Triazole Antifungals. II.[1] Synthesis and Antifungal Activities of 3-Acyl-4-methyloxazolidine Derivatives

Toshiyuki KONOSU,[a] Yawara TAJIMA,[a] Noriko TAKEDA,[a] Takeo MIYAOKA,[a] Mayumi KASAHARA,[b] Hiroshi YASUDA,[b] and Sadao OIDA*,[a]

Medicinal Chemistry Research Laboratories,[a] and Biological Research Laboratories,[b] Sankyo Co., Ltd., Hiromachi, Shinagawa-ku, Tokyo 140, Japan. *Received March 29, 1990*

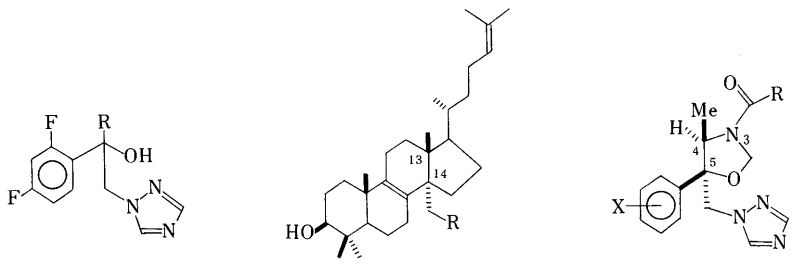
Triazole compounds with an oxazolidine ring were designed and synthesized as a potential inhibitor of the fungal cytochrome P_{450} 14α-demethylase. In testing for antifungal activity against a mouse systemic *Candida albicans* infection, (4*R*,5*R*)-3-acyl-4-methyloxazolidine derivatives 4 exhibited remarkably high efficacy after oral or parenteral dosing. The potent activity of 4 is hypothesized to be a consequence of a structural similarity between 4 and lanosterol, a target molecule of the cytochrome P_{450} 14α-demethylase. Highly stereoselective synthesis of these oxazolidines is also described.

Keywords antifungal activity; oral activity; 1,2,4-triazole; 3-acyl-4-methyloxazolidine; cytochrome P_{450} inhibitor; structure–activity relationship; stereoselective synthesis

Systemic fungal infection in man has been increasing.[2] The imidazole derivative ketoconazole[3] has been used as an orally active antifungal agent in Europe and the United States. A new antifungal azole fluconazole[4] (**1**), which is also orally effective and is claimed to have lower toxicity and more potent activity than ketoconazole, has recently been launched on the market, and two newer orally active azoles, itraconazole[5] and SM-8668[6] (**2**), have been under clinical trial.

Azole (imidazole and triazole) antifungals have been shown to inhibit the fungal biosynthesis of ergosterol, which is an important constituent of the fungal cell membrane. An important step in ergosterol biosynthesis is the 14-demethylation of lanosterol (**3**: R = H), mediated by the cytochrome P_{450} monooxygenase enzyme.[7] The 14α-methyl group of lanosterol is removed *via* three oxidation steps by sequential attacks of the oxygen atoms coordinated with the protoheme iron atom located in the binding domain of the enzyme. Inhibition of this enzyme is believed to be brought about by a mechanism in which azole antifungals bind to the heme iron atom with the lone pair electrons of the ring nitrogen atom (N-3 of imidazole and N-4 of triazole) and exclude oxygen which would normally take part in the reaction.[8] Since the target of the cytochrome P_{450} 14α-demethylase enzyme is the 14-methyl group of lanosterol, a logical inhibitor could be lanosterol with a heme binding functionality at the 14-methyl position. In pursuit of such an inhibitor, Schering chemists synthesized 14α-aminomethyl and 14α-imidazolylmethyl substituted lanosterol derivatives (**3**: R = NH_2, imidazol-1-yl), which were shown to be inhibitors of fungal ergosterol biosynthesis and were active *in vitro* against *Candida* and dermatophyte strains.[9]

As part of a program aimed at seeking an active agent against fungal infections, we designed a new triazolylmethyloxazolidine derivative represented by general formula **4** as a potential inhibitor of the cytochrome P_{450} 14α-demethylase enzyme. We presumed the 3-acyl-4-methyloxazolidine **4** with 4*R*,5*R* stereochemistry to have a mimic lanosterol skeleton. The 5β-aromatic ring and the oxazolidine ring of **4** could be regarded as the B and D rings of lanosterol, and the 4β-methyl group and the methylene carbon atom of the 5α-triazolylmethyl group of **4** as the 13β-methyl and 14α-methyl groups of lanosterol, respectively. The N-acyl group of **4** might correspond to the 17-alkyl side chain of lanosterol. To some extent, the oxygen atom in the oxazolidine ring was expected to play a role in the binding at the active site of the enzyme, since the oxygen atom at the benzylic position in such antifungals as **1**, **2** or ketoconazole appears to be important for their antifungal potency. The nitrogen atom in the oxazolidine ring is convenient for the introduction of a variety of acyl groups at this position, and selection of a proper acyl chain could match the 17-side chain of lanosterol. Among the N-acyl groups, we were initially most interested in the 5-methyl-4-hexenoyl group, as in oxazolidine **4A** (Chart 2), because of its likeness in shape and bulkiness to the alkyl side chain of lanosterol.



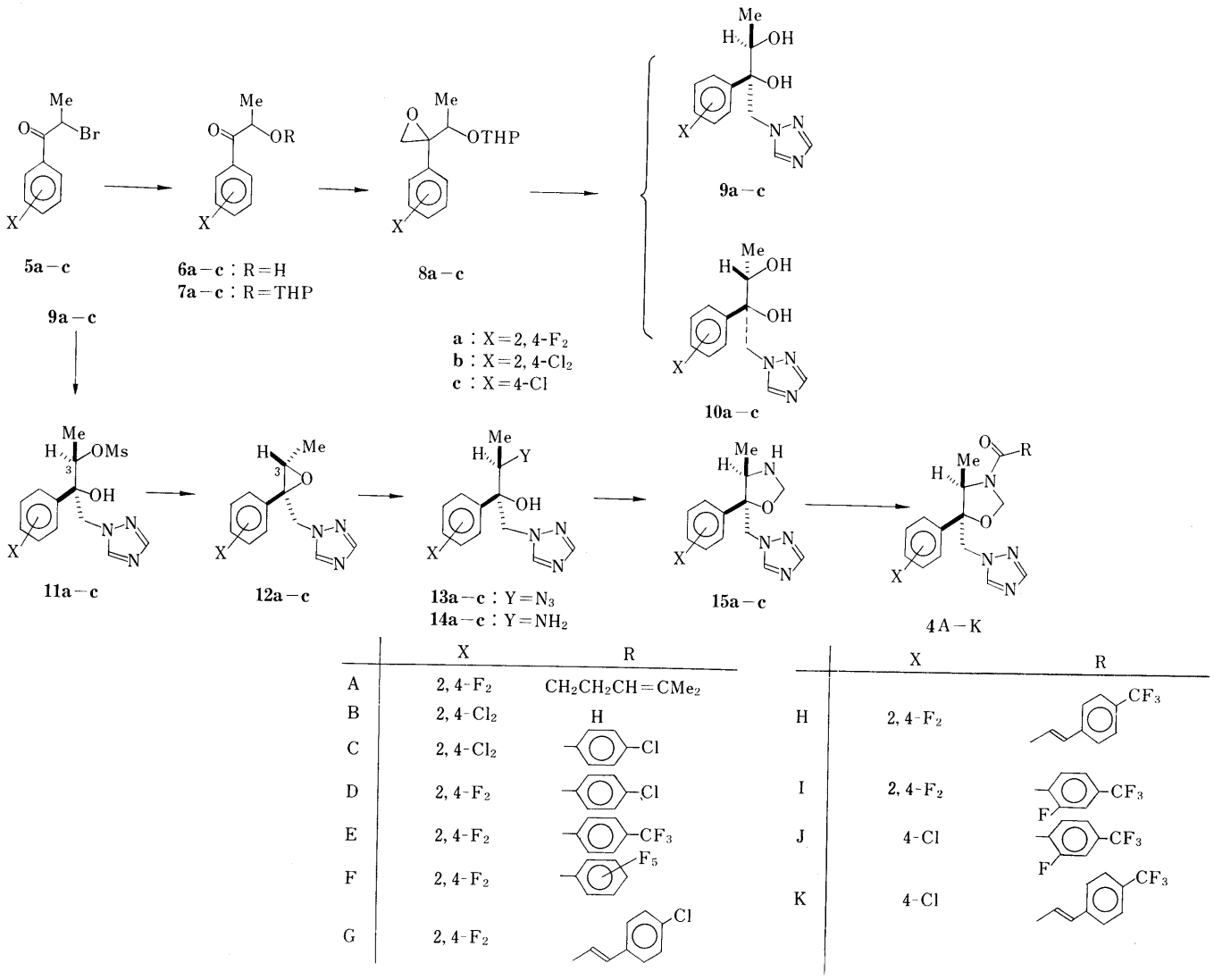
1 : R = CH_2N(triazol-1-yl)

2 : R = $CHMeS(O)_2Me$

3

4 : X = halogen(s)

Chart 1



	X	R
A	2, 4-F_2	$CH_2CH_2CH=CMe_2$
B	2, 4-Cl_2	H
C	2, 4-Cl_2	Cl
D	2, 4-F_2	Cl
E	2, 4-F_2	CF_3
F	2, 4-F_2	F_5
G	2, 4-F_2	Cl

	X	R
H	2, 4-F_2	CF_3
I	2, 4-F_2	F, CF_3
J	4-Cl	F, CF_3
K	4-Cl	F, CF_3

Chart 2

This and other *N*-acyloxazolidine derivatives (**4A**—K) were synthesized as racemates as illustrated in Chart 2. A key precursor to these oxazolidine compounds is the (2*R**, 3*R**) aminoalcohol **14**, which was prepared in three steps from the (2*R**, 3*R**) diol **9**. Stereoselective synthesis of **9** had been developed in the synthesis of SM-8668 by Saji *et al.*[6] from the α-bromopropiophenone **5** *via* **6**, **7** and **8**. According to their procedure, the diols (**9a, b, c**) were obtained in good yields. The minor (2*R**, 3*S**) diastereomers (**10a, b, c**) were separated by recrystallization and column chromatography. The diols (**9a, b, c**) were mesylated in a usual manner to give the mesylates (**11a, b, c**). Treatment of the mesylates (**11a, b, c**) with sodium azide in the presence of ammonium chloride in *N*,*N*-dimethylformamide (DMF) at 115 °C gave the (2*R**, 3*R**) azidoalcohols (**13a, b, c**). This reaction was found to proceed with double inversions of stereochemistry at the C-3 position *via* the intermediate epoxides (**12a, b, c**), which were obtained in good yields by ceasing the reaction in a shorter time. Further treatment of these epoxides with sodium azide afforded high yields of the above azidoalcohols. Catalytic hydrogenation of these azides (**13a, b, c**) using 10% palladium–charcoal in ethanol (EtOH) easily afforded the corresponding aminoalcohols (**14a, b, c**).

