Efficient synthesis of chlorogenic acid and its regioisomers

メタデータ	言語: eng
	出版者:
	公開日: 2017-10-05
	キーワード (Ja):
	キーワード (En):
	作成者:
	メールアドレス:
	所属:
URL	http://hdl.handle.net/2297/46581

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Dissertation

Efficient synthesis of chlorogenic acid and its regioisomers

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June 2016

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Abstract

Chlorogenic acid, also known as 5-caffeoylquinic acid (5-CQA), and its isomers structurally are esters of caffeic acid with quinic acids. They are secondary metabolites found in a wide variety of natural resources, such as coffee products and fruits. Regarding their antioxidant and other biological effects, convenient methods for practical synthesis have been explored.

In this work, the efficient regioselective synthesis of chlorogenic acid and its regioisomers was investigated. The common acid catalyzed esterification of caffeic acid with alcohol could not proceed well since phenolic hydroxy groups inhibit the reaction. Then we need to protect the phenolic hydroxyl groups and to activate the carbonyl group of caffeic acid. So diacetylcaffeoyl chloride and TBS-protected vinyl caffeate were prepared. In addition non-protected quinic acid leads to the formation of mixture of regioisomers, therefore regioselective protection of the hydroxyl groups of quinic acid was necessary to yield chlorogenic acid and its regioisomers selectively.

Initially regioselective protections of hydroxyl groups of quinic acid were carried out. Protected quinic acid for the synthesis of 1-caffeoylquinic acid (1-CQA), was afforded by refluxing 2,2-dimethoxypropane and *p*-TsOH in ethyl acetate, resulting in 3,4,5-protected lactone. This lactone was then treated with $NaOCH_3$ in methanol to give 3,4-protected quinic acid for the synthesis of 5-CQA. Moreover, protections of quinic acids for the starting materials of 4- and 3-CQA syntheses were performed similarly using TBS-protecting group (TBSCl) with temperature alterations; at low temperature 3,5-protected quinic acid for synthesis of 4-CQA was afforded while at higher temperature 4,5-protected quinic acid for preparation of 3-CQA was achieved.

Protection of phenolic hydroxyl group and activation of caffeic acid were conducted as follows. Caffeic acid was reacted with acetic anhydride to afford diacetylcaffeic acid and subsequently reacted with oxalyl chloride to activate the carbonyl group. The product, diacetylcaffeoyl chloride, was then reacted with regioselectively protected quinic acids to afford the protected chlorogenic acid and its isomers. Cleavage all the protecting groups using low concentrations of HCl gave the corresponding chlorogenic acid and its regioisomers, respectively.

Also we investigated the irreversible transesterification of caffeic acid vinyl ester with protected quinic acids. First TBS-protected caffeic acid prepared by treating caffeic acid with TBSCl and imidazole in DMF, then the product was reacted with vinyl acetate with Pd(II) acetate instead of Hg(II) as catalyst to obtain TBS-protected vinyl caffeate. Transesterification reactions of this vinyl caffeate with protected quinic acids were performed in refluxed toluene with $La(NO_3)_3{\cdot}H_2O$ catalyst and $(n\text{-Oct})_3P$ additive. The products were hydrolyzed using low concentration of HCl to yield the corresponding caffeoylquinic acids.

Two new efficient methods showing great success for syntheses of chlorogenic acid and its regioisomers were introduced. First, 3- and 5-CQA were efficiently synthesized using diacetylcaffeoyl chloride with 4,5-protected quinic acid and 3,4-protected one, respectively. Second, 1-, 3- and 4-CQA were efficiently synthesized via irreversible transesterification reaction of TBS-protected vinyl caffeate with regioselectively protected quinic acids.

CHAPTER 1

General Introduction

1.1 Chlorogenic acids among phenolic phytochemicals

Chlorogenic acid, as an individual compound, also known as 5-caffeoylquinic acid (5-CQA), is arguable the most widespread of all monoesters formed between caffeic and quinic acids (CQA).[1] It is commonly considered to be a storage form of cinnamic acid derivatives and has been considered as an intermediate in the lignin pathway.[2] As a group, chlorogenic acids are referred to a related family of esters of hydroxycinnamic acids.[3] Hydroxycinnamic acids are one of the most abundant of phenolic phytochemicals. Phenolic phytochemicals also known as phenolic phytonutrients are any of various bioactive chemical compounds found in plants and important part of human and animal diets.[4-6] Originally, these compounds occur naturally that have important roles to protect plants against pathogenic diseases and to protect them from high energy radiation exposure.[7,8] Owing to their essential protective biological functions, these substances are widely distributed, almost in all plants including food groups, fruits, fruit juices, grains, vegetables, legumes[6].

As one of the most important groups of phenolic phytochemicals, hydroxycinnamic acids have been at the center of studies for years. The most widely distributed hydroxycinnamic acids in fruits are *p*-coumaric, caffeic and ferulic acids.[9] Hydroxycinnamic acids usually exist in various conjugated forms of esters of hydroxyacids such as quinic, shikimic and tartaric acids.[10] Isomers of

chlorogenic acid include the ester of caffeic acids with different position of hydroxyl groups on the quinic acid ring. These regioisomers are: 4-*O*-caffeoylquinic acid (4-CQA), 3-*O*-caffeoylquinic acid (3-CQA) and 1-*O*-caffeoylquinic acid (1-CQA). In addition to that, Birgul[11] had synthesized some di, tri, and tetra caffeoylquinic acids as other isomers of chlorogenic acids.

1.2 Chemical structure of some chlorogenic acids

Classically, chlorogenic acids (CGAs) are a family of esters formed between certain *trans*-cinnamic acids and quinic acid. The numbering of quinic acid in its structure refers to IUPAC numbering, depicted in Figure 1.1[12] Thus the names of chlorogenic acids are commonly derived from this numbering rule other than their trivial names. The schematic reaction of the formation of 5-CQA is presented in Figure 1.2.

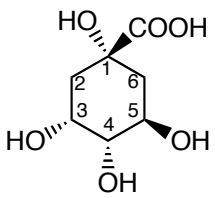
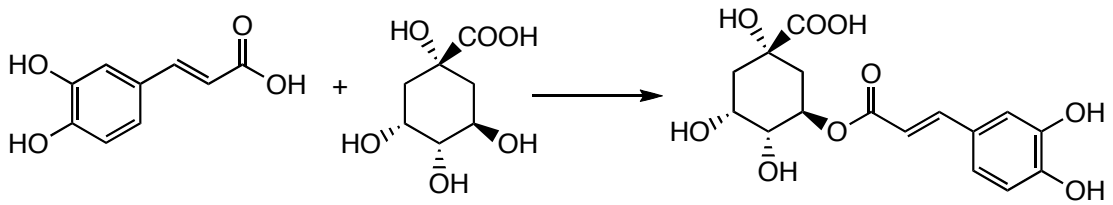


Figure 1.1 (-)-Quinic acid numbering based on the IUPAC rules

This numbering system is applied through the whole pages of this report. One example is the naming for compound **3**, which is a 5-caffeoylquinic acid (chlorogenic acid) since the caffeoyl group is bonded to carbon number 3 of the quinic acid. This is important to mention earlier to avoid any confusion with old literatures giving the name of chlorogenic acid as 3-caffeoylquinic acid.

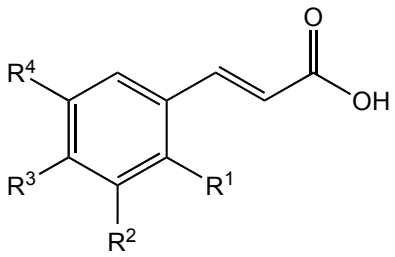


1 **2** **3**

Caffeic acid Quinic acid Chlorogenic acid (5-CQA)

Figure 1.2 Schematic reaction of caffeic acid and quinic acid to form 5-CQA

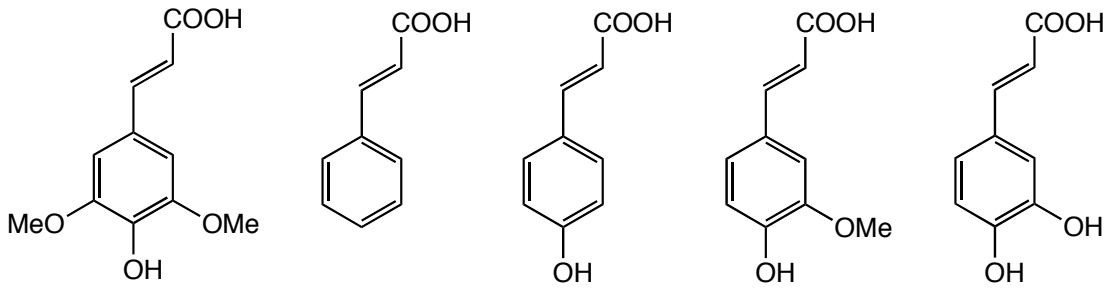
Cinnamic acid and its derivatives composing the commonest chlorogenic acids are summarized in Figure 1.3, and the structures of five commonest cinnamic acids is shown in Figure 1.4, while the chemical structure of the chlorogenic acid and its isomers is shown in Figure 1.5.



Cinnamic acids	R^1	R^2	R^3	R^4
Cinnamic acid	H	H	H	H
o-Hydroxycinnamic acid	OH	H	H	H
Caffeic acid	H	OH	OH	H
Ferulic acid	H	OCH_3	OH	H
p-Coumaric acid	H	H	OH	H
Isoferulic acid	H	OH	OCH_3	H
Sinapic acid	H	OCH_3	OH	OCH_3

Figure 1.3 Cinnamic acid and its primary derivatives of chlorogenic acids

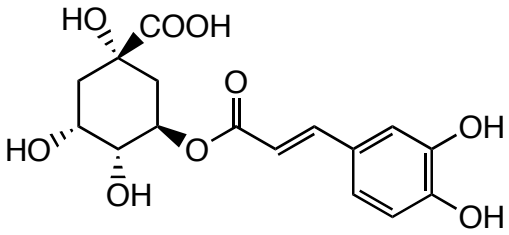
From Figure 1.3 and Figure 1.4, all common hydroxycinnamic acids constitute of a single hydroxyl group on their structures, except for caffeic acid. Caffeic acid has two hydroxyl groups, thus occasionally caffeic acid also called as dihydroxycinnamic acid.



4 **5** **6** **7** **8**

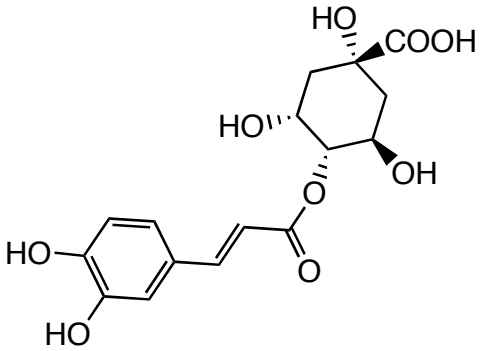
Sinapic acid Cinnamic acid *p*-Coumaric acid Ferulic acid Caffeic acid

Figure 1.4 Structure of cinnamic acid and its commonest derivatives of hydroxycinnamic acids



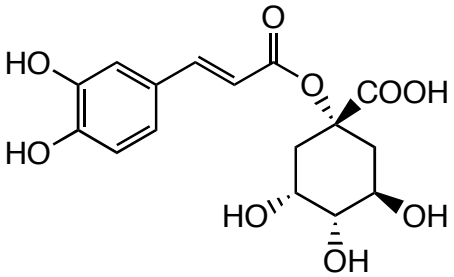
5-CQA

3



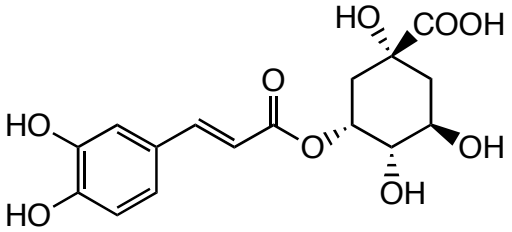
4-CQA

9



1-CQA

10



3-CQA

11

Figure 1.5 Chlorogenic acid, 5-CQA (**3**) and its isomers: 4-CQA (**9**), 1-CQA (**10**) and 3-CQA (**11**)

1.3 Chemical synthesis of chlorogenic acid

To afford chlorogenic acids, methods reported in the literature were involving condensation reactions of an acid chloride with protected quinic acids. The resulted protected esters are then hydrolyzed with mild concentration of acid to remove all the protecting groups. And the corresponding chlorogenic acids are isolated mostly after purification over column chromatography.

