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Synthesis of 6-(perfluoroalkyl)salicylates by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 3-ethoxy-1-(perfluoroalkyl)prop-2-en-1-ones

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Abstract—6-(Perfluoroalkyl)salicylates were prepared by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 3-ethoxy-1-(perfluoroalkyl)-prop-2-en-1-ones.

1. Introduction

(Perfluoroalkyl)arenes are important building blocks for the synthesis of pharmaceuticals and new materials.[1–3] Perfluoroalkyl groups are chemically and biologically inert and are, therefore, not metabolized. A number of amphiphilic perfluoroalkyl derivatives represent promising liquid crystals.[4] One of the most common methods for the synthesis of (perfluoroalkyl)arenes relies on the reaction of iodoarenes with (perfluoroalkyl)cuprates.[5] However, the preparative scope of this method is limited, since a number of side-reactions are frequently observed and the starting materials are often not readily available. Some years ago, Chan and Brownbridge reported[6] an elegant approach to salicylates based on the cyclization of 1,3-bis(silyl enol ethers)[7] with 3-(silyloxy)alk-2-en-1-ones.[8] Recently, we developed a convenient access to 2-acetyl- and 2-alkoxycarbonyl-3-(trifluoromethyl)phenols by cyclization of 1,3-bis(silyl enol ethers) with 4-ethoxy- and 4-silyloxy-1,1,1-trifluoroalk-3-en-2-ones.[9] In previous papers, Kostyuk and co-workers reported the formation of 3,5-bis(trifluoromethyl)anilines by reaction of enamines with 1,1,1,5,5,5-hexafluoroacetylacetone.[10] Herein, we report a new and efficient approach to 6-(perfluoroalkyl)salicylates by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 3-ethoxy-1-(perfluoroalkyl)prop-2-en-1-ones. These transformations provide a convenient and regioselective synthesis of novel (perfluoroalkyl)salicylates, which are not readily available by other methods, from readily available starting materials.

Keywords: Arenes; Cyclizations; Organic fluorine compounds; Silyl enol ethers.
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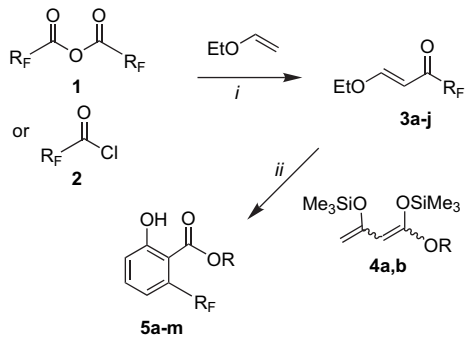
2. Results and discussion

The pyridine-mediated reaction of ethyl vinyl ether with (perfluoroalkyl)carboxylic anhydrides **1** or (perfluoroalkyl)-carboxylic chlorides **2** afforded the 3-ethoxy-1-(perfluoroalkyl)prop-2-en-1-ones **3a–j** in 39–71% yield (Scheme 1, Table 1). The reactions were carried out in analogy to the synthesis of trifluoromethyl-substituted 3-(alkoxy)prop-2-en-1-ones.[11] (Perfluoroalkyl)carboxylic anhydrides[12a] and chlorides[12b] are known and were prepared according to a literature method. The synthesis of 3-ethoxy-1-(perfluoroalkyl)prop-2-en-1-ones **3a–j** has, except for **3a**,[13] not yet been reported. Due to their rather unstable nature, **3a–j** could be characterized in most cases only by NMR experiments. All products reside as a single *E*/*Z*-diastereomer; comparison of the values of the vicinal coupling constants with those reported in the literature[11c,13b] suggest that the double bonds possess an *E*-configuration.



Scheme 1. Synthesis of **5a–m**, (*i*) CH_2Cl_2, pyridine, 0→20 °C, 12 h; (*ii*) $TiCl_4$, CH_2Cl_2, −78→20 °C, 20 h.

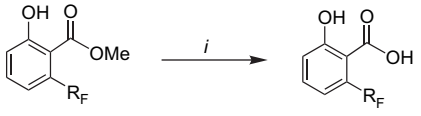
Table 1. Products **3a–j**, **5a–m** and their yields

3	5	R_F	R	% (3)[a]	% (5)[a]
a	**a**	C_3F_7	Me	56	41
b	**b**	C_5F_{11}	Me	40	43
c	**c**	C_6F_{13}	Me	41	53
d	**d**	C_7F_{15}	Me	72	58
e	**e**	C_8F_{17}	Me	52	52
f	**f**	C_9F_{19}	Me	71	47
g	**g**	$C_{10}F_{21}$	Me	59	38
h	**h**	$C_{11}F_{23}$	Me	40	40
i	**i**	$C_{13}F_{27}$	Me	39	26
j	**j**	$C_{15}F_{31}$	Me	39	24
e	**k**	C_8F_{17}	Et	52	48
f	**l**	C_9F_{19}	Et	71	40
g	**m**	$C_{10}F_{21}$	Et	59	52

[a] Isolated yields.

