Asymmetric Synthesis of SM-9164, a Biologically Active Enantiomer of Antifungal Agent SM-8668

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SM-9164, a biologically active enantiomer of antifungal agent SM-8668, was prepared by asymmetric synthesis in 10 steps in 13% overall yield from commercially available 2-chloro-1-(2,4-difluorophenyl)ethanone. The crucial steps were Katsuki-Sharpless asymmetric epoxidation of the (*E*)-allylic alcohol and epimerization of the *erythro*-sulfone to the desired *threo*-isomer under basic conditions.

During the course of our search for antifungal azole compounds, we found that *dl-threo*-2-(2,4-difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (SM-8668) (**1**)[1,2] had excellent antifungal activity with oral administration on various deep fungal infection models.[3] Recently, we also found that only a (2*R*,3*R*)-isomer of **1**, namely SM-9164, showed potent activity both in vitro and in vivo.[4] Three reports on the synthesis of SM-9164 [(2*R*,3*R*)-**1**] are available at present; the first synthesis used (*S*)-2-chloropropionic acid as a chiral synthon,[5] the second started from *L*-threonine,[6] and the third applied Katsuki-Sharpless asymmetric epoxidation[7] of (*Z*)-allylic alcohol **4**.[8] However, these synthetic routes took many steps and resulted in low overall yields.

In searching for a convenient and efficient synthetic method for optically active **1**, we investigated an enantioselective synthesis of (2*R*,3*R*)-**1** using Katsuki-Sharpless asymmetric epoxidation of *E*-selectively prepared allylic alcohol **8**.

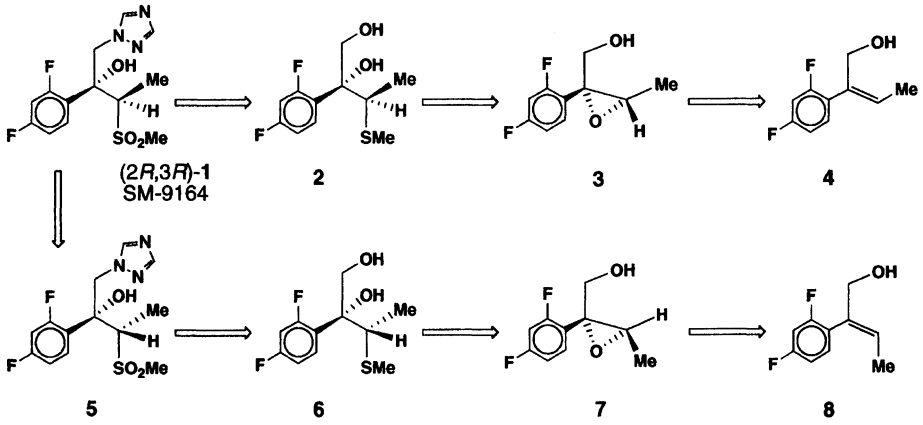
Results and Discussion

Two synthetic strategies using Katsuki-Sharpless asymmetric epoxidation[7] can be constructed for the synthesis of (2*R*,3*R*)-**1** as outlined in Scheme 1. One involves asymmetric epoxidation of (*Z*)-olefin **4** which should give (2*R*,3*S*)-epoxide **3**. The obtained **3** would generate sulfide **2**, which was reported to be an intermediate in the preparation of (2*R*,3*R*)-**1**.[4,9] Indeed, this synthetic route was recently proved to be successful by Bennett et al.[8] However, they also reported that they faced a problem in the stereoselectivity of the asymmetric epoxidation (only 76% ee), as expected from the prior report.[10] The other strategy involves asymmetric epoxidation of (*E*)-allylic alcohol **8** which should give (2*R*,3*R*)-epoxide **7**. This should give a good result since it is also reported that (*E*)-α-(hydroxymethyl)stilbene was converted into (2*S*,3*S*)-α-(hydroxymethyl)stilbene oxide both in a high yield (87%) and in excellent selectivity (>95% ee).[7] Therefore, we investigated the latter method to synthesize (2*R*,3*R*)-**1** enantioselectively, though this synthetic route requires a conversion of the resulting *erythro*-sulfone **5** into the desired *threo*-one **1** in the last step. In a preliminary examination with racemic **5**, the epimerization went well to give *threo*-racemate **1** in 74% yield as detailed later.

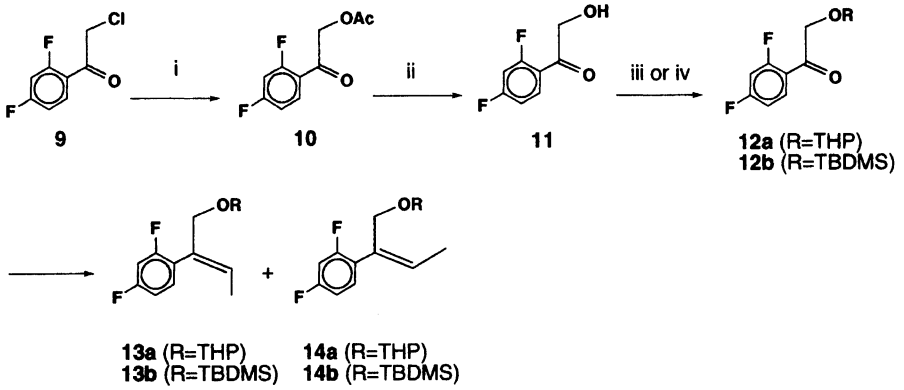
(*E*)-Allylic alcohol **8**[9] as an important precursor for asymmetric epoxidation was stereoselectively prepared by Wittig olefination from ketone **12** which was derived from acetate **10**, as shown in Scheme 2. Commercially available α-chloro ketone **9** was treated with sodium acetate in *N*, *N*-dimethylformamide to afford acetate **10** in 94% yield. Because of the instability of α-hydroxy ketone **11** under basic conditions, alkaline hydrolysis of acetate **10** failed. In contrast, acid hydrolysis of **10** using hydrochloric acid gave **11** in 69% yield. The hydroxy group of **11** was then protected with a tetrahydropyranyl (THP) or *t*-butyldimethylsilyl (TBDMS) group to give the desired ketone **12a** or **12b**, respectively.

