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Synthesis of 2-Perfluoroalkyl 4*H*- and 2*H*-Chromenylphosphonates Mediated by Amines and Phosphines

Blazej Duda,[†] Sergey N. Tverdomed,*[,†,‡] and Gerd-Volker Röschenthaler[†]

[†]*School of Engineering and Science, Jacobs University Bremen, Campus Ring 1, 28759 Bremen, Germany, and* [‡]*Department of Organic Chemistry, St. Petersburg State Institute of Technology (Technical University), Moskovskii pr. 26, St. Petersburg 190013, Russia*

s.tverdomed@jacobs-university.de

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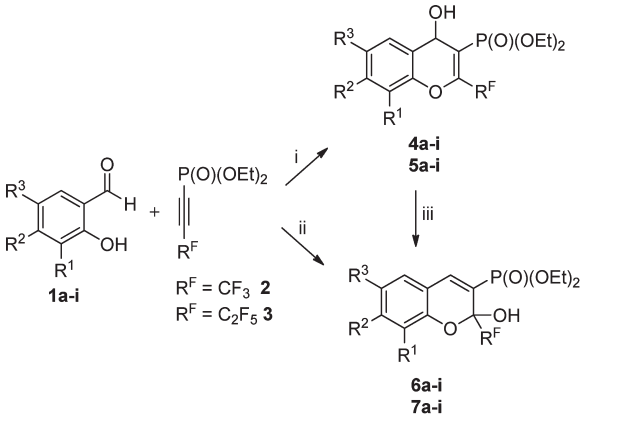

i: $R^4{}_2XR^5$ where X = N or P; DMSO, RT, 3-18h; ii: PPh_3, DMSO, RT, 4-18h; iii: 6 N HCl (10 mol%), CH_2Cl_2, RT, 6-18h.

An efficient synthesis of 2-perfluoroalkyl 4*H*-chromen-3-ylphosphonates **4a**−**i** ($R^F = CF_3$) and **5a**−**i** ($R^F = C_2F_5$) has been accomplished via regioselective cycloaddition of 2-hydroxybenzaldehydes to diethyl 3,3,3-trifluoropropyn-1-yl- and diethyl 3,3,4,4,4-pentafluorobutyn-1-ylphosphonate, using trialkyl amines or phosphines as mediators. 2*H*-Chromen-3-ylphosphonates **6a**−**i** were regioselectively obtained in the presence of triphenylphosphine. A convenient method for the isomerization of 4*H*-chromen-3-ylphosphonates into 2*H*-chromen-3-ylphosphonates **6a**−**i** ($R^F = CF_3$) and **7a**−**i** ($R^F = C_2F_5$) was established.

Introduction

Six-membered oxygen-containing heterocycles are of great interest as they are common fragments of many biologically active molecules and drugs.[1,2] Among them, special attention has been paid to 4*H*-chromenes which represent one of the most important class of such compounds connected to widespread applications in pharmaceutical and mechanistic studies of biochemical processes.[2] Until today, several 4*H*-chromenes have been proven to be efficient DNA polymerase β inhibitors (Miroestrol, **A**),[2a,b] antitrypanosomal agents (antibiotic Rhodomyrtone, **B**),[2c,d] antibacterial

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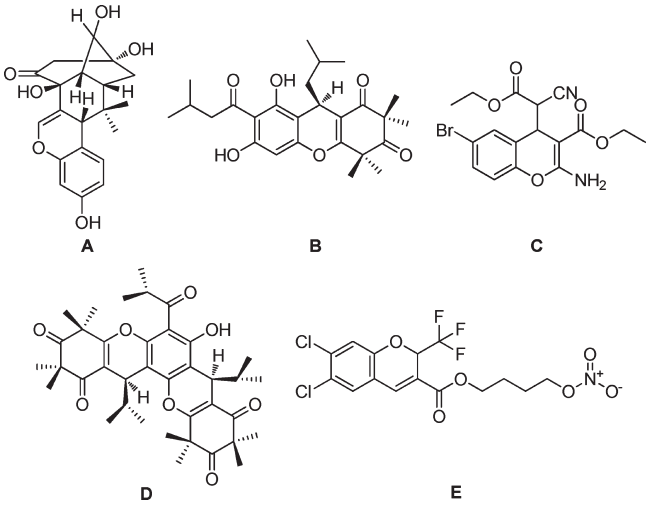
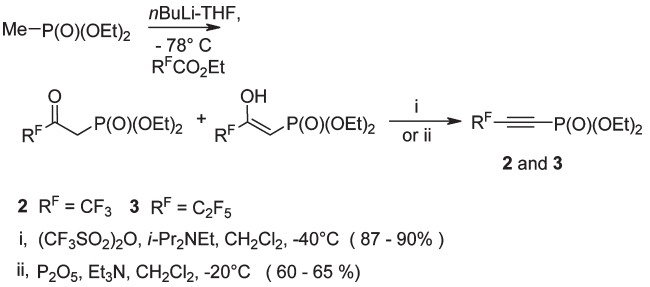
agents (α-glucosidase inhibitor myrtucommulone-E, **D**)[2e] or apoptosis inducers (**C**).[2f]



In contrast to 4*H*-chromenes, the use of 2*H*-chromenes as biologically active substances has not been widely studied but growing interest in the chemistry of these compounds is currently being observed.[2g−m] For instance, compound **E** carrying a trifluoromethyl substituent at the 2-position has been identified as a novel COX-2 selective inhibitor that donates nitric oxide, exhibiting analgesic and anti-inflammatory properties that facilitate wound healing.[1b]

The syntheses of 2,3-functionalized chromenes are mostly based on the Knoevenagel condensation of salicylaldehydes with 1,3-diketones[3] which generally offer poor possibilities for ring functionalization due to the limited availability of respective 1,3-diketones. To look for synthetic approaches that overcome this disadvantage, alternative routes using unsaturated carboxylic derivatives in reactions with various 2-hydroxybenzaldehydes have been accomplished.[4] These methods, however, are based on symmetrical substrates, therefore avoiding the regioselectivity of the process.[4] To the best of our knowledge, a synthetic methodology for phosphorus-containing chromenes has not yet been described.

SCHEME 1. Synthetic Pathway for the Synthesis of Corresponding Acetylenephosphonates 2 and 3



The presence of a phosphonate motif in a vast array of molecules has been shown to play a significant role in pharmaceutical researches.[5] The introduction of the phosphoryl group into the chromenyl ring could serve as a promising approach toward designing a novel class of phosphorus heterocycles with enhanced chemical and biological features. Consequently, to achieve the regioselectivity, the additional presence of an "active auxiliary" such as a perfluoroalkyl group would be necessary.[4f] This could be achieved by the use of highly electrophilic perfluoroacetylenephosphonates[6] as starting materials, whose synthesis has slightly been improved in our laboratory (Scheme 1).[7]

In this paper, we report a new convenient approach for the regioselective synthesis of 2*H*- and 4*H*-chromenes containing both the phosphoryl and perfluoralkyl substituents in the 3- and 2-position via the cycloaddition of various 2-hydroxybenzaldehydes to unsymmetrical perfluoroacetylenephosphonates. A useful method for the isomerization of 4*H*-chromenylphosphonates into 2*H*-chromenylphosphonates will also be disclosed.

Results and Discussions

Our first experiments involved the reaction of substituted 2-hydroxybenzaldehydes **1a**−**i** with diethyl 3,3,3-trifluoropropyn-1-ylphosphonate **2** or diethyl 3,3,4,4,4-pentafluorobutyn-1-ylphosphonate **3** and led to the corresponding 4*H*-chromen-3-ylphosphonates **4a**−**i** and **5a**−**i** in moderate to excellent yields (Table 1). The reaction proceeded smoothly by the action of equimolar amounts of substrates in dry DMSO and in the presence of *i*-Pr_2NEt at RT. The conversion of either **2** or **3** was monitored by ^{19}F and ^{31}P NMR spectroscopy and was completed at ambient temperature within a few hours. The crude products were purified by flash column chromatography and recrystallized from cyclohexane (Method A). Apparently, the cycloaddition was effectively influenced by the presence of substituents at both the 6-position electronically and the 8-position sterically. The electron-withdrawing effect of e.g.

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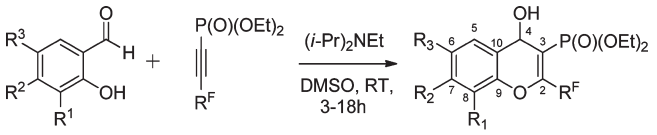
TABLE 1. Cycloaddition Reactions of Substituted Salicylaldehydes 1a−i with 2 and 3



1a-i **2** $R^F = CF_3$ **3** $R^F = C_2F_5$ **4a-i** $R^F = CF_3$ **5a-i** $R^F = C_2F_5$

entry	compd[a]	R^F	R^1	R^2	R^3	time (h)	yield[b] (%)
1	**4a**	CF_3	H	H	H	5	95
2	**4b**	CF_3	H	H	Me	5	94
3	**4c**	CF_3	H	H	OMe	13	42
4	**4d**	CF_3	H	H	Cl	8	61
5	**4e**	CF_3	H	H	NO_2	3	98
6	**4f**	CF_3	Br	H	Br	10	54
7	**4g**	CF_3	*t*-Bu	H	*t*-Bu	9	58
8	**4h**	CF_3	H	NEt_2	H	6	90
9	**4i**	CF_3	OMe	H	H	8	68
10	**5a**	C_2F_5	H	H	H	6	90
11	**5b**	C_2F_5	H	H	Me	6	91
12	**5c**	C_2F_5	H	H	OMe	18	30
13	**5d**	C_2F_5	H	H	Cl	11	50
14	**5e**	C_2F_5	H	H	NO_2	5	93
15	**5f**	C_2F_5	Br	H	Br	14	42
16	**5g**	C_2F_5	*t*-Bu	H	*t*-Bu	10	54
17	**5h**	C_2F_5	H	NEt_2	H	7	86
18	**5i**	C_2F_5	OMe	H	H	8	65

[a]Compounds were synthesized according to Method A. [b]Isolated yields.

