Electronic Supplementary Information for

First Synthesis, Full Characterization, and Evidence for the Presence in Human Biological Fluids, of Hydroxycinnamic acid Sulphate and Glucuronide Conjugates, as a Result of Coffee Consumption.

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Part A: Synthetic procedures

Abstract - A systematic investigation of the human metabolism of hydroxycinnamic acid conjugates was carried out. A set of 24 potential human metabolites of coffee polyphenols has been chemically prepared, and used as analytical standards for unequivocal identifications. These included glucuronide conjugates and sulphate esters of caffeic, ferulic, isoferulic, *m*-coumaric and *p*-coumaric acids as well as their dihydro derivatives. A particular focus has been made on caffeic and 3,4-dihydroxyphenylpropionic acid derivatives, especially the sulphate conjugates, for which regioselective preparation was particularly challenging, and have so far never been identified as human metabolites. Ten, out of the 24 synthesized conjugates have been identified in human plasma and/or urine after coffee consumption. A number of these conjugates were synthesized, characterized and detected as hydroxycinnamic acid metabolites for the first time. This was the case of dihydroisoferulic acid 3'-*O*-glucuronide, caffeic acid 3'-sulphate, as well as the sulphate and glucuronide derivatives of 3,4-dihydroxyphenylpropionic acid.

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Table of contents

1. Source of Chemicals and materials, General methods, and General procedures A to G.

These have been detailed in the Experimental Section of the main body of the paper.

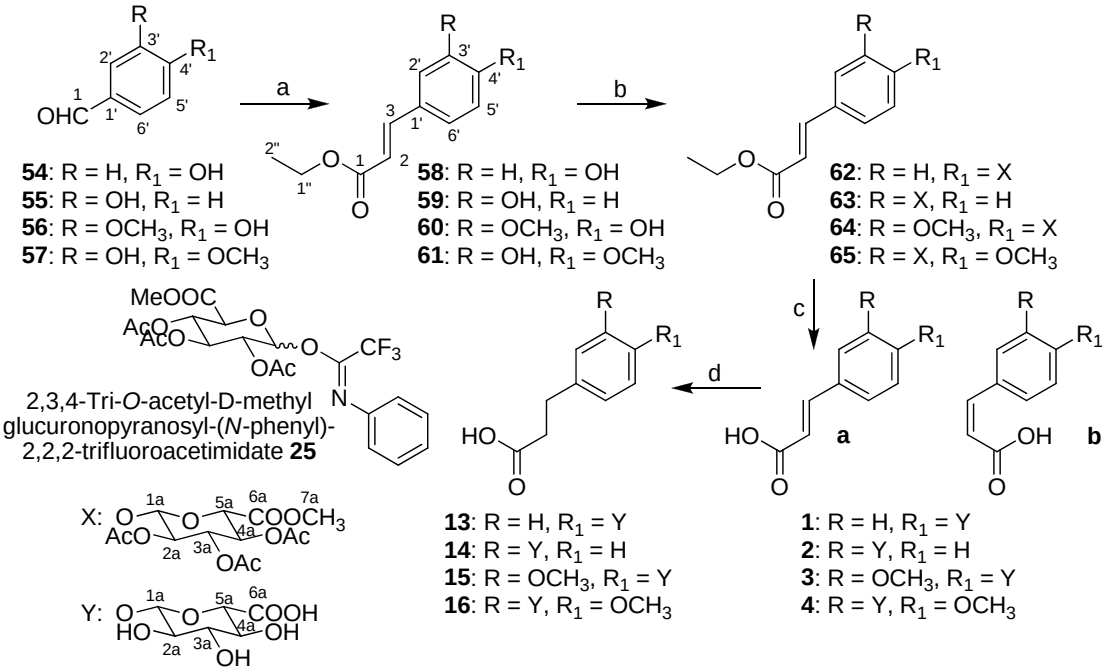
2. General procedure H: Synthesis and purification of monohydroxycinnamic and 3-(monohydroxyphenyl)propionic acid sulphates.

A suspension of 1 part of the monohydroxycinnamic or 3-(monohydroxyphenyl)propionic acid, 10 parts of sulphur trioxide-trimethylamine complex, and 12 parts of sodium carbonate in water (100 mL/g of acid), was stirred at room temperature for 48 h. The evolution of the reaction was followed after withdrawing an aliquot (2-3 drops) of the medium, acidification with 1 drop of AcOH, and TLC on RP-18 WF_{254} using water/methanol (8/2) as solvent: R_f 0-0.1 (acids) and 0.4-0.6 (sulphates). The insoluble components were removed by filtration. The water solution was brought to pH 6 to 6.5 with Ambertite® CG50. The medium was filtered through a P zero sintered glass filter, and the solid material was washed with one volume of water. Finally, lyophilization of the filtrate yielded a crude product with a high salt content. This residue was treated with MeOH (10 mL/g), the solids were removed by filtration, and washed with a small amount of MeOH. The solution was concentrated to 2-5 mL, and purified by CC on Sephadex® LH 20, using MeOH/water (1/1) as solvent. Alternatively, when the sulphate ester was contaminated with some free acid, CC was carried out on RP-18, using a gradient of MeOH in water.

3. Synthetic strategy for the preparation of monohydroxycinnamic- and monohydroxyphenyl propionic acid *O*-glucuronides.

The Horner-Wadsworth-Emmons reaction of hydroxybenzaldehydes **54**-**57** with ethyl (triphenylphosphoranyliden)acetate,[1] afforded *p*-coumaric, *m*-coumaric, ferulic, and isoferulic acid ethyl esters **58**-**61** (Scheme S1) in very good yields (84-97%). The reaction of **58**-**61** with glucuronic acid donor **25**,[2] in the presence of BF_3-etherate as catalyst, yielded the corresponding protected β-glucuronides **62**-**65** as sole products, and in very good yield (84-89%). Some problems have been encountered in the past with the deprotection of peracetylated hydroxycinnamic acid glucuronides, and a two-step deprotection sequence was set up.[3] In contrast, when we submitted compounds **62**-**65** to alkaline hydrolysis in 1 N aqueous NaOH, both the elimination of acetyl protective groups, and the hydrolysis of the methyl- and ethyl carboxylic ester functions took place in a single step. This yielded *p*-coumaric acid 4′-*O*-β-D-glucuronide **1** (85%), *m*-coumaric acid 3′-*O*-β-D-glucuronide **2** (89 %), ferulic acid 4′-*O*-β-D-glucuronide **3** (88%), and isoferulic acid 4′-*O*-β-D-glucuronide **4** (75%). In all cases, the final hydroxycinnamic acid glucuronides were obtained as a mixture of (*E*)-, and (*Z*)-isomers from which the very major (*E*)-isomer, but not the minor (*Z*)-isomer, could be isolated in pure form. However, considering that i) during the biosynthesis of hydroxycinnamic acid derivatives in plants, the (*E*)-isomer is the sole product of the phenylalanine ammonia-lyase activity, and ii) in fact the (*E*)-isomers

represent the major constituents of coffee,[4] only the (*E*)-isomers were relevant for metabolic studies. In only one case, both (*E*)-*p*-coumaric acid 4′-*O*-β-D-glucuronide **1a**, and (*Z*)-*p*-coumaric acid 4′-*O*-β-D-glucuronide **1b** were isolated in pure form from the mixture of isomers. In contrast, (*E*)- and (*Z*)-isoferulic glucuronides **4a** & **4b**, could not be separated on a preparative scale. Finally catalytic hydrogenation of hydroxycinnamic acid glucuronides **1**-**4** yielded the corresponding dihydro derivatives **13**-**16** in 75-100% yield.



Scheme S1 The preparation of *p*-coumaric acid 4'-*O*-β-D-glucuronide **1**, *m*-coumaric acid 3'-*O*-β-D-glucuronide **2**, ferulic acid 4'-*O*-β-D-glucuronide **3**, isoferulic acid 3'-*O*-β-D-glucuronide **4**, dihydro-*p*-coumaric acid 4'-*O*-β-D-glucuronide **13**, dihydro-*m*-coumaric acid 3'-*O*-β-D-glucuronide **14**, dihydroferulic acid 4'-*O*-β-D-glucuronide **15**, and dihydroisoferulic acid 3'-*O*-β-D-glucuronide **16**. a) Ethyl (triphenylphosphoranyliden) acetate, CH_2Cl_2/THF, **58**: 92%, **59**: 95%, **60**: 97%, **61**: 84%; b) 2,3,4-Triacetyl-D-methyl glucuronopyranosyl-(*N*-phenyl)-2,2,2-trifluoroacetimidate **25**, BF_3 etherate, CH_2Cl_2, **62**: 89%, **63**: 85%, **64**: 84%, **65**: 84%; c) 1 N aq. NaOH, MeOH/H_2O, then Amberlite® IR-120, **1**: 85%, **2**: 89%, **3**: 88%, **4**: 75%; d) H_2, 5% Pd/C, MeOH-H_2O, **13**: 100%, **14**: 75%, **15**: 90%, **16**: 90%).

