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Stereoselective addition of ethyl 3-morpholino(piperidino)-crotonates to 2-trihalomethyl-3-nitro-2*H*-chromenes. Synthesis of 4-acetonyl-3-nitrochromans

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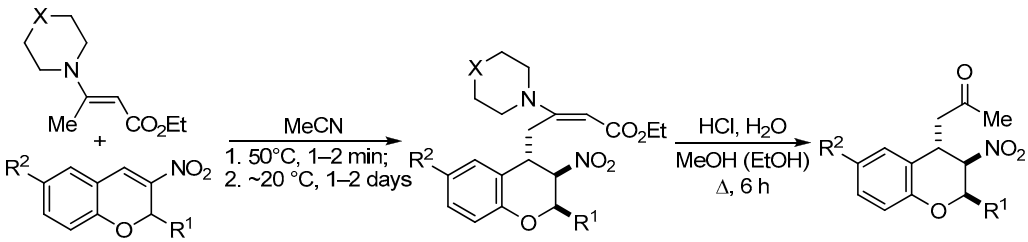


Tertiary enamines of acetoacetic ester, obtained with morpholine and piperidine, add to 2-R^1-3-nitro-2*H*-chromenes (R^1 = CF_3, CCl_3, Ph) *via* the vinylogue β-methyl group and give the respective *cis,trans*-2,3,4-trisubstituted chromans, the stereoconfiguration of which was established by X-ray structural analysis. Acidic hydrolysis of these compounds was accompanied by decarboxylation and produced 4-acetonyl-3-nitrochromans with retention of configuration.

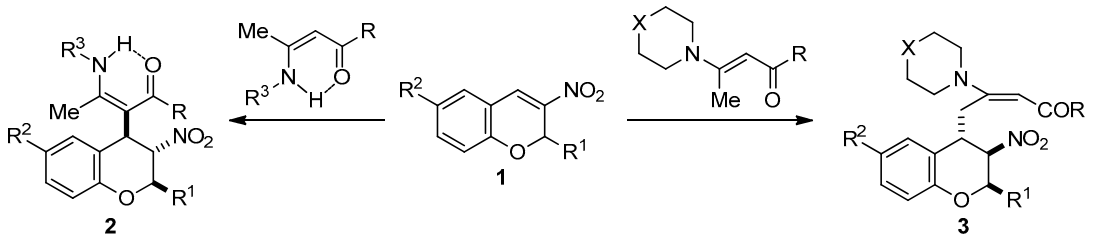
Keywords: chromans, 3-nitro-2*H*-chromenes, push-pull enamines, hydrolysis, stereochemistry.

2*H*-Chromene and its derivatives belong to an important class of oxygen-containing heterocyclic compounds, which are common in plants and show various types of biological activity.[1] The presence of electron-withdrawing substituents in the pyran fragment of these molecules increases the reactivity of C(3)=C(4) bond with regard to nucleophiles, and for this reason 2*H*-chromenes are valuable substrates for the preparation of more complex heterocycles. Of particular synthetic value are 3-nitro-2*H*-chromenes, featuring a double bond conjugated with a nitro group.[2] The introduction of a trihalomethyl group at position 2 of nitrochromene system further increases the reactivity of double bond in pyran ring and offers rich synthetic possibilities for interactions of 3-nitro-2-trihalomethyl-2*H*-chromenes[3] with various *C*-, *N*-, *S*-nucleophiles, which have been studied in detail.[4] However, their reactions with push-pull enamines remain little known. Only one study[5] describes the reactions of 2-aryl-3-nitro-2*H*-chromenes with methyl β-methylaminocrotonate, leading to mixtures consisting of product from nucleophilic addition at the C-4 atom of chromene and the respective chromeno[3,4-*b*]-pyrrole formed by its further Grob cyclization.

Recently we studied the reactions of 2-trifluoromethyl- and 2-trichloromethyl-3-nitro-2*H*-chromenes **1** with enamines of acetoacetic ester, acetylacetone, and benzoylacetone,[6,7] and showed that the regio- and stereochemistry of the addition products changed in the direction from primary and secondary enamines (obtained from ammonia, methylamine, and benzylamine) to tertiary enamines (obtained from morpholine and piperidine). While in the first case the reaction involved the most nucleophilic α-carbon atom of enamine and led to the formation of chromans **2** as *trans,trans* diastereomers with *Z*-configuration of double bond, tertiary enamines added *via* their β-Me vinylogous group and gave *cis,trans*-chromans **3** with *E*-configuration of double bond (preliminary report,[6] Scheme 1).

Due to the rare occurrence of the latter direction involving methyl group of enamine, usually observed only in the series of highly electrophilic ketones and imines,[8] we undertook a more detailed study of the reaction between 3-nitro-2*H*-chromenes and tertiary enamines, based on acetoacetic ester. In the current work, we present complete data about the interaction of 2-substituted 3-nitro-

Scheme 1



2*H*-chromenes with ethyl β-morpholino- and β-piperidinocrotonates, as well as conversion of the obtained addition products to 4-acetonylchromans under the conditions of acidic hydrolysis.

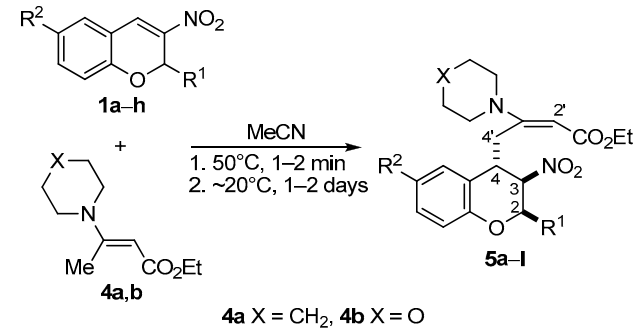
We established that 2-trifluoromethyl-, 2-trichloromethyl-, and 2-phenyl-3-nitro-2*H*-chromenes **1a**–**h** smoothly reacted with acetoacetic ester enamines **4a**,**b** in a minimum amount of acetonitrile (0.2–0.4 ml for 1.0 mmol of reagent) over 1–2 days at room temperature, and gave ethyl 3-morpholino(piperidino)-4-(3-nitrochroman-4-yl)-2-butenoates **5a**–**l** in 14–79% yields after recrystallization from a 2:1 hexane–dichloromethane system. The lowest yields of adducts **5e**,**f**,**j**,**k** (14–41%) were obtained from chromenes **1d**,**g** containing an electron-donating MeO group at position 6 (Scheme 2, Table 1).

The structure of the obtained compounds was established from elemental analysis, IR spectroscopy, ^{1}H and ^{19}F NMR spectroscopy, and X-ray structural analysis. The addition reaction occurred at the C-4 atom of chromene *via* the vinylogous β-Me group without elimination of nitrous acid fragments, and compounds **5a**–**l** were formed only as the *cis*,*trans* diastereomers ($^3J_{H2,H3} \approx {}^3J_{H3,H4} \approx 1.5$ Hz, *ct*-isomer)[9] with *E*-configuration of the double bond. The stereoconfiguration of 2,3,4-trisubstituted chromans **5a**–**l** was confirmed by monocrystal X-ray structural analysis of compounds **5b**,**i** (Fig. 1 and 2). The CF_3 group was observed in ^{19}F NMR spectra of trifluoromethylated chromans **5a**–**f** in $CDCl_3$ as a doublet at 86.7 ppm (J = 6.0 Hz). We should note that an analogous reaction between conjugated nitroalkenes and enamines of β-dicarbonyl compounds was previously described only for the example of α-(trichloroethylidene)nitroalkanes.[10]

We have recently shown[7] that adducts **3** (R = Me) during refluxing in methanol in the presence of hydrochloric acid either underwent hydrolysis to the respective chroman β-diketones **7** (R^1 = CCl_3) or cyclized to chromenopyridines **8** (R^1 = CF_3) (Scheme 3). For this reason, we were interested in studying the behavior of addition products **5a**–**l** under analogous conditions. We found that the ester group hydrolysis in *ct*-chromans **5a**–**l** upon heating for 6 h in 70% ethanol or methanol in the presence of a catalytic amount of hydrochloric acid was accompanied by decarboxylation and gave the acetonyl derivatives **6a**–**l** with the same pyran ring configuration ($^3J_{H2,H3} \approx {}^3J_{H3,H4} \approx 2.0$ Hz, *ct*-isomer)[9] in 16–91% yields (Scheme 3, Table 1). The lowest yields (16–19%) were observed in the case of 4-acetonylchroman **6e**, obtained by hydrolysis of adducts **5e**,**f** with the MeO group at position 6.

