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New preparation of difluoroiodomethylsulfanylbenzenes and their radical addition to unsaturated compounds initiated by sodium dithionite

Xueyan Yang [a], Xiang Fang [a], Xianjin Yang [a], Min Zhao [a], Yizheng Han [a], Yongjia Shen [a], Fanhong Wu [a,b,*]

[a] *Laboratory for Advanced Material and Institute of Fine Chemicals, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, PR China*

[b] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China*

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Abstract

Difluoroiodomethylsulfanylbenzene (**3a**) and 1-chloro-4-difluoroiodomethylsulfanylbenzene (**3b**) are novel and efficient difluoromethylating reagents via the reaction with unsaturated compounds, such as alkenes, ethynylbenzene, pent-4-en-1-ols, and pent-4-enoic acids initiated by $Na_2S_2O_4$, to afford the corresponding adducts, tetrahydrofuran derivatives, and γ-butyrolactones containing difluoromethylene group in moderate to good yields.

Keywords: Difluoroiodomethylsulfanylbenzene; Difluoromethylene; γ-Butyrolactone; Addition; Tetrahydrofuran derivatives

1. Introduction

The selective introduction of a *gem*-difluoromethylene (CF_2) moiety into organic compounds is of great importance because this group is usually considered as an isopolar and isosteric replacement for oxygen[1] and some molecules containing CF_2 group are potential broad spectrum antibiotics,[2] inhibitors of HIV-1 reverse transcriptase,[3,4] and antitumor agents.[5] Introduction of CF_2 group into organic molecules is often realized through the conversion of a carbonyl into a difluoromethylene group with (diethylamino)sulfur trifluoride (DAST)[6] or other reagents.[7] Compounds with CF_2 moiety, such as XCF_2COOEt and CF_2X_2 (X=I, Br, Cl), are also used to introduce CF_2 group into organic compounds via radical,[8] carbene,[9] and ionic reactions.[3,10] Recently, $PhSCF_2Br$ has been demonstrated to be a versatile *gem*-difluoromethylating reagent via the radical reaction promoted by SmI_2[11] or the formation of Grignard reagents.[12] However, it is still highly desirable to develop new effective, convenient, and general preparation methods and new difluoromethylating reagents.

Polyfluoroalkyl iodides, which can react with various unsaturated substrates via free radical addition, an efficient method for the preparation of polyfluoroalkylated derivatives, have better reactivity than the corresponding bromides.[13] We are convinced that, similar to polyfluoroalkyl iodides, functionalized difluoromethyl iodides may proceed by free radical addition reaction under the appropriate conditions giving adducts and the formed C–I bond could be further elaborated. This promoted us to develop new functionalized difluoromethyl iodides. In recent years, *gem*-difluoromethylated compounds with CF_2 adjacent to sulfur atom have been attractive due to their synthetic utilities.[11,14] But limited examples were reported on the introduction of CF_2 bonding to sulfur atom, especially difluoromethylated sulfanyl group,[11,12,15] into organic compounds. Here, we wish to describe the new preparation of novel difluoromethylating reagents, difluoroiodomethylsulfanylbenzene (**3a**) and 1-chloro-4-difluoroiodomethylsulfanylbenzene (**3b**),

* Corresponding author.
E-mail address: wfh@ecust.edu.cn (F. Wu).

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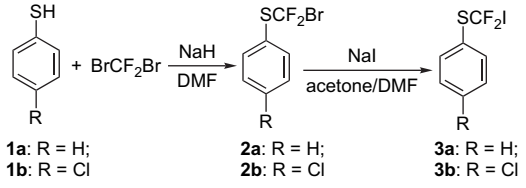
by halogen exchange and the study of their radical addition to unsaturated compounds initiated by $Na_2S_2O_4$. The reaction of **3a** and **3b** with alkenes and alkynes afforded the corresponding adducts. The reaction of **3a** and **3b** with pent-4-en-1-ols and pent-4-enoic acids followed by the intramolecular replacement of C–I bond gave tetrahydrofuran derivatives and γ-butyrolactones containing phenylsulfanyl difluoromethyl moiety.

2. Results and discussion

2.1. Preparation of *3a* and *3b*

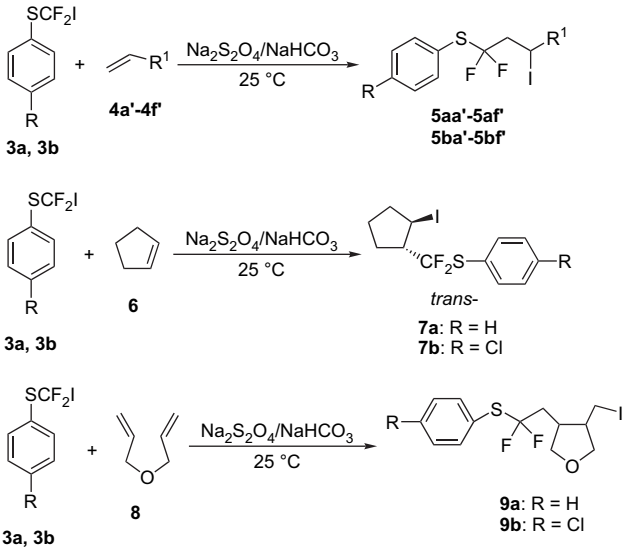
Difluoroiodomethylsulfanylbenzene (**3a**) and 1-chloro-4-difluoroiodomethylsulfanylbenzene (**3b**) can be prepared by nucleophilic reaction of benzenethiol (**1a**) and 4-chloro-benzenethiol (**1b**) with CF_2I_2 in very low yields as reported in the literature.[16] Herein, we developed a convenient and efficient method to prepare **3a** and **3b** by halogen exchange reaction of bromodifluoromethylsulfanylbenzene (**2a**) and 1-chloro-4-bromodifluoromethylsulfanylbenzene (**2b**) in the presence of sodium iodide (Scheme 1). While **2a** and **2b** were easily obtained by the reaction of sodium phenylthiolate with dibromodifluoromethane,[17] conversion of CF_2Br to CF_2I by halogen exchange reaction was usually difficult to occur and there were limited reports on such a transformation. Previous reports showed that the reaction usually proceeded in acetone[18] and butanone.[19] However, the reaction of **2** with NaI didn't occur when only acetone or butanone was used as the solvent. While in DMF, **2** converted completely in several hours giving a complicated mixture with less than 10% of **3** formed. When the reaction of **2a** with NaI was carried out in the mixture of acetone and DMF (4.4:1 v/v) under reflux for a week, **3a** was obtained in 56% yield. For **2b**, the reaction proceeded in acetone and DMF (2.0–4.0:1 v/v) to afford 50% of **3b**.



Scheme 1.

2.2. Reactions of *3a* and *3b* with alkenes and alkynes

The addition of polyfluoroalkyl iodides to alkenes or alkynes can be realized under conditions of photolysis,[20] electrolysis,[21] thermal,[22] and free radical initiators.[23] Since $Na_2S_2O_4$ has been shown to be a good initiator and gave high yields of adducts under mild conditions,[23a] it was chosen in this study. This type of reaction typically took place at low temperature (5–10 °C), while the addition of **3a** and **3b** to alkenes didn't occur when the reaction temperature was lower than 10 °C. At higher temperature (20–30 °C), the reaction proceeded smoothly for 0.5–1 h affording the corresponding



Scheme 2.

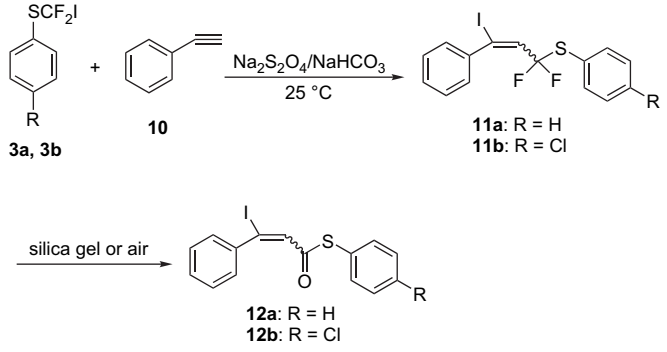
adducts and 1–1.5 mol equiv of alkenes were used (Scheme 2). The detailed results are summarized in Table 1. For terminal alkenes **4a′–4f′**, the reaction gave the corresponding adducts **5aa′–5af′** and **5ba′–5bf′** with CF_2 group adding to terminal carbon of the double bond in 50–70% yields (Table 1, entries 1–6 and 9–14). When cyclopentene **6** was used as the substrate, the reaction gave only trans isomers **7a** and **7b**. The NMR signal of the proton of CHI in **7a** and **7b** exhibited a quartet at δ 4.49 ppm (J=5.2 Hz) and δ 4.46 ppm (J=5.1 Hz) with coupling to adjacent R_FCH and CH_2, which resembled closely to those of the polyfluoroalkyl analog characterized previously.[25,26] Free radical addition of **3** in a trans mode to cyclopentene conformed to the pattern observed in reactions of this type, since the cis adducts would be disfavored because of steric interactions between R_F and I groups.[25,26] The reaction of **3a** and **3b** with diallyl ether **8** gave tetrahydrofuran

Table 1
Addition of **3** to alkenes and ethynylbenzene

Entry	3	4	R^1	Product	Yield (%)
1	**3a**	**4a′**	$(CH_2)_5CH_3$	**5aa′**	75.1
2	**3a**	**4b′**	$(CH_2)_3CH_3$	**5ab′**	78.3
3	**3a**	**4c′**	CH_2OH	**5ac′**	77.2
4	**3a**	**4d′**	CH_2CN	**5ad′**	70.5
5	**3a**	**4e′**	$CH_2OCOCH_2CH_3$	**5ae′**	80.0
6	**3a**	**4f′**	CH_2CH_2Br	**5af′**	55.6
7	**3a**	**6**	Cycloheptene	**7a**	69.2
8	**3a**	**8**	Diallyl ether	**9a**	66.7
9	**3b**	**4a′**	$(CH_2)_5CH_3$	**5ba′**	73.8
10	**3b**	**4b′**	$(CH_2)_3CH_3$	**5bb′**	71.8
11	**3b**	**4c′**	CH_2OH	**5bc′**	75.3
12	**3b**	**4d′**	CH_2CN	**5bd′**	63.8
13	**3b**	**4e′**	$CH_2OCOCH_2CH_3$	**5be′**	67.9
14	**3b**	**4f′**	CH_2CH_2Br	**5bf′**	65.9
15	**3b**	**6**	Cycloheptene	**7b**	69.6
16	**3b**	**8**	Diallyl ether	**9b**	75.2
17	**3a**	**10**	Ph–	**12a**	55.0
18	**3b**	**10**	Ph–	**12b**	52.0

derivatives **9a** and **9b**, indicating a radical mechanism.[8b] The addition of **2a** to 1-hexene was also investigated, giving a complicated mixture with low conversion of **2a**. This indicated that **3a** has better reactivity than the corresponding bromides.

