Optically Active Antifungal Azoles. I. Synthesis and Antifungal Activity of (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-mercapto-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol and Its Stereoisomers

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(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-mercapto-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(2*R*,3*R*)-7] and its stereoisomers [(2*S*,3*R*)-, (2*S*,3*S*)- and (2*R*,3*S*)-7] were prepared from the optically active oxiranes 6 by a newly developed ring-opening reaction and evaluated for antifungal activity. The thiol (2*R*,3*R*)-7 showed extremely potent antifungal activity *in vitro* and *in vivo*.

The optically active oxirane (2*R*,3*S*)-6, a useful intermediate for the synthesis of sulfur-containing antifungal azoles 5, was synthesized from methyl (*R*)-lactate [(*R*)-8] *via* eight steps in a stereocontrolled manner. The key step in the synthesis is the Grignard reaction of an amide derivative [(*R*)-12a] of (*R*)-lactic acid with 2,4-difluorophenylmagnesium bromide (13).

Keywords optically active antifungal triazole; chiral synthesis; triazolylmercaptobutanol; methyl (*R*)-lactate; antifungal activity; structure–activity relationship

The incidence of systemic fungal infections has been increasing recently due to an increase in the number of immunocompromised hosts.[1] Patients undergoing organ transplants or anticancer chemotherapy and patients with acquired immunodeficiency syndrome (AIDS) are immunosuppressed to some extent and susceptible to life-threatening fungal infections such as candidosis, cryptococcosis and aspergillosis. For the treatment of these infections, orally active antifungal azoles, ketoconazole (**1**),[2] fluconazole (**2**)[3] and itraconazole (**3**),[4] have been developed and are currently used in antifungal chemotherapy.

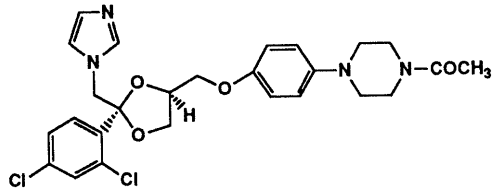
Recently Saji *et al.* reported the extremely potent antifungal agent SM-8668 (**4**, genaconazole) and showed that the active enantiomer has a (2*R*,3*R*)-configuration.[5]

In an effort to find a new antifungal agent, we planned the synthesis of a variety of sulfur-containing optically active triazole derivatives represented by the general formula **5**. The key intermediates for the synthesis of **5** were considered to be (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-methyl-2-(1*H*-1,2,4-triazol-1-yl)methyloxirane [(2*R*,3*S*)-**6**][6] and (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(2*R*,3*R*)-**7**].[7]

In this paper, we describe an efficient and practical route for the synthesis of the optically active oxirane (2*R*,3*S*)-**6** starting from methyl (*R*)-lactate [(*R*)-**8**] and the subsequent ring-opening reaction of **6** to afford the thiol (2*R*,3*R*)-**7** (Table I).[8] In the course of this research, we found that the thiol (2*R*,3*R*)-**7** has potent antifungal activity. Therefore, three stereoisomers of the thiol, (2*S*,3*R*)-**7**, (2*S*,3*S*)-**7** and (2*R*,3*S*)-**7** (Table I), were prepared to investigate the relationship between antifungal activity and stereochemistry.

Chemistry

Our protocol for the practical synthesis of the optically active oxirane (2*R*,3*S*)-**6** is illustrated by a retrosynthetic formula in Chart 2. We chose (*R*)-lactic acid [(*R*)-**8**′] or its



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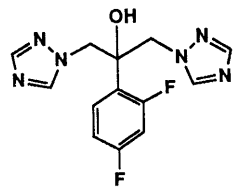

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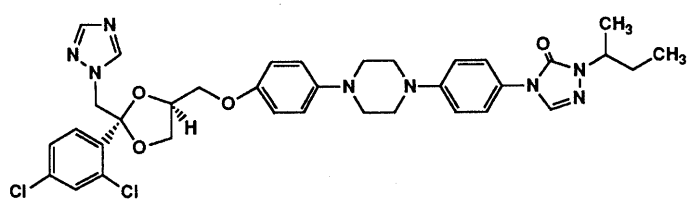

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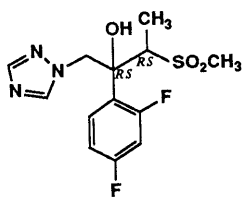

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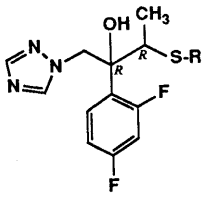

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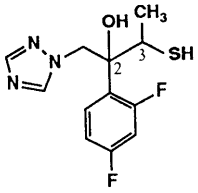
Chart 1

TABLE I. 2-(2,4-Difluorophenyl)-3-mercapto-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols



Compd.	Yield (%)	mp °C (Solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR δ (in $CDCl_3$)	IR ν_{max}^{KBr} (cm^{-1})	$[\alpha]_D$ (c, %) {°C} in MeOH
(2*R*,3*R*)-**7**	82	176—178[b] (EA–H)	$C_{12}H_{13}F_2N_3O_2$	50.52 (50.81	4.59 4.64	14.73 14.64)	1.17 (3H, d, J=7 Hz), 1.96 (1H, d, J=10 Hz), 3.45 (1H, m), 4.76 (1H, s), 4.82 (1H, d, J=14 Hz), 5.01 (1H, d, J=14 Hz), 6.69—6.81 (2H, m), 7.33—7.45 (1H, m), 7.79 (2H, s)	3230, 1610, 1500, 1420, 1260, 1190	−56.8 (0.7) {23}
(2*S*,3*R*)-**7**	41	141—144 (EA–H)	$C_{12}H_{13}F_2N_3O_2$	50.52 (50.51	4.59 4.59	14.73 14.49)	1.52 (3H, d, J=7 Hz), 1.54 (1H, d, J=6 Hz), 3.69 (1H, m), 4.56 (1H, s), 4.62 (1H, d, J=14 Hz), 4.94 (1H, dd, J=14, 1.8 Hz), 6.68—6.81 (2H, m), 7.30—7.43 (1H, m), 7.73 (1H, s), 7.95 (1H, s)	3260, 1615, 1500, 1420, 1260, 1200	+64.1 (1.0) {25}
(2*S*,3*S*)-**7**	71	175—178 (EA–H)	$C_{12}H_{13}F_2N_3O_2$	50.52 (50.54	4.59 4.69	14.73 14.48)	1.17 (3H, d, J=7 Hz), 1.96 (1H, d, J=10 Hz), 3.45 (1H, m), 4.75 (1H, s), 4.81 (1H, d, J=14 Hz), 5.01 (1H, d, J=14 Hz), 6.69—6.81 (2H, m), 7.30—7.46 (1H, m), 7.79 (1H, s), 7.80 (1H, s)	3230, 1615, 1500, 1420, 1265, 1190	+55.7 (1.0) {25}
(2*R*,3*S*)-**7**	42	141—143 (EA–H)	$C_{12}H_{13}F_2N_3O_2$	50.52 (50.51	4.59 4.68	14.73 14.53)	1.52 (3H, d, J=7 Hz), 1.54 (1H, d, J=6 Hz), 3.69 (1H, m), 4.55 (1H, s), 4.62 (1H, d, J=14 Hz), 4.94 (1H, dd, J=14, 1.8 Hz), 6.68—6.82 (2H, m), 7.29—7.45 (1H, m), 7.72 (1H, s), 7.95 (1H, s)	3260, 1615, 1500, 1420, 1260, 1200	−63.4 (1.0) {25}

