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Synthesis of *gem*-Difluoromethylenated Spiro-γ-butyrolactones by Employing $PhSCF_2Si(CH_3)_3$ as a *gem*-Difluoromethylenating Agent

Adisak Chatupheeraphat,[a] Darunee Soorukram,[a] Chutima Kuhakarn,[a] Patoomratana Tuchinda,[a] Vichai Reutrakul,[a] Chaveng Pakawatchai,[b] Saowanit Saithong,[b] and Manat Pohmakotr*[a]

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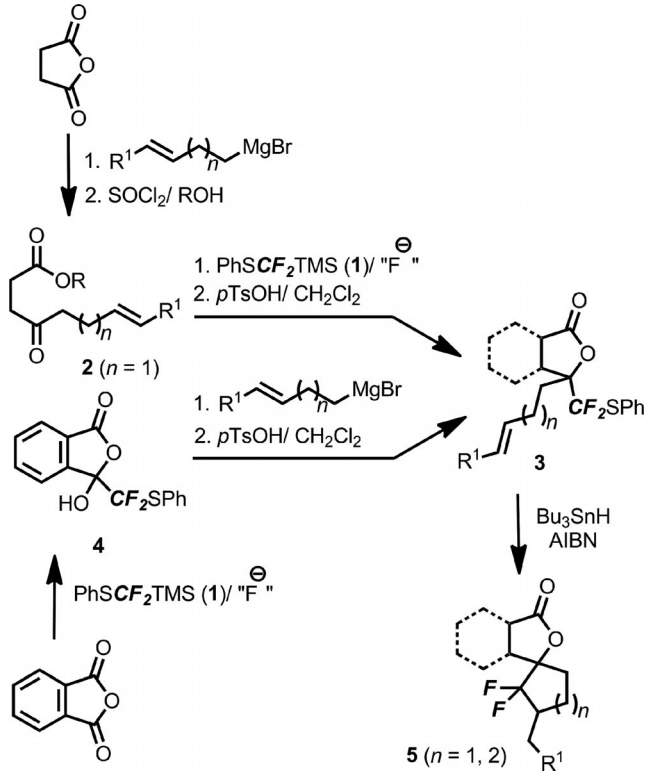
$PhSCF_2TMS$ was utilized as a useful *gem*-difluoromethylene building block for the synthesis of *gem*-difluoromethylenated spiro-γ-butyrolactones. The radical cyclization of γ-alkenyl-γ-*gem*-difluoro(phenylsulfanyl)methyl-γ-butyrolactones provided *gem*-difluoromethylenated spiro-γ-butyrolactones.

Introduction

Fluorine-containing organic molecules are important structural motifs in a number of drug candidates, agrochemical reagents, and functional materials.[1] Their unique properties stem from the enhanced chemical, physical, and metabolic stability of the fluorinated moiety. Accordingly, there has been great interest in the syntheses of fluorine-containing natural product analogs and materials.[2] Despite this interest, general synthetic methods for the introduction of the *gem*-difluoromethylene group into organic compounds are still highly desirable. Among several fluorinated reagents, $PhSCF_2TMS$ (**1**; TMS = trimethylsilyl), first introduced by Prakash and co-workers, has gained popularity as a useful and convenient *gem*-difluoromethylene building block.[3] In connection with our work on the synthesis of fluorine-containing organic molecules by using **1** as a *gem*-difluoromethylene radical anion equivalent ($CF_2^{\bullet-}$),[4] we report herein a synthetic strategy to *gem*-difluoromethylenated spiro-γ-butyrolactones. It was envisaged that the *gem*-difluoromethylenated spiro-γ-butyrolactones **5** could be derived from the key intermediates **3** by an intramolecular radical cyclization (Scheme 1). Compounds **3** should be obtained by sequential chemoselective fluoride-catalyzed nucleophilic addition of **1** and lactonization of γ-keto esters **2**, prepared by treatment of succinic anhydride with alkenylmagnesium bromides followed by esterification. Alternatively, the key compounds **3** should also be derived from γ-*gem*-difluoro(phenylsulfanyl)methylated γ-butyrolactones **4**, which could be prepared by the fluoride-catalyzed nucleophilic addition of **1** with phthalic anhydride. The treatment of **4** with alkenylmagnesium bromides followed by lactonization gave the key intermediates **3**. Notably, the functionalized cyclopentanes and cyclohexanes bearing a spiro-γ-



Scheme 1. Proposed synthetic route to *gem*-difluoromethylenated spiro-γ-butyrolactones.

[a] Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Mahidol University,
Rama VI Road, Bangkok 10400, Thailand
E-mail: manat.poh@mahidol.ac.th
http://chemistry.sc.mahidol.ac.th
[b] Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Prince of Songkla University,
Hat Yai, Songkla 90112, Thailand

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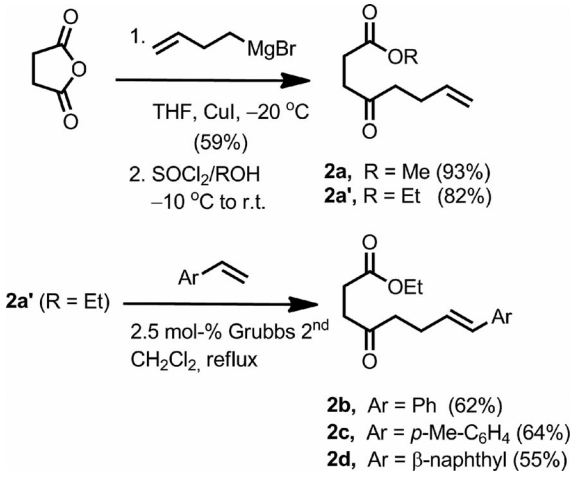
butyrolactone moiety have been found in natural products that exhibit potential bioactivities.[5] Therefore, there has been considerable interest in the development of efficient methods for the syntheses of spiro-γ-butyrolactones.[6]

Results and Discussion

Preparation of 3 from Succinic Anhydride

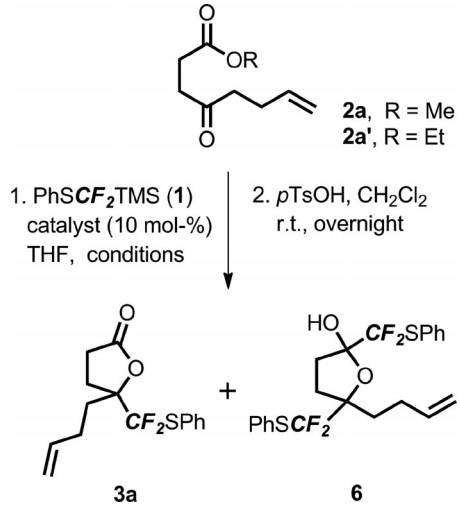
To begin with, the requisite γ-keto esters **2a** and **2a′** were prepared in good yields by treatment of succinic anhydride with homoallylmagnesium bromide (2 equiv.) in the presence of a catalytic amount of CuI[7] at –20 °C followed by esterification of the resulting ketocarboxylic acid with a mixture of $SOCl_2$/MeOH or $SOCl_2$/EtOH at –10 °C to room temp. for 2 h. The olefin cross-metathesis of **2a′** with styrene derivatives mediated by the 2nd generation Grubbs catalyst (2.5 mol-%) in CH_2Cl_2 at reflux gave keto esters **2b–d** as *E* isomers (Scheme 2).



Scheme 2. Preparation of γ-keto esters **2**.

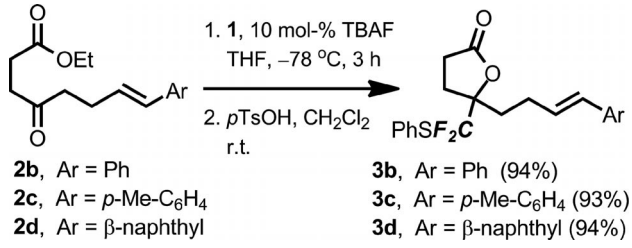
We initially screened for the optimized conditions for chemoselective fluoride-catalyzed nucleophilic addition of **1** with γ-keto ester **2a**.[4d] The treatment of **1** (2 equiv.) with **2a** in the presence of 10 mol-% of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) at –78 °C to room temp. for 5 h followed by lactonization [*p*TsOH (cat.), CH_2Cl_2, room temp.] gave the expected γ-butyrolactone **3a** in 46% yield together with **6** in 49% yield (Table 1, Entry 1). The formation of **3a** can be explained by the chemoselective fluoride-catalyzed nucleophilic addition of **1** to the keto group of **2a** followed by lactonization under acidic treatment of the firstly formed γ-hydroxy ester adduct. The undesired adduct **6** was believed to derive from the nonselective fluoride-catalyzed addition of **1** to both of the keto and the ester groups of **2a** followed by lactol formation upon acidic workup. A similar result was observed when tetrabutylammonium triphenyldifluorosilicate (TBAT) was employed in place of TBAF (Table 1, Entry 2). The reduction of the amount of **1** employed (from 2 equiv. to 1.5 equiv.) led to an improved yield of **3a** (75%, Table 1, Entry 3). Fortunately, the reaction with 1.2 equivalents of **1** in THF at –78 °C for 3.5 h gave an excellent yield of **3a** (92%) along with **6** (1%) (Table 1, Entry 4). Under the optimized reaction conditions (Table 1, Entry 4), the reaction of **2a′** readily proceeded to yield the expected γ-butyrolactone **3a** in 97% yield as a single product (Table 1, Entry 5). Under similar reaction conditions, keto esters **2b–d** afforded γ-*gem*-difluoro(phenylsulfanyl)methyl-γ-butyrolactones **3b–d** in high yields (93–94%) after lactonization. The reactions are summarized in Scheme 3.

Table 1. Fluoride-catalyzed nucleophilic addition of **1** to γ-keto esters **2** under various conditions.



Entry	2	Catalyst	1 [equiv.]	*T* [°C]	Time [h]	3a (% yield)[a]	6 (% yield)[a]
1	**2a**	TBAF	2	–78 to r.t.	5	46	49
2	**2a**	TBAT	2	–78 to r.t.	5	31	51
3	**2a**	TBAF	1.5	–78 to r.t.	5	75	17
4	**2a**	TBAF	1.2	–78	3.5	92	1
5	**2a′**	TBAF	1.2	–78	3	97	–

[a] Yield of isolated product.

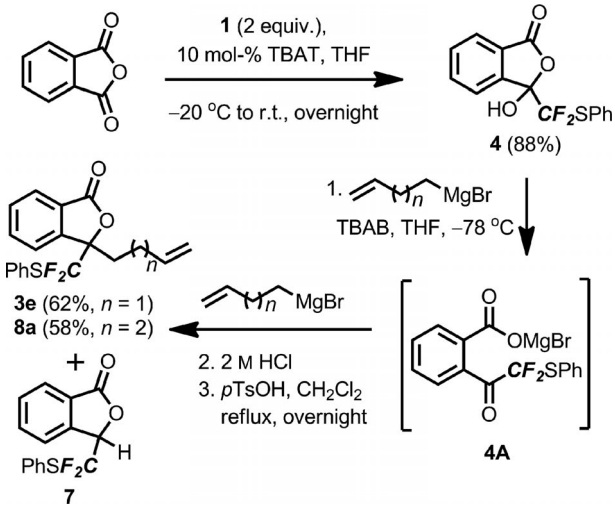


Scheme 3. Fluoride-catalyzed nucleophilic addition of **1** to γ-keto esters **2b–d**.

Preparation of 3 from Phthalic Anhydride

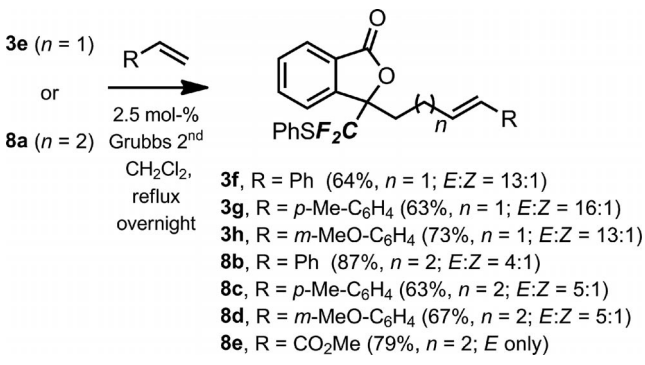
γ-Lactol **4** was readily prepared in good yield (88%) by the TBAT-catalyzed nucleophilic addition of **1** (2 equiv.) to phthalic anhydride (Scheme 4) according to our previous report.[3a] Primarily, the treatment of **4** with homoallylmag-

nesium bromide (5 equiv.) at –10 °C for 0.5 h gave the expected product **3e** (27% yield) along with **7** (53%) after lactonization. An improved yield of **3e** (52% yield) was achieved when the reaction with the Grignard reagent was performed at –78 °C for 3 h. However, a significant amount of **7** was also isolated (31% yield). In the presence of an additive, tetrabutylammonium bromide (TBAB, 5 equiv.), homoallylmagnesium bromide reacted with **4** at –78 °C for 3 h to provide **3e** (62% yield) and **7** (23% yield).[8] Under similar reaction conditions, compounds **8a** and **7** were obtained in 58 and 29% yields, respectively, from the reaction of **4** with 1-pentenylmagnesium bromide. The formation of **7** could be rationalized by competitive reduction of the intermediate **4A** owing to a β-hydrogen transfer from the Grignard reagent during the reaction.



Scheme 4. Preparation of **3e** and **8a** from phthalic anhydride.

With compounds **3e** and **8a** in hand, we used them to prepare the alkenyl-substituted compounds **3f**–**h** and **8b**–**e** in good yields through olefin cross-metathesis, as summarized in Scheme 5. Except for **8e**, the alkenyl-substituted compounds were obtained as mixtures of *E* and *Z* isomers with the *E* isomer as the major isomer.

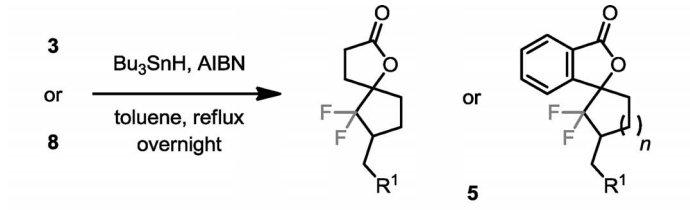


Scheme 5. Synthesis of **3f**–**h** and **8b**–**e** by olefin cross-metathesis of **3e** and **8a** with styrene derivatives.

Preparation of *gem*-Difluoromethylenated Spiro-γ-butyrolactones 5

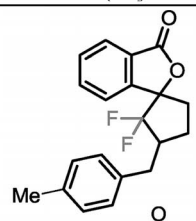
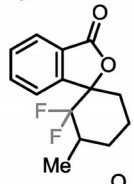
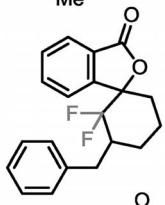
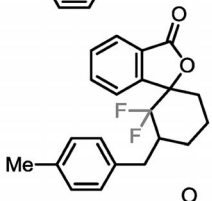
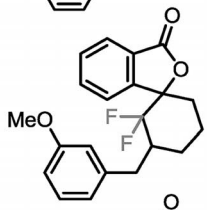
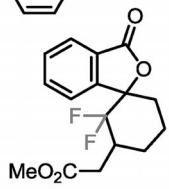
Having achieved the preparation of γ-difluoro(phenylsulfanyl)methyl-γ-butyrolactones **3** and **8**, which are the key intermediates for the syntheses of the desired γ-(*gem*-difluoromethylenated) spiro-γ-butyrolactones, we next investigated an intramolecular radical cyclization (Table 2). Thus, the exposure of **3a**–**d** to Bu_3SnH in the presence of a cata-

Table 2. Preparation of *gem*-difluoromethylenated spiro-γ-butyrolactones **5** by intramolecular radical cyclization of **3** and **8**.



3 or **8**	**5** (% yield) (isomeric ratio)
3a	**5aA** (34%)[a] **5aB** (33%)[b]
3b	**5bA** (47%)[a] **5bB** (35%)[b]
3c	**5cA** (42%)[a] **5cB** (32%)[a]
3d	**5dA** (44%)[b] **5dB** (32%)[b]
3e	**5e** (89%)[c] (1:3)[d]
3f	**5f** (82%)[c] (1:1.6)[d]

Table 2. *(continued)*

3 or 8	5 (% yield) (isomeric ratio)
3g	 **5g** (83%)[c] (1:1.6)[d]
3h	 **5h** (85%)[c] (1:1.6)[d]
8a	 **5iA** (48%)[b] **5iB** (34%)[a]
8b	 **5jA** (68%)[b] **5jB** (23%)[b]
8c	 **5kA** (63%)[b] **5kB** (24%)[b]
8d	 **5lA** (64%)[b] **5lB** (19%)[b]
8e	 **5m** (92%)[c] (3:1)[d]

[a] Isolated yield; a small amount of its diastereomer is included, see Supporting Information. [b] Isolated yield of pure diastereomer. [c] Isolated yield of a mixture of diastereomers. [d] The ratio of diastereoisomers was determined by ^{19}F NMR spectroscopy of the crude mixture.

lytic amount of azobisisobutyronitrile (AIBN) in toluene at reflux overnight yielded the expected γ-(*gem*-difluoromethylenated) spiro-γ-butyrolactones **5a**–**d** in good yields (68–83%) as mixtures of two diastereomers, which could be chromatographically separated.

