded 2-(2′*S*-methylbutyl)-2-(2″*S*-methylbutyl)-1,3-benzodithiole 1-oxide **10** of (1*S*,2′*S*,2″*S*) configuration exclusively. The same stereoisomer of the sulfoxide **10** was also obtained by dialkylation of the early eluting (−)-enantiomer of 1,3-benzodithiole 1-oxide ($\mathbf{5}_{1S}$) using (+)-1-iodo-2-methylbutane, thus enabling the unequivocal establishment of the absolute configurations of the enantiomers of 1,3-benzodithiole 1-oxides listed in Table 1. A comparison of circular dichroism (CD) spectra for sulfoxides **5**–**9** indicates that this method may also be used to correlate absolute configurations of 2-alkyl substituted 1,3-benzodithiole 1-oxides.

1,3-Benzodithiole **1** and 2-alkyl-1,3-benzodithioles **2**–**4** in the presence of strong bases yield carbanions which are valuable acyl carbanion equivalents and can undergo both mono- and di-alkylation reactions.[1] Similarly, the 1-oxide derivatives of the corresponding 1,3-benzodithioles **5**–**8** also form stable carbanions which react with electrophiles. The presence of a chiral sulfoxide group in compounds **5**–**8** could, in principle, be used in asymmetric synthesis.

As part of a continuing programme to investigate the ability of enzyme systems to stereodifferentiate between prochiral lone pairs on a sulfur atom and between prochiral sulfur atoms on a carbon atom,[2,3] studies on the enzyme-catalysed oxidations of 1,3-benzodithioles **1**–**4** are currently in progress. A necessary prelude to the interpretation of data produced from enzymatic oxidation of the 1,3-disulfides[4] **1**–**4** is the unequivocal assignment of the absolute configurations of the resulting monosulfoxides **5**–**8**. The latter compounds were considered to be more suitable than the corresponding 1,3-dithiane 1-oxides[2] and 1,3-dithiolane 1-oxides[3] for enzyme stereoselectivity studies. The 1,3-benzodithiole 1-oxides **5**–**8** thus have the following advantages: (i) the aryl ring provides a suitable chromophore for UV detection of small quantities during HPLC analysis; (ii) these bicyclic compounds behave as alkyl aryl sulfoxides whose enantiomeric composition can readily be determined by CSP-HPLC analysis; (iii) in contrast with the 1,3-dithiolane 1-oxides, substitution at the C-2 position, stereochemical correlation, and asymmetric synthesis can be carried out on the 1,3-benzodithiole 1-oxide series **5**–**8**.



Results and Discussion

1,3-Benzodithiole **1** and 2-alkyl-1,3-benzodithioles **2**–**4** were synthesised by the literature methods[1,5] and oxidized by sodium metaperiodate to the corresponding racemic sulfoxides **5**–**8**. The *trans*-isomers **6**–**8** in each case were identified by TLC (lower R_f), HPLC (late eluting isomer) and ^{1}H NMR spectral (larger δ values for the C-2-methine signal due to deshielding by the sulfoxide group) characteristics. Conversely, the *cis*-isomers were less strongly retained during chromatography and showed smaller δ values for the methine signal. A racemic sample of 1,3-benzodithiole 1-oxide **5** was separated into enantiomers using a Chiralcel OB analytical column (250 × 4.6 mm) [propan-2-ol (30):hexane (70), α 1.4]. Larger samples

Table 1 Optical rotations ($[\alpha]_D$), CD data ($\lambda,\Delta\varepsilon$), enantiomeric excess (% e.e.) and absolute configurations of sulfoxides

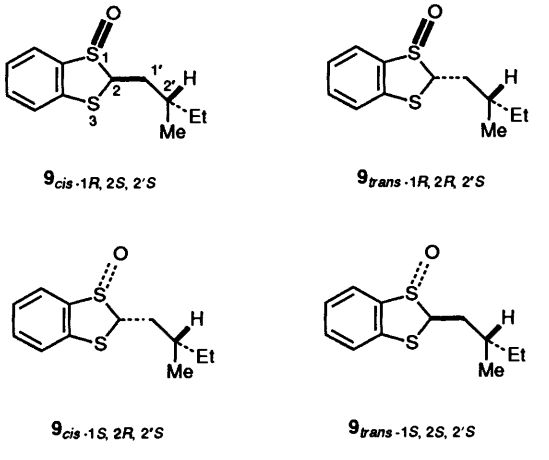
Compound	$[\alpha]_D$[a]	Analytical CD band $[\lambda/nm\ (\Delta\varepsilon)]$[b]	% E.e.[c]	Absolute configurations
$\mathbf{5}_{1R}$	+510	218 (+29.2)	>98	1*R*
$\mathbf{6}_{cis\text{-}1R,2S}$	+69	218 (+6.2)	25	1*R*,2*S*
$\mathbf{6}_{trans\text{-}1R,2R}$	+28	218 (+4.2)	25	1*R*,2*R*
$\mathbf{7}_{cis\text{-}1R,2S}$	+29	218 (+6.4)	25	1*R*,2*S*
$\mathbf{7}_{trans\text{-}1R,2R}$	+18	218 (+4.6)	25	1*R*,2*R*
$\mathbf{8}_{cis\text{-}1R,2S}$	+48	218 (+8.0)	25	1*R*,2*S*
$\mathbf{8}_{trans\text{-}1R,2R}$	+16	220 (+5.6)	25	1*R*,2*R*
$\mathbf{9}_{trans\text{-}1S,2S,2'S}$	−59	219 (−32.5)	>98	1*S*,2*S*(2′*S*)
$\mathbf{9}_{trans\text{-}1R,2R,2'S}$	+103	220 (+36.0)	>98	1*R*,2*R*(2′*S*)
$\mathbf{9}_{cis\text{-}1R,2S,2'S}$	+254	218 (+42.5)	>98	1*R*,2*S*(2′*S*)
$\mathbf{9}_{cis\text{-}1S,2R,2'S}$	−248	220 (−50.0)	>98	1*S*,2*R*(2′*S*)
$\mathbf{10}_{1S,2'S,2''S}$	−40	220 (−42.0)	>98	1*S*,(2′*S*,2″*S*)
$\mathbf{10}_{1R,2'S,2''S}$	+81	220 (+43.0)	>98	1*R*,(2′*S*,2″*S*)

[a] EtOH. [b] MeCN, $\Delta\varepsilon$($dm^3\ mol^{-1}\ cm^{-1}$). [c] Determined by CSP-HPLC analysis.

