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Regioselective Nucleophilic 1,4-Trifluoromethylation of 2-Polyfluoroalkylchromones with (Trifluoromethyl)trimethylsilane. Synthesis of Fluorinated Analogs of Natural 2,2-Dimethylchroman-4-ones and 2,2-Dimethylchromenes

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Reactions of 2-polyfluoroalkylchromones with (perfluoroalkyl)trimethylsilanes proceed as a 1,4-nucleophilic perfluoroalkylation to give 2,2-bis(polyfluoroalkyl)chroman-4-ones with high regioselectivity and good yields after acid hydrolysis. Oxidation of 6-methyl-2,2-bis(trifluoromethyl)-chroman-4-one with a mixture of $K_2S_2O_8$ and $CuSO_4$ in aqueous acetonitrile leads to fluorinated analogues of natural lactarochromal and the corresponding acid. Reduction of substituted 2,2-bis-(trifluoromethyl)chroman-4-one with sodium borohydride in methanol and subsequent dehydration of chromanols in refluxing xylene in the presence of *p*-toluene sulfonic acid gives 2,2-bis-(trifluoromethyl)chromenes, which are fluorinated analogues of natural precocenes.

Introduction

The polyfluoroalkyl groups, especially the CF_3 group, are highly important substituents in the field of organic chemistry. The introduction of these groups into organic molecules can bring about some remarkable changes in the physical properties, chemical reactivity, and biological activity of the derived fluorinated compounds.[1] In particular, due to the powerful electron-withdrawing ability of R^F groups the insertion of polyfluoroalkyl substituents into the 2-position of chromones activates these molecules and dramatic differences in the reactivity of 2-alkyl- and 2-polyfluoroalkylchromones with respect to nucleophilic reagents are observed.[2]

Regioselective perfluoroalkylation of organic compounds with various fluorinating agents is a well-established methodology for the synthesis of partially fluorinated materials applicable for agrochemistry and the pharmaceutical industry.[3] The unique properties of (trifluoromethyl)trimethylsilane (Ruppert's reagent) as a nucleophilic trifluoromethylating agent are well-known.[4] This reagent is presently the most popular tool in applications where perfluoroalkylation is involved. The reactions of aldehydes, ketones, diketones, α-keto amides, esters, and *N*-protected amino esters with CF_3SiMe_3 in the presence of a catalytic amount of tetrabutylammonium fluoride or cesium fluoride proceed as a nucleophilic 1,2-addition of the CF_3 group at the carbonyl carbon atom to give trifluoromethylated alcohols or trifluoromethyl ketones in excellent yields following acid hydrolysis.[5] However, little effort has been devoted to α,*β*-unsaturated systems especially with respect to nucleophilic 1,4-trifluoromethylation. To the best of our knowledge, there are no methods for preparative addition of a CF_3 group

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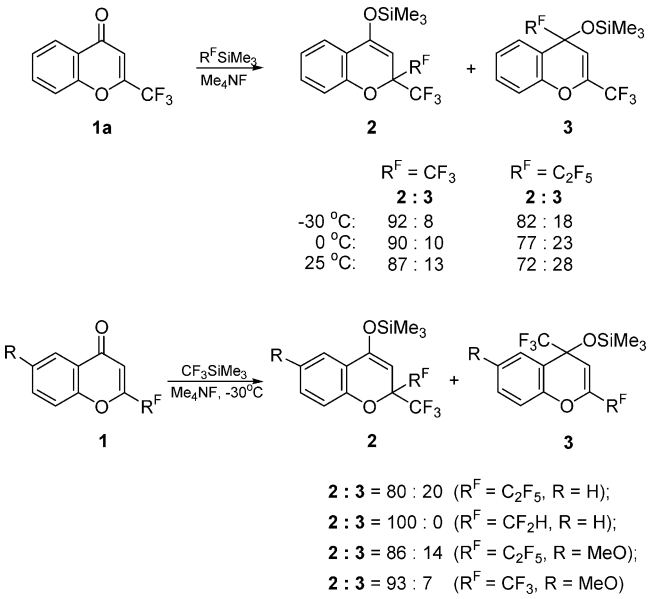
to the C=C bond of conjugated enones. In the case of 2-cyclohexen-1-one and CF_3SiMe_3/Bu_4NF, 1,2-addition predominates (>90%).[5a−c] Furthermore, nucleophilic trifluoromethylation of chalcone and (dibenzylidene)acetone with trifluoromethane and silicon-containing bases exclusively results in 1,2-addition.[6a] The adduct of trifluoromethane and *N*-formylmorpholine behaves the same way in the reaction with chalcone.[6b] The only example known to us, where a 1,4-addition takes place to a certain extent, is observed in the reaction of *trans*-1-benzoyl-2-(dimethylamino)ethylene with $CF_3H/N(SiMe_3)_3/DMF/Me_4NF$. However, in this reaction the 1,4-trifluoromethylation was followed by the elimination of dimethylamine[6a] and the initial product of 1,4-addition (36% from the ^{19}F NMR spectrum) could not be isolated. Thus, this reaction proceeding as an A_N-E process could not be strongly considered a successful nucleophilic 1,4-trifluoromethylation.

Results and Discussion

The biological activity of many of the naturally occurring compounds which incorporate a chroman ring system has resulted in several applications of substituted chroman-4-ones in synthesis.[7] Despite advances in the area, methods for preparing these valuable intermediates, especially 2-R^F-chroman-4-ones, remain limited.[8] In contrast, chromones are readily prepared by a variety of methods,[9] and could in principle provide chroman-4-ones via the conjugate addition sequence.[8] We undertook a study of 2-substituted chromones of differing electrophilicity and steric bulk to determine which of these substrates preferentially undergo 1,4-addition rather than 1,2-addition during fluoride-initiated trifluoromethylation using Ruppert's reagents (preliminary communication, see ref 10).

Here, we wish to report that (trifluoromethyl)- and (perfluoroethyl)trimethylsilanes can be employed to generate compounds with the *gem*-bis(perfluoroalkyl) group by 1,4-nucleophilic perfluoroalkylation of 2-R^F-chromones **1** (R^F = CF_2H, CF_3, C_2F_5). In our initial studies, we optimized the reaction conditions by using 2-trifluoromethylchromone **1a** and R^FSiMe_3 (R^F = CF_3, C_2F_5) and monitored the reaction progress by ^{19}F NMR. To subsequently design a preparative procedure and determine the scope of the reaction, products were not isolated but were observed by ^{19}F NMR spectroscopy. When chromone **1a** was treated with 1.4 equiv of R^FSiMe_3 in dry THF in the presence of a catalytic amount of anhydrous Me_4NF (3−4 mol %) as a nucleophilic initiator for several hours (4−24 h) at different temperatures (from 25 to −30 °C), ^{19}F NMR analysis of the reaction mixture showed almost

SCHEME 1



quantitative formation of the trimethylsilyl ethers **2** and **3** with high regioselectivity (Scheme 1). Anhydrous tetramethylammonium fluoride[11] proved to be the best source of fluoride ion. Surprisingly, no trifluoromethylation was observed in the case of CF_3SiMe_3/Bu_4NF. The use of ^tBuOK to initiate 1,4-trifluoromethylation was also not satisfactory: in the presence of this catalyst the ratio of the 1,2- and 1,4-adducts in the reaction between chromone **1** (R^F = CF_3, R = MeO) and CF_3SiMe_3 was 53:47, respectively.

