Structural Study of Triazole Antifungals. II.[1] Crystal and Molecular Structures of the Two Diastereoisomers (4*R**,5*R**)- and (4*S**,5*R**)-5-(2,4-Difluorophenyl)-4-methyl-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-3-[4-(trifluoromethyl)benzoyl]oxazolidine

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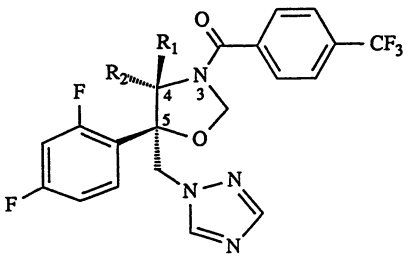
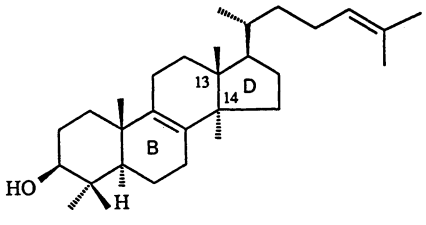
The title compounds were designed and synthesized as potential inhibitors of cytochrome P-450 14α-demethylase. The antifungal activity of (4*R**,5*R**)-isomer is markedly higher than that of (4*S**,5*R**)-isomer. The crystal structures of the two diastereoisomers were determined by X-ray diffraction technique. The final *R* indices of (4*R**,5*R**)- and (4*S**,5*R**)-isomers were 0.063 and 0.070 for 2840 and 2365 reflections, respectively. The different configuration at the 4-position in the oxazolidine ring causes the differences in the ring conformation and in some torsion angles. The three-dimensional structures of the two diastereoisomers are consequently different. Among the diastereoisomers and enantiomers, the (4*R*,5*R*)-enantiomer is superimposable on lanosterol, which is a substrate of cytochrome P-450 14α-demethylase, suggesting that the 4β-methyl group plays an important role in the antifungal activity.

Compounds containing the imidazole ring or the 1,2,4-triazole ring are known to be active as antifungal agents. These compounds have been shown to inhibit biosysthesis of the cell membrane in fungi. An important step in this biosynthesis is cytochrome P-450-mediated 14α-demethylation of lanosterol to give, after several steps, ergosterol, which is an essential molecule for the formation of fungal membranes.[2] Imidazole and triazole antifungals inhibit this enzyme by a mechanism in which the heterocyclic nitrogen atom (N-3 of imidazole and N-4 of triazole) binds to the heme iron atom located in the binding site of the enzyme.[3]

In a program aimed at seeking an active agent against fungal infections, new triazolylmethyloxazolidine derivatives were designed and synthesized as potential inhibitors against fungal cytochrome P-450 14α-demethylase.[4] Among them, (4*R**,5*R**)-5-(2,4-difluorophenyl)-4-methyl-5-[(1*H*-1,2,4-triazol-1-yl)methyl]-3-[4-(trifluoromethyl)benzoyl]oxazolidine shows the excellent antifungal activity. On the other hand, the (4*S**,5*R**)-diastereoisomer exhibits significantly less activity. This paper reports the results of structural studies of the two diastereoisomers using X-ray crystallographic analysis and a structural comparison with lanosterol.



