Synthesis and Absolute Configuration of the Enantiomers of 7-Fluoro-1-methyl-3-(methylsulfinyl)-4(1*H*)-quinolinone (Flosequinan)

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The enantiomers of 7-fluoro-1-methyl-3-(methylsulfinyl)-4(1*H*)-quinolinone [(±)-1, flosequinan], a new drug for the treatment of heart failure, were synthesized from the optically active (*R*)-α-methylbenzylamine derivatives of quinoline. The key intermediates, (*R*)-α-methylbenzylamine derivatives, were prepared by diastereomeric separation. The configuration of (+)-1 was assigned on the basis of an X-ray crystallographic analysis of the synthetic precursor (4a). The absolute configuration was found to be (*R*)-(+)-1 and (*S*)-(−)-1.

Keywords flosequinan; asymmetric sulfur; absolute configuration; X-ray crystallography; diastereomeric separation; quinolinone derivative

The quinolinone derivative, 7-fluoro-1-methyl-3-(methylsulfinyl)-4(1*H*)-quinolinone [(±)-**1**, flosequinan][1] is a new orally active vasodilator which exerts both arterial and venous dilator effects.[2,3] In pharmacological and pharmacokinetic studies of flosequinan it has also been shown that the sulfone metabolite has interesting pharmacological activity.[4] This compound has an asymmetric sulfur at the 3-position of the quinolinone ring and thus two enantiomers exist. In order to investigate differences in the biological activity and stereoselective metabolism, the pure enantiomers of flosequinan were needed. Optically active sulfoxides have usually been prepared by asymmetric oxidation[5] of the corresponding sulfides. We describe here the synthesis of optically active flosequinan *via* diastereomeric separation of the (*R*)-α-methylbenzylamine derivatives and the determination of their absolute configuration by X-ray crystallographic analysis of the synthetic precursor (**4a**).

Synthesis Initially, we tried asymmetric oxidation of 7-fluoro-1-methyl-3-(methylthio)-4(1*H*)-quinolinone[1] according to Kagan's method.[5] However, this did not give a satisfactory result.

Next, we attempted to separate a racemic sulfoxide compound (**3**) *via* the diastereomeric (*R*)-α-methylbenzylamine derivatives (**4a** and **4b**). Oxidation of 4-chloro-7-fluoro-3-(methylthio)quinoline (**2**)[1] with *m*-chloroperbenzoic acid (*m*-CPBA) afforded the sulfoxide (**3**), which was converted to the benzylamine derivatives by condensation with (*R*)-α-methylbenzylamine in dioxane. The diastereomeric mixture was recrystallized twice from ethyl acetate to give **4a**. The recovered crystals from the first mother liquor of **4a** were recrystallized from ethyl acetate–diethyl ether to afford **4b**. The optical purities of **4a** and **4b** appeared to be 99.2% and 100% ee, respectively, as determined by high-performance liquid chromatography (HPLC) using a chiral stationary phase column.

Hydrolysis of the benzylamine (**4a**) with 1 N hydrochloric acid (HCl) gave (−)-4-amino-7-fluoro-3-(methylsulfinyl)quinoline [(−)-**5**]. Finally, the target compound [(−)-**1**] was prepared from the aminoquinoline [(−)-**5**] by methylation and hydrolysis with methyl iodide in the presence of potassium carbonate (K_2CO_3).

The opposite isomer [(+)-**1**] was obtained similarly from the other benzylamine (**4b**). The optical purities of (−)-**1** and (+)-**1** were determined to be 98.5% and 99.6% ee, respectively, by HPLC.

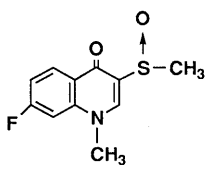
X-Ray Analysis A stereoscopic view of the molecule of **4a** is shown in Fig. 1. The absolute configuration of the chiral sulfoxide was determined as *S*, which was based on the stereochemistry of the (*R*)-α-methylbenzyl group. Consequently, the sulfoxide in a series of (−)-compounds derived from **4a** was of the *S* configuration. An ORTEP drawing of (*S*)-(−)-**1** is shown in Fig. 2.

