Synthesis and Antifungal Activities of R-102557 and Related Dioxane-Triazole Derivatives

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Novel triazole compounds with a dioxane ring were synthesized. Condensation of the diol precursor 10 with various aromatic aldehydes 11—13 under acidic conditions afforded a series of dioxane–triazole compounds 14—16. The antifungal activities of the compounds 14—16 were evaluated *in vivo* in mice infection models against *Candida* and *Aspergillus* species. High activities were seen for the derivatives with one or two double bond(s) and an aromatic ring substituted with an electron-withdrawing group in the side chain. Among the derivatives, R-102557 (16R: Ar=4-(2,2,3,3-tetrafluoropropoxy)phenyl) showed excellent *in vivo* activities against *Candida*, *Aspergillus* and *Cryptococcus* species. It also showed high tolerance in a preliminary toxicity study in rats.

Key words antifungal; triazole; R-102557; structure–activity relationship; synthesis; lanosterol 14-demethylase

There have been increasing demands for antifungal agents that are effective against systemic mycosis.[1] We are surrounded by fungi, and it is thanks to our immune system that our bodies are not invaded by fungi. But once our immune system becomes deficient or suppressed, as it does in AIDS patients and in those that have received cancer chemotherapy or organ transplants, then we become highly susceptible to such fungal infection. In many cases it is not the AIDS or cancer itself but the mycosis that is lethal to these patients.

Attention has been paid to triazole derivatives[2] because of their generally broad antifungal spectrum and low toxicity. Triazole derivatives displace lanosterol from lanosterol 14-demethylase (14DM), a cytochrome P450-dependent enzyme, and block the biosynthesis of an essential component of the fungal cell membrane, ergosterol.[3] Fluconazole[4] (**1**) has relatively low antifungal activity *in vitro*, but it is water-soluble, and has excellent pharmacokinetic properties. It is effective against candidiasis after both oral administration and injection. However, its activity against *Aspergillus* seems limited. Itraconazole[5] (±)-(**2**) has an excellent and broader antifungal spectrum. Newer triazole agents such as voriconazole[6] (**3**), Sch56592[7] (**4**) and ER-30346[8] (BMS-207147) (**5**), are active against *Aspergillus* and currently under clinical trials.

In our continuing program[9] aimed at finding a new triazole antifungal agent, we designed a series of dioxane–triazole compounds depicted by the general formula I (Chart 1). We presumed that the left-half portion of the molecule, shown in the box, is essential to the high antifungal activity. It is a common substructure seen in many other triazole antifungals. The 1,3-dioxane ring was introduced in the expectation that: 1) Since acetal moieties will make a molecule more hydrophilic and water-soluble than simple hydrocarbon moieties, the compound could become more available orally and would be more easily delivered to the target fungal enzyme; 2) since many other triazole antifungal agents have heteroatoms at the corresponding part of the molecule, complementary structure of the target enzyme would be implied; 3) a 2,5-substituted-1,3-dioxane ring would not create a chiral center and would generate *cis* and *trans* isomers only; and 4) a variety of aldehydes should be available as the side chain precursor. The sulfur atom was incorporated in the 3-position because the molecule could readily be prepared from the known epoxide **8**.[9a,b,e,10] The methyl group at the 3-position mimics the 13β-methyl group of lanosterol.[9e,f] The two fluorine atoms in the benzene ring in the left half of the molecule aim at strengthening the antifungal activity.[4b,10c]

In this paper, we will present our recent findings on synthesis and antifungal activities of the compounds I.

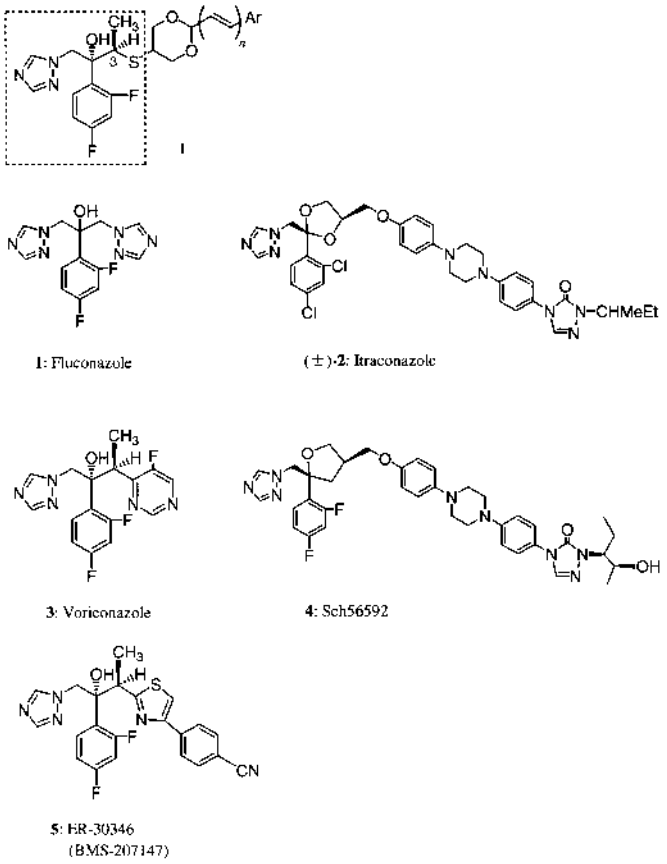

Chart 1

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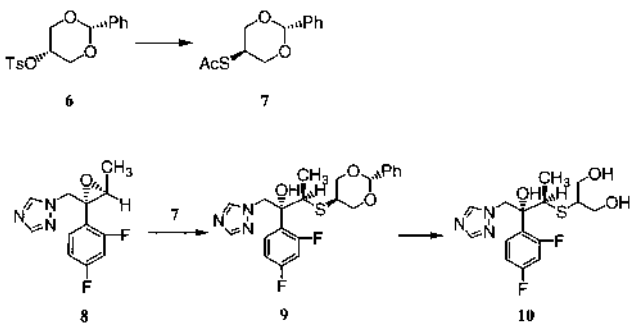


Chart 2

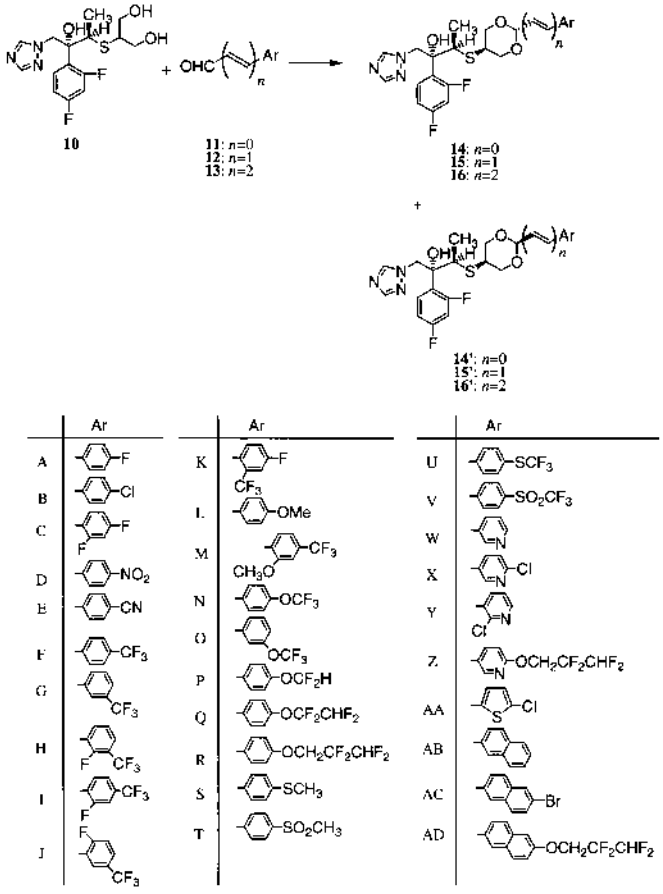


Chart 3

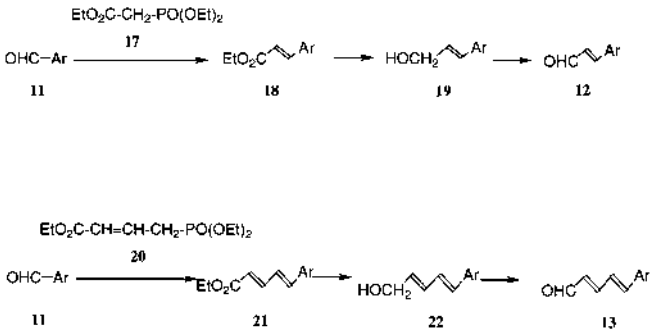


Chart 4

Chemistry In order to prepare a variety of derivatives I in an efficient manner, the diol **10** was planned as a pivotal precursor. Preparation of the diol **10** was accomplished as follows (Chart 2). The known tosylate **6**[11] was heated with potassium thioacetate in *N*,*N*-dimethylformamide (DMF) to give the thioester **7** in 43% yield. Then, the optically active known epoxide **8**[9a,b,e,10] was treated with the thioester **7** in the presence of sodium methoxide to afford the thioether **9** in 91% yield. The benzylidene protecting group was removed by acid treatment to furnish **10** in 88% yield.

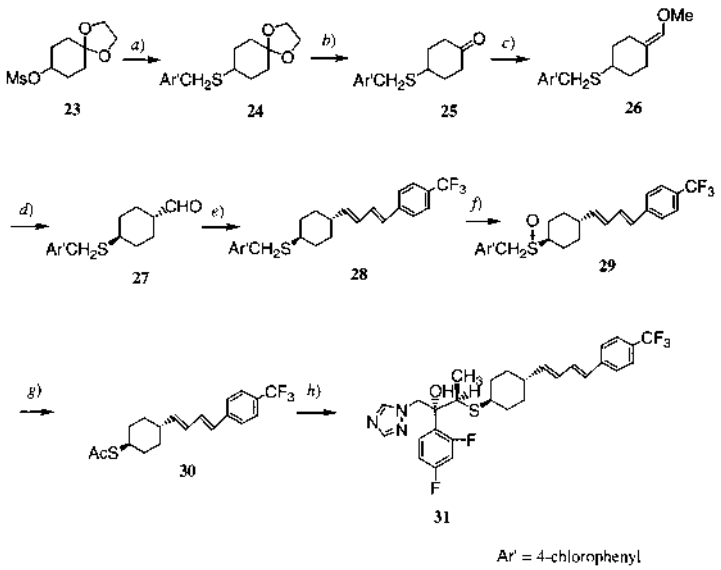
The diol **10** was coupled with a variety of aldehydes **11**, **12**, and **13** (Chart 3). The reaction was driven by stirring a solution of a mixture of diol **10** and each aldehyde **11**—**13** in dichloromethane in the presence of *p*-toluenesulfonic acid and molecular sieves 4A. The *trans* dioxane isomers **14**, **15**, and **16** were predominantly produced, and easily separated from the *cis* isomers **14′**, **15′**, and **16′** by column chromatography. The stereochemistry was elucidated by ^{1}H-NMR spectrum. The trans isomers **14**, **15**, and **16**, showed the characteristic signal for the methine proton at the 5-position of the 1,3-dioxane ring with a large coupling constant (triplet of triplets, J=*ca.* 11, 5 Hz). An analogous signal pattern was observed for the above-mentioned *trans* thioether **9**. In contrast, the *cis* isomers **14′**, **15′**, and **16′** showed small coupling constants (triplet-like, J=*ca.* 2 Hz). These data indicate that the methine protons in the isomers **14**, **15**, and **16** are axial and those in the isomers **14′**, **15′**, and **16′** are equatorial. Therefore, the sulfur atoms in the isomers **14**, **15**, and **16** are equatorial and *trans* to the olefinic substituents, whereas those in the isomers **14′**, **15′**, and **16′** are axial and *cis* to the olefinic substituents.

Most of the 3-arylacroleins **12** used in the above reactions were prepared from the corresponding aryl aldehydes **11** stereoselectively by the homologation sequence shown in Chart 4. Thus, Horner–Wadsworth–Emmons reaction with phosphonoacetate **17** gave the esters **18**; diisobutylaluminium hydride (DIBAL) reduction gave the allylic alcohols **19**; and further oxidation gave **12**. Most of the 5-aryl-2,4-pentadienals **13** were prepared from **11** in a similar manner using the phosphonocrotonate **20** *via* **21** and **22**. The 3-arylacroleins **12**D and **12**E were prepared in one step from the corresponding aryl aldehydes **11**D and **11**E using (triphenylphosphoranylidene)acetaldehyde following a literature procedure.[12] The aldehyde **13**E was prepared in a similar manner in one step from **11**E using (triphenylphosphoranylidene)crotonaldehyde.[13]

A cyclohexane analog **31** was prepared as shown in Chart 5 for comparing activities.

Antifungal Activity Since it is known that there is no good correlation between *in vitro* and *in vivo* activities of azole antifungal agents,[14] and we have experienced this discrepancy in the antifungal evaluation of the oxazolidine derivatives,[9f] the compounds were evaluated *in vivo* using a murine model of systemic candidiasis. The results are summarized in Table 1. In the model, a group of 10 mice were inoculated with fungi intravenously and the test compounds (16—20 mg/kg, *per* dose) were administered either orally (*p.o.*) or intraperitoneally (i.p.) 1, 4, and 24 h post infection. All the control (no drug) mice died within three days after infection whereas those that were given drugs survived substantially longer.

The structure–activity relationships were evaluated initially by comparing the *in vivo* activities of **9**, **14**A, **14**C, and



a) 4-Chloro-α-toluenethiol, NaH, DMF, 50℃. *b*) HCl, acetone, H_2O, 50℃.
c) $[Ph_3P^+-CH_2OMe]Cl^-$, NaH, DMSO, rt. *d*) HCl, acetone, H_2O, 55℃, then NaOMe, MeOH, rt.
e) $[Ph_3P^+-CH_2-CH=CH-C_6H_4-CF_3]Cl^-$, NaH, DMSO, rt. *f*) mCPBA, CH_2Cl_2, 0℃.
g) $(CF_3CO)_2O$, 2,6-lutidine, THF, CH_3CN, 0℃; $NaHCO_3$, H_2O; CH_3COCl, Et_3N, CH_2Cl_2, 0℃.
h) **8**, NaOMe, MeOH, DMF, 55—60℃.

Chart 5

14D, which have no olefinic carbon chain between the aryl and dioxane rings. The unsubstituted phenyl compound **9** exhibited a fair activity. Introducing an electron-withdrawing group such as a fluorine atom or a nitro group to the phenyl ring resulted in slight improvement in the survival rates.

We then fixed the aryl ring Ar to 2,4-difluorophenyl, and varied the length of the olefinic carbon chain between the dioxane and aryl rings (compounds **14**C, **15**C, and **16**C). The compound **15**C, with one olefinic double bond, showed a better *in vivo* activity against Candida albicans than the shortest compound **14**C, and it was slightly active than the longer homolog **16**C.

