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One-Pot Synthesis of Functionalized 3-(Trifluoromethyl)phenols by [3+3] Cyclization of 1,3-Bis(silyl enol ethers) with α,β-Unsaturated Trifluoromethyl Ketones

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Dedicated to Professor Dr. Ralf Miethchen

Keywords: Arenes / Cyclizations / Organic fluoro compounds / Silyl enol ethers / Regioselectivity

Functionalized 3-(trifluoromethyl)phenols were prepared by formal [3+3] cyclization of 1,3-bis(silyl enol ethers) with readily available open-chained and cyclic α,β-unsaturated trifluoromethyl ketones. The reaction of 3,4-dihydro-5-(trifluoroacetyl)-2*H*-pyran with 1,3-bis(silyl enol ethers) resulted in a domino process to give new functionalized dihydropyrans. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2008)

Introduction

The trifluoromethyl group represents, due to its unique stereoelectronic properties, a very important substituent in organic and medicinal chemistry.[1] While the size of the CF_3 group is comparable to the methyl group, its high electronegativity results in a much different electronic situation and a change of the reactivity. This plays an important role in drug–receptor interactions. In addition, the increased lipophilicity of CF_3-substituted molecules improves their in vivo transport. Undesirable metabolic transformations are often avoided, due to the high chemical and biological stability of the CF_3 group. Therefore, the synthesis of CF_3-substituted arenes and hetarenes plays an important role in drug discovery.[1] Trifluoromethyl-substituted compounds also play an increasingly important role as ligands[2] for catalytic reactions in fluorous biphase systems and supercritical carbon dioxide.[3] This takes advantage of the excellent solubility of trifluoromethyl- and perfluoroalkyl-substituted molecules in fluorophilic solvents. It is noteworthy that CF_3-substituted arenes also represent important substructures of various organocatalysts (such as CF_3-substituted *N*,*N*′-diarylthioureas).[4,5]

Trifluoromethyl-substituted arenes and hetarenes are available by trifluoromethylation of appropriate starting materials.[6,7] This includes, for example, the reaction of aryl halides with (trifluoromethyl)copper, the SF_4-mediated transformation of carboxylic acids into CF_3 groups, and the transformation of CX_3 into CF_3 groups. However, these reactions are often applicable only to specific substrates. (Trifluoromethyl)copper is rather unstable and rapidly undergoes decomposition in reactions with "difficult" substrates. In addition, it has to be taken into consideration that the synthesis of complex aromatic starting materials is often a difficult task. An important alternative for the synthesis of CF_3-substituted arenes relies on synthetic transformations of CF_3-containing building blocks.[8] This strategy is a good supplement for direct fluorination methods, and is gaining considerable importance. For example, (trifluoromethyl)phenols have been prepared based on cyclocondensation reactions,[9] metalation of (trifluoromethyl)arenes and subsequent addition of electrophiles,[10] and Diels–Alder reactions.[11] 3,5-Bis(trifluoromethyl)anilines were prepared by cyclization of enamines with 1,1,1,5,5,5-hexafluoroacetylacetone.[12] α,β-Unsaturated trifluoromethyl ketones, readily available by condensation of enol ethers with trifluoroacetic anhydride,[13] have been widely used for the synthesis of CF_3-substituted heterocycles.[14] The synthesis of CF_3-substituted benzene derivatives by this method has, despite the pharmacological and synthetic importance of these compounds, only scarcely been reported to date. 2-Acetyl-5-(trifluoromethyl)phenol was prepared by sodium hydride mediated cyclization of acetylacetone with 4-ethoxy-1,1,1-trifluorobut-3-en-2-one.[15] However, this protocol proved not to be general, and is restricted to the synthesis of only one specific example. Recently, we have reported[16] the synthesis of 2-acetyl- and 2-(alkoxycarbonyl)-3-(trifluoromethyl)phenols by formal [3+3] cyclizations[17,18] of 1,3-bis(silyl enol ethers) − electroneutral

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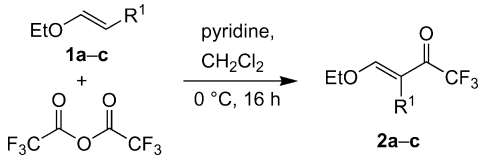
equivalents of 1,3-dicarbonyl dianions (masked dianions)[19] – with 4-ethoxy-1,1,1-trifluoroalk-3-en-2-ones. These reactions offer a convenient and regioselective approach to functionalized CF_3-substituted phenols which are not readily available by other methods. Herein we wish to report full details of these studies. With regard to our preliminary communication,[16] the preparative scope was significantly extended. In addition, we report a new domino reaction of 1,3-bis(silyl enol ethers) with 3,4-dihydro-5-(trifluoroacetyl)-2*H*-pyran.

Results and Discussion

Reactions of electron-rich olefins such as vinyl ethers or vinyl sulfides with trifluoroacetic anhydride give the corresponding trifluoroacetylated compounds in high yields. Following the procedure of Hojo[13b,13c] and Colla,[13d] the synthesis of substituted enol ethers **1a**–**c** with trifluoroacetic anhydride afforded the α,β-unsaturated trifluoromethyl ketones **2a**–**c** in good yields (Scheme 1, Table 1). This reaction is known to proceed by an addition–elimination mechanism.[20–22]



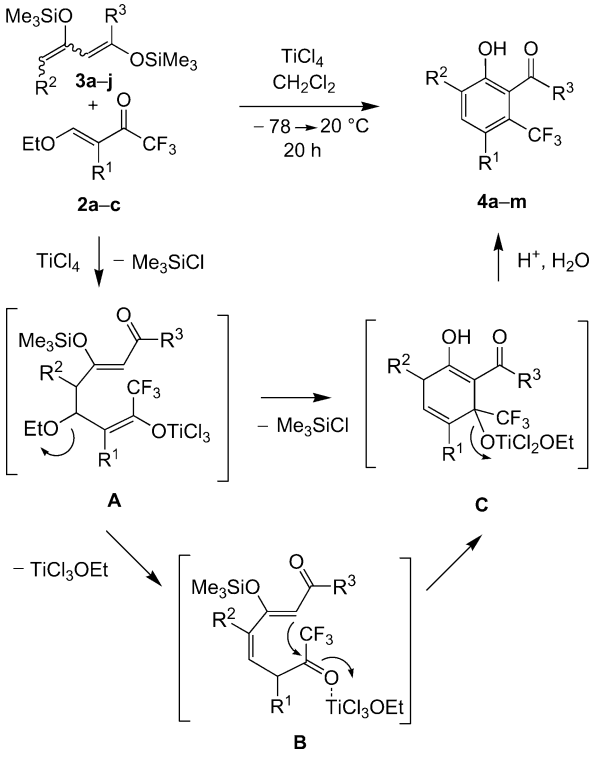
Scheme 1. Synthesis of α,β-unsaturated trifluoromethyl ketones **2a**–**c**.

Table 1. Synthesis of α,β-unsaturated trifluoromethyl ketones **2a**–**c**.

2	R^1	% Yield[a]
a	H	93[13e]
b	Me	64[13d]
c	Et	86

[a] Isolated yield.

The $TiCl_4$-mediated cyclization of enone **2a** with 1,3-bis(silyl enol ether) **3a** afforded 3-(trifluoromethyl)phenol **4a** (Scheme 2, Table 2). The reaction presumably proceeds by regioselective attack of the terminal carbon atom of **3a** onto the carbon attached to the ethoxy group of enone **2a**, cyclization by attack of the central carbon atom of **3a** onto the carbonyl group, and aromatization by elimination (either before or during the aqueous work-up). The high concentration of the reaction mixture and the employment of an excess of **3a** (2.0 equiv.) proved to be important parameters during the optimization of this reaction. The cyclization of enones **2a**–**c** with 1,3-bis(silyl enol ethers) **3a**–**j** afforded, following our optimized protocol, the 3-(trifluoromethyl)phenols **4a**–**m** in 20 to 88% yield. The best yields were generally obtained for those phenols derived from the methyl- and ethyl-substituted enones **2b** and **2c** (except for products **4j** and **4m**). The mechanism proposed for the formation of phenols **4a**–**m** is supported by the following observation: during the formation of **4f**, the non-aromatized product **5** was isolated as a side product in 21% yield. The formation of this type of side product could be explained by hydrolysis of intermediate **C**, as not all of the material underwent the final aromatization (Scheme 2). The relatively low yields of some phenols **4** can be explained by the formation of side products such as **5**.

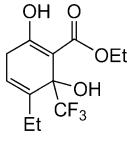


Scheme 2. Possible mechanism of the formation of 3-(trifluoromethyl)phenols **4a**–**m**.

Table 2. Synthesis of 3-(trifluoromethyl)phenols **4a**–**m**.

3	2	4	R^1	R^2	R^3	% Yield[a]
a	**a**	**a**	H	H	OEt	30
b	**a**	**b**	H	Me	OEt	20
c	**a**	**c**	H	Et	OEt	26
d	**b**	**d**	Me	H	OMe	45
e	**b**	**e**	Me	H	Me	58
a	**c**	**f**	Et	H	OEt	71[b]
d	**c**	**g**	Et	H	OMe	71
e	**c**	**h**	Et	H	Me	40
f	**c**	**i**	Et	*n*Bu	OMe	77
g	**c**	**j**	Et	$H_2C{=}CH(CH_2)_2$	OMe	20
h	**c**	**k**	Et	$Cl(CH_2)_6$	OMe	88
i	**c**	**l**	Et	*n*-C_7H_{15}	OMe	53
j	**c**	**m**	Et	$PhCH_2$	OMe	24

[a] Isolated yields. [b] Compound **5** was also isolated in 21% yield (see structure).



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The ^{1}H NMR spectra of products **4a**–**m** show a sharp signal between δ = 10 and 12 ppm which can be assigned to the proton involved in a hydrogen bond: O–H···O=C. The CF_3 group appears (^{19}F NMR) at about –63 ppm for acetophenone derivatives (**4e**,**h**) and in the range of –52 ppm for salicylate derivatives (**4a**–**d**, **f**–**g**, **i**–**m**). For comparison, CF_3 groups attached to a simple benzene moiety usually give rise to a signal at δ = –64 ppm[23] and CF_3 groups located next to a carbonyl group resonate at about –70 ppm. The structure of **4g** was independently confirmed by an X-ray single-crystal structure analysis (Figure 1).[24] The structure of **5** was elucidated by NMR, MS and IR spectroscopy. The resonance (^{19}F NMR) of the CF_3 group (δ = –80 ppm) suggests that the latter is attached to an alkene rather than to an arene moiety. In the ^{1}H NMR spectrum, no signals are observed in the aromatic region. For proton 4-H, a doublet is observed at δ = 5.73 ppm and a double doublet for 3a/b-H at δ = 2.88–3.13 ppm.

