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The synthesis of 2,4-dienyl fluoroalkyl ketones by a tandem three-stage sequence of propargyl 2-fluoroalkylvinyl ether formation, Claisen rearrangement, and allene-to-conjugated diene isomerization

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Abstract—A tandem three stages process to a series of trifluoromethyl and halodifluoromethyl 2,4-unsaturated ketones **4a-c** is described. This process started with the preparation of 2-fluoroalkyl substituted propargyl vinyl ether **3a-d** by treatment of a mixture of individual ethyl α-per(poly)fluoroalkyl acetates **1a-d** and propargyl alcohol **2** in CH_2Cl_2 with the mixed base (Na_2CO_3/TEA) at ambient temperature. When heated in toluene at 80°C, these ethers readily underwent a tandem propargyl-allenyl Claisen rearrangement and isomerization of the resultant 3,4-dienone to give 2,4-unsaturated fluoroalkyl ketones **4a-c** (*Z*/*E* mixture). The reaction of ethyl α-per(poly)fluoroalkyl acetate **1** with 1-phenyl propargyl alcohol **5** in refluxing CH_2Cl_2 in the presence of the mixed base (Na_2CO_3/TEA) directly afforded the corresponding unsaturated fluoroalkyl ketone **6a-c** in one pot. In the presence of NaH, the reaction of ethyl 3-halo-3-fluoroalkylacrylates **8a-b** with 1,1-dimethyl propargyl alcohol **9** at −50°C to 0°C also gave the unsaturated fluoroalkyl ketones **10a-b** in one pot. The difluorovinyl propargyl ether **11** produced by reduction of 2-bromodifluoromethyl substituted propargyl vinyl ether **3b** rearranged in hot benzene to give the corresponding allene **12** bearing a *gem*-difluoromethylene group in the middle of the aliphatic chain.

1. Introduction

It is well known that incorporation of fluorines or fluorine-containing groups into organic molecules can result in profound changes in the physical, chemical and biochemical properties of the original compounds.[1] Therefore there are continuing interests in the development of efficient and general methodologies to selectively introduce fluorines and fluorine-containing groups into organic molecules for the discovery of new drugs, agrochemicals and materials.[2] Two strategies including direct fluorination and building block approach, which are complementary to each other, have been adopted to resolve this problem. In contrast to the direct fluorination method,[3] the building-block approach offers greater synthetic applicability and versatility, provided that a range of suitable building blocks are readily available.[4] In our efforts to search for novel and versatile fluorine-containing synthons for fluorinated heterocycles,[5] which might have potential biological activities, we noticed that the allenic group exists in many of the natural products[6] and the allenic compounds can serve as excellent synthetic intermediates for natural products and heterocycles.[7] Thus, we had great interest in the synthesis of fluorine-containing allenes by simple procedures.

Among methods for preparing allenic compounds,[8] the propargyl to allenyl Claisen rearrangement has been studied in detail.[9] However, because the formation of a planar cyclic transition states in this type of rearrangement is unfavorable, very high temperature flash vacuum pyrolysis and catalysis by Lewis acid or Bronsted acid are necessary in most cases for the reaction to occur.[7e,9a,10] The conventional Claisen rearrangement of fluorine-containing allyl vinyl ether has been well investigated, and it was found that fluorine-containing substituents on the six-atom backbone could have a rate accelerating effect to allow the rearrangement to proceed under very mild conditions.[11] Although successful examples of the rearrangement of the fluorinated propargyl vinyl ether have rarely been reported,[12] we anticipated that fluoroalkyl groups might have the same rate-accelerating effect in the rearrangement of fluoroalkylated propargyl

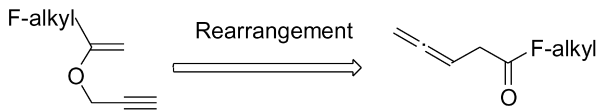

Figure 1.

Keywords: Claisen rearrangement; propargyl vinyl ether; ketone; allene; fluoroalkyl.

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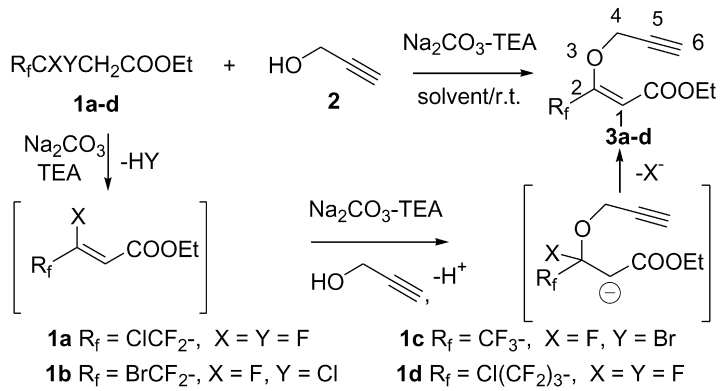
Table 1. Preparation of 2-fluoroalkyl propargyl vinyl ethers **3a-d**



Entry	Acetate	Base	Solvent	Time	Product	Yield (%)[a]
1	**1a**	Na_2CO_3/TEA	CH_2Cl_2	26 h	**3a**	65
2	**1b**	Na_2CO_3/TEA	CH_2Cl_2	24 h	**3b**	59
3	**1c**	KOH/TEA	Et_2O	4 days	**3c**	64[b]
4	**1d**	KOH/TEA	Et_2O	4 days	**3d**	65[b]

[a] Isolated yield.
[b] With Na_2CO_3–TEA as base and CH_2Cl_2 as solvent, the yield was very poor.

vinyl ethers to the corresponding allenes (Fig. 1). With the hope to synthesize fluorine-containing allenes, we prepared a series of 2-fluoroalkyl substituted propargyl vinyl ether and examined in detail their Claisen rearrangement under heating. To our delight, the reaction proceeded at unusually low temperature without catalyst. Herein, we report our finding.

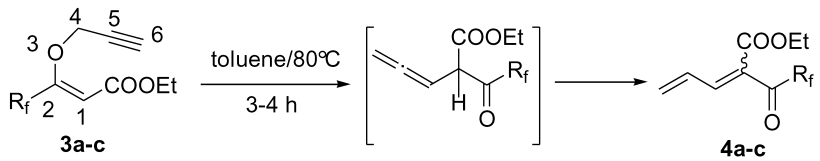
2. Results and discussion

2.1. Claisen rearrangement of 2-fluoroalkyl propargyl vinyl ethers

2.1.1. Rearrangement of 2-fluoroalkyl propargyl vinyl ethers 3a-d. By treatment of the mixture of ethyl α-per(poly)fluoroalkyl acetates **1a-d** and propargyl alcohol **2** in the solvent specified with the mixed base of Na_2CO_3 and TEA (or KOH and TEA) at room temperature, we prepared 2-fluoroalkyl propargyl vinyl ethers **3a-d** through a three-steps process in one flask (Table 1). According to the literature,[13] the double bonds of the resultant vinylethers generally have *Z* configuration, and we also found this to be the case.

