Efficient Chemical Synthesis of (Epi)catechin Glucuronides: Brain-Targeted Metabolites for Treatment of Alzheimer’s Disease and Other Neurological Disorders

Maite L. Docampo-Palacios,* Anislay Alvarez-Hernández, Ângelo de Fátima, Luciano Morais Liao, Giulio M. Pasinetti, and Richard A. Dixon*

ABSTRACT: Grape seed extract (GSE) is rich in flavonoids and has been recognized to possess human health benefits. Our group and others have demonstrated that GSE is able to attenuate the development of Alzheimer’s disease (AD). Moreover, our results have disclosed that the anti-Alzheimer’s benefits are not directly/solely related to the dietary flavonoids themselves, but rather to their metabolites, particularly to the glucuronidated ones. To facilitate the understanding of regioisomer/stereoisomer-specific biological effects of (epi)catechin glucuronides, we here describe a concise chemical synthesis of authentic standards of catechin and epicatechin metabolites 3−12. The synthesis of glucuronides 9 and 12 is described here for the first time. The key reactions employed in the synthesis of the novel glucuronides 9 and 12 include the regioselective methylation of the 4′-hydroxyl group of (epi)catechin (≤1.0/99.0%; 3′-OMe/4′-OMe) and the regioselective deprotection of the tert-butyldimethylsilyl (TBS) group at position 5 (yielding up to 79%) over the others (3, 7 and 3′ or 4′).

INTRODUCTION

Fruits, vegetables, and their juices, as well as tea, wine, and cocoa-derived products, are important dietary sources of flavonoids.1−7 Diets rich in flavonoids are linked with the prevention of a variety of degenerative diseases, most importantly, cardiovascular and neuropsychological.1,4−7 Flavonoids, a broad class of plant natural products, are based on a fifteen-carbon skeleton containing two benzene rings (A and B) connected via a heterocyclic pyran moiety (C) (Figure 1).3,8,9 The presence of different oxidation states of the C ring and different functional groups on the A, B, and C rings gives rise to diverse subclasses of flavonoids such as flavonols, flavones, flavanones, isoflavones, and flavan-3-ols. Such flavonoids are known for their pharmacological properties, which include antiallergic,10 antibacterial,11−13 anticancer,14−16 antifungal,11−13 anti-Helicobacter pylori,11,19 anti-inflammatory,20 antioxidant/antiradical,21,22 antiviral,11−13 cardioprotective,23,24 gastroprotective,25 neuroprotective,26−30 and nutraceutical.31

Grape seed extract (GSE) is rich in flavonoids and has been recognized to stimulate glucose uptake in insulin-resistant adipocytes32−34 to produce a significant decrease in systolic and diastolic blood pressure of spontaneously hypertensive rats (SHR),35 to ameliorate diabetic bladder dysfunction and reduce the apoptosis of the bladder in diabetic rats,36 to defend against fat accumulation and improve the plasma lipid profile in hamsters,37 and to improve the antioxidant status and decrease the incidence of free radical-induced lipid peroxidation in blood samples of rats exposed to X-radiation.38 Our group and others have demonstrated that GSE is also able to attenuate the development of Alzheimer’s disease (AD).39−43

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The GSE studied by us was a complex mixture of proanthocyanidins (PACs, both oligomeric and polymeric) and their monomeric units consisting of the flavan-3-ols (+)-catechin (1) and (−)-epicatechin (2) (Figure 1). The monomeric units, rather than the oligomers or polymers, are bioavailable and, therefore, candidates for being the active components in the GSE with respect to amelioration of Alzheimer’s disease symptoms.45,46 These components, in the form of glucuronidated and/or methylated phase II metabolites, reach the brain at a concentration of 300–400 nM after 10 days of repeated dosing.46 Our studies showed that the predominant plasma metabolites of 1 and 2, identified by liquid chromatography–mass spectrometry time-of-flight (LC–MS-TOF), were catechin-5-O-β-glucuronide (7), 3′-O-methyl catechin-5-O-β-glucuronide (8), epicatechin-5-O-β-glucuronide (10), and 3′-O-methyl epicatechin-5-O-β-glucuronide (11) (Figure 1). It is noteworthy that the effects of conjugation can differ depending on the type and position of conjugation, the flavonoid concentration, the pharmacological/molecular target effect studied, and the assay system used so that no general rules can be deduced.47,48 It has further been established that the ingested (epi)catechin is extensively metabolized into its related metabolites by O-methylation, sulfation, O-glucuronidation, and combinations thereof, and also that the absorption, metabolism, and biological activity of dietary flavan-3-ols are strongly influenced by stereochemistry.49−53 However, a broad study of regioisomer/stereoisomer-specific effects on the biochemical and pharmacological properties of flavan-3-ols, particularly as related to anti-Alzheimer properties, has yet to be undertaken. In part, this reflects the lack of good synthetic strategies to furnish all possible (epi)catechin-glucuronide regioisomers. In particular, the chemical synthesis of glucuronide derivatives of catechin is underexplored when compared with the chemical/enzymatic synthesis of the corresponding conjugates of epicatechin.55−61 For the series of (epi)catechin glucuronides shown in Figure 1, the synthesis of glucuronides 7, 8, 10, and 11 has been reported elsewhere, while the chemical synthesis of glucuronides 8 and 9 is described here for the first time. In this context, authentic standards of (+) catechin and...
(−) epicatechin metabolites 3–12 (Figure 1) were prepared by a chemically unambiguous synthetic approach for the further mechanism of action studies.

■ RESULTS AND DISCUSSION

Methylation of (Epi)catechin. The synthesis of methylated (+)-catechin derivatives was carried out using the procedure reported by González-Manzano et al.54 with small modifications with respect to the reaction time (Scheme 1). The original technique used 3.5 h in an ultrasonic bath, but under our experimental conditions, low quantities of methylated products were obtained at that time and the reaction was therefore stirred at room temperature for 20 h and monitored by high-performance liquid chromatography (HPLC). We observed the formation of two products, which were assigned as 3′- and 4′-O-methyl catechin (3 and 4). The methylation of catechin was preferentially at the 4′ position, as shown in Figure 2. The proportion of 3′- and 4′-O-methylcatechin isomers was 3:7 as calculated by HPLC analysis.

However, Donovan et al.62 specified that the preferential position for the methylation of catechin is position 3′. No formation of other methyl ether isomers was detected, demonstrating that the preferential site for methylation under these reaction conditions is ring B. Application of the same method for methylation of (−)-epicatechin gave similar results with the formation of the corresponding 3′- and 4′-O-methyl epicatechin derivatives (5 and 6), but in this case, the ratio between the two isomers was 4:6, respectively (Figure 2B), as calculated by HPLC analysis.