The $TiCl_4$ mediated cyclization of **3a–j** with 1,3-bis(silyl enol ethers) **4a**,**b**—prepared from methyl and ethyl acetoacetate—afforded the novel 6-(perfluoroalkyl)salicylates **5a–m** (Scheme 1, Table 1). All products were formed with very good regioselectivity. The regioselectivity can be explained—following general observations by Chan[6]—by $TiCl_4$ mediated conjugate addition of the terminal carbon atom of the 1,3-bis(silyl enol ether) onto **3a–j** and subsequent cyclization by attack of the central carbon atom of the bis(silyl enol ether) onto the carbonyl group. Satisfactory yields were obtained for all products, but they decreased with increasing length of the perfluoroalkyl group (which can be explained by the decreasing solubility).

The synthesis of free 6-(perfluoroalkyl)salicylic acids was studied next. Our initial attempts to hydrolyze the ester **5d** by treatment with NaOH/H_2O, NaOH/EtOH, NaOMe/MeOH or trifluoroacetic acid (TFA) failed. Finally, we have found that treatment of **5d** with KO*t*-Bu/THF (stirring for 3 days at 20 °C) and subsequent acidic work-up afforded the desired carboxylic acid **6a** in 78% yield (Scheme 2, Table 2). Likewise, the 6-(perfluoroalkyl)salicylic acids **6b**,**c** were prepared from **5g** and **5j**, respectively.



Scheme 2. Synthesis of **6a–c**, (*i*) (1) KO*t*-Bu, THF, 20 °C, 3 days; (2) HCl, H_2O.

In conclusion, a variety of 6-(perfluoroalkyl)salicylates were prepared by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 3-ethoxy-1-(perfluoroalkyl)prop-2-en-1-ones.

Table 2. Products **6a–c** and their yields

5	6	R_F	% (6)[a]
d	**a**	C_7F_{15}	78
g	**b**	$C_{10}F_{21}$	80
j	**c**	$C_{15}F_{31}$	86

[a] Isolated yields.

3. Experimental section

3.1. General procedure for the synthesis of 3-ethoxy-1-(perfluoroalkyl)prop-2-en-1-ones 3a–j

To a CH_2Cl_2 solution (2.5 mL/mmol) of (perfluoroalkyl)-carboxylic chloride **2** or (perfluoroalkyl)carboxylic anhydride **1** (1.0 equiv) was added dropwise a CH_2Cl_2 solution (1.5 mL/mmol) of pyridine (2.0 equiv) and of ethyl vinyl ether (1.3 equiv) at 0 °C. The temperature of the solution was allowed to slowly rise to 20 °C and the solution was stirred at 20 °C for 12 h. The solvent was removed in vacuo and the residue was purified by kugelrohr distillation or by column chromatography (silica gel, *n*-heptane/EtOAc=20:1). In the ^{13}C NMR data, the carbon atoms attached to the fluorine atoms were omitted, due to extensive couplings.

3.1.1. 1-Ethoxy-4,4,5,5,6,6,7,7,8,8,8-(undecafluoro)oct-1-en-3-one (3b). Starting with a CH_2Cl_2 solution (4 mL) of perfluorohexanoic anhydride (**1b**) (1.00 g, 1.6 mmol) and a CH_2Cl_2 solution (4 mL) of pyridine (0.23 g, 3.2 mmol) and ethyl vinyl ether (0.15 g, 2.1 mmol), **3b** was isolated by kugelrohr distillation (oven temperature=110 °C, 6 Torr) as a colourless oil (240 mg, 40%); R_f=0.79 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=7.90 (d, ^3J=12.2 Hz, 1H, H-1), 5.93 (d, ^3J=12.2 Hz, 1H, H-2), 4.10 (q, ^3J=7.0 Hz, 2H, OCH_2CH_3), 1.39 (t, ^3J=7.0 Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=181.8 (C-3), 168.0 (C-2), 98.8 (C-1), 69.2 (OCH_2CH_3), 14.2 (OCH_2CH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−88.7 (CF_3), −121.0, −121.4, −122.5 (CF_2), −126.1 (CF_2CF_3).

3.1.2. 1-Ethoxy-4,4,5,5,6,6,7,7,8,8,9,9,9-(tridecafluoro)-non-1-en-3-one (3c). Starting with a CH_2Cl_2 solution (1 mL) of perfluoroheptanoic anhydride (**1c**) (180 mg, 0.47 mmol) and a CH_2Cl_2 solution (1 mL) of pyridine (74 mg, 0.94 mmol) and ethyl vinyl ether (44 mg, 0.61 mmol), **3c** was isolated by column chromatography as a colourless oil (80 mg, 41%); R_f=0.83 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=7.91 (d, ^3J=12.2 Hz, 1H, H-1), 5.94 (d, ^3J=12.2 Hz, 1H, H-2), 4.11 (q, ^3J=7.0 Hz, 2H, OCH_2CH_3), 1.40 (t, ^3J=7.0 Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=181.8 (C-3), 168.0 (C-2), 98.8 (C-1), 69.2 (OCH_2CH_3), 14.3 (OCH_2CH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−88.6 (CF_3), −120.8, −121.4, −122.2, −122.6 (CF_2), −125.9 (CF_2CF_3).