Experimental

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on a Bruker A-200 spectrometer. Mass spectra (MS) were obtained on a Varian MAT-312 instrument. Optical rotations were measured on a DIP-360 digital polarimeter (Japan Spectroscopic Co., Ltd.).

4-Chloro-7-fluoro-3-(methylthio)quinoline (2) Phosphoryl chloride (11 ml, 116 mmol) was added to a solution of 7-fluoro-3-(methylthio)-4(1*H*)-quinolinone and 5-fluoro-3-(methylthio)-4(1*H*)-quinolinone (6.07 g, 29 mmol) in $CHCl_3$ (80 ml) and the reaction mixture was refluxed for 2.5 h, then allowed to cool. After removal of $POCl_3$, the residue was poured into ice-water, adjusted to pH 9 (NaOH aqueous solution) and extracted with CH_2Cl_2. The extract were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane : AcOEt = 5 : 1) and recrystallized from Et_2O–hexane to give **2** (5.0 g, 76%) as colorless needles, mp 119—120 °C. NMR δ: 2.66 (3H, s), 7.35—7.50 (1H, m), 7.71 (1H, dd, J = 9.62, 2.54 Hz), 8.20 (1H, dd, J = 9.32, 5.82 Hz), 8.78 (1H, s). IR (KBr): 3440, 1560, 1485, 1175 cm^{-1}. *Anal.* Calcd for $C_{10}H_7ClFNS$: C, 52.75; H, 3.10; N, 6.15. Found: C, 52.78; H, 3.24; N, 6.13.

4-Chloro-7-fluoro-3-(methylsulfinyl)quinoline (3) *m*-CPBA (80%,



1 (flosequinan)