Cyclization of the aminoalcohols (**14a, b, c**) to the oxazolidines (**15a, b, c**) was accomplished by heating with 1 equivalent of paraformaldehyde in benzene in quantitative yields. The oxazolidine **15a** was used for acylation with 5-methyl-4-hexenoyl chloride and triethylamine in methylene chloride to give the amide **4A**. This product was shown by analysis of the nuclear magnetic resonance spectrum (NMR) to be a 1 : 1 mixture of two rotamers with respect to the amide bond. The N-formyl derivative **4B** was obtained by formylation of **15a** with formic acid and *N*,*N*′-carbonyldiimidazole. Other *N*-acyloxazolidines, such as substituted benzoyl or cinnamoyl derivatives (**4C**—K), were synthesized by acylation of **15a, b** or **c** with the corresponding acyl chloride in pyridine. We selected acyl groups with the benzene ring substituted with an electron withdrawing atom(s) or group, such as a fluorine atom, a chlorine atom or a trifluoromethyl group, in expectation of increasing the metabolic stability of the benzene ring and thereby enhancing the activity.[10]

As will be shown later, several of the oxazolidines synthesized above exhibited remarkably potent antifungal *in vivo* activity. As mentioned above, one of the important

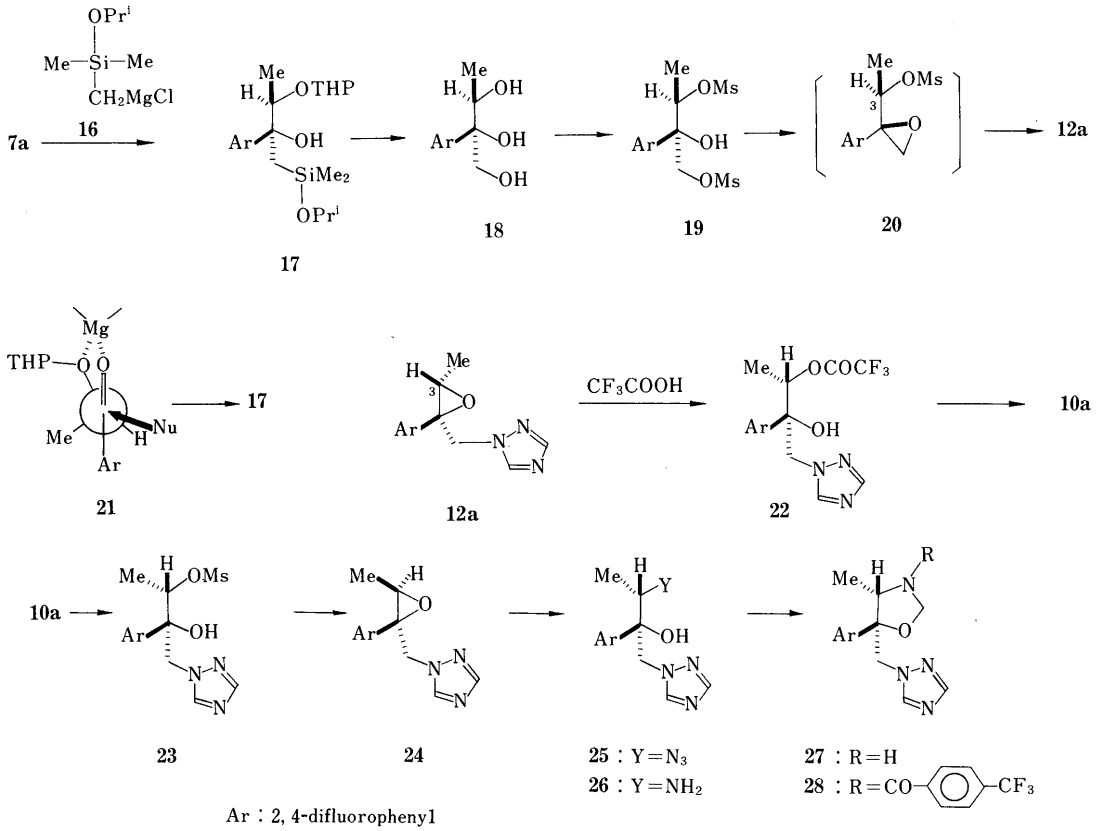


Chart 3

intermediates for the synthesis of these oxazolidines is the epoxide **12**. We developed an alternative route to **12a** in a highly stereoselective manner with no contamination of its diastereomer. The new method is shown below, and stereoselective conversion of the epoxide **12a** to the diol **10a**, a minor product of the above-mentioned literature method, is also described.

The ketone **7a** was treated with the Grignard reagent **16**[11] in ether at 0 °C to give the silylalcohol **17**. Oxidative desilylation[11] of **17** with hydrogen peroxide and sodium bicarbonate in tetrahydrofuran (THF)–H_2O afforded the diol, whose deprotection of the tetrahydropyranyl group by acid treatment in methanol (MeOH) gave the triol **18** in 73% overall yield based on **7a**. The triol **18** was mesylated to give the dimesylate **19**, which was then treated with excess sodium triazolide, prepared from sodium hydride and 1*H*-1,2,4-triazole, in DMF at 65—70 °C for 2 h to give the epoxide **12a** in 80% yield over the two steps from **18**. Monitoring of the reaction revealed that the mesylate **19** first cyclizes to the epoxide **20** which is then ring-opened by an attack of the triazolide ion. It then recyclizes concomitantly with an inversion at the C-3 position to form the (2*R**, 3*S**) epoxide **12a**. There was no formation of the diastereomeric epoxide **24**, whose preparation will be described later, as judged by NMR analysis of the product. Exclusive formation of the epoxide **12a** in the above reaction sequence suggests that in the Grignard reaction of **7a** the nucleophile attacks selectively from the less hindered face of the carbonyl group of the magnesium-chelated intermediate **21** to give the (2*R**,3*R**) alcohol **17**. The 2*R**,3*S** stereochemistry of **12a** was determined by comparing the NMRs of **12a** and its diastereomer **24**. The signal of the methyl group of **12a** appears at δ 1.64, whereas that of **24** appears at δ 1.05, remarkably shifted to a higher field. This indicates that the methyl group of **24** is influenced by the ring current of the aryl group, suggesting *cis* orientation of these two groups in **24**. Consequently, *trans* orientation of the methyl group and the aryl group in **12a** was assigned.

Treatment of the epoxide **12a** with trifluoroacetic acid at 0 °C gave the ring-opened product **22**, which was solvolyzed with MeONa in MeOH to afford the diol **10a** in 86% yield over two steps from **12a**. With a 2% yield, the diastereomeric diol **9a** was obtained only as a minor product. The NMR spectrum of the intermediate **22** was identical with that of an authentic sample prepared by trifluoroacetylation of **10a** using trifluoroacetic anhydride and triethylamine. This indicates that the cleavage of the epoxide ring of **12a** occurred not at the benzylic position, but at the C-3 position with retention of the stereochemistry. In contrast, the ring cleavage of the diastereomeric epoxide **24** under the same reaction conditions occurred predominantly with an inversion at the C-3 position to give 56% yield of **10a** accompanied with a 22% yield of **9a**. The reason why these two epoxides behave differently in the ring-opening reaction is not understood at present.

The diol **10a** obtained above was used for synthesis of the 4α-methyloxazolidine derivative **28**, a diastereomer of **4E**. The synthesis of **28** was easily performed by a procedure similar to that described in the preparation of **4**, *via* **23**, **24**, **25**, **26** and **27**. The stereochemistry of **28** and the previously described 4β-methyloxazolidines **4A**—**K** was inferable again by comparison of their NMR data. While the signal of the methyl group of **28** is observed at δ 1.47, those of **4A**—**K** appear at a significantly higher field, in the range of δ

0.84—1.11 (Table V). This suggests that the methyl and the aryl groups of **4A**—K are in *cis* and those of **28** are in *trans* orientation. This assignment was confirmed by X-ray crystallographic analyses of both **4E** and **28**, which will be reported elsewhere.[12a)]

Optically active oxazolidines of an enantiomeric pair of (4*R*,5*R*)-(+)-**4C** and (4*S*,5*S*)-(−)-**4C** were synthesized from (2*R*,3*R*)-(−)-**9b** and (2*S*,3*S*)-(+)-**9b**, respectively, following exactly the same procedure as described in the preparation of the racemic oxazolidine **4C**. Both diols, (−)-**9b** and (+)-**9b**, were easily obtained by resolution of the racemic diol **9b**, each enantiomer of which was found to form a highly crystalline salt with *d*- or *l*-10-camphorsulfonic acid. The absolute configuration of these enantiomers was determined by X-ray crystallographic analysis of the opticaly active azidoalcohol (2*R*,3*R*)-(−)-**13b**, which was derived from the diol (2*R*,3*R*)-(−)-**9b**.[12b)]

To evaluate the role of the 4-methyl group of the oxazolidine derivatives in antifungal activity, the 4-demethyloxazolidine analog **33** was prepared. The known epoxide **29a**[10)] was transformed into **33** by a reaction sequence similar to that described in the preparation of **4**, *via* **30a**, **31a** and **32**. The 2-oxazolidinone derivative **35** was also synthesized by acylation of **34**. The oxazolidinone **34** was obtained by cyclization of the known aminoalcohol **31b**,[13)] which was derived from the epoxide **29b** *via* **30b**, using diphosgene in the presence of the base.

The *in vitro* antifungal activities of these *N*-acyloxazolidine derivatives on Sabouraud dextrose agar media are presented in Table I. The minimum inhibitory concentration (MIC) values (in μg/ml) against several species of fungi in comparison with ketoconazole and fluconazole are given. Although most of the compounds showed activities more or less against *Trichophyton rubrum*, they were mostly inactive against other species of the fungi at a concentration of 50 μg/ml. All compounds synthesized exhibited no *in vitro* activity against *Candida albicans* strains at 50 μg/ml on this agar media.

It is known that *in vitro* activity among azoles is unreliable in predicting *in vivo* activity.[14)] Therefore these oxazolidines were subjected to studies in animal models of fungal infection. The results of *in vivo* studies in mice in systemic candidiasis, one of the most important pathogenic fungal infections in man, are summarized in Table II. In the experiment, groups of 10 mice were inoculated intravenously with 6 to 9×10^6 cells of *C. albicans* 427. The oxazolidines were administered orally (*p.o.*) or intraperitoneally (i.p.) at 1, 4 and 24 h post-infection. Antifungal efficacy of the compounds was compared with that of ketoconazole and fluconazole. All control mice (no drug) died within 2 d after infection, whereas most mice treated *p.o.* or i.p. with azoles (20 mg/kg/dose) survived remarkably longer.

