Optically Active Antifungal Azoles. IV.[1] Synthesis and Antifungal Activity of (2*R*,3*R*)-3-Azolyl-2-(substituted phenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols

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(2*R*,3*R*)-3-Azolyl-2-(substituted phenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (III) were prepared from (2*R*,3*S*)-3-methyl-2-(substituted phenyl)-2-(1*H*-1,2,4-triazol-1-yl)methyloxiranes (21a—f) by a ring-opening reaction with 1*H*-1,2,3-triazole and 1*H*-tetrazole and evaluated for antifungal activity against *Candida albicans in vitro* and *in vivo*. The optically active oxiranes (21a—f), which serve as the key synthetic intermediates, were synthesized from 1-[(2*R*)-2-(3,4,5,6-tetrahydro-2*H*-pyran-2-yl)oxypropanoyl]morpholine (24) and substituted phenylmagnesium bromide (23) *via* six steps in a stereocontrolled manner. The 3-(1*H*-1,2,3,-triazol-1-yl)-(IIIa) and 3-(2*H*-2-tetrazolyl)-2-butanol (IIId) derivatives showed strong protective effects against candidosis in mice.

Key words optically active antifungal azole; chiral synthesis; 1,3-bis(azolyl)-2-butanol; triazolylbutanol; antifungal activity; candidosis

The incidence of systemic fungal infections such as candidosis, cryptococcosis and aspergillosis has been increasing recently due to an increase in the number of immunocompromised hosts.[2] For the treatment of these infections, the new antifungal azoles fluconazole[3] and itraconazole,[4] which can be given orally, have been developed for clinical use.

In the course of our search for new antifungal agents, we have synthesized a variety of sulfur-containing optically active triazole derivatives I.[1,5] In the previous paper, we described the synthesis and antifungal activities of sulfide (Ia) and sulfonamide (Ib) derivatives of (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol.[1]

We next focused on the antifungal activity of a nitrogen-containing triazole derivative with the general formula II. We chose 1,2,3-triazole and tetrazole nuclei as the $-NR^4R^5$ moiety in II and designed optically active (2*R*,3*R*)-3-azolyl-2-(substituted phenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (III).[6] Varying the substituent R on the benzene ring gave a variety of derivatives with different physicochemical properties, which might influence the potency of antifungal activity as well as the pharmacokinetic characteristics. We chose 2,4-difluoro (2,4-F_2), 4-chloro (4-Cl), 4-fluoro (4-F), 4-trifluoromethyl (4-CF_3), 4-trifluoromethoxy (4-OCF_3) and 2-fluoro (2-F) groups[7] as substituents R and prepared (2*R*,3*R*)-2-(substituted phenyl)-3-(1*H*-1,2,3-triazol-1-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (IIIa), (2*R*,3*R*)-2-(substituted phenyl)-3-(2*H*-1,2,3-triazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (IIIb), (2*R*,3*R*)-2-(substituted phenyl)-3-(1*H*-1-tetrazolyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (IIIc) and (2*R*,3*R*)-2-(substituted phenyl)-3-(2*H*-2-tetrazolyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (IIId).

In this paper, we describe the synthesis of compounds IIIa—d (**1**—**20**: Table I) as well as their antifungal activities against *Candida albicans in vitro* and *in vivo*.

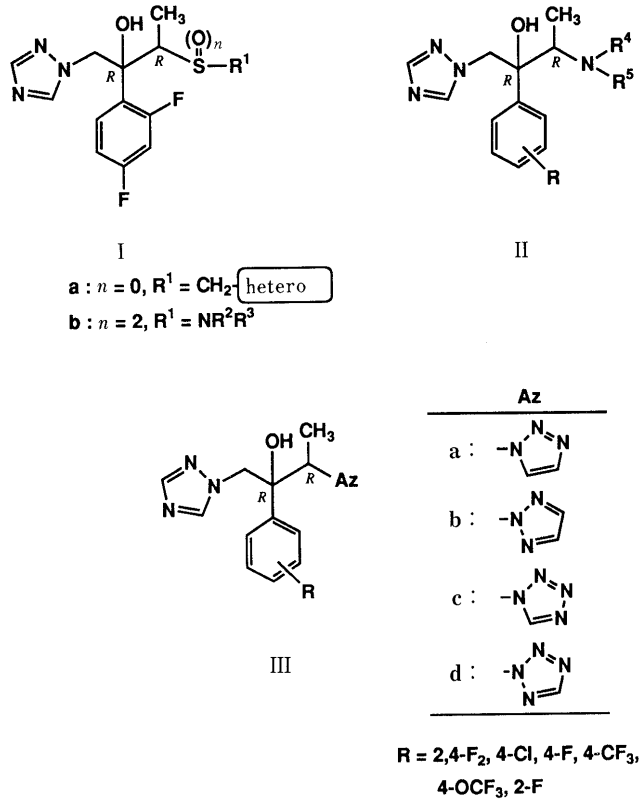

Chart 1

Chemistry

We previously established a route for the synthesis of (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-methyl-2-(1*H*-1,2,4-triazol-1-yl)methyloxirane (**21a**) starting from methyl (*R*)-lactate,[5a] and this oxirane was used as the key synthetic intermediate for the preparation of our sulfur-containing triazole derivatives (I) *via* a nucleophilic ring-opening reaction at the 3-position.[5] In the case of the synthesis of compounds IIIa—d as well, (2*R*,3*S*)-2-(substituted phenyl)oxiranes (**21a**—**f**) could serve as the key synthetic precursors. Thus, we prepared the oxiranes **21b**—**f** *via* a route similar to that used for the synthesis

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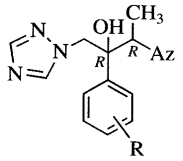
TABLE I. (2*R*,3*R*)-3-Azolyl-2-(substituted phenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (III)



