First Efficient Syntheses of 1-, 4-, and 5-Caffeoylquinic Acid

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Efficient synthesis of 1-, 4-, and 5-caffeoylquinic acid was achieved in three or four steps with suitably protected quinic acid precursors, in overall yields of 41%, 36%, and 60% [from quinic acid (**1**)]. 1-Caffeoylquinic acid was prepared by esterification of acetone quinide **7** with caffeoyl chloride **6**, followed by a two-step hydrolysis of all protecting groups. Caffeoylquinic acids **4** and **5** were prepared from known quinic acid derivatives, **13** and **25**, by selective esterification of the secondary hydroxy groups and hydrolysis with 1 M HCl. However, initial attempts to prepare fully protected quinic acid derivatives with a free hydroxy group only at either C-4 or C-5, for the synthesis of **4** and **5**, were not successful. Kinetic acetalization of pentasilylated quinic acid **15** using bis(dimethoxy acetals) afforded several crystalline reaction products which were identified by X-ray diffraction. Diacetal **20**, derived from a vicinal *cis*-diol, was unambiguously identified for the first time. Unexpectedly, it has two *trans*-diaxially oriented methoxy groups, forcing the quinide ring into a twist-boat conformation.

Introduction

Quinic acid (**1**) and its four monocaffeoyl esters **2**−**5** (Figure 1) are widespread secondary plant metabolites.[1] The caffeoylquinic acids possess a broad spectrum of biological activities.[2,3] Most intensely studied is 3-caffeoylquinic acid (chlorogenic acid, **3**), which is usually the major regioisomer,[4] and the only commercially available caffeoylquinic acid. All other isomers must either be isolated from plant sources[5] or synthesized by random isomerization of the commercially available acid **3**.[6,7] Regioselective syntheses of caffeoylquinic acids have been reported in brief for 1-caffeoylquinic acid[6c,8] and 5-caffeoylquinic acid[9] (**2** and **5**). It is to be noted that different rules exist for the numbering and stereochemical descriptors of the ring system of quinic acid (**1**).[10] By *3-caffeoylquinic acid* we refer below to chlorogenic acid (**3**), as have the majority of authors.[11]

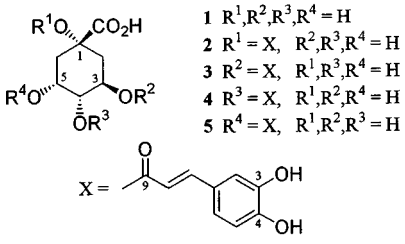
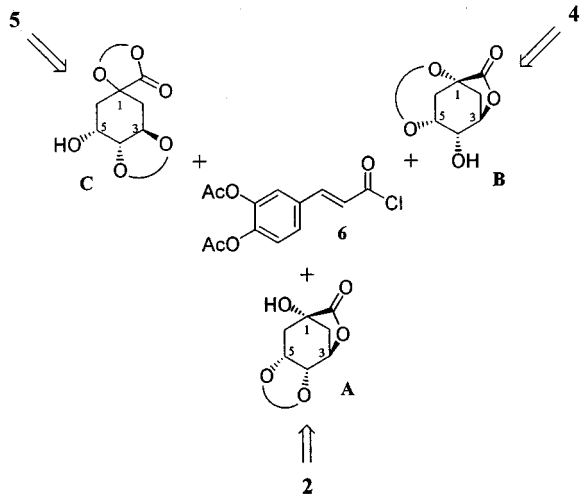


Figure 1. Quinic acid (**1**) and its monocaffeic acid esters **2**−**5**

In a preceding paper, we described a short and efficient synthesis of **3** from a new quinic acid acetal obtained by kinetic acetalization.[12] Here we report the first efficient and regioselective syntheses of the other, commercially unavailable monocaffeoylquinic acids (**2**, **4**, and **5**). Obviously, all caffeoylquinic acids can be prepared by esterification of suitable caffeic and quinic acid derivatives. Di-*O*-acetylcaffeoyl chloride (**6**) was used as the acylating agent because it had already successfully been employed for the preparation of **3**.[12] The preparations of the selectively protected quinic acids **A**−**C** (Scheme 1) were more difficult. Quinic acid derivatives corresponding to structure **A** are known[13] but those outlined in structures **B** and **C** have not yet been described.



Scheme 1. Quinic acid acetals **A**−**B** as key precursors for the synthesis of caffeoyl ester **2**, **4**, and **5**

Results and Discussion

(a) 1-Caffeoylquinic Acid

The first synthesis of 1-caffeoylquinic acid (**2**) was published in 1964. It was synthesized from acetone quinide **7**[14]

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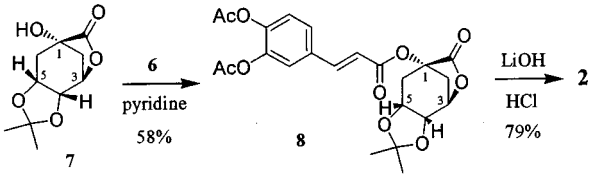
and di-*O*-ethylcarbonate-protected caffeoyl chloride, but neither yields nor conditions were described in detail.[6c,8,15]

In our hands, acetone quinide **7** reacted smoothly with acid chloride **6** under standard esterification conditions, providing ester **8** in 58% yield (Scheme 2). Hydrolysis of the protecting groups was accomplished in a two-step sequence; all labile esters were cleaved using LiOH in a degassed water/THF solution under an inert gas, and removal of the acetal group was then achieved after acidification of the reaction mixture with 2 M HCl, whereupon 1-caffeoylquinic acid (**2**) was obtained in 79% yield (41% from **1**). The yield of **2** was less than 20% when the hydrolysis was performed entirely under acidic conditions (1 M HCl) or when the solution of **8** in water/THF was not carefully degassed prior to the addition of LiOH. In this case, the solution turned deep brown after addition of the base and the color remained even after acidification, indicating that oxidation of the liberated catechol group had occurred to some extent.

