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Reaction of Polyhaloalkyl-Substituted Chromones, Pyrones, and Furanones with Salicylaldehydes as a Direct Route to Fused 2*H*-Chromenes

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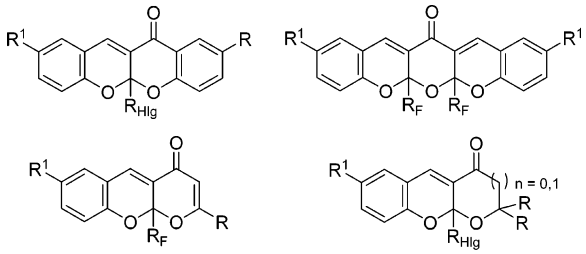

Polyhaloalkyl-substituted chromones, γ-pyrones, and β-furanones react with salicylaldehydes in the presence of piperidine to give a wide variety of fused 2*H*-chromenes in good yields. This novel annulation reaction presumably proceeds by a tandem intermolecular oxa-Michael addition and subsequent intramolecular Mannich condensation.

Introduction

Chromans (3,4-dihydro-2*H*-1-benzopyrans) and 2*H*-chromenes (2*H*-1-benzopyrans) are important classes of oxygenated heterocycles that have attracted much synthetic interest because of their reactivity and the biological activity of naturally occurring representatives.[1] It is known that the reactions of salicylaldehydes with various conjugated olefins such as nitroalkenes,[2] acrylate derivatives,[3] or α,β-unsaturated ketones[4] proceed via nucleophilic addition of phenolic hydroxyl to an activated C=C bond (oxa-Michael addition) with further cyclization at the formyl group (aldol condensation) leading to the corresponding 2*H*-chromene derivatives. When DABCO was used as a base, a sequence of the Baylis−Hillman reaction and a Michael addition was invoked.[5] The reaction of salicylaldehydes with 2-cyclohexen-1-one or 2-cyclopenten-1-one, a typical Baylis−Hillman coupling, was suggested to occur through a domino oxa-Michael addition/aldol condensation pathway in the

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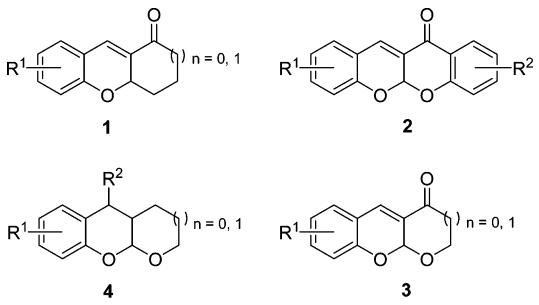

FIGURE 1. Fused 2*H*-chromenes and chromans **1**−**4**.

presence of DABCO under aqueous conditions to give tetrahydroxanthenones **1**.[6] At the same time, the reaction of salicyl *N*-tosylimines with these enones can be carried out in the presence of $PPhMe_2$, giving compounds **1** through an aza-Baylis−Hillman reaction/oxa-Michael addition pathway.[7]

Very recently, Basavaiah et al.[8] and Cheng et al.[9] reported that chromone, 6-methylchromone, and γ-pyrone can be successfully employed as novel activated alkenes in the Baylis−Hillman coupling with aromatic and aliphatic aldehydes catalyzed by methanolic trimethylamine or sodium methoxide. However, to our surprise, there are no reports on the reaction of chromones and related compounds with salicylaldehydes. This reaction could be regarded as a direct route to chromeno[2,3-*b*]chromenes **2** and pyrano- or furo[2,3-*b*]chromenes **3** with the fused acetal moiety (Figure 1), which is an important structural subunit of a variety of biologically active natural products.[10] Earlier,[11] analogous pyrano[2,3-*b*]chromenes were obtained from salicylaldehydes and dimethyl acetylenedicarboxylate in very low yields.

The observed biological activity of relatively simple fused acetals emphasizes the importance of their synthesis. Recently, several catalytic methods have been developed for the preparation of such compounds. It was found possible to form hydrogenated pyrano- and furobenzopyrans **4** (Figure 1) from salicylaldehydes or salicylaldimines on one hand, and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran on the other hand, effecting C−C bond formation by using a catalytic amount of ytterbium triflate,[12] bismuth triflate,[13] lithium tetrafluoroborate,[14] or indium trichloride.[15] Reactions of manganic acetate[16] or silver carbonate[17] with β-diketones and β-ketoesters lead to generation of radical intermediates, which add to dihydrofurans, dihydropyrans, and endocyclic lactones to afford fused acetals. Tetrahydropyrano- and tetrahydrofurobenzopyrans **4** were also obtained by the [4+2] cycloaddition of 3-nitrocoumarins with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran, followed by hydrolysis, decarboxylation, and acetalation of the cyclic nitronates.[18]

