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Synthesis of *gem*-difluoromethylenated analogues of anamarine

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ABSTRACT

Practical synthesis of two *gem*-difluoromethylenated analogues of anamarine was described. The important synthetic steps included the preparation of the key intermediates **20**–**21** through the indium-mediated *gem*-difluoropropargylation of aldehyde **18** with the fluorine-containing building block **19** and efficient construction of α,β-unsaturated-δ-lactone scaffold via BAIB/TEMPO procedure.

1. Introduction

Isolated from the flowers and leaves of a Peruvian *Hyptis* species by Valverde and co-workers in 1979 [1,2], (+)-anamarine **1** has a structure featuring *R*-configuration in the 5,6-dihydro-2H-pyran-2-one ring and L-gluco arrangement in the C6-side chain (Fig. 1). In the past years, (+)-anamarine **1** along with other members of this α,β-unsaturated lactone class of natural products [3,4] including spicigerolide **2**, hyptolide **3** and synrotolide **4** attracted considerably more attention from organic chemist, medicinal chemist and biological chemist in view of the fact that all of these compounds possessed a range of pharmacological properties, such as cytotoxicity against human tumor cells, antimicrobial or antifungal activities [5,6]. Thus, pharmacological properties of these types make these compounds and their analogues interesting synthetic goals.

So far, several groups have reported the synthesis of the anamarine and its *epi*-isomers based on two main synthetic routes (Scheme 1). One route involved the Wittig reaction between pre-modified phosphonium salt **5** and protected aldehyde **6** to afford the *Z*-olefin **7**, which was converted to anamarine or its *epi*-isomers via a series of transformations of protecting groups and *hν*-irradiated isomerization of *Z*-double bond [7–10]. Another route utilized the ring-closing metathesis (RCM) reaction of triene compounds **8** to construct 5,6-dihydro-2H-pyran-2-one ring [11–14]. Due to inconvenience of *hν* irradiation reaction and expensive Grubbs catalyst for RCM reaction, in our opinion new synthetic method for anamarine and its analogues should be developed. Additionally, structure-activity relationship (SAR) has demonstrated that the α,β-unsaturated-δ-lactone scaffold of anamarine and its *epi*-isomers played a key role for their bioactivities because such structure unit was an excellent potential Michael acceptor for nucleophilic amino acid residues of the natural receptors [15–17]. In view of the similarity in size between fluorine atom and hydrogen atom and the strong electron-withdrawing property of *gem*-difluoromethylene group (CF_2) [18,19], we intended to introduce a CF_2 group to α,β-unsaturated-δ-lactone of anamarine at the γ-position. We envisioned that the resultant γ,γ-difluoromethylenylated-α,β-unsaturated anamarine analogues would be much more electron deficient, making it a better candidate to enhance the reactivity of the conjugated double bond as an acceptor with minimum steric change. Herein we would like to describe the total synthesis of *gem*-difluoromethylenated analogues of anamarine using novel synthetic strategy.

2. Results and discussion

Our retrosynthetic analysis was outlined in Scheme 2. We proposed that γ,γ-*gem*-difluoromethylenated anamarine analogues **9**–**10** could be afforded from the intermediate **A** by means of oxidation–cyclization procedure, which was developed by Forsyth group [20] and have been successfully utilized to synthesize a series of *gem*-difluoromethylenated α,β-unsaturated-δ-lactone derivatives in our group [21,22]. Homopropargylation of aldehyde **C** with fluorine-containing building block **B** would yield compound **A**. Aldehyde **C** would be prepared via reduction of ester **D** and

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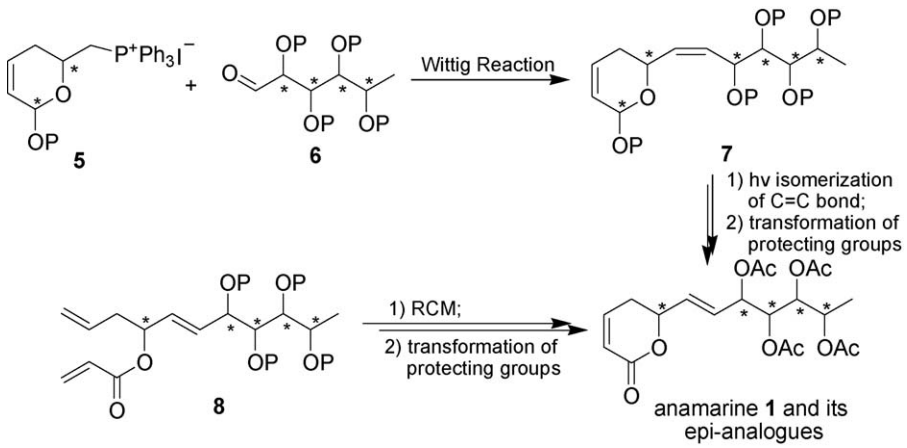


Scheme 1. Reported synthetic strategy for anamarine and its epi-analogues.

