Optically Active Antifungal Azoles. III.[1)] Synthesis and Antifungal Activity of Sulfide and Sulfonamide Derivatives of (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-mercapto-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol

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In an effort to find potent antifungal agents, optically active sulfur-containing triazole derivatives, sulfides (3) and sulfonamides (4), were prepared and evaluated for antifungal activity against *Candida albicans in vitro* and *in vivo*. The sulfides (3) were prepared by the reaction of (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (1) with various heteroarylmethyl chlorides in the presence of sodium methoxide. The sulfonamides (4) were synthesized starting from the disulfide (15) in three steps including oxidation of the corresponding sulfenamides (17). Some of the sulfur-containing triazole derivatives (3, 4) showed strong protective effects against candidosis in mice.

Keywords optically active antifungal azole; sulfide; sulfonamide; triazolylbutanol; antifungal activity; candidosis

As a part of our search for potent antifungal agents, we planned the synthesis of sulfur-containing optically active azoles with the general structure I. In our previous paper, we reported the stereoselective synthesis of the key intermediate for the optically active azoles, (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (**1**), starting from methyl (*R*)-lactate.[2)] Since compound **1** showed potent antifungal activity, we investigated the relationship between the stereochemistry of the two asymmetric carbons and the antifungal activity *in vivo* and *in vitro*, and confirmed that the (2*R*,3*R*)-configuration in **1** is essential for potent antifungal activity.[2)] We also prepared the disulfide derivatives (**2**), which can be pro-drugs of **1**.[1b)]

According to our research protocol, we continued chemical modification studies on the thiol (**1**) and designed the sulfides, (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-heteroarylmethylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (**3**), and the sulfonamides, (2*R*,3*R*)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)-2-butanesulfonamides (**4**). The introduction of various heteroarylmethyl groups into the thiol (**1**) seemed not only to improve physicochemical properties such as stability and aqueous solubility but also to modulate the hydrophobic character, which might be related to the potency of the antifungal activity. We chose imidazole, triazole, thiazole and fused imidazole nuclei as the heteroaryl moieties and prepared a variety of sulfide derivatives (**3a—o**, Chart 2).

We were also interested in a sulfonamide fragment because it has been shown to be stable to metabolism[3)] and to have a hydrophilic character.[4)] In the designed structure **4**, modification of the substituents (R^1 and R^2)

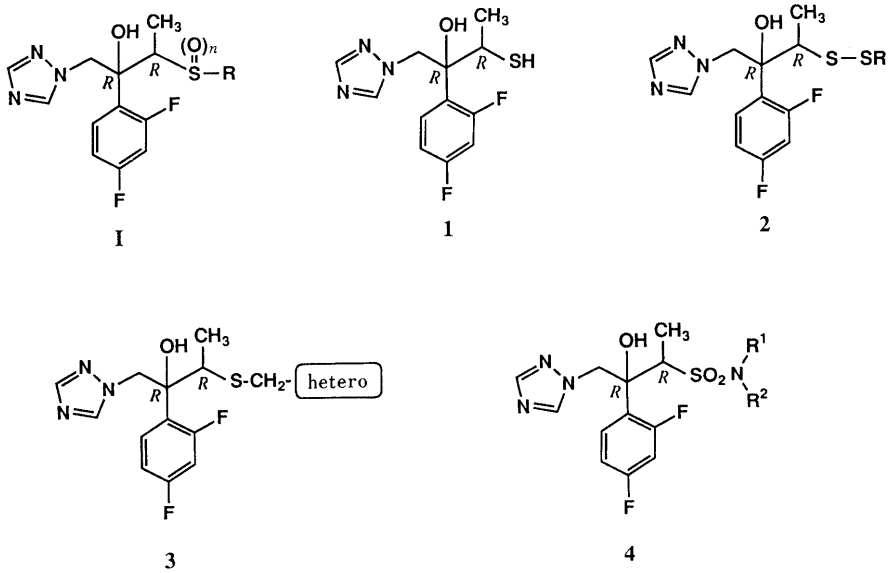


Chart 1

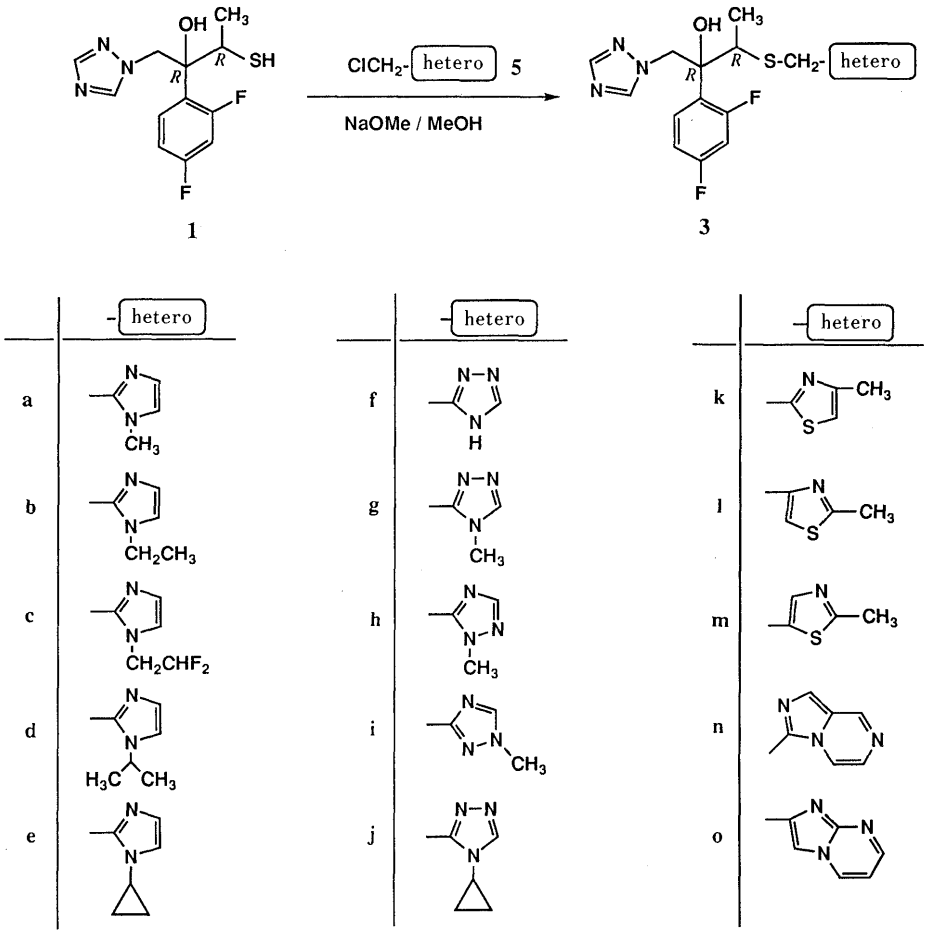


Chart 2

on the nitrogen atom gave a variety of derivatives (**4a—n**, Charts 4 and 5), which were expected to have different degrees of hydrophobicity.

In this paper, we describe the synthesis of compounds **3** and **4** as well as their antifungal activity against *Candida albicans in vitro* and *in vivo*.

Chemistry The reaction of the thiol (**1**) with various heteroarylmethyl chlorides (**5**) proceeded smoothly to yield the corresponding sulfides (**3**) as illustrated in Chart 2. 1-Substituted 2-chloromethyl imidazoles (**5a—e**) were allowed to react with **1** in the presence of sodium methoxide (NaOMe) to afford **3a—e** in 55—83% yields. The reaction of **1** with chlorides such as *N*-unsubstituted and *N*-substituted triazolylmethyl chlorides (**5f—j**), thiazolylmethyl chlorides (**5k—m**) and fused imidazolylmethyl chlorides (**5n—o**) gave the corresponding sulfides (**3f—o**) in 42—90% yields under the same conditions. Among the derivatives in this series, the 4-methyl-4*H*-1,2,4-triazolyl-3-methyl compound **3g** showed remarkable solubility in water (*ca.* 7%).

Next, the synthesis of the sulfonamides (**4**) from the thiol (**1**) was carried out. Our initial synthetic efforts are illustrated in Chart 3. Attempted conversion of the thiol (**1**) or its *S*-acetate (**6**)[2] into the corresponding sulfonyl chloride by oxidation with chlorine (Cl_2) gave a complex mixture. Since the hydroxy group on the tertiary carbon seemed to be labile under the reaction conditions, we decided to protect it with an acetyl (Ac) group. After examining the reaction conditions, treatment of **1** with acetic anhydride (Ac_2O) in pyridine in the presence of 1 eq of dimethylaminopyridine (DMAP) was found to give the desired *S*,*O*-diacetate (**7**) in a quantitative yield. Oxidation of the diacetate (**7**) with Cl_2 was conducted, and the *O*-acetyl sulfonyl chloride (**8**) was obtained successfully in 72% yield. However, the reaction of **8** with amines such as dimethylamine and 1-phenylpiperazine afforded products containing the olefins (**9a**, **b**) as the major components.[5] The reaction mechanism for the formation of the olefins (**9**) was assumed to be as follows. Increased acidity of the α-proton owing to the electron-withdrawing effect of the chlorosulfonyl group in **8** might accelerate elimination of hydrogen chloride to produce the intermediate **10** under basic conditions, and the subsequent addition of amines to **10** might give rise to elimination of the acetoxy group to form the olefins (**9**). This route is supported by the fact that the cyclopropyl analogue (**11**), which has no α-proton, gave the desired sulfonamide (**14**) *via* the same sequence of reactions (Chart 3).[6]

We, therefore, searched for an alternative method for the preparation of the sulfonamide (**4**). Sulfenamides, a reduced form of sulfonamide, have been regarded as useful intermediates for the synthesis of sulfonamides.[7] The use of a sulfenyl chloride, a precursor in the preparation of a sulfenamide, seemed to be promising for the reaction with

