STEREOSELECTIVE SYNTHESIS OF ANTIFUNGAL SULFOXIMINES, NOVEL TRIAZOLES II†

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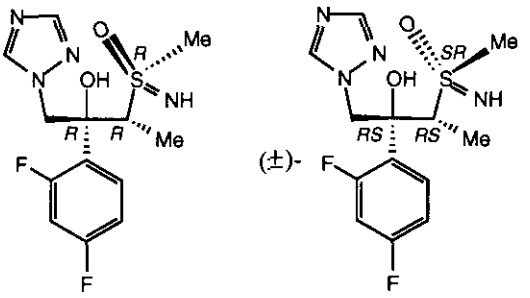
Abstract -Novel triazole derivatives with *N*-substituted sulfoximine moiety were synthesized and evaluated for antifungal activity. These compounds showed only significantly weak activity and the *N-H* sulfoximine moiety was extremely important for the activity. A more practical and effective stereoselective synthesis of *N-H* sulfoximine, (*R*)-*S*-2-[(2*R*,3*R*)-3-(2,4-difluorophenyl)-3-hydoroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-methylsulfoximine (**1**), which was considered to be the most promising compound, has been developed.

Introduction

In the previous paper,[1] we described the stereoselective synthesis and antifungal activity of (*R*)-*S*-methylsulfoximine (**1**), the epimer of *N-H* sulfoximine at sulfur [(±)-**2**], and the related compounds. As a result, we found that **1** was the most potent *in vitro* antifungal activity with a broad spectrum and then the desired stereochemistry at sulfur to show the strong activity was (*R*)-configuration (Figure 1).

In this paper, we describe the modification of sulfoximine moiety of **1** to investigate whether the hydrogen of sulfoximine moiety is essential for antifungal activity, and also the more practical stereoselective synthesis of **1**.

† This paper is dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday, and with gratitude for his many contributions in organic chemistry.

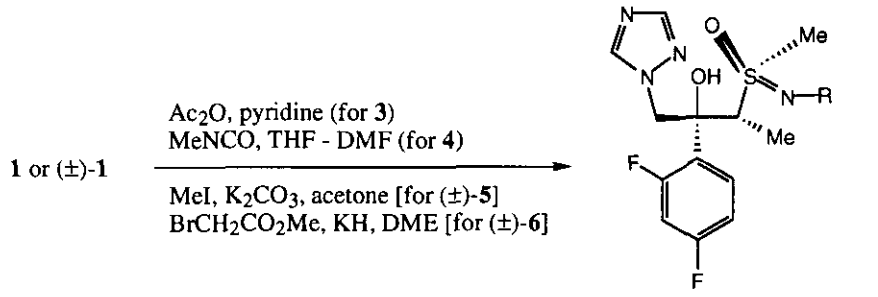


1 (±)-**2**

Figure 1

Chemistry

In general the nitrogen of *N-H* sulfoximine is sufficiently basic to form salts with mineral acids and can serve as a point for additional substitution.[2] *N*-Acylation of **1** with acetic anhydride in pyridine or methyl isocyanate proceeded smoothly at room temperature to give the corresponding *N*-substituted sulfoximines (**3** and **4**) in 83 and 78% yields, respectively. The hydroxyl group of **1** was inert under the conditions. In contrast, *N*-alkylation of (±)-**1** with methyl iodide or methyl bromoacetate gave the corresponding *N*-alkylated sulfoximines [(±)-**5** and (±)-**6**] in low yields, 19 and 47%, respectively (Scheme 1).