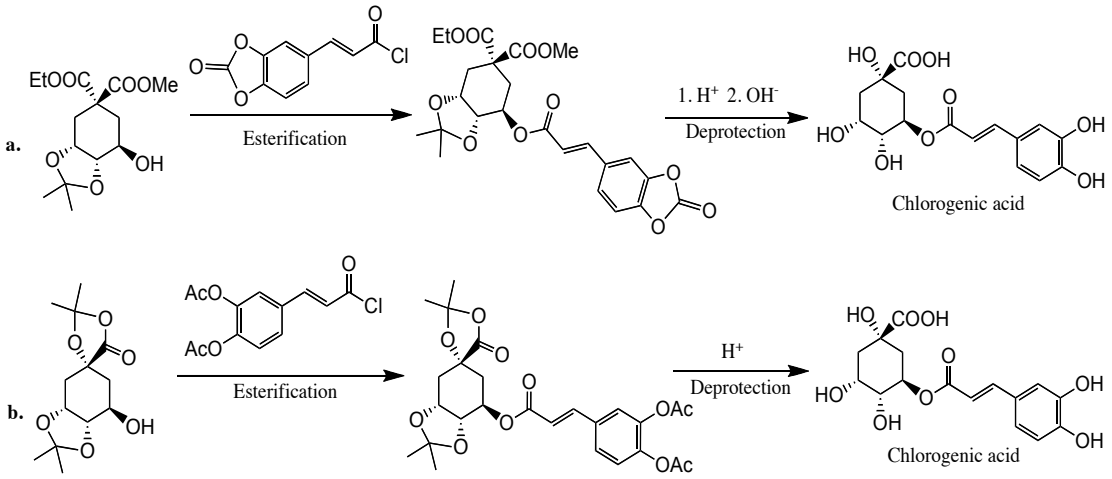
It seems that the process is quite simple; in fact, a selective-straightforward reaction is far from easy. This is a fairly complex process with regards to the

presence of hydroxyl and carboxylic groups on compounds used as starting materials namely cinnamic acids and quinic acid. Therefore, protection is required to prevent unwanted reactions, such as self-condensation of the acid chloride. Hydroxyl groups in the acyl chloride are also necessary to protect. On the other hand, certain hydroxyl groups of the quinic acid are required protections depending on the synthetic compound target. The desired products are obtained by removing all the protecting groups in dilute acid concentration, because chlorogenic acids are more stable in acidic condition [13,14] and unstable in basic condition.[15]

1.4 Reported Synthesis of chlorogenic acid and its isomers in literature

The very first efficient synthesis of 5-caffeoylquinic acid was reported by Panizzi[16] then Haslam.[17] Their study involved steps of protection-deprotection reactions to give a very low yield 5%. Not many selective chemical syntheses reported after that, until Sefkow[18] introduced a relatively short and efficient regioselective synthesis by kinetic acetalization. Synthetic pathways of Panizzi and Sefkow methods were shown in Scheme 1. Different activated caffeic acids and protected quinic acids were employed to achieve chlorogenic acid. Nonetheless in both methods the chlorogenic acid derivatives were prepared by esterification of suitable caffeic and quinic acid derivatives. In Panizzi's method (Scheme 1a) 3,4-oxomethylenedioxycinnamoyl chloride was used as an acylating agent while Sefkow (Scheme 1b) used diacetylcaffeoyl chloride. Esterifications with protected quinic acids followed by hydrolysis of all protecting groups affording the chlorogenic acid (5-CQA). Not only the activated caffeic acids and protected quinic acids used are different of the two methods but also the

removal of protecting groups. Panizzi and co-workers used two steps of deprotections. They first removed the isopropylidene group in acid, followed by removal of the cyclic carbonate, ethoxycarbonyl and methyl ester groups in basic using barium hydroxide. Meanwhile removal all protecting groups in Sefkow method was conducted in low concentration of hydrochloric acid. Although the synthesis of 5-CQA was achieved using these methods, the yield afforded in Panizzi's method was very low while the steps involved in Sefkow's method were very difficult to follow.



Scheme 1. Reaction pathway of the syntheses of chlorogenic acid (5-CQA) by Panizzi (a) and Sefkow (b)

Syntheses of 5-CQA isomers, which are 1-, 3-, and 4-CQAs had been reported. For example, synthesis of 1-*O*-caffeoylquinic acid (1-CQA) was reported by Weiss et al.[19] They reported that 1-CQA was synthesised from the by-product of the the kinetic acetalysation of the protected quinide **12**. According to Rohloff et al.,[20] the ratio of the protected quinide **12** and bisacetonide **15** became 92:8 by using conditions for a thermodynamic acetalization of quinic acid **2**. This acetalization was accomplished by refluxing quinic acid **2**, *p*-toluenesulfonic acid, 2,2-

dimethoxypropane (DMP) and acetone for 2 h in 90 % yield. Esterification of the protected quinide **12** with diacetylcaffeic acid chloride **23** was carried out in the presence of 4-(dimethylamino)pyridine (DMAP) and pyridine in dichloromethane at room temperature for 4 h. Then cleavage of the protecting groups by hydrolysis using low concentration of HCl led to the desired 1-CQA, **10**. Rúveda[21]obtained 1-*O*-caffeoylquinic acid by heating 1-*O*-caffeoylquinide in 0.1 N HCl at 100 ^{0}C for 15 min. Synthesis of 4-CQA, **9,** was realized by using the protected quinic acid introduced by Abel et al.[22] and the synthesis of 3-CQA was utilizing the protected quinic acid introduced by Montchamp.[23] These processes were clearly presented by Sefkow et al. in their report.[24] All the protected quinic used by Sefkow to synthesize chlorogenic acid and its isomers is shown in Figure 1.6.

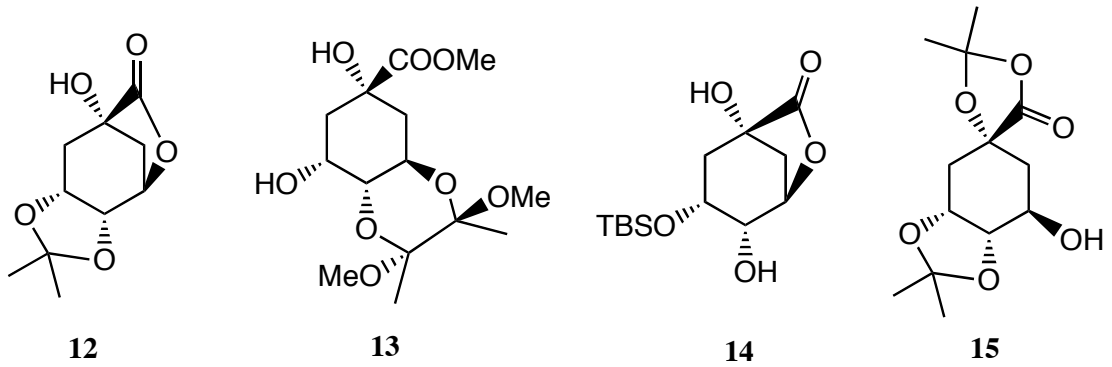


Figure 1.6 Protected quinic acids used by Sefkow et al.[18,24]

There are not many current studies focusing on the syntheses of chlorogenic acids. Several studies using enzymes as catalysts were recently reported.[25-27] However, the chemical synthetic methods of chlorogenic acids are much less explored, almost after Sefkow's publications, this approach was relatively undeveloped. Most studies related to chlorogenic acids recently were dominant

on the analysis and quantification of chlorogenic acids from natural products. Besides, techniques of isolation from natural sources were also receiving great attentions. Furthermore, health effects of chlorogenic acids either performed *in vivo* or *in vitro* are other areas of intensive investigations. To this reason, the current report is presenting results on effective syntheses of chlorogenic acid and its isomers based on chemical methods, and the highlight for this is summarized in the following subheading, the purpose of study, while the schematic syntheses are depicted in Figure 1.7.

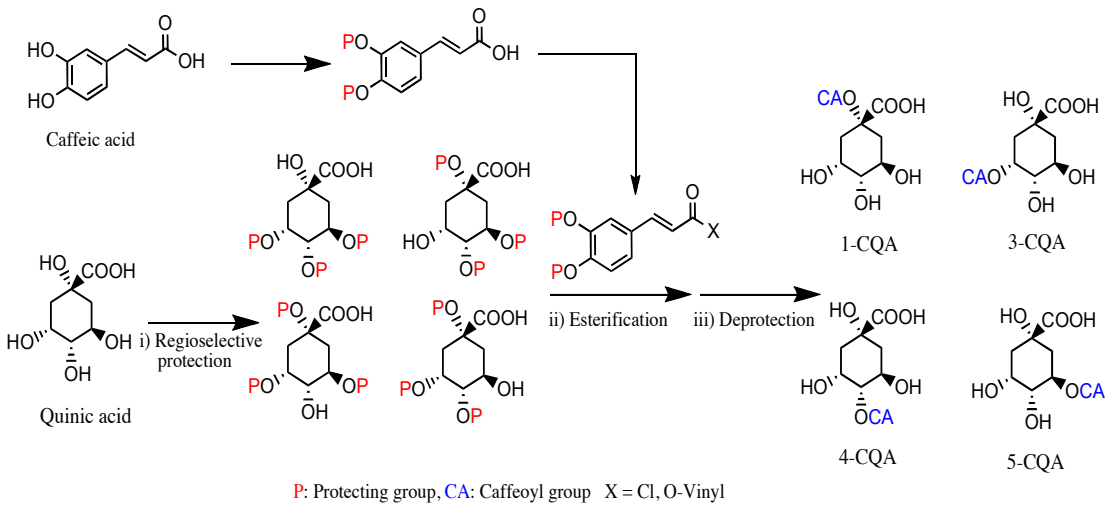


Figure 1.7 Schematic pathway of the syntheses of chlorogenic acid and its isomers

1.5 Objectives

This study was conducted to synthesize chlorogenic acid and its isomers of caffeoylquinic acids (CQAs) via regioselectively protected quinic acids (QAs). The esterification reactions of the protected quinic acids were performed in the basis of two approaches; first, condensation reactions using caffeoyl chloride and

second, transesterification using vinyl caffeate. This report is constructed into six chapters: chapter one is a general introduction, chapter two is the syntheses of regioselectively protected quinic acids, chapter three is synthesis of CQAs using caffeoyl chloride, chapter four is synthesis of vinyl esters of caffeic acid, chapter five is synthesis of CQAs using vinyl caffeate, and chapter six is the general conclusion.

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CHAPTER 2

Protection of Quininic Acid and Caffeic Acid

2.1 Introduction

Quinic acid, **2**, is a substituted cyclohexane possessing four hydroxyl and a carboxyl groups. This leads to a high potential of being oxidized through one, two, or all its hydroxyl groups. To avoid an interruption during a reaction projected to only a specific OH group in this compound, protection of other OH groups are necessary.

Different protecting groups to selectively mask hydroxyl or carboxyl groups of quinic acid, especially in esterification reactions to synthesize chlorogenic acids, have been reported by different authors in literature. Protection of the carboxyl group was suggested by de Pooter et al. as esterification with diazodiphenylmethane and this has been widely used by other authors.[1] Some of the protection process for specific hydroxyl groups with regards to the synthesis of chlorogenic acid and its isomers have also been reported. A one-step protection, compound **12** (3,4-isopropyledene) to provide a suitable protected quinic acid for 1-CQA synthesis can be achieved by heating quinic acid in acetone in the presence of *p*-toluenesulphonic acid (*p*-TsOH). This was first introduced by Rohloff et al.[2] Protected quinic acid, **15**, for making 5-CQA has been used by Sefkow.[3] Meanwhile, the protected quinic acid to make 4-CQA was utilizing compound **14** introduced by Abel et al.[4] and protected quinic acid **13** that first reported by Montchamp[5] was used to synthesize 3-CQA. Scarpati at al.[6] used an

excess of quinide in the synthesis of coumaroylquinic acid whereas Zane and Wender used 1-ethoxycarbonyl quinide in the synthesis of feruloylquinic acid.[7]

Caffeic acid, **1**, has two hydroxyl groups on aromatic ring and a carboxyl group. To avoid unwanted reaction on the catechol group, protections of these hydroxyl groups are also required. Few publications have been associated to this protection in conjunction with providing starting material for chlorogenic acids synthesis. Acetyl protecting group was used by D'Ambrosio.[8] Benzyl protecting group was employed by Yuan[9] et al. while TBS protecting group was introduced by Takahashi et al.[10]

2.2 Experimental

2.2.1 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. Solvents evaporation was performed using Iwaki Rotary Evaporator REN-1000 with reduced pressure. JEOL NMR of JNM-LA400 and ECA500 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.