III	R	Az	mp (°C) (Solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR δ (in $CDCl_3$)	IR ν (cm^{-1}) (KBr)	$[\alpha]_D$ (*c*, %) {°C} (in MeOH)
1	2,4-F_2	1*H*-1,2,3-Triazol-1-yl	119—120 (D–Et_2O)	$C_{14}H_{14}F_2N_6O$	52.50 (52.35)	4.41 (4.29)	26.24 (26.08)	1.38 (3H, d, J=7 Hz), 3.49 (1H, d, J= 14.4 Hz), 4.99 (1H, d, J=14.4 Hz), 5.39 (1H, s), 5.52 (1H, q, J=7 Hz), 6.75—6.90 (2H, m), 7.42—7.59 (1H, m), 7.74 (1H, s), 7.77 (1H, s), 7.81 (1H, s), 7.98 (1H, s)	3315, 3124, 1618, 1599, 1500, 1421	−69.4 (1.0) {20}
2	4-Cl	1*H*-1,2,3-Triazol-1-yl	145—147 (Acetone–IPE)	$C_{14}H_{15}ClN_6O$	52.75 (52.81)	4.74 (4.74)	26.36 (26.34)	1.40 (3H, d, J=7 Hz), 3.58 (1H, d, J=14.4 Hz), 4.60 (1H, d, J=14.4 Hz), 5.28 (1H, d, J=7 Hz), 5.31 (1H, s), 7.16—7.38 (4H, m), 7.64 (1H, s), 7.78 (1H, s), 7.79 (1H, s), 7.97 (1H, d, J=1 Hz)	3360, 3114, 1660, 1508, 1492, 1456	−90.8 (0.48) {20}
3	4-F	1*H*-1,2,3-Triazol-1-yl	157—158 (A)	$C_{14}H_{15}FN_6O$	55.62 (55.79)	5.00 (5.22)	27.80 (27.91)	1.40 (3H, d, J=7 Hz), 3.58 (1H, d, J=14 Hz), 4.62 (1H, d, J=14 Hz), 5.25—5.39 (1H, m), 5.30 (1H, s), 6.96—7.05 (2H, m), 7.29—7.36 (2H, m), 7.66 (1H, s), 7.78 (1H, s), 7.80 (1H, s), 7.98 (1H, s)	3275, 3125, 1600, 1510, 1482, 1275	−74.5 (1.0) {20}
4	4-CF_3	1*H*-1,2,3-Triazol-1-yl	106—107 (Et_2O)	$C_{15}H_{15}F_3N_6O$	51.14 (51.04)	4.29 (4.40)	23.85 (23.45)	1.40 (3H, d, J=7 Hz), 3.62 (1H, d, J=14 Hz), 4.70 (1H, d, J=14 Hz), 5.36 (1H, q, J=7 Hz), 5.49 (1H, s), 7.51 (2H, d, J=8.6 Hz), 7.60 (2H, d, J=8.6 Hz), 7.68 (1H, s), 7.79 (1H, s), 7.82 (1H, s), 8.00 (1H, s)	3420, 3120, 1620, 1510, 1330, 1125	−65.7 (1.04) {20}
5	4-OCF_3	1*H*-1,2,3-Triazol-1-yl	119—121 (Acetone–IPE)	$C_{15}H_{15}F_3N_6O_2$	48.92 (49.10)	4.10 (4.14)	22.82 (22.75)	1.40 (3H, d, J=7 Hz), 3.60 (1H, d, J=14.2 Hz), 4.63 (1H, d, J=14.2 Hz), 5.32 (1H, q, J=7 Hz), 5.40 (1H, s), 7.17 (2H, d, J=9 Hz), 7.40 (2H, d, J=9 Hz), 7.66 (1H, s), 7.80 (1H, s), 7.81 (1H, s), 7.99 (1H, s)	3450, 1598, 1512, 1416, 1280, 1222	−64.1 (0.5) {20}
6	2-F	1*H*-1,2,3-Triazol-1-yl	119—120 (Et_2O–IPE)	$C_{14}H_{15}FN_6O$	55.62 (55.69)	5.00 (5.08)	27.80 (28.02)	1.38 (3H, d, J=7 Hz), 3.49 (1H, dd, J=14 Hz), 5.03 (1H, d, J=14 Hz), 5.28 (1H, s), 5.58 (1H, q, J=7 Hz), 6.99—7.12 (2H, m), 7.21—7.51 (2H, m), 7.72 (2H, s), 7.80 (1H, s), 8.00 (1H, s)	3120, 1620, 1520, 1490, 1400, 1210	−76.7 (1.0) {20}
7	2,4-F_2	2*H*-1,2,3-Triazol-2-yl	99—100 (IPE)	$C_{14}H_{14}F_2N_6O$	52.50 (52.33)	4.41 (4.47)	26.24 (26.22)	1.43 (3H, d, J=7 Hz), 3.57 (1H, d, J=14.4 Hz), 4.91 (1H, dd, J=14.4, 1.2 Hz), 5.29 (1H, s), 5.54 (1H, q, J=7 Hz), 6.75—6.92 (2H, m), 7.43—7.63 (1H, m), 7.65 (1H, s), 7.77 (2H, s), 7.85 (1H, s)	3340, 3302, 1618, 1500, 1421	−83.5 (1.08) {23}
8	4-Cl	2*H*-1,2,3-Triazol-2-yl	148—149 (D–IPE)	$C_{14}H_{15}ClN_6O$	52.75 (52.71)	4.74 (4.77)	26.36 (26.37)	1.43 (3H, d, J=7 Hz), 3.73 (1H, d, J=14.4 Hz), 4.55 (1H, d, J=14.4 Hz), 5.22 (1H, s), 5.26 (1H, q, J=7 Hz), 7.16—7.38 (4H, m), 7.71 (1H, s), 7.74 (2H, s), 7.75 (1H, s)	3411, 1598, 1512, 1495, 1402, 1336	−120.0 (0.5) {20}
9	4-F	2*H*-1,2,3-Triazol-2-yl	125—127 (D–IPE)	$C_{14}H_{15}FN_6O$	55.62 (55.39)	5.00 (5.02)	27.80 (27.72)	1.43 (3H, d, J=7 Hz), 3.73 (1H, d, J=14 Hz), 4.55 (1H, d, J=14 Hz), 5.21 (1H, s), 5.26 (1H, q, J=7 Hz), 6.96—7.04 (2H, m), 7.29—7.34 (2H, m), 7.71 (1H, s), 7.75 (3H, s)	3410, 1600, 1510, 1340, 1230, 1160	−90.4 (1.0) {20}
10	4-CF_3	2*H*-1,2,3-Triazol-2-yl	118—119 (D–H)	$C_{15}H_{15}F_3N_6O$	51.14 (51.08)	4.29 (4.25)	23.85 (23.64)	1.42 (3H, d, J=7 Hz), 3.77 (1H, d, J=14 Hz), 4.61 (1H, d, J=14 Hz), 5.31 (1H, d, J=7 Hz), 5.35 (1H, s), 7.46 (2H, d, J=8.4 Hz), 7.57 (2H, d, J=8.4 Hz), 7.69 (1H, s), 7.75 (2H, s), 7.78 (1H, s)	3410, 1620, 1510, 1415, 1330, 1135	−88.0 (1.02) {20}
11	4-OCF_3	2*H*-1,2,3-Triazol-2-yl	126—127 (D–IPE)	$C_{15}H_{15}F_3N_6O_2$	48.92 (49.27)	4.10 (4.19)	22.82 (22.87)	1.43 (3H, d, J=7 Hz), 3.75 (1H, d, J=14.2 Hz), 4.57 (1H, d, J=14.2 Hz), 5.29 (1H, q, J=7 Hz), 5.30 (1H, s), 7.16 (2H, d, J=9 Hz), 7.37 (2H, d, J=9 Hz), 7.71 (1H, s), 7.76 (2H, s), 7.78 (1H, s)	3250, 1598, 1510, 1466, 1417, 1353	−84.8 (0.5) {20}
12	2-F	2*H*-1,2,3-Triazol-2-yl	164—166 (E–Et_2O)	$C_{14}H_{15}FN_6O$ ·HCl	49.64 (49.44)	4.76 (4.74)	24.81 (24.54)	1.36 (3H, d, J=7 Hz), 3.90 (1H, d, J=14 Hz), 4.93 (1H, d, J=14 Hz), 5.41 (1H, q, J=7 Hz), 7.01—7.32 (4H, m), 7.74 (1H, s), 7.92 (2H, s), 8.46 (1H, s) (in DMSO-d_6)	3360, 1620, 1520, 1490, 1420, 1230	−83.9 (1.05) {23}
13	2,4-F_2	1*H*-1-Tetrazolyl	136—137 (E–H_2O) 113—114 (A–H)	$C_{13}H_{13}F_2N_7O$	48.60 (48.49)	4.08 (4.40)	30.52 (30.81)	1.43 (3H, d, J=7 Hz), 3.56 (1H, d, J=14.2 Hz), 4.99 (1H, d, J=14.2 Hz), 5.58 (1H, q, J=7 Hz), 5.64 (1H, s), 6.75—6.95 (2H, m), 7.36—7.50 (1H, m), 7.71 (1H, s), 7.78 (1H, s), 9.01 (1H, s)	3410, 3062, 1618, 1597	−47.5 (1.0) {20}
14	4-Cl	1*H*-1-Tetrazolyl	174—176 (A)	$C_{13}H_{14}ClN_7O$ ·HCl	43.83 (43.61)	4.24 (4.39)	27.52 (27.19)	1.46 (3H, d, J=7 Hz), 4.43 (1H, d, J=14 Hz), 4.86 (1H, d, J=14 Hz), 5.31 (1H, q, J=7 Hz), 7.21—7.46 (4H, m), 7.99 (1H, s), 8.51 (1H, s), 9.32 (1H, s) (in DMSO-d_6)	3440, 3130, 1600, 1540, 1500, 1370	−50.6 (0.5) {20}
15	4-F	1*H*-1-Tetrazolyl	143—144 (IPE)	$C_{13}H_{14}FN_7O$	51.48 (51.40)	4.65 (4.60)	32.33 (32.41)	1.43 (3H, d, J=7 Hz), 3.64 (1H, d, J=14 Hz), 4.62 (1H, d, J=14 Hz), 5.32 (1H, q, J=7 Hz), 5.47 (1H, s), 6.98—7.09 (2H, m), 7.25—7.37 (2H, m), 7.64 (1H, s), 7.80 (1H, s), 9.00 (1H, s)	3140, 1600, 1510, 1470, 1410, 1280	−33.2 (0.5) {20}
16	2-F	1*H*-1-Tetrazolyl	107—108 (IPE)	$C_{13}H_{14}FN_7O$	51.48 (51.27)	4.65 (4.80)	32.33 (32.14)	1.42 (3H, d, J=7 Hz), 3.57 (1H, d, J=14 Hz), 5.03 (1H, d, J=14 Hz), 5.53 (1H, s), 5.64 (1H, q, J=7 Hz), 7.02–7.12 (2H, m), 7.24—7.48 (2H, m), 7.74 (1H, s), 7.75 (1H, s), 9.02 (1H, s)	3420, 1610, 1510, 1380, 1210, 1125	−40.6 (0.5) {20}
17	2,4-F_2	2*H*-2-Tetrazolyl	111—130 (Et_2O)	$C_{13}H_{13}F_2N_7O$ ·HCl	43.65 (43.64)	3.94 (3.90)	27.41 (27.20)	1.49 (3H, d, J=7 Hz), 4.18 (1H, d, J=14.4 Hz), 4.92 (1H, d, J=14.4 Hz), 5.67 (1H, q, J=7 Hz), 6.90—7.04 (1H, m), 7.20—7.40 (2H, m), 7.72 (1H, s), 8.32 (1H, s), 9.11 (1H, s) (in DMSO-d_6)	3400, 3060, 1620, 1616, 1597	−52.8 (0.55) {20}
18	4-Cl	2*H*-2-Tetrazolyl	118—120 (IPE)	$C_{13}H_{14}ClN_7O$	48.83 (48.75)	4.41 (4.43)	30.66 (30.43)	1.59 (3H, d, J=7 Hz), 3.96 (1H, d, J=14 Hz), 4.73 (1H, d, J=14 Hz), 5.13 (1H, s), 5.47 (1H, q, J=7 Hz), 7.21—7.32 (4H, m), 7.74 (2H, s), 8.60 (1H, s)	3450, 1600, 1510, 1330, 1270, 1210	−73.1 (0.5) {20}
19	4-F	2*H*-2-Tetrazolyl	98—99 (IPE)	$C_{13}H_{14}FN_7O$	51.48 (51.26)	4.65 (4.45)	32.33 (32.10)	1.59 (3H, d, J=7 Hz), 3.96 (1H, d, J=14 Hz), 4.73 (1H, d, J=14 Hz), 5.10 (1H, s), 5.51 (1H, q, J=7 Hz), 6.96—7.04 (2H, m), 7.26—7.32 (2H, m), 7.73 (1H, s), 7.74 (1H, s), 8.60 (1H, s)	3140, 1600, 1510, 1420, 1280, 1210	−51.6 (0.5) {20}
20	2-F	2*H*-2-Tetrazolyl	98—99 (IPE)	$C_{13}H_{14}FN_7O$	51.48 (51.52)	4.65 (4.51)	32.33 (32.45)	1.58 (3H, d, J=7 Hz), 3.80 (1H, d, J=14 Hz), 5.09 (1H, d, J=14 Hz), 5.12 (1H, s), 5.72 (1H, q, J=7 Hz), 7.00—7.12 (2H, m), 7.24—7.35 (1H, m), 7.48—7.57 (1H, m), 7.69 (1H, s), 7.77 (1H, s), 8.62 (1H, s)	3150, 1580, 1510, 1390, 1210, 1130	−46.2 (0.2) {20}

