Reactions of 3-nitro-2-trihalomethyl-2*H*-chromenes with S- and N-nucleophiles. Synthesis and stereochemistry of 2,3,4-trisubstituted chromanes

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The reactions of 3-nitro-2-trifluoromethyl- and 3-nitro-2-trichloromethyl-2*H*-chromenes with thiols and aromatic amines proceed *via* the nucleophilic addition type to the activated double bond to form 2,3,4-trisubstituted chromanes in high yields. The stereoisomeric compositions and structures of the diastereomers were determined by ^{1}H, ^{19}F NMR and 2D NOESY spectroscopies and X-ray diffraction analysis.

Key words: 2*H*-chromenes, chromanes, S- and N-nucleophiles, Michael reaction, diastereomers, conformers, NMR spectroscopy, X-ray diffraction analysis.

Many derivatives of chromane (3,4-dihydro-2*H*-1-benzopyran) and 2*H*-chromene (2*H*-1-benzopyran) are natural compounds that are widely abundant in plants.[1] Some of them, as well as a series of synthetic 2*H*-chromenes, recommended themselves as pesticides[2,3] and promising drugs.[4—9] Due to their relative availability, high reactivity, and stability, 2*H*-chromenes long ago have been used successfully as the starting materials for the preparation of natural compounds with complicated structures, for instance, pterocarpanes and pterocarpenes.[10,11] The reactions of 2*H*-chromenes with electrophiles, reducing agents, and 1,3-dipoles were studied in rather detail, which allowed one to synthesize various chromane derivatives and new related heterocyclic systems.[12—21] However, data on reactivity of the double bond in 2*H*-chromenes toward nucleophilic reagents are scarce. It is known[22] that the reactions of 2-aryl-3-nitrochromenes with dialkyl phosphites in the presence of triethylamine affords 4-phosphorylchromenes, because the addition is accompanied by the elimination of a nitrous acid molecule. The syntheses of chromeno[4,3-*c*]pyrazolines from the corresponding 3-acyl-2*H*-chromene arylhydrazones[23] by intramolecular addition and of 3-nitro-2-(3,4-methylenedioxyphenyl)-4-[(1-cyclohexenyl)nitromethyl]chromane from 1-nitromethylcyclohexene and the corresponding 2*H*-chromene[24] were described.

We have recently[25] reported the reactions of activated trifluoro(trichloro)methylalkenes with salicylic aldehydes in the presence of triethylamine giving 3-benzoyl- and 3-nitro-2-trihalomethyl-2*H*-chromenes in high yields. Since chromane derivatives are important in the biological and synthetic aspects, in the present work we studied the reactions of a series of 3-nitro-2-trihalomethyl-2*H*-chromenes with several S- and N-nucleophiles and showed that they proceed *via* the Michael reaction mechanism as the conjugated nucleophilic addition to the C(4) atom to form 2,3,4-trisubstituted chromane derivatives and is not accompanied by elimination of nitrous acid elements. In the most cases, the reactions afforded mixtures of diastereomeric products, whose structures were determined by ^{1}H, ^{19}F NMR and 2D NOESY spectroscopies and X-ray diffraction analysis (see preliminary report[26]).

Results and Discussion

We found that the reactions of chromenes **1a—e** with *p*-thiocresol, ethyl mercaptoacetate, and 2-mercaptoethanol in benzene for 5 h at 65 °C (method *A*) or in CH_2Cl_2 in the presence of K_2CO_3 for 2 days at ~20 °C (method *B*) proceed as the nucleophilic addition of thiols to the activated double bond of chromenes **1** and afford 2,3,4-trisubstituted chromanes **2a—o** (Scheme 1).

One can judge about the reactivity of chromenes **1a—e** in the reactions with S-nucleophiles from their conversion under the conditions of methods *A* and *B*. The conversion was calculated from the intensity of a doublet of the CF_3 group of unreacted chromenes **1a—c** in the

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 309—321, February, 2006.
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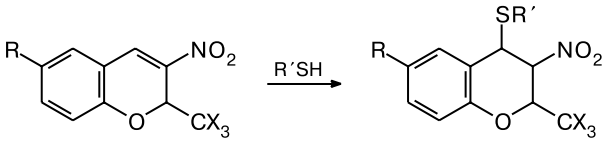
Scheme 1



1a—e **2a—o**

1: R = H, X = F (**a**); R = Br, X = F (**b**); R = NO_2, X = F (**c**); R = H, X = Cl (**d**); R = Br, X = Cl (**e**)

2	R	X	R′	**2**	R	X	R′
a	H	F	4-MeC_6H_4	**i**	H	Cl	CH_2CO_2Et
b	Br	F	4-MeC_6H_4	**j**	Br	Cl	CH_2CO_2Et
c	NO_2	F	4-MeC_6H_4	**k**	H	F	$(CH_2)_2OH$
d	H	Cl	4-MeC_6H_4	**l**	Br	F	$(CH_2)_2OH$
e	Br	Cl	4-MeC_6H_4	**m**	NO_2	F	$(CH_2)_2OH$
f	H	F	CH_2CO_2Et	**n**	H	Cl	$(CH_2)_2OH$
g	Br	F	CH_2CO_2Et	**o**	Br	Cl	$(CH_2)_2OH$
h	NO_2	F	CH_2CO_2Et				

^{19}F NMR spectra and singlets of the H(2) and/or H(4) protons of chromenes **1d,e** in the ^1H NMR spectra (Table 1). It is seen that 2-CF_3-substituted chromenes are more reactive than 2-CCl_3-substituted chromenes, and the introduction of electron-withdrawing substituents (NO_2, Br) into position 6 of the chromene system enhances the reactivity of the both (see Table 1). In the case of 6-NO_2-2-CF_3-substituted chromene **1c**, the conversion achieves almost 100% regardless of the method used and thiol structure, whereas the reaction with 2-CCl_3-containing chromene **1d** under the same conditions occurs, on the average, by 35 (method *A*) and 45% (method *B*).

The addition of thiols to the double bond of chromenes **1** is not diastereoselective, because four stereomers with *trans—trans*- (*tt*), *trans—cis*- (*tc*), *cis—trans*- (*ct*), and *cis—cis*-configurations (*cc*) at the C(2)—C(3) and C(3)—C(4) bonds, respectively, were formed in all cases. Stereochemistry of the products was determined by comparison of the spin-spin coupling (SSC) constants $J_{2,3}$ and $J_{3,4}$ with published data on the related molecules[27—29] and by the 2D NOESY spectra of adducts **2d,l** and X-ray diffraction study of crystals of *tc*-**2d** and *ct*-**2f**.

Table 1. Conversion of chromenes **1a—e** in the reactions with S-nucleophiles

Chromene	Reactant	Conversion (%)	
		Method *A*	Method *B*
1a	HSC_6H_4-4-Me	81	67
	$HSCH_2CO_2Et$	95	91
	$HS(CH_2)_2OH$	47	95
1b	HSC_6H_4-4-Me	94	96
	$HSCH_2CO_2Et$	83	65
	$HS(CH_2)_2OH$	75	93
1c	HSC_6H_4-4-Me	100	100
	$HSCH_2CO_2Et$	96	95
	$HS(CH_2)_2OH$	100	98
1d	HSC_6H_4-4-Me	41	30
	$HSCH_2CO_2Et$	48	72
	$HS(CH_2)_2OH$	12	34
1e	HSC_6H_4-4-Me	98	86
	$HSCH_2CO_2Et$	78	81
	$HS(CH_2)_2OH$	76	79

The ratio of diastereomeric chromanes **2a—o**, which depends on the reaction conditions and the nature of the substrate and S-nucleophile, was determined by analysis of the ^1H and ^{19}F NMR spectra of the reaction mixtures (Table 2). The obtained results show that the *ct*-isomer is the main for method *B* (in 11 cases of 15, its content is 35—69%), and the *cc*-isomer is minor (2—13%). Under the conditions of method *A*, the *tt*- or *tc*-isomer predominates (each in seven reactions), and the content of the *cc*-isomer varies from 5 to 40%. Recrystallization of the reaction mixtures from hexane or its mixture with dichloromethane gave the following stereoisomers in the individual state: *cc*-**2a**, *tt*-**2b**, *tc*-**2d**, *tc*-**2e**, *ct*-**2f**, *ct*-**2g**, *ct*-**2h**, *ct*-**2i**, *cc*-**2j**, *tt*-**2k**, *tt*-**2l**, *ct*-**2l**, and *ct*-**2o**, the latter was prepared by refluxing reactants in benzene in the presence of K_2CO_3. In the present study, we did not aim at isolating of all diastereomers.

The thorough analysis of the SSC values in the ^1H NMR spectra of the synthesized products gave four groups of $J_{2,3}$ and $J_{3,4}$ constants, each of which characterizes a certain diastereomeric form. The maximum (for the compounds studied) SSC values ($J_{2,3}$ = 7.4—9.5 Hz and $J_{3,4}$ = 7.9—9.9 Hz) indicate the axial arrangement of the H(2) and H(3) atoms, the pseudo-axial arrangement of the H(4) atom, and, hence, the *tt*-configuration of equatorial substituents in a conformation close to half-chair (the published values for the *tt*-isomers of 2,3,4-trisubstituted chromanes with equatorial substituents are $J_{2,3}$ = 8—11 Hz and $J_{3,4}$ = 10—12 Hz).[29,30] The medium constants ($J_{2,3}$ = 6.1—7.6 Hz and $J_{3,4}$ = 4.8—5.5 Hz) were ascribed to diastereomers with the *tc*-configuration containing the equatorial CX_3 group, because the axial-axial SSC constant is usually higher than the axial-equatorial one (in this case, a decrease in $J_{2,3}$ compared to that of the *tt*-isomer can be a consequence of a distorted half-chair conformation). The values $J_{2,3}$ = 1.2 Hz, $J_{3,4}$ = 2.5 Hz and $J_{2,3}$ = 1.2 Hz, $J_{3,4}$ = 5.0 Hz were given earlier[27] for the *ct*- and *cc*-isomers, respectively, of 3-bromo-3,4-dihydro-2-methyl-2*H*-chromen-4-yl acetate with the equatorial Me group, which made it possible to ascribe the values found by us $J_{2,3} \approx J_{3,4}$ = 1.2—1.8 Hz to the *ct*- and $J_{2,3}$ = 1.4—1.8 Hz and $J_{3,4}$ = 5.4—5.6 Hz to the *cc*-diastereomers with the equatorial CX_3 group (Scheme 2, Table 3).