We previously obtained compounds **6a**,**h** by tandem condensation of *o*-hydroxybenzylideneacetone with (*E*)-1-nitro-3,3,3-trifluoro(trichloro)propenes.[6] However, the reaction

Scheme 2



Scheme 3

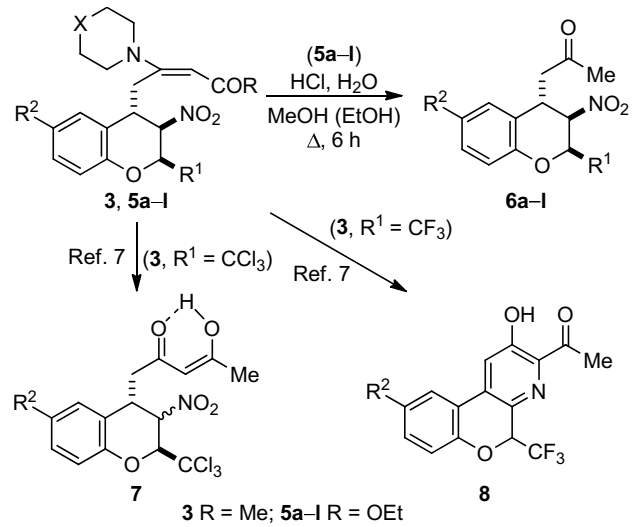


Table 1. Substituents and yields of compounds **5a**–**l** and **6a**–**l**

Cromene	R^1	R^2	X	Compound	Yield, %	Compound	Yield, % (Solvent)
1a	CF_3	H	O	**5a**	79	**6a**	44 (EtOH)
1b	CF_3	Br	CH_2	**5b**	76	–	–
1b	CF_3	Br	O	**5c**	67	**6c**	65 (EtOH), 63 (MeOH)
1c	CF_3	NO_2	CH_2	**5d**	49	**6d**	38 (EtOH)
1d	CF_3	MeO	CH_2	**5e**	37	**6e**	19 (MeOH)
1d	CF_3	MeO	O	**5f**	41	**6e**	16 (MeOH)
1e	CCl_3	H	CH_2	**5g**	54	–	–
1e	CCl_3	H	O	**5h**	41	**6h**	56 (EtOH)
1f	CCl_3	Br	O	**5i**	56	**6i**	47 (MeOH), 77 (EtOH)*
1g	CCl_3	MeO	CH_2	**5j**	26	**6j**	91 (MeOH), 68 (EtOH)**
1g	CCl_3	MeO	O	**5k**	14	**6j**	85 (MeOH), 65 (EtOH)***
1h	Ph	H	O	**5l**	63	**6l**	82 (EtOH)

* *ct*:*tc* = 84:16 (at 60°C).
** *ct*:*tc* = 89:11 (at 60°C).
*** *tc*-Isomer.

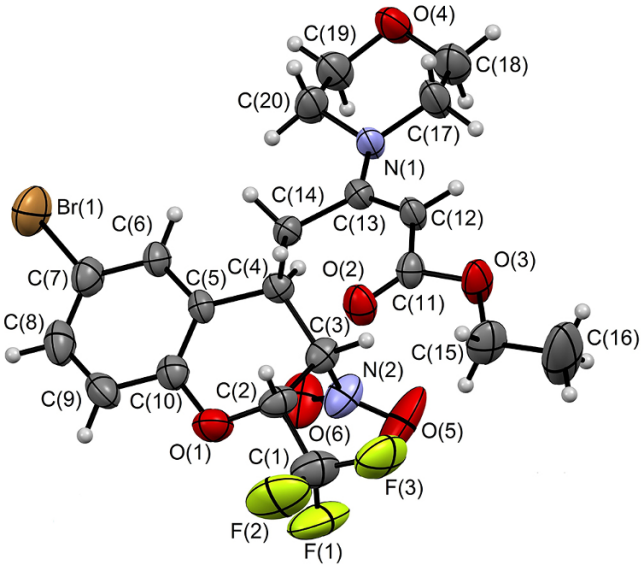


Figure 1. The molecular structure of compound *ct*-**5b** with atoms represented by thermal vibration ellipsoids of 50% probability.

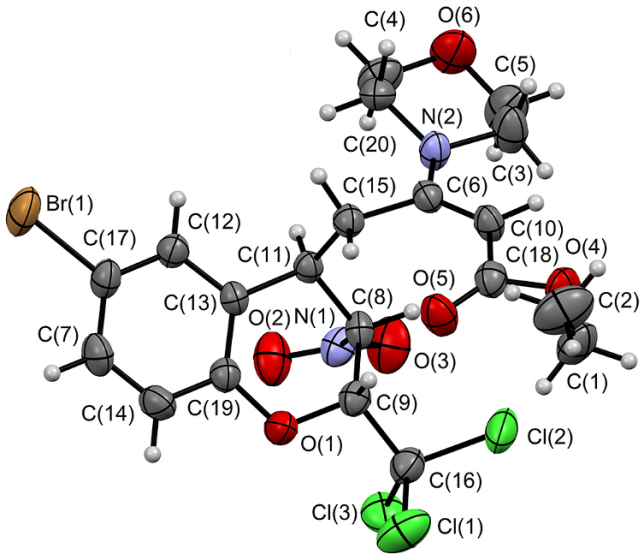


Figure 2. The molecular structure of compound *ct*-**5i** with atoms represented by thermal vibration ellipsoids of 50% probability.

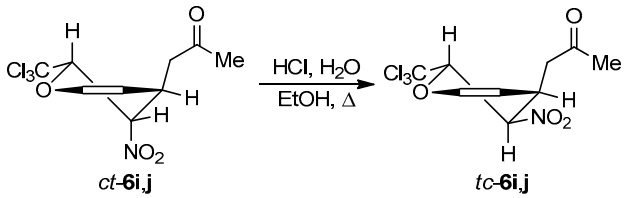
in this case was less stereoselective and chromans **6a**,**h** were formed as a mixture of two diastereomers (*ct*:*tt* = 80:20 in the case of compound **6a** and *tc*:*tt* = 72:28 in the case of compound **6h**). A whole series of *cis,trans*-4-acetonyl-2-aryl-3-nitrochromans, including chroman **6l**, was recently synthesized by direct addition of acetone to 2-aryl-3-nitro-2*H*-chromenes in the presence of pyrrolidine and benzoic acid.[11]

It should be noted that performing the hydrolysis in ethanol in the case of CCl_3-adducts **5i**–**k** led to a partial or complete epimerization at the C-3 atom linked to the NO_2 group, therefore the expected chromans *ct*-**6i**,**j** were accompanied by their isomers *tc*-**6i**,**j**, of which the isomer *tc*-**6j** was isolated as pure compound in 65% yield ($^3J_{H2,H3} \approx {}^3J_{H3,H4} \approx 5.5$ Hz, *tc*-isomer).[9] Apparently, the main factor determining the stereoconfiguration of products **5** and **6** is the preferred *trans* configuration of substituents at positions 2 and 4 of the chroman system (Scheme 4).

