Optically Active Antifungal Azoles. VI.[1] Synthesis and Antifungal Activity of *N*-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-*N'*-(4-substituted phenyl)-3(2*H*,4*H*)-1,2,4-triazolones and 5(1*H*,4*H*)-tetrazolones

Tomoyuki KITAZAKI,* Norikazu TAMURA, Akihiro TASAKA, Yoshihiro MATSUSHITA, Ryogo HAYASHI, Kenji OKONOGI, and Katsumi ITOH

Pharmaceutical Research Laboratories III, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan. Received August 10, 1995; accepted October 19, 1995

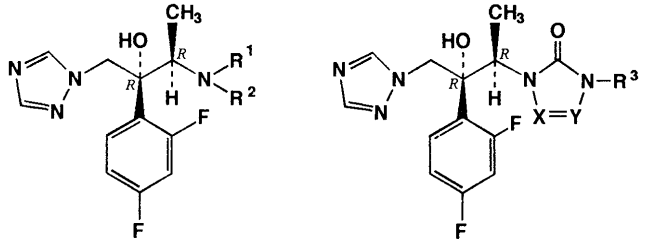
A new series of optically active antifungal azoles, *N*-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-*N'*-(4-substituted phenyl)-3(2*H*,4*H*)-1,2,4-triazolones (1,2) and 5(1*H*,4*H*)-tetrazolones (3), were prepared from the triflate derivative of (1*S*)-1-[(2*R*)-2-(2,4-difluorophenyl)-2-oxiranyl]ethanol (13) by an *S*N2 displacement reaction with the anion of an azolone (17—19) and subsequent ring-opening reaction with 1*H*-1,2,4-triazole. The optically active oxiranylethanol 13 was synthesized from methyl (*R*)-lactate in a stereocontrolled manner. The azolones 1—3 prepared showed potent antifungal activities *in vitro* and *in vivo*.

Key words optically active antifungal azole; 1,2,3-trisubstituted-2-butanol; triazolone; tetrazolone; stereocontrolled synthesis; antifungal activity

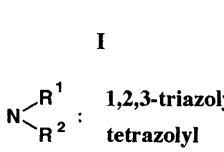
For the treatment of systemic fungal infections, orally active antifungal azoles such as fluconazole and itraconazole have been developed and widely used in antifungal therapy.[2] In recent years, the emergence of fungi resistant to fluconazole, as well as clinical failures in the treatment have been reported.[3] Therefore, there is still a need to develop new and effective antifungal agents with a broad antifungal spectrum.

In the course of our search for new antifungal azoles, we established a method for the stereocontrolled synthesis of optically active 1,2,3-trisubstituted-2-butanol derivatives starting from methyl (*R*)-lactate.[4] In a preceding report, we designed bis-azole derivatives with the general formula I and described the synthesis and the antifungal activity of optically active bis-azoles containing a 1*H*-1,2,3-triazole or 1*H*-tetrazole nucleus.[5]

Subsequently we designed a new structural type of nitrogen-containing triazole derivative, that is the azolone depicted by the general formula II. As seen from the structure of II, it is possible to vary the atoms represented with X and Y in the azolone nucleus, as well as to modify the substituent R^3, to obtain a variety of derivatives with different physicochemical properties which might influence the potency and the pharmacokinetic profiles. We chose triazolone (X=N, Y=CH and X=CH, Y=N) and tetrazolone (X=Y=N) nuclei as the azolone moiety and a 4-substituted phenyl group as the substituent R^3. Thus, we prepared the three types of derivatives (Chart 2), 2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-(4-substituted phenyl)-3(2*H*,4*H*)-1,2,4-triazolones (**1**), 4-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-2-(4-substituted phenyl)-3(2*H*,4*H*)-1,2,4-triazolones (**2**) and 1-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-(4-substituted phenyl)-5(1*H*,4*H*)-tetrazolones (**3**). For the substituent R on the benzene ring linked to the azolone moiety, we selected fluorine-containing groups, *i.e.*, F, CF_3, OCF_3, OCF_2CF_2H, OCH_2CF_3, $OCH_2CF_2CF_2H$

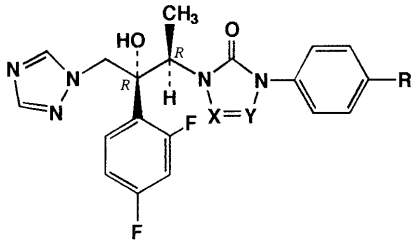


I II



1,2,3-triazolyl
tetrazolyl

Chart 1



1 : X = N, Y = CH
2 : X = CH, Y = N
3 : X = Y = N

	R
a	F
b	CF_3
c	OCF_3
d	OCF_2CF_2H
e	OCH_2CF_3
f	$OCH_2CF_2CF_2H$
g	$OCH_2CF_2CF_3$

Chart 2

* To whom correspondence should be addressed.

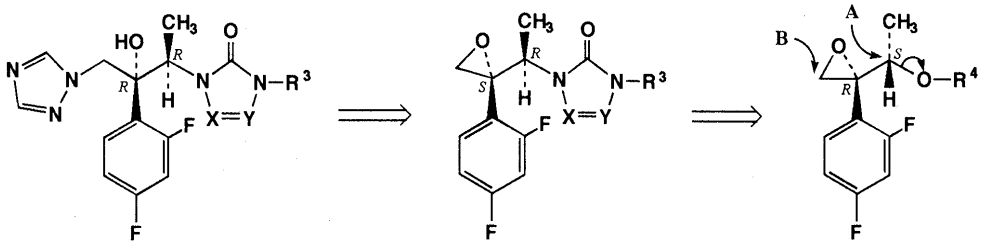
Table 1. Physicochemical and Spectral Data for the Azolones **1**—**3**

No.	Yield[a] (%)	mp (°C) (Solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ	IR (KBr) cm^{-1}	$[\alpha]_D$ {°C} MeOH (*c*)
1a	53	AP[c]	$C_{20}H_{17}F_3N_6O_2 \cdot H_2O$	53.57 (53.95)	4.27 (4.14)	18.74 (18.45)	1.30 (3H, d, J=7 Hz), 4.36 (1H, d, J=14.2 Hz), 5.01 (1H, d, J=14.2 Hz), 5.08 (1H, q, J=7 Hz), 5.44 (1H, s), 6.72—6.90 (2H, m), 7.12—7.31 (2H, m), 7.48—7.65 (3H, m), 7.69 (1H, s), 7.76 (1H, s), 7.94 (1H, s) SIMS (m/z): 431 (MH^+)	1703, 1620, 1599	—
1b	42	AP	$C_{21}H_{17}F_5N_6O_2$	52.50 (52.35)	3.57 (3.68)	17.49 (17.44)	1.31 (3H, d, J=7 Hz), 4.38 (1H, d, J=15 Hz), 5.03 (1H, d, J=15 Hz), 5.09 (1H, q, J=7 Hz), 5.35 (1H, br), 6.76—6.86 (2H, m), 7.50—7.62 (1H, m), 7.66—7.84 (5H, m), 7.87 (1H, s), 7.94 (1H, s)	1710, 1616, 1498	—
1c	47	AP	$C_{21}H_{17}F_5N_6O_3$	50.81 (50.49)	3.45 (3.50)	16.93 (16.67)	1.31 (3H, d, J=7 Hz), 4.37 (1H, d, J=14.2 Hz), 5.03 (1H, d, J=14.2 Hz), 5.09 (1H, q, J=7 Hz), 5.41 (1H, s), 6.76—6.90 (2H, m), 7.38 (2H, d, J=9 Hz), 7.51—7.64 (1H, m), 7.65 (2H, d, J=9 Hz), 7.70 (1H, s), 7.81 (1H, s), 7.94 (1H, s)	1711, 1620, 1562, 1516, 1500, 1427	—
1d	65	AP	$C_{22}H_{18}F_6N_6O_3$	50.01 (49.77)	3.43 (3.46)	15.90 (16.11)	1.31 (3H, d, J=7 Hz), 4.37 (1H, d, J=14.2 Hz), 5.02 (1H, d, J=14.2 Hz), 5.09 (1H, q, J=7 Hz), 5.41 (1H, s), 5.94 (1H, tt, J=53, 2.8 Hz), 6.75—6.90 (2H, m), 7.38 (2H, d, J=9 Hz), 7.50—7.70 (1H, m), 7.63 (2H, d, J=9 Hz), 7.70 (1H, s), 7.80 (1H, s), 7.94 (1H, s)	1710, 1691, 1620, 1564, 1511	−23.4° {20} (1.0)
1e	59	162—164 (DE-IPE)	$C_{22}H_{19}F_5N_6O_3$	51.77 (51.78)	3.75 (3.77)	16.46 (16.56)	1.30 (3H, d, J=7 Hz), 4.36 (1H, d, J=14.8 Hz), 4.41 (2H, q, J=8 Hz), 5.02 (1H, d, J=14.8 Hz), 5.09 (1H, q, J=7 Hz), 5.48 (1H, s), 6.74—6.90 (2H, m), 7.09 (2H, d, J=9 Hz), 7.48—7.65 (1H, m), 7.53 (2H, d, J=9 Hz), 7.69 (1H, s), 7.76 (1H, s), 7.95 (1H, s)	1708, 1697, 1660, 1619, 1558, 1517	−23.3° {20} (1.0)
1f	63	150—151 (IPE) 154—155 (EA-IPE)	$C_{23}H_{20}F_6N_6O_3$	50.93 (50.91)	3.72 (3.84)	15.49 (15.47)	1.30 (3H, d, J=7 Hz), 4.37 (1H, d, J=15 Hz), 4.40 (2H, tt, J=11.8, 1.4 Hz), 5.02 (1H, d, J=15 Hz), 5.09 (1H, q, J=7 Hz), 5.47 (1H, s), 6.07 (1H, tt, J=53, 4.8 Hz), 6.75—6.88 (2H, m), 7.07 (2H, dt, J=9, 2.2 Hz), 7.53 (2H, dt, J=9, 2.2 Hz), 7.50—7.64 (1H, m), 7.69 (1H, s), 7.75 (1H, s), 7.95 (1H, s)	1716, 1697, 1618, 1558, 1517, 1506	−22.0° {20} (1.0)
1g	46	166—167 (DE-IPE)	$C_{23}H_{19}F_7N_6O_3$	49.29 (49.32)	3.42 (3.36)	15.00 (15.13)	1.30 (3H, d, J=7 Hz), 4.36 (1H, d, J=14.8 Hz), 4.48 (2H, t, J=12 Hz), 5.02 (1H, d, J=14.8 Hz), 5.09 (1H, q, J=7 Hz), 5.48 (1H, s), 6.75—6.90 (2H, m), 7.09 (2H, d, J=9 Hz), 7.48—7.64 (1H, m), 7.54 (2H, d, J=9 Hz), 7.70 (1H, s), 7.76 (1H, s), 7.95 (1H, s)	1708, 1699, 1662, 1619, 1558, 1517	−19.8° {20} (1.0)
2a	55	132—133 (EA-H)	$C_{20}H_{17}F_3N_6O_2$	55.81 (55.64)	3.98 (4.05)	19.53 (19.48)	1.23 (3H, d, J=7.2 Hz), 4.15 (1H, d, J=14.2 Hz), 4.95 (1H, dq, J=7.2, 1.6 Hz), 5.08 (1H, d, J=14.2 Hz), 5.56 (1H, d, J=1.6 Hz), 6.78—6.91 (2H, m), 7.14 (2H, t, J=9.4 Hz), 7.39—7.62 (1H, m), 7.77 (1H, s), 7.80 (1H, s), 7.95 (1H, s), 7.99 (2H, dd, J=9.4, 4.8 Hz)	1691, 1620, 1599, 1566, 1512	−14.4° {20} (0.6)
2b	24	141—142 (EA-H)	$C_{21}H_{17}F_5N_6O_2$	52.50 (52.77)	3.57 (3.70)	17.49 (17.26)	1.24 (1H, d, J=7.2 Hz), 4.15 (1H, d, J=14 Hz), 4.97 (1H, dq, J=7.2, 1.4 Hz), 5.08 (1H, q, J=14 Hz), 5.56 (1H, d, J=1.4 Hz), 6.76—6.91 (2H, m), 7.38—7.59 (1H, m), 7.72 (2H, d, J=8.6 Hz), 7.77 (1H, s), 7.80 (1H, s), 8.00 (1H, s), 8.20 (2H, d, J=8.6 Hz)	1701, 1618, 1597, 1568, 1520	−12.5° {20} (1.0)
2c	68	AP	$C_{21}H_{17}F_5N_6O_3$	50.81 (50.70)	3.45 (3.43)	16.93 (16.63)	1.24 (3H, d, J=7.2 Hz), 4.14 (1H, d, J=14.4 Hz), 4.96 (1H, dq, J=7.2, 1.6 Hz), 5.08 (1H, d, J=14.4 Hz), 5.56 (1H, d, J=1.6 Hz), 6.75—6.90 (2H, m), 7.31 (2H, d, J=9.2 Hz), 7.48—7.52 (1H, m), 7.77 (1H, s), 7.80 (1H, s), 7.97 (1H, s), 8.08 (2H, d, J=9.2 Hz)	1712, 1697, 1620, 1599, 1512	−13.4° {20} (1.0)
2d	57	147—148 (EA-H)	$C_{22}H_{18}F_6N_6O_3$	50.01 (49.71)	3.43 (3.41)	15.90 (15.85)	1.24 (3H, d, J=7.2 Hz), 4.14 (1H, d, J=14.2 Hz), 4.95 (1H, dq, J=7.2, 1.6 Hz), 5.08 (1H, d, J=14.2 Hz), 5.55 (1H, d, J=1.6 Hz), 5.93 (1H, tt, J=53, 2.8 Hz), 6.71—6.90 (2H, m), 7.30 (2H, d, J=9.2 Hz), 7.34—7.51 (1H, m), 7.77 (1H, s), 7.80 (1H, s), 7.96 (1H, s), 8.06 (2H, d, J=9.2 Hz)	1699, 1619, 1508	−11.3° {20} (0.6)
2e	68	98—99 (EA-H)	$C_{22}H_{19}F_5N_6O_3$	51.77 (51.52)	3.75 (3.98)	16.46 (16.65)	1.24 (3H, d, J=7.2 Hz), 4.15 (1H, d, J=14.2 Hz), 4.39 (2H, q, J=8.2 Hz), 4.95 (1H, dq, J=7.2, 1.6 Hz), 5.09 (1H, d, J=14.2 Hz), 5.56 (1H, d, J=1.6 Hz), 6.70—6.90 (2H, m), 7.03 (2H, d, J=9.2 Hz), 7.34—7.53 (1H, m), 7.77 (1H, s), 7.81 (1H, s), 7.94 (1H, s), 7.96 (2H, d, J=9.2 Hz)	1701, 1614, 1560	−10.4° {20} (0.4)
2f	81	162—163 (EA-H)	$C_{23}H_{20}F_6N_6O_3$	50.93 (50.68)	3.72 (3.66)	15.49 (15.73)	1.23 (3H, d, J=7 Hz), 4.14 (1H, d, J=14.4 Hz), 4.49 (2H, t, J=13 Hz), 4.94 (1H, dq, J=7, 1.6 Hz), 5.08 (1H, d, J=14.4 Hz), 5.54 (1H, d, J=1.6 Hz), 6.10 (1H, tt, J=52, 5.4 Hz), 6.71—6.89 (2H, m), 7.03 (2H, d, J=9.2 Hz), 7.34—7.51 (1H, m), 7.77 (1H, s), 7.80 (1H, s), 7.93 (1H, s), 7.95 (2H, d, J=9.2 Hz)	1693, 1620, 1558, 1517	−9.6° {20} (0.6)
2g	53	111—112 (EA-H)	$C_{23}H_{19}F_7N_6O_3$	49.29 (49.13)	3.42 (3.47)	15.00 (15.09)	1.24 (3H, d, J=7.2 Hz), 4.14 (1H, d, J=14.4 Hz), 4.45 (2H, t, J=12.2 Hz), 4.95 (1H, dq, J=7.2, 1.6 Hz), 5.08 (1H, d, J=14.4 Hz), 5.54 (1H, d, J=1.6 Hz), 6.71—6.89 (2H, m), 7.03 (2H, d, J=9 Hz), 7.34—7.52 (1H, m), 7.77 (1H, s), 7.80 (1H, s), 7.93 (1H, s), 7.96 (2H, d, J=9 Hz)	1699, 1620, 1614, 1566	−9.2° {20} (0.4)
3a	51	AP	$C_{19}H_{16}F_3N_7O_2 \cdot H_2O$	50.78 (50.83)	4.04 (3.71)	21.82 (21.68)	1.46 (3H, d, J=7.2 Hz), 4.35 (1H, d, J=14.4 Hz), 5.08 (1H, d, J=14.4 Hz), 5.10 (1H, q, J=7.2 Hz), 5.50 (1H, s), 6.72—6.90 (2H, m), 7.15—7.30 (2H, m), 7.50—7.68 (1H, m), 7.72 (1H, s), 7.91 (1H, s), 7.89—8.01 (2H, m)	1726, 1618, 1598, 1512	−7.1° {20} (1.0)
3b	21	AP	$C_{20}H_{16}F_5N_7O_2$	49.90 (49.64)	3.35 (3.35)	20.37 (20.22)	1.47 (3H, d, J=7.2 Hz), 4.36 (1H, d, J=14.2 Hz), 5.08 (1H, d, J=14.2 Hz), 5.10 (1H, q, J=7.2 Hz), 5.47 (1H, s), 6.74—6.91 (2H, m), 7.50—7.68 (1H, m), 7.73 (1H, s), 7.80 (2H, d, J=8.8 Hz), 7.91 (1H, s), 8.18 (2H, d, J=8.8 Hz)	1730, 1618, 1522, 1502	−6.0° {20} (0.2)