Results and Discussion

It is well-known that the introduction of the R_F group substantially affects the electron density distribution in organic molecules, and as a result some partially fluorinated substances have become valuable synthons for the construction of novel heterocyclic compounds.[19] 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.[20] As a continuation of our studies on the synthetic potential of 2-R_F-chromones, which turned out to be highly reactive substrates in the reactions with N-,[21] S-,[22] and C-nucleophiles,[23] and owing to the increasing importance of fluorine-containing heterocycles in biology, pharmacology, and industrial applications,[19] we report herein a novel reaction of polyhaloalkyl-substituted chromones, γ-pyrones, and β-furanones with salicylaldehydes having both nucleo- and electrophilic groups in the molecules.

We have found that 2-R_F- (R_F = CF_2H, CF_3, $(CF_2)_2H$, C_2F_5) and 2-CCl_3-chromones react with salicylaldehydes in the presence of piperidine (0.2 equiv) in refluxing benzene to afford 5a-(polyhaloalkyl)-5a*H*,11*H*-chromeno[2,3-*b*]chromen-11-ones **2a**−**y** in high to moderate yields without the formation

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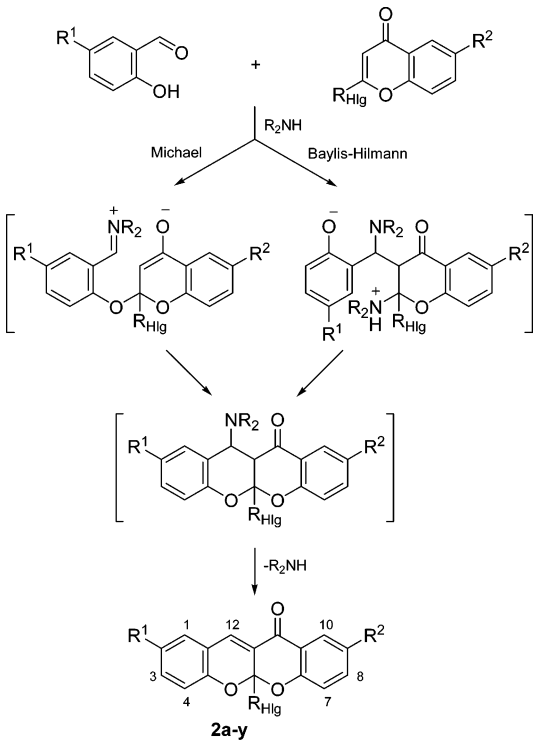
SCHEME 1



R_{Hlg} = CF_2H, CF_3, $(CF_2)_2H$, C_2F_5, CCl_3

TABLE 1. Reaction of 2-Polyhaloalkylchromones with Salicylaldehydes in the Presence of Piperidine in C_6H_6

product	R_{Hlg}	R^1	R^2	reaction time (h)	yield[a] (%)
2a	CF_2H	H	NO_2	1	94[b]
2b	CF_2H	H	Cl	5	52
2c	CF_2H	H	H	7	52
2d	CF_2H	H	Me	17	60
2e	CF_2H	Br	NO_2	3	69
2f	CF_2H	Br	Cl	7	53
2g	CF_2H	MeO	Cl	4	98
2h	CF_2H	MeO	Me	5	83
2i	CF_3	H	NO_2	30 min	90
2j	CF_3	H	H	7	55
2k	CF_3	H	Me	37	50
2l	CF_3	Br	NO_2	2	76
2m	CF_3	Br	H	12	27
2n	CF_3	Br	Me	12[c]	22
2o	CF_3	MeO	NO_2	10 min	82
2p	CF_3	MeO	H	2	74
2q	CF_3	MeO	Me	4	78
2r	$(CF_2)_2H$	H	NO_2	7	57
2s	$(CF_2)_2H$	H	H	7[c]	56
2t	C_2F_5	H	Cl	5	52
2u	C_2F_5	Br	Cl	14	74
2v	CCl_3	H	Cl	27	56
2w	CCl_3	H	H	29[c]	12
2x	CCl_3	MeO	Cl	6	69
2y	CCl_3	MeO	H	8[c]	23

[a] Isolated yields. [b] Yield 92% in toluene at 80 °C for 1 h. [c] In toluene.

of any side products arising from Baylis−Hillman reaction or ring-opening of the pyrone ring (Scheme 1). The progress of the reaction was monitored by TLC, and the results are summarized in Table 1. Among different solvents (THF, MeCN, EtOH), which have been tested to perform the reaction, benzene and toluene appeared to give the best results. The reaction works well with morpholine as a base, while the use of NEt_3, DABCO, or Ph_3P, known catalysts for the Baylis−Hillman coupling,[24] resulted in a comparable yield, but the reaction took longer (4−5 h for **2i**). When 2-hydroxyacetophenone was employed instead of salicylaldehyde, the reaction did not proceed at all.

