STEREOSELECTIVE SYNTHESIS OF ANTIFUNGAL SULFOXIMINES, NOVEL TRIAZOLES I†

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Abstract -Different types of sulfoximines, novel triazoles with three contiguous asymmetric centers on sulfur and two carbons, were stereoselectively synthesized and evaluated for antifungal activity. (*R*)-*S*-2-[(2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-methylsulfoximine (**2a**) showed extremely potent antifungal activities.

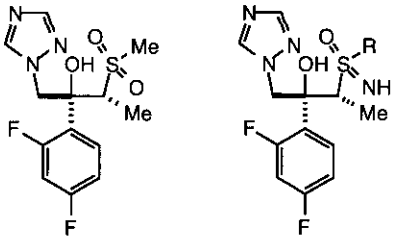
Introduction

Since the introduction of fluconazole[1] in 1990 and itraconazole[2] in 1992, these antifungal triazoles have been widely used for the systemic mycosis. However, the antifungal spectrum of these drugs is rather narrow, and the widespread use of these, especially of fluconazole, has been leading to the development of resistance, such as oral candidiasis in AIDS patients. Therefore, many triazole derivatives have been synthesized and evaluated extensively for the development of the new antifungal drugs having a broad spectrum and being effective against mycoses caused by fluconazole-resistant fungus.

Recently, a sulfone moiety-containing triazole SM-8668 (**1**) has been demonstrated to have an excellent antifungal activity against a wide range of mycoses including that by fluconazole-resistant fungus in animal experiments.[3] However, because of its low water-solubility, the route of the administration of **1** was limited only to *p.o.* And **1** was withdrawn from clinical studies because hepatocellular carcinogenesis was observed in the long-term toxicological studies.[4]

† 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.

We have taken notice of the excellent antifungal activity of **1**, and designed novel sulfoximine derivatives (**2**) as less toxic and more effective antifungal agents (Figure 1). Since sulfoximine possesses isoelectronic structure with sulfone, we expected that **2** would exhibit potent antifungal activities as reported for **1**. Moreover sulfoximine is more polar than sulfone and the nitrogen of *N-H* sulfoximine is sufficiently basic to form salts with various mineral acids, and therefore it was expected that **2** could be administered intravenously as well as *p.o.* and be less hepatotoxic for decreased accumulation in liver due to their improved water-solubility compared to that of **1**.



