Optically Active Antifungal Azoles. VIII.[1] Synthesis and Antifungal Activity of 1-[(1*R*,2*R*)-2-(2,4-Difluoro- and 2-Fluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-(4-substituted phenyl)-2(1*H*,3*H*)-imidazolones and 2-Imidazolidinones

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New optically active antifungal azoles, 1-[(1*R*,2*R*)-2-(2,4-difluoro- and 2-fluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-(4-substituted phenyl)-2(1*H*,3*H*)-imidazolones (1, 2) and 2-imidazolidinones (3, 4), were prepared in a stereocontrolled manner from (1*S*)-1-[(2*R*)-2-(2,4-difluoro- and 2-fluorophenyl)-2-oxiranyl]ethanols (15, 16). Compounds 1—4 showed potent antifungal activity against *Candida albicans in vitro* and *in vivo*, as well as a broad antifungal spectrum for various fungi *in vitro*. Furthermore, the imidazolidinones, 3b—e and 4d, e, were found to exert extremely strong growth-inhibitory activity against *Aspergillus fumigatus*.

Key words optically active antifungal azoles; 1,2,3-trisubstituted-2-butanol; imidazolone; imidazolidinone; stereocontrolled synthesis; antifungal activity

In the course of our search for therapeutically useful antifungal azoles, we designed optically active azolone derivatives depicted by the general formula I (Chart 1). We have recently reported the stereocontrolled synthesis of the triazolone (Ia, b) and tetrazolone (Ic) derivatives as well as their potent antifungal activity against *Candida albicans* (*C. albicans*) *in vitro* and *in vivo*.[2] Among these derivatives, 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-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone [TAK-187: Ia (R=$OCH_2CF_2CF_2H$)] was found to have a broad antifungal spectrum as well as a potent protective effect against various experimental fungal infections in mice.[1—3] This compound was selected as a candidate for clinical trials.

As an extension of our study on the azolones depicted by the general formula I, we planned the synthesis of analogs with carbon substitutions in the triazolone and tetrazolone nuclei: *i.e.*, the imidazolone and imidazolidinone derivatives with the general formula II. Compound II was expected to exert potent antifungal activity because of its structural similarlity to I. Furthermore, it was thought that the slight changes in physicochemical properties owing to this modification might result in the improved antifungal spectrum and pharmacokinetic profile.

Here, we describe the synthesis and antifungal activity of 1-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-(4-substituted phenyl)-2(1*H*,3*H*)-imidazolones (**1**) and 2-imidazolidinones (**3**) as well as their monofluorophenyl analogs (**2**, **4**) shown in Chart 2. The substituent R, *i.e.*, F, CF_3, OCF_3, OCF_2CF_2H and $OCH_2CF_2CF_2H$, was chosen from a series of fluorine-containing groups which was exploited in our previous work[2] as the substituent making compounds resistant to metabolic breakdown *in vivo*.

Chemistry We previously established a route for the synthesis of (1*S*)-1-[(2*R*)-2-(2,4-difluorophenyl)-2-oxiranyl]-ethanol (**15**: Chart 3) starting from compound **5** (C*, *R*:*S*=*ca*. 4:1),[4] and **15** was used as the key synthetic intermediate for the preparation of the azolone derivatives Ia—c *via* an *SN*2 reaction, with an azolone anion at the 1-position, followed by an oxirane ring-opening reaction with 1*H*-1,2,4-triazole.[2] We exploited this synthetic methodology for the preparation of the imidazolone (**1**, **2**) and imidazolidinone (**3**, **4**) derivatives.

For the synthesis of the compounds containing a 2-fluorophenyl nucleus (**2**, **4**), (1*S*)-1-[(2*R*)-2-(2-fluorophenyl)-2-oxiranyl]ethanol (**16**) was chosen as the key synthetic intermediate. Thus, compound **6** (C*, *R*:*S*=*ca*. 4:1)[5] was used as the starting material and converted to **16** *via* substantially the same reactions used for the synthesis of **15**, *i.e.*, **6**→**8**→**10**→**12**→**14**→**16**, as shown in Chart 3.

Next, we investigated a possible improvement of this synthetic process to reduce the number of reaction steps. Thus, the Mitsunobu reaction of **8** was carried out in the presence of 3,5-dinitrobenzoic acid, followed by recrystallization to give the dinitrobenzoate **17** with high diastereomeric purity, and then **17** was hydrolyzed to **16** in high yield.

The oxiranylethanols, **15** and **16**, were converted to the desired imidazolone and imidazolidinone derivatives **1**—**4** according to the method illustrated in Chart 4.

The 2,4-difluorophenyl-oxiranylethanol **15** was converted to the triflate **18** and allowed to react with 1-(4-substituted phenyl)-2(1*H*,3*H*)-imidazolones (**31a**—**e**: Table 3) in the presence of sodium hydride (NaH) at −10 °C. In the case of the 2-fluorophenyl-oxiranylethanol **16**, the corresponding triflate **19** was reacted with 1-[4-(1,1,2,2-tetrafluoroethoxy)-phenyl]- (**31d**) and 1-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2(1*H*,3*H*)-imidazolone (**31e**), which were expected to be moieties leading to high antifungal activity. This *SN*2 reaction produced a mixture of two isomers in all cases. In each case the two isomers were separated by column chromatography on silica gel to obtain *N*-substituted products (**20**, **21**: less polar) and *O*-substituted products (**24**, **25**: more polar) in 12—45% and 11—29% isolated yields, respectively (Table 5). The structures of these isomers were determined based on their IR spectra as follows: compounds **20** and **21** showed

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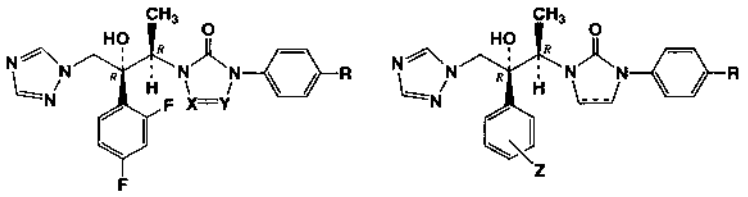
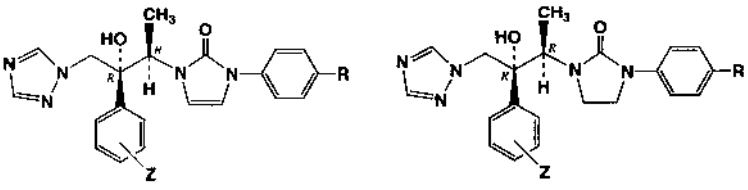


I II

a:X=N,Y=CH
(TAK-187:R=$OCH_2CF_2CF_2H$)
b:X=CH,Y=N
c:X=Y=N

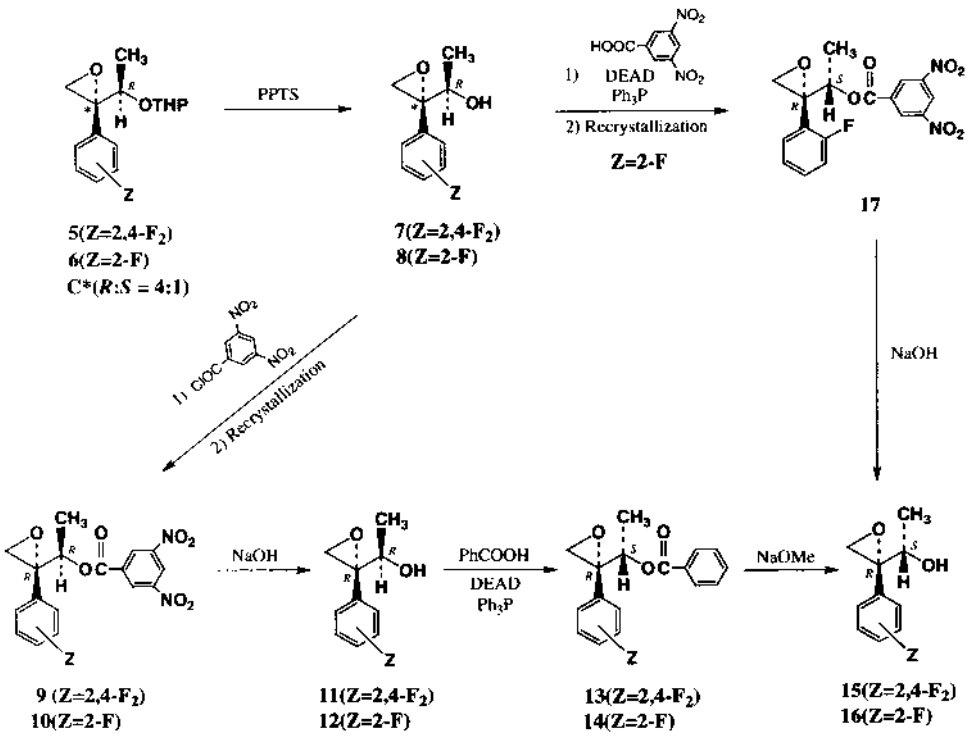
Chart 1



1 : Z=2,4-F_2
2 : Z=2-F
3 : Z=2,4-F_2
4 : Z=2-F

	R
a	F
b	CF_3
c	OCF_3
d	OCF_2CF_2H
e	$OCH_2CF_2CF_2H$

Chart 2



5(Z=2,4-F_2)
6(Z=2-F)
C*(*R*:*S* = 4:1)

