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Selective Synthesis of Caffeoylquinic Acids (CQAs) Using Transesterification of Vinyl Caffeate

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Abstract

A new method for selective synthesis of caffeoylquinic acids (CQAs) was applied. 1-, 3-, and 4-CQAs were successfully prepared from transesterification of a novel compound, 3, 4-di-*tert*-butyldimethylsiloxyvinylcinnamate, (**3**) in the presence of $La(NO_3)_3.H_2O/P(n\text{-octyl})_3$ catalyst with regioselectively protected quinic acids (QAs). Intermediate ester compounds **6**, **13** and **15** were afforded from the esterification reaction. After purifications, these novel esters were then treated with dilute HCl_{aq} to achieve the titled mono-CQAs with 45%, 51%, and 47%, respectively from their protected forms. All the new obtained compounds were confirmed to their ^{1}H NMR, ^{13}C NMR and IR spectra. Their molecular weight were calculated and confirmed to the High Resolution Mass Spectrometer (HRMS) results.

Keywords: Trans-esterification**,** chemical synthesis**,** caffeoylquinic acids**,** protected, quinic acids**,** vinyl caffeate**,** lanthanum (III) nitrate monohydrate catalyst

1. INTRODUCTION

Caffeoylquinic acids (CQAs) and derivatives are natural compounds possessing various biological activities, [1-3] which have been attracting many researchers to do extensive studies for many years. While these secondary metabolites found in a wide

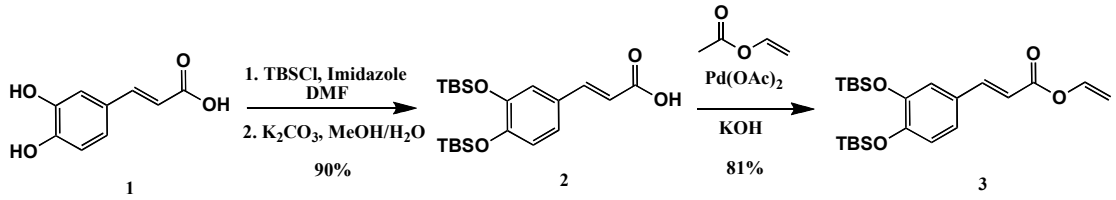
variety of natural sources, potato [4], coffee products and apple are among those sources constituting high percentage of CQAs [5-7]. Some vegetables, for example, spinach and leeks also constitute these compounds [8, 9]. Isolation from natural products has been a more commonly preferable method used to obtain the substances; convenient methods for practical synthesis of CQAs remain interesting, however, and still very tempting to deal with. In fact, the synthesis of CQAs via chemical methods is still quite challenging resulting only few publications, such as by Hemmerle*et al.* [10] and Lorentz *et al.* [11] Among these papers, Sefkow and co-workers' [12, 13] have reported the synthesis of 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*. [14] 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.

In our previous report [15], we developed a different pathway to synthesize 3-and 5-CQAs through an esterification reaction of 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 with caffeoyl chloride. In this article, we are reporting a new synthetic strategy in selective construction of CQA isomers using caffeic acid vinyl ester. The suitable synthetic method of caffeic acid vinyl esters has been relatively unknown.[16-18] So we also describe a new synthetic method for the preparation of these vinyl esters. Transesterification reactions of caffeic acid vinyl ester with protected quinic acids were assisted by lanthanum (III) nitrate monohydrate as catalyst.[19] The esterification products were protected CQAs and the corresponding CQAs were achieved after the removal of all the protecting groups using low concentration of hydrochloric acid.

2. EXPERIMENTAL

2.1 General procedures

Chemical reactions took place in argon atmosphere in dried glassware. High grade of purity of commercially available reagents were used and solvents were always purified before using them in reactions. Kieselgel 60 F_{254} plates (Merck) were used to perform thin layer chromatographic (TLC) analyses and detection was carried out under UV light or by spraying it with 20% ethanolic-sulfuric acid. Purifications of resulted products were performed using flash chromatography on Silica Gel 60N, 40-50 μm. Solvents were removed with Iwaki Rotary Evaporator REN-1000. Recording of ^{1}H and ^{13}C NMR spectra were performed in JEOL NMR of JNM-LA 500 while JEOL JMS-700 was used to record High Resolution Mass Spectrophotometer (HRMS) spectra. Infrared spectra of samples were obtained from HORIBA FT-720 FT-IR Spectrometer.



Scheme 1. Synthesis of 3, 4-di-*tert*-butyldimethylsiloxyvinylcinnamate (**3**) from caffeic acid (**1**) via ditbs-cinnamic acid (**2**)

2.2 Synthesis of 3, 4-di-*tert*-butyldimethylsiloxycinnamic acid (2)

Adapted procedure from Takahashi, M. et al. was employed in this experiment. [20] Caffeic acid, **1**, (180 mg, 1 mmol) and imidazole (477 mg, 7 mmol) were added to a two-neck round bottom flask then dissolved with DMF (1 mL). To the solution mixture, *tert*-butyldimethylsylyl chloride (TBSCl) (497 mg, 3.3 mmol) was added then stirred at room temperature for 6 hours. After cooling to room temperature, 5 ml of distilled water was added to quench the reaction. The resultant reaction was extracted with Hexane:EtOAc (1:1), (2 × 15 mL). Organic phase was separated, washed with brine (2 × 15 mL), dried over sodium sulfate and solvents were evaporated under reduced pressure to give crude product, which was used for the next step of reaction without any further purification. This crude material was dissolved in 50% methanol (w/w). To the reaction mixture, potassium carbonate (150 mg, 1.1 mmol) was added and stirred at room temperature for 1 hour then quenched with 3% HCl (w/w) (10 mL). Extraction with Hexane:EtOAc (1:1), 2 × 15 mL was performed to get the organic phase that was subsequently washed it with brine (2 × 15 mL), dried it over sodium sulfate and finally, solvents were evaporated under reduced pressure to give the desired compound **2** (**Scheme 1**) as pale yellow solid. Yield: 86%. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.22 (s, 6H, $(CH_3)_2$-Si), 0.23 (s, 6H, $(CH_3)_2$-Si), 0.99 (s, 9H, $(CH_3)_3C$), 1.00 (s, 9H, $(CH_3)_3C$), 6.25 (d, 1H, *J* = 15.5 Hz, CO-CH-CH-Ph), 6.84 (d, 1H, *J* = 9.2 Hz, Ar-H), 7.04-7.06 (m, 2H, Ar-H), 7.68 (d, 1H, *J* = 15.5 Hz, Ph-CH-CH-CO).