2.2.2 Preparation of (1*S*,3*R*,4*R*,5*R*)-3,4-*O*-isopropylidene-1,5-quinic acid lactone (12)

To a stirring solution of (-)-quinic acid (**2**) (1g, 5.20 mmol) in 30 ml of ethyl acetate, *p*-TsOH (10 mg, 0.05 mmol) and 2,2-dimethoxypropane (1,96 ml, 15.60 mmol) were added, respectively. The mixture was refluxed for 3 h and after cooling to room temperature the solvent was evaporated under reduced pressure to give crude product. This crude material was dissolved in a mixture of ethyl acetate (EtOAc) (25 ml) and *n*-hexane (25 ml). White solid was precipitated when the solution left in the refrigerator for 1 h. The solid was collected and dried to give 88% yield of the desired compound (Figure 2.1). ^{1}H NMR (400 MHz, $CDCl_3$, δ = 1.33 (s, 3H), 1.52 (s, 3H), 2.18 (dd, 1H, *J* = 14.6, 2.9 Hz), 2.28 – 2.40 (m, 2H), 2.50 (s, broad, 1H), 2.65 (d, 1H, *J* = 11.7 Hz), 4.31 (dq, 1H, *J* = 6.5, 1.3 Hz), 4.5 (td, 1H, *J* = 7.1, 2.8 Hz). NMR data were in good agreement with literature data.[2]

2.2.3 Preparation of methyl 3,4-*O*-isopropylidene-1,5-quinate (16)

To a solution of acetone quinide (**12**) (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 **16** (Figure 2.2), as white powder in 78% yield. 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.[12]

2.2.4 Preparation of (1*S*,3*R*,4*R*,5*R*)-1,3,4-trihydroxy-6-oxa-bicyclo[3.2.1] octan-7-one (17)

To a solution of (-)-quinic acid (**2**) (1.96 g, 10.20 mmol) in a mixture of toluene (20 ml) and DMF (7 ml), *p*-TsOH (100 mg, 0.52 mmol) and 2.04 g of molecular sieves (200 mg/mmol of **2**) were added, respectively. The mixture was refluxed for 24 h and after cooling to room temperature the solvent was evaporated and the residue was added with dichloromethane (20 ml) and *n*-hexane (10 ml) forming white precipitation. The white solid was collected resulting in the crude of **17** with 86% yield and this was used for the next reaction without any purification. ^{1}H NMR (400 MHz, (CD_3OD), δ = 1.86 (t, 1H, *J* =11.7 Hz), 2.01 (dq, 1H, *J* = 11.4, 3.0 Hz), 2.21 (dq, 1H, *J* = 11.4, 30 Hz), 2.46 (d, 1H, *J* = 11.5 Hz), 3.29 – 3.31 (m, 1H), 3.66 – 3.72 (m, 1H), 4.70 (t, 1H, *J* = 5.5 Hz), 4.91 (s, broad, 3H). NMR data were in good agreement with literature data.[13]

2.2.5 Preparation of (1*R*,3*R*,4*S*,5*R*)-3-*tert*-butyldimethylsiloxy-1,3-dihydroxycyclohexane-1,5-carbolactone (14)

To a solution of lactone (**17**) (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) to give the desired product **14** as white solid, Rf = 0.12, and 64 % yield and byproduct **18**, 5%, Rf = 0.17. ^{1}H NMR (400 MHz, ($CDCl_3$), δ = 0.09 (s, 6H), 0.90 (s, 9H), 1.98 – 2.03 (m, 2H), 2.30 (dq, 1H, *J* = 11.7, 2.9 Hz), 2.63 (d, 2H, *J* = 11.2 Hz), 2.96 (s, broad, 1H), 3.91 (d, 1H, 10.3 Hz), 3.98 (t, 1H, *J* = 4.6 Hz), 4.88 (t, 1H, *J* = 5.4 Hz). NMR data were in good agreement with literature data.[13]

2.2.6 Preparation of (1*R*,3*R*,4*S*,5*R*)-4-*tert*-butyldimethylsiloxy-1,3-dihydroxy cyclohexane-1,5-carbolactone (18)

To a solution of quinic acid lactone (**17**) (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 **18** (Figure 2.3), as white solid, 36% yield. R_f = 0.17 and 25% byproduct **14**. ^{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.[13]

2.2.7 Preparation of 3,4-di-*tert*-butyldimethylsiloxycinnamic acid (19)

Adapted procedure from Takahashi, M. et al. was employed in this experiment.[10] 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*-butyldimethylsilyl chloride (TBSCl) (497 mg, 3.3 mmol) was added then stirred at room temperature for 6 h. After reaction time was achieved, then 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 *n*-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 **19** as pale yellow solid. Yield: 93%. ^{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, $(CH_3)_3$C), 1.00 (s, 9H, $(CH_3)_3$C), 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). NMR data were in good agreement with literature data.[10]

2.2.8 Preparation of 2,2-dimethylbenzo [*d*] [1,3] dioxolcinnamic acid (20)

In a two neck round bottom flask contained dihydroxycinnamic acid (1.0 mmol, 180 mg), dimethoxypropane (DMP) (2.2 mmol, 156 mg), *p*-toluene sulfonic acid (0.1 mmol, 5 mg), 1,4-dioxane (5 mL) were added and the mixture was stirred for 30 h at reflux temperature of 1,4-dioxane. After cooling, the reaction solution was concentrated in an evaporator and purified by column chromatography to give **20**, as a pale yellow crystal (35%). Mp: 136-140 ℃.

IR (KBr, ν, cm^{-1}): = 3063 (C-H, alkene), 2928 (C-H, methyl), 1700 (C=O, carboxyl), 1497 (C=C, aromatic), 1421. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.62 (s, 6H, $(CH_3)_2$-C), 6.16 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.65-6.94 (m, 3H, Ar-H), 7.61 (d, 1H, *J* = 15.5 Hz, Ph-CH-CO). ^{13}C NMR ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 172.9 (1C, C=O, carboxyl), 150.1 (1C, Ar-C), 148.3 (1C, Phen-C), 147.2 (1C, Ar-C), 130.0 (1C, Ar-C), 128.2 ((1C, C-$(CH_3)_2O_2$), 124.8 (1C, Ar-C), 119.2 (1C, Ar-C), 114.6 (1C, Ar-C), 108.6 (1C, Ar-C), 106.6 (1C, benz-C), 26.0 (2C, CH_3-C). HRMS EI: m/z: calcd for $C_{12}H_{12}O_4$ [M^+] = 220.0736. Found 220.0736.

2.2.9 Preparation of 3,4-diacetoxycinnamic acid (21)

In a two neck flask contained dihydroxycinnamic acid (1.0 mmol, 180 mg), acetic anhydride (2.5 mmol, 252 mg), *N*, *N*-dimethyl-4-aminopyridine (DMAP) (0.025 mmol, 3 mg) were added. Pyridine (1 mL) was also added then the reaction mixture was stirred for 1 hour at 0 ℃. Following that, the mixture was poured into an ice bath, added with 2 M HCl aq until pH around 2. A mixture of ethyl acetate and THF (EtOAc: THF, 3:1 v/v; 10 mL × 3) was used to extract the organic phase. The organic layer was then dried over sodium sulfate and concentrated

using an evaporator, to obtain the desired product **21,** as pale yellow crystals (97%).

^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.28 (s, 3H, acetyl-H), 2.29 (s, 3H, acetyl-H), 6.53 (d, 1H, *J* = 15.9 Hz, CO-CH-CH-Ph), 7.32 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.62 (m, 2H, Ar-H), 7.66 (d, 1H, *J* = 15.9 Hz, Ph-CH-CH-CO). NMR data were in good agreement with literature data.[14]

2.2.10 Preparation of 3,4-dibenzyloxycinnamic acid (22)

Dihydroxycinnamic acid (1.0 mmol, 180 mg), THF (2.5 mL) and potassium carbonate (5 mmol, 690 mg) were placed into a two neck round bottom flask, then benzyl bromide (5 mmol, 855 mg) was also added. After stirring for 24 h at THF reflux, the reaction was quenched by addition of 5 drops of methanol. Potassium carbonate was removed by filtration and solvents were removed using an evaporator. The residue was dissolved in 1,4-dioxane (4 mL) and to this, 1M $NaOH_{aq}$ (3 mL) was added and stirred for 24 h at 40 °C. The reaction mixture was concentrated by an evaporator, and extracted as the sodium salt in the aqueous layer with ethyl acetate and water. The aqueous layer was adjusted to pH around 1 with 1M HCl_{aq} and re-extracted with ethyl acetate to gain the organic phase. After drying over sodium sulfate, the organic phase was concentrated using an evaporator, to give **22** as pale yellow crystals (80%).

^{1}H NMR (500 MHz, $(CD_3)_2CO$, δ, ppm): 5.10 (s, 2H, benzyl-H), 5.13 (s, 2H, benzyl-H), 6.27 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.98 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.07-7,42 (m, 13H, Ar-H), 7.46 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO). NMR data were in good agreement with literature data.[15]

2.3 Results and discussion

2.3.1 Preparation of (1*S*, 3*R*, 4*R*, 5*R*)-3,4-*O*-isopropylidene-1,5-quinic acid lactone (12) and methyl 3,4-*O*-isopropylidene-1,5-quinate (16)

Compound **12** was the starting material for synthesizing 1-CQA. The protection of the quinic acid here was quite straightforward as shown in Figure 2.1

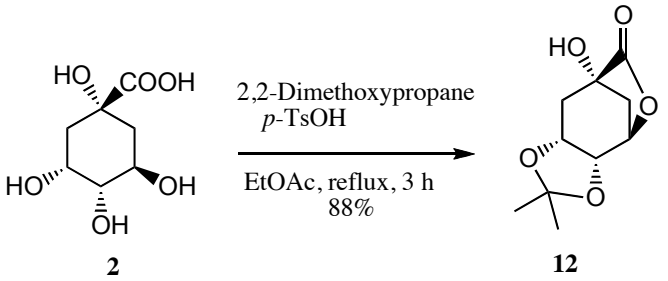
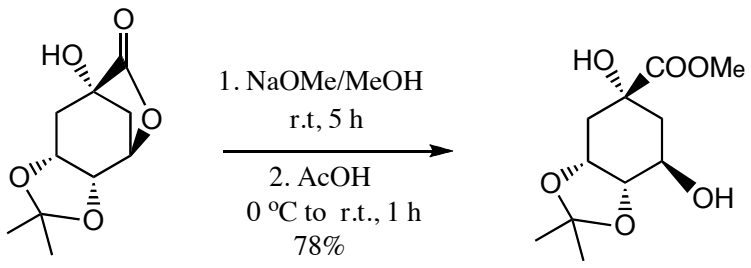


Figure 2.1 Protection of quinic acid using 2,2 dimethoxypropane in the presence of *p*-TsOH catalyst

The reaction of quinic acid with 2,2-dimethoxypropane was carried out. After being refluxed for three hours, the solution mixture underwent recrystallization to afford the desired product **12**, as much as 88%. And this was proved by the identical proton NMR spectrum to those reported in literature.[2,4] It is obviously shown from its structure in Figure 2.1 that quinic acid has been converted to a nearly complete of hydroxyl groups protected form. Compound **12** possess only one hydroxyl group at carbon number one, which is just at the right position for the esterification to synthesize 1-CQA.

This compound (**12**) was used to synthesize another protected quinic acid (**16**), which was the starting material for synthesizing chlorogenic acid (5-CQA). The schematic reaction was shown in Figure 2.2.



12 **16**

Figure 2.2 Protection of quinic acid to synthesize the precursor for 5-CQA

The reaction of protected quinic acid (**12**) with sodium methoxide in methanol was carried out. This reaction was performed at room temperature for 5 h and when acetic acid was added the temperature was lowered to 0 ^{0}C and then let it to run at room temperature for another 1 h. The desired product methyl ester **16** was achieved after purification using column chromatography in 78% yield. To prove that this product was **16**, proton NMR was analyzed and found in good agreement with the literature.[12]

2.3.2 Preparation of (1*S*, 3*R*, 4*R*, 5*R*)-1,3,4-trihydroxy-6-oxa-bicyclo [3.2.1]octan-7-one (17), lactone (14) and lactone (18)

To prepare protected quinic acids suitable for synthesizing 4-CQA and 3-CQA, the starting material for both protected quinic acids is necessary to make. The starting material **17** was prepared by heating quinic acid with *p*-TsOH in a mixture of toluene and DMF for 24 h. The lactonization proceeded smoothly to afford lactone **17**. The yield was 86%, and the proton NMR spectrum was assigned and in agreement with literature.[13] The description is shown in Figure 2.3. The synthesis of **14** as the starting material to make 4-CQA was performed at low temperature. Compound **17** was reacted with TBSCl at 0 ^{o}C for 2 h and then

at room temperature for 3 h. After purification, the 3-TBS-protected lactone **14** was achieved in 64% yield. And the byproduct was in fact the 4-TBS-protected lactone **18** in 5% isolated yield. Although compound **18** was identified, interestingly this substance has never been reported its engagement in reactions. To this reason, compound **18** was intended to utilize as a starting material in the synthesis of 3-CQA.

As an excess of the synthesis of **14**, compound **18** was only in a small portion of the total products so that enrichment of the yield of this particular lactone is necessary. To do this, the synthesis of compound **18** alone was performed in a similar fashion to the synthesis of **14** except the reaction condition was changed in which the temperature was raised to 90 ^{o}C and imidazole was replaced with Bu_4NI and triethylamine (TEA). After purification, the desired product was successfully isolated in 36% yield and the byproduct was compound **14** in 25%. For this reason, it is apparently that the synthesis of either **14** or **18** was always giving the byproduct of the isomer.

