First Efficient Synthesis of Chlorogenic Acid

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The first efficient synthesis of chlorogenic acid (**1**) was achieved in four steps (three purifications) from quinic acid (**2**). The overall yield was 65%. The key intermediate was quinic acid bisacetonide (**6**), selectively prepared by a modified kinetic acetalization protocol. Esterification of **6** with caffeic acid chloride (**3**) afforded ester **12**. Cleavage of all the protecting groups of **12** was accomplished in one step under acidic conditions. The progress of the hydrolysis was monitored by MALDI-MS.

Introduction

3-Caffeoyl quinic acid (**1**; Figure 1), chlorogenic acid, and the 1-, 4-, and 5-regioisomers are common secondary plant metabolites.[1] Particulary high contents of **1** and its congeners are found in coffee (up to 7%), potatoes, and many fruits and vegetables.[1] Humans consuming plant-rich food and drinking more than one cup of coffee a day may ingest up to 1 g of chlorogenic acids per day.[1] Chlorogenic acid (**1**) has many biological activities.[2] Most important, it has antibacterial, antimutagenic, antitumor, and antiviral properties.[3] The pharmacophore responsible for the biological function is the catechol moiety in **1**. This *ortho*-diphenyl group acts as a radical scavenger,[4] and as an antioxidant.[5] Despite their importance as non-nutritive food constituents, relatively little is known about the metabolism of caffeoyl quinic acids in mammals.[2,6] Studies on the metabolism of **1** are limited because isotope labeled chlorogenic acids are not readily available and *efficient* syntheses of **1**, or labeled derivatives thereof, have not been reported.

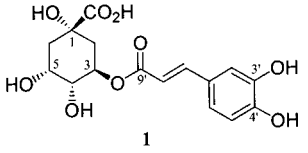

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Figure 1. 3-Caffeoylquinic acid (chlorogenic acid)

Herein we describe a short and efficient synthesis of chlorogenic acid (**1**) starting from quinic and caffeic acid.

Results and Discussion

The first and so-far only chemical[7] synthesis of chlorogenic acid (**1**) was reported by Panizzi et al. 45 years ago.[8] The natural product was prepared in seven steps from quinic acid (**2**) but the overall yield was low (<5%). The major disadvantage of this synthesis was the formation of a quinide acetal with the wrong hydroxy group unprotected. This required several protecting group manipulations and acidic and basic hydrolysis as the final steps of the synthesis.[9] Basic hydrolysis, in particular, should be avoided because chlorogenic acid is very sensitive to oxidation in basic solutions. Recently, the synthesis of a series of chlorogenic acid analogs was reported by Hemmerle et al.[10] Good overall yields (22−32%) of these analogs were achieved by using only acid-labile protecting groups, although a quinide acetal (Figure 2) was again used as the quinic acid intermediate. Key features for a short synthesis of **1** in high overall yield would therefore be a properly functionalised quinic acid derivative and the use of only acid-labile protecting groups (Scheme 1).

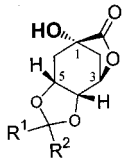
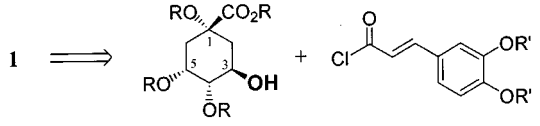
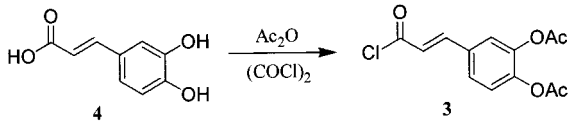


Figure 2. Quinide acetals formed by common acetalization processes



Scheme 1. Key intermediates for a synthesis of chlorogenic acid **1** (R, R′ = acid labile)

A suitably protected and activated caffeic acid was di-*O*-acetylcaffeoyl chloride (**3**)[11] obtained from caffeic acid (**4**) after optimization of standard procedures. Acylation of **4** with Ac_2O in pyridine and chlorination with two equivalents of oxalyl chloride provided the acid chloride **3** in 93% overall yield after recrystallization (Scheme 2).