3.1.3. 1-Ethoxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-(pentadecafluoro)dec-1-en-3-one (3d). Starting with a CH_2Cl_2 solution (10 mL) of perfluoroctanoic chloride (**2a**) (1.77 g, 4.10 mmol) and a CH_2Cl_2 solution (7 mL) of pyridine (0.64 g, 8.20 mmol) and ethyl vinyl ether (0.38 g, 5.33 mmol), **3d** was isolated by kugelrohr distillation (oven temperature=70 °C, 0.2 Torr) as a colourless oil (1.15 g, 72%); R_f=0.71 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=7.91 (d, ^3J=12.2 Hz, 1H, H-1), 5.94 (d, ^3J=12.2 Hz, 1H, H-2), 4.11 (q, ^3J=7.0 Hz, 2H, OCH_2CH_3), 1.40 (t, ^3J=7.0 Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=182.0 (C-3), 168.1 (C-2), 99.0 (C-1), 69.4 (OCH_2CH_3), 14.5 (OCH_2CH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.6 (CF_3), −120.9, −121.3, −121.9, −122.3, −122.6 (CF_2), −126.0 (CF_2CF_3). MS (CI, isobutane): *m*/*z* (%)=469 ($[M+1]^+$, 100), 99 (9).

3.1.4. 1-Ethoxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-(heptadecafluoro)undec-1-en-3-one (3e). Starting with a CH_2Cl_2 solution (7 mL) of perfluorononanoic chloride (**2b**) (1.50 g, 3.10 mmol) and a CH_2Cl_2 solution (5 mL) of pyridine (0.49 g, 6.2 mmol) and ethyl vinyl ether (0.29 g, 4.0 mmol), **3e** was isolated by column chromatography as a colourless oil (1.15 g, 72%); R_f=0.71 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=7.90 (d, ^3J=12.2 Hz, 1H, H-1), 5.93 (d, ^3J=12.2 Hz, 1H, H-2), 4.09 (q, ^3J=7.0 Hz, 2H, OCH_2CH$_3$), 1.38 (t, ^3J=7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=181.8 (C-3), 168.0 (C-2), 98.8 (C-1), 69.2 (OCH$_2$CH$_3$), 14.2 (OCH$_2$$CH_3$). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−81.0 (CF_3), −121.1, −121.4, −121.9, −122.4, −122.8 (CF_2), −126.2 (CF_2CF$_3$).

3.1.5. 1-Ethoxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-(nonadecafluoro)dodec-1-en-3-one (3f). Starting with a CH_2Cl_2 solution (4 mL) of perfluorodecanoic chloride (**2c**) (1.00 g, 1.9 mmol) and a CH_2Cl_2 solution (4 mL) of pyridine (0.30 g, 3.8 mmol) and ethyl vinyl ether (0.18 g, 2.4 mmol), **3f** was isolated by column chromatography as a colourless solid (754 mg, 71%); R_f=0.74 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=7.90 (d, ^3J=12.2 Hz, 1H, H-1), 5.94 (d, ^3J=12.2 Hz, 1H, H-2), 4.10 (q, ^3J=7.0 Hz, 2H, OCH_2CH$_3$), 1.39 (t, ^3J=7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=181.8 (C-3), 168.0 (C-2), 98.8 (C-1), 69.2 (OCH$_2$CH$_3$), 14.3 (OCH$_2$$CH_3$). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.8 (CF_3), −121.1, −121.4, −121.9, −122.3, −122.8 (CF_2), −126.1 (CF_2CF$_3$).

3.1.6. 1-Ethoxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-(henicosafluoro)tridec-1-en-3-one (3g). Starting with a CH_2Cl_2 solution (7 mL) of perfluoroundecanoic chloride (**2d**) (2.5 g, 4.3 mmol) and a CH_2Cl_2 solution (7 mL) of pyridine (0.68 g, 8.6 mmol) and ethyl vinyl ether (0.52 g, 5.6 mmol), **3g** was isolated by column chromatography as a colourless solid (1.55 g, 59%); R_f=0.82 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=7.91 (d, ^3J=12.2 Hz, 1H, H-1), 5.94 (d, ^3J=12.2 Hz, 1H, H-2), 4.11 (q, ^3J=7.0 Hz, 2H, OCH_2CH$_3$), 1.40 (t, ^3J=7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=181.8 (C-3), 168.0 (C-2), 98.8 (C-1), 69.2 (OCH$_2$CH$_3$), 14.3 (OCH$_2$$CH_3$). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.7 (CF_3), −121.0, −121.2, −121.7, −122.2, −122.6 (CF_2), −126.0 (CF_2CF$_3$).

3.1.7. 1-Ethoxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,14-(tricosafluoro)tridec-1-en-3-one (3h). Starting with a CH_2Cl_2 solution (4 mL) of perfluorododecanoic chloride (**2e**) (1.50 g, 2.4 mmol) and a CH_2Cl_2 solution (4 mL) of pyridine (0.38 g, 4.8 mmol) and ethyl vinyl ether (0.22 g, 3.1 mmol), **3h** was isolated by column chromatography as a colourless solid (628 mg, 40%); R_f=0.79 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=7.91 (d, ^3J=12.2 Hz, 1H, H-1), 5.95 (d, ^3J=12.2 Hz, 1H, H-2), 4.11 (q, ^3J=7.0 Hz, 2H, OCH_2CH$_3$), 1.41 (t, ^3J=7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=168.0 (C-2), 98.8 (C-1), 69.2 (OCH$_2$CH$_3$), 14.3 (OCH$_2$$CH_3$). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.5 (CF_3), −120.9, −121.1, −121.5, −122.1, −122.4 (CF_2), −125.8 (CF_2CF$_3$).

