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Asymmetric Synthesis of *gem*-Difluoromethylenated Linear Triquinanes via Cascade *gem*-Difluoroalkyl Radical Cyclization

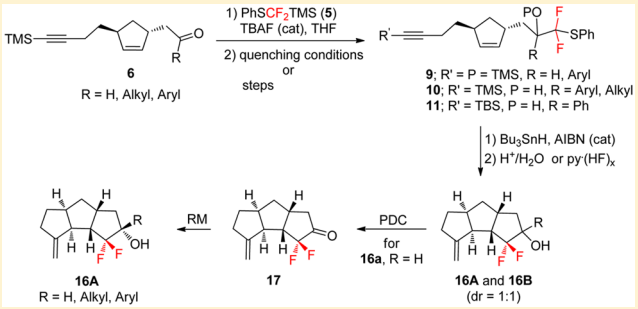
Watcharaporn Thaharn,[†] Darunee Soorukram,[†] Chutima Kuhakarn,[†] Patoomratana Tuchinda,[†] Chaveng Pakawatchai,[‡] Saowanit Saithong,[‡] Vichai Reutrakul,[†] and Manat Pohmakotr*[,†]

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

[‡]Center of Excellence for Innovation in Chemistry (PERCH−CIC) and Department of Chemistry Faculty of Science, Prince of Songkla University, Hat Yai, Songkla 90112, Thailand

Supporting Information

ABSTRACT: An asymmetric synthesis of *gem*-difluoromethylenated linear triquinanes is described exploiting the synthetic utilities of $PhSCF_2TMS$ (**5**) as a "$^{\bullet}CF_2^{-}$" building block. The strategy involves fluoride-catalyzed nucleophilic addition of $PhSCF_2TMS$ (**5**) to chiral ketocyclopentenes **6** to provide silylated adducts **9** or alcohol derivatives **10** and **11**. Subsequent cascade radical cyclization of the *gem*-difluoroalkyl radical generated from silylated adducts **9** or alcohols **10** and **11** afforded *gem*-difluoromethylenated linear triquinanes **16** as an approximate 1:1 mixture of two diastereomers (**16A** and **16B**). Alternatively, a convenient asymmetric synthesis of *gem*-difluoromethylenated linear triquinanes **16A** can be accomplished by oxidation of **16a** (R = H) to provide ketotriquinane **17** followed by a highly stereoselective nucleophilic addition to **17** employing DIBAL, $NaBH_4$, and various Grignard reagents.



INTRODUCTION

A linearly fused triquinane is a substructural unit found in hirsutene (**1**) and $\Delta^{9(12)}$-capnellene (**2**) (Figure 1). A number of hirsutene and capnellene families of triquinane natural products were isolated from plants, microorganisms, and marine organisms.[1] Some linear triquinane natural products, for example, hirsutic acid (**3**) and coriolin (**4**), exhibit antibiotic and antitumor activity,[2] respectively (Figure 1). Because of their intricate structures and significant biological properties, development of numerous synthetic methods for the construction of linear triquinane framework and related cyclopentanoids has been reported.[1,3] In recent years, organofluorine compounds are of particular interest due to their unique physical, chemical, biological and therapeutic properties. Therefore, organofluorine compounds are widely used in medicine and agriculture, as well as in materials sciences.[4] In particular, the presence of *gem*-difluoromethylene moiety in bioactive compounds was realized to enhance their biological properties.[5] As a result, substantial progress has been made toward efficient methods for the synthesis of *gem*-difluoromethylenated compounds in recent years.[6]

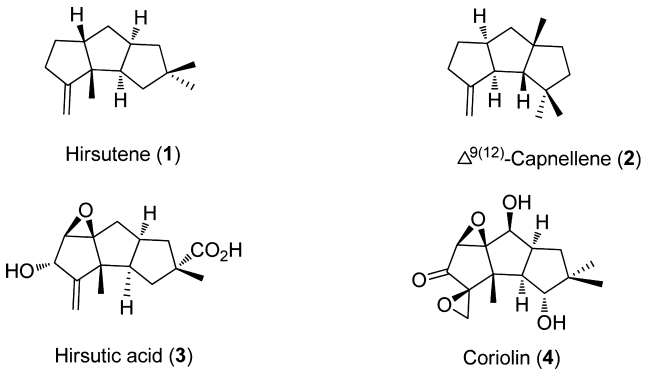


Figure 1. Triquinane-type compounds.

As a part of our research program devoted to the synthesis of *gem*-difluoromethylenated organic compounds employing $PhSCF_2TMS$ (**5**) as a *gem*-difluoromethylene building block [a difluoromethylene radical anion equivalent ($^{\bullet}CF_2^{-}$)],[7] we previously reported the preparation of *gem*-difluoromethylenated 1-azabicyclic compounds,[8] macrocyclic lactones,[9] cyclopentanols,[10] and spiro-γ-butyrolactones.[11] Recently, we described the reaction of compounds **7** (R = Ar), derived from the reaction of chiral ketocyclopentenes **6** with $PhSCF_2TMS$ (**5**), with tributyltin radical in refluxing toluene yielding a chiral bicyclic ketones **8** through a chemoselective addition of the tributyltin radical to the terminal acetylenic group of

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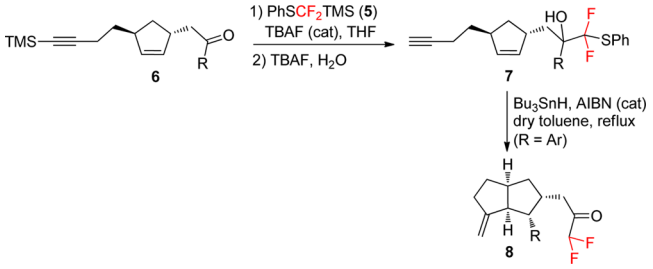
compounds **7** followed by radical cyclization/1,4-*ipso*-aryl migration cascade (Scheme 1).[12]

Scheme 1. Our Previous Report on Radical Cyclization/1,4-*ipso*-Aryl Migration Cascade for Asymmetric Synthesis of Bicyclic Compounds 8



In the present work, we disclose a general synthetic entry to an asymmetric synthesis of *gem*-difluoromethylenated linear triquinane derivatives **16**, which has never been reported in the literature. The synthesis involved fluoride-catalyzed nucleophilic addition of $PhSCF_2TMS$ (**5**) to chiral ketocyclopentenes **6** leading to adducts **9**–**12**. Upon treatment of compounds **9**–**11** with Bu_3SnH/AIBN in refluxing toluene, reductive cleavage of the PhS–C bond took place leading to the corresponding *gem*-difluoroalkyl radical of type **9A**–**11A**, which underwent a cascade radical cyclization to furnish the expected linear triquinane derivatives **13**–**15** and then **16** after protodesilylation and hydrolysis (Scheme 2).

RESULTS AND DISCUSSION

Our study commenced with the preparation of the requisite compounds **9**–**12**. Thus, treatment of $PhSCF_2TMS$ (**5**) with chiral ketocyclopentenes **6a**–**c**, readily prepared from a chiral lactone, (3*aR*,6*aS*)-3,3*a*,4,6*a*-tetrahydro-2*H*-cyclopenta[*b*]-furan-2-one,[13] in the presence of 10 mol % of TBAF in THF at 0 °C to rt for 24 h followed by quenching the reaction mixture with a saturated $NaHCO_3$ solution at 0 °C gave silylated adducts **9a**–**c** (80–87% yields), each as a 1:1 mixture of diastereomers (determined by ^{19}F NMR) (Table 1, entries 1–3). When water was employed in place of a saturated aqueous $NaHCO_3$ solution in the quenching step, the reaction of **6b** and **6d**–**f** gave the corresponding alcohols **10a**–**d** (71–97% yields), each as a 1:1 mixture of diastereomers (Table 1, entries 4–7). Finally, alcohols **11** and **12** bearing TBS and ethoxycarbonyl moieties, respectively, were prepared in two steps (Table 1, entries 8–9).[14] Indeed, treatment of **6b** with $PhSCF_2TMS$ (**5**) under the standard reaction conditions followed by quenching the reaction with excess amount of TBAF gave **7** (96% yield) (Table 1). Compound **7** was then converted to alcohols **11** or **12** by treatment of **7** with *n*-BuLi followed by trapping with either TBSCl or ethyl chloroformate, respectively.

Having succeeded in the preparation of compounds **9**–**12**, we next studied their cascade radical cyclization[15,16] to the required *gem*-difluoromethylenated linear triquinanes **16**. The reaction of **9a** (dr = 1:1) in toluene (0.02 M) with Bu_3SnH (1.75 equiv) and a catalytic amount of AIBN at refluxing temperature for 24 h provided *gem*-difluoromethylenated linear triquinane **13a** in 84% yield as a mixture of four stereoisomers (Table 2, entry 1). The observed results revealed that tributyltin radical mediated the reductive cleavage of the PhS–C bond to provide *gem*-difluoroalkyl radical intermediate of type **9A** (Scheme 2), which further underwent a cascade radical cyclization to furnish *gem*-difluoromethylenated triquinane derivative **13a** as a mixture of four diastereomers (^{19}F NMR analysis). With no attempts to separate the stereoisomers, **13a** was exposed to protodesilylation and hydrolysis (TFA, CH_2Cl_2, 0 °C, 2 h)[17] to afford a 1:1 mixture of *gem*-difluoromethylenated triquinanes **16aA** and **16aB** in 82% yield (Table 2, entry 1). Unfortunately, attempts to separate the two diastereoisomers, **16aA** and **16aB**, were not successful. With the optimum reaction conditions as for **9a**, the silylated compounds **9b** and **9c** yielded the corresponding *gem*-difluoromethylenated triquinanes **13b** and **13c** in good yields (81–89% yields), each as a mixture of four stereoisomers. Protodesilylation and hydrolysis of **13b** and **13c** gave the corresponding *gem*-difluoromethylenated linear triquinanes **16b** and **16c** in good yields, each as approximately 1:1 mixture of two diastereomers. To our delight, separation of the diastereomers for each of **16b** and **16c** was possible by means of preparative TLC (Table 2, entries 2–3). Under similar reaction conditions as for silylated compounds **9a**–**c**, the radical cyclization of the alcohol derivatives **10a**–**d** (dr = 1:1) gave the corresponding *gem*-difluoromethylenated triquinanes **14a**–**d** (each as a mixture of four diastereomers). Subsequent protodesilylation of **14a**–**d** (TFA, CH_2Cl_2, 0 °C, 1 h) gave the corresponding *gem*-difluoromethylenated triqui-

Scheme 2. Synthetic Entry to *gem*-Difluoromethylenated Linear Triquinanes 16

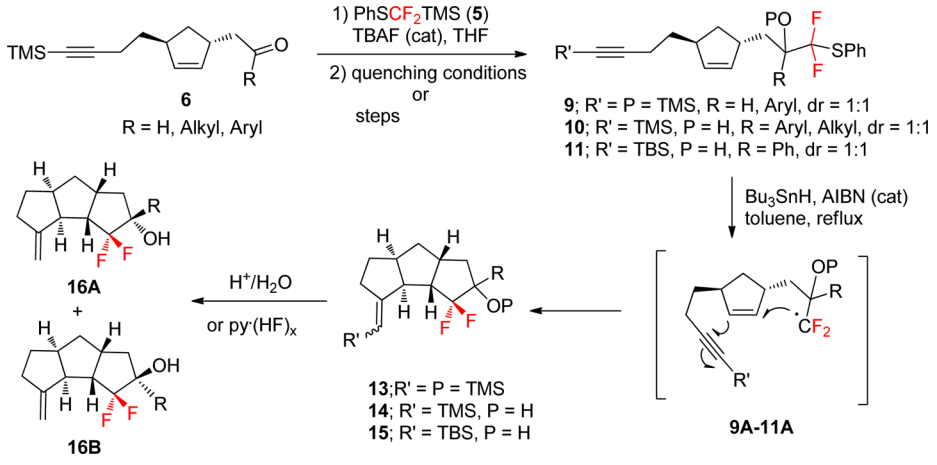


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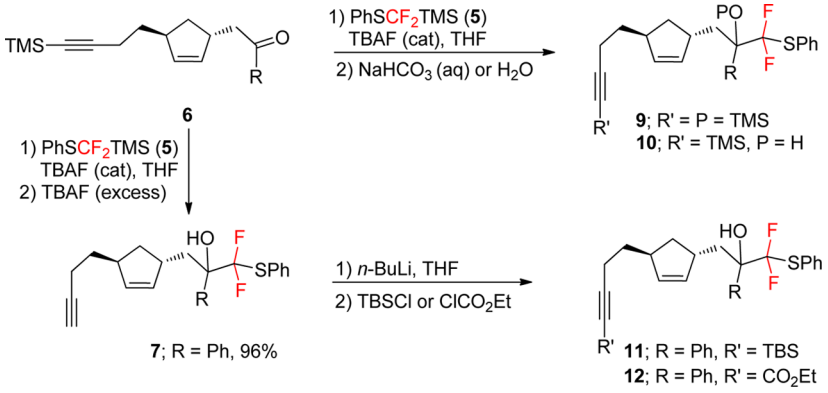
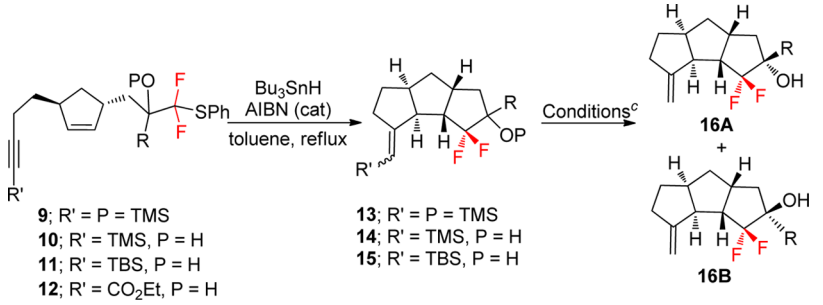
Table 1. Fluoride-Catalyzed Nucleophilic Addition of $PhSCF_2SiMe_3$ (5) to Chiral Ketocyclopentene 6



entry	substrate	R	product; yield (%)[a,b] 9[c] or 10[d] or 11 or 12
1	**6a**	H	**9a**; 80
2	**6b**	Ph	**9b**; 84
3	**6c**	4-FC_6H_4	**9c**; 87
4	**6b**	Ph	**10a**; 97
5	**6d**	4-$CF_3C_6H_4$	**10b**; 90
6	**6e**	CH_3	**10c**; 74
7	**6f**	CH_2CH_3	**10d**; 71
8	**6b**	Ph	**11**; 75
9	**6b**	Ph	**12**; 76

[a]Isolated yields after column chromatography (SiO_2). [b]In all cases, mixtures of two diastereoisomers (dr = 1:1) were obtained (^{19}F NMR analysis). [c]The reaction was quenched with sat. $NaHCO_3$. [d]The reaction was quenched with water.