7(Z=2,4-F_2)
8(Z=2-F)

17

9 (Z=2,4-F_2)
10(Z=2-F)

11(Z=2,4-F_2)
12(Z=2-F)

13(Z=2,4-F_2)
14(Z=2-F)

15(Z=2,4-F_2)
16(Z=2-F)

Chart 3

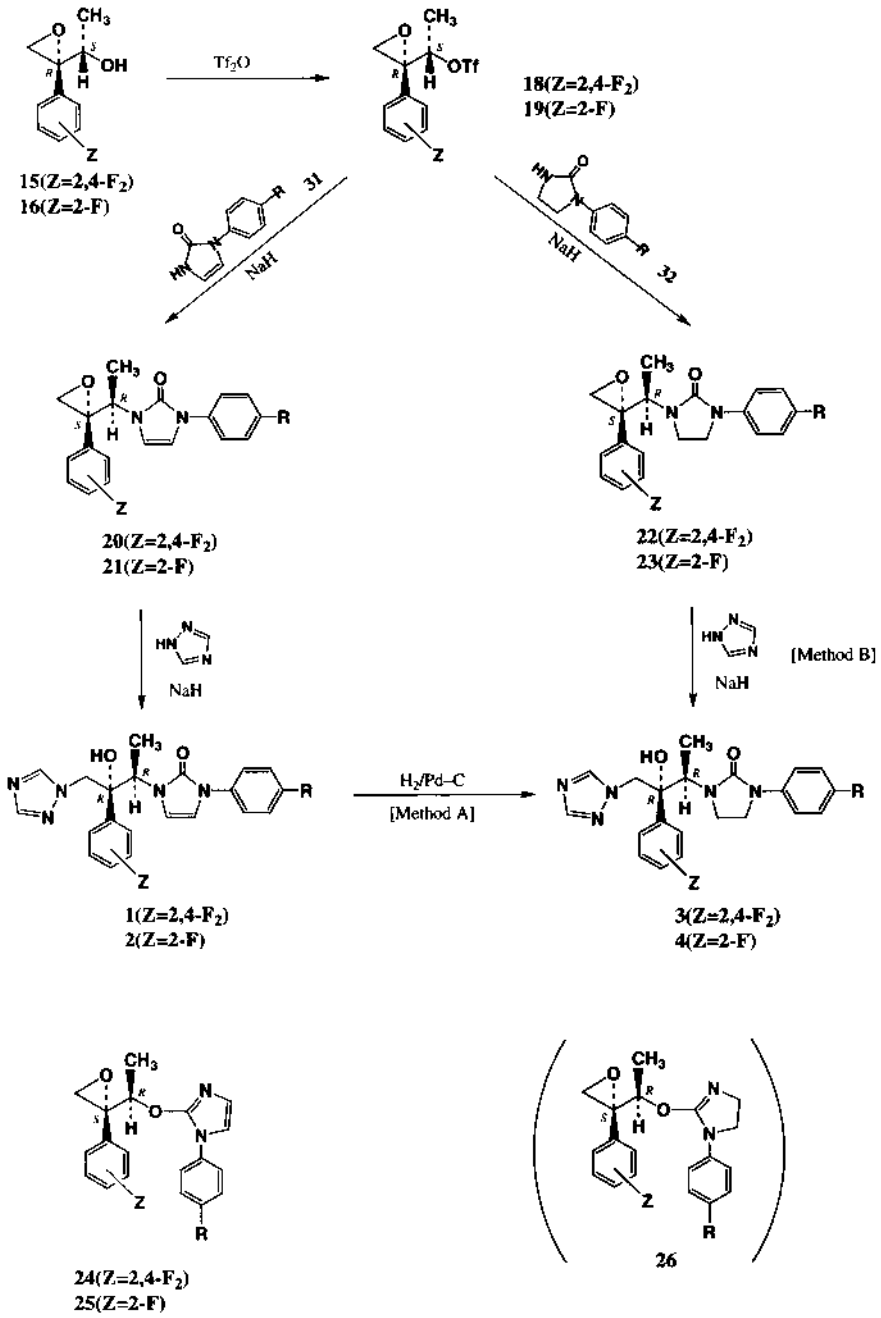


Chart 4

strong absorption at 1660—1700 cm^{-1} due to the carbonyl stretching vibration, while this absorption was not observed in compounds **24** or **25**.

The *N*-substituted compounds obtained above, **20a**—**e** and **21d**, **e**, were allowed to react with 1*H*-1,2,4-triazole in the presence of NaH in *N*,*N*-dimethylformamide (DMF) to give the imidazolone derivatives, **1a**—**e** and **2d**, **e**, in 66—83% isolated yields.

The imidazolidinone derivatives, **3a**—**e** and **4d**, **e**, were prepared by catalytic hydrogenation (method A) on palladium carbon (Pd–C) from the corresponding imidazolones (**1a**—**e**, **2d**, **e**). In addition, the imidazolidinone derivatives, **3b**—**e** and **4d**, **e**, were prepared by an alternative pathway (method B), using 1-(4-substituted phenyl)-2-imidazolidinones (**32b**—**e**: Table 4) which are hydrogenated forms of the imidazolones **31b**—**e**. Thus, the triflates, **18** and **19**, were reacted with **32b**—**e** in the same manner as above to give **22b**—**e** and **23d**, **e** in 16—53% yields based on the oxiranylethanols **15** or **16**. In these cases, formation of the *O*-substituted isomer **26** was not observed. The oxiranes, **22b**—**e** and **23d**, **e**, were then allowed to react with 1*H*-1,2,4-triazole in the presence of NaH to give the desired imidazolidinone derivatives, **3b**—**e** and **4d**, **e**, in 40—74% isolated yields. The structural confirmation of these imidazolone and imidazolidinone derivatives (**1**—**4**) was achieved using the analytical results shown in Table 1.

The imidazolones **31a**—**e** (Table 3) and the imidazolidinones **32b**—**e** (Table 4), which were used in the above synthesis, were prepared as shown in Chart 5. Among the imidazolones **31**, 1-(4-fluoro and 4-trifluoromethylphenyl)-2(1*H*,

Table 1. 1-[(1*R*,2*R*)-2-(2,4-Difluoro and 2-Fluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-(4-substituted phenyl)-2(1*H*,3*H*)-imidazolones (**1**, **2**) and 2-imidazolidinones (**3**, **4**)

