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Synthesis of 1-*O*-Methylchlorogenic Acid: Reassignment of Structure for MCGA3 Isolated from Bamboo (*Phyllostachys edulis*) Leaves

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Supporting Information

ABSTRACT: The first synthesis of 1-*O*-methylchlorogenic acid is described. The short and efficient synthesis of this compound provides laboratory-scale quantities of the material to investigate its biological properties. The synthesis involves C-1 alkylation of the known (−)-4,5-cyclohexylidenequinic acid lactone followed by methoxide opening to the hydroxyl ester. Acylation of the C-5 hydroxyl group followed by sequential removal of protecting groups afforded 1-*O*-methylchlorogenic acid. The NMR spectroscopic characteristics of this compound do not coincide with those reported for the original isolation from bamboo (*Phyllostachys edulis*) leaves of the compound designated MCGA3. Comparison of the published spectroscopic data reported for MCGA3, with both reported literature values and spectroscopic data obtained from an authentic sample, leads to the conclusion that the compound isolated from bamboo (*Phyllostachys edulis*) leaves is instead methyl chlorogenate.

KEYWORDS: *1-O-methylchlorogenic acid, MCGA3, Phyllostachys edulis, methyl chlorogenate*

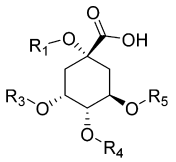
INTRODUCTION

Phenolic plant secondary metabolites composed of caffeoyl esters of small molecular weight hydroxy acids and amides have displayed significant biological activities against cancer,[1] inflammation,[2] and cardiovascular disease[3] in addition to their well-described behavior as antioxidants.[4,5] Specific examples include compounds such as rosmarinic acid (antiviral, antibacterial, anti-inflammatory),[6,7] clovamide (anti-inflammatory),[7] cafftaric acid (antimutagenic),[8] and chicoric acid (HIV-1 integrase inhibitor),[9−12] and subulatin whose antioxidant activity parallels that of α-tocopherol.[13]

As a subset of this class of secondary metabolites, caffeoyl derivatives of quinic acid have also enjoyed detailed examination toward their significant biological activities. Chlorogenic acid, **1**, is the most common and most widely distributed plant phenolic of this subclass whose antioxidant activity has been well documented.[5,14,15] The radical scavenging/antioxidant activity of chlorogenic acid[16−20] has led to investigation of its inhibitory effects on lipid peroxidation,[17,18] inhibition of hemolysis of mouse erythrocytes,[18] action in acute reduction of blood pressure in healthy humans,[19] and promising antitumor activity.[20−22] The antibacterial activity of chlorogenic acid has been attributed to disruption of outer and plasma cell membranes and discharging membrane ion gradients and leading to leakage of cell contents.[23] Tomato plants have been engineered for higher production of chlorogenic acid,[24] projected to ultimately provide even more beneficial agricultural foodstuffs.

Chlorogenic acid and its isomers, neochlorogenic acid, **3**, and cryptochlorogenic acid, **4**, have demonstrated similar antioxidant activity in vitro,[25−28] possess tyrosinase inhibitory activities, and moderate activity against several cancer cell lines,[26] including suppression of colon cancer,[21] exhibits potential neuroprotective activity,[29] and serves as an 8-hydroxydeoxyguanosine inhibitor.[22] The methyl ester of chlorogenic acid, methyl chlorogenate, **14**, has shown to be a 5-lipooxygenase inhibitor[30] and has exhibited activity as a HIV protease inhibitor with an IC_{50} measurement of 40 μg/mL.[31] Thus, discovery of any new entity belonging to the class of caffeoyl quinates attracts attention for its potential biological properties and activities and potential use as a therapeutic or as a lead compound in drug discovery efforts.

In 2001, Kweon et al.[32] reported the isolation of two new chlorogenic acid derivatives, together with the known compound 5-*O*-feruoylquinic acid, **5** (Figure 1), from an aqueous ethanol extract of bamboo (*Phyllostachys edilis*) leaves and identified them as the methyl ether derivatives of the C-1



