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Synthesis of *p*-coumaroylquinic acids and analysis of their interconversion

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ABSTRACT

The synthesis of four isomers of *p*-coumaroylquinic acids was performed by esterification of *p*-acetylcoumaroylchloride with a suitably protected (−)-quinic acid. All isomers have been characterized by means of NMR spectroscopy and circular dichroism. Acyl migration was observed in the synthesis of 3-*O*-*p*-coumaroylquinic acid and 4-*O*-*p*-coumaroylquinic acid. Calculations on the most stable conformations of all isomers have also been performed to explain the acyl migration observed during the synthesis procedure.

1. Introduction

Chlorogenic acids belong to the family of phenolic compounds often found in plants,[1,2] that are secondary metabolites involved in defense mechanisms against environmental stress.[3] Although chlorogenic acids are present in many vegetables[4] and fruits, such as potatoes, pears, apples and berries,[5] green coffee beans are particularly rich in these compounds.[6,2] Coffee is in fact the main source of chlorogenic acids in the human diet.[5] Moreover, chlorogenic acids can be used as indicators of coffee quality,[5,7] since the final content of chlorogenic acids and their corresponding lactones formed after roasting are responsible for the acidity and bitterness of the beverage.[6,8] Over the last few years, some health benefits have also been associated with chlorogenic acids and several reports have claimed that chlorogenic acids can contribute to the prevention of cardiovascular diseases and types 2 diabetes.[5,9–11] Chlorogenic acids are esters formed between *trans*-cinnamic acids (such as caffeic, ferulic and *p*-coumaric acid) and quinic acid;[12] therefore, depending on the type of cinnamic acid and on which hydroxyl group of the cyclohexane ring in the quinic acid is esterified, a great variety of chlorogenic acids can be formed, not only as monoesters but also as di- and triesters.[13] The total content of chlorogenic acids in coffee depends on the coffee species (*Coffea arabica* 4–8% and *Coffea canephora* 7–14% of the dry matter basis),[2,14] but also on the degree of roasting, the agriculture practices as well as the soil composition.[3] The most abundant CGA is 5-caffeoylquinic acid **2b** (also called chlorogenic acid, Fig. 1), but a total number of 76 chlorogenic acids have been isolated and identified in the last few years.[10] *p*-Coumaroylquinic acids are less abundant and for this reason are the less studied[10] so there is a lack of information on their contribution to the aroma of coffee. The experimental procedure for the quantification of chlorogenic acids in coffee beans is relatively complex since it comprises of extraction, separation and purification processes and their identification and quantification is usually carried out by HPLC coupled with mass spectrometry.[3,6,10,14] For this reason, it is important to have analytical standards to unequivocally determine their presence in coffee. Since Panizzi et al.[15,16] reported the first synthesis of chlorogenic acids, several literature reports have described the synthesis of different isomers of caffeoylquinic acid (Sefkow et al.)[17,18] and feruloylquinic acid (Dokli et al.).[19] In 1961 Haslam et al.[20] synthesized for the first time 5-*O*-*p*-coumaroylquinic acid using a condensation reaction and subsequently in 1964[21] the same authors synthesized the other three isomers using acyl migration as the synthetic method. It is important to highlight that a different numbering system for the substituents on the cyclohexane ring was adopted, resulting in different names.[22] In the same way, Ma et al.[23] carried out the synthesis of 5-*O*-*p*-coumaroylquinic acid by condensation between quinic acid bisacetonide and *p*-acetylcoumaroylchloride, in order to evaluate its potential antifungal activity. Even though it seems that all the methods described in the literature involve the esterification of the quinic acid with an acyl chloride, to protect selectively the hydroxyl groups of the

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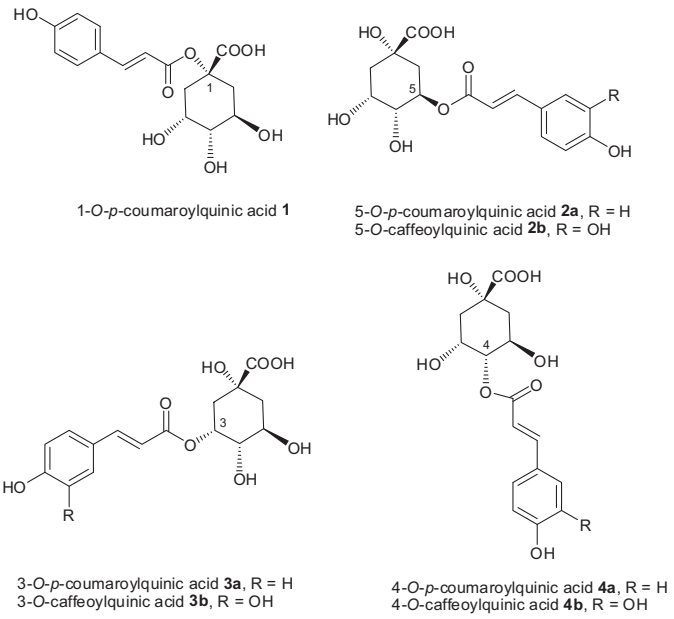


Figure 1.

cyclohexane ring, there is still a lack of information about the synthetic route and characterisation data of the different isomers of *p*-coumaroylquinic acid.

Herein we report the synthesis and characterization of four commercially unavailable isomers of *p*-coumaroylquinic acid: 1-*O*-*p*-coumaroylquinic acid **1**, 5-*O*-*p*-coumaroylquinic acid **2a**, 3-*O*-*p*-coumaroylquinic acid **3a,** 4-*O*-*p*-coumaroylquinic acid **4a** (Fig. 1) that were carried out with some modifications of the synthesis route proposed by Sefkow et al.[17,18] and Dokli et al.[19] The work is complemented by a computational study, which provided important evidence to explain the variations in outcome and chemical yields of the different reactions, as a result of the relative stability of the target products and their intermediates, together with side products resulting from interconversions.