a) Recrystallization solvents: EA, ethyl acetate; H, hexane. *b*) mp 175—178 °C.[6d]

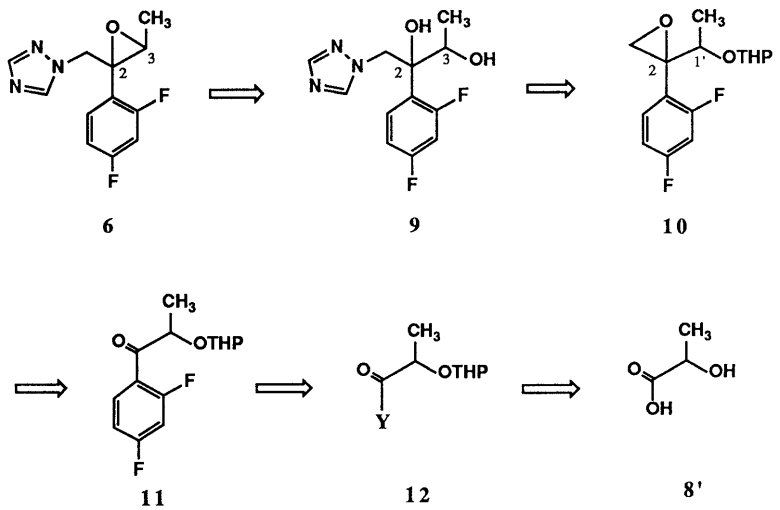


Chart 2

derivative as a chiral synthon available for large scale preparation.

Saji *et al.* reported the synthesis of the racemic oxirane (2*RS*,3*SR*)-**6** *via* diastereoselective epoxidation of 2′,4′-difluoro-2-[3,4,5,6-tetrahydro-2*H*-pyran-2-yl(THP)oxy]-propiophenone [(*RS*)-**11**] to produce (1′*RS*,2*RS*)-**10**.[5a] Therefore, we expected that asymmetric induction forming the optically active oxirane (1′*R*,2*R*)-**10** would occur under the same reaction conditions if the optically active propiophenone derivative (*R*)-**11** was used as the substrate. We therefore focused our initial efforts on the preparation of the propiophenone derivative (*R*)-**11**.

The most promising method seemed to be the Grignard reaction[9] of 2,4-difluorophenylmagnesium bromide (**13**) with the *N*,*N*-dialkylamide derivative of lactic acid, because of the liability of the THP group under acidic conditions as well as possible racemization under the basic conditions. Two type of amides (*R*)-**12** (Y=pyrrolidinyl and morpholino) were prepared from methyl (*R*)-lactate [(*R*)-**8**] by amidation with amines followed by protection with

a THP group, and these were then reacted with the Grignard reagent **13** in tetrahydrofuran (THF). The results revealed that the morpholino derivative [(*R*)-**12a**] gave (*R*)-**11** in a higher yield (88%) than the pyrrolidinyl derivative. The enantiomer excess (ee) of (*R*)-**11** was assessed by high-performance liquid chromatography (HPLC) using a chiral column after conversion to the 2-hydroxypropiophenone derivative [(*R*)-**14**], and was found to be 98.8%. This Grignard reaction proved to be efficient to obtain (*R*)-**11** in a high yield without racemization.

Diastereoselective epoxidation of (*R*)-**11** with Corey's reagent[10] in dimethyl sulfoxide (DMSO) afforded the oxirane derivative (1′*R*)-**10**, which was a diastereomeric mixture consisting of the desired diastereomer (1′*R*,2*R*)-**10** and the undesired isomer (1′*R*,2*S*)-**10** in a ratio of *ca.* 4:1.[11] The isomeric mixture was reacted with 1*H*-1,2,4-triazole in the presence of sodium hydride to give the butanol derivative (3*R*)-**16** in a 62% yield [based on (*R*)-**11**]. The THP group was removed with pyridinium *p*-toluenesulfonate (PPTS) and the resulting diol was purified by recrystallization to obtain the diastereomerically pure diol (2*R*,3*R*)-**9** in a 42% yield. Separation of the residue derived from the mother liquor by silica gel column chromatography provided an additional amount of (2*R*,3*R*)-**9** (23% yield) and its diastereoisomer (2*S*,3*R*)-**9** (6% yield). The optically active diol (2*R*,3*R*)-**9** was converted to the corresponding mesylate followed by treatment with sodium methoxide (NaOMe) in methanol (MeOH) to give the oxirane (2*R*,3*S*)-**6** in an 80% yield. The enantiomeric purity of the oxirane (2*R*,3*S*)-**6** was determined, by HPLC using a chiral column, to be 99.6% ee (Chart 3).

Next, conversion of the oxirane (2*R*,3*S*)-**6** to the optically active thiol (2*R*,3*R*)-**7** was investigated. Although various methods for the preparation of thiols are known,[12] they are not always useful for practical synthesis, because of the instability of the resulting thiol or necessity of multistep operations. Therefore, we planned to establish a one step synthesis of (2*R*,3*R*)-**7** from (2*R*,3*S*)-**6**, which would be practical for large scale synthesis.

First, we examined the ring-opening reaction of (2*R*,3*S*)-**6** with sodium hydrosulfide (NaSH). The treatment of (2*R*,3*S*)-**6** with excess NaSH gave the desired thiol (2*R*,3*R*)-**7** in a 45—50% yield (method A). However, some unidentified by-products were formed and silica gel column chromatography was necessary for purification. Our efforts then turned to the development of a new method to prepare the thiol (2*R*,3*R*)-**7**.