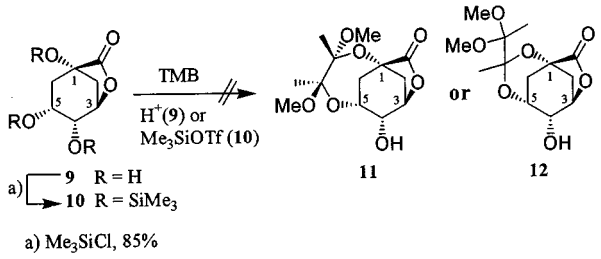


Scheme 2. Synthesis of caffeoyl ester **2**

(b) 4-Caffeoylquinic Acid

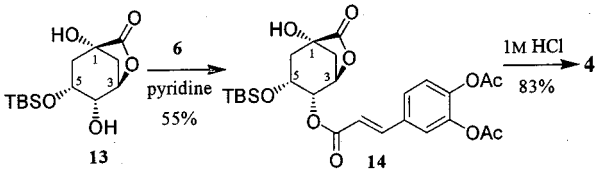
4-Caffeoylquinic acid (cryptochlorogenic acid, **4**) had not yet been synthesized regioselectively. The only methods for obtaining small quantities of this compound were extensive isolation from plant material or base-induced, random isomerization of chlorogenic acid (**3**).

Our first approach was a regioselective esterification of the hydroxy group at C-4, using a fully protected quinic acid derivative (structure **B**) as outlined in Scheme 1. Since acid-catalyzed acetalizations of quinide **9**[16] with ketones or aldehydes generally provide the corresponding dioxolanones, such as **7**, we expected, when using 2,2,3,3-tetramethoxybutane (TMB), a regioselective functionalization of the hydroxy groups at C-1 and C-5 of quinide **9** or of the corresponding tris(trimethylsilyl) ether **10**. Usually TMB does not react with vicinal *cis*-diols,[17] either acetal **11** or **12** should be formed by reaction of **9** or **10** with TMB under thermodynamic or kinetic reaction conditions (Scheme 3). Unfortunately, proton-catalyzed acetalization of **9** in the presence of MeOH and $CH(OMe)_3$ afforded a series of different acetals derived from quinide **9** or methyl quinate. Similarly, the Lewis acid catalyzed cyclization of silyl ether **10** produced several 4,5-protected quinides; these were not structurally identified, but it was apparent that neither **11** nor **12** was formed under any acetalization conditions applied.



Scheme 3. Attempted synthesis of acetals **11** or **12** from quinides **9** or **10**

As demonstrated by Abell et al., differentiation of the secondary hydroxy groups at C-4 and C-5 of quinide **9** was effectively achieved with TBSCl, providing silyl ether **13** in over 75% yield (from **9**).[18] Although **13** possesses two sterically hindered hydroxy groups, esterification of **13** with 1.2 equiv. of caffeoyl chloride **6** in pyridine exclusively provided ester **14** in 55% yield. Interestingly, no esterification was observed when the reaction was performed in CH_2Cl_2 containing several equivalents of pyridine. Hydrolysis of all protecting groups was accomplished with 1 M HCl at room temperature, and 4-caffeoylquinic acid (**4**) was obtained in 83% yield (36% from **1**) (Scheme 4). Use of the sequential basic and acidic hydrolysis procedure as described above, however, resulted in cleavage of all esters and quantitative isolation of caffeic acid.



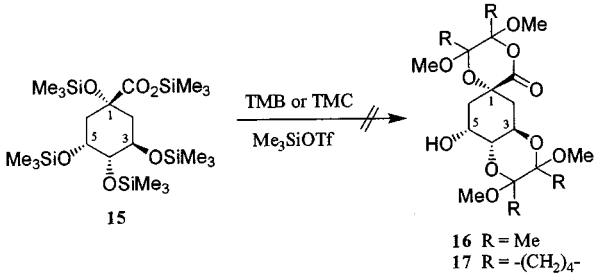
Scheme 4. Synthesis of 4-caffeoylquinic acid (**4**) from silyl ether **13**

(c) 5-Caffeoylquinic Acid

One regioselective synthesis of 5-caffeoylquinic acid (neochlorogenic acid, **5**) has been reported in the literature.[9] Haslam et al. obtained **5** in six steps from **1** and in an overall yield of only 3%. The major drawback was an unselective esterification of a quinide derivative with both secondary hydroxy groups at C-4 and C-5 unprotected, since no suitably protected quinic acid derivative (corresponding to structure **C** in Scheme 1) was available.

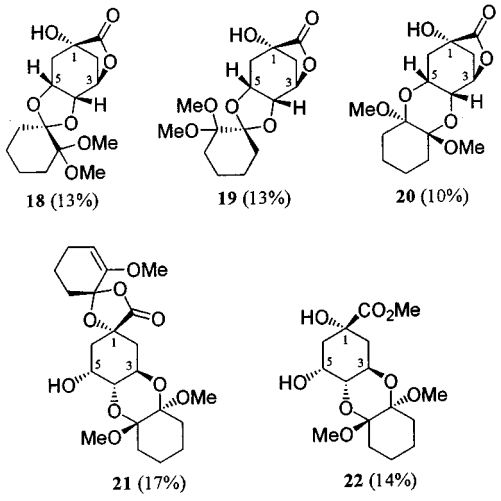
Our first attempt was the preparation of a quinic acid bis(acetal) with an unprotected hydroxy group at C-5, which it was hoped could be synthesized from quinic acid (**1**) using TMB[17] or 1,1,2,2-tetramethoxycyclohexane (TMC).[19] These acetals are common reagents for the protection of vicinal *trans*-diols and so they might also have been expected to react with α-hydroxy acids to give the corresponding dioxanones.[20] However, protic acetalization of **1** with these reagents could be ruled out, since quinides are formed under thermodynamic reaction conditions. Therefore, pentasilylquinic acid **15**[12] was treated with TMB or

TMC under Lewis acid catalysis at low temperature,[21] but neither of the expected acetals, **16** or **17**, was formed under these conditions (Scheme 5).



Scheme 5. Attempted synthesis of bis(cyclodiacetals) **16** or **17** from pentasilylquinic acid **15** and TMB or TMC, respectively

Treatment of **15** with TMC afforded at least eight quinic acid derived products: compounds **18**−**22** and corresponding silyl ethers (Scheme 6). Characterization of the reaction products by spectroscopic methods was difficult, due to the structural similarity of the hitherto unknown reaction products. For example, compounds **18**−**20**, three isomers of $C_{15}H_{22}O_7$, show very similar NMR spectra. Fortunately, all the compounds shown in Scheme 6 are crystalline and their structures were elucidated by X-ray diffraction.