(*ca.* 10 mg per injection) were separated using a Chiralcel (Daicel Chemical Industries, Ltd.) semi-preparative OB column (250 × 9.4 mm) to yield the early, $\mathbf{5}_{1S}$ ($[\alpha]_D$ −505),* and late, $\mathbf{5}_{1R}$ ($[\alpha]_D$ +510), eluting enantiomers.†

Enantiomer $\mathbf{5}_{1R}$ was diluted with the racemic sulfoxide **5** to yield a sample of 25% e.e. Treatment of this enantiomerically enriched sample of (+)-($\mathbf{5}_{1R}$) with base to yield the corresponding carbanion, followed by reaction with appropriate iodoalkanes in turn gave both *cis* and *trans* isomers **6**–**8** in optically active (25% e.e.) form (Table 1). The alkylation process thus allowed the absolute configurations of sulfoxides $\mathbf{6}_{cis\text{-}1R,2S}$, $\mathbf{6}_{trans\text{-}1R,2R}$, $\mathbf{7}_{cis\text{-}1R,2S}$, $\mathbf{7}_{trans\text{-}1R,2R}$, $\mathbf{8}_{cis\text{-}1R,2S}$ and $\mathbf{8}_{trans\text{-}1R,2R}$ to be unequivocally correlated to the absolute stereochemistry of the parent sulfoxide $\mathbf{5}_{1R}$.

Alkylation of the racemic sulfoxide $\mathbf{5}_{1R}/\mathbf{5}_{1S}$ using potassium bis(trimethylsilyl)amide, and (*S*)-(+)-1-iodo-2-methylbutane yielded four diastereoisomers of 2-(2′-methylbutyl)-1,3-benzodithiole 1-oxide ($\mathbf{9}_{trans\text{-}1S,2S,2'S}$, $\mathbf{9}_{trans\text{-}1R,2R,2'S}$, $\mathbf{9}_{cis\text{-}1R,2S,2'S}$, and



$\mathbf{9}_{cis\text{-}1S,2R,2'S}$). These diastereoisomers were separated using a semi-preparative Pirkle 1A (ionic) CSP-HPLC column [propan-2-ol (10):hexane (90)] (Fig. 1). The most strongly retained

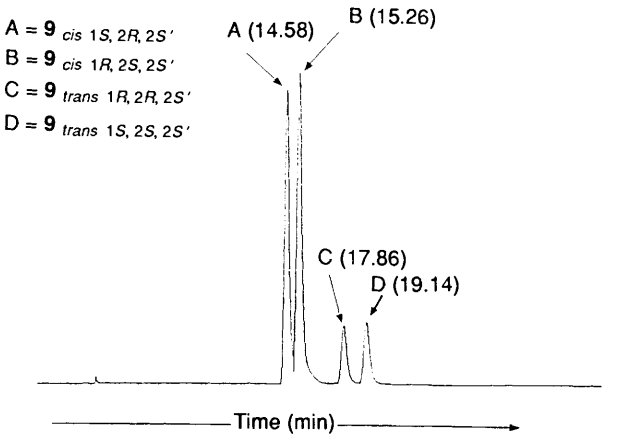
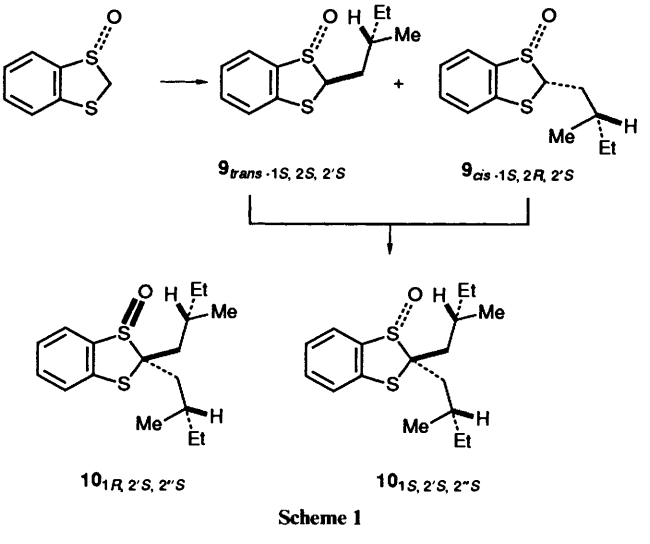


Fig. 1 HPLC trace of diastereoisomers A-D using a Pirkle 1A ionic column

diastereoisomer, $\mathbf{9}_{trans\text{-}1S,2S,2'S}$, was found to be crystalline. X-Ray crystallographic analysis of $\mathbf{9}_{trans\text{-}1S,2S,2'S}$ allowed the diaxial *trans*-relationship between the sulfoxide oxygen atoms and the 2-alkyl group to be confirmed and the absolute configuration to be assigned as (1*S*,2*S*,2′*S*) (Fig. 2). Diastereoisomer $\mathbf{9}_{trans\text{-}1S,2S,2'S}$ thus provided an 'anchor configuration' to which absolute configurations of the other chiral sulfoxides listed in Table 1 were stereochemically correlated. Dialkylation of optically pure 1,3-benzodithiole (1*S*)-oxide, $\mathbf{5}_{1S}$, ($[\alpha]_D$ −505) using an excess of (*S*)-(+)-1-iodo-2-methylbutane yielded 2-(2′*S*-methylbutyl)-2-(2″*S*-methylbutyl)-1,3-benzodithiole 1-oxide, $\mathbf{10}_{1S,2'S,2''S}$ ($[\alpha]_D$ −40). The latter procedure avoided the production (and thus separation) of *cis-trans* isomers, $\mathbf{9}_{trans\text{-}1S,2S,2'S}$ and $\mathbf{9}_{cis\text{-}1S,2R,2'S}$. A similar alkylation procedure on the crystalline diastereoisomer of the now established absolute configuration ($\mathbf{9}_{trans\text{-}1S,2S,2'S}$) yielded the 2,.2-dialkyl-1,3-benzodithiole 1-oxide, **10**, of identical (1*S*,2′*S*,2″*S*) configuration (Scheme 1). Thus, a stereochemical correlation sequence has



Scheme 1

been established between structure $\mathbf{9}_{trans\text{-}1S,2S,2'S}$ ($[\alpha]_D$ −59), the 2,2-disubstituted 1,3-benzodithiole 1-oxide, $\mathbf{10}_{1S,2'S,2''S}$ ($[\alpha]_D$ −40), the parent molecule 1,3-benzodithiole 1-oxide, $\mathbf{5}_{1S}$, ($[\alpha]_D$ −505) and the derived 2-alkyl-substituted (1*R*)-oxides **6**–**8**.