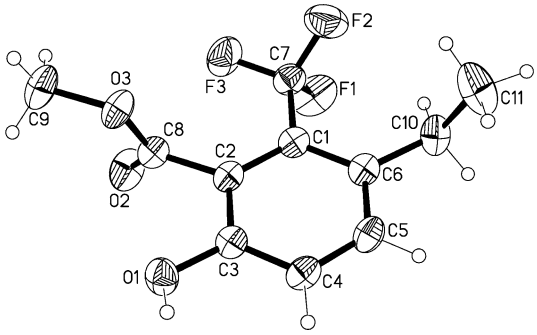
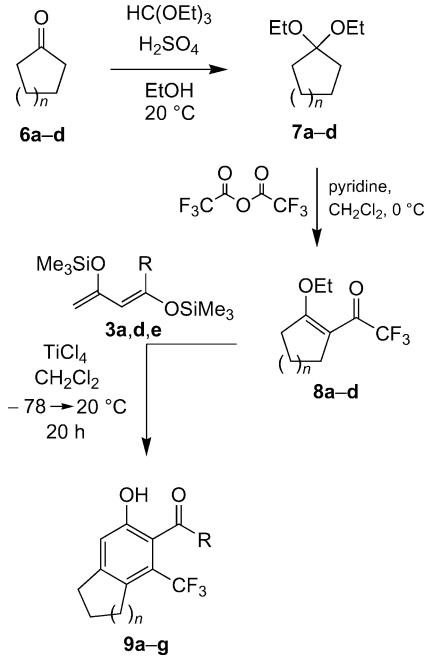


Figure 1. Molecular structure of **4g** in the crystal (ORTEP plot, 50% probability level, one of the two symmetry-independent molecules is shown).

The known cyclic α,β-unsaturated trifluoromethyl ketones **8a**–**d** were prepared, following a known procedure,[25,26] by reaction of trifluoroacetic anhydride with ketals **7a**–**d** (Scheme 3). The latter are available from cycloalkanones **6a**–**d**.[27] Notably, enol ethers **8a**–**d** were formed, in contrast to the corresponding *silyl* enol ethers,[28] with definite regioselectivity. This is an important issue for the regioselectivity of the [3+3] cyclizations, since the employment of a mixture of regioisomeric enol ethers usually results in the formation of a mixture of regioisomeric phenols. Besides, it is known that the silyl group of 3-(silyloxy)alk-2-en-1-ones can undergo a $TiCl_4$-mediated rearrangement from one oxygen atom to the other, which may also result in the formation of regioisomeric mixtures of phenols (depending on the substitution pattern).[17,18] In fact, this type of rearrangement is *not* observed for 3-alkoxyalk-2-en-1-ones.

The $TiCl_4$-mediated cyclization of enones **8a**–**d** with 1,3-bis(silyl enol ethers) **3a**,**d**,**e** afforded the annulated 3-(trifluoromethyl)phenols **9a**–**g** in moderate to good yields (except for **9b**) and with excellent regioselectivity (Table 3). The formation of the other regioisomer was not observed. The products are presumably formed by the mechanism proposed for the formation of **4a**–**m**. In most cases, the yields of phenols **9b**,**d**,**e**,**g**, prepared from acetylacetone-derived 1,3-bis(silyl enol ether) **3e**, were lower than those of phenols **9a**,**f** which were prepared from β-keto-ester-derived 1,3-bis(silyl enol ethers) **3a**,**d**. This can be explained by the lower reactivity of **3e** compared to **3a**,**d**. The structures of products **9a**–**g** were established by spectroscopic methods. The resonances of the CF_3 groups (^{19}F NMR) were observed in the expected range of δ = –51 ppm (ester derivatives) and –63 ppm (keto derivatives). In addition the structure of **9c** was independently confirmed by an X-ray single-crystal diffraction analysis (Figure 2).[24] The unit cell hosts two symmetric independent molecules of **9a**, which are interconnected by hydrogen bonds.



Scheme 3. Synthesis of annulated 3-(trifluoromethyl)phenols **9a**–**g**.

Table 3. Synthesis of annulated 3-(trifluoromethyl)phenols **9a**–**g**.

3	8	9	*n*	R	% Yield[a]
d	**a**	**a**	1	OMe	68
e	**a**	**b**	1	Me	14
d	**b**	**c**	2	OMe	30
e	**b**	**d**	2	Me	37
e	**c**	**e**	3	Me	40
a	**d**	**f**	4	OEt	84
e	**d**	**g**	4	Me	40

[a] Isolated yields.

The reaction of hexane-2,5-dione (**10**) with trimethyl orthoformate in the presence of *p*-toluenesulfonic acid (*p*TsOH) afforded the known bis(ketal) **11**.[29] The latter was transformed into bis(enone) **12** by treatment with trifluoroacetic anhydride (Scheme 4).[30] The $TiCl_4$-mediated cyclization of **12** with 1,3-bis(silyl enol ether) **3a** afforded bis[4-(trifluoromethyl)salicylate] **13**.

The aryl-substituted α,β-unsaturated trifluoromethyl ketones **16a**–**c** were prepared by reaction of trifluoroacetic anhydride with ketals **15a**–**c**, which are available from acetophenones **14a**–**c**.[31] In the $TiCl_4$-mediated cyclization of **16a**

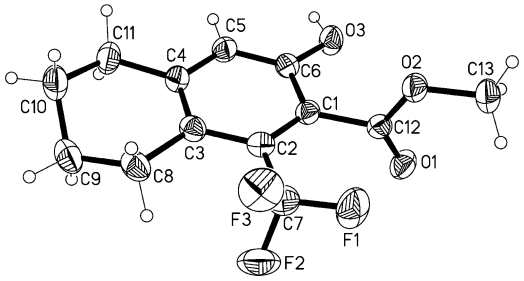
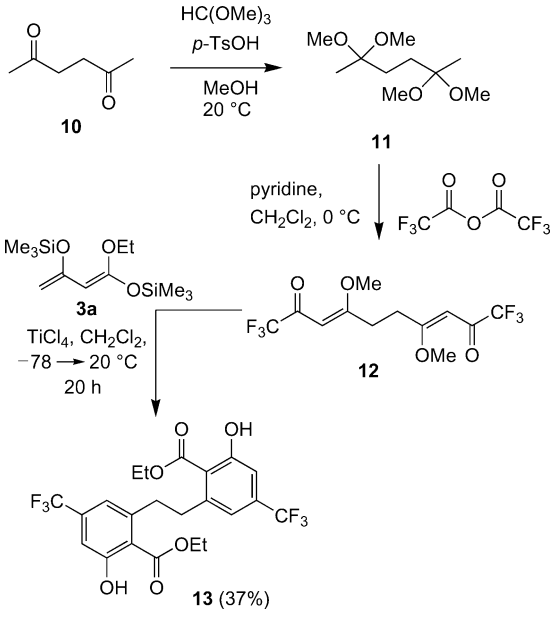


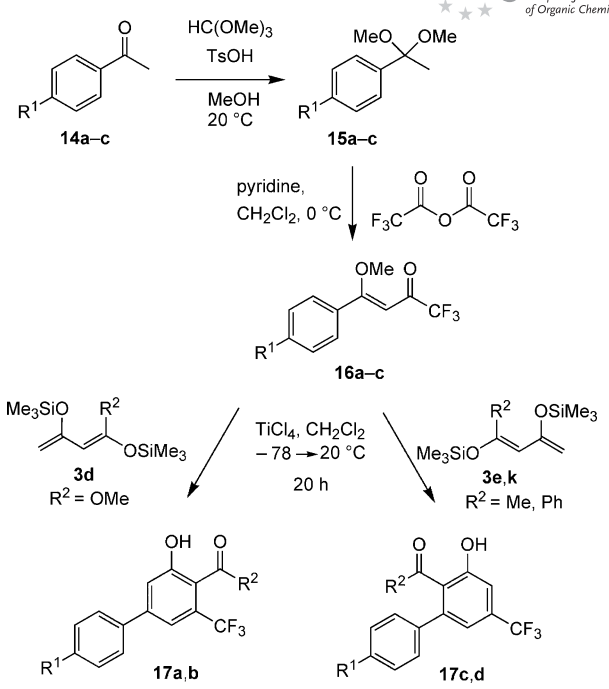
Figure 2. Molecular structure of **9c** in the crystal (ORTEP plot, 50% probability level).



Scheme 4. Synthesis of bis[4-(trifluoromethyl)salicylate] **13**.

and **16b** with 1,3-bis(silyl enol ether) **3d**, the appropriate CF_3-substituted biaryls **17a** and **17b** were obtained (Scheme 5, Table 4). The cyclization of 1,3-bis(silyl enol ethers) **3e** and **3k** with **16a** and **16c** afforded the biaryls **17c** and **17d**, respectively. It is noteworthy that different regioisomers were obtained for the reactions of β-keto-ester- and 1,3-diketone-derived 1,3-bis(silyl enol ethers), as evidenced by X-ray structural analysis (Figures 3 and 4).[24] Both compounds **17b** and **17d** were independently characterized by this method. Any formation of the opposite regioisomer could not be detected. This can be explained based on the different reactivities of the starting materials **3d**,**e**,**k**.

Treatment of 3,4-dihydro-2*H*-pyran (**18**) with trifluoroacetic anhydride afforded the known[13d,22] cyclic enone **19**. The $TiCl_4$-mediated reaction of **19** with 1,3-bis(silyl enol ethers) **3a**,**e**,**l**,**k** afforded the 2-(trifluoroalkylated) 5,6-dihydro-4*H*-pyran derivatives **20a**–**d** (Scheme 6, Table 5). The formation of the products can be explained by a domino reaction: the $TiCl_4$-mediated conjugate addition of the terminal carbon atom of the 1,3-bis(silyl enol ether) to **19** gave intermediate **A**. Ring opening of the pyran ring by a retro-Michael reaction afforded intermediate **B**. Attack of the



Scheme 5. Synthesis of biaryls **17a**–**d**.

Table 4. Products and yields of **17a**–**d**.

3	16	17	R^1	R^2	% Yield[a]
d	**a**	**a**	Cl	OMe	25
d	**b**	**b**	Br	OMe	20
e	**a**	**c**	Cl	Me	40
k	**c**	**d**	H	Ph	28

[a] Isolated yields.

