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Synthesis of γ,γ-difluoro-β-hydroxy-δ-lactones as new precursors of HMG-CoA reductase inhibitor

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This paper is dedicated to Professor Wei-Yuan Huang on the occasion of his 90th birthday.

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ABSTRACT

A series of γ,γ-difluoro-β-hydroxy-δ-lactones **1** were efficiently synthesized as new precursors of HMG-CoA reductase inhibitor in one pot by treatment of readily prepared *gem*-difluoromethylenated acetonides **3** with trifluoroacetic acid. Contrarily, acetonides **3** could be transformed to the γ,γ-*gem*-difluoromethylenated α,β-unsaturated δ-lactones **2** through hydrolyzation and lactonization in refluxing toluene.

1. Introduction

Statins are well-known inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which have become the most frequently prescribed agents for the treatment of hypercholesterolemia due to their compelling action on significantly reducing the rates of cardiovascular events [1]. A large number of statin analogs including Lovastatin, Pravastatin, Fluvastatin, Simvastatin, Atorvastatin, Rosuvastatin and Pitavastatin (Fig. 1) have been synthesized, in which modifications were mainly focused on the variation of their lipophilic fragment to improve the biological activity and reduce the side effects [2]. It has been revealed by structure–activity relationship (SAR) studies that the hydroxyl-valerolactone fragment was essentially responsible for the biological activity of statins [3], whereas studies on the modification of the hydroxyl-valerolactone precursor have rarely been documented. To the best of our knowledge, only Reardon and Abeles have disclosed series of fluorinated hydroxyl valerolactones as HMG-CoA reductase inhibitors till date [4].

The strong electronegativity and relatively small size of fluorine atom combined with the chemical inertness of C-F bonds make fluorine-substitution a powerful tool for medicinal chemistry study [5]. Recently, special attention has been paid to the *gem*-difluoromethylene group because many compounds with this functional group exhibited extraordinary biological activities with potential pharmaceutical applications [6]. With a long-term interest in the methodology studies on fluorine-containing δ-lactones [7] and other related bioactive small molecules, the introduction of *gem*-difluoromethylene group (CF_2) to β-hydroxy δ-lactones at the γ-position (Fig. 2) was investigated. Herein, we described the synthesis of γ,γ-difluoro-β-hydroxy-δ-lactones as new precursors of HMG-CoA reductase inhibitor.

2. Results and discussion

gem-Difluoromethylenated acetonides **3** were first obtained in their *syn* forms in 15–20% overall yields (Scheme 1) according to literature methods [8]. Zinc-mediated Reformatsky reaction of cinnamyl aldehyde derivatives **4** with ethyl bromodifluoroacetate gave the corresponding esters **5**. Subsequent Claisen condensation of **5** with *tert*-butyl acetate produced δ-hydroxy-β-keto esters **6** which were then reduced to β,δ-diols **7** in the presence of $NaBH_4$.

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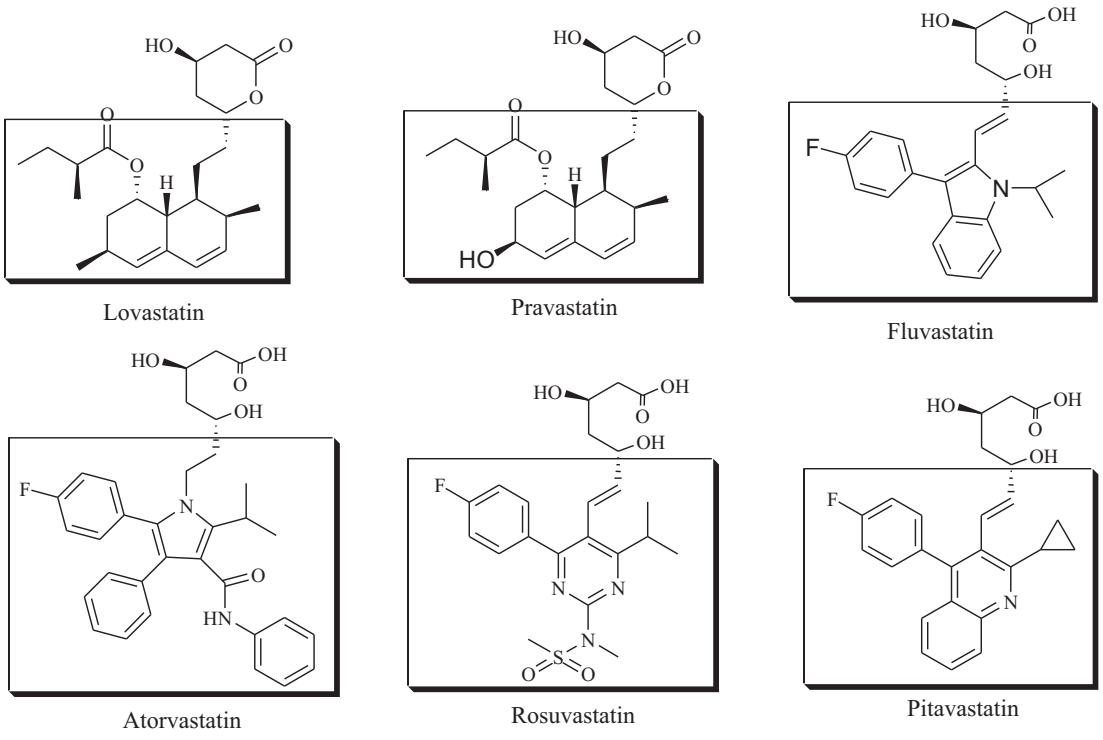