The addition reaction of **3** with ethynylbenzene **10** was carried out under the similar conditions affording adducts **11** and a trace of **12**. After prolonged standing in air or during column chromatography on silica gel **12** was obtained as the main product (Scheme 3). For **3a**, only *E*-**12a** was observed. For **3b**, a mixture of *E*/*Z* isomers was obtained in 7.6:1 ratio based on ^{1}H NMR with *E* isomer as the main product. The NMR signal of alkenyl hydrogen of *E*-**12b** (δ 7.14 ppm) appeared more downfield than that of *Z* isomer (δ 7.08 ppm).[26] The major or only *E* isomer may be derived from the vinyl radical **11**$^{\bullet}$, which was more stable than **11**$^{\bullet\prime}$ for the lower steric hindrance between $RSCF_2$ (R=Ph, C_6H_4Cl-*p*) (Fig. 1) and the electron donor.[27] In vinyl radicals **11**$^{\bullet}$ and **11**$^{\bullet\prime}$, phenyl group was usually thought to favor the linear form in order to ensure a better orbital overlap for resonance.[27] It was reported that oxygen, sulfur, or nitrogen atom adjacent to carbon–fluorine bond greatly increased the adduct's reactivity toward nucleophiles.[28] Therefore, compounds **11** with CF_2 adjacent to sulfur and double bond were readily hydrolyzed to give compounds **12** on prolonged standing in the air or during the column chromatographic purification on silica gel.



Scheme 3.

2.3. Their reactions with pent-4-en-1-ols

We have described that fluoroalkylation of pent-4-en-1-ols initiated by $Na_2S_2O_4$ gave adducts, which could be cyclized by heating in DMF or acetonitrile giving fluorinated tetrahydrofuran derivatives.[29] The addition reaction of **3a** and **3b** to pent-4-en-1-ols **13a**$'$–**13d**$'$ was realized under the similar conditions

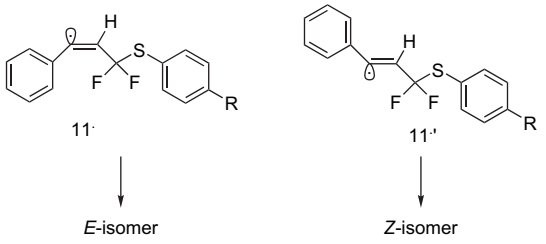
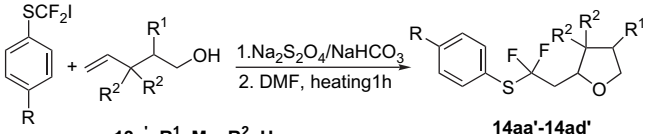


Figure 1.

Table 2
Reaction of **3** with pent-4-en-1-ols **13a**$'$–**d**$'$



13a$'$: R^1=Me, R^2=H
13b$'$:R^1=H, R^2=H
13c$'$: R^1=H, R^2=Me
13d$'$:R^1=Ph, R^2=H

14aa'-14ad'
14ba'-14bd'

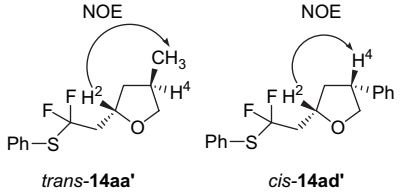
Entry	3	13	Temperature (°C)	Product	Yield (%)	Trans/cis[a]
1	**3a**	**13a**$'$	130	**14aa**$'$	52.1	1.51:1
2	**3a**	**13b**$'$	130	**14ab**$'$	54.3	—
3	**3a**	**13c**$'$	110	**14ac**$'$	60.0	—
4	**3a**	**13d**$'$	130	**14ad**$'$	65.2	2.73:1
5	**3b**	**13a**$'$	130	**14ba**$'$	66.1	1.44:1
6	**3b**	**13b**$'$	130	**14bb**$'$	66.4	—
7	**3b**	**13c**$'$	110	**14bc**$'$	65.0	—
8	**3b**	**13d**$'$	130	**14bd**$'$	56.0	2.70:1

[a] Based on ^{1}H NMR.

with alkenes to give the corresponding adducts, which were converted to phenylsulfanyl difluoromethylated tetrahydrofuran derivatives **14** by heating in DMF for 1 h. For 2-methyl-pent-4-en-1-ol (**13a**$'$) and 2-phenyl-pent-4-en-1-ol (**13d**$'$), a mixture of trans/cis isomers was obtained (Table 2, entries 1, 4, 5, and 8) with trans isomer as the major product. Significant chemical shift differences between the two protons at C-3 (for example, $\Delta\delta$=1.10 ppm for *cis*-**14aa**$'$, 0.82 ppm for *cis*-**14ad**$'$) indicated a cis isomer. Small differences (for example, $\Delta\delta$=0.0 ppm for *trans*-**14aa**$'$, 0.12 ppm for *trans*-**14ad**$'$) pointed to trans configuration. The results were consistent with the established stereochemistry of 2,4-disubstituted tetrahydrofurans.[30] The stereochemistry of **14aa**$'$ and **14ad**$'$ was further ascertained by analysis of their ^{1}H–^{1}H NOESY spectra. For **14aa**$'$, the apparent correlated peaks between H-2 (δ=4.33–4.28 ppm) and the three protons on CH_3 (δ=1.03 ppm) showed that CH_3 group and H-2 lied in cis position, which indicated a trans orientation of H-2 and H-4. For **14ad**$'$, the apparent correlated peaks between H-2 (δ=4.40–4.38 ppm) and H-4 (δ=3.58–3.43 ppm) were observed in its cis isomer (Fig. 2).

2.4. Their reactions with pent-4-enoic acids

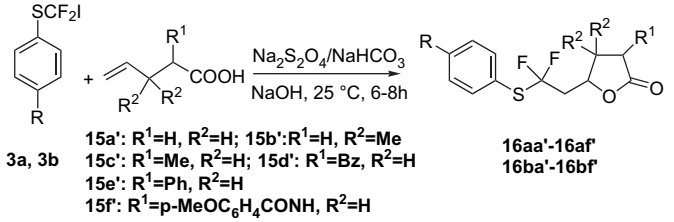
The reaction of **3** and pent-4-enoic acids **15a**$'$–**15f**$'$ was carried out in the presence of 1–1.2 equiv NaOH for 6–8 h at 20–30 °C yielding difluoromethylated γ-butyrolactones **16** in 55–74% yields. The data are summarized in Table 3. The results showed that for 2-substituted-pent-4-enoic acids **15c**$'$–**15f**$'$, a mixture of cis/trans isomers was obtained.



trans-**14aa'** *cis*-**14ad'**

Figure 2. ^{1}H–^{1}H NOESY of *trans*-**14aa**$'$ and *cis*-**14ad**$'$.

Table 3
Reaction of **3** with pent-4-enoic acids



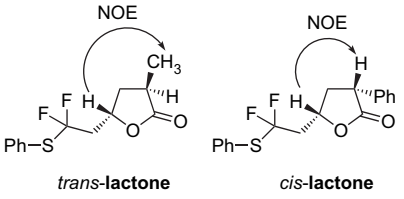
3a, 3b

15a': R^1=H, R^2=H; 15b':R^1=H, R^2=Me
15c': R^1=Me, R^2=H; 15d': R^1=Bz, R^2=H
15e': R^1=Ph, R^2=H
15f': R^1=p-MeOC$_6$H$_4$CONH, R^2=H

16aa'-16af'
16ba'-16bf'

Entry	3	15	Product	Trans/cis[a]	Yield (%)
1	**3a**	**15a′**	**16aa′**	—	74.0
2	**3a**	**15b′**	**16ab′**	—	70.0
3	**3a**	**15c′**	**16ac′**	1:1.02	66.2
4	**3a**	**15d′**	**16ad′**	1:1.30	72.1
5	**3a**	**15e′**	**16ae′**	2.33:1	57.0
6	**3a**	**15f′**	**16af′**	1.28:1	55.3
7	**3b**	**15a′**	**16ba′**	—	64.8
8	**3b**	**15b′**	**16bb′**	—	64.2
9	**3b**	**15c′**	**16bc′**	1:1.07	63.9
10	**3b**	**15e′**	**16bd′**	1:1.28	71.0
11	**3b**	**15d′**	**16be′**	2.11:1	59.2
12	**3b**	**15f′**	**16bf′**	1.09:1	58.3

[a] Based on ^{1}H NMR.



trans-**lactone** *cis*-**lactone**

Figure 3. ^{1}H–^{1}H NOESY of *trans*-lactone and *cis*-lactone.

Analysis of the crude products by ^{1}H NMR spectrum and integration of signals attributed to the CH–O indicated that the cis/trans ratio ranged from 1:1.02 to 2.33:1. For alkyl group on C2, cis isomer was obtained as the main product (entries 3, 4, 9, and 10). While for Ph or NH group on C2, trans isomer dominated in the reaction. Similar to tetrahydrofuran derivatives, the differences of the chemical shifts between the two protons on C-4 in *cis*-**16** were more significant than those in trans isomer.[31] The further confirmation of the stereochemistry of the lactones was obtained by analysis of the ^{1}H–^{1}H NOESY spectra of each isomer (Fig. 3).

Similar to the addition reaction of polyfluoroalkyl iodides to alkenes initiated by sodium dithionite,[24] we proposed that the mechanism of addition of **3** to olefins **4** may involve a single electron transfer (SET) process for the anion radical. The reaction of **3** with pent-4-en-1-ols **13** and pent-4-enoic acids **15** to give the corresponding tetrahydrofuran derivatives **14** and γ-butyrolactones **16** may involve the addition of R_FI to double bond through a SET process and then followed by intramolecular S_N2 reaction.[29,32] The *syn*- and *anti*-diastereomer obtained in radical addition cyclized to give the corresponding trans and cis isomers (Fig. 4).[33] The weak steric hinderance between the groups on C2 (R^1 and R^2) and the groups on C4 (I and $PhSCF_2CH_2$) may affect the ratio of *syn*/*anti* isomers.

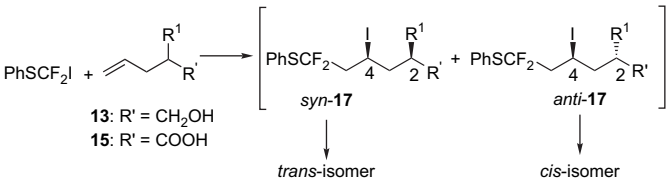


Figure 4.

Most of the products exhibited a typical AB pattern signal in the ^{19}F NMR spectrum.[8d] For example, ^{19}F NMR of **5be′** exhibited two doublets of multiplets at −72.10 ppm and −73.47 ppm. The lower field signal was a doublet of doublet of doublets with J=206.5, 16.9, 10.8 Hz. The higher field signal was also a doublet of doublet of doublets with J=206.5, 16.0, 13.2 Hz.

3. Conclusion

In summary, a new method for the preparation of difluoroiodomethylsulfanylbenzene (**3a**) and 1-chloro-4-difluoroiodomethylsulfanylbenzene (**3b**) was developed from bromodifluoromethylsulfanylbenzene (**2a**) and 1-chloro-4-bromodifluoromethylsulfanylbenzene (**2b**) through a halogen exchange process in the presence of NaI in a mixture of DMF/acetone. The reaction of **3a** and **3b** with unsaturated compounds, such as alkenes, alkynes, pent-4-en-1-ols, and pent-4-enoic acids, initiated by $Na_2S_2O_4$ afforded the corresponding adducts, tetrahydrofuran derivatives, and γ-butyrolactones containing phenylsulfanyl difluoromethyl moiety, in moderate to good yields.