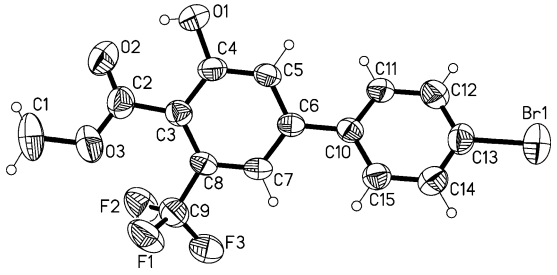


Figure 3. Molecular structure of **17b** in the crystal (ORTEP plot, 50% probability level, one out of the four symmetry-independent molecules is shown).

oxygen atom onto the carbonyl group gave intermediate **C**, and subsequent elimination afforded the products **20a**–**d**. The structure was independently confirmed by an X-ray crystal structure analysis (Figure 5).[24] In solution ($CDCl_3$), the β-keto-ester-derived product **20a** exists as a tautomeric mixture (ketone/enol ratio 2:1), which is supported by NMR spectroscopic observations. All 1,3-diketone-derived products **20b**–**d** exclusively exist in their enol tautomeric form. In case of the synthesis of **20b**, side product **21** was isolated in 40% yield. The formation of **21** can be explained by attack of the terminal carbon atom of the 1,3-bis(silyl enol ether) onto carbon atom C-6 of the 3,4-dihydro-2*H*-

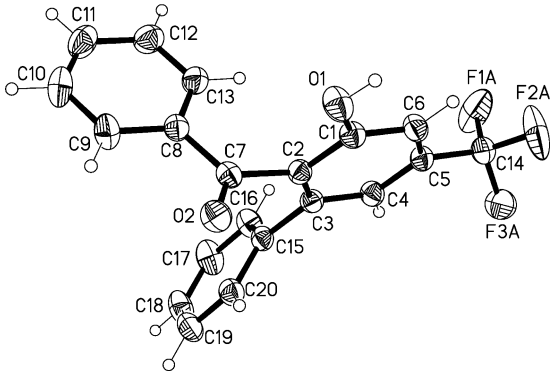


Figure 4. Molecular structure of **17d** in the crystal (ORTEP plot, 50% probability level, only one of the two disorderd orientations of the CF_3 group is shown).

pyran **19**, ring opening, and subsequent re-cyclization via the central carbon atom of the 1,3-dicarbonyl moiety. Related transformations were reported for the reaction of cyclic enol ethers, such as **19**, with carbon,[32] nitrogen,[33] and oxygen nucleophiles.[13c] The formation of products **20a**–**d** is not unexpected, since the alcohol released by the retro-Michael reaction is a good nucleophile and can compete easily (6-*exo*-*trig* ring closure) with the enol ether [6-(enol-*endo*)-*exo*-*trig* ring closure].

Table 5. Synthesis of dihydropyrans **20a**–**d**.

3	20	R	Ketone/enol	% Yield[a]
a	**a**	OEt	2:1	24
e	**b**	Me	0:1	53[b]
k	**c**	Ph	0:1	29
l	**d**	CF_3	0:1	26

[a] Isolated yields. [b] Compound **21** was also isolated in 40% yield (see structure).

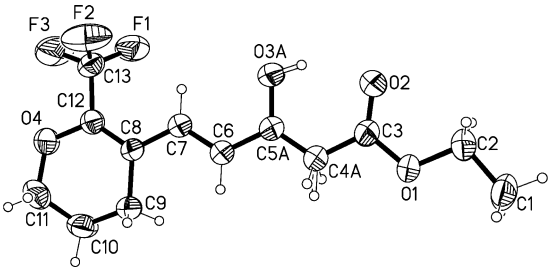
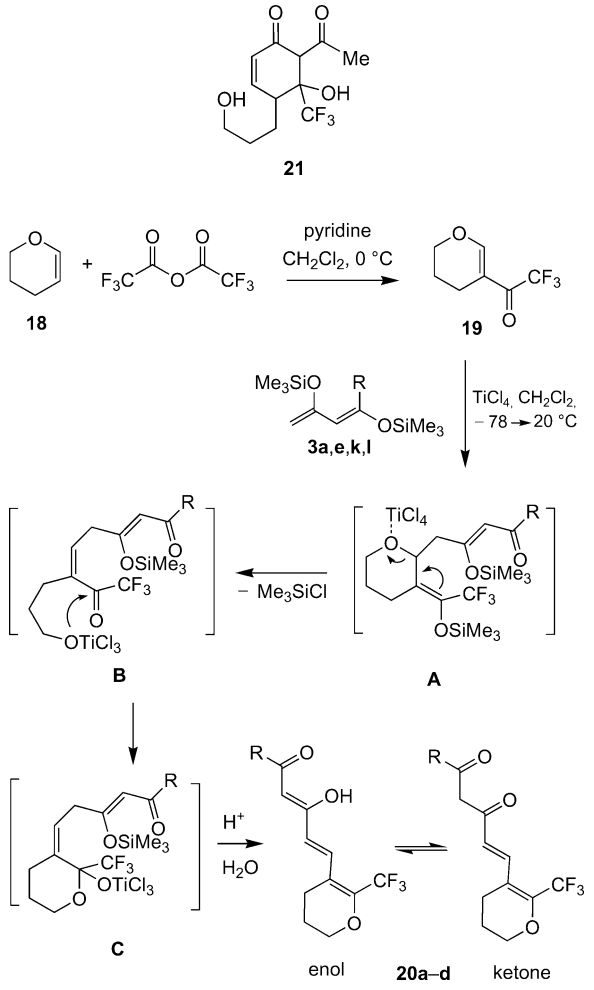


Figure 5. Molecular structure of **20a** in the crystal (ORTEP plot, 50% probability level, one out of the four symmetry independent molecules is shown).



Scheme 6. Reaction of enone **19** with 1,3-bis(silyl enol ethers) **3a**,**e**,**l**,**k**.

Conclusions

In conclusion, we have reported a new and versatile approach to functionalized 3-(trifluoromethyl)phenols based on [3+3] cyclizations of 1,3-bis(silyl enol ethers) with open-chain and cyclic α,β-unsaturated trifluoromethyl ketones. These products are not readily available by other synthetic strategies. The reaction of 3,4-dihydro-5-(trifluoroacetyl)-2*H*-pyran with different 1,3-bis(silyl enol ethers) resulted in an unexpected domino process to give new 2-(trifluoroalkylated) 5,6-dihydro-4*H*-pyrans.

Experimental Section

General: Chemical shifts of the ^1H and ^{13}C NMR spectra were reported in parts per million (ppm) using the solvent as internal standard (chloroform, δ = 7.26 and 77.0 ppm, respectively). Infrared spectra were recorded with an FTIR spectrometer. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). Melting points are uncorrected. The solvent CH_2Cl_2 (anhydrous, 99.8%) was purchased directly from ACROS, and was used without further purification. $TiCl_4$ was purchased from Aldrich and freshly distilled prior to use. Analytical thin-layer chromatography was performed on 0.20 mm 60-Å silica gel plates. Column chromatography was performed using 60-Å silica gel (60–200 mesh). All cyclization reactions were carried out in Schlenk tubes under an argon atmosphere. The α,β-unsaturated ketones and bis(silyl enol ethers) were prepared as described in the literature. Crystallographic data were collected with a Bruker-Nonius Apex-X8 CCD-diffractometer with Mo-K_α radiation (λ = 0.71073 Å). The structures were solved by direct methods using SHELXS-97

and refined against F^2 on all data by full-matrix least-squares with SHELXL-97.[34] All non-hydrogen atoms were refined anisotropically; all hydrogen atoms were placed on geometrically calculated positions and refined by using a riding model.

4-Ethoxy-3-ethyl-1,1,1-trifluorobuten-2-one (2c): To a mixture of 1-butenyl ethyl ether (**1c**) (5.00 g, 50.0 mmol) and pyridine (3.7 mL, 45.0 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic anhydride (7.0 mL, 45.0 mmol) at 0 °C, and the temperature of the reaction mixture was allowed to rise to 20 °C during 14 h. The pyridinium salt was filtered off and washed with CH_2Cl_2, and the solvent of the filtrate was removed in vacuo. After distillation in vacuo, **2c** (8.42 g, 86%) was obtained as a colourless liquid; b.p. 68 °C (10 mbar). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.48 (q, $J_{H,F}$ = 1.2 Hz, 1 H, 4-H), 4.20 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH$_3$), 2.32 (q, ^3J = 7.6 Hz, 2 H, CH_2CH$_3$), 1.38 (t, ^3J = 7.0 Hz, 3 H, OCH$_2$CH_3), 0.96 (t, ^3J = 7.6 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 179.7 (q, $^2J_{C,F}$ = 33.4 Hz, C=O), 164.3 (q, $^3J_{C,F}$ = 4.8 Hz, C-4), 118.5 (C-3), 117.1 (q, $^1J_{C,F}$ = 293 Hz, CF_3), 71.8 (OCH$_2$CH$_3$), 16.6 (CH$_2$CH$_3$), 15.4 (OCH$_2$$CH_3$), 12.8 (CH$_2$$CH_3$) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –68.8 (CF_3) ppm. IR (neat): $\tilde{\nu}$ = 1626 (OH), 1683 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 196 (16) [M$^+$], 127 (63) [M$^+$ – CF_3], 99 (100) [M$^+$ – COCF_3]. HRMS (EI): calcd. for $C_8H_{11}F_3O_2$ 196.0706; found 196.0704 [M$^+$].

General Procedure for the Synthesis of 4a–m, 5 and 17a–d: To a solution of 1,3-bis(silyl enol ether) **3a**–**k** (2.0 equiv.) and the respective enone **2a**–**c**, **16a**–**c** (1.0 equiv.) in CH_2Cl_2 (5 mL) was added $TiCl_4$ (1.0 equiv.) at –78 °C under argon. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h, and an aqueous HCl solution (10%, 20 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-heptane/EtOAc = 20:1).

Ethyl 6-(Trifluoromethyl)salicylate (4a): Following the general procedure, **2a** (500 mg, 2.97 mmol), **3a** (5.95 mmol) and $TiCl_4$ (0.33 mL, 2.97 mmol) yielded **4a** as a colourless syrup (208 mg, 30%). The spectroscopic data were identical with those reported.[11b]

Ethyl 3-Methyl-6-(trifluoromethyl)salicylate (4b): Following the general procedure, **2a** (500 mg, 2.97 mmol), **3b** (1.07 g, 5.95 mmol) and $TiCl_4$ (0.33 mL, 2.97 mmol) yielded **4b** as a colourless syrup (150 mg, 20%); R_f = 0.56 (*n*-heptane/EtOAc = 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.00 (s, 1 H, OH), 7.33 (d, $^3J_{4,5}$ = 8.0 Hz, 1 H, 5-H), 7.20 (d, $^3J_{4,5}$ = 8.0 Hz, 1 H, 4-H), 4.44 (q, ^3J = 7.3 Hz, 2 H, OCH_2CH$_3$), 2.30 (s, 3 H, CH_3), 1.41 (t, ^3J = 7.3 Hz, 3 H, OCH$_2$CH_3) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.6 (C=O), 160.1 (C-2), 133.9 (C-4), 131.9 (C-3), 127.8 (q, $^2J_{C,F}$ = 33.0 Hz, C-6), 123.5 (q, $^1J_{C,F}$ = 273.0 Hz, CF_3), 118.3 (q, $^3J_{C,F}$ = 7.0 Hz, C-5), 110.5 (C-1), 62.5 (OCH$_2$CH$_3$), 16.3 (CH_3), 13.5 (OCH$_2$$CH_3$) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –57.6 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3203 (OH), 1672 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 248 (25) [M$^+$], 202 (54) [M$^+$ – OCH$_2$CH$_3$]. $C_{11}H_{11}F_3O_3$ (248.20): calcd. C 53.23, H 4.47; found C 53.34, H 4.93.