Accordingly, a number of the derivatives **15**, which have one double bond, were prepared and tested. Compounds with an electron-donating substituent at the phenyl ring (*e.g.* the compound **15**L) showed modest activity whereas those with an electron-withdrawing substituent such as a chlorine atom or a trifluoromethyl group (*e.g.* the compounds **15**B, **15**F, and **15**G) showed good activity.

The 4-position seems to be the most suitable position in the phenyl ring for modification. As we can see by comparing **15**A and **15**K, introduction of a trifluoromethyl group at the 2-position, in addition to the fluorine atom at the 4-position, brought about only a small improvement in activity. The 3-trifluoromethyl derivatives **15**G, **15**H and **15**J showed much higher activities than **15**K, and the 4-trifluoromethyl derivatives **15**F and **15**I exhibited the highest activities.

The trifluoromethoxy derivatives **15**N and **15**O also showed high activities.

The *cis* (in terms of the stereochemistry on the 1,3-dioxane ring) isomers showed lower activities than the *trans* counterpart, as we can see by comparing **15**B and **15**′B, **15**F and **15**′F, and, **15**Q and **15**′Q.

The activities of the pyridyl (**15**W, **15**X, **15**Y, and **15**Z) and thienyl (**15**AA) analogs were lower than those of the phenyl analogs. However, the naphthyl ring analog **15**AC exhibited excellent activity, comparable to that of the substituted phenyl compounds.

We then prepared the homologs **16**, which have two double bonds. The relationship between the Ar groups and the antifungal activities paralleled that of the derivatives **15**. Among the compounds, **16**B, **16**F, **16**N, **16**R, **16**U and **16**V showed high *in vivo* potency.

The cyclohexane ring analog **31** showed only fair activity, implying the importance of the 1,3-dioxane ring for antifungal activity.

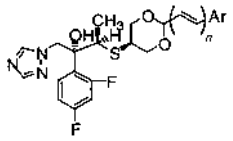
Some of the compounds were evaluated further by a murine model of systemic aspergillosis. The results are summarized in Table 2. In this model, a group of 10 mice were inoculated with either *Aspergillus fumigatus* or *Aspergillus flavus* intravenously, and the test compounds (20 mg/kg, *per* dose) were administered orally 1, 4, 24, 31, 48 and 55 h post infection.

Among the compounds tested, **15**F, **15**R, **15**V, **15**AC, **15**AD, **16**R, and **16**V protected all mice for 14 d from both *Aspergillus fumigatus* and *Aspergillus flavus*.

In a preliminary toxicity study in rats (F344 strain, male, 5 weeks old, given drugs of 100 mg/kg/dose orally once daily for 14 d, each group consisting of five rats), all cases given **15**F (a derivative with one double bond) died in the second week of the administration, but all rats given **16**F, **16**R and **16**V (derivatives with two double bonds) survived without any apparent toxic symptoms. Among **16**F, **16**R and **16**V, the compound **16**R showed the lowest influence on adrenal glands and thyroid glands.

Finally, the compound **16**R was tested in a murine infection model of *Cryptococcus neoformans* (Table 3). In the model, a group of 10 mice were inoculated with *C. neoformans* intravenously and the test compounds were administered orally once daily for 5 d. The results are summarized in

Table 1. Comparative Antifungal Efficacies of Various Dioxane–Triazole Compounds against Systemic Infection with *Candida albicans*[a)]



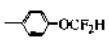
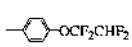
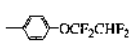
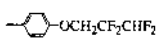
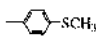
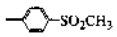
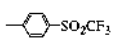
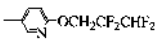
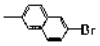
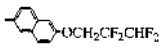
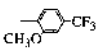
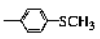
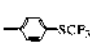
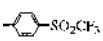
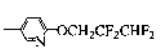
Compd.[b)]	Ar	*n*	Stereo-chemistry	Dose[c)] (mg/kg)	Route	% Survival rate on day				
						3	9	14	21	30
9		0	*trans*	20	*p.o.*	100	100	50	20	—
					i.p.	100	100	40	30	—
14A		0	*trans*	19	*p.o.*	100	80	40	20	—
					i.p.	100	100	80	70	—
14C		0	*trans*	19	*p.o.*	100	100	90	60	—
					i.p.	100	100	80	30	—
14D		0	*trans*	19	*p.o.*	100	100	70	20	—
					i.p.	100	100	80	40	—
15A		1	*trans*	20	*p.o.*	100	100	60	30	—
					i.p.	100	100	100	40	—
15B		1	*trans*	19	*p.o.*	100	100	100	60	—
					i.p.	100	100	100	70	—
15′B		1	*cis*	17	*p.o.*	100	100	70	50	—
					i.p.	100	100	80	50	—
15C		1	*trans*	19	*p.o.*	100	100	90	60	—
					i.p.	100	100	100	70	—
15D		1	*trans*	19	*p.o.*	100	100	70	60	—
					i.p.	100	100	100	80	—
15E		1	*trans*	20	*p.o.*	100	80	50	20	—
					i.p.	90	80	80	80	—
15F		1	*trans*	18	*p.o.*	100	100	100	100	—
					i.p.	100	100	100	100	—
15′F		1	*cis*	19	*p.o.*	100	100	100	90	—
					i.p.	100	100	100	100	—
15G		1	*trans*	20	*p.o.*	100	100	100	100	—
					i.p.	100	100	100	90	—
15H		1	*trans*	18	*p.o.*	100	100	100	80	—
					i.p.	100	100	100	100	—
15I		1	*trans*	20	*p.o.*	100	100	100	100	90
					i.p.	100	100	100	100	100
15J		1	*trans*	20	*p.o.*	100	100	100	90	70
					i.p.	100	100	100	100	90
15K		1	*trans*	18	*p.o.*	100	100	90	40	—
					i.p.	100	100	100	50	—
15L		1	*trans*	18	*p.o.*	100	100	50	20	—
					i.p.	100	100	60	40	—
15N		1	*trans*	18	*p.o.*	100	100	100	100	90
					i.p.	100	100	100	100	100
15O		1	*trans*	18	*p.o.*	100	100	100	100	100
					i.p.	100	100	100	100	50
15P		1	*trans*	19	*p.o.*	100	100	100	70	—
					i.p.	100	100	100	80	—
15Q		1	*trans*	20	*p.o.*	100	100	100	100	80
					i.p.	100	100	100	100	100
15′Q		1	*cis*	20	*p.o.*	100	100	100	60	—
					i.p.	100	100	100	70	—
15R		1	*trans*	19	*p.o.*	100	100	100	100	80
					i.p.	100	100	100	100	100
15S		1	*trans*	19	*p.o.*	100	100	70	50	—
					i.p.	100	100	100	70	—
15T		1	*trans*	18	*p.o.*	100	90	50	20	—
					i.p.	100	100	70	50	—
15V		1	*trans*	20	*p.o.*	100	100	100	100	—
					i.p.	100	100	100	100	—
15W		1	*trans*	16	*p.o.*	100	100	50	40	—
					i.p.	100	100	40	20	—
15X		1	*trans*	19	*p.o.*	100	100	80	50	—
					i.p.	100	100	100	80	—
15Y		1	*trans*	16	*p.o.*	100	100	80	50	—
					i.p.	100	100	100	80	—

Table 1. (Continued)

Compd.[b]	Ar	*n*	Stereo-chemistry	Dose[c] (mg/kg)	Route	% Survival rate on day				
						3	9	14	21	30
15Z		1	*trans*	20	*p.o.*	100	100	100	80	—
					i.p.	100	100	100	100	—
15AA		1	*trans*	17	*p.o.*	100	100	80	60	—
					i.p.	100	100	90	90	—
15AB		1	*trans*	20	*p.o.*	100	100	90	60	—
					i.p.	100	100	90	70	—
15AC		1	*trans*	20	*p.o.*	100	100	100	100	—
					i.p.	100	100	100	100	—
15AD		1	*trans*	20	*p.o.*	100	100	100	100	—
					i.p.	70	70	70	70	—
16B		2	*trans*	20	*p.o.*	100	100	100	100	80
					i.p.	100	100	100	100	100
16C		2	*trans*	18	*p.o.*	100	90	50	40	—
					i.p.	100	100	100	80	—
16E		2	*trans*	20	*p.o.*	100	100	100	70	50[d]
					i.p.	100	100	100	100	90[d]
16F		2	*trans*	18	*p.o.*	100	100	100	100	100
					i.p.	100	100	100	100	100
16M		2	*trans*	20	*p.o.*	100	100	60	50	—
					i.p.	100	100	100	70	—
16N		2	*trans*	20	*p.o.*	100	100	100	100	100
					i.p.	100	100	100	100	100
16R		2	*trans*	20	*p.o.*	100	100	100	100	100
					i.p.	100	100	100	100	100
16S		2	*trans*	20	*p.o.*	100	100	80	60	—
					i.p.	100	100	100	100	—
16U		2	*trans*	18	*p.o.*	100	100	100	100	—
					i.p.	100	100	100	100	—
16V		2	*trans*	20	*p.o.*	100	100	100	100	100
					i.p.	100	100	100	100	100
16X		2	*trans*	20	*p.o.*	100	100	90	40	—
					i.p.	100	100	100	100	—
16Z		2	*trans*	20	*p.o.*	100	100	100	60	—
					i.p.	100	100	100	90	—
16AA		2	*trans*	20	*p.o.*	100	70	40	20	—
					i.p.	90	90	70	40	—
31		2	*trans* (cyclohexane analog)	20	*p.o.*	70	70	70	30	—
					i.p.	60	60	60	60	—
Itraconazole				20	*p.o.*	50	20	0		
					i.p.	30	0			
Fluconazole				20	*p.o.*	100	100	70	60	—
Control (no drug)				0		0				

—: No data. *a*) *In vivo* activity was determined in mice (each group consisted of ten male mice, ddY strain, 5 weeks old) infected systemically using an intravenous challenge of 6 to 9×10^6 cells of *Candida albicans* SANK 51486. The triazole compounds were administered orally (*p.o.*) or intraperitoneally (i.p.) 1, 4, 24 h post infection. 0.5% Aqueous tragacantha pulverata (for **16**E and **16**V, 0.5% aqueous carboxymethyl cellulose sodium salt) was used as a vehicle for *p.o.* administration. *b*) Oxalic acid salts of the triazole derivatives except for **15**E, **15**V, **15**X, **15**AC, **15**AD, **16**E, **16**M, **16**R, **16**X and **31** were prepared and tested. *c*) *Per* administration. *d*) On day 29.

Table 3. All the control mice started to die after 10 d post infection. Here again, **16**R showed an excellent protecting effect. This is a remarkable feature of compound **16**R, since currently used antifungal agents have low efficacies against *Cryptococcus.*

The *in vitro* antifungal activity of **16**R, compared with those of fluconazole and itraconazole, against various fungi is shown in Table 4.

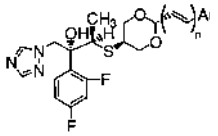
Compound **16**R has now been named R-102557, and its preclinical study is under way.

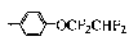
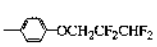
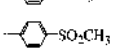
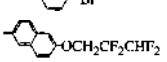
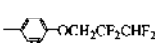
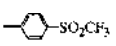
Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded either on a JASCO A-102 or Nic 5SCX spectrometer. Proton magnetic resonance (^{1}H-NMR) spectra were recorded either on a JEOL GX-270 (270 MHz), Varian EM-360L (60 MHz) or JNM GSX-400 (400 MHz) spectrometer. Mass spectra (MS) and high-resolution MS (HR-MS) were recorded on JEOL JMS D300 spectrometer. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; td, triplet of doublets; tt, triplet of triplets; q, quartet; quint, quintet; m, multiplet; br, broad. Rotations were determined on a Perkin-Elmer 241 spectrometer at 25 °C. Chromatography columns were prepared with silica gel (60—110 mesh, Kanto Chemical Co., Inc.). The amount of the silica gel used is shown in parentheses. The Lobar® column used was LiChroprep® Si 60, E. Merck, 40—63 μm, Size B (310-25).

***S*-(*trans*-2-Phenyl-1,3-dioxan-5-yl) Thioacetate (7)** A solution of *cis*-2-phenyl-1,3-dioxan-5-yl *p*-toluenesulfonate[11] (**6**, 29.0 g, 86.8 mmol) and sodium thioacetate (17.0 g, 149 mmol) in DMF (200 ml) was stirred at 115—120 °C for 1 h. After the mixture was cooled, it was partitioned between benzene and H_2O. The organic layer was dried and concentrated to give a brown oily residue, which was chromatographed (300 g, benzene : hexane = 2 : 1, v/v) to afford a crude product of **7** as a crystalline solid. Recrystallization from benzene–hexane gave **7** (8.99 g, 43%) as needles, mp 95—96 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.37 (3H, s), 3.79 (2H, t, J=11 Hz), 4.03 (1H, tt, J=11, 5 Hz), 4.31 (2H, dd, J=11, 5 Hz), 5.47 (1H, s), 7.35—7.5 (5H, m). IR ($CHCl_3$) cm^{-1}: 1690, 1383, 1146, 1084. MS *m/z*:

Table 2. Comparative Antifungal Efficacies of Various Dioxane–Triazole Compounds against Systemic Infection with *Aspergillus*[a)]



Compd.[b)]	Ar	*n*	Species	% Survival rate on day			
				3	6	9	14
15A		1	*A. fumigatus*	80	40	0	
			A. flavus	100	70	10	10
15B		1	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	50	0
15C		1	*A. fumigatus*	90	70	60	50
			A. flavus	90	70	10	10
15D		1	*A. fumigatus*	100	100	100	70
			A. flavus	100	100	80	0
15E		1	*A. fumigatus*	100	80	80	80
			A. flavus	100	40	0	
15F		1	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	100	100
15G		1	*A. fumigatus*	100	70	60	60
			A. flavus	80	40	30	0
15H		1	*A. fumigatus*	100	30	20	20
			A. flavus	100	100	90	20
15I		1	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	90	30
15J		1	*A. fumigatus*	100	20	20	10
			A. flavus	40	20	10	0
15N		1	*A. fumigatus*	100	100	100	100
			A. flavus	100	90	90	70
15O		1	*A. fumigatus*	90	40	10	10
			A. flavus	30	0		
15P		1	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	80	0
15Q		1	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	100	80
15R		1	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	100	100
15S		1	*A. fumigatus*	100	60	40	30
			A. flavus	100	80	0	
15T		1	*A. fumigatus*	100	80	70	50
			A. flavus	100	40	0	
15V		1	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	100	100
15AC		1	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	100	100
15AD		1	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	100	100
16B		2	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	100	90
16C		2	*A. fumigatus*	30	20	20	20
			A. flavus	90	30	0	
16E		2	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	100	40
16F		2	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	100	90
16N		2	*A. fumigatus*	100	100	100	100
			A. flavus	100	80	80	70
16R		2	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	100	100
16U		2	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	90	90
16V		2	*A. fumigatus*	100	100	100	100
			A. flavus	100	100	100	100
Itraconazole			*A. fumigatus*	100	60	50	30
			A. flavus	80	30	0	0
Control (no drug)			*A. fumigatus*	80	0		
			A. flavus	50	0		

a) *In vivo* activity was determined in mice (each group consisted of ten male mice, ddY strain, 5 weeks old) infected systemically using an intravenous challenge of either 5×10^6 conidia of *Aspergillus fumigatus* SANK 10569 or 3×10^6 conidia of *Aspergillus flavus* SANK 18497. The triazole compounds (20 mg/kg/dose) were administered orally 1, 4, 24, 31, 48 and 55 h post infection. 0.5% Aqueous tragacantha pulverata (for **16**E and **16**V, 0.5% aqueous carboxymethyl cellulose sodium salt) was used as a vehicle for administration. *b*) Oxalic acid salts of the triazole derivatives except for **15**E, **15**AC, **15**AD and **16**R were prepared and tested.