Under similar reaction conditions, the radical cyclizations of **3e**–**h** and **8a**–**e** were achieved without difficulty to form the expected *gem*-difluoromethylenated spiro-γ-butyrolactones **5e**–**m**. The results are summarized in Table 2.

The relative stereochemistry of **5dA** and **5iA** were assigned on the basis of X-ray crystallography (Figure 1).[9] Therefore, we speculate that the relative stereochemistries of **5aA**–**5cA** and **5jA**–**5lA** are similar to those of **5dA** and **5iA**.

Conclusions

In conclusion, we have developed a synthetic entry to *gem*-difluoromethylenated spiro-γ-butyrolactones by employing $PhSCF_2TMS$ (**1**) as a "$CF_2^{\cdot-}$" building block. The present method proves potentially useful as a general synthetic entry to *gem*-difluoromethylenated spiro-γ-butyrolactones, which are versatile building blocks for the synthesis of natural products containing spiro-γ-butyrolactone moieties.

Experimental Section

General: All reactions were performed under an argon atmosphere, and glassware, needles, and syringes were oven-dried and then kept in a desiccator before use. THF was distilled from sodium–benzophenone ketyl. Dichloromethane, toluene, and ethanol were distilled from calcium hydride and stored over activated molecular sieves (4 Å). Methanol was distilled from Mg turnings. Column chromatography was performed by using Merck silica gel 60 PF_{254} (Art 7736). Other common solvents [hexanes, ethyl acetate (EtOAc), and acetone] were distilled before use. The ^1H NMR spectra were recorded with a Bruker DPX-300 (300 MHz), Bruker-400 (400 MHz), or Bruker-500 (500 MHz) spectrometer with samples in $CDCl_3$ and tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded with a Bruker DPX-300 (75 MHz), Bruker-400 (100 MHz), or Bruker-500 (125 MHz) spectrometer with samples in $CDCl_3$ and residual non-deuterated solvent peaks as an internal standard. The ^{19}F NMR spectra were recorded with a Bruker-400 (376 MHz) or a Bruker-500 (470 MHz) spectrometer, and chemical shifts (δ) were measured with trichlorofluoromethane (δ = 0 ppm) as an internal standard. The IR spectra were recorded with either a Jasco A-302 or a Perkin–Elmer 683 infrared spectrometer. The mass spectra were recorded by using a Thermo Finnigan Polaris Q mass spectrometer. The high-resolution mass spectra were recorded with either an HR-TOF-MS Micromass model VQ-TOF2 or Finnigan MAT 95 mass spectrometer. Melting points were recorded with a Buchi 501 melting point apparatus. The X-ray crystallographic analysis was performed with a Bruker SMART APEX CCD diffractometer.

4-Oxooct-7-enoic Acid: To a suspension of magnesium turnings (6.5 g, 268 mmol) in dry THF (80 mL) was slowly added a solution of homoallyl bromide (8.1 mL, 80 mmol) in dry THF (80 mL) with a cannula over a period of 1 h at room temperature. The reaction mixture was stirred at room temperature for 2 h. The resulting Grignard reagent was then added dropwise over a period of 30 min to a suspension of succinic anhydride (4 g, 40 mmol) and copper iodide (1.1 g, 6 mmol) in dry THF (40 mL) at –20 °C. The reaction mixture was stirred at –20 °C and then warmed to 0 °C for 3 h. The reaction mixture was quenched with HCl (2 M, 20 mL) at 0 °C and extracted with EtOAc (4× 50 mL). The combined organic

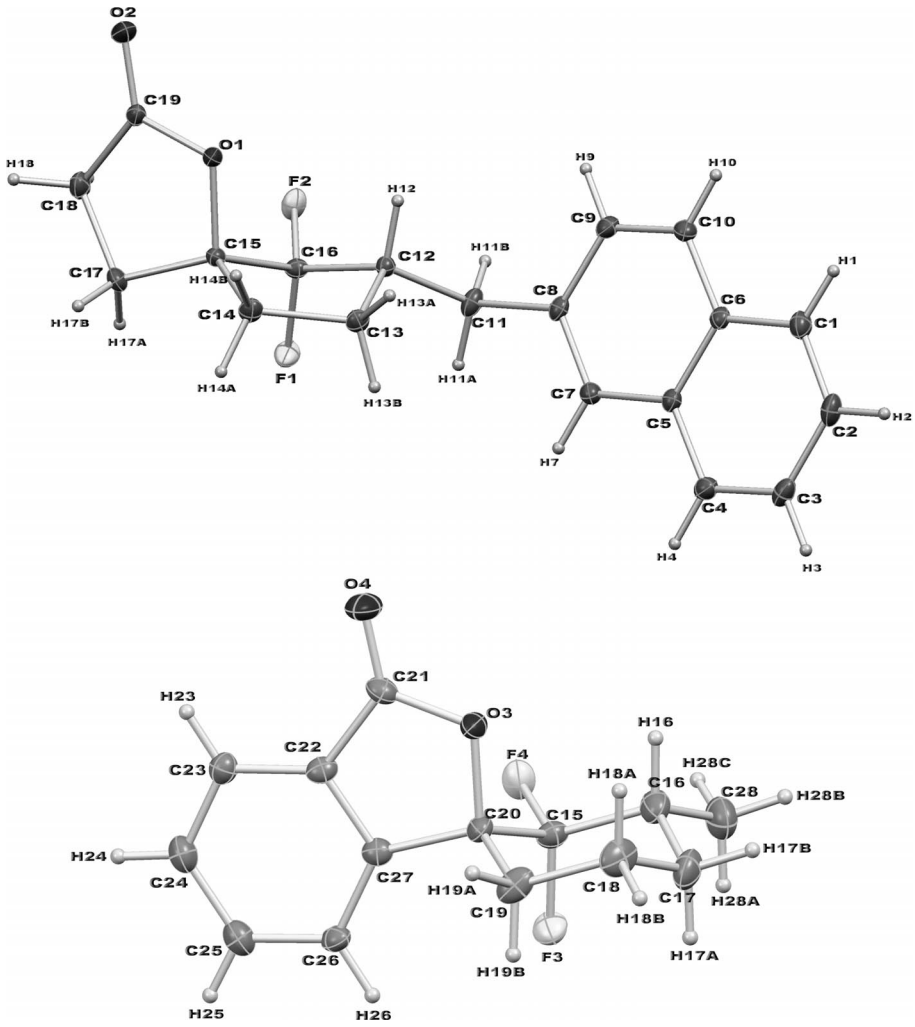


Figure 1. X-ray crystallographic structures of **5dA** and **5iA**.

phase was washed with brine (50 mL) and dried with anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, 30% EtOAc/0.5% AcOH in hexanes) to afford 4-oxooct-7-enoic acid (3.7 g, 59%) as a pale yellow viscous oil. FTIR ($CHCl_3$): $\tilde{\nu}$ = 3029, 1713, 1404, 1368, 1286, 1256, 920 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 10.58–8.80 (br, 1 H, OH), 5.79 (ddt, J = 16.7, 12.9, 6.4 Hz, 1 H, CH_2=C*H*), 5.09–4.90 (m, 2 H, CH_2=CH), 2.75–2.68 (m, 2 H, CH_2), 2.67–2.59 (m, 2 H, CH_2), 2.58–2.50 (m, 2 H, CH_2), 2.40–2.27 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0 (C), 178.7 (C), 136.8 (CH), 115.3 (CH_2), 41.7 (CH_2), 36.8 (CH_2), 27.7 (CH_2), 27.6 (CH_2) ppm. MS: *m*/*z* (%) = 157 (100) $[M + H]^+$, 139 (7), 111 (34), 95 (32), 55 (2). HRMS (ESI-TOF): calcd. for $C_8H_{12}O_3Na$ $[M + Na]^+$ 179.0684; found 179.0688.

General Procedure A for the Preparation of Keto Esters 2

Methyl 4-Oxooct-7-enoate (2a): A solution of 4-oxooct-7-enoic acid (704 mg, 4.5 mmol) in dry MeOH (20 mL) was treated with thionyl chloride (0.8 mL, 11 mmol) at –10 °C, and the mixture was slowly warmed to room temperature for 2 h. The reaction mixture was quenched with saturated Na_2CO_3 (10 mL), and the resulting mixture was evaporated and extracted with EtOAc (3× 20 mL). The combined organic phase was washed successively with water (10 mL) and brine (10 mL) and dried with anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, 20% EtOAc in hexanes) to give **2a** (713 mg, 93% yield) as a colorless liquid. FTIR ($CHCl_3$): $\tilde{\nu}$ = 1733, 1719, 1439, 1411, 1365, 1178, 919 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.73 (ddt, J = 16.7, 12.9, 6.5 Hz, 1 H, CH_2=C*H*), 5.02–4.85 (m, 2 H, CH_2=CH), 3.60 (s, 3 H, OCH_3), 2.73–2.64 (m, 2 H, CH_2), 2.58–2.43 (m, 4 H, 2× CH_2), 2.30–2.20 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0 (C), 173.2 (C), 136.9 (CH), 115.2 (CH_2), 51.7 (CH_3), 41.7 (CH_2), 37.0 (CH_2), 27.6 (2× CH_2) ppm. MS: *m*/*z* (%) = 171 (100) $[M + H]^+$, 169 (18), 159 (4), 115 (13), 111 (20), 95 (25), 93 (2). HRMS (ESI-TOF): calcd. for $C_9H_{14}O_3Na$ $[M + Na]^+$ 193.0841; found 193.0840.

Ethyl 4-Oxooct-7-enoate (2a′): According to general procedure A, a mixture of 4-oxooct-7-enoic acid (1.6 g, 10 mmol) in dry EtOH (50 mL) and thionyl chloride (2.5 mL, 30 mmol) gave **2a′** (1.52 g, 82% yield) as a colorless liquid after purification by column chromatography (SiO_2, 20% EtOAc in hexanes). FTIR ($CHCl_3$): $\tilde{\nu}$ = 1718, 1412, 1376, 1351, 1096, 919 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.78 (ddt, J = 16.7, 12.9, 6.5 Hz, 1 H, CH_2=C*H*), 5.07–4.90 (m, 2 H, CH_2=CH), 4.10 (q, J = 7.2 Hz, 2 H, OCH_2), 2.75–2.63 (m, 2 H, CH_2), 2.61–2.48 (m, 4 H, 2× CH_2), 2.40–2.20 (m, 2 H, CH_2), 1.22 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.1 (C), 172.7 (C), 136.9 (CH), 115.2 (CH_2), 60.5 (CH_2), 41.7 (CH_2), 37.0 (CH_2), 27.9 (CH_2), 27.6 (CH_2), 14.1 (CH_3) ppm. MS: *m*/*z* (%) = 185 (100) $[M + H]^+$, 129 (4), 111

(16), 95 (18). HRMS (ESI-TOF): calcd. for $C_{10}H_{16}O_3Na$ [M + Na]$^+$ 207.0997; found 207.1003.

General Procedure B for the Preparation of Keto Esters 2b–d

(*E*)-Ethyl 4-Oxo-8-phenyloct-7-enoate (2b): A solution of **2a′** (1.9 g, 10 mmol) and styrene (4.5 mL, 40 mmol) in dry CH_2Cl_2 (40 mL) was treated with a catalytic amount of Grubbs' 2nd generation catalyst (212 mg, 0.3 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was heated to reflux overnight. After completion of the reaction, the solvent was evaporated, and the crude product was purified by column chromatography (SiO_2, 100% hexanes to 10% EtOAc in hexanes) to give **2b** (1.6 g, 62% yield) as a pale yellow viscous oil. FTIR ($CHCl_3$): $\tilde{\nu}$ = 1721, 1447, 1412, 1376, 1350, 1192, 1097, 966 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 4 H, 4× ArH), 7.25–7.16 (m, 1 H, ArH), 6.42 (d, J = 15.9 Hz, 1 H, CH=C*H*), 6.21 (dt, J = 15.9, 6.7 Hz, 1 H, CH=C*H*), 4.15 (q, J = 7.2 Hz, 2 H, OCH_2), 2.83–2.71 (m, 2 H, CH_2), 2.71–2.58 (m, 4 H, 2× CH_2), 2.58–2.46 (m, 2 H, CH_2), 1.27 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0 (C), 172.7 (C), 137.3 (C), 130.7 (CH), 128.7 (CH), 128.4 (2× CH), 127.0 (CH), 125.9 (2× CH), 60.6 (CH_2), 42.2 (CH_2), 37.1 (CH_2), 27.9 (CH_2), 27.0 (CH_2), 14.1 (CH_3) ppm. MS: *m*/*z* (%) = 261 (100) [M + H]$^+$, 259 (11), 215 (3), 169 (4), 117 (3). HRMS (ESI-TOF): calcd. for $C_{16}H_{20}O_3Na$ [M + Na]$^+$ 283.1310; found 283.1297.

(*E*)-Ethyl 4-Oxo-8-(4-tolyl)oct-7-enoate (2c): According to general procedure B, the reaction of **2a′** (1.8 g, 10 mmol), 4-methylstyrene (5 mL, 40 mmol), and Grubbs' 2nd generation catalyst (212 mg, 0.3 mmol) in dry CH_2Cl_2 (50 mL) gave **2c** (1.7 g, 64% yield) as a pale yellow viscous oil after purification by column chromatography (SiO_2, 100% hexanes to 10% EtOAc in hexanes). FTIR ($CHCl_3$): $\tilde{\nu}$ = 1720, 1514, 1445, 1412, 1376, 1192, 1034, 969 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.1 Hz, 2 H, 2× ArH), 7.09 (d, J = 8.1 Hz, 2 H, 2× ArH), 6.37 (d, J = 15.8 Hz, 1 H, CH=C*H*), 6.13 (dt, J = 15.8, 6.8 Hz, 1 H, CH=C*H*), 4.13 (q, J = 7.1 Hz, 2 H, OCH_2), 2.74 (t, J = 6.4 Hz, 2 H, CH_2), 2.63 (t, J = 7.2 Hz, 2 H, CH_2), 2.59 (t, J = 6.3 Hz, 2 H, CH_2), 2.53–2.41 (m, 2 H, CH_2), 2.32 (s, 3 H, CH_3), 1.25 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.0 (C), 172.7 (C), 136.8 (C), 134.6 (C), 130.6 (CH), 129.1 (2× CH), 127.7 (CH), 125.9 (2× CH), 60.6 (CH_2), 42.3 (CH_2), 37.1 (CH_2), 28.0 (CH_2), 27.0 (CH_2), 21.1 (CH_3), 14.1 (CH_3) ppm. MS: *m*/*z* (%) = 275 (8) [M + H]$^+$, 247 (48), 257 (14), 256 (66), 229 (19), 228 (40), 169 (75), 168 (30), 131 (100), 129 (95), 128 (51), 115 (47), 91 (50), 77 (14), 55 (21). HRMS (ESI-TOF): calcd. for $C_{17}H_{22}O_3Na$ [M + Na]$^+$ 297.1467; found 297.1462.

(*E*)-Ethyl 8-(Naphthalen-2-yl)-4-oxooct-7-enoate (2d): According to general procedure B, the reaction of **2a′** (1.4 g, 8 mmol), 2-vinylnaphthalene (3.6 g, 23 mmol), and Grubbs' 2nd generation catalyst (141 mg, 0.2 mmol) in dry CH_2Cl_2 (50 mL) gave **2d** (1.3 g, 55%) as a pale yellow viscous oil after purification by column chromatography (SiO_2, 100% hexanes to 10% EtOAc in hexanes). FTIR ($CHCl_3$): $\tilde{\nu}$ = 1718, 1410, 1375, 1187, 1098, 1019, 966 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.62 (m, 3 H, 3× ArH), 7.58 (s, 1 H, ArH), 7.46 (dd, J = 8.6, 1.7 Hz, 1 H, ArH), 7.42–7.26 (m, 2 H, 2× ArH), 6.48 (d, J = 15.8 Hz, 1 H, CH=C*H*), 6.23 (dt, J = 15.8, 6.7 Hz, 1 H, CH=C*H*), 4.05 (q, J = 7.1 Hz, 2 H, OCH_2), 2.75–2.35 (m, 8 H, 4× CH_2), 1.16 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.1 (C), 172.7 (C), 134.8 (C), 133.6 (C), 132.7 (C), 130.8 (CH), 129.1 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 126.1 (CH), 125.3 (CH), 125.5 (CH), 123.4 (CH), 60.6 (CH_2), 42.2 (CH_2), 37.1 (CH_2), 28.0 (CH_2), 27.1 (CH_2), 14.1 (CH_3) ppm. MS: *m*/*z* (%) = 311 (9) [M + H]$^+$, 310 (27) [M]$^+$, 292 (100), 264 (14), 218 (11), 204 (23), 191 (10), 179 (59), 165 (65), 152 (34), 141 (21), 129 (15), 115 (8), 101 (26). HRMS (ESI-TOF): calcd. for $C_{20}H_{22}O_3Na$ [M + Na]$^+$ 333.1467; found 333.1467.

