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Short communication

α,α-Difluoro-α-phenylsulfanyl-α-trimethylsilylmethane as "$^{\bullet}CF_2^{-}$" synthetic building block for the preparation of *gem*-difluoromethylenated cyclopentanols

Krisana Peewasan, Chutima Kuhakarn, Darunee Soorukram, Patoomratana Tuchinda, Vichai Reutrakul, Manat Pohmakotr *

Center of Excellence for Innovation in Chemistry (PERCH-CIC) and Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Road, Bangkok 10400, Thailand

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ABSTRACT

A general strategy for the preparation of *gem*-difluoromethylenated cyclopentanols has been demonstrated; it involves sequential fluoride-catalyzed nucleophilic addition of α,α-difluoro-α-phenylsulfanyl-α-trimethylsilylmethane ($PhSCF_2SiMe_3$; **1**) to homoallyl ketones followed by intramolecular radical cyclization.

1. Introduction

Organofluorine compounds are of importance due to their unique physical properties. More importantly, they are widely used in pharmaceutical chemistry and material sciences [1,2]. The presence of *gem*-difluoromethylene moiety in organic compounds led to the enhancement of biological properties of drug molecules [3]. Consequently, the development of general and efficient methodologies for the preparation of structurally different fluorine containing molecules has attracted considerable attention in organic communities [4,5].

Recently, $PhSCF_2SiMe_3$ (**1**) has been shown to react with carbonyl compounds [6], γ-ketoesters [7], imines [8], imides [5d], and alkyl bromides [9] to provide the corresponding *gem*-difluoromethylenated alcohols, γ-lactones, amines, 1-azabicyclic compounds, and alkanes, respectively. In continuation with our research work on using **1** as a *gem*-difluoromethylene building block [10], we now wish to report a general synthetic entry to *gem*-difluoromethylenated cyclopentanols [11]. Since it has been demonstrated that carbonyl compounds can undergo fluoride-catalyzed nucleophilic difluoro(phenylsulfanyl)methylation reaction using **1**, it is anticipated that **1** would similarly react with homoallyl ketones **2** leading to adducts **3**. Subsequent reductive cleavage of the phenylsulfanyl moiety should provide radical intermediate **4** that should then undergo intramolecular radical cyclization, providing the desired *gem*-difluoromethylenated cyclopentanol **5** (Scheme 1).

2. Results and discussion

To begin with, treatment of **1** with homoallyl ketone **2a** in the presence of 10 mol% of anhydrous tetrabutylammonium fluoride (TBAF) in THF at −78 °C to room temperature overnight (16 h) followed by acidic workup (1 M HCl) afforded the expected adduct **3a** in 93% yield (Table 1, entry 1). Under similar reaction conditions as for **3a**, the reaction of **1** with **2d–g** provided the corresponding adducts **3d–g** in moderate to good yields (Table 1, entries 4–7). Alternatively, compounds **3b**, **3c**, and **3h** were prepared in high yields (entries 2, 3, and 8) by cross-olefin metathesis of **3a** and **3g** with styrene or methyl acrylate, respectively, employing Grubbs second-generation catalyst in refluxing CH_2Cl_2 for 20 h.

Having succeeded in preparing adducts **3a–h**, reductive desulfenylation of **3** employing Bu_3SnH/AIBN should provide *gem*-difluoromethylenated radical intermediate **4**, which should then be trapped intramolecularly by an alkenyl moiety to afford *gem*-difluoromethylenated cyclopentanols **5**. Under the standard reaction conditions (1.75 equiv. Bu_3SnH, 15 mol% AIBN, toluene, reflux, 5 h), reductive desulfenylation followed by radical cyclization of **3a** yielded **5a** in 68% yield as a mixture of two diastereomers (Table 1, entry 1). Pure *trans*-**5a** was partially obtained in 40% yield by chromatography. The relative yields of the two diastereomers were carefully determined by ^1H NMR (500 MHz) to be approximately 2:1. Under the standard radical reaction conditions, a

* Corresponding author. Tel.: +66 2201 5158; fax: +66 2644 5126.
E-mail address: scmpk@mahidol.ac.th (M. Pohmakotr).

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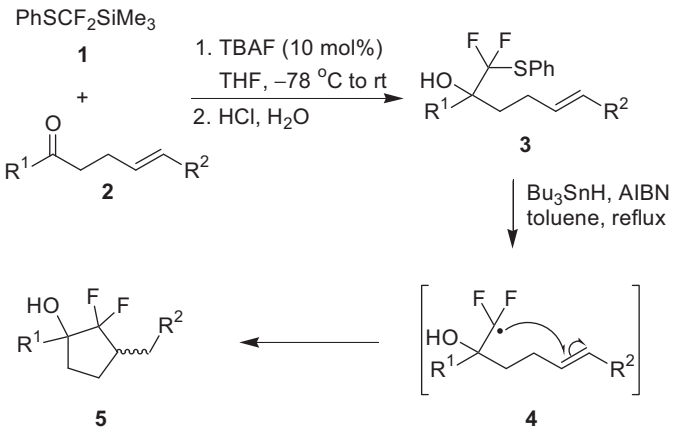
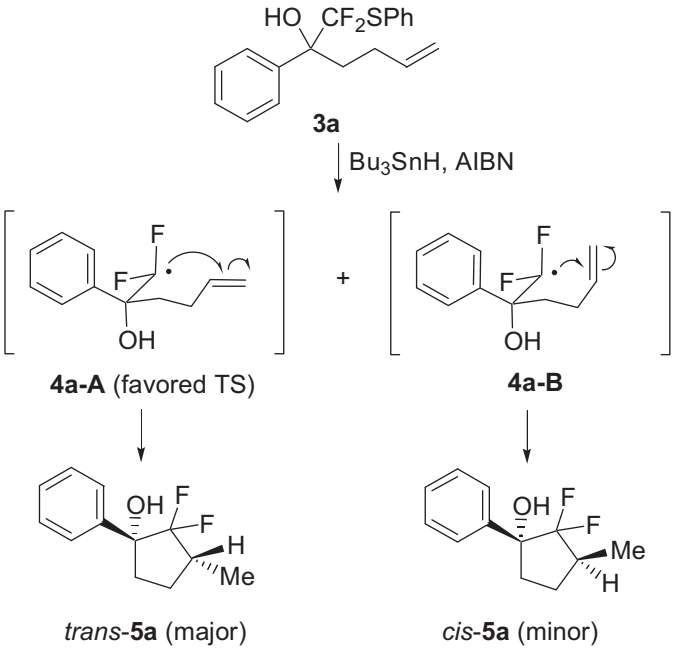


Scheme 1.

collection of *gem*-difluoromethylenated cyclopentanols **5b**–**h**, each as mixtures of isomers, were synthesized in moderate to good yields (56–87%) (Table 1, entries 2–8). Unfortunately, attempts to separate each isomer of compounds **5b**–**h** by chromatographic techniques were unsuccessful.