2. Results and discussion

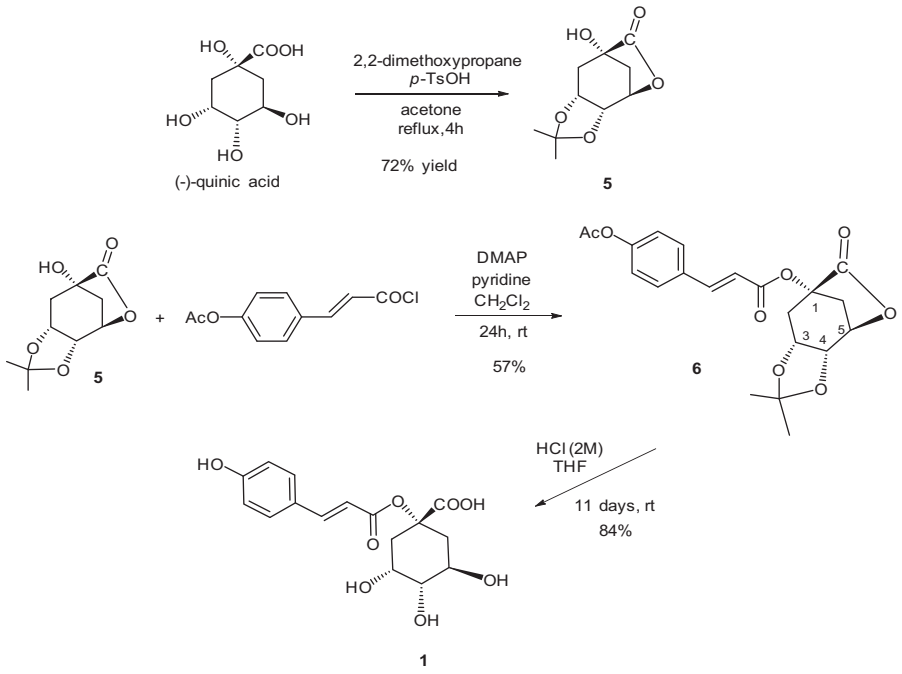
All *p*-coumaroylquinic acids were synthesized by coupling *p*-acetylcoumaroylchloride[18,24] with the different targeted (−)-quinic acids containing only one free hydroxyl group and all the other hydroxyl groups protected in different ways. Although there is no report in the literature of quinic acid rings esterified at position 1 occurring in coffee beans,[25] this compound was identified as one of the targets. It was envisaged that its availability would allow it to be used as a standard to further confirm the absence of these compounds in the natural source. The synthesis of 1-*O*-*p*-coumaroylquinic acid **1** was carried out according to Scheme 1. In the first step, the protection of the hydroxyl groups in positions 3,4 and 5 was achieved by a modified literature procedure.[19,26] Lactone **5** was synthesized in 72% yield and used in the next step without further purification. The second step involved the condensation reaction with *p*-acetylcoumaroylchloride, using DMAP with pyridine in dichloromethane at room temperature. The protected ester **6** was obtained in 57% yield after purification by column chromatography. The deprotection of all hydroxyl groups was performed under acidic conditions using HCl (2 M)/THF (4:1) with stirring for 11 days to give 1-*O*-*p*-coumaroylquinic acid **1** in 84% yield (Scheme 1).

The same lactone **5** was also used as the starting building block for the synthesis of 5-*O*-*p*-coumaroylquinic acid **2a**, following Scheme 2. The ethyl carboxylate **7**[19] was directly obtained by treatment with sodium ethoxide in ethanol resulting in an opening of the lactone ring of compound **5** and protection of the carboxylic group. ^{1}H NMR of the crude product revealed the presence of the ethyl carboxylate **7**, although in a mixture with lactone **5** in a 13:1 ratio. The crude product was esterified following the same protocol as with **1** and purified by column chromatography to give compound **8** in 48% yield. Protection of the hydroxyl group was not necessary since Pooter et al. demonstrated that under mild conditions, no esterification occurs at the axial C-1 hydroxyl group of quinic acid.[27] Deprotection was performed in 6 days in the presence of HCl (2 N)/THF to obtain 5-*O*-*p*-coumaroylquinic acid **2a** in 77% from the protected ester **8**.

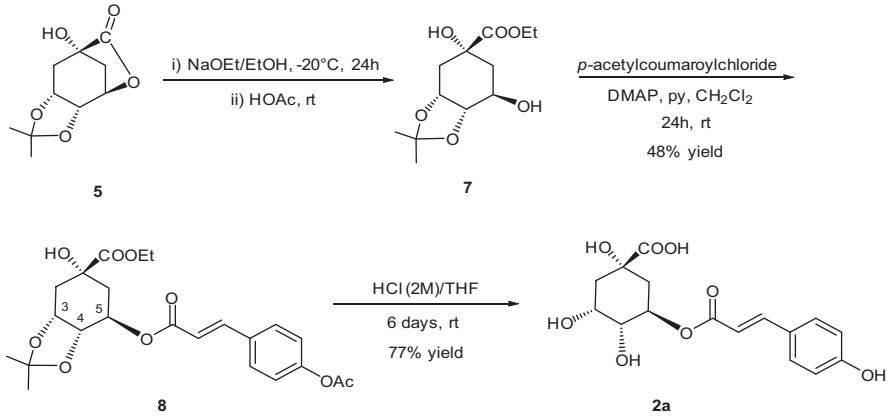
^{1}H NMR data are very similar to that of an authentic sample of 5-*O*-*p*-caffeoylquinic acid **2b** except for the aromatic ring protons, showing the same stereochemistry and conformation of the cyclohexane ring. The most stable conformation of compound **2a**, as well as that of **2b**, is the one with the ester and carboxylic groups in equatorial positions, the hydroxyl group at C-4 equatorial and hydroxyl group at C-3 axial. In compound **2b** this is clearly evidenced by the coupling constants and W_H of the proton signals at C-3, C-4 and C-5 (see Table 1). H-5 resonates at 5.34 with a W_H of 23.2, indicating an axial position while H-3 resonates at 4.16 with a W_H of 10.7 indicating an equatorial position. Compound **2a** had almost an identical spectra for the protons of the quinic ring thus demonstrating that both have the same conformation.

3-*p*-Coumaroylquinic acid **3a** was synthesized following Scheme 3. The carboxyl group of (−)-quinic acid was protected by esterification with MeOH, followed by protection of the hydroxyl groups at positions 4 and 5 using 2,2,3,3-tetramethoxybutane to give the protected methyl quinate **10**[17,19,29] with 15% overall yield from (−)-quinic acid. Coupling between *p*-acetylcoumaroylchloride and **10** under standard esterification conditions gave the corresponding ester **11** in 74% yield, after purification by column chromatography. Deprotection under acidic conditions by HCl (2 M)/THF (3:1) for 6 days afforded a 4:1 mixture of 3-*O*-*p*-coumaroylquinic acid **3a** and 4-*O*-*p*-coumaroylquinic acid **4a** (62% conversion yield) as determined by ^{1}H NMR. It is necessary to monitor the reaction by ^{1}H NMR since after a prolonged time, the hydrolysis reaction of the ester bond between quinic acid and *p*-coumaroyl moiety occurs. Compound **4a** could be recognized by ^{1}H NMR since a double of doublet at lower field (4.81 ppm) appeared, due to the presence of the acyl group at C-4, together with an overlapped signal of two protons at C-3 and C-5 at 4.32 ppm. Also in this case, the ^{1}H NMR spectrum of **3a** is very similar to the one of 3-*O*-caffeoylquinic acid **3b** (see Table 1) with respect to the most stable conformation. The W_H 17.8 of H-5 clearly shows that it is an axial proton while H-3 is an equatorial proton due to the lower W_H (13.7).

4-*O*-*p*-Coumaroylquinic acid **4a** was obtained after protection at positions 5 and 3 of the quinic acid ring following Scheme 4. 1,5-γ-Quinide was synthesized from (−)-quinic acid through dehydration in the absence of any solvent, as described by Wolinsky et al.[30] and the crude product was purified by heating under reflux in ethyl acetate as suggested by Raheem et al.[31] Recrystallizations of the brown sticky residue with EtOH or MeOH as suggested by Wolinsky et al. and other literature procedures[30,2] were not successful since compound **4** was obtained in less than 5% yield. Subsequently, protection with *tert*-butyldimethylsilylchloride (TBS) following a literature procedure[30,32] gave a mixture of monosilylated isomers in positions 3 and 4 of the cyclohexane ring in a 70:30 ratio (3-OTBDMS): (4-OTBDMS) with the protection at position 3 in the major product, as determined by ^{1}H NMR spectroscopy. Although several eluents were tried in order to separate the two isomers by flash chromatography, it



Scheme 1. Synthesis of 1-*O*-*p*-coumaroylquinic acid **1**.

