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New route for synthesis of 3- and 5-caffeoylquinic acids via protected quinic acids

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ABSTRACT

Caffeoylquinic acids (CQAs) are a group of the phenylpropanoids produced by certain plant species, which have various biological activities including antioxidant, antibacterial, anticancer, and others. Several synthetic routes have been developed using quinic acids (QAs) and caffeic acid derivatives as starting materials. In this study, alternative pathways of 3- and 5-CQAs preparation using protected quinic acids are described. Both CQAs were achieved by removal of the protecting groups of compound 9 and 18 with acid hydrolysis using dilute HCl solution. These compounds (9 and 18) are novel, resulted from esterification reaction of diacetyl caffeoyl chloride and protected quinic acids. The hydroxyl groups of quinic acid in this case were protected with 2,2-dimethoxy propane or tert-butyldimethylsilyl (TBS) chloride.

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1. Introduction

Caffeoylquinic acids (CQAs) and its derivatives are secondary metabolites that are found in a wide variety of natural sources. Coffee products and apple are among those sources constituting high percentage of CQAs [1-3]. Some vegetables, for example, sweet potato and leeks also constitute these compounds [4,5]. Owing to their antioxidant and other biological effects [6-8], convenient methods of CQAs have been sought for practical synthesis. As a result, numerous scientific papers have been published on the chemical and enzymatic synthetic methods, such as by Hemmerle *et al.* [9] and Lorentz *et al.* [10] Among these methods, Sefkow and co-workers' [11,12] have reported for the first time a complete package of CQAs syntheses. They synthesized 1-, 3-, 4-, and 5-CQA with performing esterification of suitable protected quinic acids with acid chloride of caffeic acid. However, the preparation of protected quinic acids (QAs) of Sefkow's method is really hard to trace. Meanwhile, Dokli *et al.* [13] reported the syntheses of 3-, 4- and 5-feruloylquinic acids utilizing but with little modifications of the Sefkow's protocol, especially on protected quinic acids.

Inspired by the aforementioned reports, the present article is reporting the synthesis of 3- and 5-CQAs utilizing methyl 3,4-*o*-isopropylidene-1,5-quinate and an overlooked protected quinic acid, (1*R*, 3*R*, 4*S*, 5*R*)-4-*tert*-butyldimethylsiloxy-1, 3-di hydroxycyclohexane-1,5-carbolactone as the starting materials. These quinic acid derivatives were then esterified with caffeoyl chloride to obtain the correspondent esters of protected CQAs. Removal of all protected groups was carried out in dilute concentrations of HCl to attain the relevant CQAs. To complement the description of the synthesis of 3- and 5-CQAs, 1- and 4-CQAs were also synthesized and described in this article.

2. Experimental

2.1. General procedures

All reactions were conducted in dried glassware under argon atmosphere. Reagents used were commercially available with high grade of purity and solvents were purified using known methods. Thin layer chromatographic (TLC) analyses were performed on Kieselgel 60 F_{254} plates from Merck. Detection was carried out under UV light or spraying with 20% ethanolic sulfuric acid. Flash chromatography for substance purifications was performed on Silica Gel 60N, 40-50 μm.

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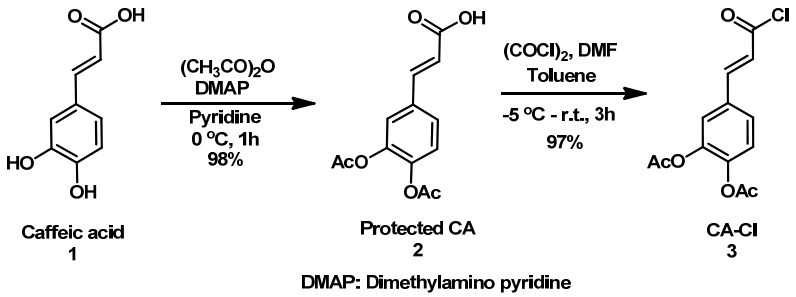


Scheme 1

Solvents evaporation was performed using Iwaki Rotary Evaporator REN-1000 with reduced pressure. JEOL NMR of JNM-LA400 and 500 were utilized in analyses of ^{1}H and ^{13}C NMR spectra. JEOL JMS-700 was used to record High Resolution Mass Spectrophotometer (HRMS) spectra. HORIBA FT-720 FT-IR Spectrometer was used to record infrared spectra. Compound **5** and **12** were prepared according to references [14,15], respectively.

2.2. Preparation of protected 1-CQA (7)

To a solution of acetone quinide (**5**) (400 mg, 1.87 mmol) in dichloromethane (10 mL), pyridine (8 mL), DMAP (11.4 mg, 0.09 mmol) and diacetyl caffeoyl chloride (**3**) (Scheme 1) (580 mg, 2.06 mmol) were added, respectively. The mixture was stirred for 15 h at room temperature. The resultant reaction mixture was diluted with dichloromethane (80 mL), washed with 2 M HCl and brine (2 × 10 mL) each. The organic phase was dried over $MgSO_4$ and the solvents were evaporated under reduced pressure to give crude product. This product was purified over column chromatography on silica gel (*n*-hexane:EtOAc, 2:1, *v*:*v*) to give the desired compound **7** (Scheme 2), as powder. Color: White. Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.35 (s, 3H, CH_3-CO_2CH_3), 1.54 (s, 3H, $CH_3CO_2CH_3$), 2.30 (s, 3H, CH_3CO-O), 2.31 (s, 3H, CH_3CO-O), 2.42 (dd, 1H, *J* = 14.5, 3.0 Hz, Cyclohexyl-H), 2.53 (ddd, 1H, *J* = 14.4, 7.7, 2.3 Hz, Cyclohexyl-H), 2.64 (d, 1H, *J* = 11.5 Hz, Cyclohexyl-H), 3.11 (dd, 1H, *J* = 11.6, 6.2 Hz, Cyclohexyl-H), 4.35 (d, 1H, *J* = 5.4 Hz, CH-O-CO), 4.57 (dd, 1H, *J* = 7.1, 3.0 Hz, CH-O-CO), 4.82 (dd, 1H, *J* = 6.3, 2.4 Hz, CH-O-CH_2), 6.39 (d, 1H, *J* = 15.9 Hz, CO-CH-CH-Ph), 7.24 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.36 (d, 1H, *J* = 2.0 Hz, Ar-H), 7.41 (dd, 1H, *J* = 8.4, 2.1 Hz, Ar-H), 7.66 (d, 1H, *J* = 15.9 Hz, Ph-CH-CH-CO). NMR data were in good agreement with literature data [11].

