Optical Resolution of *dl-threo*-2-(2,4-Difluorophenyl)-2-[1-(methylthio)ethyl]oxirane: Its Application to the Synthesis of SM-9164, a Biologically Active Enantiomer of Antifungal Agent SM-8668

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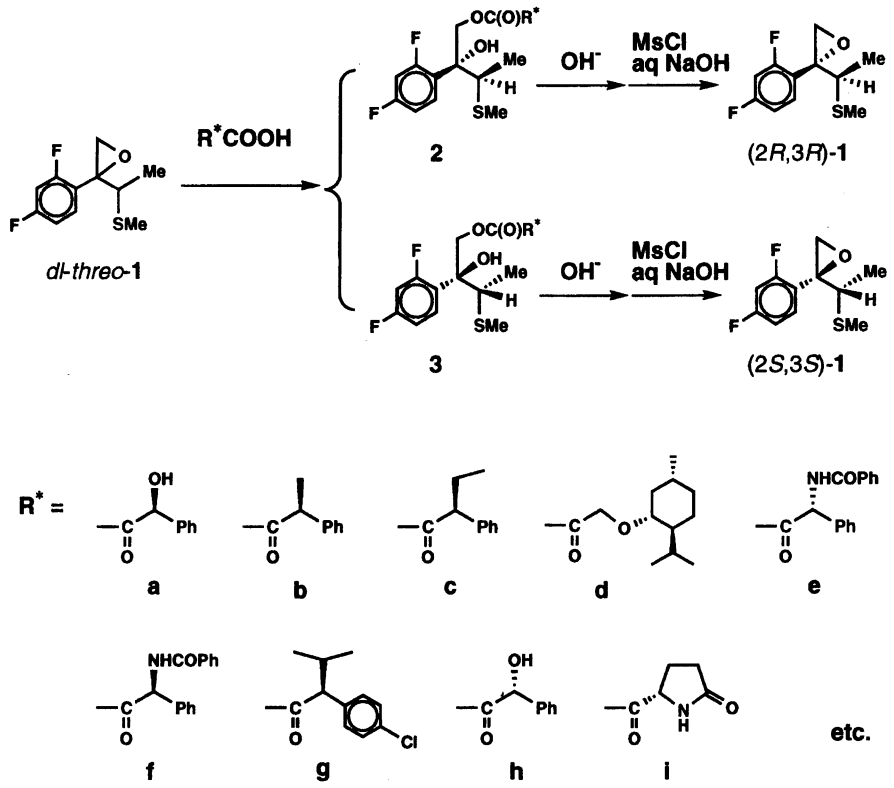
A racemate of *threo*-2-(2,4-difluorophenyl)-2-[1-(methylthio)ethyl]oxirane was separated into two enantiomers by reaction with a chiral carboxylic acid, followed by separation of the resultant diastereomers, hydrolysis of the ester, and dehydration of the 1,2-diol to the oxirane. This new optical resolution method was applied to the synthesis of SM-9164, a biologically active enantiomer of antifungal agent SM-8668. Thus, the optically active isomer of SM-8668 was prepared efficiently in eight steps from *m*-difluorobenzene.

α-Substituted styrene oxides are important intermediates for the preparation of antifungal compounds.[1—3] We previously reported that *threo*-2-(2,4-difluorophenyl)-2-[1-(methylthio)ethyl]oxirane (**1**) was reacted with acetic acid to give *threo*-1-acetoxy-2-aryl-3-methylthio-2-butanols in high yield.[4] As expected from our recent result that **1** could react with a variety of carboxylic acids as well as acetic acid, reaction of *dl*-**1** with a chiral carboxylic acid should give a separable mixture of optically active diastereomers **2** and **3**. As outlined in Scheme 1, thus obtained **2** and **3** should regenerate oxirane **1** in an optically active form. We herein describe this new methodology of optical resolution of *dl*-**1**, and its application to the synthesis of (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (SM-9164) (**5**), which is a biologically active enantiomer of antifungal agent SM-8668[1,6] and shows higher antifungal activity than SM-8668 both in vitro and in vivo.[5]

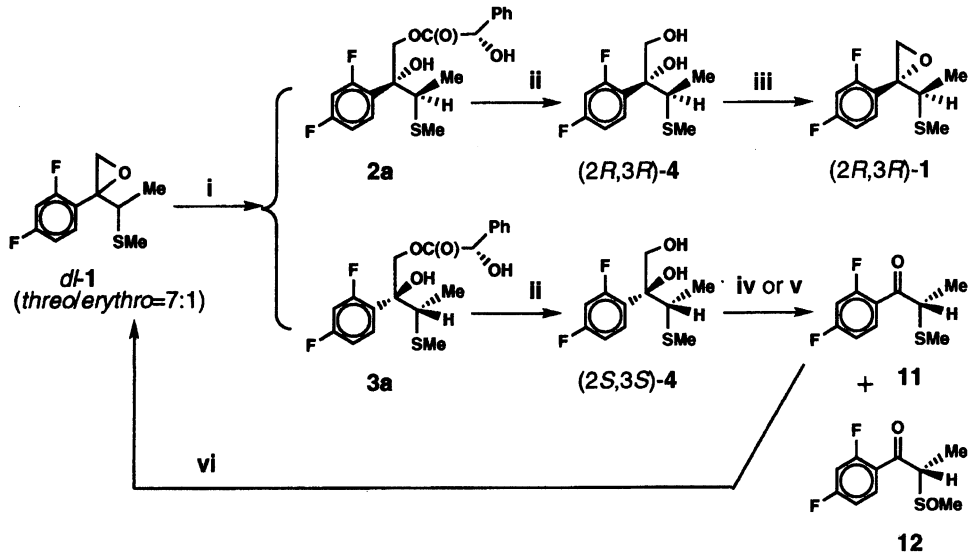
Results and Discussion

A racemate of oxirane **1** was prepared in 84% overall yield in three steps from *m*-difluorobenzene, as described in our previous report.[2] This oxirane **1** was reacted with various chiral carboxylic acids to give a 1 : 1 diastereomeric mixture of **2** and **3**, which was easily separated by silica-gel column chromatography or fractional crystallization. In the case of reaction of *dl-threo*-**1** with R*COOH, the mixture could be separated by silica-gel column chromatography, when R*COOH was chosen from (+)-2-phenylpropionic acid, (+)-2-phenylbutyric acid, (−)-menthoxyacetic acid, *N*-benzoyl-D-phenylglycine,[7] (+)-2-(4-chlorophenyl)-3-methylbutyric acid,[8] and their enantiomers. In contrast, in the case of reaction with R*COOH, **2** could be separated from the mixture by fractional crystallization, when R*COOH was chosen from L-mandelic acid [(+)-2-hydroxy-2-phenylacetic acid], (+)-2-(4-chlorophenyl)-3-methylbutyric acid, and *N*-benzoyl-D-phenylglycine. Similarly, in the case of reaction with R*COOH, **3** could be separated from the mixture by fractional crystallization, when R*COOH was chosen from D-mandelic acid, (−)-pyroglutamic acid [(−)-2-oxoproline], and *N*-benzoyl-L-phenylglycine. The resulting single isomer of **2** or **3** could respectively regenerate optically active oxirane **1** by alkaline hydrolysis followed by dehydration of the resulting 1,2-diol **4** consisting of regioselective mesylation and alkaline treatment. These steps proceeded with complete retention of absolute configuration of **2**.