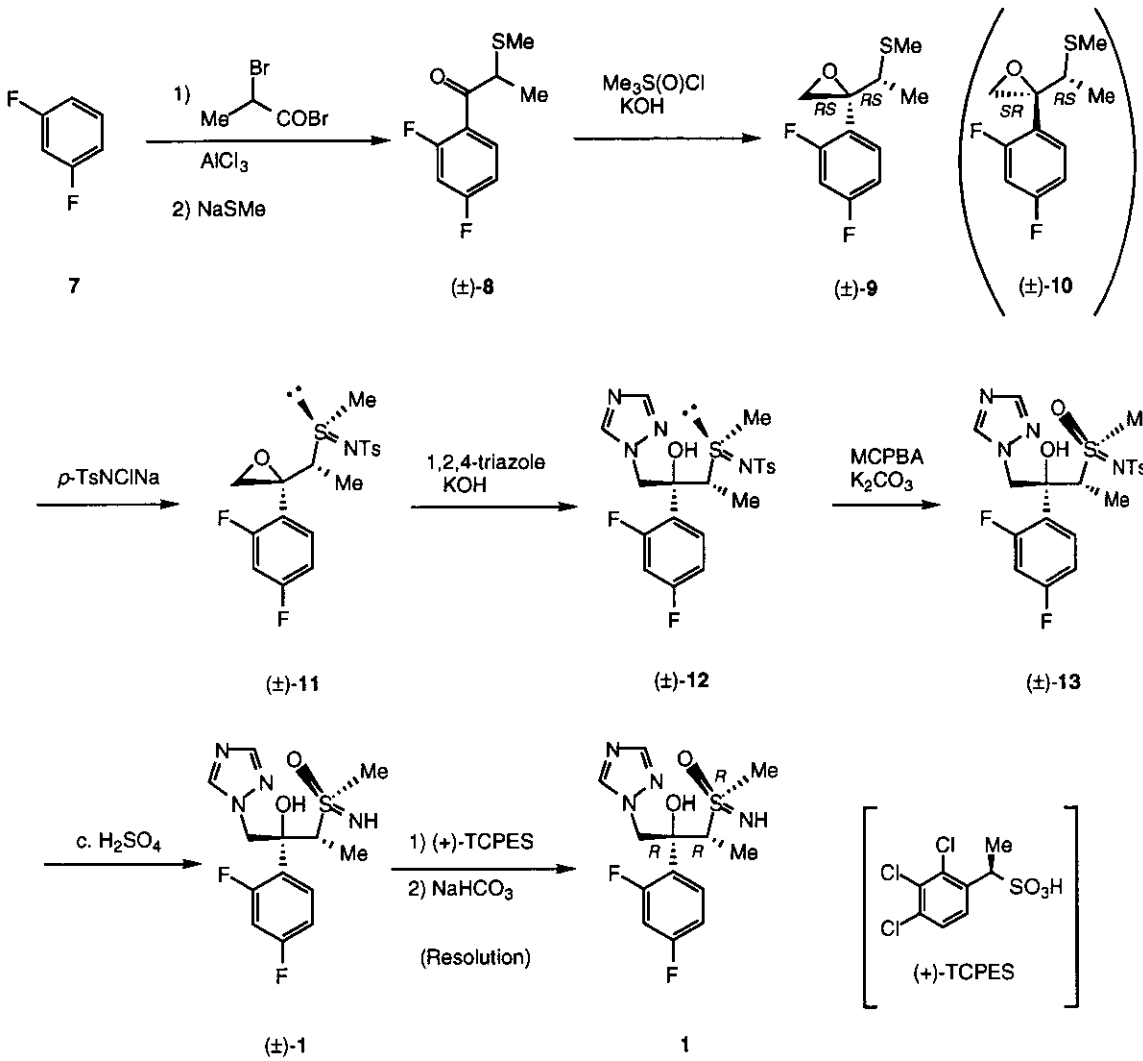


3 (R = Ac)
4 (R = CONHMe)
(±)-**5** (R = Me)
(±)-**6** (R = CH_2CO_2Me)

Scheme 1

The *in vitro* antifungal activity of **3**, **4**, (±)-**5** and (±)-**6** was evaluated and found to be very weak compared to that of **1** (data not shown). These results reveal that the *N-H* sulfoximine moiety is extremely important to

show the potent antifungal activity.



Scheme 2

Since the sulfoximine (**1**), which was prepared by the reported procedure,[1] was found to be the most promising compound as an antifungal drug candidate, more practical and effective synthetic procedure was investigated for a large scale synthesis of **1**. Thus the racemic sulfide [(±)-**8**][3] was prepared from 1,3-difluorobenzene (**7**) in two steps as shown in Scheme 2. Diastereoselective epoxidation of (±)-**8** was subsequently performed by slightly modified literature method[3] and the resulting crude mixture was purified by