Scheme 6. Structural diversity in the reaction of **15** with TMC under aprotic conditions

It was known that five-membered ring acetals − **18** and **19**, for example[22] − can be formed as minor side products from the reaction between TMC and vicinal *cis*-diols.[19] However, a *cis*-diol-derived cyclodiacetal, such as **20** (Figure 2, Table 1), had not been unambiguously identified before. Recently, Shih and Wu reported that methyl shikimate reacted with TMB to give a mixture of *cis*- and *trans*-diacetals, but no evidence for the structural assignment was provided. Since it is known that two diastereoisomeric acetals can be formed from diequatorial diols,[19b] the given assignment of the shikimate acetals is not certain.[23] Surprisingly, the crystal structure of acetal **20** revealed two perfectly *trans*-diaxially oriented (179.6°) methoxy groups despite the "unfavorable" *cis* configuration of the vicinal diol moiety. As the consequence, the quinide ring was forced into a twist-boat conformation (Figure 2).

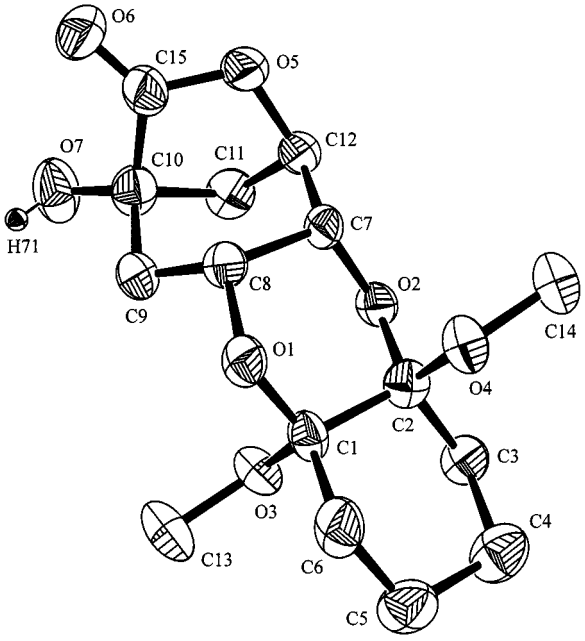


Figure 2. X-ray structure of *cis*-cyclodiacetal **20**; ORTEP plot with 50% probability displacement ellipsoids; H atoms have been omitted for clarity (except H71);[26] selected bond lengths [Å] and angles [°]: O5−C12 1.483(8), C15−O5 1.363(7), O7−C10 1.378(7), O6−C15 1.198(8); C1−O3−C13 115.6(4), C2−O4−C14 115.1(4), O6−C15−O5 120.5(6), O6−C15−C10 129.6(6), O7−C10−C11 112.7(5), C10−C11−C12 98.8(5); the molecules are linked by hydrogen bonds between O7 and O6 via H71 [O7···O6 2.813(8), H71···O6 2.09(8) Å, O5−O51···O4 158(1)°; symmetry operator of O6: $x - 1/2, 1/2 - y, -z$]

Two appropriate quinic acid derivatives for the regioselective synthesis of **5**, compounds **21** and **22** (Scheme 6), could be formed from **15** and TMC, but the yields were too low to proceed with one of these materials. Unlike the diastereoisomers **18** and **19**, bis(acetal) **21** (Figure 3) was obtained in a high diastereoisomeric excess. Two structural features of diacetal **21** were surprising: (i) a dioxolanone moiety[20] and (ii) an enol ether adjacent to the dioxolanone acetal. Both observations could be explained if **15** were to react with 2-methoxycyclohexenone rather than with TMC. 2-Methoxycyclohexenone was formed as a side product from TMC under the influence of the Lewis acid.

Aprotic acetalization of **15** with TMB gave similar results, but in this case only compounds **23** and **24** were isolated as major products (Scheme 7). The two compounds were structurally related to quinide **19** and bis(acetal) **21**, respectively. The structures of **23** and **24** were established by comparison of their ^1H and ^{13}C NMR spectra with those obtained for **19** and **21**.

As demonstrated, fully protected bis(acetals) of quinic acid possessing a free hydroxy group at C-5, such as **21** and **24**, can be prepared from **15**, although not in useful yields. For an efficient synthesis of **5**, an alternative strategy invol-

Table 1. Crystal data and measurement conditions for the compounds **20** and **21**

	20	**21**
Empirical formula	$C_{15}H_{22}O_7$	$C_{22}H_{32}O_9$
Molecular mass	314.33	440.48
Crystal size [mm]	1.29 × 0.19 × 0.19	1.56 × 0.75 × 0.57
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Lattice parameters		
a [Å]	6.301(3)	9.002(3)
b [Å]	13.539(6)	12.945(2)
c [Å]	17.333(8)	19.412(2)
V [Å^3]	1477.4(8)	2262.0(8)
Z	4	4
$D_{calcd.}$ [g·cm^{-3}]	1.412	1.293
F (000)	672	944
μ [mm^{-1}]	0.112	0.100
Radiation type	Mo-K_α	Mo-K_α
λ [Å]	0.71073	0.71073
2 Θ_{max} [°]	55.0	60.0
h_{min}/h_{max}	0/7	−12/12
k_{min}/k_{max}	0/16	−18/18
l_{min}/l_{max}	0/20	−27/27
No. of measured reflections	1529	7397
No. of unique reflections	1529	6582
No. of observed reflections [$I > 2\sigma(I)$]	770	4638
No. of parameters	232	341
R factor [$I > 2\sigma(I)$]	0.0469	0.0411
Goodness of fit	0.969	0.991

ving *trans*-acetal **25**[17] (85% from **1**) was therefore developed. The suitability of compound **25** was proved by quantitative conversion of **25** into quinic acid (**1**) using 1 M HCl. Selective esterification of the hydroxy group at C-5 was achieved using 1.2 equiv. of acid chloride **6** under standard conditions. Ester **26** was obtained in 88% yield (Scheme 8). Cleavage of the protecting groups with 1 M HCl afforded 5-caffeoylquinic acid (**5**) in 81% yield (60% from **1**).

Conclusion

We have shown for the first time that syntheses of 1-, 4-, and 5-caffeoylquinic acid may be efficiently achieved in three or four steps, using appropriately protected quinic acid derivatives. Our initial strategy to prepare the caffeoylquinic acids from fully protected quinic acid precursors with only the desired hydroxy group unprotected was successful only for caffeoylquinic acid **2**. This acid was prepared in 41% overall yield from **1** by esterification of acetone quinide **7** with caffeoyl chloride **6**, followed by a two-step hydrolysis of all protecting groups. Caffeoylquinic acids **4** and **5** were prepared according to alternative routes based on the known quinic acid derivatives **13** and **25**. Both intermediates possess two unprotected hydroxy groups, a tertiary at C-1 and a secondary at C-4 or C-5, respectively. Selective esterifications of the secondary hydroxy groups were achieved in moderate to good yields (55% and 88%).