a) Recrystallization solvents; D: dichloromethane, Et_2O: diethyl ether, M: methanol, IPE: diisopropyl ether, A: ethyl acetate, H: hexane, E: ethanol.

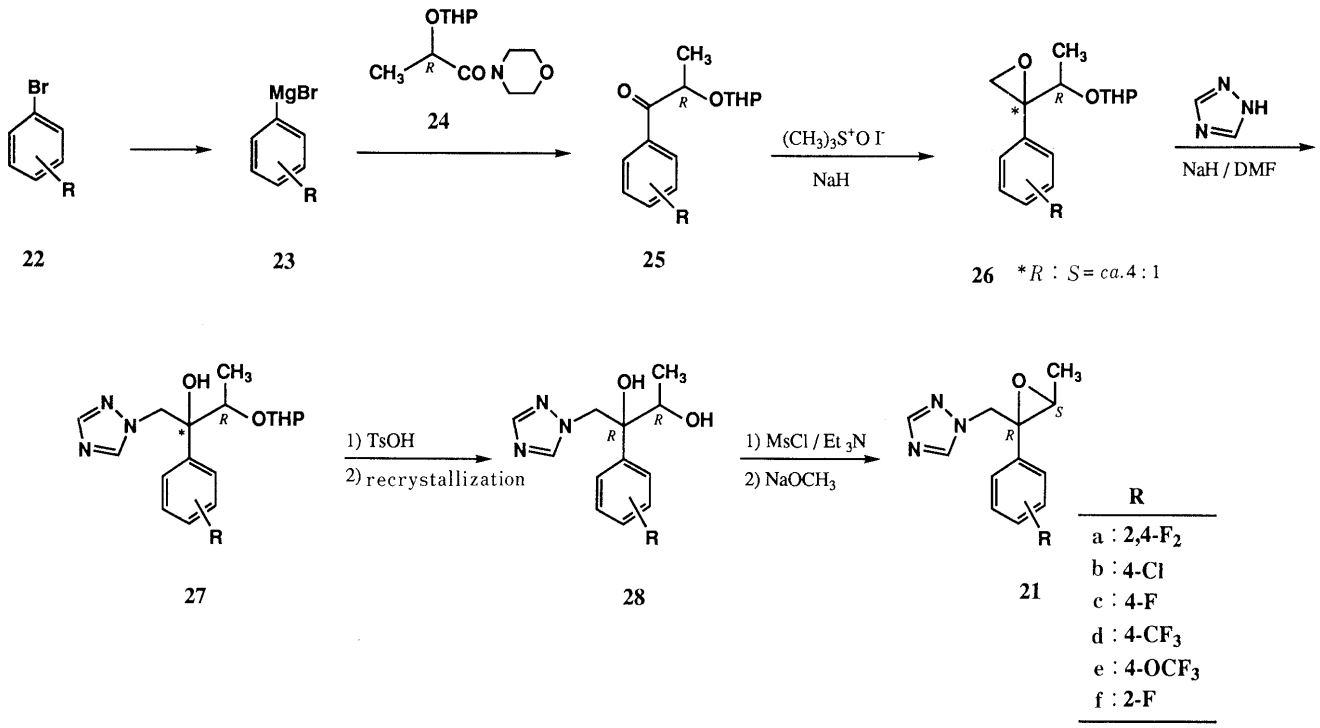


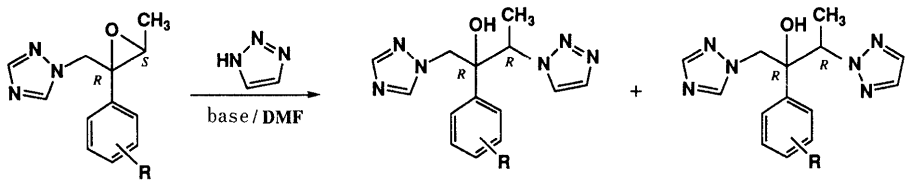
Chart 2

of **21a** as shown in Chart 2.

Grignard reaction of the amide **24**, which was derived from methyl (*R*)-lactate,[5a] with 4-Cl- (**23b**), 4-F- (**23c**), 4-CF_3- (**23d**) and 4-CF_3O-phenylmagnesium bromide (**23e**) proceeded smoothly to give (*R*)-2-(3,4,5,6-tetrahydro-2*H*-pyran-2-yl)oxypropiophenone derivatives (**25b—e**) in 74—100% yields. It has been reported that 2-F-phenylmagnesium bromide (**23f**) is unstable and liable to produce triphenylene and polymers, presumably *via* a benzyne intermediate.[8] In fact, the reaction of 2-bromofluorobenzene (**22f**) with magnesium (Mg) to produce **23f** followed by the addition of compound **24** gave highly lipophilic substances as the major product, but formation of a trace amount of the desired compound **25f** was observed. We then investigated the reaction conditions necessary to obtain compound **25f** in a reasonable yield. Dawson and Burger reported that Grignard reaction of **23f** with diethyl chlorophosphate could be conducted by the entrainment method using ethyl bromide (EtBr).[9] According to this method, **23f** was prepared in the presence of EtBr and allowed to react with **24**. The desired propiophenone **25f** was isolated in a 27% yield. We continued our search for reaction conditions to improve the yield and found that addition of the reagents in reverse order was quite effective for this purpose, that is, addition of Mg to a mixture of **22f**, **24** and EtBr in tetrahydrofuran (THF) followed by stirring brought about the Grignard reaction to afford compound **25f** in a 66% yield. Finally, it was found that EtBr was unnecessary when adding the reagents in reverse order.

