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Palladium-Catalyzed Stereoconvergent Formylation of (*E*/*Z*)-β-Bromo-β-fluorostyrenes: Straightforward Access to (*Z*)-α-Fluorocinnamic Aldehydes and (*Z*)-β-Fluorocinnamic Alcohols

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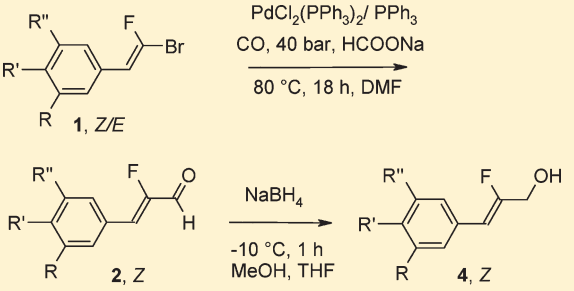
Supporting Information

ABSTRACT: We report here the stereoconvergent formylation of (*E*/*Z*)-β-bromo-β-fluorostyrene mixtures with carbon monoxide and sodium formate catalyzed by palladium. Optimization of reaction conditions leads to the corresponding pure (*Z*)-α-fluorocinnamaldehydes in good yields. The reaction was extended to styrenes bearing electro-attracting or electro-donating groups. The obtained α-fluoroaldehydes were smoothly reduced to the corresponding (*Z*)-β-fluorocinnamic alcohol by $NaBH_4$. The reaction could be performed on functionalized substrates as demonstrated by the access to the glucoside of β-fluoroconiferyl alcohol, (*Z*)-β-fluoroconiferin, a strong inhibitor of lignin polymerization.



INTRODUCTION

In the past few years, there has been an increased interest in fluoroorganic compounds in the pharmaceutical and agrochemical industries.[1,2] Indeed, the introduction of only one fluorine atom in a strategic position often leads to analogues of natural compounds with the same Michaelis−Menten affinity constant but with very different reaction rates or completely different reaction pathways.[3] Among this class of monofluorinated molecules, 2-fluoropropenal and 2-fluoropropenol derivatives have attracted much attention. 2-Fluoropropenals are key intermediates for the synthesis of more complex structures.[4] (*Z*)-α-Fluorocinnamic aldehydes themselves have been transformed in a conjugated chain by reaction with a Wittig−Horner reagent during the synthesis of retinoid X receptor agonists or RXR-selective modulators. They have also been used as precursors to obtain chiral 2-fluoro-3-phenylpropionic acid or transformed into an imine, which leads to chiral fluorinated allyl amines by addition of Grignard reagents.[5] The 2-fluoropropenol motif is also the key structure of several biologically active compounds[6] and is used as a building block.[7] Introduction of a fluorine atom in the cinnamic alcohol part of the Factor Xa inhibitor leads to the most active compound, which furthermore responds negatively to the Ames test, unlike the nonfluorinated analogue.[8] (*Z*)-α-Fluorocinnamic aldehydes and (*Z*)-β-fluorocinnamic alcohols themselves are found in several patents either as intermediate or final products.[9] In most syntheses, 2-fluoropropenol is obtained by the reduction of the corresponding ester synthesized by Wittig−Horner condensation of triethylfluorophosponacetate with a strong reducing reagent such as DIBAL-H. Unlike nonfluorinated conjugated acids, reduction by $NaBH_4$ also may yield the alcohol. The corresponding 2-fluoropropenal is obtained by mild oxidation of the corresponding alcohol, using for example the tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide (TPAP/NMO) system or Dess−Martin reagent. There are few syntheses leading directly to the aldehyde, and they use even harsher conditions, which are not compatible with functionalized molecules.[10] We were confronted with this problem during the synthesis the *O*-glucoside of fluoroconiferyl alcohol, (*Z*)-β-fluoroconiferin, a strong inhibitor of lignin polymerization.[11] The final step involves the reduction of the fully protected glucoside ester by $NaBH_4$ (7.4 equiv), in the presence of LiCl (10 equiv) in glyme (80 °C, 18 h), and leads to a time-consuming purification due to the deprotection of the pentaacetate glucose moiety. As a result, we are particularly interested in applying the same strategy we developed for the synthesis of the natural compound coniferin, which is based on the mild reduction of the corresponding aldehyde by $NaBH_4$.[12]

Our group and others have proposed an efficient methodology for the stereoselective access to fluoroolefins starting from α-bromo-α-fluoroolefins by palladium-catalyzed coupling reactions.[13] These olefins could be easily obtained via a Zn(Cu)- or Et_2Zn-promoted Wittig−Burton reaction of CBr_3F and PPh_3 with aldehydes, which gave an *E*/*Z* α-bromo-α-fluorolefins mixture in good yields.[14] Recently, Burton et al. have described

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Scheme 1. Reaction of β-Bromo-β-fluorostyrene 1 with CO and HCOONa Catalyzed by $PdCl_2(PPh_3)_2$

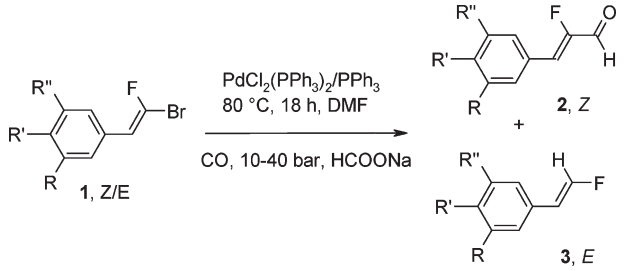


Table 1. Effects of Several Parameters on the Formylation of β-Bromo-β-fluorostyrene 1a[a]

						isolated yield (%)	
entry	solvent	HCOONa (equiv)	T (°C)	P(CO)	t (h)	**2a**, Z	**3a**, E
a	ACN	1.0	100	1	48	0	30
b	THF	1.0	100	1	48	0	30
c	DMSO	1.0	100	1	48	0	20
d	DMF	1.0	100	1	48	20	51
e	DMF	0.5	100	1	48	6	21
f	DMF	5.0	100	1	48	0	0
g	DMF	1.0	80	10	18	31	41
h	DMF	1.0	80	40	18	78	20

[a] **1a** E/Z mixture (26/74), (1.83 mmol), PPh_3 (0.18 mmol), powdered HCOONa (1 equiv: 1.83 mmol), $PdCl_2(PPh_3)_2$ (0.091 mmol), solvent (13 mL), CO (P bar)) at T °C for t h.

the convergent carbonylation reactions of 1,2-difluoro-1-iodoolefins or 1-bromo-1-fluoroolefins with carbon monoxide in the presence of an alcohol or amine, catalyzed by palladium, leading to (E)- and (Z)-α-fluoro-α,β-unsaturated esters and amides.[15]

Starting from these interesting results, we decided to investigate the formylation of α-bromo-α-fluoroolefins by CO in the presence of a reducing reagent and catalyzed by palladium. The palladium-catalyzed formylation of aryl or vinyl halides[16] is less documented than their carbonylation.[17] Whereas the carbonylation of nonfluorinated gemdihalides has previously been described by one of the authors,[18] their formylation has not been documented. Nevertheless, several mild conditions have been described for the formylation of aryl or vinyl halides.[19] Among those, we chose to use as hydrogen source for the formylation sodium formate, a very weak reducing agent that is easily handled and does not introduce any toxic reagents which could be deleterious for biological tests.[20]