Contrary to expectation, the *in vivo* activity of the oxazolidine **4A** having a 5-methyl-4-hexenoyl group was disappointing. Lack of activity of **4A** might be due to metabolic instability of its side chain aliphatic group, although no definite evidence is available at present. In contrast, the N-formyl derivative **4B** showed good oral

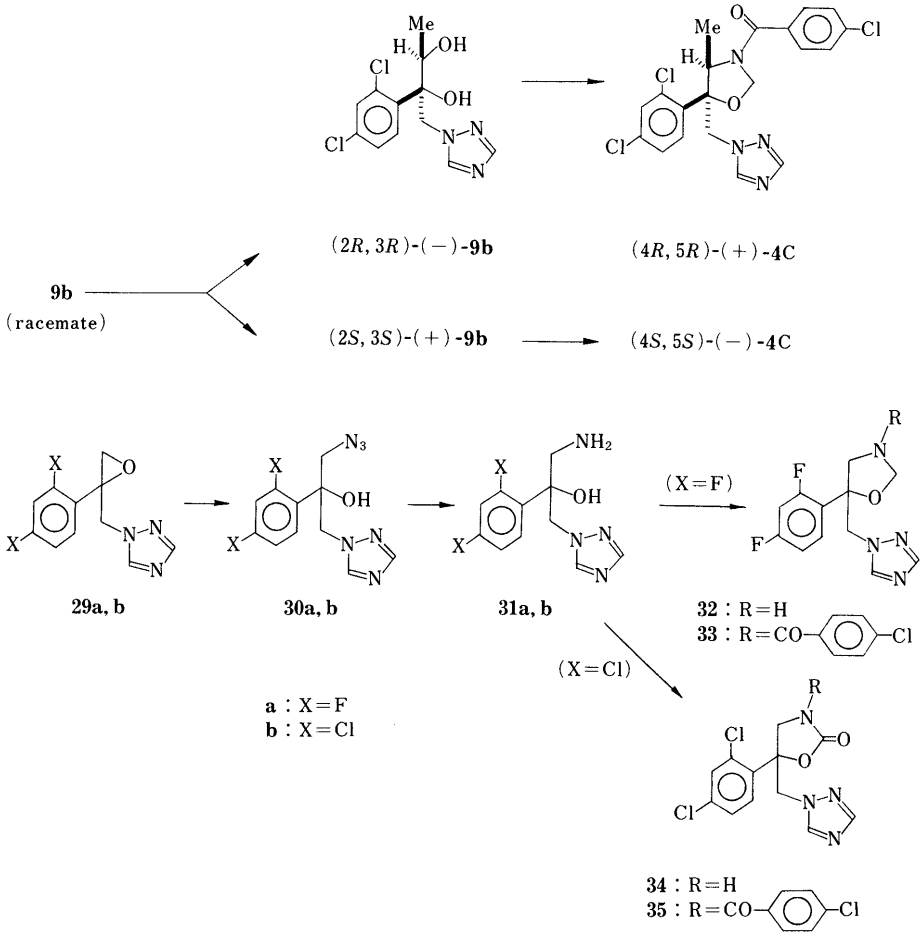


Chart 4

TABLE I. The *in Vitro* Antifungal Activities of Oxazolidine Derivatives (**4A—K**, **28** and **33**)

Compound[a]	MIC[b] (μg/ml)							
	C.a. (1)	*C.a.* (2)	*C.n.*	*M.m.*	*A.f.*	*M.g.*	*T.m.*	*T.r.*
4A	>50	>50	>50	>50	>50	>50	>50	12.5
4B	>50	>50	>50	>50	>50	>50	>50	>50
4C	>50	>50	12.5	>50	50	25	25	6.2
(+)-**4C**	>50	>50	12.5	>50	>50	25	25	6.2
(−)-**4C**	>50	>50	>50	>50	>50	>50	>50	25
4D	>50	>50	>50	>50	>50	>50	>50	25
4E	>50	>50	>50	>50	>50	>50	>50	50
4F	>50	>50	>50	>50	>50	>50	>50	50
4G	>50	>50	>50	50	>50	>50	>50	1.5
4H	>50	>50	>50	>50	>50	>50	>50	3.1
4I	>50	>50	>50	>50	>50	>50	>50	12.5
4J	>50	>50	50	>50	>50	>50	>50	3.1
4K	>50	>50	>50	>50	>50	>50	>50	1.5
28	>50	>50	>50	>50	>50	>50	>50	>50
33	>50	>50	>50	>50	>50	>50	>50	12.5
Ketoconazole	50	50	1.5	50	12.5	6.2	3.1	0.4
Fluconazole	>50	>50	>50	>50	>50	>50	>50	12.5

a) All compounds except for (+)-**4C** and (−)-**4C** are racemic. Oxalic acid salts of the oxazolidine derivatives except for **4H**, **4K** and **28** were prepared and submitted to the test. *b*) The values were determined on Sabouraud dextrose agar media buffered to pH 6.0. Plates were incubated at 27 °C. The strains of yeasts and fungi used were *C.a.* (1), *Candida albicans* Sc.; *C.a.* (2), *Candida albicans* 427; *C.n.*, *Cryptococcus neoformans* 58063; *M.m.*, *Mucor mucedo* 14358; *A.f.*, *Aspergillus fumigatus* 10569; *M.g.*, *Microsporum gypseum* 11268; *T.m.*, *Trichophyton mentagrophytes* Sc.; *T.r.*, *Trichophyton rubrum* Sc. *C.a.* (1), *C.a.* (2) and *C.n.* were grown for 2 d. *M.m.*, *A.f.* and *M.g.* were grown for 5 d. *T.m.* and *T.r.* were grown for 7 d.

activity which seemed superior to that of ketoconazole. The benzoyl derivatives (**4C**, D, I, J) with the 4*R**,5*R** stereochemistry showed markedly enhanced activity. The antifungal potency of both the 2,4-dichlorophenyl and 2,4-difluoropheny analogs, **4C** and **4D**, with the same benzoyl group was shown to be approximately equal. The activity of the 4-(trifluoromethyl)benzoyl derivative **4E** was excellent as shown, apparently more potent than that of fluconazole. Extremely potent activity was observed in the 2-fluoro-4-(trifluoromethyl)benzoyl derivatives, **4I** and **4J**, as after being administered *p.o.* or i.p., almost all mice survied to even 3 weeks after infection. On the other hand, the pentafluorobenzoyl derivative **4F** was almost devoid of activity. The *N*-cinnamoyloxazolidines (**4G**, H, K), with the benzene ring of the acyl group substituted with a chlorine atom or a trifluoromethyl group, retained potent antifungal activity.

The 4-demethyloxazolidine analog **33** was shown to have considerable activity, comparable to ketoconazole, though it was less active than the corresponding 4β-methyl analog **4D**; the 4α-methyloxazolidine **28**, a diastereomer of **4E**, showed significantly decreased activity. Comparison of the activity of the enantiomeric pair of the oxazolidines, (+)-**4C** and (−)-**4C**, revealed that the (+)-enantiomer with the 4*R*, 5*R* absolute configuration was far more potent than the (−)-enantiomer. These results are in accord with the presumption that among diastereomers and enantiomers of 4-methyloxazolidine derivatives, only the oxazolidine **4** with the 4*R*, 5*R* absolute configuration could fit sterically to superimpose on the lanosterol skeleton and could be a good inhibitor of cytochrome P_{450} 14α-demethylase. The oxazolidinone analog **35** was almost inactive *in vivo*.

In a preliminary toxicity study of the selected oxazolidine compounds, all three mice (ddY strain, male, 5 weeks old) tested survived after oral administration of a single dose (300 mg/kg) of **4C** (oxalic acid salt), **4E** (oxalic acid salt) or **4H**.

Experimental

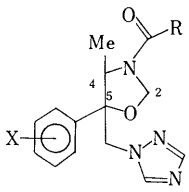
Melting points are uncorrected. Infrared spectra (IR) were recorded on a JASCO A-2 spectrometer and proton magnetic resonance spectra (^{1}H-NMR) on a Varian EM-360L spectrometer in $CDCl_3$ using Me_4Si as an internal standard. Mass spectra (MS) were obtained on a JEOL JMS D300 spectrometer. Rotations were determined on a Perkin–Elmer 141 spectrometer at 25 °C. Thin-layer chromatography (TLC) was performed on TLC plates, Silica gel 60 F_{254} precoated, layer thickness 0.25 mm (E. Merck) and spots were made visible by ultraviolet (UV) irradiation, by spraying with vanadic acid–sulfuric acid followed by heating, or by iodine treatment. Chromatography columns were prepared with silica gel (60—110 mesh, Kanto Chemical Co., Inc.) and preparative TLC was carried out on plates of Silica gel 60 F_{254}, layer thickness 2 mm (E. Merck). The amount of silica gel used and the developing solvents are shown in parentheses. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; td, triplet of doublets; q, quartet; m, multiplet; br, broad.

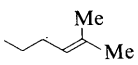
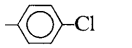
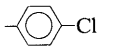
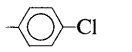
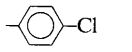
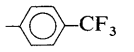
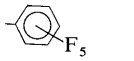
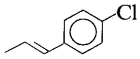
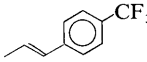
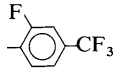
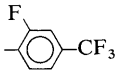
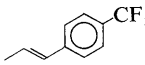
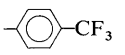
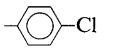
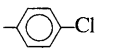
(2*R,3*R**)-2-Aryl-1-(1*H*-1,2,4-triazol-1-yl)-2,3-butanediols (9a, b, c) and the (2*R**,3*S**) Diastereomers (10a, b, c)** The diols, **9a**, **b**, **c** and **10a**, **b**, **c**, were prepared according to the method developed by Saji *et al.*[6] The relative ratio of the diastereomeric diols obtained by employing this method was 8:1 for **9a** and **10a**, 17:1 for **9b** and **10b**, and 4.3:1 for **9c** and **10c**. Since the detailed description of the procedure is not yet available, the preparation of **9c** and **10c**, which are so far unknown in literature, from the starting material is described below in detail as a typical example.

1-Bromoethyl 4-Chlorophenyl Ketone (5c) Aluminum chloride (7.53 g, 56.6 mmol) was added portionwise to a stirred mixture of chlorobenzene (12.7 g, 113 mmol) and 2-bromopropionyl bromide (12.2 g, 56.6 mmol) at 0 °C. The whole was then stirred at the same temperature for 1.5 h. At the end of this time, the mixture was poured carefully into ice-water with stirring. The separated oily product was extracted with CH_2Cl_2 and washed with a diluted aqueous solution of $NaHCO_3$ and brine. Evaporation of the solvent *in vacuo* afforded a crystalline residue which was recrystallized from hexane to give **5c** (12.8 g, 91%), mp 79—80 °C. *Anal.* Calcd for C_9H_8BrClO: C, 43.67; H, 3.26; Br, 32.28; Cl, 14.32. Found: C, 43.57; H, 3.33; Br, 32.48; Cl, 14.43. IR ν_{max}^{KBr} cm^{-1}: 1682, 1589. NMR ($CDCl_3$) δ: 1.86 (3H, d, *J*=7 Hz), 5.21 (1H, q, *J*=7 Hz), 7.45 (2H, d-like, *J*=9 Hz), 7.98 (2H, d-like, *J*=9 Hz).