No.	Yield[a] (%)	mp[b] (°C) (Solv.)[c]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ	IR (KBr) cm^{-1}	$[\alpha]_D$ {°C} MeOH (*c*)
1a	74	AP	$C_{21}H_{18}F_3N_5O_2$	58.47 (58.87)	4.23 4.42	16.31 16.14)	1.20 (3H, d, *J*=7 Hz), 4.20 (1H, d, *J*=14.2 Hz), 4.95 (1H, q, *J*=7 Hz), 5.10 (1H, d, *J*=14.2 Hz), 5.58 (1H, br), 6.60 (1H, d, *J*=3.2 Hz), 6.74 (1H, d, *J*=3.2 Hz), 6.70—6.88 (2H, m), 7.05—7.20 (2H, m), 7.40—7.65 (3H, m), 7.73 (1H, s), 7.85 (1H, s) [SI-MS (*m*/*z*): 430 (MH^+)]	1687, 1618, 1599, 1513	−24.8° {20} (0.4)
1b	83	AP	$C_{22}H_{18}F_5N_5O_2$	55.12 (54.81	3.78 3.97	14.61 14.39)	1.21 (3H, d, *J*=7.2 Hz), 4.19 (1H, d, *J*=14.2 Hz), 5.00 (1H, q, *J*=7.2 Hz), 5.11 (1H, d, *J*=14.2 Hz), 5.46 (1H, s), 6.71 (1H, d, *J*=3.2 Hz), 6.83 (1H, d, *J*=3.2 Hz), 6.72—6.90 (2H, m), 7.40—7.56 (1H, m), 7.72 (2H, d, *J*=8.4 Hz), 7.75 (1H, s), 7.83 (2H, d, *J*=8.4 Hz), 7.84 (1H, s)	1693, 1618, 1599, 1524, 1500, 1429	−20.4° {20} (0.5)
1c	71	AP	$C_{22}H_{18}F_5N_5O_3$	53.34 (53.08	3.66 3.79	14.14 13.89)	1.20 (3H, d, *J*=7 Hz), 4.19 (1H, d, *J*=14.4 Hz), 4.97 (1H, q, *J*=7 Hz), 5.10 (1H, d, *J*=14.4 Hz), 5.51 (1H, br), 6.39 (1H, d, *J*=3.2 Hz), 6.64 (1H, d, *J*=3.2 Hz), 6.70—6.86 (2H, m), 7.31 (2H, d, *J*=9 Hz), 7.38—7.54 (1H, m), 7.69 (2H, d, *J*=9 Hz), 7.74 (1H, s), 7.84 (1H, s)	1691, 1620, 1599, 1514, 1427, 1252	—
1d	66	126—127 (DE)	$C_{23}H_{19}F_6N_5O_3$	52.38 (52.22	3.63 3.83	13.28 13.08)	1.21 (3H, d, *J*=7 Hz), 4.18 (1H, d, *J*=14 Hz), 4.97 (1H, q, *J*=7 Hz), 5.10 (1H, d, *J*=14 Hz), 5.40—5.60 (1H, br), 5.93 (1H, tt, *J*=53, 2.8 Hz), 6.64 (1H, d, *J*=3 Hz), 6.77 (1H, d, *J*=3 Hz), 6.74—6.84 (2H, m), 7.30 (2H, d, *J*=9 Hz), 7.40—7.55 (1H, m), 7.67 (2H, d, *J*=9 Hz), 7.74 (1H, s), 7.84 (1H, s)	1685, 1510, 1430, 1270, 1200	−18.4° {20} (0.6)
1e	79	144—145 (DCM–IPE) 124.5—125.5 (DE)	$C_{24}H_{21}F_6N_5O_3$	53.24 (53.12	3.91 4.19	12.93 12.76)	1.20 (3H, d, *J*=7 Hz), 4.20 (1H, d, *J*=14 Hz), 4.37 (2H, t, *J*=12 Hz), 4.94 (1H, q, *J*=7 Hz), 5.09 (1H, d, *J*=14 Hz), 5.55—5.74 (1H, br), 6.06 (1H, tt, *J*=53, 5 Hz), 6.59 (1H, d, *J*=3 Hz), 6.72 (1H, d, *J*=3 Hz), 6.74—6.85 (2H, m), 7.01 (2H, d, *J*=9 Hz), 7.42—7.55 (1H, m), 7.58 (2H, d, *J*=9 Hz), 7.73 (1H, s), 7.86 (1H, s)	1682, 1610, 1516, 1428	−17.9° {20} (0.3)
2d	76	AP	$C_{23}H_{20}F_5N_5O_3$	54.23 (53.94	3.96 3.93	13.75 13.64)	1.20 (3H, d, *J*=7 Hz), 4.19 (1H, d, *J*=14 Hz), 5.05 (1H, q, *J*=7 Hz), 5.16 (1H, d, *J*=14 Hz), 5.25—5.50 (1H, br), 5.93 (1H, tt, *J*=53, 2.8 Hz), 6.65 (1H, d, *J*=3 Hz), 6.81 (1H, d, *J*=3 Hz), 6.98—7.08 (2H, m), 7.19—7.50 (2H, m), 7.31 (2H, d, *J*=9 Hz), 7.69 (2H, d, *J*=9 Hz), 7.73 (1H, s), 7.81 (1H, s)	1685, 1510, 1430, 1270, 1200	–23.3 ° {20} (1.0)
2e	77	135—137 (IPE)	$C_{24}H_{22}F_5N_5O_3$	55.07 (54.98	4.24 4.18	13.38 13.35)	1.20 (3H, d, *J*=7 Hz), 4.21 (1H, d, *J*=14 Hz), 4.37 (2H, t, *J*=12 Hz), 4.95—5.11 (1H, m), 5.15 (1H, d, *J*=14 Hz), 5.34—5.56 (1H, br), 6.07 (1H, tt, *J*=53, 5 Hz), 6.59 (1H, d, *J*=3 Hz), 6.76 (1H, d, *J*=3 Hz), 6.97—7.07 (2H, m), 7.01 (2H, d, *J*=9 Hz), 7.17—7.29 (1H, m), 7.44—7.52 (1H, m), 7.59 (2H, d, *J*=9 Hz), 7.72 (1H, s), 7.82 (1H, s)	1675, 1515, 1430, 1255, 1200	−20.7° {20} (0.5)
3a	35[A]	74—78 (EA–H)	$C_{21}H_{20}F_3N_5O_2$	58.46 (58.62	4.67 4.88	16.24 15.87)	1.06 (3H, d, *J*=7 Hz), 3.65—3.73 (1H, m), 3.79—4.00 (3H, m), 4.51 (1H, d, *J*=14 Hz), 4.60 (1H, m), 5.07 (1H, d, *J*=14 Hz), 5.3—5.7 (1H, br), 6.71—6.82 (2H, m), 6.99—7.11 (2H, m), 7.36—7.56 (3H, m), 7.74 (1H, s), 7.87 (1H, s)	1690, 1615, 1510, 1480, 1420	−64.7° {20} (0.7)
3b	17[A] 48[B]	AP	$C_{22}H_{20}F_5N_5O_2$	54.89 (54.72	4.19 4.19	14.55 14.29)	1.07 (3H, d, *J*=7 Hz), 3.60—4.12 (4H, m), 4.49 (1H, d, *J*=14.2 Hz), 4.60—4.80 (1H, m), 5.11 (1H, d, *J*=14.2 Hz), 5.36 (1H, br), 6.70—6.85 (2H, m), 7.32—7.48 (1H, m), 7.60 (2H, d, *J*=8.8 Hz), 7.70 (1H, d, *J*=8.8 Hz), 7.76 (1H, s), 7.85 (1H, s)	1700, 1616, 1523, 1498, 1486	−63.1° {23} (0.6)
3c	66[A] 40[B]	AP	$C_{22}H_{20}F_5N_5O_3$	53.12 (52.83	4.05 4.12	14.08 14.11)	1.08 (3H, d, *J*=7 Hz), 3.65—4.05 (4H, m), 4.53 (1H, d, *J*=14.2 Hz), 4.60—4.80 (1H, m), 5.10 (1H, d, *J*=14.2 Hz), 5.40 (1H, br), 6.68—6.85 (2H, m), 7.31 (2H, d, *J*=9 Hz), 7.32—7.48 (1H, m), 7.69 (2H, d, *J*=9 Hz), 7.76 (1H, s), 7.88 (1H, s)	1695, 1610, 1510, 1480, 1420	−58.5° {20} (0.5)
3d	64[A] 58[B]	164—165 (EA–IPE)	$C_{23}H_{21}F_6N_5O_3$	52.18 (52.30	4.00 3.95	13.23 13.28)	1.07 (3H, d, *J*=7 Hz), 3.67—3.75 (1H, m), 3.82—4.01 (3H, m), 4.50 (1H, d, *J*=15 Hz), 4.65 (1H, m), 5.10 (1H, d, *J*=15 Hz), 5.3—5.6 (1H, br), 5.91 (1H, tt, *J*=53, 3 Hz), 6.72—6.83 (2H, m), 7.21 (2H, d, *J*=9.2 Hz), 7.36—7.49 (1H, m), 7.58 (2H, d, *J*=9.2 Hz), 7.75 (1H, s), 7.86 (1H, s)	1680, 1615, 1510, 1480, 1425	−55.4° {20} (0.8)
3e	70[A] 55[B]	125—126 (EA–IPE)	$C_{24}H_{23}F_6N_5O_3$	53.04 (53.04	4.27 4.50	12.89 12.82)	1.06 (3H, d, *J*=7 Hz), 3.66—3.73 (1H, m), 3.80—3.95 (3H, m), 4.33 (2H, tt, *J*=12, 1.6 Hz), 4.52 (1H, d, *J*=14.4 Hz), 4.5—4.65 (1H, m), 5.08 (1H, d, *J*=14.4 Hz), 5.45—5.65 (1H, br), 6.06 (1H, tt, *J*=53, 4.8 Hz), 6.70—6.83 (2H, m), 6.94 (2H, d, *J*=9.2 Hz), 7.39—7.54 (1H, m), 7.50 (2H, d, *J*=9.2 Hz), 7.74 (1H, s), 7.88 (1H, s)	1690, 1665, 1510, 1485, 1440	−52.7° {20} (0.8)
4d	89[A] 74[B]	142—143 (EA–IPE)	$C_{23}H_{22}F_5N_5O_3$	54.01 (53.96	4.34 4.48	13.69 13.69)	1.06 (3H, d, *J*=7 Hz), 3.68—4.05 (4H, m), 4.51 (1H, d, *J*=14.4 Hz), 4.65—4.80 (1H, m), 5.15 (1H, d, *J*=14.4 Hz), 5.25 (1H, br), 5.91 (1H, tt, *J*=53.2, 3 Hz), 6.95—7.63 (8H, m), 7.74 (1H, s), 7.82 (1H, s)	1680, 1610, 1515, 1480, 1425	−61.8° {23} (1.0)
4e	79[A] 73[B]	126—127 (IPE)	$C_{24}H_{24}F_5N_5O_3$	54.86 (54.66	4.60 4.57	13.33 13.26)	1.06 (3H, d, *J*=7 Hz), 3.66—4.05 (4H, m), 4.33 (2H, tt, *J*=12, 1.6 Hz), 4.52 (1H, d, *J*=14 Hz), 4.60—4.77 (1H, m), 5.13 (1H, d, *J*=14 Hz), 5.35 (1H, br), 6.07 (1H, tt, *J*=53, 5 Hz), 6.91—7.53 (8H, m), 7.73 (1H, s), 7.83 (1H, s)	1690, 1610, 1510, 1480, 1430	−56.3° {23} (1.0)