The positions of the methoxyl substituents on (epi)catechin were confirmed by heteronuclear multiple bond correlation (HMBC) spectra using a long-range correlation between the methoxy protons and C-3′ of 3 and 5 (Figures S4 and S12) and C-4′ of 4 and 6 (Figures S8 and S16).1H- and 13C NMR and liquid chromatography coupled to mass spectrometry (LC/MS) data derived from 3′-O-methyl (epi)catechin (3 and 5) and 4′-O-methyl (epi)catechin (4 and 6) were in complete agreement.

Table 1. Different Methylation Reaction Conditions for the Preparation of 4′-O-Methyl Catechin (4)

| entry | equiv (K₂CO₃) | equiv (CH₃I) | time (h) | 3′-/4′-O-methyl catechin yield (%) |
|-------|---------------|--------------|----------|----------------------------------|
| 1     | 5.0           | 18.0         | 24       | 40/60                            |
| 2     | 1.0           | 1.0          | 24       | ≤1/20                            |
| 3     | 2.0           | 2.0          | 48       | 5/50                             |
| 4     | 2.5           | 3.0          | 48       | 10/70                            |
| 5     | 2.5 (1.0 + 0.5)² | 4.0 (1.5 + 1.5 + 1.0)² | 72       | ≤1/99                            |

²Reagents were added in batch (periods of time of 24 h).²Yield was calculated by HPLC without purification.
agreement with the assigned structure of these compounds and those already published in the literature. \textsuperscript{54,61} The relative configurations of H-2/H-3 (C-ring) of the diastereoisomers catechin and epicatechin were established as trans (catechin) and cis (epicatechin), respectively, by comparing the \(^1H\) coupling constants of the protons of two chiral centers on the ring (\(J_{2H,3H} = 8.0\) Hz, 3 and \(J_{2H,3H} < 2\) Hz, 5 and 6).

Finally, the LC−MS analyses of 3′-O-methyl catechin (3), 4′-O-methyl catechin (4), 3′-O-methyl epicatechin (5), and 4′-O-methyl epicatechin (6) showed the expected quasimolecular ion at \(m/z\) 303.1 [M − H]− (calcld for 3−6, 303.1).

The above-described procedure for the synthesis of methyl ethers of epi(catechin) was modified to obtain a regioselective methylation of (epi)catechin at position 4′. Table 1 shows the different conditions used in the methylation of catechin and the relationship between both regioisomers (3′-/4′-O-methyl catechin). The best conditions were reached by applying intermittent injection of methyl iodide and potassium carbonate, reducing the amounts of methylating agent and the base, and increasing the reaction time (Table 1, entry 5).

The reactions were monitored by HPLC, and Figure 3 shows the HPLC chromatograms for the optimal conditions in the regioselective methylation of (epi)catechin.

To the best of our knowledge, regioselective methylation of epi(catechin) to obtain 4′-O-methyl catechin and 4′-O-methyl epicatechin has not been previously reported.

**Synthesis of (Epi)catechin-5-O-Glucuronides.** The semisynthesis of metabolites that contain phenol groups commonly requires the protection of hydroxyl groups to prevent unwanted side reactions since these compounds are sensitive to pH changes. For example, catechins and epicatechins are unstable at pH < 5, entering into polymerization reactions, whereas in basic conditions (pH > 9) opening of the C ring occurs, leading to epimerization reactions.\textsuperscript{63} The most common protective groups used for phenolic compounds include acetyl, benzyl, methoxymethyl acetal, tetrafluoropyridyl, and dichlorodiphenylmethane;\textsuperscript{55,58,59,64} however, there have been few reports where silyl groups were used to protect hydroxyl groups in phenolic compounds. The tert-butyldimethylsilyl (TBS) substituent can be installed in one-step, is stable under a range of commonly employed reaction conditions, and is selectively cleaved under mild conditions.

The synthetic strategy implemented to obtain (epi)catechin-5-O-glucuronides is shown in Scheme 2. In the first step, as specified above, it was essential to protect phenolic hydroxyl groups. This reaction was carried out using tert-butyldimethylsilyl chloride (TBSCl) in excess, imidazole, and dropwise addition of dimethylformamide (DMF) according to the methodology developed by Cruz et al.\textsuperscript{65} Compounds 13−18 were obtained with excellent yields (92−97%) after purification by flash chromatography (silica gel, hexane/ethyl acetate 15:1 v/v). This is the first time that compounds 14, 15, 17, and 18 were synthesized and a complete characterization was therefore performed.

The hydroxyl group to be glucuronidated was selectively deprotected by the removal of TBS at position 5 using trifluoroacetic acid (TFA) to afford the intermediates 19−24 with yield ranging between 61 and 79%. Better yields were

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**Figure 3.** (A) HPLC of the crude reaction product from the regioselective methylation of catechin: 4′-O-methyl catechin (4). (B) HPLC of the crude reaction product from the regioselective methylation of epicatechin: 4′-O-methyl epicatechin (6).
found for 4′-O-methyl derivatives, and the amount of TFA added and the reaction time were critical. For best results, it was necessary to start the reaction with 3 equivalents of TFA added drop by drop and, after 12 h, one more equivalent of TFA was added and the reaction was quenched after 36 h. The crude reaction mixture was purified by flash chromatography (silica gel, hexane/ethyl acetate 10:1 v/v). The intermediates 20, 21, 23, and 24 have not been reported previously and, therefore, a complete characterization was performed. The next step was the acid glucuronidation of the phenolic intermediates 19−24 using methyl 2,3,4-tri-O-(trichloroacetamidoyl)-α-D-glucuronate as a sugar donor and catalyzed by BF3·Et2O as Lewis acid (Scheme 2, step 3) under known reaction conditions.55,59 Compounds 25−30 were not purified to proceed to the next steps. The last two steps for the synthesis of (epi)catechin-5-O-glucuronides (7−12) involved the hydrolysis of the methyl ester and acetyl groups and the removal of TBS groups (Scheme 2, steps d, e).