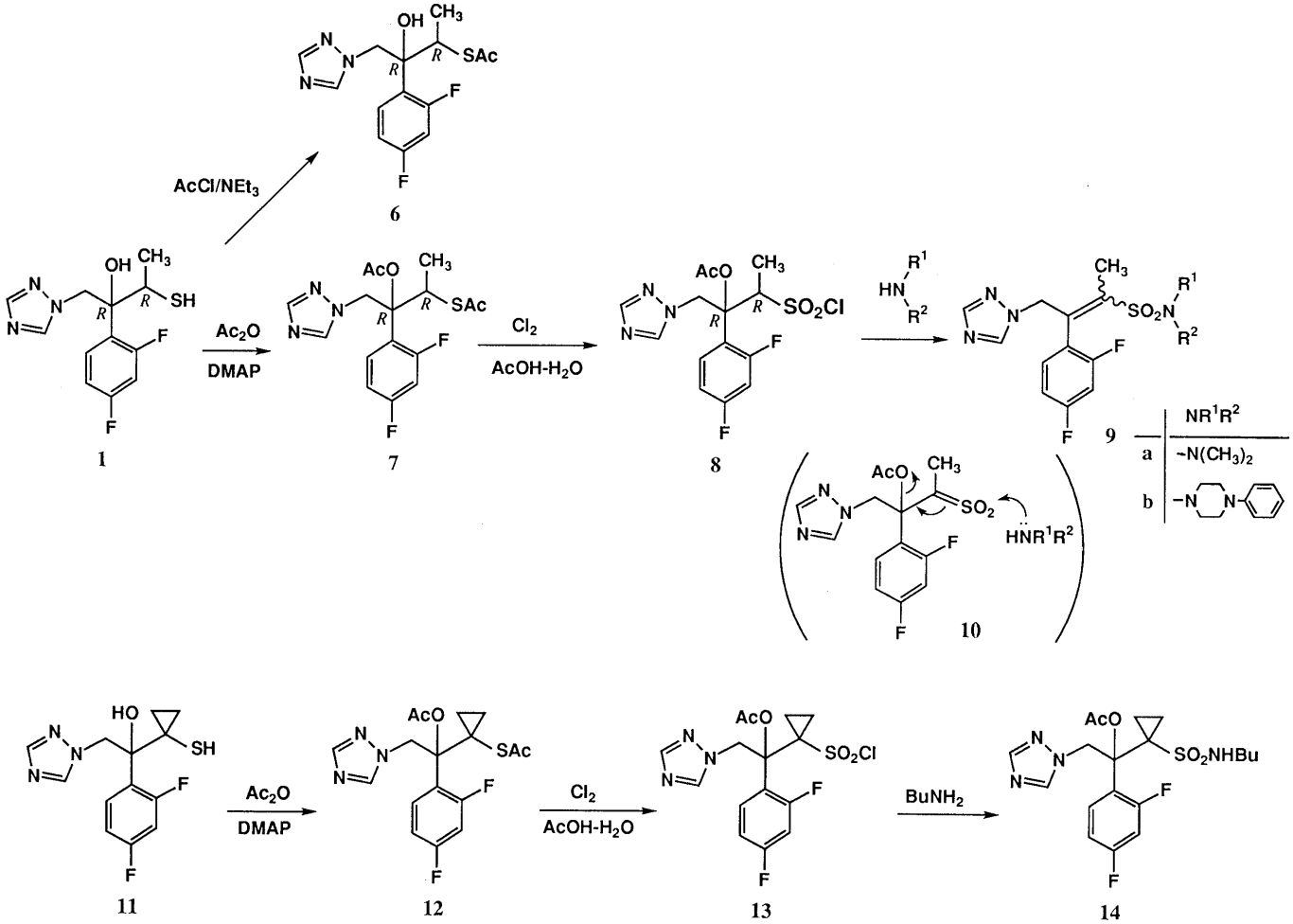


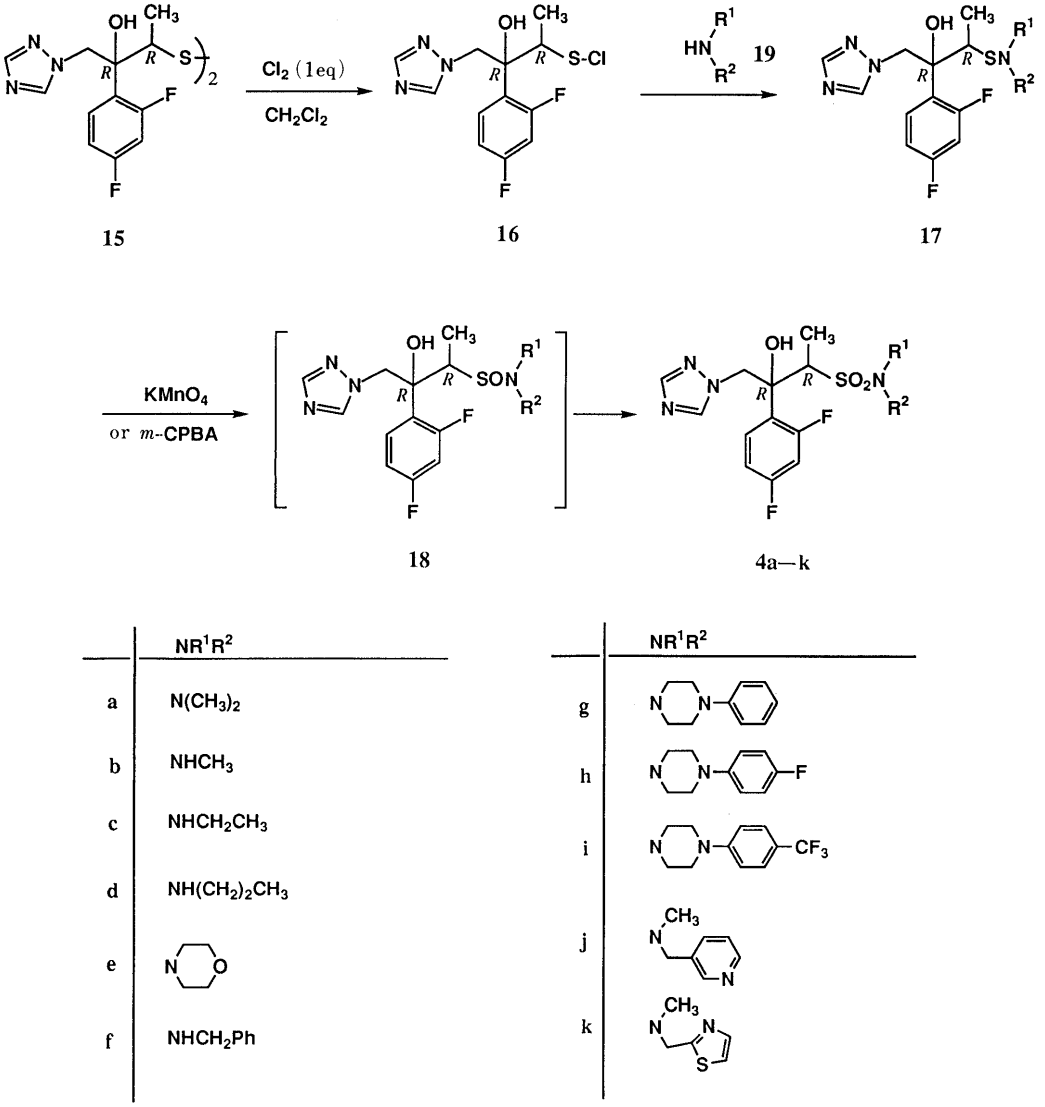
Chart 3

amines, as the low electron-withdrawing effect of the chlorothio group compared with that of the chlorosulfonyl group might diminish the hydrogen chloride-elimination.

Therefore, we investigated the synthetic route *via* the sulfenamide (**17**, Chart 4). First, we examined the reaction conditions for the synthesis of the sulfenyl chloride (**16**), and found that the disulfide (**15**)[1b] was the best precursor for the preparation of **16**. Treatment of **15** with 1 eq of Cl_2 in dichloromethane (CH_2Cl_2) at 0 °C gave **16**, which was then allowed to react with various amines (**19**) *in situ* to give the sulfenamides (**17**). In the case of the synthesis of the morpholinosulfonyl derivative (**4e**), the sulfenamide **17e** was isolated in 40% yield after purification by silica gel chromatography. Then, **17e** was subjected to oxidation with potassium permanganate ($KMnO_4$, 2 eq) in acetone to give **4e** in 59% isolated yield. In addition, the mono-oxygenated compound **18e**, which was considered to be the intermediate in this oxidation reaction, was isolated in 17% yield. On the other hand, oxidation of **17e** with 2 eq of *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 gave **4e** exclusively in 71% isolated yield. Compounds **4a—d**, **f—k** listed in Chart 4 were prepared *via* the same sequence of reactions. In these cases, the preparation was carried out without isolation of the sulfenamide (**17**), and the isolated yields of **4** were 13—44% based on the disulfide (**15**).

N-Alkylation of the *N*-monoalkylated product was adopted as an alternative procedure for the synthesis of the *N*,*N*-disubstituted sulfonamide derivatives. For example, alkylation of the *N*-monomethyl compound **4b** with 3-chloromethylpyridine in MeOH in the presence of NaOMe at 60 °C gave **4j** in 40% yield.

We next investigated the synthesis of the *N*-unsubstituted sulfonamide (**4n**), which seemed to be most hydrophilic among this series of sulfonamide derivatives. Wang and Hu reported that an *N*-benzylsulfamoyl compound could be converted to the corresponding sulfamoyl compound by means of the sulfuric acid (H_2SO_4)-catalyzed debenzylation reaction.[8] Thus, we examined this procedure for the synthesis of **4n** under several reaction conditions, and the results are shown in Chart 5. First, the *N*-benzyl compound **4f** was treated with H_2SO_4 in a mixture of toluene and ethanol (EtOH). However, the acid-catalyzed elimination reaction producing the olefin **20**[9] occurred predominantly. Therefore the benzyl group of **4f** was replaced by benzhydryl (**4l**) and 3,4-dimethoxybenzyl (**4m**) groups because the latter substituents are readily susceptible to acidic elimination. Upon treatment with H_2SO_4, both **4l** and **4m** afforded the desired compound (**4n**, entries 3 and 4), though the yields were low. Further examination of the reaction conditions was carried out to optimize the yield using compound **4m**,



15 16 17 18 4a—k

	NR^1R^2
a	$N(CH_3)_2$
b	$NHCH_3$
c	$NHCH_2CH_3$
d	$NH(CH_2)_2CH_3$
e	morpholino
f	$NHCH_2Ph$
g	4-phenylpiperazin-1-yl
h	4-(4-fluorophenyl)piperazin-1-yl
i	4-(4-trifluoromethylphenyl)piperazin-1-yl
j	methyl(4-pyridyl)amino
k	methyl(2-thiazolyl)amino

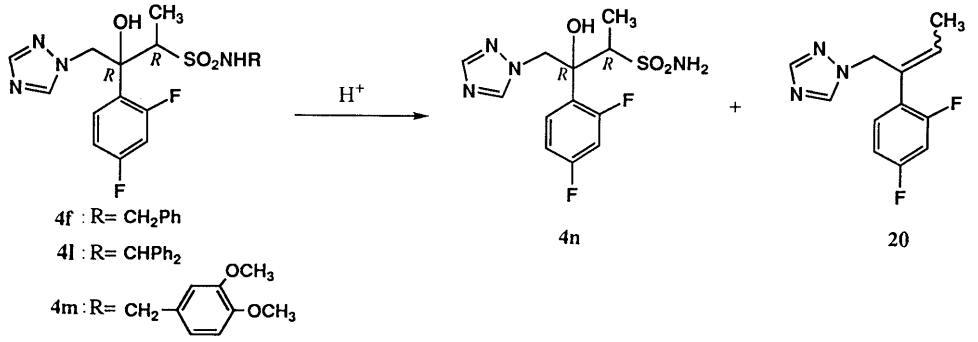
Chart 4

as **4m** was obtained in a better overall yield (26%) from **15** than **4l** (overall yield 14%). Dramatic improvement (69%) of the yield was attained by shortening the reaction time and lowering the reaction temperature (entry 5). Compound **4n** was found to have moderate water-solubility (*ca.* 2%).

