Tetrahedron: *Asymmetry* 24 (2013) 785–790

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Syntheses of 3-, 4-, and 5-*O*-feruloylquinic acids

Irena Dokli [a,*], Luciano Navarini [b], Zdenko Hameršak [a]

[a] *Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, PO Box 180, 10002 Zagreb, Croatia*
[b] *illycaffè s.p.a, via Flavia 110, I 34147 Trieste, Italy*

ARTICLE INFO

Article history:
Received 3 March 2013
Accepted 13 June 2013

ABSTRACT

The efficient synthesis of 3-, 4-, and 5-*O*-feruloylquinic acids starting from D-(−)-quinic acid is described. Esterification of suitably protected quinic acid derivatives with 3-(4-acetoxy-3-methoxyphenyl)-acryloyl chloride and subsequent hydrolysis of all the protecting groups afforded the title products in overall yields of 33%, 15%, and 45%, respectively, (from quinic acid).

1. Introduction

Numerous studies have shown a protective effect of moderate coffee drinking on several chronic and degenerative diseases such as diabetes, cardiovascular, and neurodegenerative disorders, however the mechanism behind this effect has yet to be elucidated.[1] Several researchers have suggested that the oxidative stress induced by reactive oxygen species may be neutralized by the antioxidant activity of some coffee compounds; caffeine,[2] melanoidins,[3] and polyphenols.[4] Chlorogenic acids (CGAs) represent the most abundant class of phenolic compounds in coffee, which may account for up to 12% of the dry matter of green coffee beans.[5] The term 'chlorogenic acid' in fact comprises of quinic acid derivatives, including caffeoyl, dicaffeoyl, *p*-coumaroyl, feruloyl, and caffeoylferuloyl among many others. The most abundant CGAs in coffee are caffeic acid esters, including 5-*O*-caffeoylquinic and its isomers 3- and 4-*O*-caffeoylquinic.[6] Additionally, the isomers of dicaffeoylquinic acids, feruloylquinic acids, diferuloylquinic acids, and *p*-coumaroylquinic acids, and many others are found in green coffee beans.[4,6]

Feruloylquinic acid isomers are minor CGAs from a quantitative point of view and are approximately 4% of the total CGA content in green coffee beans.[7] For this reason feruloylquinic acid isomers have not yet been the subject of detailed investigations. The absence of commercially available standards has led to the necessity of employing hyphenated techniques, such as LC–MS/MS, in order to investigate this class of compounds.[8] Their quantitative determination in coffee brews is not routinely performed and their biological activity and metabolic fate are scarcely investigated.[9]

There are several synthetic approaches to quinic acid esters. Sefkow et al., described the synthesis of 1-, 3-, 4-, and 5-caffeoylquinic acids based on the esterification of quinic acid by cinnamic acid derivatives.[10,11] In another approach, the key reaction was a Knoevenagel condensation of a suitable aldehyde and a malonate ester of quinic acid to form a cinnamic (*E*)-double bond.[12]

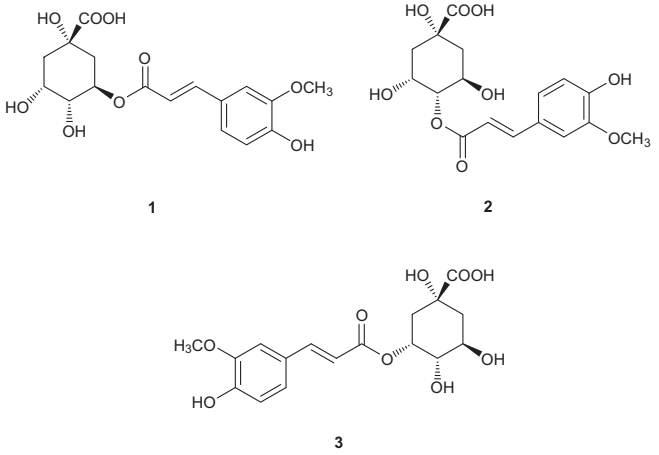


Figure 1. 3-, 4-, and 5-*O*-feruloylquinic acid isomers.

Herein we report the preparation of three feruloylquinic acid isomers: 3-*O*-feruloylquinic acid **1**, 4-*O*-feruloylquinic acid **2,** and 5-*O*-feruloylquinic acid **3** shown in Figure 1. We used Sefkow's synthetic strategy for the synthesis of caffeoylquinic acids with a few modifications.