1 R_5 = Caffeoyl, R_1, R_3, R_4 = H, 5-*O*-Caffeoylquinic acid (Chlorogenic Acid)
2 R_1 = Caffeoyl, R_3-R_5 = H, 1-*O*-Caffeoylquinic acid
3 R_3 = Caffeoyl, R_1, R_4, R_5 = H, 3-*O*-Caffeoylquinic acid (Neochlorogenic Acid)
4 R_4 = Caffeoyl, R_1, R_3, R_5 = H, 4-*O*-Caffeoylquinic acid (Crytochlorogenic acid)
5 R_5 = Feruloyl, R_1, R_3, R_4 = H, 5-*O*-Feruloylquinic acid
6 R_3 = Caffeoyl, R_4 = CH_3, R_1, R_5 = H, 4-*O*-Methyl-3-*O*-caffeoylquinic acid (4-*O*-methylneochlorogenic acid)
7 R_5 = Caffeoyl, R_1 = CH_3, R_3, R_4 = H, 1-*O*-Methyl-5-*O*-caffeoylquinic acid (1-*O*-methylchlorogenic acid, MCGA3)

Figure 1. The monocaffeoylquinic acids, **1**−**4**, and the three compounds isolated from aqueous ethanol extraction of bamboo (*Phyllostachys edulis*) leaves, **5**−**7**.

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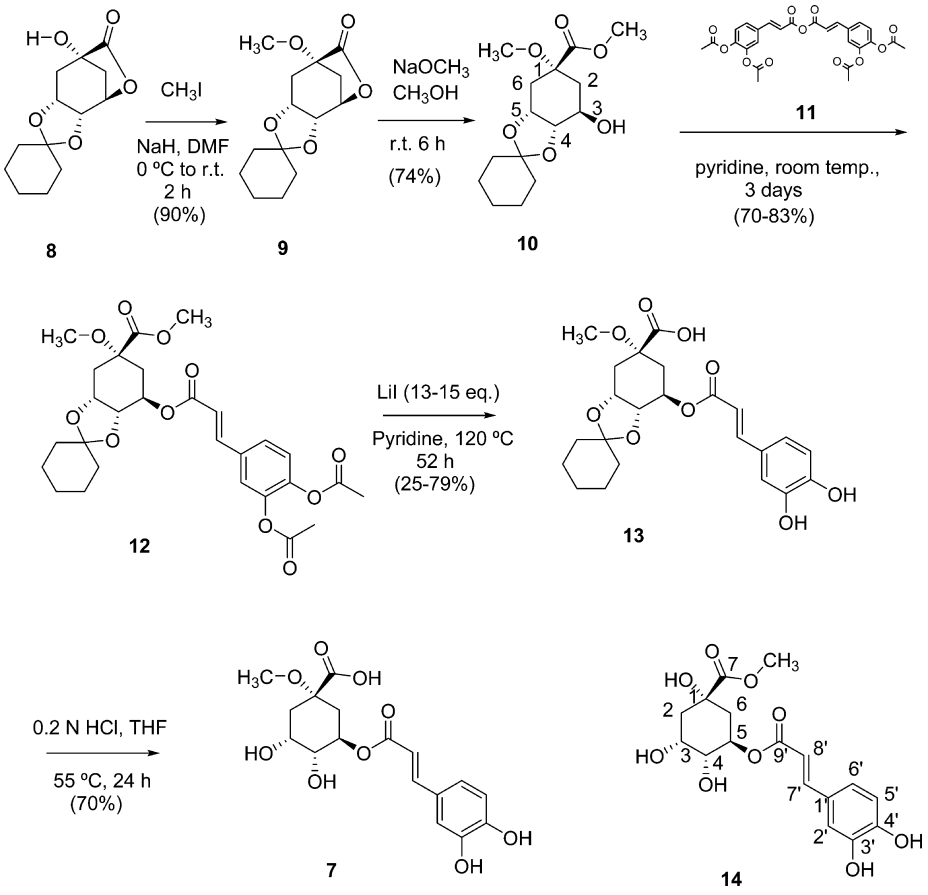

Figure 2. Synthesis of 1-*O*-methylchlorogenic acid, **7**.

and C-4 hydroxyl groups of chlorogenic acid, **7** and **6**, respectively. Evaluation of these compounds revealed strong antioxidant properties in standard tests with compound **7** showing activity superior to that of chlorogenic acid and compound **6** in both the DPPH scavenging assay and the iron-induced rat microsomal lipid peroxidation system.[32] Compound **7** was reported to possess unique antioxidant properties, including induction of heme oxygenase-1 mRNA and protein and providing protection of bovine aortic pulmonary endothelial cells against ROS-mediated necrosis when challenged with the oxidant *tert*-butyl hydroperoxide.[33] Further studies have shown that this compound also induces additional selected phase II genes including ferretin, γ-glutamylcysteine lygase, glutathione reductase, and glutathione transferase at the micromolar level.[34] Lastly, the compound assigned structure **7** was shown to enhance ultraviolet A-mediated apoptosis via activation of p21 in HaCaT keratinocytes, potentially leading to prevention of sunlight-induced photocarcinogenesis.[35]