NO_2− at the 6-position in compound **1e**, which tends to stabilize the phenolate **8** by resonance (Scheme 2), slightly increases the reactivity of **1e**, compared to salicylaldehyde **1a** (Table 1, entries 1 and 5). On the other hand, π-electron-donating groups, for instance Cl− (**1d**), Br− (**1f**), and MeO− (**1c**) in 2-hydroxybenzaldehyde at the 6-position, rendered the hydroxyl group less acidic and thus decreased its reactivity (Table 1, entries 3, 4, and 6), as was monitored by ^{19}F and ^{31}P NMR. We proposed that those differences in the reactivity of salicylaldehydes with acetylenephosphonates are connected to equilibrium of an acid−base-type reaction, where the concentration of the phenolate anion **8** is lower for electron-donating groups (EDG) compared to electron-withdrawing substituents (EWG). Apparently, electron-donating groups with lone pairs on the atoms adjacent to the π-system increase the nucleophilicity of the phenolate anion **8**, which subsequently might decompose the acetylenephosphonates **2** and **3**. We found that the more acidic and less nucleophilic hydroxyl group of salicylaldehydes **1** gave rise to a higher yield of cycloaddition products. In contrast, the reactivity of the salicylaldehyde with a methyl substituent at the 6-position of **1b** was observed to be similar to 2-hydroxybezaldehyde **1a**, possibly because of the absence of the mesomeric destabilization in phenolate **8** and its comparable nucleophilicity to unsubstituted **1a**.

The bulky *tert*-butyl substituent at the 8-position of **1g**, due to its steric hindrance and proximity to the hydroxyl group (ortho-position), reduces the ability of the latter to react with the triple bond of **2** and **3** and thus increases the reaction time (Table 1, entries 7 and 16). In contrast to the aforementioned examples, the presence of a strong π-electron-donating substituent at the 7-position, such as the diethylamino group, did not affect the overall reactivity of the salicylaldehyde **1h** compared to **1a**. However, compounds **4h** and **5h** were found to be acid-sensitive and thus could not be isolated and purified by a standard workup procedure due to their rapid and quantitative isomerization to 2*H*-chromenes **6h** and **7h** upon contact with silica gel. However, using neutral Al_2O_3, we isolated the corresponding 4*H*-chromenylphosphonates **4h** and **5h** in excellent yields (Table 1, entries 8 and 17). Generally, electron-withdrawing groups at the 6-position of a 2-hydroxybenzaldehyde have been demonstrated as key factors enabling cycloaddition to be more efficient and lead to respective heterocyclic compounds with very good results (Table 1).

At elevated temperatures, the yield of the target products **4a−i** and **5a−i** decreased. The ^{19}F and ^{31}P NMR analysis of reaction mixtures showed the presence of byproduct at $\delta_F = -75$ to -80 and at $\delta_P = 10$ to 14 ppm, respectively. These findings could be due to the thermal instability of intermediates formed from acetylenephosphonates **2** or **3** and salicylaldehydes **1a−i**. However, at lower temperatures (−20 to 0 °C) cyclization products were not detected.

A wide range of solvents were used for the synthesis of chromenes **4a−i** and **5a−i**, such as dichloromethane, *N*,*N*-dimethylformamide, tetrahydrofuran, dimethyl sulfoxide, and toluene (Table 2). The best results were observed for DMSO probably because of its solvation properties (Table 2, entries 13−15).[8] As expected, in the case of weaker solvating agents such as DCM and toluene, the yield of the products was noticeably reduced (Table 2, entries 1−3 and 10−12). Interestingly beside the high conversion of acetylenephosphonate **2** in DCM significant amounts of byproduct (ca. 25%) are also observed. Additional purification (second column chromatography) subsequently gave the target product with lower yields (Table 2, entries 1−3). When using DMF as a solvent in the reaction of 2-hydroxybenzaldehyde **1a** with **2** we obtained not only cyclization product **4a**, but also traces of the corresponding vinyl ether ($\delta_F \approx -70$ and $\delta_P \approx 10$ ppm) (Table 2, entries 4−6). The reaction carried out in THF did not proceed toward the chromenyl ring (Table 2, entries 7−9).

Such reactions (see Table 2) are dramatically affected by the choice of the mediator studied, such as tri-*n*-butylphosphine, tri-*tert*-butylphosphine, tricyclohexylphosphine, and methyldiphenylphosphine, or amines, e.g. *N*,*N*-diisopropyl-*N*-ethylamine and DABCO (1,4-diazabicyclo[2.2.2]octane). In this cycloaddition process the best results were achieved by using *i*-Pr_2NEt (Method A). DABCO showed a significant yield reduction in the case of compounds **4a** and **5a**. Also trivalent phosphorus compounds bearing cyclic and/or aliphatic substituents used furnished 4*H*-chromenes **4a−i** and **5a−i** in good yields. Taking $MePPh_2$, the reactivity of **1a** with **2** was found to be comparable with its trialkyl analogues. Thus, 2-perfluoroalkyl 4*H*-chromen-3-ylphosphonate **4a** was regioselectively obtained. In the absence of a mediator the reaction of 2-hydroxybenzaldehydes **1a−i** with either **2** or **3** did not proceed. Indeed, the hydroxyl group of **1a−i** was not nucleophilic enough to attack the triple bond of acetylene derivatives **2** or **3**. The structure of all perfluoroalkyl 4*H*-chromenylphosphonates **4a−i** and **5a−i** was established by ^1H, ^{19}F, ^{31}P, and ^{13}C NMR spectroscopy and mass spectrometry (ESI). Characteristic signals in the ^{19}F NMR spectra were found at $\delta_F = -66$ to -69 ppm for **4a−i**, at $\delta_F = -81$ to -83 ppm, $\delta_F = -112$ to -115 ppm for **5a−i** and for ^1H NMR a doublet at $\delta_H = 5.5$ ppm ($J_{H-P} = 4-8$ Hz). In the ^{13}C NMR spectra a

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SCHEME 2. Proposed Mechanism for the Formation of 4*H*- and 2*H*-Chromenes

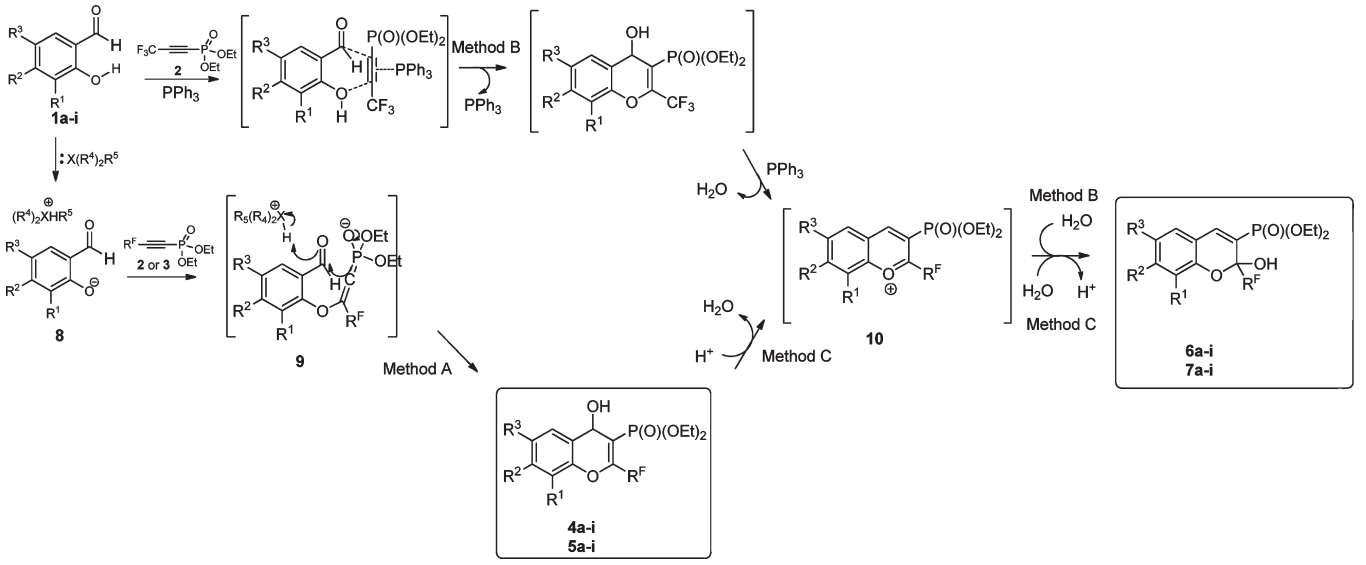
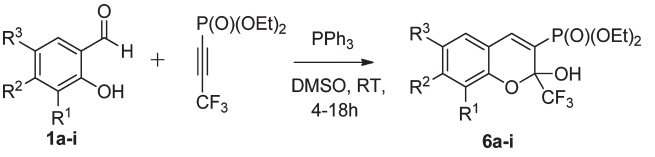


TABLE 2. Reaction of 2-Hydroxybenzaldehyde 1a with 2: Screening of Different Reaction Conditions

					yield[d] (%)	
entry	solvent	base	convn[c](%)	time (h)	4*H*-chromene	2*H*-chromene
1[b]	CH_2Cl_2	PPh_3	89	16		50
2[a]	CH_2Cl_2	*i*-Pr_2NEt	92	9	57	
3[a]	CH_2Cl_2	P(*n*-Bu)$_3$	91	10	56	
4[b]	DMF	PPh_3	60	10		58
5[a]	DMF	*i*-Pr_2NEt	67	8	60	
6[a]	DMF	P(*n*-Bu)$_3$	65	8	60	
7[b]	THF	PPh_3	0	24		
8[a]	THF	*i*-Pr_2NEt	0	24		
9[a]	THF	P(*n*-Bu)$_3$	0	24		
10[b]	toluene	PPh_3	55	15		40
11[a]	toluene	*i*-Pr_2NEt	60	10	45	
12[a]	toluene	P(*n*-Bu)$_3$	58	11	43	
13[b]	DMSO	PPh_3	95	6		92
14[a]	DMSO	*i*-Pr_2NEt	100	5	95	
15[a]	DMSO	P(*n*-Bu)$_3$	98	6	90	

[a]The reaction was carried out according to Method A. [b]The reaction was afforded according to Method B. [c]Reaction progress was monitored by ^{19}F and ^{31}P NMR. [d]Isolated yield.