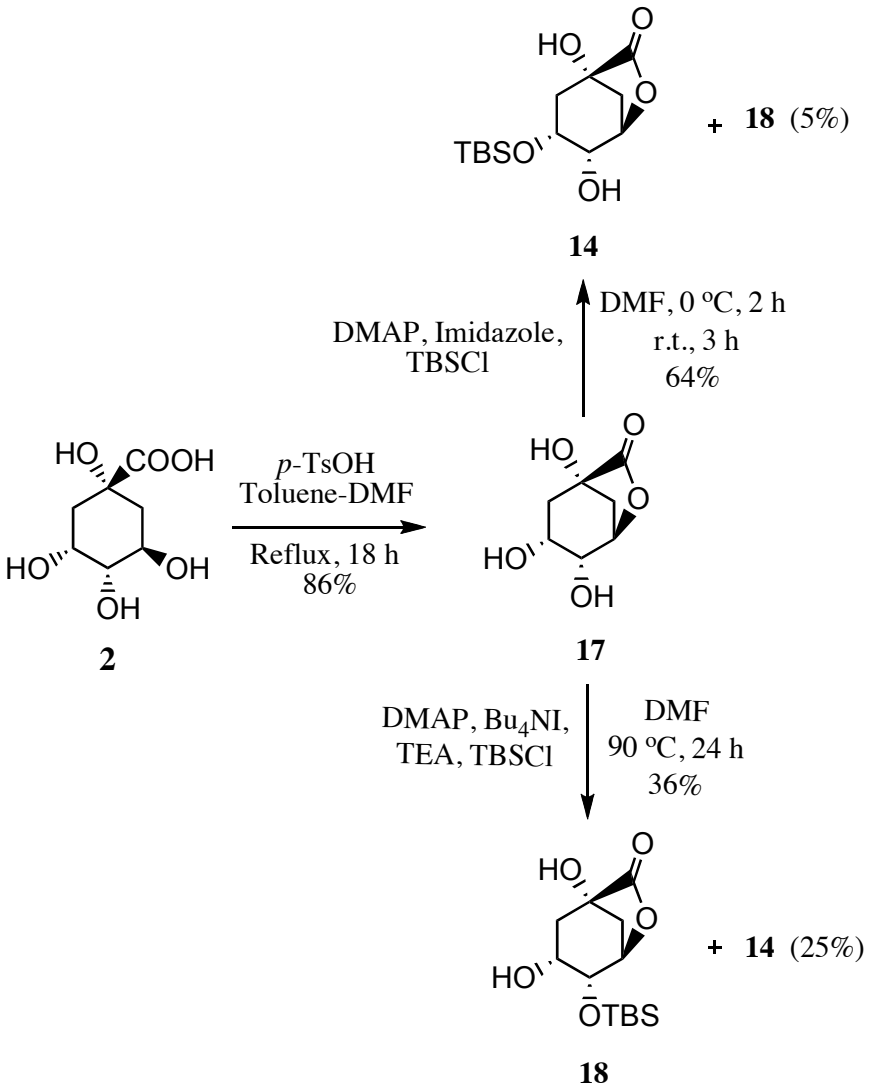


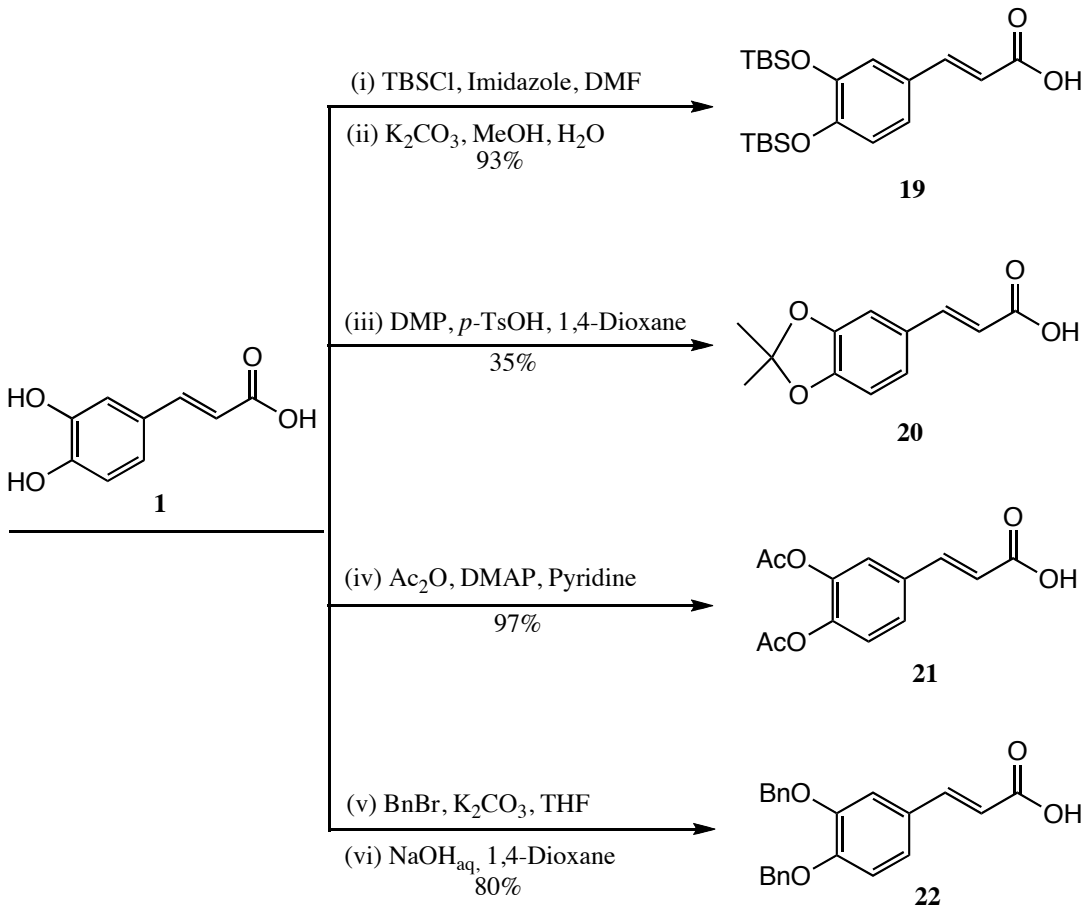
Figure 2.3 Synthesis route of protection of quinic acid to prepare starting material of 4-CQA, 3-CQA via an intermediate compound **17**

2.3.3 Protection of phenolic hydroxyl groups

Dihydroxycinnamic acid or caffeic acid (**1**) possesses two phenolic hydroxyl groups with high degree of oxidation similar to alcohol compounds. To avoid of being involved in reactions in a multi-step synthesis, these hydroxyl groups are necessary to protect. In this experiment, silyl-based protective, acetal protection, acyl-based protective and benzyl (Bn) protection, were carried out, as depicted

in Figure 2.4. Using *tert*-butyldimethylchlorosilane (TBSCl) as silyl-based protective, the desired product **19** was afforded in two steps. First, caffeic acid was reacted with TBSCl in the presence of imidazole in DMF to give a crude intermediate product (tri-TBS-protected caffeic acid), which was used in the next step of reaction without any purification. In the second step of the reaction, the crude intermediate material was treated with potassium carbonate in methanol-water to cleave the TBS-protected ester. This process resulted the di-TBS-protected caffeic acid (**19**) in 93% yield.

Acetal protection of caffeic acid was achieved in one step of reaction. Caffeic acid was reacted with dimethoxypropane (DMP) in the presence *p*-TsOH as catalyst in a refluxed 1,4-dioxane for 30 h, to give the acetal-protected caffeic acid **20** as pale yellow crystal, 35% yield. Meanwhile, diacetyl-protected caffeic acid **21** was prepared using acetic anhydride. Caffeic acid was reacted with acetic anhydride in the presence of DMAP as catalyst and pyridine at 0 ^{0}C for 1 h. Acidified with HCl 2M, gave the acyl-based protective **21** with 97% yield. The last protecting group applied was a benzyl-based protective. This reaction was a two-step process. Initially, caffeic acid was reacted with benzyl bromide in the presence of potassium carbonate as catalyst to give a crude intermediate product, which was used for the next step of reaction without any purification. Then, the crude material was treated with NaOH 1M in 1,4-dioxane for 24 h. The reaction proceeded quite well to give the Bn-protected caffeic acid **22** in 80% of isolated yield after purification.



Reagents and conditions: (i) TBSCl (3.3 equiv.), Imidazole (7 equiv.), DMF, r.t., 6 h; (ii) K_2CO_3 (1.1 equiv.), MeOH/H_2O, r.t., 1 h, 93%; (iii) DMP (2.2 equiv.), *p*-TsOH (0.1 equiv.), 1.4-Dioxane, reflux, 48 h, 35%; (iv) Ac_2O (2.5 equiv.), DMAP (0.025 equiv.), Pyridine, 0 °C, 1 h, 97%; (v) BnBr (5 equiv.), K_2CO_3 (5 equiv.), THF, reflux, 24 h; (vi) 1M NaOHaq, 1,4-Dioxane, r.t., 24 h, 80%. TBSCl = *tert*-butyldimethylchlorosilane, DMF = *N,N*-Dimethylformamide, DMP = 2,2-Dimethoxypropane, DMAP = *N,N*-Dimethyl-4-aminopyridine, THF = Tetrahydrofuran.

Figure 2.4 Protections of phenolic hydroxyl group

2.4 Conclusions

Regioselectively protected quinic acid that suitable for syntheses of chlorogenic acid (5-CQA) and its regioisomers were successfully prepared in relatively simple ways. To get protected quinic acid for 1-CQA and 5-CQA was using in line procedure. Quinic acid was reacted with 2,2-dimethoxypropane in the presence of acid catalyst, *p*-TsOH, and the process took place in refluxed ethyl acetate resulting in the protected quinic acid for making 1-CQA, 62% yield. Lactonization

of this compound by heating it with $NaOCH_3$ in methanol at room temperature gave the protected quinic acid for making 5-CQA, 36% yield.

On the other hand, protected quinic acids for 4-CQA and 3-CQA used the same intermediate compound, lactone **17.** When this lactone was reacted with TBSCl at 0 ^{o}C, the main product was 3-TBS protected lactone, the starting material for making 4-CQA. Conversely, 4-TBS protected lactone, the starting material to synthesize 3-CQA was a dominant product when lactone **17** was reacted with TBSCl at higher temperature.

Protections of hydroxyl groups on caffeic acid were readily performed with common protecting hydroxyl groups of acetyl, benzyl and TBS groups in satisfying results, over 80% yields.

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CHAPTER 3

Synthesis of Caffeoylquinic Acids via Condensation Reaction of Caffeoyl Chloride with Protected Quinic Acids

3.1 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[11,12] and co-workers 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.

This chapter will describe the synthesis of 5- and 3-CQAs utilizing methyl 3,4-*O*-isopropylidene-1,5-quinate **16** and an overlooked protected quinic acid, (1*R*,3*R*,4*S*,5*R*)-4-*tert*-butyldimethylsiloxy-1,3-dihydroxycyclohexane-1,5-

carbolactone, **18**, 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.

3.2 Experimental

3.2.1 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. Solvents evaporation was performed using Iwaki Rotary Evaporator REN-1000 with reduced pressure. JEOL NMR of JNM-LA400 and ECA500 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.

3.2.2 Synthesis of diacetylcaffeoyl chloride (23)

To a solution of caffeic acid (720 mg, 4 mmol) and DMAP (12 mg, 0.1 mmol) in 5ml pyridine, acetyc acid anhydride (940 μl, 10 mmol) was added at 0 ^{o}C. The reaction mixture was stirred for 1 h and then poured onto crushed ice. The

aqueous phase was acidified with 2M aq. HCl (pH ≈ 2) and extracted with EtOAc/THF (3:1, 3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvents were removed by evaporation under reduced pressure. Trituration of the residue with hexane containing a small amount of ethyl acetate afforded quantitative di-*O*-acetylcaffeic acid as colorless powder. This product was then suspended in toluene (20 ml) containing 2 drops of DMF. Oxalyl chloride (700 µL, 8 mmol) was added at -5 ^{o}C. After stirring for 3 hours at room temperature, all starting material had dissolved resulting in a pale-brown solution. Toluene and unreacted oxalyl chloride were removed under reduced pressure and the residual brownish product was triturated with hexane containing a small amount of acetyl acid to afford acid chloride 97%.

^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.29 (s, 3H, acetyl-H), 2.29 (s, 3H, acetyl-H), 6.91 (d, 1H, *J* = 15.6 Hz, CO-CH-CH-Ph), 7.38 (d, 1H, *J* = 9.0 Hz, Ar-H), 7.61 (m, 2H, Ar-H), 7.94 (d, 1H, *J* = 15.6 Hz, Ph-CH-CH-CO).[12]

3.2.3 Synthesis of protected ester of 1-CQA (24)

To a solution of acetone quinide (**12**) (400 mg, 1.87 mmol) in dichloromethane (10 mL), pyridine (8 mL), DMAP (11.4 mg, 0.09 mmol) and diacetylcaffeoyl chloride (**23**) (Figure 3.1) (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 **24** (Figure 3.2) as white

powder, 75% yield. ^{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]

3.2.4 Preparation of 1-CQA (10)

As much as 184 mg (0.40 mmol) of protected 1-CQA (**24**) 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 **10** (Figure 3.2) as pale yellow powder, 89% yield. ^{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]

3.2.5 Synthesis of protected 5-CQA (25) and 1,5-diCQA (26)

To a stirred solution of methyl quinate (**16**) (400 mg, 1.62 mmol) in dichloromethane (15 mL), pyridine (6 mL), DMAP (11.4 mg, 0.09 mmol) and diacetylcaffeoyl chloride (**23**) (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 (**25**) as waxy white solid, 58% yield and methyl 3,4-*O*-isopropylidene-1,5-diacetylcaffeoyl quinate (**26**), Figure 3.3, as waxy white solid, 3% isolated yield. Methyl 3,4-*o*-isopropylidene-5-diacetylcaffeoyl quinate (**25**): 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-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, Cyclohexyl-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, Cyclohexyl-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 (**26**) : 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). ^1H 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* = 16.0 Hz, Ph-CH-CH-CO). HRMS FAB+: *m/z*: calculated for $C_{37}H_{39}O_{16}$ $[M+H^+]$ = 739.2238, found 739.2229.