4-Chlorophenyl 1-Hydroxyethyl Ketone (6c) Lithium hydroxide (1.11 g, 46.5 mmol) was added to a solution of **5c** (11.5 g, 46.5 mmol) in a 4:1 mixture of DMF and water (110 ml) at 0 °C. The mixture was stirred at the same temperature for 2 h and then diluted with AcOEt. After washing with water and brine, the solvent was evaporated *in vacuo* to afford

TABLE II. Comparative Antifungal Efficacy of Oxazolidine Derivatives (**4A—K**, **28**, **33** and **35**) against Systemic Infection of *Candida albicans*[a]



Compd.[b]	X	R	Stereochemistry	Dose (mg/kg)	Route	% survival rate on day				
						3	6	9	14	21
4A	2,4-F_2		4*R**,5*R**	20	*p.o.*	0				
					i.p.	0				
4B	2,4-Cl_2	H	4*R**,5*R**	20	*p.o.*	100	90	60	40	40
					i.p.	100	80	40	30	30
4C	2,4-Cl_2		4*R**,5*R**	20	*p.o.*	100	100	90	80	70
					i.p.	100	100	90	50	0
(+)-**4C**	2,4-Cl_2		4*R*,5*R*	20	*p.o.*	100	100	100	70	40
					i.p.	100	100	100	60	30
				5	*p.o.*	100	100	100	60	40
					i.p.	100	100	90	40	10
(−)-**4C**	2,4-Cl_2		4*S*,5*S*	20	*p.o.*	50	30	10	0	
					i.p.	60	40	20	0	
4D	2,4-F_2		4*R**,5*R**	20	*p.o.*	100	100	90	40	10
					i.p.	100	100	70	70	40
4E	2,4-F_2		4*R**,5*R**	20	*p.o.*	100	100	100	100	80
					i.p.	100	100	100	100	70
4F	2,4-F_2		4*R**,5*R**	20	*p.o.*	20	20	20	20	20
					i.p.	0				
4G	2,4-F_2		4*R**,5*R**	20	*p.o.*	100	100	100	70	50
					i.p.	100	100	100	80	40
4H	2,4-F_2		4*R**,5*R**	20	*p.o.*	100	100	100	100	60
					i.p.	80	80	80	80	50
4I	2,4-F_2		4*R**,5*R**	20	*p.o.*	100	100	100	100	90
					i.p.	100	100	100	100	100
4J	4-Cl		4*R**,5*R**	20	*p.o.*	100	100	100	100	100
					i.p.	100	100	100	100	100
4K	4-Cl		4*R**,5*R**	20	*p.o.*	60	60	60	60	40
					i.p.	60	60	60	60	60
28	2,4-F_2		4*S**,5*R**	20	*p.o.*	10	10	10	10	10
					i.p.	20	20	20	10	10
33	2,4-F_2		(4-Demethyl)	20	i.p.	100	70	30	ND	ND
35	2,4-Cl_2		(2-Oxo-4-demethyl)	20	*p.o.*	20	10	0		
					i.p.	10	0			
Ketoconazole				20	*p.o.*	100	80	50	30	10
					i.p.	100	80	50	20	0
Fluconazole				20	*p.o.*	100	100	100	70	60
				5	*p.o.*	100	100	80	50	30
Control (no drug)						0				

a) *In vivo* activity was determined in mice (each group consisted of ten male mice, 5 weeks old, of the ddY strain) infected systemically using an intravenous challenge of 6 to 9×10^6 cells of *Candida albicans* 427. The triazole was administrated orally (*p.o.*) or intraperitoneally (i.p.) at 1, 4, 24 h post infection. *b*) All compounds except for (+)-**4** and (−)-**4** are racemic. Oxalic acid salts of the oxazolidine derivatives except for **4H**, **4K**, **28**, and **35** were prepared and submitted to the test. ND: not determined.

the crude hydroxyketone **6c** (8.70 g, 100%) as an oil which contained a small amount of DMF as determined by the NMR spectrum, but was pure enough for the next reaction. NMR ($CDCl_3$) δ: 1.42 (3H, d, J=7 Hz), 3.84 (1H, br d, J=6.5 Hz), 5.1 (1H, m), 7.42 (2H, d-like, J=9 Hz), 7.92 (2H, d-like, J=9 Hz).

4-Chlorophenyl 1-(Tetrahydropyran-2-yloxy)ethyl Ketone (7c) A solution of **6c** (9.60 g, 52 mmol), 2,3-dihydropyran (5.25 g, 62.4 mmol) and pyridinium *p*-toluenesulfonate (0.65 g, 2.6 mmol) in CH_2Cl_2 (100 ml) was stirred at room temperature for 5 h. At the end of this time, the mixture was treated with a diluted aqueous solution of $NaHCO_3$, washed with brine and dried. Removal of the solvent under reduced pressure gave an oily residue which was chromatographed on silica gel (100 g, 3—10% AcOEt–hexane, v/v) to yield **7c** (10.8 g, 78% yield from **5c**) as an oil. IR $\nu_{max}^{CHCl_3}$: 1695 cm^{-1}. NMR ($CDCl_3$) δ: 1.45 and 1.51 (1 : 1, 3H, d, J=7 Hz), 1.2—2.0 (6H, br), 3.1—4.1 (2H, m), 4.55 and 4.72 (1 : 1, 1H, br), 4.85 and 5.10 (1 : 1, 1H, q, J=7 Hz), 7.40 (2H, d-like, J=9 Hz), 7.8—8.2 (2H, m).

2-(4-Chlorophenyl)-2-[1-(tetrahydropyran-2-yloxy)ethyl]oxirane (8c) Sodium hydride (55% mineral oil dispersion, 2.13 g, 48.8 mmol, washed with hexane) was dissolved in dimethyl sulfoxide (DMSO) (150 ml) at 60 °C for 1 h. After cooling, trimethylsulfoxonium iodide (17.9 g, 81.4 mmol) was

added to this solution and the whole was stirred for 1 h at room temperature. A solution of **7c** (10.9 g, 40.7 mmol) in DMSO (100 ml) was added and this mixture was stirred at room temperature for 1 h. The mixture was partitioned between benzene and water. The organic layer was collected, washed and dried. Evaporation of the solvent gave **8c** (11.5 g, 100%) as an oil which was used for the next reaction without further purification. NMR ($CDCl_3$) δ: 1.11 and 1.21 (1 : 1, 3H, d, J=6.5 Hz), 2.6—4.1 (4H, m), 4.08 and 4.23 (1 : 1, 1H, q, J=6.5 Hz), 4.8 (1H, m), 7.34 (4H, s).

(2*R,3*R**)-2-(4-Chlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2,3-butanediol (9c) and the (2*R**,3*S**) Diastereomer (10c)** A mixture of the epoxide **8c** (11.5 g, 40.7 mmol) obtained above, 1*H*-1,2,4-triazole (11.2 g, 163 mmol), *tert*-BuOK (9.13 g, 81.3 mmol) and DMF (100 ml) was stirred at 100 °C for 1 h. At the end of this time, the mixture was concentrated *in vacuo* and partitioned between benzene and water. The organic layer was collected, washed and dried. Removal of the solvent under reduced pressure gave an oily product which was chromatographed on silica gel (120 g, AcOEt) to afford the protected triazolyl alcohol (11.95 g, 84%) as an oil. Deprotection of this product was carried out by treatment with *p*-toluenesulfonic acid (6.58 g, 1 eq) in MeOH (110 ml) at room temperature for 1 h. After the addition of a diluted aqueous solution of $NaHCO_3$, the mixture was concentrated by the brief removal of MeOH and was extracted with AcOEt. The extract was washed with brine, dried and evaporated *in vacuo*. The crystalline residue was recrystallized from AcOEt to yield **9c** (5.25 g), mp 168—169 °C. After evaporation of the solvent from the mother liquor, the residue (*ca.* 2 g) was chromatographed (30 g, 2—4% MeOH–AcOEt) to give the less polar isomer **10c** (1.27 g, 12% yield from the ketone **7c**), mp 111—112 °C, and an additional amount (0.33 g) of **9c** (52% overall yield from **7c**). The relative ratio of **9c** and **10c** was thus 4.3 : 1. *Anal.* Calcd for $C_{12}H_{14}ClN_3O_2$: C, 53.84; H, 5.27; Cl, 13.24; N, 15.70. Found for **9c**: C, 53.63; H, 5.46; Cl, 13.33; N, 15.55. Found for **10c**: C, 53.91; H, 5.46; Cl, 12.99; N, 15.50. IR ν_{max}^{KBr} cm^{-1}: for **9c**, 3430; for **10c**, 3450. NMR (DMSO-d_6) δ: for **9c**, 0.80 (3H, d, J=6.5 Hz), 4.00 (1H, m), 4.67 (2H, s), 5.08 (1H, d, J=5.5 Hz), 5.22 (1H, s), 7.29 (4H, s), 7.66 (1H, s), 8.18 (1H, s); for **10c**, 0.80 (3H, d, J=6.5 Hz), 3.73 (1H, m), 4.58 (1H, d, J=14 Hz), 4.69 (1H, d, J=14 Hz), 5.07 (1H, d, J=5 Hz), 5.40 (1H, s), 7.30 (2H, d-like, J=9 Hz), 7.59 (2H, d-like, J=9 Hz), 7.79 (1H, s), 8.23 (1H, s).

Optical Resolution of the (2*R,3*R**) Diol 9b** (2*R**,3*R**)-**9b** (2.50 g, 8.26 mmol) was dissolved in hot MeOH (50 ml) and *l*-10-camphorsulfonic acid (2.02 g, 8.67 mmol) was added to this solution. After cooling, ether (160 ml) was added and the resulting precipitates were collected by filtration. The yield was 2.03 g. $[\alpha]_D$ −92° (c=0.90, MeOH). This solid salt was dissolved in MeOH (25 ml), and recrystallization by the addition of ether (75 ml) gave a pure *l*-camphorsulfonic acid salt of (2*R*,3*R*)-**9b** (1.42 g), mp 209—212 °C, $[\alpha]_D$ −99° (c=1.00, MeOH). The free base (2*R*,3*R*)-**9b** was obtained by treatment of the pure salt (1.35 g) obtained above with a diluted aqueous solution of $NaHCO_3$, followed by extraction with AcOEt. Evaporation of the solvent and recrystallization of the residue from AcOEt–hexane afforded (2*R*,3*R*)-**9b** (658 mg), mp 109—111 °C, $[\alpha]_D$ −111° (c=0.74, MeOH).