Chart 1

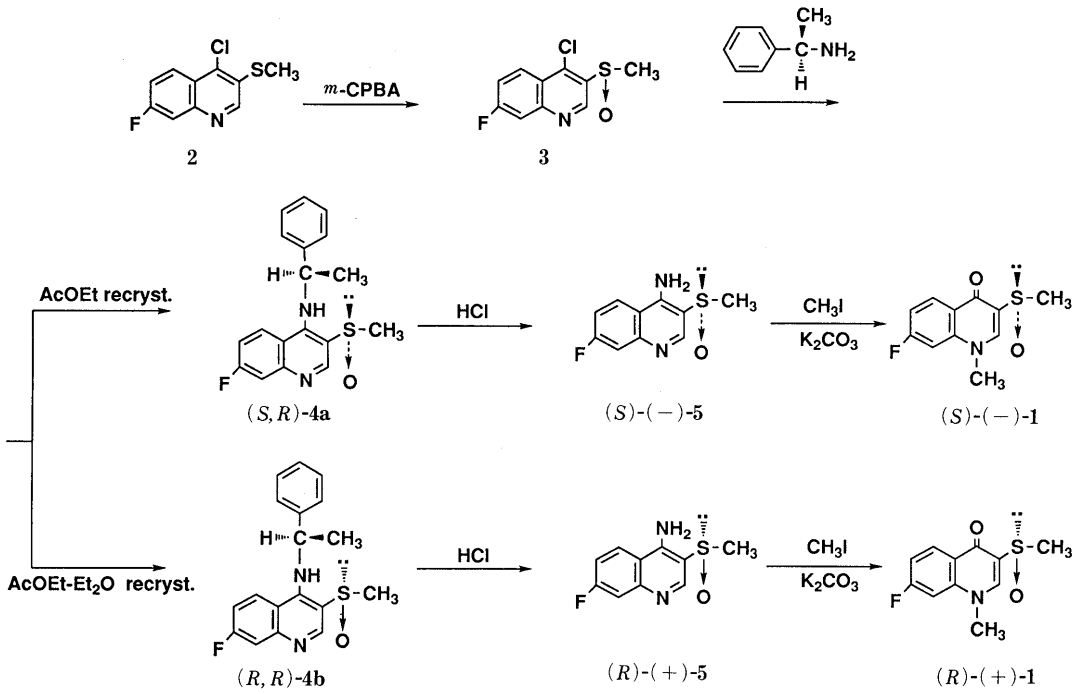


Chart 2

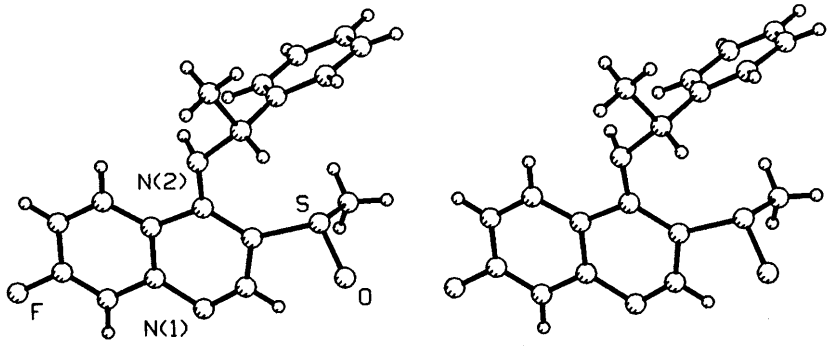


Fig. 1. Stereoscopic View of **4a**

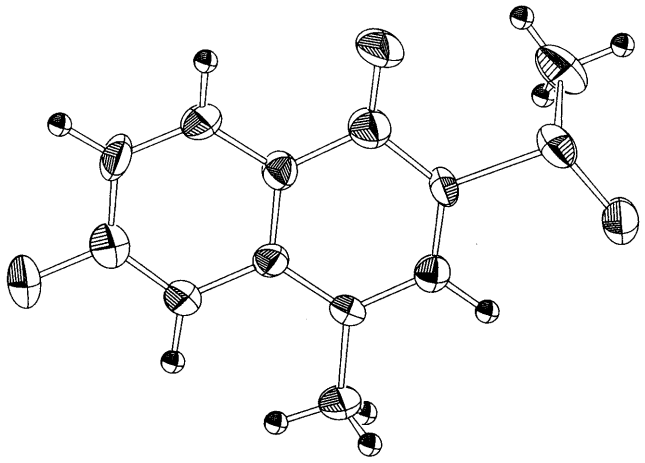


Fig. 2. ORTEP Drawing of (*S*)-(−)-**1**

Thermal ellipsoids are drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

5.2 g, 24.2 mmol) was added to a stirred and ice-cooled solution of **2** (4.78 g, 21 mmol) in $CHCl_3$ (100 ml) and the reaction mixture was stirred at the same temperature for 30 min. The mixture was washed with Na_2CO_3 aqueous solution and dried over $MgSO_4$. After removal of $CHCl_3$, the residue was purified by column chromatography (silica gel, hexane : AcOEt = 1 : 2) and recrystallized from MeOH to give **3** (5.1 g, 95%) as colorless needles, mp 197—197.5 °C. NMR δ: 2.98 (3H, s), 7.50—7.60 (1H, m), 7.86 (1H, dd, J=9.48, 2.53 Hz), 8.29 (1H, dd, J=9.33, 5.73 Hz), 9.31 (1H, s). IR (KBr): 3430, 1625, 1490, 1060 cm^{-1}. *Anal.* Calcd for $C_{10}H_7ClFNOS$: C, 49.29; H, 2.90; N, 5.75. Found: C, 49.47; H, 2.88; N, 5.74.