As can be seen from Table 1, the electron-withdrawing nitro group at the 6-position of chromones facilitates the initial nucleophilic addition at the C(2) atom and the electron-donating methyl group complicates this process, which most likely is the key rate-determining step. 5-Bromosalicylaldehyde gave products **2m**,**n** in low yields (22−27%) and with 5-nitrosalicylaldehyde no reaction was observed, probably due to the lower nucleophilicity of the corresponding phenolate anions. According to this, 5-methoxysalicylaldehyde gave the best results. At the same time, it is known that the Baylis−Hilmann reaction is faster with electron-poor aldehydes.[25] Unlike 2-unsubstituted chromones, which reacted with aromatic aldehydes to furnish Baylis−Hillman products,[8,9] we could not obtain analogous compounds with 2-CF_3-chromones and *m*-nitrobenzaldehyde in the presence of Et_3N or DABCO, most likely due to steric repulsion between the CF_3 group and tertiary amine at the initial stage.

The reaction presented should therefore be regarded as an oxa-Michael addition of phenolate anion to the activated double bond of chromone, followed by intramolecular Mannich condensation between enolate anion and iminium cation arising from the formyl group and piperidine in situ. This transformation is a novel C−C bond-forming reaction at the 3-position of the chromone system to give the chromeno[2,3-*b*]chromen-11-ones **2**. Clearly the electron-withdrawing R_{Hlg} group enhances the electrophilicity of the substrate and encourages conjugate addition at the initial stage. It should be noted that the reaction rate seems to depend on both the electronic and steric nature of the R_{Hlg} substituent. For instance, in the case of 2-trichloromethylchromones (compounds **2w**,**y**), the reaction time was longer, the yield was lower, and the use of toluene instead of benzene was necessary. Efforts to affect an analogous cyclization with nonhalogenated substrates, such as flavone and chromone, were unsuccessful. Flavone was recovered unchanged after treatment with piperidine and salicylaldehyde in refluxing benzene for 8 h, but the more reactive chromone reacted readily with piperidine to give the previously known aminoenone, *trans*-1-(2-hydroxyphenyl)-3-piperidinoprop-2-en-1-one.[26] This fact suggests an important electronic effect of the R_F and CCl_3 groups at the C(2) atom in chromones on the course of the annulation reaction.

In attempting to ascertain if related cyclic enones can participate in this reaction, we found that 2,3-dihydro-4*H*-pyran-4-ones[27] and 2,2-dimethylfuran-3(2*H*)-ones[28] activated by the polyhaloalkyl group also react under the above experimental conditions in the presence of a catalytic amount of concentrated

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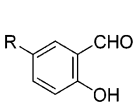
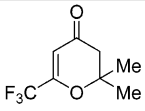
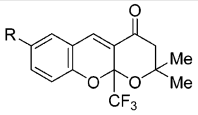
TABLE 2. Reaction of Dihydropyrones and Furanones with Salicylaldehydes

aldehyde	R_{Hlg}-substrate	product	yield,[a] % (time, h)
			