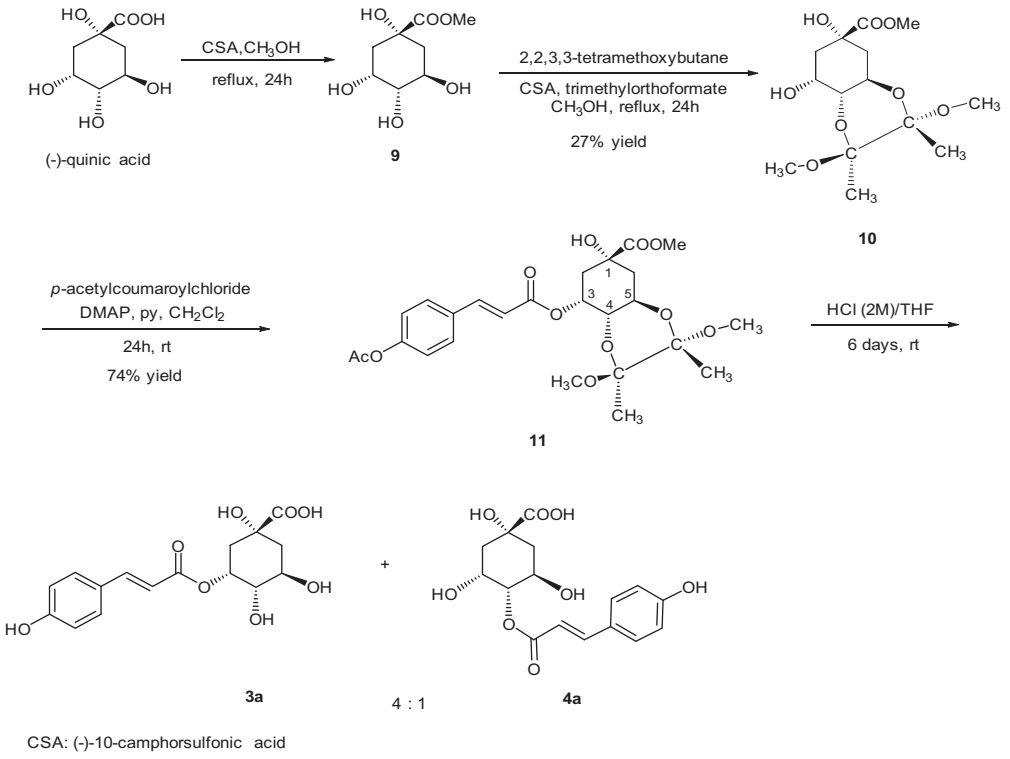


Scheme 2. Synthesis of 5-*O*-*p*-coumaroylquinic acid **2a**.

Table 1
^{1}H NMR in CD_3OD at 500 MHz

Compound	Ar protons	Vinyl protons	H-3	H-4	H-5	H-2 H-6
2a	7.47 (d, *J* 8.5), 6.81 (d, *J* 8.5)	7.62 (d, *J* 16.0), 6.32 (d, *J* 16.0)	4.17 (m, W_H 10.7)	3.72 (dd, J_1 3.6, J_2 8.2)	5.34 (dt, J_1 8.9, J_2 4.3, W_H 22.0)	2.16–2.25 (2H, m), 2.01–2.11 (2H,m)
2b[28]	7.05 (d, *J* 2.9), 6.96 (dd, J_1 8.8, J_2 2.9), 6.78 (d, *J* 8.8)	7.56 (d, *J* 14.7), 6.26 (d, *J* 14.7)	4.16 (m, W_H 10.7)	3.72 (dd, J_1 7.0, J_2 3.6)	5.34 (dt, J_1 8.9, J_2 5.3, W_H 23.2)	2.16–2.24 (2H, m), 2.02–2.10 (2H, m)
3a	7.47 (d, *J* 8.5), 6.81 (d, *J* 8.5)	7.67 (d, *J* 15.9), 6.39 (d, *J* 15.9)	5.39 (m, W_H 13.7)	3.71 (dd, J_1 7.6, J_2 2.7)	4.10 (m, W_H 17.8)	2.10–2.20 (3H, m), 1.93–2.02 (1H, m)
3b[28]	7.04 (d, *J* 2.4), 6.94 (dd, J_1 8.8, J_2 2.4), 6.78 (d, *J* 8.8)	7.58 (d, *J* 16.7), 6.31 (d, *J* 16.7)	5.35 (m, W_H 11.9)	3.65 (dd, J_1 8.7, J_2 4.3)	4.14 (dt, J_1 8.7, J_2 4.3, W_H 21.7)	2.11–2.22 (3H, m), 1.93–1.99 (1H, m)
4a	7.49 (d, *J* 8.6), 6.82 (d, *J* 8.6)	7.73 (d, *J* 15.9), 6.45 (d, *J* 15.9)	4.32 (m)	4.81 (dd, $J_1$10.0, J_2 2.8)	4.32 (m)	2.17–2.22 (2H, m), 2.00–2.10 (2H, m)
4b[28]	7.07 (d, *J* 3.1), 6.96 (dd, J_1 9.4, J_2 3.1), 6.78 (d, *J* 9.4)	7.64 (d, *J* 15.6), 6.37 (d, *J* 15.6)	4.28 (m)	4.80 (dd, J_1 9.6, J_2 3.8)	4.28 (m)	2.16–2.22 (2H, m), 1.98–2.08 (2H, m)

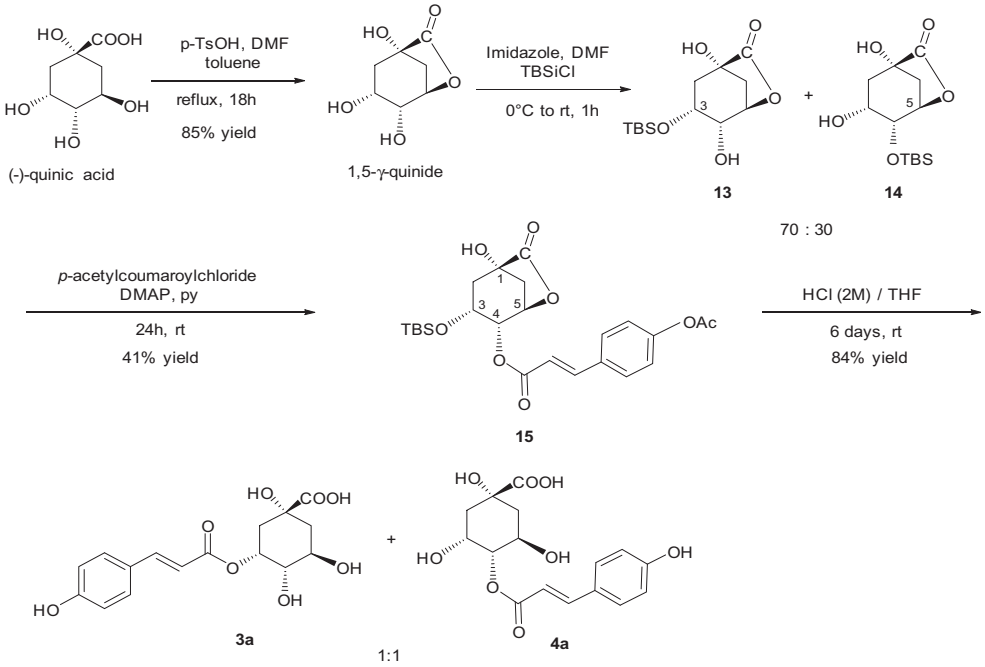
was not possible to isolate the 3-OTBDMS isomer as a pure compound so the mixture of the two was used in the next step. Esterification with *p*-acetylcoumaroylchloride**,** using pyridine as the solvent, as suggested by Sefkow et al.[17] and Dokli et al.,[19] gave only **15** as a pure compound**,** while no esterification at position 3 was observed as confirmed by ^{1}H NMR analysis of the crude product. Compound **15** was obtained in 41% yield after purification by column chromatography and subsequently deprotected under acidic



