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Synthesis of *gem*-Difluoromethylene Containing Cycloalkenes via Ring-opening Reaction of *gem*-Difluorocyclopropanes and Subsequent RCM Reaction

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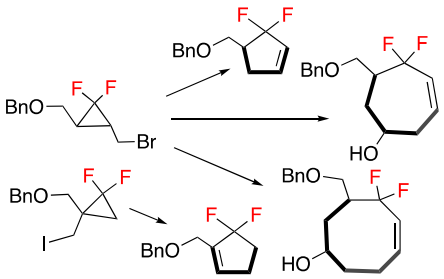
KEYWORDS. Gem-difluorocyclopropane; Ring-opening allylation reaction; Ring-closing metathesis; Medium sized cycloalkane; *gem*-Difluoromethylene.

Supporting information

ABSTRACT: The radical type ring-opening reaction of *gem*-difluorocyclopropanes and subsequent regioselective mono-epoxidation of the products were demonstrated. Introduction of a vinyl or allyl group to the epoxide produced the diene derivatives that were subjected to the Ring Closing Metathesis (RCM) reaction to furnish the *gem*-difluoromethylene containing cyclopentene, cycloheptene, and cyclooctene derivatives in good to excellent yields.



1. INTRODUCTION

The incorporation of a fluorine atom into an organic molecule can alter the chemical reactivity of the resulting compound due to the strong electron-withdrawing nature of the fluorine with no significant modification of their molecular sizes. Using this characterisitic of the *gem*-fluorinated compounds, we can create a new molecule that exhibits unique physical and biological properties.[1,2,3] For example, Ahmeda and co-workers recently succeeded in synthesizing a strong musk-smelling compound which contains the *gem*-difluoromethylene moiety.[3] Therefore, the development of an efficient means to access *gem*-fluorinated compounds has gained strong attention from the synthetic organic chemistry community.[1,2,4-9]

The syntheses of *gem*-difluoromethylene compounds have been generally achieved by the difluorination of carbonyl or thiocarbonyl functional groups.[5] Recently, great progress in the synthesis of *gem*-difluoromethylene compounds has been accomplished using various methodologies.[6-9] Synthetic strategies that use economical building blocks containing a *gem*-difluoromethylene moiety have also been recognized as an attractive route to access *gem*-difluoromethylene compounds.[10] Among such methodologies, the strategy of the ring-opening of *gem*-difluorocyclopropane derivatives is very attractive; Amii[11] and Gilman[12] independently reported the formation of 2,2-difluoroketones via the ring-opening reaction of siloxy-*gem*-difluorocyclopropane derivatives in the same year. Since then, siloxy-*gem*-difluorocyclopropane has fascinated many researchers; Fuchibe and co-workers reported the preparation of Nazarov reaction precursors through the ring-opening reaction of siloxy-*gem*-difluorocyclopropane.[13] Recently, Wang also developed the ring-opening diarylation of the same compound.[14] Specklin[15] reported the stereoselective ring-opening reaction of *gem*-difluorocyclopropanes.[15] The ring-opening methodology of *gem*-difluorocyclopropanes is now recognized as a useful method for the synthesis of fluorinated organic compounds.

We have synthesized *gem*-difluorocyclopropane derivatives and revealed their unique physical and biological properties.[2] We next accomplished the synthesis of various types of *gem*-difluoromethylene compounds via the radical type regioselective ring-opening allylation of *gem*-difluorocyclopropane derivatives.[16] Furthermore, we recently found that aerobic oxidation took place after the visible light-mediated ring-opening reaction of *gem*-difluorocyclopropane in the presence of an organic dye and amine to furnish 2,2-difluoro-homoallylic alcohols in good yields.[17] Since our ring-opening products have two olefin moieties with different reactivities, they are expected to become key intermediates for various types of cycloalkenes through the ring closing methathesis (RCM) reaction. The RCM reaction is now

considered as one of the most powerful tools for preparing cyclic compounds.[18,19] In fact, this methodology has been applied for preparing *gem*-difluoromethylenes containing cyclic compounds.[20,21] Qing et al. first reported the use of the RCM reaction for the synthesis of *gem*-difluorinated cyclic compounds, and they prepared analogues of massoialactone[20a] and 7-epi-castanospermine.[20b] O'Hagan and coworkers reported the synthesis of *gem*-difluoromethylene groups containing macrocyclic compounds that exhibited an olfactory property via the RCM reaction.[3,19] Inspired by these results, we planned the synthesis of five types of medium-sized cyclic compounds, such as **3**, **4**, **5**, **6,** and **7** from *gem*-difluorocyclopropanes **1** or **2** as the starting molecules (Figure 1).

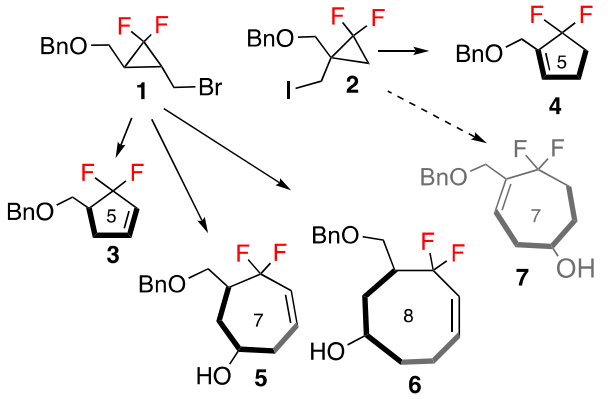


Figure 1. Synthetic plan for *gem*-difluorinated cycloalkenes **3**, **4**, **5**, **6**, and **7** using two types of *gem*-difluorocyclopropanes 1 and 2 as starting molecules through the RCM reaction.

2. RESULTS AND DISCUSSION

Figure 2 shows the retrosynthetic analysis of the target cycloalkenes using *gem*-difluorocyclopropane **1** as the starting molecule. The benzyloxy moiety in the starting compounds **1** and **2** allows easy handling of the products due to increased boiling point, though fluorinated small molecules are generally easily escaped during the purification process due to their high volatility. We used different protecting groups, such as allyl, methoxymethyl (MOM), and *p*-methoxybenzyl groups, as the starting compounds considering a further synthesizing process.[2d,2e,2h] We postulated that cyclopentene **3**, cycloheptene **5**, and cyclooctane **6** might be derived from the dienes **8**, **12**, and **13** *via* the RCM reaction, respectively. The dienes **12** and **13** might be derived from the epoxide **10** that could be produced by the regioselective oxidation of the diene **8** that was prepared by the ring-opening allylation of the *gem*-difluorocyclopropane **1**.[16] The cyclopentene **4** might be derived from the diene **9** and this compound might be derived from the *gem*-difluorocyclopropane **2**.

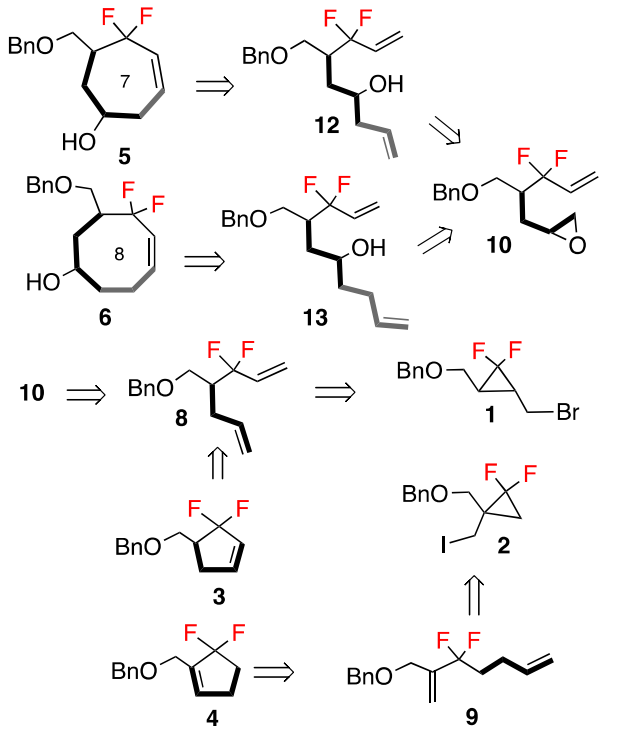


Figure 2. Retrosynthetic analysis for synthesizing three types of *gem*-difluorinated cycloalkenes, **3**, **4**, **5**, and **6**.

2.1. PREPARATION OF TWO TYPES OF GEM-DIFLUORINATED CYCLOPENTENES 3 AND 4.

As already mentioned, we prepared diene **8** through the regioselective allylation of the *gem*-difluorocyclopropane derivative **1** through a radical-type ring-opening reaction.[16] The RCM reaction of the diene **8** smoothly took place using 10 mol% of the 1st generation Grubbs catalyst (Grubbs I) to afford the desired cyclopentene **3** in 97% yield (Figure 3).