Reaction of 4-Chloro-7-fluoro-3-(methylsulfinyl)quinoline (3) with (*R*)-α-methylbenzylamine A solution of **3** (5.1 g, 21 mmol) and (*R*)-α-methylbenzylamine (5.1 g, 42 mmol) in dioxane (60 ml) was refluxed for 16 h. After removal of dioxane, the residue was purified by column chromatography (silica gel, hexane : AcOEt : MeOH = 2 : 6 : 0.05) to give **4a** and **4b** (6.3 g) as a pale yellow powder. Two recrystallizations from AcOEt gave (*S*,*R*)-**4a** (2.6 g, 38%) as colorless needles, mp 183—184 °C, $[\alpha]_D^{25}$ −288° (c=1, MeOH). NMR δ: 1.72 (3 H, d, J=6.70 Hz), 2.67 (1H, s), 5.15—5.35 (1H, m), 7.05—7.20 (1H, m), 7.25—7.50 (5H, m), 7.56 (1H, dd, J=9.98, 2.75 Hz), 7.88 (1H, br s), 7.98 (1 H, dd, J=9.45, 5.83 Hz), 8.45 (1H, s). IR (KBr): 3370, 1625, 1535, 1025 cm^{-1}. *Anal.* Calcd for $C_{18}H_{17}FN_2OS$: C, 65.83; H, 5.22; N, 8.53. Found: C, 65.83; H, 5.22; N, 8.39. The recovered crystals from the first mother liquor of (*R*,*S*)-**4a** were recrystallized from AcOEt–Et_2O to give (*R*,*R*)-**4b** (1.8 g, 26%) as colorless needles, mp 109—109.5 °C, $[\alpha]_D^{25}$ +20.0° (c=1, MeOH). NMR δ: 1.74 (3H, d, J=6.66 Hz), 2.98 (3H, s), 5.15—5.35 (1H, m), 6.95—7.10 (1H, m), 7.20—7.45 (5H, m), 7.52 (1H, dd, J=10.00, 2.75 Hz), 8.02 (1H, dd, J=9.46, 5.86 Hz), 8.05 (1H, br s), 8.44 (1H, s). IR (KBr): 3350, 1630, 1575, 1015 cm^{-1}. *Anal.* Calcd for $C_{18}H_{17}FN_2OS$·

H_2O: C, 62.41; H, 5.53; N, 8.09. Found: C, 62.54; H, 5.49; N, 8.07.

Determination of the Optical Purities of 4a and 4b Compounds **4a** and **4b** were each subjected to HPLC (column, Chiralcel OD, 4.6 mm i.d. × 15 cm; solvent, EtOH; flow rate, 0.5 ml/min; detection, UV 254 nm). The optical purities were determined to be as follows; **4a**, 99.2% ee (t_R 8.0 min); **4b**, 100% ee (t_R 9.1 min).

(3*S*)-4-Amino-7-fluoro-3-(methylsulfinyl)quinoline [(*S*)-(−)-5] A solution of (*S*,*R*)-**4a** (0.39 g, 1.2 mmol) in 1 N HCl (35 ml) was stirred at 75—80 °C for 1 h, then allowed to cool. The mixture was extracted with Et_2O. The aqueous layer was made alkaline with Na_2CO_3 aqueous solution and concentrated *in vacuo*. The residue was recrystallized from AcOEt to give (*S*)-(−)-**5** (0.27 g, 98%) as colorless needles, mp 208—210 °C, $[\alpha]_D^{25}$ −138° (c=1, MeOH). NMR δ: 3.01 (3H, s), 6.74 (2H, br s), 7.25—7.40 (1H, m), 7.62 (1H, dd, J=10.00, 2.58 Hz), 7.82 (1H, dd, J=9.20, 5.64 Hz), 8.41 (1H, s). IR (KBr): 3350, 3195, 1650, 1450, 1015 cm^{-1}. *Anal.* Calcd for $C_{10}H_9FH_2OS$: C, 53.56; H, 4.05; N, 12.49. Found: C, 53.54; H, 4.04; N, 12.35.

(3*R*)-4-Amino-7-fluoro-3-(methylsulfinyl)quinoline [(*R*)-(+)-5] Compound (*R*)-(+)-**5** (0.27g, 98%) was prepared by a similar procedure to that used for (*S*)-(−)-**5** with (*R*,*R*)-**4b** (0.39 g, 1.2 mmol) and 1 N HCl (35 ml), $[\alpha]_D^{25}$ +146° (c=1, MeOH). *Anal.* Calcd for $C_{10}H_9FN_2OS$: C, 53.56; H, 4.05; N, 12.49. Found: C, 53.55; H, 3.94; N, 12.49.

