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Fluoride-catalyzed nucleophilic addition of $PhSCF_2SiMe_3$ to anhydrides: synthesis of γ-difluoromethylated γ-lactams†

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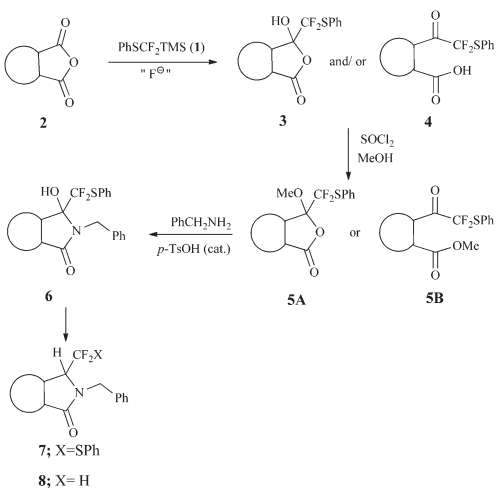
$PhSCF_2SiMe_3$ (**1**) underwent fluoride-catalyzed nucleophilic addition to the carbonyl group of anhydrides to provide the corresponding γ-difluoro(phenylsulfanyl)methyl γ-lactols, which were employed for the synthesis of γ-difluoromethylated γ-lactams.

Introduction

Organofluorines are important in pharmaceuticals, agrochemicals and materials, as they often enhance their chemical and metabolic stability, lipophilicity and binding selectivity.[1] As a consequence, the development of efficient methodology for the synthesis of organofluorine compounds has attracted considerable attention in organic synthesis.[2] Mostly, syntheses of organofluorines have involved the use of sulfur tetrafluoride,[3] diethylaminosulfur trifluoride (DAST),[4] Selectfluor,[5] *N*-fluoro-bis[(trifluoromethyl)sulfonyl]imide (NFSI),[6] and zinc difluoromethylsulfinate[7] as fluorinating agents. More recently, electrochemical fluorination,[8] electrophilic perfluoroalkylation[9] of organic compounds as well as palladium- and copper-catalyzed coupling reactions of nucleophilic fluorinated reagents[10] with aryl halides, vinyl halides, alkynes and terminal alkenes have been continuously reported.

First introduced by Prakash and co-workers as a nucleophilic (phenylsulfanyl)difluoromethylating agent,[11a–c] difluoro(phenylsulfanyl)trimethylsilane ($PhSCF_2SiMe_3$, **1**) was employed as a useful difluoromethyl and *gem*-difluoromethylene building block and its synthetic utilities were reported by several research groups. Fluoride-catalyzed nucleophilic addition of **1** with carbonyl compounds,[11] ketoesters,[12] imines,[13] alkyl iodides[14] and cyclic imides[15] has been demonstrated and the resulting adducts have been transformed into the corresponding difluoromethylated and *gem*-difluoromethylenated products. However, to the best of our knowledge, there are no reports on the fluoride-catalyzed nucleophilic addition of **1** to succinic anhydrides. As part of our efforts to demonstrate the synthetic utility of **1**, we report here for the first time fluoride-catalyzed nucleophilic addition of **1** to succinic anhydrides. It was anticipated that the resulting adducts **3** and/or **4** could be utilized for the synthesis of γ-difluoromethylated γ-lactams **8** by sequential esterification, lactamization, reductive cleavage of the hydroxyl group followed by reductive removal of the phenylsulfanyl group as summarized in Scheme 1. It should be emphasized that the γ-lactam moiety is an important subunit found in a number of biologically active natural products.[16] Additionally, a number of synthetic approaches toward the synthesis of the γ-lactam units and their synthons are still of great interest.[17]



Scheme 1

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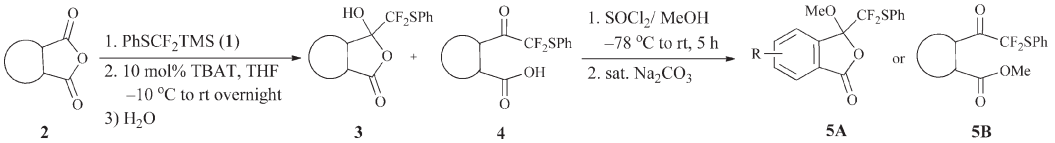
†Electronic supplementary information (ESI) available: Copies of ^1H, ^{13}C, and ^{19}F NMR of all compounds, and COSY-45, HMBC and HMQC of **3fA** and **3fB**. See DOI: 10.1039/c3ob27193e

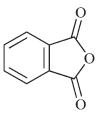
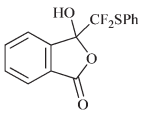
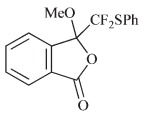
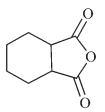
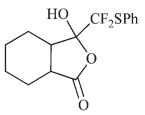
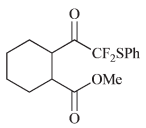
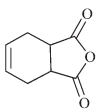
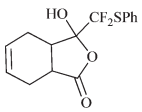
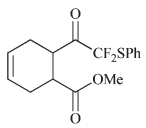
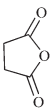
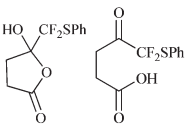
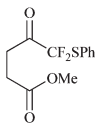
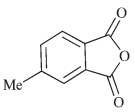
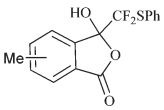
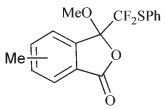
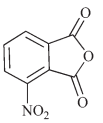
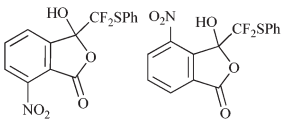
Results and discussion

At first, we examined the reaction conditions of the fluoride-catalyzed nucleophilic addition of **1** with phthalic anhydride (**2a**) as a model reaction. It was found that treatment of **1** (2 equiv.) with **2a** (1 equiv.) in THF in the presence of 10 mol% of TBAF (tetrabutylammonium fluoride) at −78 °C to room temperature overnight followed by quenching with H_2O gave the expected adduct **3a** in 56% yield. The best yield (91%) of **3a** was obtained when 10 mol% of TBAT (tetrabutylammonium triphenyldifluorosilicate) in THF was employed and the reaction was carried out at −10 °C to room temperature overnight (Table 1, entry 1). The reaction of **1** with **2b** using 10 mol% of TBAT provided good yields of the expected adduct **3b** as an inseparable 4 : 1 mixture of diastereomers after aqueous work-up. The reaction, however, afforded a mixture of **3b** and the corresponding ketoacid **4b** in 43% and 18% yields, respectively, after work-up with 1 M HCl. The formation of **4b** resulted from acid-catalyzed ring-opening of the lactol adduct **3b**. To get more insight into the generality of the fluoride-catalyzed nucleophilic addition of **1** to the carbonyl group of anhydrides, anhydrides **2c–f** were chosen as substrates. Under the standard conditions as for **2a**, **1** reacted smoothly with anhydride **2c** to give the desired adduct **3c** in 88% yield as an inseparable 12.6 : 3.4 : 1 mixture of three diastereomers as revealed by ^{19}F NMR. We proposed that the major isomers of compounds **3b** and **3c** arose from the fluoride-catalyzed nucleophilic attack on the carbonyl group of the anhydride from the less hindered

Table 1 Preparation of compounds **3**, **4** and **5**



2 **3** **4** **5A** **5B**

Entry	Anhydrides **2**	**3**[a] (yield)	**5**[a] (yield)
1	 **2a**	 **3a** (91%)	 **5Aa** (94%)
2	 **2b** (*cis*:*trans* = 19:1)[b]	 **3b** (88%, 4:1)[c]	 **5Bb** (97%, *cis*:*trans* = 8:1)[b,d]
3	 **2c** (*cis*:*trans* = 19:1)[b]	 **3c** (88%, 12.6:3.4:1)[c]	 **5Bc** (92%, *cis*:*trans* = 5.6:1)[b,d]
4	 **2d**	 **3d** and **4d** (85%, 1:7)[b,e]	 **5Bd** (91%)
5	 **2e**	 **3e** (77%, 1:1)[b]	 **5Ae** (94%, 1:1)[c]
6	 **2f**	 **3fA** (37%),[a] **3fB** (41%)[a]	—[f]

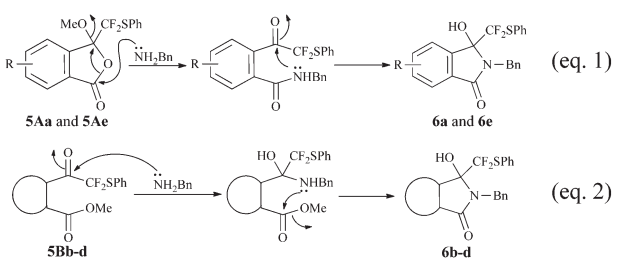
[a] Isolated yield. [b] The ratio was determined by ^1H NMR. [c] The ratio was determined by ^{19}F NMR. [d] Combined yield of the mixture of *cis*- and *trans*-isomers. [e] Combined yield of the mixture of products **3d** and **4d**. [f] The reaction was not performed.

exo-face. Low chemoselectivities for the addition of **1** to unsymmetrical anhydrides **2e** and **2f** were observed. As shown in Table 1 (entries 5–6), 1 : 1 ratios of isomers of the corresponding adducts **3e** and **3f** were obtained. The regioisomers **3fA** and **3fB** were separated by chromatography and their structures were established by COSY-45, HMQC and HMBC. Having established a general access to γ-(difluoro(phenylsulfanyl)-methyl)-γ-lactols **3**, we demonstrated that these compounds can be used as precursors for preparation of γ-difluoromethylated γ-lactams **8**. Thus, treatment of lactol **3a** with thionyl chloride in methanol at −78 °C to room temperature for 5 h afforded a good yield of the corresponding lactol ether **5Aa** in 94% yield.

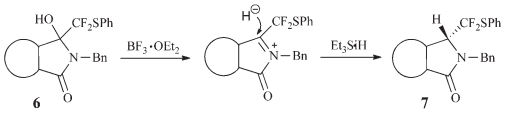
A similar result was obtained when a diastereomeric mixture of **3e** was employed leading to lactol ether **5Ae** as a 1 : 1 diastereomeric mixture (Table 1, entries 1and 5). The formation of lactol ether **5A** from **3a** and **3e** could be rationalized as the initial generation of the corresponding benzylic cation, followed by trapping by methanol. However, under similar reaction conditions, **3b**, **3c** and a mixture of **3d** and **4d** gave high yields (91–97%) of the corresponding ketoesters **5Bb**, **5Bc**, and **5Bd**, respectively (Table 1, entries 2–4). The formation of the ketoester **5B** resulted from acid-catalyzed ring-opening of **3b–d** to the corresponding ketoacid **4** followed by esterification. As shown in Table 1, the 8 : 1 and 5.6 : 1 mixtures of **5Bb** and **5Bc**, respectively, were obtained. The results could be explained by isomerization of the α-carbon next to the keto group of the expected *cis*-isomer of the ketoesters **5Bb** and **5Bc** partly occurring during work-up conditions to lead to their *trans*-isomers.