Table 2. Preparation of *gem*-Difluoromethylenated Linear Triquinanes 16



entry	substrate	R	13 or 14 or 15; yield (%)[a] (dr)[b]	16[c]; yield (%)[a] (dr)[b]
1	**9a**	H	**13a**; 84 (40:38:12:10)	**16aA** + **16aB**; 82[d] (1:1)[b]
2	**9b**	Ph	**13b**; 81 (40:38:12:10)	**16bA**; 40
				16bB; 40
3	**9c**	4-FC_6H_4	**13c**; 89 (41:38:11:10)	**16cA**; 45
				16cB; 44
4	**10a**	Ph	**14a**; 88 (42:41:9:8)	**16bA**; 38
				16bB; 39
5	**10b**	4-$CF_3C_6H_4$	**14b**; 79 (42:41:9:8)	**16dA**; 42
				16dB; 42
6	**10c**	CH_3	**14c**; 83 (37:15:37:11)	**16eA** + **16eB**; 90[d] (1:1)[b]
7	**10d**	CH_2CH_3	**14d**; 91 (35:16:34:15)	**16fA** + **16fB**; 82[d] (1:1)[b]
8	**11**	Ph	**15**; 76 (33:33:18:16)	**16bA**; 45
				16bB; 46

[a]Isolated yields after column chromatography (SiO_2). [b]Determined by ^{19}F NMR. [c]The TMS group was removed by using trifluoroacetic acid in CH_2Cl_2, while the TBS group was removed by using py·$(HF)_x$. [d]The two diastereoisomers could not be separated by means of chromatography.

nanes **16b**, **16d**, **16e** and **16f**, each as a mixture of two diastereomers, in good yields (Table 1, entries 4–7). While the diastereoisomers of **16b** and **16d** can be separated (preparative TLC), compounds **16e** and **16f** were obtained each as a 1:1 mixture of two diastereoisomers. It is worth mentioning here that the stereochemistries of **16aA** and **16bA–16dA** were later confirmed on the basis of the NOE experiments and X-ray crystallographic data of their derivatives. Next, the effect of the

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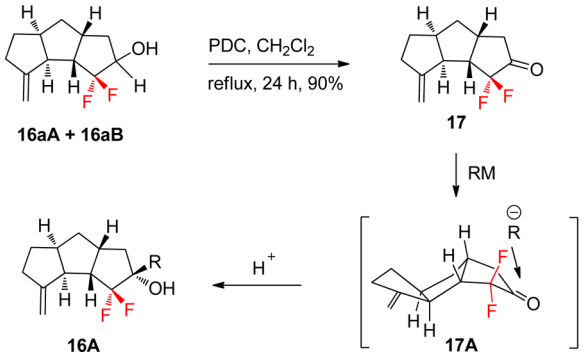
TMS-protected terminal acetylene on the present cascade radical cyclization was evaluated. Compounds **11** and **12** bearing the TBS group and the ethoxycarbonyl moiety respectively in place of the TMS-protected terminal acetylene were exposed to our standard radical cyclization reaction. Compound **11** (TBS-protected terminal acetylene) gave comparable results leading to *gem*-difluoromethylenated triquinane **15** in 76% yield as a mixture of four diastereomers (Table 2, entry 8). Subsequent protodesilylation of **15** employing py·$(HF)_x$[18] yielded **16bA** and **16bB** in 45% and 46% yields, respectively. Unfortunately, compound **12** bearing the ethoxycarbonyl moiety failed to undergo the reaction; indefinite spots were observed by TLC analysis.

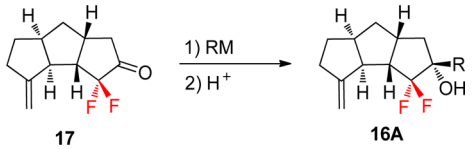
From the above-mentioned results, the *gem*-difluoromethylenated linear triquinanes of type **16** can be readily prepared in good yields by the cascade radical cyclization followed by protodesilylation and hydrolysis of *gem*-difluoroalkyl radical generated from both trimethylsilyloxy derivatives **9** (TMS-protected terminal acetylene) and alcohol derivatives **10** (TMS-protected terminal acetylene) and **11** (TBS-protected terminal acetylene), which in turn were prepared from nonstereoselective fluoride-catalyzed nucleophilic addition of $PhSCF_2TMS$ (**5**) to chiral ketocyclopentenes **6a**–**f**. Even though the two diastereoisomers of compound **16** where R = Aryl could be separated by means of thin-layer chromatography, those possessing R = Me and Et were obtained as a mixture of two isomers. To circumvent this drawback, it is anticipated that a *gem*-difluoromethylenated ketotriquinane **17**, derived from a mixture of **16aA** and **16aB** (1:1 dr) upon oxidation, would undergo highly stereoselective nucleophilic addition by nucleophiles such as a hydride from a reducing agent or a Grignard reagent to provide *gem*-difluoromethylenated linear triquinanes **16A**. Thus, oxidation of a mixture of **16aA** and **16aB** (1:1 dr) with pyridinium dichromate (PDC) in refluxing dichloromethane for 24 h gave the expected ketotriquinane **17** in 90% yield (Scheme 3).[19] To our delight, the reaction of

Scheme 3. Preparation of *gem*-Difluoromethylenated Linear Triquinanes 16A by Stereoselective Nucleophilic Addition of Hydride or Grignard Reagents to Ketotriquinane 17



ketotriquinane **17** with diisobutylaluminum hydride (DIBAL) in THF at −78 °C for 1 h gave only **16aA** as a single diastereomer in 87% yield (Scheme 3 and Table 3, entry 1). Similar results were obtained when sodium borohydride in methanol was employed in place of DIBAL. The stereochemical outcome of the reduction of **17** providing only **16aA** can be rationalized as depicted in Scheme 3. Hydride from the reducing agent attacks the carbonyl carbon of the *gem*-difluoromethylenated linear ketotriquinane **17** from its less

Table 3. Preparation of *gem*-Difluoromethylenated Linear Triquinanes 16A



entry	RM	R	**16A** (% yield)[a]
1	DIBAL	H	**16aA** (87)
2	$NaBH_4$	H	**16aA** (74)
3	PhMgCl	Ph	**16bA** (83)
4	$4\text{-}FC_6H_4MgBr$	$4\text{-}FC_6H_4$	**16cA** (89)
5	$4\text{-}CF_3C_6H_4MgBr$	$4\text{-}CF_3C_6H_4$	**16dA** (86)
6	MeMgCl	Me	**16eA** (92)
7	EtMgCl	Et	**16fA** (83)
8	*n*-BuMgCl	*n*-Bu	**16gA** (85)
9	$4\text{-}MeOC_6H_4MgBr$	$4\text{-}MeOC_6H_4$	**16hA** (92)
10	$2,4\text{-}(MeO)_2C_6H_3MgBr$	$2,4\text{-}(MeO)_2C_6H_3$	**16iA** (87)

[a]Isolated yields after column chromatography (SiO_2).

hindered convex face through the transition state **17A** to provide the adduct **16aA** as a single isomer. The stereochemistry of **16aA** was also confirmed by NOE experiments (see the Supporting Information). On the basis of this approach, *gem*-difluoromethylenated linear triquinanes **16bA**–**16iA**, each as a single isomer, were also obtained in high yields from the reaction of ketotriquinane **17** with various Grignard reagents at 0 °C for 1 h followed by treatment with a saturated NH_4Cl solution. The results are summarized in Table 3. The stereochemistry of **16hA** was confirmed by X-ray crystallography (see the Supporting Information). On the same basis of X-ray data of **16hA**, we assumed that the relative stereochemistries of **16bA**–**16gA** and **16iA** are similar to those of **16hA**. Thus, the addition reaction of the Grignard reagent and the reduction proceeded through the proposed transition state **17A** as depicted in Scheme 3.

CONCLUSION

We have demonstrated the synthetic utilities of $PhSF_2TMS$ (**5**) as a *gem*-difluoromethylene radical anion building block ($^{\bullet}CF_2^-$) for asymmetric synthesis of *gem*-difluoromethylenated linear triquinanes **16**. The strategy involved fluoride-catalyzed nucleophilic addition of **5** to chiral ketocyclopentenes **6** followed by cascade cyclization of *gem*-difluoroalkyl radical derived from the corresponding silylated adducts **9** or alcohol derivatives **10** and **11**. Alternatively, highly stereoselective nucleophilic addition of DIBAL, $NaBH_4$ and various Grignard reagents to *gem*-difluoromethylenated ketotriquinane **17**, obtained by oxidation of a 1:1 mixture of diastereomers of **16a** with PDC in dichloromethane, provided a convenient asymmetric synthesis of *gem*-difluoromethylenated linear triquinanes **16**. We expect that the method developed has the potential of being applied in synthesis of other related *gem*-difluoromethylenated linear triquinanes as well as their heteroatom substituted analogues.

EXPERIMENTAL SECTION

General Procedures. ^1H NMR spectra were recorded on 400 MHz spectrometers and are reported in ppm. Proton decoupled ^{13}C NMR spectra were recorded on 100 MHz spectrometer and are reported in ppm. The ^{19}F NMR spectra were recorded on a 376 MHz spectrometer and chemical shifts (δ) were measured with fluorotri-

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chloromethane (δ = 0) as an internal standard. Reactions were monitored by thin-layer chromatography and visualized by UV and a solution of $KMnO_4$. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride and stored over activated molecular sieves (4 Å). All glasswares and syringes were oven-dried and kept in a desiccator before use. Purification of the reaction products were carried out by preparative thin-layer chromatography plates or column chromatography on silica gel.

2-((1*R*,4*S*)-4-(4-(Trimethylsilyl)but-3-yn-1-yl)cyclopent-2-en-1-yl)acetaldehyde (6a). To a solution of *N*-methoxy-*N*-methyl-2-((1*R*,4*S*)-4-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopent-2-en-1-yl)-acetamide (**18**)[12] (587 mg, 2 mmol) in dry THF (10 mL) at −78 °C was added dropwise diisobutylaluminum hydride (DIBAL) (1 M in hexane, 3 mL, 3 mmol). After stirring at −78 °C for 1 h, the reaction was quenched by the addition of EtOAc (10 mL), and then poured into a mixture of tartaric acid (0.5 M aqueous solution, 10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography (SiO_2, 5% EtOAc in hexanes) to give **6a** (380 mg, 81% yield) as a colorless oil: $[\alpha]^{26}_D$ −51.4 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.8 Hz, 1H), 5.76−5.71 (m, 1H), 5.70−5.63 (m, 1H), 3.23−3.13 (m, 1H), 2.89−2.75 (m, 1H), 2.55−2.18 (m, 4H), 1.83−1.45 (m, 4H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2 (CO), 135.4 (CH), 133.3 (CH), 107.2 (C), 84.6 (C), 49.8 (CH_2), 44.0 (CH), 39.0 (CH), 36.0 (CH_2), 34.4 (CH_2), 18.3 (CH_2), 0.1 (3 × CH_3); IR (neat) ν_{max} 2174*s*, 1713*s*, 1250*s*, 843*s*, 760*m* cm^{-1}; MS *m*/*z* (%) relative intensity 234 (M^+, 2), 145 (16), 131 (25), 117 (54), 91 (100), 73 (35); HRMS (ESI-TOF) calcd for $C_{14}H_{22}NaOSi$ $[M + Na]^+$ 257.1338, found 257.1330.

1-Phenyl-2-((1*R*,4*S*)-4-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopent-2-en-1-yl)ethanone (6b). *General Procedure A.* A solution of aryl bromide (3 mmol) in dry THF (3 mL) was added dropwise to a suspension of Mg (turnings) (365 mg, 15 mmol) in dry THF (3 mL) under an argon atmosphere at room temperature. After stirring for 2 h, the resulting Grignard reagent was transferred dropwise via a canular to a solution of **18** (176 mg, 0.6 mmol) in dry THF (6 mL) at 0 °C under an argon atmosphere. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography (SiO_2, 2% EtOAc in hexanes) to yield **6b** (167 mg, 90% yield) as a colorless oil: $[\alpha]^{29}_D$ −73.6 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.1 Hz, 2H), 7.61−7.53 (m, 1H), 7.49−7.42 (m, 2H), 5.73 (br s, 2H), 3.37−3.25 (m, 1H), 3.05 (dd, *J* = 16.6, 6.2 Hz, 1H), 2.95 (dd, *J* = 16.6, 7.9 Hz, 1H), 2.90−2.78 (m, 1H), 2.34−2.16 (m, 2H), 1.87−1.77 (m, 1H), 1.76−1.68 (m, 1H), 1.67−1.59 (m, 1H), 1.58−1.46 (m, 1H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7 (CO), 137.1 (C), 134.9 (CH), 134.3 (CH), 133.0 (CH), 128.6 (2 × CH), 128.1 (2 × CH), 107.4 (C), 84.5 (C), 44.6 (CH_2), 43.9 (CH), 40.7 (CH), 36.3 (CH_2), 34.5 (CH_2), 18.3 (CH_2), 0.1 (3 × CH_3); IR (neat) ν_{max} 2174*s*, 1687*s*, 1598*m*, 1449*m*, 1250*s*, 843*s*, 759*s* cm^{-1}; MS *m*/*z* (%) relative intensity 310 (M^+, 4), 219 (18), 205 (24), 116 (18), 105 (98), 91 (20), 77 (100), 73 (35); HRMS (ESI-TOF) calcd for $C_{20}H_{26}OSiNa$ $[M + Na]^+$ 333.1651, found 333.1651.

1-(4-Fluorophenyl)-2-((1*R*,4*S*)-4-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopent-2-en-1-yl) ethanone (6c). According to the *general procedure A*, the reaction of **18** (235 mg, 0.8 mmol) and 4-FC_6H_4MgBr (0.5 M, 4 mmol) in dry THF (8 mL) at 0 °C gave **6c** (231 mg, 88% yield) as a colorless oil after column chromatography (SiO_2, 2% EtOAc in hexanes): $[\alpha]^{23}_D$ −76.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.93 (m, 2H), 7.15−7.07 (m, 2H), 5.77−5.68 (m, 2H), 3.35−3.23 (m, 1H), 3.01 (dd, *J* = 16.5, 6.6 Hz, 1H), 2.91 (dd, *J* = 16.5, 7.9 Hz, 1H), 2.87−2.77 (m, 1H), 2.31−2.17 (m, 2H), 1.81 (ddd, *J* = 13.3, 8.2, 5.1 Hz, 1H), 1.70 (ddd, *J* = 13.2, 8.2, 5.0 Hz, 1H), 1.67−1.46 (m, 2H), 0.13 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.49 (s, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0 (CO), 165.7 (d, *J* = 253.0 Hz, C), 135.0 (CH), 134.1 (CH), 133.6 (d, *J* = 2.6 Hz, C), 130.7 (d, *J* = 9.1 Hz, 2 × CH), 115.6 (d, *J* = 21.7 Hz, 2 × CH), 107.4 (C), 84.5 (C), 44.5 (CH_2), 43.9 (CH), 40.7 (CH), 36.3 (CH_2), 34.5 (CH_2), 18.3 (CH_2), 0.1 (3 × CH_3); IR (neat) ν_{max} 2174*s*, 1687*s*, 1598*s*, 1507*m*, 1250*s*, 1157*m*, 842*s*, 735*m* cm^{-1}; MS *m*/*z* (%) relative intensity 328 (M^+, 4), 203 (17), 123 (50), 91 (23), 74 (100), 65 (8), 51 (20); HRMS (ESI-TOF) calcd for $C_{20}H_{25}FNaOSi$ $[M + Na]^+$ 351.1556, found 351.1579.

1-(4-(Trifluoromethyl)phenyl)-2-((1*R*,4*S*)-4-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopent-2-en-1-yl)ethanone (6d). According to the *general procedure A*, the reaction of **18** (235 mg, 0.8 mmol) and 4-$CF_3C_6H_4MgBr$ (0.5 M, 4 mmol) in dry THF (8 mL) at 0 °C gave **6d** (245 mg, 81% yield) as a colorless oil after column chromatography (SiO_2, 5% EtOAc in hexanes): $[\alpha]^{26}_D$ −83.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 5.79−5.68 (m, 2H), 3.36−3.25 (m, 1H), 3.07 (dd, *J* = 16.8, 6.5 Hz, 1H), 2.97 (dd, *J* = 16.8, 7.8 Hz, 1H), 2.90−2.79 (m, 1H), 2.33−2.16 (m, 2H), 1.83 (ddd, *J* = 13.3, 8.2, 5.2 Hz, 1H), 1.71 (ddd, *J* = 13.2, 8.3, 5.0 Hz, 1H), 1.67−1.46 (m, 2H), 0.14 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.11 (s, 3 × F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6 (CO), 139.8 (C), 135.3 (CH), 134.3 (q, *J* = 31.2 Hz, C), 133.9 (CH), 128.4 (2 × CH), 125.6 (q, *J* = 3.4 Hz, 2 × CH), 123.6 (q, *J* = 271.1 Hz, CF_3), 107.3 (C), 84.6 (C), 44.9 (CH_2), 43.9 (CH), 40.6 (CH), 36.3 (CH_2), 34.5 (CH_2), 18.3 (CH_2), 0.1 (3 × CH_3); IR (neat) ν_{max} 2174*s*, 1694*s*, 1410*s*, 1326*s*, 1171*s*, 1134*s*, 1067*s*, 843*s* cm^{-1}; MS *m*/*z* (%) relative intensity 379 (M^+, 3), 273 (13), 219 (14), 173 (100), 145 (90), 91 (25), 65 (8), 51 (16). HRMS (ESI-TOF) calcd for $C_{21}H_{25}F_3NaOSi$ $[M + Na]^+$ 401.1524, found 401.1526.