It was found that the Claisen rearrangement of the propargyl vinyl ethers **3a-d** occurred readily at very mild conditions. Gentle thermolysis could promote the rearrangement, and after being heated in toluene at 80°C for only 3–4 h, the substrate was consumed completely. Evaporation of solvent and direct chromatography afforded 2,4-unsaturated fluoroalkyl ketones **4a-c** in moderate to high yield as *Z*/*E* mixtures as shown by the ^{19}F NMR spectroscopy. The yields of and the ratios of the two stereoisomeric products are shown in Table 2. It was noted that the rearrangement product of ether **3d** underwent rapid degradation, which was rationalized as the consequence of the more strong electron withdrawing nature of fluoroalkyl group (R_f=$Cl(CF_2)_3^-$) than the other fluoroalkyl groups.[14] In fact, all of the other 2,4-unsaturated fluoroalkyl ketones became a gel and decomposed as complicated mixtures after several weeks at room temperature. Ketones **4a-c** were presumably formed

Table 2. Rearrangement of propargyl vinyl ethers **3a-d**



Substrate	Product	Yield (%)[a]	Isomer ratio (*E*/*Z*)[b]
3a R_f=$ClCF_2^-$	**4a**	51	1:3.9
3b R_f=$BrCF_2^-$	**4b**	78	1:2.8
3c R_f=CF_3^-	**4c**	82	1:2.0
3d R_f=$Cl(CF_2)_3^-$	Decomposed	–	–

[a] Isolated yield.
[b] Determined by ^{19}F NMR analysis of the crude product.

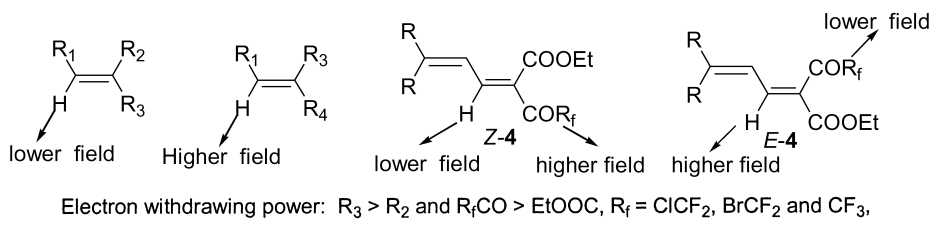


Figure 2. Determination of the double bond configuration in unsaturated ketone **4**.

by a propargyl-allenyl Claisen rearrangement of the fluoroalkylated ethers **3** followed by a moderately stereoselective double bond isomerization (Table 2). Because the α-proton in the ketoallenes is appreciably very acidic, they rapidly underwent isomerization to the thermodynamically more stable conjugated dienones as a mixture of *Z*/*E* isomers. Compared with what have been reported in the literature,[11a] it is obvious that the fluoroalkyl groups appended at 2-position of the propargyl vinyl ether systems in our study accelerate the rearrangement considerably.

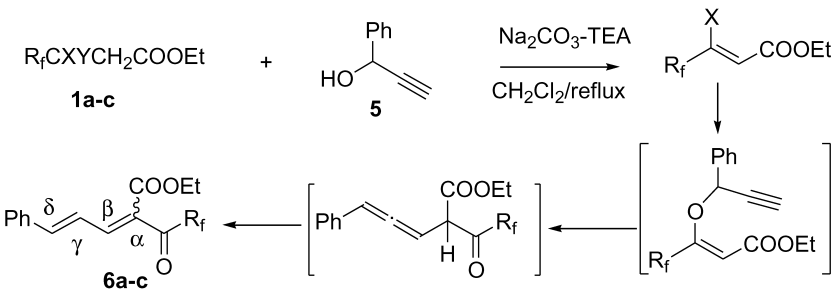
It should be pointed out that the two stereoisomeric products in **4a-c** were difficult to be separated. The rearrangement product of propargyl vinyl ether **3a** is illustrated here as an example. ^{19}F NMR spectroscopy showed two signals at −61.5 and −64.0 ppm in an integration ratio of 1:3.9. In the ^{1}H NMR spectroscopy, except the ethyl group protons, the chemical shifts of the other protons appeared in the vinylic range, without signal at the 3–4 ppm range corresponding to the proton at the α position of the two carbonyl groups. The IR spectrum exhibited no absorption at 1950 cm^{-1}, characteristic of the allene moiety, but one very strong and broad carbonyl group absorption at 1731 cm^{-1} and two medium intensive absorption of C=C bond at 1625 and 1589 cm^{-1}. All these data indicated that the product formed should be characterized as 2-ethoxycarbonyl group substituted 2,4-unsaturated fluoroalkyl ketone **4a**, as a *Z*/*E* mixture, rather than the expected terminal allenic compound (Table 2).

It was well documented by the literature that when the proton and a strong electron-withdrawing group (R_3 in Fig. 2) are in *cis* in a trisubstituted alkene, the proton signal generally appears at lower field than that in *trans* counterpart.[15] Thus, when observing the ^{1}H NMR spectra of the two-component product mixture of **4a** (also illustrated as an example), because the fluoroalkylcarbonyl group exhibits more strong electron-withdrawing ability than ethoxycarbonyl group the lowest field doublet pattern signal at 7.50 ppm should be assigned to the β-proton of *Z* stereoisomeric product, consequently the higher field doublet signal at 7.35 ppm must be attributed to β-proton of the *E* stereoisomeric product, these two signals have an integration ratio as 3.9:1. While in the ^{19}F NMR spectra of this product mixture, the higher field signal (−64.0 ppm) and the lower field signal (−61.5 ppm) also have an integration ratio as 3.9:1. Base on these two same integration ratios, the higher field ^{19}F NMR signal should arise from the *Z* isomeric product, and lower field signal from *E* isomeric product (Fig. 2).

This type of conjugated diene structure is contained in a variety of aliphatic natural products[16] and is conventionally constructed by condensation of α,β-unsaturated aldehyde with Witting reagent,[17] reduction of acetylenic compounds[18] and transition metal catalyzed coupling of vinyl halide with alkenyl-metallic compounds.[15b] Our procedure should provide a new access to this type of compounds.