General Procedure C for the Preparation of γ-(Difluorophenylsulfanylmethyl)-γ-butyrolactones 3

γ-[Difluoro(phenylsulfanyl)methyl]-γ-(butyl-3-ene)-γ-butyrolactone (3a): A solution of **1** (241 mg, 1 mmol) and **2a** (92 mg, 0.5 mmol) in dry THF (1 mL) was treated with 10 mol-% TBAF solution (0.25 mL, 0.1 mmol, 0.4 M solution in dry THF) at –78 °C, and the mixture was slowly warmed to room temperature for 5 h. The reaction was quenched at room temperature with excess TBAF solution, and the resulting mixture was stirred at room temperature for 15 min, diluted with water (10 mL), and then extracted with EtOAc (3× 10 mL). The combined organic phase was washed successively with water (10 mL) and brine (10 mL) and dried with anhydrous Na_2SO_4. After removal of the solvent, the crude product was treated with a catalytic amount of *p*TsOH in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature overnight. After removal of the solvent, water (10 mL) was added, and the mixture was extracted with EtOAc (4× 10 mL). The combined organic phase was washed with water (15 mL) and brine (15 mL) and dried with anhydrous Na_2SO_4. The crude product was purified by column chromatography (SiO_2, 10% EtOAc in hexanes) to give **3a** (68 mg, 46% yield) as a white solid [m.p. 44–45 °C (hexanes)] and **6** (119 mg, 49% yield) as a white solid [m.p. 90–92 °C (CH_2Cl_2/hexanes)]. Compound **3a**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1787, 1643, 1475, 1441, 1214, 1211, 1151, 1063, 971, 920 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (d, J = 7.3 Hz, 2 H, 2× ArH), 7.43–7.35 (m, 1 H, ArH), 7.35–7.25 (m, 2 H, 2× ArH), 5.75 (ddt, J = 16.5, 10.3, 6.1 Hz, 1 H, C*H*=CH_2), 5.02 (dd, J = 16.1, 1.1 Hz, 1 H, CH=CH*H*), 4.96 (d, J = 10.2 Hz, 1 H, CH=CH*H*), 2.70–2.60 (m, 1 H, CH*H*), 2.55–2.45 (m, 2 H, CH_2), 2.25–2.05 (m, 4 H, 2× CH_2), 1.95–1.80 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.3 (C), 136.8 (2× CH), 136.6 (CH), 130.1 (t, J = 287.0 Hz, CF_2), 130.1 (CH), 129.1 (2× CH), 124.7 (C), 115.7 (CH_2), 88.0 (t, J = 25.0 Hz, C), 33.8 (CH_2), 28.3 (CH_2), 26.8 (CH_2), 26.0 (CH_2) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –84.1 (d, J = 210.4 Hz, 1 F), –85.0 (d, J = 210.4 Hz, 1 F) ppm. MS: *m*/*z* (%) = 299 (100) [M + H]$^+$, 279 (31), 251 (54), 241 (11), 231 (8), 169 (9), 149 (17), 147 (26), 121 (18), 111 (20), 93 (6), 83 (3), 55 (13). HRMS (ESI-TOF): calcd. for $C_{15}H_{16}F_2O_2Na$ [M + Na]$^+$ 321.0737; found 321.0757. Compound **6**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 3570, 1642, 1475, 1441, 1214, 1067, 1033, 971, 918 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, J = 7.0 Hz, 2 H, 2× ArH), 7.65 (d, J = 7.1 Hz, 2 H, 2× ArH), 7.55–7.30 (m, 6 H, 6× ArH), 5.91 (ddt, J = 16.8, 12.9, 6.5 Hz, 1 H, C*H*=CH_2), 5.14 (dd, J = 17.2, 1.6 Hz, 1 H, CH=CH*H*), 5.06 (d, J = 10.2, 1.6 Hz, 1 H, CH=CH*H*), 3.28 (s, 1 H, OH), 2.66–2.54 (m, 1 H, CH*H*), 2.49 (dd, J = 13.3, 9.6 Hz, 1 H, CH*H*), 2.40–2.24 (m, 3 H, 3× CH*H*), 2.22–2.10 (m, 2 H, 2× CH*H*), 2.06–2.15 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.0 (CH), 136.9 (2× CH), 136.7 (2× CH), 131.0 (dd, J = 288.5, 284.4 Hz, CF_2), 129.9 (CH), 129.7 (CH), 129.0 (2× CH), 128.9 (2× CH), 126.3 (d, J = 285.6 Hz, CF_2), 125.9 (C), 115.0 (CH_2), 125.7 (C), 107.0 (t, J = 28.0 Hz, C), 91.5 (dd, J = 24.0, 21.0 Hz, C), 35.7 (CH_2), 33.5 (CH_2), 29.9 (CH_2), 27.9 (CH_2) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –80.9 (d, J = 210.8 Hz, 1 F), –83.3 (d, J = 210.8 Hz, 1 F), –85.9 (s, 2 F) ppm. MS: *m*/*z* (%) = 458 (7) [M]$^+$, 440 (47) [M – H_2O]$^+$, 331 (74), 279 (68), 271 (31), 251 (28), 231 (40), 189 (47), 159 (36), 147 (100), 135 (71), 109 (54), 77 (52). HRMS (ESI-TOF): calcd. for $C_{22}H_{22}F_4O_2S_2Na$ [M + Na]$^+$ 481.0895; found 481.0896.

Preparation of 3a from 2a′: According to general procedure C, a solution of **1** (143 mg, 0.6 mmol) and **2a′** (97 mg, 0.5 mmol) in dry

THF (1 mL) was treated with 10 mol-% TBAF solution (0.25 mL, 0.1 mmol, 0.24 M solution in dry THF) at –78 °C, followed by treatment with a catalytic amount of *p*TsOH in CH_2Cl_2 (2 mL) to give **3a** (145 mg, 97% yield) as a white solid.

γ-[Difluoro(phenylsulfanyl)methyl]-γ-(4-phenylbutyl-3-ene)-γ-butyrolactone (3b): According to general procedure C, the reaction of **1** (289 mg, 1.2 mmol) and **2b** (262 mg, 1 mmol) and purification by column chromatography (SiO_2, 8% EtOAc and 2% CH_2Cl_2 in hexanes) provided **3b** (350 mg, 94% yield) as a white solid [m.p. 68–69 °C (hexanes)]. FTIR ($CHCl_3$): $\tilde{\nu}$ = 1787, 1497, 1475, 1463, 1442, 1214, 1215, 1173, 1063, 969 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.54 (d, J = 7.26 Hz, 2 H, 2× ArH), 7.40–7.34 (m, 1 H, ArH), 7.31–7.18 (m, 6 H, 6× ArH), 7.17–7.09 (m, 1 H, ArH), 6.37 (d, J = 15.9 Hz, 1 H, C*H*=CH), 6.10 (dt, J = 15.8, 6.6 Hz, 1 H, CH=C*H*), 2.73–2.58 (m, 1 H, CH*H*), 2.57–2.43 (m, 2 H, CH_2), 2.33–2.05 (m, 4 H, 2× CH_2), 2.00–1.80 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.3 (C), 137.1 (C), 136.8 (2× CH), 131.2 (CH), 130.1 (t, J = 281.6 Hz, CF_2), 130.1 (CH), 129.1 (2× CH), 128.5 (2× CH), 128.2 (CH), 127.2 (CH), 126.0 (2× CH), 124.7 (C), 87.9 (t, J = 24.9 Hz, C), 34.3 (CH_2), 28.3 (CH_2), 26.2 (CH_2), 26.1 (CH_2) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –84.2 (d, J = 210.9 Hz, 1 F), –84.9 (d, J = 210.9 Hz, 1 F) ppm. MS: *m*/*z* (%) = 375 (100) $[M + H]^+$, 335 (22), 311 (3), 225 (18), 177 (13), 179 (20), 165 (10), 117 (7), 91 (4). HRMS (ESI-TOF): calcd. for $C_{21}H_{20}F_2O_2SNa$ $[M + Na]^+$ 397.1050; found 397.1072.

γ-[Difluoro(phenylsulfanyl)methyl]-γ-(4-tolylbutyl-3-ene)-γ-butyrolactone (3c): According to general procedure C, the reaction of **1** (297 mg, 1.2 mmol) and **2c** (295 mg, 1 mmol) and purification by column chromatography (SiO_2, 8% EtOAc and 2% CH_2Cl_2 in hexanes) provided **3c** (376 mg, 93% yield) as a white solid [m.p. 89–90 °C (hexanes)]. FTIR ($CHCl_3$): $\tilde{\nu}$ = 1787, 1513, 1475, 1442, 1235, 1172, 1150, 1060, 970 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, J = 7.2 Hz, 2 H, 2× ArH), 7.38 (dd, J = 7.4, 7.4 Hz, 1 H, ArH), 7.32 (dd, J = 7.7, 7.7 Hz, 2 H, 2× ArH), 7.17 (d, J = 7.6 Hz, 2 H, 2× ArH), 7.04 (d, J = 8.0 Hz, 2 H, 2× ArH), 6.35 (d, J = 15.9 Hz, 1 H, C*H*=CH), 6.06 (dt, J = 15.7, 6.6 Hz, 1 H, CH=C*H*), 2.73–2.58 (m, 1 H, CH*H*), 2.57–2.43 (m, 2 H, 2× CH*H*), 2.33–2.05 (m, 7 H, CH_3, 2× CH_2), 2.00–1.80 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.4 (C), 137.1 (C), 136.9 (2× CH), 134.4 (C), 131.1 (CH), 130.2 (t, J = 288.5 Hz, CF_2), 130.2 (CH), 129.2 (2× CH), 129.1 (2× CH), 127.1 (CH), 125.9 (2× CH), 124.7 (C), 88.0 (t, J = 25.1 Hz, C), 34.4 (CH_2), 28.4 (CH_2), 26.3 (CH_2), 26.1 (CH_2), 21.1 (CH_3) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –84.3 (d, J = 210.4 Hz, 1 F), –85.0 (d, J = 210.4 Hz, 1 F) ppm. MS: *m*/*z* (%) = 389 (18) $[M + H]^+$, 388 (76) $[M]^+$, 280 (8), 279 (39), 259 (25), 241 (33), 239 (42), 231 (16), 213 (36), 199 (29), 131 (62), 91 (39). HRMS (ESI-TOF): calcd. for $C_{22}H_{22}F_2O_2SNa$ $[M + Na]^+$ 411.1206; found 411.1216.

γ-[Difluoro(phenylsulfanyl)methyl]-γ-[4-(2-naphthyl)butyl-3-ene]-γ-butyrolactone (3d): According to general procedure C, the reaction of **1** (336.2 mg, 1.2 mmol) and **2c** (312 mg, 1 mmol) and purification by column chromatography (SiO_2, 8% EtOAc and 2% CH_2Cl_2 in hexanes) afforded **3d** (403 mg, 94% yield) as a white solid [m.p. 97–98 °C (hexanes)]. FTIR ($CHCl_3$): $\tilde{\nu}$ = 1787, 1508, 1475, 1441, 1174, 1152, 1061, 970 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.50 (t, J = 7.6 Hz, 3 H, 3× ArH), 7.60 (s, 1 H, ArH), 7.55 (d, J = 7.1 Hz, 2 H, 2× ArH), 7.49 (dd, J = 10.2, 1.7 Hz, 1 H, ArH), 7.43–7.25 (m, 5 H, 5× ArH), 6.53 (d, J = 15.9 Hz, 1 H, C*H*=CH), 6.23 (dt, J = 15.7, 6.5 Hz, 1 H, CH=C*H*), 2.73–2.58 (m, 1 H, CH*H*), 2.57–2.43 (m, 2 H, CH_2), 2.33–2.05 (m, 4 H, 2× CH_2), 2.00–1.80 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.4 (C), 136.9 (2× CH), 134.6 (C), 133.6 (C), 132.8 (C), 131.3 (CH), 130.2 (CH), 130.2 (t, J = 287.5 Hz, CF_2), 129.1 (2× CH), 128.7 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 126.2 (CH), 125.7 (2× CH), 124.7 (C), 123.4 (CH), 88.0 (t, J = 24.9 Hz, C), 34.4 (CH_2), 28.4 (CH_2), 26.4 (CH_2), 26.2 (CH_2) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –84.2 (d, J = 210.8 Hz, 1 F), –84.9 (d, J = 210.8 Hz, 1 F) ppm. MS: *m*/*z* (%) = 425 (2) $[M + H]^+$, 424 (3) $[M]^+$, 310 (23), 293 (26), 292 (100), 265 (4), 205 (16), 191 (15), 179 (55), 165 (56), 152 (26), 141 (31), 129 (15), 101 (10), 73 (5), 55 (6). HRMS (ESI-TOF): calcd. for $C_{25}H_{22}F_2O_2SNa$ $[M + Na]^+$ 447.1206; found 447.1208.

γ-[Difluoro(phenylsulfanyl)methyl]-γ-hydroxyisobenzo-furan-1(3*H*)-one (4): According to the literature procedure,[3a] a mixture of **1** (1.4 g, 6 mmol) and phthalic anhydride (0.4 g, 3 mmol) in dry THF (8 mL) was treated with 10 mol-% TBAT (0.4 g, 0.7 mmol) at –20 °C. The reaction mixture was stirred at –20 °C and slowly warmed to room temperature overnight. The reaction was quenched with H_2O (3 mL) and extracted with EtOAc (3× 25 mL). The organic phase was washed successively with water and brine and dried with anhydrous Na_2SO_4. After solvent removal, a crude product was purified by column chromatography (SiO_2, 20% EtOAc in hexanes) to give **4** (0.85 g, 88% yield) as white needles [m.p. 79–80 °C (CH_2Cl_2/hexanes)]. FTIR ($CHCl_3$): $\tilde{\nu}$ = 3120, 1757, 1468, 1441, 1063, 1044, 764, 747 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.3 Hz, 1 H, ArH), 7.80–7.74 (m, 2 H, 2× ArH), 7.73–7.68 (m, 1 H, ArH), 7.60 (d, J = 7.4 Hz, 2 H, 2× ArH), 7.50–7.44 (m, 1 H, ArH), 7.43–7.36 (m, 2 H, 2× ArH), 4.69 (br, 1 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.8 (C), 143.0 (2× C), 136.8 (2× CH), 134.9 (CH), 131.9 (CH), 130.3 (CH), 129.2 (2× CH), 127.4 (C), 126.4 (t, J = 287.3 Hz, CF_2), 124.5 (CH), 124.0 (CH), 102.9 (t, J = 30.4 Hz, C) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –84.5 (d, J = 213.4 Hz, 1 F), –87.1 (d, J = 213.4 Hz, 1 F) ppm. MS: *m*/*z* (%) = 309 (12) $[M + H]^+$, 308 (8) $[M]^+$, 160 (38), 149 (100), 121 (22), 110 (10), 93 (10), 77 (5), 65 (17), 51 (5). HRMS (ESI-TOF): calcd. for $C_{15}H_{10}F_2O_3SNa$ $[M + Na]^+$ 331.0216; found 331.0231.

General Procedure D for the Preparation of γ-[Difluoro(phenylsulfanyl)methyl]-γ-butyrolactones 3e and 8a

3-(But-3-enyl)-3-[difluoro(phenylsulfanyl)methyl]isobenzofuran-1(3*H*)-one (3e): A solution of homoallyl bromide (5 mL, 50 mmol) in dry THF (40 mL) was slowly added by cannula over a period of 1 h to a suspension of magnesium turnings (1.9 g, 80 mmol) in dry THF (40 mL). The reaction mixture was stirred at room temperature for 2 h. The resulting homoallylmagnesium bromide was added dropwise over 45 min to a suspension of **4** (3.1 g, 10 mmol) and tetra-*n*-butylammonium bromide (16.1 g, 50 mmol) in dry THF (20 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 3 h. After the reaction was completed, it was quenched with HCl (2 M, 20 mL) at –78 °C and extracted with EtOAc (4× 50 mL). The organic phase was washed with brine (50 mL) and dried with anhydrous Na_2SO_4. After removal of the solvent, the crude product was treated with a catalytic amount of *p*TsOH in dry CH_2Cl_2 (20 mL) under reflux overnight. After the solvent was removed, the residue was diluted with water (20 mL) and extracted with EtOAc (4× 20 mL). The combined organic phase was washed with water (20 mL) and brine (20 mL) and dried with anhydrous Na_2SO_4. The crude product was purified by column chromatography (SiO_2, 10% EtOAc in hexanes) to afford **3e** (2.2 g, 62% yield) as a pale yellow viscous oil and **7** (642 mg, 23% yield) as a white solid [m.p. 75–76 °C (CH_2Cl_2/hexanes)]. Compound **3e**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1783, 1644, 1467, 1287, 920 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.87 (d, J = 7.6 Hz, 1 H, ArH), 7.63 (ddd, J = 7.5, 7.5, 1.1 Hz, 1 H, ArH), 7.55 (ddd, J = 7.5, 7.5, 1.1 Hz, 1 H, ArH), 7.48 (d, J = 7.7 Hz, 1 H, ArH), 7.42 (d, J = 7.1 Hz, 2 H, 2× ArH), 7.36–7.29

(m, 1 H, ArH), 7.28–7.21 (m, 2 H, 2× ArH), 5.59 (ddt, J = 16.4, 13.1, 6.5 Hz, 1 H, C*H*=CH$_2$), 4.88–4.75 (m, 2 H, CH=C*H*$_2$), 2.49 (ddd, J = 14.5, 11.3, 5.1 Hz, 1 H, CH*H*), 2.25 (ddd, J = 14.6, 11.3, 5.0 Hz, 1 H, CH*H*), 1.92–1.80 (m, 1 H, CH*H*), 1.52–1.39 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7 (C), 145.7 (C), 136.7 (2× CH), 136.3 (CH), 134.4 (CH), 130.5 (CH), 130.0 (CH), 129.0 (2× CH), 128.3 (t, J = 287.6 Hz, CF_2), 127.4 (C), 125.8 (CH), 125.1 (C), 123.4 (CH), 115.6 (CH_2), 89.2 (t, J = 27.8 Hz, C), 31.2 (CH_2), 26.7 (CH_2) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –80.8 (d, J = 212.7 Hz, 1 F), –82.3 (d, J = 212.7 Hz, 1 F) ppm. MS: m/z (%) = 347 (100) [M + H]$^+$, 346 (9), 327 (4), 261 (3), 237 (9), 217 (21), 197 (17), 187 (42), 169 (100), 151 (8), 141 (30), 129 (8), 77 (7), 65 (6). HRMS (ESI-TOF): calcd. for $C_{19}H_{16}F_2O_2SNa$ [M + Na]$^+$ 369.0737; found 369.0734. Compound **7**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1784, 1602, 1475, 1286, 976 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.5 Hz, 1 H, ArH), 7.73 (ddd, J = 8.4, 8.4, 1.1 Hz, 1 H, ArH), 7.66 (d, J = 7.5 Hz, 2 H, 2× ArH), 7.60 (d, J = 7.1 Hz, 2 H, 2× ArH), 7.50–7.43 (m, J = 6.5, 1.3 Hz, 1 H, ArH), 7.42–7.34 (m, 2 H, 2× ArH), 5.65 (dd, J = 10.5, 5.3 Hz, 1 H, CF_2C*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8 (C), 142.3 (C), 136.7 (2× CH), 134.5 (CH), 130.6 (CH), 130.3 (CH), 129.2 (2× CH), 126.5 (t, J = 282.0 Hz, CF_2), 126.5 (C), 125.9 (CH), 124.9 (C), 124.1 (CH), 79.6 (t, J = 32.4 Hz, CH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –79.0 (d, J = 216.5 Hz, 1 F), –85.5 (dd, J = 216.5, 10.6 Hz, 1 F) ppm. MS: m/z (%) = 293 (28) [M + H]$^+$, 292 (59) [M]$^+$, 160 (14), 159 (100), 133 (70), 127 (12), 105 (17), 99 (1), 77 (30). HRMS (ESI-TOF): calcd. for $C_{15}H_{10}F_2O_2SNa$ [M + Na]$^+$ 315.0267; found 315.0261.

