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Formal [3+3] cyclocondensations of 1,3-bis(silyloxy)-1,3-butadienes with 1-chloro-1,1-difluoro-4,4-dimethoxybut-3-en-2-one and 1,1-difluoro-4,4-dimethoxybut-3-en-2-one. Regioselective synthesis of fluorinated salicylates and pyran-4-ones

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ABSTRACT

The $TiCl_4$-mediated [3+3] cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 1-chloro-1,1-difluoro-4,4-dimethoxybut-3-en-2-one or 1,1-difluoro-4,4-dimethoxybut-3-en-2-one afforded CF_2Cl- and CF_2H-substituted salicylates, respectively. The Me_3SiOTf-mediated [3+3] cyclocondensation of the same building blocks provided CF_2Cl- and CF_2H-substituted pyran-4-ones and CF_2Cl-substituted cyclohexenones. The formation of CF_2H-substituted cyclohexenones was not observed. Besides the type of Lewis acid, the product distribution is also influenced by the substitution pattern of the 1,3-bis(silyloxy)-1,3-butadiene: The Me_3SiOTf mediated cyclization of C4-unsubstituted dienes resulted in the formation of CF_2Cl-substituted pyran-4-ones, while the cyclization of C4-substituted dienes afforded CF_2Cl-substituted cyclohexenones. The $TiCl_4$-mediated cyclization of C4-substituted dienes with 1,1-difluoro-4,4-dimethoxybut-3-en-2-one failed. Therefore, 3-substituted CF_2H-salicylates were prepared by transformation of the respective CF_2Cl-salicylates with tributyltin hydride.

The unique properties of fluorine-containing carba- and heterocycles are of considerable importance in organic and medicinal chemistry. The replacement of hydrogen by fluorine in organic molecules has often led to dramatic changes in their physicochemical and biological properties.[1,2] This has a drastic effect on the overall electronic distribution within the molecule thereby affecting dipole moments and the acidity, basicity or activity of neighboring groups; any of which can affect molecular interactions with receptors or other interacting molecules [3]. Therefore, the synthesis of fluorinated molecules plays an important role in drug discovery and many pharmaceuticals, such as well known ciprofloxacin, ofloxacin, or norfloxacin which all contain fluorine atoms [4,5]. In this context, fluorinated natural product analogues have been developed which often show a better biological activity than the natural products themselves. Last but not the least, highly fluorinated arenes show a very good solubility in fluorophilic solvents. These properties make them excellent ligands for catalytic reactions in fluorous biphase systems [6] and useful organocatalysts [7].

A large number of methods have been developed for the introduction of fluorine into different organic compounds [8]. In particular, transition-metal-catalyzed and organo-catalyzed C–F and C–CF_3 bond-forming reactions, on both aromatic rings and aliphatic chains, were explored in recent years [9,10]. However, molecules containing a CF_2Cl- or CF_2H group have been studied much more rarely. These molecules can be interesting for pharmacological studies, like antibacterial and cytotoxicity screenings, and investigations of AChE inhibitions. In fact, CF_2H-substituted arenes have been reported to be of considerable pharmacological relevance, for example, as tyrosine kinase inhibitors [11].

CF_2Cl-substituted arenes have been prepared by reaction of arenes with bis(chlorodifluoroacetyl)peroxide [12], by UV-mediated reaction of difluoromethylarenes with chlorine [13], reaction of (ethylthio)difluoromethyl-arenes with BrF_3 [14] and fluorination of trichloromethyl-arenes (using Olah's reagent or KF in ionic liquids) [15]. CF_2H-substituted arenes can be prepared by direct introduction of fluorine into the desired positions of organic compounds (e.g. benzaldehyde) using fluorinating agents, such as

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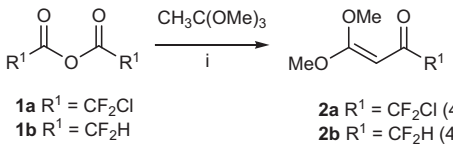
sulfur tetrafluoride [16], 4-*tert*-butyl-2,6-dimethylsulfur-trifluoride [17] and dimethylaminosulfur-trifluoride (DAST) [18]. All these methods rely on the fluorination or chlorination of suitable benzene derivatives. Despite their utility, they have severe drawbacks with regard to the preparative scope. Moreover, some halogenation reagents are toxic and the starting materials, functionalized benzene derivatives, are not readily available.

An alternative strategy for the synthesis of halogenated arenes relies on the application of a building block strategy. In recent years, we have studied various cyclization reactions of 1,3-bis(silyloxy)-1,3-butadienes with electrophiles and found that the type of Lewis acid can have an important influence on the regioselectivity of cyclization [19–22]. Recently, the synthesis of 1-chloro-1,1-difluoro-4,4-dimethoxybut-3-en-2-one [23] and its diethoxy derivative [24] and their reactions with a primary amine have been studied. Furthermore Grée et al. described the synthesis of pyrimidine derivatives containing a difluoromethyl side chain starting with easily accessible propargylic fluoride building blocks [25].

Herein, we report the first cyclocondensation reactions of 1,3-bis(silyloxy)-1,3-butadienes with 1-chloro-1,1-difluoro-4,4-dimethoxybut-3-en-2-one and 1,1-difluoro-4,4-dimethoxybut-3-en-2-one. These reactions provide a convenient approach to CF_2Cl and CF_2H salicylates and pyran-4-ones which are not readily available by other methods. The products, fluorinated salicylates and pyran-4-ones, are of general interest as potentially biologically relevant analogues of natural products and drugs.

1. Results and discussion

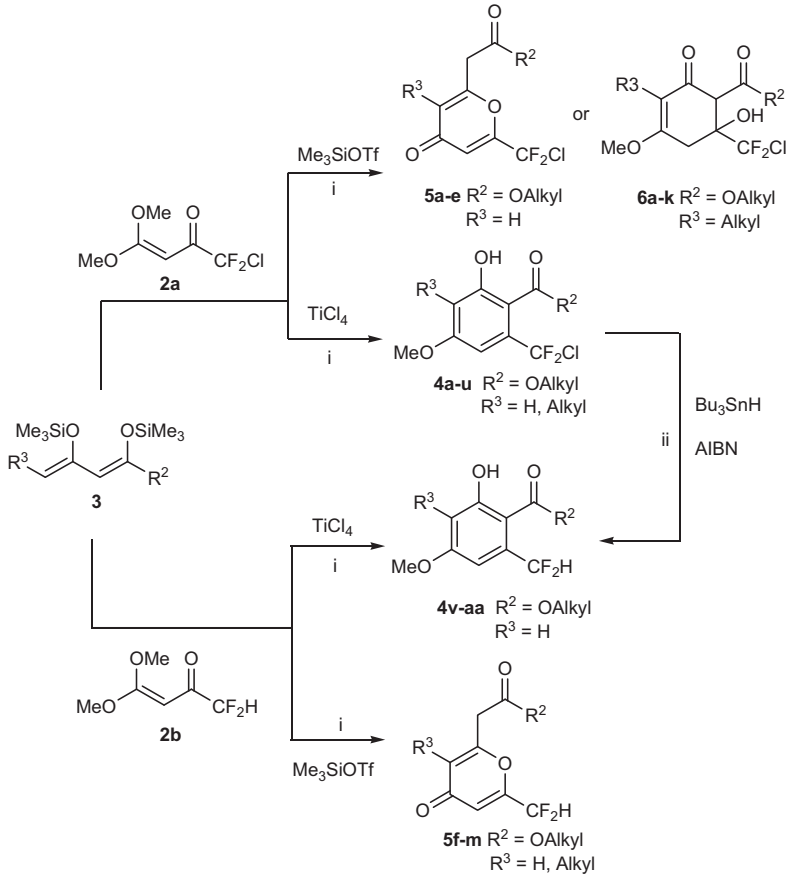
1-Chloro-1,1-difluoro-4,4-dimethoxybut-3-en-2-one 2a and 1,1-difluoro-4,4-dimethoxybut-3-en-2-one 2b were prepared by reaction of chlorodifluoroacetic anhydride 1a or difluoro acetic anhydride (1b) with 1,1,1-trimethoxyethane (Scheme 1) [23,26]. 1,3-Bis(silyloxy)-1,3-butadienes 3a-x were prepared according to the literature from the corresponding β-ketoester in two steps [20,27,28].



Scheme 1. Synthesis of **2a,b**: i, pyridine, CH_2Cl_2, 0 → 20 °C, 18 h.

The reaction of **2a,b** with 1,3-bis(silyloxy)-1,3-butadienes **3a-v**, carried out in the presence of $TiCl_4$, afforded the salicylates **4a**–**aa**, with excellent regioselectivity in moderate to good yields (Scheme 2, Table 1). The CF_2Cl and the CF_2H groups were located *ortho* to the ester moiety. The formation of the *para* regioisomer was not observed.

The yields depend on the type of diene employed. It is noteworthy that the presence of long alkyl groups located at the terminal carbon atom of the diene afforded the expected salicylates (**4m**,**n**,**q**), albeit, in lower yields. The moderate yields can be explained by steric hindrance and competing $TiCl_4$-mediated oxidative dimerization of the diene as a side-reaction. This type of process has been previously reported [29]. In some reactions, the formation of a small amount of β-ketoester, formed by hydrolysis of the diene, was observed. Its chromatographic separation from the product was difficult in some cases. Therefore, practical problems during the chromatographic purification also influenced the yields. The synthesis of C-3-substituted CF_2H-salicylates ($R^3 \neq H$) was *not* possible.



Scheme 2. Synthesis of **4**, **5** and **6**: i, CH_2Cl_2, −78 → 20 °C, 12–14 h; ii, benzene, 90 °C, 20 h.

Table 1
Synthesis of **4a–aa**.

2	3	4	R^1	R^2	R^3	%[a] [4]
a	**a**	**a**	CF_2Cl	OMe	H	86
a	**b**	**b**	CF_2Cl	OEt	H	50
a	**c**	**c**	CF_2Cl	O*i*Pr	H	50
a	**d**	**d**	CF_2Cl	O*i*Bu	H	56
a	**e**	**e**	CF_2Cl	OBn	H	50
a	**f**	**f**	CF_2Cl	$O(CH_2)_2OMe$	H	48
a	**g**	**g**	CF_2Cl	OMe	Me	68
a	**h**	**h**	CF_2Cl	OMe	Et	89
a	**i**	**i**	CF_2Cl	OMe	*i*Pr	69
a	**j**	**j**	CF_2Cl	OMe	*n*Pr	62
a	**k**	**k**	CF_2Cl	OEt	Et	42
a	**l**	**l**	CF_2Cl	OEt	*n*Pent	57
a	**m**	**m**	CF_2Cl	OMe	*n*Hex	30
a	**n**	**n**	CF_2Cl	OEt	*n*Hept	31
a	**o**	**o**	CF_2Cl	OMe	*n*Oct	55
a	**p**	**p**	CF_2Cl	OMe	*n*Dodec	42
a	**q**	**q**	CF_2Cl	OMe	*n*Hexadec	30
a	**r**	**r**	CF_2Cl	OMe	$BnCH_2$	40
a	**s**	**s**	CF_2Cl	OMe	$Cl(CH_2)_4$	35
a	**t**	**t**	CF_2Cl	OMe	$Cl(CH_2)_3$	36
a	**u**	**u**	CF_2Cl	OMe	MeO	42
b	**a**	**v**	CF_2H	OMe	H	35
b	**b**	**w**	CF_2H	OEt	H	33
b	**e**	**x**	CF_2H	OBn	H	30
b	**c**	**y**	CF_2H	O*i*Pr	H	58
b	**f**	**z**	CF_2H	$O(CH_2)_2OMe$	H	30
b	**v**	**aa**	CF_2H	OnBu	H	37

[a] Yields of isolated products.

The reaction conditions were optimized for the synthesis of salicylates **4a** and **4y** (Table 2). It is obvious that the temperature and the stoichiometry play an important role. The best yield was obtained when the solution was slowly warmed from −78 to 20 °C. The reaction was carried out in a concentrated solution using an excess (2.0 equiv.) of the diene.

The structures were confirmed by spectroscopic methods. The hydroxyl proton of salicylates **4a–aa** showed low field resonances ($\delta \sim 11.00$ ppm, ^{1}H NMR) which indicates that the protons are involved in an intramolecular hydrogen bond O–H···O. The carbon atoms were unambigiously assigned by analysis of the C–F coupling constants (J_{C-F}) in the ^{13}C NMR-spectra and by 2D NMR experiments. The absence of any J_{C-F} coupling at C-3 (Fig. 1) prooves that the CF_2Cl group is located *ortho* to the ester group.

Besides routine IR spectroscopy, RAMAN experiments were carried out for derivatives **4g** and **4r**. Broad signals were observed in the region of ca. 150 cm^{-1} which are diagnostic for intermolecular hydrogen bonds. Strong signals are observed at 1300 cm^{-1} (C–F stretch vibrations) and 1450 cm^{-1} (C–Cl stretch vibrations). As expected from the 2:1 ratio of fluorine and chlorine atoms present in the CF_2Cl group, the intensity of the C–F signal is two times higher than the C–Cl signal. These signals are much more pronounced in RAMAN compared to IR spectra. Two signals were detected, during IR experiments, in the region of 1650 cm^{-1}

Table 2
Optimization of the synthesis of **4a** and **4y**.

	Ratio of **2**:**3** [mmol]	V (CH_2Cl_2) [mL]	Yield (**4**) [%][a]
4a	1:2	2	86
	1:2	5	72
	1:3	2	82
	1:1	2	48
4y	1:2	2	48
	1:2	5	58
	1:2	10	55
	1:1	5	38
	1:3	5	42

[a] Yields of isolated products.

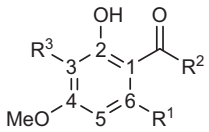


Fig. 1. Numbering of salicylates **4a–aa**.

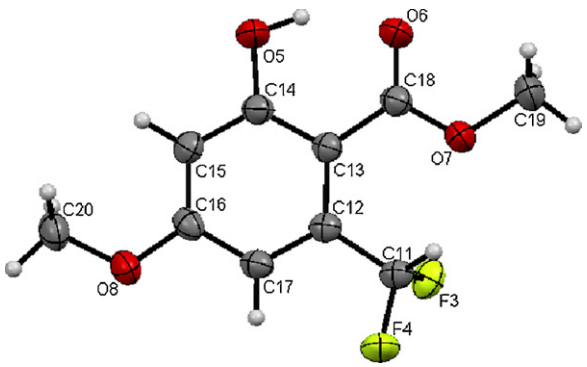


Fig. 2. Ortep drawing of **4v**.

assigned to the C=O stretch vibration of the ester group and of the C–O stretch vibration of the OH group. The signals indicate that both groups are involved in an intramolecular hydrogen bond.

The structure of product **4v** was independently confirmed by X-ray structure analysis (Fig. 2).[30]

The reaction of **2a** with 1,3-bis(silyloxy)-1,3-butadienes **3**, carried out in the presence of Me_3SiOTf, resulted in the formation of CF_2H-substituted 4H-pyran-4-ones **5a–m** and CF_2Cl-substituted cyclohexenones **6a–k** (Scheme 1, Table 3). On the other hand, the reaction of **2b** with 1,3-bis(silyloxy)-1,3-butadienes **3**, carried out in the presence of Me_3SiOTf, yielded the CF_2H-substituted 4H-pyran-4-ones **5f–m** (Scheme 1, Table 3). The formation of cyclohexenones was not observed.

It is obvious that the reactions of **2a** with 4-unsubstituted dienes (R^3 = H) afforded pyran-4-ones **5a–e**, while the reaction

Table 3
Synthesis of **5a–m** and **6a–k**.

2	3	5/6	R^1	R^2	R^3	%	
						5	**6**
a	**a**	**5a**	CF_2Cl	OMe	H	32	–
a	**b**	**5b**	CF_2Cl	OEt	H	44	–
a	**c**	**5c**	CF_2Cl	O*i*Pr	H	51	–
a	**d**	**5d**	CF_2Cl	O*i*Bu	H	43	–
a	**f**	**5e**	CF_2Cl	$O(CH_2)_2OMe$	H	50	–
b	**b**	**5f**	CF_2H	OEt	H	60	–
b	**c**	**5g**	CF_2H	O*i*Pr	H	57	–
b	**d**	**5h**	CF_2H	O*i*Bu	H	52	–
b	**g**	**5i**	CF_2H	OMe	Me	31	–
b	**h**	**5j**	CF_2H	OMe	Et	45	–
b	**k**	**5k**	CF_2H	OEt	Et	31	–
b	**j**	**5l**	CF_2H	OMe	*n*Pr	32	–
b	**w**	**5m**	CF_2H	OMe	*n*Non	26	–
a	**g**	**6a**	CF_2Cl	OMe	Me	–	32
a	**h**	**6b**	CF_2Cl	OMe	Et	–	56
a	**l**	**6c**	CF_2Cl	OEt	*n*Pent	–	57
a	**x**	**6d**	CF_2Cl	OEt	*n*Hex	–	57
a	**n**	**6e**	CF_2Cl	OEt	*n*Hept	–	58
a	**o**	**6f**	CF_2Cl	OMe	*n*Oct	–	57
a	**w**	**6g**	CF_2Cl	OMe	*n*Non	–	46
a	**p**	**6h**	CF_2Cl	OMe	*n*Dodec	–	64
a	**q**	**6i**	CF_2Cl	OMe	*n*Hexadec	–	80
a	**y**	**6j**	CF_2Cl	OMe	*i*Bu	–	80
a	**z**	**6k**	CF_2Cl	OMe	Cl	–	52

[a] Yields of isolated products.

Table 4
Optimization of the synthesis of **5c**, **5f** and **6a**.

	Ratio of **2**:**3** [mmol]	V (CH_2Cl_2) [mL]	Yield (**5**) [%][a]
5c	1:2	10	51
	1:2	5	41
	1:2	15	36
	1:3	10	49
	1:1	10	22
5f	1:2	5	34
	1:2	10	60
	1:2	15	55
6a	1:2	10	32
	1:2	5	23
	1:2	15	30

[a] Yields of isolated products.

with dienes containing an alkyl or a chloride group located at carbon C-4 ($R^3 \neq H$) of the diene afforded cyclohexenones **6a–k**. In contrast, the reaction of substrate **2b** led only to the formation of pyran-4-ones **5f–m**. All products were obtained in moderate to good yields and the cyclohexenones were formed with very good 1,2-diastereoselectivity (*vide infra*).

The Me_3SiOTf-mediated reaction was optimized for products **5c**, **5f** and **6a** (Table 4). The best yield was obtained when an excess of diene **3** was employed. In contrast to the $TiCl_4$-mediated reaction, which is carried out in a highly concentrated solution (c(**2**) = 0.5 M), the yield of **5** and **6** can be improved when the reaction is carried out in a more dilute solution (c(**2**) = 0.1 M). However, the change of the solvent from dichloromethane to acetone and tetrahydrofuran failed.

