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Triazole Antifungals. IV.[1] Synthesis and Antifungal Activities of 3-Acylamino-2-aryl-2-butanol 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 25, 1991*

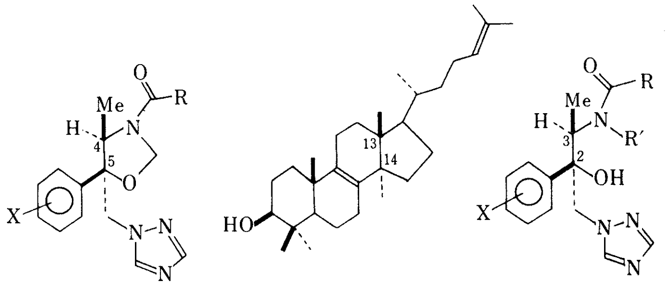
New triazole compounds were designed and synthesized as potential inhibitors of the fungal cytochrome P-450 14α-demethylase. In testing for antifungal activity against a mouse systemic *Candida albicans* infection, (2*R*,3*R*)-3-acylamino-2-aryl-2-butanol derivatives III exhibited remarkably high efficacy after oral or parenteral administration. The structure–activity relationships of these amidoalcohols were evaluated.

Keywords antifungal activity; 1,2,4-triazole; 3-acylamino-2-aryl-1-(triazol-1-yl)-2-butanol; cytochrome P-450 inhibitor; structure–activity relationship; oral activity

In a previous paper,[2] we reported the synthesis and antifungal activities of triazole compounds I, which have a methyl-substituted oxazolidine ring. Remarkably potent *in vivo* activity was observed in this series of derivatives. The antifungal activities of these oxazolidines were presumed to arise from the potential ability of I to inhibit the fungal cytochrome P-450 14α-demethylase. This enzyme catalyzes 14-demethylation of lanosterol (II) in the biosynthesis of ergosterol,[3] which is an important constituent of the fungal membrane. A structural similarity between the oxazolidine I and lanosterol was hypothesized to be an essential factor accounting for the antifungal potency of I. The oxazolidine I was favorably overlaid to fit to the lanosterol skeleton in a manner such that the 5β-aromatic ring and the oxazolidine ring of I are located on the B and D rings of the steroid, and that the 4β-methyl group and the methylene carbon atom of the 5α-triazolylmethyl group of I respectively occupy the positions of the 13β-methyl and 14α-methyl groups of lanosterol. The N-acyl group of I was regarded as corresponding to the 17-side chain of lanosterol.

The 4*R*,5*R* absolute configuration, as well as the location of the methyl substituent at the C(4) position of I, was identified as a key structural element of antifungal potency. Changing the stereochemistry at the C(4) and/or C(5) position or 4-demethylation resulted in a profound decrease in activity, confirming the validity of the hypothesis described above.

There is, however, some divergence in overlaying the oxazolidine I onto lanosterol. As can be seen by inspection of the Dreiding model, the four carbon atoms, Me–C(13)–C(14)–Me, of lanosterol adopt a nearly *anti* coplaner conformation, whereas X-ray crystallographic analysis of the oxazolidine I [X=2,4-F_2, R=4-(CF_3)C_6H_4] revealed that the dihedral angle between the 4-methyl group and the 5-methylene group of I was *ca.* 137°.[4] Meanwhile, X-ray crystallographic analysis of the azidoalcohol (2*R*,3*R*)-**2b**, one of the synthetic intermediates for I, established that the four carbon centers, Me–C(3)–C(2)–CH_2, of **2b** are approximately *anti* coplanar.[5] This conformation of **2b** can fit more favorably around these centers to match lanosterol than the oxazolidine I, and **2b** was found to exhibit fairly good *in vivo* antifungal activity, superior to that of ketoconazole. From these facts, we were interested in the antifungal activity of the acylaminoalcohol derivatives represented by the general formula III, which corresponds to the ring-opened analog of the oxazolidine I. It was anticipated that a better fitting of molecule III than oxazolidine I to the space, which should be occupied by lanosterol in the binding site of the cytochrome P-450 14α-demethylase, could be obtained by rotating the C(2)–C(3) bond appropriately, and that triazole III might form a stable complex with the enzyme, resulting in good inhibitory activity.

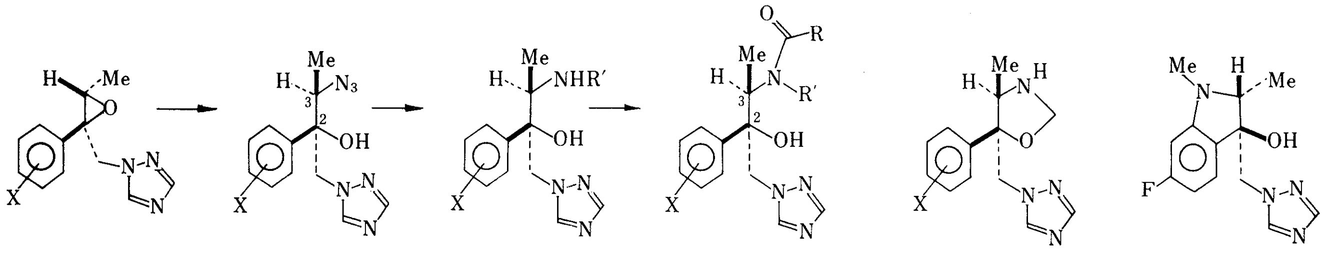


I II III : R′=H or Me

Chart 1

A variety of acylaminoalcohol derivatives (**7**—**49**), as shown in Chart 2, was synthesized, as racemates and/or in optically active forms, by acylation of aminoalcohol intermediates **3** and **4**. Racemic aminoalcohols **3a**—**c** were provided as described previously from the epoxides **1a**—**c** *via* the azidoalcohols **2a**—**c**. Preparation of the optically active aminoalcohol **3b** has already been reported.[2] Stereoselective synthesis of enantiomeric epoxides, (2*R*,3*S*)- and (2*S*,3*R*)-**1a**, and azidoalcohols, (2*R*,3*R*)- and (2*S*,3*S*)-**2a**, key intermediates for the preparation of optically active aminoalcohols, **3a** and **4a**, has been disclosed.[1] *N*-Methylaminoalcohols **4a** and **4c** were obtained by lithium aluminum hydride reduction of the oxazolidine derivatives **5a** and **5c**, which were formed by treatment of **3a** and **3c**, respectively, with paraformaldehyde.[2] These *N*-methylaminoalcohols were alternatively prepared by a ring-opening reaction of the epoxides **1a** and **1c** with methylamine on heating in methanol, although the 2,4-difluorophenyl analog **4a** was accompanied by a substantial amount of the indoline derivative **6**, which was shown to be formed by cyclization of **4a**.

For structure–activity relationship studies, some addi-



1a, b, c **2a, b, c** **3a, b, c** : R′=H **4a, c** : R′=Me **7**−**44** : R′=H **45**−**49** : R′=Me **5a, c** **6**

a : X= 2, 4-F_2
b : X= 2, 4-Cl_2
c : X= 4-Cl

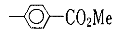
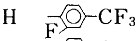
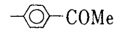
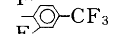
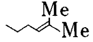
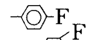
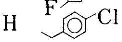
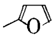
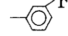
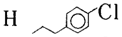
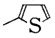
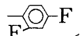
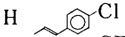
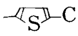
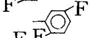
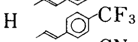
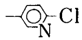
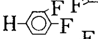
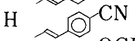
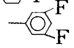
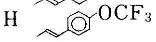
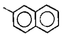
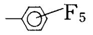
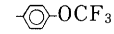
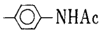
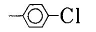
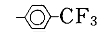
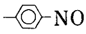
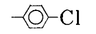
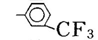
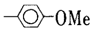
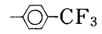
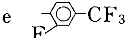
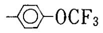
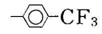
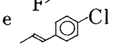
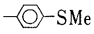
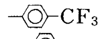
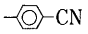
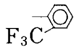
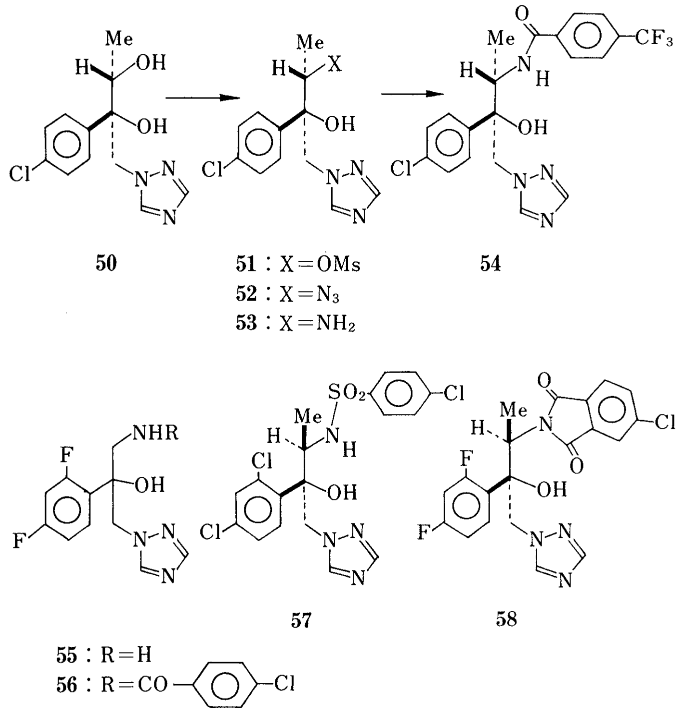
	X	R′	R		X	R′	R		X	R′	R
7	2, 4-Cl_2	H	H	22	2, 4-Cl_2	H		37	2, 4-F_2	H	
8	2, 4-Cl_2	H	*tert*-Bu	23	2, 4-Cl_2	H		38	4-Cl	H	
9	2, 4-F_2	H		24	2, 4-F_2	H		39	2, 4-F_2	H	
10	2, 4-F_2	H		25	2, 4-F_2	H		40	2, 4-F_2	H	
11	2, 4-F_2	H		26	2, 4-F_2	H		41	2, 4-F_2	H	
12	2, 4-F_2	H		27	2, 4-F_2	H		42	2, 4-F_2	H	
13	2, 4-F_2	H		28	2, 4-F_2	H		43	2, 4-F_2	H	
14	2, 4-F_2	H	Ph	29	2, 4-F_2	H		44	2, 4-F_2	H	
15	2, 4-F_2	H		30	2, 4-F_2	H		45	2, 4-F_2	Me	
16	2, 4-F_2	H		31	2, 4-F_2	H		46	2, 4-F_2	Me	
17	2, 4-Cl_2	H		32	2, 4-Cl_2	H		47	2, 4-F_2	Me	
18	4-Cl	H		33	2, 4-F_2	H		48	4-Cl	Me	
19	4-Cl	H		34	2, 4-Cl_2	H		49	2, 4-F_2	Me	
20	2, 4-Cl_2	H		35	4-Cl	H					
21	2, 4-Cl_2	H		36	2, 4-F_2	H					