1-((1*R*,4*S*)-4-(4-(Trimethylsilyl)but-3-yn-1-yl)cyclopent-2-en-1-yl)propan-2-one (6e). According to the *general procedure A*, the reaction of **18** (293 mg, 1 mmol) and MeMgBr (2 M, 5 mmol, 2.5 mL) in dry THF (8 mL) at 0 °C gave **6e** (216 mg, 87% yield) as a colorless oil after column chromatography (SiO_2, 5% EtOAc in hexanes): $[\alpha]^{26}_D$ −79.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59−5.54(m, 1H), 5.53−5.46 (m, 1H), 3.04−2.93 (m, 1H), 2.71−2.60 (m, 1H), 2.36 (dd, *J* = 16.6, 6.7 Hz, 1H), 2.27 (dd, *J* = 16.6, 7.9 Hz, 1H), 2.16−2.04 (m, 2H), 1.99 (s, 3H), 1.67−1.54 (m, 1H), 1.53−1.43 (m, 2H), 1.42−1.30 (m, 1H), −0.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4 (C), 134.9 (CH), 133.9 (CH), 107.4 (C), 84.5 (C), 49.7 (CH_2), 43.9 (CH), 40.2 (CH), 36.1 (CH_2), 34.5 (CH_2), 30.3 (CH_2), 18.3 (CH_3), 0.1 (3 × CH_3); IR (neat) ν_{max} 2174*s*, 1716*s*, 1361*m*, 1249*s*, 843*s*, 760*m* cm^{-1}; MS *m*/*z* (%) relative intensity 248 (M^+, 8), 233 (87), 159 (45), 131 (53), 117 (90), 93 (56), 73 (100), 59 (14); HRMS (ESI-TOF) calcd for $C_{15}H_{24}NaOSi$ $[M + Na]^+$ 271.1494, found 271.1487.

1-((1*R*,4*S*)-4-(4-(Trimethylsilyl)but-3-yn-1-yl)cyclopent-2-en-1-yl)butan-2-one (6f). According to the *general procedure A*, the reaction of **18** (293 mg, 1 mmol) and EtMgBr (2 M, 5 mmol, 2.5 mL) in dry THF (8 mL) at 0 °C gave **6f** (241 mg, 92% yield) as a colorless oil after column chromatography (SiO_2, 5% EtOAc in hexanes): $[\alpha]^{26}_D$ −56.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71−5.68 (m, 1H), 5.66−5.62 (m, 1H), 3.19−3.07 (m, 1H), 2.85−2.73 (m, 1H), 2.52−2.34 (m, 4H), 2.29−2.18 (m, 2H), 1.73 (ddd, *J* = 13.2, 8.2, 5.1 Hz, 1H), 1.67−1.56 (m, 2H), 1.55−1.44 (m, 1H), 1.05 (t, *J* = 7.3 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1 (C), 134.8 (CH), 134.1 (CH), 107.4 (C), 84.5 (C), 48.4 (CH_2), 43.9 (CH), 40.3 (CH), 36.3 (CH_2), 36.2 (CH_2), 34.5 (CH_2), 18.3 (CH_2), 7.8 (CH_3), 0.1 (3 × CH_3); IR (neat) ν_{max} 2170*s*, 1709*s*, 1410*w*, 1251*s*, 844*s* cm^{-1}; MS *m*/*z* (%) relative intensity 262 (M^+, 8), 238 (26), 179 (56), 125 (52), 98 (73), 81 (91), 67 (79), 57 (100); HRMS (ESI-TOF) calcd for $C_{16}H_{26}NaOSi$ $[M + Na]^+$ 285.1651, found 285.1653.

((1,1-Difluoro-1-(phenylthio)-3-((1*R*,4*S*)-4-(4-(trimethylsilyl)-but-3-yn-1-yl)cyclopent-2-en-1-yl)propan-2-yl)oxy)trimethylsilane (9a). *General Procedure B.* A solution of $PhSCF_2TMS$ (**5**) (928 mg, 4 mmol) and **6a** (469 mg, 2 mmol) in dry THF (3 mL) was treated with a solution of 10 mol % TBAF (1 M in dry THF, 0.4 mL, 0.4 mmol) at 0 °C to room temperature under an argon atmosphere for 24 h. The reaction mixture was quenched with saturated aqueous

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$NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography (SiO_2, 5−10% EtOAc in hexanes) to give a 50:50 diastereomeric mixture of **9a** (747 mg, 80% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$, isomer **A** marked*) δ 7.65−7.57 (m, 4H of isomers **A** and **B**), 7.45−7.33 (m, 6H of isomers **A** and **B**), 5.80−5.65 (m, 4H of isomers **A** and **B**), 4.07−3.93 (m, 2H of isomers **A** and **B**), 2.93−2.78 (m, 4H of isomers **A** and **B**), 2.34−2.17 (m, 4H of isomers **A** and **B**), 1.88−1.47 (m, 12H of isomers **A** and **B**), 0.18 (s, 18H of isomers **A** and **B**), 0.16 (s, 18H of isomers **A** and **B**); ^{19}F NMR (376 MHz, $CDCl_3$, isomer **A** marked*) δ −83.17 (ddt, J = 209.8, 41.7, 8.3 Hz, 2 × F*), −85.81 (ddt, J = 209.1, 53.3, 9.8 Hz, 2 × F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$, isomer **A** marked*) δ 136.6 (2 × CH of isomers **A** and **B**), 136.5 (2 × CH of isomers **A** and **B**), 135.3 (CH*), 135.0 (CH of isomer **B**), 134.1 (CH of isomer **B**), 133.4 (CH*), 130.2 (dd, J = 282.7, 282.7 Hz, 2 × CF_2 of isomers **A** and **B**), 129.6 (2 × CH of isomers **A** and **B**), 128.9 (4 × CH of isomers **A** and **B**), 126.3 (2 × C of isomers **A** and **B**), 107.4 (C*), 107.3 (C of isomer **B**), 84.5 (C of isomer **B**), 84.4 (C*), 74.6 (dd, J = 25.0, 11.4 Hz, CH*), 74.3 (dd, J = 25.9, 11.4 Hz, CH of isomer **B**), 43.9 (CH*), 43.8 (CH of isomer **B**), 40.6 (2 × CH of isomers **A** and **B**), 38.3 (CH_2 of isomer **B**), 37.7 (CH_2*), 36.8 (CH_2*), 35.4 (CH_2 of isomer **B**), 34.6 (2 × CH_2 of isomers **A** and **B**), 18.3 (2 × CH_2 of isomers **A** and **B**), 0.3 (3 × CH_3*), 0.2 (3 × CH_3 of isomer **B**), 0.1 (6 × CH_3 of isomers **A** and **B**); IR (neat) ν_{max} 2175*s*, 1584*w*, 1475*m*, 1442*s*, 1251*s*, 1135*s*, 843*s*, 750*s* cm^{-1}; MS m/z (%) relative intensity 466 (M^+ − 1, 2), 267 (14), 153 (50), 129 (69), 115 (100), 91 (71), 73 (97), 65 (18) cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{36}F_2NaOSSi_2$ $[M + Na]^+$ 489.1891, found 489.1890.

((1,1-Difluoro-2-phenyl-1-(phenylthio)-3-((1*R*,4*S*)-4-(4-(trimethylsilyl)but-3-yn-1-yl)cyclo pent-2-en-1-yl)propan-2-yl)oxy)trimethylsilane (9b). According to the *general procedure B*, the reaction of **6b** (311 mg, 1 mmol) with **5** (464 mg, 2 mmol) in dry THF (2 mL) in the presence of 10 mol % TBAF (1.0 M in dry THF, 0.2 mL, 0.2 mmol) gave a 50:50 diastereomeric mixture of **9b** (456 mg, 84% yield) as a pale yellow oil after column chromatography (SiO_2, 5−10% EtOAc in hexanes): ^{1}H NMR (400 MHz, $CDCl_3$, isomer **A** marked*) δ 7.65−7.55 (m, 4H of isomers **A** and **B**), 7.51−7.44 (m, 4H of isomers **A** and **B**), 7.42−7.27 (m, 12H of isomers **A** and **B**), 5.66−5.54 (m, 2H of isomer **B**), 5.35 (d, J = 5.6 Hz, 1H*), 4.44 (d, J = 5.6 Hz, 1H*), 2.76−2.55 (m, 4H of isomers **A** and **B**), 2.29−2.02 (m, 8H of isomers **A** and **B**), 1.75−1.66 (m, 2H*), 1.56−1.29 (m, 4H of isomers **A** and **B**), 1.23−1.11 (m, 1H of isomer **B**), 1.07−0.75 (m, 1H of isomer **B**), 0.36 (s, 9H*), 0.34 (s, 9H of isomer **B**), 0.14 (s, 9H*), 0.13 (s, 9H of isomer **B**); ^{19}F NMR (376 MHz, $CDCl_3$, isomer **A** marked*) δ −79.57 (dd, J = 201.5, 186.9 Hz, 2 × F*), −82.89 (dd, J = 202.1, 130.7 Hz, 2 × F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$, isomer **A** marked*) δ 140.5 (C of isomer **B**), 140.2 (C*), 136.2 (2 × CH of isomers **A** and **B**), 135.5 (CH*), 135.0 (CH of isomer **B**), 133.9 (CH*), 133.3 (CH of isomer **B**), 131.7 (dd, J = 290.0, 290.0 Hz, 2 × CF_2 of isomers **A** and **B**), 129.3 (2 × CH of isomers **A** and **B**), 128.7 (6 × CH of isomers **A** and **B**), 127.8 (6 × CH of isomers **A** and **B**), 127.2 (2 × CH of isomers **A** and **B**), 127.1 (2 × CH of isomers **A** and **B**), 126.8 (2 × C of isomers **A** and **B**), 107.5 (C*), 107.4 (C of isomer **B**), 84.4 (C of isomer **B**), 84.3 (C*), 83.7 (t, J = 23.2 Hz, C*), 83.6 (t, J = 23.3 Hz, C of isomer **B**), 44.0 (CH*), 43.1 (CH of isomer **B**), 41.1 (CH_2*), 39.8 (CH_2 of isomer **B**), 39.6 (CH*), 39.2 (CH of isomer **B**), 38.3 (CH_2 of isomer **B**), 37.3 (CH_2*), 34.4 (CH_2 of isomer **B**), 34.3 (CH_2*), 18.3 (CH_2 of isomer **B**), 18.2 (CH_2*), 2.6 (3 × CH_3*), 2.5 (3 × CH_3 of isomer **B**), 0.1 (6 × CH_3 of isomers **A** and **B**); IR (neat) ν_{max} 2174*s*, 1584*m*, 1441*s*, 1251*s*, 1143*s*, 1052*s*, 843*s*, 758*s* cm^{-1}; MS m/z (%) relative intensity 542 (M^+, 0.1), 217 (17), 131 (12), 118 (100), 117 (72), 115 (63), 91 (24), 74 (39); HRMS (ESI-TOF) calcd for $C_{30}H_{40}F_2NaOSSi_2$ $[M + Na]^+$ 565.2204, found 565.2208.

((1,1-Difluoro-2-(4-fluorophenyl)-1-(phenylthio)-3-((1*R*,4*S*)-4-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopent-2-en-1-yl)propan-2-yl)oxy)trimethylsilane (9c). According to the *general procedure B*, the reaction of **6c** (328 mg, 1 mmol) with **5** (464 mg, 2 mmol) in dry THF (2 mL) in the presence of 10 mol % TBAF (1.0 M in dry THF, 0.2 mL, 0.2 mmol) gave a 50:50 diastereomeric mixture of **9c** (488 mg, 87% yield) as a pale yellow oil after column chromatography (SiO_2, 5−10% EtOAc in hexanes): ^{1}H NMR (400 MHz, $CDCl_3$, isomer **A** marked*) δ 7.60−7.51 (m, 4H of isomers **A** and **B**), 7.50−7.43 (m, 4H of isomers **A** and **B**), 7.41−7.27 (m, 6H of isomers **A** and **B**), 7.11−7.02 (m, 4H of isomers **A** and **B**), 5.63 (d, J = 5.6 Hz, 1H of isomer **B**), 5.58 (d, J = 5.7 Hz, 1H of isomer **B**), 5.38 (d, J = 5.7 Hz, 1H*), 4.46 (d, J = 5.7 Hz, 1H*), 2.74−2.54 (m, 4H of isomers **A** and **B**), 2.29−2.04 (m, 8H of isomers **A** and **B**), 1.73−1.64 (m, 2H*), 1.56−1.32 (m, 4H of isomers **A** and **B**), 1.20−1.10 (m, 1H of isomer **B**), 1.08−0.90 (m, 1H of isomer **B**), 0.34 (s, 9H*), 0.33 (s, 9H of isomer **B**), 0.13 (m, 18H of isomers **A** and **B**); ^{19}F NMR (376 MHz, $CDCl_3$, isomer **A** marked*) δ −79.75 (dd, J = 199.5, 199.5 Hz, 2 × F*), −83.20 (dd, J = 202.5, 117.5 Hz, 2 × F of isomer **B**), −114.74 (s, 1F*), −114.87 (s, 1F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$, isomer **A** marked*) δ 162.6 (d, J = 245.3 Hz, C*), 162.5 (d, J = 245.2 Hz, C of isomer **B**), 136.2 (d, J = 3.0 Hz, 4 × CH of isomers **A** and **B**), 135.2 (CH of isomer **B**), 134.8 (CH*), 134.5 (2 × C of isomers **A** and **B**), 134.1 (CH of isomer **B**), 133.5 (CH*), 131.6 (t, J = 283.2, 283.2 Hz, 2 × CF_2 of isomers **A** and **B**), 129.4 (4 × CH of isomers **A** and **B**), 128.9 (2 × CH of isomers **A** and **B**), 128.8 (4 × CH of isomers **A** and **B**), 126.9 (2 × C of isomers **A** and **B**), 114.8 (d, J = 21.1 Hz, 4 × CH of isomers **A** and **B**), 107.4 (C of isomer **B**), 107.3 (C*), 84.4 (2 × C of isomers **A** and **B**), 83.5 (t, J = 23.6 Hz, C*), 83.4 (t, J = 23.3 Hz, C of isomer **B**), 44.0 (CH of isomer **B**), 43.1 (CH*), 41.0 (CH_2*), 39.8 (CH_2 of isomer **B**), 39.6 (CH of isomer **B**), 39.2 (CH*), 38.2 (CH_2*), 37.4 (CH_2 of isomer **B**), 34.4 (CH_2*), 34.3 (CH_2 of isomer **B**), 18.3 (CH_2*), 18.2 (CH_2 of isomer **B**), 2.5 (6 × CH_3 of isomers **A** and **B**), 0.1 (6 × CH_3 of isomers **A** and **B**); IR (neat) ν_{max} 2174*s*, 1584*w*, 1441*s*, 1251*s*, 1144*s*, 1053*s*, 843*s*, 757*s* cm^{-1}; MS m/z (%) relative intensity 561 (M^+, 0.2), 401 (14), 235 (13), 215 (22), 117 (100), 115 (46), 91 (23), 77 (11), 65 (5); HRMS (ESI-TOF) calcd for $C_{30}H_{39}F_3NaOSSi_2$ $[M + Na]^+$ 583.2110, found 583.2119.

