

Retention of Configuration in Ligand Coupling Reactions in σ -Sulphuranes

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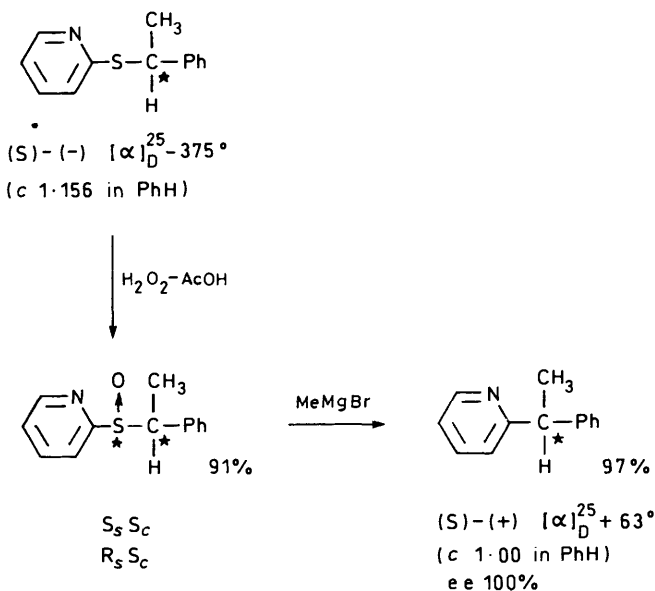
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In accord with the ligand coupling concept, an axial and an equatorial ligand are considered to be extruded from the valence-shell-expanded heteroatom in a concerted fashion which thus affords the coupling product. Therefore, the coupling ligands should retain the original configuration. Indeed, the ligand coupling product, *p*-(1-Phenylethyl)phenylsulphonylbenzene (**3**) formed in the reaction of 1-phenylethyl benzene-*p*-sulphonylphenyl sulphoxide (**2**) with ethylmagnesium bromide is found to retain completely the 1-phenylethyl group configuration, as in our earlier example of the coupling reaction of optically active 1-phenylethyl 2-pyridyl sulphoxide with Grignard reagents and that of allylic and vinylic sulphoxides with Grignard reagents. The absolute configuration of (+)-(**2**) and (+)-(**3**) are determined unequivocally to be $S_S R_C$ and R_C , respectively, by X-ray methods.

We have previously shown that optically active 1-phenylethyl 2-pyridyl sulphoxide reacts either with an alkyl or with a phenyl Grignard reagent to afford optically active 2-(1-phenylethyl)pyridine quantitatively, regardless of the configuration of the chiral sulphur atom, as shown below.^{1,2} Because of the



Scheme 1.

complete retention of configuration of the 1-phenylethyl group in the resultant 2-(1-phenylethyl)pyridine, the ligand coupling reaction has been suggested to proceed concertedly between an axial and equatorial ligands within the hypervalent σ -sulphurane formed by the nucleophilic attack of the Grignard reagent on the sulphinyl sulphur atom. One drawback of our previous example of the complete retention of configuration of 1-phenylethyl group in the coupling product, *i.e.*, 2-(1-phenylethyl)pyridine in the ligand coupling reaction of 1-phenylethyl 2-pyridyl sulphoxide with either an alkyl or an aryl Grignard

reagent could be caused by the facile chelation of the nitrogen atom in the 2-pyridyl group with the sulphinyl oxygen atom in the incipient σ -sulphurane formed by the nucleophilic attack of the Grignard reagent.

In order to avoid the possible chelating interaction of the magnesium atom in the Grignard reagent with the nitrogen atom in the 2-pyridyl group and the sulphinyl oxygen atom, it is desirable to use a ligand which does not contain a nitrogen atom which could chelate with the magnesium atom of the Grignard reagent. Our choice of reaction is the ligand coupling between 1-phenylethyl benzene-*p*-sulphonylphenyl sulphoxide (**2**) with ethylmagnesium bromide, which gives the coupling product in more than 85% yield.