As expected, regioselectivity of the nucleophilic attack by R^FSiMe_3 on the pyrone ring will depend on the steric effects of the C(2) fluorinated group. In fact, upon increasing the length of the perfluoroalkyl chain in Ruppert's reagent to C_2F_5 the regioselectivity drops, most likely due to steric repulsion between R^F moieties. When the temperature was decreased from 25 to −30 °C, regioselectivity increased by 5% and 10% for R^F = CF_3 and C_2F_5, respectively. Similarly, the reaction of 2-perfluoroethylchromone with CF_3SiMe_3 leads to a mixture of the 1,4- and 1,2-addition products in the molar **2**:**3** ratio 80:20 at −30 °C and 73:27 at 0 °C. Note that steric hindrance in the carbonyl compounds is also a limiting factor in the reactions of R^FSiMe_3.[5b] The reaction was markedly favored in regioselectivity when carried out with chromone bearing the CF_2H group at C(2). However, in the case of 2-(1,1,2,2-tetrafluoroethyl)- and 6-methoxy-2-(1,1,2,2-tetrafluoroethyl)chromones, the reaction mixture almost immediately becomes dark-red and resinifies under the same conditions. This can be explained by the abstraction of the terminal hydrogen atom of the $(CF_2)_2H$ group with Ruppert's reagent, which inhibits a nucleophilic addition of the CF_3 group.

The formation of trimethylsilyl ethers **2** clearly indicates that the 2-polyfluoroalkylchromones **1** easily undergo 1,4-trifluoromethylation due to the presence of the fluorinated group at the C(2) atom of the chromone

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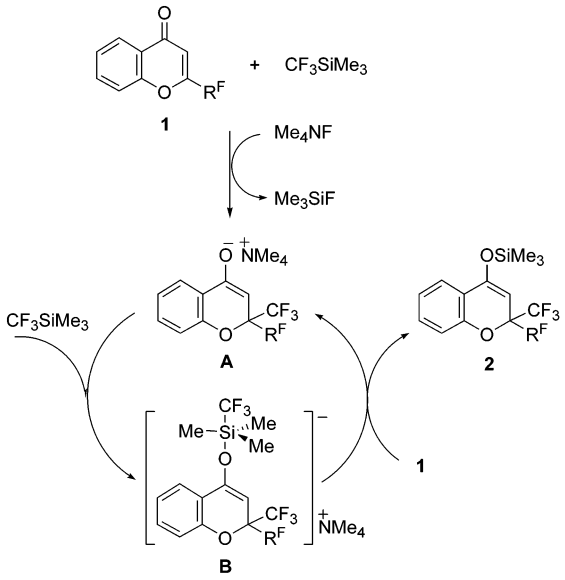
SCHEME 2



system. In regards to this, it is worth noting that in our hands neither the chromone nor the 2-methylchromone react with CF_3SiMe_3. In the latter case, the only product was the 1,2-adduct (12 h, ~20 °C, 13% from the ^{19}F NMR spectrum, singlet at −82.07). The reaction of indenone with CF_3SiMe_3 in the presence of KF gives the corresponding trifluoromethylated alcohol after acid hydrolysis.[4l] In attempting to ascertain if related systems can participate in this reaction, we found that 2-trichloromethylchromone[12] and *N*-benzyl-2-trifluoromethylchromen-4*H*-imine[8] fail to react under the above experimental conditions and only the starting materials were recovered with small amounts of decomposition products. In addition, 6-methyl-4-trifluoromethylcoumarin[13] gives a complex reaction mixture containing about 40% of the 1,2-adduct with other unidentifiable products. The fact that 1,4-adducts were not observed in these reactions suggests an important electronic effect of the R^F group at the C(2) atom in compounds **1** on the course of the reaction with R^FSiMe_3. Clearly the electron-withdrawing R^F group enhances the electrophilicity of the substrate and encourages conjugate addition.

The nucleophilic reaction mechanism for the 1,4-trifluoromethylation of 2-R^F-chromones with CF_3SiMe_3 should be the same as that reported for carbonyl compounds.[4b,c] The reaction involves fluoride ion initiation to form the trifluoromethylated enolate anion **A**, which then via hypervalent silicon intermediate **B** catalyzes the subsequent reaction (Scheme 2).

Our optimum conditions for the fluoride-induced 1,4-trifluoromethylation were applied to the preparative synthesis of chromanones **4a**−**f**. When chromones **1a**,**b** are treated in THF with CF_3SiMe_3/Me_4NF for 4 h at −10 °C followed by acid hydrolysis at room temperature, 2,2-bis(trifluoromethyl)chroman-4-ones **4a**,**b** were obtained as colorless oils after vacuum distillation in 86% and 61% isolated yields, respectively. Each product contained as an admixture ~10% trimethylsilyl ethers **3**, which are more stable than ethers **2** at the acid hydrolysis. The

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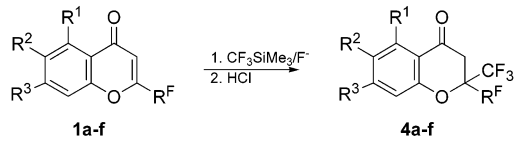
SCHEME 3



$R^F = CF_3$, $R^1 = R^2 = R^3 = H$ (**a**);
$R^F = CF_3$, $R^1 = R^3 = H$, $R^2 = Me$ (**b**);
$R^F = CF_3$, $R^1 = R^3 = H$, $R^2 = MeO$ (**c**);
$R^F = CF_3$, $R^1 = R^2 = H$, $R^3 = MeO$ (**d**);
$R^F = CF_3$, $R^2 = H$, $R^1 = R^3 = MeO$ (**e**);
$R^F = CF_2H$, $R^1 = R^3 = H$, $R^2 = MeO$ (**f**)

reactions of chromones **1c**−**f** with CF_3SiMe_3 were carried out at −30 °C for 24 h and crystalline chromanones **4c**−**f** were isolated in 50−76% yields. No side products were observed. This reaction is the first example of successful preparative regioselective 1,4-trifluoromethylation of a conjugated enone system that proceeds as an A_N process (Scheme 3).

The introduction of fluorine in place of hydrogen has become a common practice by medicinal chemists in attempts to improve the biological activity of organic compounds.[3] In our opinion, the approach described here represents the best overall route to fluorinated analogues of natural chromanones, chromanes, and chromenes with *gem*-dimethyl groups at the C(2) atom.[9] Thus, 4-oxo-2,2-bis(trifluoromethyl)chroman-6-carbaldehyde **5a**, the analogue of natural lactarochromal, a metabolite of the fungus *Lactarius deliciosus*[14] in which both methyl groups are replaced by the trifluoromethyl groups, was synthesized by the oxidation of the 6-Me group of chromanone **4b** with a mixture of $K_2S_2O_8$ and CuSO4 in aqueous acetonitrile[15] in 17% yield (the reaction conditions are not optimized). In addition to hexafluorolactarochromal **5a**, this reaction gives the corresponding hexafluoro acid **5b** (yield 35%), which is also a fluorinated analogue of the natural acid isolated from *Chrysothamnus viscidiflorus*[16] (Scheme 4).