Treatment of the racemic parent sulfoxide, $\mathbf{5}_{1R}/\mathbf{5}_{1S}$ with base followed by dialkylation with (*S*)-(+)-1-iodo-2-methylbutane yielded two diastereoisomers, $\mathbf{10}_{1R,2'S,2''S}$ and $\mathbf{10}_{1S,2'S,2''S}$. This diastereoisomeric pair was separated by means of CSP-HPLC using a semi-preparative Pirkle 1A (ionic) column [propan-2-

* $[\alpha]_D$ Values are recorded in units of 10^{-1} deg cm^2 g^{-1} throughout.
† **Warning**: This type of column was found to have a very short lifetime, despite use of the recommended solvent system.

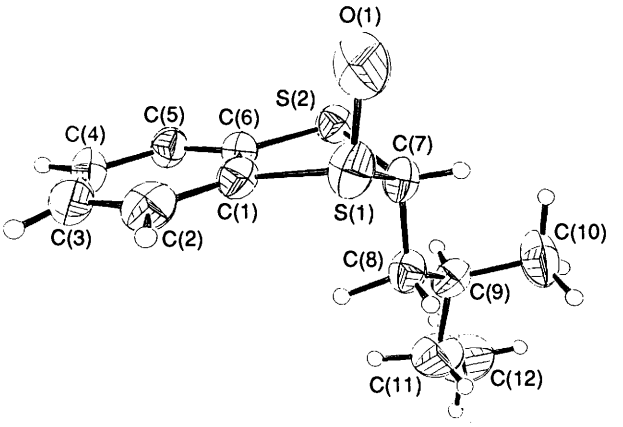


Fig. 2 ORTEP[11] plot and crystallographic numbering for one of the two crystallographically independent molecules of sulfoxide $\mathbf{9}_{trans\text{-}1S,2S,2'S}$. Thermal ellipsoids for non-H atoms are drawn at the 40% probability level

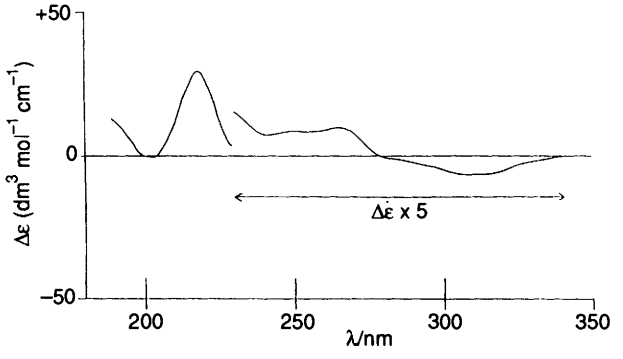


Fig. 3 CD spectrum of $\mathbf{5}_{1R}$

ol–hexane (4:96) as eluent] and provided a sample of diastereoisomer $\mathbf{10}_{1R,2S',2''S}$ ($[\alpha]_D$ +81) which was unavailable from the procedure shown in Scheme 1.

As shown by Fig. 2, absolute configurations can be established by X-ray crystallography. Although this can be achieved by CD spectroscopy with the application of the 'Exciton coupling' method, assignments are more generally achieved relatively. However, strict limits are required to ensure that valid comparisons can be made between CD spectra. It is important to relate chiroptical data pertaining to the same excitation (transition) with optical activity derived from the same spectroscopic mechanism. Schoenfelder and Snatzke have claimed[7] that more than one mechanism is required to fully explain the CD associated with electronic transitions localised on an aromatic ring.

The basic chromophore in the sulfoxides **5–10** is well represented by compound **5**. This compound presents a CD spectrum (Fig. 3) with a prominent magnetic dipole allowed transition around 218 nm derived from an n-π* transition associated with the sulfur/sulfoxide substituents in line with previous observations.[2,3] The sign of this dichroism is inevitably linked to the chirality of the sulfoxide group and its disposition with respect to the 'conjugated' aromatic ring, in the present cases a positive sign correlates with 1*R* sulfoxide stereochemistry. This is clearly demonstrated in Fig. 5, where the CD around 218 nm can be correlated with the sulfoxide chirality of pseudo-enantiomeric pairs, being only slightly dependent on the identity of the substitution at position 2. The 218 nm CD component is flanked by weaker dichroisms, often requiring amplification for presentation at longer wavelengths (Figs. 3–5, Table 1), that are derived from π-π* transitions localised on the phenyl group. The latter will inevitably be more susceptible to the molecular environment (chirality at positions 1 and 2).

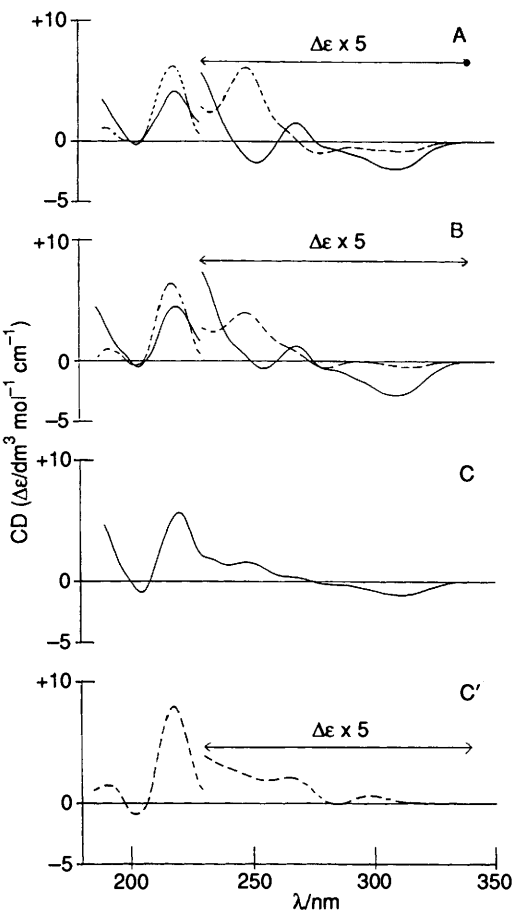


Fig. 4 CD spectrum of A —— $\mathbf{6}_{trans\text{-}1R,2R}$; - - - - $\mathbf{6}_{cis\text{-}1R,2S}$; B —— $\mathbf{7}_{trans\text{-}1R,2R}$; - - - - $\mathbf{7}_{cis\text{-}1R,2S}$; C —— $\mathbf{8}_{trans\text{-}1R,2R}$; C' - - - - $\mathbf{8}_{cis\text{-}1R,2S}$

Nevertheless, patterns should emerge. In particular, there is a noticeable correlation between the CD spectra of diastereoisomers (Figs. 4 and 5). Compounds having 1*R*,2*R* configuration all show a similar negative peak around 310 nm, differentiating them from their 2*S* counterparts, confirming the relative assignment of the C-2 centre of chirality. $\mathbf{10}_{1R,2S',2''S}$ Has a CD spectrum very similar to $\mathbf{5}_{1R}$ which also lacks C-2 chirality.