SM-8668 (racemic) **Sulfoximine**
1 **2**

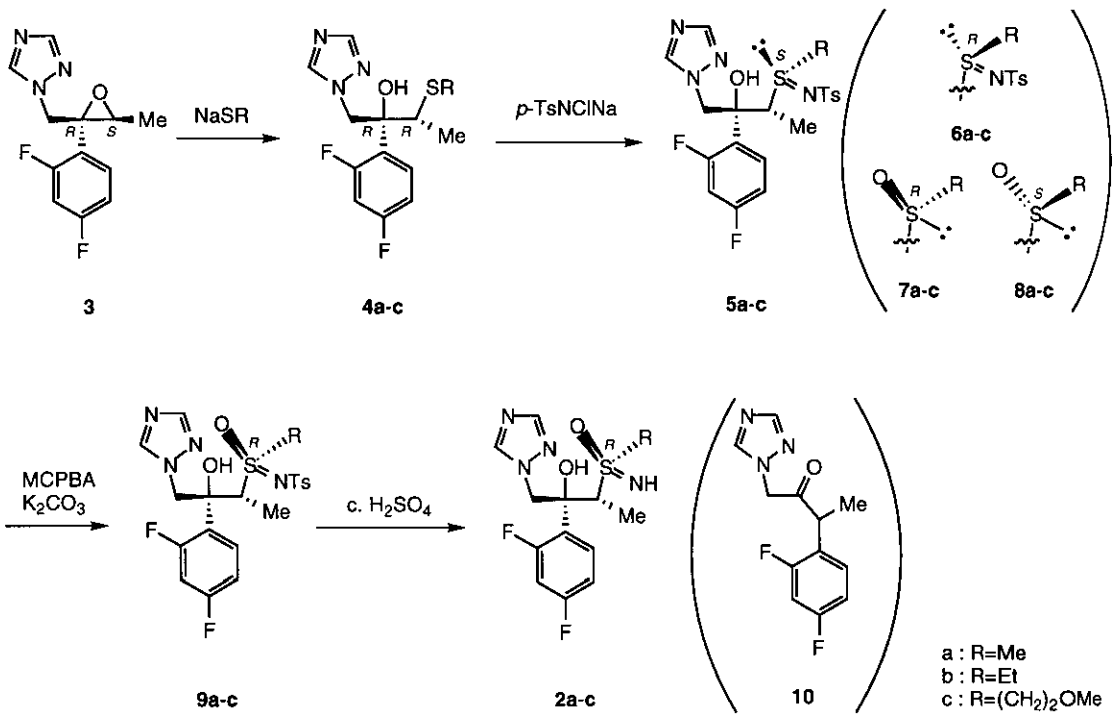
Figure 1

In this paper, we report an efficient stereoselective synthesis and antifungal activity of structurally unique sulfoximines (**2**) as new sulfur-containing antifungal triazole derivatives.

Chemistry

Studies on sulfur-containing triazoles revealed that the active enantiomer had a (2*R*,3*R*)-configuration.[5] Therefore, we selected the sulfides [**4** and (±)-**4**] with (2*R*,3*R*)- and (2*RS*,3*RS*)-configurations as key intermediates for the synthesis of sulfoximines. The sulfides [**4** and (±)-**4**] were readily prepared from the epoxides [**3**[5,6] and (±)-**3**[7a]] with sodium alkanethiolates in good yields.[5c,7] The reaction of **4a**[5a,7] with chloramine T trihydrate, which is known as a useful reagent for the facile synthesis of *N*-tosylsulfilimine,[8] proceeded diastereoselectively to give the *N*-tosylsulfilimine (**5a**, 43% yield) with (*S*)-configuration at sulfur as a sole isomer together with the undesired sulfoxides (**7a** and **8a**, 28:1, 41% yield). The absolute configuration at sulfur of **5a** and **7a** was determined to be (*S*) and (*R*) by the X-Ray crystallographic analysis of the final product [(**2a**) and (±)-**7a**], respectively. As described below, **2a** was obtained by the following

two-step procedure, oxidation (**5a**→**9a**) and acidic detosylation (**9a**→**2a**), with the retention of configuration at sulfur.[9] Diastereoselectivity at sulfur of **5a** might be resulted from the chlorosulfonium intermediate formation, following the displacement of chlorine with tosylamidate anion to give **5a**.[8a] However, it is still uncertain whether the isolated **5a** was produced by kinetically steric effect or the thermodynamic inversion at sulfur of *N*-tosylsulfilimine.[10]



Scheme 1

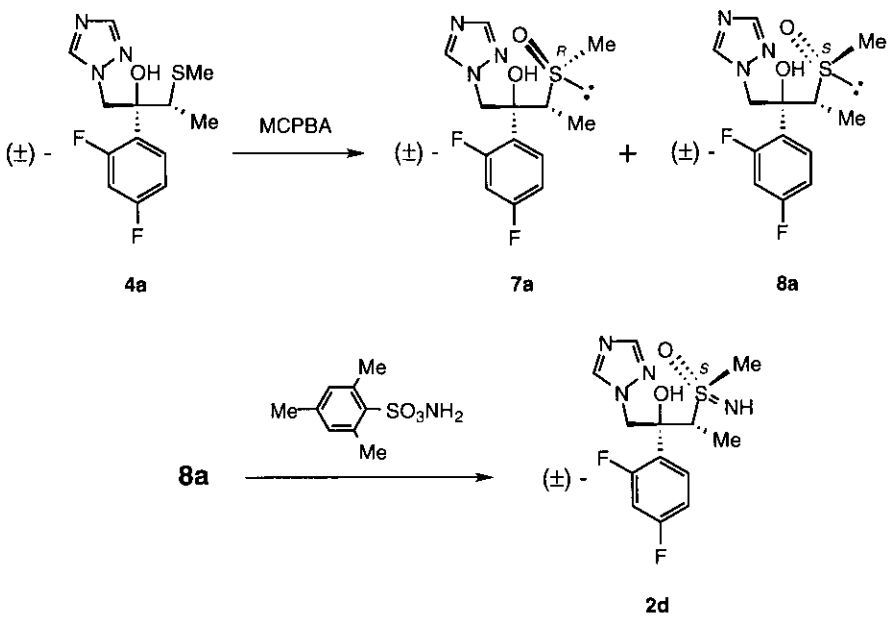
The sulfoxides (**7a** and **8a**) were reported to be produced by the reaction of the chlorosulfonium intermediate with water.[8] Therefore, the crystal water of chloramine T trihydrate was removed azeotropically by evaporation with EtOH, and expectedly the yield of **5a** was dramatically improved to be 90% by using the anhydrous chloramine T in MeOH. However, in the case of the more hindered sulfide [(±)-**4b**], the *N*-tosylsulfilimine [(±)-**5b**][11] was obtained in low yield (39%) and the corresponding sulfoxide [(±)-**7b** or (±)-**8b**] was isolated in 34% yield as a sole isomer.[12] In the case of **4c**, in MeOH, the yield of **5c**[11] was low (31%). It was slightly improved (54%) when the reaction was carried out in EtOH, but a small amount of the epimer of **5c** at sulfur (**6c**) was obtained (4%). Using a mixed solvent system (DMF and *i*-PrOH, 10:1), the total yield of the