Recently we have shown that the reaction of *N*-benzyl-2-trifluoromethylchromen-4-imines with malonic acid is a convenient method for the synthesis of 2-methyl-2-trifluoromethylchroman-4-ones. Using this method, an analogue of lactarochromal in which one of the methyl groups in the *gem*-dimethyl moiety is replaced by the CF_3 group was described.[8c]

Substituted 2,2-dimethylchromans of various levels of saturation and oxidation are common natural products which are widely distributed among many plants.[9] Furthermore, they have considerable biological importance, especially as potentially useful modern pesticides[17] and drug candidates in the field of potassium channel openers.[18] Because of their ease of preparation, reactivity, and relative stability, 2,2-dimethylchromenes have an im-

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SCHEME 4

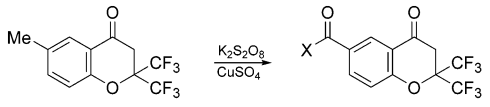
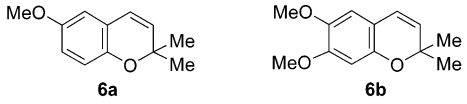


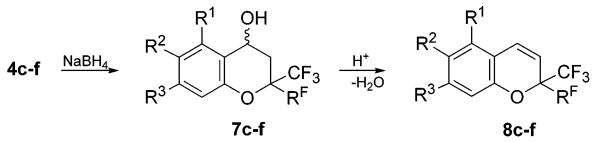
CHART 1



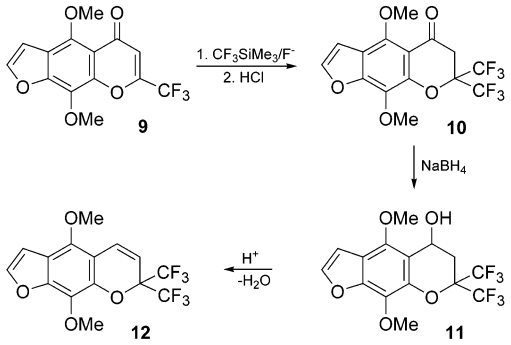
portant role and are valuable intermediates for synthetic purposes in 2,2-dimethylchroman chemistry. For example, precocene I (**6a**) and precocene II (**6b**) are antijuvenile hormones which have been isolated from the plant *Ageratum houstonianum*. Although precocenes are nature-friendly in the general sense, they cause precocious metamorphosis, sterility and other pronounced biological effects in various insects.[19]

The central position of the 2*H*-chromene ring system in large and diverse classes of naturally occurring and biologically active heterocycles has led to the development of a number of methods for their preparation,[20] and properties of these compounds were investigated.[21] However, published data on the synthesis of partially fluorinated 2,2-dimethylchromenes are lacking. In view of the unique biological properties displayed by precocenes **6**[19] on one hand and by many CF_3-containing heterocycles[1,3] on the other hand, it was of interest to obtain fluorine-containing precocenes by using our approach with (trifluoromethyl)trimethylsilane. Synthesis of these compounds was achieved by reduction of chromanones **4c**−**f** with sodium borohydride in methanol and subsequent dehydration of chromanols **7c**−**f** in refluxing xylene for 2 h in the presence of *p*-toluene sulfonic acid as a catalyst. Reduction of **4f** exhibits relatively high stereoselectivity and the diastereomer ratio was 79:21. Expectedly, these reactions proceeded smoothly for all substrates and 2,2-bis(trifluoromethyl)chroman-4-ols **7c**−**f** and 2,2-bis(trifluoromethyl)chromenes **8c**−**f**, fluorinated analogues of natural precocenes **6**, were isolated as crystalline products (except for **8f**) in 76−89% yields for **7c**−**f** and 51−72% yields for **8c**−**f**. The structures of these compounds were confirmed by ^{1}H, ^{19}F NMR, and IR spectroscopy and mass spectrometry. In the ^{19}F NMR spectra the bis(trifluoromethyl) moiety of **4a**,**c**−**e** and **8c**−**e** manifests itself as a singlet ranging between −76 and −78 ppm; CF_3 groups of the trifluoromethylated chromanols **7c**−**e**

SCHEME 5



SCHEME 6



appeared as quartets at about −76 and −77 ppm with $^4J_{F,F} = 10.3$ Hz due to the chiral center in their molecules, and the signal for the CF_3 group of compounds **4f** and **8f** appeared as a doublet of doublets at about −79 ppm ($^4J_{F,F}$ = 5.1−6.1 H and 10.6−11.1 Hz). Two sets of signals in the ^{19}F and ^{1}H NMR spectra of **7f** showed the presence of two diastereomers. The ^{1}H NMR spectra of chromenes **8c**−**f** showed signals for the aromatic protons and a characteristic AX-system ranging between 5.4−5.7 and 6.8−7.2 ppm for the CH=CH moiety; the coupling constant was $J_{AX} = 10.1$ Hz (Scheme 5).

Recently[22] the condensation of khellinone with CF_3CO_2-Et allowed us to obtain 7-trifluoromethylnorkhellin **9**, viz., the fluorinated analogue of natural furochromone khellin, which is an efficient medicinal substance[23] and present in plant *Ammi visnaga L* known by its therapeutic properties.[24] The replacement of Me by the CF_3 group in khellin affects the electron density distribution in the khellin system and makes trifluorokhellin **9** a promising substrate for the preparation of potentially bioactive compounds.[25] Using the above method we were able to synthesize three new khellin derivatives **10**−**12**. Trifluorokhellin **9** reacted easily and cleanly with CF_3-$SiMe_3$ at −30 °C for 24 h to afford the desired furochromanone **10** in 70% isolated yields without any formation of 1,2-adduct (monitoring by ^{19}F NMR). Treatment of **10** with $NaBH_4$ in methanol at room temperature for 10 min gave furochromanol **11** (70%), which was easily converted into furochromene **12** (73%) by refluxing in xylene for 2 h with a catalytic amount of *p*-toluene sulfonic acid (Scheme 6).