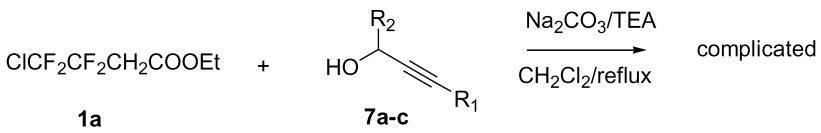
2.1.2. One-pot reaction of ethyl α-per(poly)fluoroalkyl acetate 1a-c with 1-phenyl propargyl alcohol 5 to 2,4-unsaturated fluoroalkyl ketones 6a-c. It was shown that increasing the degree of substitution on the propargyl vinyl ether systems could accelerate the rate of their Claisen

Table 3. One flask reaction of ethyl α-per(poly)fluoroalkyl acetate **1a-c** with 1-phenyl propargyl alcohol **5** to 2,4-unsaturated fluoroalkyl ketones **6a-c**



Substrate	Time (h)	Product	Yield (%)[a]	Isomer ratio (*E*/*Z*)[b]
1a R_f=$ClCF_2^-$, X=Y=F	40	**6a**	45	1:2.0
1b R_f=$BrCF_2^-$, X=F, Y=Cl	12	**6b**	38	1:1.2
1c R_f=CF_3^-, X=F, Y=Br	12	**6c**	69	1:1.2

[a] Isolated yield.
[b] Determined by ^{19}F NMR analysis of the crude product.



7a R_1= H, R_2 = Me; **7b** R_1= butyl, R_2 = H; **7c** R_1= butyl, R_2 = Me

Scheme 1.

rearrangement.[9b,19] We therefore turned our attention to 1-phenylpropargyl alcohol-derived propargyl vinyl ethers. At first, when 1-phenyl propargyl alcohol **5** was used to react with ethyl 4-chloro-3,3,4,4-tetrafluorobutanoate **1a**, no product was obtained under the same reaction condition as that described above for preparing propargyl vinyl ether **3**. However, when the individual mixtures in CH_2Cl_2 were heated under reflux for the durations specified in Table 3, the conjugated dienones **6a-c** were obtained directly in one-pot. The yields were moderate and products were mixture of geometric isomers with respect to the configuration of the α,β-double bonds (Table 3). The rearrangement appeared to be rapid, as we were unable to detect the intermediate propargyl vinyl ether by ^{19}F NMR and TLC analysis.

To determine the configuration of γ,δ-double bond, the two isomers in **6a** were partially separated through careful chromatography using CH_2Cl_2/hexane as eluent to give two slightly contaminated samples. The ^{1}H NMR spectroscopy of the individual partially purified isomer indicated that although the α,β-double bond in each case different in configuration, the γ,δ-double bond was formed exclusively in *E* configuration ($J_{\gamma,\delta}$=15 Hz in both isomers).

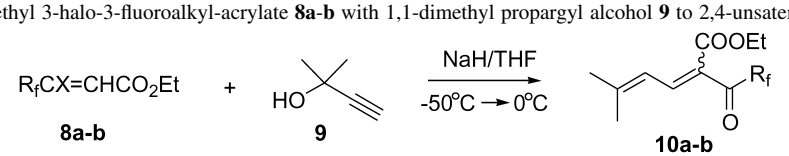
It should mentioned that the reactions of the following three substituted propargyl alcohols **7a-c** with acetate **1a** under the same conditions for 1-phenyl propargyl alcohol **5** gave complicated product mixtures from which a pure substance could not be isolated (Scheme 1).

2.1.3. One-pot reaction of ethyl 3-halo-3-fluoroalkyl-acrylate 8a-b with 1,1-dimethyl propargyl alcohol 9 to 2,4-unsaturated fluoroalkyl ketone 10a-b. With Na_2CO_3–TEA as base, the reaction of 1,1-dimethyl propargyl alcohol **9** with acetate **1a** did not afford the anticipated 2,4-unsaturated fluoroalkyl ketone apparently because of the steric hindrance of the tertiary propargyl alcohol. Consequently, we allowed **9** to react directly with ethyl 3-halo-3-fluoroalkyl-acrylates **8a-b** in THF in the presence of NaH. Upon stirring at −50°C for half an hour and warming up to 0°C over 2 h, the reaction mixture was quenched with 1N HCl. ^{19}F NMR analysis of crude product obtained after work-up showed the formation of the two isomers of the expected fluoroalkyl ketones **10a-b** and an unknown by-product whose ^{19}F NMR signal appeared at considerably lower field. The yields and isomer ratios from the ^{19}F NMR data are indicated in Table 4. Chromatography using CH_2Cl_2/hexane as eluent afforded one isomer contaminated with trace amount of the unknown by-product, while another isomer could not be separated out from this by-product.

2.2. Claisen rearrangement of 1,1-difluorovinyl propargyl ether

Reduction of the 2-bromodifluoromethyl substituted propargyl vinyl ether **3b** by treatment with zinc powder in DMF followed by quenched with aqueous NH_4Cl, or by treatment with $Na_2S_2O_4$/$NaHCO_3$ in CH_3CN/H_2O afforded the 1,1-difluorovinyl propargyl ether compound **11** in good yield, which readily underwent a propargyl-allene Claisen rearrangement at 80°C in benzene to yield the difluoromethene intermediated allenic β-ketoester **12** in nearly quantitative yield as a mixture of ketone, enol and its hydrate (Scheme 2). The absorption at 1983 and 1956 cm^{-1} in the IR spectrum confirmed the formation of the allenic moiety, and so did the triplet signals at 195.2 and 194.9 ppm in the ^{13}C NMR spectra. A double bond isomerization by fluorine atom shift being an unlikely process, the allenic moiety in **12** endures. This allenic product was rather stable and was not prone to polymerization. It was anticipated that this first reported, novel and multifunctional compound would be an excellent synthon to access *gem*-difluoromethene substituent containing compounds,[20] which has received much more attention in the development of new