The proposed transition structure for radical cyclization was shown in Scheme 2. Based on Zimmermann–Beckwith–Houk Model [12], we assumed that the preferred transition structure for cyclization that proceeds through an exo-1,5-ring closure mode was found to be cyclopentane chair-like transition state with substituent occupied at pseudoequatorial position. Therefore, for radical cyclization of compound **3a** to yield compound **5a**, a chair-like transition structure **4a**-**A** should be more favorable, giving rise to the *trans*-**5a** as a major isomer. On the contrary, the minor *cis*-**5a** should occur through a less favorable boat-like transition structure **4a**-**B**. Additionally, for compounds **5a**–**e**, the evidence in supporting the *trans*-isomer as the major isomer was the ^{1}H NMR chemical shifts of the methine protons of compounds **5a**–**e**. The influence caused by anisotropic effect of the phenyl ring [13] made the methine protons of the *trans*-isomers **5a**–**e** to appear at higher field region than those of the *cis*-isomers. The *trans*-isomers of **5f** and **5h** were also proposed, based on the transition structure in Scheme 2, to be the major isomers.



Scheme 2.

In conclusion, we have demonstrated a convenient two-step synthesis of *gem*-difluoromethylenated cyclopentanols. The synthetic approach entails fluoride-catalyzed nucleophilic addition of $PhSCF_2SiMe_3$ to homoallyl ketones followed by intramolecular radical cyclization.

3. Experimental

The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker Advance-500 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{19}F NMR (470 MHz) spectra were recorded on a Bruker Advance-500 spectrometer and chemical shifts (δ) were measured with fluorotrichloromethane ($\delta = 0$) as an internal standard. The IR spectra were recorded on either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer. The electron impact mass spectra were recorded by using Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded using TOF mode on a Micromass model VQ-TOF2 mass spectrometer. Elemental analyses were performed using a Perkin Elmer Elemental Analyzer 2400 CHN. Melting points were recorded on a Buchi 501 melting point apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Column chromatography was performed by using Merck silica gel 60H (mesh Art. 7736). Preparative TLC plates were prepared by using Merck silica gel 60 PF_{254} (mesh Art. 7747).

3.1. General procedure for the synthesis of compound 3

To a mixture of $PhSCF_2SiMe_3$ (**1**) (1.39 g, 6 mmol) and **2a** (481 mg, 3 mmol) in dry THF (6 mL), was added 10 mol% TBAF (0.6 mL, 0.6 mmol, 1 M solution in THF) at −78 °C. The reaction mixture was stirred and slowly warmed up to room temperature overnight (16 h), then quenched with 1 M HCl (3 mL) and extracted with EtOAc (3× 50 mL). The organic layer was washed with water (10 mL), brine (10 mL), and dried (anh. Na_2SO_4). Purification by preparative TLC (SiO_2, 15% EtOAc-hexanes) afforded **3a**.

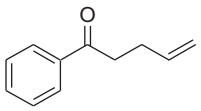
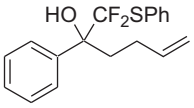
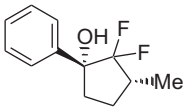
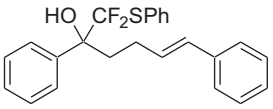
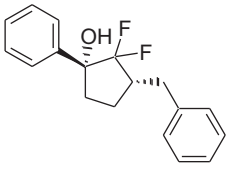
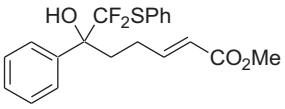
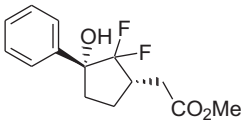
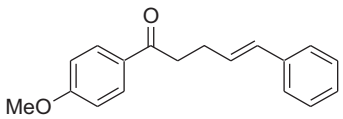
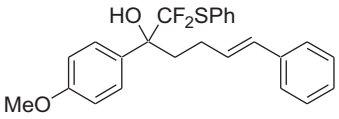
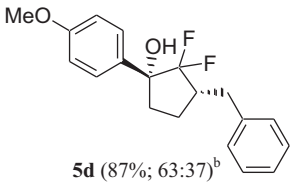
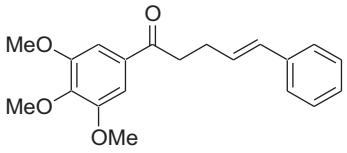
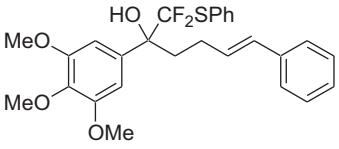
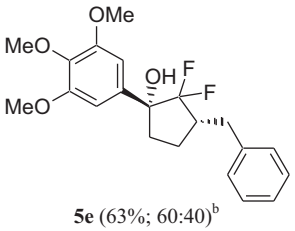
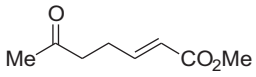
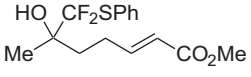
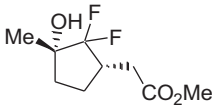
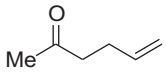
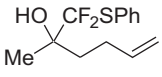
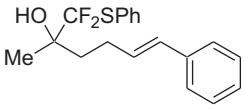
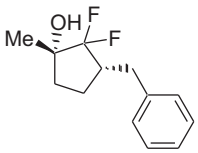
3.1.1. 1,1-Difluoro-2-phenyl-1-(phenylsulfanyl)hex-5-en-2-ol (3a)