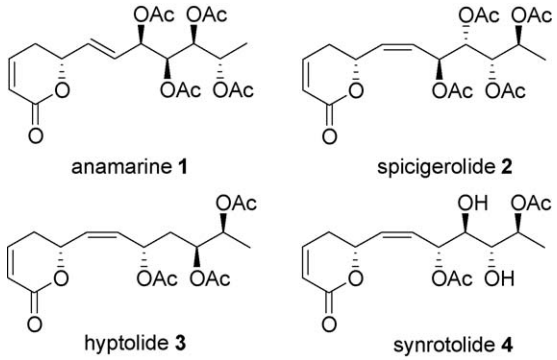


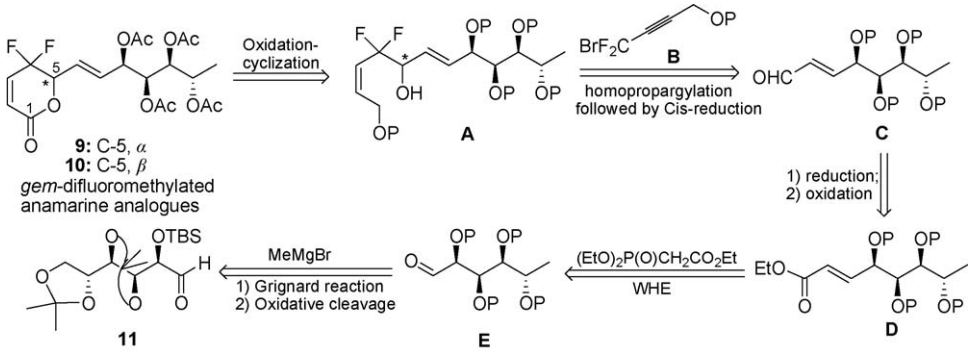
Fig. 1. The anamarine-type α,β-unsaturated lactones.

subsequent oxidation. The ester **D** could be obtained by means of WHE reaction between $(EtO)_2P(O)CH_2CO_2Et$ and aldehyde **E**, which, in turn, would be produced from readily prepared aldehyde **11** via Grigard reaction followed by oxidative cleavage.

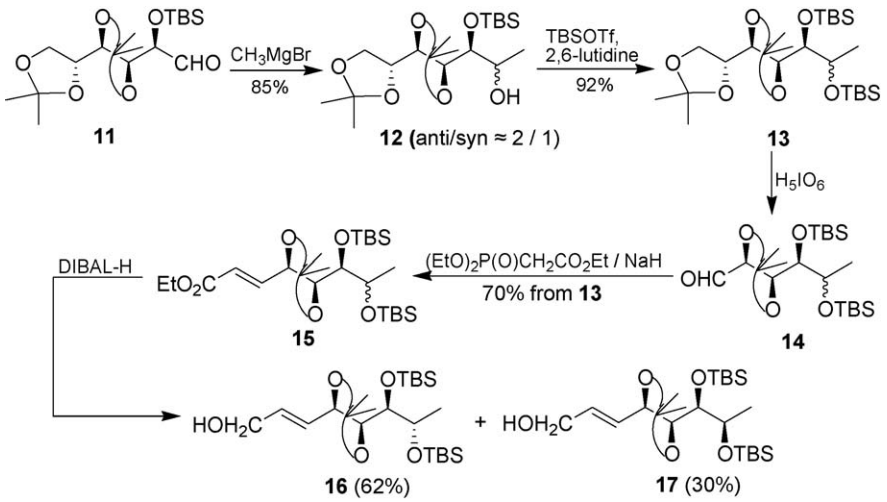
Based on our retrosynthetic analysis, our synthesis embarked from the aldehyde **11** (Scheme 3), which was prepared from commercially available D-glucono-δ-lactone in 3 steps according to reported procedure [23,24]. The nucleophilic addition of aldehyde **11** with MeMgBr gave alcohol **12** as a mixture of two diastereomers with *anti*-isomer as the major product [25] and two diastereoisomers could not be separated by flash chromatography. Silylation of alcohol **12** with TBSOTf/2,6-lutidine produced the compound **13** in good yield. When **13** was treated with periodic acid hydrate (H_5IO_6) [26], the selective hydrolysis of terminal isopropylidene acetal in **13** and *in situ* glycol cleavage proceeded smoothly in one pot to give aldehyde **14**, which was used in next step without purification. Then, treatment of **14** with ethyl 2-(diethoxyphosphoryl)acetate in the presence of NaH afforded ester **15** in 70% yields over two steps. Reduction of ester **15** with DIBAL-H smoothly provided the alcohols **16** and **17** in good yield. Fortunately, two diastereomers **16** and **17** could be readily separated by silica gel chromatography.

Oxidation of the alcohol **16** with Dess-Martin oxidant gave the desired aldehyde **18** in almost quantitative yield (Scheme 4). At this point, we focused our efforts on the homopropargylation of aldehyde **18** with fluorine-containing building block **19** [21]. Initially, the reaction conditions developed by Hammond group [27] were used. However, we found that treatment of aldehyde **18** with (4-bromo-4,4-difluorobut-2-ynyloxy)(tert-butyl)dimethylsilane **19** with THF–H_2O (1:4, v/v) as solvent in the presence of indium at room temperature gave the expected product **20** in low yield along with its diastereomer **21** (*anti*/*syn* = 1.6:1, determined by ^{19}F NMR before column chromatography). Diastereoisomer **20** and **21** could be separated by silica gel chromatography. After further optimization, we were pleased to find that substitution of DMF–H_2O (2:1, v/v) for THF–H_2O (1:4, v/v) as solvent would significantly improve the yield of alcohols **20**–**21** and *anti*-alcohol **20** was still the major diastereoisomer [28,29].