Table 1. (continued)

No.	Yield[a] (%)	mp (°C) (Solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ	IR (KBr) cm^{-1}	$[\alpha]_D$ {°C} MeOH (*c*)
3c	43	AP	$C_{20}H_{16}F_5N_7O_3 \cdot 1/2H_2O$	47.44 (47.64)	3.38 (3.32)	19.36 (19.03)	1.46 (3H, d, J=7.2 Hz), 4.35 (1H, d, J=13.8 Hz), 5.08 (1H, d, J=13.8 Hz), 5.10 (1H, q, J=7.2 Hz), 5.51 (1H, s), 6.71—6.90 (2H, m), 7.38 (2H, d, J=9.2 Hz), 7.48—7.63 (1H, m), 7.72 (1H, s), 7.91 (1H, s), 8.04 (2H, d, J=9.2 Hz)	1722, 1684, 1618, 1599	−5.7° {20} (1.0)
3d	48	93—94 (EA–H)	$C_{21}H_{17}F_6N_7O_3$	47.64 (47.47	3.24 3.24	18.52 18.36)	1.46 (3H, d, J=7.2 Hz), 4.34 (1H, d, J=14.4 Hz), 5.08 (1H, d, J=14.4 Hz), 5.10 (1H, q, J=7.2 Hz), 5.50 (1H, s), 5.95 (1H, tt, J=52.8, 2.8 Hz), 6.73—6.91 (2H, m), 7.38 (2H, d, J=9 Hz), 7.49—7.64 (1H, m), 7.72 (1H, s), 7.91 (1H, s), 8.01 (2H, d, J=9 Hz)	1730, 1618, 1514, 1502	−3.9° {20} (1.0)
3e	27	AP	$C_{21}H_{18}F_5N_7O_3$	49.31 (49.50	3.55 3.86	19.17 18.65)	1.46 (3H, d, J=7 Hz), 4.35 (1H, d, J=16 Hz), 4.41 (2H, q, J=8 Hz), 5.08 (1H, d, J=16 Hz), 5.10 (1H, q, J=7 Hz), 5.51 (1H, s), 6.75—6.88 (2H, m), 7.09 (2H, d, J=9 Hz), 7.51—7.63 (1H, m), 7.72 (1H, s), 7.90 (2H, d, J=9 Hz), 7.91 (1H, s)	1720, 1618, 1515	—
3f	57	AP	$C_{22}H_{19}F_6N_7O_3 \cdot 1/2H_2O$	47.83 (47.60	3.65 3.52	17.75 17.45)	1.45 (3H, d, J=7.2 Hz), 4.35 (1H, d, J=14.2 Hz), 4.41 (2H, t, J=11.8 Hz), 5.08 (1H, d, J=14.2 Hz), 5.11 (1H, q, J=7.2 Hz), 5.53 (1H, s), 6.09 (1H, tt, J=53.2, 4.8 Hz), 6.75—6.90 (2H, m), 7.08 (2H, d, J=9 Hz), 7.50—7.68 (1H, m), 7.72 (1H, s), 7.90 (2H, d, J=9 Hz), 7.92 (1H, s)	1726, 1618, 1599, 1516	−2.3° {20} (0.4)
3g	53	AP	$C_{22}H_{18}F_7N_7O_3$	47.07 (47.38	3.23 3.13	17.46 17.30)	1.45 (3H, d, J=7.2 Hz), 4.35 (1H, d, J=14.2 Hz), 4.47 (2H, dt, J=12.2, 1 Hz), 5.08 (1H, d, J=14.2 Hz), 5.10 (1H, q, J=7.2 Hz), 5.50 (1H, s), 6.74—6.90 (2H, m), 7.09 (2H, d, J=9.2 Hz), 7.49—7.65 (1H, m), 7.72 (1H, s), 7.90 (2H, d, J=9.2 Hz), 7.91 (1H, s)	1726, 1618, 1599, 1516	−2.3° {20} (1.0)

a) Based on compounds **20**—**22**. *b*) Recrystallization solvent: E, ethanol; W, water; DE, diethyl ether; IPE, diisopropyl ether; EA, ethyl acetate; H, hexane. *c*) Amorphous powder.



II III IV

Chart 3

and $OCH_2CF_2CF_3$, expecting them to afford compounds refractory to metabolic breakdown *in vivo*.

In this paper, we describe the establishment of a new route for the stereocontrolled synthesis of the azolones II (**1a**—**g**, **2a**—**g** and **3a**—**g**, Table 1), as well as their antifungal activities against *Candida albicans in vitro* and *in vivo*.

Chemistry Our protocol for the new synthetic route to the optically active azolones II is illustrated in Chart 3 by a retrosynthetic formula. The final step is the introduction of 1*H*-1,2,4-triazole into an oxirane derivative III. The key step of this synthetic plan seemed to be the displacement reaction of the (2*R*)-oxiranyl-(1*S*)-ethanol derivative with an azolone anion, IV→III. It is essential that this displacement reaction with an anion occurs at the 1-position (course A; *SN*2 process), not at the 3-position of the oxirane ring (course B; *SN*2′ process).

We examined this key step by using the model reaction (Chart 4) of a pyrazole anion and the (2*R*)-oxiranyl-(1*R*)-ethanol **7**, because compound **7** was readily available from the oxirane derivative **5**[4a] *via* three steps [deprotection of the tetrahydropyranyl (THP) group, 3,5-dinitrobenzoylation followed by recrystallization to obtain **6** in high purity and alkaline hydrolysis], although the stereochemistry of **7** was inadequate for the preparation of the final (*R*,*R*)-1,2,3-trisubstituted-2-butanol derivatives.

First, we carried out the reaction of the mesylate **8** with pyrazole in the presence of sodium hydride (NaH) in *N*,*N*-dimethylformamide (DMF). The reaction proceeded at around 50 °C, but the undesirable product **9**, which would be formed *via* course B (*SN*2′ process), was obtained exclusively.[6] We then exploited the trifluoromethanesulfonyloxy (TfO) group as a leaving group because it was expected that the triflate **10** might react with an anion under mild conditions.[7] The alcohol **7** was converted to the triflate **10** by reaction with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of *N*,*N*-diisopropylethylamine (iso-Pr_2NEt). The displacement reaction of **10** with a pyrazole anion, as expected, proceeded smoothly at low temperature (−10 °C) and compound **11** was obtained in 40% yield. ^{1}H-NMR and HPLC analyses indicated that **11** was a single isomer, and therefore, **11** was considered to have the (1*S*)-configuration generated *via* the *SN*2 process (course A), although stereochemical assignment was not carried out.

On the basis of the successful result in the above model

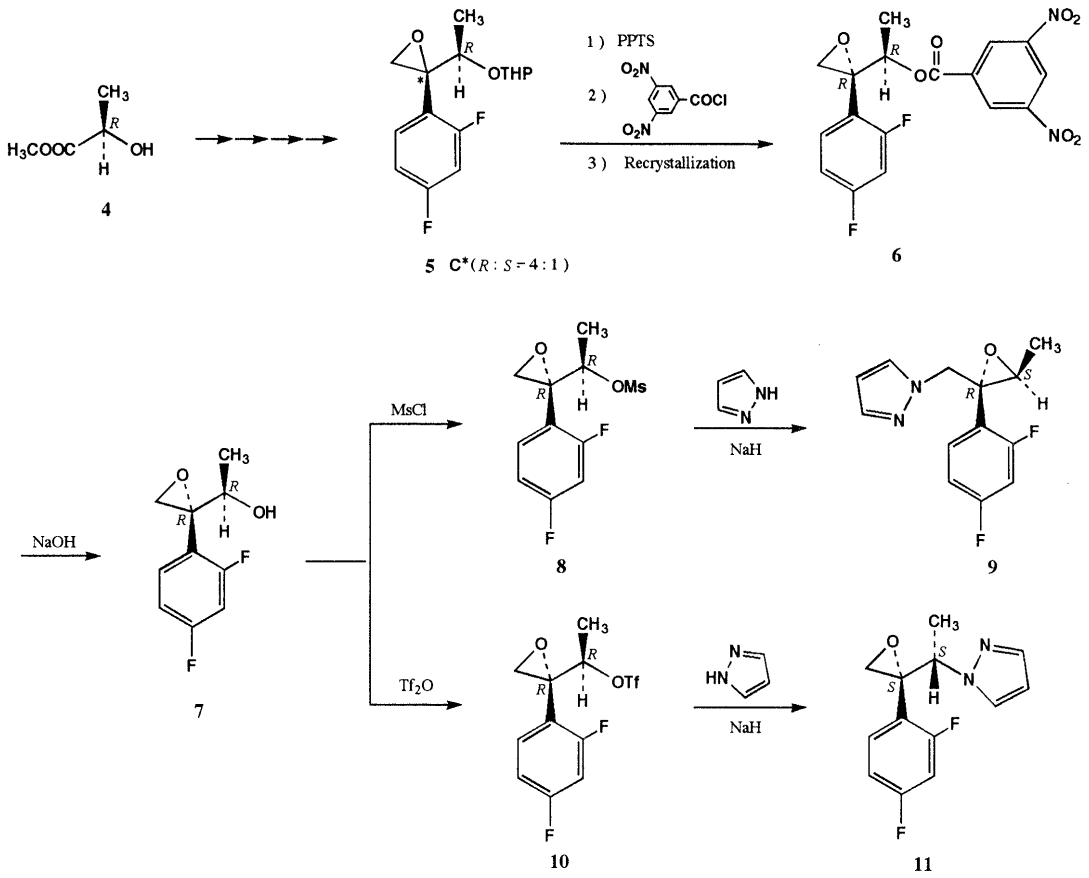


Chart 4

reaction, we directed our efforts to the preparation of compounds with the desired stereochemistry. Thus, the (2*R*)-oxiranyl-(1*R*)-ethanol **7** was submitted to Mitsunobu reaction to invert the configuration of the 1-position from *R* to *S*. The subsequent debenzoylation of the product **12** with sodium methoxide (NaOMe) in methanol (MeOH) gave the (2*R*)-oxiranyl-(1*S*)-ethanol **13**. To confirm that our new synthetic processes proceeded in a stereocontrolled manner, we undertook the preparation of the tetrazole derivative **16** with the use of **13** (Chart 5), since the structure of **16** prepared by an alternative route was determined by X-ray crystallographic analysis in our preceding report.[5] The (1*S*)-triflate **14** was prepared in the same manner as described for **10** and allowed to react with 1*H*-tetrazole in the presence of NaH at $-10\,^{\circ}C$. Two products (**15a** and **15b**), the substitution position isomers at the tetrazole nitrogen atom, were isolated in 50% total yield based on **13**. The more polar **15a** was assigned to be the 1-substituted isomer based on the observation of nuclear Overhauser effect (NOE) between the methyl group and the 5-proton on the tetrazole ring. Reaction of **15a** and 1*H*-1,2,4-triazole in the presence of NaH gave compound **16**, which was identical with an authentic sample.[5]

Our new route for the synthesis of (*R*,*R*)-1,2,3-trisubstituted-2-butanols was thus proved to proceed in a stereocontrolled manner. Then, the synthesis of the azolones **1**—**3** was undertaken by utilizing this route (Chart 5). The triflate **14** was reacted with 4-(4-substituted phenyl)-3(2*H*,4*H*)-1,2,4-triazolones **17a**—**g** (Table 3) in the presence of NaH at $-10\,^{\circ}C$ to give the desired products **20a**—**g** (Table 6) exclusively in 24—57% yields based on **13**. On the other hand, in the case of the reaction with 2-(4-substituted phenyl)-3(2*H*,4*H*)-1,2,4-triazolones **18a**—**g** (Table 4), a mixture of two isomers was formed and separated by column chromatography on silica gel to give **21a**—**g** (less polar) and **23a**—**g** (more polar) in 21—45% and 11—24% isolated yields, respectively (Table 6). The structures of these isomers were assigned based on their IR spectra as follows: *N*-substituted compounds **21a**—**g** showed a strong absorption around 1700 cm^{-1} due to the carbonyl stretching vibration, while this absorption was not observed in *O*-substituted isomers **23a**—**g**. Reaction of **14** with 1-(4-substituted phenyl)-5(1*H*,4*H*)-tetrazolones **19a**—**g** (Table 5) also gave two isomers, **22a**—**g** (less polar, Table 6) and **24a**—**g** (more polar, Table 6). The structural assignment of these isomers was done similarly to those of **21** and **23**.