distillation (bp 99-114 °C at 1.0-1.5 mmHg) to give predominantly desired epoxide [(±)-**9**] as a mixture [(±)-**9**:(±)-**10** = 7-8:1]. The following reaction with anhydrous chloramine T[1,4] proceeded diastereoselectively and the crude products were recrystallized from AcOEt to give the *N*-tosylsulfilimine [(±)-**11**] in 49% yield as colorless crystals, mp 138.5-139.5 °C. The relative configuration at sulfur of obtained (±)-**11** was confirmed to be desired (*S*)-configuration by leading to (±)-**12**[1] as follows. Thus obtained (±)-**11** reacted with 1,2,4-triazole in the presence of potassium hydroxide in DMSO at room temperature and the resulting crude product was triturated with *i*-PrOH to give (±)-**12** in 49% yield as colorless crystals, mp 171-173 °C. (±)-**12** was subsequently reacted with MCPBA in the presence of potassium carbonate in DMF and the resulting mixture was diluted with water. The separated products were collected by filtration to afford (±)-**13** as colorless crystals in 97% yield, mp 180-181 °C. Detosylation of (±)-**13** was carried out in concentrated sulfuric acid and the crude product was recrystallized from AcOEt to give (±)-**1** in 73% yield as colorless crystals, mp 162-163°C. Resolution of (±)-**1** proceeded very effectively by using (+)-2-(2,3,4-trichlorophenyl)ethanesulfonic acid [(+)-TCPES][5] as a resolving agent to afford the diastereomeric salt of **1** and (+)-TCPES (1:2) as colorless crystals, mp 210.0-210.5 °C (acetone), $[\alpha]_D^{20}$ +28.8° (c. 1.01, MeOH). **1** was easily obtained from the salt in a usual manner, mp 173.5-174.0 °C (AcOEt), $[\alpha]_D^{20}$ -40.0° (c. 0.10, MeOH). Thus the improved synthetic procedure was confirmed to be very practical for the large scale synthesis of optical pure **1**.

1 was considered to be the most promising compound as an antifungal drug candidate.[1] The detailed pharmacological data of **1** will be submitted in the near future.

EXPERIMENTAL

Melting points were determined on a Yamato MP-21 apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian Gemini-300 spectrometer. Optical rotation was measured on a Horiba polarimeter SEPA-200. MS spectra were obtained on a JEOL JMS-HX100 mass spectrometer. Flash chromatography was performed by using Katayama K230 silica gel.

(*R*)-*N*-Acetyl-*S*-2-[(2*R*, 3*R*)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-methylsulfoximine (3) To a solution of **1** (200 mg, 0.61 mmol) in pyridine (0.5 mL) was added acetic anhydride (0.5 mL, 5.30 mmol) at rt. The mixture was stirred for 2 h, diluted with AcOEt (30 mL), washed with 5% citric acid (40 mL), brine (40 mL), saturated $NaHCO_3$ (30 mL), and brine (30

mL), dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography ($CHCl_3$ - MeOH, 15:1). The obtained products were recrystallized from CH_2Cl_2 - *i*-Pr_2O to give **3** as colorless needles (189 mg, 83%), mp 157-159 °C. IR (Nujol) cm^{-1}: 3100, 1620, 1500, 1280, 1160. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, *J*=7.2 Hz), 2.11 (3H, s), 3.33 (3H, s), 4.89 (1H, dq, *J*=7.0, 1.2 Hz), 5.06 (1H, br d, *J*=14.7 Hz), 5.49 (1H, d, *J*=14.6 Hz), 5.75 (1H, d, *J*=2.0 Hz), 6.7-6.8 (2H, m), 7.29 (1H, ddd, *J*=8.8, 8.8, 6.3 Hz), 7.76 (1H, s), 7.78 (1H, s). FAB-MS *m/z*: 373 (MH^+). Anal. Calcd for $C_{15}H_{18}N_4O_3F_2S$: C, 48.38; H, 4.87; N, 15.04; F, 10.20; S, 8.61. Found: C, 48.32; H, 4.88; N, 14.78; F, 10.16; S, 8.80.