Next, we investigated a synthetic conversion of the lactol ethers **5A** and ketoesters **5B** to *N*-benzyl-γ-hydroxy-γ-lactams **6**, which was expected to be a precursor to for further transformation to the required γ-difluoromethylated γ-lactams **8** as shown in Scheme 2. Thus, the reaction of **5Aa** with benzylamine and a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in toluene under reflux overnight (15 h) led to the formation of **6a** in good yield (96%). Under similar reaction conditions, the 8 : 1 mixture of *cis*- and *trans*-isomers of **5Bb** afforded the corresponding lactam **6b** as a single isomer in 48% yield, together with the recovered starting material **5Bb** (52% yield). Unfortunately, the stereochemistry of **6b** could not be established by means of any spectroscopic methods. However, we thought that **6b** should possess *cis*-stereochemistry at the fused ring junction in order to allow the cyclization to take place. It is worth mentioning that the ^{1}H NMR patterns of the recovered **5Bb** are in good agreement with those of the starting *trans*-**5Bb**. This implied that the thermodynamically less stable *cis*-**5Bb** readily underwent isomerization to the more stable *trans*-**5Bb** under the reaction conditions (*p*-TsOH in refluxing $PhCH_3$). The *trans*-**5Bb** can react with benzylamine to yield the corresponding hemiaminal but it was unable to undergo cyclization. Upon aqueous work-up, the hemiaminal derived from the *trans*-**5Bb** underwent hydrolysis, leading to the recovery of *trans*-**5Bb**. Due to the low solubility of **5Bc** in toluene, the reaction of **5Bc** (5.6 : 1 mixture of *cis*- and *trans*-isomers) with benzylamine and a catalytic amount of *p*-TsOH was carried out in refluxing CH_2Cl_2 to give **6c** as a mixture of two separable isomers in 45% and 36% yields. Similarly to the case of **6b**, the two isomers of **6c** should have *cis*-stereochemistry at the fused ring junction. The difference should be derived from the stereochemistry at the carbinol carbon. Unfortunately, we were unable to precisely correlate each of the NMR spectra with the exact structures. In the case of **5Ae**, a 1 : 1 mixture of isomers of **6e** was obtained, as the reaction started from a 1 : 1 mixture of isomers of the ketoester **5Ae**. Compounds **6a** and **6e** resulted presumably from acid-catalyzed nucleophilic attack of benzylamine at the carboxyl group of **5Aa** and **5Ae** followed by intramolecular nucleophilic addition of the resulting ketoamides (Scheme 2, eqn (1)). The formation of **5Bb–5Bd** was explained by acid-catalyzed nucleophilic attack of benzylamine at the keto group of **5Bb–5Bd** followed by lactamization of the initially formed aminol adduct (Scheme 2, eqn (2)).

Our next task was to accomplish the preparation of γ-difluoromethylated γ-lactams **8** from γ-diflurorinated γ-hydroxy γ-lactams **6** by consecutive acid-catalyzed reduction reaction of compound **6** to **7** followed by reductive cleavage of the PhS–C bond of compound **7**.[12] Thus, compounds **6a–e** were transformed into the corresponding γ-(difluoro(phenylsulfanyl)methyl)-γ-lactams **7a–e** in good yields (83–96%) by reacting with Et_3SiH (10 equiv.) and $BF_3{\cdot}OEt_2$ (3 equiv.) in dry CH_2Cl_2 at −78 °C to room temperature overnight. The mechanism for the reduction of **6** to **7** could be rationalized by inital formation of an iminium ion intermediate **6A**, followed by hydride addition from the same side of the hydrogen atom at the ring-junction in order to avoid the steric interaction with the cyclohexane or cyclohexene ring to provide **7b** or **7c** as the sole stereoisomer (Scheme 3). Our proposed mechanism was further confirmed when a mixture of two diastereomers (1.3 : 1) of **6c** was subjected to the acid-catalyzed reduction reaction. Compound **7c** was isolated in 81% yield as a single isomer. Its ^{1}H NMR patterns are similar to those obtained when a major isomer of **6c** was employed as a starting material

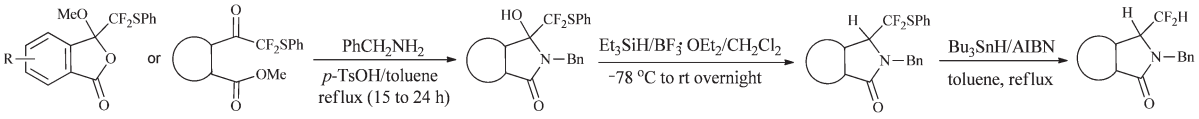


Scheme 2 Proposed mechanism for the formation of **6**.

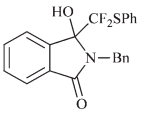
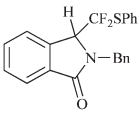
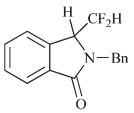
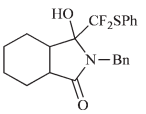
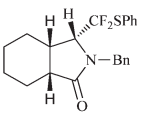
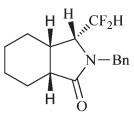
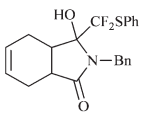
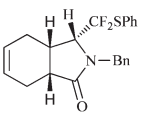
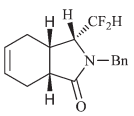
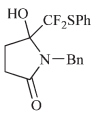
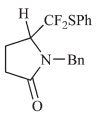
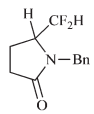
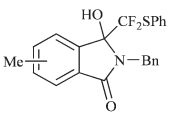
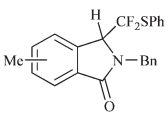
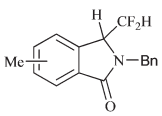


Scheme 3 Proposed mechanism for the reduction of 6.

Table 2 Preparation of compounds **6**, **7** and **8**



5A **5B** **6** **7** **8**

Entry	5	6[a] (yield)	7[a] (yield)	8[a] (yield)
1	**5Aa**	 **6a** (96%)	 **7a** (87%)	 **8a** (82%)
2	**5Bb** (*cis* : *trans* = 8 : 1)	 **6b** (48%)	 **7b** (83%)	 **8b** (98%)
3	**5Bc** (*cis* : *trans* = 5.6 : 1)	 **6c** (87%, *dr* = 1.3:1)[b,c]	 **7c** (88%)[e]	 **8c** (97%)
4	**5Bd**	 **6d** (56%)	 **7d** (96%)	 **8d** (69%)
5	**5Ae**	 **6e** (63%, 1:1)[d]	 **7e** (83%, 1:1)[d]	 **8e** (79%, 1:1)[d]

[a] Isolated yield. [b] The ratio was determined by ^{1}H NMR. [c] The reaction was carried out in CH_2Cl_2. [d] The ratios were determined by ^{19}F NMR. [e] The major diastereomer of **6c** was used.

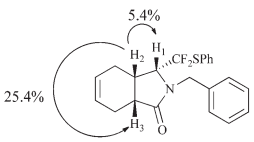


Fig. 1 Observed NOE of **7c**.

(Table 2, entry 3). The relative stereochemistry of **7c** as shown in entry 3 (Table 2) was confirmed by NOE experiments as depicted in Fig. 1. Similarly, we assumed therefore that the relative stereochemistry of **7b** is as shown in Table 2 (entry 2).

Finally, reductive cleavage of the phenylsulfanyl group of **7** to the required γ-difluoromethylated γ-lactams **8** was smoothly achieved by treatment of **7** with Bu_3SnH and a catalytic amount of AIBN in refluxing toluene. The results of our investigation are summarized in Table 2. γ-Difluoromethylated γ-lactams **8a–e** were obtained in 69–98% yields as listed in Table 2.

Conclusions

In summary, we have successfully demonstrated for the first time a fluoride-catalyzed nucleophilic addition of $PhSCF_2SiMe_3$ (**1**) to various anhydrides to afford γ-phenylsulfanyldifluoromethyl-γ-lactol derivatives, which were employed as the starting materials for the synthesis of γ-difluoromethylated γ-lactams. Thus, the research results provided a general entry to γ-difluoromethylated γ-lactams and described a synthetic application of $PhSCF_2SiMe_3$ as a difluoromethyl synthon.

Experimental

General

The ^{1}H NMR spectra were recorded on either a Bruker-300 (300 MHz) or a Bruker-500 (500 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on either a Bruker DPX-300 (75 MHz) or a Bruker-500 (125 MHz) spectrometer in $CDCl_3$ using

tetramethylsilane as an internal standard. The ^{19}F NMR spectra were recorded on a Bruker-500 (470 MHz) spectrometer and chemical shifts (δ) were measured with fluorotrichloromethane (δ = 0) as an internal standard. The IR spectra were recorded on either a Jasco A-302 or 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 on either a HR-TOF-MS Micromass model VQ-TOF2 or a Finnigan MAT 95 mass spectrometer. Melting points were recorded on a Büchi 501 melting point apparatus and are uncorrected. Tetrahydrofuran was distilled from sodium-benzophenone ketyl. Dichloromethane and toluene were distilled over calcium hydride and stored over activated molecular sieves (4 Å). Dry methanol was obtained by distilling over magnesium turnings. All glassware and syringes were oven-dried and kept in a desiccator before use. Preparative thin-layer chromatography (PLC) was performed by using Merck silica gel 60 PF_{254} (Art 7747). Column and flash column chromatography were performed by using Merck silica gel 60 (Art 7734 and 7736, respectively).

General procedure A for the preparation of compounds 3

3-(Difluoro(phenylsulfanyl)methyl)-3-hydroxyisobenzofuran-1(3*H*)-one (3a). To a solution of **1** (0.93 g, 4.0 mmol) in THF (3 mL) and phthalic anhydride (0.30 g, 2.0 mmol) at −10 °C was added a solution of 10 mol% TBAT (0.22 g, 0.4 mmol) in THF (2 mL). The reaction mixture was stirred at −10 °C (6 h) then quenched with water (3 mL) and extracted with AcOEt (3 × 15 mL). The combined organic phase was washed with water (10 mL), brine (10 mL) and dried (anh. Na_2SO_4). Purification of the crude product by flash column chromatography (SiO_2, 20% AcOEt in hexanes) gave **3a** as a white solid (0.56 g, 91% yield): m.p. 79–80 °C (CH_2Cl_2/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 7.96–7.92 (m, 1H, Ar*H*), 7.80–7.74 (m, 2H, Ar*H*), 7.74–7.68 (m, 1H, Ar*H*), 7.63–7.58 (m, 2H, Ar*H*), 7.50–7.45 (m, 1H, Ar*H*), 7.43–7.36 (m, 2H, Ar*H*), 4.75–4.50 (br, 1H, O*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8 (C), 143.0 (2 × C), 136.8 (CH), 134.9 (CH), 131.9 (CH), 130.3 (CH), 129.2 (2 × CH), 127.4 (C), 126.3 (t, J = 287.3 Hz, CF_2), 125.7 (2 × CH), 124.5 (CH), 102.9 (t, J = 30.4 Hz, C). ^{19}F NMR (470 MHz, $CDCl_3$): δ −87.1 (d, J = 213.4 Hz, 1F), −84.5 (d, J = 213.4 Hz, 1F). IR (KBr): ν_{max} 3120*br*, 1757*s*, 1276*m*, 945*s* cm^{-1}. MS: *m*/*z* (% relative intensity) 309 (M^+ + 1, 11), 308 (M^+, 7), 160 (38), 149 (100), 121 (22), 65 (17). HRMS (ESI-TOF) calcd $C_{15}H_{10}F_2O_3SNa$ $[M + Na]^+$: 331.0216; found: 331.0231.