Fig. 1. The reported HMG-CoA reductase inhibitors.

Considering the difficulty in separating *syn* and *anti* diols, crude diols **7** were transformed to the desired acetonide **3** without further purification in the presence of *iso*-propylidene acetal which is useful for removing traces of the hydroxy epimers produced in the stereoselective reduction of the δ-hydroxy-β-keto esters **6**. Finally, the intermediates **3a**–**3e** were isolated as single *syn* forms by column chromatography on silica gel [9].

With acetonides **3** in hand, we then examined the conversion of **3** into the desired γ,γ-difluoro-β-hydroxy-δ-lactones **1** (Scheme 2). Treatment of **3** with TsOH and then NaOH for hydrolyzing, respectively, the acetonide and ester protecting groups led to the crude dihydroxy acids **8**, which was then subjected to the lactonization reaction under the condition (in dry toluene at 110 °C for 5 h) reported by Reddy's group [10]. However, the γ,γ-difluoro-α,β-unsaturated-δ-lactones **2** were unexpectedly obtained in 30–70% yields instead of the titled products **1**.

We deduced that at high reaction temperature, acids **8** were converted correspondingly to the α,β-unsaturated δ-lactones **2** [12], similar to the reported synthesis of **2a** through ring-closing metathesis (RCM) reaction by Qing et al. [11]. Since **route I** failed to give the desired products, an alternative method reported by Takahashi et al. which may convert the acetonides into δ-lactones in one-pot was attempted [13]. To our delight, the desired lactones **1** were thus obtained in 40–50% yields by treating acetonides **3** with CF_3COOH in CH_2Cl_2 (Scheme 2, **route II**).

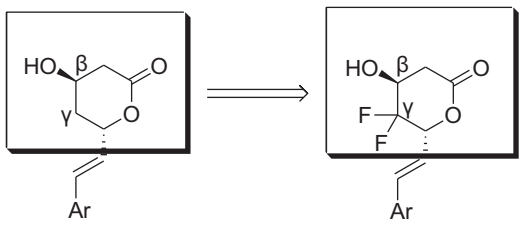


Fig. 2. Design of new precursors of HMG-CoA reductase inhibitor.