In conclusion, CD spectroscopy has been shown to provide a simple direct means of relating the absolute configurations of a range of mono- and di-alkylated 1,3-benzodithiole 1-oxides and should be applicable to other similar derivatives which have been used in enzyme-catalysed sulfoxidation studies.[4]

Experimental

^{1}H NMR spectra were recorded at 250 MHz (Bruker WH250), 300 MHz (General Electric QE300) and 500 MHz (General Electric Omega 500) as specified. All ^{1}H NMR spectra were obtained using $CDCl_3$ solvent and tetramethylsilane as internal reference. Coupling constants have been expressed in Hz. Mass spectra were recorded at 70 eV on an AE1-MS902 instrument updated by VG Instruments. Accurate molecular weights were determined by the peak matching method using perfluorokerosene as standard reference. Circular dichroism spectra were recorded using Jasco J600 and J720 instruments, spectroscopic grade acetonitrile and cell path lengths of 10 nm, 0.5 mm and 0.2 mm where appropriate. Optical rotation measurements were determined using a Perkin-Elmer Model 241 instrument.

1,3-Benzodithiolylium tetrafluoroborate and 2-(3-methylbutoxy)-1,3-benzodithiole, were prepared by the literature methods.[5,6]

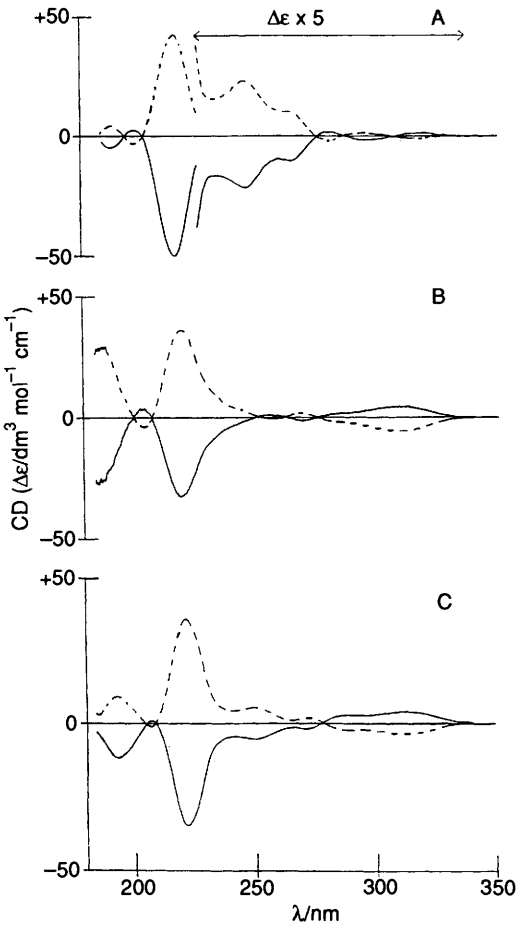


Fig. 5 CD spectrum of: A —— $\mathbf{9}_{cis\text{-}1S.2R.2'S}$; - - - - $\mathbf{9}_{cis\text{-}1R.2S.2'S}$; B —— $\mathbf{9}_{trans\text{-}1S.2S.2'S}$; - - - - $\mathbf{9}_{trans\text{-}1R.2R.2'S}$; C —— $\mathbf{10}_{1S,2S.2''S}$; - - - - $\mathbf{10}_{1S,2'S.2''S}$

1,3-*Benzodithiole* **1**.—To a stirred solution of sodium borohydride (1 g, 0.026 mol) in anhydrous THF (150 cm^3) was added 1,3-benzodithiolylium tetrafluoroborate (6.3 g, 26 mmol) portionwise at room temperature. After being stirred for 2 h the mixture was poured into iced water and extracted with diethyl ether (3 × 200 cm^3). The ethereal extract was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to give an oily residue. Distillation of the residue gave 1,3-benzodithiole **1** (2.9 g, 72%), b.p. 78–80 °C/0.2 mmHg (lit.,[5] 103–104 °C/3 mmHg).

2-*Methyl*-1,3-*benzodithiole* **2**.—Tetrafluoroboric acid–diethyl ether complex (1 cm^3) was added to a solution of benzene-1,2-dithiol (1.49 g, 10.5 mmol) and acetaldehyde (0.44 g, 10 mmol) in dry benzene (50 cm^3). The stirred mixture was heated at 50–60 °C for 30 min and then poured into water and extracted with diethyl ether. The extract was washed with 5% aqueous sodium hydroxide and water, dried ($MgSO_4$) and evaporated under reduced pressure to yield an oil. Distillation of this under reduced pressure gave 2-methyl-1,3-benzodithiole **2** (1.62 g, 97%), b.p. 62–64 °C/0.02 mmHg. The product **2** was found to recrystallize from aqueous methanol to give a colourless solid, m.p. 41–43 °C (Found: C, 57.3; H, 4.8. $C_8H_8S_2$ requires C, 57.1; H, 4.8%); δ_H(250 MHz) 1.69 (3 H, d, *J* 6.7, Me), 4.98 (1 H, q, *J* 6.7, 2-H), 7.02–7.05 (2 H, m, ArH) and 7.21–7.27 (2 H, m, ArH).

2-*Ethyl*-1,3-*benzodithiole* **3**.—2-Ethyl-1,3-benzodithiole **3** was obtained in 95% yield in a similar manner to that described for 2-methyl-1,3-benzodithiole **2** and was purified by distillation, b.p. 72–76 °C/0.01 mmHg (Found: C, 59.6; H, 5.7. $C_9H_{10}S_2$ requires C, 59.3; H, 5.5%); δ_H(250 MHz) 0.99 (3 H, t, *J* 7.3, CH_2Me), 1.91 (2 H, m, CH_2Me), 4.73 (1 H, t, *J* 7.0, 2-H), 6.96–7.00 (2 H, m, ArH) and 7.17–7.22 (2 H, m, ArH).