Chart 2

tional analogs (racemates), as shown in Chart 3, were synthesized and tested for antifungal activity. The (2*R**, 3*S**) amidoalcohol **54** was prepared from diol **50**[2] in the usual manner *via* **51**, **52** and **53**. The demethyl derivative **56** was obtained from the aminoalcohol **55**,[2] and the sulfonamide **57** was obtained from **3b**. The phthalimide analog **58** was formed by heating the aminoalcohol **3a** with 4-chlorophthalic anhydride in toluene in the presence of triethylamine.

The *in vitro* antifungal activities of these acylaminoalcohols and their analogs were evaluated on Sabouraud dextrose agar media. Most of the compounds were shown to have slight or some degree of activity against *Trichophyton rubrum*. As observed with the oxazolidine derivatives I, however, almost all of the synthesized compounds described above were inactive against most of the other yeast and fungi (*Candida albicans*, *Cryptococcus neoformans*, *Mucor mucedo*, *Aspergillus fumigatus*, *Microsporum gypseum* and *Trychophyton mentagrophytes*) at a concentration of 50 μg/ml. It is known that there is no good correlation between *in vitro* and *in vivo* activities of azole antifungals, as was also seen in the oxazolidine series I. Therefore, these triazoles were subjected to animal model studies of fungal infection. The results of *in vivo* studies in mice in systemic *Candida albicans* infection are summarized



50 **51** : X=OMs **54**
52 : X=N_3
53 : X=NH_2

57 **58**

55 : R=H
56 : R=CO—⟨◯⟩—Cl

Chart 3

TABLE I. Comparative Antifungal Efficacy of Acylaminoalcohol Derivatives (**7**—**49**,**54** and **56**) and Related Compounds (**57** and **58**) against Systemic Infection of *Candida albicans*[a]

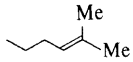
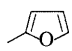
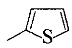
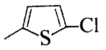
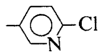
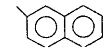
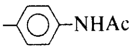
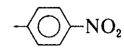
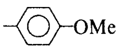
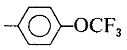
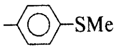
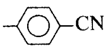
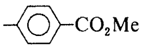
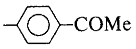
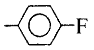
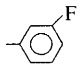
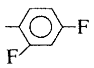
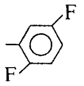
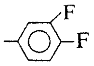
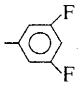
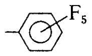
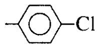
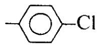
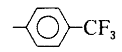
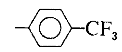
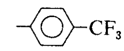
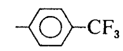
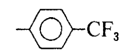
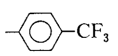
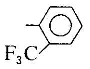
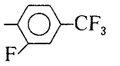
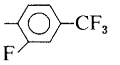
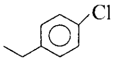
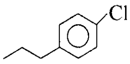
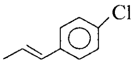
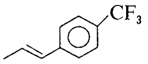
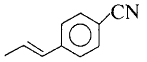
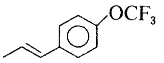
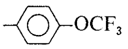
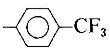
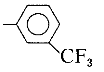
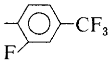
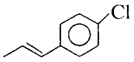
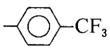
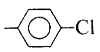
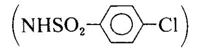
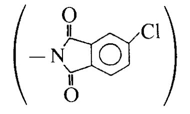
Compd.[b]	X	R′	R	Stereochemistry	Dose (mg/kg)	Route	% survival rate on day			
							3	9	14	21
7	2, 4-Cl_2	H	H	$2R^*, 3R^*$	20	*p.o.*	100	30	10	0
						i.p.	100	30	0	
8	2, 4-Cl_2	H	*tert*-Bu	$2R^*, 3R^*$	20	*p.o.*	20	0		
						i.p.	40	20	0	
9	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	10	10	10	10
						i.p.	0			
10	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	30	10	0	
						i.p.	10	0		
11	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	80	60	60	30
						i.p.	100	70	60	60
12	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	100	60	10	0
						i.p.	100	80	50	50
13	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	100	70	40	30
						i.p.	100	40	10	0
14	2, 4-F_2	H	Ph	$2R^*, 3R^*$	20	*p.o.*	60	10	10	10
						i.p.	20	0		
15	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	40	0		
						i.p.	90	40	30	0
16	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	100	100	20	0
						i.p.	80	70	40	20
17	2, 4-Cl_2	H		$2R^*, 3R^*$	20	*p.o.*	100	90	70	60
						i.p.	100	100	100	100
18	4-Cl	H		$2R^*, 3R^*$	20	*p.o.*	40	0		
						i.p.	20	0		
19	4-Cl	H		$2R^*, 3R^*$	20	*p.o.*	100	90	90	90
						i.p.	100	100	100	100
20	2, 4-Cl_2	H		$2R^*, 3R^*$	20	*p.o.*	80	80	40	30
						i.p.	80	80	40	20
21	2, 4-Cl_2	H		$2R^*, 3R^*$	20	*p.o.*	100	100	100	100
						i.p.	100	100	100	100
22	2, 4-Cl_2	H		$2R^*, 3R^*$	20	*p.o.*	30	10	10	0
						i.p.	0			
23	2, 4-Cl_2	H		$2R^*, 3R^*$	20	*p.o.*	0			
						i.p.	0			
24	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	100	80	40	30
						i.p.	100	100	100	70
25	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	20	10	0	
						i.p.	30	20	20	0
26	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	100	100	90	60
						i.p.	100	100	80	50
27	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	70	70	60	40
						i.p.	80	50	20	10
28	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	100	100	100	70
						i.p.	100	100	100	60
29	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	100	100	90	70
						i.p.	100	100	90	70
30	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	10	0		
						i.p.	0			
31	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	100	60	40	30
						i.p.	100	100	90	90
32	2, 4-Cl_2	H		$2R^*, 3R^*$	20	*p.o.*	100	100	70	30
						i.p.	100	100	100	80
33	2, 4-F_2	H		$2R^*, 3R^*$	20	*p.o.*	100	100	100	90
						i.p.	100	100	100	90
(−)-**33**	2, 4-F_2	H		$2R, 3R$	20	*p.o.*	100	100	100	100
						i.p.	100	100	100	100
(+)-**33**	2, 4-F_2	H		$2S, 3S$	20	*p.o.*	50	10	10	10
						i.p.	30	0		
34	2, 4-Cl_2	H		$2R^*, 3R^*$	20	*p.o.*	100	100	100	100
						i.p.	100	100	100	100
(−)-**34**	2, 4-Cl_2	H		$2R, 3R$	2.5	*p.o.*	100	100	100	100
						i.p.	100	100	100	100

Table I. (continued)