(4*R**,5*R**)-isomer: R_1=CH_3, R_2=H
(4*S**,5*R**)-isomer: R_1=H, R_2=CH_3



lanosterol

Experimental

(4*R,5*R**)-Isomer.** Colorless plates were grown by slow evaporation of a benzen–hexane solution at room temperature. Diffraction experiments were performed with a crystal, 0.1×0.3×0.8 mm, on a Rigaku AFC-5 diffractometer, using the monochromated Cu *Kα* radiation. The crystal data are as follows: $C_{21}H_{17}N_4O_2F_5$, F.W.=452.4, triclinic, space group $P\bar{1}$, a=14.076(3), b=10.715(2), c=7.017(3) Å, α=95.12(3), β=96.29(4), γ=101.86(2)°, V=1022.7(4) Å^3, Z=2, D_c=1.47 g cm^{-3}, μ(Cu*Kα*)=11.4 cm^{-1}. The ω-2θ scanning mode was employed up to 2θ=128°. A total of 3523 reflections were measured, of which 2843 unique reflections with $F \geqslant 3\sigma(F)$ were used for the analysis. Three references measured every 200 reflections showed no significant variation in intensity. Correction was made for Lorentz and polarization factors, but not absorption. The structure was solved by the direct methods using MULTAN 78,[5] and refined by the block-diagonal least-squares technique with anisotropic thermal parameters. Hydrogen atoms were located on a difference Fourier synthesis and refined isotropically. A difference Fourier map revealed two positions of trifluoromethyl F atoms: both positions were included with population parameters of 0.7 and 0.3. Three low-angle reflections seemed to be affected by secondary extinction and were excluded from the data set. The final refinement converged at R=0.063 and R_w=0.062. The weighting scheme applied was $w=1/\sigma(F)$. Atomic scattering factors were taken from Ref. 6. Calculations were carried out with the DIRECT-SEARCH program system.[7] The final fractional coordinates and equivalent iso-

Table 1. Fractional Atomic Coordinates and Equivalent Isotropic Parameters for Non-H Atoms, with esd's in Parentheses