The *cis*,*trans* configuration of chromans **5**, identified from the analysis of NMR coupling constants, was confirmed by monocrystal X-ray structural study of compounds **5b**,**i**. The structure of diastereomer *ct*-**5b** is presented in Figure 1, showing that the methylene and nitro groups occupy axial positions, while the trifluoromethyl group takes an equatorial position, corresponding to the assigned configuration of diastereomer *ct*-**5b**. The pyran ring had a conformation of slightly twisted half-chair, explained by steric interactions between its bulky substituents. The C(4)–C(3)–C(2)–C(1) and C(5)–C(4)–C(3)–N(2) torsion angles were –177.8(2) and 80.8(2)°, respectively, while the angle formed by C(6)–C(5)–C(4) plane and methylene group was 74.0(3)°. The same conformation of heterocycle was also found in the structurally related chroman **5i**, containing a trichloromethyl group instead of trifluoromethyl group (Fig. 2).

The aminoenone fragment was practically planar in both cases, explained by delocalization of the lone electron pair of

Scheme 4



ct-**6i**,**j** *tc*-**6i**,**j**

nitrogen atom with the ester carbonyl group. For example, the N(1)–C(13)–C(12)–C(11) torsion angle in chroman **5b** was equal to –174.9(2)°, while the analogous angle in chroman **5i** was smaller by only 3.6°. The angles between benzene and aminoenone fragment planes in molecules of compounds **5b**,**i** were respectively 172.0(2)° (i.e., these fragments were nearly coplanar) and 134.0(2)° (i.e., the presence of relatively bulky trichloromethyl group forced a rotation of aminoenone fragment with respect to the chroman system).

Thus, reactions of 2-substituted 3-nitro-2*H*-chromenes with tertiary enaminoesters obtained from cyclic amines produced *cis,trans*-3-amino-4-(3-nitrochroman-4-yl)-2-butenoates, which gave 4-acetonylchromans upon acidic hydrolysis. The described polyfunctional products are promising intermediates for the synthesis of more complex heterocyclic compounds, including molecules with trifluoro- and trichloromethyl groups.

Experimental

IR spectra were recorded on a PerkinElmer Spectrum BX-II instrument using an ATR accessory for compounds **5e**, **6d**, **6e**, *tc*-**6j** and in KBr for the rest of the compounds. ^{1}H and ^{19}F NMR spectra were acquired on a Bruker DRX-400 spectrometer (400 and 376 MHz, respectively), ^{13}C NMR spectra were acquired on a Bruker Avance-500 spectrometer (126 MHz) in $CDCl_3$, internal standards were TMS

and C_6F_6 (–162.9 ppm). Elemental analysis was performed on an automated PE 2400 analyzer. Melting points were determined on an SMP40 apparatus. 3-Nitro-2*H*-chromenes **1** were obtained according to a published procedure.[3]

Preparation of chromans 5a–l (General method). A mixture of the appropriate chromene **1** (1.0 mmol) and ethyl (*E*)-3-piperidinocrotonate (**4a**) (0.20 g, 1.0 mmol) or ethyl (*E*)-3-morpholinocrotonate (**4b**) (1.0 mmol) in anhydrous acetonitrile (0.4 ml) was heated at 50°C until dissolution (1–2 min) and maintained for 1–2 days at ~20°C. The precipitate that formed was filtered off and recrystallized from a 1:2 mixture of hexane–dichloromethane.

Ethyl (*E*)-3-morpholino-4-[(2*S,3*R**,4*S**)-3-nitro-2-(trifluoromethyl)chroman-4-yl]but-2-enoate (5a)**. Yield 79%. White powder. Mp 174–175°C (decomp.). IR spectrum, ν, cm^{-1}: 1677, 1585, 1557, 1495, 1481, 1449, 1394, 1379. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.1, CH_3); 2.79 (1H, dd, *J* = 15.3, *J* = 4.4, 4'-C$\underline{H}_aH_b$); 3.22 (2H, dt, *J* = 12.8, *J* = 4.9) and 3.33 (2H, dt, *J* = 12.8, *J* = 4.9, $N(CH_2)_2$); 3.39 (1H, dd, *J* = 12.2, *J* = 4.4, 4-CH); 3.76 (4H, t, *J* = 4.9, $O(CH_2)_2$); 4.05 (1H, dq, *J* = 10.9, *J* = 7.1) and 4.12 (1H, dq, *J* = 10.9, *J* = 7.1, OCH_2); 4.18 (1H, dd, *J* = 15.3, *J* = 12.2, 4'-$CH_a\underline{H}_b$); 5.06 (1H, s, 2'-CH); 5.15 (1H, br. s, 3-CH); 5.20 (1H, qd, *J* = 6.0, *J* = 1.4, 2-CH); 7.06 (1H, td, *J* = 7.5, *J* = 1.2, H-6); 7.07 (1H, dd, *J* = 8.2, *J* = 1.2, H-8); 7.17 (1H, d, *J* = 7.7, H-5); 7.26 (1H, ddd, *J* = 8.2, *J* = 7.3, *J* = 1.5, H-7). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.3; 32.6; 38.4; 47.4; 59.7, 66.3; 70.6 (q, *J* = 34.1, C-2); 77.4, 94.2; 117.6; 120.8; 122.2 (q, *J* = 280.7, CF_3); 122.9; 128.3; 128.8; 152.0; 159.2; 168.4 (C=O). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 86.7 (d, *J* = 6.0, CF_3). Found, %: C 54.12; H 5.11; N 6.34. $C_{20}H_{23}F_3N_2O_6$. Calculated, %: C 54.05; H 5.22; N 6.30.

Ethyl (*E*)-4-[(2*S,3*R**,4*S**)-6-bromo-3-nitro-2-(trifluoromethyl)chroman-4-yl]-3-(1-piperidinyl)but-2-enoate (5b)**. Yield 76%. White powder. Mp 154–155°C (decomp.). IR spectrum, ν, cm^{-1}: 1666, 1583, 1559, 1478, 1448, 1411, 1395, 1378. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.1, CH_3); 1.56–1.72 (6H, m, $3CH_2$); 2.75 (1H, dd, *J* = 15.5, *J* = 4.5, 4'-C$\underline{H}_aH_b$); 3.27–3.40 (5H, m, $N(CH_2)_2$, 4-CH); 4.02 (1H, dq, *J* = 10.9, *J* = 7.1) and 4.09 (1H, dq, *J* =10.9, *J* = 7.1, OCH_2); 4.25 (1H, br. t, *J* = 14.0, 4'-$CH_a\underline{H}_b$); 5.00 (1H, s, 2'-CH); 5.11 (1H, br. s, 3-CH); 5.27 (1H, qd, *J* = 6.0, *J* = 1.3, 2-CH); 6.95 (1H, d, *J* = 8.8, H-8); 7.30 (1H, d, *J* = 2.3, H-5); 7.35 (1H, dd, *J* = 8.8, *J* = 2.3, H-7). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.4; 24.3; 25.6; 32.6; 38.2; 48.5; 59.4; 70.7 (q, *J* = 34.4, C-2); 91.8; 114.9; 119.3; 122.1 (q, *J* = 280.9, CF_3); 123.4; 131.0; 131.7; 151.2; 158.4; 169.0 (C=O). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 86.7 (d, *J* = 6.0, CF_3). Found, %: C 48.49; H 4.58; N 5.43. $C_{21}H_{24}BrF_3N_2O_5$. Calculated, %: C 48.38; H 4.64; N 5.37.