The structures of all products were confirmed by spectroscopic methods. The CF_2Cl-substituted cyclohexenones **6a–k** show interesting spectroscopic properties. The two fluorine atoms of the CF_2Cl-group are diastereotopic (Fig. 3). Therefore, two signals are observed in the ^{19}F NMR spectra at $\delta \approx -64$ ppm and $\delta \approx -66$ ppm. The ^1H NMR spectra of **6a–k** show two characteristic doublets in the range of $\delta = 2.80–3.10$ ppm for protons H-5 ($^2J \approx 17.7$ Hz). The proton of the OH group appears as a singlet at $\delta \approx 5.66$ ppm. The chemical shift suggests that the latter is not involved in an intramolecular hydrogen bond in the solution.

The structures of **6b,e,k** were independently confirmed by X-ray crystal structure analysis (Figs. 4–6) [30]. The crystal structures unambiguously prove the relative configuration of these molecules. The hydroxyl and the ester group are located cis to each other. In the solid state an intramolecular hydrogen bond O–H···O is present. In solution, beside the major isomer, a small amount of the minor isomer is detected.

Under the conditions of mass spectrometry (EI, electron ionization), elimination of water from cyclohexenones **6** is observed and only the molecular ions of the aromatized products can be detected. The correct molecular ions are observed when the measurements are carried out using the milder ESI technique (electrospray ionization).

The formation of **4** can be explained by reaction of **2** with $TiCl_4$ to give A containing an allylic carbon unit. The attack of the terminal carbon atom of the diene **3** onto A afforded intermediate **B**. The elimination of Me_3SiOMe (intermediate **C**) and subsequent cyclization gave intermediate **D** (Scheme 3). The elimination of

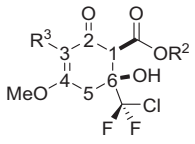


Fig. 3. Numbering scheme of cyclohexenones 6 and diastereotopic nature of the fluorine atoms.

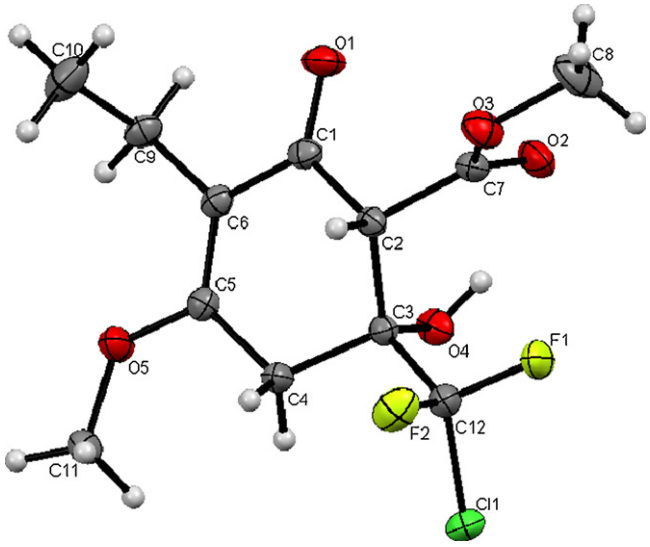


Fig. 4. Ortep drawing of **6b**.

titanium hydroxide (before or during the aqueous work-up) and aromatization resulted in the formation of product **4** (Scheme 4).

The formation of **5** and **6** presumably proceeds by formation of allylic cation **E**. The attack of the terminal carbon atom of **3** onto **E** provides intermediate **F**. We consider two pathways which either lead to pyran-4-one **5** or to cyclohehexenone **6**. *Pathway I*: The rotation of the C3–C4-bond of the diene (intermediate **F**) followed by elimination of Me_3SiOMe (intermediate **G**) and subsequent cyclization via the oxygen rather than the carbon atom provides intermediate **H**. The elimination of silanol (before or during the aqueous work-up) results in the formation of pyran-4-ones **5**. *Pathway II*: The formation of product **6** can be explained by a mechanism which is similar to the one leading to salicylates **4**. The cyclization of intermediate **I** proceeds via the central carbon atom of the diene moiety. In contrast to the formation of salicylates **4**, no elimination of the hydroxyl group and aromatization occurs. This result is surprising since the aromatization should be a facile process. It might be explained by the assumption that intermediate

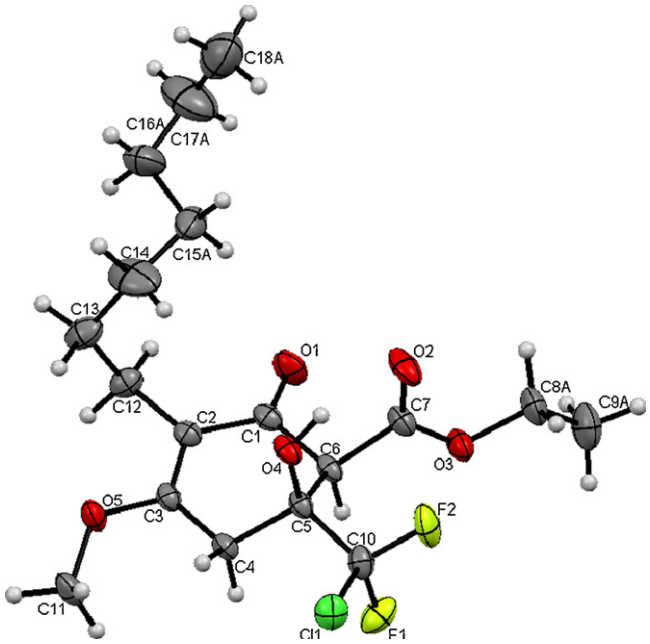


Fig. 5. Ortep drawing of **6e**.

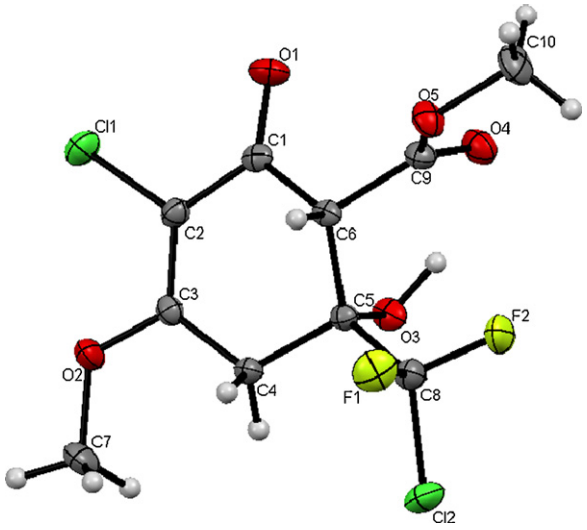
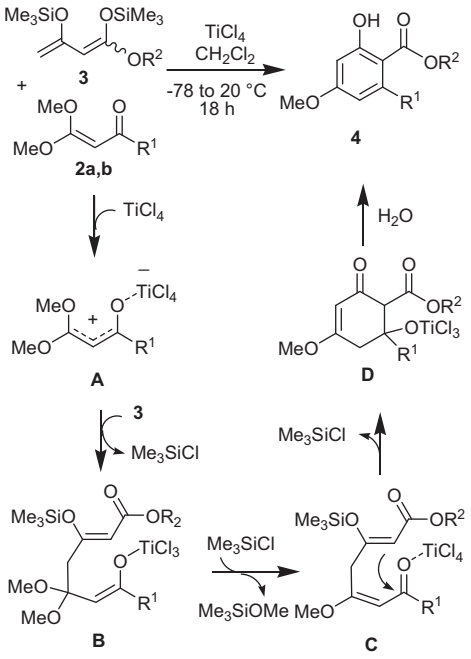
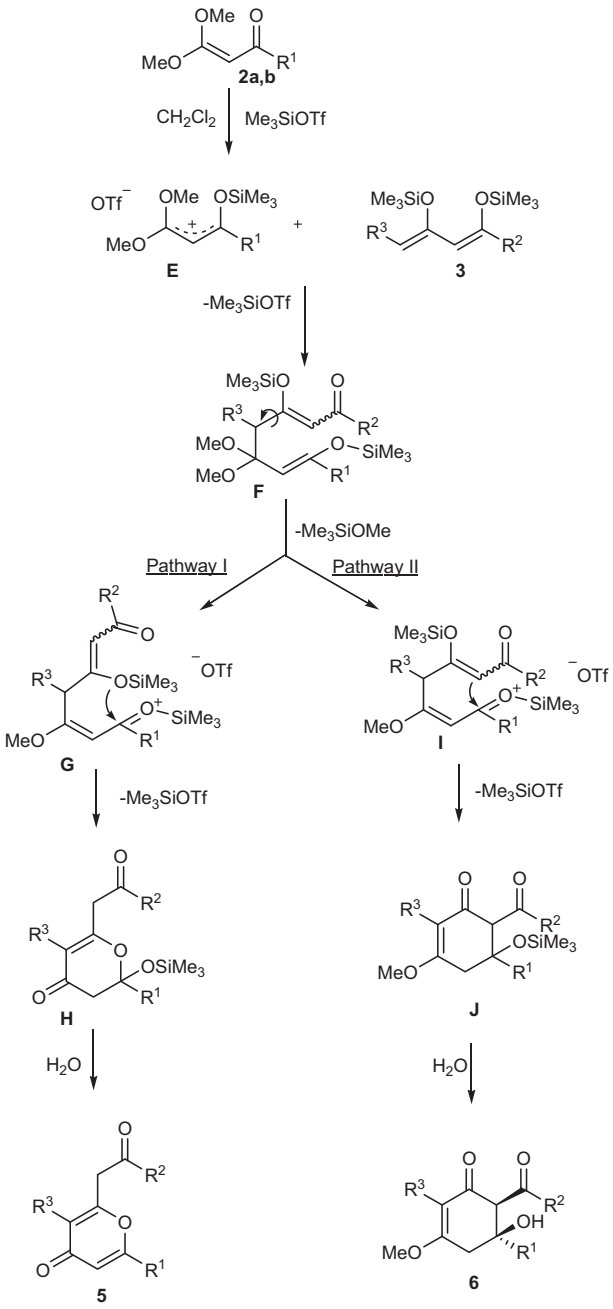


Fig. 6. Ortep drawing of **6k**.



Scheme 3. Possible mechanism of the formation of **4**.



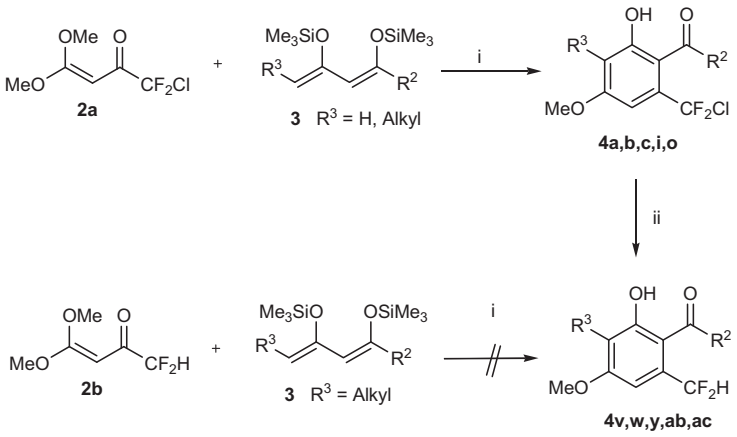
Scheme 4. Possible mechanism of the formation of **5** and **6**.

D, containing a titanium alkoxide moiety, readily undergoes an elimination of $TiCl_3OH$ and aromatization before the aqueous work up (*vide supra*). In contrast, intermediate **J**, containing a silanolate moiety, is more stable and no elimination occurs. The addition of hydrochloric acid (10%) (aqueous work up) results in cleavage of Si–O bond, but no elimination and aromatization occurs. The stability of compounds **6** might be explained by the presence of the electron-withdrawing CF_2Cl group. The rate of the acid-mediated elimination of water is decreased because a cation located next to the CF_2Cl group is expected to be unstable and an elimination requires more drastic conditions.

As mentioned before, the $TiCl_4$-mediated reactions of **2b** with 1,3-bis(silyloxy)-1,3-butadienes **3**, containing an alkyl or a chloride group located at carbon C-4 of the diene moiety ($R^3 \neq H$), did not result in the formation of 3-substituted CF_2H-salicylates (*vide supra*). A successful alternative is the preparation of these salicylates by radical reactions of the respective CF_2Cl-substituted salicylates with tributyltin hydride in the presence of AIBN (Scheme 5, Table 5) [21,22]. Both C-3-substituted and C-3-unsubstituted CF_2H-salicylates were successfully prepared in moderate to good yields.

In addition, CF_2Cl-substituted salicylates **4a,c,i,j,o** were transformed, by reaction with allyltributyltin and AIBN, to the corresponding CF_2H-substituted salicylates **7a–e** in good to very good yields (Scheme 6, Table 6).

Using the Density Functional Theory (DFT) B3LYP method with a 6-31g* basis set and the Natural Bond Orbital (NBO) analysis [31], we calculated the atomic charges of the electrophilic and nucleophilic centers of enones **2a,b** and 1,3-bis(silyloxy)-1,3-butadienes **3a,b,g,h**, respectively (Scheme 7, Table 7). The terminal carbon atom C-4 of dienes **3a,b** exhibits the highest nucleophilicity, while carbon atom C-3 of the enones **2a,b** represents the most electrophilic center. The difference in the substitution pattern of

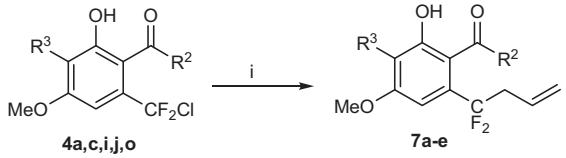


Scheme 5. Attempted synthesis of 3-substituted CF_2H-salicylates: i, $TiCl_4$, CH_2Cl_2, −78 → 20 °C; synthesis of CF_2H-substituted salicylates **4v,w,y,ab,ac** by reduction of CF_2Cl-salicylates: i, AIBN, Bu_3SnH, benzene, 90 °C, 20 h.

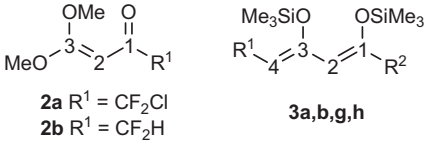
the butenone (CF_2Cl vs. CF_2H) influences the electronic situation of these molecules. The change of the CF_2Cl group to the CF_2H group decreases the NPA atomic charge on the carbon atom C-3 from 0.749 to 0.718, due to the stronger electron withdrawing effect of the CF_2Cl group compared to the CF_2H group. The substitution of carbon atom C-4 ($R^3 \neq H$) lowers the nucleophilicity of diene **3**. The decrease of the electrophilicity at carbon atom C-3 of the CF_2H-substituted enone and the decrease of the nucleophilicity at carbon atom C-4 of 4-substituted dienes (**3g,h**) might be the reason why the formation of 3-substituted ($R^3 \neq H$) CF_2H-salicylates could not be achieved.

In addition, we calculated the geometric structures of CF_2Cl- and CF_2H-substituted salicylates along with their electrostatic potential maps in the ground state and the dipole moments (Table 8) (Density Functional B3LYP method (DFT) with 6-31g* basis set). The mapped electrostatic potential (MEP) of compounds **4a** and **4v** show a high negative potential in the area of the CF_2Cl/CF_2H group while 6-unsubstituted salicylates (R = H) and 6-methylsalicylates show a more neutral area. This may have an effect on further chemical, physical and biological properties (e.g. interactions between substrate and receptor).

Conclusions. In conclusion, we reported the $TiCl_4$-mediated formal [3+3]-cyclocondensation reactions of 1,3-bis(silyloxy)-1,3-butadienes with 1-chloro-1,1-difluoro-4,4-dimethoxybut-3-en-2-one and 1,1-difluoro-4,4-dimethoxybut-3-en-2-one which afforded a variety of functionalized CF_2Cl- and CF_2H-salicylates with very good regioselectivities. The Me_3SiOTf-mediated cyclization of 1,3-bis(silyloxy)-1,3-butadienes, containing no substituent R^3 located at carbon atom C-4 of the diene (R^3 = H), resulted in the formation of CF_2Cl-substituted pyran-4-ones. CF_2Cl-substituted cyclohexenones were formed when dienes were employed which contain a substituent R^3 located at carbon C-4 ($R^3 \neq H$). In contrast, independently from the substitution pattern of the diene (R^3 = H and $R^3 \neq H$), the reaction of dienes with 1,1-difluoro-4,4-dimethoxybut-3-en-2-one resulted in the formation of pyran-4-ones when Me_3SiOTf was employed as the Lewis acid. The synthesis of 3-substituted difluoromethylsalicylates was possible by reaction of 3-substituted chlorodifluoromethyl-salicylates with tributyltin hydride and AIBN.[12] In addition, CF_2Cl-substituted salicylates could be transformed to 6-difluorobutenyl-salicylates in the presence of allyltributyltin and AIBN.[32]



Scheme 6. Synthesis of **7a**–**e**: i, AIBN, $Bu_3SnCH_2CHCH_2$, benzene, 90 °C, 20 h.



Scheme 7. Numbering scheme of enones **2a,b** and of 1,3-bis(silyloxy)-1,3-butadienes **3a,b,g,h**.

Table 5
Synthesis of **4v,w,y,ab,ac**.

4 (CF_2Cl) [a]	**4** (CF_2H)	R^2	R^3	% (**4**, CF_2H)[b]
a	**v**	Me	H	88
b	**w**	Et	H	87
c	**y**	*i*Pr	H	48
i	**ab**	Me	*i*Pr	46
o	**ac**	Me	*n*Octyl	51

[a] CF_2Cl-substituted salicylate;
[b] Yields of isolated products.

Table 6
Synthesis of **7a**–**e**.

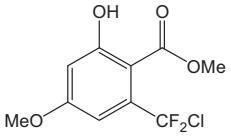
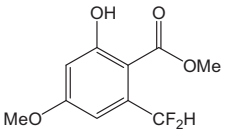
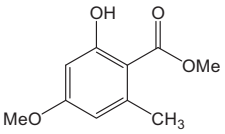
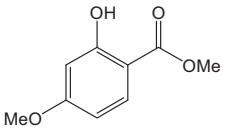
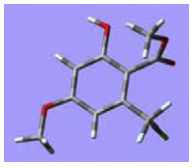
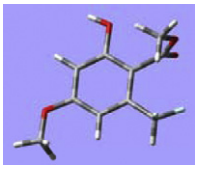
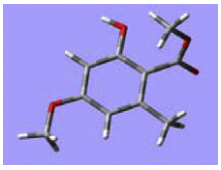
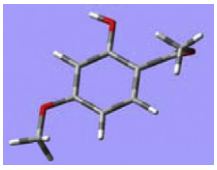
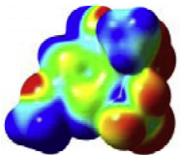
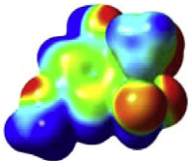
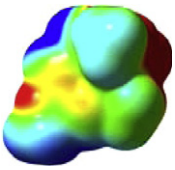
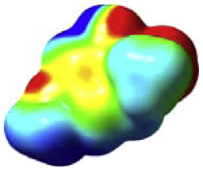
4	**7**	R^1	R^2	%[a] [7]
a	**a**	Me	H	72
c	**b**	*i*Pr	H	96
i	**c**	Me	*n*Pr	89
j	**d**	Me	*i*Pr	85
o	**e**	Me	*n*Octyl	77

[a] Yields of isolated products.

Table 7
Atomic charges calculated by NBO-analysis.