The method described in this paper was also applicable to the 1,4-trifluoromethylation of 3-chloro-2-trifluoromethylchromone (**13**)[26] and 1-methyl-2-(trifluoromethyl)-quinolin-4(1*H*)-one (**14**).[27] Reactions of these compounds

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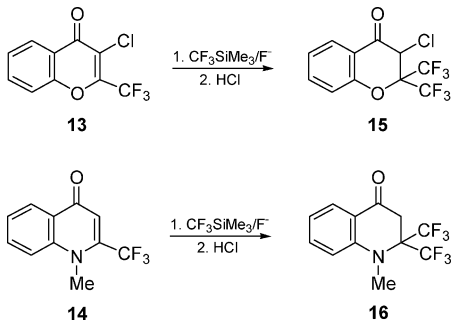
SCHEME 7



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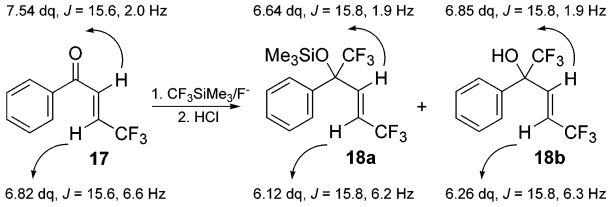
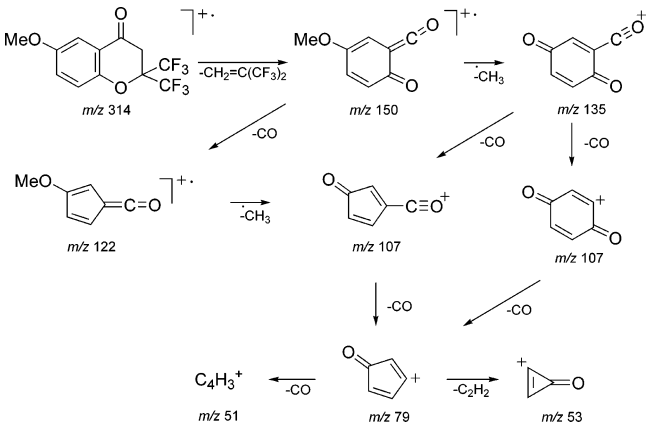


SCHEME 9



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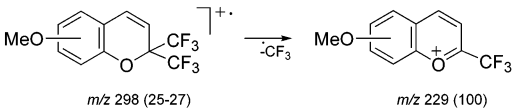

with CF_3SiMe_3 in the presence of Me_4NF led to the formation of the corresponding trifluoromethylated silyl ethers, which upon hydrolysis with 20% HCl afforded the 3-chloro-2,2-bis(trifluoromethyl)chroman-4-one (**15**) and 1-methyl-2,2-bis(trifluoromethyl)-2,3-dihydroquinolin-4(1*H*)-one (**16**) as the only isolated products. Although slightly lower yields (53−58%) were obtained, in these cases no 1,2-addition products could be detected when reaction was followed by ^{19}F NMR spectroscopy. It is noteworthy that 3-chlorochromone **13** is less reactive than 2-R^F-chromones **1** and reacted with CF_3SiMe_3 at room temperature for 24 h, whereas quinolone **14** reacted as rapidly as 2-R^F-chromones **1**. The successful reaction with quinolone **14** shows that the method is rather flexible and can be used in the preparation of previously unknown 2,2-bis(trifluoromethyl) derivatives of hydrogenated quinoline which are potentially medicinally active (Scheme 7). Earlier tri- and difluoromethylated tetra- and dihydroquinoline derivatives were obtained by cationic polar cycloaddition of α-methoxylated amines with nucleophilic unsaturated compounds in the presence of a Lewis acid.[28]

Interestingly, when a similar experiment was carried out with an acyclic analogue of **1a**, (*E*)-4,4,4-trifluoro-1-phenyl-2-buten-1-one (**17**),[29] in which the heterocyclic oxygen atom is missing, no evidence of 1,4-addition was observed by NMR spectroscopy and reaction exclusively proceeded via nucleophilic addition of the CF_3 group to the carbonyl group to form the trimethylsilyl ether **18a**. The ^1H NMR spectrum of the crude product after 12 h at −10 °C followed by acid hydrolysis showed a 92:8 mixture of ether **18a** and allylic alcohol **18b**, indicating that partial hydrolysis of **18a** had occurred (Scheme 8). This example shows again the interplay of electronic and steric factors on the course of the reaction with CF_3SiMe_3 and is consistent with Singh and Shreeve's observation that the trans α,*β*-enones, including 1,1,1-trifluoro-4-phenyl-3-buten-2-one isomeric to **17**, react cleanly with CF_3SiMe_3 in the presence of a catalytic amount of CsF to produce trimethylsilyl ether intermediates in essentially quantitative yields.[4b,5f]

The fragmentation patterns in the mass spectra of chromanones **4**, **10**, and **15** are exemplified in Scheme 8 for the parent compound **4c**. The molecular ion (the base peak) undergoes the expected retro-Diels−Alder reaction to give the peak at *m*/*z* 150. A mode of breakdown of the *m*/*z* 150 ion occurs through loss of CO, $^{\bullet}CH_3$, and C_2H_2. These degradation pathways confirmed the structure of **4c** and are characteristic of all of the 2,2-bis(trifluoromethyl)chroman-4-ones, including the 3-chloro derivative **15** (Scheme 9).

As expected, the molecular ion of 2,2-bis(trifluoromethyl)chromenes **8** loses one trifluoromethyl group to give a stable pyrilium cation as the base peak (Scheme 10).

In summary, the reaction of readily available 2-trifluoromethylchromones with Ruppert's reagent is a simple and efficient method for the synthesis of 2,2-dimethylchroman-4-ones in which the *gem*-dimethyl group is replaced by the *gem*-bis(trifluoromethyl) moiety. This approach is the first example of a preparative 1,4-trifluoromethylation and can be used for synthesis of fluorinated analogues of natural compounds.

Experimental Section

The starting 2-polyfluoroalkylchromones **1a**−**f**, **9**, and **13** were prepared by reaction of the appropriate 2-hydroxyacetophenones with R^FCO_2Et according to described procedures.[2a,22,26] 1-Methyl-2-(trifluoromethyl)quinolin-4(1*H*)-one (**14**) was obtained from 2-aminoacetophenone, CF_3CO_2Et, and MeI in the presence of ^{t}BuOK.[27] (*E*)-4,4,4-Trifluoro-1-phenyl-2-buten-1-one (**17**) was prepared according to described procedures.[29]

2,2-Bis(polyfluoroalkyl)chroman-4-ones 4a−f, 10, and 15: General 1,4-Trifluoromethylation Procedure. Chromone **1** or **9** (5 mmol) and (trifluoromethyl)trimethylsilane (1.0 g, 7 mmol) were dissolved in dry THF (15 mL) and cooled to −25 to −30 °C, and a catalytic amount of anhydrous Me_4NF (20

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mg) was added (solution changed from colorless to yellow). The reaction mixture was left to stand with stirring at that temperature for 24 h, after which it was hydrolyzed at ~20 °C by reacting with 20% HCl (1 mL) for 15 min. After the removal of solvent under reduced pressure, the residue was worked up with boiling hexane and purified by filtration through a silica gel layer (d = 10 mm, l = 10 mm) and recrystallization from the same solvent to afford the analytical samples of the compounds **4e**−**f** and **10**. In the case of **13**, the reaction was carried out at ~20 °C. The liquid products from **1a**,**b** (the reaction was carried out at 0 °C for 4 h) were extracted with $CHCl_3$ (20 mL), and the extract was dried over anhydrous K_2CO_3, filtered, and distilled under reduced pressure to give chromanones **4a**,**b** with an admixture (11−12%) of trimethylsilyl ethers **3**.