Table 3. Comparative Antifungal Efficacies of **16**R, Fluconazole and Itraconazole against Systemic Infection with *Cryptococcus neoformans*[a)]

Compound	Dose[b)] (mg/kg)	% Survival rate on day			
		10	20	30	40
16R	100	100	100	100	100
	25	100	100	100	90
	6.25	100	100	100	50
	1.56	100	100	80	0
Fluconazole	100	100	100	10	0
	25	100	90	0	
	6.25	100	80	0	
Itraconazole	100	100	70	0	
Control (no drug)	0	100	40	0	

a) *In vivo* activity was determined in mice (each group consisted of ten male mice, ddY strain, 5 weeks old) infected systemically using an intravenous challenge of 1×10^6 cells of *Cryptococcus neoformans* TIMM 0362. The triazole compounds were administered orally 4, 24, 48, 72 and 96 h post infection. 0.5% Aqueous carboxymethyl cellulose sodium salt was used as a vehicle for administration. *b*) Per administration.

Table 4. *In Vitro* Antifungal Activities[a)] of **16**R, Fluconazole and Itraconazole

Strain	MIC[b)] (μg/ml)		
	16R	Fluconazole	Itraconazole
C. albicans ATCC24433	0.125	0.5	0.125
C. albicans SANK51486	0.016	0.25	0.031
C. albicans TIMM3164	0.125	>4	0.25
C. albicans ATCC64550	1	>4	1
C. parapsilosis ATCC90018	0.063	0.5	0.125
C. glabrata ATCC90030	1	>4	1
C. krusei ATCC6258	0.125	>4	0.5
C. tropicalis ATCC750	0.125	2	0.5
C. neoformans TIMM1855	0.031	>4	0.25
A. fumigatus ATCC26430	0.125	>4	0.25
A. fumigatus SANK10569	0.125	>4	0.25
A. flavus SANK18497	0.25	>4	0.5

a) *In vitro* antifungal activities were measured at 35 °C (30 °C for *Aspergillus* spp.) in RPMI1640 (yeast nitrogen base for *C. neoformans*) at pH 7.0. *b*) Minimum inhibitory concentrations (MIC) were expressed as the minimum concentration of the test compounds that inhibit the growth of the fungi by 80%.

238(M^+), 237, 195, 162, 149, 116, 107, 73. *Anal.* Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92. Found: C, 60.25; H, 5.95.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[(*trans*-2-phenyl-1,3-dioxan-5-yl)thio]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (9) A 1.6 N solution of sodium methoxide in MeOH (2.5 ml, 4.0 mmol) was added to a solution of (2*R*,3*S*)-2-(2,4-trifluorophenyl)-3-methyl-2-[(1*H*-1,2,4-triazol-1-yl)-methyl]oxirane (**8**)[9a,b,e,10] (1.65 g, 6.57 mmol) and the thioester **7** (2.00 g, 8.40 mmol) in DMF (20 ml) at room temperature with stirring. The whole was then heated at 65 °C for 2 h. After the mixture was cooled, it was diluted with AcOEt and washed with brine. The organic layer was dried and concentrated to give a crude oil. Chromatography (60 g, AcOEt : benzene = 1 : 5, v/v) afforded **9** (2.53 g, 91%) as a crystalline solid, which was used for the next reaction without further purification. An analytical sample, mp 58—60 °C, was obtained by recrystallization from AcOEt–hexane. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.21 (3H, d, J=7 Hz), 3.36 (1H, q, J=7 Hz), 3.48 (1H, tt, J=11, 5 Hz), 3.75 (1H, t, J=11 Hz), 3.77 (1H, t, J=11 Hz), 4.40 (1H, ddd, J=11, 5, 3 Hz), 4.51 (1H, ddd, J=11, 5, 3 Hz), 4.84 (1H, d, J=14 Hz), 5.02 (1H, s), 5.05 (1H, d, J=14 Hz), 5.49 (1H, s), 7.7—7.8 (2H, m), 7.3—7.45 (4H, m), 7.45—7.53 (2H, m), 7.79 (2H, s). IR ($CHCl_3$) cm^{-1}: 3400, 1615, 1500, 1139. FAB-MS *m/z*: 448(M^++1). $[\alpha]_D^{25}$ −88 (c=1.07, $CHCl_3$). *Anal.* Calcd for $C_{22}H_{23}F_2N_3O_3S$: C, 59.05; H, 5.18; N, 9.39. Found: C, 58.97; H, 5.30; N, 9.42.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[[2-hydroxy-1-(hydroxymethyl)-ethyl]thio]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (10) A 4 M solution of HCl in 1,4-dioxane (0.35 ml, 1.4 mmol) was added to a solution of **9** (253 mg, 0.57 mmol) in MeOH (3.5 ml) at room temperature. After the mixture was stirred at room temperature for 30 min, powdered $NaHCO_3$ (250 mg, 3.0 mmol) was added. The mixture was stirred at room temperature for 10 min and then filtered. The concentrated filtrate was chromatographed (5 g, MeOH–AcOEt, 1 : 9, v/v) to afford **10** (179 mg, 88%) as a colorless, viscous oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.20 (3H, d, J=7 Hz), 3.15 (1H, br), 3.25 (1H, dddd, J=7, 7, 6, 6 Hz), 3.48 (1H, q, J=7 Hz), 3.75 (1H, dd, J=11, 6 Hz), 3.80 (1H, dd, J=11, 7 Hz), 3.81 (1H, dd, J=11, 7 Hz), 3.95 (1H, dd, J=11, 6 Hz), 4.1 (1H. br), 4.84 (1H, d, J=14 Hz), 5.19 (1H, d, J=14 Hz), 5.57 (1H, br s), 6.7—6.8 (2H, m), 7.39 (1H, td, J=9, 7 Hz), 7.75 (1H, s), 7.91 (1H, s). IR ($CHCl_3$): 3400, 1618, 1500 cm^{-1}. FAB-MS *m/z*: 360 (M^++1). $[\alpha]_D^{25}$ −61 (c=1.05, $CHCl_3$).

Aryl Aldehydes (11) The aryl aldehydes **11**A—**11**L, **11**N—**11**Q, **11**S, **11**W, and **11**AA were available at either Tokyo Kasei Kogyo Co., Ltd., Aldrich ,or Fluorochem Ltd. The aldehydes **11**T[15)] and **11**AB[16)] are known in the literature. The preparation of the other aryl aldehydes, **11**M, **11**R, **11**U, **11**V, **11**X—**11**Z, **11**AC, and **11**AD is described below.

2-Methoxy-4-(trifluoromethyl)benzaldehyde (11M) Methyl 2-fluoro-4-(trifluoromethyl)benzoate (560 mg, 2.52 mmol) was treated with NaOMe (272 mg, 5.04 mmol) in MeOH (4.2 ml) at room temperature for 5 h. The mixture was acidified with HCl, concentrated, and diluted with AcOEt. The insoluble materials were removed by filtration. The filtrate was concentrated and the residue was chromatographed (21 g, AcOEt : hexane = 1 : 3, v/v) to afford methyl 2-methoxy-4-(trifluoromethyl)benzoate (333 mg, 56%) as an oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 3.92 (3H, s), 3.96 (3H, s), 7.18 (1H, s), 7.25 (1H, d, J=8 Hz), 7.86 (1H, d, J=8 Hz).

A 1.5 M solution of DIBAL in toluene (5.9 ml, 8.9 mmol) was added to a stirred solution of methyl 2-methoxy-4-(trifluoromethyl)benzoate (1.04 g, 4.45 mmol) in toluene (10 ml) at 0 °C. After the mixture was stirred at 0 °C for 1 h, a saturated solution of NH_4Cl was added, and the mixture was filtered through Celite. The precipitates were washed with toluene. The organic layer was separated and concentrated to give crude 2-methoxy-4-(trifluoromethyl)benzyl alcohol, ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.2 (1H, br), 3.91 (3H, s), 4.73 (2H, s), 7.08 (1H, s), 7.23 (1H, d, J=8 Hz), 7.43 (1H, d, J=8 Hz), as an oil. This alcohol, without further purification, was treated with activated MnO_2 (8.6 g, 99 mmol) in CH_2Cl_2 (26 ml) at room temperature for 1.3 h. The mixture was filtered and the filtrate was concentrated to give 2-methoxy-4-(trifluoromethyl)benzaldehyde (**11**M) (756 mg, 83%) as a pale yellow solid, which was air-sensitive and unsuitable for further purification. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 3.92 (3H, s), 7.22 (1H, s), 7.29 (1H, d, J=8 Hz), 7.94 (1H, d, J=8 Hz), 10.51 (1H, s). IR (KBr) cm^{-1}: 1700.

4-(2,2,3,3-Tetrafluoropropoxy)benzaldehyde (11R) 4-Hydroxybenzaldehyde (5.3 g, 43 mmol) was added in small portions to a stirred suspension of NaH (55% mineral oil dispersion, 1.9 g, 43.5 mmol; washed with hexane) in *N*,*N*-dimethylacetamide (DMA) (25 ml) at 0 °C. When hydrogen gas ceased to evolve, 2,2,3,3-tetrafluoropropyl *p*-toluenesulfonate (11.14 g, 39 mmol) was added, and the whole was stirred at 120 °C for 2.3 h. After the solution was cooled, it was diluted with a mixture of benzene and hexane (*ca.* 1 : 1) and was washed with H_2O. The organic layer was dried and concentrated to give **11**R (8.85 g, 96%) as an air-sensitive oil, which was unsuitable for further purification. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 4.45 (2H, t, J=11.9 Hz), 6.06 (1H, tt, J=53, 5 Hz), 7.06 (2H, d, J=9 Hz), 7.88 (2H, d, J=9 Hz), 9.93 (1H, s). IR (neat) cm^{-1}: 1701.

4-(Trifluoromethylthio)benzaldehyde (11U) A 1.0 M solution of DIBAL in toluene (9.8 ml, 9.8 mmol) was added to a stirred solution of 4-(trifluoromethyl)benzonitrile (1.0 g, 4.9 mmol) in toluene (10 ml) at −30 °C. The mixture was worked up by adding a 10% aqueous solution of $KHSO_4$. The product was extracted with toluene. The organic layer was concentrated, and the residual oil was chromographed (10 g, AcOEt : hexane = 1 : 5, v/v) to afford **11**U (703 mg, 69%) as a crystalline solid, whose further purification was difficult owing to its air-sensitivity. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.81 (2H, d, J=8 Hz), 7.94 (2H, d, J=8 Hz), 10.09 (1H, s).

4-(Trifluoromethylsulfonyl)benzaldehyde (11V) A mixture of 4-(trifluoromethylthio)benzyl alcohol (500 mg, 2.4 mmol) and *m*-chloroperbenzoic acid (mCPBA, 70—75%, 1.48 g) in $CHCl_3$ (5 ml) was stirred at room temperature for 16 h and then at 70 °C for 5 h. After the mixture was cooled, it was washed with an aqueous solution of Na_2SO_3. Solvents were removed *in vacuo* to afford crude 4-(trifluoromethylsulfonyl)benzyl alcohol (507 mg, 88%) as a crystalline mass, mp 40—42 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.5 (1H, br), 4.89 (1H, d, J=8 Hz), 7.68 (2H, d, J=8 Hz), 8.01 (2H, d, J=8 Hz). IR (KBr) cm^{-1}: 3397 (br), 1597, 1370, 1217, 1205, 1187, 1141, 1072, 1052. MS *m/z*: 240 (M^+), 171, 107, 89, 77. *Anal.* Calcd for $C_8H_7F_3O_3S$: C, 40.00; H, 2.94. Found: C, 40.25; H, 3.15.

In a manner similar to that described above for the preparation of the alde-

hyde **11**M, 4-(trifluoromethylsulfonyl)benzyl alcohol (19.82 g, 82.5 mmol) was oxidized with activated MnO_2 (200 g, 2.3 mol) in CH_2Cl_2 (200 ml) to afford **11**V (14.1 g, 72%) as a crystalline solid, whose further purification was difficult owing to its air-sensitivity. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.18 (2H, d, J=8.3 Hz), 8.25 (2H, d, J=8 Hz), 10.20 (1H, s). MS (EI) *m/z*: 238 (M^+), 185, 169, 105, 77. IR ($CHCl_3$) cm^{-1}: 1700, 1373, 1218, 1141, 1074.

6-Chloropyridine-3-carbaldehyde (11X) Ethyl chloroformate (758 mg, 7.0 mmol) was added to a stirred solution of 6-chloro-3-nicotinic acid (1.0 g, 6.4 mmol) and Et_3N (642 mg, 6.3 mmol) in tetrahydrofuran (THF) (12 ml) at −15 °C. After the mixture was stirred for 15 min, a solution of $NaBH_4$ (648 mg, 17 mmol) in H_2O (6 ml) was added. The whole was stirred at −15 °C for 20 min, and then diluted with AcOEt (80 ml). The mixture was washed with brine and dried. Evaporation of the solvent and chromatographic purification (10 g, AcOEt : hexane=3 : 2) of the residue afforded (6-chloro-3-pyridyl)methanol (785 mg, 86%) as needles, mp 63—65 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.09 (1H, br t, J=6 Hz), 4.80 (2H, br d, J=6 Hz), 7.29 (1H, dd, J=8, 5 Hz), 7.89 (1H, dd, J=8, 2 Hz), 8.33 (1H, dd, J=5, 2 Hz). IR (KBr) cm^{-1}: 3266 (br), 1411, 1044. MS *m/z*: 143 (M^+), 108. *Anal.* Calcd for C_6H_6ClNO: C, 50.20; H, 4.21; N, 9.76. Found: C, 50.39; H, 4.35; N, 9.71.