The mother liquor, obtained above by separation of the crystallized

TABLE III. 2-Aryl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol Derivatives (**11a**, **b**, **c**, **13a**, **b**, **c**, **14a**, **b**, **c**, **23**, **25** and **26**)

Compd.	mp °C (solvent[a])	IR ν_{max} cm^{-1} (state) Optical Rotation	^{1}H—NMR ($CDCl_3$) δ[b]	Formula	Analysis % Calcd (Found) C	H	N	Halogen
11a	123—126 (A–H)	3400, 1620, 1500, ($CHCl_3$)	1.28 (3H, d, 6.5), 3.10 (3H, s), 4.2 (1H, br), 4.67(1H, d, 14), 5.08 (1H, d, 14), 5.31 (1H, q, 6.5), 6.6—7.1 (2H, m), 7.3—7.8 (1H, m), 7.82 (1H, s), 7.94 (1H, s)	$C_{13}H_{15}F_2N_3O_4S$	44.95 (44.79	4.35 4.15	12.10 12.03)	
11b	157—159 (A–H)	3130, 1583, 1553, 1345 (KBr)	1.20 (3H, d, 7), 3.13 (3H, s), 4.68 (1H, d, 14), 5.59 (1H, d, 14), 5.85 (1H, q, 7), 7.0—7.7 (3H, m), 7.68 (1H, s), 8.00 (1H, s)	$C_{13}H_{15}Cl_2N_3O_4S$	41.06 (40.92	3.98 3.86	11.05 10.83	Cl 18.65 Cl 18.53)
(2*R*,3*R*)-(−)-**11b**	142—145 (A–H)	$[\alpha]_D$ −145° (c=1.16, $CHCl_3$)	Identical with that of **11b**	$C_{13}H_{15}Cl_2N_3O_4S$	41.06 (40.90	3.98 3.94	11.05 10.92)	
(2*S*,3*S*)-(+)-**11b**	142—145 (A–H)	$[\alpha]_D$ +144° (c=0.91, $CHCl_3$)	Identical with that of **11b**	$C_{13}H_{15}Cl_2N_3O_4S$	41.06 (41.21	3.98 4.00	11.05 10.87)	
11c	Oil	3400, 1600, 1502, 1490 ($CHCl_3$)	1.27 (3H, d, 6.5), 3.05 (3H, s), 4.69 (2H, s), 5.03 (1H, s), 5.09 (1H, q, 6.5), 7.29 (4H, s), 7.79 (1H, s), 7.82 (1H, s)	$C_{13}H_{16}ClN_3O_4S$	45.15 (45.33	4.66 4.58	12.15 12.04)	
13a	106—108 (E–H)	3420, 2120, 1620, ($CHCl_3$)	1.14 (3H, d, 7), 3.80 (1H, q, 7), 4.70 (1H, br s), 4.80 (2H, s), 6.5—7.0 (2H, m), 7.2—7.7 (1H, m), 7.80 (1H, s), 7.86 (1H, s)	$C_{12}H_{12}F_2N_6O$	48.98 (49.05	4.11 4.07	28.56 28.49	F 12.91 F 13.09)
13b	113—114 (E)	3420, 2150, 1590, 1506 ($CHCl_3$)	1.12 (3H, d, 7), 4.27 (1H, q, 7), 4.72 (1H, d, 15), 5.05 (1H, s), 5.44 (1H, d, 15), 7.11 (1H, dd, 8, 2), 7.31 (1H, d, 2), 7.58 (1H, d, 8), 7.78 (1H, s), 7.84 (1H, s)	$C_{12}H_{12}Cl_2N_6O$	44.05 (44.06	3.70 3.86	25.69 25.41	Cl 21.67 Cl 21.19)
(2*R*,3*R*)-(−)-**13b**	154—156 (A)	$[\alpha]_D$ −100° (c=0.89, $CHCl_3$)	Identical with that of **13b**	$C_{12}H_{12}Cl_2N_6O$	44.05 (43.88	3.70 3.76	25.69 25.49)	
(2*S*,3*S*)-(+)-**13b**	154—156 (A)	$[\alpha]_D$ +100° (c=0.95, $CHCl_3$)	Identical with that of **13b**	$C_{12}H_{12}Cl_2N_6O$	44.05 (44.17	3.70 3.89	25.69 25.46)	
13c	104—105 (A–H)	3410, 2110, 1597, 1502 ($CHCl_3$)	1.15 (3H, d, 7), 3.69 (1H, q, 7), 4.50 (1H, d, 14), 4.76 (1H, d, 14), 4.90 (1H, s), 7.25 (4H, s), 7.73 (1H, s), 7.80 (1H, s)	$C_{12}H_{13}ClN_6O$	49.24 (49.56	4.48 4.59	28.71 28.46	Cl 12.11 Cl 12.01)
14a	123—124 (E)	3220 (br), 1619, 1511 (KBr)	0.85 (3H, d, 6.5), 2.2 (3H, br), 3.62 (1H, qd, 6.5, 2.5), 4.68 (2H, s), 6.6—7.0 (2H, m), 7.3—7.7 (1H, m), 7.81 (1H, s), 8.00 (1H, s)	$C_{12}H_{14}F_2N_4O$	53.73 (53.58	5.26 5.33	20.89 20.67)	
14b	104—105 (E)	3250, 1586, 1510 (KBr)	0.81 (3H, d, 7), 4.13 (1H, q, 7), 4.65 (1H, d, 15), 5.28 (1H, d, 15), 7.08 (1H, dd, 8, 2), 7.38 (1H, d, 2), 7.48 (1H, d, 8), 7.70 (1H, s), 8.24 (1H, s)[c]	$C_{12}H_{14}Cl_2N_4O$	47.86 (48.19	4.69 4.73	18.60 18.27	Cl 23.54 Cl 23.77)
(2*R*,3*R*)-(−)-**14b**	Oil	$[\alpha]_D$ −86° (c=0.50, MeOH)	Identical with that of **14b**	$C_{12}H_{14}Cl_2N_4O$	47.86 (47.91	4.69 4.55	18.60 18.43)	
(2*S*,3*S*)-(+)-**14b**	Oil	$[\alpha]_D$ +84° (c=1.18, MeOH)	Identical with that of **14b**	$C_{12}H_{14}Cl_2N_4O$	47.86 (47.81	4.69 4.70	18.60 18.39)	
14c	Oil	3400, 1595, 1500 ($CHCl_3$)	0.86 (3H, d, 6.5), 2.5 (3H, br), 3.29 (1H, q, 6.5), 4.50 (2H, s), 7.25 (4H, s), 7.85 (1H, s), 7.90 (1H, s)	$C_{12}H_{15}ClN_4O$	54.03 (53.81	5.67 5.58	21.01 20.71)	
23	157—161 (A–H)	3280, 1610, 1510, 1500 (KBr)	1.46 (3H, d, 6.5), 2.87 (3H, s), 3.43 (1H, br), 4.65 (1H, d, 14), 5.02 (1H, d, 14), 5.18 (1H, q, 6.5), 6.7—7.2 (2H, m), 7.3—7.8 (1H, m), 7.67 (1H, s), 8.33 (1H, s)[d]	$C_{13}H_{15}F_2N_3O_4S$	44.95 (45.38	4.35 4.52	12.10 12.30)	
25	80—81.5 (B–H)	3400, 2120, 1620 ($CHCl_3$)	1.37 (3H, dd, 6.5, 1), 3.85 (1H, q, 6.5), 4.50 (1H, dd, 14, 1), 4.96 (1H, dd, 14, 1.5), 5.23 (1H, br s), 6.5—7.0 (2H, m), 7.3—7.7 (1H, m), 7.73 (1H, s), 7.97 (1H, s)	$C_{12}H_{12}F_2N_6O$	48.98 (49.08	4.11 4.03	28.56 28.44)	
26	101—103 (B–H)	3400 (br), 1615, 1510 ($CHCl_3$)	1.35 (3H, d, 6.5), 3.81 (1H, q, 6.5), 4.50 (1H, dd, 14, 0.5), 5.01 (1H, dd. 14, 1), 5.02 (1H, s), 6.5—7.0 (2H, m), 7.56 (1H, td, 8.5, 6.5), 7.80 (1H, s), 8.01 (1H, s)	$C_{12}H_{14}F_2N_4O$	53.73 (53.83	5.26 5.30	20.89 20.96	F 14.16 F 14.31)

a) Recrystallization solvents: A, ethyl acetate; H, hexane; E, ether; B, benzene. *b*) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses. *c*) CD_3OD used as a solvent. *d*) A mixture of $CDCl_3$ and DMF-d_7 (1 : 1) used as a solvent.

TABLE IV. 2-Aryl-3-methyl-2-[(1*H*-1,2,4-triazol-1-yl)methyl]oxiranes (**12a**, **b**, **c** and **24**)

Compd.	mp °C	IR $\nu_{max}^{CHCl_3}$ cm^{-1} Optical rotation	^{1}H-NMR ($CDCl_3$) δ[a]	Formula	Analysis % or MS *m/z* Calcd (Found)		
					C	H	N
12a	62—64 (B–H)[b]	1619, 1600, 1503	1.64 (3H, d, 5.5), 3.16 (1H, q, 5.5), 4.40 (1H, d, 15), 4.88 (1H, d, 15), 6.5—7.2 (3H, m), 7.79 (1H, s), 7.98 (1H, s)	$C_{12}H_{11}F_2N_3O$	57.37 (57.42	4.11 4.55	16.73 17.15)
12b	Oil	1585, 1555	1.63 (3H, d, 6), 3.18 (1H, q, 6), 4.37 (1H, d, 15), 4.99 (1H, 15), 6.90 (1H, d, 8), 7.11 (1H, dd, 8, 2), 7.38 (1H, d, 2), 7.83 (1H, s), 7.99 (1H, s)	$C_{12}H_{11}Cl_2N_3O$	50.72 (51.10	3.90 3.82	14.79 14.48)
(2*R*,3*S*)-(−)-**12b**	Oil	$[\alpha]_D$ −21° (c=0.85, $CHCl_3$)	Identical with that of **12b**	$C_{12}H_{11}Cl_2N_3O$	50.72 (50.93	3.90 4.01	14.79 14.52)
(2*S*,3*R*)-(+)-**12b**	Oil	$[\alpha]_D$ +21° (c=0.97, $CHCl_3$)	Identical with that of **12b**	$C_{12}H_{11}Cl_2N_3O$	50.72 (50.95	3.90 3.96	14.79 14.50)
12c	Oil	1600, 1498	1.60 (3H, d, 5.5), 3.11 (1H, q, 5.5), 4.39 (1H, d, 15), 4.82 (1H, d, 15), 6.95—7.35 (4H, m), 7.86 (1H, s), 7.95 (1H, s)	$C_{12}H_{12}ClN_3O$	252, 250 (M^++1), 234, 204, 154, 151, 139, 125, 111, 96 (100%), 69		
24	Oil	1619, 1600, 1503	1.05 (3H, d, 5.5), 3.17 (1H, q, 5.5), 4.38 (1H, d, 15), 4.80 (1H, d, 15), 6.7—7.4 (3H, m), 7.84 (1H, s), 8.08 (1H, s)	$C_{12}H_{11}F_2N_3O$	251 (M^+), 236, 188, 169, 156, 153, 141, 139, 119, 110, 96 (100%)		

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses. b) Recrystallization solvents: B, benzene; H, hexane.

l-camphorsulfonic acid salt of (2*R*,3*R*)-**9b**, was concentrated and treated with a diluted aqueous solution of $NaHCO_3$. The resulting free base residue (1.35 g) enriched in (2*S*,3*S*)-**9b** was purified using *d*-10-camphorsulfonic acid in a similar way as described above as an enantiomeric salt (1.81 g), mp 209—211 °C, $[\alpha]_D$ +99° (c=0.95, MeOH). Liberation of the free base (2*S*,3*S*)-**9b** by alkalization of the salt obtained above, followed by recrystallization from AcOEt–hexane, afforded a pure specimen (952 mg), mp 109—110 °C, $[\alpha]_D$ +111° (c=1.07, MeOH).