1,1-Difluoro-2-phenyl-1-(phenylthio)-3-((1*R*,4*S*)-4-(4-(trimethylsilyl)but-3-yn-1-yl)cyclo pent-2-en-1-yl)propan-2-ol (10a). *General Procedure C.* A solution of $PhSCF_2TMS$ (**5**) (464 mg, 2 mmol) and **6b** (311 mg, 1 mmol) in dry THF (2 mL) was treated with a solution of 10 mol % TBAF (1 M in dry THF, 0.2 mL, 0.2 mmol) at 0 °C to room temperature under an argon atmosphere for 24 h. The reaction mixture was quenched with H_2O (20 mL) for 1 h and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography (SiO_2, 5−10% EtOAc in hexanes) to a 52:48 diastereomeric mixture of **10a** (457 mg, 97% yield) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$, isomer **A** marked*) δ 7.67−7.60 (m, 4H of isomers **A** and **B**), 7.56−7.50 (m, 4H of isomers **A** and **B**), 7.46−7.29 (m, 12H of isomers **A** and **B**), 5.86−5.80 (m, 1H of isomer **B**), 5.69−5.64 (m, 1H of isomer **B**), 5.57−5.53 (m, 1H*), 5.13−5.07 (m, 1H*), 2.80−2.53 (m, 6H of isomers **A** and **B**), 2.45−2.33 (m, 2H of isomers **A** and **B**), 2.23−2.05 (m, 6H of isomers **A** and **B**), 1.81 (ddd, J = 13.3, 7.9, 5.7 Hz, 1H*), 1.73 (ddd, J = 12.9, 8.2, 4.6 Hz, 1H of isomer **B**), 1.57−1.33 (m, 6H of isomers **A** and **B**), 0.16 (s, 18H of isomers **A** and **B**); ^{19}F NMR (376 MHz, $CDCl_3$, **A** marked*) δ − 81.28 (dd, J = 201.5, 36.1 Hz, 2 × F*), −83.98 (dd, J = 202.5, 83.3 Hz, 2 × F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$, isomer **A** marked*) δ 138.3 (C*), 138.0 (C of isomer **B**), 136.5 (4 × CH of isomers **A** and **B**), 135.5 (CH of isomer **B**),135.1 (CH*), 134.1 (CH of isomer **B**), 134.0 (CH*), 131.4 (dd, J = 290.1, 290.1 Hz, 2 × CF_2 of isomers **A** and **B**), 129.6 (2 × CH of isomers **A** and **B**), 128.8 (4 × CH of isomers **A** and **B**), 128.2 (2 × CH of isomers **A** and **B**), 128.1 (4 × CH of isomers **A** and **B**), 126.7 (4 × CH of isomers **A** and **B**), 126.2 (2 × C of isomers **A** and **B**), 107.4 (2 × C of isomers **A** and **B**), 84.4 (C*), 84.3 (C of isomer **B**), 80.6 (t, J = 23.1 Hz, 2 × C of isomers **A** and **B**), 43.9 (CH*), 43.5 (CH of isomer **B**), 41.5 (CH_2 of isomer **B**), 41.2 (CH_2*), 39.6 (CH of isomer **B**), 39.4 (CH*), 37.9 (CH_2*), 37.6 (CH_2 of isomer **B**), 34.3 (2 × CH_2 of isomers **A** and **B**), 18.3 (CH_2*), 18.2 (CH_2 of isomer **B**), 0.1 (6 ×

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CH_3 of isomers **A** and **B**); IR ($CHCl_3$) ν_{max} 3593*br*, 2170*s*, 1604*w*, 1449*s*, 1442*s*, 1251*s*, 1061*s*, 635*m* cm^{-1}; MS *m*/*z* (%) relative intensity 471 (M^+, 3), 311 (92), 245 (68), 218 (50), 180 (62), 117 (93), 91 (62), 73 (100), 65 (10); HRMS (ESI-TOF) calcd for $C_{27}H_{32}F_2NaOSSi$ $[M + Na]^+$ 493.1809, found 493.1803.

1,1-Difluoro-1-(phenylthio)-2-(4-(trifluoromethyl)phenyl)-3-((1*R*,4*S*)-4-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopent-2-en-1-yl)-propan-2-ol (10b). According to the *general procedure C*, the reaction of **6d** (379 mg, 1 mmol) with **5** (464 mg, 2 mmol) in dry THF (2 mL) in the presence of 10 mol % TBAF (1.0 M in dry THF, 0.2 mL, 0.2 mmol) gave a 50:50 diastereomeric mixture of **10b** (485 mg, 90% yield) as a pale yellow oil after column chromatography (SiO_2, 5−10% EtOAc in hexanes): ^1H NMR (400 MHz, $CDCl_3$, isomer **A** marked*) δ 7.73 (d, J = 8.1 Hz, 4H of isomers **A** and **B**), 7.65 (d, J = 8.3 Hz, 4H of isomers **A** and **B**), 7.51−7.45 (m, 4H of isomers **A** and **B**), 7.42−7.36 (m, 2H of isomers **A** and **B**), 7.35−7.29 (m, 4H of isomers **A** and **B**), 5.81−5.74 (m, 1H of isomer **B**), 5.69−5.64 (m, 1H of isomer **B**), 5.60−5.54 (m, 1H*), 5.11−5.05 (m, 1H*), 2.80−2.66 (m, 2H of isomers **A** and **B**), 2.63 (s, 2H of isomers **A** and **B**), 2.61−2.43 (m, 2H of isomers **A** and **B**), 2.42−2.32 (m, 2H of isomers **A** and **B**), 2.24−2.02 (m, 6H of isomers **A** and **B**), 1.79 (ddd, J = 13.3, 7.9, 5.6 Hz, 1H*), 1.71 (ddd, J = 12.9, 8.2, 4.6 Hz, 1H of isomer **B**), 1.54−1.33 (m, 6H of isomers **A** and **B**), 0.13 (s, 9H*), 0.12 (s, 9H of isomer **B**); ^{19}F NMR (376 MHz, $CDCl_3$, isomer **A** marked*) δ −62.55 (s, 2 × F of isomers **A** and **B**), −81.69 (dd, J = 206.2, 30.6 Hz, 2 × F*), −83.99 (dd, J = 205.7, 86.5 Hz, 2 × F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$, isomer **A** marked*) δ 142.4 (C*), 142.1 (C of isomer **B**), 136.6 (4 × CH of isomers **A** and **B**), 134.9 (CH of isomer **B**), 134.7 (CH*), 134.6 (CH of isomer **B**), 134.5 (CH*), 130.9 (t, J = 291.0 Hz, 2 × CF_2 of isomers **A** and **B**), 130.4 (q, J = 30.2 Hz, 2 × C of isomers **A** and **B**), 129.8 (2 × CH of isomers **A** and **B**), 128.9 (4 × CH of isomers **A** and **B**), 127.3 (4 × CH of isomers **A** and **B**), 125.7 (2 × C of isomers **A** and **B**), 125.1 (q, J = 3.8 Hz, 4 × CH of isomers **A** and **B**), 124.1 (q, J = 268.0 Hz, 2 × CF_3 of isomers **A** and **B**), 107.3 (2 × C of isomers **A** and **B**), 84.5 (2 × C of isomers **A** and **B**), 80.7 (t, J = 23.6 Hz, 2 × C of isomers **A** and **B**), 44.0 (CH of isomer **B**), 43.5 (CH*), 41.6 (CH_2 of isomer **B**), 41.2 (CH_2*), 39.5 (CH of isomer **B**), 39.4 (CH*), 37.9 (CH_2 of isomer **B**), 37.8 (CH_2*), 34.3 (CH_2 of isomer **B**), 34.2 (CH_2*), 18.3 (CH_2 of isomer **B**), 18.2 (CH_2*), 0.1 (6 × CH_3 of isomers **A** and **B**); IR (neat) ν_{max} 3499*s*, 2174*s*, 1621*m*, 1413*s*, 1327*s*, 1130*s*, 1070*s*, 843*s*, 750*m* cm^{-1}; MS *m*/*z* (%) relative intensity 539 (M^+, 2), 299 (38), 298 (44), 265 (53), 173 (100), 115 (69), 91 (87), 65 (24); HRMS (ESI-TOF) calcd for $C_{28}H_{31}F_5NaOSSi$ $[M + Na]^+$ 561.1683, found 561.1680.

1,1-Difluoro-2-methyl-1-(phenylthio)-3-((1*R*,4*S*)-4-(4-(trimethylsilyl)but-3-yn-1yl)cyclopent-2-en-1-yl)propan-2-ol (10c). According to the *general procedure B*, the reaction of **6e** (248 mg, 1 mmol) with **5** (464 mg, 2 mmol) in dry THF (2 mL) in the presence of 10 mol % TBAF (1.0 M in dry THF, 0.2 mL, 0.2 mmol) gave a 50:50 diastereomeric mixture of **10c** (302 mg, 74% yield) as a pale yellow oil after column chromatography (SiO_2, 5−10% EtOAc in hexanes): ^1H NMR (400 MHz, $CDCl_3$ isomer **A** marked*) δ 7.57 (d, J = 6.9 Hz, 4H of isomers **A** and **B**), 7.47−7.34 (m, 6H of isomers **A** and **B**), 5.86−5.66 (m, 4H of isomers **A** and **B**), 3.04−2.93 (m, 2H of isomers **A** and **B**), 2.87−2.75 (m, 2H of isomers **A** and **B**), 2.29−2.19 (m, 4H of isomers **A** and **B**), 1.98 (s, 2H of isomers **A** and **B**), 1.89−1.70 (m, 8H of isomers **A** and **B**), 1.67−1.48 (m, 4H of isomers **A** and **B**), 1.45 (s, 6H of isomers **A** and **B**), 0.15 (m, 18H of isomers **A** and **B**); ^{19}F NMR (376 MHz, $CDCl_3$, isomer **A** marked*) δ −85.54 (s, 2 × F*), −85.72 (s, 2 × F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7 (4 × CH of isomers **A** and **B**), 135.5 (CH of isomer **B**), 135.4 (CH*), 134.6 (CH*), 134.2 (CH of isomer **B**), 132.0 (t, J = 286.3 Hz, 2 × CF_2 of isomers **A** and **B**), 129.7 (2 × CH of isomers **A** and **B**), 128.9 (4 × CH of isomers **A** and **B**), 126.0 (2 × C of isomers **A** and **B**), 107.5 (2 × C of isomers **A** and **B**), 84.4 (2 × C of isomers **A** and **B**), 77.3 (t, J = 24.4 Hz, 2 × C of isomers **A** and **B**), 44.1 (CH*), 43.9 (CH of isomer **B**), 42.0 (CH of isomer **B**), 41.5 (CH of isomer **B**), 39.7 (CH_2*), 39.6 (CH_2 of isomer **B**), 38.3 (CH_2*), 37.9 (CH_2 of isomer **B**), 34.5 (CH_2*), 34.4 (CH_2 of isomer **B**), 21.7 (CH_2*), 21.2 (CH_2 of isomer **B**), 18.4 (CH_3*), 18.3 (CH_3 of isomer **B**), 0.1 (6 × CH_3 of isomers **A** and **B**); IR (neat) ν_{max} 3479*br*, 2173*s*, 1475*s*, 1441*s*, 1250*s*, 1044*s*, 843*s*, 750*s* cm^{-1}; MS *m*/*z* (%) relative intensity 409 (M^+, 5), 210 (49), 207 (30), 205 (49), 169 (94), 132 (100), 91 (65), 65 (15); HRMS (ESI-TOF) calcd for $C_{22}H_{30}F_2NaOSSi$ $[M + Na]^+$ 431.1652, found 431.1659.

1,1-Difluoro-1-(phenylthio)-2-(((1*R*,4*S*)-4-(4-(trimethylsilyl)-but-3-yn-1-yl)cyclopent-2-en-1-yl)methyl)butan-2-ol (10d). According to the *general procedure B*, the reaction of **6f** (262 mg, 1 mmol) with **5** (464 mg, 2 mmol) in dry THF (2 mL) in the presence of 10 mol % TBAF (1.0 M in dry THF, 0.2 mL, 0.2 mmol) gave a 50:50 diastereomeric mixture of **10d** (300 mg, 71% yield) as a pale yellow oil after column chromatography (SiO_2, 5−10% EtOAc in hexanes): ^1H NMR (400 MHz, $CDCl_3$, isomer **A** marked*) δ 7.67−7.57 (m, 4H of isomers **A** and **B**), 7.47−7.35 (m, 6H of isomers **A** and **B**), 5.86−5.78 (m, 1H*), 5.76−5.66 (m, 3H of isomers **A** and **B**), 3.01−2.90 (m, 2H of isomers **A** and **B**), 2.87−2.75 (m, 2H of isomers **A** and **B**), 2.29−2.22 (m, 4H of isomers **A** and **B**), 2.00 (s, 2H of isomers **A** and **B**), 1.93−1.70 (m, 12H of isomers **A** and **B**), 1.67−1.45 (m, 4H of isomers **A** and **B**), 1.02 (t, J = 7.5 Hz, 6H of isomers **A** and **B**), 0.15 (s, 18H of isomers **A** and **B**); ^{19}F NMR (376 MHz, $CDCl_3$, isomer **A** marked*) δ −81.62 (s, 2 × F*), −81.70 (s, 2 × F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$, isomer **A** marked*) δ 136.8 (4 × CH of isomers **A** and **B**), 135.6 (CH of isomer **B**), 135.5 (CH*), 134.4 (CH*), 134.2 (CH of isomer **B**), 132.8 (t, J = 269.0 Hz, 2 × CF_2 of isomers **A** and **B**), 129.7 (2 × CH of isomers **A** and **B**), 128.9 (4 × CH of isomers **A** and **B**), 126.1 (2 × C of isomers **A** and **B**), 107.5 (2 × C of isomers **A** and **B**), 84.4 (2 × C of isomers **A** and **B**), 78.9 (t, J = 16.3 Hz, C*), 78.8 (t, J = 21.9 Hz, C of isomer **B**), 44.0 (CH*), 43.8 (CH of isomer **B**), 39.6 (CH*), 39.5 (CH of isomer **B**), 39.4 (CH_2 of isomer **B**), 39.1 (CH_2*), 38.1 (2 × CH_2 of isomers **A** and **B**), 34.4 (2 × CH_2 of isomers **A** and **B**), 28.4 (CH_2*), 28.0 (CH_2 of isomer **B**), 18.3 (2 × CH_2 of isomers **A** and **B**), 8.0 (2 × CH_3 of isomers **A** and **B**), 0.1 (6 × CH_3 of isomers **A** and **B**); IR (neat) ν_{max} 3471*br*, 2174*s*, 1475*m*, 1441*s*, 1250*s*, 1045*s*, 843*s*, 749*s* cm^{-1}; MS *m*/*z* (%) relative intensity 423 (M^+, 3), 221 (25), 205 (48), 150 (45), 144 (58), 132 (100), 118 (85), 91 (73), 65 (7); HRMS (ESI-TOF) calcd for $C_{23}H_{32}F_2ONaSSi$ $[M + Na]^+$ 445.1809, found 445.1804.