The results of the Wittig reaction of ketone **12a** or **12b** under several conditions are summarized in Table 1. The regioselectivity of each reaction was described as a ratio of the desired *E*-isomer (**13**) and the undesired *Z*-isomer (**14**), which was determined by comparing the NMR peak area of the two inseparable isomers. We first tried the classical procedure reported by Wittig,[11] however, it did not show any regioselectivity (Entries 1 and 2). Next, we tried some reaction conditions reported for a synthesis of *E*-trisubstituted allylic alcohols.[12,13] Nevertheless, the results were not satisfactory in terms of yields and regioselectivities (Entries 3—5). Unexpectedly, however, the reaction conditions using hexamethylphosphoric triamide (HMPA) as a co-solvent afforded (*E*)-olefins **13a** and **13b** in high regioselectivities (Entries 6 and 7), though they were generally recognized as conditions for synthesis of *Z*-trisubstituted allylic alcohols.[14] The obtained (*E*)-olefin **13b** ($E:Z=97:3$) was treated with tetrabutylammonium fluoride and purified by silica-gel column chromatography to afford the desired (*E*)-allylic alcohol **8**[9] as a single isomer in 96% yield.

(*E*)-Allylic alcohol **8** was then subjected to Katsuki-



Scheme 1. Synthetic strategy.



Reagents and conditions
i) NaOAc, DMF, r.t., 4 h (94%).
ii) 1M HCl, MeOH, 40 °C, 5 h (69%).
iii) DHP, PPTS, CH_2Cl_2, 0 °C, 7 h (quant.).
iv) TBDMSCl, pyridine, CH_2Cl_2, 0 °C, 7 h (96%).

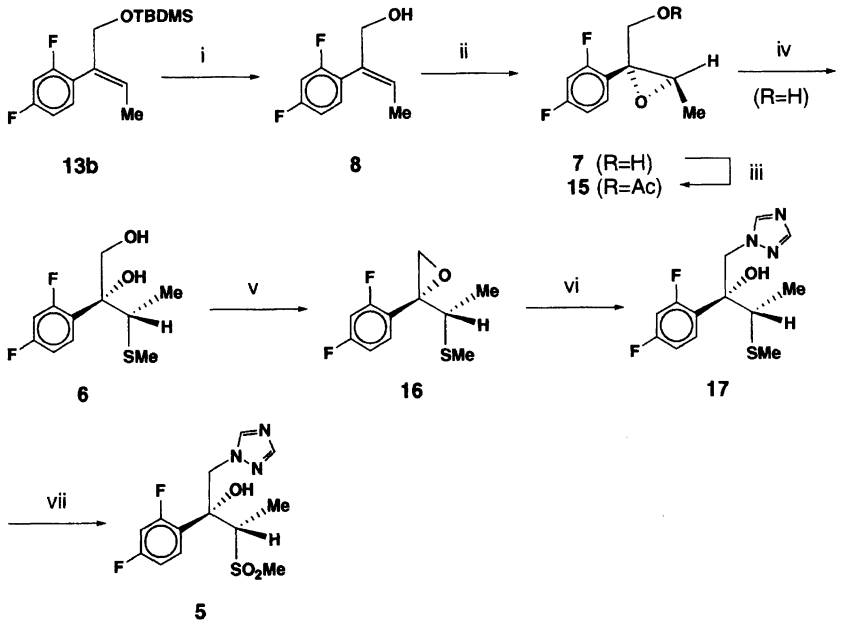
Scheme 2.

Table 1. Reaction Conditions and Regioselectivity of Wittig Reaction of Ketone **12**

Entry	Reaction conditions	Yield %	Ratio[a] **13** : **14**
1[b]	$EtPPh_3^+Br^-$ (1.5 equiv), BuLi (1.5 equiv), ether, r.t., 30 min; **12a**, r.t., 5 h	73	59 : 41
2[b]	(Using **12b**, same reaction conditions as Entry 1)	79	65 : 35
3[c]	$EtPPh_3^+Br^-$ (1.2 equiv), BuLi (1.2 equiv), THF–ether (1 : 1), r.t., 30 min; **12a**, −78 °C, 10 min; BuLi (1.2 equiv), −40 °C, 5 min; 8% HCl–ether soln. (1.5 equiv), −30 °C, 5 min; ^{t}BuOK (2.0 equiv), ^{t}BuOH, r.t., 3 h	60	79 : 21
4[c]	(Using **12b**, same reaction conditions as Entry 3)	59	91 : 9
5[d]	$EtPPh_3^+Br^-$ (1.5 equiv), *t*-BuOK (1.5 equiv), THF, r.t., 30 min ; **12b**, reflux 7 h	33	89 : 11
6[e]	$EtPPh_3^+Br^-$ (1.5 equiv), BuLi (1.4 equiv), THF–HMPA (9 : 1), r.t., 10 min; **12a**, −78 °C, 20 min, then r.t.	75	95 : 5
7[e]	(Using **12b**, same reaction conditions as Entry 7)	79	97 : 3

a) Product ratio was determined by comparing the NMR peak area of each isomers. b—e) See Refs. 11, 12, 13, and 14, respectively.

Sharpless asymmetric epoxidation[7] using (−)-diethyl (2*S*, 3*S*)-tartrate [(−)-DET], titanium tetraisopropoxide, and a solution of *t*-butyl hydroperoxide (TBHP) in dichloromethane at −20 °C to give epoxide (+)-**7** in a high yield [96% yield,



Reagents and conditions
i) $Bu_4N^+F^-$, THF, 0 °C, 1 h (96%).
ii) (−)-DET, TBHP, $Ti(OPr^i)_4$, CH_2Cl_2, −20°C, 2 d (96%).
iii) Ac_2O, pyridine, CH_2Cl_2, 0 °C, 3 h (68%).
iv) NaSMe, DMSO, 55 °C, 3 h (77%).
v) MsCl, Et_3N, CH_2Cl_2, then 35% aq KOH (quant.).
vi) 1,2,4-triazole, NaOH, DMSO, 80 °C, 3 h (72%).
vii) 31% H_2O_2, concd HCl, $Na_2WO_4 \cdot 2H_2O$, toluene, 60 °C, 1 h (98%).