We first accomplished the hydrolysis of the methyl ester and acetyl groups because catechins and epicatechins are easily oxidized, losing hydrogen atoms in alkaline solution with the generation of quinone-oxidized products and other radical species occurring via oxidation processes.66−68 Also, epicatechin and catechin molecules can undergo epimerization of the 2-position via quinomethide under basic conditions (Scheme 3).69,70 Deprotection of the acetyl groups as well as hydrolysis of the methyl ester for compounds 25−30 was easily achieved using a mixture of 5.4 M MeONa in MeOH and 0.5 M NaOH at room temperature for 3 h. Under these conditions, the desilylation reaction proceeded without obtaining degradation products.
Table 2. NMR Spectroscopic Data for Catechin-5-O-β-D-glucuronide (7), 3′-O-Methylcatechin-5-O-β-D-glucuronide (8), and 4′-O-Methylcatechin-5-O-β-D-glucuronide (9)

|     | compound 7 |     | compound 8 |     | compound 9 |
|-----|------------|-----|------------|-----|------------|
|     | position   | ¹H δ (ppm) CD$_3$OD J (Hz) | ¹³C (1H) δ (ppm) CD$_3$OD | ¹H δ (ppm) CD$_3$OD J (Hz) | ¹³C (1H) δ (ppm) CD$_3$OD | ¹H δ (ppm) acetone-d$_6$ J (Hz) | ¹³C (1H) δ (ppm) acetone-d$_6$ |
| 2   | 4.73 (1H, d, J = 7.2) | 82.7 | 4.64 (1H, d, J = 8.0) | 81.6 | 467 (1H, d, J = 7.0) | 82.1 |
| 3   | 4.09 (1H, dt, J = 5.2, 7.2, 7.8) | 68.4 | 4.01 (1H, dt, J = 5.6, 7.7, 8.0) | 68.7 | 396 (1H, dt, J = 5.1, 7.0, 7.8) | 67.8 |
| 4   | H4-α: 3.10 (1H, dd, J = 5.2, 16.4) | 28.3 | H4-α: 3.06 (1H, dd, J = 5.6, 16.4) | 28.7 | H4-α: 2.95 (1H, dd, J = 5.1, 16.3) | 28.0 |
|     | H4-β: 2.72 (1H, dd, J = 7.8, 16.4) |     | H4-β: 2.62 (1H, dd, J = 7.7, 16.4) |     | H4-β: 2.69 (1H, dd, J = 7.8, 16.3) |     |
| COOH | 175.6 |     | 170.8 |     | 175.9 |
| 5   | 158.0 |     | 158.0 |     | 157.7 |
| 6   | 6.41 (1H, d, J = 2.0) | 97.1 | 6.33 (1H, d, J = 1.8) | 97.2 | 6.42 (1H, d, J = 2.0) | 97.2 |
| 7   | 158.1 |     | 158.1 |     | 158.1 |
| 8   | 6.12 (1H, d, J = 2.0) | 98.2 | 6.03 (1H, d, J = 1.8) | 98.2 | 6.01 (1H, d, J = 2.0) | 97.7 |
| 9   | 156.7 |     | 156.7 |     | 156.2 |
| 10  | 103.4 |     | 103.6 |     | 103.0 |
| 1′  | 132.2 |     | 132.0 |     | 133.9 |
| 2′  | 6.93 (1H, d, J = 1.8) | 115.3 | 6.97 (1H, d, J = 1.6) | 111.8 | 6.92 (1H, d, J = 1.9) | 112.5 |
| 3′  | 146.2 |     | 148.9 |     | 145.8 |
| 4′  | 146.2 |     | 147.5 |     | 148.1 |
| 5′  | 6.87 (1H, d, J = 8.1) | 116.2 | 6.80 (1H, d, J = 8.2) | 116.0 | 6.88 (1H, d, J = 8.3) | 115.0 |
| 6′  | 6.82 (1H, dd, J = 1.8, 8.1) | 119.9 | 6.85 (1H, dd, J = 1.6, 8.2) | 121.2 | 6.81 (1H, dd, J = 1.9, 8.2) | 119.0 |
| 1″  | 4.95 (1H, d, J = 7.3) | 102.6 | 4.86 (inside of CD$_3$OD signal) | 102.8 | 4.84 (1H, d, J = 7.1) | 102.9 |
| 2′, 3′, 4″ | 3.64–3.58 (3H, m) | 77.9, 747, 73.5 | 3.51–3.58 (3H, m) | 78.0, 73.5, 73.5 | 3.51–3.44 (3H, m) | 77.7, 744, 73.0 |
| 5″  | 3.84 (1H, d, J = 9.4) | 76.6 | 3.75 (1H, d, J = 7.3) | 74.7 | 3.78 (1H, d, J = 9.2) | 75.6 |
| OCH$_3$ | 3.85 (3H, s) |     | 3.85 (3H, s) |     | 3.81 (3H, s) |     |

R$_1$=R$_2$=H: catechin-5-O-β-D-glucuronide (7)
R$_1$=CH$_3$, R$_2$=H: 3′-O-methylcatechin-5-O-β-D-glucuronide (8)
R$_1$=H, R$_2$=CH$_3$: 4′-O-methylcatechin-5-O-β-D-glucuronide (9)
Table 3. NMR Spectroscopic Data for Epicatechin-5-O-β-D-glucuronide (10), 3′-O-Methylepicatechin-5-O-β-D-glucuronide (11), and 4′-O-Methylepicatechin-5-O-β-D-glucuronide (12)