A colorless oil (894 mg, 93% yield); IR (neat): 3543s, 1642m, 1475m, 1449s, 1441s, 1047s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 8.0 Hz, 2H, Ph*H*), 7.59–7.54 (m, 2H, Ph*H*), 7.48–7.33 (m, 6H, Ph*H*), 5.83 (ddt, J = 17.0, 10.4, 6.5 Hz, 1H, C*H*=CHH), 5.04–4.94 (m, 2H, CH=C*HH*), 2.69 (s, 1H, O*H*), 2.44–2.35 (m, 1H, CHH–C*H*H), 2.28–2.10 (m, 2H, C*H*H–CH*H*), 1.85–1.75 (m, 1H, CH*H*–CHH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0 (CH), 137.9 (C), 136.6 (2CH), 131.3 (t, J = 288.5 Hz, CF_2), 129.6 (2CH), 128.8 (2CH), 128.1 (2CH), 126.7 (2CH), 126.2, (C), 115.1 (CH_2), 80.4 (t, J = 23.6 Hz, C), 34.6 (CH_2), 27.2 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −81.55 (d, J = 204.5 Hz, F), −84.02 (d, J = 204.5 Hz, F). MS (EI): m/z (%) = 320 $[M]^+$ (1), 303 (45), 225 (20), 161 (95), 105 (100), 77 (19). HRMS (ESI-TOF): calcd. for $C_{18}H_{18}F_2OSNa$ $[M+Na]^+$: 343.0944; Found: 343.1002.

3.1.2. (E)-1,1-Difluoro-2,6-diphenyl-1-(phenylsulfanyl)hex-5-en-2-ol (3b)

Cross-olefin metathesis of **3a** (665 mg, 2 mmol) with styrene (0.9 mL, 8 mmol) using Grubbs' catalyst (2nd generation, 5 mol%) in reflux CH_2Cl_2 (10 mL) for 20 h gave **3b** (681 mg, 86% yield) as a colorless oil after purification by preparative TLC (SiO_2, 10% EtOAc-hexanes); IR (neat): 3473s, 1496s, 1475s, 1449s, 1048s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 7.9 Hz, 2H, Ph*H*), 7.54–7.50 (m, 2H, Ph*H*), 7.45–7.35 (m, 5H, Ph*H*), 7.35–7.29 (m, 2H, Ph*H*), 7.29–7.23 (m, 3H, Ph*H*), 7.21–7.15 (m, 1H, Ph*H*), 6.30 (d, J = 15.8 Hz, 1H, =C*H*Ph), 6.14 (dt, J = 15.8, 6.7 Hz, 1H, C*H*=CHPh), 2.67 (s, 1H,

Table 1
Preparation of *gem*-difluoromethylenated cyclopentanols **5**.

Entry	**2**	**3** (%)[a]	**5** (%;[a] *trans*:*cis*)
1	 **2a**	 **3a** (93%)	 **5a** (68%; 66:34)[b]
2	–	 **3b**[c] (86%)	 **5b** (56%; 65:35)[b]
3	–	 **3c**[c] (82%)	 **5c** (73%; 61:39)[b]
4	 **2d**	 **3d** (60%)	 **5d** (87%; 63:37)[b]
5	 **2e**	 **3e** (89%)	 **5e** (63%; 60:40)[b]
6	 **2f**	 **3f** (67%)	 **5f** (77%; 66:34)[b]
7	 **2g**	 **3g** (77%)	–[d]
8	–	 **3h** (75%)[e]	 **5h** (71%; 52:48)[b]

[a]Isolated yields by chromatography on silica gel.
[b]Determined by ^{1}H NMR spectrum.
[c]Compounds **3b** and **3c** were prepared by cross-olefin metathesis between **3a** and styrene and methyl acrylate, respectively.
[d]The reaction was not performed.
[e]Prepared by cross-olefin metathesis between **3g** and styrene.

O*H*), 2.48–2.36 (m, 1H), 2.33–2.20 (m, 2H), 1.96–1.85 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.8 (C), 137.4 (C), 136.6 (2CH), 131.3 (t, J = 288.6 Hz, CF_2), 130.5 (2CH), 129.7 (CH), 129.6 (CH), 129.0 (2CH), 128.5 (2CH), 128.2 (2CH), 127.0 (CH), 126.7 (2CH), 126.2 (C), 126.9 (2CH), 80.3 (t, J = 23.3 Hz, C), 35.1 (CH_2), 26.5 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −81.6 (d, J = 204.2 Hz, F), −84.0 (d, J = 204.2 Hz, F). MS (EI): m/z (%) = 396 $[M]^+$ (1), 253 (46), 237 (100), 117 (90), 105 (54), 91 (38), 77 (48). Anal. Calcd. for $C_{24}H_{22}F_2OS$: C, 72.70; H, 5.59; Found: C, 72.55; H, 5.56.

3.1.3. 7,7-Difluoro-6-hydroxy-6-phenyl-7-(phenylsulfanyl)hept-2-enoic acid methyl ester (3c)

Cross-olefin metathesis of **3a** (665 mg, 2 mmol) with methyl acrylate (0.7 mL, 8 mmol) using Grubbs' catalyst (2nd generation, 5 mol%) in reflux CH_2Cl_2 (10 mL) gave **3c** (620 mg, 82% yield) as a white solid after purification by preparative TLC (SiO_2, 15% EtOAc-hexanes); m.p. 127–128 °C. IR (KBr): 3439s, 1709s, 1702s, 1655s, 1436s, 1331s, 1257s, 1214s, 1053s, 1014s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, J = 8.0 Hz, 2H, Ph*H*), 7.56–7.51 (m, 2H, Ph*H*), 7.46–7.38 (m, 4H, Ph*H*), 7.38–7.33 (m, 2H, Ph*H*), 6.93 (dt, J = 15.6, 6.7 Hz, 1H, –C*H*=), 5.78 (dt, J = 15.6, 1.5 Hz, 1H, C*H*=C(O)), 3.73 (s, 3H, CH_3), 2.80 (s, 1H, O*H*), 2.44–2.36 (m, 1H), 2.36–2.21 (m, 2H), 1.94–1.83 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9 (CO), 148.4 (CH), 137.4 (C), 136.6 (2CH), 131.2 (t, J = 288.9 Hz, CF_2), 129.7 (CH), 128.9 (2CH), 128.4 (2CH), 128.3 (2CH), 126.6 (CH), 126.0 (C), 121.2 (CH), 80.0 (t, J = 23.1 Hz, C), 51.4 (OCH_3), 33.9 (CH_2), 25.8 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −81.6 (d, J = 204.9 Hz, F), −84.1 (d, J = 204.9 Hz, F). MS (EI): m/z (%) = 378 $[M]^+$ (1), 341 (13), 219 (51), 187 (100), 169 (90), 141 (89), 128 (36), 115 (18), 105 (22), 77 (27). HRMS (ESI-TOF) calcd. for $C_{20}H_{20}F_2O_3SNa$ $[M+Na]^+$: 401.0999; Found: 401.0997.