3.2.6 Synthesis of 5-CQA (3)

As much as 172 mg (0.35 mmol) of protected 5-CQA (**25**) 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 **3** (Figure 3.3) as pale yellow powder, 88% yield. ^{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]

3.2.7 Synthesis of protected 4-CQA (27) and 1,4-CQA (28)

To a solution of monosilyl protected compound **14** (465 mg, 1.62 mmol), DMAP (30 mg, 0.24 mmol), and diacetylcaffeoyl chloride (**23**) (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 **27** as off white solid, 60% yield and **28**, as waxy white solid, 15% yield. 4-((*E*)-3-(((1*R*,3*R*,4*S*,5*R*)-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 (**27**): ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.02 (s, 3H, Si-CH_3), 0.05 (s, 3H, Si-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]

(1*R*,3*R*,4*S*,5*R*)-3-*tert*-butyldimethylsiloxy-1,4-diacetylcaffeoylcyclohexane-1,5-carbolactone (**28**): 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-CH_3), 0.08 (s, 3H Si-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.

3.2.8 Synthesis of 4-CQA (9)

As much as 213 mg (0.40 mmol) of protected 4-CQA (**27**) 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 **9** (Figure 3.4), as yellow powder, 40% yield.

^{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]

3.2.9 Synthesis of protected 3-CQA (29)

To a solution of monosilyl protected compound (**18**) (335 mg, 1.46 mmol) and DMAP (22 mg, 0.17 mmol), diacetylcaffeoyl chloride (**23**) (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. 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-diacetylcaffeoylcyclohexane-1,5-carbolactone (**29**), Figure 3.5, as white solid, 53% yield. 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, Cyclohexyl-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_3COOPh), 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.

3.2.10 Synthesis of 3-CQA (11)

As much as 213 mg (0.4 mmol) of protected 3-CQA (**29**) 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 **11** (Figure 3.5) as yellow powder. 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]

3.3 Results and discussion

Although the main objective of this chapter to report the 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.

3.3.1 Preparation of diacetylcaffeoyl chloride

Acid chloride **23** used in this work was prepared, as depicted in Figure 3.1, according to a known procedure by Sefkow[12] from protected caffeic acid (**21**) in one step reaction. The reaction of diacetyl protected caffeic acid (**21**) with oxalyl chloride in toluene in the presence of DMF as catalyst proceeded to afford the corresponding acid chloride (**23**) with excellent yield of 97%. Compared to its original caffeic acid, acid chloride has a better leaving group thus more reactive, this is the basic reason of converting the free acid to the halide acid.

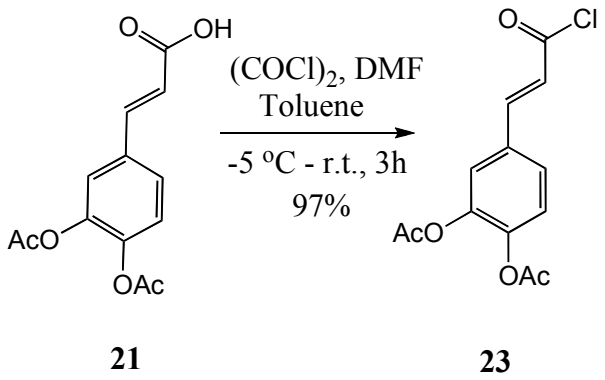

Figure 3.1 Preparation of acid chloride **23** of caffeic acid

The acid chloride **23** was used in any of the esterification with protected quinic acids to synthesize the intended caffeoylquinic acids in this chapter.

3.3.2 Synthesis of 1-CQA (10)

Synthesis of 1-CQA was adapted from Dokli's method[13] and the synthesis route was depicted in Figure 3.2. It is apparent that lactone **12** possess only one hydroxyl group located at the required site to undergo an esterification reaction with acid chloride (**23**) to produce an ester of intermediate protected 1-CQA (**24**). Synthesis of compound **24** was carried out at ambient temperature in dichloromethane in the presence of basic catalyst, DMAP, attaining 75% yield of isolating product. 1-CQA (**10**) 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 **25**.

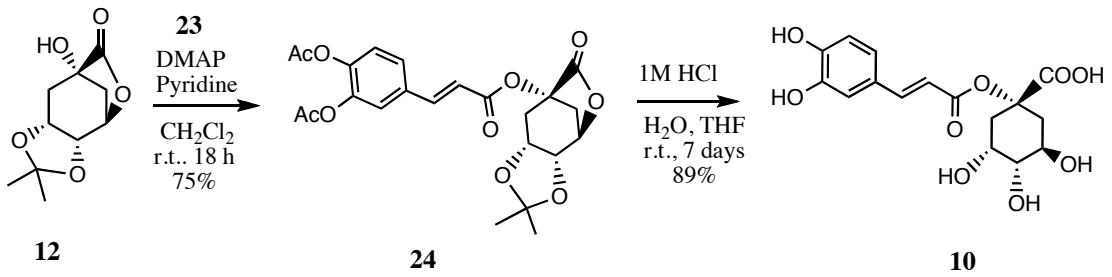

Figure 3.2 Synthesis route of 1-CQA (**10**) via protected ester of **24**

3.3.3 Synthesis of 5-CQA (3)

The ester of protected 5-CQA **25** was synthesized from esterification of diacetylcaffeoyl chloride **23** with protected qunic acid **16**, employing exactly the same condition as for the synthesis of ester **24**. The reaction scheme is depicted in Figure 3.3. Diacetylcaffeoyl chloride was reacted with methyl ester of quinic acid derivative **16** at ambient temperature in dichloromethane. The reaction proceeded well in the presence of DMAP as catalyst and pyridine. This reaction resulted in 58% yield of the isolated desired product (**25**) and minute amounts of compound **26** (3%). It seems that hydroxyl group at carbon 1 of quinic acid, which is a tertiary alcohol was less favorable to engage in a reaction with acid chloride compared to the secondary alcohol of hydroxyl group at number 5. The secondary alcohol reacted faster than a tertiary alcohol with acid chloride. The 5-CQA (**3**) was achieved at 88% yield after treating compound **25** with 1 M HCl to remove all the protecting groups for 4 days at room temperature.

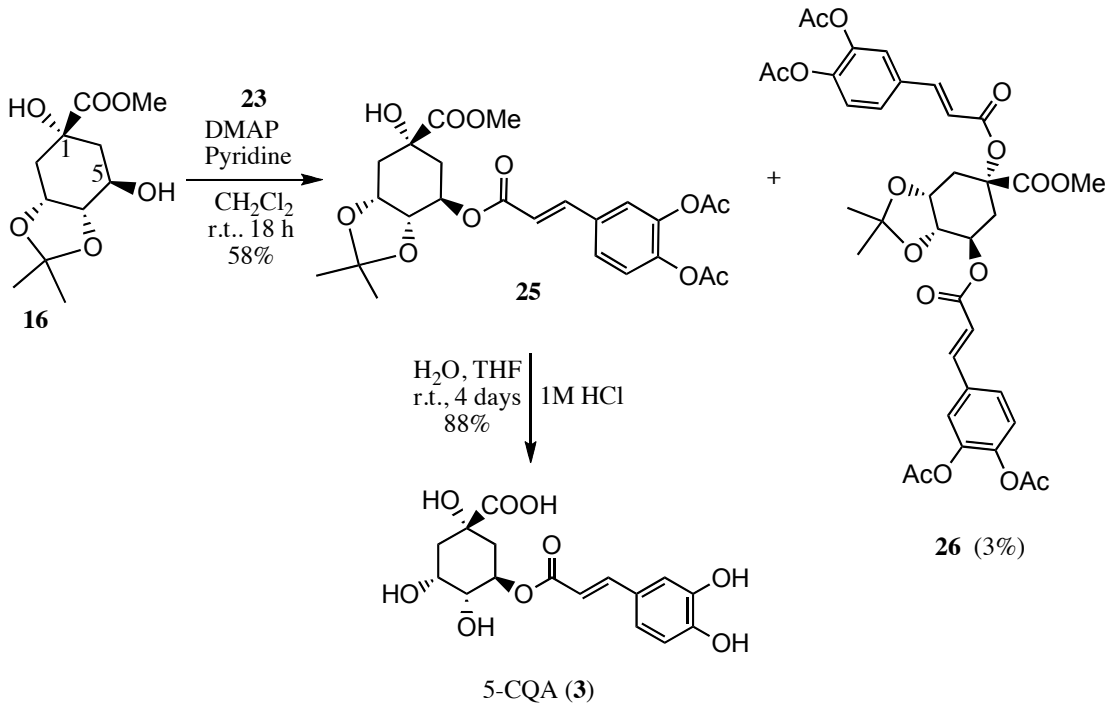

Figure 3.3 Synthesis route of making 5-CQA (**3**) and di-1,5-CQA (**26**) via intermediate ester (**25**)

3.3.4 Synthesis of 4-CQA (9)

Lactone **14** was used to synthesize protected 4-CQA, **27** by reacting it with compound **23**. 3-TBS protected quinic acid, lactone **14**, was reacted with diacetylcaffeoyl chloride in pyridine with the presence of DMAP as catalyst and the conditions of reaction were identical to the synthesis of ester **24** and **25.** This reaction, after purification with column chromatography, gave the desired ester **27** and byproduct of a diester **28** in 60% and 15% yield, respectively. This is interesting to see the fact that the diester **28** was obtained in a quite significant increase in yield compared to the compound **26** in the previous reaction. This may happen because of the proximity reasons between hydroxyl groups at carbon 1 and 5 compared to carbon 1 and 4 of the quinic acid derivatives. It is understood that secondary alcohol reacted faster with acid chloride than tertiary

alcohol and this applied to both reactions in Figure 3.3 and Figure 3.4. However, the distance of hydroxyl groups at carbon number 1 to 5 is relatively closer than the distance of hydroxyl groups at carbon number 1 to 4. Therefore, the formation of **25** resulted a bulkier structure than the formation of **27** towards the free hydroxyl group at carbon number 1 of the quinic acid derivative. In other words, the hydroxyl group of quinic acid at compound **27** is less hindrance than that of at compound **25**. Consequently, the formation of **28** is relative more easily than the formation of **26** and this was reflected by the obtained yields of the two compounds. 4-CQA was attained in 40% yield after removing all the protecting groups of **27** by stirring compound this ester with 1 M HCl for 8 days.

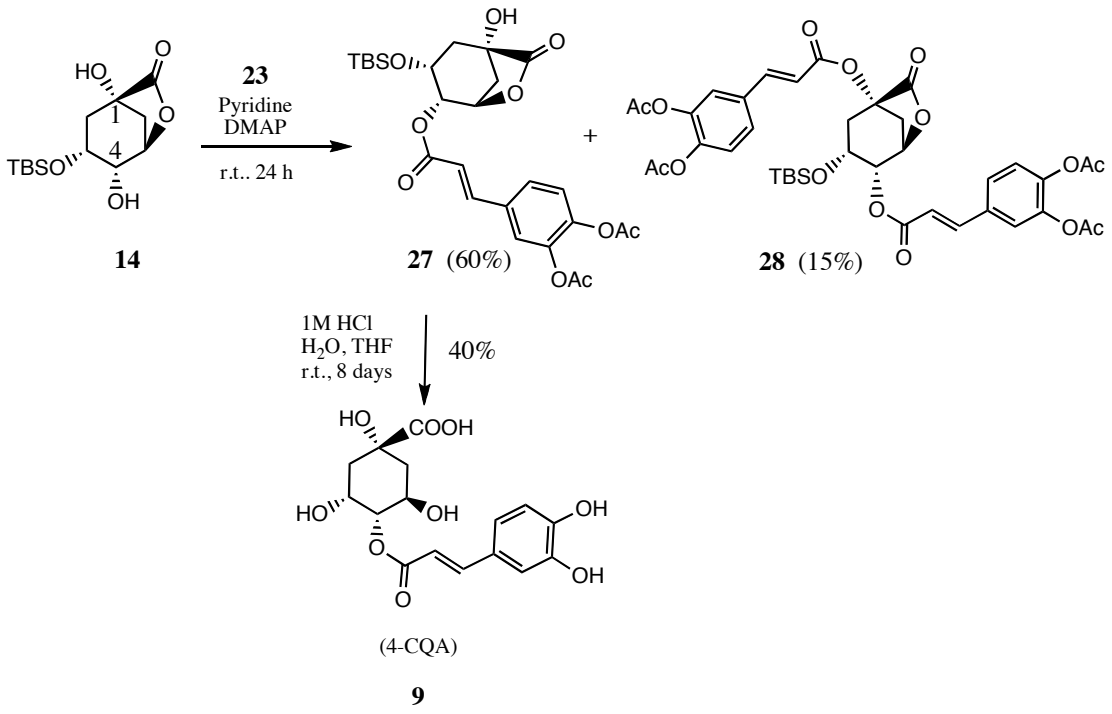

Figure 3.4 Synthesis route of making 4-CQA (**9**) and di-1,4-CQA via intermediate ester **27**

3.3.5 Synthesis of 3-CQA (11)

Lactone **18** was esterified with **23** using identical procedure to the synthesis of protected 4-CQA, as shown in Figure 3.5. 4-TBS protected quinic acid, lactone **18**, was reacted with diacetylcaffeoyl chloride in the presence DMAP as catalyst in pyridine for 24 h. This reaction gave the desired product of protected ester **29** in 53%. This ester was hydrolyzed with 1 M HCl for 7 days to remove all the protecting groups attaining 3-CQA **11** in 41% yield.