Kakehi *et al.* reported the utility of an alkoxycarbonylethylthio moiety as a new protected thiol, which regenerates the thiol *via* retro-Michael reaction upon treatment with a strong base such as potassium *tert*-butoxide.[13] We anticipated that the ring-opening reaction of the oxirane [(2*R*,3*S*)-**6**] with mercaptopropionic acid ester and the subsequent retro-Michael reaction might occur in one pot. Thus, a variety of reaction conditions were examined, and we found that the oxirane (2*R*,3*S*)-**6** reacted with 12 eq of methyl mercaptopropionate in the presence of 5 eq of NaOMe at reflux temperature in MeOH to give the desired thiol (2*R*,3*R*)-**7** in an 82% yield (method B). The majority (55%) of the product was obtained in a highly pure form by simple crystallization. Silica gel chroma-

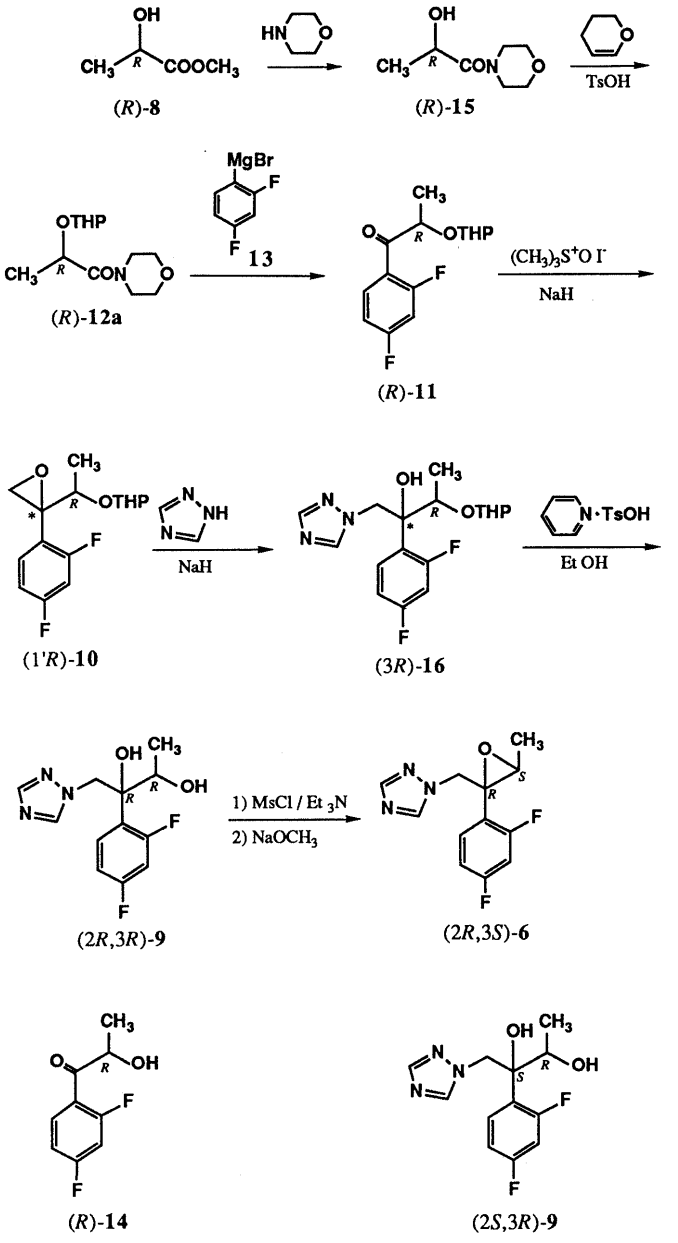


Chart 3

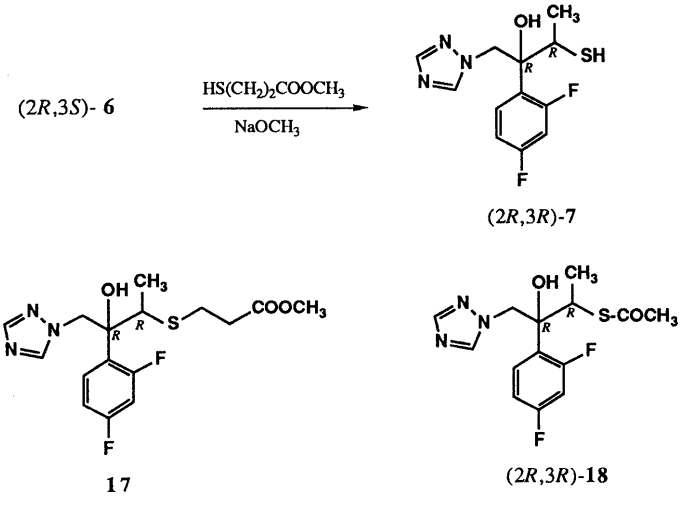


Chart 4

tography of the residue gave additional (2*R*,3*R*)-**7** (27% yield).

The intermediate in this reaction was predicted to be the Michael product **17**. However, compound **17** was not detected in the reaction course as the major component under the above conditions, probably because of its lability in favor of (2*R*,3*R*)-**7** under basic conditions. In order to confirm our predicted mechanism, compound **17** was prepared by an alternative method, *i.e.*, the reaction of (2*R*,3*R*)-**7** with methyl acrylate in the presence of tetrabutylammonium fluoride. Compound **17** was treated with NaOMe in MeOH under the same conditions as those in the synthesis of (2*R*,3*R*)-**7**. The product was (2*R*,3*R*)-**7**, as expected.

The absolute configuration of (2*R*,3*R*)-**7** was confirmed by X-ray crystallographic analysis as shown in Fig. 1.[14] Furthermore, the enantiomeric purity of (2*R*,3*R*)-**7** was assessed by HPLC using a chiral column after conversion to the corresponding thioacetate (2*R*,3*R*)-**18** and was found to be 99.7% ee. This one-step synthesis would be convenient and versatile to prepare various thiol derivatives.

The evaluation of the thiol (2*R*,3*R*)-**7** for *in vivo* antifungal activity revealed that this enantiomer is highly active against candidosis in mice. Therefore, we were interested in the structure–activity relationships of the stereoisomers of the thiol, and the other three stereoisomers, (2*S*,3*R*)-**7**, (2*S*,3*S*)-**7** and (2*R*,3*S*)-**7**, were synthesized. The diastereoisomer (2*S*,3*R*)-**7** was prepared starting from (2*S*,3*R*)-**9**, which was the by-product obtained in the synthesis of (2*R*,3*R*)-**9**, through a similar route to the above, *i.e.*, (2*S*,3*R*)-**9**→(2*S*,3*S*)-**6**→(2*S*,3*R*)-**7**. The enantioisomer (2*S*,3*S*)-**7** was synthesized starting from ethyl (*S*)-lactate [(*S*)-**8**] *via* substantially the same route as that for (2*R*,3*R*)-**7**: (*S*)-**8**→(*S*)-**15**→(*S*)-**12a**→(*S*)-**11**→(1′*S*)-**10**→(3*S*)-**16**→(2*S*,3*S*)-**9**→(2*S*,3*R*)-**6**→(2*S*,3*S*)-**7**. In the case of the preparation of the other diastereomer (2*R*,3*S*)-**7**, compound (2*R*,3*S*)-**9** which was the minor product in the synthesis of (2*S*,3*S*)-**9** was used as the starting material and converted to (2*R*,3*S*)-**7** in the same manner as described for the preparation of (2*S*,3*R*)-**7**: (2*R*,3*S*)-**9**→(2*R*,3*R*)-**6**→(2*R*,3*S*)-**7**.