The oxirane derivatives obtained above, **20a**—**g**, **21a**—**g** and **22a**—**g**, were allowed to react with 1*H*-1,2,4-triazole in the presence of NaH in DMF to give the desired azolones, **1a**—**g**, **2a**—**g** and **3a**—**g** (Table 1), in 42—65%, 24—81% and 21—57% isolated yields, respectively. The structural confirmation of these azolones was carried out using the analytical results shown in Table 1. Furthermore, compound **1f** was submitted to X-ray crystallographic analysis and the structure was determined unequivocally as shown in Fig. 1.[8]

In the above ring-opening reaction of the oxiranes, in most cases the desired azolones **1**—**3** were obtained exclusively, but in the case of compounds **2a**, **b**, additional products **26a**, **b** were isolated in a considerable yield. The

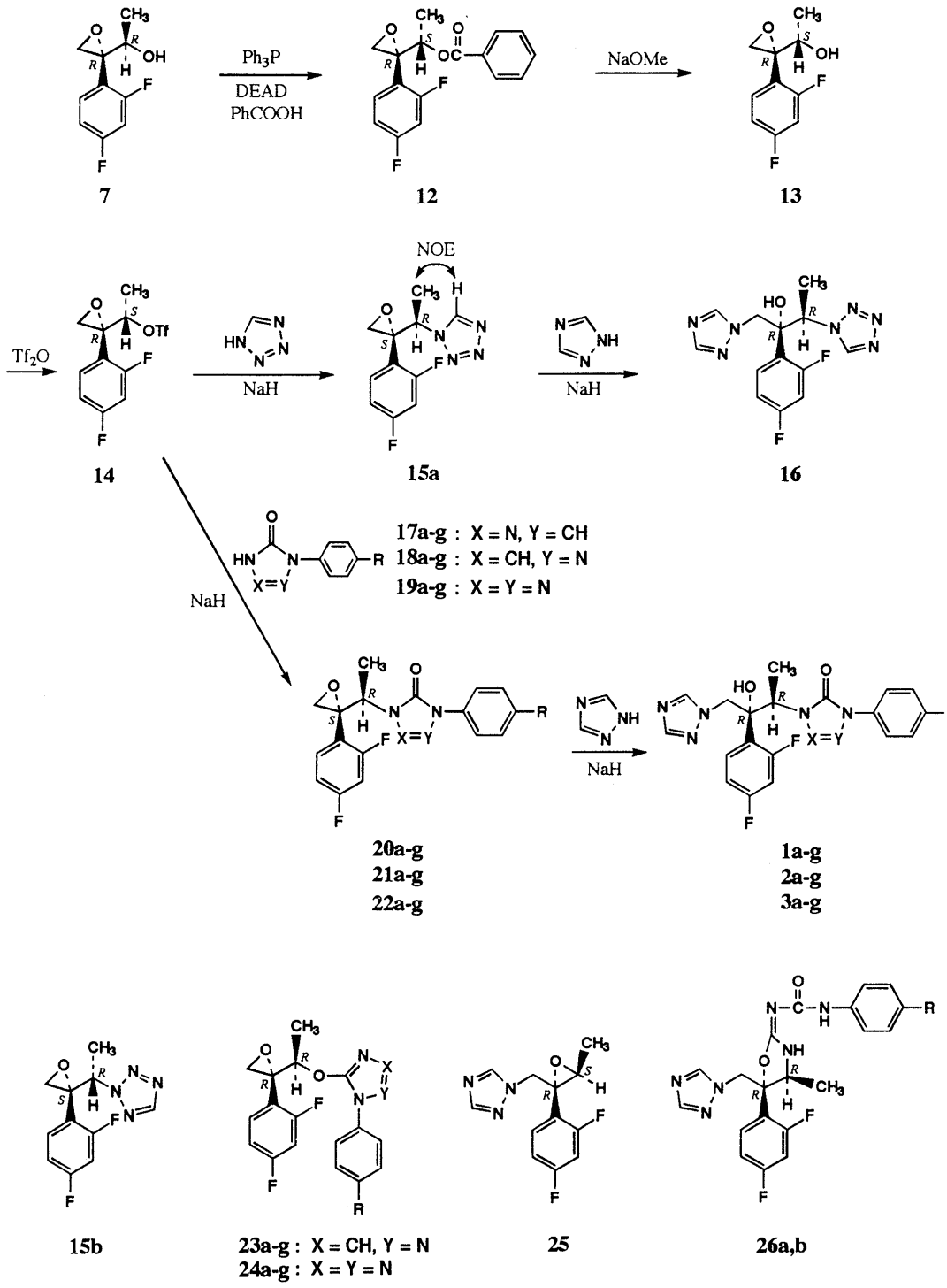


Chart 5

structure of these by-products could not be clarified from the ^{1}H-NMR and IR spectra. Compounds **26a** and **26b** showed the same molecular weights as those of **2a** and **2b**, respectively, by secondary ion mass spectrometry (SIMS), so it was clear that an unexpected side reaction or a rearrangement had occurred during the ring-opening reaction of the oxiranes **21a, b** with 1*H*-1,2,4-triazole under the basic conditions. Finally, the structure of **26a** was determined by X-ray crystallographic analysis to be the oxazolidine derivative represented in Fig. 2.

The structure of **26a** suggests that a peculiar rearrangement of **2a** might occur under basic conditions. The product **2a** was treated with NaH under a condition similar to that used for its preparation from **21a**, and compound **26a** was obtained, as expected, in 51% isolated yield. On the basis of these results, we postulate the mechanism of this rearrangement to be as illustrated in Chart 6,[9] although there is no evidence for the existence of the diaziridinone intermediate **28**.[10]

In addition to the synthesis of the azolones **1**—**3**, we attempted the synthesis of their *O*-azolyl substituted isomers using the by-products, **23** and **24**, in order to investigate the structure–activity relationship. However, treatment of **23** and **24** with 1*H*-1,2,4-triazole in the presence of NaH gave no ring-opening product of the oxirane, but gave the triazolylmethyl oxirane **25**[4a] *via* an

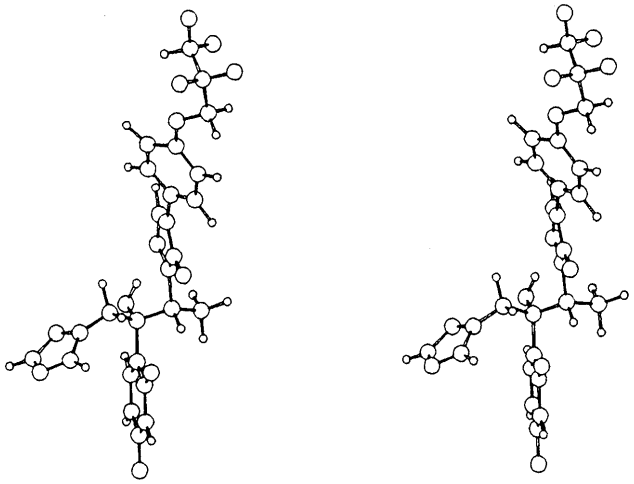


Fig. 1. Stereoscopic Molecular View of Compound **1f**

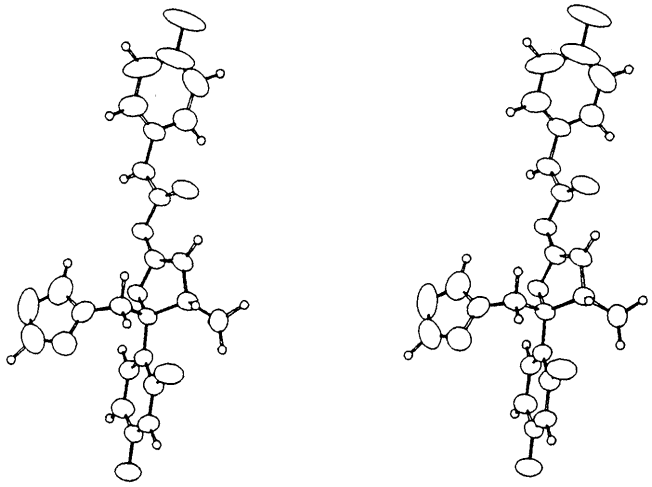


Fig. 2. Stereoscopic Molecular View of Compound **26a**

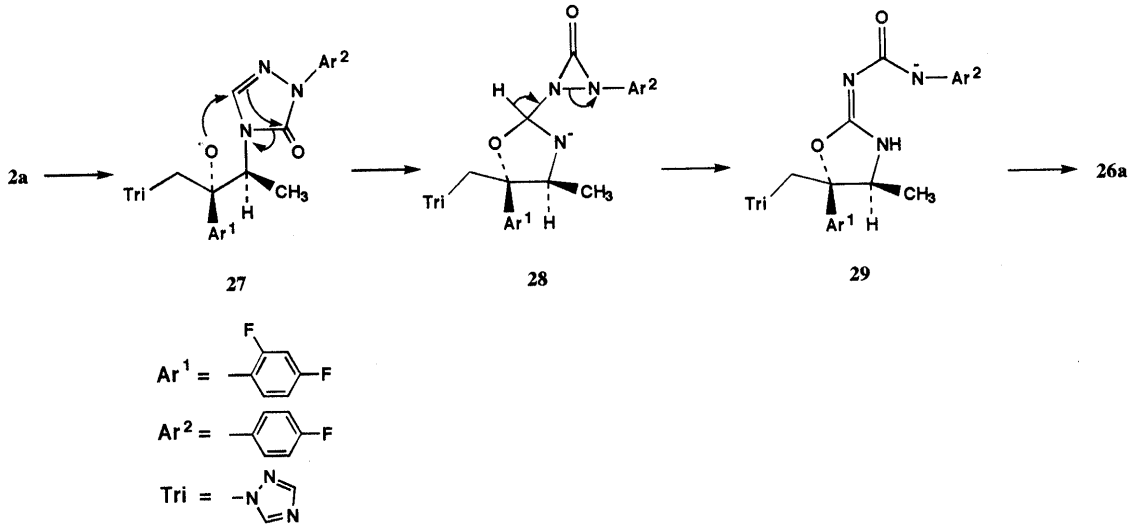


Chart 6

S_N2' process with the azolyloxy group as the leaving group.

The triazolones, **17a—g** and **18a—g**, and the tetrazolones **19a—g** which were used in the above synthesis were prepared as shown in Chart 7. Thus, the 4-(4-substituted phenyl)anilines **30a—g** were converted to the phenylcarbamates **31a—g** followed by treatment with hydrazine hydrate to give the semicarbazides **32a—g**, and subsequent cyclization[11] with formamidine afforded the corresponding 4-(4-substituted phenyl)-3(2*H*,4*H*)-1,2,4-triazolones (**17a—g**, Table 3). On the other hand, 2-(4-substituted phenyl)-3(2*H*,4*H*)-1,2,4-triazolones (**18a—g**, Table 4) were prepared from the corresponding phenylhydrazines **33a—g** *via* two steps: condensation with glyoxylic acid and Curtius rearrangement accompanying cyclization.[12] 4-Polyfluoroalkoxyphenylhydrazines, **33d—g**, which were used in the synthesis of **18d—g**, were synthesized from the anilines **30d—g** by diazotization and subsequent reduction. Among the tetrazolones **19** (Table 5), 1-(4-fluoro, 4-trifluoromethyl and 4-trifluoromethoxyphenyl)-5(1*H*,4*H*)-tetrazolones (**19a—c**) were synthesized from the commercially available phenyl isocyanates (**34a—c**) in one step (method a)[13] with trimethylsilyl azide ($TMSN_3$). For the synthesis of the other tetrazolones **19d—g**, the starting 4-substituted benzoic acids (**35d—g**) were converted to the corresponding isocyanates, followed by treatment with $TMSN_3$ to obtain **19d—g** (method b).

Antifungal Activity The azolones **1—3** and the rearranged product **26** obtained above were evaluated for *in vitro* and *in vivo* antifungal activity against *Candida albicans*. The *in vitro* assay using *C. albicans* TA was carried out by a paper disc method (Disc) on yeast nitrogen base (YNB) medium and by an agar-dilution method on YNB and peptone-yeast extract-glucose (PYG) media at pH 7.0. The 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). In addition, the *in vitro* activity to inhibit the hyphal outgrowth of *C. albicans* IFO 0583 in serum was measured and expressed in terms of *MIC* against the hyphal outgrowth (*MICH*, μg/ml).[1] On the other hand, *C. albicans* TA-infected mice were used for the *in vivo* assay, and the activity is expressed in terms of ED_{50} (mg/kg, the dose of the test compound which allows 50% of infected mice to survive after a single oral administration). The results of these *in vitro* and *in vivo* assays are shown in Table 2.