(3*S*)-7-Fluoro-1-methyl-3-(methylsulfinyl)-4(1*H*)-quinolinone [(*S*)-(−)-1] A mixture of (*S*)-(−)-**5** (0.23 g, 1 mmol), methyl iodide (0.62 ml, 10 mmol) and K_2CO_3 (0.42 g, 3 mmol) in methyl ethyl ketone (25 ml) was stirred at 70—80 °C for 24 h. After removal of the solvent, the residue was poured into water and extracted with CH_2Cl_2. The extract were washed with dilute HCl and saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (eluent, CH_2Cl_2 : MeOH = 30 : 1) and recrystallized from EtOH to give (*S*)-(−)-**1** (31 mg, 13%) as colorless prisms, mp 258—258.5 °C (dec.), $[\alpha]_D^{25}$ −393° (c=1, $CHCl_3$). NMR δ: 2.94 (3 H, s), 3.91 (3H, s), 7.10—7.35 (2H, m), 7.99 (1H, s), 8.45 (1H, dd, J=8.78, 6.32 Hz). IR (KBr): 3440, 3020, 1595, 1045 cm^{-1}. *Anal.* Calcd for $C_{11}H_{10}FNO_2S$: C, 55.22; H, 4.21; N, 5.85. Found: C, 55.29; H, 4.05; N, 5.84.

(3*R*)-7-Fluoro-1-methyl-3-(methylsulfinyl)-4(1*H*)-quinolinone [(*R*)-(+)-1] Compound (*R*)-(+)-**1** (12 mg, 10%) was prepared by a similar procedure to that used for (*S*)-(−)-**1** with (*R*)-(+)-**5** (0.11 g, 0.5 mmol), methyl iodide (0.31 g, 5 mmol) and K_2CO_3 (0.14 g, 1 mmol) in methyl ethyl ketone (12 ml), $[\alpha]_D^{25}$ +405° (c=1, $CHCl_3$). *Anal.* Calcd for $C_{11}H_{10}FNO_2S$: C, 55.22; H, 4.21; N, 5.85. Found: C, 55.15; H, 4.14; N, 5.78.

Determination of the Optical Purities of (*S*)-(−)-1 and (*R*)-(+)-1 Compounds (*S*)-(−)-**1** and (*R*)-(+)-**1** were subjected to HPLC (column, Chiralcel OD, 4.6 mm i.d. × 15 cm; solvent, EtOH; flow rate, 0.5 ml/min; detection, UV 254 nm). The optical purities were determined to be as follows; (*S*)-(−)-**1**, 98.5% ee (t_R 11.5 min); (*R*)-(+)-**1**, 99.6% ee (t_R 26.4 min).

X-Ray Analysis of 4a The needle crystal used for the X-ray study had dimensions of approximately 0.1 × 0.1 × 0.7 mm. All data were obtained on a Rigaku AFC-5S automated four-circle diffractometer with graphite-monochromated MoK_α radiation. Final lattice parameters were obtained from a least-squares refinement using 25 reflections. Crystal data: $C_{18}H_{17}FN_2OS$, M_r=328.40, monoclinic, space group $P2_1$, a=9.234(8), b=7.660(4), c=11.80(1) Å, β=97.39(7)′, V=828(2) Å^3, Z=2, D_c=1.318 g/cm^3, $F(000)$=344 and μ(MoK_α)=2.01 cm^{-1}. The intensities were measured using the $\omega/2\theta$ scan mode up to 45′ in 2θ. Three standard reflections were monitored every 150 measurements. The data were corrected for Lorentz and polarization factors, but no absorption correction was applied. Of the 1672 independent reflections which were collected, 885 reflections with $I>2\sigma(I)$ were used for the structure determination and refinement. The structure was solved using the program package TEXSAN.[6] All non-H atoms were found in the Fourier map, and H atoms at calculated positions were included for the structure calculation. Refinement by the full-matrix least-squares method with anisotropic temperature factors was carried out for non-H atoms. At final convergence, R=0.076, R_w=0.046, with $w=4F_o^2/\sigma^2(F_o)^2$, goodness of fit=2.57 and $(\Delta/\sigma)_{max}$=0.03 for 207 parameters.[7] The minimum and maximum peaks in the final difference Fourier map were −0.36 and 0.40 eÅ^{-3}. Atomic coordinates for the non-H atom of **4a** are given in Table I. Atomic scattering factors were taken from International Tables for X-ray Crystallography.[8] Computation was carried out on a Digital Micro VAX 3300.