N-tosylsulfilimines was much higher, however, the diastereoselectivity was significantly reduced (**5c** 51%, **6c** 34%).

The oxidation of **5a-c** with MCPBA was carried out under basic conditions[9] to afford the *N*-tosylsulfoximines (**9a-c**) in good yields (80-90%).

The following hydrolytic detosylation of **9a** and (±)-**9b** in concentrated sulfuric acid at 0-25 °C proceeded smoothly to give the *N-H* sulfoximines [**2a** and (±)-**2b**] in each 72% yield. In contrast, beside the *N-H* sulfoximine (**2c**, 54%), an undesired ketone (**10**) was formed by the same procedure in 45% yield. The intriguing results could not be explained only by the usual thermal cleavage of ß-hydroxysulfoximine.[8c] The detailed reaction mechanisms of the aryl-rearrangement are now under investigation.

Meanwhile the epimer of the *N-H* sulfoximine (**2a**) at sulfur [(±)-**2d**] was prepared from the sulfoxide [(±)-**8a**] (Scheme 2). Thus, (±)-**4a**[7a] was reacted with MCPBA to give (±)-**7a** (47%) and (±)-**8a** (41%). Imination of sulfoxide with *O*-mesitylsulfonylhydroxylamine (MSH) is known to occur with retention of configuration at sulfur.[13] Therefore, (±)-**8a** was reacted with MSH in CH_2Cl_2 at rt to give the epimer (±)-**2d** in 48% yield. But the *in vitro* antifungal activity of (±)-**2d** was found to be weaker than that of **2a**.



Sheme 2

Antifungal Activity[14]

Among the present sulfoximines, **2a** showed the most potent antifungal activity *in vitro* against *C. albicans* ATCC48130 (MIC, 1.56 μg/mL) . The *in vivo* antifungal activities against typical systemic mycosis are exhibited in Table 1.

Table 1. *in vivo* Antifungal Activity[a] (ED_{50}, mg/kg)

		C. albicans ATCC 48130	*A. fumigatus* Tsukuba	*C. neoformans* 145A
2a	*p.o.*	0.11 (0.30)	7.84	3.38
	i.v.	0.14		
fluconazole	*p.o.*	0.79 (1.93)	>60	>60
	i.v.	0.49		

a. Data in parentheses are those of immunocompromised mice pretreated with cyclophosphoamide.

It was thus revealed that **2a** had very potent antifungal activities with a broad spectrum in normal and immunocompromised mice both by oral and intravenous administrations. This compound was also very effective (ED_{50}, 2.87 mg/kg, *p.o.*) in immunocompromised mice against fluconazole-resistant *C. albicans* (ED_{50} of fluconazole, >30 mg/kg, *p.o.*), which was clinically isolated from AIDS patients. At the present, the noticeable pharmacological properties[14] of **2a** have been elucidated as follows: 1) highly potent antifungal activity with a broad spectrum; 2) good oral absorption (99% in mice, 93% in rats); 3) good water solubility (3-4 mg/mL in saline at 25 °C); 4) low binding affinity to serum protein (6.8% in mice, 5.1% in human); 5) lower hepatotoxicity than **1** (rat).

Conclusion

In this paper, we have demonstrated the stereoselective synthesis and antifungal activity of structurally unique triazole compounds with a sulfoximine moiety. Among these, **2a** was found to have the most potent antifungal activity and a broad spectrum against typical systemic mycoses. The compound was also very effective against fluconazole-resistant *C. albicans* in immunocompromised mice and had a number of excellent pharmacological properties as an antifungal agent.