The concerted nature of the ligand coupling has also been demonstrated by us in the reactions described below. The reaction of benzene-*p*-sulphonylphenyl crotyl sulphoxide with Grignard reagents afforded benzene-*p*-sulphonyl(crotyl)benzene, in which the geometric configuration of the crotyl group was completely preserved. No rearrangement was observed in the coupling reaction of benzene-*p*-sulphonylphenyl α -methylallyl sulphoxide. Such a complete retention of geometric configuration was also found in the reactions of 2-pyridyl and benzene-*p*-sulphonylphenyl styryl sulphoxides with Grignard reagents.³

These stereochemical studies are of importance in proving that ligand coupling within the σ -sulphurane is a concerted process. We have found that the reaction of an optically active 1-phenylethyl benzene-*p*-sulphonylphenyl sulphoxide (**2**) with ethylmagnesium bromide also gives the ligand coupling product, *p*-(1-phenylethyl)phenylsulphonylbenzene, in which the original configuration of the 1-phenylethyl group was completely retained. This paper describes the detailed account of our observation on this reaction.

Results and Discussion

In order to synthesize optically active 1-phenylethyl benzene-*p*-sulphonylphenyl sulphide (**1**), optically active (*R*)-(+)-1-phenylethyl sulphide (which was prepared by the method reported in the literature⁴) was used as an asymmetric source. Although in our early example of 1-phenylethyl 2-pyridyl sulphide, the optically active sulphide can be obtained

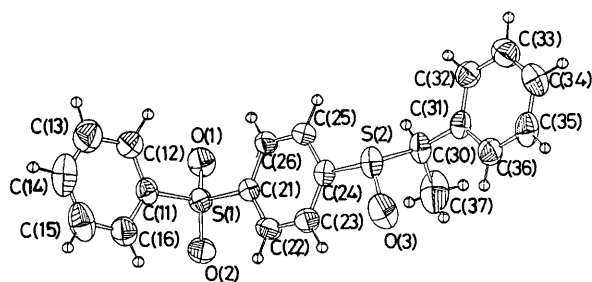


Figure 1. Molecular structure and atom numbering of S_5R_C -1-phenylethyl *p*-benzenesulphonylphenyl sulphoxide (2). The thermal ellipsoids of non-H atoms are drawn at 50% probability and H atoms are represented by spheres of radius 0.1 Å.

by mechanical resolution of the racemic crystals; this was unsuccessful in the case of optically active (1). Therefore, optically active (1) was oxidized with *m*-chloroperbenzoic acid to optically active (2) and the diastereoisomeric mixture was separated by recrystallization from absolute ethanol. One diastereoisomer was obtained as optically active crystals. The absolute configuration of the molecule (+)-(2) was determined to be S_5R_C by X-ray analysis. The *R*-configuration of 1-phenylethyl group is retained completely in the oxidation of the sulphide without racemization. The molecular structure of (2) is shown in Figure 1.

The coupling reaction of this optically active (2) with ethylmagnesium bromide was carried out and this afforded *p*-(1-phenylethyl)phenylsulphonylbenzene (3) in 70% yield as shown below. In the reaction of the 2-pyridyl sulphoxide, the reaction