Antifungal Activity The sulfide (**3**) and sulfonamide (**4**) derivatives were evaluated for antifungal activities against *C. albicans* TA *in vitro* and *in vivo*, and the results are shown in Table I. The *in vitro* assay was carried out by a paper disc method[2] and an agar-dilution method[10] on yeast nitrogen base (YNB) and peptone–yeast extract–glucose (PYG) media at pH 7.0. The *in vitro* activities are expressed as the diameter (mm) of the growth inhibition zone around the paper disc soaked in a 1 mg/ml solution of the test compound and as the minimum inhibitory concentration (MIC, μg/ml). *C. albicans* TA-infected mice were used for the *in vivo* assay,[1b] and the activity is expressed in terms of ED_{50} (mg/kg, the dose of the test compound which allowed 50% of infected mice to survive after oral administration).

All compounds (**3**, **4**) showed growth-inhibitory activity against *C. albicans* TA in the paper disc assay, though the observed MIC values were mostly in the range of 25—100 μg/ml or more. Such high MIC values against *C. albicans* on these particular culture media have often been observed with triazole antifungals such as fluconazole.

In the *in vivo* assay, the sulfide derivatives (**3**) were found to have strong protective effects against candidosis.[11] In the case of the 1-substituted-2-imidazolylmethylthio derivatives, the 1-methyl (**3a**) and 1-cyclopropyl (**3e**) derivatives were somewhat superior to the 1-ethyl (**3b**), 1-(2,2-difluoroethyl) (**3c**) and 1-isopropyl (**3d**) derivatives. The activities of these compounds (**3a**—**e**) were comparable to that of fluconazole (ED_{50}, 0.29—0.35 mg/kg). In the case of 1,2,4-triazolylmethylthio derivatives, the *N*-unsubstituted 3-triazolyl (**3f**), 4-methyl-3-triazolyl (**3g**), 2-methyl-3-triazolyl (**3h**) and 4-cyclopropyl-3-triazolyl (**3j**) derivatives showed potent activity (ED_{50}, 0.19—0.71 mg/kg). On the other hand, the activity of the 1-methyl-3-triazolyl derivative (**3i**) was moderate (ED_{50}, 2.8 mg/kg). Among the thiazolylmethylthio derivatives, the 2-methyl-4-thiazolyl derivative (**3l**) was more potent than the isomers **3k** and **3m**. Fused imidazolylmethylthio



entry	substrate	conditions		products		
1	**4f**	H_2SO_4 / toluene +EtOH	80°C, 12 h	**4f** (minor)[a]	+	**20** (48%)[b]
2	**4f**	H_2SO_4 / toluene +EtOH	80°C, 5 h	**4f** (45%)[c]	+	**20** (45%)[c]
3	**4l**	H_2SO_4 / toluene +EtOH	80°C, 5 h	**4n** (28%)[c]	+	**20** (40%)[c]
4	**4m**	H_2SO_4 / toluene +EtOH	80°C, 5 h	**4n** (10%)[b]	+	**20** (major)[a]
5	**4m**	H_2SO_4 / toluene +EtOH	70°C, 0.5 h	**4n** (69%)[b]	+	**20** (trace)[a]

a) Not isolated. *b*) Isolated yield. *c*) Determined by ^{1}H-NMR analysis.

Chart 5

TABLE I. Antifungal Activity of Sulfide (**3**) and Sulfonamide (**4**) Derivatives against *C. albicans* TA

Compound	*In vivo* (in mice) ED_{50} (mg/kg) *p.o.*	*In vitro* Disc (1 mg/ml) Diameter (mm) YNB	*In vitro* MIC (μg/ml) YNB	*In vitro* MIC (μg/ml) PYG
3a	0.28	35	>100	100
3b	0.50	40	>100	>100
3c	0.50	27	100	100
3d	0.50	35	>100	>100
3e	0.35	38	100	25
3f	0.71	28	100	50
3g	0.19	25	>100	100
3h	0.50	30	>100	100
3i	2.80	40	100	50
3j	0.40	15	>100	100
3k	1.41	35	100	100
3l	0.39	35	100	25
3m	1.41	40	100	100
3n	0.50	32	100	>100
3o	0.50	35	>100	100
4a	4.5	35	>100	>100
4b	5.0	40	>100	>100
4c	5.0	40	>100	>100
4d	5.0	43	>100	>100
4e	20	45	>100	>100
4f	8.0	40	100	100
4g	7.1	50	100	50
4h	8.0	50	50	50
4i	6.4	32	25	25
4j	2.8	40	50	12.5
4k	8.0	40	100	25
4n	11.3	30	50	25
Fluconazole	0.29—0.35	18	>100	100

derivatives (**3n** and **3o**) also showed potent activity (ED_{50}, 0.50 mg/kg). Among this series of the sulfide derivatives, compound **3g** was found to be most potent in this *in vivo* assay.

In the case of the sulfonamide derivatives (**4a**—**n**), the *N*-alkylsulfamoyl derivatives (**4a**—**d**) had moderate activity *in vivo*, but the introduction of bulky and lipophilic substituents onto the nitrogen atom of the sulfamoyl group as well as the removal of the *N*-substituent caused a slight decrease in *in vivo* activity, as seen with **4e**—**i**, **k**, **n**. The 3-pyridylmethyl derivative (**4j**) was most potent (ED_{50}, 2.8 mg/kg) in this series, but it was about ten times less active than the sulfide derivative **3g**.

Experimental

Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Hitachi 215 spectrometer or Horiba FT-200 Fourier-transform IR spectrometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken on a Varian Gemini-200 (200 MHz) spectrometer with tetramethylsilane as the internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. The optical rotations were recorded with a JASCO DIP-370 digital polarimeter. The secondary ion mass spectra (SIMS) were obtained on a Hitachi M-80A mass spectrometer.

Reactions were followed by thin layer chromatography (TLC) on Silica gel 60 F_{254} precoated TLC plate (E. Merck), or by HPLC using an octadecyl silica (ODS) column (A-303, Yamamura Chemical Laboratories Co.). Chromatographic separations were carried out on Silica gel 60 (0.063—0.200 mm, E. Merck).

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(1-methyl-1*H*-2-imidazolyl)methylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (3a, Table II) A mixture of **1** (1.0 g, 3.5 mmol), 2-chloromethyl-1-methylimidazole hydrochloride[12] (**5a**, 0.59 g, 3.5 mmol) and NaOMe (28% in MeOH, 1.37 g, 7.0 mmol) in EtOH (10 ml) was stirred at room temperature for 10 min. Water (20 ml) was added, and the resulting mixture was extracted with ethyl acetate (AcOEt, 20 ml × 3). The extracts were combined, washed with brine and dried over $MgSO_4$. The solvent was evaporated off *in vacuo* and the residue was chromatographed on silica gel. Elution with AcOEt–MeOH (10 : 1, v/v) followed by crystallization from diethyl ether (Et_2O) gave **3a** (0.72 g, 55%) as colorless prisms.

The reaction of **1** with the chlorides (**5b** and **5d**—**i**) was carried out in a manner similar to that described above to obtain the correspond-

TABLE II. (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-heteroarylmethylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (**3**)