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.

(2*R S*, 3*R S*)-2-(2,4-Difluorophenyl)-3-ethylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-4b] To a suspension of sodium hydride (60% dispersion in a mineral oil, 1.23 g, 30.7 mmol) in DMF (30 mL) was added dropwise ethanethiol (1.90 g, 30.7 mmol) at 5-10 °C under argon. The mixture was then stirred for 50 min at rt. To the mixture was added dropwise a solution of the epoxide [(±)-**3**][7a] (3.50 g, 13.9 mmol) in DMF (20 mL) and the stirring was continued for 3.5 h at rt. The reaction was quenched with brine (150 mL) under ice-cooling and the resulting mixture was extracted with AcOEt (2 x 200 mL). The combined extracts were washed with brine (5 x 300 mL), dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography (*n*-hexane - AcOEt, 2:1) to give (±)-**4b**[7b] as an amorphous solid (3.99 g, 91%). IR (Nujol) cm^{-1}: 3400-3200, 1620, 1600, 1270, 1140, 965. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, dd, *J*=7.3, 0.7 Hz), 1.32 (3H, t, *J*=7.4 Hz), 2.68 (1H, dq, *J*=12.4, 7.3 Hz), 2.76 (1H, dq, *J*=12.4, 7.5 Hz), 3.29 (1H, ddq, *J*=7.0, 1.2, 1.2 Hz), 4.62 (1H, d, *J*=1.4 Hz), 4.85 (1H, dd, *J*=14.2, 1.4 Hz), 5.07 (1H, d, *J*=14.0 Hz), 6.7-6.8 (2H, m), 7.37 (1H, ddd, *J*=8.5, 8.5, 6.6 Hz), 7.76 (1H, s), 7.83 (1H, s). FAB-MS *m/z*: 314 (MH^+).

(2*R*, 3*R*)-2-(2,4-Difluorophenyl)-3-(2-methoxyethyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4c) To a suspension of sodium hydride (60% dispersion in a mineral oil, 2.01 g, 50.2 mmol) in DMF (25 mL) was added dropwise 2-mercaptoethanol (5.88 g, 75.3 mmol) at 5-10 °C under argon. The mixture was then stirred for 40 min under ice-cooling. To the mixture was added dropwise a solution of the epoxide **3**[5,6] (6.30 g, 25.1 mmol) in DMF (12 mL). The ice-bath was removed and the mixture was heated at 50 °C for 45 min. The reaction was quenched with brine (350 mL) under ice-cooling and the resulting mixture was extracted with AcOEt (2 x 200 mL). The combined extracts were washed with brine (5 x 300 mL), dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography ($CHCl_3$ - AcOEt, 1:3 → $CHCl_3$ - MeOH, 10:1) to give (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-hydroxyethyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol as an amorphous solid (8.36 g, quant). IR (Nujol) cm^{-1}: 3340, 3230, 1615, 1500, 1270, 1130, 1050. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, dd, *J*=7.1, 0.9 Hz), 2.68

(1H, br t, *J*=5.7 Hz), 2.89 (1H, ddd, *J*=13.9, 5.9, 5.2 Hz), 2.96 (1H, ddd, *J*=13.9, 6.7, 5.4 Hz), 3.38 (1H, br q, *J*=7.0 Hz), 3.8-3.9 (2H, m), 4.87 (1H, dd, *J*=14.1, 1.5 Hz), 5.09 (1H, d, *J*=1.1 Hz), 5.10 (1H, d, *J*=14.0 Hz), 6.7-6.8 (2H, m), 7.39 (1H, ddd, *J*=8.9, 8.9, 6.6 Hz), 7.76 (1H, s), 7.83 (1H, s). FAB-MS *m/z*: 330 (MH^+). To a solution of the obtained alcohol (7.74 g, 23.5 mmol) in DMF (40 mL) was added sodium hydride (60% dispersion in a mineral oil, 0.94 g, 23.5 mmol) at -10- -7 °C and the stirring was continued for 30 min under ice-cooling. To the mixture was added dropwise methyl iodide (2.9 mL, 47.0 mmol). After the mixture was stirred for 1 h at 0 °C, the reaction was quenched with brine (120 mL) and the resulting mixture was extracted with AcOEt (2 x 120 mL, 50 mL). The combined extracts were washed with brine (5 x 120 mL), dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography ($CHCl_3$ - MeOH, 50:1) to give **4c**, as an amorphous solid (6.27 g, 78%). IR (Nujol) cm^{-1}: 3200, 1620, 1515, 1500, 1270, 1200, 1135. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, dd, *J*=7.2, 0.9 Hz), 2.85 (1H, dt, *J*=13.8, 5.9 Hz), 2.94 (1H, ddd, *J*=13.9, 6.7, 5.9 Hz), 3.42 (1H, br q, *J*=6.9 Hz), 3.44 (3H, s), 3.6-3.7 (2H, m), 4.89 (1H, dd, *J*=14.2, 1.5 Hz), 4.93 (1H, br s), 5.12 (1H, d, *J*=14.2 Hz), 6.7-6.8 (2H, m), 7.38 (1H, ddd, *J*=9.0, 9.0, 6,5 Hz), 7.75 (1H, s), 7.82 (1H, s). FAB-MS *m/z*: 344 (MH^+).