Scheme 2. Optimized synthesis of caffeic acid chloride **3**

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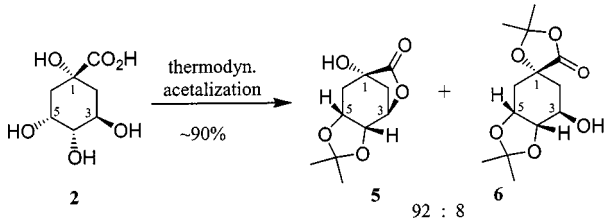
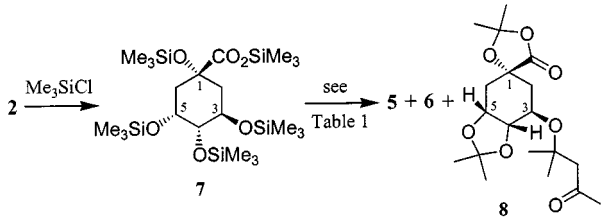
The acid-catalyzed acetalization of (−)-quinic acid (**2**) under thermodynamic conditions generally afford the quinide acetal (Figure 2) in good yields (75 to 90%).[12,13] Recently, Rohloff et al. reported that transformation of **2** under those conditions in a mixture of acetone and 2,2-dimethoxypropane (DMP) yielded, beside quinide acetal **5**, bisacetonide **6** as a minor product (Scheme 3).[14] This bisacetonide would be the ideal quinic acid derivative because the hydroxy group at C(3) is unblocked and the acetals are acid sensitive. Unfortunately, all attempts to improve the yield of **6** using a variety of thermodynamic acetalization conditions failed. In all cases the ratio of **5** and **6** remained unchanged.



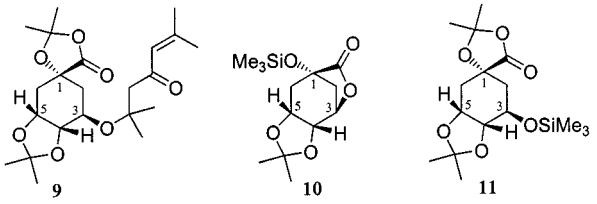
Scheme 3. Product ratio of the thermodynamic acetalization of quinic acid (**2**)

Alternatively, acetalization of carbonyl compounds can be effected under kinetic reaction conditions. In this case, a ketone or aldehyde and an alkoxysilane were reacted at low temperature with catalytic amounts of a Lewis acid.[15]

Silylation of (−)-quinic acid (**2**) with 5.5 equivalents of trimethylsilyl chloride (TMS-Cl) and six equivalents of Et_3N (5 h, −5 °C) afforded the pentasilyl derivative **7** in 95% yield (Scheme 4). Next, silyl ether **7** and acetone (4 equiv.) were treated with 11 mol-% of trimethylsilyl trifluoromethanesulfonate (TMS-OTf) at −75 °C for one hour and at −30 °C for 20 hours.[15a] Three products, quinide **5**, bisacetonide **6**, and compound **8**, derived from the addition of mesityloxide to **6**, were obtained in 42, 50 and 5% yield, respectively (Scheme 4 and Table 1, entry 1). In order to improve the yield of **6** various reaction parameters were varied (Table 1). Increasing the amount of acetone (9 equiv.) or TMS-OTf (20 mol-%), lowering the initial reaction temperature (−95 °C) or maintaining the reaction at −75 °C did not improve the yield of bisacetonide **6**. Only the ratio of quinide **5** and mesityl adduct **8** varied (entries 2−4). Even if the reaction was carried out in acetone, the ratio of **5**, **6**, and **8** was almost unchanged but, additionally, an adduct of **6** and phorone, compound **9** (Scheme 5) was isolated in 3% yield (entry 5).