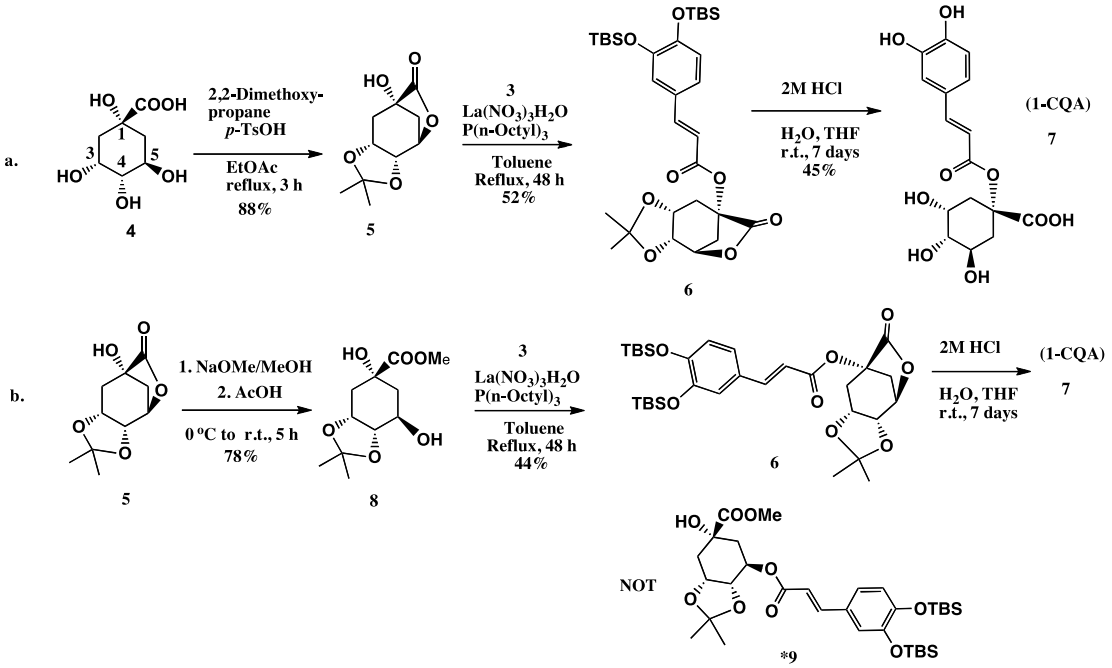
2.3 Synthesis of (*E*)-vinyl 3-[3, 4-bis(*tert*-butyldimethylsiloxy)phenyl]acrylate (3)

To a two-neck flask, 3, 4-di-*tert*-butyldimethylsiloxycinnamic acid (613 mg, 1.5 mmol), vinyl acetate (2.3 mL, 24 mmol) and palladium (II) acetate (18 mg, 0.15 mmol) were added. The reaction mixture was stirred at room temperature for 10 minutes and subsequently, potassium hydroxide (10 mg, 0.15 mmol) was added. The reaction mixture was stirred at 40 °C for 4 hours, then diluted with 20 mL of EtOAc, filtered through celite and concentrated by evaporator under reduced pressure. Purification was done over column chromatography on silica gel (Hexane:EtOAc, 5:1, v/v) to give 580 mg of (**3**), (**Scheme 1**), as yellow liquid. (Rf = 0.82 on Hexane:EtOAc, 4:1, v/v). Yield: 81%. IR (film, ν, cm^{-1}): 3005 (C-H, alkene), 2958 (C-H, methyl), 1713 (C = O, ester), 1558 (C = C, aromatic), 1508 (C = C, aromatic), 1269 (Si-CH_3), 1152 (C-O, ester), 1092 (Si-O), 915 (C = CH_2, Vinyl). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.22 (s, 6H, $(CH_3)_2$-Si), 0.23 (s, 6H, $(CH_3)_2$-Si), 0.99 (s, 9H,

$(CH_3)_3C$), 1.00 (s, 9H, $(CH_3)_3C$), 4.62 (dd, 1H, *J* = 6.6, 1.4 Hz, CH-C-vinyl), 4.97 (dd, 1H, *J* = 14.0, 1.4 Hz, CH-C-vinyl), (6.25 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.83 (d, 1H, *J* = 9.2 Hz, Ar-H), 7.03-7.05 (m, 2H, Ar-H), 7.42 (dd, 1H, *J* = 13.7, 6.3 Hz, O-CH-vinyl), 7.67 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 164.41 (1C, Carboxylic-C), 150.08 (1C, Ar-C), 147.40 (1C, Ph-CH), 146.81 (1C, Ar-C), 141.54 (1C, Ar-C), 127.84 (1C, Ar-C), 122.78 (1C, Ar-C), 121.32 (1C, Ar-C), 120.70 (1C, Ar-C), 114.22 (1C, benz-CH), 97.63 (1C, CH_2-Vin), 26.04 (3C, (CH_3)-C), 26.00 (3C, (CH_3)-C), 18.65 (1C, C-CH_3), 18.60 (1C, C-CH_3),-3.91 (2C, $(CH_3)_2$-Si),-3.95 (2C, $(CH_3)_2$-Si). HRMS (EI): m/z: calcd for $C_{23}H_{38}O_4Si_2$ $[M]^+$, 434.2309; found 434.2306.

2.4 Synthesis of (1*S*, 3*R*, 4*R*, 5*R*)-1-[3-(3, 4-di-*O*-*tert*-butyldimethylsiloxy)caffeoyl-1, 3-quinic acid lactone)] (6)

