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Synthesis and Antifungal Activities of Some Thiolane-Triazole Derivatives

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As part of our search for active agents against systemic fungal infections, a new series of triazole compounds with a thiolane ring was synthesized. Their antifungal activities were investigated *in vitro* and *in vivo*. Some of these thiolane-triazoles showed promising activity, comparable to that of ketoconazole, against a mouse systemic *Candida albicans* infection, after oral or parenteral dosing.

Keywords antifungal activity; 1*H*-1,2,4-triazole; thiolane; oral activity; synthesis; stereoisomer

Systemic fungal infection in man has been increasing. Patients who receive cancer chemotherapy or an organ transplant are immunosuppressed to some extent and are particularly susceptible to these opportunistic infections.[1] The azole derivative ketoconazole[2] (**1**) has been used as an orally active antifungal agent in Europe and the United States, but it has the drawback of side effects, including hepatotoxicity.[3] A new antifungal azole, fluconazole[4] (**2**), has recently been launched in the market. Fluconazole is orally effective and is claimed to have lower toxicity and more potent activity than ketoconazole. Another orally active azole, SM-8668[5] (**3**), from Sumitomo Pharmaceuticals is under clinical trial in the United States. In animal experiments, SM-8668 was demonstrated to have higher potency against a wide range of mycoses than fluconazole.[6]

In order to seek a safer drug with greater efficacy against an increasing number of systemic fungal infections, a research program was started in our laboratories. We were interested in cyclic analogs of SM-8668 (**3**) as represented by general formula **4**, in which two methyl groups of **3** are connected by a methylene carbon to form the thiolane ring. These thiolane-triazole compounds **4** were synthesized with 4-chloro- or 2,4-dichloro-phenyl substituents (X=4-Cl or 2,4-Cl_2) instead of the 2,4-difluorophenyl moiety, because replacement of the fluorine atoms in SM-8668 (**3**) with chlorine atom(s) did not appear to bring about a significant alteration in antifungal activity.[5]

The key intermediate **8** for the synthesis of **4** was prepared from the chloroketone **5** in three steps as shown in Chart 2. The ketone **5** was treated with 3-mercapto-1-propanol in the presence of sodium hydride in *N*,*N*-dimethylformamide (DMF) to give the hydroxyketone **6** in quantitative yield, and this was sulfonylated to give the mesylate **7**. Cyclization of **7** to **8** was accomplished by treatment with a base such as lithium diisopropylamide or lithium hexamethyldisilazide in tetrahydrofuran (THF) at 50—55 °C. A minor cyclization product **9** was obtained in *ca.* 10% yield.

Methylenation of **8a** with trimethylsulfoxonium iodide and sodium hydride in dimethyl sulfoxide[7] (DMSO) gave a 2 : 1 diastereomeric mixture of epoxides, **10a** and **11a**, which were ring-opened by sodium triazolide in DMF at 95 °C to afford a major alcohol **12a** and a minor alcohol **13a**. The yields of **12a** and **13a** from the ketone **8a**, after separation by column chromatography, were 25% and 13%, respec-

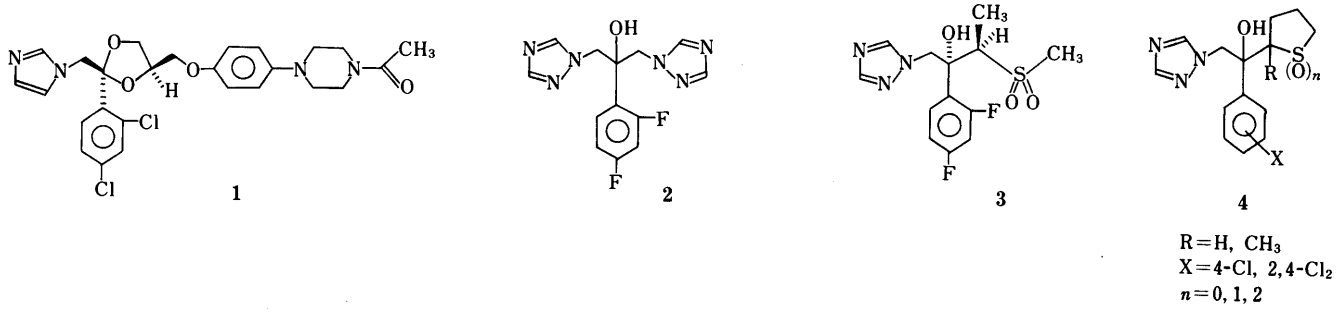


Chart 1

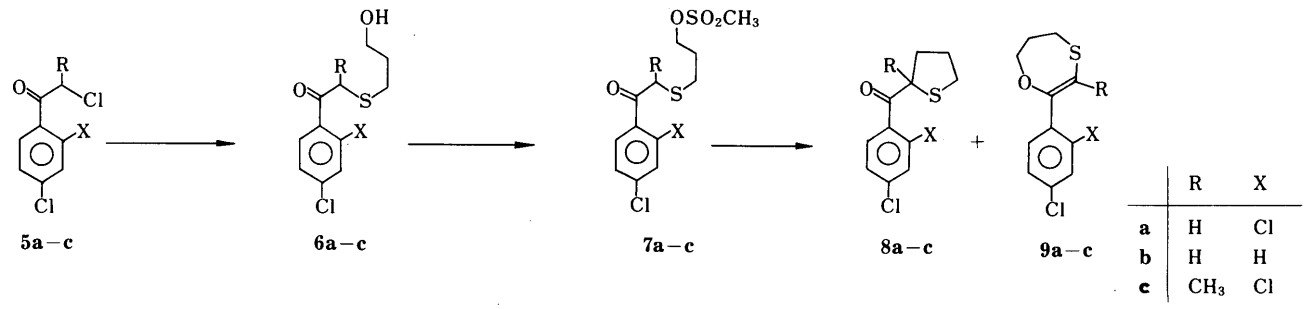
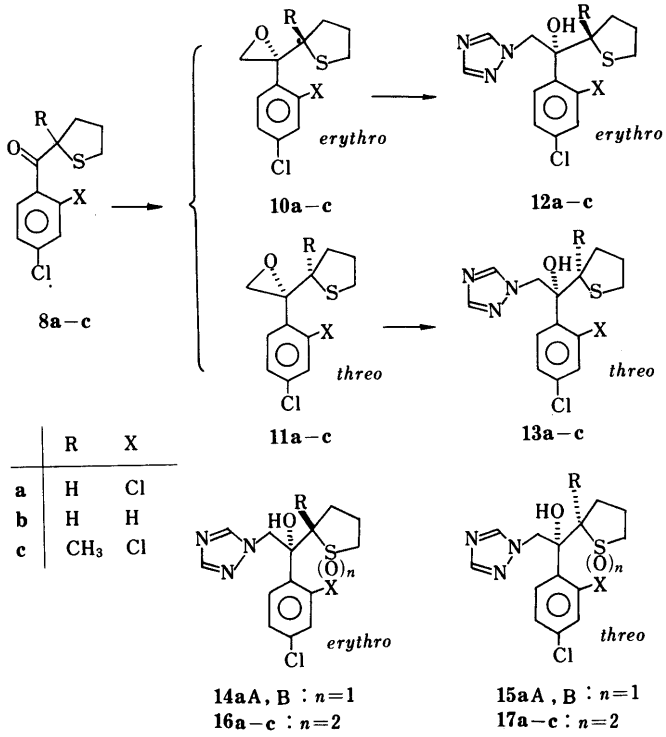


Chart 2

tively. Stereoselective methylenation of **8a** was attained by reaction with diiodomethane and *n*-butyllithium[8] in THF at −78 °C to give the *erythro* isomer **10a** from which the alcohol **12a** was obtained as a sole product by reaction with sodium triazolide as described above. The stereochemistry of the triazole alcohols, **12a** and **13a**, was inferred based on the reaction of the ketone **8a** and methylenation reagent, in which the incoming nucleophile attacks the less hindered face of the carbonyl group of **8a** as illustrated by the Felkin–Anh model[9] **18** to give the *erythro* epoxide **10a** as a major product, a precursor to the major alcohol **12a**.



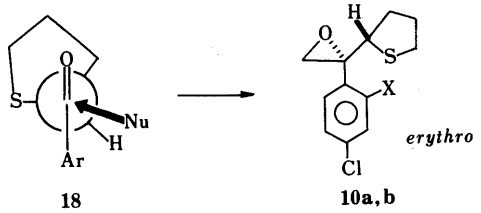
	R	X
a	H	Cl
b	H	H
c	CH_3	Cl

Oxidation of the thiolane alcohol **12a** with 1 eq of *meta*-chloroperbenzoic acid (MCPBA) afforded an isomeric mixture of two sulfoxides which could be separated to the less polar isomer **14aA** (75% yield) and the polar isomer **14aB** (19% yield). Both sulfoxides, **14aA** and **14aB**, were further oxidized to the sulfone **16a**. The minor thiolane alcohol **13a** was similarly oxidized with MCPBA into two isomeric sulfoxides, the less polar one **15aA** (52% yield) and the more polar one **15aB** (32% yield). They were further oxidized to the sulfone **17a**.

The 4-chlorophenyl ketone **8b** was also transformed into the thiolane derivatives, **12b** and **13b**, and their sulfones, **16b** and **17b**, *via* a reaction sequence similar to that described above.