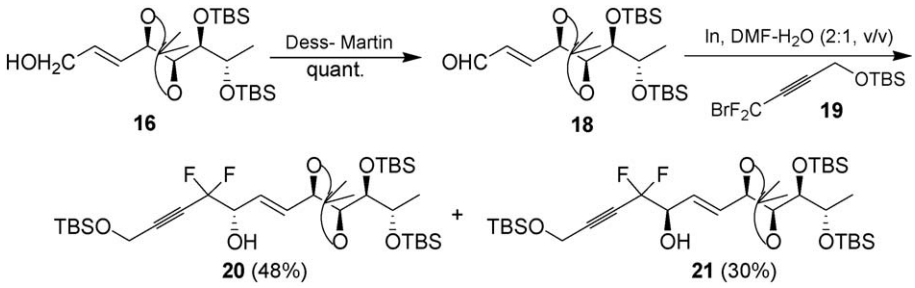
With the key intermediates **20**–**21** in hand, the synthesis of the target molecules were performed as outlined in Scheme 5. Initial attempts to hydrogenate the triple bond of in **20** and **21** to the *cis* double bond using Lindlar catalyst/quinoline system failed. Fortunately, the selective hydrogenation progressed well utilizing Pd–$BaSO_4$/–quinoline system [30] and compound **22** and **23** was provided in 96% and 93% yields, respectively. Selective deprotection of the primary TBS group in **22** and **23** with D-camphor-10-



Scheme 2. Retrosynthetic analysis of γ,γ-*gem*-difluoromethylenated anamarine analogues **9**–**10**.

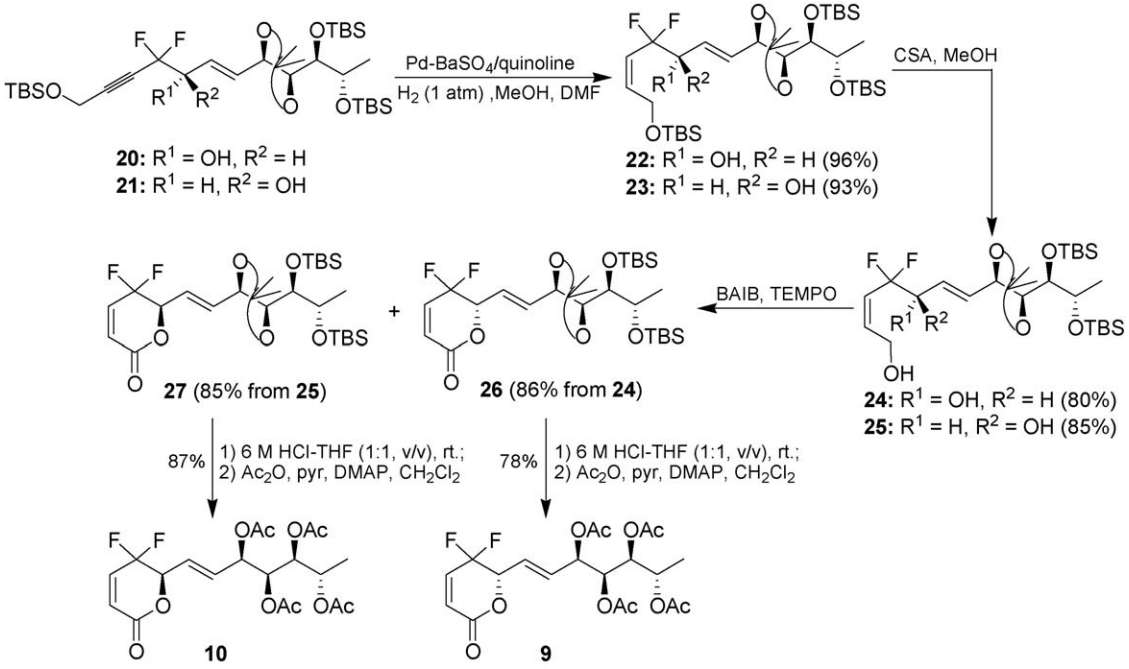


Scheme 3.



Scheme 4.

sulfonic acid (CSA) gave cyclization precursor **24** and **25** in 80% and 85% yield, respectively. Delightfully, treatment of compound **24** and **25** with 0.2 equiv. of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)/3.0 equiv. of [bis(acetoxy)iodo]benzene (BAIB) in dichloromethane at room temperature smoothly afforded cyclization compound **26** and **27** in 86% and 85% yield, respectively. Using O'Doherty reported reaction condition [14], attempts to removal of all protecting groups by heating the lactones **26** and **27** in 10% aqeous HCl/THF for 10 min at 65 °C failed. Gratifyingly, treatment of compounds **26** and **27** with 6 M aqueous HCl/THF (1:1, v/v)



Scheme 5.

followed by direct acetylation with Ac_2O/DMAP/pyridine successfully afforded out target molecules **9** and **10** in 78% and 87% yields, respectively.

3. Conclusions

We have accomplished the total synthesis of *gem*-difluoromethylenated analogues of anamarine **9** and **10** in a straightforward fashion. Our synthesis featured practical preparation of the key intermediates **20–21** through the indium-mediated *gem*-difluoropropargylation of aldehyde **18** with the fluorine-containing building block **19** and efficient construction of α,β-unsaturated-δ-lactone scaffold via BAIB/TEMPO procedure. In our opinion, herein reported synthetic route provided a novel optional method for the preparation of anamarine and its analogues.