Atom	x	y	z	B_{eq}/Å^2	Atom	x	y	z	B_{eq}/Å^2
(4*R**,5*R**)-Isomer					(4*S**,5*R**)-Isomer				
O(1)	0.1428(2)	0.6487(2)	0.5607(3)	4.26(8)	O(1)	0.2529(2)	0.2192(5)	0.2027(1)	4.0(5)
C(2)	0.2297(3)	0.6174(4)	0.6460(6)	5.0(1)	C(2)	0.2983(3)	0.2544(8)	0.2785(2)	5.3(2)
N(3)	0.2904(2)	0.6215(3)	0.4943(4)	4.21(9)	N(3)	0.2870(2)	0.4853(6)	0.2902(2)	4.4(1)
C(4)	0.2706(3)	0.7189(3)	0.3723(5)	3.9(1)	C(4)	0.2514(2)	0.5979(7)	0.2193(2)	4.0(1)
C(5)	0.1637(3)	0.7231(3)	0.4043(5)	3.8(1)	C(5)	0.2049(2)	0.4062(7)	0.1706(2)	3.6(1)
C(6)	0.0876(3)	0.6564(3)	0.2361(5)	4.4(1)	C(6)	0.1993(2)	0.4209(7)	0.0929(2)	4.1(1)
N(7)	0.0999(2)	0.5271(3)	0.1719(4)	4.07(9)	N(7)	0.1688(2)	0.2256(6)	0.0503(2)	3.8(1)
N(8)	0.1546(2)	0.5093(3)	0.0301(5)	5.1(1)	N(8)	0.0912(2)	0.1732(7)	0.0220(2)	4.8(1)
C(9)	0.1521(3)	0.3850(4)	0.0244(6)	5.3(1)	C(9)	0.0900(3)	−0.0100(8)	−0.0126(2)	4.7(2)
N(10)	0.1003(3)	0.3240(3)	0.1495(5)	5.8(1)	N(10)	0.1603(2)	−0.0806(7)	−0.0093(2)	4.9(1)
C(11)	0.0685(3)	0.4171(4)	0.2401(6)	5.5(1)	C(11)	0.2078(2)	0.0726(8)	0.0311(2)	4.6(2)
C(12)	0.3460(2)	0.5365(3)	0.4413(5)	4.1(1)	C(12)	0.2986(3)	0.5839(9)	0.3534(3)	5.7(2)
O(13)	0.3819(2)	0.5414(2)	0.2910(4)	5.24(9)	O(13)	0.2796(3)	0.7767(6)	0.3552(2)	8.8(2)
C(14)	0.3621(2)	0.4414(3)	0.5769(5)	3.9(1)	C(14)	0.3365(3)	0.4602(9)	0.4239(3)	5.9(2)
C(15)	0.3632(3)	0.3174(4)	0.4944(6)	4.9(1)	C(15)	0.4041(5)	0.348(2)	0.4376(4)	9.1(3)
C(16)	0.3819(3)	0.2259(4)	0.6102(6)	5.2(1)	C(16)	0.4410(5)	0.243(2)	0.5057(4)	10.3(4)
C(17)	0.4006(3)	0.2557(3)	0.8066(5)	4.6(1)	C(17)	0.4068(4)	0.250(1)	0.5571(3)	8.6(3)
C(18)	0.4008(3)	0.3786(4)	0.8913(5)	4.6(1)	C(18)	0.3476(7)	0.377(2)	0.5434(4)	11.9(5)
C(19)	0.3813(3)	0.4694(3)	0.7731(5)	4.4(1)	C(19)	0.3093(6)	0.480(2)	0.4763(4)	10.1(4)
C(20)	0.4230(4)	0.1587(4)	0.9346(7)	6.6(2)	C(20)	0.4427(6)	0.113(2)	0.6268(3)	15.5(5)
F(21)	0.4362(4)	0.0568(3)	0.8435(6)	9.1(2)	F(21)	0.4858(6)	−0.020(1)	0.6277(3)	28.7(6)
F(22)	0.3469(4)	0.1248(4)	1.0383(7)	10.4(2)	F(22)	0.3998(4)	0.107(2)	0.6606(3)	29.4(6)
F(23)	0.4951(3)	0.2012(4)	1.0662(6)	9.8(2)	F(23)	0.4933(4)	0.238(1)	0.6751(3)	21.8(4)
C(24)	0.1478(3)	0.8595(3)	0.4588(5)	3.9(1)	C(24)	0.1248(2)	0.3803(7)	0.1754(2)	3.6(1)
C(25)	0.1513(3)	0.9469(3)	0.3293(5)	4.4(1)	C(25)	0.0677(2)	0.5403(8)	0.1483(2)	4.4(1)
C(26)	0.1382(3)	1.0712(3)	0.3710(6)	5.0(1)	C(26)	−0.0057(3)	0.5257(9)	0.1492(3)	5.3(2)
C(27)	0.1227(3)	1.1023(4)	0.5536(6)	5.3(1)	C(27)	−0.0213(3)	0.343(1)	0.1792(3)	5.8(2)
C(28)	0.1186(3)	1.0225(4)	0.6948(6)	5.5(1)	C(28)	0.0307(3)	0.1766(9)	0.2065(3)	5.6(2)
C(29)	0.1311(3)	0.8977(4)	0.6421(5)	4.7(1)	C(29)	0.1040(3)	0.1975(8)	0.2039(2)	4.6(2)
F(30)	0.1697(2)	0.9152(2)	0.1471(3)	6.00(8)	F(30)	0.0851(2)	0.7224(4)	0.1197(2)	5.7(5)
F(31)	0.1096(2)	1.2248(2)	0.6011(4)	7.6(1)	F(31)	−0.0937(2)	0.3225(6)	0.1817(2)	8.3(1)
C(32)	0.3472(3)	0.8445(4)	0.4351(7)	6.1(1)	C(32)	0.3132(3)	0.6992(8)	0.1976(3)	5.2(2)
F(21′)	0.429(1)	0.180(1)	1.106(1)	11.9(6)	C(15′)	0.384(2)	0.556(5)	0.482(1)	8(1)
F(22′)	0.511(1)	0.136(2)	0.915(2)	20(1)	C(16′)	0.423(2)	0.430(7)	0.546(1)	10(1)
F(23′)	0.358(1)	0.0442(9)	0.890(2)	13.9(6)	C(18′)	0.348(2)	0.128(5)	0.499(1)	9(1)
					C(19′)	0.311(2)	0.241(4)	0.434(1)	7(1)

tropic thermal parameters[8] are given in Tablel 1.[9]

(4*S,5*R**)-Isomer.** Recrystallization from a benzene–ether solution gave colorless plates. The crystal used has approximate dimensions of 0.2×0.4×0.6 mm; the unit cell constants area a=18.513(3), b=6.122(2), c=19.805(1) Å, β=113.13(4)°, V=2064(2) Å^3, D_c=1.46 g cm^{-3} in space group $P2_1/a$ (Z=4), μ(Cu $K\alpha$)=11.3 cm^{-1}. Of 3432 reflections measured, 2367 were independently observed at level $F \geqslant 3\sigma(F)$. Data reduction and structure determination were carried out using the methods and procedures described for (4*R**,5*R**)-isomer. The ortho- and meta-position atoms of the trifluoromethylbenzoyl group are disordered in two orientations with weights of 0.8 and 0.2. Two low-angle reflections affected by secondary extinction were left out of the refinement. With unit weights, final residuals were R=0.070 and R_w=0.063.

