Stereospecific Acetolysis of *threo*- and *erythro*-2-Aryl-2-[1-(methylthio)ethyl]oxiranes

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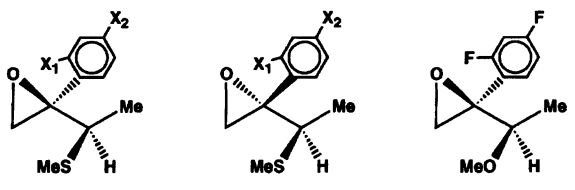
Threo-2-aryl-2-[1-(methylthio)ethyl]oxiranes (**1a—d**) were reacted with acetic acid to give two types of unexpected ring-opening products, *threo*-1-acetoxy-2-aryl-3-methylthio-2-butanols (**4a—d**) and mono-*O*-acetyl derivatives of *threo*-2-aryl-2-methylthio-1,3-butanediol (**5a—d** and **6a—d**). On the other hand, *erythro*-2-aryl-2-[1-(methylthio)ethyl]oxiranes (**2a—d**) gave *erythro*-1-acetoxy-2-aryl-3-methylthio-2-butanols (**7a—d**) and mono-*O*-acetyl derivatives of *erythro*-2-aryl-2-methylthio-1,3-butanediol (**8a—d** and **9a—d**). It is suggested that these products are generated from thiiranium ionic intermediates, because they all completely retain the relative configuration of the starting oxiranes.

α-Substituted styrene oxides are important intermediates for the preparation of potent antifungal compounds.[1—3] We previously reported the synthesis of *threo*- and *erythro*-2-aryl-2-(1-substituted ethyl)oxiranes (**1—3**) in a diastereoselective manner (Fig. 1).[2] In the course of our study on the reactivities of these oxiranes, we observed that oxiranes **1** and **2** gave two types of unexpected ring-opening products upon acetolysis. We herein describe the details of this reaction and the proposed reaction mechanisms.

Results and Discussion

threo-2-Aryl-2-[1-(methylthio)ethyl]oxiranes (**1a—d**) were treated with acetic acid in dichloromethane at 40 °C to give *threo*-1-acetoxy-2-aryl-3-methylthio-2-butanols (**4a—d**) and unexpected rearrangement products, mono-*O*-acetyl derivatives of *threo*-2-aryl-2-methylthio-1,3-butanediol (**5a—d** and **6a—d**) as shown in Scheme 1. On the other hand, *erythro*-2-aryl-2-[1-(methylthio)ethyl]oxiranes (**2a—d**) gave *erythro*-1-acetoxy-2-aryl-3-methylthio-2-butanols (**7a—d**) and mono-*O*-acetyl derivatives of *erythro*-2-aryl-2-methylthio-1,3-butanediol (**8a—d** and **9a—d**). Interestingly, *threo*-oxiranes **1a—d** gave only *threo*-products, and *erythro*-oxiranes **2a—d** gave only *erythro*-products. Moreover, neither *threo*- nor *erythro*-2-acetoxy-2-(2,4-difluorophenyl)-3-methylthio-1-butanol (**10** or **11**) were obtained at all, even though they were expected as normal ring-opening products under acidic conditions. The yield and product ratio in the acetolysis of *threo*-oxiranes **1a—d** and *erythro*-oxiranes **2a—d** are shown in Tables 1 and 2. In all cases, products **4a—d** were easily separated from the reaction mixture by silica-gel column chromatography, but **5** and **6** couldn't be. Thus, the product ratio was



1 (*threo*) **2** (*erythro*) **3** (*threo*)

Fig. 1.

Table 1. Acetilysis of *threo*-Epoxide **1a—d**

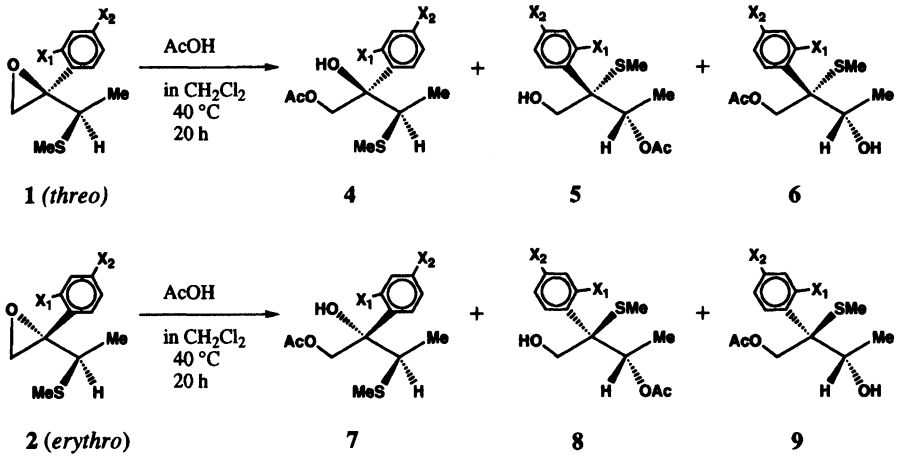
	Substituent		Total yield[a]	Product ratio[b]
	X_1	X_2	%	**4** : **5** : **6**
1a	F	F	98.6	94 : 2 : 4
1b	H	F	95.1	96 : 2 : 2
1c	H	H	96.1	94 : 3 : 3
1d	H	Me	92.1	94 : 3 : 3

a) Isolated yield of product **4**, **5**, and **6**. b) Ratio of **4** vs. (**5**+**6**) was determined by isolated yield. Ratio of **5** vs. **6** was determinated by ^{1}H NMR measurement.