As shown in Scheme 2, for a typical example, *dl*-**1** (*threo*/*erythro*=7 : 1) was treated with 1.0 equivalent of L-mandelic acid in toluene at reflux temperature for 3 h to afford a 1 : 1 diastereomeric mixture of esters **2a** and **3a**, one of which was precipitated from toluene–heptane (1 : 1) and collected by filtration. The crystalline powder was then recrystallized from toluene–heptane (2 : 3) to give L-mandelate **2a** as a single isomer[9] in 31% yield. Next, this ester was hydrolyzed with sodium hydroxide in a mixture of toluene and water to give (2*R*,3*R*)-**4**. Then, it was treated with methanesulfonyl chloride in toluene and 30% aqueous sodium hydroxide in presence of a catalytic amount of benzyltriethylammonium chloride[10] to afford (2*R*,3*R*)-**1** quantitatively. Thus, racemic **1** was resolved into optically active **1** in 30% overall yield. An optical resolution method for epoxides such as described here is novel in that diastereo-



Scheme 1.



i) L-mandelic acid, toluene, reflux, 3 h (**2a**; 31% yield, 100% e.e., **3a**; 41% yield, 62% e.e.)
ii) NaOH, toluene, 60 °C, 3 h (quant.)
iii) MsCl, BnN^+Et_3 Cl^- (cat.), 30 % aq NaOH, toluene, 0 °C, 2.5 h (quant.)
iv) $Pb(OAc)_4$, toluene, 0 °C, 3 h (**11**; 84%)
v) $NaIO_4$, MeOH, H_2O, 0 °C, 9 h (**11**; 40%, **12**; 25%)
vi) $Me_3S^+(O)$ Cl^-, 48% aq NaOH, CH_2Cl_2, r.t., 4 h (97%, *threo/erythro*=7:1)

Scheme 2.

meric esters are directly generated from epoxide *dl*-**1** and chiral carboxylic acids. Generally, *dl*-epoxides has been resolved after transformed to the corresponding *dl*-diols by ring-cleavage reaction.[11)]

The ring-opening reaction of *dl*-**1** with a chiral carboxylic acid should proceed in the same mechanism as

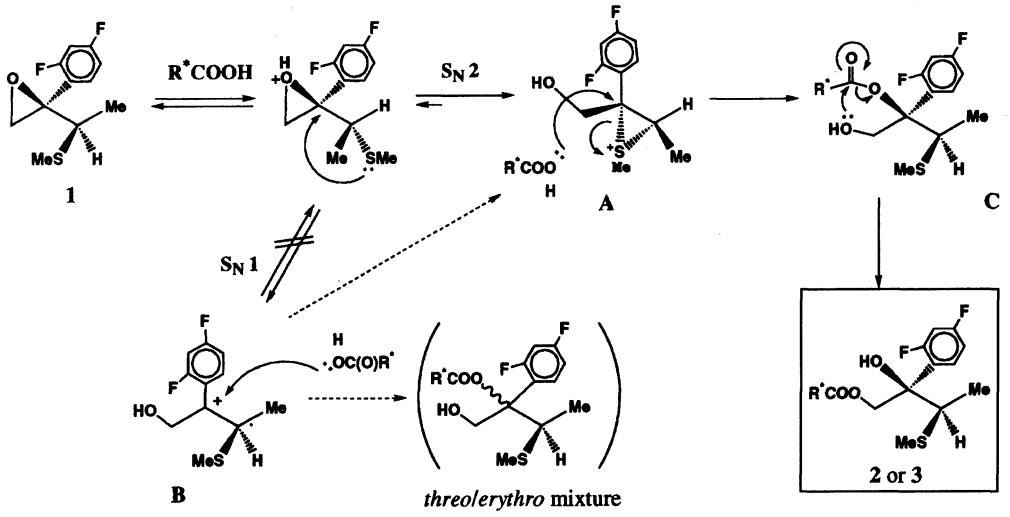
we previously reported on acetolysis of *dl*-**1**,[4] as summarized in Scheme 3. Since *dl-threo*-**1** gave diastereomers **2** and **3** in high yield and did not afford any amount of their corresponding (2*R*,3*S*)- or (2*S*,3*R*)-isomer, the mode of the reaction is not assumed to be S_N1 via benzyl cationic intermediate **B**, but rather S_N2 via thiiranium ionic intermediate **A**. The nucleophilic attack of a carboxyl group on the thiiranium ionic intermediate should take place with complete inversion to give 2-acyloxyl compound **C**. However, because of immediate rearrangement of acyl group, we could not detect **C** at all, but obtained 1-acyloxyl compounds **2** and **3**.

Attempting to improve this optical resolution method further, we investigated the reaction of *dl*-**1** with a chiral sulfonic acid instead of a chiral carboxylic acid. If we can obtain sulfonate **6** or **7** as a single isomer, the number of steps for the optical resolution will be decreased. However, reaction of *dl*-**1** with anhydrous *d*-camphorsulfonic acid gave neither sulfonate **6** nor **7**, and afforded aldehyde **8** and enal **9**, as shown in Scheme 4. When the reaction was carried out at 0 °C for 4 h, aldehyde **8** was afforded in 23% yield as a 3:2 unseparable mixture and enal **9** was afforded in 35% as a single isomer. Aldehyde **8** should be generated via 1,2-hydride shift[12] of hydrogen atom on 3-position of *dl*-**1**. In fact, the reaction of 3,3,1′-trideuterated *dl*-**1** (containing 81, 81, and 82 atom % of deuterium in order)[13] with *d*-camphorsulfonic acid gave 1,2,3-trideuterated **8** as a 2:1 mixture. The contents of deuterium on C-1, C-2, and C-3 positions of the major isomer were 79, 73, and 81 atom % in order, and those of the minor isomer were 79, 46, and 81 atom % of deuterium in order. On the other hand, enal **9** should be generated via aldehyde **8** by further treatment of **8** with *d*-camphorsulfonic acid. Indeed, a longer reaction time made the ratio of **9** increase. Geometry of the olefin on enal **9** was determined to be *E*-, since the nuclear Overhauser effect was observed on the vinyl proton of allyl alcohol **10** (derived from enal **9** by reduction with diisobutylaluminum hydride) when methylene protons of **10** was irradiated.

