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Synthesis of chromeno[3,4-*c*][1,2]oxazine-*N*-oxides via formal [4+2] cycloaddition of 3-nitro-2-trihalomethyl-2*H*-chromenes with cyclohexanone and pinacolone enamines

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ABSTRACT

3-Nitro-2-trichloro(trifluoro)methyl-2*H*-chromenes undergo a formal [4+2] cycloaddition reaction to cyclohexanone and pinacolone enamines, producing chromeno[3,4-*c*][1,2]benzoxazin-6-oxides with high diastereoselectivity and in good yields. In addition, some novel 2,3,4-trisubstituted chromanes were obtained. The stereochemistry of the products was established based on a 2D NOESY experiment and an X-ray diffraction study.

1. Introduction

Derivatives of 2*H*-1-benzopyran, also known as 2*H*-chromenes, belong to an important class of natural oxygen-containing heterocycles that are widely distributed among many plants.[1] They have considerable biological importance[2] and are useful intermediates in the synthesis of more complex natural products, such as pterocarpans.[3] In addition, 3-nitro-2*H*-chromenes, that are related to conjugated nitroalkenes, have attracted considerable attention in recent years due to the possibility of using them as dipolarophiles in 1,3-cycloadditions of diazoalkanes,[4] azomethine ylides,[5] *N*-methylnitrone,[6] and sodium azide.[7]

On the other hand, considerable interest was aroused in the synthesis of partially halogenated heterocyclic compounds, many of which have found use as agrochemicals and drugs.[8] The reactions of 3-nitro-2-trihalomethyl-2*H*-chromenes **1**,[9] which are of interest as building blocks in organic synthesis for the construction of trihalomethyl-containing heterocycles, have been studied in sufficient detail.[10] The majority of the reactions with these compounds are nucleophilic additions at the 4-position leading to various types of 4-substituted chromans.[11] However, their cycloaddition reactions are under-developed. Only two papers are known reporting the reaction of 3-nitro-2-trihalomethyl-2*H*-chromenes **1** with enol ethers[12] and nonstabilised azomethyne ylides[13] to give the corresponding cycloadducts, a fact prompting us to investigate the synthesis of chromeno[3,4-*c*][1,2]benzoxazin-6-oxides from chromenes **1** and enamines **2**, derived from cyclohexanone, pinacolone, and morpholine.

Taking into account the reactions of conjugated nitroalkenes with enamines[14] and the fact that the Michael addition is facilitated by the presence of electron-withdrawing groups in a Michael acceptor, we envisaged that the nitroolefinic system of chromenes **1** would be useful for a simple and convenient synthesis of CX_3-containing 1,2-oxazine *N*-oxides, which could be used as 1,3-dipoles for the preparation of novel polycyclic chromane derivatives.[12] Herein, we have studied the heterocyclization of 2-trichloromethyl- and 2-trifluoromethyl-3-nitro-2*H*-chromenes **1a**–**h** with *N*-cyclohexenylmorpholine (**2a**) and 1-*tert*-butyl-1-morpholinoethene (**2b**) and shown that these reactions result in the formation of cyclic nitronates **3** and **6**, which were converted into the *trans,cis*-2,3,4-trisubstituted chromane derivatives **5** and **7**, respectively.

2. Results and discussion

3-Nitro-2-trihalomethyl-2*H*-chromenes **1a**–**h** were prepared by the tandem reaction (conjugate addition followed by intramolecular

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Henry condensation) of salicylaldehydes with 3,3,3-trichloro (trifluoro)-1-nitropropenes in the presence of triethylamine reported earlier by our group.[9] We found that the reaction of chromenes **1a**–**f** with *N*-cyclohexenylmorpholine (**2a**) in acetonitrile at room temperature resulted in the formation of cycloadducts **3a**–**f** in 32–82% yields as single diastereomeric products, the structure of which was established by IR, ^{1}H, ^{19}F, and ^{13}C NMR spectroscopy as well as by elemental analysis. The reaction was complete after 1 h for 2-CCl_3-chromenes **1a**–**d** and 0.5 h for 2-CF_3-chromenes **1e**,**f** and the products could be isolated by simple filtration of the precipitate formed. The results are summarized in Table 1. To the best of our knowledge, this type of cycloaddition between 3-nitro-2*H*-chromenes and enamines has not previously been reported.

Table 1
Yields of compounds **3**–**5**

Starting materials **1**, **3**	R	X	Product	Time (h)	Yield (%)
1a	H	Cl	**3a**	1	80
1b	Br	Cl	**3b**	1	69
1c	MeO	Cl	**3c**	1	82
1d	NO_2	Cl	**3d**	1	32[a]
1e	Br	F	**3e**	0.5	59
1f	NO_2	F	**3f**	0.5	54
1g	H	F	**4g**	3 days	48
1h	MeO	F	**4h**	3 days	45
3a	H	Cl	**5a**	3	70
3b	Br	Cl	**5b**	3	78
3c	MeO	Cl	**5c**	3	53
3d	NO_2	Cl	**5d**	3	58

[a] In this case, partial dehydrochlorination took place.

All signals in the ^{1}H and ^{13}C NMR spectra of compound **3d** were assigned on the basis of 2D ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, and HMBC experiments. It should be noted that the latter exhibits a cross-peak through four bonds between H-12b and the carbon atom of the CCl_3 group. The structures of **3** were firmly established by comparison of their spectra with the spectra of **3d**. The cis,cis-stereochemistry between the H-12b, H-12c, and the morpholine residue at C-4a in the cyclic nitronates **3** was established unambiguously by the 2D NOESY spectrum of **3b**, which exhibits cross-peaks between the protons H-12c, NCH_2, and H-12b as well as between H-12b and NCH_2, indicating that they are spatially close to each other and, hence, **3b** has the structure with the indicated stereochemistry of the nodal atoms (Scheme 1). In the ^{1}H NMR spectrum of **3b**, the signal of H-12b appeared as a slightly broadened doublet at δ 4.53 ppm (for **3a**–**f**: δ 4.3–4.6 ppm) with medium coupling constants (^{3}J=6.0 Hz) due to coupling with the proton H-12c at δ 2.55 ppm (for **3a**–**f**: δ 2.5–2.7 ppm). The H-7 methine proton, which did not give any cross-peaks in the 2D NOESY spectrum, appeared as a doublet at δ 6.09 ppm (for **3a**–**f**: δ 5.9–6.2 ppm) with ^{4}J=0.8 Hz due to coupling with H-12b (in the ^{1}H–^{1}H COSY spectrum of **3b**, a weak cross-peak between H-7 and H-12b was observed). In addition, the CF_3 group in the ^{19}F NMR spectra of **3e**,**f** manifests itself as a doublet at δ 86.7 ppm with $^{3}J_{F,H}$=7.0–7.1 Hz in $CDCl_3$.

The first step of the reaction of chromenes **1** with enamine **2a** involves the diastereoselective formation of a new C–C bond in the resulting dipolar intermediate **A** (Michael addition), in which the ambident nitronate anion reacts with the iminium carbon atom to give 1,2-oxazine *N*-oxides **3** as a result of a formal [4+2] cycloaddition reaction.

Replacement of the bulky trichloromethyl group with a trifluoromethyl had no effect on the diastereoselectivity, but stability of the products shows a decreasing trend. Indeed, cyclic nitronates **3e**,**f** bearing a trifluoromethyl group are sufficiently stable in the crystalline state and can be stored in a freezer at −10 °C, without deterioration, for a long time. However, they proved to be unstable in $CDCl_3$ and C_6D_6 solutions, in which ring-opening followed by retro-Michael reaction and hydrolysis of the enamine took place. Chromenes **1e**,**f**, morpholine, and cyclohexanone were observed immediately after dissolution of **3e**,**f** (28% and 6% of **1e** in $CDCl_3$ and C_6D_6, respectively; 25% of **1f** in $CDCl_3$).