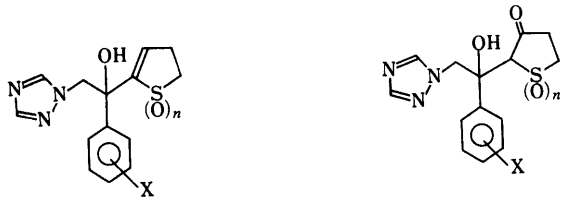
The methyl analog **8c** resisted methylenation with trimethylsulfoxonium iodide and sodium hydride, but it reacted smoothly with trimethylsulfonium methyl sulfate[10] and sodium hydride in DMSO to give a 2:1 mixture of epoxides, **10c** and **11c**, in 75% yield. Treatment of this mixture with sodium triazolide in the usual manner produced an inseparable mixture of the alcohols, **12c** and **13c**. Oxidation with 2 eq of MCPBA gave a 2:1 mixture of the sulfones, **16c** and **17c**, which were easily separated by chromatography. The relative stereochemistry of these sulfones was not determined.

The thiolane-triazole **4** was next converted to its dehydro and oxo analogs as represented by general formulae **19** and **20**, respectively. The syntheses of these compounds were performed as follows.



18 10a,b

Chart 3



19 20

Chart 4

The thiolane **8a** was oxidized with 1 eq of MCPBA to give the sulfoxide **21**, which was then dehydrated with trifluoroacetic anhydride and 2,6-lutidine[11] to give the conjugated ketone **22** in quantitative yield. Treatment of **22** with diiodomethane and *n*-butyllithium gave the epoxide **23** in 53% yield. Ring-opening reaction with sodium triazolide in the usual manner provided the triazole alcohol **24** in 60% yield. Oxidation of **24** with 1 eq of MCPBA afforded a mixture of sulfoxides **25**, and further oxidation gave the sulfone **26**.

As for the oxo analog **20**, we aimed at synthesizing a diastereomeric pair of 2,4-dichlorophenyl derivatives, **36** and **37**. The key intermediate **30** for the synthesis was obtained from the chloroketone **5a** in the following way. Treatment of **5a** with 3-mercaptopropionic acid in the

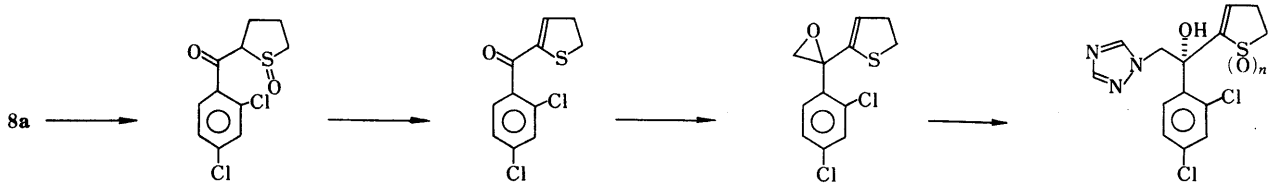


Chart 5

TABLE I. The *in Vitro* Antifungal Activities of Thiolane-Triazole Derivatives

Compound[a]	Stereochemistry	MIC[c] (μg/ml)							
		C.a. (1)	*C.a.* (2)	*C.n.*	*M.m.*	*A.f.*	*M.g.*	*T.m.*	*T.r.*
12a	*erythro*	>50	>50	1.5	12.5	12.5	50	6.2	0.4
12b	*erythro*	>50	>50	12.5	>50	>50	>50	25	0.8
13a	*threo*	>50	>50	6.2	12.5	6.2	6.2	3.1	0.4
13b	*threo*	>50	>50	12.5	50	50	50	25	6.2
12c+**13c**[b] (2:1)	*erythro* +*threo*	50	50	3.1	3.1	12.5	25	3.1	0.1
14aA	*erythro*	>50	>50	>50	>50	>50	>50	>50	>50
15aA	*threo*	>50	>50	>50	>50	>50	>50	>50	50
15aB	*threo*	>50	>50	>50	>50	>50	>50	>50	>50
16a	*erythro*	>50	>50	>50	>50	>50	>50	>50	>50
16b	*erythro*	>50	>50	>50	>50	>50	>50	>50	>50
17a	*threo*	>50	>50	>50	>50	>50	>50	>50	12.5
17b	*threo*	>50	>50	>50	>50	>50	>50	>50	25
24	—	>50	>50	25	25	50	50	6.2	0.8
25	—	>50	>50	>50	>50	>50	>50	>50	>50
26	—	>50	>50	>50	>50	>50	>50	>50	50
34	*erythro*	>50	>50	>50	1.5	25	6.2	12.5	3.1
35	*threo*	>50	>50	>50	>50	>50	>50	>50	50
36	*erythro*	>50	>50	50	1.5	25	25	6.2	0.4
37	*threo*	>50	>50	50	3.1	50	50	12.5	1.5
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) Oxalic acid salts of the thiolane derivatives except for **17a** were prepared and tested. *b*) Stereochemistries were only tentatively assigned, and may be interchanged. *c*) 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 neofermans* 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.

presence of 2 eq of sodium hydride gave the acid **27**, which was esterified to the methyl ester **28** in 89% yield over two steps. Cyclization of **28** with sodium methoxide in boiling methanol afforded the diketone **29** in 56% yield. Monoacetalization of **29** to **30** with ethylene glycol and *p*-toluenesulfonic acid in benzene was accompanied with the ring-opened byproduct **31**. To avoid substantial formation of **31**, the reaction was stopped before the starting diketone **29** was consumed. The ketone **30** was subjected to methylenation with diiodomethane and *n*-butyllithium to yield a mixture of two isomeric epoxides which were separated by chromatography to give a major crystalline isomer **32** (53% yield) and a minor oily isomer **33** (8% yield). The stereochemistry of these epoxides was not determined, but an *erythro* structure is likely for the major isomer **32** based on the same considerations as in the methylenation reaction of the ketone **8a**. The epoxide **32** was transformed into the azole alcohol **34** in the usual manner, and deprotection under acidic conditions afforded the ketoalcohol **36** in high yield. Oxidation of **36** with MCPBA gave the labile sulfoxide **38**, which easily underwent retroaldol reaction in contact with a weak base such as sodium bicarbonate to give a degradation product **39**. The minor epoxide **33** was also led to the oxothiolane derivative **37** *via* **35** in a similar manner.

The *in vitro* antifungal activities of these thiolane-triazoles on Sabouraud dextrose agar media are presented in Table I. The minimum inhibitory concentration (MIC) values (in μg/ml) against *Candida albicans*, *Cryptococcus neoformans*, *Mucor mucedo*, *Aspergillus fumigatus*, *Microsporum gypseum*, *Trichophyton mentagrophytes* and *T. rubrum*, in comparison with ketoconazole and fluconazole, are given. Most of the compounds synthesized were inactive against *C. albicans* species at a concentration of 50 μg/ml. Only a mixture of the methylated thiolanes (**12c** and **13c**) was active against *C. albicans* at 50 μg/ml. This mixture was also found to be the most potent (*in vitro*) of the thiolane derivatives against most of the yeast and fungi tested. Comparable MIC values were obtained for ketoconazole as shown in the table. In contrast, fluconazole exhibited almost no antifungal activities against these microorganisms at a concentration of 50 μg/ml on this agar media. Sulfides (**12a—c**, **13a—c**, **34**, **36** and **37**) were active against most of the fungi, whereas sulfoxides (**14a**, **15a** and **25**) and sulfones (**16a,b**, **17a,b** and **26**) were mostly inactive. There appeared to be no significant difference in activity between *erythro* and *threo* isomers (**12a**/**13a**; **12b**/**13b**), though the *erythro* isomer **34** of the protected oxothiolane showed higher activity than the *threo* isomer **35**. The dehydrothiolane derivative **24** was less active than the corresponding thiolanes (**12a** and **13a**) or oxothiolane **36**. *In vitro* activities of 4-chlorophenyl derivatives (**12b** and **13b**) were significantly decreased compared with the corresponding 2,4-dichlorophenyl analogs (**12a** and **13a**).

As noted above, the *in vitro* studies of the thiolane-triazoles demonstrated that they were mostly inactive against *C. albicans* on the agar media employed. *In vitro* activity among azoles, however, is known to be unreliable in predicting *in vivo* activity.[12] In the hope of predicting activity in humans, the thiolane-triazoles were subjected to studies in animal models of fungal infection.