All compounds prepared, **1—3** and **26**, showed growth-inhibitory activity against *C. albicans* TA in the

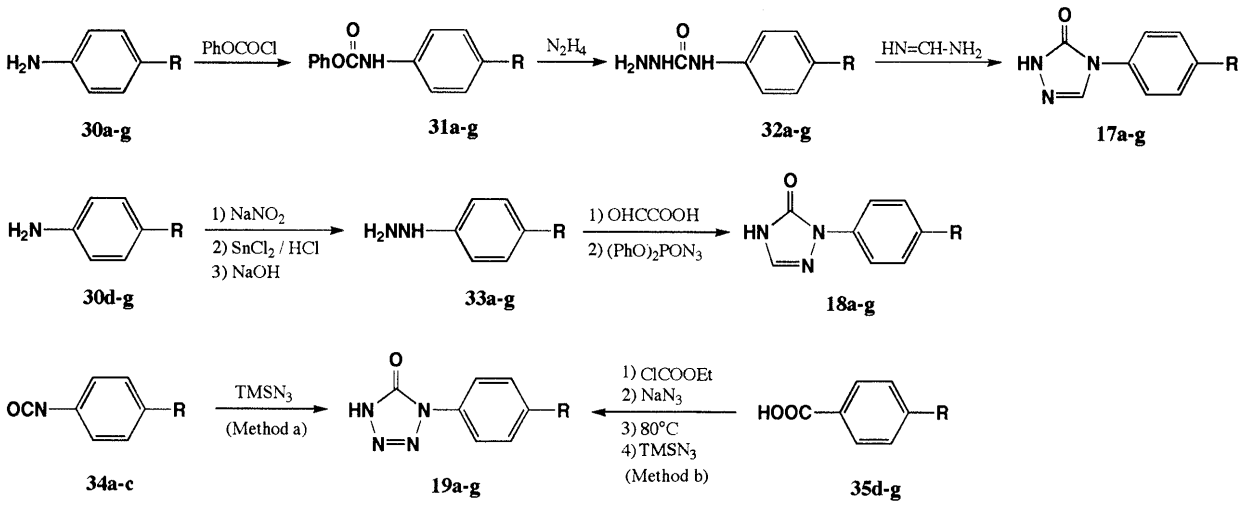


Chart 7

Table 2. Antifungal Activity against *C. albicans*

No.	*In vitro* TA Disc (mm on YNB)	*In vitro* TA *MIC* (μg/ml) YNB (PYG)	*In vitro* IFO 0583 *MICH* (μg/ml)	*In vivo* TA ED_{50} (mg/kg *p.o.*)
1a	42	>100 (100)	<0.05	0.71
1b	45	50 (50)	<0.05	0.18
1c	43	50 (50)	<0.05	0.35
1d	43	50 (50)	0.013	0.16
1e	41	50 (50)	0.08	0.18
1f	42	50 (50)	<0.05	0.32
1g	35	50 (50)	0.32	0.77
2a	45	50 (50)	<0.05	8.0
2b	26	>100 (>100)	<0.05	0.16
2c	39	6.25 (0.05)	0.013	0.19
2d	34	12.5 (12.15)	0.02	0.18
2e	43	12.5 (12.5)	0.01	0.16
2f	33	100 (25)	0.62	0.22
2g	30	6.25 (6.25)	0.01	0.89
3a	34	50 (50)	0.08	2.0
3b	37	50 (25)	0.04	2.0
3c	36	50 (25)	0.16	2.0
3d	35	25 (25)	0.15	0.71
3e	36	25 (25)	0.31	1.3
3f	34	25 (25)	0.16	2.0
3g	41	25 (25)	0.62	2.8
26a	34	>100 (>100)	1.56	8.0
26b	19	50 (50)	25	>16.0
Fluconazole	42	>100 (>100)	0.2—0.8	0.29—0.35

paper disc assay. However, the observed *MIC* values on YNB and PYG media were 25—50 μg/ml or more for all compounds except **2c**, **d**, **e**, **g** which showed lower *MIC* values of 0.05—12.5 μg/ml. It is known that azole antifungals such as fluconazole show high *MIC* values on conventional culture media. On the other hand, the azolones **1**—**3** and fluconazole showed strong inhibitory activity against hyphal outgrowth (*MICH*, <0.62 μg/ml), while **26a**, **b** were weak in the same assay. The potencies of the azolones in *MICH* assay are mostly comparable or superior to that of fluconazole.

In the *in vivo* assay, the azolones **1**—**3** were found to have a strong protective effect against candidiasis, but compounds **26a**, **b** were less active. 4-(4-Substituted phenyl)triazolone derivatives **1a**—**g** had potent activity (ED_{50}, 0.16—0.77 mg/kg) comparable to that of fluconazole. Within this series of derivatives, compound **1d** showed the lowest ED_{50} value (0.16 mg/kg). Furthermore, 2-(4-substituted phenyl)triazolone derivatives **2** also showed potent *in vivo* activity (ED_{50}, 0.16—0.89 mg/kg), except **2a** (ED_{50}, 8.0 mg/kg). The activity was comparable to that of the corresponding 4-substituted triazolone derivative **1**. Among this series of derivatives, compounds **2b** and **2e** showed the lowest ED_{50} value (0.16 mg/kg). In the case of the tetrazolone derivatives **3a**—**g**, the activities were moderate (ED_{50}, 0.71—2.8 mg/kg), and their potencies were somewhat lower than those of the corresponding triazolone derivatives **1**—**2**.

In conclusion, we have established a stereocontrolled route for the synthesis of optically active 1,2,3-trisubstituted-2-butanol derivatives, and the chiral synthesis was applied to the preparation of novel antifungal azolones II. The triazolone (**1**, **2**) and tetrazolone (**3**) derivatives described in this report included new antifungal agents with potent activities *in vitro* and *in vivo*. Further biological evaluation of this series of derivatives is in progress.

Experimental

Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured with a JASCO IR-810 spectrometer. ^{1}H-NMR spectra were taken on a Varian Gemini-200 spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. SIMS were measured with a Hitachi M-80A mass spectrometer. The optical rotations were recorded with a JASCO DIP-181 or DIP-370 digital polarimeter.

Reactions were run at room temperature unless otherwise noted and traced by TLC on Silica gel 60 F_{254} precoated TLC plates (E. Merck) or by HPLC using an octadecyl silica (ODS) column (A-303, 4.6 mm i.d. × 250 mm, Yamamura Chemical Laboratories Co.). Standard work-up procedures were as follows. The reaction mixture was partitioned between the indicated solvent and water. Organic extracts were combined and washed in the indicated order using the following aqueous solutions; water, 5% aqueous sodium bicarbonate solution (aqueous $NaHCO_3$) and saturated NaCl solution (brine). Extracts were dried over $MgSO_4$, filtered and evaporated *in vacuo*.

Chromatographic separations were carried out on Silica gel 60 (0.063—0.200 mm, E. Merck) using the indicated eluents.

4-Fluoroaniline (**30a**), 4-(trifluoromethyl)aniline (**30b**), 4-(trifluoro-

methoxy)aniline (**30c**), 4-(1,1,2,2-tetrafluoroethoxy)aniline (**30d**), 4-fluorophenylhydrazine (**33a**), 4-trifluoromethylphenylhydrazine (**33b**), 4-trifluoromethoxyphenylhydrazine (**33c**), 4-fluorophenyl isocyanate (**34a**), 4-trifluoromethylphenyl isocyanate (**34b**), 4-trifluoromethoxyphenyl isocyanate (**34c**) and 4-(1,1,2,2-tetrafluoroethoxy)benzoic acid (**35d**) were purchased from commercial suppliers (Aldrich Chemical Company, Inc. and BNFL Fluorochemicals Ltd.). 4-(1,1,2,2-Tetrafluoroethoxy)phenylhydrazine (**33d**) was prepared according to the literature.[14]

The *in vitro* and *in vivo* antifungal activities were measured by the methods described in our preceding reports.[1,4,5]

4-(2,2,2-Trifluoroethoxy)aniline (30e) A mixture of 4-chloronitrobenzene (109.5 g), K_2CO_3 (192 g), 2,2,2-trifluoroethanol (100 ml) and DMF (200 ml) was heated at 100 °C for 30 h. After having been cooled, the mixture was worked up [ethyl acetate (AcOEt)–hexane; water]. The residue was purified by chromatography on silica gel (AcOEt–hexane, 1 : 5, v/v) to give 4-(2,2,2-trifluoroethoxy)nitrobenzene (113 g, 63%) as pale yellow prisms, mp 75—76 °C (from hexane). A solution of this product (26 g) in ethanol (EtOH, 700 ml) was hydrogenated over 10% Pd–carbon (50% wet, 4 g) under atmospheric pressure. After absorption of hydrogen stopped, the catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to give **30e**[15] (22.4 g, quantitative) as a pale brown oil. ^{1}H-NMR ($CDCl_3$) δ: 3.44 (2H, br), 4.25 (2H, q, J=8.4 Hz), 6.62 (2H, d, J=9 Hz), 6.78 (2H, d, J=9 Hz).

4-(2,2,3,3,3-Pentafluoropropoxy)aniline[16] (**30g**, quantitative) was prepared from 2,2,3,3,3-pentafluoropropanol and 4-chloronitrobenzene *via* the same sequence of reactions as described above. ^{1}H-NMR ($CDCl_3$) δ: 3.48 (2H, br), 4.31 (2H, dt, J=12.4, 1 Hz), 6.61 (2H, d, J=9 Hz), 6.77 (2H, d, J=9 Hz).

4-(2,2,3,3-Tetrafluoropropoxy)aniline (30f) A mixture of 4-nitrophenol (68.8 g), K_2CO_3 (114 g), 2,2,3,3-tetrafluoropropyl iodide (40 g) and DMF (700 ml) was heated at 100 °C for 17 h. After having been cooled, the mixture was worked up (AcOEt; water, saturated aqueous $NaHCO_3$, water, 1 N HCl) to give 4-(2,2,3,3-tetrafluoropropoxy)nitrobenzene (33.2 g, 79%) as pale yellow prisms, mp 63—64 °C [from diisopropyl ether (iso-Pr_2O)]. Hydrazine hydrate (20 ml) was added dropwise to a stirred mixture of this product (33.2 g), $FeCl_3$ (0.5 g), activated carbon (5 g) and MeOH (500 ml) over the period of 1 h at 70—80 °C. The resulting mixture was stirred overnight at 70—80 °C. After having been cooled, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was worked up (AcOEt–hexane; water) to give **30f**[16,17] (24 g, 82%) as a pale brown oil. ^{1}H-NMR ($CDCl_3$) δ: 3.51 (2H, br), 4.26 (2H, t, J=12 Hz), 6.06 (1H, tt, J=53, 5 Hz), 6.64 (2H, d, J=9 Hz), 6.77 (2H, d, J=9 Hz).

4-(2,2,3,3-Tetrafluoropropoxy)phenylhydrazine Hydrochloride (33f·HCl) A solution of $NaNO_2$ (7.31 g) in water (105 ml) was added dropwise to a mixture of 4-(2,2,3,3-tetrafluoropropoxy)aniline (**30f**, 23.4 g) and concentrated HCl (80 ml) over the period of 1 h at −10 °C. A solution of $SnCl_2$ (96 g) in concentrated HCl (96 ml) was added dropwise, while the temperature was held at −5 °C. The resulting mixture was made alkaline (pH 12—14) with NaOH (110 g). The insoluble material was removed by filtration and the filtrate was worked up (CH_2Cl_2; brine). The oily residue was dissolved in AcOEt (15 ml) and 4 N HCl-AcOEt (30 ml) was added to the solution. The mixture was stirred for 1 h, then the precipitate was collected by filtration and washed with diethyl ether (Et_2O) to give **33f**·HCl (18.6 g, 65%) as a colorless powder. *Anal.* Calcd for $C_9H_{10}F_4N_2O$·HCl: C, 39.36; H, 4.04; N, 10.20. Found: C, 39.51; H, 3.96; N, 10.33. ^{1}H-NMR (DMSO-d_6) δ: 4.52 (2H, t, J=13.6 Hz), 6.67 (1H, tt, J=52.2, 5.4 Hz), 7.01 (4H, s), 8.04 (1H, br), 10.14 (3H, br).

The hydrochlorides of 4-(2,2,2-trifluoroethoxy)-(**33e**, 75%) and 4-(2,2,3,3,3-pentafluoropropoxy)phenylhydrazine (**33g**, 81%) were prepared from the corresponding anilines (**30e**, **g**) by the same method as described above. **33e**:[18] *Anal.* Calcd for $C_8H_9F_3N_2O$·HCl: C, 36.60; H, 4.15; N, 11.55. Found: C, 39.70; H, 3.91; N, 11.83. ^{1}H-NMR (DMSO-d_6) δ: 4.69 (2H, q, J=9 Hz), 7.01 (4H, s), 8.04 (1H, br), 10.15 (3H, br). **33g**: *Anal.* Calcd for $C_9H_9F_5N_2O$·HCl: C, 36.94; H, 3.44; N, 9.57. Found: C, 36.79; H, 3.47; N, 9.62. ^{1}H-NMR (DMSO-d_6) δ: 4.76 (2H, t, J=13.6 Hz), 7.01 (4H, s), 8.05 (1H, br), 10.14 (3H, br).

4-(2,2,2-Trifluoroethoxy)benzoic Acid (35e) A mixture of ethyl 4-fluorobenzoate (29 g), K_2CO_3 (100 g), 2,2,2-trifluoroethanol (25 ml) and DMF (200 ml) was stirred for 48 h, then worked up (AcOEt; water) to give ethyl 4-(2,2,2-trifluoroethoxy)benzoate (48 g) as a colorless oil. A solution of NaOH (21 g) in water (100 ml) was added to a solution of this product in EtOH (150 ml). The resulting mixture was stirred at 40—50 °C for 2 h and then EtOH was evaporated off *in vacuo*. The residue was acidified with concentrated HCl. The deposited solid was collected by filtration to give **35e**[19] (31 g, 82%). mp 155—156 °C (from EtOH–H_2O). *Anal.* Calcd for $C_9H_7F_3O_3$: C, 49.10; H, 3.20. Found: C, 48.83; H, 3.21. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 4.46 (2H, q, J=8.2 Hz), 6.99 (1H, dt, J=9, 3 Hz), 8.04 (2H, dt, J=9, 3 Hz).

The benzoic acids **35f**, **g** were prepared from 2,2,3,3-tetrafluoropropanol and 2,2,3,3,3-pentafluoropropanol, respectively, by the same method as described above. **35f**[20]: *Anal.* Calcd for $C_{10}H_8F_4O_3$: C, 47.63; H, 3.20. Found: C, 47.48; H, 3.50. ^{1}H-NMR ($CDCl_3$) δ: 4.43 (2H, t, J=11.8 Hz), 6.07 (1H, tt, J=53.2, 4.6 Hz), 7.00 (2H, d, J=8.8 Hz), 8.11 (2H, d, J=8.8 Hz). **35g**[19]: mp 156—158 °C (from EtOH–H_2O). *Anal.* Calcd for $C_{10}H_7F_5O_3$: C, 44.46; H, 2.61. Found: C, 44.16; H, 2.52. ^{1}H-NMR ($CDCl_3$) δ: 4.49 (2H, t, J=12 Hz), 7.02 (2H, dt, J=9.8, 2 Hz), 8.11 (2H, dt, J=9.8, 2 Hz).