Antifungal Activity The four stereoisomers of the thiol **7** were evaluated for antifungal activity *in vitro*. Table II shows the results of *in vitro* activity determination by a paper disc assay (measuring the diameter of the inhibition zone around a paper disc soaked in a solution of 1000 μg/ml of test compound) on yeast nitrogen base (YNB) agar and Sabouraud dextrose agar (SDA) at pH 7.0. All of the isomers showed activity against *Candida* and *Saccharomyces* species. The isomers with the (2*R*,3*R*)- and (2*R*,3*S*)-configuration had potent activity with a

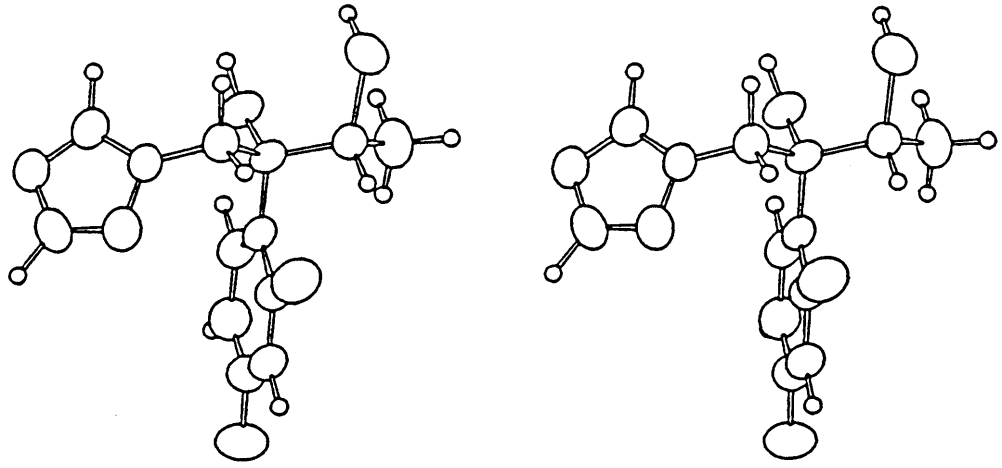


Fig. 1. Stereoscopic View of the Molecule of (2*R*,3*R*)-**7**

TABLE II. *In Vitro* Antifungal Activity of the Thiols (**7**)

Species and strain		Growth-inhibition zone diameter (mm)			
		(2*R*,3*R*)-**7**	(2*S*,3*R*)-**7**	(2*S*,3*S*)-**7**	(2*R*,3*S*)-**7**
Candida albicans	IFO 0583	40	25	34	35
Candida albicans	TA	37	23	34	40
Candida utilis	IFO 0619	38	20	20	33
Saccharomyces cerevisiae	IFO 0209	40	30	28	30
Cryptococcus neoformans	IFO 0410	35	0	+	25
Torulopsis glabrata	IFO 1085	33	0	0	30
Aspergillus niger	IFO 4066	25	0	0	20
Aspergillus fumigatus	IFO 6344	25	0	0	20
Sporothrix schenckii	IFO 8158	17	0	0	0
Trichophyton rubrum	IFO 5467[a)]	15	0	+	30
Trichophyton mentagrophytes	IFO 7522[a)]	21	0	13	30
Microsporum gypseum	IFO 6075[a)]	20	0	13	25

Media: YNB (pH 7.0) 28 °C, 2 d; *a*) SDA (pH 7.0) 28 °C, 2 d.

TABLE III. *In Vivo* Antifungal Activity of the Thiols (**7**) against *Candida albicans* TA

Compound No.	ED_{50} (mg/kg), *p.o.*
(2*R*,3*R*)-**7**	0.19
(2*R*,3*S*)-**7**	2.8

broad spectrum against yeasts as well as fungi. On the other hand, the isomers with (2*S*,3*S*)- and (2*S*,3*R*)-configuration showed a narrow antifungal spectrum. This indicates that the (*R*)-configuration of the C2 position might be the key factor for potent and broad antifungal activity *in vitro*. This clear relationship between the configuration of C2 and the activity might be due to the stereochemical requirements of the binding site in the target enzyme, cytochrome $P450_{14DM}$.[15]

The pair of isomers which had potent activity *in vitro*, (2*R*,3*R*)-**7** and (2*R*,3*S*)-**7**, were evaluated in an *in vivo* assay against candidosis, and the results are shown in Table III. The *in vivo* antifungal activity was expressed in terms of ED_{50} (mg/kg, the oral dose of the compound which allowed the 50% survival of mice infected with *C. albicans* TA).

Compound (2*R*,3*R*)-**7** showed strong *in vivo* antifungal activity (ED_{50}, 0.19 mg/kg). However, the (2*R*,3*S*)-isomer was about fourteen times less potent than the (2*R*,3*R*)-isomer. Therefore, the (*R*)-configuration of C3 proved to be an important factor for potent *in vivo* activity, although the role of the C3-stereochemistry of this agent *in vivo* is unclear.[16]

Experimental

Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Hitachi 215 spectrometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken on a Varian Gemini-200 (200 MHz) spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The optical rotations were recorded with a JASCO DIP-181 digital polarimeter.

All of the starting materials are commercially available. Reactions were followed by thin-layer chromatography (TLC) on TLC plates, Silica gel 60 F_{254} precoated (E. Merck), and chromatographic separations were carried out on Silica gel 60 (0.063—0.200 mm, E. Merck).

4-[(*R*)-2-Hydroxypropionyl]morpholine [(*R*)-15] A mixture of methyl (*R*)-lactate [(*R*)-**8**, 104 g, 1.0 mol] and morpholine (260 ml, 3.0 mol) was heated at 85 °C for 60 h. The mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel (800 g). Elution with hexane–AcOEt (1 : 1, v/v)→AcOEt gave (*R*)-**15** (141 g, 88%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, d, J=6.6 Hz), 3.43 (2H, t, J=4.8 Hz), 3.55—3.80 (6H, m), 3.79 (1H, d, J=7.4 Hz), 4.38—4.53 (1H, m). IR (neat): 1635 (C=O) cm^{-1}. $[\alpha]_D^{23}$ +0.98° (c=5.24, $CHCl_3$).