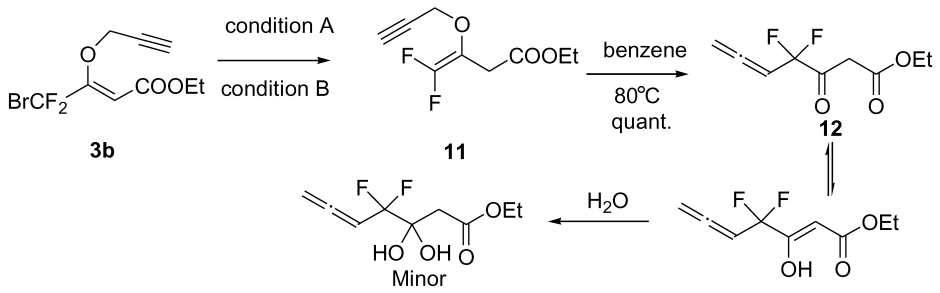
Table 4. One flask reaction of ethyl 3-halo-3-fluoroalkyl-acrylate **8a-b** with 1,1-dimethyl propargyl alcohol **9** to 2,4-unsaterated fluoroalkyl ketone **10a-b**



8a R_f = $ClCF_2$-, X = F; **8b** R_f = CF_3-, X = Cl

Substrate	Product	Yield (%)[a]	Isomer ratio (*E*/*Z*)[a]
8a R_f=$ClCF_2^-$, X=F	**10a** (*Z*)[b]	54	1:2.7
8b R_f=CF_3^-, X=Cl	**10b** (*E*)[b]	30	1:1

[a] The yields and isomer ratios were determined by ^{19}F NMR.
[b] The isomer which was isolated almost pure is indicated in parentheses.



Scheme 2. Condition A: $Na_2S_2O_4/NaHCO_3/CH_3CN/H_2O$/rt, yield=25%. Condition B: Zn/DMF/N_2/rt, yield=58%.

analogues of oxygen-containing bioactive molecules in view that the CF_2 unit is isoelectronic and isosteric to oxygen.[21] Application of this compound in synthesis of *gem*-difluorinated heterocycles is in progress and will be reported in due course.

3. Conclusions

In summary, we have investigated the thermal Claisen rearrangement of fluorine-containing propargyl vinyl ethers in detail. Through the reaction of propargyl alcohol with ethyl α-per(poly)fluoroalkyl acetate under the effect of a base, we prepared the requisite 2-fluoroalkyl substituted propargyl vinyl ethers, which at 80°C underwent a tandem propargyl-allene Claisen rearrangement and bond migration to give 2,4-unsaturated fluoroalkyl ketones as an *E*/*Z* mixture. With 1-substituted propargyl alcohols, we could obtain the fluoroalkyl ketones in an one-flask process at low temperature without isolation of the propargyl vinyl ether. A 1,1-difluorovinyl propargyl ether compound produced by reduction of bromodifluoromethyl substituted propargyl vinyl ether, could also readily undergo a propargyl-allene Claisen rearrangement at 80°C to form a novel allenic ketoester containing a CF_2-unit. From the low rearrangement temperature and short rearrangement time for some of the systems, we have come to the conclusion that the fluoroalkyl at 2-position and fluorine at 1-position of the propargyl vinyl ether system as well as increasing the substitution pattern on the α-position of the propargyl alcohol residue have the effect to facilitate the rearrangement.

4. Experimental

4.1. Instruments

NMR spectra were recorded on a Varian-360L, a Varian VXR400S or a Bruker AM-300 spectrometer with TMS as internal standards, $CFCl_3$ as external standards and $CDCl_3$ as solvent, unless otherwise stated. In ^{19}F NMR spectra, upfield shifts were quoted as negative. Coupling constants were given in Hz. For clarity, when the mixture of two stereoisomers was obtained and the NMR spectrum clearly resolved, the data of the major isomer is quoted first, then followed by the data of minor isomer in parentheses; otherwise, the absorption patterns were quoted as they appeared. Mass spectra were recorded on a HP 5989a spectrometer; accurate mass measurements were performed on a Finngan MAT instrument. IR spectra were obtained with a Perkin–Elmer 983G spectro-photometer on KBr disks and elemental analyses were performed at the author's institute. TLC was performed on silica gel Plate and column chromatography over silica gel (purchased from Qingdao Ocean Chemicals).

4.2. General method

Solvents were purified by conventional methods prior to use (toluene/P_2O_5, THF/Na wire, DMF/CaH_2), except CH_2Cl_2 and CH_3CN were used as received. Ethyl α-per(poly)fluoroalkyl acetate **1** was prepared by the sodium dithionite initiated addition of per(poly)fluoroalkylhalide to ethyl vinyl ether followed by oxidation and esterification.[5a,22] 3-Octyn-2-ol and 2-heptyn-1-ol were prepared by the addition of corresponding acetylenic magnesium reagent to paraformaldehyde and acetaldehyde according to literature procedure.[23] Ethyl 3-halo-3-fluoroalkyl-acrylates **8a**-**b** was obtained by elimination of hydrogen halide from the corresponding ethyl α-per(poly)fluoroalkyl acetate **1** by TEA and Na_2CO_3 in diethyl ether at room temperature. All the other regents were obtained from commercial sources.

4.3. Preparation of 2-fluoroalkyl propargyl vinyl ethers 3 (general procedure)

A solution of the corresponding ethyl α-per(poly)fluoroalkyl acetate **1a** (3 mmol) and propargyl alcohol **2** (4.5 mmol, 0.25 g, 0.27 mL) in 10 mL CH_2Cl_2 under ice-water bath cooling was added Na_2CO_3 (4.5 mmol, 0.38 g) in one portion and triethylamine (4.5 mmol, 0.46 g, 0.63 mL) dropwise with a syringe. After half an hour, the reaction mixture was stirred at room temperature for the time specified in Table 1. After confirmation of completion of reaction by ^{19}F NMR analysis, the reaction mixture was poured into water (20 mL). The organic layer was separated, the water layer was extracted with CH_2Cl_2 (20 mL×3), and the combined organic layers were washed once with brine (40 mL) and dried over Na_2SO_4. Upon the solvent evaporation under vacuum, the residue was purified by silica gel column chromatography with hexane/ethyl acetate as eluent and individual propargyl vinyl ethers **3** were obtained as a yellowish oil in each case.

4.3.1. Ethyl (*Z*)-4-chloro-4,4-difluoro-3-(2-propynoxy)-2-butenoate (3a). Following the general procedure above, the reaction of ethyl 4-chloro-3,3,4,4-tetrafluorobutanoate **1a** with propargyl alcohol **2** was allowed to proceed for 26 h.