4. Ethyl *p*-coumarate (58).

Procedure A was carried out using 1.00 g (8.19 mmol) of 4'-hydroxybenzaldehyde **54** in 10 mL of dry THF + 10 mL of dry CH_2Cl_2, and 2.8 g (8.04 mmol) of ethyl (triphenylphosphoranyliden)acetate. This afforded, after purification, 1.446 g (7.52 mmol; 92%) of compound **58**. TLC R_f = 0.50 (Silica 60 F254, Hexane-EtOAc 7/3). ^{1}H NMR and ^{13}C NMR data of **58** were in accordance with published values.[5,6]

5. Ethyl *m*-coumarate (59).

Procedure A was carried out using 3.05 g (25 mmol) of 3'-hydroxybenzaldehyde **55** in 10 mL of dry THF + 10 mL of dry CH_2Cl_2, and 8.71 g (25 mmol) of ethyl (triphenylphosphoranyliden)acetate. This afforded, after purification, 4.57 g (23.8 mmol; 95.2%) of compound **59**. TLC R_f = 0.47 (Silica 60 F254, Hexane-EtOAc 7/3). The ^{1}H NMR of **59** in acetone-d_6 was close to the previously published data for ethyl

m-coumarate in $CDCl_3$.[7,8] ^{1}H NMR (360 MHz, Acetone-d_6) δ 1.29 (t, 3 H, *J* = 7.1 Hz, H2"), 4.22 (q, 2H, *J* = 7.1 Hz, H1"), 6.46 (d, 1H, *J* = 16.0 Hz, H2), 6.92 (m, 1 H, H4'), 7.12 (t, 1 H, *J* = 2.0 Hz, H2'), c.a. 7.14-7.17 (m, 1 H, H6'), 7.26 (t, 1 H, *J* = 7.8 Hz, H5'),7.60 (d, 1 H, *J* = 16.0 Hz, H3). ^{13}C NMR (90 MHz, Acetone-d_6) δ 14.6 (C2"), 60.8 (C1"), 115.4 (C2'), 118.3 (C4'), 119.1 (C2), 115.4 (C2'), 120.5 (C6'), 130.9 (C5'), 136.8 (C1'), 145.2 (C3), 158.7 (C3'), 167.0 (C1).

6. Ethyl ferulate (60).

Procedure A was carried out using 2.00 g (13.15 mmol) of vanillin **56** in 10 mL of dry CH_2Cl_2, and 4.6 g (13.15 mmol) of ethyl (triphenylphosphoranyliden)acetate. This afforded, after purification, 2.8429 g (12.79 mmol; 97%) of compound **60**.[9] TLC R_f = 0.48 (Silica 60 F254, Hexane-EtOAc 7/3). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.33 (t, 3 H, *J* = 7.1 Hz, H2"), 3.91 (s, 3 H, 3'-OMe), 4.26 (q, 2H, *J* = 7.1 Hz, H1"), 6.29 (d, 1H, *J* = 15.9 Hz, H2), 6.91 (d, 1 H, *J* = 8.1 Hz, H5'), 7.03 (d, 1 H, *J* = 1.9 Hz, H2'), 7.07 (dd, 1 H, *J* = 8.1 and 1.9 Hz, H6'), 7.61 (d, 1 H, *J* = 15.9 Hz, H3). ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.4 (C2"), 55.9 (3'-OMe), 60.4 (C1"), 109.3 (C2'), 114.7 (C5'), 115.6 (C2), 123.0 (C6'), 127.0 (C1'), 144.7 (C3), 146.8 (C3'), 147.9 (C4'), 167.3 (C1).

7. Ethyl isoferulate (61).

Procedure A was carried out using 3.04 g (20 mmol) of isovanillin **57** in 10 mL of dry CH_2Cl_2, and 6.97 g (20 mmol) of ethyl (triphenylphosphoranyliden)acetate. This afforded, after purification, 3.73 g (16.8 mmol; 84%) of compound **61**. TLC R_f = 0.32 (Silica 60 F254, Hexane-EtOAc 2/1). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.33 (t, 3 H, *J* = 7.1 Hz, H2"), 3.92 (s, 3 H, 4'-OMe), 4.25 (q, 2H, *J* = 7.2 Hz, H1"), 5.70 (brs, 1 H, 3'-OH), 6.29 (d, 1H, *J* = 15.9 Hz, H2), 6.84 (d, 1 H, *J* = 8.3 Hz, H5'), 7.03 (dd, 1 H, *J* = 8.3 and 2.1 Hz, H6'), 7.14 (d, 1 H, *J* = 2.1 Hz, H2'), 7.59 (d, 1 H, *J* = 15.9 Hz, H3). ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.35 (C2"), 56.0 (4'-OMe), 60.4 (C1"), 110.5 (C5'), 113.0 (C2'), 116.3 (C2), 121.8 (C6'), 128.1 (C1'), 140.4 (C3), 145.9 (C3'), 148.5 (C4'), 167.3 (C1).). NMR data was in accordance with that previously published for ethyl isoferulate in $CDCl_3$.[10]

8. 2-Propenoic acid, 3-[4-[(2,3,4-tri-*O*-acetyl-6-methyl-β-D-glucopyranurosyl)oxy]phenyl]-, ethyl ester (62).

Using procedure B, 213.4 mg (1.11 mmol) of *p*-coumaric acid ethyl ester **58** were reacted with 1.115 g (2.21 mmol) of 2,3,4-triacetyl-D-methyl glucuronopyranosyl-(*N*-phenyl)-2,2,2-trifluoroacetimidate **25**,[2] and with 40 µl (0.32 mmol) of BF_3 etherate. This yielded, after purification by MPLC on silica and RP-18, 504.6 mg (0.99 mmol; 89%) of novel compound **62**. TLC R_f = 0.14 (Silica 60 F254, Hexane-EtOAc 7/3). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, H2" *Z*-form), 1.33 (t, 3 H, *J* = 7.1 Hz, H2" *E*-form), 2.05 (s, 3H, C$\underline{H}_3$-CO), 2.06 (s, 6H, C$\underline{H}_3$-CO), 3.73 (s, 3H, H7a), 4.21 (d, 1H, *J* = 9.6 Hz, H5a), 4.26 (q, 2H, *J* = 7.1 Hz, H1"), 5.20 (d, 1H, *J* = 7.1 Hz, H1a), 5.27-5-37 (m, 3H, H2a + H3a + H4a), 5.89 (d, *J* = 12.7 Hz, H2 *Z*-form), 6.34 (d, 1H, *J* = 16.0 Hz, H2 *E*-form), 6.86 (d, *J* = 12.7 Hz, H3 *Z*-form), 7.00 (d, 2 H, *J* = 8.7 Hz, H3'/5'), 7.48 (d, 2 H, *J* = 8.7 Hz, H2'/6'), 7.63 (d, 1 H, *J* = 16.0 Hz, H3 *E*-form). ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.3 (C2"), 20.5 (C$\underline{H}_3$-CO), 20.6 (C$\underline{H}_3$-CO), 53.0 (C7a),

60.5 (C1”), 69.0 (C4a), 71.0 (C2a), 71.7 (C3a), 72.7 (C5a), 98.6 (C1a), 117.1 (C3'/5'), 117.3 (C2 *E*-form), 118.8 (C2 *Z*-form), 129.6 (C2'/6'), 129.8 (C1'), 143.6 (C3), 158.0 (C4'), 166.8 (C6a*), 167.0 (C1*), 169.2 (CH_3-$\underline{C}O$), 169.3 (CH_3-$\underline{C}O$), 170.1 (CH_3-$\underline{C}O$).

9. 2-Propenoic acid, 3-[3-[(2,3,4-tri-*O*-acetyl-6-methyl-β-D-glucopyranurosyl)oxy]phenyl]-, ethyl ester (63).

Using procedure B, 500 mg (2.6 mmol) of *m*-coumaric acid ethyl ester **59** were reacted with 3 g (5.93 mmol) of 2,3,4-triacetyl-D-methyl glucuronopyranosyl-(*N*-phenyl)-2,2,2-trifluoroacetimidate **25**,[2] and with 85 µl (0.86 mmol) of BF_3 etherate. This yielded, after purification by MPLC on silica and RP-18, 1.12 g (2.2 mmol; 85 %) of novel compound **63**. TLC R_f = 0.18 (Silica 60 F254, Hexane-EtOAc 2/1). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, H2” *Z*-form), 1.34 (t, 3 H, *J* = 7.1 Hz, H2” *E*-form), 2.05 (s, 3H, $C\underline{H}_3$-CO), 2.06 (s, 3H, $C\underline{H}_3$-CO), 2.08 (s, 3H, $C\underline{H}_3$-CO), 3.74 (s, 3H, H7a), 4.21 (brd, 1H, *J* = 9.5 Hz, H5a), 4.27 (q, 2H, *J* = 7.1 Hz, H1”), 5.17 (d, 1H, *J* = 7.1 Hz, H1a), 5.27-5.38 (m, 3H, H2a + H3a + H4a), 5.95 (d, *J* = 12.8 Hz, H2 *Z*-form), 6.42 (d, 1H, *J* = 16.0 Hz, H2 *E*-form), 6.85 (d, *J* = 12.8 Hz, H3 *Z*-form), 7.02 (m, 1H, H4'), 7.17 (brt, 1 H, *J* = 1.9 Hz, H2'), c.a. 7.23-7.26 (m, H6'), 7.32 (t, 1H, *J* = 7.8 Hz, H5'), 7.63 (d, 1 H, *J* = 16.0 Hz, H3 *E*-form). ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.3 (C2”), 20.5 ($C\underline{H}_3$-CO), 20.6 ($C\underline{H}_3$-CO), 53.0 (C7a), 60.6 (C1”), 69.0 (C4a), 71.1 (C2a), 71.8 (C3a), 72.6 (C5a), 99.1 (C1a), 116.3 (C2'), 118.8 (C4'), 119.2 (C2), 23.4 (C6'), 130.1 (C5'), 136.2 (C1'), 143.7 (C3), 157.0 (C3'), 166.8 (C1), 169.2 (CH_3-$\underline{C}O$), 169.3 (CH_3-$\underline{C}O$), 170.1 (CH_3-$\underline{C}O$).

10. 2-Propenoic acid, 3-[3-methoxy-4-[(2,3,4-tri-*O*-acetyl-6-methyl-β-D-glucopyranurosyl)oxy]phenyl]-, ethyl ester (64).