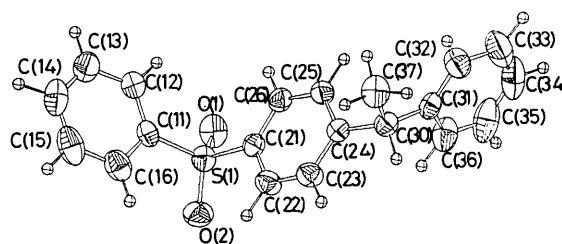
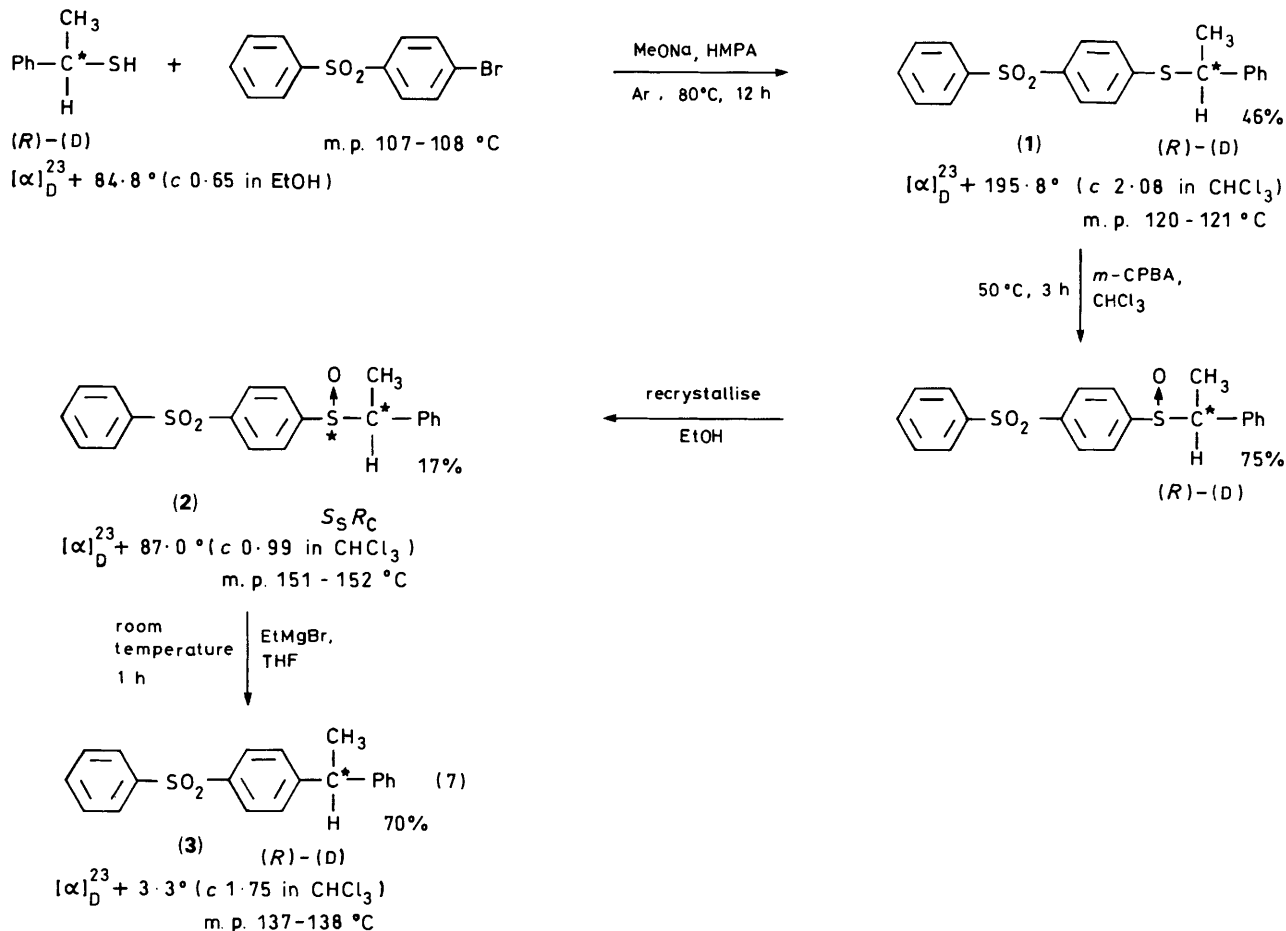


Figure 2. Molecular structure and atom numbering of R_C -*p*-(1-phenylethyl)phenylsulphonylbenzene (3).

was complete within 15 min, however, in the case of optically active (2) treated with ethylmagnesium bromide, the completion of the reaction required *ca.* 1 h. The absolute configuration of 1-phenylethyl group of (+)-(3) was unequivocally determined to be *R* by the X-ray analysis, although the specific rotation of this product is as small as $+3.3^\circ$. Figure 2 shows the molecular structure of (+)-(3). Further, without separation of the diastereoisomeric mixture of sulphoxide (2), the treatment of (2) with ethylmagnesium bromide also afforded the same product with the same specific rotation, in more than 85% yield.