The nature of the CX_3 group is important for the reaction with *N*-cyclohexenylmorpholine (**2a**). Thus, formation of the corresponding solid cycloadducts **3g**,**h** from CF_3-chromenes **1g**,**h** under the same reaction conditions was not observed. In this case, after 3 days, colorless crystals of 2,3,4-trisubstituted chromanes **4g**,**h** with a tetrasubstituted enamine fragment and with trans,trans-configuration at the C(2)–C(3) and C(3)–C(4) bonds were obtained in moderate yields. All three bulky substituents in this benzopyran system occupy equatorial positions, as indicated by X-ray crystallographic analysis after the isolation of chromanes **4g**,**h** as single crystals from the reaction mixture (Figs. 1 and 2). It should be noted that the ^{1}H NMR spectra of **4g**,**h** recorded in $CDCl_3$ and C_6D_6 at room temperature displayed broadened signals in the aliphatic region due to the restricted rotation of the chromanyl moiety about the C(4)–C(2′) bond.

It is obvious from the different relative configurations at C-12b (**3a**–**f**) and C-4 (**4g**,**h**) that non-isolable intermediates **3g**,**h** are initially formed as the kinetically controlled products, and then retro-Michael reaction of **3g**,**h** via a cleavage of the C(12b)–C(12c) bond takes place followed by slow formation of the thermodynamically controlled addition products **4g**,**h**. Obviously, the change in the reaction course is a result of the replacement of the electron-withdrawing groups (**1e**,**f**, R=Br, NO_2) by the electron-donating groups (**1g**,**h**, R=H, MeO) in the benzene ring of the CF_3-chromenes **1**.

Acid hydrolysis of cyclic nitronates **3a**–**d** containing a CCl_3 group, which were more stable than CF_3-nitronates **3e**,**f**, under reflux in aqueous ethanol in the presence of concentrated HCl for 3 h, successfully removed the amino function to give (2*R**)-[(2*S**,3*S**,4*S**)-3-nitro-2-(trichloromethyl)chroman-4-yl]cyclohexanones **5a**–**d** in 53–78% yields. The stereochemistry of these compounds was assigned as trans-C(2)–C(3) and cis-C(3)–C(4), since the vicinal coupling constants ($J_{2,3}$=7.5–7.9 Hz and $J_{3,4}$=5.5–5.9 Hz) were similar to the reported ones ($J_{2,3}$=6.1–7.6 Hz and $J_{3,4}$=4.8–5.8 Hz) of the adducts prepared from chromenes **1** and various mononucleophiles.[11]

The (*R**)-configuration at C-2′ was ascribed by analogy with formation of (2*R*)-[(2*R*,3*R*,4*S*)-3-nitro-2-arylchroman-4-yl]cyclohexanones from racemic 2-aryl-3-nitro-2*H*-chromenes and cyclohexanone with the pyrrolidinyl-camphor derivative as a bifunctional organocatalyst.[15] Finally, the indicated stereochemistry of chromane derivatives **5** was unambiguously confirmed by X-ray single crystal analysis of **5c** as a representative example (Fig. 3). Our attempt to prepare CF_3-containing cyclohexanone derivative **5f** by acid hydrolysis of **3f** led to a 54:46 mixture of **5f** and **1f**, respectively, which were not separated. Note that in this case, the vicinal coupling constants $J_{2,3}$=2.3 Hz and $J_{3,4}$=1.7 Hz for **5f** agree well with the configurations cis-C(2)–C(3) and trans-C(3)–C(4).[11a]

Next, in order to assess the influence of the phenyl substituent on the efficiency and stereoselectivity of this reaction, we turned our attention to annulation with 3-nitro-2-phenyl-2*H*-chromene. However, this compound did not give a positive result under our reaction conditions and an unidentifiable mixture of products was obtained. The observed difference in reactivity between 2-CX_3-chromenes **1** and 3-nitro-2-phenyl-2*H*-chromene is undoubtedly due to the fact that the presence of the trihalomethyl group in place of phenyl makes them more reactive.

To demonstrate the ability of other enamines to undergo a formal [4+2] cycloaddition reaction, 1-*tert*-butyl-1-morpholinoethene (**2b**), prepared from morpholine and pinacolone, was allowed to react with CCl_3-chromenes **1b**–**d** under the same reaction conditions

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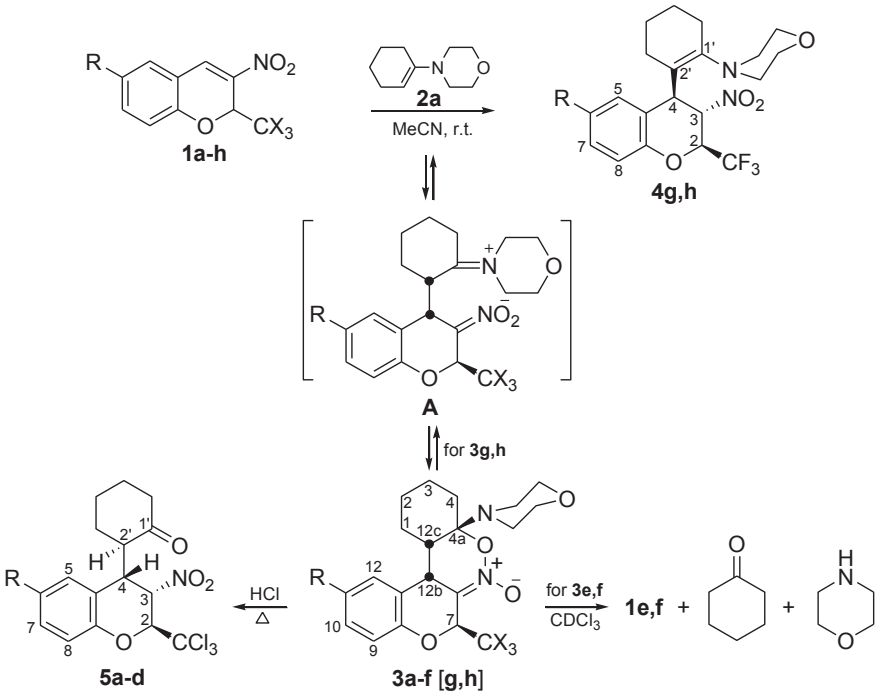


Scheme 1. Synthesis of compounds **3**–**5**.

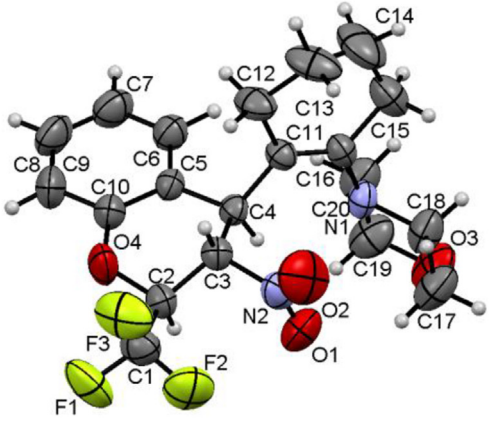


Fig. 1. Molecular structure of **4g** (thermal ellipsoids at 50% probability level).