4. Experimental

4.1. General

Unless otherwise indicated, all chemicals and solvents were used as received from commercial sources or purified by standard procedures. Optical rotations were recorded on a Jasco P-1030 polarimeter. IR Spectra were scanned with a Bio-Rad FTS185 spectrophotometer. ^{1}H- and ^{13}C NMR spectra were obtained using a Bruker AM300 and AM400 spectrometer, respectively and ^{19}F NMR spectra were recorded on a Bruker AM300 spectrometer ($CFCl_3$ as external standard and low field is positive. Chemical shifts (δ) in ppm, coupling constants (J) in Hz). LRMS were measured on Agilent system mass spectrometer and HRMS on an APEXIII (7.0 T) FTMS or waters mass spectrometer, respectively. Elemental analyses were taken on a Vario EL III elementary analysis instrument.

4.2. (1S)-1-(tert-Butyldimethylsilyloxy)-1-((4S,5R)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-ol (12)

To a solution of compound **11** (9.60 g, 26.7 mmol) in Et_2O (100 mL) at −78 °C was added MeMgBr (17.8 mL, 3 M solution in ether) dropwise. After stirring for 1 h, the reaction was quenched with saturated aqueous NH_4Cl and was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4. Removal of all the solvent in vacuo resulted in a residue, which was purified by silica gel chromatography (petroleum ether:ethyl acetate = 4:1) to give compound **12** (8.85 g, 85% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (m, 2H), 4.02 (m, 2H), 3.90 (m, 2H), 3.71 (m, 0.6H), 3.60 (m, 0.4H), 2.29 (br s, 1H), 1.41 (m, 6H), 1.35 (m, 6H), 1.24 (m, 3H), 0.94 (s, 9H), 0.13 (m, 6H); IR (thin film) ν_{max} 3492, 2932, 1474, 1254, 1070, 838 cm^{-1}; MS (ESI) m/z 391 $(M+H)^+$, 413 $(M+Na)^+$; Anal. Calcd. for $C_{19}H_{38}O_6Si$: C, 58.43; H, 9.81. Found: C, 58.53; H, 9.65.

4.3. (R)-4-((4R,5S)-5-((1R)-1,2-bis(tert-Butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-1,3-dioxolane (13)

To a solution of compound **12** (6.50 g, 16.7 mmol) in CH_2Cl_2 (100 mL) was added 2,6-lutidine (4.3 mL, 45.0 mmol) followed by TBSOTf (6.5 mL, 33.0 mmol) dropwise at −10 °C. The reaction mixture was stirred at −10 °C for 0.5 h, then warmed to room temperature and stirred overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and was extracted with CH_2Cl_2. The combined organic extracts were washed with 1 M HCl and brine, dried over anhydrous Na_2SO_4. Removal of all the solvent in vacuo gave a residue, which was purified by silica gel chromatography (petroleum ether:ethyl acetate = 20:1) to afford compound **13** (7.74 g, 92% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22–4.02 (m, 3H), 3.99–3.74 (m, 3H), 3.73 (dd, J = 4.5 Hz, 1.2 Hz, 0.4H), 3.69 (t, J = 3.9 Hz, 0.6H), 1.37 (m, 6H), 1.33 (m, 6H), 1.19 (t, J = 6.6 Hz, 3H), 0.91 (m, 18H), 0.09 (m, 12H); IR (thin film) ν_{max} 2933, 1473, 1255, 835 cm^{-1}; MS (ESI) m/z 505 $(M+H)^+$; Anal. Calcd. for $C_{25}H_{52}O_6Si_2$: C, 59.48; H, 10.38. Found: C, 59.64; H, 10.39.

4.4. (E)-Ethyl 3-((4R,5S)-5-((1R)-1,2-bis(tert-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (15)

To a solution of H_5IO_6 (4.40 g, 19.3 mmol) in Et_2O (80 mL) was added a solution of compound **13** (6.50 g, 12.9 mmol) in Et_2O (40 mL) dropwise at room temperature. After stirring for 20 h the reaction mixture was filtered through Celite and the filter cake was washed with Et_2O. The filtrate was added H_2O (50 mL) and the organic phase was separated. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4. Removal of all the solvent in vacuo gave a residue, which was used without further purification.

To a solution of $(EtO)_2P(O)CH_2CO_2Et$ (4.33 g, 19.4 mmol) in THF (80 mL) was added NaH (774 mg, 60% in oil, 19.4 mmol) at 0 °C. The reaction mixture was stirred for 30 min, then a solution of the above residue in THF (30 mL) was added dropwise. After stirring for 1 h, the reaction was quenched with saturated aqueous NH_4Cl and was extracted with Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. After filtration and removal of all the solvent, the residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 100:1) to give compound **15** (4.53 g, 70% yield two steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (dd, J = 15.6 Hz, 4.5 Hz, 0.3H), 6.88 (dd, J = 15.6 Hz, 5.4 Hz, 0.7H), 6.13 (d, J = 15.6 Hz, 1H), 4.51 (m, 1H), 4.20 (m, 2H), 3.88 (m, 2H), 3.62 (t, J = 3.9 Hz, 0.7H), 3.58 (t, J = 4.8 Hz, 0.3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.28 (m, 3H), 1.17 (d, J = 6.0 Hz, 3H), 0.91 (m, 18H), 0.09 (m, 12H); IR (thin film) ν_{max} 2933, 1728, 1662, 1473, 1257, 1104, 836 cm^{-1}; MS (ESI) m/z 525 $(M+Na)^+$, 541 $(M+K)^+$; Anal. Calcd. for $C_{25}H_{50}O_6Si_2$: C, 59.72; H, 10.02. Found: C, 59.49; H, 10.24.