We next synthesized the cyclopentene **4** through the route described in Figure 3; the *gem*-difluorocyclopropane **2**[17] was treated with 8 equiv. of allyltributylstannane and 10 mol% of AIBN, then the mixture was heated at 80°C without any solvent. The desired ring-opening reaction proceeded and the diene **9** was obtained in 76% yield. Although the RCM reaction of diene **9** proceeded using the Grubbs I catalyst, the yield of the desired compound **4** was moderate (73%) and it required the Stewart-Grubbs catalyst[22] to obtain the cyclopentene **4** in excellent yield (94 %) (Figure 3). It is postulated that the increase in the catalytic activity of the Stewart-Grubbs catalyst in the RCM reaction might occur from the significantly more open steric environment around the ruthenium center, which allows the catalytic site to accommodate larger organic fragments.[22] Since the RCM reaction of the diene **9** might proceed via a more sterically bulky in-

termediate compared to that of the cyclization of **8**, the Stewart-Grubbs catalyst thus gave a better result compared to the Grubbs I catalyst.

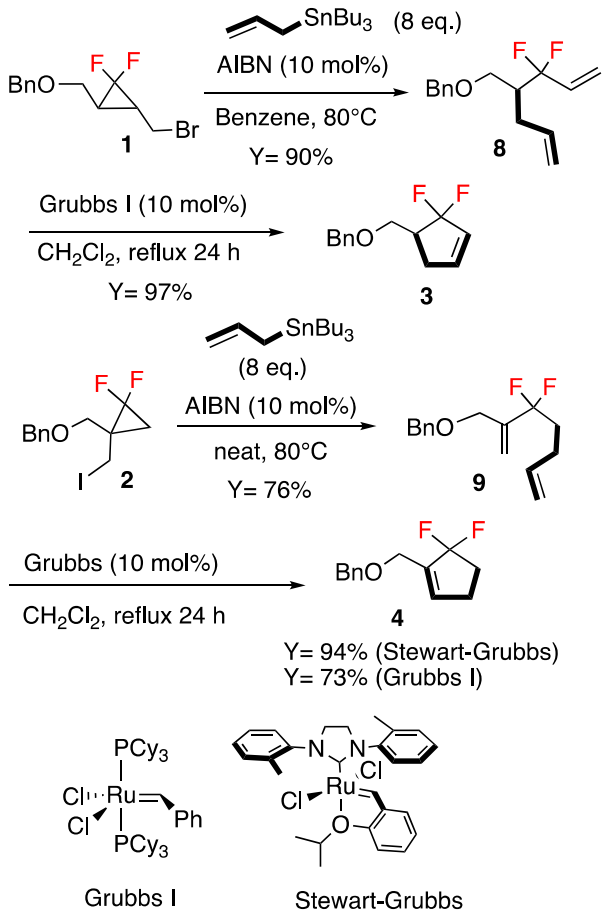


Figure 3. Synthesis of cyclopentenes **3** and **4**.

2.2 PREPARATION OF CYCLOHEPTENE 5 AND CYCLOOCTENE 6.

We next accomplished the synthesis of the cycloheptene **5** and cyclooctene **6** starting from the diene **8** as summarized in Figures 4 and 5. Selective epoxidation of **8** was easily accomplished by the treatment of **8** with *m*-CPBA (1.3 equiv.) and the desired oxirane **10** was selectively obtained in 72% yield because the olefinic group adjacent to the *gem*-difluoromethylene moiety exhibited a poor reactivity towards the oxidant compared to the other olefinic moiety.

The epoxide **10** was treated with the vinyl Grignard reagent in the presence of copper(I) cyanide (CuCN) in THF at -40°C to provide the vinylation product **12**.[23] Although the unexpected by-product **15** was produced by the defluorinated S_N2' type vinylation,[24] the separation of **12** and the by-product **15** was easily accomplished by silica gel thin layer chromatography (TLC), and the diene **12** was obtained in 68% yield. The RCM reaction under high dilution conditions using the Grubbs II catalyst[25] successfully proceeded and the desired cycloheptene **5** was obtained in 91 % yield (Figure 4). Although the Grubbs I catalyst also gave the cycloheptene **5**, the yield was insufficient (35%) compared to that of the Grubbs II-catalyzed reaction and the unreacted **12** was recovered in 62% yield.

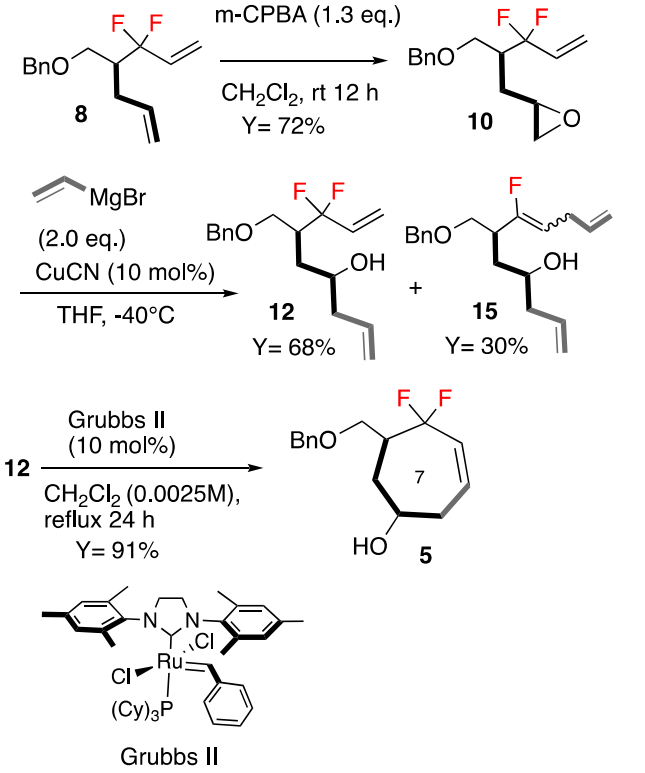


Figure 4. Synthesis of cycloheptene **5**.

We next undertook the synthesis of the cyclooctane **6** starting from the epoxide **10** (Figure 5). The epoxide **10** was reacted with the allyl Grignard reagent in the presence of 10 mol% of CuCN in THF at -40°C to afford the allylation product **13** in 80% yield. Although the undesired S_N2'-reaction product **16** was also produced, the separation of **13** and **16** was easily accomplished by silica gel TLC. The RCM reaction of **13** using the Grubbs II catalyst was successful and the desired cyclooctane **6** was obtained in 84% yield. We have thus accomplished the synthesis of four types of compounds, i.e., **3**, **4**, **5**, and **6**.

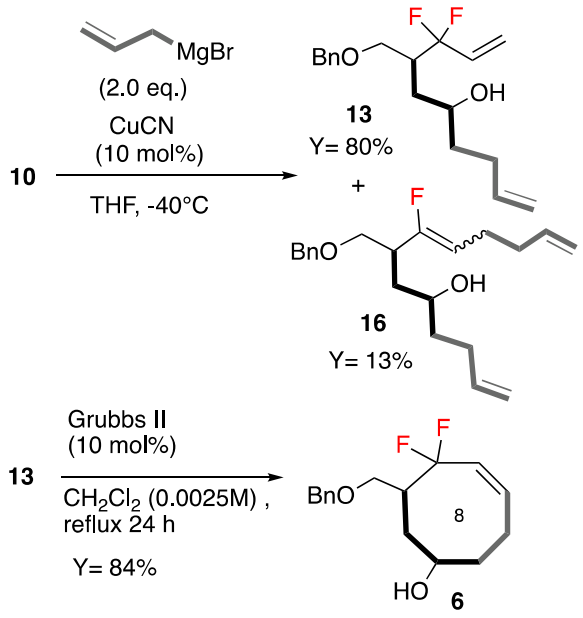


Figure 5. Synthesis of cyclooctene **6**.

2.3 ATTEMPT TO SYNTHESIZE THE CYCLOHEPTENE 7.

In order to synthesize the cycloheptene **7**, the epoxide **11** was reacted with the vinyl Grignard reagent. Different from the reaction of the epoxide **10**, the reaction of the epoxide **11** with vinyl MgBr successfully proceeded, and gave the desired diene **14** in 82% yield. Although undesired S_N2'-reaction product **17** (15%) was also produced in the reaction, the separation of **14** and the by-product **17** was easily accomplished by silica gel thin layer chromatography (TLC). However, we encountered a serious problem in the next RCM reaction; no cyclized product **7** was obtained and only the starting diene **14** and unidentified solids were obtained when using the three types of Grubbs catalysts, i.e., Grubbs I and II, and Stewart-Grubbs. Shu and co-workers reported such an example of the RCM reaction under high reaction temperature conditions; they conducted the RCM reaction at 110°C using the nitro-Hoveyda-Grubbs catalyst[26] in a toluene solvent system.[27] Bräse, Balova, and co-workers successfully overcame the thermodynamic barrier in the RCM reaction using this catalyst.[28] Hence, we attempted the RCM reaction of **14** using nitro-Hoveyda-Grubbs catalyst under toluene or 1,1-dichloroethane reflux conditions. Unfortunately, we again failed to synthesize the desired cycloheptene **7** and only decomposition of the diene **14** was observed even when the reaction was conducted under highly diluted conditions using four types of Ru catalysts (Figure 6). Even when the hydroxyl group was protected as the trimethylsilyl ether, no desired cyclization product was again obtained.