(*R*)-*S*-2-[(2*R*, 3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-methyl-*N*-methylcarbamoylsulfoximine (4) To a solution of **1** (159 mg, 0.454 mmol) in THF (10 mL) - DMF (2 mL) was added methyl isocyanate (29 μL, 0.499 mmol) under ice-cooling. The ice-bath was removed and the mixture was stirred for 5.5 h at rt. To the mixture was added methyl isocyanate (8 μL, 0.136 mmol) and the stirring was continued for an additional 2 h. The reaction was quenched with ice-water (30 mL). The resulting mixture was saturated with NaCl and extracted with AcOEt (30 mL, 20 mL). The combined extracts were washed with brine (350 mL), dried (Na_2SO_4), and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography (AcOEt - MeOH, 100:1) to give **4** as an amorphous solid (137 mg, 78%), mp 73-76 °C. IR (Nujol) cm^{-1}: 3310, 1620, 1500, 1140. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, *J*=7.2 Hz), 2.79 (3H, d, *J*=4.8 Hz), 3.26 (3H, s), 4.92 (1H, br q, *J*=4.1 Hz), 5.08 (1H, br d, *J*=15 Hz), 5.09 (1H, q like, *J*=7 Hz), 5.49 (1H, d, *J*=14.6 Hz), 5.66 (1H, d, *J*=1.8 Hz), 6.7-6.8 (2H, m), 7.2 7 (1H, s), 7.30 (1H, ddd, *J*=9.5, 8.8, 6.4 Hz), 7.76 (1H, s). FAB-MS *m/z*: 388 (MH^+).

(*R S*)-*S*-2-[(2*R S*, 3*R S*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*N*,*S*-dimethylsulfoximine [(±)-5] To a solution of (±)-**1** (2.32 g, 7 mmol) in acetone (40 mL) were added K_2CO_3 (0.97 g, 7 mmol) and methyl iodide (0.87 mL, 14 mmol) at rt. After stirring for 7 h, methyl iodide (4.4 mL, 70 mmol) was added. After stirring for 16.5 h, K_2CO_3 (2.91 g, 21 mmol) was added and the stirring was continued for 23 h. The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography ($CHCl_3$ - MeOH, 50:1) to give (±)-**5** as a colorless oil (0.46 g, 19%). IR (Neat) cm^{-1}: 3300, 1605, 1590, 1135. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, dd, *J*=7.3, 1.3 Hz), 2.82 (3H, s), 3.09 (3H, s), 3.74 (1H, q, *J*=7.2 Hz), 4.89 (1H, dd, *J*=14.2, 1.3 Hz), 5.30 (1H, d, *J*=14.3 Hz), 6.7-6.8 (3H, m), 7.39 (1H, ddd, *J*=9.1, 8.4, 6.5 Hz), 7.74 (1H, s), 7.93 (1H, s). FAB-MS *m/z*: 345 (MH^+).

(*RS*)-*S*-2-[(2*RS*,3*RS*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-methyl-*N*-methoxycarbonylmethylsulfoximine [(±)-6] To a suspension of potassium hydride (35% dispersion in a mineral oil, 229 mg, 2 mmol) in 1,2-dimethoxyethane (3 mL) was added (±)-**1** (300 mg, 0.91 mmol) under ice-cooling. The ice-bath was removed and the mixture was stirred for 50 min at rt. After addition of tetra-*n*-butylammonium bromide (15 mg, 0.045 mmol) and methyl bromoacetate (258 μL, 2.72 mmol) under ice-cooling, the ice-bath was removed and the stirring was continued for additional 1.5 h at rt. The reaction was quenched with saturated NH_4Cl (20 mL) and saturated $NaHCO_3$ (20 mL) under ice-cooling. The resulting mixture was saturated with NaCl and extracted with AcOEt (2 x 30 mL). The combined extracts were washed with brine (3 x 40 mL), dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography ($CHCl_3$ - AcOEt, 20:1 → $CHCl_3$ - AcOEt - MeOH, 200:10:1). The obtained products were recrystallized from CH_2Cl_2 - *i*-Pr_2O to give (±)-**6** as colorless needles (171 mg, 47%), mp 133-136 °C. IR (Nujol) cm^{-1}: 3120, 1750, 1620, 1500, 1205, 1145. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, dd, *J*=7.2, 1.0 Hz), 3.20 (3H, s), 3.83 (1H, q, *J*=7.3 Hz), 3.76 (3H, s), 3.96 (2H, s), 4.92 (1H, dd, *J*=13.9, 1.3 Hz), 5.46 (1H, d, *J*=13.7 Hz), 6.7-6.8 (3H, m), 7.37 (1H, ddd, *J*=9.5, 9.0, 6.5 Hz), 7.69 (1H, s), 8.00 (1H, s). FAB-MS *m/z*: 403 (MH^+). Anal. Calcd for $C_{16}H_{20}N_4O_4F_2S$: C, 47.75; H, 5.01; N, 13.92; F, 9.44; S, 7.97. Found: C, 47.19; H, 4.90; N, 13.67; F, 9.05; S, 7.82.