(*S*)-*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*-tosylsulfilimine (5a) Chloramine T trihydrate (68.84 g, 0.24 mol) was dissolved in EtOH (700 mL) and the solvent was removed *in vacuo*. The procedure was repeated again. To a solution of the sulfide (**4a**)[5a,7] (36.58 g, 0.12 mol) in MeOH (400 mL) was added dropwise a solution of the anhydrous chloramine T in MeOH (200 mL) at rt. The mixture was concentrated *in vacuo* and ice-cold 3% NaOH (1.2 L) was added to the residue. The resulting mixture was extracted with AcOEt (3 x 800 mL). The combined extracts were washed with ice-cold 5% NaOH (500 mL) and brine (2 x 1 L), dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography ($CHCl_3$ - AcOEt, 5:1 → $CHCl_3$ - MeOH, 20:1) to give **5a** as an amorphous solid (50.56 g, 90%). 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), 7.19 (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^+).

The following *N*-tosylsulfilimines were also obtained.

(*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*-ethyl-*N*-tosylsulfilimine [(±)-5b]** The reaction was carried out in MeOH; amorphous solid (39%). IR (Nujol) cm^{-1}: 3320, 1620, 1600, 1500, 1280, 1140, 965. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t, *J*=7.4 Hz), 1.18 (3H, d, *J*=7.2 Hz), 2.41 (3H, s), 2.94 (1H, dq, *J*=12.4, 7.4 Hz), 3.13 (1H, dq, *J*=12.4, 7.5 Hz), 3.78 (1H, br q, *J*=7.3 Hz), 5.01 (1H, d, *J*=14.5 Hz), 5.07 (1H, d, *J*=14.5 Hz), 5.76 (1H, d, *J*=2.2 Hz), 6.7-6.8 (2H, m), 7.20 (1H, ddd, *J*=8.8, 8.8, 6.3 Hz), 7.27 (2H, d like, *J*=8.0 Hz), 7.81 (1H, s), 7.82 (1H, s), 7.83 (2H, d like, *J*=8.5 Hz). FAB-MS *m/z*: 483 (MH^+).

S-2-[(2*RS*,3*RS*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-ethylsulfoxide was obtained as the major by-product, colorless oil (34%). IR (Neat) cm^{-1}: 3200, 1610, 1500, 1270, 1140. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, dd, *J*=7.0, 0.7 Hz), 1.38 (3H, t, *J*=7.6 Hz), 2.71 (1H, dq, *J*=12.9, 7.6 Hz), 2.95 (1H, dq, *J*=13.0, 7.5 Hz), 3.30 (1H, q, *J*=7.1 Hz), 4.92 (1H, d, *J*=14.3 Hz), 5.01 (1H, dd, *J*=14.0, 1.3 Hz), 5.33 (1H, s), 6.7-6.8 (2H, m), 7.42 (1H, ddd, *J*=9.6, 9.6, 6.6 Hz), 7.70 (1H, s), 8.03 (1H, s). FAB-MS *m/z*: 330 (MH^+).