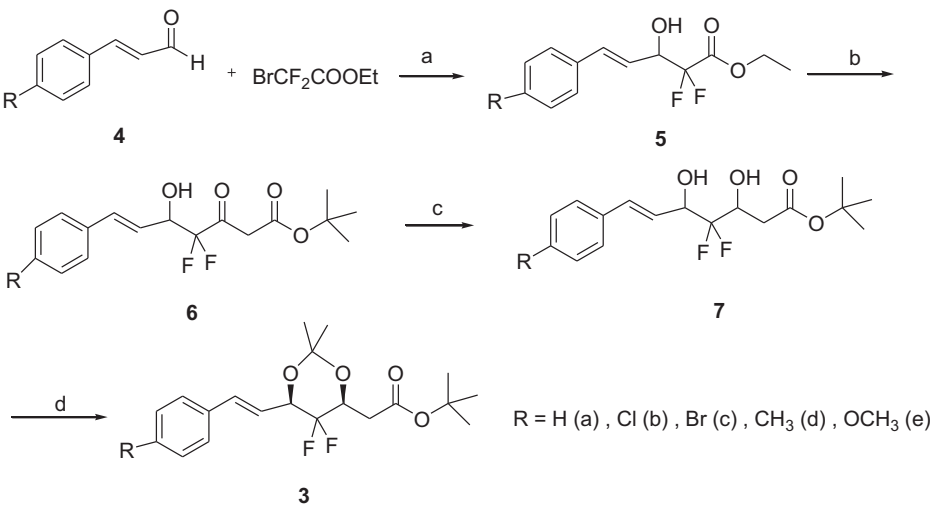
After successfully obtaining the new *gem*-difluoromethylenated δ-lactone precursors, we further projected to produce the lipophilic fragment-varied derivatives in which the phenyl rings are replaced by heterocyclic cores for establishing SAR studies. The most commonly used Wittig reaction for the preparation of statins by coupling aryl groups with fully *O*-protected 3,5-dihydroxy-6-oxohexenoic acids will be adopted [14]. As shown in Scheme 3, we preliminarily attempted the ozonolysis cleavage of **3a**, which led to *gem*-difluoromethylenated aldehyde **9** in 80% yield. This intermediate could be further coupled with various heterocyclic rings via Wittig reaction and then converted into the *gem*-difluoromethylenated δ-lactones via the method established in this study, providing a novel class of statin analogs as new inhibitors of HMG-CoA reductase. The synthesis and biological assessments will be presented in due course.

In conclusion, we have reported the efficient synthesis of γ,γ-difluoro-β-hydroxy-δ-lactones **1** as new precursors of HMG-CoA reductase inhibitor. The important *gem*-difluoromethylenated acetonide intermediates **3** were obtained via a straightforward 4-step sequence, which could also be converted into *gem*-difluoromethylenated aldehydes via ozonolysis cleavage for further structural modifications. The synthesis and biological study of other statin analogs are currently underway in our laboratories.

3. Experimental

3.1. General

IR spectra were measured on a Nicolet Magna IR-550 spectrometer. High-resolution mass spectra were carried out on a Finnigan GC-MS-4021 spectrometer. ^1H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker AC-500 spectrometer with Me_4Si as an internal standard. ^{19}F NMR spectra were obtained on a Bruker AC-500 (367.5 MHz) spectrometer in $CDCl_3$ with $CFCl_3$ as an external standard, in which downfield shifts



Scheme 1. Reagents and conditions: (a) Zn, THF, 60 °C; (b) *tert*-butyl acetate, LDA, −70 °C; (c) $NaBH_4$, THF/MeOH; (d) acetone, $(CH_3O)_2C(CH_3)_2$, TsOH.

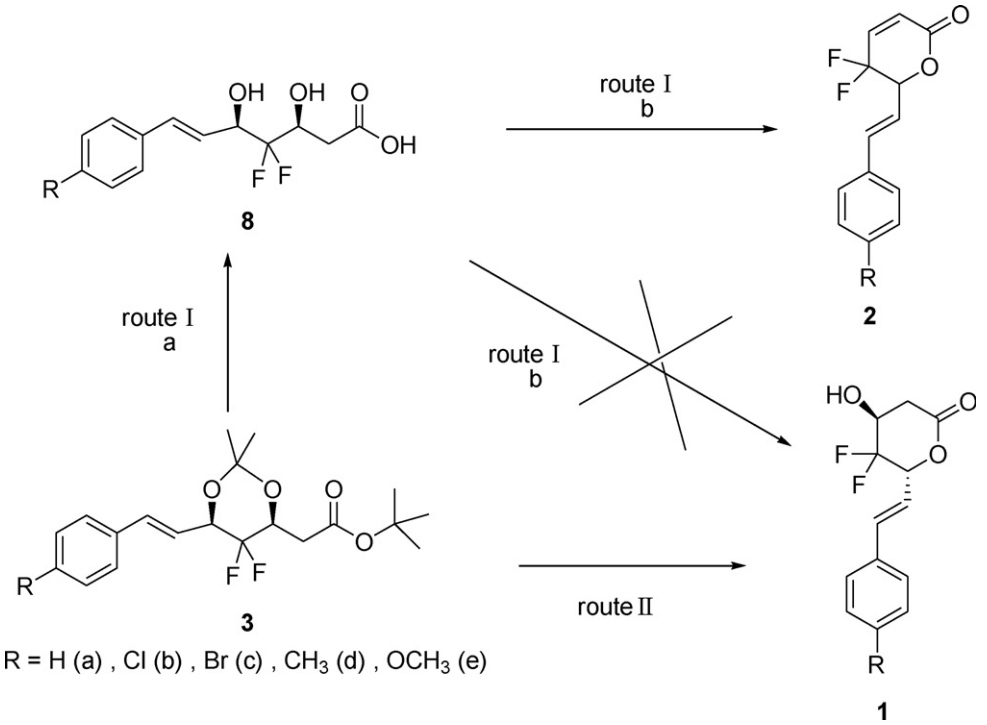
were designated as negative. All chemical shifts (δ) are expressed in parts per million and coupling constants (J) are given in hertz.