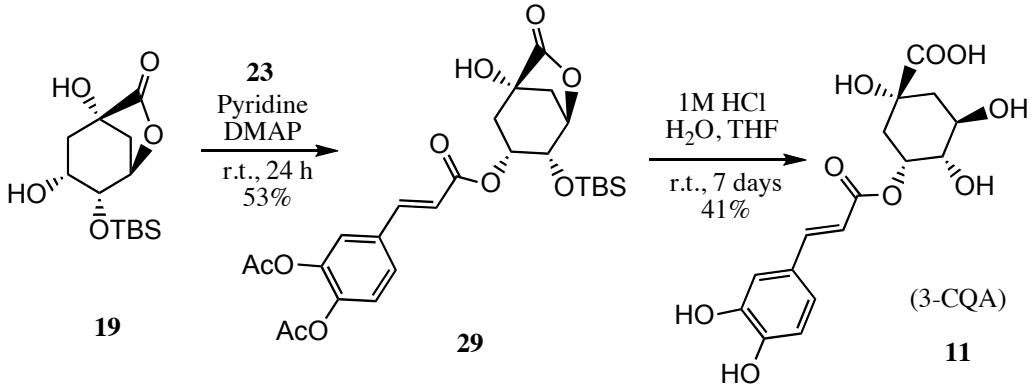

Figure 3.5 Synthesis route of making 3-CQA (**11**) via intermediate ester **29**

3.4 Conclusions

Efficient 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 was achieved. Apart from relatively moderate results, this method is considerably simpler than previous methods. The 3-CQA and 5-CQA were achieved by hydrolysis of the correspondent protected esters with dilute concentration of HCl.

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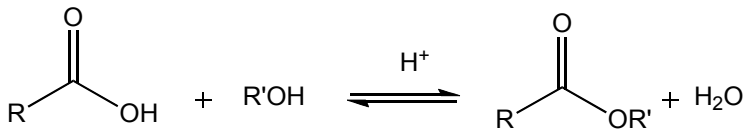
CHAPTER 4

Synthesis of Vinyl Esters

4.1 Introduction

Fischer esterification, Scheme 4.1, is the most familiar pathway of esterification reaction of carboxylic acids and alcohols catalyzed by acid.



Scheme 4.1 *Fischer esterification* of carboxylic acid with alcohol

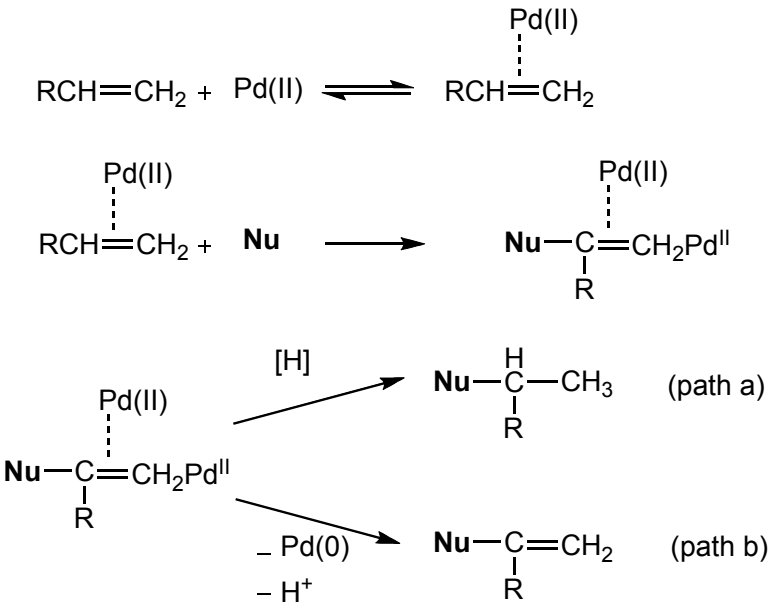
The reaction in Scheme 4.1 is an equilibrium process. Therefore there are two basic approaches to improve yields in chemical syntheses of esters of carboxylic acids and alcohols, which has been written in many Organic Chemistry textbooks. A very popular approach is employing an excess of alcohol to drive the balance of reaction equation towards products. Another familiar technique is removal of water as one of the esterification products.[1,2]

In certain conditions, for example, when esters intended to make possessing bulky structures of secondary or tertiary alcohols, such as quinic acid and its derivatives, those techniques are not enough to boost yields against steric hindrances. Thus, the use of more reactive and endorsing irreversible reaction of carboxylic acid derivatives may be complementing helpful. For instance, the use of acyl halides[1,2] as discussed in the previous chapter or anhydrides, or vinyl

esters is necessary. The use of vinyl esters is particularly interesting; however, the effective and very safe methods of making these substances remains unrevealed. Reported methods of vinyl esters syntheses were relied heavily on the use of mercuric catalysts, such as mercury(II) sulfate or mercury(II) acetate to enhance the vinyl ester products. The transvinylation reaction employing vinyl acetate alongside with mercuric salts was first introduced over seven decades ago, back to early 1940s by Herrmann et al.[3] and Toussaint et al.[4] Adelman[5] studied vinyl esterification reaction using mercuric acetate(II) based on infrared absorption spectrum. By measuring the spectrum, exchange of hydrogen atoms and the vinyl group of the carboxyl group was clearly indicated. Meanwhile, Kavitha et al.[6] reported the synthesis of vinyl caffeate with low yield in 1999 and other reports that used mercury(II) acetate as catalyst to synthesize vinyl caffeate, were also published.[7-9] Gao et al. reported the synthesis of vinyl coumarate and vinyl acetate using mercury acetate.[10] Regardless the catalysts, these reports are highlighting the ability of vinyl acetate to react with alcohols to produce another new vinyl ester or what is so called the transvinylation.

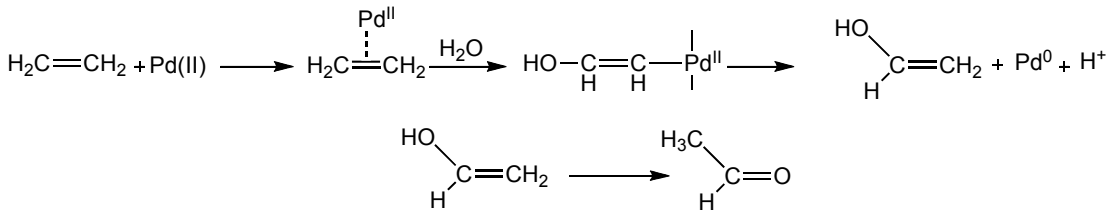
Despite being widely recognized as good catalysts, mercuric compounds in all oxidation states are highly risk to environment and human health. On the other hand, palladium (Pd), that has played an important role in modern organic synthesis, is relatively eco-friendly and less harmful to human health. Palladium has been reported in numerous publications showing its versatility as organopalladium intermediates in various synthetic organic chemistry. For example, Carey and Sundberg[2] summarized the reactions of alkenes with Pd(II) resulting in a Pd-π complex, shown in Scheme 4.2, that has a similarity to the

solvomercuration reaction in which the both type of reactions are the subject of *nucleophilic* addition.



Scheme 4.2 Nucleophillic adition via Pd-π complex

Under reductive condition, path a, Pd(II) may be replaced by hydrogen. When reducing agent is unavailable, a proton and Pd(0) are eliminated and the nucleophile is substituting the vinyl hydrogen (path b). The same fashion in path b occurs when Pd(II) salts reacted with compounds possessing potential leaving groups in an allylic position.[11,12] The *Wacker reaction* is another popular application of Pd catalyst for conversion of ethene to acetaldehyde, as shown in Scheme 4.3.



Scheme 4.3 The *Wacker reaction*, conversion of ethene to acetaldehyde

The *Heck reaction* is another popular reaction employing Pd catalyst. Usually this reaction is involving aryl and alkenyl halides reacted with alkene to provide an alkenyl group substitution on halide. Besides, many palladium-catalyzed cross coupling reactions are among the popular reactions using Pd catalyst.[2]

Although numerous reports about the versatile role of palladium(II) as catalysts in chemical reactions, no report discussed in more details about the use of palladium(II) acetate as catalyst in transvinylation of vinyl acetate with cinnamic acid and its derivatives. Palladium(II) acetate and Pd catalyst use were reported by Yang et al.[13] to provide vinyl esters by coupling carboxylic acids and alkenes but not a transvinylation. Considering the similarities in function and in some cases, interchangeable between mercuric(II) and palladium(II) catalysts,[14] this chapter presents the use of palladium(II) acetate, instead of mercuric(II) acetate as catalyst in the syntheses of several vinyl esters of cinnamic acid derivatives. The resulted vinyl esters are important to provide starting materials to react with quinic acid derivatives to form esters of caffeoylquinic acids. The reactions using vinyl esters-protected quinic acid are the subject to be discussed later in the subsequence chapter.

This chapter will discuss the impact of several additives on obtained yield of the reactions between vinyl acetate with cinnamic acid. The proposed catalyst cycle and results of transvinylation of some hydroxycinnamic acids with vinyl acetate would also be presented.

4.2 Experimental

4.2.1 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. Solvents evaporation was performed using Iwaki Rotary Evaporator REN-1000 with reduced pressure. JEOL NMR of JNM-LA400 and ECA500 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.

4.2.2 Synthesis of vinyl cinnamate (31)

The procedure of the syntheses various vinyl esters was adapted from Gao et al. [10] In a two-neck flask, cinnamic acid (**30**) (1.0 mmol, 148 mg), THF (1 mL), vinyl acetate (16 mmol, 1.4 g, 1.5 mL) and palladium(II) acetate (0.1 mmol, 9 mg) were added together and the reaction mixture was stirred for 30 minutes at room temperature. Thereafter, 10 % w/w of sulfuric acid in THF (1 drop) was added, and the mixture was continued to stir for 4 h at 40 °C, then filtered through celite. The filtrate was washed with water (15 mL × 1) and saturated brine (15 mL × 2). The organic layer was dried over sodium sulfate, and concentrated using an evaporator to get desired product (95%). ^{1}H NMR (400 MHz, $(CD_3)_2CO$, δ, ppm): 4.66 (dd, 1H, *J* = 6.3, 1.5 Hz, CH-C-vinyl), 4.96 (dd, 1H, *J* = 14.0, 1.96 Hz,

CH-C-vinyl), 6.62 (d, 1H, *J* = 16.1 Hz, CO-CH-CH-Ph), 7.39-7.47 (m, 4H; 3H, Ar-H and 1H, O-CH-vinyl), 7.37-7.81 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.83 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO). Proton NMR data is in agreement with literature.[15]

This experiment was performed in similar fashion but different additives used: *p*-TsOH, $BF_3.OEt_2$, Pyridine, K_2CO_3, KOH. The results were presented in Figure 4.1.