The results of *in vivo* studies in mice with 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

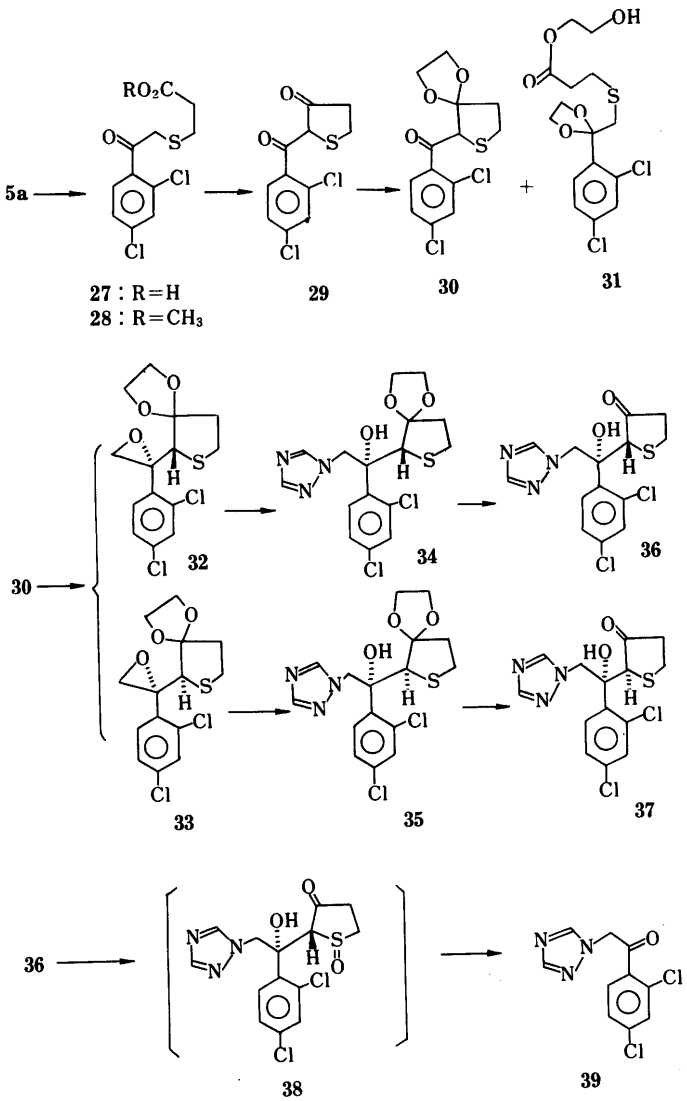


Chart 6

thiolane-triazoles were administered orally (*p.o.*) or intraperitoneally (i.p.) at 1, 4, 24 h post infection. Antifungal efficacy of the compounds was compared with that of ketoconazole. All control mice died within 2 d after infection, whereas most mice treated *p.o.* or i.p. with azoles (20 mg/kg/dose) survived appreciably longer. Sulfides (**12a** and **13a**) as well as sulfoxides (**15aA** and **15aB**) and sulfones (**16a** and **17a**) were shown to have good activity, comparable to that of ketoconazole. The methyl analog (isomeric mixture of **12c** and **13c**) was also active *in vivo* and the sulfone **17c** (one isomer derived from the above mixture) retained *in vivo* potency, whereas the isomeric sulfone **16c** showed considerably decreased activity. 4-Chlorophenyl derivatives (**12b**, **13b**, **16b** and **17b**) were less active compared with the corresponding 2,4-dichlorophenyl analogs (**12a**, **13a**, **16a** and **17a**). Dehydrothiolane derivatives (**24**, **25**, and **26**) and the oxothiolane **36** exhibited substantially decreased *in vivo* activity.

After the completion of this work, it was learned that very recently Livermore *et al.* announced the synthesis of a novel series of azole antifungal agents,[13] several of which overlapped to some extent in chemistry with the thiolane-triazole compounds described in this paper.

Table II. Comparative Antifungal Efficacy of Thiolane-Triazole Derivatives against Systemic Infection of *Candida albicans*[a]

Compound[b]	Dose (mg/kg)	Route	% survival rate on day					Mean survival days
			2	5	9	13	21	
12a	20	*p.o.*	100	100	40	0		8.4
		i.p.	100	100	20	10	0	8.5
12b	20	*p.o.*	50	40	0			3.6
		i.p.	60	30	0			3.4
13a	20	*p.o.*	100	100	40	10	0	9.6
		i.p.	100	90	10	0		6.7
13b	20	*p.o.*	100	70	30	10	0	7.7
		i.p.	100	70	20	0		7.0
12c + 13c[c]	20	i.p.	100	60	40	10	0	7.9
14aA	20	*p.o.*	70	40	10	0		4.4
		i.p.	80	60	10	0		5.2
15aA	20	*p.o.*	100	100	40	10	0	8.8
		i.p.	100	100	60	50	20	12.3
15aB	20	*p.o.*	100	100	70	40	20	12.7
		i.p.	100	100	30	10	0	8.2
16a	20	*p.o.*	100	70	50	50	30	11.0
		i.p.	70	40	20	20	0	5.2
16b	20	*p.o.*	40	30	0			2.4
		i.p.	50	10	0			2.3
16c[c]	20	i.p.	30	30	0			2.0
17a	20	*p.o.*	100	100	50	30	0	9.8
		i.p.	100	100	70	40	30	13.1
17b	20	*p.o.*	70	40	30	0		5.7
		i.p.	90	30	20	10	0	5.8
17c[c]	20	i.p.	100	100	10	10	0	8.0
24	20	*p.o.*	40	40	30	20	0	4.9
		i.p.	80	50	10	0		5.6
25	20	*p.o.*	60	40	10	0		4.1
		i.p.	30	30	0			2.0
26	20	*p.o.*	20	0				0.9
		i.p.	0					0.2
34	20	*p.o.*	30	10	0			1.7
		i.p.	20	0				1.2
36	20	*p.o.*	40	30	10	0		3.0
		i.p.	50	40	20	10	0	4.7
Ketoconazole	20	*p.o.*	100	70	40	20	0	8.2
		i.p.	100	100	70	40	20	13.0
Control (no drug)			0					0.5

a) *In vivo* activity was determined in mice (each group consisted of ten mice) 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, 24 h post infection. The mean survival days of mice were calculated based on termination of the experiment 21 d after infection.

b) Oxalic acid salts of the thiolane derivatives except for **16c**, **17a** and **17c** were prepared and tested. *c*) Stereochemistries (*erythro* or *threo*) were only tentatively assigned, and may be interchanged.

Experimental

Melting points are not corrected. Infrared spectra (IR) were recorded on a JASCO A-2 spectrometer, proton nuclear magnetic resonance spectra (^{1}H-NMR) on a Varian A-60 spectrometer using tetramethylsilane as the internal standard and mass spectra (MS) on a JEOL JMS-D300 spectrometer. Thin-layer chromatography (TLC) was performed on TLC plates, Silica gel $60F_{254}$ precoated, layer thickness 0.25 mm (E. Merck) and spots were made visible by ultraviolet (UV)-irradiation or by spraying with vanadic acid–sulfuric acid followed by heating. Chromatography columns were prepared with silica gel (60—110 mesh, Kanto Chemical Co., Inc.) and preparative TLC plates were provided with Silica gel $60F_{254}$, layer thickness 2 mm (E. Merck). The amount of silica gel used and the developing solvents are shown in parenthesis. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; br, broad.

2-(3-Hydroxypropylthio)-2′,4′-dichloroacetophenone (6a) 3-Mercapto-1-propanol (4.34 g, 47.2 mmol) was added to a stirred mixture of NaH (55% mineral oil dispersion, 1.96 g, 45 mmol, washed with hexane) and DMF (80 ml) over a period of 5 min at 0 °C. The mixture was stirred for 15 min, then 2,2′,4′-trichloroacetophenone (**5a**) (10.1 g, 45 mmol) was

added. The reaction mixture was stirred at 0 °C for 20 min, diluted with AcOEt and washed with water and brine. Removal of the solvent *in vacuo* gave **6a** (12.44 g, 99%) as an oil, which was used for the next reaction without further purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650, 1688. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (2H, m), 2.65 (2H, t, J=7 Hz), 3.67 (2H, t, J=5.5 Hz), 3.77 (2H, s), 7.30 (1H, dd, J=8.5, 2 Hz), 7.45 (1H, d, J=2 Hz), 7.55 (1H, d, J=8.5 Hz). MS *m/z*: 278 (M^+), 243, 173. High-resolution MS (HRMS) Calcd for $C_{11}H_{12}Cl_2O_2S$: 277.9235. Found: 277.9239.

2-(3-Hydroxypropylthio)-4′-chloroacetophenone (6b) Following a procedure similar to that described above, **6b** was prepared as an oil from 2,4′-dichloroacetophenone (**5b**) and 3-mercapto-1-propanol in quantitative yield. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650, 1690. ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.1 (2H, m), 2.5—2.9 (3H, m), 3.68 (2H, t, J=6 Hz), 7.44 (2H, d, J=9 Hz), 7.94 (2H, d, J=9 Hz). MS *m/z*: 244 (M^+), 139. HRMS Calcd for $C_{11}H_{13}ClO_2S$: 243.9625. Found: 243.9620.

2-(3-Hydroxypropylthio)-2′,4′-dichloropropiophenone (6c) Following a procedure similar to that described for the preparation of **5a**, **6c** was prepared as an oil from 2,2′,4′-trichloropropiophenone (**5c**) (provided by Friedel–Crafts reaction of 1,3-dichlorobenzene and 2-chloropropionyl chloride in 87% yield) and 3-mercapto-1-propanol in quantitative yield. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650, 1690. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (3H, d, J=7 Hz), 1.5—2.0 (2H, m), 2.3—2.7 (3H, m), 3.65 (2H, t, J=6 Hz), 7.2—7.6 (3H, m). MS *m/z*: 292 (M^+), 173. HRMS Calcd for $C_{12}H_{14}Cl_2O_2S$: 291.9392. Found: 291.9383.