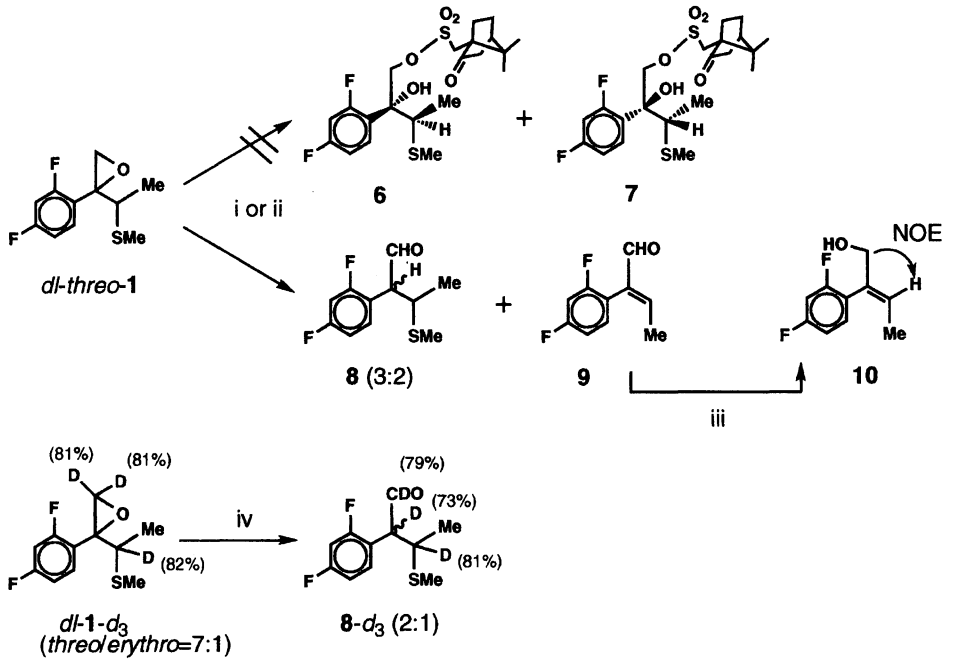
In addition, in case that only (2*R*,3*R*)-isomer of **1** is required, ester **3a**, which should give an undesirable isomer of **1**, can be recycled. As shown also in Scheme 2, **3a** was hydrolyzed with sodium hydroxide in a mixture of toluene and water to give (2*S*,3*S*)-**4**. Then, 1,2-diol (2*S*,3*S*)-**4** was oxidatively cleaved with 1.2 equivalent of lead(IV) acetate in toluene at 0 °C for 3 h to give optically active ketone **11** in 84% yield. In contrast, a considerable yield of sulfoxide **12** was afforded together with desired **11**, when sodium periodate or manganese(IV) oxide was used as an oxidizing reagent. Finally, optically active ketone **11** was treated with dimethylsulfoxonium methylide generated from trimethylsulfoxonium chloride and 48% aqueous sodium hydroxide in dichloromethane[2] to give oxirane **1** (*threo*/*erythro*=7:1) with complete loss of chirality. Thus, desirable isomer (2*R*,3*R*)-**1** was obtained from racemic **1** in more than 48% overall yield after recycling an undesirable ester **3a** three times.

Optically active oxirane (2*R*,3*R*)-**1**, obtained by the method described above, is a useful intermediate for preparation of antifungal agent SM-9164 (**5**) As shown in Scheme 5, (2*R*,3*R*)-**1** was treated with 1*H*-1,2,4-triazole in presence of sodium hydroxide at 80 °C to give **13** as a crystalline powder in 76% yield.[2] Then, sulfide **13** was oxidized with hydrogen peroxide in presence of a catalytic amount of sodium tungstate under acidic conditions to afford sulfone **5** in 92% yield.[2,14] The absolute configuration of **5** was confirmed to be 2*R*,3*R* by X-ray crystallographic analysis.

As described above, SM-9164 (**5**) was prepared in 28% overall yield in eight steps from *m*-difluorobenzene. This synthetic route for **5** should be one of the best one in the points of an overall yield and the number of

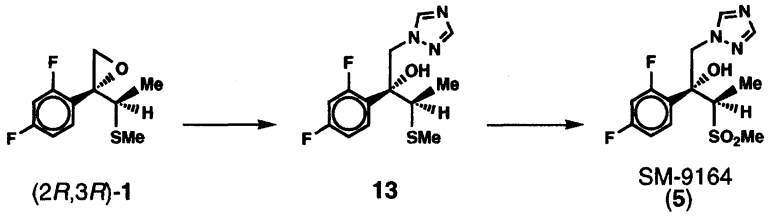


Scheme 3.



i) *d*-camphorsulfonic acid, MeCN, 0 °C, 4 h (**8**; 23%, **9**; 35%)
ii) *d*-camphorsulfonic acid, MeCN, 0 °C, 24 h (**8**; 7%, **9**; 53%)
iii) DIBAL-H, ether, -20 °C, 1 h (74%)
iv) *d*-camphorsulfonic acid, MeCN, 0 °C, 4 h (**8**-d_3; 9%)

Scheme 4.



i) 1*H*-1,2,4-triazole, NaOH, DMSO, 80 °C, 3 h (76%)
ii) 35% aq H_2O_2, concd HCl, Na_2WO_4 (cat.), H_2O, 40 °C, 2 h (92%)

Scheme 5.

steps, though there are a few other synthetic reports on **5**, including optical resolution of SM-8668,[15] synthesis from (*S*)-2-chloropropionyl chloride[16] and preparation from L-threonine.[17]

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). Measurement of optical rotations were performed with a JASCO DIP-370. 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. Ether was dried over molecular sieves 4A.

Reaction of Racemic Oxirane 1 with L-Mandelic Acid: To a solution of *dl*-oxirane **1** (71.15 g, 309.0 mmol, *threo*/*erythro*=7:1) in toluene (800 ml) was added L-mandelic acid (48.30 g, 317.4 mmol), and the mixture was stirred for 3 h at reflux temperature. After washed with saturated sodium hydrogencarbonate (200 ml), the toluene layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. A 1:1 mixture of toluene and heptane (190 ml) was added to the residue, and the resulting precipitates were collected by filtration. It was then recrystallized from a 2:3 mixture of toluene and heptane (180 ml) to give ester **2a** as a single isomer[9] (36.16 g, 31% yield based on *dl*-**1**): A colorless crystalline powder; mp 110.5—112.0 °C; $[\alpha]_D^{25}$ −0.8° (*c* 0.5, $CHCl_3$); IR (KBr) 3470, 1710, 1610, 1600, and 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.01 (3H, d, *J*=7.2 Hz, CHC<u>H</u>$_3$), 2.17 (3H, s, SCH_3), 3.10 (1H, q, *J*=7.2 Hz, <u>CH</u>CH_3), 3.23 (1H, d, *J*=5.6 Hz, CH<u>OH</u>), 3.35 (1H, s, OH), 4.62 (1H, d, *J*=11.8 Hz, CH_2), 5.03 (1H, d, *J*=11.8 Hz, CH_2), 5.00 (1H, d, *J*=5.6 Hz, <u>CH</u>OH), 6.52—6.72 (2H, m), 7.09—7.15 (2H, m), and

7.20—7.33 (4H, m). Found: C, 59.53; H, 5.33%. Calcd for $C_{19}H_{20}F_2O_4S$: C, 59.67; H, 5.27%. In addition, the resulting filtrates were combined together and concentrated under the reduced pressure. This was then purified by column chromatography on 1.0 kg of silica gel eluting with hexane and ethyl acetate (3 : 1) to give a mixture of ester **2a** and **3a** (58.85 g, 50% yield, **2a** : **3a**=19 : 81 determined by HPLC[9]): A pale yellow oil; $[\alpha]_D^{25}$ +40.5° (*c* 0.6, $CHCl_3$); ^1H NMR of **3a** ($CDCl_3$) δ=1.04 (3H, d, *J*=7.2 Hz, CH<u>CH</u>$_3$), 2.13 (3H, s, SCH_3), 2.35 (1H, s, OH), 3.12 (1H, br.s, CH<u>OH</u>), 3.17 (1H, q, *J*=7.2 Hz, <u>CH</u>CH_3), 4.72 (1H, d, *J*=11.5 Hz, CH_2), 4.78 (1H, d, *J*=11.8 Hz, CH_2), 5.00 (1H, s, <u>CH</u>OH), 6.56—6.84 (2H, m), 7.08—7.15 (2H, m), and 7.18—7.36 (4H, m).