TABLE 3. The Cycloaddition of 1a−i to 2 Mediated by Triphenylphosphine



entry	compd	R^1	R^2	R^3	time (h)	yield[a] (%)
1	**6a**	H	H	H	6	92
2	**6b**	H	H	Me	6	93
3	**6c**	H	H	OMe	14	40
4	**6d**	H	H	Cl	9	59
5	**6e**	H	H	NO_2	4	95
6	**6f**	Br	H	Br	11	51
7	**6g**	*t*-Bu	H	*t*-Bu	9	56
8	**6h**	H	NEt_2	H	8	86
9	**6i**	OMe	H	H	9	64

[a]Isolated yield.

quartet of doublets at δ_C = 145 to 148 ppm (J_{C-F} = 35−37 Hz, J_{C-P} = 17−18 Hz) of compounds **4a−i** was observed assigned to the C(2) carbon atom directly bonded to the perfluoroalkyl group. A characteristic doublet at δ_C = 60 to 63 ppm for C(4) with J_{C-P} = 7−10 Hz and a doublet for C(3) at $\delta_C \approx$ 110 ppm (J_{C-P} = 186−190 Hz) were detected for **4**,**5a−i**.

Further investigations revealed that the regioselectivity in the reaction of substituted salicylaldehydes **1a−i** with acetylene **2** (R^F = CF_3) in the presence of PPh_3 dramatically changed and the corresponding perfluoroalkyl 2*H*-chromenylphosphonates **6a−i** were formed (Table 3).

This phenomenon has not been explored before.[4e,g] Interestingly, when acetylene derivative **3** (R^F = C_2F_5) was reacted with **1a−i** in the presence of PPh_3, the regioselectivity was similar when other trivalent phosphines or amines were used. Perfluoroalkyl 4*H*-chromenylphosphonates **5a−i** have been thus isolated as sole products. The cycloaddition of **1a−i** with **2** was performed by using equimolar amounts of reagents and PPh_3 in dry DMSO at ambient temperature and was monitored by ^{19}F and ^{31}P NMR spectroscopy (Method B). We observed that the electronic and sterical features of substituents at 6-, 7-, and 8-positions in substrates **1a−i** as well as solvation effects of solvents (DMSO, DMF, DCM, toluene) and temperatures influenced the reaction progress and the yields of **6a−i**, in an analogous manner as for **4a−i** (Tables 1 and 3). We found that the reaction yield remained unchanged when the amount of the mediator increased but became lower when decreased. Therefore using catalytic amounts of the mediator prolonged the reaction time or applying elevated temperatures will be required. Moreover the increased amount of byproduct and lower yields of the target products were found.

The change in regioselectivity in the presence of various basic mediators and triphenylphosphine could be best explained by the different nature of intermediates **9** and **10** that determined the progress of the reaction. In the case of basic mediators, the phenolate anion **8** (Scheme 2) derived from

TABLE 4. 2*H*-Chromenes 6a−i and 7a−i Synthesized by the Isomerization Process of 4*H*-precursors 4,5a−i Catalyzed by 6 N HCl

entry	compd[a]	R^F	R^1	R^2	R^3	time (h)	yield[b] (%)
1	**6a**	CF_3	H	H	H	6	98
2	**6b**	CF_3	H	H	Me	6	97
3	**6c**	CF_3	H	H	OMe	7	97
4	**6d**	CF_3	H	H	Cl	8	98
5	**6e**	CF_3	H	H	NO_2	6	99
6	**6f**	CF_3	Br	H	Br	7	98
7	**6g**	CF_3	*t*-Bu	H	*t*-Bu	8	97
8	**6h**	CF_3	H	NEt_2	H	8	98
9	**6i**	CF_3	OMe	H	H	7	98
10	**7a**	C_2F_5	H	H	H	6	97
11	**7b**	C_2F_5	H	H	Me	7	96
12	**7c**	C_2F_5	H	H	OMe	8	97
13	**7d**	C_2F_5	H	H	Cl	7	98
14	**7e**	C_2F_5	H	H	NO_2	5	99
15	**7f**	C_2F_5	Br	H	Br	7	98
16	**7g**	C_2F_5	*t*-Bu	H	*t*-Bu	8	97
17	**7h**	C_2F_5	H	NEt_2	H	7	97
18	**7i**	C_2F_5	OMe	H	H	8	98

[a]Compounds were synthesized according to Method C. [b]Isolated yield.

the deprotonation of 2-hydroxybenzaldehyde derivatives **1a−i** by tertiary alkyl amines or phosphines (Method A), regioselectively reacted via a Michael-type addition with the more electrophilic carbon of the acetylenephosphonates' triple bond, containing a CF_3 (**2**) or C_2F_5 (**3**) group. As a result, a dipolar allene intermediate **9**[4e] has been formed that further intramolecularly cyclizes to give perfluoroalkyl 4*H*-chromenylphosphonates **4a−i** and **5a−i** (Scheme 2). Probably, the reaction of **1a−i** with **2** in the presence of PPh_3 proceeds through the 4*H*-chromenyl ring and consequently gives the appropriate 2*H*-chromenes **6a−i** (Method B). The elimination−addition of H_2O from the 4*H*-precursor might be achieved through the benzopyrrylium cation **10** (Scheme 2) according to Method B as well as through the acid-catalyzed isomerization of 4*H*-chromenes into 2*H*-chromenes (Method C). The function of PPh_3 in this cycloaddition reaction is not yet clear. However, the isomerization process of 4*H*-chromenes bearing carboxyl groups using mineral acids has already been examined.[4b,d]

Moreover, the role of DMSO in the stabilization of intermediates **9** and **10** in the enhancement of their reactivity might also consequently be explained. It is worth mentioning that the reactivity of **3** in the reaction with numerous 2-hydroxybenzaldehydes **1a−i** was noteworthy lower, compared to its CF_3-analogue **2** (Table 1). The same results have been detected in all cases, which is in agreement with other examples of cycloaddition reactions of these compounds, for instance Diels−Alder reaction[7] and 1,3-dipolar cycloaddition.[6]

Finally, we wish to report a facile method for the isomerization of 4*H*-chromenylphosphonates **4a−i** and **5a−i** into 2*H*-chromenylphosphonates **6a−i** and **7a−i** proceeding in the presence of a wide range of acids (Tables 4 and 5). The best results were observed at ambient temperatures in dichloromethane when 6 N HCl was used as a catalyst (Method C) (Table 5, entry 2). Under these conditions, 2*H*-chromenylphosphonates **6a−i** ($R^F = CF_3$) and **7a−i** ($R^F = C_2F_5$) were obtained in almost quantitative yields without further purification (Table 4). For compound **4a** the isomerization was also examined with other strong acids, for instance trifluoroacetic acid, triflic acid, *p*-toluenesulfonic acid, or sulfuric acid (Table 5), and took place smoothly in the absence of water (Table 5, entries 3−5 and 7). However, in the case of weak organic acids such as acetic acid the conversion of **4a** into the desired 2*H*-chromenylphosphonate **6a** was not found (Table 5, entry 6). As has been examined, 4*H*-chromenylphosphonates **5a−i** ($R^F = C_2F_5$) readily isomerize to give the corresponding 2*H*-chromenylphosphonates **7a−i** under similar conditions in very good yields (Table 4). However, it should be noted that the preparation of 2*H*-chromenylphosphonates **7a−i** using this isomerization process is the only straightforward route providing the aforementioned compounds that cannot be obtained by the cycloaddition route (Method B).

TABLE 5. The Isomerization Process of 4a into a Suitable 2*H*-Chromenylphosphonate 6a: Screening of Various Acids

entry	acid	convn[a] (%)	time (h)	yield[b] (%)
1	HCl (concd)	90	4	87
2	HCl (6 N)	100	4	97
3	TfOH	95	6	84
4	TsOH	85	6	78
5	H_2SO_4 (concd)	94	5	85
6	AcOH	∼5	10	0
7	TFA	97	5	89

[a]The reaction was monitored by ^{19}F and ^{31}P NMR . [b]Isolated yield.

The novel perfluoroalkyl 2*H*-chromenylphosphonates **6a−i** and **7a−i** were fully characterized by ^1H, ^{19}F, ^{31}P, and ^{13}C NMR spectroscopy. For these compounds the ^1H NMR spectra showed characteristic doublets belonging to the vinyl proton at C(4) at $\delta_H \approx 7.4$ ppm ($J_{H-P} = 18-20$ Hz). In the ^{19}F NMR spectra $\delta_F = -78$ to -80 ppm (CF_3) and AB-system (CF_2) $\delta_F = -121$ to -127 ppm, with the coupling constant $J_{AB} \approx 278$ Hz due to the diastereotopic effect of the CF_2 motif directly attached to the chiral center, were detected for compounds **7a−i** ($R^F = C_2F_5$). In the ^{13}C NMR spectra of these compounds, triplet of doublets belonging to C(2) substituted with perfluoroalkyl moiety at $\delta_C = 94$ to 96 ppm ($J_{C-F} = 30-35$ Hz, $J_{C-P} = 17-19$ Hz) were detected. The pentafluoroethyl group was seen as a quartet of triplets (CF_3) at around $\delta_C = 116$ to 118 ppm ($J_{C-F} = 283-289$ Hz, $J_{C-F} = 30-35$ Hz) and also as a triplet of quartets (CF_2) at $\delta_C = 112$ to 115 ppm ($J_{C-F} = 289-294$ Hz, $J_{C-F} = 34-36$ Hz). Moreover, the C(3) carbon atom connected with the phosphoryl group was split as a doublet at $\delta_C = 114$ to 117 ppm ($J_{C-P} = 187-191$ Hz). The CF_3 group for **6a−i** was found as a singlet at $\delta_F \approx -85$ ppm. In the ^{13}C NMR spectra of **6a−i**, the signals of C(2) and C(4) nuclei were split as a quartet of doublets at $\delta_C = 95$ to 97 ppm ($J_{C-F} = 30-34$ Hz, $J_{C-P} = 16-20$ Hz) and a doublet at $\delta_C = 140$ to 145 ppm ($J_{C-P} = 4-6$ Hz), respectively.