Compd.[b]	X	R′	R	Stereochemistry	Dose (mg/kg)	Route	% survival rate on day			
							3	9	14	21
					1.25	*p.o.*	60	60	60	50
						i.p	90	90	90	80
					0.63	*p.o.*	30	30	30	30
						i.p	80	80	80	80
35	4-Cl	H		2*R**, 3*R**	20	*p.o.*	100	100	100	90
						i.p.	100	100	100	100
36	2, 4-F_2	H		2*R**, 3*R**	20	*p.o.*	100	50	10	10
						i.p.	100	20	0	
37	2, 4-F_2	H		2*R**, 3*R**	20	*p.o.*	100	100	100	100
						i.p.	100	100	100	100
38	4-Cl	H		2*R**, 3*R**	20	*p.o.*	100	100	100	100
						i.p.	100	100	100	100
39	2, 4-F_2	H		2*R**, 3*R**	20	*p.o.*	60	30	0	
						i.p.	10	0		
40	2, 4-F_2	H		2*R**, 3*R**	20	*p.o.*	100	80	80	40
						i.p.	100	90	30	0
41	2, 4-F_2	H		2*R**, 3*R**	20	*p.o.*	100	100	60	60
						i.p.	100	100	100	100
42	2, 4-F_2	H		2*R**, 3*R**	20	*p.o.*	100	100	90	60
						i.p.	90	90	90	70
(−)-**43**	2, 4-F_2	H		2*R*, 3*R*	20	*p.o.*	100	100	50	40
						i.p.	100	100	60	50
(−)-**44**	2, 4-F_2	H		2*R*, 3*R*	20	*p.o.*	100	100	100	80
						i.p.	100	100	100	100
(−)-**45**	2, 4-F_2	Me		2*R*, 3*R*	20	*p.o.*	100	100	70	40
						i.p.	100	100	70	40
46	2, 4-F_2	Me		2*R**, 3*R**	20	*p.o.*	100	100	100	100
						i.p.	100	100	100	90
47	2, 4-F_2	Me		2*R**, 3*R**	20	*p.o.*	100	70	40	20
						i.p.	100	80	50	40
48	4-Cl	Me		2*R**, 3*R**	20	*p.o.*	100	100	100	100
						i.p.	100	100	100	100
49	2, 4-F_2	Me		2*R**, 3*R**	20	*p.o.*	100	100	80	60
						i.p.	100	100	100	80
54	4-Cl	H		2*R**, 3*S**	20	*p.o.*	20	10	0	
						i.p.	0			
56	2, 4-F_2	H		2*R** (3-demethyl)	20	*p.o.*	100	50	10	0
						i.p.	100	20	0	
57	2, 4-Cl_2			2*R**, 3*R**	20	*p.o.*	10	0		
						i.p.	50	0		
58	2, 4-F_2			2*R**, 3*R**	20	*p.o.*	100	40	20	0
						i.p.	100	50	10	0
Ketoconazole					20	*p.o.*	100	50	30	10
						i.p.	100	50	20	0
Fluconazole					20	*p.o.*	100	100	70	60
					6.25	*p.o.*	100	90	70	60
					3.13	*p.o.*	100	90	60	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) that were infected systemically using an intravenous challenge of 6 to 9 × 10^6 cells of *Candida albicans* 427. The triazole was administered orally (*p.o.*) or intraperitoneally (i.p.) at 1, 4, and 24 h post-infection. *b)* Compounds are racemic unless otherwise indicated. The amides **8**—**10** are oxalic acid salts, (−)-**33**, (+)-**33** and (−)-**44** are HCl salts, and (−)-**45** and **58** are HNO_3 salts.

in Table I. The compounds were administered orally (*p.o.*) or intraperitoneally (i.p.) at 1, 4, and 24 h post-infection. All control mice (no drug) died within 2 d after infection. The antifungal efficacy of the compounds was compared with that of ketoconazole and fluconazole, both of which are currently used for the treatment of fungal diseases, including deep-seated mycoses.

The structure–activity relationships were evaluated initially by varying the N-acyl groups in a series of compounds with 2*R**,3*R** stereochemistry. No significant difference was observed between the *p.o.* and i.p. activities of the compounds tested. Compound **7**, which has an N-formylamino function, was somewhat active, though it was not very potent, and the analogs **8** and **9**, which have a bulky alkyl group, showed significantly decreased activity. The latter compound, **9**, was of initial interest because of the likeness in shape of its acyl group to the 17-side chain of lanosterol. Amides **10**, **14** and **15**, with an unsubstituted (hetero)aromatic ring, showed no significant activity, although the unsubstituted thenoyl counterpart **11** showed good activity. Amides **12** and **13**, with a chlorine-substituted heteroaromatic ring, also showed high activity. These heteroaromatic amide analogs, however, were excluded from any further consideration of modification, because of their relatively less potent activity compared with the corresponding benzamide congener. The benzamide derivatives, **16** and **20**, which have an acetamido or methylthio group at the 4-position of the benzoyl group, expressed some potency, whereas the 4-methoxybenzamide **18** exhibited very poor activity, presumably as a result of rapid metabolism of both the methoxy group and the relatively electron-rich benzene ring of the acyl moiety. The trifluoromethoxy derivative **19** showed excellent activity, as did the nitro (**17**) and the cyano (**21**) compound. These compounds possess an electron-withdrawing group at the 4-position of the benzoyl group, whose benzene ring is thereby expected to be resistant to metabolism. On the other hand, the compounds with either an ester (**22**) or acetyl (**23**) function on the benzoyl group showed no significant activity, which is presumably due to the metabolic instability of these substituents. Monohalogenation at the 4-position of the benzoyl group enhanced antifungal potency, as can be seen from **24**, **31** and **32**, whereas the 3-fluorobenzoyl derivative **25** showed only poor activity. The difluoro series **26**—**29** exhibited increased potency. All 4-(trifluoromethyl)benzoyl derivatives, **33**, **34** and **35**, and the 2-fluoro-4-(trifluoromethyl)benzoyl derivatives, **37** and **38**, showed the highest activity, because after being administered *p.o.* or i.p., almost all mice survived as long as 3 weeks after infection. This activity was more potent than that of fluconazole. In contrast, the activity of the 2-(trifluoromethyl)benzoyl analog **36** was less potent. The phenylacetyl derivative **39**, a homolog of **31**, had no significant activity. The phenethyl analog **40** showed good activity, and its dehydro analog **41**, a cinnamamide derivative, enhanced *in vivo* potency. Other cinnamamides, **42**, (−)-**43** and (−)-**44**, retained the potent activity of the parent benzamide derivatives.

The *N*-methylbenzamides, (−)-**45**, **46**—**48**, and the *N*-methylcinnamamide **49** also expressed remarkably high activity. The ($2R^*,3S^*$)-benzamidoalcohol **54**, a diastereoisomer of **35**, was almost devoid of activity, and the demethyl analog **56** showed significantly less potency than the methyl equivalent **31**. Comparison of the activity of the enantiomeric pair of the benzamidoalcohols, (−)-**33** and (+)-**33**, revealed that antifungal activity resides in (−)-**33**, which has a $2R,3R$ absolute configuration, as was expected from the previous results of the oxazolidines I and also from the aforementioned discussion of the structural similarity between III and lanosterol. Interestingly, the sulfonamide **57**, an analog of the benzamide **32**, did not show any significant *in vivo* activity. The phthalimide derivative **58** was less potent than the amide analog **31**.

Table II. The ED_{50} Values of Selected Compounds in Mice Infected Systemically with *Candida albicans*

Compound	Route	ED_{50} (mg/kg) on day	
		14	15
32	*p.o.*	7.07	
	i.p.	3.84	
33	*p.o.*		0.86
	i.p.		<0.63
(−)-**33**	*p.o.*		<0.31
	i.p.		<0.31
(−)-**34**	*p.o.*	1.06	
	i.p.	<0.63	
35	*p.o.*		1.19
	i.p.		1.71
37	*p.o.*		<0.63
	i.p.		<0.63
38	*p.o.*		0.88
	i.p.		0.90
46	*p.o.*		0.66
	i.p.		<0.63
48	*p.o.*		1.31
	i.p.		1.97
Ketoconazole	*p.o.*		31.4
	i.p.		39.9
Fluconazole	*p.o.*		3.00
	i.p.		3.04

The ED_{50} values were determined by the probit method in mice (each group consisted of ten male mice, 5 weeks old, of the ddY strain) that were infected systemically using an intravenous challenge of 6 to 9×10^6 cells of *Candida albicans* 427. Compounds were tested at appropriate doses selected from the series 10, 5, 2.5, 1.25, 0.63, 0.31 mg/kg by *p.o.* or i.p. administration at 1, 4, and 24 h post-infection. All compounds are free bases except for **32** (oxalic acid salt) and (−)-**33** (HCl salt).

The structure–activity relationship patterns of the amidoalcohol variants discussed here are parallel with those of the oxazolidine derivatives I. The ED_{50} values (the dose of compound required to cause 50% of the treated animals to survive) for the selected amidoalcohols in a murine model of systemic candidiasis were evaluated, and the results are given in Table II. Antifungal potency of these amidoalcohols and the oxazolidines I was compared by the ED_{50} values. The ED_{50}'s (on day 14) of the typical oxazolidine (I: $X = 2,4\text{-}Cl_2$, R = 4-chlorobenzoyl; racemate, oxalic acid salt) were determined as 8.52 mg/kg, *p.o.* and 10.0 mg/kg, i.p., and those of the amidoalcohol equivalent **32** (racemate, oxalic acid salt) were 7.07 mg/kg, *p.o.* and 3.84 mg/kg, i.p.; the amidoalcohol showed slightly more potent activity than the oxazolidine counterpart. Among the racemic triazoles tested, the 2-fluoro-4-(trifluoromethyl)benzoyl derivative **37** was the most potent against *Candida albicans* infection; the ED_{50} (on day 15) was <0.63 mg/kg for both *p.o.* and i.p. administration, which was at least 5 times more potent than fluconazole, whose ED_{50}'s (on day 15) were 3.00 mg/kg, *p.o.* and 3.07 mg/kg, i.p.