Scheme 4. Kinetic acetalization of quinic acid (**2**)



Scheme 5. By-products of the kinetic acetalization in acetone and DMP, respectively

The workup procedure strongly affected the yield of product **6**. Quenching of the reaction by addition of pyridine[15] gave varying yields of bisacetonide **6** (20−50%) under otherwise similar conditions. More reproducible results were obtained when the cold (−30 °C) or a re-cooled (−80 °C) reaction mixture was poured into a saturated solution of $NaHCO_3$ and the aqueous phase was immediately neutralized with NH_4Cl.

Taking into account that **8** is derived from **6**, the yield of quinic acid bisacetonide was between 41 and 71%, and

Table 1. Optimization of the kinetic acetalization of silyl ether **7**

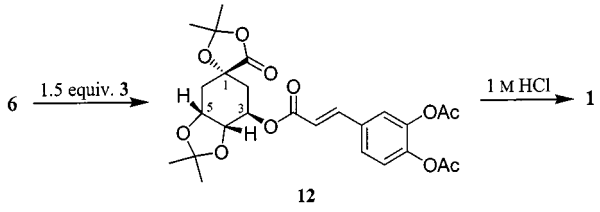
Entry	Reagent [equiv.]	Solvent	Lewis acid. [mol-%]	T [°C]	t [h]	Workup[a]	**6**, **5**, **8** [%][b]
1	acetone [4]	CH_2Cl_2	TMS-OTf [11]	−75 → −30	1 → 16	A	50:42:5
2	acetone [9]	CH_2Cl_2	TMS-OTf [20]	−75 → −30	4 → 16	A	50:19:18
3	acetone [9]	CH_2Cl_2	TMS-OTf [20]	−75	2	A	36:10:5
4	acetone [10]	CH_2Cl_2	TMS-OTf [18]	−95 → −30	2 → 70	B	48:39:10
5	acetone [87]	−	TMS-OTf [18]	−95 → −30	2 → 70	B	48:21:23[c]
6	DMP [3]	CH_2Cl_2	TMS-OTf [20]	−75 → −30	6 → 16	C	48:32:−
7	DMP [3]	CH_2Cl_2	TMS-OTf [16]	−75	24	C	5:5:−
8	DMP [3]	CH_2Cl_2	TMS-OTf [7]	−75 → −30	2 → 70	C	47:41:−
9	DMP [3]	CH_2Cl_2	TMS-OTf [15]	−98 → −30	2 → 55	B	38:30:−[d]
10	DMP [33]	−	TMS-OTf [5]	−30	4	C	20:−:−[e]
11	DMP [9]	CH_2Cl_2	$BF_3{\cdot}Et_2O$ [16]	−75 → −30	1 → 30	C	20:20:−
12	DMP [9]	CH_2Cl_2	$TiCl_4$ [8]	−75 → −30	1 → 71	C	−:25:−
13	acetone [36]/DMP [22]	−	TMS-OTf [18]	−95 → −30	2 → 24	B	82:13:−[f]
14	acetone [58]/DMP [17]	−	TMS-OTf [18]	−95 → −30	2 → 5	B	74:6:−

[a] **A**: pyridine was added, **B**: reaction cooled to −80 °C, added to a sat. $NaHCO_3$ solution and neutralized with NH_4Cl, **C**: poured at −30 °C into a sat. $NaHCO_3$ solution and neutralized with NH_4Cl. − [b] Various amounts of TMS ethers **10** and **11** were formed especially in cases when DMP was used as reagent. − [c] Phorone adduct **9** was isolated in 3% yield. − [d] About 20% of **10** and **11** were obtained. − [e] Not determined. − [f]About 3% of **10** was isolated.