Conclusions

We herein report the first regioselective synthesis of 2-perfluoralkyl 4*H*-chromen-3-ylphosphonates as useful heterocycles with potential biological activities, via the cycloaddition of 2-hydroxybenzaldehyde derivatives to perfluoroacetylenephosphonates. 2*H*-Chromenylphosphonates bearing the CF_3 substituent were obtained under cycloaddition conditions or by isomerization of corresponding 4*H*-precursors. We also demonstrated a convenient route to C_2F_5-substitued 2*H*-chromenylphosphonates via acid-catalyzed isomerization. Factors influencing the regioselectivity of the processes and the reactivity of reagents were also discussed.

Experimental Section

Method A: Preparation of 4*H*-Chromene Derivative Mediated by Trialkyl Amine (Phosphine). The salicylaldehyde derivative (5 mmol) was dissolved in dry DMSO (20 mL) at ambient temperature.

Afterward an amine (5 mmol) was rapidly added and the mixture stirred for 10 to 15 min at RT. To the reaction mixture was added the acetylene (5 mmol) dropwise and an exothermic effect was observed. The solution was stirred for an additional 3 to 5 hours at room temperature and after that diluted with Et_2O (250 mL) and washed with H_2O (3 × 150 mL). The ethereal phases were combined and dried over $MgSO_4$, filtered off, and washed with diethyl ether (2 × 50 mL). The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with DCM:EtOAc (2:1 ratio) as eluent. The product was recrystallized from cyclohexane.

Diethyl (4-hydroxy-2-(trifluoromethyl)-4*H*-chromen-3-yl)phosphonate (4a): colorless crystals (95%); mp 106−110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, J = 7.1 Hz, 6H), 4.19 (m, 4H), 4.44 (br, 1H, OH), 5.77 (d, J_{H-P} = 4.6 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 6.9 Hz, 1H), 7.34 (t, J = 8.3 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 7.1 Hz), 62.1 (d, J_{C-P} = 4.8 Hz), 63.1 (d, J_{C-P} = 5.7 Hz), 106.9 (d, J_{C-P} = 190.7 Hz), 116.4, 117.4 (q, J_{C-F} = 279.2 Hz), 120.3 (d, J_{C-P} = 9.9 Hz), 125.9, 128.9, 130.4, 147.1 (qd, J_{C-F} = 38.3 Hz, J_{C-P} = 17.3 Hz), 148.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −66.4; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.4; MS ESI m/z [M − OH]$^+$ 335, [M + Na]$^+$ 375 (72%); HRMS (EI 70 eV) calcd for $C_{14}H_{16}F_3O_5P$ [M]$^{\bullet+}$ 352.06875, found 352.06903.

Diethyl (4-hydroxy-6-methyl-2-(trifluoromethyl)-4*H*-chromen-3-yl)phosphonate (4b): colorless crystals (94%); mp 68−71 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, J = 6.9 Hz, 6H), 2.35 (s, 3H), 4.19 (m, 4H), 4.37 (br, 1H, OH), 5.74 (d, J_{H-P} = 6.9 Hz, 1H), 7.02 (d, J = 8.7 Hz, 1H), 7.14 (dd, J = 8.2 Hz, J = 1.8 Hz, 1H), 7.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 20.9, 62.2 (d, J_{C-P} = 4.8 Hz), 63.1 (d, J_{C-P} = 4.8 Hz), 106.5 (d, J_{C-P} = 191.7 Hz), 116.2, 118.8 (q, J_{C-F} = 277.0 Hz), 119.9 (d, J_{C-P} = 9.6 Hz), 129.6, 130.6, 135.7, 146.4, 147.5 (qd, J_{C-F} = 32.6 Hz, J_{C-P} = 16.3 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −66.4; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.8; MS ESI m/z [M + Na]$^+$ 389, [2M + Na]$^+$ 755 (49%); HRMS (ESI) calcd for $C_{15}H_{18}F_3O_5PNa$ [M + Na]$^+$ 389.0742, found 389.0742.

Diethyl (4-hydroxy-6-methoxy-2-(trifluoromethyl)-4*H*-chromen-3-yl)phosphonate (4c): colorless crystals (42%); mp 74−76 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, J = 7.3 Hz, 6H), 3.76 (s, 3H), 4.19 (m, 4H), 5.22 (d, J_{H-P} = 5.5 Hz, 1H), 5.7 (br, 1H, OH), 6.85 (d, J = 8.7 Hz, 1H), 6.99 (d, J = 2.7 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 55.7, 63.4 (d, J_{C-P} = 5.7 Hz), 112.6, 116.3 (d, J_{C-P} = 188.8 Hz), 116.9, 119.2 (q, J_{C-F} = 253.9 Hz), 119.5, 143.3 (d, J_{C-P} = 5.2 Hz), 145.6 (qd, J_{C-F} = 39.0 Hz, J_{C-P} = 15.3 Hz), 146.2, 154.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −66.5; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.8; MS ESI m/z [M + Na]$^+$ 405; HRMS (ESI) calcd for $C_{15}H_{18}F_3O_6PNa$ [M + Na]$^+$ 405.0685, found 405.0690.

Diethyl (4-hydroxy-6-chloro-2-(trifluoromethyl)-4*H*-chromen-3-yl)phosphonate (4d): Colorless crystals (61%); mp 95−99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, J = 7.3 Hz, 6H), 4.19 (q, J = 7.3 Hz, 4H), 5.64 (d, J_{H-P} = 7.8 Hz, 1H), 7.03 (d, J = 8.7 Hz, 1H), 7.24 (dd, J = 8.7 Hz, J = 2.3 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1 (d, J_{C-P} = 6.7 Hz), 61.4 (d, J_{C-P} = 4.8 Hz), 63.2 (d, J_{C-P} = 4.8 Hz), 106.9 (d, J_{C-P} = 191.7 Hz), 117.9, 118.6 (q, J_{C-F} = 276.0 Hz), 122.8 (d, J_{C-P} = 9.6 Hz), 129.4, 129.7, 130.7, 146.9, 146.9 (qd, J_{C-F} = 39.3 Hz, J_{C-P} = 17.3 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −66.4; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.0; MS ESI m/z: [M+Na]$^+$ 409, [M+K]$^+$ 425 (64%); HRMS (ESI) Calcd for $C_{14}H_{15}ClF_3O_5PNa$ [M+Na]$^+$ 409.0190, found 409.0209.

Diethyl (4-hydroxy-6-nitro-2-(trifluoromethyl)-4*H*-chromen-3-yl)-phosphonate (4e): colorless crystals (98%); mp 107−110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (t, J = 6.9 Hz, 6H), 4.25 (m, 4H), 5.86 (br, 1H, OH), 6.06 (d, J_{H-P} = 5.5 Hz, 1H), 7.27 (d, J = 9.2 Hz, 1H), 8.22 (d, J = 9.2 Hz, 1H), 8.62 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 61.0 (d, J_{C-P} = 4.8 Hz), 63.6 (d, J_{C-P} = 5.7 Hz), 108.1 (d, J_{C-P} = 192.6 Hz), 117.6, 118.5 (q, J_{C-F} = 276.0 Hz), 122.8 (d, J_{C-P} = 9.6 Hz), 124.9, 126.5, 145.2, 146.7 (qd, J_{C-F} = 40.2 Hz, J_{C-P} = 17.2 Hz), 152.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −66.4; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 14.3; MS ESI m/z [M + Na]$^+$ 420, [2M + Na]$^+$ 817 (85%); HRMS (ESI) calcd for $C_{14}H_{15}F_3NO_7PNa$ [M + Na]$^+$ 420.0430, found 420.0436.

Diethyl (6,8-dibromo-4-hydroxy-2-(trifluoromethyl)-4*H*-chromen-3-yl)phosphonate (4f): brown crystals (54%); mp 115−118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, J = 6.9 Hz, 6H), 4.18 (m, 4H), 5.69 (br, 1H, OH), 5.77 (d, J_{H-P} = 5.9 Hz, 1H), 7.68 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 61.7 (d, J_{C-P} = 4.8 Hz), 63.5 (d, J_{C-P} = 6.7 Hz), 107.8 (d, J_{C-P} = 191.7 Hz), 111.3, 118.5 (q, J_{C-F} = 277.9 Hz), 124.3 (d, J_{C-P} = 9.6 Hz), 131.7, 135.5, 144.7, 146.4, 146.9 (qd, J_{C-F} = 39.3 Hz, J_{C-P} = 17.2 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −66.2; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 14.4; MS ESI m/z [M − H_2O]$^+$ 492 (42%), [M + Na]$^+$ 533 (96%), [M + K]$^+$ 549; HRMS (ESI) calcd for $C_{14}H_{14}Br_2F_3O_5PNa$ [M + Na]$^+$ 532.8790, found 532.8778.

Diethyl (6,8-di-*tert*-butyl-4-hydroxy-2-(trifluoromethyl)-4*H*-chromen-3-yl)phosphonate (4g): colorless crystals (58%); mp 79−81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 1.35 (m, 6H), 1.39 (s, 9H), 4.21 (m, 4H), 4.61 (d, J_{H-P} = 4.6 Hz, 1H), 5.78 (br, 1H, OH), 7.37 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 29.9, 31.4, 34.83, 34.9, 62.8 (d, J_{C-P} = 4.8 Hz), 63.5 (d, J_{C-P} = 4.8 Hz), 106.1 (d, J_{C-P} = 190.7 Hz), 119.0 (q, J_{C-F} = 277.9 Hz), 119.9 (d, J_{C-P} = 8.6 Hz), 124.1, 124.6, 137.0, 145.2, 146.7 (qd, J_{C-F} = 38.3 Hz, J_{C-P} = 17.2 Hz), 148.2; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −66.2; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.5; MS ESI m/z [M − HF]$^+$ 444, [M − H]$^+$ 463 (15%); HRMS (ESI) calcd for $C_{22}H_{32}F_3O_5PNa$ [M + Na]$^+$ 487.1832, found 487.1840.