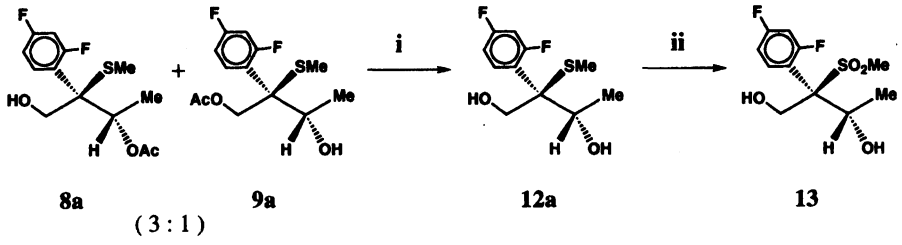
Table 2. Acetilysis of *erythro*-Epoxide **2a—d**

	Substituent		Total yield[a]	Product ratio[b]
	X_1	X_2	%	**7** : **8** : **9**
2a	F	F	87.5	24 : 57 : 19
2b	H	F	82.1	37 : 25 : 38
2c	H	H	82.4	37 : 24 : 39
2d	H	Me	81.2	58 : 17 : 25

a) Isolated yield of product **7**, **8**, and **9**. b) Ratio of **7** vs. (**8**+**9**) was determinated by isolated yield. Ratio of **8** vs. **9** was determinated by ^{1}H NMR measurement.



Scheme 1.



i) K_2CO_3 (2.0 eq.), in MeOH, room temp., 3 h, 92.9 % yield.
ii) 4-chloroperbenzoic acid (3.0 eq.), in CH_2Cl_2, room temp., 1d., 81.6 % yield.

Scheme 2.

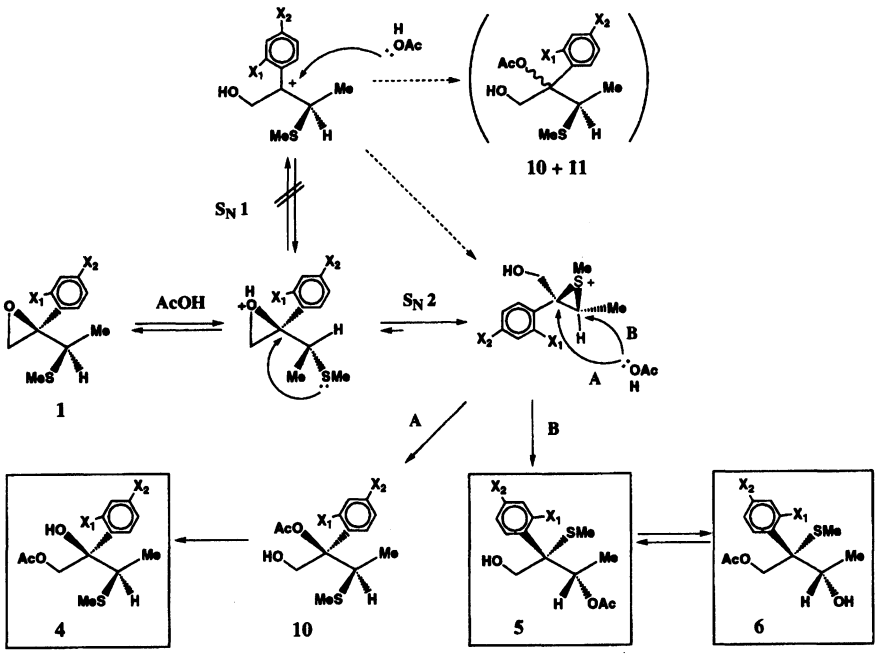


Fig. 2.

determined from the isolated yields of **4** vs. **5** and **6**, and from the NMR peak area ratio of **5** vs. **6**. The product ratio of **7**:**8**:**9** was determined by the same method.

In the reaction of *threo*-oxiranes **1a**—**d** with acetic acid, **4a**—**d** were given as main products in high yields as shown in Table 1. The ratio of products (**4**:**5**:**6**) was quite independent of the substituent pattern on the phenyl ring. On the other hand, in the reaction of *erythro*-oxiranes **2a**—**d** with acetic acid, **8a**—**d** and **9a**—**d** were given in considerable yields as shown in Table 2. In

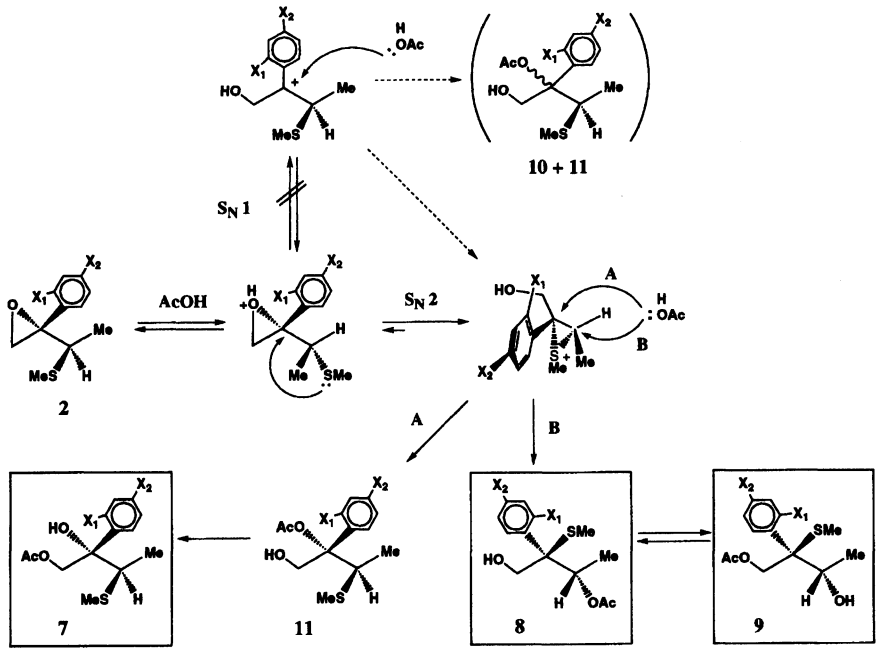
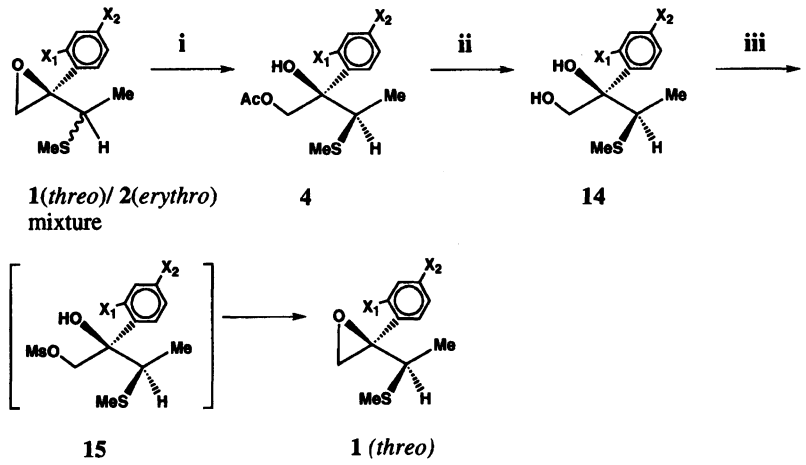