Diasteroselective epoxidation of **25b—f** with Corey's reagent[10] in dimethyl sulfoxide (DMSO) afforded the oxirane derivatives **26b—f**, which were diastereomeric mixtures consisting of the desired (1′*R*,2*R*)-diastereomer and the undesired (1′*R*,2*S*)-isomer in a ratio of *ca.* 4 : 1.[11] This product (**26b—f**) was reacted with 1*H*-1,2,4-triazole in the presence of sodium hydride (NaH) to obtain the butanol derivatives **27b—f** in 70—84% yields based on **25b—f**. The tetrahydropyranyl group was removed with *p*-toluenesulfonic acid (TsOH) followed by recrystallization of the resulting diol to obtain the diastereomerically pure (2*R*,3*R*)-diols **28b—f** in 34—71% yields. The diols **28b—f** were converted to the corresponding mesylates and subsequent treatment with sodium methoxide (NaOMe) in methanol (MeOH) gave the oxiranes **21b—f** in 77—88% yields.

The ring-opening reaction of the oxiranes **21a—f** to give the bis-azole derivatives III (**1—20**: Table I) was then investigated. The reaction of **21a** with 1*H*-1,2,3-triazole in the presence of NaH in dimethylformamide (DMF) gave a mixture of two regioisomers, which were separated by column chromatography on silica gel into the more polar 1*H*-1,2,3-triazol-1-yl (**1**) and less polar 2*H*-1,2,3-triazol-2-yl (**7**) derivatives in 24% and 18% isolated yields, respectively. Substitution position on the 1,2,3-triazole moiety in these two regioisomers was determined by ^{1}H-NMR measurement ; the two unequivalent protons of the 1*H*-1,2,3-triazole moiety in **1** appeared as two singlets, while the two equivalent protons in **7** appeared as one singlet. The 1,2,3-triazole analogues, **2—6** and **8—12**, were prepared in the same way, and the isolated yields are shown in Chart 3. As can be seen in Chart 3, the combined isolated yields of IIIa and IIIb were around 50%; therefore, we tried to improve the yields by using a base other than NaH. Alkaline metal carbonates such as lithium carbonate (Li_2CO_3), sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3) and cesium carbonate (Cs_2CO_3) were examined for effectiveness in the conversion of **21a** into **1** and **2**. Among these carbonates, K_2CO_3 was found to give the best result, and the isolated



21a–f IIIa IIIb

R	base	IIIa (isolated yield, %)	IIIb
2,4-F_2	NaH	**1** (24)	**7** (18)
	K_2CO_3	**1** (47)	**7** (36)
4-Cl	NaH	**2** (26)	**8** (28)
	K_2CO_3	**2** (38)	**8** (50)
4-F	NaH	**3** (24)	**9** (23)
	K_2CO_3	**3** (38)	**9** (48)
4-CF_3	NaH	**4** (32)	**10** (24)
4-CF_3O	NaH	**5** (23)	**11** (29)
2-F	NaH	**6** (24)	**12** (25)
	K_2CO_3	**6** (47)	**12** (32)

Chart 3

yields were 47% (**1**) and 36% (**2**). This reaction condition was also applied in the synthesis of the 4-Cl, 4-F and 2-F analogues, and a considerable improvement in isolated yield was attained, as shown in Chart 3.

The synthesis of tetrazole derivatives (IIIc,d) was first attempted by using NaH as the base, 1*H*-tetrazole and the oxirane **21a**. However, the benzofuran derivative **29**, which was possibly formed *via* isomerization followed by intramolecular substitution, was obtained as the major product instead of the desired ring-opening products (**13** and **17**: trace). We next examined bis(tributyltin)oxide [$(Bu_3Sn)_2O$], because this metal reagent has been reported to be effective in the synthesis of propanol analogues.[12] However, this reaction required a very long reaction period (>7 d), and the combined isolated yield of **13** and **17** was less than 20% (Chart 4). On the basis of the satisfactory results in the case of the 1,2,3-triazoles described above, we tested alkaline metal carbonates, Li_2CO_3, Na_2CO_3, K_2CO_3 and Cs_2CO_3. In the case of tetrazoles , Li_2CO_3 was found to be the most effective, and the 1*H*-1-tetrazolyl (**13**: more polar) and 2*H*-2-tetrazolyl (**17**: less polar) compounds were isolated by silica gel column chromatography in 29% and 35% yields, respectively (Chart 4). The structure of **13** was determined by X-ray crystallographic analysis (Fig. 1).

The 4-Cl, 4-F and 2-F analogues, IIIc (**14**—**16**) and IIId (**18**—**20**), were prepared in the same manner as that used

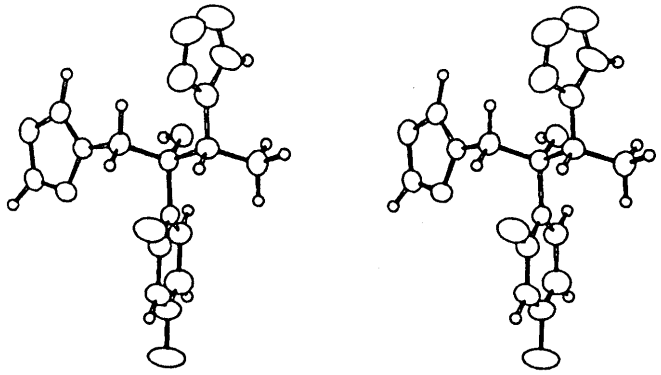
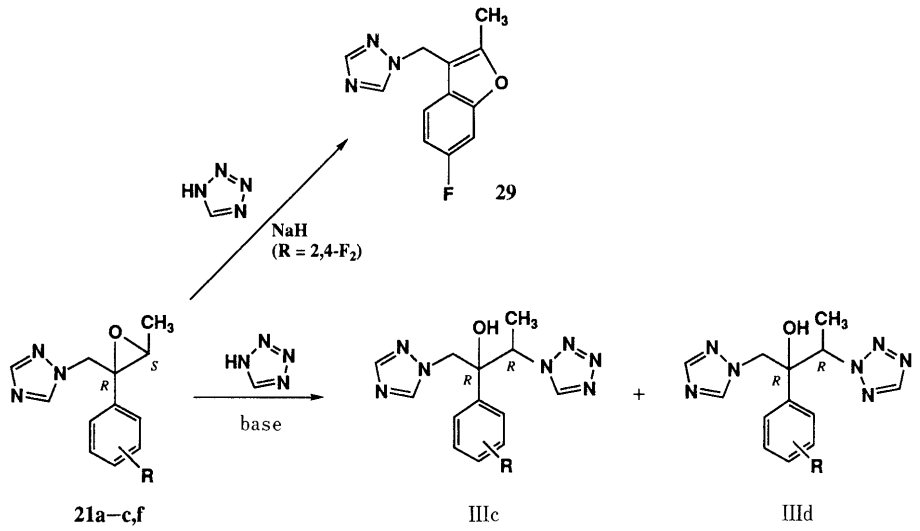


Fig. 1. Stereoscopic View of the Molecule of **13**

for the synthesis of **13** and **17** in good yields, as shown in Chart 4. In these pairs of regioisomers, the more polar substances were assumed to be the 1*H*-1-tetrazolyl compounds (**14**—**16**), and the less polar isomers were assumed to be the 2*H*-2-tetrazolyl compounds (**18**—**20**) by analogy with the case of **13** and **17**.