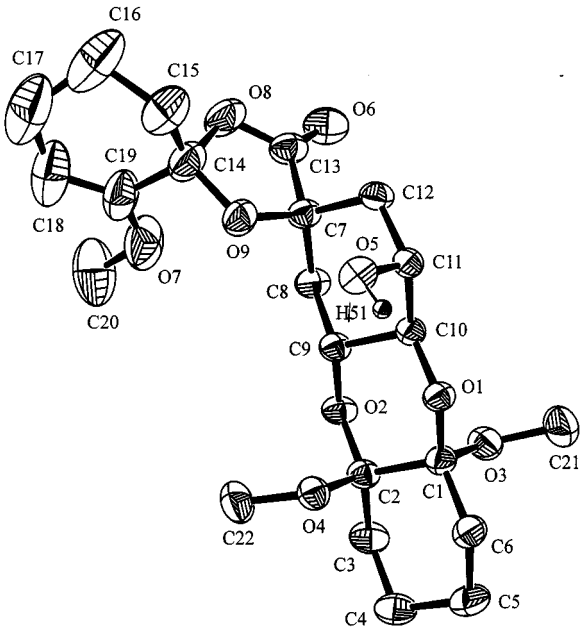
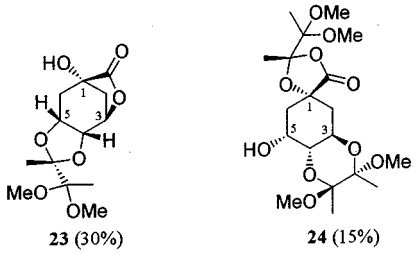
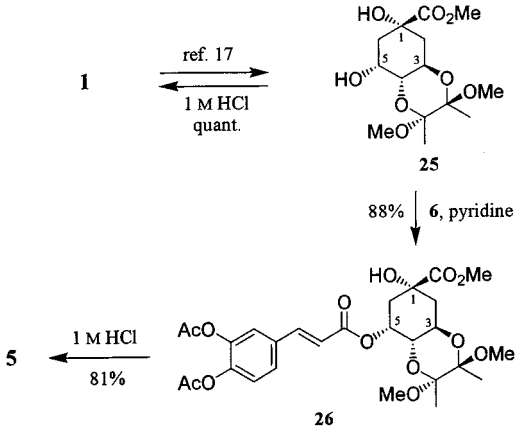


Figure 3. X-ray structure of compound **21**; ORTEP plot with 50% probability displacement ellipsoids; H atoms have been omitted for clarity (except H51);[26] selected bond lengths [Å] and angles [°]: C9−C10 1.512(2), C11−O5 1.4238(19), C13−O6 1.202(2), C14−C15 1.520(4), C14−C19 1.500(4), C15−C16 1.500(5), C16−C17 1.484(7), C17−C18 1.524(7), C18−C19 1.337(4), C19−O7 1.350(4), O7−C20 1.416(4); C1−O3−C21 115.84(15), C22−O4−C2 114.87(13), C12−C11−O5 107.79(13), C10−C11−O5 112.31(12), C11−C12−C7 114.20(12), C8−C7−C12 111.43(13), O9−C7−C13 103.38(13), O8−C13−O6 123.59(17), C7−C13−O6 127.18(8), O9−C14−O8 105.75(16), C19−C14−C15 113.1(2), C18−C19−C14 121.7(3), C17−C18−C19 123.1(4), C14−C19−O7 110.23(19), C19−O7−C20 119.8(2); intermolecular hydrogen bonds were found between O5 and O4 via H51 [O···O4 2.9728(17), H51···O4 2.23(3) Å, O5−O51···O4 146(2)°; symmetry operator of O4: $x - 1/2, 3/2 - y, 2 - z$]



Scheme 7. Major products derived from the reaction of **15** with TMB

Caffeoyl esters **4** and **5** were obtained after hydrolysis in 36% and 60% overall yields from **1**. On the other hand, quinic acid derivatives with a free hydroxy group at either C-4 or C-5, respectively, were not obtained in sufficient quantities. Neither quinide **9**, under thermodynamic conditions, nor silyl ether **10**, under kinetic reaction conditions, reacted with TMB to give acetals with an unprotected hydroxy group at C-4. Treatment of **15** with TMC or TMB afforded several crystalline reaction products, which were identified by X-ray diffraction. Unexpectedly, diacetal **20**, derived from a vicinal *cis*-diol, has two perfectly *trans*-diaxi-



Scheme 8. Synthesis of neochlorogenic acid (**5**)

ally oriented methoxy groups, forcing the quinide ring into a twist-boat conformation.

Experimental Section

General Procedures: All reactions were performed in dried glassware under N_2. Standard reagents and solvents were purified according to known procedures.[24] – Thin layer chromatographic (TLC) analyses were performed on Merck 60 F_{254} silica gel plates. Column-chromatographic purifications ("flash chromatography", FC) were performed as described.[25] – 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. – Infrared (IR) spectra were recorded with a Perkin–Elmer FT-IR 16 PC instrument either from KBr plates or neat. – Ultraviolet (UV) spectra were obtained from alcoholic solutions utilizing an ATI UNICAM UV 3 instrument. – Mass spectra were measured by electron impact (EI), using a Finnigan MAT SSQ 710 instrument, and MALDI-MS were recorded with a Bruker Reflex II (positive ion mode, matrix: THAP). – Elemental analyses were performed with a LECO CHNS-932 instrument.