3.2. General procedure for preparation of 5 [15]

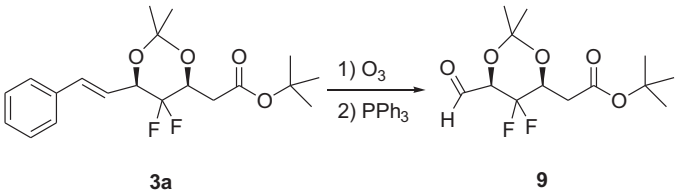
To a stirring mixture of THF (22 mL) and freshly activated zinc powder (1.7 g, 25.6 mmol), ethyl 2-bromo-2,2-difluoroacetate (5.0 g, 24.6 mmol) was added dropwise at r.t. Then, cinnamyl aldehyde **4a** (2.6 g, 19.7 mmol) dissolved in THF (22 mL) was added dropwise to the reaction mixture. After completion of the addition, the mixture was heated to 60 °C and remained for 5 h, followed by the addition of saturated ammonium chloride for quenching the reaction. The excess zinc was removed by suction filtration and the filter cake was washed with ethyl acetate. The combined filtrate was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuum. The remaining residue was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (6:1) to give **5a** (3.3 g, 66% yield).

3.3. General procedure for preparation of 6 [16]

Keeping the inner temperature below 0 °C, *n*-butyllithium (10.9 mL, 2.2 mol L^{-1}, 24 mmol) was added to a solution of diisopropylethylamine (dried over KOH) (3.4 mL, 24 mmol) in THF (5 mL) over 20 min under Ar atmosphere. The reaction mixture was stirred at −5 to −10 °C for 30 min, then was cooled to −30 to −40 °C. *tert*-Butyl acetate (6.5 mL, 24 mmol) was added over 5 min. The reaction mixture was stirred for another 30 min with the inner temperature below −20 °C. Then the mixture was cooled to approximately −70 °C, and a solution of **5** (2.0 g, 8.0 mmol) in THF (6 mL) was added over 25 min. The reaction



Scheme 2. Reagents and conditions: **route I**: (a) i. TsOH, MeOH, ii. NaOH, iii. HCl; (b) toluene, reflux; **route II**: TFA, r.t.



Scheme 3. Ozonolysis cleavage of **3a**.

mixture was stirred for 1 h, and then the temperature was raised to 0 °C over 30 min. The reaction was quenched with saturated aqueous ammonium chloride solution (10 mL) and stirred for 15 min. The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic layer was washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue **6** was used for the next step directly.

3.4. General procedure for preparation of 7 [17]

A 100 mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, funnel, and thermometer was charged with THF (12 mL) and cooled to −45 °C. Sodium borohydride (0.90 g, 24 mmol) was added and the suspension was stirred for 5 min. Then, a solution of **6** (8 mmol) in THF (10 mL) and MeOH (16 mL) was added over 25 min. The reaction mixture was stirred for another 1.5 h at −45 °C, and then was charged with saturated aqueous sodium bicarbonate solution (16 mL) for another 10 min. The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic phase was washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue **7** was used for the next step directly.

3.5. General procedure for preparation of 3

2,2-Dimethoxypropane (1.5 mL, 12 mmol) and *p*-toluensulfonic acid (21 mg, 0.12 mmol) were added to a solution of diol **7a** (8.0 mmol) in dry acetone (15 mL) and the solution was stirred at 35–40 °C for 24 h. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent, the resulting residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give **3a** (530 mg, in 18% isolated yield over the three steps).