Our interest in this class of compounds is coupled to recent reports showing that the presence of compounds containing the *o*-diphenol functionality during ensilage of dairy cow forages, containing either naturally occurring or plants transfected with polyphenoloxidase (PPO),[36] results in enhanced protein preservation of the stored forage. Thus, our interest lies in securing sufficient quantities of naturally occurring *o*-diphenols to evaluate them as PPO substrates and allow investigation of the mechanism by which these compounds alter forage protein composition toward rumen digestion. We have initiated a program to produce naturally occurring caffeoyl-containing *o*-diphenols[37] and examine their ability to serve as substrates for PPO and protein preservations.[38] The extraordinary activities reported for **7**, abbreviated as MCGA3 in reports of subsequent studies, prompted us to develop a laboratory synthesis of this compound.

MATERIALS AND METHODS

General Experimental. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance 360 instrument operating at 360 MHz (^{1}H) and 90 MHz (^{13}C), respectively. Spectra (presented in Supporting Information) obtained were referenced to the residual signals: for acetone-d_6 at 2.04 and 29.8 ppm; for methanol-d_4 at 3.30 and 49.0 ppm; for ^{1}H and ^{13}C, respectively. Mass spectra were obtained on a Waters LCT instrument. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Shimadzu IRPrestige-21 spectrometer operating in the ATR mode. Elemental analyses were performed by Midwest Microlabs, LLC, Indianapolis, IN. Optical rotations were determined on a Rudolph Research (Flanders, NJ) Autopol III Automatic Polarimeter. Thin-layer chromatography was performed on precoated DC-Fertigplatten SIL G-25 UV254 plates (Alltech, Deerfield, IL). Flash chromatography was conducted on silica gel, Merck, grade 9385, 230−400 mesh, 60 Å. Pyridine was dried over activated 4 Å sieves. For clarity in interpretation of NMR assignments, all assignments are made according to numbered structure **14** in Figure 2. Mention of trade names or commercial products in this article is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the U.S. Department of Agriculture.

Synthesis of 1-*O*-Methyl-3,4-cyclohexylidenequinic Acid Lactone, 9. To a 50 mL, two-necked, round-bottomed flask equipped with a magnetic stir bar, an equalizing addition funnel, and a septum were added sodium hydride (193 mg, 8.02 mmol, 60% in mineral oil) and anhydrous DMF (10 mL), and the flask was placed under an argon atmosphere using a gas inlet adapter. The stirring suspension

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was cooled in an ice bath, and a mixture of (−)-4,5-cyclohexylidenequinic acid lactone, **8** (1.36 g, 5.35 mmol), and iodomethane (1.14 g, 8.02 mmol) in anhydrous DMF (15 mL) was added dropwise via the addition funnel over a 30 min period. The mixture was allowed to slowly warm to room temperature over 2 h. The mixture was cautiously quenched by adding it to a stirred solution of half-saturated aqueous ammonium chloride and ethyl acetate (50 mL each). The layers were separated, the aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic extracts were washed with water (3 × 50 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated to give an off-white solid. This material was recrystallized from hexanes (10 mL/g of residue) to give 1.30 g (90%) of an off-white solid. R_f = 0.45 (7:3 hexanes/EtOAc), $[\alpha]_D^{25}$ = +1.4 (*c* = 1.02, $CHCl_3$), mp 95.5−97 °C (hexanes), ^{1}H NMR (360 MHz, acetone-d_6) δ 4.68 (dd, 1, *J* = 6.3, 2.5 Hz, H5), 4.56 (m, 1, H3), 4.30 (ddd, 1, *J* = 6.4, 2.4, 1.2 Hz, H4), 3.30 (s, 3, OCH_3), 2.57 (dddd, 1, *J* = 11.7, 6.2, 2.3, 1.3 Hz, H6a), 2.33 (d, 1, *J* = 11.7, H6b), 2.30 (ddd, 1, *J* = 14.6, 7.7, 2.4 Hz, H2a), 2.04 (dd, 1, *J* = 14.6, 3.0 Hz, H2b), 1.66−1.72 (m, 2), 1.56−1.66 (m, 4), 1.48−1.56 (m, 2), 1.35−1.42 (m, 2). ^{13}C NMR (90 MHz, acetone-d_6) δ 175.8 (C═O), 110.6 (acetal C), 77.6 (C1), 75.6 (C5), 72.9 (C4), 71.8 (C3), 52.0 (OCH_3), 37.6, 36.8 (C2), 34.3, 29.9 (C6), 25.7, 24.7, 24.2 ppm. IR (ATR) ν_{max} 2926, 2842, 1777, 1653, 1452, 1163, 1085, 983, 913 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_5$: C: 62.67; H: 7.51. Found: C; 62.99, H; 7.58.