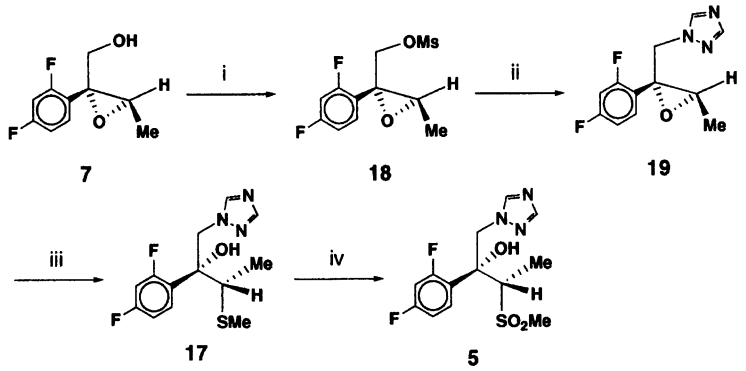
Scheme 3.

$[\alpha]_D^{25}$ +35.0° (*c* 1.0, $CHCl_3$)],[7,15] as shown in Scheme 3. In order to determine the enantioselectivity of the reaction, the hydroxy group of (+)-**7** was acetylated, and the ^1H NMR spectra of the resulting acetate (+)-**15** was measured in the presence of 10 mol% of a chiral shift reagent, europium(III) derivative of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato], i. e., $Eu(hfdc)_3$. The NMR spectrum was compared with the corresponding NMR spectrum of *dl*-**15** which was prepared by Sharpless epoxidation[16] of **8** followed by acetylation. No peaks originating from the antipode were observed in the chart of (+)-**15** at all, therefore the enantiomeric excess (ee) of (+)-**7** was determined to be > 95%.

Optically active epoxide (+)-**7** was then treated with aqueous sodium methanethiolate in dimethyl sulfoxide at 55 °C to afford *erythro*-sulfide **6** [77% yield, $[\alpha]_D^{25}$ +7.5° (*c* 1.0, MeOH)]. The primary hydroxy group of diol **6** was mesylated selectively, followed by alkaline treatment of the mesylate to give *erythro*-epoxide **16** [a quantitative yield, $[\alpha]_D^{25}$ −45.2° (*c* 0.5, toluene)]. Introduction of a 1*H*-1,2,4-triazolyl group to epoxide **16** using 1,2,4-triazole and sodium hydroxide in dimethyl sulfoxide at 80 °C gave *erythro*-triazolyl sulfide **17** [72% yield, $[\alpha]_D^{25}$ −92.3° (*c* 0.5, $CHCl_3$)]. Sulfide **17** was then oxidized with hydrogen peroxide in the presence of a catalytic amount of sodium tungstate under acidic conditions to afford *erythro*-sulfone **5** [98% yield, $[\alpha]_D^{25}$ −52.0° (*c* 0.9, $CHCl_3$)].

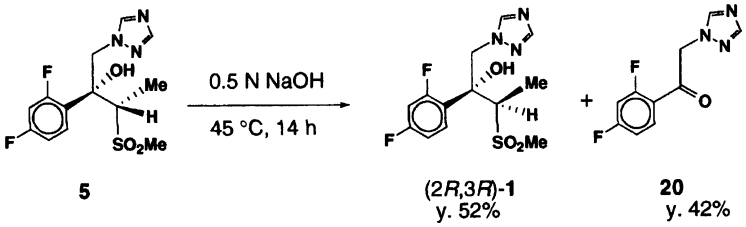
An alternative way to prepare *erythro*-sufone **5** from epoxide **7** was also investigated, as shown in Scheme 4. Mesylation of the hydroxy group of **7** followed by substitution of the mesyl group of **18** to a 1,2,4-triazolyl group afforded **19** in 49% yield. The nucleophilic attack of methanethiolate on epoxide **19** proceeded with complete inversion to give sulfide **17** as a single product in 84% yield. Sulfide **17** was oxidized to sulfone **5** under the same conditions as described above. This route could be valuable for the preparation of **5** if the yield of the first step can be improved.

Finally, epimerization of *erythro*-sulfone **5** to the desired *threo*-isomer **1** was investigated under basic conditions. When racemic **5** was treated at 60 °C in 1 M aqueous sodium hydroxide solution (1 M=1 mol dm^{-3}), the epimerization at the C-3 position went well to afford racemic **1** in 74% yield. Because of its low solubility, *threo*-racemate **1** crystallized as soon as it was generated in the reaction media. Therefore, the equilibrium between *erythro*-racemate **5** and *threo*-racemate **1** would be displaced to the more insoluble **1**. On the basis of the results of racemic **5**, we then tried the epimerization of chiral *erythro*-isomer **5** obtained above under similar conditions. The best result was obtained when the reaction was carried out at 45 °C in 0.5 M aqueous sodium hydroxide solution, as shown in Scheme 5. Thus, chiral **1** could be obtained in 52% yield. The absolute configuration of the product was determined to be (2*R*,3*R*) by the optical rotation



Reagents and conditions
i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min.
ii) 1,2,4-triazole, NaOH, DMSO, 80 °C, 1 h (49% from **7**).
iii) NaSMe, DMSO, 55 °C, 3 h (84%).
iv) 31% H_2O_2, concd HCl, $Na_2WO_4 \cdot 2H_2O$, toluene, 60 °C, 1 h (98%).

Scheme 4.



Scheme 5.