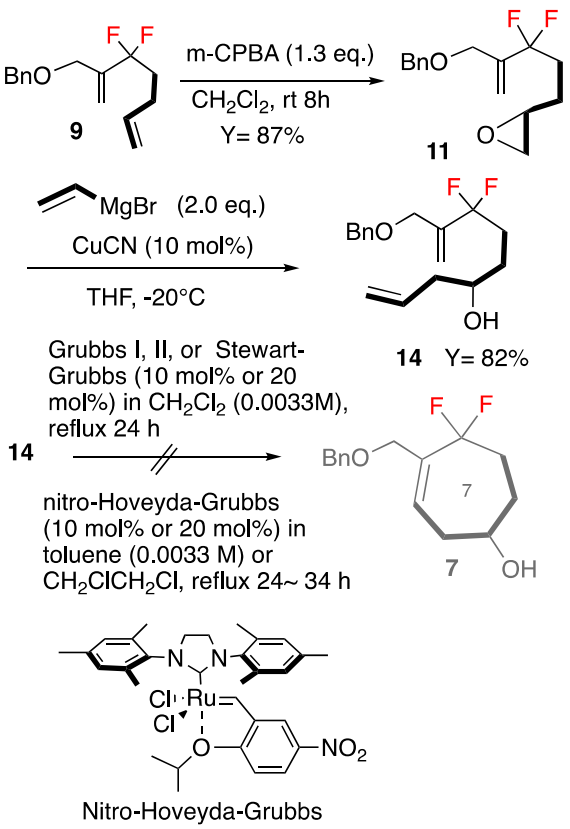


Figure 6. Unsuccessful results to produce the cycloheptene **7**.

To elucidate the reason why the RCM reaction was unsuccessful for the diene **14**, we conducted calculations and compared the energy profile for two possible intermediates using the B3LYP/6-311+G(d,p) calculations.[29-31] We used the chiral forms of (4*R*,6*R*)-6-((benzyloxy)methyl)-7,7-difluorononа-1,8-dien-4-ol **(12)** and (*S*)-8-((benzyloxy)methyl)-7,7-difluorononа-1,8-dien-4-ol **(14)** for the calculations to simplify the reaction, though racemic compounds were employed in the present RCM reactions. The optimized structures for the precursor of the cycloheptene **5** should be A# (Figures 7 and 8). On the other hand, the optimized precursor of the cycloheptene **7** should be B# as shown in Figures 7 and 8. The calculations suggested that there might be a significant difference between the two key intermediates A# and B# (Figure 7). As already mentioned, the RCM reaction of **12** easily took place and the desired cycloheptene **5** was obtained in excellent yield as shown in Figure 4. Isomerization from the A-transoid to the A-cisoid forms, which are precursors of the key intermediate A#, easily proceeded because only a small energy barrier (3.2 KJ/mol) was estimated; changing the A-cisoid form to cis-A# might more easily occur because A# is 3.5 KJ/mol more stable than the A-cisoid conformer (Figure 7). On the contrary, the calculations suggested that 57.2 KJ/mol might be needed to access

B# from the B-cisoid intermediate, because the quaternary carbon would be formed (Figures 7 and 8). We postulated that the difficulty to access B# from the B-cisoid form would be solved by elevating the reaction temperature. However, as already mentioned, we failed to obtain the desired cycloalkene **7** after extensive studies using four types of the Grubbs catalysts. On the other hand, we succeeded in synthesizing two cyclopentane derivatives **3** and **4** via the RCM reaction. To elucidate the reason why the RCM reaction was successful for dienes **8** and **9**, we investigated the energy profile for two possible intermediates (C# and D#) using the B3LYP/6-311+G(d,p) calculations (Figure 9).[29-31] The calculations suggested that the energy barrier in the synthesis of cyclopentene **3** via the possible intermediate C# by the RCM reaction of **8** is very low; it needed only 3.5 KJ/mol. Although conversion energy of the synthesis of cyclopentene **4** through D# of the RCM reaction of diene **9** was higher (45.0 KJ/mol) than that of diene **8**, it is noteworthy that the value was still lower than that needed for the synthesis of the cycloheptene **5** (55.6 KJ/mol) (Figures 7 and 9). It is well known that 7-membered cyclic compounds are conformationally more unstable than the 5-membered cyclic compounds. Therefore, the energy barrier between the B-cisoid and B# might be too high to produce the desired cyclization. It was thus concluded that the diene **14** was unsuitable for the Ru-catalyzed RCM reaction.

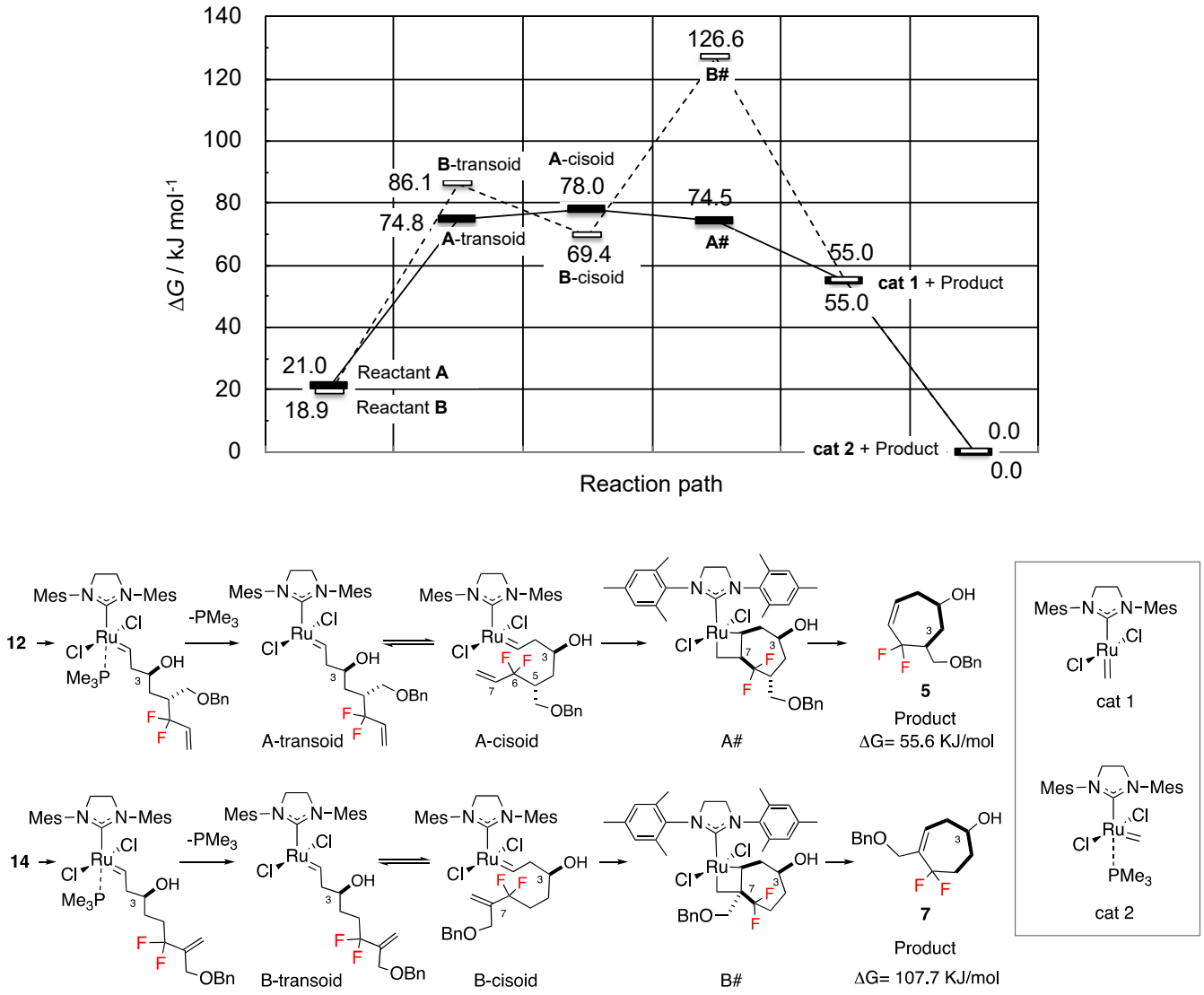
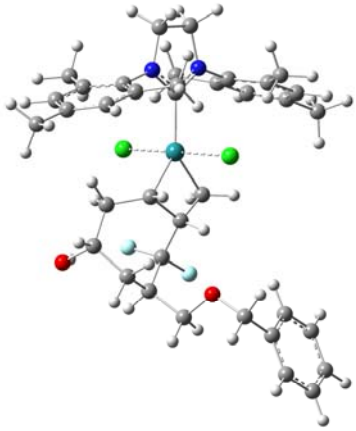
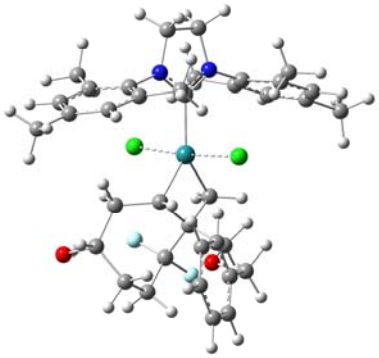


Figure 7. Plausible Gibbs energy profile for the reaction pathways to access cycloheptenes **5** and **7** based on B3LYP/ Lanl2dz calculations via cis-A#(—■—) and cis-B#(---□---). For ease of the calculations, we used model compounds in which the configuration of the 3-hydroxyl groups was tentatively fixed as (3*S*) and the tri(cyclohexyl)phosphine group was simplified to the trimethylphosphine from tri(cyclohexyl)phosphine.