a) Yield based on compounds **20**—**23** or compounds **1**, **2**. *b*) AP: Amorphous powder. *c*) Recrystallization solvent: DE, diethyl ether; IPE, diisopropyl ether; DCM, dichloromethane; EA, ethyl acetate; H, hexane. [A]: Method A. [B]: Method B.

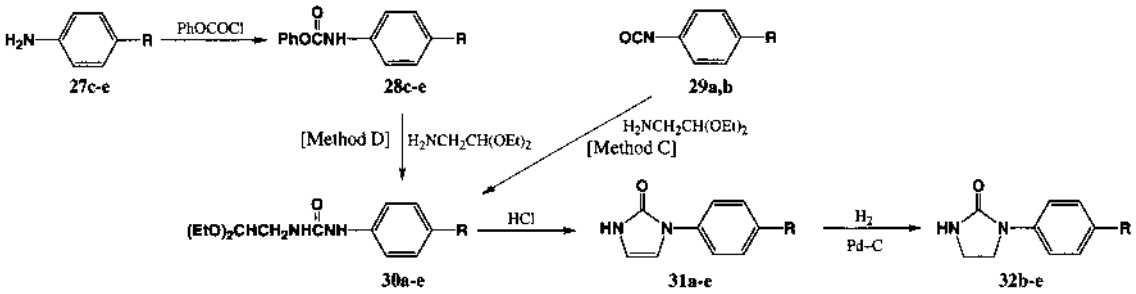


Chart 5

Table 2. Antifungal Activity of Compounds **1**—**4**

No.	*MIC* (μg/ml)[a]							ED_{50} (mg/kg) *p.o.*[d]
	C. albicans[b]		*C. neoformans*[b]		*A. fumigatus*[c]			*C. albicans*
	TA	TIMM1756	TIMM1740	TIMM1855	437	TIMM1728	IFO6344	TA
1a	<0.016	<0.016	0.25	0.5	16	8	16	2.0
1b	<0.016	<0.016	0.03	0.06	4	4	4	0.35
1c	<0.016	<0.016	0.03	0.06	4	2	2	0.56
1d	<0.016	<0.016	0.016	0.03	2	1	1	0.19
1e	<0.016	<0.016	0.06	0.13	2	2	2	0.35
2d	<0.016	<0.016	0.06	0.13	2	2	2	0.18
2e	<0.016	<0.016	0.06	0.13	2	2	4	0.32
3a	<0.016	<0.016	0.13	0.13	8	4	8	2.0
3b	<0.016	<0.016	<0.016	0.03	1	1	1	0.71
3c	<0.016	<0.016	0.03	0.06	1	0.5	0.5	0.77
3d	<0.016	<0.016	<0.016	0.016	0.25	0.25	0.25	0.35
3e	<0.016	<0.016	0.016	0.03	0.5	0.5	0.5	0.71
4d	<0.016	<0.016	<0.016	<0.016	0.5	0.25	0.5	0.35
4e	<0.016	<0.016	<0.016	0.03	1	0.5	0.5	0.65
FCZ	0.13	0.5	4	16	>64	>64	>64	0.22—0.35
TAK-187[e]	0.008	0.016	0.13	0.25	2	2	2	0.32

a) Medium: RPMI 1640 agar. *b*) Determined under 20% CO_2. *c*) Determined under air. *d*) Administered in the form of a 0.5% carboxymethylcellulose (CMC) suspension. *e*) Reported in references 1 and 2.

3*H*)-imidazolones (**31a**, **b**), were synthesized starting from the commercially available phenyl isocyanates (**29a**, **b**) *via* two reaction steps: conversion of **29a**, **b** to the ureas **30a**, **b** by treatment with 2,2-diethoxyethylamine and subsequent cyclization with hydrochloric acid (method C). For the synthesis of the other imidazolones **31c**—**e**, the starting 4-substituted anilines (**27c**—**e**) were converted to the phenylcarbamates **28c**—**e** followed by treatment with 2,2-diethoxyethylamine to give the ureas **30c**—**e** and subsequent cyclization to give **31c**—**e** (method D). On the other hand, 1-(4-substituted phenyl)-2(1*H*,3*H*)-imidazolidinones (**32b**—**e**) were prepared from the corresponding imidazolones **31b**—**e** by catalytic hydrogenation on Pd–C.

Antifungal Activity The imidazolone and imidazolidinone derivatives **1**—**4** were evaluated for *in vitro* antifungal activity against *C. albicans*, *Cryptococcus neoformans* (*C. neoformans*) and *Aspergillus fumigatus* (*A. fumigatus*), and for *in vivo* activity against *C. albicans* in mice. The *in vitro* activity is expressed as the minimum inhibitory concentration (*MIC*, μg/ml). The *MIC* values for yeast type fungi such as *C. albicans* and *C. neoformans* were determined by an agar-dilution method on RPMI 1640 medium under 20% CO_2,[6] and *MIC* values for *A. fumigatus* were measured using the same medium but in air. *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 assays are shown in Table 2.

Compounds **1**—**4** showed strong growth-inhibitory activity against *C. albicans* in the agar-dilution assay. The observed *MIC* values for *C. albicans* (TA, TIMM1756) were all lower than 0.016 μg/ml. Moreover, all compounds showed low *MIC* values of <0.016—0.5 μg/ml for *C. neoformans* (TIMM1740, TIMM1855). On the other hand, in the *in vitro* assay for *A. fumigatus* (437, TIMM1728, IFO6344), compounds **1**—**4** had a range of *MIC* values from 0.25 μg/ml to 16 μg/ml. The imidazolidinones (**3**, **4**) showed clearly lower *MIC* values for *A. fumigatus* compared with those of the corresponding imidazolones (**1**, **2**). In particular, the imidazolidinones (**3b**—**e**, **4d**, **e**) containing the polyfluoro-alkyl and alkoxyphenyl group had strong inhibitory activity (*MIC*, 0.25—1 μg/ml) against the three strains of *A. fumigatus*. In a comparison of the *in vitro* activity of 2-fluorophenyl derivatives (**2d**, **e**, **4d**, **e**) with that of the corresponding 2,4-difluorophenyl derivatives (**1d**, **e**, **3d**, **e**), no distinct differences in *MIC* values were observed. This result indicates that the 4-fluoro atom in the 2,4-difluorophenyl group is not necessary for potent *in vitro* antifungal activity.[7]

In the *in vivo* assay, the imidazolones and imidazolidinones **1**—**4** showed a strong protective effect against candidiasis. The activity (ED_{50}, 0.18—0.77 mg/kg) was comparable

with that of fluconazole (FCZ: ED_{50}, 0.22—0.35 mg/kg) and TAK-187 (ED_{50}, 0.32 mg/kg), except in the case of **1a** and **3a** which showed higher ED_{50} values of 2.0 mg/kg.

In conclusion, we found that the optically active imidazolone and imidazolidinone derivatives (**1**—**4**) showed potent *in vitro* antifungal activity against not only yeasts such as *C. albicans* and *C. neoformans* but also against molds such as *A. fumigatus* as well as potent *in vivo* activitiy against candidiasis. It is particularly noteworthy that the imidazolidinones having the polyfluoro-alkyl and alkoxyphenyl group at the 3-position, **3b**—**e** and **4d**, **e**, exhibited low *MIC* values for *A. fumigatus*. 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 recorded 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. The secondary ion mass spectra (SI-MS) 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 carried out at room temperature unless otherwise noted and followed 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, YMC Co., Ltd.). 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.