Using procedure B, 165.5 mg (0.745 mmol) of ferulic acid acid ethyl ester **60** were reacted with 0.741 g (1.47 mmol) of 2,3,4-triacetyl-D-methyl glucuronopyranosyl-(*N*-phenyl)-2,2,2-trifluoroacetimidate **25**,[2] and with 30 µl (0.24 mmol) of BF_3 etherate. This yielded, after purification by MPLC on silica and RP-18, 336.5 mg (0.625 mmol; 84%) of novel compound **64**. TLC R_f = 0.10 (Silica 60 F254, Hexane-EtOAc 7/3). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.1 Hz, H2” *Z*-form), 1.34 (t, 3 H, *J* = 7.1 Hz, H2” *E*-form), 2.04 (s, 3H, $C\underline{H}_3$-CO), 2.06 (s, 3H, $C\underline{H}_3$-CO), 2.08 (s, 3H, $C\underline{H}_3$-CO), 3.74 (s, 3H, H7a), 3.85 (s, 3H, 3'-OMe), 4.12 (d, 1H, *J* = 9.4 Hz, H5a), 4.18 (q, *J* = 7.1 Hz, H1” *Z*-form), 4.26 (q, 2H, *J* = 7.1 Hz, H1” *E*-form), 5.08 (d, 1H, *J* = 7.0 Hz, H1a), 5.27-5-36 (m, 3H, H2a + H3a + H4a), 5.90 (d, *J* = 12.8 Hz, H2 *Z*-form), 6.34 (d, 1H, *J* = 16.0 Hz, H2 *E*-form), 6.83 (d, *J* = 12.8 Hz, H3 *Z*-form), 7.05 (brs, 1 H, H2'), 7.08 (brd, 1 H, *J* = 8.1 Hz, H6'), 7.13 (d, 1 H, *J* = 8.3 Hz, H5'), 7.61 (d, 1 H, *J* = 16.0 Hz, H3 *E*-form). ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.2 (C2” *Z*-form), 14.3 (C2” *E*-form), 20.5 ($C\underline{H}_3$-CO), 20.6 ($C\underline{H}_3$-CO), 20.6 ($C\underline{H}_3$-CO), 53.0 (C7a), 56.0 (3'-OMe), 60.3 (C1” *Z*-form), 60.5 (C1” *E*-form), 69.2 (C4a), 71.0 (C2a), 71.7 (C3a), 72.7 (C5a), 100.3 (C1a), 111.4 (C2'), 117.7 (C2 *E*-form), 119.0 (C2 *Z*-form), 120.1 (C5'), 121.7 (C6'), 131.2 (C1'), 142.7 (C3 *Z*-form), 143.9 (C3 *E*-form), 147.4 (C4'), 150.8 (C3'), 166.9 (C1*), 166.9 (C6a*), 169.2 (CH_3-$\underline{C}O$), 169.4 (CH_3-$\underline{C}O$), 170.1 (CH_3-$\underline{C}O$).

11. (*E*)-2-Propenoic acid, 3-[4-methoxy-3-[(2,3,4-tri-*O*-acetyl-6-methyl-β-D-glucopyranurosyl)oxy]phenyl]-, ethyl ester (65).

Using procedure B, 149.5 mg (0.67 mmol) of isoferulic acid acid ethyl ester **61** were reacted with 0.671 g (1.328 mmol) of 2,3,4-triacetyl-D-methyl glucuronopyranosyl-(*N*-phenyl)-2,2,2-trifluoroacetimidate **25**,[2] and with 30 μl (0.24 mmol) of BF_3 etherate. This yielded, after purification by MPLC on silica and RP-18, 299.5 mg (0.56 mmol; 83.6%) of novel compound **65**. TLC R_f = 0.10 (Silica 60 F254, Hexane-EtOAc 7/3). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.33 (t, 3 H, *J* = 7.1 Hz, H2"), 2.04 (s, 3H, C$\underline{H}_3$-CO), 2.06 (s, 3H, C$\underline{H}_3$-CO), 2.09 (s, 3H, C$\underline{H}_3$-CO), 3.78 (s, 3H, H7a), 3.85 (s, 3H, 4'-OMe), 4.13 (d, 1H, *J* = 9.5 Hz, H5a), 4.25 (q, 2H, *J* = 7.1 Hz, H1"), 5.04 (d, 1H, *J* = 7.2 Hz, H1a), 5.27-5-10 (m, 3H, H2a + H3a + H4a), 6.29 (d, 1H, *J* = 15.9 Hz, H2), 6.89 (d, 1 H, *J* = 8.5 Hz, H5'), 7.25 (dd, 1 H, *J* = 8.5 and 2.1 Hz, H6'), 7.40 (d, 1 H, *J* = 2.1 Hz, H2'), 7.58 (d, 1 H, *J* = 15.9 Hz, H3). ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.3 (C2"), 20.5 (C$\underline{H}_3$-CO), 20.6 (2 × C$\underline{H}_3$-CO), 53.0 (C7a), 56.0 (4'-OMe), 60.4 (C1"), 69.1 (C4a), 71.0 (C2a), 71.9 (C3a), 72.6 (C5a), 100.7 (C1a), 112.4 (C5'), 116.7 (C2), 119.5 (C2'), 125.8 (C6'), 127.6 (C1'), 143.7 (C3), 145.8 (C3'), 152.5 (C4'), 166.8 (C6a), 167.1 (C1), 169.3 (2 × CH_3-C$\underline{O}$), 170.2 (CH_3-C$\underline{O}$).

12. (*E*)-*p*-Coumaric acid 4'-*O*-β-D-glucuronide (1a), and (*Z*)-*p*-Coumaric acid 4'-*O*-β-D-glucuronide (1b).

Following procedure C, 399 mg (0.785 mmol) of **62** were treated with 10 mL of 1 N aq. NaOH. After acidification (4 g of Amberlite® IR-120) and purification by MPLC on RP-18, 196.7 mg of (*E*)-*p*-coumaric acid 4'-*O*-β-D-glucuronide **1a**, and 32.3 mg of (*Z*)-*p*-coumaric acid 4'-*O*-β-D-glucuronide **1b** were isolated (total deprotection yield: 229 mg, 0.67 mmol, 85%). TLC R_f = 0.37 (RP-18 F254s, MeOH-H_2O-HCOOH 1/9/0.1). HPLC R_t = 5.42 (**1a**, method A; 99% purity at 280 nm). The ^{1}H- and ^{13}C NMR data of (*E*)-*p*-coumaric acid 4'-*O*-β-D-glucuronide in D_2O,[11] and in CD_3OD,[3] have been previously published. The NMR data in DMSO-d_6 is reported here for the first time. Compound **1a**: ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.26-3.37 (m, 2H, H2a + H3a), 3.40 (brt, 1H, *J* = 9.0 Hz, H4a), 3.95 (d, 1H, *J* = 9.5 Hz, H5a), 5.14 (d, 1H, *J* = 7.4 Hz, H1a), 6.41 (d, 1H, *J* = 16.0 Hz, H2), 7.05 (d, 2H, *J* = 8.8 Hz, H3'/5'), 7.55 (d, 1H, *J* = 16.0 Hz, H3), 7.65 (d, 2H, *J* = 8.8 Hz, H2'/6'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 71.2 (C4a), 72.8 (C2a), 75.2 (C5a), 75.6 (C3a), 99.3 (C1a), 116.2 (C3'/5'), 117.1 (C2), 128.0 (C1'), 129.7 (C2'/6'), 143.4 (C3), 158.3 (C4'), 167.6 (C1), 170.0 (C6a). LC-HRMS $[M-H]^-$ calc for $C_{15}H_{15}O_9$: 339.0716; found: 339.0721. Compound **1b**: ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.25-3.37 (m, 2H, H2a + H3a), 3.39 (brt, 1H, *J* = 8.9 Hz, H4a), 3.92 (d, 1H, *J* = 9.5 Hz, H5a), 5.11 (d, 1H, *J* = 7.4 Hz, H1a), 5.84 (d, 1H, *J* = 12.8 Hz, H2), 6.84 (d, 1H, *J* = 12.9 Hz, H3), 7.00 (d, 2H, *J* = 8.9 Hz, H3'/5'), 7.68 (d, 2H, *J* = 8.9 Hz, H2'/6'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 71.2 (C4a), 72.8 (C2a), 75.2 (C5a), 75.7 (C3a), 99.4 (C1a), 115.3 (C3'/5'), 118.8 (C2), 128.5 (C1'), 131.6 (C2'/6'), 140.6 (C3), 157.3 (C4'), 167.4 (C1), 170.0 (C6a).

13. (*E*)-*m*-Coumaric acid 3'-*O*-β-D-glucuronide (2a), and (*Z*)-*m*-Coumaric acid 3'-*O*-β-D-glucuronide (2b).

Following procedure C, 400 mg (0.78 mmol) of **63** were treated with 10 mL of 1N aq. NaOH. After acidification (8 g of Amberlite® IR-120) and purification by MPLC on

RP-18, 215.8 mg of (*E*)-*m*-coumaric acid 3'-*O*-β-D-glucuronide **2a**, and 20.6 mg of (*Z*)-*m*-coumaric acid 3'-*O*-β-D-glucuronide **2b** were isolated (total deprotection yield: 236.4 mg, 0.69 mmol, 89 %). Although the presence of *m*-coumaric glucuronide has been shown in rat urine after administration of γ-oryzanol,[12] both compounds **2a** and **2b** are described here for the first time. HPLC R_t = 6.18 (**2a**, method A; 97% purity at 280 nm). Compound **2a**: ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.25-3.46 (m, 3H, H2a + H3a + H4a), 3.98 (d, 1H, *J* = 9.5 Hz, H5a), 5.17 (d, 1H, *J* = 7.3 Hz, H1a), 6.55 (d, 1H, *J* = 16.0 Hz, H2), 7.05 (dt, 1H, *J* = 7.2, 2.3 Hz, H4'), 7.33 (m, 3H, H2' + H5' + H 6'), 7.56 (d, 1H, *J* = 16.0 Hz, H3). ^{13}C NMR (90 MHz, DMSO-d_6) δ 71.3 (C4a), 72.9 (C2a), 75.3 (C5a), 75.8 (C3a), 99.4 (C1a), 115.0 (C2'), 118.1 (C4'), 119.7 (C2), 122.1 (C6'), 129.9 (C5'), 135.6 (C1'), 143.7 (C3), 157.2 (C3'), 167.5 (C1), 170.1 (C6a). LC-HRMS [M-H]$^-$ calc for $C_{15}H_{15}O_9$: 339.0716; found: 339.0719.