Scheme 3. Synthesis of 3-*O*-*p*-coumaroylquinic acid **3a**.

conditions HCl (2 M)/THF (3:1) to give a mixture of isomers **3a** and **4a** in a 1:1 ratio (43% of conversion yield from the protected ester). Since the starting compound was only isomer **15**, an acyl migration from the C-4 to the C-3 of the cyclohexane ring occurred as it was observed by ^{1}H NMR spectroscopy. This kind of rearrangement was already observed by Haslam et al. in 1964[21] when isomers 3- and 5-*O*-*p*-coumaroylquinic acid were obtained from 4-*O*-*p*-coumaroylquinic acid by treatment with sodium hydrogen carbonate. Although in our case the deprotection reaction was carried out under acidic conditions, it seems that the same acyl migration occurs probably by the formation of the intermediate orthoesters.

In order to explain the interconversions observed along the syntheses of the esters, we have carried out a computational analysis on the end products and on the main intermediates leading to their formation (Fig. 2).



Scheme 4. Synthesis of 4-*O*-*p*-coumaroylquinic acid **4a**.

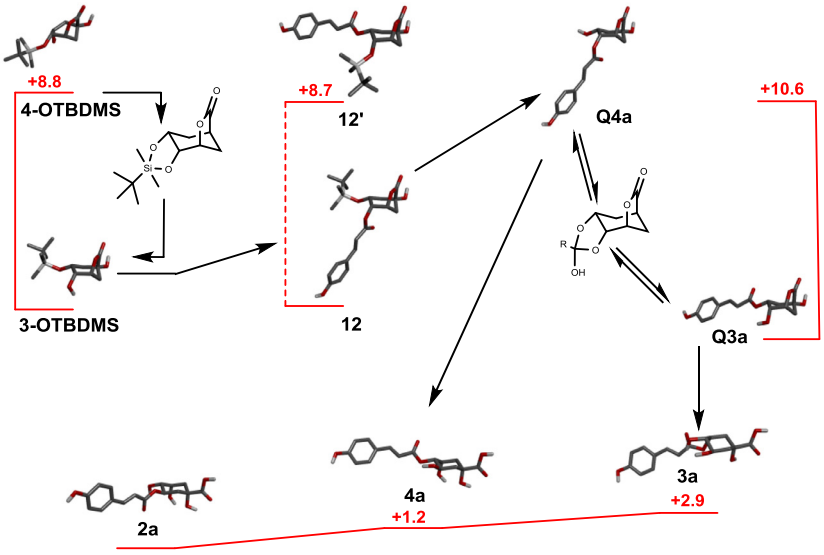


Figure 2. Computational analysis of the interconversions between products and between synthetic intermediates. The relative B3LYP/6.31G(d,p) energies are given in Kcal/mol.

The geometries of the products and intermediates were optimized first at the HF/6.31G(d) level, and then further refined with a DFT calculation carried out at the B3LYP/6.31G(d,p) level. The end products **2a**, **4a** and **3a** showed slight differences in energy, with the most stable being the 5-acyloyl derivative **2a**. This explains why its direct synthesis from compounds **7** and **8** is not affected by any isomerization. Esters **4a** and **3a** are only 1.2 and 2.9 Kcal/mol less stable, respectively. The overall conformation of the three compounds were very similar, with the carboxyl group at position 1 always found in an equatorial conformation. As a consequence, ester **3a** is the only product with the cumaroyl group in an axial conformation, as experimentally observed in the NMR spectra. The occurrence of a 20% **4a** in the synthesis of **3a** from the protected intermediate **9** (Scheme 3) can therefore be explained by the thermodynamically favored intramolecular acyl transfer from **3a** to **4a**, starting upon deprotection of **9**.

The synthesis of **4a**, as outlined in Scheme 4, involves more complex interconversions. The protection of the starting 1,5-γ-quinide may lead to two different silylated compounds and the 3-protected derivatives are the most abundant in the reaction crude, while compound **12** is the only product derived from the acylation of this mixture. 3-OTBDMS is actually much more stable that its isomer 4-OTBDMS, by 8.8 Kcal/mol. In quinides, at difference with quinic derivatives, position 4 is in fact axial, and for this reason the 4-protected compound is strongly destabilized and the bulky protecting group forces the quinide to a boat-like conformations. Full equilibration to the most stable 3-derivative is likely to occur easily, via a pentacoordinate silicon intermediate, and this may explain the fully selective transformation into compound **12**, which is even more stable than its isomer **12′** (Scheme 4). In the subsequent step of the synthesis, compound **12** was deprotected and hydrolyzed, and a 1:1 mixture of products **4a** and **3a** was obtained. Since **12** would lead directly to **4a**, and this compound is more stable than **3a**, the only explanation for the observed result may be if the deprotection occurs before the ring opening reaction of quinides intermediates **Q4a** and **Q3a** (Fig. 2). The relative stability of the two deprotected quinides is in fact reversed with respect to the end products, and **Q3a** is more stable by over 10 Kcal/mol. Interconversion thus happens at the quinide level and not at the product level in this synthetic path, and its outcome is the result of a complex competition between equilibria.

2.1. Circular dichroism

The Circular dichroism spectra of all isomers **1**–**4a** were registered and a comparison with the those obtained for the commercially available caffeoyl analogues **2b**–**4b** was made to verify the same absolute configuration of the stereocenters of the two series of compounds. Additionally, two different solvents were used, methanol and acetonitrile, in order to establish whether hydrogen bonding can modify the spectra.

In Figure 3, the circular dichroism spectra of all compounds in methanol are reported. The CD spectra of the *p*-coumaroylquinic acids **2a**–**4a** and those of the corresponding caffeoyl analogs **2b**–**4b** are very similar, indicating that they must have the same absolute configuration of the stereogenic centers. Furthermore, the same behavior is qualitatively observed for all compounds in both solvents (methanol and acetonitrile) used as it can be noticed comparing Figure 3 with Figure 4 indicating that the distributions of conformers are quite the same in both solvents.

Compounds **2a,b**–**3a,b** present a double Cotton effect, with a positive band in the range 290–340 nm and a negative band in the range 200–220 nm, while compounds **4a** and **4b** have both bands negative. It should be noted that **3a** and **3b** present also a third positive band in the range 220–260 nm.

3. Conclusion

In conclusion, all four isomers of *p*-coumaroylquinic acids were synthesized and characterized. The quantification of these compounds is very important in the area of coffee analysis and could be used as standards to evaluate a range of coffee matrices of different origins. The interconversion occurring between the isomers and during their synthesis have been explained on the basis of the relative stability of the isomers and of the intermediates leading to them.