3.5.1. (E)-tert-butyl 2-(5,5-difluoro-2,2-dimethyl-6-styryl-1,3-dioxan-4-yl)acetate (3a)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 1.50 (s, 3H), 1.62 (s, 3H), 2.51–2.73 (m, 2H), 4.38–4.60 (m, 2H), 6.23 (dd, 1H, J = 16 Hz, J = 6.8 Hz), 6.77 (d, 1H, J = 16 Hz), 7.28–7.36 (m, 5H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −135.1 (d, 1F, J = 241.4 Hz), −121.5 (d, 1F, J = 241.4 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.8, 28.1, 33.9, 69.0 (t, J = 26.7 Hz), 73.3 (t, J = 26.8 Hz), 81.2, 100.0, 119.8 (t, J = 232.0 Hz), 126.9, 128.3, 128.6, 135.3, 136.0, 136.1, 169.3. IR (cm^{-1}, KBr) 2997, 1724, 1155, 1096, 694. EI-MS (*m*/*z*) 368 (M^+, 3), 312 (22), 237 (40), 234 (40), 133 (51), 57 (100), 43 (36). HRMS calcd for $C_{20}H_{26}F_2O_4$: 368.1799, found: 368.1800.

3.5.2. tert-Butyl 2-(6-(4-chlorostyryl)-5,5-difluoro-2,2-dimethyl-1,3-dioxan-4-yl)acetate (3b)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H), 1.50 (s, 3H), 1.62 (s, 3H), 2.50–2.72 (m, 2H), 4.43–4.60 (m, 2H), 6.21 (dd, 1H, J = 16 Hz, J = 6.8 Hz), 6.74 (d, 1H, J = 16 Hz), 7.29 (d, 2H, J = 8.4 Hz), 7.35 (d, 2H, J = 8.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −134.9 (d, 1F, J = 241.8 Hz), −121.5 (d, 1F, J = 241.8 Hz,). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.1, 28.9, 33.8, 68.9 (t, J = 26.9 Hz), 72.9 (t, J = 27.2 Hz), 81.2, 100.1, 120.5 (t, J = 235.2 Hz), 122.2, 128.1, 128.8, 134.0, 134.5, 134.7, 169.3. IR (cm^{-1}, KBr) 2980, 1725, 1174, 1101, 844. EI-MS (*m*/*z*) 404 (M^++2, 5), 402 (M^+, 13), 346 (37), 271 (86), 268 (100), 167 (54), 165 (41), 138 (28), 131 (33), 57 (65). HRMS calcd for $C_{20}H_{25}ClF_2O_4$: 402.1409, found: 402.1410.

3.5.3. tert-Butyl 2-(6-(4-bromostyryl)-5,5-difluoro-2,2-dimethyl-1,3-dioxan-4-yl)acetate (3c)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H), 1.50 (s, 3H), 1.62 (s, 3H), 2.50–2.72 (m, 2H), 4.44–4.60 (m, 2H), 6.22 (dd, 1H, J = 16 Hz, J = 6.8 Hz), 6.72 (d, 1H, J = 16 Hz), 7.28 (d, 2H, J = 8.4 Hz), 7.45 (d, 2H, J = 8.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −134.9 (d, 1F, J = 241.4 Hz), −121.6 (d, 1F, J = 241.4 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.1, 28.9, 33.8, 68.6 (t, J = 26.5 Hz), 73.1(t, J = 26.8 Hz), 81.3, 100.1, 120.6 (t, J = 228.1 Hz), 122.2, 128.4, 128.9, 131.7, 134.7, 134.9, 169.3. IR (cm^{-1}, KBr) 2982, 1726, 1173, 1103, 840. EI-MS (*m*/*z*) 448 (M^++2, 13), 446 (M^+, 13), 392 (31), 312 (100), 211 (65), 131 (42), 57 (65). HRMS calcd for $C_{20}H_{25}BrF_2O_4$: 446.0904, found: 446.0935.