Synthesis of Methyl 1-*O*-Methyl-3,4-cyclohexylidenequinate, 10. To a 100 mL, pear-shaped, one-necked flask equipped with a magnetic stir bar and a ground glass stopper were added compound **9** (1.26 g, 4.69 mmol) and anhydrous methanol (28 mL). To this stirring solution was added freshly prepared 1.0 M sodium methoxide in methanol (14.0 mL, 14.0 mmol, 2.98 equiv) dropwise over ∼2 min at room temperature. After 21 h of being stirred at room temperature, the reaction was quenched through the addition of glacial acetic acid (1.70 mL, 29.6 mmol), diluted with EtOAc (150 mL), and washed with water (50 mL). The layers were separated, the aqueous layer extracted with EtOAc (50 mL), and the combined EtOAc extracts were washed with water (50 mL), saturated $NaHCO_3$ (50 mL), and brine (25 mL) and dried (Na_2SO_4). The mixture was filtered, concentrated, and dried to give a white solid residue. The residue was purified via flash chromatography on silica gel (80 g) using 9:1 $CHCl_3$/ acetone as eluent to give 1.08 g (76%) of a white solid. R_f = 0.23 (9:1 $CHCl_3$/acetone); $[\alpha]_D^{25}$ = −16.7 (*c* = 0.86, $CHCl_3$), ^{1}H NMR (360 MHz, acetone-d_6) δ 4.37 (dd, 1, *J* = 10.6, 5.2 Hz, H3), 4.08 (d, 1, *J* = 4.5 Hz, C3-O*H*), 3.99 (m, 1, H5), 3.88 (t, 1, *J* = 6.2 Hz, H4), 3.69 (s, 3, CO_2CH_3), 3.19 (s, 3, OCH_3), 2.22 (dd, 1, *J* = 15.1, 5.2 Hz, H6a), 2.14 (ddd, 1, *J* = 15.1, 4.7, 1.6 Hz, H6b), 1.99 (ddd, 1, *J* = 13.5, 4.0, 1.6 Hz, H2a), 1.70 (dd, 1, *J* = 13.5, 10.5 Hz, H2b), 1.53−1.66 (m, 4), 1.49−1.53 (m, 4), 1.30−1.40 (m, 2H). ^{13}C NMR (90 MHz, acetone-d_6) δ 174.1 (C7, C═O), 109.5 (acetal C), 80.8 (C4), 79.9 (C1), 73.5 (C5), 68.4 (C3), 52.3 (OCH_3), 52.2 (CO_2CH_3), 39.1 (C2), 39.0, 35.9, 31.2 (C6), 25.8, 24.8, 24.5. IR (ATR) ν_{max} 3203, 2938, 2851, 1721, 1450, 1436, 1160, 1078, 1066 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_6$: C: 59.98; H: 8.05. Found: C; 60.04, H; 7.97.