|  | Position | Compound 10 |  |  | Compound 11 |  | Compound 12 |  |
|---|---|---|---|---|---|---|---|---|
|  | 1H δ (ppm) CD3OD, J (Hz) | 13C (1H) δ (ppm) CD3OD | 1H δ (ppm) DMSO-d6 J (Hz) | 13C (1H) δ (ppm) DMSO-d6 | 1H δ (ppm) CD3CD J (Hz) | 13C (1H) δ (ppm) CD3CD |
| 2 | 4.84 (inside CD3OD signal) | 79.9 | 4.79 (1H, s, br) | 78.2 | 4.88–4.87 (2H, m, H2, H1″) | 79.8 |
| 3 | 4.19 (1H, s, br) | 67.3 | 4.05/4.05 (1H, s, br) | 64.8 | 4.12 (1H, s, br) | 67.1 |
| 4 | 2.98–2.91 (2H, m, H4-α, H4-β) | 29.3 | 2.75/2.73 (2H, m, H4-α, H4-β) | 28.3 | 2.93–2.84 (2H, m, H4-α, H4-β) | 29.4 |
| COOH | 175.4 | 175.4 |
| 5 | 157.9 | 157.9 |
| 6 | 6.33 (1H, d, J = 2.1) | 97.3 | 6.20/6.12 (1H, d, J = 2.3/2.5) | 95.24 | 6.30 (1H, d, J = 2.2) | 97.3 |
| 7 | 158.9 | 156.7 |
| 8 | 6.09 (1H, d, J = 2.1) | 98.6 | 6.00/5.96 (1H, d, J = 2.3/2.5) | 96.6 | 6.02 (1H, d, J = 2.2) | 98.5 |
| 9 | 157.1 | 155.3 |
| 10 | 102.8 | 100.6 |
| 11 | 132.2 | 130.1 |
| 2′ | 6.99 (1H, d, J = 2.0) | 115.3 | 7.03/7.03 (1H, s) | 111.8 | 6.96 (1H, d, J = 1.8) | 112.3 |
| 3′ | 145.8 | 147.0 |
| 4′ | 145.9 | 146.3 |
| 5′ | 6.77 (1H, d, J = 8.2) | 115.9 | 6.78/6.77 (1H, d, J = 7.8/7.8) | 114.8 | 6.89–6.85 (2H, m, H5′, H6′) | 115.2 |
| 6′ | 6.81 (1H, dd, J = 2.0, 8.2) | 119.4 | 6.83/6.81 (1H, d, J = 1.6, 8.2) | 119.6 | 6.89–6.85 (2H, m, H5′, H6′) | 119.2 |
| 1″ | 4.90 (inside CD3OD signal) | 102.8 | 4.85/4.88 (1H, d, J = 9.0/8.9) | 100.7 | 4.81–4.78 (2H, m, H2, H1″) | 102.6 |
| 2′, 3′, 4′ | 3.59–3.50 (3H, m) | 77.9, 74.7, 73.4 | 3.26–3.21 (3H, m) | 76.8, 73.1, 72.3 | 33.50–3.44 (3H, m) | 78.0, 74.7, 73.5 |
| 5′ | 3.79 (1H, d, J = 9.5) | 76.7 | 3.43/3.41 (1H, s, br) | 74.4 | 3.69 (1H, d, J = 9.2) | 75.0 |
| OCH3 | 3.74/3.74 (3H, s) | 55.6 | 3.80 (3H, s) | 56.5 |

Two stable conformations for this epicatechin glucuronide were observed in DMSO-d6, which was evident in the 1H NMR spectrum; hence, NMR shifts and coupling constants are reported in pairs (see the Supporting Information for details).
such as ortho-quinones.\textsuperscript{65} Purification of the residue by preparative HPLC furnished catechin-5-O-glucuronide (7, 68%), 3′-O-catechin-5-O-glucuronide (8, 71%), 4′-O-methyl catechin-5-O-glucuronide (9, 77%), epicatechin-5-O-glucuronide (10, 51%), 3′-O-epicatechin-5-O-glucuronide (11, 59%), and 4′-O-methyl epicatechin-5-O-glucuronide (12, 65%) is

Figure 4. $^1$H NMR spectrum of 11 in DMSO-$d_6$ performed at different temperatures. The inset shows an expanded region of H6 signals from the pair of conformational isomers present in a ratio of approximately 1:0.47 (A, 25 °C) or 1:0.23 (B, 10 °C).
performed with excellent purity. Epicatechin glucuronides showed a lower yield than catechin glucuronides, and we observed a small peak corresponding to catechin analogues in HPLC chromatograms of the crude reaction products.

The complete unambiguous assignments of the hydrogens and carbons of the three rings and the glucuronic acid moiety were accomplished using a combination of heteronuclear multiple quantum coherence (HMQC) and HMBC (Tables 2 and 3) and are in agreement with those previously reported by Zhang59 and Blount.6,61 In the HMBC spectrum, the long correlation between the anomeric proton (H-1') and C5 (Figures S44, S48, S52, S56, S62, and S66) is evident in all compounds.

The NMR spectra obtained for compound 11 in DMSO-d6 gave a set of double signals for each nucleus with a peak intensity ratio of around 1:0.47 in the 1H NMR spectrum (Figures 4A and S57). The full chemical shift assignment of the precursor ions showed a quasimolecular ion at m/z 479.1 [M − H]− (calcd for 479.1). A fragment at m/z 302.9 was also observed, corresponding to the neutral loss of 176 Da (the glucuronic moiety) from the quasimolecular precursor ions m/z 479.1 [M − H]. Compounds 7 and 10 showed a quasimolecular ion at m/z 465.3 [M − H]− (calcd for 465.4). A fragment at m/z 288.9 was also observed, corresponding to the neutral loss of 176 Da (the glucuronic moiety) from the quasimolecular precursor ions m/z 465.3 [M − H]− (Figures S75–S80).

CONCLUSIONS

This work describes the first regioselective methylation of (epi)catechin to obtain 4'-O-methyl (epi)catechin with 97 and 94% of yield, respectively. Furthermore, we developed an efficient synthetic procedure to prepare (epi)catechin-5-O-glucuronides in five (compound 7 and 10) or six (compounds 8, 9, 11, and 12) steps with an overall yield ranging between 64 and 83%. The synthesis of these compounds will allow us to study them as potentially active components (for the compounds shown to be present in the brain) as controls in mechanism of action studies in relation to neuroprotection in Alzheimer’s disease using in vitro assays to measure the regulation of oxidative stress and neuroinflammation.

We believe that the synthesis of the intermediates 14, 15, 17, 18, 20, 21, 23, and 24 has not been described previously. A number of analytical tools were applied for a complete characterization of the final products as well as the intermediates in the synthetic routes, including MS and NMR.

EXPERIMENTAL PROCEEDURES

General Information. All reactions were carried out in dried glassware and round-bottomed flasks under an argon atmosphere using commercial reagents, distilled solvents, and anhydrous solvents unless otherwise noted. High-performance liquid chromatography (HPLC) grade solvents were purchased from Fisher Scientific. Chemicals and solvents were of reagent grade and obtained from commercial sources without further purification. The reactions were monitored by thin-layer chromatography (TLC) on aluminum-backed precoated silica gel 60 F254 plates (Sigma, St. Louis, MO), and compounds were detected using a UV lamp (254 nm). Column chromatographic purification was performed using 230–400 mesh silica gel unless otherwise noted.

Preparative high-performance liquid chromatography (HPLC) was performed on an Agilent HP1200 HPLC, monitoring at 280 nm. The HPLC with ChemStation software version B.02.01.54 was equipped with a G1322A degasser, G1311A quaternary pump, G1367B autosampler, G1316A thermostatic column compartment, and G1315C diode array detector. A Phenomenex Luna 10 μm C18 250 × 21.2 mm column was used for preparative HPLC on the Agilent HPLC system. For methyl ethers of (epi)catechin, the column was eluted with an isocratic mixture of water with formic acid (0.1%) and acetonitril (87:13, v/v), and the flow rate was set at 9 mL/min. The crude methylated (epi)catechin derivatives were loaded in methanol. For (epi)catechin glucuronides, the column was eluted with a mobile phase consisting of solvent A (0.1% formic acid in water) and solvent B (acetonitril) with a gradient of 10% B for 5 min and 15% B for 35 min. The crude glucuronides were loaded in 60% (v/v) MeOH. The solubility of these compounds in 60% MeOH is poor and this limited the load amount, but this solvent gave the best compromise between the solubility and solvent polarity.