$[[\alpha]_D^{25}$ -72.0° (*c* 0.4, $CHCl_3$)] and HPLC analysis.[4,9] The enantiomeric excess of the final product was determined to be 98% by HPLC analysis. In addition, only 2% of unreacted starting *erythro*-sulfone **5** was recovered in this reaction. However, this reaction was accompanied with ketone **20**[17] as a by-product in 42% yield, which should be generated by a retro-Aldol type reaction of sulfone **1**. Higher temperatures or longer reaction times caused higher yields of by-product **20**. With regard to the reaction mechanism, it seems difficult to discuss a present. Different from the case of the racemate, the epimerization of chiral **5** proceeded homogenously because of the higher solubility of chiral **1** than racemic **1** in the reaction media.[4] Nevertheless, the equilibrium was completely displaced to **1**. In order to find the reason, we calculated the molecular dynamics of both *erythro*-sulfone **5** and *threo*-one **1** several ways, however, we could not obtain any supportable information to explain the experimental results. Further investigation to clarify the reaction mechanism is currently in progress.

In conclusion, we have found a new synthetic method for preparing SM-9164 utilizing Katsuki-Sharpless asymmetric epoxidation of (*E*)-allylic alcohol **8** and epimerization of *erythro*-sulfone **5** under basic conditions. Thus, SM-9164 could be prepared by asymmetric synthesis in only 10 steps from commercially available α-chloro ketone **9** in 13% overall yield.

Experimental

Melting points were determined on a Thomas–Hoover capillary melting point apparatus without correction. Measurements of optical rotations were performed with a JASCO DIP-370. Infrared spectra (IR) were recorded on a JASCO A-102 IR spectrometer or a Perkin–Elmer 1600 FTIR 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 ($\delta = 0.00$). 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 were used as received unless otherwise indicated. Dichloromethane, ether, *N*, *N*-dimethylformamide (DMF), and benzene were dried over molecular sieves 4A. Tetrahydrofuran (THF), dimethylsulfoxide (DMSO), and hexamethylphosphoric triamide (HMPA) were dried over molecular sieves 5A.

2-Acetoxy-1-(2,4-difluorophenyl)ethanone (10): To a solution of 2-chloro-1-(2,4-difluorophenyl)ethanone (**9**) (190.7 mg, 1.00 mmol) in DMF (2.0 ml) was added anhydrous sodium acetate (164 mg, 2.00 mmol), and the mixture was stirred at room temperature for 4 h. The mixture was then diluted with dichloromethane (50 ml) and washed with water (3×20 ml). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give acetate **10** (200.5 mg, 94% yield): A colorless oil; IR (neat) 3450, 1700, 1620, 1600, 1510, 1500, and 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta = 2.23$ (3H, s, OAc), 5.20 (2H, d, $J = 4.0$ Hz, CH_2), 6.87—7.06 (2H, m, Ph-H), and 8.03 (1H, m, Ph-H). Found: C, 55.93; H, 3.86%. Calcd for $C_{10}H_8F_2O_3$: C, 56.08; H, 3.76%.

1-(2,4-Difluorophenyl)-2-hydroxyethanone (11): To a cooled solution of acetate **10** (50.0 mg, 0.23 mmol) in methanol (1.0 ml) at 0 °C was added 1 M hydrochloric acid solution (0.1 ml, 0.10 mmol), and the mixture was stirred at 40 °C for 5 h. The reaction mixture was then poured into a stirred mixture of water (20 ml) and dichloromethane (50 ml), and the mixture was stirred for an additional 10 min. The organic layer was separated and washed with saturated sodium hydrogen carbonate (20 ml), which was then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by preparative TLC developed twice with a 4 : 1 mixture of hexane and ether to afford alcohol **11** (27.5 mg, 69% yield): A colorless crystalline powder; mp 90.0—93.0 °C; IR (KBr) 3440, 1690, 1605, 1595, 1500, and 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.52 (1H, t, J = 4.8 Hz, OH), 4.77 (2H, dd, J = 3.6 and 4.8 Hz, CH_2), 6.93 (1H, m, Ph-H), 7.04 (1H, m, Ph-H), and 8.13 (1H, m, Ph-H). Found: C, 55.92; H, 3.32%. Calcd for $C_8H_6F_2O_2$: C, 55.82; H, 3.51%.

1-(2,4-Difluorophenyl)-2-(tetrahydropyranyloxy)ethanone (12a): To a cooled solution of alcohol **11** (100 mg, 0.58 mmol) and dihydropyran (DHP, 80 μl, 0.87 mmol) in dichloromethane (2.0 ml) at 0 °C was added pyridinium *p*-toluenesulfonate (PPTS, 8.0 mg, 0.03 mmol), and the mixture was stirred at 0 °C for 7 h. The reaction mixture was then poured into a stirred mixture of saturated sodium hydrogen carbonate (10 ml) and dichloromethane (50 ml), and the mixture was stirred for an additional 10 min. The organic layer was separated and washed with water (20 ml), and then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to afford THP ether **12a** (169 mg, a quantitative yield): A colorless oil; ^1H NMR ($CDCl_3$) δ = 1.40—2.00 (6H, m, H-2, 3, and 4 of THP), 3.54 (1H, m, H-5 of THP), 3.88 (1H, m, H-5 of THP), 4.77 (1H, t, J = 3.3 Hz, H-1 of THP), 4.81 (2H, s, CH_2), 6.84—7.04 (2H, m, Ph-H), and 8.04 (1H, m, Ph-H).

2-(*t*-Butyldimethylsilyloxy)-1-(2,4-difluorophenyl)ethanone (12b): To a cooled solution of alcohol **11** (100 mg, 0.58 mmol) and pyridine (0.1 ml, 1.22 mmol) in dichloromethane (2.0 ml) at 0 °C was added *t*-butyldimethylsilyl chloride (TBDMSCl, 131 mg, 0.87 mmol), and the mixture was stirred at 0 °C for 7 h. The reaction mixture was then poured into a stirred mixture of saturated sodium hydrogen carbonate (10 ml) and dichloromethane (50 ml), and this was stirred for an additional 10 min. The organic layer was separated and washed with water (20 ml), and then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to afford TBDMS ether **12b** (159 mg, 96% yield): A colorless oil; ^1H NMR ($CDCl_3$) δ = 0.13 (6H, s, SiMe×2), 0.93 (9H, s, Si^{t}Bu), 4.80 (2H, d, J = 3.7 Hz, CH_2), 6.87 (1H, m, Ph-H), 6.99 (1H, m, Ph-H), and 7.99 (1H, m, Ph-H).