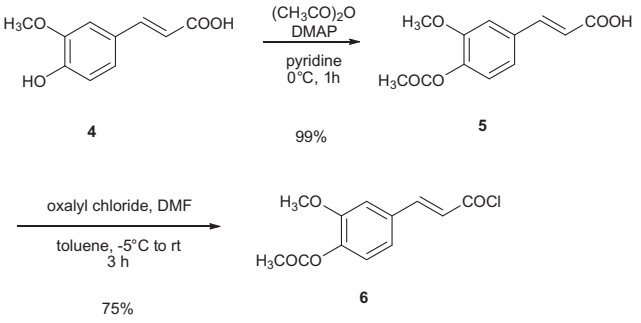
2. Results and discussion

3-(4-Acetoxy-3-methoxyphenyl)-acryloyl chloride **6** was prepared, according to a known procedure,[13] from ferulic acid **4** in two steps in a combined yield of 74% (Scheme 1).

The synthesis of 3-*O*-feruloylquinic acid **1** is shown in Scheme 2. The quadruple protection of commercially available D-(−)-quinic acid **7** to give lactone **8** was carried out with 2,2-dimethoxypropane

* Corresponding author. Tel.: +385 14561029; fax: +385 14680108.
E-mail address: Irena.Dokli@irb.hr (I. Dokli).

0957-4166/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetasy.2013.06.002



Scheme 1. Synthesis of 3-(4-acetoxy-3-methoxyphenyl)-acryloyl chloride **6**.

and *p*-toluenesulfonic acid in refluxing EtOAc. The crude lactone **8** was subjected to ethanolysis with NaOEt/EtOH at −20 °C, to obtain a mixture of lactone **8** and ester **9** in a ratio of 1:5 as indicated by ^{1}H NMR spectroscopy.[14] Pure ester **9** was isolated after column chromatography in 76% yield from **7**. Esterification of quinate **9** with chloride **6** in the presence of DMAP and pyridine in dichloromethane gave compound **9** in 64% yield. All of the protecting groups were removed using 1 M aqueous HCl in THF (4:1) at room temperature to afford 3-*O*-feruloylquinic acid **1** in 67% yield after two recrystallizations.

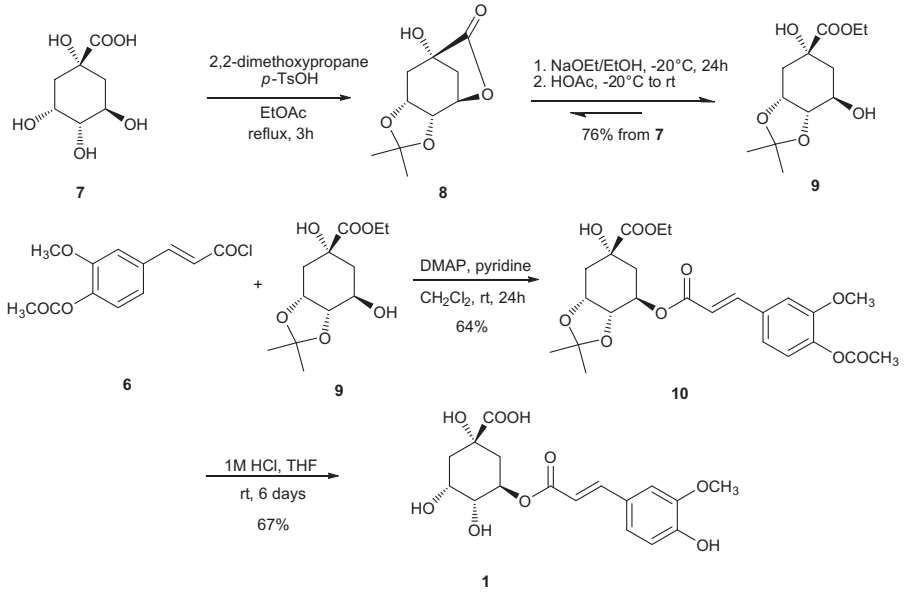
4-*O*-Feruloylquinic acid **2** was prepared according to Scheme 3. D-(−)-Quinic acid **1** was converted into lactone **11** with *p*-toluenesulfonic acid in refluxing toluene. The selective protection of the C-5 hydroxy group was achieved using *tert*-butyldimethylsilyl (TBS) chloride to provide a mixture of monosilylated compounds **12a** and **12b** in the ratio of 96:4 as indicated by ^{1}H NMR spectroscopy.[15] Pure **12a** was isolated after column chromatography in 67% yield (from **7**). Esterification of **12a** with 1.5 equiv of chloride **6** in a mixture of dichloromethane and pyridine in the presence of DMAP after 4 days at room temperature did not proceed with full conversion (90%) and resulted in a mixture of 4-monoesterificated **13a** and 1,4-diesterificated **13b** product in a molar ratio of **13a**:**13b** = 1.5:1. Pure **13a** was isolated after chromatography in 45% yield. Better results were obtained when the reaction proceeded in pyridine with 1.8 equiv of chloride **6** at room temperature. After 24 h, the conversion was 100%, and the molar ratio of products was **13a**:**13b** = 3:1. Pure **13a** was isolated after chromatography in 60% yield (Table 1).