3.5.4. (E)-tert-butyl 2-(6-(4-methylstyryl)-5,5-difluoro-2,2-dimethyl-1,3-dioxan-4-yl) acetate (3d)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 1.50 (s, 3H), 1.62 (s, 3H), 2.33 (s, 3H), 2.50–2.73 (m, 2H), 4.43–4.58 (m, 2H), 6.18 (dd, 1H, J = 16 Hz, J = 6.8 Hz), 6.74 (d, 1H, J = 16 Hz), 7.13 (d, 2H, J = 8.0 Hz), 7.32 (d, 2H, J = 8.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −134.9 (d, 1F, J = 241.4 Hz), −121.5 (d, 1F, J = 241.8 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.3, 28.1, 28.9, 33.8, 69.0 (t, J = 26.9 Hz), 73.4(t, J = 26.7 Hz), 81.2, 100.0, 113.6, 118.6 (t, J = 247.6 Hz), 126.8, 129.3, 133.2, 136.1, 138.2, 169.4. IR (cm^{-1}, KBr) 2985, 1728, 1174, 1093, 866, 841. EI-MS (*m*/*z*) 382 (M^+, 22), 326 (17), 251 (71), 248 (100), 189 (38), 147 (65), 131 (63), 57 (36). HRMS calcd for $C_{21}H_{28}F_2O_4$: 382.1956, found: 382.1959.

3.5.5. (E)-tert-butyl 2-(6-(4-methoxystyryl)-5,5-difluoro-2,2-dimethyl-1,3-dioxan-4-yl)acetate (3e)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 9H), 1.50 (s, 3H), 1.62 (s, 3H), 2.50–2.73 (m, 2H), 3.81 (s, 3H), 4.42–4.57 (m, 2H), 6.09 (dd, 1H, J = 16 Hz, J = 6.8 Hz), 6.72 (d, 1H, J = 16 Hz), 6.85 (d, 2H, J = 8.8 Hz), 7.36 (d, 2H, J = 8.8 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −135.3 (d, 1F, J = 241.4 Hz), −121.4 (d, 1F, J = 241.8 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.1, 28.9, 33.8, 55.3, 69.0 (t, J = 26.8 Hz), 73.4(t, J = 27.3 Hz), 81.2, 100.0, 112.8, 116.2 (t, J = 248.6 Hz), 117.4, 128.2, 128.8, 135.8, 159.8, 169.4. IR (cm^{-1}, KBr) 2979, 1723, 1513, 1174, 1092, 843. EI-MS (*m*/*z*) 398 (M^+, 39), 327 (17), 284 (17), 267 (59), 264 (36), 162 (100), 134 (22), 57 (33). HRMS calcd for $C_{21}H_{28}F_2O_5$: 398.1905, found: 398.1906.

3.6. General procedure for preparation of 2

p-Toluensulfonic acid (30 mg, 0.026 mmol) was added in one portion to a solution of the acetonide **3** (368 mg, 1 mmol) in MeOH (10 mL), and the mixture was stirred for 1 h at r.t. Et_3N (20 μL, 0.288 mmol) was then added, and the reaction mixture was concentrated in vacuo. The resulting residue was hydrolyzed with aqueous 1 M NaOH (1.5 mL, 1.5 mmol) in MeOH (5 mL) for 24 h at r.t. Subsequent acidic extraction gave a crude acid, which was heated in dry toluene (8 mL) at 110 °C for 6 h. The mixture was then evaporated in vacuo and the resulting residue subjected to flash column chromatography (petroleum ether/ethyl acetate = 10:1) to give **2**.

3.6.1. (E)-5,5-difluoro-6-styryl-5,6-dihydropyran-2-one (2a) [11]

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.15–5.21 (m, 1H), 6.27 (dd, 1H, J = 16 Hz, J = 6.9 Hz), 6.36 (d, 1H, J = 10.1 Hz), 6.84–6.92 (m, 2H), 7.31–7.46 (m, 5H).

*3.6.2. (E)-6-(4-chlorostyryl)-5,5-difluoro-5,6-dihydropyran-2-one (**2b**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.13–5.20 (m, 1H), 6.24 (dd, 1H, J = 16 Hz, J = 6.8 Hz), 6.36 (d, 1H, J = 10.0 Hz), 6.84–6.89 (m, 2H), 7.33 (d, 2H, J = 8.4 Hz), 7.38 (d, 2H, J = 8.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −107.7 (dd, 2F, J = 431.6 Hz, J = 281.7 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 79.9 (t, J = 28.2 Hz), 117.7 (t, J = 238.2 Hz), 126.6, 128.3, 129.0, 133.6, 134.8, 136.5, 137.8, 138.1, 160.1. IR (cm^{-1}, KBr) 3090, 2924, 1738, 1491, 1072, 811. EI-MS (m/z) 272 (M^++2, 12), 270 (M^+, 37), 138 (18), 131 (18), 104 (100). HRMS calcd for $C_{13}H_9ClF_2O_2$: 270.0259, found: 270.0261.