Lanthanum nitrate monohydrate (43 mg, 0.12 mmol) and tri-*n*-octyl phosphine (91 mg, 0.24 mmol) were added to a-two neck flask and then dissolved with toluene (4 mL). The mixture was stirred at room temperature for 10 minutes. Into the solution mixture, lactone **5** (prepared based on procedure from reference 14)(254 mg, 1.19 mmol) and vinyl ester caffeate (515 mg, 1.19 mmol) were added and then stirred at reflux temperature for 48 hours. After cooling to room temperature, 5 drops of distilled water was added to quench the reaction. Then, it was dried over sodium sulfate and solvents were evaporated under reduced pressure. Purification was done by column chromatography (Hex: EtOAc, 4:1 v/v) to give **6**, as waxy white solid. Yield: 52%. TLC (Hex: EtOAc, 5:1, v/v): Rf = 0.40. FT-IR (KBr, ν, cm^{-1}): 3046 (C-H, alkene), 2958 (C-H, methyl), 2931 (C-H, methyl), 2859 (C-H, methyl), 1806 (C = O, γ-lactone), 1720 (C = O ester) 1633 (C = C, alkenyl), 1595 (C = C, aromatic), 1511 (C = C, aromatic), 1473 (C = C, aromatic), 1463 (CH_2-sciss-Cyclohex), 1259 (Si-CH_3), 1155 (C-O, ester), 1072 (Si-O). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.21 (s, 6H, $(CH_3)_2$-Si), 0.22 (s, 6H, $(CH_3)_2$-Si), 0.98 (s, 9H, $(CH_3)_3C$), 0.99 (s, 9H, $(CH_3)_3C$), 1.34 (s, 3H, CH_3-CO_2CH_3), 1.54 (s, 3H, $CH_3CO_2CH_3$), 2.44 (dd, 1H, *J* = 14.3, 3.4 Hz, Cyclohexyl-H), 2.53 (ddd, 1H, *J* = 14.5, 7.6, 2.1 Hz, cyclohexyl-H), 2.63 (d, 1H, *J* = 11.5 Hz, Cyclohexyl-H), 3.11 (dd, 1H, *J* = 11.5, 6.9 Hz, Cyclohexyl-H), 4.35 (d, 1H, *J* = 5.2 Hz, CH-O-CO), 4.57 (td, 1H, *J* = 7.0, 3.1 Hz, CH-O-CO), 4.81 (dd, 1H, *J* = 6.3, 2.3 Hz, CH-O-CH_2), 6.22 (d, 1H, *J* = 15.5 Hz, CO-CH-CH-Ph), 6.82 (d, 1H, *J* = 8.6 Hz, Ar-H), 7.00-7.26 (m, 2H, Ar-H), 7.60 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 173.77 (1C, COO-lactone), 165.40 (1C, CO-Olefinic), 149.99 (1C, Ar-C), 147.30 (1C, Ar-C), 146.79 (1C, Olefinic-C), 127.68 (1C, Ar-C), 122.79 (1C, Ar-C), 121.22 (1C, Ar-C), 120.58 (1C, C-$(CH_3)_2$), 114.30 (1C, Ar-C), 109.99 (1C, Olefinic-C), 76.09 (1C, Cyclohexyl-C), 75.48 (1C, Cyclohexyl-C), 72.55 (1C, Cyclohexyl-C), 71.27 (1C, Cyclohexyl-C), 35.73 (1C, Cyclohexyl-C), 30.83 (1C, Cyclohexyl-C), 27.06 (2C, C-$(CH3)_3$), 25.95 (6C, Methyl-C-CSi), 24.43 (1C, Methyl-CO-lactone), 18.53 (1C, Methyl-CO-lactone),-3.98 (4C, Methyl-Si). HRMS FAB+: m/z: calcd for $C_{31}H_{49}O_8Si_2$ $[M+H^+]$, 605.2960; found 605.2973.



Scheme 2. Synthesis of 1-CQA (**7**) from esterification of protected quinic acid (**5**) with protected vinyl caffeate (**3**) (a), attempt to synthesize 5-CQA (b). ***9** should be the expected product of the reaction of **8** and **3**, but not detected from NMR and IR spectra.

2.5. Preparation of 1-CQA (7)

As much as 209 mg (0.34 mmol) of compound **6** was dissolved in a mixture of THF (15 mL) and 2 M HCl (7.5 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 crude1-CQA. Purification was attained by column chromatograph using EtOAc as eluent to remove all the impurities; followed by methanol to give the desired compound **7** (**Scheme 2**), as yellow powder. Yield: 45%. ^{1}H NMR (500 MHz, D_2O, δ, ppm): 1.90 (dd, 1H, *J* = 13.7, 10.9 Hz, Cyclohexyl-H), 2.12 (dd, 1H, *J* = 15.2, 3.2 Hz, Cyclohexyl-H), 2.41 (d, 1H, *J* = 13.7 Hz, Cyclohexyl-H), 2.50 (d, 1H, *J* = 15.5 Hz, Cyclohexyl-H), 3.56 (dd, 1H, *J* = 9.2, 3.4 Hz, CH-OHCH$_2$), 4.05 (td, 1H, *J* = 9.7, 4.8 Hz, CH-OHCH$_2$), 4.16 (d, 1H, *J* = 3.4 Hz, CH-OHCOH), 6.34 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.87 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.05 (d, 1H, *J* = 8.6 Hz, Ar-H), 7.11 (s, 1H, Ar-H), 7.53 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO).

2.6. Preparation of methyl (1*R*, 3*R*, 4*S*, 5*R*)-3, 4-*O*-isopropylidene-1, 5-quinate (8)

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 **8** (Scheme **2**), as powder, (R_f = 0.17). Color: White. Yield: 78%. ^{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 [21].

2.7 Synthesis of protected ester 5-CQA (9)

Lanthanum nitrate monohydrate (43 mg, 0.12 mmol) and tri-*n*-octyl phosphine (91 mg, 0.24 mmol) were added to a-two neck flask and then dissolved with toluene (4 mL). The mixture was stirred at room temperature for 10 minutes. Into the solution mixture, lactone **8** (320 mg, 1.3 mmol) and vinyl ester caffeate (565 mg, 1.3 mmol) were added and then stirred at reflux temperature for 48 hours. After cooling to room temperature, 5 drops of distilled water was added to quench the reaction. Then, it was dried over sodium sulfate and solvents were evaporated under reduced pressure. Purification was done by column chromatography (Hex: EtOAc, 4:1, v/v) to give product, **6** instead of **9**, **Scheme 2**, as waxy solid. TLC (Hex: EtOAc, 5:1, v/v): Rf = 0.40. Color: White. Yield: 44%. FT-IR (KBr, ν, cm^{-1}) and ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm) are identical with those for compound **6**. 5-CQA was also attempted to achieve, however, the resulted product was 1-CQA (**7**).

2.8. Preparation of (1*R*, 3*R*, 4*S*, 5*R*)-3-*tert*-butyldimethylsiloxy-1, 4-dihydroxycyclohexane-1, 5-carbolactone (11)

To a solution of lactone **10** (prepared based on procedure of reference 18) (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 **11** (**Scheme 3**), as waxy white solid (62% yield), 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 [18].