A solution of dimethyl sulfoxide (DMSO) (1.02 g, 12.9 mmol) in CH_2Cl_2 (1 ml) was added to a solution of oxalyl chloride (1.37 g, 10.8 mmol) in CH_2Cl_2 (15 ml) at −78 °C. After the mixture was stirred at −78 °C for 10 min, a solution of (6-chloro-3-pyridyl)methanol (773 mg, 5.4 mmol) and Et_3N (2.18 g, 21.5 mmol) in CH_2Cl_2 (10 ml) was added. The mixture was allowed to warm to −15 °C over 20 min, and then treated with a saturated aqueous solution of NH_4Cl (25 ml). The product was extracted with AcOEt, and the organic layer was dried and concentrated to afford an oily residue, which was chromatographed (10 g, AcOEt : hexane=1 : 4, v/v) to afford **11**X (700 mg, 92%) as needles, mp 72—73 °C, whose further purification was difficult owing to its air-sensitivity. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.43 (1H, dd, J=8, 5 Hz), 8.24 (1H, dd, J=8, 2 Hz), 8.62 (1H, dd, J=5, 2 Hz), 10.64 (1H, s). IR (KBr) cm^{-1}: 1697, 1581, 1263. MS *m/z*: 141 (M^+), 112, 105.

2-Chloropyridine-3-carbaldehyde (11Y) In a manner similar to that described above for the preparation of the aldehyde **11**X, 2-chloro-3-nicotinic acid (1.0 g, 6.4 mmol) was reduced (ethyl chloroformate, $NaBH_4$) and then oxidized (DMSO, oxalyl chloride, Et_3N) to afford, after chromatography, **11**Y (664 mg, 74%) as a crude, crystalline solid, mp 37—41 °C, whose further purification was difficult owing to its air-sensitivity. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.43 (1H, dd, J=7, 5 Hz), 8.24 (1H, dd, J=7, 2 Hz), 8.62 (1H, dd, J=5, 2 Hz), 10.46 (1H, s). IR ($CHCl_3$) cm^{-1}: 1700, 1575, 1375. MS *m/z*: 141 (M^+), 112, 105.

6-(2,2,3,3-Tetrafluoropropoxy)-3-pyridinecarbaldehyde (11Z) 2,2,3,3-Tetrafluoropropanol was added slowly to a suspension of NaH (55% mineral oil dispersion, 840 mg, 19.3 mmol; washed with hexane) in DMF (40 ml) at 0 °C. When hydrogen gas ceased to evolve, a solution of ethyl 6-chloro-3-niconinate (3.40 g, 18.3 mmol) in DMF (15 ml) was added over a period of 30 min. After the mixture was stirred at 0 °C for 30 min, it was poured into ice water and the product was extracted with benzene. The extract was dried and the solvents were evaporated to give an oily residue, which was chromatographed (50 g, benzene : hexane=2 : 3) to afford ethyl 6-(2,2,3,3-tetrafluoropropoxy)-3-nicotinate (4.42 g, 86%) as an oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 4.39 (2H, q, J=7 Hz), 4.81 (2H, br t, J=13 Hz), 6.00 (1H, tt, J=53, 5 Hz), 6.87 (1H, d, J=9 Hz), 8.24 (1H, dd, J=9, 2.5 Hz), 8.83 (1H, d, J=2.5 Hz). IR ($CHCl_3$) cm^{-1}: 1717, 1604, 1280, 1119. MS *m/z*: 281 (M^+), 236, 180, 152, 151, 123, 122, 93.

In a manner similar to that described above for the preparation of the aldehyde **11**M, ethyl 6-(2,2,3,3-tetrafluoropropoxy)-3-nicotinate (2.2 g, 7.8 mmol) was reduced (DIBAL) and then oxidized (activated MnO_2) to afford **11**Z (1.76 g, 96%) as an air-sensitive oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 4.86 (2H, br t, J=13 Hz), 6.01 (1H, tt, J=53, 4 Hz), 6.97 (1H, d, J=9 Hz), 8.15 (1H, dd, J=9, 2.3 Hz), 8.65 (1H, d, J=2.3 Hz), 10.00 (1H, s). IR ($CHCl_3$) cm^{-1}: 1701, 1605, 1574, 1489, 1364, 1118. MS *m/z*: 237 (M^+), 186, 166, 136, 107, 106, 78.

6-Bromo-2-naphthaldehyde (11AC) A solution of methyl 6-bromo-2-naphtoate (2.50 g, 9.4 mmol) in THF (10 ml) was added to a stirred suspension of $LiAlH_4$ (537 mg, 14.1 mmol) in THF (15 ml) at 5—10 °C. After the mixture was stirred at 5—10 °C for 1 h, the reaction was worked up by adding a solution of NaOH (46 mg, 1.15 mmol) in H_2O (1.6 ml). The insoluble materials were removed by filtration and the filtrate was concentrated to afford crude product of (6-bromo-2-naphthy)methanol (2.0 g, gross yield=90%) as a powder, which was used for the next reaction without further purification.

In a manner similar to that described for the preparation of the aldehyde **11**M, the crude product of (6-bromo-2-naphthyl)methanol (1.0 g) obtained above was oxidized with activated MnO_2 (2.73 g, 31.4 mmol) to afford **11**AC (900 mg, 91%) as an oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.67 (1H, dd, J=9, 2 Hz), 7.83—7.89 (2H, m), 7.98 (1H, dd, J=9, 1.5 Hz), 8.08 (1H, d, J=2 Hz), 8.32 (1H, s), 10.15 (1H, s). MS *m/z*: 236, 234 (M^+), 207, 205, 189, 155, 126.

6-(2,2,3,3-Tetrahydropropoxy)-2-naphthaldehyde (11AD) Methyl 6-hydroxy-2-naphthoate (200 mg, 0.99 mmol) was added slowly to a stirred suspension of NaH (60% mineral oil dispersion, 39.6 mg, 0.99 mmol; washed with hexane) in DMA (2 ml) at 0 °C. When hydrogen gas ceased to evolve, a solution of 2,2,3,3-tetrafluoropropyl *p*-toluenesulfonate (311 mg, 1.09 mmol) in DMA (1 ml) was added at the same temperature. The whole was stirred at 100 °C for 2 h. After the solution was cooled, it was poured into ice water and the product was extracted with AcOEt. The organic layer was dried and concentrated to give an oily residue, which was chromatographed (5 g, AcOEt : hexane=1 : 9, v/v) briefly to afford methyl 6-(2,2,3,3-tetrafluoropropoxy)-2-naphthoate (302 mg, gross yield=96%) as a crude crystalline solid, which was used for the next reaction without further purification. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 3.95 (3H, s), 4.46 (2H, br t, J=11.9 Hz), 6.14 (1H, tt, J=53, 5 Hz), 7.10 (1H, d, J=2.4 Hz), 7.17 (1H, br d, J=8.8 Hz), 7.69 (1H, d, J=8.8 Hz), 7.80 (1H, d, J=8.8 Hz), 8.02 (1H, d, J=8.8 Hz), 8.49 (1H, s).

In a manner similar to that described for the preparation of the aldehyde **11**M, the crude product of methyl 6-(2,2,3,3-tetrafluoropropoxy)-2-naphthoate (300 mg) was reduced (DIBAL) and then oxidized (MnO_2) to afford **11**AD (210 g, 75%) as a colorless, air-sensitive solid. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 4.52 (2H, br t, J=12 Hz), 6.12 (1H, tt, J=53, 5 Hz), 7.22 (1H, d, J=2.5 Hz), 7.28 (1H, br d, J=8 Hz), 7.84 (1H, d, J=8 Hz), 7.96 (2H, d, J=8 Hz), 8.29 (1H, s).

(*E*)-3-Aryl-2-propenals (12) The aldehydes **12**A—**12**C, **12**F—**12**L, **12**N—**12**T and **12**V—**12**AD were prepared from the corresponding aryl aldehydes **11**A—**11**C, **11**F—**11**L, **11**N—**11**T and **11**V—**11**AD *via* a homologation sequence using triethyl phosphonoacetate (**17**). As a typical example the preparation of **12**F is described below. The aldehyde **12**E was prepared from **11**E according to the literature[12] using (triphenylphosphoranylidene)acetaldehyde. The aldehyde **12**D was prepared from **11**D in a similar manner as follows.

(*E*)-*p*-Nitrocinnamaldehyde (12D) A mixture of *p*-nitrobenzaldehyde (**11**D) (302 mg, 2.0 mmol), (triphenylphosphoranylidene)acetaldehyde (608 mg, 2.0 mmol) and toluene (5 ml) was refluxed for 100 min. The cooled mixture was concentrated *in vacuo* to give a brown mass, which was chromatographed on silica gel (20 g, AcOEt : hexane=1 : 9, v/v) to afford a crude product of **12**D. Recrystallizaion from benzene–hexane afforded a pure material of **12**D (237 mg, 67%) as yellow needles, mp 105—110 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.80 (1H, dd, J=17, 7 Hz), 7.53 (1H, d, J=17 Hz), 7.74 (2H, d, J=9 Hz), 8.30 (2H, d, J=9 Hz), 7.98 (1H, d, J=7 Hz). IR (KBr) cm^{-1}: 1682, 1518, 1346, 1124. MS *m/z*: 177 (M^+), 160, 130, 103, 102, 77. *Anal.* Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98; N, 7.91. Found: C, 61.06; H, 4.04; N, 7.71.

(*E*)-*p*-(Trifluoromethyl)cinnamaldehyde (12F) Triethyl phosphonoacetate (**17**) (4.63 g, 20.7 mmol) was added dropwise to a stirred suspension of NaH (55% mineral oil dispersion, 903 mg, 20.7 mmol; washed with hexane) in 1,2-dimethoxyethane (DME) (60 ml) at 0 °C. After the mixture was stirred at 0 °C for 15 min, 4-(trifluoromethyl)benzaldehyde (**11**F) (2.0 g, 11.5 mmol) was added. After the mixture had been stirred for 15 min, it was diluted with AcOEt and washed with H_2O. The organic layer was dried and concentrated to give an oily residue, which was chromatographed on silica gel (50 g, AcOEt : hexane=1 : 24, v/v) to afford ethyl (*E*)-*p*-(trifluoromethyl)cinnamate (**18**F) (2.75 g, 98%) as a crystalline mass, mp 31—32.5 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.35 (3H, t, J=7 Hz), 4.28 (1H, q, J=7 Hz), 6.51 (1H, d, J=16 Hz), 7.66 (4H, s), 7.69 (1H, d, J=16 Hz). IR (KBr) cm^{-1}: 1709, 1336, 1112. MS *m/z*: 244 (M^+), 216, 199, 171. *Anal.* Calcd for $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54. Found: C, 59.22; H, 4.66.

A 1.5 M solution of DIBAL in toluene (16.4 ml, 24.6 mmol) was added to a stirred solution of **18**F (3.00 g, 12.3 mmol) in toluene (15 ml) at 0 °C. After the mixture was stirred at 0 °C for 20 min, iced water was added carefully in small portions with stirring. The mixture was diluted with AcOEt and filtered through Celite. The organic layer was separated and concentrated to give a solid residue, which was recrystallized from benzene–hexane to give (*E*)-*p*-(trifluoromethyl)cinnamyl alcohol (**19**F) (2.36 g, 96%) as colorless needles, mp 53—55 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.57 (1H, br), 4.36 (2H, br t, J=5 Hz), 6.44 (1H, dt, J=16, 5 Hz), 6.66 (1H, d, J=16 Hz), 7.47 (2H, d, J=8 Hz), 7.56 (2H, d, J=8 Hz). IR (KBr) cm^{-1}: 1332, 1127, 1067.

MS *m/z*: 202 (M^+), 160. *Anal.* Calcd for $C_{10}H_9F_3O$: C, 59.41; H, 4.49. Found: C, 59.19; H, 4.54.

A mixture of **19**F (2.15 g, 10.6 mmol) and activated MnO_2 (14 g, 161 mmol) in CH_2Cl_2 (30 ml) was stirred at room temperature for 2 h. The mixture was filtered, and the filtrate was concentrated to give a crystalline residue, which was recrystallized from from benzene–hexane to give (*E*)-*p*-(trifluoromethyl)cinnamaldehyde (**12**F) (1.92 g, 90%) as colorless needles, mp 60—61 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.78 (1H, dd, J=16, 7 Hz), 7.53 (1H, d, J=16 Hz), 7.69 (4H, s), 9.76 (1H, d, J=7 Hz). IR (KBr) cm^{-1}: 1680, 1630, 1321, 1173, 1123, 1066. MS *m/z*: 200 (M^+), 199, 171, 151, 145, 131, 103, 102. *Anal.* Calcd for $C_{10}H_7F_3O$: C, 60.01; H, 3.52. Found: C, 59.85; H, 3.55.

(2*E*,4*E*)-5-Aryl-2,4-pentadienals (13) The aldehydes **13**B, **13**C, **13**F, **13**M, **13**N, **13**R, **13**S, **13**U, **13**V, **13**X, **13**Z and **13**AA were prepared from the corresponding aryl aldehydes **11**B, **11**C, **11**F, **11**M, **11**N, **11**R, **11**S, **11**U, **11**V, **11**X, **11**Z and **13**AA *via* a homologation sequence using triethyl phosphonocrotonate (**20**). As a typical example, the preparation of **13**F is described below. The aldehyde **13**E was prepared from **11**E using (triphenylphosphoranilidene)crotonaldehyde as follows.

4-[(1*E*,3*E*)-5-Oxo-1,3-pentadienyl]benzonitrile (13E) A mixture of 4-formylbenzonitrile (**11**E) (13.1 g, 99 mmol), (triphenylphosphoranilidene)-crotonaldehyde[13] (40 g, 120 mmol) and CH_2Cl_2 (200 ml) was stirred overnight. The mixture was concentrated *in vacuo* and the residual solid was chromatographed on silica gel (250 g) to remove polar byproducts. Elution with AcOEt afforded a crude product, which contained geometrical isomers, as judged by TLC. Then the mixture was dissolved in toluene (150 ml) and the solution was irradiated and refluxed for 12 h with a 300W tungsten lamp (visible light). The mixture was cooled and concentrated *in vacuo* to leave a solid residue, which was chromatographed on silica gel (1.2 kg). The fractions eluted with AcOEt–toluene (1 : 9, v/v) was concentrated and the crystals emerged were collected by filtration to give **13**E (3.46 g, 19%) as light brown needles, mp 147—150 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.36 (1H, dd, J=15.3, 7.8 Hz), 7.00 (1H, d, J=15.6 Hz), 7.09 (1H, dd, J=15.6, 10.3 Hz), 7.27 (1H, dd, J=15.3, 10.3 Hz), 7.59 (2H, d, J=8.4 Hz), 7.67 (2H, d, J=8.4 Hz), 9.67 (1H, d, J=7.8 Hz). IR (KBr) cm^{-1}: 2226, 1683, 1670, 1626. MS *m/z*: 183 (M^+), 154, 140, 127, 115. *Anal.* Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.56; H, 5.05; N, 7.62.