Fig. 3.



i) AcOH (1.7 eq.), in CH_2Cl_2, 40 °C, 20 h
ii) K_2CO_3 (2.0 eq.), in MeOH, room temp., 3 h
iii) MsCl (1.5 eq.), Et_3N (3.0 eq.), in CH_2Cl_2, room temp., 30 min.; then 15 % aq. KOH

Scheme 3.

addition, the yield of **7** became lower, as the electron-withdrawing factor of the substituents on the phenyl ring increased. In contrast, the corresponding 3-methoxy analog, **3**, was quite stable under the same reaction conditions, and didn't give any ring-opening product. The reactivity of the oxiranes is obviously enhanced by the methylthio group.

In this connection, the relative configuration of **8a** and **9a** was confirmed to be *erythro* by X-ray crystallographic analysis of crystalline sulfone **13**, which was given from the mixture of **8a** and **9a** in 2 steps as shown in Scheme 2. The 3:1 mixture of **8a** and **9a** was hydrolyzed to give diol **12a** in a 92.2% yield, which was oxidized by 4-chloroperbenzoic acid to afford sulfone **13** as crystals after recrystallization from dichloromethane.

The proposed reaction mechanism can be summarized in Figs. 2 and 3. From the fact that all the products retain the relative configurations of the starting oxiranes, the mode of the reaction isn't assumed to be S_N1 via a benzyl cationic intermediate, but rather S_N2 via the thiiranium ionic intermediate. The nucleophilic attack of the acetoxyl group on the thiiranium ionic intermediate should take place with complete inversion. Such a thiiranium ionic intermediate will give two types of adducts, since it has two possible positions for nucleophilic attack. When the C-2 position of the intermedi-

ate suffers the nucleophilic attack, 2-acetoxy-1-ols (**10** or **11**) should be produced (path A). However, we could not detect such compounds, because they are probably transformed to the corresponding 1-acetoxy-2-ols (**4** or **7**) at once via acyl rearrangement.[4] In the meantime, when the C-3 position of the intermediate is the target of the nucleophilic attack, sulfur-rearranged product **5** or **8** is yielded (path B). Furthermore, products **6** and **9** are obtained by rearrangement of acyl group on **5** and **8**, respectively.[4]

The difference in the regioselectivities in the nucleophilic attack of the acetoxyl group on the thiiranium ionic intermediate between the *threo*-series and *erythro*-series can be explained as follows. *threo*-Isomers **1a**—**d** prefer path A, because it is easy for thiiranium ionic intermediates generated from them to undergo nucleophilic attack at the more electrophilic C-2 position. Since the phenyl group and the methyl group on these intermediates are placed in *trans* geometry, the C-2 position of the intermediates should not be so bulky (Fig. 2). On the other hand, in the case of thiiranium ionic intermediates generated from *erythro*-isomers **2a**—**d**, the *cis*-methyl group prevents the rotation of the phenyl ring, and this brings steric hindrance to the C-2 position. Thus, the nucleophilic attack occurs at the C-3 position to give rearranged products **8** and **9** in considerable yields (Fig. 3).

With respect to the preparation of the starting materials, *threo*-epoxides **1a**—**d**, free from their *erythro*-isomers, were prepared as shown in Scheme 3.[5] *threo*-Rich epoxide **1a** (*threo*/*erythro*=5 : 1) afforded by a previously reported method,[2] was reacted with acetic acid similar to the method described above. After purification, major product **4a** was hydrolyzed to give *threo*-diol **14a**. Diol **14a** was treated with methanesulfonyl chloride and triethylamine followed by treatment with aqueous KOH solution to regenerate *threo*-epoxide **1a** free from its *erythro*-isomer. Other *threo*-epoxides **1b**, **1c**, and **1d** were prepared by the same method.

Although a number of examples of neighboring sulfur participation have been studied,[6] the formation of thiiranium ions from 2,3-epoxy sulfides has not been reported to any significant degree.[7] Moreover, diols derived from **1a**—**d** by hydrolysis are also useful for synthesis of antifungal agents.[8] Further studies on applications of this reaction will be reported in the near future.