From both the result of this reaction and that of the 2-pyridyl group, the configuration of the sulphonyl group is found not to affect the stereochemistry of the coupling reaction. In addition, these two experimental results prove quite obviously that σ -sulphurane intermediates bearing an electron-withdrawing equatorial benzene-*p*-sulphonylphenyl group and a heteroaryl group undergo ligand coupling with the apicophilic 1-phenylethyl group has proceeded concertedly.



Scheme 2.

Experimental

M.p.s are uncorrected and were taken on a Yanaco micro melting point apparatus. IR spectra were obtained on a JASCO IRA-1 spectrometer and NMR spectra on a Hitachi R-24B spectrometer in CDCl_3 solution using tetramethylsilane as the internal standard. Reactions were monitored by chromatography, *i.e.*, TLC (Merck Kieselgel 60-GF₂₅₄). Silica gel used for column chromatography was Wakogel C-200, *ca.* 200 mesh. Elementary analyses were carried out at the Chemical Analysis Centre, Tsukuba University.

All reagents were obtained from Wako Pure Chemical Industries Ltd, or Tokyo Kasei Co. Solvents were further purified by general methods.

Preparation of Optically Active 1-Phenylethyl Benzene-*p*-sulphonylphenyl Sulphide (1).—To a stirred solution of benzene-*p*-sulphonylphenyl bromide⁵ (1.0 g, 3.36 mmol) and optically pure (*R*)-(+)-1-phenylethyl sulphide (0.62 g, 3.36 mmol), $[\alpha]_{\text{D}}^{23} + 84.8^\circ$ (*c* 0.65 in EtOH); {lit.,⁴ $[\alpha]_{\text{D}}^{25} + 91.0^\circ$ (*c* 6.17 in EtOH)} in HMPA (11 cm³), MeONa (0.17 g, 3.1 mmol) was added at room temperature and this solution was stirred at 80 °C under argon atmosphere. After the solution was cooled to room temperature and poured into saturated brine (30 cm³). The solution was extracted with ether (3 × 80 cm³). The combined organic layer was washed with saturated brine (3 × 30 cm³) and water (4 × 40 cm³). This layer was dried (MgSO_4) and the solvent was removed by evaporation. Chromatography on silica gel with ethyl acetate–hexane (1:9) as the eluant yielded optically active (1) (0.542 g, 46%), m.p. 120–121 °C (Found: C, 67.5; H, 5.1. $\text{C}_{20}\text{H}_{18}\text{O}_2\text{S}_2$ requires C, 67.8; H, 5.1%); $[\alpha]_{\text{D}}^{23} + 195.8^\circ$ (*c* 2.08 in CHCl_3); $\delta_{\text{H}}(\text{CDCl}_3)$ 1.49 (3 H, d, *J* 7 Hz, CH_3), 4.36 (1 H, q, *J* 7 Hz, CH), and 6.96–8.15 (14 H, m, ArH); λ_{max} 1 155 and 1 310 cm⁻¹ (SO_2).