In a preliminary toxicity study, all five mice (ddY strain, male, 5 weeks old) tested survived after oral dosing of 1000 mg/kg of **33** (racemate) once daily for 4 d.

Further evaluation of these amidoalcohols is in progress.

Experimental

Melting points are uncorrected. Infrared spectra (IR) were recorded on a JASCO A-2 spectrometer and proton nuclear magnetic resonance spectra (^1H-NMR) on a Varian EM-360L spectrometer in $CDCl_3$ using

TABLE III. 3-Acylamino-2-aryl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (**7**—**49**, and **54**) and Related Compounds (**56**—**58**)

Compd.	Yield (%)	mp (°C) (Solvent$^{a)}$) [Oxalic acid salt: mp (°C)]	IR ν_{max} cm^{-1} (State) Optical rotation	^{1}H-NMR (CDCl$_3$) $\delta^{b)}$	Formula	Analysis % or MS *m/z* Calcd (Found) C	H	N	Halogen
7	57	233—237 (A–H)	3200, 1679, 1656, 1138 (KBr)	0.95 (3H, d, 7), 4.51 (1H, d, 14), 5.45 (1H, d, 14), 5.45 (1H, q, 7), 7.0—7.7 (3H, m), 7.75 (1H, s), 8.25 (2H, s)$^{c)}$	$C_{13}H_{14}Cl_2N_4O_2$	47.43 (47.61	4.29 4.36	17.02 16.78)	
8	94	Oil [156—160]	3650, 1650, 1506 (CHCl$_3$)	0.86 (3H, d, 7), 1.27 (9H, s), 4.27 (1H, d, 14), 5.33 (1H, br d), 5.37 (1H, br), 5.62 (1H, d, 14), 6.24 (1H, br d), 7.08 (1H, dd, 9, 2), 7.32 (1H, d, 2), 7.52 (1H, d, 9), 7.80 (1H, s), 7.84 (1H, s)	$C_{17}H_{22}Cl_2N_4O_2$	387, 385 (M$^+$+1), 369, 327, 302, 257, 256, 197, 128, 85, 70 (100%)			
9	65	Oil [143—145]	3450, 1660, 1500 (CHCl$_3$)	0.92 (3H, d, 7), 1.66 (6H, s), 2.34 (4H, d, 3), 4.37 (1H, d, 14), 4.68 (1H, q, 7), 4.96 (1H, d, 14), 6.5—7.7 (3H, m), 7.76 (1H, s), 7.97 (1H, s)$^{c)}$	$C_{19}H_{24}F_2N_4O_2$	379, 378 (M$^+$), 296, 224, 186, 154, 141, 127, 82, 70, 44 (100%)			
10	87	Oil [174—176]	3430, 1658, 1595, 1515 (CHCl$_3$)	1.00 (3H, d, 7), 4.50 (1H, d, 14), 4.9 (1H, m), 5.06 (1H, d, 14), 5.25 (1H, br), 6.5—7.6 (6H, m), 7.80 (1H, s), 7.87 (1H, s)	$C_{17}H_{16}F_2N_4O_3$	363 (M$^+$+1), 343, 281, 224 (100%), 141, 138, 127, 95, 82, 70			
11	76	166—167 (A–H)	3430, 1645, 1530, 1500 (CHCl$_3$)	1.03 (3H, d, 7), 4.52 (1H, d, 14), 4.95 (1H, m), 5.09 (1H, d, 14), 5.4 (1H, br), 6.6—7.8 (6H, m), 7.79 (1H, s), 7.90 (1H, s)	$C_{17}H_{16}F_2N_4O_2S$	53.96 (54.21	4.26 4.33	14.81 14.89	F 10.04 F 10.29)
12	40	191—193 (E–H)	3400, 3270, 1620, 1550 (KBr)	0.99 (3H, d, 7), 4.43 (1H, d, 14), 4.96 (1H, m), 5.02 (1H, d, 14), 5.36 (1H, br s), 6.3—7.1 (3H, m), 6.91 (1H, d, 4), 7.1—7.6 (1H, m), 7.36 (1H, d, 4), 7.81 (2H, s)	$C_{17}H_{15}ClF_2N_4O_2S$	49.46 (49.64	3.66 3.81	13.57 13.31	Cl 8.59 Cl 8.55)
13	77	188—190 (A–H)	3430, 1662, 1583, 1500 (CHCl$_3$)	1.01 (3H, d, 7), 4.46 (1H, d, 14), 5.0 (1H, m), 5.05 (1H, d, 14), 5.3 (1H, br), 6.6—7.0 (2H, m), 7.2—7.6 (1H, m), 7.45 (1H, d, 9), 7.80 (2H, s), 8.18 (1H, dd, 9, 2.5), 8.92 (1H, d, 2.5)$^{c)}$	$C_{18}H_{16}ClF_2N_5O_2$	53.01 (52.86	3.95 3.86	17.17 17.30	Cl 8.69 Cl 8.32)
14	76	133—134 (A–H)	3380, 1658, 1616, 1518 (KBr)	1.02 (3H, d, 7), 4.48 (1H, d, 14), 4.97 (1H, br s), 5.05 (1H, m), 5.09 (1H, d, 14), 6.6—7.1 (3H, m), 7.3—7.7 (4H, m), 7.7—8.1 (2H, m), 7.81 (1H, s), 7.86 (1H, s)	$C_{19}H_{18}F_2N_4O_2$	61.28 (61.19	4.87 4.77	15.05 15.17	F 10.20 F 10.08)
15	58	187—189 (A–H)	3460, 1657, 1500 (CHCl$_3$)	1.08 (3H, d, 7), 4.54 (1H, d, 14), 5.0 (1H, m), 5.11 (1H, d, 14), 5.2 (1H, br), 6.6—7.1 (3H, m), 7.2—8.1 (8H, m), 8.40 (1H, s)	$C_{23}H_{20}F_2N_4O_2$	65.40 (65.66	4.77 4.69	13.26 12.93	F 8.99 F 8.71)
16	51	254—255.5 (A–H)	3405, 3325, 1694, 1643, 1529 (KBr)	1.05 (3H, d, 7), 4.47 (1H, d, 14), 4.97 (1H, m), 5.03 (1H, d, 14), 6.6—7.1 (2H, m), 7.1—7.5 (1H, m), 7.5—8.2 (4H, m), 7.73 (1H, s), 7.81 (1H, s)$^{c)}$	$C_{21}H_{21}F_2N_5O_3$	58.74 (58.72	4.93 5.00	16.31 16.28	F 8.85 F 9.05)
17	66	257—258.5 (M–A)	3375, 3300, 1650, 1556 (KBr)	1.14 (3H, d, 7), 4.89 (1H, d, 14), 4.98 (1H, m), 5.86 (1H, d, 14), 5.89 (1H, br), 7.15 (1H, dd, 9, 2), 7.47 (1H, d, 2), 7.81 (1H, d, 9), 7.91 (1H, s), 8.37 (1H, s)$^{d)}$	$C_{19}H_{17}Cl_2N_5O_4$	50.68 (50.45	3.81 3.78	15.55 15.31)	