Compound	NPA C^1	NPA C^2	NPA C^3	NPA C^4
2a	0.441	−0.557	0.749	–
2b	0.451	−0.525	0.718	–
3a	0.689	−0.452	0.344	−0.562
3b	0.693	−0.451	0.334	−0.563
3g	0.673	−0.452	0.302	−0.288
3h	0.675	−0.453	0.308	−0.291

Table 8
Calculated geometric structure, MEP, dipole moments of **4a** and **4v** and of **6** methyl- and 6-unsubstituted salicylates.

Numbering scheme and structure				
Geometric structure				
Electrostatic potential maps				
μ_{calc} [D]	6.9850	6.6991	5.5748	5.9910

2. Experimental

General Comments. All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^{1}H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). X-ray crystal structure analysis of 4 v: Data were collected on a Bruker APEX II CCD diffractometer using graphite-monochromated Mo Kα radiation. X-ray crystal structure analysis of **6b**, **6e** and **6k**: Data were collected on a STOE IPDS II diffractometer using graphite-monochromated Mo Kα radiation. For preparative scale chromatography silica gel 60 (0.063–0.200 mm, 70–230 mesh) was used. 1,3-bis(trimethylsilyloxy)-1,3-butadienes **3a–x** were prepared according to the literature from the corresponding β-ketoesters into two steps [20,29,30].

General procedure for the synthesis of 2a,b: To a stirred solution of methyl orthoacetate (20 mmol) and pyridine (40 mmol) in dry dichloromethane (20 mL), **1** (40 mmol) is added drop wise (ice cooling) and the mixture is stirred for 24 h at 20–25 °C. It is then washed two times with 10% sodium carbonate (20 mL), one time with ice cold dist. water and dried with sodium sulfate. The solvent and pyridine are removed in vacuo to give **2** as a white solid. It is used without further purification and can be stored at −20 °C.

1-Chloro-1,1-difluoro-4,4-dimethoxybut-3-en-2-one (2a): This compound has been previously described [23]. Starting with methyl orthoacetate (2.56 mL, 20 mmol) and pyridine (3.22 mL, 40 mmol) and chlorodifluoro acetic acid anhydride (9.70 g, 40 mmol), **2a** was isolated as a white solid (1.68 g, 42%); mp = 48–50 °C, [lit. [23] 48–49 °C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.92, 3.97 (s, 3H, OCH_3), 4.96 (s, 1H, CH).^{13}C NMR (100 MHz, $CDCl_3$) δ = 55.5, 57.6 (OCH_3), 70.9 (CH), 121.1 (t, ^{1}J = 307.2 Hz, CF_2Cl), 172.4 (C4), 177.5 (t, ^{2}J = 27.2 Hz, C-2). ^{19}F NMR (282 MHz, $CDCl_3$) δ = −65.51 (s, CF_2Cl).

1,1-Difluoro-4,4-dimethoxybut-3-en-2-one (2b): Starting with methyl orthoacetate (2.56 mL, 20 mmol) and pyridine (3.22 mL, 40 mmol) and difluoro-acetic acid anhydride (6.96 g, 40 mmol), **2b** was isolated as a white solid (1.54 g, 45%); mp = 49–51 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.99 (t, ^{4}J = 1.3 Hz, 1H, CH), 5.76 (t, ^{2}J = 55.0 Hz, 1H, CF_2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.4, 57.5 (OCH_3), 73.3 (CH), 110.8 (q, J_{C-F} = 252.0 Hz, CF_2H), 171.4 (C), 184.0 (t, J_{C-F} = 23.3 Hz, CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −124.5 (2F, d, $^{2}J_{F-H}$ = 54.6 Hz, CF_2H).

General procedure (I) for the synthesis of 4a–aa: To a CH_2Cl_2 solution (2 mL/1 mmol of 2) of **2** (1 mmol) was added **3** (2 mmol) and, subsequently, $TiCl_4$ (0.1 mL, 1 mmol) at −78 °C. The temperature of the solution was allowed to warm up to 20 °C during a 12–14 h period with stirring. Hydrochloric acid (10%, 15 mL) was added to the solution and the organic and aqueous layers were separated. The latter was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by a column chromatography.

Methyl 2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)-benzoate (4a): Starting with **2a** (1.0 mmol, 200 mg), **3a** (2.0 mmol, 0.521 g) and $TiCl_4$ (1.0 mmol, 0.11 mL) in 2 mL of CH_2Cl_2, **4a** was isolated (228 mg, 86%) by chromatography (silica gel, heptanes/EtOAc = 100:0 → 15:1) as a slightly yellow solid; mp 50–51 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.59 (d, 1H, ^{4}J = 2.5 Hz, H3), 6.85 (d, 1H, ^{4}J = 2.5 Hz, H5), 11.13 (s, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 52.3 (OCH_3), 55.8 (OCH_3), 103.1 (C1), 103.3 (C3), 107.9 (t, ^{3}J = 9.5 Hz, C5), 124.8 (t, ^{1}J = 290.5 Hz, $CClF_2$), 137.7 (t, ^{2}J = 26.4 Hz, C6), 163.4 (C4), 164.4 (C2), 169.8 (CO); ^{19}F NMR (235 MHz, $CDCl_3$) δ = −45.8 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3120 (w), 3093 (w), 3032 (w), 3015 (w), 2974 (w), 2958 (w), 2945 (w), 2847 (w), 1674 (s), 1615 (s); MS (EI, 70 eV): *m*/*z* = 266 (M^+, 35), 236 (35), 235 (23), 234 (100), 171 (71); HRMS (EI, 70 eV): calcd. for $C_{10}H_9O_4ClF_2$ (M^+) 266.014859, found: *m*/*z* = 266.01519.

Ethyl 2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)-benzoate (4b): Starting with **2a** (0.200 g, 1 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3b**) (0.549 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4b** was isolated as a colorless solid (0.139 g, 50%); mp = 33–35 °C; R_F = 0.47 (*n*-hexane/CH_2Cl_2 = 3:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (t, ^{3}J = 6.8 Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.51 (q, ^{3}J = 6.8 Hz, 2H,

CH_2), 6.58 (d, ^4J = 2.4 Hz, 1H, CH), 6.84 (d, ^4J = 2.4 Hz, 1H, CH), 11.26 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (CH_3), 55.8 (OCH_3), 62.3 (CH_2), 103.2 (C-1), 103.2 (C-3), 107.8 (t, J_{C-F} = 9.0 Hz, C-5), 124.9 (t, J_{C-F} = 289.0 Hz, CF_2Cl), 137.7 (t, J_{C-F} = 26.0 Hz, C-6), 163.3 (C-2), 164.6 (C-4), 169.4 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.8 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3091 (w), 3014 (w), 2990 (w), 2944 (w), 2906 (w), 2784 (w), 2744 (w), 2712 (w), 2656 (w), 2570 (w), 1645 (s), 1595 (s), 1485 (w), 1368 (s), 1331 (s), 1266 (s), 1230 (m), 1210 (s), 1106 (s), 1043 (m), 991 (s), 954 (s), 805 (s), 703 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 280 (M^+, 28), 236 (36), 234 (100), 197 (13), 171 (50), 149 (7). Anal. calcd. for $C_{11}H_{11}ClF_2O_4$ (280.65): C, 47.08; H, 3.95. Found: C, 47.02; H, 4.072.

Isopropyl 2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)-benzoate (4c): Starting with **2a** (0.200 g, 1 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3c**) (0.577 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4c** was isolated as a white solid (0.147 g, 50%); mp = 35–36 °C; R_F = 0.54 (*n*-hexane/CH_2Cl_2 = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 5.28–5.36 (m, 1H, CH), 6.58 (d, ^4J = 2.4 Hz, 1H, CH), 6.83 (d, ^4J = 2.7 Hz, 1H, CH), 11.41 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (CH_3), 55.7 (OCH_3), 70.8 (CH), 103.3 (C-3), 103.6 (C-1), 107.8 (t, J_{C-F} = 10.0 Hz, C-5), 124.9 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 137.6 (t, J_{C-F} = 26.0 Hz, C-6), 163.2, 164.6 (C), 169.0 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.5 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3232 (w), 3122 (w), 3091 (w), 3028 (w), 2980 (m), 2940 (w), 2846 (w), 1672 (s), 1616 (s), 1359 (s), 1094 (s), 996 (s), 948 (s), 839 (s), 794 (s), 841 (s), 794 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 294 (M^+, 16), 252 (14), 236 (35), 235 (24), 234 (100), 171 (35). Anal. calcd. for $C_{12}H_{13}ClF_2O_4$ (294.68): C, 48.10; H, 4.45; Cl, 12.03. Found: C, 48.03; H, 4.539; Cl, 11.93.

Isobutyl 2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)-benzoate (4d): Starting with **2a** (0.200 g, 1 mmol), 1-isobutyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3d**) (0.604 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4d** was isolated as a colorless oil (0.174 g, 56%); R_F = 0.44 (*n*-hexane/CH_2Cl_2 = 3:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00, 1.02 (s, 3H, CH_3), 2.09–2.20 (m, 1H, CH), 3.85 (s, 3H, OCH_3), 4.16 (d, ^3J = 6.8 Hz, CH_2), 6.59 (d, ^4J = 2.4 Hz, 1H, CH), 6.85 (d, ^4J = 2.8 Hz, 1H, CH), 11.24 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3 (CH_3), 27.4 (CH), 55.8 (OCH_3), 72.8 (CH_2), 103.3 (C-3), 103.4 (C-1), 107.8 (t, J_{C-F} = 9.0 Hz, C-5), 124.9 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 137.6 (t, J_{C-F} = 26.0 Hz, C-6), 163.2, 164.5 (C), 169.7 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.9 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3098 (w), 3012 (w), 2964 (w), 2914 (w), 2876 (w), 2850 (w), 1656 (m), 1614 (m), 1581 (m), 1377 (m), 1260 (s), 1146 (m), 1042 (s), 996 (s), 954 (s), 794 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 308 (M^+, 14), 252 (10), 236 (35), 235 (23), 234 (100), 171 (21). Anal. calcd. for $C_{13}H_{15}ClF_2O_4$ (308.71): C, 50.58; H, 4.90. Found: C, 50.56; H, 4.90.

Benzyl 2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)-benzoate (4e): Starting with **2a** (0.200 g, 1 mmol), 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3e**) (0.673 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4e** was isolated as a slightly yellow oil (0.170 g, 50%); R_F = 0.42 (*n*-hexane/CH_2Cl_2 = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 3H, OCH_3), 5.39 (s, 2H, CH_2), 6.57 (d, ^4J = 2.7 Hz, 1H, CH), 6.83 (d, ^4J = 2.7 Hz, 1H, CH), 7.34–7.47 (m, 5H, Ph), 11.17 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.8 (OCH_3), 68.2 (CH_2), 103.1 (C-1), 103.3 (C-3), 107.9 (t, J_{C-F} = 6.75 Hz, C-5), 124.8 (t, J_{C-F} = 216.0 Hz, CF_2Cl), 128.5, 128.7, 129.3, 134.5 (Ph), 137.7 (t, J_{C-F} = 19.5 Hz, C-6), 163.4 (C-2), 164.6 (C-4), 169.2 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.8 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3092 (w), 3067 (w), 3034 (w), 2934 (w), 2849 (w), 1657 (s), 1615 (s), 1376 (s), 1260 (s), 1146 (s), 1041 (s), 952 (s), 793 (s), 695 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 342 (M^+, 15), 92 (9), 91 (100), 65 (7). Anal. calcd. for $C_{16}H_{13}ClF_2O_4$ (342.72): C, 56.07; H, 3.82. Found: C, 56.26; H, 4.093.

2-Methoxyethyl 2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)benzoate (4f): Starting with **2a** (0.200 g, 1 mmol), 1-(2-methoxyethoxy)-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3f**) (0.610 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4f** was isolated as a slight yellow oil (0.147 g, 48%); R_F = 0.47 (*n*-hexane/EtOAc = 3:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.47 (s, 3H, OCH_3), 3.75 (t, ^3J = 4.8 Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.51 (t, ^3J = 4.8 Hz, 2H, CH_2), 6.58 (d, ^4J = 2.8 Hz, 1H, CH), 6.84 (d, ^4J = 2.8 Hz, 1H, CH), 10.84 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 58.9 (OCH_3), 64.7, 69.5 (CH_2), 103.4 (C-1), 103.5 (C-3), 107.8 (t, J_{C-F} = 10.0 Hz, C-5), 124.9 (t, J_{C-F} = 289.0 Hz, CF_2Cl), 137.6 (t, J_{C-F} = 26.0 Hz, C-6), 163.3 (C-2), 164.0 (C-4), 168.9 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −45.1 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3092 (w), 2941 (w), 2895 (w), 2848 (w), 2823 (w), 1659 (s), 1614 (s), 1440 (w), 1372 (w), 1262 (s), 1206 (m), 1107 (s), 1041 (s), 952 (s), 795 (s), 702 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 310 (M^+, 19), 275 (16), 237 (11), 236 (36), 235 (30), 234 (100), 171 (32), 157 (9), 59 (8). Anal. calcd. for $C_{12}H_{13}ClF_2O_4$ (310.86): C, 46.39; H, 4.22. Found: C, 46.42; H, 4.50.

Methyl 2-hydroxy-4-methoxy-3-methyl-6-(chlorodifluoromethyl)benzoate (4g): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3g**) (0.549 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4g** was isolated as a white solid (0.191 g, 68%); mp = 56–57 °C; R_F = 0.63 (*n*-hexane/CH_2Cl_2 = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.82 (s, 1H, H-5), 10.86 (s, 1-H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.4 (CH_3), 52.3, 55.8 (OCH_3), 101.3 (t, J_{C-F} = 9.4 Hz, C-5), 104.0 (t, J_{C-F} = 1.5 Hz, C-1), 117.3 (C-3), 125.3 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 134.8 (t, J_{C-F} = 25.9 Hz, C-6), 160.5, 160.6 (C), 170.2 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.5 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3019 (w), 2976 (w), 2923 (w), 2851 (m), 1671 (s), 1605 (s), 1510 (s), 1437 (s), 1238 (s), 1194 (s), 1168 (s), 1108 (s), 1003 (s), 973 (s), 884 (s), 841 (s), 794 (s), 766 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 280 (M^+, 60), 250 (27), 249 (30), 248 (76), 245 (16), 230 (32), 229 (14), 228 (80), 225 (15), 213 (13), 212 (100), 201 (10), 198 (11), 190 (12), 185 (21), 182 (11), 162 (18), 142 (12). Anal. calcd. for $C_{11}H_{11}ClF_2O_4$ (280.65): C, 47.08; H, 3.95. Found: C, 47.25; H, 4.156.

Methyl 3-ethyl-2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)benzoate (4h): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-hexa-1,3-diene (**3 h**) (0.577 g, 2 mmol) and $TiCl_4$ (0.11 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4 h** was isolated as a white solid (0.257 g, 89%); mp = 39–40 °C; R_F = 0.54 (*n*-hexane/CH_2Cl_2 = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, ^3J = 7.5 Hz, 3H, CH_3), 2.70 (q, ^3J = 7.5 Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.81 (s, 1H, H-5), 10.78 (s, 1-H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8 (CH_3), 16.5 (CH_2), 52.3, 55.8 (OCH_3), 101.5 (t, J_{C-F} = 9.5 Hz, C-5), 104.2 (t, J_{C-F} = 1.8 Hz, C-1), 123.2 (C-3), 125.3 (t, J_{C-F} = 289.8 Hz, CF_2Cl), 134.9 (t, J_{C-F} = 26.0 Hz, C-6), 160.2, 160.3 (C), 170.2 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.5 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3005 (w), 2968 (w), 2939 (w), 2877 (w), 2852 (w), 1667 (m), 1603 (m), 1579 (m), 1509 (w), 1438 (m), 1290 (s), 1235 (s), 1132 (s), 1105 (s), 980 (s), 802 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 294 (M^+, 24), 262 (16), 242 (11), 227 (12), 226 (100). Anal. calcd. for $C_{12}H_{13}ClF_2O_4$ (294.68): C, 48.91; H, 4.45. Found: C, 48.93; H, 4.663.

Methyl 3-isopropyl-2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)benzoate (4i): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-5-methyl-hexa-1,3-diene (**3i**) (0.605 g, 2 mmol) and $TiCl_4$ (0.11 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4i** was isolated as a slight yellow oil (0.211 g, 69%); R_F = 0.51 (*n*-hexane/CH_2Cl_2 = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 2.26 (m, ^3J = 6.7 Hz, 1H, CH), 3.71 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.63 (s, 1H, H-5), 10.62 (s, 1H, OH). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 21.0 (CH), 23.6, 24.0 (CH_3), 53.1, 56.91 (OCH_3), 103.1 (t, $^3J_{C-F}$ = 36.0 Hz, C-5), 105.7 (C-1),

129.5 (CF_2Cl), 127.5 (C-3), 136.1 (t, $^2J_{C-F}$ = 26.6 Hz, C-6), 161.8 (C-2), 169.6 (C-4), 171.5 (CO). ^{19}F NMR (300 MHz, $CDCl_3$): δ = −45.0 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958 (w), 2903 (w), 2873 (w), 1702 (m), 1602 (w), 1437 (w), 1312 (w), 1235 (m), 1098 (s), 983 (m), 839 (m), 802 (w), 696 (w), 627 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 308 (M^+, 45), 275 (28), 237 (14), 236 (33), 235 (44), 171 (31), 157 (15). HRMS (EI, 70 eV): calcd. for $C_{13}H_{14}ClO_4F_2$ ($[M^+H]^-$) 307.0554, found 307.0561.

Methyl 3-npropyl-2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)benzoate (4j): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-hepta-1,3-diene (**3j**) (0.605 g, 2 mmol) and $TiCl_4$ (0.11 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4j** was isolated as a slight yellow oil (0.198 g, 62%); R_F = 0.59 (*n*-hexane/CH_2Cl_2 = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.75 (t, ^3J = 7.2 Hz, 1H, 3H, CH_3), 1.89 (m, ^3J = 7.6 Hz, 2H, CH_2), 2.48 (t, ^3J = 7.8 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.64 (s, 1H, H-5), 10.58 (s, 1H, OH). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 15.3 (CH_3), 21.7, 22.8 (CH_2), 53.0, 57.0 (OCH_3), 102.65 (t, $^3J_{C-F}$ = 36.0 Hz, C-5), 105.4 (C-1), 126.5 (CF_2Cl), 130.3 (C-3), 135.7 (t, $^2J_{C-F}$ = 26.6 Hz, C-6), 161.6 (C-2), 169.67 (C-4), 171.4 (CO). ^{19}F NMR (300 MHz, $CDCl_3$): δ = −44.9 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957 (w), 2934 (w), 2873 (w), 1934 (m), 1604 (w), 1510 (w), 1437 (w), 1402 (m), 1288 (s), 1236 (m), 1135 (m), 1110 (w), 983 (m), 902 (s), 840 (w), 800 (m), 694 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 308 (M^+, 41), 276 (21), 237 (10), 236 (30), 235 (40), 171 (38), 157 (8). HRMS (EI, 70 eV): calcd. for $C_{13}H_{14}ClO_4F_2$ ($[M^+H]^-$) 307.0554, found 307.0561.