A#



B#

Figure 8. Optimized structure of the key intermediates A# and B# by B3LYP/ Lanl2dz calculation.

3. CONCLUSION

We have accomplished the synthesis of four types of novel *gem*-difluorinated cycloalkenes, i.e., (((2,2-difluorocyclopent-3-en-1-yl)methoxy)methyl)benzene (**3**), (((5,5-difluorocyclopent-1-en-1-yl)methoxy)methyl)benzene (**4**), 6-((benzyloxy)methyl)-5,5-difluorocyclohept-3-enol (**5**), and 7-((benzyloxy)methyl)-6,6-difluorocyclooct-4-enol (**6**) starting from the *gem*-difluorocyclopropanes through four straightforward sequences, i.e., (1) ring-opening allylation, (2) chemoselective epoxidation, (3) vinylation or allylation of the epoxide moiety, and finally, (4) the RCM reaction. However, unfortunately, the synthesis of (benzyloxy)methyl)-5,5-difluorocyclohept-3-enol (**7**) by the present methodology was unsuccessful. Since the synthesized cycloalkenes have three important functional groups, i.e., the hydroxyl, olefinic, and *gem*-difluoromethylene groups, we expect that our compounds may become useful key intermediates for preparing fluorine-containing biologically-active or functional compounds.

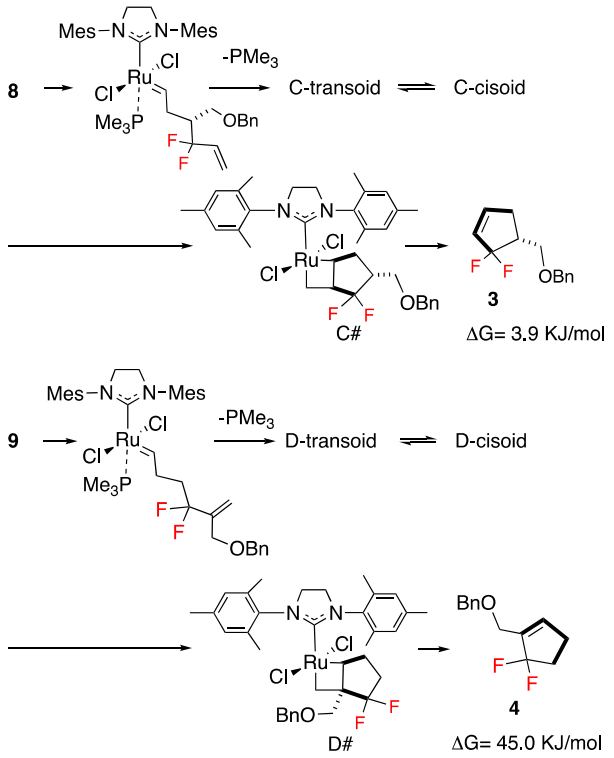


Figure 9. Plausible Gibbs energy profile for the reaction pathways to access cycloheptenes **3** and **4** based on B3LYP/ Lanl2dz calculations via cis-C# and cis-D.

EXPERIMENTAL SECTION

General Experimental Details. The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded by a Bruker Avance III (600 MHz for ^{1}H, 565 MHz for ^{19}F, and 151 MHz for ^{13}C). Chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) in $CDCl_3$ as the internal reference. The high resolution mass spectra were recorded by a Thermo Fisher Scientific EXACTIVE mass spectrometer. Quantum mechanical calculations were carried out with Gaussian 16[29] at the Research Center for Computational Science (RCCS, Okazaki, Japan). Geometry optimizations were performed and followed by the vibrational analysis to ensure the energetic stability of the optimized structures using the B3LYP/LanL2dz level of theory.[30,31]

Synthesis of the starting *gem*-difluorocyclopropanes (1 and 2)

(((3-(bromomethyl)-2,2-difluorocyclopropyl)methoxy)methyl)benzene (**1**).[17]

(1) A solution of sodium chlorodifluoroacetate (84 g, 440 mmol) in dry diglyme (100 mL) was dropwise added to a dry diglyme (150 mL) solution of (*E*)-but-2-ene-1,4-diyl diacetate (15.1 g, 88 mmol) at 180°C for over 5 h under Ar. The reaction mixture was stirred for 30 min at rt, then the reaction was quenched by the addition of water (50 mL) and extracted with hexane (4×50 mL). The combined organic layers were washed with water (3×50 mL), dried over $MgSO_4$ and concentrated to give a yellow liquid oil (24 g). To a methanol (300 mL) solution of this oil (24 g) was added potassium carbonate (24.8 g, 180 mmol) at rt and the mixture was stirred for 12 h at rt, then the reaction was quenched by the addition of water (50 mL) and evaporated to dryness. The resulting residue was extracted with ethyl acetate (3×30 mL) and the combined organic layers were dried over $MgSO_4$, evaporated and purified by silica gel (SiO_2) column chromatography (hexane/ethyl acetate=4/1) to give (3,3-difluorocyclopropane-1,2-diyl)dimethanol (CAS 1393563-23-9, 11.2 g, 81 mmol) in 92% yield.

(2) To a solution of NaH (0.90 g, 60%, 22.5 mmol) in DMF (45 mL) was added a DMF (5 mL) solution of (3,3-difluorocyclopropane-1,2-diyl)dimethanol (2.6 g, 18.8 mmol) at 0°C and the mixture was stirred at the same temperature for 0.5 h, then benzyl bromide (2.9 mL, 20.7 mmol) was dropwise added at 0°C. The resulting mixture was stirred at rt for 12 h, then the reaction was quenched by the addition of water, and extracted 3 times with ethyl acetate. The combined organic layers were washed 3 times with water, dried over $MgSO_4$, then evaporated to dryness. The resulting residue was purified by SiO_2 flash column chromatography (hexane/ethyl acetate = 20:1) to give (3-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol (**18**)[2g] (3.13 g, 13.7 mmol) in 73% yield.

(3) To a dry CH_2Cl_2 (70 mL) solution of **18** (3.0 g, 13.1 mmol) was added pyridine (10.0 mL, 126 mmol), triphenylphosphine (8.1 g, 31 mmol) and CBr_4 (5.0 g, 15 mmol) at rt and the mixture was stirred for 30 min, then the solvent was removed by evaporation. The residue was purified by SiO_2 column chromatography (hexane/ethyl acetate=9/1) to give **1** (2.82 g, 9.69 mmol) in 74% yield: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 4.57(d, 1H, J=11.9 Hz), 4.50 (d, 1H, *J*=11.9 Hz), 3.64-3.60 (m, 1H), 3.55-3.52 (m, 1H), 3.47-3.38 (m, 2H), 1.92-1.86 (m, 1H), 1.75 (sext, 1H, *J*=7.0 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.8, 128.5, 127.9, 127.7, 114.8 (t, $J_{C\text{-}F}$ = 287.9 Hz), 72.7, 65.6 (d, $J_{C\text{-}F}$ = 4.5 Hz), 30.0 (t, $J_{C\text{-}F}$ = 10.0 Hz), 28.9 (t, $J_{C\text{-}F}$= 10.8 Hz), 27.5 (d, $J_{C\text{-}F}$ = 5.5 Hz); ^{19}F NMR (565 MHz, $CDCl_3$) δ 25.16 (dd, *J*=161.8 Hz, 13.0 Hz), 22.05 (dd, *J*=161.8 Hz, 13.0 Hz). IR (neat) 3033, 2867, 1473, 1455, 1366, 1291, 1211, 1089, 1028, 980, 739, 698, 658 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{13}F_2OBrNa$ 313.0016; Found 313.0010.

(((2,2-difluoro-1-(iodomethyl)cyclopropyl)methoxy)methyl)benzene (**2**).[17]

(1) A mixture of 1,1-bis(chloromethyl)ethylene (CAS 1871-57-4, 10.0 g, 80 mmol), triethylamine (33.5 mL, 240 mmol) and acetic acid (11.4 mL, 200 mmol) was stirred at 70°C for 12 h. After being allowed to cool to rt, the mixture was diluted with water (ca. 100 mL) and extracted with ethyl acetate (3 times). The combined organic layers were washed with brine (2 times) and dried over $MgSO_4$, then evaporation and subsequent purification by silica gel flash chromatograohy (hexane/ ethyl acetate = 17:3) afforded 2-methylenepropane-1,3-diyl diacetate (10.7 g, 62. 4 mmol) in 78 % yield. To a solution of 2-methylenepropane-1,3-diyl diacetate (10.4 g, 60 mmol) in dry diglyme (100 mL) was dropwise added a solution of sodium chlorodifluoroacetate (45.7 g, 300 mmol) in dry diglyme (50 mL) at 180°C over 3 h, then the mixture was stirred at the same temperature for 1 h. The reaction was quenched by the addition of water (50 mL), then extracted with hexane (3×50 mL). The combined organic layers were washed with water (8×5 mL), dried over $MgSO_4$ and concentrated to give a yellow liquid oil (10.30 g). To a methanol (200 mL) solution of this oil (10.30 g) was added potassium carbonate (K_2CO_3) (8.3 g, 60 mmol) at rt and the mixture was stirred for 3 h at rt, then the reaction was quenched by the addition of water (30 mL) and evaporated to dryness. The resulting residue was extracted with ethyl acetate (3×20 mL) and the combined organic layers were dried over $MgSO_4$, evaporated and purified by SiO_2 column chromatography (hexane/ethyl acetate=4/1) to give (2,2-difluorocyclopropane-1,1-diyl)dimethanol (**19**)(CAS 228580-15-2) (7.73 g, 56 mmol) in 70% yield (3 steps).