The relative stereochemistry of 2,3,4-trisubstituted chromanes **2** was confirmed by the 2D NOESY experi-

Table 2. Ratio of stereoisomeric chromanes **2a—o** in reaction mixtures formed upon the reactions of chromenes **1a—e** with S-nucleophiles

Chromane	Isomer	Content of isomers (%)	
		Method *A*	Method *B*
3-Nitro-4-(*p*-tolylsulfanyl)-2-(trifluoromethyl)-chromane (**2a**)	*tt*	13	38
	tc	44	3
	ct	3	57
	cc	40	2
6-Bromo-3-nitro-4-(*p*-tolylsulfanyl)-2-(trifluoromethyl)-chromane (**2b**)	*tt*	44	38
	tc	40	8
	ct	10	49
	cc	6	5
3,6-Dinitro-4-(*p*-tolylsulfanyl)-2-(trifluoromethyl)-chromane (**2c**)	*tt*	64	17
	tc	5	1
	ct	15	69
	cc	16	13
3-Nitro-4-(*p*-tolylsulfanyl)-2-(trichloromethyl)-chromane (**2d**)	*tt*	11	20
	tc	67	43
	ct	0	31
	cc	22	6
6-Bromo-3-nitro-4-(*p*-tolylsulfanyl)-2-(trichloromethyl)-chromane (**2e**)	*tt*	12	23
	tc	75	45
	ct	2	26
	cc	11	6
Ethyl [2-(3,4-dihydro-3-nitro-2-trifluoromethyl-2*H*-chromen-4-yl)]sulfanyl acetate (**2f**)	*tt*	21	36
	tc	55	11
	ct	6	50
	cc	18	3
Ethyl [2-(6-bromo-3,4-dihydro-3-nitro-2-trifluoromethyl-2*H*-chromen-4-yl)]-sulfanyl acetate (**2g**)	*tt*	51	18
	tc	8	7
	ct	32	69
	cc	9	6
Ethyl [2-(3,4-dihydro-3,6-dinitro-2-trifluoromethyl-2*H*-chromen-4-yl)]-sulfanyl acetate (**2h**)	*tt*	45	25
	tc	19	10
	ct	20	57
	cc	16	8
Ethyl [2-(3,4-dihydro-3-nitro-2-trichloromethyl-2*H*-chromen-4-yl)]sulfanyl acetate (**2i**)	*tt*	19	32
	tc	59	27
	ct	0	35
	cc	22	6
Ethyl [2-(6-bromo-3,4-dihydro-3-nitro-2-trichloromethyl-2*H*-chromen-4-yl)]-sulfanyl acetate (**2j**)	*tt*	24	25
	tc	60	45
	ct	1	25
	cc	15	5
2-(3,4-Dihydro-3-nitro-2-trifluoromethyl-2*H*-chromen-4-yl)sulfanyl-ethan-1-ol (**2k**)	*tt*	55	38
	tc	6	10
	ct	34	48
	cc	5	4
2-(6-Bromo-3,4-dihydro-3-nitro-2-trifluoromethyl-2*H*-chromen-4-yl)sulfanylethan-1-ol (**2l**)	*tt*	40	30
	tc	7	7
	ct	46	58
	cc	7	5
2-(3,4-Dihydro-3-nitro-2-trifluoromethyl-2*H*-chromen-4-yl)sulfanyl-ethan-1-ol (**2m**)	*tt*	41	20
	tc	11	19
	ct	33	55
	cc	15	6
2-(3,4-Dihydro-3-nitro-2-trichloromethyl-2*H*-chromen-4-yl)sulfanyl-ethan-1-ol (**2n**)	*tt*	42	36
	tc	38	24
	ct	10	36
	cc	10	4
2-(6-Bromo-3,4-dihydro-3-nitro-2-trichloromethyl-2*H*-chromen-4-yl)sulfanylethan-1-ol (**2o**)	*tt*	40	40
	tc	47	28
	ct	4	26
	cc	9	6

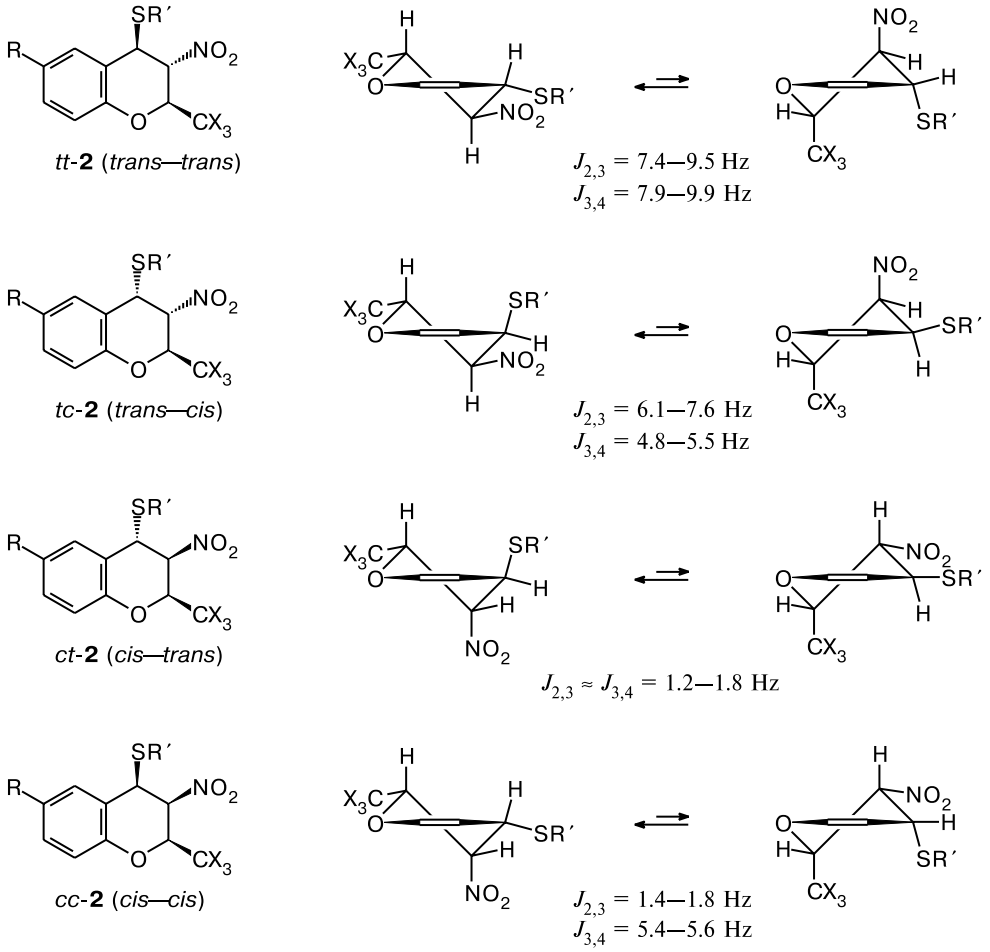
ment of adducts **2d** (a mixture of the *cc*- and *tc*-isomers in a ratio of 30 : 70) and **2l** (a mixture of the *tt*- and *ct*-isomers in a ratio of 40 : 60). In the case of minor isomer **2d**, cross-peaks were observed between the H(2)—H(3), H(3)—H(4), and H(2)—H(4) protons, whereas in the main isomer **2d** the cross-peak of H(2)—H(4) was absent, which agrees with the configurations *cc* and *tc*. In adduct **2l**, the cross-peak of H(2)—H(4) was observed only for the minor isomer with the *tt*-configuration. Thus, an analysis of the SSC values and data on the 2D NOESY spectra indicate that compounds **2** exist in $CDCl_3$ solutions predominantly in the half-chair conformation with the equatorial trihalomethyl group (see Scheme 2; the half-chair conformation in a real molecule can be distorted).

An analysis of the ^{1}H NMR spectra of compounds **2a—o** (see Table 3) revealed several empirical rules, which can be useful for configuration determination in the series of 2,3,4-trisubstituted chromanes.

1. When the H(2) atom exists in the *trans*-position toward the NO_2 and SR´ groups (*cc*-isomer), its chemical shift (CS) moves to the high field, while for the *cis*-position (*tc*-isomer) the shift is downfield, which is related to the deshielding influence of the substituents. As a result, the difference between the CS of the H(2) atoms in the *tc*- and *cc*-isomers is 1.0—1.2 and 0.7—1.0 ppm for CCl_3- and CF_3-substituted chromanes, respectively, which allows one to identify the *tc*- and *cc*-isomers.