Ethyl 3-ethyl-2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)benzoate (4k): Starting with **2a** (0.200 g, 1 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-hexadiene (**3k**) (0.533 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4k** was isolated as a slight yellow oil (0.129 g, 42%); R_F = 0.69 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.10 (t, ^3J = 7.5 Hz, 3H, CH_3), 1.43 (t, ^3J = 7.2 Hz, 3H, CH_3), 2.70 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.90 (s, CH_3, OCH_3), 4.43 (q, ^3J = 7.2 Hz, CH_2), 6.81 (s, 1H, H-5), 10.91 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 13.7 (CH_3), 16.5 (CH_2), 55.8 (OCH_3), 62.3 (CH_2), 101.5 (t, J_{C-F} = 9.0 Hz, C-5), 104.5 (C-1), 123.2 (C-3), 125.4 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 134.8 (t, J_{C-F} = 26.0 Hz, C-6), 160.2 (C-2), 160.3 (C-4), 169.8 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −43.7 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2970 (w), 2939 (w), 2908 (w), 2877 (w), 2849 (w), 1662 (s), 1603 (m), 1579 (m), 1508 (w), 1462 (m), 1396 (m), 1287 (s), 1235 (s), 1107 (s), 1057 (m), 973 (m), 897 (w), 804 (s), 659 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 308 (M^+, 21), 263 (10), 262 (18), 242 (11), 227 (13), 226 (100), 198 (7). Anal. calcd. for $C_{13}H_{15}ClF_2O_4$ (308.71): C, 50.58; H, 4.90. Found: C, 50.58; H, 5.049.

Ethyl 3-pentyl-2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)benzoate (4l): Starting with **2a** (0.200 g, 1 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-nonadiene (**3l**) (0.717 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4l** was isolated as a slight yellow oil (0.199 g, 57%); R_F = 0.61 (*n*-heptane/EtOAc = 3:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.32–1.51 (m, 9H, CH_3, $(CH_2)_3$), 2.66 (t, ^3J = 7.8 Hz, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.43 (q, ^3J = 7.2 Hz, 2H, OCH_2), 6.80 (s, 1H, H-5), 10.89 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 14.0 (CH_3), 22.5, 23.0, 28.1, 31.1, 31.9 (CH_2), 55.8 (OCH_3), 62.3 (OCH_2), 101.4 (t, J_{C-F} = 10.0 Hz, C-5), 104.4 (C-1), 122.1 (C-3), 125.4 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 134.8 (t, J_{C-F} = 26.3 Hz, C-6), 160.4 (C-2), 160.5 (C-4), 169.9 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −43.9 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957 (w), 2929 (w), 2859 (w), 1663 (m), 1604 (w), 1509 (w), 1465 (w), 1396 (m), 1287 (s), 1235 (m), 1150 (m), 1109 (w), 1023 (m), 988 (s), 844 (w), 801 (m), 726 (w), 694 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 350 (M^+, 36), 305 (17), 287 (24), 275 (43), 274 (16), 273 (100), 268 (57), 267 (16), 250 (31), 249 (36), 248 (91), 247 (78), 230 (22), 229 (13), 228 (47), 213 (12), 212 (59), 197 (11), 181 (28). Anal. calcd. for $C_{16}H_{21}ClF_2O_4$ (350.79): C, 54.78; H, 6.03. Found: C, 55.14; H, 6.422.

Methyl 3-hexyl-2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)benzoate (4m): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-decadiene (**3m**) (0.689 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4m** was isolated as a colorless oil (0.105 g, 30%); R_F = 0.41 (*n*-hexane/CH_2Cl_2 = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 6.8 Hz, 3H, CH_3), 1.28–1.51 (m, 8H, $(CH_2)_4$), 2.66 (t, ^3J = 7.8 Hz, 2H, CH_2Ar), 3.89 (s, 3H, OCH_3), 3.95(s, 3H, OCH_3), 6.81 (s, 1H, H-5), 10.77 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 23.1, 28.3, 29.5, 31.7 (CH_2), 52.3, 55.8 (OCH_3), 101.4 (t, J_{C-F} = 9.0 Hz, C-5), 104.2 (C-1), 122.1 (C-3), 125.3 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 134.8 (t, J_{C-F} = 25.5 Hz, C-6), 160.4 (C-2), 160.5 (C-4), 170.2 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.5 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3006 (w), 2955 (w), 2929 (w), 2857 (w), 1669 (s), 1604 (m), 1579 (w), 1510 (w), 1438 (s), 1402 (m), 1298 (s), 1236 (s), 979 (s), 801 (s), 693 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 350 (M^+, 44), 319 (16), 315 (18), 301 (16), 289 (30), 288 (12), 287 (78), 283 (18), 282 (69), 261 (10), 250 (34), 249 (43), 248 (100), 247 (97), 230 (22), 228 (49), 213 (12), 212 (61), 209 (23), 197 (14), 181 (33). Anal. calcd. for $C_{16}H_{21}ClF_2O_4$ (350.79): C, 54.78; H, 6.03. Found: C, 54.75; H, 6.17.

Ethyl 3-heptyl-2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)benzoate (4n): Starting with **2a** (0.200 g, 1 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-undecadiene (**3n**) (0.747 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4n** was isolated as a colorless oil (0.110 g, 31%); R_F = 0.69 (*n*-hexane/CH_2Cl_2 = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.26–1.55 (m, 13H, CH_3, $(CH_2)_5$), 2.66 (t, ^3J = 7.8 Hz, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.43 (q, ^3J = 7.2 Hz, 2H, OCH_2), 6.80 (s, 1H, H-5), 10.90 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 14.1 (CH_3), 22.7, 23.1, 28.4, 29.2, 29.8, 31.9 (CH_2), 55.8 (OCH_3), 62.3 (OCH_2), 101.4 (t, J_{C-F} = 9.8 Hz, C-5), 104.4 (C-1), 121.5 (C-3), 125.3 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 134.8 (t, J_{C-F} = 26.3 Hz, C-6), 160.4 (C-2), 160.5 (C-4), 169.9 (CO). ^{19}F NMR (282 MHz, CDCl3): δ = −44.1 (CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2957 (w), 2926 (w), 2856 (w), 1664 (m), 1604 (w), 1501 (w), 1396 (m), 1288 (s), 1235 (s), 1150 (w), 1111 (w), 1023 (m), 986 (s), 845 (w), 801 (m), 723 (w), 694 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 378 (M^+, 36), 333 (18), 315 (20), 303 (31), 302 (13), 301 (84), 297 (16), 296 (76), 295 (17), 293 (10), 250 (34), 249 (38), 248 (100), 247 (80), 230 (22), 229 (14), 228 (48), 213 (13), 212 (58), 209 (11), 197 (10), 181 (29), 29 (9). Anal. calcd. for $C_{18}H_{25}Cl_1F_2O_4$ (378.81): C, 57.07; H, 6.65. Found: C, 57.26; H, 6.764.

Methyl 3-octyl-2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)benzoate (4o): Starting with **2a** (0.200 g, 1 mmol) and 1-methoxy-1,3-bis(trimethylsilyloxy)-dodeca-1,3-diene (**3o**) (0.745 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4o** was isolated as a colorless oil (0.207 g, 55%); R_F = 0.60 (*n*-hexane/CH_2Cl_2 = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 6.6 Hz, 3H, CH_3), 1.27–1.30 (m, 10H, $(CH_2)_5CH_3$), 1.43–1.51 (m, 2H, CH_2), 2.66 (t, ^3J = 7.6 Hz, 2H, CH_2Ar), 3.89 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.81 (s, 1H, H-5), 10.78 (s, 1-H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 23.1, 28.4, 29.3, 29.4, 29.5, 29.8, 31.9 (CH_2), 52.3, 55.8 (OCH_3), 101.5 (t, J_{C-F} = 9.4 Hz, C-5), 104.2 (t, J_{C-F} = 1.9 Hz, C-1), 122.1 (C-3), 125.3 (t, J_{C-F} = 287.9 Hz, CF_2Cl), 134.8 (t, J_{C-F} = 25.7 Hz, C-6), 160.4, 160.5 (C), 170.2 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.5 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3006 (w), 2954 (w), 2925 (w), 2854 (w), 1668 (m), 1604 (m), 1579 (m), 1509 (w), 1438 (m), 1288 (s), 1235 (s), 1167 (m), 1146 (s), 1111 (s), 1092 (s), 982 (s), 801 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 380 (12), 378 (M^+, 35), 347 (14), 343 (17), 329 (15), 317 (27), 316 (13), 315 (77), 311 (28), 310 (78), 261 (11), 250 (35), 249 (43), 248 (100), 247 (96), 230 (20), 228 (48), 224 (11), 213 (12), 212 (59), 209 (23), 197 (13), 181 (29). Anal. calcd. for $C_{18}H_{25}ClF_2O_4$ (378.84): C, 57.07; H, 6.65. Found: C, 57.24; H, 6.55.

Methyl 3-dodecyl-2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)benzoate (4p): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-hexadeca-1,3-diene (**3p**)

(0.857 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4p** was isolated as a colorless solid (0.179 g, 41%); mp = 47–48 °C; R_F = 0.73 (*n*-hexane/DCM = 3:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.25–1.35 (m, 18H, $(CH_2)_9CH_3$), 1.44–1.49 (m, 2H, CH_2), 2.66 (t, ^3J = 7.7 Hz, 2H, CH_2Ar), 3.89 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.81 (s, 1H, H-5), 10.75 (s, 1-H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 23.1, 28.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.8 31.9 (CH_2), 52.3, 55.8 (OCH_3), 101.5 (t, J_{C-F} = 9.3 Hz, C-5), 104.2 (t, J_{C-F} = 1.9 Hz, C-1), 122.1 (C-3), 125.3 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 134.8 (t, J_{C-F} = 25.5 Hz, C-6), 160.4, 160.5 (C), 170.2 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.5 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3024 (w), 2953 (w), 2914 (s), 2849 (s), 1655 (m), 1606 (m), 1582 (m), 1499 (w), 1466 (m), 1438 (m), 1301 (s), 1242 (s), 1138 (s), 977 (s), 803 (m), 784 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 434 (M^+, 26), 403 (12), 399 (15), 385 (12), 373 (26), 372 (17), 371 (69), 367 (37), 366 (29), 261 (11), 250 (32), 249 (43), 248 (100), 247 (93), 230 (20), 228 (43), 224 (11), 213 (13), 212 (54), 209 (22), 197 (13), 182 (24), 43 (15), 41 (11). Anal. Calcd. for $C_{22}H_{33}ClF_2O_4$ (434.94): C, 60.75; H, 7.65. Found: C, 60.73; H, 7.56.

Methyl 3-hexadecyl-2-hydroxy-4-methoxy-6-(chlorodifluoromethyl)benzoate (4q): Starting with **2a** (0.300 g, 1.5 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-icosa-1,3-diene (**3q**) (1.41 g, 3 mmol) and $TiCl_4$ (0.16 mL, 1.5 mmol) in CH_2Cl_2 (3 mL), product **4q** was isolated as a colorless solid (0.160 g, 30%); mp = 63–64 °C; R_F = 0.76 (*n*-hexane/CH_2Cl_2 = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 6.7 Hz, 3H, CH_3), 1.25–1.31 (m, 26H, $(CH_2)_{13}CH_3$), 1.43–1.52 (m, 2H, CH_2), 2.65 (t, ^3J = 7.6 Hz, 2H, CH_2Ar), 3.89 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.81 (s, 1H, H-5), 10.77 (s, 1-H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 23.1, 28.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.8 31.9 (CH_2), 52.3, 55.8 (OCH_3), 101.5 (t, J_{C-F} = 9.4 Hz, C-5), 104.2 (t, J_{C-F} = 1.8 Hz, C-1), 122.1 (C-3), 125.3 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 134.8 (t, J_{C-F} = 25.8 Hz, C-6), 160.4, 160.5 (C), 170.2 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.5 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3022 (w), 2953 (w), 2913 (s), 2849 (s), 1655 (m), 1606 (m), 1582 (m), 1498 (w), 1466 (m), 1438 (m), 1304 (s), 1282 (s), 1138 (s), 985 (m), 975 (s), 803 (m), 784 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 491 (M^+, 5), 490 (18), 427 (26), 423 (10), 250 (30), 249 (32), 248 (100), 247 (67), 228 (21), 212 (28), 209 (13), 57 (15), 55 (15), 43 (31), 41 (17). Anal. calcd. for $C_{26}H_{41}ClF_2O_4$ (491,05): C, 63.59; H, 8.42. Found: C, 63.51; H, 8.427.

Methyl 2-hydroxy-4-methoxy-3-phenethyl-6-(chlorodifluoromethyl)benzoate (4r): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-6-phenyl-1,3-hexadiene (**3r**) (0.577 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4r** was isolated as a colorless solid (0.144 g, 39%); mp = 52–53 °C; R_F = 0.62 (*n*-hexane/CH_2Cl_2 = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.79 (t, ^3J = 5.1 Hz, 2H, CH_2), 2.97 (t, ^3J = 5.1 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.80 (s, 1H, H-5), 7.15–7.31 (m, 5H, Ph), 10.87 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3, 34.4 (CH_2), 52.4, 55.8 (OCH_3), 101.5 (t, J_{C-F} = 9.8 Hz, C-5), 104.2 (C-1), 120.9 (C-3), 125.3 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 128.2, 128.5, 129.1 (Ph), 135.2 (t, J_{C-F} = 26.3 Hz, C-6), 160.5 (C-2), 160.5 (C-4), 169.9 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.6 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3087 (w), 3065 (w), 3028 (w), 3004 (w), 2960 (w), 2942 (w), 2849 (w), 1668 (s), 1579 (w), 1497 (w), 1440 (m), 1405 (m), 1297 (s), 1237 (m), 1099 (s), 1072 (m), 1013 (m), 973 (s), 892 (m), 841 (m), 799 (s), 749 (s), 698 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 370 (M^+, 12), 279 (21), 249 (33), 248 (11), 247 (100), 181 (12), 91 (19). Anal. calcd. for $C_{18}H_{17}ClF_2O_4$ (370.77): C, 58.31; H, 4.62. Found: C, 58.28; H, 4.657.

Methyl 2-hydroxy-4-methoxy-3-(4-chlorobutyl)-6-(chlorodi- fluoromethyl)benzoate (4s): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-8-chloro-1,3-octadiene (**3s**) (0.702 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4s** was isolated as a colorless oil (0.122 g, 35%); R_F = 0.52 (*n*-hexane/CH_2Cl_2 = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.61–1.71 (m, 2H, CH_2), 1.76–1.86 (m, 2H, CH_2), 2.71 (t, ^3J = 7.2 Hz, 2H, CH_2), 3.57 (t, ^3J = 6.9 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.80 (s, 1H, H-5), 10.84 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 25.6, 32.4, 45.0 (CH_2), 52.4, 55.8 (OCH_3), 101.4 (t, J_{C-F} = 9.8 Hz, C-5), 104.2 (C-1), 120.9 (C-3), 125.2 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 135.2 (t, J_{C-F} = 26.3 Hz, C-6), 160.5 (C-2), 160.5 (C-4), 170.1 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.7 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3011 (w), 2954 (w), 2865 (w), 1667 (m), 1604 (w), 1438 (m), 1284 (s), 1235 (s), 1144 (s), 1100 (s), 981 (s), 801 (s), 693 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 357 (M^+, 2), 356 (11), 291 (34), 290 (16), 289 (100), 249 (12), 247 (32). Anal. calcd. for $C_{14}H_{16}Cl_2F_2O_4$ (357.18): C, 47.08; H, 4.52. Found: C, 47.02; H, 4.901.

Methyl 2-hydroxy-4-methoxy-3-(4-chloropropyl)-6-(chloro-difluoromethyl)benzoate (4t): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-7-chloro-1,3-heptadiene (**3t**) (0.674 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4t** was isolated as a colorless oil (0.122 g, 36%); R_F = 0.50 (*n*-hexane/CH_2Cl_2 = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.95–2.05 (m, 2H, CH_2), 2.82 (t, ^3J = 7.8 Hz, 2H, CH_2), 3.55 (t, ^3J = 6.9 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.80 (s, 1H, H-5), 10.87 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 31.4, 44.9 (CH_2), 52.4, 55.9 (OCH_3), 101.4 (t, J_{C-F} = 9.8 Hz, C-5), 104.2 (C-1), 120.0 (C-3), 125.2 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 135.5 (t, J_{C-F} = 26.3 Hz, C-6), 160.5 (C-2), 160.6 (C-4), 170.1 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −44.7 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3007 (w), 2955 (w), 2851 (w), 1667 (m), 1605 (w), 1438 (m), 1291 (s), 1235 (s), 1144 (s), 1098 (s), 982 (s), 800 (s), 693 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 343 (M^+, 1), 342 (11), 306 (17), 277 (34), 276 (14), 275 (100), 271 (12), 248 (16), 247 (18), 212 (11). Anal. calcd. for $C_{13}H_{14}Cl_2F_2O_4$ (343.15): C, 45.50; H, 4.11. Found: C, 45.59; H, 4.264.

Methyl 2-hydroxy-3,4-dimethoxy-6-(chlorodifluoromethyl)benzoate (4u): Starting with **2a** (0.200 g, 1 mmol), 1,4-dimethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3u**) (0.581 g, 2 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (2 mL), product **4u** was isolated as a slightly yellow oil (0.126 g, 42%); R_F = 0.64 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.84 (s, 1H, H-5), 9.20 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.6, 56.3, 60.9 (OCH_3), 102.6 (t, J_{C-F} = 8.0 Hz, C-5), 107.9 (C-1), 125.1 (t, J_{C-F} = 288.0 Hz, CF_2Cl), 130.8 (t, J_{C-F} = 27.0 Hz, C-6), 138.4 (C-3), 152.9, 154.3 (C), 168.3 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −45.1 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3333 (m), 3096 (w), 3008 (w), 2957 (w), 2853 (w), 1732 (s), 1612 (m), 1513 (w), 1431 (m), 1353 (m), 1278 (s), 1104 (m), 1023 (s), 982 (s), 874 (m), 808 (s), 739 (m), 689 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 296 (M^+, 45), 267 (11), 266 (28), 265 (34), 264 (79), 261 (11), 245 (14), 241 (24), 237 (11), 236 (26), 235 (23), 229 (21), 228 (100), 223 (11), 221 (31), 204 (12), 193 (9), 183 (11), 178 (23), 157 (12) 115 (11), 93 (14). Anal. calcd. for $C_{11}H_{11}ClF_2O_4$ (296.65): C, 44.54; H, 3.74. Found: C, 44.65; H, 4.050.

Methyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (4v): Starting with **2b** (0.166 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **(3a)** (0.521 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1 mmol) in CH_2Cl_2 (5 mL), the product **4v** was isolated as a white solid (0.081 g, 35%); mp = 72–73 °C; R_F = 0.70 (heptane/EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.85, 3.97 (s, 3H, OCH_3), 6.55, 6.88 (d, ^4J = 2.4 Hz, 1H, CH), 7.24 (t, ^2J = 55.6 Hz, 1H, CF_2H), 11.60 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.5, 55.7 (OCH_3), 102.7 (t, J_{C-F} = 1.6 Hz, C-3), 102.8 (bs, C-1), 106.7 (t, J_{C-F} = 10.5 Hz, C-5), 111.9 (t, J_{C-F} = 237.7 Hz, CF_2H), 136.9 (t, J_{C-F} = 21.4 Hz, C-6), 164.5, 165.4, 170.2 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −113.3 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3097 (w), 2950 (w), 2923 (w), 2848 (w), 1652 (s), 1620 (s), 1583 (s), 1519 (w), 1436 (s) 1259 (s), 999,6 (s), 752 (s). MS (EI, 70 eV): *m*/*z* (%): 232 (M^+, 41), 201 (21), 200 (100), 172 (34), 157 (21). HRMS

(EI, 70 eV): calcd. for $C_{10}H_{10}F_2O_4$ (M^+) 232.05417, found 232.05483.

Ethyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (4w): Starting with **2b** (0.166 g, 1.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3b**) (0.549 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) in CH_2Cl_2 (5 mL), the product **4b** was isolated as a white solid (0.082 g, 33%); mp = 71–72 °C; R_F = 0.60 (*n*-heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, ^3J = 7.0 Hz, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.44 (q, ^3J = 7.2 Hz, 2H, CH_2), 6.55, 6.88 (d, ^4J = 2.7 Hz, 1H, CH), 7.28 (t, ^2J = 55.5 Hz, 1H, CF_2H), 11.71 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 55.6 (OCH_3), 62.0 (CH_2), 102.7 (t, J_{C-F} = 1.5 Hz, C-3), 103.1 (t, J_{C-F} = 4.4 Hz, C-1), 106.6 (t, J_{C-F} = 10.5 Hz, C-5), 111.9 (t, J_{C-F} = 237.7 Hz, CF_2H), 136.9 (t, J_{C-F} = 21.3 Hz, C-6), 164.4, 165.5, 169.7 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −113.2 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3094 (w), 2983 (w), 2925 (w), 2854 (w), 1649 (m), 1617 (m), 1589 (m), 1527 (w), 1445 (m), 1370 (s), 1255 (s), 996 (s), 862 (s), 624 (s), 411 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 246 (M^+, 31), 201 (22), 200 (100), 172 (31), 157 (15). HRMS (EI, 70 eV): calcd. for $C_{11}H_{12}F_2O_4$ (M^+) 246.06982, found 246.07028.

Benzyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (4x): Starting with **2b** (0.166 g, 1.0 mmol), 1-benzyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**2e**) (0.673 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) in CH_2Cl_2 (5 mL), the product **4x** was isolated as a yellow oil (0.091 g, 30%); R_F = 0.62 (*n*-heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3H, OCH_3), 5.40 (s, 2H, CH_2), 6.55 (d, ^4J = 2.7 Hz, 1H, CH), 6.84 (d, ^4J = 2.7 Hz, 1H, CH), 7.20 (t, ^2J = 57.0 Hz, 1H, CF_2H), 7.37–7.47 (m, 5H, Ph), 11.65 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 67.9 (CH_2), 102.7 (bs, C-3), 102.8 (t, J_{C-F} = 4.0 Hz, C-1), 106.8 (t, J_{C-F} = 11.0 Hz, C-5), 111.7 (t, J_{C-F} = 237.5 Hz, CF_2H), 128.6, 128.8, 134.5 (Ph), 137.0 (t, J_{C-F} = 21.5 Hz, C-6), 164.5, 165.6, 169.5 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −113.0 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3066 (w), 3033 (w), 2959 (w), 2852 (w), 1655 (s), 1618 (s), 1581 (m), 1498 (w), 1441 (w), 1373 (s), 1248 (s), 1161 (s), 1030 (s), 951 (s), 749 (s), 695 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 308 (M^+, 18), 91 (100). HRMS (EI, 70 eV): calcd. for $C_{16}H_{14}F_2O_4$ (M^+) 308.08547, found 308.08601.

Isopropyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (4y): Starting with **2b** (0.166 g, 1.0 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3c**) (0.577 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) in CH_2Cl_2 (5 mL), the product **4y** was isolated as a yellow oil (0.151 g, 58%); R_F = 0.57 (*n*-heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 5.26 − 5.38 (m, 1H, CH), 6.54 (d, ^4J = 2.7 Hz, 1H, CH), 6.84 (d, ^4J = 2.7 Hz, 1H, CH), 7.28 (t, ^2J = 55.5 Hz, 1H, CF_2H), 11.79 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 (CH_3), 55.6 (OCH_3), 70.4 (CH), 102.7 (bs, C-3), 103.5 (t, J_{C-F} = 4.1 Hz, C-1), 106.5 (t, J_{C-F} = 10.5 Hz, C-5), 111.8 (t, J_{C-F} = 237.7 Hz, CF_2H), 137.0 (t, J_{C-F} = 21.3 Hz, C-6), 164.3, 165.5, 169.3 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −113.1 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3062 (w), 2983 (w), 2935 (w), 2853 (w), 1654 (s), 1617 (s), 1583 (m), 1444 (w), 1360 (s), 1254 (s), 1098 (s), 1032 (s), 954 (s), 757 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 260 (M^+, 17), 218 (17), 201 (20), 200 (100), 172 (22). Anal. calcd. for $C_{12}H_{14}F_2O_4$ (260.23): C, 55.38; H, 5.42. Found: C, 55.77; H, 5.74.

2-Methoxyethyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (4z): Starting with **2b** (0.166 g, 1.0 mmol), 1-(2-methoxyethoxy)-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3f**) (0.609 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) in CH_2Cl_2 (5 mL), the product **4z** was isolated as a white solid (0.082 g, 30%); mp = 63–64 °C; R_F = 0.61 (*n*-heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.43 (s, 3H, OCH_3), 3.72 (t, ^3J = 4.8 Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.50 (t, ^3J = 4.8 Hz, 2H, CH_2), 6.54 (d, ^4J = 2.7 Hz, 1H, CH), 6.89 (d, ^4J = 2.7 Hz, 1H, CH), 7.31 (t, ^2J = 55.3 Hz, 1H, CF_2H), 11.47 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.6, 58.9 (OCH_3), 64.5, 69.8 (CH_2), 102.6 (bs, C-3), 103.0 (t, J_{C-F} = 4.5 Hz, C-1), 106.7 (t, J_{C-F} = 10.5 Hz, C-5), 112.0 (t, J_{C-F} = 237.5 Hz, CF_2H), 137.3 (t, J_{C-F} = 21.5 Hz, C-6), 164.5, 165.3, 169.4 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −113.1 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3339 (w), 3095 (w), 2995 (w), 2922 (w), 2852 (w), 2820 (w), 1649 (s), 1613 (s), 1590 (s), 1488 (w), 1436 (s), 1372 (s), 1258 (s), 1205 (s), 1107 (s), 1024 (s), 995 (s), 755 (s), 543 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 276 (M^+, 27), 218 (12), 201 (41), 200 (100), 172 (18). HRMS (EI, 70 eV): calcd. for $C_{12}H_{14}F_2O_5$ (M^+) 276.08038, found 276.08054.

n-Butyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (4aa): Starting with **2b** (0.166 g, 1.0 mmol), 1-butoxy-1,3-bis(-trimethylsilyloxy)-1,3-butadiene (**3v**) (0.605 g, 2.0 mmol) and $TiCl_4$ (0.1 mL, 1.0 mmol) in CH_2Cl_2 (5 mL), the product **4aa** was isolated as a white solid (0.101 g, 37%); mp = 43 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.99 (t, ^3J = 7.3 Hz, 3H, CH_3), 1.40–1.54 (m, 2H, CH_2), 1.73–1.84 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 4.39 (t, ^3J = 6.7 Hz, 2H, OCH_2), 6.55 (d, ^4J = 2.7 Hz, 1H, CH), 6.88 (d, ^4J = 2.7 Hz, 1H, CH), 7.26 (t, ^2J = 55.6 Hz, 1H, CF_2H) 11.74 (s, 1H, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.6 (CH_3), 19.2, 30.4 (CH_2), 55.6 (OCH_3), 66.0 (OCH_2), 102.8 (C-3), 103.1 (t, J_{C-F} = 4.3 Hz, C-1), 106.6 (t, J_{C-F} = 10.8 Hz, C-5), 111.9 (t, J_{C-F} = 239.2 Hz, CF_2H), 136.9 (t, J_{C-F} = 21.5 Hz, C-6), 164.4, 165.5, 169.9 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −113.4 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 2937 (w), 2875 (w), 1724 (w), 1658 (s), 1618 (s), 1582 (m), 1504 (w), 1463 (m), 1444 (m), 1433 (m), 1396 (m), 1372 (s), 1330 (s), 1249 (s), 1205 (s), 1162 (s), 1108 (s), 1051 (m), 1032 (s), 1002 (s), 954 (s), 843 (m), 757 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 274 (M^+, 21), 201 (20), 200 (100), 172 (18), 157 (8), 153 (8). Anal. calcd. for $C_{13}H_{16}F_2O_4$ (274.26): C, 56.93; H, 5.88. Found: C, 57.19; H, 5.95.

General procedure (II) for the synthesis of 4 v,w,y,ab,ac: The reaction was carried out in a pressure tube. To a benzene suspension (10 mL/1 mmol of **4**) of **4** (1 mmol) was added Bu_3SnH (1.2 mmol) and AIBN (azobisisobutyronitrile) (0.12 mmol) and the resultant solution was degassed by bubbling argon through the solution for 5 min. The mixture was heated up to 90 °C under Argon atmosphere for 20 h with stirring. The temperature of the solution was allowed to warm to room temperature. The pressure tube was rinsed with benzene and the organic solution was concentrated in vacuo. The residue was purified by a column chromatography (*n*-heptane/EtOAc).

Methyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (4v): Starting with **4a** (0.266 g, 1.0 mmol), Bu_3SnH (0.349 g, 1.2 mmol), AIBN (0.020 g, 0.12 mmol), the product **4v** was isolated as a white solid (0.204 g, 88%); mp = 72–73 °C; R_F = 0.60 (heptane/EtOAc = 3:2). Product **4v** was analytically characterized.

Ethyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (4w): Starting with **4b** (0.246 g, 1.0 mmol), Bu_3SnH (0.349 g, 1.2 mmol), AIBN (0.020 g, 0.12 mmol), the product **4w** was isolated as a white solid (0.214 g, 87%); mp = 71–72 °C; R_F = 0.62 (heptane/EtOAc = 3:2). Product **4w** was analytically characterized.

Isopropyl 2-(difluoromethyl)-6-hydroxy-4-methoxybenzoate (4y): Starting with **4c** (0.294 g, 1.0 mmol), Bu_3SnH (0.349 g, 1.2 mmol), AIBN (0.020 g, 0.12 mmol), the product **4y** was isolated as a colorless oil (0.126 g, 48%); R_F = 0.67 (heptane/EtOAc = 3:2). Product **4y** was analytically characterized.

Methyl 2-(difluoromethyl)-6-hydroxy-4-methoxy-3-propyl-benz oate (4ab): Starting with **4i** (0.308 g, 1.0 mmol), Bu_3SnH (0.349 g, 1.2 mmol), AIBN (0.020 g, 0.12 mmol), the product **4ab** was isolated as a colorless oil (0.126 g, 46%); R_F = 0.61 (heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 3.57 (t, ^3J = 7.0 Hz, 1H, CH), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.78 (s, 1H, H-5), 11.59 (s, 1H, OH), 12.56 (s, 1H, CF_2). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 23.1, 28.4, 29.5, 29.8, 31.9 (CH_2), 52.3, 55.8 (OCH_3), 101.5 (t, $^3J_{C-F}$ = 36.0 Hz, C-5), 104.2 (C-1), 121.5 (CF_2), 125.3 (C-3), 134.8 (t, $^2J_{C-F}$ = 102.0 Hz, C-6), 160.4

(C-2), 160.5 (C-4), 170.19 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −112.5 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2960 (w), 2904(w), 2874 (w), 1699 (m), 1604 (w), 1308 (w), 1234 (m), 1095 (s), 840 (m), 802 (w), 696 (w), 626 (m). GC–MS (EI, 70 eV): *m/z* (%): 274 (M^+, 22), 201 (20), 200 (98), 170 (24), 157 (10). HRMS (EI, 70 eV): calcd. for $C_{13}H_{16}F_2O_4$ (M^+) 274.10167, found 274.10162.

Methyl 2-(difluoromethyl)-6-hydroxy-4-methoxy-3-octylbenzoate (4ac): Starting with 4o (0.308 g, 1.0 mmol), Bu_3SnH (0.349 g, 1.2 mmol), AIBN (0.020 g, 0.12 mmol), the product 4ac was isolated as a colorless oil (0.175 g, 51%); R_F = 0.67 (heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, ^3J = 7,14 Hz, 3H, CH_3), 1.14–1.44 (m, 12H, $(CH_2)6$), 2.47 (t, ^3J = 7.5 Hz, 2H, CH_2), 2.62 (t, ^3J = 7.7 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.74 (s, 1H, H-5), 10.68 (s, 1H, OH), 11.64 (s, 1H, CF_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.67, 23.1, 28.4, 29.5, 29.8, 31.9 (CH_2), 52.3, 55.8 (OCH_3), 101.5 (t, $^3J_{C-F}$ = 36.0 Hz, C-5), 104.2 (C-1), 121.5 (CF_2), 125.3 (C-3), 134.8 (t, $^2J_{C-F}$ = 102.0 Hz, C-6), 160.4 (C-2), 160.5 (C-4), 170.2 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −112.5 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm − 1): $\tilde{\nu}$ = 2959 (w), 2903(w), 2874 (w), 1700 (m), 1612 (w), 1608 (w), 1234 (m), 1180 (m), 1144 (m), 1130 (m), 1109 (m), 1099 (m), 1082 (s), 840 (m), 802 (w), 693 (w), 627 (m). GC–MS (EI, 70 eV): *m/z* (%): 344 (M^+, 33), 322 (33), 298 (12), 256 (13), 223(22), 201 (20), 200 (98), 170 (24), 157 (10). HRMS (EI, 70 eV): calcd. for $C_{13}H_{16}F_2O_4$ (M^+) 344.17992, found 344.17986.

General procedure for the synthesis of 5a–m and 6a–k: To a CH_2Cl_2 solution (10 mL/1 mmol of **2**) of **2** (1 mmol) was added **3** (2 mmol) and, subsequently, Me_3SiOTf (0.18 mL, 1 mmol) at −78 °C. The temperature of the solution was allowed to warm up to 20 °C during 12–14 h with stirring. To the solution was added hydrochloric acid (10%, 20 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography.

Methyl 2-(4-oxo-6-(chlorodifluoromethyl)-4H-pyran-2-yl)acetate (5a): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3a**) (0.520 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5a** was isolated as a yellow oil (0.079 g, 32%); R_F = 0.23 (*n*-heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 6.36 (d, ^4J = 2.1 Hz, 1H, CH), 6.65 (d, ^4J = 2.1 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.0 (CH_2), 52.9 (OCH_3), 112.6 (t, J_{C-F} = 3.0 Hz, C-5), 116.2 (C-3), 120.0 (t, J_{C-F} = 288.8 Hz, CF_2Cl), 156.4 (t, J_{C-F} = 33.8 Hz, C-6), 161.3, 166.9, 177.8 (C). ^{19}F NMR (282 MHz, CDCl3): δ = −59.9 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3082 (w), 2957 (w), 2921 (w), 2850 (w), 1743 (s), 1668 (s), 1639 (m), 1615 (m), 1400 (m), 1233 (m), 1152 (s), 1081 (s), 927 (s), 876 (m), 823 (s), 749 (w). GC–MS (EI, 70 eV): *m/z* (%): 252 (M^+, 100), 210 (14), 208 (40), 189 (47), 165 (29), 147 (16), 130 (25), 123 (27), 101 (10), 95 (19), 80 (11), 69 (39), 59 (72). Anal. calcd. for $C_9H_7ClF_2O_4$ (252.60): C, 42.79; H, 2.79. Found: C, 42.79; H, 2.974.

Ethyl 2-(4-oxo-6-(chlorodifluoromethyl)-4H-pyran-2-yl)acetate (5b): Starting with **2a** (0.200 g, 1 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3b**) (0.548 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5b** was isolated as a yellow oil (0.118 g, 44%); R_F = 0.27 (*n*-heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, ^3J = 6.9, 3H, CH_3), 3.62 (s, 2H, CH_2), 4.24 (q, ^3J = 7.2, 3H, OCH_2), 6.35 (d, ^4J = 2.1 Hz, 1H, CH), 6.64 (d, ^4J = 2.1 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 39.3 (CH_2), 62.2 (OCH_2), 112.6 (t, J_{C-F} = 2.3 Hz, C-5), 117.3 (C-3), 120.1 (t, J_{C-F} = 288.8 Hz, CF_2Cl), 156.4 (t, J_{C-F} = 33.8 Hz, C-6), 161.5, 166.5, 177.8 (C). ^{19}F NMR (282 MHz, CDCl3): δ = −59.9 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3080 (w), 2948 (w), 2936 (w), 2853 (w), 1739 (m), 1669 (s), 1616 (m), 1398 (m), 1233 (m), 1153 (s), 1081 (s), 1027 (m), 928 (s), 823 (m). GC–MS (EI, 70 eV): *m/z* (%): 266 (M^+, 64), 221 (25), 203 (36), 196 (31), 195 (12), 194 (100), 165 (30), 157 (10), 109 (20), 69 (42), 52 (11), 29 (55). Anal. calcd. for $C_{10}H_9ClF_2O_4$ (266.63): C, 45.05; H, 3.40. Found: C, 44.96; H, 3.88.

Isopropyl 2-(4-oxo-6-(chlorodifluoromethyl)-4H-pyran-2-yl)acetate (5c): Starting with **2a** (0.200 g, 1 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3c**) (0.577 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5c** was isolated as a slightly yellow oil (0.142 g, 51%); R_F = 0.35 (*n*-heptane/EtOAc = 3:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26, 1.27 (s, 3H, CH_3), 3.59 (s, 2H, CH_2), 5.06–5.12 (m, 1H, CH), 6.35 (d, ^4J = 2.4 Hz, 1H, CH), 6.63 (d, ^4J = 2.4 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 21.7 (CH_3), 39.7 (CH_2), 70.0 (OCH), 112.6 (t, J_{C-F} = 3.0 Hz, C-5), 117.2 (C-3), 120.1 (t, J_{C-F} = 288.8 Hz, CF_2Cl), 156.4 (t, J_{C-F} = 33.8 Hz, C-6), 161.7, 166.0, 177.9 (C). ^{19}F NMR (282 MHz, CDCl3): δ = −59.8 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3367 (w), 3085 (w), 2983 (w), 2940 (w), 2881 (w), 1734 (m), 1668 (s), 1617 (m), 1232 (m), 1159 (m), 1102 (s), 1082 (s), 928 (s), 813 (m). GC–MS (EI, 70 eV): *m/z* (%): 280 (M^+, 19), 223 (16), 221 (47), 217 (19), 196 (18), 194 (54), 193 (11), 167 (10), 165 (31), 69 (21), 43 (100), 41 (19). Anal. calcd. for $C_{11}H_{11}ClF_2O_4$ (280.65): C, 47.08; H, 3.95. Found: C, 47.26; H, 4.305.