4.2.3 Vinyl caffeate (32)

Dihydroxycinnamic acid (**1**) (1.0 mmol, 194 mg) was placed into a two-necked flask, THF (1 mL), vinyl acetate (16 mmol, 1.4 g, 1.5 mL and palladium(II) acetate (0.1 mmol, 9 mg) were also added, and the mixture was stirred for 30 minutes at room temperature. Thereafter, 10% w/w of sulfuric acid in THF (1 drop) was added, and the mixture was stirred for 4 h at 40 °C, filtered through celite, and the filtrate was concentrated using an evaporator. The crude material was purified over chromatography column (*n*-Hexane : EtOAc, 1:1) to give desired product **32**, as yellow solid, R_f = 0.41, (21% yield). ^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 4.61 (dd, 1H, *J* = 6.3, 1.1 Hz, CH-C-vinyl), 4.94 (dd, 1H, *J* = 14.0, 1.4 Hz, CH-C-vinyl), 6.29 (d, 1H, *J* = 15.5 Hz, CO-CH-CH-Ph), 6.79 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.99 (dd, 1H, *J* = 8.3, 2.0 Hz, Ar-H), 7.07 (d, 1H, *J* = 2.3 Hz, Ar-H), 7.40 (dd, 1H, *J* = 13.7, 6.3 Hz, O-CH-vinyl), 7.66 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO). Data is in agreement with literature.[6]

4.2.4 Vinyl coumarate (34)

4-Hydroxycinnamic acid (**33**) (1.0 mmol, 164 mg) was placed into a two-necked flask, THF (1 mL), vinyl acetate (16 mmol, 1.4 g, 1.5 mL) and palladium(II)

acetate (0.1 mmol, 9 mg) were also added, and the mixture was stirred for 30 minutes at room temperature. Thereafter, 10% w/w of sulfuric acid in THF (1 drop) was added, and the mixture was stirred for 4 h at 40 °C. The mixture was filtered through celite, and the filtrate was concentrated using an evaporator. The crude material was purified over chromatography column (*n*-Hexane : EtOAc, 2:1) to give desired product **34**, as yellow solid, R_f = 0.35, (35% yield). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 4.63 (dd, 1H, *J* = 6.3, 1.1 Hz, CH-C-vinyl), 4.98 (dd, 1H, *J* = 13.7, 1.7 Hz, CH-C-vinyl), 5.6 (s, broad, 1H, OH), 6.32 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.87 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.42 (dd, 1H, *J* = 13.7, 6.3 Hz, O-CH-vinyl), 7.48 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.74 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO). Data is in agreement with literature.[10]

4.2.5 Vinyl ferulate (36)

Ferulic acid (**35**) (1.0 mmol, 194 mg) was placed into a two-necked flask, THF (1 mL), vinyl acetate (16 mmol, 1.4 g, 1.5 mL) and palladium(II) acetate (0.1 mmol, 9 mg) were also added, and the mixture was stirred for 30 minutes at room temperature. Thereafter, 10% w/w of sulfuric acid in THF (1 drop) was added, and the mixture was stirred for 4 h at 40 °C. The mixture was filtered through celite, and the filtrate was concentrated using an evaporator. The crude material was purified over chromatography column (*n*-Hexane : EtOAc, 2:1) to give desired product **36**, as yellow solid, R_f = 0.42, (16% yield). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 3.93 (s, 3H, CH_3), 4.62 (d, 1H, *J* = 6.3 Hz, CH-C-vinyl), 4.96 (d, 1H, *J* = 13.7 Hz, CH-C-vinyl), 5.98 (s, broad, 1H, OH), 6.31 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.92 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.09 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.43 (1H, dd, *J*

= 13.7, 6.3 Hz, O-CH-vinyl), 7.72 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO). Data is in agreement with literature.[10]

4.2.6 Vinyl 4-t*ert*-butyldimethylsiloxycinnamate (38)

4-t*ert*-butyldimethylsiloxycinnamic acid (**37**) (1.0 mmol, 278 mg) was placed into a two-necked flask, to this, vinyl acetate (16 mmol, 1.4 g, 1.5 mL) and palladium(II) acetate (0.1 mmol, 9 mg) were also added and the reaction mixture was stirred for 30 minutes at room temperature. Then, KOH (0.1 mmol, 6 mg) was added, and the reaction mixture was stirred for 4 h at 40 °C. The mixture was filtered through celite, and the filtrate was concentrated using evaporator and purified with column chromatography over silica to give 70% the desired product (**38**). (*n*-Hexane:EtOAc, 30:1, v/v, R_f = 0.40). IR (film, ν, cm^{-1}): 3087 (C-H, alkene), 3033 (C-H, aromatic), 2955 (C-H, methyl), 1731 (C=O, carbonyl), 1509 (C=C, aromatic), 1149 (C-O, ester). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.23 (s, 6H, $(CH_3)_2$-Si)), 0.99 (s, 9H, $(CH_3)_3C$), 4.62 (dd, 1H, *J* = 6.3, 1.5 Hz, CH-C-vinyl), 4.97 (dd, 1H, *J* = 14.0, 1.6 Hz, CH-C-vinyl), 6.32 (d, 1H, *J* = 16.1 Hz, CO-CH-CH-Ph), 6.86 (t, 2H, *J* = 4.3 Hz, Ar-H), 7.40-7.46 (m, 2H, Ar-H; 1H, CH-vinyl), 7.74 (d, 1H, *J* = 16.1 Hz, Ph-CH-CH-CO). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 164.3 (1C, carboxylic-C),158.4 (1C, Ar-C), 146.5 (1C, Ph-C), 141.5 (1C, Ar-C), 130.1 (1C, CH-Vin), 127.5 (2C, Ar-C), 120.7 (2C, Ar-C), 114.3 (1C, benz-C), 97.5 (1C, CH_2-Vin), 25.7 (3C, (CH_3)-C), 18.3 (1C, C-CH_3), -4.3 (2C, $(CH_3)_2$-Si). HRMS (EI): m/z: calcd for $C_{17}H_{24}O_3Si$ $[M]^+$, 304.1495; found 304.1488.

4.2.7 Vinyl 4-t*ert*-butyldimethylsiloxy-3-methoxycinnamate (40)

4-t*ert*-butyldimethylsiloxy-3-cinnamic acid (**39**) (1.0 mmol, 317 mg) was placed into a two-necked flask, to this, vinyl acetate (16 mmol, 1.4 g, 1.5 mL) and palladium(II) acetate (0.1 mmol, 9 mg) were also added and the reaction mixture was stirred for 30 minutes at room temperature. Then, KOH (0.1 mmol, 6 mg) was added, and the reaction mixture was stirred for 4 h at 40 °C. The mixture was filtered through celite, and the filtrate was concentrated using evaporator and purified with column chromatography over silica to give 50% the desired product (**40**). (*n*-Hexane:EtOAc, 30:1, R_f = 0.40). IR (film, ν, cm^{-1}): 3086 (C-H, alkene), 3047 (C-H, aromatic), 2929 (C-H, methyl), 1727 (C=O, carbonyl), 1511 (C=C, aromatic), 1146 (C-O, ester), 1036 ($C=CH_2$, vinyl). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.12 (s, 6H, $(CH_3)_2$-Si)), 0.94 (s, 9H, $(CH_3)_3C$), 3.78 (s, 3H, CH_3-O), 4.56 (dd, 1H, *J* = 6.3, 1.7 Hz, CH-C-vinyl), 4.90 (dd, 1H, *J* = 14.0, 1.4 Hz, CH-C-vinyl), 6.26 (d, 1H, *J* = 15.5 Hz, CO-CH-CH-Ph), 6.80 (d, 1H, *J* = 8.0 Hz), 6.99 (t, 2H, *J* = 4.9 Hz), 7.37 (1H, dd, *J* = 14.3, 6.3 Hz), 7.67 (d, 1H, *J* = 16.0 Hz, Ph-CH-CH-CO). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 164.3 (1C, Carboxylic-C), 151.3 (1C, Ar-C), 148.1 (1C, Ph-CH), 146.9 (1C, Ar-C), 141.5 (1C, CH-Vin), 128.1 (1C, Ar-C), 122.7 (1C, Ar-C), 121.2 (1C, Ar-C), 114.3 (1C, Ar-C), 111.0 (1C, benz-CH), 97.5 (1C, CH_2-Vin), 55.5 (1C, CH_3-O), 25.7 (3C, (CH_3)-C), 18.6 (1C, C-CH_3), -4.5 (2C, $(CH_3)_2$-Si). HRMS (EI): m/z: calcd for $C_{18}H_{26}O_4Si$ $[M]^+$, 334.1600; found 334.1605.

4.2.8 Vinyl 3,4-di-*tert*-butyldimethylsiloxycinnamate (41)

To a two-neck flask, 3,4-di-*tert*-butyldimethylsiloxycinnamic acid (**19**) (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 h, 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 (*n*-Hexane:EtOAc, 5:1, v/v) to give 580 mg of (**41**), (Figure 4.3), as yellow liquid. (Rf = 0.82 on *n*-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, $(CH_3)_3$C), 1.00 (s, 9H, $(CH_3)_3$C), 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, CH-Vin), 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.

4.2.9 Vinyl 2,2-dimethylbenzo [*d*] [1,3] dioxolcinnamate (42)

In a two-necked flask, **20** (1.0 mmol, 220 mg), vinyl acetate (16 mmol, 1.4 g, 1.5 mL) and palladium(II) acetate (0.1 mmol, 9 mg) were added. After stirring for 10 minutes at room temperature, potassium hydroxide (0.1 mmol, 6 mg) was added and the mixture was stirred for 4 h at 40 °C. The reaction mixture was filtered

through celite and the filtrate was concentrated by an evaporator and purified by column chromatography to give **42** as a pale yellow oil (84%). TLC (*n*-Hexane: EtOAc, 4: 1 v/v): Rf = 0.64. IR (film, ν, cm^{-1}): 3087 (C-H, alkene), 2992 (C-H, methyl), 1727 (C=O, carboxyl, 1496 (C=C, aromatic), 951 (C-H, vinyl), 809 (C-H, vinyl terminal). ^1H NMR(500 MHz, $CDCl_3$, δ, ppm): 1.69 (s, 6H, $(CH_3)_2$-C), 4.61 (dd, 1H, *J* = 6.3, 1.7 Hz, CH-C-vinyl), 4.96 (dd, 1H, *J* = 13.7, 1.7 Hz, CH-C-vinyl), 6.25 (d, 1H, *J* = 15.5 Hz, CO-CH-CH-Ph), 6.71-7.01 (m, 3H, Ar-H), 7.42 (dd, 1H, *J* = 13.7, 6.3 Hz, O-CH-vinyl), 7.69 (d, 1H, *J* = 15.5 Hz, Ph-CH-CO). ^{13}C NMR ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 164.4 (1C, C=O, carboxyl), 150.1 (1C, Ar-C), 148.4 (1C, Phenyl-C), 146.8 (1C, Ar-C), 141.5 (1C, CH-vin), 128.1 (1C, C-$(CH_3)_2O_2$), 124.8 (1C, Ar-C), 119.2 (1C, Ar-C), 113.9 (1C, Ar-C), 108.6 (1C, Ar-C), 106.5 (1C, Benz-C), 97.6 (1C, CH_2-Vin), 26.0 (2C, CH_3-C). HRMS (EI): m/z: calcd for $C_{14}H_{14}O_4$ $[M]^+$, 246.0892; found, 246.0899.

4.2.10 Vinyl 3,4-diacetoxycinnamate (43)

In a two-necked flask **21** (1 mmol, 290 mg), THF (1 mL), vinyl acetate (16 mmol, 1.4 g, 1.5 mL) and palladium(II) acetate (0.1 mmol, 9mg) were added. The reaction mixture was stirred for 30 minutes at room temperature. Thereafter, 10% w/w of sulfuric acid in THF (1 drop) was added, and the mixture was stirred for 4 h at 40 °C. The mixture was filtered through celite and the filtrate was extracted with ethyl acetate (15 mL × 3) then washed with saturated brine (15 mL × 2). The organic layer was dried over sodium sulfate, and concentrated using an evaporator. Purification was done by column chromatography to give **43** as pale yellow oil (84%). TLC (*n*-Hexane: EtOAc, 3: 1 v/v): R_f = 0.30. IR (film, ν, cm^{-1}) : 3090 (C-H, alkene), 2932 (C-H, methyl), 1722 (C=O, carbonyl), 1506

(C=C, aromatic), 1167 (C-O, ester), 903(C=CH_2, vinyl). ^{1}H NMR(500 MHz, $CDCl_3$, δ, ppm): 2.31 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.65 (dd, 1H, *J* = 6.3, 1.7 Hz, CH-C-vinyl), 4.98 (dd, 1H, *J* = 13.7, 1.7 Hz, CH-C-vinyl), 6.40 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 7.24 (d, 1H, *J* = 8.6 Hz, O-CH-vinyl), 7.38-7.45 (m, 3H, aromatic-H), 7.73 (d, 1H, *J* = 16.0 Hz, Ph-CH-CO). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 168.0 (1C, C=O, acetyl), 167.9(1C, C=O, acetyl), 163.4 (1C, C=O, ester), 144.6 (1C, Ar-C), 143.8 (1C, Phenyl-C), 142.5 (1C, Ar-C), 141.2 (1C, CH-vin), 132.8 (1C, Ar-C), 126.6 (1C, Ar-C), 124.0 (1C, Ar-C), 122.9 (1C, Ar-C), 117.7 (1C, Benz-C), 97.9 (1C, CH_2-Vin), 20.6 (1C, CH_3), 20.5 (1C, CH_3). HRMS (EI) : m/z: calcd for $C_{15}H_{14}O_6$ $[M]^+$: 290.0790; found : 290.0786.