14. (*E*)-Ferulic acid 4'-*O*-β-D-glucuronide (3a) and (*Z*)-Ferulic acid 4'-*O*-β-D-glucuronide (3b).

Following procedure C, 331 mg (0.615 mmol) of **64** were treated with 10 mL of 1 N aq. NaOH. After acidification (7.2 g of wet Amberlite® IR-120) and purification by MPLC on RP-18, 157.2 mg of (*E)* -ferulic acid 4'-*O*-β-D-glucuronide **3a**, and 42.6 mg of (*Z*)-ferulic acid 4'-*O*-β-D-glucuronide **3b** (containing 30% **3a**) were isolated (total deprotection yield: 199.8 mg, 0.54 mmol, 88%). TLC R_f = 0.47 (Silica 60 F254, BuOH-AcOOH-water 4/1/1). HPLC R_t = 5.83 (**3a**, method A; 99% purity at 280 nm). The ^{1}H- and ^{13}C NMR data of (*E)* -ferulic acid 4'-*O*-β-D-glucuronide in CD_3OD, has been previously published.[3] The NMR data in DMSO-d_6 is reported here for the first time. Compound **3a:** ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.29-3.41 (m, 3H, H2a + H3a + H4a), 3.82, (s, 3H, 3'-OMe), 3.90 (d, 1H, *J* = 9.5 Hz, H5a), 5.16 (d, 1H, *J* = 7.4 Hz, H1a), 6.48 (d, 1H, *J* = 15.9 Hz, H2), 7.09 (d, 1H, *J* = 8.5 Hz, H5'), 7.20 (dd, 1H, *J* = 8.5 and 1.8 Hz, H6'), 7.35 (d, 1H, *J* = 1.8 Hz, H2'), 7.53 (d, 1H, *J* = 15.9 Hz, H3). ^{13}C NMR (90 MHz, DMSO-d_6) δ 55.61 (3'-OMe), 71.2 (C4a), 72.7 (C2a), 75.3 (C5a), 75.9 (C3a), 99.1 (C1a), 111.2 (C2'), 114.8 (C5'), 117.3 (C2), 122.0 (C6'), 128.3 (C1'), 143.8 (C3), 147.7 (C4'), 149.0 (C3'), 167.7 (C1), 170.0 (C6a). LC-HRMS [M-H]$^-$ calc for $C_{16}H_{17}O_{10}$: 369.0821; found: 369.0834.

15. (*E*)- and (*Z*)-Isoferulic acid 3'-*O*-β-D-glucuronide (4a) and (4b).

Following procedure C, 300 mg (0.557 mmol) of **65** were treated with 10 mL of 1 N aq. NaOH. After acidification (10.9 g of wet Amberlite® IR-120) and purification by MPLC on RP-18, 154 mg of isoferulic acid 3'-*O*-β-D-glucuronide **4** (mixture of 9/1 *E*-**4a** and *Z*- **4b** forms) were isolated (yield: 154 mg, 0.416 mmol, 75%). Isoferulic acid glucuronide has been detected in rat urine and plasma by LC-ESI-MS after dosing of isoferulic acid.[13] However both compounds **4a** and **4b** are characterized here for the first time. TLC R_f = 0.47 (Silica 60 F254, BuOH-AcOOH-water 4/1/1). HPLC R_t = 6.53 (**4a**, method A; 99% purity at 280 nm). ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.29-3.42 (m, 3H, H2a + H3a + H4a *E*- and *Z*-forms), 3.80, (s, 3H, 4'-OMe *E*- and *Z*-forms), 4.00 (d, 1H, *J* = 9.5 Hz, H5a *E*- and *Z*-forms), 5.29 (d, 1H, *J* = 7.3 Hz, H1a *E*- and *Z*-forms), 5.81 (0.1H, d, *J* = 12.8 Hz, H2 *Z*-form), 6.44 (d, 0.9H, *J* = 15.9 Hz, H2 *E*-form), 6.77 (d, 0.1H, *J* = 13.0 Hz, H3 *Z*-form), 7.02 (d, 1H, *J* = 8.5 Hz, H5' *E*- and *Z*-forms), 7.27 (dd, 1H, *J* = 8.4 and 1.7 Hz, H6' *E*- and *Z*-forms), 7.44 (d, 1H, *J* = 1.8 Hz,

H2' *E*- and *Z*-forms), 7.51 (d, 0.9H, *J* = 15.9 Hz, H3 *E*-form). ^{13}C NMR (90 MHz, DMSO-d_6) δ 55.5 (4'-OMe), 71.2 (C4a), 72.8 (C2a), 75.2 (C5a), 76.0 (C3a), 98.7 (C1a), 112.2 (C5'), 113.4 (C2'), 116.8 (C2), 123.6 (C6'), 126.8 (C1'), 143.9 (C3), 145.9 (C3'), 150.8 (C4'), 167.8 (C1), 170.1 (C6a). LC-HRMS [M-H]$^-$ calc for $C_{16}H_{17}O_{10}$: 369.0821; found: 369.0825.

16. Dihydro-*p*-coumaric acid 4'-*O*-β-D-glucuronide (13).

Following procedure D, 65 mg (0.19 mmol) of crude compound **1** were hydrogenated for 2 h. This yielded, after filtration and freeze-drying, 70 mg (0.20 mmol; 100%) of compound **13**. Compound **13** has been identified in rat urine by mass spectrometry,[14] however its full characterization is made her for the first time. HPLC R_t = 5.42 (method A; 99% purity at 280 nm). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.49 (t, 2H, H2), 2.75 (t, 2H, *J* = 7.6, H3), 3.24-3.40 (m, 5H, H2a + H3a + H4a + 2OH), 3.85 (d, 1H, *J* = 9.5 Hz, H5a), 4.97 (d, 1H, *J* = 7.42 Hz, H1a), 6.92 (d, 2H, J = 8.7 Hz, H3' + H 5',), 7.14 (d, 2H, J = 8.7 Hz, H2' + H 6'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 29.4 (C3), 35.4 (C2), 71.3 (C4a), 72.8 (C2a), 75.2 (C5a), 75.7 (C3a), 100.0 (C1a), 116.0 (C3' + C5'), 129.0 (C2' + C6'), 134.3 (C1'), 155.2 (C4'), 170.1 (C6a) 173.7 (C1). LC-HRMS [M-H]$^-$ calc for $C_{15}H_{17}O_9$: 341.0872; found: 341.0882.

17. Dihydro-*m*-coumaric acid 3'-*O*-β-D-glucuronide (14).

Following procedure D, 250 mg (0.73 mmol) of crude compound **2** were hydrogenated for 2 h. Purification by MPLC yielded 186 mg (0.54 mmol; 75%) of compound **14**. The presence of dihydro-*m*-coumaric glucuronide has been shown in rat urine after administration of γ-oryzanol,[12] However compound **14** is characterized here for the first time. HPLC R_t = 5.95 (method A; 99% purity at 210 nm). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.51 (t, 2H, H2), 2.78 (t, 2H, *J* = 7.5, H3), 3.21-3.41 (m, 5H, H2a + H3a + H4a + 2OH), 3.88 (d, 1H, *J* = 9.5 Hz, H5a), 5.02 (d, 1H, *J* = 7.4 Hz, H1a), 6.82-6.87 (m, 3H, H2' + H4' + H 6'), 7.19 (t, 1H, *J* = 8.1 Hz, H5'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 30.3 (C3), 35.1 (C2), 71.3 (C4a), 72.9 (C2a), 75.4 (C5a), 75.8 (C3a), 99.8 (C1a), 113.5 (C4'), 116.2 (C2'), 121.9 (C6'), 129.2 (C5'), 142.4 (C1'), 157.0 (C3'), 170.1 (C6a) 173.7 (C1). LC-HRMS [M-H]$^-$ calc for $C_{15}H_{17}O_9$: 341.0872; found: 341.0878.

18. Dihydroferulic acid 4'-*O*-β-D-glucuronide (15).

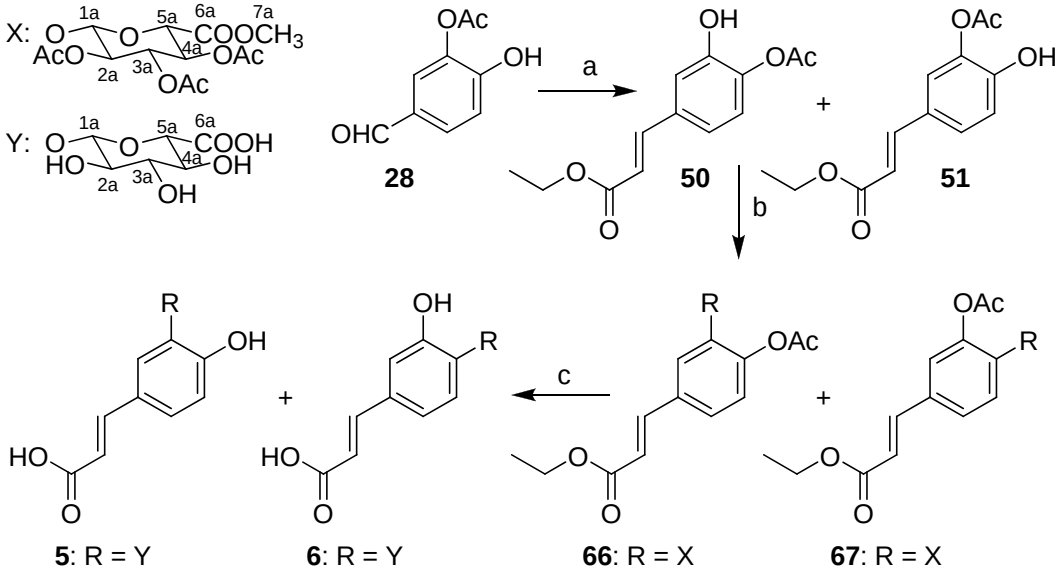
Following procedure D, 40 mg (0.108 mmol) of compound **3** were hydrogenated for 2 h. This yielded after filtration and freeze-drying 35.8 mg (0.096 mmol; 90%) of novel compound **15**. HPLC R_t = 5.78 (method A; 99% purity at 280 nm). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.51 (t, 2H, H2), 2.75 (t, 2H, *J* = 7.4, H3), 3.23-3.37 (m, 3H, H2a + H3a + H4a), 3.74 (s, 3H, 3'-OMe), 3.75 (m, 1H, H5a), 4.98 (d, 1H, *J* = 7.2 Hz, H1a), 6.70 (dd, 1H, *J* = 8.3 and 1.8 Hz H6'), 6.87 (d, 1H, *J* = 1.8 Hz, H2') 6.95 (d, 1H, *J* = 8.3 Hz, H5'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 29.9 (C3), 35.4 (C2), 35.4 (3'-OMe), 71.3 (C4a), 72.9 (C2a), 75.1 (C5a), 76.0 (C3a), 99.9 (C1a), 112.8 (C2'), 115.4 (C5'), 119.9 (C6'), 134.9 (C1'), 144.2 (C4'), 148.8 (C3'), 170.3 (C6a) 173.7 (C1). LC-HRMS [2M-H]$^-$ calc for $C_{32}H_{39}O_{20}$: 743.2040; found: 743.2019.