Ethyl 3-Ethyl-6-(trifluoromethyl)salicylate (4c): Following the general procedure, **2a** (500 mg, 2.97 mmol), **3c** (1.80 g, 5.95 mmol) and $TiCl_4$ (0.33 mL, 2.97 mmol) yielded **4c** as a colourless syrup (150 mg, 20%); R_f = 0.62 (*n*-heptane/EtOAc = 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.96 (s, 1 H, OH), 7.34 (d, $^3J_{4,5}$ = 7.9 Hz, 1 H, 5-H), 7.24 (d, $^3J_{4,5}$ = 7.9 Hz, 1 H, 4-H), 4.44 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH$_3$), 2.72 (q, ^3J = 7.5 Hz, 2 H, CH_2CH$_3$), 1.41 (t, ^3J = 7.2 Hz, 3 H, OCH$_2$CH_3), 1.41 (t, ^3J = 7.5 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.7 (C=O), 159.7 (C-2), 137.5 (C-3), 132.3 (C-4), 127.7 (q, $^2J_{C,F}$ = 32.0 Hz, C-6), 123.6 (q, $^1J_{C,F}$ = 273.0 Hz, CF_3), 118.4 (q, $^3J_{C,F}$ = 7.0 Hz, C-5), 110.6 (C-1), 62.5 (OCH$_2$CH$_3$), 23.2 (CH$_2$CH$_3$), 13.5 (OCH$_2$$CH_3$), 13.2 (CH$_2$$CH_3$) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –57.7 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3200 (OH), 1672 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 262 (29) [M$^+$], 216 (55) [M$^+$ – OCH$_2$CH$_3$]. HRMS (EI): calcd. for $C_{13}H_{15}F_3O_3$ 262.0811; found 262.0804 [M$^+$].

Methyl 5-Methyl-6-(trifluoromethyl)salicylate (4d): Following the general procedure, **2b** (500 mg, 2.75 mmol), **3d** (1.43 g, 5.49 mmol) and $TiCl_4$ (0.30 mL, 2.75 mmol) yielded **4d** as a colourless solid (289 mg, 45%); m.p. 83 °C; R_f = 0.53 (*n*-heptane/EtOAc = 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.21 (s, 1 H, OH), 7.26 (d, $^3J_{3,4}$ = 8.7 Hz, 1 H, 3-H), 7.04 (d, $^3J_{3,4}$ = 8.7 Hz, 1 H, 4-H), 3.94 (s, 3 H, OCH_3), 2.43 (q, $^5J_{H,F}$ = 2.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 169.4 (C=O), 155.2 (C-2), 136.5 (C-5), 129.8 (q, $^3J_{C,F}$ = 2.0 Hz, C-4), 127.7 (q, $^2J_{C,F}$ = 31.0 Hz, C-6), 123.8 (q, $^1J_{C,F}$ = 276.0 Hz, CF_3), 120.3 (C-3), 115.2 (q, $^3J_{C,F}$ = 3.0 Hz, C-1), 53.0 (OCH_3), 20.2 (q, $^4J_{C,F}$ = 4 Hz, CH_3) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –55.7 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3283 (OH), 1705 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 234 (24) [M$^+$], 202 (100) [M$^+$ – OCH_3]. HRMS (EI): calcd. for $C_{10}H_9F_3O_3$ 234.0498; found 234.0502 [M$^+$].

2-Acetyl-4-methyl-3-(trifluoromethyl)phenol (4e): Following the general procedure, **2b** (500 mg, 2.75 mmol), **3e** (1.34 g, 5.49 mmol) and $TiCl_4$ (0.30 mL, 2.75 mmol) yielded **4e** as a colourless solid (346 mg, 58%); m.p. 96 °C; R_f = 0.56 (*n*-heptane/EtOAc = 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.20 (d, $^3J_{5,6}$ = 8.5 Hz, 1 H, 6-H), 6.98 (d, $^3J_{5,6}$ = 8.5 Hz, 1 H, 5-H), 2.51 (q, $^6J_{H,F}$ = 1.7 Hz, 3 H, C(O)-CH_3), 2.42 (q, $^5J_{H,F}$ = 2.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 205.5 (C=O), 151.2 (C-1), 134.3 (C-4), 129.2 (q, $^3J_{C,F}$ = 2.0 Hz, C-5), 127.1 (q, $^3J_{C,F}$ = 3.0 Hz, C-2), 125.5 (q, $^2J_{C,F}$ = 30.0 Hz, C-3), 124.1 (q, $^1J_{C,F}$ = 276.0 Hz, CF_3), 120.0 (C-6), 32.1 (q, $^3J_{C,F}$ = 3.0 Hz, C(O)CH$_3$), 19.3 (q, $^3J_{C,F}$ = 3.0 Hz, CH_3) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –54.9 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3275 (OH), 1697 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 218 (25) [M$^+$], 203 (100) [M$^+$ – CH_3]. HRMS (EI: calcd. for $C_{10}H_9F_3O_2$ 218.0549; found 218.0546 [M$^+$].

Ethyl 5-Ethyl-6-(trifluoromethyl)salicylate (4f): Following the general procedure, **2c** (750 mg, 3.8 mmol), **3a** (2.00 g, 7.7 mmol) and $TiCl_4$ (0.42 mL, 3.8 mmol) yielded **4f** as a colourless solid (670 mg, 71%); m.p. 84 °C; R_f = 0.55 (*n*-heptane/EtOAc = 2:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.37 (br. s, 1 H, OH), 7.31 (d, $^3J_{3,4}$ = 8.5 Hz, 1 H, 3-H), 7.09 (d, $^3J_{3,4}$ = 8.5 Hz, 1 H, 4-H), 4.39 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH$_3$), 2.68–2.80 (m, ^3J = 7.4 Hz, 2 H, CH_2CH$_3$), 1.38 (t, ^3J = 7.1 Hz, 3 H, OCH$_2$CH_3), 1.29 (t, ^3J = 7.4 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.2 (C=O), 155.4 (C-2), 136.4 (C-5), 135.4 (C-4), 126.4 (q, $^2J_{C,F}$ = 33.0 Hz, C-6), 124.3 (q, $^1J_{C,F}$ = 274.0 Hz, CF_3), 120.8 (C-3), 117.6 (C-1), 62.7 (OCH$_2$CH$_3$), 26.7 (CH$_2$CH$_3$), 16.1 (OCH$_2$$CH_3$), 13.8 (CH$_2$$CH_3$) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –53.8 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3288 (OH), 1700 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 262 (19) [M$^+$], 217 (31) [M$^+$ – OCH$_2$CH$_3$], 216 (100) [M$^+$ – HOCH$_2$CH$_3$]. $C_{12}H_{13}F_3O_3$ (262.22): calcd. C 54.96, H 5.00; found C 55.07, H 5.06.

During the synthesis of **4f**, compound **5** was isolated as a side product. The reaction of **2c** (750 mg, 3.8 mmol), **3a** (2.00 g, 7.7 mmol) and $TiCl_4$ (0.42 mL, 3.8 mmol) yielded **5** as a colourless syrup (223 mg, 21%); R_f = 0.76 (*n*-heptane/EtOAc = 2:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.73 (d, $^3J_{3a,4}$ = 1.9 Hz, 1 H, 4-H), 5.40 (br. s, 1 H, OH), 4.42 (q, ^3J = 7.2 Hz, 2 H, OCH_2CH$_3$), 2.88–3.13 (dd, $^2J_{3a,3b}$ = 17.0 Hz, $^3J_{4,3a}$ = 1.9 Hz, 2 H, 3a-H, 3b-H), 2.17–2.52

(m, $^2J_{7a,7b}$ = 16.0 Hz, ^3J = 7.4 Hz, 2 H, 7a-H, 7b-H), 1.39 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 1.09 (t, ^3J = 7.4 Hz, 3 H, 8-H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 177.6 (C=O), 170.9 (C-2), 139.0 (C-1), 126.4 (q, $^1J_{C,F}$ = 290.0 Hz, CF_3), 119.5 (C-4), 96.1 (C-5), 74.0 (q, $^2J_{C,F}$ = 30.0 Hz, C-6), 62.2 (OCH_2CH_3), 31.8 (C-3), 22.4 (C-7), 14.2 (OCH_2CH_3), 13.0 (C-8) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –79.9 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3529, 3353 (OH), 1689 cm^{-1} (C=O). MS (EI, 70 eV): *m/z* (%) = 262 (17) [$M^+ - H_2O$], 216 (100) [$M^+ - H_2O$ – EtOH]. $C_{12}H_{15}F_3O_4$ (280.24): calcd. C 51.43, H 4.06; found C 50.97, H 4.12.

Methyl 5-Ethyl-6-(trifluoromethyl)salicylate (4g): Following the general procedure, **2c** (750 mg, 3.8 mmol), **3d** (2.00 g, 7.7 mmol) and $TiCl_4$ (0.42 mL, 3.8 mmol) yielded **4g** as a colourless solid (670 mg, 71%); m.p. 84 °C; R_f = 0.45 (*n*-heptane/EtOAc = 2:3). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.14 (br. s, 1 H, OH), 7.32 (d, $^3J_{3,4}$ = 8.5 Hz, 1 H, 3-H), 7.09 (d, $^3J_{3,4}$ = 8.5 Hz, 1 H, 4-H), 3.93 (s, 3 H, OCH_3), 2.75 (dq, ^3J = 7.3 Hz, $^5J_{H,F}$ = 2.4 Hz, 2 H, CH_2CH_3), 1.23 (t, ^3J = 7.3 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.6 (C=O), 155.2 (C-2), 136.5 (C-5), 135.4 (C-4), 127.2 (q, $^2J_{C,F}$ = 31.0 Hz, C-6), 124.1 (q, $^1J_{C,F}$ = 276.0 Hz, CF_3), 120.8 (C-3), 115.2 (C-1), 53.1 (OCH_3), 26.6 (q, $^4J_{C,F}$ = 2.9 Hz, CH_2CH_3), 16.1 (CH_2CH_3) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –54.4 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3663 (OH), 1710 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 248 (27) [M^+], 217 (29) [$M^+ - OCH_3$], 216 (100) [$M^+ - HOCH_3$]. $C_{11}H_{11}F_3O_3$ (248.20): calcd. C 53.23, H 4.47; found C 53.59, H 4.93.

2-Acetyl-4-ethyl-3-(trifluoromethyl)phenol (4h): Following the general procedure, **2c** (800 mg, 4.1 mmol), **3e** (2.00 g, 8.2 mmol) and $TiCl_4$ (0.45 mL, 4.1 mmol) yielded **4h** as a colourless solid (376 mg, 40%); m.p. 83 °C; R_f = 0.4 (*n*-heptane/EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.78 (br. s, 1 H, OH), 7.14 (d, $^3J_{5,6}$ = 8.2 Hz, 1 H, 6-H), 6.94 (d, $^3J_{5,6}$ = 8.2 Hz, 1 H, 5-H), 2.70 (q, ^3J = 7.6 Hz, 2 H, CH_2CH_3), 2.52 (s, 3 H, $COCH_3$), 1.18 (t, ^3J = 7.6 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 206.0 (C=O), 151.2 (C-1), 135.8 (C-4), 133.3 (C-5), 126.8 (q, $^3J_{C,F}$ = 2.8 Hz, C-2), 125.1 (q, $^2J_{C,F}$ = 30.0 Hz, C-3), 124.8 (q, $^1J_{C,F}$ = 275.6 Hz, CF_3), 120.5 (C-6), 32.2 (q, $^5J_{C,F}$ = 2.8 Hz, $COCH_3$), 25.8 (q, $^4J_{C,F}$ = 2.0 Hz, CH_2CH_3), 16.2 (CH_2CH_3) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –53.3 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3419 (OH), 1702 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 232 (29) [M^+], 217 (100) [$M^+ - CH_2CH_3$]. HRMS (EI): calcd. for $C_{11}H_{11}F_3O_2$ 232.0706; found 232.0707 [M^+].