RESULTS AND DISCUSSION

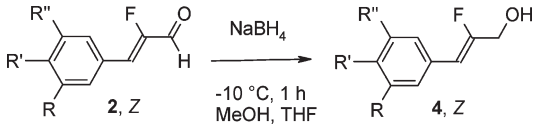
Formylation Optimization. We were delighted to find that under Okano's standard conditions (HCOONa, 1 equiv; CO pressure 1 bar; DMF, 100 °C for 18 h)[20] an E/Z mixture (26/74) of β-bromo-β-fluorostyrene itself **1a** gave the expected (Z)-α-fluorocinnamicaldehyde in pure Z configuration (Scheme 1). However, the reaction mixture also contained the expected reduction product, α-fluorolefin byproduct **3a**, but in pure E configuration (Table 1, entry d). Carbon−fluorine bond reduction is much more difficult than carbon−chlorine bond reduction, as observed during the reaction of 1-chloro-1-fluoroethylene in the presence of Et_3SiH using $(PPh_3)_3RhCl$ as catalyst at 35 °C.[21] So, as expected for a palladium-catalyzed reaction, no fluorine atom loss was observed even in our strongly reducing conditions due to the presence of carbon monoxide and sodium formate. The reduction of the double bond, which has been previously described on α-fluoroconjugated aldehydes using Pd/C as catalyst, was also not detected.[22]

Table 2. Formylation of Substituted β-Bromo-β-fluorostyrenes 1 with Sodium Formate (1 equiv) under 40 bar Pressure of CO in DMF[a]

1	R, *meta*	R′, *para*	R″, *meta*	**1** (E/Z)[c]	**2/3**	isolated yield (%) **2**
1a	H	H	H	26/74	87/13	78
1b	H	Cl	H	90/10	85/15	74
1c	H	F	H	74/26	90/10	81
1d	H	NO_2	H		91/9	76
1e	MeO	H	MeO		95/5	85
1f	Br	MeO	H	73/27	90/10	84
1g	MeO	GluO[b]	H		67/33	61
1h	H	GluO[b]	H		67/33	61
1i	MeO	GluO[b]	MeO		67/33	60

[a] Substrate **1** (1.83 mmol), PPh_3 (0.18 mmol), powdered HCOONa (1.83 mmol), $PdCl_2(PPh_3)_2$ (0.091 mmol), DMF (13 mL), and CO (40 atm) at 80 °C for 18 h. [b] GluO = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl. [c] From ^{19}F NMR and checked by GC−MS.

Scheme 2. Reduction of (Z)-α-Fluorocinnaldehydes 2 by Sodium Borohydride



In order to optimize the reaction, several parameters were examined: (i) nature of the solvent, (ii) number of sodium formate equivalents, (iii) temperature, (iv) CO pressure, and (v) reaction time.

The trend observed is very similar to the behavior of bromobenzene.[20] The reaction in apolar solvents such as acetonitrile and THF gave only reduction product **3a** (Table 1, entries a, b). However, formylation of β-bromo-β-fluorostyrene appears to be more sensitive as no product is observed in DMSO (Table 1, entry c), unlike bromobenzene, which gave a fair yield.

The reaction yield and the product repartition also depend on the amount of sodium formate used. Formation of the reduction byproduct **3a** was favored when only 0.5 equiv of HCOONa was added to the mixture, leading to a **2**/**3** ratio of 0.3 (Table 1, entry e). The **2**/**3** ratio increased to 0.4 when 1 equiv of HCOONa was used (Table 1, entry d). However, no reaction was observed when an excess of sodium formate was used (Table 1, entry f), unlike the result observed for bromobenzene. The data shown in Table 1 (entries d and e) suggest that (Z)-β-bromo-β-fluorostyrene **1a**, Z reacts preferentially to give the reduced (E)-β-fluorostyrene **3a**, E, whereas (E)-β-bromo-β-fluorostyrene **1a**, E leads to (Z)-α-fluorocinnamaldehyde **2a**, Z.

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As expected, the use of high CO pressures resulted in an increase of the aldehyde yield but also in a sharp increase of the reaction rate, allowing a decrease in temperature from 100 to 80 °C and in reaction time from 48 to 18 h (Table 1, entries g, h). In these optimized conditions, no (*E*)-α-fluorocinnamicaldehyde **2a**, *E* was detected and the percentage of (*Z*)-α-fluorocinnamaldehyde **2a**, *Z* (74%) was higher than the percentage of (*E*)-*β*-bromo-*β*-fluorostyrene **1a**, *E* (26%). This result suggests that (*E*)-α-fluorocinnamaldehyde **2a**, *E* obtained from (*Z*)-*β*-bromo-*β*-fluorostyrene **1a** is isomerized in the reaction conditions. The same isomerization was previously observed during the palladium-catalyzed formylation of (*Z*)-*β*-bromostyrene by CO/H_2, which yielded (*E*)-cinnamaldehyde.[16d] The fact that we obtain (*E*)-α-fluorocinnamaldehyde **2a** instead of the reduced product (*E*)-*β*-fluorostyrene **3a** at higher CO pressure can be explained by an easier insertion of CO on the *π*-allylpalladium intermediate, which is less stable in the case of the (*Z*)-*β*-bromo-*β*-fluorostyrene **1a** isomer. In summary, high CO pressure favors orienting the reaction toward the formation of α-fluorocinnamaldehyde **2a** and so decreases the formation of the reduced (*E*)-*β*-fluorostyrene **3a**. This is shown by the **2a**/**3a** ratio, which increases from 0.4 to nearly 4 when CO pressure is increased from 1 to 40 bar (Table 1, entries d and h). As (*E*)-α-fluorocinnamaldehyde **2a** isomerizes in the reaction medium, the combination of a 80 °C temperature and high CO pressures (40 bar) allowed us to isolate pure (*Z*)-α-fluorocinnamaldehyde **2a** in 78% yield.

Table 3. Reduction of Substituted (*Z*)-α-Fluorocinnaldehydes 2 by $NaBH_4$

4	R, *meta*	R′, *para*	R″, *meta*	isolated yield (%) **4**
4a	H	H	H	86
4b	H	Cl	H	84
4c	H	F	H	87
4d	H	NO_2	H	90
4e	MeO	H	MeO	93
4f	Br	MeO	H	83
4g	MeO	GluO[a]	H	80
4h	H	GluO[a]	H	78
4i	MeO	GluO[a]	MeO	74

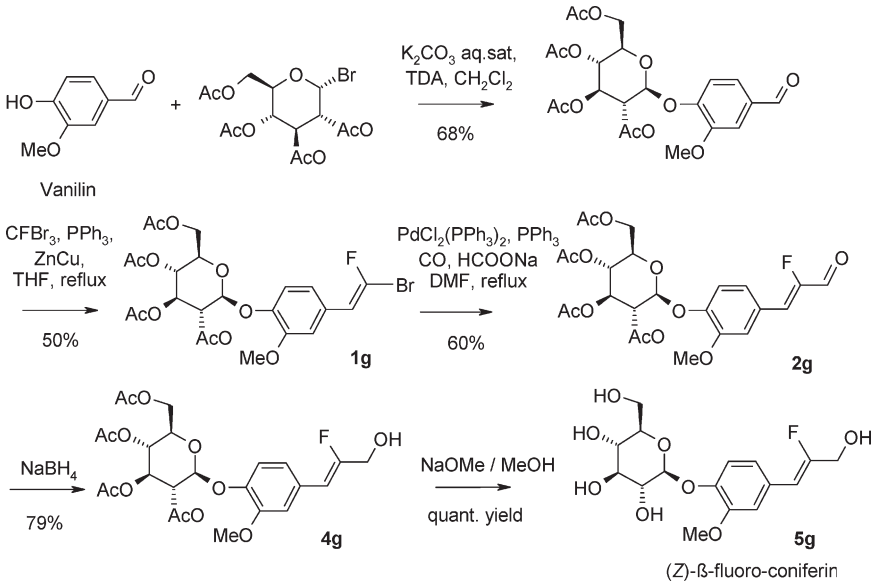
[a] GluO = 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl.

