Stereoselective Synthesis of Antifungal Agent *threo*-2-(2,4-Difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (SM-8668)

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The stereoselective synthesis of antifungal agent *threo*-2-(2,4-difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (SM-8668) is described. The key step is the selective synthesis of intermediate *threo*-2-(2,4-difluorophenyl)-2-(1-substituted ethyl)oxirane. *threo*-2-(2,4-Difluorophenyl)-2-(1-methylthioethyl)oxirane was synthesized *threo*-selectively by the reaction of 1-(2,4-difluorophenyl)-2-methylthio-1-propanone with dimethyloxosulfonium methylide in a heterogeneous media consisting of a hydrophobic solvent and aqueous alkaline solution.

During the course of our search for antifungal azole compounds, we found that *threo*-2-(2,4-difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (**1**, SM-8668)[1] had excellent antifungal activity with oral administration on various deep fungal infection models.[2] We report herein the *threo*-selective synthesis of **1**. The crucial step in the synthesis involves a diastereoselective conversion of 2-substituted 1-(2,4-difluorophenyl)-1-propanone (**2** or **4**) to *threo*-2-(2,4-difluorophenyl)-2-(1-substituted ethyl)oxirane (**7** or **11**).

Results and Discussion

In order to obtain *threo*-2-(2,4-difluorophenyl)-2-(1-substituted ethyl)oxirane (**7**, **9** or **11**) in practical yield, the stereoselectivities of the oxirane formation by the reaction of 2-substituted 1-(2,4-difluorophenyl)-1-propanone (**2**, **3** or **4**) with dimethylsulfonium methylide (**5**) or dimethyloxosulfonium methylide (**6**)[3] were investigated (Scheme 1).

Starting materials **2** (R=OTHP), **3** (R=OMe), and **4** (R=SMe) were prepared from 2-bromo-1-(2,4-difluorophenyl)-1-propanone (**13**) as shown in Scheme 2. Bromo ketone **13**, prepared by Friedel–Crafts acylation of 1,3-difluorobenzene with 2-bromopropionyl bromide, was treated with potassium carbonate in methanol to give oxirane **14** as a 5:2 mixture of diastereomers. Treatment of the mixture with catalytic amount of hydrogen chloride afforded 2-hydroxy ketone **15**. The hydroxyl group in **15** was protected with dihydropyran to give tetrahydropyranyl ether **2** as a 1:1 diastereomeric mixture at the pyranyl ether anomeric center. On the other hand, direct methylation of hydroxyl group in **15** was failed because of its unstability under the basic conditions. In contrast, we found that methyl ether **3** could be synthesized via acetal **16** which was afforded by acid-catalyzed opening of oxirane **14** in methanol. Methylation of hydroxyl group in **16** followed by deprotection of dimethyl acetal in **17** gave the desired methyl ether **3** in a good yield. Methylthio ether **4** was prepared by displacement of bromide in **13** with sodium methanethiolate.

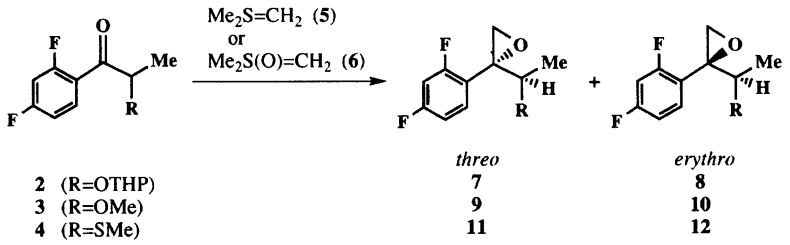
When sulfonium methylide **5** was used as a reagent for oxirane formation reaction in tetrahydrofuran (THF), it was found that alkoxy ketone **2** was transformed to *erythro*-oxirane **8** as a major product. In completely the same manner, *erythro*-**12** was mainly obtained from methylthio ketone **4**. These *erythro*-oxiranes were kinetic products as expected from Cram's rule.[4] On the other hand, when oxosulfonium methylide **6** was used as a reagent in dimethyl sulfoxide (DMSO)–THF, alkoxy ketones **2** and **3** were transformed *threo*-oxiranes **7** and **9** as major products respectively, but methylthio ketone **4** gave a 1:1 mixture of *threo*-oxirane **11** and *erythro*-**12** unfortunately (Table 1).[5,6]

Thus, *threo*-oxirane **7** was found to be a desirable intermediate for synthesis of antifungal agent **1**. Opening the oxirane **7** with 1*H*-1,2,4-triazole sodium salt, followed by hydrolysis of the pyranyl ether afforded crystalline diol **18**. Mesylation of the secondary hydroxyl group in **18** followed by treatment with base gave oxirane **19** as a single isomer. The relative configuration at C-2 and C-3 position in **19** was presumed to be *erythro*, because the elimination of methanesulfoxyl group at C-3 position was caused by the manner of S_N2-type substitution of hydroxyl group at C-2 position. The resultant oxirane **19** was reacted with sodium methanethiolate to give 3-methylthio compound **20** in high yield. It should easily be presumed that the relative configuration at C-2 and C-3 position in **20** was *threo*,