(2) To a solution of NaH (0.90 g, 60%, 22.5 mmol) in DMF (45 mL) was added a DMF (5 mL) solution of the diol **19** (2.6 g, 18.8 mmol) at 0°C and the mixture was stirred at the same temperature for 0.5 h, then benzylbromide (2.9 mL, 20.7 mmol) was dropwise added at 0°C. The resulting mixture was stirred at rt for 12 h, then the reaction was quenched by the addition of water, and extracted 3 times with ethyl acetate. The combined organic layers were washed 3 times with water, dried over $MgSO_4$, then evaporated to dryness. The resulting residue was purified by SiO_2 flash column chromatography (hexane/ethyl acetate = 20:1) to give the mono-benzyl ether, (1-((benzyloxy)methyl)-2,2-difluorocyclopropyl)methanol (**20**)(2.78 g, 12.2 mmol) in 65% yield: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.29-7.38 (m, 5 H), 4.60 (d, 1 H, *J* = 12.0 Hz), 4.55 (d, 1 H, *J* = 12.0 Hz), 3.77-3.83 (m, 2 H), 3.68 (, 2 H), 2.35 (brs, OH), 1.36-1.41 (m, 1H), 1.25-1.29 (m, 1H);^{13}C NMR ($CDCl_3$, 151 MHz) δ 137.5, 128.5, 128.0, 127.7, 114.7 (t, *J* = 286 Hz), 73.3, 69.0 (d, $J_{C\text{-}F}$= 6.2 Hz), 61.9 (d, $J_{C\text{-}F}$ = 6.4 Hz), 31.8,18.9; ^{19}F NMR ($CDCl_3$, MHz) δ 24.92 (d, 1F, *J* =164 Hz), 23.00 (d, 1F, *J* = 158 Hz); IR (neat) 3400, 2932, 2871, 1472, 1455, 1192, 1092, 1006, 901, 735, 697 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{14}F_2O_2Na$ 251.0860; Found 251.0854.

(3) To a dichloromethane (CH_2Cl_2)(12 mL) solution of **20** (3.78 g, 14.6 mmol) were added triethylamine (2.2 mL, 21.9 mmol) and methylsulfonyl chloride (2.5 g, 21.9 mmol) at 0°C, then the mixture was stirred at rt for 4 h. The reaction mixture was quenched by addition of a saturated $NaHCO_3$ aqueous solution, then extracted with CH_2Cl_2 (3 times). The combined organic layers were evaporated to dryness and the residue was diluted with acetone (73 mL). To this mixture was added sodium iodide (NaI) powder (21.8 g, 146 mmol) at rt and the mixture was stirred at 60°C for 6 h. After being allowed cool to rt, the mixture was evaporated to dryness,

then washed with a saturated $NaHSO_4$ aqueous solution (3 times), and purified by SiO_2 flash column chromatography (hexane/ethyl acetate = 9/1) to furnish **2** (3.78 g, 11.2 mmol) in 77% yield (2 steps); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37-7.30 (m, 5 H), 4.58 (d, 1 H, J = 12.0 Hz), 4.53 (d, 1 H, J = 12.0 Hz), 3.76 (ddd, 1 H, J = 10.8 Hz, 4.2 Hz, 1.2 Hz), 3.59 (dd, 1 H, J = 10.8 Hz, 1.8 Hz), 3.44 (dd, 1 H, J = 10.2 Hz, 0.6 Hz,), 3.33 (dd, 1 H, J = 1.8 Hz, 0.6 Hz), 1.34 (m, 1 H), 1.21 (m, 1 H);^{13}C NMR ($CDCl_3$, 151 MHz) δ 137.8, 128.6, 127.9, 127.8, 116.4 (dd, J_{C-F} = 292.9 Hz, 4.7 Hz), 77.2 (t, J_{C-F} = 31.9 Hz), 68.3 (d, J_{C-F} = 5.4 Hz), 32.6 (t, J_{C-F} = 9.8 Hz), 22.8 (t, J_{C-F} = 45.3 Hz), 5.8; ^{19}F NMR ($CDCl_3$, MHz) δ 29.91 (ddd, 1F, J = 158.2 Hz, 11.3 Hz, 11.3 Hz), 23.02 (ddd, 1F, J = 158.2 Hz, 11.3 Hz, 11.3 Hz); IR (neat) 3031, 2863, 1455, 1375, 1212, 1093, 994, 901, 735, 696 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{13}F_2OINa$ 360.9877; Found 360.9870.

Ring-opening allylation

(((2-Allyl-3,3-difluoropent-4-en-1-yl)oxy)methyl)benzene (**8**).[16] Into a solution of allyltributylstannane (129 μL, 0.4 mmol), AIBN (8.2 mg, 0.05 mmol) and **1** (58.2 mg, 0.2 mmol) in dry benzene (2.0 mL) was bubbled nitrogen gas for 10 min, then the mixture was stirred for 12 h at 80℃. After allowing to cool to rt, the reaction mixture was concentrated under reduced pressure, then diluted with ether and stirred with an aq. solution of KF for 3 h at rt and filtered through a glass sintered filter to remove the produced filtrate. The filtrate was washed with water, dried over anhydrous $MgSO_4$, concentrated and the residue was purified by SiO_2 column chromatography (hexane/ ethyl acetate=4/1) to give **8** (45.4 mg, 0.18 mmol) in 77% yield: bp130°C, 1.5 torr (Kugelrohr); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 5.96 (m, 1H), 5.79 (m, 1H), 5.62 (dt, 1H, J = 17.3 Hz, 2.1 Hz), 5.41 (d, 1H, J = 11.0 Hz), 5.05 (dd, 2H, J = 24.0 Hz, 17.3 Hz), 4.47 (dd, 2H, J = 18.0 Hz, 12.0 Hz), 3.55 (ddd, 2H, J = 18.0 Hz, 6.0 Hz, 4.4Hz), 2.39-2.37 (m, 1H), 2.27-2.20 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.2, 135.7, 132.3 (t, J_{C-F} = 25.7 Hz), 128.4, 127.60, 127.58, 121.9 (t, J_{C-F} = 238.4 Hz), 119.2 (t, J_{C-F} = 9.7 Hz), 117.0, 73.2, 67.3 (t, J_{C-F} = 5.1 Hz), 46.1 (t, J_{C-F} = 24.2 Hz), 30.3 (t, J_{C-F} = 3.3 Hz); ^{19}F NMR (565 MHz, $CDCl_3$) δ 62.38 (dt, J = 245.1Hz, 9.7 Hz), 58.5 (dt, J=244.6 Hz, 14.0Hz); IR (neat) 3067, 3033, 2924, 2871, 1641, 1454, 1420, 1365, 1114, 1060, 698 cm^{-1}; HRMS (ESI-TOF) m/z: $[M]^+$ Calcd for $C_{15}H_{18}F_2O$ 253.1404; Found 253.1362.

(((3,3-Difluoro-2-methylenehept-6-en-1-yl)oxy)methyl)benzene (**9**). Using the same method, the diene **9** was prepared in 76% yield from **2**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36-7.31 (m, 5 H), 5.80 (1H, ddt, J = 19.8 Hz, 6.6 Hz, 3.6 Hz), 5.57 (1H, s), 5.52 (1H, s), 5.03 (1H, dd, J = 24.6 Hz, 1.8 Hz), 4.99 (1H, dd, J = 10.3 Hz, 1.8 Hz). 4.55 (2H, s), 4.10 (2H, s), 2.43-2.21 (2H, m), 2.11-2.06 (2H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 141.1, 137.8, 136.8, 128.4, 127.8, 127.6, 122.1 (t, J_{C-F} = 242 Hz), 117.1, 117.0, 116.9, 115.2, 72.5, 68.3, 68.2, 35.8 (t, J_{C-F} = 26.4 Hz), 26.5 (t, J_{C-F} = 4.8 Hz) ; ^{19}F NMR ($CDCl_3$, 565 MHz) δ 62.70; IR (neat) 3067, 2933, 2862, 1643, 1453, 1364, 1173, 1071, 1028, 915, 734, 697cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{18}F_2ONa$ 275.1223; Found 275.1218.

Synthesis of cyclopentenes (**3** and **4**).