2.9. Synthesis of (1*R*, 3*R*, 4*S*, 5*R*)-4-[3-(3, 4-di-*O*-*tert*-butydimthylsiloxy)caffeoyl-3-*tert*-butydimthylsiloxy-1-hydroxycyclohexane-1, 5-carbolactone] (13)

Lanthanum nitrate monohydrate (37 mg, 0.10 mmol) and tri-*n*-octyl phosphine (77 mg, 0.20 mmol) were added to a-two neck round bottom flask and then dissolved with toluene (4 mL). The mixture was stirred at room temperature for 10 minutes. Into the solution mixture, lactone **11** (288 mg, 1.0 mmol) and vinyl ester caffeate (435 mg, 1.0 mmol) were added and then stirred at reflux temperature for 48 hours. After cooling to room temperature, 5 drops of distilled water was added to quench the reaction. Then, it was dried over sodium sulfate and solvents were evaporated under reduced pressure. Purification was done by column chromatography (Hex: EtOAc, 4:1, v/v) to give **13** as yellow liquid. TLC (Hex: EtOAc, 5: 1 v / v): R_f = 0.40. Yield: 46%. FT-IR (KBr, ν, cm^{-1}): 3442 (OH), 3042 (C-H, alkene) 2955 (C-H, methyl), 2930 (C-H, methyl), 2859 (C-H, methyl), 1805 (C = O, γ-lactone), 1721 (C = O, ester), 1632 (C = C, alkenyl), 1596 (C = C, aromatic), 1509 (C = C, aromatic), 1473 (C = C, aromatic), 1464 (CH_2-sciss-Cyclohex), 1426 (C = C, aromatic), 1255 (Si-CH_3), 1152 (C-O, ester), 1064 (Si-O). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.10 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si), 0.20 (s, 6H, $(CH_3)_2$-Si), 0.22 (s, 6H, $(CH_3)_2$-Si), 0.91 (s, 9H, $(CH_3)_3$C), 0.98 (s, 9H, $(CH_3)_3$C), 0.99 (s, 9H, $(CH_3)_3$C), 2.22 (d, 2H, *J* = 8.6 Hz, Cyclohexyl-H), 2.68 (d, 1H, *J* = 11.5 Hz, cyclohexyl-H), 2.97 (s, 1H,-OH), 3.06 (dd, 1H, *J* = 11.5, 6.3 Hz, Cyclohexyl-H), 3.98-4.03 (m, 2H, Cyclohexyl-H), 4.96 (dd, 1H, *J* = 6.0, 4.3 Hz, Cyclohexyl-H), 6.22 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.81 (d, 1H, *J* = 8.6 Hz, Ar-H), 6.99-7.01 (m, 2H, Ar-H), 7.60 (d, 1H, *J* = 15.5 Hz, Ph-CH-CH-CO). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 172.95 (1C, COO-lactone), 165.46 (1C, CO-Olefinic), 150.05 (1C, Ar-C), 147.35 (1C, Ar-C), 146.82 (1C, Olefinic-C), 127.72 (1C, Ar-C), 122.92 (1C, Ar-C), 121.26 (1C, Ar-C), 120.54 (1C, Ar-C), 114.37 (1C, Olefinic-C), 76.41 (1C, Cyclohexyl-C), 76.37 (1C, Cyclohexyl-C), 67.03 (1C, Cyclohexyl-C), 66.51 (1C, Cyclohexyl-C), 37.29 (1C, Cyclohexyl-C), 33.17 (1C, Cyclohexyl-C), 26.00 (6C, $(CH_3)_3$-C), 25.79 (3C, $(CH_3)_3$-C), 18.59 (2C, C-$(CH_3)_3$), 18.06 (1C, C-$(CH3)_3$),-3.95 (4C, Methyl-Si),-3.98 (2C, Methyl-Si). HRMS EI+: m/z: calcd for $C_{34}H_{58}O_8Si_3$ [M^+], 678.3439; found 678.3438.

2.10. Synthesis of 4-CQA (14)

As much as 213 mg (0.40 mmol) of protected 4-CQA (**13**) was suspended in a mixture of THF (15 mL) and 2 M HCl (7.5 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 (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 give crude 4-CQA. Purification was attained by column chromatograph using EtOAc as eluent to remove all the impurities; followed by methanol to give the desired compound **14** (**Scheme 3**), as yellow powder. Yield: 51%. ^{1}H NMR (400 MHz, D_2O, δ, ppm): 1.89 (t, 1H, *J* = 10.0 Hz, Cyclohexyl-H), 2.09 (d, 1H, *J* = 15.6 Hz, Cyclohexyl-H), 2.38 (d, 1H, *J* = 11.5 Hz, Cyclohexyl-H, 2.50 (d, 1H, *J* = 15.9 Hz, Cyclohexyl-H), 3.55 (d, 1H, *J* = 8.1Hz,

CH-OHCH$_2$), 4.02 (s, 1H, *J* = 9.5, 4.2 Hz, CH-OHCH$_2$), 4.14 (s, 1H, CH-OHCOH), 6.37 (d, 1H, *J* = 15.9 Hz, CO-CH-CH-Ph), 6.89 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.08 (d, 1H, *J* = 7.3 Hz, Ar-H), 7.15 (s, 1H, Ar-H), 7.55 (d, 1H, *J* = 16.1 Hz, Ph-CH-CH-CO).