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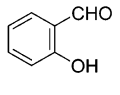
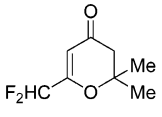
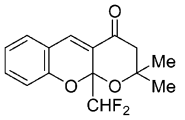
		3b: R = Br	49 (18)
		3c: R = MeO	61 (10)
			59 (14)
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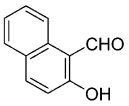
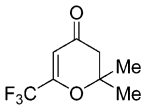
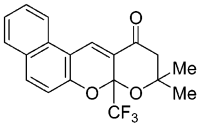
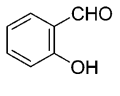
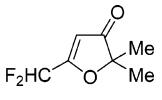
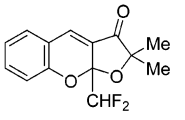
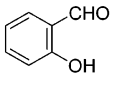
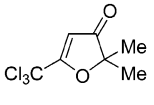
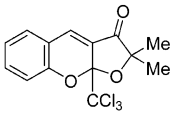
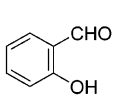
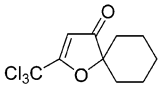
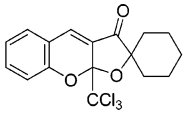
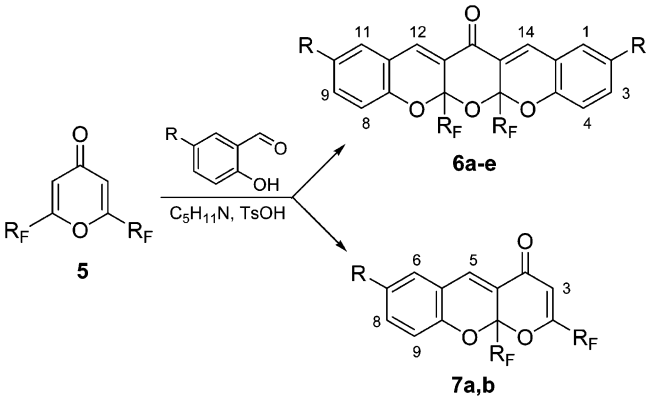
			8 (0.5)
		3e	
			44 (30)
		3f	
			55 (2)[b]
		3g	
			34 (36)
		3h	

[a] Isolated yields. [b] In toluene.

H_2SO_4 to give compounds **3a**−**h** in 34−61% yields (Table 2). This result clearly shows that the present methodology could be applicable to various types of cyclic polyhaloalkyl-containing Michael acceptors, providing a rapid route to the synthesis of a wide variety of fused 2*H*-chromenes. Unfortunately, when sterically hindered 2-hydroxy-1-naphthaldehyde was used for the reaction with 2,2-dimethyl-6-trifluoromethyl-2,3-dihydro-4*H*-pyran-4-one, the corresponding tetracyclic adduct **3e** was only obtained in an 8% yield due to the strong resinification of the reaction mixture.

The structures of compounds **2** and **3** agree well with the data from elemental analysis and with results of IR and NMR spectroscopy. The IR spectra of these compounds showed intense absorption bands in the ranges 1670−1680 (compounds **2**) and 1690−1730 cm^{-1} (compounds **3**), corresponding to the carbonyl group, and 1560−1580 cm^{-1} (compounds **2** and **3**) due to the C═C double bond; a characteristic feature of the ^1H NMR spectra is the appearance of a singlet at δ 7.6−8.1 ppm for the olefinic proton (in $CDCl_3$). In the ^1H NMR spectra of

SCHEME 2



R_F = CF_3, R = H (**a**); R_F = CF_2H, R = H (**b**);
R_F = $(CF_2)_2H$, R = H (**c**); R_F = CF_3, R = Br (**d**);
R_F = CF_2H, R = Br (**e**)

3a−**e**, an AB-system of the CH_2 group (J_{AB} = 17.4−17.7 Hz) due to the chiral center in these molecules is observed. In the ^{19}F NMR spectra the CF_3 group manifests itself as a singlet at 75.8−76.2 and 74.1−74.6 ppm (C_6F_6) for compounds **2i**−**q** and **3a**−**c**,**e**, respectively.

Next, we were interested in the reactivity of γ-pyrones **5**, carrying two R_F groups (R_F = CF_3, CF_2H, $(CF_2)_2H$) on the 2- and 6-positions.[29] The double annulation reaction of **5** with two molecules of salicylaldehyde would furnish directly linear polycyclic compounds **6**, which contain three oxygen atoms in the adjacent three rings. Indeed, using this reaction with an excess of salicylaldehydes (3 equiv) in the presence of piperidine and *p*-TsOH in benzene under reflux for 15 h, we were able to obtain 5a,6a-bis(polyfluoroalkyl)-5a*H*,6a*H*,13*H*-chromeno[3′,2′:5,6]pyrano[2,3-*b*]chromen-13-ones **6a**−**e** in 52−82% yields (Scheme 2). When 2-(difluoromethyl)-6-(trifluoromethyl)-4*H*-pyran-4-one was used as a Michael acceptor the pentacyclic diadduct **6f** with different R_F groups was formed in 70% yield (Figure 2). The reactions could also occur in the absence of *p*-TsOH but the yields were lower (42−48%).