(*S*)-*S*-2-[(2*R*, 3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-(2-methoxy)ethyl-*N*-tosylsulfimine (5c) The reaction was carried out in EtOH; **5c** (less polar), amorphous solid (54%). IR (Nujol) cm^{-1}: 3400, 1610, 1600, 1500, 1280, 1140. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, d, *J*=7.1 Hz), 2.41 (3H, s), 2.9-3.0 (1H, m), 2.99 (3H, s), 3.3-3.5 (2H, m), 3.5-3.6 (1H, m), 3.83 (1H, br q, *J*=7.3 Hz), 5.06 (1H, d, *J*=14.3 Hz), 5.12 (1H, d, *J*=14.6 Hz), 5.77 (1H, d, *J*=2.2 Hz), 6.7-6.8 (2H, m), 7.22 (1H, ddd, *J*=8.9, 8.9, 6.4 Hz), 7.29 (2H, d like, *J*=8.1 Hz), 7.80 (1H, s), 7.84 (1H, s), 7.86 (2H, d like, *J*=8.3 Hz). FAB-MS *m/z*: 513 (MH^+). The epimer at sulfur was obtained as a minor product. **6c** (more polar), colorless oil (4%), IR (Neat) cm^{-1}: 3320, 1620, 1600, 1500, 1280, 1140, 970. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, dd, *J*=7.0, 0.7 Hz), 2.40 (3H, s), 3.11 (3H, s), 3.16 (1H, ddd, *J*=12.9, 3.1, 3.1 Hz), 3.29 (1H, ddd, *J*=12.9, 10.5, 4.1 Hz), 3.48 (1H, ddd, *J*=10.1, 10.1, 2.9 Hz), 3.62 (1H, ddd, *J*=10.7, 3.9, 3.9 Hz), 3.81 (1H, br q, *J*=7.0 Hz), 4.84 (1H, d, *J*=14.3 Hz), 5.00 (1H, d, *J*=14.2 Hz), 5.66 (1H, s), 6.73 (1H, ddd, *J*=12.3, 8.4, 2.6 Hz), 6.8-6.9 (1H, m), 7.27 (2H, d like, *J*=8.1 Hz), 7.52 (1H, ddd, *J*=9.1, 9.1, 6.5 Hz), 7.70 (1H, s), 7.82 (2H, d like, *J*=8.3 Hz), 7.87 (1H, s). FAB-MS *m/z*: 513 (MH^+).

(*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*-tosylsulfoximine (9a) To a solution of **5a** (46.86 g, 0.1 mol) in DMF (0.7 L) were added by portions K_2CO_3 (21.20 g, 0.2 mol) and 80% MCPBA (43.14 g, 0.2 mol) at rt. After stirring for 1.5 h, ice-cold saturated $NaHCO_3$ (2 L) and ice-water (0.7 L) were added. The resulting mixture was then extracted

with AcOEt (2 x 1.2 L). The combined extracts were washed with brine (5 x 0.6 L), dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography ($CHCl_3$ - AcOEt, 3:1) to give **9a** as an amorphous solid (42.64 g, 88%). 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^+).

The following sulfoximines were also obtained.

(*RS*)-*S*-2-[(2*RS*,3*RS*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-ethyl-*N*-tosylsulfoximine [(±)-9b] amorphous solid (85%). IR (Nujol) cm^{-1}: 3360, 1620, 1600, 1500, 1060. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, *J*=7.2 Hz), 1.44 (3H, t, *J*=7.3 Hz), 2.42 (3H, s), 3.41 (1H, dq, *J*=13.6, 7.4 Hz), 3.70 (1H, dq, *J*=13.6, 7.4 Hz), 5.05 (1H, d, *J*=15.3 Hz), 5.09 (1H, dq, *J*=7.2, 1.9 Hz), 5.35 (1H, d, *J*=14.5 Hz), 5.69 (1H, d, *J*=2.0 Hz), 6.7-6.8 (2H, m), 7.26 (2H, d like, *J*=8.0 Hz), 7.75 (1H, s), 7.77 (1H, s), 7.88 (2H, d like, *J*=8.4 Hz). FAB-MS *m/z*: 499 (MH^+).

(*R*)-*S*-2-[(2*R*, 3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-(2-methoxy)ethyl-*N*-tosylsulfoximine (9c) amorphous solid (83%). IR (Nujol) cm^{-1}: 3140, 1620, 1600, 1325, 1205, 1155. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, d, *J*=7.3 Hz), 2.42 (3H, s), 3.35 (3H, s), 3.7-3.8 (1H, m), 3.9-4.0 (3H, m), 4.87 (1H, dq, *J*=7.2, 1.4 Hz), 4.98 (1H, d, *J*=14.7 Hz), 5.31 (1H, d, *J*=14.3 Hz), 5.73 (1H, d, *J*=1.5 Hz), 6.6-6.7 (1H, m), 6.78 (1H, ddd, *J*=11.7, 8.4, 2.5 Hz), 7.24 (1H, ddd, *J*=9.0, 9.0, 6.4 Hz), 7.75 (1H, s), 7.78 (1H, s), 7.29 (2H, d like, *J*=8.0 Hz), 7.88 (2H, d like, *J*=8.4 Hz). FAB-MS *m/z*: 529 (MH^+).