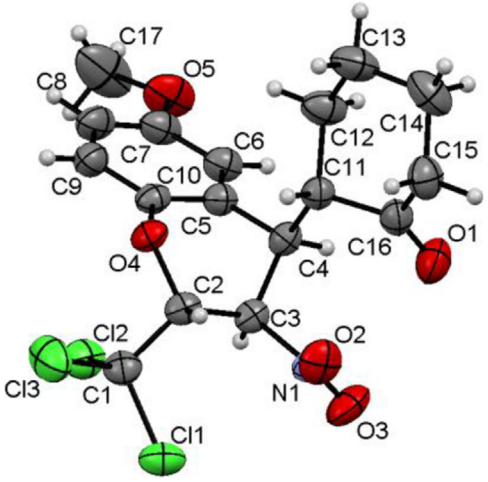


Fig. 3. Molecular structure of **5c** (thermal ellipsoids at 50% probability level).

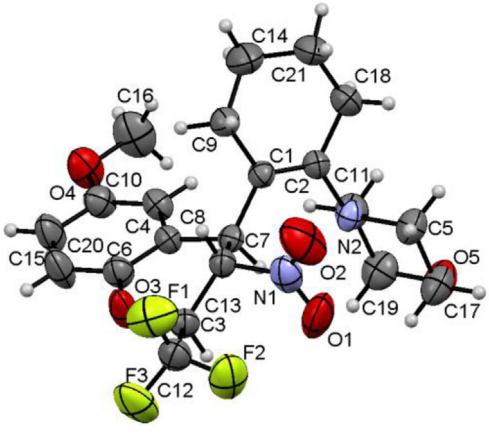
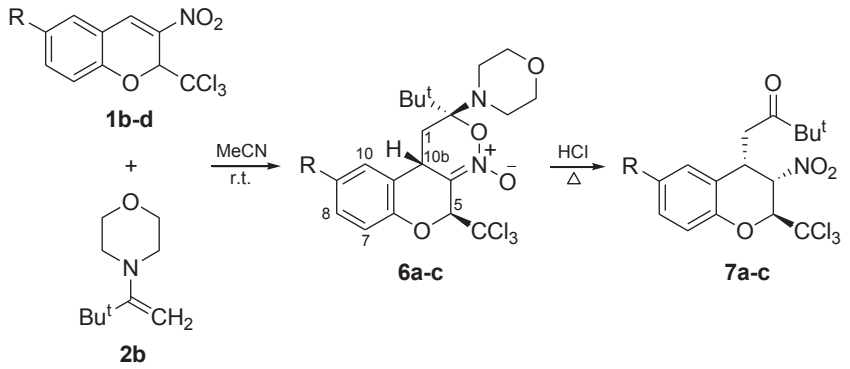


Fig. 2. Molecular structure of **4h** (thermal ellipsoids at 50% probability level).

(MeCN, ~20 °C, 5–20 min). We found that enamine **2b** also smoothly reacted with these chromenes to produce the expected products **6a**–**c** in moderate to good yields (43–67%). The reaction proceeded under kinetic reaction control with very good stereoselectivity (only one diastereomer could be observed by ^{1}H NMR spectroscopy of the crude products).

The stereochemistry of **6b** was firmly established by 2D NOESY (H-10b↔NCH$_2$ and H-10b↔OCH$_2$); assignment of all the signals was achieved by 2D ^{1}H–^{13}C HSQC and HMBC experiments for **6b** in CDCl$_3$. In the ^{1}H NMR spectrum of **6a**, the signal of H-10b appeared as a doublet of doublets at δ 4.19 ppm with ^3J=11.8 and 6.7 Hz due to coupling with the CH$_2$ group at δ 2.47 ppm. The H-5 methine proton, which did not give any cross-peaks in the 2D NOESY spectrum, appeared as a doublet at δ 6.12 ppm with ^4J=0.6 Hz due to coupling with H-10b (Scheme 2)

Hydrolysis of nitronates **6a**–**c** under reflux in aqueous ethanol in the presence of concentrated HCl gave the expected (2*S**,3*S**,4*S**)-



Chromene **1**	R	Product **6**	Yield (%)	Product **7**	Yield (%)
1b	Br	**6a**	64	**7a**	63
1c	MeO	**6b**	43	**7b**	77
1d	NO_2	**6c**	67	**7c**	52

Scheme 2. Synthesis of compounds **6** and **7**.

4-methylpivaloyl-3-nitro-2-(trichloromethyl)chromanes **7a**–**c** in 52–77% yields. As in the case of chromanes **5**, the stereochemistry of these compounds was assigned as trans-C(2)–C(3) and cis-C(3)–C(4), since the vicinal coupling constants were $J_{2,3}$=4.3–5.9 Hz and $J_{3,4}\approx$5.5 Hz. The coupling constants $J_{2,3}$ are found to be somewhat different for **7b** (5.9 Hz) and **7c** (4.3 Hz). This may be due to difference in dihedral angle of the H–C2–C3–H unit.

3. Conclusion

In conclusion, we have shown, for the first time, that the cycloaddition reaction between 3-nitro-2-trihalomethyl-2*H*-chromenes and enamines provides a regio- and stereoselective approach to the synthesis of CF_3- and CCl_3-containing cyclic nitronates, which can be considered as 1,3-dipoles for the preparation of new fused chromane derivatives of biological interest. Thus, a novel reactivity of 3-nitro-2*H*-chromenes was revealed.

4. Experimental

4.1. General

^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on Bruker DRX-400 (400, 376, 100 MHz) and Bruker Avance^{III}-500 (500, 471, 126 MHz) spectrometers in $CDCl_3$ or C_6D_6 with TMS and C_6F_6 as internal standards, respectively. IR spectra were recorded on a Perkin–Elmer Spectrum BX-II instrument as KBr discs. Elemental analyses were performed at the Microanalysis Services of the Postovsky Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points are uncorrected. All solvents used were dried and distilled as per standard procedures. The starting chromenes **1a**–**h** were prepared according to described procedure.[9]

4.2. General procedure for the synthesis of compounds 3a–f

A mixture of the corresponding chromene **1** (1.0 mmol) and *N*-cyclohexenylmorpholine (**2a**) (0.17 g, 1.0 mmol) was stirred at room temperature in dry acetonitrile (0.6 mL) for 1 h (**3a**–**d**) and 0.5 h (**3e**,**f**). The solid that formed was filtered and recrystallized from CH_2Cl_2/hexane (2:3) as a white powder.

4.2.1. (7S,12bS*,12cS*,4aS*)-4a-Morpholino-7-(trichloromethyl)-2,3,4,4a,12b,12c-hexahydro-1H,7H-chromeno[3,4-c][1,2]benzoxazin-6-oxide (**3a**).* Yield 0.37 g (80%), mp 155–156 °C (decomp.). IR (KBr): 1605, 1585, 1493, 1455 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10–1.76 (m, 7H, 3CH_2, C*H*H), 2.09 (d, *J*=13.9 Hz, 1H, CH*H*), 2.59 (ddd, *J*=11.8, 5.7, 4.3 Hz, 1H, H-12c), 2.71 (dt, *J*=11.5, 4.4 Hz, 2H, N(C*H*H)$_2$), 2.89 (br s, 2H, N(CH*H*)$_2$), 3.71 (s, 4H, O(CH_2)$_2$), 4.55 (d, *J*=5.9 Hz, 1H, H-12b), 6.10 (s, 1H, H-7), 6.98–7.07 (m, 3H, Ar), 7.21 (t, *J*=7.6 Hz, 1H, Ar). Anal. Calcd for $C_{20}H_{23}Cl_3N_2O_4$: C, 52.02; H, 5.02; N, 6.07. Found: C, 51.99; H, 5.00; N, 6.05.