3.1.8. 1-Ethoxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16,16-(heptacosafluoro)hexadec-1-en-3-one (3i). Starting with a CH_2Cl_2 solution (1.5 mL) of perfluorotetradecanoic chloride (**2f**) (381 mg, 0.52 mmol) and a CH_2Cl_2 solution (1.5 mL) of pyridine (82 mg, 1.04 mmol) and ethyl vinyl ether (48 mg, 0.68 mmol), **3i** was isolated by column chromatography as a colourless solid (156 mg, 39%); R_f=0.75 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=7.91 (d, ^3J=12.2 Hz, 1H, H-1), 5.95 (d, ^3J=12.2 Hz, 1H, H-2), 4.11 (q, ^3J=7.0 Hz, 2H, OCH_2CH$_3$), 1.41 (t, ^3J=7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=168.0 (C-2), 98.8 (C-1), 69.2 (OCH$_2$CH$_3$), 14.4 (OCH$_2$$CH_3$). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.4 (CF_3), −120.8, −120.8, −121.0, −121.3, −122.0, −122.4 (CF_2), −125.8 (CF_2CF$_3$).

3.1.9. 1-Ethoxy-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,15,16,16,17,17,18,18,18-(hentriconta-fluoro)octadec-1-en-3-one (3j). Starting with a CH_2Cl_2 solution (1.5 mL) of perfluorohexadecanoic chloride (**2g**) (458 mg, 0.55 mmol) and a CH_2Cl_2 solution (1.5 mL) of pyridine (87 mg, 1.10 mmol) and ethyl vinyl ether (52 mg, 0.72 mmol), **3j** was isolated by column chromatography as a colourless solid (185 mg, 39%); R_f=0.75 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=7.91 (d, ^3J=12.2 Hz, 1H, H-1), 5.95 (d, ^3J=12.2 Hz, 1H, H-2), 4.11 (q, ^3J=7.0 Hz, 2H, OCH_2CH$_3$), 1.41 (t, ^3J=7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=168.0 (C-2), 98.8 (C-1), 69.2 (OCH$_2$CH$_3$), 14.4 (OCH$_2$$CH_3$). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.5 (CF_3), −120.8, −121.2, −121.5, −122.1, −122.4 (CF_2), −125.9 (CF_2CF$_3$).

3.2. General procedure for the synthesis of 6-(perfluoroalkyl)salicylates 5a–m

To a CH_2Cl_2 solution (2.5 mL/mmol) of 3-ethoxy-3-(perfluoroalkyl)alk-2-en-1-one **3** (1.0 equiv) and 1,3-bis(silyl enol ether) **4a**,**b** (1.3 equiv) was added $TiCl_4$ (1.0 equiv) at −78 °C under argon atmosphere. The temperature of the solution was allowed to slowly rise to 20 °C and the solution was stirred at this temperature for 12 h. To the solution was added hydrochloric acid (10%) and the organic and the aqueous layers were separated and 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 column chromatography (silica gel, *n*-heptane/EtOAc=20:1). In the ^{13}C NMR data, the carbon atoms attached to the fluorine atoms were omitted, due to extensive couplings.

3.2.1. Methyl 6-(heptafluoropropyl)salicylate (5a). Starting with **3a** (402 mg, 1.5 mmol), **4a** (521 mg, 2.0 mmol) and $TiCl_4$ (284 mg, 1.5 mmol) in CH_2Cl_2 (3 mL), **5a** was isolated as a colourless oil (195 mg, 41%); R_f=0.43 (*n*-heptane/EtOAc=1:1). A small amount of an unknown impurity could not be separated. ^{1}H NMR ($CDCl_3$, 250 MHz): δ=9.37 (s, 1H, OH), 7.50 (t, ^3J=8.5 Hz, 1H, H-4), 7.24–7.17 (m, 2H, H-3, H-5), 3.93 (s, 3H, OCH$_3$). ^{13}C NMR ($CDCl_3$, 63 MHz): δ=169.0 (C=O), 159.1 (C-2), 132.8 (C-3), 129.0 (C-6), 121.6 (C-4), 120.6 (C-5), 115.9 (C-1), 52.8 (OCH$_3$). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.5 (CF_3), −99.4 (ArCF_2), −126.9 (CF_2CF$_3$). MS (EI, 70 eV): *m*/*z* (%)=320 (M^+, 21), 288 (100, [M^+−MeOH]), 241 (8),

141 (37). HRMS (EI, 70 eV): calcd for $C_{11}H_7F_7O_3$ (M^+) 320.02779, found 320.02728.