18	71	200—202 (A–B)	3450, 1645, 1604, 1493 (CHCl$_3$)	1.03 (3H, d, 7), 3.85 (3H, s), 4.47 (1H, d, 14), 4.70 (1H, m), 4.72 (1H, d, 14), 5.33 (1H, br), 6.74 (1H, br d, 9), 6.94 (2H, d, 8), 7.27 (4H, s), 7.65 (1H, s), 7.80 (1H, s), 7.84 (2H, d, 8)	$C_{20}H_{21}ClN_4O_3$	59.93 (59.59	5.28 5.21	13.98 13.83)	
19	60	172—177 (A–H)	3360, 1638, 1543, 1502 (KBr)	1.03 (3H, d, 7), 4.45 (1H, d, 14), 4.65 (1H, m), 4.74 (1H, d, 14), 5.30 (1H, s), 6.82 (1H, br d, 9), 7.30 (4H, s), 7.34 (2H, d, 9), 7.66 (1H, s), 7.82 (1H, s), 7.93 (2H, d, 9)	$C_{20}H_{18}ClF_3N_4O_3$	52.81 (52.55	3.99 4.16	12.32 12.20	F 12.53 F 12.54)
20	41	167—168 (A–H)	3300, 1627, 1545 (KBr)	0.98 (3H, d, 7), 2.51 (3H, s), 4.42 (1H, d, 15), 5.47 (2H, m), 5.67 (1H, d), 6.83 (1H, br d), 7.11 (1H, dd, 9, 2), 7.32 (2H, d, 8), 7.39 (1H, d, 2), 7.58 (1H, d, 9), 7.80 (1H, s), 7.82 (2H, d, 8), 7.86 (1H, s)	$C_{20}H_{20}Cl_2N_4O_2S$	53.22 (53.04	4.47 4.58	12.41 12.39	Cl 15.71 Cl 15.14)
21	74	246—248 (A)	3520, 3250, 2220, 1660, 1554 (KBr)	1.11 (3H, d, 7), 4.83 (1H, d, 15), 5.00 (1H, br), 5.84 (1H, d, 15), 7.15 (1H, dd, 9, 2), 7.44 (1H, d, 2), 7.80 (1H, d, 9), 7.85 (2H, d, 8), 8.25 (2H, d, 8), 8.36 (2H, s)$^{d)}$	$C_{20}H_{17}Cl_2N_5O_2$	55.83 (55.95	3.98 3.87	16.28 16.02)	
22	82	122—130 (dec.) (M)	3560, 3330, 1711, 1634, 1560 (KBr)	1.01 (3H, d, 7), 3.92 (3H, s), 4.61 (1H, d, 15), 5.42 (1H, br), 5.51 (1H, d, 15), 6.11 (1H, s), 7.23 (1H, dd, 9, 2), 7.51 (1H, d, 2), 7.63 (1H, d, 9), 7.8—8.3 (4H, m), 8.15 (2H, s)$^{e)}$	$C_{21}H_{20}Cl_2N_4O_4$	54.44 (54.63	4.35 4.33	12.09 11.88)	
23	57	169—172 (A–H)	3430, 3110, 1677, 1650, 1525 (KBr)	0.98 (3H, d, 7), 2.63 (3H, s), 4.45 (1H, d, 15), 5.49 (2H, br), 5.67 (1H, d, 15), 6.90 (1H, br d), 7.12 (1H, dd, 9, 2), 7.38 (1H, d, 2), 7.58 (1H, d, 9), 7.82 (1H, s), 7.95 (1H, s), 8.06 (2H, s)	$C_{21}H_{20}Cl_2N_4O_3$	56.39 (56.00	4.51 4.48	12.53 12.24	Cl 15.85 Cl 15.39)
24	89	205 (A)	3280, 1634, 1530 (KBr)	1.04 (3H, d, 7), 4.47 (1H, d, 15), 4.96 (1H, m), 5.08 (1H, d, 15), 6.5—7.1 (2H, m), 7.1—7.9 (1H, m), 7.19 (2H, t, 9), 7.78 (1H, s), 7.97 (2H, dd, 9, 6), 8.01 (1H, s)$^{f)}$	$C_{19}H_{17}F_3N_4O_2$	58.46 (58.62	4.39 4.71	14.35 14.25	F 14.60 F 14.52)
25	44	164—165 (A–E)	3400, 3280, 1638, 1553 (KBr)	1.02 (3H, d, 7), 4.47 (1H, d, 15), 4.96 (1H, m), 5.09 (1H, d, 15), 5.38 (1H, br), 6.5—7.0 (3H, m), 7.2—7.9 (5H, m), 7.82 (2H, s)	$C_{19}H_{17}F_3N_4O_2$	58.46 (58.38	4.39 4.41	14.35 14.17	F 14.60 F 14.85)
26	37	165—166 (A)	3370, 3230, 1668, 1535 (KBr)	1.02 (3H, d, 7), 4.51 (1H, d, 14), 4.99 (1H, br), 5.06 (1H, d, 14), 5.32 (1H, br d), 6.5—7.7 (5H, m), 7.81 (2H, s), 7.9—8.4 (1H, m)	$C_{19}H_{16}F_4N_4O_2$	55.88 (55.94	3.95 3.81	13.72 13.73	F 18.61 F 18.59)
27	39	150—151 (E—H)	3420, 1662, 1528 (KBr)	1.02 (3H, d, 7), 4.52 (1H, d, 14), 4.99 (1H, br), 5.07 (1H, d, 14), 5.32 (1H, br d), 6.6—7.1 (3H, m), 7.1—7.6 (3H, m), 7.6—8.1 (1H, m), 7.82 (2H, s)	$C_{19}H_{16}F_4N_4O_2$	55.88 (56.11	3.95 4.07	13.72 13.82	F 18.61 F 18.61)
28	38	168—169 (E–H)	3400, 3300, 1637, 1540 (KBr)	1.01 (3H, d, 7), 4.45 (1H, d, 14), 5.00 (1H, br), 5.07 (1H, d, 14), 5.39 (1H, br d), 6.5—7.1 (3H, m), 7.1—8.0 (4H, m), 7.83 (2H, s)	$C_{19}H_{16}F_4N_4O_2$	55.88 (56.12	3.95 4.18	13.72 13.51	F 18.61 F 18.37)
29	39	178 (E–H)	3420, 1640, 1620, 1595 (KBr)	1.02 (3H, d, 7), 4.43 (1H, d, 14), 4.98 (1H, br), 5.06 (1H, d, 14), 5.39 (1H, br s), 6.4—7.1 (3H, m), 7.1—7.6 (4H, m), 7.81 (2H, s)	$C_{19}H_{16}F_4N_4O_2$	55.88 (55.40	3.95 4.42	13.72 13.46	F 18.61 F 18.87)
30	47	111—116 (A–B–H)	3425, 1680, 1500 (CHCl$_3$)	0.98 (3H, d, 7), 4.53 (1H, d, 14), 5.09 (1H, d, 14), 5.1 (2H, m), 6.6—7.8 (4H, m), 7.82 (1H, s), 7.85 (1H, s)	$C_{19}H_{13}F_7N_4O_2$	49.36 (49.02	2.83 3.23	12.12 10.02)	