4.5. (E)-3-((4R,5S)-5-((1R,2S)-1,2-bis(tert-Butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (16) and (E)-3-((4R,5S)-5-((1R,2R)-1,2-bis(tert-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (17)

To a solution of **15** (4.20 g, 8.4 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added DIBAL-H (12.5 mL, 1 M solution in toluene, 12.5 mmol) dropwise. After stirring for 1 h, the reaction was quenched with saturated aqueous Rochelle's salt. Warmed up to room temperature, the mixture was stirred for 3 h. The aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4. After filtration and removal of all the solvent in vacuo, the residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 20:1) to afford compound **16** (2.39 g, 62% yield) and **17** (1.16 g, 30% yield). Compound **16**: clear oil; $[\alpha]_D^{27}$ = +13.6° (c 1.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (dt, J = 15.6 Hz, 5.4 Hz, 1H), 5.70 (dd, J = 15.3 Hz, 7.5 Hz, 1H), 4.30 (t, J = 8.4 Hz, 1H), 4.17 (d, J = 4.8 Hz, 2H), 3.82 (m, 1H), 3.75 (dd, J = 9.0 Hz, 3.6 Hz, 1H), 3.58 (t, J = 3.6 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.12 (d, J = 6.3 Hz, 3H), 0.93 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 128.1, 108.6, 81.7, 77.5, 76.7, 69.7, 62.5, 27.0, 26.0, 25.9, 18.8, 18.5, 18.1, −3.9, −4.3, −4.4, −4.8; IR (thin film) ν_{max} 3420, 2931, 1473, 1254, 1101, 835 cm^{-1}; MS (ESI) m/z 483 $(M+Na)^+$; HRMS Calcd. for

$C_{23}H_{48}O_5Si_2Na$: 483.2933; found: 483.2939. Compound **17**: clear oil; $[\alpha]_D^{25}$ = +24.4° (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (dt, *J* = 15.3 Hz, 5.4 Hz, 1H), 5.79 (dd, *J* = 15.3 Hz, 6.9 Hz, 1H), 4.37 (t, *J* = 7.8 Hz, 1H), 4.16 (d, *J* = 5.1 Hz, 2H), 3.92 (dd, *J* = 9.0 Hz, 3.6 Hz, 1H), 3.83 (m, 1H), 3.50 (t, *J* = 3.6 Hz, 1H), 1.41 (s, 6H), 1.17 (d, *J* = 6.3 Hz, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 129.2, 108.6, 79.7, 77.5, 73.8, 70.6, 62.9, 27.1, 27.0, 25.8, 18.1, −4.4, −4.9; IR (thin film) ν_{max} 3413, 2858, 1473, 1254, 1102, 835 cm^{-1}; MS (ESI) *m*/*z* 483 $(M+Na)^+$; HRMS Calcd. for $C_{23}H_{48}O_5Si_2Na$: 483.2933; found: 483.2937.

4.6. (S,E)-1-((4R,5S)-5-((1R,2S)-1,2-bis(tert-Butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-(tert-butyldimethylsilyloxy)-4,4-difluorohept-1-en-5-yn-3-ol (20) and (R,E)-1-((4R,5S)-5-((1R,2S)-1,2-bis(tert-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-(tert-butyldimethylsilyloxy)-4,4-difluorohept-1-en-5-yn-3-ol (21)

To a solution of **16** (0.74 g, 1.61 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin reagent (1.02 g, 2.41 mmol). After stirring for 1 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4. After filtration and removal of all the solvent, the residue was used for next step without further purification.

To a stirred suspension of the above residue and compound **19** (0.48 g, 1.39 mmol) in DMF–H_2O (20 mL, 2:1, v/v) was added indium power (0.20 g, 1.77 mmol) at room temperature. After stirring for 5 h, the reaction mixture was quenched with 1 M HCl. The aqueous phase was extracted with EtOAc, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4. After filtration and removal of all the solvent, the residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 20:1) to afford compound **20** (0.52 g, 48% yield) and **21** (0.33 g, 30% yield). Compound **20**: yellow oil; $[\alpha]_D^{24}$ = +1.2° (*c* 0.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (m, 2H), 4.36 (m, 4H), 3.78 (m, 2H), 3.59 (t, *J* = 3.9 Hz, 1H), 2.02 (br s, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.90 (m, 27H), 0.09 (m, 18H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −95.1 (d, *J* = 286.1 Hz, 1F), −96.6 (d, *J* = 272.4 Hz, 1F); IR (thin film) ν_{max} 3460, 2932, 2230, 1473, 1256, 1104, 836 cm^{-1}; MS (ESI) *m*/*z* 701 $(M+Na)^+$, 717 $(M+K)^+$; Anal. Calcd. for $C_{33}H_{64}F_2O_6Si_3$: C, 58.36; H, 9.50. Found: C, 58.68; H, 9.24. Compound **21**: yellow oil; $[\alpha]_D^{25}$ = +25.2° (*c* 2.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (m, 2H), 4.36 (m, 4H), 3.81 (m, 1H), 3.75 (dd, *J* = 8.4 Hz, 4.5 Hz, 1H), 3.60 (t, *J* = 3.6 Hz, 1H), 1.80 (br s, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.12 (d, *J* = 6.3 Hz, 3H), 0.91 (m, 27H), 0.09 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0, 127.7, 120.9 (t, *J* = 237.3 Hz), 109.0, 88.2 (t, *J* = 6.4 Hz), 81.8, 77.0, 76.7, 75.5 (t, *J* = 38.9 Hz), 74.4 (t, *J* = 29.8 Hz), 69.8, 51.2, 27.0, 26.9, 26.1, 25.9, 25.7, 18.7, 18.5, 18.2, 18.1, −3.9, −4.4, −4.5, −4.8, −5.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −94.5 (d, *J* = 274.4 Hz, 1F), −96.6 (d, *J* = 280.7 Hz, 1F); IR (thin film) ν_{max} 3460, 2932, 2258, 1650, 1473, 1257, 1108, 836 cm^{-1}; MS (ESI) *m*/*z* 696 $(M+NH_4)^+$; HRMS Calcd. for $C_{33}H_{64}F_2O_6Si_3Na$: 701.3871; found: 701.3838.