All protecting groups were, as above, removed using 1 M aqueous HCl in THF (4:1) at room temperature. However, we observed that under the given reaction conditions, acyl migration from the C-4 hydroxy to the C-5 hydroxy occurred to some extent to give 5-*O*-feruloylquinic acid **3** as a side product. This made the purification and isolation of pure 4-*O*-feruloylquinic acid **2** by recrystallization difficult because 4-*O*-feruloylquinic acid **2** was found to be more soluble than 5-*O*-feruloylquinic acid **3** in all of the tested mixtures of solvents. The longer reaction time required for the full conversion (8 days), resulted in more acyl migration product **3** (20%). This problem was solved by stopping the reaction at 90% conversion (5 days), followed by column chromatography (EtOAc) in order to remove 5-*O*-feruloylquinic acid (up to 5%), and then recrystallization from a mixture of THF/diisopropyl ether to afford pure 4-*O*-feruloylquinic acid **2** in 36% yield.

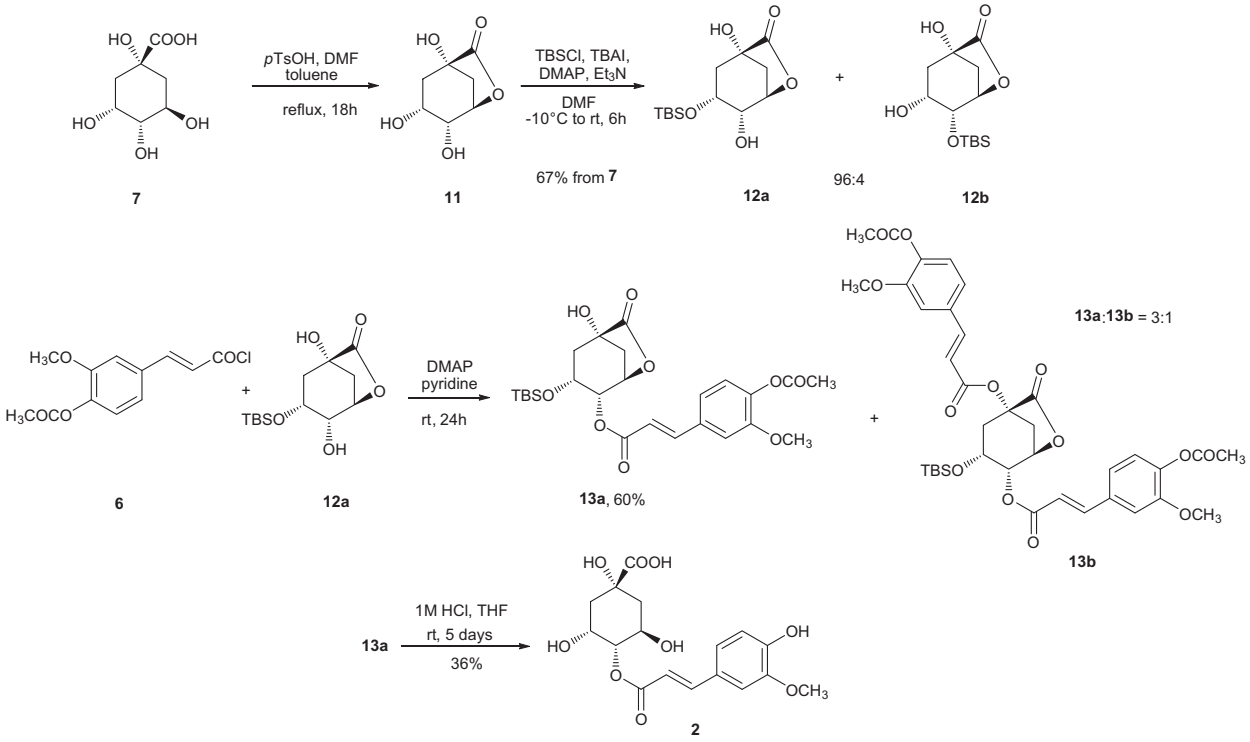
5-*O*-Feruloylquinic acid **3** was prepared according to Scheme 4. D-(−)-Quinic acid **7** was first converted into ester **14** using (±)-10-camphorsulfonic acid (CSA) in refluxing methanol. Selective protection of the C-3 and C-4 vicinal diequatorial hydroxyls with 2,2,3,3-tetramethoxybutane **15** in the presence of CSA and trimethyl orthoformate resulted in butane 2,3-bisacetal (BBA) protected methyl quinate **16** in 76% yield from **7**.[16] Esterification of **16** with feruloyl chloride **6** was carried out in a mixture of pyridine and dichloromethane in the presence of DMAP at room temperature to provide ester **17** in 86% yield. All of the protecting groups were removed using 1 M aqueous HCl in THF (3:1) at room temperature after 5 days. Again, under the given conditions, acyl migration from the C-5 hydroxy to the C-4 hydroxy was observed (up to 10%). Pure 5-*O*-feruloylquinic acid **3** was isolated after two recrystallizations from a mixture of THF/diisopropyl ether in 69% yield.