Ethyl (*E*)-4-[(2*S,3*R**,4*S**)-6-bromo-3-nitro-2-(trifluoromethyl)chroman-4-yl]-3-morpholinobut-2-enoate (5c)**. Yield 67%. Colorless prisms. Mp 169–170°C (decomp.). IR spectrum, ν, cm^{-1}: 1673, 1582, 1561, 1482, 1450, 1413, 1371. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.1, CH_3); 2.77 (1H, dd, *J* = 15.2, *J* = 4.6, 4'-C$\underline{H}_aH_b$); 3.21 (2H, dt, *J* = 12.8, *J* = 4.9) and 3.30 (2H, dt, *J* = 12.8, *J* = 4.9, $N(CH_2)_2$); 3.36 (1H, dd, *J* = 12.2, *J* = 4.6, 4-CH); 3.76 (4H, t, *J* = 4.9, $O(CH_2)_2$); 4.03 (1H, dq, *J* = 10.9, *J* = 7.1) and 4.12 (1H, dq, *J* = 10.9, *J* = 7.1, OCH_2); 4.15 (1H, br. t, *J* = 13.3, 4'-$CH_a\underline{H}_b$); 5.07 (1H, s, 2'-CH); 5.12 (1H, br. s, 3-CH); 5.21 (1H, qd, *J* = 6.0, *J* = 1.4, 2-CH); 6.96 (1H, d, *J* = 8.8, H-8); 7.27 (1H, d, *J* = 2.3, H-5); 7.36 (1H, dd, *J* = 8.8, *J* = 2.3, H-7). ^1H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 1.06 (3H, t, *J* = 7.1, CH_3); 2.19 (2H, dt, *J* = 12.8, *J* = 4.9, $N(C\underline{H}_aH_b)_2$); 2.34 (2H, dt, *J* = 12.8, *J* = 4.9, $N(CH_a\underline{H}_b)_2$); 3.03 (4H, t, *J* = 4.9, $O(CH_2)_2$); 3.15 (1H, dd, *J* = 12.1, *J* = 4.6, 4-CH); 3.79 (1H, br. s, 4'-$CH_a\underline{H}_b$); 3.96 (1H, dq, *J* = 10.9, *J* = 7.1) and 4.04 (1H, dq, *J* = 10.9, *J* = 7.1, OCH_2); 4.78 (1H, s, 2'-CH); 5.31 (1H, br. s, 3-CH); 5.41 (1H, br. q, *J* = 6.1, 2-CH); 6.56 (1H, d, *J* = 8.8, H-8); 6.94 (1H, dd, *J* = 8.8, *J* = 2.3, H-7); 7.13 (1H, d, *J* = 2.3, H-5); the signal of the 4'-C$\underline{H}_aH_b$ proton is masked at about 2.19 ppm. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 14.3; 32.4; 38.2; 47.5; 59.8; 66.3; 70.7 (q, *J* = 34.4, C-2); 94.6; 115.0; 119.4; 122.1 (q, *J* = 280.9, CF_3); 123.0; 131.0; 131.9; 151.2; 158.8; 168.5 (C=O). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 86.7 (d, *J* = 6.0, CF_3). ^{19}F NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 88.0 (d, *J* = 6.1, CF_3). Found, %: C 45.99; H 4.22; N 5.36. $C_{20}H_{22}BrF_3N_2O_6$. Calculated, %: C 45.90; H 4.24; N 5.35.

Ethyl (*E*)-4-[(2*S,3*R**,4*S**)-3,6-dinitro-2-(trifluoromethyl)-chroman-4-yl]-3-(1-piperidinyl)but-2-enoate (5d)**. Yield 49%. Light-yellow powder. Mp 142–143°C (decomp.). IR spectrum, ν, cm^{-1}: 1673, 1600, 1555, 1527, 1484, 1445, 1382, 1349. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (3H, t, *J* = 7.1, CH_3); 1.60–1.75 (6H, m, $3CH_2$); 2.90 (1H, br. d, *J* = 15.0, 4'-C$\underline{H}_aH_b$); 3.30–3.40 (4H, m, $N(CH_2)_2$); 3.44 (1H, dd, *J* = 12.1, *J* = 4.9, 4-CH); 4.00 (1H, dq, *J* = 10.9, *J* = 7.1) and 4.08 (1H, dq, *J* = 10.9, *J* = 7.1, OCH_2); 4.14–4.27 (1H, m, 4'-$CH_a\underline{H}_b$); 5.02 (1H, s, 2'-CH); 5.17 (1H, br. s, 3-CH); 5.47 (1H, br. q, *J* = 6.0, 2-CH); 7.18 (1H, d, *J* = 9.0, H-8); 8.12 (1H, d, *J* = 2.5, H-5); 8.17 (1H, dd, *J* = 9.0, *J* = 2.5, H-7). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.4; 24.3; 25.6; 32.5; 38.4; 48.6; 59.5; 71.0 (q, *J* = 34.8, C-2); 92.2; 118.3; 121.9 (q, *J* = 280.9, CF_3); 122.0; 124.5; 124.9; 142.9; 156.9; 157.9; 169.1 (C=O). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 86.7 (d, *J* = 5.9, CF_3). Found, %: C 51.75; H 4.99; N 8.55. $C_{21}H_{24}F_3N_3O_7$. Calculated, %: C 51.75; H 4.96; N 8.62.

Ethyl (*E*)-4-[(2*S,3*R**,4*S**)-6-methoxy-3-nitro-2-(trifluoromethyl)chroman-4-yl]-3-(1-piperidinyl)but-2-enoate (5e)**. Yield 37%. White powder. Mp 147–148°C (decomp.). IR spectrum, ν, cm^{-1}: 1668, 1575, 1556, 1488, 1447, 1429, 1395, 1371. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.1, CH_3); 1.52−1.72 (6H, m, $3CH_2$); 2.70–2.82 (1H, m, 4'-C$\underline{H}_aH_b$); 3.27−3.41 (5H, m, $N(CH_2)_2$, 4-CH); 3.80 (3H, s, CH_3O); 4.02 (1H, dq, *J* = 10.8, *J* = 7.1) and 4.09 (1H, dq, *J* = 10.8, *J* = 7.1, OCH_2); 4.27 (1H, br. t, *J* = 13.4, 4'-$CH_a\underline{H}_b$); 5.00 (1H, s, 2'-CH); 5.11 (1H, br. s, 3-CH); 5.21 (1H, br. q, *J* = 6.0, 2-CH); 6.73 (1H, d, *J* = 2.8, H-5); 6.82 (1H, dd, *J* = 9.0, *J* = 2.8, H-7); 6.99 (1H, d, *J* = 9.0, H-8). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.4; 24.4; 25.5; 32.8; 38.6; 48.4; 55.8; 59.3; 71.8 (q, *J* = 34.2, C-2); 91.5; 113.6; 113.9; 118.1; 122.1; 122.3 (q, *J* = 280.6, CF_3); 124.5; 146.1; 154.9; 158.9; 169.0 (C=O). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 86.7 (d, *J* = 6.0, CF_3). Found, %: C 55.64;

H 5.81; N 5.95. $C_{22}H_{27}F_3N_2O_6$. Calculated, %: C 55.93; H 5.76; N 5.93.

Ethyl (*E*)-4-[(2*S,3*R**,4*S**)-6-methoxy-3-nitro-2-(trifluoromethyl)chroman-4-yl]-3-morpholinobut-2-enoate (5f)**. Yield 41%. White powder. Mp 145–146°C (decomp.). IR spectrum, ν, cm^{-1}: 1687, 1675, 1581, 1558, 1500, 1450, 1374. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.1, CH_3); 2.79 (1H, dd, *J* = 15.0, *J* = 4.5, 4'-C$\underline{H}_a$H$_b$); 3.21 (2H, dt, *J* = 13.0, *J* = 4.9) and 3.31 (2H, dt, *J* = 13.0, *J* = 4.9, $N(CH_2)_2$); 3.36 (1H, dd, *J* = 12.2, *J* = 4.5, 4-CH); 3.75 (4H, t, *J* = 4.9, $O(CH_2)_2$); 3.80 (3H, s, CH_3O); 4.04 (1H, dq, *J* = 10.9, *J* = 7.1) and 4.11 (1H, dq, *J* = 10.9, *J* = 7.1, OCH_2); 4.17 (1H, br. t, *J* = 13.4, 4'-CH$_a\underline{H}_b$); 5.06 (1H, s, 2'-CH); 5.11 (1H, br. s, 3-CH); 5.13 (1H, br. q, *J* = 6.0, 2-CH); 6.69 (1H, d, *J* = 2.8, H-5); 6.83 (1H, dd, *J* = 9.0, *J* = 2.8, H-7); 7.00 (1H, d, *J* = 9.0, H-8). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.3; 32.5; 38.6; 47.4; 55.8; 59.6; 66.3; 70.8 (q, *J* = 34.1, C-2); 77.4; 94.3; 113.7; 113.9; 118.2; 121.7; 122.3 (q, *J* = 280.7, CF_3); 146.0; 155.0; 159.2; 168.4 (C=O). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 86.7 (d, *J* = 6.0 Hz, CF_3). Found, %: C 53.10; H 5.19; N 5.88. $C_{21}H_{25}F_3N_2O_7$. Calculated, %: C 53.16; H 5.31; N 5.90.