Characterization Data. For NMR analysis, the synthesized substances were dissolved in a specific deuterated solvent and then transferred to a 5 mm Shigemi tube (Wilmad Glass, Vineland, NJ) or a normal NMR tube.

The proton and carbon nuclear magnetic resonance (1H NMR and 13C NMR, respectively) spectra were recorded using a Varian-INOVA 500 NMR spectrometer (Varian, CA, 1H NMR 500 MHz, and 13C NMR 125 MHz). Varian-INOVA 400 NMR spectrometer (Varian, CA, 1H NMR 400 MHz, and 13C NMR 100 MHz), or Bruker Avance III spectrometer (Bruker, CA, 1H NMR 600 MHz, and 13C NMR 150 MHz) equipped with a 5 mm inverse detection BBI probe at ambient temperature unless otherwise indicated.

Chemical shifts were reported in ppm relative to the CDCl3 peak (7.26 ppm for 1H NMR, 77.0 ppm for 13C(1)H) NMR), CD2OD peak (4.78 ppm for 1H NMR, 49.3 ppm for 13C(1)H) NMR), DMSO-d6 peak (2.50 ppm for 1H NMR, 39.5 ppm for 13C(1)H) NMR), or acetone-d6 peak (2.05 ppm for 1H NMR, 29.9 ppm for 13C(1)H) NMR). Data for 1H were reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, and br = broad singlet), coupling constants (Hz), and integration.

Analytical HPLC was used to monitor some reactions and analyze the products. A sample volume of 10 μL was applied to an Agilent 1290 UHPLC system equipped with an Eclipse Plus C18 column (3.5 μm particle, 100 × 4.6 mm) and separated in a mobile phase consisting of solvent A (0.1% formic acid in water) and solvent B (acetonitril) with 15% isocratic gradient of solvent B and a flow rate of 1 mL/min for 30 min. Chromatograms were monitored at 280 nm.

LC–MS/MS analysis was performed using an Agilent 1290 Infinity II liquid 645 chromatography system coupled to an Agilent 6400 Series Triple Quadrupole System with an electrospray ionization source in a negative ionization mode. A reverse-phase ZORBAX RR Eclipse Plus capillary column,
0.3 mm × 150 mm (3.5 μm particle size), was used for separation. The gradient for LC separation was 0.1% (v/v) formic acid in water (A) and 0.1% (v/v) formic acid in acetonitrile (B) with the following gradient of solvent B: 5 min 10%, 10 min 20%, 15 min 30%, 20 min 50%, 25 min 70%, and 30 min 95% with a flow rate of 0.5 mL/min for 30 min. The injection volume was 5 μL. The eluted compounds were analyzed by ESI-MS/MS in the range of m/z 100–800 and processed using Agilent MassHunter Qualitative Analysis software.

The detection of the newly synthesized metabolites was achieved using a hybrid triple quadrupole/ion trap mass spectrometer (QTRAP 5500) from AB Sciex. Each compound was injected individually and directly into the mass spectrometer at a flow rate of 7 μL/min using electrospray ionization. Full and product ion scan modes were utilized to assess the precursor ion mass and MS/MS spectrum, respectively.

All high-resolution mass spectra (HRMS) were recorded using a high-resolution mass spectrometer TripleTOF6600+ from AB Sciex. Each compound was diluted 20-fold with a solution of 100% methanol. Metabolites were injected individually and directly into the mass spectrometer apparatus at a flow rate of 10 μL/min. The parameters such as decluttering potential, collision energy, and collision spray energy were set up at 80 V, 35 V, and 5 V, respectively. The mass spectra were acquired using Turbo Spray Ionization set to 5500 V in a positive ion mode with an accumulation time of 100 ms. The curtain gas (nitrogen), nebulizing, and heating gas were set to 25, 20, and 15 psi, respectively. The temperature of the source was 25 °C. MS spectra were acquired and processed using Analyst TF 1.8.1 software.

**Synthesis of 3′- and 4′-O-Methyl (Epi)catechin and Their Glucuronide Derivatives.**

**Representative Procedure for Methylation of (Epi)catechin: Synthesis of (2R,3S)-2-(4-Hydroxy-3-methoxyphenyl)chromene-3,5,7-triol (3), (2R,3S)-2-(3-Hydroxy-4-methoxyphenyl)chromene-3,5,7-triol (4), (2R,3R)-2-(4-Hydroxy-3-methoxyphenyl)chromene-3,5,7-triol (5), and (2R,3R)-2-(3-Hydroxy-4-methoxyphenyl)chromene-3,5,7-triol (6).** A suspension of (epi)catechin (2.0 g, 6.89 mmol) methyl iodide (8.0 mL, 0.12 mol), potassium carbonate (4.76 g, 34.45 mmol), and ground 3A molecular sieves (2 g) in aceton (120 mL) was sonicated for 4 h and then stirred at room temperature for 20 h under argon. The progress of the reaction was monitored by HPLC. After 24 h, the solvent was filtered and concentrated to dryness in vacuo (no heat). The crude product was further purified by preparative HPLC in 20 injections. The purity of the fractions was checked by analytical HPLC. The fractions of each methyl ether of (epi)catechin were combined and evaporated under nitrogen flow to afford 733. 8 mg of compound 3 (35%), 1.25 g of compound 4 (60%), 838.1 mg of compound 5 (40%), and 1.15 g of compound 6 (55%).

**Compound 4**\(^{54,61,62}\) \(^{1}H\) NMR (500 MHz, DMSO-d6) δ (ppm): 6.91 (1H, d, J = 1.4 Hz, H2′); 6.77–6.73 (2H, m, H5′, H6′); 5.90 (1H, d, J = 2.2 Hz, H6); 5.69 (1H, d, J = 2.2 Hz, H8); 4.51 (1H, d, J = 8.0 Hz, H3′); 3.89 (1H, td, J = 5.6, 8.0, 8.1 Hz, H3); 3.75 (3H, s, OCH3); 2.73 (1H, dd, J = 5.6, 16.0 Hz, H4′α); 2.36 (1H, dd, J = 8.1, 16.0 Hz, H4′β). \(^{13}C\) (1H) NMR (125 MHz, DMSO-d6) δ (ppm): 156.5 (C7); 156.2 (C5); 155.4 (C9); 157.2 (C3); 146.2 (C4); 130.4 (C1′); 120.2 (C6′); 115.0 (C5′); 111.6 (C2′); 99.2 (C10); 95.2 (C6); 93.9 (C8); 81.3 (C2); 66.3 (C3); 55.6 (OCH3); 28.5 (C4). MS m/z: [M – H]\(^+\) calcd for C14H13O6 303.1; found 303.1.