Results and Discussion

The atom labelling and thermal ellipsoids are shown in Fig. 1. Bond lengths and angles are given in Table 2. Some bond lengths and angles in the two diastereoisomers, particularly in the oxazolidine rings, are significantly different from each other.

The oxazolidine ring of the (4*R**,5*R**)-isomer takes the half-chair conformation, as in the (4*S**,5*R**)-isomer. However in the (4*R**,5*R**)-isomer, the C(2) and N(3) atoms of the oxazolidine ring are displaced form the plane descried by the remaining atoms, O(1), C(4), and C(5) by −0.21(1) Å and 0.25(1) Å, while in the (4*S**,5*R**)-isomer the C(4) and C(5) atoms lie out of the plane containing the other ring atoms by 0.33(2) Å and −0.22(2) Å, respectively. This discrepancy in the ring puckering might be accounted for by the difference of the configuration at the C(4) atom in the oxazolidine ring.

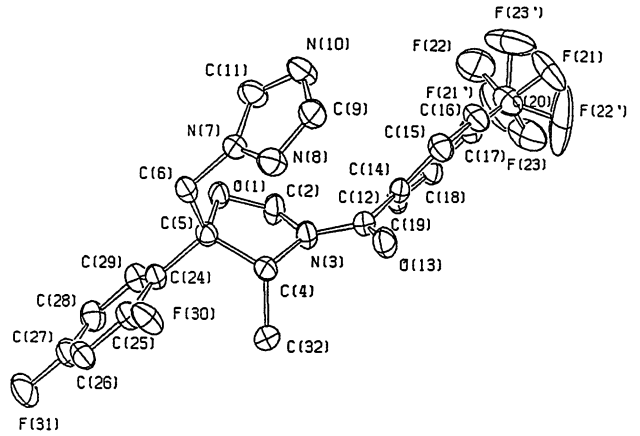
Remarkable differences of some torsion angles are recognized between the two molecules, as shown in Table 3. The C(32) methyl group and the triazolylmethyl group are *trans* in the (4*R**,5*R**)-isomer, contrary to the *cis* configuration in the (4*S**,5*R**)-isomer, resulting in the C(32)–C(4)–C(5)–C(6) torsion angles of 137.2(3)° in the former and −28.1(6)° in the latter. The triazole ring of the (4*R**,5*R**)-isomer is located above the oxazolidine ring with a C(4)–C(5)–C(6)–N(7) torsion angle of 49.4(4)°. The (4*S**,5*R**)-isomer can not take

Table 2. Bond Distances (l/Å) and Angles (θ/°)