31	76	221—222 (A–H)	3310, 1635, 1536 (KBr)	1.02 (3H, d, 7), 4.50 (1H, d, 15), 4.95 (1H, m), 5.06 (1H, d, 15), 6.5—7.1 (2H, m), 7.1—7.9 (1H, m), 7.50 (2H, d, 8), 7.77 (1H, s), 7.90 (2H, d, 8), 8.00 (1H, s)[f]	$C_{19}H_{17}ClF_2N_4O_2$	56.10 (56.30	4.21 4.23	13.77 13.68	Cl Cl	8.71 8.67)
32	74	217—219 (E–H)	3430, 1655, 1585, 1505 ($CHCl_3$)	0.95 (3H, d, 7), 4.40 (1H, d, 15), 5.46 (2H, m), 5.63 (1H, d, 15), 6.88 (1H, br d), 7.11 (1H, dd, 9, 2), 7.35 (1H, d, 2), 7.45 (2H, d, 8), 7.54 (1H, d, 9), 7.78 (1H, s), 7.83 (2H, d, 8), 7.84 (1H, s)	$C_{19}H_{17}Cl_3N_4O_2$	51.89 (51.64	3.90 3.95	12.74 12.48)		
33	77	201—205 (A–H)	3375, 1666, 1540 (KBr)	1.08 (3H, d, 7), 4.50 (1H, d, 15), 4.98 (1H, m), 5.11 (1H, d, 15), 6.6—7.2 (2H, m), 7.2—7.9 (1H, m), 7.77 (1H, s), 7.80 (2H, d, 8), 8.10 (1H, s), 8.11 (2H, d, 8)[f]	$C_{20}H_{17}F_5N_4O_2$	54.55 (54.75	3.89 4.07	12.72 12.85)		
(2*R*,3*R*)-(−)-**33**	81	Oil [140—148][h]	$[\alpha]_D$ −105° (c=0.96, $CHCl_3$)	Identical with that of **33**	$C_{20}H_{17}F_5N_4O_2$	441 (M^++1), 421, 358, 224, 216, 173 (100%), 145, 131, 127, 82, 70				
(2*S*,3*S*)-(+)-**33**	82	Oil [140—148][h]	$[\alpha]_D$ +106° (c=0.98, $CHCl_3$)	Identical with that of **33**	$C_{20}H_{17}F_5N_4O_2$					
34	67	186 (A–H)	3360, 1665, 1530 (KBr)	0.99 (3H, d, 7), 4.40 (1H, d, 15), 5.49 (2H, m), 5.68 (1H, d, 15), 6.84 (1H, br d), 7.10 (1H, dd, 9, 2), 7.37 (1H, d, 2), 7.56 (1H, d, 9), 7.79 (2H, d, 9), 7.83 (1H, s), 7.87 (1H, s), 8.04 (2H, d, 9)	$C_{20}H_{17}Cl_2F_3N_4O_2$	50.76 (51.14	3.62 3.59	11.84 11.82)		
(2*R*,3*R*)-(−)-**34**	75	88—91 (A–H)	$[\alpha]_D$ −115° (c=1.01, $CHCl_3$)	Identical with that of **34**	$C_{20}H_{17}Cl_2F_3N_4O_2$	475, 473 (M^++1), 455, 453, 392, 390, 258, 256, 216, 173 (100%), 145, 70				
35	62	204—207 (A–H)	3450, 1660, 1525, 1500 ($CHCl_3$)	1.04 (3H, d, 7), 4.48 (1H, d, 14), 4.76 (1H, d, 14), 4.4—5.0 (2H, m), 7.1 (1H, br d), 7.28 (4H, s), 7.69 (2H, d, 9), 7.69 (1H, s), 7.78 (1H, s), 7.99 (2H, d, 9)	$C_{20}H_{18}ClF_3N_4O_2$	54.74 (54.41	4.13 4.51	12.77 12.76	F F	12.99 12.95)
36	69	184—186 (A)	3370, 3220, 1671, 1500 (KBr)	1.06 (3H, d, 7), 4.55 (1H, d, 15), 4.96 (1H, m), 5.08 (1H, d, 15), 6.5—7.1 (2H, m), 7.2—7.9 (1H, m), 7.40 (1H, s), 7.64 (2H, br s), 7.76 (1H, s), 8.00 (1H, s)[f]	$C_{20}H_{17}F_5N_4O_2$	54.55 (54.23	3.89 4.07	12.72 12.30)		
37	48	176—177 (M)	3360, 3250, 1668, 1546 (KBr)	1.02 (3H, d, 7), 4.52 (1H, d, 15), 5.06 (1H, d, 15), 5.36 (1H, br s), 6.5—7.1 (2H, m), 7.1—7.8 (4H, m), 7.81 (2H, br s), 8.1—8.5 (1H, m)	$C_{20}H_{16}F_6N_4O_2$	52.41 (52.31	3.52 3.82	12.22 12.54	F F	24.87 24.96)
38	68	223—225 (A–H)	3310, 1668, 1534 (KBr)	0.93 (3H, d, 7), 4.57 (1H, d, 14), 4.63 (1H, m), 4.83 (1H, d, 14), 5.67 (1H, s), 7.38 (4H, s), 7.5—8.1 (3H, m), 7.73 (1H, s), 8.10 (1H, s), 8.46 (1H, br d, 9)[g]	$C_{20}H_{17}ClF_4N_4O_2$	52.58 (52.82	3.75 3.96	12.26 12.38	F F	16.63 16.61)
39	77	185—186 (A–H)	3420, 3280, 1644 (KBr)	0.92 (3H, d, 7), 3.42 (1H, br s), 3.68 (2H, s), 4.48 (1H, d, 14), 4.70 (1H, m), 4.90 (1H, d, 14), 5.95 (1H, br s), 6.5—7.6 (3H, m), 7.63 (1H, s), 8.26 (1H, s)[e]	$C_{20}H_{19}ClF_2N_4O_2$	57.08 (57.08	4.55 4.61	13.31 13.06	F F	9.03 8.75)
40	66	133—134 (A–H)	3270, 1646, 1546 (KBr)	0.79 (3H, d, 7), 2.3—2.8 (2H, m), 2.8—3.2 (2H, m), 3.91 (1H, d, 15), 4.64 (1H, br), 4.76 (1H, d, 15), 5.17 (1H, br d), 6.05 (1H, br d), 6.5—7.0 (2H, m), 7.0—7.6 (1H, m), 7.21 (4H, s), 7.78 (1H, s), 7.81 (1H, s)	$C_{21}H_{21}ClF_2N_4O_2$	58.00 (58.09	4.87 4.81	12.88 12.74)		
41	26	204—206 (A–H)	3450, 1665, 1622, 1500 ($CHCl_3$)	1.00 (3H, d, 7), 4.49 (1H, d, 14), 4.9 (1H, m), 5.05 (1H, d, 14), 5.45 (1H, br s), 6.53 (1H, d, 16), 6.5—7.0 (3H, m), 7.1—7.6 (5H, m), 7.66 (1H, d, 16), 7.80 (1H, s), 7.84 (1H, s)	$C_{21}H_{19}ClF_2N_4O_2$	58.27 (58.68	4.42 4.45	12.94 12.75	F F	8.78 8.59)
42	93	166—167 (A–H)	3300, 1657, 1617 (KBr)	1.00 (3H, d, 7), 4.51 (1H, d, 14), 5.0 (1H, m), 5.08 (1H, d, 14), 5.39 (1H, br s), 6.64 (1H, d, 16), 6.4—7.1 (3H, m), 7.2—7.4 (1H, m), 7.65 (4H, s), 7.77 (1H, d, 16), 7.84 (2H, s)	$C_{22}H_{19}F_5N_4O_2$	56.65 (56.95	4.11 4.47	12.01 12.02	F F	20.37 20.18)
(2*R*,3*R*)-(−)-**43**	71	209—210 (A–H)	$[\alpha]_D$ −83° (c=1.04, $CHCl_3$)	0.98 (3H, d, 7), 4.46 (1H, d, 14), 4.9 (1H, m), 5.03 (1H, d, 14), 5.4 (1H, br), 6.59 (1H, d, 16), 6.5—7.5 (3H, m), 7.2—7.6 (1H, m), 7.65 (4H, s), 7.72 (1H, d, 16), 7.80 (1H, s), 7.85 (1H, s)	$C_{22}H_{19}F_2N_5O_2$	62.40 (62.33	4.52 4.55	16.54 16.40	F F	8.97 8.87)
(2*R*,3*R*)-(−)-**44**	72	Oil [60 (dec.)][h]	$[\alpha]_D$ −56° (c=0.78, $CHCl_3$)	0.98 (3H, d, 7), 4.48 (1H, d, 14), 4.9 (1H, m), 5.03 (1H, d, 14), 6.53 (1H, d, 16), 6.5—7.7 (8H, m), 7.70 (1H, d, 16), 7.77 (1H, s), 7.83 (1H, s)	$C_{22}H_{19}F_5N_4O_3$	483 (M^++1), 400, 258, 224, 215 (100%), 161, 82, 70				
(2*R*,3*R*)-(−)-**45**	69	Oil [103—106][i]	$[\alpha]_D$ −106° (c=1.39, $CHCl_3$)	1.14 (3H, d, 7), 3.18 (3H, s), 4.42 (1H, d, 14), 5.30 (1H, br), 5.32 (1H, d, 14), 6.5—7.1 (2H, m), 7.1—7.8 (1H, m), 7.30 (2H, d, 10), 7.47 (2H, s)	$C_{21}H_{19}F_5N_4O_3$ $\cdot HNO_3$	47.29 (47.44	3.78 4.06	13.13 12.87	F F	17.81 17.70)
46	73	144—146 (E)	3110, 1638, 1610 (KBr)	1.17 (3H, d, 7), 3.16 (3H, s), 4.43 (1H, d, 14), 5.30 (1H, br), 5.35 (1H, d, 14), 6.4—7.1 (2H, m), 7.2—8.2 (5H, m), 7.60 (1H, s), 7.69 (1H, s)	$C_{21}H_{19}F_5N_4O_2$	55.51 (55.64	4.21 4.49	12.33 12.12	F F	20.90 20.90)
47	52	155—157.5 (E–H)	3430, 3170, 1646, 1501 (KBr)	1.16 (3H, d, 7), 3.16 (3H, s), 4.43 (1H, d, 14), 5.22 (1H, br), 5.33 (1H, d, 14), 5.46 (1H, br), 6.5—7.1 (2H, m), 7.2—8.2 (5H, m), 7.72 (1H, s), 7.78 (1H, s)	$C_{21}H_{19}F_5N_4O_2$	55.51 (55.54	4.21 4.38	12.33 12.24	F F	20.90 20.75)
48	54	174—175 (A–H)	3420, 1680, 1626 ($CHCl_3$)	1.12 (3H, d, 7), 3.11 (3H, s), 4.48 (1H, d, 14), 4.91 (1H, d, 14), 5.20 (2H, br), 7.1—7.9 (3H, m), 7.29 (4H, s), 7.69 (1H, s), 7.78 (1H, s)	$C_{21}H_{19}ClF_4N_4O_2$	53.57 (53.31	4.07 4.22	11.90 11.21	F F	16.14 16.01)
49	61	169—171 (E–H)	3430, 3100, 1648, 1494 (KBr)	1.08 (3H, d, 7), 3.34 (3H, s), 4.32 (1H, d, 14), 5.13 (1H, br), 5.24 (1H, d, 14), 5.37 (1H, br), 6.6—6.9 (2H, m), 7.17 (1H, d, 15), 7.2—8.1 (5H, m), 7.43 (1H, s), 7.47 (1H, s), 7.78 (1H, d, 15)	$C_{22}H_{21}ClF_2N_4O_2$	59.13 (59.47	4.74 4.98	12.54 12.40	F F	8.50 8.28)
54	60	175—177 (B–H)	3430, 1659, 1621, 1599 ($CHCl_3$)	1.41 (3H, d, 6.5), 4.60 (2H, s), 4.5—5.0 (1H, m), 6.41 (1H, br d, 9), 7.29 (4H, s), 7.65 (4H, s), 7.82 (1H, s), 7.87 (1H, s)	$C_{20}H_{18}ClF_3N_4O_2$	54.74 (54.77	4.13 4.18	12.77 12.64	F F	12.99 12.83)
56	87	170—172 (E–C)	3400, 1655 ($CHCl_3$)	3.8—4.0 (2H, m), 4.62 (2H, s), 5.85 (1H, br), 6.6—7.0 (3H, m), 7.3—7.7 (1H, m), 7.35 (2H, d, 9), 7.61 (2H, d, 9), 7.83 (1H, s), 8.09 (1H, s)	$C_{18}H_{15}ClF_2N_4O_2$	55.04 (55.24	3.85 3.65	14.26 14.11)		
57	40	104—108 (E)	3390, 1588 ($CHCl_3$)	0.64 (3H, d, 6.5), 4.56 (1H, dq, 9, 6.5), 4.78 (1H, d, 15), 5.5 (1H, br), 5.54 (1H, d, 15), 5.60 (1H, d, 9), 7.05 (1H, dd, 8.5, 2), 7.31 (1H, d, 2), 7.47 (1H, d, 8.5), 7.51 (2H, d, 9), 7.80 (1H, s), 7.85 (1H, s), 7.92 (2H, d, 9)	$C_{18}H_{17}Cl_3N_4O_3S$	45.44 (45.47	3.60 3.72	11.78 11.76)		
58	98	Foam [143—150][i]	3380, 1770, 1705, 1615 ($CHCl_3$)	1.35 (3H, d, 7), 4.40 (1H, d, 15), 4.90 (1H, d, 15), 5.16 (1H, q, 7), 5.3 (1H, br), 6.6—7.1 (2H, m), 7.54 (1H, s), 7.4—8.1 (4H, m), 8.13 (1H, s)	$C_{20}H_{15}ClF_2N_4O_3$	435, 433 (M^++1), 352, 350, 334, 332, 279, 277, 224 (100%), 210, 208, 141				