Reaction of Racemic Oxirane 1 with Other Chiral Carboxylic Acid: The following esters were obtained by the same method as described above. They were separated and purified by either column chromatography or fractional crystallization.

2b [R=(*S*)-2-Phenylpropionyl]: Colorless crystals; mp 85.0—87.0 °C; $[\alpha]_D^{25}$ −37.1° (*c* 0.5, $CHCl_3$); IR (KBr) 3450, 1715, 1615, 1600, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.03 (3H, d, *J*=6.9 Hz, CH(SCH_3)<u>CH</u>$_3$), 1.31 (3H, d, *J*=6.9 Hz, CHPh<u>CH</u>$_3$), 2.17 (3H, s, SCH_3), 3.11 (1H, q, *J*=6.9 Hz, <u>CH</u>(SCH_3)CH_3), 3.53 (1H, d, *J*=7.2 Hz, <u>CH</u>PhCH$_3$), 3.74 (1H, s, OH), 4,56 (1H, d, *J*=11.9 Hz, CH_2), 4.92 (1H, d, *J*=11.9 Hz, CH_2), 6.58—6.74 (2H, m), 6.98—7.03 (2H, m), 7.18—7.24 (3H, m), and 7.35 (1H, m). Found: C, 62.79; H, 5.76%. Calcd for $C_{20}H_{22}F_2O_3S$·1/5 H_2O: C, 62.55; H, 5.88%.

3b [R=(*S*)-2-Phenylpropionyl]: Colorless crystals; mp 98.0—102.0 °C; $[\alpha]_D^{25}$ +54.1° (*c* 0.5, $CHCl_3$); IR (KBr) 3500, 1720, 1615, 1600, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.05 (3H, d, *J*=6.9 Hz, CH(SCH_3)<u>CH</u>$_3$), 1.29 (3H, d, *J*=7.2 Hz, CHPh<u>CH</u>$_3$), 2.16 (3H, s, SCH_3), 3.15 (1H, q, *J*=6.9 Hz, <u>CH</u>(SCH_3)CH_3), 3.52 (1H, d, *J*=7.2 Hz, <u>CH</u>PhCH$_3$), 3.60 (1H, s, OH), 4.66 (1H, d, *J*=11.9 Hz, CH_2), 4.76 (1H, d, *J*=11.9 Hz, CH_2), 6.66 (1H, m), 6.76 (1H, m), 7.00—7.06 (2H, m), 7.18—7.23 (3H, m), and 7.45 (1H, m). Found: C, 62.76; H, 5.79%. Calcd for $C_{20}H_{22}F_2O_3S$·1/5 H_2O: C, 62.55; H, 5.88%.

2c [R=(*S*)-2-Phenylbutyryl]: Colorless crystals; mp 48.0—54.0 °C; $[\alpha]_D^{25}$ −18.6° (*c* 0.5, $CHCl_3$); IR (KBr) 3450, 1740, 1615, 1600, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.73 (3H, t, *J*=7.2 Hz, $CHCH_2$<u>CH</u>$_3$), 1.03 (3H, d, *J*=6.9 Hz, CH<u>CH</u>$_3$), 1.63 (1H, m, CH<u>CH</u>$_2$CH$_3$), 1.88 (1H, m, CH<u>CH</u>$_2$CH$_3$), 2.17 (3H, s, SCH_3), 3.11 (1H, q, *J*=6.9 Hz, <u>CH</u>CH_3), 3.25 (1H, t, *J*=7.9 Hz, <u>CH</u>CH_2CH_3), 3.73 (1H, s, OH), 4.59 (1H, d, *J*=11.9 Hz, CH_2), 4.90 (1H, d, *J*=11.9 Hz, CH_2), 6.59—6.71 (2H, m), 6.98—7.05 (2H, m), 7.18—7.24 (3H, m), and 7.33 (1H, m). Found: C, 63.63; H, 6.07%. Calcd for $C_{21}H_{24}F_2O_3S$: C, 63.94; H, 6.13%.

3c [R=(*S*)-2-Phenylbutyryl]: A colorless oil; $[\alpha]_D^{25}$ +40.0° (*c* 0.5, $CHCl_3$); IR (neat) 3350, 1735, 1615, 1600, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.72 (3H, t, *J*=7.2 Hz, $CHCH_2$<u>CH</u>$_3$), 1.05 (3H, d, *J*=6.9 Hz, CH<u>CH</u>$_3$), 1.61 (1H, m, CH<u>CH</u>$_2$CH$_3$), 1.86 (1H, m, CH<u>CH</u>$_2$CH$_3$), 2.16 (3H, s, SCH_3), 3.14 (1H, q, *J*=6.9 Hz, <u>CH</u>CH_3), 3.25 (1H, t, *J*=7.9 Hz, <u>CH</u>CH_2CH_3), 3.69 (1H, s, OH), 4,65 (1H, d, *J*=11.9 Hz, CH_2), 4.78 (1H, d, *J*=11.9 Hz, CH_2), 6.65 (1H, m), 6.75 (1H, m), 6.98—7.06 (2H, m), 7.18—7.24 (3H, m), and 7.46 (1H, m). Found: C, 63.32; H, 6.04%. Calcd for $C_{21}H_{24}F_2O_3S$·1/5 H_2O: C, 63.36; H, 6.18%.

2d [R=*l*-Menthoxyacetyl]: A colorless oil; $[\alpha]_D^{25}$ −69.2° (*c* 0.5, $CHCl_3$); IR (neat) 3450, 1740, 1610, 1600, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.71 (3H, d, *J*=6.9 Hz, CH_3), 0.86 (3H, d, *J*=7.2 Hz, CH_3), 0.89 (3H, d, *J*=6.9 Hz, CH_3), 0.73—1.00 (2H, m), 1.09 (3H, d, *J*=6.9 Hz, CH(SCH_3)<u>CH</u>$_3$), 1.15—1.26 (2H, m), 1.56—1.64 (3H, m), 1.89 (1H, d, *J*=12.2 Hz), 2.14 (1H, m), 2.21 (3H, s, SCH_3), 2.98 (1H, dt, *J*=4.3 and 10.6 Hz), 3.22 (1H, q, *J*=6.9 Hz, <u>CH</u>(SCH_3)CH_3), 3.68 (1H, s, OH), 3.87 (1H, d, *J*=7.6 Hz, O<u>CH</u>$_2$CO$_2$), 3.91 (1H, d, *J*=7.6 Hz, O<u>CH</u>$_2$CO$_2$), 4.69 (1H, d, *J*=11.9 Hz, CH_2), 4.93 (1H, d, *J*=11.9 Hz, CH_2), 6.76 (1H, m), 6.87 (1H, m), and 7.61 (1H, m). Found: C, 61.73; H, 7.46%. Calcd for $C_{23}H_{34}F_2O_4S$·1/5 H_2O: C, 61.64; H, 7.74%.