*3.6.3. (E)-6-(4-bromostyryl)-5,5-difluoro-5,6-dihydropyran-2-one (**2c**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.12–5.20 (m, 1H), 6.26 (dd, 1H, J = 6.2 Hz, J = 16.2 Hz), 6.36 (d, 1H, J = 10.0 Hz), 6.82–6.89 (m, 2H), 7.31 (d, 2H, J = 8.4 Hz), 7.49 (d, 2H, J = 8.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −107.7 (dd, 2F, J = 473.2 Hz, J = 281.7 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 79.9 (t, J = 30.4 Hz), 117.8 (t, J = 238.2 Hz), 123.0, 126.6, 126.7, 128.5, 132.0, 134.1, 136.6, 137.8, 160.1. IR (cm^{-1}, KBr) 3088, 2924, 1738, 1487, 1070, 809. EI-MS (m/z) 315 (M^++2, 26), 313 (M^+, 28), 181 (14), 131 (14), 104 (100). HRMS calcd for $C_{13}H_9BrF_2O_2$: 313.9754, found: 331.9755.

*3.6.4. (E)-6-(4-methylstyryl)-5,5-difluoro-5,6-dihydropyran-2-one (**2d**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H), 5.12–5.19 (m, 1H), 6.21 (dd, 1H, J = 16 Hz, J = 7.2 Hz), 6.35 (d, 1H, J = 10.0 Hz), 6.84–6.88 (m, 2H), 7.17 (d, 2H, J = 8.0 Hz), 7.34 (d, 2H, J = 8.0 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −107.6 (s, 2F). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.3, 80.4 (t, J = 30.3 Hz), 112.1 (t, J = 228.2 Hz), 115.9, 126.6, 127.0, 129.5, 132.4, 137.9, 138.0, 139.1, 160.4. IR (cm^{-1}, KBr) 3086, 2924, 1738, 1291, 1074, 811. EI-MS (m/z) 250 (M^+, 67), 146 (20), 131 (100), 118 (22), 104 (54). HRMS calcd for $C_{14}H_{12}F_2O_2$: 250.0805, found: 250.0807.

3.7. General procedure for preparation of **1**

A solution of trifluoroacetic acid (1.7 g, 15 mmol) in methylene chloride (15 mL) was added to a solution of **3** (1 mmol) in methylene chloride (15 mL) at 0 °C dropwise within 30 min. Then the reaction mixture was stirred at room temperature for 12 h and cooled with ice water bath. 5% sodium bicarbonate solution was then added, and the mixture was extracted with methylene chloride. The combined organic phase was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the remaining residue was purified through column chromatography (petroleum ether/ethyl acetate = 3:1) to obtain **1**.

*3.7.1. (E)-5,5-difluoro-4-hydroxy-6-styryl-tetrahydropyran-2-one (**1a**)*

^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.95 (dd, 1H, J = 18.2 Hz, J = 1.4 Hz), 3.06–3.11 (m, 1H), 4.33–4.37 (m, 1H), 5.37–5.43 (m, 1H), 6.24 (dd, 1H, J = 15.9 Hz, J = 7.1 Hz), 6.87 (d, 1H, J = 15.9 Hz), 7.30–7.45 (m, 5H). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −124.2 (dd, 2F, J = 433.8 Hz, J = 254.5 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 34.9, 66.9 (t, J = 27.5 Hz), 77.0 (t, J = 30.4 Hz), 114.5, 116.4 (t, J = 242.4 Hz), 118.1, 122.9, 132, 134.2, 136.4, 167. IR (cm^{-1}, KBr) 3382, 2924, 1723, 1487, 1092, 815. EI-MS (m/z) 254 (M^+, 58), 146 (28), 133 (100), 131 (54), 115 (44), 77 (31). HRMS calcd for $C_{13}H_{12}F_2O_3$: 254.0755, found: 254.0753.