2.3. Preparation of 1-CQA (8)

As much as 184 mg (0.40 mmol) of protected 1-CQA (**7**) was suspended in a mixture of THF (4 mL) and 2 M HCl (16 mL). The mixture was stirred at room temperature and TLC (MeOH:EtOAc, 1:1, *v*:*v*) was used to monitor the progress of reaction. After the complete disappearance of the protected 1-CQA spot (7 days), the reaction is stopped and added with dichloromethane (5 mL) forming two layers. The aqueous phase was separated, saturated with solid NaCl, and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give desired 1-CQA, compound **8** (Scheme 2) as powder. Color: Pale yellow. Yield: 89%. ^{1}H NMR (400 MHz, CD_3OD, δ, ppm): 1.89 (dd, 1H, *J* = 13.8, 9.9 Hz, Cyclohexyl-H), 2.19 (dd, 1H, *J* = 14.8, 3.3 Hz, Cyclohexyl-H), 2.42 (d, 1H, *J* = 12.4 Hz, Cyclohexyl-H), 2.56 (d, 1H, *J* = 12.9 Hz, Cyclohexyl-H), 3.46 (dd, 1H, *J* = 8.4, 3.5 Hz, CH-OHCH_2), 4.07 (ddd, 1H, *J* = 15.5, 6.0, 3.0 Hz, CH-OHCH_2), 4.14 (dd, 1H, *J* = 8.2, 3.8 Hz, CH-OHCOH), 6.27 (d, 1H, *J* =15.9 Hz, CO-CH-CH-Ph), 6.77 (d, 1H, *J* = 8.1 Hz, Ar-H), 6.94 (dd, 1H, *J* = 8.2, 1.8 Hz, Ar-H), 7.04 (d, 1H, *J* = 2.0 Hz, Ar-H), 7.54 (d, 1H, *J* = 15.9 Hz, Ph-CH-CH-CO). NMR data were in good agreement with literature data [11].

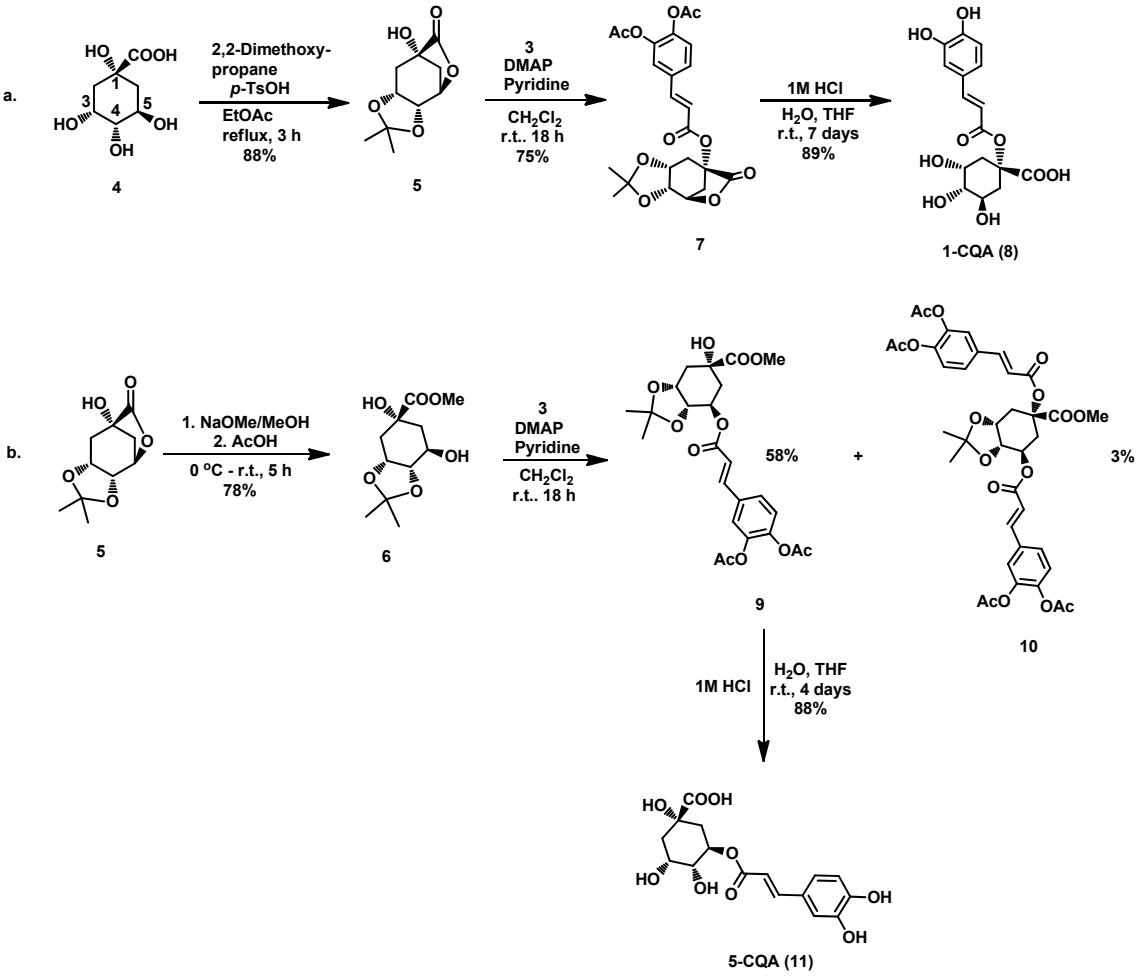
2.4. Preparation of methyl 3,4-O-isopropylidene-1,5-quinate (6)