Methyl 3-Butyl-5-ethyl-6-(trifluoromethyl)salicylate (4i): Following the general procedure, **2c** (465 mg, 2.37 mmol), **3f** (1.50 g, 4.74 mmol) and $TiCl_4$ (0.26 mL, 2.4 mmol) yielded **4i** as a colourless syrup (555 mg, 77%); R_f = 0.65 (*n*-heptane/EtOAc = 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.43 (s, 1 H, OH), 7.16 (s, 1 H, 4-H), 3.92 (s, 3 H, OCH_3), 2.72 (dq, $^5J_{H,F}$ = 1.7 Hz, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 2.65 (t, ^3J = 7.1 Hz, 2 H, $CH_2(CH_2)_2CH_3$), 1.53–1.64 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.31–1.44 (m, 2 H, $(CH_2)_2CH_2CH_3$), 1.22 (t, ^3J = 7.4, 3 H, CH_2CH_3), 0.94 (t, ^3J = 7.4 Hz, 3 H, $(CH_2)_3CH_3$) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 170.3 (C=O), 153.5 (C-2), 135.8 (C-5), 135.5 (C-4), 135.1 (C-3), 124.6 (q, $^2J_{C,F}$ = 31.0 Hz, C-6), 124.3 (q, $^1J_{C,F}$ = 275.0 Hz, CF_3), 114.4 (q, $^3J_{C,F}$ = 3.5 Hz, C-1), 53.0 (OCH_3), 31.5, 30.0 (CH_2), 26.7 (CH_2CH_3), 22.7 (CH_2), 16.2, 14.1 (CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –53.8 ppm. IR (neat): $\tilde{\nu}$ = 3427 (OH), 1746 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 304 (31) [M^+], 273 (18) [$M^+ - OCH_3$]. HRMS (EI): calcd. for $C_{15}H_{19}F_3O_3$ 304.1281; found 304.1275 [M^+].

Methyl 3-(But-3-enyl)-5-ethyl-6-(trifluoromethyl)salicylate (4j): Following the general procedure, **2c** (468 mg, 2.38 mmol), **3g** (1.50 g, 4.77 mmol) and $TiCl_4$ (0.26 mL, 2.4 mmol) yielded **4j** as a colourless syrup (137 mg, 20%); R_f = 0.75 (*n*-heptane/EtOAc = 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.49 (s, 1 H, OH), 7.16 (s, 1 H, 4-H), 5.85 (ddd, ^3J = 6.8 Hz, ^3J = 10.2 Hz, 1 H, HC=), 4.95–5.03 (m, 2 H, H_2C=), 3.92 (s, 3 H, OCH_3), 2.74 (dd, ^3J = 7.2 Hz, 2 H, $ArCH_2$), 2.71 (dd, $^5J_{H,F}$ = 1.9 Hz, ^3J = 7.4 Hz, 2 H, CH_2CH_3), 2.37 (dd, ^3J = 7.2 Hz, 2 H, $ArCH_2CH_2$), 1.22 (t, ^3J = 7.4 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 170.3 (C=O), 153.6 (C-2), 137.8 (H_2C=), 135.8 (C-5), 135.7 (C-4), 124.6 (q, $^2J_{C,F}$ = 29.6 Hz, C-6), 124.3 (q, $^1J_{C,F}$ = 275.9 Hz, CF_3), 123.1 (C-3), 115.5 (HC=), 114.4 (C-1), 53.1 (OCH_3), 33.2, 29.8 (CH_2), 26.8 (CH_2CH_3), 16.2 (CH_2CH_3) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –53.9 (CF_3) ppm. IR (neat): $\tilde{\nu}$ = 3420 (OH), 1716 cm^{-1} (C=O). MS (EI, 70 eV): *m/z* (%) = 302 (25) [M^+], 270 (22) [$M^+ - CH_3OH$]. HRMS (EI): calcd. for $C_{15}H_{17}F_3O_3$ 302.11243; found 302.112124 [M^+].

Methyl 3-(6-Chlorohexyl)-5-ethyl-6-(trifluoromethyl)salicylate (4k): Following the general procedure, **2c** (388 mg, 1.98 mmol), **3h** (1.50 g, 3.96 mmol) and $TiCl_4$ (0.22 mL, 1.98 mmol) yielded **4k** as a colourless syrup (636 mg, 88%); R_f = 0.74 (*n*-heptane/EtOAc = 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.47 (s, 1 H, OH), 7.15 (s, 1 H, 4-H), 3.92 (s, 3 H, OCH_3), 3.53 (t, ^3J = 7.5 Hz, 2 H, CH_2Cl), 2.71 (dq, $J_{H,F}$ = 2.3 Hz, ^3J = 7.5 Hz, 2 H, CH_2CH_3), 2.65 (t, ^3J = 7.4 Hz, 2 H, $CH_2(CH_2)_5Cl$), 1.32–1.82 (m, 8 H, $CH_2(CH_2)_4CH_2Cl$), 1.22 (t, ^3J = 7.5 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 170.2 (C=O), 153.5 (C-2), 135.8 (C-5), 135.5 (C-4), 124.7 (q, $^2J_{C,F}$ = 31.0 Hz, C-6), 124.3 (q, $^1J_{C,F}$ = 274.3 Hz, CF_3), 114.3 (C-1), 53.1 (OCH_3), 45.2 (CH_2Cl), 32.6, 30.1, 29.1, 28.8, 27.1, 26.8 (CH_2), 16.3 (CH_2CH_3). ^{19}F NMR (235 MHz, $CDCl_3$): δ = –53.8 (CF_3) ppm. IR (neat): $\tilde{\nu}$ = 3420 (OH), 1748 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 368 (3) [M^+, ^{37}Cl], 366 (17) [M^+, ^{35}Cl], 334 (16) [$M^+ - CH_3OH$]. HRMS (EI): calcd. for $C_{17}H_{22}ClF_3O_3$ 366.12041; found 366.120050 [M^+].

Ethyl 5-Ethyl-3-heptyl-6-(trifluoromethyl)salicylate (4l): Following the general procedure, **2c** (410 mg, 2.09 mmol), **3i** (1.50 g, 4.18 mmol) and $TiCl_4$ (0.45 mL, 4.1 mmol) yielded **4l** as a colourless syrup (387 mg, 53%); R_f = 0.75 (*n*-heptane/EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.43 (br. s, 1 H, OH), 7.15 (s, 1 H, 4-H), 3.92 (s, 3 H, OCH_3), 2.71 (dq, ^3J = 7.5 Hz, $^5J_{H,F}$ = 1.8 Hz, 2 H, CH_2CH_3), 2.63 (t, ^3J = 7.9 Hz, 2 H, $ArCH_2$), 1.54–1.65 (m, ^3J = 7.9 Hz, 2 H, $ArCH_2CH_2$), 1.24–1.39 (m, 8 H, $Ar(CH_2)_2(CH_2)_4CH_3$), 1.22 (t, ^3J = 7.5 Hz, 3 H, CH_2CH_3), 0.88 (t, ^3J = 7.3 Hz, 3 H, $Ar(CH_2)_6CH_3$) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 170.3 (C=O), 153.2 (C-2), 135.5 (C-5), 135.5 (C-4), 124.7 (q, $^2J_{C,F}$ = 30.9 Hz, C-6), 124.4 (q, $^1J_{C,F}$ = 274.2 Hz, CF_3), 122.5 (C-3), 114.3 (q, $^3J_{C,F}$ = 2.5 Hz, C-1), 53.0 (OCH_3), 31.9, 30.2, 29.3, 29.2, 26.7 ($Ar(CH_2)_6CH_3$), 26.7 (q, $^4J_{C,F}$ = 3.4 Hz, CH_2CH_3), 22.8 ($Ar(CH_2)_6CH_3$), 16.2 (CH_2CH_3), 14.2 ($Ar(CH_2)_6CH_3$) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –53.8 (CF_3) ppm. IR (neat): $\tilde{\nu}$ = 3415 (OH), 1746 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 346 (31) [M^+], 314 (32) [$M^+ - CH_3OH$], 285 (49) [$M^+ - HC(O)OCH_3$].

Methyl 3-Benzyl-5-ethyl-6-(trifluoromethyl)salicylate (4m): Following the general procedure, **2c** (420 mg, 2.14 mmol), **3j** (1.50 g, 4.28 mmol) and $TiCl_4$ (0.26 mL, 2.1 mmol) yielded **4m** as a colourless syrup (175 mg, 24%); R_f = 0.65 (*n*-heptane/EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, OH), 7.15–7.44 (m, 5 H, Ph), 7.03 (s, 1 H, 4-H), 3.91 (s, 2 H, CH_2), 3.82 (s, 3 H, OCH_3), 2.59 (dq, $^5J_{H,F}$ = 1.9 Hz, ^3J = 7.5 Hz, 2 H, CH_2CH_3), 1.09 (t, ^3J = 7.5 Hz, 3 H, CH_3CH_3) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 170.1 (C=O), 153.4 (C-2), 141.5 (C_{Ph}), 136.1 (C-5), 134.8 (C-4), 133.4 (C-3), 129.0, 128.7, 126.6 (CH_{Ph}), 123.7 (q, $^1J_{C,F}$ = 273.0 Hz, CF_3), 114.8 (q, $^3J_{C,F}$ = 3.5 Hz, C-1), 53.1 (OCH_3), 36.0 (CH_2), 26.6 (CH_2CH_3), 16.2 (CH_2CH_3) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ

= –53.9 (CF_3) ppm. IR (neat): ṽ = 3625 (OH), 1741 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 338 (47) [M^+], 306 (40) [$M^+ – CH_3OH$], 278 (31) [$M^+ – HC(O)OCH_3$]. HRMS (EI): calcd. for $C_{18}H_{17}F_3O_3$ 338.11243; found 338.111978 [M^+].

General Procedure for the Synthesis of 9a–g: To a solution of the 1,3-bis(silyl enol ether) **3a**,**d**,**e** (2.0 equiv.) and the respective enone **8a**–**d** (1 equiv.) in CH_2Cl_2 (5 mL) was added $TiCl_4$ (1 equiv.) at –78 °C under argon. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h, and then an aqueous HCl solution (10%, 20 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-heptane/EtOAc = 20:1).