2-[3-(Methanesulfonyloxy)propylthio]-2′,4′-dichloroacetophenone (7a) Methanesulfonyl chloride (6.10 g, 53.3 mmol) was added dropwise to a stirred solution of **6a** (12.4 g, 44.5 mmol) and triethylamine (5.85 g, 58 mmol) in CH_2Cl_2 (80 ml) at −15 °C. The mixture was stirred for 5 min at the same temperature and then washed with brine. After evaporation of the solvent, the residue was chromatographed on silica gel (150 g, AcOEt : cyclohexane = 1 : 3, v/v) to yield **7a** (11.3 g, 71%) as an oil. IR $\nu_{max}^{CHCl_3}$ 1688 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (2H, m), 2.68 (2H, t-like, J=7 Hz), 3.04 (3H, s), 3.83 (2H, s), 4.34 (2H, t, J=6 Hz), 7.30 (1H, dd, J=8.5, 2 Hz), 7.43 (1H, d, J=2 Hz), 7.55 (1H, d, J=8.5 Hz). MS *m/z*: 356 (M^+), 260, 221, 173. HRMS Calcd for $C_{12}H_{14}Cl_2O_4S_2$: 355.8311. Found: 355.8308.

2-[3-(Methanesulfonyloxy)propylthio]-4′-chloroacetophenone (7b) The hydroxyketone **6b** was mesylated as described above to give **7b** as an oil in 82% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.3 (2H, m), 2.67 (2H, t-like, J=7 Hz), 2.97 (3H, s), 3.76 (2H, s), 4.29 (2H, t, J=6 Hz), 7.44 (2H, d, J=9 Hz), 7.93 (2H, d, J=9 Hz). MS *m/z*: 322 (M^+), 226, 139. HRMS Calcd for $C_{12}H_{15}ClO_4S_2$: 321.8700. Found: 321.8696.

2-[3-(Methanesulfonyloxy)propylthio]-2′,4′-dichloropropiophenone (7c) The hydroxyketone **6c** was mesylated as described above to give **7c** as an oil in 74% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, d, J=7 Hz), 1.7—2.2 (2H, m), 2.4—2.8 (2H, m), 2.98 (3H, s), 3.13 (1H, q, J=7 Hz), 3.24 (2H, t, J=6 Hz), 7.2—7.6 (3H, m). MS *m/z*: 370 (M^+), 173. HRMS Calcd for $C_{13}H_{16}Cl_2O_4S_2$: 369.8467. Found: 369.8467.

2,4-Dichlorophenyl 2-Thiolanyl Ketone (8a) A 1.5 M *n*-butyllithium hexane solution (13.3 ml, 20.0 mmol) was added to a solution of hexamethyldisilazane (3.38 g, 21.0 mmol) in THF (26 ml) at −20 °C and the mixture was stirred at 0 °C for 10 min. To this solution was added a solution of **7a** (6.50 g, 18.2 mmol) in THF (60 ml) and the whole was heated at 50—55 °C for 30 min. The mixture was cooled and then partitioned between AcOEt and water. The organic layer was collected, washed with brine and dried. After evaporation of the solvent, the residue was chromatographed on silica gel (60 g, 5% AcOEt–cyclohexane) to give a 7 : 1 mixture of **8a** and **9a** (3.66 g, 77%) as an oil whose ratio was determined by ^{1}H-NMR analysis. This mixture was used for the next reaction without further purification. Pure samples of **8a** and **9a** were obtained as oils by chromatography over a Lobar column-A (E. Merck) using 1% AcOEt–hexane as the eluent. IR $\nu_{max}^{CHCl_3}$ cm^{-1}; for **8a**: 1698, 1583; for **9a**: 1581, 1468. ^{1}H-NMR ($CDCl_3$) δ; for **8a**: 1.8—2.8 (4H, m), 2.89 (2H, t, J=6 Hz), 4.65 (1H, m), 7.15—7.55 (3H, m); for **9a**: 2.21 (2H, quintet, J=6 Hz), 3.22 (2H, t, J=6 Hz), 4.63 (2H, t, J=6 Hz), 5.38 (1H, s), 7.1—7.4 (3H, m). MS *m/z*; for **8a**: 260 (M^+), 225, 173, 87.

4-Chlorophenyl 2-Thiolanyl Ketone (8b) A 1.5 M *n*-butyllithium hexane solution (9.0 ml, 13.5 mmol) was added to a solution of hexamethyldisilazane (2.29 g, 14.2 mmol) in THF (18 ml) at −20 °C and the mixture was stirred at 0 °C for 20 min. To this solution was added a solution of **7b** (3.95 g, 12.3 mmol) in THF (40 ml) and the whole was heated at 50—55 °C for 30 min. The mixture was cooled and partitioned between AcOEt and water. The organic layer was collected, washed with brine and dried. After evaporation of the solvent, the rsidue was chromatographed on silica gel (50 g, 1% AcOEt–cyclohexane) to give a crystalline mass (1.93 g), which was recrystallized from AcOEt–hexane to afford **8b** (1.75 g, 63%), mp 84—85 °C. *Anal.* Calcd for $C_{11}H_{11}ClOS$: C, 58.27; H, 4.89; S, 14.14. Found: C, 58.21; H, 4.85; S, 14.03. IR $\nu_{max}^{CHCl_3}$ 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.8—3.8 (4H, m), 2.91 (2H, t-like, J=6 Hz), 4.65 (1H, m), 7.44 (2H, d, J=9 Hz), 7.90 (2H, d, J=9 Hz). MS *m/z*: 226 (M^+), 139, 87.

2,4-Dichlorophenyl 2-Methylthiolan-2-yl Ketone (8c) A 1.5 M *n*-butyllithium hexane solution (5.18 ml, 7.77 mmol) was added to a solution of diisopropylamine (855 mg, 8.47 mmol) in THF (20 ml) at −20 °C and the mixture was stirred at 0 °C for 10 min. To this solution was added a solution of **7c** (2.62 g, 7.06 mmol) in THF (10 ml) and the whole was heated at 50—55 °C for 30 min. The mixture was cooled and partitioned between AcOEt and water. The organic layer was collected, washed with brine and dried. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (15 g, AcOEt : hexane = 1 : 3, v/v) to afford **8c** (1.06 g, 52%) as an oil. IR $\nu_{max}^{CHCl_3}$ 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, s), 1.8—3.3 (6H, m), 7.23 (1H, dd, J=9, 2 Hz), 7.39 (1H, d, J=2 Hz), 7.65 (1H, d, J=9 Hz). The ^{1}H-NMR spectrum showed this oil to be contaminated with the byproduct **9c** (*ca.* one-sixth of the product), whose characteristic signals appeared at δ 1.60 (s, CH_3–$\overset{\|}{C}$–S) and 4.52 (t, J=6 Hz, O–CH_2–CH_2). This product was used for the next reaction without further purification.

2-(2,4-Dichlorophenyl)-2-(2-thiolanyl)oxirane (10a and 11a) i) Sodium hydride (55% mineral oil dispersion, 467 mg, 10.7 mmol, washed with hexane) was dissolved in DMSO (20 ml) at 60 °C for 50 min. After cooling of the mixture, trimethylsulfoxonium iodide (2.52 g, 11.5 mmol) was added, and the whole was stirred for 15 min at room temperature. A solution of **8a** (2.00 g, 7.65 mmol) in DMSO (5 ml) was added and the whole was stirred at room temperature overnight. The mixture was partitioned between AcOEt and water. The organic layer was collected, washed and dried. After evaporation of the solvent, the residue was chromatographed on silica gel (15 g, 5% AcOEt–hexane) to give a mixture of **10a** and **11a** (1.63 g, 77%) as an oil, which was shown to be contaminated by a small amount of **9a** by ^{1}H-NMR. The ratio of **10a** and **11a** in the mixture was determined by ^{1}H-NMR to be *ca.* 2 : 1. An attempt to separate **10a** and **11a** using a Lobar column resulted in the isomerization of both epoxides to aldehyde products [^{1}H-NMR ($CDCl_3$) δ: 9.70 and 9.75 (1 : 1, s each)] and only a small amount of the less polar isomer **11a** could be obtained. ^{1}H-NMR ($CDCl_3$) δ (selected absorptions); for **10a**: 2.82 (1H, d, J=5 Hz), 3.29 (1H, d, J=5 Hz); for **11a**: 2.77 (1H, d, J=5 Hz), 2.97 (1H, d, J=5 Hz).

ii) A 1.5 M *n*-butyllithium hexane solution (0.60 ml, 0.90 mmol) was added dropwise to a solution of **8a** (166 mg, 0.64 mmol) and diiodomethane (212 mg, 0.80 mmol) in THF (2 ml) at −78 °C in 1 min with stirring. The mixture was stirred for 10 min and then partitioned between benzene and water. The organic layer was collected and evaporated *in vacuo*. The crude product was purified by chromatography on silica gel as described above to yield **10a** (96 mg, 55%) as an oil, and did not contain **11a** as judged by ^{1}H-NMR and TLC.