Preparation of Ester 8: DMAP (0.18 g, 1.5 mmol) and acid chloride **6**[12] (1.97 g, 7.0 mmol) were added at room temperature to a solution of acetone quinide **7**[14] (1.07 g, 5.0 mmol) and pyridine (1 mL) in CH_2Cl_2 (40 mL). The reaction mixture was stirred at room temperature (4 h) and was then quenched by slow addition of 1 M aqueous HCl solution (pH ≈ 3). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried with $MgSO_4$ and filtered, and the solvents were removed under reduced pressure. Chromatography of the residue (SiO_2, 4 × 35 cm, 33% EtOAc/light petroleum ether) followed by recrystallization afforded 1.33 g (58%) of ester **8** as white crystals. – M.p. 126–128 °C. – $[\alpha]_D^{25}$ = +1.8 (*c* = 0.2, CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ = 2987, 1803, 1774, 1720, 1639, 1212, 1169 cm^{-1}. – ^{1}H NMR: δ = 7.65 (d, *J* = 15.9 Hz, 1 H), 7.40 (dd, *J* = 8.3, 1.8 Hz, 1 H), 7.36 (d, *J* = 1.8 Hz, 1 H), 7.28 (d, *J* = 8.3 Hz, 1 H), 6.38 (d, *J* = 15.9 Hz, 1 H), 4.81 (dd, *J* = 6.3, 2.3 Hz, 1 H), 4.56 (ddd, *J* = 7.4, 6.7, 3.2 Hz, 1 H), 4.34 (br. d, *J* = 6.4 Hz, 1 H), 3.11 (br. dd, *J* = 11.4, 6.4 Hz, 1 H), 2.63 (d, *J* = 11.4 Hz, 1 H), 2.53 (ddd, *J* = 14.5, 7.6, 2.0 Hz, 1 H), 2.41 (dd, *J* = 14.5, 3.1 Hz, 1 H), 2.31 (s, 3 H), 2.30 (s, 3 H), 1.54 (s, 3 H), 1.34 (s, 3 H). – ^{13}C NMR: δ = 173.4 (s), 168.0 (s), 167.9 (s), 164.5 (s), 144.7 (d), 143.8 (s), 142.4 (s), 132.8 (s), 126.5 (d), 124.0 (d), 122.9 (d), 117.9 (d), 109.9 (s), 76.3 (s), 75.4 (d), 72.4 (d), 71.1 (d), 35.5 (t), 30.6 (t), 26.9 (q), 24.3 (q), 20.6 (q), 20.6 (q). – MS (70 eV): *m*/*z* (%) = 461 (4), 445 (6), 418 (14), 376 (100), 247 (9), 205 (29), 163 (95). – UV (EtOH): λ_{max} (ε) = 285 (14000), 204 (70000) nm. – $C_{23}H_{24}O_{10}$ (460.44): calcd. C 60.00, H 5.26; found C 59.74, H 5.42.

Preparation of 1-Caffeoylquinic Acid (2): A solution of ester **8** (0.46 g, 1.0 mmol) in a mixture of degassed THF (25 mL) and water (10 mL) was treated with LiOH (1 M in H_2O, 4.1 mL, 4.1 mmol) at room temperature. The brownish solution was stirred for 5 h at room temperature and acidified using aqueous 2 M HCl solution (pH ≈ 1). The yellow reaction mixture was stirred for an additional 17 h at room temperature and diluted by the addition of CH_2Cl_2 (50 mL). The aqueous layer was separated, saturated with solid NaCl, and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. The residue was triturated with warm Et_2O, providing 0.28 g (79%) of 1-caffeoylquinic acid (**1**) as amorphous solid. – ^{1}H NMR ([D$_4$]MeOH): δ = 7.56 (d, *J* = 15.9 Hz, 1 H), 7.05 (d, *J* = 1.7 Hz, 1 H), 6.96 (dd, *J* = 8.1, 1.7 Hz, 1 H), 6.79 (d, *J* = 8.1 Hz, 1 H), 6.28 (d, *J* = 15.9 Hz, 1 H), 4.17 (dd, *J* = 4.2, 3.3 Hz, 1 H), 4.09 (ddd, *J* = 10, 8, 4.2 Hz, 1 H), 3.52 (dd, *J* = 8.2, 3.1 Hz, 1 H), 2.57 (br. dd, *J* = 14.8, 3.1 Hz, 1 H), 2.45 (br. d, *J* = 13 Hz, 1 H), 2.20 (dd, *J* = 14.8, 3.0 Hz, 1 H), 1.96 (dd, *J* = 13.3, 9.9 Hz, 1 H). – ^{13}C NMR ([D$_4$]MeOH): δ = 175.4 (s), 168.1 (s), 149.6 (d), 147.3 (s), 146.8 (s), 127.8 (s), 123.0 (d), 116.5 (d), 115.3 (d), 115.1 (d), 81.6 (s), 76.2 (d), 69.5 (d), 67.9 (d), 39.6 (t), 35.9 (t). – MS (70 eV): *m*/*z* (%) = 336 (0.4), 180 (32), 163 (29), 60 (100).

Preparation of Ester 14: DMAP (0.05 g, 0.4 mmol) and caffeic acid chloride **6** (1.51 g, 5.3 mmol) were added at –10 °C to a solution of silyl ether **13**[18] (1.53 g, 5.3 mmol) in pyridine (15 mL). Additional chloride **6** was added after 2.5 h (0.37 g, 1.3 mmol) and 5 h (0.20 g, 0.7 mmol), and the reaction mixture was stirred at room temperature for 17 h. The brownish solution was poured onto ice/CH_2Cl_2. The mixture was acidified using 2 M HCl and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The residue was purified by FC (SiO_2, 5 × 30 cm, 25–70% EtOAc/light petroleum ether) and recrystallization from EtOAc/light petroleum ether to afford 1.55 g (55%) of ester **14** as colorless crystals. – M.p. 171–172 °C. – $[\alpha]_D^{23}$ = +12 (*c* = 0.2, CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ = 3447, 2954, 1791, 1742, 1711, 1638, 1229, 1206, 1119, 839 cm^{-1}. – ^{1}H NMR: δ = 7.66 (d, *J* = 15.9 Hz, 1 H), 7.43 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.40 (d, *J* = 1.8 Hz, 1 H), 7.25 (d, *J* = 8.4 Hz, 1 H), 6.44 (d, *J* = 15.9 Hz, 1 H), 5.43 (t, *J* = 4.7 Hz, 1 H), 4.85 (t, *J* = 5.3 Hz, 1 H), 4.04 (ddd, *J* = 9.6, 8.1, 4.7 Hz, 1 H), 2.79 (br. s, 1 H), 2.53 (d, *J* = 11.7 Hz, 1 H), 2.42 (dd, *J* = 11.7, 5.6 Hz, 1 H), 2.32 (s, 3 H), 2.31 (s, 3 H), 2.12–2.08 (m, 2 H), 0.81 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H). – ^{13}C NMR: δ = 177.3 (s), 168.0 (s), 165.2 (s), 144.2 (d), 143.8 (s), 142.5 (s), 132.9 (s), 126.6 (d), 124.0 (d), 122.8 (d), 118.3 (d), 74.2 (d), 72.0 (s), 66.6 (d), 65.9 (d), 40.9 (t), 37.5 (t), 26.5 (q), 20.6 (q), 17.9 (s), –5.1 (q). – MS (70 eV): *m*/*z* (%) = 535 (4), 477 (43), 321 (33), 279 (49), 247 (59), 205 (100), 163 (48). – UV (EtOH): λ_{max} (ε)= 282 (24000), 220 (17000) nm. – $C_{26}H_{34}O_{10}Si$ (534.63): calcd. C 58.41, H 6.42; found C 58.27, H 6.21.