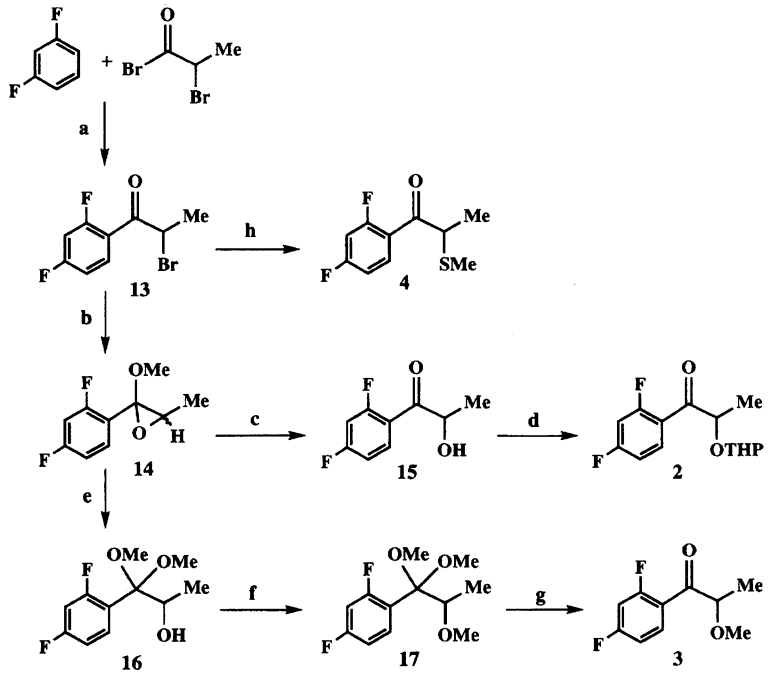
Table 1. Oxirane Formation Reaction in a Homogeneous System[a]

Ylide	Ketone	Yield[b]/%	Product ratio
5	**2** (R=OTHP)		**7** : **8**= 1 : 10[c]
5	**4** (R=SMe)		**11** : **12**= 1 : 16[d]
6	**2** (R=OTHP)	97	**7** : **8**=15 : 1[c]
6	**3** (R=OMe)	90	**9** : **10**= 5 : 1[c]
6	**4** (R=SMe)	95	**11** : **12**= 1 : 1[d]

a) Reaction was carried out in THF at 0 °C (in the case of ylide **5**) or carried out in DMSO–THF (3:1) at r.t. (in the case of ylide **6**). b) Isolated yield. All samples gave satisfactory ^{1}H NMR. c) Ratio was determinated by ^{1}H NMR measurement. d) Ratio was determinated by HPLC analysis.[6]



Scheme 1.



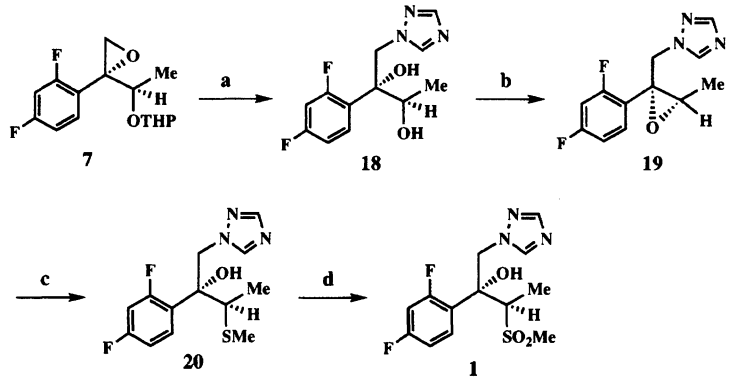
a) $AlCl_3$, r.t., 4 h (96.0%); b) K_2CO_3, MeOH, 0 °C, 5 h (99.0%); c) 2% aq HCl, CH_2Cl_2, 0 °C, 3 h (87.4%); d) DHP, $POCl_3$, CH_2Cl_2, 0 °C, 7 h (quant.); e) HCl–ether soln, MeOH, 0 °C, 1.5 h (98.7%); f) NaH, MeI, DMF, 0 °C, 3 h; g) 1 M HCl, MeCN, r.t., 3 h (57.5% from **16**); h) 15 wt% aq NaSMe, $(CH_2Cl)_2$, 10—20 °C, 3 h (91.1%).

Scheme 2.

because those reactions proceeded with complete double inversion onto C-3 position in *threo*-diol **18**. Finally, methylthio compound **20** was oxidized under acidic conditions with hydrogen peroxide in presence of a catalytic amount of sodium tungstate to give desired antifungal agent **1** (Scheme 3).

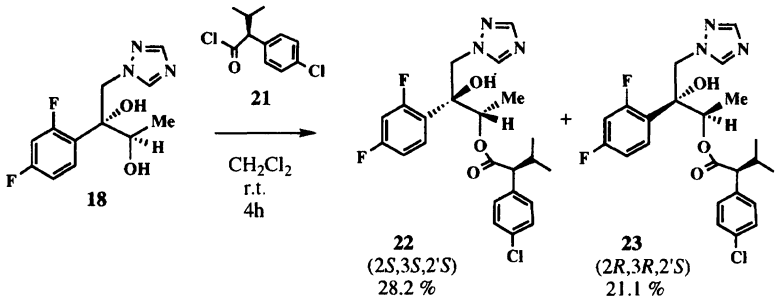
The relative configuration of oxirane **7** and antifungal agent **1** was determined as follows: Diol **18** was acylated with (*S*)-2-(4-chlorophenyl)-3-methylbutyryl chloride (**21**)[7] to give a 1 : 1 mixture of diastereomeric esters **22** and **23** (Scheme 4). After purification of **22** by fractional crystallization, the absolute configuration of **22** was determined to be (2*S*,3*S*,2′*S*) by X-ray crystallographic analysis. This result revealed that the relative configuration of diol **18** was determined to be (2*R**,3*R**)-*threo*. Therefore, the relative configuration of oxirane **7** was concluded to be (2*R**,3*R**)-*threo*, because diol **18** should keep the configuration of oxirane **7**. The relative configuration of **1** was also determined to be (2*R**,3*R**)-*threo* from the above-mentioned reaction mechanism.