3-(Difluoro(phenylsulfanyl)methyl)-3-hydroxy-hexahydroisobenzofuran-1(3*H*)-one (3b). According to the *general procedure A*, the reaction of **1** (0.93 g, 4.0 mmol) and hexahydrophthalic anhydride (0.31 g, 2.0 mmol) provided a white solid of **3b** (0.55 g, 88% yield) as a 4 : 1 mixture of isomers after flash column chromatrography (SiO_2, 20% AcOEt in hexanes): m.p. 90–97 °C (AcOEt/hexanes). ^1H NMR (500 MHz, $CDCl_3$, minor isomer marked*): δ 7.66–7.58 (m, 4H, Ar*H* of major and minor isomers), 7.50–7.46 (m, 6H, Ar*H* of major and minor isomers), 4.11 (br, 1H, O*H*), 3.40* (br, 1H, O*H*), 3.25* (t, J = 6.2 Hz, 1H, C*H*H), 2.98–2.88 (m, 2H, 2 × C*H*), 2.88–2.78* (m, 1H, C*H*H), 2.65* (dt, J = 5.5, 12.1 Hz, 2H, CH_2), 2.28–2.19* (m, 2H, CH_2), 2.19–2.10* (m, 2H, CH_2), 2.03–1.93 (m, 1H, C*H*H), 1.85–1.70 (m, 3H, 3 × C*H*H), 1.68–1.55 (m, 1H, CH*H*), 1.53–1.30 (m, 3H, 3 × CH*H*), 1.19–1.05* (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$, minor isomer marked*): δ 175.8* (C), 175.4 (C), 136.9* (2 × CH), 136.8 (2 × CH), 136.7* (CH), 130.4 (CH), 129.2 (2 × CH), 129.1* (2 × CH), 128.1 (t, J = 279.9 Hz, CF_2), 124.4 (C), 104.4 (dd, J = 28.4, 28.5 Hz, C), 43.9* (CH), 39.9 (CH), 39.0* (CH), 37.6 (CH), 24.2* (CH_2), 23.6 (CH_2), 23.2* (CH_2), 22.7 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 22.3* (CH_2), 22.1 (CH_2). Some peaks of the minor isomer could not be detected by ^{13}C NMR due to their low intensity. ^{19}F NMR (470 MHz, $CDCl_3$, minor isomer marked*): δ −87.2 (d, J = 212.7 Hz, 1F), −86.5 (d, J = 212.7 Hz, 1F), −85.1* (d, J = 215.0 Hz, 1F), −83.2* (d, J = 215.0 Hz, 1F). IR (KBr): ν_{max} 3381*s*, 1780*s*, 1260*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 314 (M^+, 2), 160 (43), 155 (75), 126 (21), 109 (74), 81 (100). HRMS (ESI-TOF) calcd $C_{15}H_{16}F_2O_3SNa$ $[M + Na]^+$: 337.0686; found: 337.0673.

3-(Difluoro(phenylsulfanyl)methyl-3-hydroxy-3a,4,7,7a-tetrahydroisobenzofuran-1(3*H*)-one (3c). According to the *general procedure A*, the reaction of **1** (0.93 g, 4.0 mmol) and *cis*-1,2,3,6-tetrahydrophthalic anhydride (0.30 g, 2.0 mmol, 19 : 1 *cis*-dominant) provided a 12.6 : 3.4 : 1 mixture of isomers of **3c** (0.55 g, 88% yield) as a white solid after flash column chromatography (SiO_2, 20% AcOEt in hexanes): m.p. 80–87 °C (AcOEt/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 7.60–7.50 (m, 4H, Ar*H* of major and minor isomers), 7.42–7.28 (m, 6H, Ar*H* of major and minor isomers), 6.00–5.38 (m, 2H, 2 × C*H* of major and minor isomers), 4.75–3.75 (br, 2H, O*H* of major and minor isomers), 3.50–2.80 (m, 4H, 2 × C*H* of major and minor isomers), 2.75–2.20 (m, 8H, 2 × CH_2 of major and minor isomer). ^{13}C NMR (125 MHz, $CDCl_3$,): δ 176.3 (C), 136.8 (2 × CH), 135.1 (C), 130.4 (CH), 129.2 (2 × CH), 127.9 (CH), 126.9 (CH), 125.4 (t, J = 314.6 Hz, CF_2), 124.4 (CH), 104.8 (C), 38.2 (CH), 36.3 (CH), 23.5 (CH_2), 20.7 (CH_2). Due to low intensity, the minor isomer could not be detected by ^{13}C NMR. ^{19}F NMR (470 MHz, $CDCl_3$): δ −88.1 (d, J = 212.7 Hz, 1F), −87.2 (d, J = 212.7 Hz, 1F), −84.4 (d, J = 214.8 Hz, 1F), −83.1 (d, J = 214.8 Hz, 1F), −82.0 (d, J = 222.1 Hz, 1F), −80.9 (d, J = 222.1 Hz, 1F). IR (KBr): ν_{max} 3447*br*, 1734*s*, 1698*s*, 1442*m*, 1385*m*, 1119*m*, 1036*w*, 943*w*, 751*w*, 691*w* cm^{-1}. MS: *m*/*z* (% relative intensity) 312 (M^+, 6), 293 (19), 273 (11), 160 (15), 153 (34), 126 (13), 97 (14), 79 (100), 76 (44), 51 (9). HRMS (ESI-TOF) calcd $C_{15}H_{14}F_2O_3SNa$ $[M + Na]^+$: 335.0529; found: 335.0545.

A mixture of 5-(difluoro(phenylsulfanyl)methyl)-5-hydroxydihydrofuran-2(3*H*)-one (3d) and 5,5-difluoro-4-oxo-5-(phenylsulfanyl)pentanoic acid (4d). According to the *general procedure A*, the reaction of **1** (0.93 g, 4.0 mmol) and succinic anhydride (0.20 g, 2.0 mmol) gave a 1 : 7 mixture of **3d** and **4d** (0.44 g, 85% yield) as colorless oil after flash column chromatography (SiO_2, 20% AcOEt in hexanes). ^1H NMR (300 MHz, $CDCl_3$, **3d** marked*): δ 8.39 (br, 1H, O*H*), 7.75–7.65 (m, 4H, Ar*H* of **3d** and **4d**), 7.65–7.32 (m, 6H, Ar*H* of **3d** and **4d**), 3.03 (t, J = 6.3 Hz, 2H, CH_2), 2.95–2.75* (m, 2H, CH_2), 2.68 (t, J = 6.3 Hz, 2H, CH_2), 2.41–2.30* (m, 2H, CH_2).^{13}C NMR (75 MHz, $CDCl_3$, **3d** marked*): δ 194.5 (t, J = 29.5 Hz, C), 177.4 (C), 174.8* (C),

136.7* (2 × CH), 136.4 (2 × CH), 130.5 (CH), 130.2* (CH), 129.3 (2 × CH), 129.1* (2 × CH), 124.4* (t, J = 266.1 Hz, CF_2), 124.3 (C), 124.2* (C), 122.2 (t, J = 287.5 Hz, CF_2), 105.0* (dt, J = 7.3, 29.1 Hz, C), 31.1 (CH_2), 29.0* (CH_2), 28.0* (CH_2), 26.8 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$, **3d** marked*): δ −85.4 (s, 2F), −88.4* (s, 2F). IR (neat): ν_{max} 3205*br*, 3064*br*, 2928*br*, 1739*s*, 1714*s*, 1442*m*, 1232*m*, 1176*m*, 1089*m*, 1066*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 260 (M^+, 14), 241 (6), 196 (4), 162 (5), 161 (11), 160 (100), 159 (23), 139 (6), 111 (5), 110 (23), 101 (60), 78 (5), 73 (21), 65 (13), 55 (40). HRMS (ESI-TOF) calcd $C_{11}H_{10}F_2O_3SNa$ $[M + Na]^+$: 283.0216; found: 283.0211.

A mixture of 3-(difluoro(phenylsulfanyl)methyl)-3-hydroxy-6-methylisobenzofuran-1(3*H*)-one and 3-(difluoro(phenylsulfanyl)methyl)-3-hydroxy-5-methylisobenzofuran-1(3*H*)-one (3e). According to the *general procedure A*, the reaction of **1** (0.93 g, 4.0 mmol) and 4-methylpthalic anhydride (0.33 g, 2.0 mmol) provided a 1 : 1 mixture of regioisomers of **3e** (0.52 g, 77%) as a white solid after flash column chromatography (SiO_2, 20% AcOEt in hexanes): m.p. 110–117 °C (AcOEt/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76–7.72 (m, 1H, Ar*H*), 7.66–7.16 (m, 2H, Ar*H*), 7.60 (m, 4H, Ar*H*), 7.55–7.50 (m, 2H, Ar*H*), 7.46–7.41 (m, 3H, Ar*H*), 7.39–7.33 (m, 4H, Ar*H*), 2.48 (s, 3H, CH_3), 2.47 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.7 (C), 167.6 (C), 146.6 (C), 143.7 (C), 142.5 (C), 140.6 (C), 136.7 (2 × CH), 136.7 (2 × CH), 135.9 (CH), 132.8 (CH), 130.1 (3 × CH), 129.0 (3 × CH), 127.3 (2 × C), 126.3 (t, J = 286.9 Hz, CF_2), 126.3 (t, J = 287.0 Hz, CF_2), 125.7 (CH), 125.4 (CH), 124.8 (CH), 124.7 (C), 124.5 (C), 124.1 (CH), 103.8 (t, J = 30.9 Hz, C), 103.4 (t, J = 30.3 Hz, C). 22.0 (CH_3), 21.3 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −85.5 (s, 4F). IR (KBr): ν_{max} 3379*br*, 3179*br*, 1758*s*, 1613*m*, 1475*m*, 1442*m*, 1281*m*, 1117*m*, 1094*m*, 1064*s*, 1041*s*, 948*s*, 780*m*, 758*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 322 (M^+, 2), 255 (4), 165 (7), 164 (12), 163 (100), 160 (17), 135 (11), 79 (5), 77 (18). HRMS (ESI-TOF) calcd $C_{16}H_{12}F_2O_3SNa$ $[M + Na]^+$: 345.03723; found: 345.0359.