3.1.4. 1,1-Difluoro-2-(4-methoxyphenyl)-6-phenyl-1-(phenylsulfanyl)hex-5-en-2-ol (3d)

The reaction of **1** (1.39 g, 6 mmol) with **2d** (799 mg, 3 mmol) and purification by preparative TLC (SiO_2, 5% EtOAc-hexanes) gave **3d** (768 mg, 60% yield) as a colorless oil. IR (neat): 3479s, 1612s, 1515s, 1254s, 1181s, 1038s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61–7.50 (m, 4H, Ph*H*), 7.45–7.39 (m, 1H, Ph*H*), 7.39–7.33 (m, 2H, Ph*H*), 7.33–7.27 (m, 4H, Ph*H*), 7.25–7.18 (m, 1H, Ph*H*), 7.00–6.94 (m, 2H, Ar*H*), 6.34 (d, J = 15.8 Hz, 1H, =C*H*Ph), 6.18 (dt, J = 15.8, 6.7 Hz, 1H, C*H*=CH), 3.87 (s, 3H, CH_3), 2.64 (s, 1H, O*H*), 2.47–2.38 (m, 1H), 2.36–2.22 (m, 2H), 2.02–1.92 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5 (C), 137.5 (2C), 136.5 (2CH), 131.5 (t, J = 288.4 Hz, CF_2), 130.4 (CH), 129.8 (CH), 129.6 (CH), 128.8 (2CH), 128.5 (2CH), 128.0 (2CH), 127.0 (CH), 126.3 (C), 125.9 (2CH), 113.5 (2CH), 80.1 (t, J = 23.6 Hz, C), 55.2 (OCH_3), 35.1 (CH_2), 26.6 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −81.7 (d, J = 203.7 Hz, F), −84.3 (d, J = 203.7 Hz, F). MS (EI): m/z (%) = 426 $[M]^+$ (2), 295 (7), 267 (100), 135 (97), 117 (55), 77 (25). HRMS (ESI-TOF) calcd. for $C_{25}H_{24}F_2O_2SNa$ $[M+Na]^+$: 449.1363; Found: 449.1397. Anal. Calcd. for $C_{25}H_{24}F_2O_2S$: C, 70.40; H, 5.67; Found: C, 70.28; H, 5.89.

3.1.5. 1,1-Difluoro-6-phenyl-1-(phenylsulfanyl)-2-(3,4,5-trimethoxyphenyl)hex-5-en-2-ol (3e)

The reaction of **1** (1.39 g, 6 mmol) with **2e** (979 mg, 3 mmol) and purification by preparative TLC (SiO_2, 15% EtOAc-hexanes) gave **3e** (1.30 g, 89% yield) as a white solid. m.p. 141–143 °C. IR (KBr): 3407s, 1592s, 1506s, 1461s, 1451s, 1417s, 1318s, 1244s, 1126s, 1060s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56–7.50 (m, 2H, Ph*H*), 7.43–7.37 (m, 1H, Ph*H*), 7.37–7.31 (m, 2H, Ph*H*), 7.31–7.26 (m, 4H, Ph*H*), 7.22–7.16 (m, 1H, Ph*H*), 6.82 (s, 2H, Ar*H*), 6.32 (d, J = 15.8 Hz, 1H, =C*H*Ph), 6.15 (dt, J = 15.8, 6.5 Hz, 1H, C*H*=CH), 3.89 (s, 9H, 3OCH_3), 2.67 (s, 1H, O*H*), 2.41–2.20 (m, 3H), 2.03–1.91 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9 (2C), 138.0 (C), 137.4 (C), 136.6 (2CH), 133.3 (C), 131.2 (t, J = 289.5 Hz, CF_2), 130.5 (CH), 130.0 (CH), 129.6 (CH), 128.9 (2CH), 128.5 (2CH), 127.1 (CH), 126.2 (C), 125.9 (2CH), 104.3 (2CH), 80.3 (t, J = 23.5 Hz, C), 60.9 (OCH_3), 56.2 (2OCH_3), 35.3 (CH_2), 26.5 (CH_2). ^{19}F NMR (470 MHz, $CDCl_3$): δ −81.3 (d, J = 205.4 Hz, F), −83.5 (d, J = 205.4 Hz, F). MS (EI): m/z (%) = 486 $[M]^+$ (20), 355 (27), 327 (100), 251 (18), 195 (57), 117 (36). HRMS (ESI-TOF) calcd. for $C_{27}H_{28}F_2O_4SNa$ $[M+Na]^+$: 509.1574; Found: 509.1616. Anal. Calcd. for $C_{27}H_{28}F_2O_4S$: C, 66.65; H, 5.80; Found: C, 66.44; H, 5.49.

3.1.6. 7,7-Difluoro-6-hydroxy-6-methyl-7-(phenylsulfanyl)hept-2-enoic acid methyl ester (3f)

The reaction of **1** (1.39 g, 6 mmol) with **2f** (469 mg, 3 mmol) and purification by column chromatography (SiO_2, 5% EtOAc-hexanes) gave **3f** (636 mg, 67% yield) as a colorless oil. IR (neat): 3445s, 1723s, 1714s, 1699s, 1659s, 1440s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65–7.58 (m, 2H, Ph*H*), 7.46–7.40 (m, 1H, Ph*H*), 7.40–7.34 (m, 2H, Ph*H*), 7.02 (dt, J = 15.7, 6.7 Hz, 1H, –C*H*=CH), 5.89 (dt, J = 15.7, 1.5 Hz, 1H, C*H*=C(O)), 3.73 (s, 3H, OCH_3), 2.66–2.50 (br. s, 1H, O*H*), 2.50–2.41 (m, 1H), 2.41–2.30 (m, 1H), 2.01–1.91 (m, 1H), 1.89–1.80 (m, 1H), 1.42 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0 (CO), 148.6 (CH), 136.6 (2CH), 131.8 (t, J = 286.0 Hz, CF_2), 129.7 (CH), 128.9 (2CH), 125.8, (C), 121.2 (CH), 76.5 (t, J = 23.1 Hz, C), 51.4 (OCH_3), 34.4 (CH_2), 26.0 (CH_2), 21.0 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −85.0 (s, 2F). MS (EI): m/z (%) = 316 $[M]^+$ (3), 297 (11), 278 (8), 249 (11), 184 (89), 157 (44), 141 (70), 129 (84), 125 (63), 109 (48), 97 (47), 79 (100). HRMS (ESI-TOF) calcd. for $C_{15}H_{18}F_2O_3SNa$ $[M+Na]^+$: 339.0843; Found: 339.0842.