2,2-Bis(trifluoromethyl)chroman-4-one (4a): yield 86% as a colorless liquid; bp 94−97 °C (15 mmHg); IR (neat) 1710 (C═O), 1670, 1615, 1590 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) **4a** (89%) δ 3.22 (2H, s, CH_2), 7.13 (1H, dd, ^oJ = 8.4 Hz, ^mJ = 1.0 Hz), 7.17 (1H, ddd, ^oJ = 8.4, 7.3 Hz, ^mJ = 1.0 Hz), 7.60 (1H, ddd, ^oJ = 8.4, 7.3 Hz, ^mJ = 1.8 Hz), 7.89 (1H, dd, ^oJ = 7.8 Hz, ^mJ = 1.8 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) **3a** (11%) δ −0.03 (9H, s, $SiMe_3$), 5.81 (1H, s, ═CH), 7.18 (1H, dd, ^oJ = 8.4 Hz, ^mJ = 1.1 Hz), 7.27 (1H, ddd, °J = 8.4, 7.3 Hz, ^mJ = 1.1 Hz), 7.44 (1H, ddd, ^oJ = 8.4, 7.3 Hz, ^mJ = 1.7 Hz), 7.72 (1H, d quint, ^oJ = 8.0 Hz, $^mJ = {}^5J_{H,F}$ = 1.4 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) **4a** δ −77.78 (s, CF_3); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) **3a** δ −73.70 (s, C^2−CF_3), −81.98 (s, C^4−CF_3); ^{13}C NMR (50 MHz, $CDCl_3$) **4a** δ 34.7 (s, C^3), 80.0 (sept, $^2J_{C,F}$ = 30.9 Hz, C^2), 117.5 (s, C^8), 119.2 (s, C^{4a}), 121.9 (q, $^1J_{C,F}$ = 287.8 Hz, CF_3), 123.4 (s, C^6), 126.5 (s, C^5), 137.1 (s, C^7), 157.2 (s, C^{8a}), 184.5 (s, C^4).

6-Methyl-2,2-bis(trifluoromethyl)chroman-4-one (4b): yield 61% as a colorless liquid; bp 122−125 °C (27 mmHg); IR (neat) 1710 (C═O), 1670, 1620, 1590 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) **4b** (88%) δ 2.34 (3H, s, Me), 3.19 (2H, s, CH_2), 7.02 (1H, d, ^oJ = 8.5 Hz), 7.40 (1H, ddq, ^oJ = 8.5 Hz, ^mJ = 2.3 Hz, $^4J_{H,Me}$ = 0.6 Hz), 7.67 (1H, dq, ^mJ = 2.3 Hz, $^4J_{H,Me}$ = 0.4 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) **3b** (12%) δ −0.03 (9H, s, $SiMe_3$), 2.38 (3H, s, Me), 5.77 (1H, s, ═CH), 7.07 (1H, d, ^oJ = 8.5 Hz), 7.23 (1H, ddq, ^oJ = 8.5 Hz, ^mJ = 2.2 Hz, $^4J_{H,Me}$ = 0.6 Hz), 7.48 (1H, br s).

6-Methoxy-2,2-bis(trifluoromethyl)chroman-4-one (4c): yield 76% as colorless needles; mp 91−92 °C; IR (KBr) 1705 (C═O), 1619, 1493, 1435 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (2H, s, CH_2), 3.82 (3H, s, MeO), 7.06 (1H, dd, ^oJ = 9.1 Hz), 7.18 (1H, dd, ^oJ = 9.1 Hz, ^mJ = 3.2 Hz), 7.30 (1H, d, ^mJ = 3.2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −76.44 (s, CF_3); MS m/z (I_{rel} (%)) 314 (M^+, 100), 150 (63), 135 (17), 122 (13), 107 (29), 79 (29), 53 (15), 51 (13); HRMS calcd for $C_{12}H_8F_6O_3$ (M^+) 314.0378, found 314.0389.

7-Methoxy-2,2-bis(trifluoromethyl)chroman-4-one (4d): yield 67% as colorless needles; mp 88−89 °C; IR (KBr) 1688 (C═O), 1620, 1583, 1504, 1440 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.16 (2H, s, CH_2), 3.88 (3H, s, MeO), 6.57 (1H, d, ^mJ = 2.5 Hz), 6.70 (1H, dd, ^oJ = 8.9 Hz, ^mJ = 2.5 Hz), 7.83 (1H, d, ^oJ = 8.9 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −76.59 (s, CF_3); MS m/z (I_{rel} (%)) 314 (M^+, 81), 150 (100), 122 (36), 107 (17), 79 (5), 51 (4); HRMS calcd for $C_{12}H_8F_6O_3$ (M^+) 314.0378, found 314.0383.

5,7-Dimethoxy-2,2-bis(trifluoromethyl)chroman-4-one (4e): yield 64% as colorless crystals; mp 77−78 °C; IR (KBr) 1687 (C═O), 1618, 1577, 1467, 1425 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.12 (2H, s, CH_2), 3.87 (3H, s, MeO), 3.90 (3H, s, MeO), 6.18 (1H, d, ^mJ = 1.9 Hz), 6.23 (1H, d, ^mJ = 1.9 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −76.73 (s, CF_3); MS m/z (I_{rel} (%)) 344 (M^+, 100), 315 (47), 180 (82), 152 (62), 137 (72), 122 (19), 109 (15), 69 (73); HRMS calcd for $C_{13}H_{10}F_6O_4$ (M^+) 344.0483, found 344.0483.

2-(Difluoromethyl)-6-methoxy-2-(trifluoromethyl)chroman-4-one (4f): yield 50% as colorless crystals; mp 58−59 °C; IR (Nujol) 1700 (C═O), 1615, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (1H, d, J = 17.6 Hz, CHH), 3.21 (1H, d, J = 17.6 Hz, CHH), 3.81 (3H, s, MeO), 6.07 (1H, t, $^2J_{H,F}$ = 54.2 Hz, CF_2H), 7.00 (1H, d, ^oJ = 9.1 Hz), 7.15 (1H, d, ^oJ = 9.1 Hz, ^mJ = 3.2 Hz), 7.29 (1H, d, ^mJ = 3.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$) δ −78.42 (3F, dd, $^4J_{F,F}$ = 11.1 Hz, $^4J_{F,F}$ = 5.1 Hz, CF_3), −130.12 (1F, ddq, $^2J_{F,F}$ = 300.8 Hz, $^2J_{F,H}$ = 53.8 Hz, $^4J_{F,F}$ = 11.1 Hz, CFFH), −132.75 (1F, ddq, $^2J_{F,F}$ = 300.8 Hz, $^2J_{F,H}$ = 54.7 Hz, $^4J_{F,F}$ = 5.1 Hz, CFFH). Anal. Calcd for $C_{12}H_9F_5O_3$: C, 48.66; H, 3.06. Found: C, 48.63; H, 3.17.