The most frequently described mechanism for the formylation of aryl bromide in presence of formate involves (i) the oxidative addition of the substrate to the Pd(0) catalyst, (ii) the insertion of CO, (iii) the exchange of the bromide by the formate anion, (iv) the expulsion of carbon dioxide leading to a palladium hydride species, and (v) the transfer of the hydride leading to the aldehyde.[20] This mechanism implies that the hydrogen on the aldehyde comes from the formate anion. However, recently Zawisza et al. have shown that in the palladium-catalyzed reduction of aryl halides using dimethylformamide as solvent DMF is the hydride source.[23a] In order to check the origin of the hydrogen in the aldehyde group, the reaction was performed in DMF-d_7 under the optimized reaction on substrate **1d**. The mass spectrum obtained by GC−MS analysis using electron ionization at 70 eV shows no incorporation of deuterium in the aldehyde **2d**. This result is highly in favor of a mechanism identical to the one described previously for the formylation of aryl bromide in which the hydrogen on the aldehyde comes from the formate anion. Dimethylformamide was also described as a source of CO in Pd-catalyzed reaction under microwave irradiation.[23b] The strong dependency of the formylation reaction yield on CO pressure precludes this mechanism.

These conditions were applied to the formylation of a wide variety of *β*-bromo-*β*-fluorostyrenes (Table 2) bearing either simple electron-donating groups (substrate **1h**), weakly or strongly electron-attractive groups (substrates **1b**, **c** and **1d**, **e** respectively), mixed groups (substrates **1f**, **g**, **i**), and functionalized groups (substrates **1g**, **h**, **i**). In each case, (*Z*)-α-fluorocinnaldehydes were exclusively isolated and the observed formylation yields ranged from good to excellent. The comparison of *E*/*Z* ratio from the starting material **1** to the **2**/**3** ratio demonstrates that the reaction is steroconvergent.

Reduction of (*Z*)-α-Fluoro Conjugated Aldehydes to (*Z*)-*β*-Fluoro Conjugated Alcohols. The reduction of

Scheme 3. Synthesis of (*Z*)-*β*-Fluoroconiferin



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(*Z*)-α-fluorocinnaldehydes by sodium borohydride in cold methanol (−10 °C), not previously described to the best of our knowledge, afforded the corresponding (*Z*)-*β*-fluorocinnamyl alcohols **4** in good yield (74−93%) without saturation of the double bond (Scheme 2 and Table 3) as observed for other (*Z*)-α-substituted α,*β*-conjugated aldehydes bearing a chlorine, a bromine, an iodine, or an alkoxy group.[24]

Synthesis of (*Z*)-*β*-Fluoroconiferin and Analogues. This methodology gave us a new and straightforward access to (*Z*)-*β*-fluoroconiferin (Scheme 3). Vanilin was first *O*-glucosylated by reaction with 1-bromo-2,3,4,6-tetraacetyl-*β*-D-glucopyranoside in biphasic conditions, using tris-2-(2-methoxy-ethoxy-ethyl)-amine (TDA) as the phase transfer agent.[25] The corresponding α-bromo-α-fluoroolefin **1g** was obtained via a Zn(Cu)-promoted Wittig−Burton-type reaction with CBr_3F and PPh_3 in THF.[13e]

Formylation of **1g** was achieved with CO, sodium formate, and Pd under the optimized conditions previously mentioned to give the corresponding pure (*Z*)-α-fluoroaldehyde **2g** (Table 2, entry 1g). Reduction of aldehyde **2g** into alcohol **4g** was accomplished by sodium borohydride in THF. Finally, (*Z*)-*β*-fluoroconiferin **5g** was obtained by deprotection of acetyl groups by sodium methanoate in quantitative yields.[11,12] The two others fluorinated analogues of lignin precursors **5h** (R = R′ = H) and **5i** (*Z*)-*β*-fluorosyringin (R = R′ = OMe) were obtained in a similar way.

CONCLUSION

We report on a new and efficient synthesis of (*Z*)-α-fluoroaldehydes that involves formylation of α-bromo-α-fluoroolefins *Z*/*E* mixture with carbon monoxide and sodium formate and is catalyzed by palladium. Optimization of the reaction parameters allowed us to drive the formylation toward the formation of pure (*Z*)-α-fluoroaldehydes in good yields.

This method can be extended to functionalized substrates such as α-bromo-α-fluorostyrene *p*-*O*-glucoside derivative **1g**, which leads to pure (*Z*)-*β*-fluoroconiferin **5g** after reduction and deprotection. By using this straightforward synthesis, several hundred milligrams of (*Z*)-*β*-fluoroconiferin **5g** and analogues **5h** and **5i** were obtained and will be used to further understand the inhibition of lignin biosynthesis in plantlets growing in an artificial medium.[11,26] Experiments are in progress and results will be published in a forthcoming paper.

EXPERIMENTAL SECTION

All commercially available products were used as received. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl under argon before use. Dimethylformamide (DMF) was distilled under reduced pressure before use. For flash chromatography, silica- gel 60 (230−400 mesh ASTM) was used. The melting points were not corrected. NMR spectra were recorded at 300 MHz for ^1H and ^{13}C, using $CDCl_3$ or CD_3OD as solvents and TMS as internal standard; chemical shifts and *J* values are given in ppm and Hz, respectively. Deuterated solvents were 99.9% or better. GC−MS were recorded on an ion trap mass spectrometer fitted with a 60 m × 0.32 mm apolar column using electron ionization (EI) at 70 eV. Fast atom bombardment (FAB) mass spectra were measured on a high resolution double focusing magnetic sector mass spectrometer.

General Procedure for the Preparation of *β*-Bromo-*β*-fluorostyrenes. Glucosyloxy-benzaldehydes (1 mmol), fluorotribromethane (1.5 equiv, 2 mmol), triphenylphosphine (1 equiv, 1 mmol), and 5 mL of freshly distilled THF were added under argon to a flask fitted with a reflux condenser. Then freshly prepared Zn(Cu) (1.5 equiv 2 mmol) was added. The solution was refluxed for 7 h. After cooling, the organic phase was diluted in diethyl ether, then washed with water, and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was purified by flash column chromatography using a mixture of ethyl acetate/dichloromethane as eluent to obtain the desired *β*-bromo-*β*-fluoroolefins as an *E*/*Z* mixture (50/50).