Experimental

Melting points were determined on Thomas–Hoover capillary melting point apparatus and were uncorrected. Infrared spectra (IR) were recorded on a JASCO A-102 IR spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were obtained on a JEOL JNM-GX270 spectrometer (270 MHz) in the designated solvent using tetramethylsilane as an internal standard (δ=0.00). FD-mass spectra were recorded on a Hitachi DF/GC/MS M-80 spectrometer. TLC was performed on precoated glass sheets of silica gel 60 F-254 (E. Merck). Chromatography columns were prepared with silica gel 60 (70—230 mesh, E. Merck). All reagents were obtained from commercial suppliers and used as received unless otherwise indicated. Dichloromethane was dried over molecular sieves 4A.

Acetolysis of *threo*-2-(2,4-Difluorophenyl)-2-[1-(methylthio)ethyl]oxirane (1a): To a solution of *threo*-2-(2,4-difluorophenyl)-2-[1-(methylthio)ethyl]oxirane (**1a**) (230.0 mg, 1.00 mmol) in dichloromethane (3.0 ml) was added acetic acid (0.10 ml, 1.7 equiv), and the mixture was stirred at 40 °C for 20 h. The above reaction mixture was diluted with 50 ml of dichloromethane and washed with 20 ml of saturated sodium hydrogencarbonate. The organic layer was dried over anhydrous sodium sulfate, and then filtered and evaporated in vacuo. The residue was purified by column chromatography on 10 g of silica gel and eluted with hexane and ethyl acetate (4 : 1) to give *threo*-1-acetoxy-2-(2,4-difluorophenyl)-3-methylthio-2-butanol (**4a**, 230.6 mg, 0.930 mmol, 93.0% yield, R_f=0.5 developed with a 1 : 1 mixture of hexane and ether) as a colorless oil, and to give a 1 : 2 mixture of *threo*-3-acetoxy-2-(2,4-difluorophenyl)-2-methylthio-1-butanol (**5a**) and *threo*-4-acetoxy-3-(2,4-difluorophenyl)-3-methylthio-2-butanol (**6a**) (13.9 mg as a mixture, 0.056 mmol, 5.6% yield, R_f=0.3 developed with a 1 : 1 mixture of hexane and ether) as a colorless oil.

4a: IR (neat) 3470, 1740, 1615, 1595, and 1500 cm^{-1}; FD-MS *m*/*z* (%) 290 (M^+, 100); ^{1}H NMR ($CDCl_3$) δ=1.09 (3H, d, *J*=6.9 Hz, CH<u>CH$_3$</u>), 1.88 (3H, s, SCH_3), 2.21 (3H, s, $COCH_3$), 3.22 (1H, q, *J*=6.9 Hz, <u>CH</u>CH_3), 3.69 (1H, s, OH), 4.60 (1H, d, *J*=12.0 Hz, CH_2), 4.97 (1H, d, *J*=12.0 Hz, CH_2), 6.73—6.93 (2H, m), and 7.62 (1H, m).

5a: ^{1}H NMR ($CDCl_3$) δ=1.25 (3H, d, *J*=6.9 Hz, CH<u>CH$_3$</u>), 1.87 (3H, s, SCH_3), 2.00 (3H, s, $COCH_3$), 2.68 (1H, dd, *J*=4.0 and 9.2 Hz, OH), 4.06 (1H, dd, *J*=4.0 and 12.2 Hz, CH_2), 4.30 (1H, dd, *J*=9.2 and 12.2 Hz, CH_2), 5.57 (1H, q, *J*=6.9 Hz, <u>CH</u>CH_3), 6.76—6.96 (2H, m), and 7.81 (1H, m).

6a: ^{1}H NMR ($CDCl_3$) δ=1.22 (3H, d, *J*=7.0 Hz, CH<u>CH$_3$</u>), 1.97 (3H, s, SCH_3), 2.03 (3H, s, $COCH_3$), 2.29 (1H, d, *J*=7.0 Hz, OH), 4.39 (1H, quint., *J*=7.0 Hz, <u>CH</u>CH_3), 4.74 (1H, d, *J*=12.2 Hz, CH_2), 4.85 (1H, d, *J*=12.2 Hz, CH_2), 6.76—6.96 (2H, m), and 7.71 (1H, m).

Acetolysis of *threo*- and *erythro*-2-Aryl-2-[1-(methylthio)ethyl]oxiranes: The following compounds were obtained by the same method as that described for the acetolysis of *threo*-oxirane **1a**. Yields and product ratios are shown in Tables 1 and 2 respectively.

4b: ^{1}H NMR ($CDCl_3$) δ=1.15 (3H, d, *J*=7.2 Hz, CH<u>CH$_3$</u>), 1.96 (3H, s, SCH_3), 2.08 (3H, s, $COCH_3$), 3.06 (1H, q, *J*=7.2 Hz, <u>CH</u>CH_3), 3.16 (1H, s, OH), 4.52 (1H, d, *J*=12.6 Hz, CH_2), 4.58 (1H, d, *J*=12.6 Hz, CH_2), 7.04 (2H, t, *J*=8.9 Hz), and 7.41 (2H, dd, *J*=5.3 and 8.9 Hz).

5b: ^{1}H NMR ($CDCl_3$) δ=1.16 (3H, d, *J*=6.3 Hz, CH<u>CH$_3$</u>), 1.86 (3H, s, SCH_3), 2.03 (3H, s, $COCH_3$), 2.71 (1H, dd, *J*=4.0 and 9.0 Hz, OH), 3.97 (1H, dd, *J*=4.0 and 12.0 Hz, CH_2), 4.10 (1H, dd, *J*=9.0 and 12.0 Hz, CH_2), 5.41 (1H, q, *J*=6.3 Hz, <u>CH</u>CH_3), 6.91—7.11 (2H, m), and 7.30—7.60 (2H, m).