3d [R=*l*-Menthoxyacetyl]: A colorless oil; $[\alpha]_D^{25}$ −11.4° (*c* 0.5, $CHCl_3$); IR (neat) 3450, 1740, 1615, 1600, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.72 (3H, d, *J*=6.9 Hz, CH_3), 0.86 (3H, d, *J*=7.2 Hz, CH_3), 0.89 (3H, d, *J*=6.9 Hz, CH_3), 0.73—1.00 (2H, m), 1.09 (3H, d, *J*=6.9 Hz, CH(SCH_3)<u>CH</u>$_3$), 1.15—1.26 (2H, m), 1.56—1.65 (3H, m), 1.88 (1H, d, *J*=12.2 Hz), 2.14 (1H, m), 2.21 (3H, s, SCH_3), 2.97 (1H, dt, *J*=4.3, 10.6 Hz), 3.21 (1H, q, *J*=6.9 Hz, <u>CH</u>(SCH_3)CH_3), 3.73 (1H, s, OH), 3.82 (1H, d, *J*=16.5 Hz, O<u>CH</u>$_2$CO$_2$), 3.95 (1H, d, *J*=16.5 Hz, O<u>CH</u>$_2$CO$_2$), 4.68 (1H, d, *J*=11.9 Hz, CH_2), 4.93 (1H, d, *J*=11.9 Hz, CH_2), 6.77 (1H, m), 6.88 (1H,m), and 7.61 (1H, m). Found: C, 61.76; H, 7.46%. Calcd for $C_{23}H_{34}F_2O_4S$·1/5 H_2O: C, 61.64; H, 7.74%.

2e [R=(*R*)-2-Benzamide-2-phenylacetyl]: Colorless crystals; mp 119.0—120.5 °C; $[\alpha]_D^{25}$ −58.6° (*c* 0.5, $CHCl_3$); IR (KBr) 3400, 1730, 1645, 1615, 1605, 1580, 1530, and 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.06 (3H, d, *J*=7.2 Hz, CH<u>CH</u>$_3$), 2.14 (3H, s, SCH_3), 3.17 (1H, q, *J*=7.2 Hz, <u>CH</u>CH_3), 3.27 (1H, s, OH), 4.76 (1H, d, *J*=11.6 Hz, CH_2), 4.86 (1H, d, *J*=11.6 Hz, CH_2), 5.54 (1H, d, *J*=6.6 Hz, <u>CH</u>NH), 6.61 (1H, m), 6.74 (1H, m), 6.93 (1H, d, *J*=6.6 Hz, CH<u>NH</u>), 7.15—7.55 (9H, m), and 7.72—7.77 (2H, m). Found: C, 63.91; H, 5.16; N, 2.89; S, 6.72%. Calcd for $C_{26}H_{25}F_2NO_4S$·1/2 H_2O: C, 63.84; H, 5.23; N, 2.86; S, 6.55%.

3e [R=(*R*)-2-Benzamide-2-phenylacetyl]: A colorless oil; $[\alpha]_D^{25}$ +2.7° (*c* 0.5, $CHCl_3$); IR (KBr) 3400, 1730, 1645, 1620, 1600, 1580, 1520, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.03 (3H, d, *J*=6.9 Hz, CH<u>CH</u>$_3$), 2.17 (3H, s, SCH_3), 3.12 (1H, q, *J*=6.9 Hz, <u>CH</u>CH_3), 3.52 (1H, s, OH), 4.60 (1H, d, *J*=11.9 Hz, CH_2), 5.14 (1H, d, *J*=11.9 Hz, CH_2), 5.55 (1H, d, *J*=6.2 Hz, <u>CH</u>NH), 6.52—6.64 (2H, m), 6.89 (1H, d, *J*=6.2 Hz, CH<u>NH</u>), 7.17—7.55 (9H, m), and 7.71—7.75 (2H, m). Found: C, 63.74; H, 5.13; N, 2.80%. Calcd for $C_{26}H_{25}F_2NO_4S$·1/2 H_2O: C, 63.84; H, 5.23; N, 2.86%.

2f [R=(*S*)-2-Benzamide-2-phenylacetyl]: A colorless oil; $[\alpha]_D^{25}$ −3.5° (*c* 0.5, $CHCl_3$). Found: C, 63.75; H, 4.97; N, 2.84; S, 6.85%. Calcd for $C_{26}H_{25}F_2NO_4S$·1/2 H_2O: C, 63.84; H, 5.23; N, 2.86; S, 6.55%. Ester **2f** showed identical spectral (IR and ^1H NMR) with those recorded for its enantiomer **3e**.

3f [R=(*S*)-2-Benzamide-2-phenylacetyl]: Colorless crystals; mp 119.0—120.5 °C; $[\alpha]_D^{25}$ +59.3° (*c* 0.5, $CHCl_3$). Found: C, 63.53; H, 5.35; N, 2.70; S, 6.70%. Calcd for $C_{26}H_{25}F_2NO_4S$·1/2 H_2O: C, 63.84; H, 5.23; N, 2.86; S, 6.55%. Ester **3f** showed identical spectral (IR and ^1H NMR)

with those recorded for its enantiomer **2e**.

2g [R=(*S*)-2-(4-Chlorophenyl)3-methylbutyryl]: Colorless crystals; mp 82.5—83.0 °C; $[\alpha]_D^{25}$ +41.1° (*c* 0.6, $CHCl_3$); IR (KBr) 3450, 1735, 1615, 1595, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.58 (3H, d, *J*=6.6 Hz, $CHCH(\underline{CH_3})_2$), 0.82 (3H, d, *J*=6.6 Hz, $CHCH(\underline{CH_3})_2$), 1.03 (3H, d, *J*=7.2 Hz, $CH\underline{CH_3}$), 2.10 (1H, m, $CH\underline{CH}(CH_3)_2$), 2.18 (3H, s, SCH_3), 2.92 (1H, d, *J*=11.0 Hz, $\underline{CH}CH(CH_3)_2$), 3.12 (1H, q, *J*=7.2 Hz, $\underline{CH}CH_3$), 3.70 (1H, br, OH), 4.61 (1H, d, *J*=11.9 Hz, CH_2), 4.87 (1H, d, *J*=11.9 Hz, CH_2), 6.60—6.71 (2H, m), 6.97 (2H, d, *J*=8.6 Hz), 7.18 (2H, d, *J*=8.6 Hz), and 7.31 (1H, m). Found: C, 59.63; H, 5.65; S, 6.90; Cl, 8.46%. Calcd for $C_{22}H_{25}ClF_2O_3S$: C, 59.66; H, 5.69; S, 7.24; Cl, 8.00%.