19. Dihydroisoferulic acid 3'-*O*-β-D-glucuronide (16).

Following procedure D, 60 mg (0.16 mmol) of compound **4** were hydrogenated for 4 h. This yielded after filtration and freeze-drying 54.1 mg (0.145 mmol; 90%) of compound novel **16**. HPLC R_t = 6.32 (method A; 98% purity at 280 nm). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.47 (t, 2H, H2), 2.72 (t, 2H, *J* = 7.6, H3), 3.24-3.40 (m, 3H, H2a + H3a + H4a), 3.72 (s, 3H, 4'-OMe), 3.82 (d, *J* = 9.5 Hz, 1H, H5a), 5.05 (d, 1H, *J* = 7.4 Hz, H1a), 6.79 (dd, 1H, *J* = 8.2 and 1.9 Hz H6'), 6.88 (d, 1H, *J* = 8.4 Hz, H5') 6.96 (d, 1H, *J* = 1.9 Hz, H2'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 29.9 (C3), 35.6 (C2), 55.7 (4'-OMe), 71.4 (C4a), 72.9 (C2a), 75.3 (C5a), 76.1 (C3a), 99.7 (C1a), 112.7 (C5'), 115.6 (C2'), 121.6 (C6'), 133.2 (C1'), 145.9 (C3'), 147.4 (C4'), 170.3 (C6a) 173.9 (C1). LC-HRMS $[M-H]^-$ calc for $C_{16}H_{19}O_{10}$: 371.0978; found: 371.0974.

20. Synthetic strategy for the preparation of caffeic acid *O*-glucuronides

3'-Acetoxy-4'-hydroxybenzaldehyde **28** was used as a precursor of caffeic acid glucuronide (Scheme S2).



Scheme S2 The preparations of caffeic acid 3'-*O*-β-D-glucuronide **5** and of caffeic acid 4'-*O*-β-D-glucuronide **6**. a) Ethyl (triphenylphosphoranyliden) acetate, CH_2Cl_2, 83% of **50** + **51**; b) Compound **25**, BF_3 etherate, CH_2Cl_2, 100% of **66** + **67**; c) NaOH, MeOH/H_2O, then Amberlite® IR-120, **5**: 55%, **6**: 81%.

During the Horner-Wadsworth-Emmons reaction, some ester migration took place, and a mixture of compounds **50** and **51** was obtained, although the 4′-hydroxy compound **51** was major (2/3), compared to the 3'-hydroxy compound **50** (1/3). The direct glucuronidation of the mixture of **50** and **51** using **25** as glucuronic acid donor yielded a mixture of the two protected caffeic acid glucuronides **66** and **67** in quantitative yield. The two isomers were easily separated by MPLC on silica. In compound **66**, the 3'-glucuronidation was unequivocally shown by the presence, on its HMBC spectrum, of a long distance correlation between the anomeric proton H1a at 5.18 ppm, and C3' of caffeic acid at 148.39 ppm. Similarly, from the HMBC spectrum of **67**, the long distance correlation between H1a at 5.19 ppm, and C4' at 149.43 ppm,

indicated 4'-glucuronidation. We individually submitted compounds **66** and **67** to alkaline hydrolysis using 1N NaOH in 50% aq. MeOH, to give caffeic acid 3'-*O*-β-D-glucuronide **5** (55%), and caffeic acid 4'-*O*-β-D-glucuronide **6** (81%). Both compounds were isolated as inseparable mixtures of the major (*E*)- and the minor (*Z*)-isomers **5a** + **5b** and **6a** + **6b**, respectively.

21. 4'-Acetoxy-3'-hydroxy-, and 3'-acetoxy-4'-hydroxycinnamic acids ethyl esters (50) and (51) from 3'-acetoxy-4'-hydroxybenzaldehyde (28).

Procedure A was carried out using 0.5498 g (3.05 mmol) of 3'-acetoxy-4'-hydroxybenzaldehyde **28** in 5 mL of dry THF + 5 mL of dry CH_2Cl_2, and 1.063 g (3.05 mmol) of ethyl (triphenylphosphoranyliden)acetate, except that the reaction was carried out for 24 h. This afforded, after purification by MPLC on silica, 0.6324 g (2.53 mmol; 83%) of a mixture of 4'-acetoxy-3'-hydroxycinnamic acids ethyl ester **50**, and of 3'-acetoxy-4'-hydroxycinnamic acids ethyl ester **51** (about 1/3 to 2/3 ratio, respectively, according to NMR analysis). Compounds **50** and **51** were directly submitted to the next synthetic step, without purification. TLC R_f **50** & **51** = 0.49 (Silica 60 F254, Hexane-EtOAc 6/4).

22. 2-Propenoic acid, 3-[4-acetyloxy-3-[(2,3,4-tri-*O*-acetyl-6-methyl-β-D-glucopyranurosyl)oxy]phenyl]-, ethyl ester (66), and 2-propenoic acid, 3-[3-acetyloxy-4-[(2,3,4-tri-*O*-acetyl-6-methyl-β-D-glucopyranurosyl)oxy]phenyl]-, ethyl ester (67).

268.5 mg (1.07 mmol) of the above mixture of esters **50** plus **51**, and 1.0639 g (2.10 mmol) of 2,3,4-triacetyl-D-methyl glucuronopyranosyl-(*N*-phenyl)-2,2,2-trifluoroacetimidate **25**,[2] were dissolved in 14 mL of dry CH_2Cl_2. 40 µl (0.32 mmol) of BF_3 etherate were added and the mixture was stirred at rt for 15 h. The medium was diluted with 50 mL of CH_2Cl_2, washed with 3 x 50 mL of H_2O, and concentrated under reduced pressure. The residue was purified by MPLC on silica using a gradient of EtOAc in hexane-EtOAc 9/1 as solvent. This yielded 154.9 mg of pure protected caffeic acid 3'-*O*-β-D-glucuronide **66**, 109.5 mg of a mixture of protected caffeic acid 3'- and 4'-*O*-β-D-glucuronides **66** and **67**, and 339.6 mg of pure protected caffeic acid 4'-*O*-β-D-glucuronide **67** (total glucuronidation yield: 604 mg, 1.07 mmol, 100%). Both compounds **66** and **67** are described here for the first time. TLC R_f = 0.31 (**67**) & 0.37 (**66**) (Silica 60 F254, Hexane-EtOAc 6/4). Compound **66**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.36 (t, 3 H, *J* = 7.1 Hz, H2"), 2.05 (s, 3H, C$\underline{H}_3$-CO), 2.06 (s, 3H, C$\underline{H}_3$-CO), 2.08 (s, 3H, C$\underline{H}_3$-CO), 2.28 (s, 3H, 4'-C$\underline{H}_3$-CO), 3.78 (s, 3H, H7a), 4.26 (d, 1H, *J* = 9.4 Hz, H5a), 4.27 (q, 2H, *J* = 7.1 Hz, H1"), 5.18 (d, 1H, *J* = 7.4 Hz, H1a), 5.33-5-36 (m, 3H, H2a + H3a + H4a), 6.36 (d, 1H, *J* = 16.0 Hz, H2), 7.06 (d, 1 H, *J* = 8.7 Hz, H5'), 7.23 (d, 1H, *J* = 1.8 Hz, H2'), 7.24 (dd, 1H, *J* = 8.7 and 1.8 Hz, H6'), 7.62 (d, 1 H, *J* = 16.0 Hz, H3). ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.3 (C2"), 20.4 (4'-C$\underline{H}_3$-CO), 20.5 (C$\underline{H}_3$-CO), 20.6 (C$\underline{H}_3$-CO), 20.7 (C$\underline{H}_3$-CO), 53.1 (C7a), 60.7 (C1"), 69.0 (C4a), 70.4 (C2a), 71.8 (C3a), 72.5 (C5a), 98.7 (C1a), 114.8 (C2'), 119.0 (C2), 123.4 (C6'), 123.8 (C5'), 133.6 (C1'), 141.6 (C4'), 143.3 (C3), 148.4 (C3'), 166.5 (C6a*), 166.7 (C1*), 168.7 (4'-CH$_3$-C$\underline{O}$), 169.3 (CH$_3$-C$\underline{O}$), 169.4 (CH$_3$-C$\underline{O}$), 170.0 (CH$_3$-C$\underline{O}$). Compound **67**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.33 (t, 3 H, *J* = 7.1 Hz, H2"), 2.05 (s,