From the synthetic point of view, it is more desirable to prepare compound **20** directly from **11** instead of **7** in the above reactions. It is reported that sulfonium methylide **5** results in products directed by kinetic control of betaine formation, whereas oxosulfonium methylide **6** results in products predicted by thermodynamic conditions.[8] Based on this fact, it is expected that the thermodynamically controlled reaction conditions are favorable for *threo*-controlled oxirane formation from ketone **2**, **3** or **4**. After screening various reaction conditions with using oxosulfonium methylide **6**, we found that *threo*-oxirane **7**, **9** or **11** was given respectively in high yield with the reaction of ketone **2**, **3** or **4** in heterogeneous media consisting of hydrophobic solvent and aqueous alkaline solution[9] (*threo*/*erythro* => 5 : 1)



a) i) 1*H*-1,2,4-triazole, K_2CO_3, DMF, 90 °C, 4 h; ii) 5% aq HCl, toluene, r.t., 3 h (56.0%); b) i) MsCl, Et_3N, CH_2Cl_2, 0—5 °C, 30 min. ii) 15% aq NaOH, 0—5 °C, 1 h (94.7%); c) 15 wt % aq NaSMe, MeOH, 60 °C, 4 h (86.7%); d) H_2O_2, Na_2WO_4, concd HCl, MeOH, reflux, 3 h (90.0%).

Scheme 3.



Scheme 4.

(Table 2). Especially, it is noted that *threo*-oxirane **11** was prepared for the first time with enough diastereoselectivity by using this method (≥92% yield, *threo*/*erythro*=5—7:1). When trimethyloxosulfonium chloride was used for the source of oxosulfonium methylide **6** the reaction proceeded at room temperature for 2—4 h, while trimethyloxosulfonium iodide required longer reaction time (7—15 h) and higher temperature (70 °C). Moreover, we found that the less amount of hydrophobic solvent or the more concentrated aqueous alkaline solution was used, the faster the reaction rate becomes. Benzene, toluene, dichloromethane or 1,2-dichloroethane was favorable for hydrophobic solvent in this reaction.

Table 2. Oxirane Formation Reaction with Dimethyloxosulfonium Methylide **6** in a Heterogeneous Media[a)]

Ketone	Hydrophobic solvent	Product (oxirane) Yield[b)]/%	Product ratio
2 (R=OTHP)	CH_2Cl_2	97	**7** : **8**=11 : 1[c)]
3 (R=OMe)	CH_2Cl_2	93	**9** : **10**=13 : 1[c)]
4 (R=SMe)	CH_2Cl_2	99	**11** : **12**= 7 : 1[d)]
4 (R=SMe)	$(CH_2Cl)_2$	99	**11** : **12**= 6 : 1[d)]
4 (R=SMe)	Toluene	92	**11** : **12**= 5 : 1[d)]
4 (R=SMe)	PhCl	92	**11** : **12**= 5 : 1[d)]

a) Reaction was carried out in hydrophobic solvent–48% aq NaOH at r.t. b) Isolated yield. All samples gave satisfactory ^{1}H NMR. c) Ratio was determinated by ^{1}H NMR measurement. d) Ratio was determinated by HPLC analysis.[6)]

It is easily understood that *threo*-oxirane **11** is better intermediate for synthesis of antifungal agent **1**. Oxirane **11** was treated with 1*H*-1,2,4-triazole in presence of sodium hydroxide in DMSO at 80 °C for 4 h to give directly triazolyl compound **20**. Thus, antifungal agent **1** was synthesized in only 5 steps from 1,3-difluorobenzene in more than 35% overall yield.

Experimental

All boiling and melting points were uncorrected. Infrared spectra (IR) were recorded on a JASCO A-102 spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were obtained on a JEOL GX270 spectrometer using tetramethylsilane as an internal standard. Measurement of optical rotations were performed with a JASCO DIP-370. Chromatography columns were prepared with silica gel (Kieselgel 60, 70—230 mesh, E. Merck).

2-Bromo-1-(2,4-difluorophenyl)-1-propanone (13): To a suspension of *m*-difluorobenzene (100.0 g, 0.877 mol) and anhydrous aluminum chloride (128.7 g, 0.965 mol) was added dropwise 2-bromopropionyl bromide (208.4 g, 0.965

mol) at 25—30 °C over 1.5 h period, and the mixture was further stirred for 2.5 h. The above reaction mixture was added dropwise to 3% aq HCl (986 g) below 25 °C with cooling by an ice-water bath, and the resulting white slurry was stirred at room temperature for 1 h. Then it was extracted with 1,2-dichloroethane (500 ml×2) and the organic layer was successively washed with 240 g of water, 255 g of 5% aq $NaHCO_3$ and 240 g of water. The organic layer was dried over anhydrous Na_2SO_4 and then filtered and evaporated in vacuo. The residue was distilled under reduced pressure to give 2-bromo ketone **13** (209.6 g, 96.0% yield): A colorless oil; bp 70—71 °C at 0.9 mmHg (1 mmHg=133.322 Pa); IR ($CHCl_3$) 1690 and 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.89 (3H, d, J=6.6 Hz), 5.25 (1H, q, J=6.6 Hz), 6.85—7.05 (2H, m), and 7.93—8.03 (1H, m). Found: C, 43.43; H, 2.93; Br 31.91%. Calcd for $C_9H_7OF_2Br$: C, 43.40; H, 2.83; Br 32.08%.