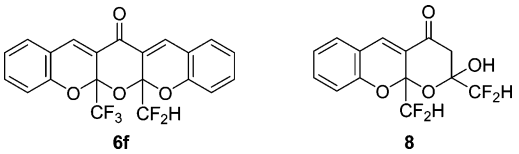
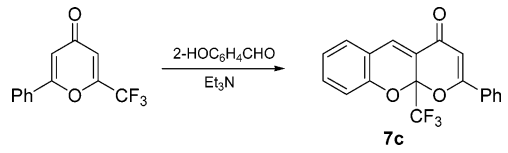


FIGURE 2. Di- and monoadducts **6f** and **8**.

Attempts to synthesize monoadducts **7a**,**b** by direct reaction of salicylaldehyde with a 2 equimolar amount of **5** in the presence of piperidine and *p*-TsOH failed. Because the reaction described presumably involved generation of iminium salts in situ, salicylaldehyde was converted to the compounds **7a**,**b** by pregeneration of its iminium salt and subsequent addition of the corresponding pyrone **5** (2 equiv). In the case of **7b**, using a similar procedure and allowing the reaction mixture to react with a 5% solution HCl, hydrate **8** was obtained in 40% yield (Figure 2). This clearly indicates that the C(2) atom of **7** is susceptible to nucleophilic attack and makes monoadducts **7** attractive building blocks for the synthesis of various hetero-

(29) (a) Yachevskii, D. S.; Chizhov, D. L.; Ratner, V. G.; Pashkevich, K. I. *Izv. Acad. Nauk, Ser. Khim.* **2001**, 1176−1180 (*Russ. Chem. Bull.* **2001**, *50*, 1233−1237). (b) Yachevskii, D. S.; Chizhov, D. L.; Pashkevich, K. I.; Charushin, V. N. *ARKIVOC* **2004**, *xi*, 71−76.

SCHEME 3



7c

cyclic systems containing the R_F group and the 2*H*-chromene ring. The subsequent dehydration of **8** to **7b** was performed in refluxing benzene for 2 h in the presence of a catalytic amount of *p*-toluenesulfonic acid and molecular sieves (3 Å, 1 g) in 64% yield. It is worth pointing out that 4*H*-pyran-4-one and 2,6-dimethyl-4*H*-pyran-4-one did not react with salicylaldehyde under our reaction conditions; the failure of the reactions may be attributed to the instability and lower electrophilicity of the nonhalogenated pyrones as compared to pyrones **5**.

Compounds **6a**−**f** were obtained as mixtures of the corresponding *trans*- and *cis*-isomers in variable proportions, depending on the nature of the starting materials and catalysts. Note that stereoisomers **6** could be easily distinguished by the chemical shift of the olefinic protons (H-12, H-14) in a $CDCl_3$ solution. For *trans*-**6**, this signal is observed as a singlet at δ 7.83−7.91 ppm, whereas for *cis*-**6** it is more shielded (δ 7.56−7.67 ppm). In some cases, the products **6** were formed exclusively as the thermodynamically more stable *trans*-isomers (usually in the presence of piperidine and *p*-TsOH). Surprisingly, when the piperidine/Me_2NH·HCl/AcONa system was employed the stereoselectivity obtained was the opposite and the *cis*-isomer was the major product (*cis*/*trans* = 75/25−95/5). The stereochemistry was determined by the X-ray diffraction analysis of the *trans*- and *cis*-isomers of **6a**. The ORTEP drawings of these compounds are shown in the Supporting Information. The only example where a similar oxygenated linear system was mentioned is a hetero-Diels−Alder reaction of 1-pentyne with two molecules of 3-methylene-2,4-chromandione.[30]

As expected, regioselectivity of the nucleophilic attack by the phenolic hydroxyl of salicylaldehyde on the pyrone ring will depend on the electronic effects of the substituents. In fact, the reaction of 2-phenyl-6-trifluoromethyl-4*H*-pyran-4-one and salicylaldehyde in the presence of Et_3N at room temperature occurs only at the carbon atom connected to the CF_3 group to give compound **7c** as the sole product in 56% isolated yield (Scheme 3).

In conclusion, we have shown, for the first time, that the reaction of salicylaldehydes with chromones, γ-pyrones, and β-furanones activated by the polyhaloalkyl group provides a convenient and short approach to the synthesis of a variety of fused 2*H*-chromene derivatives. The reaction occurred most likely through an oxa-Michael addition/Mannich condensation pathway, which well fits with our experimental results. The simplicity of the reaction and ready availability of the starting materials make it attractive.

Experimental Section

General Procedure for the Synthesis of Compounds 2. A solution of 2-R_F- or 2-CCl_3-chromone (1.0 mmol), salicylaldehyde (1.0 mmol), and piperidine (0.2 mmol) in anhydrous benzene (5 mL) was refluxed until the reaction was completed (TLC, Table 1). The reaction mixture was then evaporated, and the residue was washed with hexane. The solid product was recrystallized from hexane (or hexane/CH_2Cl_2) to give pure product **2** as light-yellow or yellow crystals.