3g [R=(*S*)-2-(4-Chlorophenyl)3-methylbutyryl]: A colorless oil; $[\alpha]_D^{25}$ −42.4° (*c* 1.0, $CHCl_3$); IR (neat) 3450, 1735, 1615, 1595, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.58 (3H, d, *J*=6.6 Hz, $CHCH(\underline{CH_3})_2$), 0.81 (3H, d, *J*=6.6 Hz, $CHCH(\underline{CH_3})_2$), 1.04 (3H, d, *J*=7.2 Hz, $CH\underline{CH_3}$), 2.10 (1H, m, $CH\underline{CH}(CH_3)_2$), 2.18 (3H, s, SCH_3), 2.92 (1H, d, *J*=10.6 Hz, $\underline{CH}CH(CH_3)_2$), 3.13 (1H, q, *J*=7.2 Hz, $\underline{CH}CH_3$), 3.70 (1H, br, OH), 4.66 (1H, d, *J*=11.9 Hz, CH_2), 4.80 (1H, d, *J*=11.9 Hz, CH_2), 6.65 (1H, m), 6.74 (1H, m), 7.00 (2H, d, *J*=8.6 Hz), 7.18 (2H, d, *J*=8.6 Hz), and 7.46 (1H, m). Found: C, 59.01; H, 5.56%. Calcd for $C_{22}H_{25}ClF_2O_3S \cdot 1/5\ H_2O$: C, 59.17; H, 5.73%.

3h [R=(*R*)-2-Hydroxy-2-phenylacetyl (D-Mandelyl)]: Colorless crystals; mp 105.0—108.0 °C; $[\alpha]_D^{25}$ −3.2° (*c* 0.5, $CHCl_3$). Found: C, 59.45; H, 5.30%. Calcd for $C_{19}H_{20}F_2O_4S$: C, 59.67; H, 5.27%. Ester **3h** showed identical spectral (IR and ^1H NMR) with those recorded for its enantiomer **2a**.

3i [R=(*S*)-2-Pyrrolidone-5-carboyl]: Colorless crystals; mp 97.0—100.0 °C; $[\alpha]_D^{25}$ +34.8° (*c* 0.5, $CHCl_3$); IR (KBr) 3450, 1750, 1685, 1615, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.09 (3H, d, *J*=6.9 Hz, $CH\underline{CH_3}$), 1.90 (1H, m), 2.14—2.35 (3H, m), 2.21 (3H, s, SCH_3), 3.24 (1H, q, *J*=6.9 Hz, $\underline{CH}CH_3$), 3.75 (1H, s, OH), 4.05 (1H, t, *J*=6.0 Hz, $\underline{CH}CO_2$), 4.78 (1H, d, *J*=11.6 Hz, CH_2), 4.84 (1H, d, *J*=11.6 Hz, CH_2), 6.18 (1H, br, NH), 6.79 (1H, m), 6.91 (1H, m), and 7.63 (1H, m). Found: C, 53.33; H, 5.22; N, 3.89%. Calcd for $C_{16}H_{19}F_2NO_4S$: C, 53.47; H, 5.33; N, 3.90%.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-methylthio-1,2-butanediol [(2*R*,3*R*)-4]: To a solution of L-mandelate **2a** (35.66 g, 93.2 mmol) in toluene (350 ml) were added water (124 ml) and sodium hydroxide (15.7 g, 98% assay, 384.6 mmol), and the mixture was stirred at 60 °C for 3h. The organic layer was separated and washed with water (100 ml×2). It was dried over anhydrous sodium sulfate, then filtered and evaporated in vacuo to give diol (2*R*,3*R*)-**4** (23.18 g, quantitative yield): A colorless oil; $[\alpha]_D^{25}$ −25.7° (*c* 0.5, $CHCl_3$); IR (neat) 3400, 1610, 1595, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.12 (3H, d, *J*=7.3 Hz, $CH\underline{CH_3}$), 2.20 (3H, s, SCH_3), 2.64 (1H, dd, *J*=5.6, 8.6 Hz, OH), 3.25 (1H, q, *J*=7.3 Hz, $\underline{CH}CH_3$), 3.54 (1H, s, OH), 3.84 (1H, dd, *J*=8.6, 11.5 Hz, CH_2), 4.33 (1H, dd, *J*=5.6, 11.5 Hz, CH_2), 6.78 (1H, m), 6.90 (1H, m), and 7.68 (1H, m). Found: C, 53.18; H, 5.73; S, 12.90%. Calcd for $C_{11}H_{14}F_2O_4S$: C, 53.21; H, 5.68; S, 12.91%.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-2-[1-(methylthio)-ethyl]oxirane [(2*R*,3*R*)-1]: Diol (2*R*,3*R*)-**4** (15.00 g, 56.4 mmol) and benzyltriethylammonium chloride (1.38 g, 6.0 mmol) were added to the two phase solution consisting of toluene (150 ml) and 30% aqueous sodium hydroxide (240.0 g, 1.80 mol), and the mixture was stirred vigorously at 0 °C. Methanesulfonyl chloride (10.39 g, 90.7 mmol) was added dropwise over a 1.5 h period at 0 °C, and it was then stirred at 0 °C for an additional hour. The organic layer was separated and washed with water (100 ml×2). It was dried over anhydrous sodium sulfate, then filtered and evaporated in vacuo to give optically active oxirane **1** (13.01 g, quantitative yield): A colorless oil; $[\alpha]_D^{25}$ −54.4° (*c* 0.5, $CHCl_3$); IR (neat) 1615, 1595, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.26 (3H, d, *J*=7.3 Hz, $CH\underline{CH_3}$), 2.18 (3H, s, SCH_3), 2.86 (1H, d, *J*=5.1 Hz, CH_2), 2.95 (1H, q, *J*=7.3 Hz, $\underline{CH}CH_3$), 3.18 (1H, q, *J*=5.1 Hz, CH_2), 6.75—6.94 (2H, m), and 7.50 (1H, m).

Reaction of Racemic Oxirane 1 with *d*-Camphorsulfonic Acid: To a solution of *dl*-**1** (230.0 mg, 1.00 mmol, *threo*/*erythro*=360:1[4]) in 3.0 ml of acetonitrile was added anhydrous *d*-camphorsulfonic acid (232 mg, 1.0 mmol). The mixture was stirred at 0 °C for 4 h, then it was diluted with chloroform (50 ml), and washed with saturated sodium hydrogencarbonate (10 ml). The organic layer was dried over anhydrous sodium sulfate, then filtered and evaporated in vacuo. The resulting residue was separated by column chromatography on 7.5 g of silica gel, eluting with hexane and ethyl acetate (20:1) to give aldehyde **8** (53.7 mg, 23% yield, a 3:2 mixture of diastereomers, R_f=0.33 developed with 5:1 mixture of hexane and ether) and enal **9** (63.3 mg, 35% yield, R_f=0.25 developed with 5:1 mixture of hexane and ether).

8: A pale yellow oil; ^1H NMR of major isomer ($CDCl_3$) δ=1.17 (3H, d, *J*=7.2 Hz, $CH\underline{CH_3}$), 2.14 (3H, s, SCH_3), 3.41 (1H, dq, *J*=8.0 and 7.2 Hz, $\underline{CH}CH_3$), 3.81 (1H, d, *J*=8.0 Hz, $\underline{CH}$Ph), 6.82—6.95 (2H, m), 7.14—7.28 (1H, m), and 9.83 (1H, s, CHO). ^1H NMR of minor isomer ($CDCl_3$) δ=1.42 (3H, d, *J*=7.2 Hz, $CH\underline{CH_3}$), 2.02 (3H, s, SCH_3), 3.41 (1H, dq, *J*=8.0, 7.2 Hz, $\underline{CH}CH_3$), 3.95 (1H, d, *J*=8.0 Hz, $\underline{CH}$Ph), 6.82—6.95 (2H, m), 7.14—7.28 (1H, m), and 9.79 (1H, s, CHO).