Synthesis of Methyl 1-*O*-Methyl-3,4-cyclohexylidene-5-*O*-bis(3′,4′-*O*-acetylcaffeoyl)quinate, 12. To a pear-shaped, one-necked flask equipped with a magnetic stir bar and a septum were added ester alcohol **10** (855 mg, 2.85 mmol) and pyridine (12 mL). To this stirred solution was added caffeic acid anhydride tetraacetate (**11**, 2.17 g, 4.27 mmol, 1.5 equiv) in one portion, and the resulting mixture was capped with a septum and stirred at room temperature for 72 h. The mixture was diluted with EtOAc (350 mL) and transferred to a 500 mL separatory funnel. The mixture was washed with 2 N aqueous HCl (2 × 75 mL, second washing acidic w/litmus), saturated aqueous $NaHCO_3$ (4 × 60 mL), brine (50 mL) and dried ($MgSO_4$). The solution was filtered, concentrated, and dried to give an off-white foam (2.0 g). The residue was purified via chromatography on flash silica gel (200 g) using 96:4 $CHCl_3$/acetone (1.5 L) followed by 9:1 $CHCl_3$/acetone (500 mL) as eluent to afford 1.10 g (71%) of an off-white foam. $[\alpha]_D^{25}$ = −28.3 (*c* = 1.05, $CHCl_3$), ^{1}H NMR (360 MHz, acetone-d_6) δ 7.67 (d, 1, *J* = 16.0 Hz, H7′), 7.64−7.60 (m, 2, H2′, H6′), 7.31 (d, 1, *J* = 7.9 Hz, H5′), 6.54 (d, 1, *J* = 16.0 Hz, H8′), 5.34 (ddd, 1, *J* = 11.5, 7.5, 4.2 Hz, H5), 4.48 (ddd, 1, *J* = 5.3, 5.3, 2.9 Hz, H3), 4.17 (dd, 1, *J* = 7.3, 5.8 Hz, H4), 3.70 (s, 3, CO_2CH_3), 3.27 (s, 3, OCH_3), 2.43 (br d, 1, *J* = 15.8 Hz, H2a), 2.27−2.17 (m, 8, H2b, H6a, O_2CCH_3, O_2CCH_3), 1.82 (dd, 1, *J* = 13.2, 11.3 Hz, H6b), 1.71−1.65 (m, 2), 1.60−1.50 (m, 6), 1.40−1.25 (m, 2) ppm. ^{13}C NMR (90 MHz, acetone-d_6) δ 173.6 (COOH), 168.6 (O_2CCH_3), 168.5 (O_2CCH_3), 166.2 (C9′), 145.0 (C3′ or C4′), 143.9 (C3′ or C4′), 134.0 (C1′), 127.3 (C6′), 125.0 (C5′), 123.9 (C2′), 120.0 (C8′), 110.1 (acetal C), 80.0 (C1), 77.2 (C4), 73.7 (C3), 72.2 (C5), 52.6 (OCH_3), 52.5 (CO_2CH_3), 38.8, 36.0, 35.4 (C2), 31.1 (C6), 25.7, 24.7, 24.5, 20.5 (O_2CCH_3), 20.4 (O_2CCH_3) ppm. IR (ATR) ν_{max} 2930, 2853, 1770, 1710, 1635, 1505, 1368, 1199, 1166, 1111, 1070, 1008, 903 cm^{-1}. HRMS: Calcd for $C_{28}H_{34}O_{11}$ [M + NH_4]$^+$: 564.2440 *m*/*z*. Found: 564.2445 *m*/*z*.

Synthesis of 1-*O*-Methyl-3,4-cyclohexylidene-5-*O*-caffeoylquinic Acid, 13. To an 8 mL vial equipped with a magnetic stir bar and a screw cap were added compound **12** (200 mg, 0.366 mmol) and anhydrous pyridine (5.0 mL). To this solution was added LiI (740 mg 5.53 mmol) in one portion, and the mixture was degassed by bubbling Ar gas through the solution for 2 min by which time the LiI had completely dissolved. The vial was sealed and heated in an oil bath at 120 °C for 52 h. The cooled reaction mixture was diluted with EtOAc (70 mL) and washed with 1 N aqueous HCl (30 mL). The aqueous layer was extracted with EtOAc (30 mL), and the combined EtOAc extracts were washed with 0.5 M aqueous sodium thiosulfate (2 × 30 mL), water (30 mL), brine (30 mL) and dried ($MgSO_4$). The solution was filtered, concentrated, and dried to give a light tan foam. This residue was purified via column chromatography on flash silica gel (30 g) using 92:8:1 CH_2Cl_2/CH_3OH/AcOH as eluent to give 131 mg (79%) of an off-white foam. R_f = 0.25 (92:8:1 CH_2Cl_2/CH_3OH/AcOH); $[\alpha]_D^{25}$ = −37.2 (*c* = 1.04, MeOH), mp 118−120 °C. ^{1}H NMR (360 MHz, acetone-d_6) δ 7.55 (d, 1, *J* = 15.9 Hz, H7′), 7.16 (d, 1, *J* = 2.0 Hz, H2′), 7.04 (dd, 1, *J* = 8.2, 2.0 Hz, H6′), 6.86 (d, 1, *J* = 8.2 Hz, H5′), 6.27 (d, 1, *J* = 15.9 Hz, H8′), 5.34 (ddd, 1, *J* = 11.5, 7.5, 4.2 Hz, H5), 4.49 (m, 1, H3), 4.17 (dd, 1, *J* = 7.4, 5.7 Hz, H4), 3.32 (s, 3, OCH_3), 2.41 (m, 1, H2a), 2.29−2.22 (m, 2, H2b, H6a), 1.83 (dd, 1, *J* = 13.2, 11.3 Hz, H6b), 1.70−1.60 (m, 2), 1.60−1.50 (m, 6), 1.45−1.30 (m, 2). ^{13}C NMR (90 MHz, acetone-d_6) δ 174.2 (CO_2H), 166.8 (C9′), 148.7 (C4′), 146.3 (C3′), 145.9 (C7′), 127.6 (C1′), 122.6 (C6′), 116.3 (C5′), 115.7 (C8′), 115.2 (C2′), 110.0 (acetal C), 79.9 (C1), 77.3 (C4), 73.8 (C3), 71.7 (C5), 52.6 (OCH_3), 38.8, 36.0, 35.5 (C6), 31.2 (C2), 25.7, 24.7, 24.5. IR (ATR) ν_{max} 3255, 2878, 1770, 1684, 1596, 1514, 1269, 1154, 810 cm^{-1}. HRMS: Calcd for $C_{23}H_{28}O_9$ [M + H]$^+$: 449.1807 *m*/*z*. Found: 449.1799 *m*/*z*.