5a-(Difluoromethyl)-9-nitro-5a*H*,11*H*-chromeno[2,3-*b*]chromen-11-one (2a): mp 175−176 °C; IR (KBr) 1678, 1620, 1592, 1569, 1529, 1470, 1439, 1349 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (t, 1H, J = 54.7 Hz), 7.10−7.16 (m, 2H), 7.26 (d, 1H, J = 9.1 Hz), 7.41−7.49 (m, 2H), 7.79 (s, 1H), 8.43 (dd, 1H, J = 9.1, 2.8 Hz), 8.89 (d, 1H, J = 2.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$/C_6F_6) δ 27.05 (dd, 1F, J = 292.8, 55.0 Hz), 29.57 (dd, 1F, J = 292.8, 54.5 Hz). Anal. Calcd for $C_{17}H_9F_2NO_5$: C, 59.14; H, 2.63; N, 4.06. Found: C, 59.31; H, 2.82; N, 3.96.

5a-(Trifluoromethyl)-5a*H*,11*H*-chromeno[2,3-*b*]chromen-11-one (2j): mp 143−144 °C; IR (KBr) 1679, 1629, 1607, 1571, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.21 (m, 4H), 7.40−7.48 (m, 2H), 7.61 (ddd, 1H, J = 8.4, 7.3, 1.7 Hz), 7.96 (s, 1H), 8.02 (dd, 1H, J = 7.8, 1.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$/C_6F_6) δ 75.96 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.2 (q, J = 35.1 Hz), 115.8, 117.5, 118.0, 118.5, 120.1, 122.1 (q, J = 294.5 Hz), 123.4, 123.6, 127.3, 130.4, 134.1, 136.5, 136.9, 151.3, 156.0, 178.3. Anal. Calcd for $C_{17}H_9F_3O_3$: C, 64.16; H, 2.85. Found: C, 64.13; H, 2.92.

9-Nitro-5a-(1,1,2,2-tetrafluoroethyl)-5a*H*,11*H*-chromeno[2,3-*b*]chromen-11-one (2r): mp 136−137 °C; IR (KBr) 1679, 1624, 1610, 1570, 1531, 1472, 1440, 1352 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (tdd, 1H, J = 52.4, 7.6, 4.1 Hz), 7.12 (br d, 1H, J = 8.2 Hz), 7.17 (td, 1H, J = 7.6, 1.0 Hz), 7.26 (d, 1H, J = 9.1 Hz), 7.44−7.52 (m, 2H), 8.05 (s, 1H), 8.45 (dd, 1H, J = 9.1, 2.8 Hz), 8.91 (d, 1H, J = 2.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$/C_6F_6) δ 24.59 (dddd, 1F, J = 305.7, 52.5, 8.3, 5.7 Hz), 27.06 (dddd, 1F, J = 305.7, 52.5, 8.3, 5.7 Hz), 30.19 (dtd, 1F, J = 282.6, 7.8, 5.7 Hz), 35.11 (ddt, 1F, J = 282.6, 8.0, 4.0 Hz). Anal. Calcd for $C_{18}H_9F_4NO_5$: C, 54.70; H, 2.30; N, 3.54. Found: C, 54.60; H, 2.33; N, 3.43.

General Procedure for the Synthesis of Compounds 3. A solution of R_F- or CCl_3-dihydropyrone or furanone (1.0 mmol), salicylaldehyde (1.0 mmol), piperidine (1.0 mmol), and concentrated H_2SO_4 (0.3 mmol) in anhydrous benzene (5 mL) was refluxed until the reaction was completed (TLC, Table 2). The reaction mixture was then evaporated, and the residue was washed with hexane. The solid product was recrystallized from hexane (or hexane/CH_2Cl_2) to give pure product **3** as light-yellow or yellow crystals.

7-Methoxy-2,2-dimethyl-10a-(trifluoromethyl)-2,3-dihydro-4*H*,10a*H*-pyrano[2,3-*b*]chromen-4-one (3c): mp 112−113 °C; IR (KBr) 1698, 1621, 1574, 1489 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.50 (s, 3H), 2.53 (d, 1H, J = 17.6 Hz), 2.74 (d, 1H, J = 17.6 Hz), 3.79 (s, 3H), 6.83 (d, 1H, J = 2.8 Hz), 6.95 (dd, 1H, J = 8.9, 2.8 Hz), 6.98 (d, 1H, J = 8.9 Hz), 7.72 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$/C_6F_6) δ 74.64 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 30.1, 49.8, 55.8, 97.5 (q, J = 34.0 Hz), 113.7, 116.8, 118.9, 119.4, 120.3, 122.3 (q, J = 291.9 Hz), 136.7, 147.4, 154.9, 193.0. Anal. Calcd for $C_{16}H_{15}F_3O_4$: C, 58.54; H, 4.61. Found: C, 58.52; H, 4.37.

