Substrate-Controlled Hydrogenation of Flavanones: Selective Synthesis of 2′-Hydroxy-1,3-Diarylpropanes and Flavans

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A new substrate-controlled hydrogenation of flavanones to selectively obtain different hydrogenation products is herein reported. Thus, hydrogenation of flavanones bearing different electron-donating and electron withdrawing substituents (Cl, Br, Me, OMe, OH) provided the corresponding 1,3-diarylpropanes in excellent yields. This procedure offers a straightfor-ward, simple, and cost-effective method for the preparation of glycosylated 2′-hydroxy-1,3-diarylpropanes derived from natural flavanones such as Naringin and Hesperedin. On the contrary, when the hydrogenation was performed over fluorinated flavanones, the corresponding flavans were selectively obtained in excellent yields.

Introduction

1,3-Diarylpropanes are a subclass of flavonoids which are precursors for flavonoid biosynthesis in plants and exhibit significant cytotoxic activity in several cancer cell lines.[1] In addition, 1,3-diarylpropanes have shown antifungal,[2] anti-inflammatory,[3] antiadipogenic,[4] antitubercular,[5] antimalarial,[6] anti-Alzheimer[7] and antioxidant activities,[8] to name a few. 1,3-Diarylpropanes have also shown strong inhibition of tyrosinase and exhibited strong skin-whitening effects; therefore, these natural compounds are of growing industrial interest for the development of depigmenting agents.[9]

Despite 1,3-diarylpropanes have been isolated from several natural sources, its low abundance requires their preparation in the laboratory.[10] In this regard, we have recently reported a straightforward, simple, and cost-effective method for the preparation of a wide variety of 2′-hydroxy-1,3-diarylpropanes based on the catalytic hydrogenation of chalcones under mild conditions (room temperature, atmospheric pressure) and in a green solvent such as ethanol [Scheme 1, (a)].[11] Hydrogenation with molecular hydrogen is an atom economic transformation and undoubtedly the cleanest possible method for reducing a compound.[12] Combined with the use of green solvents such as ethanol, selective catalytic hydrogenation certainly meets the demand for environmentally friendly catalytic processes. Yet another requirement for the development of sustainable

Previous work: hydrogenation of chalcones
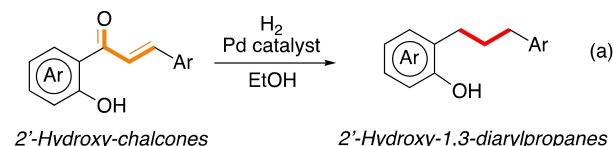
This work: hydrogenation of flavanones
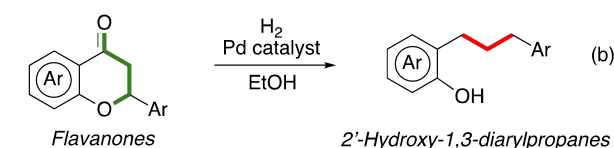
Scheme 1. Hydrogenation-based synthesis of 2′-hydroxy-1,3-diarylpropanes.

chemical processes is the use renewable feedstocks as starting materials.[13] Although chalcones are intermediates in flavonoid biosynthesis, they do not accumulate to appreciable degree in most plants.[14] In this regard, a more attractive approach for the preparation of 2′-hydroxy-1,3-diarylpropanes would be the reduction of naturally abundant flavanones.[15] Flavanones such as Hesperetin, Naringenin, and their respective glycosides are widespread in citrus fruits, occurring in quantities up to 740 mg/L (depending on the Citrus species and cultivar).[16] In addition, flavanones can be extracted from citrus waste using environmentally benign techniques, so the development of processes to convert them to high-value-added products are of paramount importance from the point of view of bio-circular economy.[17]

Herein we describe a practical process for catalytic hydrogenation of flavanones using a mixture of Pd/C and Pd(OH)$_2$/C as a heterogeneous catalyst [Scheme 1, (b)].

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Results and Discussion

To investigate the hydrogenation of flavanones, commercially available flavanone was used as model substrate. Considering our recent results on the catalytic hydrogenation of chalcones, ethanol was the solvent of choice for our studies.[11] Flavanone **1a** was hydrogenated over Pd/C catalyst (20 mol%) (Catalyst A) in ethanol, obtaining the corresponding 1,3-diarylpropane **3a** as the sole hydrogenation product (Table 1, entry 1). However, under the same conditions, hydrogenation of less reactive 4'-methylflavanone **1b** afforded a mixture of 1,3-diarylpropane **3b** and dihydrochalcone **2b** (Table 1, entry 2). Similarly, when 4'-methoxyflavanone **1c** was hydrogenated over Pd/C catalyst (20 mol%) (Catalyst A) in ethanol, a mixture of 1,3-diarylpropane **3c** and dihydrochalcone **2c** was obtained (Table 1, entry 3).