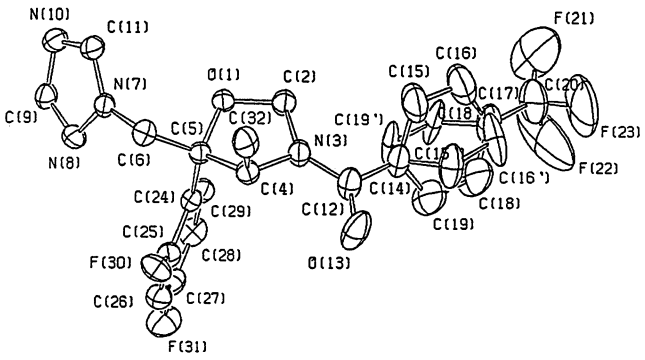
	(4*R**,5*R**)-Isomer	(4*S**,5*R**)-Isomer		(4*R**,5*R**)-Isomer	(4*S**,5*R**)-Isomer
O(1)–C(2)	1.417(5)	1.419(5)	C(4)–C(5)–C(24)	114.1(3)	110.8(4)
O(1)–C(5)	1.435(4)	1.436(5)	C(6)–C(5)–C(24)	109.2(3)	113.0(3)
C(2)–N(3)	1.434(5)	1.461(6)	C(5)–C(6)–N(7)	112.4(3)	113.7(4)
N(3)–C(4)	1.459(5)	1.466(5)	C(6)–N(7)–N(8)	120.3(3)	122.9(4)
N(3)–C(12)	1.370(5)	1.330(6)	C(6)–N(7)–C(11)	129.6(3)	128.4(4)
C(4)–C(5)	1.554(5)	1.549(5)	N(8)–N(7)–C(11)	110.0(3)	108.7(3)
C(4)–C(32)	1.536(5)	1.504(8)	N(7)–N(8)–C(9)	101.6(3)	102.5(4)
C(5)–C(6)	1.519(5)	1.503(7)	N(8)–C(9)–N(10)	115.5(4)	115.5(4)
C(5)–C(24)	1.545(5)	1.530(7)	C(9)–N(10)–C(11)	102.3(3)	101.7(4)
C(6)–N(7)	1.469(5)	1.444(5)	N(7)–C(11)–N(10)	110.6(4)	111.6(4)
N(7)–N(8)	1.346(5)	1.360(5)	N(3)–C(12)–O(13)	120.7(3)	121.2(4)
N(7)–C(11)	1.322(5)	1.326(6)	N(3)–C(12)–C(14)	117.1(3)	119.5(5)
N(8)–C(9)	1.322(5)	1.309(6)	O(13)–C(12)–C(14)	122.2(3)	119.3(5)
C(9)–N(10)	1.333(6)	1.349(7)	C(12)–C(14)–C(15)	116.9(3)	119.9(6)
N(10)–C(11)	1.316(6)	1.320(6)	C(12)–C(14)–C(19)	124.2(3)	119.9(6)
C(12)–O(13)	1.218(5)	1.236(7)	C(15)–C(14)–C(19)	118.8(3)	119.7(6)
C(12)–C(14)	1.489(5)	1.499(7)	C(14)–C(15)–C(16)	120.2(3)	119.0(8)
C(14)–C(15)	1.404(5)	1.36(1)	C(15)–C(16)–C(17)	120.1(4)	119.8(8)
C(14)–C(19)	1.368(5)	1.32(1)	C(16)–C(17)–C(18)	120.6(4)	117.4(7)
C(15)–C(16)	1.376(6)	1.41(1)	C(16)–C(17)–C(20)	121.0(4)	118.8(7)
C(16)–C(17)	1.370(5)	1.39(3)	C(18)–C(17)–C(20)	118.4(3)	123.8(8)
C(17)–C(18)	1.395(5)	1.28(1)	C(17)–C(18)–C(19)	118.6(3)	123(1)
C(17)–C(20)	1.492(6)	1.53(1)	C(14)–C(19)–C(18)	121.7(3)	120(1)
C(18)–C(19)	1.384(6)	1.39(1)	C(17)–C(20)–F(21)	113.6(4)	117.6(8)
C(20)–F(21)	1.273(6)	1.14(2)	C(17)–C(20)–F(22)	109.0(4)	111.2(9)
C(20)–F(22)	1.367(7)	1.23(1)	C(17)–C(20)–F(23)	114.3(4)	105.9(9)
C(20)–F(23)	1.272(6)	1.29(1)	F(21)–C(20)–F(22)	107.9(4)	125(1)
C(24)–C(25)	1.359(5)	1.386(6)	F(21)–C(20)–F(23)	108.8(5)	96.5(8)
C(24)–C(29)	1.375(5)	1.374(7)	F(22)–C(20)–F(23)	102.5(4)	92.8(8)
C(25)–C(26)	1.393(5)	1.370(7)	C(5)–C(24)–C(25)	121.6(3)	120.8(4)
C(25)–F(30)	1.359(4)	1.345(6)	C(5)–C(24)–C(29)	120.9(3)	123.0(4)
C(26)–C(27)	1.348(6)	1.348(8)	C(25)–C(24)–C(29)	117.5(3)	116.1(4)
C(27)–C(28)	1.363(6)	1.361(7)	C(24)–C(25)–C(26)	124.0(4)	124.0(5)
C(27)–F(31)	1.380(5)	1.367(7)	C(24)–C(25)–F(30)	120.0(3)	118.5(4)
C(28)–C(29)	1.407(6)	1.385(8)	C(26)–C(25)–F(30)	116.0(3)	117.5(4)
C(14)–C(15′)		1.29(3)	C(25)–C(26)–C(27)	115.3(4)	116.4(5)
C(14)–C(19′)		1.46(3)	C(26)–C(27)–C(28)	125.4(4)	123.8(5)
C(15′)–C(16′)		1.42(4)	C(26)–C(27)–F(31)	117.2(4)	118.4(5)
C(16′)–C(17)		1.18(4)	C(28)–C(27)–F(31)	117.5(4)	117.8(5)
C(17)–C(18′)		1.44(3)	C(27)–C(28)–C(29)	116.3(4)	117.8(5)
C(18′)–C(19′)		1.39(3)	C(24)–C(29)–C(28)	121.5(4)	121.9(4)
C(20)–F(21′)	1.20(1)		C(12)–C(14)–C(15′)		121(1)
C(20)–F(22′)	1.33(2)		C(12)–C(14)–C(19′)		121.9(9)
C(20)–F(23′)	1.36(1)		C(15′)–C(14)–C(19′)		116(2)
			C(14)–C(15′)–C(16′)		119(3)
C(2)–O(1)–C(5)	109.9(3)	110.8(3)	C(15′)–C(16′)–C(17)		126(3)
O(1)–C(2)–N(3)	104.0(3)	104.6(3)	C(16′)–C(17)–C(18′)		120(2)
C(2)–N(3)–C(4)	109.2(3)	110.0(3)	C(16′)–C(17)–C(20)		129(1)
C(2)–N(3)–C(12)	128.4(3)	127.4(4)	C(18′)–C(17)–C(20)		111(1)
C(4)–N(3)–C(12)	121.5(3)	122.3(4)	C(17)–C(18′)–C(19′)		116(3)
N(3)–C(4)–C(5)	101.4(3)	99.8(3)	C(14)–C(19′)–C(18′)		121(2)
N(3)–C(4)–C(32)	109.5(3)	111.2(3)	C(17)–C(20)–F(21′)	120.8(7)	
C(5)–C(4)–C(32)	115.8(3)	115.7(4)	C(17)–C(20)–F(22′)	110.4(9)	
O(1)–C(5)–C(4)	105.8(3)	103.4(3)	C(17)–C(20)–F(23′)	112.1(7)	
O(1)–C(5)–C(6)	104.7(3)	106.5(4)	F(21′)–C(20)–F(22′)	101(1)	
O(1)–C(5)–C(24)	108.5(3)	109.6(3)	F(21′)–C(20)–F(23′)	104.2(9)	
C(4)–C(5)–C(6)	113.8(3)	113.0(4)	F(22′)–C(20)–F(23′)	107(1)	