3-((1*R*,4*S*)-4-(4-(*tert*-Butyldimethylsilyl)but-3-yn-1-yl)-cyclopent-2-en-1-yl)-1,1-difluoro-2-phenyl-1-(phenylthio)-propan-2-ol (11). To a solution of **7** (199 mg, 0.5 mmol) in THF (5 mL) was added *n*-BuLi (0.3 mL, 0.6 mmol, 1.95 M solution in hexane) at −78 °C. After stirring at −78 °C for 1 h, a solution of TBSCl (106 mg, 0.7 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at −78 °C for 6 h and then gradually warmed to rt for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography (SiO_2, 5% EtOAc in hexanes) to give a 50:50 diastereomeric mixture of **11** (192 mg, 75% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$ isomer **A** marked*) δ 7.64−7.57 (m, 4H of isomers **A** and **B**), 7.54−7.47 (m, 4H of isomers **A** and **B**), 7.44−7.28 (m, 12H of isomers **A** and **B**), 5.81−5.75 (m, 1H*), 5.67−5.61 (m, 1H*), 5.56−5.50 (m, 1H of isomer **B**), 5.11−5.03 (m, 1H of isomer **B**), 2.81−2.67 (m, 2H of isomers **A** and **B**), 2.68−2.49 (m, 4H of isomers **A** and **B**), 2.35 (ddd, J = 14.3, 6.8, 6.8 Hz, 2H of isomers **A** and **B**), 2.21−2.01 (m, 6H of isomers **A** and **B**), 1.84−1.66 (m, 2H of isomers **A** and **B**), 1.55−1.31 (m, 6H of isomers **A** and **B**), 0.91 (s, 18H, of isomers **A** and **B**), 0.06 (s, 12H, of isomers **A** and **B**); ^{19}F NMR (376 MHz, $CDCl_3$, isomer **A** marked*) δ −81.40 (dd, J = 204.7, 31.4 Hz, 2 × F*), −84.14 (dd, J = 204.0, 93.1 Hz, 2 × F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$, isomer **A** marked*) δ 138.4 (C of isomer **B**), 138.0 (C*), 136.6 (4 × CH of isomers **A** and **B**), 135.5 (CH*), 135.1 (CH of isomer **B**), 134.2 (CH*), 134.1 (CH of isomer **B**), 131.4 (t, J = 287.9 Hz, 2 × CF_2 of isomers **A** and **B**), 129.6 (2 × CH of isomers **A** and **B**), 128.9 (4 × CH of isomers **A** and **B**), 128.2 (2 × CH of isomers **A** and **B**), 128.1 (4 × CH of isomers **A** and **B**), 126.8 (4 × CH of isomers **A** and **B**), 126.3 (C*), 126.1 (d, J = 3.2 Hz, C of isomer **B**), 107.9 (2 × C of isomers **A** and **B**), 82.5 (2 × C of isomers **A** and **B**), 80.5 (t, J = 23.5

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Hz, 2 × C of isomers **A** and **B**), 43.9 (CH of isomer **B**), 43.5 (CH*), 41.5 (CH_2*), 41.2 (CH_2 of isomer **B**), 39.6 (CH*), 39.5 (CH of isomer **B**), 38.0 (CH_2 of isomer **B**), 37.7 (CH_2*), 34.4 (2 × CH_2 of isomers **A** and **B**), 26.1 (6 × CH_3 of isomers **A** and **B**), 18.3 (CH_2 of isomer **B**), 18.2 (CH_2*), 16.5 (2 × C of isomers **A** and **B**), −4.5 (4 × CH_3 of isomers **A** and **B**); IR (neat) ν_{max} 3534*br*, 2349*s*, 1497*s*, 1472*s*, 1249*s*, 1049*s*, 836*s*, 774*s*, 704*s* cm^{-1}; MS *m*/*z* (%) relative intensity 513 (M^+, 0.5), 129 (53), 97 (76), 85 (63), 73 (88), 57 (100), 55 (48); HRMS (ESI-TOF) calcd for $C_{30}H_{38}F_2NaOSSi$ $[M + Na]^+$ 535.2278, found 535.2271.

Ethyl 5-((1*S*,4*R*)-4-(3,3-difluoro-2-hydroxy-2-phenyl-3-(phenylthio)propyl)cyclopent-2-en-1-yl)pent-2-ynoate (12). To a solution of 7 (80 mg, 0.2 mmol) in THF (5 mL) was added *n*-BuLi (0.12 mL, 0.24 mmol, 1.95 M solution in hexane) at −78 °C. After stirring at −78 °C for 1 h, a solution of ethyl chloro fomate (28 mg, 0.26 mmol) in THF (1 mL) was added. The mixture was stirred at −78 °C for 5 h and then gradually warmed to rt for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography (SiO_2, 5% EtOAc in hexanes) to give a 50:50 diastereomeric mixture of **12** (72 mg, 76% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$ isomer **A** marked*) 7.63−7.56 (m, 4H of isomers **A** and **B**), 7.54−7.47 (m, 4H of isomers **A** and **B**), 7.45−7.28 (m, 12H of isomers **A** and **B**), 5.85−5.78 (m, 1H*), 5.65−5.56 (m, 1H*), 5.54−5.47 (m, 1H of isomer **B**), 5.14−5.08 (m, 1H of isomer **B**), 4.20 (dd, *J* = 14.3, 7.2 Hz, 2H*), 4.21 (dd, *J* = 14.3, 7.1 Hz, 2H of isomer **B**), 2.81−2.65 (m, 2H of isomers **A** and **B**), 2.66−2.51 (m, 4H of isomers **A** and **B**), 2.41−2.19 (m, 6H of isomers **A** and **B**), 2.15−2.10 (m, 2H of isomers **A** and **B**), 1.76−1.86 (m, 1H*), 1.73−1.64 (m, 1H of isomer **B**), 1.57−1.34 (m, 6H of isomers **A** and **B**), 1.30 (t, *J* = 7.1 Hz, 3H*), 1.29 (t, *J* = 7.2 Hz, 3H of isomer **B**); ^{19}F NMR (376 MHz, $CDCl_3$, isomer **A** marked*) δ −81.39 (dd, *J* = 202.3, 32.3 Hz, 2 × F*), −84.14 (dd, *J* = 204.2, 78.6 Hz, 2 × F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$, isomer **A** marked*) δ 153.8 (2 × CO of isomers **A** and **B**), 138.3 (C*), 138.0 (C of isomer **B**), 136.6 (4 × CH of isomers **A** and **B**), 136.1 (CH*), 135.7 (CH of isomer **B**), 133.5 (CH*), 133.4 (CH of isomer **B**), 131.4 (t, *J* = 290.4 Hz, 2 × CF_2 of isomers **A** and **B**), 129.6 (2 × CH of isomers **A** and **B**), 128.9 (4 × CH of isomers **A** and **B**), 128.2 (6 × CH of isomers **A** and **B**), 126.7 (4 × CH of isomers **A** and **B**), 126.2 (C*), 126.1 (C of isomer **B**), 89.3 (C*), 89.2 (C of isomer **B**), 80.5 (dd, *J* = 22.9, 24.7 Hz, 2 × C of isomers **A** and **B**), 73.2 (2 × C of isomers **A** and **B**), 61.8 (2 × CH_2 of isomers **A** and **B**), 43.8 (CH of isomer **B**), 43.6 (CH*), 41.5 (CH_2*), 41.1 (CH_2 of isomer **B**), 39.7 (CH*), 39.6 (CH of isomer **B**), 37.8 (CH_2*), 37.5 (CH_2 of isomer **B**), 33.1 (2 × CH_2 of isomers **A** and **B**), 17.0 (2 × CH_2 of isomers **A** and **B**), 14.0 (2 × CH_3 of isomers **A** and **B**); IR (neat) ν_{max} 3460*br*, 2235*s*, 1705*s*, 1442*s*, 1250*s*, 1045*br*, 749*s*, 704*s* cm^{-1}; MS *m*/*z* (%) relative intensity 471 (M^+, 1), 470 (0.5), 183 (99), 117 (59), 105 (100), 73 (87); HRMS (ESI-TOF) calcd for $C_{27}H_{28}F_2NaO_3S$ $[M + Na]^+$ 493.1625, found 493.1624.

Mixture of (2*S*,3a*S*,3b*S*,6a*S*,7a*R*)- and (2*R*,3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-4-methylenedecahydro-1*H*-cyclopenta[*a*]-pentalen-2-ol (16aA and 16aB). *General Procedure D.* An argon gas was bubbled through a solution of compound **9a** (467 mg, 1 mmol) in dry toluene (25 mL) for 1 h. The solution was heated to reflux and a solution of Bu_3SnH (0.5 mL, 1.75 mmol) and AIBN (16 mg, 0.1 mmol) in dry toluene (25 mL) was added dropwise at reflux over a 1 h period. After the completion of the reaction (24 h), the reaction mixture was concentrated and the tin byproduct were removed by column chromatography [SiO_2, hexanes (500 mL)] and then 5% EtOAc in hexanes to give a 40:38:12:10 diastereomeric mixture of **13a** (301 mg, 84% yield) as a colorless oil which was treated with CF_3CO_2H (0.2 mL, 2.5 mmol) at 0 °C in CH_2Cl_2 (10 mL) for 1 h. The reaction mixture was cautiously neutralized by adding a saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed successively with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 10% EtOAc in hexanes) to afford an inseparable 49:51 diastereomeric mixture of **16aA** and **16aB** (147 mg, 82% yield) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$, isomer **A** marked*) δ 4.97−4.92 (m, 2H of isomers **A** and **B**), 4.89 (d, *J* = 2.1 Hz, 1H*), 4.88 (d, *J* = 2.0 Hz, 1H of isomer **B**), 4.17−4.04 (m, 2H of isomers **A** and **B**), 3.18−3.11 (m, 1H*), 3.01−2.95 (m, 1H of isomer **B**), 2.93−2.82 (m, 1H of isomer **B**), 2.79−2.51 (m, 7H of isomers **A** and **B**), 2.49−2.32 (m, 4H of isomers **A** and **B**), 2.30−2.18 (m, 1H*), 1.95−1.73 (m, 3H of isomers **A** and **B**), 1.72−1.31 (m, 8H of isomers **A** and **B**); ^{19}F NMR (376 MHz, $CDCl_3$, isomer **A** marked*) δ −107.58 (ddd, *J* = 231.2, 10.2, 10.2 Hz, 1F*), −113.73 (dd, *J* = 230.1, 8.3 Hz, 1F*), −116.36 (ddd, *J* = 230.1, 17.5, 6.4 Hz, 1F of isomer **B**), −122.27 (ddd, *J* = 228.2, 13.0, 13.0 Hz, 1F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$, isomer **A** marked*) δ 156.3 (C of isomer **B**), 156.1 (C*), 129.3 (t, *J* = 253.5 Hz, CF_2*), 127.9 (t, *J* = 253.1 Hz, CF_2 of isomer **B**), 106.6 (CH_2 of isomer **B**), 106.4 (CH_2*), 75.1 (dd, *J* = 28.0, 22.6 Hz, CH*), 74.8 (dd, *J* = 31.3, 22.0 Hz, CH of isomer **B**), 54.7 (dd, *J* = 21.8, 19.3 Hz, CH*), 54.6 (dd, *J* = 22.2, 18.8 Hz, CH of isomer **B**), 48.8 (dd, *J* = 5.7, 3.1 Hz, CH of isomer **B**), 48.7 (d, *J* = 6.1 Hz, CH*), 46.0 (CH of isomer **B**), 45.5 (CH*), 38.8 (d, *J* = 5.3 Hz, CH of isomer **B**), 38.2 (CH_2 of isomer **B**), 38.1 (CH_2*), 37.5 (d, *J* = 6.0 Hz, CH*), 36.3 (d, *J* = 5.1 Hz, CH_2*), 35.9 (CH_2 isomer **B**), 32.3 (CH_2*), 32.2 (CH_2 of isomer **B**), 29.1 (2 × CH_2 of isomers **A** and **B**); IR (neat) ν_{max} 3597*s*, 3410*br*, 1652*m*, 1457*s*, 1356*s*, 1096*s*, 1038*s*, 889*s*, cm^{-1}; MS *m*/*z* (%) relative intensity 214 (M^+, 6), 167 (22), 149 (100), 121 (18), 115 (17), 91 (30), 79 (15); HRMS (ESI-TOF) calcd for $C_{12}H_{16}F_2ONa$ $[M + Na]^+$ 237.1067, found 237.1063.

Mixture of (2*R*,3a*S*,3b*S*,6a*S*,7a*R*)- and (2*S*,3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-4-methylene-2-phenyldecahydro-1*H*-cyclopenta-[*a*]pentalen-2-ol (16bA and 16bB). According to the *general procedure D*, the reaction of **9b** (217 mg, 0.4 mmol) in dry toluene (10 mL) with a solution of Bu_3SnH (0.2 mL, 0.7 mmol), AIBN (7 mg, 0.04 mmol) in dry toluene (10 mL) at reflux followed by the removal of tin byproduct and column chromatography (SiO_2, 2% EtOAc in hexane) gave a 40:38:12:10 diastereomeric mixture of **13b** (141 mg, 81% yield) as a colorless oil which was treated with CF_3CO_2H (0.08 mL, 1.0 mmol) at 0 °C in CH_2Cl_2 for 2 h to afford compound **16bA** (38 mg, 40% yield) and **16bB** (38 mg, 40% yield) as a colorless oil after preparative thin-layer chromatography (SiO_2, 10% diethyl ether in hexanes ×3). **16bA**: $[\alpha]^{26}_D$ −26.5 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 2H), 7.42−7.30 (m, 3H), 4.91 (s, 1H), 4.87 (s, 1H), 3.36−3.25 (m, 1H), 2.97−2.85 (m, 1H), 2.84−2.76 (m, 1H), 2.72−2.57 (m, 2H), 2.51−2.28 (m, 3H), 1.96−1.76 (m, 4H), 1.39 (ddt, *J* = 15.6, 12.6, 7.8 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.01 (dd, *J* = 231.1, 19.0 Hz, 1F), −119.06 (dd, *J* = 229.4, 8.6 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0 (C), 139.5 (C), 128.9 (dd, *J* = 258.5, 258.5 Hz, CF_2), 128.2 (4 × CH), 126.7 (CH), 106.5 (CH_2), 82.6 (dd, *J* = 26.0, 21.7 Hz, C), 56.9 (dd, *J* = 22.5, 19.9 Hz, CH), 50.3 (t, *J* = 4.0 Hz, CH), 47.0 (CH), 42.1 (CH_2), 39.4 (CH_2), 38.0 (t, *J* = 3.3 Hz, CH), 33.0 (CH_2), 30.0 (CH_2); IR ($CHCl_3$) ν_{max} 3591*s*, 3408*br*, 1653*m*, 1498*s*, 1449*s*, 1188*s*, 1047*s*, 890*s* cm^{-1}; MS *m*/*z* (%) relative intensity 290 (M^+, 1), 272 ($M^+ - H_2O$, 100), 253 (23), 162 (46), 120 (24), 106 (22), 91 (20), 77 (29); HRMS (ESI-TOF) calcd for $C_{18}H_{20}F_2ONa$ $[M + Na]^+$ 313.1380, found 313.1382. **16bB**: $[\alpha]^{26}_D$ −34.5 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 2H), 7.43−7.31 (m, 3H), 5.00 (d, *J* = 1.7 Hz, 1H), 4.93 (d, *J* = 2.0 Hz, 1H), 3.22−3.00 (m, 3H), 2.78−2.66 (m, 1H), 2.54−2.38 (m, 3H), 2.34 (ddd, *J* = 13.5, 8.9, 4.4 Hz, 1H), 2.03 (ddd, *J* = 13.5, 8.7, 4.4 Hz, 1H), 1.84 (ddd, *J* = 14.9, 13.6, 6.4 Hz, 1H), 1.69−1.45 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.59 (dd, *J* = 231.4, 21.2 Hz, 1F), −119.71 (dd, *J* = 232.0, 12.0 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0 (C), 138.8 (C), 128.9 (dd, *J* = 263.6, 255.0 Hz, CF_2), 128.3 (2 × CH), 128.2 (2 × CH), 126.5 (CH), 106.4 (CH_2), 83.3 (dd, *J* = 29.7, 21.2 Hz, C), 55.4 (dd, *J* = 19.5, 6.8 Hz, CH), 47.6 (d, *J* = 8.8 Hz, CH), 46.2 (CH), 41.5 (d, *J* = 2.9 Hz, CH_2), 38.6 (d, *J* = 9.3 Hz, CH), 37.1 (CH_2), 32.0 (CH_2), 28.8 (CH_2); IR (neat) ν_{max} 3592*s*, 3390*br*, 1652*m*, 1450*s*, 1352*s*, 1188*s*, 1054*s*, 1038*s*, 900*m* cm^{-1}; MS *m*/*z* (%) relative intensity 290 (M^+, 4), 273 (49), 272 ($M^+ - H_2O$, 69), 253 (100), 162

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(51), 119 (39), 91 (28), 77 (33), 65 (8); HRMS (ESI-TOF) calcd for $C_{18}H_{20}F_2ONa$ $[M + Na]^+$ 313.1380, found 313.1381.