On view of these unsatisfactory results, we envisioned the use of a more active palladium catalyst, namely $Pd(OH)_2$ (Pearlman's catalyst). There are several reports in the literature of the enhanced catalytic activity of $Pd(OH)_2$ for C—O bond cleavage.[18] In fact, a mixture of Pd/C and $Pd(OH)_2/C$ has proven its effectiveness in the cleavage of difficult benzyl protecting groups.[19] Taking into account these previous results, we then hydrogenated 4'-methylflavanone **1b** over a mixture of Pd/C 10% catalyst (10 mol%) and $Pd(OH)_2$ 20% (10 mol%) (Catalyst B) in ethanol, obtaining 1,3-diarylpropane **3b** in excellent yield (Table 1, entry 5). Under these conditions, hydrogenation flavanones **1a** and **1c** afforded almost quantitatively 1,3-diarylpropanes **3b** and **3c** respectively (Table 1, entries 4,6).

With the optimal conditions for the formation of the 1,3-diarylpropanes, we investigated the scope of the process. A series of flavanones **1** bearing electron-donor and electron withdrawing groups were hydrogenated over a mixture of Pd/C 10% (10 mol%) and $Pd(OH)_2$ 20% (10 mol%) (Catalyst B) in ethanol at r.t. under hydrogen atmosphere, obtaining in all cases the total reduced products **3a–g** in good yields (Scheme 2).

The hydrogenation rate is highly dependent on the electronic character of the substituents. Thus, flavanones bearing electron-withdrawing groups (**1d**, **1e**) required 24 h to achieve the total reduction. On contrary, unsubstituted flavanone (**1a**) was fully reduced in 12 h, whereas the hydrogenation of flavanones bearing electron-donor groups just required 6 h (**1c**, **1f**, **1g**).

The hydrogenation polyhydroxylated natural flavanones Naringenin **1h** and Hesperetin **1i** was considerably slower, and the reaction time was increased to 48 h to achieve the formation of the corresponding 1,3-diarylpropanes as the major hydrogenation products. On the other hand, the presence of the *O*-disaccharide moiety in the aromatic ring of natural Naringin **1j** and Hesperedin **1k** resulted in a dramatic decrease in the reaction rate. Thus, total hydrogenation of flavanones **1j,k** required 96 h (Scheme 1). The low hydrogenation rate of natural flavanones **1h–k** is in accordance with their low solubility in the reaction media, as is widely known that a low solubility of reagents leads to a decreased rate of hydrogenation compared to highly soluble reagents.[20]

The physical data of known 1,3-diarylpropanes **3a–h** were comparable to those previously reported in the literature.[11,21] 1,3-Diarylpropane **3i** was fully characterized by ^1H (300 MHz), ^{13}C (75 MHz) NMR spectroscopy and HRMS (ESI-TOF). Highly polar 1,3-diarylpropanes **3j** and **3k** were fully acetylated prior to full characterization.