4.2.2. (7S,12bS*,12cS*,4aS*)-11-Bromo-4a-morpholino-7-(trichloromethyl)-2,3,4,4a,12b,12c-hexahydro-1H,7H-chromeno[3,4-c][1,2]benzoxazin-6-oxide (**3b**).* Yield 0.37 g (69%), mp 147–148 °C (decomp.). IR (KBr): 1602, 1575, 1481 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12–1.31 (m, 2H, CH_2), 1.48–1.79 (m, 5H, 2CH_2, C*H*H), 2.09 (d, *J*=13.9 Hz, 1H, CH*H*), 2.55 (ddd, *J*=12.0, 6.0, 4.3 Hz, 1H, H-12c), 2.70 (dt, *J*=10.8, 4.7 Hz, 2H, N(C*H*H)$_2$), 2.88 (m, 2H, N(CH*H*)$_2$), 3.70 (s, 4H, O(CH_2)$_2$), 4.53 (br d, *J*=6.0 Hz, 1H, H-12b), 6.09 (d, *J*=0.8 Hz, 1H, H-7), 6.92 (d, *J*=8.8 Hz, 1H, H-9), 7.15 (dd, *J*=2.3, 1.0 Hz, 1H, H-12), 7.31 (ddd, *J*=8.8, 2.3, 1.0 Hz, 1H, H-10). Anal. Calcd for $C_{20}H_{22}BrCl_3N_2O_4$: C, 44.43; H, 4.10; N, 5.18. Found: C, 44.48; H, 3.98; N, 5.29.

4.2.3. (7S,12bS*,12cS*,4aS*)-11-Methoxy-4a-morpholino-7-(trichloromethyl)-2,3,4,4a,12b,12c-hexahydro-1H,7H-chromeno[3,4-c][1,2]benzoxazin-6-oxide (**3c**).* Yield 0.40 g (82%), mp 145–146 °C (hexane, decomp.). IR (KBr): 1606, 1497, 1429 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.28 (m, 2H, CH_2), 1.45–1.75 (m, 5H, 2CH_2, C*H*H), 2.08 (d, *J*=14.2 Hz, 1H, CH*H*), 2.53 (ddd, *J*=11.4, 5.8, 4.3 Hz, 1H, H-12c), 2.70 (dt, *J*=11.4, 4.3 Hz, 2H, N(C*H*H)$_2$), 2.82–2.96 (m, 2H, N(CH*H*)$_2$), 3.70 (s, 4H, O(CH_2)$_2$), 3.78 (s, 3H, MeO), 4.51 (d, *J*=5.7 Hz, 1H, H-12b), 6.06 (s, 1H, H-7), 6.54 (d, *J*=2.7 Hz, 1H, H-12), 6.78 (dd, *J*=9.0, 2.7 Hz, 1H, H-10), 6.96 (d, *J*=9.0 Hz, 1H, H-9). Anal. Calcd for $C_{21}H_{25}Cl_3N_2O_5$: C, 51.29; H, 5.12; N, 5.70. Found: 50.90; H, 5.15; N, 5.61.

4.2.4. (7S,12bS*,12cS*,4aS*)-4a-Morpholino-11-nitro-7-(trichloromethyl)-2,3,4,4a,12b,12c-hexahydro-1H,7H-chromeno[3,4-c][1,2]benzoxazin-6-oxide (**3d**).* Yield 0.16 g (32%), mp 151–152 °C (decomp.). IR (KBr): 1604, 1583, 1521, 1484, 1365, 1342 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12–1.22 (m, 2H, H-1′, H-2′), 1.48–1.80 (m, 5H, H-1″, H-2″, H-3′, H-3″, H-4′), 2.12 (br d, *J*=13.4 Hz, 1H, H-4″), 2.68–2.77 (m, 3H, H-12c, N(C*H*H)$_2$), 2.89 (m, 2H, N(CH*H*)$_2$), 3.72 (m, 4H, O(CH_2)$_2$), 4.63 (br d, *J*=6.1 Hz, 1H, H-12b), 6.20 (s, 1H, H-7), 7.16 (d, *J*=9.1 Hz, 1H, H-9), 8.01 (d, *J*=2.1 Hz, 1H, H-12), 8.12 (dd, *J*=9.1,

2.1 Hz, 1H, H-10); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.2 (C-3), 23.7 (C-1), 24.1 (C-2), 26.0 (C-4), 33.1 (C-12b), 33.8 (C-12c), 45.4 ($N(CH_2)_2$), 67.3 ($O(CH_2)_2$), 80.2 (C-7), 96.8 (C-4a), 98.4 (CCl_3), 111.6 (C-6a), 118.4 (C-9), 119.8 (C-12a), 123.1 (C-12), 124.5 (C-10), 142.6 (C-11), 157.5 (C-8a). Anal. Calcd for $C_{20}H_{22}Cl_3N_3O_6$: C, 47.40; H, 4.38; N, 8.29. Found: C, 47.23; H, 4.23; N, 8.21.

4.2.5. (7S,12bS*,12cS*,4aS*)-11-Bromo-4a-morpholino-7-(trifluoromethyl)-2,3,4,4a,12b,12c-hexahydro-1H,7H-chromeno[3,4-c][1,2]benzoxazin-6-oxide (**3e**).* Yield 0.29 g (59%), mp 138–139 °C (decomp.). IR (KBr): 1615, 1577, 1484 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.30 (m, 2H, CH_2), 1.48–1.90 (m, 5H, $2CH_2$, C*H*H), 2.09 (d, *J*=14.0 Hz, 1H, CH*H*), 2.53 (ddd, *J*=12.1, 5.7, 4.6 Hz, 1H, H-12c), 2.68 (dt, *J*=11.3, 4.4 Hz, 2H, $N(CHH)_2$), 2.82–2.93 (m, 2H, $N(CHH)_2$), 3.68 (br s, 2H, $O(CH_2)_2$), 4.31 (d, *J*=5.7 Hz, 1H, H-12b), 5.92 (q, *J*=7.1 Hz, 1H, H-7), 6.89 (d, *J*=8.8 Hz, 1H, H-9), 7.17 (d, *J*=2.3, 1H, H-12), 7.31 (ddd, 1H, H-10, *J*=8.8, 2.3, 0.8 Hz); ^{1}H NMR (400 MHz, C_6D_6) δ 0.54–0.80 (m, 2H, CH_2), 1.04–1.58 (m, 6H, $3CH_2$), 1.73 (ddd, *J*=11.7, 5.8, 4.2 Hz, 1H, H-12c), 1.95–2.03 (m, 2H, $N(CHH)_2$), 2.40–2.52 (m, 2H, $N(CHH)_2$), 3.33–3.41 (m, 2H, $O(CHH)_2$), 3.42–3.49 (m, 2H, $O(CHH)_2$), 4.07 (d, *J*=5.8 Hz, 1H, H-12b), 6.07 (q, *J*=7.2 Hz, 1H, H-7), 6.55 (d, *J*=8.8 Hz, 1H, H-9), 6.93 (ddd, *J*=8.8, 2.3, 0.8 Hz, 1H, H-10), 6.99 (dd, *J*=2.3, 1.0 Hz, 1H, H-12); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.7 (d, *J*=7.1 Hz, CF_3); ^{19}F NMR (376 MHz, C_6D_6) δ 87.8 (d, *J*=7.2 Hz, CF_3). Anal. Calcd for $C_{20}H_{22}BrF_3N_2O_4$: C, 48.89; H, 4.51; N, 5.70. Found: C, 48.96; H, 4.56; N, 5.78.