3.1.7. 1,1-Difluoro-2-methyl-1-(phenylsulfanyl)hex-5-en-2-ol (3g)

The reaction of **1** (1.39 g, 6 mmol) with hex-5-en-2-one (295 mg, 3 mmol) and purification by column chromatography (SiO_2, 5% EtOAc-hexanes) gave **3g** (596 mg, 77% yield) as a colorless oil. IR (neat): 3441s, 1710s, 1642s, 1475s, 1441s, 1381s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46–7.41 (m, 2H, Ph*H*), 7.27–7.22 (m, 1H, Ph*H*), 7.22–7.16 (m, 2H, Ph*H*), 5.68 (ddt, J = 17.1, 10.2, 6.6 Hz, 1H, C*H*=CHH), 4.90 (ddt, J = 1.7, 17.1, 1.7 Hz, 1H, =C*H*H), 4.82 (ddt, J = 1.7, 10.2, 1.4 Hz, 1H, =CH*H*), 2.16–1.98 (m, 2H, CH_2), 1.88 (s, 1H, O*H*), 1.74–1.66 (m, 1H), 1.66–1.58 (m, 1H), 1.23 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.1 (CH), 136.7 (2CH), 132.0 (t, J = 285.0 Hz, CF_2), 129.7 (CH), 128.9 (2CH), 126.1, (C), 115.0 (CH_2), 76.9 (t, J = 23.0 Hz, C), 35.4 (CH_2), 27.4 (CH_2), 21.1 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −85.1 (s, 2F). MS (EI): m/z (%) = 258 $[M]^+$ (66), 240 (32), 201 (16), 160 (22), 131 (100), 109 (40). HRMS (ESI-TOF) calcd. for $C_{13}H_{16}F_2OSNa$ $[M+Na]^+$: 281.0788; Found: 281.0787.

3.1.8. 1,1-Difluoro-2-methyl-6-phenyl-1-(phenylsulfanyl)hex-5-en-2-ol (3h)

Cross-olefin metathesis of **3g** (512 mg, 2 mmol) with styrene (0.9 mL, 8 mmol) using Grubbs' catalyst (2nd generation, 5 mol%) in reflux CH_2Cl_2 (10 mL) gave **3h** (496 mg, 75% yield) as a colorless oil after purification by column chromatography (SiO_2, 5% EtOAc-hexanes); IR (neat): 3436s, 1475s, 1441s, 1380s, 1047s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 8.1 Hz, 2H, Ph*H*), 7.53–7.43 (m, 5H, Ph*H*), 7.43–7.37 (m, 2H, Ph*H*), 7.34–7.28 (m, 1H, Ph*H*), 6.56 (d, J = 15.8 Hz, 1H, =C*H*Ph), 6.35 (dt, J = 15.8, 6.9 Hz, 1H, C*H*=CHPh), 2.63–2.42 (m, 3H), 2.14–2.04 (m, 1H), 2.04–1.96 (m, 1H), 1.56 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.5 (C), 136.6 (2CH), 132.0 (t, J = 286.1 Hz, CF_2), 130.4 (CH), 129.8 (CH), 129.6 (CH), 128.9 (2CH), 128.4 (2CH), 126.9 (CH), 126.0 (C), 125.9 (2CH), 76.8 (t, J = 23.0 Hz, C), 35.7 (CH_2), 26.6 (CH_2), 20.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −84.7 (s, 2F). MS (EI): m/z (%) = 335 $[M+H]^+$ (30), 243 (55), 187 (69), 175 (100), 117 (67), 91 (28). HRMS (ESI-TOF) calcd. for $C_{19}H_{20}F_2OSH$ $[M+H]^+$: 335.1281; Found: 335.1288.

3.2. General procedure for the synthesis of compound 5

Argon was bubbled through a solution of **3a** (320 mg, 1 mmol) in toluene (5 mL) for 30 min. Bu_3SnH (0.47 mL, 1.75 mmol) was added to the solution and deoxygenation was continued for 5 min. AIBN (25 mg, 0.15 mmol) was added and the solution was heated to reflux for 5 h. Evaporation and purification by column chromatography (SiO_2, 10% EtOAc-hexanes) gave a colorless oil of **5a** (144 mg, 68% yield) as a 66:34 mixture of *trans*- and *cis*-isomers. The major *trans*-isomer was obtained in 40% yield by column chromatography (SiO_2, 5% EtOAc-hexanes).

3.2.1. 2,2-Difluoro-3-methyl-1-phenylcyclopentanol (5a)

IR (neat): 3450s, 1460s, 1455s, 1449s, 1204s, 1122s, 1059s cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.55–7.48 (m, 2H, Ph*H*), 7.40–7.28 (m, 3H, Ph*H*), 2.60–2.28 (m, 3H, O*H*, C*H*, and C*H*H), 2.15–2.04 (m, 2H, C*HH*), 1.79–1.68 (m, 1H, CH*H*), 1.17 (dd, J = 7.2, 2.0 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5 (C), 128.8 (dd, J = 261.3, 255.4 Hz, CF_2), 128.2 (2CH), 128.1 (CH), 126.5 (2CH), 81.4 (dd, J = 27.4, 20.7 Hz, C), 38.7 (dd, J = 24.1, 22.4 Hz, CH), 34.4 (d, J = 2.3 Hz, CH_2), 27.6 (dd, J = 4.9, 3.2 Hz, CH_2), 15.1 (dd, J = 7.9, 3.6 Hz, CH_3). ^{19}F NMR (470 MHz, $CDCl_3$): δ −98.1 (dd, J = 230.9, 23.3 Hz, F), −126.3 (d, J = 230.9 Hz, F). MS (EI): m/z (%) = 212 $[M]^+$ (18), 161 (14), 149 (14), 133 (100), 115 (43), 105 (36), 91 (24), 77 (54). HRMS (ESI-TOF): calcd. for $C_{12}H_{14}F_2ONa$ $[M+Na]^+$: 235.0911; Found: 235.0863.