9: Colorless needles; ^1H NMR ($CDCl_3$) δ=1.96 (3H, d, *J*=7.2 Hz, CH_3), 6.84—7.15 (3H, m), 7.02 (1H, q, *J*=7.2 Hz, CH), and 9.60 (1H, s, CHO).

Similarly, anhydrous *d*-camphorsulfonic acid (9.29 g, 40.0 mmol) was added to a solution of *dl*-**1** (9.21 g, 40.0 mmol, *threo*/*erythro*=360:1[4]) in 3.0 ml of acetonitrile, and the mixture was stirred at 0 °C for 24 h. It was worked up in the same manner as described above to give aldehyde **8** (0.67 g, 7 % yield, a 3:2 mixture of diastereomers) and enal **9** (3.86 g, 53% yield).

***dl*-3,3-Dideuterio-2-(2,4-difluorophenyl)-2-[1-deuterio-1-(methylthio)ethyl]oxirane (1-d_3):** To a solution of 1-(2,4-difluorophenyl)-2-methylthio-1-propanone[2] (216 mg, 1.00 mmol) in dichloromethane (3.4 ml) were added trimethyloxosulfonium chloride (195 mg, 1.5 mmol) and 48% sodium hydroxide in deuterium oxide (6.0 g). The resultant mixture was stirred at room temperature for 5 h. The reaction mixture was then diluted with dichloromethane (20 ml), and the organic layer was separated. It was washed with deuterium oxide (10 ml×2), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give **1**-d_3 (223 mg, 97% yield, *threo*/*erythro*=7:1): A colorless oil; ^1H NMR ($CDCl_3$) δ=1.26 (3H, d, *J*=7.2 Hz, CH_3), 2.18 (3H, s, SMe),

2.86 (0.19H, d, J=5.1 Hz), 2.95 (0.18H, q, J=7.2 Hz, CH), 3.18 (0.19H, d, J=5.1 Hz), 6.75—6.94 (2H, m) and 7.50 (1H, m).

Reaction of Trideuterated Oxirane *dl*-1-d_3 with *d*-Camphorsulfonic Acid: To a solution of *dl*-**1**-d_3 obtained above (223 mg, 0.97 mmol, *threo*/*erythro*=7:1) in 3.0 ml of acetonitrile was added anhydrous *d*-camphorsulfonic acid (232.0 mg, 1.0 mmol), and the mixture was stirred at 0 °C for 4 h. It was diluted with chloroform (50 ml) and washed with saturated sodium hydrogencarbonate (10 ml). It was dried over anhydrous sodium sulfate, then filtered and evaporated in vacuo. The resulting residue was separated by column chromatography on 10 g of silica gel eluting with hexane and ethyl acetate (20:1) to give trideuterated aldehyde **8**-d_3 (16.1 mg, 9% yield, a 2:1 mixture of diastereomers): A pale yellow oil; ^{1}H NMR of major isomer ($CDCl_3$) δ=1.17 (3H, d, J=7.2 Hz, CHC<u>H</u>$_3$), 2.14 (3H, s, SCH_3), 3.41 (0.19H, dq, J=8.0 and 7.2 Hz, C<u>H</u>CH_3), 3.81 (0.27H, d, J=8.0 Hz, C<u>H</u>Ph), 6.82—6.95 (2H, m), 7.14—7.28 (1H, m), and 9.83 (0.21H, s, CHO). ^{1}H NMR of minor isomer ($CDCl_3$) δ=1.42 (3H, d, J=7.2 Hz, CHC<u>H</u>$_3$), 2.02 (3H, s, SCH_3), 3.41 (0.19H, dq, J=8.0, 7.2 Hz, C<u>H</u>CH_3), 3.95 (0.54H, d, J=8.0 Hz, C<u>H</u>Ph), 6.82—6.95 (2H, m), 7.14—7.28 (1H, m), and 9.79 (0.21H, s, CHO).

(*E*)-2-(2,4-Difluorophenyl)-2-buten-1-ol (10): A solution of enal **9** (3.85 g, 21.2 mmol) in dry ether (40 ml) was cooled to −20 °C in carbon tetrachloride–dry ice bath under argon atmosphere. To the mixture was added dropwise 1.0 M (M=mol dm^{-3}) diisobutylaluminum hydride solution in toluene (25.0 ml, 25.0 mmol), and the solution was stirred at −20 °C for 1 h. Methanol (1.0 ml) was added dropwise to the mixture over a 10 min period at −20 °C, and then 1.25 M sulfuric acid (30 ml) was added. After the mixture was stirred vigorously, the aqueous layer was separated and extracted with ether (50 ml×2). The organic layers were combined together, and washed with water (50 ml) and saturated sodium hydrogencarbonate (50 ml) in order. It was dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography on 50 g of silica gel eluting with hexane and ethyl acetate (5:1) to give allyl alcohol **10** (2.89 g, 74% yield): A colorless oil; IR (neat) 3350, 1610, 1590, and 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.53 (1H, br, OH), 1.56 (3H, d, J=6.9 Hz, CH_3), 4.28 (2H, s, CH_2), 5.97 (1H, q, J=6.9 Hz, CH), 6.80—6.93 (2H, m), and 7.16(1H, m).

Oxidative Cleavage of 1,2-Diol (2*S*,3*S*)-4 with Lead(IV) Acetate: To a solution of (2*S*,3*S*)-**4** (1.00 g, 4.03 mmol, 100% ee) in toluene (40 ml) was added lead(IV) acetate (2.14 g, 4.82 mmol) at 0 °C over a 10 min period. The mixture was then stirred at 0 °C for 3 h. The insoluble material was filtered off and washed with toluene (30 ml). Silica gel (10 g) was added to the resulting filtrate, and the mixture was stirred at room temperature for 10 min. This mixture was filtered off again, washed with toluene (100 ml), and concentrated under the reduced pressure to give ketone **11** (0.734 g, 84% yield): A colorless oil; $[\alpha]_D^{25}$ −22.1° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=1.52 (3H, d, J=6.9 Hz, CHC<u>H</u>$_3$), 1.89 (3H, s, SCH_3), 4.22 (1H, q, J=6.9 Hz, C<u>H</u>CH_3), 6.82—7.02 (2H, m), and 7.96 (1H, m).

Oxidative Cleavage of 1,2-Diol (2*S*,3*S*)-4 with Sodium Periodate: To a solution of (2*S*,3*S*)-**4** (1.00 g, 4.03 mmol, 100% ee) in methanol (10.0 ml) and water (1.0 ml) was added sodium periodate (1.12 g, 4.83 mmol) at 0 °C, and the mixture was stirred at 0 °C for 9 h. Water (30 ml) was added to the mixture, and the solution was extracted with chloroform (50 ml×3). The organic layers were combined together and washed with 10% aqueous sodium sulfite (50 ml). The organic layer was dried over anhydrous sodium sulfate, then filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on 60 g of silica gel eluting with dichloromethane to give ketone **11** (0.350 g, 40% yield), and then eluting with dichloromethane and ether (7:3) to give sulfoxide **12** as a 3:2 mixture of diastereomers (0.267 g, 25% yield).