2,2-Dimethyl-9a-(trichloromethyl)-9a*H*-furo[2,3-*b*]chromen-3(2*H*)-one (3g): mp 112−113 °C; IR (KBr) 1733, 1641, 1607, 1567, 1480, 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.62 (s, 3H), 7.08 (td, 1H, J = 7.5, 1.1 Hz), 7.15 (d, 1H, J = 8.2 Hz), 7.40−7.46 (m, 2H), 7.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 28.1, 86.4, 103.1, 104.1, 116.1, 119.3, 120.5, 122.9, 130.5, 134.0, 134.9, 154.7, 199.6. Anal. Calcd for $C_{14}H_{11}Cl_3O_3$: C, 50.41; H, 3.32. Found: C, 50.61; H, 3.38.

General Procedure for the Synthesis of *trans*-6. A solution of 2,6-bis(polyfluoroalkyl)pyrone **5** (1.0 mmol), salicylaldehyde (3.0 mmol), piperidine (2.5 mmol), and *p*-toluenesulfonic acid (2.0 mmol) in anhydrous benzene (10 mL) was refluxed for 15 h. The reaction mixture was then evaporated, and the residue was purified by chromatography (silica gel, benzene) and recrystallized from a mixture of hexane/CH_2Cl_2 (4:1) to give product *trans*-**6** as yellow or yellow-orange crystals.

General Procedure for the Synthesis of *cis*-6. A solution of 2,6-bis(polyfluoroalkyl)pyrone **5** (1.0 mmol), salicylaldehyde (3.0

(30) Appendino, G.; Cravotto, G.; Toma, L.; Annunziata, R.; Palmisano, G. *J. Org. Chem.* **1994**, *59*, 5556−5564.

mmol), $Me_2NH{\cdot}HCl$ (2.5 mmol), and AcONa (10 mol %) in anhydrous benzene (20 mL) was refluxed for 15−20 h. The reaction mixture was then filtered, the precipitate was washed with boiling benzene (3 × 5 mL), and the benzene solution was purified by chromatography (silica gel, benzene) and recrystallized from a mixture of hexane/CH_2Cl_2 (4:1) to give product *cis*-**6** as yellow crystals.

***trans*-5a,6a-Bis(trifluoromethyl)-5a*H*,6a*H*,13*H*-chromeno[3′,2′:5,6]pyrano[2,3-*b*]chromen-13-one (*trans*-6a):** yield 52%; mp 237−238 °C (subl.); IR (Nujol) 1681, 1626, 1605, 1568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08−7.16 (m, 4H), 7.38−7.48 (m, 4H), 7.91 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 75.67 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 97.6 (q, J = 36.4 Hz), 116.2, 117.5, 118.1, 121.7 (q, J = 291.5 Hz), 123.6, 130.6, 134.6, 137.4, 152.2, 178.9. Anal. Calcd for $C_{21}H_{10}F_6O_4$: C, 57.29; H, 2.29; F, 25.89. Found: C, 57.31; H, 2.20; F, 25.83.

***cis*-5a,6a-Bis(trifluoromethyl)-5a*H*,6a*H*,13*H*-chromeno[3′,2′:5,6]pyrano[2,3-*b*]chromen-13-one (*cis*-6a):** yield 56%; mp 201−202 °C; IR (Nujol) 1693, 1621, 1607, 1569 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06−7.15 (m, 4H), 7.34−7.44 (m, 4H), 7.64 (s, 2H); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 76.35 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.2 (q, J = 36.0 Hz), 116.0, 117.4, 119.1, 121.8 (q, J = 294.1 Hz), 123.3, 130.3, 134.1, 136.9, 153.2, 180.7. Anal. Calcd for $C_{21}H_{10}F_6O_4$: C, 57.29; H, 2.29; F, 25.89. Found: C, 57.35; H, 2.37; F, 25.78.