Wittig Reaction of Ketone 12a [Entry 1]:[11] To a suspension of ethyltriphenylphosphonium bromide (195 mg, 0.53 mmol) in ether (2.0 ml) under nitrogen was added dropwise a solution of butyllithium in hexane (1.66 M, 0.32 ml, 0.53 mmol). After being stirred at room temperature for 30 min, the solution was treated with ketone **12a** (91 mg, 0.35 mmol), and was then stirred at room temperature for an additional 5 h. The reaction mixture was worked up by the same method as described above to give a 59 : 41 mixture of **13a** and **14a** (67 mg, 73% yield) as a colorless oil.

13a: ^1H NMR ($CDCl_3$) δ = 1.40—1.90 (6H, m), 1.53 (3H, d, J = 6.9 Hz, Me), 3.46 (1H, m), 3.72 (1H, m), 4.13 (1H, d, J = 12.5 Hz), 4.36 (1H, d, J = 12.5 Hz), 4.65 (1H, t, J = 3.3 Hz), 5.98 (1H, q, J = 6.9 Hz, CH), 6.72—6.91 (2H, m), and 7.17 (1H, m).

14a: ^1H NMR ($CDCl_3$) δ = 1.40—1.90 (6H, m), 1.89 (3H, d, J = 6.9 Hz, Me), 3.46 (1H, m), 3.72 (1H, m), 4.38 (1H, d, J = 12.5 Hz), 4.53 (1H, d, J = 12.5 Hz), 4.65 (1H, t, J = 3.3Hz), 5.87 (1H, q, J = 6.9 Hz, CH), 6.72—6.91 (2H, m), and 7.22 (1H, m).

Wittig Reaction of Ketone 12b [Entry 2]:[11] Ketone **12b** (101 mg, 0.35 mmol) was treated by the same method as described above to afford a 65 : 35 mixture of **13b** and **14b** (83 mg, 79% yield).

13b: ^1H NMR ($CDCl_3$) δ = 0.00 (6H, s, SiMe×2), 0.86 (9H, s, Si^{t}Bu), 1.53 (3H, d, J = 6.9 Hz, Me), 4.25 (2H, s, CH_2), 5.93 (1H, q, J = 6.9 Hz, CH), 6.70—6.90 (2H, m), and 7.13 (1H, m).

14b: ^1H NMR ($CDCl_3$) δ = 0.00 (6H, s, SiMe×2), 0.86 (9H, s, Si^{t}Bu), 1.83 (3H, d, J = 6.9 Hz, Me), 4.49 (2H, s, CH_2), 5.68 (1H, q, J = 6.9 Hz, CH), 6.70—6.90 (2H, m), and 7.22 (1H, m).

Wittig Reaction of Ketone 12a [Entry 3]:[12] To a suspension of ethyltriphenylphosphonium bromide (156 mg, 0.43 mmol) in a mixture of ether (1.5 ml) and THF (2.5 ml) under nitrogen was added dropwise a solution of butyllithium in hexane (1.66 M, 0.25 ml, 0.42 mmol). After being stirred at room temperature for 30 min, the solution was cooled to −78 °C, and was treated with a solution of ketone **12a** (91 mg, 0.35 mmol) in ether (1.0 ml). After being stirred at −78 °C for 5 min, additional butyllithium in hexane (1.66 M, 0.25 ml, 0.43 mmol) was added dropwise to the mixture at −40 °C. After 5 min, 8 wt% hydrochloric acid solution in ether (0.25 ml, 0.55 mmol) was added dropwise to the mixture at −30 °C. After an additional 5 min, potassium *t*-butoxide (79 mg) and *t*-butyl alcohol (0.1 ml) were added to the mixture at −30 °C, and the resulting mixture was allowed to warm to room temperature. The mixture was then stirred at room temperature for an additional 3 h. The reaction mixture was worked up by the same method as described above to give a 79 : 21 mixture of **13a** and **14a** (58 mg, 60% yield) as a colorless oil.

Wittig Reaction of Ketone 12b [Entry 4]:[12] Ketone **12b** (102 mg, 0.36 mmol) was treated by the same method as described above to afford a 91 : 9 mixture of **13b** and **14b** (62 mg, 59% yield). A small amount of starting material was also recovered (22 mg, 22% recovered).

Wittig Reaction of Ketone 12b [Entry 5]:[13] To a suspension of ethyltriphenylphosphonium bromide (215 mg, 0.58 mmol) in THF (2.0 ml) was added potassium *t*-butoxide (65 mg, 0.58 mmol), and the mixture was stirred at room temperature for 30 min. Ketone **12b** (110 mg, 0.38 mmol) was then added to the mixture, and the resulting suspension was stirred at room temperature for 5 h. Additional ethyltriphenylphosphonium bromide (215 mg, 0.58 mmol) and potassium *t*-butoxide (65 mg, 0.58 mmol) were added to the mixture, and the mixture was refluxed for 7 h. The resultant reaction mixture was worked up and purified in the same method as described above to give an 89 : 11 mixture of **13a** and **14a** (38 mg, 33% yield).

Modified Wittig Reaction of Ketone 12a [Entry 6]:[14] To a suspension of ethyltriphenylphosphonium bromide (292 mg, 0.84 mmol) in THF (2.4 ml) and HMPA (0.26 ml) under nitrogen was added dropwise a solution of butyllithium in hexane (1.66 M, 0.44 ml, 0.73 mmol). After being stirred at room temperature for 10 min, the solution was cooled at −78 °C, and was treated with ketone **12a** (143 mg, 0.56 mmol). After being stirred at −78 °C for 20 min, the reaction mixture was allowed to warm to room temperature. The mixture was then stirred at room temperature for an additional 2 h. Water (20 ml) was added to the reaction mixture, and the mixture was extracted with ether (3×20 ml). The combined organic layers were washed with water (2×20 ml) and brine (20 ml) in order, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography on 5 g of silica gel eluting with hexane and ether (10 : 1) to give a 95 : 5 mixture of **13a** and **14a** (99 mg, 75% yield) as a colorless oil.