3.2.2. Methyl 6-(undecafluoropentyl)salicylate (5b). Starting with **3b** (220 mg, 0.60 mmol), **4a** (203 mg, 0.78 mmol) and $TiCl_4$ (114 mg, 0.60 mmol) in CH_2Cl_2 (1.2 mL), **5b** was isolated as a colourless solid (108 mg, 43%); mp=68–69 °C; R_f=0.53 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=9.31 (s, 1H, OH), 7.51 (t, ^3J=8.5 Hz, 1H, H-4), 7.24–7.18 (m, 2H, H-3, H-5), 3.93 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=168.9 (C=O), 159.1 (C-2), 132.8 (C-3), 127.5 (C-6), 121.7 (C-4), 120.8 (C-5), 114.7 (C-1), 52.8 (OCH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.4 (CF_3), −99.6 (CF_2Ar), −117.2, −122.7 (CF_2), −125.7 (CF_2CF_3). MS (EI, 70 eV): *m/z* (%)=420 (M^+, 24), 388 (100, [M^+−MeOH]), 341 (10), 169 (21), 141 (61). HRMS (EI, 70 eV): calcd for $C_{13}H_7F_{11}O_3$ (M^+) 420.02141, found 420.02112.

3.2.3. Methyl 6-(tridecafluorohexyl)salicylate (5c). Starting with **3c** (80 mg, 0.19 mmol), **4a** (65 mg, 0.25 mmol) and $TiCl_4$ (36 mg, 0.19 mmol) in CH_2Cl_2 (0.5 mL), **5c** was isolated as a colourless solid (47 mg, 53%); mp=75–76 °C; R_f=0.50 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=9.29 (s, 1H, OH), 7.50 (t, ^3J=8.5 Hz, 1H, H-4), 7.24–7.18 (m, 2H, H-3, H-5), 3.93 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.0 (C=O), 159.1 (C-2), 132.9 (C-4), 129.1 (C-6), 121.7 (C-5), 120.8 (C-3), 114.8 (C-1), 52.8 (OCH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.5 (CF_3), −99.7 (CF_2Ar), −117.1 (CF_2), −121.9 (CF_2), −122.4 (CF_2), −125.8 (CF_2CF_3). MS (EI, 70 eV): *m/z* (%)=470 (M^+, 17), 438 (100, [M^+−MeOH]), 419 (7), 169 (9), 141 (60). HRMS (EI, 70 eV): calcd for $C_{14}H_7O_3F_{13}$ (M^+) 470.01821, found 470.01904.

3.2.4. Methyl 6-(pentadecafluoroheptyl)salicylate (5d). Starting with **3d** (1.00 g, 2.1 mmol), **4a** (1.12 g, 2.7 mmol) and $TiCl_4$ (0.40 g, 2.1 mmol) in CH_2Cl_2 (5.5 mL), **5d** was isolated as a colourless solid (650 mg, 58%); mp=83–84 °C; R_f=0.50 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=9.28 (s, 1H, OH), 7.48 (t, ^3J=8.5 Hz, 1H, H-4), 7.23–7.16 (m, 2H, H-3, H-5), 3.92 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.1 (C=O), 159.1 (C-2), 132.9 (C-3), 129.2 (C-6), 121.8 (C-4), 120.9 (C-5), 115.2 (C-1), 52.9 (OCH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.7 (CF_3), −100.2 (CF_2Ar), −117.3, −121.8, −122.5 (CF_2), −126.0 (CF_2CF_3). IR ($CHCl_3$, cm^{-1}): $\tilde{\nu}$ = 3277, 1685. MS (EI, 70 eV): *m/z* (%)=520 (M^+, 18), 488 (100, [M^+−MeOH]), 461 (8, [M^+−COOMe]). HRMS (EI, 70 eV): calcd for $C_{15}H_7F_{15}O_3$ (M^+) 520.0150, found 520.0128.

3.2.5. Methyl 6-(heptadecafluorooctyl)salicylate (5e). Starting with **3e** (777 mg, 1.5 mmol), **4a** (521 mg, 2.0 mmol) and $TiCl_4$ (284 mg, 1.5 mmol) in CH_2Cl_2 (3 mL), **5e** was isolated as a colourless solid (443 mg, 52%); mp=102–104 °C; R_f=0.50 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=9.31 (s, 1H, OH), 7.51 (t, ^3J=8.5 Hz, 1H, H-4), 7.24–7.18 (m, 2H, H-3, H-5), 3.94 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.0 (C=O), 159.3 (C-2), 132.9 (C-3), 129.2 (C-6), 121.7 (C-4), 120.8 (C-5), 114.6 (C-1), 52.8 (OCH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.7 (CF_3), −99.8 ($ArCF_2$), −117.7, −121.9, −122.6 (CF_2), −126.0 (CF_2CF_3). MS (EI, 70 eV): *m/z* (%)=570 (M^+, 15), 538 (100, [M^+−MeOH]), 519 (11), 169 (12), 141 (64). HRMS (EI, 70 eV): calcd for $C_{16}H_7O_3F_{17}$ (M^+) 570.01183, found 570.01008. Anal. Calcd for $C_{16}H_7F_{17}O_3$ (570.20): C, 33.70; H, 1.24. Found: C, 33.83; H, 1.28.