4,9-Dimethoxy-7,7-bis(trifluoromethyl)-6,7-dihydro-5*H*-furo[3,2-*g*]chromen-5-one (10): yield 70% as yellow crystals; mp 146−147 °C; IR (KBr) 1694 (C═O), 1609, 1545, 1484, 1441 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.21 (2H, s, CH_2), 4.06 (3H, s, MeO), 4.11 (3H, s, MeO), 6.98 (1H, d, J = 2.5 Hz), 7.59 (1H, d, J = 2.5 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −76.44 (s, CF_3); MS m/z (I_{rel} (%)) 384 (M^+, 100), 369 (38), 355 (18), 220 (9), 205 (72), 192 (6), 177 (62), 147 (8), 119 (10), 69 (15); HRMS calcd for $C_{15}H_{10}F_6O_5$ (M^+) 384.0432, found 384.0429.

3-Chloro-2,2-bis(trifluoromethyl)chroman-4-one (15): yield 58% as colorless needles; mp 49−50 °C; IR (KBr) 1708 (C═O), 1609, 1591, 1465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (1H, q, $^4J_{H,F}$ = 0.7 Hz, CH), 7.17 (1H, d, ^oJ = 8.5 Hz), 7.24 (1H, ddd, ^oJ = 7.8, 7.2 Hz, ^mJ = 0.9 Hz), 7.66 (1H, ddd, ^oJ = 8.5, 7.2 Hz, ^mJ = 1.7 Hz), 7.95 (1H, dd, ^oJ = 7.8 Hz, ^mJ = 1.7 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −68.28 (q, $J_{F,F}$ = 9.2 Hz, CF_3), −72.47 (q, $J_{F,F}$ = 9.2 Hz, CF_3); MS m/z (I_{rel} (%)) 318 (M^+, 22), 249 (6), 120 (100), 92 (46), 69 (7); HRMS calcd for $C_{11}H_5ClF_6O_2$ (M^+) 317.9882, found 317.9881.

1-Methyl-2,2-bis(trifluoromethyl)-2,3-dihydroquinolin-4(1*H*)-one (16): yield 53% as colorless needles; mp 52−53 °C; IR (Nujol) 1700 (C═O), 1610, 1580 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (2H, s, CH_2), 3.19 (3H, sept, $^5J_{H,F}$ = 1.0 Hz, Me), 6.90 (1H, d, ^oJ = 8.7 Hz), 6.92 (1H, ddd, ^oJ = 7.7, 7.2 Hz, ^mJ = 0.9 Hz), 7.53 (1H, ddd, ^oJ = 8.7, 7.2 Hz, ^mJ = 1.8 Hz), 7.88 (1H, dd, ^oJ = 7.7 Hz, ^mJ = 1.8 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −70.55 (s, CF_3). Anal. Calcd for $C_{12}H_9F_6NO$: C, 48.50; H, 3.05; N, 4.71. Found: C, 48.23; H, 3.11; N, 4.69.

(*E*)-4,4,4-Trifluoro-1-phenyl-1-(trifluoromethyl)but-2-enyl trimethylsilyl ether (18a): yield 85% as dark yellow oil after acid hydrolysis and evaporation of THF in vacuo; ^{1}H NMR (400 MHz, $CDCl_3$) **18a** (92%) δ 0.10 (9H, s, $SiMe_3$), 6.12 (1H, dq, $^3J_{H,H}$ = 15.8 Hz, $^3J_{H,F}$ = 6.2 Hz), 6.64 (1H, dq, $^3J_{H,H}$ = 15.8 Hz, $^4J_{H,F}$ = 1.9 Hz), 7.38−7.48 (5H, m, Ph); ^{1}H NMR (400 MHz, $CDCl_3$) **18b** (8%) δ 6.26 (1H, dq, $^3J_{H,H}$ = 15.8 Hz, $^3J_{H,F}$ = 6.3 Hz), 6.85 (1H, dq, $^3J_{H,H}$ = 15.8 Hz, $^4J_{H,F}$ = 1.9 Hz), 7.38−7.48 (5H, m, Ph); ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$, in 2 weeks after preparation) **18a** (75%) δ −76.93 (s, CF_3), −65.77 (dd, ^3J = 6.2 Hz, ^4J = 1.9 Hz, CF_3); ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$, in 2 weeks after preparation) **18b** (25%) δ −79.28 (s, CF_3), −65.70 (dd, ^3J = 6.3 Hz, ^4J = 1.9 Hz, CF_3).

4-Oxo-2,2-bis(trifluoromethyl)chroman-6-carbaldehyde (5a) and 4-oxo-2,2-bis(trifluoromethyl)chroman-6-carboxylic acid (5b). The title compounds were obtained by using a slight modification of a published procedure.[11a] A mixture of chromanone **4h** (0.92 g, 2.6 mmol), $K_2S_2O_8$ (1.80 g, 6.7 mmol), and $CuSO_4 \cdot 5H_2O$ (0.19 g, 0.76 mmol) in acetonitrile (22 mL) and H_2O (15 mL) was boiled for 2 h. Then the reaction mixture was diluted with 150 mL of H_2O, and the product was extracted with chloroform (3 × 30 mL). The combined extract was treated with a saturated solution of $NaHCO_3$ (50 mL), and the aqueous layer was separated and acidified by concentrated HCl (5 mL). The resulting precipitate was collected, washed with H_2O, and dried to give acid **5b** as a colorless solid (0.30 g, 35%), mp 182−183 °C; IR (Nujol) 1740, 1715 (C═O), 1630, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29 (2H, s, CH_2), 7.26 (1H, d, ^oJ = 8.7 Hz), 8.33 (1H, dd, ^oJ = 8.7 Hz, ^mJ = 2.2 Hz), 8.67 (1H, d, ^mJ = 2.2 Hz). Anal. Calcd for $C_{12}H_6F_6O_4$: C, 43.92; H, 1.84. Found: C, 44.02; H, 1.85.

The chloroform layer was dried over anhydrous K_2CO_3 and filtered, chloroform was distilled off, and aldehyde **5a** was extracted from the residue with hot hexane (50 mL). The hexane extract was passed through a silica gel layer (d = 10

mm, l = 10 mm) and eluted with boiling hexane (15 mL). Hexane excess was distilled off, and aldehyde **5a** was crystallized from the remaining solution (~20 mL) upon cooling to −10 °C and stirring. The resulting precipitate was collected, washed with cold hexane, and recrystallized from hexane to give aldehyde **5a** as colorless needles (0.14 g, 17%), mp 85 °C; IR (Nujol) 1710 (C=O), 1615, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.30 (2H, s, CH_2), 7.31 (1H, d, ^oJ = 8.6 Hz), 8.17 (1H, dd, ^oJ = 8.6 Hz, ^mJ = 2.1 Hz), 8.40 (1H, d, ^mJ = 2.1 Hz), 9.99 (1H, s, CHO). Anal. Calcd for $C_{12}H_6F_6O_3$: C, 46.17; H, 1.94. Found: C, 46.14; H, 1.87.

2,2-Bis(trifluoromethyl)chroman-4-ols 7c−f and 11: General Procedure. To a solution of chroman-4-one **4** or **10** (2.5 mmol) in methanol (5 mL) was added powdered sodium borohydride (0.47 g, 12.4 mmol) slowly (5 min) at room temperature, and the mixture was stirred for 10 min. After dilution with water (25 mL), the residue was filtered off, washed with water, dried, and purified by recrystallization from hexane or by SiO_2 flash chromatography to give the compounds **7c−f** and **11**.