4-(4-Trifluoromethoxyphenyl)-3(2*H*,4*H*)-1,2,4-triazolone (17c, Table 3) Phenyl chloroformate (PhOCOCl, 19.5 g) was added dropwise to a stirred mixture of 4-trifluoromethoxyaniline (**30c**, 20 g), pyridine (9.8 g) and AcOEt (150 ml) at 0 °C. The mixture was stirred for 15 min at 0 °C, then washed with water and concentrated *in vacuo*. The deposited crystals were collected and washed with hexane to give phenyl 4-trifluoromethoxyphenylcarbamate (**31c**: 34.1 g). mp 150—151 °C (from CH_2Cl_2–hexane). *Anal.* Calcd for $C_{14}H_{10}F_3NO_3$: C, 56.57; H, 3.39; N, 4.71. Found: C, 56.54; H, 3.32; N, 4.64.

A mixture of **31c** (15 g), hydrazine hydrate (6 ml) and EtOH (50 ml) was stirred for 2 h. It was concentrated *in vacuo* and the residue was washed with AcOEt to give 4-(4-trifluoromethoxyphenyl)semicarbazide (**32c**: 11.7 g) as colorless crystals, mp 128—130 °C (from AcOEt–iso-Pr_2O). *Anal.* Calcd for $C_8H_8F_3N_3O_2$: C, 40.86; H, 3.43; N, 17.87. Found: C, 40.79; H, 3.22; N, 17.33. ^{1}H-NMR (DMSO-d_6) δ: 4.36 (2H, br), 7.21 (2H, d, J=9 Hz), 7.48 (1H, br), 7.64 (2H, d, J=9 Hz), 8.83 (1H, br).

A mixture of **32c** (7 g), formamidine acetate (15.5 g) and DMF (150 ml) was stirred for 30 min. AcOH (8.9 g) was added, and the resulting mixture was heated for 6 h at 80 °C. The solvent was removed *in vacuo* and the residue was worked up (AcOEt, brine). The residue was recrystallized from AcOEt–hexane to give **17c** (3.44 g, 47% from **30c**) as colorless crystals.

The triazolones **17a**, **b**, **d**—**g** (Table 3) were prepared from the corresponding anilines (**30a**, **b**, **d**—**g**) *via* the same sequence of reactions as described above.

2-(4-Trifluoromethylphenyl)-3(2*H*,4*H*)-1,2,4-triazolone (18b, Table 4) Glyoxylic acid hydrate (2.9 g) was added to a mixture of 4-trifluoromethylphenylhydrazine (**33b**, 5 g), concentrated HCl (3.1 ml) and water (31 ml). The resulting mixture was stirred for 1 h. The deposited precipitate was collected by filtration, washed with water and dried over P_2O_5 to give 4-trifluoromethylphenylhydrazonoacetic acid (6.26 g, 95%) as a pale yellow powder. This compound (6.26 g) was suspended in toluene (176 ml). Triethylamine (Et_3N, 4 ml) and diphenylphosphoryl azide [$(PhO)_2PON_3$, 6.1 ml] were added to the suspension, and the resulting mixture was heated at 120 °C for 1 h. It was then cooled, and extracted with 10% aqueous NaOH (200 ml). The aqueous extract was acidified (pH 1) with concentrated HCl. The deposited precipitate was collected by filtration and washed with water and hexane, successively, to give **18b** (4.48 g, 68% from **33b**) as a colorless powder.

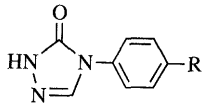
The triazolones **18a**, **c**—**g** (Table 4) were prepared from the corresponding phenylhydrazines (**33a**, **c**—**g**) *via* the same sequence of reactions as described above.

1-(4-Trifluoromethylphenyl)-5(1*H*,4*H*)-tetrazolone (19b, Table 5) Method a: A mixture of $TMSN_3$ (5.36 ml) and 4-trifluoromethylphenyl isocyanate (**34b**, 2.89 ml) was heated at 110 °C for 24 h, then cooled, and chromatographed on silica gel (AcOEt–hexane, 1 : 1→2 : 1, v/v). The product was recrystallized from AcOEt–hexane to obtain **19b** (3.64 g, 78%) as colorless needles.

The tetrazolones **19a**, **c** (Table 5) were prepared from the corresponding phenyl isocyanates (**34a**, **c**) in a manner similar to that described above.

1-[4-(2,2,3,3-Tetrafluoropropoxy)phenyl]-5(1*H*,4*H*)-tetrazolone (19f, Table 5) Method b: Et_3N (1.53 ml) and ethyl chloroformate (ClCOOEt, 1 ml) were added to a solution of 4-(2,2,3,3-tetrafluoropropoxy)benzoic acid (**35f**, 2.52 g) in CH_2Cl_2 (35 ml) at −20 °C. The mixture was stirred for 40 min at −20 °C, then NaN_3 (1.37 g) and tetrabutylammonium hydrogen sulfate (Bu_4NHSO_4, 0.719 g) were added at 0 °C. The resulting mixture was stirred for 1 h at 0 °C and worked up (CH_2Cl_2; water, brine). The oily residue was dissolved in toluene (30 ml). The solution was heated

Table 3. 4-(4-Substituted Phenyl)-3(2*H*,4*H*)-1,2,4-Triazolones (**17**)



17	R	Yield[a] (%)	mp (°C) (Solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR δ [DMSO-d_6] (IR (KBr) cm^{-1})
17a	F	20	214 (dec.) (EA–DCM)	$C_8H_6FN_3O$	53.63 (53.87	3.38 3.62	23.45 23.57)	7.35 (2H, t, J=8.6 Hz), 7.72 (2H, dd, J=8.6, 4.8 Hz), 8.34 (1H, s) (3080, 3000, 1709, 1655, 1616, 1576, 1508, 1458)
17b	CF_3	12	225—226 (EA)	$C_9H_6F_3N_3O$	47.17 (47.05	2.64 2.50	18.34 18.11)	7.87 (2H, d, J=8 Hz), 7.96 (2H, d, J=8 Hz), 8.53 (1H, s), 12.1 (1H, br s) (3220, 3080, 1700, 1620, 1570, 1330)
17c	OCF_3	47	193–195 (EA–H)	$C_9H_6F_3N_3O_2$	44.09 (43.91	2.47 2.43	17.14 17.32)	7.37 (2H, d, J=9 Hz), 7.63 (2H, dt, J=9, 2 Hz), 7.73 (1H, d, J=1.4 Hz), 10.23 (1H, br s) [$CDCl_3$] (3286, 1697, 1567, 1513, 1407, 1282, 1224)
17d	OCF_2CF_2H	50	216—217 (EA)	$C_{10}H_7F_4N_3O_2$	43.33 (43.31	2.55 2.43	15.16 15.23)	6.82 (1H, tt, J=52, 2.8 Hz), 7.43 (2H, d, J=9 Hz), 7.82 (2H, d, J=9 Hz), 8.42 (1H, s) {3210, 3074, 1712, 1702, 1573, 1519)
17e	OCH_2CF_3	47	177—178 (EA–IPE)	$C_{10}H_8F_3N_3O_2$	46.34 (46.23	3.11 3.07	16.21 16.42)	4.40 (2H, q, J=8 Hz), 7.07 (2H, d, J=9 Hz), 7.51 (2H, d, J=9 Hz), 7.67 (1H, s), 10.27 (1H, br) [$CDCl_3$] (3210, 3077, 1708, 1697, 1573, 1523)
17f	$OCH_2CF_2CF_2H$	58	163—165 (EA–IPE)	$C_{11}H_9F_4N_3O_2$	45.27 (45.17	3.12 3.07	14.43 14.40)	4.39 (2H, tt, J=11.8, 1.6 Hz), 6.06 (1H, tt, J=4.8, 53 Hz), 7.06 (2H, dt, J=9.2, 2.2 Hz), 7.50 (2H, dt, J=9.2, 2.2 Hz), 7.66 (1H, d, J=1.4 Hz), 9.87 (1H, br s) [$CDCl_3$] (3185, 1716, 1708, 1699, 1562, 1515)
17g	$OCH_2CF_2CF_3$	39	187—188 (AC–IPE)	$C_{11}H_8F_5N_3O_2$	42.73 (42.82	2.61 2.56	13.59 14.04)	4.46 (2H, t, J=12.4 Hz), 7.07 (2H, d, J=9 Hz), 7.51 (2H, d, J=9 Hz), 7.67 (1H, d, J=1.4 Hz), 9.91 (1H, br) [$CDCl_3$] (3209, 3126, 3085, 1714, 1571, 1519)

a) Overall yield from anilines **30**. *b*) Recrystallization solvent: EA, ethyl acetate; DCM, dichloromethane; H, hexane; IPE, diisopropyl ether; AC, acetone.

at 80 °C for 1.5 h and evaporated *in vacuo* to give the isocyanate as an oily residue. $TMSN_3$ (2.7 ml) was added to the residue and the resulting mixture was heated at 110 °C for 18 h under an argon atmosphere, then cooled, and chromatographed on silica gel (AcOEt–hexane, 1 : 1→2 : 1→AcOEt, v/v). The product was recrystallized from AcOEt–hexane to obtain **19f** (1.5 g, 51%) as colorless prisms.

The tetrazolones **19d, e, g** (Table 5) were prepared from the corresponding benzoic acids (**35d, e, g**) in a manner similar to that described above.

[(1*R*)-1-[(2*R*)-2-(2,4-Difluorophenyl)-2-oxiranyl]ethyl] 3,5-Dinitrobenzoate (6) A mixture of **5**[4a] (82 g), pyridinium *p*-toluenesulfonate (PPTS, 6.3 g) and EtOH (600 ml) was stirred for 1 h at 55 °C, then concentrated *in vacuo* and worked up (AcOEt; water, brine). The residue was purified by column chromatography on silica gel (hexane–AcOEt, 10 : 1→8 : 1→3 : 1, v/v) to give (1*R*)-1-[2-(2,4-difluorophenyl)-2-oxiranyl]ethanol (31.5 g, 55%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.14—1.23 (3H, m), 1.77, 2.22 (1H), 2.80, 2.92 (1H), 3.27—3.32 (1H), 4.00—4.20 (1H, m), 6.75—6.94 (2H, m), 7.36—7.48 (1H, m).

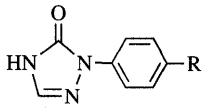
This oil (31.5 g) and 3,5-dinitrobenzoyl chloride (40 g) were dissolved in CH_2Cl_2 (500 ml). Et_3N (24.1 ml) was added dropwise to this solution at 0 °C. After having been stirred for 3.5 h, the mixture was washed (water, aqueous $NaHCO_3$) and concentrated *in vacuo*. The precipitated crystals were collected by filtration and washed with CH_2Cl_2. The mother liquor and washings were combined and evaporated *in vacuo*. AcOEt (25 ml) and MeOH (300 ml) were added to the residue, and the resulting mixture was cooled in an ice bath. The precipitated crystals were collected by filtration and recrystallized from AcOEt–MeOH to give **6** (28.7 g, 46%) as colorless needles, mp 104—107 °C (from AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, dd, J=6.6, 1.2 Hz), 3.01 (1H, d, J=4.6 Hz), 3.23 (1H, d, J=4.6 Hz), 5.33 (1H, q, J=6.6 Hz), 6.85—7.07 (2H, m), 7.54 (1H, m), 9.13 (2H, d, J=2.2 Hz), 9.25 (1H, t, J=2.2 Hz). *Anal.* Calcd for $C_{17}H_{12}F_2N_2O_7$: C, 51.79; H, 3.10; N, 7.10. Found: C, 51.58; H, 3.05; N, 7.05. IR (KBr): 1738, 1630, 1610, 1595, 1540, 1340, 1270, 1165 cm^{-1}. $[\alpha]_D^{25}$ −23.4° (c=1.0, $CHCl_3$). The enantiomeric excess (% ee) of **6** was determined to be >99% by HPLC using a chiral stationary phase column (Chiralcel OJ, 4.6 mm × 250 mm, Daicel Chemical Industries, Tokyo, Japan) under the following conditions: mobile phase (hexane–EtOH, 7 : 3), flow rate (1.0 ml/min), detection (UV at 254 nm). The retention times of the enantiomers, **6** and the (*S,S*)-isomer,[21] were 18.9 and 15.9 min, respectively.

(1*R*)-1-[(2*R*)-2-(2,4-Difluorophenyl)-2-oxiranyl]ethanol (7) A 1 N aqueous NaOH solution (255 ml) was added dropwise to a solution of **6** (50 g) and MeOH (2000 ml). The mixture was stirred for 1 h, then 1 N HCl (127 ml) was added. The whole was concentrated *in vacuo* and worked up (AcOEt; brine) to afford a residue, which was purified by silica gel column chromatography (hexane–AcOEt, 3 : 1, v/v) to give **7** (25 g, 99%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, dd, J=6.6, 1.2 Hz), 1.83 (1H, d, J=8 Hz), 2.80 (1H, d, J=5.2 Hz), 3.30 (1H, d, J=5.2 Hz), 4.01—4.17 (1H, m), 6.75—6.93 (2H, m), 7.36—7.48 (1H, m). IR (neat): 3420, 2980, 1615, 1600, 1505, 1425, 1270, 1140, 1100 cm^{-1}. $[\alpha]_D^{25}$ −52.3° (c=2.6, $CHCl_3$).

[(1*S*)-1-[(2*R*)-2-(2,4-Difluorophenyl)-2-oxiranyl]ethyl] Benzoate (12) Triphenylphosphine (Ph_3P, 63.3 g), benzoic acid (PhCOOH, 29.5 g) and diethyl azodicarboxylate (DEAD, 42 g) were added to an ice-cooled solution of **7** (16.1 g) in THF (320 ml). The mixture was stirred for 6 h, then worked up (AcOEt; water, brine), and the residue was chromatographed on silica gel (hexane–AcOEt, 15 : 1→7 : 1, v/v) to give **12** (19.2 g, 78%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, d, J=6.6 Hz), 2.90 (1H, d, J=5.2 Hz), 3.28 (1H, d, J=5.2 Hz), 5.36 (1H, q, J=6.6 Hz), 6.74—6.94 (2H, m), 7.38—7.60 (4H, m), 7.94—8.01 (2H, m). IR (neat): 1725, 1615, 1600, 1505, 1450, 1425, 1260, 1100 cm^{-1}.