2-(4-Chlorophenyl)-2-(2-thiolanyl)oxirane (10b and 11b) Following a procedure similar to that described above, the reaction of **9b** and trimethylsulfoxonium iodide in the presence of a base afforded a mixture of **10b** and **11b** as an oil in 80% yield. The ratio of **10b** and **11b** in the mixture was determined by ^{1}H-NMR to be *ca.* 3 : 2. ^{1}H-NMR ($CDCl_3$) δ (selected absorptions); for **10b**: 2.73 (1H, d, J=5 Hz), 3.13 (1H, d, J=5 Hz), 3.87 (1H, t-like, J=7 Hz); for **11b**: 2.65 (1H, d, J=5 Hz), 3.18 (1H, d, J=5 Hz), 4.02 (1H, m).

2-(2,4-Dichlorophenyl)-2-(2-methylthiolan-2-yl)oxirane (10c and 11c) A solution of sodium methylsulfinylmethylide was prepared by dissolving NaH (55 mineral oil dispersion, 454 mg, 10.4 mmol, washed with hexane) in DMSO (18 ml) as described above. To this was added trimethylsulfonium methyl sulfate (1.96 g, 10.4 mmol) and then a solution of **8c** (1.01 g, 3.47 mmol) in DMSO (3 ml). The mixture was stirred at room temperature for 30 min and then diluted with benzene and washed with water and brine. Evaporation of the solvent *in vacuo* afforded a mixture of **10c** and **11c** (860 mg, 75%) as an oil, which contained a small amount of **9c** and was used for the next reaction without further purification. The ratio of these two epoxides were assessed by ^{1}H-NMR as 2 : 1, though assignment of *threo*/*erythro* stereochemistry to these epoxides could not be made. ^{1}H-NMR ($CDCl_3$) δ (selected absorptions); for the major epoxide: 1.50 (3H, s), 2.89 (1H, d, J=5 Hz), 3.45 (1H, d, J=5 Hz), 7.74 (1H, d, J=9 Hz); for the minor epoxide: 1.47 (3H, s), 2.85 (1H, d, J=5 Hz), 3.42 (1H, d, J=5 Hz), 7.70 (1H, d, J=9 Hz).

1-(2,4-Dichlorophenyl)-1-(2-thiolanyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol (12a and 13a) i) The diastereomeric 2 : 1 mixture of **10a** and **11a** (1.63 g, 5.93 mmol) obtained above was added to a solution of sodium triazolide in

DMF, prepared by mixing NaH (55% mineral oil dispersion, 517 mg, 11.8 mmol) and 1*H*-1,2,4-triazole (1.00 g, 14.5 mmol) in DMF (25 ml) at 0 °C, and the reaction mixture was stirred at 95 °C for 2 h. The cooled mixture was diluted with benzene–AcOEt (1 : 1, v/v) and washed with water and brine. After removal of the solvent, the residue was chromatographed on silica gel (20 g, AcOEt : hexane = 1 : 2—3 : 1, v/v) to give **12a** (650 mg, 25% over two steps from **8a**), mp 146—149 °C (recrystallized from AcOEt–hexane), and the less polar isomer **13a** (346 mg, 13% over two steps from **8a**), mp 146—148 °C (recrystallized from AcOEt–hexane). *Anal.* Calcd for $C_{14}H_{15}Cl_2N_3OS$: C, 48.84; H, 4.39; N, 12.21. Found for **12a**: C, 48.90; H, 4.34; N, 12.12. Found for **13a**: C, 48.72; H, 4.31; N, 11.98. IR $\nu_{max}^{CHCl_3}$ cm^{-1}; for **12a**: 3420; for **13a**: 3405. ^{1}H-NMR ($CDCl_3$) δ: for **12a**: 1.5—2.5 (4H, m), 2.6—2.9 (2H, m), 4.15 (1H, d, J = 1.5 Hz), 4.51 (1H, d, J = 14 Hz), 4.85 (1H, m), 5.34 (1H, dd, J = 14, 1.5 Hz), 7.06 (1H, dd, J = 9, 2 Hz), 7.35 (1H, d, J = 2 Hz), 7.42 (1H, d, J = 9 Hz), 7.60 (1H, s), 8.00 (1H, s); for **13a**: 1.3—2.4 (4H, m), 2.7—3.1 (2H, m), 4.35 (1H, s), 4.45 (1H, d, J = 14 Hz), 4.80 (1H, m), 5.20 (1H, d, J = 14 Hz), 7.10 (1H, dd, J = 9, 2 Hz), 7.37 (1H, d, J = 2 Hz), 7.61 (1H, d, J = 9 Hz), 7.72 (1H, s), 7.97 (1H, s). MS *m/z*; for **12a**: 344 ($M^+ + 1$), 256, 87; for **13a**: 344 ($M^+ + 1$), 256, 87.

The *erythro* isomer **12a** formed its oxalic acid salt, mp 150—152 °C, on being mixed with 1 eq of oxalic acid in AcOEt. Similarly, the *threo* isomer **13a** formed its oxalic acid salt, mp 120—140 °C.

ii) The *erythro* epoxide **10a** obtained by reaction of **8a** with diiodomethane and *n*-butyllithium as described above was similarly treated with sodium triazolide in DMF to give the *erythro* alcohol **12a** in 71% yield.

1-(4-Chlorophenyl)-1-(2-thiolanyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol (12b and 13b) Following a procedure similar to that described above, the diastereomeric 3 : 2 mixture of **10b** and **11b** (780 mg) was treated with 2.5 eq of sodium triazolide at 95 °C for 1 h. The products were separated by chromatography to give **12b** (429 mg, 34% over two steps from **8b**) as an oil and the less polar isomer **13b** (310 mg, 25% over two steps from **8b**), mp 179—180 °C (recrystallized from AcOEt). *Anal.* Calcd for $C_{14}H_{16}ClN_3OS$: C, 54.27; H, 5.21; N, 13.56; S, 10.35. Found for **13b**: C, 54.28; H, 5.17; N, 13.73; S, 10.53. IR ν_{max}^{KBr} cm^{-1}; for **12b**: 3250 (br); for **13b**: 3230 (br). ^{1}H-NMR ($CDCl_3$) δ; for **12b**: 1.5—2.5 (4H, m), 2.6—2.9 (2H, m), 4.04 (1H, s), 4.1 (1H, m), 4.48 (2H, s), 7.26 (4H, s), 7.80 (2H, s); for **13b**: 1.2—2.4 (4H, m), 2.7—3.1 (2H, m), 3.90 (1H, s), 4.1 (1H, m), 4.42 (2H, br s), 7.26 (4H, s), 7.78 (2H, s). MS *m/z*; for **12b**: 310 ($M^+ + 1$), 222, 87; for **13b**: 310 ($M^+ + 1$), 222, 87. HRMS Calcd for $C_{14}H_{17}ClN_3OS$ ($M^+ + 1$): 310.0081. Found for **12b**: 310.0075.

The *erythro* isomer **12b** formed its oxalic acid salt, mp 160—163 °C, and the *threo* isomer **13b** formed its oxalic acid salt, mp 153—155 °C.

1-(2,4-Dichlorophenyl)-1-(2-methylthiolan-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol (12c and 13c) The diastereomeric 2 : 1 mixture of **10c** and **11c** (820 mg, 2.70 mmol) described above was treated with sodium triazolide, prepared from NaH (55% mineral oil dispersion, 236 mg, 5.40 mmol, washed with hexane) and 1*H*-1,2,4-triazole (410 mg, 5.94 mmol) in DMF (10 ml), at 95 °C for 8.5 h. The cooled mixture was diluted with AcOEt and washed with water and brine. The crude product, obtained by evaporation of the solvent, was chromatographed on silica gel (10 g, 5% MeOH–CH_2Cl_2) to afford a mixture of **12c** and **13c** (480 mg, 50%) as a crystalline mass, mp 100—115 °C (washed with AcOEt–hexane), which was not further purified or separated. The ^{1}H-NMR spectrum showed that the diastereomeric ratio of the mixture was *ca.* 2 : 1, though relative stereochemistry (*threo* or *erythro*) could not be assigned to each diastereomer. *Anal.* Calcd for $C_{15}H_{17}ClN_3OS$: C, 50.28; H, 4.78; N, 11.73; S, 8.95; Cl, 19.79. Found: C, 50.41; H, 4.76; N, 11.68; S, 9.10; Cl, 19.64. ^{1}H-NMR ($CDCl)_3$) δ (selected absorptions); for a major isomer: 1.43 (3H, s), 4.95 (1H, d, J = 15 Hz), 5.63 (1H, br s), 5.85 (1H, br d, J = 15 Hz), 7.77 (1H, s), 8.22 (1H, s); for a minor isomer: 1.64 (3H, s), 4.64 (1H, d, J = 15 Hz), 5.05 (1H, br s), 5.97 (1H, br d, J = 15 Hz), 7.95 (1H, s), 8.22 (1H, s).

The mixture of **12c** and **13c** obtained above formed its oxalic acid salt, mp 146—150 °C.