Unexpectedly, the presence of a fluorine substituent in flavanone **1l** resulted in the quantitative formation of the corresponding flavan **4a** instead of the expected 1,3-diarylpropane (Scheme 3).
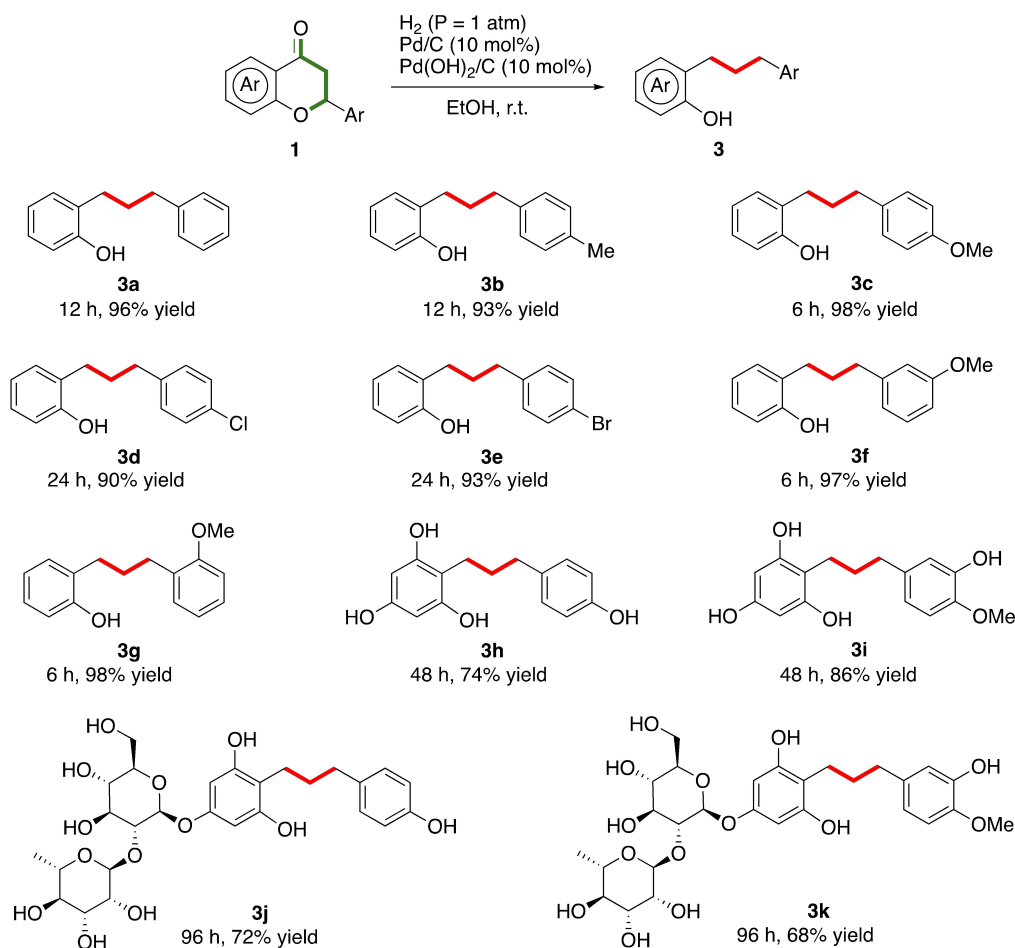
On view of this interesting result, we decided to focus on the possibility of selectively obtain fluorinated flavans, so the above hydrogenation conditions were applied to a series of fluorinated flavanones. Thus, a series of mono, di and trifluorinated flavanones were hydrogenated over a mixture of Pd/C 10% (10 mol%) and $Pd(OH)_2$ 20% (10 mol%) (Catalyst B) in ethanol at r.t. under hydrogen atmosphere for 24 h, obtaining in all cases the corresponding flavans **4a–h** as the sole hydrogenation products in excellent yields (Scheme 4).

The effect of both the catalyst and the substrate in the reaction outcome can be explained considering that flavanones can undergo chalcone–flavanone equilibrium under the catalytic hydrogenation conditions (Scheme 5). The chalcone–flavanone equilibrium has been extensively investigated and it is widely assumed that is strongly influenced on the pH. Thus, in the acidic and neutral pH ranges, flavanones **1** are the predominant species, while in the alkaline region the chalcone form **9** prevails.[22] Even though Pearlman's catalyst structure is commonly written as palladium(II) hydroxide supported on carbon, that is $Pd(OH)_2/C$, recent studies demonstrate that this catalyst should be formulated as C/PdO/OH/ H_2O.[23] Due to the presence of variable amounts of water and hydroxyls, the flavanone–chalcone equilibrium is more displaced to the chalcone **9** when the hydrogenation is performed in the presence of a mixture of Pearlman's catalyst and Pd/C
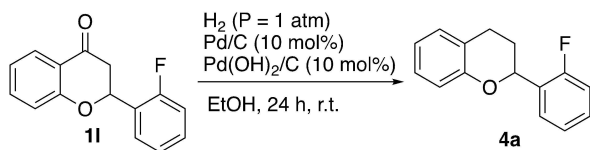
Table 1. Hydrogenation of flavanones **1**.

Entry	1	R	Catalyst[a]	Ratio 2/3[b]	Yield of 3 [%][c]
1	**1a**	H	A	0/100	96
2	**1b**	Me	A	44/56	48
3	**1c**	OMe	A	48/52	43
4	**1a**	H	B	0/100	96
5	**1b**	Me	B	0/100	93
6	**1c**	OMe	B	0/100	98

[a] Catalyst A: Pd/C (20 mol%); Catalyst B: Pd/C (10 mol%) and $Pd(OH)_2/C$ (10 mol%). [b] Determined by ^1H NMR (300 MHz) of the crude reaction mixtures. [c] Isolated yield.

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Scheme 2. Synthesis of diarylpropanes **3** from flavanones **1**.