2,3,4,6-Tetra-*O*-acetyl-1-[4-((2*Z*)-2-fluoro-2-bromoethenyl)-2-methoxyphenyl]-*β*-D-glucopyranoside (1g). Mp 79−80 °C; ^{19}F NMR ($CDCl_3$) *δ* −69.22 (d, *E*, $^3J_{HF}$ = 32.5 Hz, 1 F), −65.99 (d, *Z*, $^3J_{HF}$ = 14.9 Hz, 1 F) ppm; ^1H NMR ($CDCl_3$) *δ* 2.02 (s, 6 H), 2.06 (s, 3 H), 2.15 (s, 3 H), 3.72−3.78 (m, 1 H), 3.79 (s, *Z*, 1.5 H), 3.81 (s, *E*, 1.5 H), 4.11 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 2.5 Hz, 1 H), 4.22 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 5.1 Hz, 1 H), 4.90−5.17 (m, 2 H),5.25−5.30 (m, 2 H), 5.90 (d, *E*, $^3J_{HF}$ = 32.2 Hz, 0.5 H), 6.59 (d, Z, $^3J_{HF}$ = 14.9 Hz, 0.5 H), 6.86 (d, *Z*, $^3J_{HH}$ = 8.4 Hz, 0.5 H), 6.87 (d, *E*, $^3J_{HH}$ = 8.4 Hz, 0.5 H), 6.95 (dd, *Z*, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.9 Hz, 0.5 H), 6.96 (dd, *E*, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.9 Hz, 0.5 H), 7.05 (d, *Z*, $^4J_{HH}$ = 1.9 Hz, 0.5 H), 7.06 (d, *E*, $^4J_{HH}$ = 1.9 Hz, 0.5 H) ppm. Elemental analysis: theoretical for $C_{23}H_{26}BrFO_{11}$ ($C_4H_8O_2$) C, 48.73, H, 5.15, O, 31.26; observed C, 48.40, H, 5.04, O, 31.52.

2,3,4,6-Tetra-*O*-acetyl-1-[4-((2*Z*)-2-fluoro-2-bromoethenyl)-phenyl]-*β*-D-glucopyranoside (1h). Mp 72−73 °C; ^{19}F NMR ($CDCl_3$) *δ* −69.79 (d, *E*, $^3J_{HF}$ = 32.8 Hz, 1 F) ppm, −66.47 (d, *Z*, $^3J_{HF}$ = 15.0 Hz, 1 F) ppm; ^1H NMR ($CDCl_3$) *δ* 2.03 (s, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 2.06 (s, 3 H), 3.82−3.89 (m, 1 H), 4.13 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 2.5 Hz, 1 H), 4.22 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 5.1 Hz, 1 H), 5.06−5.19 (m, 2 H), 5.25−5.35 (m, 2 H), 5.91 (d, *E*, $^3J_{HF}$ = 32.4 Hz, 0.5 H), 6.59 (d, *Z*, $^3J_{HF}$ = 14.5 Hz, 0.5 H), 6.94 (d, Z, $^3J_{HH}$ = 8.6 Hz, 1 H), 6.96 (d, *E*, $^3J_{HH}$ = 8.7 Hz, 1 H), 7.32 (d, *Z*, $^3J_{HH}$ = 8.9 Hz, 1 H), 7.40 (d, *E*, $^3J_{HH}$ = 8.8 Hz, 1 H) ppm. Elemental analysis: theoretical for $C_{22}H_{24}BrFO_{10}$ ($C_4H_8O_2$) C, 49.14, H, 5.08, O, 30.21; observed C, 49.87, H, 4.91; O, 30.62.

2,3,4,6-Tetra-*O*-acetyl-1-[4-((2*Z*)-2-fluoro-2-bromoethenyl)-2,6-dimethoxyphenyl]-*β*-D-glucopyranoside (1i). Mp 83−84 °C; NMR ^{19}F ($CDCl_3$, 300 MHz) *δ* −68.52 (d, *E*, $^3J_{HF}$ = 32.3 Hz, 1 F), - 65.52 (d, *Z*, $^3J_{HF}$ = 15.1 Hz, 1 F) ppm; ^1H NMR ($CDCl_3$) *δ* 1.99 (s, 3 H), 2.01 (s, 3 H), 2.02 (s, 3 H), 2.04 (s, 3 H), 3.64−3.72 (m, 1 H), 3.79 (s, *Z*, 3 H), 3.81 (s, *E*, 3 H), 4.13 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 2.5 Hz, 1 H), 4.22 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 5.1 Hz, 1 H), 5.03−5.31 (m, 4 H), 5.88 (d, *E*, $^3J_{HF}$ = 32.2 Hz, 0.5 H), 6.57 (d, *Z*, $^3J_{HF}$ = 14.5 Hz, 0.5 H), 6.59 (s, *Z*, 1 H), 6.69 (s, *E*, 1 H) ppm. Elemental analysis: theoretical for $C_{24}H_{28}BrFO_{12}$ C, 47.46, H, 4.65, O, 31.61; observed C, 47.51, H, 4.92, O, 32.23.

General Procedure for the Preparation of (*Z*)-α-Fluorocinnamic aldehydes. A 50 mL stainless steel autoclave equipped with a magnetic stirrer bar was charged with *β*-bromo-*β*-fluoroolefins (0.5 mmol), $PdCl_2(PPh_3)_2$ (5%), PPh_3 (10%), HCOONa (0.5 mmol), and 5 mL of DMF under nitrogen. The autoclave was pressurized to 40 bar with CO, and the mixture was agitated and warmed at 80 °C for 18 h. After cooling to room temperature, the reactor was vented, the crude solution was filtered, then the resulting precipitate was washed with dichloromethane, and the solvents were evaporated. The resulting residue was diluted in dichloromethane and washed with water (3 × 50 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated. The product was isolated by flash column chromatography using a mixture of ethyl acetate/petroleum ether as eluent.

(2*Z*)-2-Fluoro-3-phenyl-2-propenal (2a). ^{19}F NMR ($CDCl_3$) *δ* −126.54 (dd, $^3J_{HF}$ = 33.2 Hz, $^3J_{HF}$ = 17.2 Hz) ppm; ^1H NMR ($CDCl_3$) *δ* 6.61 (d, $^3J_{HF}$ = 33.1 Hz, 1 H), 7.33 (m, 1 H), 7.47 (d, $^3J_{HH}$ = 8.4 Hz, 2 H), 7.73 (d, $^3J_{HH}$ = 8.4 Hz, 2 H), 9.37 (d, $^3J_{HF}$ = 17.2 Hz, 1 H) ppm; ^{13}C NMR ($CDCl_3$) *δ* 121.14 (d, $^2J_{CF}$ = 4.2 Hz), 128.45, 129.02, 130.28, 131.25, 155.24 (d, $^1J_{CF}$ = 264.8 Hz), 183.15 (d, $^2J_{CF}$ = 26.4 Hz) ppm. MS (EI) *m*/*z* (relative intensity): 150 (M^+, 42), 149 (100),

121 (16), 101 (21), 96 (19), 75 (18). HRMS (m/z): observed 151.0554, calcd for C_9H_8OF 151.0553 $[M + H]^+$.