such a conformation because of the upward *cis* methyl group attached to C(4) atom.

In order to avoid the repulsion between the O(13) atom and C(32) methyl group attached to the 4-position in the oxazolidine ring, the torsion angle of C(12)–N(3)–C(4)–C(5) to take the value of 143.6(3)° in the (4*R**,5*R**)-isomer, while it is −145.3(4)° in the (4*S**,5*R**)-isomer. Consequently, the directions of the two phenyl groups in these molecules differ from each other, as shown in Fig. 1. It may be concluded that the



(a)



(b)

Fig. 1. ORTEP plots of the two diastereoisomers with thermal ellipsoids at the 30% probability level. (a) (4*R**,5*R**)-isomer. (b) (4*S**,5*R**)-isomer.

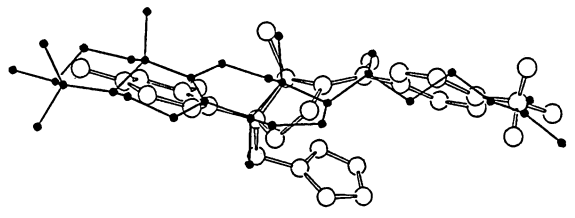


Fig. 2. Comparison of (4*R*,5*R*)-enantiomer (large open circles) and lanosterol (small closed circles).

different configurations at the 4-position in the oxazolidine rings make the two diastereoisomers adopt the different overall structures.