(*RS*)-(((2,2-difluorocyclopent-3-en-1-yl)methoxy)methyl)benzene (**3**). A CH_2Cl_2 (80 mL) solution of a mixture of the Grubbs (I) catalyst (16.7 mg, 0.020 mmol) and diene **8** (50.8 mg, 0.20 mmol) was stirred at reflux conditions under Ar for 24. After being allowed to cool to rt, the mixture was evaporated to dryness and the residue was purified by SiO_2 TLC (hexane/ ethyl acetate = 4:1) to afford the cyclopentane **3** (42.6 mg, 0.19 mmol) in 95% yield: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36-7.31 (m, 5 H), 6.31 (1H, dt, J= 6.0 Hz, 2.4 Hz), 5.84 (1H, dt, J= 4.5 Hz, 2.0 Hz), 4.57 (1H, d, J= 27.0 Hz), 4.55 (1H, d, J= 27 Hz), 3.77 (1H, dd, J= 9.6 Hz, 6.0 Hz), 3.46 (1H, dd, J= 9.0 Hz, 0.6 Hz), 2.75-2.68 (2H, m), 2.34-2.33 (1H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 141.2, 141.1, 141.0, 138.2, 132.6 (t, J_{C-F}= 245 Hz), 128.5, 127.7, 127.4 (t, J_{C-F}= 27.2 Hz), 73.3, 68.3, 44.4 (dd, J_{C-F}= 22.7 Hz, 24.2 Hz), 34.3; ^{19}F NMR ($CDCl_3$, 565 MHz) δ76.43 (1F, d, J= 255 Hz), 63.78 (1F, d, J= 256 Hz) ; IR (neat) 3031, 2939, 2861, 1367, 1207, 1174, 1051, 1027, 740, 698 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{14}F_2ONa$ 247.0910; Found 247.0903.

(((5,5-Difluorocyclopent-1-en-1-yl)methoxy)methyl)benzene (**4**). By the same method using the Stewart-Grubbs catalyst, the cyclopentene **4** (42.2 mg, 0.188 mmol) was obtained in 94 % yield from the diene **9** (50.8 mg, 0.20 mmol): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.38-7.29 (5H, m), 6.26-6.25 (1H, m), 4.57 (2H, s), 4.18 (2H, s), 2.50-2.46 (2H, m), 2.42-2.35 (2H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 141.1, 137.8, 136.8, 128.4, 138.1, 137.4 (t, J_{C-F}= 9.0 Hz), 137.0 (t, J_{C-F}= 25.7 Hz), 132.9 (t, J_{C-F}= 243 Hz), 128.5, 127.8, 127.7, 72.8, 63.7, 34.2 (t, J_{C-F}= 25.6 Hz), 27.4 (t, J_{C-F}= 3.0 Hz); ^{19}F NMR ($CDCl_3$, 565 MHz) δ 73.03-72.95 (2F, m); IR (neat) 3031, 2930, 2860, 1454, 1369, 1331, 1157, 1058, 935, 698 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{14}F_2ONa$ 247.0910; Found 247.0904.

Chemo-selective epoxidation and subsequent vinylation or allylation

(*RS*)-2-((*SR*)-2-((benzyloxy)methyl)-3,3-difluoropent-4-en-1-yl)oxirane (**10**). To *m*-CPBA (280 mg, 1.13 mmol, purity 70%) in a CH_2Cl_2 (7.0 mL) solution was added a CH_2Cl_2 (2.0 mL) solution of the diene **8** (220. mg, 0.87 mmol) at 0°C, then the mixture was stirred at rt for 12 h. The mixture was washed 3 times with a 1.0 M-NaOH aqueous solution, then extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, evaporated to dryness, then purified by SiO_2 flash column chromatography (hexane/ ethyl acetate= 9:1) to afford the epoxide **10** (170 mg, 0.63 mmol) in 72% yield as an ca. 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36-7.29 (5H, m), 5.99-5.95 (1H,m), 5.63 (1H, d, J = 17.4 Hz), 5.44 (1H, d, J = 11.4 Hz), 4.50 (2H, s), 3.71-3.57 (2H, m), 3.07-3.02 (1H, m), 2.77-2.75 (1H, m), 2.47-2.46 (1H, m), 2.40-2.36 (1H, m), 1.84-1.73 (2H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 138.0, 137.9, 131.9 (t, J_{C-F} = 3.47 Hz), 131.8 (t, J_{C-F} = 3.47 Hz), 128.5, 128.4, 127.8, 127.7, 127.6, 121.6 (t, J_{C-F} = 242 Hz), 121.5 (t, J_{C-F} = 242 Hz), 119.79, 119.75, 119.73, 119.68, 119.66, 119.62, 73.3, 73.3, 67.8 (t, J_{C-F} = 5.1 Hz), 63.4 (t, J_{C-F} = 5.3 Hz), 50.9, 50.4, 47.9, 47.4, 44.5 (t, J_{C-F} = 24.9 Hz), 43.9 (t, J_{C-F} = 25.0 Hz), 29.9 (t, J_{C-F} = 3.0 Hz), 29.6 (t, J_{C-F} = 3.3 Hz) ; ^{19}F

NMR ($CDCl_3$, 565 MHz) δ 63.21 (0.5 F, d, J = 248 Hz), 62.13 (0.5F, d, J = 248 Hz), 58.02 (0.5 F, d, J = 249 Hz), 57.33 (0.5 F, d, J = 249 Hz); IR (neat) 3032, 2926, 2871, 1454, 1420, 1366, 1204, 1058, 987 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{18}F_2O_2Na$ 291.1173; Found 291.1163.

(*4RS,6RS*)-6-((benzyloxy)methyl)-7,7-difluorononа-1,8-dien-4-ol (**12**). To a THF (2.0 mL) suspension of dry Cu(I)CN (2.0 mg, 0.02 mmol) was added the epoxide **10** (53.9 mg, 0.20 mmol) under Ar and the mixture was cooled to -40°C. To this mixture was dropwise added a vinyl MgBr-THF solution (1.0 M, 0.4 mL) and stirred for 12 h at the same temperature. The reaction was quenched by the addition of a saturated NH_4Cl aqueous solution and extracted 3 times with ether. The combined organic layers were dried over $MgSO_4$, evaporated dryness, and purified by SiO_2 TLC to give the diene **12** (40.3 mg, 0.136 mmol) in 68% yield. Since **12** is a mixture of diastereomers (ca. 1:1), the NMR spectra were complicated: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36-7.29 (5H, m), 5.62 (1H, dt, J = 17.4 Hz, 4.2 Hz), 5.44 (1H, dd, J = 10.8 Hz, 5.4 Hz), 5.13-5.11 (1H, m), 5.09 (1H, d, J = 1.2 Hz), 4.52 (2H, d (germinal coupling), J = 14.4 Hz), 3.81-3.70 (2H, m), 3.53-3.46 (1H, m), 2.52-2.46 (0.5H, m), 2.41-2.36 (0.5H, m), 2.36-2.33 (0.5 H, m), 2.28-2.17 (2H, m), 1.91 (0.5H, dt, J = 14.4 Hz, 3.6 Hz), 1.71 (0.5H, dt, J= 10.7 Hz, 3.6 Hz), 1.63 (0.5H, dt, J = 10.8 Hz, 3.6 Hz), 1.52-1.47 (1H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 137.6, 137.3, 134.8, 132.0 (t, J_{C-F} = 27.2 Hz), 131.6 (t, J_{C-F} = 26.6 Hz), 128.6, 128.5, 128.0, 127.9, 127.84, 127.79, 121.9 (t, J_{C-F} = 243 Hz), 121.7 (t, J_{C-F} = 242 Hz), 120.0 (t, J_{C-F} = 9.5 Hz), 119.7 (t, J_{C-F} = 9.5 Hz), 117.8, 117.7, 73.5, 73.5, 70.3, 69.6 (t, J_{C-F} = 5.1 Hz), 68.2 (t, J_{C-F} = 4.9 Hz), 67.7, 44.7 (t, J_{C-F} = 24.2 Hz), 42.4 (t, J_{C-F} = 24.3 Hz), 42.4, 42.2, 34.9, 33.9 ; ^{19}F NMR ($CDCl_3$, 565 MHz) δ 61.28 (0.5F, dt, J= 242 Hz, 16.9 Hz), 60.18 (0.5F, dt, J = 299 Hz, 11.3 Hz), 59.19 (0.5F, dt, J = 248 Hz, 11.3 Hz), 58.86 (0.5F, dt, J = 242 Hz, 16.9 Hz); IR (neat) 3423, 2933, 2865, 1454, 1366, 1174, 1073, 1029, 920, 738 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{22}F_2O_2Na$ 319.1486, found 319.1468.