6-Methoxy-2,2-bis(trifluoromethyl)chroman-4-ol (7c): yield 89% as colorless crystals; mp 76−77 °C; IR (KBr) 3370 (OH), 1617, 1499, 1468, 1429 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.06 (1H, d, J = 7.9 Hz, OH), 2.19 (1H, ddq, ^2J = 14.2 Hz, ^3J = 10.4 Hz, $^4J_{H,F}$ = 1.5 Hz, C*H*H), 2.77 (1H, dd, ^2J = 14.2 Hz, ^3J = 5.9 Hz, CH*H*), 3.79 (3H, s, MeO), 4.97 (1H, dt, $J \approx$ 10.0 Hz, $J \approx$ 7.0 Hz), 6.82 (1H, ddd, ^oJ = 8.9 Hz, ^mJ = 3.0 Hz, J = 0.7 Hz), 6.95 (1H, d, ^oJ = 8.9 Hz), 7.03 (1H, dd, ^mJ = 3.0 Hz, J = 0.9 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −76.25 (q, $J_{F,F}$ = 10.3 Hz, CF_3), −77.83 (q, $J_{F,F}$ = 10.3 Hz, CF_3); MS m/z (I_{rel} (%)) 316 (M^+, 100), 315 (2), 299 (5), 152 (72), 151 (15), 137 (48), 109 (8), 69 (6); HRMS calcd for $C_{12}H_{10}F_6O_3$ (M^+) 316.0534, found 316.0545.

7-Methoxy-2,2-bis(trifluoromethyl)chroman-4-ol (7d): yield 83% as colorless crystals; mp 74−75 °C; IR (KBr) 3259 (OH), 1631, 1591, 1512, 1442 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.0 (1H, br s, OH), 2.24 (1H, dd, ^2J = 14.4 Hz, ^3J = 10.4 Hz, C*H*H), 2.76 (1H, dd, ^2J = 14.4 Hz, ^3J = 6.0 Hz, CH*H*), 3.81 (3H, s, MeO), 4.97 (1H, m), 6.57 (1H, d, ^mJ = 2.5 Hz), 6.68 (1H, dd, ^oJ = 8.9 Hz, ^mJ = 2.5 Hz), 7.40 (1H, d, ^oJ = 8.9 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −76.02 (q, $J_{F,F}$ = 10.3 Hz, CF_3), −77.47 (q, $J_{F,F}$ = 10.3 Hz, CF_3); MS m/z (I_{rel} (%)) 316 (M^+, 85), 315 (29), 299 (41), 152 (58), 151 (100), 69 (23), 28 (94); HRMS calcd for $C_{12}H_{10}F_6O_3$ (M^+) 316.0534, found 316.0552.

5,7-Dimethoxy-2,2-bis(trifluoromethyl)chroman-4-ol (7e): yield 76% as a yellow powder; mp 140−141 °C; IR (KBr) 3547 (OH), 1632, 1600, 1500, 1464, 1436 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.43 (1H, dd, ^2J = 15.3 Hz, ^3J = 7.2 Hz, C*H*H), 2.67 (1H, dd, ^2J = 15.3 Hz, ^3J = 6.2 Hz, CH*H*), 3.65 (1H, s, OH), 3.79 (3H, s, MeO), 3.87 (3H, s, MeO), 5.10 (1H, t, J = 6.5 Hz), 6.19 (2H, s); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −75.54 (q, $J_{F,F}$ = 10.3 Hz, CF_3), −76.33 (q, $J_{F,F}$ = 10.3 Hz, CF_3); MS m/z (I_{rel} (%)) 346 (M^+, 93), 345 (41), 329 (100), 182 (42), 181 (23), 164 (41), 136 (14), 69 (43), 28 (18); HRMS calcd for $C_{13}H_{12}F_6O_4$ (M^+) 346.0640, found 346.0637.

2-(Difluoromethyl)-6-methoxy-2-(trifluoromethyl)chroman-4-ol (7f): yield 88% as colorless crystals; mp 59−60 °C; IR (Nujol) 3300 (OH), 1620, 1500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major diastereomer (79%) δ 2.03 (1H, d, J = 7.6 Hz, OH), 2.08 (1H, dd, ^2J = 14.0 Hz, ^3J = 9.9 Hz, C*H*H), 2.76 (1H, dd, ^2J = 14.0 Hz, ^3J = 5.8 Hz, CH*H*), 3.79 (3H, s, MeO), 5.00 (1H, dt, J = 9.7 Hz, J = 6.7 Hz), 6.01 (1H, t, $^2J_{H,F}$ = 54.8 Hz, CF_2H), 6.81 (1H, ddd, ^oJ = 8.9 Hz, ^mJ = 3.0 Hz, J = 0.7 Hz), 6.89 (1H, d, ^oJ = 8.9 Hz), 7.02 (1H, dd, ^mJ = 3.0 Hz, J = 0.9 Hz); ^1H NMR (400 MHz, $CDCl_3$) minor diastereomer (21%) δ 2.03 (1H, d, J = 7.6 Hz, OH), 2.29 (1H, ddt, ^2J = 14.4 Hz, ^3J = 8.6 Hz, J = 1.2 Hz, C*H*H), 2.57 (1H, ddd, ^2J = 14.4 Hz, ^3J = 5.5 Hz, J = 2.1 Hz, CH*H*), 3.79 (3H, s, MeO), 4.94 (1H, q, J = 7.1 Hz), 6.10 (1H, t, $^2J_{H,F}$ = 54.6 Hz, CF_2H), 6.82 (1H, ddd, ^oJ = 8.9 Hz, ^mJ = 3.0 Hz, J = 0.6 Hz), 6.90 (1H, d, ^oJ = 8.9 Hz), 6.97 (1H, dd, ^mJ = 3.0 Hz, J = 0.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$) major diastereomer (79%) δ −79.31 (3F, dd, $^4J_{F,F}$ = 10.8 Hz, $^4J_{F,F}$ = 4.6 Hz, CF_3), −130.37 (1F, ddq, $^2J_{F,F}$ = 297.8 Hz, $^2J_{F,H}$ = 54.4 Hz, $^4J_{F,F}$ = 10.8 Hz, C*F*FH), −134.30 (1F, ddqd, $^2J_{F,F}$ = 297.8 Hz, $^2J_{F,H}$ = 55.1 Hz, $^4J_{F,F}$ = 4.6 Hz, $^4J_{F,H}$ = 1.3 Hz, CF*F*H); ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$) minor diastereomer (21%) δ −77.46 (3F, dd, $^4J_{F,F}$ = 11.5 Hz, $^4J_{F,F}$ = 5.7 Hz, CF_3), −131.67 (1F, ddqd, $^2J_{F,F}$ = 293.0 Hz, $^2J_{F,H}$ = 54.4 Hz, $^4J_{F,F}$ = 11.5 Hz, $^4J_{F,H}$ = 2.0 Hz, C*F*FH), −134.66 (1F, ddq, $^2J_{F,F}$ = 293.0 Hz, $^2J_{F,H}$ = 54.6 Hz, $^4J_{F,F}$ = 5.7 Hz, CF*F*H). Anal. Calcd for $C_{12}H_{11}F_5O_3$: C, 48.33; H, 3.72. Found: C, 48.42; H, 3.75.