3-(Difluoro(phenylsulfanyl)methyl)-3-hydroxy-7-nitroisobenzofuran-1(3*H*)-one (3fA) and 3-(difluoro(phenylsulfanyl)methyl)-3-hydroxy-4-nitroisobenzofuran-1(3*H*)-one (3fB). According to the *general procedure A*, the reaction of **1** (0.93 g, 4.0 mmol) and 3-nitrophthalic anhydride (0.39 g, 2.0 mmol) provided a pale yellow solid of **3fA** (0.26 g, 37% yield) and a yellow solid of **3fB** (0.29 g, 41% yield) after flash column chromatography (SiO_2, 40% AcOEt in hexanes). **3fA**: m.p. 149–150 °C. ^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD): δ 8.12 (dd, J = 1.0, 7.7 Hz, 1H, Ar*H*), 8.06 (dd, J = 0.6, 7.7 Hz, 1H, Ar*H*), 8.01 (t, J = 8.0 Hz, 1H, Ar*H*), 7.56–7.52 (m, 2H, Ar*H*), 7.48–7.42 (m, 1H, Ar*H*), 7.41–7.35 (m, 2H, Ar*H*). ^{13}C NMR (125 MHz, CD_3OD): δ 163.0 (C), 147.9 (C), 147.8 (C), 137.8 (2 × CH), 137.6 (CH), 131.4 (CH), 130.3 (2 × CH), 129.9 (CH), 127.7 (t, J = 285.8 Hz, CF_2), 127.7 (CH), 126.1 (C), 120.7 (C), 104.5 (C). ^{19}F NMR (470 MHz, CD_3OD): δ −89.1 (s, 2F). IR (KBr): ν_{max} 3429*br*, 1787*s*, 1617*w*, 1536*s*, 1474*w*, 1441*w*, 1360*s*, 1039*s*, 762*m*, 754*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 354 (M^+ + 1, 40), 194 (74), 178 (100), 159 (58), 148 (53), 139 (21), 120 (7), 110 (24), 104 (74), 92 (13), 77 (33), 76 (39), 63 (19). HRMS (ESI-TOF) calcd $C_{15}H_9F_2NO_5SNa$ $[M + Na]^+$: 376.0067; found: 376.0041. **3fB**: m.p. 170–171 °C (CH_2Cl_2/hexanes). ^{1}H NMR (500 MHz, CD_3OD): δ 8.29 (dd, J = 0.8, 8.0 Hz, 1H, Ar*H*), 8.24 (dd, J = 0.9, 7.6 Hz, 1H, Ar*H*), 7.97 (t, J = 7.9 Hz, 1H, Ar*H*), 7.53–7.48 (m, 2H, Ar*H*), 7.47–7.42 (m, 1H, Ar*H*), 7.39–7.33 (m, 2H, Ar*H*). ^{13}C NMR (125 MHz, CD_3OD): δ 166.3 (C), 148.6 (C), 137.9 (2 × CH), 136.1 (C), 135.0 (CH), 132.4 (C), 131.5 (CH), 131.4 (CH), 131.1 (CH), 130.2 (2 × CH), 128.3 (t, J = 285.6 Hz, CF_2), 126.0 (C), 100.0 (C). ^{19}F NMR (470 MHz, CD_3OD): δ −84.2 (d, J = 211.3 Hz, 1F), −85.1 (d, J = 211.3 Hz, 1F). IR (KBr): ν_{max} 3427*br*, 1796*s*, 1535*s*, 1471*m*, 1441*m*, 1361*s*, 765*m*, 777*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 353 (M^+, 3), 196 (15), 194 (100), 178 (60), 177 (8), 159 (99), 150 (28), 148 (19), 125 (8), 110 (38), 104 (59), 78 (12), 77 (51), 76 (30), 75 (21), 63 (17). HRMS (ESI-TOF) calcd $C_{15}H_9F_2O_5NSNa$ $[M + Na]^+$: 376.0067; found: 376.0020.

General procedure B for the preparation of compounds 5

3-(Difluoro(phenylsulfanyl)methyl)-3-methoxyisobenzofuran-1(3*H*)-one (5Aa). To a solution of **3a** (32 mg, 0.1 mmol) in dry MeOH (2 mL) was slowly added $SOCl_2$ (0.02 mL, 0.3 mmol) under an argon atmosphere. The reaction mixture was stirred at −78 °C followed by slowly warming up to room temperature for 5 h. The reaction was quenched with sat. Na_2CO_3 (1 mL) at 0 °C and then methanol was removed under *vacuo*. The aqueous layer was extracted with AcOEt (3 × 3 mL). The combined organic phase was washed with water, brine and dried (anh. Na_2SO_4). The crude was purified by column chromatography (SiO_2, 10% AcOEt in hexanes) to afford a colorless oil of **5Aa** (30 mg, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 7.7 Hz, 1H, Ar*H*), 7.73–7.57 (m, 3H, Ar*H*), 7.56–7.51 (m, 2H, Ar*H*), 7.37–7.33 (m, 1H, Ar*H*), 7.31–7.25 (m, 2H, Ar*H*), 3.16 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5 (C), 140.8 (C), 137.0 (2 × C), 134.7 (CH), 132.0 (CH), 130.1 (CH), 129.0 (2 × CH), 128.6 (C), 126.4 (t, J = 285.6 Hz, CF_2), 125.9 (CH), 125.0 (C), 124.9 (CH), 106.9 (t, J = 30.2 Hz, C), 52.0 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −84.7 (d, J = 213.1 Hz, 1F), −83.8 (d, J = 213.1 Hz, 1F). IR (neat): ν_{max} 1782*s*, 1588*m*, 1563*m*, 1475*m*, 1442*m*, 1387*s*, 1277*m*, 751*s*, 692*s* cm^{-1}. MS: *m*/*z* (% relative intensity) 322 (M^+, trace), 160 (30), 149 (100), 121 (13), 109 (6), 93 (7), 77 (6), 65 (15), 51 (7). HRMS (ESI-TOF) calcd. $C_{16}H_{12}F_2O_3SNa$ $[M + Na]^+$: 345.0373; found: 345.0380.

Methyl 2-(2,2-difluoro-2-(phenylsulfanyl)acetyl)cyclo hexane carboxylate (5Bb). According to the *general procedure B*, the reaction of a 4 : 1 mixture of **3b** (0.19 g, 0.6 mmol) with $SOCl_2$ (0.14 mL, 1.8 mmol) provided a 8 : 1 mixture of *cis*- and *trans*-isomers of **5Bb** (0.19 g, 97% yield) as a colorless oil after column chromatography (SiO_2, 10% AcOEt in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$, minor isomer marked*): δ 7.64 (d, J = 7.1 Hz, 4H, Ar*H* of major and minor isomers), 7.51–7.45 (m, 2H, Ar*H* of major and minor isomers), 7.44–7.38 (m, 4H, Ar*H* of major and minor isomers), 3.68 (s, 6H, CH_3 of major and minor isomers), 3.68–3.63* (m, 1H, C*H*), 3.44–3.39 (m, 1H, C*H*), 3.00–2.90* (m, 1H, C*H*), 2.89–2.83 (m, 1H, C*H*), 2.25–2.03 (m, 4H, CH_2 of major and minor isomers), 2.00–1.65 (m, 6H, 3 × CH*H* of major and minor isomers), 1.58–1.30 (m, 6H, 3 × C*H*H of major and minor isomers). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.3 (t, J = 27.2 Hz, C), 173.5 (C), 136.7 (2 × CH), 130.3 (CH),

129.1 (2 × CH), 125.0 (C), 123.1 (t, J = 291.5 Hz, CF_2), 51.8 (CH_3), 43.6 (CH), 43.0 (CH), 25.9 (CH_2), 25.7 (CH_2), 23.8 (CH_2), 22.6 (CH_2). Due to low intensity, the minor isomer could not be detected by ^{13}C NMR. ^{19}F NMR (470 MHz, $CDCl_3$, minor isomer marked*): δ −81.8 (d, J = 217.6 Hz, 1F), −81.8* (d, J = 212.8 Hz, 1F), −81.2 (d, J = 217.6 Hz, 1F), −79.5* (d, J = 212.8 Hz, 1F). IR (neat): ν_{max} 1798*w*, 1736*s*, 1475*w*, 1442*m*, 1199*m*, 1180*m*, 1040*m*, 1017*m*, 921*m*, 751*m*, 691*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 328 (M^+, 5), 310 (10), 309 (55), 297 (4), 277 (10), 170 (9), 169 (84), 141 (22), 110 (8), 109 (49), 81 (100), 80 (31), 77 (13). HRMS (ESI-TOF) calcd $C_{16}H_{18}F_2O_3SNa$ $[M + Na]^+$: 351.0842; found: 351.0840.

Methyl 6-(2,2-difluoro-2-(phenylsulfanyl)acetyl)cyclohex-3-enecarboxylate (5Bc). According to the *general procedure B*, the reaction of a 12.6 : 3.4 : 1 mixture of **3c** (0.31 g, 1.0 mmol) with $SOCl_2$ (0.20 mL, 3 mmol) provided 5.6 : 1 mixture of *cis*- and *trans*-isomers of **5Bc** (0.30 g, 92% yield) as a colorless oil after column chromatography (SiO_2, 10% AcOEt in hexanes). ^1H NMR (500 MHz, $CDCl_3$, minor isomer marked*): δ 7.68–7.61 (m, 4H, Ar*H* of major and minor isomers), 7.51–7.46 (m, 2H, Ar*H* of major and minor isomers), 7.44–7.38 (m, 4H, Ar*H* of major and minor isomers), 5.80–5.65 (m, 4H, 2 × C*H* of major and minor isomers), 3.70 (s, 3H, OCH_3), 3.69* (s, 3H, OCH_3), 3.51* (d, J = 2.4, 5.8 Hz, 1H, C*H*), 3.46 (dt, J = 5.2, 11.2 Hz, 1H, C*H*), 3.13* (dt, J = 2.5, 5.8 Hz, 1H, C*H*), 3.02 (dt, J = 5.7, 11.2 Hz, 1H, C*H*), 2.74–2.64* (m, 2H, CH_2), 2.63–2.50 (m, 2H, CH_2), 2.48–2.38* (m, 2H, CH_2), 2.29–2.18 (m, 1H, C*H*H), 2.15–2.04 (m, 1H, CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$, minor isomer marked*): δ 199.0 (t, J = 28.4 Hz, C), 196.2* (t, J = 27.6 Hz, C), 174.3 (C), 173.1* (C), 136.7 (2 × CH), 135.0* (C), 130.4* (CH), 130.3* (2 × CH), 129.2 (2 × CH of major and minor isomers), 127.9 (C), 125.5* (CH), 125.0 (2 × CH), 124.8 (C), 124.5 (2 × CH), 123.7* (CH), 123.0* (dd, J = 287.4, 289.7 Hz, CF_2), 122.7 (dd, J = 290.4, 292.4 Hz, CF_2), 52.1 (CH_3), 51.9* (CH_3), 42.2 (CH), 41.2 (CH), 41.1* (CH), 39.5* (CH), 28.7 (CH_2), 27.8 (CH_2), 26.0* (CH_2), 24.7* (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$, minor isomer marked*): δ −83.2 (d, J = 217.8 Hz, 1F), −82.6 (d, J = 217.8 Hz, 1F), −82.2* (d, J = 218.6 Hz, 1F), −81.1* (d, J = 218.6 Hz, 1F). IR ($CHCl_3$): ν_{max} 1796*s*, 1733*s*, 1562*w*, 1475*m*, 1442*m*, 1398*m*, 1101*m*, 1042*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 325 ($M^+ - 1$, 8), 281 (12), 256 (23), 227 (13), 213 (17), 199 (17), 179 (23), 178 (70), 161 (36), 149 (100), 125 (49), 111 (41), 97 (65), 79 (94), 69 (87), 55 (89). HRMS (ESI-TOF) calcd $C_{16}H_{16}F_2O_3SNa$ $[M + Na]^+$: 349.0685; found: 349.0684.