TABLE I. Atomic Coordinates for the Non-H Atoms of **4a** with Their e.s.d.'s in Parentheses

$$B_{eq}=(8/3)\pi^2\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*a_ia_j$$

Atom	x	y	z	B_{eq}
S	0.2937 (4)	0.2632	0.7014 (3)	4.0 (2)
F	0.072 (1)	0.861 (1)	0.1406 (7)	5.9 (5)
O	0.231 (1)	0.085 (1)	0.6672 (9)	5.4 (6)
N(1)	0.205 (1)	0.368 (2)	0.371 (1)	4.9 (7)
N(2)	0.191 (1)	0.679 (2)	0.6662 (8)	3.4 (6)
C(1)	0.237 (2)	0.310 (2)	0.473 (1)	4.0 (8)
C(2)	0.248 (1)	0.395 (2)	0.579 (1)	3.7 (8)
C(3)	0.205 (1)	0.576 (2)	0.576 (1)	2.7 (6)
C(4)	0.172 (2)	0.663 (2)	0.464 (1)	3.5 (8)
C(5)	0.144 (2)	0.835 (2)	0.445 (1)	3.5 (8)
C(6)	0.113 (2)	0.902 (2)	0.339 (1)	3.8 (8)
C(7)	0.106 (2)	0.792 (2)	0.246 (1)	3.9 (8)
C(8)	0.133 (2)	0.625 (2)	0.257 (1)	4.2 (8)
C(9)	0.169 (2)	0.550 (2)	0.366 (1)	4 (1)
C(10)	0.217 (2)	0.635 (2)	0.788 (1)	4.3 (8)
C(11)	0.376 (2)	0.633 (2)	0.838 (1)	3.4 (7)
C(12)	0.414 (2)	0.554 (2)	0.943 (1)	4.6 (9)
C(13)	0.557 (2)	0.539 (2)	0.992 (1)	6 (1)
C(14)	0.665 (2)	0.613 (2)	0.938 (2)	5 (1)
C(15)	0.630 (2)	0.692 (2)	0.835 (1)	5 (1)
C(16)	0.485 (2)	0.704 (2)	0.786 (1)	3.8 (8)
C(17)	0.132 (1)	0.776 (2)	0.850 (1)	4.8 (7)
C(18)	0.487 (2)	0.248 (3)	0.697 (1)	7 (1)

e.s.d., estimated standard deviations.

TABLE II. Atomic Coordinates for the Non-H Atoms of **1** with Their e.s.d.'s in Parentheses

$$B_{eq}=(8/3)\pi^2\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*a_ia_j$$