3.2.6. Methyl 6-(nonadecafluorononyl)salicylate (5f). Starting with **3f** (568 mg, 1.0 mmol), **4a** (338 mg, 1.3 mmol) and $TiCl_4$ (189 mg, 1.0 mmol) in CH_2Cl_2 (2.5 mL), **5f** was isolated as a colourless solid (290 mg, 47%); mp=109–110 °C; R_f=0.50 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=9.28 (s, 1H, OH), 7.50 (t, ^3J=8.5 Hz, 1H, H-4), 7.24–7.18 (m, 2H, H-3, H-5), 3.93 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.0 (C=O), 159.3 (C-2), 132.9 (C-3), 129.2 (C-6), 121.7 (C-4), 120.8 (C-5), 114.6 (C-1), 52.8 (OCH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.4 (CF_3), −99.6 (CF_2Ar), −116.9, −121.5, −122.4 (CF_2), −125.8 (CF_2CF_3). MS (EI, 70 eV): *m/z* (%)=620 (M^+, 23), 588 (100, [M^+−MeOH]), 569 (20), 169 (18), 141 (75). HRMS (EI, 70 eV): calcd for $C_{17}H_7F_{19}O_3$ (M^+) 620.00863, found 620.00875. Anal. Calcd for $C_{17}H_7F_{19}O_3$ (620.01): C, 32.92; H, 1.14. Found: C, 33.02; H, 1.15.

3.2.7. Methyl 6-(henicosafluorodecyl)salicylate (5g). Starting with **3g** (1.00 g, 1.6 mmol), **4a** (547 mg, 2.1 mmol) and $TiCl_4$ (303 mg, 1.6 mmol) in CH_2Cl_2 (3.2 mL), **5g** was isolated as a colourless solid (405 mg, 38%); mp=118–119 °C; R_f=0.50 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=9.30 (s, 1H, OH), 7.50 (t, ^3J=8.5 Hz, 1H, H-4), 7.24–7.18 (m, 2H, H-3, H-5), 3.94 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.0 (C=O), 159.3 (C-2), 132.9 (C-3), 129.3 (C-6), 121.8 (C-4), 120.8 (C-5), 114.6 (C-1), 52.8 (OCH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.5 (CF_3), −99.5 (CF_2Ar), −117.0, −121.4, −122.4 (CF_2), −125.8 (CF_2CF_3). MS (EI, 70 eV): *m/z* (%)=670 (M^+, 16), 638 (100, [M^+−MeOH]), 619 (17), 169 (13), 141 (44). HRMS (EI, 70 eV): calcd for $C_{18}H_7F_{21}O_3$ (M^+) 670.00544, found 670.00601. Anal. Calcd for $C_{18}H_7F_{21}O_3$ (670.21): C, 32.26; H, 1.05. Found: C, 32.70; H, 1.18.

3.2.8. Methyl 6-(tricosafluoroundecyl)salicylate (5h). Starting with **3h** (620 mg, 0.93 mmol), **4a** (315 mg, 1.21 mmol) and $TiCl_4$ (176 mg, 0.93 mmol) in CH_2Cl_2 (1.9 mL), **5h** was isolated as a colourless solid (262 mg, 40%); mp=119–120 °C; R_f=0.50 (*n*-heptane/EtOAc=1:1). ^1H NMR ($CDCl_3$, 250 MHz): δ=9.30 (s, 1H, OH), 7.51 (t, ^3J=8.5 Hz, 1H, H-4), 7.24–7.18 (m, 2H, H-3, H-5), 3.93 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.0 (C=O), 159.3 (C-2), 132.9 (C-3), 121.8 (C-4), 121.0 (C-5), 52.8 (OCH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.5 (CF_3), −99.7 (CF_2Ar), −117.1, −121.5, −122.5 (CF_2), −125.9 (CF_2CF_3). MS (EI, 70 eV): *m/z* (%)=720 (M^+, 22), 688 (100, [M^+−MeOH]), 669 (25), 169 (13), 141 (47). HRMS (EI, 70 eV): calcd for $C_{19}H_7F_{19}O_3$ (M^+) 720.00224, found 720.00280.

3.2.9. Methyl 6-(heptacosafluorotridecyl)salicylate (5i). Starting with **3i** (155 mg, 0.15 mmol), **4a** (52 mg, 0.20 mmol) and $TiCl_4$ (28 mg, 0.15 mmol) in CH_2Cl_2

(0.3 mL), **5i** was isolated as a colourless solid (31 mg, 26%); mp=114–115 °C; R_f=0.35 (*n*-heptane/EtOAc=1:1). A small amount of an unknown impurity could not be separated. ^{1}H NMR ($CDCl_3$, 250 MHz): δ=9.30 (s, 1H, OH), 7.50 (t, ^3J=8.5 Hz, 1H, H-4), 7.24–7.18 (m, 2H, H-3, H-5), 3.93 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.0 (C=O), 159.2 (C-2), 132.9 (C-3), 121.7 (C-4), 120.8 (C-5), 52.8 (OCH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.5 (CF_3), −99.7 ($ArCF_2$), −116.9 (CF_2), −121.4, −122.4 (CF_2), −126.5 (CF_2CF_3). MS (EI, 70 eV): *m*/*z* (%)=820 (M^+, 24), 788 (100, [M^+−MeOH]), 750 (62), 141 (64). HRMS (EI, 70 eV): calcd for $C_{21}H_7O_3F_{27}$ (M^+) 819.99586, found 819.994578.