Ethyl (*E*)-4-[(2*S,3*R**,4*S**)-3-nitro-2-(trichloromethyl)-chroman-4-yl]-3-(1-piperidinyl)but-2-enoate (5g)**. Yield 54%. White powder. Mp 171–172°C (decomp.). IR spectrum, ν, cm^{-1}: 1678, 1588, 1554, 1488, 1456, 1397, 1377. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (3H, t, *J* = 7.1, CH_3); 1.54–1.72 (6H, m, $3CH_2$); 2.84 (1H, dd, *J* = 15.4, *J* = 4.5, 4'-C$\underline{H}_a$H$_b$); 3.26–3.42 (5H, m, $N(CH_2)_2$, 4-CH); 4.04 (1H, dq, *J* = 10.9, *J* = 7.1) and 4.08 (1H, dq, *J* = 10.9, *J* = 7.1, OCH_2); 4.45 (1H, br. t, *J* = 13.6, 4'-CH$_a\underline{H}_b$); 5.02 (1H, s, 2'-CH); 5.26 (1H, s, 2-CH); 5.57 (1H, s, 3-CH); 7.06 (1H, t, *J* = 7.6, H-6); 7.12 (1H, d, *J* = 8.1, H-8); 7.22 (1H, d, *J* = 7.6, H-5); 7.26 (1H, t, *J* = 7.5, H-7). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.5; 24.4; 25.6; 32.6; 39.9; 48.5; 59.3; 59.4; 78.3; 80.1; 91.9; 96.0; 117.4; 121.2; 122.6; 128.5; 152.7; 159.2; 168.9 (C=O). Found, %: C 51.19; H 5.08; N 5.67. $C_{21}H_{25}Cl_3N_2O_5$. Calculated, %: C 51.29; H 5.12; N 5.70.

Ethyl (*E*)-3-morpholino-4-[(2*S,3*R**,4*S**)-3-nitro-2-(trichloromethyl)chroman-4-yl]but-2-enoate (5h)**. Yield 41%. White powder. Mp 190–191°C (decomp.). IR spectrum, ν, cm^{-1}: 1680, 1588, 1553, 1489, 1455, 1397, 1378. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.1, CH_3); 2.91 (1H, dd, *J* = 15.4, *J* = 4.5, 4'-C$\underline{H}_a$H$_b$); 3.20 (2H, dt, *J* = 12.8, *J* = 4.9) and 3.29 (2H, dt, *J* = 12.8, *J* = 4.9, $N(CH_2)_2$); 3.40 (1H, dd, *J* = 11.9, *J* = 5.5, 4-CH); 3.68–3.75 (4H, m, $O(CH_2)_2$); 4.06 (1H, dq, *J* = 10.9, *J* = 7.1) and 4.11 (1H, dq, *J* = 10.9, *J* = 7.1, OCH_2); 4.32 (1H, br. t, *J* = 13.7, 4'-CH$_a\underline{H}_b$); 5.08 (1H, s, 2'-CH); 5.17 (1H, br. d, *J* = 0.7, 2-CH); 5.60 (1H, br. s, 3-CH); 7.06 (1H, t, *J* = 7.6, H-6); 7.13 (1H, d, *J* = 8.1, H-8); 7.19 (1H, d, *J* = 7.6, H-5); 7.28 (1H, t, *J* = 7.8, H-7). Found, %: C 48.55; H 4.58; N 5.63. $C_{20}H_{23}Cl_3N_2O_6$. Calculated, %: C 48.65; H 4.70; N 5.67.

Ethyl (*E*)-4-[(2*S,3*R**,4*S**)-6-bromo-3-nitro-2-(trichloromethyl)chroman-4-yl]-3-morpholinobut-2-enoate (5i)**. Yield 56%. Colorless prisms. Mp 209–210°C (decomp.). IR spectrum, ν, cm^{-1}: 1673, 1583, 1556, 1480, 1449, 1400, 1354. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.1, CH_3); 2.85 (1H, dd, *J* = 15.2, *J* = 5.4, 4'-C$\underline{H}_a$H$_b$); 3.19 (2H, dt, *J* = 12.8, *J* = 4.9) and 3.27 (2H, dt, *J* = 12.8, *J* = 4.8, $N(CH_2)_2$); 3.36 (1H, dd, *J* = 11.6, *J* = 5.4, 4-CH); 3.73 (4H, t, *J* = 4.8, $O(CH_2)_2$); 4.06 (1H, dq, *J* = 10.9, *J* = 7.1) and 4.10 (1H, dq, *J* = 10.9, *J* = 7.1, OCH_2); 4.31 (1H, br. t, *J* = 13.4, 4'-CH$_a\underline{H}_b$); 5.08 (1H, s, 2'-CH); 5.18 (1H, d, *J* = 1.4, 2-CH); 5.56 (1H, br. s, 3-CH); 7.03 (1H, d, *J* = 8.8, H-8); 7.28 (1H, d, *J* = 2.2, H-5); 7.38 (1H, dd, *J* = 8.8, *J* = 2.2, H-7). ^1H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 1.05 (3H, t, *J* = 7.1, CH_3); 2.21–2.38 (5H, m, 4'-C$\underline{H}_a$H$_b$, $N(CH)_2$); 3.07 (4H, t, *J* = 4.8, $O(CH_2)_2$); 3.12 (1H, dd, *J* = 11.4, *J* = 5.9, 4-CH); 3.96–4.08 (3H, m, 4'-CH$_a\underline{H}_b$, OCH_2); 4.86 (1H, s, 2'-CH); 5.43 (1H, d, *J* = 1.0, 2-CH); 5.76 (1H, br. s, 3-CH); 6.69 (1H, d, *J* = 8.8, H-8); 6.96 (1H, dd, *J* = 8.8, *J* = 2.2, H-7); 7.11 (1H, d, *J* = 2.2, H-5). Found, %: C 41.78; H 3.74; N 4.95. $C_{20}H_{22}BrCl_3N_2O_6$. Calculated, %: C 41.95; H 3.87; N 4.89.

Ethyl (*E*)-4-[(2*S,3*R**,4*S**)-6-methoxy-3-nitro-2-(trichloromethyl)chroman-4-yl]-3-(1-piperidinyl)but-2-enoate (5j)**. Yield 26%. White powder. Mp 172–173°C (decomp.). IR spectrum, ν, cm^{-1}: 1673, 1579, 1555, 1497, 1456, 1421, 1380. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (3H, t, *J* = 7.1, CH_3); 1.54–1.72 (6H, m, $3CH_2$); 2.83 (1H, dd, *J* = 15.4, *J* = 4.5, 4'-C$\underline{H}_a$H$_b$); 3.24–3.40 (5H, m, 4-CH, $N(CH_2)_2$); 3.81 (3H, s, CH_3O); 4.04 (1H, dq, *J* = 10.9, *J* = 7.1) and 4.07 (1H, dq, *J* = 10.9, *J* = 7.1, OCH_2); 4.45 (1H, br. t, *J* = 13.4, 4'-CH$_a\underline{H}_b$); 5.02 (1H, s, 2'-CH); 5.19 (1H, s, 2-CH), 5.54 (1H, s, 3-CH); 6.73 (1H, d, *J* = 2.8, H-5); 6.84 (1H, dd, *J* = 8.9, *J* = 2.8, H-7); 7.06 (1H, d, *J* = 8.9, H-8). ^{13}C NMR spectrum, δ, ppm: 14.5; 24.3; 25.6; 32.5; 40.1; 44.5; 48.5; 55.8; 59.3; 78.2; 80.3; 92.0; 96.0; 113.6; 118.0; 122.0; 146.7; 154.8; 159.2; 168.8 (C=O). Found, %: C 50.43; H 5.51; N 5.63. $C_{22}H_{27}Cl_3N_2O_6$. Calculated, %: C 50.64; H 5.22; N 5.37.