Chromatography using hexane/ethyl acetate (20:1, R_f=0.3) as eluent afforded compound **3a** (466 mg, 1.95 mmol, yield 65%) as yellow oil; [Found: C, 45.23; H, 3.88. $C_9H_9ClF_2O_3$ requires C, 45.30; H, 3.80%]; ν_{max} (liquid film) 3307, 2985, 2965, 2128, 1724, 1658, 1248, 1194, 1148, 1104, 1034, 986, 791 cm^{-1}; δ_F (56.4 MHz, $CDCl_3$, $CFCl_3$) −59.8; δ_H (60 MHz, $CDCl_3$, Me_3Si) 1.28 (3H, t, J=7.0 Hz, CH_2CH_3), 2.62 (1H, s, OCH_2CCH), 4.33 (2H, q, J=7.0 Hz, CH_2CH_3), 5.09 (2H, s, OCH_2CCH), 6.90 (1H, s, =CH); m/z (EI) 239/241 (M^+, 6/2), 210/212 (7/2), 193/195 (56/18), 165/167 (6/2), 153 (98), 125 (100), 97 (35), 69 (9%).

4.3.2. Ethyl (*Z*)-4-bromo-4,4-difluoro-3-(2-propynoxy)-2-butenoate (3b). Following the general procedure above, the reaction of ethyl 4-bromo-3,3,4,4-tetrafluorobutanoate **1b** with propargyl alcohol **2** was allowed to proceed for 26 h. Chromatography using hexane/ethyl acetate (20:1, R_f=0.3) as eluent afforded compound **3b** (501 mg, 1.77 mmol, yield 59%) as yellow oil; [Found: C, 38.39; H, 3.44. $C_9H_9BrF_2O_3$ requires C, 38.19; H, 3.20%]; ν_{max} (liquid film) 3304, 2985, 2128, 1720, 1656, 1245, 1194, 1146, 1104, 1032, 972, 638 cm^{-1}; δ_F (56.4 MHz, $CDCl_3$, $CFCl_3$) −56.2; δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.32 (3H, t, J=7.2 Hz, CH_2CH_3), 2.63 (1H, t, J=2.7 Hz, OCH_2CCH), 4.23 (2H, q, J=7.2 Hz, CH_2CH_3), 5.08 (2H, d, J=2.7 Hz, OCH_2CCH), 5.88 (1H, s, =CH); m/z (EI) 283/285 (M^+, 28/27), 255/257 (22/20), 237/239 (20/19), 209/211 (20/21), 175 (13), 130 (89), 97 (100), 69 (67%).

4.3.3. Ethyl (*Z*)-4,4,4-trifluoro-3-(2-propynoxy)-2-butenoate (3c). Following the general procedure above using KOH and TEA as base instead of Na_2CO_3 and TEA (and diethyl ether as solvent instead of dichloromethene), the reaction of ethyl 3-bromo-3,4,4,4-tetrafluorobutanoate with propargyl alcohol **2** was allowed to proceed for 4 days. Chromatography using hexane/ethyl acetate (20:1, R_f=0.3) as eluent afforded compound **3c** (426 mg, 1.92 mmol, yield 64%) as yellowish oil; ν_{max} (liquid film) 3307, 2985, 2120, 1723, 1668, 1297, 1201, 1150, 1104, 1031 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −72.9; δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.32 (3H, t, J=7.2 Hz, CH_2CH_3), 2.62 (1H, t, J=2.4 Hz, OCH_2CCH), 4.23 (2H, q, J=7.2 Hz, CH_2CH_3), 5.03 (2H, d, J=2.4 Hz, OCH_2CCH), 5.94 (1H, s, =CH); m/z (EI) 222 (M^+, 21), 194 (55), 177 (100), 153 (67), 149 (20), 125 (93), 109 (5), 97 (43), 69 (36%); HRMS (EI): M^+, found 222.0512. $C_9H_9F_3O_3$ requires 222.0504.

4.3.4. Ethyl (*Z*)-6-chloro-4,4,5,5,6,6-hexafluoro-3-(2-propynoxy)-2-hexenoate (3d). Following the general procedure above using KOH and TEA as base instead of Na_2CO_3 and TEA (and diethyl ether as solvent instead of dichloromethene), the reaction of ethyl 6-chloro-3,3,4,4,5,5,6,6-octafluorohexanoate **1d** with propargyl alcohol **2** was allowed to proceed for 4 days. Chromatography using hexane/ethyl acetate (20:1, R_f=0.3) as eluent afforded **3d** (659 mg, 1.95 mmol, yield 65%) as yellow oil; [Found: C, 39.23; H, 2.80. $C_{11}H_9ClF_6O_3$ requires C, 39.02; H, 2.68%]; ν_{max} (liquid film) 3313, 2987, 2130, 1723, 1661, 1294, 1191, 1128, 1021, 841, 778 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −120.5 (2F, s, $ClCF_2CF_2CF_2$), −115.9 (2F, s, $ClCF_2CF_2CF_2$), −68.0 (2F, s, $ClCF_2CF_2CF_2$); δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.33 (3H, t, J=7.2 Hz, CH_2CH_3), 2.63 (1H, t, J=2.4 Hz, OCH_2CCH), 4.24 (q, 2H, J=7.2 Hz, CH_2CH_3), 5.05 (2H, d, J=2.4 Hz, OCH_2CCH) 5.92 (1H, s, =CH); m/z (EI) 338 (M^+, 1), 309 (1), 293/295 (46/16), 282/284 (17/5), 265/267 (50/17), 255/257 (10/4), 153 (9), 69 (100%).

4.4. Claisen rearrangement of propargyl vinyl ether 3a-c

A dilute solution of the appropriate propargyl vinyl ether **3** in 40–50 mL toluene was heated at 80°C for 4 h under nitrogen atmosphere. After evaporation of solvent under vacuum, the resulting residue was analyzed by ^{19}F NMR to determine the *E*/*Z* ratio, and cleaned up by chromatography (hexane/ethyl acetate) to give the unsaturated fluoroalkyl ketone **4** as an *E*/*Z* mixture in oil form.