2. The high difference between the CS of the H(3) and H(2) atoms ($\Delta\delta$ 1.1—1.5 and 0.7—1.1 for CCl_3- and

Scheme 2



CF_3-containing chromanes, respectively) has the diagnostic significance for the *cc*-isomer. In the case of the *ct*-isomer in which these atoms are arranged similarly, the value $\Delta\delta = \delta_{H(3)} - \delta_{H(2)}$ is substantially affected by the CX_3 groups and also by the nature of the substituent at the sulfur atom.

3. The SR′ group in the pseudo-equatorial position exerts a greater deshielding effect on the H(5) aromatic proton than that in the pseudo-axial position. Due to this, the presence of the *tt*- and *cc*-isomers in a diastereomeric mixture can be concluded from the signal of the H(5) atom, which is observed in a low field and, in addition, appears as a characteristic doublet of triplets or a doublet of doublets because of splitting on the H(4) atom.

4. The CS value of the H(3) atom increases in the series *tt* < *tc* < *ct* < *cc*, *i.e.*, the H(3) axial proton is more shielded than the equatorial proton. This regularity is violated only for CF_3-containing chromanes **2a—c** in which this atom of the *ct*-isomer falls into the region of shielding of the *p*-tolyl substituent, and its signal undergoes an upfield shift of ~0.5 ppm.

It should be mentioned that the transition from CF_3- to CCl_3-substituted chromanes is accompanied by the downfield shift of signals of the H(2) proton in the *tt*- and *tc*-isomers (by ~0.3 ppm) and of the H(3) proton in the *ct*- and *cc*-isomers (by ~0.4 ppm). The replacement of the *p*-tolyl substituent at the sulfur atom by the CH_2CO_2Et and $(CH_2)_2OH$ groups affects mainly the CS of the H(3) atom in the *ct*- and *cc*-isomers, which exhibits a downfield shift (by 0.4—0.5 ppm). The presence of the bromine atom in position 6 of the chromane system does not change substantially the CS of the H(2)—H(4) atoms. However, when the 6-NO_2 group appears, the H(2) atom of the *tt*-isomer and H(3) of the *tc*-isomer are deshielded by 0.2—0.3 ppm.

In the ^{19}F NMR spectra, the CF_3 groups in the *tt*-, *tc*-, and *cc*-isomers appear as doublets in a narrow region of δ 84.7—86.3, whereas for the *ct*-isomers this region is δ 86.8—87.1, which allows the latter to be detected easily, and their percentage content in a mixture can be calculated. The $^3J_{CF_3,H(2)}$ SSC constant can also be useful for determination of the diastereomeric composition of a

Table 3. ^{1}H, ^{19}F NMR and IR spectra of diastereomers of chromanes **2a—o**

Chromane	NMR, δ (*J*/Hz)							IR, ν/cm^{-1}
	^{1}H						^{19}F	
	H(2)	H(3)	H(4)	H(5)	H(6)—H(8)	R′	CF_3 (d)	
tt-**2a**	4.77 (dq, *J* = 8.5, *J* = 5.5)	4.93 (t, *J* = 8.7)	4.88 (br.d, *J* = 8.8)	7.89 (dt, *J* = 7.6, *J* = 1.2)[a]	6.93 (dd, H(8), *J* = 8.2, *J* = 1.2); 7.18 (td, H(6), *J* = 7.5, *J* = 1.2); 7.30 (m, H(7))	2.32 (s, Me); 7.10 (m, H(3′), H(5′)); 7.38 (m, H(2′), H(6′))	85.45 (*J* = 5.5)	—
tc-**2a**	5.47 (dq, *J* = 7.6, *J* = 6.1)	5.13 (dd, *J* = 7.6, *J* = 5.0)	4.75 (d, *J* = 5.0)	—[b]	6.95—7.04 (m, H(6), H(8)); 7.28 (m, H(7))	2.34 (s, Me); 7.09—7.19 (m, H(3′), H(5′), H(2′), H(6′))	84.72 (*J* = 6.1)	—
ct-**2a**	5.11 (qd, *J* = 6.1, *J* = 1.5)	5.04 (t, *J* = 1.7)	4.73 (br.s)	7.51 (dd, *J* = 7.7, *J* = 1.6)	7.04 (dd, H(8), *J* = 8.2, *J* = 1.1); 7.12 (td, H(6), *J* = 7.6, *J* = 1.1); 7.30 (ddd, H(7), *J* = 8.2, *J* = 7.4, *J* = 1.6)	2.40 (s, Me); 7.25 (m, H(3′), H(5′)); 7.41 (m, H(2′), H(6′))	86.84 (*J* = 6.1)	—
cc-**2a**	4.49 (qd, *J* = 5.6, *J* = 1.7)	5.20 (dd, *J* = 5.5, *J* = 1.7)	4.61 (br.d, *J* = 5.5)	7.94 (dt, *J* = 7.9, *J* = 1.2)[a]	7.03 (dd, H(8), *J* = 8.2, *J* = 1.2); 7.15 (td, H(6), *J* = 7.6, *J* = 1.2); 7.31 (dddd, H(7), *J* = 8.2, *J* = 7.3, *J* = 1.5, *J* = 0.9)	2.40 (s, Me); 7.24 (d, H(3′), H(5′), *J* = 8.0); 7.56 (d, H(2′), H(6′), *J* = 8.0)	85.51 (*J* = 5.7)	1630, 1555, 1489, 1381
tt-**2b**	4.77 (dq, *J* = 8.8, *J* = 5.5)	4.90 (t, *J* = 8.9)	4.82 (d, *J* = 9.2)	8.02 (dd, *J* = 2.4, *J* = 1.0)[a]	6.83 (d, H(8), *J* = 8.7); 7.37 (ddd, H(7), *J* = 8.7, *J* = 2.4, *J* = 0.7)	2.33 (s, Me); 7.12 (d, H(3′), H(5′), *J* = 8.0); 7.25 (d, H(2′), H(6′), *J* = 8.0)	85.65 (*J* = 5.5)	1656, 1597, 1555, 1492, 1476, 1366
tc-**2b**	5.43 (quint, *J* = 6.5)	5.12 (dd, *J* = 7.2, *J* = 5.1)	4.64 (d, *J* = 5.0)	—[b]	6.85—6.95 (d, H(8), *J* = 8.7); 7.35—7.42 (m, H(7))	2.32—2.40 (s, Me); 7.08—7.14 (m, H(3′), H(5′)); 7.23—7.27 (m, H(2′), H(6′))	84.91 (*J* = 6.1)	—
ct-**2b**	5.07 (qd, *J* = 6.0, *J* = 1.7)	5.03 (t, *J* = 1.7)	4.65 (br.s)	7.62 (d, *J* = 2.4)	6.85—6.95 (d, H(8), *J* = 8.7); 7.35—7.42 (m, H(7))	2.32—2.40 (s, Me); 7.08—7.14 (m, H(3′), H(5′)); 7.23—7.27 (m, H(2′), H(6′))	86.87 (*J* = 6.0)	—
cc-**2b**	4.47 (qd, *J* = 5.5, *J* = 1.7)	5.18 (dd, *J* = 5.5, *J* = 1.7)	4.53 (br.d, *J* = 5.5)	8.07 (dd, *J* = 2.4, *J* = 1.3)[a]	6.85—6.95 (d, H(8), *J* = 8.7); 7.35—7.42 (m, H(7))	2.32—2.40 (s, Me); 7.08—7.14 (m, H(3′), H(5′)); 7.23—7.27 (m, H(2′), H(6′))	85.59 (*J* = 5.6)	—
tt-**2c**	4.93 (m)	4.96 (m)	4.89 (d, *J* = 9.3)	8.85 (dd, *J* = 2.6, *J* = 1.0)[a]	7.08 (d, H(8), *J* = 9.0); 8.15 (ddd, H(7), *J* = 9.1, *J* = 2.6, *J* = 0.7)	2.33 (s, Me); 7.13 (m, H(3′), H(5′)); 7.30 (m, H(2′), H(6′))	86.03 (*J* = 5.3)	—
tc-**2c**	5.51 (quint, *J* = 6.1)	5.22 (br.t, *J* = 5.7)	4.72 (br.d, *J* = 5.3)	—[b]	—[b]	—[b]	85.33 (*J* = 6.1)	—
ct-**2c**	5.22 (qd, *J* = 5.9, *J* = 1.8)	5.09 (t, *J* = 1.8)	4.74 (br.s)	8.42 (d, *J* = 2.7)	7.19 (d, H(8), *J* = 9.1); 8.21 (dd, H(7), *J* = 9.1, *J* = 2.7)	2.42 (s, Me); 7.29 (m, H(3′), H(5′)); 7.44 (m, H(2′), H(6′))	86.95 (*J* = 5.9)	1623, 1589, 1562, 1524, 1488, 1368
cc-**2c**	4.61 (qd, *J* = 5.5, *J* = 1.8)	5.26 (dd, *J* = 5.4, *J* = 1.8)	4.59 (br.d, *J* = 5.4)	8.89 (dd, *J* = 2.6, *J* = 1.2)[a]	7.16 (d, H(8), *J* = 9.1); 8.22 (ddd, H(7), *J* = 9.1, *J* = 2.6, *J* = 0.7)	2.41 (s, Me); 7.30 (m, H(3′), H(5′)); 7.59 (m, H(2′), H(6′))	85.75 (*J* = 5.5)	—

(*to be continued*)

Table 3 (*continued*)