**Compound 5**\(^{54,61,62}\) \(^{1}H\) NMR (500 MHz, DMSO-d6) δ (ppm): 7.03 (1H, d, J = 2.0 Hz, H2′); 6.83 (1H, dd, J = 2.0, 8.1 Hz, H6′); 6.73 (1H, d, J = 8.0 Hz, H5); 6.73 (1H, d, J = 2.2 Hz, H8); 4.79 (1H, s, H2); 4.70 (1H, s, H3); 3.84 (1H, s, H3′); 3.74 (3H, s, OCH3); 2.69 (1H, dd, J = 4.5, 16.4 Hz, H4′β); 2.51 (1H, dd, J = 2.5, 16.40 Hz, H4′α). \(^{13}C\) (1H) NMR (125 MHz, DMSO-d6) δ (ppm): 156.5 (C7); 156.3 (C5); 155.8 (C9); 146.9 (C3′); 145.8 (C4′); 130.6 (C1′); 119.6 (C6′); 114.8 (C5′); 111.6 (C2′); 98.4 (C10); 95.6 (C6); 94.5 (C8); 78.1 (C2); 64.9 (C3); 55.6 (OCH3); 28.4 (C4). MS m/z: [M – H]\(^+\) calcd for C14H13O6 303.1; found 303.1.

**Compound 6**\(^{54,61,62}\) \(^{1}H\) NMR (500 MHz, DMSO-d6) δ (ppm): 6.93 (1H, d, J = 2.0 Hz H2′); 6.85 (1H, d, J = 8.4 Hz, H5′); 6.78 (1H, d, J = 2.0, 8.4 Hz, H6′); 5.91 (1H, d, J = 2.3 Hz, H6); 5.73 (1H, d, J = 2.3 Hz, H8); 4.78 (1H, s, H2); 4.02 (1H, td, J = 1.7, 4.6, 3.6 Hz, H3); 3.74 (3H, s, OCH3); 2.69 (1H, dd, J = 4.6, 16.3 Hz, H4′β); 2.47 (1H, m, H4′α). \(^{13}C\) (1H) NMR (125 MHz, DMSO-d6) δ (ppm): 156.6 (C7); 156.3 (C5); 155.7 (C9); 146.8 (C4′); 145.9 (C3′); 132.4 (C1′); 117.7 (C5′); 114.8 (C2′); 111.6 (C6′); 98.4 (C10); 95.2 (C6); 94.1 (C8); 77.9 (C2); 64.9 (C3); 55.7 (OCH3); 28.2 (C4). MS m/z: [M – H]\(^+\) calcd for C14H13O6 303.1; found 303.1.

**Representative Procedure for Regioselective Methylation of (Epi)catechin: Synthesis of (2R,3S)-2-(3,5-Dimethoxyphenyl)chromene-3,5,7-triol (4) and (2R,3R)-2-(4,5-Dimethoxyphenyl)chromene-3,5,7-triol (6).** A suspension of (epi)catechin (2.0 g, 6.89 mmol) methyl iodide (0.6 mL, 10.33 mmol), potassium carbonate (952.2 mg, 6.89 mmol), and ground 3A molecular sieves (1 g) in aceton (80 mL) was vigorously stirred for 24 h under argon. Then, another batch of methyl iodide (0.6 mL, 10.33 mmol) and potassium carbonate (952.2 mg, 6.89 mmol) was added. After 24 h, methyl iodide (0.4 mL, 6.89 mmol) and potassium carbonate (476.1 mg, 3.44 mmol) were added again. The progress of the reaction was monitored by HPLC. After 72 h, the solvent was removed under vacuum, and the residue was further purified by preparative HPLC in 20 injections using the same procedure described for the methylation of (epi)catechin. The yield was 2.03 g of compound 4 (97%) and 1.97 g of compound 6 (94%).

**Representative Procedure for Protecting Hydroxyl Groups with Tert-butyldimethylsilyl chloride: Synthesis of (((2R,3S)-2-(3,4-Bis(tert-butyldimethylsilyl)oxy)phenyl)chromene-3,5,7-triyi)triis(tert-butyldimethylsilyl)oxy)triis(tert-butyldimethylsilyl)oxy)triis(tert-butyldimethylsilyl)oxy)triis(tert-butyldimethylsilyl)oxy)trimethylsilane) (13),**
Representative Procedure for Selective Removal of the TBS Protective Group: Synthesis of (2R,3S)-2-(4-((tert-Butyl(dimethyl)silyl)oxy)-4-methoxyphenyl)chroman-5-ol (19), (2R,3S)-3,7-Bis((tert-butyl(dimethyl)silyl)oxy)-4-methoxyphenyl)chroman-5-ol (20), (2R,3S)-3,7-Bis((tert-butyl(dimethyl)silyl)oxy)-4-methoxyphenyl)chroman-5-ol (21), (2R,3R)-2-(3,4-Bis((tert-butyl(dimethyl)silyl)oxy)-4-methoxyphenyl)chroman-5-ol (22), and (2R,3R)-3,7-Bis((tert-butyl(dimethyl)silyl)oxy)-4-methoxyphenyl)chroman-5-ol (24).