ED_{50} values of the compounds against candidiasis were determined by the method described in our preceding report.[4)]

1-(4-Trifluoromethylphenyl)-2(1*H*,3*H*)-imidazolone (31b: Table 3) Method C: 4-Trifluoromethylphenyl isocyanate (**29b**, 10 g) was added dropwise to 2,2-diethoxyethylamine (7.8 ml) over the period of 5 min at 0 °C with stirring. The resulting mixture was stirred for 1 h at room temperature. The precipitated colorless crystals were collected by filtration and washed with hexane to give 1-(2,2-diethoxyethyl)-3-(4-trifluoromethylphenyl)urea (**30b**, 16.2 g, 95%). mp 135—136 °C [from ethanol (EtOH)]. *Anal*. Calcd for $C_{14}H_{19}F_3N_2O_3$: C, 52.50; H, 5.98; N, 8.75. Found: C, 52.62; H, 5.92; N, 8.69. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (6H, t, J=7 Hz), 3.42 (2H, dd, J=6, 5 Hz), 3.56—3.85 (4H, m), 4.56 (1H, t, J=5 Hz), 7.43 (2H, d, J=9 Hz), 7.50 (2H, d, J=9 Hz).

Compound **30b** (9.2 g) was dissolved in a mixture of EtOH (113 ml) and water (57 ml), then 0.48 N HCl (67.5 ml) was added to the solution. The resulting mixture was stirred for 48 h, then neutralized (pH 7.0) with 1 N aqueous NaOH, and concentrated *in vacuo*. The residue was worked up [ethyl acetate (AcOEt); water, brine] and crystallized from AcOEt–diisopropyl ether (iso-Pr_2O) to give **31b** (4.87 g) as colorless prisms.

1-(4-Fluorophenyl)-2(1*H*,3*H*)-imidazolone (**31a**: Table 3) was prepared from 4-fluorophenyl isocyanate (**29a**) *via* the same sequence of reactions as described above.

1-(4-Trifluoromethoxyphenyl)-2(1*H*,3*H*)-imidazolone (31c: Table 3) Method D: 4-Trifluoromethoxyaniline (**27c**) was converted to phenyl 4-trifluoromethoxyphenylcarbamate (**28c**).[1)] A mixture of **28c** (37.5 g), pyridine (10 ml) and 2,2-diethoxyethylamine (20.1 g) was heated at 50 °C for 2 h. The mixture was evaporated *in vacuo* and the residue was crystallized from petroleum ether to give 1-(2,2-diethoxyethyl)-3-(4-trifluoromethoxyphenyl)-urea (**30c**, 32.3 g, 76%).

Compound **30c** (32.1 g) was dissolved in a mixture of methanol (MeOH, 520 ml), water (200 ml) and 0.48 N HCl (240 ml). The resulting solution was stirred for 14 h at room temperature and then concentrated *in vacuo*. The residue was worked up (AcOEt; water, brine) and crystallized from AcOEt–hexane to give **31c** (17.7 g, 75%) as colorless prisms.

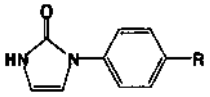
1-[4-(1,1,2,2-Tetrafluoroethoxy)phenyl]-2(1*H*,3*H*)-imidazolone (**31d**: Table 3) and 1-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2(1*H*,3*H*)-imidazolone (**31e**: Table 3) were prepared from the corresponding carbamates **28d**, **e**[1)] *via* the same sequence of reactions as described above.

1-(4-Trifluoromethylphenyl)-2-imidazolidinone (32b: Table 4) A solution of **31b** (1.15 g) in acetic acid (AcOH, 20 ml) was hydrogenated over 10% Pd–C (0.3 g) under room temperature and atmospheric pressure for 6 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was crystallized from AcOEt–iso-Pr_2O to give **32b** (0.95 g) as colorless prisms.

1-(4-Trifluoromethoxyphenyl)-, 1-[4-(1,1,2,2-tetrafluoroethoxy)phenyl]- and 1-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2-imidazolidinone (**32c**—**e:** Table 4) were prepared from the corresponding imidazolones (**31c**—**e**) in the same manner as above.

[(1*R*)-1-[(2*R*)-2-(2-Fluorophenyl)-2-oxiranyl]ethyl] 3,5-Dinitrobenzoate (10) A mixture of **6**[5)] (73.02 g), pyridinium *p*-toluenesulfonate (PPTS, 3.26 g) and EtOH (250 ml) was stirred for 1 h at 55 °C. The mixture was concentrated *in vacuo* and worked up (AcOEt; water, brine). The residue was purified by column chromatography on silica gel (hexane–AcOEt, 5 : 1→4 : 1, v/v) to give **8** (31.72 g, 67%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (2.4H, d, J=6.6 Hz), 1.21 (0.6H, d, J=6.6 Hz), 1.79 (0.8H, d, J=8.4 Hz), 2.27 (0.2H, s), 2.81 (0.8H, d, J=5.2 Hz), 2.95 (0.2H, d, J=5.2 Hz), 3.30 (0.2H, d, J=5.2 Hz), 3.32 (0.8H, d, J=5.2 Hz), 4.11—4.20 (1H,

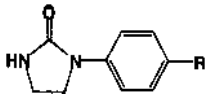
Table 3. 1-(4-Substituted phenyl)-2(1*H*, 3*H*)-imidazolones (**31**)



31	R	Yield[a)] (%)	mp (°C) (Solv.)[b)]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ {IR (KBr) cm^{-1}}
a	F	59 [C]	166—167 (EA–IPE)	$C_9H_7FN_2O$	60.67 (60.65	3.96 4.02	15.72 15.67)	6.43 (1H, t, J=2.8 Hz), 6.49 (1H, t, J=2.8 Hz), 7.14 (2H, dd, J=9, 8.2 Hz), 7.54 (2H, dd, J=9, 4.8 Hz) {3182, 3076, 1670, 1516, 1429}
b	CF_3	70 [C]	170—171 (EA–IPE)	$C_{10}H_7F_3N_2O$	52.64 (52.60	3.09 3.20	12.28 12.15)	6.50 (1H, t, J=3 Hz), 6.62 (1H, t, J=3 Hz), 7.71 (2H, d, J=8.8 Hz), 7.79 (2H, d, J=8.8 Hz) {3360, 3050, 1690, 1610,1520, 1420}
c	OCF_3	48 [D]	145—146 (EA–H)	$C_{10}H_7F_3N_2O_2$	49.19 (49.21	2.89 3.10	11.47 11.44)	6.40—6.65 (2H, m), 7.31 (2H, d, J=9 Hz), 7.63 (2H, dt, J=9, 2 Hz), 10.78 (1H, br) {3147, 1683, 1519, 1429}
d	OCF_2CF_2H	28 [D]	161—163 (EA)	$C_{11}H_8F_4N_2O_2$	47.84 (47.55	2.92 2.96	10.14 10.07)	5.93 (1H, tt, J=53, 2.8 Hz), 6.46 (1H, t, J=2.6 Hz), 6.55 (1H, t, J=2.6 Hz), 7.30 (2H, d, J=9 Hz), 7.63 (2H, d, J=9 Hz), 10.47 (1H, br) {3150, 1685, 1510, 1430, 1200, 1110}
e	$OCH_2CF_2CF_2H$	48 [D]	157—159 (EA)	$C_{12}H_{10}F_4N_2O_2$	49.66 (49.72	3.47 3.52	9.65 9.58)	4.37 (2H, t, J=11 Hz), 6.07(1H, tt, J=53, 4.8 Hz), 6.42 (1H, s), 6.48 (1H, s), 7.01 (2H, d, J=9 Hz), 7.52 (2H, d, J=9 Hz), 10.81 (1H, br s) {3130, 3020, 1690, 1515, 1420, 1255, 1085}

a) Overall yield from isocyanates **29** [Method C] or anilines **27** [Method D]. *b*) Recrystallization solvent: EA, ethyl acetate; IPE, diisopropyl ether; H, hexane.