Scheme 3. Hydrogenation of 4'-fluoroflavanone **1 l**.

compared to Pd/C alone (Scheme 5). As chalcones are much easier to hydrogenate than flavanones, the enhanced hydrogenation rate using a mixture of Pd(OH)$_2$/C and Pd/C in comparison to Pd/C alone can be explained by the prevalence of the chalcone form under these conditions.
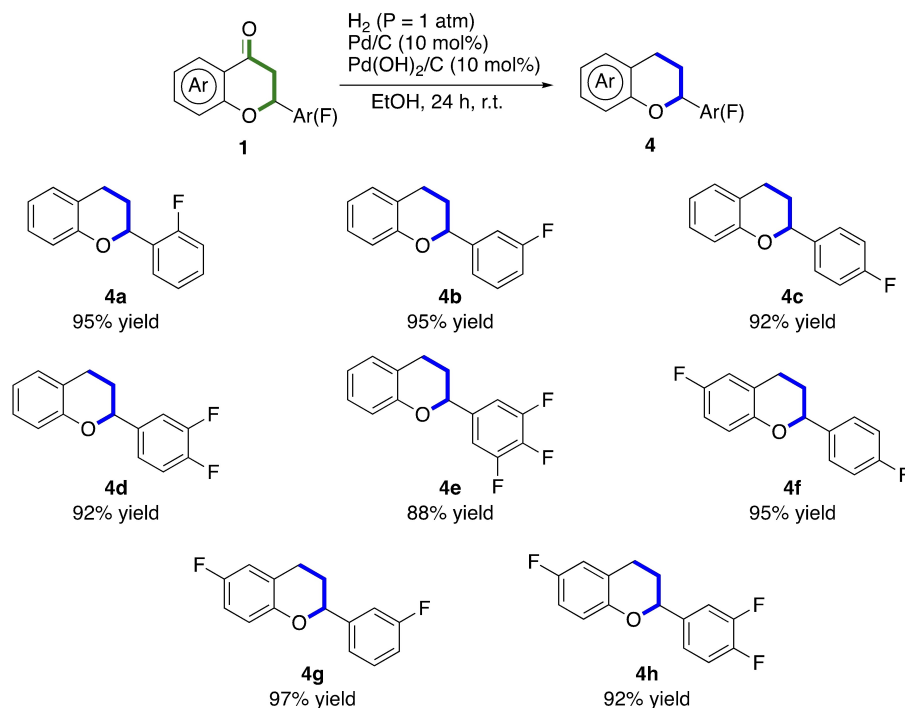
The chalcone–flavanone equilibrium would also explain the quantitative formation of fluoroflavans **4**. Electron-withdrawing fluorine group enhance the electrophilicity of β-carbon, hindering the ring-opening to the chalcone **9** and displacing the equilibrium to the flavanone form **1** (Scheme 5). From here, the hydrogenation of the C=O bond is relatively easy, but the total reduction to 2'-hydroxy-1,3-diarylpropanes **3** would require the hydrogenolysis of the cyclic C–O bond, which is recognized to be considerably difficult.[24] In the case of flavanones bearing electron-donor groups, the β-carbon is less electrophilic, thus

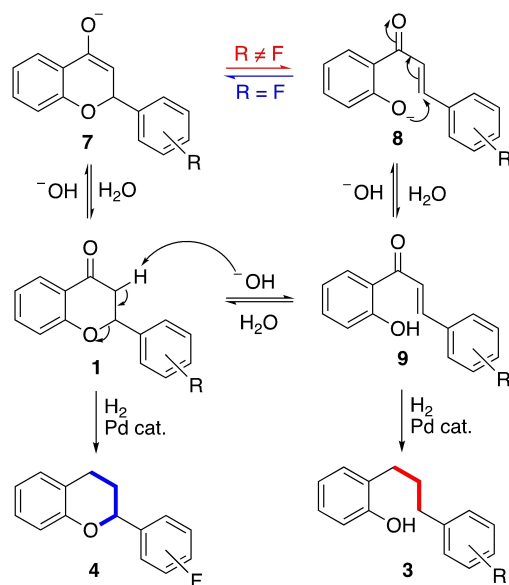displacing the equilibrium to the chalcone and increasing the hydrogenation rate.