Ethyl (*E*)-4-[(2*S,3*R**,4*S**)-6-methoxy-3-nitro-2-(trichloromethyl)chroman-4-yl]-3-morpholinobut-2-enoate (5k)**. Yield 14%. White powder. Mp 180–181°C (decomp.). IR spectrum, ν, cm^{-1}: 1679, 1578, 1554, 1498, 1448, 1397, 1354. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.1, CH_3); 2.89 (1H, dd, *J* = 15.5, *J* = 5.2, 4'-C$\underline{H}_a$H$_b$); 3.19 (2H, dt, *J* = 12.9, *J* = 4.9) and 3.27 (2H, dt, *J* = 12.9, *J* = 4.9, $N(CH_2)_2$); 3.36 (1H, dd, *J* = 11.7, *J* = 5.2, 4-CH); 3.72 (4H, t, *J* = 4.9, $O(CH_2)_2$); 3.80 (3H, s, CH_3O); 4.06 (1H, dq, *J* = 10.7, *J* = 7.1) and 4.09 (1H, dq, *J* = 10.7, *J* = 7.1, OCH_2); 4.31 (1H, br. t, *J* = 13.6, 4'-CH$_a\underline{H}_b$); 5.07 (1H, s, 2'-CH); 5.10 (1H, s, 2-CH); 5.56 (1H, s, 3-CH); 6.70 (1H, d, *J* = 2.9, H-5); 6.85 (1H, dd, *J* = 9.0, *J* = 2.9, H-7); 7.07 (1H, d, *J* = 9.0, H-8). ^{13}C NMR spectrum, δ, ppm: 14.4; 32.2; 40.2; 47.6; 55.9; 59.6; 66.3; 78.2; 80.4; 94.8; 96.0; 113.6; 113.9; 118.1; 121.7; 146.8; 154.9; 159.5; 168.2 (C=O). Found, %: C 47.94; H 4.83; N 5.30. $C_{21}H_{25}Cl_3N_2O_7$. Calculated, %: C 48.15; H 4.81; N 5.35.

Ethyl (*E*)-3-morpholino-4-[(2*S,3*R**,4*S**)-3-nitro-2-phenylchroman-4-yl]but-2-enoate (5l)**. Yield 63%. White powder. Mp 178–179°C (decomp.). IR spectrum, ν, cm^{-1}: 1685, 1584, 1549, 1489, 1451, 1391, 1377. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 7.1, CH_3); 2.83

(1H, dd, *J* = 15.3, *J* = 4.0, 4'-C$\underline{H}_a$H$_b$); 3.20 (2H, dt, *J* = 12.8, *J* = 5.0) and 3.36 (2H, dt, *J* = 12.8, *J* = 5.0, N(CH$_2$)$_2$); 3.45 (1H, dd, *J* = 12.3, *J* = 4.0, 4-CH); 3.68–3.78 (4H, m, O(CH$_2$)$_2$); 4.15 (1H, dq, *J* = 10.8, *J* = 7.1) and 4.20 (1H, dq, *J* = 10.8, *J* = 7.1, OCH$_2$); 4.43 (1H, dd, *J* = 15.3, *J* = 12.3, 4'-CH$_a\underline{H}_b$); 5.06 (1H, d, *J* = 1.9, 2-CH); 5.07 (1H, s, 2'-CH); 5.78 (1H, d, *J* = 1.9, 3-CH); 7.03 (1H, t, *J* = 7.6, H-6); 7.06 (1H, d, *J* = 8.4, H-8); 7.20–7.27 (2H, m, H-5, H-7); 7.34–7.53 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 14.5; 32.9; 38.1; 47.4; 59.5; 66.3; 72.9; 85.5; 94.0; 117.7; 121.4; 121.8; 125.9; 128.1; 128.4; 128.5; 128.6; 136.2; 153.9; 160.2; 168.6 (C=O). Found, %: C 66.42; H 6.34; N 6.24. $C_{25}H_{28}N_2O_6$. Calculated, %: C 66.36; H 6.24; N 6.19.

Preparation of 4-acetonylchromans 6a–l (General method). A mixture of the appropriate chroman **5a–l** (1.0 mmol), H$_2$O (1.0 ml), EtOH or MeOH (3.0 ml), and conc. HCl (0.4 ml) was stirred and refluxed for 6 h. The mixture was then cooled to room temperature, the precipitate was filtered off, washed with water (2×1 ml), dried, and recrystallized from a 1:1 mixture of hexane and dichloromethane, yielding compounds **6a–l** as white powders.

1-[(2*S,3*R**,4*S**)-3-Nitro-2-(trifluoromethyl)chroman-4-yl]propan-2-one (*ct*-6a)**. Yield 44% (EtOH). Mp 109–110°C. IR spectrum, ν, cm^{-1}: 1719, 1585, 1564, 1490, 1375. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.23 (3H, s, CH$_3$); 2.80 (1H, dd, *J* = 18.8, *J* = 9.7) and 3.05 (1H, dd, *J* = 18.8, *J* = 3.8, CH$_2$); 3.97 (1H, br. d, *J* = 8.8, 4-CH); 4.52 (1H, qd, *J* = 5.9, *J* = 2.2, 2-CH); 5.16 (1H, t, *J* = 2.0, 3-CH); 7.02 (1H, dd, *J* = 8.3, *J* = 1.0, H-8); 7.06 (1H, td, *J* = 7.3, *J* = 1.0, H-6); 7.13 (1H, dd, *J* = 7.7, *J* = 1.3, H-5); 7.24 (1H, td, *J* = 7.6, *J* = 1.3, H-7). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 87.0 (d, *J* = 5.9, CF$_3$). Found, %: C 51.62; H 4.03; N 4.49. $C_{13}H_{12}F_3NO_4$. Calculated, %: C 51.49; H 3.99; N 4.62.

1-[(2*S,3*R**,4*S**)-6-Bromo-3-nitro-2-(trifluoromethyl)-chroman-4-yl]propan-2-one (*ct*-6c)**. Yield 65% (EtOH), 63% (MeOH). Mp 135–136°C. IR spectrum, ν, cm^{-1}: 1715, 1563, 1481, 1409, 1368. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (3H, s, CH$_3$); 2.80 (1H, dd, *J* = 19.0, *J* = 9.5) and 3.04 (1H, dd, *J* = 19.0, *J* = 3.5, CH$_2$); 3.94 (1H, br. d, *J* = 8.8, 4-CH); 4.51 (1H, qd, *J* = 5.8, *J* = 2.0, 2-CH); 5.15 (1H, t, *J* = 1.5, 3-CH); 6.92 (1H, d, *J* = 8.8, H-8); 7.27 (1H, d, *J* = 2.3, H-5); 7.35 (1H, dd, *J* = 8.8, *J* = 2.3, H-7). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 30.1; 33.3; 49.3; 70.7 (q, *J* = 34.6, C-2); 78.4; 115.6; 119.1; 121.8 (q, *J* = 281.5, CF$_3$); 123.0; 131.1; 131.8; 150.8; 203.7 (C=O). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 87.0 (d, *J* = 5.8, CF$_3$). Found, %: C 40.76; H 2.80; N 3.67. $C_{13}H_{11}BrF_3NO_4$. Calculated, %: C 40.86; H 2.90; N 3.67.