3-[Difluoro(phenylsulfanyl)methyl]-3-(pent-4-enyl)isobenzofuran-1(3*H*)-one (8a): According to general procedure D, a solution of the Grignard reagent generated from magnesium turnings (2.0 g, 80 mmol) and 5-bromopent-1-ene (6 mL, 50 mmol) in dry THF (80 mL) was treated with **4** (3 g, 10 mmol) and tetra-*n*-butylammonium bromide (16 g, 50 mmol) in dry THF (20 mL) to give **8a** (2 g, 58% yield) as a pale yellow viscous oil and **7** (0.85 g, 29% yield) as a white solid after purification by column chromatography (SiO_2, 10% EtOAc in hexanes). Compound **8a**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1783, 1644, 1467, 1287, 920 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.6 Hz, 1 H, ArH), 7.69 (ddd, J = 7.5, 7.5, 1.1 Hz, 1 H, ArH), 7.69 (ddd, J = 7.6, 7.6, 0.8 Hz, 1 H, ArH), 7.54 (d, J = 7.7 Hz, 1 H, ArH), 7.49 (d, J = 7.1 Hz, 2 H, 2× ArH), 7.45–7.34 (m, 1 H, ArH), 7.31 (t, J = 7.7 Hz, 2 H, 2× ArH), 5.64 (ddt, J = 17.0, 13.4, 6.7 Hz, 1 H, C*H*=CH$_2$), 5.00–4.85 (m, 2 H, CH=C*H*$_2$), 2.50–2.35 (m, 1 H, CH*H*), 2.30–2.18 (m, 1 H, CH*H*), 2.10–1.90 (m, 2 H, CH$_2$), 1.38–1.20 (m, 1 H, CH*H*), 0.90–0.70 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8 (C), 145.9 (C), 137.3 (CH), 136.7 (2× CH), 134.4 (CH), 130.4 (CH), 130.0 (CH), 128.9 (2× CH), 128.3 (t, J = 286.3 Hz, CF_2), 127.2 (C), 125.8 (CH), 125.1 (CH), 123.3 (C), 115.4 (CH_2), 89.4 (t, J = 27.4 Hz, C), 33.1 (CH_2), 31.3 (CH_2), 21.5 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.8 (d, J = 212.7 Hz, 1 F), –82.3 (d, J = 212.7 Hz, 1 F) ppm. MS: m/z (%) = 361 (28) [M + H]$^+$, 360 (8) [M]$^+$, 251 (19), 211 (14), 201 (30), 183 (70), 165 (100), 159 (22), 155 (17), 147 (12), 131 (11), 103 (14), 91 (3), 77 (9), 76 (3). HRMS (ESI-TOF): calcd. for $C_{20}H_{18}F_2O_2SNa$ [M + Na]$^+$ 383.0893; found 383.0896.

General Procedure E for the Preparation of γ-[Difluoro(phenylsulfanyl)methyl]-γ-butyrolactones 3f–3h and 8b–8e

***E*/*Z* Mixture of 3-[Difluoro(phenylsulfanyl)methyl]-3-(4-phenylbut-3-enyl)isobenzofuran-1(3*H*)-one (3f):** A solution of **3e** (1 g, 3 mmol), styrene (1.4 mL, 12 mmol), and Grubbs' 2nd generation catalyst (64 mg, 75 μmol) in dry CH_2Cl_2 (20 mL) was heated at reflux overnight. After completion of the reaction, the solvent was evaporated, and the crude product was purified by column chromatography (SiO_2, 100% hexanes to 10% EtOAc in hexanes) to give **3f** (*E*/*Z* = 13:1; 814 mg, 64% yield) as a colorless viscous oil. FTIR ($CHCl_3$): $\tilde{\nu}$ = 1789, 1600, 1467, 1287, 966 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, *major* isomer marked *): δ = 7.84 (ddd, J = 7.6, 0.7, 0.7 Hz, 1 H, ArH*), 7.80 (ddd, J = 7.7, 0.8, 0.8 Hz, 1 H, ArH *minor*), 7.64–7.55 (m, 2 H, 2× ArH *major* and *minor*), 7.53–7.45 (m, 4 H, 4× ArH *major* and *minor*), 7.38–7.33 (m, 4 H, 4× ArH *major* and *minor*), 7.33–7.26 (m, 2 H, 2× ArH *major* and *minor*), 7.26–7.19 (m, 4 H, 4× ArH *major* and *minor*), 7.19–7.12 (m, 8 H, 8× ArH *major* and *minor*), 7.11–7.05 (m, 1 H, ArH*), 7.04–6.93 (m, 1 H, ArH *minor*), 6.28 (d, J = 15.8 Hz, 1 H, CH=C*H minor*), 6.11 (d, J = 15.8 Hz, 1 H, CH=C*H**), 5.89 (dt, J = 15.8, 6.9 Hz, 1 H, CH=C*H**), 5.57 (dt, J = 15.3, 7.4 Hz, 1 H, CH=C*H minor*), 3.21 (dd, J = 14.8, 7.2 Hz, 1 H, CH*H minor*), 3.06 (dd, J = 14.5, 7.3 Hz, 1 H, CH*H minor*), 2.65–2.45 (m, 1 H, CH*H**), 2.40–2.25 (m, 1 H, CH*H**), 2.10–1.95 (m, 2 H, 2× CH*H major* and *minor*), 1.70–1.55 (m, 2 H, 2× CH*H major* and *minor*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6 (C), 145.6 (C), 137.1 (C), 136.7 (2× CH), 134.5 (CH), 131.0 (CH), 130.5 (CH), 130.0 (CH), 129.0 (2× CH), 128.4 (2× CH), 128.3 (t, J = 288.0 Hz, CF_2), 127.9 (CH), 127.3 (C), 127.1 (CH), 125.9 (2× CH), 125.8 (CH), 125.0 (C), 123.4 (CH), 89.2 (t, J = 27.6 Hz, C), 31.5 (CH_2), 26.1 (CH_2) ppm. Owing to low signal intensity, the *minor* isomer could not be detected by ^{13}C NMR spectroscopy. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.1 (d, J = 225.6 Hz, 1 F *minor*), –67.5 (d, J = 212.5 Hz, 1 F*), –68.5. (d, J = 225.6 Hz, 1 F *minor*), –68.8 (d, J = 212.8 Hz, 1 F*) ppm. MS: m/z (%) = 423 (51) [M + H]$^+$, 422 (35) [M]$^+$, 333 (12), 332 (35), 313 (20), 276 (13), 273 (16), 223 (22), 203 (51), 183 (16), 175 (59), 159 (35), 149 (25), 131 (22), 117 (62), 115 (100), 105 (31), 91 (55), 77 (54), 65 (22). HRMS (ESI-TOF): calcd. for $C_{25}H_{20}F_2O_2SNa$ [M + Na]$^+$ 445.1050; found 445.1059.

***E*/*Z* Mixture of 3-[Difluoro(phenylsulfanyl)methyl]-3-(4-tolylbut-3-enyl)isobenzofuran-1(3*H*)-one (3g):** According to general procedure E, the reaction of **3e** (1 g, 3 mmol), 4-methylstyrene (1.6 mL, 12 mmol), and Grubbs' 2nd generation catalyst (64 mg, 75 μmol) in dry CH_2Cl_2 (20 mL) gave **3g** (*E*/*Z* = 16:1; 872 mg, 63% yield) as a colorless viscous oil after purification by column chromatography (SiO_2, 100% hexanes to 10% EtOAc in hexanes). FTIR ($CHCl_3$): $\tilde{\nu}$ = 1789, 1600, 1513, 1467, 1287, 968 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, *major* isomer marked *): δ = 8.19 (d, J = 7.6 Hz, 1 H, ArH*), 8.14 (d, J = 7.6 Hz, 1 H, ArH *minor*), 8.00–7.90 (m, 2 H, 2× ArH *major* and *minor*), 7.83–7.79 (m, 4 H, 4× ArH *major* and *minor*), 7.78–7.70 (m, 4 H, 4× ArH *major* and *minor*), 7.70–7.60 (m, 2 H, 2× ArH *major* and *minor*), 7.60–7.53 (m, 4 H, 4× ArH *major* and *minor*), 7.43–7.30 (m, 4 H, 4× ArH *major* and *minor*), 7.30–7.27 (m, 4 H, 4× ArH *major* and *minor*), 6.59 (d, J = 15.8 Hz, 1 H, CH=C*H minor*), 6.43 (d, J = 15.8 Hz, 1 H, CH=C*H**), 6.19 (dt, J = 15.7, 6.9 Hz, 1 H, CH=C*H**), 5.86 (dt, J = 15.7, 7.8 Hz, 1 H, CH=C*H minor*), 3.55 (dd, J = 14.6, 7.3 Hz, 1 H, CH*H minor*), 3.39 (dd, J = 14.4, 7.4 Hz, 1 H, CH*H minor*), 3.00–2.80 (m, 1 H, CH*H**), 2.73–2.60 (m, 1 H, CH*H**), 2.56 (s, 3 H, C*H*$_3$*), 2.52 (s, 3 H, C*H*$_3$ *minor*), 2.43–2.30 (m, 2 H, CH*H major* and *minor*), 2.10–1.83 (m, 2 H, CH*H major* and *minor*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6 (C), 145.7 (C), 136.9 (C), 136.7 (2× CH), 134.4 (CH), 134.3 (C), 130.8 (CH), 130.5 (CH), 130.0 (CH), 129.1 (2× CH), 129.0 (2× CH), 128.8 (t, J = 276.1 Hz, CF_2), 127.3 (C), 126.8 (CH), 125.8 (3× CH), 125.8 (C), 123.4 (CH), 89.1 (t, J = 27.6 Hz, C), 31.6 (CH_2), 26.0 (CH_2), 21.1 (CH_3) ppm. Owing to low signal intensity, the *minor* isomer could not be detected by ^{13}C NMR spectroscopy. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.5 (d, J = 214.5 Hz, 1 F *minor*), –80.9 (d, J = 214.5 Hz, 1 F*), –81.8 (d, J =

214.5 Hz, 1 F *minor*), –82.3 (d, *J* = 214.5 Hz, 1 F*) ppm. MS: *m*/*z* (%) = 437 (28) $[M + H]^+$, 436 (43) $[M]^+$, 347 (43), 327 (61), 323 (93), 289 (48), 279 (55), 259 (30), 251 (57), 235 (18), 159 (39), 131 (80), 129 (77), 115 (58), 105 (69), 91 (100), 77 (72), 65 (24). HRMS (ESI-TOF): calcd. for $C_{26}H_{22}F_2O_2SNa$ $[M + Na]^+$ 459.1206; found 459.1206.

***E*/*Z* Mixture of 3-[Difluoro(phenylsulfanyl)methyl]-3-[4-(3-methoxyphenyl)but-3-enyl]isobenzofuran-1(3*H*)-one (3h):** According to general procedure E, the reaction of **3e** (1 g, 3 mmol), 3-methoxystyrene (1.6 mL, 12 mmol), and Grubbs' 2nd generation catalyst (64 mg, 75 μmol) in dry CH_2Cl_2 (20 mL) gave **3h** (*E*/*Z* = 13:1; 1 g, 73% yield) as a colorless viscous oil after purification by column chromatography (SiO_2, 100% hexanes to 10% EtOAc in hexanes). FTIR (neat): $\tilde{\nu}$ = 1789, 1600, 1580, 1470, 1288, 1156, 968 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, *major* isomer marked *): δ = 7.84 (dd, *J* = 7.6, 0.8 Hz, 1 H, ArH*), 7.79 (d, *J* = 7.6 Hz, 1 H, ArH *minor*), 7.63–7.54 (m, 2 H, 2× ArH *major* and *minor*), 7.53–7.55 (m, 4 H, 4× ArH *major* and *minor*), 7.43–7.33 (m, 4 H, 4× ArH *major* and *minor*), 7.32–7.26 (m, 2 H, 2× ArH *major* and *minor*), 7.25–7.18 (m, 4 H, 4× ArH *major* and *minor*), 7.08 (t, *J* = 7.9 Hz, 1 H, ArH*), 7.02 (t, *J* = 7.9 Hz, 1 H, ArH *minor*), 6.73 (d, *J* = 7.7 Hz, 1 H, ArH*), 6.70–6.58 (m, 4 H, 4× ArH *major* and *minor*), 6.56–6.45 (m, 1 H, ArH *minor*), 6.25 (d, *J* = 15.8 Hz, 1 H, CH=C*H minor*), 6.08 (d, *J* = 15.8 Hz, 1 H, CH=C*H**), 6.19 (dt, *J* = 15.7, 6.9 Hz, 1 H, CH=C*H**), 5.56 (dt, *J* = 15.2, 7.4 Hz, 1 H, CH=C*H minor*), 3.68 (s, 3 H, OCH_3*), 3.63 (s, 3 H, CH_3 *minor*), 3.20 (dd, *J* = 14.6, 7.4 Hz, 1 H, CH*H minor*), 3.05 (dd, *J* = 14.5, 7.5 Hz, 1 H, CH*H minor*), 2.60–2.49 (m, 1 H, CH*H**), 2.39–2.25 (m, 1 H, CH*H**), 2.10–1.95 (m, 2 H, CH*H major* and *minor*), 1.70–1.55 (m, 2 H, CH*H major* and *minor*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6 (C), 159.7 (C), 145.6 (C), 138.5 (C), 136.6 (2× CH), 134.4 (CH), 130.9 (CH), 130.5 (CH), 130.0 (CH), 129.3 (CH), 128.9 (2× CH), 128.2 (t, *J* = 277.5 Hz, CF_2), 128.2 (CH), 127.3 (C), 125.8 (CH), 125.0 (C), 123.4 (CH), 118.6 (CH), 112.8 (CH), 111.3 (CH), 89.0 (t, *J* = 28.0 Hz, C), 55.1 (CH_3), 31.5 (CH_2), 26.0 (CH_2) ppm. Owing to low signal intensity, the *minor* isomer could not be detected by ^{13}C NMR spectroscopy. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.5 (d, *J* = 209.8 Hz, 1 F *minor*), –80.9 (d, *J* = 213.2 Hz, 1 F*), –81.8 (d, *J* = 209.8 Hz, 1 F *minor*), –82.3 (d, *J* = 213.2 Hz, 1 F*) ppm. MS: *m*/*z* (%) = 452 (58) $[M + H]^+$, 451 (64) $[M]^+$, 343 (26), 323 (17), 305 (30), 303 (64), 275 (51), 215 (16), 161 (53), 147 (100), 145 (47), 117 (15), 115 (34), 91 (86), 77 (19), 65 (9). HRMS (ESI-TOF): calcd. for $C_{26}H_{22}F_2O_3SNa$ $[M + Na]^+$ 475.1155; found 475.1151.