According to the *general procedure D*, the reaction of **10a** (188 mg, 0.4 mmol) in dry toluene (10 mL) with a solution of Bu_3SnH (0.2 mL, 0.7 mmol), AIBN (7 mg, 0.04 mmol) in dry toluene (10 mL) at reflux followed by the removal of tin byproduct and column chromatography (SiO_2, 5% EtOAc in hexane) gave a 42:41:9:8 diastereomeric mixture of **14a** (128 mg, 88% yield) as a colorless oil which was treated with CF_3CO_2H (0.04 mL, 0.5 mmol) at 0 °C in CH_2Cl_2 for 1 h to afford compound **16bA** (39 mg, 38% yield) and **16bB** (40 mg, 39% yield) as a colorless oil after preparative thin-layer chromatography (SiO_2, 10% diethyl ether in hexanes ×3).

According to the *general procedure D*, the reaction of **11** (154 mg, 0.3 mmol) in dry toluene (8 mL) with a solution of Bu_3SnH (0.1 mL, 0.5 mmol), AIBN (5 mg, 0.03 mmol) in dry toluene (7 mL) at reflux followed by the removal of tin byproduct and column chromatography (SiO_2, 5% EtOAc in hexane) gave a 33:33:18:16 diastereomeric mixture of **15** (92 mg, 76% yield) as a colorless oil which was treated with py·$(HF)_x$ (20 μL) at 0 °C in CH_2Cl_2 (5 mL) for 3 h to afford compound **16bA** (30 mg, 45% yield) and **16bB** (31 mg, 46% yield) as a colorless oil after preparative thin-layer chromatography (SiO_2, 10% diethyl ether in hexanes ×3).

Mixture of (2*R*,3a*S*,3b*S*,6a*S*,7a*R*)- and (2*S*,3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-2-(4-fluorophenyl)-4-methylenedecahydro-1*H*-cyclopenta[*a*]pentalen-2-ol (16cA and 16cB). According to the *general procedure D*, the reaction of **9c** (224 mg, 0.4 mmol) in dry toluene (10 mL) with a solution of Bu_3SnH (0.2 mL, 0.7 mmol), AIBN (7 mg, 0.04 mmol) in dry toluene (10 mL) at reflux followed by the removal of tin byproduct and column chromatography (SiO_2, 5% EtOAc in hexane) gave a 41:38:11:10 diastereomeric mixture of **13c** (161 mg, 89% yield) as a colorless oil which was treated with CF_3CO_2H (0.08 mL, 1.1 mmol) at 0 °C in CH_2Cl_2 for 2 h to afford compound **16cA** (49 mg, 45% yield) as a white solid and **16cB** (48 mg, 44% yield) as a colorless oil after preparative thin-layer chromatography (SiO_2, 15% diethyl ether in hexanes ×3). **16cA**: mp 88−90 °C; $[\alpha]^{27}_D$ −24.4 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.57−7.44 (m, 2H), 7.11−7.02 (m, 2H), 4.91 (s, 1H), 4.86 (s, 1H), 3.32−3.23 (m, 1H), 2.95−2.83 (m, 1H), 2.82−2.75 (m, 1H), 2.68−2.55 (m, 2H), 2.49−2.29 (m, 2H), 1.92−1.74 (m, 5H), 1.45−1.32 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.40 (dd, *J* = 230.5, 19.2 Hz, 1F), −114.16 (s, 1F), −119.24 (dd, *J* = 231.2, 9.0 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, *J* = 245.7 Hz, CF), 156.9 (C), 135.3 (d, *J* = 4.1 Hz, C), 128.8 (dd, *J* = 263.6, 253.2 Hz, CF_2), 128.6 (d, *J* = 8.0 Hz, 2 × CH), 115.1 (d, *J* = 21.1 Hz, 2 × CH), 106.5 (CH_2), 82.1 (dd, *J* = 23.7, 23.7 Hz, C), 56.8 (dd, *J* = 22.4, 20.0 Hz, CH), 50.2 (t, *J* = 4.0 Hz, CH), 47.0 (CH), 42.3 (CH_2), 39.4 (CH_2), 37.9 (t, *J* = 3.4 Hz, CH), 33.0 (CH_2), 30.0 (CH_2); IR ($CHCl_3$) ν_{max} 3589*s*, 1606*m*, 1513*s*, 1352*m*, 1164*s*, 1093*m*, 891*m*, 840*s* cm^{-1}; MS *m*/*z* (%) relative intensity 309 (M^+ + 1, 0.3), 290 ($M^+ - H_2O$, 100), 270 (46), 255 (27), 179 (94), 91 (32), 77 (12), 65 (6); HRMS (ESI-TOF) calcd for $C_{18}H_{19}F_3NaO$ $[M + Na]^+$ 331.1286, found 331.1287. **16cB**: $[\alpha]^{24}_D$ −33.9 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.03 (t, *J* = 8.6 Hz, 2H), 4.50 (d, *J* = 1.8 Hz, 1H), 4.49 (d, *J* = 3.0 Hz, 1H), 3.16−2.89 (m, 4H), 2.72−2.61 (m, 1H), 2.54−2.35 (m, 2H), 2.30 (ddd, *J* = 13.0, 8.6, 4.1 Hz, 1H), 2.04 (ddd, *J* = 13.8, 9.0, 5.1 Hz, 1H), 1.81 (ddd, *J* = 14.0, 14.0, 7.4 Hz, 1H), 1.65−1.44 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.29 (dd, *J* = 226.0, 24.1 Hz, 1F), −114.23 (s, 1F), −121.28 (dd, *J* = 225.4, 10.3 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, *J* = 245.3 Hz, CF), 156.1 (C), 135.2 (C), 129.4 (d, *J* = 7.9 Hz, 2 × CH), 128.4 (dd, *J* = 269.3, 250.4 Hz, CF_2), 114.8 (d, *J* = 21.1 Hz, 2 × CH), 106.5 (CH_2), 84.7 (dd, *J* = 33.2, 18.8 Hz, C), 55.0 (dd, *J* = 22.0, 19.5 Hz, CH), 47.7 (d, *J* = 8.6 Hz, CH), 46.1 (CH), 40.6 (CH_2), 38.5 (d, *J* = 9.1 Hz, CH), 36.7 (CH_2), 31.8 (CH_2), 28.5 (CH_2). IR ($CHCl_3$) ν_{max} 3589*s*, 3382*br*, 1622*s*, 1412*s*, 1328*s*, 1170*s*, 1131*s*, 1070*s*, 846*s* cm^{-1}; MS *m*/*z* (%) relative intensity 308 (M^+, 1), 291 (21), 290 ($M^+ - H_2O$), 289 (41), 270 (44), 255 (36), 179 (97), 123 (41), 91 (39), 77 (14); HRMS (ESI-TOF) calcd for $C_{18}H_{19}F_3NaO$ $[M + Na]^+$ 331.1286, found 331.1288.

Mixture of (2*R*,3a*S*,3b*S*,6a*S*,7a*R*)- and (2*S*,3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-4-methylene-2-(4-(trifluoromethyl)phenyl)decahydro-1*H*-cyclopenta[*a*]pentalen-2-ol (16dA and 16dB). According to the *general procedure D*, the reaction of **10b** (162 mg, 0.3 mmol) in dry toluene (8 mL) with a solution of Bu_3SnH (0.14 mL, 0.53 mmol), AIBN (5 mg, 0.03 mmol) in dry toluene (7 mL) at reflux followed by the removal of tin byproduct and column chromatography (SiO_2, 10% EtOAc in hexane) gave a 42:41:9:8 diastereomeric mixture of **14b** (102 mg, 79% yield) as a colorless oil which was treated with CF_3CO_2H (0.03 mL, 0.4 mmol) at 0 °C in CH_2Cl_2 for 1 h to afford compound **16dA** (36 mg, 42% yield) and **16dB** (36 mg, 42% yield) as a colorless oil after preparative thin-layer chromatography (SiO_2, 5% diethyl ether in hexanes ×4). **16dA**: $[\alpha]^{24}_D$ −21.5 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 4.92 (d, *J* = 1.3 Hz, 1H), 4.87 (d, *J* = 1.3 Hz, 1H), 3.32−3.23 (m, 1H), 2.99−2.87 (m, 1H), 2.86−2.76 (m, 1H), 2.71−2.58 (m, 2H), 2.50−2.41 (m, 2H), 2.40−2.30 (m, 1H), 1.97−1.76 (m, 4H), 1.39 (ddt, *J* = 12.6, 7.8, 7.8 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.69 (s, 3 × F), −103.63 (dd, *J* = 231.1, 19.7 Hz, 1F), −119.04 (dd, *J* = 232.6, 7.3 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (C), 143.4 (C), 130.3 (q, *J* = 32.2 Hz, C), 128.8 (dd, *J* = 260.3, 257.0 Hz, CF_2), 127.2 (2 × CH), 125.2 (q, *J* = 3.5 Hz, 2 × CH), 124.0 (q, *J* = 270.5 Hz, CF_3), 106.7 (CH_2), 82.5 (dd, *J* = 26.1, 21.8 Hz, C), 57.0 (dd, *J* = 22.4, 19.8 Hz, CH), 50.3 (t, *J* = 4.0 Hz, CH), 47.0 (CH), 42.4 (CH_2), 39.4 (CH_2), 38.1 (t, *J* = 3.5 Hz, CH), 33.0 (CH_2), 30.0 (CH_2); IR ($CHCl_3$) ν_{max} 3589*s*, 3378*br*, 1622*m*, 1328*s*, 1171*s*, 1070*s*, 845*m* cm^{-1}; MS *m*/*z* (%) relative intensity 358 (M^+, 0.1), 340 ($M^+ - H_2O$, 100), 229 (75), 173 (59), 145 (71), 115 (37), 91 (69), 77 (38), 51 (24); HRMS (ESI-TOF) calcd for $C_{19}H_{19}F_5NaO$ $[M + Na]^+$ 381.1254, found 381.1253. **16dB**: $[\alpha]^{27}_D$ −29.3 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 5.00 (d, *J* = 1.6 Hz, 1H), 4.92 (d, *J* = 1.9 Hz, 1H), 3.24−3.01 (m, 3H), 2.79−2.67 (m, 1H), 2.54−2.39 (m, 3H), 2.34 (ddd, *J* = 13.5, 8.8, 4.3 Hz, 1H), 2.08−1.97 (m, 1H), 1.84 (ddd, *J* = 17.0, 11.5, 7.2 Hz, 1H), 1.75−1.45 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.7 (s, 1F), −109.73 (dd, *J* = 232.7, 22.2 Hz, 1F), −120.05 (dd, *J* = 232.6, 10.0 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (C), 140.5 (C), 130.4 (q, *J* = 32.4 Hz, C), 128.8 (dd, *J* = 263.6, 255.6 Hz, CF_2), 127.1 (2 × CH), 125.2 (q, *J* = 3.6 Hz, 2 × CH), 124.0 (q, *J* = 268.9 Hz, CF_3), 106.5 (CH_2), 83.5 (dd, *J* = 38.8, 25.3 Hz, C), 55.5 (dd, *J* = 21.4, 19.6 Hz, CH), 47.6 (d, *J* = 8.8 Hz, CH), 46.2 (CH), 41.8 (d, *J* = 2.6 Hz, CH_2), 38.7 (d, *J* = 9.1 Hz, CH), 37.1 (CH_2), 32.0 (CH_2), 28.8 (CH_2); IR ($CHCl_3$) ν_{max} 3589*s*, 3378*br*, 1622*m*, 1328*s*, 1171*s*, 1070*s*, 845*m* cm^{-1}; MS *m*/*z* (%) relative intensity 358 (M^+, 0.4), 340 ($M^+ - H_2O$, 100), 320 (25), 305 (17), 229 (67), 173 (50), 145 (55), 91 (54), 77 (26), 65 (13); HRMS (ESI-TOF) calcd for $C_{19}H_{19}F_5NaO$ $[M + Na]^+$ 381.1254, found 381.1256.

Mixture of (2*R*,3a*S*,3b*S*,6a*S*,7a*R*)- (2*S*,3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-2-methyl-4-methylenedecahydro-1*H*-cyclopenta[*a*]-pentalen-2-ol (16eA and 16eB). According to the *general procedure D*, the reaction of **10c** (163 mg, 0.4 mmol) in dry toluene (10 mL) with a solution of Bu_3SnH (0.2 mL, 0.7 mmol), AIBN (7 mg, 0.04 mmol) in dry toluene (10 mL) at reflux followed by the removal of tin byproduct and column chromatography (SiO_2, 1% EtOAc in hexane) gave a 37:15:37:11 diastereomeric mixture of **14c** (100 mg, 83% yield) as a colorless oil which was treated with CF_3CO_2H (0.04 mL, 0.5 mmol) at 0 °C in CH_2Cl_2 for 2 h to give an inseparable 50:50 diastereomeric mixture of **16eA** and **16eB** (68 mg, 90% yield) as a colorless oil after chromatography (SiO_2, 10% CH_2Cl_2 in hexanes): ^1H NMR (400 MHz, $CDCl_3$ isomer **A** marked*) δ 4.96−4.85 (m, 2H of isomers **A** and **B**), 4.84−4.78 (m, 2H of isomers **A** and **B**), 3.16−3.11 (m, 1H*), 3.04−3.01 (m, 1H of isomer **B**), 2.95−2.57 (m, 6H of isomers **A** and **B**), 2.51−2.20 (m, 4H of isomers **A** and **B**), 2.06−1.90 (m, 2H of isomers **A** and **B**), 1.80−1.66 (m, 4H of isomers **A** and **B**), 1.65−1.33 (m, 8H of isomers **A** and **B**), 1.30 (s, 3H*), 1.28 (s, 3H of isomer **B**); ^{19}F NMR (376 MHz, $CDCl_3$, isomer **A** marked*) δ −114.52 (dd, *J* = 225.8, 13.0 Hz, 1F*), −116.97 (dd, *J* = 225.0, 15.8 Hz, 1F of isomer **B**), −120.47 (d, *J* = 223.3 Hz, 1F*), −121.95 (dd, *J* = 225.6, 15.0 Hz, 1F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$, isomer **A** marked*) δ 156.3 (2 × C of isomers A and B), 128.6 (dd, *J* = 280.1, 278.1 Hz, 2 × CF_2 of isomers **A** and **B**), 106.2 (2 × CH_2 of isomers A and B), 81.7 (dd, *J* = 26.3, 26.3 Hz, 2 × C of isomers **A** and **B**), 54.8 (t,

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J = 21.2 Hz, 2 × CH of isomers **A** and **B**), 47.5 (d, J = 8.7 Hz, CH*), 47.0 (CH of isomer **B**), 46.3 (2 × CH of isomers **A** and **B**), 42.8 (CH_2 of isomer **B**), 41.9 (d, J = 3.0 Hz, CH_2*), 39.2 (2 × CH of isomers **A** and **B**), 37.4 (2 × CH_2 of isomers **A** and **B**), 32.2 (2 × CH_2 of isomers **A** and **B**), 29.7 (CH_2 of isomer **B**), 29.0 (CH_2*), 19.6 (2 × CH_3 of isomers **A** and **B**); IR ($CHCl_3$) ν_{max} 3439*br*, 1670*m*, 1448*m*, 1247*s*, 1021*s*, 824*s* cm^{-1}; MS m/z (%) relative intensity 228 (M^+ + 1, 3), 210 ($M^+ - H_2O$, 4), 167 (12), 131 (100), 121 (10), 73 (87); HRMS (ESI-TOF) calcd for $C_{13}H_{18}F_2NaO$ $[M + Na]^+$ 251.1223, found 251.1245.