4.4.1. Ethyl 2-chlorodifluoroacetyl-2,4-hexadienonate (4a). Using the general procedure above, **3a** (428 mg) afforded **4a** (217 mg, yield 51%) as *E*/*Z* (1:3.9) mixture in the form of a yellow oil; [Found: C, 45.18; H, 3.77. $C_9H_9ClF_2O_3$ requires C, 45.30; H, 3.80%]; ν_{max} (liquid film) 2986, 1731, 1625, 1589, 1242, 1190, 1150, 1096, 775 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −64.0 (*Z*) [−61.5 (*E*)]; δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.28–1.37 (3H, m, CH_2CH_3), 4.26–4.35 (2H, m, CH_2CH_3), 5.79–5.99 (2H, m, CH_2=CH–CH=), 6.51 (1H, ddd, J=16.7, 11.7, 9.9 Hz, CH_2=CH–CH=) (*Z*) [7.03 (1H, ddd, J=16.8, 11.3, 9.9 Hz, CH_2=CH–CH=) (*E*)], 7.50 (1H, d, J=11.7 Hz, CH_2=CH–CH=) (*Z*) [7.35 (1H, d, J=11.3 Hz, CH_2=CH–CH=) (*E*)]; m/z (EI) 238/240 (M^+, 3/1), 193/195 (25/9), 153 (97), 125 (100), 97 (38), 85/87 (21/9), 53 (41%).

4.4.2. Ethyl 2-bromodifluoroacetyl-2,4-hexadienonate (4b). Using the general procedure above, **3b** (244 mg) afforded **4b** (190 mg, yield 78%) in a *E*/*Z* (1:2.8) mixture in the form of a yellow oil; [Found: C, 38.40; H, 3.43. $C_9H_9BrF_2O_3$ requires C, 38.19; H, 3.20%]; ν_{max} (liquid film) 2985, 1729, 1623, 1589, 1240, 1188, 1151, 1091, 1025 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −60.3 (*Z*), [−58.4 (*E*)]; δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.28–1.35 (3H, m, CH_2CH_3), 4.26–4.35 (2H, m, CH_2CH_3), 5.81–5.99 (2H, m, CH_2=CH–CH=), 6.54 (1H, dddd, J=16.7, 11.4, 9.9, 1.3 Hz, CH_2=CH–CH=) (*Z*) [7.04 (1H, dddd, J=16.7, 11.1, 10.0, 1.1 Hz, CH_2=CH–CH=) (*E*), 7.49 (1H, d, J=11.4 Hz, CH_2=CH–CH=) (*Z*) [7.36 (1H, d, J=11.1 Hz, CH_2=CH–CH=) (*E*); m/z (EI) 282/284 (M^+, 3/3), 254/256 (1/1), 237/239 (10/11), 203 (3), 175 (10), 153 (100), 125 (69), 97 (23), 81 (10), 69 (7), 52 (18%).

4.4.3. Ethyl 2-trifluoroacetyl-2,4-hexadienonate (4c). Using the general procedure above, **3c** (372 mg) afforded **4c** (305 mg, yield 82%) as *E*/*Z* (1:2.0) mixture in the form of a yellow oil; ν_{max} (liquid film) 2987, 1716, 1620, 1581, 1202, 1127, 1021 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −75.4 (*Z*), [−72.4 (*E*)]; δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.19–1.43 (3H, m, CH_2CH_3), 4.21–4.39 (2H, m, CH_2CH_3), 5.82–6.02 (2H, m, CH_2=CH–CH=), 6.55 (1H, ddd, J=16.8, 11.8, 9.9 Hz, CH_2=CH–CH=) (*Z*) [7.03 (1H, ddd, J=16.8, 11.8, 9.9 Hz, CH_2=CH–CH=) (*E*)], 7.52 (1H, d, J=11.8 Hz, CH_2=CH–CH=) (*Z*) [7.37 (1H, d, J=11.8 Hz, CH_2=CH–CH=) (*E*)]; m/z (EI) 222 (M^+, 15), 194 (37), 177 (65), 153 (52), 125 (90), 97 (63), 81 (32), 69

(100) and 53 (70%); HRMS (EI): M^+, found 222.0520. $C_9H_9F_3O_3$ requires 222.0504.

4.5. One pot reaction of ethyl α-per(poly)fluoroalkyl acetates 1a-c with 1-phenyl propargyl alcohol 5 to unsaturated fluoroalkyl ketones 6a-c

A solution of the corresponding ethyl α-per(poly)fluoroalkyl acetate **1** (1.5 mmol) and 1-phenyl propargyl alcohol **5** (1.8 mmol, 0.24 g, 0.21 mL) in 10 mL CH_2Cl_2 cooled in an ice-water bath was added Na_2CO_3 (3 mmol, 0.33 g) in one portion and triethylamine (3 mmol, 0.30 g, 0.42 mL) dropwise with a syringe. After half an hour, the reaction mixture was held under reflux for the time specified in Table 2 until completion of reaction by TLC analysis. The reaction mixture was poured into water (20 mL). The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (20 mL×3), and the combined organic layers were washed once with brine (40 mL) and dried over Na_2SO_4. Upon solvent evaporation under vacuum, the residue was analyzed by ^{19}F NMR to determine the *E*/*Z* ratio, and then clean up by chromatography using hexane/ethyl acetate as eluent gave the unsaturated fluoroalkyl ketone **6** as oil in a *E*/*Z* mixture form.

4.5.1. Ethyl (2*E*/*Z*, 4*E*)-2-chlorodifluoroacetyl-5-phenyl-2,4-hexadienonate (6a). Following the general procedure above, a mixture of **1a** and 1-phenyl propargyl alcohol **5** was held under reflux for 40 h. The crude product had an *E*/*Z* ratio of 1:2. Chromatography afforded **6a** (210 mg, 0.67 mmol, yield 45%) an *E*/*Z* mixture in the form of a yellow oil; [Found: C, 57.31; H, 4.09. $C_{15}H_{13}ClF_2O_3$ requires C, 57.25; H, 4.16%]; ν_{max} (liquid film) 2985, 1724, 1607, 1578, 1209, 1154, 752 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −63.5 (*Z*) [−61.1 (*E*)]; δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.28–1.46 (3H, m, CH_2CH_3), 4.31–4.45 (2H, m, CH_2CH_3), 7.01–7.76 (8H, m, all the other protons); *m*/*z* (EI) 314/316 (M^+, 13/4), 279 (1), 269/271 (9/2), 229 (46), 201 (7), 183 (31), 155 (15), 128 (34), 115 (100), 102 (9), 77 (6%). When the *E*/*Z* mixture was further chromatographed with hexane/CH_2Cl_2 (2.5:1) as eluent, the two stereoisomers were separated from each other with slight cross-contamination. *Z*-**6a**: δ_F (282 MHz, [D_6] acetone, $CFCl_3$) −64.0; δ_H (300 MHz, [D_6] acetone, Me_3Si) 1.31 (3H, t, *J*=7.1 Hz, CH_2CH_3), 4.31 (2H, q, *J*=7.1 Hz, CH_2CH_3), 7.06 (1H, dd, *J*=15.3, 11.9 Hz, PhCH=CH–CH=), 7.42–7.69 (6H, m, Ph and PhCH=CH–CH=), 7.82 (1H, d, *J*=11.9 Hz, PhCH=CH–CH=). *E*-**6a**: δ_F (282 MHz, [D_6] acetone, $CFCl_3$) −61.8; δ_H (300 MHz, [D_6] acetone, Me_3Si) 0.97 (3H, t, *J*=5.5 Hz, CH_2CH_3), 4.03 (2H, q, *J*=5.5 Hz, CH_2CH_3), 6.41 (1H, d, *J*=15.4 Hz, PhCH=CH–CH=), 6.93–7.16 (5H, m, Ph), 7.28 (1H, d, *J*=11.5 Hz, PhCH=CH–CH=), 7.67 (1H, dd, *J*=15.4, 11.5 Hz, PhCH=CH–CH=).