4,9-Dimethoxy-7,7-bis(trifluoromethyl)-6,7-dihydro-5*H*-furo[3,2-*g*]chroman-5-ol (11): yield 70% as a yellow powder; mp 91−92 °C; IR (KBr) 3543 (OH), 1628, 1554, 1492, 1451 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.50 (1H, dd, ^2J = 14.6 Hz, ^3J = 7.0 Hz, C*H*H), 2.72 (1H, dd, ^2J = 14.6 Hz, ^3J = 6.4 Hz, CH*H*), 3.89 (1H, s, OH), 4.01 (3H, s, MeO), 4.16 (3H, s, MeO), 5.28 (1H, t, J = 6.7 Hz, CH), 6.89 (1H, d, J = 2.5 Hz), 7.55 (1H, d, J = 2.5 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −75.51 (q, $J_{F,F}$ = 10.3 Hz, CF_3), −76.22 (q, $J_{F,F}$ = 10.3 Hz, CF_3); MS m/z (I_{rel} (%)) 386 (M^+, 100), 371 (24), 343 (13), 222 (13), 207 (57), 192 (10), 69 (11); HRMS calcd for $C_{15}H_{12}F_6O_5$ (M^+) 386.0589, found 386.0594.

2,2-Bis(trifluoromethyl)-2*H*-chromenes 8c−f and 12: General Procedure. A mixture of chroman-4-ol **7** or **11** (1.5 mmol) and a catalytic amount of *p*-toluene sulfonic acid (~10 mg) in xylene (2 mL) was heated at reflux for 2 h. After the removal of solvent under reduced pressure, the residue was worked up with boiling hexane and purified by filtration through a silica gel layer (d = 10 mm, l = 10 mm) and recrystallization from the same solvent (except for **8f**) to afford the compounds **8c−f** and **12**.

6-Methoxy-2,2-bis(trifluoromethyl)-2*H*-chromene (8c): yield 72% as colorless crystals; mp 34−35 °C; IR (KBr) 1652, 1625, 1587 (C=C), 1495, 1469, 1457, 1438 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (3H, s, MeO), 5.68 (1H, d, J = 10.1 Hz), 6.62 (1H, d, ^mJ = 3.0 Hz), 6.79 (1H, dd, ^oJ = 8.9 Hz, ^mJ = 3.0 Hz), 6.85 (1H, d, J = 10.1 Hz), 6.89 (1H, d, ^oJ = 8.9 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −78.15 (s, CF_3); MS m/z (I_{rel} (%)) 298 (M^+, 27), 229 (100), 69 (4); HRMS calcd for $C_{12}H_8F_6O_2$ (M^+) 298.0429, found 298.0431.

7-Methoxy-2,2-bis(trifluoromethyl)-2*H*-chromene (8d): yield 68% as colorless crystals; mp 49−50 °C; IR (KBr) 1651, 1626, 1575 (C=C), 1513, 1487, 1468, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (3H, s, MeO), 5.51 (1H, d, J = 10.1 Hz), 6.53 (2H, m), 6.83 (1H, d, J = 10.1 Hz), 6.99 (1H, d, ^oJ = 9.0 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −78.28 (s, CF_3); MS m/z (I_{rel} (%)) 298 (M^+, 25), 229 (100), 69 (9), 28 (15); HRMS calcd for $C_{12}H_8F_6O_2$ (M^+) 298.0429, found 298.0414.

5,7-Dimethoxy-2,2-bis(trifluoromethyl)-2*H*-chromene (8e): yield 67% as colorless crystals; mp 86−87 °C; IR (KBr) 1651, 1624, 1588 (C=C), 1504, 1467, 1437 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.80 (3H, s, MeO), 3.81 (3H, s, MeO), 5.42 (1H, d, J = 10.1 Hz), 6.09 (1H, s), 6.17 (1H, s), 7.17 (1H, d, J = 10.1 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −78.34 (s, CF_3); MS m/z (I_{rel} (%)) 328 (M^+, 18), 259 (100), 69 (13), 28 (2); HRMS calcd for $C_{13}H_{10}F_6O_3$ (M^+) 328.0534, found 328.0549.

2-(Difluoromethyl)-6-methoxy-2-(trifluoromethyl)-2*H*-chromene (8f): yield 51% as a colorless oil; IR (neat) 1650, 1615, 1590 (C=C), 1500, 1475, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (3H, s, MeO), 5.69 (1H, d, J = 10.1 Hz), 5.94 (1H, t, $^2J_{H,F}$ = 54.7 Hz, CF_2H), 6.61 (1H, d, ^mJ = 3.0 Hz), 6.76 (1H, dd, ^oJ = 8.9 Hz, ^mJ = 3.0 Hz), 6.82 (1H, d, J = 10.1 Hz), 6.83 (1H, d, ^oJ = 8.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$) δ −80.00 (3F, dd, $^4J_{F,F}$ = 10.6 Hz, $^4J_{F,F}$ = 6.1 Hz, CF_3), −132.22 (1F, ddqd, $^2J_{F,F}$ = 298.0 Hz, $^2J_{F,H}$ = 54.3 Hz, $^4J_{F,F}$ = 10.6 Hz, $^4J_{F,H}$ = 0.8 Hz, C*F*FH), −133.47 (1F, ddq, $^2J_{F,F}$ = 298.0 Hz, $^2J_{F,H}$ = 55.1 Hz, $^4J_{F,F}$ = 6.1 Hz, CF*F*H). Anal. Calcd for $C_{12}H_9F_5O_2$: C, 51.44; H, 3.24. Found: C, 51.53; H, 3.10.

4,9-Dimethoxy-7,7-bis(trifluoromethyl)-7*H*-furo[3,2-*g*]-chromene (12): yield 73% as yellow crystals; mp 75−76 °C; IR (KBr) 1647, 1607 (C=C), 1490 cm^{-1}; ^1H NMR (200 MHz,

$CDCl_3$) δ 4.03 (3H, s, MeO), 4.06 (3H, s, MeO), 5.62 (1H, d, J = 10.2 Hz), 6.87 (1H, d, J = 2.5 Hz), 7.33 (1H, d, J = 10.2 Hz), 7.53 (1H, d, J = 2.5 Hz); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −77.84 (s, CF_3); MS m/z (I_{rel} (%)) 368 (M^+, 86), 353 (23), 338 (13), 325 (6), 299 (100), 269 (55), 69 (14), 28 (8); HRMS calcd for $C_{15}H_{10}F_6O_4$ (M^+) 368.0483, found 368.0494.

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Supporting Information Available: General experimental details and ^{1}H and ^{19}F NMR spectra for compounds **4f**, **7f**, **8f**, and **18a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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