4.2.6. (7S,12bS*,12cS*,4aS*)-4a-Morpholino-11-nitro-7-(trifluoromethyl)-2,3,4,4a,12b,12c-hexahydro-1H,7H-chromeno[3,4-c][1,2]benzoxazin-6-oxide (**3f**).* Yield 0.25 g (54%), mp 139–140 °C (decomp.). IR (KBr): 1617, 1586, 1529, 1487, 1344 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.34 (m, 2H, CH_2), 1.50–1.80 (m, 5H, $2CH_2$, C*H*H), 2.12 (d, *J*=13.4 Hz, 1H, CH*H*), 2.67 (ddd, *J*=12.1, 5.8, 4.1 Hz, 1H, H-12c), 2.72 (dt, *J*=11.5, 4.3 Hz, 2H, $N(CHH)_2$), 2.86–2.97 (m, 2H, $N(CHH)_2$), 3.70 (br s, 4H, $O(CH_2)_2$), 4.39 (d, *J*=5.9 Hz, 1H, H-12b), 6.03 (q, *J*=7.0 Hz, 1H, H-7), 7.14 (d, *J*=9.1 Hz, 1H, H-9), 8.01 (dd, *J*=2.5, 1.1 Hz, 1H, H-12), 8.22 (ddd, *J*=9.1, 2.5, 0.8 Hz, 1H, H-10); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.7 (d, *J*=7.0 Hz, CF_3). Anal. Calcd for $C_{20}H_{22}F_3N_3O_6$: C, 52.52; H, 4.85; N, 9.19. Found: C, 52.43; H, 4.78; N, 9.13.

4.3. Compounds 4g,h

4.3.1. (2S,3S*,4R*)-4-[2-(3-Nitro-2-(trifluoromethyl)-3,4-dihydro-2H-chromen-4-yl)-1-cyclohexen-1-yl]morpholine (**4g**).* A mixture of chromene **1g** (0.25 g, 1.0 mmol) and enamine **2a** (0.17 g, 1.0 mmol) was stirred at room temperature in dry acetonitrile (0.2 mL) for 3 days. After addition of methanol (0.2 mL), the solid that formed was filtered and recrystallized from CH_2Cl_2/hexane (1:2) as colorless crystals. Yield 0.20 g (48%), mp 151–152 °C. IR (KBr): 1585, 1561, 1486, 1458, 1372 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–2.7 (m, 12H, $4CH_2$, $N(CH_2)_2$), 3.72 (br s, 4H, $O(CH_2)_2$), 4.91 (br s, 1H, H-4), 4.97 (br s, 1H, H-3), 5.81 (br s, 1H, H-2), 6.87–7.25 (m, 4H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$) δ 84.7 (d, *J*=4.8 Hz, CF_3). Anal. Calcd for $C_{20}H_{23}F_3N_2O_4$: C, 58.25; H, 5.62; N, 6.79. Found: C, 58.11; H, 5.65; N, 6.72.

4.3.2. (2S,3S*,4R*)-4-[2-(6-Methoxy-3-nitro-2-(trifluoromethyl)-3,4-dihydro-2H-chromen-4-yl)-1-cyclohexen-1-yl]morpholine (**4h**).* This compound was prepared from **1h** and **2a** according to the procedure described for compound **4g**. Yield 0.20 g (45%), colorless crystals, mp 165–166 °C. IR (KBr): 1661, 1614, 1560, 1498, 1464, 1372 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45–2.20 (m, 8H, $4CH_2$), 2.47–2.64 (m, 4H, $N(CH_2)_2$), 3.70 (br s, 4H, $O(CH_2)_2$), 3.74 (s, 3H, MeO), 4.90 (br s, 2H, H-3, H-4), 5.73 (br s, 1H, H-2), 6.43 (br s, 1H, H-5), 6.75 (dd, *J*=8.9, 2.6 Hz, 1H, H-7), 6.93 (d, *J*=8.9 Hz, 1H, H-8); ^{19}F NMR (376 MHz, $CDCl_3$) δ 84.8 (d, *J*=4.6 Hz, CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.3, 22.5, 22.9, 29.7, 41.7, 51.0, 55.7, 67.1, 73.5 (q, *J*=32.7 Hz, C-2), 80.3, 112.7, 113.5, 117.6, 122.1, 122.6 (q, *J*=281.3 Hz, CF_3), 124.7, 145.9, 150.1, 155.3; ^{1}H NMR (500 MHz, C_6D_6) δ 0.9–1.8 (m, 8H, $4CH_2$), 2.33 (br s, 4H, $N(CH_2)_2$), 3.25 (s, 3H, MeO), 3.57–3.72 (m, 4H, $O(CH_2)_2$), 4.35 (br s, 1H, H-4), 4.91 (br s, 1H, H-3), 5.73 (br s, 1H, H-2), 6.41 (dd, *J*=8.9, 3.0 Hz, 1H, H-7), 6.51 (dd, *J*=3.0, 1.0 Hz, 1H, H-5), 6.76 (d, *J*=8.9 Hz, 1H, H-8); ^{19}F NMR (471 MHz, C_6D_6) δ 86.1 (d, *J*=5.3 Hz, CF_3). Anal. Calcd for $C_{21}H_{25}F_3N_2O_5$: C, 57.01; H, 5.70; N, 6.33. Found: C, 56.97; H, 5.38; N, 5.96.

4.4. General procedure for the synthesis of compounds 5a–d,f and 7a–c

The corresponding nitronate **3** or **6** (1.0 mmol) was refluxed in a mixture of EtOH (4 mL), H_2O (1 mL), and concentrated HCl (0.2 mL) with stirring for 3 h. The reaction mixture was cooled to room temperature and the solid that formed was filtered, washed with H_2O (2×1 mL), dried, and recrystallized from CH_2Cl_2/hexane (1:5) as a white powder or yellow crystals.

4.4.1. (2R)-[(2S*,3S*,4S*)-3-Nitro-2-(trichloromethyl)-3,4-dihydro-2H-chromen-4-yl]cyclohexanone (**5a**).* Yield 0.27 g (70%), mp 148–149 °C, white powder. IR (KBr): 1703, 1556, 1488, 1364 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (qd, *J*=12.8, 3.5 Hz, 1H, C*H*H), 1.50–1.82 (m, 4H, $2CH_2$), 2.04–2.12 (m, 1H, CH*H*), 2.36–2.49 (m, 2H, CH_2), 2.98 (ddd, *J*=12.8, 6.9, 5.4 Hz, 1H, H-2′), 4.51 (dd, *J*=6.9, 5.5 Hz, 1H, H-4), 5.25 (dd, *J*=7.9, 5.5 Hz, 1H, H-3), 5.63 (d, *J*=7.9 Hz, 1H, H-2), 7.04 (m, 1H, H-6), 7.06 (d, *J*=7.8 Hz, 1H, H-8), 7.19 (dd, *J*=8.2, 1.6 Hz, 1H, H-5), 7.26 (td, *J*=7.8, 1.6 Hz, 1H, H-7). Anal. Calcd for $C_{16}H_{16}Cl_3NO_4$: C, 48.94; H, 4.11; N, 3.57. Found: C, 48.83; H, 4.14; N, 3.58.