To confirm this hypothesis, the hydrogenation of flavanols was next investigated. Thus, when flavanols **5 a,b** were hydrogenated in ethanol in the presence of a mixture of Pd/C and Pd(OH)$_2$/C (Catalyst B) for 24 h, flavans **4 i,j** were obtained quantitatively (Scheme 6).
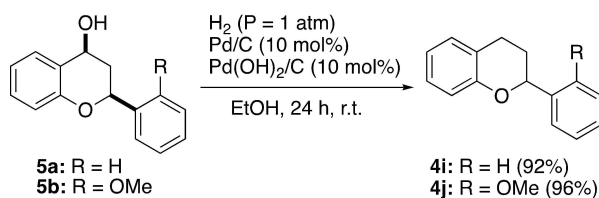
Conclusion

In conclusion, we have developed a new procedure for the effective total hydrogenation of flavanones. The reaction proceeds at atmospheric pressure and under mild conditions and tolerates a wide variety of functional groups and substitution patterns. The procedures described herein offer a straightforward, simple and cost-effective method for the preparation of a wide variety of 2'-hydroxy-1,3-diarylpropanes. Using this approach, natural flavanones of biological and industrial relevance such as Naringin and Hesperidin were successfully transformed into the corresponding 2'-hydroxy-1,3-diarylpropanes. To the best of our knowledge, this is the first report in the literature of such glycosylated 1,3-diarylpropanes.

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Scheme 4. Synthesis of fluorinated flavans **4** from flavanones **1**.

Scheme 5. Mechanistic proposal.

Scheme 6. Hydrogenation of flavanols **5**.

In addition, when fluorinated flavanones are used as starting materials, the hydrogenation afforded exclusively the corresponding fluorinated flavans.

Experimental Section

General Methods: All reagents were purchased in the highest quality available and were used without further purification. Column chromatography was carried out on silica gel 230–400 mesh. Compounds were visualized on analytical thin layer chromatograms (TLC) by UV light (254 nm) and potassium permanganate stain. NMR experiments were registered in an AV-Bruker spectrometer (^{1}H NMR, 300 MHz, ^{13}C NMR and DEPT-135, 75 MHz). Chemical shifts are given in ppm relative to the residual non deuterated solvent, which is used as an internal standard, and coupling constants (J) are reported in Hz. Diastereoisomeric ratios were obtained using ^{1}H NMR (300 MHz) analysis of crude products. HPLC analyses were performed on an Agilent HP 1100 chromatograph equipped with a UV-Vis detector. HRMS were measured at 70 eV using electrospray ionization in positive mode (ESI$^+$).

General procedure for the synthesis of diarylpropanes 3 from flavanones 1: 10 % Pd/C (106 mg, 0.1 mmol Pd) and 20 % Pd(OH)$_2$ (70 mg, 0.1 mmol Pd(OH)$_2$) were added to a deoxygenated solution of the corresponding flavanone **1 a–k** (1.0 mmol) in ethanol (20 mL) under inert atmosphere. The reaction flask was thrice evacuated and flushed with hydrogen gas and the resulting mixture was stirred at room temperature under hydrogen atmosphere. After 24–96 h, the mixture was filtered through a Celite® pad and the solvent was removed under reduced pressure, to afford the corresponding 1,3-diarylpropanes **3 a–k** (**3 a**: 204 mg, 96 % yield; **3 b**: 210 mg, 93 % yield; **3 c**: 237 mg, 98 % yield; **3 d**: 222 mg, 90 % yield; **3 e**: 271 mg, 93 % yield; **3 f**: 235 mg, 97 % yield; **3 g**: 237 mg, 98 % yield; **3 h**: 193 mg, 74 % yield; **3 i**: 250 mg, 86 % yield; **3 j**: 409 mg, 72 % yield;

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3k: 407 mg, 68% yield). 1,3-Diarylpropanes **3a–h** were previously described in the literature.[11,21] The data for new 1,3-diarylpropane **3i** is shown below.

2-[3-(4-Hydroxy-3-methoxyphenyl)propyl]benzene-1,3,5-triol (3i): Clear oil. $R_f = 0.23$ (Hex:EtOAc 2:3); ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.78 (d, $J = 8.2$ Hz, 1H), 6.79–6.61 (m, 2H), 5.88 (s, 2H), 3.79 (s, 3H), 2.82 (dt, $J = 16.8$, 4.8 Hz, 1H), 2.59–2.49 (m, 4H), 1.78–1.68 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 157.6, 156.7, 147.0, 146.8, 137.6, 120.5, 116.4, 112.7, 108.7, 56.4, 36.5, 32.8, 23.8; ESI-TOF-HRMS: $[M+H]^+$ calcd. for C$_{16}$H$_{19}$O$_5$ 291.1227; found, 291.1226.

1,3-Diarylpropanes **3j** and **3k** were acetylated prior to their characterization.