Preparation of 4-Caffeoylquinic Acid (4): THF (ca. 4 mL) was added to a suspension of ester **14** (0.29 g, 0.54 mmol) in aq. HCl (1

M, 20 mL) until the solid was completely dissolved. The clear solution was stirred for 6 d at 23 °C and the reaction progress was monitored by TLC. The solution was saturated with solid NaCl and the aqueous layer extracted with EtOAc/THF (3:1, 3 × 20 mL). The combined organic extracts were dried with $MgSO_4$ and filtered, and the solvents were removed under reduced pressure. The pale yellow residue was recrystallized twice from a mixture of THF, Et_2O, and light petroleum ether, affording 0.16 g (83%) of **4** as a pale yellow powder containing small amounts of 5-caffeoylquinic acid (**5**) as indicated by the ^1H NMR spectrum. − ^1H NMR ([D$_4$]MeOH): δ = 7.64 (d, *J* = 15.9 Hz, 1 H), 7.06 (d, *J* = 1.8 Hz, 1 H), 6.96 (dd, *J* = 8.1, 1.8 Hz, 1 H), 6.78 (d, *J* = 8.1 Hz, 1 H), 6.37 (d, *J* = 15.9 Hz, 1 H), 4.80 (dd, *J* = 9.3, 3.0 Hz, 1 H), 4.37−4.23 (m, 2 H), 2.29−1.92 (m, 4 H). − ^{13}C NMR ([D$_6$]DMSO): δ = 175.2 (s), 166.3 (s), 148.3 (s), 145.6 (s), 144.8 (d), 125.6 (s), 121.2 (d), 115.8 (d), 114.7 (d), 114.6 (d), 77.0 (d), 74.1 (s), 66.6 (d), 63.8 (d), 40.9 (t), 37.6 (t). − MS (70 eV): *m*/*z* (%) = 336 (0.4), 180 (32), 163 (29), 60 (100).

Preparation of Compounds 18−22: TMSOTf (40 μL, 0.22 mmol) was added at −76 °C to a solution of silyl ether **15** (2.73 g, 4.94 mmol) and 1,1,2,2-tetramethoxycyclohexane (TMC, 2.32 g, 10.0 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at that temperature for 1 h and then maintained at −30 °C for 19 h. An additional quantity of TMSOTf (40 μL, 0.22 mmol) was added at −30 °C and the solution was maintained for a further 48 h at that temperature. The brownish solution was poured into a 1:1 mixture of sat. $NaHCO_3$ and NH_4Cl (40 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried using $MgSO_4$ and filtered, and the solvent was removed in vacuo. The residue was purified by FC (6 × 30 cm, 20−100% EtOAc/light petroleum ether → 5−20% MeOH/EtOAc), yielding 0.20 g (13%) of compound **18**, 0.20 g (13%) of compound **19**, 0.15 g (10%) of compound **20**, 0.36 g (17%) of compound **21**, and 0.29 g (17%) of compound **22** as pale yellow solids. Recrystallization of these compounds gave colorless crystals, suitable for X-ray crystallography (except for compound **22**). − **Compound 18:** M.p. 105−106 °C. − $[\alpha]_D^{30}$ = −25 (*c* = 0.16, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3585, 3477, 3195, 2948, 1787, 1640, 1165, 1068 cm^{-1}. − ^1H NMR: δ = 4.75 (dd, *J* = 5.7, 2.2 Hz, 1 H), 4.74 (td, *J* = 7.3, 3.0 Hz, 1 H), 4.51 (br. d, *J* = 6.4 Hz, 1 H), 3.28 (s, 6 H), 2.99 (s, 1 H), 2.55 (d, *J* = 11.7 Hz, 1 H), 2.35 (ddd, *J* = 14.7, 8.0, 2.2 Hz, 1 H), 2.30 (br. dd, *J* = 11.7, 6.4 Hz, 1 H), 2.15 (dd, *J* = 14.6, 2.8 Hz, 1 H), 1.80−1.68 (m, 4 H), 1.64−1.55 (m, 2 H), 1.54−1.44 (m, 2 H). − ^{13}C NMR: δ = 179.0 (s), 111.6 (s), 101.8 (s), 75.8 (d), 73.6 (s), 73.2 (d), 71.5 (d), 49.1 (q), 49.1 (q), 39.1 (t), 35.2 (t), 34.3 (t), 30.6 (t), 22.8 (t), 21.4 (t). − MS (70 eV): *m*/*z* (%) = 314 (0.2), 299 (2), 283 (2), 270 (1), 224 (10), 175 (6), 143 (10), 111 (32), 101 (100). − **Compound 19:** M.p. 146−147 °C. − $[\alpha]_D^{30}$ = −24 (*c* = 0.23, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3527, 3461, 2944, 1799, 1764, 1131, 1060 cm^{-1}. − ^1H NMR: δ = 4.82 (dd, *J* = 6.1, 2.9 Hz, 1 H), 4.47 (ddd, *J* = 7.8, 6.5, 4.0 Hz, 1 H), 4.29 (ddd, *J* = 6.5, 2.8, 0.9 Hz, 1 H), 3.31 (s, 3 H), 3.31 (s, 3 H), 3.27 (s, 1 H), 3.06 (d, *J* = 11.6 Hz, 1 H), 2.46 (dd, *J* = 14.2, 4.0 Hz, 1 H), 2.34−2.24 (m, 2 H), 1.86−1.72 (m, 2 H), 1.68−1.63 (m, 2 H), 1.56−1.47 (m, 4 H). − ^{13}C NMR: δ = 179.2 (s), 112.5 (s), 98.9 (s), 76.1 (d), 71.7 (d), 71.6 (d), 71.6 (s), 49.7 (q), 49.4 (q), 38.0 (t), 34.3 (t), 31.9 (t), 31.2 (t), 22.4 (t), 21.5 (t). − MS (70 eV): *m*/*z* (%) = 314 (0.2), 299 (2), 283 (1), 270 (1), 224 (10), 175 (7), 143 (8), 111(29), 101 (100). − **Compound 20:** M.p. 248−249 °C. − $[\alpha]_D^{30}$ = −120 (*c* = 0.06, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3471, 2955, 1773, 1081, 1049 cm^{-1}. − ^1H NMR: δ = 4.74 (dd, *J* = 6.0, 4.4 Hz, 1 H), 4.40 (t, *J* = 4.7 Hz, 1 H), 3.88 (ddd, *J* = 11.6, 7.3, 5.2 Hz, 1 H), 3.24 (s, 3 H), 3.24 (s, 3 H), 2.86 (s, 1 H), 2.79 (t, *J* = 11.6 Hz, 1 H), 2.62 (d, *J* = 11.6 Hz, 1 H), 2.38 (ddd, *J* = 11.4, 6.0, 2.7 Hz, 1 H), 2.17 (ddd, *J* = 11.7, 7.3, 2.7 Hz, 1 H), 1.87−1.65 (m, 4 H), 1.62−1.48 (m, 2 H), 1.47−1.24 (m, 2 H). − ^{13}C NMR: δ = 177.8 (s), 98.5 (s), 97.6 (s), 75.8 (d), 72.3 (s), 66.8 (d), 62.4 (d), 47.7 (q), 47.0 (q), 39.2 (t), 37.3 (t), 27.9 (t), 26.8 (t), 21.3 (t), 21.0 (t). − MS (70 eV): *m*/*z* (%) = 315 (30), 299 (32), 283 (68), 175 (70), 111 (89), 67 (100). − **Compound 21:** M.p. 190−192 °C. − $[\alpha]_D^{29}$ = +74 (*c* = 0.25, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3556, 2944, 1797, 1664, 1271, 1102, 1058 cm^{-1}. − ^1H NMR: δ = 4.99 (t, *J* = 4.1 Hz, 1 H), 4.37 (ddd, *J* = 12.5, 10.5, 4.2 Hz, 1 H), 4.17 (br. s, 1 H), 3.72 (dd, *J* = 10.5, 2.9 Hz, 1 H), 3.54 (s, 3 H), 3.22 (s, 3 H), 3.20 (s, 3 H), 2.72 (br. d, *J* = 5 Hz, 1 H), 2.46 (ddd, *J* = 12.9, 4.1, 1.4 Hz, 1 H), 2.18−2.05 (m, 6 H), 1.90 (t, *J* = 12.8 Hz, 1 H), 1.85−1.71 (m, 6 H), 1.57−1.34 (m, 4 H). − ^{13}C NMR: δ = 173.6 (s), 150.0 (s), 106.8 (s), 102.2 (d), 99.1 (s), 98.6 (s), 80.3 (s), 73.3 (d), 68.6 (d), 62.8 (d), 54.6 (q), 46.8 (q), 46.7 (q), 39.4 (t), 37.6 (t), 36.7 (t), 27.0 (t), 27.0 (t), 23.4 (t), 21.3 (t), 20.1 (t). − MS (70 eV): *m*/*z* (%) = 440 (4), 425 (38), 409 (100), 377 (11), 283 (4), 127 (12). − **Compound 22:** M.p. 149−150 °C. − $[\alpha]_D^{29}$ = +105 (*c* = 0.16, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3457, 3288, 2929, 1744, 1181, 1100, 1060 cm^{-1}. − ^1H NMR: δ = 4.48 (ddd, *J* = 12.0, 10.5, 4.1 Hz, 1 H), 4.27 (br. s, 1 H), 4.21 (m, 1 H), 3.79 (s, 3 H), 3.74 (dd, *J* = 10.4, 2.7 Hz, 1 H), 3.36 (br. s, 1 H), 3.22 (s, 3 H), 3.22 (s, 3 H), 2.18 (dt, *J* = 14.8, 2.8 Hz, 1 H), 2.10 (ddd, *J* = 12.9, 4.6, 2.8 Hz, 1 H), 2.05 (dd, *J* = 14.8, 2.9 Hz, 1 H), 1.97 (t, *J* = 12.4 Hz, 1 H), 1.88−1.67 (m, 4 H), 1.60−1.30 (m, 4 H). − ^{13}C NMR: δ = 174.3 (s), 99.1 (s), 98.7 (s), 75.8 (s), 73.6 (d), 69.4 (d), 63.0 (d), 52.9 (q), 46.8 (q), 38.9 (t), 37.6 (t), 27.1 (t), 26.9 (t), 21.3 (t), 21.3 (t). − MS (70 eV): *m*/*z* (%) = 346 (4), 331 (32), 315 (100), 283 (13), 255 (7), 175 (10), 143 (70).