4-[(*S*)-2-Hydroxypropionyl]morpholine [(*S*)-**15**] was prepared from ethyl (*S*)-lactate [(*S*)-**8**] in a 72% yield in a manner similar to that described above, $[\alpha]_D^{23}$ −0.98° (c=5.23, $CHCl_3$).

4-[(2*R*)-2-(3,4,5,6-Tetrahydro-2*H*-pyran-2-yloxy)propionyl]morpholine [(*R*)-12a] 3,4-Dihydro-2*H*-pyran (89.3 g, 1.06 mol) was added dropwise to a mixture of (*R*)-**15** (141 g, 0.88 mol) and *p*-toluenesulfonic acid monohydrate (1.67 g, 8.8 mmol) in CH_2Cl_2 (500 ml) over a period of 15 min with stirring at 0 °C. After being stirred for 30 min at 0 °C, the mixture was washed with aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (800 g). Elution with hexane–AcOEt (8 : 1, v/v)→AcOEt gave (*R*)-**12a** (184 g, 85%) as a pale yellow oil. *Anal.* Calcd for $C_{12}H_{21}NO_4$: C, 59.14; H, 8.70; N, 5.76. Found: C, 58.87; H, 8.54; N, 5.50. IR (neat): 1662, 1650 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39, 1.44 (3H, d each J=6.8 Hz), 1.40—1.95 (6H, m), 3.40—3.95 (10H, m), 4.48—4.75 (2H, m).

4-[(2*S*)-2-(3,4,5,6-Tetrahydro-2*H*-pyran-2-yloxy)propionyl]morpholine [(*S*)-**12a**] was prepared from (*S*)-**15** in an 89% yield in a manner similar to that described above. IR (neat): 1662, 1650 (C=O) cm^{-1}.

(2*R*)-2′,4′-Difluoro-2-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)propiophenone [(*R*)-11] A mixture of magnesium (turnings, 22.6 g, 0.93 mol) and 1-bromo-2,4-difluorobenzene (50 g, 0.26 mol) in THF (950 ml) was vigorously stirred to initiate the reaction. When the temperature reached 40—45 °C, the mixture was cooled to 35 °C in a water bath and 1-bromo-2,4-difluorobenzene (129.7 g, 0.67 mol) was added dropwise to the mixture over a period of 30 min, keeping the temperature at 35—45 °C. The resulting mixture was stirred at room temperature for 1 h and then cooled at −20 °C. A solution of (*R*)-**12a** (188.5 g, 0.78 mol) in THF (150 ml) was added dropwise over a period of 15 min to the mixture. The whole was stirred at room temperature for 4 h, then a saturated aqueous solution of NH_4Cl (400 ml) and water (400 ml) were added, and the resulting mixture was extracted with AcOEt (1 l and 500 ml × 2). The extracts were combined, washed successively with water and brine and dried over $MgSO_4$. The solvent was evaporated off under reduced pressure and the residue was chromatographed on silica gel (2 kg). Elution with hexane–AcOEt (30 : 1→5 : 1, v/v) gave (*R*)-**11** (184 g, 88%) as a pale yellow oil. IR (neat): 1695 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.96 (9H, m), 3.26—3.58 (1H, m), 3.65—3.98 (1H, m), 4.65, 4.76 (1H, t each, J=3.5 Hz), 4.80—4.95, 5.02—5.18 (1H, m each), 6.80—7.05 (2H, m), 7.84—8.00 (1H, m).

According to a procedure similar to that described above, (2*S*)-2′,4′-difluoro-2-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)propiophenone [(*S*)-**11**] was prepared in a 76% yield from (*S*)-**12a** as a pale yellow oil. IR (neat): 1695 (C=O) cm^{-1}.

(*R*)-2′,4′-Difluoro-2-hydroxypropiophenone [(*R*)-14] A mixture of (*R*)-**11** (0.29 g, 1.1 mmol) and PPTS (63 mg, 0.25 mmol) in EtOH (10 ml) was stirred at 60 °C for 30 min. The mixture was concentrated *in vacuo* and the residue was partitioned between AcOEt and water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give an oil, which was chromatographed on silica gel. Elution with hexane–AcOEt (5 : 1, v/v) gave (*R*)-**14** as a colorless oil. IR (neat): 1690 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, dd, J=7, 1.6 Hz), 3.74 (1H, d, J=7 Hz), 4.90—5.10 (1H, m), 6.86—7.08 (2H, m), 7.96—8.08 (1H, m), $[\alpha]_D^{23}$ +68.7° (c=1.8, $CHCl_3$).

(*S*)-2′,4′-Difluoro-2-hydroxypropiophenone [(*S*)-**14**] was obtained from (*S*)-**11** by the same procedure as above.

The enantiomeric purity was determined by HPLC using Chiralcel OB® (4.6 mm i.d. × 250 mm, Daicel Chemical Industries, Tokyo, Japan) under the following conditions: mobile phase, hexane–isopropanol, 8 : 2, v/v; flow rate 1.0 ml/min; detection, UV at 254 nm. The retention times of the enantiomers, (*R*)-**14** and (*S*)-**14**, were 13.3 and 10.9 min, respectively. The ee values of (*R*)-**14** and (*S*)-**14** were determined to be 98.8% and 98.4%, respectively.

2-(2,4-Difluorophenyl)-2-[(1*R*)-1-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)-ethyl]oxirane [(1′*R*)-10] Trimethylsulfoxonium iodide (122.3 g, 0.55 mol) was added portionwise to a stirred mixture of sodium hydride (60% mineral oil dispersion, 21.3 g, 0.53 mol) and DMSO (800 ml) under ice cooling over a period of 75 min. The resulting mixture was stirred at room temperature for 30 min and then cooled in an ice bath. A solution of (*R*)-**11** (124 g, 0.46 mol) in DMSO (150 ml) was added to the mixture. After being stirred for 2 h at room temperature, the mixture was poured into water (1.2 l) and extracted with AcOEt (800 ml and 600 ml × 2). The organic extracts were combined, washed successively with water and brine, and dried over $MgSO_4$. Evaporation of the solvent gave (1′*R*)-**10** (126 g) as a pale yellow oil, which was contaminated with a mineral oil, and was used for the next step without purification. A part of the product was purified by chromatography on silica gel (hexane–AcOEt–CH_2Cl_2, 10 : 1 : 1, v/v) to afford (1′*R*)-**10** as a pale yellow oil. IR (neat): 2950, 1618, 1600, 1510, 1425, 1270, 1140, 1120, 1075, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10—1.30 (3H, m), 1.40—1.95 (6H, m), 2.83 (1H, m), 3.05, 3.32 (1H, d each, J=5.2 Hz), 3.42—3.60 (1H, m), 3.76—4.14 (2H, m), 4.70—4.87, 4.88—4.97 (1H, m each), 6.72—6.95 (2H, m), 7.32—7.60 (1H, m).