3.2.2. 3-Benzyl-2,2-difluoro-1-phenylcyclopentanol (5b)

Radical cyclization of **3b** (396 mg, 1 mmol) afforded a colorless oil of **5b** (161 mg, 56% yield) as a 65:35 mixture of *trans*- and *cis*-isomers after purification by column chromatography (SiO_2, 5% EtOAc-hexanes). IR (neat): 3550s, 1498s, 1455s, 1447s, 1190s, 1065s cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, *trans*-isomer marked*): δ 7.57–7.50 (m, 4H, Ph*H* of *trans*- and *cis*-isomers), 7.42–7.26 (m, 10H, Ph*H* of *trans*- and *cis*-isomers), 7.26–7.19 (m, 6H, Ph*H* of *trans*- and *cis*-isomers), 3.17* (dd, J = 13.1, 4.2 Hz, 1H, C*H*HPh), 3.12–2.97 (m, 2H, C*H*HPh and C*H*), 2.74–2.55 (m, 3H of *trans*- and *cis*-isomers), 2.50–2.28 (m, 3H of *trans*- and *cis*-isomers), 2.16–2.03 (m, 4H of *trans*- and *cis*-isomers), 1.94–1.84* (m, 2H, CH_2), 1.66–1.52 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$, *trans*-isomer marked*): δ 139.7 (C), 139.6* (C), 139.3* (C), 138.9 (C), 128.4 (4CH), 128.7 (t, J = 251.9 Hz, CF_2), 128.5* (dd, J = 262.5, 256.5 Hz, CF_2), 128.4 (4CH), 128.3 (2CH), 128.2 (4CH), 128.1 (CH), 126.6 (CH), 126.5 (2CH), 126.2 (2CH), 81.5* (dd, J = 27.5, 20.6 Hz, C), 80.9 (dd, J = 28.3, 20.6 Hz, C), 45.5* (dd, J = 23.7, 20.7 Hz, CH), 43.6 (t, J = 21.1 Hz, CH), 36.3* (dd, J = 7.1, 3.3 Hz, CH_2), 34.2* (d, J = 2.4 Hz, CH_2), 33.9 (d, J = 3.5 Hz, CH_2), 33.7 (d, J = 7.4 Hz, CH_2), 25.7* (dd, J = 4.3, 3.4 Hz, CH_2), 24.0 (d, J = 9.4 Hz, CH_2). ^{19}F NMR (470 MHz, $CDCl_3$, *trans*-isomer marked*): δ −96.6* (dd, J = 232.3, 22.3 Hz, F), −118.7 (dd, J = 230.2, 25.6 Hz, F), −124.6* (d, J = 232.3 Hz, F), −124.8 (d, J = 230.2 Hz, F). MS (EI): m/z (%) = 288 $[M]^+$ (1), 270 (79), 161 (100), 133 (48), 129 (35), 115 (30), 105 (71), 91 (54), 77 (76). HRMS (ESI-TOF): calcd. for $C_{18}H_{18}F_2ONa$ $[M+Na]^+$: 311.1224; Found: 311.1182.

3.2.3. (2,2-Difluoro-3-hydroxy-3-phenylcyclopentyl)acetic acid methyl ester (5c)

Radical cyclization of **3c** (378 mg, 1 mmol) afforded a colorless oil of **5c** (197 mg, 73% yield) as a 61:39 mixture of *trans*- and *cis*-isomers after purification by column chromatography (SiO_2, 15% EtOAc-hexanes). IR (neat): 3472s, 1732s, 1440s, 1280s, 1209s, 1106s, 1066s cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, *trans*-isomer marked*): δ 7.55–7.46 (m, 4H, Ph*H* of *trans*- and *cis*-isomers), 7.39–7.27 (m, 6H, Ph*H* of *trans*- and *cis*-isomers), 3.65 (s, 6H, OCH_3 of *trans*- and *cis*-isomers), 3.28–3.11 (m, 1H, C*H*), 3.11–2.96 (s, 2H, O*H* of *trans*- and *cis*-isomers), 2.89–2.75* (m, 1H, C*H*), 2.75* (dd, J = 16.4, 5.9 Hz, 1H, CH*H*–CO), 2.69 (dd, J = 16.2, 4.7 Hz, 1H, CH*H*CO), 2.53* (dd, J = 16.4, 8.7 Hz, 1H, C*H*HCO), 2.40 (dd, J = 16.2, 10.3 Hz, 1H, C*H*H–CO), 2.45–2.36 (m, 1H, C*H*H), 2.36–2.27 (m, 2H, C*H*H of *trans*- and *cis*-isomers), 2.25–2.12* (m, 1H, C*H*H), 2.12–2.03 (m, 2H, C*H*H of *trans*- and *cis*-isomers), 1.85–1.73* (m, 1H, C*H*H), 1.56–1.45 (m, 1H, C*H*H). ^{13}C NMR (125 MHz, $CDCl_3$, *trans*-isomer marked*): δ 172.6* (CO), 172.5 (CO), 138.8* (C), 138.6 (C), 128.4 (dd, J = 265.1, 253.0 Hz, CF_2), 128.3* (dd, J = 264.6, 255.1 Hz, CF_2), 128.2* (2CH), 128.1 (2CH), 128.0 (2CH), 126.5 (2CH), 126.4* (2CH) 81.1* (dd, J = 28.4, 20.4 Hz, C), 80.3 (dd, J = 27.9, 20.3 Hz, C), 51.7 (OCH_3), 51.6* (OCH_3), 40.4* (dd, J = 26.4, 20.3 Hz, CH), 38.5 (t, J = 21.1 Hz, CH), 35.5* (dd, J = 6.6, 4.7 Hz, CH_2), 33.9 ($2CH_2$), 32.4 (d, J = 7.9 Hz, CH_2), 25.8* (t, J = 3.8 Hz, CH_2), 24.0 (d, J = 8.6 Hz, CH_2). ^{19}F NMR (470 MHz, $CDCl_3$, *trans*-isomer marked*): δ −94.9* (dd, J = 233.6, 24.4 Hz, F), −118.1 (dd, J = 230.3, 25.3 Hz, F), −125.0* (d, J = 233.6 Hz, F), −125.7 (dt, J = 230.3, 3.4 Hz, F). MS (EI): m/z (%) = 270 $[M]^+$ (11), 233 (100), 199 (8), 171 (8), 157 (22), 133 (22), 115 (13), 105 (15), 77 (16). HRMS (ESI-TOF): calcd. for $C_{14}H_{16}F_2O_3Na$ $[M+Na]^+$: 293.0966; Found: 293.0936. Anal. Calcd. for $C_{14}H_{16}F_2O_3$: C, 62.22; H, 5.97; Found: C, 62.18; H, 5.84.