2-*Isopropyl*-1,3-*benzodithiole* **4**.—2-Isopropyl-1,3-benzodithiole **4** was synthesised in 87% yield by the method described for 2-methyl-1,3-benzodithiole **2** and was purified by distillation, b.p. 68–71 °C/0.05 mmHg (lit.,[1] b.p. 76–80 °C/0.1 mmHg); δ_H(250 MHz) 0.99 (6 H, d, *J* 6.6, $CHMe_2$), 1.95 (1 H, m, $CHMe_2$), 4.77 (1 H, d, *J* 6.2, 2-H), 6.92–6.95 (2 H, m, ArH) and 7.12–7.15 (2 H, m, ArH).

Oxidation of 1,3-*Benzodithioles* **1–4**.—Sodium metaperiodate (2.8 g, 13 mmol) in water (60 cm^3) was added dropwise with stirring to a cooled (0 °C) solution of 1,3-benzodithiole (10 mmol) in methanol (150 cm^3) and the mixture was stirred overnight at room temperature. The solid inorganic by-product of the reaction was filtered off and washed with chloroform (3 × 20 cm^3). The filtrate was concentrated under reduced pressure to *ca.* 15 cm^3, saturated with NaCl and extracted with chloroform (4 × 30 cm^3). The combined chloroform extracts and washings were dried ($MgSO_4$), concentrated under reduced pressure and the crude product was purified by flash chromatography or preparative TLC on silica gel (100% diethyl ether as eluent). The *cis*- and *trans*-isomers were also separated by semipreparative HPLC [α > 1.2, Zorbax SIL, 9.4 × 250 mm; propan-2-ol (0.2%)–dichloromethane (99.8%), at a flow rate of 7 cm^3 min^{-1}]. In each case the early eluted or high R_f isomer had the *cis*-configuration.

1,3-*Benzodithiole* 1-*oxide* $\mathbf{5}_R/\mathbf{5}_S$. This compound was obtained in 85% yield; m.p. 90–91 °C (ethanol–pentane) (Found: C, 49.6; H, 3.4. $C_7H_6S_2O$ requires C, 49.4; H, 3.5%); δ_H(250 MHz) 4.19 (1 H, d, *J* 13, 2-H), 4.35 (1 H, d, *J* 13, 2-H), 7.27–7.32 (1 H, m, ArH), 7.50–7.53 (2 H, m, ArH) and 7.91 (1 H, d, *J* 7.2, ArH).

An enantiomeric separation of 1,3-benzodithiole 1-oxide, $\mathbf{5}_R/\mathbf{5}_S$, was achieved using a Chiralcel OB semipreparative column (9.4 × 250 mm) [propan-2-ol–hexane (30:70), at a flow rate of 2.0 cm^3 min^{-1}, 0.01 g injections, α 1.4]. Early eluting isomer, $\mathbf{5}_{1S}$, $[\alpha]_D$ −505 (EtOH). Late eluting isomer, $\mathbf{5}_{1R}$, $[\alpha]_D$ +510 (EtOH).

cis-2-*Methyl*-1,3-*benzodithiole* 1-*oxide* $\mathbf{6}_{cis\text{-}1R,2S}$. This compound was obtained in 25% yield; m.p. 88–90 °C (ethanol–pentane) (Found: C, 52.1; H, 4.4. $C_8H_8S_2O$ requires C, 52.2; H, 4.35%); δ_H(250 MHz) 1.84 (3 H, d, *J* 7.0, Me), 4.45 (1 H, q, *J* 6.9, 2-H), 7.28–7.34 (1 H, m, ArH), 7.44–7.49 (2 H, m, ArH) and 7.85 (1 H, d, *J* 7.7, ArH).

trans-2-*Methyl*-1,3-*benzodithiole* 1-*oxide*, $\mathbf{6}_{trans\text{-}1R,2R}$. This compound was obtained in 50% yield; m.p. 132–134 °C (ethanol–pentane) (Found: C, 52.3; H, 4.3. $C_8H_8S_2O$ requires C, 52.2; H, 4.35%); δ_H(250 MHz) 1.84 (3 H, d, *J* 7.3, Me), 4.60 (1 H, q, *J* 7.3, 2-H), 7.28–7.34 (1 H, m, ArH), 7.42–7.49 (2 H, m, ArH) and 7.85 (1 H, d, *J* 7.7, ArH).

cis-2-*Ethyl*-1,3-*benzodithiole* 1-*oxide* $\mathbf{7}_{cis\text{-}1R,2S}$. This compound was obtained in 19% yield; m.p. 55–56 °C (ethanol–pentane) (Found: M, 198.018 09. $C_9H_{10}S_2O$ requires 198.018 06); δ_H(300 MHz) 1.30 (3 H, t, *J* 7.4, CH_2Me), 2.11 (1 H, m, CH_2Me), 2.39 (1 H, m, CH_2Me), 4.26 (1 H, t, *J* 7.6, 2-H), 7.26–7.31 (1 H, m, ArH), 7.44–7.47 (2 H, m, ArH) and 7.87 (1 H, d, *J* 7.7, ArH).

trans-2-*Ethyl*-1,3-*benzodithiole* $\mathbf{7}_{trans\text{-}1R,2R}$. This compound was obtained in 64% yield; m.p. 75–76 °C (ethanol–pentane) (Found: C, 54.5; H, 5.1. $C_9H_{10}S_2O$ requires C, 54.54; H, 5.05%); δ_H(300 MHz) 1.18 (3 H, t, *J* 7.3, CH_2Me), 1.65 (1 H, m, CH_2Me), 2.00 (1 H, m, CH_2Me), 4.48 (1 H, dd, *J* 7.0, 7.0, 2-H), 7.26–7.32 (1 H, m, ArH), 7.45–7.47 (2 H, m, ArH) and 7.84 (1 H, d, *J* 7.7, ArH).

cis-2-*Isopropyl*-1,3-*benzodithiole* 1-*oxide* $\mathbf{8}_{cis\text{-}1R,2S}$. This compound was obtained in 15% yield; m.p. 126–127 °C (ethanol–pentane) (Found: M, 212.034 28. $C_{10}H_{12}S_2O$ requires *M*, 212.033 71); δ_H(300 MHz) 1.20 (3 H, d, *J* 6.4, Me), 1.42 (3 H, d, *J* 6.5, Me), 2.57 (1 H, m, C*H*Me$_2$), 4.05 (1 H, d, *J* 10.6, 2-H), 7.24–7.29 (1 H, m, ArH), 7.45–7.47 (2 H, m, ArH) and 7.86 (1 H, d, *J* 8.2, ArH).

trans-2-*Isopropyl*-1,3-*benzodithiole* 1-*oxide* $\mathbf{8}_{trans\text{-}1R,2R}$. This compound was obtained in 73% yield; m.p. 97–98 °C (ethanol–pentane) (Found: C, 56.2; H, 5.8. $C_{10}H_{12}S_2O$ requires C, 56.6; H, 5.7%); δ_H(300 MHz) 1.06 (3 H, d, *J* 6.7, Me), 1.16 (3 H, d, *J* 6.7, Me), 2.60 (1 H, m, C*H*Me$_2$), 4.45 (1 H, d, *J* 6.6, 2-H), 7.26–7.28 (1 H, m, ArH), 7.43–7.46 (2 H, m, ArH) and 7.79 (1 H, d, *J* 7.5, ArH).