Trifluoroacetic acid (117 μL, 1.50 mmol) was added dropwise to an ice-cooled stirred solution of compound 13 (430.0 mg, 0.50 mmol) in anhydrous methylene chloride (200 mL) under argon and stirred on an ice bath for 2 h. Then, another batch of trifluoroacetic acid (38 μL, 0.50 mmol) was added and the reaction mixture was stirred for 24 h on an ice bath. After 36 h, a saturated solution of sodium hydroxide (90 mL) was added and the mixture was stirred for 30 min and separated. The aqueous solution was extracted with methylene chloride (100 mL). The combined organic phase was washed with brine (100 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was dissolved in methylene chloride for purification by flash column chromatography (silica gel, hexane/EtOAc (10:1)) to yield the following products:
Compound 19 (259.8 mg, 70%). 1H NMR (500 MHz, CDCl3) δ (ppm): 6.89 (1H, d, J = 2.0 Hz, H2); 6.85 (1H, dd, J = 2.0, 8.2 Hz, H6); 6.82 (1H, d, J = 2.2 Hz, H1); 5.96 (1H, d, J = 2.2 Hz, H6); 4.83 (1H, s, br, OH-5); 4.55 (1H, d, J = 8.8 Hz, H2); 3.91 (1H, td, J = 5.8, 8.8, 9.1 Hz, H3); 2.97 (1H, dd, J = 5.8, 15.9 Hz, H4-α); 2.59 (1H, dd, J = 9.1, 15.9 Hz, H4-β); 1.00 – (−0.36), (60H, CH3-TBS). 13C NMR (125 MHz, CDCl3) δ (ppm): 156.0; 155.4; 154.3; 146.9; 146.7; 132.6; 121.0; 120.9; 106.1; 100.9; 100.2; 81.9; 69.4; 29.9; 26.2; 26.1; 25.9; 25.8; 18.6; 18.3; 18.0; 0.2; −3.9; −3.9; −4.0; −4.0; −4.3; −4.3; −4.5; −4.5. −5.2. ESI-MS m/z: [M + H+] calculated for C39H60O14Si6, 647.3621 [M + H]+; found, 647.3619.

Representative Procedure for Synthesis by Glucuronidation of (2S,3R,4S,5R,6S)-2-(((2R,3S)-2-(3,4-bis((tert-butyldimethylsilyl)oxy)-4-methoxyphenyl)-3,7-bis((tert-butyldimethylsilyl)oxy)-2-(3-((tert-butyldimethylsilyl)oxy)-4-methoxyphenyl)oxy)-6-(methoxy-carbonyl)tetrahydro-2H-pyran-3,4,5-triyl Triacetate (25, 3R,4S,5R,6S)-2-(((2R,3S)-3,7-Bis((tert-butyldimethylsilyl)oxy)-2-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)chroman-5-yl)oxy)-6-(methoxy-carbonyl)tetrahydro-2H-pyran-3,4,5-triyl Triacetate (26), (2S,3R,4S,5R,6S)-2-(((2R,3S)-3,7-Bis((tert-butyldimethylsilyl)oxy)-2-(3-((tert-butyldimethylsilyl)oxy)-4-methoxyphenyl)oxy)-6-(methoxy-carbonyl)tetrahydro-2H-pyran-3,4,5-triyl Triacetate (27), (2S,3R,4S,5R,6S)-2-(((2R,3S)-3,7-Bis((tert-butyldimethylsilyl)oxy)-oxy)-2-(3-((tert-butyldimethylsilyl)oxy)-4-methoxyphenyl)oxy)-6-(methoxy-carbonyl)tetrahydro-2H-pyran-3,4,5-triyl Triacetate (30).

A suspension of the dried compound 19 (240.0 mg, 0.32 mmol) and (2S,3S,4S,5R,6S)-2-(methoxy-carbonyl)-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (228.0 mg, 0.48 mmol) was dissolved in anhydrous methylene chloride (8 mL) in the presence of 4 Å molecular sieves (0.5 g). The reaction was stirred at room temperature for 30 min under argon and then cooled in an ice-H2O bath for 15 min. A solution of the Lewis acid [BF3·OEt2 (32 mL, 0.22 mmol) in 0.5 mL of CH2Cl2] was added slowly via a syringe. The resulting suspension was continuously stirred at 0 °C in an ice-H2O bath for 12 h. Then, another batch of (2S,3S,4S,5R,6S)-2-(methoxy-carbonyl)-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (76.0 mg, 0.16 mmol) was added and the suspension was stirred for 30 min. A solution of BF3·OEt2 (10 μL mL, 0.08 mmol) in anhydrous methylene chloride (0.2 mL) was added slowly via a syringe and stirred at 0 °C in an ice-H2O bath for 12 h. After 24 h, the reaction was quenched by saturated sodium hydrogen carbonate solution (10 mL). The organic layer was separated, washed with brine (5 mL), dried over anhydrous sodium sulfate, and evaporated. The crude product (25) was directly subjected to subsequent hydrolysis of acetyl and methyl ester groups.

Representative Procedure for Methyl Ester Hydrolysis and Removal of Acetyl Groups: Synthesis of (2S,3R,4S,5R,6S)-6-(((2R,3S)-2-(3,4-Dihydroxyphenyl)-3,7-dihydroxycroman-5-
(3H, m, H2", H3", H4"); 3.06 (1H, dd, J = 5.6, 16.4 Hz, H4-6); 2.62 (1H, dd, J = 7.7, 16.4 Hz, H4-β). $^{13}$C NMR (150 MHz, CD$_2$OD) δ (ppm): 170.8 (COOH); 158.1 (C7); 158.0 (C5); 156.7 (C9); 148.9 (C3′); 147.5 (C4′); 132.0 (C1′); 121.2 (C6′); 116.0 (C5′); 111.8 (C2′); 103.6 (C10); 102.8 (C2′); 98.2 (C8); 97.2 (C6); 81.6 (C2); 78.0, 73.5, 73.5 (C2′, C3′, C4′); 74.7 (C5′); 68.7 (C3); 56.4 (OCH$_3$); 28.7 (C4). ESI-MS m/z: [M - H]$^-$ calculated for C$_{22}$H$_{23}$O$_{12}$, 479.13; found 479.40.

Compound 9$^{41}$ (263.1 mg, 77% overall yield of the last three steps): $^1$H NMR (600 MHz, acetone-$d_6$) δ (ppm): 6.92 (1H, d, J = 1.9 Hz, H2); 6.88 (1H, d, J = 8.3 Hz, H5′); 6.81 (1H, dd, J = 1.9, 8.3 Hz, H6); 6.42 (1H, d, J = 2.0 Hz, H8); 6.01 (1H, d, J = 2.0 Hz, H8); 4.84 (1H, d, J = 7.1 Hz, H1′); 4.67 (1H, d, J = 7.0 Hz, H2); 3.96 (1H, td, J = 5.1, 16.3 Hz, H4-α); 2.69 (1H, dd, J = 7.8, 16.3 Hz, H4-β). $^{13}$C NMR (150 MHz, acetone-$d_6$) δ (ppm): 175.9 (COOH); 158.1 (C7); 157.7 (C5); 156.2 (C9); 148.1 (C4′); 145.8 (C3′); 133.9 (C1′); 119.0 (C6′); 115.0 (C5′); 112.5 (C2′) 103.0 (C10); 102.9 (C1′); 97.7 (C8); 97.2 (C6); 82.1 (C2); 77.7, 74.4, 73.0 (C2′, C3′, C4′); 75.6 (C5′); 67.8 (C3); 56.4 (OCH$_3$); 28.0 (C4). ESI-MS m/z: [M - H]$^-$ calculated for C$_{22}$H$_{23}$O$_{12}$, 479.13; found 479.40.