Atom	x	y	z	B_{eq}
S(11)	0.9158 (3)	0.1670 (1)	0.5713 (1)	3.16 (7)
F(12)	0.6044 (7)	−0.1051 (2)	0.9224 (2)	5.0 (2)
O(14)	0.9692 (4)	0.1125 (3)	0.5076 (2)	4.4 (2)
O(15)	0.7671 (9)	0.2105 (3)	0.7184 (2)	5.4 (3)
N(7)	0.8021 (8)	−0.0481 (3)	0.6810 (3)	2.6 (3)
C(1)	0.652 (1)	−0.0481 (4)	0.8695 (4)	3.4 (4)
C(2)	0.702 (1)	−0.0793 (4)	0.8041 (4)	2.9 (3)
C(3)	0.748 (1)	−0.0202 (3)	0.7488 (4)	2.4 (2)
C(4)	0.738 (1)	0.0683 (3)	0.7637 (4)	2.6 (3)
C(5)	0.688 (1)	0.0950 (4)	0.8333 (3)	3.1 (3)
C(6)	0.644 (1)	0.0385 (4)	0.8867 (3)	3.4 (4)
C(8)	0.8483 (8)	0.0101 (4)	0.6287 (3)	2.4 (3)
C(9)	0.839 (1)	0.0957 (4)	0.6405 (3)	2.4 (3)
C(10)	0.782 (1)	0.1319 (4)	0.7083 (4)	3.3 (4)
C(13)	0.700 (1)	0.2134 (4)	0.5478 (3)	4.6 (4)
C(16)	0.813 (1)	−0.1394 (4)	0.6642 (3)	3.8 (4)

Determination of the Absolute Configurations of (+)- and (−)-1 The absolute stereochemistry of the levo enantiomer [(−)-**4a**] was determined to be 3*S*, 4*R* by X-ray crystallographic analysis of (−)-**4a** which derived from commercially available (*R*)-α-methylbenzylamine. Compound (+)-**4b** was then established to possess a 3*R*, 4*R* configuration. Thus, the absolute configurations at S(O) for the isomers of **1** and **5** are assigned as depicted in Chart 2.

X-Ray Analysis of (*S*)-(−)-1 The prism crystal used for the X-ray study had dimensions of approximately 0.3 × 0.3 × 0.3 mm. Data collection, reduction, and refinement were the same as in the previous case. Crystal data: $C_{11}H_{10}FNO_2S$, M_r=232.21, orthorhombic, space group $C222_1$, a=7.33(1), b=15.59(1), c=18.413(8) Å, V=2103(5) Å^3, Z=8, D_c=1.511 g/cm^3, $F(000)$=992 and μ (MoK_α)=2.91 cm^{-1}. Of the 1391 independent reflections which were collected, 881 reflections with $I>3\sigma$ (I) were used for the structure determination and refinement. At

final convergence, $R=0.050$, $R_w=0.037$, goodness of fit $=1.98$ and $(\Delta/\sigma)_{max}=0.02$ for 145 parameters.[7] The minimum and maximum peaks in the final difference Fourier map were -0.29 and $0.28\,e\text{Å}^{-3}$. Atomic coordinates for the non-H atoms of **1** are given in Table II.

References

1) M. F. Sim, D. B. Yates, U.S. Patent 4552884 (1985) [*Chem. Abstr.* **103**, 183569*e* (1985)].
2) A. J. Cowley, R. D. Wynne, J. R. Hampton, *J. Hypertens.*, **2** (suppl. 3), 547 (1984).
3) S. S. Gottlieb, J. L. Halpern, P. D. Kessler, E. Rothlauf, M. Packer, *Circulation*, **76**, IV-445 (1987).
4) R. Falotico, B. J. Haertlein, C. S. Lakas-Weiss, J. J. Salata, A. J. Tobia, *J. Cardiovasc. Pharmacol.*, **14**, 412 (1989).
5) P. Pitchen, E. Dunach, M. N. Deshmukh, H. B. Kagan, *J. Am. Chem. Soc.*, **106**, 8188 (1984); S. Zhao, O. Samuel, H. B. Kagan, *Tetrahedron*, **43**, 5135 (1987).
6) "TEXSAN, TEXRAY Structure Analysis Package," Molecular Structure Corporation, 3200A, Research Forest Drive, The Woodlands, TX77381, U.S.A., 1985.
7) Tables of coordinates and geometry for each compound are available from the authors on request.
8) "International Tables for X-Ray Crystallography," Vol. IV, The Kynoch Press, Birmingham, England, 1964, Table 2.2A.