Antifungal Activity

The bis-azole derivatives III (**1**—**20**) were evaluated for antifungal activity against *C. albicans* TA *in vitro* and *in vivo*, and the results are shown in Table II. The *in vitro* assay was carried out by a paper disc method (Disc)[5a] on



R	base	solvent	IIIc (isolated yield, %)	IIId
2,4-F_2	$(Bu_3Sn)_2O$	toluene	**13** (6)	**17** (9)
	$(Bu_3Sn)_2O$	DMF	**13** (5)	**17** (12)
	Li_2CO_3	DMF	**13** (29)	**17** (35)
4-Cl	Li_2CO_3	DMF	**14** (28)	**18** (49)
4-F	Li_2CO_3	DMF	**15** (20)	**19** (44)
2-F	Li_2CO_3	DMF	**16** (29)	**20** (33)

Chart 4

yeast nitrogen base (YNB) medium and an agar-dilution method[13] on 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 a 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 CDF_1 mice (Charles River, Japan) were used for the *in vivo* assay,[5a] 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). *C. albicans* TA cells were infected intravenously, and the test compounds were administered orally.

All bis-azole derivatives (**1**—**20**) showed growth-inhibitory activity against *C. albicans* TA in the paper disc assay, but the observed MIC values against *C. albicans* TA on YNB and PYG media were mostly in the range of 50—100 μg/ml or more. Lower MIC values (6.25—12.5 μg/ml on PYG medium) were though observed with **7** and **17**. Such high MIC values against *C. albicans* on conventional culture media have often been observed with triazole antifungals such as fluconazole.

In the *in vivo* assay, most of the bis-azoles III were found to have a strong protective effect against *C. albicans* TA infection in mice. All 1*H*-1,2,3-triazol-1-yl derivatives (IIIa), 2,4-F_2- (**1**: ED_{50}, 0.28 mg/kg), 4-Cl- (**2**: ED_{50}, 0.18 mg/kg), 4-F- (**3**: ED_{50}, 0.45 mg/kg), 4-CF_3- (**4**: ED_{50}, 0.18 mg/kg), 4-CF_3O- (**5**: ED_{50}, 0.32 mg/kg) and 2-F-phenyl (**6**: ED_{50}, 0.35 mg/kg), had potent activity comparable or superior to that of fluconazole (ED_{50}, 0.29—0.35 mg/kg). 2*H*-1,2,3-Triazol-2-yl derivatives (IIIb), 2,4-F_2- (**7**: ED_{50}, 0.39 mg/kg), 4-Cl- (**8**: ED_{50}, 2.0 mg/kg), 4-F- (**9**: ED_{50}, 2.0 mg/kg), 4-CF_3- (**10**: ED_{50}, 0.71 mg/kg), 4-CF_3O- (**11**: ED_{50}, >4.0 mg/kg) and 2-F-phenyl (**12**: ED_{50}, 1.41 mg/kg), also showed *in vivo* antifungal activity but were inferior to the corresponding 1*H*-1,2,3-triazol-1-yl derivatives (IIIa).

In the case of 1*H*-1-tetrazolyl derivatives (IIIc), the 2,4-F_2- (**13**: ED_{50}, 0.38 mg/kg) and 2-F-phenyl (**16**: ED_{50}, 0.35 mg/kg) compounds were more potent than the 4-Cl- (**14**: ED_{50}, 0.77 mg/kg) and 4-F- phenyl (**15**: ED_{50}, 2.0 mg/kg) derivatives. Activities of 2*H*-2-tetrazolyl compounds (IIId), 2,4-F_2- (**17**: ED_{50}, 0.18 mg/kg), 4-Cl- (**18**: ED_{50}, 0.35 mg/kg), 4-F- (**19**: ED_{50}, 1.54 mg/kg) and 2-F-phenyl (**20**: ED_{50}, 0.32 mg/kg), were superior to those of the corresponding 1*H*-1-tetrazoyl compounds (IIIc). Within this tetrazole series (IIIc, d), the 2,4-F_2-phenyl-2*H*-2-tetrazolyl derivative (**17**) was the most potent, being about two times more active than fluconazole.

Experimental

Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured with a Horiba FT-200 Fourier-transform IR spectrometer. ^{1}H-NMR spectra were taken on a Varian Gemini-200 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.

Reactions were followed by TLC on TLC plates, Silica gel 60 F_{254} precoated (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).

TABLE II. Antifungal Activity of Bis-azoles (III) against *C. albicans* TA

		In vivo	*In vitro*		
	III	*p.o.* ED_{50} (mg/kg)	Disc YNB (mm)	MIC YNB (μg/ml)	MIC PYG (μg/ml)
IIIa					
	1	0.28	45	>100	100
	2	0.18	35	>100	50
	3	0.45	36	>100	100
	4	0.18	37	>100	>100
	5	0.32	40	>100	>100
	6	0.35	18	>100	100
IIIb					
	7	0.39	48	>100	6.25
	8	2.0	40	100	50
	9	2.0	37	100	50
	10	0.71	41	>100	>100
	11	>4.0[a]	42	>100	>100
	12	1.41	28	>100	100
IIIc					
	13	0.38	40	>100	100
	14	0.77	32	>100	100
	15	2.0	27	>100	100
	16	0.35	39	>100	100
IIId					
	17	0.18	40	100	12.5
	18	0.35	40	>100	100
	19	1.54	30	>100	100
	20	0.32	40	>100	50
Fluconazole		0.29—0.35	18	>100	100

a) A life-span-prolonging effect was observed at the dose of 4 mg/kg.

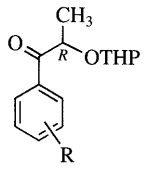
(2*R*)-4′-Chloro-2-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)propiophenone (25b, Table III) A mixture of Mg (turnings, 7.47 g, 307 mmol) and **22b** (20 g, 104.4 mmol) in THF (350 ml) was stirred vigorously to initiate the reaction. When the reaction temperature reached 40 °C, the mixture was cooled to 35 °C in a water bath and **22b** (38.9 g, 203 mmol) was added dropwise to the mixture over a period of 10 min, keeping the reaction temperature at 34—40 °C. The mixture was stirred at 30 °C for 1 h and then cooled at 0 °C in an ice bath. A solution of **24** (60 g, 246 mmol) in THF (60 ml) was added dropwise to the mixture over a period of 15 min. The resulting mixture was stirred at room temperature for 3 h, then a saturated aqueous solution of ammonium chloride (aqueous NH_4Cl, 120 ml) and water (100 ml) were added, and the whole was extracted with ethyl acetate (AcOEt, 500 ml). The extract was washed with water and brine and dried over magnesium sulfate ($MgSO_4$). The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel (900 g). Elution with hexane–AcOEt (30 : 1→10 : 1, v/v) gave **25b** (66 g) as a pale yellow oil.

The reaction of **24** with Grignard reagents (**23c—e**) was carried out in a manner similar to that described above to afford the corresponding propiophenone derivatives (**25c—e**), and their spectral data are summarized in Table III.

(2*R*)-2′-Fluoro-2-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)propiophenone (25f, Table III) Method 1: Mg (turnings, 2.36 g, 98 mmol) was added to a mixture of **22f** (15.8 g, 90.1 mmol), EtBr (0.95 g, 8.7 mmol) and **24** (20 g, 82 mmol) in THF (200 ml) and the resulting mixture was stirred vigorously to initiate the reaction. Stirring was continued for 2 h, then aqueous NH_4Cl (80 ml) and water (80 ml) were added, and the whole was extracted with AcOEt (400 ml). The extract was washed with water and brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel (150 g). Elution with hexane–AcOEt (10 : 1→7 : 1, v/v) gave **25f** (13.7 g) as a pale yellow oil.

Method 2: Mg (11 g, 452 mmol) was added to a mixture of **22f** (37.5 g, 213 mmol) and **24** (100 g, 410 mmol) in THF (450 ml) and the mixture was stirred vigorously to initiate the reaction. When the reaction temperature reached 40 °C, the mixture was cooled to 35 °C in a water bath and **22f** (41.75 g, 239 mmol) was added dropwise to the mixture over a period of 25 min, keeping the reaction temperature at 40—55 °C.