3.2.10. Methyl 6-(hentricontafluoropentadecyl)salicylate (5j). Starting with **3j** (185 mg, 0.21 mmol), **4a** (71 mg, 0.27 mmol) and $TiCl_4$ (38 mg, 0.21 mmol) in CH_2Cl_2 (0.5 mL), **5j** was isolated as a colourless solid (45 mg, 24%); mp=84–86 °C; R_f=0.35 (*n*-heptane/EtOAc=1:1). ^{1}H NMR ($CDCl_3$, 250 MHz): δ=9.30 (s, 1H, OH), 7.50 (t, ^3J=8.5 Hz, 1H, H-4), 7.24–7.18 (m, 2H, H-3, H-5), 3.93 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.0 (C=O), 159.2 (C-2), 132.9 (C-3), 121.7 (C-4), 120.8 (C-5), 114.6 (C-1), 52.8 (OCH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.8 (CF_3), −99.8 ($ArCF_2$), −117.3 (CF_2), −121.6, −122.7 (CF_2), −126.1 (CF_2CF_3). MS (EI, 70 eV): *m*/*z* (%)=920 (M^+, 13), 888 (31, [M^+−MeOH]), 850 (100), 788 (43), 750 (58), 688 (13), 141 (33). HRMS (EI, 70 eV): calcd for $C_{23}H_7O_3F_{31}$ (M^+) 919.98947, found 919.98842.

3.2.11. Ethyl 6-(heptadecafluorooctyl)salicylate (5k). Starting with **3e** (160 mg, 0.31 mmol), **4b** (170 mg, 0.62 mmol) and $TiCl_4$ (59 mg, 0.31 mmol) in CH_2Cl_2 (0.8 mL), **5k** was isolated as a colourless solid (84 mg, 46%); mp=95–96 °C; R_f=0.45 (*n*-heptane/EtOAc=1:1). A small amount of an unknown impurity could not be separated. ^{1}H NMR ($CDCl_3$, 250 MHz): δ=9.21 (s, 1H, OH), 7.49 (t, ^3J=8.5 Hz, 1H, H-4), 7.24–7.17 (m, 2H, H-3, H-5), 4.43 (q, ^3J=7.0 Hz, 2H, OCH_2CH_3), 1.36 (t, ^3J=7.0 Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=168.5 (C=O), 158.9 (C-2), 132.5 (C-3), 128.8 (C-6), 121.6 (C-4), 120.9 (C-5), 115.5 (C-1), 62.7 (OCH_2CH_3), 13.4 (OCH_2CH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.5 (CF_3), −99.8 ($ArCF_2$), −117.5, −121.6, −122.4 (CF_2), −125.8 (CF_2CF_3). MS (EI, 70 eV): *m*/*z* (%)=584 (M^+, 14), 538 (100, [M^+−EtOH]), 519 (11), 169 (11), 141 (36). HRMS (EI, 70 eV): calcd for $C_{17}H_9O_3F_{17}$ (M^+) 584.02748, found 584.02769.

3.2.12. Ethyl 6-(nonadecafluorononyl)salicylate (5l). Starting with **3f** (568 mg, 1.0 mmol), **4b** (338 mg, 1.3 mmol) and $TiCl_4$ (189 mg, 1.0 mmol) in CH_2Cl_2 (2.5 mL), **5l** was isolated as a colourless solid (35 mg, 40%); mp=103–104 °C; R_f=0.45 (*n*-heptane/EtOAc=1:1). A small amount of an unknown impurity could not be separated. ^{1}H NMR ($CDCl_3$, 250 MHz): δ=9.19 (s, 1H, OH), 7.48 (t, ^3J=8.5 Hz, 1H, H-4), 7.23–7.16 (m, 2H, H-3, H-5), 4.42 (q, ^3J=7.0 Hz, 2H, OCH_2CH_3), 1.36 (t, ^3J=7.0 Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=169.0 (C=O), 159.3 (C-2), 132.9 (C-3), 129.2 (C-6), 121.7 (C-4), 120.8 (C-5), 114.6 (C-1), 52.8 (OCH_2CH_3), 13.4 (OCH_2CH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.5 (CF_3), −100.0 (CF_2Ar), −117.6, −121.5, −122.4 (CF_2), −125.8 (CF_2CF_3). MS (EI, 70 eV): *m*/*z* (%)=634 (M^+, 12), 588 (100, [M^+−EtOH]), 569 (10), 169 (9), 141 (29). HRMS (EI, 70 eV): calcd for $C_{18}H_9O_3F_{19}$ (M^+) 634.02428, found 634.025582.