(2*E*,4*E*)-5-[4-(Trifluoromethyl)phenyl]-2,4-pentadienal (13F) Triethyl phosphonocrotonate (**20**) (25.9 g, 103 mmol) was added dropwise to a stirred suspension of NaH (55% mineral oil dispersion, 4.51 g, 103 mmol; washed with hexane) in DME (70 ml) at 0 °C. After the mixture was stirred at 0 °C for 15 min, 4-(trifluoromethyl)benzaldehyde (**11**F) (10.0 g, 57.4 mmol) was added slowly. After the mixture had been stirred for 10 min, it was poured into ice water and the product was extracted with AcOEt. The organic layer was dried and concentrated to give an oily residue, which was chromatographed (150 g, AcOEt : hexane = 3 : 47, v/v) to afford **21**F (11.2 g, 72%) as an oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.32 (3H, t, J=7 Hz), 4.24 (2H, q, J=7 Hz), 6.05 (1H, d, J=15 Hz), 6.85—7.0 (2H, m), 7.44 (1H, ddd, J=15, 8, 2.6 Hz), 7.55 (2H, d, J=9 Hz), 7.61 (2H, d, J=9 Hz). IR ($CHCl_3$) cm^{-1}: 1707, 1631, 1326, 1171, 1133, 1068. MS *m/z*: 270 (M^+), 225, 197, 177, 128.

A 1.5 M solution of DIBAL in toluene (27.7 ml, 41.6 mmol) was added to a stirred solution of **21**F (5.31 g, 19.6 mmol) in toluene (50 ml) at 0 °C. After the mixture was stirred at 0 °C for 45 min, ice water were added in small portions with stirring. The mixture was diluted with AcOEt and filtered through Celite. The organic layer was separated and concentrated to give a solid residue, which was chromatographed (100 g, AcOEt : hexane = 1 : 4, v/v) and recrystallized from benzene–hexane to give **22**F (2.47 g, 55%) as colorless needles, mp 72—75 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.47 (1H, t, J=6 Hz), 4.28 (1H, t, J=6 Hz), 6.04 (1H, dt, J=15 Hz, J=6 Hz), 6.45 (1H, dd, J=15, 11 Hz), 6.57 (1H, d, J=16 Hz), 6.87 (1H, dd, J=16, 11 Hz), 7.47 (2H, d, J=9 Hz), 7.56 (2H, d, J=9 Hz). IR (KBr) cm^{-1}: 1327, 1120, 1070. MS *m/z*: 228 (M^+), 172, 159. *Anal.* Calcd for $C_{11}H_{11}F_3O$: C, 63.16; H, 4.86. Found: C, 62.90; H, 4.69.

A mixture of **22**F (1.19 g, 5.21 mmol) and activated MnO_2 (14.28 g, 164.2 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 0.5 h. The mixture was filtered, and the filtrate was concentrated to give **13**F (1.09 g, 92%) as an oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.33 (1H, dd, J=15, 7 Hz), 7.0—7.35 (3H, m), 7.60 (2H, d, J=9 Hz), 7.64 (2H, d, J=9 Hz), 9.65 (1H, d, J=7 Hz). IR (neat) cm^{-1}: 1674, 1622, 1323, 1067. MS *m/z*: 226 (M^+), 177, 129.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[(*trans*-2-substituted-1,3-dioxan-5-yl)thio]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (14—16) and Their *cis* Isomers (14′—16′) These compounds were prepared by acetalization reaction between the alcohol **10** and the corresponding aldehydes **11**, **12** and **13**. The *trans* isomers **14**—**16** were predominantly produced and easily separated from the *cis* isomers **14′**—**16′** by silica gel column chromatography. The *trans/cis* ratio was between 5 : 1 and 10 : 1. As a typical example the preparation of **15**F and **15′**F is described below. The spectral data are listed in Table 5.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-[[*trans*-2-[(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl]-1,3-dioxan-5-yl]thio]-2-butanol (15F) Molecular sieves 4A (pellet, 57.6 g) was added to a stirred solution of the alcohol **10** (5.90 g, 16.4 mmol), aldehyde **12**F (4.93 g, 24.6 mmol), and *p*-toluenesulfonic acid hydrate (4.69 g, 24.6 mmol) in CH_2Cl_2 (200 ml) at room temperature. After the mixture was stirred at room temperature for 4 h, it was treated with a diluted aqueous solution of $NaHCO_3$. The mixture was filtered, and the organic layer was dried and concentrated to give an oily residue, which was purified by column chromatography (250 g). Elution with AcOEt–hexane (1 : 24, v/v) gave the recovered aldehyde **12**F (2.19 g). Elution with AcOEt–hexane (1 : 1, v/v) afforded **15**F (5.93 g, 67%) as colorless crystals, mp 73—75 °C. Further elution with AcOEt–hexane (4 : 1, v/v) afforded the *cis* isomer **15′**F (753 mg, 8%) as a colorless oil.

8-(4-Chlorobenzylthio)-1,4-dioxaspiro[4.5]decane (24) 4-Chloro-α-toluenethiol (430 mg, 2.7 mmol) was added to a stirred suspension of NaH (55% mineral oil dispersion, 106 mg, 2.4 mmol; washed with hexane) in DMF (4 ml) at 0 °C. After the mixture was stirred at 0 °C for 5 min, 1,4-dioxaspiro[4.5]decan-8-yl methanesulfonate[17] (**23**, 512 mg, 2.2 mmol) was added. The whole was heated at 50 °C for 1 h. After the mixture was cooled, it was diluted with AcOEt and wshed with brine. The organic layer was dried over $MgSO_4$ and the solvents were removed *in vacuo* to leave an oily residue, which was purified by column chromatography (30 g). Elution with AcOEt–hexane (1 : 24, v/v) afforded **24** (438 mg, 68%) as an oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.4—2.0 (8H, m), 2.61 (1H, tt, J=6, 4 Hz), 3.70 (2H, s), 3.93 (4H, br s), 7.30 (4H, br s). IR ($CHCl_3$) cm^{-1}: 1496, 1371, 1208, 1123, 1110, 1033, 925. MS *m/z*: 298 (M^+), 173, 125, 99.

4-(4-Chlorobenzylthio)cyclohexanone (25) A 2 M solution of HCl (12.5 ml, 25 mmol) was added to a solution of **24** (11.0 g, 37 mmol) in a mixture of acetone (101 ml) and H_2O (25 ml), and the whole was stirred at 50 °C for 2 h. The cooled mixture was diluted with benzene and washed with brine. The organic layer was dried over $MgSO_4$. Solvents were removed *in vacuo* to leave **25** (9.4 g, 100%) as an oil, which was used for the next reaction without further purification. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.89 (2H, dddd, J=12, 9, 8, 6 Hz), 2.1—2.2 (2H, m), 2.29 (2H, ddd, J=14, 9, 5 Hz), 2.54 (1H, dt, J=14, 6 Hz), 2.97 (1H, tt, J=8, 4 Hz), 3.75 (2H, s), 7.29 (4H, br s).

1-(4-Chlorobenzylthio)-4-(methoxymethylene)cyclohexane (26) A suspension of sodium hydride (55% mineral oil dispersion, 146 mg, 3.34 mmol; washed with hexane) in degassed DMSO (18 ml) was heated at 55 °C for 2 h to obtain an almost clear solution of dimsyl sodium. (Methoxymethyl)triphenylphosphonium chloride (1.26 g, 3.67 mmol) was then added to the mixture at room temperature to obtain an orange-red solution. Then a solution of **25** (426 mg, 1.67 mmol) in DMSO (5 ml) was added at room temperature. The reaction was quenched by addition of H_2O. The product was extracted with toluene. The organic layer was dried over $MgSO_4$ and concentrated to afford an oily residue, which was chromatographed on silica gel (20 g). Elution with CH_2Cl_2–hexane (1 : 4, v/v) afforded **26** (370 mg, 78%) as an oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.2—1.5 (2H, m), 1.7—2.0 (3H, m), 2.0—2.2 (1H, m), 2.5—2.8 (2H, m), 3.53 (3H, s), 3.71 (2H, s), 5.77 (1H, s), 7.27 (4H, s). IR ($CHCl_3$) cm^{-1}: 1689, 1491, 1123, 1094. MS *m/z*: 282 (M^+), 157, 124.

***trans*-4-(4-Chlorobenzylthio)cyclohexanecarbaldehyde (27)** A mixture of **26** (955 mg, 3.4 mmol), 5 M HCl solution (1 ml, 5 mmol), acetone (20 ml), and H_2O (5 ml) was heated at 55 °C for 2 h. Then the mixture was concentrated *in vacuo* at room temperature. The residue was taken up in AcOEt, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent afforded an oily residue, which was chromatographed on silica gel (15 g). Elution with CH_2Cl_2–hexane (1 : 3, v/v) afforded a *ca.* 1 : 1 mixture of **27** and its *cis* isomer (865 mg, 95%). The isomeric ratio was determined by ^{1}H-NMR in $CDCl_3$; the benzylic protons of **27** appeared at δ 3.73 as a singlet whereas those of the *cis* isomer appeared at δ 3.67.

The above obtained mixture (865 mg) was treated, at room temperature for 2 h, with a solution of sodium methoxide prepared by dissolving sodium metal (23 mg, 1.0 mmol) in MeOH (15 ml). Acetic acid (0.2 ml) was then added and the mixture was concentrated *in vacuo.* The residue was taken up in AcOEt, and the extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvents afforded a solid residue, which was a *ca.* 4 : 1 mixture of **27** and its *cis* isomer, as indicated by ^{1}H-NMR. The residue was

Table 5. (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[(2-subustituted-1,3-dioxan-5-yl)thio]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (**14**—**16**) and the *cis* Isomers (**15′**B, **15′**F, **15′**Q)

Compd.	Yield (%)	mp (°C) (Solvent[a]) [Oxalic acid salt: mp (°C)]	IR cm^{-1} (State) Optical rotation[b]	^{1}H-NMR (270 MHz, $CDCl_3$)[c]	Formula	MS *m/z* Analysis % Calcd (Found)		
						C	H	N
14A	54	Oil [140—142]	1500, 1140, 1080 ($CHCl_3$) $[\alpha]_D$ −79.2 (c=1.45, $CHCl_3$)	1.20 (3H, d, 7), 3.35 (1H, q, 7), 3.44 (1H, tt, 11, 5), 3.73 (1H, t, 11), 3,75 (1H, t, 11), 4.39 (1H, ddd, 11, 5, 2), 4.50 (1H, ddd, 11, 5, 2), 4.85 (1H, d, 14), 5.02 (1H, s), 5.05 (1H, d, 14), 5.45 (1H, s), 6.65—6.8 (2H, m), 7.0—7.1 (3H, m), 7.37 (1H, td, 9, 7), 7.47 (2H, dd, 9, 6), 7.78 (2H, s)	$C_{22}H_{22}F_3N_3O_3S$	466 (M^++1), 342, 224		
14C[d]	56	Oil [159—159]	1500, 1140 ($CHCl_3$) $[\alpha]_D$ −75.2 (c=1.01, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.5—4.0 (3H, m), 4.2—4.6 (2H, m), 4.78 (1H, d, 14), 5.01 (1H, d, 1.5), 5.07 (1H, d, 14), 5.70 (1H, s), 6.5—7.8 (6H, m), 7.79 (2H, s)	$C_{22}H_{21}F_4N_3O_3S$	483 (M^+), 224		
14D	27	Oil [149—152]	1520, 1350 ($CHCl_3$) $[\alpha]_D$ −74.2 (c=1.02, $CHCl_3$)	1.20 (3H, d, 7), 3.15—4.0 (4H, m), 4.1—4.6 (2H, m), 4.77 (1H, d, 14), 5.00 (1H, d, 1.5), 5.02 (1H, d, 14), 5.48 (1H, s), 6.5—7.0 (2H, m), 7.2—7.6 (1H, m), 7.76 (2H, d, 8), 7.80 (2H, s), 8.26 (2H, d, 8)	$C_{22}H_{22}F_2N_4O_5S$	492 (M^+), 224		
15A	62	Oil [132—136]	1500, 1140 ($CHCl_3$) $[\alpha]_D$ −72.2 (c=1.00, $CHCl_3$)	1.19 (3H, d, 7), 3.34 (1H, q, 7), 3.42 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,67 (1H, t, 11), 4.32 (1H, ddd, 11, 5, 2), 4.44 (1H, ddd, 11, 5, 2), 4.82 (1H, d, 14), 5.01 (1H, s), 5.04 (1H, d, 14), 5.11 (1H, d, 4), 6.09 (1H, dd, 16, 4), 6.65—6.8 (2H, m), 6.77 (1H, d, 16), 7.02 (1H, t, 9), 7.3—7.4 (3H, m), 7.79 (2H, s)	$C_{24}H_{24}F_3N_3O_3S$	491 (M^+), 224		
15B	67	Oil [88—91]	1500, 1140 ($CHCl_3$) $[\alpha]_D$ −68.2 (c=1.22, $CHCl_3$)	1.19 (3H, d, 7), 3.34 (1H, q, 7), 3.41 (1H, tt, 11, 5), 3.64 (1H, t, 11), 3,66 (1H, t, 11), 4.32 (1H, ddd, 11, 5, 2), 4.44 (1H, ddd, 11, 5, 2), 4.82 (1H, d, 14), 5.01 (1H, s), 5.04 (1H, d, 14), 5.11 (1H, d, 5), 6.15 (1H, dd, 16, 5), 6.65—6.8 (2H, m), 6.76 (1H, d, 16), 7.2—7.4 (5H, m), 7.78 (2H, s)	$C_{24}H_{24}ClF_2N_3O_3S$	507 (M^+), 284, 224		
15′B	8	Oil [94—98]	1500, 1270, 1140 ($CHCl_3$) $[\alpha]_D$ −79.8 (c=1.30, $CHCl_3$)	1.21 (3H, d, 7), 3,11 (1H, t-like, 2), 3.50 (1H, q, 7), 4.2—4.4 (4H, m), 4.88 (1H, d, 15), 4.93 (1H, s), 5.16 (1H, d, 15), 5.23 (1H, d, 5), 6.21 (1H, dd, 17, 5), 6.65—6.8 (2H, m), 6.76 (1H, d, 17), 7.2—7.4 (5H, m), 7.77 (1H, s), 7.80 (1H, s)	$C_{24}H_{24}ClF_2N_3O_3S$	507 (M^+), 284, 224		
15C[d]	56	Oil [143—145]	1500, 1140 ($CHCl_3$) $[\alpha]_D$ −68.2 (c=1.02, $CHCl_3$)	1.20 (3H, d, 7), 3.1—3.9 (4H, m), 4.1—4.6 (2H, m), 4.79 (2H, d, 14), 5.01 (1H, d, 1.5), 5.06 (1H, d, 14), 5.12 (1H, d, 4.5), 6.19 (1H, dd, 16, 4.5), 6.5—7.0 (5H, m), 6.92 (1H, d, 16), 7.1—7.6 (1H, m), 7.80 (2H, s)	$C_{24}H_{23}F_4N_3O_3S$	509 (M^+), 284, 224		
15D	40	Oil [157—160]	1500, 1270, 1140 ($CHCl_3$) $[\alpha]_D$ −64.1 (c=2.43, $CHCl_3$)	1.19 (3H, d, 7), 3.35 (1H, q, 7), 3.42 (1H, tt, 11, 5), 3.66 (1H, t, 11), 3,68 (1H, t, 11), 4.34 (1H, ddd, 11, 5, 2), 4.46 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.04 (1H, d, 14), 5.04 (1H, s), 5.16 (1H, d, 4), 6.32 (1H, dd, 16, 4), 6.65—6.8 (2H, m), 6.87 (1H, d, 16), 7.36 (1H, td, 9, 8), 7.53 (2H, d, 9), 7.79 (1H, s), 7.80 (1H, s), 8.19 (2H, d, 9)	$C_{24}H_{24}F_2N_4O_5S$	518 (M^+), 284, 224		
15E	66	164—165 (A–H)	2230, 1499, 1141 ($CHCl_3$) $[\alpha]_D$ −77.9 (c=0.52, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.41 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,67 (1H, t, 11), 4.33 (1H, ddd, 11, 5, 2), 4.46 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.03 (1H, s), 5.04 (1H, d, 14), 5.14 (1H, d, 4), 6.28 (1H, dd, 16, 4), 6.7—6.8 (2H, m), 6.82 (1H, d, 16), 7.3—7.45 (1H, m), 7.49 (2H, d, 8), 7.62 (2H, d, 8), 7.79 (2H, s)	$C_{25}H_{24}F_2N_4O_5S$	498 (M^+), 284, 224 60.23 4.85 11.24 (60.34 5.05 11.03)		
15F	67	73—75 (A–H))	1617, 1500, 1326, 1136 (KBr) $[\alpha]_D$ −73.8 (c=1.00, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.43 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,67 (1H, t, 11), 4.33 (1H, ddd, 11, 5, 2), 4.46 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.03 (1H, s), 5.04 (1H, d, 14), 5.14 (1H, d, 4), 6.26 (1H, dd, 16, 4), 6.7—6.8 (2H, m), 6.84 (1H, d, 16), 7.36 (1H, td, 9, 7), 7.50 (2H, d, 8), 7.58 (2H, d, 8), 7.79 (2H, s)	$C_{25}H_{24}F_5N_4O_5S$	541 (M^+), 521, 224 55.45 4.47 7.76 (55.70 4.57 7.37)		
15′F	8	Oil [112—114]	1618, 1499, 1326, 1140, 1131 ($CHCl_3$) $[\alpha]_D$ −83.1 (c=1.03, $CHCl_3$)	1.22 (3H, d, 7), 3,14 (1H, t-like), 3.50 (1H, q, 7), 4.2—4.4 (4H, m), 4.88 (1H, d, 15), 4.94 (1H, s), 5.16 (1H, d, 15), 5.27 (1H, d, 5), 6.33 (1H, dd, 17, 5), 6.6—6.8 (2H, m), 6.84 (1H, d, 17), 7.37 (1H, td, 9, 7), 7.50 (2H, d, 8), 7.58 (2H, d, 8), 7.78 (1H, s), 7.81 (1H, s	$C_{25}H_{24}F_5N_4O_5S$	541 (M^+), 521, 224		
15G	57	Oil [63—69]	1499, 1334, 1135 ($CHCl_3$) $[\alpha]_D$ −73.9 (c=0.59, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.43 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,68 (1H, t, 11), 4.33 (1H, ddd, 11, 5, 2), 4.45 (1H, ddd, 11, 5, 2), 4.84 (1H, d, 14), 5.03 (1H, s), 5.04 (1H, d, 14), 5.14 (1H, d, 4), 6.24 (1H, dd, 16, 4), 6.7—6.8 (2H, m), 6.84 (1H, d, 16), 7.73—7.76 (4H, s), 7.65 (1H, s), 7.79 (2H, s)	$C_{25}H_{24}F_5N_3O_5S$	541 (M^+), 318, 284, 224		
15H	60	Oil [56—71]	1499, 1468, 1334, 1142 ($CHCl_3$) $[\alpha]_D$ −73.4 (c=1.06, $CHCl_3$)	1.20 (3H, d, 7), 3.35 (1H, q, 7), 3.43 (1H, tt, 11, 5), 3.66 (1H, t, 11), 3,68 (1H, t, 11), 4.33 (1H, ddd, 11, 5, 2), 4.45 (1H, ddd, 11, 5, 2), 4.84 (1H, d, 14), 5.03 (1H, s), 5.04 (1H, d, 14), 5.15 (1H, d, 4), 6.31 (1H, dd, 16, 4), 6.7—6.8 (2H, m), 6.98 (1H, d, 16), 7.21 (1H, t), 7.36 (1H, q, 8), 7.52 (1H, t, 8), 7.67 (1H,t), 7.79 (2H, s)	$C_{25}H_{23}F_6N_3O_5S$	559 (M^+), 540, 336, 224		
15I	66	Oil [149—152]	1499, 1332, 1137 ($CHCl_3$) $[\alpha]_D$ −72.1 (c=0.63, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.41 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,68 (1H, t, 11), 4.34 (1H, m), 4.46 (1H, m), 4.83 (1H, d, 14), 5.04 (1H, d, 14), 5.04 (1H, s), 5.15 (1H, d, 4), 6.36 (1H, dd, 16, 4), 6.7—6.8 (2H, m), 6.97 (1H, d, 16), 7.3—7.45 (3H, m), 7.58 (1H, t, 8), 7.79 (2H, s)	$C_{25}H_{23}F_6N_3O_5S$	559 (M^+), 540, 336, 224		