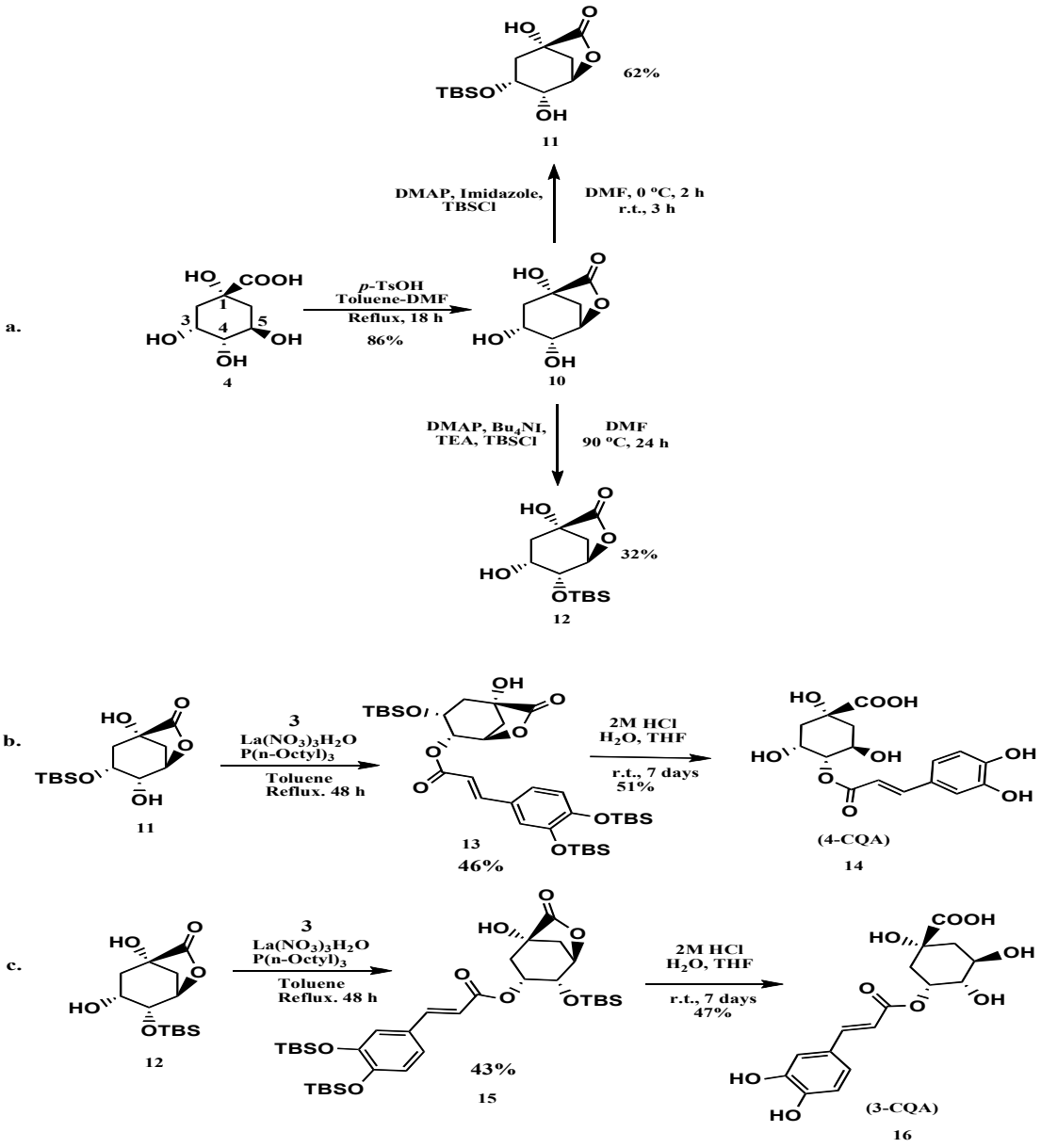
2.11. Preparation of (1*R*, 3*R*, 4*S*, 5*R*)-4-*tert*-butyldimethylsiloxy-1, 3-dihydroxy cyclohexane-1, 5-carbolactone (12)

To a solution of quinic acid lactone (**10**) (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 **12** (**Scheme 3**), as solid. R_f = 0.09. Color: White. Yield: 32%. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.14 (s, 3H, Si-CH$_3$), 0.17 (s, 3H, Si-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 [18].

2.12. Synthesis of (1*R*, 3*R*, 4*S*, 5*R*)-3-[3-(3, 4-di-*O*-*tert*-butydimthylsiloxy)caffeoyl-4-*tert*-butydimthylsiloxy-1-hydroxycyclohexane-1, 5-carbolactone (15)

Lanthanum nitrate monohydrate (37 mg, 0.10 mmol) and tri-*n*-octyl phosphine (77 mg, 0.20 mmol) were added to a-two neck round bottom flask and then dissolved with toluene (4 mL). The mixture was stirred at room temperature for 10 minutes. Into the solution mixture, lactone **12** (288 mg, 1.0 mmol) and vinyl ester caffeate (435 mg, 1.0 mmol) were added and then stirred at reflux temperature for 48 hours. After cooling to room temperature, 5 drops of distilled water was added to quench the reaction. Then, it was dried over sodium sulfate and solvents were evaporated under reduced pressure. Purification was done by column chromatography (Hex: EtOAc, 4:1 v/v) to give **15**, as waxy white solid, TLC (Hex: EtOAc, 5:1 v/v): Rf = 0.40. Yield: 43%. FT-IR (KBr, ν, cm^{-1}): 3566 (OH), 3063 (C-H, alkene) 2954 (C-H, methyl), 2932 (C-H, methyl), 2858 (C-H, methyl), 1804 (C = O, γ-lactone), 1720 (C = O, ester), 1633 (C = C, alkenyl), 1596 (C = C, aromatic), 1510 (C = C, aromatic), 1473 (C = C, aromatic), 1463 (CH$_2$-sciss-Cyclohex), 1425 (C = C, aromatic), 1256 (Si-CH$_3$), 1155 (C-O, ester), 1062 (Si-O). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.15 (s, 3H, CH$_3$Si), 0.18 (s, 3H, CH$_3$Si), 0.21 (s, 6H, (CH$_3$)$_2$-Si), 0.22 (s, 6H, (CH$_3$)$_2$-Si), 0.95 (s, 9H, (CH$_3$)$_3$C), 0.98 (s, 9H, (CH$_3$)$_3$C), 0.99 (s, 9H, (CH$_3$)$_3$C), 2.13 (dt, 2H, *J* = 22.5, 10.5 Hz, Cyclohexyl-H), 2.38 (dq, *J* = 11.9, 3.2 Hz, Cyclohexyl-H), 2.61 (d, 1H, *J* = 11.5 Hz, cyclohexyl-H), 3.06 (dq, 1H, *J* = 11.2, 3.2 Hz, Cyclohexyl-H), 3.89-3.96 (m, 1H, Cyclohexyl-H), 4.14 (1H, t, *J* = 4.6 Hz, OH), 4.75 (dd, 1H, *J* = 6.3, 4.6 Hz, Cyclohexyl-H), 6.23 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.82 (d, 1H, *J* = 9.2 Hz, Ar-H), 7.00-7.02-7.01 (m, 2H, Ar-H), 7.59 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO). ^{13}C

NMR (125 MHz, $CDCl_3$, δ, ppm): 172.43 (1C, COO-lactone), 165.52 (1C, CO-Olefinic), 150.06 (1C, Ar-C), 147.36 (1C, Ar-C), 146.79 (1C, Olefinic-C), 127.73 (1C, Ar-C), 122.84 (1C, Ar-C), 121.28 (1C, Ar-C), 120.66 (1C, Ar-C), 114.41 (1C, Olefinic-C), 76.54 (1C, Cyclohexyl-C), 76.35 (1C, Cyclohexyl-C), 67.40 (1C, Cyclohexyl-C), 66.10 (1C, Cyclohexyl-C), 37.72 (1C, Cyclohexyl-C), 33.33 (1C, Cyclohexyl-C), 26.01 (6C, $(CH_3)_3$-C), 25.82 (3C, $(CH_3)_3$-C), 18.60 (2C, C-$(CH_3)_3$), 18.16 (1C, C-$(CH3)_3$),-3.94 (4C, Methyl-Si),-4.55 (2C, Methyl-Si). HRMS FAB+: m/z: calcd for $C_{34}H_{59}O_8Si_3$ [$M+H^+$], 679.3512; found 679.3504.