According to a procedure similar to that described above, 2-(2,4-difluorophenyl)-2-[(1*S*)-1-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)ethyl]-oxirane [(1′*S*)-**10**] was obtained from (*S*)-**11** and used for the next step without purification.

(3*R*)-2-(2,4-Difluorophenyl)-3-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(3*R*)-16] 1*H*-1,2,4-Triazole (94 g, 1.37 mol) was added portionwise to a mixture of sodium hydride (60%

oil dispersion, 47.2 g, 1.24 mol) and *N*,*N*-dimethylformamide (DMF) (650 ml) over a period of 30 min under a nitrogen atmosphere at 0 °C. The mixture was stirred for 15 min at room temperature and a solution of (1′*R*)-**10** (126 g) obtained above in DMF (150 ml) was added. The resulting mixture was heated at 80 °C for 4 h with stirring. After being cooled, the mixture was poured into water (2 l) and the whole was extracted with AcOEt (1 l and 500 ml × 2). The extract was washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel. Elution with hexane–AcOEt (4 : 1→1 : 1, v/v) gave (3*R*)-**16** [100 g, 62% based on (*R*)-**11**] as a light brown oil. IR (neat): 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.99, 1.12 (3H, d each, J=6.4 Hz), 1.40—2.00 (6H, m), 3.40—3.65 (1H, m), 3.80—4.06 (1H, m), 4.25—4.45 (1H, m), 4.29 (1H, s), 4.62 (1H, d, J=14.2 Hz), 4.62—4.78 (1H, m), 4.90 (1H, d, J=14.2 Hz), 6.65—6.83 (2H, m), 7.35—7.50 (1H, m), 7.71, 7.72 (1H, s each), 7.91, 7.94 (1H, s each).

According to a procedure similar to that described above, (3*S*)-**16** was obtained from (1′*S*)-**10** and used for the next step without purification.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2,3-butanediol [(2*R*,3*R*)-9] and (2*S*,3*R*)-2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2,3-butanediol [(2*S*,3*R*)-9] A mixture of (3*R*)-**16** (11.7 g, 33.1 mmol) and PPTS (2.49 g, 9.9 mmol) in EtOH (130 ml) was heated at 55 °C for 2 h. Further PPTS (0.5 g) was added and the mixture was heated at 55 °C for another 2 h. The mixture was concentrated *in vacuo* and extracted with AcOEt (400 ml). The extract was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. Diethyl ether (Et_2O, 50 ml) was added to the residue to precipitate (2*R*,3*R*)-**9** (3.80 g, 42%) as white powdery crystals. The mother liquor was concentrated *in vacuo* and the residue was chromatographed on silica gel. Elution with AcOEt–MeOH (30 : 1, v/v) gave (2*S*,3*R*)-**9** (0.53 g, 6%) as a less polar substance. The eluent containing a more polar isomer was concentrated, followed by recrystallization from Et_2O, to give additional (2*R*,3*R*)-**9** (1.95 g, 23%). The diastereomeric purity of (2*R*,3*R*)-**9** and (2*S*,3*R*)-**9** was measured by HPLC under the following conditions: A-303® column (ODS, 4.6 mm i.d. × 250 mm, Yamamura Chemical Laboratories Co.), mobile phase (MeOH–H_2O–AcOH, 7 : 3 : 0.02, v/v; flow rate, 0.8 ml/min; detection, UV at 254 nm). The diastereomeric excess (de) values were determined to be 99.4% and 99.3%, respectively. The retention times of the diastereomers, (2*R*,3*R*)-**9** and (2*S*,3*R*)-**9**, were 4.8 and 4.1 min.

(2*R*,3*R*)-**9**: mp 115—117 °C. *Anal.* Calcd for $C_{12}H_{13}F_2N_3O_2$: C, 53.53; H, 4.87; N, 15.61. Found: C, 53.71; H, 4.87; N, 15.47. IR (KBr): 3550, 3420, 3150, 2990, 1615, 1600, 1500, 1420, 1265, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, J=6.4 Hz), 2.50 (1H, br), 4.25—4.40 (1H, m), 4.70—4.93 (3H, m), 6.70—6.85 (2H, m), 7.36—7.48 (1H, m), 7.84 (1H, s), 7.85 (1H, s). $[\alpha]_D^{23}$ −80.3° (c=1.0, MeOH).

(2*S*,3*R*)-**9**: Amorphous powder. *Anal.* Calcd for $C_{12}H_{13}F_2N_3O_2$: C, 53.53; H, 4.87; N, 15.61. Found: C, 53.39; H, 4.94; N, 15.33. IR (KBr): 3400, 1615, 1595, 1500, 1420, 1275, 1200, 1135 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, dd, J=6.4, 1.6 Hz), 2.44 (1H, d, J=5.4 Hz), 3.90—4.10 (1H, m), 4.56 (1H, dd, J=14, 1.6 Hz), 5.04 (1H, s), 5.05 (1H, dd, J=14, 1.6 Hz), 6.65—6.86 (2H, m), 7.50—7.62 (1H, m), 7.80 (1H, s), 8.05 (1H, s). $[\alpha]_D^{20}$ +69.0° (c=1.0, MeOH).

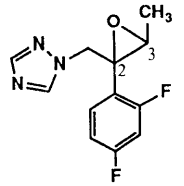
(2*S*,3*S*)-2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2,3-butanediol [(2*S*,3*S*)-**9**] and (2*R*,3*S*)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2,3-butanediol [(2*R*,3*S*)-**9**] were prepared from (3*S*)-**16** in a manner similar to that described above. The yields were 38% and 2.8%, respectively, based on (*S*)-**11**.

(2*S*,3*S*)-**9**: mp 115—117 °C. *Anal.* Calcd for $C_{12}H_{13}F_2N_3O_2$: C, 53.53; H, 4.87; N, 15.61. Found: C, 53.47; H, 4.95; N, 15.38. IR (KBr): 3550, 3440, 3145, 1615, 1600, 1500, 1420, 1270, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, J=6.4 Hz), 2.50 (1H, br), 4.25—4.40 (1H, m), 4.70—4.93 (3H, m), 6.70—6.85 (2H, m), 7.36—7.48 (1H, m), 7.84 (1H, s), 7.85 (1H, s). $[\alpha]_D^{23}$ +80.1° (c=1.05, MeOH).