Methyl 5,5-difluoro-4-oxo-5-(phenylsulfanyl)pentanoate (5Bd). According to the *general procedure B*, the reaction of a 1 : 7 mixture of **3d** and **4d** (0.26 g, 1.0 mmol) with $SOCl_2$ (0.20 mL, 3.0 mmol) gave a pale yellow oil of **5Bd** (0.25 g, 91% yield) after column chromatography (SiO_2, 10% AcOEt in hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 7.1 Hz, 2H, Ar*H*), 7.62–7.47 (m, 1H, Ar*H*), 7.44–7.40 (m, 2H. Ar*H*), 3.72 (s, 3H, OCH_3), 3.04 (t, J = 6.6 Hz, 2H, CH_2), 2.65 (t, J = 6.6 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.7 (t, J = 29.1 Hz, C), 172.1 (C), 136.7 (2 × CH), 130.5 (CH), 129.3 (2 × CH), 124.4 (d, J = 2.1 Hz, C), 122.3 (t, J = 288.9 Hz, CF_2), 51.9 (CH_3), 31.5 (CH_2), 27.0 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −85.3 (s, 2F). IR (neat): ν_{max} 1741*s*, 1475*w*, 1441*m*, 1217*m*, 1172*m*, 1102*m*, 1069*m*, 752*m*, 691*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 275 ($M^+ + 1$, trace), 274 (M^+, 6), 255 (16), 181 (7), 175 (13), 159 (15), 147 (9), 116 (7), 115 (100), 109 (14), 87 (34), 77 (14), 65 (8), 59 (11), 55 (39). HRMS (ESI-TOF) calcd $C_{12}H_{12}F_2O_3SNa$ $[M + Na]^+$: 297.0372; found: 297.0418.

A mixture of 3-(difluoro(phenylthio)methyl)-3-methoxy-5-methylisobenzofuran-1(3*H*)-one and 3-(difluoro(phenylthio)methyl)-3-methoxy-6-methylisobenzofuran-1(3*H*)-one (5Ae). According to the *general procedure B*, the reaction of a 1 : 1 mixture of **3e** (0.34 g, 1.0 mmol) with $SOCl_2$ (0.20 mL, 3.0 mmol) gave a colorless oil of **5Ae** (0.33 g, 94% yield) as a 1 : 1 mixture of isomers. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, J = 8.3 Hz, 1H, Ar*H*), 7.66 (s, 1H, Ar*H*), 7.58–7.44 (m, 6H, Ar*H*), 7.43–7.21 (m, 8H, Ar*H*), 3.14 (s, 3H, OCH_3), 3.13 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7 (C), 166.6 (C), 146.4 (2 × C), 142.8 (2 × C), 141.2 (C), 137.9 (C), 136.9 (4 × CH), 135.8 (CH), 133.1 (CH), 130.0 (2 × CH), 128.9 (4 × CH), 126.4 (t, J = 285.7 Hz, CF_2), 126.0 (C), 125.9 (C and CH), 125.6 (CH), 125.1 (d, J = 2.2 Hz, CH), 124.9 (t, J = 283.7 Hz, CF_2) 124.6 (d, J = 2.1 Hz, CH), 106.8 (t, J = 30.2 Hz, C), 106.5 (t, J = 30.2 Hz, C), 51.9 (CH_3), 51.8 (CH_3), 22.1 (CH_3), 21.4 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −84.9 (d, J = 212.9 Hz, 2F), −84.8 (d, J = 212.9 Hz, 1F), −84.0 (d, J = 212.9 Hz, 1F). IR ($CHCl_3$): ν_{max} 1787*s*, 1709*w*, 1615*w*, 1475*w*, 1442*w*, 1286*m*, 1164*w*, 1140*w*, 1114*m*, 991*m*, 948*m*, 909*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 337 ($M^+ + 1$, 4), 317 (5), 305 (9), 191 (4), 178 (9), 177 (100), 147 (4), 91 (5). HRMS (ESI-TOF) calcd. $C_{17}H_{14}F_2O_3SNa$ $[M + Na]^+$: 359.0529; found: 359.0530.

General procedure C for the preparation of compounds 6

2-Benzyl-3-(difluoro(phenylsulfanyl)methyl)-3-hydroxyisoindolin-1-one (6a). A mixture of **5Aa** (65 mg, 0.2 mmol), benzylamine (43 mg, 0.4 mmol) and a catalytic amount of *p*-TsOH in toluene (4 mL) was heated at reflux for 15 h. The reaction mixture was diluted with AcOEt (10 mL) and washed with water (3 × 10 mL), brine (10 mL) and dried (anh. Na_2SO_4). Purification of the crude product by column chromatography (SiO_2, 20% AcOEt in hexanes) gave **6a** (72 mg, 96% yield) as a white needle: m.p. 143–144 °C (CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ 7.86–7.83 (m, 1H, Ar*H*), 7.72–7.68 (m, 1H, Ar*H*), 7.60–7.58 (m, 2H, Ar*H*), 7.35–7.25 (m, 3H, Ar*H*), 7.20–7.10 (m, 7H, Ar*H*), 4.95 (d, J = 15.6 Hz, 1H, C*H*H), 4.45 (d, J = 15.6 Hz, 1H, CH*H*), 3.85 (br, 1H, O*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.3 (C), 141.9 (C), 137.5 (2 × C), 136.7 (2 × CH), 132.8 (CH), 131.5 (C), 131.0 (2 × CH), 130.1 (CH), 129.2 (t, J = 187.5 Hz, CF_2), 129.0 (2 × CH), 128.5 (3 × CH), 127.4 (CH), 124.2 (CH), 123.8 (CH), 91.2 (t, J = 25.0 Hz, C), 43.5 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −81.6 (d, J = 211.0 Hz, 1F), −80.5 (d, J = 211.0 Hz, 1F). IR (nujol): ν_{max} 3207*br*, 1682*s*, 1471*s*, 1456*s*, 1455*m*, 1163*s*, 770*s* cm^{-1}. MS: *m*/*z* (% relative intensity) 398 (M^+, 10), 380 (7), 250 (6), 238 (47), 161 (11), 160 (100), 91 (20), 65 (7). HRMS (ESI-TOF) calcd. $C_{22}H_{17}F_2NO_2SNa$ $[M + Na]^+$: 420.0846; found: 420.0851.

2-Benzyl-3-(difluoro(phenylsulanyl)methyl)-3-hydroxyoctahydro-1*H*-isoindol-1-one (6b). According to the *general procedure*

C, the reaction of a 8 : 1 mixture of **5Bb** (82 mg, 0.25 mmol), and benzylamine (54 mg, 0.5 mmol) gave a single isomer of **6b** (48 mg, 48% yield) as a white needle after column chromatography (SiO_2, 20% AcOEt in hexanes): m.p. 171–172 °C (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69–7.60 (m, 2H, Ar*H*), 7.52–7.46 (m, 1H, Ar*H*), 7.45–7.37 (m, 4H, Ar*H*), 7.36–7.31 (m, 2H, Ar*H*), 7.31–7.25 (m, 1H, Ar*H*), 5.04 (d, J = 15.4 Hz, 1H, C*H*H), 4.38 (d, J = 15.4 Hz, 1H, CH*H*), 2.97–2.85 (m, 2H, CH_2), 2.71 (d, J = 6.6 Hz, 1H, O*H*), 2.24–2.15 (m, 1H, C*H*), 1.80–1.69 (m, 2H, CH_2), 1.69–1.53 (m, 2H, CH_2), 1.32–1.07 (m, 3H, CH_2 and C*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.3 (C), 138.6 (C), 136.7 (2 × CH), 130.7 (dd, J = 286.5, 289.9 Hz, CF_2), 130.2 (CH), 129.1 (2 × CH), 128.6 (2 × CH), 128.0 (2 × CH), 127.3 (CH), 125.1 (C), 93.4 (dd, J = 22.8, 26.3 Hz, C), 44.0 (d, J = 3.3 Hz, CH_2), 39.5 (d, J = 3.6 Hz, CH), 39.4 (CH), 23.3 (CH_2), 23.1 (CH_2), 22.9 (CH_2), 22.5 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −83.6 (d, J = 208.7 Hz, 1F), −81.4 (d, J = 208.7 Hz, 1F). IR (KBr): ν_{max} 3171*br*, 1686*s*, 1448*m*, 1385*w*, 1360*w*, 1171*m*, 1141*w*, 1045*m*, 781*w*, 750*m*, 703*w*, 691*w* cm^{-1}. MS: *m*/*z* (% relative intensity) 404 (M^+ + 1, 1), 334 (2), 278 (5), 245 (17), 244 (100), 167 (12), 166 (97), 138 (16), 109 (9), 95 (42), 91 (75), 65 (14). HRMS (ESI-TOF) calcd. $C_{22}H_{23}F_2NO_2SNa$ $[M + Na]^+$: 426.1315; found: 426.1317.