2-(2,4-Difluorophenyl)-2-methoxy-3-methyloxirane (14): To a solution of 2-bromo ketone **13** (12.08 g 48.5 mmol) in 1,2-dichloroethane (48 g) was added anhydrous potassium carbonate (13.4 g, 97.0 mmol) at 0 °C, and the mixture was stirred at the same temperature for 1 h. Methanol (31.2 ml, dried over molecular sieve 3A) was added dropwise to the reaction mixture, which was stirred at 0 °C for 5 h. The resulting suspension was filtered and the solid deposited was washed with 1,2-dichloroethane (10 g×2). The filtrate was concentrated under reduced pressure to give oxirane **14** as 5:2 diastereo mixture (9.61 g, 99.0% yield), which was subjected to the sequential reactions without further purification: A colorless oil; ^1H NMR of major isomer ($CDCl_3$) δ=1.04 (3H, d, J=5.6 Hz), 3.28 (3H, s), 3.63 (1H, q, J=5.6 Hz), 6.85—6.96 (2H, m), and 7.41—7.51 (1H, m). ^1H NMR of minor isomer ($CDCl_3$) δ=1.52 (3H, d, J=5.3 Hz), 3.08 (1H, q, J=5.3 Hz), 3.31 (3H, s), 6.81—6.92 (2H, m), and 7.41—7.51 (1H, m).

1-(2,4-Difluorophenyl)-2-hydroxy-1-propanone (15): To a solution of oxirane **14** (34.77 g, 0.174 mol) in 1,2-dichloroethane (55 g) was added water (93 g) and 35% aq HCl (2.74 g, 0.026 mol) at 0 °C. After stirred at 0 °C for 3 h, 5% aq NaOH (16.86 g) and sodium hydrogencarbonate (0.88 g) were added to the reaction mixture, and further stirred at 0 °C for 1 h. After then sodium chloride (36.5 g) was added to the stirred solution, which was evaporated in vacuo to remove 1,2-dichloroethane. The resulting suspension was cooled at 0 °C and filtered off. Then, the crystals isolated were washed with 16 g of water, and dried under reduced pressure to give 2-hydroxy ketone **15** (28.26 g, 87.4% yield): Colorless crystals; mp 52—53 °C; IR ($CHCl_3$) 1690 and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.41 (3H, d, J=6.9 Hz), 3.74 (1H, d, J=5.9 Hz), 5.01 (1H, m), 6.87—7.07 (2H, m), and 7.97—8.07 (1H, m). Found: C, 57.98; H, 4.38%. Calcd for $C_9H_8O_2F_2$: C, 58.07; H, 4.33%.

1-(2,4-Difluorophenyl)-2-(tetrahydropyranyloxy)-propan-1-one (2): To a solution of 2-hydroxy ketone **15** (13.5 g, 72.5 mmol) in dichloromethane (25 g, dried over molecular sieve 4A) was added 3,4-dihydro-2*H*-pyran (7.59 g, 90.2 mmol) and phosphoryl chloride (0.20 g, 1.3 mmol) at 0 °C, and the mixture was stirred at 0 °C for 7 h. 5% aq NaOH (57 g) was added dropwise to the reaction mixture, and further stirred at room temperature for 30 min. The aqueous layer was separated and extracted with dichloromethane (15 g×3). The organic layers were combined together, washed with water (20 g×3), and dried over anhydrous Na_2SO_4. It was then filtered and evaporated in vacuo to give THP ether **2** as 1:1 diastereo mixture (19.7 g, quantitative yield): A colorless oil; IR ($CHCl_3$) 1700 and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.47 (3H, d, J=7.2 Hz), 1.4—1.9 (6H, m), 3.52 (1H, m), 3.89 (1H, m), 4.65 (1H, br.s), 5.11 (1H, q, J=7.2 Hz), 6.83—7.02 (2H, m), and 7.87—7.97 (1H, m).

1-(2,4-Difluorophenyl)-1,1-dimethoxy-2-propanol (16): To a solution of methoxyoxirane **14** (1.525 g, 7.62 mmol) in methanol (10 ml) was added 9% HCl–ether solution at 0 °C, and the mixture was stirring at 0 °C for 40 min. It was neutralized with 3% aq $NaHCO_3$ and extracted with dichloromethane (50 ml×2). The organic layers were combined and washed with sat. NaCl (30 ml), and dried over anhydrous Na_2SO_4. It was then filtered and evaporated in vacuo to give alcohol **16** (1.67 g, 94.5% yield): A colorless oil; IR (neat) 3500, 1605, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.98 (3H, d, J=6.3 Hz), 2.61 (1H, br.s), 3.25 (3H, s), 3.40 (3H, s), 4.20 (1H, br.q, J=6.3 Hz), 6.74—6.92 (2H, m), and 7.51—7.61 (1H, m).