General procedure for the synthesis of acetyl 1,3-diarylpropanes 6a and 6b: 1,3-Diarylpropanes **3j** or **3k** (0.1 mmol) stirred in a mixture of pyridine (1.5 mL) and acetic anhydride (3.0 mL) in the presence of catalytic DMAP (2 mg). After 24 h, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were washed with aqueous saturated NaHCO$_3$ (2×15 mL), aqueous saturated CuSO$_4$ (2×15 mL) and water (15 mL), dried (Na$_2$SO$_4$), filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO$_2$) eluting with EtOAc/Hex 1:1 to yield acetylated derivatives **6a** or **6b** in 62% and 54% yield respectively.

5-[2-O-(3,4,5-Tri-O-acetyl-6-deoxy-α-L-mannopyranosyl)-(3,4,6-tri-O-acetyl-β-D-glucopyranosyl)]oxy]-2-[3-(4-acetoxyphenyl)propyl]benzene-1,3-phenylene diacetate (6a): 56 mg, 62% yield. Clear oil. $R_f = 0.31$ (Hex:EtOAc 1:1); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.19 (d, $J = 8.5$ Hz, 1H), 7.01 (d, $J = 8.5$ Hz, 1H), 6.67 (s, 2H), 5.32 (t, $J = 9.4$ Hz, 1H), 5.21 (dd, $J = 10.1$, 3.3 Hz, 1H), 5.10–5.00 (m, 5H), 4.25 (dd, $J = 12.2$, 5.6 Hz, 1H), 4.16–4.09 (m, 2H), 3.95 (dd, $J = 9.3$, 7.6 Hz, 1H), 3.86 (ddd, $J = 9.8$, 5.5, 2.3 Hz, 1H), 2.64 (t, $J = 7.0$ Hz, 2H), 2.50–2.33 (m, 2H), 2.18 (s, 6H), 2.16 (s, 3H), 2.15 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.82–1.74 (m, 2H), 1.20 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 170.6, 170.24, 170.19, 170.1, 169.7, 169.7, 169.6, 168.7, 154.7, 150.1, 148.9, 139.3, 129.5, 122.0, 121.4, 109.4, 99.1, 98.1, 74.2, 71.9, 70.9, 68.4, 66.9, 62.1, 35.1, 30.4, 23.7, 21.1, 20.9, 20.7, 20.6, 17.4; ESI-TOF-HRMS: $[M+K]^+$ calcd. for C$_{45}$H$_{54}$KO$_{22}$ 985.2738; found, 985.2730.

5-[2-O-(3,4,5-Tri-O-acetyl-6-deoxy-α-L-mannopyranosyl)-(3,4,6-tri-O-acetyl-β-D-glucopyranosyl)]oxy]-2-[3-(3-acetoxy-4-methoxy)phenyl)propyl]benzene-1,3-phenylene diacetate (6b): 53 mg, 54% yield. Clear oil. $R_f = 0.24$ (Hex:EtOAc 1:1); ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.98 (dd, $J = 8.3$, 2.2 Hz, 1H), 6.89–7.00 (m, 2H), 6.60 (s, 2H), 5.26–5.20 (m, 5H), 5.07–4.99 (m, 2H), 3.85–3.77 (m, 4H), 3.80 (s, 3H), 3.61 (dd, $J = 11.3$, 4.8 Hz, 1H), 2.55 (t, $J = 7.1$ Hz, 2H), 2.32–2.30 (m, 2H), 2.30 (s, 3H), 2.18 (s, 6H), 2.10 (s, 3H), 2.06 (s, 3H), 2.04 (s, 6H), 2.02 (s, 3H), 1.97 (s, 3H), 1.75–1.67 (m, 2H), 1.12 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 170.2, 170.1, 169.9, 169.8, 169.4, 169.3, 169.0, 168.9, 154.9, 150.1, 149.3, 139.6, 134.4, 126.7, 122.8, 121.9, 112.4, 111.7, 109.2, 98.8, 97.9, 73.0, 72.6, 71.0, 70.9, 69.4, 69.0, 68.8, 66.6, 66.3, 56.0, 34.7, 30.4, 23.8, 20.8, 20.7, 17.4; ESI-TOF-HRMS: $[M+Na]^+$ calcd. for C$_{46}$H$_{56}$NaO$_{23}$ 999.3105; found, 999.3090.