Chromane	NMR, δ (*J*/Hz)							IR, ν/cm^{-1}
	^{1}H						^{19}F	
	H(2)	H(3)	H(4)	H(5)	H(6)—H(8)	R′	CF_3 (d)	
tt-**2d**	5.08 (d, *J* = 7.6)	5.18 (t, *J* = 7.8)	4.79 (d, *J* = 8.0)	7.69 (dt, *J* = 7.9, *J* = 1.2)[a]	—[b]	—[b]	—	—
tc-**2d**	5.74 (d, *J* = 6.7)	5.31 (dd, *J* = 6.7, *J* = 5.5)	4.78 (d, *J* = 5.5)	—[b]	6.96—7.06 (m, H(6), H(8)); 7.28 (m, H(7))	2.34 (s, Me); 7.08 (m, H(3′), H(5′)); 7.19 (m, H(2′), H(6′))	—	—
ct-**2d**	5.17 (d, *J* = 1.2)	5.53 (t, *J* = 1.5)	4.70 (br.s)	7.53 (dd, *J* = 7.9, *J* = 1.6)	—[b]	—[b]	—	1655, 1589, 1560, 1487, 1372
cc-**2d**	4.55 (d, *J* = 1.5)	5.63 (dd, *J* = 5.5, *J* = 1.5)	4.64 (br.d, *J* = 5.5)	7.95 (dt, *J* = 7.8, *J* = 1.3)[a]	7.12 (m, H(6), H(8)); 7.33 (m, H(7))	2.39 (s, Me); 7.24 (m, H(3′), H(5′)); 7.57 (m, H(2′), H(6′))	—	—
tt-**2e**	5.09 (d, *J* = 7.7)	5.15 (t, *J* = 7.8)	4.71 (d, *J* = 7.9)	7.81 (dd, *J* = 2.3, *J* = 0.9)[a]	6.94 (d, H(8), *J* = 8.6); 7.40 (ddd, H(7), *J* = 8.6, *J* = 2.3, *J* = 0.6)	2.34 (s, Me); 7.13 (m, H(3′), H(5′)); 7.28 (m, H(2′), H(6′))	—	—
tc-**2e**	5.71 (d, *J* = 6.5)	5.30 (dd, *J* = 6.5, *J* = 5.5)	4.70 (d, *J* = 5.5)	7.12 (m)	6.93 (d, H(8), *J* = 8.6); 7.37 (dd, H(7), *J* = 8.6, *J* = 2.4)	2.36 (s, Me); 7.12 (m, H(3′), H(5′)); 7.20 (m, H(2′), H(6′))	—	1642, 1566, 1490, 1472, 1362
ct-**2e**	5.13 (s)	5.50 (t, *J* = 1.5)	4.62 (br.s)	7.64 (dd, *J* = 2.3, *J* = 0.6)	7.02 (d, H(8), *J* = 8.6); 7.45 (m, H(7))	—[b]	—	—
cc-**2e**	4.53 (d, *J* = 1.4)	5.60 (dd, *J* = 5.5, *J* = 1.5)	4.56 (dt, *J* = 5.4, *J* = 1.0)	8.08 (dd, *J* = 2.4, *J* = 1.2)[a]	6.98 (d, H(8), *J* = 8.7); 7.43 (ddd, H(7), *J* = 8.7, *J* = 2.4, *J* = 1.0)	2.40 (s, Me); 7.23—7.26 (m, H(3′), H(5′)); 7.55—7.59 (m, H(2′), H(6′))	—	—
tt-**2f**	4.83 (dq, *J* = 9.0, *J* = 5.5)	5.35 (t, *J* = 9.2)	4.87 (br.d, *J* = 9.0)	7.69 (dt, *J* = 7.9, *J* = 1.3)[a]	7.05—7.16 (m, H(6), H(8)); 7.29 (m, H(7))	1.26 (t, Me, *J* = 7.1); 3.17 (AB system, SCH_2, *J* = 15.2); 4.12 (ABX_3 system, OCH_2, *J* = 10.8, *J* = 7.1)	85.43 (*J* = 5.5)	—
tc-**2f**	5.52 (quint, *J* = 6.2)	5.26 (dd, *J* = 7.0, *J* = 5.0)	4.94 (d, *J* = 5.0)	7.37 (dd, *J* = 7.9, *J* = 1.7)	—[b]	1.30 (t, Me, *J* = 7.1); 3.58 (s, SCH_2); 4.22 (q, OCH_2, *J* = 7.1)	84.98 (*J* = 6.2)	—
ct-**2f**	5.02 (qd, *J* = 5.8, *J* = 1.8)	5.49 (t, *J* = 1.8)	4.70 (br.s)	7.41 (dd, *J* = 7.9, *J* = 1.7)	7.02 (dd, H(8), *J* = 8.4, *J* = 1.0); 7.09 (td, H(6), *J* = 7.6, *J* = 1.0); 7.28 (ddd, H(7), *J* = 8.4, *J* = 7.4, *J* = 1.5)	1.33 (t, Me, *J* = 7.1); 3.47 (AB system, SCH_2, *J* = 15.7); 4.27 (qd, OCH_2, *J* = 7.1, *J* = 0.6)	87.02 (*J* = 6.0)	1728, 1612, 1590, 1556, 1489, 1369
cc-**2f**	4.63 (qd, *J* = 5.7, *J* = 1.7)	5.63 (dd, *J* = 5.6, *J* = 1.7)	—[b]	7.70 (dt, *J* = 7.9, *J* = 1.2)[a]	—[b]	1.29 (t, Me, *J* = 7.1); 3.23 (AB system, SCH_2, *J* = 15.5); 4.21 (qd, OCH_2, *J* = 7.1, *J* = 0.9)	85.62 (*J* = 5.7)	—

(*to be continued*)

Table 3 (*continued*)

Chromane	NMR, δ (*J*/Hz)							IR, ν/cm^{-1}
	^{1}H						^{19}F	
	H(2)	H(3)	H(4)	H(5)	H(6)—H(8)	R′	CF_3 (d)	
tt-**2g**	4.85 (dq, *J* = 8.9, *J* = 5.5)	5.33 (t, *J* = 8.9)	4.84 (d, *J* = 9.2)	7.83 (dd, *J* = 2.4, *J* = 1.0)[a]	6.91 (d, H(8), *J* = 8.8); 7.39 (ddd, H(7), *J* = 8.8, *J* = 2.4, *J* = 0.7)	1.29 (t, Me, *J* = 7.1); 3.23 (AB system, SCH_2, *J* = 15.2); 4.16 (q, OCH_2, *J* = 7.1)	85.67 (*J* = 5.5)	—
tc-**2g**	5.44 (quint, *J* = 6.1)	5.33 (t, *J* = 5.5)	—[b]	7.65 (d, *J* = 2.4)	—[b]	1.35 (t, Me, *J* = 7.1); 3.30 (AB system, SCH_2, *J* = 15.4); 4.25 (q, OCH_2, *J* = 7.1)	85.37 (*J* = 6.3)	—
ct-**2g**	4.98 (qd, *J* = 5.9, *J* = 1.6)	5.49 (t, *J* = 1.8)	4.65 (br.s)	7.55 (d, *J* = 2.4)	6.92 (d, H(8), *J* = 8.8); 7.39 (dd, H(7), *J* = 8.8, *J* = 2.4)	1.34 (t, Me, *J* = 7.1); 3.49 (AB system, SCH_2, *J* = 15.8); 4.28 (q, OCH_2, *J* = 7.1)	87.06 (*J* = 5.9)	1739, 1605, 1567, 1479, 1378
cc-**2g**	4.64 (qd, *J* = 5.7, *J* = 1.7)	5.62 (dd, *J* = 5.5, *J* = 1.7)	4.78 (br.d, *J* = 5.0)	7.84 (dd, *J* = 2.4, *J* = 1.0)[a]	—[b]	—[b]	85.69 (*J* = 5.7)	—
tt-**2h**	5.06 (dq, *J* = 8.2, *J* = 5.7)	5.39 (t, *J* = 8.4)	4.96 (br.d, *J* = 8.5)	8.68 (dd, *J* = 2.6, *J* = 1.2)[a]	7.15 (d, H(8), *J* = 9.1); 8.19 (m, H(7))	1.30 (t, Me, *J* = 7.1); 3.33 (AB system, SCH_2, *J* = 15.4); 4.22 (q, OCH_2, *J* = 7.1)	86.27 (*J* = 5.7)	—
tc-**2h**	5.46 (qd, *J* = 6.4, *J* = 4.4)	5.55 (t, *J* = 4.7)	4.83 (d, *J* = 4.7)	8.58 (dd, *J* = 2.6, *J* = 0.6)	—[b]	—[b]	86.05 (*J* = 6.4)	—
ct-**2h**	5.12 (qd, *J* = 5.8, *J* = 1.8)	5.62 (t, *J* = 1.8)	4.77 (br.s)	8.39 (d, *J* = 2.7)	7.17 (d, H(8), *J* = 9.1); 8.19 (dd, H(7), *J* = 9.1, *J* = 2.6)	1.33 (t, Me, *J* = 7.1); 3.57 (AB system, SCH_2, *J* = 16.0); 4.30 (q, OCH_2, *J* = 7.1)	87.13 (*J* = 5.8)	1745, 1622, 1585, 1567, 1517, 1484, 1368
cc-**2h**	4.78 (qd, *J* = 5.5, *J* = 1.8)	5.72 (dd, *J* = 5.6, *J* = 1.8)	4.87 (d, *J* = 5.6)	8.69 (dd, *J* = 2.6, *J* = 1.2)[a]	—[b]	—[b]	85.85 (*J* = 5.5)	—
tt-**2i**	5.17 (d, *J* = 7.6)	5.35 (t, *J* = 7.9)	4.79 (d, *J* = 8.0)	7.60 (dt, *J* = 7.6, *J* = 1.2)[a]	—[b]	1.26 (t, Me, *J* = 7.1); 3.24 (s, SCH_2); 4.16 (q, OCH_2, *J* = 7.1)	—	—
tc-**2i**	5.76 (d, *J* = 6.8)	5.38 (dd, *J* = 5.4, *J* = 6.8)	5.01 (d, *J* = 5.4)	7.32 (dd, *J* = 7.8, *J* = 1.6)	—[b]	1.29 (t, Me, *J* = 7.1); 3.16 (AB system, SCH_2, *J* = 15.5); 4.19 (m, OCH_2)	—	—
ct-**2i**	5.01 (dd, *J* = 1.5, *J* = 0.6)	5.88 (t, *J* = 1.5)	4.68 (br.s)	7.43 (ddd, *J* = 7.9, *J* = 1.6, *J* = 0.6)	7.09 (td, H(6), *J* = 7.6, *J* = 1.1); 7.10 (d, H(8), *J* = 8.3); 7.31 (dddd, H(7), *J* = 8.3, *J* = 7.3, *J* = 1.6, *J* = 0.6)	1.34 (t, Me, *J* = 7.1); 3.49 (AB system, SCH_2, *J* = 15.5); 4.28 (q, OCH_2, *J* = 7.1)	—	1731, 1613, 1589, 1554, 1486, 1367
cc-**2i**	4.69 (d, *J* = 1.4)	6.05 (dd, *J* = 5.6, *J* = 1.5)	4.84 (d, *J* = 5.6)	7.71 (dt, *J* = 7.8, *J* = 1.2)[a]	—[b]	1.34 (t, Me, *J* = 7.1); 3.47 (AB system, SCH_2, *J* = 14.8); 4.27 (m, OCH_2)	—	—
tt-**2j**	5.19 (d, *J* = 7.5)	5.30 (dd, *J* = 8.4, *J* = 7.5)	4.75 (br.d, *J* = 8.4)	7.75 (dd, *J* = 2.3, *J* = 0.9)[a]	7.00 (d, H(8), *J* = 8.6); 7.44 (dd, H(7), *J* = 8.6, *J* = 2.3)	1.28 (t, Me, *J* = 7.2); 3.28 (AB system, SCH_2, *J* = 15.2); 4.19 (q, OCH_2, *J* = 7.2)	—	—