1-(2,4-Difluorophenyl)-1,1,2-trimethoxypropane (17): To a solution of alcohol **16** (1.367 g, 5.89 mmol) in *N*,*N*-dimethylformamide (14 ml) was added sodium hydride (353 mg, 60% assay, 8.8 mmol) at 0 °C. After 10 min methyl iodide (0.55 ml, 8.8 mmol) was added dropwise to the mixture, and which was stirred at 0 °C for 2 h. Water (50 ml) was added and extracted with dichloromethane (60 ml×3). The organic layers were combined and washed with 50 ml of water and dried over anhydrous Na_2SO_4. It was then filtered and evaporated in vacuo to give methyl ether **17** (1.403 g, 96.7% yield): A colorless oil; IR (neat) 1690, 1605 and 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.00 (3H, d, J=6.6 Hz), 3.22 (3H, s), 3.37 (3H, s), 3.44 (3H, s), 3.74 (1H, q, J=6.6 Hz), 6.72—6.90 (2H, m), and 7.51—7.61 (1H, m).

1-(2,4-Difluorophenyl)-2-methoxy-1-propanone (3): To a solution of acetal **17** (1.403 g, 5.70 mmol) in acetonitrile (20 ml) was added 1 M HCl (0.5 ml, 0.5 mmol) (1 M=1 mol dm^{-3}) at room temperature, and the mixture was stirred for 3 h. After the solvent was evaporated in vacuo, 20 ml of sat. $NaHCO_3$ was added and extracted with dichloromethane (30 ml×3). The organic layer was washed with 20 ml of sat. NaCl and dried over anhydrous Na_2SO_4. It was then filtered and evaporated in vacuo. The residue was purified by column chromatography on 50 g of silica gel eluting with hexane and ethyl acetate (10:1) to give methyl ether **3** (807 mg, 70.7% yield): A colorless oil; IR ($CHCl_3$) 1695 and 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.42 (3H, d, J=6.9 Hz), 3.42 (3H, s), 4.57 (1H, q, J=6.9 Hz), 6.77—7.03 (2H, m), and 7.89—7.99 (1H, m).

1-(2,4-Difluorophenyl)-2-methylthio-1-propanone (4): To a solution of 2-bromo ketone **13** (209.4 g, 0.841 mol) in 1,2-dichloroethane (840 g) was added dropwise 15 wt% aq NaSMe (594 g, 1.27 mol) under 10 °C with cooling by ice-water bath, and the mixture was stirred at 10—20 °C for 3 h. 13% aq NaOCl (745 g) was added dropwise to the mixture under 20 °C, which was stirred for 15 min. The organic layer was separated, washed twice with 200 ml of water, dried over anhydrous Na_2SO_4, and then filtered and evaporated in vacuo. The residue was distilled under reduced pressure to give 2-methylthio ketone **4** (165.6 g,

91.1% yield): A colorless oil; bp 79.5—80 °C at 0.8 mmHg; IR ($CHCl_3$) 1685 and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.52 (3H, d, J=6.9 Hz), 1.89 (3H, s), 4.22 (1H, q, J=6.9 Hz), 6.82—7.02 (2H, m), and 7.91—8.01 (1H, m). Found: C, 55.28; H, 4.73; S, 14.90%. Calcd for $C_{10}H_{10}OF_2S$: C, 55.54; H, 4.66; S, 14.83%.

Oxirane Formation Reaction of Ketone 2 with Ylide 5 or 6. a) Reaction of Ketone 2 with Dimethylsulfonium Methylide (5): To a suspension of trimethylsulfonium iodide (245 mg, 1.2 mmol) in THF (3.0 ml) was added dropwise 1.55 M butyllithium in hexane (0.71 ml) at 0 °C under nitrogen atmosphere. After 5 min the solution of ketone **2** (270 mg, 1.0 mmol) in THF (1.0 ml) was added to the mixture, and which was stirred at 0 °C for 3 h. Water (20 ml) was added to the reaction mixture, and which was extracted with ether (20 ml×2). The organic layers were combined, washed with 20 ml of water, and dried over anhydrous Na_2SO_4. It was then filtered and evaporated in vacuo. The residue was dissolved in 10 ml of toluene, and the solution was filtered to remove insoluble materials. The filtrate was evaporated in vacuo to give the mixture of oxiranes **7** and **8** (293 mg). Product ratio is shown in Table 1.

7: A colorless oil; ^1H NMR ($CDCl_3$) δ=1.14 and 1.22 (3H, d, J=6.6 Hz), 1.4—1.9 (6H, m), 2.82 and 2.84 (1H, d, J=5.3 Hz), 3.05 and 3.32 (1H, d, J=5.3 Hz), 3.5—3.9 (2H, m), 3.98 and 4.05 (1H, q, J=6.6 Hz), 4.76 and 4.92 (1H, t, J=3.2 Hz), 6.7—6.9 (2H, m), and 7.3—7.5 (1H, m).