*3.7.2. (E)-6-(4-chlorostyryl)-5,5-difluoro-4-hydroxy-tetrahydropyran-2-one (**1b**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.92–2.96 (m, 1H), 3.03–3.09 (m, 1H), 4.31–4.34 (m, 1H), 5.40 (dt, 1H, J = 20.4 Hz, J = 5.8 Hz), 6.20 (dd, 1H, J = 16 Hz, J = 7.2 Hz), 6.80 (d, 1H, J = 16 Hz), 7.31 (d, 2H, J = 8.4 Hz), 7.35 (d, 2H J = 8.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −124.2 (dd, 2F, J = 432.2 Hz, J = 254.3 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 36.0, 65.8 (t, J = 26.6 Hz), 76.2 (t, J = 29.8 Hz), 116.5, 117.9 (t, J = 238.4 Hz), 128.2, 129.0, 133.8, 134.7, 136.4, 167.1. IR (cm^{-1}, KBr) 3283, 2925, 1704, 1492, 1086, 821. EI-MS (m/z) 290 (M^++2, 13), 288 (M^+, 44), 169 (29), 167 (100), 131 (24). HRMS calcd for $C_{13}H_{11}ClF_2O_3$: 288.0365, found: 288.0355.

*3.7.3. (E)-6-(4-bromostyryl)-5,5-difluoro-4-hydroxy-tetrahydropyran-2-one (**1c**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.92–2.98 (m, 1H), 3.04–3.10 (m, 1H), 4.32–4.35 (m, 1H), 5.39 (dt, 1H, J = 20.3 Hz, J = 5.6 Hz), 6.22 (dd, 1H, J = 16 Hz, J = 7.2 Hz), 6.80 (d, 1H, J = 16 Hz), 7.29 (d, 2H, J = 8.4 Hz), 7.47 (d, 2H J = 8.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −124.2 (dd, 2F, J = 433.8 Hz, J = 254.5 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 35.9, 65.9 (t, J = 28.4 Hz), 76.0 (t, J = 29.5 Hz), 116.4, 118.1 (t, J = 229.8 Hz), 122.8, 128.5, 131.9, 134.2, 136.4, 166.7. IR (cm^{-1}, KBr) 3382, 2925, 1724, 1488, 1092, 815. EI-MS (m/z) 334 (M^++2, 33), 332 (M^+, 33), 213 (80), 211 (100), 131 (42). HRMS calcd for $C_{13}H_{11}BrF_2O_3$: 331.9860, found: 331.9859.

*3.7.4. (E)-6-(4-methylstyryl)-5,5-difluoro-4-hydroxy-tetrahydropyran-2-one (**1d**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H), 2.68–2.76 (m, 2H), 4.22–4.28 (m, 1H), 5.36 (d, 1H, J = 2.0 Hz), 6.09–6.13 (m, 1H), 6.50 (dd, 1H, J = 10.4 Hz, J = 3.2 Hz), 7.17 (d, 2H, J = 8.0 Hz), 7.23 (d, 2H, J = 8.0 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −107.7 (dd, 2F, J = 848.3 Hz, J = 267.4 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.2, 32.9, 68.9 (t, J = 23.5 Hz), 73.8 (t, J = 29.7 Hz), 113.5, 121.8 (t, J = 231.5 Hz), 128.0, 129.2, 133.1, 137.1, 138.6, 175.5. IR (cm^{-1}, KBr) 3422, 2925, 1737, 1324, 1145, 789. EI-MS (m/z) 268 (M^+, 0.3), 248 (20), 189 (100), 119 (17). HRMS calcd for $C_{14}H_{14}F_2O_3$: 268.0911, found: 268.0914.

*3.7.5. (E)-6-(4-methoxystyryl)-5,5-difluoro-4-hydroxy-tetrahydropyran-2-one (**1e**)*

^{1}H NMR ($CDCl_3$,400 MHz) δ 2.68–2.86 (m, 2H), 3.73 (s, 3H), 4.24–4.31 (m, 1H), 5.10–5.12 (m, 1H), 6.92–6.97 (m, 1H), 6.14 (dd, 1H, J = 10.4 Hz, J = 1.2 Hz), 6.82 (d, 2H, J = 8.8 Hz), 7.18 (d, 2H, J = 8.4 Hz). ^{19}F NMR ($CDCl_3$, 367.5 MHz) δ −107.7 (dd, 2F, J = 848.3 Hz, J = 267.4 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 31.6, 54.3, 68.9 (t, J = 24.5 Hz), 72.6 (t, J = 29.3 Hz), 113.1, 119.8 (t, J = 234.2 Hz), 120.1, 127.8, 129.6, 137.9, 158.9, 174.2. IR (cm^{-1}, KBr) 3422, 2962, 1701, 1258, 1034, 812. EI-MS (m/z) 268 (M^+, 11), 264 (11), 205 (100), 135 (80). HRMS calcd for $C_{14}H_{14}F_2O_4$: 284.0860, found: 284.0861.

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