4. Experimental

4.1. General

All reagents and solvents were purchased from Sigma–Aldrich and used without further purification. Dichloromethane was dried

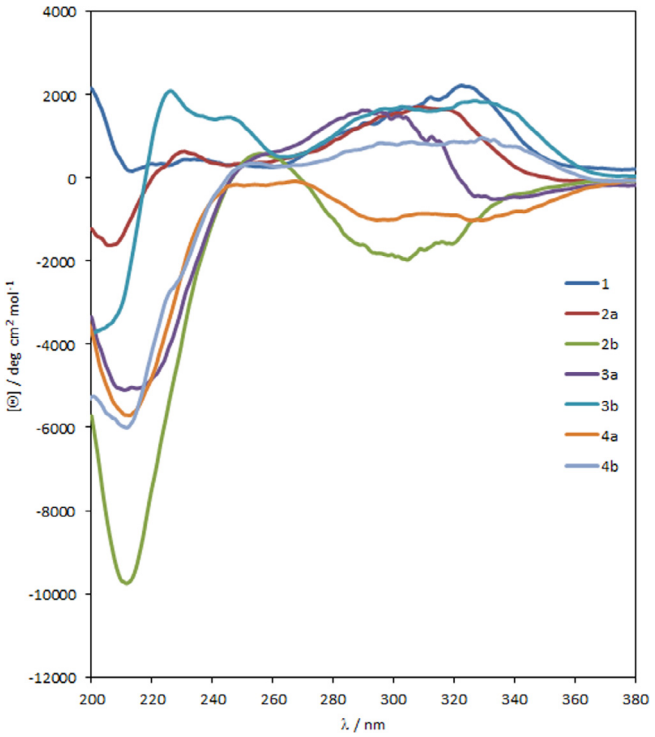


Figure 3. Circular dichroism spectra of compounds **1**–**4** in MeOH.

over $CaCl_2$. Caffeoylquinic acids **2b**–**4b** were purchased from Phytolab. Esterification reactions were performed under argon atmosphere. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} silica gel plates. ^1H and ^{13}C NMR spectra were recorded with a Varian 500 spectrometer (residual solvent peaks, δ = 7.26 ppm for $CDCl_3$ and 3.31 ppm for CD_3OD, were used as the internal standard). Electrospray Ionization (ESI) mass spectrometry measurements were performed with an Esquire 400 (Bruker-Daltonics) spectrometer. HRMS-ESI were obtained with a Waters Xevo Q-Tof spectrometer in negative mode. Infrared spectra (IR) were recorded with an Avatar 320-IR FTIR (ThermoNicolet). Optical rotations were recorded on a Jasco P2000 polarimeter at the wavelength of sodium D band (λ = 589) using a quartz cell of 1 dm length. Circular dichroism spectra were recorded on a Jasco J-710 spectropolarimeter. Melting points were measured with a Sanyo Gallenkamp apparatus and were uncorrected.

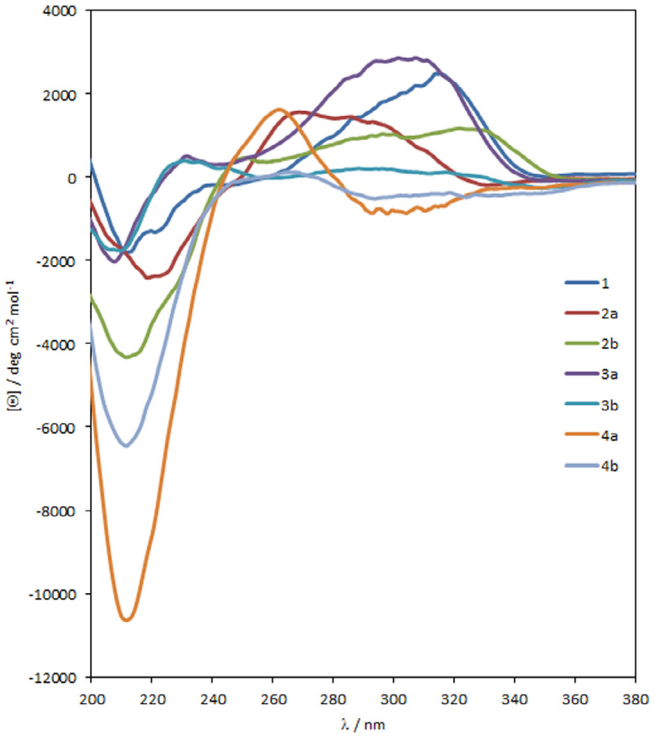


Figure 4. Circular dichroism spectra of compounds **1**–**4** in MeCN.

4.2. *p*-Acetylcoumaroylchloride

Acetic anhydride was added (4.66 g, 45.69 mmol) at 0 °C to a suspension of *p*-coumaric acid (5 g, 30.46 mmol) and DMAP (93 mg, 0.76 mmol) in pyridine (10 mL). The reaction was stirred for 3 h at room temperature and then poured onto crushed ice. After acidification with aq. HCl (pH < 2) acetyl *p*-coumaric acid was obtained as a white solid, which was filtered and washed with water (93% yield). Oxalyl chloride was added at −5 °C, to a suspension of acetyl *p*-coumaric acid (1 g, 4.85 mmol) in toluene (17 mL) containing two drops of DMF and the reaction was stirred at −5 °C for 2 h and then overnight at room temperature. The solvent was removed under reduced pressure to afford *p*-acetylcoumaroylchloride as a yellow solid in 95% yield. NMR data were in accordance with the literature data.[24]

4.3. 3,4-*O*-Isopropylidene-1,5-quinic lactone 5

2,2-Dimethoxypropane (4.87 g, 46.83 mmol) was added to a suspension of quinic acid (3 g, 15.61 mmol) and *p*-toluenesulfonic acid (216 mg, 1.15 mmol) in acetone (60 mL) and the mixture was heated at reflux for 2 h. After cooling, neutralization with $NaHCO_3$ (5%) was performed and the mixture was stirred for 1 h at room temperature. The reaction mixture was sequentially extracted with CH_2Cl_2 (three times, 20 mL at time) and washed with water (two times, 20 mL at time). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Lactone **5** was obtained as a white solid in 72% yield and was used in the next step without further purification. NMR data were in accordance with the literature.[26]