Table 5. (Continued)

Compd.	Yield (%)	mp (°C) (Solvent[a]) [Oxalic acid salt: mp (°C)]	IR cm^{-1} (State) Optical rotation[b]	^{1}H-NMR (270 MHz, $CDCl_3$)[c]	Formula	MS *m/z* Analysis % Calcd (Found)		
						C	H	N
15J	66	Oil [105—113]	1500, 1334, 1135 ($CHCl_3$) $[\alpha]_D$ −72.7 (c=0.55, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.42 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,67 (1H, t, 11), 4.33 (1H, ddd, 11, 5, 2), 4.46 (1H, ddd, 11, 5, 2), 4.84 (1H, d, 14), 5.03 (1H, s), 5.04 (1H, d, 14), 5.14 (1H, d, 4), 6.34 (1H, dd, 16, 4), 6.7—6.8 (2H, m), 6.96 (1H, d, 16), 7.16 (1H, t, 9), 7.36 (1H, q, 8), 7.52 (1H, m), 7.74 (1H, dd, 6, 2), 7.79 (2H, s)	$C_{25}H_{23}F_6N_3O_5S$	559 (M^+), 540, 336, 224		
15K	43	Oil [124—130]	1499, 1479, 1134, 1142 ($CHCl_3$) $[\alpha]_D$ −73.7 (c=1.00, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.41 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,67 (1H, t, 11), 4.33 (1H, ddd, 11, 5, 2), 4.45 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.03 (1H, s), 5.04 (1H, d, 14), 5.13 (1H, d, 4), 6.10 (1H, dd, 16, 4), 6.7—6.8 (2H, m), 7.11 (1H, d, 16), 7.22 (1H, td, 8, 3), 7.3—7.4 (2H, m), 7.63 (1H, dd, 9, 5), 7.79 (2H, s)	$C_{25}H_{23}F_6N_3O_5S$	559 (M^+), 540, 336, 224		
15L	44	Oil [70—72]	1510, 1240, 1140, 965 ($CHCl_3$) $[\alpha]_D$ −75.9 (c=1.45, $CHCl_3$)	1.19 (3H, d, 7), 3.34 (1H, q, 7), 3.41 (1H, tt, 11, 5), 3.64 (1H, t, 11), 3,66 (1H, t, 11), 3.81 (3H, s), 4.32 (1H, ddd, 11, 5, 2), 4.43 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.01 (1H, s), 5.04 (1H, d, 14), 5.10 (1H, d, 4), 6.04 (1H, dd, 16, 4), 6.65—6.8 (2H, m), 6.74 (1H, d, 16), 6.86 (2H, d, 9), 7.3—7.4 (1H, m), 7.34 (2H, d, 9), 7.79 (1H, s), 7.80 (1H, s)	$C_{25}H_{27}F_2N_3O_4S$	503 (M^+), 265, 224, 219		
15N	43	Amorphous [68—71]	1500, 1255, 1140, 965 ($CHCl_3$) $[\alpha]_D$ −77.1 (c=0.52, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.42 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,67 (1H, t, 11), 4.32 (1H, ddd, 11, 5, 2), 4.45 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.01 (1H, s), 5.03 (1H, d, 14), 5.12 (1H, d, 4), 6.15 (1H, dd, 16, 4), 6.7—6.8 (2H, m), 6.79 (1H, d, 16), 7.17 (2H, d, 9), 7.3—7.45 (1H, m), 7.42 (2H, d, 9), 7.79 (2H, s)	$C_{25}H_{24}F_5N_3O_4S$	557 (M^+), 538, 334, 224		
15O	53	Amorphous [72—77]	1500, 1257, 1217, 1140 ($CHCl_3$) $[\alpha]_D$ −73.2 (c=0.62, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.42 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,67 (1H, t, 11), 4.33 (1H, ddd, 11, 5, 2), 4.45 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.01 (1H, s), 5.04 (1H, d, 14), 5.13 (1H, d, 4), 6.20 (1H, dd, 16, 4), 6.7—6.8 (2H, m), 6.79 (1H, d, 16), 7.13 (1H, d, 7), 7.2—7.4 (3H, m), 7.79 (2H, s)	$C_{25}H_{24}F_5N_3O_4S$	557 (M^+), 538, 334, 224		
15P	64	Oil [71—76]	1509, 1499, 1382, 1132 ($CHCl_3$) $[\alpha]_D$ −68.4 (c=0.57, $CHCl_3$)	1.19 (3H, d, 7), 3.34 (1H, q, 7), 3.42 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,67 (1H, t, 11), 4.32 (1H, ddd, 11, 5, 2), 4.45 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.02 (1H, s), 5.04 (1H, d, 14), 5.12 (1H, d, 4), 6.13 (1H, dd, 16, 4), 6.51 (1H, t, 74), 6.7—6.8 (2H, m), 6.78 (1H, d, 16), 7.08 (2H, d, 9), 7.3—7.4 (1H, m), 7.40 (2H, d, 9),7.79 (2H, s)	$C_{25}H_{25}F_4N_3O_4S$	539 (M^+), 520, 284, 265, 224		
15Q	60	Oil [71—78]	1507, 1500, 1278, 1184, 1133 ($CHCl_3$) $[\alpha]_D$ −71.7 (c=0.66, $CHCl_3$)	1.19 (3H, d, 7), 3.34 (1H, q, 7), 3.42 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,67 (1H, t, 11), 4.33 (1H, ddd, 11, 5, 2), 4.45 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.02 (1H, s), 5.04 (1H, d, 14), 5.12 (1H, d, 4), 5.91 (1H, tt, 53, 3), 6.15 (1H, dd, 16, 4), 6.7—6.8 (2H, m), 6.79 (1H, d, 16), 7.17 (2H, d, 9), 7.3—7.45 (1H, m), 7.41 (2H, d, 9),7.79 (2H, s)	$C_{26}H_{25}F_6N_3O_4S$	589 (M^+), 570, 538, 366, 224		
15′Q	7	Oil [99—101]	1508, 1500, 1278, 1184, 1130 ($CHCl_3$) $[\alpha]_D$ −74.6 (c=0.89, $CHCl_3$)	1.22 (3H, d, 7), 3.12 (1H, t-like, 2), 3.51 (1H, q, 7), 4.2—4.4 (4H, m), 4.89 (1H, d, 15), 4.93 (1H, s), 5.17 (1H, d, 15), 5.25 (1H, d, 5), 5.90 (1H, tt, 53, 3), 6.22 (1H, dd, 17, 5), 6.65—6.8 (2H, m), 6.79 (1H, d, 17), 7.17 (2H, d, 9), 7.37 (1H, td, 9, 7), 7.42 (2H, d, 9), 7.78 (1H, s), 7.81 (1H, s)	$C_{26}H_{25}F_6N_3O_4S$	589 (M^+), 570, 538, 342, 224		
15R	63	Oil [72—79]	1511, 1499, 1277, 1140, 1133 ($CHCl_3$) $[\alpha]_D$ −73.1 (c=0.55, $CHCl_3$)	1.19 (3H, d, 7), 3.34 (1H, q, 7), 3.41 (1H, tt, 11, 5), 3.64 (1H, t, 11), 3,67 (1H, t, 11), 4.33 (1H, m), 4.35 (2H, t, 12), 4.44 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.01 (1H, s), 5.04 (1H, d, 14), 5.11 (1H, d, 4), 6.06 (1H, tt, 53, 5), 6.08 (1H, dd, 16, 4), 6.65—6.8 (2H, m), 6.75 (1H, d, 16), 6.88 (2H, d, 9), 7.3—7.45 (1H, m), 7.33 (2H, d, 9),7.79 (2H, s)	$C_{27}H_{27}F_6N_3O_4S$	603 (M^+), 319, 265, 224		
15S	37	Oil [79—81]	1517, 1497, 1275, 1136, 965 ($CHCl_3$) $[\alpha]_D$ −62.9 (c=0.75, $CHCl_3$)	1.19 (3H, d, 7), 2.48 (3H, s), 3.33 (1H, q, 7), 3.41 (1H, tt, 11, 5), 3.64 (1H, t, 11), 3,67 (1H, t, 11), 4.32 (1H, ddd, 11, 5, 2), 4.44 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.01 (1H, s), 5.04 (1H, d, 14), 5.11 (1H, d, 4), 6.13 (1H, dd, 16, 4), 6.65—6.8 (2H, m), 6.74 (1H, d, 16), 7.19 (2H, d, 9), 7.3—7.4 (1H, m), 7.32 (2H, d, 9), 7.79 (2H, s)	$C_{25}H_{27}F_2N_3O_3S_2$	519 (M^+), 284, 265, 234, 224		
15T[e]	58	Oil [87—92]	1500, 1140 ($CHCl_3$) $[\alpha]_D$ −62.2 (c=0.95, $CHCl_3$)	1.20 (3H, d, 7), 3.00 (3H, s), 3.33 (1H, q, 7), 3.5—4.0 (3H, m), 4.2—4.8 (2H, m), 4.80 (1H, d, 14), 5.08 (1H, d, 14), 5.15 (1H, d, 4), 6.30 (1H, dd, 17, 4), 6.55—7.0 (2H, m), 6.90 (1H, d, 17), 7.2—7.6 (1H, m), 7.58 (2H, d, 9), 7.80 (2H, s), 7.94 (2H, d, 8)	$C_{25}H_{27}F_2N_3O_5S_2$	551 (M^+), 284, 265, 224		
15V	65	Amorphous [86—88]	1594, 1500, 1368, 1218, 1141 (KBr) $[\alpha]_D$ −62.7 (c=1.01, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.44 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,68 (1H, t, 11), 4.34 (1H, ddd, 11, 5, 2), 4.47 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.03 (1H, s), 5.03 (1H, d, 14), 5.16 (1H, d, 4), 6.38 (1H, dd, 16, 4), 6.65—6.8 (2H, m), 6.89 (1H, d, 16), 7.36 (1H, td, 9, 7), 7.66 (2H, d, 9), 7.80 (2H, s), 8.00 (2H, d, 9)	$C_{25}H_{24}F_5N_3O_5S_2$	606 (M^++1, FAB) 49.58 (49.51	4.00 3.94	6.94 6.69)