4.5.2. Ethyl (2*E*/*Z*, 4*E*)-2-bromodifluoroacetyl-5-phenyl-2,4-hexadienonate (6b). Following the general procedure above, a mixture of **1b** (3 mmol, 801 mg) and 1-phenyl propargyl alcohol **5** (3.6 mmol, 0.48 g, 0.42 mL) was held under reflux for 12 h. The crude product had an *E*/*Z* ratio of 1:1.2. Chromatography afforded **6b** (412 mg, 1.15 mmol, yield 38%) as an *E*/*Z* mixture in the form of a yellow oil; [Found: C, 50.39; H, 3.66. $C_{15}H_{13}BrF_2O_3$ requires C, 50.16; H, 3.65]; ν_{max} (liquid film) 2984, 1723, 1608, 1575, 1281, 1236, 1163, 751, 689 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −59.8 (*Z*) [−57.8 (*E*)]; δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.31–1.47 (3H, m, CH_2CH_3), 4.29–4.43 (2H, m, CH_2CH_3), 6.99 (1H, dd, *J*=15.3, 11.6 Hz, PhCH=CH–CH=) (*Z*), 7.17–7.72 (ca. 8H, m); *m*/*z* (EI) 358/360 (M^+, 20/19), 313/315 (8/8), 279 (6), 229 (100), 201 (13), 155 (34), 128 (79), 115 (100), 77 (14%).

4.5.3. Ethyl (2*E*/*Z*,4*E*)-2-trifluoroacetyl-5-phenyl-2,4-hexadienonate (6c). Following the general procedure above, a mixture of **1c** (3 mmol, 801 mg) and 1-phenyl propargyl alcohol **5** (3.6 mmol, 0.48 g, 0.42 mL) was held under reflux for 12 h. The crude product had an *E*/*Z* ratio of 1:1.2. Chromatography afforded **6c** (619 mg, 2.1 mmol, yield 69%) as a *E*/*Z* mixture in the form of a yellow oil; [Found: C, 60.32; H, 4.39. $C_{15}H_{13}F_3O_3$ requires C, 60.41; H, 4.39]; ν_{max} (liquid film) 2986, 1708, 1607, 1579, 1290, 1248, 1208, 1157, 1085, 751, 688 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −74.7 (*Z*) [−72.2 (*E*)]; δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.31–1.41 (3H, m, CH_2CH_3), 4.29–4.42 (2H, m, CH_2CH_3), 7.14 (1H, dd, *J*=15.3, 11.2 Hz, PhCH=CH–CH=) (*Z*), 7.08–7.58 (ca. 7H, m), 7.74 (1H, d, *J*=11.2 Hz, PhCH=CH–CH=) (*Z*); *m*/*z* (EI) 298 (M^+, 71), 278 (17), 269 (9), 253 (100), 229 (19), 201 (8), 183 (10), 155 (17), 128 (22), 115 (28), 69 (3%).

4.6. One pot reaction of ethyl 3-halo-3-fluoroalkyl-acrylates 8a-b with 1,1-dimethyl propargyl alcohol 9 to unsaturated fluoroalkyl ketones 10a-b

To a suspension of 60% NaH (10 mmol, 400 mg) in 5 mL anhydrous THF at −50°C was added a solution of 1,1-dimethyl propargyl alcohol **9** (3 mmol, 0.25 g, 0.3 mL) in 5 mL THF dropwise. The mixture was then stirred for half an hour at −50°C before a solution of the ethyl 3-halo-3-fluoroalkyl-acrylate **8** (2 mmol) in 5 mL THF was added dropwise over half an hour. The reaction mixture was allowed to warm up to 0°C over 2 h before quenching with 1N HCl (5 mL) under cooling by an ice-salt bath. The crude mixture was extracted with ether (20 mL×3) and the ether solution was washed with brine (30 mL) and dried (Na_2SO_4). After evaporation of solvent under vacuum, the residue was analyzed by ^{19}F NMR to determine the *E*/*Z* ratio and yield. Subsequent chromatography with hexane/CH_2Cl_2 as eluent on a silica gel column afforded one isomer which was relatively pure, but still contaminated by a minor unknown by-product whose ^{19}F NMR signal appeared at considerably lower field. Another isomer was mixed with the main by-product, which was hard to be separated out.

4.6.1. Ethyl (2*Z*)-2-chlorodifluoroacetyl-5-methyl-2,4-heptadienonate (*Z*-10a). Following the general procedure above, for the reaction of ethyl 4-chloro-3,4,4-trifluoro-2-butenoate **8a** (2 mmol, 405 mg) and 1,1-dimethyl propargyl alcohol **9**, chromatography with haxene/CH_2Cl_2 (2.5:1) as eluent afforded essentially pure *Z*-**10a** as a yellowish oil (the *E* isomer could not be separated from the unknown by-product) 2984, 2938, 1727, 1627, 1589, 1303, 1247, 1154, 1103, 772 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −63.7; δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.31 (3H, t, *J*=7.1 Hz, CH_2CH_3),

1.97 (3H, s, Me_2C═CH–CH═), 2.01 (3H, s, Me_2C═CH–CH═), 4.33 (2H, q, J=7.1 Hz, CH_2CH_3), 6.12 (1H, d, J=12.5 Hz, Me_2C═CH–CH═), 7.84 (1H, d, J=12.5 Hz, Me_2C═CH–CH═); m/z (EI) 266/268 (M^+, 4/1), 251/253 (24/8), 231 (1), 221/223 (18/10), 203 (2), 181 (6), 135 (10), 107 (20), 79 (34%); HRMS (EI): M^+, found 266.0480. $C_{11}H_{13}ClF_2O_3$ requires 266.0521.