suppression of compound **8** was therefore desirable. Acetone was therefore replaced by DMP as carbonyl synthon. As expected, no mesityl adduct **8** was formed under a variety of reaction conditions (entries 6−12), although DMP had several disadvantages. In particular: (i) the yields of compound **6** were generally lower than those achieved with acetone as reactant; (ii) the reaction mixture soon turned deep red-brown after addition of the Lewis acid. The brownish reaction product obtained after workup was difficult to purify because several by-products, derived from DMP, were formed; (iii) cleavage of the remaining silyl ether during the reaction was always incomplete, and silyl ether **10** and **11** (Scheme 5) were generally isolated, each in 5−10% yield. Both silyl ethers **10** and **11** could be cleaved quantitatively to **5** and **6**, respectively, with tetrabutylammonium fluoride (TBAF) at −30 °C. The reaction temperature was critical because quinide **5** was exclusively formed from a 1:1 mixture of **10** and **11** when the reaction was carried out at 0 °C. It was assumed that the lability of the dioxolanone moiety of **6** was caused by a proximity of the hydroxy group at C(3) and the carboxyl group at C(1) resulting in a rapid cyclization to the lactone although the X-ray crystal structure of **6** provided no evidence for this assumption.[16]

As a consequence, a mixture of both carbonyl components, DMP and acetone, gave the best yields of **6** (up to 82%) (Table 1, entries 13 and 14). No adduct **8** was formed under these conditions and the amount of silyl ethers **10** and **11** was below 3%.

Esterification of **6** with 1.5 equivalents of **3** was realized in dichloromethane at 0 °C under standard esterification



Scheme 6. Final steps to chlorogenic acid (**1**)

conditions. Ester **12** was obtained in 92% yield (Scheme 6).

Cleavage of all protecting groups of ester **12** was achieved with 1 N aqueous HCl containing 15% THF. When 2 N HCl was used,[10] saponification of the caffeic ester was observed to some extent (15%) whereas deprotection was very slow with 0.5 N HCl. The progress of the hydrolysis of the two acetonides and of the two phenol acetates was monitored by MALDI-TOF mass spectra. Hydrolysis of the protecting groups was complete after 10 days at room temperature, and chlorogenic acid (**1**) was isolated in 91% yield (Scheme 6).

Conclusion

We have developed the first efficient synthesis of chlorogenic acid (**1**) starting from caffeic and quinic acid. In only four steps (three purifications), compound **1** was obtained in 65% overall yield from **2** and in 51% overall yield from **3** (based on 1.5 equivalents of **3** employed for the esterification reaction). The key intermediate was bisacetonide **6** which was prepared as the major product (82%) for the first time using a kinetic acetalization protocol. By using this strategy, isotope labeled chlorogenic acid derivatives should be obtained in high yields from the corresponding starting materials[7b,17]

Experimental Section

General Procedures: All reactions were performed in dried glassware under an inert (N_2) atmosphere. Standard reagents and solvents were purified according to known procedures.[18] Thin layer chromatographic (TLC) analyses were performed on silica gel plates Merck 60 F_{254}. Column chromatographic purifications ("flash chromatography", FC) were performed as described elsewhere.[19] Melting points were determined using a Büchi SMP-20 apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-1000 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker ARX 300 instrument at 300.1 and 75.4 MHz, respectively. Unless otherwise stated, $CDCl_3$ was used as solvent. IR spectra were recorded with a Perkin−Elmer FT-IR 16 PC instrument either from KBr plates or neat. UV spectra were obtained from alcoholic solutions utilizing an ATI UNICAM UV 3 instrument. Mass spectra were achieved by electron impact (EI) using a Finnigan MAT SSQ 710 instrument and MALDI-MS were recorded on a Bruker Reflex II (positive ion mode, matrix: THAP). Elemental analyses were performed on a LECO CHNS-932 instrument.