Epoxydation of ketone [(±)-8)][4] To a suspension of (±)-**8** (68.01 g, 0.315 mol) and trimethylsulfoxonium chloride (60.71 g, 0.472 mol) in CH_2Cl_2 (680 mL) was added dropwise 43% aq. KOH (830 g) at rt. The mixture was vigorously stirred for 16.5 h and diluted with water (2 L). The resulting organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (300 mL). The organic layer and extracts were combined, washed with brine (2 x 600 mL), dried (Na_2SO_4), and filtered. The filtrate was removed *in vacuo* and the residue was dissolved in toluene (300 mL). The insoluble materials were removed by filtration. The filtrate was removed *in vacuo* and the residue was purified by distillation under reduced pressure to give a 7.9:1 mixture of the diastereomeric epoxides [(±)-**9** and (±)-**10**] as a colorless oil (62.38 g, 86%), bp 99-114 °C (1.0-1.5 mmHg). The ratio of two diastereomers was determined by the ^{1}H-NMR analysis. IR (Neat) cm^{-1}: 1615, 1600, 1505, 1135. ^{1}H-NMR ($CDCl_3$) δ: [(±-**9**)] 1.27 (3H, dd, *J*=7.3, 1.8 Hz), 2.18 (3H, s), 2.86 (1H, dd, *J*=5.1, 0.9 Hz), 2.95 (1H, q, *J*=7.3 Hz), 3.18 (1H, d, *J*=5.1 Hz), 6.7-7.0 (2H, m), 7.4-7.6 (1H, m); [(±)-**10**)] 1.31 (3H, dd, *J*=7.0, 0.9 Hz), 2.15 (3H, s), 2.8-3.2 (3H, partly hidden behind the signals of **9**), 6.7-7.0 (2H, m), 7.3-7.5 (1H, m). EI-MS *m/z*: 230 (M^+).

(*R S*)-*S*-2-[(2*S R*, 3*S R*)-3-(2,4-Difluorophenyl)-3,4-epoxy]butyl-*S*-methyl-*N*-tosylsulfoximine [(±)-11] Chloramine T trihydrate (51.90 g, 184 mmol) was treated with EtOH (2 x 500 mL) as described in the previous paper.[1] To a solution of the epoxide (7.9:1 mixture of **9** and **10**, 20.20 g, 87.7 mmol) in DMF (50 mL) was added dropwise a solution of the pretreated anhydrous chloramine T in DMF (150 mL) under ice-cooling. After stirring for 1 h, the ice-bath was removed and the stirring was continued for an additional 2 h at rt. The mixture was poured into ice-water (2.3 L) and extracted with AcOEt (2 x 500 mL). The combined extracts were washed with ice-cold 5% NaOH (2 x 200 mL), and brine (200 mL), dried (Na_2SO_4), and filtered. The filtrate was evaporated *in vacuo* and the residue was recrystallized from AcOEt to give (±)-**11** as colorless prisms (17.31 g, 49%), mp 138.5-139.5 °C. IR (Nujol) cm^{-1}: 1610, 1590, 1140. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, dd, *J*=7.5, 1.0 Hz), 2.41 (3H, s), 2.50 (3H, s), 2.90 (1H, d, *J*=4.0 Hz), 3.40 (1H, d, *J*=4.0 Hz), 3.76 (1H, q, *J*=7.5 Hz), 6.8-6.9 (2H, m), 7.2-7.3 (2H, m), 7.34 (1H, ddd, *J*=9.0, 6.5, 6.5 Hz), 7.7-7.8 (2H, m). FAB-MS *m/z*: 400 (MH^+). Anal. Calcd for $C_{18}H_{19}NO_3F_2S_2$: C, 54.12; H, 4.79; N, 3.51; F, 9.51; S, 16.01. Found: C, 54.15; H, 4.66; N, 3.40; F, 9.68; S, 16.27.