4. Experimental

4.1. General information

Melting points are uncorrected. IR spectra were measured on a Nicolet Magna IR-550 spectrometer. High-resolution mass spectra were recorded on a Finnigan GC–MS-4021 spectrometer. NMR spectra were recorded in $CDCl_3$ solution at 20 °C on a Bruker AC-500 spectrometer operating at 500 MHz (^{1}H), 125.8 MHz (^{13}C), and 470.5 MHz (^{19}F). Chemical shifts (δ) are given in parts per million relative to TMS for ^{1}H and ^{13}C, and relative to $CFCl_3$ for ^{19}F. Column chromatography was performed using silica gel H, particle size 20–30 μm.

4.2. General procedure for the preparation of 3

The mixture of **2** (0.126 mol), NaI (57 g, 0.38 mol), and acetone/DMF (100 mL) was stirred under reflux for a week. After evaporation of acetone, the residue was cooled to room temperature and water (60 mL) was added. The mixture was extracted with ethyl ether (3×50 mL). The combined organic layers were washed with saturated Na_2SO_3, brine, and water. After drying and removal of solvent, the residue was purified by fractional distillation to give a pale yellow oil **3a** (56.0%

yield, bp 70–72 °C/1 mmHg) and **3b** (50.0% yield, bp 80–84 °C/1 mmHg).

4.3. General procedure for the addition of **3** to olefins and ethynylbenzene

To the mixture of **3** (2 mmol), alkenes, or ethynylbenzene (2–3 mmol), acetonitrile (6 mL), and water (2 mL) was added the mixture of sodium dithionite (560 mg, 3.2 mmol) and sodium bicarbonate (270 mg, 3.2 mmol) at 20–30 °C in 20 min. After stirring for 0.5–1 h at the same temperature, water (ca. 15 mL) was added and the mixture was extracted with ethyl ether (3×15 mL). The combined organic layers were washed with saturated brine and dried over anhydrous sodium sulfate. After evaporation of ethyl ether, the crude product was purified by column chromatography eluting with PE and EA to give the corresponding product.

4.3.1. (1,1-Difluoro-3-iodo-nonylsulfanyl)-benzene (**5aa′**)

Colorless oil. IR (film): 3062, 1575, 1215, 1190, 1155, 1111, 1048, 1026 cm^{-1}. ^1H NMR: δ 7.30–7.53 (m, 5H, PhH), 4.30–4.25 (m, 1H, CHI), 2.93–2.82 (m, 1H, CF_2CH_2), 2.79–2.68 (m, 1H, CF_2CH_2), 1.72–1.67 (m, 2H), 1.45–1.39 (m, 1H), 1.33–1.18 (stack, 7H), 0.82 (t, 3H, J=7.7 Hz, CH_3). ^{13}C NMR: δ 136.9, 130.7, 129.8, 129.7 (t, J=281.4 Hz), 127.5, 50.1 (t, J=23.5 Hz), 40.7, 32.3, 30.2, 28.9, 25.9, 23.2, 14.7. ^{19}F NMR: δ −70.61 (ddd, 1F, J_{F-F}=206.6 Hz, J_{1H-F}=17.4 Hz, J_{2H-F}=9.9 Hz), −73.36 (dt, 1F, J_{F-F}=206.6 Hz, J_{2H-F}=14.8 Hz). HRMS (EI), $C_{15}H_{21}F_2IS$ calcd: 398.0377; found: 398.0368.

4.3.2. (1,1-Difluoro-3-iodo-heptylsulfanyl)-benzene (**5ab′**)

Colorless oil. IR (film): 3062, 1575, 1230, 1209, 1155, 1116, 1048, 1026 cm^{-1}. ^1H NMR: δ 7.61–7.37 (m, 5H, PhH), 4.38–4.33 (m, 1H, CHI), 3.00–2.90 (m, 1H, CF_2CH_2), 2.86–2.78 (m, 1H, CF_2CH_2), 1.80–1.76 (m, 2H), 1.51–1.46 (m, 1H), 1.43–1.33 (stack, 3H), 0.92 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR: δ 136.9, 130.7, 129.8, 129.7 (t, J=281.2 Hz), 127.0, 50.1 (t, J=23.3 Hz), 40.4, 32.4, 25.8, 22.4, 14.6. ^{19}F NMR: δ −70.62 (ddd, 1F, J_{F-F}=206.6 Hz, J_{1H-F}=17.4 Hz, J_{2H-F}=9.9 Hz), −73.38 (dt, 1F, J_{F-F}=206.6 Hz, J_{H-F}=15.1 Hz). HRMS (EI), $C_{13}H_{17}F_2IS$ calcd: 370.0064; found: 370.0069.

4.3.3. 4,4-Difluoro-2-iodo-4-phenylsulfanyl-butan-1-ol (**5ac′**)

Colorless oil. IR (film): 3383 (br), 3060, 1581, 1366, 1264, 1206, 1153, 1068, 1028 cm^{-1}. ^1H NMR: δ 7.61–7.37 (m, 5H, PhH), 4.48–4.44 (m, 1H, CHI), 3.81–3.62 (m, 2H, CH_2O), 3.03–2.93 (m, 1H, CF_2CH_2), 2.87–2.77 (m, 1H, CF_2CH_2), 1.25 (t, 1H, J=7.0 Hz, OH). ^{13}C NMR: δ 136.9, 130.8, 129.8, 129.5 (t, J=292.1 Hz), 126.7, 68.4, 45.9 (t, J=24.0 Hz), 27.1. ^{19}F NMR: δ −71.50 (ddd, 1F, J_{F-F}=207.5 Hz, J_{1H-F}=17.4 Hz, J_{2H-F}=9.9 Hz), −73.40 (dt, 1F, J_{F-F}=207.5 Hz, J_{H-F}=15.3 Hz). HRMS (EI), $C_{10}H_{11}F_2IOS$ calcd: 343.9543; found: 343.9543.

4.3.4. 5,5-Difluoro-3-iodo-5-phenylsulfanyl-pentanenitrile (**5ad′**)

Colorless oil. IR (film): 3061, 2252, 1580, 1364, 1328, 1237, 1213, 1150, 1061, 1025 cm^{-1}. ^1H NMR: δ 7.60–7.26 (m, 5H, PhH), 4.45–4.41 (m, 1H, CHI), 3.23 (dd, 1H, J_1=17.6 Hz, J_2=6.3 Hz, CH_2CN), 3.15 (dd, 1H, J_1=17.6 Hz, J_2=3.9 Hz, CH_2CN), 2.97–2.91 (m, 2H, CF_2CH_2). ^{13}C NMR: δ 136.9, 131.1, 130.0, 129.3 (t, J=287.5 Hz), 126.0, 117.5, 48.6 (t, J=24.2 Hz), 30.5, 10.1. ^{19}F NMR: δ −75.69 (dt, 1F, J_{F-F}=210.3 Hz, J_{H-F}=13.4 Hz), −74.9 (dt, 1F, J_{F-F}=210.3 Hz, J_{H-F}=15.1 Hz). HRMS (EI), $C_{11}H_{10}F_2INS$ calcd: 352.9547; found: 352.9546.

4.3.5. Propionic acid 4,4-difluoro-2-iodo-4-phenylsulfanyl-butyl ester (**5ae′**)

Colorless oil. IR (film): 3026, 1744, 1579, 1422, 1383, 1354, 1271, 1217, 1167, 1082, 1028 cm^{-1}. ^1H NMR: δ 7.61–7.38 (m, 5H, PhH), 4.47–4.42 (m, 1H, CHI), 4.35–4.27 (m, 2H, CH_2O), 2.94–2.80 (m, 2H, CF_2CH_2), 2.37 (q, 2H, J=7.6 Hz, CH_2CO), 1.16 (t, 3H, J=7.6 Hz, CH_3). ^{13}C NMR: δ 174.2, 136.9, 130.8, 129.9, 129.3 (t, J=280.1 Hz), 126.7, 68.9, 46.3 (t, J=24.3 Hz), 28.1, 17.0, 9.7. ^{19}F NMR ($CDCl_3$) δ −71.97 (ddd, 1F, J_{F-F}=208.5 Hz, J_{1H-F}=16.9 Hz, J_{2H-F}=11.3 Hz), −73.37 (dt, 1F, J_{F-F}=208.5 Hz, J_{H-F}=14.4 Hz). HRMS (EI), $C_{13}H_{15}F_2IO_2S$ calcd: 399.9806; found: 399.9819.

4.3.6. (5-Bromo-1,1-difluoro-3-iodo-pentylsulfanyl)-benzene (**5af′**)

Colorless oil. IR (film): 3059, 1475, 1439, 1246, 1200, 1160, 1054, 1028 cm^{-1}. ^1H NMR: δ 7.62–7.38 (m, 5H, PhH), 4.48–4.54 (m, 1H, CHI), 3.61–3.57 (m, 1H, CH_2Br), 3.50–3.45 (m, 1H, CH_2Br), 3.05–2.96 (m, 1H, CF_2CH_2), 2.82–2.79 (m, 1H, CF_2CH_2), 2.28–2.23 (m, 2H, CH_2CH_2Br). ^{13}C NMR: δ 137.0, 130.9, 129.9, 129.7 (t, J=281.0 Hz), 126.7, 49.9 (t, J=23.7 Hz), 42.6, 33.9, 22.7. ^{19}F NMR: δ −70.00 (ddd, 1F, J_{F-F}=208.4 Hz, J_{1H-F}=17.4 Hz, J_{2H-F}=9.4 Hz), −73.09 (dt, 1F, J_{F-F}=208.4 Hz, J_{H-F}=15.3 Hz). HRMS (EI), $C_{11}H_{12}BrF_2IS$ calcd: 419.8835; found: 419.8827.

4.3.7. trans-[Difluoro-(2-iodo-cyclopentyl)-methylsulfanyl]-benzene (**7a**)

Colorless oil. IR (film): 3060, 1346, 1305, 1194, 1149, 1065, 1026 cm^{-1}. ^1H NMR: δ 7.62–7.36 (m, 5H, PhH), 4.49 (q, 1H, J=5.2 Hz, CHI), 3.13–3.11 (m, 1H, CF_2CH), 2.18–2.12 (m, 2H), 2.05–1.97 (m, 1H), 1.91–1.85 (m, 2H), 1.78–1.62 (m, 1H). ^{13}C NMR: δ 137.0, 131.8 (t, J=282.2 Hz), 130.5, 129.7, 127.0, 59.9 (t, J=22.1 Hz), 41.8, 27.7, 26.1, 22.9. ^{19}F NMR: δ −78.50 (dd, 1F, J_{F-F}=205.2 Hz, J_{H-F}=13.2 Hz), −80.32 (dd, 1F, J_{F-F}=205.2 Hz, J_{H-F}=14.8 Hz). HRMS (EI), $C_{12}H_{13}F_2IS$ calcd: 353.9751; found: 353.9763.