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a) Recrystallization solvent: A, AcOEt; H, hexane; B, benzene; E, ether; M, MeOH; C, $CHCl_3$. *b*) Chemical shifts are given with proton numbers, absorption patterns, and coupling constants in Hz in parentheses. *c*) CD_3OD was used as a solvent. *d*) Pyridine-d_5 was used as a solvent. *e*) DMF-d_7 was used as a solvent. *f*) A mixture of $CDCl_3$ and CD_3OD (10 : 1) was used as a solvent. *g*) DMSO-d_6 was used as a solvent. *h*) HCl salt. *i*) HNO_3 salt.

Me_4Si as an internal standard. Mass spectra (MS) were obtaind on a JEOL JMS D300 spectrometer. Optical 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; dq, doublet of quartets; t, triplet; q, quartet; qd, quartet of doublets; m, multiplet; br, broad.

(2*R*,3*R*)-3-Amino-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(2*R*,3*R*)-3a] A solution of (2*R*,3*R*)-**2a**[1] (5.00 g) in EtOH (100 ml) was shaken with 10% palladium–carbon (1.30 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 (2*R*,3*R*)-**3a** (4.56 g, 100%) as a solid, which was recrystallized from benzene to afford a pure specimen, mp 154—155 °C: $[\alpha]_D$ −73° (c=1.06, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{14}F_2N_4O$: C, 53.73; H, 5.26; N, 20.89. Found: C, 53.59; H, 5.35, N, 20.71. IR ν_{max} (KBr) cm^{-1}: 3210, 1620, 1600. The NMR spectrum was identical with that of the corresponding racemate.[2]

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-(*N*-methylamino)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4a) and the (2*R*,3*R*) Enantiomer [(2*R*,3*R*)-4a]** i) A solution of (4*R**,5*R**)-5-(2,4-difluorophenyl)-4-methyl-5-[(1*H*-1,2,4-triazol-1-yl)methyl]oxazolidine[2] (**5a**, 941 mg, 3.36 mmol) in tetrahydrofuran (THF, 25 ml) was added dropwise to a suspension of lithium aluminum hydride (127 mg, 3.36 mmol) in THF (8 ml), with ice-cooling and stirring. After stirring at the same temperature for 30 min, a 1 N aqueous solution of NaOH (0.5 ml) was added and the whole was stirred for an additional 1 h. At the end of this time, the mixture was filtered using Celite, and the filtrate was concentrated under reduced pressure to afford **4a** (868 mg, 92%) as a solid, which was used without further purification for the next reaction. An analytical sample of **4a**, mp 141—145 °C, was obtained by recrystallization from AcOEt–hexane. *Anal.* Calcd for $C_{13}H_{16}F_2N_4O$: C, 55.31; H, 5.71; F, 13.46; N, 19.85. Found: C, 55.39; H, 5.78; F, 13.63; N, 20.01. IR ν_{max} (KBr) cm^{-1}: 3210, 1610, 1580, 1499. NMR ($CDCl_3$) δ: 0.90 (3H, dd, J=7, 2 Hz), 2.48 (3H, s), 2.96 (1H, qd, J=7, 2 Hz), 4.80 (2H, s), 6.55—7.1 (2H, m), 7.1—7.7 (1H, m), 7.77 (1H, s), 7.96 (1H, s).

In a similar way, (2*R*,3*R*)-**4a** was obtained as a crude cake in 95% yield from (4*R*,5*R*)-**5a**, which was prepared as described previously[2] by heating equimolar amounts of (2*R*,3*R*)-**3a** and paraformaldehyde in benzene. An analytical sample of (2*R*,3*R*)-**4a**, mp 168—170 °C, $[\alpha]_D$ −97.4° (c=0.96, $CHCl_3$), was obtained by recrystallization from AcOEt–MeOH. The NMR spectrum was identical with that of the racemate **4a** described above.

ii) A 40% methylamine solution in MeOH (0.7 ml) was added to a solution of **1a**[2] (racemate, 180 mg) in MeOH (1 ml), and the whole in a sealed tube was heated at 70 °C for 21 h. The solvent was evaporated off under reduced pressure to give a viscous oil (202 mg), which was shown by the NMR spectrum to be a mixture of **4a**, **6** and **1a** in approximately a 3 : 1 : 1 ratio.

This reaction in a scale using 1.00 g of **1a** (racemate) at a higher temperature (100 °C) during a longer time (46 h) afforded an almost pure product **6** as a solid, which was purified by recrystallization from AcOEt–benzene to give a pure specimen (943 mg, 84%), mp 170—173 °C. *Anal.* Calcd for $C_{13}H_{15}FN_4O$: C, 59.53; H, 5.76; F, 7.24; N, 21.36. Found: C, 59.62; H, 5.89; F, 6.95; N, 21.24. IR ν_{max} (KBr) cm^{-1}: 3138, 1621, 1602, 1514, 1492. NMR (DMF-d_7) δ: 1.35 (3H, d, J=6.5 Hz), 2.73 (3H, s), 3.32 (1H, q, J=6.5 Hz), 4.28 (1H, d, J=15 Hz), 4.42 (1H, d, J=15 Hz), 5.85 (1H, br), 6.1—6.5 (3H, m), 7.84 (1H, s), 8.34 (1H, s).

(2*R,3*R**)-2-(4-Chlorophenyl)-3-(*N*-methylamino)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4c)** i) Following a procedure similar to that described for **4a**, **4c** was prepared as a cake in 90% yield by treatment of **5c**[2] (racemate) with lithium aluminum hydride in THF. MS m/z: 281 (M^++1), 223, 222, 198, 139, 125, 111, 70, 58 (100%). NMR ($CDCl_3$) δ: 0.96 (3H, d, J=6.5 Hz), 2.38 (3H, s), 2.55 (1H, q, J=6.5 Hz), 3.41 (1H, s), 4.46 (1H, d, J=15 Hz), 4.80 (1H, d, J=15 Hz), 7.29 (4H, s), 7.83 (1H, s), 8.05 (1H, s).

ii) A 40% methylamine solution in MeOH (12 ml) was added to a solution of **1c**[2] (racemate, 3.00 g) in MeOH (15 ml), and the whole in a sealed tube was heated at 70 °C for 24 h. Removal of the solvent by evaporation *in vacuo* afforded **4c** (3.45 g) as a solid, which was used without further purification for the next reaction. The NMR spectrum was identical with that of the sample obtained above.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-formamido-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (7)** A solution of *N*-formylimidazole in CH_2Cl_2, prepared *in situ* from formic acid (42 mg, 0.91 mmol) and *N*,*N*′-carbonyldiimidazole (147 mg, 0.91 mmol) in CH_2Cl_2 (1.5 ml), was added to a solution of **3b**[2] (racemate, 120 mg, 0.40 mmol) in CH_2Cl_2 (0.5 ml). The mixture was stirred at room temperature for 10 h, after which it was diluted with AcOEt, washed successively with water and brine, and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a solid, which was recrystallized from AcOEt–hexane to give **7** (75 mg, 57%) as a colorless powder, mp 233—237 °C. Spectroscopic data and elementary analysis data are given in Table III.

(2*R,3*R**)-2-(2,4-Dichlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-[(trimethylacetyl)amino]-2-butanol (8)** Trimethylacetyl chloride (100 mg, 0.83 mmol) was added to a solution of **3b** (150 mg, 0.50 mmol) in pyridine (2.5 ml), with stirring at 0 °C. After being stirred at the same temperature for 30 min, the mixture was concentrated under reduced pressure and the residue was partitioned between AcOEt and a diluted aqueous solution of $NaHCO_3$. The organic layer was washed with brine, dried and concentrated *in vacuo* to afford an oily residue, which was chromatographed on silica gel (2 g, benzene–AcOEt, 4 : 1—1 : 1, v/v) to give **8** (180 mg, 94%) as an oil. Spectroscopic data is given in Table III.