To a solution of acetone quinide (**5**) (750 mg, 3.51 mmol) in methanol (30 mL), sodium methoxide (302.8 mg, 4.21 mmol) was added and the mixture was stirred at room temperature for 5 h. Acetic acid (150 µL) was added to the mixture after which was cooled to 0 °C, then let it to warm back to room temperature. Solvent was evaporated under reduced pressure to get crude product that was purified over column chromatography on silica gel (*n*-hexane:EtOAc, 1:1, *v*:*v*) to give the desired product, compound **6** (Scheme 2). Color: Colorless liquid. Yield: 78%. R_f = 0.17. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.38 (s, 3H, $CH_3CO_2CH_3$), 1.55 (s, 3H $CH_3CO_2CH_3$), 1.88 (dd, 1H, *J* = 13.5, 10.9 Hz, Cyclohexyl-H), 2.08 (dd, 1H, *J* = 13.7, 4.1 Hz, Cyclohexyl-H), 2.26 (d, 2H, *J* = 3.9 Hz, Cyclohexyl-H), 2.63 (s, broad, 1H, OH), 3.41 (s, broad, 1H, OH), 3.82 (s, 3H, CO-O-CH_3), 3.99 (t, 1H, *J* = 6.3 Hz, CH-O), 4.11-4.17 (m, 1H, CH-O), 4.46-4.49 (m, 1H, CH-OH). NMR data were in good agreement with literature data [16].

2.5. Synthesis of protected 5-CQA (9) and 1,5-diCQA (10)

To a stirred solution of methyl quinate (**6**) (400 mg, 1.62 mmol) in dichloromethane (15 mL), pyridine (6 mL), DMAP (11.4 mg, 0.09 mmol) and diacetyl caffeoyl chloride (**3**) (690 mg, 2.44 mmol) were respectively added. The mixture was continued to stir up to 15 h at room temperature. The resultant reaction mixture was diluted with dichloromethane (80 mL), washed with 2 M HCl, $NaHCO_3$ and brine (2 × 20 mL) each. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford crude ester. This was purified over column chromatography on silica gel (dichloromethane:diethyl ether, 1:1, *v*:*v*) to give methyl 3,4-*O*-isopropylidene-5-diacetylcaffeoyl quinate (**9**) and methyl 3,4-*O*-isopropylidene-1,5-diacetylcaffeoyl quinate (**10**), Scheme **2**, as waxy solid.

Methyl 3,4-o-isopropylidene-5-diacetylcaffeoyl quinate (**9**): Color: Off white. Yield: 58%. FT-IR (KBr, ν, cm^{-1}): 3482 (OH), 3072 (C-H, aromatic) 2987 (C-H, alkyl), 1774 (C=O, ester), 1716 (C=O, ester), 1638 (C=C, alkenyl), 1506 (C=C, aromatic), 1207 (C-O-C, ester), 1179 (C-O-C, ester). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.38 (s, 3H, $CH_3CO_2CH_3$), 1.60 (s, 3H $CH_3CO_2CH_3$), 1.93 (dd, 1H, *J* = 13.2, 11.0 Hz, Cyclohexyl-H), 2.22-2.27 (1H, Cyclohexyl-H), 2.31 (s, 3H, CH_3CO-O), 2.32 (s, 3H, CH_3CO-O), 2.33 (d, 2H, *J* = 3.4 Hz, Cyclohexyl-H), 3.45 (s, broad, 1H, OH), 3.79 (s, 3H, CO-O-CH_3), 4.21 (dd, 1H, *J* = 7.2, 5.7 Hz, CH-O-lactone), 4.55 (dd, 1H, *J* = 8.8, 3.7 Hz, CH-O-lactone) 5.42-5.48 (m, 1H, CH-O-Caff), 6.38 (d, 1H, *J* = 15.9 Hz, CO-CH-



Scheme 2

CH-Ph), 7.22 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.35 (d, 1H, *J* = 1.7 Hz, Ar-H), 7.40 (dd, 1H, *J* = 8.3, 1.7 Hz, Ar-H), 7.63 (d, 1H, *J* = 15.9 Hz, Ph-CH-CH-CO). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 174.68 (1C, $COOCH_3$), 168.07 (1C, COOPh), 168.00 (1C, COOPh), 165.58 (1C, COCH-Olefinic), 143.47 (1C, Olefinic-C), 143.24 (1C, Ar-C), 142.36 (1C, Ar-C), 133.17 (1C, Ar-C), 126.37 (1C, Ar-C), 123.92 (1C, Ar-C), 122.74 (1C, Ar-C), 119.04 (1C, C-$(CH_3)_2$), 109.61 (1C, Olefinic-C), 77.20 (1C, Cyclohexyl-C), 73.79 (1C, Cyclo hexyl-C), 73.57 (1C, Cyclohexyl-C), 70.90 (1C, Cyclohexyl-C), 53.10 (1C, CH_3-O), 36.84 (1C, Cyclohexyl-C), 34.28 (1C, Cyclo hexyl-C), 27.967 (1C, CH_3-C), 25.78 (1C, CH_3-C), 20.66 (1C, CH_3-COOPh), 20.62 (1C, CH_3-COOPh). HRMS FAB+: *m/z*: calculated for $C_{24}H_{29}O_{11}$ [M+H$^+$] = 493.1710, found 493.1716.