4.3.8. 3-(2,2-Difluoro-2-phenylsulfanyl-ethyl)-4-iodomethyl-tetrahydro-furan (**9a**)

Colorless oil. IR (film): 3059, 1580, 1311, 1240, 1214, 1167, 1115, 1051, 961, 914, 750, 691 cm^{-1}. ^1H NMR: δ (major) 7.61–7.38 (m, 5H, PhH), 4.03 (t, 1H, J=8.4 Hz), 3.99 (ddd, 1H, J_1=9.0 Hz, J_2=6.1 Hz, J_3=0.80 Hz), 3.75 (dd, 1H,

J_1=9.0 Hz, J_2=4.1 Hz), 3.61 (t, 1H, J=8.4 Hz), 3.19 (ddd, 1H, J_1=9.9 Hz, J_2=4.8 Hz, J_3=0.67 Hz), 3.02 (t, 1H, J=9.9 Hz), 2.79–2.74 (m, 1H, CF_2CH_2), 2.72–2.65 (m, 1H, CF_2CH_2), 2.45–2.08 (stack, 2H, CHCH); δ (minor) 7.61–7.38 (m, 5H, PhH), 4.18 (t, 1H, J=8.1 Hz), 3.98 (dd, 1H, J_1=9.3 Hz, J_2=6.9 Hz), 3.58 (dd, 1H, J_1=9.3 Hz, J_2=5.9 Hz), 3.53 (t, 1H, J_1=8.1 Hz), 3.29 (dd, 1H, J_1=9.8 Hz, J_2=4.9 Hz), 3.13 (t, 1H, J=9.8 Hz), 2.45–2.08 (stack, 4H, CF_2CH_2, CHCH). ^{13}C NMR: δ (major) 136.9, 130.7, 129.9 (t, J=276.8 Hz), 129.8, 127.1, 74.4, 72.4, 45.8, 38.7, 36.9 (t, J=23.9 Hz), 4.4; δ (minor) 136.9, 130.7, 129.9 (t, J=276.8 Hz), 129.8, 127.1, 74.9, 74.6, 48.3, 42.2 (t, J=22.2 Hz), 42.0, 7.9. ^{19}F NMR: δ (major) −72.00 (ddd, 1F, J_{F-F}=206.1 Hz, J_{1H-F}=17.9 Hz, J_{2H-F}=10.4 Hz), −74.00 (ddd, 1F, J_{F-F}=206.1 Hz, J_{1H-F}=17.9 Hz, J_{2H-F}=14.1 Hz); δ (minor) −71.44 (ddd, 1F, J_{F-F}=207.0 Hz, J_{1H-F}=18.3 Hz, J_{2H-F}= 10.4 Hz), −74.23 (dt, 1F, J_{F-F}=207.0 Hz, J_{H-F}=16.2 Hz). HRMS (EI), $C_{13}H_{15}OF_2IS$ calcd: 383.9856; found: 383.9856.

4.3.9. 3-Iodo-3-phenyl-thioacrylic acid S-phenyl ester (**12a**)

White crystal with mp: 130–131 °C. IR (KBr): 3051, 1689, 1577 cm^{-1}. ^{1}H NMR: δ 7.37–7.27 (m, 10H, PhH), 7.15 (s, 1H, =CH). ^{13}C NMR: δ 185.8, 142.6, 137.9, 135.1, 130.3, 130.2, 129.9, 128.7, 128.6, 127.8, 117.3. MS (EI, *m/z*): 366 (M^+, 0.2), 257 (100), 129 (12), 102 (36). Anal. Calcd for $C_{15}H_{11}IOS$: C, 49.20; H, 3.03. Found: C, 49.36; H, 2.96.

4.3.10. 1-Chloro-4-(1,1-difluoro-3-iodo-nonylsulfanyl)-benzene (**5ba′**)

Pale yellow oil. IR (film): 1574, 1476, 1261, 1216, 1156, 1094, 1048, 1014 cm^{-1}. ^{1}H NMR: δ 7.45–7.26 (m, 4H, PhH), 4.28–4.22 (m, 1H, CHI), 2.90–2.82 (m, 1H, CF_2CH_2), 2.79–2.70 (m, 1H, CF_2CH_2), 1.71–1.67 (m, 2H), 1.45–1.41 (m, 1H), 1.34–1.18 (stack, 7H), 0.81 (t, 3H, J=6.9 Hz, CH_3). ^{13}C NMR: δ 136.4, 135.7, 128.3, 127.7 (t, J=281.9 Hz), 123.6, 48.4 (t, J=23.0 Hz), 39.0, 30.6, 28.5, 27.2, 23.8, 21.5, 13.0. ^{19}F NMR: δ −70.48 (ddd, 1F, J_{F-F}=207.5 Hz, J_{1H-F}=17.9 Hz, J_{2H-F}= 9.9 Hz), −73.27 (dt, 1F, J_{F-F}=207.5 Hz, J_{H-F}=14.8 Hz). HRMS (EI), $C_{15}H_{20}ClF_2IS$ calcd: 431.9987; found: 431.9987.

4.3.11. 1-Chloro-4-(1,1-difluoro-3-iodo-heptylsulfanyl)-benzene (**5bb′**)

Pale yellow oil. IR (film): 1573, 1262, 1230, 1158, 1113, 1095, 1041, 1013 cm^{-1}. ^{1}H NMR: δ 7.46–7.28 (m, 4H, PhH), 4.27–4.24 (m, 1H, CHI), 2.90–2.84 (m, 1H, CF_2CH_2), 2.77–2.72 (m, 1H, CF_2CH_2), 1.72–1.68 (m, 2H), 1.49–1.41 (m, 1H), 1.29–1.24 (stack, 3H), 0.85 (t, 3H, J=7.0 Hz). ^{13}C NMR: δ 138.2, 137.4, 130.1, 129.4 (t, J=281.8 Hz), 125.2, 50.1 (t, J=23.0 Hz), 40.4, 32.3, 25.4, 22.3, 14.6. ^{19}F NMR: δ −70.53 (ddd, 1F, J_{F-F}= 204.7 Hz, J_{1H-F}=17.9 Hz, J_{2H-F}=9.9 Hz), −73.33 (ddd, 1F, J_{F-F}=204.7 Hz, J_{1H-F}=16.0 Hz, J_{2H-F}=14.6 Hz). HRMS (EI), $C_{13}H_{16}ClF_2IS$ calcd: 403.9674; found: 403.9646.

4.3.12. 4-(4-Chlorophenylthio)-4,4-difluoro-2-iodobutan-1-ol (**5bc′**)

Pale yellow oil. IR (film): 3325 (br), 1570, 1207, 1166, 1092, 1020 cm^{-1}. ^{1}H NMR: δ 7.46–7.29 (m, 4H, PhH), 4.39–4.35 (m, 1H, CHI), 3.74–3.61 (m, 2H, CH_2O), 2.95–2.87 (m, 1H, CF_2CH_2), 2.79–2.71 (m, 1H, CF_2CH_2), 1.99 (s, 1H, OH). ^{13}C NMR: δ 136.5, 135.9, 128.5, 127.5 (t, J=281.4 Hz), 123.4, 66.7, 44.2 (t, J=23.8 Hz), 25.1. ^{19}F NMR: δ −71.66 to −72.13 (m, 1F), −73.40 to −73.80 (m, 1F). HRMS (EI), $C_{10}H_{10}ClF_2IOS$ calcd: 377.9154; found: 377.9147.

4.3.13. 5-(4-Chloro-phenylsulfanyl)-5,5-difluoro-3-iodo-pentanenitrile (**5bd′**)

Pale yellow oil. IR (film): 3086, 2253, 1605, 1572, 1262, 1237, 1212, 1148, 1093, 1061 cm^{-1}. ^{1}H NMR: δ 7.44–7.28 (m, 4H, PhH), 4.36–4.31 (m, 1H, CHI), 3.15 (dd, 1H, J_1=17.6 Hz, J_2=6.3 Hz, CH_2CN), 3.06 (dd, 1H, J_1=17.6 Hz, J_2=4.3 Hz, CH_2CN), 2.92–2.84 (m, 2H, CF_2CH_2). ^{13}C NMR: δ 136.5, 136.1, 128.6, 127.3 (t, J=281.4 Hz), 122.7, 115.9, 46.9 (t, J=23.8 Hz), 28.9, 8.2. ^{19}F NMR: δ −71.60 (dt, 1F, J_{F-F}=207.5 Hz, J_{H-F}=13.6 Hz), −74.92 (dt, 1F, J_{F-F}= 207.5 Hz, J_{H-F}=15.0 Hz). HRMS (EI), $C_{11}H_9ClF_2INS$ calcd: 386.9157; found: 386.9157.

4.3.14. Propionic acid 4-(4-chloro-phenylsulfanyl)-4,4-difluoro-2-iodo-butyl ester (**5be′**)

Pale yellow oil. IR (film): 1744, 1573, 1261, 1230, 1162, 1091, 1015 cm^{-1}. ^{1}H NMR: δ 7.46–7.29 (m, 4H, PhH), 4.36–4.33 (m, 1H, CHI), 4.28–4.20 (m, 2H, CH_2O), 2.90–2.69 (m, 2H, CF_2CH_2), 2.31 (q, 2H, J=7.6 Hz, CH_2CO), 1.09 (t, 3H, J=7.6 Hz, CH_3). ^{13}C NMR: δ 174.2, 138.2, 137.6, 130.2, 129.0 (t, J=281.3 Hz), 125.0, 68.9, 46.4 (t, J=24.0 Hz), 28.1, 16.7, 9.7. ^{19}F NMR: δ −72.10 (ddd, 1F, J_{F-F}=206.5 Hz, J_{1H-F}=16.9 Hz, J_{2H-F}=10.8 Hz), −73.47 (ddd, 1F, J_{F-F}= 206.5 Hz, J_{1H-F}=16.0 Hz, J_{2H-F}=13.2 Hz). HRMS (EI), $C_{13}H_{14}ClF_2IO_2S$ calcd: 433.9416; found: 433.9415.

4.3.15. 1-(5-Bromo-1,1-difluoro-3-iodo-pentylsulfanyl)-4-chloro-benzene (**5bf′**)

Pale yellow oil. IR (film): 1573, 1288, 1247, 1200, 1161, 1094, 1054, 1033, 1012 cm^{-1}. ^{1}H NMR: δ 7.46–7.28 (m, 4H, PhH), 4.44–4.38 (m, 1H, CHI), 3.53–3.49 (m, 1H, CH_2Br), 3.42–3.37 (m, 1H, CH_2Br), 2.98–2.88 (m, 1H, CF_2CH_2), 2.81–2.71 (m, 1H, CF_2CH_2), 2.20–2.15 (m, 2H, CH_2CH_2Br). ^{13}C NMR: δ 138.0, 137.4, 130.0, 129.2 (t, J=281.8 Hz), 124.8, 49.7 (t, J=23.4 Hz), 42.4, 33.8, 22.2. ^{19}F NMR: δ −69.86 (ddd, 1F, J_{F-F}=206.1 Hz, J_{1H-F}=16.9 Hz, J_{2H-F}= 9.9 Hz), −72.85 (dt, 1F, J_{F-F}=206.1 Hz, J_{H-F}=15.3 Hz). HRMS (EI), $C_{11}H_{11}BrClF_2IS$ calcd: 453.8446; found: 453.8451.