1-(2,4-Dichlorophenyl)-1-(2-thiolanyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol *S*-Oxide (14aA and 14aB) MCPBA (85% purity, 141 mg, 0.70 mmol) was added to a solution of **10a** (221 mg, 0.64 mmol) in CH_2Cl_2 (4 ml) at 0 °C with stirring. The mixture was stirred for 10 min and then treated with Na_2SO_3 solution. The organic layer was collected, washed with dilute $NaHCO_3$ and brine, and dried. The product, after evaporation of the solvent, was chromatographed on silica gel (10 g). Elution with 3% MeOH–AcOEt gave **14aA** as a crystalline mass (173 mg, 75%), mp 143—144 °C (recrystallized from benzene–hexane). Further elution with 20% MeOH–AcOEt gave **14aB**, as a crystalline mass (44 mg, 19%), mp 169—171 °C (recrystallized from AcOEt). *Anal.* Calcd for $C_{14}H_{15}Cl_2N_3O_2S$: C, 46.68; H, 4.20; N, 11.66. Found: for **14aA**: C, 46.54; H, 4.17; N, 11.61; for **14aB**: C, 46.57; H, 4.12; N, 11.71. IR $\nu_{max}^{CHCl_3}$ cm^{-1}; for **14aA**: 3280; for **14aB**: 3360. ^{1}H-NMR ($CDCl_3$) δ; for **14aA**: 1.7—3.3 (6H, m), 3.8—4.3 (1H, m), 4.62 (1H, d, J = 14 Hz), 4.98 (1H, dd, J = 14, 1.5 Hz), 5.93 (1H, d, J = 1.5 Hz), 7.20 (1H, dd, J = 9, 2 Hz), 7.42 (1H, d, J = 2 Hz), 7.63 (1H, d, J = 9 Hz), 7.75 (1H, s), 8.13 (1H, s); for **14aB**: 1.9—3.2 (6H, m), 3.8—4.3 (1H, m), 4.38 (1H, d, J = 14 Hz), 5.38 (1H, s), 5.48 (1H, d, J = 14 Hz), 7.15 (1H, dd, J = 9, 2 Hz), 7.40 (1H, d, J = 2 Hz), 7.69 (1H, d, J = 9 Hz), 7.84 (1H, s), 7.90 (1H, s). MS *m/z*; for **14aA**: 359 (M^+), 277, 70; for **14aB**: 359 (M^+), 277.

These triazoles, **14aA** and **14aB**, formed their oxalic acid salts, mp 141—145 °C and mp 159—160 °C, respectively.

1-(2,4-Dichlorophenyl)-1-(2-thiolanyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol *S*-Oxide (15aA and 15aB) Following a procedure similar to that described above, **13a** was oxidized with 1 eq of MCPBA to give **15aA** (52%), mp 181—184 °C, and the polar isomer **15aB** (32%), mp 202—204 °C. *Anal.* Calcd for $C_{14}H_{15}Cl_2N_3O_2S$: C, 46.68; H, 4.20; N, 11.66. Found; for **15aA**: C, 46.67; H, 4.05; N, 11.71; for **15aB**: C, 46.51; H, 4.07; N, 11.48. IR $\nu_{max}^{CHCl_3}$ cm^{-1}; for **15aA**: 3260; for **15aB**: 3390. ^{1}H-NMR ($CDCl_3$) δ; for **15aA**: 1.5—2.8 (4H, m), 2.9—3.5 (2H, m), 3.8—4.2 (1H, m), 4.99 (1H, d, J = 14 Hz), 5.51 (1H, d, J = 14 Hz), 6.42 (1H, s), 7.10 (1H, dd, J = 9, 2 Hz), 7.34 (1H, d, J = 2 Hz), 7.57 (1H, d, J = 9 Hz), 7.65 (1H, s), 8.27 (1H, s); for **15aB**: 1.2—3.4 (6H, m), 4.09 (1H, br t, J = 8 Hz), 5.01 (1H, d, J = 14 Hz), 5.58 (1H, d, J = 2 Hz), 5.73 (1H, d, J = 14 Hz), 7.09 (1H, dd, J = 9, 2 Hz), 7.35 (1H, d, J = 2 Hz), 7.40 (1H, d, J = 9 Hz), 7.82 (1H, s), 7.88 (1H, s). MS *m/z*; for **15aA**: 359 (M^+), 277, 70; for **15aB**: 359 (M^+), 277, 70.

These triazoles, **15aA** and **15aB**, formed their oxalic acid salts, mp 198 °C (dec.) and mp 166—167 °C (dec.), respectively.

1-(2,4-Dichlorophenyl)-1-(2-thiolanyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol *S,S*-Dioxide (16a) MCPBA (85% purity, 120 mg, 0.59 mmol) was added to a solution of **12a** (102 mg, 0.30 mmol) in CH_2Cl_2 (3 ml) at room temperature with stirring. The mixture was stirred for 1 h and then treated with Na_2SO_3 solution. The organic layer was collected, washed with dilute $NaHCO_3$ and brine and dried. The crystalline residue, after evaporation of the solvent, was recrystallized from AcOEt–hexane to give **16a** (87 mg, 78%), mp 172—173 °C. *Anal.* Calcd for $C_{14}H_{15}Cl_2N_3O_3S$: C, 44.69; H, 4.02; N, 11.17. Found: C, 44.52; H, 3.96; N, 11.03. IR $\nu_{max}^{CHCl_3}$ 3480 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.8 (4H, m), 2.8—3.3 (2H, m), 4.56 (1H, d, J = 14 Hz), 4.6 (1H, m), 4.90 (1H, s), 5.01 (1H, d, J = 14 Hz), 7.15 (1H, dd, J = 9, 2 Hz), 7.42 (1H, d, J = 2 Hz), 7.46 (1H, d, J = 9 Hz), 7.71 (1H, s), 8.02 (1H, s). MS *m/z*: 376 (M^+), 293, 214, 173, 147, 83.

This triazole sulfone **16a** formed its oxalic acid salt, mp 180—182 °C (dec.).

1-(2,4-Dichlorophenyl)-1-(2-thiolanyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol *S,S*-Dioxide (17a) Following a procedure similar to that described above, **13a** was oxidized with 2 eq of MCPBA to yield **17a** (88%) as prisms, mp 205—208 °C (recrystallized from AcOEt–hexane). *Anal.* Calcd for $C_{14}H_{15}Cl_2N_3O_3S$: C, 44.69; H, 4.02; N, 11.17. Found: C, 44.78; H, 3.88; N, 11.19. IR $\nu_{max}^{CHCl_3}$ 3450 cm^{-1}. ^{1}H-NMR ($CDCl)_3$) δ: 1.6—2.5 (4H, m), 2.0—3.4 (2H, m), 4.28 (1H, t-like, J = 9 Hz), 5.12 (1H, d, J = 14 Hz), 5.15 (1H, s), 5.56 (1H, d, J = 14 Hz), 7.07 (1H, dd, J = 9, 2 Hz), 7.33 (1H, d, J = 2 Hz), 7.48 (1H, d, J = 9 Hz), 7.67 (1H, s), 7.89 (1H, s). MS *m/z*: 376 (M^+), 147, 83.

1-(Chlorophenyl)-1-(2-thiolanyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol *S,S*-Dioxide (16b and 17b) Following a procedure similar to that described above, **12b** and **13b** were separately oxidized with 2 eq of MCPBA to afford **16b** (81%) as an oil and **17b** (85%), mp 153—155 °C (recrystallized from $CHCl_3$–hexane), respectively. *Anal.* Calcd for $C_{14}H_{16}ClN_3O_3S$: C, 49.19; H, 4.72; N, 12.29. Found for **17b**: C, 49.02; H, 4.69; N, 12.37. ^{1}H-NMR ($CDCl_3$) δ; for **16b**: 1.6—2.4 (4H, m), 3.0—3.4 (2H, m), 3.59 (1H, t-like, J = 9 Hz), 4.80 (1H, d, J = 14 Hz), 4.80 (1H, s), 5.12 (1H, d, J = 14 Hz), 7.0—7.4 (4H, m), 7.75 (1H, s), 7.79 (1H, s), for **17b**: 1.7—3.4 (6H, m), 3.93 (1H, t-like, J = 9 Hz), 4.10 (1H, d, J = 14 Hz), 4.44 (1H, d, J = 14 Hz), 4.47 (1H, br s), 7.0—7.4 (4H, m), 7.49 (1H, s), 7.85 (1H, s). MS *m/z*; for **16b**: 342 ($M^+ + 1$), 259, 180, 147; for **17b**: 342 ($M^+ + 1$). HRMS Calcd for $C_{14}H_{17}ClN_3O_3S$ ($M^+ + 1$): 341.9979. Found for **16b**: 341.9972.

These triazole sulfones, **16b** and **17b**, formed their oxalic acid salts, mp 177—182 °C and mp 110—112 °C, respectively.