Diethyl (7-(diethylamino)-4-hydroxy-2-(trifluoromethyl)-4*H*-chromen-3-yl)phosphonate (4h): orange crystals (90%); mp 91−93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (m, 6H), 1.24 (m, 6H), 3.24 (m, 4H), 4.10 (m, 4H), 5.51 (d, J_{H-P} = 6.1 Hz, 1H), 6.20 (d, J = 2.4 Hz, 1H), 6.46 (dd, J = 2.3 Hz, J = 8.7 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.3, 16.0 (d, J_{C-P} = 6.7 Hz), 44.6, 61.5 (d, J_{C-P} = 5.1 Hz), 62.8 (d, J_{C-P} = 6.0 Hz), 97.4, 106.2 (d, J_{C-P} = 187.3 Hz), 110.3, 119.4 (q, J_{C-F} = 288.5 Hz), 130.0, 131.1, 147.0 (qd, J_{C-F} = 35.0 Hz, J_{C-P} = 17.6 Hz), 148.8, 149.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −66.4; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.9; MS ESI m/z [M + Na]$^+$ 446 (87%), [2M + Na]$^+$ 869; HRMS (ESI) calcd for $C_{18}H_{25}F_3NO_5$-PNa [M + Na]$^+$ 446.1315, found 446.1319.

Diethyl (4-hydroxy-8-methoxy-2-(trifluoromethyl)-4*H*-chromen-3-yl)phosphonate (4i): colorless crystals (68%); mp 85−87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, J = 6.8 Hz, 6H), 3.89 (s, 3H), 4.19 (m, 4H), 4.33 (br, 1H, OH), 5.76 (d, J_{H-P} = 4.1 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 56.4, 62.1 (d, J_{C-P} = 4.8 Hz), 63.1 (d, J_{C-P} = 5.7 Hz), 106.7 (d, J_{C-P} = 191.7 Hz), 111.9, 120.2 (q, J_{C-F} = 276.0 Hz), 120.7, 121.3 (d, J_{C-P} = 8.6 Hz), 125.7, 138.5, 147.1 (qd, J_{C-F} = 39.3 Hz, J_{C-P} = 17.2 Hz), 147.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −66.1; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.6; MS ESI m/z [M + Na]$^+$ 405, [2M + Na]$^+$ 787 (23%); HRMS (ESI) calcd for $C_{15}H_{18}F_3O_6PNa$ [M + Na]$^+$ 405.0691, found 405.0887.

Diethyl (4-hydroxy-2-(pentafluoroethyl)-4*H*-chromen-3-yl)phosphonate (5a): colorless crystals (90%); mp 70−73 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, J = 6.9 Hz, 6H), 4.20 (m, 4H), 4.46 (br, 1H, OH), 5.81 (d, J_{H-P} = 6.9 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 7.26 (t, J = 7.3 Hz, 1H), 7.34 (t, J = 7.3 Hz, 1H), 7.52 (d, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 62.2 (d, J_{C-P} = 3.8 Hz), 63.1 (d, J_{C-P} = 7.1 Hz), 109.3 (tq, J_{C-F} = 287.0 Hz, J_{C-F} = 37.4 Hz), 109.7 (d, J_{C-P} = 172.5 Hz), 116.2, 118.4 (qt, J_{C-F} = 259.1 Hz, J_{C-F} = 33.4 Hz), 120.4 (d, J_{C-P} = 9.6 Hz), 126.0, 129.7, 147.1 (td, J_{C-F} = 30.7 Hz, J_{C-P} = 17.2 Hz), 148.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −81.5 (s, 3F), −114.6 (d, J_{F-P} = 23.1 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.8; MS ESI m/z [M + Na]$^+$ 425

(29%), $[2M + Na]^+$ 827; HRMS (ESI) calcd for $C_{15}H_{16}F_5O_5PNa$ $[M + Na]^+$ 425.0548, found 425.0558.

Diethyl (4-hydroxy-6-methyl-2-(pentafluoroethyl)-4*H*-chromen-3-yl)phosphonate (5b): colorless crystals (91%); mp 72−74 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, J = 6.9 Hz, 6H), 2.34 (s, 3H), 4.19 (m, 4H), 4.60 (br, 1H, OH), 5.76 (d, J_{H-P} = 6.9 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 7.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1 (d, J_{C-P} = 6.7 Hz), 20.9, 62.8 (d, J_{C-P} = 1.9 Hz), 63.3 (d, J_{C-P} = 5.7 Hz), 109.2 (d, J_{C-P} = 191.7 Hz), 109.4 (tq, J_{C-F} = 265.5 Hz, J_{C-F} = 39.4 Hz), 119.0 (qt, J_{C-F} = 277.0 Hz, J_{C-F} = 36.4 Hz), 128.9, 129.5, 130.5, 134.1, 135.7, 146.2, 147.2 (td, J_{C-F} = 29.7 Hz, J_{C-P} = 17.2 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −81.5 (s, 3F), −114.5 (d, J_{F-P} = 21.6 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.99; MS ESI m/z $[M - OH]^+$ 399, $[M + Na]^+$ 439 (20%), $[M + K]^+$ 455 (25%); HRMS (ESI) calcd for $C_{16}H_{18}F_5O_5PNa$ $[M + Na]^+$ 439.0710, found 439.0704.

Diethyl (4-hydroxy-6-methoxy-2-(pentafluoroethyl)-4*H*-chromen-3-yl)phosphonate (5c): colorless crystals (30%); mp 115−120 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, J = 7.3 Hz, 6H), 3.80 (s, 3H), 4.19 (m, 4H), 4.79 (br, 1H, OH), 5.77 (d, J_{H-P} = 6.9 Hz, 1H), 6.88 (dt, J = 9.2 Hz, J = 3.2 Hz, 1H), 7.00 (dt, J = 9.2 Hz, J = 3.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 7.8 Hz), 55.8, 62.8 (d, J_{C-P} = 4.8 Hz), 63.1 (d, J_{C-P} = 6.7 Hz), 108.2 (d, J_{C-P} = 190.7 Hz), 108.9 (tq, J_{C-F} = 260.7 Hz, J_{C-F} = 35.5 Hz), 112.1, 117.2, 117.2 (qt, J_{C-F} = 276.1 Hz, J_{C-F} = 20.1 Hz), 117.4, 120.9 (d, J_{C-P} = 9.6 Hz), 142.5, 147.2 (td, J_{C-F} = 29.7 Hz, J_{C-P} = 16.3 Hz), 157.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −81.4 (s, 3F), −114.4 (d, J_{F-P} = 26.0 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 16.1; MS ESI m/z $[M + Na]^+$ 455; HRMS (ESI) calcd for $C_{16}H_{18}F_5O_6PNa$ $[M + Na]^+$ 455.0653, found 455.0658.

Diethyl (4-hydroxy-6-chloro-2-(pentafluoroethyl)-4*H*-chromen-3-yl)phosphonate (5d): colorless crystals (61%); mp 95−99 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, J = 6.1 Hz, 6H), 4.21 (m, 4H), 4.83 (br, 1H, OH), 5.76 (d, J = 6.7 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 7.30 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.9 Hz), 62.2 (d, J = 5.4 Hz), 63.3 (d, J_{C-P} = 2.1 Hz), 104.2 (tq, J_{C-F} = 270.4 Hz, J_{C-F} = 32.5 Hz), 109.8 (d, J_{C-P} = 186.9 Hz), 121.6, 117.8 (d, J_{C-P} = 21.1 Hz), 116.3 (qt, J_{C-F} = 266.6 Hz, J_{C-F} = 35.4 Hz), 129.4, 130.0, 131.0, 146.7 (d, J_{C-P} = 4.8 Hz), 149.3 (td, J_{C-F} = 30.5 Hz, J_{C-P} = 17.0 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −81.5 (s, 3F), −114.7 (d, J_{F-P} = 18.3 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.3; MS ESI m/z $[M + Na]^+$ 459; HRMS (ESI) calcd for $C_{15}H_{15}ClF_5O_5PNa$ $[M + Na]^+$ 459.0158, found 459.0147.

Diethyl (4-hydroxy-6-nitro-2-(pentafluoroethyl)-4*H*-chromen-3-yl)-phosphonate (5e): colorless crystals (93%); mp 139−142 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, J = 6.9 Hz, 6H), 4.23 (m, 4H), 5.88 (br, 1H, OH), 6.25 (d, J_{H-P} = 5.0 Hz, 1H), 7.23 (d, J = 9.4 Hz, 1H), 8.21 (dd, J = 9.2 Hz, J = 2.7 Hz, 1H), 8.64 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 61.3 (d, J_{C-P} = 4.8 Hz), 63.6 (d, J_{C-P} = 5.7 Hz), 110.8 (d, J_{C-P} = 193.6 Hz), 109.2 (tq, J_{C-F} = 287.5 Hz, J_{C-F} = 36.4 Hz), 117.4, 118.0 (qt, J_{C-F} = 260.7 Hz, J_{C-F} = 40.3 Hz), 122.7 (d, J_{C-P} = 10.5 Hz), 124.9, 126.5, 145.3, 146.6 (td, J_{C-F} = 46.9 Hz, J_{C-P} = 17.3 Hz), 152.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −81.4 (s, 3F), −115.2 (d, J_{F-P} = 19.5 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 14.4; MS ESI m/z $[M + Na]^+$ 470; HRMS (ESI) calcd for $C_{15}H_{15}F_5NO_7PNa$ $[M + Na]^+$ 470.0399, found 470.0395.

Diethyl (6,8-dibromo-4-hydroxy-2-(pentafluoroethyl)-4*H*-chromen-3-yl)phosphonate (5f): colorless crystals (42%); mp 115−119 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (t, J = 6.9 Hz, 6H), 4.18 (q, J = 6.9 Hz, 4H), 5.48 (br, 1H, OH), 5.73 (d, J_{H-P} = 7.3 Hz, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.69 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d J_{C-P} = 6.7 Hz), 61.0 (d, J_{C-P} = 4.8 Hz), 63.4 (d, J_{C-P} = 5.7 Hz), 109.2 (tq, J_{C-F} = 288.5 Hz, J_{C-F} = 36.4 Hz), 110.5 (d, J_{C-P} = 192.6 Hz), 111.1, 118.1, 119.8 (qt, J_{C-F} = 256.9 Hz, J_{C-F} = 39.4 Hz), 124.3 (d, J_{C-P} = 10.5 Hz), 131.6, 135.6, 144.5, 146.9 (td, J_{C-F} = 30.6 Hz, J_{C-P} = 16.3 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −81.1 (s, 3F), −114.2 (d, J_{F-P} = 17.3 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 14.7; MS ESI m/z $[M + Na]^+$ 583; HRMS (ESI) calcd for $C_{15}H_{14}Br_2F_5O_5PNa$ $[M + Na]^+$ 582.8758, found 582.8766.