4.4. 1-Acetyl *p*-coumaroyl-3,4-*O*-isopropylidene quinide 6

3,4-*O*-Isopropylidene-1,5-quinic lactone **5** (500 mg, 2.33 mmol) was suspended in CH_2Cl_2 (20 mL), DMAP (86 mg, 0.7 mmol), pyridine (0.47 mL, 4.66 mmol) and *p*-acetylcoumaroylchloride (783 mg, 3.49 mmol) were added. The mixture was stirred 24 h at room temperature. The reaction mixture was diluted with CH_2Cl_2, and sequentially extracted with 1 M aqueous HCl solution (three times, 10 mL at time), $NaHCO_3$ (5%) (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (diethyl ether/CH_2Cl_2 = 1/1) to afford ester **6** (57%) as a colorless solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (1H, d, J = 16.0 Hz, CH=CH), 7.55 (2H, d, J = 8.6 Hz, Ar), 7.14 (2H, d, J = 8.6 Hz, Ar), 6.41 (1H, d, J = 16.0 Hz, CH=CH), 4.82 (1H, dd, J = 6.5, 2.5 Hz, H-4), 4.59 (1H, dt, J = 2.19, 6.9, H-5), 4.36 (1H, m, H-3), 3.11 (1H, m, H-6), 2.65 (1H, apparent d, H-6), 2.53 (1H, ddd, J = 14.0, 6.5, 2.3 Hz, H-2ax), 2.45 (1H, dd, J = 14.5, 3.2 Hz, H-2 eq), 2.31 (3H, s, CH_3CO), 1.54 (3H, s, CH_3), 1.35 (3H, s, CH_3); ^{13}C NMR (500 MHz, $CDCl_3$) δ 173.65 (s, COO), 169.21 (s, COO), 164.99 (s, COO), 152.59 (s, Ar), 145.71 (d, CH=CH), 131.86 (s, Ar), 129.59 (d, Ar), 122.37 (d, Ar), 117.09 (d, CH=CH), 110.14 (s, $C(CH_3)_2$), 76.39 (s, C-1), 75.57 (d, C-5), 72.64 (d, C-4), 71.33 (d, C-3), 35.82 (t, C-2), 30.87 (t, C-6), 27.15 C_{18} (q, $C(CH_3)_2$), 24.50 (q, $C(CH_3)_2$), 21.29 (q, CH_3CO).

4.5. 1-*O*-*p*-Coumaroylquinic acid 1

Ester **6** (500 mg, 1.24 mmol) was dissolved in a mixture of THF (10 mL) and aq. 2 M HCl (40 mL) and the yellowish solution formed was stirred for 11 days at room temperature. The solution was saturated with solid NaCl and then extracted with EtOAc (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. 1-*p*-coumaroylquinic acid **1** was obtained as a colorless solid in 84% from the corresponding protected ester **6**. Mp. 130–135 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.61 (1H, d, J = 15.9 Hz, CH=CH), 7.45 (2H, d, J = 8.6 Hz, Ar), 6.81 (2H, d, J = 8.6 Hz, Ar), 6.35 (1H, d, J = 15.9 Hz, CH=CH), 4.15 (1H, q, J = 4.3, Hz, H-5), 4.06 (1H, dt, J = 9.1, 3.6 Hz, H-3), 3.48 (1H, dd, J = 8.3, 3.3 Hz, H-4), 2.57 (1H, m, H-6), 2.44 (1H, m, H-2), 2.21 (dd, J = 14.9, 3.5 Hz, H-6), 1.91 (1H, dd, J = 13.8, 8.5 Hz, H-2);^{13}C NMR (500 MHz, CD_3OD) δ 174.91 (s, COO), 167.55 (s, COO), 160.79 (s, Ar), 146.40 (d, CH=CH), 130.67 (d, Ar), 126.73 (s, Ar), 116.30 (d, Ar), 114.97 (d, CH=CH), 80.95 (s, C-1), 75.77 (d, C-4), 69.13 (d, C-5), 67.40 (d, C-3), 39.40 (t, C-2), 35.38 (t, C-6); IR (nujol): $\tilde{\nu}$ = 3582.61, 3358.97, 2950, 1693.99, 1631.07, 1170.67, 1113.35, 831.61 cm^{-1}. MS (ESI$^+$): m/z [M+Na] = 361.0; HRMS (ESI$^-$): [M−H] = 337.092 (calculated: 337.092345); $[\alpha]_D^{20}$ = +5.1 (*c* 1.10, MeOH) (lit.[21] $[\alpha]_D^{22}$ = −5.0 (*c* 2, MeOH)); UV (MeOH): ε_{314} = 84200.

4.6. Ethyl 3,4-*O*-isopropylidene quinate 7

A suspension of crude lactone **5** (1 g, 4.67 mmol) in absolute EtOH (30 mL) was treated with NaOEt (12.71 mg, 0.19 mmol) dissolved in EtOH (160 μL). The brownish solution was stirred at room temperature for 2 h and then stored at −20 °C for 24 h. After quenching the unreacted NaOEt by the addition of acetic acid (13 μL) the solvent was removed under reduced pressure at 30 °C. The residue was a mixture of lactone **5** and ester **7** in a ratio 13:1 determined by ^{1}H NMR analysis. This crude mixture was used without further purification in the next step.[26,33]

4.7. Ethyl 5-*O*-acetyl-*p*-coumaroyl-3,4-*O*-isopropylidene quinate 8

To a solution of ethyl-3,4-*O*-isopropylidene quinate **7** (500 mg, 1.92 mmol), DMAP (35 mg, 0.15 mmol) and pyridine (6 mL) in CH_2Cl_2 (25 mL), *p*-acetylcoumaroylchloride (645.18 mg, 2.88 mmol) was added. The mixture was stirred for 24 h at room temperature and acidified with aq. HCl 1 M (pH 2–3) and then extracted with CH_2Cl_2 (three times, 50 mL at time). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brownish residue was purified by column chromatography on silica gel (diethyl ether/CH_2Cl_2 = 1/1) to afford ester **8** in 48% yield as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (1H, d, J = 15.9 Hz, CH=CH), 7.53 (2H, d, J = 8.6 Hz, Ar), 7.13 (2H, d, J = 8.6 Hz, Ar), 6.40 (1H, d, J = 15.9 Hz, CH=CH), 5.49 (1H, dt, J = 11.7, 4.5 Hz, H-5), 4.55 (1H, dt, J_1 = 3.7, J_2 = 5.6, H-3), 4.28–4.20 (3H, m, OCH_2+H-4), 2.31 (3H, CH_3CO), 2.32–2.28 (2H, m, H-2), 2.25 (1H, dd, J = 13.2, 4.4 Hz, H-6_{eq}), 1.94 (1H, dd, J = 13.3, 11.3 Hz, H-6_{ax}), 1.60 (s, C(CH_3)$_2$), 1.38 (s, C(CH_3)$_2$), 1.30 (3H, t, J = 7.2 Hz, CH_3CH_2);^{13}C NMR (500 MHz, $CDCl_3$) δ 174.48 (s, COO), 169.27 (s, COO), 166.03 (s, COO), 152.27 (s, Ar), 144.19 (d, CH=CH), 132.24 (s, Ar), 129.37 (d, Ar), 122.30 (d, Ar), 118.29 (d, CH=CH), 109.76 (s, *C*(CH_3)$_2$), 77.05 (d, C-3), 75.65 (s, C-1), 73.81(d, C-4), 71.11 (d, C-5), 62.36 (t, *C*H_2CH$_3$), 37.13 (t, C-6), 34.56 (t, C-2), 28.17 (q, C(*C*H_3)$_2$), 26.01 (q, C(*C*H_3)$_2$), 21.30 (q, *C*H_3CO), 14.28 (q, CH_3CH_2).

4.8. 5-*O*-*p*-Coumaroylquinic acid 2a

Ethyl 1-acetyl *p*-coumaroyl-3,4-*O*-isopropylidene quinate **12** (290 mg, 0.65 mmol) was dissolved in a mixture of THF (10 mL) and aq. 2 M HCl (40 mL) and the solution was stirred for 6 days at room temperature. After saturation with solid NaCl, the mixture was extracted with EtOAc (3 * 30 mL) and the organic phase was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave 5-*O*-*p*-coumaroylquinic acid as a colorless solid in 77% yield from the corresponding protected ester **12**.