(*to be continued*)

Table 3 (*continued*)

Chromane	NMR, δ (*J*/Hz)							IR, ν/cm^{-1}
	^{1}H						^{19}F	
	H(2)	H(3)	H(4)	H(5)	H(6)—H(8)	R′	CF_3 (d)	
tc-**2j**	5.69 (d, *J* = 6.2)	5.42 (dd, *J* = 6.2, *J* = 5.4)	4.96 (d, *J* = 5.4)	7.55 (d, *J* = 2.3)	6.99 (d, H(8), *J* = 8.6); 7.44 (dd, H(7), *J* = 8.6, *J* = 2.3)	1.31 (t, Me, *J* = 7.2); 3.21 (AB system, SCH_2, *J* = 15.3); 4.22 (q, OCH_2, *J* = 7.2)	—	1724, 1638, 1561, 1478, 1368
ct-**2j**	4.97 (d, *J* = 0.8)	5.88 (t, *J* = 1.5)	4.65 (br.s)	7.56 (d, *J* = 2.3)	7.02 (d, H(8), *J* = 8.6); 7.41 (dd, H(7), *J* = 8.6, *J* = 2.3)	1.34 (t, Me, *J* = 7.1); 3.50 (AB system, SCH_2, *J* = 15.5); 4.28 (q, OCH_2, *J* = 7.1)	—	—
cc-**2j**	4.67 (d, *J* = 1.4)	6.04 (dd, *J* = 5.6, *J* = 1.4)	4.80 (br.d, *J* = 5.6)	7.85 (dd, *J* = 2.3, *J* = 1.1)[a]	6.97 (d, H(8), *J* = 8.7); 7.40 (ddd, H(7), *J* = 8.7, *J* = 2.3, *J* = 0.9)	1.35 (t, Me, *J* = 7.2); 3.46 (AB system, SCH_2, *J* = 14.9); 4.28 (m, OCH_2)	—	—
tt-**2k**	4.83 (dq, *J* = 9.5, *J* = 5.4)	5.19 (t, *J* = 9.7)	4.76 (br.d, *J* = 9.9)	7.73 (dt, *J* = 7.9, *J* = 1.2)[a]	7.01 (dd, H(8), *J* = 8.2, *J* = 1.1); 7.14 (td, H(6), *J* = 7.7, *J* = 1.1); 7.28 (m, H(7))	1.90 (br.s, OH); 2.57—2.71 (m, SCH_2); 3.70—3.82 (m, OCH_2)	85.24 (*J* = 5.4)	3368, 1603, 1572, 1484, 1371
tc-**2k**	5.53 (dq, *J* = 7.6, *J* = 6.1)	5.22 (dd, *J* = 7.6, *J* = 4.9)	4.80 (d, *J* = 4.9)	7.39 (dd, *J* = 7.6, *J* = 1.5)	—[b]	—[b]	84.85 (*J* = 6.2)	—
ct-**2k**	5.03 (qd, *J* = 6.1, *J* = 1.2)	5.54 (t, *J* = 1.7)	4.66 (br.s)	7.42 (dd, *J* = 7.8, *J* = 1.2)	7.00 (dd, H(8), *J* = 8.2, *J* = 1.2); 7.07 (td, H(6), *J* = 7.6, *J* = 1.2); 7.26 (m, H(7))	2.00 (br.s, OH); 2.84—3.07 (m, SCH_2); 3.90—4.05 (m, OCH_2)	86.97 (*J* = 6.1)	—
cc-**2k**	4.61 (qd, *J* = 5.8, *J* = 1.8)	5.68 (dd, *J* = 5.6, *J* = 1.8)	4.72 (br.s)	—[b]	—[b]	—[b]	85.50 (*J* = 5.8)	—
tt-**2l**	4.84 (dq, *J* = 9.2, *J* = 5.5)	5.21 (t, *J* = 9.4)	4.73 (d, *J* = 9.6)	7.88 (dd, *J* = 2.4, *J* = 1.1)[a]	6.90 (d, H(8), *J* = 8.7); 7.38 (ddd, H(7), *J* = 8.7, *J* = 2.4, *J* = 0.8)	1.90 (br.s, OH); 2.64 (ddd, SC<u>H</u>H, *J* = 13.9, *J* = 7.3, *J* = 5.0); 2.73 (ddd, SCH<u>H</u>, *J* = 13.9, *J* = 5.8, *J* = 4.6); 3.75—3.87 (m, OCH_2)	85.46 (*J* = 5.5)	—
tc-**2l**	5.44 (quint, *J* = 6.1)	5.31 (dd, *J* = 6.1, *J* = 4.8)	4.74 (d, *J* = 4.8)	7.68 (d, *J* = 2.4)	—[b]	—[b]	85.22 (*J* = 6.3)	—
ct-**2l**	4.99 (qd, *J* = 5.9, *J* = 1.5)	5.55 (t, *J* = 1.7)	4.65 (br.s)	7.56 (dd, *J* = 2.4, *J* = 0.5)	6.91 (d, H(8), *J* = 8.7); 7.36 (ddd, H(7), *J* = 8.8, *J* = 2.4, *J* = 0.5)	1.80 (br.s, OH); 2.88 (ddd, SC<u>H</u>H, *J* = 14.6, *J* = 7.6, *J* = 3.7); 3.05 (ddd, SCH<u>H</u>, *J* = 14.6, *J* = 6.2, *J* = 3.8); 3.96 (ddd, OC<u>H</u>H, *J* = 11.0, *J* = 7.6, *J* = 3.7); 4.06 (ddd, OCH<u>H</u>, *J* = 11.0, *J* = 6.2, *J* = 3.8)	86.98 (*J* = 5.9)	3484, 1553, 1479, 1367
cc-**2l**	4.59 (qd, *J* = 5.7, *J* = 1.6)	5.70 (dd, *J* = 5.5, *J* = 1.7)	4.70 (br.d, *J* = 5.5)	7.91 (dd, *J* = 2.4, *J* = 1.2)[a]	—[b]	—[b]	85.57 (*J* = 5.7)	—

(*to be continued*)

Table 3 (*continued*)