Isobutyl 2-(4-oxo-6-(chlorodifluoromethyl)-4H-pyran-2-yl)acetate (5d): Starting with **2a** (0.200 g, 1 mmol), 1-isobutyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3d**) (0.605 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5d** was isolated as a slightly yellow oil (0.126 g, 43%); R_F = 0.44 (*n*-heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91, 0.94 (s, 3H, CH_3), 1.88–1.99 (m, 1H, CH), 3.64 (s, 2H, CH_2), 3.97 (d, ^3J = 6.6, 2H, CH_2), 6.36 (d, ^4J = 2.1 Hz, 1H, CH), 6.64 (d, ^4J = 2.1 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 19.2 (CH_3), 27.6 (CH), 39.3 (CH_2), 72.1 (OCH_2), 112.6 (t, J_{C-F} = 3.0 Hz, C-5), 117.3 (C-3), 120.1 (t, J_{C-F} = 288.8 Hz, CF_2Cl), 156.4 (t, J_{C-F} = 33.8 Hz, C-6), 161.5, 166.5, 177.8 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −59.7 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3078 (w), 2959 (w), 2921 (w), 2875 (w), 2851 (w), 1739 (m), 1672 (s), 1641 (m), 1618 (m), 1397 (m), 1233 (m), 1152 (s), 1082 (s), 991 (s), 963 (s), 929 (s), 876 (s), 824 (s), 720 (w). GC–MS (EI, 70 eV): *m/z* (%): 294 (M^+, 7), 241 (35), 240 (11), 239 (100), 231 (20), 221 (21), 196 (20), 194 (60), 167 (12), 130 (12), 69 (27), 57 (70), 56 (16), 43 (10), 41 (48), 39 (13), 29 (18). HRMS (EI, 70 eV): calcd. for $C_{12}H_{13}ClF_2O_4$ (M^+): 294.04649. Found: 294.046922.

2-Methoxyethyl 2-(4-oxo-6-(chlorodifluoromethyl)-4H-pyran-2-yl)acetate (5e)

Starting with **2a** (0.200 g, 1 mmol), 1-(2-methoxyethyl)-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3f**) (0.609 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5e** was isolated as a yellow oil (0.148 g, 50%); R_F = 0.15 (*n*-heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.38 (s, 2H, CH_2), 3.61 (t, ^3J = 4.8, 2H, CH_2), 3.68 (s, 3H, OCH_3), 4.34 (t, ^3J = 4.5, 2H, OCH_2), 6.37 (d, ^4J = 2.4 Hz, 1H, CH), 6.64 (d, ^4J = 2.4 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.0 (CH_2), 59.0 (OCH_3), 64.9 (CH_2, OCH_2), 70.0 (CH_2, CH_2OCH_3), 112.6 (t, J_{C-F} = 3.0 Hz, C-5), 117.4 (C-3), 120.1 (t, J_{C-F} = 288.8 Hz, CF_2Cl), 156.4 (t, J_{C-F} = 33.8 Hz, C-6), 161.2, 166.6, 177.8 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −59.8 (s, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3081 (w), 2952 (w), 2920 (w), 2850 (w), 1741 (m), 1669 (s), 1639 (m), 1399 (m), 1236 (m), 1155 (m), 1080 (s), 990 (s), 927 (s), 876 (m), 821 (m), 668 (m). GC–MS (EI, 70 eV): *m/z* (%): 296 (M^+, 29), 238 (11), 230 (15), 196 (27), 194 (81), 167 (13), 165 (39), 161 (36), 157 (10), 130 (16), 99 (10), 69 (32), 59 (15), 58 (42), 45 (100), 43 (12), 31 (10), 29 (18). Anal. calcd. for $C_{11}H_{11}ClF_2O_5$ (296.65): C, 44.54; H, 3.74. Found: C, 44.97; H, 3.945.

Ethyl 2-(6-(difluoromethyl)-4-oxo-4H-pyran-2-yl)acetate (5f): Starting with **2b** (0.166 g, 1.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3b**) (0.549 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5f** was

isolated as a orange solid (0.140 g, 60%); mp = 49–51 °C; R_F = 0.17 (*n*-heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, ^3J = 6.0 Hz, 3H, CH_3), 3.59 (s, 2H, CH_2), 4.23 (q, ^3J = 7.1 Hz, 2H, CH_2), 6.32 (d, ^4J = 3.0 Hz, 1H, CH), 6.36 (t, ^2J = 52.5 Hz, 1H, CF_2H), 6.56 (d, ^4J = 3.0 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 39.3 (CH_2), 62.0 (CH_2), 108.7 (t, J_{C-F} = 241.1 Hz, CF_2H), 114.1 (t, J_{C-F} = 3.7 Hz, C-5),117.3 (C-3), 157.5 (t, J_{C-F} = 27.3 Hz, C-6), 161.4, 166.7, 178.1 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.3 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3233 (w), 3055 (w), 2987 (w), 2973 (w), 2934 (w), 2855 (w), 1724 (s), 1668 (s), 1622 (s), 1416 (m), 1371 (s), 1337 (s), 1223 (s), 1114 (s), 1026 (s), 905 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 232 (M^+, 63), 187 (24), 160 (100), 131 (42), 121 (17), 109 (28), 69 (45), 29 (62). Anal. calcd. for $C_{10}H_{10}F_2O_4$ (232.18): C, 51.73; H, 4.34. Found: C, 51.14; H, 4.58.

Isopropyl 2-(6-(difluoromethyl)-4-oxo-4H-pyran-2-yl)acetate (5g): Starting with **2b** (0.166 g, 1.0 mmol), 1-isopropyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3c**) (0.577 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5 g** was isolated as a orange oil (0.139 g, 57%); R_F = 0.31 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (d, ^3J = 6.3 Hz, 6H, CH_3), 3.46 (s, 2H, CH_2), 4.91–5.04 (m, 1H, CH), 6.24 (d, ^4J = 2.4 Hz, 1H, CH), 6.25 (t, ^2J = 53.4 Hz, 1H, CF_2H), 6.56 (d, ^4J = 9.0 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 21.8 (CH_3), 39.6 (CH_2), 70.0 (OCH), 108.7 (t, J_{C-F} = 242.0 Hz, CF_2H), 114.2 (t, J_{C-F} = 3.8 Hz, C-5),117.3 (C-3), 157.5 (t, J_{C-F} = 27.3 Hz, C-6), 161.8, 166.3, 178.4 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.3 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2985 (w), 1731 (s), 1670 (s), 1616 (s), 1467 (s), 1467 (w), 1376 (s), 1261 (s), 1101 (s), 926 (s), 876 (s), 905 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 246 (M^+, 38), 187 (63), 160 (76), 159 (17), 131 (54), 83 (12), 81 (10), 69 (25), 43 (100), 41 (20), 39 (11). HRMS (EI, 70 eV): calcd. for $C_{11}H_{12}F_2O_4$ (M^+) 246.069117, found 246.06982. Anal. calcd. for $C_{11}H_{12}F_2O_4$ (246.21): C, 53.66; H, 4.91. Found: C, 53.34; H, 4.87.

Isobutyl 2-(6-(difluoromethyl)-4-oxo-4H-pyran-2-yl)acetate (5h): Starting with **2b** (0.166 g, 1.0 mmol), 1-isobutyloxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**3d**) (0.605 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5 h** was isolated as a slight yellow oil (0.125 g, 52%); R_F = 0.37 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (d, ^3J = 6.9 Hz, 6H, CH_3), 1.73–1.84 (m,1H, CH), 3.46 (s, 2H, CH_2), 3.80 (d, ^3J = 6.6 Hz, 2H, OCH_2), 6.18 (d, ^4J = 2.3 Hz, 1H, CH), 6.21 (t, ^2J = 53.3 Hz, 1H, CF_2H), 6.42 (d, ^4J = 8.6 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9 (6H, CH_3), 27.6 (CH), 39.4 (CH_2), 72.0 (OCH_2), 108.7 (t, J_{C-F} = 241.9 Hz, CF_2H), 114.2 (t, J_{C-F} = 3.9 Hz, C-5),117.4 (C-3), 157.6 (t, J_{C-F} = 27.4 Hz, C-6), 161.6, 166.8, 178.2 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.2 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2961 (w), 2922 (w), 2852 (w), 1737 (s), 1671 (s), 1632 (s), 1470 (w), 1378 (m), 1259 (s), 1056 (s), 925 (s), 876 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 260 (M^+, 12), 205 (100), 187 (25), 160 (70), 159 (17), 131 (44), 69 (16), 57 (41), 41 (26), 39 (11). HRMS (EI, 70 eV): calcd. for $C_{12}H_{14}F_2O_4$ (M^+) 260.08547, found 260.086103.

Methyl 2-(6-(difluoromethyl)-4-oxo-3-methyl-4H-pyran-2-yl)acetate (5i): Starting with **2b** (0.166 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3g**) (0.549 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5i** was isolated as a colorless oil (0.071 g, 31%); R_F = 0.28 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82 (s, 3H, CH_3), 3.54 (s, 2H, CH_2), 3.61 (s, 3H, OCH_3), 6.18 (t, ^2J = 54.0 Hz, 1H, CF_2H), 6.40 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.9 (CH_3), 37.4 (CH_2), 52.9 (OCH_3), 108.8 (t, J_{C-F} = 242.2 Hz, CF_2H), 112.5 (t, J_{C-F} = 3.9 Hz, C-5), 125.2 (C-3), 156.7 (t, J_{C-F} = 27.8 Hz, C-6), 157.0, 167.6, 178.4 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.1 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3466 (w), 2957 (m), 1739 (s), 1667 (s), 1610 (s), 1434 (m), 1329 (m), 1082 (s), 794 (m), 562 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 232 (M^+, 100), 201 (89), 175 (10), 174 (78), 173 (51), 145 (48), 121 (23), 69 (20), 59 (23), 53 (23), 52 (12), 51 (14). HRMS (EI, 70 eV): calcd. for $C_{10}H_{10}F_2O_4$ (M^+) 232.05417, found 232.054580. Anal. calcd. for $C_{10}H_{10}F_2O_4$ (232.181): C, 51.73; H, 4.34. Found: C, 51.78; H, 4.507.

Methyl 2-(6-(difluoromethyl)-4-oxo-3-ethyl-4H-pyran-2-yl)acetate (5j): Starting with **2b** (0.166 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-hexadiene (**3h**) (0.577 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5j** was isolated as a slight yellow oil (0.125 g, 52%); R_F = 0.46 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, ^3J = 7.5 Hz, 3H, CH_3), 2.45 (q, ^3J = 7.5 Hz, 2H, CH_2), 3.69 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 6.31 (t, ^2J = 53.6 Hz, 1H, CF_2H), 6.51 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7 (CH_3), 18.2, 36.9 (CH_2), 52.9 (OCH_3), 108.8 (t, J_{C-F} = 242.2 Hz, CF_2H), 112.9 (t, J_{C-F} = 3.9 Hz, C-5), 130.5 (C-3), 156.7 (t, J_{C-F} = 27.8 Hz, C-6), 157.1, 167.9, 178.0 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.4 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959 (s), 1741 (s), 1667 (s), 1609 (s), 1434 (s), 1382 (s), 1056 (s), 797 (m), 564 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 260 (M^+, 100), 215 (71), 199 (17), 188 (43), 187 (83), 186 (11), 185 (28), 173 (12), 121 (11), 69 (11), 67 (18). HRMS (EI, 70 eV): calcd. for $C_{11}H_{12}F_2O_4$ (M^+) 246.06982, found 246.069858. Anal. calcd. for $C_{11}H_{12}F_2O_4$ (246.07): C, 53.66; H, 4.91. Found: C, 54.15; H, 5.26.

Ethyl 2-(6-(difluoromethyl)-4-oxo-3-ethyl-4H-pyran-2-yl)acetate (5k): Starting with **2b** (0.166 g, 1.0 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-hexadiene (**3k**) (0.605 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5k** was isolated as a yellow oil (0.081 g, 31%); R_F = 0.28 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.8 Hz, 3H, CH_3), 1.12 (t, ^3J = 6.9 Hz, 3H, CH_3), 2.28 (q, ^3J = 6.9 Hz, 2H, CH_2), 3.50 (s, 2H, CH_2), 4.05 (q, ^3J = 6.9 Hz, 2H, OCH_2), 6.16 (t, ^2J = 53.6 Hz, 1H, CF_2H), 6.41 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 14.1 (CH_3), 18.2, 37.2 (CH_2), 62.1 (OCH_2), 108.8 (t, J_{C-F} = 242.1 Hz, CF_2H), 112.9 (t, J_{C-F} = 3.8 Hz, C-5), 130.4 (C-3), 156.7 (t, J_{C-F} = 27.8 Hz, C-6), 157.4, 167.4, 178.1 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.2 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2979 (m), 1736 (s), 1607 (s), 1423 (m), 1328 (m), 1056 (s), 795 (m), 564 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 260 (M^+, 44), 215 (31), 189 (12), 187 (83), 187 (77), 185 (19), 173 (9), 69 (11), 67 (22), 29 (13). ESI-MS: calcd. for $C_{12}H_{15}F_2O_4$ (M^+H^+) 261.0933, found 261.0933; calcd. for $C_{12}H_{14}F_2NaO_4$ (M^+Na^+) 283.0752, found 283.0753. Anal. calcd. for $C_{12}H_{14}F_2O_4$ (260.23): C, 55.38; H, 5.42. Found: C, 55.31; H, 5.525.

Methyl 2-(6-(difluoromethyl)-4-oxo-3-propyl-4H-pyran-2-yl)acetate (5l): Starting with **2b** (0.166 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-heptadiene **(3j)** (0.605 g, 2.0 mmol) and Me_3SiOTf (0.18 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5l** was isolated as a orange oil (0.082 g, 32%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.41–1.53 (m, 2H, CH_2), 2.38 (t, ^3J = 7.8 Hz, 2H, CH_2), 3.67 (s, 2H, CH_2), 3.76 (s, 3H, OCH_3), 6.31 (t, ^2J = 53.7 Hz, 1H, CF_2H), 6.54 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 21.5, 26.5, 37.0 (CH_2), 52.7 (OCH_3), 108.8 (t, J_{C-F} = 242.4 Hz, CF_2H), 112.8 (t, J_{C-F} = 3.9 Hz, C-5), 129.1 (C-3), 156.6 (t, J_{C-F} = 27.8 Hz, C-6), 157.3, 167.8, 178.1 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.7 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3083 (w), 2961 (w), 2936 (w), 2874 (w), 1741 (s), 1668 (s), 1631 (m), 1609 (s), 1456 (w), 1434 (m), 1420 (m), 1380 (m), 1338 (m), 1309 (m), 1262 (m), 1195 (m), 1177 (m), 1158 (m), 1136 (s), 1092 (s), 1051 (s), 1011 (m), 873 (m), 801 (m), 649 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 260 (M^+, 24), 259 (10), 246 (11), 245 (100), 232 (50), 229 (17), 228 (24), 213 (14), 201 (41), 200 (12), 199 (25), 187 (63), 185 (31), 174 (44), 173 (22), 121 (13), 79 (16), 77 (11), 69 (18), 59 (18), 53 (14), 51 (14). Anal. calcd. for $C_{12}H_{14}F_2O_4$ (260.23): C, 55.38; H, 5.42. Found: C, 55.16; H, 5.44.

Methyl 2-(6-(difluoromethyl)-4-oxo-3-nonyl-4H-pyran-2-yl)acetate (5m): Starting with **2b** (0.166 g, 1.0 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-tridecadiene (**3w**) (0.773 g,

2.0 mmol) and Me_3SiOTf (0.18 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **5 m** was isolated as a slight yellow solid (0.071 g, 31%); mp = 41–42 °C; R_F = 0.38 (*n*-heptane/EtOAc = 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.78 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.62–1.22 (m, 16H, CH_2), 3.59 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3), 6.23 (t, ^2J = 54.2 Hz, 1H, CF_2H), 6.41 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.4, 24.7, 28.3, 29.3, 29.4, 29.5, 29.7, 31.9 (CH_2), 52.8 (OCH_3), 108.8 (t, J_{C-F} = 242.5 Hz, CF_2H), 112.8 (t, J_{C-F} = 3.7 Hz, C-5), 129.4 (C-3), 156.6 (t, J_{C-F} = 27.8 Hz, C-6), 157.3, 167.9, 178.2 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.3 (2F, d, $^2J_{F-H}$ = 56.4 Hz, CF_2H). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2952 (w), 2916 (m), 2850 (w), 1730 (m), 1669 (s), 1636 (s), 1424 (m), 1382 (m), 1067 (s), 790 (m), 573 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 344 (M^+, 3), 312 (14), 272 (20), 271 (100), 259 (26), 245 (24), 232 (40), 201 (18), 199 (17), 185 (11), 174 (22). HRMS (EI, 70 eV): calcd. for $C_{18}H_{26}F_2O_4$ (M^+) 344.17937, found 344.179242. Anal. calcd. for $C_{18}H_{26}F_2O_4$ (344.39): C, 62.77; H, 7.61. Found: C, 62.68; H, 7.498.

Methyl 6-(chlorodifluoromethyl)-6-hydroxy-4-methoxy-3-methyl-2-oxocyclohex-3-ene-carboxylate (6a): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene (**3 g**) (0.549 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **6a** was isolated as a yellow solid (0.094 g, 32%); mp = 73–75 °C, R_F = 0.51 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.72–1.74 (m, 3H, CH_3), 2.84 (brd, ^2J = 17.7 Hz, 1H, H-5a), 2.99 (d, ^2J = 17.1 Hz, 1H, H-5b), 3.81 (s, 0.5H, H-1a), 3.81 (s, 0.5H, H-1b), 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.65 (s, 0.5H, OH-a), 5.66 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.4 (CH_3), 31.5 (C-5), 53.2 (C-1), 53.2, 55.8 (OCH_3), 78.0 (t, J_{C-F} = 24.8 Hz, C-6), 113.3 (C-3), 130.2 (t, J_{C-F} = 299.3 Hz, CF_2Cl), 166.8, 171.6, 188.7 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −64.0 (d, $^2J_{F-F}$ = 166.4, 1F, CF_2Cl), −66.5 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3428 (w), 3009 (w), 2965 (w), 2932 (w), 2865 (w), 1748 (s), 1666 (m), 1601 (s), 1434 (w), 1256 (m), 1096 (s), 1020 (s), 948 (s), 706 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 298 (M^+, 1), 280 (61), 223 (17), 213 (31), 212 (17), 201 (100), 187 (23), 181 (72), 137 (15), 83 (17), 69 (32), 59 (15). ESI-MS: calcd. for $C_{11}H_{14}ClF_2O_5$ ($M+H^+$) 299.04923, found 299.04978; calcd. for $C_{11}H_{13}ClF_2NaO_5$ ($M+Na^+$) 321.03118, found 321.03204.