Synthesis of 1-*O*-Methyl-5-*O*-caffeoylquinic Acid (1-*O*-Methylchlorogenic Acid), 7. To an 8 mL vial containing acetal **13** (20.8 mg, 0.0463 mmol) was added tetrahydrofuran (5 mL) followed by 0.2 M aqueous HCl (600 μL). The resulting solution was degassed by bubbling Ar gas through the solution for 1 min, and the vial was sealed with a screw cap and placed in a 55 °C oil bath for 24 h. The resulting mixture was cooled to room temperature, diluted with ethyl acetate (40 mL), washed with water (5 mL) and 80% brine (2 × 5 mL), and dried ($MgSO_4$). The solution was filtered and concentrated to give a light brown residue. The residue was diluted with water (1 mL) to provide a suspension which was frozen in liquid nitrogen and freeze-dried on a vacuum line to give 12.0 mg (70%) of a fluffy white solid. Attempted melting point determination of this hygroscopic material resulted in formation of a glass below 140 °C. $[\alpha]_D^{25}$ = −16.1 (*c* = 0.55, MeOH), ^{1}H NMR (360 MHz, CD_3OD) δ 7.52 (d, 1, *J* = 15.9 Hz, H7′), 7.04 (d, 1, *J* = 1.9 Hz, H2′), 6.94 (dd, 1, *J* = 8.2, 1.9 Hz, H6′), 6.76 (d, 1, *J* = 8.0 Hz, H5′), 6.21 (d, 1, *J* = 15.9 Hz, H8′), 5.13, (m, 1, H5), 4.11 (m, 1, H3), 3.75 (m, 1, H4), 3.31 (s, 3, OCH_3), 2.32−2.24 (m, 2, H2a, H6a), 2.11 (m, 1, H6b), 2.01 (m, H2b) ppm. ^{13}C NMR (90 MHz, CD_3OD) δ 175.0 (COOH), 168.4 (C9′), 149.6 (C4′), 147.2 (C7′), 146.8 (C3′), 127.8 (C1′), 123.0 (C6′), 116.4 (C5′), 115.2 (C2′), 115.1 (C8′), 81.2 (C1), 72.2 (C4), 72.0 (C5), 69.7 (C3), 52.2 (OCH_3), 35.9 (C2), 34.2 (C6) ppm. IR (ATR) ν_{max} 2951, 2906 1700, 1595, 1516, 1436, 1254, 1151, 1111, 976, 808 cm^{-1}. HRMS: Calcd for $C_{17}H_{20}O_{\backslash 9}$ + Na [M + Na]$^+$: 391.1000 *m*/*z*. Found: 391.1013 *m*/*z*.