No.	Yield[a] (%)	mp (°C) (solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$)	IR ν_{max}^{KBr} (cm^{-1})	$[\alpha]_D$ (*c*) in MeOH (°C)
3a	55	98—99 (Et_2O)	$C_{17}H_{19}F_2N_5OS$	53.81 (53.90)	5.05 (5.01)	18.46 (18.44)	1.21 (3H, d, J=7.2 Hz), 3.51 (1H, q, J=7.2 Hz), 3.68 (3H, s), 3.78 (1H, d, J=15.4 Hz), 4.03 (1H, d, J=15.4 Hz), 4.55 (1H, d, J=14.2 Hz), 4.83 (1H, d, J=14.2 Hz), 6.67—6.78 (2H, m), 6.85 (1H, d, J=1.2 Hz), 6.98 (1H, d, J=1.2 Hz), 7.00 (1H, s), 7.38—7.51 (1H, m), 7.67 (1H, s), 7.96 (1H, s)	3000, 1610, 1500, 1270, 1130	−131.9° (0.98) (25)
3b	79	120—121 (Et_2O)	$C_{18}H_{21}F_2N_5OS$	54.95 (54.96)	5.38 (5.46)	17.80 (17.79)	1.22 (3H, d, J=7 Hz), 1.45 (3H, t, J=7.4 Hz), 3.54 (1H, q, J=7 Hz), 3.75 (1H, d, J=15.4 Hz), 3.99 (2H, q, J=7.4 Hz), 4.06 (1H, d, J=15.4 Hz), 4.59 (1H, d, J=14.4 Hz), 4.84 (1H, d, J=14.4 Hz), 6.68—6.77 (2H, m), 6.90 (1H, s), 7.00 (1H, s), 7.34 (1H, br), 7.39—7.52 (1H, m), 7.66 (1H, s), 8.00 (1H, s)	2980, 1610, 1500, 1260, 1110	−108.4° (1.1) (25)
3c	83	105—110 (E–Et_2O)	$C_{18}H_{19}F_4N_5OS \cdot 2HCl$	43.04 (43.06)	4.21 (4.23)	13.94 (13.96)	1.07 (3H, d, J=7 Hz), 3.51 (1H, q, J=7 Hz), 4.42 (1H, d, J=15 Hz), 4.55 (1H, d, J=15 Hz), 4.65 (1H, d, J=14 Hz), 4.94 (2H, dt, J=3, 14 Hz), 4.97 (1H, d, J=14 Hz), 6.60 (1H, tt, J=3, 55 Hz), 6.80—7.30 (3H, m), 7.79 (2H, s), 8.00 (1H, s), 8.85 (1H, s) (in DMSO-d_6)	1610, 1590, 1500, 1420, 1120	−51.8° (1.0) (25)
3d	79	159—160 (Et_2O)	$C_{19}H_{23}F_2N_5OS$	56.00 (55.96)	5.69 (5.73)	17.19 (17.11)	1.22 (3H, d, J=6.8 Hz), 1.47 (6H, d, J=6.8 Hz), 3.54 (1H, q, J=6.8 Hz), 3.77 (1H, d, J=15.4 Hz), 4.08 (1H, d, J=15.4 Hz), 4.44 (1H, septet, J=6.8 Hz), 4.62 (1H, d, J=14.6 Hz), 4.83 (1H, d, J=14.6 Hz), 6.68—6.79 (2H, m), 6.96 (1H, s), 7.02 (1H, s), 7.33 (1H, br), 7.43—7.52 (1H, m), 7.66 (1H, s), 8.00 (1H, s)	3100, 2980, 1610, 1500, 1270, 1130	−90.1° (1.0) (25)
3e	77	127—128 (Et_2O)	$C_{19}H_{21}F_2N_2OS$	56.28 (56.34)	5.22 (5.26)	17.27 (17.14)	0.95—1.17 (4H, m), 1.26 (3H, d, J=7 Hz), 3.20—3.33 (1H, m), 3.60 (1H, q, J=7 Hz), 3.94 (1H, d, J=15 Hz), 4.03 (1H, d, J=15 Hz), 4.62 (1H, d, J=14 Hz), 4.88 (1H, d, J=14 Hz), 6.67—6.80 (2H, m), 6.87 (1H, s), 6.93 (1H, s), 7.40—7.53 (1H, m), 7.65 (1H, s), 7.68 (1H, s), 8.03 (1H, s)	3000, 1620, 1500, 1270, 1130	−119.5° (1.0) (23)
3f	42	170—172 (IPE)	$C_{15}H_{16}F_2N_6OS$	49.17 (49.14)	4.40 (4.40)	22.94 (22.59)	1.24 (3H, d, J=7.2 Hz), 3.45 (1H, q, J=7.2 Hz), 3.97 (1H, d, J=15.2 Hz), 4.09 (1H, d, J=15.2 Hz), 4.73 (1H, d, J=14.4 Hz), 5.08 (1H, d, J=14.4 Hz), 5.85 (1H, s), 6.69—6.82 (2H, m), 7.39—7.51 (1H, m), 7.77 (1H, s), 7.92 (1H, s), 8.20 (1H, s)	3150, 2900, 1610, 1490, 1410, 1260, 1130	−96.4° (1.0) (25)
3g	90	134—136 (Acetone)	$C_{16}H_{18}F_2N_6OS$	50.52 (50.55)	4.77 (4.56)	22.09 (22.13)	1.14 (3H, d, J=7 Hz), 3.48 (1H, q, J=7 Hz), 3.78 (3H, s), 3.99 (1H, d, J=15 Hz), 4.08 (1H, d, J=15 Hz), 4.61 (1H, d, J=14 Hz), 4.83 (1H, d, J=14 Hz), 5.44 (1H, s), 6.67—6.78 (2H, m), 7.29—7.41 (1H, m), 7.73 (1H, s), 7.83 (1H, s), 8.14 (1H, s)	3110, 1605, 1530, 1500, 1408. 1270, 1195, 1130	−104.9° (1.0) (25)
3h	90	AP[c]	$C_{16}H_{18}F_2N_6OS \cdot 2HCl$	42.39 (42.30)	4.45 (4.86)	18.54 (18.24)	1.02 (3H, d, J=7 Hz), 3.55 (1H, q, J=7 Hz), 4.13 (1H, d, J=15 Hz), 3.93 (3H, s), 4.25 (1H, d, J=15 Hz), 4.55 (1H, d, J=14.2 Hz), 4.90 (1H, d, J=14.2 Hz), 6.87—7.29 (3H, m), 7.97 (1H, s), 8.08 (1H, s), 8.76 (1H, s), (in DMSO-d_6)	3400, 1600, 1490, 1410, 1260, 1120	−57.6° (1.0) (25)
3i	62	AP[c] (Lyophilization)	$C_{16}H_{18}F_2N_6OS$	50.52 (50.28)	4.77 (5.00)	22.09 (22.03)	1.24 (3H, d, J=7.2 Hz), 3.50 (1H, q, J=7.2 Hz), 3.85 (1H, d, J=15 Hz), 3.92 (3H, s), 4.02 (1H, d, J=15 Hz), 4.71 (1H, d, J=15 Hz), 5.08 (1H, d, J=15 Hz), 6.07 (1H, s), 6.68—6.79 (2H, m), 7.37—7.50 (1H, m), 7.71 (1H, s), 7.87 (1H, s), 8.03 (1H, s)	3400, 3130, 1615, 1500, 1420, 1270, 1140	−96.4° (1.0) (25)
3j	74	88—90 (E–EA)	$C_{18}H_{20}F_2N_6OS \cdot 2HCl$	45.10 (44.80)	4.63 (4.80)	17.53 (17.13)	1.00—1.10 (4H, m), 1.18 (3H, d, J=6.8 Hz), 3.28—3.40 (1H, m), 3.57 (1H, q, J=6.8 Hz), 4.04 (1H, d, J=15 Hz), 4.16 (1H, d, J=15 Hz), 4.64 (1H, d, J=14 Hz), 4.84 (1H, d, J=14 Hz), 5.58 (1H, s), 6.66—6.80 (2H, m), 7.30—7.43 (1H, m), 7.73 (1H, s), 7.86 (1H, s), 8.12 (1H, s) (in DMSO-d_6) SIMS m/z: 407 (MH^+)	3100, 2700, 1740, 1620, 1500, 1420	−75.6° (1.0) (23)
3k	65	158—160 (E–EA)	$C_{17}H_{18}F_2N_4OS_2 \cdot 2HCl \cdot H_2O$	41.89 (42.05)	4.55 (4.26)	11.49 (11.52)	1.03 (3H, d, J=7 Hz), 2.37 (3H, s), 3.55 (1H, q, J=7 Hz), 4.07 (1H, d, J=15 Hz), 4.21 (1H, d, J=15 Hz), 4.62 (1H, d, J=14 Hz), 4.95 (1H, d, J=14 Hz), 6.80—6.93 (1H, m), 7.02—7.29 (2H, m), 7.20 (1H, s), 7.71 (1H, s), 8.46 (1H, s) (in DMSO-d_6)	3300, 1610, 1590, 1500, 1410, 1270, 1130	−70.0° (1.0) (23)
3l	43	165—167 (EA)	$C_{17}H_{18}F_2N_4OS_2 \cdot 2HCl \cdot 1/2H_2O$	42.68 (42.64)	4.42 (4.37)	11.71 (11.59)	1.03 (3H, d, J=7 Hz), 2.68 (3H, s), 3.49 (1H, q, J=7 Hz), 3.91 (1H, d, J=15 Hz), 4.01 (1H, d, J=15 Hz), 4.50 (1H, d, J=14 Hz), 4.90 (1H, d, J=14 Hz), 6.82—6.92 (1H, m), 7.05—7.27 (2H, m), 7.38 (1H, s), 7.78 (1H, s), 8.58 (1H, s) (in DMSO-d_6)	3100, 1610, 1500, 1410, 1270, 1130	−83.1° (1.0) (23)
3m	81	52—54 (E–Et_2O)	$C_{17}H_{18}F_2N_4OS_2 \cdot 2HCl$	43.50 (43.57)	4.29 (4.78)	11.94 (11.57)	1.02 (3H, d, J=7 Hz), 2.69 (3H, s), 3.32 (1H, q, J=7 Hz), 4.02 (1H, d, J=15 Hz), 4.17 (1H, d, J=15 Hz), 4.61 (1H, d, J=14 Hz), 4.95 (1H, d, J=14 Hz), 6.82—6.94 (1H, m), 7.06—7.28 (2H, m), 7.67 (1H, s), 7.88 (1H, s), 8.65 (1H, s) (in DMSO-d_6)	3400, 1610, 1500, 1420, 1270, 1130	−74.1° (1.0) (23)
3n	70	102—105 (E–Et_2O)	$C_{19}H_{18}F_2N_6OS \cdot 2HCl \cdot 3/2H_2O$	44.19 (44.49)	4.48 (4.23)	16.27 (15.88)	0.99 (3H, d, J=6.6 Hz), 3.52 (1H, q, J=6.6 Hz), 4.50 (1H, d, J=14 Hz), 4.55 (1H, d, J=15 Hz), 4.69 (1H, d, J=15 Hz), 4.85 (1H, d, J=14 Hz), 6.80—7.30 (3H, m), 7.89 (1H, d, J=5.4 Hz), 8.12 (1H, s), 8.62 (1H, s), 8.89 (1H, d, J=5.4 Hz), 8.98 (1H, s), 9.73 (1H, s), (in DMSO-d_6) SIMS m/z: 417 (MH^+)	3050, 2750, 1640, 1610, 1420, 1160	−130.3° (1.0) (23)
3o	70	105—110 (EA)	$C_{19}H_{18}F_2N_6OS \cdot 2HCl \cdot 3/2H_2O$	44.19 (44.39)	4.49 (4.59)	16.27 (15.86)	1.11 (3H, d, J=6.8 Hz), 3.49 (1H, q, J=6.8 Hz), 4.20 (1H, d, J=14.8 Hz), 4.32 (1H, d, J=14.8 Hz), 4.76 (1H, d, J=13.8 Hz), 4.99 (1H, d, J=13.8 Hz), 6.80—7.40 (3H, m), 7.69 (1H, dd, J=4.4, 6.6 Hz), 7.83 (1H, s), 8.34 (1H, s), 8.69 (1H, s), 9.04 (1H, dd, J=1.6, 4.4 Hz), 9.41 (1H, dd, J=1.6, 6.6 Hz) (in DMSO-d_6)	3400, 1650, 1615, 1530, 1500, 1420	−66.2° (1.0) (25)

a) Based on compound **1**. *b*) Recrystallization solvent: EA, ethyl acetate; IPE, diisopropyl ether; M, methanol; Et_2O, diethyl ether; D, dichloromethane; E, ethanol; H, hexane. *c*) Amorphous powder.

ing sulfides (**3b**, **d**—**i**, Table II). The chlorides, **5f**[13] and **5h**,[14] were prepared according to the cited methods.

(2*R*,3*R*)-3-(4-Cyclopropyl-4*H*-1,2,4-triazol-3-yl)methylthio-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol Dihydrochloride (3j, Table II) A mixture of **1** (0.25 g, 0.88 mmol), 3-chloromethyl-4-cyclopropyl-4*H*-1,2,4-triazole hydrochloride (**5j**, 0.17 g, 0.88 mmol) and NaOMe (28% in MeOH, 0.34 g, 1.77 mmol) in EtOH (2.5 ml) was stirred at room temperature for 10 min. The mixture was diluted with brine (3 ml) and extracted with AcOEt (10 ml × 3). The extracts were combined, dried over $MgSO_4$ and evaporated *in vacuo*. Purification of the residue by chromatography on silica gel (CH_2Cl_2–MeOH, 98 : 2→9 : 1, v/v) followed by the treatment with HCl (4 M solution in AcOEt, 0.5 ml) and crystallization from EtOH–AcOEt gave **3j** (0.31 g, 74%) as a colorless crystalline powder.