Preparation of Compounds 23 and 24: TMSOTf (40 μL, 0.22 mmol) was added at −76 °C to a solution of silyl ether **15** (2.75 g, 4.97 mmol) and 2,2,3,3-tetramethoxybutane (TMB, 4.5 g, 25 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at that temperature for 1 h and maintained at −30 °C for 46 h. An additional quantity of TMSOTf (40 μL, 0.22 mmol) was added at −30 °C and the solution was maintained at that temperature for a further 6 d. The brownish solution was poured into a 1:1 mixture of sat. $NaHCO_3$ and NH_4Cl (40 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried using $MgSO_4$ and filtered, and the solvent was removed in vacuo. The residue was purified by FC (6 × 30 cm, 20−100% EtOAc/light petroleum ether → 5−20% MeOH/EtOAc), yielding 0.44 g (13%) of compound **23**, and 0.20 g (17%) of compound **24** as pale brown solids. Recrystallization of these compounds gave colorless crystals. − **Compound 23:** M.p. 140−141 °C. − $[\alpha]_D^{30}$ = −18 (*c* = 0.23, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3486, 3374, 2954, 1789, 1100, 1068 cm^{-1}. − ^1H NMR: δ = 4.81 (dd, *J* = 6.1, 2.7 Hz, 1 H), 4.49 (ddd, *J* = 7.6, 6.8, 4.0 Hz, 1 H), 4.32 (dd, *J* = 6.3, 2.2 Hz, 1 H), 3.29 (s, 3 H), 3.01 (d, *J* = 11.6 Hz, 1 H), 2.81 (s, 1 H), 2.41 (dd, *J* = 14.4, 4.0 Hz, 1 H), 2.32−2.22 (m, 1 H), 1.37 (s, 3 H), 1.33 (s, 3 H). − ^{13}C NMR: δ = 179.0 (s), 113.2 (s), 100.9 (s), 76.1 (d), 71.9 (d), 71.8 (d), 71.7 (s), 49.9 (q), 38.2 (t), 34.4 (t), 20.1 (q), 18.7 (q). − MS (70 eV): *m*/*z* (%) = 257 (2), 199 (13), 185 (2), 139 (4), 111 (12), 89 (100). − **Compound 24:** M.p. 148−149 °C. − $[\alpha]_D^{26}$ = +106 (*c* = 0.3, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3478, 2948, 1797, 1130, 1033 cm^{-1}. − ^1H NMR: δ = 4.19 (ddd, *J* = 12.5, 10.2, 4.3 Hz, 1 H), 4.15 (br. q, *J* = 3 Hz, 1 H), 3.56 (dd, *J* = 10.2, 3.1 Hz, 1 H), 3.29 (s, 3 H), 3.27 (s, 6 H), 3.23 (s, 3 H), 2.50 (br. s, 1 H), 2.44 (ddd, *J* = 13.0, 4.1, 2.6 Hz, 1 H), 2.09 (dt, *J* = 15.0, 2.7 Hz, 1 H), 2.01 (dd, *J* = 15.0, 3.2 Hz, 1 H), 1.81 (dd, *J* = 13.0, 12.5 Hz, 1 H), 1.62 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 1.30 (s, 3 H). − ^{13}C NMR: δ = 173.3 (s), 111.8 (s), 100.7 (s), 100.1 (s), 99.7 (s), 80.1 (s), 72.4 (d), 68.2 (d),