Methyl 3,4-O-isopropylidene-1,5-diacetylcaffeoyl quinate (**10**): Color: White. Yield: 3%. FT-IR (KBr, ν, cm^{-1}): 3068 (C-H, aromatic) 2926 (C-H, alkyl), 1775 (C=O, ester), 1716 (C=O, ester), 1638 (C=C, alkenyl), 1505 (C=C, aromatic), 1205 (C-O-C, ester), 1179 (C-O-C, ester). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.33 (s, 3H, $CH_3CO_2CH_3$), 1.50 (s, 3H, $CH_3CO_2CH_3$), 1.92 (t, 1H, *J* = 12.3 Hz, Cyclohexyl-H), 2.28 (s, 3H, CH_3CO-O), 2.29 (s, 3H, CH_3CO-O), 2.30 (s, 3H, CH_3CO-O), 2.31 (s, 3H, CH_3CO-O), 2.48 (dd, 1H, *J* = 16.0, 4.6 Hz, Cyclohexyl-H), 2.54 (d, 1H, *J* = 11.5 Hz, Cyclohexyl-H), 2.89 (d, 1H, *J* = 16.6 Hz, Cyclohexyl-H), 3.73 (s, 3H, CO-O-CH_3), 4.18 (t, 1H, *J* = 6.6 Hz, CH-O-lactone), 4.51 (dd, 1H, *J* = 7.4, 5.2 Hz, CH-O-lactone), 5.45-5.50 (m, 1H, CH-O-caff), 6.38 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.41 (d, 1H, *J* = 17.2 Hz, CO-CH-CH-Ph), 7.21 (d, 1H, *J* = 5.2 Hz, Ar-H), 7.23 (d, 1H, *J* = 5.2 Hz, Ar-H), 7.35 (d, 2H, J = 10.3 Hz, Ar-H), 7.40 (t, 2H, *J* = 9.5 Hz, Ar-H), 7.64 (d, 1H, *J* = 15.5 Hz, Ph-CH-CH-CO), 7.68 (d, 1H, *J* = 6.0 Hz, Ph-CH-CH-CO). HRMS FAB+: *m/z*: calculated for $C_{37}H_{39}O_{16}$ [M+H$^+$] = 739.2238, found 739.2229.

2.6. Synthesis of 5-CQA (11)

As much as 172 mg (0.35 mmol) of protected 5-CQA (**9**) was suspended in a mixture of THF (3 mL) and 1 M HCl (15 mL). The mixture was stirred at room temperature and TLC (MeOH:EtOAc, 1:1, *v:v*) was used to monitor the progress of reaction. After the complete disappearance of the protected 5-CQA spot (4 days), the reaction is stopped and added with dichloromethane (5 mL) forming two layers. The aqueous phase was separated, saturated with solid NaCl, and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated with evaporator under reduced pressure to give the desired product, compound **11** (Scheme 2) as powder. Color: Pale Yellow. Yield: 88%. ^{1}H NMR (400 MHz, CD_3OD, δ, ppm): 2.04-2.08 (m, 2H, CH_2, Cyclohexyl-H), 2.19 -2.23 (m, 2H, CH_2, Cyclohexyl-H), 3.73 (dd, 1H, *J* = 8.6, 2.9 Hz, CH-OH), 4.16-4.18 (m, 1H, CH-OH), 5.33 (td, 1H, *J* = 8.9, 4.4 Hz, CH-O-Caff), 6.26 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.78 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.96 (dd, 1H, *J* = 8.3, 2.0 Hz, Ar-H), 7.05 (d, 1H, *J* =1.7 Hz, Ar-H), 7.56 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO). NMR data were in good agreement with literature data [11].

2.7. Preparation of (1R,3R,4S,5R)-3-tert-butyldimethyl siloxy-1,4-dihydroxycyclohexane -1,5-carbolactone (13)

To a solution of lactone (**12**) (400 mg, 2.28 mmol) in DMF (4 mL) at 0 °C, imidazole (204 mg, 3.01 mmol), DMAP (65 mg, 0.48 mmol), and TBSCl (448 mg, 3.00 mmol) were respectively added. The mixture was stirred for 2 h at 0 °C and extended 3 more hours at room temperature. The resultant reaction mixture was added with EtOAc (20 mL) forming some white precipitant. The mixture was filtered through celite and solvents were evaporated under reduced pressure to afford crude material. Purification was done by column chromatography on silica gel (*n*-hexane:diethyl ether, 1:1, *v*:*v*) to give the desired product, compound **13** (Scheme 3), as waxy solid. Color: White. Yield: 62%. R_f = 0.12. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.09 (s, 6H, $Si(CH_3)_2$, 0.90 (s, 9H, $C(CH_3)_3$, 1.98-2.03 (m, 2H, Cyclohexyl-H), 2.30 (dq, 1H, *J* = 11.7, 2.9 Hz, Cyclohexyl-H), 2.60 (s, broad, 1H, OH), 2.64 (d, 1H, *J* = 11.5 Hz, Cyclohexyl-H), 2.96 (s, broad, 1H, OH), 3.91 (d, 1H, 10.3 Hz, CH-OTBS), 3.98 (t, 1H, *J* = 4.6 Hz, CH-OH), 4.88 (t, 1H, *J* = 5.4 Hz, CH-O-CO). NMR data were in good agreement with literature data [15].