Diethyl (6,8-di-*tert*-butyl-4-hydroxy-2-(pentafluoroethyl)-4*H*-chromen-3-yl)phosphonate (5g): colorless crystals (54%); mp 68−71 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 1.34 (t, J = 7.2 Hz, 6H), 1.37 (s, 9H), 4.18 (m, 4H), 5.78 (d, J_{H-P} = 6.9 Hz, 1H), 7.36 (d, J = 2.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 29.7, 31.4, 34.42, 34.8, 60.5 (d, J_{C-P} = 5.8 Hz), 63.4 (d, J_{C-P} = 5.9 Hz), 111.2 (tq, J_{C-F} = 288.0 Hz, J_{C-F} = 35.6 Hz), 111.3 (d, J_{P-C} = 190.7 Hz), 116.6 (d, J_{C-P} = 13.5 Hz), 119.2 (qt, J_{C-F} = 264.9 Hz, J_{C-F} = 35.6 Hz), 124.0, 128.9, 137.9, 144.7, 147.4 (td, J_{C-F} = 29.9 Hz, J_{C-P} = 16.4 Hz), 147.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −81.4 (s, 3F), −115.2 (d, J_{F-P} = 17.3 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 16.2; MS ESI m/z $[M - OH]^+$ 497, $[M + Na]^+$ 537 (75%); HRMS (ESI) calcd for $C_{23}H_{32}F_5O_5PNa$ $[M + Na]^+$ 537.1805, found 537.1807.

Diethyl (7-(diethylamino)-4-hydroxy-2-(pentafluoroethyl)-4*H*-chromen-3-yl)phosphonate (5h): orange crystals (86%); mp 115−119 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00 (m, 6H), 1.16 (m, 6H), 3.23 (m, 4H), 4.03 (m, 4H), 5.00 (br, 1H, OH), 5.29 (d, J_{H-P} = 6.5 Hz, 1H), 6.14 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.2, 15.9 (d, J_{C-P} = 6.9 Hz), 45.1, 62.6 (d, J_{C-P} = 5.4 Hz), 64.5 (d, J_{C-P} = 4.8 Hz), 99.9, 106.1 (d, J_{C-P} = 190.3 Hz), 108.6, 109.0 (tq, J_{C-F} = 289.4 Hz, J_{C-F} = 33.0 Hz), 109.1 (d, J_{C-P} = 14.4 Hz), 109.6 (qt, J_{C-F} = 241.9 Hz, J_{C-F} = 33.5 Hz), 130.0, 143.5 (d, J_{C-P} = 4.8 Hz), 148.8 (td, J_{C-F} = 29.7 Hz, J_{C-P} = 19.6 Hz), 152.0, 154.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −78.3 (s, 3F), −125.1 (s, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 18.9; MS ESI m/z $[M + H]^+$ 474, $[M + Na]^+$ 496 (99%); HRMS (ESI) calcd for $C_{19}H_{24}F_5NO_5P$ $[M - H]^+$ 472.1308, found 472.1312.

Diethyl (4-hydroxy-8-methoxy-2-(pentafluoroethyl)-4*H*-chromen-3-yl)phosphonate (5i): colorless crystals (65%); mp 125−129 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, J = 7.3 Hz, 6H), 3.86 (s, 3H), 4.19 (m, 4H), 4.34 (br, 1H, OH), 5.80 (d, J_{H-P} = 6.9 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 56.5, 62.3 (d, J_{C-P} = 4.8 Hz), 63.1 (d, J_{C-P} = 6.7 Hz), 109.2 (d, J_{C-P} = 191.7 Hz), 109.4 (tq, J_{C-F} = 288.5 Hz, J_{C-F} = 36.4 Hz), 111.9, 118.5 (qt, J_{C-F} = 261.2 Hz, J_{C-F} = 39.3 Hz), 120.6, 121.3 (d, J_{C-P} = 9.6 Hz), 125.8, 138.5, 147.1 (td, J_{C-F} = 30.7 Hz, J_{C-P} = 16.3 Hz), 147.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −81.6 (s, 3F), −114.3 (d, J_{F-P} = 14.4 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.8; MS ESI m/z $[M + Na]^+$ 455, $[M - OH]^+$ 415 (37%), $[2M + Na]^+$ 887 (76%); HRMS (ESI) calcd for $C_{16}H_{18}F_5O_6PNa$ $[M + Na]^+$ 455.0653, found 455.0666.

Method B: Preparation of 2*H*-Chromene Derivative Mediated by Triphenylphosphine. The salicylaldehyde derivative (5 mmol) was dissolved in dry DMSO (20 mL) at ambient temperature. Afterward triphenylphosphine (5 mmol) was rapidly added and the mixture stirred for 5 min at RT. To the reaction mixture was added the acetylene (5 mmol) dropwise and an exothermic effect was observed. The solution was stirred for an additional 2−3 h at room temperature and after that diluted with Et_2O (250 mL) and then washed with H_2O (3 × 150 mL). The ethereal phases were combined and dried over $MgSO_4$, filtered off, and washed with diethyl ether (2 × 50 mL). The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with DCM:EtOAc (2:1 ratio) as eluent.

Diethyl (2-hydroxy-2-(trifluoromethyl)-2*H*-chromen-3-yl)phosphonate (6a): colorless crystals, 92% (Method B), 98% (Method C); mp 160−164 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, J = 6.8 Hz, 6H), 4.20 (m, 4H), 7.03 (d, J = 7.3 Hz, 2H), 7.20 (dd, J = 8.3 Hz, J = 1.9 Hz, 1H), 7.36 (dt, J = 7.8 Hz, J = 1.5 Hz, 1H), 7.48 (d,

J_{H-P} = 19.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5 (d, J_{C-P} = 6.7 Hz), 63.9 (d, J_{C-P} = 6.5 Hz), 95.9 (qd, J_{C-F} = 35.1 Hz, J_{C-P} = 16.4 Hz), 115.5 (d, J_{P-C} = 188.6 Hz), 116.5, 118.0 (d, J_{C-P} = 14.9 Hz), 122.5 (q, J_{C-F} = 290.9 Hz), 122.9, 129.3, 143.2 (d, J_{C-P} = 4.6 Hz), 152.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −86.5; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 16.1; MS EI 70 eV *m*/*z* $[M]^{\bullet+}$ 352; HRMS (EI 70 eV) calcd for $C_{14}H_{16}F_3O_5P$ $[M]^{\bullet+}$ 352.06875, found 352.06903.

Diethyl (2-hydroxy-6-methyl-2-(trifluoromethyl)-2*H*-chromen-3-yl)phosphonate (6b): colorless crystals, 93% (Method B), 97% (Method C); mp 100−105 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 (t, *J* = 6.9 Hz, 6H), 2.26 (s, 3H), 4.14 (m, 4H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.98 (s, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.39 (d, J_{H-P} = 19.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 4.3 Hz), 20.5, 63.6 (d, J_{C-P} = 4.8 Hz), 95.5 (qd, J_{C-F} = 35.6 Hz, J_{C-P} = 17.3 Hz), 114.6 (d, J_{C-P} = 187.8 Hz), 115.6, 117.4 (d, J_{C-P} = 14.4 Hz), 122.4 (q, J_{C-F} = 290.9 Hz), 129.1, 132.0, 134.3, 143.1, 150.4; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −85.5; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.8; MS ESI *m*/*z*: $[M - OH]^+$ 349, $[M + Na]^+$ 389 (4%), $[2M + Na]^+$ 755 (95%); HRMS (ESI) calcd for $C_{15}H_{18}F_3O_5PNa$ $[M + Na]^+$ 389.0742, found 389.0742.

Diethyl (2-hydroxy-6-methoxy-2-(trifluoromethyl)-2*H*-chromen-3-yl)phosphonate (6c): colorless crystals, 40% (Method B), 97% (Method C); mp 92−96 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, *J* = 7.3 Hz, 6H), 3.76 (s, 3H), 4.20 (m, 4H), 6.70 (s, 1H), 6.92 (m, 2H), 7.07 (br, 1H, OH), 7.41 (d, J_{H-P} = 19.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 55.8, 63.6 (d, J_{C-P} = 5.7 Hz), 95.5 (qd, J_{C-F} = 35.5 Hz, J_{C-P} = 16.3 Hz), 112.7, 115.6 (d, J_{C-P} = 186.9 Hz), 117.0, 117.9 (d, J_{C-P} = 15.3 Hz), 119.6, 122.4 (q, J_{C-F} = 291.4 Hz), 142.9 (d, J_{C-P} = 3.8 Hz), 146.4, 154.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −85.2; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.5; MS ESI *m*/*z* $[M - OH]^+$ 365 (6%), $[M + Na]^+$ 405 (15%), $[2M + Na]^+$ 787; HRMS (ESI) calcd for $C_{15}H_{18}F_3O_6PNa$ $[M + Na]^+$ 405.0685, found 405.0690.

Diethyl (2-hydroxy-6-chloro-2-(trifluoromethyl)-2*H*-chromen-3-yl)phosphonate (6d): colorless crystals, 59% (Method B), 98% (Method C); mp 84−87 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, *J* = 7.3 Hz, 6H), 4.22 (q, *J* = 7.3 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 2.3 Hz, 1H), 7.30 (dd, *J* = 8.7 Hz, *J* = 2.3 Hz, 1H), 7.37 (d, J_{H-P} = 19.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 5.7 Hz), 63.7 (d, J_{C-P} = 6.7 Hz), 95.7 (qd, J_{C-F} = 35.4 Hz, J_{C-P} = 16.3 Hz), 117.1 (d, J_{C-P} = 188.8 Hz), 117.6, 118.8 (d, J_{C-P} = 15.3 Hz), 122.2 (q, J_{C-F} = 290.4 Hz), 127.5, 128.2, 133.0, 141.6 (d, J_{C-P} = 4.8 Hz), 150.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −85.5; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 14.9; MS ESI *m*/*z* $[M - OH]^+$ 369 (36%), $[M + Na]^+$ 409 (21%), $[M + K]^+$ 425 (35%), $[2M + Na]^+$ 795; HRMS (ESI) calcd for $C_{14}H_{15}ClF_3O_5P$-Na $[M + Na]^+$ 409.0190, found 409.0209.