4.3.16. trans-1-Chloro-4-[difluoro-(2-iodo-cyclopentyl)-methylsulfanyl]-benzene (**7b**)

Pale yellow oil. IR (film): 1571, 1475, 1256, 1195, 1176, 1148, 1093, 1064, 1043 cm^{-1}. ^{1}H NMR: δ 7.56–7.34 (m, 4H, PhH), 4.46 (q, 1H, J=5.1 Hz, CHI), 3.17–3.07 (m, 1H, CF_2CH), 2.18–2.12 (m, 2H), 2.01–1.97 (m, 1H), 1.90–1.77 (m, 2H), 1.78–1.71 (m, 1H). ^{13}C NMR: δ 138.3, 137.2, 131.6 (t, J=282.5 Hz), 130.0, 125.4, 59.9 (t, J=21.9 Hz), 41.8, 27.8, 26.1, 22.5. ^{19}F NMR: δ −78.82 (dd, 1F, J_{F-F}= 204.7 Hz, J_{H-F}=14.1 Hz), −79.93 (dd, 1F, J_{F-F}=204.7 Hz,

J_{H-F}=14.6 Hz). HRMS (EI), $C_{12}H_{12}ClF_2IS$ calcd: 387.9361; found: 387.9361.

4.3.17. 3-[(4-Chloro-phenylsulfanyl)-difluoro-methyl]-4-iodomethyl-tetrahydro-furan (**9b**)

Pale yellow oil. IR (film): 1573, 1476, 1260, 1241, 1215, 1168, 1093, 1014 cm^{-1}. ^1H NMR: δ (major) 7.43–7.25 (m, 4H), 3.91 (t, 1H, J=8.0 Hz), 3.87 (dd, 1H, J_1=8.9 Hz, J_2=6.3 Hz), 3.63 (dd, 1H, J_1=8.9 Hz, J_2=4.3 Hz), 3.51 (t, 1H, J=8.0 Hz), 3.08 (dd, 1H, J_1=9.7 Hz, J_2=4.9 Hz), 2.92 (t, 1H, J=9.7 Hz), 2.67–2.62 (m, 1H, CF_2CH_2), 2.60–2.53 (m, 1H, CF_2CH_2), 2.30–2.01 (stack, 2H, CHCH); δ (minor) 7.43–7.25 (m, 4H, PhH), 4.06 (t, 1H, J=7.8 Hz), 3.83 (dd, 1H, J_1=9.0 Hz, J_2=7.3 Hz), 3.47 (dd, 1H, J_1=9.0 Hz, J_2=6.0 Hz), 3.41 (t, 1H, J=7.8 Hz), 3.19 (dd, 1H, J_1=9.1 Hz, J_2=4.0 Hz), 3.03 (t, 1H, J=9.1 Hz), 2.32–2.01 (stack, 4H, CF_2CH_2, CHCH). ^{13}C NMR: δ (major) 137.9, 137.1, 129.9, 129.5 (t, J=279.9 Hz), 125.2, 74.0, 72.0, 45.6, 38.4, 36.6 (t, J=23.5 Hz), 4.3; δ (minor) 137.9, 137.0, 129.9, 129.4 (t, J=279.9 Hz), 125.3, 74.5, 74.3, 48.0, 41.9 (t, J=23.2 Hz), 41.8, 7.9. ^{19}F NMR: δ (major) −71.62 (ddd, 1F, J_{F-F}=203.7 Hz, J_{1H-F}=17.9 Hz, J_{2H-F}=10.4 Hz), −73.67 (dt, 1F, J_{F-F}=203.7 Hz, J_{H-F}=15.8 Hz); δ (minor) −71.3 (ddd, 1F, J_{F-F}=204.7 Hz, J_{1H-F}=18.3 Hz, J_{2H-F}=9.9 Hz), −73.75 (dt, 1F, J_{F-F}=204.7 Hz, J_{H-F}=16.2 Hz). HRMS (EI), $C_{13}H_{14}ClF_2IOS$ calcd: 417.9467; found: 417.9467.

4.3.18. 3-(4-Chloro-phenyl)-3-iodo-thioacrylic acid S-phenyl ester (**12b**)

White crystal with mp: 103–104 °C. E/Z=7.6:1. IR (KBr): 3050, 1691, 1570, 1092 cm^{-1}. ^1H NMR: δ (Z) 7.42–7.22 (m, 9H, PhH), 7.08 (s, 1H, =CH); δ (E) 7.42–7.22 (m, 9H, PhH), 7.14 (s, 1H, =CH). ^{13}C NMR: δ (Z) 186.0, 143.9, 136.8, 136.4, 131.5, 131.2, 130.2, 129.7, 129.2, 126.1, 114.0; δ (E) 185.1, 142.5, 137.5, 136.7, 136.3, 130.4, 130.1, 128.7, 128.5, 126.2, 118.1. MS (EI, m/z): 400 (M^+, 0.1), 257 (100), 102 (41). Anal. Calcd for $C_{15}H_{10}ClIOS$: C, 44.97; H, 2.52. Found: C, 45.39; H, 2.36.

4.4. General procedure for the reaction of **3** with pent-4-en-1-ols **13**

The addition of **3** (2 mmol) to pent-4-en-1-ols **13** (2 mmol) was carried out under the same conditions as alkenes. After usual work-up, the crude adduct was dissolved in DMF (4 mL), the mixture was heated in 130 °C oil bath for 1 h, and then cooled to room temperature. The mixture was treated with 10% Na_2SO_3 (10 mL) and then extracted with ethyl ether (3×10 mL). The combined organic layers were washed with saturated brine and water, and then dried over anhydrous sodium sulfate. After removal of ethyl ether, the residue was purified by column chromatography eluting with PE and EA to give the corresponding tetrahydrofuran derivatives.

4.4.1. 2-(2,2-Difluoro-2-phenylsulfanyl-ethyl)-4-methyl-tetrahydro-furan (**14aa′**)

Colorless oil. IR (film): 3060, 1612, 1582, 1441, 1169, 1136, 1101, 1025 cm^{-1}. ^1H NMR: δ (trans) 7.62–7.34 (m, 5H, PhH), 4.33–4.28 (m, 1H, CHO), 3.99 (dd, 1H, J_1=8.4 Hz, J_2=6.9 Hz, CH_2O), 3.30 (dd, 1H, J_1=8.4 Hz, J_2=6.6 Hz, CH_2O), 2.58–2.42 (m, 1H, CF_2CH_2), 2.38–2.19 (stack, 2H, CF_2CH_2, $CHCH_3$), 1.81–1.70 (m, 2H, CH_2CHCH_3), 1.03 (d, 3H, J=6.8 Hz, CH_3); δ (cis) 7.62–7.34 (m, 5H, PhH), 4.23–4.19 (m, 1H, CHO), 3.90 (t, 1H, J=8.0 Hz, CH_2O), 3.36 (t, 1H, J=8.0 Hz, CH_2O), 2.58–2.42 (m, 1H, CF_2CH_2), 2.38–2.19 (stack, 3H, CF_2CH_2, $CHCH_3$, CH_2CHCH_3), 1.21–1.15 (m, 1H, CH_2CHCH_3), 1.04 (d, 3H, J=6.4 Hz, CH_3). ^{13}C NMR: δ (trans) 136.8, 130.4, 129.6, 129.3 (t, J=278.8 Hz), 127.6, 75.5, 75.1, 45.3 (t, J=22.5 Hz), 40.8, 33.6, 18.6; δ (cis) 136.8, 130.4, 129.6, 129.3 (t, J=278.8 Hz), 127.6, 75.3, 74.0, 45.5 (t, J=22.7 Hz), 42.1, 34.9, 18.1. ^{19}F NMR: δ (trans) −71.08 (ddd, 1F, J_{F-F}=207.0 Hz, J_{1H-F}=15.1 Hz, J_{2H-F}=12.2 Hz), −72.86 (dt, 1F, J_{F-F}=207.0 Hz, J_{H-F}=16.0 Hz); δ (cis) −70.93 (ddd, 1F, J_{F-F}=207.0 Hz, J_{1H-F}=15.1 Hz, J_{2H-F}=12.7 Hz), −72.94 (dt, 1F, J_{F-F}=207.0 Hz, J_{H-F}=16.5 Hz). HRMS (EI), $C_{13}H_{16}F_2OS$ calcd: 258.0890; found: 258.0887.

4.4.2. 2-(2,2-Difluoro-2-phenylsulfanyl-ethyl)-tetrahydro-furan (**14ab′**)

Colorless oil. IR (film): 3060, 1581, 1440, 1240, 1168, 1126, 1083, 1025 cm^{-1}. ^1H NMR: δ 7.62–7.34 (m, 5H, PhH), 4.19–4.11 (m, 1H, CHO), 3.90–3.85 (m, 1H, CH_2O), 3.79–3.74 (m, 1H, CH_2O), 2.55–2.45 (m, 1H, CF_2CH_2), 2.33–2.22 (m, 1H, CF_2CH_2), 2.16–2.10 (m, 1H), 1.94–1.83 (m, 2H), 1.60–1.52 (m, 1H). ^{13}C NMR: δ 136.3, 129.8, 129.3, 128.7 (t, J=278.7 Hz), 127.0, 74.0, 67.8, 44.5 (t, J=22.7 Hz), 36.4, 25.6. ^{19}F NMR: δ −71.16 (ddd, 2F, J_{F-F}=207.0 Hz, J_{1H-F}=15.5 Hz, J_{2H-F}=12.7 Hz), −72.93 (dt, 2F, J_{F-F}=207.0 Hz, J_{H-F}=16.2 Hz). HRMS (EI), $C_{12}H_{14}F_2OS$ calcd: 244.0733; found: 244.0724.

4.4.3. 2-(2,2-Difluoro-2-phenylsulfanyl-ethyl)-3,3-dimethyl-tetrahydro-furan (**14ac′**)

Colorless oil. IR (film): 3023, 1583, 1473, 1261, 1176, 1051, 1021 cm^{-1}. ^1H NMR: δ 7.64–7.35 (m, 5H, PhH), 3.95–3.86 (stack, 2H, CH_2O, CHO), 3.71 (dd, 1H, J_1=8.3 Hz, J_2=2.9 Hz, CH_2O), 2.29–2.15 (m, 2H, CF_2CH_2), 1.84–1.78 (m, 1H, CH_2C), 1.75–1.70 (m, 1H, CH_2C), 1.04 (s, 3H, CH_3), 0.88 (s, 3H, CH_3). ^{13}C NMR: δ 136.9, 130.3, 130.1 (t, J=279.2 Hz), 129.6, 127.7, 82.2, 66.5, 41.6, 41.3, 40.4 (t, J=23.3 Hz), 25.3, 22.0. ^{19}F NMR: δ −70.64 (dt, 1F, J_{F-F}=205.1 Hz, J_{H-F}=15.3 Hz), −71.67 (dt, 1F, J_{F-F}=205.1 Hz, J_{H-F}=14.5 Hz). HRMS (EI), $C_{14}H_{18}F_2OS$ calcd: 272.1046; found: 272.1028.