2-Benzyl-3-(difluoro(phenylsulfanyl)methyl)-3-hydroxy-2,3,3*a*,4,7,7*a*-hexahydro-1*H*-isoindol-1-one (6c). According to the *general procedure C*, the reaction of a 5.6 : 1 mixture of **5Bc** (0.33 g, 1.0 mmol) and benzylamine (0.14 g, 1.3 mmol) gave a mixture of isomers of **6c** (0.35 g, 87% yield) as a white solid after purification by column chromatography (SiO_2, 50% AcOEt in hexanes). Separation of the mixture of **6c** was achieved by preparative thin-layer chromatography (SiO_2, 30% AcOEt in hexanes × 2) to give **6cA** (more polar, 0.18 g, 45%, m.p. 164–165 °C) and **6cB** (less polar, 0.15 g, 37%, m.p. 170–171 °C). **6cA**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52–7.44 (m, 2H, Ar*H*), 7.44–7.33 (m, 1H, Ar*H*), 7.33–7.26 (m, 4H, Ar*H*), 7.26–7.11 (m, 3H, Ar*H*), 5.76–5.61 (m, 2H, 2 × C*H*), 4.47 (d, J = 15.7 Hz, 1H, C*H*H), 4.37 (d, J = 15.7 Hz, 1H, CH*H*), 3.34 (br, 1H, O*H*), 2.68 (dt, J = 5.5, 12.3 Hz, 1H, C*H*H), 2.60–2.37 (m, 3H, 3 × CH*H*), 2.23–2.11 (m, 1H, C*H*), 2.11–2.00 (m, 1H, C*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5 (C), 138.2 (C), 136.8 (2 × CH), 130.3 (CH), 129.4 (t, J = 286.1 Hz, CF_2), 129.2 (2 × CH), 128.4 (2 × CH), 128.0 (2 × CH), 127.2 (CH), 126.9 (CH), 126.1 (CH), 124.6 (C), 92.6 (t, J = 25.1 Hz, C), 49.6 (CH), 43.8 (CH_2), 41.2 (CH), 27.2 (CH_2), 26.8 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −79.5 (d, J = 213.6 Hz, 1F), −79.0 (d, J = 213.6 Hz, 1F). IR (KBr): ν_{max} 1683*s*, 1442*m*, 1412*m*, 1385*m*, 1065*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 402 (M^+ + 1, 9), 276 (6), 243 (17), 242 (100), 166 (3), 164 (54), 106 (8), 93 (22), 91 (60), 79 (16), 77 (12). HRMS (ESI-TOF) calcd $C_{22}H_{21}F_2NO_2SNa$ $[M + Na]^+$: 424.1158; found: 424.1179. **6cB**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62–7.50 (m, 2H, Ar*H*), 7.46–7.39 (m, 1H, Ar*H*), 7.39–7.27 (m, 2H, Ar*H*), 7.27–7.15 (m, 5H, Ar*H*), 5.76–5.65 (m, 2H, 2 × C*H*), 5.21 (d, J = 15.5 Hz, 1H, C*H*H), 4.25 (d, J = 15.5 Hz, 1H, CH*H*), 2.58–2.47 (m, 3H, 2 × C*H* and O*H*), 2.41–2.30 (m, 1H, C*H*H), 2.30–2.21 (m, 2H, CH_2), 2.20–2.08 (m, 1H, CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.8 (C), 137.8 (C), 136.8 (2 × CH), 130.3 (CH), 129.8 (t, J = 285.4 Hz, CF_2), 129.2 (2 × CH), 128.9 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 127.0 (CH), 125.9 (CH), 124.7 (C), 92.4 (dd, J = 23.6, 27.8 Hz, C), 44.0 (CH_2), 42.7 (CH), 40.3 (CH), 25.5 (CH_2), 25.4 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −81.4 (d, J = 213.9 Hz, 1F), −80.8 (d, J = 213.9 Hz, 1F). IR (KBr): ν_{max} 3219*br*, 1683*s*, 1499*m*, 1474*m*, 1443*s*, 1413*s*, 1349*m*, 1297*m*, 1212*m*, 1183*s*, 1076*s*, 1046*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 402 (M^+ + 1, 3), 276 (5), 243 (18), 242 (100), 165 (9), 164 (57), 106 (6), 93 (16), 91 (53), 79 (15), 77 (17), 65(12). HRMS (ESI-TOF) calcd. $C_{22}H_{21}F_2NO_2SNa$ $[M + Na]^+$: 424.1158; found: 424.1164.

1-Benzyl-5-(difluoro(phenylsulfanyl)methyl)-5-hydroxypyrrolidin-2-one (6d). According to the *general procedure C*, the reaction of **5Bd** (55 mg, 0.2 mmol) and benzylamine (43 mg, 0.4 mmol) gave **6d** (39 mg, 56% yield) as a white needle after purification by column chromatography (SiO_2, 20% AcOEt in hexanes): m.p. 130–131 °C (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, J = 7.4 Hz, 2H, Ar*H*), 7.51–7.45 (m, 1H, Ar*H*), 7.44–7.39 (m, 2H, Ar*H*), 7.39–7.35 (m, 2H, Ar*H*), 7.35–7.30 (m, 2H, Ar*H*), 7.30–7.24 (m, 1H, Ar*H*), 4.95 (d, J = 15.5 Hz, 1H, C*H*H), 4.41 (d, J = 15.5 Hz, 1H, CH*H*), 3.82 (br, 1H, O*H*), 2.79–2.68 (m, 1H, C*H*H), 2.63–2.51 (m, 2H, CH_2), 2.16 (dt, J = 8.6, 15.5 Hz, 1H, CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.7 (C), 137.5 (C), 136.7 (2 × CH), 130.2 (CH), 129.6 (t, J = 287.2 Hz, CF_2), 129.1 (2 × CH), 128.5 (2 × CH), 128.2 (2 × CH), 127.4 (CH), 124.7 (C), 93.2 (t, J = 25.5 Hz, C), 44.2 (C), 30.4 (CH_2), 28.6 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −84.9 (d, J = 207.7 Hz, 1F), −83.4 (d, J = 207.7 Hz, 1F). IR (nujol): ν_{max} 3354*br*, 1678*s*, 1456*m*, 1441*m*, 1203*m*, 1152*m*, 1069*s*, 748*m*, 715*s* cm^{-1}. MS: *m*/*z* (% relative intensity) 350 (M^+, 12), 284 (7), 191 (13), 190 (100), 168 (2), 165 (2), 160 (6), 140 (5), 121 (3), 112 (49), 106 (5), 92 (5), 91 (65), 84 (23), 77 (6), 65 (15). HRMS (ESI-TOF) calcd. $C_{18}H_{17}F_2NO_2SNa$ $[M + Na]^+$: 372.0846; found: 372.0847.

A mixture of 2-benzyl-3-(difluoro(phenylsulfanyl)methyl)-3-hydroxy-6-methylisoindolin-1-one and 2-benzyl-3-(difluoro(phenylsulfanyl)methyl)-3-hydroxy-5-methylisoindolin-1-one (6e). According to the *general procedure C*, the reaction of a 1 : 1 mixture of **5Ae** (71 mg, 0.2 mmol) and benzylamine (47 mg, 0.4 mmol) gave a 1 : 1 isomeric mixture of **6e** (54 mg, 63% yield) as a white solid after purification by column chromatography (SiO_2, 30% AcOEt in hexanes): m.p. 140–150 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 7.7 Hz, 1H, Ar*H*), 7.66 (br, 1H, Ar*H*), 7.61 (dd, J = 1.7, 7.8 Hz, 1H, Ar*H*), 7.51 (br, 1H, Ar*H*), 7.46–7.36 (m, 8H, Ar*H*), 7.35–7.24 (m, 14H, Ar*H*), 5.02 (d, J = 15.6 Hz, 1H, C*H*H), 5.01 (d, J = 15.6 Hz, 1H, C*H*H), 4.55 (d, J = 15.6 Hz, 1H, CH*H*), 4.54 (d, J = 15.6 Hz, 1H, CH*H*), 3.81 (br, 1H, O*H*), 3.76 (br, 1H, O*H*), 2.49 (s, 3H, CH_3), 2.47 (s, 3H, CH_3).^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5 (C), 168.4 (C), 143.8 (C), 142.3 (C), 141.5 (C), 139.3 (C), 137.7 (C), 137.6 (C), 136.7 (2 × CH), 136.6 (2 × CH), 133.6 (2 × CH), 131.8 (2 × CH), 131.6 (2 × C), 130.0 (2 × CH), 128.9 (2 × CH), 128.6 (t, J = 282.5 Hz, 2 × CF_2), 128.4 (4 × CH), 127.3 (2 × CH), 125.0 (C), 124.9 (C), 124.7 (CH), 124.6 (CH), 124.1 (2 × CH), 123.9 (CH), 123.8 (CH), 123.6 (2 × CH), 91.1 (t, J = 26.5 Hz, 2 × C), 43.5 (CH_2), 43.4 (CH_2), 22.0 (CH_3), 21.5 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −81.8 (d, J = 210.3 Hz, 1F), −81.7 (d, J = 211.5 Hz, 1F), −80.6 (d, J = 211.5 Hz, 1F), −80.5 (d, J = 210.3 Hz, 1F). IR (KBr): ν_{max}

3362*br*, 1698*s*, 1684*s*, 1618*m*, 1443*m*, 1385*s*, 1358*m*, 1152*m*, 1118*m*, 1067*s*, 1011*m*, 753*m*, 699*s*, 692*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 412 (M^+ + 1, trace), 253 (8), 252 (45), 175 (12), 174 (100), 91 (26), 65 (9). HRMS (ESI-TOF) calcd $C_{23}H_{19}F_2NO_2SNa$ $[M + Na]^+$: 434.1002; found: 434.0979.

General procedure D for the preparation of compounds 7

2-Benzyl-3-(difluoro(phenylsulfanyl)methyl)isoindolin-1-one (7a). To a solution of **6a** (78 mg, 0.2 mmol) in dry CH_2Cl_2 (3 mL) at −78 °C was slowly added triethylsilane (0.3 mL, 2.0 mmol) and $BF_3{\cdot}OEt_2$ (0.1 mL, 0.6 mmol) under an argon atmosphere. The reaction mixture was slowly warmed up to room temperature overnight (15 h) then quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was washed with water (3 mL), brine (3 mL) and dried (anh. Na_2SO_4). Purification of the crude product by column chromatography (SiO_2, 20% AcOEt in hexanes) gave a white solid of **7a** (66 mg, 87% yield): m.p. 96–97 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01–7.96 (m, 1H, Ar*H*), 7.64–7.55 (m, 3H, Ar*H*), 7.49–7.40 (m, 3H, Ar*H*), 7.39–7.26 (m, 7H, Ar*H*), 5.54 (d, *J* = 15.1 Hz, 1H, C*H*H), 4.83 (dd, *J* = 3.3, 7.8 Hz, 1H, C*H*), 4.25 (dd, *J* = 1.9, 15.1 Hz, 1H, CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1 (C), 138.5 (d, *J* = 6.6 Hz, C), 136.7 (2 × CH), 136.4 (C), 132.4 (C), 132.2 (CH), 130.0 (CH), 129.7 (CH), 129.6 (dd, *J* = 282.1, 284.6 Hz, CF_2), 129.0 (2 × CH), 128.8 (2 × CH), 128.6 (2 × CH), 127.7 (CH), 124.8 (C), 124.60 (d, *J* = 3.8 Hz, CH), 124.1 (CH), 63.4 (dd, *J* = 25.9, 26.1 Hz, C), 44.9 (d, *J* = 3.4 Hz, CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −73.4 (d, *J* = 221.8 Hz, 1F), −67.5 (dd, *J* = 7.1, 221.8 Hz, 1F). IR (neat): ν_{max} 1705*s*, 1471*m*, 1442*m*, 1393*s*, 1130*s*, 1033*s*, 705*s*, 694*s* cm^{-1}. MS: *m*/*z* (% relative intensity) 382 (M^+ + 1, 7), 381 (M^+, 10), 223 (17), 222 (98), 167 (13), 139 (4), 109 (3), 92 (100), 65 (13). HRMS (ESI-TOF) calcd. $C_{22}H_{17}F_2NOSNa$ $[M + Na]^+$: 404.0896; found: 404.0912.