(*R S*)-*S*-2-[(2*S R*, 3*S R*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-methyl-*N*-tosylsulfilimine [(±)-12] A mixture of 1,2,4-triazole (20.71 g, 0.3 mol) and 96% KOH (11.78 g, 0.21 mol) in DMSO (80 mL) was heated at 75°C for 10 min. After cooling, a solution of (±)-**11** (79.90 g, 0.2 mol) in DMSO (320 mL) was added to the mixture at rt. After stirring for 2 h, the mixture was poured into ice-water (10 L) and the separated product was collected by filtration. The air-dried product was triturated with *i*-PrOH (150 mL) and collected by filtration to give (±)-**12** as colorless crystals (46.22 g, 49%), mp 171-173 °C (AcOEt). IR (Nujol) cm^{-1}: 3360, 1500, 1280, 1140, 1090. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, d, *J*=7.1 Hz), 2.42 (3H, s), 2.70 (3H, s), 3.81 (1H, ddq, *J*=0.7, 0.7, 7.0 Hz), 5.01 (2H, s), 5.76 (1H, d, *J*=2.2 Hz), 6.7-6.8 (2H, m), 7.1 (1H, ddd, *J*=8.9, 8.9, 6.2 Hz), 7.28 (2H, d like, *J*=8.4 Hz), 7.81 (1H, s), 7.82 (1H, s), 7.83 (2H, d like, *J*=8.4 Hz). FAB-MS *m/z*: 469 (MH^+). Anal. Calcd for $C_{20}H_{22}N_4O_3F_2S_2$: C, 51.27; H, 4.73; N, 11.96; F, 8.11; S, 13.69. Found: C, 51.29; H, 4.68; N, 11.90; F, 8.01; S, 13.80.

(*R S*)-*S*-2-[(2*R S*, 3*R S*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-methyl-*N*-tosylsulfoximine [(±)-13] To a suspension of (±)-**12** (46.05 g, 98 mmol) and K_2CO_3 (20.83 g, 197 mmol) in DMF (400 mL) was added 80% MCPBA (25.45 g, 118 mmol) under ice-cooling. The ice-bath was removed and the mixture was stirred for 2 h at rt. After addition of 80% MCPBA (2.16 g, 10 mmol), the stirring was continued for an additional 2 h. The mixture was poured into ice-water (8 L) and the

separated product was collected by filtration. After washing with water (2 x 2 L), the product was dissolved in AcOEt (2.5 L), dried ($MgSO_4$), and filtered. The filtrate was removed *in vacuo* to give (±)-**13** as colorless crystals (45.90 g, 97%), mp 180-181 °C (AcOEt). IR (Nujol) cm^{-1}: 3380, 1155, 1060. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, d, *J*=7.1 Hz), 2.40 (3H, s), 3.40 (3H, s), 4.82 (1H, dq like, *J*=1.1, 7.0 Hz), 5.00 (1H, d, *J*=14.7 Hz), 5.40 (1H, d, *J*=14.6 Hz), 5.75 (1H, d, *J*=2.0 Hz), 6.7-6.8 (2H, m), 7.26 (1H, ddd, *J*=6.2, 9.0, 9.0 Hz), 7.30 (2H, d like, *J*=7.7 Hz), 7.73 (1H, s), 7.78 (1H, s), 7.89 (2H, d like, *J*=8.4 Hz). FAB-MS *m/z*: 485 (MH^+). Anal. Calcd for $C_{20}H_{22}N_4O_4F_2S_2$: C, 49.58; H, 4.58; N, 11.56; F, 7.84; S, 13.24. Found: C, 49.75; H, 4.57; N, 11.37; F, 7.76; S, 13.10.