3.2.13. Ethyl 6-(henicosafluorodecyl)salicylate (5m). Starting with **3g** (230 mg, 0.37 mmol), **4b** (203 mg, 0.48 mmol) and $TiCl_4$ (70 mg, 0.37 mmol) in CH_2Cl_2 (1 mL), **5m** was isolated as a colourless solid (130 mg, 52%); mp=105–106 °C; R_f=0.45 (*n*-heptane/EtOAc=1:1). A small amount of an unknown impurity could not be separated. ^{1}H NMR ($CDCl_3$, 250 MHz): δ=9.21 (br s, 1H, OH), 7.49 (t, ^3J=8.5 Hz, 1H, H-4), 7.24–7.17 (m, 2H, H-3, H-5), 4.43 (q, ^3J=7.0 Hz, 2H, OCH_2CH_3), 1.36 (t, ^3J=7.0 Hz, 3H, OCH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=168.5 (C=O), 158.9 (C-2), 132.6 (C-3), 128.9 (C-6), 121.6 (C-4), 121.0 (C-5), 115.5 (C-1), 62.7 (OCH_2CH_3), 13.4 (OCH_2CH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ=−80.5 (CF_3), −99.7 (CF_2Ar), −117.5 (CF_2), −121.4 (CF_2), −122.4 (CF_2), −125.8 (CF_2CF_3). MS (EI, 70 eV): *m*/*z* (%)=684 (M^+, 10), 638 (100, [M^+−EtOH]), 141 (18). HRMS (EI, 70 eV): calcd for $C_{19}H_9O_3F_{21}$ (M^+) 684.02109, found 684.01984.

3.3. General procedure for the synthesis of 6-(perfluoroalkyl)salicylic acids 6a–c

To a THF solution (20 mL/mmol) of **5** (1.0 equiv) was added KO*t*-Bu (4.0 equiv) at 20 °C and the solution was stirred for 3 days at 20 °C. To the solution was added hydrochloric acid (10%) until the solution reached pH=1. The organic and the aqueous layers were separated and the latter was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane/EtOAc=1:1). In the ^{13}C NMR data, the carbon atoms attached to the fluorine atoms were omitted, due to extensive couplings.

3.3.1. 6-(Pentadecafluoroheptyl)salicylic acid (6a). Starting with **5d** (110 mg, 0.21 mmol), KO*t*-Bu (94 mg, 0.84 mmol), THF (6.0 mL), **6a** was isolated as a colourless solid (83 mg, 78%); mp=157 °C (dec); R_f=0.24 (*n*-heptane/EtOAc=1:1). ^{1}H NMR (CD_3OD, 250 MHz): δ=7.33 (t, ^3J=7.9 Hz, 1H, H-4), 7.13–7.00 (m, 2H, H-3, H-5). ^{13}C NMR (CD_3OD, 75 MHz): δ=173.5 (C=O), 156.5 (C-2), 130.2 (C-3), 126.8 (C-6), 120.6 (C-4), 119.8 (C-5), 112.4 (C-1). ^{19}F NMR (CD_3OD, 235 MHz): δ=−78.8 (CF_3), −102.0 (CF_2Ar), −116.4, −118.8, −119.3, −120.2 (CF_2), −123.7 (CF_2CF_3). MS (EI, 70 eV): *m*/*z* (%)=506 (M^+, 18), 488 (100), 469 (11). HRMS (EI, 70 eV): calcd for $C_{14}H_5F_{15}O_3$ (M^+) 505.99863, found 505.99937.

3.3.2. 6-(Henicosafluorodecyl)salicylic acid (6b). Starting with **5g** (55 mg, 0.08 mmol), KO*t*-Bu (36 mg, 0.32 mmol) in THF (2.0 mL), **6b** was isolated as a colourless solid (42 mg, 80%); mp=161 °C (dec); R_f=0.24 (*n*-heptane/EtOAc=1:1). ^{1}H NMR (CD_3OD, 250 MHz): δ=7.29 (t, ^3J=8.2 Hz, 1H, H-4), 7.12–7.00 (m, 2H, H-3, H-5). ^{13}C NMR (CD_3OD, 75 MHz): δ=170.2 (C=O), 156.2 (C-2), 131.3 (C-3), 120.6 (C-4), 119.6 (C-5). ^{19}F NMR (CD_3OD, 235 MHz): δ=−78.8 (CF_3), −103.4 (CF_2Ar), −117.1, −119.1, −120.1 (CF_2), −123.7 (CF_2CF_3).

3.3.3. 6-(Hentricontafluoropentadecyl)salicylic acid (6c). Starting with **5k** (40 mg, 0.04 mmol), KO*t*-Bu (18 mg, 0.16 mmol) in THF (2.0 mL), **6c** was isolated as a colourless solid (31 mg, 86%); mp=168 °C (dec); R_f=0.24 (*n*-heptane/EtOAc=1:1). ^{1}H NMR (CD_3OD, 250 MHz): δ=7.38 (t, ^3J=8.2 Hz, 1H, H-4), 7.14–7.02 (m, 2H, H-3, H-5). ^{19}F NMR (CD_3OD, 235 MHz): δ=−85.1 (CF_3), −105.4 (CF_2Ar), −119.1, −123.4, −123.6 (CF_2), −127.1 (CF_2CF_3). Due to the low solubility of **6c**, a ^{13}C NMR spectrum could not be obtained.

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