Synthesis and Stereochemical Correlation of Sulfoxides $\mathbf{5}_{1R}$, $\mathbf{6}_{cis\text{-}1R,2S}$, $\mathbf{6}_{trans\text{-}1R,2R}$, $\mathbf{7}_{cis\text{-}1R,2S}$ *and* $\mathbf{7}_{trans\text{-}1R,2R}$.—To a solution of 1,3-benzodithiole 1-oxide, $\mathbf{5}_{1R}$ {0.04 g, 0.24 mmol, $[\alpha]_D$ +128 (EtOH), 25% e.e.} and iodomethane (0.15 cm^3, 2.4 mmol) in dry THF was added sodium hydride (60% dispersion in mineral oil; 0.015 g, 0.38 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for 3 days at room temperature before water was added cautiously to destroy excess of sodium hydride. The mixture was filtered and the filtrate and diethyl ether washings were dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product which was purified by preparative TLC on silica gel using diethyl ether as eluent. This yielded a mixture (0.032 g, 73% yield) of $\mathbf{6}_{cis\text{-}1R,2S}$ (75%) and $\mathbf{6}_{trans\text{-}1R,2R}$ (25%). The mixture was separated by preparative HPLC as outlined earlier. The enantiomeric excess values for compounds $\mathbf{6}_{cis\text{-}1R,2S}$ and $\mathbf{6}_{trans\text{-}1R,2R}$ were determined by ^{1}H NMR analysis (300 MHz) in $CDCl_3$ solvent containing (+)-(*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol: $\mathbf{6}_{cis\text{-}1R,2S}$, $[\alpha]_D$ +69 (EtOH), 25% e.e.; $\mathbf{6}_{trans\text{-}1R,2R}$, $[\alpha]_D$ +28 (EtOH) 25% e.e. By a similar procedure 1,3-benzodithiole 1-oxide, $\mathbf{5}_{1R}$, ($[\alpha]_D$ +128 (EtOH), 25% e.e.) was treated with iodoethane to yield a mixture of the sulfoxides, $\mathbf{7}_{cis\text{-}1R,2S}$/$\mathbf{7}_{trans\text{-}1R,2R}$. Similar purification, separation and % e.e. determination methods were used for the *cis* and *trans* isomers: $\mathbf{7}_{cis\text{-}1R,2S}$, $[\alpha]_D$ +29 (EtOH), 25% e.e.; $\mathbf{7}_{trans\text{-}1R,2R}$, $[\alpha]_D$ +18 (EtOH), 25% e.e.

Synthesis and Stereochemical Correlation of Sulfoxides $\mathbf{8}_{cis\text{-}1R,2S}$ *and* $\mathbf{8}_{trans\text{-}1R,2R}$ *with* $\mathbf{5}_{1R}$.—To a solution of 1,3-benzodithiole 1-oxide (0.04 g, 0.24 mmol, $[\alpha]_D$ +128 (EtOH), 25% e.e.) and 2-iodopropane (0.24 cm^3, 2.4 mmol) in dry THF under nitrogen was added potassium bis(trimethylsilylamide) (0.5 mol dm^{-3} solution in toluene; 0.85 cm^3, 0.43 mmol) and the resultant mixture was stirred in the dark for 3 days at room temperature. With the same work-up and purification procedures as for the sulfoxides $\mathbf{6}_{cis\text{-}1R,2S}$, $\mathbf{6}_{trans\text{-}1R,2R}$, $\mathbf{7}_{cis\text{-}1R,2S}$ and $\mathbf{7}_{trans\text{-}1R,2R}$ the pure sulfoxides $\mathbf{8}_{cis\text{-}1R,2S}$ and $\mathbf{8}_{trans\text{-}1R,2R}$ were obtained: $\mathbf{8}_{cis\text{-}1R,2S}$, 75%, $[\alpha]_D$ +48 (EtOH), 25% e.e.; $\mathbf{8}_{trans\text{-}1R,2R}$, 25%, $[\alpha]_D$ +16 (EtOH), 25% e.e.

Synthesis and Separation of the Diastereoisomers of 2-(2′-*Methylbutyl*)-1,3-*benzodithiole* 1-*Oxide*, $\mathbf{9}_{cis\text{-}1R,2S,2'S}$, $\mathbf{9}_{trans\text{-}1R,2R,2'S}$, $\mathbf{9}_{cis\text{-}1S,2R,2'S}$ *and* $\mathbf{9}_{trans\text{-}1S,2S,2'S}$.—Treatment of racemic 1,3-benzodithiole 1-oxide ($\mathbf{5}_R$/$\mathbf{5}_S$) (1 g, 5.9 mmol) with (*S*)-(+)-1-iodo-2-methylbutane (3.8 cm, 29 mmol) and potassium bis(trimethylsilyl)amide in a manner identical with that described for the synthesis of the sulfoxides $\mathbf{8}_{cis\text{-}1R,2S}$ and $\mathbf{8}_{trans\text{-}1R,2R}$, yielded a mixture of the four diastereoisomers of 2-(2′-methylbutyl)-1,3-benzodithiole-1-oxide (total yield 0.8 g, 56%) (Found: C, 60.2; H, 6.9. $C_{12}H_{16}S_2O$ requires C, 60.0; H, 6.7%).

Separation of the four diastereoisomers (0.05 g) was achieved with a Pirkle 1A, ionic chiral stationary phase HPLC column (250 × 9.4 mm) using isopropyl alcohol–hexane (10:90) solvent at a flow rate of 2.0 cm^3 min^{-1} (Fig. 1).