***E*/*Z* Mixture of 3-[Difluoro(phenylsulfanyl)methyl]-3-(5-phenylpent-4-enyl)isobenzofuran-1(3*H*)-one (8b):** According to general procedure E, the reaction of **8a** (936 mg, 2.6 mmol), styrene (1.6 mL, 12 mmol), and Grubbs' 2nd generation catalyst (64 mg, 75 μmol) in dry CH_2Cl_2 (20 mL) gave **8b** (*E*/*Z* = 4:1; 972 mg, 87% yield) a as a colorless viscous oil after purification by column chromatography (SiO_2, 100% hexanes to 10% EtOAc in hexanes). FTIR ($CHCl_3$): $\tilde{\nu}$ = 1790, 1600, 1493, 1468, 1287, 1048, 967 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, *major* isomer marked *): δ = 7.87 (ddd, *J* = 7.6, 0.9, 0.9 Hz, 1 H, ArH*), 7.82 (ddd, *J* = 7.5, 0.8, 0.8 Hz, 1 H, ArH *minor*), 7.65–7.59 (m, 2 H, 2× ArH *major* and *minor*), 7.58–7.49 (m, 2 H, 2× ArH *major* and *minor*), 7.48–7.44 (m, 2 H, 2× ArH *major* and *minor*), 7.44–7.39 (m, 4 H, 4× ArH *major* and *minor*), 7.35–7.29 (m, 2 H, 2× ArH *major* and *minor*), 7.28–7.14 (m, 12 H, 12× ArH *major* and *minor*), 7.14–7.08 (m, 1 H, ArH*), 7.05–7.00 (m, 1 H, ArH *minor*), 6.24 (d, *J* = 15.8 Hz, 1 H, CH=C*H**), 6.13 (d, *J* = 15.8 Hz, 1 H, CH=C*H minor*), 5.96 (dt, *J* = 15.8, 7.0 Hz, 1 H, CH=C*H**), 5.92 (dt, *J* = 15.3, 6.9 Hz, 1 H, CH=C*H minor*), 2.58 (ddd, *J* = 15.7, 10.9, 5.1 Hz, 1 H, CH*H minor*), 2.41 (ddd, *J* = 16.5, 12.2, 4.4 Hz, 1 H, CH*H**), 2.33 (ddd, *J* = 15.9, 10.9, 5.3 Hz, 1 H, CH*H minor*), 2.21 (ddd, *J* = 13.3, 13.3, 4.6 Hz, 1 H, CH*H**), 2.16–2.00 (m, 4 H, 4× CH*H major* and *minor*), 1.50–1.04 (m, 1 H, CH*H minor*), 1.38–1.24 (m, 1 H, CH*H**), 0.88–0.72 (m, 2 H, 2× CH*H major* and *minor*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8 (C), 145.9 (C), 137.4 (C), 136.7 (2× CH), 134.4 (CH), 130.9 (CH), 130.5 (CH), 130.0 (CH), 129.2 (CH), 129.0 (2× CH) 128.5 (2× CH), 128.3 (t, *J* = 230.3 Hz, CF_2), 127.3 (C), 127.0 (CH), 126.0 (2× CH), 125.9 (CH), 125.1 (C), 123.3 (CH), 89.4 (t, *J* = 27.8 Hz, C), 32.5 (CH_2), 31.5 (CH_2), 26.1 (CH_2) ppm. Owing to low signal intensity, the *minor* isomer could not be detected by ^{13}C NMR spectroscopy. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.9 (d, *J* = 218.5 Hz, 1 F, CF*F**), –81.0 (d, *J* = 218.5 Hz, 1 F, CF*F minor*), –82.2 (d, *J* = 210.2 Hz, 1 F, CF*F**), –82.3 (d, *J* = 218.8 Hz, 1 F, CF*F minor*) ppm. MS: *m*/*z* (%) = 437 (9) $[M + H]^+$, 436 (17) $[M]^+$, 327 (52), 307 (11), 287 (35), 259 (22), 133 (26), 130 (10), 129 (42), 115 (36), 91 (35), 77 (9) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{26}H_{22}F_2O_2SNa$ $[M + Na]^+$ 459.1206; found 459.1202.

***E*/*Z* Mixture of 3-[Difluoro(phenylsulfanyl)methyl]-3-(4-tolylpent-4-enyl)isobenzofuran-1(3*H*)-one (8c):** According to general procedure E, the reaction of **8a** (1 g, 2.6 mmol), 4-methylstyrene (1.6 mL, 12 mmol), and Grubbs' 2nd generation catalyst (64 mg, 75 μmol) in dry CH_2Cl_2 (20 mL) gave **8c** (*E*/*Z* = 5:1; 872 mg, 63% yield) as a colorless viscous oil after purification by column chromatography (SiO_2, 100% hexanes to 10% EtOAc in hexanes). FTIR (neat): $\tilde{\nu}$ = 1779, 1601, 1513, 1467, 1287, 969 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, *major* isomer marked *): δ = 7.85 (ddd, *J* = 7.6, 1.0, 1.0 Hz, 1 H, ArH*), 7.68 (d, *J* = 8.1 Hz, 1 H, ArH *minor*), 7.63–7.55 (m, 2 H, 2× ArH *major* and *minor*), 7.54–7.48 (m, 2 H, 2× ArH *major* and *minor*), 7.47–7.43 (m, 2 H, 2× ArH *major* and *minor*), 7.43–7.30 (m, 4 H, 4× ArH *major* and *minor*), 7.34–7.23 (m, 2 H, 2× ArH *major* and *minor*), 7.21–7.13 (m, 4 H, 4× ArH *major* and *minor*), 7.13–7.06 (m, 2 H, 2× ArH*), 7.05–7.02 (m, 2 H, 2× ArH *minor*), 7.02–6.95 (m, 4 H, 4× ArH *major* and *minor*), 6.19 (d, *J* = 15.8 Hz, 1 H, CH=C*H**), 6.08 (d, *J* = 15.8 Hz, 1 H, CH=C*H minor*), 5.98–5.80 (m, 2 H, 2× CH=C*H**), 2.60–2.50 (m, 1 H, CH*H**), 2.45–2.32 (m, 2 H, 2× CH*H major* and *minor*), 2.28–2.15 (m, 7 H, CH*H**, 2× CH_3 *major* and *minor*), 2.14–1.98 (m, 2 H, 2× CH*H**), 1.98–1.85 (m, 2 H, 2× CH*H minor*), 1.38–1.20 (m, 2 H, 2× CH*H major* and *minor*), 0.88–0.70 (m, 2 H, 2× CH*H major* and *minor*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.8 (C), 145.9 (C), 136.7 (C), 136.7 (2× CH), 134.6 (C), 134.4 (CH), 130.7 (CH), 130.4 (CH), 130.0 (CH), 129.1 (2× CH), 128.9 (2× CH), 128.3 (t, *J* = 287.8 Hz, CF_2), 128.1 (CH), 127.3 (C), 125.8 (3× CH), 125.1 (C), 123.3 (CH), 89.4 (t, *J* = 27.4 Hz, C), 32.4 (CH_2), 31.4 (CH_2), 22.2 (CH_2), 21.1 (CH_3) ppm. Owing to low signal intensity, the *minor* isomer could not be detected by ^{13}C NMR spectroscopy. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.8 (d, *J* = 212.0 Hz, 1 F*), –80.9 (d, *J* = 210.4 Hz, 1 F *minor*), –82.2 (d, *J* = 212.0 Hz, 1 F*), –82.3 (d, *J* = 210.4 Hz, 1 F *minor*) ppm. MS: *m*/*z* (%) = 451 (16) $[M + H]^+$, 450 (33) $[M]^+$, 341 (34), 301 (50), 145 (23), 144 (100), 131 (83), 129 (70), 115 (15), 105 (23), 91 (20), 77 (10). HRMS (ESI-TOF): calcd. for $C_{27}H_{24}F_2O_2SNa$ $[M + Na]^+$ 473.1363; found 473.1357.

***E*/*Z* Mixture of 3-[Difluoro(phenylsulfanyl)methyl]-3-[(3-methoxyphenyl)pent-4-enyl]isobenzofuran-1(3*H*)-one (8d):** According to general procedure E, the reaction of **8a** (936 g, 2.6 mmol), 3-methoxystyrene (1.6 mL, 12 mmol), and Grubbs' 2nd generation catalyst (64 mg, 75 μmol) in dry CH_2Cl_2 (20 mL) gave **8d** (*E*/*Z* = 5:1; 817 mg, 67% yield) as a colorless viscous oil after purification by column chromatography (SiO_2, 100% hexanes to 10% EtOAc in hexanes). FTIR ($CHCl_3$): $\tilde{\nu}$ = 1790, 1500, 1580, 1468, 1288, 1265, 1156, 968 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *major* isomer marked

*): δ = 8.00–7.86 (m, 2 H, 2× ArH *major* and *minor*), 7.74–7.65 (m, 2 H, 2× ArH *major* and *minor*), 7.65–7.44 (m, 8 H, 8× ArH *major* and *minor*), 7.44–7.36 (m, 2 H, 2× ArH *major* and *minor*), 7.36–7.27 (m, 4 H, 4× ArH *major* and *minor*), 7.23–7.07 (m, 2 H, 2× ArH *major* and *minor*), 6.93–6.85 (m, 2 H, 2× ArH *major* and *minor*), 6.85–6.78 (m, 2 H, 2× ArH *major* and *minor*), 6.78–6.60 (m, 2 H, 2× ArH *major* and *minor*), 6.28 (d, *J* = 15.8 Hz, 1 H, CH=C*H**), 6.18 (d, *J* = 15.8 Hz, 1 H, CH=C*H minor*), 6.10–5.92 (m, 2 H, 2× CH=C*H major* and *minor*), 3.79 (s, 3 H, OCH_3*), 3.74 (s, 3 H, OCH_3 *minor*), 2.54–2.52 (m, 1 H, CH*H minor*), 2.51–2.47 (m, 2 H, 2× CH*H major* and *minor*), 2.47–2.00 (m, 5 H, 3× CH*H**, 2× CH*H minor*), 1.49–1.30 (m, 2 H, 2× CH*H major* and *minor*), 0.99–0.79 (m, 2 H, 2× CH*H major* and *minor*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9 (C), 159.8 (C), 145.9 (C), 138.9 (C), 136.8 (2× CH), 134.5 (CH), 130.8 (CH), 130.5 (CH), 130.1 (CH), 129.6 (CH), 129.5 (CH), 129.0 (2× CH), 128.3 (t, *J* = 287.0 Hz, CF_2), 127.3 (C), 125.9 (CH), 125.0 (C), 123.4 (CH), 118.7 (CH), 112.8 (CH), 111.3 (CH), 89.0 (t, *J* = 27.0 Hz, C), 55.2 (OCH_3), 32.5 (CH_2), 31.5 (CH_2), 21.1 (CH_2) ppm. Owing to low signal intensity, the *minor* isomer could not be detected by ^{13}C NMR spectroscopy. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.8 (d, *J* = 213.2 Hz, 1 F*), –80.9 (d, *J* = 210.9 Hz, 1 F *minor*), –82.2 (d, *J* = 213.2 Hz, 1 F*), –82.3 (d, *J* = 210.9 Hz, 1 F *minor*) ppm. MS: *m*/*z* (%) = 467 (19) $[M + H]^+$, 466 (50) $[M]^+$, 317 (20), 161 (29), 160 (100), 147 (95), 129 (27), 121 (15), 115 (9), 91 (20), 77 (8). HRMS (ESI-TOF): calcd. for $C_{27}H_{24}F_2O_3SNa$ $[M + Na]^+$ 489.1312; found 489.1309.

(*E*)-Methyl 6-{1-[Difluoro(phenylsulfanyl)methyl]-3-oxo-1,3-dihydroisobenzofuran-1-yl}hex-2-enoate (8e): According to general procedure E, the reaction of **8a** (936 mg, 2.6 mmol), methyl acrylate (1.1 mL, 12 mmol), and Grubbs' 2nd generation catalyst (64 mg, 75 μmol) in dry CH_2Cl_2 (20 mL) gave **8e** (989 mg, 79% yield) as a white solid after purification by column chromatography (SiO_2, 100% hexanes to 10% EtOAc in hexanes) [m.p. 85–86 °C (CH_2Cl_2/hexanes)]. FTIR ($CHCl_3$): $\tilde{\nu}$ = 1781, 1717, 1659, 1468, 1288, 1051, 982 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.6 Hz, 1 H, ArH), 7.71 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1 H, ArH), 7.63 (ddd, *J* = 7.5, 7.5, 0.8 Hz, 1 H, ArH), 7.53 (d, *J* = 7.7 Hz, 1 H, ArH), 7.48 (d, *J* = 7.1 Hz, 2 H, 2× ArH), 7.43–7.36 (m, 1 H, ArH), 7.35–7.28 (m, 2 H, 2× ArH), 6.79 (d, *J* = 15.6, 6.9 Hz, 1 H, CH=C*H*), 5.74 (dt, *J* = 15.7, 1.5 Hz, 1 H, CH=C*H*), 3.70 (s, 3 H, OCH_3), 2.44 (ddd, *J* = 14.3, 12.1, 4.4 Hz, 1 H, CH*H*), 2.33–2.08 (m, 3 H, 3× CH*H*), 1.45–1.30 (m, 1 H, CH*H*), 1.95–0.83 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6 (C), 166.7 (C), 147.5 (CH), 145.6 (C), 136.7 (2× CH), 134.6 (CH), 130.6 (CH), 130.1 (CH), 129.0 (2× CH), 128.2 (t, *J* = 296.4 Hz, CF_2), 127.2 (C), 126.0 (CH), 125.0 (C), 123.3 (CH), 121.8 (CH), 89.2 (t, *J* = 28.0 Hz, C), 51.4 (OCH_3), 31.6 (CH_2), 31.4 (CH_2), 21.0 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.9 (d, *J* = 214.9 Hz, 1 F, CF*F*), –82.3 (d, *J* = 214.9 Hz, 1 F, CF*F*) ppm. MS: *m*/*z* (%) = 419 (4) $[M + H]^+$, 418 (3) $[M]^+$, 385 (15), 359 (21), 358 (70), 329 (17), 288 (21), 286 (18), 227 (22), 182 (20), 181 (100), 180 (13), 159 (51), 131 (12), 103 (7), 77 (7). HRMS (ESI-TOF): calcd. for $C_{22}H_{20}F_2O_4SNa$ $[M + Na]^+$ 441.0948; found 441.0947.

General Procedure F for the Preparation of γ-*gem*-Difluoromethylenated Spiro-γ-butyrolactones 5a–m

6,6-Difluoro-7-methyl-1-oxaspiro[4.4]nonan-2-one (5a): Argon was bubbled through a solution of **3a** (451 mg, 1.5 mmol) in dry toluene (50 mL) for 30 min, and a mixture of Bu_3SnH (0.95 mL, 3 mmol) and AIBN (37 mg, 0.2 mmol) in dry toluene (8 mL) was added dropwise at reflux over 1 h. The resulting reaction mixture was heated at reflux for 8 h and then evaporated to dryness to give a crude product, which was firstly purified by column chromatography (SiO_2, hexanes and then CH_2Cl_2) to remove organotin byproducts. A colorless oil was obtained, which was then purified again by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) to give **5aA** (less polar; 135 mg, 35% yield, which contains 1% of **5aB** as determined by ^{1}H NMR spectroscopy) as a colorless liquid and **5aB** (more polar; 127 mg, 33% yield) as a colorless liquid. Compound **5aA**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1781, 1459, 1252, 1219, 1184, 1118, 1049, 1021, 993, 927 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.73–2.58 (m, 1 H, C*H*HCO), 2.58–2.35 (m, 3 H, CH*H*CO and 2× C*H*H), 2.07–1.89 (m, 3 H, 3× C*H*H), 1.89–1.83 (m, 1 H, C*H*H), 1.37–1.25 (m, 1 H, C*H*H), 1.02 (d, *J* = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.7 (CO), 127.2 (dd, *J* = 264.5, 249.4 Hz, CF_2), 89.5 (dd, *J* = 32.4, 21.3 Hz, C), 36.0 (t, *J* = 21.4 Hz, CH), 32.2 (d, *J* = 4.0 Hz, CH_2), 28.5 (CH_2), 25.6 (d, *J* = 9 Hz, CH_2), 24.8 (d, *J* = 3.1 Hz, CH_2), 10.8 (d, *J* = 7.3 Hz, CH_3) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –125.2 (dd, *J* = 230.3, 27.7 Hz, 1 F), –128.6 (dd, *J* = 230.3, 3.8 Hz, 1 F, CF*F*) ppm. MS: *m*/*z* (%) = 191 (8) $[M + H]^+$, 181 (55), 180 (33), 178 (13), 169 (7), 167 (21), 151 (14), 133 (14), 131 (39), 129 (11), 115 (13), 106 (10), 105 (100), 91 (37), 79 (31), 77 (51), 67 (12). HRMS (ESI-TOF): calcd. for $C_9H_{12}F_2O_2Na$ $[M + Na]^+$ 213.0703; found 213.0700. Compound **5aB**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1782, 1459, 1252, 1218, 1184, 1118, 1049, 1021, 993, 927 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.67–2.56 (m, 1 H, C*H*HCO), 2.52–2.42 (m, 2 H, CH*H*CO and C*H*H), 2.38–2.24 (m, 1 H, CH), 2.07–1.94 (m, 3 H, 3× CH*H*), 1.84–1.73 (m, 1 H, C*H*H), 1.59–1.49 (m, 1 H, C*H*H), 1.02 (dd, *J* = 7.3, 2.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.6 (CO), 127.2 (dd, *J* = 265.6, 250.4 Hz, CF_2), 89.5 (dd, *J* = 31.8, 20.3 Hz, C), 38.0 (dd, *J* = 21.1, 24.6 Hz, CH), 33.0 (d, *J* = 3.3 Hz, CH_2), 28.2 (CH_2), 27.4 (t, *J* = 4.1 Hz, CH_2), 26.0 (d, *J* = 4.3 Hz, CH_2), 14.5 (dd, *J* = 4.9, 7.4 Hz, CH_3) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –102.6 (dd, *J* = 236.0, 1.41 Hz, 1 F), –126.5 (d, *J* = 236.0 Hz, 1 F) ppm. MS: *m*/*z* (%) = 191 (9) $[M + H]^+$, 171 (5), 151 (69), 123 (8), 111 (33), 95 (4), 83 (22), 65 (3), 55 (32). HRMS (ESI-TOF): calcd. for $C_9H_{12}F_2O_2Na$ $[M + Na]^+$ 213.0703; found 213.0693.