General procedure for the synthesis of fluorinated flavans 4 from fluorinated flavanones 1l–s: 10% Pd/C (106 mg, 0.1 mmol Pd) and 20% Pd(OH)$_2$ (70 mg, 0.1 mmol Pd(OH)$_2$) were added to a deoxygenated solution of the corresponding flavanone **1h–s** (1.0 mmol) in ethanol (20 mL) under inert atmosphere. The reaction flask was thrice evacuated and flushed with hydrogen gas and the resulting mixture was stirred at room temperature under hydrogen atmosphere. After 24 h, the mixture was filtered through a Celite® pad and the solvent was removed under reduced pressure, to afford the corresponding fluorinated flavans **4a–h** (**4a**: 217 mg,

95% yield; **4b**: 217 mg, 95% yield; **4c**: 210 mg, 92% yield; **4d**: 226 mg, 92% yield; **4e**: 232 mg, 88% yield; **4f**: 234 mg, 95% yield; **4g**: 239 mg, 97% yield; **4h**: 243 mg, 92% yield). Flavans **4c** and **4f** were previously described in the literature.[25,26] Data for new flavans **4a–b,d–e,g–h** are shown below.

2′-Fluoroflavan (4a): 95% yield. Clear oil. $R_f = 0.63$ (Hex:EtOAc 9:1); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.59 (td, $J = 7.6$, 1.9 Hz, 1H), 7.38–7.30 (m, 1H), 7.25–7.08 (m, 4H), 6.99–6.91 (m, 2H), 5.45 (dd, $J = 10.1$, 2.5 Hz, 1H), 3.07 (ddd, $J = 16.5$, 11.3, 5.9 Hz, 1H), 2.83 (ddd, $J = 16.5$, 5.3, 3.4 Hz, 1H), 2.35–2.27 (m, 1H), 2.17–2.03 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 159.6 (d, $J = 246.1$ Hz), 155.0, 129.6, 129.2 (d, $J = 8.3$ Hz), 129.0 (d, $J = 12.9$ Hz), 127.4, 127.4, 124.3 (d, $J = 3.6$ Hz), 121.9, 120.5, 116.9, 115.3 (d, $J = 21.5$ Hz), 71.8 (d, $J = 3.3$ Hz), 28.9, 25.0; ESI-TOF-HRMS: $[M+H]^+$ calcd. for C$_{15}$H$_{14}$FO 229.1023; found, 229.1026.

3′-Fluoroflavan (4b): 95% yield. Clear oil. $R_f = 0.70$ (Hex:EtOAc 9:1); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.39 (td, $J = 8.2$, 5.9 Hz, 1H), 7.27–7.11 (m, 4H), 7.10–7.01 (m, 1H), 7.01–6.90 (m, 2H), 5.11 (dd, $J = 10.0$ Hz, $J = 2.5$ Hz, 1H), 2.31–2.22 (m, 1H), 2.16–2.03 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 163.0 (d, $J = 245.8$ Hz), 154.8, 144.4 (d, $J = 7.2$ Hz), 130.1 (d, $J = 8.1$ Hz), 129.6, 127.5, 121.5 (d, $J = 2.9$ Hz), 120.5, 116.9, 114.6 (d, $J = 21.2$ Hz), 113.0 (d, $J = 22.4$ Hz), 77.0, 29.9, 24.9; ESI-TOF-HRMS: $[M+H]^+$ calcd. for C$_{15}$H$_{14}$FO 229.1023; found, 229.1024.

3′,4′-Difluoroflavan (4d): 92% yield. White solid. mp 66–68 °C. $R_f = 0.65$ (Hex:EtOAc 9:1); ^{1}H NMR (300 MHz, CDCl$_3$): ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.35–7.28 (m, 1H), 7.23–7.12 (m, 4H), 6.97–6.91 (m, 2H), 5.06 (dd, $J = 10.2$, 2.5 Hz, 1H), 3.04 (ddd, $J = 16.6$, 11.3, 5.9 Hz, 1H), 2.84 (ddd, $J = 16.6$, 5.4, 3.4 Hz, 1H), 2.29–2.20 (m, 1H), 2.13–1.99 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 159.6 (d, $J = 246.1$ Hz), 155.0, 129.6, 129.2 (d, $J = 8.3$ Hz), 129.0 (d, $J = 12.9$ Hz), 127.4, 127.4, 124.3 (d, $J = 3.6$ Hz), 121.9, 120.5, 116.9, 115.3 (d, $J = 21.5$ Hz), 76.5, 30.0, 24.8; ESI-TOF-HRMS: $[M+H]^+$ calcd. for C$_{15}$H$_{13}$F$_2$O 247.0929; found 247.0928.