3. Conclusion

In conclusion, we have described an efficient synthesis of 3-, 4-, and 5-*O*-feruloylquinic acid starting from D-(−)-quinic acid. Esterification of suitably protected quinic acid derivatives with feruloyl chloride **6** and subsequent hydrolysis of all the protecting



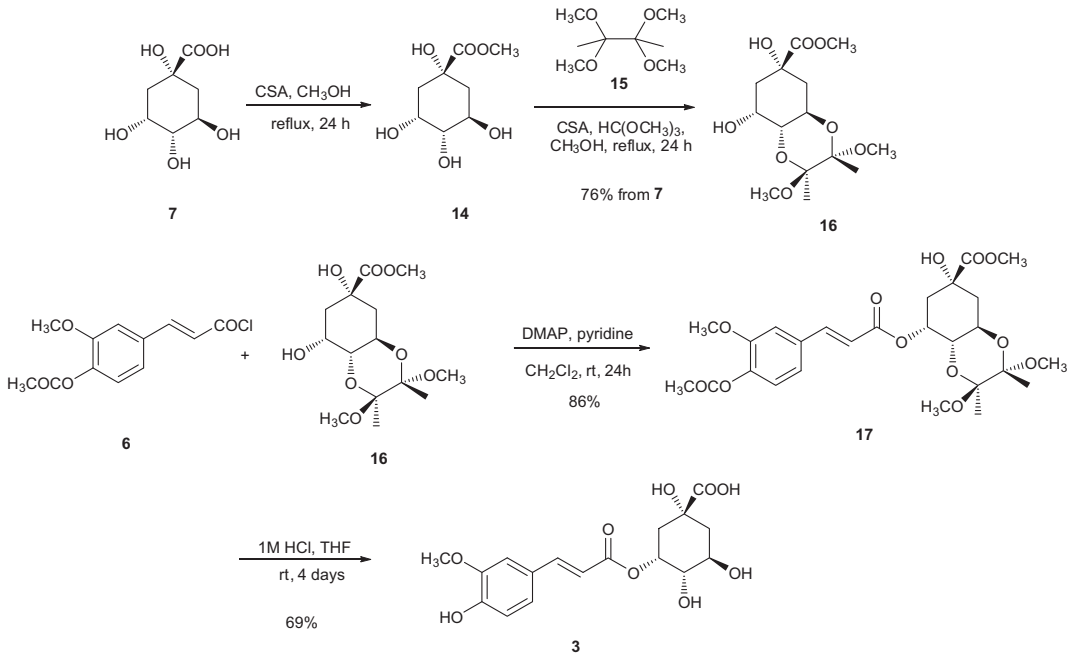
Scheme 2. Synthesis of 3-*O*-feruloylquinic acid **1**.



Scheme 3. Synthesis of 4-*O*-feruloylquinic acid **2**.

Table 1
Esterification of **12a** (1 equiv) with chloride **6** in the presence of DMAP (0.15 equiv)

Entry	**6** (equiv)	Solvent	Time (days)	Conversion (%)	**13a**:**13b**	Combined yield (%)	Yield **13a** (%)
1	1.5	CH_2Cl_2/pyridine (4:1)	4	90	1.5:1	75	45
2	1.5	Pyridine	1	90	3:1	–	46
3	1.8	Pyridine	1	100	3:1	81	60



Scheme 4. Synthesis of 5-*O*-feruloylquinic acid **3**.

groups afforded the title products in overall yields of 33%, 15%, and 45%, respectively, (from quinic acid).

4. Experimental

4.1. General methods

All of the reactions were conducted under an argon atmosphere. Solvents were *puriss p.a.* quality. All other reagents were purchased from commercial sources and used without purification. TLC was performed on aluminum baked silica plates (60 F_{254}, Merck). UV light (254 nm) or phosphomolibdic acid reagent was used for visualizing. Column chromatography was performed on silica gel (Silica gel 60, 70–230 mesh, Fluka). ^{1}H and ^{13}C NMR were recorded on Bruker AV 300 and AV 600 spectrometers. Chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm), referenced to TMS. Chemical purity determination, and progression of the reactions was performed by HPLC on a Eurospher 100-5 C18, 250 mm × 4.6 mm column. Optical rotations were measured using Optical Activity AA-10 automatic polarimeter. High resolution mass spectrometry (HRMS) was performed on a 4800 Plus MALDI TOF/TOF Analyzer. Compounds **5**,[13] **6**,[13] and **15**[16] were prepared according to literature procedures.