8: A colorless oil; ^1H NMR ($CDCl_3$) δ=1.12 and 1.22 (3H, d, J=6.6 Hz), 1.4—1.9 (6H, m), 2.84 and 2.88 (1H, d, J=5.3 Hz), 3.17 and 3.19 (1H, d, J=5.3 Hz), 3.3—3.9 (2H, m), 4.02 and 4.02 (1H, q, J=6.6 Hz), 4.73 and 4.83 (1H, t, J=3.1 Hz), 6.7—6.9 (2H, m), and 7.3—7.5 (1H, m).

b) Reaction of Ketone 2 with Dimethyloxosulfonium Methylide (6) in Homogeneous Solvent: To a suspension of trimethyloxosulfonium iodide (264 mg, 1.2 mmol) in DMSO (3.0 ml) was added sodium hydride (44 mg, 60% assay, 1.1 mmol) at 10 °C under nitrogen atmosphere. After stirred at 10 °C for 5 min, the mixture was stirred at room temperature for further 30 min. Then the solution of ketone **2** (270 mg, 1.0 mmol) in THF (1.0 ml) was added, and stirred at room temperature for 3 h. Water (20 ml) was added to the reaction mixture, and which was extracted with ether (20 ml×2). The organic layers were combined, washed with 20 ml of water, and dried over anhydrous Na_2SO_4. It was then filtered and evaporated in vacuo. The residue was dissolved in 10 ml of toluene, and the solution was filtered to remove insoluble materials. The filtrate was evaporated in vacuo to give the mixture of oxiranes **7** and **8** (276 mg, 97.1% yield). Yield and product ratio is shown in Table 1.

c) Reaction of Ketone 2,3 or 4 with Dimethyloxosulfonium Methylide (6) in Heterogeneous Solvent: To a solution of ketone **2**,**3** or **4** (1 mmol) in dichloromethane (4.2 g) was added trimethyloxosulfonium chloride (193 mg, 1.5 mmol) and 48% aq NaOH (6.0 g), and the mixture was stirred at room temperature for 3 h. Water (20 ml) was added to the reaction mixture, and which was extracted with dichloromethane (20 ml×2). The organic layers were combined, washed with 20 ml of water, and dried over anhydrous Na_2SO_4. It was then filtered and evaporated in vacuo. The residue was dissolved in 10 ml of toluene, and the solution was filtered to remove insoluble materials. The filtrate was evaporated in vacuo to give the mixture of oxiranes **7** and **8** (276 mg, 97.1% yield). Yield and product ratio is shown in Table 2.

Oxirane Formation Reaction of Ketone 3 or 4 with Ylide 5 or 6: The following compounds were obtained by methods **a**—**c** described in the reaction of ketone **2**. Yield and product ratio is shown in Tables 1 and 2 respectively.

9: A colorless oil; ^1H NMR ($CDCl_3$) δ=1.16 (3H, d, J=6.6 Hz), 2.82 (1H, d, J=5.3 Hz), 3.10 (1H, d, J=5.3 Hz), 3.45 (1H, q, J=6.6 Hz), 3.48 (3H, s), 6.75—6.93 (2H, m), and 7.40—7.49 (1H, m).

10: A colorless oil; ^1H NMR ($CDCl_3$) δ=1.66 (3H, d, J=6.6 Hz), 2.88 (1H, d, J=5.1 Hz), 3.17 (1H, d, J=5.1 Hz), 3.43 (3H, s), 3.46 (1H, q, J=6.6 Hz), 6.75—6.93 (2H, m), and 7.35—7.45 (1H, m).

11: A colorless oil; ^1H NMR ($CDCl_3$) δ=1.26 (3H, d, J=7.3 Hz), 2.18 (3H, s), 2.86 (1H, d, J=5.1 Hz), 3.18 (1H, d, J=5.1 Hz), 2.95 (1H, q, J=7.3 Hz), 6.75—6.94 (2H, m), and 7.45—7.55 (1H, m).

12: A colorless oil; ^1H NMR ($CDCl_3$) δ=1.31 (3H, d, J=6.9 Hz), 2.15 (3H, s), 2.86 (1H, d, J=5.0 Hz), 3.17 (1H, d, J=5.0 Hz), 2.97 (1H, q, J=6.9 Hz), 6.76—6.92 (2H, m), and 7.36—7.45 (1H, m).

***threo*-2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2,3-butanediol (18):** To a solution of *threo*-rich oxirane **7** (19.5 g, 68.6 mmol, **7**:**8**=15:1) in *N*,*N*-dimethylformamide (120 g) were added 1*H*-1,2,4-triazole (14.2 g, 205.6 mmol) and potassium carbonate (28.5 g, 206.2 mmol). The mixture was warmed to 90 °C and stirred at 90 °C for 4 h. The reaction mixture was cooled to room temperature, and the solid deposited was filtered and washed with toluene (50 g×3). The filtrate was poured into 390 g of water and stirred vigorously for 20 min. The aqueous layer was separated and extracted with toluene (50 g×2). The toluene layers were combined together and washed several times with 500 ml of water. To the above solution, included THP ether of **18**, was added 5% aq HCl (120 g, 165 mmol), and the mixture was stirred at room temperature for 3 h. The aqueous layer was separated and washed with 80 g of hexane. The above aqueous layer, included HCl salt of **18**, was neutralized with diluted sodium hydroxide solution to give pale yellow precipitate. The resulting slurry was cooled to 0—5 °C, and stirred at 0—5 °C for 1 h. The precipitate was collected by filtration, washed with cold water, and dried under reduced pressure. This was purified by column chromatography on 300 g of silica gel eluting with ethyl acetate to give *threo*-diol **18** (10.34 g, 56.0% yield): Colorless crystals; mp 156—157 °C; IR (KBr) 3500—3200, 1620, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.97 (3H, d, J=6.7 Hz), 2.64 (1H, d, J=9.2 Hz), 4.33 (1H, m), 4.80 (2H, q, J=7.3 Hz), 4.82 (1H, s), 6.71—6.81 (2H, m), 7.37—7.46 (1H, m), 7.82 (1H, s), and 7.85 (1H, s). Found: C, 53.51; H, 4.98; N, 15.59%. Calcd for $C_{12}H_{13}O_2F_2N_3$: C, 53.53; H, 4.87; N, 15.61%.