TABLE III. (2*R*)-2-(3,4,5,6-Tetrahydro-2*H*-pyran-2-yloxy)propiophenones (**25**)



25	R	Yield (%)	Appearance	^{1}H-NMR (in $CDCl_3$) δ	IR (neat) $_{max}\nu_{C=O}$ cm^{-1}	$[\alpha]_D$ (*c*, %) {°C} (in MeOH)
b	4-Cl	99	Colorless oil	1.46, 1.52 (3H, d each, *J* = 7 Hz), 1.10—2.10 (6H, m), 3.30—4.02 (2H, m), 4.57—4.76 (1H, m), 4.90, 5.15 (1H, q each, *J* = 7 Hz), 7.30—7.60 (2H, m), 7.85—8.20 (2H, m)	1697	+41.5 (2.5) {25}
c	4-F	99	Pale yellow oil	1.46, 1.53 (3H, d each, *J* = 7 Hz), 1.40—1.92 (6H, m), 3.31—3.58 (1H, m), 3.63—3.96 (1H, m), 4.55—4.80 (1H, m), 4.92, 5.17 (1H, q each, *J* = 7 Hz), 7.06—7.18 (2H, m), 8.03—8.17 (2H, m)	1695	+7.8 (0.61) {20}
d	4-CF_3	74	Pale yellow oil	1.48, 1.54 (3H, d each, *J* = 7 Hz), 1.36–1.92 (6H, m), 3.31—3.58 (1H, m), 3.63—3.97 (1H, m), 4.58—4.78 (1H, m), 4.92, 5.18 (1H, q each, *J* = 7 Hz), 7.70—7.76 (2H, m), 8.14 (1H, d, *J* = 8.2 Hz), 8.2 (1H, d, *J* = 8.2 Hz)	1700	+45.6 (0.66) {20}
e	4-OCF_3	100	Pale yellow oil	1.47, 1.52 (3H, d each, *J* = 7 Hz), 1.33—2.0 (6H, m), 3.30—4.0 (2H, m), 4.55—4.85 (1H, m), 4.91, 5.16 (1H, q each, *J* = 7 Hz), 7.20—7.38 (2H, m), 8.07—8.24 (2H, m)	1699	+42.8 (2.8) {25}
f	2-F	66[a] 48[b]	Pale yellow oil	1.43, 1.56 (3H, d each, *J* = 7 Hz), 1.39—2.01 (6H, m), 3.32—3.61 (1H, m), 3.71—3.98 (1H, m), 4.65—4.88 (1H, m), 4.97, 5.19 (1H, q each, *J* = 7 Hz), 7.08—7.29 (2H, m), 7.46—7.57 (1H, m), 7.83—7.88 (1H, m)	1700	+14.5 (0.5) {20}

a) In the presence of EtBr. *b*) Without EtBr.

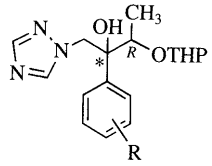
The resulting mixture was stirred at 35—40°C for 1.5 h then cooled in an ice bath. Aqueous NH_4Cl (200 ml) and water (200 ml) were added, and the whole was extracted with AcOEt (300 ml × 2, 100 ml). The extracts were combined, washed with water and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel (1 kg). Elution with hexane–AcOEt (15 : 1→6 : 1, v/v) gave **25f** (49 g) as a pale yellow oil.

2-(4-Chlorophenyl)-2-[(1*R*)-1-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)-ethyl]oxirane (26b) Under a nitrogen atmosphere, trimethylsulfoxonium iodide (67.8 g, 308 mmol) was added portionwise to a stirred mixture of NaH (60% oil dispersion, 11.8 g, 295 mmol) and DMSO (450 ml) under ice cooling over a period of 45 min. The resulting mixture was stirred at room temperature for 45 min and then cooled in an ice bath. A solution of **25b** (69 g, 257 mmol) in DMSO (100 ml) was added to the mixture and the whole was stirred at room temperature for 2 h. The mixture was poured into cold water (600 ml) and extracted with AcOEt (400 ml, 300 ml × 2). The extracts were combined, washed successively with water (150 ml × 2) and brine (100 ml), and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give **26b** (74.5 g) as a pale yellow oil, which contained a mineral oil and was used for the next step without purification. A part of the product was purified by chromatography on silica gel (hexane–AcOEt, 20 : 1→5 : 1, v/v) to afford **26b** as a colorless oil. IR (neat): 2493, 1558, 1540, 1508, 1456, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10—1.26 (3H, m), 1.40—1.95 (6H, m), 2.68—2.80 (1H, m), 3.00—3.37 (1H, m), 3.42—3.95 (2H, m), 4.09, 4.25 (1H, q each, J=6.6 Hz), 4.68—4.94 (1H, m), 7.22—7.58 (4H, m).

In a similar manner, **26c—f** were prepared and used for the next step without purification.

(3*R*)-2-(4-Chlorophenyl)-3-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (27b, Table IV) 1*H*-1,2,4-triazole (42.1 g, 610 mmol) was added portionwise to a stirred mixture of NaH (60% oil dispersion, 22.2 g, 560 mmol) and DMF (300 ml) over a period of 30 min under a nitrogen atmosphere at 0 °C. The mixture was stirred for 15 min at room temperature and the solution of **26b** obtained above (52 g) in DMF (50 ml) was added. The resulting mixture was stirred at 80 °C for 4 h with stirring. After being cooled, the mixture was diluted with water (400 ml) and the whole was extracted with AcOEt (200 ml × 3). The extract was washed with water and brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (500 g). Elution with hexane–AcOEt (3 : 2)→AcOEt–acetone

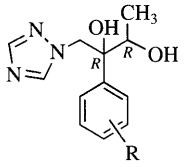
TABLE IV. (3*R*)-2-(Substituted phenyl)-3-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (**27**)



27	R	Yield[a] (%)	Appearance	^{1}H-NMR (in $CDCl_3$) δ
b	4-Cl	84	Pale yellow oil	0.92—1.18 (3H, m), 1.40—1.95 (6H, m), 3.40—3.66 (1H, m), 3.70—4.95 (6H, m), 7.15—8.06 (6H, m)
c	4-F	72.7	Pale yellow oil	0.99, 1.13 (3H, d each, J=6.4 Hz), 1.40—1.95 (6H, m), 3.40—3.60 (1H, m), 3.74—4.17 (2H, m), 4.30—5.01 (4H, m), 6.90—7.55 (4H, m), 7.74—8.07 (2H, m)
d	4-CF_3	81.7	Pale yellow oil	1.02, 1.13 (3H, d each, J=6.4 Hz), 1.45—1.98 (6H, m), 3.46—3.63 (1H, m), 3.88—4.32 (3H, m), 4.55—4.91 (3H, m), 7.36—7.58 (4H, m), 7.77—7.97 (2H, m)
e	4-OCF_3	80.8	Pale yellow oil	0.95—1.95 (9H, m), 3.40—3.60 (1H, m), 3.75—5.00 (6H, m), 7.05—8.09 (6H, m)
f	2-F	70	Pale yellow oil	0.99, 1.12 (3H, d each, J=6.2 Hz), 1.45—1.89 (6H, m), 3.40—3.60 (1H, m), 3.74—4.17 (2H, m), 4.29—5.02 (4H, m), 6.92—7.50 (4H, m), 7.71—8.09 (2H, m).

a) Based on the propiophenone **25**.