Compound 10$^{59,61}$ (105.4 mg, 51% overall yield of the last three steps): $^1$H NMR (600 MHz, CD$_2$OD) δ (ppm): 6.99 (1H, d, J = 2.0 Hz, H2); 6.81 (1H, dd, J = 2.0, 8.2 Hz, H6); 6.77 (1H, d, J = 8.2 Hz, H5′); 6.33 (1H, d, J = 2.1 Hz, H6); 6.09 (1H, d, J = 2.1 Hz, H8); 4.90 (inside of CD$_2$OD signal H1′); 4.84 (inside of CD$_2$OD signal H1′); 4.19 (1H, s, br H3); 3.79 (1H, d, J = 9.5 Hz, H5′); 3.59-3.50 (3H, m, H2′, H3′, H4′); 2.98-2.91 (2H, m, H4-α and H4-β). $^{13}$C NMR (150 MHz, CD$_2$OD) δ (ppm): 175.4 (COOH); 158.5 (C7); 157.9 (C5); 157.1 (C9); 154.9 (C4′); 154.8 (C3′); 132.2 (C1′); 119.4 (C6′); 115.9 (C5′); 115.3 (C2′); 102.8 (C10); 102.8 (C1′); 98.6 (C8); 97.3 (C6); 79.9 (C2); 77.9, 74.7, 73.4 (C2′, C3′, C4′); 76.7 (C5′); 67.3 (C3); 29.3 (C4). ESI-MS m/z: [M - H]$^-$ calculated for C$_{22}$H$_{23}$O$_{12}$, 466.11; found 465.30.

Compound 11$^{59,61}$ (220.3 mg, 59% overall yield of the last three steps): $^1$H NMR (600 MHz, DMSO-$d_6$) δ (ppm): 7.03/ 7.03 (1H, s, H2′); 6.83/6.81 (1H, d, J = 7.8/7.8 Hz, H6); 6.78/6.77 (1H, d, J = 7.8/7.8 Hz, H5′); 6.20/6.12 (1H, d, J = 2.3/2.5 Hz, H8); 6.00/5.96 (1H, d, J = 2.3/2.5 Hz, H8); 4.79 (1H, s, br H2); 4.85/4.68 (1H, d, J = 9.0/8.9 Hz, H1′); 4.05/ 4.05 (1H, s, br H3); 3.74/3.74 (3H, s, OCH$_3$); 3.43/3.41 (1H, s, br H5′); 3.26-3.21 (3H, m, H2′, H3′, H4′); 2.75/2.73 (2H, m, H4-α and H4-β). $^{13}$C NMR (150 MHz, DMSO-$d_6$) δ (ppm): 172.0 (COOH); 156.8 (C5); 156.7 (C7); 155.3 (C9); 147.0 (C3′); 146.3 (C4′); 130.1 (C1′); 119.6 (C6′); 114.8 (C5′); 111.8 (C2′); 100.7 (C1′); 100.6 (C10); 96.6 (C8); 95.4 (C6); 78.2 (C2); 76.8 (C3); 74.4 (C5′); 73.1 (C2′); 72.3 (C4′); 64.8 (C3); 55.6 (OCH$_3$); 28.3 (C4). ESI-MS m/z: [M - H]$^-$ calculated for C$_{22}$H$_{23}$O$_{12}$, 479.13; found 479.10.

Compound 12$^{59,61}$ (264.6 mg, 65% overall yield of the last three steps): $^1$H NMR (500 MHz, CD$_2$OD) δ (ppm): 6.96 (1H, d, J = 1.8 Hz, H2); 6.89-6.85 (2H, m, H5′, H6′); 6.30 (1H, d, J = 2.2 Hz, H6); 6.02 (1H, d, J = 2.2 Hz, H8); 4.81- 4.78 (2H, m, H2, H1′); 4.15 (1H, s, br H3); 3.80 (3H, s, OCH$_3$); 3.69 (1H, d, J = 9.2 Hz, H5′); 3.50-3.44 (3H, m, H2′, H3′, H4′); 2.93-2.84 (2H, m, H4-α, H4-β). $^{13}$C NMR (125 MHz, CD$_2$OD) δ (ppm): 158.5 (C7); 157.9 (C5);
157.0 (C9); 148.5 (C4’); 147.2 (C3’); 133.5 (C1’); 119.2 (C6’); 115.2 (C5’); 112.3 (C2’); 102.8 (C10); 102.6 (C1’); 98.5 (C8); 97.3 (C6); 79.8 (C2); 78.0, 74.7, 73.5 (C2’, C3’, C4’); 75.0 (C5’); 67.1 (C3); 56.5 (OCH3); 29.4 (C4). ESI-MS m/z: [M – H]− calcld for C22H23O12, 479.13; found 479.20.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c04512.

Copies of 1H NMR and 13C NMR, HMBC, and HMQC spectra for all compounds; copies of MS, MS/MS, and HRMS spectra of intermediate compounds and glucuronide derivatives (PDF)

**AUTHOR INFORMATION**

Corresponding Authors

Maite L. Docampo-Palacios — BioDiscovery Institute and Department of Biological Sciences, University of North Texas, Denton, Texas 76203, United States; orcid.org/0000-0001-5205-3989; Phone: +1-214-601-5892; Email: md@precisionplantmolecules.com; Fax: +1-580-224-6692

Richard A. Dixon — BioDiscovery Institute and Department of Biological Sciences, University of North Texas, Denton, Texas 76203, United States; orcid.org/0000-0001-8393-9408; Phone: +1-940-565-2308; Email: Richard.Dixon@unt.edu

Authors

Anislay Alvarez-Hernández — BioDiscovery Institute and Department of Biological Sciences, University of North Texas, Denton, Texas 76203, United States

Ángel de Fátima — Department of Chemistry, Universidade Federal de Minas Gerais, Belo Horizonte, MG 31270-901, Brazil; orcid.org/0000-0001-9985-2980

Luciano Moraes Lião — Institute of Chemistry, Universidade Federal de Goiás, Goiânia, GO 74690-900, Brazil; orcid.org/0000-0001-5205-3989

Giulio M. Pasinetti — Department of Psychiatry, The Mount Sinai School of Medicine, New York, New York 10029, United States; orcid.org/0000-0002-1524-5196

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acsomega.0c04512

Notes

The authors declare no competing financial interest.

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