(1*S*)-1-[(2*R*)-2-(2,4-Difluorophenyl)-2-oxiranyl]ethanol (13) A 28% NaOMe–MeOH (12.9 ml) solution was added to an ice-cooled solution of **12** (15.9 g) in MeOH (800 ml). The mixture was stirred for 6 h, then 1 N HCl (63.2 ml) was added and the whole was concentrated to afford a residue, which was submitted to silica gel column chromatography (hexane–AcOEt, 6 : 1→2 : 1, v/v) to give **13** (9.7 g, 93%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, dd, J=6.4, 1 Hz), 2.24 (1H, d,

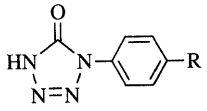
Table 4. 2-(4-Substituted Phenyl)-3(2*H*,4*H*)-1,2,4-Triazolones (**18**)



18	R	Yield[a] (%)	mp (°C) (Solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR δ [in DMSO-d_6] (IR (KBr) cm^{-1})
18a	F	39	206 (dec.)	$C_8H_6FN_3O$	53.63 (53.93	3.38 3.51	23.45 23.68)	7.28 (2H, t, J=9 Hz), 7.91 (2H, dd, J=9, 5 Hz), 8.10 (1H, s) (3159, 3068, 2856, 1714, 1566, 1512, 1508, 1446)
18b	CF_3	68	221 (dec.)	$C_9H_6F_3N_3O$	47.17 (47.26	2.64 2.64	18.34 18.10)	7.81 (2H, d, J=8.4 Hz), 8.15 (2H, d, J=8.4 Hz), 8.19 (1H, s) (3157, 3086, 2872, 1693, 1614, 1568, 1520, 1448)
18c	OCF_3	59	174–175	$C_9H_6F_3N_3O_2$	44.09 (44.10	2.47 2.57	17.14 17.35)	7.46 (2H, d, J=8.2 Hz), 8.03 (2H, d, J=8.2 Hz), 8.16 (1H, s) (3155, 3026, 2823, 1722, 1512, 1450)
18d	OCF_2CF_2H	42	192—193	$C_{10}H_7F_4N_3O_2$	43.33 (43.13	2.55 2.45	15.16 15.10)	6.81 (1H, tt, J=49.8, 1.8 Hz), 7.37 (2H, d, J=8.4 Hz), 8.00 (2H, d, J=8.4 Hz), 8.15 (1H, s) {3018, 2999, 1713, 1600, 1508)
18e	OCH_2CF_3	20	179—180	$C_{10}H_8F_3N_3O_2$	46.34 (46.08	3.11 3.07	16.21 15.95)	4.77 (2H, q, J=8.8 Hz), 7.14 (2H, d, J=9.2 Hz), 7.82 (2H, d, J=9.2 Hz), 8.09 (1H, s) (3152, 3031, 2870, 1697, 1600, 1512, 1450)
18f	$OCH_2CF_2CF_2H$	32	186—187	$C_{11}H_9F_4N_3O_2$	45.37 (45.59	3.12 3.23	14.43 14.13)	4.60 (2H, t, J=12.8 Hz), 6.68 (1H, tt, J=52.2, 5.6 Hz), 7.13 (2H, d, J=9 Hz), 7.81 (2H, d, J=9 Hz), 8.08 (1H, s) (3150, 3050, 2860, 1703, 1560, 1516, 1468)
18g	$OCH_2CF_2CF_3$	2	180—181	$C_{11}H_8F_5N_3O_2$	42.73 (42.74	2.61 2.75	13.59 13.23)	4.84 (2H, t, J=13.6 Hz), 7.15 (2H, d, J=9.2 Hz), 7.83 (2H, d, J=9.2 Hz), 8.08 (1H, s) (3153, 3028, 2910, 1694, 1652, 1558, 1512, 1456)

a) Overall yield from hydrazines **33**. *b*) Recrystallized from ethyl acetate–diisopropyl ether.

Table 5. 1-(4-Substituted Phenyl)-5(1*H*,4*H*)-Tetrazolones (**19**)



19	R	Yield[a] (%) [Method]	mp (°C) (Solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR δ [DMSO-d_6] (IR (KBr) cm^{-1})
19a	F	79 [a]	195—196 (EA–H)	$C_7H_6FN_4O$	46.67 (46.90	2.80 3.02	31.10 31.27)	7.41 (2H, t, J=9 Hz), 7.87 (2H, dd, J=9, 5 Hz) (3077, 2929, 1720, 1674, 1518, 1431)
19b	CF_3	78 [a]	191—192 (EA–H)	$C_9H_5F_3N_4O$	41.75 (41.85	2.19 2.28	24.34 24.09)	7.94 (2H, d, J=9 Hz), 8.14 (2H, d, J=9 Hz) (3165, 3093, 1712, 1616, 1522, 1431)
19c	OCF_3	76 [a]	152—153 (EA–H)	$C_8H_5F_3N_4O_2$	39.04 (38.97	2.05 2.10	22.76 22.76)	7.40 (2H, d, J=8.4 Hz), 8.04 (2H, d, J=8.4 Hz) (3093, 1716, 1647, 1540, 1473)
19d	OCF_2CF_2H	55 [b]	164—165 (EA–H)	$C_9H_6F_4N_4O_2$	38.86 (39.13	2.17 2.20	20.14 20.25)	6.84 (1H, tt, J=51.8, 3.2 Hz), 7.49 (2H, d, J=9.2 Hz), 7.97 (2H, d, J=9.2 Hz) (3080, 2998, 1699, 1514, 1340)
19e	OCH_2CF_3	14 [b]	148—151 (EA–H)	$C_9H_7F_3N_4O_2$	SIMS: 261 (MH^+)			4.42 (2H, q, J=8 Hz), 7.10 (2H, d, J=9.2 Hz), 7.89 (2H, d, J=9.2 Hz) [$CDCl_3$]
19f	$OCH_2CF_2CF_2H$	51 [b]	156—157 (EA–IPE)	$C_{10}H_8F_4N_4O_2$	41.11 (41.32	2.76 2.85	19.17 18.92)	4.65 (2H, t, J=13.2 Hz), 6.68 (1H, tt, J=51.8, 5.6 Hz), 7.24 (2H, d, J=9 Hz), 7.78 (2H, d, J=9 Hz) (3093, 1726, 1650, 1558, 1513, 1473)
19g	$OCH_2CF_2CF_3$	40 [b]	151—152 (EA–H)	$C_{10}H_7F_5N_4O_2$	38.72 (38.94	2.27 2.33	18.06 18.33)	4.91 (2H, t, J=13.4 Hz), 7.25 (2H, d, J=9 Hz), 7.78 (2H, d, J=9 Hz) (3084, 2988, 1707, 1516, 1464)

a) Overall yield from isocyanates **34** or benzoic acids **35**. *b*) Recrystallization solvent: EA, ethyl acetate; H, hexane; IPE, diisopropyl ether.

$J=2$ Hz), 2.92 (1H, d, $J=5$ Hz), 3.28 (1H, d, $J=5$ Hz), 4.12 (1H, dq, $J=6.4$, 2 Hz), 6.77—6.95 (2H, m), 7.32—7.44 (1H, m). IR (neat): 3420, 2980, 1615, 1600, 1500, 1425 cm^{-1}. $[\alpha]_D^{24}$ −33.3° ($c=2.4$, $CHCl_3$).

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-methyl-2-(1*H*-pyrazol-1-ylmethyl)-oxirane (9) Et_3N (1.04 ml) was added dropwise to an ice-cooled solution of **7** (1 g) and methanesulfonyl chloride (MsCl, 0.85 g) in CH_2Cl_2 (15 ml). The mixture was stirred for 30 min, then worked up (CH_2Cl_2; water, aqueous $NaHCO_3$) to give the mesylate **8**[22] (1.4 g, quantitative). 1*H*-Pyrazole (1 g) was added to a stirred mixture of NaH (60% in oil, 0.49 g) and DMF (4 ml) at 0 °C. The whole was stirred for 15 min, then **8** (1 g) was added. The resulting mixture was stirred for 20 min and then for 1 h at 50—55 °C, and worked up (AcOEt; water). The residue was purified by silica gel column chromatography (hexane–AcOEt, 4 : 1, v/v) to give **9** (0.86 g, 85%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (3H, d, $J=5.6$ Hz), 3.16 (1H, q, $J=5.6$ Hz), 4.39 (1H, d, $J=15$ Hz), 4.62 (1H, dd, $J=15$, 1 Hz), 6.13 (1H, t, $J=2$ Hz), 6.63—6.80 (2H, m), 6.91—7.03 (1H, m), 7.28 (1H, d, $J=2$ Hz), 7.36 (1H, d, $J=2$ Hz).

(2*S*)-2-(2,4-Difluorophenyl)-2-[(1*S*)-1-(1*H*-pyrazol-1-yl)ethyl]oxirane (11) Tf_2O (0.91 ml) was added dropwise to a stirred solution of **7** (1 g) and iso-Pr_2NEt (0.95 ml) in CH_2Cl_2 (30 ml) over a period of 3 min at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 20 min at −78 °C and then for 20 min at −20 °C. It was concentrated to about 5 ml *in vacuo* at −10 °C and the residue was submitted to flash chromatography on silica gel (CH_2Cl_2–hexane, 1 : 1, v/v). The eluates containing the triflate 10 were combined and concentrated to about 5 ml.[23] This solution was added to a mixture of 1*H*-pyrazole (0.34 g), NaH (60% in oil, 0.2 g) and DMF (4 ml) at −10 °C. The resulting mixture was stirred for 10 min at −10 °C and then for 20 min at 0 °C, and worked up (AcOEt; water). The residue was purified by chromatography on silica gel (hexane–AcOEt, 2 : 1, v/v) to give **11** (0.5 g, 40%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.56 (3H, d, $J=7$ Hz), 2.82 (1H, q, $J=5$ Hz), 3.15 (1H, d, $J=5$ Hz), 4.83 (1H, q, $J=7$ Hz), 6.19 (1H, t, $J=2$ Hz), 6.66—6.80 (2H, m), 6.94—7.06 (1H, m), 7.35 (1H, d, $J=2$ Hz), 7.41 (1H, d, $J=2$ Hz).

(2*S*)-2-(2,4-Difluorophenyl)-2-[(1*R*)-1-(1*H*-tetrazol-1-yl)ethyl]oxirane (15a) and (2*S*)-2-(2,4-Difluorophenyl)-2-[(1*R*)-1-(2*H*-tetrazol-2-yl)ethyl]-oxirane (15b) Tf_2O (0.97 ml) was added dropwise to a stirred solution of **13** (1.06 g) and iso-Pr_2NEt (1.01 ml) in CH_2Cl_2 (30 ml) over a period of 3 min at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 20 min at −78 °C and then for 20 min at −20 °C. It was concentrated to about 5 ml *in vacuo* at −10 °C and the residue was submitted to flash chromatography on silica gel (CH_2Cl_2–hexane, 1 : 1, v/v). The eluates containing the triflate **14** were combined and concentrated to about 5 ml.[23] This solution was added to a stirred mixture of 1*H*-tetrazole (371 mg), NaH (60% in oil, 136 mg) and DMF (4.2 ml) at −10 °C. The resulting mixture was stirred for 10 min at −10 °C and then for 20 min at 0 °C. Water (50 ml) was added and the mixture was worked up (AcOEt; water, brine). The residue was purified by chromatography on silica gel (hexane–AcOEt, 4 : 1→1 : 1→1 : 2, v/v) to give **15b** (0.42 g, 31%, less polar) as a colorless oil and **15a** (0.25 g, 19%, more polar) as colorless prisms.

15a: mp 122—123 °C (from AcOEt–hexane). *Anal.* Calcd for $C_{11}H_{10}F_2N_4O$: C, 52.38; H, 4.00; N, 22.21. Found: C, 52.08; H, 3.97; N, 22.32. ^{1}H-NMR ($CDCl_3$) δ: 1.69 (3H, d, $J=7.2$ Hz), 2.58 (1H, q, $J=4$ Hz), 2.84 (1H, d, $J=4$ Hz), 5.27 (1H, q, $J=7.2$ Hz), 6.75—7.20 (3H, m), 8.71 (1H, s). IR (KBr): 3060, 1620, 1600, 1506, 1489, 1480 cm^{-1}.

15b: ^{1}H-NMR ($CDCl_3$) δ: 1.76 (3H, dd, $J=7.2$, 1.2Hz), 2.93 (1H, d, $J=4.6$ Hz), 2.98 (1H, d, $J=4.6$ Hz), 5.41 (1H, q, $J=7.2$ Hz), 6.72—7.15 (3H, m), 8.52 (1H, s). IR (neat): 3150, 3060, 1620, 1600, 1506, 1480 cm^{-1}.

(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 (16) A solution of **15a** (0.062 g) in DMF (0.5 ml) was added to a mixture of 1*H*-1,2,4-triazole (0.034 g), NaH (60% in oil, 0.019 g) and DMF (0.8 ml). The mixture was stirred for 5 h at 50 °C, then worked up (AcOEt; water, brine) to afford a residue, which was purified by chromatography on silica gel (AcOEt–hexane, 1 : 1→2 : 1→AcOEt, v/v) to give **16** (0.012 g, 15%). This product was identical with **16** prepared from the oxirane **25** in our preceding report[5] upon direct comparison with the authentic sample.

2-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2,3-epoxy-1-methylpropyl]-4-(4-fluorophenyl)-3(2*H*,4*H*)-1,2,4-triazolone (20a, Table 6) Compound **13** (1.35 g) was converted to **14** in the same manner as that described for the synthesis of **15a**. A solution of **14** in CH_2Cl_2 (28 ml) was added to a stirred mixture of **17a** (963 mg), NaH (60% in oil, 0.198 g) and DMF (8 ml) at −10 °C. The resulting mixture was stirred at −10 °C for 10 min and then at 0 °C for 20 min. Water (15 ml) was added and the mixture was worked up (AcOEt; water, brine). The residue was purified by chromatography on silica gel (hexane–AcOEt, 4 : 1→3 : 1→2 : 1→1 : 1, v/v) to give **20a** (0.583 g, 24%) as colorless needles.

The reaction of **14** with the triazolones (**17b—g**) was carried out in a manner similar to that described above to obtain the corresponding oxirane derivatives (**20b—g**, Table 6).