(*R*)-*S*-2-[(2*R*, 3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-methylsulfoximine (2a) To a solution of **9a** (8.89 g, 18.3 mmol) in $CHCl_3$ (25 mL) was added dropwise ice-cold conc. H_2SO_4 (30 mL) at 0 °C. After stirring for 4 h , the mixture was poured into ice-water (300 mL). The resulting mixture was basified with 10% NaOH and solid $NaHCO_3$ to pH 8, saturated with NaCl, and extracted with AcOEt (4 x 500 mL). The combined extracts were washed with brine (2 x 500 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, 100:10:1). The obtained product was recrystallized from CH_2Cl_2 - MeOH - *i*-Pr_2O to give **2a** as colorless crystals (4.39 g, 72%), mp 171-172 °C,

$[\alpha]_D^{20}$ -40.0° (c. 0.10, MeOH). 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^+). 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, 47.19; H, 4.86; N, 16.68; F, 11.37; S, 9.58. 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*)-**2a** and (*S*)-**2a**, 13.7 and 9.1 min, respectively. No (*S*)-**2a** was detected. For X-Ray crystallographic analysis, purified **2a** was recrystallized again from water to give colorless prisms, mp 164.5-165.5 °C.

The following sulfoximines were also obtained.

(*RS*)-*S*-2-[(2*RS*, 3*RS*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-ethylsulfoximine [(±)-2b] Colorless amorphous solid (72%). IR (Nujol) cm^{-1}: 3200, 1620, 1600, 1500, 1140. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, dd, *J*=7.3, 1.4 Hz), 1.46 (3H, t, *J*=7.4 Hz), 2.82 (1H, br s), 3.19 (1H, dq, *J*=13.4, 7.4 Hz), 3.36 (1H, dq, *J*=13.4, 7.5 Hz), 3.64 (1H, q, *J*=7.3 Hz), 4.90 (1H, d, *J*=14.2 Hz), 5.35 (1H, d, *J*=14.1 Hz), 6.60 (1H, br s), 6.7-6.8 (2H, m), 7.41 (1H, ddd, *J*=8.9, 8.9, 6.7 Hz), 7.73 (1H, s), 7.94 (1H, s). FAB-MS *m/z*: 345 (MH^+).

(*R*)-*S*-2-[(2*R*, 3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-(2-methoxy)ethylsulfoximine (2c) Colorless oil (54%). IR (Neat) cm^{-1}: 3280, 3150, 1620, 1600, 1210, 1110. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, dd, *J*=7.3, 1.3 Hz), 3.04 (1H, br s), 3.43 (3H, s), 3.4-3.6 (2H, m), 3.9-4.0 (2H, m), 3.99 (1H, q, *J*=7.2 Hz), 4.97 (1H, dd, *J*=13.9, 1.1 Hz), 5.27 (1H, d, *J*=13.8 Hz), 6.7-6.8 (2H, m), 7.05 (1H, s), 7.42 (1H, ddd, *J*=8.9, 8.9, 6.5 Hz), 7.68 (1H, s), 8.01 (1H, s). FAB-MS *m/z*: 375 (MH^+). The following ketone was obtained as a by-product.

3-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanone (**10**) Colorless oil (45%). IR (Neat) cm^{-1}: 1740, 1505, 1140. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, d, *J*=7.0 Hz), 4.12 (1H, q, *J*=7.0 Hz), 4.95 (1H, d, *J*=18.0 Hz), 5.03 (1H, d, *J*=18.0 Hz), 6.9-7.0 (2H, m), 7.17 (1H, ddd, *J*=8.6, 8.6, 6.1 Hz), 7.94 (1H, s), 8.01 (1H, s). FAB-MS *m/z*: 252 (MH^+).