4.4.2. (2R)-[(2S*,3S*,4S*)-2-[6-Bromo-3-nitro-2-(trichloromethyl)-3,4-dihydro-2H-chromen-4-yl]cyclohexanone (**5b**).* Yield 0.32 g (78%), mp 183–184 °C, white powder. IR (KBr): 1709, 1567, 1478, 1367 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (qd, *J*=12.8, 3.3 Hz, 1H, C*H*H), 1.48–1.87 (m, 4H, $2CH_2$), 2.04–2.14 (m, 1H, CH*H*), 2.34–2.52 (m, 2H, CH_2), 2.92 (ddd, *J*=12.8, 6.8, 5.4 Hz, 1H, H-2′), 4.49 (t, *J*=6.1 Hz, 1H, H-4), 5.22 (dd, *J*=7.8, 5.8 Hz, 1H, H-3), 5.63 (d, *J*=7.8 Hz, 1H, H-2), 6.95 (d, *J*=8.5 Hz, 1H, H-8), 7.36 (d, *J*=2.0 Hz, 1H, H-7), 7.39 (dd, *J*=8.5, 2.0 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.4, 28.0, 32.5, 38.2, 42.4, 49.2, 84.2, 84.3, 99.2, 113.1, 119.9, 124.8, 132.1, 132.8, 152.6, 209.1 (C=O). Anal. Calcd for $C_{16}H_{15}BrCl_3NO_4$: C, 40.75; H, 3.21; N, 2.94. Found: C, 40.68; H, 3.18; N, 2.71.

4.4.3. (2R)-[(2S*,3S*,4S*)-2-[6-Methoxy-3-nitro-2-(trichloromethyl)-3,4-dihydro-2H-chromen-4-yl]cyclohexanone (**5c**).* Yield 0.22 g (53%), mp 137–138 °C, yellow prisms. IR (KBr): 1708, 1638, 1561, 1521, 1496, 1462, 1364 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (qd, *J*=13.3, 3.4 Hz, 1H, C*H*H), 1.52–1.82 (m, 4H, $2CH_2$), 2.05–2.13 (m, 1H, CH*H*), 2.36–2.49 (m, 2H, CH_2), 2.98 (ddd, *J*=12.7, 6.8, 5.5 Hz, 1H, H-2′), 3.77 (s, 3H, MeO), 4.45 (dd, *J*=6.8, 5.5 Hz, 1H, H-4), 5.23 (dd, *J*=7.7, 5.5 Hz, 1H, H-3), 5.58 (d, *J*=7.7 Hz, 1H, H-2), 6.72 (d, *J*=2.9 Hz, 1H, H-5), 6.80 (dd, *J*=8.8, 2.9 Hz, 1H, H-7), 6.95 (d, *J*=8.8 Hz, 1H, H-8). Anal. Calcd for $C_{17}H_{18}Cl_3NO_5$: C, 48.31; H, 4.29; N, 3.31. Found: 48.14; H, 4.18; N, 3.14.

4.4.4. (2R)-[(2S*,3S*,4S*)-2-[3,6-Dinitro-2-(trichloromethyl)-3,4-dihydro-2H-chromen-4-yl]cyclohexanone (**5d**).* Yield 0.25 g (58%), mp 192–193 °C, white powder. IR (KBr): 1706, 1561, 1518, 1484, 1345 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (qd, *J*=13.8, 3.2 Hz, 1H, C*H*H), 1.50–1.87 (m, 4H, $2CH_2$), 2.06–2.14 (m, 1H, CH*H*), 2.36–2.53 (m, 2H, CH_2), 2.92 (dt, *J*=13.3, 6.4 Hz, 1H, H-2′), 4.64 (t, *J*=5.9 Hz, 1H, H-4), 5.30 (dd, *J*=7.8, 5.9 Hz, 1H, H-3), 5.74 (d, *J*=7.8 Hz, 1H, H-2), 7.20 (m, 1H, H-8), 8.18–8.23 (m, 2H, H-5, H-7). Anal. Calcd for

$C_{16}H_{15}Cl_3N_2O_6$: C, 43.91; H, 3.45; N, 6.40. Found: C, 43.88; H, 3.47; N, 6.35.

4.4.5. (2R)-[(2S*,3R*,4S*)-2-[3,6-Dinitro-2-(trifluoromethyl)-3,4-dihydro-2H-chromen-4-yl]cyclohexanone (**5f**).* This compound was isolated as a mixture of **5f** (54%) with chromene **1f** (46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (qd, J=13.8, 3.6 Hz, 1H, C*H*H), 1.69–2.11 (m, 4H, $2CH_2$), 2.16–2.26 (m, 1H, CH*H*), 2.34–2.57 (m, 2H, CH_2), 2.82 (dt, J=12.7, 6.4 Hz, 1H, H-2′), 3.74 (br d, J=7.0 Hz, 1H, H-4), 5.07 (qd, J=6.0, 2.3 Hz, 1H, H-2), 5.22 (dd, J=2.3, 1.7 Hz, 1H, H-3), 7.19 (d, J=9.1 Hz, 1H, H-8), 8.03 (d, J=2.7 Hz, 1H, H-5), 8.16 (dd, J=9.1, 2.7 Hz, 1H, H-7); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.9 (d, J=6.0 Hz, CF_3).

4.5. Compounds 6a–c

4.5.1. (2R,5S*,10bS*)-9-Bromo-2-tert-butyl-2-morpholino-5-(trichloromethyl)-1,10b-dihydro-2H,5H-chromeno[3,4-c][1,2]oxazine-4-oxide (**6a**).* A mixture of chromene **1b** (0.37 g, 1.0 mmol) and enamine **2b** (0.17 g, 1.0 mmol) was kept at room temperature in dry acetonitrile (1.0 mL) for 10 min. The solid that formed was filtered and washed with acetonitrile (3×0.2 mL). Yield 0.34 g (64%), mp 166–167 °C (decomp.), white powder. IR (KBr): 1612, 1577, 1480 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H, *t*-Bu), 2.06 (dd, J=14.2, 11.8 Hz, 1H, C*H*H), 2.88 (dd, J=14.2, 6.7 Hz, 1H, CH*H*), 3.01–3.07 (m, 2H, N(C*H*H)$_2$), 3.22–3.30 (m, 2H, N(CH*H*)$_2$), 3.56–3.65 (m, 2H, O(CH$_2$)$_2$), 4.19 (dd, J=11.8, 6.7 Hz, 1H, H-10b), 6.12 (d, J=0.6 Hz, 1H, H-5), 6.93 (d, J=8.8 Hz, 1H, H-7), 6.99 (ddd, J=8.8, 2.3, 0.7 Hz, 1H, H-8), 7.20 (dd, J=2.3, 1.0 Hz, 1H, H-10). Anal. Calcd for $C_{20}H_{24}BrCl_3N_2O_4$: C, 44.27; H, 4.46; N, 5.16. Found: C, 43.86; H, 4.27; N, 5.05.

4.5.2. (2R,5S*,10bS*)-2-tert-Butyl-9-methoxy-2-morpholino-5-(trichloromethyl)-1,10b-dihydro-2H,5H-chromeno[3,4-c][1,2]oxazine-4-oxide (**6b**).* This compound was prepared from chromene **1c** and enamine **2b** according to the procedure described for compound **6a** for 20 min. Yield 0.21 g (43%), mp 154–155 °C (decomp.), white powder. IR (ATR): 1604, 1497, 1430 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 9H, *t*-Bu), 2.07 (dd, J=14.3, 11.8 Hz, 1H, C*H*H), 2.87 (dd, 1H, J=14.3, 6.7 Hz, CH*H*), 3.00–3.08 (m, 2H, N(C*H*H)$_2$), 3.22–3.30 (m, 2H, N(CH*H*)$_2$), 3.57–3.68 (m, 4H, O(CH$_2$)$_2$), 3.80 (s, 3H, MeO), 4.18 (dd, J=11.8, 6.7 Hz, 1H, H-10b), 6.08 (s, 1H, H-5), 6.66 (dd, J=2.9, 0.8 Hz, 1H, H-10), 6.80 (dd, J=8.9, 2.9 Hz, 1H, H-8), 6.97 (d, J=8.9 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.2 (C*Me*$_3$), 27.3 (C-1), 29.4 (C-10b), 43.5 (C*Me*$_3$), 48.1 (NCH$_2$), 55.8 (OMe), 68.2 (OCH$_2$), 79.8 (C-5), 99.0 (C-2), 99.2 (CCl$_3$), 111.8 (C-10), 113.6 (C-8), 113.9 (C-4a), 117.7 (C-7), 121.6 (C-10a), 145.3 (C-6a), 154.6 (C-9). Anal. Calcd for $C_{21}H_{27}Cl_3N_2O_5$: C, 51.08; H, 5.51; N, 5.67. Found: C, 51.13; H, 5.43; N, 5.67.