6b: ^{1}H NMR ($CDCl_3$) δ=1.22 (3H, d, *J*=6.6 Hz, CH<u>CH$_3$</u>), 1.82 (3H, s, SCH_3), 2.08 (3H, s, $COCH_3$), 2.24 (1H, d, *J*=5.6 Hz, OH), 4.19 (1H, m, <u>CH</u>CH_3), 4.60 (1H, d, *J*=12.0 Hz, CH_2), 4.83 (1H, d, *J*=12.0 Hz, CH_2), 6.91—7.11 (2H, m), and 7.30—7.60 (2H, m).

4c: ^{1}H NMR ($CDCl_3$) δ=1.16 (3H, d, J=7.0 Hz, $CHCH_3$), 1.95 (3H, s, SCH_3), 2.06 (3H, s, $COCH_3$), 3.10 (1H, q, J=7.0 Hz, $CHCH_3$), 3.15 (1H, s, OH), 4.54 (1H, d, J=11.5 Hz, CH_2), 4.62 (1H, d, J=11.5 Hz, CH_2), and 7.24—7.45 (5H, m).

5c: ^{1}H NMR ($CDCl_3$) δ=1.15 (3H, d, J=6.4 Hz, $CHCH_3$), 1.85 (3H, s, SCH_3), 2.02 (3H, s, $COCH_3$), 2.71 (1H, dd, J=3.6 and 8.9 Hz, OH), 3.99 (1H, dd, J=3.6 and 11.9 Hz, CH_2), 4.17 (1H, dd, J=8.9 and 11.6 Hz, CH_2), 5.45 (1H, q, J=6.4 Hz, $CHCH_3$), and 7.20—7.60 (5H, m).

6c: ^{1}H NMR ($CDCl_3$) δ=1.24 (3H, d, J=6.6 Hz, $CHCH_3$), 1.81 (3H, s, SCH_3), 2.08 (3H, s, $COCH_3$), 2.22 (1H, d, J=5.6 Hz, OH), 4.23 (1H, m, $CHCH_3$), 4.64 (1H, d, J=11.9 Hz, CH_2), 4.87 (1H, d, J=11.9 Hz, CH_2), and 7.20—7.60 (5H, m).

4d: ^{1}H NMR ($CDCl_3$) δ=1.17 (3H, d, J=7.3 Hz, $CHCH_3$), 1.96 (3H, s, SCH_3), 2.05 (3H, s, $COCH_3$), 2.34 (3H, s, $PhCH_3$), 3.08 (1H, q, J=7.3 Hz, $CHCH_3$), 3.11 (1H, s, OH), 4.52 (1H, d, J=11.5 Hz, CH_2), 4.59 (1H, d, J=11.5 Hz, CH_2), 7.15 (1H, d, J=8.0 Hz), and 7.30 (2H, d, J=8.0 Hz).

5d: ^{1}H NMR ($CDCl_3$) δ=1.16 (3H, d, J=6.3 Hz, $CHCH_3$), 1.82 (3H, s, SCH_3), 2.06 (3H, s, $COCH_3$), 2.34 (3H, s, $PhCH_3$), 2.54 (1H, dd, J=5.3 and 7.6 Hz, OH), 3.88 (1H, dd, J=5.3 and 11.5 Hz, CH_2), 4.16 (1H, dd, J=7.6 and 11.5 Hz, CH_2), 5.40 (1H, q, J=6.3 Hz, $CHCH_3$), 7.18 (2H, d, J=8.0 Hz), and 7.40 (2H, d, J=8.0 Hz).

6d: ^{1}H NMR ($CDCl_3$) δ=1.13 (3H, d, J=6.6 Hz, $CHCH_3$), 1.80 (3H, s, SCH_3), 2.11 (3H, s, $COCH_3$), 2.22 (1H, d, J=7.0 Hz, OH), 2.34 (3H, s, $PhCH_3$), 4.22 (1H, quint., J=7.0 Hz, $CHCH_3$), 4.72 (1H, d, J=11.9 Hz, CH_2), 4.82 (1H, d, J=11.9 Hz, CH_2), 7.18 (2H, d, J=8.0 Hz), and 7.40 (2H, d, J=8.0 Hz).

7a: IR ($CHCl_3$) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.42 (3H, d, J=7.0 Hz, $CHCH_3$), 1.77 (3H, s, SCH_3), 1.89 (3H, s, $COCH_3$), 3.36 (1H, q, J=7.0 Hz, $CHCH_3$), 3.60 (1H, s, OH) 4.46 (1H, d, J=11.5 Hz, CH_2), 4.64 (1H, d, J=11.5 Hz, CH_2), 6.77 (1H, m), 6.92 (1H, m), and 7.65 (1H, m).

8a: ^{1}H NMR ($CDCl_3$) δ=1.17 (3H, d, J=6.6 Hz, $CHCH_3$), 1.89 (3H, s, SCH_3), 2.04 (3H, s, $COCH_3$), 2.64 (1H, t, J=7.0 Hz, OH), 4.01 (1H, dd, J=7.0 and 12.0 Hz, CH_2), 4.35 (1H, dd, J=7.0 and 12.0 Hz, CH_2), 5.52 (1H, q, J=6.6 Hz, $CHCH_3$), 6.78—6.97 (2H, m), and 7.81 (1H, m).

9a: ^{1}H NMR ($CDCl_3$) δ=1.20 (3H, d, J=6.6 Hz, $CHCH_3$), 1.86 (3H, s, SCH_3), 2.05 (3H, s, $COCH_3$), 2.44 (1H, d, J=5.6 Hz, OH), 4.39 (1H, m, $CHCH_3$), 4.77 (1H, d, J=12.0 Hz, CH_2), 4.86 (1H, d, J=12.0 Hz, CH_2), 6.78—6.97 (2H, m), and 7.56 (1H, m).