4.2. (1*S*,3*R*,4*R*,5*R*)-4,5-*O*-Isopropylidene-1,3-quinic acid lactone 8

At first, D-(−)-quinic acid **7** (1 g, 5.2 mmol) was suspended in EtOAc (30 mL). *p*-Toluenesulfonic acid monohydrate (10 mg, 0.052 mmol) and 2,2-dimethoxypropane (1.96 mL, 15.6 mmol) were then added. The mixture was heated at reflux for 3 h. After cooling, the solvent was removed under reduced pressure. The residual solid, lactone **8** was used in the next step without further purification. NMR data were in accordance with the literature data.[14]

4.3. Ethyl (1*R*,3*R*,4*S*,5*R*)-4,5-*O*-isopropylidene-1,3-quinate 9

To a solution of crude lactone **8** in absolute EtOH (30 mL) was added NaOEt in EtOH (0.208 mmol, 0.16 mL, 0.04 equiv with respect to quinic acid). The mixture was stirred at room temperature for 1 h, and then overnight at −20 °C. The reaction mixture was neutralized at −20 °C with acetic acid (13 μL) and then warmed to room temperature. The solvent was removed under reduced pressure. ^{1}H NMR spectroscopy showed that the crude product was a mixture of lactone **8** and ester **9** (ratio 1:5). Column chromatography on silica gel (*n*-hexane/EtOAc = 1/1) yielded pure **9** (1.03 g, 76% from **7**) as a white solid. NMR data were in accordance with the literature data.[14]

4.4. Ethyl (1*S*,3*R*,4*R*,5*R*)-3-[3-(4-acetoxy-3-methoxyphenyl)-acryloyloxy]-4,5-*O*-isopropylidene-1-quinate 10

To a solution of ethyl 4,5-*O*-isopropylidene-1,3-quinate **9** (500 mg, 1.9 mmol) and DMAP (35 mg, 0.29 mmol) in CH_2Cl_2 (25 mL) were added pyridine (6 mL) and 3-(4-acetoxy-3-methoxyphenyl)-acryloyl chloride **6** (734 mg, 2.9 mmol). The mixture was stirred overnight at room temperature and then acidified with 1 M aq HCl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (diethyl ether/CH_2Cl_2 = 1/1) to afford ester **10** (590 mg, 64%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, 3H, J = 6.9 Hz), 1.38 (s, 3H), 1.59 (s, 3H), 1.91 (dd, 1H, J_1 = 11.3 Hz, J_2 = 13.1 Hz), 2.21–2.32 (m, 6H), 3.41 (s, 1H), 3.85 (s, 3H), 4.19–4.27 (m, 3H), 4.51–4.56 (m, 1H), 5.42–5.50 (m, 1H), 6.37 (d, 1H, J = 16.1 Hz), 7.02–7.12 (m, 3H), 7.65 (d, 1H, J = 16.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.10, 20.61, 25.84, 28.01, 34.45, 36.96, 55.91, 62.17, 71.03, 73.65, 73.73, 76.91, 109.61, 111.31, 118.23, 121.21, 123.25, 133.34, 141.51, 144.42, 151.41, 165.82, 168.71, 174.32.

4.5. 3-*O*-Feruloylquinic acid 1

To a solution of ester **10** (580 mg, 1.21 mmol) in THF (10 mL) was added 1 M aq HCl (40 mL). The mixture was then stirred for 6 days at 25 °C. The solution was saturated with solid NaCl and the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was recrystallized twice from a mixture of MTBE/diisopropyl ether to afford 3-*O*-feruloylquinic acid **1** (300 mg, 67%) as a white powder. NMR data were in accordance with the literature data.[12,13] ^{1}H NMR (300 MHz, methanol-d_4): δ = 2.06–2.28 (m, 4H), 3.75 (dd, 1H, J_1 = 3.1 Hz, J_2 = 8.4 Hz), 3.91 (s, 1H), 4.18–4.20 (m, 1H), 5.36 (ddd, 1H, J_1 = 4.5 Hz, J_2 = 8.9 Hz, J_3 = 9.1 Hz), 6.37 (d, 1H, J = 15.9 Hz), 6.83 (d, 1H, J = 8.2 Hz), 7.10 (dd, 1H, J_1 = 1.8 Hz, J_2 = 8.2 Hz), 7.21 (d, 1H, J = 1.8 Hz), 7.64 (d, 1H, J = 15.9 Hz). ^{13}C NMR (75 MHz, methanol-d_4): δ = 36.83, 37.38, 55.08, 69.87, 70.61, 72.08, 74.73, 110.44, 114.27, 115.08, 122.70, 126.40, 145.54, 147.97, 149.23, 167.20, 175.62. HRMS (MALDI): *m*/*z*: calcd for $C_{17}H_{20}O_9Na$ [M+Na$^+$] 391.0999; found: 391.0994. $[\alpha]_D^{25} = -35.1$ (*c* 1.14, CH_3OH). {lit.[12] $[\alpha]_D^{25} = -19.6$ (*c* 1.12 g l^{-1}, CH_3OH)).