2.8. Synthesis of protected 4-CQA (15) and 1,4-CQA (16)

To a solution of monosilyl protected compound **13** (465 mg, 1.62 mmol), DMAP (30 mg, 0.24 mmol), and caffeoyl chloride (**3**) (846 mg, 2.92 mmol) were added. The mixture was stirred for 24 h at room temperature. Upon the completion of reaction, the mixture was dissolved with dichloromethane (30 mL), poured into crushed ice before titrating it with 1 M HCl to pH ≈ 2. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered and solvent was evaporated under reduced pressure to give 1.1 g crude. Purification was done by column chromatography on silica gel (*n*-hexane:diethyl ether:dichloromethane, 1:1:1, *v*:*v*:*v*) to give compound **15** and **16**, Scheme 3, as waxy solid.

4-((E)-3-(((1R,3R,4S,5R)-3-((tert-butyldimethylsilyl)oxy)-1-hydroxy-7-oxo-6-oxabicyclo[3.2.1]octan-4-yl)oxy)-3-oxoprop-1-en-1-yl)-1,2-phenylene diacetate (**15**): Color: Off white. Yield: 52%. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.02 (s, 3H, $Si\text{-}CH_3$), 0.05 (s, 3H, $Si\text{-}CH_3$), 0.80 (s, 9H, $C(CH_3)_3$, 2.05 -2.09 (m, 2H, Cyclohexyl-H), 2.30 (s, 3H, CH_3CO-O), 2.31 (s, 3H, CH_3CO-O), 2.42 (dd, 1H, *J* = 12.2, 5.9 Hz, Cyclohexyl-H), 2.54 (d, 1H, *J* = 12.0 Hz, Cyclohexyl-H), 3.20 (s, broad, 1H, OH), 4.04 (td, 1H, *J* = 8.8, 4.7 Hz, CH-OTBS), 4.85 (t, 1H, *J* = 5.4 Hz, CH-O-Caff), 5.44 (t, 1H, *J* = 4.9 Hz, CH-O-CO), 6.44 (d, 1H, *J* = 16.1Hz, CO-CH-CH-Ph), 7.25 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.40 (d, 1H, *J* = 2.2 Hz, Ar-H), 7.43 (dd, 1H, *J* = 8.4, 2.1 Hz, Ar-H), 7.66 (d, 1H, *J* =15.9 Hz, Ph-CH-CH-CO). NMR data were in good agreement with literature data [11].

(1R, 3R, 4S, 5R)-3-tert-butyldimethylsiloxy-1,4-diacetyl caffeoylcyclohexane-1,5-carbolactone (**16**): Color: Off white. Yield: 15%. FT-IR (KBr, ν, cm^{-1}): 3077 (C-H, aromatic) 2933 (C-H, alkyl), 2857 (C-H, alkyl), 1775 (C=O, ester), 1724 (C=O, ester), 1637 (C=C, alkenyl), 1506 (C=C, aromatic), 1255 ($SiCH_3$), 1205 (C-O-C, ester), 1179 (C-O-C, ester), 1060 (Si-O). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.05 (s, 3H, $Si\text{-}CH_3$), 0.08 (s, 3H $Si\text{-}CH_3$), 0.82 (s, 9H, $C(CH_3)_3$), 2.27 (d, 1H, *J* = 12.4 Hz, Cyclohexyl-H), 2.31 (s, 3H, CH_3CO-O), 2.31 (s, 3H, CH_3CO-O), 2.32 (s, 3H, CH_3CO-O), 2.32 (s, 3H, CH_3CO-O), 2.36 (d, 1H, *J* = 11.5 Hz, Cyclohexyl-H), 2.64 (d, 1H, Cyclohexyl-H), 3.17 (dq, 1H, *J* = 11.0, 3.0 Hz, Cyclohexyl-H), 4.12 – 4.16 (m, 1H, CH-OTBS), 4.93 (t, 1H, *J* = 5.4 Hz, CH-O-Caff), 5.48 (t, 1H, *J* = 4.6 Hz, CH-O-CO), 6.42 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.46 (d, 1H, J = 15.5 Hz, CO-CH-CH-Ph), 7.24 (d, 1H, *J* = 1.7 Hz, Ar-H), 7.26 (d, 1H, *J* = 1.7 Hz, Ar-H), 7.39 (d, 2H, *J* = 13.2, 1.7 Hz, Ar-H), 7.43 (td, 2H, *J* = 7.7, 1.7 Hz, Ar-H), 7.66 (d, 1H, *J* = 5.7 Hz, Ph-CH-CH-CO), 7.70 (d, 1H, *J* = 5.7 Hz, Ph-CH-CH-CO). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 171.99 (1C, COO-lactone), 168.07 (1C, 1C, $COOCH_3$), 168.00 (1C, 1C, $COOCH_3$), 167.97 (1C, 1C, $COOCH_3$), 167.92 (1C, 1C, $COOCH_3$), 165.08 (1C, COOCH-Olefinic), 164.52 (1C, COOH-Olefinic), 144.75 (2C, Olefinic-C), 144.15 (1C, Olefinic-C), 143.83 (1C, Ar-C), 143.72 (1C, Ar-C), 142.44 (1C, Ar-C), 132.92 (1C, Ar-C), 132.74 (1C, Ar-C), 126.58 1C, Ar-C), 126.54 (1C, Ar-C), 124.02 (1C, Ar-C), 124.00 (1C, Ar-C), 122.97 (1C, Ar-C), 122.84 (1C, Ar-C), 118.23 (1C, Ar-C), 117.89 (1C, Olefinic-C), 76.51 (1C, Cyclohexyl-C), 74.22 (1C, Cyclohexyl-C), 66.89 (1C, Cyclohexyl-C), 65.69 (1C, Cyclohexyl-C), 37.61 (1C, Cyclohexyl-C), 34.23 (1C, Cyclohexyl-C), 25.53 (1C, $C(CH_3)_3$), 20.64 (3C, CH_3-C), 20.60 (2C, CH_3COOPh), 17.87 (2C, CH_3COOPh), -5.14 (2C, CH_3-Si). HRMS FAB+: *m/z*: calculated for $C_{39}H_{45}O_{15}Si$ $[M+H^+]$ = 781.2528, found 781.2531.