Mixture of (2*R*,3a*S*,3b*S*,6a*S*,7a*R*)- and (2*S*,3a*S*,3b*S*,6a*S*,7a*R*)-2-Ethyl-3,3-difluoro-4-methylenedecahydro-1*H*-cyclopenta[*a*]-pentalen-2-ol (16fA and 16fB). According to the *general procedure D*, the reaction of **10d** (169 mg, 0.4 mmol) in dry toluene (10 mL) with a solution of Bu_3SnH (0.2 mL, 0.7 mmol), AIBN (7 mg, 0.04 mmol) in dry toluene (10 mL) at reflux followed by the removal of tin byproduct and column chromatography (SiO_2, 1% EtOAc in hexane) gave a 35:16:34:15 diastereomeric mixture of **14d** (114 mg, 91% yield) as a colorless oil which was treated with CF_3CO_2H (0.04 mL, 0.5 mmol) at 0 °C in CH_2Cl_2 for 2 h to give an inseparable 50:50 diastereomeric mixture of **16fA** and **16fB** (72 mg, 82% yield) as a colorless oil after column chromatography (SiO_2, 10% EtOAc in hexanes): ^{1}H NMR (400 MHz, $CDCl_3$ isomer **A** marked*) δ 4.97–4.92 (m, 2H of isomers **A** and **B**), 4.90–4.85 (m, 2H of isomers **A** and **B**), 3.21–3.11 (m, 1H*), 3.09–3.03 (m, 1H of isomer **B**), 3.02–2.81 (m, 2H*), 2.76–2.57 (m, 4H of isomers **A** and **B**), 2.50–2.30 (m, 4H of isomers **A** and **B**), 2.10–2.06 (m, 2H of isomers **A** and **B**), 1.85–1.52 (m, 14H of isomers **A** and **B**), 1.48–1.37 (m, 2H of isomers **A** and **B**), 0.99 (t, J = 7.4 Hz, 3H*), 0.98 (t, J = 7.5 Hz, 3H of isomer **B**); ^{19}F NMR (376 MHz, $CDCl_3$, isomer **A** marked*) δ −110.93 (dd, J = 228.6, 15.4 Hz, 1F*), −114.54 (dd, J = 231.8, 25.0 Hz, 1F of isomer **B**), −119.23 (d, J = 232.0 Hz, 1F*), −121.98 (d, J = 227.9 Hz, 1F of isomer **B**); ^{13}C NMR (100 MHz, $CDCl_3$, isomer **A** marked*) δ 156.8 (C of isomer **B**), 156.4 (C*), 129.8 (dd, J = 236.6, 236.6 Hz, CF_2 of isomers **B**), 129.7 (dd, J = 235.5, 235.5 Hz, CF_2*), 106.3 (CH_2 of isomer **B**), 106.2 (CH_2*), 83.0 (dd, J = 28.1, 21.0 Hz, 2 × C of isomers **A** and **B**), 56.2 (dd, J = 23.3, 19.4 Hz, CH of isomer **B**), 55.5 (dd, J = 21.7, 19.9 Hz, CH*), 47.4 (d, J = 8.7 Hz, 2 × CH of isomers **A** and **B**), 46.3 (CH*), 46.1 (CH of isomer **B**), 40.2 (d, J = 3.4 Hz, CH_2*), 39.8 (CH_2 of isomer **B**), 38.6 (d, J = 9.6 Hz, CH*), 38.3 (s, CH of isomer **B**), 37.6 (2 × CH_2 of isomers **A** and **B**), 32.4 (CH_2*), 32.3 (CH_2 of isomer **B**), 29.1 (2 × CH_2 of isomers **A** and **B**), 26.5 (d, J = 3.6 Hz, CH_2 of isomer **B**), 26.0 (CH_2*), 7.4 (CH_3*), 7.2 (CH_3 of isomer **B**); IR ($CHCl_3$) ν_{max} 3593*br*, 1651*m*, 1463*s*, 1442*m*, 1262*s*, 1098*s*, 1036*m*, 1012*s*, 844*s* cm^{-1}; MS m/z (%) relative intensity 242 (M^+, 3), 224 ($M^+ - H_2O$, 100), 195 (22), 168 (13), 120 (34), 91 (43); HRMS (ESI-TOF) calcd for $C_{14}H_{20}F_2NaO$ $[M + Na]^+$ 265.1380, found 265.1381.

(3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-4-methyleneoctahydro-1*H*-cyclopenta[*a*]pentalen-2(3b*H*)-one (17). A 50:50 mixture of **16a** (214 mg, 1 mmol) and pyridinium dichromate (PDC) (451 mg, 1.2 mmol) in dry CH_2Cl_2 (10 mL) was stirred at reflux under an argon atmosphere. After stirring for 24 h, the reaction mixture was allowed to cool to room temperature, filtered and washed with CH_2Cl_2 (3 × 20 mL). The combined filtrates were washed successively with water (20 mL), brine (20 mL), and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography (SiO_2, 20% CH_2Cl_2 in hexanes) to give a colorless oil of **17** (191 mg, 90% yield): $[\alpha]^{26}_D$ −18.3 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (d, J = 1.8 Hz, 1H), 4.90 (d, J = 1.7 Hz, 1H), 3.11–3.03 (m, 1H), 2.92–2.81 (m, 1H), 2.80–2.71 (m, 1H), 2.70–2.59 (m, 2H), 2.46–2.26 (m, 2H), 2.21–2.12 (m, 1H), 1.86 (ddt, J = 12.6, 7.5, 7.5 Hz, 1H), 1.79–1.66 (m, 2H), 1.46–1.35 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.45 (dd, J = 273.5, 17.1 Hz, 1F), −116.86 (dd, J = 274.1, 8.6 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0 (t, J = 270.0 Hz, CO), 155.3 (C), 118.1 (dd, J = 260.2 Hz, 253.6 Hz, CF_2), 106.7 (CH_2), 54.8 (dd, J = 20.5, 17.6 Hz, CH), 47.2 (t, J = 3.6 Hz, CH), 44.4 (CH), 38.7 (CH_2), 38.2 (CH_2), 35.6 (t, J = 3.5 Hz, CH), 33.6 (CH_2), 31.0 (CH_2); IR (neat) ν_{max} 1777*s*, 1657*m*, 1402*m*, 1221*m*, 1046*s*, 889*m* cm^{-1}; MS m/z (%) relative intensity 212 (M^+, 16), 211 (30), 173 (30), 165 (38), 131 (61), 117 (50), 91 (100), 77 (56); HRMS (ESI-TOF) calcd for $C_{12}H_{14}F_2ONa$ $[M + Na]^+$ 235.0910, found 235.0908.

(2*S*,3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-4-methylenedecahydro-1*H*-cyclopenta[*a*]pentalen-2-ol (16aA). To a solution of **17** (42 mg, 0.2 mmol) in THF (5 mL) at −78 °C was added dropwise diisobutylaluminum hydride DIBAL (1 M in hexane, 1 mL, 1 mmol). After 1 h, the excess DIBAL was quenched by the addition of EtOAc (2 mL) at −78 °C. The reaction mixture was then poured into a solution of tartaric acid (0.5 M aqueous solution, 5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation gave a crude product, which was purified by column chromatography (SiO_2, 15% CH_2Cl_2 in hexanes) to give **16aA** as a colorless oil (37 mg, 87% yield): $[\alpha]^{28}_D$ −22.5 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (d, J = 2.0 Hz, 1H), 4.89 (d, J = 2.1 Hz, 1H), 4.16–4.03 (m, 1H), 3.19–3.11 (m, 1H), 2.75–2.52 (m, 3H), 2.46–2.32 (m, 2H), 2.31–2.21 (m, 1H), 2.01–1.94 (m, 1H), 1.85–1.74 (m, 1H), 1.64–1.54 (m, 2H), 1.47–1.31 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.59 (ddd, J = 229.1, 10.1, 10.1 Hz, 1F), −122.29 (ddd, J = 227.7, 13.0, 12.6 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (C), 127.9 (dd, J = 252.9, 252.9 Hz, CF_2), 106.4 (CH_2), 75.1 (dd, J = 27.7, 22.6 Hz, CH), 54.7 (dd, J = 22.0, 19.2 Hz, CH), 48.7 (d, J = 5.6 Hz, CH), 45.5 (CH), 38.1 (CH_2), 37.5 (d, J = 6.0 Hz, CH), 36.3 (d, J = 5.1 Hz, CH_2), 32.3 (CH_2), 29.1 (CH_2); IR (neat) ν_{max} 3597*s*, 3410*br*, 1652*m*, 1456*m*, 1356*m*, 1096*m*, 1038*s*, 889*m*; MS m/z (%) relative intensity 214 (M^+, 5), 199 (21), 129 (51), 128 (48), 117 (50), 115 (39), 105 (34), 91 (100), 79 (33); HRMS (ESI-TOF) calcd for $C_{12}H_{16}F_2ONa$ $[M + Na]^+$ 237.1067, found 237.1068.

The reaction employing sodium borohydide was carried out as follows: sodium borohydide (38 mg, 1 mmol) was added over a period of 10 min to a stirred solution of **17** (42 mg, 0.2 mmol) in methanol (10 mL) at 0 °C. The reaction mixture was allowed to stir for 1 h followed by addition of H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 15% CH_2Cl_2 in hexanes) to give **16aA** (32 mg, 74% yield).

(2*R*,3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-4-methylene-2-phenyldecahydro-1*H*-cyclopenta[*a*]pentalen-2-ol (16bA). According to the *general procedure A*, the solution of **17** (42 mg, 0.2 mmol) in dry THF (5 mL) was treated with phenyl magnesium bromide (0.5 M in THF, 2 mL, 1 mmol) at 0 °C for 1 h to give **16bA** (48 mg, 83% yield) as a colorless oil after column chromatography (SiO_2, 10% EtOAc in hexanes). The spectral data and its optical rotation were identical to those of **16bA** obtained from the radical cyclization of **9b** or **10a** (Table 2).

(2*R*,3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-2-(4-fluorophenyl)-4-methylenedecahydro-1*H*-cyclopenta[*a*]pentalen-2-ol (16cA). According to the *general procedure A*, the solution of **17** (42 mg, 0.2 mmol) in dry THF (5 mL) was treated with 4-FC_6H_4MgBr (0.5 M in THF, 2 mL, 1 mmol) at 0 °C for 1 h to give **16cA** (55 mg, 89% yield) as a colorless oil after column chromatography (SiO_2, 5% EtOAc in hexanes). The spectral data and its optical rotation were identical to those of **16cA** obtained from the radical cyclization of **9c** (Table 2).

(2*R*,3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-4-methylene-2-(4-(trifluoromethyl)phenyl)decahydro-1*H*-cyclopenta[*a*]pentalen-2-ol (16dA). According to the *general procedure A*, the solution of **17** (64 mg, 0.3 mmol) in dry THF (6 mL) was treated with 4-$CF_3C_6H_4MgBr$ (0.5 M in THF, 3 mL, 1.5 mmol) at 0 °C for 1 h to give **16dA** (92 mg, 86% yield) as a colorless oil after column chromatography (SiO_2, 5% EtOAc in hexanes). The spectral data and its optical rotation were identical to those of **16dA** obtained from the radical cyclization of **10b** (Table 2).

(2*S*,3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-2-methyl-4-methylenedecahydro-1*H*-cyclopenta[*a*]pentalen-2-ol (16eA). According to the *general procedure A*, the reaction of **17** (42 mg, 0.2 mmol) and methylmagnesium chloride (2 M in THF, 0.5 mL, 1 mmol) in dry THF (5 mL) at 0 °C gave **16eA** (42 mg, 92% yield) as a colorless oil after column chromatography (SiO_2, 10% EtOAc in hexanes): $[\alpha]^{28}_D$ −59.2 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (d, J = 2.0

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Hz, 1H), 4.89 (d, J = 2.1 Hz, 1H), 3.17−3.11 (m, 1H), 2.74−2.57 (m, 3H), 2.49−2.30 (m, 2H), 2.06−1.98 (m, 1H), 1.96 (s, 1H), 1.84−1.73 (m, 1H), 1.66−1.47 (m, 3H), 1.46−1.36 (m, 1H), 1.32 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.52 (dd, J = 225.8, 13.0 Hz, 1F), −120.48 (dd, J = 219.4, 10.2 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 (C), 128.9 (dd, J = 260.6, 254.9 Hz, CF_2), 106.1 (CH_2), 80.6 (dd, J = 29.0, 22.8 Hz, C), 54.8 (dd, J = 21.6, 19.4 Hz, CH), 47.4 (d, J = 9.0 Hz, CH), 46.3 (CH), 41.9 (d, J = 3.0 Hz, CH_2), 38.7 (d, J = 9.0 Hz, CH), 37.4 (CH_2), 32.2 (CH_2), 29.0 (CH_2), 19.6 (CH_3); IR ($CHCl_3$) ν_{max} 3589*s*, 3385*br*, 1670*m*, 1457*m*, 1262*s*, 1098*s*, 1021*s*, 8112*s* cm^{-1}; MS m/z (%) relative intensity 228 (M^+, 5), 210 ($M^+ - H_2O$, 4), 167 (25), 149 (100), 121 (26), 77 (24); HRMS (ESI-TOF) calcd for $C_{13}H_{18}F_2NaO$ $[M + Na]^+$ 251.1223, found 251.1232.

(2*S*,3a*S*,3b*S*,6a*S*,7a*R*)-2-Ethyl-3,3-difluoro-4-methylenedecahydro-1*H*-cyclopenta[*a*]pentalen-2-ol (16fA). According to the *general procedure A*, the reaction of **17** (21 mg, 0.1 mmol) and ethylmagnesium chloride (2 M in THF, 0.25 mL, 0.5 mmol) in dry THF (4 mL) at 0 °C gave **16fA** (20 mg, 83% yield) as a colorless oil after column chromatography (SiO_2, 10% EtOAc in hexanes): $[\alpha]^{26}_D$ −21.3 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (d, J = 2.1 Hz, 1H), 4.87 (d, J = 2.1 Hz, 1H), 3.20−3.12 (m, 1H), 2.80−2.55 (m, 3H), 2.49−2.30 (m, 2H), 2.10−1.95 (m, 1H), 1.88−1.51 (m, 7H), 1.44−1.37 (m, 1H), 0.98 (t, J = 7.5 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.93 (dd, J = 229.2, 14.1 Hz, 1F), −119.24 (d, J = 230.9 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4 (C), 129.7 (dd, 237.9, 237.9 Hz, CF_2) 106.2 (CH_2), 83.0 (dd, J = 28.4, 22.7 Hz, C), 55.5 (dd, J = 21.9, 19.6 Hz, CH), 47.4 (d, J = 8.7 Hz, CH), 46.3 (CH), 40.2 (d, J = 3.4 Hz, CH_2), 38.6 (d, J = 9.3 Hz, CH), 37.6 (CH_2), 32.4 (CH_2), 29.1 (CH_2), 26.0 (CH_2), 7.4 (CH_3); IR ($CHCl_3$) ν_{max} 3598*m*, 3405*br*, 1651*m*, 1463*s*, 1262*s*, 1098*s*, 1012*s*, 844*s* cm^{-1}; MS m/z (%) relative intensity 242 (M^+, 3), 224 ($M^+ - H_2O$, 100), 195 (23), 120 (34), 117 (33), 91 (43); HRMS (ESI-TOF) calcd for $C_{14}H_{20}F_2NaO$ $[M + Na]^+$ 265.1380, found 265.1376.