Table 5. (Continued)

Compd.	Yield (%)	mp (°C) (Solvent[a]) [Oxalic acid salt: mp (°C)]	IR cm^{-1} (State) Optical rotation[b]	^{1}H-NMR (270 MHz, $CDCl_3$)[c]	Formula	MS *m/z* Analysis % Calcd (Found)		
						C	H	N
15W	52	Oil [*ca.* 80]	1500, 1140 ($CHCl_3$) $[\alpha]_D$ −62.2 (*c*=0.90, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.43 (1H, tt, 11, 5), 3.65 (1H, t, 11), 3,68 (1H, t, 11), 4.33 (1H, ddd, 11, 5, 2), 4.46 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.04 (1H, s), 5.04 (1H, d, 14), 5.14 (1H, d, 4), 6.25 (1H, dd, 17, 4), 6.7—6.8 (2H, m), 6.81 (1H, d, 17), 7.29 (1H, dd, 8, 5), 7.3—7.45 (1H, m), 7.73 (dt, 8, 1), 7.80 (2H, s), 8.51 (dd, 5, 1), 8.62 (1H, d, 1)	$C_{23}H_{24}F_2N_4O_3S$	474 (M^+), 284, 265, 224		
15X	63	73—76 (A–H)	1500, 1460, 1275, 1140, 1100 ($CHCl_3$) $[\alpha]_D$ −75.6 (*c*=0.52, $CHCl_3$)	1.19 (3H, d, 7), 3.33 (1H, q, 7), 3.43 (1H, tt, 11, 5), 3.64 (1H, t, 11), 3,67 (1H, t, 11), 4.32 (1H, ddd, 11, 5, 2), 4.46 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.03 (1H, d, 14), 5.04 (1H, s), 5.13 (1H, d, 4), 6.23 (1H, dd, 17, 4), 6.7—6.8 (2H, m), 6.78 (1H, d, 17), 7.30 (1H, d, 8), 7.35 (1H, td, 9, 7), 7.70 (1H, dd, 8, 2), 7.79 (2H, s), 8.38 (1H, d, 2)	$C_{23}H_{23}ClF_2N_4O_3S$	508 (M^+), 285, 265, 224		
15Y[f]	73	Oil	1500, 1400, 1140, 965 ($CHCl_3$) $[\alpha]_D$ −69.7 (*c*=0.69, $CHCl_3$)	1.20 (3H, d, 7), 3.34 (1H, q, 7), 3.43 (1H, tt, 11, 5), 3.66 (1H, t, 11), 3,68 (1H, t, 11), 4.33 (1H, ddd, 11, 5, 2), 4.46 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.04 (1H, d, 14), 5.04 (1H, s), 5.17 (1H, d, 5), 6.23 (1H, dd, 17, 5), 6.7—6.8 (2H, m), 7.13 (1H, d, 17), 7.24 (1H, dd, 8, 5), 7.36 (1H, td, 9, 7), 7.79 (2H, s), 7.85 (1H, dd, 8, 2), 8.31 (1H, dd, 5, 2)	$C_{23}H_{23}ClF_2N_4O_3S$	508 (M^+), 342, 285, 224		
15Z	39	Oil [101—109]	1602, 1490, 1278, 1139, 1128 ($CHCl_3$) $[\alpha]_D$ −61.4 (*c*=0.74, $CHCl_3$)	1.19 (3H, d, 7), 3.33 (1H, q, 7), 3.42 (1H, tt, 11, 5), 3.64 (1H, t, 11), 3,67 (1H, t, 11), 4.33 (1H, ddd, 11, 5, 2), 4.45 (1H, ddd, 11, 5, 2), 4.74 (2H, tt, 13, 1), 4.82 (1H, d, 14), 5.01 (1H, s), 5.03 (1H, d, 14), 5.12 (1H, d, 5), 6.01 (1H, tt, 53, 5), 6.11 (1H, dd, 16, 5), 6.65—6.85 (4H, m), 7.36 (1H, td, 9, 7), 7.73 (1H, dd, 9, 2), 7.79 (2H, s), 8.13 (1H, d, 2)	$C_{26}H_{26}F_6N_4O_4S$	604 (M^+), 489, 381, 320, 224		
15AA	50	Oil [53—57]	1500, 1275, 1140, 960 ($CHCl_3$) $[\alpha]_D$ −75.7 (*c*=0.56, $CHCl_3$)	1.19 (3H, d, 7), 3.33 (1H, q, 7), 3.40 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 4.30 (1H, ddd, 11, 5, 2), 4.42 (1H, ddd, 11, 5, 2), 4.82 (1H, d, 14), 5.01 (1H, d, 5), 5.04 (1H, d, 14), 5.05 (1H, s), 5.89 (1H, dd, 16, 5), 6.65—6.85 (3H, m), 6.78 (2H, s), 7.36 (1H, m), 7.87 (2H, s)	$C_{22}H_{22}ClF_2N_3O_3S_2$	513 (M^+), 284, 224		
15AB	22	Oil [78—79.5]	1618, 1499, 1141, 966 ($CHCl_3$) $[\alpha]_D$ −70.7 (*c*=0.88, $CHCl_3$)	1.20 (3H, d, 7), 3.35 (1H, q, 7), 3.44 (1H, tt, 11, 5), 3.68 (1H, t, 11), 3,70 (1H, t, 11), 4.34 (1H, ddd, 11, 5, 2), 4.46 (1H, ddd, 11, 5, 2), 4.84 (1H, d, 14), 5.01 (1H, s), 5.05 (1H, d, 14), 5.18 (1H, d, 5), 6.30 (1H, dd, 16, 5), 6.65—6.80 (2H, m), 6.98 (1H, d, 16), 7.37 (1H, td, 9, 7), 7.4—7.5 (2H, m), 7.60 (1H, dd, 10, 1), 7.7—7.9 (4H, m), 7.79 (2H, s)	$C_{28}H_{27}F_2N_3O_3S$	525 (M^++1, FAB)		
15AC	44	167—168 (A–H)	1617, 1596, 1499, 1135 (KBr) $[\alpha]_D$ −40.6 (*c*=0.50, MeOH)	1.20 (3H, d, 7), 3.35 (1H, q, 7), 3.4—3.5 (1H, m), 3.67 (1H, t, 11), 3.69 (1H, t, 7), 4.35 (1H, dd, 11, 5, 2), 4.46 (1H, dd, 11, 5, 2), 4.85 (1H, d, 14), 5.02 (1H, s), 5.05 (1H, d, 14), 5.17 (1H, d, 4), 6.30 (1H, dd, 16, 4), 6.7—6.8 (2H, m), 6.94 (1H, d, 16), 7.3—7.4 (1H, m), 7.5—7.8 (7H, m), 7.96 (1H, s)	$C_{28}H_{26}BrF_2N_3O_3S$	601 (M^+), 523, 448, 378, 318, 262, 224 55.82 4.35 6.97 (55.65 4.31 6.90)		
15AD	45	115—117 (A–H)	1617, 1620, 1500, 1274, 1135 (KBr) $[\alpha]_D$ −65.9 (*c*=1.00, $CHCl_3$)	1.20 (3H, d, 7), 3.35 (1H, q, 7), 3,4—3.5 (1H, m), 3.67 (1H, t, 11), 3.69 (1H, t, 7), 4.35 (1H, dd, 11, 5, 2), 4.4—4.5 (1H, m), 4.47 (2H, t, 11), 4.84 (1H, d, 14), 5.02 (1H, s), 5.05 (1H, d, 14), 5.17 (1H, d, 5), 6.11 (1H, tt, 53, 5), 6.27 (1H, dd, 16, 5), 6.7—6.8 (2H, m), 6.94 (1H, d, 16), 7.1—7.2 (2H, m), 7.3—7.4 (1H, m), 7.6—7.9 (6H, m)	$C_{31}H_{29}F_6N_3O_4S$	653 (M^+), 613, 589, 511, 402, 369, 342, 284 56.96 4.47 6.43 (56.75 4.25 6.68)		
16B	65	Amorphous [112—114]	1499, 1275, 1140, 1050, 966 (KBr) $[\alpha]_D$ −76.8 (*c*=1.02, $CHCl_3$)	1.19 (3H, d, 7), 3.33 (1H, q, 7), 3.39 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 4.30 (1H, ddd, 11, 5, 2), 4.41 (1H, ddd, 11, 5, 2), 4.82 (1H, d, 14), 5.00 (1H, s), 5.03 (1H, d, 14), 5.05 (1H, d, 5), 5.79 (1H, dd, 16, 5), 6.57 (1H, dd, 16, 10), 5,57 (1H, d, 15), 6.65—6.80 (3H, m), 7.2—7.4 (5H, m), 7.79 (2H, s)	$C_{26}H_{26}ClF_2N_3O_3S$	533 (M^+), 284, 252, 224 58.48 4.91 7.87 (58.15 5.07 7.67)		
16C	61	Amorphous [88—91]	1614, 1500, 1276, 1139 ($CHCl_3$) $[\alpha]_D$ −79.1 (*c*=1.04, $CHCl_3$)	1.18 (3H, d, 7), 3.33 (1H, q, 7), 3.39 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 3.90 (3H, s), 4.30 (1H, ddd, 11, 5, 2), 4.42 (1H, ddd, 11, 5, 2), 4.82 (1H, d, 14), 5.00 (1H, s), 5.03 (1H, d, 14), 5.05 (1H, d, 5), 5.80 (1H, dd, 16, 5), 6.62 (1H, dd, 15, 10), 6.65—6.80 (2H, m), 6.85 (1H, dd, 16, 10), 6.96 (1H, d, 16), 7.06 (1H, s), 7.18 (1H, d, 8), 7.36 (1H, q, 8), 7.54 (1H, d, 8), 7.79 (2H, s)	$C_{26}H_{25}F_4N_3O_3S$	536 (M^++1, FAB)		
16E	81	147—149 (A–H)	2225, 1617, 1603, 1500, 1140 (KBr) $[\alpha]_D$ −73.4 (*c*=1.30, $CHCl_3$)	1.19 (3H, d, 7), 3.33 (1H, q, 7), 3.40 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 4.31 (1H, ddd, 11, 5, 2), 4.43 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.00 (1H, s), 5.03 (1H, d, 14), 5.06 (1H, d, 4), 5.87 (1H, dd, 15, 4), 6.59 (1H, dd, 15, 10), 6.61 (1H, 15), 6.7—6.8 (2H, m), 6.87 (1H, 15, 10), 7.35 (1H, td, 8, 7), 7.48 (2H, d, 8), 7.60 (2H, 8), 7.79 (2H, s)	$C_{27}H_{26}F_2N_4O_3S$	525 (M^++1, FAB) 61.82 5.00 10.68 (62.00 5.01 10.56)		
16F	64	Oil [62—64]	1651, 1456, 1325, 1128, 1068 ($CHCl_3$) $[\alpha]_D$ −69.8 (*c*=1.00, $CHCl_3$)	1.19 (3H, d, 7), 3.33 (1H, q, 7), 3.40 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 4.30 (1H, ddd, 11, 5, 2), 4.42 (1H, ddd, 11, 5, 2), 4.82 (1H, d, 14), 5.00 (1H, s), 5.03 (1H, d, 14), 5.06 (1H, d, 5), 5.84 (1H, dd, 15, 5), 6.60 (1H, dd, 15, 11), 6.7—6.8 (2H, m), 6.73 (1H, d, 16), 6.85 (1H, dd, 16, 11), 7.3—7.45 (1H, m), 7.49 (2H, d, 9), 7.56 (2H, d, 9), 7.78 (2H, s)	$C_{27}H_{26}F_5N_3O_3S$	567 (M^+), 547, 284, 224		

Table 5. (Continued)