4.7. (S,1E,5Z)-1-((4R,5S)-5-((1R,2S)-1,2-bis(tert-Butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-(tert-butyldimethylsilyloxy)-4,4-difluorohepta-1,5-dien-3-ol (22)

To a mixture of Pd–$BaSO_4$ (28 mg, 42 mg/mmol) in MeOH (20 mL) was added a solution of quinoline (28 mg, 42 mg/mmol) in MeOH (2 mL) at 0 °C. Warming up to room temperature, the suspension mixture was stirred for 15 min before a solution of compound **20** (450 mg, 0.66 mmol) in DMF (10 mL) was added. After the mixture was stirred for 3.5 h under hydrogen atmosphere (1 atm) at 35 °C, ^{19}F NMR indicated the absence of starting material **20**. The reaction mixture was filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 20:1) to afford compound **22** (449 mg, 96% yield) as a yellow oil: $[\alpha]_D^{24}$ = +4.8° (*c* 0.60, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (m, 1H), 5.90 (m, 2H), 5.47 (m, 1H), 4.44 (m, 2H), 4.33 (m, 2H), 3.80 (m, 1H), 3.75 (dd, *J* = 8.1 Hz, 3.9 Hz, 1H), 3.58 (t, *J* = 3.6 Hz, 1H), 2.10 (br s, 1H) 1.42 (s, 3H), 1.38 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 0.90 (m, 27H), 0.07 (m, 18H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −101.6 (d, *J* = 260.9 Hz, 1F), −104.4 (dt, *J* = 261.5 Hz, 13.2 Hz, 1F); IR (thin film) ν_{max} 3460, 2932, 1473, 1256, 1104, 836 cm^{-1}; MS (ESI) *m*/*z* 703 $(M+Na)^+$, 719 $(M+K)^+$; Anal. Calcd. for $C_{33}H_{66}F_2O_6Si_3$: C, 58.19; H, 9.77. Found: C, 57.95; H, 9.72.

4.8. (R,1E,5Z)-1-((4R,5S)-5-((1R,2R)-1,2-bis(tert-Butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-(tert-butyldimethylsilyloxy)-4,4-difluorohepta-1,5-dien-3-ol (23)

Compound **23** was prepared from compound **21** (300 mg, 0.44 mmol) in 93% yield using the same conditions as described for compound **22**. Yellow oil; $[\alpha]_D^{24}$ = +20.0° (*c* 1.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 (m, 1H), 5.86 (m, 2H), 5.48 (m, 1H), 4.44 (m, 2H), 4.30 (m, 2H), 3.80 (m, 1H), 3.74 (dd, *J* = 8.1 Hz, 3.9 Hz, 1H), 3.58 (t, *J* = 3.3 Hz, 1H), 2.29 (br s, 1H) 1.42 (s, 3H), 1.38 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 0.90 (m, 27H), 0.08 (m, 18H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −101.6 (d, *J* = 274.1 Hz, 1F), −104.9 (dt, *J* = 259.7 Hz, 12.6 Hz, 1F); IR (thin film) ν_{max} 3480, 2932, 1650, 1473, 1256, 1104, 836 cm^{-1}; MS (ESI) *m*/*z* 703 $(M+Na)^+$, 719 $(M+K)^+$; Anal. Calcd. for $C_{33}H_{66}F_2O_6Si_3$: C, 58.19; H, 9.77. Found: C, 58.53; H, 9.54.

4.9. (S,2Z,6E)-7-((4R,5S)-5-((1R,2R)-1,2-bis(tert-Butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4,4-difluorohepta-2,6-diene-1,5-diol (24)

To a solution of **22** (400 mg, 0.59 mmol) in MeOH (10 mL) was added 10-CSA (9 mg, 0.029 mmol). After stirring for 1 h, the reaction mixture was quenched with saturated $NaHCO_3$. The aqueous phase was extracted with EtOAc, and the organic phase was washed with brine, dried over anhydrous Na_2SO_4. After filtration and removal of all the solvent in vacuo, the residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 4:1) to give compound **24** (267 mg, 80% yield) as a clear oil: $[\alpha]_D^{23}$ = +7.3° (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (m, 1H), 5.88 (m, 2H), 5.51 (m, 1H), 4.36 (m, 4H), 3.79 (m, 2H), 3.57 (t, *J* = 3.3 Hz, 1H), 2.62 (br s, 2H), 1.42 (s, 3H), 1.39 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0 (t, *J* = 4.6 Hz), 131.9, 129.1, 121.7 (t, *J* = 26.3 Hz), 120.4 (dd, *J* = 244.8 Hz, 243.4 Hz), 109.0, 81.8, 77.0, 76.6, 73.0 (t, *J* = 30.1 Hz), 69.8, 58.6, 27.0, 26.8, 26.1, 25.9, 18.9, 18.5, 18.1, −3.9, −4.4, −4.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −101.1 (dt, *J* = 270.1 Hz, 13.5 Hz, 1F), −102.5 (dt, *J* = 258.0 Hz, 12.9 Hz, 1F); IR (thin film) ν_{max} 3450, 2956, 1473, 1255, 1109, 836 cm^{-1}; MS (ESI) *m*/*z* 611 $(M+COOH)^-$; HRMS Calcd. for $C_{28}H_{53}F_2O_8Si_2$: 611.3253; found: 611.3262.