$\mathbf{9}_{cis\text{-}1S,2R,2'S}$. A gum (0.015 g, 30%), $[\alpha]_D$ −248 (EtOH); δ_H(300 MHz) 0.96 (3 H, t, *J* 7.4, *Me*CH$_2$), 1.06 (3 H, d, *J* 6.6, *Me*CH), 1.29 and 1.59 (1 H, each, m, MeC*H*$_2$), 1.72 (1 H, m, MeC*H*), 1.91 and 2.33 (1 H each, m, 1′-H), 4.38 (1 H, dd, *J* 7.6, 2-H), 7.27 (1 H, m, 5-H), 7.46 (2 H, m, 4-H, 6-H) and 7.87 (1 H, d, *J* 7.7, 7-H).

$\mathbf{9}_{cis\text{-}1R,2S,2'S}$. A gum (0.012 g, 24%), $[\alpha]_D$ +254; δ_H(300 MHz) 0.95 (3 H, t, *J* 7.4, *Me*CH$_2$), 1.05 (3 H, d, *J* 6.6, *Me*CH), 1.34 and 1.51 (1 H each, m, MeC*H*$_2$), 1.61 (1 H, m, MeC*H*), 2.12 (2 H, m, 1′-H), 4.39 (1 H, dd, *J* 6.8, 8.6, 2-H), 7.28 (1 H, m, 5-H), 7.46 (2 H, m, 4-H, 6-H) and 7.86 (1 H, d, *J* 7.6, 7-H).

$\mathbf{9}_{trans\text{-}1R,2R,2'S}$. A crystalline solid (0.004 g, 8%), m.p. 58–59 °C (pentane) $[\alpha]_D$ +103 (EtOH); δ_H(300 MHz) 0.90 (3 H, t, *J* 7.4, *Me*CH$_2$), 1.00 (3 H, d, *J* 6.6, *Me*CH), 1.20 and 1.47 (1 H, each, m, MeC*H*$_2$), 1.57 (1 H, m, MeC*H*), 1.76 and 1.88 (1 H each, m, 1′-H), 4.60 (1 H, dd, *J* 6.9, 8.9, 2-H), 7.29 (1 H, m, 5-H), 7.46 (2 H, m, 4-H, 6-H) and 7.83 (1 H, d, *J* 7.7, 7-H).

$\mathbf{9}_{trans\text{-}1S,2S,2'S}$. A crystalline solid (0.004 g, 8%), m.p. 60–61 °C (pentane), $[\alpha]_D$ −59 (EtOH); δ_H(500 MHz) 0.88 (3 H, t, *J* 7.4, *Me*CH$_2$), 0.97 (3 H, d, *J* 6.3, *Me*CH), 1.27 and 1.40 (1 H each, m, MeC*H*$_2$), 1.54 (2 H, m, MeC*H*, 1′-H), 1.73 (1 H, m, 1′-H), 4.60 (1 H, dd, *J* 4.8, 11.0, 2-H), 7.28 (1 H, m, 5-H), 7.46 (2 H, m, 4-H, 6-H) and 7.84 (1 H, d, *J* 7.9, 7-H).

X-Ray Crystallographic Analysis of 2-(2′-*Methylbutyl*)-1,3-*benzodithiole* 1-*Oxide*, $\mathbf{9}_{trans\text{-}1S,2S,2'S}$.—*Crystal Data for* $\mathbf{9}_{trans\text{-}1S,2S,2'S}$. $C_{12}H_{16}S_2O$, M = 240.4, monoclinic, a = 10.581(2), b = 11.403(3), c = 11.038(3) Å, β = 106.21(2)°, U = 1278.8(5)Å^3, Z = 4, D_x = 1.249 g cm^{-3} $F(000)$ = 512, space group $P2_1$ (No. 4), Mo-$K\alpha$ radiation, λ = 0.710 73 Å, μ(Mo-$K\alpha$) = 3.4 cm^{-1}.

Analysis and Refinement.—7444 Diffraction intensities, including Friedel pairs, were measured on a Siemens P3/V2000 diffractometer. The structure was determined by direct methods (SHELX S86)[8] and refined by least squares (SHELX 76).[9] The asymmetric unit consists of two crystallographically independent, but chemically equivalent, molecules in one of which the $CH_3CH_2(CH_3)CH$ part of the 2-methylbutyl group is disordered, occupying two different conformations about the C(7)–C(8) and C(8)–C(9) bonds, in equal proportions. In each molecule the dithiole ring has an envelope conformation with an axial 2-methylbutyl group and a quasi-axial S=O (Fig. 2). In the refinement process non-hydrogen atoms were allowed anisotropic vibrations (except the carbons of the disordered group, which were isotropic); the hydrogens of the disordered groups and of the methyl groups were included at positions calculated from the geometry of the molecule while the other 17 hydrogens were included as independent isotropic atoms, having been located in a ΔF map. The enantiomer was chosen to correspond to the *known* absolute configuration of the (*S*)-2-methylbutyl group and this established the overall configuration as 1*S*, 2*S*, 2′*S*. [In addition the absolute configuration was established independently by least-squares refinement of the alternative enantiomer. Hamilton's[10] R_w ratio of 1.0127, for 330 variables and 3699 degrees of freedom, allowed rejection of the second enantiomer at a probability level of 2.5 × 10^{-18}.] The 4029 data with $F > 6\sigma(F)$ gave R = 0.051, R_w = 0.055 with weighting scheme $w = 1.52/[\sigma^2(F) + 0.000\,87F^2]$. There are no intermolecular contacts below 3.0 Å between non-hydrogen atoms. Fractional atomic coordinates for non-hydrogen atoms are listed in Table 2. Other crystallographic results (hydrogen atom coordinates, bond lengths, bond angles and thermal parameters have been deposited with the Cambridge Crystallophic Data Centre.*

* For details, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1992, Issue 1.