(2*R,3*R**)-2-Aryl-3-methanesulfonyloxy-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (11a, b, c), the (2*R**,3*S**) Diastereomer (23) and the (2*R*,3*R*) and (2*S*,3*S*) Enantiomers [(−)-11b and (+)-11b]** As a typical example, the preparation of (−)-**11b** is described. Methanesulfonyl chloride (1.30 g, 11.0 mmol) was added, while ice-cooling and stirring, to a suspension of (−)-**9b** (2.10 g, 6.95 mmol) in pyridine (80 ml). The reaction mixture was allowed to rise to room temperature, and then was stirred for 2 h. At the end of this time, the pyridine was distilled off under reduced pressure. The residue was mixed with a diluted aqueous solution of $NaHCO_3$ and extracted with ether. The extract was washed with brine and concentrated *in vacuo* to yield a crystalline mass which was recrystallized from AcOEt–hexane to furnish (−)-**11b** (2.37 g, 90%), mp 142—145 °C, $[\alpha]_D$ −145° (c=1.16, $CHCl_3$). In a similar way, **11a, b, c** and (+)-**11b** were obtained in 93, 96, 87 and 93% yields, respectively. Methanesulfonylation of **10a** under the reaction conditions described above gave **23** (36%), mp 157—161 °C (recrystallized from AcOEt–hexane), and the oily epoxide **24** (59%). Specroscopic data and elementary analysis data of these sulfonates are given in Table III, and those of **24** are in Table IV.

(2*R,3*R**)-2-Aryl-3-azido-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (13a, b, c), the (2*R**, 3*S**) Diastereomer (25) and the (2*R*,3*R*) and (2*S*,3*S*) Enantiomers [(−)-13b and (+)-13b]** As a typical example, the preparation of (−)-**13b** is described. A mixture of (−)-**11b** (2.36 g, 6.21 mmol), sodium azide (2.09 g, 32.1 mmol), ammonium chloride (337 mg, 6.30 mmol) and DMF (35 ml) was stirred at 115 °C for 15 h. At the end of this time, the solvent was evaporated under reduced pressure. The residue was partitioned between benzene and water. The organic layer was washed with brine, dried and evaporated *in vacuo*. The product was recrystallized from AcOEt to give (−)-**13b** (1.42 g, 70%), mp 154—156 °C, $[\alpha]_D$ −100° (c=0.89, $CHCl_3$). In a similar way, **13a, b, c** and (+)-**13b** were obtained in 84, 75, 88 and 88% yields, respectively. The azide **25** was similarly obtained in 78% overall yield from **10a** using the crude product containing **23** and **24**. Spectroscopic data and elementary analysis data are given in Table III.

By work-up of the above-mentioned reaction mixture after a shorter reaction time (30 min), the intermediate epoxide (2*R*,3*S*)-**12b**, $[\alpha]_D$ −21° (c=0.85, $CHCl_3$), was obtained as an oil in good yield (>80% yield). The epoxides, **12a, b, c** and (2*S*,3*R*)-(+)-**12b**, were similarly obtained from **11a, b, c** and (+)-**11b**, respectively. Spectroscopic data and elementary analysis data of these epoxides are given in Table IV.

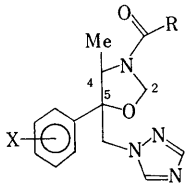
(2*R,3*R**)-3-Amino-2-aryl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (14a, b, c), the (2*R**,3*S**) Diastereomer (26) and the (2*R*,3*R*) and (2*S*,3*S*) Enantiomers [(−)-14b and (+)-14b]** As a typical example, the preparation of (−)-**14b** is described. A solution of (−)-**13b** (1.20 g) in EtOH (30 ml) was shaken with 10% palladium–charcoal (0.33 g) under an H_2 atmosphere for 1 h. The catalyst was filtered off using Celite and the filtrate was concentrated under reduced pressure to give (−)-**14b** (1.08 g, 98%) as an oil, $[\alpha]_D$ −86° (c=0.50, MeOH). In a similar way, **14a, b, c, 26** and (+)-**14b** were obtained in quantitative yields. Spectroscopic data and elementary analysis data are given in Table III.

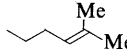
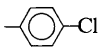
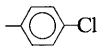
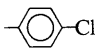
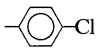
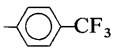
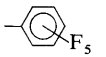
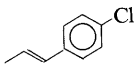
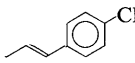
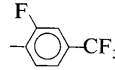
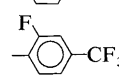
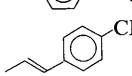
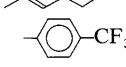
(4*R,5*R**)-5-Aryl-4-methyl-5-[(1*H*-1,2,4-triazol-1-yl)methyl]oxazolidine (15a, b, c), the (4*S**,5*R**) Diastereomer (27) and the (4*R*,5*R*) and (4*S*,5*S*) Enantiomers [(−)-15b and (+)-15b]** As a typical example, the preparation of **15a** (racemate) is described. A mixture of **14a** (300 mg, 1.12 mmol), paraformaldehyde (34 mg, 1.13 mmol) and benzene (10 ml) was heated under reflux for 3 h. Evaporation of benzene under reduced pressure gave **15a** (325 mg, 100%) as a viscous oil which solidified on standing, mp 60—70 °C. Recrystallization of **15a** from any kind of solvent was difficult. MS *m/z*: 281 (M^++1), 250, 224 (100%), 211, 198, 181, 170, 141, 127. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340, 1618, 1600, 1500. NMR ($CDCl_3$) δ: 0.93 (3H, dd, J=6.5, 2.5 Hz), 2.1 (1H, br s), 3.65 (1H, q, J=6.5 Hz), 4.2—4.8 (2H, m), 4.63 (2H, s), 6.5—7.0 (2H, m), 7.2—7.6 (1H, m), 7.80 (1H, s), 8.08 (1H, s). In a similar way, **15b, c, 27**, (−)-**15b** and (+)-**15b** were obtained in quantitative yields. Elementary analysis, IR and NMR data of **27**, mp 110—113 °C (recrystallized from AcOEt–hexane), are given below. *Anal.* Calcd for $C_{13}H_{14}F_2N_4O$: C, 55.71; H, 5.04; F, 13.56; N, 19.99. Found: C, 55.46; H, 5.07; F, 13.55; N, 20.06. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3310, 1619, 1600, 1500. NMR ($CDCl_3$) δ: 1.48 (3H, d, J=6.5 Hz), 2.05 (1H, br), 3.55 (1H, m), 4.2—5.0 (4H, m), 6.5—7.4 (3H, m), 7.70 (1H, s), 8.03 (1H, s).

(4*R,5*R**)-5-(2,4-Difluorophenyl)-4-methyl-3-(5-methyl-4-hexenoyl)-5-[(1*H*-1,2,4-triazol-1-yl)methyl]oxazolidine (4A)** A solution of 5-methyl-4-hexenoyl chloride in CH_2Cl_2, prepared *in situ* from 5-methyl-4-hexenoic acid (130 mg, 1.02 mmol) and oxalyl chloride (120 mg, 0.94 mmol) in the presence of a catalytic amount of DMF in CH_2Cl_2 (2 ml) at room temperature, was added to a stirred solution of **15a** (96 mg, 0.33 mmol) and triethylamine (200 mg, 2.0 mmol) in CH_2Cl_2 (2 ml) at 0 °C. Stirring was continued for 30 min, and then the mixture was partitioned between AcOEt and a diluted aqueous solution of $NaHCO_3$. The organic layer was collected, washed with brine, dried and concentrated *in vacuo* to give an oily residue which was purified by preparative TLC (AcOEt–hexane, 5:1, v/v) to yield **4A** (47 mg, 34%) as an oil. The amide **4A** formed its oxalic acid salt (31 mg), mp 108—110 °C, on being mixed with oxalic acid (13 mg) in AcOEt–benzene–hexane. Spectroscopic data of **4A** are given in Table V.

(4*R,5*R**)-5-(2,4-Dichlorophenyl)-3-formyl-4-methyl-5-[(1*H*-1,2,4-triazol-1-yl)methyl]oxazolidine (4B)** A solution of *N*-formylimidazole in CH_2Cl_2, prepared *in situ* from formic acid (107 mg, 2.3 mmol) and *N*,*N*′-carbonyl diimidazole (380 mg, 2.3 mmol) in CH_2Cl_2 (2 ml), was added to a solution of **15b** (208 mg, 0.69 mmol) in CH_2Cl_2 (2 ml). The mixture was allowed to stand at room temperature for 2 h. The mixture was diluted

TABLE V. 3-Acyl-5-aryl-4-methyl-5-[(1*H*-1,2,4-triazol-1-yl)methyl]oxazolidines (**4A—K** and **28**)