2,10a-Bis(trifluoromethyl)-4*H*,10a*H*-pyrano[2,3-*b*]chromen-4-one (7a). A solution of salicylaldehyde (1.0 mmol) and piperidine (2.0 mmol) in anhydrous benzene (10 mL) in the presence of a catalytic amount of *p*-toluenesulfonic acid (5 mol %) was refluxed for 2 h. The reaction mixture was then concentrated up to half of the volume and, after addition of *p*-TsOH (1.0 mmol) and 2,6-bis-(trifluoromethyl)-4*H*-pyran-4-one (2.0 mmol), was heated under reflux for 4 h. After evaporation of the solvent, the residue was purified by chromatography (silica gel, benzene) and then recrystallized from hexane/CH_2Cl_2 (4:1) to give product **7a** as yellow crystals. Yield 44%; mp 109−110 °C; IR (Nujol) 1681, 1651, 1624, 1613, 1571 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (s, 1H), 7.15−7.19 (m, 2H), 7.42 (dd, 1H, J = 7.7, 1.6 Hz), 7.49 (ddd, 1H, J = 8.2, 7.5, 1.6 Hz), 7.89 (d, 1H, J = 0.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 75.60 (s), 88.29 (s). Anal. Calcd for $C_{14}H_6F_6O_3$: C 50.02; H, 1.80; F, 33.91. Found: C, 49.95; H, 2.02; F, 33.79.

2,10a-Bis(difluoromethyl)-4*H*,10a*H*-pyrano[2,3-*b*]chromen-4-one (7b). This compound was prepared analogously to **7a** in 11% yield as light-yellow crystals (yield 64% from **8**). Mp 131−132 °C; IR (Nujol) 1674, 1648, 1624, 1609, 1572 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (t, 1H, J = 54.6 Hz), 5.97 (s, 1H), 6.18 (t, 1H, J = 53.7 Hz), 7.07−7.12 (m, 2H), 7.37 (dd, 1H, J = 7.7, 1.6 Hz), 7.43 (ddd, 1H, J = 8.1, 7.5, 1.6 Hz), 7.79 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 26.89 (dd, 1F, J = 292.5, 54.6 Hz), 28.59 (dd, 1F, J = 292.5, 54.6 Hz), 35.61 (dd, 1F, J = 308.9, 53.7 Hz), 36.98 (dd, 1F, J = 308.9, 53.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.4 (t, J = 27.8 Hz), 105.4 (td, J = 4.4, 1.5 Hz), 108.9 (t, J = 243.6 Hz), 112.9 (t, J = 256.0 Hz), 115.8, 117.6, 117.9, 123.6, 130.5, 134.0, 135.6, 150.6 (d, J = 0.8 Hz), 158.2 (ddd, J = 26.5, 25.5, 1.1 Hz), 179.1. Anal. Calcd for $C_{14}H_8F_4O_3$: C, 56.01; H, 2.69; F, 25.31. Found: C, 55.85; H, 2.63; F, 25.29.

2-Phenyl-10a-(trifluoromethyl)-4*H*,10a*H*-pyrano[2,3-*b*]chromen-4-one (7c). A mixture of 2-phenyl-6-(trifluoromethyl)-4*H*-pyran-4-one (1.0 mmol) and salicylaldehyde (4.0 mmol) in Et_3N (1 mL) was allowed to stand at room temperature for 2 weeks. The reaction mixture was evaporated under reduced pressure, and the resulting precipitate was purified by chromatography (silica gel, CH_2Cl_2). Then the CH_2Cl_2 solution was diluted with hexane and the crystalline material was collected by filtration to give product **7c** as light-yellow powder. Yield 56%; mp 187−188 °C; IR (Nujol) 1666, 1624, 1606, 1573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (s, 1H), 7.12−7.16 (m, 2H), 7.40 (dd, 1H, J = 7.7, 1.6 Hz), 7.44 (ddd, 1H, J = 8.2, 7.5, 1.6 Hz), 7.47−7.58 (m, 3H), 7.84−7.86 (m, 2H), 7.85 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 75.95 (s). Anal. Calcd for $C_{19}H_{11}F_3O_3$: C, 66.28; H, 3.22; F, 16.55. Found: C, 66.02; H, 3.23; F, 16.53.

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Supporting Information Available: General experimental details and X-ray crystal data of *trans*- and *cis*-**6a**; complete listing of IR and ^1H, ^{19}F NMR peaks and elemental analyses of compounds **2**, **3**, **6**, and **8**; copies of ^1H and ^{19}F NMR spectra for compounds **2c**,**e**,**h**,**i**,**j**,**o**,**r**,**t**,**x**, **3c**,**d**,**f**, *trans*- and *cis*-**6a**, and **7a**,**c**; copies of ^{13}C NMR spectra for **3c** and *trans*-**6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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