4.6. (1*S*,3*R*,4*R*,5*R*)-1,3,4-Trihydroxy-6-oxa-bicyclo[3.2.1]octan-7-one 11

A solution of D-(−)-quinic acid (1.96 g, 10.2 mmol) and *p*-toluenesulfonic acid (100 mg, 0.52 mmol) in anhydrous toluene (20 mL) and anhydrous DMF (7 mL) was refluxed under a Dean–Stark trap for 18 h. The reaction mixture was cooled and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 (20 mL) and hexane (10 mL). The precipitated product was collected by vacuum filtration to afford the crude lactone **11** (1.77 g) which was used in the next reaction step without further purification.

4.7. (1*R*,3*R*,4*S*,5*R*)-5-*tert*-Butyldimethylsiloxy-1,4-dihydroxycyclohexane-1,3-carbolactone 12a

Crude lactone **11** (1.77 g), DMAP (175 mg, 1.43 mmol), tetrabutylammonium iodide (189 mg, 0.51 mmol) and triethylamine (1.7 mL, 12.2 mmol) were suspended in dry DMF (20 mL) at −10 °C, after which *tert*-butyldimethylsilyl chloride (1.9 g, 12.5 mmol) was added. The solution was stirred at −10 °C for 1 h and then 5 h at room temperature. The reaction mixture was diluted with ethyl acetate (100 mL) and filtered over Celite. The filtrate was washed successively with 1 M aq HCl (100 mL) and brine (3 × 100 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (diethyl ether/*n*-hexane = 1/1) to afford monosilyl product **12a** (1.98 g, 67.3%). NMR data were in accordance with the literature data.[15]

4.8. (1*R*,3*R*,4*S*,5*R*)-4-[3-(4-Acetoxy-3-methoxyphenyl)-acryloyloxy]-5-*tert*-butyldimethylsiloxy-1-hydroxycyclohexane-1,3-carbolactone 13a and (1*R*,3*R*,4*S*,5*R*)-1,4-di-[3-(4-acetoxy-3-methoxyphenyl)-acryloyloxy]-5-*tert*-butyldimethylsiloxy-cyclohexane-1,3-carbolactone 13b

To a solution of monosilyl protected compound **12a** (310 mg, 1.07 mmol) and DMAP (20 mg, 0.16 mmol) in pyridine (15 mL) at room temperature, was added 3-(4-acetoxy-3-methoxyphenyl)-

acryloyl chloride **6** (490 mg, 1.92 mmol). The mixture was stirred overnight at room temperature and then poured onto crushed ice, after which CH_2Cl_2 (20 mL) was added. The reaction mixture was acidified with 1 M aq HCl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was a mixture of **13a** and **13b** (3:1). The residue was purified by column chromatography on silica gel (diethyl ether/CH_2Cl_2 = 1/1) to afford ester **13a** (330 mg, 60%) as a colorless solid, and **13b** (160 mg) as a white solid. Compound **13a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 3H), 0.08 (s, 3H), 0.83 (s, 9H), 2.11–2.12 (m, 2H), 2.33 (s, 3H), 2.41–2.44 (m, 1H), 2.56 (d, 1H, J = 11.8 Hz), 2.72 (s, 1H), 3.89 (s, 3H), 4.04–4.08 (m, 1H), 4.86–4.87 (m, 1H), 5.43–5.45 (m, 1H), 6.43 (d, 1H, J_1 = 15.8 Hz), 7.07–7.16 (m, 3H), 7.69 (d, 1H, J_1 = 15.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.56, 17.41, 20.08, 25.07, 37.00, 40.54, 55.48, 65.46, 66.10, 71.49, 73.75, 110.98, 116.79, 120.87, 122.85, 132.55, 141.32, 144.91, 151.02, 164.89, 168.18, 176.75.