6H, C$\underline{H}_3$-CO), 2.08 (s, 3H, C$\underline{H}_3$-CO), 2.28 (s, 3H, 3'-C$\underline{H}_3$-CO), 3.75 (s, 3H, H7a), 4.27 (d, 1H, *J* = 9.2 Hz, H5a), 4.25 (q, 2H, *J* = 7.1 Hz, H1"), 5.19 (d, 1H, *J* = 7.4 Hz, H1a), 5.29-5-36 (m, 3H, H2a + H3a + H4a), 6.31 (d, 1H, *J* = 16.0 Hz, H2), 7.04 (d, 1 H, *J* = 8.6 Hz, H5'), 7.23 (d, 1H, *J* = 2.1 Hz, H2'), 7.35 (dd, 1H, *J* = 8.6 and 2.1 Hz, H6'), 7.56 (d, 1 H, *J* = 16.0 Hz, H3). ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.3 (C2"), 20.4 (3'-C$\underline{H}_3$-CO), 20.5 (C$\underline{H}_3$-CO), 20.6 (2 × C$\underline{H}_3$-CO), 53.1 (C7a), 60.6 (C1"), 69.1 (C4a), 70.2 (C2a), 71.6 (C3a), 72.7 (C5a), 98.3 (C1a), 115.3 (C5'), 118.2 (C2), 122.4 (C2'), 127.3 (C6'), 130.2 (C1'), 140.3 (C3'), 142.8 (C3), 149.4 (C4'), 166.5 (C6a*), 166.8 (C1*), 168.8 (3'-CH$_3$-C$\underline{O}$), 169.3 (CH$_3$-C$\underline{O}$), 169.5 (CH$_3$-C$\underline{O}$), 169.9 (CH$_3$-C$\underline{O}$).

23. (*E*)- and (*Z*)-Caffeic acid 3'-*O*-β-D-glucuronide (5a) and (5b).

Following procedure C, 123.3 mg (0.217 mmol) of 2-propenoic acid, 4-[4-acetoxy-3-[(2,3,4-tri-*O*-acetyl-6-methyl-β-D-glucopyranurosyl)oxy]phenyl]-, ethyl ester **66** were treated with 5 mL of 1 N aq. NaOH. After acidification (4.3 g of wet Amberlite® IR-120) and purification by MPLC on RP-18, 41.1 mg of caffeic acid 3'-*O*-β-D-glucuronide **5** (mixture of 75/25 *E*- **5a** and *Z*- **5b** forms) were isolated (total deprotection yield: 42.1 mg, 0.118 mmol, 55%). The ^{1}H- and ^{13}C NMR data of (*E)* - caffeic acid 3'-*O*-β-D-glucuronide in CD_3OD has been previously published.[3] The NMR data in DMSO-d_6 is reported here for the first time. HPLC R_t = 5.88 (method A; 94% purity at 280 nm). ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.29-3.43 (m, 3H, H2a + H3a + H4a *E*- and *Z*-forms), 3.76, (d, 0.25H, *J* = 9.7 Hz, H5a *Z*-form), 4.00 (d, 0.75H, *J* = 9.5 Hz, H5a *E*-form), 4.78 (d, 0.25H, *J* = 7.2 Hz, H1a *Z*-form), 5.07 (d, 0.75H, *J* = 7.2 Hz, H1a *E*-form), 5.75 (d, 0.25H, *J* = 12.7 Hz, H2 *Z*-form), 6.31 (d, 0.75H, *J* = 15.9 Hz, H2 *E*-form), 6.66 (d, 0.25H, *J* = 13.0 Hz, H3 *Z*-form), 6.79 (d, 0.25H, *J* = 8.3 Hz, H5' *Z*-form), 6.84 (d, 0.75H, *J* = 8.2 Hz, H5' *E*-form), 7.16-7.20 (m, 1H, H6' *E and Z*-form), 7.37 (d, 0.75H, *J* = 1.7 Hz, H2' *E*-form), 7.46 (d, 0.75H, *J* = 15.9 Hz, H3 *E*-form), 7.66 (d, 0.25H, *J* = 1.7 Hz, H2' *Z*-form). ^{13}C NMR (90 MHz, DMSO-d_6) δ 71.3 (C4a), 72.9 (C2a), 75.1 (C5a), 75.3 (C3a), 100.5 (C1a), 115.0 (C2'), 115.9 (C2), 116.2 (C5'), 124.0 (C6'), 125.7 (C1'), 144.1 (C3), 145.3 (C3'), 149.1 (C4'), 167.8 (C1), 170.3 (C6a). LC-HRMS $[M-H]^-$ calc for $C_{15}H_{15}O_{10}$: 355.0665; found: 355.0653.

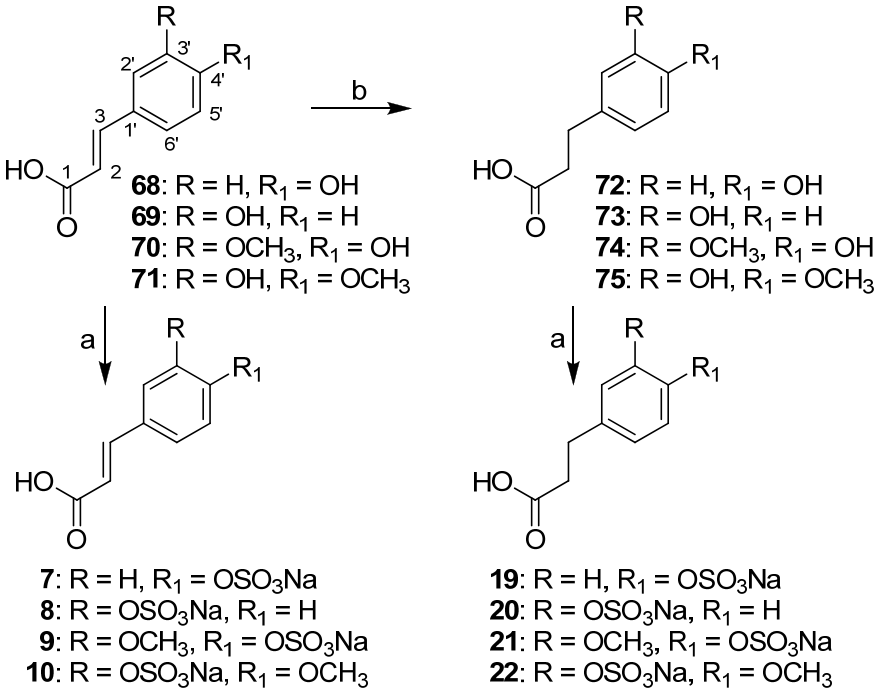
24. (*E*)- and (*Z*)-Caffeic acid 4'-*O*-β-D-glucuronide (6a) and (6b).

Following procedure C, 176.3 mg (0.311 mmol) of **67** were treated with 5 mL of 1 N aq. NaOH. After acidification (4.3 g of wet Amberlite® IR-120) and purification by MPLC on RP-18, 89.4 mg of caffeic acid 4'-*O*-β-D-glucuronide **6** (mixture of 95/5 *E*- **6a** and *Z*- **6b** forms) were isolated (total deprotection yield: 89.4 mg, 0.251 mmol, 81%). The ^{1}H- and ^{13}C NMR data of (*E)* - caffeic acid 4'-*O*-β-D-glucuronide in CD_3OD, has been previously published.[3] The NMR data in DMSO-d_6 is reported here for the first time. HPLC R_t = 5.28 (method A; 99% purity at 280 nm). ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.29-3.44 (m, 3H, H2a + H3a + H4a *E*- and *Z*-forms), 3.91 (d, 1H, *J* = 9.5 Hz, H5a *E*- and *Z*-forms), 4.98 (d, 1H, *J* = 7.4 Hz, H1a *E*- and *Z*-forms), 5.82 (d, 0.05H, *J* = 12.8 Hz, H2 *Z* -form), 6.32 (d, 0.95H, *J* = 15.9 Hz, H2 *E*-form), 6.73 (d, 0.05H, *J* = 13.0 Hz, H3 *Z* -form), 6.99 (d, 0.05 H, *J* = 8.4 Hz, H5' *Z* -form), 7.04 (d, 0.95H, *J* = 8.4 Hz, H5' *E* -form), 7.11 (dd, 0.95H, *J* = 8.4 and 1.9 Hz, H6' *E*-form), 7.14 (m, 0.95H, *J* = 2.0 Hz, H2' *E*-form), 7.29 (d, 0.05H, *J* = 2.0 Hz, H2' *Z* -form), 7.46 (d, 0.95H, *J* = 15.9 Hz, H3 *E*-form). ^{13}C NMR (90 MHz, DMSO-d_6) δ 71.3 (C4a), 72.8 (C2a), 75.0 (C5a), 75.3 (C3a), 100.8 (C1a), 115.0 (C2'), 115.9 (C2), 116.2 (C5'),

124.0 (C6'), 128.9 (C1'), 143.7 (C3), 146.7 (C3' or C4'), 146.8 (C4' or C3'), 167.6 (C1), 170.0 (C6a). LC-HRMS $[M-H]^-$ calc for $C_{15}H_{15}O_{10}$: 355.0665; found: 355.0664.