Antifungal azole derivatives interfere with the microsomal P-450-dependent 14α-demethylation of lanosterol, resulting in the accumulation of 14α-methyl sterols and a decreased availability of ergosterol.[10] Oxazolidine derivatives with a (4*R**,5*R**)-configuration show markedly enhanced activities, while (4*S**,5*R**)-diastereomers possess significantly decreased activities. Of the enantiomeric pair, the activity of (4*R*,5*R*)-enantiomer is far more potent than that of (4*S*,5*S*)-enantiomer.[4] Thus, we presumed that only (4*R*,5*R*)-enantiomer, among the diastereoisomers and enantiomers, has a favorable framework to fit in the active site of the enzyme, and using it we carried out a structural comparison with lanosterol. The lanosterol model was built by use of the typical bond lengths and angles and minimized by the force-field calculation of the MM2′ program.[11]

Table 3. Selected Torsion Angles (τ/°)

	(4*R**,5*R**)-Isomer	(4*S**,5*R**)-Isomer
C(5)–O(1)–C(2)–N(3)	−25.1(4)	−9.3(5)
C(2)–O(1)–C(5)–C(4)	9.2(4)	27.1(5)
O(1)–C(2)–N(3)–C(4)	32.5(4)	−13.8(5)
C(2)–N(3)–C(4)–C(5)	−26.0(4)	28.8(5)
N(3)–C(4)–C(5)–O(1)	10.0(4)	−32.8(4)
C(12)–N(3)–C(4)–C(5)	143.6(3)	−145.3(4)
C(4)–N(3)–C(12)–C(14)	179.7(3)	−178.9(4)
N(3)–C(4)–C(5)–C(6)	−104.4(3)	−147.5(3)
N(3)–C(4)–C(5)–C(24)	129.3(3)	84.6(4)
C(32)–C(4)–C(5)–O(1)	−108.4(3)	86.6(4)
C(32)–C(4)–C(5)–C(6)	137.2(3)	−28.1(6)
C(4)–C(5)–C(6)–N(7)	49.4(4)	169.4(3)
C(4)–C(5)–C(24)–C(25)	69.8(5)	66.3(5)
C(5)–C(6)–N(7)–N(8)	−92.1(4)	77.0(5)

Computer graphics showed how (4*R*,5*R*)-enantiomer can be superposed on lanosterol (Fig. 2). The 5β-difluorophenyl group and the oxazolidine ring 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 as the 13β-methyl and 14α-methyl group of lanosterol, respectively. The *N*-trifluoromethylbenzoyl group might correspond to the 17-alkyl side chain of lanosterol. The 4β-methyl group is expected to play an important role in antifungal potency, since a 4-demethyloxazolidine analogue exhibits an intermediate activity between (4*R**,5*R**)- and (4*S**,5*R**)-diastereoisomers.[4]

References

1) Part I: T. Hata, H. Hanzawa, T. Konosu, and S. Oida, *Anal. Sci.*, **6**, 789 (1990).

2) Y. Aoyama, Y. Yoshida, and R. Sato, *J. Biol. Chem.*, **259**, 1661 (1984).

3) P. Gadher, E. I. Mercer, B. C. Baldwin, and T. E. Wiggins, *Pestic. Biochem. Physiol.*, **19**, 1 (1983).

4) T. Konosu, Y. Tajima, N. Takeda, T. Miyaoka, M. Kasahara, H. Yasuda, and S. Oida, *Chem. Pharm. Bull.*, **38**, 2476 (1990).

5) P. Main, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, and M. M. Woolfson, "MULTAN 78. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data," Univs. of York,

England and Louvain, Belgium (1978).
6) "International Tables for X-Ray Crystallography," Kynoh Press, Birmingham (1974), Vol. IV.
7) Y. Koyama and K. Okada, *Acta Crystallogr., Sect. A,* **31**, S18 (1975).
8) W. C. Hamilton, *Acta Crystallogr.,* **18**, 502 (1965).
9) Lists of structure factors, anisotropic thermal parameters, and atomic parameters for hydrogen atoms have been deposited as Document No. 8961 at the Office of the Editor of Bull. Chem. Soc. Jpn.
10) H. Van den Bossche, G. Willemsens, W. Cools, W. F. J. Lauwers, and L. Le Jeune, *Chem.-Biol. Interact.,* **21**, 59 (1978).
11) C. Jaime and E. Ōsawa, *Tetrahedron,* **39**, 2769 (1983).