Compd.	Yield (%)	mp (°C) (Solvent[a]) [Oxalic acid salt: mp (°C)]	IR cm^{-1} (State) Optical rotation[b]	^{1}H-NMR (270 MHz, $CDCl_3$)[c]	Formula	MS *m/z* Analysis % Calcd (Found)		
						C	H	N
16M	61	Amorphous	1501, 1418, 1328, 1241, 1140 (KBr) $[\alpha]_D$ −65.1 (*c*=1.06, $CHCl_3$)	1.18 (3H, d, 7), 3.33 (1H, q, 7), 3.39 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 3.90 (3H, s), 4.30 (1H, ddd, 11, 5, 2), 4.41 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.00 (1H, s), 5.03 (1H, d, 14), 5.05 (1H, d, 5), 5.79 (1H, dd, 15, 5), 6.58 (1H, dd, 15, 9), 6.7—6.9 (6H, m), 7.2—7.6 (2H, m), 7.79 (2H, s)	$C_{28}H_{28}F_5N_3O_4S$	597 (M^+), 284, 224		
16N	66	Amorphous [75—79]	1507, 1500, 1262, 1141 ($CHCl_3$) $[\alpha]_D$ −73.3 (*c*=0.70, $CHCl_3$)	1.18 (3H, d, 7), 3.33 (1H, q, 7), 3.40 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 4.30 (1H, ddd, 11, 5, 2), 4.42 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.01 (1H, s), 5.03 (1H, d, 14), 5.05 (1H, d, 4), 5.80 (1H, dd, 16, 4), 6.58 (1H, dd, 16, 10), 6.60 (1H, d, 16), 6.7—6.9 (3H, m), 7.17 (2H, d, 9), 7.36 (1H, m), 7.42 (2H,d, 9), 7.79 (2H, s)	$C_{27}H_{26}F_5N_3O_4S$	583 (M^+), 564, 360, 342, 284, 224		
16R	66	73—76 (E–H)	1605, 1510, 1277, 1254, 1140 (KBr) $[\alpha]_D$ −68.1 (*c*=1.22, $CHCl_3$)	1.18 (3H, d, 7), 3.33 (1H, q, 7), 3.39 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 4.30 (1H, ddd, 11, 5, 2), 4.35 (1H, t, 12), 4.41 (1H, ddd, 11, 5, 2), 4.82 (1H, d, 14), 4.99 (1H, s), 5.03 (1H, d, 14), 5.04 (1H, d, 5), 5.75 (1H, dd, 16, 5), 6.06 (1H, tt, 53, 5), 6.56 (1H, dd, 16, 10), 6.57 (1H, d, 15), 6.68 (1H, dd, 15, 10), 6.7—6.9 (2H, m), 6.88 (2H, d, 9), 7.3—7.4 (1H, m), 7.37 (2H,d, 9), 7.79 (2H, s)	$C_{29}H_{29}F_6N_3O_4S$	629 (M^+), 345, 285, 259, 224 55.32 4.64 6.67 (55.26 4.64 6.73)		
16S	40	Amorphous [78—80]	1618, 1595, 1499, 1277, 1141 (KBr) $[\alpha]_D$ −68.1 (*c*=1.44, $CHCl_3$)	1.18 (3H, d, 7), 2.48 (3H, s), 3.33 (1H, q, 7), 3.38 (1H, tt, 11, 5), 3.61 (1H, t, 11), 3,63 (1H, t, 11), 4.30 (1H, ddd, 11, 5, 2), 4.41 (1H, ddd, 11, 5, 2), 4.82 (1H, d, 14), 5.00 (1H, s), 5.02 (1H, d, 14), 5.04 (1H, d, 5), 5.75 (1H, dd, 16, 5), 6.56 (1H, dd, 16, 10), 6.57 (1H, d, 15), 6.68 (1H, dd, 15, 10), 6.5—6.65 (2H, m), 6.65—6.8 (3H, m), 7.23 (2H, d, 9), 7.3—7.4 (1H, m), 7.32 (2H,d, 9), 7.78 (2H, s)	$C_{27}H_{29}F_2N_3O_3S_2$	545 (M^+), 370, 284, 261 , 224		
16U	56	Foam [83—85]	1621, 1680, 1621, 1501, 1117 (KBr) $[\alpha]_D$ −68.2 (*c*=0.72, $CHCl_3$)	1.19 (3H, d, 7), 3.33 (1H, q, 7), 3.40 (1H, tt, 11, 5), 3.62 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 4.31 (1H, ddd, 11, 5, 2), 4.42 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.01 (1H, d, 5), 5.03 (1H, d, 14), 5.06 (1H, d, 5), 5.83 (1H, dd, 15, 5), 6.60 (1H, dd, 15, 9), 6.62 (1H, d, 16), 6.7—6.8 (2H, m), 6.84 (1H, dd, 16, 10), 7.3—7.4 (1H, m), 7.44 (2H, d, 8), 7.60 (2H, d, 8), 7.79 (2H, s)	$C_{27}H_{26}F_5N_3O_3S_2$	599 (M^+), 376, 346, 284, 224		
16V[g]	71	Amorphous	1591, 1500, 1368, 1217, 1139 (KBr) $[\alpha]_D$ −59.0 (*c*=1.05, $CHCl_3$)	1.19 (3H, d, 7), 3.33 (1H, q, 7), 3.41 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 4.31 (1H, ddd, 11, 5, 2), 4.44 (1H, ddd, 11, 5, 2), 4.83 (1H, d, 14), 5.02 (1H, s), 5.03 (1H, d, 14), 5.08 (1H, d, 4), 5.96 (1H, dd, 16, 4), 6.63 (1H, dd, 15, 11), 6.68 (1H, d, 15), 6.7—6.8 (2H, m), 6.98 (1H, dd, 16, 11), 7.36 (1H, td, 9, 7), 7.65 (2H, d, 8), 7.787 (1H, s), 7,793 (1H, s), 7.97 (2H, d, 8)	$C_{27}H_{26}F_5N_3O_5S_2$	632 (M^++1, FAB) 51.34 4.15 6.65 (51.26 4.20 6.40)		
16X	69	88—90 (A–H)	1618, 1499, 1463, 1277, 1141 (KBr) $[\alpha]_D$ −55.2 (*c*=0.62, $CHCl_3$)	1.18 (3H, d, 7), 3.33 (1H, q, 7), 3.40 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 4.30 (1H, ddd, 11, 5, 2), 4.42 (1H, ddd, 11, 5, 2), 4.82 (1H, d, 14), 5.01 (1H, s), 5.03 (1H, d, 14), 5.05 (1H, d, 4), 5.82 (1H, dd, 16, 4), 6.56 (1H, d, 15), 6.58 (1H, dd, 15, 11), 6.65—6.75 (3H, m), 7.28 (1H, d, 8), 7.39 (1H, td, 9, 7), 7.70 (1H, dd, 8, 2), 7,79 (2H, s), 8.37 (1H, d, 2)	$C_{27}H_{25}ClF_2N_4O_5S_2$	534 (M^+), 499, 311, 284, 224		
16Z	63	Amorphous [64—69]	1598, 1488, 1278, 1140, 1128 ($CHCl_3$) $[\alpha]_D$ −58.6 (*c*=0.52, $CHCl_3$)	1.19 (3H, d, 7), 3.33 (1H, q, 7), 3.39 (1H, tt, 11, 5), 3.62 (1H, t, 11), 3,64 (1H, t, 11), 4.30 (1H, ddd, 11, 5, 2), 4.42 (1H, ddd, 11, 5, 2), 4,74 (2H, brt, 13), 4.82 (1H, d, 14), 5.01 (1H, s), 5.03 (1H, d, 14), 5.05 (1H, d, 5), 5.78 (1H, dd, 16, 5), 6.01 (1H, tt, 53, 5), 6.51—6.62 (2H, m), 6.65—6.78 (3H, m), 6.81 (1H, d, 9), 7.35 (1H, m), 7.74 (1H, dd, 9, 2), 7,79 (2H, s), 8.11 (1H, d, 2)	$C_{28}H_{28}F_6N_4O_4S$	630 (M^+), 284, 224		
16AA	69	Oil [90—110]	1500, 1275, 1140 ($CHCl_3$) $[\alpha]_D$ −55.2 (*c*=0.56, $CHCl_3$)	1.18 (3H, d, 7), 3.32 (1H, q, 7), 3.38 (1H, tt, 11, 5), 3.60 (1H, t, 11), 3.63 (1H, t, 11), 4.29 (1H, m), 4.41 (1H, m), 4.82 (1H, d, 14), 5.00 (1H, s), 5.02 (1H, d, 14), 5.03 (1H, d, 14), 5.74 (1H, dd, 14, 5), 6.4—6.55 (2H, m), 6.60 (1H, d, 15), 6.7—6.8 (4H, m), 7.36 (1H, q, 8.2), 7.79 (2H, s)	$C_{24}H_{24}ClF_2N_3O_3S$	507 (M^+), 284, 224		

a) Recrystallization solvent: A, AcOEt; H, hexane; E, ether. *b*) Rotations were measured at 25 °C. *c*) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parenthesis. *d*) The ^{1}H-NMR spectra of **14**C and **15**C were taken using a 60 MHz spectrometer in $CDCl_3$. *e*) The ^{1}H-NMR spectrum of **15**T was taken using a 60 MHz spectrometer in $CDCl_3$ containing D_2O. *f*) The $[\alpha]_D$ value shows the optical rotation of the oxalic acid salt of **15**Y. The melting point of the oxalic acid salt was difficult to measure because of the hygroscopicity. *g*) The ^{1}H-NMR spectrum of **16**V was taken using a 400 MHz spectrometer in $CDCl_3$.

recrystallized twice from cold Et_2O–hexane to afford pure isomer **27** (220 mg, 24% from **26**) as colorless plates, mp 44—46 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.2—1.5 (4H, m), 1.95—2.15 (2H, m), 2.15—2.35 (1H, m), 2.35—2.55 (1H, m), 3.73 (2H, s), 7.27 (5H, s), 9.61 (1H, s). IR (KBr) cm^{-1}: 1732, 1493, 1448, 1092. MS *m/z*: 268 (M^+), 125, 110. *Anal.* Calcd for $C_{14}H_{17}ClOS$: C, 62.56; H, 6.38. Found: C, 62.44; H, 6.31.

***trans*-1-(4-Chlorobenzylthio)-4-[(1*E*,3*E*)-4-[4-(trifluoromethyl)-phenyl]-1,3-butadienyl]cyclohexane (28)** A suspension of sodium hydride (55% mineral oil dispersion, 50 mg, 1.14 mmol) in DMSO (7 ml) was heated at 55 °C for 2.5 h to obtain an almost clear solution of dimsyl sodium. [(*E*)-(*p*-(Trifluoromethyl)cinnamyl)triphenylphosphonium chloride (607 mg, 1.26 mmol) was then added to the mixture at room temperature to obtain an orange solution. Then **27** (170 mg, 0.63 mmol) was added at room temperature. After the mixture was stirred at room temperature for 15 min, it was treated with H_2O. Then it was diluted with toluene and washed successively with H_2O and brine. The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo* to afford an oily residue, which was chromatographed on silica gel (5 g). Elution with CH_2Cl_2–hexane (1 : 2, v/v) af-

forded a mixture of geometrical isomers of olefins (303 mg) as a yellow solid, which was recrystallized from hexane to afford a pure *E*,*E*-isomer **28** (86 mg, 31%) as pale yellow needles, mp 142—144 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.1—1.3 (2H, m), 1.3—1.5 (2H, m), 1.7—2.0 (2H, m), 2.46 (1H, tt, J=12, 4 Hz), 3.74 (2H, s), 5.81 (1H, dd, J=15, 7 Hz), 6.20 (1H, dd, J=15, 10 Hz), 6.47 (1H, d, J=16 Hz), 6.81 (1H, dd, J=16, 10 Hz), 7.29 (4H, s), 7.46 (2H, d, J=8 Hz), 7.55 (2H, d, J=8 Hz). IR (KBr) cm^{-1}: 1612, 1490, 1326, 1127, 1068. MS *m/z*: 436 (M^+), 311, 277, 235, 159, 125. *Anal.* Calcd for $C_{24}H_{24}ClF_3S$: C, 65.97; H, 5.54. Found: C, 65.68; H, 5.45.

***trans*-1-(4-Chlorobenzylsulfinyl)-4-[(1*E*,3*E*)-4-[4-(trifluoromethyl)-phenyl]-1,3-butadienyl]cyclohexane (29)** *m*CPBA (80% purity, 104 mg, 0.48 mmol) was added to a solution of **28** (211 mg, 0.48 mmol) in CH_2Cl_2 (20 ml) at 0 °C. After the mixture was stirred for 5 min, it was treated with an aqueous solution of Na_2SO_3 and the product was extracted with AcOEt. The organic layer was washed with an aqueous solution of $NaHCO_3$ and brine, successively. The extract was dried over $MgSO_4$, and the solvents were removed to afford a solid residue, which was recrystallized from AcOEt–hexane to afford **29** (168 mg, 77%) as a colorless, crystalline powder, mp 212—214 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.1—1.3 (2H, m), 1.5—1.8 (2H, m), 1.9—2.3 (5H, m), 2.42 (1H, tt, J=12, 4 Hz), 3.87 (1H, d, J=13 Hz), 3.97 (1H, d, J=13 Hz), 5.80 (1H, dd, J=15, 7 Hz), 6.22 (1H, dd, J=15, 10 Hz), 6.48 (1H, d, J=16 Hz), 6.80 (1H, dd, J=16, 10 Hz), 7.25 (2H, d, J=8 Hz), 7.36 (2H, d, J=8 Hz), 7.45 (2H, d, J=8 Hz), 7.55 (2H, d, J=8 Hz). IR (KBr) cm^{-1}: 1612, 1492, 1325, 1168, 1128, 1069. MS *m/z*: 452 (M^+), 327, 278, 277, 159, 125. *Anal.* Calcd for $C_{24}H_{24}ClF_3OS$: C, 63.64; H, 5.34. Found: C, 63.61; H, 5.38.

***S*-[*trans*-4-[(1*E*,3*E*)-4-[4-(Trifluoromethyl)phenyl]-1,3-butadienyl]cyclohexyl] Thioacetate (30)** Trifluoroacetic anhydride (165 mg, 0.79 mmol) was added to a mixture of **29** (178 mg, 0.39 mmol), 2,6-lutidine (168 mg, 1.6 mmol), THF (8 ml) and CH_3CN (3 ml) at 0 °C. After the mixture was stirred at room temperature for 3 min, it was treated with an aqueous solution of $NaHCO_3$. The product was extracted with AcOEt. The extract was dried over $MgSO_4$ and solvents were removed *in vacuo* to leave an oily residue of crude thiol. This residue was treated with triethylamine (119 mg, 1.17 mmol) and acetyl chloride (62 mg, 0.79 mmol) in CH_2Cl_2 (10 ml) at 0 °C. After the mixture was stirred at room temperature for 1 h, it was diluted with AcOEt and washed with an aqueous solution of $NaHCO_3$ and brine, successively. The organic layer was dried over $MgSO_4$ and the solvents were removed *in vacuo* to leave an oily residue, which was purified by column chromatography (5 g). Elution with CH_2Cl_2–hexane (1 : 1, v/v) gave a crude product, which was purified further with a Lobar® column using AcOEt–hexane (1 : 19, v/v)] as an eluent to afford **30** (98 mg, 70%) as a crystalline powder, mp 113—115 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.2—1.5 (4H, m), 1.7—1.9 (2H, m), 2.0—2.2 (3H, m), 2.31 (3H, s), 3.37 (1H, tt, J=12, 4 Hz), 5.82 (1H, dd, J=15, 7 Hz), 6.20 (1H, dd, J=15, 10 Hz), 6.47 (1H, d, J=16, 7 Hz), 6.81 (1H, dd, J=16, 10 Hz), 7.45 (2H, d, J=8 Hz), 7.54 (2H, d, J=8 Hz). IR (KBr) cm^{-1}: 1688, 1326, 1117, 1068. HR-MS *m/z*: 354.1252 (Calcd for $C_{19}H_{21}F_3OS$: 354.1265). MS *m/z*: 354 (M^+), 311, 277, 236, 159, 43.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-[[*trans*-4-[(1*E*,3*E*)-4-[4-(trifluoromethyl)phenyl]-1,3-butadienyl]cyclohexyl]thio]-2-butanol (31) A solution of sodium methoxide (0.4 M in MeOH, 0.2 ml, 0.08 mmol) was added to a mixture of **30** (96 mg, 0.27 mmol), **8** (70 mg, 0.28 mmol) and DMF (5 ml), and the mixture was heated at 55—60 °C for 2 h. After the mixture was cooled, it was diluted with toluene and washed with H_2O and brine, successively. The organic layer was dried over $MgSO_4$, and the solvents were removed *in vacuo* to afford an oily residue, which was chromatographed on silica gel (5 g). Elution with AcOEt–CH_2Cl_2 (1 : 5, v/v) afforded **31** (90 mg, 59%) as a crystalline powder, mp 74—76 °C. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.1—1.6 (4H, m), 1.17 (3H, d, J=7 Hz), 1.8—2.0 (2H, m), 2.0—2.2 (3H, m), 2.69 (1H, tt, J=12, 3 Hz), 3.35 (1H, q, J=7 Hz), 4.64 (1H, s), 4.83 (1H, d, J=15 Hz), 5.10 (1H, d, J=15 Hz), 5.83 (1H, dd, J=15, 7 Hz), 6.22 (1H, dd, J=15, 10 Hz), 6.48 (1H, d, J=15 Hz), 6.74 (2H, t-like, J=8 Hz), 6.81 (1H, dd, J=15, 10 Hz), 7.2—7.5 (1H, m), 7.45 (2H, d, J=8 Hz), 7.54 (2H, d, J=8 Hz), 7.76 (1H, s), 7.84 (1H, s). IR ($CHCl_3$) cm^{-1}: 1615, 1500, 1325, 1125, 1068. HR-MS *m/z*: 563.2036 (Calcd for $C_{29}H_{30}F_5N_3OS$: 563.2030). MS (EI) *m/z*: 563 (M^+), 544, 340, 310, 277, 224 (100%). $[\alpha]_D^{25}$ −82.8 (c=0.90, $CHCl_3$).

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