Chromane	NMR, δ (*J*/Hz)							IR, ν/cm^{-1}
	^{1}H						^{19}F	
	H(2)	H(3)	H(4)	H(5)	H(6)—H(8)	R′	CF_3 (d)	
tt-**2m**	5.03 (dq, *J* = 8.8, *J* = 5.6)	5.32 (t, *J* = 8.9)	4.86 (d, *J* = 9.0)	8.72 (dd, *J* = 2.6, *J* = 1.2)[a]	7.14 (d, H(8), *J* = 9.1); 8.15—8.20 (dd, H(7), *J* = 9.1, *J* = 2.6)	2.70—3.15 (m, SCH_2); 3.87—4.15 (m, OCH_2)	85.97 (*J* = 5.6)	—
tc-**2m**	5.44 (qd, *J* = 6.4, *J* = 4.7)	5.57 (t, *J* = 4.8)	4.83 (d, *J* = 5.0)	8.60 (dd, *J* = 2.6, *J* = 0.9)[a]	7.12 (d, H(8), *J* = 9.1); 8.15—8.20 (dd, H(7), *J* = 9.1, *J* = 2.6)	2.70—3.15 (m, SCH_2); 3.87—4.15 (m, OCH_2)	85.88 (*J* = 6.4)	—
ct-**2m**	5.11 (qd, *J* = 5.8, *J* = 1.7)	5.71 (t, *J* = 1.8)	4.80 (br.s)	8.40 (d, *J* = 2.7)	7.15 (d, H(8), *J* = 9.1); 8.16 (dd, H(7), *J* = 9.1, *J* = 2.7)	2.70—3.15 (m, SCH_2); 3.87—4.15 (m, OCH_2)	87.04 (*J* = 5.9)	3535, 1535, 1657, 1565, 1621, 1521, 1480, 1345
cc-**2m**	4.74 (qd, *J* = 5.5, *J* = 1.7)	5.83 (dd, *J* = 5.5, *J* = 1.5)	—[b]	8.76 (dd, *J* = 2.6, *J* = 1.0)[a]	7.13 (d, H(8), *J* = 9.1); 8.15—8.20 (dd, H(7), *J* = 9.1, *J* = 2.6)	2.70—3.15 (m, SCH_2); 3.87—4.15 (m, OCH_2)	85.70 (*J* = 5.6)	—
tt-**2n**	5.20 (d, *J* = 7.6)	5.22 (t, *J* = 7.6)	4.64 (d, *J* = 7.6)	7.65 (dt, *J* = 7.6, *J* = 1.2)[a]	7.06—7.18 (m, H(8), H(6)); 7.26—7.44 (m, H(7))	1.90 (br.s, OH); 2.70—3.10 (m, SCH_2); 3.72—4.06 (m, OCH_2)	—	—
tc-**2n**	5.77 (d, *J* = 6.8)	5.36 (dd, *J* = 6.8, *J* = 5.4)	4.82 (d, *J* = 5.3)	—[b]	7.06—7.18 (m, H(8), H(6)); 7.26—7.44 (m, H(7))	1.90 (br.s, OH); 2.70—3.10 (m, SCH_2); 3.72—4.06 (m, OCH_2)	—	—
ct-**2n**	5.06 (dd, *J* = 1.5, *J* = 0.8)	5.91 (t, *J* = 1.5)	4.67 (br.s)	—[b]	7.06—7.18 (m, H(8), H(6)); 7.26—7.44 (m, H(7))	1.90 (br.s, OH); 2.70—3.10 (m, SCH_2); 3.72—4.06 (m, OCH_2)	—	—
cc-**2n**	—[b]	6.09 (dd, *J* = 5.6, *J* = 1.5)	4.75 (br.d, *J* = 5.6)	7.77 (dt, *J* = 7.6, *J* = 1.2)[a]	7.06—7.18 (m, H(8), H(6)); 7.26—7.44 (m, H(7))	1.90 (br.s, OH); 2.70—3.10 (m, SCH_2); 3.72—4.06 (m, OCH_2)	—	—
tt-**2o**	5.23 (d, *J* = 7.5)	5.18 (dd, *J* = 8.8, *J* = 7.5)	4.62 (br.d, *J* = 8.8)	7.81 (dd, *J* = 2.4, *J* = 1.0)[a]	6.98 (d, H(8), *J* = 8.6); 7.43 (ddd, H(7), *J* = 8.6, *J* = 2.4, *J* = 0.9)	1.90 (t, OH, *J* = 5.6); 2.70—2.81 (m, SCH_2); 3.80—3.86 (m, OCH_2)	—	3472, 1561, 1474, 1365
tc-**2o**	5.68 (d, *J* = 6.3)	5.40 (dd, *J* = 6.3, *J* = 5.5)	4.80 (d, *J* = 5.5)	7.52 (d, *J* = 2.4)	6.99 (d, H(8), *J* = 8.6); 7.43 (dd, H(7), *J* = 8.6, *J* = 2.4)	1.85 (t, OH, *J* = 5.6); 2.70—2.81 (m, SCH_2); 3.80—3.86 (m, OCH_2)	—	—
ct-**2o**	5.01 (dd, *J* = 1.5, *J* = 0.6)	5.92 (t, *J* = 1.5)	4.66 (br.s)	7.56 (d, *J* = 2.4)	6.98 (d, H(8), *J* = 8.8); 7.39 (dd, H(7), *J* = 8.8, *J* = 2.4)	1.90 (br.s, OH); 2.89 (ddd, SC<u>H</u>H, *J* = 14.5, *J* = 6.8, *J* = 4.2); 3.08 (ddd, SCH<u>H</u>, *J* = 14.5, *J* = 6.5, *J* = 4.0); 3.98—4.09 (m, OCH_2)	—	—
cc-**2o**	4.65 (d, *J* = 1.4)	6.12 (dd, *J* = 5.6, *J* = 1.4)	4.74 (br.d, *J* = 5.6)	7.91 (dd, *J* = 2.4, *J* = 1.2)[a]	6.96 (d, H(8), *J* = 8.6); 7.39 (ddd, H(7), *J* = 8.6, *J* = 2.3, *J* = 1.1)	3.96—4.08 (m, OCH_2)	—	—

[a] $J_{5,4} \approx J_{5,7}$ = 1.0—1.2 Hz.
[b] Chemical shifts were not determined because of superposition of signals or a low content of the diastereomer.

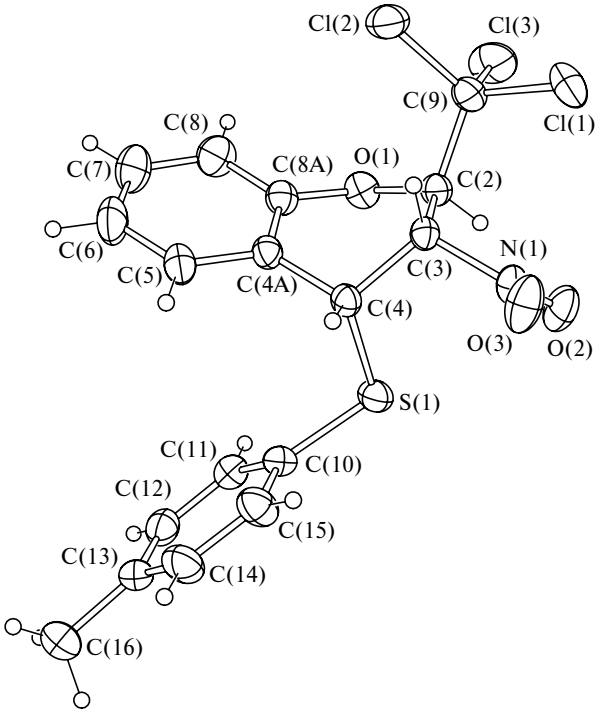


Fig. 1. General view of a molecule of *trans*—*cis*-isomer **2d**.

Fig. 2. Distorted boat conformation of isomer *tc*-**2d** in crystal.

mixture, because this value is 6.1—6.4 in *tc*-, 5.8—6.1 in *ct*-, and 5.3—5.8 Hz in the *tt*- or *cc*-isomers (see Table 3).

The X-ray diffraction study of crystals of individual diastereomers *tc*-**2d** and *ct*-**2f** was carried out for the ultimate confirmation of the structures of diastereomeric forms drawn on the basis of analysis of the SSC values and 2D NOESY spectra. The structure of a molecule of *tc*-**2d** is shown in Figs 1 and 2 and confirms the configuration ascribed to this molecule. The bond lengths in *tc*-**2d** are close to mean statistical values,[31] and the pyran fragment takes the form of a distorted boat, which is related, most likely, to steric interactions between the bulky substituents. The endocyclic torsion angles in the pyran fragment are given below.

Angle	Value/deg
O(1)—C(2)—C(3)—C(4)	22.9(2)
C(2)—C(3)—C(4)—C(4a)	–51.7(2)
C(3)—C(4)—C(4a)—C(8a)	40.4(2)
C(4)—C(4a)—C(8a)—O(1)	2.5(3)
C(4a)—C(8a)—O(1)—C(2)	–36.9(3)
C(8a)—O(1)—C(2)—C(3)	22.0(2)

Note that of approximately 300 chromane structures available at the Cambridge Structure Database[32] only in four structures the pyran fragment has a boat or a distorted boat conformation.

The dihedral angles between the mean plane drawn through the atoms of the pyran cycle and the C(3)—N(1) and C(2)—C(9) bonds are 68.0 and 139.8°, respectively, and the dihedral angle between the sulfanyl fragment and *p*-tolyl ring is 66.9°. The aromatic rings are unfolded relatively to each other at an angle of 48.6°. Molecules of *tc*-**2d** in crystal form a complicated supramolecular motive of 1d-architecture (chains along the crystallographic axis *c*) due to van der Waals interactions of the C—H...O and C—H...S types: O(1)...H(4a), 2.58 Å; O(2)...H(6a), 2.64 Å; O(3)...H(2a), 2.31 Å; S(1)...H(3a), 2.92 Å (Fig. 3).

The structure of isomer *ct*-**2f** is presented in Fig. 4 showing that the sulfanyl and nitro groups occupy the axial positions and the trifluoromethyl group is in the equatorial position. The pyran cycle exists in the conformation of a weakly distorted half-chair with the deviation of the C(2) and C(3) atoms from the plane of other atoms by –0.363(3) and 0.308(4) Å, respectively. In crystal of compound *ct*-**2f**, one can distinguish the C(13)—H...F(2) intermolecular interactions with an H...F distance of 2.48 Å (the sum of van der Waals radii is 2.56 Å),[33] which link the molecules to form centrosymmetric dimers. Also note π-stacking of the interaction between the benzene rings of the neighboring molecules with intercenter and interplanar distances of 3.915 and 3.531 Å, respectively.