4-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2,3-epoxy-1-methylpropyl]-2-(4-fluorophenyl)-3(2*H*,4*H*)-1,2,4-triazolone (21a, Table 6) and (2*R*)-2-(2,4-Difluorophenyl)-2-[(1*R*)-1-[1-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-yloxy]-ethyl]oxirane (23a, Table 6) Compound **13** (2.27 g) was converted to **14** in the same manner as that described for the synthesis of **15a**. A solution of **14** in CH_2Cl_2 (45 ml) was added to a stirred mixture of **18a** (1.8 g), NaH (60% in oil, 0.374 g) and DMF (12 ml) at −10 °C. The resulting mixture was stirred at −10 °C for 10 min and then at 0 °C for 20 min. Water (20 ml) was added and the whole was worked up (AcOEt; water, brine) to afford a residue, which was chromatographed on silica gel (hexane–AcOEt, 4 : 1→3 : 1→2 : 1→1 : 1, v/v). The eluate containing the less polar isomer was concentrated and the residue was crystallized from AcOEt–hexane to give **21a** (0.848 g, 21%) as colorless prisms. The eluate containing the more polar isomer was concentrated *in vacuo* to give **23a** (0.446 g, 11%) as a colorless oil.

The reaction of **14** with the triazolones (**18b—g**) was carried out in a manner similar to that described above to give compounds **21b—g** (Table 6) and **23b—g** (Table 6).

1-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2,3-epoxy-1-methylpropyl]-4-(4-fluorophenyl)-5(1*H*,4*H*)-tetrazolone (22a, Table 6) and (2*R*)-2-(2,4-Difluorophenyl)-2-[(1*R*)-1-[1-(4-fluorophenyl)-1*H*-tetrazol-5-yloxy]-ethyl]oxirane (24a, Table 6) Compound **13** (1.43 g) was converted to **14** in the same manner as that described for the synthesis of **15a**. The triflate **14** was allowed to react with **19a** (1.03 g) in the presence of NaH (60% in oil, 0.206 g) in a manner similar to that described for the synthesis of **20a**, and the product was chromatographed on silica gel (hexane–AcOEt, 4 : 1→3 : 1→2 : 1, v/v). The eluate containing the less polar isomer was concentrated *in vacuo* to give **22a** (1.22 g, 47%) as a colorless oil. The eluate containing the more polar isomer was concentrated *in vacuo* to give **24a** (0.205 g, 7.9%) as a colorless oil.

The reaction of **14** with the tetrazolones (**19b—g**) was carried out in a manner similar to that described above to give compounds **22b—g** (Table 6) and **24b—g** (Table 6).

2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-(4-fluorophenyl)-3(2*H*,4*H*)-1,2,4-triazolone (1a, Table 1) A solution of **20a** (0.85 g) in DMF (2 ml) was added to a stirred mixture of 1*H*-1,2,4-triazole (0.315 g), NaH (60% in oil, 0.17 g) and DMF (8 ml). The resulting mixture was stirred for 5 h at 50 °C and worked up (AcOEt; water, brine) to afford a residue, which was chromatographed on silica gel (hexane–AcOEt, 2 : 1→1 : 1→1 : 2→AcOEt, v/v) to give **1a** (0.532 g, 53%) as a colorless powder.

The reaction of **20b—g** with 1*H*-1,2,4-triazole was carried out in a manner similar to that described above to give compounds **1b—g** (Table 1).

The high optical purity (>99%) of **1d** and **1f** was confirmed by HPLC using a chiral stationary phase column (Chiralcel OG and Chiralpak AD, 4.6 mm × 250 mm, Daicel Chemical Industries, Tokyo, Japan) under the following conditions [column; mobile phase; flow rate; detection]: **1d** [OG; hexane–isopropyl alcohol (iso-PrOH), 1 : 1; 1 ml/min; UV at 262 nm], **1f** [AD; hexane–iso-PrOH, 4 : 1; 1 ml/min; UV at 262 nm]. The corresponding racemate used in this analysis was prepared independently.

4-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-2-(4-fluorophenyl)-3(2*H*,4*H*)-1,2,4-triazolone (2a, Table 1) and (4*R*,5*R*)-5-(2,4-Difluorophenyl)-2-(4-fluorophenyl)aminocarbonylimino-4-methyl-5-(1*H*-1,2,4-triazol-1-yl)methyloxazolidine (26a) 1) Compound **21a** (0.84 g) was allowed to react with 1*H*-1,2,4-triazole (0.315 g) in the presence of NaH (60% in oil, 0.17 g) in a manner similar to that described for the synthesis of **1a**. The product was chromatographed on silica gel (hexane–AcOEt, 4 : 1→3 : 1→2 : 1→1 : 1→1 : 2, v/v). The eluate containing the less polar isomer was concentrated *in vacuo* and crystallized from AcOEt–hexane to give **2a** (0.545 g, 55%) as colorless crystals. The eluate containing the more polar isomer was concentrated *in vacuo* and the residue was crystallized from AcOEt–hexane to give **26a** (0.16 g, 16%) as colorless prisms.

26a: mp 99 °C (dec.). *Anal.* Calcd for $C_{20}H_{17}F_3N_6O_2 \cdot 3/2H_2O$: C, 52.52; H, 4.41; N, 18.37. Found: C, 52.76; H, 4.13; N, 18.06. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, d, $J=6.2$ Hz), 4.50 (1H, q, $J=6.2$ Hz), 4.68 (1H, d, $J=14.8$ Hz), 4.83 (1H, d, $J=14.8$ Hz), 6.77—6.95 (2H, m), 6.99 (2H,

Table 6. Oxirane Derivatives (**20**—**24**)

No.	Yield[a] (%)	mp (°C) (Solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ	IR (cm^{-1})
20a	24	100—101 (EA–H)	$C_{18}H_{14}F_3N_3O_2$	59.84 (59.85	3.91 3.93	11.63 11.74)	1.47 (3H, d, J=7.2 Hz), 2.88 (1H, d, J=4.6 Hz), 3.16 (1H, d, J=4.6 Hz), 4.94 (1H, q, J=7.2 Hz), 6.70—6.91 (2H, m), 7.08—7.22 (2H, m), 7.25—7.51 (3H, m), 7.63 (1H, s)	1693, 1618, 1514 (neat)
20b	37	124—125 (EA–H)	$C_{19}H_{14}F_5N_3O_2$	55.48 (55.56	3.43 3.43	10.22 10.15)	1.48 (3H, d, J=7.4 Hz), 2.89 (1H, d, J=4.6 Hz), 3.16 (1H, d, J=4.6 Hz), 4.95 (1H, q, J=7.2 Hz), 6.74—6.90 (2H, m), 7.28—7.42 (1H, m), 7.64—7.86 (5H, m)	1700, 1620, 1390 (KBr)
20c	50	103—106 (IPE–H)	$C_{19}H_{14}F_5N_3O_3$	53.40 53.35	3.30 3.41	9.83 9.84)	1.48 (3H, d, J=7 Hz), 2.88 (1H, d, J=4.8 Hz), 3.16 (1H, d, J=4.8 Hz), 4.94 (1H, q, J=7 Hz), 6.72—6.92 (2H, m), 7.25—7.45 (3H, m), 7.56 (2H, d, J=9.2 Hz), 7.66 (1H, s)	1697, 1620, 1562, 1514, 1430 (KBr)
20d	43	Oil	$C_{20}H_{15}F_6N_3O_3$	52.30 (52.20	3.29 3.24	9.15 9.13)	1.47 (3H, d, J=7.2 Hz), 2.89 (1H, d, J=4.6 Hz), 3.16 (1H, d, J=4.6 Hz), 4.95 (1H, q, J=7.2 Hz), 5.93 (1H, tt, J=53, 2.8 Hz), 6.74—6.90 (2H, m), 7.25—7.45 (3H, m), 7.55 (2H, dt, J=9, 2.2 Hz), 7.67 (1H, s) $[\alpha]_D^{20}$ +16.7° (c=0.91, MeOH)	1699, 1619, 1600, 1554, 1510, 1400 (neat)
20e	46	Oil	$C_{20}H_{16}F_5N_3O_3$	—	—	—[c]	1.46 (3H, d, J=7 Hz), 2.88 (1H, d, J=4.6 Hz), 3.15 (1H, d, J=4.6 Hz), 4.38 (2H, q, J=8 Hz), 4.94 (1H, q, J=7 Hz), 6.74—6.90 (2H, m), 7.02 (2H, d, J=9.2 Hz), 7.36—7.50 (1H, m), 7.44 (2H, d, J=9.2 Hz), 7.62 (1H, s)	1704, 1619, 1558, 1516 (neat)
20f	57	Oil	$C_{21}H_{17}F_6N_3O_3$	SIMS: 474 (MH^+)			1.47 (3H, d, J=7 Hz), 2.88 (1H, d, J=4.8 Hz), 3.16 (1H, d, J=4.8 Hz), 4.38 (2H, d, J=11.8 Hz), 4.94 (1H, q, J=7 Hz), 6.07 (1H, tt, J=53, 4.8 Hz), 6.75—6.90 (2H, m), 6.95—7.12 (2H, m), 7.28—7.55 (3H, m), 7.63 (1H, s) $[\alpha]_D^{20}$ +14.6° (c=1.0, MeOH)	1716, 1705, 1616, 1558, 1516 (neat)
20g	29	Oil	$C_{21}H_{16}F_7N_3O_3$	—	—	—[c]	1.46 (3H, d, J=7 Hz), 2.88 (1H, d, J=4.6 Hz), 3.15 (1H, d, J=4.6 Hz), 4.44 (2H, t, J=12 Hz), 4.94 (1H, q, J=7 Hz), 6.72—6.92 (2H, m), 7.02 (2H, dt, J=9.2, 2.2 Hz), 7.30—7.50 (1H, m), 7.44 (2H, dt, J=9.2, 2.2 Hz), 7.62 (1H, s)	1708, 1619, 1558, 1515, 1427 (neat)
21a	21	163—164 (EA–H)	$C_{18}H_{14}F_3N_3O_2$	59.84 (59.51	3.91 3.83	11.63 11.83)	1.43 (3H, d, J=7.2 Hz), 2.73 (1H, d, J=4.2 Hz), 2.77 (1H, d, J=4.2 Hz), 5.01 (1H, q, J=7.2 Hz), 6.82—7.01 (2H, m), 7.12 (2H, t, J=8.8 Hz), 7.35—7.50 (1H, m), 7.60 (1H, s), 7.96 (2H, dd, J=8.8, 4.6 Hz)	1714, 1620, 1603, 1562, 1512 (KBr)
23a	11	Oil	$C_{18}H_{14}F_3N_3O_2$	SIMS: 362 (MH^+)			1.50 (3H, dd, J=6.6, 1.6 Hz), 2.93 (1H, d, J=4.8 Hz), 3.20 (1H, d, J=4.8 Hz), 5.27 (1H, q, J=6.6 Hz), 6.76—6.98 (2H, m), 7.13 (2H, t, J=8.2 Hz), 7.30—7.49 (1H, m), 7.63 (2H, dd, J=8.2, 4.6 Hz), 7.64 (1H, s)	1618, 1601, 1548 (neat)
21b	22	164—165 (EA–H)	$C_{19}H_{14}F_5N_3O_2$	55.48 (55.17	3.43 3.39	10.22 10.19)	1.44 (3H, d, J=7.2 Hz), 2.74 (1H, d, J=4.2 Hz), 2.78 (1H, d, J=4.2 Hz), 5.02 (1H, q, J=7.2 Hz), 6.80—7.01 (2H, m), 7.35—7.51 (1H, m), 7.64 (1H, s), 7.70 (2H, d, J=8.8 Hz), 8.18 (2H, d, J=8.8 Hz)	1722, 1619, 1601, 1564, 1524 (KBr)
23b	12	Oil	$C_{19}H_{14}F_5N_3O_2$	SIMS: 412 (MH^+)			1.53 (3H, dd, J=6.6, 1.6 Hz), 2.94 (1H, d, J=4.8 Hz), 3.22 (1H, d, J=4.8 Hz), 5.37 (1H, q, J=6.6 Hz), 6.75—6.98 (2H, m), 7.38—7.52 (1H, m), 7.68 (1H, s), 7.70 (2H, d, J=8.4 Hz), 7.85 (2H, d, J=8.4 Hz)	1618, 1599, 1558, 1540 (neat)
21c	25	116—117 (EA–IPE)	$C_{19}H_{14}F_5N_3O_3$	53.40 (53.09	3.30 3.23	9.83 9.83)	1.43 (3H, d, J=7.2 Hz), 2.74 (1H, d, J=4 Hz), 2.77 (1H, d, J=4 Hz), 5.01 (1H, q, J=7.2 Hz), 6.80—7.00 (2H, m), 7.28 (2H, d, J=9.2 Hz), 7.33—7.50 (1H, m), 7.61 (1H, s), 8.05 (2H, d, J=9.2 Hz)	1712, 1618, 1600, 1514 (KBr)
23c	24	Oil	$C_{19}H_{14}F_5N_3O_3$	SIMS: 428 (MH^+)			1.51 (3H, d, J=6.6 Hz), 2.94 (1H, d, J=4.8 Hz), 3.20 (1H, d, J=4.8 Hz), 5.31 (1H, q, J=6.6 Hz), 6.78—6.98 (2H, m), 7.29 (2H, d, J=9 Hz), 7.35—7.50 (1H, m), 7.65 (1H, s), 7.71 (2H, d, J=9 Hz)	1620, 1603, 1549, 1518, 1429 (neat)
21d	45	105—106 (EA–IPE)	$C_{20}H_{15}F_6N_3O_3$	52.30 (52.10	3.29 3.34	9.15 9.13)	1.43 (3H, d, J=7.2 Hz), 2.74 (1H, d, J=4.4 Hz), 2.77 (1H, d, J=4.4 Hz), 5.01 (1H, q, J=7.2 Hz), 5.92 (1H, tt, J=53, 2.8 Hz), 6.81—7.01 (2H, m), 7.28 (2H, d, J=9.2 Hz), 7.30—7.49 (1H, m), 7.61 (1H, s), 8.04 (2H, d, J=9.2 Hz)	1718, 1618, 1601, 1560 (KBr)
23d	11	Oil	$C_{20}H_{15}F_6N_3O_3$	SIMS: 460 (MH^+)			1.51 (3H, dd, J=6.6, 1.4 Hz), 2.94 (1H, d, J=4.8 Hz), 3.21 (1H, d, J=4.8 Hz), 5.30 (1H, q, J=6.6 Hz), 5.97 (1H, tt, J=52.8, 3 Hz), 6.74—6.97 (2H, m), 7.29 (2H, d, J=9.2 Hz), 7.36—7.48 (1H, m), 7.65 (1H, s), 7.70 (2H, d, J=9.2 Hz)	1618, 1599, 1558, 1539 (neat)
21e	38	118—119 (EA–IPE)	$C_{20}H_{16}F_5N_3O_3$	54.43 (54.20	3.65 3.70	9.52 9.58)	1.42 (3H, d, J=7.2 Hz), 2.73 (1H, d, J=4.2 Hz), 2.77 (1H, d, J=4.2 Hz), 4.37 (2H, q, J=8.2 Hz), 5.00 (1H, q, J=7.2 Hz), 6.81—7.02 (2H, m), 7.00 (2H, d, J=9.2 Hz), 7.31—7.50 (1H, m), 7.59 (1H, s), 7.93 (2H, d, J=9.2 Hz)	1712, 1618, 1559, 1497 (KBr)
23e	12	Oil	$C_{20}H_{16}F_5N_3O_3$	SIMS: 442 (MH^+)			1.49 (3H, dd, J=6.6, 1.6 Hz), 2.93 (1H, d, J=5 Hz), 3.20 (1H, d, J=5 Hz), 4.40 (2H, q, J=8.2 Hz), 5.26 (1H, q, J=6.6 Hz), 6.75—6.94 (2H, m), 7.00 (2H, d, J=9.2 Hz), 7.32—7.48 (1H, m), 7.59 (2H, d, J=9.2 Hz), 7.63 (1H, s)	1618, 1598, 1542, 1508 (neat)
21f	37	116—117 (EA–IPE)	$C_{21}H_{17}F_6N_3O_3$	53.28 (53.13	3.62 3.72	8.88 8.86)	1.42 (3H, d, J=7.2 Hz), 2.73 (1H, d, J=4.2 Hz), 2.77 (1H, d, J=4.2 Hz), 4.37 (2H, tt, J=11.8, 1.6 Hz), 5.00 (1H, q, J=7.2 Hz), 6.08 (1H, tt, J=53, 5 Hz), 6.79—7.04 (2H, m), 6.99 (2H, d, J=9.4 Hz), 7.32—7.49 (1H, m), 7.59 (1H, s), 7.93 (2H, d, J=9.4 Hz)	1713, 1618, 1514 (KBr)