Compd.	X	R	Stereo-chemistry	mp °C (Solvent[a]) [Oxalic acid salt: mp °C]	Yield %	IR $\nu_{max}^{CHCl_3}$ cm^{-1} Optical rotation	^{1}H-NMR ($CDCl_3$) δ[b]	Formula	Analysis % or MS *m/z* Calcd (Found) C	H	N	Halogen
4A	2,4-F_2		4*R**,5*R**	Oil [108—110]	34	1645, 1622	0.95, 0.97 (1 : 1, 3H, d, 6.5), 1.66 (6H, br s), 2.0—2.7 (4H, m), 4.55 (2H, s), 4.7—5.3 (1H, m), 5.18 (0.5H, d, 5.5), 5.19 (0.5H, d, 3.5), 5.36 (0.5H, d, 3.5), 5.47 (0.5H, d, 5.5), 5.6—7.5 (3H, m), 7.60, 7.72, 7.75, 7.77 (0.5H, each, s)	$C_{20}H_{24}F_2N_4O_2$	391, 390(M^+), 321, 308, 281, 279, 224, 212, 198, 182, 170, 166(100%), 141, 127, 82			
4B	2,4-Cl_2	H	4*R**,5*R**	Oil [147—157 (dec.)]	41	1670, 1586	0.99, 1.05 (1 : 2, 3H, d, 7), 4.3—5.6 (5H, m), 7.0—7.5 (3H, m), 7.6—7.9 (2H, m), 8.13, 8.30 (1 : 2, 1H, s)	$C_{14}H_{14}Cl_2N_4O_2$	340(M^+), 305, 273, 271, 260, 258(100%), 232, 230, 204, 202, 175, 173, 161, 159			
4C	2,4-Cl_2		4*R**,5*R**	166—167 (A–H)	60	1640, 1590	1.03 (3H, d, 6.5), 4.50 (1H, d, 16), 4.95 (1H, d, 16), 5.25 (3H, br), 7.0—7.7 (9H, m)	$C_{20}H_{17}Cl_3N_4O_2$	53.17	3.79	12.40	Cl 23.55
									(53.02	3.83	12.28	Cl 23.32)
(+)-**4C**	2,4-Cl_2		4*R*,5*R*	Oil [122—126]	64	$[\alpha]_D$ +5.42 (c = 1.07, $CHCl_3$)	Identical with that of **4C**	$C_{20}H_{17}Cl_3N_4O_2$	453, 451(M^+ + 1), 383, 381, 370, 368, 342, 340, 141, 139(100%), 111, 70			
(−)-**4C**	2,4-Cl_2		4*S*,5*S*	Oil [123—127]	62	$[\alpha]_D$ −5.40 (c = 0.94, $CHCl_3$)	Identical with that of **4C**	$C_{20}H_{17}Cl_3N_4O_2$	—			
4D	2,4-F_2		4*R**,5*R**	Oil [161—164]	89	1638, 1615	1.01 (3H, d, 7), 4.55 (2H, s), 4.8—5.5 (3H, m), 6.6—8.0 (9H, m)	$C_{22}H_{19}ClF_2N_4O_6$ (Oxalate)	51.93	3.76	11.01	F 7.47
									(51.60	3.96	10.68	F 7.15)
4E	2,4-F_2		4*R**,5*R**	121—122 (B–H)	66	1645, 1620	1.01 (3H, br d, 6.5), 4.57 (2H, s), 4.7—5.6 (3H, m), 6.7—8.0 (9H, m)	$C_{21}H_{17}F_5N_4O_2$	55.76	3.79	12.39	
									(55.72	3.93	12.32)	
4F	2,4-F_2		4*R**,5*R**	Oil [140 (dec.)]	87	1665, 1620	0.92, 1.11 (1 : 1, 3H, d, 7), 4.2 (0.5H, m), 4.60 (2H, s), 5.0 (0.5H, m), 5.14 (1H, s), 5.45, 5.75 (1 : 1, 1H, d, 6), 6.6—7.5 (3H, m), 7.62, 7.68, 7.71, 7.77 (0.5H each, s)	$C_{20}H_{13}F_7N_4O_2$	50.64	2.76	11.81	
									(50.43	2.58	11.51)	
4G	2,4-F_2		4*R**,5*R**	Oil [162—165]	81	1645, 1615	1.01 (3H, d, 7), 4.55 (2H, s), 4.75 (1H, br), 5.33 (1H, br), 5.56 (1H, d, 5), 6.2—8.1 (11H, m)	$C_{22}H_{19}ClF_2N_4O_2$	59.40	4.30	12.60	
									(59.71	4.39	12.37)	
4H	2,4-F_2		4*R**,5*R**	168—169 (A–H)	59	1655, 1618	1.03 (3H, d, 7), 4.59 (2H, s), 4.8 (1H, br), 5.34 (1H, br d, 5), 5.58 (1H, d, 5), 6.3—8.0 (11H, m)	$C_{23}H_{19}F_5N_4O_2$	57.74	4.00	11.71	F 19.85
									(57.53	4.03	11.75	F 19.70)
4I	2,4-F_2		4*R**,5*R**	Oil [167—168]	60	1650, 1620	0.84, 1.10 (2 : 3, 3H, d, 7), 4.3 (1H, m), 4.61, 4.67 (3 : 2, 2H, s), 4.9—5.9 (2H, m), 6.6—7.9 (8H, m)	$C_{21}H_{16}F_6N_4O_2$	53.62	3.43	11.91	
									(53.89	3.70	11.57)	
4J	4-Cl		4*R**,5*R**	Oil [175—177]	33	1650, 1620	0.76, 1.00 (2 : 3, 3H, d, 7), 4.3 (1H, m), 4.59 (2H, s), 4.8—5.9 (2H, m), 6.8—7.9 (9H, m)	$C_{21}H_{17}ClF_4N_4O_2$	53.80	3.66	11.95	
									(53.95	3.54	11.70)	
4K	4-Cl		4*R**,5*R**	180—181 (A–H)	69	1650, 1610	0.91 (3H, d, 6.5), 4.53 (2H, br s), 4.88 (1H, q, 6.5), 5.37 (1H, br d, 5), 5.57 (1H, d, 5), 7.0—8.0 (12H, m)	$C_{23}H_{20}ClF_3N_4O_2$	57.93	4.23	11.75	F 11.95
									(58.40	4.54	11.98	F 11.68)
28	2,4-F_2		4*S**,5*R**	120—121 (B–H)	59	1640, 1618	1.47 (3H, d, 7), 4.55 (1H, d, 15), 4.80 (1H, d, 15), 4.3—5.6 (3H, m), 6.5—7.1 (3H, m), 7.28 (2H, d, s), 7.65 (1H, s), 7.66 (2H, d, 8), 7.93 (1H, s)	$C_{21}H_{17}F_5N_4O_2$	55.76	3.79	12.39	F 21.00
									(56.06	3.93	12.46	F 21.12)

a) Recrystallization solvents: A, ethyl acetate; H, hexane; B, benzene. *b*) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses.

with AcOEt and washed with a diluted aqueous solution of $NaHCO_3$ and brine. After evaporation of the solvent, the crude product was purified by preparative TLC (10% v/v EtOH–AcOEt) to give **4B** (94 mg, 41%) as an oil. The amide **4B** (94 mg) formed its oxalic acid salt (84 mg), mp 147—157 °C (dec.), on being mixed with 1 eq of oxalic acid in acetone–hexane. Spectroscopic data of **4B** are given in Table V.

(4*R,5*R**)-3-Acyl-5-aryl-4-methyl-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-oxazolidine (4C—J), the (4*S**,5*R**) Diastereomer (28) and the (4*R*,5*R*) and (4*S*,5*S*) Enantiomers [(−)-4C and (+)-4C]** As a typical example of N-benzoylation or N-cinnamoylation, the preparation of **4C** is described. 4-Chlorobenzoyl chloride (350 mg, 2.00 mmol) was added to a solution of **15b** (420 mg, 1.34 mmol) in pyridine (10 ml) with stirring and ice-cooling. After 1 h, MeOH (0.8 ml) was added to the mixture, which was then stirred for 10 min. The solvent was removed under reduced pressure, and a diluted aqueous solution of $NaHCO_3$ was added to the residue. Extraction with AcOEt and evaporation of the solvent gave an oily product which was chromatographed on silica gel (15 g, benzene–AcOEt, 2 : 1—1 : 1, v/v) to yield a crystalline mass. Recrystallization from AcOEt–hexane gave a pure specimen of **4C** (360 mg, 60%), mp 166—167 °C. The amide **4C** formed an amorphous salt of oxalic acid, on being mixed with 1 eq of oxalic acid in AcOEt–hexane. Spectroscopic data and elementary analysis of **4C** and other amide analogs are given in Table V.

(2*S,3*R**)-2-(2,4-Difluorophenyl)-1-(dimethylisopropoxysilyl)-3-(tetrahydropyran-2-yloxy)-2-butanol (17)** To a solution of (dimethylisopropoxysilyl)methylmagnesium chloride[11] (**16**), prepared from chloromethyldimethylisopropoxysilane (2.45 g, 14.7 mmol) and magnesium (0.40 g, 16.5 mmol) in ether (50 ml), was added dropwise a solution of **7a** (2.10 g, 7.76 mmol) in THF (12 ml) over a period of 10 min, while stirring at 0 °C. The mixture was then warmed to room temperature. After 10 min, the mixture was cooled to 10 °C and a saturated aqueous solution of NH_4Cl was added to the mixture, which was extracted with AcOEt. The extract was washed with brine, and the solvent was evaporated *in vacuo* to give the crude product **17** (3.22 g) as an oil which was used without further purification for the next reaction. IR $\nu_{max}^{CHCl_3}$: 3425 cm^{-1}. NMR ($CDCl_3$) δ: −0.30 (3H, s), 0.00 (3H, s), 0.90 and 1.00 (1 : 1, 3H, d, J=6.5 Hz), 1.06 (3H, d, J=6 Hz), 1.10 (3H, d, J=6 Hz), 1.4—2.0 (8H, m), 3.3—4.2 (4H, m), 4.12 and 4.26 (1 : 1, 1H, s), 4.71 (1H, m), 6.5—7.0 (2H, m), 7.71 (1H, td, J=9, 6.5 Hz).

(2*R,3*R**)-2-(2,4-Difluorophenyl)-1,2,3-butanetriol (18)** To a solution of the above-mentioned crude product **17** (3.22 g) in a 1 : 1 mixture of THF and MeOH (35 ml) was added $NaHCO_3$ (0.50 g, 5.88 mmol) and 35% H_2O_2 (5.0 ml), and then the mixture was stirred at 70 °C for 1.5 h. After cooling, the mixture was diluted with AcOEt and washed with brine. The solvent was distilled off under reduced pressure to give the oily product (3.19 g). IR $\nu_{max}^{CHCl_3}$: 3550 cm^{-1}. NMR ($CDCl_3$) δ: 0.92 (1.5H, d, J=6.5 Hz), 1.03 (1.5H, d, J=6.5 Hz), 1.3—2.0 (6H, m), 3.2—4.8 (8H, m), 6.5—7.1 (2H, m), 7.78 (1H, td, J=9, 7 Hz). The crude product obtained above was treated with *p*-toluenesulfonic acid (85 mg, 0.45 mmol) in MeOH (30 ml) at room temperature for 30 min. After addition of triethylamine (0.50 g, 0.50 mmol), the mixture was concentrated under reduced pressure to give an oily product, which was chromatographed on silica gel (15 g, AcOEt) to afford **18** (1.23 g, 73% overall yield from **7a**) as a viscous oil. IR $\nu_{max}^{CHCl_3}$: 3400 (br) cm^{-1}. NMR (acetone-d_6) δ: 0.87 (3H, d, J=6.5 Hz), 3.5—4.7 (6H, m), 6.7—7.2 (2H, m), 7.81 (1H, td, J=9, 7 Hz).

(2*R,3*R**)-2-(2,4-Difluorophenyl)-1,3-bis(methanesulfonyloxy)-2-butanol (19)** Methanesulfonyl chloride (1.18 ml, 15.2 mmol) was added, while stirring at 0 °C, to a solution of **18** (1.20 g, 5.50 mmol) in pyridine (5 ml), and then the mixture was stirred at the same temperature for 30 min. At the end of this time, pyridine was distilled off under reduced pressure to leave an oil, which was diluted with AcOEt and washed, in turn, with a diluted aqueous solution of $NaHCO_3$ and with brine. Removal of the solvent gave **19** (2.06 g, 96%) as an oil, which was pure enough, as judged by NMR, for the next reaction. NMR ($CDCl_3$) δ: 1.23 (3H, d, J=6.5 Hz), 2.95 (3H, s), 3.10 (3H, s), 3.82 (1H, s), 4.70 (2H, s), 5.32 (1H, q, J=6.5 Hz), 6.7—7.2 (2H, m), 7.6—8.0 (1H, m).