Then we studied the interaction of chromenes **1a,c** with aromatic amines and found that reflux of 3-nitro-2-trifluoromethyl-2*H*-chromene (**1a**) with aniline, *p*-toluidine, and *p*-anisidine in benzene for 4—6 h afforded 4-arylamino-3-nitro-2-trifluoromethylchromanes **3a—c**

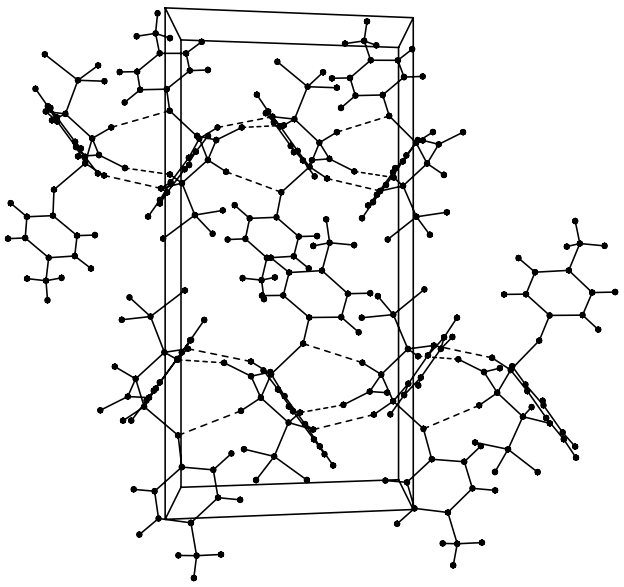


Fig. 3. Packing of molecules *tc*-**2d** in crystal.

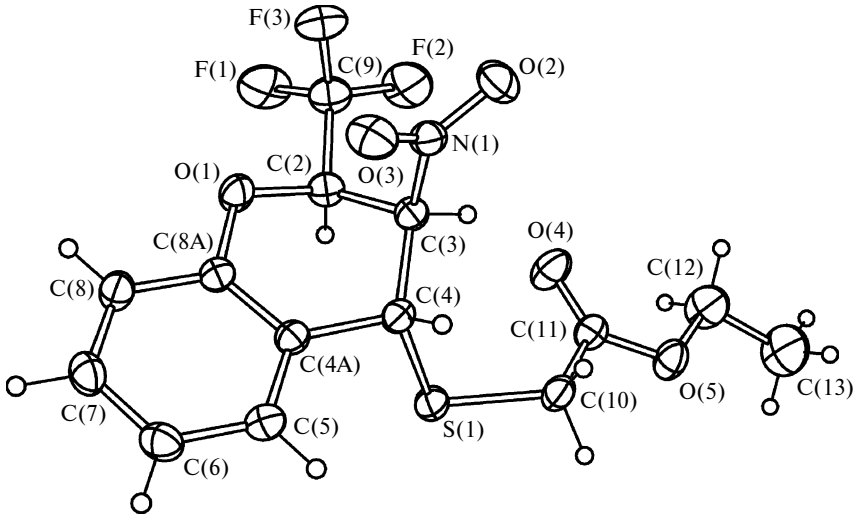
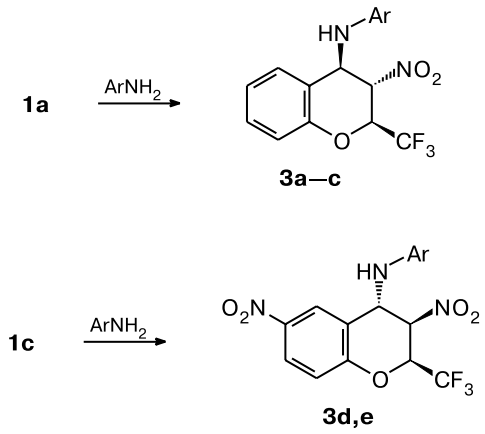


Fig. 4. General view of a molecule of *cis—trans*-isomer **2f**.

(Scheme 3). After the reaction mixture was recrystallized from hexane or its mixture with dichloromethane, only one diastereomer was isolated in each case (30—63% yields), whose configuration and conformation were determined on the basis of the ^{1}H NMR spectral data. For instance, the high SSC values ($J_{2,3}$ = 10.5—10.6 Hz and $J_{3,4}$ = 9.7 Hz) indicate the existence of the pyran fragment in the half-chair conformation with the 2-CF_3 and 3-NO_2 substituents in the equatorial positions and the 4-NHAr group in the pseudo-equatorial position. Therefore, compounds **3a—c** have the *tt*-configuration. It is interesting that the reaction of 3,6-dinitro-2-trifluoromethyl-2*H*-chromene (**1c**) with aniline and *p*-toluidine ceases within 2 h and affords chromanes **3d,e** as *ct*-diastereomers with $J_{2,3} \approx J_{3,4}$ = 1.9 Hz (Table 4). It should be mentioned that the replacement of trihalomethyl group by phenyl in chromenes **1** decreases sharply their reactivity. For example, 3-nitro-2-phenyl-2*H*-chromene[34] and 6-bromo-3-nitro-2-phenyl-2*H*-chromene react with neither aniline nor ethyl mercaptoacetate under the studied conditions, or a complicated mixture of products is formed, indicating a considerable contribution of the CF_3 and CCl_3 groups to the activation of the double bond of chromenes **1**.

To conclude, the reaction of 3-nitro-2-trihalomethyl-2*H*-chromenes with thiols proceeds as nucleophilic addition to the activated double bond according to the Michael reaction mechanism and leads to diastereomeric mixtures of 2,3,4-trisubstituted chromanes, whose structures were determined by the analysis of the SSC values and 2D NOESY spectra and confirmed by X-ray diffraction data. Similar reactions with aromatic amines afford *trans—trans*- or *cis—trans*-4-arylamino-3-nitro-2-trifluoromethylchromanes.

Scheme 3



3: Ar = Ph (**a**, **d**), 4-MeC_6H_4 (**b**, **e**), 4-MeOC_6H_4 (**c**)

Experimental

IR spectra were recorded on a Perkin—Elmer Spectrum BX-II instrument in KBr pellets. ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer in $CDCl_3$ with working frequencies of 400.1 (^{1}H) and 376.5 MHz (^{19}F) using Me_4Si and C_6F_6, respectively, as internal standards. 2D NOESY experiments were conducted using standard impulse sequences from the Bruker NMR Suite 2.6 software with a mixing time of 1.7 s.

The starting chromenes **1a,b,d,e** were synthesized according to known procedures.[25]

3,6-Dinitro-2-trifluoromethyl-2*H*-chromene (1c) was synthesized according to a known procedure[25] with the only difference that the reaction was conducted for 48 h. The yield was 75%, m.p. 128—129 °C (from ethanol), light yellow powder. Found (%): C, 41.29; H, 1.40; N, 9.61. $C_{10}H_5F_3N_2O_5$. Calculated (%): C, 41.40; H, 1.74; N, 9.65. IR, ν/cm^{-1}: 3072, 1664, 1619, 1582, 1514, 1476, 1344. ^{1}H NMR, δ: 6.22 (q, 1 H, H(2),

Table 4. ^{1}H, ^{19}F NMR and IR spectra of 4-ArNH-chromanes **3a—e**

Chromane	NMR, δ (*J*/Hz)							IR, ν/cm^{-1}
	^{1}H						^{19}F	
	H(2)	H(3) (t)	H(4)	H(5)	H(6)—H(8)	ArNH	CF_3 (d)	
tt-**3a**	5.19 (dq, *J* = 7.9, *J* = 6.0)	5.08 (*J* = 8.0)	5.45 (br.t, *J* = 8.7)	7.37 (dt, *J* = 7.9, *J* = 1.2)*	7.05 (d, H(8), *J* = 8.4); 7.06 (td, H(6), *J* = 7.6, *J* = 1.2); 7.31 (dddd, H(7), *J* = 8.2, *J* = 7.4, *J* = 1.7, *J* = 0.7)	3.97 (br.d, *J* = 9.4); 6.68—6.72 (m, H(2′), H(6′)); 6.85 (tt, H(4′), *J* = 7.6, *J* = 1.0); 7.20—7.25 (m, H(3′), H(5′))	85.67 (*J* = 6.0)	3389, 1603, 1565, 1512, 1488, 1376
tt-**3b**	5.17 (dq, *J* = 8.0, *J* = 5.9)	5.07 (*J* = 8.0)	5.40 (br.d, *J* = 7.9)	7.38 (dt, *J* = 7.9, *J* = 1.1)*	7.01—7.07 (m, H(6), H(8)); 7.30 (dddd, H(7), *J* = 8.3, *J* = 7.4, *J* = 1.6, *J* = 0.6)	2.26 (s, Me); 3.80—3.90 (br.s); 6.59—6.63 (m, H(2′), H(6′)); 7.01—7.07 (m, H(3′),H(5′))	85.61 (*J* = 5.9)	3378, 1616, 1566, 1520, 1488, 1375
tt-**3c**	5.15 (dq, *J* = 8.1, *J* = 5.9)	5.07 (*J* = 8.1)	5.34 (br.d, *J* = 8.1)	7.40 (dt, *J* = 7.7, *J* = 1.0)*	7.03 (dd, H(8), *J* = 8.2, *J* = 1.2); 7.06 (td, H(6), *J* = 7.5, *J* = 1.2); 7.30 (br.t, H(7), *J* = 8.0)	3.40—3.90 (br.s); 3.76 (s, OMe); 6.63—6.67 (m, H(2′), H(6′)); 6.78—6.82 (m, H(3′), H(5′))	85.58 (*J* = 5.9)	3371, 1610, 1570, 1518, 1488, 1372
ct-**3d**	4.86 (qd, *J* = 5.8, *J* = 1.9)	5.31 (*J* = 1.9)	5.04 (br.d, *J* = 4.0)	8.34 (d, *J* = 2.6)	7.28 (d, H(8), *J* = 9.1); 8.28 (dd, H(7), *J* = 9.1, *J* = 2.6)	4.03 (br.d, *J* = 4.2); 6.74—6.78 (m, H(2′), H(6′)); 6.99 (tt, H(4′), *J* = 7.5, *J* = 0.9); 7.32—7.38 (m, H(3′), H(5′))	87.30 (*J* = 5.8)	3392, 1658, 1622, 1603, 1564, 1526, 1499, 1484, 1345, 1326
ct-**3e**	4.85 (qd, *J* = 5.9, *J* = 1.9)	5.30 (*J* = 1.9)	5.00 (br.d, *J* = 4.0)	8.33 (d, *J* = 2.6)	7.27 (d, H(8), *J* = 9.1); 8.27 (dd, H(7), *J* = 9.1, *J* = 2.6)	2.32 (s, Me); 3.91 (br.d, *J* = 4.2); 6.67 (d, H(2′), H(6′), *J* = 8.3); 7.15 (d, H(3′), H(5′), *J* = 8.3)	87.26 (*J* = 5.9)	3393, 1622, 1590, 1557, 1524, 1485, 1348, 1329

* $J_{5,4} \approx J_{5,7}$ = 1.0—1.2 Hz.