4.4.4. 2-(2,2-Difluoro-2-phenylsulfanyl-ethyl)-4-phenyl-tetrahydro-furan (**14ad′**)

Colorless oil. IR (film): 3061, 1603, 1494, 1253, 1223, 1170, 1081, 1026 cm^{-1}. ^1H NMR: δ (trans): 7.64–7.25 (m, 10H, PhH), 4.53–4.48 (m, 1H, CHO), 4.26 (dd, 1H, J_1=8.5 Hz, J_2=7.4 Hz, CH_2O), 3.75 (t, 1H, J=8.5 Hz, CH_2O), 3.58–3.43 (m, 1H, CHPh), 2.68–2.52 (m, 1H, CF_2CH_2), 2.45–2.31 (m, 1H, CF_2CH_2), 2.30–2.22 (m, 1H,

CH_2CHPh), 2.17–2.11 (m, 1H, CH_2CHPh); δ (cis) 7.64–7.25 (m, 10H, PhH), 4.40–4.38 (m, 1H, CHO), 4.19 (t, 1H, J=8.2 Hz, CH_2O), 3.85 (t, 1H, J=8.2 Hz, CH_2O), 3.58–3.43 (m, 1H, CHPh), 2.68–2.52 (stack, 2H, CF_2CH_2, CH_2CHPh), 2.45–2.31 (m, 1H, CF_2CH_2), 1.79–1.77 (m, 1H, CH_2CHPh). ^{13}C NMR: δ (trans) 142.8, 137.0, 130.6, 129.8, 129.4, 129.3 (t, J=278.4 Hz), 128.0, 127.6, 127.1, 75.4, 74.8, 45.6 (t, J=22.7 Hz), 45.1, 41.0; δ (cis) 142.5, 137.0, 130.6, 129.8, 129.4, 129.3 (t, J=278.4 Hz), 127.9, 127.6, 127.4, 75.6, 74.9, 46.1, 45.3 (t, J=22.3 Hz), 42.2. ^{19}F NMR: δ (trans) −70.97 (dt, 1F, J_{F-F}=207.5 Hz, J_{H-F}=15.5 Hz), −72.63 (dt, 1F, J_{F-F}=207.5 Hz, J_{H-F}=16.0 Hz); δ (cis) −70.80 (dt, 1F, J_{F-F}=207.5 Hz, J_{H-F}=13.2 Hz), −72.87 (dt, 1F, J_{F-F}=207.5 Hz, J_{H-F}=15.4 Hz). HRMS (EI), $C_{18}H_{18}F_2OS$ calcd: 320.1046; found: 320.1046.

*4.4.5. 2-[2-(4-Chloro-phenylsulfanyl)-2,2-difluoro-ethyl]-4-methyl-tetrahydro-furan (**14ba′**)*

Colorless oil. IR (film): 3065, 1574, 1477, 1259, 1230, 1171, 1137, 1095, 1015 cm^{-1}. ^{1}H NMR: δ (trans) 7.55–7.34 (m, 4H, PhH), 4.34–4.26 (m, 1H, CHO), 4.01 (dd, 1H, J_1=8.3 Hz, J_2=6.7 Hz, CH_2O), 3.32 (dd, 1H, J_1=8.3 Hz, J_2=6.9 Hz, CH_2O), 2.58–2.42 (m, 1H, CF_2CH_2), 2.39–2.18 (stack, 2H, CF_2CH_2, CHCH$_3$), 1.85–1.74 (stack, 2H, CH_2CHCH$_3$), 1.04 (d, 3H, J=6.8 Hz, CH_3); δ (cis) 7.55–7.34 (m, 4H, PhH), 4.24–4.15 (m, 1H, CHO), 3.93 (t, 1H, J=7.8 Hz, CH_2O), 3.37 (t, 1H, J=7.8 Hz, CH_2O), 2.58–2.42 (m, 1H, CF_2CH_2), 2.39–2.18 (m, 3H, CF_2CH_2, CHCH$_3$, CH_2CHCH$_3$), 1.21–1.18 (m, 1H, CH_2CHCH$_3$), 1.05 (d, 3H, J=6.5 Hz, CH_3). ^{13}C NMR: δ (trans) 138.1, 137.1, 129.9, 129.1 (t, J=279.2 Hz), 126.0, 75.7, 73.9, 45.4 (t, J=22.4 Hz), 40.8, 33.7, 18.6; δ (cis) 138.1, 137.1, 129.9, 129.1 (t, J=279.2 Hz), 126.0, 75.3, 75.2, 45.5 (t, J=22.4 Hz), 42.1, 35.0, 18.1. ^{19}F NMR: δ (trans) −70.65 (dt, 1F, J_{F-F}=205.6 Hz, J_{H-F}=13.6 Hz), −72.70 (dt, 1F, J_{F-F}=205.6 Hz, J_{H-F}=16.5 Hz); δ (cis) −70.73 (dt, 1F, J_{F-F}=205.6 Hz, J_{H-F}=13.9 Hz), −72.78 (dt, 1F, J_{F-F}=205.6 Hz, J_{H-F}=16.2 Hz). HRMS (EI), $C_{13}H_{15}ClF_2OS$ calcd: 292.0500; found: 292.0500.

*4.4.6. 2-[2-(4-Chloro-phenylsulfanyl)-2,2-difluoro-ethyl]-tetrahydro-furan (**14bb′**)*

IR (film): 3063, 1574, 1477, 1258, 1171, 1093, 1016 cm^{-1}. ^{1}H NMR: δ 7.55–7.26 (m, 4H, PhH), 4.18–4.12 (m, 1H, CHO), 3.91–3.86 (m, 1H, CH_2O), 3.98–3.76 (m, 1H, CH_2O), 2.51–2.43 (m, 1H, CF_2CH_2), 2.32–2.27 (m, 1H, CF_2CH_2), 2.17–2.12 (m, 1H), 2.00–1.85 (m, 2H), 1.60–1.53 (m, 1H). ^{13}C NMR: δ 138.2, 137.1, 129.9, 129.2 (t, J=279.2 Hz), 126.0, 74.5, 68.6, 45.1 (t, J=22.9 Hz), 32.8, 26.2. ^{19}F NMR ($CDCl_3$) δ −70.69 (ddd, 1F, J_{F-F}=205.6 Hz, J_{1H-F}=15.1 Hz, J_{2H-F}=12.2 Hz), −72.69 (dt, 1F, J_{F-F}=205.6 Hz, J_{H-F}=16.2 Hz). HRMS (EI), $C_{12}H_{13}ClF_2OS$ calcd: 278.0344; found: 278.0344.

*4.4.7. 2-[2-(4-Chloro-phenylsulfanyl)-2,2-difluoro-ethyl]-3,3-dimethyl-tetrahydro-furan (**14bc′**)*

Colorless oil. IR (film): 3066, 1574, 1259, 1177, 1093, 1050, 1015 cm^{-1}. ^{1}H NMR: δ 7.56–7.34 (m, 4H, PhH), 3.96–3.86 (stack, 2H, CHO, CH_2O), 3.69 (dd, 1H, J_1=7.9 Hz, J_2=3.1 Hz, CH_2O), 2.29–2.18 (m, 2H, CF_2CH_2), 1.85–1.79 (m, 1H, CH_2C), 1.76–1.71 (m, 1H, CH_2C), 1.05 (s, 3H, CH_3), 0.89 (s, 3H, CH_3). ^{13}C NMR: δ 138.2, 137.0, 129.9, 129.8 (t, J=262.0 Hz), 126.1, 81.6, 66.6, 41.7, 41.3, 40.4 (t, J=23.1 Hz), 25.3, 22.0. ^{19}F NMR: δ −70.99 to −71.06 (m, 2F). HRMS (EI), $C_{14}H_{17}ClF_2OS$ calcd: 306.0657; found: 306.0657.

*4.4.8. 2-[2-(4-Chloro-phenylsulfanyl)-2,2-difluoro-ethyl]-4-phenyl-tetrahydro-furan (**14bd′**)*

Colorless oil. IR (film): 3086, 1568, 1386, 1251, 1163, 1094, 1043, 1001 cm^{-1}. ^{1}H NMR: δ (trans) 7.58–7.24 (m, 9H, PhH), 4.52–4.47 (m, 1H, CHO), 4.26 (dd, 1H, J_1=8.5 Hz, J_2=7.6 Hz, CH_2O), 3.76 (t, 1H, J=8.5 Hz, CH_2O), 3.52–3.43 (m, 1H, CHPh), 2.68–2.54 (m, 1H, CF_2CH_2), 2.48–2.30 (m, 1H, CF_2CH_2), 2.29–2.23 (m, 1H, CH_2CHPh), 2.16–2.10 (m, 1H, CH_2CHPh); δ (cis) 7.58–7.24 (m, 9H, PhH), 4.42–4.10 (m, 1H, CHO), 4.19 (t, 1H, J=8.3 Hz, CH_2O), 3.83 (t, 1H, J=8.3 Hz, CH_2O), 3.52–3.43 (m, 1H, CHPh), 2.68–2.54 (stack, 2H, CF_2CH_2, CH_2CHPh), 2.48–2.30 (m, 1H, CF_2CH_2), 1.78–1.72 (m, 1H, CH_2CHPh). ^{13}C NMR: δ (trans) 142.0, 137.5, 136.5, 129.3, 128.7, 128.4 (t, J=279.4 Hz), 127.2, 126.6, 125.2, 74.6, 74.0, 44.8 (t, J=22.4 Hz), 44.3, 40.3; δ (cis) 141.6, 137.5, 136.5, 129.3, 128.6, 128.4 (t, J=279.4 Hz), 127.1, 126.7, 125.2, 74.8, 74.2, 45.3, 44.5 (t, J=22.4 Hz), 41.4. ^{19}F NMR: δ (trans) −70.64 (dt, 1F, J_{F-F}=206.5 Hz, J_{H-F}=14.1 Hz), −72.54 (dt, 1F, J_{F-F}=206.5 Hz, J_{H-F}=16.0 Hz); δ (cis) −70.72 (dt, 1F, J_{F-F}=206.1 Hz, J_{H-F}=14.1 Hz), −72.67 (dt, 1F, J_{F-F}=206.1 Hz, J_{H-F}=16.0 Hz). HRMS (EI), $C_{18}H_{17}ClF_2OS$ calcd: 354.0657; found: 354.0657.

*4.5. General procedure for the reaction of **3** with pent-4-enoic acids **15***

Pent-4-enoic acid **15** (2 mmol) was dissolved in a solution of NaOH (80 mg, 2 mmol) in water (2 mL). Acetonitrile (6 mL) and **3** (2 mmol) were then added while stirring. Sodium dithionite (560 mg, 3.2 mmol) and sodium bicarbonate (270 mg, 3.2 mmol) were added to the solution at 25 °C in 20 min. After stirring for 6–8 h at this temperature, water (ca. 15 mL) was added. The mixture was extracted with ethyl ether (3×15 mL). The combined organic layers were washed with saturated brine and dried over anhydrous sodium sulfate. After evaporation of ethyl ether, the crude product was purified by column chromatography eluting with PE and EA to give the corresponding lactones.

*4.5.1. 5-(2,2-Difluoro-2-phenylsulfanyl-ethyl)-dihydro-furan-2-one (**16aa′**)*

Colorless oil. IR (film): 3062, 1780, 1603, 1250, 1219, 1187, 1154, 1073, 1023 cm^{-1}. ^{1}H NMR: δ 7.62–7.34 (m, 5H, PhH), 4.84–4.78 (m, 1H, CHO), 2.73–2.63 (m, 1H, CF_2CH_2), 2.59–2.36 (stack, 4H, CF_2CH_2, CH_2CO, CH_2CH_2CO), 2.01–1.93 (m, 1H, CH_2CH_2CO). ^{13}C NMR: δ 176.8, 136.9, 130.8, 129.9, 128.5 (t, J=278.8 Hz), 126.8, 75.7, 44.5 (t, J=23.8 Hz), 29.3, 29.1. ^{19}F NMR: δ −71.45 (ddd, 1F, J_{F-F}=210.8 Hz,

J_{1H-F}=16.9 Hz, J_{2H-F}=10.8 Hz), −73.56 (dt, 1F, J_{F-F}= 210.8 Hz, J_{H-F}=15.8 Hz). HRMS (EI), $C_{12}H_{12}O_2F_2S$ calcd: 258.0526; found: 258.0527.