During the course of the reaction, the defluorinated allylic alkylation simultaneously took place to afford the mono-fluorinated diene **15** (18.2 mg, 0.060 mmol) in 30 % yield:

(*4RS,6RS,ZE*)-6-((benzyloxy)methyl)-7-fluoroundeca-1,7,10-trien-4-ol (**15**)(ca. 1:1 mixture of *E,Z* and diastereomers): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36-7.25 (5H, m), 5.85-5.76 (2H, m), 5.13 (2H, g, J = 14.4 Hz), 5.05 (1H, dt, J = 16.8 Hz, 3.6 Hz), 4.99 (1H, d, J = 10.2 Hz), 4.71 (0.5 H, dt, J=38.4 Hz, 7.2 Hz), 4.69 (0.5 H, dt, J = 43.2 Hz, 7.8 Hz), 4.53 (2H, d (germinal coupling), J = 4.3 Hz), 3.79-3.71 (1H, m), 3.60 (0.5 H, dd, J = 8.4 Hz, 6.0 Hz), 3.58 (0.5 H, dd, J = 11.4 Hz, 6.6 Hz), 3.01 (0.5 H, dd, J = 6.6 Hz, 4.8 Hz), 3.45 (0.5 H, dd, 7.2 Hz, 6.6 Hz), 2.84 (2H, dt, J = 7.8 Hz, 1.8 Hz), 2.76-2.68 (1H, m), 2.30-2.25 (1H, m), 2.21-2.17 (1H, m), 2.14-2.02 (1H, m), 1.72-1.67 (1H, m), 1.65-1.50 (1H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 160.7 (d, J_{C-F} = 207 Hz), 160.3 (d, J_{C-F} = 182 Hz), 159.1 (d, J_{C-F} = 257 Hz), 138.1, 137.9, 136.4, 136.3, 134.7, 134.6, 128.5, 128.4, 127.8, 127.71, 127.69, 127.67, 127.6, 118.17, 118.14, 118.07, 115.2, 114.92, 114.88, 104.8 (d, J_{CF} = 14.8 Hz), 104.6 (d, J_{C-F} = 22.9 Hz), 103.9 (d, J_{C-F} = 22.8 Hz), 73.3, 73.1, 71.4, 71.1, 70.8, 68.8, 68.5, 68.4, 42.6, 41.83, 41.75, 40.6, 40.5, 39.9, 39.7, 36.4, 36.1, 35.7, 35.6, 29.3 (d, J_{C-F} = 9.8 Hz), 27.83 (d, J_{C-F}= 3.6 Hz), 27.79 (d, J_{C-F} = 4.3 Hz); ^{19}F NMR ($CDCl_3$, 565 MHz) δ 46.15 (dd, J = 22.6 Hz, 11.3 Hz), 45.20 (dd, J = 39.5 Hz, 22.6 Hz), 42.08 (dd, J = 39.5 Hz, 28.2 Hz); IR (neat) 3429, 3077, 2917, 2862, 1704, 1454, 1100, 914, 737 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{25}FO_2Na$ 327.1737; Found 327.1728.

Synthesis of cycloheptene (5) and cyclooctane (6)

(1*RS,6RS*)-6-((benzyloxy)methyl)-5,5-difluorocyclohept-3-enol (**5**). A CH_2Cl_2 (30 mL) solution of a mixture of the Grubbs (II) catalyst (8.6 mg, 0.01 mmol) and the diene **12** (30.2 mg, 0.10 mmol) was stirred at reflux conditions under Ar for 24. After being allowed to cool to rt, the mixture was evaporated to dryness and the residue was purified by SiO_2 TLC (hexane/ ethyl acetate = 3:2) to afford the cycloheptene **5** (24.4 mg, 0.091 mmol) in 91% yield (ca. 1:1 diastereomixture): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36-7.27 (5H, m), 5.97-5.9 (1H, m), 5.84-5.74 (1H, m), 4.56 (1H, d, J = 12.0 Hz), 4.51 (1H, d, J = 12.0 Hz), 4.00 (0.5 H, dt, J = 12.0 Hz, 6.0 Hz), 3.88-3.84 (0.5 H, m), 3.82 (1H, dd, J = 9.6 Hz, 3.2 Hz), 3.79 (1H, dd, J = 9.6 Hz, 4.2 Hz), 3.5 (1H, OH, dt, J = 9.0 Hz, 6.6 Hz), 2.71-2.62 (0.5 H, m), 2.50-2.38 (2.5 H, m), 2.38-2.32 (0.5 H, m), 2.13-2.04 (0.5 H, m), 2.13-2.04 (1H, m), 1.85 (0.5H, dt, J = 13.8 Hz, 9.6 Hz); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 137.97, 137.93, 132.5 (t, J_{C-F} = 13.6 Hz), 131.9 (dd, J_{C-F} = 13.6 Hz, 9.1 Hz), 129.6 (dd, J_{C-F} = 36.2 Hz, 27.2 Hz), 129.0 (t, J_{C-F} = 31.7 Hz), 128.5, 127.86, 127.85, 127.83, 127.82, 122.0 (t, J_{C-F} = 237 Hz), 121.9 (t, J_{C-F} = 193 Hz), 73.5, 73.3, 68.5 (t, J_{C-F} = 31.7 Hz), 65.9, 43.1 (t, J_{C-F} = 24.2 Hz), 40.7 (t, J_{C-F} = 22.7 Hz), 36.2, 36.2, 36.0, 34.4 (t, J_{C-F} = 4.5 Hz) ; ^{19}F NMR ($CDCl_3$, 565 MHz) δ 73.16 (0.5F, dd, J = 267 Hz, 10.2 Hz), 72.60 (0.5F, dt, J = 267 Hz, 13.0 Hz), 66.40 (0.5F, dd, J = 268 Hz, 122.6 Hz), 63.76 (0.5F, dd, J = 266 Hz, 22.6 Hz); IR (neat) 3395, 3032, 2931, 1497, 1454, 1370, 1207, 1100, 1055, 1001, 698 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{18}F_2O_2Na$ 291.1173; Found 291.1163.

(*5RS,7RS*)-7-((benzyloxy)methyl)-8,8-difluorodeca-1,9-dien-5-ol (**13**). To a THF (2.0 mL) suspension of dry Cu(I)CN (6.6 mg, 0.065 mmol) was added the epoxide **10** (175.0 mg, 0.65 mmol) under Ar and the mixture was cooled to -40°C. To this mixture was dropwise added an allyl MgBr-Et_2O solution (0.7 M, 1.3 mL) and stirred for 12 h at the same temperature. The reaction was quenched by the addition of a saturated NH_4Cl aqueous solution and extracted 3 times with ether. The combined organic layers were dried over $MgSO_4$, evaporated to dryness, and underwent SiO_2 TLC (hexane/ ethyl acetate= 4:1) to give the diene **13** (162 mg, 0.52 mmol) in 80% yield as an ca. 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37-7.30 (5H, m), 5.93-5.79 (2H, m), 5.63 (1H, d, J = 30.7 Hz), 5.45 (1H, dd, J = 13.2 Hz, 6.0 Hz), 5.03 (1H, d, J = 17.4 Hz), 4.97 (1H, dd, J = 9.6 Hz, 4.0 Hz), 4.73 (1H, brs, OH), 4.54 (2H, s), 3.77-3.73 (1.5H, m), 3.67-3.63 (0.5 H, m), 3.48 (1H, m), 2.52-2.44 (0.5 H, m), 2.40-2.33 (0.5 H, m), 2.23-2.09 (2H, m), 1.93-1.89 (0.5 H, m), 1.73-1.68 (0.5 H, m), 1.61-1.46 (3H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 138.6, 138.5, 137.5,

137.2, 132.1 (t, J_{C-F} = 26.7 Hz), 131.6 (t, J_{C-F} = 26.5 Hz), 128.6, 128.5, 128.0, 127.9, 127.8, 121.8 (t, J_{C-F} = 243 Hz), 121.7 (t, J_{C-F} = 245 Hz), 120.1 (t, J_{C-F} = 17.5 Hz), 119.7 (t, J_{C-F} = 9.5 Hz), 114.8, 114.6, 73.6, 70.6, 69.6 (t, J_{C-F} = 5.1 Hz), 68.5 (t, J_{C-F} = 5.0 Hz), 67.9, 44.8 (t, J_{C-F} = 23.9 Hz), 42.5 (t, J_{C-F} = 24.2 Hz), 37.1, 36.7, 34.7, 30.2, 30.0; ^{19}F NMR ($CDCl_3$, 565 MHz) δ 461.16-59.91 (1F, m), 59.10-58.04 (1F, m); IR (neat) 3424, 2929, 2864, 1640, 1454, 1420, 1365, 1204, 1059, 988, 699 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{24}F_2O_2Na$ 333.1544; Found 333.2209.

(*5RS,7RS*)-7-((benzyloxy)methyl)-8-fluorotrideca-1,8,12-trien-5-ol (**16**). The mono-fluorinated diene **16** (28.3 mg, 0.085 mmol) was formed in 13 % yield *(ca. 1:1 mixture of E,Z and diastereomers)*: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37-7.29 (5H, m),5.86-5.76 (2H, m), 5.06-4.96 (4H, m), 4.67 (0.5 H, t, *J*= 7.2 Hz), 4.61 (0.5 H, t, *J* = 7.2 Hz), 4.54 (2H, s), 3.69-6.67 (1H, m), 3.57 (1H, dd, *J* = 9.6 Hz, 6.6 Hz), 3.43 (1H, dd, *J* = 9.0 Hz, 6.6 Hz), 2.79-2.70 (1H, m), 2.23-2.08 (6H, m), 1.99 (1H, OH, d, *J* = 4.8 Hz), 1.66-1.62 (1H, m), 1.59-1.47 (3H, m) ; ^{13}C NMR ($CDCl_3$, 151 MHz) δ 158.9 (d, J_{C-F} = 256 Hz), 138.9,138.1,138.0, 128.4, 127.7, 127.7, 115.0, 114.8, 106.7 (d, J_{C-F} = 15.2 Hz), 73.1, 71.6, 69.1, 40.7, 40.5, 37.2, 36.8, 33.6, 30.1, 22.9 (d, J_{C-F} = 5.1 Hz); ^{19}F NMR ($CDCl_3$, 565 MHz) δ 42.30; IR (neat) 3412, 3076, 2921, 2858, 1706, 1641, 1454, 1102, 913., 737, 698 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{29}FO_2Na$ 355.2050; Found 355.2042.