Preparation of Acid Chloride 3: To a solution of caffeic acid (7.20 g, 40.0 mmol) and DMAP (0.12 g, 1.0 mmol) in pyridine (20 mL) was acetic anhydride added (9.4 mL, 0.1 mol) at 0 °C. The reaction mixture was stirred for 1 h and then poured onto crushed ice. The aqueous phase was acidified with 2 M aq. HCl (pH ≈ 2) and extracted with EtOAc/THF (3:1; 3 × 80 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Trituration of the residue with light petroleum containing small amounts of EtOAc afforded di-*O*-acetylcaffeic acid (10.4 g, 39 mmol) as a colorless powder. This was suspended in toluene (200 mL) containing five drops of DMF. Oxalyl chloride (7.0 mL, 0.08 mol) was added at −5 °C. After stirring for 3 h at room temperature, all starting material had dissolved resulting in a pale-brown solution. Toluene and unreacted oxalyl chloride were removed under reduced pressure. The residual brownish product was recrystallized from toluene to afford 6.0 g of acide chloride **3**. The mother liquid was concentrated and the residue triturated with light petroleum containing small amounts of EtOAc. A total of 10.6 g (93%) of acid chloride **3** was obtained as a pale yellow powder. − ^{1}H NMR: δ = 7.77 (d, *J* = 15.5 Hz, 1 H), 7.46 (dd, *J* = 8.4, 1.9 Hz, 1 H), 7.43 (d, *J* = 1.9 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 6.49 (d, *J* = 15.5 Hz, 1 H), 2.32 (s, 3 H), 2.31 (s, 3 H). − ^{13}C NMR: δ = 167.91 (s), 167.72 (s), 165.78 (s), 148.44 (d), 144.78 (s), 142.60 (s), 131.59 (s), 127.39 (d), 124.27 (d), 123.65 (d), 123.28 (d), 20.59 (q), 20.53 (q). − MS (70 eV): *m/z* (%) = 284 (3), 282 (8), 247 (74), 242 (8), 240 (24), 205 (41), 200 (9), 198 (28), 163 (100).

Preparation of Bisacetonide 6: To a suspension of quinic acid **2** (2.00 g, 10.4 mmol; dried for 4 h, 30 °C, 5 × 10^{-3} mbar) in CH_2Cl_2 (40 mL) was added Et_3N (8.0 mL, 58 mmol) at −15 °C. The reac-

tion mixture turned clear within a few minutes and trimethylsilyl chloride (7.0 mL, 55 mol) was added at that temperature. A white precipitate was immediately formed. The suspension was stirred for 4.5 h while the temperature was maintained below 0 °C. Pentane (100 mL) was added and the precipitate was filtered off. The filter cake was washed with hot pentane (2 × 100 mL). The solvents were removed under reduced pressure. The residue was redissolved in pentane (200 mL) and any remaining traces of ammonium salt were filtered off. Pentane was removed in vacuo to give silyl ether **7** (5.47 g, 95%) as a pale yellow liquid (in an attempt to purify **7** by vacuum distillation, decomposition of **7** occurred).