Table 2 Fractional atomic coordinates for $\mathbf{9}_{trans\text{-}1S,2S,2'S}$

Atom	*x*	*y*	*z*
S(1)	0.142 46(10)	0.249 81(13)	0.165 43(12)
S(2)	0.103 92(10)	0.000 00	0.104 28(10)
O(1)	0.117 7(3)	0.284 3(3)	0.031 0(4)
C(1)	−0.007 0(4)	0.187 3(4)	0.178 7(4)
C(2)	−0.104 2(4)	0.251 4(5)	0.210 4(4)
C(3)	−0.221 0(5)	0.197 5(6)	0.205 8(5)
C(4)	−0.242 2(5)	0.082 6(6)	0.170 5(5)
C(5)	−0.145 1(4)	0.018 3(5)	0.138 6(4)
C(6)	−0.026 6(4)	0.070 5(4)	0.144 1(4)
C(7)	0.224 2(4)	0.107 1(4)	0.189 9(4)
C(8)	0.273 7(4)	0.080 7(4)	0.328 8(4)
C(9)	0.363 4(4)	−0.026 7(4)	0.361 6(5)
C(10)	0.492 9(5)	−0.008 1(6)	0.328 8(6)
C(11)	0.383 5(7)	−0.058 6(6)	0.499 1(5)
C(12)	0.457 0(8)	−0.173 2(7)	0.539 1(7)
S(1a)	−0.583 22(10)	0.264 09(13)	−0.044 19(11)
S(2a)	−0.637 61(11)	0.020 60(14)	−0.132 64(13)
O(1a)	0.448 8(3)	0.231 8(3)	0.093 3(3)
C(1a)	−0.461 8(4)	0.193 9(4)	−0.102 5(4)
C(2a)	−0.343 5(4)	0.248 8(5)	−0.100 9(4)
C(3a)	−0.248 5(5)	0.183 4(5)	−0.134 9(5)
C(4a)	−0.269 8(5)	0.067 5(5)	−0.166 5(5)
C(5a)	−0.386 9(5)	0.012 9(5)	−0.168 2(5)
C(6a)	−0.484 9(4)	0.076 9(4)	−0.137 8(4)
C(7a)	−0.709 0(4)	0.166 3(5)	−0.136 4(5)
C(8a)	−0.762 8(6)	0.218 5(6)	−0.265 9(6)
C(9a)*	−0.904 0(12)	0.232 9(13)	−0.329 2(11)
C(10a)	−0.911 5(19)	0.325 8(20)	−0.463 3(19)
C(11a)	−0.961 8(21)	0.101 7(18)	−0.358 3(19)
C(12a)	−1.104 8(19)	0.118 0(19)	−0.420 2(19)
C(9b)	−0.882 6(14)	0.135 9(13)	−0.340 1(13)
C(10b)	−0.981 7(14)	0.110 7(13)	−0.280 7(15)
C(11b)	−0.937 0(14)	0.218 3(14)	−0.471 9(13)
C(12b)	−0.992 3(18)	0.323 1(16)	−0.448 9(14)

* Atoms C(9a)–C(12a) and C(9b)–C(12b) are the disordered portion of the second (crystallographically independent) molecule and have occupation numbers of 0.5.

Synthesis of 2-[(S)-2′-*Methylbutyl*]-2-[(S)-2″-*methylbutyl*]-1,3-*benzodithiole* 1-*Oxide* $\mathbf{10}_{1S,2'S,2''S}$.—Treatment of the laevorotatory enantiomer (1*S*)-1,3-benzodithiole 1-oxide, $\mathbf{5}_{1S}$, $[\alpha]_D$ −505 (0.002 g, 0.012 mmol) with (*S*)-(+)-1-iodo-2-methylbutane (0.02 g, 0.10 mmol) in the presence of potassium bis(trimethylsilyl)amide (0.5 mol dm^{-3}; 0.10 cm^3, 0.050 mmol) using an identical procedure to that previously outlined for the synthesis of sulfoxides $\mathbf{8}_{cis\text{-}1R,2S}$ and $\mathbf{8}_{trans\text{-}1R,2R}$ gave the 2,2-dialkylated product 2-[(*S*)-2′-methylbutyl]-2-[(*S*)-2″-methylbutyl]-1,3-benzodithiole 1-oxide, $\mathbf{10}_{1S,2'S,2''S}$, which was isolated as an oil (0.002 g, 54% yield) after purification by TLC. The electronic CD spectrum of the 2,2-dialkylated sulfoxide $\mathbf{10}_{1S,2'S,2''S}$ was identical with that of the dialkylated sulfoxide of 2-(2′-methylbutyl)-1,3-benzodithiole 1-oxide, $\mathbf{9}_{trans\text{-}1S,2S,2'S}$, also prepared by the above method using (*S*)-(+)-1-iodo-2-methylbutane. The two dialkyl sulfoxides showed exactly the same retention time on a Pirkle 1A ionic column (250 × 4.9 mm) with propan-2-ol–hexane (4:96) as eluent.

Treatment of the racemic 1,3-benzodithiole-1-oxide, $\mathbf{5}_{1S}/\mathbf{5}_{1R}$ (0.250 g, 1.48 mmol) with (*S*)-(+)-1-iodo-2-methylbutane (2.5 g, 12.6 mmol) under similar conditions gave a diastereoisomeric mixture of sulfoxides $\mathbf{10}_{1S,2'S,2''S}$ and $\mathbf{10}_{1R,2'S,2''S}$ which was purified by PLC (Silica gel) (0.275 g, 60% yield) followed by distillation b.p. 90–95 °C/0.01 mmHg (Found: C, 65.8; H, 8.5. $C_{17}H_{26}S_2O$ requires C, 65.8; H, 8.4%). The colourless viscous oil (0.015 g), consisting of the two dialkyl sulfoxide diastereoisomers, was separated into pure diastereoisomers using a Pirkle 1A ionic column (250 × 9.4 mm) and propan-2-ol–hexane (4:96) as eluent (α, 1.35). $\mathbf{10}_{1S,2'S,2''S}$. Early isomer, a gum (0.006 g, 40%), $[\alpha]_D$ −40 (EtOH); δ_H(300 MHz) 0.81 (3 H, t, *J* 7.4, *Me*CH_2), 0.94 (3 H, t, *J* 7.3, *Me*CH_2), 0.95 (3 H, d, *J* 6.8, *Me*CH), 1.04 (3 H, d, *J* 6.5, *Me*CH), 1.16–2.30 (10 H, m, 2 × CH_2CHCH_2), 7.25 (1 H, m, 5-H), 7.36 (2 H, m, 4-H, 6-H) and 7.78 (1 H, d, *J* 7.6, 7-H).

$\mathbf{10}_{1R,2'S,2''S}$. Late isomer, a gum (0.007 g, 47%), $[\alpha]_D$ +81 (EtOH), δ_H(300 MHz) 0.84 (3 H, t, *J* 7.4, $MeCH_2$), 0.91 (3 H, t, *J* 7.4, *Me*CH_2), 0.98 (3 H, d, *J* 6.2, *Me*CH), 1.1 (3 H, d, *J* 6.5, *Me*CH), 1.14–2.13 (10 H, m, 2 × CH_2CHCH_2), 7.25 (1 H, m, 5-H), 7.39 (2 H, m, 4-H, 6-H) and 7.82 (1 H, d, *J* 7.6, 7-H).

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