Methyl 6-(chlorodifluoromethyl)-6-hydroxy-4-methoxy-3-ethyl-2-oxocyclohex-3-ene-carboxylate (6b): Starting with **2b** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-hexadiene (**3 h**) (0.577 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **6b** was isolated as a yellow solid (0.176 g, 56%); mp = 100–102 °C, R_F = 0.42 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.5 Hz, 3H, CH_3), 2.28–2.32 (m, 2H, CH_2), (brd, ^2J = 17.7 Hz, 1H, H-5a), 2.99 (d, ^2J = 17.7 Hz, 1H, H-5b), 3.78 (s, 0.5H, H-1a), 3.78 (s, 0.5H, H-1b), 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.66 (s, 0.5H, OH-a), 5.67 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8 (CH_3), 15.7 (CH_2), 31.5 (C-5), 53.2 (C-1), 53.3, 55.7 (OCH_3), 78.0 (t, J_{C-F} = 24.0 Hz, C-6), 119.5 (C-3), 130.3 (t, J_{C-F} = 298.5 Hz, CF_2Cl), 166.6, 171.7, 188.3 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −64.0 (d, $^2J_{F-F}$ = 166.4, 1F, CF_2Cl), −66.5 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3413 (w), 3024 (w), 2997 (w), 2964 (w), 2957 (w), 2934 (w), 2871 (w), 1714 (s), 1653 (m), 1619 (s), 1442 (m), 1409 (m), 1355 (m), 1246 (s), 1206 (s), 1172 (s), 1079 (s), 1026 (s), 997 (s), 964 (s), 887 (m), 802 (m), 699 (s). GC–MS (EI, 70 eV): *m*/*z* (%): 312 (M^+, 1), 294 (43), 274 (15), 258 (21), 237 (47), 235 (97), 227 (46), 226 (33), 195 (100), 170 (20), 155 (17), 83 (27), 69 (45), 59 (15). ESI-MS: calcd. for $C_{12}H_{16}ClF_2O_5$ ($M+H^+$) 313.06488, found 313.06457; calcd. for $C_{12}H_{15}ClF_2NaO_5$ ($M+Na^+$) 335.04683, found 335.04684. Anal. calcd. for $C_{12}H_{15}ClF_2O_5$ (312.69): C, 46.09; H, 4.84. Found: C, 46.15; H, 4.82.

Ethyl 6-(chlorodifluoromethyl)-6-hydroxy-4-methoxy-3-pentyl-2-oxocyclohex-3-ene-carboxylate (6c): Starting with **2a** (0.200 g, 1 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-nonadiene (**3l**) (0.577 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **6c** was isolated as a yellow solid (0.208 g, 56%); mp = 55–57 °C, R_F = 0.57 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 7.2 Hz, 3H, CH_3), 1.25–1.38 (m, 9H,$CH_3(CH_2)_4$), CH_3), 2.22–2.34 (m, 2H, CH_2), 2.84 (d, ^2J = 17.1 Hz, 1H, H-5a), 2.99 (d, ^2J = 17.4 Hz, 1H, H-5b), 3.76 (s, 0.5H, H-1a), 3.76 (s, 0.5H, H-1b), 3.88 (s, 3H, OCH_3), 4.35 (q, ^3J = 6.6 Hz, CH_2, OCH_2), 5.76 (s, 0.5H, OH-a), 5.77 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.1 (CH_3), 22.2, 22.5, 28.0, 31.8 (CH_2), 31.5 (C-5), 53.3 (C-1), 55.7 (OCH_3), 62.5 (OCH_2), 78.0 (t, J_{C-F} = 24.0 Hz, C-6), 118.2 (C-3), 130.3 (t, J_{C-F} = 299.3 Hz, CF_2Cl), 166.7, 171.3, 188.7 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −64.0 (d, $^2J_{F-F}$ = 166.4, 1F, CF_2Cl), −66.5 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3435 (w), 3014 (w), 2964 (w), 2924 (w), 2874 (w), 2858 (w), 1732 (s), 1651 (s), 1615 (s), 1374 (m), 1336 (m), 1255 (s), 1164 (s), 1074 (s), 1024 (s), 933 (m), 879 (m), 814 (m), 788 (m), 708 (w), 675 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 368 (M^+, 1), 350 (8), 330 (10), 314 (23), 283 (31), 265 (15), 249 (21), 248 (19), 247 (20), 237 (30), 223 (35), 221 (100), 211 (21), 153 (29), 69 (21), 29 (16). ESI-MS: calcd. for $C_{16}H_{24}ClF_2O_5$ ($M+H^+$) 369.12748, found 369.12795; calcd. for $C_{16}H_{23}ClF_2NaO_5$ ($M+Na^+$) 391.10943, found 391.10963. Anal. calcd. for $C_{16}H_{23}ClF_2O_5$ (368.80): C, 52.11; H, 6.29. Found: C, 52.13; H, 6.359.

Ethyl 6-(chlorodifluoromethyl)-6-hydroxy-4-methoxy-3-hexyl-2-oxocyclohex-3-ene-carboxylate (6d): Starting with **1** (0.200 g, 1 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-decadiene (**3x**) (0.740 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **6d** was isolated as a yellow solid (0.218 g, 57%); mp = 64–66 °C, R_F = 0.61 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.22–1.29 (m, 8H, $CH_3(CH_2)_5$), 1.35 (t, ^3J = 7.2 Hz, 3H, CH_3), 2.22–2.32 (m, 2H, CH_2), 2.84 (d, ^2J = 17.4 Hz, 1H, H-5a), 2.98 (d, ^2J = 17.4 Hz, 1H, H-5b), 3.76 (s, 0.5H, H-1a), 3.76 (s, 0.5H, H-1b), 3.88 (s, 3H, OCH_3), 4.34 (q, ^3J = 7.2 Hz, CH_2, OCH_2), 5.75 (s, 0.5H, OH-a), 5.76 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.1 (CH_3), 22.3, 22.7, 28.3, 29.3, 31.7 (CH_2), 31.6 (C-5), 53.3 (C-1), 55.7 (OCH_3), 62.5 (OCH_2), 78.0 (t, J_{C-F} = 24.0 Hz, C-6), 118.3 (C-3), 130.4 (t, J_{C-F} = 299.3 Hz, CF_2Cl), 166.7, 171.3, 188.7 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −64.0 (d, $^2J_{F-F}$ = 166.4, 1F, CF_2Cl), −66.5 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3419 (w), 2955 (w), 2931 (w), 2851 (w), 1721 (m), 1637 (w), 1604 (s), 1374 (s), 1333 (m), 1254 (m), 1091 (s), 1021 (s), 954 (m), 901 (m), 799 (m), 668 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 382 (M^+, 1), 364 (13), 344 (11), 328 (32), 297 (34), 287 (23), 282 (20), 255 (16), 251 (31), 249 (25), 248 (30), 247 (25), 225 (19), 223 (41), 221 (100), 212 (19), 186 (15), 153 (30), 69 (21), 43 (22), 29 (22). Anal. calcd. for $C_{17}H_{27}ClF_2O_5$ (384.84): C, 53.06; H, 7.07. Found: C, 53.02; H, 6.848.

Ethyl 6-(chlorodifluoromethyl)-6-hydroxy-4-methoxy-3-heptyl-2-oxocyclohex-3-ene-carboxylate (6e): Starting with **2a** (0.200 g, 1 mmol), 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-undecadiene (**3n**) (0.745 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **6e** was isolated as a yellow solid (0.231 g, 58%); mp = 65–67 °C, R_F = 0.60 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 6.5 Hz, 3H, CH_3), 1.23–1.29 (m, 10H, $CH_3(CH_2)_6$), 1.36 (t, ^3J = 7.2 Hz, 3H, CH_3), 2.24–2.30 (m, 2H, CH_2), 2.83 (d, ^2J = 17.7 Hz, 1H, H-5a), 2.98 (d, ^2J = 17.4 Hz, 1H, H-5b), 3.76 (s, 0.5H, H-1a), 3.76 (s, 0.5H, H-1b), 3.88 (s, 3H, OCH_3), 4.35 (q, ^3J = 7.0 Hz, CH_2, OCH_2), 5.76 (s, 0.5H, OH-a), 5.76 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 14.1 (CH_3), 22.3, 22.7, 28.3, 29.2, 29.6, 31.9 (CH_2), 31.5 (C-5), 53.3 (C-1), 55.7 (OCH_3), 62.5 (OCH_2), 78.0 (t, J_{C-F} = 24.8 Hz, C-6), 118.3 (C-3), 130.3 (t, J_{C-F} = 298.5 Hz, CF_2Cl), 166.6, 171.3, 188.7 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −64.0 (d, $^2J_{F-F}$ = 166.4, 1F, CF_2Cl), −66.5 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3424 (w), 3036 (w), 2960 (w), 2928 (w), 2856 (w), 1722 (s), 1638 (s), 1604 (s), 1445 (m), 1374 (m), 1334 (s), 1255 (s), 1162 (s), 1089 (s), 1022 (s), 976 (m), 800 (m), 669 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 396 (M^+, 1), 378 (15),

358 (11), 342 (32), 311 (35), 301 (31), 296 (28), 293 (20), 269 (15), 265 (25), 249 (24), 248 (39), 247 (34), 239 (18), 228 (17), 223 (37), 221 (100), 212 (22), 153 (26), 69 (15), 29 (15). ESI-MS: calcd. for $C_{18}H_{28}ClF_2O_5$ ($M+H^+$) 397.15878, found 397.15921; calcd. for $C_{18}H_{27}ClF_2NaO_5$ ($M+Na^+$) 419.14073, found 419.14074. Anal. calcd. for $C_{18}H_{27}ClF_2O_5$ (396.85): C, 54.48; H, 6.86. Found: C, 54.57; H, 6.807.

Methyl 6-(chlorodifluoromethyl)-6-hydroxy-4-methoxy-3-octyl-2-oxocyclohex-3-ene-carboxylate (6f): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-dodecadiene (**3n**) (0.745 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **6f** was isolated as a slight yellow solid (0.225 g, 58%); mp = 59–61 °C, R_F = 0.50 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, ^3J = 7.2 Hz, 3H, CH_3), 1.25–1.29 (m, 12H, $CH_3(CH_2)_7$), 2.24–2.29 (m, 2H, CH_2), 2.84 (d, ^2J = 17.7 Hz, 1H, H-5a), 2.99 (d, ^2J = 17.7 Hz, 1H, H-5b), 3.80 (s, 0.5H, H-1a), 3.80 (s, 0.5H, H-1b), 3.88, 3.90 (s, 3H, OCH_3), 5.66 (s, 0.5H, OH-a), 5.67 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.3, 22.7, 28.3, 29.3, 29.4, 29.6, 31.9 (CH_2), 31.5 (C-5), 53.2 (OCH_3), 53.3 (C-1), 55.7 (OCH_3), 78.0 (t, J_{C-F} = 24.0 Hz, C-6), 118.3 (C-3), 130.3 (t, J_{C-F} = 298.5 Hz, CF_2Cl), 166.7, 171.7, 188.5 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −64.0 (d, $^2J_{F-F}$ = 166.4, 1F, CF_2Cl), −66.5 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3400 (w), 3008 (w), 2955 (w), 2925 (w), 2855 (w), 1721 (m), 1658 (m), 1619 (s), 1459 (m), 1379 (s), 1348 (s), 1250 (s), 1167 (s), 1114 (s), 1024 (s), 988 (s), 943 (m), 795 (w), 666 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 396 (M^+, 1), 378 (26), 358 (23), 343 (24), 342 (61), 317 (19), 315 (50), 311 (86), 310 (47), 293 (57), 283 (32), 279 (100), 250 (22), 249 (31), 248 (64), 247 (62), 235 (20), 228 (28), 223 (37), 221 (99), 212 (32), 209 (18), 181 (23), 153 (29), 69 (36), 59 (18), 55 (16). ESI-MS: calcd. for $C_{18}H_{28}ClF_2O_5$ ($M+H^+$) 397.15878, found 397.15943; calcd. for $C_{18}H_{27}ClF_2NaO_5$ ($M+Na^+$) 419.14073, found 419.1409. Anal. calcd. for $C_{18}H_{27}ClF_2O_5$ (396.85): C, 54.48; H, 6.86. Found: C, 54.22; H, 6.783.

Methyl 6-(chlorodifluoromethyl)-6-hydroxy-4-methoxy-3-nonyl-2-oxocyclohex-3-ene-carboxylate (6g): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-tridecadiene (**3w**) (0.773 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), **6 g** was isolated as a slightly yellow solid (0.189 g, 46%); mp = 52–54 °C, R_F = 0.58 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 7.2 Hz, 3H, CH_3), 1.25–1.32 (m, 14H, $CH_3(CH_2)_8$), 2.24–2.27 (m, 2H, CH_2), 2.84 (brd, ^2J = 17.7 Hz, 1H, H-5a), 2.99 (d, ^2J = 17.7 Hz, 1H, H-5b), 3.80 (s, 0.5H, H-1a), 3.80 (s, 0.5H, H-1b), 3.87, 3.88 (s, 3H, OCH_3), 5.66 (s, 0.5H, OH-a), 5.67 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 22.2, 22.7, 28.3, 29.4, 29.5, 29.5, 29.6, 31.9 (CH_2), 31.5 (C-5), 53.2 (OCH_3), 53.3 (C-1), 55.7 (OCH_3), 78.0 (t, J_{C-F} = 24.0 Hz, C-6), 118.3 (C-3), 130.3 (t, J_{C-F} = 299.3 Hz, CF_2Cl), 166.7, 171.7, 188.5 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −64.0 (d, $^2J_{F-F}$ = 166.4, 1F, CF_2Cl), −66.5 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3447 (w), 3025 (w), 2958 (w), 2923 (w), 2855 (w), 1741 (s), 1651 (m), 1614 (s), 1393 (m), 1258 (s), 1167 (s), 1127 (s), 1023 (s), 983 (s), 945 (s), 918 (m), 815 (w), 664 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 410 (M^+, 1), 392 (8), 372 (10), 356 (29), 326 (15), 325 (100), 307 (25), 293 (90), 248 (20), 221 (45), 153 (12),69 (15). ESI-MS: calcd. for $C_{19}H_{30}ClF_2O_5$ ($M+H^+$) 411.17443, found 411.1748; calcd. for $C_{19}H_{29}ClF_2NaO_5$ ($M+Na^+$) 433.16638, found 433.15629. Anal. calcd. for $C_{19}H_{29}ClF_2O_5$ (410.88): C, 55.54; H, 7.11. Found: C, 55.63; H, 7.187.

Methyl 6-(chlorodifluoromethyl)-6-hydroxy-4-methoxy-3-dodecyl-2-oxocyclohex-3-ene-carboxylate (6h): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadecadiene (**3p**) (0.857 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **6h** was isolated as slightly yellow solid (0.291 g, 64%); mp = 45–46 °C, R_F = 0.63 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.25–1.32 (m, 20H, $CH_3(CH_2)_{11}$), 2.22–2.31 (m, 2H, CH_2), 2.84 (brd, ^2J = 17.7 Hz, 1H, H-5a), 2.99 (d, ^2J = 17.7 Hz, 1H, H-5b), 3.80 (s, 0.5H, H-1a), 3.80 (s, 0.5H, H-1b), 3.88, 3.88 (s, 3H, OCH_3), 5.66 (s, 0.5H, OH-a), 5.67 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.3, 22.7, 28.3, 29.4, 29.5, 29.6, 29.7, 29.7, 29.7, 32.0 (CH_2), 31.5 (C-5), 53.2 (OCH_3), 53.3 (C-1), 55.7 (OCH_3), 78.0 (t, J_{C-F} = 24.0 Hz, C-6), 118.3 (C-3), 130.2 (t, J_{C-F} = 299.3 Hz, CF_2Cl), 166.7, 171.7, 188.5 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −64.0 (d, $^2J_{F-F}$ = 166.4, 1F, CF_2Cl), −66.5 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3420 (w), 3014 (w), 2956 (w), 2914 (m), 2850 (m), 1717 (m), 1652 (m), 1610 (s), 1382 (m), 1346 (m), 1255 (s), 1167 (s), 1081 (s), 1025 (w), 986 (s), 956 (m), 833 (w), 799 (w), 715 (m), 673 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 452 (M^+, 1), 434 (22), 414 (26), 399 (26), 398 (52), 373 (35), 371 (42), 368 (17), 367 (76), 366 (19), 349 (56), 335 (48), 250 (19), 249 (25), 248 (63), 247 (57), 244 (21), 235 (21), 228 (19), 223 (45), 221 (100), 216 (19), 212 (28), 209 (19), 181 (20), 153 (20), 69 (23), 43 (32), 41 (21), 29 (15). ESI-MS: calcd. for $C_{22}H_{36}ClF_2O_5$ ($M+H^+$) 453.22138, found 453.22163; calcd. for $C_{22}H_{35}ClF_2NaO_5$ ($M+Na^+$) 475.20333, found 475.20363. Anal. calcd. for $C_{22}H_{35}ClF_2O_5$ (452.96): C, 58.34; H, 7.79. Found: C, 58.26; H, 7.680.

Methyl 6-(chlorodifluoromethyl)-6-hydroxy-4-methoxy-3-hexadecyl-2-oxocyclohex-3-ene-carboxylate (6i): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-icosandiene (**3q**) (0.969 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **6i** was isolated as a slightly yellow solid (0.409 g, 80%); mp = 58–59 °C, R_F = 0.62 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.24–1.33 (m, 28H, $CH_3(CH_2)_{15}$), 2.22–2.31 (m, 2H, CH_2), 2.84 (brd, ^2J = 17.7 Hz, 1H, H-5a), 2.99 (d, ^2J = 17.7 Hz, 1H, H-5b), 3.80 (s, 0.5H, H-1a), 3.80 (s, 0.5H, H-1b), 3.88, 3.88 (s, 3H, OCH_3), 5.66 (s, 0.5H, OH-a), 5.67 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.3, 22.7, 28.2, 28.3, 29.4, 29.5, 29.5, 29.6, 29.6, 29.7, 29.7, 29.7, 31.9, 32.0 (CH_2), 31.5 (C-5), 53.2 (OCH_3), 53.3 (C-1), 55.7 (OCH_3), 78.0 (t, J_{C-F} = 24.0 Hz, C-6), 118.3 (C-3), 130.3 (t, J_{C-F} = 299.3 Hz, CF_2Cl), 166.7, 171.7, 188.5 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −64.0 (d, $^2J_{F-F}$ = 166.4, 1F, CF_2Cl), −66.5 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3382 (w), 3015 (w), 2954 (w), 2915 (s), 2849 (s), 1744 (m), 1715 (w), 1653 (w), 1614 (s), 1385 (m), 1249 (s), 1165 (s), 1082 (s), 1021 (s), 985 (s),955 (m), 940 (m), 837 (w), 718 (m), 665 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 508 (M^+, 1), 590 (22), 470 (15), 455 (21), 454 (45), 429 (15), 427 (38), 424 (22), 423 (75), 422 (19), 405 (29), 391 (30), 279 (18), 250 (33), 249 (40), 248 (100), 247 (69), 245 (21), 244 (27), 235 (19), 230 (20), 228 (34), 223 (40), 221 (98), 214 (29), 213 (46), 212 (41), 211 (19), 209 (24), 195 (20), 187 (33), 181 (27), 153 (22), 97 (20), 83 (28), 71 (25), 69 (51), 67 (18), 59 (19), 57 (52), 55 (58), 44 (49), 43 (79), 41 (52). ESI-MS: calcd. for $C_{26}H_{44}ClF_2O_5$ ($M+H^+$) 509.28399, found 509.28398; calcd. for $C_{26}H_{43}ClF_2NaO_5$ ($M+Na^+$) 531.26593, found 531.26622. Anal. calcd. for $C_{26}H_{43}ClF_2O_5$ (509.07): C, 61.34; H, 8.51. Found: C, 61.38; H, 8.478.