Table 6. (continued)

No.	Yield[a] (%)	mp (°C) (Solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ	IR (cm^{-1})
23f	11	Oil	$C_{21}H_{17}F_6N_3O_3$	SIMS: 474 (MH^+)			1.49 (3H, dd, J=6.4, 1.6 Hz), 2.93 (1H, d, J=4.8 Hz), 3.20 (1H, d, J=4.8 Hz), 4.40 (2H, t, J=11.8 Hz), 5.27 (1H, q, J=6.4 Hz), 6.09 (1H, tt, J=53.2, 4.8 Hz), 6.78—6.94 (2H, m), 6.99 (2H, d, J=9 Hz), 7.32—7.49 (1H, m), 7.59 (2H, d, J=9 Hz), 7.63 (1H, s)	1620, 1602, 1550, 1518 (neat)
21g	37	128—129 (EA–IPE)	$C_{21}H_{16}F_7N_3O_3$	51.33 (51.04)	3.28 (3.24)	8.55 (8.46)	1.43 (3H, d, J=7.2 Hz), 2.73 (1H, d, J=4.2 Hz), 2.77 (1H, d, J=4.2 Hz), 4.44 (2H, t, J=12.2 Hz), 5.01 (1H, q, J=7.2 Hz), 6.80—7.01 (2H, m), 7.01 (2H, d, J=9.2 Hz), 7.32—7.49 (1H, m), 7.59 (1H, s), 7.94 (2H, d, J=9.2 Hz)	1712, 1618, 1513, 1383 (KBr)
23g	13	Oil	$C_{21}H_{16}F_7N_3O_3$	SIMS: 492 (MH^+)			1.49 (3H, dd, J=6.6, 1.8 Hz), 2.93 (1H, d, J=4.8 Hz), 3.20 (1H, d, J=4.8 Hz), 4.47 (2H, dt, J=12.2, 1 Hz), 5.27 (1H, q, J=6.6 Hz), 6.76—6.95 (2H, m), 7.00 (2H, d, J=9 Hz), 7.30—7.48 (1H, m), 7.60 (2H, d, J=9 Hz), 7.64 (1H, s)	1620, 1604, 1550, 1518 (neat)
22a	47	Oil	$C_{17}H_{13}F_3N_4O_2$	SIMS: 363 (MH^+)			1.60 (3H, d, J=7.2 Hz), 2.93 (1H, d, J=4.4 Hz), 3.17 (1H, d, J=4.4 Hz), 4.93 (1H, q, J=7.2 Hz), 6.75—6.92 (2H, m), 7.10—7.40 (3H, m), 7.82—7.99 (2H, m)	1734, 1618, 1600, 1558, 1508 (neat)
24a	7.9	Oil	$C_{17}H_{13}F_3N_4O_2$	SIMS: 363 (MH^+)			1.56 (3H, dd, J=6.6, 1.6 Hz), 2.96 (1H, d, J=4.6 Hz), 3.20 (1H, d, J=4.6 Hz), 5.31 (1H, q, J=6.6 Hz), 6.74—6.96 (2H, m), 7.23 (2H, t, J=9 Hz), 7.30—7.49 (1H, m), 7.65 (2H, dd, J=9, 4.6 Hz)	1618, 1600, 1558, 1515, 1425 (neat)
22b	47	Oil	$C_{18}H_{13}F_5N_4O_2$	SIMS: 413 (MH^+)			1.61 (3H, d, J=7.2 Hz), 2.93 (1H, d, J=4.6 Hz), 3.16 (1H, d, J=4.6 Hz), 4.97 (1H, q, J=7.2 Hz), 6.72—6.94 (2H, m), 7.23—7.40 (1H, m), 7.75 (2H, d, J=8.4 Hz), 8.13 (2H, d, J=8.4 Hz)	1734, 1618, 1522, 1508, 1429 (neat)
24b	5.8	Oil	$C_{18}H_{13}F_5N_4O_2$	SIMS: 413 (MH^+)			1.59 (3H, dd, J=6.6, 1.6 Hz), 2.98 (1H, d, J=4.6 Hz), 3.23 (1H, d, J=4.6 Hz), 5.39 (1H, q, J=6.6 Hz), 6.75—6.98 (2H, m), 7.32—7.49 (1H, m), 7.80 (2H, d, J=9 Hz), 7.82 (2H, d, J=9 Hz)	1618, 1600, 1508, 1458, 1423 (neat)
22c	53	Oil	$C_{18}H_{13}F_5N_4O_3$	SIMS: 429 (MH^+)			1.60 (3H, d, J=7.4 Hz), 2.93 (1H, d, J=4.4 Hz), 3.17 (1H, d, J=4.4 Hz), 4.93 (1H, q, J=7.4 Hz), 6.75—6.96 (2H, m), 7.24—7.43 (1H, m), 7.35 (2H, d, J=9.2 Hz), 8.00 (2H, d, J=9.2 Hz)	1732, 1620, 1601, 1514, 1427 (neat)
24c	4	Oil	$C_{18}H_{13}F_5N_4O_3$	SIMS: 429 (MH^+)			1.57 (3H, dd, J=6.6, 1.2 Hz), 2.98 (1H, d, J=4.6 Hz), 3.22 (1H, d, J=4.6 Hz), 5.34 (1H, q, J=6.6 Hz), 6.78—6.98 (2H, m), 7.31—7.50 (1H, m), 7.39 (2H, d, J=8.4 Hz), 7.74 (2H, d, J=8.4 Hz)	1620, 1605, 1514, 1425 (neat)
22d	53	Oil	$C_{19}H_{14}F_6N_4O_3$	SIMS: 461 (MH^+)			1.61 (3H, d, J=7 Hz), 2.93 (1H, d, J=4.4 Hz), 3.17 (1H, d, J=4.4 Hz), 4.93 (1H, q, J=7 Hz), 5.94 (1H, tt, J=52.8, 2.6 Hz), 6.75—6.94 (2H, m), 7.24—7.40 (1H, m), 7.34 (2H, d, J=9 Hz), 7.98 (2H, d, J=9 Hz)	1734, 1618, 1599, 1510, 1427 (neat)
24d	5	Oil	$C_{19}H_{14}F_6N_4O_3$	SIMS: 461 (MH^+)			1.58 (3H, dd, J=6.6, 1.6 Hz), 2.98 (1H, d, J=4.8 Hz), 3.22 (1H, d, J=4.8 Hz), 5.32 (1H, q, J=6.6 Hz), 5.98 (1H, tt, J=52.8, 2.8 Hz), 6.76—6.94 (2H, m), 7.30—7.42 (1H, m), 7.39 (2H, d, J=9 Hz), 7.71 (2H, d, J=9 Hz)	1618, 1601, 1560, 1550, 1508 (neat)
22e	—	Oil[d]	—	—			1.55 (d, J=7 Hz), 1.60 (d, J=8 Hz), 2.93 (d, J=4.5 Hz), 2.96 (d, J=4.8 Hz), 3.17 (d, J=4.5 Hz), 3.20 (d, J=4.8 Hz), 4.40 (q, J=8 Hz), 4.44 (q, J=8 Hz), 4.93 (q, J=8 Hz), 5.31 (q, J=7 Hz), 6.77—6.95 (m), 7.06 (d, J=9.2 Hz), 7.09 (d, J=9.2 Hz), 7.27—7.45 (m), 7.61 (d, J=9.2 hz), 7.86 (d, J=9.2 Hz)	—
22f	38	Oil	$C_{20}H_{16}F_6N_4O_3$	SIMS: 475 (MH^+)			1.60 (3H, d, J=7.2 Hz), 2.93 (1H, d, J=4.4 Hz), 3.17 (1H, d, J=4.4 Hz), 4.40 (2H, t, J=11.8 Hz), 4.93 (1H, q, J=7.2 Hz), 6.08 (1H, tt, J=53.2, 4.6 Hz), 6.73—6.94 (2H, m), 7.05 (2H, d, J=9 Hz), 7.23—7.41 (1H, m), 7.86 (2H, d, J=9 Hz)	1745, 1622, 1601, 1522, 1431 (neat)
24f	15	Oil	$C_{20}H_{16}F_6N_4O_3$	SIMS: 475 (MH^+)			1.56 (3H, dd, J=6.4, 1.6 Hz), 2.96 (1H, d, J=4.8 Hz), 3.21 (1H, d, J=4.8 Hz), 4.44 (2H, t, J=13.2 Hz), 5.31 (1H, q, J=6.4 Hz), 6.10 (1H, tt, J=53.2, 4.6 Hz), 6.78—6.95 (2H, m), 7.08 (2H, d, J=9.2 Hz), 7.30—7.50 (1H, m), 7.61 (2H, d, J=9.2 Hz)	1620, 1599, 1554, 1462 (neat)
22g	55	Oil	$C_{20}H_{15}F_7N_4O_3$	SIMS: 493 (MH^+)			1.60 (3H, d, J=7 Hz), 2.92 (1H, d, J=4.4 Hz), 3.16 (1H, d, J=4.4 Hz), 4.46 (2H, dt, J=12, 1 Hz), 4.92 (1H, q, J=7 Hz), 6.75—6.93 (2H, m), 7.05 (2H, d, J=9.2 Hz), 7.20—7.38 (1H, m), 7.86 (2H, d, J=7 Hz)	1732, 1618, 1601, 1558, 1516, 1427 (neat)
24g	4	Oil	$C_{20}H_{15}F_7N_4O_3$	SIMS: 493 (MH^+)			1.56 (3H, dd, J=6.6, 1.4 Hz), 2.96 (1H, d, J=4.8 Hz), 3.20 (1H, d, J=4.8 Hz), 4.51 (2H, dt, J=12, 1 Hz), 5.31 (1H, q, J=6.6 Hz), 6.74—6.96 (2H, m), 7.09 (2H, d, J=9 Hz), 7.28—7.48 (1H, m), 7.62 (2H, d, J=9 Hz)	1618, 1601, 1558, 1518, 1427 (neat)

a) Yield based on compound **13**. *b*) Recrystallization solvent: EA, ethyl acetate; H, hexane; IPE, diisopropyl ether. *c*) Not determined. *d*) Compounds **22e** and **24e** were inseparable on silica gel chromatography and were obtained as a mixture.

t, J=9 Hz), 7.15—7.35 (1H, m), 7.42 (2H, dd, J=9 Hz, 4.8 Hz), 7.78 (1H, s), 8.09 (1H, s), 8.77 (1H, br). SIMS m/z: 431 (MH^+).

The reaction of **21b** with 1*H*-1,2,4-triazole was carried out in a manner similar to that described above to give compound **2b** (24% yield, Table 1) and compound **26b** (53% yield).

26b: oil. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, J=6.4 Hz), 4.57 (1H, q, J=6.4 Hz), 4.69 (1H, d, J=15 Hz), 4.87 (1H, d, J=15 Hz), 6.80—7.01 (2H, m), 7.24—7.45 (1H, m), 7.54 (2H, d, J=9.8 Hz), 7.60 (2H, d, J=9.8 Hz), 7.82 (1H, s), 8.12 (1H, s), 8.74 (1H, br). SIMS m/z: 481 (MH^+).

The reaction of **21c—g** with 1*H*-1,2,4-triazole was carried out in a manner similar to that described above to give compounds **2c—g** (Table

1).

The high optical purity (>99%) of **2c** was confirmed by HPLC using a chiral stationary phase column (Chiralcel OF, 4.6 mm × 250 mm, Daicel Chemical Industries, Tokyo, Japan) under the following conditions: mobile phase [hexane–iso-PrOH–diethylamine (4 : 1 : 0.025)], flow rate (1 ml/min), detection (UV at 262 nm). The corresponding racemate used in this analysis was prepared independently.

2) A mixture of **2a** (0.1 g), NaH (60% in oil, 0.016 g) and DMF (2 ml) was stirred for 5 h at 80 °C, then cooled, and worked up (AcOEt; water, brine) to afford a residue, which was purified by preparative TLC (AcOEt) to give **26a** (0.051 g, 51%).

1-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-(4-fluorophenyl)-5(1*H*,4*H*)-tetrazolone (3a, Table 1) Compound **22a** (1.22 g) was allowed to react with 1*H*-1,2,4-triazole (0.457 g) in the presence of NaH (60% in oil, 0.247 g) in a manner similar to that described for the synthesis of **1a**. The product was purified by chromatography on silica gel (hexane–AcOEt, 2 : 1 → 1 : 1 → 1 : 2, v/v) to give **3a** (0.748 g, 51%) as a colorless powder.

The reaction of **22b—g** with 1*H*-1,2,4-triazole was carried out in a manner similar to that described above to give compounds **3b—g** (Table 1).

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