Preparation of Optically Active 1-Phenylethyl Benzene-*p*-sulphonylphenyl Sulphoxide (2).—To a stirred solution of the optically active sulphide (1) (449 mg, 1.27 mmol) in chloroform (10 cm³), *m*-chloroperbenzoic acid (330 mg, 1.91 mmol) was added at –50 °C for 1 h. After the solution had been stirred at the same temperature for 2 h, the reaction temperature was raised to room temperature slowly. The solution was diluted in chloroform (5 cm³) and washed with saturated sodium thiosulphate solution. The combined chloroform layer was neutralized with a saturated sodium hydrogencarbonate solution and washed with water (3 × 30 cm³) and dried (MgSO_4). After removal of the solvent, chromatography on silica gel with benzene–ethylacetate (4:1) as the eluant yielded a diastereoisomer of (2) (353 mg, 75%). This diastereoisomer (2) was further purified by being dissolved in absolute ethanol and one diastereoisomer of *S*-configuration at the sulphanyl group and *R*-configuration at the 1-phenylethyl group (81.5 mg, 17%) was obtained, m.p. 151–152 °C (Found: C, 64.8; H, 4.9; S, 17.3. $\text{C}_{20}\text{H}_{18}\text{O}_3\text{S}_2$ requires C, 64.8; H, 4.9; S, 17.3%); $[\alpha]_{\text{D}}^{23} + 87.0^\circ$ (*c* 0.99 in CHCl_3); $\delta_{\text{H}}(\text{CDCl}_3)$ 1.67 (3 H, d, *J* 7 Hz, CH_3), 3.73 (1 H, q, *J* 7 Hz, CH), and 6.79–8.07 (14 H, m, ArH); λ_{max} 1 035 (SO_2), 1 155, and 1 325 cm⁻¹ (SO_2).

Coupling Reaction of Optically Active (2) with Ethylmagnesium Bromide.—To a solution of optically active (2) (56 mg, 0.15 mmol) in tetrahydrofuran (THF) (1.5 cm³), ethylmagnesium bromide (0.15 cm³, 0.15 mmol) in THF solution (1.0 mmol cm⁻³) was added using a syringe, with stirring under an atmosphere of argon at room temperature. After 1 h, water was added and the solution was extracted with dichloromethane (3 × 10 cm³). The combined dichloromethane layer was dried (MgSO_4) and the solvent was evaporated. Chromatography on silica gel with hexane–ethylacetate (5:1) as the eluant yielded optically active (*R*)-(+)-(3) (34 mg, 70%), m.p. 137–138 °C

Table. Positional parameters ($\times 10^5$ for *S*, $\times 10^4$) and equivalent isotropic temperature factors (\AA^2) for non-H atoms. ESD values are in parentheses.