7-Benzyl-6,6-difluoro-1-oxaspiro[4.4]nonan-2-one (5b): According to general procedure F, radical cyclization of **3b** (528 mg, 1.5 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) gave **5bA** (less polar; 184 mg, 48% yield, which contains 1% of **5bB** as determined by ^{1}H NMR spectroscopy) as a white solid [m.p. 75–76 °C (CH_2Cl_2/hexanes)] and **5bB** (more polar; 136 mg, 35% yield) as a white solid [m.p. 72–73 °C (CH_2Cl_2/hexanes)]. Compound **5bA**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1784, 1497, 1456, 1346, 1275, 1224, 1182, 1152, 1089, 1072, 1012, 936 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.17 (m, 2 H, 2× ArH), 7.16–7.09 (m, 3 H, 3× ArH), 2.97 (dd, *J* = 13.8, 5.1 Hz, 1 H, C*H*), 2.83–2.37 (m, 5 H, 5× CH*H*), 2.08–1.75 (m, 4 H, 4× CH*H*), 1.48–1.35 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.6 (CO), 138.9 (C), 128.7 (2× CH), 128.4 (2× CH), 127.0 (dd, *J* = 265.6, 249.6 Hz, CF_2), 126.3 (CH), 89.5 (dd, *J* = 32.4, 21.3 Hz, C), 42.9 (t, *J* = 20.9 Hz, CH), 33.0 (d, *J* = 6.1 Hz, CH_2), 31.9 (d, *J* = 4.1 Hz, CH_2), 28.5 (CH_2), 24.7 (d, *J* = 3.4 Hz, CH_2), 24.0 (d, *J* = 8.7 Hz, CH_2) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –125.2 (dd, *J* = 230.3, 27.7 Hz, 1 F), –128.6 (dd, *J* = 230.3, 3.8 Hz, 1 F) ppm. MS: *m*/*z* (%) = 267 (14) $[M + H]^+$, 266 (80) $[M]^+$, 247 (8), 246 (26), 227 (13), 226 (66), 209 (1), 208 (5), 167 (85), 166 (42), 117 (72), 115 (72), 115 (33), 111 (10), 109 (5), 91 (100), 77 (16), 65 (28), 50 (10). HRMS (ESI-TOF): calcd. for $C_{15}H_{16}F_2O_2Na$ $[M + Na]^+$ 289.1016; found 289.1030. Compound **5bB**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1787, 1497, 1455, 1254, 1189, 1141, 1096, 1060, 989 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.17 (m, 2

H, 2× ArH), 7.16–7.09 (m, 3 H, 3× ArH), 3.09–2.94 (m, 1 H, C*H*), 2.72–2.41 (m, 5 H, 5× CH*H*), 2.09–1.47 (m, 2 H, 2× CH*H*), 1.84–1.73 (m, 2 H, 2× CH*H*), 1.72–1.59 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.6 (CO), 139.1 (C), 128.8 (2× CH), 128.5 (2× CH), 127.0 (dd, *J* = 266.4, 251.6 Hz, CF_2), 126.3 (CH), 89.5 (dd, *J* = 31.3, 20.0 Hz, C), 44.8 (dd, *J* = 23.3, 19.6 Hz, CH), 35.4 (dd, *J* = 6.5, 4.5 Hz, CH_2), 32.9 (d, *J* = 3.0 Hz, CH_2), 28.2 (CH_2), 26.0 (d, *J* = 4.3 Hz, CH_2), 25.6 (d, *J* = 3.6 Hz, CH_2) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –100.9 (dd, *J* = 235.9, 22.6 Hz, 1 F, CF*F*), –124.9 (d, *J* = 235.9 Hz, 1 F, CF*F*) ppm. MS: *m*/*z* (%) = 267 (19) $[M + H]^+$, 266 (66) $[M]^+$, 247 (6), 246 (38), 227 (11), 226 (79), 209 (2), 208 (3), 167 (91), 166 (38), 117 (68), 115 (40), 111 (9), 109 (4), 91 (100), 77 (16), 65 (28), 50 (11). HRMS (ESI-TOF): calcd. for $C_{15}H_{16}F_2O_2Na$ $[M + Na]^+$ 289.1016; found 289.1013.

6,6-Difluoro-7-(4-methylbenzyl)-1-oxaspiro[4.4]nonan-2-one (5c): According to general procedure F, radical cyclization of **3c** (396 mg, 1 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) gave **5cA** (less polar; 135 mg, 46% yield, which contains 4% of **5cB** as determined by ^{1}H NMR spectroscopy) as a white solid [m.p. 61–62 °C (CH_2Cl_2/hexanes)] and **5cB** (more polar; 104 mg, 35% yield, which contains 4% of **5cA** as determined by ^{1}H NMR spectroscopy) as a white solid [m.p. 59–60 °C (CH_2Cl_2/hexanes)]. Compound **5cA**: FTIR ($CHCl_3$): ṽ = 1784, 1516, 1459, 1346, 1183, 1155, 1083, 1013, 934 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90–7.80 (m, 4 H, 4× ArH), 2.87 (dd, *J* = 13.5, 5.1 Hz, 1 H, C*H*), 2.75–2.35 (m, 5 H, 5× CH*H*), 2.20 (s, 3 H, CH_3), 2.04–1.75 (m, 4 H, 4× CH*H*), 1.45–1.30 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.6 (CO), 135.8 (2× C), 129.1 (2× CH), 128.6 (2× CH), 127.0 (dd, *J* = 268.5, 252.3 Hz, CF_2), 89.5 (dd, *J* = 32.1, 20.9 Hz, C), 42.9 (t, *J* = 20.9 Hz, CH), 32.6 (d, *J* = 6.3 Hz, CH), 31.9 (d, *J* = 3.9 Hz, CH_2), 28.5 (CH_2), 24.7 (d, *J* = 3.3 Hz, CH_2), 24.0 (d, *J* = 8.4 Hz, CH_2), 20.9 (CH_3) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –123.2 (dd, *J* = 231.0, 27.7 Hz, 1 F, CF*F*), –128.6 (dd, *J* = 231.0 Hz, 1 F, CF*F*) ppm. MS: *m*/*z* (%) = 281 (12) $[M + H]^+$, 280 (43) $[M]^+$, 260 (4), 240 (10), 181 (21), 180 (8), 131 (43), 106 (12), 105 (100), 91 (12), 77 (27). HRMS (ESI-TOF): calcd. for $C_{16}H_{18}F_2O_2Na$ $[M + Na]^+$ 303.1173; found 303.1172. Compound **5cB**: FTIR ($CHCl_3$): ṽ = 1783, 1515, 1459, 1253, 1188, 1142, 1091, 1056, 990 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90–7.80 (m, 4 H, 4× ArH), 2.97 (d, *J* = 9.0 Hz, 1 H, CH), 2.70–2.57 (m, 1 H, CH*H*), 2.56–2.40 (m, 4 H, 4× CH*H*), 2.24 (s, 3 H, C*H*$_3$), 2.10–1.93 (m, 2 H, 2× CH*H*), 1.83–1.72 (m, 2 H, 2× CH*H*), 1.71–1.54 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5 (CO), 135.9 (C), 135.8 (C), 129.1 (2× CH), 128.7 (2× CH), 127.3 (dd, *J* = 266.5, 251.8 Hz, CF_2), 89.4 (dd, *J* = 31.0, 19.8 Hz, C), 44.8 (dd, *J* = 23.0, 19.6 Hz, CH), 34.8 (dd, *J* = 6.5, 3.8 Hz, CH_2), 32.9 (d, *J* = 3.0 Hz, CH_2), 28.2 (CH_2), 26.1 (d, *J* = 4.3 Hz, CH_2), 25.5 (t, *J* = 3.8 Hz, CH_2), 20.9 (CH_3) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –101.2 (dd, *J* = 235.7, 22.1 Hz, 1 F), –124.9 (d, *J* = 235.7 Hz, 1 F) ppm. MS: *m*/*z* (%) = 281 (8) $[M + H]^+$, 280 (49) $[M]^+$, 261 (3), 241 (12), 240 (37), 181 (31), 180 (13), 131 (53), 106 (9), 105 (100), 91 (15), 77 (30). HRMS (ESI-TOF): calcd. for $C_{16}H_{18}F_2O_2Na$ $[M + Na]^+$ 303.1173; found 303.1172.

6,6-Difluoro-7-(naphthalen-2-ylmethyl)-1-oxaspiro[4.4]nonan-2-one (5d): According to general procedure F, radical cyclization of **3d** (608 mg, 1.4 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) gave **5dA** (less polar; 199 mg, 44% yield) as a white solid [m.p. 106–117 °C (CH_2Cl_2/hexanes)] and **5dB** (more polar; 148 mg, 32% yield) as a white solid [m.p. 105–106 °C (CH_2Cl_2/hexanes)]. Compound **5dA**: FTIR ($CHCl_3$): ṽ = 1784, 1509, 1459, 1346, 1188, 1140, 1085, 1014, 990 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87–7.73 (m, 3 H, 3× ArH), 7.65 (s, 1 H, ArH), 7.53–7.38 (m, 2 H, 2× ArH), 7.34 (dd, *J* = 8.4, 1.4 Hz, 1 H, ArH), 3.22 (dd, *J* = 13.7, 4.9 Hz, 1 H, CH), 3.03–2.84 (m, 1 H, CH*H*), 2.84–2.60 (m, 3 H, 3× CH*H*), 2.60–2.45 (m, 1 H, CH*H*), 2.13–1.85 (m, 4 H, 4× CH*H*), 1.62–1.43 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5 (CO), 136.4 (C), 133.5 (C), 132.2 (C), 128.1 (CH), 127.6 (CH), 127.4 (CH), 127.1 (CH), 127.0 (dd, *J* = 262.1, 247.9 Hz, CF_2), 127.0 (CH), 126.1 (CH), 125.4 (CH), 89.6 (dd, *J* = 32.3, 21.1 Hz, C), 42.8 (t, *J* = 10.2 Hz, CH), 33.2 (d, *J* = 6.0 Hz, CH_2), 32.0 (d, *J* = 4.1 Hz, CH_2), 28.5 (CH_2), 24.7 (d, *J* = 3.3 Hz, CH_2), 24.0 (d, *J* = 8.5 Hz, CH_2) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –121.6 (dd, *J* = 231.0, 28.2 Hz, 1 F), –125.5 (d, *J* = 231.0 Hz, 1 F) ppm. MS: *m*/*z* (%) = 317 (5) $[M + H]^+$, 316 (33) $[M]^+$, 310 (20), 292 (44), 265 (4), 205 (12), 181 (13), 179 (40), 165 (48), 141 (100), 115 (30), 91 (12), 77 (13), 55 (13). HRMS (ESI-TOF): calcd. for $C_{19}H_{18}F_2O_2Na$ $[M + Na]^+$ 339.1173; found 339.1175. Compound **5dB**: FTIR ($CHCl_3$): ṽ = 1784, 1509, 1459, 1188, 1140, 1085, 1056, 990 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87–7.73 (m, 3 H, 3× ArH), 7.66 (s, 1 H, ArH), 7.53–7.40 (m, 2 H, 2× ArH), 7.34 (d, *J* = 8.2 Hz, 1 H, ArH), 3.26 (dd, *J* = 13.4, 4.2 Hz, 1 H, C*H*), 3.88–2.65 (m, 3 H, 3× CH*H*), 2.64–2.50 (m, 2 H, 2× CH*H*), 2.18–2.00 (m, 2 H, 2× CH*H*), 2.93–1.70 (m, 3 H, 3× CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5 (CO), 136.5 (C), 133.5 (C), 132.2 (C), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.3 (d, *J* = 266.6 Hz, CF_2), 127.3 (CH), 127.1 (CH), 126.1 (CH), 125.4 (CH), 89.6 (dd, *J* = 31.5, 20.3 Hz, C), 44.7 (dd, *J* = 23.3, 19.8 Hz, CH), 35.5 (dd, *J* = 6.1, 4.1 Hz, CH_2), 32.8 (d, *J* = 2.8 Hz, CH_2), 28.2 (CH_2), 25.9 (d, *J* = 3.6 Hz, CH_2), 25.6 (t, *J* = 3.6 Hz, CH_2) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –99.2 (dd, *J* = 236.2, 23.5 Hz, 1 F), –123.4 (d, *J* = 236.2 Hz, 1 F) ppm. MS: *m*/*z* (%) = 317 (8) $[M + H]^+$, 316 (31) $[M]^+$, 293 (15), 292 (67), 264 (8), 219 (10), 205 (16), 204 (21), 191 (9), 180 (17), 179 (57), 167 (75), 165 (54), 152 (30), 141 (100), 129 (18), 115 (23), 105 (14), 95 (18), 77 (21), 67 (16), 55 (11). HRMS (ESI-TOF): calcd. for $C_{19}H_{18}F_2O_2Na$ $[M + Na]^+$ 339.1173; found 339.1173.

2,2-Difluoro-3-methyl-3′*H*-spiro[cyclopentane-1,1′-isobenzofuran]-3′-one (5e): According to general procedure F, radical cyclization of **3e** (522 mg, 1.5 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) gave a 1:3 mixture of diastereoisomers [determined by ^{19}F NMR spectroscopy (376 MHz)] of **5e** (317 mg, 89% yield) as a colorless liquid: FTIR (neat): ṽ = 1777, 1614, 1467, 1340, 1052, 986 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, *major* isomer marked *): δ = 7.90–7.83 (m, 2 H, 2× ArH *major* and *minor*), 7.73–7.63 (m, 2 H, 2× ArH *major* and *minor*), 7.60–7.50 (m, 4 H, 4× ArH *major* and *minor*), 2.83–2.65 (m, 1 H, C*H*, *minor*), 2.64–2.50 (m, 1 H, C*H**), 2.48–2.39 (m, 1 H, CH*H minor*), 2.38–2.22 (m, 3 H, 2× CH*H** and CH*H minor*), 2.20–2.03 (m, 2 H, 2× CH*H major* and *minor*), 1.90–1.73 (m, 1 H, CH*H**), 1.68–1.53 (m, 1 H, CH*H minor*), 1.21 (dd, *J* = 7.3, 2.1 Hz, 3 H, CH_3*), 1.14 (d, *J* = 6.9 Hz, 3 H, CH_3 *minor*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, *major* isomer marked *): δ = 168.5 (CO*), 168.5 (CO *minor*), 145.2 (C*), 145.0 (C *minor*), 134.2 (CH *minor*), 134.1 (CH*), 130.0 (2× CH *major* and *minor*), 127.6 (dd, *J* = 271.4, 248.1 Hz, CF_2*), 126.7 (dd, *J* = 268.1, 248.6 Hz, CF_2 *minor*), 126.7 (2× C *major* and *minor*), 125.4 (2× CH *major* and *minor*), 123.9 (d, *J* = 4.8 Hz, CH*), 123.9 (d, *J* = 6.4 Hz, CH *minor*), 90.6 (dd, *J* = 33.1, 21.8 Hz, C*), 90.0 (dd, *J* = 32.5, 22.1 Hz, C *minor*), 38.9 (dd, *J* = 24.0, 20.6 Hz, CH*), 37.1 (t, *J* = 21.1 Hz, CH *minor*), 33.2 (d, *J* = 3.1 Hz, CH_2*), 32.4 (d, *J* = 2.8 Hz, CH_2 *minor*), 28.3 (t, *J* = 3.9 Hz, CH_2*), 25.9 (d, *J* = 8.9 Hz, CH_2 *minor*), 15.1 (t, *J* = 6.4 Hz, CH_3*), 10.8 (d, *J* = 7.1 Hz, CH_3 *minor*) ppm. ^{19}F NMR (376 MHz, $CDCl_3$, *major* isomer marked *): δ = –96.1 (dd, *J* = 236.9, 26.8 Hz, 1 F*), –124.6 (dd, *J* = 230.3, 28.2 Hz, 1 F *minor*),

–124.9 (d, J = 236.9 Hz, 1 F*), –127.2 (d, J = 230.3 Hz, 1 F *minor*) ppm. MS: *m/z* (%) = 239 (61) $[M + H]^+$, 238 (21), 201 (16), 181 (9), 141 (3), 159 (100), 143 (3), 131 (21), 115 (7), 105 (13), 89 (14). HRMS (ESI-TOF): calcd. for $C_{13}H_{12}F_2O_2Na$ $[M + Na]^+$ 261.0703; found 261.0700.