(*R S*)-*S*-2-[(2*R S*, 3*R S*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-methylsulfoximine [(±)-1] To a solution of (±)-**13** (3.61 g, 7.45 mmol) in $CHCl_3$ (12 mL) was added dropwise conc. H_2SO_4 (7 mL) under ice-cooling. After stirring for 30 min, the ice-bath was removed and the stirring was continued for 4 h at rt. The mixture was poured into ice-water (50 mL), basified with ice-cold 10% NaOH (115 mL), and extracted with $CHCl_3$ (2 x 100 mL). The combined extracts were washed with brine (2 x 50 mL), dried ($MgSO_4$), and filtered. The filtrate was removed *in vacuo* and the residue was recrystallized from AcOEt to give (±)-**1** as colorless prisms (1.79 g, 73%), mp 162-163 °C. IR (Nujol) cm^{-1}: 3260, 3200, 1505, 1210, 1035. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, dd, *J*=7.3, 0.9 Hz), 2.67 (1H, br s), 3.14 (3H, s), 3.57 (1H, q, *J*=7.2 Hz), 4.93 (1H, dd, *J*=14.4, 0.8 Hz), 5.45 (1H, d, *J*=14.4 Hz), 6.02 (1H, s), 6.7-6.8 (2H, m), 7.36 (1H, ddd, *J*=9.3, 9.3, 6.5 Hz), 7.76 (1H, s), 7.88 (1H, s). FAB-MS *m/z*: 331 (MH^+).

Resolution of (±)-1 To a solution of (±)-**1** (300 mg, 0.908 mmol) in $CHCl_3$ (6 mL) was added a solution of lyophilized (*S*)-2-(2,3,4-trichlorophenyl)ethanesulfonic acid [(+)-TCPES][5] (421 mg, 1.45 mmol) in $CHCl_3$ (1.5 mL) at rt. After stirring for 3 h, the separated needles were collected by filtration and recrystallized from acetone to give a diastereomeric salt of **1** and (+)-TCPES (1:2) as colorless needles (275 mg, 33%), mp 208.5-209.0 °C; $[\alpha]_D^{20}$ +28.8° (c. 1.01, MeOH). IR (Nujol) cm^{-1}: 1615, 1170, 1010. ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, d, *J*=7.0 Hz), 1.44 (2 x 3H, d, *J*=7.0 Hz), 3.72 (3H, s), 4.26 (2 x 1H, q, *J*=7.0 Hz), 4.84 (1H, d, *J*=14.5 Hz), 4.87 (1H, q, *J*=7.0 Hz), 5.14 (1H, d, *J*=14.5 Hz), 7.02 (1H, ddd, *J*=9.0, 9.0, 2.0 Hz), 7.2-7.3 (3H, m), 7.58 (2 x 1H, d, *J*=8.5 Hz), 7.69 (2 x 1H, d, *J*=8.5 Hz), 7.76 (1H, s), 8.32 (1H, s). FAB-MS *m/z*: 331 (MH^+). Anal. Calcd for $C_{13}H_{16}N_4O_2F_2S \cdot 2C_8H_7O_3Cl_3S \cdot 0.5\ H_2O$: C, 37.92; H, 3.40; N, 6.10; Cl, 23.16; F, 4.14; S, 10.47. Found: C, 37.83; H, 3.32; N, 6.01; Cl, 23.45; F, 4.26; S, 10.77. The obtained diastereomeric salt (265 mg) was basified with saturated $NaHCO_3$ (10 mL) and the resulting mixture was

extracted with AcOEt (2 x 20 mL). The combined extracts were washed with brine (2 x 10 mL), dried ($MgSO_4$), and filtered. The filtrate was removed *in vacuo* and the residue was recrystallized from AcOEt to give **1**[1] as colorless prisms (83 mg, 86%), mp 173.5-174.0°C; $[\alpha]_D^{20}$ -40.0° (c. 0.10, MeOH). Anal. Calcd for $C_{13}H_{16}N_4O_2F_2S$: C, 47.26; H, 4.88; N, 16.96; F, 11.50; S, 9.71. Found: C, 47.23; H, 4.78; N, 16.81; F, 11.63; S, 9.74. The enantiomeric purity was determined by HPLC using Opti-Pak XC (3.9 mm i.d. x 300 mm, Nihon Millipore Ltd.) under the following conditions; mobile phase, *n*-hexane - *i*-PrOH (1:1), v/v; flow rate, 0.7 mL/min; detection, UV at 220 nm; retention time, (*R*)-**1** and (*S*)-**1**, 13.7 and 9.1 min. No (*S*)-**1** was detected.

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5. The details of preparation and application of (+)-TCPES as a resolving reagent are prepared to be submitted.

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