The amide **8** (140 mg) formed its oxalic acid salt (120 mg), mp 156—160 °C, on being mixed with 1 eq of oxalic acid in ether.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[(5-methyl-4-hexenoyl)amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (9)** A solution of 5-methyl-4-hexenoic acid (192 mg, 1.50 mmol) and *N*,*N*′-carbonyldiimidazole (243 mg, 0.15 mmol) in THF (5 ml) was warmed at 40 °C for 30 min. To this solution was added **3a**[2] (racemate, 200 mg, 0.75 mmol), and the mixture was stirred at 60—65 °C for 2.5 h. After cooling, the mixture was partitioned between AcOEt and a 5% aqueous solution of $NaHCO_3$. The organic layer was collected, washed with brine and dried over $MgSO_4$. The solvent was evaporated off under reduced pressure to give an oily residue, which was chromatographed on silica gel (10 g, benzene–AcOEt, 1 : 2—1 : 4, v/v) to afford **9** (193 mg, 65%) as an oil. Spectroscopic data of **9** is given in Table III.

The amide **9** formed its oxalic acid salt, mp 143—145 °C, on being mixed with 1 eq of oxalic acid in AcOEt–hexane.

(2*R,3*R**)-3-Acylamino-2-aryl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (10—42), the (2*R*,3*R*) Enantiomers [(−)-33, (−)-34, (−)-43 and (−)-44] and the (2*S*,3*S*) Enantiomer [(+)-33]** As a typical example, the preparation of (−)-**33** is described. 4-(Trifluoromethyl)benzoyl chloride (218 mg, 1.04 mmol) was added to a solution of (2*R*,3*R*)-**3a** (200 mg, 0.75 mmol) in pyridine (2 ml), with stirring and ice-cooling. After 1 h, MeOH (0.3 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 *in vacuo* gave an oily residue, which was chromatographed on silica gel (10 g, benzene–AcOEt, 1 : 1, v/v) to afford (−)-**33** (266 mg, 81%) as an oil, $[\alpha]_D$ −105° (c=0.96, $CHCl_3$). Spectroscopic data is given in Table III.

The amide (−)-**33** formed its HCl salt, mp 140—148 °C, on being mixed with a 4 N HCl dioxane solution (1 eq) in AcOEt–benzene.

In a similar way, other amidoalcohols were prepared by acylation of the aminoalcohols **3a—c** with the corresponding acyl chloride. Crystalline compounds were purified by recrystallization of the crude products from an appropriate solvent. The amide **32** was converted to its oxalic acid salt, mp 222—226 °C, on being mixed with 1 eq of oxalic acid in AcOEt–hexane. Oily products were purified by column chromatography, then converted to crystalline salts by mixing them with oxalic acid or HCl in an organic solvent. The yields, physical and spectroscopic data and elementary analysis data (or MS data) of these amidoalcohols are given in Table III.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[*N*-methyl-*N*-[4-(trifluoromethoxy)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(−)-45] and the (2*R,3*R**)-*N*-Methylamidoalcohols (46—49)** As a typical example, the preparation of **46** is described. 4-(Trifluoromethyl)benzoyl chloride (375 mg, 1.80 mmol) was added to a solution of **4a** (428 mg, 1.50 mmol) and triethylamine (404 mg, 4.00 mmol) in CH_2Cl_2 (8 ml). The mixture was stirred at room temperature for 30 min. At the end of this time, MeOH (0.5 ml) was added to this mixture and stirring was continued for 15 min, after which the solvent was removed by evaporation 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 a crystalline mass, which was recrystallized from ether to afford **46** (504 mg, 73%), mp 144—146 °C. Spectroscopic data and elementary analysis data are given in Table III.

In a similar way, other *N*-methylamidoalcohols were prepared by acylation of *N*-methylaminoalcohol **4a** or **4c** with the corresponding acyl chloride. The amide (−)-**45** was obtained from (−)-**4a** as an oil, which formed its HNO_3 salt, mp 103—106 °C, on being mixed with 1 eq of concentrated HNO_3 in ether. Amides **47**—**49** were crystalline and purified by recrystallization from an appropriate solvent. The yields, physical and spectroscopic data and elementary analysis data of these *N*-methylamidoalcohols are given in Table III.

(2*R,3*S**)-2-(4-Chlorophenyl)-3-methanesulfonyloxy-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (51)** Methanesulfonyl chloride (140 mg, 1.31 mmol) was added to a solution of **50**[2] (racemate, 157 mg, 0.59 mmol) in pyridine (2 ml) with stirring at 0 °C. After 2 h, the mixture was partitioned between ether and water. The organic layer was washed with brine and dried. Evaporation of the solvent under reduced pressure gave **51** (193 mg, 95%) as an oil, which was used without further purification for the next reaction. NMR ($CDCl_3$) δ: 1.27 (3H, d, $J=6$ Hz), 2.97 (3H, s), 4.6 (1H, br), 4.66 (2H, s), 4.85 (1H, q, $J=6$ Hz), 7.1—7.4 (4H, m), 7.78 (1H, s), 8.03 (1H, s).

(2*R,3*S**)-3-Azido-2-(4-chlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (52)** A mixture of **51** (193 mg, 0.56 mmol), sodium azide (188 mg, 2.89 mmol), ammonium chloride (30 mg, 0.56 mmol) and *N*,*N*-dimethylformamide (DMF, 3 ml) was stirred at 120 °C for 2 h. After cooling, the mixture was partitioned between benzene and water. The organic layer was washed with brine and concentrated *in vacuo* to give an oily residue, which was purified by column chromatography (5 g, AcOEt–hexane, 2 : 1, v/v) to give **52** (150 mg, 92%) as an oil. MS *m/z*: 295, 293 ($M^+ + 1$), 224, 222 (100%), 141, 139, 127, 125. IR ν_{max} ($CHCl_3$) cm^{-1}: 3410, 2110. NMR ($CDCl_3$) δ: 1.11 (3H, d, $J=6.5$ Hz), 3.55 (1H, q, $J=6.5$ Hz), 4.58 (2H, s), 5.14 (1H, br s), 7.2—7.6 (4H, m), 7.82 (1H, s), 8.01 (1H, s).

(2*R,3*S**)-2-(4-Chlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-[[4-(trifluoromethyl)benzoyl]amino]-2-butanol (54)** A solution of **52** (122 mg, 0.42 mmol) in EtOH (3 ml) was shaken with 10% palladium–carbon (35 mg) 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 the aminoalcohol **53** (111 mg, 100%) as an oil, which was then dissolved in pyridine (1.5 ml) and treated with 4-(trifluoromethyl)benzoyl chloride (97 mg, 0.47 mmol) at 0 °C for 30 min. Work-up in the usual manner, followed by purification by column chromatography (5 g, AcOEt–hexane, 2 : 1, v/v), and then by recrystallization from benzene–hexane gave **54** (109 mg, 60% yield from **52**), mp 175—177 °C. Spectroscopic data and elementary analysis data are given in Table III.

(±)-1-[(4-Chlorobenzoyl)amino]-2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2-propanol (56) To a solution of **55**[2] (racemate, 81 mg, 0.32 mmol) in pyridine (1 ml) was added 4-chlorobenzoyl chloride (72 mg, 0.41 mmol), with stirring at 0 °C. After 10 min, the mixture was partitioned between AcOEt and water. The organic layer was washed with brine and concentrated *in vacuo* to give a crystalline residue, which was recrystallized from $CHCl_3$–ether to afford **56** (109 mg, 87%), mp 170—172 °C. Spectroscopic data and elementary analysis data are given in Table III.

(2*R,3*R**)-3-[(4-Chlorobenzenesulfonyl)amino]-2-(2,4-dichlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (57)** A solution of **3b** (racemate, 50 mg, 0.166 mmol) and 4-chlorobenzenesulfonyl chloride (53 mg, 0.25 mmol) in pyridine (1 ml) was stirred at 0 °C. After quenching the reaction with MeOH (0.1 ml), the mixture was partitioned between AcOEt and water. The organic layer was dried and concentrated *in vacuo* to give an oily residue, which was purified by column chromatography (1 g, AcOEt–benzene, 1 : 3, v/v) to yield **57** (32 mg, 40%) as a solid. Recrystallization from ether gave an analytical sample, mp 104—108 °C. Spectroscopic data and elementary analysis data are given in Table III.

(2*R,3*R**)-3-(4-Chlorophthalimido)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (58)** A solution of **3a** (150 mg, 0.56 mmol), 4-chlorophthalic anhydride (124 mg, 0.68 mmol) and triethylamine (5 mg, 0.05 mmol) in toluene (4 ml) was heated under reflux for 4 h with azeotropic removal of water. The mixture was then diluted with AcOEt and washed with a diluted aqueous solution of $NaHCO_3$. The organic layer was dried and the solvent was distilled off under reduced pressure. The residue was purified by preparative TLC (AcOEt) to give **58** (238 mg, 98%) as a colorless foam. Spectroscopic data of **58** is given in Table III.

The imide **58** formed its HNO_3 salt, mp 143—150 °C, on being mixed with 1 eq of concentrated HNO_3 in ether.

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