Scheme 3. Synthesis of lactones as starting materials (a), synthesis of 4-CQA (b) and synthesis of 3-CQA (c).

2.13. Synthesis of 3-CQA (16)

As much as 213 mg (0.4 mmol) of protected 3-CQA (**13**) was suspended in a mixture of THF (15 mL) and 2 M HCl (7.5 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 give crude 3-CQA. Purification was attained by column chromatograph using EtOAc as eluent to remove all the impurities; followed by methanol to give the desired compound **16** (**Scheme 3**), as yellow powder. Yield: 47%. ^{1}H NMR (500 MHz, D_2O, δ, ppm): 1.92 (t, 1H, *J* = 12.9 Hz, Cyclohexyl-H), 2.09 (d, 1H, *J* = 14.3 Hz, Cyclohexyl-H), 2.41 (d, 1H, *J* = 13.7 Hz, Cyclohexyl-H), 2.50 (d, 1H, *J* = 14.9 Hz, Cyclohexyl-H), 3.57 (d, 1H, *J* = 8.6 Hz, CH-OHCH_2), 4.05 (td, 1H, *J* = 9.5, 4.2 Hz, CH-OHCH_2), 4.16 (s, 1H, CH-OHCOH), 6.29 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.81 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.97 (d, 1H, *J* = 8.6 Hz, Ar-H), 7.02 (s, 1H, Ar-H), 7.46 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO).

3. RESULTS AND DISCUSSION

3.1. Preparation of ditbs vinyl caffeate

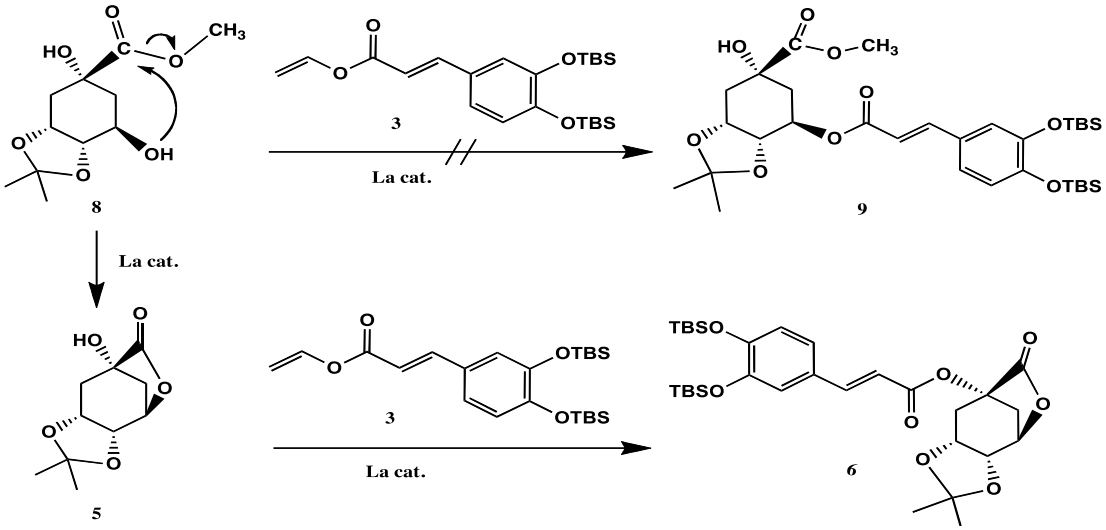
Vinyl caffeate ester **3** used in this work was prepared as depicted in **Scheme 1**, from caffeic acid (**1**) in two steps. The first step of reaction was protection of catechol group with TBSCl in the presence of imidazole in DMF, followed by treatment of the resulted product with potassium carbonate in 50% of methanol/water (w/w) to yield 90% of acid **2,** based on known procedure.[17] The resulted acid was then reacted with vinyl acetate in the presence of palladium acetate as catalyst in basic condition to yield new compound, **3**, (81%) as a handful starting material used to synthesize the proposed CQAs. The success in the formation of this compound was confirmed by results of spectroscopy analysis. From IR spectra, the most characteristic one is the C-H bending for vinyl group at 915 cm^{-1}. Also the appearance of peaks at1713 $cm^{-1}$for C = O ester, 1269 $cm^{-1}$for Si-CH_3, 1152 cm^{-1} C-O ester, 1092 cm^{-1}Si-O.Moreover, the appearance of signals at 4.62 (dd, 1H, *J* = 6.6, 1.4 Hz, CH-C-vinyl), 4.97 (dd, 1H, *J* = 14.0, 1.4 Hz, CH-C-vinyl) and 7.42 (dd, 1H, *J* = 13.7, 6.3 Hz, O-CH-vinyl) on proton NMR spectrum clearly indicated the conversion of carboxylic acid**2**to vinyl ester**3**. HRMS result concluded that **3**was achieved and completely isolated, showing an agreement result of the calculated data with the figure found from HRMS analysis.

3.2. Synthesis of 1-CQA and 5-CQA

Synthesis of 1-CQA is shown in **Scheme 2(a)**. Reaction of (-)-quinic acid(**4**) with 2, 2-dimethoxypropane in a refluxing EtOAc, with the presence of acid catalyst, *p*-TsOH, according to Dokli's method [14], produced the desired lactone (**5**). This lactone has only one hydroxyl group located at the required site to undergo an esterification reaction with tbs-protected vinyl caffeate (**3**) producing protected 1-CQA (**6**). Reaction was performed at refluxed toluene in the presence of

$La(NO_3)_3.H_2O$/P(*n*-octyl)$_3$ as catalyst, attaining 52% yield from compound **5**.The formation of compound **6** was assessed from its IR and NMR spectra, as well as from HRMS result. Disappearance of peak at 915 cm^{-1} was an evident that transesterification occurred, supported also by the appearance of some peaks from lactone. For example, a very strong peak at 1806 $cm^{-1}$is a typical C = O absorption for γ-lactone and the peak at 1463 cm^{-1} represented CH_2 scissoring for cyclohexane.[23]From the proton NMR spectrum, all protons/signals attributed to compound **6** are well indicated (in the experimental section). So do the 13 carbon NMR signals. From HRMS analysis, the m/z found is consistent with calculation result concluding the achievement of **6**.1-CQA (**7**) was obtained from removing all the protecting groups using 2 M HCl_{aq}:THF (4:1, v/v) at room temperature for 7 days, with 45% yield from compound **6**.