2.9. Synthesis of 4-CQA (17)

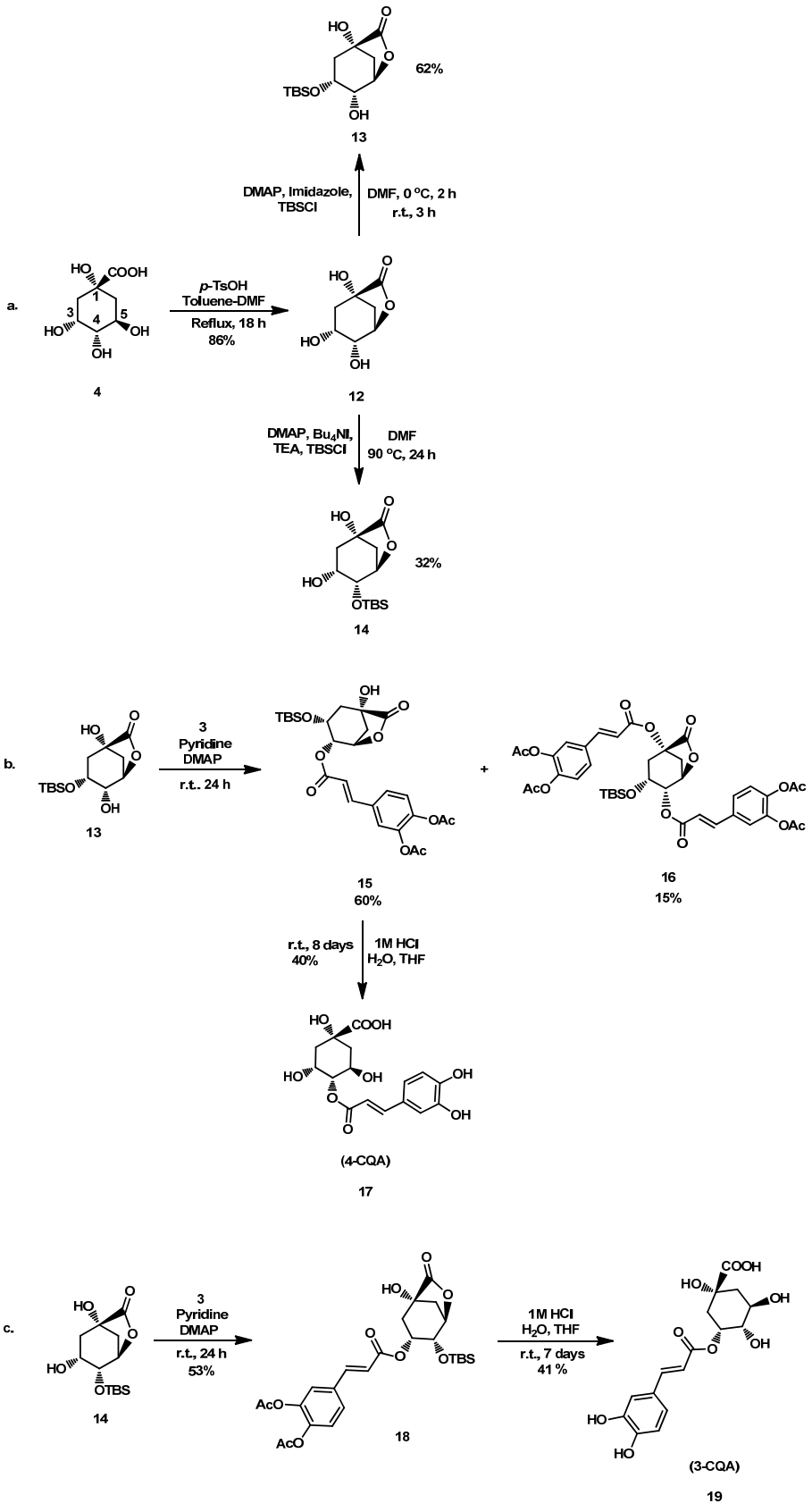
As much as 213 mg (0.40 mmol) of protected 4-CQA (**15**) was suspended in a mixture of THF (3 mL) and 1 M HCl (15 mL). The mixture was stirred at room temperature and TLC (MeOH:EtOAc, 1:1, *v*:*v*) was used to monitor the progress of reaction. After the complete disappearance of the protected 4-CQA spot (8 days), the reaction is stopped and added with dichloromethane (5 mL) forming two layers. The aqueous phase was separated, saturated with solid NaCl, and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated with evaporator under reduced pressure to give 4-CQA, compound **17** (Scheme 3), as powder. Color: Yellow. Yield: 40%. ^{1}H NMR (400 MHz, CD_3OD, δ, ppm): 1.99-2.22 (m, 4H, Cyclohexyl-H), 4.26-4.30 (m, 2H, 2CH-OH), 4.80 (dd, 1H, *J* = 9.2, 2.9 Hz, CH-O-CO), 6.37 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.78 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.94-7.07 (m, 2H, Ar-H), 7.65 (d, 1H, *J* = 15.5 Hz, Ph-CH-CH-CO). NMR data were in good agreement with literature data [11].