Methyl 6-(chlorodifluoromethyl)-6-hydroxy-4-methoxy-3-isobutyl-2-oxocyclohex-3-ene-carboxylate (6j): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-6-methyl-1,3-heptadiene (**3y**) (0.661 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **6j** was isolated as a slightly yellow solid (0.271 g, 80%); mp = 85–87 °C, R_F = 0.53 (*n*-heptane/EtOAc = 3:2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88, 088 (d, ^3J = 6.6 Hz, 3H, CH_3), 1.19–1.26 (m, 2H, CH_2), 1.45–1.54 (m, 1H, CH), 2.22–2.32 (m, 2H, CH_2), 2.84 (brd, ^2J = 17.7 Hz, 1H, H-5a), 2.99 (d, ^2J = 17.7 Hz, 1H, H-5b), 3.79 (s, 0.5H, H-1a), 3.80 (s, 0.5H, H-1b), 3.88, 3.89 (s, 3H, OCH_3), 5.66 (s, 0.5H, OH-a), 5.67 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3 (CH_2), 22.4, 22.5 (CH_3), 28.2 (CH), 31.5 (C-5), 37.3 (CH_2), 53.2 (OCH_3), 53.3 (C-1), 55.7 (OCH_3), 78.0 (t, J_{C-F} = 24.0 Hz, C-6), 118.4 (C-3), 130.2 (t, J_{C-F} = 299.3 Hz, CF_2Cl), 166.6, 171.7, 188.5 (C). ^{19}F NMR (282 MHz, $CDCl_3$):

δ = −64.0 (d, $^2J_{F-F}$ = 166.4, 1F, CF_2Cl), −66.5 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3431 (w), 3018 (w), 2962 (w), 2905 (w), 2871 (w), 2849 (w), 1740 (s), 1652 (s), 1615 (s), 1439 (m), 1341 (m), 1253 (s), 1167 (s), 1132 (s), 1093 (s), 986 (s), 972 (s), 943 (s), 918 (s), 817 (s), 795 (m), 709 (w), 664 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 354 (M^+, 1), 336 (35), 316 (18), 300 (51), 279 (34), 269 (64), 261 (16), 260 (30), 251 (87), 249 (30), 248 (86), 247 (49), 244 (39), 241 (22), 238 (19), 237 (91), 235 (20), 228 (30), 223 (43), 221 (100), 216 (30), 212 (39), 209 (27), 199 (20), 181 (28), 155 (20), 153 (41), 83 (16), 69 (53), 59 (26), 55 (16), 53 (18), 43 (28), 41 (26). ESI-MS: calcd. for $C_{15}H_{22}ClF_2O_5$ ($M+H^+$) 355.11183, found 355.11211; calcd. for $C_{15}H_{21}ClF_2NaO_5$ ($M+Na^+$) 377.09378, found 377.09392. Anal. calcd. for $C_{15}H_{21}ClF_2O_5$ (354.77): C, 50.78; H, 5.97. Found: C, 51.03; H, 5.987.

Methyl 6-(chlorodifluoromethyl)-6-hydroxy-4-methoxy-3-chloro-2-oxocyclohex-3-ene-carboxylate (6k): Starting with **2a** (0.200 g, 1 mmol), 1-methoxy-1,3-bis(trimethylsilyloxy)-4-chloro-1,3-butadiene (**3z**) (0.589 g, 2 mmol) and Me_3SiOTf (0.181 mL, 1 mmol) in CH_2Cl_2 (10 mL), product **6k** was isolated as a yellow solid (0.165 g, 52%); mp = 98–100 °C, R_F = 0.32 (*n*-heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.01 (brd, ^2J = 17.7 Hz, 1H, H-5a), 3.13 (d, ^2J = 17.7 Hz, 1H, H-5b), 3.89 (s, 3H, OCH_3), 3.93 (s, 0.5H, H-1a), 3.94 (s, 0.5H, H-1b), 4.05 (s, 3H, OCH_3), 5.66 (s, 0.5H, OH-a), 5.67 (s, 0.5H, OH-b). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.5 (C-5), 53.5 (C-1), 53.9 (OCH_3), 57.2 (OCH_3), 77.7 (t, J_{C-F} = 24.0 Hz, C-6), 109.5 (C-3), 129.7 (t, J_{C-F} = 299.3 Hz, CF_2Cl), 166.3, 170.4, 182.2 (C). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −64.1 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl), −66.4 (d, $^2J_{F-F}$ = 166.4 Hz, 1F, CF_2Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3404 (w), 3005 (w), 2958 (w), 2857 (w), 1726 (w), 1669 (m), 1595 (s), 1375 (m), 1347 (m), 1261 (s), 1169 (s), 1090 (m), 1041 (s), 1008 (m), 947 (s), 797 (m), 662 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 318 (M^+, 1), 300 (22), 233 (33), 223 (35), 221 (100), 207 (21), 174 (41), 103 (12), 69 (35), 59 (25). ESI-MS: calcd. for $C_{10}H_{11}Cl_2F_2O_5$ ($M+H^+$) 318.99461, found 318.99511; calcd. for $C_{10}H_{10}Cl_2F_2NaO_5$ ($M+Na^+$) 340.97656, found 340.97701. Anal. calcd. for $C_{10}H_{10}Cl_2F_2O_5$ (319.09): C, 37.64; H, 3.16. Found: C, 37.86; H, 3.452.

General procedure for the synthesis of 7a–e: The reaction was carried out in a pressure tube. To a benzene suspension (10 mL/1 mmol of **4**) of **4** (1 mmol) was added $Bu_3SnCH_2CH{=}CH_2$ (5.0 mmol) and AIBN (azobisisobutyronitrile) (0.12 mmol) and the resultant solution was degassed by bubbling argon through the solution for 5 min. The mixture was heated up to 90 °C under Argon atmosphere for 20 h with stirring. The temperature of the solution was allowed to warm to room temperature. The pressure tube was rinsed with benzene and the organic solution was concentrated in vacuo. The residue was purified by a column chromatography (*n*-heptane/EtOAc).

Methyl 2-(1,1-difluorobut-3-enyl)-6-hydroxy-4-methoxy-benzoate (7a): Starting with **4a** (0.266 g, 1 mmol), $Bu_3SnCH_2CH{=}CH_2$ (1.65 g, 5.0 mmol), AIBN (0.020 g, 0.12 mmol), the product **7a** was isolated as a colorless oil (0.196 g, 72%); R_F = 0.45 (heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.16 (dt, $^3J_{HH}$ = 7.1 Hz, $^3J_{HF}$ = 17.1 Hz, 2H, CH_2), 3.82, 3.92 (s, 3H, OCH_3), 5.16 (d, $^3J_{trans}$ = 1.5 Hz, 1H, $CH{=}CH_2$), 5.21 (d, $^3J_{cis}$ = 1.5 Hz, 1H, $CH{=}CH_2$), 5.80–5.94 (m, 1H, $CH{=}CH_2$), 6.52 (s, 1H, H-3), 6.65 (s, 1H, H-5), 10.50 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.1 (t, $^2J_{C-F}$ = 27 Hz, CH), 52.4, 55.6 (OCH_3), 101.9 (CH), 104.3 (t, $^3J_{C-F}$ = 2.25 Hz, C-5), 108.5 (t, $^3J_{C-F}$ = 10.5 Hz, C-6), 120.3 (CH_2), 121.8 (t, $^1J_{C-F}$ = 243.75 Hz, CF_2), 129.4 (t, $^3J_{C-F}$ = 4.5 Hz, CH), 139.6 (t, $^3J_{C-F}$ = 26.25 Hz, C-6), 163.2 (C–OH), 163.3 (C–OMe), 170.2 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −88.67 (CF_2). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2982 (w), 1653 (m), 1614 (s), 1426 (m), 1356 (m), 1260 (s), 1098 (s), 978 (s), 730 (m), 620 (m), 538 (m), 429 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 272 (M^+, 92), 241 (22), 240 (74), 231 (16), 221 (15), 220 (26), 212 (28), 211 (32), 201 (12), 198 (13), 194 (13), 193 (100), 192 (33), 177 (10), 171 (25), 168 (11), 149 (34), 133 (28), 121 (14), 101 (13), 69 (15). HRMS (EI, 70 eV): calcd. for $C_{13}H_{14}F_2O_4$ (M^+) 272.08547, found 272.085365. Anal. calcd. for $C_{13}H_{14}F_2O_4$ (232.181): C, 57.35; H, 5.18. Found: C, 56.98; H, 4.907.

Isopropyl 2-(1,1-difluorobut-3-enyl)-6-hydroxy-4-methoxy-benzoate (7b): Starting with **4c** (0.294 g, 1 mmol), $Bu_3SnCH_2CH{=}CH_2$ (1.65 g, 5.0 mmol), AIBN (0.020 g, 0.12 mmol), the product **7b** was isolated as a slight yellow oil (0.289 g, 96%); R_F = 0.69 (heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38, 1.40 (s, 6H, CH_3), 3.16 (dt, $^3J_{HH}$ = 7.1 Hz, $^3J_{HF}$ = 17.1 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 5.17 (d, $^3J_{trans}$ = 1.8 Hz, 1H, $CH{=}CH_2$), 5.22 (d, $^3J_{cis}$ = 1.6 Hz, 1H, $CH{=}CH_2$), 5.28–5.37 (m, 1H, CH), 5.82–5.93 (m, 1H, $CH{=}CH_2$), 6.52 (s, 1H, H-3), 6.63 (s, 1H, H-5), 10.70 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 21.6 (CH_3), 43.1 (t, $^2J_{C-F}$ = 27 Hz, CH), 55.6 (OCH_3), 70.3 (CH), 101.9 (CH), 105.0 (t, $^3J_{C-F}$ = 2.25 Hz, C-5), 108.4 (t, $^3J_{C-F}$ = 10.5 Hz, C-6), 120.3 (CH_2), 121.9 (t, $^1J_{C-F}$ = 243.75 Hz, CF_2), 129.3 (t, $^3J_{C-F}$ = 4.5 Hz, CH), 139.4 (t, $^3J_{C-F}$ = 26.25 Hz, C-6), 163.0 (C–OH), 163.2 (C–OMe), 169.5 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −87.85 (CF_2). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2984 (w), 1655 (m), 1580 (s), 1466 (m), 1426 (w), 1356 (m),1261 (s), 1204 (m), 1099 (s), 1024 (m), 979 (m), 842 (m), 620 (s), 591 (w), 476 (w), 429 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 300 (M^+, 46), 258 (18), 241 (30), 240 (67), 221 (16), 220 (32), 214 (22), 213 (30), 212 (28), 198 (15), 197 (28), 194 (18), 193 (100), 192 (26), 177 (23), 171 (11), 163 (10), 162 (11), 150(13), 149 (35), 69 (12), 43 (22), 41 (16). HRMS (EI, 70 eV): calcd. for $C_{15}H_{18}F_2O_4$ (M^+) 300.11677, found 300.116729. Anal. calcd. for $C_{13}H_{14}F_2O_4$ (300.30): C, 59.99; H, 6.04. Found: C, 59.72; H, 6.031.

Methyl 2-(1,1-difluorobut-3-enyl)-6-hydroxy-4-methoxy-5-npropylbenzoate (7c): Starting with **4i** (0.314 g, 1 mmol), $Bu_3SnCH_2CH{=}CH_2$ (1.65 g, 5.0 mmol), AIBN (0.020 g, 0.12 mmol), the product **7c** was isolated as a colorless oil (0.281 g, 89%); R_F = 0.61 (heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.35 (m, ^3J = 7.5 Hz, 2H, CH_2), 2.46 (t, ^3J = 7.7 Hz, 2H, CH_2), 2.96 (dt, $^3J_{HH}$ = 7.1 Hz, $^3J_{HF}$ = 17.1 Hz, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.03 (d, $^3J_{trans}$ = 16.9 Hz, 1H, $CH{=}CH_2$), 5.06 (d, $^3J_{cis}$ = 8.7 Hz, 1H, $CH{=}CH_2$), CH_2), 5.72 (dt, $^3J_{H-H}$ = 7.1 Hz, $^4J_{H-F}$ = 27.3 Hz, dd, $^3J_{cis}$ = 7.0 Hz, $^3J_{trans}$ = 12,7 Hz, 1H, $CH{=}CH_2$), 6.44 (s, 1H, H-5), 9.96 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.31 (CH_3), 19.48, 20.97 (CH_2), 41.10 (t, $^2J_{C-F}$ = 27.0 Hz, CH_2), 50.01 (OCH_3), 53.36 (OCH_3), 100.14 (t, $^3J_{C-F}$ = 2.25 Hz, C-5), 103.01 (C-1), 117.58 (C-3), 117.86 (CH_2), 119.87 (t, $^1J_{C-F}$ = 243.75 Hz, CF_2), 127.25 (t, $^3J_{C-F}$ = 4.5 Hz, CH), 134.40 (t, $^2J_{C-F}$ = 26.25 Hz, C-6), 156.97 (C-2), 158.29 (C-4), 168.41 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −88.80 (CF_2). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2956 (w), 2936 (w), 2873 (w), 1935 (m), 1655 (m), 1611 (w), 1509 (w), 1395 (m), 1288 (s), 1167 (m), 1132 (m), 1109 (w), 985 (m), 906 (s), 839 (w), 784 (m), 695 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 314 (M^+, 92), 288 (45), 245 (22), 241 (22), 240 (70), 231 (16), 221 (9), 220 (20), 212 (30), 211 (32), 201 (10), 198 (13), 194 (18), 193 (100), 192 (33), 177 (10), 171 (25), 168 (11), 149 (38), 133 (18), 121 (14), 102 (15), 69 (8). HRMS (ESI): calcd. for $C_{16}H_{20}O_4F_2$ ($M+Na]^+$) 337.1222, found 337.1231.

Methyl 2-(1,1-difluorobut-3-enyl)-6-hydroxy-4-methoxy-5-isopropylbenzoate (7d): Starting with **4j** (0.314 g, 1 mmol), $Bu_3SnCH_2CH{=}CH_2$ (1.65 g, 5.0 mmol), AIBN (0.020 g, 0.12 mmol), the product **7d** was isolated as a slight yellow oil (0.267 g, 85%); R_F = 0.57 (heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 3.05 (dt, $^3J_{HH}$ = 7.1 Hz, $^3J_{HF}$ = 17.1 Hz, 2H, CH_2), 3.54 (m, ^3J = 7.1 Hz, 1H, CH), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.13 (d, $^3J_{trans}$ = 12.1 Hz, 1H, $CH{=}CH_2$), 5.18 (d, $^3J_{cis}$ = 4.5 Hz, 1H, $CH{=}CH_2$), 5.83 (dt, $^3J_{H-H}$ = 7.1 Hz, $^4J_{H-F}$ = 27.4 Hz, dd, $^3J_{cis}$ = 7.0 Hz, $^3J_{trans}$ = 13.65 Hz, 1H, $CH{=}CH_2$), 6.52 (s, 1H, H-5), 10.09 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9 (CH_3), 24.2 (CH), 43.4 (t, $^2J_{C-F}$ = 27.0 Hz, CH_2), 52.3, 55.6 (OCH_3), 102.9 (t, $^3J_{C-F}$ = 2.4 Hz, C-5), 105.6 (C-1), 120.2 (t, $^1J_{C-F}$ = 243.7 Hz,

CF_2), 122.1 (CH_2), 124.4 (C-3), 129.5 (t, $^3J_{C-F}$ = 4.5 Hz, CH), 136.6 (t, $^2J_{C-F}$ = 26.25 Hz, C-6), 159.3 (C-2), 160.7 (C-4), 170.8 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −88.96 (CF_2). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2958 (w), 2903 (w), 2869 (w), 1697 (m), 1655 (m), 1602 (w), 1438 (w), 1310 (w), 1234 (m), 1148 (m), 1103 (w), 1095 (s), 842 (m), 804 (w), 702 (w), 626 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 314 (M^+, 92), (M^+, 92), 288 (40), 243 (22), 240 (20), 241 (75), 231 (10), 221 (13), 212 (33), 210 (35), 194 (14), 191 (100), 192 (30), 177 (15), 171 (12), 168 (10), 133 (16), 121 (12), 102 (10), 69 (13). HRMS (EI, 70 eV): calcd. for $C_{16}H_{20}O_4F_2$ (M^+) 314.13242, found 314.132385.

Methyl 2-(1,1-difluorobut-3-enyl)-6-hydroxy-4-methoxy-5-octylbenzoate (7e): Starting with **4o** (0.384 g, 1 mmol), $Bu_3SnCH_2CH{=}CH_2$ (1.65 g, 5.0 mmol), AIBN (0.020 g, 0.12 mmol), the product **7e** was isolated as a colorless oil (0.296 g, 77%); R_F = 0.59 (heptane/EtOAc = 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70 (t, ^3J = 7,0 Hz, 3H, CH_3) 1.00–1.35 (m, 12H, $(CH_2)_6$), 2.47 (t, ^3J = 7,5 Hz, 2H, CH_2), 2.96 (dt, $^3J_{HH}$ = 7.1 Hz, $^3J_{HF}$ = 17.0 Hz, 2H, CH_2), 3.68 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.02 (d, $^3J_{trans}$ = 12.2 Hz, 1H, CH=CH_2), 5.07 (d, $^3J_{cis}$ = 4.7 Hz, 1H, CH=CH_2), 5.72 (dt, $^3J_{H-H}$ = 7.0 Hz, $^4J_{H-F}$ = 27.3 Hz, dd, $^3J_{cis}$ = 7.2 Hz, $^3J_{trans}$ = 13.65 Hz, 1H, CH=CH_2), 6.44 (s, 1H, H-5), 9.96 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 22.9, 28.5, 29.4, 29.7, 31.9 (CH_2), 43.3 (t, $^2J_{C-F}$ = 27.0 Hz, CH_2), 52.2, 55.6 (OCH_3), 102.4 (t, $^3J_{C-F}$ = 2.25 Hz, C-5), 105.3 (C-1), 120.1 (CF_2), 122.1 (CH_2), 126.0 (C-3), 129.5 (t, $^3J_{C-F}$ = 4.5 Hz, CH), 136.5 (t, $^2J_{C-F}$ = 26.25 Hz, C-6), 159.2 (C-2), 160.4 (C-4), 170.65 (CO). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −88.79 (CF_2). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2959 (w), 2903(w), 2874 (w), 1700 (m), 1612 (w), 1608 (w), 1234 (m), 1180 (m), 1144 (m), 1130 (m), 1109 (m), 1099 (m), 1082 (s), 840 (m), 802 (w), 693 (w), 627 (m). GC–MS (EI, 70 eV): *m*/*z* (%): 384 (M^+, 88), 354 (12), 323 (22), 301 (34), 288 (42), 243 (21), 240 (13), 241 (66), 231 (10), 221 (13), 212 (33), 191 (100), 192 (22), 177 (13), 171 (10), 168 (22), 133 (11), 121 (11), 102 (10), 69 (10). HRMS (EI): calcd. for $C_{21}H_{30}O_4F_2$ (M^+) 384.21122, found 384.21119.

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