*4.5.2. 5-(2,2-Difluoro-2-phenylsulfanyl-ethyl)-4,4-dimethyl-dihydro-furan-2-one (**16ab′**)*

Colorless oil. IR (film): 3062, 1784, 1580, 1396, 1377, 1311, 1288, 1255, 1232, 1199, 1172, 1152 cm^{-1}. ^1H NMR: δ 7.63–7.39 (m, 5H, PhH), 4.35 (d, 1H, J=8.4 Hz, CHO), 2.45 (d, 1H, J=16.8 Hz, CH_2C), 2.51–2.50 (m, 2H, CF_2CH_2), 2.31 (d, 1H, J=16.8 Hz, CH_2C), 1.16 (s, 3H, CH_3), 0.99 (s, 3H, CH_3). ^{13}C NMR: δ 175.8, 136.9, 130.7, 129.8, 129.0 (t, J=279.5 Hz), 126.9, 82.8, 44.9, 40.3, 39.1 (t, J=24.6 Hz), 24.8, 21.8. ^{19}F NMR: δ −72.02 (dt, 1F, J_{F-F}=208.9 Hz, J_{H-F}=14.6 Hz), −72.61 (dt, 1F, J_{F-F}=208.9 Hz, J_{H-F}=13.9 Hz). HRMS (EI), $C_{14}H_{16}F_2O_2S$ calcd: 286.0839; found: 286.0840.

*4.5.3. 5-(2,2-Difluoro-2-phenylsulfanyl-ethyl)-3-methyl-dihydro-furan-2-one (**16ac′**)*

Colorless oil. IR (film): 2833, 1760, 1580, 1368, 1210, 1179, 1160, 1115, 1072, 1044 cm^{-1}. ^1H NMR: δ (cis) 7.32–7.55 (m, 5H, PhH), 4.65–4.58 (m, 1H, CHO), 2.70–2.50 (stack, 3H, CF_2CH_2, CHCO, CH_2CHCO), 2.38–2.25 (m, 1H, CF_2CH_2), 1.60–1.52 (m, 1H, CH_2CHCO), 1.21 (d, 3H, J=6.8 Hz, CH_3); δ (trans) 7.32–7.55 (m, 5H, PhH), 4.84–4.77 (m, 1H, CHO), 2.70–2.50 (stack, 2H, CF_2CH_2, CHCO), 2.38–2.25 (m, 1H, CF_2CH_2), 2.25–2.17 (m, 1H, CH_2CHCO), 2.09–2.05 (m, 1H, CH_2CHCO), 1.24 (d, 3H, J=7.4 Hz, CH_3). ^{13}C NMR: δ (cis) 179.1, 136.9, 130.8, 129.9, 128.5 (t, J=278.8 Hz), 126.9, 73.5, 44.7 (t, J=24.6 Hz), 38.5, 36.5, 15.5; δ (trans) 179.6, 136.9, 130.8, 129.9, 128.5 (t, J=278.8 Hz), 126.9, 73.5, 44.4 (t, J=23.4 Hz), 36.1, 34.3, 16.3. ^{19}F NMR: δ −71.37 (ddd, 1F, J_{F-F}=210.8 Hz, J_{1H-F}=16.0 Hz, J_{2H-F}=10.8 Hz), −73.73 (dt, 1F, J_{F-F}=210.8 Hz, J_{H-F}=15.5 Hz). HRMS (EI), $C_{13}H_{14}F_2O_2S$ calcd: 272.0683; found: 272.0689.

*4.5.4. 3-Benzyl-5-(2,2-difluoro-2-phenylsulfanyl-ethyl)-dihydro-furan-2-one (**16ad′**)*

Colorless oil. IR (film): 3060, 1769, 1600, 1363, 1280, 1244, 1216, 1183, 1150, 1093, 1070, 1054, 1024 cm^{-1}. ^1H NMR: δ (cis) 7.59–7.17 (m, 10H, PhH), 4.68–4.60 (m, 1H, CHO), 3.29 (dd, 1H, J_1=14.0 Hz, J_2=4.2 Hz, $PhCH_2$), 2.93–2.91 (m, 1H, CHBn), 2.73 (dd, 1H, J_1=14.0 Hz, J_2=9.5 Hz, $PhCH_2$), 2.59–2.53 (m, 1H, CF_2CH_2), 2.48–2.43 (m, 1H, CH_2CHCO), 2.36–2.29 (m, 1H, CF_2CH_2), 1.71–1.64 (m, 1H, CH_2CHCO); δ (trans) 7.59–7.17 (m, 10H, PhH), 4.62–4.59 (m, 1H, CHO), 3.16 (dd, 1H, J_1=13.7 Hz, J_2=4.6 Hz, $PhCH_2$), 2.96–2.90 (m, 1H, CHBn), 2.83 (dd, 1H, J_1=13.7 Hz, J_2=9.1 Hz, $PhCH_2$), 2.59–2.53 (m, 1H, CF_2CH_2), 2.36–2.29 (m, 1H, CF_2CH_2), 2.28–2.21 (m, 1H, CH_2CHCO), 2.11–2.05 (m, 1H, CH_2CHCO). ^{13}C NMR: δ (cis) 177.5, 138.7, 136.6, 130.6, 129.6, 129.2, 129.1, 128.2 (t, J=278.1 Hz), 127.3, 126.6, 73.6, 44.3 (t, J=23.8 Hz), 42.8, 36.7, 36.4; δ (trans) 178.4, 138.5, 136.9, 130.8, 129.9, 129.6, 129.4, 128.4 (t, J=275.6 Hz), 127.6, 127.3, 73.6, 44.4 (t, J=23.8 Hz), 41.4, 34.8, 33.6. ^{19}F NMR: δ −71.31 to −71.91 (m, 1F), −73.52 to −74.11 (m, 1F). HRMS (EI), $C_{19}H_{18}F_2O_2S$ calcd: 348.0996; found: 348.0956.

*4.5.5. 5-(2,2-Difluoro-2-phenylsulfanyl-ethyl)-3-phenyl-dihydro-furan-2-one (**16ae′**)*

White powder with mp: 78–80 °C. IR (KBr): 3085, 3062, 1767, 1603, 1362, 1274, 1252, 1159, 1091, 1064, 1039 cm^{-1}. ^1H NMR: δ (cis) 7.63–7.26 (m, 10H, PhH), 4.87–4.81 (m, 1H, CHO), 3.93–3.87 (m, 1H, CHPh), 2.95–2.91 (m, 1H, CH_2CHCO), 2.88–2.68 (m, 1H, CF_2CH_2), 2.56–2.45 (m, 1H, CF_2CH_2), 2.24–2.20 (m, 1H, CH_2CHCO); δ (trans) 7.63–7.26 (m, 10H, PhH), 4.99–4.94 (m, 1H, CHO), 3.93–3.87 (m, 1H, CHPh), 2.88–2.68 (stack, 2H, CF_2CH_2, CH_2CHCO), 2.56–2.45 (stack, 2H, CF_2CH_2, CH_2CHCO). ^{13}C NMR: δ (cis) 176.4, 136.9, 136.5, 130.8, 129.9, 129.7, 129.5 (t, J=274.6 Hz), 128.7, 128.1, 126.3, 73.5, 47.3, 44.5 (t, J=23.7 Hz), 39.1; δ (trans) 176.8, 136.9, 137.0, 130.8, 129.9, 129.7, 129.5 (t, J=274.6 Hz), 128.4, 128.1, 126.8, 74.0, 45.7, 44.4 (t, J=23.64 Hz), 37.2. ^{19}F NMR: δ −71.13 to −71.64 (m, 1F), −73.38 to −73.89 (m, 1F). HRMS (EI), $C_{18}H_{16}F_2O_2S$ calcd: 334.0839; found: 334.0833.

*4.5.6. N-[5-(2,2-Difluoro-2-phenylsulfanyl-ethyl)-2-oxo-tetrahydro-furan-3-yl]-4-methoxy-benzamide (**16af′**)*

White powder with mp: 152–153 °C. IR (KBr, cm^{-1}): 3417, 3058, 1774, 1661, 1607, 1373, 1311, 1254, 1185, 1099, 1062, 1038 cm^{-1}. ^1H NMR: δ (cis) 7.75–7.38 (m, 7H, PhH), 7.02 (br, 1H, NH), 6.87–6.84 (m, 2H, PhH), 4.71–4.78 (stack, 2H, CHO, CHNH), 3.81 (s, 3H, OCH_3), 3.10–3.00 (m, 1H, CH_2CHCO), 2.79–2.71 (m, 1H, CF_2CH_2), 2.49–2.35 (m, 1H, CF_2CH_2), 2.12–1.02 (m, 1H, CH_2CHCO); δ (trans) 7.75–7.38 (m, 7H, PhH), 7.16 (br, 1H, NH), 6.87–6.84 (m, 2H, PhH), 5.10–5.08 (m, 1H, CHNH), 4.70–4.65 (m, 1H, CHO), 3.81 (s, 3H, OCH_3), 2.69–2.50 (stack, 2H, CF_2CH_2, CH_2CHCO), 2.49–2.35 (stack, 2H, CF_2CH_2, CH_2CHCO). ^{13}C NMR: δ (cis) 175.5, 167.8, 137.0, 130.8, 130.0, 129.8, 129.7, 128.3 (t, J=276.8 Hz), 126.7, 125.7, 114.5, 73.5, 56.0, 51.0, 44.4 (t, J=23.8 Hz), 37.0; δ (trans) 175.9, 163.3, 137.0, 130.8, 130.0, 129.8, 129.7, 128.4 (t, J=276.8 Hz), 126.7, 125.6, 114.5, 74.1, 56.0, 49.3, 44.4 (t, J=23.8 Hz), 35.1. ^{19}F NMR: δ −71.69 to −72.23 (m, 1F), −72.90 to −73.46 (m, 1F). HRMS (EI), $C_{20}H_{19}F_2NO_4S$ calcd: 407.1003; found: 407.1007.

*4.5.7. 5-[2-(4-Chloro-phenylsulfanyl)-2,2-difluoro-ethyl]-dihydro-furan-2-one (**16ba′**)*

Colorless oil. IR (film): 3087, 1780, 1251, 1218, 1185, 1154, 1093, 1075, 1013 cm^{-1}. ^1H NMR: δ 7.46–7.40 (m, 4H, PhH), 4.74–4.68 (m, 1H, CHO), 2.64–2.53 (m, 1H, CF_2CH_2), 2.48–2.30 (stack, 4H, CF_2CH_2, CH_2CO, CH_2CH_2CO), 1.94–1.85 (m, 1H, CH_2CH_2CO). ^{13}C NMR: δ 176.7, 138.1, 137.4, 130.1, 128.2 (t, J=279.4 Hz), 125.1, 44.5 (t, J=23.5 Hz), 75.6, 29.3, 29.0. ^{19}F NMR: δ −73.72 (ddd, 1F, J_{F-F}=209.4 Hz, J_{1H-F}=16.5 Hz, J_{2H-F}=11.3 Hz), −71.50 (dt, 1F, J_{F-F}= 209.4 Hz, J_{H-F}=15.1 Hz). HRMS (EI), $C_{12}H_{11}ClF_2O_2S$ calcd: 292.0136; found: 292.0136.