25. Synthetic strategy for the preparation of monohydroxycinnamic- and monohydroxyphenyl propionic acid acid sulphates.

A number of conditions have been reported for the *O*-sulphonylation of phenolic hydroxyl groups. One of the first efficient methods made use of tetrabutylammonium hydrogen sulphate as the sulphate donor, and of *N*,*N'*-dicyclohexylcarbodiimide (DCC) as esterification reagent.[15] However, as usual when using DCC, the reaction was accompanied by the formation of a huge precipitate of dicyclohexyl urea, from which the desired sulphated compounds were tedious to purify. More recently, a procedure making use of chlorosulphonic acid/pyridine as reagents has been introduced for the sulphation of hydroxycinnamic acids.[16] However, this method did not work in our hands, neither in the sulphation of quercetin, nor in that of ferulic acid (both unpublished results). The limitations of the chlorosulphonic acid method was also pointed out in a recent paper.[17] In contrast, sulphation by means of sulphur trioxide complexes is known to be very efficient,[18] and was applied the synthesis of polysulphated catechins.[19,20] However, when Jones *et al.* used such reagent in conditions for the monosulphation of quercetin, a complex mixture of at least 7 sulphated conjugates was obtained, with an overall sulphation yield of only 44%.[21] One of the major sulphated compounds of the mixture was quercetin 7-sulphate, illustrating the fact that under neutral conditions, the most acidic hydroxyl of the quercetin ring was the most susceptible to attack the sulphur trioxide complex. On the other hand, we previously observed that sulphation of the less reactive 3′-hydroxyl group of quercetin with sulphur trioxide-trimethylamine complex was very efficient in basic conditions.[22] Based on this observation, we were expecting a dramatic increase in the yield of sulphated products if the reaction was carried out under basic conditions, leading to an ionization of the hydroxyl group and increasing its nucleophilic character. Thus we directly submitted *p*-coumaric, *m*-coumaric, ferulic, and isoferulic acids **68**-**71**, or their reduced forms dihydro-*p*-coumaric, dihydro-*m*-coumaric, dihydroferulic, and dihydroisoferulic acids **72**-**75** (prepared by catalytic hydrogenation of the former) to sulphation with sulphur trioxide-trimethylamine complex, in aqueous Na_2CO_3 (Scheme S3). *p*-Coumaric acid 4′-sulphate **7**, *m*-coumaric acid 3'-sulphate **8**, ferulic acid 4′-sulphate **9**, isoferulic acid 4′-sulphate **10**, dihydro-*p*-coumaric acid 4′-sulphate **19**, dihydro-*m*-coumaric acid 3'-sulphate **20**, dihydroferulic acid 4'-sulphate **21**, and dihydroisoferulic acid 4'-sulphate **22**, were obtained as the major products of the reaction.



Scheme S3 The preparation of *p*-coumaric- **7**, *m*-coumaric- **8**, ferulic- **9**, isoferulic- **10**, dihydro-*p*-coumaric- **19**, dihydro-*m*-coumaric- **20**, dihydroferulic- **21**, and dihydroisoferulic **22** acid sulphates. a) Sulphur trioxide-trimethylamine complex, aqueous Na_2CO_3 , **7**: 92%, **8**: 88%, **9**: 53%, **10**: 43%, **19**: 40%, **20**: 36%, **21**: 37%, **22**: 39%; b) H_2, 5% Pd/C, MeOH-H_2O, **72**: 99%, **73**: 100%, **74**: 96%, **75**: 96%.

26. Dihydro-*p*-coumaric acid (72).

Following procedure D, 1 g (6.09 mmol) of *p*-coumaric acid **68** were hydrogenated during 3 hours. This yielded, after filtration, evaporation and drying under high vacuum, 970 mg (6.02 mmol; 99%) of compound **72**. The ^{1}H and ^{13}C NMR data for dihydro-*p*-coumaric acid in CD_3OD has already been published.[23] However, for comparison purposes with the sulphate conjugates, the spectra in DMSO-d_6 are given here. HPLC R_t = 7.10 (method A). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.45 (t, 2H, J = 7.6 Hz, H2), 2.70 (t, 2H, J = 7.7 Hz, H3), 6.66 (d, 2H, J = 1.9 Hz H2' + H6'), 7.01 (t, 2H, J = 1.8 Hz, H3' + H5'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 29.6 (C3) 35.8 (C2), 115.1 (C3'/C5') 129.1 (C2'/C6'), 131.0 (C1'), 155.6 (C4'), 173.9 (C1).

27. Dihydro-*m*-coumaric acid (73).

Following procedure D, 1 g (6.09 mmol) of *m*-coumaric acid **69** was hydrogenated for 4 h. This yielded, after filtration, evaporation and drying under high vacuum, 970 mg (6.08 mmol; 100%) of compound **73**.[24] HPLC R_t = 7.56 (method A). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.48 (t, 2H, J = 7.5 Hz, H2), 2.73 (t, 2H, J = 7.6 Hz, H3) 6.55-6.66 (m, 3H, H2' + H4' + H6'), 7.05 (t, 1H, J = 7.1 Hz, H5'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 30.2 (C3) 35.1 (C2), 112.8 (C4') 115.0 (C2'), 118.7 (C6'), 129.1 (C5'), 142.2 (C1'), 157.2 (C3'), 173.7 (C1).

28. Dihydroferulic acid (74).

Following procedure D, 1 g (5.14 mmol) of ferulic acid **70** was hydrogenated during 4 hours. This yielded, after filtration, evaporation and drying under high vacuum, 970

mg (4.94 mmol; 96%) of compound **74**. The ^{1}H and ^{13}C NMR data for dihydroferulic acid in CD_3OD has already been published.[25] However, for comparison purposes with the sulphate conjugates, the spectra in DMSO-d_6 are given here. HPLC R_t = 7.52 (method A). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.49 (t, 2H, J = 7.9 Hz, H2), 2.72 (t, 2H, J = 7.5 Hz, H3) 3.74 (s, 3H, 3'-OMe) 6.59 (dd, 1H, J = 8.0 and 2.0 Hz H6'), 6.67 (d, 1H, J = 8.0 Hz, H5') 6.79 (d, 1H, J = 8.0 Hz, H2'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 30.0 (C3) 35.7 (C2), 55.4 (3'-OMe) 112.4 (C2') 115.2 (C5'), 120.2 (C6'), 131.6 (C1'), 144.6 (C4'), 147.3 (C3'), 173.9 (C1).

29. Dihydroisoferulic acid (75).

Following procedure D, 1 g (5.14 mmol) of isoferulic acid **71** was hydrogenated for 4 h. This yielded, after filtration, evaporation and drying under high vacuum, 970 mg (4.94 mmol; 96%) of compound **75**. HPLC R_t = 7.94 (method A). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.44 (t, 2H, J = 7.5 Hz, H2), 2. 72 (t, 2H, J = 7.5 Hz, H3) 3.71 (s, 3H, 3'-OMe) 6.58 (brd, 1H, J = 8.2 Hz H6'), 6.63 (brs, 1H, H2') 6.79 (d, 1H, J = 8.1 Hz, H5'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 29.7 (C3) 35.6 (C2), 55.7 (3'-OMe) 112.3 (C5') 115.6 (C2'), 118.6 (C6'), 133.5 (C1'), 145.9 (C4'), 146.3 (C3'), 173.9 (C1). NMR data was in accordance with published values.[26]

30. (*E*)-*p*-Coumaric acid 4'-sulphate (7).

Following procedure H, 300 mg (1.83 mmol) of *p*-coumaric acid **68** were reacted with 2.5 g (23.6 mmol) of sodium carbonate, and with 2.1 g (15 mmol) of sulphur trioxide-trimethylamine complex in 50 mL water. This yielded, after purification by CC on LH-20, 600 mg (Quantification of the sulphate ester content following procedure G: 2.81 µmol/mg; 1.69 mmol; 92%) of compound **7.** HPLC R_t = 5.56 (method A). *p*-Coumaric acid **68** (for chemical shift comparison purpose): ^{1}H NMR (360 MHz, DMSO-d_6) δ 6.31 (d, 1H, J = 16.0 Hz, H2), 6.81 (d, 2 H, J = 8.4 Hz, H3' + H5'), 7.49-7.54 (m, 4 H, H3 + H2' + H6'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 115.2 (C2), 115.6 (C3' + C5'), 125.2 (C1'), 130.0 (C2' + C6'), 144.1 (C3), 159.5 (C4'), 167.9 (C1). NMR data of **7** in CD_3OD has been previously reported.[16,27] However the data in DMSO-d_6 is presented here for the first time. Compound **7**: ^{1}H NMR (360 MHz, DMSO-d_6) δ 6.41 (d, 1H, J = 16.0 Hz, H2), , 7.20 (d, 2 H, J = 8.7 Hz, H3'/5'), 7.52 (d, 1 H, J = 16.0 Hz, H3), 7.60 (d, 2 H, J = 8.7 Hz, H2'/6'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 118.1 (C2), 120.2 (C3'/5'), 128.9 (C1'), 128.9 (C2'/6'), 143.0 (C3), 155.1 (C4'), 168.0 (C1). LC-HRMS $[M-H]^-$ calc for $C_9H_7O_6S$: 242.9963; found: 242.9994.

31. (*E*)-*m*-Coumaric acid 3'-sulphate (8).

Following procedure H, 300 mg (1.83 mmol) of *m*-coumaric acid **69** were reacted with 2.5 g (23.6 mmol) of sodium carbonate, and with 2.1 g (15 mmol) of sulphur trioxide-trimethylamine complex in 50 mL water. This yielded, after purification by CC on LH-20, 600 mg (Quantification of the sulphate ester content following procedure G: 2.70 µmol/mg; 1.62 mmol; 88%) of compound **8.** HPLC R_t = 5.86 (method A). *m*-Coumaric acid **69** (for chemical shift comparison purpose): ^{1}H NMR (360 MHz, DMSO-d_6) δ 6.42 (d, 1H, J = 16.0 Hz, H2), 6.79 (ddd, 1 H, J = 8.0, 0.9 and 2.4 Hz, H4'), 7.03 (brt, 1 H, J = 2.0 Hz, H2'), 7.11 (brd, 1 H, J = 7.7 Hz, H6'), 7.11 (t, 1 H, J = 7.8 Hz, H5') 7.51 (d, 1 H, J = 16.0 Hz, H3). ^{13}C NMR (90 MHz,

DMSO-d_6) δ 114.4 (C2'), 117.3 (C4'), 118.8 (C2), 119.1 (C6'), 129.8 (C5'), 135.4 (C1'), 144.1 (C3), 157.6 (C3'), 167.5 (C1). NMR data for compound **8** in CD_3OD has been previously reported.[24] However the data in DMSO-d_6 is presented here for the first time. Compound **8**: ^{1}H NMR (360 MHz, DMSO-d_6) δ 6.45 (d, 1H, J = 16.0 Hz, H2), 7.24-7.42 (m, 4H, H2' + H4' + H 5' + H6'), 7.55 (d, 1 H, J = 16.0 Hz, H3). ^{13}C NMR (90 MHz, DMSO-d_6) δ 119.1 (C2), 119.6 (C2'), 122.3 (C4'), 123.0 (C6'), 129.3 (C5'), 134.9 (C1'), 143.6 (C3), 153.8 (C3'), 167.3 (C1). LC-HRMS $[M-H]^-$ calc for $C_9H_7O_6S$: 242.9963; found: 243.0001.