The reaction of **1** with the chlorides (**5c** and **5k**—**o**) was carried out in a manner similar to that described above to obtain the corresponding sulfides (**3c** and **3k**—**o**, Table II) as the hydrochlorides.

The chlorides, **5k**,[15] **5l**,[16] **5m**[17] and **5o**,[18] were prepared according to the cited methods.

2-Chloromethyl-1-ethyl-1*H*-imidazole Hydrochloride (5b) $NaBH_4$ (0.18 g, 4.8 mmol) was added portionwise to an ice-cooled solution of 1-ethyl-2-imidazolecarbaldehyde[19] (2.0 g, 16.1 mmol) in MeOH (12 ml). The resulting mixture was stirred at 0 °C for 40 min, and then a saturated aqueous solution of NaCl (5 ml) was added. After being stirred for 50 min, the mixture was extracted with AcOEt (30 ml × 3). The extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Crystallization of the residue from AcOEt–hexane gave 1-ethyl-2-imidazolemethanol (1.6 g, 79%) as colorless plates. mp 80—83 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7.4 Hz), 4.07 (2H, q, J=7.4 Hz), 4.63 (2H, s), 6.30 (1H, br s), 6.85 (2H, s). This compound (0.8 g, 6.35 mmol) was added portionwise to ice-cooled $SOCl_2$ (8 ml) and the mixture was heated under reflux for 40 min. After cooling, the mixture was concentrated *in vacuo* and the residue was crystallized from Et_2O to give **5b** (0.44 g, 55%) as colorless needles, mp 146—147 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.44 (3H, t, J=7 Hz), 4.27 (2H, q, J=7 Hz), 5.26 (2H, s), 7.70 (1H, d, J=1.8 Hz), 7.92 (1H, d, J=1.8 Hz).

2-Chloromethyl-1-(2,2-difluoroethyl)-1*H*-imidazole Hydrochloride (5c) Sodium hydride (60% oil dispersion, 10 g, 25 mmol) was added to a solution of 2-imidazolecarbaldehyde (2.0 g, 21 mmol) in dimethylformamide (DMF, 20 ml) and the mixture was stirred at room temperature for 25 min. 2,2-Difluoroethyl *p*-toluenesulfonate (5.9 g, 29.8 mmol) was added to the mixture and the whole was heated at 110 °C for 30 min. After being cooled, the mixture was diluted with water (80 ml), and extracted with AcOEt (30 ml × 3). The extracts were combined, washed successively with water (20 ml × 2) and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeOH (20 ml). To the stirred solution, $NaBH_4$ (0.3 g, 7.9 mmol) was added portionwise at 0 °C. The mixture was stirred at 0 °C for 15 min, then neutralized with 1 N HCl aqueous solution and extracted with AcOEt (30 ml × 3). The extracts were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (CH_2Cl_2–MeOH, 9 : 1) followed by recrystallization from MeOH–CH_2Cl_2–Et_2O gave 1-(2,2-difluoroethyl)-2-imidazolemethanol (1.6 g, 61%) as colorless needles, mp 97—100 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.44—4.62 (4H, m), 5.44 (1H, t, J=5.6 Hz), 6.31 (1H, tt, J=55.4, 3.2 Hz), 6.82 (1H, d, J=1.2 Hz), 7.14 (1H, s). IR (KBr): 3400, 3150, 2850, 1500, 1460, 1410, 1380. *Anal.* Calcd for $C_6H_8F_2N_2O$: C, 44.45; H, 4.97; N, 17.28. Found: C, 44.30: H, 4.99; 17.39. This compound was converted to **5c** by reaction with $SOCl_2$ in a manner similar to that described for the synthesis of **5b**.

5c (94% Yield): Colorless prisms, mp 107—108 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.91 (2H, dt, J=3.2, 15.4 Hz), 5.25 (2H, s), 6.55 (1H, tt, J=54, 3.2 Hz), 7.81 (1H, s), 7.82 (1H, s). IR (KBr): 3450, 3170, 3000, 2950, 1590, 1520, 1485, 1455, 1400 cm^{-1}. *Anal.* Calcd for $C_6H_7ClF_2N_2$·HCl: C, 33.20; H, 3.72; N, 12.91. Found: C, 33.25; H, 3.71; N, 12.65.

2-Chloromethyl-1-isopropyl-1*H*-imidazole Hydrochloride (5d) Compound **5d** was prepared starting from 1-isopropyl-2-imidazolecarbaldehyde[20] in a manner similar to that described for the synthesis of **5b**.

5d (78% Overall Yield): Colorless plates, mp 124—130 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.49 (6H, d, J=6.6 Hz), 4.82 (1H, septet, J=6.6 Hz), 5.28 (2H, s), 7.81 (1H, d, J=2 Hz), 8.08 (1H, d, J=2 Hz).

2-Chloromethyl-1-cyclopropyl-1*H*-imidazole Hydrochloride (5e) A mixture of cyclopropylamine (6.3 g, 110 mmol), NH_3 (28% aqueous solution, 7.6 g, 125 mmol) and MeOH (5 ml) was added dropwise to an ice-cooled mixture of formaldehyde (37% aqueous solution, 8.9 g, 110 mmol) and glyoxal (49% aqueous solution, 16 g, 135 mmol) in MeOH (31 ml) over a period of 25 min. The resulting mixture was stirred at 0 °C for 1 h. After removal of MeOH *in vacuo*, the resulting aqueous solution was filtered and the filtrate was diluted with water (200 ml). The mixture was extracted successively with hexane (100 ml × 4) and hexane–Et_2O (1 : 2.6, 130 ml). The aqueous layer was saturated with NaCl and extracted with AcOEt (100 ml × 8). The extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give 1-cyclopropylimidazole (4.2 g, 35%). A mixture of 1-cyclopropylimidazole (3.5 g, 33 mmol) and paraformaldehyde (2 g, 67 mmol) was heated at 170 °C for 20 min, and then further paraformaldehyde (2 g, 67 mmol) was added and the whole was heated at 170 °C for another 20 min. After being cooled, the mixture was dissolved in MeOH (20 ml) and diluted with brine (20 ml). The resulting mixture was extracted with AcOEt (40 ml × 2). The extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (CH_2Cl_2–MeOH, 9 : 1, v/v) followed by recrystallization from AcOEt–Et_2O gave 1-cyclopropyl-2-imidazolemethanol (0.70 g, 15.6%) as colorless needles, mp 90—95 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.2 (4H, m), 3.25—3.40 (1H, m), 4.76 (2H, m), 5.9 (1H, br), 6.86 (2H, s). IR (KBr): 3150, 2830, 1490, 1445, 1370, 1335, 1240 cm^{-1}. *Anal.* Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.29; N, 20.27. Found: C, 60.83; H, 7.29; N, 20.24. This compound (0.70 g, 5.1 mmol) was added to ice-cooled $SOCl_2$ (7 ml) and the mixture was heated under reflux for 5 min. After being cooled, the mixture was concentrated *in vacuo* and the residue was recrystallized from EtOH–Et_2O to give **5e** (0.75 g, 76%) as colorless prisms, mp 100—101 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.1—1.3 (4H, m), 3.65—3.80 (1H, m), 5.21 (2H, s), 7.72 (1H, d, J=2 Hz), 7.80 (1H, d, J=2 Hz). IR (KBr): 3100, 2550, 1590, 1520, 1480, 1425, 1390, 1350 cm^{-1}. *Anal.* Calcd for $C_7H_9ClN_2$·HCl: C, 43.55; N, 5.22; N, 14.51. Found: C, 43.61; H, 5.22; N, 14.37.

3-Chloromethyl-4-methyl-4*H*-1,2,4-triazole Hydrochloride (5g) 4-Methyl-4*H*-1,2,4-triazole-3-methanol[21] was allowed to react with $SOCl_2$ in a manner similar to that described for the synthesis of **5b** to afford compound **5g**.

5g (85% Overall Yield): Colorless needles, mp 95—100 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.88 (3H, s), 5.16 (2H, s), 9.65 (1H, s). IR (KBr): 3075, 2800, 1600, 1550, 1460, 1440, 1420, 1400, 1350 cm^{-1}. *Anal.* Calcd for $C_4H_6ClN_3$·HCl: C, 28.59; H, 4.20; N, 25.01. Found: C, 28.70; H, 4.18; N, 24.91.

3-Chloromethyl-1-methyl-1*H*-1,2,4-triazole Hydrochloride (5i) A mixture of 1*H*-1,2,4-triazole-3-methanol[13] (25 g, 0.25 mol) and *tert*-butyldimethylsilyl chloride (25 g, 165 mmol) in DMF (150 ml) was stirred at room temperature for 1 h. The mixture was concentrated *in vacuo*, and the residue was poured into an aqueous solution of $NaHCO_3$ (10%, 50 ml) and extracted with CH_2Cl_2 (30 ml × 3). The extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (hexane–AcOEt, 1 : 3, v/v) gave 3-*tert*-butyldimethylsilyloxymethyl-1*H*-1,2,4-triazole (15 g, 43%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.13 (6H, s), 0.93 (9H, s), 4.94 (2H, s), 8.03 (1H, s). IR (neat): 3150, 2950, 1460, 1360, 1340, 1260 cm^{-1}. SIMS *m/z*: 214 (MH^+). This compound (8.0 g, 37.5 mmol) was dissolved in DMF (20 ml). To the solution were added NaH (60% oil dispersion, 1.5 g, 37.5 mmol) and a solution of iodomethane (2.8 ml, 45 mmol) in DMF (80 ml) over a period of 10 min at 0 °C. The mixture was stirred for a further 10 min, poured into water (300 ml) and extracted with AcOEt (100 ml × 3). The extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (hexane–AcOEt, 1 : 1, v/v) gave 3-*tert*-butyldimethylsilyloxymethyl-1-methyl-1*H*-1,2,4-triazole (2.4 g, 28%) as a colorless oil.[22] ^{1}H-NMR ($CDCl_3$) δ: 0.13 (6H, s), 0.93 (9H, s), 3.90 (3H, s), 4.77 (2H, s), 7.97 (1H, s). IR (neat): 2950, 2860, 1520, 1460, 1360, 1255, 1200 cm^{-1}. SIMS *m/z*: 228 (MH^+). A mixture of 3-*tert*-butyldimethylsilyloxymethyl-1-methyl-1*H*-1,2,4-triazole (2 g, 8.8 mmol) and an aqueous solution of NaOH (5 N, 2.6 ml) in MeOH (20 ml) was stirred at room temperature for 27 h and at 45 °C for a further 21 h. The mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel. Elution with CH_2Cl_2–MeOH (9 : 1) followed by evaporation of the solvent gave 1-methyl-1*H*-1,2,4-triazole-3-methanol (1.0 g, quantitative) as colorless needles, mp 72—75 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.91 (3H, s), 4.75 (2H, d, J=3.6 Hz), 4.06 (1H, br), 8.02 (1H, s). IR (neat): 3250, 1530, 1450, 1340, 1210, 1190 cm^{-1}. SIMS *m/z*: 114 (MH^+). This compound was converted to **5i** upon treatment with $SOCl_2$ in a manner similar to that described for the

synthesis of **5b**.