Compound **13b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 3H), 0.08 (s, 3H), 0.83 (s, 9H), 2.26–2.32 (m, 1H), 2.32 (s, 3H), 2.33 (s, 3H), 2.33–2.46 (m, 1H), 2.72 (d, 1H, J = 11.5 Hz), 3.07–3.15 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.11–4.19 (m, 1H), 4.91–4.96 (m, 1H), 5.45–5.49 (m, 1H), 6.41 (d, 1H, J_1 = 15.9 Hz), 6.45 (d, 1H, J_1 = 15.9 Hz), 7.03–7.16 (m, 6H), 7.67 (d, 2H, J_1 = 15.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.60, −5.57 17.41, 20.09, 25.07, 34.01, 37.19, 55.48, 55.49, 65.34, 66.47, 73.80, 76.12, 110.86, 110.92, 116.56, 116.79, 120.99, 121.02, 122.84, 122.86, 132.41, 132.57, 141.32, 141.44, 144.95, 145.50, 151.03, 164.31, 164.86, 168.12, 168.15, 171.55.

4.9. 4-*O*-Feruloylquinic acid 2

To a solution of ester **13a** (1.0 g, 1.97 mmol) in THF (15 mL) was added 1 M aq HCl (60 mL), after which the mixture was stirred for 5 days at room temperature. The solution was saturated with solid NaCl and the aqueous phase extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc) and then recrystallized from the mixture of THF/diisopropyl ether to afford **2** (260 mg, 36%) as a white powder. NMR analysis showed that the obtained powder was an adduct with THF in a molar ratio 4:1 = **2**:THF. Next, 100 mg of this adduct was dissolved in CH_3OH and the solvent was again evaporated to provide THF free product **2**. NMR data were in accordance with the literature data.[17] ^{1}H NMR (300 MHz, methanol-d_4): δ = 1.99–2.28 (m, 4H), 3.92 (s, 3H), 4.27–4.35 (m, 2H), 6.47 (d, 1H, J = 15.9 Hz), 6.84 (d, 1H, J = 8.4 Hz), 7.12 (dd, 1H, J_1 = 1.8 Hz, J_2 = 8.4 Hz), 7.22 (d, 1H, J = 1.8 Hz), 7.73 (d, 1H, J = 15.9 Hz). ^{13}C NMR (75 MHz, methanol-d_4): δ = 37.04, 41.31, 55.06, 64.16, 68.24, 75.17, 77.92, 110.43, 114.38, 115.11, 122.63, 126.47, 145.56, 147.98, 149.20, 167.53, 175.88. HRMS (MALDI): m/z: calcd for $C_{17}H_{20}O_9Na$ [M+Na$^+$] 391.0999; found: 391.0999. $[\alpha]_D^{25}$ = −55.7 (c 0.79, CH_3OH).

4.10. (1*S*,3*R*,4*R*,5*R*)-3,4-*O*-(2′,3′-Dimethoxybutane-2′,3′-diyl)-1,5-dihydroxycyclohexanecarboxylic acid methyl ester 16

To a suspension of D-(−)-quinic acid (1 g, 5.2 mmol) in MeOH (30 mL), (±)-10-camphorsulfonic acid (12 mg, 0.052 mmol) was added. Reaction mixture was then refluxed overnight. After cooling, 2,2,3,3-tetramethoxybutane **15** (927 mg, 5.7 mmol), trimethyl orthoformate (2.6 mL, 0.024 mol), and (±)-10-camphorsulfonic acid (12 mg, 0.052 mmol) were added and mixture again refluxed overnight. Powdered $NaHCO_3$ (0.1 g) was added to the cold reaction mixture. Solution was concentrated under reduced pressure and the residue partitioned between EtOAc (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted once with EtOAc (30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. Crude product was recrystallized from EtOAc/n-hexane = 1/5 to afford compound **16** (1.28 g, 76% from quinic acid) as a white solid. NMR data are in accordance with the literature data.[16]

4.11. (1*R*,3*R*,4*S*,5*R*)-5-[3-(4-Acetoxy-3-methoxyphenyl)-acryloyloxy]-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1-hydroxycyclohexanecarboxylic acid methyl ester 17

To a solution of 3,4-BBA protected methyl quinate **16** (750 mg, 2.34 mmol) and DMAP (30 mg, 0.23 mmol) in CH_2Cl_2 (20 mL) were added pyridine (2 mL) and 3-(4-acetoxy-3-methoxyphenyl)-acryloyl chloride **3** (894 mg, 3.51 mmol). The mixture was stirred overnight at room temperature and then acidified with 1 M aq HCl. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (diethyl ether/CH_2Cl_2 = 1/1) to afford ester **17** (1.09 g, 86%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3H), 1.32 (s, 3H), 1.99–2.34 (m, 4H), 2.35 (s, 3H), 3.23 (s, 1H), 3.29 (s, 3H), 3.33 (s, 3H), 3.75 (dd, 1H, J_1 = 3.2 Hz, J_2 = 10.2 Hz), 3.81 (s, 3H), 3.91 (s, 3H), 4.40–4.99 (m, 1H), 5.38–5.41 (m, 1H), 6.48 (d, 1H, J = 15.9 Hz), 7.06–7.16 (m, 3H), 7.69 (d, 1H, J = 15.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.12, 17.35, 20.08, 36.20, 38.23, 47.44, 47.54, 52.66, 55.50, 62.30, 69.35, 70.74, 74.14, 99.12, 99.65, 110.74, 118.16, 121.06, 122.67, 133.04, 140.98, 143.95, 150.91, 165.91, 168.16, 174.93.