A solution of **7** (5.14 g, 9.3 mmol) in acetone (25 mL) and DMP (25 mL) was cooled to −95 °C and a solution of TMS-OTf (0.3 mL, 1.7 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The reaction mixture was stirred for 2 h while warming to −45 °C. The yellow solution was kept at −30 °C for 24 h, re-cooled to −80 °C and added to a sat. aq. $NaHCO_3$ solution (100 mL), whereupon the color faded. The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue (SiO_2, 6 × 20 cm, 25−65% EtOAc/light petroleum) afforded 0.30 g (13%) of quinide **5** and 2.10 g (82%) of bisacetonide **6** as colorless crystals. M.p. 124 °C (ref.[14]: oil). − $[\alpha]_D^{23}$ = −27.0 (*c* = 0.2, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3501, 2993, 1779, 1291, 1218, 1051 cm^{-1}. − ^1H NMR: δ = 4.48 (dt, *J* = 5.5, 4.3 Hz, 1 H), 4.05−3.98 (m, 2 H), 2.88 (br. s, 1 H), 2.31 (dd, *J* = 15.3, 4.7 Hz, 1 H), 2.20 (br. dd, *J* = 15.3, 3.9 Hz, 1 H), 2.13 (br. d, *J* = 13.9 Hz, 1 H). − 1.94 (dd, *J* = 13.9, 9.3 Hz, 1 H), 1.62 (s, 3 H), 1.61 (s, 3 H), 1.52 (s, 3 H), 1.37 (s, 3 H). − ^{13}C NMR: δ = 176.10 (s), 111.43 (s), 108.97 (s), 78.34 (s), 78.22 (d), 71.69 (d), 67.46 (d), 37.26 (t), 34.95 (t), 28.52 (q), 27.79 (q), 25.25 (q). − MS (70 eV): *m/z* (%) = 271 (13), 257 (100), 43 (50). − $C_{13}H_{20}O_6$ (272.30): calcd. C 54.34, H 7.40; found C 54.31, H 7.61.

By using pure acetone instead of acetone/DMP as solvent, compounds **5** (21%),[14] **6** (48%), **8** (23%) and **9** (3%) were isolated.

Compound 8: M.p. 76 °C. − $[\alpha]_D^{23}$ = −61.5 (*c* = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2981, 1790, 1711, 1369, 1273, 1224, 1034 cm^{-1}. − ^1H NMR: δ = 4.45 (dt, *J* = 5.0, 4.0 Hz, 1 H), 3.95−3.84 (m, 2 H), 2.68/2.58 (AB, *J* = 13.9 Hz, 2 H), 2.24 (dd, *J* = 15.4, 4.9 Hz, 1 H), 2.20 (s, 3 H), 2.15 (ddd, *J* = 15.5, 3.7, 1.8 Hz, 1 H), 1.94 (ddd, *J* = 13.8, 3.7, 1.7 Hz, 1 H), 1.78 (dd, *J* = 13.8, 10.6 Hz, 1 H), 1.60 (s, 3 H), 1.59 (s, 3 H), 1.53 (s, 3 H), 1.36 (s, 3 H), 1.32 (s, 3 H), 1.27 (s, 3 H). − ^{13}C NMR: δ = 208.14 (s), 174.39 (s), 110.32 (s), 108.62 (s), 78.57 (s), 78.53 (d), 75.69 (s), 72.62 (d), 67.78 (d), 55.43 (t), 39.42 (t), 35.04 (t), 32.48 (q), 28.58 (q), 28.41 (q), 27.94 (q), 26.21 (q), 26.07 (q), 25.48 (q). − MS (70 eV): *m/z* (%) = 371 (36), 313 (13), 273 (74), 254 (100). − $C_{19}H_{30}O_7$ (370.45): calcd. C 61.60, H 8.16; found C 61.62, H 8.40.

Compound 9: ^1H NMR: δ = 6.19 (s, 1 H), 4.45 (dt, *J* = 5.0, 3.7 Hz, 1 H), 3.96−3.85 (m, 2 H), 2.66/2.60 (AB, *J* = 13.5 Hz, 2 H), 2.25 (dd, *J* = 15.3, 4.9 Hz, 1 H), 2.14 (ddd, *J* = 15.3, 2.7, 1.2 Hz, 1 H), 2.12 (s, 3 H), 1.95 (ddd, *J* = 13.9, 3.6, 1.3 Hz, 1 H), 1.87 (s, 3 H), 1.78 (dd, *J* = 13.9, 10.6 Hz, 1 H), 1.60 (s, 3 H), 1.59 (s, 3 H), 1.53 (s, 3 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.28 (s, 3 H). − ^{13}C NMR: δ = 199.42 (s), 174.39 (s), 154.20 (s), 125.77 (d), 110.17 (s), 108.50 (s), 78.48 (s), 78.43 (d), 76.04 (s), 72.53 (d), 67.50 (d), 55.74 (t), 39.28 (t), 34.95 (t), 28.52 (q), 28.34 (q), 27.84 (q), 27.56 (q), 26.31 (q), 26.18 (q), 25.38 (q), 20.54 (q).