5i (90% Yield): Colorless needles, mp 69—70 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.87 (3H, s), 4.72 (2H, s), 8.57 (1H, s). IR (KBr): 3400, 3000, 1570, 1440, 1415, 1160 cm^{-1}. *Anal.* Calcd for $C_4H_6ClN_3 \cdot HCl$: C, 28.59; H, 4.20; N, 25.01. Found: C, 28.16; H, 4.08; N, 24.51.

3-Chloromethyl-4-cyclopropyl-4*H*-1,2,4-triazole Hydrochloride (5j) A mixture of glycolohydrazide (5.0 g, 80 mmol) and cyclopropylisothiocyanate (5.5 g, 56 mmol) in MeOH (50 ml) was stirred at room temperature for 1 h. Water (30 ml) and an aqueous solution of NaOH (5 N, 11 ml) were added at 0 °C and the resulting mixture was stirred at 20 °C for 3 h. The mixture was concentrated to *ca.* 10 ml *in vacuo* and the residue was diluted with EtOH (100 ml). An aqueous solution of HCl (5 N, 11 ml) was added dropwise to the solution under ice-cooling. The precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to give crude crystals of 4-cyclopropyl-5-mercapto-4*H*-1,2,4-triazole-3-methanol (6.4 g). This compound (3 g, 17.6 mmol) was added to a stirred mixture of concentrated HNO_3 (d=1.38, 4.6 ml) and water (10 ml) at 60 °C. The reaction was initiated by the addition of sodium nitrite ($NaNO_2$, 10 mg) and the reaction temperature rose to 90—100 °C. After being cooled, the mixture was neutralized with an aqueous solution of NaOH and then concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (CH_2Cl_2–MeOH, 4:1, v/v) afforded 4-cyclopropyl-4*H*-1,2,4-triazole-3-methanol (2.0 g, 82%), mp 159—160 °C. ^{1}H-NMR (DMSO-d_6): 1.0—1.2 (4H, m), 2.9—3.0 (1H, m), 3.37 (1H, br), 4.51 (2H, s), 5.60 (1H, br). *Anal.* Calcd for $C_6H_9N_3OS$: C, 42.09; H, 5.30; N, 24.54. Found: C, 42.11; H, 4.51; N, 24.50. This compound (1.0 g, 7.2 mmol) was converted to **5j** (1.34 g, 97%) upon treatment with $SOCl_2$ in a manner similar to that described for the synthesis of **5b**.

5j: Colorless needles, mp 60—65 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.0—1.3 (4H, m), 3.5—3.7 (1H, m), 5.12 (2H, s), 9.51 (1H, s). *Anal.* Calcd for $C_6H_8ClN_3 \cdot HCl$: C, 42.09; H, 4.96; N, 20.69. Found: C, 41.86; H, 5.30; N, 20.69.

3-Chloromethylimidazo[1,5-*a*]pyrazine Hydrochloride (5n) A mixture of *N*-(2-pyrazinylmethyl)chloroacetamide[23] (4.0 g, 21.6 mmol) and $POCl_3$ (20 ml) in CH_2Cl_2 (20 ml) was stirred at room temperature for 3 d and then concentrated *in vacuo*. AcOEt (200 ml) was added to the residue and stirred vigorously. The precipitate was collected by filtration followed by recrystallization from EtOH to yield **5n** (2.6 g, 59%) as pale yellow needles, mp 240 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 5.45 (2H, s), 7.92 (1H, d, J=5 Hz), 8.45 (1H, s), 8.81 (1H, d, J=5 Hz), 9.65 (1H, s). IR (KBr): 3000, 1635, 1555, 1475, 1435, 1360, 1320 cm^{-1}. *Anal.* Calcd for $C_7H_6ClN_3 \cdot HCl$: C, 41.20; H, 3.46; N, 20.59. Found: C, 41.26; H, 3.62; N, 20.31.

(2*R*,3*R*)-3-Acetylthio-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butyl Acetate (7) A mixture of **1** (10 g, 35 mmol), Ac_2O (50 ml), DMAP (4.26 g, 35 mmol) and pyridine (100 ml) was heated at 80 °C for 20 h. The mixture was cooled and concentrated *in vacuo*, then the residue was taken up in AcOEt (100 ml). The insoluble material was filtered off, and the filtrate was washed successively with water and brine and then dried over $MgSO_4$. The solvent was evaporated off *in vacuo* and the residue was chromatographed on silica gel (hexane–AcOEt, 1:2, v/v) to give **7** (11.7 g, quantitative) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, dd, J=7, 2 Hz), 2.16 (3H, s), 2.33 (3H, s), 4.62 (1H, q, J=7 Hz), 5.15 (1H, d, J=15 Hz), 5.49 (1H, dd, J=15, 2.2 Hz), 6.80—6.98 (2H, m), 7.21—7.45 (1H, m), 7.82 (1H, s), 7.87 (1H, s).

(2*R*,3*R*)-3-Acetoxy-3-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-yl)-2-butanesulfonyl Chloride (8) Chlorine gas was introduced into a solution of **7** (11.8 g, 31.9 mmol) in a 50% aqueous solution of acetic acid (150 ml) at 5 °C over a period of 3 h. The resulting mixture was concentrated *in vacuo* and the residue was diluted with AcOEt (150 ml). The solution was washed with an aqueous solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from AcOEt to give **8** (7.6 g, 72%) as a pale brown crystalline powder, mp 110—115 °C. IR (KBr): 1758, 1618, 1504, 1371, 1226 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (3H, dd, J=7, 2.6 Hz), 2.16 (3H, s), 5.15 (1H, q, J=7 Hz), 5.36 (1H, d, J=15 Hz), 5.45 (1H, dd, J=15, 2.2 Hz), 6.8—7.00 (2H, m), 7.32—7.48 (1H, m), 7.92 (1H, s), 7.94 (1H, s). *Anal.* Calcd for $C_{14}H_{14}ClF_2N_3O_4S$: C, 42.70; H, 3.58; N, 10.67. Found: C, 42.59; H, 3.74; N, 10.67.

3-(2,4-Difluorophenyl)-*N*,*N*-dimethyl-4-(1*H*-1,2,4-triazol-1-yl)-2-buten-2-ylsulfonamide (9a) A solution of dimethylamine (0.6 g, 13 mmol) in toluene (3 ml) was added to an ice-cooled solution of **8** (3.3 g, 8.4 mmol) in CH_2Cl_2 (15 ml) and the resulting mixture was stirred for 10 min at 0 °C. The mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel. Elution with hexane–AcOEt (1:2)→AcOEt gave **9a** (isomer B as the less polar substance and isomer A as the more polar isomer).

Isomer A (0.8 g, 29%): A pale yellow oil. IR (neat): 1630, 1605, 1500, 1420, 1330, 1270, 1160, 1135, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 2.73 (6H, s), 4.95 (1H, d, J=15 Hz), 5.24 (1H, d, J=15 Hz), 6.65—6.85 (3H, m), 7.69 (1H, s), 7.89 (1H, s).

Isomer B (0.48 g, 17%): A pale yellow oil. IR (neat): 1630, 1605, 1500, 1420, 1335, 1265, 1160, 1135, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (3H, s), 2.99 (6H, s), 5.51 (1H, d, J=15 Hz), 5.87 (1H, d, J=15 Hz), 6.75—7.00 (3H, m), 7.77 (1H, s), 7.98 (1H, s).

1-[2-(2,4-Difluorophenyl)-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)-1-propenylsulfonyl]-4-phenylpiperazine (9b) The reaction of **8** (0.5 g, 1.28 mmol) with 1-phenylpiperazine (0.27 g, 1.67 mmol) was carried out in a manner similar to that described in the preparation of **9a**. Compound **9b** was obtained as a mixture of two stereoisomers, which was separated by silica gel chromatography (hexane–AcOEt, 1:3, v/v) into isomer A (more polar substance, 0.18 g, 29.5%) and isomer B (less polar substance, 0.05 g, 8.1%).

Isomer A: Brown solid. IR (neat): 1590, 1500, 1330, 1260, 1220, 1160, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 3.15 (4H, m), 3.32 (4H, m), 4.95 (1H, d, J=15 Hz), 5.24 (1H, d, J=15 Hz), 6.65—7.00 (6H, m), 7.20—7.35 (2H, m), 7.70 (1H, s), 7.89 (1H, s).

Isomer B: Brown solid. IR (neat): 1590, 1500, 1330, 1260, 1220, 1160, 1135 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 3.30 (4H, m), 3.57 (4H, m), 5.49 (1H, d, J=15 Hz), 5.90 (1H, d, J=15 Hz), 6.75—7.10 (6H, m), 7.25—7.40 (2H, m), 7.79 (1H, s), 7.94 (1H, s).

(*RS*)-1-(1-Acetylthio-1-cyclopropyl)-1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethyl Acetate (12) According to a procedure similar to that described for the synthesis of **7**, compound **12** was prepared from **11**[24] in 83% yield, mp 159—160 °C (colorless prisms from AcOEt–diisopropyl ether). IR (KBr): 1740, 1710, 1610, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.43—0.56 (1H, m), 0.70—1.00 (2H, m), 1.60—1.80 (1H, m), 2.06 (3H, s), 2.10 (3H, s), 5.35 (1H, d, J=15 Hz), 5.42 (1H, d, J=15 Hz), 6.75—6.92 (2H, m), 7.15—7.30 (1H, m), 7.95 (1H, s), 8.40 (1H, s). *Anal.* Calcd for $C_{17}H_{17}F_2N_3O_3$: C, 53.54; H, 4.49; N, 11.02. Found: C, 53.59; H, 4.47; N, 11.21.