7b: ^{1}H NMR ($CDCl_3$) δ=1.27 (3H, d, J=7.2 Hz, $CHCH_3$), 1.92 (3H, s, SCH_3), 2.00 (3H, s, $COCH_3$), 3.07 (1H, q, J=7.2 Hz, $CHCH_3$), 3.21 (1H, s, OH), 4.47 (1H, d, J=11.6 Hz, CH_2), 4.62 (1H, d, J=11.6 Hz, CH_2), 7.04 (2H, t, J=8.6 Hz), and 7.48 (2H, dd, J=5.3 and 8.6 Hz).

8b: ^{1}H NMR ($CDCl_3$) δ=1.16 (3H, d, J=6.6 Hz, $CHCH_3$), 1.82 (3H, s, SCH_3), 2.06 (3H, s, $COCH_3$), 2.52 (1H, dd, J=5.6 and 7.9 Hz, OH), 3.87 (1H, dd, J=5.6 and 11.9 Hz, CH_2), 4.14 (1H, dd, J=7.9 and 11.9 Hz, CH_2), 5.38 (1H, q, J=6.6 Hz, $CHCH_3$), 7.08 (2H, t, J=8.9 Hz), and 7.53 (2H, dd, J=5.3 and 8.9 Hz).

9b: ^{1}H NMR ($CDCl_3$) δ=1.12 (3H, d, J=6.6 Hz, $CHCH_3$), 1.83 (3H, s, SCH_3), 2.11 (3H, s, $COCH_3$), 2.28 (1H, d, J=6.6 Hz, OH), 4.20 (1H, quint., J=6.6 Hz, $CHCH_3$), 4.67 (1H, d, J=11.9 Hz, CH_2), 4.83 (1H, d, J=11.9 Hz, CH_2), 7.07 (2H, t, J=9.2 Hz), and 7.53 (2H, dd, J=5.3 and 8.9 Hz).

7c: ^{1}H NMR ($CDCl_3$) δ=1.28 (3H, d, J=7.2 Hz, $CHCH_3$), 1.89 (3H, s, SCH_3), 1.99 (3H, s, $COCH_3$), 3.11 (1H, q, J=7.2 Hz, $CHCH_3$), 3.19 (1H, s, OH), 4.49 (1H, d, J=11.5 Hz, CH_2), 4.65 (1H, d, J=11.5 Hz, CH_2), and 7.28—7.52 (5H, m).

8c: ^{1}H NMR ($CDCl_3$) δ=1.17 (3H, d, J=6.3 Hz, $CHCH_3$), 1.82 (3H, s, SCH_3), 2.06 (3H, s, $COCH_3$), 2.55 (1H, dd, J=5.6 and 7.6 Hz, OH), 3.91 (1H, dd, J=5.6 and 11.5 Hz, CH_2), 4.19 (1H, dd, J=7.6 and 11.5 Hz, CH_2), 5.43 (1H, q, J=6.3 Hz, $CHCH_3$), and 7.26—7.56 (5H, m).

9c: ^{1}H NMR ($CDCl_3$) δ=1.13 (3H, d, J=6.6 Hz, $CHCH_3$), 1.81 (3H, s, SCH_3), 2.11 (3H, s, $COCH_3$), 2.24 (1H, d, J=6.6 Hz, OH), 4.24 (1H, quint., J=6.6 Hz, $CHCH_3$), 4.74 (1H, d, J=11.9 Hz, CH_2), 4.85 (1H, d, J=11.9 Hz, CH_2), and 7.28—7.55 (5H, m).

7d: ^{1}H NMR ($CDCl_3$) δ=1.27 (3H, d, J=7.0 Hz, $CHCH_3$), 1.92 (3H, s, SCH_3), 2.00 (3H, s, $COCH_3$), 2.34 (3H, s, $PhCH_3$), 3.09 (1H, q, J=7.0 Hz, $CHCH_3$), 3.14 (1H, s, OH), 4.48 (1H, d, J=11.5 Hz, CH_2), 4.62 (1H, d, J=11.5 Hz, CH_2), 7.16 (2H, d, J=8.0 Hz), and 7.37 (2H, d, J=8.0 Hz).

8d: ^{1}H NMR ($CDCl_3$) δ=1.16 (3H, d, J=6.6 Hz, $CHCH_3$), 1.82 (3H, s, SCH_3), 2.06 (3H, s, $COCH_3$), 2.35 (3H, s, $PhCH_3$), 2.53 (1H, dd, J=5.6 and 7.6 Hz, OH), 3.88 (1H, dd, J=5.6 and 11.5 Hz, CH_2), 4.16 (1H, dd, J=7.6 and 11.5 Hz, CH_2), 5.40 (1H, q, J=6.6 Hz, $CHCH_3$), 7.18 (2H, d, J=8.0 Hz), and 7.40 (2H, d, J=8.0 Hz).

9d: ^{1}H NMR ($CDCl_3$) δ=1.13 (3H, d, J=6.6 Hz, $CHCH_3$), 1.80 (3H, s, SCH_3), 2.11 (3H, s, $COCH_3$), 2.21 (1H, d, J=7.0 Hz, OH), 2.35 (3H, s, $PhCH_3$), 4.22 (1H, quint., J=7.0 Hz, $CHCH_3$), 4.72 (1H, d, J=11.9 Hz, CH_2), 4.82 (1H, d, J=11.9 Hz, CH_2), 7.18 (2H, d, J=8.0 Hz), and 7.40 (2H, d, J=8.0 Hz).