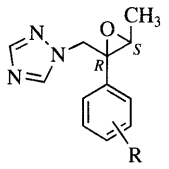
TABLE V. (2*R*,3*R*)-2-(Substituted phenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2,3-butanediol (**28**)



28	R	Yield (%)	mp (°C) (Solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ	IR ν (KBr) cm^{-1}
b	4-Cl	60	90—91 (A)	$C_{12}H_{14}ClN_3O_2$	53.84 (53.62)	5.27 5.39	15.70 15.75)	0.97 (3H, d, J=7 Hz), 3.48 (1H, s), 4.12 (1H, q, J= 7 Hz), 4.36 (1H, br), 4.54 (1H, d, J=14.2 Hz), 4.71 (1H, d, J=14.2 Hz), 7.16 (2H, d, J=8.8 Hz), 7.23 (2H, d, J=8.8 Hz), 7.87 (1H, s), 7.95 (1H, s)	3380, 1600, 1512, 1493, 1365, 1277
c	4-F	50	102—103 (A–H)	$C_{12}H_{14}FN_3O_2$	57.36 (57.59	5.62 5.77	16.72 16.73)	0.97 (3H, d, J=6.4 Hz), 2.87 (1H, d, J=8.2 Hz), 4.12 (1H, q, J= 6.4 Hz), 4.33 (1H, s), 4.54 (1H, d, J=14 Hz), 4.72 (1H, d, J=14 Hz), 6.92—7.03 (2H, m), 7.15—7.24 (2H, m), 7.72 (1H, s), 7.87 (1H, s)	3240, 1604, 1512, 1360, 1280, 1225
d	4-CF_3	47	133—135 (A–H)	$C_{13}H_{14}F_3N_3O_2$	51.83 (51.74	4.68 4.65	13.95 13.98)	0.97 (3H, d, J=6.4 Hz), 2.98 (1H, d, J=8 Hz), 4.17 (1H, q, J= 6.4 Hz), 4.49 (1H, s), 4.59 (1H, d, J=14 Hz), 4.75 (1H, d, J=14 Hz), 7.37 (2H, d, J=9 Hz), 7.55 (2H, d, J=9 Hz), 7.75 (1H, s), 7.87 (1H, s)	3520, 1620, 1515, 1412, 1340, 1135
e	4-OCF_3	71	103—104 (IPE)	$C_{13}H_{14}F_3N_3O_3$	49.21 (49.49	4.45 4.50	13.24 13.26)	0.98 (3H, d, J=6.4 Hz), 2.90 (1H, d, J=7.6 Hz), 4.14 (1H, m), 4.38 (1H, s), 4.56 (1H, d, J=14.4 Hz), 4.73 (1H, d, J=14.4 Hz), 7.14 (2H, d, J=8.4 Hz), 7.20—7.32 (2H, m), 7.75 (1H, s), 7.88 (1H, s)	3180, 1595, 1511, 1415, 1371, 1279
f	2-F	62	65—66 (Et_2O)	$C_{12}H_{14}FN_3O_2$	57.36 (57.48	5.62 5.58	16.72 16.88)	0.98 (3H, d, J=6.4 Hz), 2.54 (1H, d, J=9.8 Hz), 4.32—4.42 (1H, m), 4.72 (1H, s), 4.80 (1H, d, J=14 Hz), 4.89 (1H, d, J=14 Hz), 6.92—7.03 (2H, m), 7.19—7.45 (2H, m), 7.80 (1H, s), 7.82 (1H, s)	3400, 1510, 1490, 1405, 1270, 1210

a) Recrystallization solvents: A, ethyl acetate; H, hexane; IPE, diisopropyl ether; Et_2O, diethyl ether.

TABLE VI. (2*R*,3*S*)-3-Methyl-2-(substituted phenyl)-2-(1*H*-1,2,4-triazol-1-yl)methyloxiranes (**21**)



21	R	Yield (%)	mp (°C) (Solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ	IR ν (KBr) cm^{-1}	$[\alpha]_D$ (*c*, %) {20°C} (in MeOH)
b	4-Cl	88	51—53 (IPE)	$C_{12}H_{12}ClN_3O$	57.72 (57.63)	4.84 (4.89)	16.83 (16.83)	1.63 (3H, d, J=5.8 Hz), 3.15 (1H, q, J=5.8 Hz), 4.44 (1H, d, J=14.8 Hz), 4.87 (1H, d, J=14.8 Hz), 7.10 (2H, dt, J=6.6, 7.24 Hz), 7.24 (2H, dt, J=6.6, 2.2 Hz), 7.87 (1H, s), 7.95 (1H, s)	1597, 1508, 1484, 1344, 1273	−32.5 (1.0)
c	4-F	77	54—55 (IPE)	$C_{12}H_{12}FN_3O$	61.79 (61.32	5.19 5.23	18.02 17.92)	1.64 (3H, d, J=5.6 Hz), 3.16 (1H, q, J=5.6 Hz), 4.45 (1H, d, J=15 Hz), 4.84 (1H, d, J=15 Hz), 6.89—7.00 (2H, m), 7.09—7.19 (2H, m), 7.87 (1H, s), 7.93 (1H, s)	1605, 1515, 1435, 1350, 1272, 1220	−9.8 (1.0)
d	4-CF_3	85	81—82 (IPE)	$C_{13}H_{12}F_3N_3O$	55.12 (54.86	4.27 4.28	14.83 14.80)	1.65 (3H, d, J=5.6 Hz), 3.17 (1H, q, J=5.6 Hz), 4.47 (1H, d, J=15 Hz), 4.94 (1H, d, J=15 Hz), 7.30 (2H, d, J=8 Hz), 7.53 (2H, d, J=8 Hz), 7.87 (1H, s), 7.98 (1H, s)	1620, 1510, 1425, 1330, 1270, 1165	−15.7 (1.05)
e	4-OCF_3	82	82—83 (IPE)	$C_{13}H_{12}F_3N_3O_2$	52.18 (52.37	4.04 4.10	14.04 14.07)	1.64 (3H, d, J=5.4 Hz), 3.17 (1H, q, J=5.4 Hz), 4.46 (1H, d, J=14.6 Hz), 4.88 (1H, d, J=14.6 Hz), 7.11 (2H, d, J=9 Hz), 7.21 (2H, d, J=9 Hz), 7.89 (1H, s), 7.97 (1H, s)	1598, 1512, 1450, 1346, 1272, 1228	−24.8 (1.0)
f	2-F	77	72—74 (IPE–H)	$C_{12}H_{12}FN_3O$	61.79 (61.49	5.19 5.17	18.02 18.29)	1.65 (3H, d, J=5.6 Hz), 3.22 (1H, q, J=5.6 Hz), 4.46 (1H, d, J=14 Hz), 4.92 (1H, d, J=14 Hz), 6.98—7.10 (3H, m), 7.18—7.29 (1H, m), 7.82 (1H, s), 7.93 (1H, s)	1598, 1480, 1410, 1350, 1250, 1105	−7.3 (1.0)

a) Recrystallization solvents: IPE, diisopropyl ether; H, hexane.

(4 : 1) gave **27b** (53 g) as a colorless oil.

The reaction of **26c—f** with 1*H*-1,2,4-triazole was carried out in a manner similar to that described above to give **27c—f** (Table IV).

(2*R*,3*R*)-2-(4-Chlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2,3-butanediol (28b, Table V) TsOH hydrate (28.6 g, 150 mmol) was added to a solution of **27b** (53 g, 150 mmol) in MeOH (500 ml). The mixture was stirred at room temperature for 1 h and then neutralized with an aqueous solution of sodium bicarbonate (aqueous $NaHCO_3$). The resulting mixture was concentrated *in vacuo* to *ca.* 100 ml and extracted with AcOEt (400 ml × 3). The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Crystallization of the residue from AcOEt gave **28b** (12.5 g, 31.2%) as white powdery crystals. The mother liquor was concentrated *in vacuo* and the residue was chromatographed on silica gel (350 g). Elution with AcOEt–MeOH (50 : 1→25 : 1, v/v) followed by crystallization from a mixture of dichloromethane (CH_2Cl_2) and diisopropyl ether (iso-Pr_2O) gave additional **28b** (11.5 g, 28.7%).

The diols **28c—f** (Table V) were prepared from **27c—f** in a manner similar to that described above.

(2*R*,3*S*)-2-(4-Chlorophenyl)-3-methyl-2-(1*H*-1,2,4-triazol-1-yl)methyloxirane (21b, Table VI) Methanesulfonyl chloride (6.25 g, 54.5 mmol) was added to a mixture of **28b** (12.4 g, 46.3 mmol) and triethylamine (7.6 ml, 54.5 mmol) in AcOEt (200 ml) at 0 °C. The mixture was stirred at room temperature for 45 min, then washed successively with water and brine, and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave an oil, which was dissolved in a mixture of NaOMe (28% in MeOH, 10.5 g, 55 mmol) and MeOH (150 ml). The mixture was stirred at 0 °C for 15 min, and then concentrated *in vacuo*. The residue was extracted with AcOEt (150 ml), and the extract was washed successively with water and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a solid mass, which was purified by silica gel column chromatography (150 g, AcOEt–CH_2Cl_2–MeOH, 16 : 4 : 1, v/v). Evaporation of the eluent and crystallization of the residue from iso-Pr_2O gave **21b** (10.2 g)[14] as colorless needles.