1-[(2*S,3*R**,4*S**)-3,6-Dinitro-2-(trifluoromethyl)-chroman-4-yl]propan-2-one (*ct*-6d)**. Yield 38% (MeOH). Mp 166–167°C. IR spectrum, ν, cm^{-1}: 1720, 1588, 1560, 1521, 1486, 1434, 1409, 1352. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.27 (3H, s, CH$_3$); 2.90 (1H, dd, *J* = 19.1, *J* = 9.5) and 3.11 (1H, dd, *J* = 19.1, *J* = 3.6, CH$_2$); 4.03 (1H, br. d, *J* = 9.0, 4-CH); 4.68 (1H, qd, *J* = 5.8, *J* = 2.0, 2-CH); 5.26 (1H, t, *J* = 1.8, 3-CH); 7.17 (1H, d, *J* = 9.0, H-8); 8.13 (1H, d, *J* = 1.8, H-5); 8.16 (1H, dd, *J* = 9.0, *J* = 1.8, H-7). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 30.1; 33.5; 48.8; 71.0 (q, *J* = 35.0, C-2); 77.9; 118.2; 121.6 (q, *J* = 281.6, CF$_3$); 121.9; 124.6; 124.7; 143.4; 156.3; 203.4 (C=O). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): 87.1 (d, *J* = 5.8, CF$_3$). Found, %: C 45.06; H 3.00; N 7.80. $C_{13}H_{11}F_3N_2O_6$. Calculated, %: C 44.84; H 3.18; N 8.04.

1-[(2*S,3*R**,4*S**)-6-Methoxy-3-nitro-2-(trifluoromethyl)-chroman-4-yl]propan-2-one (*ct*-6e)** was extracted from the reaction mixture with chloroform (2×1 ml), dried over Na$_2$SO$_4$, and purified by column chromatography (eluent – chloroform). The solvents were removed at reduced pressure and the residue was recrystallized from a 1:1 mixture of hexane–dichloromethane. Yield 19% (from **5e** in MeOH), 16% (from **5f** in MeOH). Mp 88–89°C. IR spectrum, ν, cm^{-1}: 1711, 1566, 1495, 1444, 1423, 1412, 1400, 1365, 1348. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.23 (3H, s, CH$_3$); 2.79 (1H, dd, *J* = 18.8, *J* = 9.3) and 3.06 (1H, dd, *J* = 18.8, *J* = 3.8, CH$_2$); 3.77 (3H, s, MeO); 3.94 (1H, br. d, *J* = 7.8, 4-CH); 4.47 (1H, qd, *J* = 5.9, *J* = 1.5, 2-CH); 5.11 (1H, br. t, *J* = 1.5, 3-CH); 6.63 (1H, d, *J* = 2.6, H-5); 6.80 (1H, dd, *J* = 9.0, *J* = 2.6, H-7); 6.95 (1H, d, *J* = 9.0, H-8). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 30.2; 33.8; 49.6; 55.7; 70.8 (q, *J* = 34.3, C-2); 78.9; 112.9; 114.7; 118.1; 121.5; 122.0 (q, *J* = 281.4, CF$_3$); 145.6; 155.4; 204.1 (C=O). ^{19}F NMR spectrum, δ, ppm: 87.0 (d, *J* = 5.9, CF$_3$). Found, %: C 50.40; H 3.93; N 4.05. $C_{14}H_{14}F_3NO_5$. Calculated, %: C 50.46; H 4.23; N 4.20.

1-[(2*S,3*R**,4*S**)-3-Nitro-2-(trichloromethyl)chroman-4-yl]propan-2-one (*ct*-6h)**. Yield 56% (EtOH). Mp 79–80°C (hexane). IR spectrum, ν, cm^{-1}: 1717, 1591, 1559, 1487, 1371. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (3H, s, CH$_3$); 2.78 (1H, dd, *J* = 18.8, *J* = 9.8) and 3.06 (1H, dd, *J* = 18.8, *J* = 3.8, CH$_2$); 3.96 (1H, br. dd, *J* = 9.8, *J* = 3.5, 4-CH); 4.46 (1H, br. s, 2-CH); 5.56 (1H, s, 3-CH), 7.04–7.18 (3H, m, H Ar), 7.24–7.30 (1H, m, H Ar). Found, %: C 44.31; H 3.23; N 3.72. $C_{13}H_{12}Cl_3NO_4$. Calculated, %: C 44.28; H 3.43; N 3.97.

1-[(2*S,3*R**,4*S**)-6-Bromo-3-nitro-2-(trichloromethyl)-chroman-4-yl]propan-2-one (*ct*-6i)**. Yield 47% (MeOH). Mp 183−184°C. IR spectrum, ν, cm^{-1}: 1715, 1561, 1483, 1408, 1365. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.26 (3H, s, CH$_3$); 2.78 (1H, dd, *J* = 19.0, *J* = 9.8) and 3.04 (1H, dd, *J* = 19.0, *J* = 3.7, CH$_2$); 3.93 (1H, dd, *J* = 9.8, *J* = 3.7, 4-CH); 4.45 (1H, s, 2-CH); 5.54 (1H, s, 3-CH); 7.00 (1H, d, *J* = 8.8, H-8); 7.29 (1H, d, *J* = 2.0, H-5); 7.37 (1H, dd, *J* = 8.8, *J* = 2.0, H-7). ^{13}C NMR spectrum, δ, ppm: 30.2; 35.2; 50.1; 79.1; 80.7; 95.2; 115.4; 119.0; 123.1; 131.1; 131.7; 151.8; 203.6 (C=O). Hydrolysis of compound **5i** in ethanol at 60°C gave a mixture of *ct*- and *tc*-isomers in 84:16 ratio and 77% total yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *tc*-**6i** (16%): 2.22 (3H, s, CH$_3$); 2.82 (1H, dd, *J* = 18.3, *J* = 7.0) and 2.98 (1H, dd, *J* = 18.3, *J* = 6.9, CH$_2$); 4.12 (1H, q, *J* = 6.0, 4-CH); 5.36 (1H, d, *J* = 5.3, 2-CH); 5.48 (1H, t, *J* = 5.5, 3-CH); 7.01 (1H, d, *J* = 8.8, H-8); 7.30 (1H, d, *J* = 2.3, H-5); 7.41 (1H, dd, *J* = 8.8, *J* = 2.3, H-7). Found, %: C 36.07; H 2.39; N 3.20. $C_{13}H_{11}BrCl_3NO_4$. Calculated, %: C 36.19; H 2.57; N 3.25.

1-[(2*S,3*R**,4*S**)-6-Methoxy-3-nitro-2-(trichloromethyl)-chroman-4-yl]propan-2-one (*ct*-6j)**. Yield 91% (from **5j** in MeOH), 85% (from **5k** in MeOH). Mp 165–166°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (3H, s, CH$_3$); 2.79 (1H, dd, *J* = 18.8, *J* = 9.7) and 3.06 (1H, dd, *J* = 18.8, *J* = 3.8,

CH_2); 3.78 (3H, s, CH_3O); 3.93 (1H, dd, *J* = 9.7, *J* = 3.7, 4-CH); 4.42 (1H, s, 2-CH); 5.51 (1H, s, 3-CH); 6.64 (1H, d, *J* = 2.8, H-5); 6.83 (1H, dd, *J* = 9.0, *J* = 2.8, H-7); 7.04 (1H, d, *J* = 9.0, H-8). ^{13}C NMR spectrum, δ, ppm: 30.2; 35.7; 50.3; 55.7; 79.6; 80.9; 95.5, 112.9; 114.7; 118.0; 121.5; 146.6; 155.3; 204.0 (C=O). Hydrolysis of compound **5j** in EtOH at 60°C gave a mixture of *ct*- and *tc*-isomers in 89:11 ratio and 68% total yield. Found, %: C 43.95; H 3.48; N 3.60. $C_{14}H_{14}Cl_3NO_5$. Calculated, %: C 43.95; H 3.69; N 3.66.