(*1RS,7RS*)-7-((benzyloxy)methyl)-6,6-difluorocyclooct-4-enol (**6**). A CH_2Cl_2 (40 mL) solution of a mixture of the Grubbs (II) catalyst (8.7 mg, 0.01 mmol) and the diene **13** (31.2 mg, 0.10 mmol) was stirred at reflux conditions under Ar for 24. After being allowed to cool to rt, the mixture was evaporated to dryness and the residue was purified by SiO_2 TLC (hexane/ ethyl acetate = 3:2) to afford the cyclooctene **6** (23.8 mg, 0.084 mmol) in 70% yield (ca. 2:3 *cis*/*trans* mixture): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36-7.27 (5H, m), 5.96-5.90 (1H, m), 5.84-5.74 (1H, m), 4.567-4.49 (2H, m),4.04-4.01 (0.4 H, m), 3.99-3.84 (0.6 H, m), 3.78 (1H, dd, *J* = 9.0 Hz, 4.2 Hz), 3.51 (1H, t, *J* = 9.0 Hz), 2.70-2.60 (0.4 H, m), 2.52-2.32 (3H, m), 2.13-2.08 (1H, m), 1.88-1.83 (0.4H, m), 1.60-1.49 (0.6H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) ; 138.0, 137.9, 132.3 (t, J_{C-F} = 12.2 Hz), 131.8 (dd, J_{C-F}= 15.1 Hz, 10.6 Hz), 129.7 (dd, J_{C-F} = 36.2 Hz, 27.5 Hz), 129.3 (t, J_{C-F} = 31.7 Hz), 128.5, 128.4, 127.79, 127.75, 127.71, 127.69, 121.9 (t, J_{CF} = 238 Hz), 121.8 (t, J_{C-F} = 204 Hz), 73.4, 73.3, 71.3, 68.6 (dd, J_{C-F} = 142 Hz, 7.4 Hz), 68.53, 68.49 (dd, J_{C-F} = 135 Hz, 4.5 Hz), 66.1, 45.4 (t, J_{C-F} = 24.0 Hz), 43.1 (t, J_{C-F} = 22.3 Hz), 40.8 (t, J_{C-F} = 23.4 Hz), 36.2 (t, J_{C-F} = 5.6 Hz), 36.1, 35.7, 34.6 (t, J_{C-F} = 3.8 Hz), 22.49, 22.48;^{19}F NMR ($CDCl_3$, 565 MHz) δ 59.58 (t, *J*= 17.0 Hz); IR (neat) 3396, 2932, 2868, 1454, 1370, 1158, 1100, 1055, 1001, 752 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{20}F_2O_2Na$ 305.1329; Found 305.1307.

(*RS*)-2-(4-((benzyloxy)methyl)-3,3-difluoropent-4-en-1-yl)oxirane (**11**). To *m*-CPBA (226mg, 1.10 mmol, purity 70%) in a CH_2Cl_2 (5.0 mL) solution was added a CH_2Cl_2 (2.0 mL) solution of the diene **9** (181 mg, 0.70 mmol) at 0°C, then the mixture was stirred at rt for 12 h. The mixture was washed 3 times with a 1.0 M-NaOH aqueous solution, then extracted 3 times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, evaporated to dryness, then purified by SiO_2 flash column chromatography (hexane/ ethyl acetate= 9:1) to afford the epoxide **11** (164 mg, 0.61 mmol) in 87% yield as an ca. 1:1 diastereo-mixture: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36-7.29 (5H, m), 5.55 (2H, d, *J* = 27.6 Hz), 4.55 (2H, s), 4.10 (2H, s), 2.96-2.93 (1H, m), 2.75 (1H, t, *J* = 4.8 Hz), 2.47 (1H, dd, *J* = 5.4 Hz, 3.0 Hz), 2.20-2.01 (1H, m), 1.82-1.76 (1H, m), 1.69-1.63 (1H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 140.9 (t, J_{C-F} = 24.7 Hz), 128.5, 127.8, 127.7, 121.9 (t, J_{C-F} = 242 Hz), 117.3 (t, J_{C-F} = 8.2 Hz), 72.5 (t, J_{C-F} = 23.4 Hz), 68.2, 51.3, 47.1, 32.9 (t, J_{C-F} = 26.7 Hz), 25.5; ^{19}F NMR ($CDCl_3$, 565 MHz) δ 62.58 (dddd, *J* = 379 Hz, 254 Hz, 17.0 Hz, 11.3 Hz); IR (neat) 2931, 2864, 1454,1175,1092, 1062, 944, 738, 639 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ Calcd for $C_{15}H_{18}F_2O_2(NH_4)$ 286.1619; Found 286.1619.

(*RS*)-8-((benzyloxy)methyl)-7,7-difluorononona-1,8-dien-4-ol (**14**). To a THF (2.0 mL) suspension of dry Cu(I)CN (2.0 mg, 0.02 mmol) was added epoxide **11** (53.7 mg, 0.20 mmol) under Ar and the mixture was cooled to -20°C. To this mixture was dropwise added a vinyl MgBr-THF solution (1.0 M, 0.40 mL) and stirred for 12 h at the same temperature. The reaction was quenched by the addition of a saturated NH_4Cl aqueous solution and extracted 3 times with ether. The combined organic layers were dried over $MgSO_4$, evaporated to dryness, and purified by SiO_2 TLC to give the diene **14** (48.6 mg, 0.164 mmol) in 82% yield: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.36-7.29 (5H, m), 5.90-5.57 (1H, m), 5.57 (2H, d, *J* = 31.8 Hz), 5.15-5.11 (2H, m), 4.55 (2H, s), 4.10 (2H, s), 3.65-3.63 (1H, m), 2.27-2.13 (3H, m), 1.67-1.58 (1H, m), 1.57-1.55 (1H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 141.0 (t, J_{C-F} = 24.3 Hz), 137.8, 128.5, 127.8, 127.7, 122.4 (t, J_{C-F} = 242 Hz), 118.4, 117.1 (t, J_{C-F} = 8.0 Hz), 72.5, 69.8, 68.2 (t, J_{C-F} = 3.0 Hz), 42.0, 32.7 (t, J_{C-F} = 27.2 Hz), 29.3 (t, J_{C-F} = 3.0 Hz); ^{19}F NMR ($CDCl_3$, 565 MHz) δ 63.94-62.56 (2F, m); IR (neat) 3412, 3069, 2933, 2865,1641, 1453, 1365, 1173, 1064, 1027, 916, 735, 697 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{22}F_2O_2Na$ 319.1486; Found 319.1483.

8-((benzyloxy)methyl)-7-fluoroundeca-1,7,10-trien-4-ol (**17**). The mono-fluorinated diene **17** (9.13 mg, 0.030 mmol) was also obtained in 15% yield as a by-product as an ca. 1:1 (*E,Z)* mixture. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37-7.28 (5H, m), 5.85-5.71 (2H, m), 5.17-5.06 (4H, m), 4.49 (1H, s), 4.45 (1H, s), 4.11 (2H, d (geminal coupling), *J* = 3.0 Hz), 3.79 (1H, s, OH), 3.69-3.60 (1H, m), 2.97-2.80 (2H, m), 2.54-2.35 (2H, m), 2.33-2.31 (1H, m), 2.26-2.23 (0.5 H, m), 2.18-2.14 (1H, m), 1.78-1.71 (1H, m), 1.65-1.59 (1H, m), 1.59-1.53 (1.5 H, m); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 159.8 (d, J_{C-F} = 125 Hz), 158.2 (d, J_{C-F}=123 Hz), 138.5, 137.9, 135.6 (d, J_{C-F} = 2.9 Hz), 135.5, 134.8, 134.4, 128.5, 128.4, 128.0,127.84, 127.81, 127.6, 118.5, 117.7, 115.8, 112.3 (d, J_{C-F} =16.1 Hz), 111.7 (d, J_{C-F}= 12.9 Hz), 72.3, 71.9, 69.6, 69.0, 67.4 (d, J_{C-F} =10.6 Hz), 64.5 (d, J_{C-F} = 9.7 Hz), 42.1, 42.0, 33.3, 33.2, 31.8 (d, J_{CF} = 5.1 Hz), 31.3 (d, J_{C-F} = 7.2 Hz), 25.1, 24.9; ^{19}F NMR ($CDCl_3$, 565 MHz) δ 56.43 (t, *J*= 17.0 Hz), 54.18 (t, *J* = 22.6 Hz); IR (neat) 3418, 3077, 2917, 2862, 1704, 1640, 1454, 1100, 914, 737, 698 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{25}FO_2Na$ 327.1638; Found 327.1730.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXXX

The ^{1}H, ^{13}C, and ^{19}F NMR spectra for all the new compounds, **3**-**6**, and **9**-**17** (PDF) and the details of the MO calculations reported in Figures 7, 8, and 9 (Tables S1, S2, S3, S4, S5, S6, S7, and S8).

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YM, HT, and TM equally contributed for the synthetic studies and SH contributed to the MO calculations. The manuscript was prepared by TN and TI.

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The authors declare no competing financial interest.

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