4.6.2. Ethyl (2*E*)-2-trifluoroacetyl-5-methyl-2,4-heptadienonate (*E*-10b). Following the general procedure above for the reaction of ethyl 3-chloro-4,4,4-trifluoro-2-butenoate **8b** (2 mmol, 405 mg) and 1,1-dimethyl propargyl alcohol **9**, chromatography with haxene/CH_2Cl_2 (2:1) as eluent afforded essentially *E*-**10b** as a yellowish oil (the *Z* isomer could not be separated from the unknown by-product); ν_{max} (liquid film) 2985, 2941, 1731, 1708, 1617, 1574, 1383, 1210, 1162, 724 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −72.6; δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.35 (3H, t, J=7.2 Hz, CH_2CH_3), 2.04 (6H, s, Me_2C═CH–CH═), 4.34 (2H, q, J=7.2 Hz, CH_2CH_3), 6.60 (1H, d, J=12.3 Hz, Me_2C═CH–CH═), 7.77 (1H, d, J=12.3 Hz, Me_2C═CH–CH═); m/z (EI) 250 (M^+, 1), 235 (3), 219 (1), 207 (3), 178 (18), 135 (13), 108 (3), 69 (38), 43 (100%); HRMS (EI): M^+, found 250.0819. $C_{11}H_{13}F_3O_3$ requires 250.0817.

4.7. Preparation of difluorovinyl propargyl ether 11 by reduction of 2-bromo-difluoromethyl substituted propargyl vinyl ether 3b

4.7.1. Ethyl 4,4-difluoro-3-(2-propynoxy)-3-butenoate (11). *Method A*. To a solution of 2-bromodifluoromethyl propargyl vinyl ether **3b** (2.1 mmol, 600 mg) in CH_3CN (8.4 mL) and H_2O (6.3 mL), was added the mixture of $Na_2S_2O_4$ (2.4 mmol, 420 mg) and $NaHCO_3$ (2.5 mmol, 210 mg) at 10–15°C portionwisely, then the mixture was stirred at the same temperature for 4 h. After TLC analysis showed reaction completed, 10 mL H_2O was added to the mixture, then the resulted mixture was extracted with ether (20 mL×3). The combined ether solution was washed with brine (30 mL) and dried (Na_2SO_4). After evaporation of the solvent under vacuum, the resulted residue was chromatographed on silica gel column using hexane/ethyl acetate (15:1, R_f=0.3) as eluent to give the difluorovinyl propargyl ether **11** (100 mg, 0.49 mmol, yield 25%) as light bright liquid; ν_{max} (liquid film) 3294, 2986, 2940, 2124, 1769, 1739, 1287, 1097, 1029 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −111.3 (1F, d, J=66.6 Hz), −98.6 (1F, d, J=66.6 Hz); δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.32 (3H, t, J=7.2 Hz, CH_2CH_3), 2.56 (1H, t, J=2.4 Hz, OCH_2CCH), 3.24 (2H, dd, J=3.9, 2.4 Hz, CH_2CO_2Et), 4.22 (2H, q, J=7.2 Hz, CH_2CH_3), 4.51 (2H, d, J=2.4 Hz, OCH_2CCH); m/z (EI) 204 (M^+, 1), 176 (1), 165 (31), 159 (8), 137 (100), 131 (29), 120 (14), 93 (8%). HRMS (EI): M^+, found 204.0608. $C_9H_{10}F_2O_3$ requires 204.0598.

Method B. To the solution of **3b** (1.35 mmol, 381 mg) in DMF (8 mL) was added activated zinc powder (2.0 mmol, 131 mg) at room temperature under nitrogen atmosphere. The reaction completed through observation of TLC analysis after half an hour reaction, and then was quenched with saturated NH_4Cl solution (8 mL). Through the same deal-up and separation procedure as in the method A the difluorovinyl propargyl ether **11** (161 mg, 0.79 mmol, 58% yield) was obtained.

4.8. Rearrangement of the difluorovinyl propargyl ether 11 to the allenic β-ketoester 12

4.8.1. Ethyl 4,4-difluoro-3-oxo-5,6-heptadienoate (12). A solution of difluorovinyl propargyl ether **11** (320 mg) in 50 mL benzene was heated at 80°C for 4 h under nitrogen atmosphere to complete the conversion of the ether **11** (shown by TLC analysis). Then the mixture was then concentrated to dryness in vacuum, the resulted residue was pure enough for spectra analysis, but further chromatography using hexane/ethyl acetate (5:1, R_f=0.2) as eluent afforded the allenic β-ketoester **12** as brown oil in nearly quantitative yield; [Found: C, 52.63; H, 5.15. $C_9H_{10}F_2O_3$ require C, 52.95; H, 4.94]; ν_{max} (liquid film) 2987, 1983, 1956, 1761, 1738, 1667, 1329, 1215, 1072, 1024, 861 cm^{-1}; δ_F (282 MHz, $CDCl_3$, $CFCl_3$) −100.6 (enolized), −101.7 (nonenolized) and −111.2 (hydrated), integration ratio=2.6:3.2: trace; δ_H (300 MHz, $CDCl_3$, Me_3Si) 1.27–1.35 (3H, m, CH_2CH_3), 2.80 (s, hydrated CH_2CO_2Et), 3.71 (s, nonenolized CH_2CO_2Et), 4.20–4.31 (2H, m, CH_2CH_3), 4.61 (s, Hydrated hydroxyl proton), 5.15–5.26 (2H, m, allenic proton), 5.50–5.56 (m, allenic proton and enolized vinyl proton), 12.0 (br.s, enolized hydroxyl proton); δ_c (100.6 MHz, $CDCl_3$, Me_3Si) 29.6 (s), 47.1 (s), 47.8 (s), 63.2 (t, J=31.6 Hz), 66.1 (t, J=1.6 Hz), 67.0 (s), 67.4 (t, J=1.7 Hz), 72.2 (s), 74.3 (t, J=31.4 Hz), 99.9 (t, J=275.8 Hz), 100.0 (t, J=244.0 Hz), 151.5 (s), 152.7 (t, J=31.3 Hz), 158.2 (s), 177.7 (t, J=33.9 Hz), 194.9 (t, J=8.8 Hz), 195.2 (t, J=8.8 Hz); m/z (EI) 204 (M^+, 2), 185 (10), 159 (27), 130 (7), 117 (31), 155 (36), 89 (73), 69 (100%).

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