4.10. (R,2Z,6E)-7-((4R,5S)-5-((1R,2R)-1,2-bis(tert-Butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4,4-difluorohepta-2,6-diene-1,5-diol (25)

Compound **25** was prepared from compound **23** (250 mg, 0.37 mmol) in 85% yield using the same conditions as described for compound **24**. Clear oil; $[\alpha]_D^{26}$ = +26.2° (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.05 (m, 1H), 5.88 (m, 2H), 5.52 (m, 1H), 4.35 (m, 4H), 3.79 (m, 2H), 3.58 (t, *J* = 4.5 Hz, 1H), 2.05 (br s, 2H), 1.42 (s, 3H), 1.39 (s, 3H), 1.13 (d, *J* = 5.7 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ

−99.5 (dt, *J* = 259.7 Hz, 9.8 Hz, 1F), −103.1 (d, *J* = 260.3 Hz, 1F); IR (thin film) ν_{max} 3450, 2933, 1469, 1379, 1107, 834 cm^{-1}; MS (ESI) *m/z* 611 $(M+COOH)^-$; Anal. Calcd. for $C_{27}H_{52}F_2O_6Si_2$: C, 57.21; H, 9.25. Found: C, 57.42; H, 9.25.

4.11. (S)-6-((E)-2-((4R,5S)-5-((1R,2R)-1,2-bis(tert-Butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)vinyl)-5,5-difluoro-5,6-dihydropyran-2-one (26)

To a solution of **24** (220 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) was added BAIB (520 mg, 1.17 mmol) and TEMPO (12 mg, 20 mmol%) at room temperature. After stirring for 3 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$ and brine; dried over anhydrous Na_2SO_4. After filtration and removal of all the solvent in vacuo, the residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 10:1) to afford compound **26** (188 mg, 86% yield) as a clear oil: $[\alpha]_D^{24}$ = +41.8° (*c* 1.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (m, 1H), 6.32 (d, *J* = 9.9 Hz, 1H), 6.08 (dd, *J* = 15.3 Hz, 6.0 Hz, 1H), 5.94 (dd, *J* = 15.6 Hz, 5.4 Hz, 1H), 5.06 (dt, *J* = 15.6 Hz, 6.6 Hz, 1H), 4.40 (t, *J* = 6.6 Hz, 1H), 3.80 (m, 2H), 3.60 (t, *J* = 3.3 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (t, *J* = 2.0 Hz), 137.6 (dd, *J* = 31.3 Hz, 26.8 Hz), 135.8, 126.6 (dd, *J* = 9.8 Hz, 8.3 Hz), 121.7 (dd, *J* = 3.2 Hz, 1.0 Hz), 111.8 (dd, *J* = 243.9 Hz, 238.1 Hz), 109.2, 81.7, 78.7 (dd, *J* = 32.7 Hz, 28.6 Hz), 76.6, 76.5, 69.8, 27.0, 26.8, 26.0, 25.9, 19.0, 18.5, 18.1, −3.9, −4.4, −4.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −107.1 (dd, *J* = 293.9 Hz, 15.2 Hz, 1F), −108.7 (dd, *J* = 293.3 Hz, 8.9 Hz, 1F); IR (thin film) ν_{max} 2932, 1754, 1615, 1473, 1383, 1258, 1106, 835 cm^{-1}; MS (EI) *m/z* (%) 505 (2), 303 (21), 159 (54), 131 (73), 73 (100); HRMS Calcd. for $C_{23}H_{39}F_2O_6Si_2$: 505.2253; found: 505.2249.

4.12. (R)-6-((E)-2-((4R,5S)-5-((1R,2R)-1,2-bis(tert-Butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)vinyl)-5,5-difluoro-5,6-dihydropyran-2-one (27)

Compound **27** was prepared from compound **25** (200 mg, 0.35 mmol) in 85% yield using the same conditions as described for compound **26**. White solid, mp 92–94 °C; $[\alpha]_D^{25}$ = −3.7° (*c* 1.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (m, 1H), 6.32 (d, *J* = 10.5 Hz, 1H), 6.04 (dd, *J* = 15.6 Hz, 6.0 Hz, 1H), 5.93 (dd, *J* = 15.0 Hz, 6.0 Hz, 1H), 5.02 (m, 1H), 4.40 (t, *J* = 6.6 Hz, 1H), 3.82 (m, 1H), 3.77 (dd, *J* = 8.4 Hz, 3.9 Hz, 1H), 3.61 (t, *J* = 3.3 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.13 (d, *J* = 6.3 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 137.6 (dd, *J* = 31.2 Hz, 26.5 Hz), 136.5, 126.5 (dd, *J* = 9.7 Hz, 8.3 Hz), 121.6 (dd, *J* = 3.5 Hz, 0.9 Hz), 111.7 (dd, *J* = 244.1 Hz, 237.5 Hz), 109.2, 81.8, 79.1 (dd, *J* = 32.7 Hz, 28.6 Hz), 76.6, 76.5, 69.8, 27.0, 26.8, 26.0, 25.9, 18.9, 18.4, 18.1, −3.9, −4.5, −4.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −107.1 (dd, *J* = 293.9 Hz, 15.5 Hz, 1F), −108.7 (dd, *J* = 293.6 Hz, 9.8 Hz, 1F); IR (thin film) ν_{max} 2932, 1754, 1650, 1473, 1257, 1107, 835 cm^{-1}; MS (EI) *m/z* (%) 547 (2), 505 (4), 303 (32), 73 (100); HRMS Calcd. for $C_{23}H_{39}F_2O_6Si_2$: 505.2253; found: 505.2260.