(2*S*,3a*S*,3b*S*,6a*S*,7a*R*)-2-Butyl-3,3-difluoro-4-methylenedecahydro-1*H*-cyclopenta[*a*] pentalen-2-ol (16gA). According to the *general procedure A*, the reaction of **17** (21 mg, 0.1 mmol) and butylmagnesium chloride (2 M in THF, 0.25 mL, 0.5 mmol) in dry THF (4 mL) at 0 °C gave **16gA** (23 mg, 85% yield) as a colorless oil after column chromatography (SiO_2, 10% EtOAc in hexanes): $[\alpha]^{26}_D$ −41.4 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (d, J = 1.4 Hz, 1H), 4.89 (d, J = 1.6 Hz, 1H), 3.19−3.10 (m, 1H), 2.77−2.53 (m, 3H), 2.50−2.28 (m, 2H), 2.11−1.98 (m, 1H), 1.84−1.71 (m, 2H), 1.68−1.24 (m, 10H), 0.90 (t, J = 7.1 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.73 (dd, J = 229.0, 14.3 Hz, 1F), −119.58 (d, J = 229.4 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (C), 121.0 (dd, J = 260.8, 260.8 Hz, CF_2), 106.3 (CH_2), 79.7 (dd, J = 23.9, 23.9 Hz, C), 56.0 (dd, J = 23.7, 19.2, Hz, CH), 50.0 (dd, J = 5.9, 3.6 Hz, CH), 46.1 (CH), 40.1 (CH_2), 38.2 (CH_2), 37.8 (t, J = 2.8 Hz, CH), 33.4 (d, J = 2.3 Hz, CH_2), 32.3 (CH_2), 29.1 (CH_2), 25.1 (CH_2), 23.2 (CH_2), 14.0 (CH_3); IR ($CHCl_3$) ν_{max} 3593*s*, 3445*br*, 1652*m*, 1457*s*, 1187*s*, 1031*s*, 889*s* cm^{-1}; MS m/z (%) relative intensity 270 (M^+, 2), 252 ($M^+ - H_2O$, 100), 223 (30), 119 (50), 91 (47), 77 (18); HRMS (ESI-TOF) calcd for $C_{16}H_{24}F_2NaO$ $[M + Na]^+$ 293.1693, found 293.1698.

(2*R*,3a*S*,3b*S*,6a*S*,7a*R*)-3,3-Difluoro-2-(4-methoxyphenyl)-4-methylenedecahydro-1*H*-cyclopenta[*a*]pentalen-2-ol (16hA). According to the *general procedure A*, the solution of **17** (42 mg, 0.2 mmol) in dry THF (5 mL) was treated with 4-$OMeC_6H_4MgBr$ (0.5 M in THF, 2 mL, 1 mmol) at 0 °C for 1.5 h to give **16hA** (59 mg, 92% yield) as a white solid after column chromatography (SiO_2, 10% EtOAc in hexanes): mp 95−96 °C; $[\alpha]^{28}_D$ −13.0 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.2 Hz, 2H), 6.94−6.86 (m, 2H), 4.90 (s, 1H), 4.86 (s, 1H), 3.81 (s, 3H), 3.32−3.23 (m, 1H), 2.94−2.84 (m, 1H), 2.83−2.74 (m, 1H), 2.68−2.54 (m, 2H), 2.49−2.27 (m, 3H), 1.92−1.74 (m, 4H), 1.44−1.33 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.68 (dd, J = 229.2, 18.6 Hz, 1F), −119.13 (dd, J = 229.0, 9.4 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (C), 157.0 (C), 131.6 (C), 128.9 (dd, J = 259.6, 256.9 Hz, CF_2), 128.0 (2 × CH), 113.6 (2 × CH), 106.4 (CH_2), 82.2 (dd, J = 25.4, 21.7 Hz, C), 56.6 (dd, J = 22.4, 20.0 Hz, CH), 55.2 (OCH_3), 50.1 (t, J = 4.0 Hz, CH), 47.0 (CH), 42.1 (CH_2), 39.3 (CH_2), 37.8 (t, J = 3.7 Hz, CH), 33.0 (CH_2), 30.0 (CH_2); IR ($CHCl_3$) ν_{max} 3591*s*, 1652*w*, 1611*s*, 1515*s*, 1463*m*, 1255*s*, 1183*s*, 1036*s*, 835*s* cm^{-1}; MS m/z (%) relative intensity 320 (M^+, 1), 301 (100), 300 (81), 282 (26), 191 (19), 135 (38), 91 (12), 77 (8); HRMS (ESI-TOF) calcd for $C_{19}H_{22}F_2NaO_2$ $[M + Na]^+$ 343.1486, found 343.1482.

(2*R*,3a*S*,3b*S*,6a*S*,7a*R*)-2-(2,4-Dimethoxyphenyl)-3,3-difluoro-4-methylenedecahydro-1*H*-cyclopenta[*a*]pentalen-2-ol (16iA). According to the *general procedure A*, the reaction of **17** (42 mg, 0.2 mmol) and 2,4-$(OMe)_2C_6H_3MgBr$ (0.5 M in THF, 2 mL, 1 mmol) in dry THF (5 mL) at 0 °C gave **16iA** (61 mg, 87% yield) as a white solid after column chromatography (SiO_2, 10% EtOAc in hexanes): mp 52−53 °C; $[\alpha]^{27}_D$ −40.6 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.6 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.49 (dd, J = 8.6, 2.5 Hz, 1H), 5.09 (s, 1H), 4.88 (s, 1H), 4.85 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.36−3.27 (m, 1H), 2.90−2.75 (m, 2H), 2.71−2.62 (m, 1H), 2.54 (dddd, J = 19.2, 9.8, 9.8, 4.6 Hz, 1H), 2.46−2.37 (m, 1H), 2.36−2.26 (m, 1H), 1.95−1.73 (m, 4H), 1.36 (ddt, J = 12.5, 8.0, 8.0 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.24 (dd, J = 226.4, 18.8 Hz, 1F), −118.65 (dd, J = 226.5, 8.8 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7 (C), 159.4 (C), 157.4 (C), 129.1 (dd, J = 264.7, 254.5 Hz, CF_2), 128.7 (CH), 119.6 (C), 106.1 (CH_2), 104.6 (CH), 100.1 (CH), 83.5 (dd, J = 26.8, 22.0 Hz, C), 57.2 (dd, J = 23.3, 20.1 Hz, CH), 56.0 (OCH_3), 55.3 (OCH_3), 50.2 (t, J = 4.0 Hz, CH), 47.0 (CH), 40.5 (CH_2), 39.4 (CH_2), 38.0 (t, J = 3.4 Hz, CH), 33.3 (CH_2), 30.4 (CH_2); IR ($CHCl_3$) ν_{max} 3501*br*, 1615*s*, 1584*s*, 1507*s*, 1458*s*, 1306*s*, 1262*s*, 1162*s*, 1035*s*, 890*m* cm^{-1}; MS m/z (%) relative intensity 350 (M^+, 1), 332 ($M^+ - H_2O$, 17), 274 (57), 273 (100), 228 (21), 166 (39), 91 (3); HRMS (ESI-TOF) calcd for $C_{20}H_{24}F_2NaO_3$ $[M + Na]^+$ 373.1591, found 373.1592.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H, ^{13}C, ^{19}F NMR spectra for compounds **6**−**17**, NOE of **16aA** and CIF data for single crystal X-ray analysis of **16hA** (CCDC 1024130). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: manat.poh@mahidol.ac.th. Tel: (+)-66-2-2015158. Fax: (+)-66-2-6445126.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671−719. (b) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647−3692. (c) Marchand, A. P. *Synlett* **1991**, 73−79.

(2) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41−165.

(3) (a) Mehta, G.; Umarye, J. D. *Tetrahedron Lett.* **2001**, *42*, 1991−1993. (b) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855−5857.

(4) (a) Hiyama, T., Ed.; *Organofluorine Compounds, Chemistry and Applications*; Springer: New York, 2000. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214−231 and references cited. (c) Welch, J. T., Ed.; *Selective Fluorination in Organic and Bioorganic Chemistry*; American Chemical Society: Washington, D.C., 1991. (d) Fried, J.; Mitra, D. K.; Nagarajan, M.; Mehrotra, M. M. *J. Med. Chem.* **1980**, *23*, 234−237. (e) Nakano, T.; Makino, M.; Morizawa, Y.; Matsumura, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1019−1021.

DOI: 10.1021/jo5022579
J. Org. Chem. 2015, 80, 816−827

(f) Chang, C.-S.; Negishi, M.; Nakano, T.; Morizawa, Y.; Matsumura, Y.; Ichikawa, A. *Prostaglandins* **1997**, *53*, 83−90.
(5) For selected recent references, see: (a) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Blackwell: Oxford, 2009. (b) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071−1081. (c) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308−319. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (e) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359−4369.
(6) For some recent examples for the syntheses *gem*-difluoromethylenated compounds, see: (a) Zemtsov, A. A.; Kondratyev, N. S.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2014**, *79*, 818−822. (b) Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16*, 1216−1219. (c) Salomon, P.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 1482−1485. (d) Min, Q.-Q.; Yin, Z.; Feng, Z.; Guo, W.-H.; Zhang, X. *J. Am. Chem. Soc.* **2014**, *136*, 1230−1233. (e) Ni, C.; Hu, J. *Synthesis* **2014**, *46*, 842−863. (f) Munemori, D.; Narita, K.; Nokami, T.; Itoh, T. *Org. Lett.* **2014**, *16*, 2638−2641. (g) Hashimoto, R.; Iida, T.; Aikawa, K.; Ito, S.; Mikami, K. *Chem.—Eur. J.* **2014**, *20*, 2750−2754. (h) Gao, B.; Zhao, Y.; Hu, M.; Ni, C.; Hu, J. *Chem.—Eur. J.* **2014**, *20*, 7803−7810. (i) Prakash, G. K. S.; Krishnamoorthy, S.; Ganesh, S. K.; Kulkarni, A.; Haiges, R.; Olah, G. A. *Org. Lett.* **2014**, *16*, 54−57. (j) Feng, Z.; Min, Q.-Q.; Xiao, Y.-L.; Zhang, B.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 1669−1673. (k) Lee, G. M.; Harrison, D. J.; Korobkov, I.; Baker, R. T. *Chem. Commun.* **2014**, *50*, 1128−1130. (l) Wang, J.-Y.; Su, Y.-M.; Yin, F.; Bao, Y.; Zhang, X.; Xu, Y.-M.; Wang, X.-S. *Chem. Commun.* **2014**, *50*, 4108−4111. (m) Li, W.; Zhu, X.; Mao, H.; Tang, Z.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2014**, *50*, 7521−7523. (n) Ma, G.; Wan, W.; Hu, Q.; Jiang, H.; Wang, J.; Zhu, S.; Hao, J. *Chem. Commun.* **2014**, *50*, 7527−7530. (o) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 17302−17305. (p) Prakash, G. K. S.; Ni, C.; Wang, F.; Zhang, Z.; Haiges, R.; Olah, G. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10835−10839. (q) Zhou, Q.; Ruffoni, A.; Gianatassio, R.; Fujiwara, Y.; Sella, E.; Shabat, D.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3949−3952. (r) Chia, P. W.; Bello, D.; Slawin, A. M. Z.; O'Hagan, D. *Chem. Commun.* **2013**, *49*, 2189−2191. (s) Thomoson, C. S.; Dolbier, W. R., Jr. *J. Org. Chem.* **2013**, *78*, 8904−8908. (t) Li, L.; Wang, F.; Ni, C.; Hu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12390−12394. (u) Zhao, Y.; Huang, W.; Zheng, J.; Hu, J. *Org. Lett.* **2011**, *13*, 5342−5345. (v) Yue, X.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2009**, *11*, 73−76. (w) Diab, S. A.; Sene, A.; Pfund, E.; Lequeux, T. *Org. Lett.* **2008**, *10*, 3895−3898. (x) Xu, W.; Dolbier, W. R., Jr.; Salazar, J. *J. Org. Chem.* **2008**, *73*, 3535−3538. (y) Jakowiecki, J.; Loska, R.; Makosza, M. *J. Org. Chem.* **2008**, *73*, 5436−5441. (z) Verniest, G.; Surmont, R.; Hende, E. V.; Deweweire, A.; Deroose, F.; Thuring, J. W.; De Kimpe, N. *J. Org. Chem.* **2008**, *73*, 5458−5461.
(7) (a) Soorukram, D.; Kuhakarn, C.; Reutrakul, V.; Pohmakotr, M. *Synlett* **2014**, *25*, 2558−2573. (b) Pharikronburee, V.; Punirun, T.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *Org. Biomol. Chem.* **2013**, *11*, 2022−2033. (c) Boonkitpattarakul, K.; Soorukram, D.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Fluorine Chem.* **2011**, *132*, 987−990. (d) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921−930. (e) Mizuta, S.; Shibata, N.; Ogawa, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Chem. Commun.* **2006**, 2575−2577. (f) Pohmakotr, M.; Boonkitpattarakul, K.; Ieawsuwan, W.; Jarussophon, S.; Duangdee, N.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2006**, *62*, 5973−5985. (g) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *J. Fluorine Chem.* **2005**, *126*, 527−532. (h) Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Org. Chem.* **2003**, *68*, 4457−4463.
(8) (a) Thaharn, W.; Bootwicha, T.; Soorukram, D.; Kuhakarn, C.; Prabpai, S.; Kongsaeree, P.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Org. Chem.* **2012**, *77*, 8465−8479. (b) Bootwicha, T.; Panichakul, D.; Kuhakarn, C.; Prabpai, S.; Kongsaeree, P.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Org. Chem.* **2009**, *74*, 3798−3805.
(9) Punirun, T.; Peewasan, K.; Kuhakarn, C.; Soorukram, D.; Tuchinda, P.; Reutrakul, V.; Kongsaeree, P.; Prabpai, S.; Pohmakotr, M. *Org. Lett.* **2012**, *14*, 1820−1823.
(10) Peewasan, K.; Kuhakarn, C.; Soorukram, D.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Fluorine Chem.* **2012**, *135*, 367−372.
(11) Chatupheeraphat, A.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pakawatchai, C.; Saithong, S.; Pohmakotr, M. *Eur. J. Org. Chem.* **2013**, 6844−6858.
(12) Thaharn, W.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 2212−2215.
(13) (a) Jacquet, O.; Bergholz, T.; Magnier-Bouvier, C.; Mellah, M.; Guillot, R.; Fiaud, J.-C. *Tetrahedron* **2010**, *66*, 222−226. (b) Miyazaki, T.; Yokoshima, S.; Simizu, S.; Osada, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 4737−4740. (c) Seemann, M.; Schöller, M.; Kudis, S.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 2122−2127. (d) Tucker, J. W.; Nguyen, J. D.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Chem. Commun.* **2010**, *46*, 4985−4987.
(14) (a) Mukherjee, S.; Kontokosta, D.; Patil, A.; Rallapalli, S.; Lee, D. *J. Org. Chem.* **2009**, *74*, 9206−9209. (b) Rosen, T.; Taschner, M. J.; Thoma, J. A.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 1190−1201. (c) Fischer, D. F.; Xin, Z.-Q; Peters, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 7704−7707.
(15) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943−3958.
(16) For reviews on radical cyclization, see: (a) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: Oxford, 2003. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996. (c) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1991. (d) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301−856. (e) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224−2248.
(17) Lee, H.-Y.; Sha, C.-K. *J. Org. Chem.* **2012**, *77*, 598−605.
(18) Shimizu, M.; Morita, O.; Itoh, S.; Fujisawa, T. *Tetrahedron Lett.* **1992**, *33*, 7003−7006.
(19) Tanaka, Y.; Ishihara, T.; Konno, T. *J. Fluorine Chem.* **2012**, *137*, 99−104.

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