***erythro*-2-(2,4-Difluorophenyl)-2-methylthio-1,3-butanediol (12a):** To a solution of *erythro*-3-acetoxy-2-(2,4-difluorophenyl)-2-methylthio-1-butanol (**8a**) and *erythro*-4-acetoxy-3-(2,4-difluorophenyl)-3-methylthio-2-butanol (**9a**) (152.0 mg, 0.524 mmol, **8a**/**9a**=3 : 1) in methanol (1.5 ml) was added anhydrous potassium carbonate (150 mg, 2.0 equiv), and the mixture was stirred at room temperature for 3 h. Water (20 ml) was added to the reaction mixture, which was then extracted with chloroform (30 ml×3). The combined organic layers were washed with 30 ml of saturated ammonium chloride, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give diol **12a** (120.7 mg, 0.487 mmol, 92.9% yield: Colorless crystals; mp 62.5—64.5 °C; IR (KBr) 3400, 1610, 1590, and 1500 cm^{-1}; FD-MS m/z (%) 248 (M^+, 100); ^{1}H NMR ($CDCl_3$) δ=1.18 (3H, d, J=6.9 Hz, $CHCH_3$), 1.77 (3H, s, SCH_3), 2.77 (1H, d, J=8.0 Hz, OH), 2.94 (1H, dd, J=4.3 and 8.9 Hz, OH), 4.05 (1H, dd, J=4.3 and 12.0 Hz, CH_2), 4.37 (1H, dq, J=8.0 and 6.9 Hz, $CHCH_3$), 4.56 (1H, dd, J=8.9 and 12.0 Hz, CH_2), 6.77—6.95 (2H, m), and 7.56 (1H, m). Found: C, 53.20; H, 5.71; S, 13.24%. Calcd. for $C_{11}H_{14}O_2F_2S$: C, 53.21; H, 5.68; S, 12.91%.

***erythro*-2-(2,4-Difluorophenyl)-2-methylsulfonyl-1,2-butanediol (13):** To a solution of diol **12a** (189.6 mg, 0.764 mmol) in dichloromethane (3.0 ml) was added 4-chloroperbenzoic acid (494 mg, 80% assay, 3.0 equiv) at 0

°C. After being stirred at 0 °C for 30 min, the mixture was stirred at room temperature overnight. The reaction mixture was quenched with 20 ml of 10% aq Na_2SO_3 and diluted with 100 ml of ethyl acetate. The mixture was stirred for 5 min, and the aqueous layer was then separated and extracted with 50 ml of ethyl acetate. The combined organic layers were washed with 30 ml of saturated sodium hydrogencarbonate, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give 223 mg of sulfone **13** as a crude crystalline powder. This was recrystallized from dichloromethane to give pure **13** as colorless crystals (174.7 mg, 0.623 mmol, 81.6% yield: mp 128.5—129.0 °C; IR (KBr) 3400, 1615, 1600, and 1510 cm^{-1}; ^1H NMR (CD_3OD) δ=1.14 (3H, d, J=6.9 Hz, $CH\underline{CH_3}$), 3.03 (3H, s, SO_2CH_3), 4.67 (2H, s, CH_2), 5.16 (1H, q, J=6.9 Hz, $\underline{CH}CH_3$), 6.92—7.06 (2H, m), and 7.85 (1H, m). Found: C, 46.97; H, 5.07; S, 11.80%. Calcd for $C_{11}H_{14}O_4F_2S$: C, 47.14; H, 5.03; S, 11.44%.

Preparation of *threo*-Epoxide 1a Free from Its *erythro*-Isomer 2a: To a solution of a *threo*-rich mixture of oxiranes **1a** and **2a** (300.0 mg, 1.303 mmol) in dichloromethane (3.0 ml) was added acetic acid (0.10 ml, 1.35 equiv), and the mixture was stirred at 40 °C for 16 h. This reaction mixture was diluted with 50 ml of dichloromethane and washed with 20 ml of saturated sodium hydrogencarbonate. The organic layer was dried over anhydrous sodium sulfate, and then filtered and evaporated in vacuo. The residue was purified by column chromatography on 15 g of silica gel being eluted with hexane and ethyl acetate (4:1) to give *threo*-1-acetoxy-2-(2,4-difluorophenyl)-3-methylthio-2-butanol (**4a**, 265.3 mg, 0.915 mmol, 70.2% yield). The above obtained **4a** (97.6 mg, 0.336 mmol) was dissolved in 1.0 ml of methanol. To the solution was added anhydrous potassium carbonate (100 mg, 2.0 equiv), and the mixture was stirred at room temperature for 3 h. Water (20 ml) was added to the reaction mixture, which was then extracted with chloroform (30 ml×3). The combined organic layers were washed with 30 ml of saturated ammonium chloride, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give *threo*-diol **14a** (74.0 mg, 0.298 mmol, 88.8% yield): A colorless oil; IR (neat) 3350, 1610, 1595, and 1500 cm^{-1}; FD-MS m/z (%) 290 (M^+, 100); ^1H NMR ($CDCl_3$) δ=1.12 (3H, d, J=6.9 Hz, $CH\underline{CH_3}$), 2.00 (1H, br, OH), 2.20 (3H, s, SCH_3), 3.26 (1H, q, J=6.9 Hz, $\underline{CH}CH_3$), 3.55 (1H, br, OH), 3.83 (1H, d, J=11.5 Hz, CH_2), 4.32 (1H, d, J=11.5 Hz, CH_2), 6.72—7.02 (2H, m), and 7.70 (1H, m). Found: C, 53.15; H, 5.56; S, 12.90%. Calcd for $C_{11}H_{14}O_4F_2S$: C, 53.21; H, 5.68; S, 12.91%.