Oxidation of (±)-4a To a solution of (±)-**4a**[7a] (300 mg, 1 mmol) in $CHCl_3$ (3 mL) was added dropwise a solution of 80% MCPBA (217 mg, 1 mmol) in $CHCl_3$ (3 mL) under ice-cooling. The mixture was stirred for

1.5 h at 0 ℃ and diluted with $CHCl_3$ (80 mL). The resulting solution was washed with saturated $NaHCO_3$ (3 x 50 mL) and brine (3 x 50 mL), dried (Na_2SO_4), and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography ($CHCl_3$ - MeOH, 200:1 → 50:1). Less polar sulfoxide (±)-**8a**: colorless crystals (41%), mp 158-160 ℃ (*i*-Pr_2O). IR (Nujol) cm^{-1}: 3310, 3110, 1620, 1510, 1020. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, dd, *J*=1.3, 7.2 Hz), 2.71 (3H, s), 3.33 (1H, ddq, *J*=7.1, 1.3, 1.3 Hz), 4.88 (1H, d, *J*=14.3 Hz), 5.22 (1H, d, *J*=14.2 Hz), 5.77 (1H, d, *J*=1.4 Hz), 6.7-6.8 (2H, m), 7.40 (1H, ddd, *J*=9.4, 8.8, 6.4 Hz), 7.81 (1H, s), 7.89 (1H, s). FAB-MS *m/z*: 316 (MH^+). More polar sulfoxide (±)-**7a**: colorless prisms (47%), mp 160-163 ℃ (*i*-Pr_2O). IR (Nujol) cm^{-1}: 3120, 1615, 1500, 1010. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, *J*=7.0 Hz), 2.66 (3H, s), 3.28 (1H, q, *J*=7.1 Hz), 4.94 (1H, d, *J*=13.9 Hz), 5.01 (1H, dd, *J*=14.0, 1.1 Hz), 5.35 (1H, s), 6.7-6.8 (2H, m), 7.43 (1H, ddd, *J*=9.6, 8.8, 6.5 Hz), 7.71 (1H, s), 8.02 (1H, s). FAB-MS *m/z*: 316 (MH^+). The relative configuration was determined by the X-Ray crystallographic analysis of the more polar sulfoxide [(±)-**7a**].

***(RS)*-*S*-2-[(2*S*,3*S*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)]butyl-*S*-methylsulfoximine [(±)-2d]** To a solution of (±)-**8a** (200 mg, 0.63 mmol) in CH_2Cl_2 (3 mL) was added *O*-mesitylsulfonylhydroxylamine (MSH) (270 mg, 1.27 mmol) at rt. After stirring for 5 h, MSH (120 mg, 0.56 mmol) was added and the stirring was continued for an additional 2 h. The ice-cold mixture was poured into 10% NaOH (6 mL) under ice-cooling. The resulting mixture was diluted with brine (20 mL), saturated with NaCl, and extracted with AcOEt (4 x 30 mL). The combined extracts were washed with brine (3 x 50 mL), dried ($MgSO_4$), and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography (AcOEt - MeOH, 200:1 → 50:1) to give (±)-**2d** as a colorless amorphous solid (100 mg, 48%). IR (Nujol) cm^{-1}: 3280, 3130, 1620, 1600, 1500, 1100. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, dd, *J*=7.0, 0.9 Hz), 3.0-3.3 (1H, br), 3.74 (1H, q, *J*=7.0 Hz), 5.03 (1H, dd, *J*=14.5, 1.6 Hz), 5.47 (1H, d, *J*=14.4 Hz), 6.67 (1H, br s), 6.7-6.8 (2H, m), 7.34 (1H, ddd, *J*=9.2, 9.0, 6.5 Hz), 7.66 (1H, s), 7.94 (1H, s). FAB-MS *m/z*: 331 (MH^+).

Antifungal Activity *In vivo* antifungal activity was determined as follows. Normal and immunocompromised ddY mice, 4-week-old, were inoculated *via* tail vein with 1 x 10^6 CFU of *C. albicans* ATCC48130, 6 x 10^6 conidia of *A. fumigatus* Tsukuba, or 8 x 10^5 CFU of *C. neoformans* 145A. Immunocompromised mice were prepared by intraperitoneal injection of cyclophosphoamide, 200 mg/kg on

day -4 and 100 mg/kg on day -1 before infection. The test compounds were administered orally (*p.o.*) or intravenously (i.v.) immediately after the inoculation and once daily for the following 4 days. The ED_{50} values were calculated from the survival rate on day 10 (*Candida*), on day 7 (*Aspergillus*), and on day 13 (*Cryptococcus*) after infection.

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