1-[(*RS*)-1-Acetoxy-1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-ethyl]cyclopropanesulfonyl Chloride Hydrochloride (13) Chlorine gas was introduced into a solution of **12** (0.20 g, 0.52 mmol) in a 50% aqueous solution of acetic acid (8 ml) at 5 °C over a period of 2 h. The resulting mixture was concentrated *in vacuo* and the residue was crystallized from AcOEt to give **13** (0.20 g, 94%) as pale yellow prisms, mp 163—165 °C. IR (KBr): 1755, 1610, 1500, 1425, 1375, 1210 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.50—0.70 (1H, m), 1.40—2.20 (3H, m), 2.09 (3H, s), 5.39 (1H, d, J=15 Hz), 5.83 (1H, d, J=15 Hz), 7.15—7.45 (2H, m), 7.70—7.88 (1H, m), 8.11 (1H, s), 8.45 (1H, s). *Anal.* Calcd for $C_{15}H_{14}ClF_2N_3O_4S \cdot HCl$: C, 40.73; H, 3.42; N, 9.50. Found: C, 40.54; H, 3.49; N, 9.32.

1-[(*RS*)-1-Acetoxy-1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-ethyl]-*N*-butylcyclopropanesulfonamide (14) A mixture of **13** (50 mg, 0.11 mmol), butylamine (80 mg, 0.22 mmol) and DMAP (13.8 mg, 0.11 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 14 h. AcOEt (30 ml) was added to the mixture, and the whole was washed with water (5 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (hexane–AcOEt, 1:2, v/v) followed by recrystallization from diisopropyl ether gave **14** (11 mg, 22%) as colorless needles, mp 119—121 °C. IR (KBr): 1750, 1690, 1510, 1365, 1290, 1265, 1210, 1135 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, J=7 Hz), 0.75—1.70 (8H, m), 2.07 (3H, s), 2.48—2.65 (1H, m), 2.70—3.00 (2H, m), 5.52 (1H, d, J=14 Hz), 6.11 (1H, d, J=14 Hz), 6.84—7.10 (2H, m), 7.45—7.62 (1H, m), 7.97 (1H, s), 8.39 (1H, s). *Anal.* Calcd for $C_{19}H_{24}F_2N_4O_4S$: C, 51.57; H, 5.47; N, 12.66. Found: C, 51.42; H, 5.65; N, 12.52. SIMS m/z: 443 (MH^+).

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-morpholinothio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17e) A solution of Cl_2 (1 M solution in CCl_4, 2.2 ml, 2.2 mmol) was added dropwise to an ice-cooled solution of **15** (1.0 g, 1.76 mmol) in CH_2Cl_2 (30 ml) over a period of 5 min and the resulting mixture was stirred at 0 °C for 20 min, then added to a solution of morpholine (0.61 g, 7.04 mmol) in CH_2Cl_2 (10 ml). The reaction mixture was stirred at 0 °C for 20 min, washed with water (10 ml) and dried over $MgSO_4$. The solvent was evaporated off *in vacuo* and the residue was chromatographed on silica gel. Elution with hexane–AcOEt (1:2, v/v) gave **17e** (0.53 g, 40%) as a colorless oil, which solidified upon standing

in a freezer, mp 119—121 °C. IR (KBr): 3270, 1610, 1500, 1278, 1265, 1105 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=7.4 Hz), 2.90—3.25 (4H, m), 3.42 (1H, q, J=7.4 Hz), 3.60—3.90 (4H, m), 4.86 (1H, d, J=14 Hz), 5.10 (1H, d, J=14 Hz), 5.81 (1H, s), 6.70—6.88 (2H, m), 7.39 (1H, m), 7.74 (1H, s), 7.88 (1H, s). *Anal.* Calcd for $C_{16}H_{20}F_2N_4O_2S$: C, 51.88; H, 5.44; N, 15.13. Found: C, 51.99; H, 5.40; N, 14.86.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-morpholinosulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4e, Table III) and (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-morpholinosulfinyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (18e) Method A: An aqueous solution of $KMnO_4$ (7.5%, 6 ml, 2.8 mmol) was added dropwise to a solution of **17e** (0.50 g, 1.35 mmol) in acetone (25 ml) at room temperature and the mixture was stirred for 30 min. The precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in AcOEt (40 ml), and the solution was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography on silia gel. Elution with hexane–AcOEt (1 : 2, v/v) followed by crystallization from AcOEt–diisopropyl ether gave **4e** (0.32 g, 59% based on **17e**) as colorless needles. Elution with AcOEt–MeOH

TABLE III. (2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)-2-butanesulfonamides (**4**)

No.	Yield[a] (%)	mp (°C) (solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$)	IR ν_{max}^{KBr} (cm^{-1})	$[\alpha]_D^{20}$ (*c*) in MeOH 20 °C
4a	20	182—183 (EA–IPE)	$C_{14}H_{18}F_2N_4O_3S$	46.66 (46.59)	5.03 4.95	15.55 15.67)	1.16 (3H, d, J=7 Hz), 3.02 (6H, s), 3.88 (1H, q, J=7 Hz), 4.92 (1H, s), 5.04 (1H, dd, J=14, 1.4 Hz), 5.14 (1H, d, J=14 Hz), 6.68—6.85 (2H, m), 7.25—7.40 (1H, m), 7.65 (1H, s), 7.95 (1H, s)	3400, 1615, 1500, 1325, 1145, 1120	−56.3° (1.0)
4b	22	148—163 (M–EA)	$C_{13}H_{16}F_2N_4O_3S\cdot$ HCl	40.79 (40.99)	4.48 4.58	14.64 14.58)	1.07 (3H, d, J=7 Hz), 2.69 (3H, br s), 3.75 (1H, q, J=7 Hz), 4.89 (1H, d, J=14 Hz), 6.80—6.96 (1H, m), 7.10—7.28 (2H, m), 7.35 (1H, m, NH), 7.84 (1H, s), 8.75 (1H, s) (DMSO-d_6)	3100, 1615, 1500, 1420, 1320, 1150, 1130	−78.4° (1.0)
4c	17	128—140 (M–EA)	$C_{14}H_{18}F_2N_4O_3S\cdot$ HCl	42.37 (42.51)	4.83 5.07	14.12 14.02)	1.07 (3H, d, J=7 Hz), 1.12 (3H, t, J=7 Hz), 3.09 (2H, m), 3.70 (1H, q, J=7 Hz), 4.88 (1H, d, J=14 Hz), 5.24 (1H, d, J=14 Hz), 6.80—6.95 (1H, m), 7.10—7.30 (2H, m), 7.45 (1H, m, NH), 7.76 (1H, s), 8.63 (1H, s) (DMSO-d_6)	3125, 1615, 1500, 1420, 1320, 1155, 1135	−73.3° (1.0)
4d	44	149—164 (M–EA)	$C_{15}H_{20}F_2N_4O_3S\cdot$ HCl	43.85 (44.04)	5.15 5.30	13.64 13.72)	0.90 (3H, t, J=7 Hz), 1.07 (3H, d, J=7 Hz), 1.50 (2H, q, J=7 Hz), 3.01 (2H, m), 3.70 (1H, q, J=7 Hz), 4.89 (1H, d, J=15 Hz), 5.26 (1H, d, J=15 Hz), 6.80—6.96 (1H, m), 7.10—7.30 (2H, m), 7.46 (1H, m, NH), 7.79 (1H, s), 8.69 (1H, s) (DMSO-d_6)	3130, 1615, 1500, 1420, 1320, 1150, 1130	−72.2° (1.0)
4e	23	157—158 (EA–IPE)	$C_{16}H_{20}F_2N_4O_2S$	47.75 (47.87)	5.01 5.18	13.92 14.00)	1.18 (3H, d, J=7.2 Hz), 3.35—3.60 (4H, m), 3.64—4.00 (4H, m), 3.83 (1H, q, J=7.2 Hz), 5.01 (1H, dd, J=14, 1.4 Hz), 5.04 (1H, s), 5.21 (1H, d, J=14 Hz), 6.68—6.85 (2H, m), 7.23—7.40 (2H, m), 7.70 (1H, s), 7.89 (1H, s)	3410, 1620, 1600, 1505, 1340, 1255, 1155, 1130	−48.0° (1.0)
4f	16	149—150 (Et_2O)	$C_{19}H_{20}F_2N_4O_3S$	54.02 (54.07)	4.77 4.70	13.26 13.26)	1.20 (3H, d, J=7 Hz), 3.77 (1H, q, J=7 Hz), 4.45 (2H, m), 4.95 (1H, d, J=14 Hz), 5.09 (1H, t, J=5.8 Hz), 5.35 (1H, d, J=14 Hz), 6.68—6.85 (2H, m), 7.20—7.55 (6H, m), 7.70 (1H, s), 7.84 (1H, s)	1615, 1500, 1320, 1270, 1200, 1135	−28.5° (1.0)
4g	18	135—137 (EA–IPE)	$C_{22}H_{25}F_2N_5O_3S$	55.33 (55.40)	5.28 5.52	14.67 14.58)	1.20 (3H, d, J=7 Hz), 3.27 (4H, m), 3.64 (4H, m), 3.86 (1H, q, J=7 Hz), 5.03 (1H, s), 5.03 (1H, dd, J=14, 1 Hz), 5.23 (1H, d, J=14 Hz), 6.68—6.85 (2H, m), 6.90—7.02 (3H, m), 7.28—7.40 (3H, m), 7.69 (1H, s), 7.90 (1H, s)	3430, 1615, 1600, 1500, 1340, 1280, 1130	−40.7° (1.0)
4h	37	131—132 (E)	$C_{22}H_{24}F_3N_5O_3S$	53.33 (53.00)	4.88 5.01	14.13 14.04)	1.20 (3H, d, J=7 Hz), 3.17 (4H, m), 3.63 (4H, m), 3.85 (1H, q, J=7 Hz), 5.03 (1H, dd, J=14.6, 1.4 Hz), 5.03 (1H, s), 5.22 (1H, d, J=14.6 Hz), 6.68—7.10 (6H, m), 7.32 (1H, m), 7.69 (1H, s), 7.90 (1H, s)	3400, 1620, 1510, 1325, 1150	−37.3° (1.0)
4i	22	158—159 (Et_2O–H)	$C_{23}H_{24}F_5N_5O_3S$	50.64 (50.42)	4.43 4.39	12.84 12.57)	1.20 (3H, d, J=7 Hz), 3.36 (4H, m), 3.63 (4H, m), 3.86 (1H, q, J=7 Hz), 5.03 (1H, d, J=14.4 Hz), 5.08 (1H, s), 5.25 (1H, d, J=14.4 Hz), 6.70—6.85 (2H, m), 6.95 (2H, d, J=8.6 Hz), 7.25—7.40 (1H, m), 7.53 (2H, d, J=8.6 Hz), 7.71 (1H, s), 7.89 (1H, s)	1620, 1500, 1330, 1150, 1120	−32.5° (1.0)
4j	24 40[d]	AP[c]	$C_{19}H_{23}F_2N_5O_3S\cdot$ $2HCl\cdot H_2O$	43.18 (43.24)	4.77 4.92	13.25 12.99)	Free base: 1.22 (3H, d, J=7 Hz), 2.89 (3H, s), 3.93 (1H, q, J=7 Hz), 4.38 (1H, d, J=15 Hz), 4.60 (1H, d, J=15 Hz), 5.06 (1H, dd, J=14.6, 1.6 Hz), 5.07 (1H, s), 5.23 (1H, d, J=14.6 Hz), 6.70—6.86 (2H, m), 7.27—7.41 (2H, m), 7.69 (1H, s), 7.82 (1H, m), 7.92 (1H, s), 8.59 (2H, m)	3350, 1616, 1558, 1500, 1423, 1326, 1132	−32.6° (1.0)
4k	14	121—123 (Et_2O)	$C_{17}H_{19}F_2N_5O_3S_2$	46.04 (46.15)	4.32 4.42	15.79 15.30)	1.20 (3H,d, J=7 Hz), 3.06 (3H, s), 4.00 (1H, q, J=7 Hz), 4.07 (1H, d, J=16 Hz), 4.95 (1H, d, J=16 Hz), 5.04 (1H, d, J=14.6 Hz), 5.24 (1H, s), 5.24 (1H, d, J=14.6 Hz), 6.70—6.86 (2H, m), 7.34 (1H, m), 7.41 (1H, d, J=3.4 Hz), 7.67 (1H, s), 7.78 (1H, d, J=3.4 Hz), 7.93 (1H, s)	1616, 1500, 1328, 1139	−21.0° (1.0)
4l	14	120—128 (Et_2O)	$C_{25}H_{24}F_2N_4O_3S\cdot$ HCl	56.12 (56.60)	4.71 4.91	10.47 10.12)	Free base: 0.98 (3H, d, J=7 Hz), 3.50 (1H, q, J=7 Hz), 4.83 (1H, dd, J=15, 1.2 Hz), 5.18 (1H, s), 5.25 (1H, d, J=15 Hz), 5.85 (1H, s, NH), 6.60—6.78 (2H, m), 7.15—7.60 (11H, m), 7.60 (1H, s), 7.80 (1H, s)	1610, 1500, 1420, 1310, 1145	−13.5° (1.0)
4m	26	134—157 (EA–IPE)	$C_{21}H_{24}F_2N_4O_5S\cdot$ HCl	48.60 (48.61)	4.86 4.73	10.80 10.77)	1.21 (3H, d, J=7 Hz), 3.78 (1H, q, J=7 Hz), 3.89 (3H, s), 3.90 (3H, s), 4.38 (2H, m), 4.93 (1H, s), 4.98 (1H, d, J=15 Hz), 5.32 (1H, br, NH), 5.36 (1H, d, J=15 Hz), 6.70—6.95 (5H, m), 7.22—7.38 (1H, m), 7.72 (1H, s), 7.88 (1H, s)	1615, 1598, 1505, 1420, 1325, 1270, 1160, 1140	−29.4° (0.1)
4n	69	195—197 (M–D)	$C_{12}H_{14}F_2N_4O_3S$	43.37 (43.11)	4.25 4.22	16.86 16.77)	1.24 (3H, d, J=7 Hz), 3.84 (1H, q, J=7 Hz), 4.92 (1H, d, J=15 Hz), 4.93 (2H, br s), 5.53 (1H, d, J=15 Hz), 5.77 (1H, d, J=1.4 Hz), 6.70—6.84 (2H, m), 7.21—7.35 (1H, m), 7.77 (1H, s), 7.78 (1H, s)	3410, 1610, 1500, 1315, 1275, 1165	−49.9° (1.0)