Mp. 215–218 °C (lit.[20] 247–248 °C); IR (nujol): $\tilde{\nu}$ = 3582.67, 3302.38, 2917.48, 1687.13, 1633.37, 1170.30, 1080.85, 825.27 cm^{-1}; ^{1}H NMR is in accordance with literature data.[23] ^{13}C NMR (126 MHz, CD_3OD): δ 177.02 (s, C-7), 168.61 C_8 (s), 161.28 C_{14} (s), 146.68 C_{10} (d), 131.18 $C_{12,12'}$ (d), 127.23 C_{11} (s), 116.80 $C_{13,13'}$ (d), 115.33 C_9 (d), 76.15 C_1 (s), 73.41 C_4 (d), 72.00 C_5 (d), 71.15 C_3 (d), 38.77 C_2 (t), 38.22 C_6 (t).; MS (ESI$^+$): m/z [M+Na]: 361.4; $[\alpha]_D^{20}$ = −39.5 (*c* 0.79, MeOH).

4.9. 4,5-*O*-(2′,3′-Dimethoxybutane-2′,3′-dyil)-1,3-dihydroxycyclohexanecarboxylic acid methyl ester 10

To a suspension of quinic acid (1 g, 5.20 mmol) in MeOH (30 mL), (−)-10-camphorsulfonic acid (15 mg, 0.065 mmol) was added and the mixture was refluxed for 15 h under an Ar atmosphere. The methyl quinate **9** thus obtained was added with 2,2,3,3-tetramethoxybutane (1.01 g, 5.7 mmol), trimethylorthoformate (2.6 mL, 0.024 mmol) and (−)-10-camphorsulfonic acid (12 mg, 0.052 mmol) and the mixture was refluxed again. After 15 h the mixture was cooled and $NaHCO_3$ (0.1 g) was added. Solution was concentrated under reduced pressure and the orange suspension was partitioned between EtOAc (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted with EtOAc (30 mL) and the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Recrystallization of the brownish residue from EtOAc and hexane (1:5, v/v) afforded **10** in 27% yield as an orange oil. NMR data were in accordance with the literature.[19,29]

4.10. 3-Acetyl-*p*-coumaroyl-4,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1-hydroxycyclohexanecarboxylic acid methyl ester 11

4,5-*O*-(2′,3′-Dimethoxybutane-2′,3′-diyl)-1,3-dihydroxycyclohexanecarboxylic acid methyl ester **10** (122 mg, 0.38 mmol) was suspended in CH_2Cl_2 (20 mL) and DMAP (4.17 mg, 0.034 mmol), pyridine (320 μL, 4.03 mmol) and *p*-acetylcoumaroylchloride (128 mg, 0.57 mmol) were added. The mixture was stirred 24 h at room temperature and then acidified with aq. HCl 1 M (pH 2–3). After extraction with CH_2Cl_2 (three times, 30 mL at time) the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brownish residue was purified by column chromatography on silica gel (diethyl ether/CH_2Cl_2 = 1/1) to afford ester **11** in 74% yield as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (1H, d, J = 15.8 Hz, CH=CH), 7.57 (2H, d, J = 8.6 Hz, Ar), 7.14 (2H, d, J = 8.6 Hz, Ar), 6.47 (1H, d, J = 15.9 Hz, CH=CH), 5.38 (1H, q, J = 9.1 Hz, H-3), 4.45 (dt, J = 10.2, 5.6 Hz, H-5), 3.79 (3H, s, $COOCH_3$), 3.71 (1H, dd, J = 9.9, 3.2 Hz, H-4), 3.31 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 2.29 (3H, s, CH_3-CO), 2.28 (2H, m, H-2+H-6), 2.14 (1H, dd, J = 15.7, 3.2 Hz, H-2), 2.04 (1H, m, H-6); ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.62 (s, COO), 169.26 (s, COO), 166.61 (s, COO), 152.19 (s, Ar), 144.19 (d, CH=CH), 132.45 (s, Ar), 129.47 (d, Ar), 122.21 (d, Ar), 118.79 (d, CH=CH), 100.29 (s, *C*(OCH_3)), 99.73 (s, *C*(OCH_3)), 74.78 (s, C-1), 71.38 (d, C-4), 70.02 (d, C-3), 62.94 (d, C-5), 53.39 (q, *C*H_3COO), 48.3 (q, OCH_3), 48.14 (q,

OCH_3), 38.91 (t, C-6), 36.81 (t, C-2), 21.3 (q, CH_3CO), 18.03 (q, $CH_3C(OCH_3)$), 17.81 (q, $CH_3C(OCH_3)$).

4.11. 3-*O*-*p*-Coumaroylquinic acid 3a

3-Acetyl-*p*-coumaroyl-4,5-*O*-(2′,3′-dimethoxybutane-2′,3′-dyil)-1-hydroxycyclohexanecarboxylic acid methyl ester **11** (35 mg, 0.069 mmol) was dissolved in a mixture of THF (0.5 mL) and aq. 2 M HCl (1.5 mL) and the solution was stirred for 6 days at room temperature. After saturation with solid NaCl, the mixture was extracted with EtOAc (3 × 20 mL) and the organic phase dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a yellowish solid (62% yield), which was defined to be a mixture of 3-*p*-coumaroylquinic acid **3a** and 4-*p*-coumaroylquinic acid **4a** in a ratio of 8:2 as determined from ^{1}H NMR. The crude was purified by semi-preparative RP-HPLC on a Phenomenex Gemini C18 5 μm 10 × 250 mm column, using a gradient of H_2O+0,1% formic acid (A) and MeOH+0,1% formic acid (B), (20 min A 80% B 20%, from 20 to 90 min increase of B until A 40% B 60%, from 90 to 110 min A 5% B 95%, from 110 to 125 min A 95% B 5%) at a flow rate of 2 mL/min. The elution was monitored with an UV/vis detector λ 325 nm and the fractions corresponding to each peak were collected and keep at −80 °C and then freeze dried and analyzed by ^{1}H NMR. 3-*O*-*p*-coumaroylquinic acid **3a** (3 mg) was obtained as a white solid. Mp. 192–194 °C [lit.[21] 194 °C]; IR (nujol): $\tilde{\nu}$ = 3582.64, 3381.37, 2921.16, 1694.22, 1631.26, 1171.87, 1019.74, 831.37 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.67 (1H, d, J = 15.9 Hz, H-10), 7.47 (2H, d, J = 8.5 Hz, H-12), 6.81 (2H, d, J = 8.3 Hz, H-13), 6.39 (1H, d, J = 15.9 Hz, H_9), 5.39 (1H, m, W_H 13.7, H-3), 4.10 (1H, m, W_H 17.8, H-5), 3.71 (1H, dd, J = 7.6, 2.7 Hz, H-4), 2.20–1.93 (4H, m, H-2+H-6); ^{13}C NMR (500 MHz, CD_3OD) δ 177.59 (s, COO), 168.91(s, COO), 161.15 (s, Ar), 146.43 (d, CH=CH), 131.09 (d, Ar), 127.39 (s, Ar), 116.79 (d, Ar), 115.85 (d, CH=CH), 76.42 (s, C-1), 74.22 (d, C-4), 72.61 (d, C-3), 68.93 (d, C-5), 36.93 (t, C-2), 36.22 (t, C-6). MS (ESI$^+$): m/z [M+Na]: 361.0 $[\alpha]_D^{20}$ = +2.2 (c 0.12 MeOH) [lit.[21] $[\alpha]_D^{20}$ = −5.6 (c 0.6, MeOH)]; UV (MeOH): ε_{314} = 73,000.