*4.5.8. 2-[2-(4-Chloro-phenylsulfanyl)-2,2-difluoro-ethyl]-3,3-dimethyl-tetrahydro-furan (**16bb′**)*

Colorless oil. IR (film): 3065, 1780, 1573, 1287, 1260, 1232, 1198, 1152, 1094, 1069, 1013 cm^{-1}. ^1H NMR: δ 7.44–7.23 (m,

4H, PhH), 4.31 (dd, 1H, J_1=8.6 Hz, J_2=2.3 Hz, CHO), 2.31 (d, 1H, J=16.8 Hz, CH_2C), 2.18 (d, 1H, J=16.8 Hz, CH_2C), 2.35–2.17 (m, 2H, CF_2CH_2), 1.03 (s, 3H, CH_3), 0.87 (s, 3H, CH_3). ^{13}C NMR: δ 174.1, 136.5, 135.6, 128.4, 127.2 (t, J=280.0 Hz), 123.7, 80.9, 43.0, 37.4 (t, J=24.2 Hz), 38.6, 23.0, 20.0. ^{19}F NMR: δ −72.32 to −72.21 (m, 2F). HRMS (EI), $C_{14}H_{15}ClF_2O_2S$ calcd: 320.0449; found: 320.0450.

*4.5.9. 5-[2-(4-Chloro-phenylsulfanyl)-2,2-difluoro-ethyl]-3-methyl-dihydro-furan-2-one (**16bc′**)*

Colorless oil. IR (film): 3086, 1780, 1573, 1261, 1165, 1094, 1073, 1040, 1015 cm^{-1}. ^{1}H NMR: δ (cis) 7.47–7.28 (m, 4H, PhH), 4.61–4.56 (m, 1H, CHO), 2.67–2.52 (stack, 3H, CF_2CH_2, C*H*CH_3, C*H*$_2$CHCO), 2.34–2.31 (m, 1H, CF_2CH_2), 1.58–1.51 (m, 1H, C*H*$_2$CHCO), 1.20 (d, 3H, J=6.7 Hz, CH_3); δ (trans) 7.47–7.28 (m, 4H, PhH), 4.80–4.75 (m, 1H, CHO), 2.67–2.52 (stack, 2H, CF_2CH_2, C*H*CH_3), 2.34–2.31 (m, 1H, CF_2CH_2), 2.19–2.15 (m, 1H, C*H*$_2$CHCO), 2.09–2.04 (m, 1H, C*H*$_2$CHCO), 1.22 (d, 3H, J=7.35 Hz, CH_3). ^{13}C NMR: δ (cis) 179.0, 138.2, 137.2, 130.1, 128.2 (t, J=279.5 Hz), 125.1, 73.3, 44.6 (t, J=23.7 Hz), 38.4, 36.1, 15.4; δ (trans) 179.6, 138.2, 137.5, 130.1, 128.3 (t, J=279.5 Hz), 125.1, 73.3, 44.4 (t, J=23.4 Hz), 36.4, 34.3, 16.3. ^{19}F NMR: δ −73.19 to −71.71 (m, 1F), −71.44 (ddd, 1F, J_{F-F}=209.4 Hz, J_{1H-F}=16.5 Hz, J_{2H-F}=14.5 Hz). HRMS (EI), $C_{13}H_{13}ClF_2O_2S$ calcd: 306.0293; found: 306.0293.

*4.5.10. 3-Benzyl-5-[2-(4-chloro-phenylsulfanyl)-2,2-difluoro-ethyl]-dihydro-furan-2-one (**16bd′**)*

Colorless oil. IR (film): 3085, 3061, 1780, 1260, 1167, 1092, 1014 cm^{-1}. ^{1}H NMR: δ (cis) 7.38–7.05 (m, 9H, PhH), 4.47–4.44 (m, 1H, CHO), 3.14 (dd, 1H, J_1=14.0 Hz, J_2=4.1 Hz, CH_2Ph), 2.82–2.78 (m, 1H, CHBn), 2.61 (dd, 1H, J_1=14.0 Hz, J_2=9.5 Hz, CH_2Ph), 2.47–2.44 (m, 1H, CF_2CH_2), 2.32–2.25 (m, 1H, C*H*$_2$CHCO), 2.21–2.08 (m, 1H, CF_2CH_2), 1.57–1.50 (m, 1H, C*H*$_2$CHCO); δ (trans) 7.38–7.05 (m, 9H, PhH), 4.53–4.48 (m, 1H, CHO), 3.02 (dd, 1H, J_1=13.7 Hz, J_2=4.1 Hz, CH_2Ph), 2.82–2.78 (m, 1H, CHBn), 2.70 (dd, 1H, J_1=13.7 Hz, J_2=9.5 Hz, CH_2Ph), 2.47–2.44 (m, 1H, CF_2CH_2), 2.21–2.08 (stack, 3H, CF_2CH_2, CH_2CHCO). ^{13}C NMR: δ (cis) 176.1, 137.2, 136.5, 135.7, 128.4, 127.9, 127.7, 126.6 (t, J=279.2 Hz), 125.7, 123.5, 72.0, 42.8 (t, J=23.7 Hz), 41.3, 34.8, 34.0; δ (trans) 176.7, 136.8, 136.5, 135.7, 128.4, 130.0, 127.8, 126.7 (t, J=279.2 Hz), 125.9, 123.5, 71.9, 42.7 (t, J=23.4 Hz), 39.6, 35.2, 31.9. ^{19}F NMR: δ (cis) −71.24 (ddd, 1F, J_{F-F}=209.4 Hz, J_{1H-F}=15.5 Hz, J_{2H-F}=11.3 Hz), −73.24 to −73.75 (m, 1F); δ (trans) −71.37 (ddd, 1F, J_{F-F}=209.4 Hz, J_{1H-F}=15.5 Hz, J_{2H-F}=11.3 Hz), −73.24 to −73.75 (m, 1F). HRMS (EI), $C_{19}H_{17}ClF_2O_2S$ calcd: 382.0606; found: 382.0606.

*4.5.11. 5-[2-(4-Chloro-phenylsulfanyl)-2,2-difluoro-ethyl]-3-phenyl-dihydro-furan-2-one (**16be′**)*

White solid with mp: 105–107 °C. IR (KBr): 1774, 1571, 1251, 1170, 1156, 1091, 1061, 1014 cm^{-1}. ^{1}H NMR: δ (cis) 7.55–7.26 (m, 9H, PhH), 4.85–4.79 (m, 1H, CHO), 3.93–3.88 (m, 1H, CHPh), 2.92–2.90 (m, 1H, CH_2CHCO), 2.77–2.71 (m, 1H, CF_2CH_2), 2.55–2.44 (m, 1H, CF_2CH_2), 2.18–2.15 (m, 1H, CH_2CHCO); δ (trans) 7.55–7.26 (m, 9H, PhH), 4.98–4.93 (m, 1H, CHO), 3.93–3.88 (m, 1H, CHPh), 2.70–2.62 (stack, 4H, CF_2CH_2, CH_2CHCO). ^{13}C NMR: δ (cis) 176.5, 138.2, 137.6, 136.4, 130.2, 129.6, 128.7, 128.5, 128.2 (t, J=279.4 Hz), 125.0, 73.3, 47.3, 44.5 (t, J=23.6 Hz), 39.1; δ (trans) 176.8, 138.2, 137.6, 136.9, 130.2, 129.8, 128.5, 128.2 (t, J=279.4 Hz), 128.1, 125.0, 73.8, 45.8, 44.6 (t, J=23.6 Hz), 37.3. ^{19}F NMR: δ (cis) −71.39 (ddd, 1F, J_{F-F}=209.4 Hz, J_{1H-F}=16.0 Hz, J_{2H-F}=10.8 Hz), −73.75 (dt, 1F, J_{F-F}=209.4 Hz, J_{H-F}=15.5 Hz); δ (trans) −71.39 (ddd, 1F, J_{F-F}=209.4 Hz, J_{1H-F}=16.0 Hz, J_{2H-F}=10.8 Hz), −73.77 (dt, 1F, J_{F-F}=209.4 Hz, J_{H-F}=12.2 Hz). HRMS (EI), $C_{18}H_{15}ClF_2O_2S$ calcd: 368.0449; found: 368.0448.

*4.5.12. N-{5-[2-(4-Chloro-phenylsulfanyl)-2,2-difluoro-ethyl]-2-oxo-tetrahydro-furan-3-yl}-4-methoxy-benzamide (**16bf′**)*

White solid with mp: 179–181 °C. IR (KBr): 3415, 1774, 1659, 1607, 1575, 1260, 1181, 1094, 1064, 1039, 1016 cm^{-1}. ^{1}H NMR: δ (cis) 7.69–6.83 (m, 8H, PhH), 6.63 (d, 1H, J=5.2 Hz, NH), 4.79–4.75 (m, 1H, CHNH), 4.73–4.68 (m, 1H, CHO), 3.78 (s, 3H, OCH_3), 3.09–3.03 (m, 1H, C*H*$_2$CHCO), 2.65–2.54 (m, 1H, CF_2CH_2), 2.47–2.38 (m, 1H, CF_2CH_2), 2.20–1.93 (m, 1H, C*H*$_2$CHCO); δ (trans) 7.69–6.83 (m, 8H, PhH), 6.69 (d, 1H, J=5.0 Hz, NH), 5.05–5.03 (m, 1H, CHNH), 4.61–4.56 (m, 1H, CHO), 3.78 (s, 3H, OCH_3), 2.65–2.54 (stack, 2H, CF_2CH_2, CH_2CHCO), 2.47–2.38 (stack, 2H, CF_2CH_2, CH_2CHCO). ^{13}C NMR: δ (cis) 174.8, 165.6, 161.9, 137.7, 135.7, 129.6, 129.1, 127.3 (t, J=278.3 Hz), 125.5, 124.7, 113.7, 71.3, 55.4, 49.1, 43.3 (t, J=23.1 Hz), 33.9; δ (trans) 179.5, 165.5, 161.9, 137.6, 135.6, 129.5, 129.2, 127.3 (t, J=278.3 Hz), 125.4, 124.7, 113.7, 72.5, 55.4, 47.9, 43.4 (t, J=23.4 Hz), 33.2. ^{19}F NMR: δ (cis) −71.95 (ddd, 1F, J_{F-F}=209.4 Hz, J_{1H-F}=15.5 Hz, J_{2H-F}=11.8 Hz), −73.29 to −73.80 (m, 1F); δ (trans) −71.79 (ddd, 1F, J_{F-F}=209.4 Hz, J_{1H-F}=15.1 Hz, J_{2H-F}=11.8 Hz), −73.29 to −73.80 (m, 1F). HRMS (EI), $C_{20}H_{18}ClF_2NO_4S$ calcd: 441.0613; found: 441.0612.

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