Table 4. 1-(4-Substituted phenyl)-2-imidazolidinones (**32**)



32	R	Yield[a] (%)	mp (°C) (Solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ {IR (KBr) cm^{-1}}
b	CF_3	82	169—171 (EA–IPE)	$C_{10}H_9F_3N_2O$	52.18 (51.94	3.94 3.89	12.17 12.23)	3.63 (2H, t, J=8 Hz), 3.99 (2H, t, J=8 Hz), 4.95 (1H, br), 7.59 (2H, d, J=9 Hz), 7.68 (2H, d, J=9 Hz) {3230, 1700, 1616, 1523, 1488, 1410}
c	OCF_3	88	146—147 (ET–IPE)	$C_{10}H_9F_3N_2O_2$	48.79 (48.96	3.68 3.52	11.38 11.36)	3.59 (2H, t, J=8 Hz), 3.93 (2H, t, J=8 Hz), 5.55 (1H, br), 7.19 (2H, d, J=9 Hz), 7.55 (2H, d, J=9 Hz) {3250, 1705, 1680, 1515, 1485}
d	OCF_2CF_2H	90	169—171 (IPE)	$C_{11}H_{10}F_4N_2O_2$	47.49 (47.48	3.62 3.70	10.07 10.03)	3.59 (2H, t, J=8 Hz), 3.94 (2H, t, J=8 Hz), 5.08 (1H, br), 5.90 (1H, tt, J=53, 3 Hz), 7.19 (2H, d, J=9 Hz), 7.56 (2H, d, J=9 Hz) {3240, 1700, 1505, 1482, 1430}
e	$OCH_2CF_2CF_2H$	92	180—181 (IPE)	$C_{12}H_{12}F_4N_2O_2$	49.32 (49.24	4.14 3.96	9.59 9.59)	3.53—3.61 (2H, m), 3.87—3.95 (2H, m), 4.32 (2H, tt, J=11.8, 1.6 Hz), 4.97 (1H, br), 6.06 (1H, tt, J=53, 5 Hz), 6.91 (2H, d, J=9.2 Hz), 7.47 (2H, d, J=9.2 Hz) {3250, 1705, 1680, 1515, 1485}

a) Yield from imidazolones **31**. *b*) Recrystallization solvent: EA, ethyl acetate; IPE, diisopropyl ether; ET, ethanol.

m), 6.99—7.47 (4H, m).

Compound **8** (31.72 g) and 3,5-dinitrobenzoyl chloride (44.04 g) were dissolved in CH_2Cl_2 (350 ml). Triethylamine (Et_3N, 19.33 g) was added dropwise to this solution at 0 °C. After stirring for 30 min at 0 °C and for 1.5 h at room temperature, 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 (150 ml) was added to the residue. The resulting mixture was cooled in an ice bath. The precipitated crystals were collected by filtration and recrystallized from AcOEt–MeOH to give **10** (14.72 g, 22%) as colorless prisms. mp 183—184 °C (from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, dd, J=6.6, 1.6 Hz), 3.03 (1H, d, J=4.7 Hz), 3.23 (1H, d, J=4.7 Hz), 5.35 (1H, q, J=6.6 Hz), 7.09—7.59 (4H, m), 9.13 (2H, d, J=2.2 Hz), 9.23 (1H, t, J=2.2 Hz). *Anal*. Calcd for $C_{17}H_{13}FN_2O_7$: C, 54.26; H, 3.48; N, 7.44. Found: C, 54.23; H, 3.25; N, 7.41. $[\alpha]_D^{23}$ −24.7° (c=1.0, $CHCl_3$). IR (KBr): 3100, 1720, 1540, 1340, 1270 cm^{-1}.

(1*R*)-1-[(2*R*)-2-(2-Fluorophenyl)-2-oxiranyl]ethanol (12) 1 N aqueous NaOH (76.6 ml) was added dropwise to a solution of **10** (14.36 g) in MeOH (650 ml). The mixture was stirred for 1 h, then 1 N HCl (38.3 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, 4 : 1, v/v) to give **12** (6.39 g, 92%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, dd, J=6.6, 1.0 Hz), 1.78 (1H, d, J=8.2 Hz), 2.81 (1H, d, J=5.3 Hz), 3.32 (1H, d, J=5.3 Hz), 4.09—4.23 (1H, m), 6.99—7.47 (4H, m). $[\alpha]_D^{20}$ −66.2° (c=1.0, MeOH). IR (KBr): 3420, 2970, 1615, 1580, 1490, 1450 cm^{-1}.

[(1*S*)-1-[(2*R*)-2-(2-Fluorophenyl)-2-oxiranyl]ethyl] Benzoate (14) Triphenylphosphine (Ph_3P, 23.08 g), benzoic acid (PhCOOH, 10.74 g) and diethyl azodicarboxylate (DEAD, 13.82 ml) were added to an ice-cooled solution of **12** (6.39 g) in tetrahydrofuran (THF, 120 ml). The mixture was stirred overnight, then worked up (AcOEt; water, brine), and the residue was chromatographed on silica gel (hexane–AcOEt, 30 : 1→10 : 1, v/v) to give **14** (6.65 g, 66%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, J=7 Hz), 2.92 (1H, d, J=5 Hz), 3.29 (1H, d, J=5 Hz), 5.39 (1H, q, J=7 Hz), 6.98—7.18 (2H, m), 7.26—7.59 (5H, m), 7.95—7.99 (2H, m).

(1*S*)-1-[(2*R*)-2-(2-Fluorophenyl)-2-oxiranyl]ethanol (16) i) A 28% sodium methoxide (NaOMe)–MeOH (5.37 g) solution was added to an ice-cooled solution of **14** (6.64 g) in MeOH (200 ml). The mixture was stirred for 3.5 h, then 1 N HCl (27.8 ml) was added. The mixture was concentrated and the residue was submitted to silica gel column chromatography (hexane–AcOEt, 6 : 1→2 : 1, v/v) to give **16** (3.83 g, 91%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J=7 Hz), 2.27 (1H, d, J=2 Hz), 2.96 (1H, d, J=5 Hz), 3.30 (1H, d, J=5 Hz), 4.16 (1H, dq, J=7, 2 Hz), 7.03—7.44 (4H, m). IR (neat): 3450, 2980, 1620, 1580, 1490, 1450 cm^{-1}. $[\alpha]_D^{20}$ −52.3° (c=1.0, MeOH).

ii) Ph_3P (127.2 g), 3,5-dinitrobenzoic acid (102.88 g) and DEAD (84.47 g) were added to an ice-cooled solution of **8** (34.77 g) in THF (600 ml). The mixture was stirred for 7 h under an argon atmosphere, then worked up (AcOEt–iso-Pr_2O; water, brine). The residue was purified by chromatography on silica gel (hexane–AcOEt, 5 : 1, v/v) followed by crystallization from AcOEt to give **17** (23.15 g, 27%) as colorless needles. mp 147—148 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, d, J=7 Hz), 2.97 (1H, d, J=5 Hz), 3.29 (1H, d, J=5 Hz), 5.43 (1H, q, J=7 Hz), 7.02—7.56 (4H, m), 9.06 (2H, d, J=2 Hz), 9.21 (1H, t, J=2 Hz). *Anal*. Calcd for $C_{17}H_{13}FN_2O_7$: C, 54.26; H, 3.48; N, 7.44. Found: C, 54.09; H, 3.45; N, 7.31. IR (KBr): 3120, 1720, 1540, 1340, 1280 cm^{-1}. $[\alpha]_D^{20}$ −14.7° (c=1.0, $CHCl_3$).

Aqueous 1 N NaOH (146.5 ml) was added to an ice-cooled solution of **17** (22.91 g) in MeOH (700 ml). The mixture was stirred for 1 h, then 1 N HCl (85.5 ml) was added. The whole was concentrated and worked up (AcOEt; water, brine) to afford a residue, which was submitted to silica gel column chromatography (hexane–AcOEt, 3 : 1, v/v) to give **16** (10.76 g, 97%) as a colorless oil.

1-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2,3-epoxy-1-methylpropyl]-3-(4-trifluoromethylphenyl)-2(1*H*,3*H*)-imidazolone (20b: Table 5) and (2*R*)-2-(2,4-Difluorophenyl)-2-[(1*R*)-1-[1-(4-trifluoromethylphenyl)-2-imidazolyloxy]ethyl]oxirane (24b: Table 5) Trifluoromethanesulfonic anhydride (Tf_2O, 0.49 ml) was added dropwise to a stirred solution of **15** (0.535 g) and diisopropylethylamine (iso-Pr_2NEt, 0.51 ml) in CH_2Cl_2 (15 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. The mixture was condensed to about 9 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 **18** were combined and concentrated to about 3 ml.[8] This solution was added to a stirred mixture of **31b** (0.606 g), NaH (60% in oil, 0.085 g) and DMF (3 ml) at −10 °C. The resulting mixture was stirred at −10 °C for 10 min and then at 0 °C for 20 min. The mixture was then worked up (AcOEt; water, brine) and the residue was purified by chromatography on silica gel (hexane–AcOEt, 3 : 1→2 : 1→1 : 1, v/v) to give **20b** (0.362 g) as colorless crystals and **24b** (0.209 g) as a colorless oil.

The reaction of **18** with the imidazolones (**31a**, **c**—**e**) was carried out as described above to obtain the corresponding oxirane derivatives (**20a**, **c**—**e**, **24a**, **c**—**e**: Table 5).