62.3 (d), 49.8 (q), 49.7 (q), 47.9 (q), 47.4 (q), 39.5 (t), 36.0 (t), 23.0 (q), 18.6 (q), 17.7 (q), 17.6 (q). − MS (70 eV): *m/z* (%) = 389 (11), 357 (6), 331 (3), 240 (9), 115 (52), 101 (93), 89 (100).

Preparation of Ester 26: DMAP (0.06 g, 0.5 mmol) and acid chloride **6** (1.65 g, 5.8 mmol) were added at room temperature to a solution of alcohol **25**[17] (1.54 g, 4.8 mmol) in CH_2Cl_2 (20 mL) and pyridine (4.0 mL). The reaction mixture was stirred for 24 h and quenched by the addition of 1 M HCl (pH ≈ 3). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried with $MgSO_4$ and filtered, and the solvents were evaporated in vacuo. The residue was purified by FC (SiO_2, 4 × 30 cm, 33−100% EtOAc/light petroleum ether), providing 2.40 g (88%) of ester **26** as a colorless, amorphous powder. − M.p. 72−74 °C. − $[\alpha]_D^{23}$ = +56 (*c* = 0.2, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3504, 2953, 1777, 1735, 1713, 1639, 1207, 1132 cm^{-1}. − ^1H NMR: δ = 7.65 (d, *J* = 15.9 Hz, 1 H), 7.42 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.38 (d, *J* = 1.8 Hz, 1 H), 7.23 (d, *J* = 8.4 Hz, 1 H), 6.45 (d, *J* = 15.9 Hz, 1 H), 5.36 (t, *J* = 3 Hz, 1 H), 4.42 (td, *J* = 9.9, 6.7 Hz, 1 H), 3.79 (s, 3 H), 3.72 (dd, *J* = 10.1, 3.2 Hz, 1 H), 3.31 (s, 3 H), 3.27 (s, 3 H), 3.19 (s, 1 H), 2.31 (s, 3 H), 2.30 (s, 3 H), 2.26 (br. d, *J* = 15.7 Hz, 1 H), 2.12 (dd, *J* = 15.5, 3.2 Hz, 1 H), 2.06−1.96 (m, 2 H), 1.30 (s, 3 H), 1.28 (s, 3 H). − ^{13}C NMR: δ = 175.5 (s), 168.1 (s), 168.0 (s), 166.2 (s), 143.4 (s), 143.1 (d), 142.4 (s), 133.3 (s), 126.5 (d), 123.8 (d), 122.7 (d), 119.6 (d), 74.5 (s), 71.2 (d), 69.9 (d), 62.7 (d), 53.2 (q), 48.04 (q), 47.95 (q), 38.7 (t), 36.6 (t), 20.63 (q), 20.58 (q), 17.8 (q), 17.6 (q). − MS (70 eV): *m/z* (%) = 535 (100), 503 (12), 477 (34), 334 (23), 247 (23), 205 (76), 197 (43), 180 (55), 163 (82). − UV (EtOH): λ_{max} (ε)= 280 (20000), 219 (15000) nm. − $C_{27}H_{34}O_{13}$ (566.56): calcd. C 57.24, H 6.05; found C 57.08, H 6.17.

Preparation of 5-Caffeoylquinic Acid (5): Ester **26** (2.40 g, 4.24 mmol) was dissolved in a mixture of 1 M aq. HCl (120 mL) and THF (40 mL) at 23 °C. The mixture was stirred at that temperature for 7 d, during which it turned yellow (formation of diacetyl). The progress of hydrolysis was monitored by TLC. After completion of the reaction, the aqueous phase was saturated with solid NaCl and extracted with EtOAc/THF (3:1, 4 × 60 mL). The combined organic extracts were dried with $MgSO_4$ and filtered, and the solvents were removed under reduced pressure. The yellow residue was recrystallized twice from a mixture of THF, Et_2O, and light petroleum ether, providing compound **5** (1.22 g, 81%) as a pale yellow powder containing small amounts of 4-caffeoylquinic acid (**4**) as indicated by ^1H NMR. − ^1H NMR ([D$_4$]MeOH): δ = 7.58 (d, *J* = 15.9 Hz, 1 H), 7.04 (d, *J* = 1.8 Hz, 1 H), 6.94 (dd, *J* = 8.1, 1.8 Hz, 1 H), 6.77 (d, *J* = 8.1 Hz, 1 H), 6.31 (d, *J* = 15.9 Hz, 1 H), 5.35 (m, 1 H), 4.16 (ddd, *J* = 9.5, 8.5, 3.8 Hz, 1 H), 3.64 (dd, *J* = 8.5, 3.2, 1 H), 2.25−1.91 (m, 4 H). − ^{13}C NMR ([D$_6$]DMSO): δ = 176.0 (s), 166.1 (s), 148.2 (s), 145.6 (s), 144.4 (d), 125.7 (s), 121.1 (d), 115.8 (d), 115.1 (d), 114.6 (d), 72.9 (s), 71.3 (d), 71.0 (d), 67.2 (d), 39.2 (t), 35.1 (t). − MS (70 eV): *m/z* (%) = 336 (0.4), 180 (32), 163 (29), 60 (100).

Crystal Structure Determinations: The crystals were measured with a STADI-4, four-circle, computer-controlled, single-crystal diffractometer. Crystal data and details of structure determinations and refinements are summarized in Table 1. − Crystallographic data (excluding structure factors) for the structures included in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-154963 (**20**) and -154964 (**21**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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