4.12. 1,5-γ-Quinide

Quinic acid (3 g, 15.61 mmol) was heated in an open flask at 220 °C for 90 min. The brown sticky residue was refluxed with EtOAc (60 mL) for 4 h and then the solution was cooled to room temperature. The solvent was removed under pressure to give 1,5-γ-quinide as a colorless solid in 85% yield. NMR data were in accordance with the literature.[28,29]

4.13. 3-*tert*-Butyldimethylsiloxy-1,4-dihydroxy-cyclohexane-1,5-carbolactones 13 and 14

TBSi-Cl (1.31 g, 8.68 mmol) was added to a stirred solution of 1,5-γ-quinide (1.31 g, 7.55 mmol) and imidazole (1.9 g, 28 mmol) in anhydrous DMF (14 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min followed by 1 h at room temperature and then poured into water (50 mL) and extracted with EtOAc (50 ml) and diethyl ether (40 mL). The organic layer was washed with water (3 × 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a white solid in 57% yield containing esters **13** and **14** in a ratio of 7:3. The crude was used in the next step without further purification. NMR data were in accordance with the literature.[31,32]

4.14. 4-Acetyl-*p*-coumaroyl-3-*tert*-butyldimethylsiloxy-1-hydroxycyclohexane-1,5-carbolactone 15

To a solution of 3-*tert*-butyldimethylsiloxy-1,4-dihydroxy-cyclohexane-1,5-carbolactone, as a mixture of **13** and **14**, (500 mg, 1.74 mmol) and DMAP (32 mg, 0.26 mmol) in pyridine (15 mL), *p*-acetylcoumaroylchloride (700 mg, 3.12 mmol) was added. The mixture was stirred for 24 h at room temperature and then poured onto crushed ice, after which CH_2Cl_2 (20 mL) was added. The mixture was acidified with aq. HCl 1 M (pH 2–3) and then extracted with CH_2Cl_2 (three times, 30 mL at time). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brownish residue was purified by column chromatography on silica gel (diethyl ether/CH_2Cl_2 = 1/1) to afford the only ester **15**, in 41% yield, as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (1H, d, J = 15.9 Hz, CH=CH), 7.57 (2H, d, J = 8.6 Hz, Ar), 7.15 (2H, d, J = 8.6 Hz, Ar), 6.46 (1H, d, J = 15.9 Hz, CH=CH), 5.43 (1H, t, J = 4.8 Hz, H-4), 4.88 (1H, dt, J = 12.6, 5.3 Hz, H-5), 4.03 (1H, dt, J = 10.7, 4.6 Hz, H-3), 2.55 (1H, d, J = 11.8 Hz, H-6), 2.43 (1H, dd, J = 11.8, 5.8 Hz, H-6), 2.32 (3H, s, CH_3CO), 2.11 (2H, apparent d, H-2), 0.81 (9H, s, $C(CH_3)_3$), 0.06 (3H, s, CH_3Si), 0.03 (3H, s, CH_3Si); ^{13}C NMR (500 MHz, $CDCl_3$) δ 177.48 (s, COO), 169.27 (s, COO), 165.61 (s, COO), 152.50 (s, Ar), 145.15 (d, CH=CH), 131.98 (s, Ar), 129.53 (d, Ar), 122.38 (d, Ar), 117.40 (d, CH=CH), 74.42 (d, C-5), 72.15 (s, C-1), 66.68 (d, C-4), 66.06 (d, C-3), 41.14 (t, C-2), 37.64 (t, C-6), 25.71 (q, $C(CH_3)_3$), 21.28 (q, CH_3CO), 18.05 (s, $C(CH_3)_3$), −4.92 (q, $(CH_3)_2Si$).

4.15. 4-*O*-*p*-Coumaroylquinic acid 4a

4-*O*-Acetyl-*p*-coumaroyl-3-*tert*-butyldimethylsiloxy-1-hydroxycyclohexane-1,5-carbolactone **15** (332 mg, 0.7 mmol) was dissolved in a mixture of THF (5 mL) and aq. 2 M HCl (15 mL) and the solution was stirred for 6 days at room temperature. After saturation with solid NaCl, the mixture was extracted with EtOAc (3 x 50 mL) and the organic phase was dried over Na_2SO_4. Evaporation of the solvent gave a yellowish solid in 43% yield, which was a mixture of 3-*p*-coumaroylquinic acid **3a** and 4-*p*-coumaroylquinic acid **4a** as determined by ^{1}H NMR. The crude was purified by semi-preparative RP-HPLC on a Phenomenex Gemini C18 5 μm 10 x 250 mm column, using a gradient of H_2O+0,1% formic acid (A) and MeOH+0,1% formic acid (B) (20 min A 80% B 20%, from 20 to 90 min increase of B until A 40% B 60%, from 90 to 110 min A 5% B 95%, from 110 to 125 min A 95% B 5%) at a flow rate of 2 mL/min. A total of 4 runs were performed each one injecting 15 mg of crude. The elution was monitored with UV/vis detector λ 325 nm and the fractions corresponding to each peak were collected and kept at −80 °C and then freeze dried and analyzed by ^{1}H NMR. 4-*p*-coumaroylquinic acid **4a** (5 mg) was obtained as a white solid. Mp. 179–182 °C [lit.[21] 192–193 °C]; IR (nujol): $\tilde{\nu}$ = 3580, 3382.60, 2952.03, 1689.11, 1604.93, 1172.21, 1024.40.85, 830.63 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.73 (1H, d, J = 15.9 Hz, CH=CH), 7.49 (2H, d, J = 8.6 Hz, Ar), 6.82 (2H, d, J = 8.6 Hz, Ar), 6.45 (1H, d, J = 15.9 Hz, CH=CH), 4.81 (1H, dd, J = 10.0, 2.8 Hz, H-4), 4.32 (2H, m, H-3+H-5), 2.22 (4H, m, H-2+H-6); ^{13}C NMR (126 MHz, CD_3OD) δ 177.97 (s, COO), 168.97 (s, COO), 161.25 (s, Ar), 146.73 (d, CH=CH), 131.16 (d, Ar), 127.31 (s, Ar), 116.82 (d, Ar), 115.44 (d, CH=CH), 79.26 (d, C-4), 76.95 (s, C-1), 69.65 (d, C-5), 65.69 (d, C-3), 42.64 (t, C-6), 38.49 (t, C-2). MS (ESI$^+$): m/z [M+Na]: 361.0 $[\alpha]_D^{20}$ = −28.3 (c 0.3, MeOH) [lit.[21] $[\alpha]_D^{20}$ = −47.3 (c 1.4, MeOH); UV (MeOH): ε_{316} = 63,200.

4.16. Calculations

Preliminary molecular mechanics calculations and HF optimizations were performed using the Spartan 14 package[34] which was installed on an Antec P193 V3, with two six core AMD opteron Processor 2427 2.20 GHz, 4 GB RAM, 1 TB physical memory, and 64-bit Windows 7 Enterprise as operating system. Convergence criteria for geometry optimization were set as follows: energy 1.0 × 10^{-6} - hartrees, gradient tolerance 3 × 10^{-4} hartrees, distance tolerance 1.2 × 10^{-3} Å. The DFT simulations were performed on the same

machine with the Schrodinger suite of programmes using the B3LYP functional[35] and a localized 6-31G(d,p) basis set.

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