(2*R*,3*S*)-**9**: Amorphous powder. *Anal.* Calcd for $C_{12}H_{13}F_2N_3O_2$: C, 53.53; H, 4.87; N, 15.61. Found: C, 53.53; H, 4.73; N, 15.20. IR (KBr): 3350, 1615, 1510, 1490, 1275, 1200, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, dd, J=6.4 Hz, J=1.6 Hz), 2.42 (1H, d, J=5.4 Hz), 3.90—4.10 (1H, m), 4.57 (1H, dd, J=14, 1.6 Hz), 5.05 (1H, dd, J=14, 1.6 Hz), 6.67—6.86 (2H, m), 7.50—7.62 (1H, m), 7.80 (1H, s), 8.04 (1H, s). $[\alpha]_D^{20}$ −70° (c=0.5, MeOH).

(2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-methyl-2-(1*H*-1,2,4-triazol-1-yl)-methyl)oxirane [(2*R*,3*S*)-6, Table IV] Methanesulfonyl chloride (3.04 g, 26.6 mmol) was added to a mixture of (2*R*,3*R*)-**9** and AcOEt–CH_2Cl_2

TABLE IV. 2-(2,4-Difluorophenyl)-3-methyl-2-(1*H*-1,2,4-triazol-1-yl)methyloxirane



Compd.	Yield (%)	mp °C (Solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR δ (in $CDCl_3$)	IR ν_{max}^{KBr} (cm^{-1})	$[\alpha]_D$ (c, %) {°C} in MeOH	ee (%)
(2*R*,3*S*)-**6**	80	89—90[b] (EA–H)	$C_{12}H_{11}F_2N_3O$	57.37 (57.27	4.41 4.43	16.73 16.83)	1.65 (3H, d, J=5.8 Hz), 3.20 (1H, q, J=5.8 Hz), 4.43 (1H, d, J=14.6 Hz), 4.88 (1H, d, J=14.6 Hz), 6.68—6.85 (2H, m), 6.93—7.09 (1H, m), 7.82 (1H, s), 7.96 (1H, s)	3120, 1610, 1595, 1510, 1420, 1265	−8.3 (1.0) {23}	99.6
(2*S*,3*S*)-**6**	70	41—43	$C_{12}H_{11}F_2N_3O$	57.37 (57.19	4.41 4.41	16.73 16.52)	1.06 (3H, d, J=5.4 Hz), 3.18 (1H, q, J=5.4 Hz), 4.42 (1H, d, J=15 Hz), 4.80 (1H, d, J=15 Hz), 6.66—6.90 (2H, m), 7.06—7.20 (1H, m), 7.85 (1H, s), 8.06 (1H, s)	3150, 1615, 1595, 1502, 1420, 1270	+4.7 (1.0) {23}	98.1
(2*S*,3*R*)-**6**	78	89—90 (EA–H)	$C_{12}H_{11}F_2N_3O$	57.37 (56.98	4.41 4.40	16.73 16.53)	1.65 (3H, d, J=5.8 Hz), 3.20 (1H, q, J=5.8 Hz), 4.43 (1H, d, J=14.6 Hz), 4.88 (1H, d, J=14.6 Hz), 6.68—6.85 (2H, m), 6.93—7.09 (1H, m), 7.82 (1H, s), 7.96 (1H, s)	3120, 1610, 1595, 1510, 1420, 1265	+7.8 (1.0) {23}	99.5
(2*R*,3*R*)-**6**	92	Oil[c]	$C_{12}H_{11}F_2N_3O$	57.37 (56.93	4.41 4.48	16.73 16.51)	1.06 (3H, d, J=5.4 Hz), 3.18 (1H, q, J=5.4 Hz), 4.42 (1H, d, J=15 Hz), 4.80 (1H, d, J=15 Hz), 6.66—6.90 (2H, m), 7.06—7.21 (1H, m), 7.85 (1H, s), 8.06 (1H, s)	3150, 1615, 1595, 1502, 1420, 1270	−4.8 (1.02) {22}	99.6

a) Recrystallization solvents: EA, ethyl acetate; H, hexane. *b*) mp 88—88.5 °C.[6a,c] *c*) Although (2*S*,3*S*)-**6** solidified in a freezer, attempted crystallization of the enantioisomer (2*R*,3*R*)-**6** was unsuccessful. This material was used for the next step without further purification.

(4:1, v/v, 150 ml) with stirring at 0 °C. The resulting mixture was stirred at room temperature for 45 min, then washed successively with water and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the mesylate as an oil, which was dissolved in a mixture of NaOMe (28% in MeOH, 5.34 g, 27.7 mmol) and MeOH (120 ml). After being stirred for 15 min at 0 °C, the mixture was concentrated under reduced pressure. The residue was extracted with AcOEt (120 ml), and the extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a solid mass, which was purified by silica gel column chromatography (100 g, AcOEt–CH_2Cl_2, 4:1, v/v) to give a crystalline solid. Recrystallization of the solid from AcOEt–hexane gave (2*R*,3*S*)-**6** (4.89 g, 80%) as colorless needles. In a similar manner, (2*S*,3*S*)-**6**, (2*S*,3*R*)-**6** and (2*R*,3*R*)-**6** (Table IV) were prepared from (2*S*,3*R*)-**9**, (2*S*,3*S*)-**9** and (2*R*,3*S*)-**9**, respectively.

The enantiomeric purity was determined by HPLC using Chiralcel OF® (4.6 mm i.d. × 250 mm, Daicel Chemical Industries, Tokyo, Japan) under the following conditions: mobile phase, hexane–EtOH, 7:3, v/v; flow rate, 1.0 ml/min; detection, UV at 254 nm. The results are shown in Table IV.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-mercapto-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(2*R*,3*R*)-7, Table I] Method A: A mixture of (2*R*,3*S*)-**6** (0.40 g, 1.59 mmol) and $NaSH \cdot nH_2O$ (1.3 g) in MeOH (12 ml) was refluxed for 5 h. After being cooled, the mixture was neutralized with diluted aqueous HCl and extracted with CH_2Cl_2 (20 ml × 3). The extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane–AcOEt, 1:1, v/v), followed by crystallization from diisopropyl ether to yield (2*R*,3*R*)-**7** (0.22 g, 50%) as colorless prisms.