Preparation of Compound 12: To a solution of bisacetonide **6** (2.72 g, 10.0 mmol) and DMAP (0.18 g, 1.5 mmol) in CH_2Cl_2 (100 mL) were added pyridine (30 mL) and acid chloride **3** (4.23 g, 15.0 mmol) at room temperature. The reaction mixture was stirred for 5 h and acidified with 1 M aq. HCl (pH ≈3). The layers were separated and the aqueous phase re-extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvents were removed in vacuo. The residue was purified by FC (6 × 30 cm, 30−40% EtOAc/light petroleum) to afford 4.81 g (92%) of ester **12** as a colorless amorphous solid. M.p. 73−75 °C. − $[\alpha]_D^{23}$ = −33.6 (*c* = 1.0, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 2991, 1784, 1715, 1640, 1209, 1175 cm^{-1}. − ^1H NMR: δ = 7.67 (d, *J* = 16.0 Hz, 1 H), 7.40 (dd, *J* = 8.3, 1.8 Hz, 1 H), 7.35 (d, *J* = 1.8 Hz, 1 H), 7.22 (d, *J* = 8.3 Hz, 1 H), 6.40 (d, *J* = 16.0 Hz, 1 H), 5.27 (ddd, *J* = 11.0, 7.2, 3.8 Hz, 1 H), 4.53 (dt, *J* = 5.6, 3.8 Hz, 1 H), 4.21 (dd, *J* = 7.2, 6.1 Hz, 1 H), 2.33−2.29 (m, 2 H), 2.31 (s, 3 H), 2.30 (s, 3 H), 2.25 (br. dd, *J* = 13.6, 3.8 Hz, 1 H), 1.93 (dd, *J* = 13.6, 11.0 Hz, 1 H), 1.65 (s, 3 H), 1.63 (s, 3 H), 1.56 (s, 3 H), 1.38 (s, 3 H). − ^{13}C NMR: δ = 174.13 (s), 167.97 (s), 167.90 (s), 165.80 (s), 143.55 (s), 143.46 (d), 142.40 (s), 133.13 (s), 126.37 (d), 123.91 (d), 122.82 (d), 118.94 (d), 110.84 (s), 109.43 (s), 78.04 (s), 75.95 (d), 72.39 (d), 70.22 (d), 35.83 (t), 34.75 (t), 28.59 (q), 28.28 (q), 27.77 (q), 25.49 (s), 20.59 (q). − MS (70 eV): *m/z* (%) = 519 (43), 503 (57), 476 (24), 461 (43), 434 (45), 418 (39), 376 (100), 318 (30), 254 (62), 247 (41). − UV (EtOH): λ_{max} (ε) = 281 (21000), 220 (14000) nm. − $C_{26}H_{30}O_{11}$ (518.52): calcd. C 60.23, H 5.83; found C 60.19, H 5.93.

Preparation of Chlorogenic Acid (1): Ester **12** (1.56 g, 3.0 mmol) was dissolved in a mixture of THF (20 mL) and aq. 1 M HCl (80 mL) at room temperature. The reaction mixture was stirred at room temperature, and progress was monitored by MALDI-MS. After 10 days, the solution was saturated with solid NaCl and the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed in vacuo. The crystalline residue was triturated with hot Et_2O to afford 0.75 g (70%) of chlorogenic acid (**1**). The mother liquid was concentrated and the trituration step was repeated. An additional 0.22 g (21%) of **1** was obtained. All analytical data of synthetic **1** were in agreement with those obtained from purchased chlorogenic acid (Merck).

Acknowledgments

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