Modified Wittig Reaction of Ketone 12b [Entry 7]:[14] Ketone

12b (150 mg, 0.53 mmol) was treated by the same method as described above to afford a 97 : 3 mixture of **13b** and **14b** (123 mg, 79% yield) as a colorless oil.

(*E*)-2-(2,4-Difluorophenyl)-2-buten-1-ol (8): To a cooled solution of TBDMS ether **13b** (77 mg, 0.26 mmol, including 3% of **14b**) in THF (1.0 ml) at 0 °C was added a solution of tetrabutylammonium fluoride in THF (1.0 M, 0.4 ml, 0.80 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction mixture was then poured into water (20 ml) and extracted with ether (3×20 ml). The combined organic layers were washed with brine (20 ml), dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The resulting residue was purified by preparative TLC developed by hexane and ether (1 : 1) to afford (*E*)-allylalcohol **8** (46 mg, 96% yield) as a single isomer: A colorless oil; IR (neat) 3350, 2910, 2850, 1615, 1595, 1500, 1420, and 1260 cm^{-1}; ^1H 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). Found: C, 64.08; H, 5.60%. Calcd for $C_{10}H_{10}F_2O \cdot 1/5\ H_2O$: C, 63.96; H, 5.58%.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-2-hydroxymethyl-3-methyloxirane [(+)-7]: A 100 ml, 1-neck round-bottom flask equipped with a Teflon®-coated magnetic stir bar was dried and then fitted with a septum cap and flushed with nitrogen. The flask was charged with dichloromethane (16 ml) and cooled by stirring at −20 °C. The following liquids were then added sequentially via syringe while stirring at −20 °C: titanium tetraisopropoxide (distilled, 4.62 ml, 16.2 mmol); (−)-diethyl (2*S*,3*S*)-tartrate (2.73 ml, 15.9 mmol), stirred for 5 min before the next addition; alcohol **8** (2.89 g, 15.7 mmol); and finally, a solution of anhydrous *t*-butyl hydroperoxide in dichloromethane which was prepared by extraction of aqueous *t*-butyl hydroperoxide[11] (67.1%, 4.30 g, 32.0 mmol) with dichloromethane (20.0 ml) followed by drying over molecular sieves 4A. The resulting homogeneous solution was then stored for 2 d in the freezer at −20 °C in a sealed reaction vessel. The flask was then placed cooled to −20 °C and 10% aqueous tartaric acid solution (50 ml) was added while stirring; the aqueous layer solidified. After 30 min, the cooling bath was removed and stirring was continued at room temperature for 30 min. After separation of the aqueous layer, the organic layer was washed with water (20 ml), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The residue was diluted with ether (120 ml), and the resulting solution was cooled to 0 °C and 1 M sodium hydroxide (50 ml) was then added. This produced a two-phase mixture which was stirred at 0 °C for 30 min. The ether phase was washed with brine (50 ml), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give oxirane (+)-**7** (3.01 g, 96% yield): A colorless oil; $[\alpha]_D^{25}$ +35.0° (*c* 1.0, $CHCl_3$); IR (neat) 3400, 2960, 2920, 1615, 1600, 1500, 1420, and 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.08 (3H, d, J = 5.6 Hz, CH_3), 1.77 (1H, dd, J = 5.0 and 8.5 Hz, OH), 3.53 (1H, q, J = 5.6 Hz, CH), 3.84 (1H, dd, J = 8.5 and 12.5 Hz), 3.95 (1H, dd, J = 5.0 and 12.5 Hz), 6.78—6.95 (2H, m), and 7.36 (1H, m). Found: C, 58.25; H, 5.49%. Calcd for $C_{10}H_{10}F_2O_2 \cdot 1/3\ H_2O$: C, 58.25; H, 5.21%.

(2*R*,3*R*)-2-Acetoxymethyl-2-(2,4-difluorophenyl)-3-methyloxirane [(+)-15]: To a cooled solution of alcohol **8** (34.0 mg, 0.17 mmol) and pyridine (50 μl, 0.62 mmol) in dichloromethane (1.0 ml) at 0 °C was added acetic anhydride (40 μl, 0.42 mmol), and the mixture was stirred at 0 °C for 3 h. The reaction mixture was then poured into water (20 ml) and extracted with ethyl acetate (3×20 ml). The combined organic layer were washed with water (2×20 ml) and brine (20 ml) in order, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography on 6 g of Florisil eluting with hexane and ether (5 : 1) to afford acetate (+)-**15** (28.0 mg, 68% yield): A colorless oil; $[\alpha]_D^{25}$ +51.8° (*c* 0.9, $CHCl_3$); IR (KBr) 1740, 1605, 1595, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.07 (3H, d, J = 5.6 Hz, CH_3), 2.01 (3H, s, OAc), 3.40 (1H, q, J = 5.6 Hz, CH), 4.09 (1H, d, J = 12.2 Hz), 4.63 (1H, d, J = 12.2 Hz), 6.81—6.95 (2H, m), and 7.39 (1H, m). Found: C, 59.37; H, 5.28%. Calcd for $C_{12}H_{12}F_2O_3$: C, 59.50; H, 4.99%.