2-Benzyl-3-(difluoro(phenylsulfanyl)methyl)octahydro-1*H*-isoindol-1-one (7b). According to the *general procedure D*, reduction of **6b** (0.20 g, 0.5 mmol) followed by column chromatography (SiO_2, 1 : 3 : 6 CH_2Cl_2 : AcOEt : hexanes) afforded a white solid of **7b** (0.16 g, 83% yield): m.p. 165–166 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59–7.52 (m, 2H, Ar*H*), 7.41–7.37 (m, 1H, Ar*H*), 7.37–7.30 (m, 2H, Ar*H*), 7.26–7.15 (m, 3H, Ar*H*), 7.15–7.11 (m, 2H, Ar*H*), 5.22 (d, *J* = 15.1 Hz, 1H, C*H*H), 4.06 (dd, *J* = 2.3, 15.1 Hz, 1H, CH*H*), 3.53 (dd, *J* = 9.6, 10.3 Hz, 1H, C*H*), 2.23–2.15 (m, 1H, C*H*), 2.13–1.95 (m, 1H, C*H*), 1.93–1.69 (m, 5H, C*H*H), 1.36–1.24 (m, 2H, 2 × CH*H*), 1.24–1.11 (m, 1H, 5 × CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.7 (C), 136.7 (2 × CH), 136.5 (C), 131.0 (t, *J* = 281.3 Hz, CF_2), 130.0 (CH), 129.1 (2 × CH), 128.6 (2 × CH), 128.5 (2 × CH), 127.5 (CH), 125.0 (C), 65.0 (t, *J* = 29.1 Hz, C), 48.0 (CH), 45.2 (CH_2), 43.2 (CH), 29.3 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 25.6 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −75.1 (d, *J* = 220.2 Hz, 1F), −65.8 (dd, *J* = 9.9, 220.2 Hz, 1F). IR (KBr): ν_{max} 1706*s*, 1474*w*, 1449*w*, 1390*m*, 1246*w*, 1155*w*, 1111*w*, 706*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 388 (M^+ + 1, 7), 387 (M^+, 20), 278 (9), 229 (17), 228 (100), 200 (5), 109 (6), 106 (18), 95 (34), 91 (44), 65 (10). HRMS (ESI-TOF) calcd $C_{22}H_{23}F_2NOSNa$ $[M + Na]^+$: 410.1365; found: 410.1344.

2-Benzyl-3-(difluoro(phenylsulfanyl)methyl)-2,3,3*a*,4,7,7*a*-hexahydro-1*H*-isoindol-1-one (7c). According to the *general procedure D*, reduction of **6cA** (40 mg, 0.1 mmol) followed by column chromatography (SiO_2, 30% AcOEt in hexanes) afforded a colorless oil of **7c** (34 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57–7.49 (m, 2H, Ar*H*), 7.43–7.36 (m, 1H, Ar*H*), 7.36–7.30 (m, 2H, Ar*H*), 7.27–7.12 (m, 5H, Ar*H*), 5.77–5.69 (m, 1H, *H*C), 5.69–5.62 (m, 1H, C*H*), 5.25 (d, *J* = 15.1 Hz, 1H, C*H*H), 4.07 (dd, *J* = 2.2, 15.1 Hz, 1H, CH*H*), 3.61 (dd, *J* = 9.4, 9.9 Hz, 1H, C*H*), 2.54–2.39 (m, 2H, C*H*, and C*H*H), 2.23–2.04 (m, 3H, 3 × C*H*H), 2.04–1.92 (m, 1H, C*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.4 (C), 136.7 (2 × CH), 136.3 (C), 130.9 (t, *J* = 279.8 Hz, CF_2), 130.1 (CH), 129.1 (2 × CH), 128.6 (2 × CH), 128.5 (2 × CH), 127.6 (CH), 126.7 (CH), 126.5 (CH), 124.8 (C), 65.5 (dd, *J* = 23.5, 32.0 Hz, C), 45.2 (CH_2), 43.6 (CH), 38.7 (d, *J* = 2.4 Hz, CH), 29.8 (d, *J* = 3.3 Hz, CH_2), 26.1 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −75.5 (d, *J* = 219.0 Hz, 1F), −66.9 (dd, *J* = 10.1, 219.0 Hz, 1F). IR ($CHCl_3$): ν_{max} 1699*s*, 1603*m*, 1404*w*, 1354*w*, 1270*w*, 1157*w*, 1009*w* cm^{-1}. MS: *m*/*z* (% relative intensity) 385 (M^+, 9), 309 (2), 276 (6), 240 (4), 227 (15), 226 (88), 198 (5), 167 (7), 109 (7), 106 (15), 93 (27), 91 (100), 77 (28). HRMS (ESI-TOF) calcd $C_{22}H_{21}F_2NOSNa$ $[M + Na]^+$: 408.1209; found: 408.1202.

1-Benzyl-5-(difluoro(phenylsulfanyl)methyl)pyrrolidin-2-one (7d). According to the *general procedure D*, reduction of **6d** (0.18 g, 0.5 mmol) followed by column chromatography (SiO_2, 50% EtOAc in hexanes) afforded an off-white solid of **7d** (0.16 g, 96% yield): m.p. 112–113 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64–7.58 (m, 2H, Ar*H*), 7.51–7.44 (m, 1H, Ar*H*), 7.44–7.39 (m, 2H, Ar*H*), 7.36–7.27 (m, 3H, Ar*H*), 7.26–7.20 (m, 2H, Ar*H*), 5.27 (d, *J* = 14.9 Hz, 1H, C*H*H), 3.99 (d, *J* = 14.9 Hz, 1H, CH*H*), 3.86 (ddd, *J* = 3.2, 7.1, 16.5 Hz, 1H, C*H*), 2.75 (dt, *J* = 9.8, 18.2 Hz, 1H, C*H*H), 2.45 (ddd, *J* = 2.9, 10.5, 12.0 Hz, 1H, CH*H*), 2.31 (m, 1H, C*H*H), 2.16 (dq, *J* = 10.1, 14.0 Hz, 1H, CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.6 (C), 136.5 (2 × CH), 135.8 (C), 130.9 (t, *J* = 283.6 Hz, CF_2), 130.1 (CH), 129.2 (2 × CH), 128.7 (2 × CH), 128.5 (2 × CH), 127.7 (CH), 125.0 (C), 61.0 (t. *J* = 25.3 Hz, C), 45.6 (CH_2), 29.3 (CH_2), 20.5 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −77.1 (d, *J* = 211.7 Hz, 1F), −77.0 (d, *J* = 211.7 Hz, 1F). IR (KBr): ν_{max} 1699*s*, 1457*w*, 1450*w*, 1410*m*, 1232*m*, 1063*m*, 989*m*, 755*m*, 698*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 333 (M^+, 4), 175 (12), 174 (100), 109 (4), 92 (7), 91 (92), 77 (4), 65 (14). HRMS (ESI-TOF) calcd $C_{18}H_{17}F_2NOSNa$ $[M + Na]^+$: 356.0896; found: 356.0889.

A mixture of 2-benzyl-3-(difluoro(phenylsulfanyl)methyl)-6-methylisoindolin-1-one and 2-benzyl-3-(difluoro(phenylsulfanyl)methyl)-5-methyl isoindolin-1-one (7e). According to the *general procedure D*, reduction of a 1 : 1 mixture of **6e** (30 mg, 0.07 mmol) followed by column chromatography (SiO_2, 50% AcOEt in hexanes) gave a pale yellow oil of a 1 : 1 isomeric mixture of **7e** (24 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.67 (s, 1H, Ar*H*), 7.38–7.12 (m, 24H, Ar*H*), 5.40 (dd, *J* = 3.0, 15.0 Hz, 2H, 2 × C*H*H), 4.66 (dt, *J* = 3.1, 11.2 Hz, 2H, 2 × C*H*), 4.12 (ddd, *J* = 1.6, 4.5, 15.0 Hz, 2H,

2 × CH*H*), 2.38 (s, 3H, C*H*$_3$), 2.33 (s, 3H, C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2 (C), 169.1 (C), 142.9 (C), 140.0 (C), 138.8 (d, J = 6.6 Hz, C), 137.7 (d, J = 6.6 Hz, C), 136.7 (2 × CH), 136.6 (CH), 136.5 (C), 136.4 (C), 135.7 (d, J = 6.6 Hz, C), 133.2 (CH), 132.5 (C), 130.7 (CH), 129.9 (2 × CH), 129.7 (dd, J = 282.8, 284.9 Hz, CF_2), 129.6 (t, J = 283.9 Hz, CF_2), 129.6 (C), 129.0 (2 × CH), 128.9 (2 × CH), 128.7 (4 × CH), 128.5 (2 × CH), 128.0 (C), 127.7 (CH), 125.1 (CH), 125.1 (CH), 125.0 (CH), 124.9 (CH), 124.4 (CH), 124.3 (CH), 124.3 (CH), 123.9 (CH), 63.3 (dd, J = 9.0, 25.9 Hz, C), 63.0 (dd, J = 9.0, 26.0 Hz, C), 44.9 (CH_2), 44.8 (CH_2), 21.9 (CH_3), 21.4 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −73.8 (d, J = 222.3 Hz, 1F), −73.7 (d, J = 220.9 Hz, 1F), −67.8 (dd, J = 7.1, 220.9 Hz, 1F), −67.5 (dd, J = 7.1, 222.3 Hz, 1F). IR ($CHCl_3$): ν_{max} 1698*s*, 1496*w*, 1475*w*, 1456*w*, 1442*w*, 1396*w*, 1035*w* cm^{-1}. MS: *m*/*z* (% relative intensity) 396 (M^+ + 1, 4), 395 (16), 252 (4), 237 (18), 236 (100), 182 (3), 181 (13), 174 (6), 109 (6), 91 (62), 65 (11). HRMS (ESI-TOF) calcd $C_{23}H_{19}F_2NOSNa$ $[M + Na]^+$: 418.1052; found: 418.1050.