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Table 1. Comparison of ^{1}H NMR Data for MCGA3,[32] for Methyl Chlorogenate from the Current Study and from Kancheva et al.,[43] and for Compound 7

MCGA3 (Kweon et al.)[32]	methyl chlorogenate (current study, **14**)	methyl chlorogenate (Kancheva et al)[43]	compound **7**
7.51 (d, 1, J = 15.9 Hz, H7′)	7.52 (d, 1, J = 15.9 Hz, H7′)	7.52 (d, 1, J = 15.9 Hz)	7.52 (d, 1, J = 15.9 Hz, H7′)
7.04(d, 1, J = 2.0 Hz, H2′)	7.04 (d, 1, J = 1.9 Hz, H2′)	7.04 (d, 1, J = 2.0 Hz)	7.04 (d, 1, J = 1.9 Hz, H2′)
6.94 (dd, 1, J = 8.2, 2.0 Hz, H6′)	6.94 (dd, 1, J = 8.2, 1.9 Hz, H6′)	6.95 (dd, 1, J = 8.2, 2.0 Hz)	6.94 (dd, 1, J = 8.0, 1.2 Hz, H6′)
6.77 (d, 1, J = 8.4 Hz, H5′)	6.78 (d, 1, J = 8.2 Hz, H5′)	6.78 (d, 1, J = 8.2 Hz)	6.76 (d, 1, J = 8.0 Hz, H5′)
6.20 (d, 1, J = 15.9 Hz, H8′)	6.21 (d, 1, J = 15.9 Hz, H8′)	6.21 (d, 1, J = 15.9 Hz)	6.21 (d, 1, J = 15.9 Hz, H8′)
5.26−5.30 (m, 1, H5)	5.27 (m, 1, H5)	5.27 (m, 1)	5.13 (m, 1, H5)
4.12−4.15 (m, 1, H3)	4.13, (dt, 1, J = 6.6, 3.3 Hz, H3)	4.13 (m, 1)	4.11 (m, 1, H3)
3.71 (dd, 1, J = 7.5, 3.1 Hz, H4)	3.73 (dd, 1, J = 7.5, 3.1 Hz, H4)	3.73 (m, 1)	3.75 (m, 1, H4)
3.70 (s, 3, OCH_3)	3.69 (s, 3, OCH_3)	3.69 (s, 3, OCH_3)	3.31 (s, 3, OCH_3)
1.93−2.23 (m, 4, H2, H6)	2.23−2.19 (m, 3)	2.23−2.11 (m, 3)	2.32−2.24 (m, 2, H2a, H6a)
	2.00 (dd, 1, J = 13.4, 6.8 Hz, H2a)	2.03−1.99 (m, 1)	2.11 (m, 1, H6b)
			2.01 (m, 1, H2b)

RESULTS AND DISCUSSION

The approach taken for the production of MCGA3 was similar in design to a previous report outlining a synthesis of a closely related derivative.[39] However, detailed synthetic procedures were not presented in this communication. Previous reports have indicated that alkylation of the C-1 hydroxyl of the 4,5-ketal-protected quinic acid lactone can be accomplished with iodomethane.[39] Reaction of lactone **8** with methyl iodide and sodium hydride in DMF afforded methyl ether **9** in 90% yield after recrystallization from hexanes (Figure 2). Hydroxide opening of lactone **9** afforded the corresponding hydroxyl carboxylate. In our hands, acylation of this carboxylate with acetate-protected caffeoyl chloride and imidazole derivatives[39] resulted in poor isolated yields from complex mixtures. We opted to examine the feasibility of unmasking the lactone functionality to the hydroxyl methyl ester **10**. Reaction of lactone **9** with freshly prepared sodium methoxide (Na, CH_3OH)[40] afforded hydroxy ester **10** in 74% yield after chromatographic purification. The caffeoyl moiety was introduced through acylation of the secondary alcohol using caffeic acid anhydride tetraacetate, **11**,[37] a reagent developed specifically for construction of caffeoyl-containing compounds, and afforded the fully protected target compound **12**. The methyl ester functionality was cleaved with lithium iodide in pyridine (120 °C, 52 h)[41] which also resulted in concomitant loss of the caffeoyl acetate protecting groups to give the intermediate acetal **13** in 79% yield after chromatographic purification. Completion of the first synthesis of 1-*O*-methyl chlorogenic acid, **7**, was accomplished after treatment of acetal **13** with aqueous HCl in THF (70%).

Extensive NMR examination of **7** (^{1}H, ^{13}C, HSQC, and HMBC) confirmed the structure as assigned. Conclusive evidence for the assigned structure comes from diagnostic absorption in the HMBC spectrum of compound **7** where, as predicted, the methyl ether protons show only a single cross-peak interaction with the assigned C-1 carbon atom. The C-5 hydrogen atom shows three-bond correlations with C-1, C-3, and the carbonyl carbon of the caffeoyl group, as the expected arrangement for the C-5 attachment of the caffeoyl group to the quinic acid unit.