1-(2,4-Dichlorophenyl)-1-(2-methylthiolan-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol *S,S*-Dioxide (16c and 17c) The 2 : 1 diastereomeric mixture of **12c** and **13c** (relative stereochemistry interchangeable) previously obtained was oxidized with 2 eq of MCPBA as described above to give a *ca.* 2 : 1 mixture of **16c** and **17c** (76%) as a crystalline mass. Separation of this mixture using a Lobar column-A (eluent: AcOEt) gave a major isomer **16c**, mp 250—251 °C, and a less polar minor one **17c**, mp 207—208 °C. Stereochemistries of these sulfones were tentatively assigned for con-

venience, and may be interchanged. *Anal.* Calcd for $C_{15}H_{17}Cl_2N_3O_3S$: C, 46.16; H, 4.39; N, 10.77. Found; for **16c**: C, 46.08; H, 4.45; N, 10.55; for **17c**: C, 46.22; H, 4.38; N, 10.51. ^{1}H-NMR (DMF-d_7) δ; for **16c**: 1.15 (3H, s), 1.8—3.5 (6H, m), 5.45 (1H, d, J=15 Hz), 6.05 (1H, d, J=15 Hz), 6.19 (1H, s), 7.2—7.6 (2H, m), 7.78 (1H, s), 7.91 (1H, d, J=9 Hz), 8.46 (1H, s); for **17c**: 1.57 (3H, s), 1.5—2.5 (4H, m), 3.2—3.5 (2H, m), 5.27 (1H, d, J=15 Hz), 6.03 (1H, s), 6.19 (1H, d, J=15 Hz), 7.2—7.6 (2H, m), 7.80 (1H, s), 8.04 (1H, d, J=9 Hz), 8.48 (1H, s). MS m/z; for **16c**: 390 (M^++1), 307, 228, 173, 161, 83; for **17c**: 390 (M^++1).

2,4-Dichlorophenyl 2-Thiolanyl Ketone *S*-Oxide (21) MCPBA (85% purity, 1.16 g, 5.71 mmol) was added to a solution of **8a** (1.49 g, 5.71 mmol) in CH_2Cl_2 (20 ml) at 0 °C with stirring. Stirring was continued for 10 min at the same temperature, then the mixture was treated with Na_2SO_3 solution and the organic layer was collected. After washing with dilute $NaHCO_3$ and brine, the solvent was evaporated off *in vacuo* to give a crystalline mass, which was recrystallized from benzene–hexane, giving **21** (1.12 g, 71%), mp 135—142 °C. *Anal.* Calcd for $C_{11}H_{10}Cl_2O_2S$: C, 47.67; H, 3.64; S, 11.57; Cl, 25.58. Found: C, 47.85; H, 3.67; S, 11.68; Cl, 25.58. ^{1}H-NMR ($CDCl_3$) δ: 1.8—3.4 (6H, m), 4.76 (1H, m), 7.2—7.7 (3H, m). MS m/z: 276 (M^+), 241, 173, 103.

2,4-Dichlorophenyl 2-Thiolen-2-yl Ketone (22) Trifluoroacetic anhydride (302 mg, 0.73 mmol) was added to a solution of **21** (200 mg, 0.72 mmol) and 2,6-lutidine (154 mg, 1.44 mmol) in acetonitrile (4 ml) at 0 °C. The mixture was stirred for 5 min, then diluted with benzene, and washed with water, dilute HCl and brine. The solvent was distilled off *in vacuo* to provide **22** (187 mg, 100%) as a yellow oil, which was used for the next reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 2.7—3.5 (4H, m), 6.15 (1H, t, J=3 Hz), 7.2—7.5 (3H, m).

2-(2,4-Dichlorophenyl)-2-(2-thiolen-2-yl)oxirane (23) A 1.5 M *n*-butyllithium hexane solution (0.33 ml, 0.50 mmol) was added dropwise to a solution of **22** (92 mg, 0.36 mmol) and diiodomethane in THF (1 ml) at −78 °C over 1 min with stirring. The mixture was stirred for 10 min and then partitioned between benzene and water. The organic layer was collected, washed with brine and evaporated *in vacuo*. The crude product was purified by chromatography on silica gel (3 g, 20% AcOEt–hexane) to give **23** (51 mg, 53%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.5—3.5 (4H, m), 3.00 (1H, d, J=5 Hz), 3.45 (1H, d, J=5 Hz), 5.30 (1H, t, J=2.5 Hz), 7.1—7.6 (3H, m). HRMS Calcd for $C_{12}H_{10}Cl_2OS$: 271.9129. Found: 271.9118.

1-(2,4-Dichlorophenyl)-1-(2-thiolen-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol (24) Following a procedure similar to that described for the preparation of **12a** and **13a**, the epoxide **23** (88 mg, 0.32 mmol) was treated with 2 eq of sodium triazolide in DMF at 95 °C for 2 h. Work-up and chromatography of the crude product afforded **24** (66 mg, 60%), mp 59—62 °C (recrystallized from benzene). *Anal.* Calcd for $C_{14}H_{13}Cl_2N_3OS$: C, 49.13; H, 3.83; N, 12.28; S, 9.37. Found: C, 49.28; H, 3.83; N, 12.35; S, 9.39. IR $\nu_{max}^{CHCl_3}$ 3390 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.5—3.5 (4H, m), 4.75 (1H, d, J=14 Hz), 4.90 (1H, s), 5.39 (1H, d, J=14 Hz), 5.45 (1H, t, J=2.5 Hz), 7.10 (1H, dd, J=9, 2 Hz), 7.31 (1H, d, J=2 Hz), 7.57 (1H, d, J=9 Hz), 7.75 (1H, s), 7.98 (1H, s).

This triazole **24** formed its oxalic acid salt, mp 160—162 °C.

1-(2,4-Dichlorophenyl)-1-(2-thiolen-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol *S*-Oxide (25) The triazole **24** (152 mg) was oxidized with 1 eq of MCPBA in CH_2Cl_2 in the same way as described before to give a *ca.* 1:1 diastereomeric mixture of **25** (109 mg, 69%), from which the less polar isomer (45 mg), mp 162—164 °C, was separated by recrystallization from AcOEt. *Anal.* Calcd for $C_{14}H_{13}Cl_2N_3O_2S$: C, 46.94; H, 3.66; N, 11.73. Found: C, 46.77; H, 3.58; N, 11.52. ^{1}H-NMR ($CDCl_3$) δ: 2.6—3.6 (4H, m), 5.00 (1H, d, J=14 Hz), 5.29 (1H, d, J=14 Hz), 5.70 (1H, s), 6.63 (1H, t, J=2 Hz), 7.23 (1H, dd, J=9, 2 Hz), 7.39 (1H, d, J=2 Hz), 7.72 (1H, d, J=9 Hz), 7.75 (1H, s), 8.20 (1H, s).

This crystalline isomer **25** formed its oxalic acid salt, mp 132—135 °C.

1-(2,4-Dichlorophenyl)-1-(2-thiolen-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethanol *S,S*-Dioxide (26) The 1:1 diastereomeric mixture of **25** obtained above was oxidized with 1 eq of MCPBA in CH_2Cl_2 to give **26** (84%), mp 111—113 °C (recrystallized from $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.6—3.0 (2H, m), 3.35 (2H, t-like, J=7 Hz), 5.13 (1H, d, J=14 Hz), 5.43 (1H, d, J=14 Hz), 5.49 (1H, s), 6.40 (1H, t, J=3 Hz), 7.19 (1H, dd, J=9, 2 Hz), 7.37 (1H, J=2 Hz), 7.63 (1H, d, J=9 Hz), 7.77 (1H, s), 8.08 (1H, s). MS m/z: 374 (M^++1), 256, 173. HRMS Calcd for $C_{14}H_{14}Cl_2N_3O_3S$ (M^++1): 373.9433. Found: 373.9431.

2-[2-(Methoxycarbonyl)ethylthio]-2′,4′-dichloroacetophenone (28) 3-Mercaptopropionic acid (5.22 g, 49.2 mmol) was added dropwise to a stirred mixture of NaH (55% mineral oil dispersion, 3.90 g, 89.5 mmol, washed with hexane) and DMF (100 ml) at 0 °C over a period of 5 min. The mixture was stirred for 15 min, then 2,2′,4′-trichloroacetophenone (**5a**) (10.0 g, 44.8 mmol) and MeOH (50 ml) were added and stirring was continued at 0 °C for 30 min. The mixture was diluted with water (150 ml) and washed with benzene. The aqueous layer was then acidified with dilute HCl and extracted with benzene. The extract was washed with brine and dried. Evaporation of the solvent furnished **27** (1.31 g, 95%) as a crystalline mass. The crude product **27** was then dissolved in MeOH (220 ml), and concentrated H_2SO_4 (22 ml) and trimethyl orthoformate (5 ml) were added. The mixture was allowed to stand at room temperature overnight, then diluted with benzene, and washed with water and dilute $NaHCO_3$. The solvent was removed by evaporation *in vacuo* to give **28** as an oil, which was shown by ^{1}H-NMR to be partly acetalized. Therefore, **28** thus obtained was treated with concentrated HCl (20 ml) in acetone (200 ml) at room temperature for 10 min. Work-up and purification of the product by chromatography afforded **28** (12.1 g, 88% over two steps from **5a**) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.4—3.0 (4H, m), 3.68 (3H, s), 3.82 (2H, s), 7.2—7.7 (3H, m). MS m/z: 306 (M^+), 247, 173.

2,4-Dichlorophenyl 3-Oxothiolan-2-yl Ketone (29) The ketoester **28** (6.90 g, 22.5 mmol) was added to a solution of sodium methoxide in methanol, prepared by dissolving sodium (786 mg, 34.2 mmol) in MeOH (140 ml), and refluxed for 30 min. The mixture was cooled, acidified with dilute HCl and partitioned between benzene and water. The organic layer was collected, washed with dilute $NaHCO_3$ and dried. Evaporation of the solvent gave an oily residue which was chromatographed on silica gel (20 g, AcOEt : hexane = 1 : 8—1 : 7, v/v) to provide **29** (4.41 g, 72%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1648, 1608. ^{1}H-NMR ($CDCl_3$ + D_2O) δ: 2.7—3.3 (4H, m), 7.2—7.6 (3H, m). MS m/z: 274 (M^+), 173.