Attempt to synthesize 5-CQA is depicted in **Scheme 2(b)**. Protected quinic acid (**8**) was reacted with (**3**) at the same condition applied for making 1-CQA. Interestingly, the resulted product was not compound **9**, as expected. Based on proton NMR spectrum, the product was compound **6**, this was also supported by the IR spectrum. It seems that at high temperature, lactone **8**, which is an ester underwent an intramolecular transesterification between the methoxy group with hydroxyl group at number 5 of the compound rather than an intermolecular transesterification with **3**. It may occur by the help of catalyst, $La(NO_3)_3.H_2O$, being used in this experiment. As acid catalyst, lanthanum(III) nitrate functions like *p*-TsOH, [24] as for the formation of **10** from **4**. It could also be boosted by the involvement of P(*n*-octyl)$_3$ to generate an acid-base catalyst of lanthanum alkoxide (**Scheme 4**)[25]. Hence, this process led to the formation of lactone **5**, which then reacted with vinyl caffeate to form ester **6** (protected 1-CQA). To obtain 5-CQA, we have to prepare the alternative protected quinic acid that does not possess ester-protecting groups. The approaches are in progress.



Scheme 4. Reaction route to provide protected-1CQA (**6**) via intramolecular transesterification

3.3.Synthesis of 4-and 3-CQAs

4-and 3-CQAs were synthesized according to **Scheme 3**. Lactone **10** was afforded with high yield by refluxing quinic acid **4** in the mixture of toluene and DMF and with the presence of *p*-TsOH. Selective hydroxyl group protection with TBSCl was conducted by adjusting the temperature condition applied for the reaction. At lower temperature, compound **11** was more favorable while at higher temperature the isomer **12** was dominant. TBS protected lactone **11** was prepared by stirring compound **10** with TBSCl in DMF, 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 **10**. This substance was used in the synthesis of protected 4-CQA by reacting it with compound **3** to give 46% yield of the desired compound **13**. The confirmation that compound**13** had been obtained was examined from its IR and NMR spectra as well as HRMS data. As for compound **6**, peak at 915 cm^{-1} was also unidentified in the product proofing that transesterification occurred, this also was supported by the appearance some peaks from lactone. For example, a very strong peak at 1805 $cm^{-1}$is a typical C = O absorption for γ-lactone. Also the peak at 1463 cm^{-1} represented CH_2 scissoring for cyclohexane.[23]A typical broad peak at 3442 is assigned for OH absorption. All protons/signals attributed to compound **13** are clearly presented in the experimental section. So do the 13 carbon NMR signals. The m/z found from HRMS analysis is consistent with calculation result.4-CQA was attained (51% yield) of column chromatograph after which compound **13** was stirred with 2 M HCl for 7 days.

Employing a similar procedure to the synthesis of **11**, except at higher temperature, compound **12** was prepared by using *tetra*-butylammonium iodide and triethylamine (TEA) instead of imidazole. With this procedure, 32% of the desired compound **12** was afforded then used in the synthesis of the protected 3-CQA (**15**), obtaining 43% yield. Spectrophotometry data analysis supported the formation**15**.For instance, the peak at 915 cm^{-1} disappeared. Strong peak at 1804 $cm^{-1}$for C = O absorption for γ-lactone was also found.[23] Also the peak at 1463 cm^{-1} representing CH_2 scissoring for cyclohexane was also found as well asa broad peak at 3441for OH absorption was found. All protons/signals attributed to compound **13** are clearly presented in the experimental section. The m/z found from HRMS analysis is consistent with calculation result. This ester was hydrolyzedwith 2 M HCl for 7 days followed by purification over column chromatograph attaining the unprotected ester of compound **16** with 47% yield.

4. CONCLUSION

We have developed a new method for selective synthesis of 1-, 3-and 4-CQAs via transesterification reaction of tbs-protected vinyl caffeate with regioselectively protected quinic acids. This approach is quite convenient and promising because it is innovating another way for obtaining esters. Nonetheless, efforts to improve the yields of esterification are needed since the yields afforded so far are still moderate.

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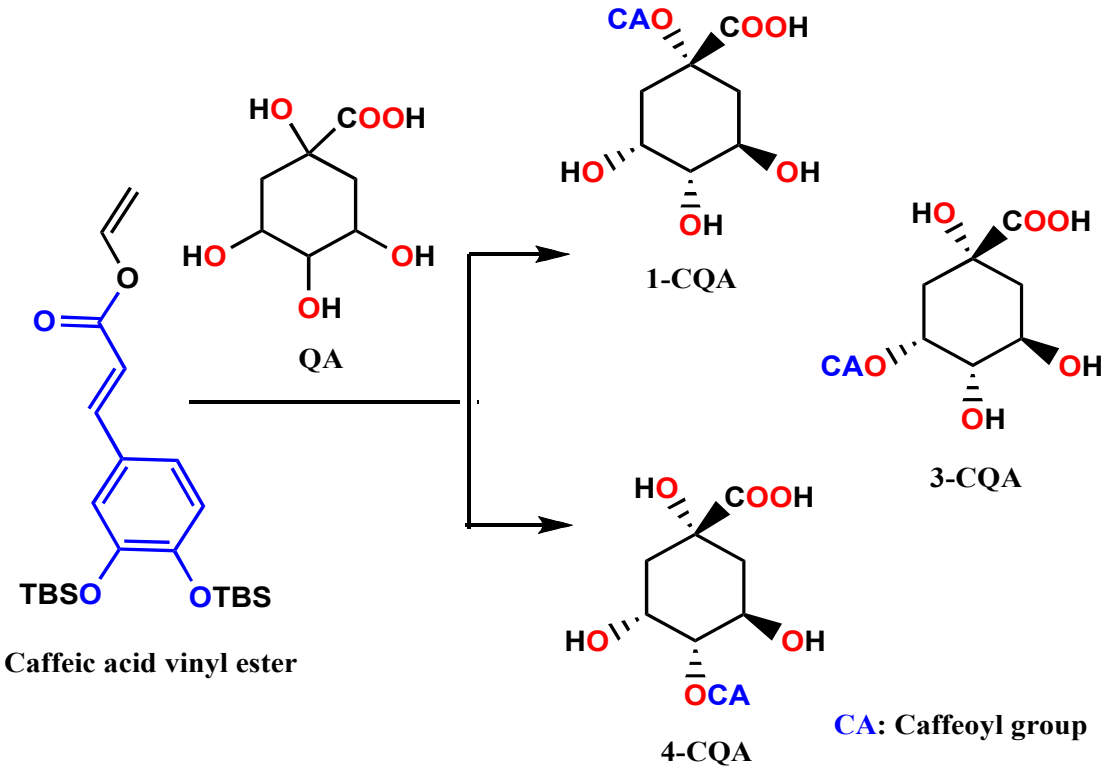

Biographical sketch

REFERENCES

[1] Fujioka, K. andShibamoto, T., Quantitation of volatiles and nonvolatile acids in an extract from coffee beverages: Correlation with antioxidant activity, *J. Agr. Food Chem.* **2006**, *54*, 6054-6058.