Diol **14a** (50.6 mg, 0.204 mmol) was then dissolved in 2.0 ml of dry dichloromethane under argon atmosphere. To the solution was added triethylamine (0.1 ml, 3.6 equiv), and the mixture was cooled to 0 °C. Methanesulfonyl chloride was added dropwise to the mixture over a 5 min period, and the mixture was stirred at 0 °C. After 30 min, 15% potassium hydroxide solution in water (0.30 g, 4.0 equiv) was added to the reaction mixture, and the resultant two-phase solution was stirred vigorously at 0 °C for 3 h. Water (10 ml) was added to the mixture, which was then extracted with dichloromethane (20 ml×2). The combined organic layers were washed with water (30 ml×3), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give *threo*-epoxide **1a** in a quantitative yield (47.1 mg, 0.204 mmol). The ratio of **1a** vs. **2a** was determined to be 360:1 by HPLC.[5]

Preparation of *threo*-Epoxides 1b—d Free from Their *erythro*-Isomers 2b—d: *threo*-Epoxides **1b—d** free from their *erythro*-isomers **2b—d** were obtained by the same method as that described in the preparation of *threo*-oxirane **1a**. The ^1H NMR spectra of intermediate diols **14b—d** are shown below.

14b: ^1H NMR ($CDCl_3$) δ=1.18 (3H, d, J=6.9 Hz, $CH\underline{CH_3}$), 2.09 (3H, s, SCH_3), 2.50 (1H, t, J=6.8 Hz, OH), 3.11 (1H, q, J=6.9 Hz, $\underline{CH}CH_3$), 3.41 (1H, s, OH), 3.78 (1H, dd, J=6.8 and 11.5 Hz, CH_2), 4.06 (1H, dd, J=6.8 and 11.5 Hz, CH_2), 7.04 (2H, t, J=8.9 Hz), and 7.70 (2H, dd, J=5.3 and 8.9 Hz).

14c: ^1H NMR ($CDCl_3$) δ=1.19 (3H, d, J=7.2 Hz, $CH\underline{CH_3}$), 2.09 (3H, s, SCH_3), 2.43 (1H, t, J=6.9 Hz, OH), 3.14 (1H, q, J=7.2 Hz, $\underline{CH}CH_3$), 3.38 (1H, s, OH), 3.81 (1H, dd, J=6.9, 11.5 Hz, CH_2), 4.11 (1H, dd, J=6.9, 11.5 Hz, CH_2), and 7.25—7.45 (5H, m).

14d: ^1H NMR ($CDCl_3$) δ=1.20 (3H, d, J=7.0 Hz, $CH\underline{CH_3}$), 2.08 (3H, s, SCH_3), 2.34 (3H, s, $PhCH_3$), 2.36 (1H, dd, J=6.3 and 7.6 Hz, OH), 3.12 (1H, q, J=7.0 Hz, $\underline{CH}CH_3$), 3.35 (1H, s, OH), 3.80 (1H, dd, J=6.3 and 11.6 Hz, CH_2), 4.08 (1H, dd, J=7.6 and 11.6 Hz, CH_2), 7.17 (2H, d, J=8.0 Hz), and 7.70 (2H, d, J=8.0 Hz).

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References

1) a) I. Saji, K. Tamoto, T. Tanio, T. Okuda, and T. Atsumi, "8th Medicinal Chemistry Symposium," Osaka, Nov. 1986, Abstr., pp. 9—12; b) I. Saji, Y. Tanaka, K. Ichise, T. Tanio, T. Okuda, and T. Atsumi, European Patent 178533 (1986); *Chem. Abstr.*, **105**, 35613r (1986).

2) I. Saji, K. Tamoto, Y. Tanaka, H. Miyauchi, K. Fujimoto, and N. Ohashi, *Bull. Chem. Soc. Jpn.*, **67**, 1427 (1994).

3) a) A. Tasaka, N. Tamura, Y. Matusita, K. Teranishi, R. Hayashi, K. Okonogi, and K. Itoh, *Chem. Pharm. Bull.*, **41**, 1035 (1993); b) T. Konosu, T. Miyaoka, Y. Tajima, and S. Oida, *Chem. Pharm. Bull.*, **39**, 2241 (1991); c) M. Ogata, H. Matsumoto, S. Shimizu, S. Kida, M. Shiro, and K. Tawara, *Eur. J. Med. Chem.*, **24**, 137 (1989).

4) K. Yamakawa, K. Nishitani, and K. Kasahara, *Chem. Pharm. Bull.*, **27**, 953 (1979), and references cited therein.

5) The ratio of *threo*-/*erythro*-epoxides was determined by HPLC. HPLC conditions are as follows: Column; Sumipax ODS A-212 (5 μm, 6 mmϕ×25 cm), mobile phase; acetonitrile/water=55/45, flow rate; 1.0 ml min^{-1}, detection; UV 210 nm: In the case of **1a**/**2a**, the peak at 17.4 min. corresponded to *threo*-epoxide **1a**, and the peak at 16.3 min. corresponded to *erythro*-one **2a**.

6) M. Ladika, B. Jursic, Z. Mihalic, and D. E. Sanko, *Tetrahedron Lett.*, **27**, 1703 (1986), and references cited therein.

7) a) A. R. Derzhinskii, L. D. Konyushkin, and A. I. Lutsenko, *Izv. Akad. Nauk SSSR*, **11**, 2652 (1984); b) D. M. Gill, N. A. Pegg, and C. M. Rayner, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1371.

8) Y. Tanaka, T. Yuasa, Y. Kawakami, K. Terashima, T. Morita, A. Nishikawa, K. Bando, and M. Kawashima, European Patent 552974 (1993); *Chem. Abstr.*, **120**, 134499 (1993).