4.5.3. (2R,5S*,10bS*)-2-tert-Butyl-2-morpholino-9-nitro-5-(trichloromethyl)-1,10b-dihydro-2H,5H-chromeno[3,4-c][1,2]oxazine-4-oxide (**6c**).* This compound was prepared from chromene **1d** and enamine **2b** according to the procedure described for compound **6a** for 5 min. Yield 0.34 g (67%), mp 175–176 °C (decomp.), white powder. IR (ATR): 1613, 1584, 1530, 1484, 1366, 1339 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H, *t*-Bu), 2.09 (dd, J=14.2, 12.0 Hz, 1H, C*H*H), 3.01 (dd, J=14.2, 6.7 Hz, 1H, CH*H*), 3.03–3.11 (m, 2H, N(C*H*H)$_2$), 3.24–3.33 (m, 2H, N(CH*H*)$_2$), 3.55–3.71 (m, 4H, O(CH$_2$)$_2$), 4.28 (d, J=12.0, 6.7 Hz, 1H, H-10b), 6.22 (s, 1H, H-5), 7.17 (d, J=9.0 Hz, 1H, H-7), 8.10–8.18 (m, 2H, H-8, H-10). Anal. Calcd for $C_{20}H_{24}Cl_3N_3O_6$: C, 47.22; H, 4.75; N, 8.26. Found: C, 46.95; H, 4.63; N, 8.44.

4.6. Compounds 7a–c

4.6.1. 1-[(2S,3S*,4S*)-6-Bromo-3-nitro-2-(trichloromethyl)chroman-4-yl]-3,3-dimethylbutan-2-one (**7a**).* Yield 0.30 g (63%), mp 128–129 °C, white powder. IR (KBr): 1703, 1561, 1479, 1408, 1361 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (s, 9H, *t*-Bu), 2.42 (dd, J=17.9, 7.9 Hz, 1H, C*H*H), 2.50 (dd, J=17.9, 6.4 Hz, 1H, CH*H*), 3.82–3.89 (m, 1H, H-4), 5.22 (d, J=5.0 Hz, 1H, H-2), 5.55 (t, J=5.2 Hz, 1H, H-3), 6.58 (d, J=8.5 Hz, 1H, H-8), 7.01 (dd, J=8.5, 2.2 Hz, 1H, H-7), 7.05 (d, J=2.2 Hz, 1H, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.3, 34.8, 34.9, 44.4, 85.2, 85.3, 98.2, 116.3, 119.7, 126.5, 129.8, 132.4, 152.3, 211.7. Anal. Calcd for $C_{16}H_{17}BrCl_3NO_4$: C, 40.58; H, 3.62; N, 2.96. Found: C, 40.44; H, 3.44; N, 3.00.

4.6.2. 1-[(2S,3S*,4S*)-6-Methoxy-3-nitro-2-(trichloromethyl)chroman-4-yl]-3,3-dimethylbutan-2-one (**7b**).* Yield 0.33 g (77%), mp 114–115 °C, white powder. IR (ATR): 1696, 1554, 1491, 1432, 1360 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H, *t*-Bu), 2.74 (dd, J=17.8, 6.8 Hz, 1H, C*H*H), 3.10 (dd, J=17.8, 7.3 Hz, 1H, CH*H*), 3.77 (s, 1H, MeO), 4.10–4.15 (m, 1H, H-4), 5.39 (d, J=5.9 Hz, 1H, H-2), 5.44 (t, J=5.6 Hz, 1H, H-3), 6.67 (d, J=2.9 Hz, 1H, H-5), 6.79 (dd, J=8.8, 2.9 Hz, 1H, H-7), 7.03 (d, J=8.8 Hz, 1H, H-8); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.1, 35.0, 35.7, 44.3, 55.7, 85.2, 85.9, 98.5, 112.6, 114.1, 118.7, 125.5, 146.9, 155.8, 212.0. Anal. Calcd for $C_{17}H_{20}Cl_3NO_5$: C, 48.08; H, 4.75; N, 3.30. Found: C, 48.09; H, 4.81; N, 3.33.

4.6.3. 1-[(2S,3S*,4S*)-3,6-Dinitro-2-(trichloromethyl)chroman-4-yl]-3,3-dimethylbutan-2-one (**7c**).* Yield 0.23 g (52%), mp 141–142 °C, white powder. IR (ATR): 1702, 1557, 1529, 1477, 1342 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (s, 9H, *t*-Bu), 2.91 (dd, J=18.2, 7.5 Hz, 1H, C*H*H), 3.19 (dd, J=18.2, 6.4 Hz, 1H, CH*H*), 4.19–4.25 (m, 1H, H-4), 5.41 (d, J=4.3 Hz, 1H, H-2), 5.68 (t, J=4.8 Hz, 1H, H-3), 7.26 (d, J=8.9 Hz, 1H, H-8), 8.07 (d, J=2.6 Hz, 1H, H-5), 8.23 (dd, J=8.9, 2.6 Hz, 1H, H-7); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.4, 33.8, 34.8, 44.4, 84.3, 85.3, 97.4, 118.6, 122.6, 124.7, 125.3, 143.6, 157.8, 211.8. Anal. Calcd for $C_{16}H_{17}Cl_3N_2O_6$: C, 43.71; H, 3.90; N, 6.37. Found: C, 43.69; H, 4.06; N, 6.35.

4.7. Crystallographic data for compounds 4g,h and 5c

Intensity data for the compounds **4g**,**h** and **5c** were collected on a 'Xcalibur 3' automatic four-circle diffractometer at 295(2) K (Mo Kα radiation, graphite monochromator, ω-scan). The structures were solved by direct methods and refined by full-matrix least-squares method using the SHELX-97 program package.[16] All non-hydrogen atoms were refined with anisotropic atomic displacement and hydrogen atoms were included at calculated position using a riding model.

*4.7.1. Crystal data for **4g**.* $C_{20}H_{23}F_3N_2O_4$, M=412.41, triclinic crystals space group $P\bar{1}$, a=9.0654(13), b=10.3076(14), c=11.8956(10) Å, α=87.281(9), β=71.727(10), γ=71.711(12)°, V=1000.6(2) Å^3, D_c=1.369 g/cm^3, absorption coefficient μ=0.114 mm^{-1}, Z=2. The intensities of 6651 independent reflections (R_{int}=0.0198) were measured. The final discrepancy factors R_1=0.0467, wR_2=0.1154, GooF=1.000 for 1990 reflections with $I>2\sigma(I)$; R_1=0.1439, wR_2=0.1210 (all data). Largest different peak and hole: 0.210 and −0.196 eÅ^{-3}. Completeness to θ=26° (85.0%). Deposition number CCDC 933119.