[2] Miyamae, Y., Kurisu, M., Murakami, K., Han, J. Isoda, H.; Irie, K. andShigemori, H., Protective effects of caffeoylquinic acids on the aggregation and neurotoxicity of the 42-residue amyloid β-protein, *Bioorgan. Med. Chem*. **2012**, *20*, 5844–5849.

[3] Kamiyama, M., Moon, J-K., Jang, H. W. andShibamoto, T., Role of degradation products of chlorogenic acid in the antioxidant activity of roasted coffee, *J. Agr. Food Chem.* **2015**, *63*, 1996-2005.
[4] Dao, L. and Friedman, M., Distribution of glycoalkaloids in potato plants and commercial potato products, *J.Agric. Food Chem*. **1992**, 40, 419-423.
[5] Clifford, M. N., Chlorogenic acids and other cinnamates – Nature, occurrence and dietary burden, *J. Sci. Food Agr.* **1999**, *79*, 362-372.
[6] Jaiswal, R., Matei, M. F., Golon, A., Wittb, M. andKuhnert, N., Understanding the fate of chlorogenic acids in coffee roasting using mass spectrometry based targeted and non-targeted analytical strategies, *Food Funct*. **2012**, *3*, 976-984.
[7] Upadhyay, R. andRao, L. J. M., An outlook on chlorogenic acids-occurrence, chemistry, technology, and biological activities, *Crit. Rev. Food Sci.* **2013**, *53*, 968-984.
[8] Tadera, K. andMitsuda, H., Isolation and chemical structure of a new fluorescent compound in spinach leaves, *J. Agric. Biol. Chem*. 1971, *35*, 1431-1435.
[9] El-Rehem, F. A., El-Rehem, A. A. and Ali, R. F. M., Proximate compositions, phytochemical constituents, antioxidant activities and phenolic contents of seed and leaves extracts of Egyptian leek (Allium ampeloprasum var. kurrat, *Eur. J. Chem*. **2013**, *4*(*3*), 185-190.
[10] Hemmerle, H., Burger, H-J., Below, P., Schubert, G., Rippel, R., Schindler, P. W., Paulus, E. andHerling, A. W., Chlorogenic acid and synthetic chlorogenic acid derivatives: Novel inhibitors of hepatic glucose-6-phosphate translocase, *J. Med. Chem*. **1997**, *40 (2)*, 137-145.
[11] Lorentz, C., Dulac, A., Pencreac'h, G., Ergan, F., Richomme, P. andSoultani-Vigneron, S., Lypase-catalyzedsynthesis of two new antioxidants: 4-O and 3-O-palmytoil chlorogenicacids, *Biotechnol*. *Lett*. **2010**, *32*, 1955-1960.
[12] Sefkow, M., Kelling, A. andSchilde, U., First efficient syntheses of 1-, 4-, and 5-caffeoylquinic acid, *Eur. J. Org. Chem*. **2001**, *14*, 2735-2742
[13] Sefkow, M., First efficient synthesis of chlorogenicacid, *Eur. J. Org. Chem.* **2001**, *6*, 1137-1141.
[14] Dokli, I., Navarini, L. andHamersak, Z., Syntheses of 3-, 4-, and 5-O-feruloylquinic acids, *Tetrahedron: Asym.* **2001**, *24 (13-14)*, 785-790.
[15] Kadidae, L., Usami, A., Koyama, T., Honda, M. andKunimoto, K., New route for synthesis of 3-and 5-caffeoylquinic acids via protected quinic acids, *Eur. J. Chem.***2015**, *6(4)*, 367-373
[16] Swern, D. and Jordan, E. F., Jr., *Org. Synth., Coll. Vol. IV*, **1963**, *30*, 977-980.
[17] Mastihubová, M. andMastihuba, V., Donor specificity and regioselectivity in lipolase mediated acylations of methyl α-d-glucopyranoside by vinyl esters of phenolic acids and their analogues, *Bioorg. Med. Chem. Lett*. **2013**, *23*, 5389-5392.
[18] Tang, Z. and Shahidi, F., A novel chemoenzymatic synthesis of phytosterylcaffeates and assessmentof their antioxidant activity, *Food Chemistry*, **2012**, *133*, 1427–1434.
[19] Hatano, M., Komiya, S. and Ishihara, K., In situ generated "lanthanum(III)

nitrate alkoxide" as highly active and nearly neutral transesterification catalyst, *Chem. Commun.***2012**, *48*, 9465-9467.

[20] Takahashi, M., Murata, Y., Hakamata, Y., Suzuki, K., Sengoku, T. and Yoda, H., First total synthesis and absolute stereochemical assignment of vittarilide-A, and antioxidant extractive component isolated from Vittariaanguste-elongataHayata, *Tetrahedron,* **2012**, *68*, 7997-8002.

[21] Maring, C. J., Giranda, V. L., Gu, Y. G., Hanessian, S., Kempf, D. J., Madigan, D. L., Stewart, K., Stoll, V. S., Sun, M., Wang, G. T., Wang, J. and Zhao, C., Neuraminidase inhibitors, *United States Patent* No. US *6, 593, 314 B1,* July *15,* **2003**.

[22] Manthey, M. K., Gonzalez-Bello, C. andAbell, C., Synthesis of (2R)-2-bromodehydroquinic acid and (2R)-2-fluorodehydroquinic acid, *J. Chem. Soc., Perk. T. 1.* **1997**, *5*, 625-628.

[23] Silverstein, R. M., Webster, F. X. and Kiemle, D. J., *Spectrometric identification of organic compounds*, 7th edition, New York: John Wiley and Sons, **2005**.

[24] Narasimhulu, M., Mahesh, K. C., Reddy, T. S., Rajesh, K. andVenkateswarlu, Y., Lanthanum(III) hexahydrate or p-toluenesulfonic acid catalyzed one-pot synthesis of 4(3H)-quinazolinones under solvent-free conditions, *Tetrahedron Letters*, **2006**, *47*, 4381-4383.

[25] Hatano, M. and Ishihara, K., Lanthanum(III) catalysts for highly efficient and chemoselectivetransesterification, *Chem. Commun.***2013**, *49*, 1983-1997.