2,4-Dichlorophenyl 3,3-(Ethylenedioxy)thiolan-2-yl Ketone (30) A mixture of **29** (514 mg), ethylene glycol (500 mg), *p*-toluenesulfonic acid (25 mg) and benzene (10 ml) was refluxed for 3.5 h. The cooled mixture was washed with dilute $NaHCO_3$ and brine. Evaporation of the solvent gave an oily mixture which was separated by chromatography on silica gel. Elution with AcOEt–hexane (1 : 5, v/v) gave the starting diketone **29** (226 mg, 44%) and **30** (178 mg, 30%), mp 75—76 °C (recrystallized from benzene–hexane), in that order of elution. *Anal.* Calcd for $C_{13}H_{12}Cl_2O_3S$: C, 48.92; H, 3.79; S, 10.04. Found: C, 48.96; H, 3.73; S, 10.26. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1584. ^{1}H-NMR ($CDCl_3$) δ: 1.8—3.2 (4H, m), 3.6—4.2 (4H, m), 4.54 (1H, s), 7.2—7.6 (3H, m). MS m/z: 318 (M^+), 173.

Further elution with AcOEt–hexane (1 : 1, v/v) gave **31** (100 mg, 14%) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610, 3490, 1730. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (2H, s), 2.4—3.0 (4H, m), 3.6—4.4 (4H, m), 4.18 (4H, br s), 7.19 (1H, dd, J=9, 2 Hz), 7.37 (1H, d, J=2 Hz), 7.78 (1H,d, J=9 Hz).

2-(2,4-Dichlorophenyl)-2-[3,3-(ethylenedioxy)thiolan-2-yl]oxirane (32 and 33) A 1.5 M *n*-butyllithium hexane solution (2.80 ml, 4.20 mmol) was added dropwise to a solution of **30** (987 mg, 3.09 mmol) and diiodomethane (1.00 g, 3.73 mmol) in THF (14 ml) at −78 °C over a period of 2.5 min with stirring. The mixture was stirred for 10 min and then partitioned between benzene and water. The organic layer was collected, washed with brine and evaporated *in vacuo* to give a crystalline mass, whose recrystallization from benzene–hexane afforded a major epoxide **32** (425 mg), mp 142—144 °C. Chromatography of the mother liquor on silica gel (15 g, 2.5—3.5% AcOEt–hexane) gave a less polar minor epoxide **33** (85 mg, 8%) as an oil and an additional amount of the major epoxide **32** (117 mg, total yield 53%), mp 141—143 °C. *Anal.* Calcd for $C_{14}H_{14}Cl_2O_3S$: C, 50.46; H, 4.23; S, 9.62. Found for **32**: C, 50.49; H, 4.41; S, 9.75. ^{1}H-NMR ($CDCl_3$) δ: for **32**: 1.9—2.2 (2H, m), 2.73 (2H, t-like, J=7 Hz), 2.91 (1H, d, J=5 Hz), 3.65 (1H, d, J=5 Hz), 3.7—3.9 (4H, m), 3.89 (1H, s), 7.19 (1H, dd, J=9, 2 Hz), 7.35 (1H, d, J=2 Hz), 7.61 (1H, d, J=9 Hz); for **33**: 1.7—2.9 (4H, m), 2.45 (1H, d, J=5.5 Hz), 3.0—3.9 (4H, m), 3.60 (1H, d, J=5.5 Hz), 3.95 (1H, s), 7.1—7.4 (2H, m), 7.58 (1H, d, J=9 Hz). HRMS Calcd for $C_{14}H_{14}Cl_2O_3S$: 331.9341. Found for **33**: 331.9346.

1-(2,4-Dichlorophenyl)-1-[3,3-(ethylenedioxy)thiolan-2-yl]-2-(1*H*-1,2,4-triazol-1-yl)ethanol (34 and 35) According to a procedure similar to that described for the preparation of **12a** and **13a**, **32** (579 mg) was heated with 3 eq of sodium triazolide at 100 °C in DMF for 4 h. Usual work-up and purification by chromatography afforded **34** (572 mg, 82%), mp 185—188 °C (recrystallized from AcOEt–benzene). *Anal.* Calcd for $C_{16}H_{17}Cl_2N_3O_3S$: C, 47.77; H, 4.26; N, 10.45; S, 7.97. Found: C, 47.54; H, 4.22; N, 10.29; S, 8.10. IR $\nu_{max}^{CHCl_3}$ 3470 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.9 (4H, m), 4.0—4.3 (4H, m), 4.75 (1H, s), 4.84 (1H, d, J=15 Hz), 4.95 (1H, s, OH), 5.42 (1H, d, J=15 Hz), 7.04 (1H, dd, J=9, 2 Hz), 7.31 (1H, d, J=2 Hz), 7.47 (1H, d, J=9 Hz), 7.62 (1H, s), 7.90 (1H, s). MS m/z: 402 (M^++1), 256, 173.

The minor epoxide **33** was similarly transformed to the triazole **35**, mp 148—149 °C (recrystallized from AcOEt), in 69% yield. *Anal.* Found: C, 47.66; H, 4.19; N, 10.15; S, 8.06. IR $\nu_{max}^{CHCl_3}$ 3450 cm^{-1}. ^{1}H-NMR ($CDCl_3$)

δ: 1.8—2.4 (2H, m), 2.6—3.8 (6H, m), 4.51 (1H, d, J=14 Hz), 4.72 (1H, d, J=1 Hz), 4.88 (1H, s), 5.15 (1H, dd, J=14, 1 Hz), 7.05 (1H, dd, J=9, 2 Hz), 7.34 (1H, d, J=2 Hz), 7.46 (1H, d, J=9 Hz), 7.61 (1H, s), 8.00 (1H, s). MS m/z: 402 (M^++1), 256, 173.

These triazoles, **34** and **35**, formed their oxalic acid salts, mp 173—175 °C (dec.) and mp 165—167 °C (dec.), respectively.

1-(2,4-Dichlorophenyl)-1-(3-oxothiolan-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)-ethanol (36 and 37) A mixture of **34** (520 mg), acetone (10 ml) and 2 N HCl (10 ml) was heated at 60 °C for 2 h. The resulting white precipitates were collected by filtration to afford the hydrochloride of **36** (475 mg, 93%), mp 190—200 °C (dec.), which was treated with Na_2CO_3 solution to give the free base **36**, mp 144—147 °C (recrystallized from AcOEt), in quantitative yield. *Anal.* Calcd for $C_{14}H_{13}Cl_2N_3O_2S$: C, 46.94; H, 3.66; N, 11.73; S, 8.95. Found: C, 46.84; H, 3.67; N, 11.98; S, 9.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1725. ^{1}H-NMR ($CDCl_3$) δ: 2.5—3.4 (4H, m), 4.48 (1H, s), 4.91 (1H, d, J=14 Hz), 5.30 (1H, br s), 5.50 (1H, d, J=14 Hz), 7.09 (1H, dd, J=9, 2 Hz), 7.31 (1H, d, J=2 Hz), 7.45 (1H, d, J=9 Hz), 7.73 (1H, s), 7.80 (1H, s).

Deacetalization of **35** with dilute HCl followed by neutralization as described above yielded **37**, mp 144—146 °C (recrystallized from AcOEt–hexane), in 89% yield. *Anal.* Found: C, 46.74; H, 3.77; N, 11.68. IR $\nu_{max}^{CHCl_3}$ cm^{-1}; 3400, 1733. ^{1}H-NMR ($CDCl_3$) δ: 2.2—3.6 (4H, m), 4.33 (1H, s), 4.86 (1H, d, J=14 Hz), 5.23 (1H, s, OH), 5.35 (1H, d, J=14 Hz), 7.01 (1H, dd, J=9, 2 Hz), 7.29 (1H, d, J=2 Hz), 7.35 (1H, d, J=9 Hz), 7.75 (1H, s), 7.78 (1H, s).

These triazoles, **36** and **37**, formed their oxalic acid salts, both of which melted at 165—167 °C with decomposition.

Oxidation of 36 with MCPBA The ketone **36** (31 mg, 0.087 mmol) was treated with MCPBA (85% purity, 17 mg, 0.087 mmol) in CH_2Cl_2 (3 ml) at 0 °C for 10 min. Monitoring of the reaction by TLC indicated the formation of a polar product. The mixture was washed with dilute $NaHCO_3$. The polar product initially formed disappeared and a less polar substance (23 mg) was obtained. ^{1}H-NMR ($CDCl_3$) δ: 5.59 (2H, s), 7.35 (1H, dd, J=8, 2 Hz), 7.50 (1H, d, J=2 Hz), 7.65 (1H, d, J=8 Hz), 7.97 (1H, s), 8.23 (1H, s). This product was identical with a sample of **39** prepared by reaction of 2,2′,4′-trichloroacetophenone (**5a**) and 1*H*-1,2,4-triazole according to a standard procedure.

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