1-[(1*R*,2*S*)-2-(2-Fluorophenyl)-2,3-epoxy-1-methylpropyl]-3-[4-(1,1,2,2-tetrafluoroethoxy)phenyl]-2(1*H*,3*H*)-imidazolone (21d: Table 5) and (2*R*)-2-(2-Fluorophenyl)-2-[(1*R*)-1-[1-[4-(1,1,2,2-tetrafluoroethoxy)phenyl]-2-imidazolyloxy]ethyl]oxirane (25d: Table 5) Compound **16** (1.004 g) was converted to the triflate **19** as described in the synthesis of **20b**. The solution of **19** in CH_2Cl_2 (28 ml)[8] was added to a stirred mixture of **31d** (1.215 g), NaH (60% in oil, 0.168 g) and DMF (10 ml) at −10 °C. The resulting mixture was stirred at −10 °C for 30 min and then at 0 °C for 20 min. The mixture was then worked up (AcOEt; water, brine) and the residue was purified by chromatography on silica gel (hexane–AcOEt, 5 : 1→2 : 1, v/v) to give **21d** (0.825 g) as a colorless powder and **25d** (0.538 g) as a colorless oil.

The reaction of **19** with **31e** was carried out as described above to obtain **21e** (Table 5).

1-[(1*R*,2*S*)-2-(2,4-Difluoro- and 2-Fluorophenyl)-2,3-epoxy-1-methylpropyl]-3-(4-substituted phenyl)-2-imidazolidinone (22b—e, 23d, e: Table 5) The triflates **18** and **19** were allowed to react with **32b**—**e** as de-

Table 5. Oxirane Derivatives (**20**—**25**)

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	31	Oil	$C_{19}H_{15}F_3N_2O_2$	[SI-MS (*m*/*z*): 361(MH^+)]			1.37 (3H, d, *J*=7.2 Hz), 2.70 (1H, d, *J*=4.8 Hz), 2.81 (1H, d, *J*=4.8 Hz), 5.07 (1H, q, *J*=7.2 Hz), 6.44 (1H, d, *J*=3.2 Hz), 6.52 (1H, d, *J*=3.2 Hz), 6.79—6.98 (2H, m), 7.02—7.20 (2H, m), 7.35—7.50 (1H, m), 7.50— 7.68 (2H, m)	1693, 1618, 1600, 1512 (neat)
24a	25	Oil	$C_{19}H_{15}F_3N_2O_2$	[SI-MS (*m*/*z*): 361(MH^+)]			1.44 (3H, dd, *J*=6.4, 1.6 Hz), 2.88 (1H, d, *J*=4.8 Hz), 3.14 (1H, d, *J*=4.8 Hz), 5.16 (1H, q, *J*=6.4 Hz), 6.65—6.80 (4H, m), 7.01—7.19 (2H, m), 7.20—7.38 (3H, m)	1618, 1601 (neat)
20b	33	135—136 (EA–H)	$C_{20}H_{15}F_5N_2O_2$	58.54 (58.80	3.68 3.90	6.83 6.81)	1.37 (3H, d, *J*=7.2 Hz), 2.72 (1H, d, *J*=4.4 Hz), 2.82 (1H, d, *J*=4.4 Hz), 5.09 (1H, q, *J*=7.2 Hz), 6.50 (1H, d, *J*=3.2 Hz), 6.64 (1H, d, *J*=3.2 Hz), 6.80—6.97 (2H, m), 7.35—7.50 (1H, m), 7.69 (2H, d, *J*=8.4 Hz), 7.82 (2H, d, *J*=8.4 Hz)	1684, 1616, 1523 (KBr)
24b	19	Oil	$C_{20}H_{15}F_5N_2O_2$	[SI-MS (*m*/*z*): 411(MH^+)]			1.46 (3H, dd, *J*=6.6, 1.6 Hz), 2.89 (1H, d, *J*=4.8 Hz), 3.16 (1H, d, *J*=4.8 Hz), 5.24 (1H, q, *J*=6.6 Hz), 6.70—6.91 (4H, m), 7.22—7.40 (1H, m), 7.50 (2H, d, *J*=8.4 Hz), 7.70 (2H, d, *J*=8.4 Hz)	1620, 1616, 1599 (neat)
20c	21	99—100 (EA–H)	$C_{20}H_{15}F_5N_2O_3$	56.34 (56.36	3.55 3.50	6.57 6.60)	1.37 (3H, d, *J*=7.2 Hz), 2.71 (1H, d, *J*=4.8 Hz), 2.80 (1H, d, *J*=4.8 Hz), 5.07 (1H, q, *J*=7.2 Hz), 6.46 (1H, d, *J*=3.2 Hz), 6.56 (1H, d, *J*=3.2 Hz), 6.80—6.96 (2H, m), 7.28 (2H, d, *J*=9 Hz), 7.40 (1H, m), 7.67 (2H, d, *J*=9 Hz)	1682, 1620, 1606, 1516, 1433 (KBr)
24c	16	Oil	$C_{20}H_{15}F_5N_2O_3$	—	—	—	1.45 (3H, dd, *J*=6.6, 1.6 Hz), 2.90 (1H, d, *J*=5 Hz), 3.14 (1H, d, *J*=5 Hz), 5.19 (1H, q, *J*=6.6 Hz), 6.70—6.90 (4H, m), 7.18—7.50 (5H, m)	1616, 1558, 1541 (neat)
20d	14	117—118 (DE)	$C_{21}H_{16}F_6N_2O_3$	—	—	—	1.37 (3H, d, *J*=7.2 Hz), 2.71 (1H, d, *J*=5 Hz), 2.81 (1H, d, *J*=5 Hz), 5.08 (1H, q, *J*=7.2 Hz), 5.93 (1H, tt, *J*=53, 2.8 Hz), 6.46 (1H, d, *J*=3 Hz), 6.57 (1H, d, *J*=3 Hz), 6.80—6.95 (2H, m), 7.28 (2H, d, *J*=9 Hz), 7.36—7.48 (1H, m), 7.67 (2H, d, *J*=9 Hz)	—
24d	11	Oil	$C_{21}H_{16}F_6N_2O_3$	—	—	—	1.45 (3H, dd, *J*=6.6, 2 Hz), 2.90 (1H, d, *J*=5 Hz), 3.15 (1H, d, *J*=5 Hz), 5.16 (1H, q, *J*=6.6 Hz), 5.97 (1H, tt, *J*=53, 3 Hz), 6.7—6.9 (2H, m), 6.74 (1H, d, *J*=1.8 Hz), 6.80 (1H, d, *J*=1.8 Hz), 7.2—7.4 (1H, m), 7.28 (2H, d, *J*=9 Hz), 7.38 (2H, d, *J*=9 Hz)	—
20e	18	AP[c]	$C_{22}H_{18}F_6N_2O_3$	55.94 (56.01	3.84 3.74	5.93 6.28)	1.36 (3H, d, *J*=7.2 Hz), 2.70 (1H, d, *J*=4.7 Hz), 2.81 (1H, d, *J*=4.7 Hz), 4.36 (2H, t, *J*=12 Hz), 5.07 (1H, q, *J*=7.2 Hz), 6.06 (1H, tt, *J*=53, 4.8 Hz), 6.43 (1H, d, *J*=3 Hz), 6.51 (1H, d, *J*=3 Hz), 6.79—7.02 (4H, m), 7.26—7.47 (1H, m), 7.52—7.60 (2H, m)	1662,1516, 1426, 1258, 1100 (KBr)
24e	12	Oil	$C_{22}H_{18}F_6N_2O_3$	—	—	—	1.43 (3H, d, *J*=6.6 Hz), 2.86 (1H, d, *J*=5.2 Hz), 3.14 (1H, d, *J*=5.2 Hz), 4.32—4.47 (2H, m), 5.19 (1H, q, *J*=6.6 Hz), 6.09 (1H, tt, *J*=53, 4.8 Hz), 6.72—6.83 (4H, m), 6.90—7.02 (2H, m), 7.24—7.47 (3H, m)	—
21d	45	104—105 (IPE–H)	$C_{21}H_{17}F_5N_2O_3$	57.28 (57.46	3.89 3.62	6.36 6.55)	1.38 (3H, d, *J*=7 Hz), 2.73 (1H, d, *J*=4.8 Hz), 2.81 (1H, d, *J*=4.8 Hz), 5.13 (1H, q, *J*=7 Hz), 5.92 (1H, tt, *J*=53, 3 Hz), 6.48 (1H, d, *J*=3 Hz), 6.56 (1H, d, *J*=3 Hz), 7.05—7.20 (2H, m), 7.27 (2H, d, *J*=9 Hz), 7.31—7.63 (2H, m), 7.67 (2H, d, *J*=9 Hz)	1690, 1515, 1490, 1425, 1300 (KBr)
25d	29	Oil	$C_{21}H_{17}F_5N_2O_3$	—	—	—	1.47 (3H, dd, *J*=6.6, 1.8 Hz), 2.92 (1H, d, *J*=5 Hz), 3.16 (1H, d, *J*=5 Hz), 5.19 (1H, q, *J*=6.6 Hz), 5.96 (1H, tt, *J*=53, 3 Hz), 6.74 (1H, d, *J*=1.8 Hz), 6.80 (1H, d, *J*=1.8 Hz), 6.98—7.08 (2H, m), 7.25—7.39 (2H, m), 7.26 (2H, d, *J*=9 Hz), 7.38 (2H, d, *J*=9 Hz)	—
21e	12	118—119 (IPE)	$C_{22}H_{19}F_5N_2O_3$	58.15 (58.17	4.21 4.12	6.16 6.23)	1.37 (3H, d, *J*=7 Hz), 2.72 (1H, d, *J*=5 Hz), 2.81 (1H, d, *J*=5 Hz), 4.36 (2H, tt, *J*=12, 2 Hz), 5.12 (1H, q, *J*=7 Hz), 6.07 (1H, tt, *J*=53, 5 Hz), 6.45 (1H, d, *J*=3 Hz), 6.51 (1H, d, *J*=3 Hz), 6.98 (2H, d, *J*=9 Hz), 7.04—7.19 (2H, m), 7.28—7.47 (2H, m), 7.57 (2H, d, *J*=9 Hz)	1690, 1665, 1515, 1455, 1435 (KBr)
25e	Not isolated							
22b	30	144—146 (EA–H)	$C_{20}H_{17}F_5N_2O_2$	58.26 (58.23	4.16 3.91	6.79 6.87)	1.24 (3H, d, *J*=7.2 Hz), 2.76 (1H, d, *J*=4.8 Hz), 3.14 (1H, d, *J*=4.8 Hz), 3.48—3.70 (2H, m), 3.78—3.90 (2H, m), 4.83 (1H, q, *J*=7.2 Hz), 6.78—6.95 (2H, m), 7.37—7.48 (1H, m), 7.57 (2H, d, *J*=8.8 Hz), 7.67 (2H, d, *J*=8.8 Hz)	1704, 1618, 1506, 1486, 1430 (KBr)
22c	30	101—102 (EA–H)	$C_{20}H_{17}F_5N_2O_3$	56.08 (56.06	4.00 4.07	6.54 6.61)	1.22 (3H, d, *J*=7 Hz), 2.76 (1H, d, *J*=5 Hz), 3.14 (1H, d, *J*=5 Hz), 3.44—3.65 (2H, m), 3.76—3.84 (2H, m), 4.81 (1H, q, *J*=7 Hz), 6.77—6.93 (2H, m), 7.19 (2H, d, *J*=9 Hz), 7.34—7.46 (1H, m), 7.56 (2H, d, *J*=9 Hz)	1695, 1510, 1480, 1420 (KBr)
22d	16	131—132 (EA–H)	$C_{21}H_{18}F_6N_2O_3$	54.79 (54.78	3.94 3.86	6.08 6.13)	1.22 (3H, d, *J*=7.4 Hz), 2.75 (1H, d, *J*=5 Hz), 3.14 (1H, d, *J*=5 Hz), 3.44—3.65 (2H, m), 3.73—3.84 (2H, m), 4.80 (1H, q, *J*=7.4 Hz), 5.89 (1H, tt, *J*=53, 2.8 Hz), 6.77—6.93 (2H, m), 7.17 (2H, d, *J*=9 Hz), 7.34 —7.46 (1H, m), 7.55 (2H, d, *J*=9 Hz)	1680, 1615, 1510, 1485, 1425 (KBr)
22e	21	121—122 (EA–H)	$C_{22}H_{20}F_6N_2O_3$	55.70 (55.65	4.25 4.15	5.90 6.02)	1.21 (3H, d, *J*=7.2 Hz), 2.75 (1H, d, *J*=7 Hz), 3.15 (1H, d, *J*=7 Hz), 3.42—3.64 (2H, m), 3.71—3.81 (2H, m), 4.32 (2H, tt, *J*=12, 1.4 Hz), 4.80 (1H, q, *J*=7.2 Hz), 6.06 (1H, tt, *J*=53, 5 Hz), 6.76—6.9 (2H, m), 6.91 (2H, d, *J*=9.2 Hz), 7.35 —7.5 (1H, m), 7.48 (2H, d, *J*=9.2 Hz)	1692, 1615, 1512, 1480, 1422 (KBr)
23d	53	148—149 (IPE)	$C_{21}H_{19}F_5N_2O_3$	57.02 (56.90	4.33 4.36	6.33 6.31)	1.24 (3H, d, *J*=7.2 Hz), 2.78 (1H, d, *J*=5 Hz), 3.15 (1H, d, *J*=5 Hz), 3.45—3.84 (4H, m), 4.85 (1H, q, *J*=7.2 Hz), 5.90 (1H, tt, *J*=53.2, 2.8 Hz), 7.02—7.60 (8H, m)	1680, 1510, 1495 (KBr)
23e	45	144—145 (IPE)	$C_{22}H_{21}F_5N_2O_3$	57.90 (57.94	4.64 4.60	6.14 6.19)	1.22 (3H, d, *J*=7.4 Hz), 2.77 (1H, d, *J*=5 Hz), 3.16 (1H, d, *J*=5 Hz), 3.47—3.77(4H, m), 4.32 (2H, tt, *J*=12, 1.6 Hz), 4.85 (1H, q, *J*=7.4 Hz), 6.07 (1H, tt, *J*=53, 5 Hz), 6.89 —7.52 (8H, m)	1690, 1510, 1480 (KBr)