***erythro*-2-(2,4-Difluorophenyl)-3-methyl-2-[(1*H*-1,2,4-triazol-1-yl)methyl]oxirane (19):** To a solution of *threo*-diol **18** (12.0 g, 44.56 mmol) in dichloromethane (115 g) was added triethylamine (13.5 g, 133.7 mmol), and the mixture was cooled to 0—5 °C. To the above solution was added dropwise methanesulfonyl chloride (7.66 g, 66.87 mmol) at 0—5 °C over 1 h period, and which was stirred at 0—5 °C for the additional 30 min. After then,

to the reaction mixture was added dropwise 15% aq NaOH (50 g) at 0—5 °C over 30 min period. After stirring at 0—5 °C for 1 h, the aqueous layer was separated and extracted again with dichloromethane (50 g). The organic layers were combined together, washed with water (50 g×3), dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo to give the amorphous residue, which was crystallized with ether to give *erythro*-oxirane **19** (10.6 g, 94.7% yield): Colorless crystals; mp 60.5—62.5 °C; IR (Nujor) 1620, and 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.64 (3H, d, J=5.6 Hz), 3.22 (1H, q, J=5.6 Hz), 4.49 (1H, d, J=14.5 Hz), 4.93 (1H, d, J=14.5 Hz), 6.69—6.83 (2H, m), 6.97—7.07 (1H, m), 7.89 (1H, s), and 8.31 (1H, br.s). Found: C, 56.99; H, 4.30; N, 16.62%. Calcd for $C_{12}H_{11}OF_2N_3$: C, 57.37; H, 4.41; N, 16.73%.

***threo*-2-(2,4-Difluorophenyl)-3-methylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (20):** To a solution of *erythro*-oxirane **19** (10.6 g, 42.19 mmol) in methanol (40 g) was added 15 wt % aq NaSMe (29.5 g, 63.1 mmol) under N_2 atmosphere. The mixture was warmed to 60 °C and stirred at 60 °C for 4 h. After cooling to room temperature, water (100 g) was added dropwise to the reaction mixture, and methanol was evapolated under reduced pressure. The aqueous suspension was then extracted with toluene (100 g×3). The toluene layers were combined together, washed with 5% aq NaOCl (100 g), and washed several times with 150 g of water. It was then dried on anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on 500 g of silica gel eluting with hexane and ethyl acetate (1 : 1) to give *threo*-triazolyl compound **20** (10.95 g, 86.7% yield): Colorless crystals; mp 122—123 °C; IR (KBr) 3200, 1615, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.15 (3H, d, J=6.9 Hz), 2.26 (3H, s), 3.22 (1H, q, J=6.9 Hz), 4.70 (1H, s), 4.87 (1H, d, J=14.2 Hz), 5.07 (1H, d, J=14.2 Hz), 6.68—6.78 (2H, m), 7.32—7.42 (1H, m), 7.77 (1H, s), and 7.82 (1H, s). Found: C, 52.13; H, 5.07; N, 13.87; S, 10.81%. Calcd for $C_{13}H_{15}OF_2N_3S$: C, 52.16; H, 5.05; N, 14.04; S, 10.71%.

***threo*-2-(2,4-Difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (1):** To a suspension of *threo*-triazolyl compound **20** (21.1 g, 70.5 mmol) in methanol (125 g) were added sodium tungstate dihydrate (55 mg, 0.17 mmol) and concd HCl (13.0 g, 125 mmol), and the resultant mixture was stirred at room temperature while dropwise addition of 35% aq H_2O_2 (19.5 g, 200 mmol). The reaction mixture was heated at 60 °C and stirred for 3 h. Then it was cooled to room temperature, followed by addition of 5% aq $Na_2S_2O_3$ to reduce excess H_2O_2. The resulting mixture was neutralized with 10% aq NaOH, and the precipitated crystals were collected by filtration to give 22.6 g of sulfone **1**. The resulting crystals were recrystallized from methanol to give pure crystalline **1** (21.0 g, 63.4 mmol, 90.0% yield): Colorless crystals; mp 209—210 °C; IR (KBr) 3200, 1615, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.27 (3H, d, J=6.9 Hz), 3.12 (3H, s), 3.60 (1H, q, J=6.9 Hz), 4.99 (1H, d, J=14.2 Hz), 5.43 (1H, d, J=14.2 Hz), 5.57 (1H, s), 6.71—6.82 (2H, m), 7.24—7.33 (1H, m), 7.76 (1H, s), and 7.78 (1H, s). Found: C, 46.93; H, 4.53; N, 12.56; S, 9.60%. Calcd for $C_{13}H_{15}O_3F_2N_3S$: C, 47.13; H, 4.56; N, 12.68; S, 9.68%.