3′,4′,5′-Trifluoroflavan (4e): 88% yield. White solid. mp: 64–66 °C. $R_f = 0.65$ (Hex:EtOAc 9:1); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.20–6.98 (m, 4H), 6.95–6.90 (m, 2H), 5.01 (ddd, $J = 10.1$, 5.3, 2.6 Hz, 1H), 3.01 (ddd, $J = 16.8$, 11.1, 5.9 Hz, 1H), 2.82 (dt, $J = 16.8$, 4.8 Hz, 1H), 2.27–2.19 (m, 1H), 2.10–1.95 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 157.8 (d, $J = 6.0$ Hz), 154.5, 154.4 (d, $J = 21.5$ Hz), 137.2 (t, $J = 8.0$ Hz), 129.5, 127.5, 121.5, 121.5 (d, $J = 9.6$ Hz), 120.7, 116.9, 109.9 (dd, $J = 30.7$, 7.4 Hz), 109.7 (d, $J = 24.3$ Hz), 76.3, 29.7, 24.8; APCI-HRMS: $[M+H]^+$ calcd. for C$_{15}$H$_{12}$F$_3$O 265.0835; found, 265.0846.

6,3′-Difluoroflavan (4g): 97% yield. White solid. mp: 40–42 °C. $R_f = 0.58$ (Hex:EtOAc 9:1); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.42–7.35 (m, 1H), 7.22–7.16 (m, 2H), 7.08–7.01 (m, 1H), 6.89–6.81 (m, 3H), 5.06 (d, $J = 10.1$, 2.5 Hz, 1 H), 3.06–2.95 (m, 1H), 2.80 (ddd, $J = 16.8$, 5.3, 3.5 Hz, 1H), 2.28–2.20 (m, 1H), 2.13–1.99 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 163.0 (d, $J = 245.9$ Hz), 156.9 (d, $J = 238.3$ Hz), 150.7, 144.1 (d, $J = 7.1$ Hz), 130.1 (d, $J = 8.2$ Hz), 122.8 (d, $J = 7.4$ Hz), 121.5 (d, $J = 2.9$ Hz), 117.7 (d, $J = 8.0$ Hz), 115.3 (d, $J = 22.5$ Hz), 114.7 (d, $J = 21.1$ Hz), 114.1 (d, $J = 23.1$ Hz), 113.0 (d, $J = 22.3$ Hz), 77.0, 29.5, 25.0; ESI-TOF-HRMS: $[M+H]^+$ calcd. for C$_{15}$H$_{13}$F$_2$O 247.0929; found, 247.0927.

6,3′,4′-Trifluoroflavan (4h): 92% yield. White solid. mp: 54–56 °C; $R_f = 0.61$ (Hex:EtOAc 9:1); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.31–7.15 (m, 3H), 6.87–6.80 (m, 3H), 5.00 (d, $J = 9.7$ Hz, 1 H), 3.06–2.83 (m, 1H), 2.80 (dt, $J = 16.8$, 4.0 Hz, 1H), 2.25–2.17 (m, 1H), 2.09–1.96 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 156.9 (d, $J = 238.7$ Hz), 150.6, 150.4 (dd, $J = 246.8$, 12.8 Hz), 149.8 (dd, $J = 246.6$, 12.8 Hz), 148.5 (dd, $J = 41.5$, 12.7 Hz), 122.6 (d, $J = 7.3$ Hz), 121.9 (dd, $J = 6.3$, 3.7 Hz), 117.7 (d, $J = 8.1$ Hz), 117.3 (d, $J = 17.3$ Hz), 115.3 (d, $J = 19.4$ Hz), 115.1 (d, $J = 14.6$ Hz), 114.2 (d, $J = 23.2$ Hz), 76.5, 29.6, 25.0; APCI-HRMS: $[M+H]^+$ calcd. for C$_{15}$H$_{12}$F$_3$O 265.0835; found, 265.0840.

General procedure for the synthesis of flavans 4i,j from flavanols 5: 10% Pd/C (106 mg, 0.1 mmol Pd) and 20% Pd(OH)$_2$ (70 mg, 0.1 mmol Pd(OH)$_2$) were added to a deoxygenated solution of the corresponding flavanol **5a,b** (1.0 mmol) in ethanol (20 mL) under inert atmosphere. The reaction flask was thrice evacuated and flushed with hydrogen gas and the resulting mixture was stirred at room temperature under hydrogen atmosphere. After 24 h, the mixture was filtered through a Celite® pad and the solvent was removed under reduced pressure, to afford the corresponding fluorinated flavans **4i,j** which were previously described in the literature[27] (**4i**: 193 mg, 92% yield; **4j**: 233 mg, 97% yield).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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