(2*R,3*S**)-2-(2,4-Difluorophenyl)-3-methyl-2-[(1*H*-1,2,4-triazol-1-yl)-methyl]oxirane (12a)** Triazole (1.53 g, 22.2 mmol) was slowly added to a suspension of sodium hydride (55% mineral oil dispersion, 0.87 g, 20.0 mmol, washed with hexane) in DMF (20 ml), while stirring at 0 °C. When the hydrogen gas ceased to evolve, a solution of **19** (2.06 g, 5.54 mmol) in DMF (5 ml) was added. The mixture was then stirred at 65—70 °C for 2 h, after which the solvent was distilled off under reduced pressure and the residue was partitioned between benzene and water. The organic layer was collected, dried and concentrated *in vacuo* to leave an oil, which was purified by column chromatography (20 g, 2 : 1 benzene–AcOEt, v/v) to give a crystalline mass. This solid was recrystallized from benzene–hexane to give **12a** (1.10 g, 80% yield over two steps from **18**), mp 62—64 °C, whose NMR and TLC properties were identical with those of the epoxide obtained from **11a**.

By work-up of the above-mentioned reaction mixture, after a shorter reaction time (15 min), the intermediate epoxide **20** was obtained as an oil in good yield (>80%) after purification by column chromatography using benzene as the eluent. NMR ($CDCl_3$) δ: 1.41 (3H, dd, J=6.5, 1.5 Hz), 3.01 (1H, d, J=5 Hz), 3.08 (3H, s), 3.20 (1H, d, J=5 Hz), 4.75 (1H, q, J=6.5 Hz), 6.6—7.1 (2H, m), 7.2—7.7 (1H, m).

Conversion of the Epoxide 12a to the Diol 10a A solution of **12a** (90 mg) in CF_3COOH (1 ml) was stirred at 0 °C for 6 h. This mixture was poured into a stirred mixture of AcOEt (10 ml) and 1.5 N $NaHCO_3$ (10 ml) at 0 °C. The organic layer was collected. The aqueous layer was saturated with NaCl and extracted with AcOEt. The combined AcOEt layer was washed with brine and dried. Evaporation of the solvent gave the crude product **22** (*ca.* 150 mg) as a viscous oil. MS *m/z*: 366 (M^++1), 283, 251, 224 (100%), 182, 169, 141, 127, 113, 83, 82. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1787. NMR ($CDCl_3$) δ (selected signals): 1.37 (3H, d, J=6.5 Hz), 4.53 (1H, d, J=14 Hz), 4.99 (1H, d, J=14 Hz), 5.44 (1H, q, J=6.5 Hz), 6.5—7.1 (2H, m), 7.55 (1H, td, J=10, 7 Hz). NMR and TLC properties of this product were identical with those of a sample of **22**, prepared by trifluoroacetylation of **10a** by treatment with trifluoroacetic anhydride and triethylamine in CH_2Cl_2. The crude product **22** obtained above was dissolved in 5% NaOH–MeOH (2 ml) and the mixture was allowed to stand at room temperature for 15 min. The mixture was then diluted with AcOEt, washed with brine, dried and concentrated *in vacuo* to give a crystalline residue. Recrystallization of this residue from AcOEt–hexane gave **10a** (69 mg), mp 159—160 °C, whose physical and spectroscopic data were identical with those of the above-mentioned minor diol **10a** obtained from the epoxide **8a**. The mother liquor was concentrated and the residue was purified by preparative TLC (AcOEt–hexane, 5 : 1, v/v) to give an additional amount of **10a** (14 mg, 86% total yield from **12a**) and the more polar diastereomeric diol **9a** (*ca.* 2 mg, 2%), mp 154—156 °C (recrystallized from AcOEt).

Similar treatment of the diastereomeric epoxide **24** with trifluoroacetic acid followed by solvolysis afforded a mixture of diols, which were separated by preparative TLC to give **9a** (22%) and **10a** (53%).

1-Azido-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (30a) and Its 2-(2,4-Dichlorophenyl) Analog (30b) A mixture of **29a** (5.10 g, 22.0 mmol), sodium azide (2.8 g, 43 mmol), ammonium chloride (1.4 g, 26 mmol) and DMF (60 ml) was stirred at 60 °C for 20 min. The cooled mixture was partitioned between benzene and a diluted aqueous solution of $NaHCO_3$. The organic layer was washed with brine, dried and concentrated *in vacuo* to give **30a** (6.0 g, *ca.* 100%) as an oil, which was used for the next reaction without further purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 2130. NMR ($CDCl_3$) δ: 3.56 (1H, d, J=13 Hz), 3.70 (1H, d, J=13 Hz), 4.72 (2H, br s), 6.5—7.9 (3H, m), 7.82 (1H, s), 8.03 (1H, s).

The 2,4-dichlorophenyl analog **30b** was similarly obtained, by reaction of **29b** with sodium azide at 90 °C for 1.5 h, as an oil in 90% yield after purification by chromatography (benzene–AcOEt, 1 : 1, v/v). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 2130. NMR ($CDCl_3$) δ: 3.81 (2H, s-like), 4.70 (1H, d, J=14 Hz), 5.21 (1H, s), 5.22 (1H, d, J=14 Hz), 7.17 (1H, dd, J=8.5, 2 Hz), 7.35 (1H, d, J=2 Hz), 7.67 (1H, d, J=8.5 Hz), 7.82 (1H, s), 7.94 (1H, s).

1-Amino-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (31a) and Its 2-(2,4-Dichlorophenyl) Analog (31b) A solution of **30a** (3.02 g) in EtOH (40 ml) was shaken with 10% palladium–charcoal (1.0 g) under an H_2 atmosphere at room temperature for 1 h. The catalyst was filtered off using Celite and the filtrate was concentrated under reduced pressure to give **31a** (2.65 g, 97%) as a cake, which was used without further purification for the next reaction. NMR ($CDCl_3$) δ: 2.98 (1H, J=14 Hz), 3.18 (1H, J=14 Hz), 4.58 (2H, br s), 6.5—7.7 (3H, m), 7.83 (1H, s), 8.10 (1H, s).

The 2,4-dichlorophenyl analog **31b** was similarly obtained as a cake by hydrogenation of **30b** in EtOH for 1 h in 98% yield. NMR ($CDCl_3$ + CD_3OD) δ: 3.02 (1H, d, J=13 Hz), 3.55 (1H, d, J=13 Hz), 4.65 (1H, d, J=14 Hz), 4.98 (1H, d, J=14 Hz), 7.21 (1H, dd, J=8.5, 2 Hz), 7.40 (1H, d, J=2 Hz), 7.69 (1H, d, J=8.5 Hz), 7.82 (1H, s), 8.16 (1H, s).

5-(2,4-Difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)methyl]oxazolidine (32) A mixture of **31a** (400 mg, 1.57 mmol), paraformaldehyde (78 mg, 2.60 mmol) and toluene (15 ml) was stirred at 80 °C for 2 h. After cooling, insoluble excess paraformaldehyde was filtered off. Evaporation of the solvent gave **32** (420 mg, *ca.* 100%) as an oil, which was used for the next reaction without further purification. MS *m/z*: 267 (M^++1), 236, 224

(100%), 197, 184, 141, 127.

3-(4-Chlorobenzoyl)-5-(2,4-difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]oxazolidine (33) 4-Chlorobenzoyl chloride (92 mg, 0.53 mmol) was added to a solution of **32** (140 mg, 0.33 mmol) and triethylamine (53 mg, 0.53 mmol) at 0 °C. The mixture was stirred at the same temperature for 30 min. MeOH (0.2 ml) was added to this mixture and stirring was continued for 20 min. The mixture was partitioned between AcOEt and a diluted aqueous solution of $NaHCO_3$. The organic layer was washed with brine, dried and concentrated *in vacuo*. The crystalline residue was recrystallized from $CHCl_3$–hexane to give **33** (106 mg, 50%), mp 152—155 °C. *Anal.* Calcd for $C_{19}H_{15}ClF_2N_4O_2$: C, 56.38; H, 3.73; N, 13.86. Found: C, 56.37; H, 3.68; N, 13.40. IR $\nu_{max}^{CHCl_3}$: 1640 cm^{-1}. NMR ($CDCl_3$) δ: 4.00 (1H, d, J=12 Hz), 4.31 (1H, d, J=12 Hz), 4.48 (1H, d, J=15 Hz), 4.68 (1H, d, J=15 Hz), 5.0—5.3 (2H, m), 6.5—7.5 (3H, m), 7.40 (4H, m), 7.82 (1H, s), 8.03 (1H, s).

The amide **33** (108 mg) formed its oxalic acid salt (107 mg), mp 150—155 °C, on being mixed with 1 eq of oxalic acid in AcOEt–hexane.

3-(4-Chlorobenzoyl)-5-(2,4-dichlorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)-methyl]-2-oxazolidinone (35) Trichloromethyl chloroformate (48 mg, 0.24 mmol) was added to a stirred solution of **31b** (70 mg, 0.24 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 60 mg, 0.49 mmol) in CH_2Cl_2 (2 ml) at −15 °C. After 20 min, the mixture was treated with a diluted aqueous solution of $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried and concentrated *in vacuo* to give a mixture of **34** and DMAP (131 mg) as a viscous oil. This mixture was dissolved in THF (2 ml) and a 1.5 M *n*-butyllithium hexane solution (0.15 ml, 0.23 mmol) was added at −78 °C under an N_2 atmosphere. After 5 min, a solution of 4-chlorobenzoyl chloride (42 mg, 0.24 mmol) in THF (1 ml) was added to this solution. The reaction temperature was allowed to rise to −20 °C over a period of 30 min. At the end of this time, the mixture was partitioned between AcOEt and water. The organic layer was washed, dried and concentrated under reduced pressure to give a crystalline residue which was recrystallized from MeOH–$CHCl_3$–benzene to yield **35** (50 mg, 48%), mp 232—234.5 °C. *Anal.* Calcd for $C_{19}H_{13}Cl_3N_4O_3$: C, 50.52; H, 2.90; Cl, 23.55; N, 12.40. Found: C, 50.23; H, 2.99; Cl, 23.63; N, 12.07. IR ν_{max}^{KBr} cm^{-1}: 1798, 1678. NMR ($CDCl_3$) δ: 4.39 (1H, d, J=12 Hz), 4.56 (1H, d, J=15 Hz), 4.95 (1H, d, J=12 Hz), 5.12 (1H, d, J=15 Hz), 7.36 (4H, s), 7.38 (1H, dd, J=9, 2 Hz), 7.58 (1H, d, J=2 Hz), 7.70 (1H, d, J=9 Hz), 8.00 (1H, s), 8.30 (1H, s).

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