The oxiranes **21c—f** (Table VI) were prepared in a manner similar to that described above.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(1*H*-1,2,3-triazol-1-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (1, Table I) and (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(2*H*-1,2,3-triazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (7, Table I) Method A: NaH (60% oil dispersion, 0.87 g, 21.8 mmol) was added portionwise to a solution of 1*H*-1,2,3-triazole (2.06 g, 29.9 mmol) in DMF (50 ml) at 0 °C and the mixture was stirred at room temperature for 10 min. Compound **21a** (5.0 g, 19.9 mmol) was added and the resulting mixture was heated at 80 °C for 10 h. After being cooled, it was poured into ice water and the whole was extracted with AcOEt (200 ml × 3). The extract was washed with brine (100 ml × 2), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (150 g, AcOEt→CH_2Cl_2–acetone, 1 : 1, v/v). The eluent containing a less polar isomer was concentrated and the residue was crystallized from iso-Pr_2O to afford **7** (1.14 g) as a colorless crystalline powder. The eluent containing the more polar isomer was concentrated *in vacuo* and the residue was crystallized from iso-Pr_2O to give **1** (1.53 g) as colorless crystals.

Method B: A mixture of **21a** (14.6 g, 58.1 mmol), 1*H*-1,2,3-triazole (6.2 g, 87.1 mmol) and K_2CO_3 (24 g, 174 mmol) in DMF (140 ml) was heated at 80 °C for 21 h. AcOEt (140 ml) was added to the mixture, and the insoluble material was filtered off. The filtrate was evaporated *in vacuo* and the residue was partitioned between AcOEt (200 ml) and water (200 ml). The organic layer was washed with brine (150 ml × 2) and dried over $MgSO_4$. Purification by silica gel chromatography followed by crystallization in the same manner as that described in method A gave **1** (8.7 g) and **7** (6.7 g).

The reaction of **21b—f** with 1*H*-1,2,3-triazole in the presence of NaH or K_2CO_3 was carried out in a manner similar to that described above to give the compounds **2—6** and **8—12** (Table I).

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(1*H*-tetrazol-1-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (13, Table I) and (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(2*H*-tetrazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17, Table I) Method C: A mixture of **21a** (11 g, 43.8 mmol), 1*H*-tetrazole (3.3 g, 47 mmol), $(Bu_3Sn)_2O$ (2.2 ml, 4.3 mmol) and DMF (220 ml) was heated at 110 °C for 7 d. The mixture was cooled, the solvent was evaporated *in vacuo* and the residue was partitioned between AcOEt (500 ml) and brine (150 ml). The organic layer was washed with brine (150 ml), and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel (2 kg). Elution with AcOEt→CH_2Cl_2–acetone (2 : 1, v/v) gave **17** as a less polar substance, which was treated with 4 N HCl in AcOEt to give **17**·HCl (1.8 g) as a colorless powder. The eluent containing the more polar isomer was concentrated to give **13** (0.65 g) as a colorless crystalline powder.

(2*R*,3*R*)-2-(4-Chlorophenyl)-3-(1*H*-tetrazol-1-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (14, Table I) and (2*R*,3*R*)-2-(4-Chlorophenyl)-3-(2*H*-tetrazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (18, Table I) Method D: A mixture of **21b** (2.0 g, 8.0 mmol), 1*H*-tetrazole (1.11 g, 15.9 mmol), Li_2CO_3 (5.86 g, 79 mmol) and DMF (40 ml) was heated at 110 °C for 8 h with stirring. The mixture was cooled, AcOEt (100 ml) was added, and the insoluble material was removed by filtration. The filtrate was concentrated *in vacuo* and then the residue was dissolved in AcOEt

(150 ml). This solution was washed with brine (50 ml × 2) and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel (200 g, CH_2Cl_2–acetone, 3 : 1→2 : 1, v/v). The eluent containing the less polar isomer was concentrated and the residue was crystallized from iso-Pr_2O to give **18** (1.26 g) as a colorless crystalline powder. The eluent containing the more polar isomer was concentrated to give **14** (0.72 g) as a colorless oil. This oil was dissolved in AcOEt and treated with HCl to give **14**·HCl (0.80 g) as a colorless powder.

The reaction of **21a, c, f** with 1*H*-tetrazole in the presence of Li_2CO_3 was carried out in a manner similar to that described in method D to obtain 1-tetrazolyl (**13**, **15**, **16**) and 2-tetrazolyl (**17**, **19**, **20**) derivatives (Table I).

6-Fluoro-2-methyl-3-(1*H*-1,2,4-triazol-1-yl)methylbenzofuran (29) Compound **21a** (0.502 g, 2 mmol) was allowed to react with 1*H*-tetrazole (0.28 g, 4 mmol) according to method A. The product was purified by silica gel chromatography (AcOEt–CH_2Cl_2, 4 : 1) to give **29** (0.045 g, 10%) as colorless crystals. mp 105—106 °C (from iso-Pr_2O). ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 5.38 (2H, s), 6.96—7.01 (1H, m), 7.12—7.28 (2H, m), 7.96 (1H, s), 8.00 (1H, s). *Anal.* Calcd for $C_{12}H_{10}FN_3O$: C, 62.33; H, 4.35; N, 18.28. Found: C, 62.11; H, 4.39; N, 18.15.

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References and Notes

1) Part III: A. Tasaka, K. Teranishi, Y. Matsushita, N. Tamura, R. Hayashi, K. Okonogi, K. Itoh, *Chem. Pharm. Bull.*, **42**, 85 (1994).
2) V. St. Georgiev, *Ann. N. Y. Acad. Sci.*, **544**, 1 (1988).
3) H. Washton, *Diagn. Microbiol. Infec. Dis.*, **12**, 229S (1989).
4) J. Heeres, L. J. J. Backx, J. Van Cutsem, *J. Med. Chem.*, **27**, 894 (1984).
5) *a*) A. Tasaka, N. Tamura, Y. Matsushita, K. Teranishi, R. Hayashi, K. Okonogi, K. Itoh, *Chem. Pharm. Bull.*, **41**, 1035 (1993); *b*) A. Tasaka, N. Tamura, Y. Matsushita, R. Hayashi, K. Okonogi, K. Itoh, *ibid.*, **41**, 1043 (1993).
6) The racemate of 1,3-bis(1*H*-1,2,4-triazol-1yl)-2-halogenophenyl-2-butanol was reported in patents. Pfizer Ltd., Eur. Pat. Appl. EP 122056 [*Chem. Abstr.*, **102**, 132042*z* (1985)], Imperial Chemical Industries PLC, Eur. Pat. Appl. EP 122693 [*Chem. Abstr.*, **102**, 149273*y* (1985)].
7) The 4-Cl, 4-F and 4-CF_3-phenyl analogues of fluconazole were reported to have potent *in vivo* antifungal activities. K. Richardson, K. Cooper, M.S. Marriott, M. H. Tarbit, P. F. Troke, P. J. Whittle, *Ann. N.Y. Acad. Sci.*, **544**, 4 (1988).
8) D. D. Mazza, M. G. Reinecke, *J. Org. Chem.*, **53**, 5800 (1988).
9) N. D. Dawson, A. Burger, *J. Org. Chem.*, **18**, 207 (1953).
10) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
11) The ratio was determined by HPLC analysis after conversion to the diol **28**.
12) Pfizer Ltd., Eur. Pat. Appl. EP 195557 [*Chem. Abstr.*, **106**, 50226*f* (1987)].
13) The Japanese Society for Medical Mycology, *Jpn. J. Med. Mycol.*, **32**, 239 (1991).
14) Synthesis of compound **21b** was reported in a patent: Sankyo Co., Ltd., Eur. Pat. Appl. EP 332387 A1 [*Chem. Abstr.*, **113**, 231379 (1990)].