Methyl 6-Hydroxy-4-(trifluoromethyl)indan-5-carboxylate (9a): Following the general procedure, **8a** (500 mg, 2.4 mmol), **3d** (1.30 g, 4.8 mmol) and $TiCl_4$ (0.26 mL, 2.4 mmol) yielded **9a** as a colourless solid (423 mg, 68%); m.p. 76 °C; R_f = 0.47 (*n*-heptane/EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 9.33 (s, 1 H, OH), 7.03 (s, 1 H, 7-H), 3.93 (s, 3 H, OCH_3), 2.98–3.09 (m, 2 H, 3-H), 2.89 (t, $^3J_{1,2}$ = 7.6 Hz, 2 H, 3-H), 2.04 (quint, $^3J_{1,2}$ = 7.6 Hz, 2 H, 2-H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 170.8 (C=O), 158.5 (C-6), 152.7 (C-7a), 135.9 (q, $^3J_{C,F}$ = 2.3 Hz, C-3a), 125.5 (q, $^2J_{C,F}$ = 32.3 Hz, C-4), 124.1 (q, $^1J_{C,F}$ = 274.7 Hz, CF_3), 116.8 (C-7), 110.8 (C-5), 52.9 (OCH_3), 33.0 (C-1), 32.8 (q, $^4J_{C,F}$ = 3.3 Hz, C-3), 25.2 (C-2) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –56.1 (CF_3) ppm. IR (Nujol): ṽ = 3273 (OH), 1707 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 260 (17) [M^+], 228 (100) [$M^+ – CH_3OH$], 200 (3) [$M^+ – HCOOCH_3$]. $C_{12}H_{11}F_3O_3$ (260.21): calcd. C 55.39, H 4.26; found C 55.19, H 4.28.

5-Acetyl-6-hydroxy-4-(trifluoromethyl)indane (9b): Following the general procedure, **8a** (770 mg, 3.7 mmol), **3e** (1.80 g, 7.4 mmol) and $TiCl_4$ (0.41 mL, 3.7 mmol) yielded **9b** as a colourless solid (130 mg, 14%); m.p. 68 °C; R_f = 0.51 (*n*-heptane/EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 12.56 (s, 1 H, OH), 7.10 (s, 1 H, 7-H), 3.24 (t, $^3J_{1,3}$ = 7.5 Hz, 2 H, 3-H), 3.01 (t, $^3J_{1,2}$ = 7.5 Hz, 2 H, 1-H), 2.68 (s, 3 H, $COCH_3$), 1.18 (t, $^3J_{1,2}$ = $^3J_{2,3}$ = 7.5 Hz, 2 H, 2-H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 205.4 (C=O), 161.9 (C-6), 147.8 (C-7a), 132.9 (q, $^3J_{C,F}$ = 1.9 Hz, C-3a), 132.3 (q, $^2J_{C,F}$ = 32.3 Hz, C-4), 123.4 (q, $^1J_{C,F}$ = 273.4 Hz, CF_3), 120.5 (C-5), 114.5 (C-7), 36.3 (C-1), 32.6 ($CO\mathit{C}H_3$), 30.5 (C-3), 25.4 (C-2) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –63.9 (CF_3) ppm. IR (Nujol): ṽ = 3214 (OH), 1731 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 244 (38) [M^+], 229 (100) [$M^+ – CH_3$], 201 (4) [$M^+ – COCH_3$]. $C_{12}H_{11}F_3O_2$ (244.21): calcd. C 59.02, H 4.54; found C 58.78, H 4.70.

Methyl 3-Hydroxy-1-(trifluoromethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (9c): Following the general procedure, **8b** (500 mg, 2.25 mmol), **3d** (1.17 g, 4.5 mmol) and $TiCl_4$ (0.25 mL, 2.25 mmol) yielded **9c** as a colourless solid (300 mg, 48%); m.p. 153 °C; R_f = 0.34 (*n*-heptane/EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.04 (br. s, 1 H, OH), 6.85 (s, 1 H, 4-H), 3.91 (s, 3 H, OCH_3), 2.72–2.89 (m, 4 H, 5-H, 8-H), 1.68–1.83 (m, 4 H, 6-H, 7-H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 169.7 (C=O), 154.1 (C-3), 144.4 (C-4a), 130.2 (q, $^3J_{C,F}$ = 1.6 Hz, C-8a), 127.7 (q, $^2J_{C,F}$ = 30.2 Hz, C-1), 124.2 (q, $^1J_{C,F}$ = 276.9 Hz, CF_3), 120.6 (C-4), 114.0 (q, $^3J_{C,F}$ = 3.0 Hz, C-2), 53.0 (OCH_3), 30.3 (C-6), 26.7 (q, $^4J_{C,F}$ = 3.8 Hz, C-8), 22.8, 22.0 (C-6, C-7) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –55.0 (CF_3) ppm. IR (Nujol): ṽ = 3343 (OH), 1712 cm^{-1} (C=O). MS (EI, 70 eV): *m*/*z* (%) = 274 (17) [M^+], 243 (100) [$M^+ – HOCH_3$], 214 (10) [$M^+ – HCOOCH_3$]. $C_{13}H_{13}F_3O_3$ (274.23): calcd. C 56.94, H 4.78; found C 57.33, H 4.67.

2-Acetyl-3-hydroxy-1-(trifluoromethyl)-5,6,7,8-tetrahydronaphthalene (9d): Following the general procedure, **8b** (815 mg, 3.67 mmol), **3e** (1.8 g, 7.34 mmol) and $TiCl_4$ (0.40 mL, 3.67 mmol) yielded **9d** as a colourless solid (350 mg, 37%); m.p. 134 °C; R_f = 0.48 (*n*-heptane/EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.12 (s, 1 H, 4-H), 2.80–2.94 (m, 4 H, 5-H, 8-H), 2.63 (s, 3 H, Me) 1.70–1.87 (m, 4 H, 6-H, 7-H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 206.6 (C=O), 155.3 (C-3), 139.1 (C-4a), 132.9 (q, $^2J_{C,F}$ = 29.9 Hz, C-1), 127.6 (C-8a), 127.3 (C-2), 123.8 (q, $^1J_{C,F}$ = 273.7 Hz, CF_3), 114.2 (q, $^3J_{C,F}$ = 3.0 Hz, C-4), 33.1 (Me), 30.1 (C-6), 25.1 (q, $^4J_{C,F}$ = 2.6 Hz, C-8), 22.2, 22.0 (C-6, C-7) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –61.9 (CF_3) ppm. IR (Nujol): ṽ = 3256 (OH), 1684 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 258 (64) [M^+], 243 (100) [M^+ – Me], 215 (9) [$M^+ – COCH_3$]. $C_{13}H_{13}F_3O_2$ (258.24): calcd. C 60.46, H 5.07; found C 60.77, H 5.51.

2-Acetyl-3-hydroxy-1-(trifluoromethyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohept-2-ene (9e): Following the general procedure, **8c** (500 mg, 2.12 mmol), **3e** (1.03 g, 4.2 mmol) and $TiCl_4$ (0.23 mL, 2.12 mmol) yielded **9e** as a colourless solid (231 mg, 40%); m.p. 152 °C; R_f = 0.42 (*n*-heptane/EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.16 (s, 1 H, OH), 6.88 (s, 1 H, 4-H), 2.50–2.90 (m, 4 H, 5-H, 9-H), 2.48 (s, 3 H, $COCH_3$), 1.57–1.85 (m, 6 H, 6-H, 7-H, 8-H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 204.6 (C=O), 152.4 (C-3), 150.2 (C-4a), 135.9 (q, $^3J_{C,F}$ = 1.9 Hz, C-9a), 126.4 (C-2), 125.7 (q, $^2J_{C,F}$ = 29.0 Hz, C-1), 124.5 (q, $^1J_{C,F}$ = 273.8 Hz, CF_3), 122.2 (q, $^5J_{C,F}$ = 2.7 Hz, C-4), 36.1 (C-5), 32.1 (q, $^4J_{C,F}$ = 4.6 Hz, C-9), 31.4 ($CO\mathit{C}H_3$), 29.8 (q, $^5J_{C,F}$ = 2.8 Hz, C-8), 27.7, 27.2 (C-6, C-7) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –51.1 (CF_3) ppm. IR (Nujol): ṽ = 3253 (OH), 1700 cm^{-1} (C=O). MS (EI, 70 eV): *m*/*z* (%) = 272 (29) [M^+]; 257 (100) [$M^+ – CH_3$]. $C_{14}H_{15}F_3O_2$ (272.26): calcd. C 61.76, H 5.55; found C 61.64, H 5.63.

Ethyl 3-Hydroxy-1-(trifluoromethyl)-5,6,7,8,9,10-hexahydrobenzocyclooctene-2-carboxylate (9f): Following the general procedure, **8d** (400 mg, 1.6 mmol), **3a** (922 mg, 3.2 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol) yielded **9f** as a colourless solid (400 mg, 79%); m.p. 105 °C; R_f = 0.5 (*n*-heptane/EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 8.08 (s, 1 H, OH), 6.95 (s, 1 H, 4-H), 4.37 (q, ^3J = 7.1 Hz, 2 H, $OC\mathit{H}_2CH_3$), 2.84–3.92 (m, 2 H, 10-H), 2.73–2.80 (m, 2 H, 5-H), 1.65–1.78 (m, 4 H, 6-H, 9-H), 1.36 (t, ^3J = 7.1 Hz, 3 H, $OCH_2C\mathit{H}_3$), 1.34–1.43 (m, 4 H, 7-H, 8-H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 169.3 (C=O), 154.7 (C-3), 149.4 (C-4a), 133.6 (q, $^3J_{C,F}$ = 2.9 Hz, C-10a), 127.7 (q, $^2J_{C,F}$ = 29.9 Hz, C-1), 124.5 (q, $^1J_{C,F}$ = 275.8 Hz, CF_3), 121.1 (C-4), 114.6 (q, $^3J_{C,F}$ = 2.9 Hz, C-2), 62.5 ($O\mathit{C}H_2CH_3$), 32.6, 32.0 (C-5, C-10), 31.6, 27.9 (C-6, C-9), 26.2, 26.1 (C-7, C-8), 13.8 ($OCH_2\mathit{C}H_3$) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –52.7 (CF_3) ppm. IR (Nujol): ṽ = 3317 (OH), 1714 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 316 (19) [M^+], 271 (26) [$M^+ – OCH_2CH_3$], 270 (100) [$M^+ – HOCH_2CH_3$]. $C_{16}H_{19}F_3O_3$ (316.32): calcd. C 60.75, H 6.05; found C 60.52, H 6.19.