4.12. 5-*O*-Feruloylquinic acid 3

To a solution of ester **17** (1.4 g, 2.60 mmol) in THF (20 mL), 1 M aq HCl (60 mL) was added. The mixture was stirred for 4 days at room temperature. The solution was saturated with solid NaCl and aqueous phase extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was recrystallized twice from the mixture of THF/diisopropyl ether to afford **3** (660 mg, 69%) as a white powder. ^{1}H NMR (300 MHz, methanol-d_4): δ = 1.94–2.22 (m, 4H), 3.67 (dd, 1H, J_1 = 3.3 Hz, J_2 = 8.5 Hz), 3.92 (s, 3H), 4.14–4.22 (m, 1H), 5.37–5.41 (m, 1H), 6.42 (d, 1H, J = 15.9 Hz), 6.83 (d, 1H, J = 8.1 Hz), 7.09 (dd, 1H, J_1 = 1.9 Hz, J_2 = 8.1 Hz), 7.21 (d, 1H, J = 1.9 Hz), 7.67 (d, 1H, J = 15.9 Hz). ^{13}C NMR (75 MHz, methanol-d_4): δ = 35.35, 40.18, 55.05, 66.88, 71.65, 73.46, 74.01, 110.33, 114.84, 115.07, 122.59, 126.57, 145.26, 147.96, 149.08, 167.56, 176.89. HRMS (MALDI): m/z: calcd for $C_{17}H_{20}O_9Na$ [M+Na$^+$] 391.0999; found: 391.0995. $[\alpha]_D^{25}$ = +10.9 (c 0.64, CH_3OH).

Acknowledgments

We thank the Ministry of Science, Education and Sports of the Republic of Croatia (Grant no. 098-0982933-2908). This work is also a part of a joint project with illycaffè s.p.a in the framework of the project: 'Nutrigenomica e consumo di caffè: effetti fisiologici, genetica del gusto e genetica della pianta' partially supported by the POR-FESR 2007-2013 Regione Autonoma Friuli Venezia Giulia, Italy.

References

1. *Coffee: Emerging Health Effects and Disease Prevention*; Chu, Y.-F., Ed.; Wiley-Blackwell: Oxford, UK, 2012.
2. Shi, X.; Dalal, N. S.; Jain, A. C. *Food Chem. Toxicol.* **1991**, *29*, 1–6.
3. Morales, F. J.; Somoza, V.; Fogliano, V. *Amino Acids* **2012**, *42*, 1097–1109.

4. Crozier, A.; Jaganath, I. B.; Clifford, M. N. *Nat. Prod. Rep.* **2009**, *26*, 1001–1043.
5. Ky, C. L.; Louarn, J.; Dussert, S.; Guyot, B.; Hamon, S.; Noirot, M. *Food Chem.* **2001**, *75*, 223–230.
6. Farah, A.; Donangelo, C. M. *Braz. J. Plant Physiol.* **2006**, *18*, 23–36.
7. Monteiro, M. C.; Farah, A. *Food Chem.* **2012**, *134*, 611–614.
8. Clifford, M. N.; Knight, S.; Surucu, B.; Kuhnert, N. *J. Agric. Food Chem.* **2006**, *54*, 1957–1969.
9. Menozzi-Smarrito, C.; Wong, C. C.; Meinl, W.; Glatt, H.; Fumeaux, R.; Munari, C.; Robert, F.; Williamson, G.; Barron, D. *J. Agric. Food Chem.* **2011**, *59*, 5671–5676.
10. Sefkow, M. *Eur. J. Org. Chem.* **2001**, 1137–1141.
11. Sefkow, M.; Kelling, A.; Schilde, U. *Eur. J. Org. Chem.* **2001**, 2735–2742.
12. Menozzi-Smarrito, C.; Munari, C.; Robert, F.; Barron, D. *Org. Biomol. Chem.* **2008**, *6*, 986–987.
13. Frank, O.; Zehentbauer, G.; Hofmann, T. *Eur. Food Res. Technol.* **2006**, *222*, 492–508.
14. Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Göckel, V.; Götzö, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Röckel-Stäbler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266–274.
15. Manthey, M. K.; González-Bello, C.; Abell, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 625–628.
16. Montchamp, J.-L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897–3899.
17. Morishita, H.; Iwahashia, H.; Kidoa, R. *Phytochemistry* **1986**, *25*, 1496–1497.