2.10. Preparation of (1R,3R,4S,5R)-4-tert-butyldimethyl siloxy-1,3-dihydroxy cyclohexane-1,5-carbolactone (14)

To a solution of quinic acid lactone (**12**) (510 mg, 2.93 mmol) in DMF (4.8 mL) at 0 °C, dry triethylamine (0.5 mL), DMAP (50 mg, 0.41 mmol), tetrabutyl ammonium iodide (54 mg, 0.145 mmol) and TBSCl (505 mg, 3.37 mmol) were respectively added. The mixture was stirred for 24 h at 90 °C. After cooling to room temperature, the resultant reaction mixture was added with EtOAc (50 mL) forming some white precipitant which was filtered through celite and solvents were evaporated under reduced pressure to afford crude material. Purification was done by column chromatography on silica gel (*n*-hexane:diethyl ether, 1:1, *v*:*v*) to give the desired product, compound 14 (Scheme 3), as solid. Color: White. Yield: 32%. R_f = 0.09. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.14 (s, 3H, $Si\text{-}CH_3$), 0.17 (s, 3H, $Si\text{-}CH_3$), 0.94 (s, 9H, $C(CH_3)_3$), 1.85 (t, 1H, *J* = 11.5 Hz, Cyclohexyl-H), 2.07 (s, broad 1H, OH), 2.18 (dq, 1H, *J* = 12.0, 3.2 Hz, Cyclohexyl-H), 2.30 (dq, 1H, *J* = 11.5, 3.1 Hz, Cyclohexyl-H), 2.53 (d, 1H, *J* = 11.5 Hz, Cyclohexyl-H), 2.73 (s, broad, 1H, OH), 3.79 – 3.84 (m, 1H, CH-OTBS), 4.10 (t, 1H, *J* = 4.6 Hz, CHOH), 4.68 (t, 1H, *J* = 5.4 Hz, CH-O-CO). NMR data were in good agreement with literature data [15].

2.11. Synthesis of protected 3-CQA (18)

To a solution of monosilyl protected compound (**14**) (335 mg, 1.46 mmol) and DMAP (22 mg, 0.17 mmol), caffeoyl chloride (**3**) (583 mg, 2.63 mmol) were added. The mixture was stirred for 24 h at room temperature. Upon the completion of reaction, the resultant reaction mixture was dissolved with 22 ml dichloromethane then poured into crushed ice before titrating it with 1 M HCl to pH ≈ 2. The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered and solvent was evaporated under reduced pressure to give 824 mg crude.


62%
13
DMAP, Imidazole, TBSCl
DMF, 0 °C, 2 h
r.t., 3 h
a.
p-TsOH
Toluene-DMF
Reflux, 18 h
86%
4
12
DMAP, Bu4NI, TEA, TBSCl
DMF
90 °C, 24 h
32%
14
b.
3
Pyridine
DMAP
r.t.. 24 h
13
15
60%
16
15%
r.t., 8 days
40%
1M HCl
H2O, THF
(4-CQA)
17
c.
3
Pyridine
DMAP
r.t., 24 h
53%
14
18
1M HCl
H2O, THF
r.t., 7 days
41 %
(3-CQA)
19

Scheme 3

Purification by column chromatography on silica gel (*n*-hexane:EtOAc, 1:1, *v*:*v*), gave the desired product of (1*R*, 3*R*, 4*S*, 5*R*)-4-*tert*-butyldimethylsiloxy-1-hydroxy,3-diacetyl caffeoyl cyclohexane-1,5-carbolactone (**18**), Scheme 3, as solid. Color: White. Yield: 53%. FT-IR (KBr, ν, cm^{-1}): 3448 (OH), 3059 (C-H, aromatic) 2954 (C-H, alkyl), 2931 (C-H, alkyl), 1780 (C=O, ester), 1716 (C=O, ester), 1638 (C=C, alkenyl), 1506 (C=C, aromatic), 1255 (Si-CH_3), 1206 (C-O-C, ester), 1178 (C-O-C, ester), 1094 (Si-O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.03 (s, 3H, Si-CH_3), 0.05 (s, 3H, Si-CH_3), 0.91 (s, 9H, C(CH_3)$_3$), 2.15-2.21 (m, 2H, Cyclohexyl-H), 2.31 (s, 3H, CH_3CO-O), 2.32 (s, 3H, CH_3CO-O), 2.33-2.38 (m, 1H, Cyclohexyl-H), 2.64 (d, 1H, *J* = 11.5 Hz, Cyclohexyl-H), 2.97 (s, broad, 1H, OH), 4.37 (t, 1H, *J* = 4.6 Hz, CH-OTBS), 4.60 (t, 1H, *J* = 5.1 Hz, CH-O-Caff), 4.99 – 5.04 (m, 1H, CH-O-CO), 6.33 (d, 1H, *J* = 15.9 Hz, CO-CH-CH-Ph), 7.20 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.37 (d, 1H, *J* = 2.0 Hz, Ar-H), 7.37 (1H, dd, *J* = 8.5, 2.0 Hz, Ar-H), 7.62 (d, 1H, *J* =16.1 Hz Ph-CH-CH-CO). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 177.47 (1C, COO-lactone), 168.09 (1C, $COOCH_3$), 168.03 (1C, $COOCH_3$), 165.25 (1C, COOCH-Olefinic), 143.73 (1C, Olefinic-C), 143.52 (1C, Ar-C), 142.27 (1C, Ar-C), 132.79 (1C, Ar-C), 126.35 (1C, Ar-C), 123.88 (1C, Ar-C), 122,65 (1C, Ar-C), 118.28 (1C, Olefinic-C), 77.21 (1C, Cyclohexyl-C), 72.07 (1C, Cyclohexyl-C), 68.74 (1C, Cyclo hexyl-C), 64.36 (1C, Cyclohexyl-C), 36.32 (1C, Cyclohexyl-C), 35.71 (1C, Cyclohexyl-C), 25.51 (1C, C(CH_3)$_3$), 25.49 (1C, CH_3-C), 25.45 (1C, CH_3-C), 20.50 (1C, CH_3-C), 20.45 (1C, CH_3 COOPh), 17.77 (1C, CH_3COOPh), -4.93 (1C, CH_3Si), -5.03 (1C, CH_3-Si). HRMS FAB+: *m/z*: calculated for $C_{26}H_{35}O_{10}Si$ [M+H$^+$] = 535.1999, found 535.2005.