Diethyl (2-hydroxy-6-nitro-2-(trifluoromethyl)-2*H*-chromen-3-yl)phosphonate (6e): colorless crystals, 95% (Method B), 99% (Method C); mp 95−98 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, *J* = 6.9 Hz, 6H), 4.21 (m, 4H), 7.13 (d, *J* = 9.2 Hz, 1H), 7.57 (d, J_{H-P} = 19.2 Hz, 1H), 7.70 (br, 1H, OH), 8.17 (d, *J* = 2.3 Hz, 1H), 8.23 (dd, *J* = 9.2 Hz, *J* = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 64.3 (d, J_{C-P} = 6.7 Hz), 96.5 (qd, J_{C-F} = 35.5 Hz, J_{C-P} = 16.3 Hz), 117.1, 117.7 (d, J_{C-P} = 15.3 Hz), 118.4 (d, J_{C-P} = 190.7 Hz), 121.8 (q, J_{C-F} = 290.8 Hz), 124.7, 128.6, 141.2 (d, J_{C-P} = 4.8 Hz), 142.8, 156.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −84.7; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 13.1; MS ESI *m*/*z* $[M - OH]^+$ 380, $[M]^+$ 397 (18%), $[M + Na]^+$ 420 (25%), $[2M + Na]^+$ 817 (6%); HRMS (ESI) calcd for $C_{14}H_{15}F_3NO_7PNa$ $[M + Na]^+$ 420.0430, found 420.0436.

Diethyl (6,8-dibromo-2-hydroxy-2-(trifluoromethyl)-2*H*-chromen-3-yl)phosphonate (6f): brown crystals, 51% (Method B), 98% (Method C); mp 132−136 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 (t, *J* = 6.9 Hz, 6H), 4.18 (m, 4H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.34 (d, J_{H-P} = 19.0 Hz, 1H), 7.68 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (d, J_{C-P} = 5.7 Hz), 64.0 (d, J_{C-P} = 5.7 Hz), 96.6 (qd, J_{C-F} = 33.5 Hz, J_{C-P} = 19.2 Hz), 111.2, 114.6, 117.8 (d, J_{C-P} = 186.9 Hz), 120.3 (d, J_{C-P} = 15.3 Hz), 122.0 (q, J_{C-F} = 291.4 Hz), 130.3, 138.6, 140.9 (d, J_{C-P} = 4.8 Hz), 148.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −85.5; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 14.1; MS ESI *m*/*z*: $[M - OH]^+$ 493 (56%), $[M]^+$ 510 (7%), $[M + Na]^+$ 533, $[M + K]^+$ 549 (81%); HRMS (ESI) calcd for $C_{14}H_{14}Br_2F_3O_5PNa$ $[M + Na]^+$ 532.8790, found 532.8778.

Diethyl (6,8-di-*tert*-butyl-2-hydroxy-2-(trifluoromethyl)-2*H*-chromen-3-yl)phosphonate (6g): colorless crystals, 56% (Method B), 97% (Method C); mp 128−132 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 9H), 1.37 (t, *J* = 7.1 Hz, 6H), 1.41 (s, 9H), 4.21 (m, 4H), 7.04 (d, *J* = 2.3 Hz, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.47 (d, J_{H-P} = 20.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (d, J_{C-P} = 6.7 Hz), 29.7, 31.4, 34.4, 34.8, 63.5 (d, J_{C-P} = 4.8 Hz), 95.5 (qd, J_{C-F} = 34.7 Hz, J_{C-P} = 17.3 Hz), 113.1 (d, J_{C-P} = 188.8 Hz), 117.1 (d, J_{C-P} = 14.4 Hz), 122.4 (q, J_{C-F} = 290.9 Hz), 123.9, 128.7, 136.9, 144.4 (d, J_{C-P} = 4.8 Hz), 144.5, 148.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −84.3; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 16.0; MS ESI *m*/*z* $[M - OH]^+$ 447, $[2M + Na]^+$ 951 (26%); HRMS (ESI) calcd for $C_{22}H_{32}F_3O_5PNa$ $[M + Na]^+$ 487.1832, found 487.1840.

Diethyl (7-(diethylamino)-2-hydroxy-2-(trifluoromethyl)-2*H*-chromen-3-yl)phosphonate (6h): yellowish crystals (86%); mp 97−100 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (t, *J* = 6.9 Hz, 6H), 1.34 (t, *J* = 8.2 Hz, 6H), 3.35 (m, 4H), 4.17 (m, 4H), 6.25 (s, 2H), 6.99 (dd, *J* = 9.1 Hz, *J* = 1.8 Hz, 1H), 7.31 (d, J_{H-P} = 18.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.6, 16.3 (d, J_{C-P} = 6.9 Hz), 44.8, 63.1 (d, J_{C-P} = 6.0 Hz), 95.8 (qd, J_{C-F} = 34.5 Hz, J_{C-P} = 17.3 Hz), 97.5, 104.8 (d, J_{C-P} = 195.2 Hz), 105.8, 106.3 (d, J_{C-P} = 15.3 Hz), 122.8 (q, J_{C-F} = 291.4 Hz), 130.4, 143.3 (d, J_{C-P} = 4.8 Hz), 152.2, 154.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −86.3; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 18.6; MS ESI *m*/*z*: $[M + Na]^+$ 446 (87%), $[2M + Na]^+$ 869; HRMS (ESI) calcd for $C_{18}H_{25}F_3NO_5PNa$ $[M + Na]^+$ 446.1315, found 446.1319.

Diethyl (2-hydroxy-8-methoxy-2-(trifluoromethyl)-2*H*-chromen-3-yl)phosphonate (6i): colorless crystals, 64% (Method B), 98% (Method C); mp 140−145 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, *J* = 6.9 Hz, 6H), 3.86 (s, 3H), 4.19 (m, 4H), 6.83 (t, *J* = 6.5 Hz, 1H), 6.95 (m, 2H), 7.48 (d, J_{H-P} = 19.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 8.6 Hz), 56.5, 63.5 (d, J_{C-P} = 4.8 Hz), 96.7 (qd, J_{C-F} = 34.5 Hz, J_{C-P} = 16.3 Hz), 115.2 (d, J_{C-P} = 187.8 Hz), 116.6, 118.4 (d, J_{C-P} = 14.4 Hz), 120.7, 122.3, 122.3 (q, J_{C-F} = 291.4 Hz), 141.7, 143.3 (d, J_{C-P} = 4.8 Hz), 147.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −86.1; ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.4; MS ESI *m*/*z* $[M + Na]^+$ 405 (12%), $[2M + Na]^+$ 787; HRMS (ESI) calcd for $C_{15}H_{18}F_3O_6P$-Na $[M + Na]^+$ 405.0691, found 405.0870.

Method C: General Procedure for the Isomerization of 2-Perfluoralkyl 4*H*-Chromen-3-ylphosphonate Derivative into 2*H*-Chromenyl Analogues. The benzopyran derivative **4**,**5a**−**i** (2 mmol) was dissolved in dichloromethane (20 mL) at ambient temperature. A solution of 6 N HCl (10 mol %) was then slowly added and the mixture was stirred for 3−7 h at RT. Afterward solvents were removed under reduced pressure and the remaining solid was dried under vacuum (0.1 mmHg).

Diethyl (2-hydroxy-2-(pentafluoroethyl)-2*H*-chromen-3-yl)phosphonate (7a): colorless crystals (97%); **5a** (2 mmol), HCl (0.2 mmol); mp 137−141 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, *J* = 6.4 Hz, 6H), 4.21 (m, 4H), 6.99 (t, *J* = 7.3 Hz, 2H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.43 (d, J_{H-P} = 19.2 Hz, 1H), 7.54 (br, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 5.7 Hz), 63.7 (d, J_{C-P} = 6.7 Hz), 97.5 (td, J_{C-F} = 29.7 Hz, J_{C-P} = 17.2 Hz), 112.3 (tq, J_{C-F} = 288.5 Hz, J_{C-F} = 34.5 Hz), 114.5 (d, J_{C-P} = 187.8 Hz), 116.2, 117.7 (d, J_{C-P} = 15.3 Hz), 118.8 (qt, J_{C-F} = 283.2 Hz, J_{C-F} = 35.4 Hz), 122.6, 128.8, 133.5, 142.8 (d, J_{C-P} = 3.8 Hz), 152.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −78.1

(s, 3F), −124.2, −125.2 (AB-system, J_{AB} = 278.8 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 16.0; MS ESI m/z $[M + Na]^+$ 425; HRMS (ESI) calcd for $C_{15}H_{16}F_5O_5PNa$ $[M + Na]^+$ 425.0558, found 425.0548.

Diethyl (2-hydroxy-6-methyl-2-(pentafluoroethyl)-2*H*-chromen-3-yl)phosphonate (7b): colorless crystals (96%); **5b** (2 mmol), HCl (0.2 mmol); mp 114−116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, J = 6.4 Hz, 6H), 2.26 (s, 3H), 4.19 (m, 4H), 6.85 (d, J = 8.2 Hz, 1H), 6.98 (s, 1H), 7.13 (d, J = 8.2 Hz, 1H), 7.38 (d, J_{H-P} = 19.2 Hz, 1H), 7.57 (br, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 20.5, 63.7 (d, J_{C-P} = 5.7 Hz), 97.5 (td, J_{C-F} = 29.7 Hz, J_{C-P} = 17.2 Hz), 112.0 (tq, J_{C-F} = 289.4 Hz, J_{C-F} = 34.5 Hz), 114.3 (d, J_{C-P} = 186.9 Hz), 115.9, 117.5 (d, J_{C-P} = 15.3 Hz), 120.3 (qt, J_{C-F} = 266.4 Hz, J_{C-F} = 35.4 Hz), 129.0, 132.0, 134.2, 143.1 (d, J_{C-P} = 4.8 Hz), 150.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −78.9 (s, 3F), −124.1, −125.1 (AB-system, J_{AB} = 278.8 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 16.2; MS ESI m/z $[M + Na]^+$ 439; HRMS (ESI) calcd for $C_{16}H_{18}F_5O_5PNa$ $[M + Na]^+$ 439.0704, found 439.0710.