4.13. (6S)-5,5-Difluoro-6-[(1E,3R,4S,5S,6S)-3,4,5,6-tetrakis(acetyloxy)-1-hepten-1-yl]-5,6-dihydro-2H-Pyran-2-one (9)

To a solution of **26** (80 mg, 0.14 mmol) in THF (3.5 mL) was added 6 M HCl (3.5 mL) at room temperature. After TLC demonstrated that starting material was completely consumed, the reaction was concentrated to give a residue, which was used without further purification.

To a solution of above residue in CH_2Cl_2 (5 mL) was added dropwise pyridine (0.15 mL), DMAP (3 mg) followed by Ac_2O (0.1 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and was extracted with CH_2Cl_2. The combined organic extracts were washed with 1 M HCl and brine, dried over anhydrous Na_2SO_4. After filtration and removal of all the solvent, the residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 1:1) to afford compound **9** (50 mg, 78% yield) as a clear oil: $[\alpha]_D^{24}$ = +0.3° (*c* 1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (m, 1H), 6.32 (d, *J* = 10.2 Hz, 1H), 6.01 (dd, *J* = 15.9 Hz, 5.4 Hz, 1H), 5.87 (dd, *J* = 15.9 Hz, 5.1 Hz, 1H), 5.48 (t, *J* = 5.7 Hz, 1H), 5.30 (dd, *J* = 6.0 Hz, 4.8 Hz, 1H), 5.23 (dd, *J* = 5.7 Hz, 4.5 Hz, 1H), 5.04 (ddd, *J* = 16.8 Hz, 8.1 Hz, 5.7 Hz, 1H), 4.91 (dt, *J* = 12.6 Hz, 6.0 Hz, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.21 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.8, 169.6, 159.8, 137.5 (t, *J* = 28.9 Hz), 131.5, 126.5 (t, *J* = 0.9 Hz), 123.7, 111.8 (t, *J* = 240.1 Hz), 78.6 (t, *J* = 30.9 Hz), 71.4, 70.9, 70.1, 67.4, 21.0, 20.8, 20.7, 20.5, 15.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −105.8 to −109.1 (m, 2F); IR (thin film) ν_{max} 2929, 1753, 1648, 1459, 1375, 1215, 1068 cm^{-1}; MS (ESI) *m/z* 480 $(M+NH_4)^+$, 485 $(M+Na)^+$; HRMS Calcd. for $C_{20}H_{24}F_2O_{10}Na$: 485.1230; found: 485.1243.

4.14. (6R)-5,5-Difluoro-6-[(1E,3R,4S,5S,6S)-3,4,5,6-tetrakis(acetyloxy)-1-hepten-1-yl]-5,6-dihydro-2H-Pyran-2-one (10)

Compound **10** (36 mg, 87%) was prepared from compound **27** (50 mg, 0.089 mmol) using the same conditions as described for compound **9**. Clear oil: $[\alpha]_D^{24}$ = −54.6° (*c* 0.79, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (m, 1H), 6.32 (d, *J* = 9.6 Hz, 1H), 6.04 (dd, *J* = 16.5 Hz, 6.0 Hz, 1H), 5.85 (dd, *J* = 15.6 Hz, 5.4 Hz, 1H), 5.47 (t, *J* = 6.3 Hz, 1H), 5.30 (dd, *J* = 6.3 Hz, 3.9 Hz, 1H), 5.23 (dd, *J* = 6.0 Hz, 4.5 Hz, 1H), 5.04 (dt, *J* = 16.8 Hz, 6.0 Hz, 1H), 4.92 (dt, *J* = 12.6 Hz, 6.0 Hz, 1H), 2.13 (s, 6H), 2.07 (s, 3H), 2.03 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.9, 169.8, 169.6, 159.7, 137.6 (t, *J* = 25.9 Hz), 131.5, 126.5 (dd, *J* = 11.5 Hz, 8.2 Hz), 123.5 (t, *J* = 3.0 Hz), 111.7 (dd, *J* = 244.3 Hz, 237.3 Hz), 78.4 (dd, *J* = 32.9 Hz, 28.1 Hz), 71.5, 71.0, 70.2, 67.3, 21.0, 20.8, 20.5, 15.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −107.2 (dd, *J* = 289.1 Hz, 16.9 Hz, 1F), −109.4 (dt, *J* = 289.1 Hz, 6.2 Hz, 1F); IR (thin film) ν_{max} 2929, 1758, 1640, 1433, 1374, 1216, 1067 cm^{-1}; MS (ESI) *m/z* 485 $(M+Na)^+$; HRMS Calcd. for $C_{20}H_{24}F_2O_{10}Na$: 485.1230; found: 485.1226.

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