2.12. Synthesis of 3-CQA (19)

As much as 213 mg (0.4 mmol) of protected 3-CQA (**18**) was suspended in a mixture of THF (4 mL) and 2 M HCl (16 mL). The mixture was stirred at room temperature and TLC (MeOH:EtOAc, 1:1, *v*:*v*) was used to monitor the progress of reaction. After the complete disappearance of the protected 3-CQA spot (7 days), the reaction is stopped and added with dichloromethane (5 mL) forming two layers. The aqueous phase was separated, saturated with solid NaCl, and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated with evaporator under reduced pressure to the desired product, 3-CQA, compound **19** (Scheme 3) as powder. Color: Yellow. Yield: 41%. ^{1}H NMR (400 MHz, CD_3OD, δ, ppm): 1.96-3.3 (m, 4H, Cyclohexyl-H), 3.64 (dd, 1H, *J* = 8.4, 3.3 Hz, CH-OH-COH), 4.15 (td, 1H, *J* = 9.1, 3.9 Hz, CH-OH-OCaff), 5.36 (m, 1H, CH-O-Caff), 6.31 (d, 1H, *J* = 15.9 Hz, CO-CH-CH-Ph), 6.77 (d, 1H, *J* = 8.1 Hz, Ar-H), 6.94 (dd, 1H, *J* = 8.1, 20 Hz, Ar-H), 7.05 (d, 1H, *J* = 2.0 Hz, Ar-H), 7.59 (d, 1H, *J* = 15.9 Hz, Ph-CH-CH-CO). NMR data were in good agreement with literature data [11].

3. Results and discussion

Although the main objective of this article is reporting our findings in the preparations of the 3- and 5-CQAs using precursors as mentioned in the introduction section, the optimized synthetic results of the 1- and 4-CQAs are also inclusive. This is necessary since the methods employed and the routes of syntheses are in correlation to one and another.

3.1. Preparation of diacetyl caffeic acid chloride

Acid chloride **3** used in this work was prepared as depicted in Scheme 1, according to a known procedure [12], from caffeic acid (**1**) in two steps with the overall yield of 97%.

3.2. Synthesis of 1- and 5-CQA

Syntheses of 1- and 5-CQA were depicted in Scheme 2. Treatment of (-)-quinic acid (**4**) with 2,2-dimethoxypropane in a refluxing EtOAc and in the presence of acid catalyst, *p*-TsOH, was a simple way to prepare lactone (**5**), according to Dokli's method [13]. This lactone, in fact, possess only one hydroxyl group located at the required site to undergo an esterification reaction with acid chloride (**3**) to produce protected 1-CQA (**7**). Synthesis of compound **7** was carried out at ambient temperature in dichloromethane in the presence of basic catalyst, DMAP, attaining 75% yield from compound **5**. 1-CQA (**8**) was obtained from cleaving all the protecting groups using 2 M HCl_{aq}:THF (4:1, *v*:*v*) at room temperature for 7 days, with 89% yield from compound **7**. The lower side of the Scheme 2 is the stages for synthesizing 5-CQA. Lactone **5** underwent methanolysis with NaOMe:MeOH at room temperature, to give crude product. After purification with column chromatography over silica gel, the desired compound **6** was obtained with 78% yield from compound **5**. Protected 5-CQA was synthesized from esterification of compound **3** with compound **6**, employing exactly the same condition as synthesizing compound **7**, to give 58% of the protected CQA (**9**) and minute amounts of compound **10**. The 5-CQA (**11**) was achieved at 88% yield after treating compound **9** with 1 M HCl for 4 days at room temperature.

3.3. Synthesis of 3- and 4-CQAs

3- and 4-CQAs were synthesized according to Scheme 3. Lactone **12** was afforded with high yield by refluxing quinic acid **4** in the mixture of toluene and DMF and in the presence of *p*-TsOH. Selective hydroxyl group protection with TBSCl is governed by altering the temperature condition applied in the reaction. At lower temperature, compound **13** was more favorable while at higher temperature the isomer **14** was dominant. TBS lactone **13** was prepared by stirring compound **12** with TBSCl in DMF and in the presence of basic catalyst DMAP and imidazole, and adjusting the temperature from 0 °C to room temperature. After purification with column chromatography, the desired product was obtained, with 62% yield from compound **12**. This substance was used to synthesize protected 4-CQA by reacting it with compound **3** to give 60% yield of compound **15** and 15% of compound **16**. 4-CQA was attained (40% yield) after stirring compound **15** with 1 M HCl for 8 days. Employing the same procedure as synthesizing compound **13**, except at higher temperature, compound **14** was unsuccessful to afford. Products were traces of the two isomers. To overcome this drawback, *tetra*-butylammonium iodide and triethylamine (TEA) were used instead of imidazole. With this procedure, 32% of the desired compound **14** was afforded and used to synthesize the protected 3-CQA (**18**) with 53% yield. This ester was hydrolyzed with 1 M HCl for 7 days attaining the unprotected ester of compound **19**, 41% yield.

4. Conclusion

We have developed a convenient method for the synthesis of 3- and 5-CQAs utilizing the methyl 3,4-*o*-isopropylidene-1,5-quinate and (1*R*,3*R*,4*S*,5*R*)-4-*tert*-butyldimethylsiloxy-1,3-dihydroxycyclohexane-1,5-carbolactone as their starting materials. These starting materials underwent esterification with diacetylcaffeoyl chloride to give protected 3- and 5-CQAs. The 3-CQA and 5-CQA were achieved by hydrolysis of the protected esters with dilute concentration of HCl.

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