32. (*E*)-Ferulic acid 4'-sulphate (9).

Following procedure H, 300 mg (1.53 mmol) of ferulic acid **70** were reacted with 2.5 g (23.6 mmol) of sodium carbonate, and with 2.1 g (15.1 mmol) of sulphur trioxide-trimethylamine complex in 50 mL water. This yielded, after purification by CC on RP-18, 420 mg (Quantification of the sulphate ester content following procedure G: 1.93 µmol/mg; 0.81 mmol; 53%) of compound **9.** HPLC R_t = 5.63 (method A). Ferulic acid **70** (for chemical shift comparison purpose): ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.82 (s, 3 H, 3'-OMe), 6.37 (d, 1H, J = 15.9 Hz, H2), 6.79 (d, 1 H, J = 8.1 Hz, H5'), 7.09 (dd, 1 H, J = 8.3 and 1.9 Hz, H6'), 7.29 (d, 1 H, J = 1.9 Hz, H2'), 7.49 (d, 1 H, J = 15.9 Hz, H3). ^{13}C NMR (90 MHz, DMSO-d_6) δ 55.6 (3'-OMe), 111.0 (C2'), 115.4 (C5'), 115.5 (C2), 122.7 (C6'), 125.7 (C1'), 144.4 (C3), 147.8 (C3'), 149.0 (C4'), 167.9 (C1). The ^{1}H and ^{13}C NMR data of **9** in DMSO-d_6 have been previously reported.[24] However, a number of signals were wrongly attributed, and have been correctly assigned here on the basis of direct and long distance NMR proton-carbon correlations. Compound **9**: ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.79 (s, 3 H, 3'-OMe), 6.46 (d, 1H, J = 15.9 Hz, H2), 7.16 (dd, 1 H, J = 8.4 and 1.9 Hz, H6'), 7.30 (d, 1 H, J = 1.9 Hz, H2'), 7.49 (d, 1 H, J = 8.4 Hz, H5'), 7.51 (d, 1 H, J = 15.9 Hz, H3). ^{13}C NMR (90 MHz, DMSO-d_6) δ 55.6 (3'-OMe), 111.3 (C2'), 117.4 (C2), 120.2 (C5'), 121.2 (C6'), 129.1 (C1'), 143.9 (C3), 144.6 (C4'), 150.3 (C3'), 167.7 (C1). LC-HRMS $[M-H]^-$ calc for $C_{10}H_9O_7S$: 273.0069; found: 273.0099.

33. (*E*)-Isoferulic acid 3'-sulphate (10).

Following procedure H, 300 mg (1.53 mmol) of isoferulic acid **71** were reacted with 2.5 g (23.6 mmol) of sodium carbonate, and with 2.1 g (15 mmol) of sulphur trioxide-trimethylamine complex in 50 mL water. This yielded, after purification by CC on LH-20, 420 mg (Quantification of the sulphate ester content following procedure G: 1.57 µmol/mg; 0.66 mmol; 43%) of novel compound **10**. HPLC R_t = 6.09 (method A). Isoferulic acid **71** (for chemical shift comparison purpose): ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.81 (s, 3 H, 4'-OMe), 6.26 (d, 1H, J = 15.9 Hz, H2), 6.95 (d, 1 H, J = 8.7 Hz, H5'), 7.10 (brd, 2 H, H2' et H6'), 7.47 (d, 1 H, J = 15.9 Hz, H3). ^{13}C NMR (90 MHz, DMSO-d_6) δ 55.5 (4'-OMe), 111.9 (C5'), 114.0 (C2'), 116.1 (C2), 120.9 (C6'), 127.0 (C1'), 144.1 (C3), 146.6 (C3'), 149.8 (C4'), 167.7 (C1). Compound **10**: ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.78 (s, 3 H, 4'-OMe), 6.21 (d, 1H, J = 15.9 Hz, H2), 7.01 (d, 1 H, J = 8.7 Hz, H5'), 7.33 (brd, 1 H, J = 8.0 Hz H6'), 7.48 (d, 1 H, J = 15.9 Hz, H3), 7.72 (brs, 1 H, H2'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 55.6 (4'-OMe), 112.3 (C5'), 116.3 (C2), 119.3 (C2'), 124.6 (C6'), 126.1 (C1'), 142.6 (C3'), 143.8 (C3), 152.4 (C4'), 167.5 (C1). LC-HRMS $[M-H]^-$ calc for $C_{10}H_9O_7S$: 273.0069; found: 273.0112.

34. Dihydro-*p*-coumaric acid 4'-sulphate (19).

Following procedure H, 300 mg (1.81 mmol) of compound **72** were reacted with 2.5 g (23.6 mmol) of sodium carbonate, and with 2.1 g (15 mmol) of sulphur trioxide-trimethylamine complex in 50 mL water. This yielded, after purification by CC on LH-20, 330 mg (Quantification of the sulphate ester content following procedure G: 2.22 µmol/mg; 0.73 mmol; 40%) of novel compound **19**. HPLC R_t = 5.08 (method A). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.35 (brt, 2H, J = 7.6 Hz, H2), 2.74 (brt, 2H, J = 7.6 Hz, H3), 7.03-7.11 (m, 4H, H2'/H6'/H3'/H5'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 30.7 (C3), 37.7 (C2) 120.4 (C3'/C5'), 128.3 (C2'/C6'), 136.7 (C1'), 151.3 (C4'), 175.6 (C1). LC-HRMS $[M-H]^-$ calc for $C_9H_9O_6S$: 245.0119; found: 245.0164.

35. Dihydro-*m*-coumaric acid 3'-sulphate (20).

Following procedure H, 297 mg (1.79 mmol) of compound **73** were reacted with 2.5 g (23.6 mmol) of sodium carbonate, and with 2.1 g (15 mmol) of sulphur trioxide-trimethylamine complex in 50 mL water. This yielded, after purification by CC on LH-20, 310 mg (Quantification of the sulphate ester content following procedure G: 2.10 µmol/mg; 0.65 mmol; 36%) of novel compound **20**. HPLC R_t = 5.34 (method A). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.29 (brt, 2H, J = 7.8 Hz, H2), 2.75 (brt, 2H, J = 7.8 Hz, H3) 6.89 (brd, 1H, J = 7.8 Hz, H6') 6.96-7.00 (m, 2H, H2' + H4'), 7.13 (t, 1H, J = 7.8 Hz, H5'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 31.7 (C3), 38.3 (C2), 117.6 (C4') 120.2 (C2'), 122.8 (C6'), 128.2 (C5'), 143.2 (C1'), 153.3 (C3'), 175.8 (C1). LC-HRMS $[M-H]^-$ calc for $C_9H_9O_6S$: 245.0119; found: 245.0161.

36. Dihydroferulic acid 4'-sulphate (21).

Following procedure H, 308 mg (1.57 mmol) of compound **74** were reacted with 2.5 g (23.6 mmol) of sodium carbonate, and with 2.1 g (15 mmol) of sulphur trioxide-trimethylamine complex in 50 mL water. This yielded, after purification by CC on LH-20, 370 mg (Quantification of the sulphate ester content following procedure G: 1.57 µmol/mg; 0.58 mmol; 37%) of novel compound **21**. HPLC R_t = 5.25 (method A). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.43 (t, 2H, J = 8.1 Hz, H2), 2.74 (t, 2H, J = 7.5 Hz, H3) 3.71 (s, 3H, 3'-OMe) 6.66 (dd, 1H, J = 8.2 and 2.0 Hz H6'), 6.82 (d, 1H, J = 1.9 Hz, H2') 7.31 (d, 1H, J = 8.2 Hz, H5'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 30.4 (C3) 36.1 (C2), 55.4 (3'-OMe) 112.6 (C2') 119.4 (C6'), 120.8 (C5'), 136.4 (C1'), 140.6 (C4'), 150.2 (C3'), 174.3 (C1). LC-HRMS $[M-H]^-$ calc for $C_{10}H_{11}O_7S$: 275.0225; found: 275.0270.

37. Dihydroisoferulic acid 3'-sulphate (22).

Following procedure H, 301 mg (1.53 mmol) of compound **75** were reacted with 2.5 g (23.6 mmol) of sodium carbonate, and with 2.1 g (15 mmol) of sulphur trioxide-trimethylamine complex in 50 mL water. This yielded, after purification by CC on LH-20, 280 mg (Quantification of the sulphate ester content following procedure G: 2.15 µmol/mg; 0.60 mmol; 39%) of novel compound **22**. HPLC R_t = 5.60 (method A). ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.45 (t, 2H, J = 7.7 Hz, H2), 2.71 (t, 2H, J = 7.4 Hz, H3) 3.71 (s, 3H, 4'-OMe), 6.81-6.87 (m, 2H, H5' and H6'), 7.30 (brd, 1H, J = 0.9 Hz, H2'). ^{13}C NMR (90 MHz, DMSO-d_6) δ 29.7 (C3) 35.5 (C2), 55.6 (4'-OMe) 112.5 (C5')

120.9 (C2'), 122.6 (C6'), 132.4 (C1'), 142.4 (C3'), 148.8 (C4'), 173.7 (C1). LC-HRMS $[M-H]^-$ calc for $C_{10}H_{11}O_7S$: 275.0225; found: 275.0270.

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