a) Based on compound **15**. *b*) Recrystallization solvent: EA, ethyl acetate; IPE, diisopropyl ether; M, methanol; Et_2O, diethyl ether; D, dichloromethane; E, ethanol; H, hexane. *c*) Amorphous powder. *d*) Prepared from **4b**.

(10 : 1, v/v) gave **18e** (90 mg, 17% based on **17e**) as a pale brown oil.

18e: IR (neat): 1690, 1610, 1500, 1445, 1415, 1270, 1105 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, dd, J=7, 2 Hz), 3.00—3.40 (5H, m), 3.60—3.95 (4H, m), 4.67 (1H, d, J=14.2 Hz), 5.37 (1H, d, J=14.2 Hz), 6.02 (1H, s), 6.70—6.95 (2H, m), 7.40—7.58 (1H, m), 7.83 (1H, s), 7.94 (1H, s). SIMS m/z: 387 (MH^+).

Method B: *m*-CPBA (100 mg, 0.54 mmol) was added to an ice-cooled solution of **17e** (100 mg, 0.27 mmol) in CH_2Cl_2 (8 ml). The mixture was stirred at room temperature for 4 h, then washed with an aqueous solution of $NaHCO_3$ (2 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (hexane–AcOEt, 1 : 2, v/v) followed by recrystallization from AcOEt–diisopropyl ether gave **4e** (75 mg, 71%) as colorless needles. The ^{1}H-NMR spectrum of the product was identical with that of **4e** obtained by method A.

(2*R*,3*R*)-3-(2,4-Difluorophenyl)-*N*,*N*-dimethyl-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)-2-butanesulfonamide (4a, Table III) A solution of Cl_2 (1 M solution in CCl_4, 3.5 ml, 3.5 mmol) was added dropwise to an ice-cooled solution of **15** (2.0 g, 3.5 mmol) in CH_2Cl_2 (60 ml) over a period of 5 min and the resulting mixture was stirred at 0 °C for 20 min, then added to an ice-cooled solution of dimethylamine (0.64 g, 14 mmol) in toluene (3.2 ml). The reaction mixture was stirred at 0 °C for 30 min, washed with water and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a crude product containing the sulfenamide (**17a**), which was dissolved in acetone (80 ml). To the solution was added dropwise a saturated aqueous solution of $KMnO_4$ until the permanganate color persisted (10 ml of $KMnO_4$ solution was consumed). The precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in AcOEt (80 ml), and the solution was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (hexane–AcOEt, 1 : 2, v/v) followed by crystallization from AcOEt–diisopropyl ether gave **4a** (0.78 g, 31% based on **15**) as colorless needles.

According to the same procedure as that described above, compounds **4b**—**d** and **4f**—**m** were prepared (Table III).

(2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-*N*-methyl-*N*-(3-pyridylmethyl)-4-(1*H*-1,2,4-triazol-1-yl)-2-butanesulfonamide (4j, Table III) A stirred mixture of **4b** (0.40 g, 1.04 mmol), 3-chloromethylpyridine hydrochloride (0.83 g, 5.2 mmol) and NaOMe (28% in MeOH, 2.0 g 10.4 mmol) in MeOH (20 ml) was heated at 60 °C for 4 h. After cooling, the mixture was concentrated *in vacuo* and the residue was dissolved in AcOEt (50 ml). The resulting solution was washed with water (10 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (AcOEt–MeOH, 10 : 1, v/v) gave **4j** (0.18 g, 40%) as a colorless oil, which (0.15 g, 0.34 mmol) was treated with HCl (4 M solution in AcOEt, 2 ml) to give **4j**·2HCl (0.13 g, 76%) as a white amorphous powder. The spectral data (^{1}H-NMR, IR) of the product were identical with those of **4j** obtained by the procedure *via* the oxidation of the sulfenamide.

2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butene (20) Entry 1: A mixture of **4f** (0.10 g, 0.24 mmol), concentrated H_2SO_4 (72 mg, 0.75 mmol) and EtOH (55 mg, 1.2 mmol) in toluene (25 ml) was stirred vigorously at 80 °C for 12 h. After being cooled, the mixture was neutralized with an aqueous solution of $NaHCO_3$ and concentrated *in vacuo*. The residue was purified by preparative TLC (20 × 20 cm). Development with hexane–AcOEt (1 : 2) and extraction of the product with AcOEt followed by evaporation of the solvent gave **20** (35 mg, 48%) as a colorless oil, which solidified upon standing at room temperature, mp 67—70 °C (colorless prisms). IR (KBr): 1618, 1594, 1500, 1423, 1280, 1265 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, d, J=6.8 Hz), 4.99 (2H, s), 6.02 (1H, q, J=6.8 Hz), 6.75—6.95 (3H, m), 7.88 (1H, s), 7.90 (1H, s). SIMS m/z: 235 (MH^+).

(2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)-2-butanesulfonamide (4n, Table III) Entry 5: A mixture of **4m** (0.71 g, 1.47 mmol), concentrated H_2SO_4 (0.63 g, 6.4 mmol) and EtOH (0.75 g, 16 mmol) in toluene (200 ml) was stirred vigorously at 70 °C for 30 min. After being cooled, the mixture was neutralized with an aqueous solution of $NaHCO_3$ and concentrated *in vacuo*. The residue was partitioned between AcOEt (100 ml) and water (20 ml), and the organic layer was separated, dried over $MgSO_4$ and then concentrated *in vacuo*. Purification of the residue by chromatography on silica gel (hexane–AcOEt, 1 : 2, v/v) followed by recrystallization from MeOH–CH_2Cl_2 gave **4n** (0.34 g, 69%) as colorless prisms.

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References and Notes

1) *a*) A part of this paper was presented at the 113th Annual Meeting of the Pharmaceutical Society of Japan, Osaka, March 1993; Abstracts of Papers, Vol. II, p. 279; *b*) Part II: A. Tasaka, N. Tamura, Y. Matsushita, R. Hayashi, K. Okonogi, K. Itoh, *Chem. Pharm. Bull.*, **41**, 1043 (1993).
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4) The hydrophobic parameters (substituent constants) derived from partition coefficients were reported as $\pi_{SO_2NH_2} = -1.82$ and $\pi_{SO_2N(CH_3)_2} = -0.78$. T. Fujita, J. Iwasa, C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964); C. Hansch, S. D. Rockwell, P. Y. C. Jow, A. Leo, E. E. Steller, *J. Med. Chem.*, **20**, 304 (1977).
5) Although the olefins could be separated by silica gel column chromatography into two stereoisomers, which were presumably (*E*)- and (*Z*)-diastereomers, stereochemical assignment has not been carried out.
6) The referee suggested another mechanism for formation of compound **9** : **8**→(2*R*,3*R*)-3-acetoxy-3-(2,4-difluorophenyl)-*N*,*N*-dimethyl-4-(1*H*-1,2,4-triazol-1-yl)-2-butansulfonamide (**21**)→**9**. To examine the feasibility of this pathway, we prepared the suggested intermediate **21** by the reaction of **4a** with acetic anhydride. Compound **21** proved to be stable to treatment with dimethylamine under conditions similar to those used in the preparation of **9a**. Therefore, it may be concluded that **10** is the intermediate for formation of **9** as shown in Chart 3. The elimination–addition mechanism of sulfonyl chlorides has been described.[7a]
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