Diethyl (2-hydroxy-6-chloro-2-(pentafluorethyl)-2*H*-chromen-3-yl)phosphonate (7d): colorless crystals (98%); **5d** (2 mmol), HCl (0.2 mmol); mp 87−90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, J = 6.9 Hz, 6H), 4.17 (q, J = 7.3 Hz, 4H), 6.92 (d, J = 8.7 Hz, 1H), 7.19 (d, J = 1.8 Hz, 1H), 7.30 (dd, J = 8.7 Hz, J = 2.3 Hz, 1H), 7.35 (d, J_{H-P} = 19.2 Hz, 1H), 7.65 (br, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (d, J_{C-P} = 5.7 Hz), 63.9 (d, J_{C-P} = 4.8 Hz), 97.7 (td, J_{C-F} = 29.7 Hz, J_{C-P} = 17.3 Hz), 112.2 (tq, J_{C-F} = 274.1 Hz, J_{C-F} = 34.5 Hz), 116.1 (d, J_{C-P} = 186.9 Hz), 117.6, 118.9 (d, J_{C-P} = 21.1 Hz), 119.0 (qt, J_{C-F} = 266.6 Hz, J_{C-F} = 35.4 Hz), 127.6, 128.2, 133.2, 141.7 (d, J_{C-P} = 4.8 Hz), 150.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −78.6 (s, 3F), −124.5, −125.5 (AB-system, J_{AB} = 278.8 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.3; MS ESI m/z $[M + Na]^+$ 459, $[2M + Na]^+$ 895 (16%); HRMS (ESI) calcd for $C_{15}H_{15}ClF_5O_5PNa$ $[M + Na]^+$ 459.0147, found 459.0158.

Diethyl (2-hydroxy-6-nitro-2-(pentafluorethyl)-2*H*-chromen-3-yl)phosphonate (7e): colorless crystals (99%); **5e** (2 mmol), HCl (0.2 mmol); mp 120−124 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (t, J = 6.9 Hz, 6H), 4.22 (m, 4H), 7.08 (d, J = 9.2 Hz, 1H), 7.47 (d, J_{H-P} = 19.2 Hz, 1H), 7.89 (br, 1H, OH), 8.14 (s, 1H), 8.22 (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 7.6 Hz), 64.2 (d, J_{C-P} = 6.7 Hz), 98.3 (td, J_{C-F} = 30.6 Hz, J_{C-P} = 17.2 Hz), 111.9 (tq, J_{C-F} = 288.5 Hz, J_{C-F} = 34.5 Hz), 117.0, 117.9 (d, J_{C-P} = 15.3 Hz), 117.9 (d, J_{C-P} = 187.8 Hz), 118.6 (qt, J_{C-F} = 265.5 Hz, J_{C-F} = 35.4 Hz), 124.5, 128.6, 140.4 (d, J_{C-P} = 3.8 Hz), 142.8, 156.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −78.5 (s, 3F), −124.2, −125.3 (AB-system, J_{AB} = 280.3 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 14.1; MS ESI m/z $[M - OH]^+$ 430 (98%), $[M + Na]^+$ 470; HRMS (ESI) calcd for $C_{15}H_{15}F_5NO_7PNa$ $[M + Na]^+$ 470.0399, found 470.0395.

Diethyl (6,8-dibromo-2-hydroxy-2-(pentafluorethyl)-2*H*-chromen-3-yl)phosphonate (7f): colorless crystals (98%); **5f** (2 mmol), HCl (0.2 mmol); mp 123−127 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (t, J = 7.3 Hz, 6H), 4.19 (q, J = 7.3 Hz, 4H),7.25 (s, 1H), 7.32 (d, J_{H-P} = 19.2 Hz, 1H), 7.65 (s, 1H), 7.80 (br, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3 (d, J_{C-P} = 5.7 Hz), 64.0 (d, J_{C-P} = 6.7 Hz), 98.5 (td, J_{C-F} = 30.7 Hz, J_{C-P} = 15.3 Hz), 110.9, 111.8 (tq, J_{C-F} = 288.5 Hz, J_{C-F} = 34.5 Hz), 114.6, 117.8 (d, J_{C-P} = 188.8 Hz), 118.7 (qt, J_{C-F} = 266.5 Hz, J_{C-F} = 36.4 Hz), 120.3 (d, J_{C-P} = 15.3 Hz), 130.3, 138.5, 140.8 (d, J_{C-P} = 3.8 Hz), 148.6; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −78.0 (s, 3F), −123.9, −124.9 (AB-system, J_{AB} = 278.8 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 14.1; MS ESI m/z $[M + Na]^+$ 583; HRMS (ESI) calcd for $C_{15}H_{14}Br_2F_5O_5PNa$ $[M + Na]^+$ 582.8758, found 582.8766.

Diethyl (6,8-di-*tert*-butyl-2-hydroxy-2-(pentafluorethyl)-2*H*-chromen-3-yl)phosphonate (7g): colorless crystals (97%); **5g** (2 mmol), HCl (0.2 mmol); mp 68−71 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 1.33 (t, J = 7.1 Hz, 6H), 1.39 (s, 9H), 4.10 (m, 4H), 6.53 (br, 1H, OH), 7.05 (s, 1H), 7.44 (s, 1H), 7.50 (d, J_{H-P} = 19.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 29.7, 31.4, 34.4, 34.8, 63.3 (d, J_{C-P} = 5.8 Hz), 97.4 (td, J_{C-F} = 29.8 Hz, J_{C-P} = 16.4 Hz), 112.2 (tq, J_{C-F} = 288.0 Hz, J_{C-F} = 35.6 Hz), 114.3 (d, J_{C-P} = 190.7 Hz), 116.8 (d, J_{C-P} = 13.5 Hz), 118.9 (qt, J_{C-F} = 264.9 Hz, J_{C-F} = 35.6 Hz), 124.1, 128.8, 136.9, 143.7 (d, J_{C-P} = 3.8 Hz), 144.7, 147.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −77.7 (s, 3F), −121.6, −126.4 (AB-system, J_{AB} = 277.4 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.8; MS ESI m/z $[M - OH]^+$ 497 (65%), $[M + Na]^+$ 537; HRMS (ESI) calcd for $C_{23}H_{32}F_5O_5PNa$ 537.1805, found 537.1807.

Diethyl (7-(diethylamino)-2-hydroxy-2-(pentafluorethyl)-2*H*-chromen-3-yl)phosphonate (7h): orange crystals (97%); **5h** (2 mmol), HCl (0.2 mmol); mp 91−95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (t, J = 6.9 Hz, 6H), 1.35 (t, J = 7.3 Hz, 6H), 3.35 (q, J = 6.9 Hz, 4H), 4.18 (m, 4H), 6.18 (br, 1H, OH), 6.25 (dd, J = 8.7 Hz, J = 2.3 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 7.3 (d, J_{H-P} = 18.3 Hz, 1H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.5, 16.2 (d, J_{C-P} = 6.7 Hz), 44.8, 63.2 (d, J_{C-P} = 4.8 Hz), 97.4, 97.9 (td, J_{C-F} = 30.7 Hz, J_{C-P} = 18.2 Hz), 104.3 (d, J_{C-P} = 192.3 Hz), 105.6, 106.3 (d, J_{C-P} = 14.4 Hz), 112.4 (tq, J_{C-F} = 288.5 Hz, J_{C-F} = 35.4 Hz), 119.2 (qt, J_{C-F} = 247.3 Hz, J_{C-F} = 34.5 Hz), 130.3, 143.5 (d, J_{C-P} = 4.8 Hz), 152.1, 154.5; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −78.3 (s, 3F), −125.1 (s, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 18.9; MS ESI m/z $[M + H]^+$ 474, $[M + Na]^+$ 496 (99%); HRMS (ESI) calcd for $C_{19}H_{24}F_5NO_5P$ $[M - H]^+$ 472.1308, found 472.1312.

Diethyl (2-hydroxy-8-methoxy-2-(pentafluorethyl)-2*H*-chromen-3-yl)phosphonate (7i): colorless crystals (98%); **5i** (2 mmol), HCl (0.2 mmol); mp 135−140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, J = 6.8 Hz, 6H), 3.85 (s, 3H), 4.16 (m, 4H), 6.8 (dd, J = 6.6 Hz, J = 2.3 Hz, 1H), 6.94 (t, J = 6.6 Hz, 1H), 7.44 (d, J_{H-P} = 19.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (d, J_{C-P} = 6.7 Hz), 56.3, 63.7 (d, J_{C-P} = 6.7 Hz), 97.5 (td, J_{C-F} = 29.8 Hz, J_{C-P} = 17.3 Hz), 112.2 (tq, J_{C-F} = 288.0 Hz, J_{C-F} = 33.7 Hz), 114.4 (d, J_{C-P} = 187.8 Hz), 116.4, 118.4 (d, J_{C-P} = 14.5 Hz), 118.8 (qt, J_{C-F} = 265.8 Hz, J_{C-F} = 35.6 Hz), 120.4, 122.3, 141.7, 143.2 (d, J_{C-P} = 3.9 Hz), 147.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −78.5 (s, 3F), −124.5, −125.5 (AB-system, J_{AB} = 278.8 Hz, 2F); ^{31}P NMR ($CDCl_3$, 161 MHz) δ 15.9; MS ESI m/z $[M - OH]^+$ 415 (42%), $[M + Na]^+$ 455, $[2M + Na]^+$ 887 (15%); HRMS (ESI) calcd for $C_{16}H_{18}F_5O_6PNa$ $[M + Na]^+$ 455.0653, found 455.0666.

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Supporting Information Available: Copies of ^{1}H, ^{19}F, ^{31}P, and ^{13}C NMR spectra, and MS and HRMS spectrometry for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.