*4.7.2. Crystal data for **4h**.* $C_{21}H_{25}F_3N_2O_5$, M=442.44, monoclinic crystals space group $P2_1/c$, a=9.1861(11), b=19.6737(18), c=12.6447(12) Å, α=γ=90.00, β=111.228(10)°, V=2130.1(4) Å^3, D_c=1.380 g/cm^3, absorption coefficient μ=0.115 mm^{-1}, Z=4. The intensities of 5025 independent reflections (R_{int}=0.0323) were measured. The final discrepancy factors R_1=0.0403, wR_2=0.0728, GooF=1.005 for 1754 reflections with $I>2\sigma(I)$; R_1=0.1304, wR_2=0.0776 (all data). Largest different peak and hole: 0.473 and −0.311 eÅ^{-3}. Completeness to θ=28° (95.0%). Deposition number CCDC 943430.

*4.7.3. Crystal data for **5c**.* $C_{17}H_{18}Cl_3NO_5$, M=422.70, monoclinic crystals space group $C2/c$, a=22.8867(9), b=5.5527(3),

c=29.3817(18) Å, $\alpha=\gamma$=90.00, β=97.871(6)°, V=3698.7(3) Å^3, D_c=1.518 g/cm^3, absorption coefficient μ=0.524 mm^{-1}, Z=8. The intensities of 3769 independent reflections (R_{int}=0.0364) were measured. The final discrepancy factors R_1=0.0408, wR_2=0.0936, GooF=1.004 for 2241 reflections with $I>2\sigma(I)$; R_1=0.0749, wR_2=0.0984 (all data). Largest different peak and hole: 0.326 and −0.294 eÅ^{-3}. Completeness to θ=26° (99.0%). Deposition number CCDC 943431.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.05.100.

References and notes

1. (a) Schweizer, E. E.; Meeder-Nycz, D. In *The Chemistry of Heterocyclic Compounds: Chromenes, Chromanones, and Chromones*; Ellis, G. P., Ed.; Wiley: New York, NY, 1977; Vol. 31, pp 11–140; (b) *The Chemistry of Heterocyclic Compounds: Chromans and Tocopherols*; Ellis, G. P., Lockhard, I. M., Eds.; Wiley: New York, NY, 1981; Vol. 36; (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
2. (a) Bowers, W. S.; Ohta, T.; Cleere, J. S.; Marsella, P. A. *Science* **1976**, *193*, 542; (b) Ishizuka, N.; Matsumura, K.; Sakai, K.; Fujimoto, M.; Mihara, S.; Yamamori, T. *J. Med. Chem.* **2002**, *45*, 2041; (c) Bergmann, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492; (d) Burrell, G.; Cassidy, F.; Evans, J. M.; Lightowler, D.; Stemp, G. *J. Med. Chem.* **1990**, *33*, 3023; (e) Gericke, R.; Harting, J.; Lues, I.; Schittenhelm, C. *J. Med. Chem.* **1991**, *34*, 3074; (f) Weston, A. H.; Edwards, G. *Biochem. Pharmacol.* **1992**, *43*, 47.
3. (a) Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Velde, D. V. *J. Org. Chem.* **1990**, *55*, 1248; (b) Murugesh, M. G.; Subburaj, K.; Trivedi, G. K. *Tetrahedron* **1996**, *52*, 2217; (c) Engler, T. A.; LaTessa, K. O.; Iyengar, R.; Chai, W.; Agrios, K. *Bioorg. Med. Chem.* **1996**, *4*, 1755.
4. Kodukulla, R. P. K.; Hariharan, S.; Trivedi, G. K. *Tetrahedron* **1994**, *50*, 4623.
5. (a) Nyerges, M.; Virányi, A.; Marth, G.; Dancsó, A.; Blaskó, G.; Tőke, L. *Synlett* **2004**, 2761; (b) Virányi, A.; Marth, G.; Dancsó, A.; Blaskó, G.; Tőke, L.; Nyerges, M. *Tetrahedron* **2006**, *62*, 8720.
6. Haran, S. H.; Mathur, H. H.; Trivedi, G. K. *Indian J. Chem.* **1988**, *27B*, 994.
7. Habib, P. M.; Raju, B. R.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. *Tetrahedron* **2009**, *65*, 5799.
8. (a) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, the Netherlands, 1993; (b) Hiyama, T. *Organofluorine Compounds: Chemistry and Application*; Springer: Berlin, 2000; (c) Menezes, F. G.; Gallardo, H.; Zucco, C. *Quim. Nova* **2010**, *33*, 2233.
9. Korotaev, V. Y.; Kutyashev, I. B.; Sosnovskikh, V. Y. *Heteroatom Chem.* **2005**, *16*, 492.
10. Korotaev, V. Y.; Barkov, A. Y.; Sosnovskikh, V. Y. *Russ. Chem. Rev.* **2013**, *82*, 1081.
11. (a) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Kodess, M. I. *Izv. Akad. Nauk, Ser. Khim.* **2006**, 309; *Russ. Chem. Bull. Int. Ed.* **2006**, *55*, 317; (b) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Kodess, M. I. *Izv. Akad. Nauk, Ser. Khim.* **2006**, 1945; *Russ. Chem. Bull. Int. Ed.* **2006**, *55*, 2020; (c) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B. *Izv. Akad. Nauk, Ser. Khim.* **2007**, 1985; *Russ. Chem. Bull. Int. Ed.* **2007**, *56*, 2054.
12. Korotaev, V. Y.; Sosnovskikh, V. Y.; Barabanov, M. A.; Yasnova, E. S.; Ezhikova, M. A.; Kodess, M. I.; Slepukhin, P. A. *Tetrahedron* **2010**, *66*, 1404.
13. Korotaev, V. Y.; Barkov, A. Y.; Moshkin, V. S.; Matochkina, E. G.; Kodess, M. I.; Sosnovskikh, V. Y. *Tetrahedron* **2013**, *69*, 8602.
14. (a) Brook, M. A.; Seebach, D. *Can. J. Chem.* **1987**, *65*, 836; (b) Seebach, D.; Lyapkalo, I. M.; Dahinden, R. *Helv. Chim. Acta* **1999**, *82*, 1829; (c) Ioffe, S. L. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd ed.; Feuer, H., Ed.; John Wiley & Sons: Chichester, UK, 2008; pp 435–748; (d) Smirnov, V. O.; Ioffe, S. L.; Tishkov, A. A.; Khomutova, Y. A.; Nesterov, I. D.; Antipin, M. Y.; Smit, W. A.; Tartakovsky, V. A. *J. Org. Chem.* **2004**, *69*, 8485; (e) Klenov, M. S.; Lesiv, A. V.; Khomutova, Y. A.; Nesterov, I. D.; Ioffe, S. L. *Synthesis* **2004**, 1159; (f) Korotaev, V. Y.; Barkov, A. Y.; Slepukhin, P. A.; Sosnovskikh, V. Y. *Izv. Akad. Nauk, Ser. Khim.* **2011**, 137; *Russ. Chem. Bull. Int. Ed.* **2011**, *60*, 143; (g) Korotaev, V. Y.; Barkov, A. Y.; Slepukhin, P. A.; Kodess, M. I.; Sosnovskikh, V. Y. *Mendeleev Commun.* **2011**, *21*, 112; (h) Korotaev, V. Y.; Barkov, A. Y.; Slepukhin, P. A.; Kodess, M. I.; Sosnovskikh, V. Y. *Tetrahedron Lett.* **2011**, *52*, 5764; (i) Korotaev, V. Y.; Barkov, A. Y.; Slepukhin, P. A.; Kodess, M. I.; Sosnovskikh, V. Y. *Tetrahedron Lett.* **2011**, *52*, 3029.
15. Magar, D. R.; Chen, K. *Tetrahedron* **2012**, *68*, 5810.
16. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.