(2*Z*)-2-Fluoro-3-(4-chlorophenyl)-2-propenal (2b). ^{19}F NMR ($CDCl_3$) δ −128.04 (dd, $^3J_{HF}$ = 33.7 Hz, $^3J_{HF}$ = 16.9 Hz) ppm. ^1H NMR ($CDCl_3$) δ 6.57 (d, $^3J_{HF}$ = 33.7 Hz, 1 H), 7.41 (d, $^3J_{HH}$ = 8.6 Hz, 2 H), 7.64 (d, $^3J_{HH}$ = 8.6 Hz, 2 H), 9.35 (d, $^3J_{HF}$ = 16.7 Hz, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 125.15 (d, $^2J_{CF}$ = 3.8 Hz), 129.05 (d, $^4J_{CF}$ = 4.2 Hz), 129.42, 131.76, 136.18, 155.24 (d, $^1J_{CF}$ = 271.72), 183.15 (d, $^2J_{CF}$ = 25.75 Hz) ppm. MS (EI) m/z (relative intensity): 186 (M^+ + 2, 7), 184 (M^+, 21), 183 (15), 150 (10), 149 (100), 121 (14), 120 (18), 112 (7), 101 (25), 99 (9), 75 (14), 74 (11). HRMS (m/z): observed 185.0160, calcd for C_9H_7OClF 185.0164 $[M + H]^+$.

(2*Z*)-2-Fluoro-3-(4-fluorophenyl)-2-propenal (2c). ^{19}F NMR ($CDCl_3$) δ −129.86 (dd, $^3J_{HF}$ = 33.9 Hz, $^3J_{HF}$ = 16.9 Hz, 1 F), 107.53 (m, 1 F) ppm; ^1H NMR ($CDCl_3$) δ 6.57 (d, $^3J_{HF}$ = 34.0 Hz, 1 H), 7.14 (dd, $^3J_{HF}$ = 8.7 Hz, $^3J_{HH}$ = 8.7 Hz, 2 H), 7.72 (dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HF}$ = 5.4 Hz, 2 H), 9.34 (d, $^3J_{HF}$ = 16.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$) δ 116.37 (d, $^2J_{CF}$ = 21.9 Hz), 125.41 (d, $^2J_{CF}$ = 3.6 Hz), 126.9, 132.80 (dd, $^3J_{CF}$ = 8.4 Hz, $^4J_{CF}$ = 8.4), 154.41(d, $^1J_{CF}$ = 267.5 Hz), 163.95 (d, $^1J_{CF}$ = 250.0), 183.76 (d, $^2J_{CF}$ = 25.7 Hz) ppm. MS (EI) m/z (relative intensity): 168 (M^+, 48), 167 (100), 149 (7), 140 (9), 139 (19), 120 (18), 119 (27), 114 (11), 99 (22), 96 (20), 75 (7), 74 (10). HRMS (m/z): observed 169.0456, calcd for $C_9H_7OF_2$ 169.0459 $[M + H]^+$.

(2*Z*)-2-Fluoro-3-(4-nitrophenyl)-2-propenal (2d). ^{19}F NMR ($CDCl_3$) δ −124.04 (dd, $^3J_{HF}$ = 33.1 Hz, $^3J_{HF}$ = 15.7 Hz) ppm; ^1H NMR ($CDCl_3$) δ 6.68 (d, $^3J_{HF}$ = 33.1 Hz, 1 H), 7.86 (d, $^3J_{HH}$ = 8.8 Hz, 2 H), 8.27 (d, $^3J_{HH}$ = 8.8, 2 H), 9.44 (d, $^3J_{HF}$ = 15.7 Hz, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 122.54 (d, $^2J_{CF}$ = 3.5 Hz), 124.17, 131.25, 136.53 (d, $^3J_{CF}$ = 4.2), 148.45, 155,70 (d, $^1J_{CF}$ = 277.1 Hz), 183,61 (d, $^2J_{CF}$ = 27.5 Hz) ppm. MS (EI) m/z (relative intensity): 195 (M^+, 27), 179 (18), 178 (100) 165 (12), 149 (20), 148 (70), 120 (12), 109 (14), 101 (48), 95 (7), 83 (13), 75 (53), 74 (19). HRMS (m/z): observed 196.0400, calcd for $C_9H_7O_3NF$: 196.0404 $[M + H]^+$.

(2*Z*)-2-Fluoro-3-(3,5-dimethoxyphenyl)-2-propenal (2e). ^{19}F NMR ($CDCl_3$) δ −127.94 (dd, $^3J_{HF}$ = 33.6 Hz, $^3J_{HF}$ = 16.9 Hz) ppm; ^1H NMR ($CDCl_3$) δ 3.81 (s, 6 H), 6.55 (s, 1 H), 6.58 (d, $^3J_{HF}$ = 33.6 Hz, 1 H), 6.85 (s, 2 H), 9.33 (d, $^3J_{HF}$ = 17.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 55.47, 103.34, 108.53, 126.87, 132.15, 154.09 (d, $^1J_{CF}$ = 271.4 Hz), 160.86, 183.98 (d, $^2J_{CF}$ = 25.4 Hz) ppm. MS (EI) m/z (relative intensity): 210 (M^+, 100), 182 (80), 153 (58), 152 (15), 123 (10), 122 (22), 121 (10), 109 (20), 107 (12), 105 (40), 103 (20), 96 (20). HRMS (m/z): observed 211.0764, calcd for $C_{11}H_{12}O_3F$ 211.0765 $[M + H]^+$.

(2*Z*)-2-Fluoro-3-(3-bromo-4-methoxyphenyl)-2-propenal (2f). ^{19}F NMR ($CDCl_3$) δ −130.23 (dd, $^3J_{HF}$ = 34.2 Hz, $^3J_{HF}$ = 17.2 Hz) ppm.^1H NMR ($CDCl_3$) δ 3.94 (s, 3 H), 6.51 (d, $^3J_{HF}$ = 34.1 Hz, 1 H), 6.95 (d, $^3J_{HH}$ = 9.0 Hz, 1 H), 7.66 (d, $^3J_{HH}$ = 9.0 Hz, 1 H), 7.90 (s, 1 H), 9.29 (d, $^3J_{HF}$ = 17.2 Hz, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 56.41, 111.95, 112.34, 124.61, 125.29, 131.48 (d, $^4J_{CF}$ = 8.4 Hz), 135.48 (d, $^4J_{CF}$ = 8.1 Hz), 154.30 (d, $^1J_{CF}$ = 269.1 Hz), 157.77, 183.53 (d, $^2J_{CF}$ = 24.9 Hz) ppm. MS (EI) m/z (relative intensity): 260 (M^+ + 1, 68), 259 (M^+, 18), 258 (M^+ - 1, 70), 229 (30), 227(30), 215 (10), 188 (12), 179 (100), 164 (13), 136 (41), 1107 (41), 81 (12), 75 (10). HRMS (m/z): observed 258.9760, calcd for $C_{10}H_9O_2BrF$ 258.9764 $[M + H]^+$.

(2*Z*)-2-Fluoro-3-[4-(2,3,4,6-tetra-*O*-acetyl)-β-D-glucopyranosyloxy-3-methoxyphenyl]-2-propenal (2g). Mp 123−125 °C; ^{19}F NMR ($CDCl_3$) δ −130.17 (dd, $^3J_{HF}$ = 33.9 Hz, $^3J_{HF}$ = 17.1 Hz, 1 F) ppm; ^1H NMR ($CDCl_3$) δ 2.02 (s, 6 H), 2.05 (s, 6 H), 3.76−3,82 (m, 1 H), 3.83 (s, 3 H), 4.15 (dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 7.1 Hz, 1 H), 4.25 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 4.9 Hz, 1 H), 5.01−5.17 (m, 2 H), 5.24−5.33 (m, 2 H), 6.55 (d, $^3J_{HF}$ = 34.0 Hz, 1 H), 7.12 (d, $^3J_{HH}$ = 8 Hz, 1 H), 7.20 (d, $^3J_{HH}$ = 7.8 Hz, 1 H), 7.29 (s, 1 H), 9.30 (d, $^3J_{HF}$ = 17.2 Hz, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.61, 56.12, 61.84, 68.29, 71.04, 72.14, 72.41, 100.02, 114.25, 119.14, 124.43, 126.32, 126.91, 148.07, 150.61, 154.44, 169.22, 169.39, 170.25, 170.53, 183.72 ppm. HRMS (NH_3) (m/z): observed 544.1833, calcd for $C_{24}H_{31}O_{12}NF$ 544.1825.