***dl*-2-Acetoxymethyl-2-(2,4-difluorophenyl)-3-methyloxirane (*dl*-15):** To a solution of alcohol **8** (19.0 mg, 0.10 mmol) in benzene (1.0 ml) was added vanadyl acetoacetonate [$VO(acac)_2$, 1.0 mg, 0.004 mmol], and the mixture was stirred at room temperature for 10 min. To this solution was then added *t*-butyl hydroperoxide in benzene which was prepared by a method similar to that described previously[11] (ca. 1.5 M, 0.1 ml, 0.15 mmol). The resulting solution was stirred at room temperature for 20 h. The reaction mixture was then diluted with ether (50 ml) and washed with water (20 ml), 5% aqueous sodium thiosulfate solution (20 ml), water (20 ml), and brine (20 ml) in order. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue containing *dl*-**7** (13.1 mg) was dissolved in dichloromethane (1.0 ml), and the solution was cooled to 0 °C. Pyridine (50 μl) and acetic anhydride (40 μl) were added to the solution, and the mixture was stirred at 0 °C for 5 h. The resulting reaction mixture was then worked up by the same procedure as described above to afford acetate *dl*-**15** (6.1 mg, 24% overall yield from **8**).

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-methylthio-1,2-butanediol (6): To a solution of oxirane (+)-**7** (2.20 g, 11.0 mmol) in DMSO (50 ml) was added dropwise 15% aqueous sodium methanethiolate solution (15.0 ml, 46.8 mmol), and the mixture was stirred at 55 °C for 3 h. The reaction mixture was then poured into water (200 ml) and extracted with toluene (3×200 ml). The combined organic layers were washed with saturated ammonium chloride solution (200 ml), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography on 100 g of silica gel eluting with hexane and ethyl acetate (4 : 1) to afford sulfide **6** (2.10 g, 77% yield): A colorless oil; $[\alpha]_D^{25}$ +7.5° (*c* 1.0, MeOH); IR (neat) 3300, 2970, 2920, 1615, 1600, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.37 (3H, d, J = 7.2 Hz, CH_3), 1.78 (1H, br., OH), 1.80 (3H, s, SCH_3), 3.34 (1H, q, J = 7.2 Hz, CH), 4.01 (2H, s, CH_2), 6.75—6.83 (2H, m), and 6.93 (1H, m). Found: C, 53.11; H, 5.82%. Calcd for $C_{11}H_{14}F_2O_2S$: C, 53.21; H, 5.68%.

(2*R*)- 2- (2, 4- Difluorophenyl)- 2- [(*S*)- 1- (methylthio)ethyl]-oxirane (16): To a cooled solution of diol **6** (503 mg, 2.03 mmol) and triethylamine (0.85 ml, 6.10 mmol) in toluene (20 ml) at 0 °C was added dropwise methanesulfonyl chloride (0.25 ml, 3.25 mmol), and the mixture was stirred at 0 °C for 30 min. 15% Aqueous potassium hydroxide solution (10 ml, 26.8 mmol) was then added, and the mixture was stirred vigorously at 0 °C for an additional 2 h. The aqueous layer was separated and extracted with toluene (30 ml). The combined organic layers were washed with water (20 ml), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to afford oxirane **16** (474 mg, a quantitative yield): A colorless oil; $[\alpha]_D^{25}$ −45.2° (*c* 0.5, toluene); IR (neat) 2970, 2920, 1610, 1600, 1500, and 1267 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.31 (3H, d, J = 6.9 Hz, CH_3), 2.15 (3H, s, SCH_3), 2.86 (1H, d, J = 5.0 Hz), 2.97 (1H, q, J = 6.9 Hz, CH), 3.17 (1H, d, J = 5.0 Hz), 6.76—6.92 (2H, m), and 7.40 (1H, m).

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-methylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17) from Oxirane 16: To a solution of oxirane **16** (434 mg, 1.88 mmol) in DMSO (4.0 ml) were added

1*H*-1,2,4-triazole (195 mg, 2.82 mmol) and sodium hydroxide (95 mg, 95% assay, 2.26 mmol), and the mixture was stirred at 80 °C for 3 h. The resulting mixture was poured into saturated ammonium chloride solution (10 ml) followed by extraction with dichloromethane (2×50 ml). The organic layers were combined together, washed with water (2×30 ml), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography on 20 g of silica gel eluting with hexane and ethyl acetate (3 : 2) to give triazolyl compound **17** (407 mg, 72% yield): A colorless crystalline powder; mp 68.0—72.0 °C; $[\alpha]_D^{25}$ −92.3° (*c* 0.5, $CHCl_3$); IR (KBr) 3500, 1615, 1600, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.51 (3H, d, *J* = 6.9 Hz, $CH\underline{CH_3}$), 1.79 (3H, s, SCH_3), 3.37 (1H, q, *J* = 6.9 Hz, $\underline{CH}CH_3$), 4.48 (1H, s, OH), 4.58 (1H, d, *J* = 13.9 Hz), 4.92 (1H, d, *J* = 13.9 Hz), 6.68—6.80 (2H, m), 7.39 (1H, m), 7.71 (1H, s), and 7.96 (1H, s). Found: C, 52.11; H, 5.32; N, 13.72%. Calcd for $C_{13}H_{15}F_2N_3OS$: C, 52.16; H, 5.05; N, 14.04%.