General procedure E for the preparation of compounds 8

2-Benzyl-3-(difluoromethyl)isoindolin-1-one (8a). A solution of **7a** (77 mg, 0.2 mmol) in toluene (3 mL) was bubbled with argon gas. The deoxygenated solution of AIBN (6 mg, 0.03 mmol) in toluene (4 mL) and Bu_3SnH (0.04 mL, 0.35 mmol) was then added dropwise. The reaction mixture was heated at reflux overnight (15 h). Toluene was evaporated to provide a crude product, which was purified by column chromatography (SiO_2, 20% AcOEt in hexanes) to give a colorless oil of **8a** (45 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99–7.93 (m, 1H, Ar*H*), 7.64–7.57 (m, 2H, Ar*H*), 7.57–7.52 (m, 1H, Ar*H*), 7.39–7.33 (m, 2H, Ar*H*), 7.33–7.29 (m, 3H, Ar*H*), 5.71 (dt, J = 5.5, 55.7 Hz, 1H, CF_2H), 5.49 (d, J = 15.1 Hz, 1H, C*H*H), 4.58 (ddd, J = 5.5, 8.5, 8.5 Hz, 1H, C*H*), 4.40 (d, J = 15.1 Hz, 1H, CH*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1 (C), 138.0 (d, J = 7.0 Hz, C), 136.5 (C), 132.4 (CH), 132.2 (CH), 129.7 (CH), 128.9 (2 × CH), 128.4 (2 × CH), 127.9 (CH), 124.3 (CH), 124.2 (d, J = 1.9 Hz, CH), 115.6 (t, J = 246.5 Hz, CF_2H), 59.9 (dd, J = 23.5, 27.0 Hz, C), 45.5 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −120.2 (ddd, J = 8.2, 54.6, 293.0 Hz, 1F), −118.1 (ddd, J = 8.9, 55.8, 293.0 Hz, 1F). IR (neat): ν_{max} 1694*s*, 1456*m*, 1470*w*, 1409*m*, 1120*s*, 1060*s*, 752*s*, 720*s*, 702*s* cm^{-1}. MS: *m*/*z* (% relative intensity) 274 (M^+ + 1, 37), 273 (58), 223 (20), 222 (77), 196 (11), 169 (6), 149 (17), 129 (5), 93 (10), 92 (100), 66 (14). HRMS (ESI-TOF) calcd $C_{16}H_{13}F_2NONa$ $[M + Na]^+$: 296.0862; found: 296.0864.

2-Benzyl-3-(difluoromethyl)octahydro-1*H*-isoindol-1-one (8b). According to the *general procedure E*, reductive cleavage of **7b** (59 mg, 0.15 mmol) provided a colorless oil of **8b** (41 mg, 98% yield) after column chromatography (SiO_2, 20% AcOEt in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.08 (m, 5H, Ar*H*), 5.65 (dt, J = 4.2, 54.8 Hz, 1H, CF_2H), 4.95 (d, J = 15.2 Hz, 1H, C*H*H), 4.04 (d, J = 15.2 Hz, 1H, CH*H*), 3.28 (dq, J = 4.2, 9.7 Hz, 1H, C*H*), 2.27–2.08 (m, 1H, C*H*), 2.04–1.92 (m, 1H, C*H*), 1.92–1.69 (m, 3H, CH_2, and C*H*H), 1.69–1.58 (m, 1H, CH*H*), 1.39–1.04 (m, 4H, 2 × CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4 (C), 136.5 (C), 128.7 (2 × CH), 128.0 (2 × CH), 127.6 (CH), 115.8 (t, J = 243.2 Hz, CF_2H), 61.5 (dd, J = 23.0, 25.2 Hz, C), 47.6 (CH), 45.0 (d, J = 1.9 Hz, CH_2), 41.4 (t, J = 3.4 Hz, CH), 28.8 (d, J = 2.0 Hz, CH_2), 25.8 (CH_2), 25.7 (CH_2), 25.5 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −124.6 (ddd, J = 8.9, 54.7, 293.3 Hz, 1F), −120.3 (ddd, J = 9.9, 54.7, 293.3 Hz, 1F). IR ($CHCl_3$): ν_{max} 1695*s*, 1456*w*, 1395*w*, 1377*w*, 1252*w*, 1134*w*, 1113*w*, 1068*w* cm^{-1}. MS: *m*/*z* (% relative intensity) 279 (M^+, 69), 229 (24), 228 (100), 202 (11), 107 (21), 106 (51), 92 (85), 79 (17). HRMS (ESI-TOF) calcd $C_{16}H_{19}F_2NONa$ $[M + Na]^+$: 302.1332; found: 302.1350.

2-Benzyl-3-(difluoromethyl)-2,3,3*a*,4,7,7*a*-hexahydro-1*H*-isoindol-1-one (8c). According to the *general procedure E*, reductive cleavage of **7c** (39 mg, 0.1 mmol) provided a colorless oil of **8c** (27 mg, 97% yield) after column chromatography (SiO_2, 20% AcOEt in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.04 (m, 5H, Ar*H*), 5.75–5.69 (m, 1H, C*H*), 5.68 (dt, J = 4.4, 54.9 Hz, 1H, CF_2H), 5.67–5.61 (m, 1H, C*H*), 4.98 (d, J = 14.7 Hz, 1H, C*H*H), 4.07 (d, J = 14.7 Hz, 1H, CH*H*), 3.37 (dq, J = 4.5, 9.3 Hz, 1H, C*H*), 2.54–2.41 (m, 1H, C*H*), 2.39–2.24 (m, 1H, C*H*), 2.21–2.05 (m, 2H, CH_2), 2.05–1.85 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2 (C), 136.4 (C), 128.8 (2 × CH), 128.1 (2 × CH), 127.7 (CH), 126.6 (CH), 126.4 (CH), 115.8 (t, J = 242.8 Hz, CF_2H), 62.1 (t, J = 24.9 Hz, C), 45.1 (CH_2), 43.3 (CH), 36.9 (CH), 29.3 (CH_2), 26.0 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −125.1 (ddd, J = 8.9, 54.5, 294.7 Hz, 1F), −119.9 (ddd, J = 8.9, 54.5, 294.7 Hz, 1F). IR ($CHCl_3$): ν_{max} 1696*s*, 1398*w*, 1271*w*, 1122*w*, 1072*w*, 909*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 278 (M^+ + 1, 27), 277 (M^+, 100), 276 (6), 227 (12), 226 (66), 186 (7), 146 (13), 106 (14), 93 (18), 91 (75), 77 (24). HRMS (ESI-TOF) calcd $C_{16}H_{17}F_2NONa$ $[M + Na]^+$: 300.1175; found: 300.1175.

1-Benzyl-5-(difluoromethyl)pyrrolidin-2-one (8d). According to the *general procedure E*, reductive cleavage of **7d** (0.30 g, 0.9 mmol) provided a colorless oil of **8d** (0.14 g, 69% yield) after column chromatography (SiO_2, 20% AcOEt in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.35 (m, 2H, Ar*H*), 7.35–7.30 (m, 1H, Ar*H*), 7.30–7.25 (m, 2H, Ar*H*), 5.72 (dt, J = 3.4, 55.3 Hz, 1H, CF_2H), 5.08 (d, J = 15.0 Hz, 1H, C*H*H), 4.17 (d, J = 15.0 Hz, 1H, CH*H*), 3.73–3.65 (m, 1H, C*H*), 2.61 (dt, J = 8.6, 9.5 Hz, 1H, C*H*H), 2.45 (ddd, J = 4.7, 9.1, 17.2 Hz, 1H, CH*H*), 2.17–2.05 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.4 (C), 136.0 (C), 128.8 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 115.4 (t, J = 244.1 Hz, CF_2H), 57.8 (t, J = 23.9 Hz, C), 45.7 (CH_2), 29.3 (CH_2), 18.5 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −126.6 (ddd, J = 10.8, 55.3, 288.0 Hz, 1F), −125.7 (ddd, J = 12.2, 55.3, 288.0 Hz, 1F). IR (neat): ν_{max} 1682*s*, 1446*w*, 1418*m*, 1237*m*, 1072*m*, 1059*m*, 703*s* cm^{-1}. MS: *m*/*z* (% relative intensity) 226 (M^+ + 1, 25), 225 (M^+, 50), 223 (7), 175 (10), 174 (75), 146 (19), 104 (14), 91 (100), 65 (16). HRMS (ESI-TOF) calcd $C_{12}H_{13}F_2NONa$ $[M + Na]^+$: 248.0862; found: 248.0862.

A mixture of 2-benzyl-3-(difluoromethyl)-6-methyl isoindolin-1-one and 2-benzyl-3-(difluoromethyl)-5-methyl isoindolin-1-one (8e). According to the *general procedure E*, reductive cleavage of 1 : 1 mixture of **7e** (19 mg, 0.05 mmol) provided colorless oil of a 1 : 1 isomeric mixture of **8e** (12 mg, 79% yield) after column chromatography (SiO_2, 50% AcOEt in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78–7.70 (m, 1H, Ar*H*), 7.70–7.60 (m, 2H, Ar*H*), 7.39–7.10 (m, 13H, Ar*H*), 5.58 (tt, J =

5.5, 55.6 Hz, 2H, 2 × CF_2H), 5.38 (d, J = 14.3 Hz, 2H, 2 × CHH), 4.52–4.36 (m, 2H, 2 × HC), 4.29 (d, J = 14.3 Hz, 2H, 2 × CHH), 1.20 (s, 3H, CH_3), 1.19 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3 (2 × C), 155.5 (C), 152.8 (C), 143.0 (C), 140.0 (C), 136.5 (C), 135.2 (C), 133.2 (CH), 132.5 (C), 130.6 (CH), 129.8 (C), 128.8 (3 × CH), 128.3 (2 × CH), 127.8 (CH), 124.7 (CH), 124.5 (3 × CH), 124.0 (2 × CH), 123.9 (2 × CH), 115.7 (t, J = 246.4 Hz, 2 × CF_2), 59.7 (t, J = 25.4 Hz, 2 × CH), 45.4 (2 × CH_2), 21.9 (CH_3), 21.4 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$) δ −120.2 (dd, J = 54.5, 292.3 Hz, 1F), −120.1 (dd, J = 54.5, 292.6 Hz, 1F), −118.6 (ddd, J = 8.9, 55.9, 292.6 Hz, 1F), −118.5 (ddd, J = 8.9, 55.9, 292.3 Hz, 1F). IR ($CHCl_3$): ν_{max} 1697*s*, 1603*m*, 1559*w*, 1542*w*, 1508*w*, 1497*w*, 1457*w*, 1077*m* cm^{-1}. MS: *m*/*z* (% relative intensity) 288 (M^+ + 1, 11), 287 (61), 286 (4), 237 (17), 236 (93), 210 (6), 178 (7), 163 (21), 115 (12), 91 (100), 65 (18). HRMS (ESI-TOF) calcd. $C_{17}H_{15}F_2NONa$ $[M + Na]^+$: 310.1019; found: 310.1020.

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