12: Colorless crystals; $[\alpha]_D^{25}$ +2.1° (*c* 1.0, $CHCl_3$); ^{1}H NMR of major isomer ($CDCl_3$) δ=1.60 (3H, d, J=7.0 Hz, CHC<u>H</u>$_3$), 2.60 (3H, s, SCH_3), 4.54 (1H, q, J=7.0 Hz, C<u>H</u>CH_3), 6.88—7.06 (2H, m), and 7.94 (1H, m). ^{1}H NMR of minor isomer ($CDCl_3$) δ=1.57 (3H, d, J=6.9 Hz, CHC<u>H</u>$_3$), 2.52 (3H, s, SCH_3), 4.80 (1H, q, J=6.9 Hz, C<u>H</u>CH_3), 6.88—7.06 (2H, m), and 7.94 (1H, m).

Two Phase Reaction of Optically Active Ketone 11 with Dimethylsulfoxonium Methylide: To a solution of optically active ketone **11** (157 mg, 0.73 mmol) in dichloromethane (3.2 g) were added trimethylsulfoxonium chloride (141 mg, 1.10 mmol) and 48% aqueous sodium hydroxide (4.5 g, 54 mmol) at room temperature, and the mixture was stirred at room temperature for 4 h. Dichloromethane (30 ml) was added to the mixture, and then, the organic layer was separated after the mixture was stirred for 5 min. It was washed with water (20 ml×2), dried over anhydrous sodium sulfate, then filtered and evaporated in vacuo to give *dl*-oxirane **1** as a mixture of diastereomers (163 mg, 97% yield, *threo*/*erythro*=7:1 determined by HPLC): A colorless oil; $[\alpha]_D^{25}$ 0.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR of *threo*-isomer ($CDCl_3$) δ=1.26 (3H, d, J=7.2 Hz, CHC<u>H</u>$_3$), 2.18 (3H, s, SCH_3), 2.86 (1H, d, J=5.2 Hz, CH_2), 2.95 (1H, q, J=7.2 Hz, C<u>H</u>CH_3), 3.18 (1H, d, J=5.2 Hz, CH_2), 6.75—6.94 (2H, m), and 7.50 (1H, m). ^{1}H NMR of *erythro*-isomer ($CDCl_3$) δ=1.31 (3H, d, J=6.9 Hz, CHC<u>H</u>$_3$), 2.15 (3H, s, SCH_3), 2.86 (1H, d, J=5.0 Hz, CH_2), 2.97 (1H, q, J=6.9 Hz, C<u>H</u>CH_3), 3.17 (1H, d, J=5.0 Hz, CH_2), 6.76—6.92 (2H, m), and 7.41 (1H, m).

Regeneration of *dl*-Oxirane 1 from Ester 3a: Ester **3a** obtained after fractional crystallization of **2a** (3.824 g, 100 mmol, 62% d.e.) was hydrolyzed with sodium hydroxide, oxidized with lead(IV) acetate, and treated with dimethylsulfoxonium methylide in the same methods as described above. Thus, oxirane *dl*-**1** was obtained in 80% overall yield (1.844 g, *threo*/*erythro*=7:1).

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-methylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (13): To a solution of epoxide (2*R*,3*R*)-**1** (13.93 g, 60.49 mmol) in dimethyl sulfoxide (70 ml) were added 1-*H*-1,2,4-triazole (6.27 g, 90.78 mmol) and sodium hydroxide (2.55 g, 98% assay, 62.47 mmol), and the mixture was stirred at 80 °C for 3 h. The resulting mixture was poured into 2% aqueous hydrochloric acid (120 ml), followed by extraction with toluene (120 ml×2). The organic layers were combined together, washed with water (120 ml×2), dried over anhydrous sodium sulfate, then filtered and evaporated in vacuo. The resulting residue was purified by column chromatography on 250 g of silica gel, eluting with hexane and ethyl acetate (1:1) to give optically active triazolyl compound **13** (13.77 g, 76% yield):

A colorless crystalline powder; mp 137.0—138.0 °C; $[\alpha]_D^{25}$ −126.7° (*c* 0.5, $CHCl_3$); IR (KBr) 3200, 1615, 1600, 1510, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.15 (3H, d, J=6.9 Hz, $CH\underline{CH}_3$), 2.26 (3H, s, SCH_3), 3.22 (1H, q, J=6.9 Hz, $\underline{CH}CH_3$), 4.70 (1H, s, OH), 4.87 (1H, d, J=14.2 Hz, CH_2), 5.07 (1H, d, J=14.2 Hz, CH_2), 6.68—6.78 (2H, m), 7.37 (1H, m), 7.77 (1H, s), and 7.82 (1H, s). Found: C, 51.92; H, 5.04; N, 14.06; S, 10.51%. Calcd for $C_{13}H_{15}F_2N_3OS$: C, 52.16; H, 5.05; N, 14.04; S, 10.71%.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (SM-9164) (5): To a suspension of optically active triazol compound **13** (4.00 g, 13.36 mmol) in water (15 ml) were added sodium tungstate dihydrate (9.0 mg, 0.027 mmol) and concd hydrochloric acid (2.24 g, 35% assay, 21.51 mmol), and the mixture was stirred at room temperature during dropwise addition of 35% aqueous hydrogen peroxide (2.73 g, 28.09 mmol). After being stirred at 40 °C for 2 h, the resulting mixture was cooled to 0 °C, followed by addition of 10% aqueous sodium sulfite to reduce excess hydrogen peroxide (checked by potassium iodide-starch paper). Then it was neutralized with 10% sodium hydroxide, and the precipitated crystals were collected by filtration. The resulting crystals were recrystallized from water to give SM-9164 (**5**) (4.08 g, 92% yield): Colorless crystals; mp 147.0—148.0 °C; $[\alpha]_D^{25}$ −38.5° (*c* 1.0, MeOH); IR (KBr) 3200, 1615, 1600, 1510, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.27 (3H, d, J=6.9 Hz, $CH\underline{CH}_3$), 3.12 (3H, s, SCH_3), 3.60 (1H, q, J=6.9 Hz, $\underline{CH}CH_3$), 4.99 (1H, d, J=14.2, Hz, CH_2), 5.43 (1H, d, J=14.2, Hz, CH_2), 5.57 (1H, s, OH), 6.71—6.82 (2H, m), 7.29 (1H, m), 7.76 (1H, s), and 7.78 (1H, s). Found: C, 47.17; H, 4.49; N, 12.73; S, 9.81%. Calcd for $C_{13}H_{15}F_2N_3O_3S$: C, 47.13; H, 4.56; N, 12.68; S, 9.68%.

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14) The optical purity of **5** was determined to be 100% ee by HPLC in following conditions: column; Sumipax OA-4400 (5 μm, 4 mmϕ×25 cm), mobile phase; hexane/1,2-dichloromethane/ethanol/acetic acid=1000/200/16/1, flow rate; 1.0 ml min^{-1}, detection; UV 260 nm: The peak at 20.7 min corresponded to (2*R*,3*R*)-isomer **5**, and the peak at 18.0 min corresponded to its enantiomer (2*S*,3*S*)-isomer of SM-8668.

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