$$B_{\text{eq}} = 4/3 \sum_i \sum_j \beta_{ij} a_i a_j$$

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}
(a) (2)				
S(1)	34 714(18)	29 305(10)	–15 649(4)	3.44(3)
S(2)	7 919(22)	62 359(11)	1 447(4)	4.20(3)
O(1)	5 924(5)	2 844(3)	–1 582(1)	4.64(9)
O(2)	2 145(6)	1 844(3)	–1 544(1)	4.71(9)
O(3)	–1 573(6)	5 881(4)	279(1)	6.40(12)
C(11)	2 600(8)	3 775(4)	–2 054(1)	3.50(11)
C(12)	4 053(10)	4 624(5)	–2 228(2)	5.16(16)
C(13)	3 416(12)	5 308(6)	–2 616(2)	6.73(20)
C(14)	1 315(12)	5 122(6)	–2 813(2)	6.56(20)
C(15)	–143(11)	4 280(6)	–2 639(2)	6.42(19)
C(16)	441(9)	3 588(5)	–2 247(2)	4.82(14)
C(21)	2 748(7)	3 835(4)	–1 076(1)	3.13(11)
C(22)	689(8)	3 678(4)	–862(1)	3.99(12)
C(23)	101(8)	4 404(4)	–482(2)	3.95(12)
C(24)	1 643(8)	5 253(4)	–324(1)	3.52(11)
C(25)	3 720(8)	5 423(4)	–544(2)	3.80(12)
C(26)	4 278(8)	4 699(4)	–921(1)	3.70(12)
C(30)	2 721(9)	5 621(5)	596(2)	4.15(13)
C(31)	2 747(8)	6 521(4)	992(1)	3.54(12)
C(32)	4 649(9)	7 262(4)	1 050(2)	4.16(13)
C(33)	4 743(10)	8 064(5)	1 420(2)	5.27(15)
C(34)	2 964(9)	8 163(5)	1 729(2)	4.97(15)
C(35)	1 067(9)	7 458(5)	1 669(2)	5.05(15)
C(36)	956(8)	6 639(5)	1 303(2)	4.48(14)
C(37)	2 051(14)	4 358(5)	730(2)	7.50(23)
(b) (3)				
S(1)	–1 673(6)	9 152(5)	–6 348(8)	3.38(1)
O(1)	–1 484(2)	1 350(1)	200(3)	4.56(5)
O(2)	–65(2)	872(1)	–3 024(3)	4.84(5)
C(11)	–246(3)	–72(1)	376(4)	3.33(5)
C(12)	–999(4)	–222(2)	2 296(5)	4.22(7)
C(13)	–1 182(4)	–1 009(2)	3 003(5)	5.46(9)
C(14)	–595(4)	–1 622(2)	1 781(6)	5.42(9)
C(15)	167(4)	–1 473(2)	–108(8)	5.64(9)
C(16)	364(3)	–690(2)	–857(5)	4.61(7)
C(21)	1 669(3)	1 344(1)	573(3)	2.91(5)
C(22)	3 011(3)	1 339(2)	–655(4)	3.76(6)
C(23)	4 407(3)	1 742(2)	158(4)	3.86(6)
C(24)	4 465(3)	2 171(1)	2 154(4)	2.99(5)
C(25)	3 129(3)	2 144(1)	3 407(4)	3.47(5)
C(26)	1 729(3)	1 731(1)	2 622(4)	3.37(5)
C(30)	5 999(3)	2 648(1)	2 930(4)	3.34(5)
C(31)	5 605(3)	3 485(1)	3 668(4)	3.47(6)
C(32)	4 715(4)	3 987(2)	2 145(6)	5.13(8)
C(33)	4 403(4)	4 768(2)	2 708(8)	6.78(11)
C(34)	4 933(5)	5 057(2)	4 790(9)	6.81(11)
C(35)	5 803(6)	4 572(2)	6 334(8)	6.90(11)
C(36)	6 138(4)	3 784(2)	5 767(5)	4.95(8)
C(37)	7 061(3)	2 170(2)	4 695(5)	4.67(7)

(Found: C, 74.4; H, 5.7; S, 10.1. $\text{C}_{20}\text{H}_{18}\text{O}_2\text{S}$ requires C, 74.5; H, 5.6; S, 9.9%); $[\alpha]_{\text{D}}^{23} + 3.3^\circ$ (*c* 1.75 in CHCl_3); $\delta_{\text{H}}(\text{CDCl}_3)$ 1.57 (3 H, d, *J* 7 Hz, CH_3), 4.12 (1 H, q, *J* 7 Hz, CH), and 6.66–8.01 (14 H, m, ArH); λ_{max} 1 150 and 1 315 cm⁻¹ (SO_2).

X-Ray Crystallography.—The crystals were grown from an ethanolic solution.

Crystal data. (2) $\text{C}_{20}\text{H}_{18}\text{O}_3\text{S}_2$, *M* = 370.49, Orthorhombic, *a* = 5.868 2(6), *b* = 11.070(1), *c* = 28.603(2) Å, *V* = 1 858.0(3) Å³ (by least-squares refinement using 25 reflections, $64 < 2\theta < 73^\circ$, $\lambda = 1.541 82$ Å), space group $P2_12_12_1$, *Z* = 4, *D*_x = 1.325 Mg m⁻³, *T* = 293 K. Colourless crystal with dimensions of 0.10 × 0.18 × 0.20 mm, $\mu = 2.676$ mm⁻¹. (3) $\text{C}_{20}\text{H}_{18}\text{O}_2\text{S}$,

$M = 322.43$, monoclinic, $a = 8.250\ 6(4)$, $b = 16.774(1)$, $c = 5.976\ 5(4)$ Å, $\beta = 95.597(5)^\circ$, $V = 823.18(8)$ Å³ (by least-squares refinement using 21 reflections, $69 < 2\theta < 74^\circ$, $\lambda = 1.541\ 82$ Å), space group $P2_1$, $Z = 2$, $D_x = 1.301$ Mg m⁻³, $T = 293$ K. Colourless crystal with dimensions of $0.30 \times 0.25 \times 0.07$ mm, $\mu = 1.751$ mm⁻¹.