3.2.4. 3-Benzyl-2,2-difluoro-1-(4-methoxyphenyl)cyclopentanol (5d)

Radical cyclization of **3d** (427 mg, 1 mmol) afforded a white solid of **5d** (277 mg, 87% yield) as a 63:37 mixture of *trans*- and *cis*-isomers after purification by PLC (SiO_2, 15% EtOAc-hexanes). m.p. = 90–93 °C. IR (neat): 3461s, 1612s, 1515s, 1455s, 1252s, 1183s, 1035s cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, *trans*-isomer marked*): δ 7.55–7.46 (m, 4H, Ar*H* of *trans*- and *cis*-isomers), 7.38–7.31 (m, 4H, Ph*H* of *trans*- and *cis*-isomers), 7.31–7.23 (m, 6H, Ph*H* of *trans*- and *cis*-isomers), 6.98–6.92 (m, 4H, Ar*H* of *trans*- and *cis*-isomers), 3.86 (s, 3H, OCH_3), 3.85* (s, 3H, OCH_3), 3.21* (dd, J = 13.3, 4.3 Hz, 1H, C*H*HPh), 3.13 (dd, J = 13.5, 5.2 Hz, 1H, C*H*HPh), 3.14–3.00 (m, 1H, CH), 2.78–2.55 (m, 3H), 2.55–2.50* (br.s, 1H, O*H*), 2.50–2.41 (m, 2H, O*H* and C*H*H), 2.39–2.28* (m, 1H, C*H*H), 2.18–2.05 (m, 3H), 1.97–1.85* (m, 2H, CH_2), 1.67–1.58 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, *trans*-isomer marked*): δ 159.5* (C), 159.4 (C), 139.7 (C), 139.6* (C), 131.4* (C), 131.1 (C), 128.6 (dd, J = 262.5, 255.0 Hz, CF_2), 128.5* (dd, J = 262.3, 255.8 Hz, CF_2), 128.8 (4CH), 128.4 (4CH), 128.3 (2CH), 128.0 (2CH), 127.8* (2CH), 126.2 (4CH), 113.6 (4CH), 81.1* (dd, J = 27.4, 20.6 Hz, C), 80.7 (dd, J = 27.9, 21.1 Hz, C), 55.2 ($2OCH_3$), 45.3* (dd, J = 23.6, 20.9 Hz, CH), 43.5 (t, J = 21.4 Hz, CH), 36.3* (dd, J = 7.3, 3.4 Hz, CH_2), 34.2* (CH_2), 33.9 (d, J = 3.9 Hz, CH_2), 33.7 (d, J = 7.6 Hz, CH_2), 25.6* (CH_2), 24.0 (d, J = 9.4 Hz, CH_2). ^{19}F NMR (470 MHz, $CDCl_3$, *trans*-isomer marked*): δ −97.0* (dd, J = 230.3, 23.5 Hz, F), −118.5 (dd, J = 230.3, 28.2 Hz, F), −124.9* (d, J = 230.3 Hz, F), −125.1 (d, J = 230.3 Hz, F). MS (EI): m/z (%) = 318 $[M]^+$ (56), 300 (98), 191 (19), 163 (58), 150 (86), 135 (100), 91 (37), 77 (30). HRMS (ESI-TOF): calcd. for $C_{19}H_{20}F_2O_2Na$ $[M+Na]^+$: 341.1329; Found: 341.1364.

3.2.5. 3-Benzyl-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)cyclo pentanol (5e)

Radical cyclization of **3e** (487 mg, 1 mmol) afforded a white solid of **5e** (238 mg, 63% yield) as a 60:40 mixture of *trans*- and *cis*-isomers after purification by PLC (SiO_2, 20% EtOAc-hexanes). m.p. = 116–120 °C. IR (neat): 3502s, 1591s, 1507s, 1462s, 1413s, 1338m, 1127s cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, *trans*-isomer marked*): δ 7.34–7.27 (m, 4H, Ph*H* of *trans*- and *cis*-isomers), 7.27–7.18 (m, 6H, Ph*H* of *trans*- and *cis*-isomers), 6.78 (s, 2H, Ar*H*), 6.76* (s, 2H, Ar*H*), 3.87* (s, 9H, OCH_3), 3.86 (s, 9H, OCH_3), 3.24–3.13* (m, 1H, C*H*HPh), 3.13–2.99 (m, 2H), 2.75–2.57 (m, 3H), 2.47–2.34 (m, 3H), 2.34–2.24* (m, 1H), 2.15–2.02 (m, 3H), 1.94–1.81* (m, 2H, CH_2), 1.66–1.54 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, *trans*-isomer marked*): δ 152.9 (2C), 139.6 (C), 139.5* (C), 138.2* (C), 138.1 (C), 134.8* (C), 134.6 (C), 128.8 (4CH), 128.7 (dd, J = 262.5,

255.3 Hz, CF_2), 128.6* (dd, J = 262.5, 255.2 Hz, CF_2), 128.5* (2CH), 128.4 (2CH), 126.2 (2CH), 104.2 (4CH), 81.5* (dd, J = 27.7, 20.4 Hz, C), 80.9 (dd, J = 27.9, 20.6 Hz, C), 60.9 ($2OCH_3$), 56.3 ($2OCH_3$), 56.2 ($2OCH_3$), 45.7* (dd, J = 23.9, 20.9 Hz, CH), 43.5 (t, J = 21.0 Hz, CH), 36.5* (dd, J = 7.2, 3.7 Hz, CH_2), 34.4* (d, J = 2.9 Hz, CH_2), 34.1 (d, J = 3.8 Hz, CH_2), 33.7 (d, J = 7.8 Hz, CH_2), 25.8* (t, J = 3.8 Hz, CH_2), 23.9 (d, J = 9.3 Hz, CH_2). ^{19}F NMR (470 MHz, $CDCl_3$, *trans*-isomer marked*): δ −94.8* (dd, J = 230.3, 23.5 Hz, F), −118.6 (dd, J = 230.3, 23.5 Hz, F), −124.1* (d, J = 230.3 Hz, F), −125.0 (d, J = 230.3 Hz, F). MS (EI): m/z (%) = 378 $[M]^+$ (100), 257 (29), 223 (25), 210 (56), 195 (53), 91 (19). HRMS (ESI-TOF): calcd. for $C_{21}H_{24}F_2O_4Na$ $[M+Na]^+$: 401.1541; Found: 401.1550.