1-[(2*S,3*S**,4*S**)-6-Methoxy-3-nitro-2-(trichloromethyl)-chroman-4-yl]propan-2-one (*tc*-6j)**. Yield 65% (from **5k** in EtOH). Mp 86–87°C. IR spectrum, ν, cm^{-1}: 1714, 1560, 1499, 1409, 1369. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (3H, s, CH_3); 2.82 (1H, dd, *J* = 18.3, *J* = 7.1, C<u>H</u>H); 2.97 (1H, dd, *J* = 18.3, *J* = 6.9, CH<u>H</u>); 3.78 (3H, s, CH_3O); 4.11 (1H, q, *J* = 6.0, 4-CH); 5.34 (1H, d, *J* = 5.8, 2-CH); 5.42 (1H, t, *J* = 5.4, 3-CH); 6.70 (1H, d, *J* = 2.8, H-5); 6.80 (1H, dd, *J* = 9.0, *J* = 2.8, H-7); 7.04 (1H, d, *J* = 9.0, H-8).

1-[(2*S,3*R**,4*S**)-3-Nitro-2-phenylchroman-4-yl]-propan-2-one (*ct*-6l).** Yield 82% (EtOH). Mp 185–186°C (mp 170.5–171.5°C).[11] IR spectrum, ν, cm^{-1}: 1710, 1587, 1545, 1490, 1371. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.27 (3H, s, CH_3); 2.92 (1H, dd, *J* = 18.4, *J* = 9.8) and 3.13 (1H, dd, *J* = 18.4, *J* = 4.0, CH_2); 3.98 (1H, dd, *J* = 9.8, *J* = 4.0, 4-CH); 5.04 (1H, t, *J* = 2.0, 3-CH); 5.26 (1H, d, *J* = 2.1, 2-CH); 7.00–7.06 (2H, m, H-6,8); 7.17 (1H, dd, *J* = 8.3, *J* = 1.4, H-5); 7.23 (1H, ddd, *J* = 8.7, *J* = 7.3, *J* = 1.4, H-7); 7.35–7.45 (5H, m, H Ph). Found, %: C 69.40; H 5.50; N 4.42. $C_{18}H_{17}NO_4$. Calculated, %: C 69.44; H 5.50; N 4.50.

X-Ray structural study of chromans 5b,i was performed at 20°C temperature on an Xcalibur S diffractometer with a CCD-detector according to standard method (MoKα-radiation, graphite monochromator, ω-scanning, $2\theta_{max}$ 52°). **Compound 5b**. The crystals of compound **5b** ($C_{21}H_{24}BrF_3N_2O_5$, *M* 523.31) were monoclinic; *a* 11.3487(10), *b* 8.7553(7), *c* 22.362(2) Å; β 95.612(7)°; *V* 2211.3(3) $Å^3$; *Z* 4; space group *P*2(1)*/n*; d_{calc} 1.345 $g·cm^{-3}$; μ 1.923 cm^{-1}; *F*(000) 1064. A total of 18370 reflections were collected, including 5168 independent, and 1874 reflections were used for refinement ($I > 2\sigma(I)$). The final probability factor values: R_1 0.0392, wR_2 0.0530, *GOF* 1.001 ($\Delta\rho_{min}/\Delta\rho_{max}$ = 0.436/–0.436 $e·Å^{-3}$).

Compound 5i. Crystals of compound **5i** ($C_{20}H_{22}BrCl_3N_2O_6$, *M* 572.66) were monoclinic; *a* 12.0862 (11), *b* 12.0044(7), *c* 17.4391(16) Å; β 106.161(8)°; *V* 2430.2(3) $Å^3$; *Z* 4; space group *P*2(1)*/n*; d_{calc} 1.565 $g·cm^{-3}$; μ 2.059 cm^{-1}; *F*(000) 1160. A total of 22261 reflections were collected, including 7908 independent, and 2997 reflections were used for refinement ($I > 2\sigma(I)$). The final probability factor values: R_1 0.0334, wR_2 0.0512, *GOF* 1.008 ($\Delta\rho_{min}/\Delta\rho_{max}$ = 0.585/–0.560 $e·Å^{-3}$).

The structures of compounds **5b**,**i** were solved by direct method, using the SHELX97 software suite.[12] All non-hydrogen atoms were refined independently in anisotropic approximation, while hydrogen atoms were placed in geometrically calculated positions and included in refinement according to the "rider" model with dependent thermal parameters. The complete X-ray structural data sets for compounds **5b**,**i** were deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1046820 and CCDC 915041, respectively).

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References

1. (a) Paul, N. D.; Mandal, S.; Otte, M.; Cui, X.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2014**, *136*, 1090. (b) Majumdar, N.; Paul, N. D.; Mandal, S.; de Bruin, B.; Wulff, W. D. *ACS Catal.* **2015**, *5*, 2329. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (d) Bergmann, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492. (e) Burrell, G.; Cassidy, F.; Evans, J. M.; Lightowler, D.; Stemp, G. *J. Med. Chem.* **1990**, *33*, 3023. (f) Gericke, R.; Harting, J.; Lues, I.; Schittenhelm, C. *J. Med. Chem.* **1991**, *34*, 3074.
2. (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (b) Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* **1985**, *18*, 284. (c) Bhanja, C.; Jena, S.; Nayak, S.; Mohapatra, S. *Beilstein J. Org. Chem.* **2012**, *8*, 1668. (d) Zhang, D.; Ma, Y.; Liu, Y.; Liu, Z.-P. *Arch. Pharm.* **2014**, *347*, 576.
3. Korotaev, V. Yu.; Kutyashev, I. B.; Sosnovskikh, V. Ya. *Heteroat. Chem*. **2005**, *16*, 492.
4. (a) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Barkov, A. Yu. *Russ. Chem. Rev*. **2013**, *82*, 1081. [*Usp. Khim.* **2013**, *82*, 1081.] (b) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B.; Kodess, M. I. *Russ. Chem. Bull.*, *Int. Ed*. **2006**, *55*, 2020. [*Izv. Akad. Nauk*, *Ser. Khim.* **2006**, 1945.] (c) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B. *Russ. Chem. Bull.*, *Int. Ed*. **2007**, *56*, 2054. [*Izv. Akad. Nauk*, *Ser. Khim.* **2007**, 1985.] (d) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Barabanov, M. A.; Yasnova, E. S.; Ezhikova, M. A.; Kodess, M. I.; Slepukhin, P. A. *Tetrahedron* **2010**, *66*, 1404. (e) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Barkov, A. Yu.; Slepukhin, P. A.; Ezhikova, M. A.; Kodess, M. I.; Shklyaev, Yu. V. *Tetrahedron* **2011**, *67*, 8685.
5. Gupta, R. C.; Seth, M.; Bhaduri, A. P. *Indian J. Chem*. **1991**, *30B*, 297.
6. Korotaev, V. Yu.; Barkov, A. Yu.; Sokovnina, A. A.; Sosnovskikh, V. Ya. *Mendeleev Commun.* **2013**, *23*, 150.
7. (a) Korotaev, V. Yu.; Barkov, A. Yu.; Sosnovskikh, V. Ya. *Tetrahedron Lett.* **2013**, *54*, 3091. (b) Korotaev, V. Yu.; Barkov, A. Yu.; Kutyashev, I. B.; Kotovich, I. V.; Ezhikova, M. A.; Kodess, M. I.; Sosnovskikh, V. Ya. *Tetrahedron* **2015**, *71*, 2658.
8. Kostyuk, A. N.; Volochnyuk, D. M.; Sibgatulin, D. A. *Synthesis* **2008**, 161.
9. (a) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B.; Kodess, M. I. *Lett. Org. Chem*. **2005**, *2*, 616. (b) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B.; Kodess, M. I. *Russ. Chem. Bull., Int. Ed*. **2006**, *55*, 317. [*Izv. Akad. Nauk*, *Ser. Khim.* **2006**, 309.]
10. Korotaev, V. Yu.; Barkov, A. Yu.; Slepukhin, P. A.; Kodess, M. I.; Sosnovskikh, V. Ya. *Tetrahedron Lett.* **2011**, *52*, 5764.
11. Wang, P.-A.; Zhang, D.-X.; Liu, X.-Y. *ARKIVOC* **2014**, (v), 408.
12. Sheldrick, G. M. *Acta Crystallogr.*, *Sect. A: Found. Crystallogr.* **2008**, *A64*, 112.