(2*Z*)-2-Fluoro-3-[4-(2,3,4,6-tetra-*O*-acetyl)-β-D-glucopyranosyloxy-phenyl]-2-propenal (2h). Mp 114−115 °C; ^{19}F NMR ($CDCl_3$, 300 MHz) δ −130.63 (dd, $^3J_{HF}$ = 34.2 Hz, $^3J_{HF}$ = 17.4 Hz, 1 F) ppm; ^1H ($CDCl_3$) δ 2.02 (s, 6 H), 2.04 (s, 3 H), 2.08 (s, 3 H), 3.86−3.91 (m, 1 H), 4.1 (dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 7.09 Hz, 1 H), 4.27 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 4.9 Hz, 1 H), 5.13−5.20 (m, 2 H), 5.27−5.31 (m, 2 H), 6.56 (d, $^3J_{HF}$ = 34.2 Hz, 1 H), 7.02 (d, $^3J_{HH}$ = 8.4 Hz, 2 H), 7.66 (d, $^3J_{HH}$ = 8.4 Hz, 2 H), 9.30 (d, $^3J_{HF}$ = 17.4 Hz, 1 H) ppm; NMR ^{13}C ($CDCl_3$) δ 20.61, 61.81, 68.13, 71.03, 72.28, 72.52, 98.29, 117.01, 125.82, 126.10, 132.54, 154.41, 158.41, 169.18, 169.42, 170.22, 170.41, 183.74 ppm. HRMS (NH_3) (m/z): observed 514.1722, calcd for $C_{23}H_{29}O_{11}NF$ 514.1719.

(2*Z*)-2-Fluoro-3-[4-(2,3,4,6-tetra-*O*-acetyl)-β-D-glucopyranosyloxy-3,5-dimethoxyphenyl]-2-propenal (2i). Mp 125−127 °C; ^{19}F NMR ($CDCl_3$) δ −129.49 (dd, $^3J_{HF}$ = 33.6 Hz, $^3J_{HF}$ = 17.1 Hz, 1 F); ^1H NMR ($CDCl_3$) δ 2.02 (s, 6 H), 2.04 (s, 3 H), 2.07 (s, 3 H), 3.40−3.69 (m, 1 H), 3.85 (s, 6 H), 4.12 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 7.3 Hz, 1 H), 4.27 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 4.9 Hz, 1 H), 4.98−5.17 (m, 2 H), 5.26−5.30 (m, 2 H), 6.52 (d, $^3J_{HF}$ = 33.6 Hz, 1 H), 6.93 (s, 2 H), 9.32 (d, $^3J_{HF}$ = 17.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.60, 56.41, 62.20, 68.45, 71.23, 72.02, 72.88, 100.81, 108.10, 126.43, 127.09, 136.58, 153.22, 154.61, 169.23, 169.44, 170.26, 170.51, 183.70 ppm. HRMS (NH_3) (m/z): observed 574.1927, calcd for $C_{25}H_{33}O_{13}NF$ 574.1930.

General Procedure for the Preparation of (*Z*)-β-Fluorocinnamic Alcohols. $NaBH_4$ (1.3 mmol) was added to a solution of α-fluoroaldehydes (1 mmol) in a mixture of MeOH/THF (50:50) at −10 °C. The solution was stirred at room temperature for 2 h, and then 20 mL of HCl (1%) was added to reach pH = 4. After solvent evaporation, the residue was extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated. The product was isolated by flash column chromatography using a mixture of ethyl acetate/petroleum ether as eluent.

(2*Z*)-2-Fluoro-3-phenyl-2-propen-1-ol (4a). ^{19}F NMR ($CDCl_3$) δ −110.86 (dt, $^3J_{HF}$ = 38.9 Hz, $^3J_{HF}$ = 14.8 Hz) ppm; ^1H NMR ($CDCl_3$) δ 4.46 (d, $^3J_{HF}$ = 14.8 Hz, 2 H), 5.56 (d, $^3J_{HF}$ = 38.9 Hz, 1 H), 7.26 (m, 1 H), 7.32 (d, $^3J_{HH}$ = 8.4 Hz, 2 H), 7.52 (d, $^3J_{HH}$ = 8.4 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ 61.22 (d, $^2J_{CF}$ = 28.8 Hz) 102.26 (d, $^2J_{CF}$ = 6.7 Hz), 128.17, 128.92, 130.18, 131.97, 157.93 (d, $^1J_{CF}$ = 265.9 Hz) ppm. MS (EI) m/z (relative intensity): 152 (M^+, 76), 133 (39), 131 (100), 106 (43), 91 (45), 78 (48), 77 (34), 51 (16). HRMS (m/z): observed 153.0710, calcd for $C_9H_{10}OF$ 153.0710 $[M + H]^+$.

(2*Z*)-2-Fluoro-3-(4-chlorophenyl)-2-propen-1-ol (4b). ^{19}F NMR ($CDCl_3$) δ −112.76 (dt, $^3J_{HF}$ = 38.3 Hz, $^3J_{HF}$ = 13.7 Hz) ppm; ^1H NMR ($CDCl_3$) δ 4.27 (d, $^3J_{HF}$ = 13.7 Hz, 2 H) 6.57 (d, $^3J_{HF}$ = 38.5 Hz, 1 H), 7.27 (d, $^3J_{HH}$ = 8.6 Hz, 2 H), 7.41 (d, $^3J_{HH}$ = 8.6 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ 61.47 (d, $^2J_{CF}$ = 32.9 Hz), 106.38 (d, $^2J_{CF}$ = 6.5 Hz), 128.69, 129.86, 131.17, 133.11, 158.58 (d, $^1J_{CF}$ = 267.4 Hz) ppm. MS (EI) m/z (relative intensity): 188 (M^+ + 2, 23), 186 (M^+, 59), 167 (28), 149 (47), 131 (100), 125 (59), 111 (45), 103 (33), 97 (24), 81 (24), 57 (40). HRMS (m/z): observed 187.0317, calcd for C_9H_9OClF 187.0320 $[M + H]^+$.