J = 6.0 Hz); 7.24 (m, 1 H, H(8)); 8.17 (s, 1 H, H(4)); 8.35 (m, 2 H, H(5), H(7)). ^{19}F NMR, δ: 83.99 (d, CF_3, *J* = 6.0 Hz).

Reaction of chromenes 1a—e with thiols (general procedure *A*). A mixture of chromene **1** (1.0 mmol) and the corresponding thiol (1.0 mmol) in benzene (5 mL) was kept for 5 h at 65 °C. Then the solution was cooled to room temperature, the solvent was removed, and the residue was washed with hexane.

General procedure *B*. A mixture of chromene **1** (1.0 mmol), the corresponding thiol (1.0 mmol), and anhydrous K_2CO_3 (0.1 mmol) in dichloromethane (5 mL) was stirred for 2 days at ~20 °C. Then a 5% solution of HCl was added to the mixture to reach an acidic pH, and the solution was extracted with dichloromethane (2×2 mL). Combined extracts were washed with water (2×1 mL) and dried with anhydrous Na_2SO_4, the solvent was removed, and the residue was washed with hexane.

Chromane *ct*-**2o** is formed as one stereoisomer on refluxing in benzene in the presence of K_2CO_3. Individual stereoisomers of other chromanes were isolated by recrystallization from hexane (chromanes *tt*-**2b**, *tc*-**2d**, and *ct*-**2f,i,l**) or a hexane—dichloromethane (3 : 1) mixture (*cc*-**2a,j** and *tt*-**2k,l**). Chromane *tc*-**2e** was isolated from the mother liquor after the reaction mixture was washed with hexane. Since the conversion was low, a diastereomeric mixture of **2n** was not isolated.

The data on the ^{1}H, ^{19}F NMR and IR spectra of diastereomers of chromanes **2a—o** are presented in Table 3. The yields, melting points, and elemental analysis data for chromanes **2a—m,o** are given in Table 5.

Reaction of chromenes 1a,c with aromatic amines. A mixture of chromene **1** (1.0 mmol) and the corresponding amine (1.0 mmol) was refluxed for 4—6 h in benzene (8 mL). Then the solution was cooled, the solvent was removed, and the residue was recrystallized from hexane (chromanes **3a—c**) or a hexane—dichloromethane (3 : 1) mixture (chromanes **3d,e**).

The ^{1}H, ^{19}F NMR and IR spectral data for chromanes **3a—e** are presented in Table 4. The yields, melting points, and elemental analysis data for chromanes **3a—e** are given in Table 5.

X-ray diffraction study of compound *tc*-2d was carried out on a Bruker P4 diffractometer (Mo-Kα radiation, graphite monochromator, 2θ/θ scan mode in the range $2\theta < 54°$). A crystalline sample of compound *tc*-**2d** 1.10×0.36×0.34 mm in size was chosen for experiment. The crystals are monoclinic: a = 10.035(3) Å, b = 19.642(4) Å, c = 10.109(4) Å, β = 106.08(2)°, V = 1914.6(10) Å^3, space group $P2_1/c$, Z = 4, $C_{17}H_{14}Cl_3NO_3S$, d_{calc} = 1.453 g cm^{-3}, μ = 0.603 mm^{-1}. Intensities of 4184 independent reflections were measured. An absorption correction was applied by crystal facet (transmission 0.79—0.83). The struc-

Table 5. Physicochemical properties and elemental composition of chromanes **2a—m,o** and **3a—e**

Chromane	Yield (%)	M.p./°C (isomeric composition (%))	Found / Calculated (%)			Molecular formula
			C	H	N	
cc-**2a**	37	187—188	54.92 55.28	3.82 3.82	3.79 3.93	$C_{17}H_{14}F_3NO_3S$
tt-**2b**	36	104—105	45.55 45.55	2.81 2.92	3.24 3.12	$C_{17}H_{13}BrF_3NO_3S$
2c	100	143—145 (17 (*tt*), 1 (*tc*), 69 (*ct*), 13 (*cc*))	49.66 49.28	3.22 3.16	6.75 6.76	$C_{17}H_{13}F_3N_2O_5S$
tc-**2d**	39	117—118	48.60 48.76	3.41 3.37	3.28 3.35	$C_{17}H_{14}Cl_3NO_3S$
tc-**2e**	41	102—103	41.10 41.03	2.68 2.63	2.83 2.81	$C_{17}H_{13}BrCl_3NO_3S$
ct-**2f**	42	95—96	46.24 46.03	3.82 3.86	3.85 3.83	$C_{14}H_{14}F_3NO_5S$
ct-**2g**	28	74—75	37.89 37.85	2.71 2.95	3.27 3.15	$C_{14}H_{13}BrF_3NO_5S$
ct-**2h**	15	121—122	41.17 40.98	3.22 3.19	6.78 6.83	$C_{14}H_{13}F_3N_2O_7S$
ct-**2i**	27	129—130	40.58 40.55	3.26 3.40	3.30 3.38	$C_{14}H_{14}Cl_3NO_5S$
cc-**2j**	10	149—150	34.04 34.07	2.68 2.65	2.75 2.84	$C_{14}H_{13}BrCl_3NO_5S$
tt-**2k**	15	87—88	44.32 44.58	3.68 3.74	4.38 4.33	$C_{12}H_{12}F_3NO_4S$
2l	29 (*tt*), 35 (*ct*)	90—92 (*tt*) 115—116 (*ct*)	35.89 35.84	2.89 2.76	3.54 3.48	$C_{12}H_{11}BrF_3NO_4S$
2m	15	125—126 (22 (*tt*), 8 (*tc*), 67 (*ct*), 3 (*cc*))	39.01 39.14	3.12 3.01	7.52 7.61	$C_{12}H_{11}F_3N_2O_6S$
ct-**2o**	32	137—138	32.08 31.92	2.45 2.46	3.07 3.10	$C_{12}H_{13}BrCl_3NO_4S$
tt-**3a**	63	151—152	56.77 56.81	3.82 3.87	8.37 8.28	$C_{16}H_{13}F_3N_2O_3$
tt-**3b**	30	146—147	57.74 57.96	4.21 4.29	7.95 7.95	$C_{17}H_{15}F_3N_2O_3$
tt-**3c**	47	127—128	55.55 55.44	4.15 4.11	7.64 7.61	$C_{17}H_{15}F_3N_2O_4$
ct-**3d**	65	199—200	49.94 50.14	3.09 3.16	10.84 10.96	$C_{16}H_{12}F_3N_3O_5$
ct-**3e**	70	201—202	51.21 51.39	3.32 3.55	10.36 10.58	$C_{17}H_{14}F_3N_3O_5$

ture was solved by a direct method using the SHELXS-97 program.[35] Structural parameters were refined by the least-squares method in the full-matrix anisotropic approximation according to the SHELXL-97 program.[35] Parameters of H atoms were calculated in each refinement cycle by coordinates of the corresponding carbon atoms (riding model). The final refinement of the structure was performed for all F^2 to $wR_2 = 0.1220$, $S = 1.030$, and 226 parameters were refined ($R = 0.0431$ for 3547 $F > 4\sigma$). The number in the Cambridge Structure Database is 269115.

X-ray diffraction study of compound *ct*-2f was carried out on a Bruker P4 diffractometer (Mo-Kα radiation, graphite monochromator). Triclinic crystal system, $a = 9.1219(6)$ Å, $b = 10.0004(8)$ Å, $c = 10.7195(8)$ Å, $\alpha = 67.597(6)°$, $\beta = 65.697(6)°$, $\gamma = 70.162(6)°$, $V = 804.4(1)$ Å^3, space group $P\bar{1}$, $Z = 2$, $C_{14}H_{14}F_3NO_5S$, $d_{calc} = 1.508$ g cm^{-3}. Intensities of 3335 reflections with $2\theta < 52°$ were measured in the $\theta/2\theta$ scan mode, of which 3113 reflections were independent ($R_{int} = 0.013$). Absorption was applied by the empirical method from the psi-curves (transmission 0.875—0.901). The structure was solved by a direct method and refined by the least-squares method in the anisotropic-isotropic (for H atoms) approximation using the SHELX-97 program package.[35] Positions of H atoms were calculated geometrically (riding model). The final values of the divergence factors are $wR_2 = 0.1167$,

GOOF = 1.088 for all reflections, $R = 0.0408$ for 2614 $I > 2\sigma(I)$. The number in the Cambridge Structure Database is 289242.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 04-03-32463).

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Received December 6, 2005;
in revised form January 17, 2006