3.2.6. (2,2-Difluoro-3-hydroxy-3-methylcyclopentyl)acetic acid methyl ester (**5f**)

Radical cyclization of **3f** (281 mg, 1 mmol) afforded a colorless oil of **5f** (161 mg, 77% yield) as a 66:34 mixture of *trans*- and *cis*-isomers after purification by column chromatography (SiO_2, 5% EtOAc-hexanes). IR (neat): 3461s, 1732s, 1440m, 1310s, 1212s, 1175s, 1116s, 1068s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, *trans*-isomer marked*): δ 3.70 (s, 6H, $2OCH_3$ of *trans*- and *cis*-isomers), 3.09–2.92 (m, 1H, C*H*), 2.81–2.64 (m, 3H, C*H**, C*H**HCO, and C*H*HCO), 2.46* (dd, J = 17.2, 10.1 Hz, 1H, CH*H*CO), 2.37 (dd, J = 16.0, 10.0 Hz, 1H, CH*H*CO), 2.24–2.13 (m, 2H, O*H* and C*H*H), 2.13–2.00* (m, 2H, O*H* and C*H*H), 1.91–1.69 (m, 4H), 1.66–1.54* (m, 1H), 1.45–1.29 (m, 1H, C*H*H), 1.34* (d, J = 2.3 Hz, 3H, CH_3), 1.33 (d, J = 2.5 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, *trans*-isomer marked*): δ 172.5* (CO), 172.4 (CO), 128.4 (dd, J = 260.9, 253.1 Hz, CF_2), 128.3* (t, J = 257.5 Hz, CF_2), 78.0* (dd, J = 26.4, 20.9 Hz, C), 77.5 (dd, J = 27.6, 21.6 Hz, C), 51.7 ($2OCH_3$), 39.6* (dd, J = 25.1, 20.4 Hz, CH), 38.0 (t, J = 21.4 Hz, CH), 34.9* (CH_2), 34.8* (dd, J = 7.0, 3.3 Hz, CH_2), 34.0 (d, J = 3.9 Hz, CH_2), 32.4 (d, J = 7.3 Hz, CH_2), 25.3* (dd, J = 4.5, 2.4 Hz, CH_2), 24.2 (d, J = 8.8 Hz, CH_2), 20.9* (d, J = 3.3 Hz, CH_3), 19.9 (d, J = 3.4 Hz, CH_3). ^{19}F NMR (470 MHz, $CDCl_3$, *trans*-isomer marked*): δ −106.6* (dd, J = 230.3, 18.8 Hz, F), −122.6 (dd, J = 230.3, 28.2 Hz, F), −127.9 (dd, J = 230.3, 7.1 Hz, F), −128.7 (dd, J = 230.3, 7.1 Hz, F). MS (EI): m/z (%) = 209 $[M+H]^+$ (7), 201 (21), 193 (31), 184 (66), 149 (92), 141 (53), 125 (69), 109 (62), 79 (100). HRMS (ESI-TOF): calcd. for $C_9H_{14}F_2O_3Na$ $[M+Na]^+$: 231.0809; Found: 231.0837.

3.2.7. 3-Benzyl-2,2-difluoro-1-methylcyclopentanol (**5h**)

Radical cyclization of **3h** (334 mg, 1 mmol) afforded a colorless oil of **5h** (161 mg, 71% yield) as a 52:48 mixture of *trans*- and *cis*-isomers after purification by column chromatography (SiO_2, 5% EtOAc-hexanes). IR (neat): 3418s, 1497m, 1455s, 1380s, 1177s, 1101s, 1071s cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, *trans*-isomer marked*): δ 7.31–7.25 (m, 4H, Ph*H* of *trans*- and *cis*-isomers), 7.23–7.16 (m, 6H, Ph*H* of *trans*- and *cis*-isomers), 3.09* (dd, J = 13.7, 4.6 Hz, 1H, C*H*HPh), 3.03 (dd, J = 13.7, 5.1 Hz, 1H, C*H*HPh), 2.90–2.73 (m, 1H, C*H*), 2.60* (dd, J = 13.7, 3.8 Hz, 1H, CH*H*Ph), 2.58 (dd, J = 13.7, 3.4 Hz, 1H, CH*H*Ph), 2.55–2.42* (m, 1H, C*H*), 2.13–2.00* (br.s, 1H, O*H*), 1.99–1.75 (m, 5H), 1.75–1.66* (m, 2H, CH_2), 1.66–1.56* (m, 1H, C*H*H), 1.46–1.35 (m, 1H, C*H*H), 1.33* (d, J = 2.4 Hz, 3H, CH_3), 1.32 (d, J = 2.4 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$, *trans*-isomer marked*): δ 139.8* (C), 139.6 (C), 128.7 (dd, J = 260.6, 252.8 Hz, CF_2), 128.4* (t, J = 257.1 Hz, CF_2), 128.8* (2CH), 128.7 (2CH), 128.4* (2CH), 128.3 (2CH), 126.1* (CH), 126.0 (CH), 78.1* (dd, J = 25.8, 21.0 Hz, C), 78.0 (dd, J = 27.6, 21.8 Hz, C), 44.6* (t, J = 21.8 Hz, CH), 43.0 (t, J = 21.1 Hz, CH), 35.5* (dd, J = 6.9, 1.8 Hz, CH_2), 35.1* (CH_2), 33.9 (d, J = 4.3 Hz, CH_2), 33.6 (d, J = 7.4 Hz, CH_2), 24.8* (dd, J = 5.9, 1.6 Hz, CH_2), 24.1 (d, J = 9.3 Hz, CH_2), 21.5* (d, J = 3.8 Hz, CH_3), 20.0 (d, J = 3.6 Hz, CH_3). ^{19}F NMR (470 MHz, $CDCl_3$, *trans*-isomer marked*): δ −108.9* (dd, J = 229.4, 18.3 Hz, F), −123.1 (dd, J = 228.6, 25.1 Hz, F), −127.3* (dd, J = 229.4, 13.2 Hz, F), −128.0 (dd, J = 228.6, 8.5 Hz, F). MS (EI): m/z (%) = 226 $[M]^+$ (28), 208 (60), 129 (36), 117 (98), 91 (100), 77 (19). HRMS (ESI-TOF): calcd. for $C_{13}H_{16}F_2ONa$ $[M+Na]^+$: 249.1067; Found: 249.1076.

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