(2*Z*)-2-Fluoro-3-(4-fluororophenyl)-2-propen-1-ol (4c). ^{19}F NMR ($CDCl_3$) δ −114.81 (dt, $^3J_{HF}$ = 37.9 Hz, $^3J_{HF}$ = 14.3 Hz, 1 F), 113.97 (m, 1 F) ppm; ^1H NMR ($CDCl_3$) δ 4.28 (d, $^3J_{HF}$ = 14.5 Hz, 2 H), 5.75 (d, $^3J_{HF}$ = 37.9 Hz, 1 H), 7.02 (dd, $^3J_{HF}$ = 8.7 Hz, $^3J_{HH}$ = 8.7 Hz, 2 H), 7.48 (dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HF}$ = 5.4 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ 61.83 (d, $^2J_{CF}$ = 32.6 Hz), 106.53 (d, $^2J_{CF}$ = 6.8 Hz), 115.62 (d, $^2J_{CF}$ = 21.5 Hz), 128.79, 130.37 (dd, $^3J_{CF}$ = 8.4 Hz, $^4J_{CF}$ = 8.4 Hz), 157.54 (d, $^1J_{CF}$ = 263.8 Hz), 162.36 (d, $^1J_{CF}$ = 247.5 Hz) ppm. MS (EI) m/z (relative intensity): 170 (M^+, 91), 151 (38), 149 (100), 133 (53), 122 (29), 121 (39), 109 (79), 101 (41), 99 (16), 96 (38), 75 (26), 74

(14). HRMS (m/z): observed 171.0615, calcd for $C_9H_9OF_2$ 171.0616 $[M + H]^+$.

(2*Z*)-2-Fluoro-3-(4-nitrophenyl)-2-propen-1-ol (4d). ^{19}F NMR ($CDCl_3$) δ −107.53 (dt, $^3J_{HF}$ = 37.9 Hz, $^3J_{HF}$ = 11.2 Hz) ppm; ^1H NMR ($CDCl_3$) δ 4.32 (d, $^3J_{HF}$ = 11.2 Hz, 2 H), 5.91 (d, $^3J_{HF}$ = 37.9 Hz, 1 H), 7.63 (d, $^3J_{HH}$ = 8.8 Hz, 2 H), 8.19 (d, $^3J_{HH}$ = 8.8 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 61.25 (d, $^2J_{CF}$ = 33.9 Hz), 105.21 (d, $^2J_{CF}$ = 5.5 Hz), 123.82, 129.22, 139.39 (d, $^3J_{CF}$ = 4.2 Hz), 146.53, 161.24 (d, $^1J_{CF}$ = 272.7 Hz) ppm. MS (EI) m/z (relative intensity): 197 (M^+, 54), 161 (10), 160 (100) 149 (21), 133 (25), 131 (17), 130 (50), 109 (18), 103 (25), 102 (15), 91 (18), 77 (23), 75 (14). HRMS (m/z): observed 198.0560, calcd for $C_9H_9O_3NF$ 198.0561 $[M + H]^+$.

(2*Z*)-2-Fluoro-3-(3,5-dimethoxyphenyl)-2-propen-1-ol (4e). ^{19}F NMR ($CDCl_3$) δ −112.21 (dt, $^3J_{HF}$ = 38.4 Hz, $^3J_{HF}$ = 14.0 Hz) ppm; ^1H NMR ($CDCl_3$) δ 3.78 (s, 6 H), 4.26 (d, $^3J_{HF}$ = 14.0 Hz, 2 H), 5.71 (d, $^3J_{HF}$ = 38.4 Hz, 1 H), 6.38 (s), 6.67 (s) ppm; ^{13}C NMR ($CDCl_3$) δ 55.32, 61.81 (d, $^2J_{CF}$ = 32.8 Hz), 99.97, 106.80 (d, $^2J_{CF}$ = 7.4 Hz), 107.41 (d, $^4J_{CF}$ = 6.0 Hz), 134.40, 158.71 (d, $^1J_{CF}$ = 267.6 Hz), 160.28 ppm. MS (EI) m/z (relative intensity): 212 (M^+, 100), 184 (15), 183 (70), 153 (12), 135 (14), 121 (11), 109 (15), 105 (11), 91 (10), 77 (10), 57 (9). HRMS (m/z): observed 213.0919, calcd for $C_{11}H_{14}O_3F$ 213.0921 $[M + H]^+$.

(2*Z*)-2-Fluoro-3-(3-bromo-4-methoxyphenyl)-2-propen-1-ol (4f). ^{19}F NMR ($CDCl_3$) δ −114.62 (dt, $^3J_{HF}$ = 38.4 Hz, $^3J_{HF}$ = 14.5 Hz) ppm; ^1H NMR ($CDCl_3$) δ 3.89 (s, 3 H), 4.26 (d, $^3J_{HF}$ = 14.5 Hz, 2 H), 5.67 (d, $^3J_{HF}$ = 38.6 Hz, 1 H), 6.84 (d, $^3J_{HH}$ = 8.5 Hz, 1 H), 7.42 (d, $^3J_{HH}$ = 8.5 Hz, 1 H), 7.72 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 56.23, 61.80 (d, $^2J_{CF}$ = 32.5 Hz), 105.94 (d, $^2J_{CF}$ = 6.7 Hz), 111.69, 114.54, 126.72, 128.87 (d, $^4J_{CF}$ = 7.4 Hz), 132.01 (d, $^4J_{CF}$ = 7.8 Hz), 155.13, 157.73 (d, $^1J_{CF}$ = 265.8 Hz) ppm. MS (EI) m/z (relative intensity): 262 (M^+ + 1, 80), 261 (M^+, 14), 260 (M^+ - 1, 91), 253 (31), 231 (20), 219 (14), 181 (100), 166 (100), 152 (65), 136 (24), 109 (26), 55 (23). HRMS (m/z): observed 260.9920, calcd for $C_{10}H_{11}O_2BrF$ 260.9921 $[M + H]^+$.

2,3,4,6-Tetra-*O*-acetyl-1-[4-((2*Z*)-2-fluoro-3-hydroxyprop-1-enyl)-2-methoxyphenyl]-β-D-glucopyranoside (4g). Mp 133−134 °C; ^{19}F NMR ($CDCl_3$) δ −114.17 (dt, $^3J_{HF}$ = 38.5 Hz, $^3J_{HF}$ = 14.3 Hz, 1 F) ppm; ^1H NMR ($CDCl_3$) δ 2.00 (s, 6 H), 2.04 (s, 6 H), 3.67−3.75 (m, 1 H), 3.77 (s, 3 H), 4.11 (dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 7.1 Hz, 1 H), 4.20 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 4.9 Hz, 1 H), 4.22 (d, $^3J_{HF}$ = 14.3 Hz, 2 H), 5.09−5.15 (m, 2 H), 5.24−5.26 (m, 2 H), 5.68 (d, $^3J_{HF}$ = 38.5 Hz, 1 H), 6.93 (d, $^3J_{HH}$ = 7.8 Hz, 1 H), 7.02 (d, $^3J_{HH}$ = 8.0 Hz, 1 H), 7.08 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.61, 55.91, 61.52, 61.93, 68.38, 71.20, 71.92, 72.66, 100.61, 106.60, 112.92, 113.02, 121.53, 128.61, 145.35, 150.34, 158.10, 169.20, 169.44, 170.31, 170.72 ppm. HRMS (NH_3) (m/z): observed 546.1987, calcd for $C_{24}H_{33}O_{12}NF$ 546.1981.