Synthesis and Separation of (*S*)-2-(4-Chlorophenyl)-3-methylbutyric Ester 22 and 23: To an ice cooling solution of racemic diol **18** (29.2 g, 0.108 mol) in dichloromethane was added (*S*)-2-(4-chlorophenyl)-3-methylbutyryl chloride (**21**, 30.0 g, 0.13 mol). The resultant mixture was stirred at 0 to 10 °C for 1 h and then at room temperature for 4 h. The reaction mixture was washed with 5% aq NaOH and water, dried over anhydrous $MgSO_4$, and concentrated to give an oily residue (67.8 g) which contained diastereomer esters **22** and **23**. The mixture was dissolved in acetone (60 ml) and stirred at room temperature for 3 h. The resulting precipitate was collected by filtration, washed with ether and dried to give nearly pure crystals (16 g). Recrystallization from acetone gave ester **22** as pure crystals (14.1 g, 28.2% yield): Mp 169—170 °C; $[\alpha]_D^{25}$ +70.0° (c=1.00, MeOH); IR (KBr) 3200, 1740, 1620, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.73 (3H, d, J=6.9 Hz), 1.07 (3H, d, J=6.6 Hz), 1.10 (3H, d, J=6.3 Hz), 2.36 (1H, m), 3.26 (1H, d, J=10.6 Hz), 4.10 (1H, d, J=14.2 Hz), 4.64 (1H, d, J=14.2 Hz), 4.69 (1H, s), 5.38 (1H, q, J=6.6 Hz), 6.61—6.77 (2H, m), 7.28—7.44 (5H, m), 7.71 (1H, s), and 7.73 (1H, s). Found: C, 59.49; H, 5.22; N, 9.07%. Calcd for $C_{23}H_{24}O_3F_2N_3Cl$: C, 59.55; H, 5.21; N, 9.06%. The mother liquor was concentrated under reduced pressure and purified by column chromatography on 500 g of silica gel eluting with chloroform to give ester **23** as colorless crystals (10.6 g, 21.1%): Mp 108.5—110°C; $[\alpha]_D^{25}$ −21.2 ° (c=1.00, MeOH); IR (KBr) 3200, 1740, 1620, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.75 (3H, d, J=6.9 Hz), 0.95 (3H, d, J=6.3 Hz), 1.07 (3H, d, J=6.6 Hz), 2.39 (1H, m), 3.23 (1H, d, J=10.9 Hz), 4.32 (1H, d, J=14.2 Hz), 4.82 (1H, d, J=14.2 Hz), 4.66 (1H, s), 5.44 (1H, q, J=6.6 Hz), 6.69—6.80 (2H, m), 7.28—7.47 (5H, m), and 7.78 (2H, s). Found: C, 59.19; H, 5.17; N, 8.70%. Calcd for $C_{23}H_{24}O_3F_2N_3Cl$: C, 59.55; H, 5.21; N, 9.06%.

***threo*-2-(2,4-Difluorophenyl)-3-methylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (20) from Oxirane 11:** To a solution of *threo*-rich oxirane **11** (24.0 g, 104 mmol, **11**:**12**=5:1) in dimethyl sulfoxide (110 g) were added 1*H*-1,2,4-triazol (9.0 g, 130 mol) and sodium hydroxide (3.5 g, 88 mmol), and the resultant mixture was heated at 80 °C for 3 h. The reaction mixture was combined with toluene (150 g) and 2% aq HCl (150 g), followed by extraction. The aqueous layer was separated and extracted again with toluene (100 g). The toluene layers were combined together, washed with water (150 g) and concentrated under reduced pressure. The resulting residue was purified by column chromatography on 500 g of silica gel eluting with *n*-hexane and ethyl acetate (1 : 1) to give *threo*-triazolyl compound **20** (17.0 g, 57 mmol, 54.6% yield from mixture of **11** and **12**): Colorless crystals; mp 122—123 °C. This sample showed identical spectral properties (IR and ^1H NMR) with those recorded on **20** synthesized from oxirane **19**.

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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) T. Tanio, K. Ichise, T. Nakajima, and T. Okuda, *Antimicrob. Agents Chemother.*, **34**, 980 (1990).

3) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867, 3782 (1962); **87**, 1353 (1965).

4) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 4828 (1952).

5) In all cases *threo*-epoxides couldn't be separated from the *threo*/*erythro* mixture because of their instability for silica gel. Fractional distillation also failed because of their almost same boiling points.

6) HPLC conditions for determining **11**/**12** ratio 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: The peak at 17.4 min. corresponded to *threo*-isomer **11**, and the peak at 16.3 min. corresponded to *erythro*-one **12**.

7) Y. Suzuki, T. Umeyoshi, M. Miyamoto, and K. Akita, Japan Kokai Tokkyo Koho JP 54-027532 (1979); *Chem. Abstr.*, **91**, 19913a (1979).

8) C. R. Johnson, *Acc. Chem. Res.*, **6**, 341 (1973).

9) This reaction condition was already reported, but they didn't discuss about the stereochemistry: Cf. A. Merz and G. Märkl, *Angew. Chem.*, **85**, 867 (1973); Y. Yano, T. Okonogi, M. Sunaga, and W. Takagi, *J. Chem. Soc., Chem. Commun.*, **1973**, 527.