Method B: A mixture of (2*R*,3*S*)-**6** (37 g, 147 mmol), methyl 3-mercaptopropionate (141 g, 1.18 mol) and NaOMe (28% in MeOH, 114 g, 589 mmol) in MeOH (600 ml) was heated under reflux for 4 h. Additional methyl 3-mercaptopropionate (35.4 g, 294 mmol) and NaOMe (28% in MeOH, 15.4 g, 79.6 mmol) were added to the mixture at 2 and 3 h after starting the reaction. After the mixture had cooled, aqueous HCl (1 M solution, 880 ml) was added and the whole was extracted with CH_2Cl_2 (2.5 l). The extract was washed successively with water and brine and dried over $MgSO_4$. Evaporation of the solvent and recrystallization of the residue from diisopropyl ether afforded (2*R*,3*R*)-**7** (23.1 g, 55%) as a colorless crystalline powder. Purification of the mother liquor by column chromatography (1 kg, hexane–AcOEt, 3:1→1:3, v/v), followed by recrystallization from hexane–AcOEt, gave additional (2*R*,3*R*)-**7** (11.1 g, 27%). Contamination with the diastereomer (2*S*,3*R*)-**7** was not observed on HPLC analysis under the following conditions: A-303® column (octadecyl silica (ODS), 4.6 mm i.d. × 250 mm, Yamamura Chemical Laboratories Co.), mobile phase (MeOH–H_2O–AcOH, 7:3:0.02, v/v; flow rate, 0.8 ml/min; detection, UV at 254 nm). The retention times of the diastereomers, (2*R*,3*R*)-**7** and (2*S*,3*R*)-**7**, were 7.5 and 5.9 min, respectively.

The isomers, (2*S*,3*R*)-**7**, (2*S*,3*S*)-**7** and (2*R*,3*S*)-**7** (Table I), were prepared by method B.

Methyl 3-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]thiopropionate (17) A solution of tetrabutylammonium fluoride (1 M solution, 3.6 ml) in THF was added to a mixture of (2*R*,3*R*)-**7** (1.0 g, 3.5 mmol) and methyl acrylate (0.48 ml, 5.3 mmol) in CH_2Cl_2 (30 ml) at 0 °C. The resulting mixture was stirred for 5 min at 0 °C, washed with water (20 ml) and dried over Na_2SO_4. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–AcOEt, 1:1, v/v) to give **17** (1.3 g, 100%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=7 Hz), 2.69 (2H, t, J=7 Hz), 2.88—3.12 (2H, m), 3.32 (1H, q, J=7 Hz), 3.74 (3H, s), 4.83 (1H, d, J=14.2 Hz), 4.86 (1H, s), 5.06 (1H, d, J=14.2 Hz), 6.68—6.80 (2H, m), 7.27—7.42 (1H, m), 7.75 (1H, s), 7.84 (1H, s). IR (neat): 3400, 2950, 1740, 1615, 1595, 1500, 1435, 1420, 1360, 1270, 1240, 1200 cm^{-1}.

A mixture of **17** (93 mg, 0.27 mmol) and NaOMe (28% in MeOH, 0.14 g, 0.73 mmol) in MeOH (3 ml) was refluxed for 4 h. After being cooled, the mixture was neutralized with diluted aqueous HCl and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (7 g, AcOEt) to yield (2*R*,3*R*)-**7** (40 mg, 57%). The spectral data (^{1}H-NMR, IR) were identical with those of (2*R*,3*R*)-**7** obtained by method B.

(2*R*,3*R*)-3-Acetylthio-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(2*R*,3*R*)-18] Acetyl chloride (121 mg, 1.54 mmol) was added to a mixture of (2*R*,3*R*)-**7** (400 mg, 1.40 mmol) and triethylamine (0.22 ml, 1.54 mmol) in CH_2Cl_2 (15 ml) with stirring at 0 °C. The resulting mixture was stirred for 30 min at room temperature and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–AcOEt, 1:1, v/v) to give (2*R*,3*R*)-**18** (450 mg, 98%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, J=7 Hz), 2.42 (3H, s), 4.31 (1H, q, J=7 Hz), 4.67 (1H, d, J=14 Hz), 4.92 (1H, d, J=14 Hz), 5.11 (1H, d, J=1.8 Hz), 6.69—6.88 (1H, m), 7.27—7.43 (1H, m), 7.78 (2H, s). This compound (440 mg) was converted to the hydrochloride by treatment with HCl (4 M solution in AcOEt). Recrystallization from MeOH–AcOEt gave (2*R*,3*R*)-**18**·HCl (420 mg) as a colorless crystalline powder, mp 120—127 °C. IR (KBr): 3250, 1688, 1615, 1500, 1270, 1135 cm^{-1}. *Anal.* Calcd for $C_{14}H_{15}F_2N_3O_2S \cdot HCl$: C, 46.22; H, 4.46; N, 11.55. Found: C, 46.20; H, 4.46; N, 11.52. $[\alpha]_D^{23}$ −97.2° (c=1.0, MeOH).

(2*S*,3*S*)-3-Acetylthio-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(2*S*,3*S*)-**18**] was prepared from (2*S*,3*S*)-**7** in a 79% yield in the same manner as described above. (2*S*,3*S*)-**18**·HCl, mp 120—128 °C (MeOH–diethyl ether). *Anal.* Calcd for $C_{14}H_{15}F_2N_3O_2S \cdot HCl$: C, 46.22; H, 4.46; N, 11.55. Found: C, 45.94; H, 4.36; N, 11.55. $[\alpha]_D^{25}$ +97.3° (c=0.53, MeOH). The spectral data (^{1}H-NMR, IR) were identical with those of (2*R*,3*R*)-**18**·HCl.

The enantiomeric purity was determined by HPLC using Chiralcel OF® (4.6 mm i.d. × 250 mm, Daicel Chemical Industries, Tokyo, Japan) under the following conditions: mobile phase, hexane–isopropanol, 7:3, v/v; flow rate 1.0 ml/min; detection, UV at 254 nm. The retention times of the enantiomers, (2*R*,3*R*)-**18** and (2*S*,3*S*)-**18**, were 16.8 and 9.9 min, respectively. The ee values of (2*R*,3*R*)-**18** and (2*S*,3*S*)-**18** were determined to be 99.7%.

Antifungal Activity *In vitro* antifungal activity was measured by the following method: a filter paper disc (manufactured by Toyo Seisakusho, 8 mm in diameter) was soaked in a 1000 μg/ml solution of the test compound in MeOH, dried and placed on an agar plate containing fungal cells, which was incubated at 28 °C for 2 d. The diameter of the growth inhibition zone around the filter paper disc was measured.

In vivo antifungal activity was determined by the following method, five-week-old Crj:CDF1 mice were inoculated intravenously with 2 × 10^6 CFU per mouse of *C. albicans* TA. The test compound was administered orally (*p.o.*) immediately after the inoculation. The efficacy of the compound was expressed in terms of ED_{50} (mg/kg) calculated by the method of Reed and Muench[17] from the survival rate on day 7 after infection. The mice of the untreated group died within 3 d.

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