Data collection and processing. Rigaku AFC-4 diffractometer, $2\theta - \omega$ mode, with graphite-monochromated Cu-K α radiation. Bijvoet pair reflections were included. Background counting time at both ends was 10 s. Three reflections were monitored every 50 reflections. For (2), scan width $\Delta\omega = 1.3 + 0.5^\circ \tan \theta$, scan speed 2° min^{-1} in 2θ , 3 903 reflections measured ($2 < 2\theta < 130^\circ$, $0 \leq h \leq 6$, $0 \leq k \leq 12$, $-33 \leq l \leq 33$), 3 671 unique, giving 2 651 with $|F_o| \leq 3\sigma(F)$. Numerical absorption correction (max and min transmission factors 0.772 and 0.642 respectively). Variation of intensities was less than 7%. For (3), scan width = $1.5 + 0.4 \tan \theta$, scan speed 4° min^{-1} in 2θ , 3 265 reflections measured ($2 < 2\theta < 130^\circ$, $-9 \leq h \leq 9$, $-19 \leq k \leq 19$, $0 < l < 7$), 2 797 unique, giving 2 684 with $|F_o| > 3\sigma(F)$. Numerical absorption correction (max and min transmission factors 0.885 and 0.667 respectively). Variation of intensities was less than 5%.

Structure analysis and refinement. Direct method (MULTAN78⁶), followed by normal Fourier synthesis procedures, hydrogen atoms were found from the D-maps and the remaining ones were obtained from calculation. Block-diagonal least-squares with anisotropic temperature factors for non-H atoms and isotropic ones for H. Further cycles of refinements were carried out on two enantiomorphic structures independently, taking into account the anomalous dispersion effect. $\Sigma w(|F_c| - k^{-1}|F_o|)^2$ was minimized. For (2), $w = 1/(1.560 - 0.0478|F_o| + 0.0008|F_o|^2)$; the final R value with $S_S R_C$ configuration was 0.051 ($wR = 0.051$) while that with $R_S S_C$ was 0.062. For 230 Bijvoet paired reflections under the conditions of $|F_o| > 5.0$, $0.1 < (\sin \theta/\lambda) < 0.5$ and $\Delta F/\langle F \rangle = 2 \{ |F_o(hkl)| - |F_o(\bar{h}\bar{k}l)| \} / \{ |F_o(hkl)| + |F_o(\bar{h}\bar{k}l)| \} > 0.1$, R values were 0.060 for $S_S R_C$ and 0.091 for $R_S S_C$. $\Delta\rho_{\text{max}} = 0.38$ e

Å⁻³, ($\Delta/\sigma_{\text{max}} = 0.121$, $s = 1.013$). For (3), $w = 1/\{\sigma^2(F_o) + 0.003|F_o|^2\}$; the final R value with R_C configuration was 0.046 ($wR = 0.39$) while that with S_C was 0.060 ($wR = 0.056$). For 84 paired reflections under the conditions of $|F_o| > 3.0$, $0.1 < (\sin \theta/\lambda) < 0.5$ and $\Delta F/\langle F \rangle > 0.1$, R values were 0.046 for R_C and 0.130 for S_C . $\Delta\rho_{\text{max}} = 0.31$ e Å⁻³, ($\Delta/\sigma_{\text{max}} = 0.114$, $s = 1.001$).

Atomic scattering factors from International Tables for X-Ray Crystallography.⁷ All computations were performed on a HITAC M260D Computer of the Data Processing Centre of the University of Electro-Communications with the programs MULTAN78, UNICS III,⁸ and ORTEP II.⁹ The atomic parameters of non-H atoms are listed in the Table. Tables of atomic parameters for H-atoms, bond lengths and angles and anisotropic temperature factors for non-H atoms are available on request from the Cambridge Crystallographic Data Centre.*

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* For details see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, 1990, p. xviii, section 5.0.