a) Yield based on compounds **15** or **16**. *b*) Recrystallization solvent: EA, ethyl acetate; H, hexane; DE, diethyl ether; IPE, diisopropyl ether. *c*) Amorphous powder

scribed in the synthesis of compound **20b** to give the corresponding imidazolidinone-containing oxirane derivatives (**22b**—**e**, **23d**, **e**).

1-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-(4-trifluoromethylphenyl)-2(1*H*,3*H*)-imidazolone (1b: Table 1) A solution of **20b** (0.362 g) in DMF (2 ml) was added to a stirred mixture of 1*H*-1,2,4-triazole (0.118 g), NaH (60% in oil, 0.065 g) and DMF (4 ml). The resulting mixture was stirred for 5 h at 50 °C and worked up (AcOEt; water, brine). The residue was then chromatographed on silica gel (hexane–AcOEt, 1 : 1→1 : 2→AcOEt, v/v) to give **1b** (0.035 g) as a colorless powder.

The reaction of **20a**, **c**—**e** and **21d**, **e** with 1*H*-1,2,4-triazole was carried out as described above to give the corresponding imidazolone derivatives (**1a**, **c**—**e**, **2d**, **e**: Table 1).

The high optical purity (>99% ee) was confirmed with compounds, **1d**, **e** and **2d**, **e**, by HPLC using a chiral column (Chiralcel OF for **2d** and Chiralpak AD for **1d**, **e** and **2e**, 4.6 mm×250 mm, Daicel Chemical Industries, Tokyo, Japan) under the following conditions: mobile phase [hexane–isopropyl alcohol (iso-PrOH), 1 : 1 for **1e** and **2e**, 5 : 1 for **1d** and 2 : 1 for **2d**], flow rate (1 ml/min), detection (UV at 262 nm). The corresponding racemate used in this analysis was prepared independently.

1-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-(4-trifluoromethylphenyl)-2-imidazolidinone (3b: Table 1) Method A: A solution of **1b** (0.1 g) in AcOH (10 ml) was hydrogenated over 10% Pd–C (0.05 g) at room temperature and atmospheric pressure for 14 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel (CH_2Cl_2–acetone, 5 : 1, v/v) to give **3b** (0.017 g) as a colorless amorphous powder.

Catalytic hydrogenation of **1a**, **c**—**e** and **2d**, **e** as above afforded the corresponding imidazolidinones (**3a**, **c**—**e**, **4d**, **e**: Table 1).

Method B: Compound **22b** was allowed to react with 1*H*-1,2,4-triazole as described in the synthesis of **1b** to give **3b**. The reaction of **22c**—**e** and **23d**, **e** with 1*H*-1,2,4-triazole was carried out in a similar fashion to give the corresponding imidazolidinone derivatives (**3c**—**e**, **4d**, **e**: Table 1).

The high optical purity (>99% ee) was confirmed with compounds, **3d**, **e** and **4d**, **e**, by HPLC using a chiral column (Chiralcel OF for **4d** and Chiralpak AD for **3d**, **e** and **4e**) under the following conditions: mobile phase (hexane–iso-PrOH, 2 : 1), flow rate (1 ml/min), detection (UV at 262 nm). The corresponding racemate used in this analysis was prepared independently.

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8) Considerable decomposition was observed during attempted isolation of the triflate. Therefore, the concentrated eluate containing the triflate was used directly in the subsequent nucleophilic displacement reaction.