2-Acetyl-3-hydroxy-1-(trifluoromethyl)-5,6,7,8,9,10-hexahydrobenzocyclooctene (9g): Following the general procedure, **8d** (400 mg, 1.6 mmol), **3e** (782 mg, 3.2 mmol) and $TiCl_4$ (0.18 mL, 1.6 mmol) yielded **9g** as a colourless solid (138 mg, 40%); m.p. 105 °C; R_f = 0.38 (*n*-heptane/EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.50 (br. s, 1 H, OH), 6.85 (s, 1 H, 4-H), 2.82–2.90 (m, 2 H, 10-H), 2.68–2.75 (m, 2 H, 5-H), 2.49 (s, 3 H, $COCH_3$), 1.62–1.74 (m, 4 H, 6-H, 9-H), 1.32–1.39 (m, 4 H, 7-H, 8-H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 205.5 (C=O), 151.4 (C-3), 147.9 (C-4a), 133.0 (q, $^3J_{C,F}$ = 1.7 Hz, C-10a), 125.8 (q, $^2J_{C,F}$ = 29.4 Hz, C-1), 124.8 (q, $^1J_{C,F}$ = 276.2 Hz, CF_3), 125.1 (q, $^3J_{C,F}$ = 3.0 Hz, C-2), 121.3 (C-4), 32.6 (C-5), 32.4 (q, $^4J_{C,F}$ = 3.7 Hz, C-10), 32.0 (C-6), 31.6 (q, $^5J_{C,F}$ =

1.5 Hz, C-9), 27.4 (q, $^5J_{C,F}$ = 2.1 Hz, CO*C*H$_3$), 26.3, 26.1 (C-7, C-8) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –51.6 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3317 (OH), 1714 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 286 (30) [M$^+$], 271 (100) [M$^+$ – CH_3], 243 (4) [M$^+$ – $COCH_3$]. $C_{15}H_{17}F_3O_2$ (286.29): calcd. C 62.93, H 5.99; found C 62.73, H 6.08.

Ethyl 6,6′-(1,2-Ethanediyl)-4,4′-bis(trifluoromethyl)salicylate (13): To a solution of **3a** (1.48 g, 5.39 mmol) and **12** (600 mg, 1.8 mmol) in CH_2Cl_2 (5 mL) was added $TiCl_4$ (0.40 mL, 3.6 mmol) at –78 °C under argon. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h, and then an aqueous HCl solution (10%, 20 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (silica gel, *n*-heptane/EtOAc = 20:1) yielded **13** as a colourless solid (350 mg, 37%); m.p. 139 °C; R_f = 0.5 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.20 (s, 2 H, OH), 7.14 (d, ^4J = 1.8 Hz, 2 H, 3-H, 3′-H), 6.80 (d, ^4J = 1.8 Hz, 2 H, 5-H, 5′-H), 4.50 (q, ^3J = 7.2 Hz, 4 H, OC*H*$_2$CH$_3$), 3.28 (s, 4 H, CH_2), 1.43 (t, ^3J = 7.2 Hz, 6 H, OCH$_2$C*H*$_3$) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 170.4 (C=O), 162.8 (C-2, C-2′), 145.3 (C-1, C-1′), 135.4 (q, $^2J_{C,F}$ = 33.4 Hz, C-4, C-4′), 127.6 (C-6, C-6′), 123.4 (q, $^1J_{C,F}$ = 254.6 Hz, CF_3), 118.4 (q, $^3J_{C,F}$ = 2.8 Hz, C-3, C-3′), 113.7 (q, $^3J_{C,F}$ = 3.0 Hz, C-5, C-5′), 62.7 (O*C*H$_2$CH$_3$), 37.8 (CH_2), 14.2 (OCH$_2$*C*H$_3$) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –64.1 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 1662 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 494 (34) [M$^+$], 448 (60) [M$^+$ – CH_2CH_3OH], 402 (100) [M$^+$ – 2CH_2CH_3OH]. HRMS (EI): calcd. for $C_{22}H_{20}F_6O_6$ 494.1159; found 494.1161 [M$^+$].

Methyl 4′-Chloro-3-hydroxy-5-(trifluoromethyl)biphenyl-4-carboxylate (17a): Following the general procedure given for the synthesis of **4a**–**m**, **16a** (557 mg, 2.0 mmol), **3d** (1.04 g, 4.0 mmol) and $TiCl_4$ (0.22 mL, 2.0 mmol) yielded **17a** as a pale yellow solid (170 mg, 25%); m.p. 84–85 °C; R_f = 0.4 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.83 (s, 1 H, OH), 7.55 (d, ^3J = 8.8 Hz, 2 H, 3′-H, 5′-H), 7.50 (d, $^4J_{2,6}$ = 1.8 Hz, 1 H, 2-H), 7.45 (d, ^3J = 8.8 Hz, 2 H, 2′-H, 6′-H), 7.38 (d, $^4J_{2,6}$ = 1.8 Hz, 1 H, 6-H), 4.01 (s, 3 H, OCH_3) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 169.6 (C=O), 162.4 (C-3), 145.5, 136.8 (C-1, C-1′), 135.5 (C-4′), 131.2 (q, $^2J_{C,F}$ = 31.5 Hz, C-5), 129.5, 128.5 (C-2′/C-6′, C-3′/C-5′), 123.4 (q, $^1J_{C,F}$ = 273.6 Hz, CF_3), 119.8, 117.9 (C-2, C-6), 109.9 (C-4), 53.1 (CH_3) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –58.5 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 1678 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 332 (16) [M$^+$, ^{37}Cl], 330 (48) [M$^+$, ^{35}Cl], 298 (100) [M$^+$ – CH_3OH], 270 (41) [M$^+$ – $HCOOCH_3$]. $C_{15}H_{10}ClF_3O_3$ (330.69): calcd. C 54.48, H 3.05; found C 54.91, H 3.42.

Methyl 4′-Bromo-3-hydroxy-5-(trifluoromethyl)biphenyl-4-carboxylate (17b): Following the general procedure given for the synthesis of **4a**–**m**, **16b** (500 mg, 1.55 mmol), **3d** (807 mg, 3.1 mmol) and $TiCl_4$ (0.17 mL, 1.55 mmol) yielded **17b** as a yellow solid (110 mg, 20%); m.p. 103 °C; R_f = 0.4 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.83 (s, 1 H, OH), 7.61 (d, ^3J = 8.5 Hz, 2 H, 3′-H, 5′-H), 7.50 (d, $^4J_{2,6}$ = 1.5 Hz, 1 H, 2-H), 7.47 (d, ^3J = 8.5 Hz, 2 H, 6′-H, 2′-H), 7.38 (d, $^4J_{2,6}$ = 1.5 Hz, 1 H, 6-H), 4.00 (s, 3 H, OCH_3) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 169.6 (C=O), 162.4 (C-3), 145.6, 137.3 (C-1, C-1′), 132.5 (C-4′), 131.2 (q, $^2J_{C,F}$ = 32.2 Hz, C-5), 128.8, 123.8 (C-2′/C-6′, C-3′/C-5′), 123.3 (q, $^1J_{C,F}$ = 273.4 Hz, CF_3), 119.8, 117.9 (C-2, C-6), 110.0 (C-4), 53.1 (CH_3) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –58.5 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 1678 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 332 (16) [M$^+$, ^{37}Cl], 330 (48) [M$^+$, ^{35}Cl], 298 (100) [M$^+$ – CH_3OH], 270 (41) [M$^+$ – $HCOOCH_3$]. $C_{15}H_{10}ClF_3O_3$ (330.69): calcd. C 54.48, H 3.05; found C 54.91, H 3.42.

2-Acetyl-4′-chloro-3-hydroxy-5-(trifluoromethyl)biphenyl (17c): Following the general procedure given for the synthesis of **4a**–**m**, **16a** (500 mg, 1.89 mmol), **3e** (968 mg, 3.96 mmol) and $TiCl_4$ (0.21 mL, 1.89 mmol) yielded **17c** as a yellow solid (234 mg, 39%); m.p. 117 °C; R_f = 0.4 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.39 (s, 1 H, OH), 7.47 (d, $^3J_{3',5'}$ = 8.6 Hz, 2 H, 3′-H, 5′-H), 7.30 (d, $^3J_{2',6'}$ = 8.6 Hz, 2 H, 2′-H, 6′-H), 7.27 (d, $^4J_{4,6}$ = 1.9 Hz, 1 H, 6-H), 7.05 (d, $^4J_{4,6}$ = 1.9 Hz, 1 H, 4-H), 1.92 (s, 3 H, CH_3) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 206.5 (C=O), 161.0 (C-3), 144.3, 139.2 (C-1, C-1′), 135.5 (C-4′), 135.3 (q, $^2J_{C,F}$ = 32.7 Hz, C-5), 130.3 (C-3′, C-5′), 129.5 (C-2′, C-6′), 123.5 (C-2), 123.1 (q, $^1J_{C,F}$ = 273.7 Hz, CF_3), 118.5 (q, $^3J_{C,F}$ = 3.8 Hz, C-6), 115.1 (q, $^3J_{C,F}$ = 3.8 Hz, C-4), 32.0 (CH_3) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –63.8 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 1678 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 316 (25) [M$^+$, ^{37}Cl], 314 (72) [M$^+$, ^{35}Cl], 299 (91) [M$^+$ – CH_3], 279 (100) [M$^+$ – ^{35}Cl]. $C_{15}H_{10}ClF_3O_2$ (314.69): calcd. C 57.25, H 3.20; found C 57.44, H 3.48.

1-Hydroxy-6-phenyl-3-(trifluoromethyl)benzophenone (17d): Following the general procedure given for the synthesis of **4a**–**m**, **16c** (500 mg, 2.0 mmol), **3k** (1.30 g, 4.1 mmol) and $TiCl_4$ (0.22 mL, 2.0 mmol) yielded **17d** as a yellow solid (193 mg, 28%); m.p. 117 °C; R_f = 0.4 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.13 (br. s, 1 H, OH), 7.00–7.60 (m, 12 H, Ph) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 200.4 (C=O), 158.6 (C-2), 144.9, 139.5, 138.1 (C_{Ph}), 134.5 (q, $^2J_{C,F}$ = 32.9 Hz, C-4), 132.9, 129.5, 129.0, 128.5, 128.2, 128.0, 127.2, 124.6 (CH_{Ph}), 123.4 (q, $^1J_{C,F}$ = 272.9 Hz, CF_3), 118.4 (q, $^3J_{C,F}$ = 3.5 Hz, C-5), 113.6 (q, $^3J_{C,F}$ = 3.5 Hz, C-3) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –63.2 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3342 (OH), 1663 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 342 (69) [M$^+$], 273 (3) [M$^+$ – CF_3], 265 (28) [M$^+$ – Ph]. $C_{20}H_{13}F_3O_2$ (342.31): calcd. C 70.17, H 3.83; found C 69.85, H 4.05.

General Procedure for the Synthesis of 20a–d and 21: To a solution of 1,3-bis(silyl enol ether) **3a**,**e**,**k**,**l** (2.0 equiv.) and **19** (1.0 equiv.) in CH_2Cl_2 (5 mL) was added $TiCl_4$ (1.0 equiv.) at –78 °C under argon. The temperature of the reaction mixture was allowed to rise to 20 °C during 14 h, and then an aqueous HCl solution (10%, 20 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-heptane/EtOAc = 20:1).