2,3,4,6-Tetra-*O*-acetyl-1-[4-((2*Z*)-2-fluoro-3-hydroxyprop-1-enyl)-phenyl]-β-D-glucopyranoside (4h). Mp 120−122 °C; NMR ^{19}F ($CDCl_3$) δ −114.79 (dt, $^3J_{HF}$ = 38.9 Hz, $^3J_{HF}$ = 14.3 Hz, 1 F); ^1H NMR ($CDCl_3$) δ 2.03 (s, 6 H), 2.05 (s, 6 H), 3.80−3.89 (m, 1 H), 4.10 (dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HH}$ = 7.09 Hz, 1 H), 4.20 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 4.9 Hz, 1 H), 4.23 (d, $^3J_{HF}$ = 14.3 Hz, 2 H), 5.05−5.17 (m, 2 H), 5.24−5.27 (m, 2 H), 5.71 (d, $^3J_{HF}$ = 38.9 Hz, 1 H), 6.92 (d, $^3J_{HH}$ = 8.1 Hz, 2 H), 7.41 ($^3J_{HH}$ = 8.1 Hz, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.62, 61.60, 61.93, 68.32, 71.14, 72.03, 72.69, 98.88, 106.44, 116.90, 128.61, 129.93, 155.92, 157.79, 169.29, 169.43, 170.31, 170.63. HRMS (NH_3) (m/z): observed 516.1871, calcd for $C_{23}H_{31}O_{11}NF$ 516.1876.

2,3,4,6-Tetra-*O*-acetyl-1-[4-((*Z*)-2-fluoro-3-hydroxyprop-1-enyl)-2,6-dimethoxyphenyl]-β-D-glucopyranoside (4i). Mp 129−130 °C; ^{19}F NMR ($CDCl_3$) δ −113.67 (dt, $^3J_{HF}$ = 38.1 Hz, $^3J_{HF}$ = 13.9 Hz, 1 F) ppm; ^1H NMR ($CDCl_3$) δ 2.01 (s, 6 H), 2.07 (s, 6 H), 3.59−3.73 (m, 1 H), 3.81 (s, 6 H), 4.12 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 7.3 Hz, 1 H), 4.21 (dd, $^2J_{HH}$= 12.3 Hz, $^3J_{HH}$ = 4.9 Hz, 1 H), 4.26 (d, $^3J_{HF}$ = 13.9 Hz, 2 H), 5.05−5.10 (m, 2 H), 5.19−5.32 (m, 2 H), 5.69 (d, $^3J_{HF}$ = 38.1 Hz, 1 H), 6.72 (s, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.71, 56.30, 61.71, 62.23, 68.54, 71.30, 71.91, 73.14, 101.17, 106.28, 107.10, 128.51, 132.11, 152.80, 158.22, 169.34, 169.41, 170.38, 170.63 ppm. HRMS (NH_3) (m/z): observed 576.2090, calcd for $C_{25}H_{35}O_{13}NF$ 576.2086.

General Procedure for the Deprotection of (*Z*)-β-Fluorocinnamic Alcohols. The (*Z*)-β-fluorocinnamic alcohol (0.5 mmol) was dissolved in 40 mL of a mixture of MeOH/THF (50:50). A sodium methylate solution prepared from 10 mg of sodium metal in methanol (10 mL) was added. When the deprotection was completed, the solution was neutralized by adding 2.0 g of an ion-exchange resin (H^+ form). The agitation was maintained during 30 min, and then the resin was filtered. The methanol was eliminated by vacuum evaporation, at room temperature. The product was isolated by chromatography on 5 mL C18 cartridge (LC-SPE) using a mixture of MeOH/H_2O.

1-[4-((2*Z*)-2-Fluoro-3-hydroxyprop-1-enyl)-2-methoxyphenyl]-β-D-glucopyranoside, (*Z*)-β-Fluoroconiferin (5g). Mp 140−141 °C; ^{19}F NMR (CD_3OD) δ −113.11 (dt, $^3J_{HF}$ = 38.9 Hz, $^3J_{HF}$ = 15.4 Hz, 1 F) ppm; ^1H NMR (CD_3OD) δ 3.34−3.48 (m, 4 H), 3.63 (m, 1 H), 3.69 (m, 1 H), 3.85 (s, 3 H), 4.17 (d, $^3J_{HF}$ = 15.4 Hz, 2 H), 4.88 (d, $^3J_{HH}$ = 7 Hz, 1 H), 5.79 (d, $^3J_{HF}$ = 38.9 Hz, 1 H), 7.05 (d, $^3J_{HH}$ = 8.3 Hz, 1 H), 7.12 (d, $^3J_{HH}$ = 8.1 Hz, 1 H), 7.19 (s, 1 H) ppm; ^{13}C NMR (CD_3OD) δ 56.71, 61.80, 62.43, 71.31, 74.92, 77.78, 78.06, 102.61, 107.65, 113.90, 117.71, 123.11, 129.60, 147.21, 150.54, 159.80, ppm. HRMS (NH_3) (m/z): observed 378.1557, calcd for $C_{16}H_{25}O_8NF$ 378.1559.

1-[4-((2*Z*)-2-Fluoro-3-hydroxyprop-1-enyl)-phenyl]-β-D-glucopyranoside (5h). Mp 127−129 °C; ^{19}F NMR (CD_3OD) δ −112.53 (dt, $^3J_{HF}$ = 39.2 Hz, $^3J_{HF}$ = 15.2 Hz, 1 F) ppm; ^1H NMR (CD_3OD) δ 3.32−3.48 (m, 4 H), 3.71 (m, 1 H), 3.89 (m, 1 H), 4.16 (d, $^3J_{HF}$ = 15.2 Hz, 2 H), 4.80 (d, $^3J_{HH}$ = 7.0 Hz, 1 H), 5.79 (d, $^3J_{HF}$ = 39.2 Hz, 1 H), 7.05 (d, $^3J_{HH}$ = 8.2 Hz, 2 H), 7.44 (d, $^3J_{HH}$ = 8.3 Hz, 2 H) ppm; ^{13}C NMR (CD_3OD) δ 61.81, 62.40, 71.41, 71.91, 74.80, 77.92, 102.13, 107.44, 117.69, 128.76, 130.91, 158.22, 159.54 ppm. HRMS (NH_3) (m/z): observed 348.1462, calcd for $C_{15}H_{23}O_7NF$ 348.1453.

1-[4-((2*Z*)-2-Fluoro-3-hydroxyprop-1-enyl)-2,6-dimethoxyphenyl]-β-D-glucopyranoside, (*Z*)-β-Fluorosyringin (5i). Mp 137−138 °C; ^{19}F NMR ($CDCl_3$) δ −110.94 (dt, $^3J_{HF}$ = 38.7 Hz, $^3J_{HF}$ = 14.5 Hz, 1 F) ppm; ^1H NMR ($CDCl_3$) δ 3.16−3.48 (m, 4 H), 3.59 (m, 1 H), 3.69 (m, 1 H), 3.84 (s, 6 H), 4.17 (d, $^3J_{HF}$ = 14.5 Hz, 2 H), 4.25 (d, $^3J_{HH}$ = 7.0 Hz, 1 H), 5.81 (d, $^3J_{HF}$ = 38.7 Hz, 1 H), 6.87 (s, 2 H) ppm; ^{13}C NMR ($CDCl_3$) δ 57.12, 61.70, 62.43, 71.31, 75.73, 77.78, 78.29, 105.28, 107.60, 107.92, 131.21, 135.62, 154.15, 160.53 ppm. HRMS (NH_3) (m/z): observed 408.1670, calcd for $C_{17}H_{27}O_9NF$ 408.1664.

■ ASSOCIATED CONTENT

Supporting Information. ^1H, ^{13}C, and ^{19}F spectra for the model compounds and for the coniferin series. This material is available free of charge via the Internet at http://pubs.acs.org.

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