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (5): To a solution of sulfide **17** (300 mg, 1.00 mmol) in toluene (6.0 ml) were added sodium tungstate dihydrate (9.0 mg, 0.03 mmol) and concd hydrochloric acid (240 mg, 35% assay, 2.30 mmol), and the mixture was stirred at room temperature while adding 35% aqueous hydrogen peroxide (300 mg, 3.09 mmol) dropwise. After stirring at 60 °C for 1 h, the resulting mixture was cooled to room temperature, followed by addition of 10% aqueous sodium sulfite to reduce excess hydrogen peroxide (checked by potassium iodide–starch paper). The mixture was then poured into saturated sodium hydrogen carbonate solution (20 ml), and extracted with dichloromethane (3×30 ml). The organic layers were combined, washed with water (20 ml) and brine (20 ml) in order, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to afford sulfone **5** (326 mg, 98% yield): Colorless crystals; mp 89.0—91.0 °C; $[\alpha]_D^{25}$ −52.0° (*c* 0.9, $CHCl_3$); IR (KBr) 3500, 1620, 1600, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.72 (3H, d, *J* = 7.2 Hz, $CH\underline{CH_3}$), 2.79 (3H, s, SO_2CH_3), 3.71 (1H, q, *J* = 7.2 Hz, $\underline{CH}CH_3$), 4.72 (1H, d, *J* = 13.9 Hz), 4.90 (1H, d, *J* = 13.9 Hz), 5.53 (1H, s, OH), 6.73—6.84 (2H, m), 7.39 (1H, m), 7.72 (1H, s), and 7.95 (1H, s). Found: C, 44.66; H, 4.86; N, 11.79%. Calcd for $C_{13}H_{15}F_2N_3O_3S \cdot H_2O$: C, 44.70; H, 4.90; N, 12.03%.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-2-[(methylsulfonyloxy)methyl]-3-methyloxirane (18): To a cooled solution of oxirane (+)-**7** (350 mg, 1.75 mmol) in dichloromethane at 0 °C was added triethylamine (0.50 ml, 3.50 mmol) followed by dropwise addition of methanesulfonyl chloride (0.20 ml, 2.62 mmol). After being stirred at 0 °C for 30 min, the mixture was diluted by ether (70 ml) and washed with water (20 ml), saturated ammonium chloride solution (20 ml), saturated sodium hydrogen carbonate solution (20 ml) and brine (20 ml) in order. The organic layer was then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to afford mesylate **18** (495 mg), which was subjected to the sequential reactions without further purification: A colorless oil; ^1H NMR ($CDCl_3$) δ = 1.09 (3H, d, *J* = 5.3 Hz, $CH\underline{CH_3}$), 2.99 (3H, s, Ms), 3.44 (1H, q, *J* = 5.3 Hz, $\underline{CH}CH_3$), 4.28 (1H, d, *J* = 11.9 Hz), 4.73 (1H, d, *J* = 11.9 Hz), 6.82—6.98 (2H, m), and 7.39 (1H, m).

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-methyl-2-[(1*H*-1,2,4-triazol-1-yl)methyl]oxirane (19): To a solution of mesylate **18** obtained above in DMSO (4.0 ml)were added 1*H*-1,2,4-triazole (183mg, 2.65 mmol) and sodium hydroxide (95 mg, 95% assay, 2.26 mmol), and the mixture was stirred at 80 °C for 1 h. The resulting mixture was then poured into water (20ml) and extracted with dichloromethane (2×30 ml). The combined organic layers were washed with saturated ammonium chloride solution (20 ml), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resultant residue was purified by column chromatography on 24 g of Florisil® eluting with hexane and ether (1 : 1) to give **19** [216 mg, 49% yield from (+)-**7**]: Colorless crystals; mp 62.0—63.0 °C; $[\alpha]_D^{25}$ +6.6° (*c* 0.9, $CHCl_3$); IR (KBr) 1620, 1600, 1510, 1425, and 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.06 (3H, d, *J* = 5.3 Hz, $CH\underline{CH_3}$), 3.18 (1H, q, *J* = 5.3 Hz, $\underline{CH}CH_3$), 4.42 (1H, d, *J* = 14.9 Hz), 4.80 (1H, d, *J* = 14.9 Hz), 6.78—6.89 (2H, m), 7.13 (1H, m), 7.85 (1H, s), and 8.06 (1H, s). Found: C, 56.01; H, 4.76; N, 16.17%. Calcd for $C_{12}H_{11}F_2N_3O \cdot 1/3\ H_2O$: C, 56.03; H, 4.57; N, 16.33%.

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-methylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17) from Oxirane 19: To a solution of oxirane **19** (204 mg, 0.81 mmol) in DMSO (3.0 ml) was added dropwise 15% aqueous sodium methanethiolate solution (1.5 ml), and the mixture was stirred at 55 °C for 3 h. The resulting mixture was poured into water (30 ml) followed by extraction with dichloromethane (2×50 ml). The organic layers were combined together, washed with saturated ammonium chloride solution (30 ml), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography on 6 g of silica gel eluting with hexane and ethyl acetate (3 : 2) to give triazolyl compound **17** (203 mg, 84% yield): A colorless crystalline powder; $[\alpha]_D^{25}$ −92.8° (*c* 0.6, $CHCl_3$). This sample showed identical spectral properties (IR and ^1H NMR) to those recorded for **17** synthesized from oxirane **16**.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(2*R*,3*R*)-1]: A solution of *erythro*-isomer **5** (41.0 mg, 0.124 mmol) in 0.5 M aqueous sodium hydroxide solution (4.0 ml) was stirred at 45 °C for 14 h. Saturated ammonium chloride solution (10 ml) was then added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate (3×30 ml). The combined organic layers were washed with brine (20 ml), dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by preparative TLC developed by chloroform and methanol (19 : 1) to give *threo*-sulfone **1** (21.3 mg, 52% yield), ketone **20** (11.7 mg, 42% yield), and unreacted starting *erythro*-sulfone **5** (0.8 mg, 2% recovered). Obtained sulfone **1** showed identical spectral properties (IR and ^1H NMR) to those recorded previously:[9] Colorless crystals; 98%ee by a HPLC analysis; $[\alpha]_D^{25}$ −72.0° (*c* 0.4, $CHCl_3$).

20: Mp 109.0—110.0 °C; IR (KBr) 1690, 1610, 1600, 1510, and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.59 (2H, s, CH_2), 6.94—7.10 (2H, m), 8.02 (1H, s, Tz-H), 8.04 (1H, m), and 8.22 (1H, s, Tz-H). Found: C, 53.69; H, 3.39; N, 18.67%. Calcd for $C_{10}H_7F_2N_3O$: C, 53.82; H, 3.16; N, 18.83%.

Determination of the Optical Purity of 1 by HPLC Analysis: The optical purity of **1** was determined by HPLC analysis under the following conditions: Column; Sumipax OA-4400 (5 μm, 4 mmϕ×25 cm), mobile phase; hexane/1,2-dichloroethane/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*)-**1**, and the peak at 18.0 min corresponded to its enantiomer (2*S*, 3*S*)-**1**.

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