3-Benzyl-2,2-difluoro-3′*H*-spiro[cyclopentane-1,1′-isobenzofuran]-3′-one (5f): According to general procedure F, radical cyclization of **3f** (635 mg, 1.5 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) gave a 1:1.6 mixture of diastereoisomers [determined by ^{19}F NMR spectroscopy (376 MHz)] of **5f** (388 mg, 82% yield) as a colorless liquid: FTIR (neat): $\tilde{\nu}$ = 1773, 1615, 1467, 1347, 1042, 987 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, *major* isomer marked *): δ = 7.97 (d, J = 7.5 Hz, 1 H, ArH*), 7.94 (d, J = 7.7 Hz, 1 H, ArH* *minor*), 7.80–7.70 (m, 2 H, 2× ArH *major* and *minor*), 7.68–7.57 (m, 4 H, 4× ArH *major* and *minor*), 7.40–7.33 (m, 4 H, 4× ArH *major* and *minor*), 7.32–7.20 (m, 6 H, 6× ArH *major* and *minor*), 3.22 (dd, J = 13.5, 4.2 Hz, 1 H, CH*), 3.16 (dd, J = 13.6, 5.1 Hz, 1 H, CH *minor*), 3.13–2.98 (m, 1 H, CH*), 2.96–2.74 (m, 2 H, 2× CH*H* *major* and *minor*), 2.75 (dd, J = 13.5, 10.0 Hz, 1 H, CH*H* *minor*), 2.58–2.45 (m, 1 H, CH*H* *minor*), 2.44–2.30 (m, 1 H, CH*H**), 2.25–2.14 (m, 3 H, CH*H* *major* and 2× CH*H* *minor*), 2.14–2.06 (m, 1 H, CH*H**), 2.06–1.95 (m, 1 H, CH*H**), 1.85–1.73 (m, 1 H, CH*H* *minor*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, *major* isomer marked *): δ = 168.6 (CO*), 168.5 (CO *minor*), 145.0 (C*), 144.8 (C *minor*), 139.1 (C*), 138.8 (C *minor*), 134.2 (2× CH *major* and *minor*), 130.0 (2× CH *major* and *minor*), 128.9 (2× CH *major* and *minor*), 128.7 (2× CH *major* and *minor*), 128.5 (4× CH *major* and *minor*), 126.4 (CH *minor*), 126.3 (CH*), 125.7 (CH*), 125.6 (CH *minor*), 127.2 (dd, J = 273.0, 249.3 Hz, CF_2*), 126.6 (dd, J = 269.4, 248.4 Hz, CF_2 *minor*), 127.1 (C*), 126.9 (C *minor*), 124.0 (d, J = 3.6 Hz, CH*), 123.9 (d, J = 3.5 Hz, CH *minor*), 90.8 (dd, J = 33.0, 21.6 Hz, C*), 90.1 (dd, J = 32.0, 21.8 Hz, C *minor*), 45.8 (dd, J = 23.3, 19.0 Hz, CH*), 44.1 (dd, J = 20.5, 20.5 Hz, CH *minor*), 35.8 (t, J = 5.8 Hz, CH*), 33.2 (d, J = 3.0 Hz, CH*), 33.1 (d, J = 6.3 Hz, CH_2*), 32.1 (d, J = 3.1 Hz, CH_2*), 26.4 (t, J = 3.5 Hz, CH_2*), 24.4 (d, J = 8.1 Hz, CH_2 *minor*) ppm. ^{19}F NMR (376 MHz, $CDCl_3$, *major* isomer marked *): δ = –94.6 (dd, J = 238.8, 23.3 Hz, 1 F*), –122.7 (dd, J = 232.0, 27.5 Hz, 1 F *minor*), –124.8 (d, J = 238.8 Hz, 1 F*), –125.5 (d, J = 232.0 Hz, 1 F *minor*) ppm. MS: *m/z* (%) = 315 (69) $[M + H]^+$, 314 (21) $[M]^+$, 223 (4), 197 (41), 177 (9), 159 (12), 129 (7), 118 (100), 117 (20), 115 (8), 91 (31), 77 (13), 65 (10). HRMS (ESI-TOF): calcd. for $C_{19}H_{16}F_2O_2Na$ $[M + Na]^+$ 337.1016; found 337.1017.

2,2-Difluoro-3-(4-methylbenzyl)-3′*H*-spiro[cyclopentane-1,1′-isobenzofuran]-3′-one (5g): According to general procedure F, radical cyclization of **3g** (656 mg, 1.5 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) gave a 1:1.6 mixture of diastereoisomers [determined by ^{19}F NMR spectroscopy (376 MHz)] of **5g** (407 mg, 83% yield) as a colorless liquid. FTIR (neat): $\tilde{\nu}$ = 1779, 1614, 1468, 1345, 1041, 983 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, *major* isomer marked *): δ = 7.83 (d, J = 7.6 Hz, 1 H, ArH*), 7.80 (d, J = 7.7 Hz, 1 H, ArH *minor*), 7.65–7.58 (m, 2 H, 2× ArH *major* and *minor*), 7.55–7.45 (m, 4 H, 4× ArH *major* and *minor*), 7.25–7.10 (m, 4 H, 4× ArH *minor*), 7.08–6.98 (m, 4 H, 4× ArH*), 3.05 (dd, J = 13.1, 3.7 Hz, 1 H, CH*H**), 2.99 (dd, J = 13.5, 5.0 Hz, 1 H, CH*H* *minor*), 2.98–2.83 (m, 1 H, C*H**), 2.80–2.62 (m, 2 H, CH*H* *major* and CH *minor*), 2.59 (dd, J = 13.5, 9.9 Hz, 1 H, CH*H* *minor*), 2.45–2.33 (m, 1 H, CH*H* *minor*), 2.30–2.18 (m, 7 H, CH*H**, 2× CH_3 *major* and *minor*), 2.12–2.01 (m, 3 H, CH*H* *major* and 2× CH*H* *minor*), 2.01–1.93 (m, 1 H, CH*H**), 1.93–1.80 (m, 1 H, CH*H**), 1.72–1.58 (m, 1 H, CH*H* *minor*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, *major* isomer marked *): δ = 168.6 (CO*), 168.4 (CO *minor*), 145.0 (C*), 144.7 (C *minor*), 135.9 (CH*), 135.8 (CH *minor*), 135.8 (CH*), 135.7 (CH *minor*), 134.2 (C *minor*), 134.1 (C*), 130.1 (2× CH *major* and *minor*), 129.2 (4× CH *major* and *minor*), 128.7 (4× CH *major* and *minor*), 127.2 (dd, J = 272.1, 249.3 Hz, CF_2*), 127.0 (C *minor*), 126.8 (C*), 126.6 (dd, J = 270.0, 249.0 Hz, CF_2 *minor*), 125.6 (CH*), 125.5 (CH *minor*), 123.9 (d, J = 4.5 Hz, CH*), 123.8 (d, J = 4.3 Hz, CH *minor*), 90.8 (dd, J = 32.9, 21.6 Hz, C*), 90.2 (dd, J = 37.5, 25.0 Hz, C *minor*), 45.8 (dd, J = 23.3, 19.1 Hz, CH*), 44.1 (dd, J = 20.4, 20.4 Hz, CH *minor*), 35.3 (dd, J = 5.6, 5.6 Hz, CH_2*), 33.1 (d, J = 2.9 Hz, CH*), 32.6 (d, J = 6.1 Hz, CH *minor*), 32.1 (d, J = 2.5 Hz, CH_2 *minor*), 26.3 (dd, J = 3.3, 3.3 Hz, CH_2*), 24.3 (d, J = 8.1 Hz, CH_2 *minor*), 20.9 (2× CH_3 *minor*) ppm. ^{19}F NMR (376 MHz, $CDCl_3$, *major* isomer marked *): δ = –94.7 (dd, J = 238.6, 26.7 Hz, 1 F*), –122.6 (dd, J = 230.9, 27.4 Hz, 1 F *minor*), –123.7 (d, J = 238.6 Hz, 1 F*), –125.4 (d, J = 230.9 Hz, 1 F *minor*) ppm. MS: *m/z* (%) = 329 (67) $[M + H]^+$, 328 (54) $[M]^+$, 197 (21), 133 (15), 132 (100), 117 (15), 105 (66), 103 (18), 91 (8), 77 (28). HRMS (ESI-TOF): calcd. for $C_{20}H_{18}F_2O_2Na$ $[M + Na]^+$ 351.1173; found 351.1176.

2,2-Difluoro-3-(3-methoxybenzyl)-3′*H*-spiro[cyclopentane-1,1′-isobenzofuran]-3′-one (5h): According to general procedure F, radical cyclization of **3h** (635 mg, 1.5 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) gave a 1:1.6 mixture of diastereoisomers [determined by ^{19}F NMR spectroscopy (376 MHz)] of **5h** (489 mg, 85% yield) as a colorless liquid. FTIR (neat): $\tilde{\nu}$ = 1778, 1601, 1585, 1491, 1467, 1262, 1041, 987 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, *major* isomer marked *): δ = 7.88–7.77 (m, 2 H, 2× ArH *major* and *minor*), 7.68–7.58 (m, 2 H, 2× ArH *major* and *minor*), 7.57–7.45 (m, 4 H, 4× ArH *major* and *minor*), 7.20–7.02 (m, 2 H, 2× ArH *major* and *minor*), 6.80–6.61 (m, 6 H, 6× ArH *major* and *minor*), 3.72 (s, 6 H, 2× OCH_3 *major* and *minor*), 3.14–2.98 (m, 2 H, 2× ArH *major* and *minor*), 2.98–2.85 (m, 1 H, CH*), 2.85–2.64 (m, 2 H, CH*H** and CH *minor*), 2.60 (dd, J = 13.5, 10.3 Hz, 1 H, CH*H* *minor*), 2.46–2.32 (m, 1 H, CH*H* *minor*), 2.32–2.18 (m, 1 H, CH*H**), 2.14–1.81 (m, 5 H, 3× CH*H** and 2× CH*H* *minor*), 1.75–1.58 (m, 1 H, CH*H* *minor*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, *major* isomer marked *): δ = 168.6 (CO*), 168.5 (CO *minor*), 160.0 (2× C *major* and *minor*), 144.9 (C*), 144.7 (C *minor*), 140.6 (C*), 140.3 (C *minor*), 134.3 (CH *minor*), 134.2 (CH*), 130.1 (2× CH *major* and *minor*), 129.4 (2× CH *major* and *minor*), 127.1 (dd, J = 272.0, 249.0 Hz, CF_2*), 126.5 (dd, J = 270.0, 249.0 Hz, CF_2 *minor*), 126.9 (C *minor*), 126.7 (C*), 125.6 (CH*), 125.6 (CH *minor*), 124.0 (d, J = 5.0 Hz, CH*), 123.9 (d, J = 4.0 Hz, CH *minor*), 121.1 (CH*), 121.0 (CH *minor*), 114.5 (CH*), 114.2 (CH *minor*), 111.7 (2× CH *major* and *minor*), 90.3 (dd, J = 33.0, 22.0 Hz, C*), 90.1 (dd, J = 32.0, 22.0 Hz, C *minor*), 55.1 (2× OCH_3 *major* and *minor*), 45.6 (dd, J = 24.0, 19.0 Hz, CH*), 43.9 (dd, J = 20.0, 20.0 Hz, CH *minor*), 35.8 (dd, J = 6.0, 6.0 Hz, 2× CH *major* and *minor*), 33.1 (d, J = 4.0 Hz, CH*), 32.0 (d, J = 3.0 Hz, CH_2 *minor*), 26.3 (d, J = 3.0 Hz, CH_2*), 24.3 (d, J = 8.0 Hz, CH_2 *minor*) ppm. ^{19}F NMR (376 MHz, $CDCl_3$, *major* isomer marked *): δ = –94.6 (dd, J = 238.2, 27.1 Hz, 1 F*), –122.7 (dd, J = 230.0, 27.5 Hz, 1 F *minor*), –123.8 (d, J = 238.2 Hz, 1 F*), –125.6 (d, J = 230.0 Hz, 1 F *minor*) ppm. MS: *m/z* (%) = 345 (69) $[M + H]^+$, 344 (21) $[M]^+$, 287 (9), 178 (8), 149 (19), 148 (10), 123 (50), 91 (13) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{18}F_2O_3Na$ $[M + Na]^+$ 367.1122; found 367.1120.

2,2-Difluoro-3-methyl-3′*H*-spiro[cyclohexane-1,1′-isobenzofuran]-3′-one (5i): According to general procedure F, radical cyclization of **8a** (528 mg, 1.5 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) gave **5iA** (less polar; 184 mg, 48% yield) as a white solid [m.p. 104–105 °C (CH_2Cl_2/hexanes)] and **5iB** (more polar; 136 mg, 35% yield, which contains

1% of **5iA** as determined by ^{1}H NMR spectroscopy) as a white solid [m.p. 102–103 °C (CH_2Cl_2/hexanes)]. Compound **5iA**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1773, 1467, 1272, 1226, 1087, 1013, 960 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.6 Hz, 1 H, ArH), 7.72 (dd, J = 7.4, 7.4 Hz, 1 H, ArH), 7.66–7.54 (m, 2 H, 2× ArH), 2.54–2.35 (m, 1 H, CH), 2.34–2.20 (m, 1 H, C*H*H), 2.02–1.71 (m, 4 H, 4× C*H*H), 1.66–1.45 (m, 1 H, C*H*H), 1.11 (d, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1 (CO), 147.5 (C), 134.2 (CH), 130.0 (CH), 126.5 (C), 125.7 (CH), 123.5 (d, J = 5.0 Hz, CH), 121.4 (dd, J = 256.0, 244.0 Hz, CF_2), 85.5 (dd, J = 34.0, 34.0 Hz, C), 35.5 (dd, J = 21.4, 21.4 Hz, CH), 34.4 (d, J = 3.0 Hz, CH_2), 30.4 (d, J = 8.0 Hz, CH_2), 20.5 (CH_2), 12.2 (t, J = 4.0 Hz, CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –118.1 (d, J = 247.8 Hz, 1 F), –124.6 (dd, J = 247.8, 28.3 Hz, 1 F) ppm. MS: *m*/*z* (%) = 253 (68) [M + H]$^+$, 252 (63) [M]$^+$, 212 (10), 160 (15), 159 (100), 146 (53), 131 (31), 104 (10), 103 (19). HRMS (ESI-TOF): calcd. for $C_{14}H_{14}F_2O_2Na$ [M + Na]$^+$ 275.0860; found 275.0854. Compound **5iB**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1773, 1468, 1272, 1087, 1013, 960 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (d, J = 7.6 Hz, 1 H, ArH), 7.69 (ddd, J = 7.4, 7.4, 1.1 Hz, 1 H, ArH), 7.63 (ddd, J = 7.1, 0.9, 0.9 Hz, 1 H, ArH), 7.58 (ddd, J = 7.5, 1.0, 1.0 Hz, 1 H, ArH), 2.50–2.37 (m, 1 H, CH*H*), 2.20–2.09 (m, 1 H, CH*H*), 2.08–1.93 (m, 3 H, 3× CH*H*), 1.80–1.63 (m, 2 H, 2× CH*H*), 1.25 (d, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (CO), 147.8 (C), 134.0 (CH), 130.0 (CH), 126.6 (C), 125.8 (CH), 123.6 (d, J = 4.0 Hz, CH), 121.1 (dd, J = 257.3, 242.5 Hz, CF_2), 86.1 (dd, J = 31.0, 22.9 Hz, C), 36.4 (dd, J = 21.8, 21.8 Hz, CH), 34.7 (2× CH_2), 28.9 (d, J = 5.8 Hz, CH_2), 17.3 (CH_2), 12.9 (dd, J = 7.8, 3.4 Hz, CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –100.0 to –112.0 (br s, 1 F), –114.0 to –121.0 (br d, J = 205.7 Hz, 1 F) ppm. MS: *m*/*z* (%) = 253 (41) [M + H]$^+$, 252 (65) [M]$^+$, 160 (13), 159 (100), 146 (69), 131 (36), 105 (12), 103 (23), 77 (8). HRMS (ESI-TOF): calcd. for $C_{14}H_{14}F_2O_2Na$ [M + Na]$^+$ 275.0860; found 275.0865.