However, these spectroscopic absorptions differ significantly from those reported for MCGA3.[32] Unfortunately, an authentic sample or spectroscopic data of MCGA3 is not available for comparison purposes. No response was received through attempted contact (e-mail) with the corresponding author of the original isolation/activity paper.[32] The corresponding author of another laboratory which utilized MCGA3 in additional studies[34,35] indicated that they are not in possession of any authentic sample of the isolated MCGA3 and have no spectroscopic data for the compound. After closer examination of the reported spectroscopic data, we surmised that the CH_3 signal at 3.7 ppm in the reported ^{1}H NMR data for MCGA3 was most likely arising from a methyl ester and not an aliphatic methyl ether (typically absorbing at 3.2−3.3 ppm) and that the ^{1}H NMR data as a whole was strikingly similar to that reported for methyl chlorogenate. Literature NMR spectroscopic data appearing both before[42] and after[43] the initial structure assignment disclosure[32] supports these observations. To verify this conjecture, we converted commercially available chlorogenic acid to methyl chlorogenate, **14**, in methanolic HCl[11] at room temperature. Comparison of reported ^{1}H and ^{13}C NMR absorption data for MCGA3 with the data obtained for **14** and **7** in CD_3OD are given in Tables 1 and 2. Both the ^{1}H and ^{13}C NMR data of methyl chlorogenate from the published literature

Table 2. Comparison of ^{13}C NMR Data for MCGA3,[32] for Methyl Chlorogenate from the Current Study and from Deyama et al.,[42] and for Compound 7

MCGA3, Kweon et al.[32] (assignment)	methyl chlorogenate, **14**, current study (assignment)	methyl chlorogenate, Deyama et al.[42] (assignment)	compound **7**, current study (assignment)
175.4 (COOR)	175.6 (COOR)	175.3 (COOR)	175.0 (COOR)
168.3 (C-9′)	168.5 (C-9′)	168.3 (C-9′)	168.4 (C-9′)
149.7 (C-3′)	149.8 (C-4′)	149.4 (C-4′)	149.6 (C-4′)
147.2 (C-4′)	147.4 (C-7′)	147.0 (C-3′ or C-7′)	147.2 (C-7′)
146.8 (C-7′)	147.0 (C-3′)	146.6 (C-3′ or C7′)	146.8 (C-3′)
127.7 (C-6′)	127.8 (C-1′)	127.7 (C-1′)	127.8 (C-1′)
123.0 (C-1′)	123.2 (C-6′)	122.9 (C-6′)	123.0 (C6′)
116.5 (C-5′)	116.7 (C-5′)	116.5 (C-5′)	116.4 (C-5′)
115.1 (C-2′)	115.3 (C-2′)	115.2 (C2′ or C8′)	115.2 (C-2′)
115.1 (C-8′)	115.1(C-8′)	115.2 (C2′ or C8′)	115.1 (C-8′)
75.8 (C-4)	75.8 (C-1)	76.0 (C-1)	81.2 (C-1)
72.6 (C-1)	72.6 (C-4)	73.0 (C-5 or C-4)	72.2 (C-4)
72.1 (C-5)	72.1 (C-5)	72.0 (C-5 or C-4)	72.0 (C-5)
70.3 (C-3)	70.3 (C-3)	70.7 (C-3)	69.7 (C-3)
53.0 (OCH_3)	53.0 (OCH_3)	53.0 (OCH_3)	52.2 (OCH_3)
38.1 (C-2)	38.1 (C-2)	38.2 (C-2 or C-6)	35.9 (C-2)
37.8 (C-6)	37.8 (C-6)	38.2 (C-2 or C-6)	34.2 (C-6)

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values and the authentic sample correlate well with the data reported from the isolation paper[32] for MCGA3, leading to the conclusion that the compound isolated from bamboo (*Phyllostachys edulis*) leaves is instead methyl chlorogenate, **14**. In addition, subsequent reports[33−35] detailing the biological activities of MCGA3 need to be amended to indicate the correct structural formula.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **9**, **10**, **12**, and **13**, along with ^{1}H, ^{13}C, $^{1}H-^{13}C$ HSQC, and $^{1}H-^{13}C$ HMBC NMR spectra for compounds **7** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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