Keto-Enol Mixture of Ethyl (*E*)-3-Oxo-5-[2-(trifluoromethyl)-5,6-dihydro-4*H*-pyran-3-yl]pent-4-enoate and Ethyl (2*Z*,4*E*)-3-Hydroxy-5-[2-(trifluoromethyl)-5,6-dihydro-4*H*-pyran-3-yl]penta-2,4-dienoate (20a): Following the general procedure, **19** (660 mg, 3.66 mmol), **3a** (2.01 g, 7.33 mmol) and $TiCl_4$ (0.40 mL, 3.66 mmol) yielded **20a** as a colourless solid (245 mg, 24%); m.p. 52 °C; R_f = 0.32 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$, ketone:enol = 2:1): δ = 11.91 (s, 1 H, OH_{enol}), 7.65 (d, $^3J_{4,5}$ = 15.8 Hz, 1 H, 4-H_{keto}), 7.49 (d, $^3J_{4,5}$ = 15.6 Hz, 1 H, 4-H_{enol}), 6.21 (d, $^3J_{4,5}$ = 15.8 Hz, 1 H, 5-H_{keto}), 5.87 (d, $^3J_{4,5}$ = 15.6 Hz, 1 H, 5-H_{enol}), 5.06 (s, 1 H, 2-H_{enol}), 4.11–4.26 (m, 8 H, OC*H*$_2$CH$_3$, 6′-H_{keto}, 6′-H_{enol}), 3.61 (s, 2 H, 2-H_{keto}), 2.29–2.40 (m, 4 H, 5′-H_{keto}, 5′-H_{enol}), 1.93–2.05 (m, 4 H, 4′-H_{keto}, 4′-H_{enol}), 1.30 (t, ^3J = 7.1 Hz, 3 H, OCH$_2$C*H*$_{3,enol}$), 1.27 (t, ^3J = 7.0 Hz, 3 H, OCH$_2$C*H*$_{3,keto}$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 191.9 (C-3$_{keto}$), 172.9 (C-3$_{enol}$), 169.3 (C-1$_{enol}$), 167.6 (C-1$_{keto}$), 147.4 (q, $^2J_{C,F}$ = 34.8 Hz, C-2′$_{enol}$), 144.6 q, $^2J_{C,F}$ = 33.9 Hz, C-2′$_{keto}$), 138.8 (q, $^4J_{C,F}$ = 2.8 Hz, C-5$_{keto}$), 130.9 (q, $^4J_{C,F}$ = 2.8 Hz, C-5$_{enol}$), 124.8 (C-4$_{keto}$), 121.2 (C-4$_{enol}$), 120.5 (q, $^1J_{C,F}$ = 275.8 Hz, $CF_{3,enol}$), 120.1 (q, $^1J_{C,F}$ = 275.8 Hz, $CF_{3,keto}$), 113.3,

112.6 (C-3′$_{keto}$, C-3′$_{enol}$), 91.6 (C-2$_{enol}$), 67.7 (C-6′$_{keto}$), 67.2 (C-6′$_{enol}$), 61.6 (O*C*H$_2$CH$_{3,keto}$), 60.3 (O*C*H$_2$CH$_{3,enol}$), 47.3 (C-2$_{keto}$), 21.2 (C-4′$_{enol}$), 21.0 (C-5′$_{enol}$), 20.9 (C-4′$_{keto}$, C-5′$_{keto}$), 14.4 (OCH$_2$-*C*H$_{3,enol}$), 14.2 (OCH$_2$*C*H$_{3,keto}$). ^{19}F NMR (235 MHz, $CDCl_3$): δ = –62.6 (CF$_{3,keto}$), –62.9 (CF$_{3,enol}$). IR (Nujol): $\tilde{\nu}$ = 3419 (OH), 1738 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 292 (19) [M$^+$], 246 (6) [M$^+$ – CH_2CH_3OH], 223 (100) [M$^+$ – CF_3]. $C_{13}H_{15}F_3O_4$ (292.25): calcd. C 53.43, H 5.17; found C 53.29, H 5.59.

(3*Z*,5*E*)-4-Hydroxy-6-[2-(trifluoromethyl)-5,6-dihydro-4*H*-pyran-3-yl]hexa-3,5-dien-2-one (20b): Following the general procedure, **19** (370 mg, 2.05 mmol), **3e** (1.00 g, 4.11 mmol) and $TiCl_4$ (0.23 mL, 2.05 mmol) yielded **20b** as a colourless solid (617 mg, 53%); m.p. 62 °C; R_f = 0.32 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.64 (d, $^3J_{5,6}$ = 15.4 Hz, 1 H, 6-H), 5.89 (d, $^3J_{5,6}$ = 15.4 Hz, 1 H, 5-H), 5.56 (s, 1 H, 3-H), 4.16 (m, 2 H, 6′-H), 2.31–2.39 (m, 2 H, 4′-H), 2.13 (s, 3 H, 1-H), 1.93–2.04 (m, 2 H, 5′-H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 197.6 (C-4), 177.3 (C-2), 145.6 (q, $^2J_{C,F}$ = 34.0 Hz, C-2′), 133.8 (q, $^4J_{C,F}$ = 2.9 Hz, C-6), 122.1 (C-5), 120.5 (q, $^1J_{C,F}$ = 275.0 Hz, CF_3), 113.2 (q, $^3J_{C,F}$ = 1.8 Hz, C-3′), 100.8 (C-3), 67.3 (C-6′), 27.1 (C-1), 21.1, 21.0 (C-4′, C-5′) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –62.6 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 1628 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 262 (64) [M$^+$], 247 (5) [M$^+$ – Me], 219 (10) [M$^+$ – $COCH_3$], 193 (100) [M$^+$ – CF_3]. HRMS (EI): calcd. for $C_{12}H_{13}F_3O_3$ 262.08168; found 262.08188 [M$^+$].

(2*Z*,4*E*)-3-Hydroxy-1-phenyl-5-[2-(trifluoromethyl)-5,6-dihydro-4*H*-pyran-3-yl]penta-2,4-dien-1-one (20c): Following the general procedure, **19** (500 mg, 2.78 mmol), **3k** (1.70 g, 5.55 mmol) and $TiCl_4$ (0.31 mL, 2.78 mmol) yielded **20c** as a yellow solid (260 mg, 30%); m.p. 90 °C; R_f = 0.28 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.78–7.85 (m, 2 H, Ph), 7.65 (d, $^3J_{4,5}$ = 15.3 Hz, 1 H, 4-H), 7.31–7.47 (m, 3 H, Ph), 6.14 (s, 1 H, 2-H), 5.98 (d, $^3J_{4,5}$ = 15.3 Hz, 1 H, 5-H), 4.07 (t, $^3J_{5',6'}$ = 5.2 Hz, 2 H, 6′-H), 2.24–2.35 (m, 2 H, 4′-H), 1.86–1.95 (m, $^3J_{5',6'}$ = 5.2 Hz, 2 H, 5′-H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 189.1 (C-3), 179.7 (C-1), 145.8 (q, $^2J_{C,F}$ = 34.0 Hz, C-2′), 136.4 (C$_{Ph}$), 134.1 (q, $^4J_{C,F}$ = 2.5 Hz, C-5), 132.6, 128.7, 127.4 (CH$_{Ph}$), 122.7 (C-4), 120.5 (q, $^1J_{C,F}$ = 275.8 Hz, CF_3), 113.3 (q, $^3J_{C,F}$ = 2.0 Hz, C-3′), 97.4 (C-2), 67.4 (C-6′), 21.2, 21.1 (C-4′, C-5′) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –62.5 (CF_3) ppm. MS (EI, 70 eV): *m*/*z* (%) = 324 (16) [M$^+$], 255 (71) [M$^+$ – CF_3], 227 (10) [M$^+$ – $COCF_3$]. $C_{17}H_{15}F_3O_3$ (324.29): calcd. C 62.96, H 4.66; found C 62.56, H 4.67.

(3*Z*,5*E*)-1,1,1-Trifluoro-4-hydroxy-6-[2-(trifluoromethyl)-5,6-dihydro-4*H*-pyran-3-yl]hexa-3,5-dien-2-one (20d): Following the general procedure, **19** (450 mg, 2.5 mmol), **3l** (1.49 g, 5.0 mmol) and $TiCl_4$ (0.28 mL, 2.5 mmol) yielded **20d** as a colourless solid (205 mg, 43%); m.p. 53 °C; R_f = 0.18 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.84 (d, $^3J_{5,6}$ = 15.3 Hz, 1 H, 6-H), 6.00 (d, $^3J_{5,6}$ = 15.3 Hz, 1 H, 5-H), 5.93 (s, 1 H, 3-H), 4.21 ("t", $^3J_{5',6'}$ = 5.2 Hz, 2 H, 6′-H), 2.32–2.42 (m, 2 H, 4′-H), 1.96–2.07 (m, $^3J_{5',6'}$ = 5.2 Hz, 2 H, 5′-H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 181.1 (C-4), 180.4 (q, $^2J_{C,F}$ = 35.8 Hz, C-2), 147.8 (q, $^2J_{C,F}$ = 34.0 Hz, C-2′), 137.7 (q, $^3J_{C,F}$ = 2.7 Hz, C-6), 120.2 (q, $^1J_{C,F}$ = 276.4 Hz, CF_3), 120.1 (C-5), 116.9 (q, $^1J_{C,F}$ = 283.3 Hz, C-1), 112.8 (q, $^3J_{C,F}$ = 2.1 Hz, C-3′), 95.5 (C-3), 67.7 (C-6′), 20.9, 20.8 (C-4′, C-5′) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –76.8 (C-1), –62.5 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 1628 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 316 (11) [M$^+$], 247 (100) [M$^+$ – CF_3], 219 (24) [M$^+$ – $COCF_3$]. HRMS (EI): calcd. for $C_{12}H_{10}F_6O_3$ 316.0529; found 316.0523 [M$^+$].

6-Acetyl-5-hydroxy-4-(3-hydroxypropyl)-5-(trifluoromethyl)cyclohex-2-enone (21): During the synthesis of **20b**, product **21** was isolated as a side product. Starting with **19** (370 mg, 2.05 mmol), **3e** (1.00 g, 4.11 mmol) and $TiCl_4$ (0.23 mL, 2.05 mmol), **21** was isolated as a colourless syrup (230 mg, 40%); R_f = 0.76 (*n*-heptane/EtOAc = 2:3). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.81 (dd, ^3J = 15.6 Hz, 1 H, 3-H), 5.86 (d, ^3J = 15.6 Hz, 1 H, 2-H), 5.53 (s, 1 H, OH), 3.80–4.00 (m, 2 H, 3′-H), 2.58–2.71 (m, 1 H, 4-H), 2.12 (s, 3 H, $COCH_3$), 1.59–1.81 (m, 4 H, 1′-H, 2′-H) ppm. ^{13}C NMR (76 MHz, $CDCl_3$): δ = 197.9, 177.3 (C=O), 141.9 (C-3), 126.9 (C-2), 122.8 (q, $^1J_{C,F}$ = 287.5 Hz, CF_3), 100.4 (C-6), 94.8 (q, $^2J_{C,F}$ = 30.5 Hz, C-5), 61.4 (C-3′), 42.2 (C-4), 27.0 (CO*C*H$_3$), 25.7, 24.1 (C-1′, C-2′) ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = –67.4 (CF_3) ppm. IR (Nujol): $\tilde{\nu}$ = 3240 (OH), 1658 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 280 (33) [M$^+$], 262 (6) [M$^+$ – H_2O], 193 (22) [M$^+$ – H_2O – CF_3]. HRMS (EI): calcd. for $C_{12}H_{15}F_3O_4$ 280.0917; found 280.0915 [M$^+$].

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