2,2-Difluoro-3-benzyl-3′*H*-spiro[cyclohexane-1,1′-isobenzofuran]-3′-one (5j): According to general procedure F, radical cyclization of **8b** (658 mg, 1.5 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) gave **5jA** (less polar; 335 mg, 68% yield) as a white solid [m.p. 107–108 °C (CH_2Cl_2/hexanes)] and **5jB** (more polar; 113 mg, 23% yield) as a white solid [m.p. 109–110 °C (CH_2Cl_2/hexanes)]. Compound **5jA**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1773, 1496, 1468, 1271, 1081, 1024, 1004, 967 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.7 Hz, 1 H, ArH), 7.72 (ddd, J = 7.5, 7.5, 1.0 Hz, 1 H, ArH), 7.63 (dd, J = 7.7, 2.4 Hz, 1 H, ArH), 7.60 (ddd, J = 7.5, 7.5, 0.8 Hz, 1 H, ArH), 7.35–7.28 (m, 2 H, 2× ArH), 7.26–7.18 (m, 3 H, 3× ArH), 3.19 (dd, J = 3.1, 2.9 Hz, 1 H, CH*H*), 2.65–2.46 (m, 1 H, CH*H*), 2.48 (dd, J = 13.3, 10.6 Hz, 1 H, CH*H*), 2.35–2.20 (m, 1 H, CH*H*), 1.93–1.84 (m, 1 H, CH*H*), 1.84–1.68 (m, 3 H, 3× CH*H*), 1.50–1.38 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (CO), 147.4 (C), 138.9 (C), 134.2 (CH), 130.1 (CH), 129.2 (2× CH), 128.4 (2× CH), 126.5 (C), 126.3 (CH), 125.7 (CH), 123.5 (d, J = 27.9 Hz, CH), 121.3 (dd, J = 256.6, 245.0 Hz, CF_2), 85.4 (dd, J = 33.0, 23.5 Hz, C), 42.4 (dd, J = 21.3, 19.8 Hz, CH), 34.6 (d, J = 3.6 Hz, CH_2), 33.1 (d, J = 5.8 Hz, CH_2), 27.1 (d, J = 6.9 Hz, CH_2), 20.3 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –117.5 (d, J = 247.6 Hz, 1 F), –122.0 (dd, J = 247.6, 27.8 Hz, 1 F) ppm. MS: *m*/*z* (%) = 329 (94) [M + H]$^+$, 328 (100) [M]$^+$, 310 (24), 308 (27), 270 (24), 199 (22), 172 (28), 169 (27), 159 (21), 147 (22), 91 (38). HRMS (ESI-TOF): calcd. for $C_{20}H_{18}F_2O_2Na$ [M + Na]$^+$ 351.1173; found 351.1178. Compound **5jB**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1773, 1496, 1468, 1270, 1081, 1025, 1004, 967 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (ddd, J = 8.4, 0.8, 0.8 Hz, 1 H, ArH), 7.72 (ddd, J = 7.6, 7.6, 1.1 Hz, 1 H, ArH), 7.65 (ddd, J = 7.6, 0.8, 0.8 Hz, 1 H, ArH), 7.61 (ddd, J = 7.5, 7.5, 0.2 Hz, 1 H, ArH), 7.35–7.28 (m, 2 H, 2× ArH), 7.25–7.18 (m, 3 H, 3× ArH), 3.11 (dd, J = 14.1, 3.3 Hz, 1 H, CH*H*), 3.00 (dd, J = 11.6, 11.6 Hz, 1 H, CH*H*), 2.60–2.45 (m, 1 H, CH), 2.28–2.15 (m, 1 H, CH*H*), 2.14–1.98 (m, 2 H, 2× CH*H*), 1.80–1.65 (m, 3 H, 3× CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (CO), 147.8 (C), 139.8 (C), 134.2 (CH), 130.1 (CH), 129.2 (2× CH), 128.5 (2× CH), 126.7 (C), 126.3 (CH), 125.9 (CH), 123.8 (d, J = 3.3 Hz, CH), 120.9 (dd, J = 258.4, 242.8 Hz, CF_2), 85.4 (dd, J = 31.9, 23.0 Hz, C), 43.9 (dd, J = 20.8, 20.8 Hz, CH), 34.8 (d, J = 2.6 Hz, CH_2), 32.5 (d, J = 5.0 Hz, CH_2), 24.7 (d, J = 5.0 Hz, CH_2), 17.1 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –100.0 to –109.0 (br s, 1 F), –114.0 to –119.0 (br d, J = 251.9 Hz, 1 F) ppm. MS: *m*/*z* (%) = 329 (50) [M + H]$^+$, 328 (100) [M]$^+$, 308 (21), 270 (13), 199 (16), 172 (18), 169 (16), 159 (18), 147 (19), 131 (14), 129 (16), 91 (30), 111 (9), 109 (4), 91 (100), 77 (16), 65 (28), 50 (11). $C_{20}H_{18}F_2O_2Na$ [M + Na]$^+$ 351.1173; found 351.1170.

2,2-Difluoro-3-(4-methylbenzyl)-3′*H*-spiro[cyclohexane-1,1′-isobenzofuran]-3′-one (5k): According to general procedure F, radical cyclization of **8c** (680 mg, 1.5 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) gave **5kA** (less polar; 323 mg, 63% yield) as a white solid [m.p. 106–107 °C (CH_2Cl_2/hexanes)] and **5kB** (more polar; 123 mg, 24% yield) as a white solid [m.p. 105–107 °C (CH_2Cl_2/hexanes)]. Compound **5kA**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1773, 1601, 1515, 1468, 1289, 1251, 1172, 1059, 975 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, J = 7.5 Hz, 1 H, ArH), 7.65–7.57 (m, 1 H, ArH), 7.56–7.44 (m, 2 H, 2× ArH), 7.06–6.95 (m, 4 H, 4× ArH), 3.05 (dd, J = 12.7, 2.1 Hz, 1 H, CH*H*), 2.54–2.29 (m, 2 H, CH, CH*H*), 2.28–2.06 (m, 4 H, CH_3, CH*H*), 1.83–1.53 (m, 4 H, 4× CH*H*), 1.41–1.24 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (CO), 147.3 (C), 135.7 (2× C), 134.2 (CH), 130.0 (CH), 129.1 (4× CH), 126.4 (C), 125.6 (CH), 123.5 (d, J = 4.0 Hz, CH), 121.3 (dd, J = 257.0, 245.0 Hz, CF_2), 85.4 (dd, J = 33.0, 23.0 Hz, C), 42.5 (dd, J = 20.0, 20.0 Hz, CH), 34.5 (d, J = 3.0 Hz, CH_2), 32.5 (CH_2), 27.0 (d, J = 7.0 Hz, CH_2), 21.3 (CH_3), 20.2 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –117.5 (d, J = 247.6 Hz, 1 F), –122.0 (dd, J = 247.6, 27.8 Hz, 1 F) ppm. MS: *m*/*z* (%) = 343 (34) [M + H]$^+$, 342 (95) [M]$^+$, 322 (56), 302 (19), 199 (20), 106 (24), 105 (100), 103 (22), 79 (15), 77 (21). HRMS (ESI-TOF): calcd. for $C_{21}H_{20}F_2O_2Na$ [M + Na]$^+$ 365.1329; found 365.1323. Compound **5kB**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1773, 1601, 1515, 1468, 1289, 1251, 1117, 1086, 1058, 975 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.7 Hz, 1 H, ArH), 7.71 (ddd, J = 7.8, 7.8, 1.0 Hz, 1 H, ArH), 7.67–7.55 (m, 2 H, 2× ArH), 7.16–7.05 (m, 4 H, 4× ArH), 3.06 (dd, J = 14.1, 3.2 Hz, 1 H, ArC*H*H), 2.95 (dd, J = 11.5, 11.5 Hz, 1 H, ArC*H*H), 2.57–2.42 (m, 1 H, CH), 2.33 (s, 3 H, CH_3), 2.26–2.14 (m, 1 H, C*H*H), 2.13–1.95 (m, 2 H, 2× C*H*H), 1.84–1.63 (m, 3 H, 3× C*H*H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0 (CO), 147.8 (C), 136.7 (C), 135.8 (C), 134.2 (CH), 130.1 (CH), 129.2 (2× CH), 129.1 (2× CH), 126.6 (C), 125.9 (CH), 123.7 (d, J = 4.0 Hz, CH), 121.0 (dd, J = 258.0, 243.0 Hz, CF_2), 86.0 (dd, J = 23.0, 23.0 Hz, C), 44.0 (dd, J = 21.0, 21.0 Hz, CH), 34.8 (CH_2), 32.0 (d, J = 4.0 Hz, CH_2), 24.7 (d, J = 4.0 Hz, CH_2), 21.0 (CH_3), 17.1 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –101.0 to –109 (br s, 1 F), –114.0 to –118.0 (br d, J = 251.9 Hz, 1 F) ppm. MS: *m*/*z* (%) = 343 (24) [M + H]$^+$, 342 (94) [M]$^+$, 322 (53), 199 (19), 106 (24), 105 (100), 77 (25). HRMS (ESI-TOF): calcd. for $C_{21}H_{20}F_2O_2Na$ [M + Na]$^+$ 365.1329; found 365.1329.

2,2-Difluoro-3-(3-methoxybenzyl)-3′*H*-spiro[cyclohexane-1,1′-isobenzofuran]-3′-one (5l): According to general procedure F, radical cyclization of **8d** (702 mg, 1.5 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes)

gave **5lA** (less polar; 344 mg, 64% yield) as a colorless viscous oil and **5lB** (more polar; 102 mg, 19% yield) as a colorless viscous oil. Compound **5lA**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1778, 1601, 1467, 1264, 1079, 1024, 1004, 965 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.6 Hz, 1 H, ArH), 7.72 (ddd, J = 7.6, 7.6, 1.5 Hz, 1 H, ArH), 7.63 (dd, J = 7.6, 2.3 Hz, 1 H, ArH), 7.60 (ddd, J = 7.7, 7.7, 0.7 Hz, 1 H, ArH), 7.23 (dd, J = 7.8, 7.8 Hz, 1 H, ArH), 6.83–6.70 (m, 3 H, 3× ArH), 3.82 (s, 3 H, OCH_3), 3.16 (dd, J = 13.3, 3.2 Hz, 1 H, CH*H*), 2.65–2.48 (m, 1 H, CH), 2.45 (dd, J = 13.2, 10.8 Hz, 1 H, CH*H*), 2.85–2.20 (m, 1 H, CH*H*), 1.93–1.84 (m, 1 H, C*HH*), 1.84–1.67 (m, 3 H, 3× CH*H*), 1.50–1.40 (m, 1 H, CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0 (CO), 159.7 (C), 147.4 (C), 140.5 (C), 134.2 (CH), 130.1 (CH), 129.4 (CH), 126.5 (C), 125.7 (CH), 123.5 (d, J = 3.8 Hz, CH), 121.7 (CH), 121.3 (dd, J = 256.5, 244.5 Hz, CF_2), 114.8 (CH), 111.8 (CH), 85.5 (dd, J = 33.1, 23.1 Hz, C), 55.2 (CH_3), 42.4 (dd, J = 19.8, 19.8 Hz, CH), 34.6 (d, J = 3.3 Hz, CH_2), 33.2 (dd, J = 3.1, 3.1 Hz, CH_2), 27.2 (d, J = 6.9 Hz, CH_2), 20.3 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –123.2 (dd, J = 231.0, 27.7 Hz, 1 F), –128.6 (dd, J = 231.0 Hz, 1 F) ppm. MS: m/z (%) = 359 (30) $[M + H]^+$, 358 (100) $[M]^+$, 199 (15), 122 (36), 91 (11). HRMS (ESI-TOF): calcd. for $C_{21}H_{20}F_2O_3Na$ $[M + Na]^+$ 381.1278; found 381.1279. Compound **5lB**: FTIR ($CHCl_3$): $\tilde{\nu}$ = 1779, 1601, 1585, 1489, 1467, 1264, 1079, 1004, 965 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.94 (ddd, J = 7.6, 0.9, 0.9 Hz, 1 H, ArH), 7.72 (ddd, J = 7.3, 7.3, 1.1 Hz, 1 H, ArH), 7.65 (ddd, J = 7.8, 0.9, 0.9 Hz, 1 H, ArH), 7.61 (ddd, J = 7.5, 0.9, 0.9 Hz, 1 H, ArH) 7.23 (dd, J = 7.8, 7.8 Hz, 1 H, ArH), 6.84–6.73 (m, 3 H, 3× ArH), 3.81 (s, 3 H, OCH_3), 3.09 (dd, J = 14.0, 3.1 Hz, 1 H, CH*H*), 2.98 (dd, J = 11.7, 11.7 Hz, 1 H, CH*H*), 2.63–2.45 (m, 1 H, CH), 2.30–2.13 (m, 1 H, C*HH*), 2.12–1.75 (m, 2 H, 2× C*HH*), 1.88–1.63 (m, 3 H, 3× C*HH*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9 (CO), 159.8 (C), 147.7 (C), 141.4 (C), 134.2 (CH), 130.1 (CH), 129.5 (CH), 126.6 (C), 125.9 (CH), 123.7 (d, J = 4.1 Hz, CH), 121.5 (CH), 120.9 (dd, J = 257.9, 242.9 Hz, CF_2), 115.0 (CH), 111.6 (CH), 85.4 (dd, J = 31.8, 23.0 Hz, C), 55.2 (CH_3), 43.7 (dd, J = 20.8, 20.8 Hz, CH), 34.8 (d, J = 2.0 Hz, CH_2), 32.5 (dd, J = 7.1, 2.9 Hz, CH_2), 24.8 (d, J = 4.6 Hz, CH_2), 17.0 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –100.0 to –109.0 (br s, 1 F), –114.0 to –118.0 (dd, J = 253.1 Hz, 1 F) ppm. MS: m/z (%) = 359 (29) $[M + H]^+$, 358 (100) $[M]^+$, 199 (14), 122 (44), 121 (11), 91 (11). HRMS (ESI-TOF): calcd. for $C_{21}H_{20}F_2O_3Na$ $[M + Na]^+$ 381.1278; found 381.1275.

Methyl 2-(2,2-Difluoro-3′-oxo-3′*H*-spiro[cyclohexane-1,1′-isobenzofuran]-3-yl)acetate (5m): According to general procedure F, radical cyclization of **8e** (629 mg, 1.5 mmol) and purification by column chromatography (SiO_2, 15% CH_2Cl_2 and 2% EtOAc in hexanes) gave a 1:3 mixture of diastereomers [determined by ^{19}F NMR spectroscopy (376 MHz)] of **5m** (428 mg, 92% yield) as a white solid, m.p. 109–110 °C (CH_2Cl_2/hexanes). FTIR ($CHCl_3$): $\tilde{\nu}$ = 1774, 1736, 1614, 1601, 1467, 1439, 1291, 1257, 1172, 1085, 1067, 978 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, *major* isomer marked *): δ = 7.95–7.85 (m, 2 H, 2× ArH *major* and *minor*), 7.75–7.68 (m, 2 H, 2× ArH *major* and *minor*), 7.68–7.55 (m, 4 H, 4× ArH *major* and *minor*), 3.70 (s, 6 H, 2× OCH_3 *major* and *minor*), 2.99–2.82 (m, 2 H, 2× CH *major* and *minor*), 2.81–2.71 (m, 3 H, CH*H major* and 2× CH*H minor*), 2.35–2.14 (m, 3 H, 2× CH*H major* and CH*H minor*), 2.11–1.80 (m, 6 H, 3× CH*H major* and 3× CH*H minor*), 1.80–1.71 (m, 3 H, CH*H major* and 2× CH*H minor*), 1.60–1.45 (m, 1 H, CH*H**) ppm.^{13}C NMR (125 MHz, $CDCl_3$, *major* isomer marked *): δ = 172.4 (CO *minor*), 171.8 (CO*), 168.7 (CO*), 168.6 (CO *minor*), 147.3 (C *minor*), 146.9 (C*), 134.2 (2× CH *major* and *minor*), 130.1 (2× CH *major* and *minor*), 126.4 (2× C *major* and *minor*), 125.8 (CH *minor*), 125.7 (d, J = 1.4 Hz, CH*), 123.6 (d, J = 3.6 Hz, CH *minor*), 123.4 (d, J = 4.3 Hz, CH*), 120.7 (dd, J = 256.5, 244.0 Hz, CF_2*), 120.3 (dd, J = 257.6, 243.0 Hz, CF_2 *minor*), 85.5 (dd, J = 31.9, 22.9 Hz, C *minor*), 84.9 (dd, J = 32.9, 23.0 Hz, C*), 51.8 (2× CH_3 *major* and *minor*), 38.1 (dd, J = 24.0, 20.3 Hz, CH *minor*), 37.7 (dd, J = 20.5, 20.5 Hz, CH*), 34.4 (d, J = 3.0 Hz, 2× CH_2 *major* and *minor*), 32.7 (CH_2*), 31.7 (d, J = 7.8 Hz, CH_2 *minor*), 28.1 (d, J = 6.8 Hz, CH_2*), 26.3 (d, J = 4.8 Hz, CH_2 *minor*), 20.1 (CH_2*), 17.0 (CH_2 *minor*) ppm. ^{19}F NMR (376 MHz, $CDCl_3$, *major* isomer marked *): δ = –104.0 to –110.0 (br s, 1 F *minor*), –115.0 to –117.5 (br d, J = 252.3 Hz, 1 F *minor*), –117.3 (d, J = 249.3 Hz, 1 F*), –121.6 (dd, J = 249.3, 31.2 Hz, 1 F*) ppm. MS: m/z (%) = 311 (20) $[M + H]^+$, 310 (100) $[M]^+$, 279 (25), 278 (54), 270 (27), 258 (22), 233 (21), 199 (24), 172 (40), 144 (17) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{16}H_{16}F_2O_4Na$ $[M + Na]^+$ 333.0914; found 333.0914.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for all reported compounds.

Acknowledgments

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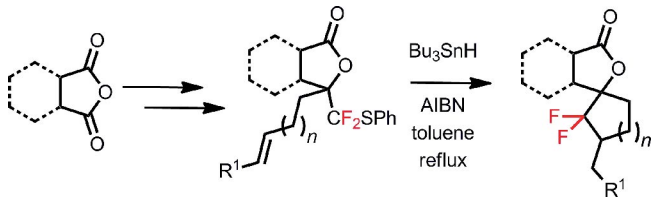
Organofluorine Compounds



$PhSCF_2TMS$ (TMS = trimethylsilyl) is utilized as a *gem*-difluoromethylenating agent for the synthesis of *gem*-difluoromethylenated spiro-γ-butyrolactones.

Keywords: Lactones / Difluoromethylenation / Cyclization / Fluorine