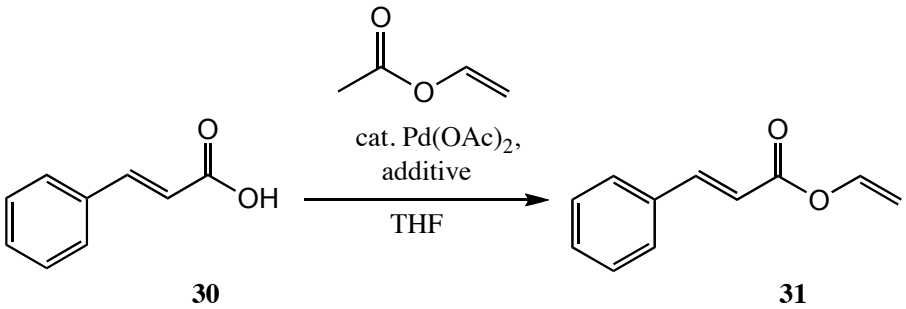
4.2.11 Vinyl 3,4-dibenzyloxycinnamate (44)

In a two-necked flask, **22** (1.0 mmol, 360 mg), vinyl acetate (16 mmol, 1.4 g, 1.5 mL) and palladium(II) acetate (0.1 mmol, 9 mg) were added. After stirring for 10 minutes at room temperature, potassium hydroxide (0.1 mmol, 6 mg) was added and the mixture was stirred for 4 h at 40 °C. The reaction mixture was filtered through celite. The filtrate was concentrated by an evaporator and purified by column chromatography to give **44** as pale yellow waxy solid (64%). TLC (*n*-Hexane: EtOAc, 5: 1 v/v): Rf = 0.58. ^{1}H NMR(500 MHz, ($CDCl_3$, δ, ppm): 4.61 (dd, 1H, *J* = 6.3, 1.7 Hz, CH-C-vinyl), 4.95 (dd, 1H, *J* = 14.0, 1.4 Hz, CH-C-vinyl), 5.17 (s, 2H, benzyl-H), 5.19 (s, 2H, Benzyl-H), 6.24 (d, 1H, *J* = 16.0 Hz, CO-CH-CH-Ph), 6.91 (d, 1H, *J* = 8.6 Hz, Ar-H), 7.08 (dd, 1H, *J* = 8.3, 2.0 Hz, O-CH-vinyl), 7.13 (d, 1H, *J* = 2.3 Hz, Ar-H), 7.31-7.46 (m, 11 H, Ar-H), 7.67 (d, 1H, *J* = 15.5 Hz, Ph-CH-CO). Data is in good agreement with literature.[6]

4.3 Results and Discussion

4.3.1 Effect of additives

Cinnamic acid (**30**) and vinyl acetate underwent acyl rearrangement in the presence of palladium acetate(II) as catalyst. The influence of various additives on obtained yields in synthesizing vinyl ester of cinnamic acid (**31**) was investigated, as depicted in Figure **4.1**. The type of additives used in this reaction was determined according to Mastihubová's procedure.[9]



Entry	Additive	Yield[a] (%)
1	-	66
2	*p*-TsOH	67
3	$BF_3.OEt_2$	68
4	H_2SO_4	95[b]
5	Pyridine	No reaction
6	K_2CO_3	94
7	KOH	96[b]

[a]Yield was determined by ^{1}H NMR spectroscopy
[b]Isolated yield
p-TsOH = *p*-toluenesulfonic acid

Figure 4.1 Additive effect on transvinylation catalyzed by Pd(II) acetate

From Figure 4.1, it is obvious that certain additives can improve the reaction's yield. Sulfuric acid, potassium carbonate and potassium hydroxide (entries 4, 6, 7) had significant impact on increasing yield of compound **31**. On the other hand, *p*-TsOH and $BF_3{\cdot}OEt_2$ when added (entries 2, 3, 5) to the reactions was apparently no effect, showing similar yields when reaction carried out without additive. While addition of pyridine, the reaction did not proceed.

4.3.2 Proposed catalytic cycle of palladium(II) acetate

The most likely catalytic cycle of palladium(II) acetate in the transvinylation process is presented in Figure 4.2. Palladium increases the electrophilic and promotes nucleophillic addition to alkene. Olefin of vinyl acetate is coordinated to the palladium to form a π complex. As the consequence, electrophile of the alkene increases. Cinnamic acid as nucleophilic is attacking the electrophilic complex at the more substituted of olefin following the Markovnikov's rule to form an intermediate of a six-membered ring.

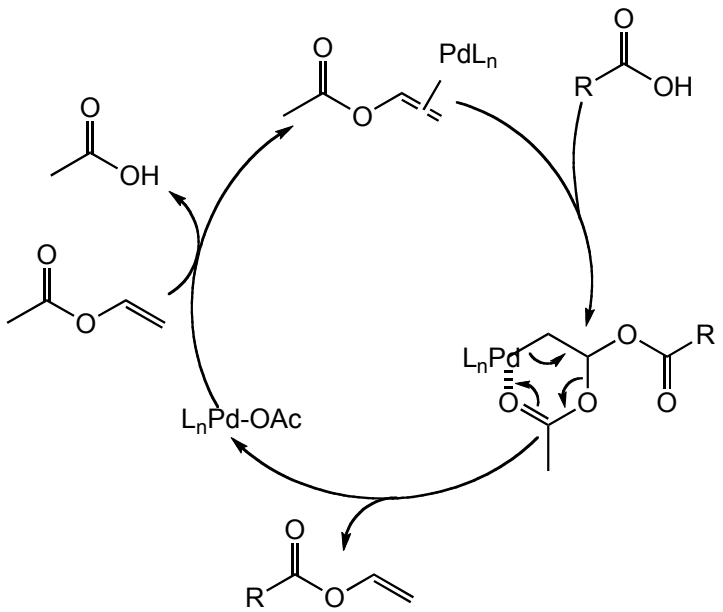


Figure 4.2 Proposed catalytic cycle of Pd(II) acetate in transvinylation reaction

After rearrangement, the vinyl ester is produced alongside with palladium acetate complex. This complex interacts with vinyl acetate eliminating acetic acid, vinyl acetate and palladium form a complex again.

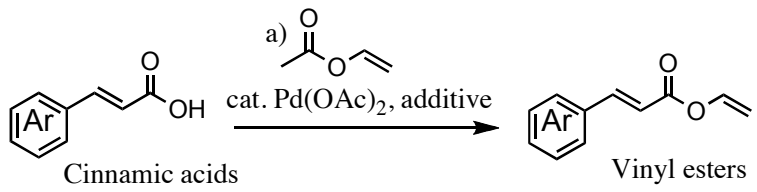
4.3.3 Synthesis of vinyl esters

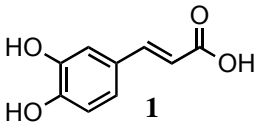
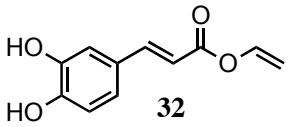
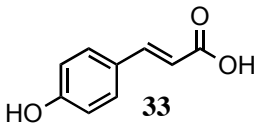
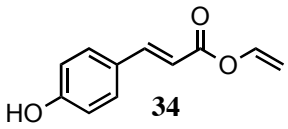
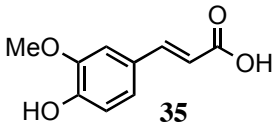
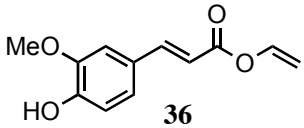
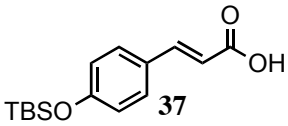
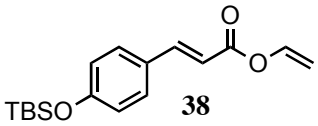
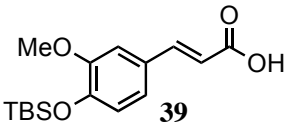
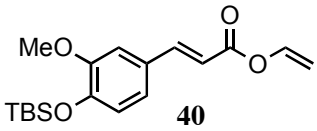
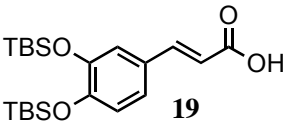
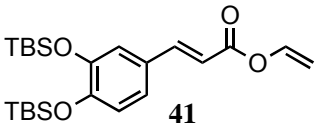
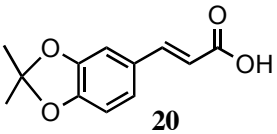
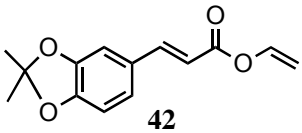
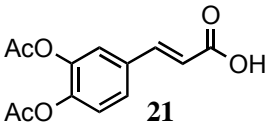
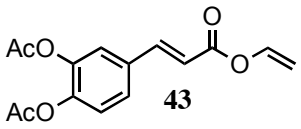
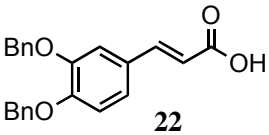
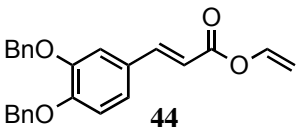
The reactions were conducted in mild temperature, at 40 ^{o}C using tetrahydrofuran (THF) as solvent for four hours. From the previous section 4.3.1, H_2SO_4 and KOH were the additives that performed better than other tested additives when cinnamic acid was reacted with vinyl caffeate. Therefore, these additives were employed in the transvinylation reaction of cinnamic acid derivatives. Dihydroxy cinnamic acid (**1**) reacted with vinyl acetate in the presence of palladium(II) acetate and sulfuric acid as additive in THF to achieve vinyl caffeate was first investigated giving the isolated yield in 21%. Coumaric acid and ferulic acid were also reacted with vinyl acetate in a similar fashion to caffeic acid giving the yields 35% and 16%, respectively. The summary was presented in Figure 4.3 and as shown in Figure 4.3, the unprotected hydroxyl groups (entry 1 to 3) had lower yields compared to those protected ones. This may be related to the vulnerability of hydroxyl groups on oxidation to produce side products; hence it decreased the yields.

When the protection using electron-withdrawing groups, such as Acetyl (Ac) group (Entry 8), product was obtained in high yield (84%). On the other hand, when the electron-donating groups, such as benzyloxy (Bn) group protection (Entry 9), yield obtained was moderate. Based on these results, the protection of

hydroxyl groups of the hydroxycinnamic acid was affecting the yields of transvinylation.

The two additives, H_2SO_4 and KOH were used differently in reactions. It was related to the stability of protecting groups. For example, *tert*-butyldimethylsilyl (TBS) protecting group is stable in both basic and acidic condition.[16] Acetals for diol protecting group is stable in base and susceptible with mild acid condition, while acetyl is more stable in acidic than in basic condition, that is why to cleave this protecting groups usually mild basic condition was used. Methyl ether and benzyl ether (Bn) protecting group are stable in both acidic and basic condition.[16]



Entry	Cinnamic acids	Additive	Vinyl esters	Yield (%)
1	 **1**	H_2SO_4	 **32**	21
2	 **33**	H_2SO_4	 **34**	35
3	 **35**	H_2SO_4	 **36**	16
4	 **37**	KOH	 **38**	70
5	 **39**	KOH	 **40**	50
6	 **19**	KOH	 **41**	81
7	 **20**	KOH	 **42**	84
8	 **21**	H_2SO_4	 **43**	84
9	 **22**	KOH	 **44**	64

Reagents and conditions; a) vinyl acetate (16 equiv.), $Pd(OAc)_2$ (0.1 equiv.), additive (0.1 equiv.), THF, 40 ºC, 4 h.

Figure 4.3 Transvinylation of hydroxycinnamic acid and its derivatives

4.4 Conclusions

Palladium(II) acetate is capable of acting as good catalyst in the syntheses of vinyl esters of cinnamic acid and its derivatives, replacing the functionality of mercury(II) catalysts. The performance of the catalyst improved with the presence of additives, such as H_2SO_4 and KOH. Obtained yields are low in the transvinylation reactions of hydroxycinnamic acids, but it turned to be significant higher when hydroxyl groups was protected prior to transvinylation.

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CHAPTER 5

Synthesis of Caffeoylquinic Acids via Transesterification of Vinyl Caffeate

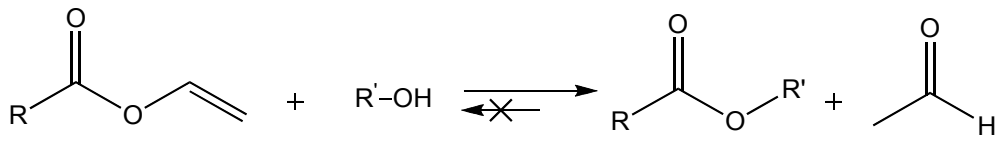
5.1 Introduction

Chlorogenic acid and its isomers are among natural compounds that have been a magnet of intensive research for many years due to their various biological activities.[1-3] These secondary metabolites occurred 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 contain these compounds.[8,9]

Techniques to provide these CQAs are still dominated by directly isolation from natural products. Meanwhile convenient methods for practical synthesis of CQAs remain interesting to synthetic chemists. In fact, the synthesis of CQAs via chemical methods is still quite challenging and relatively less developed with only few reports published, such as by Hemmerle *et al.*[10] and Lorentz *et al.*[11] And more spesifically, Sefkow and co-workers' have reported the synthesis of 1-, 3-, 4-, and 5-CQA via esterification of suitable protected quinic acids with acid chloride of caffeic acid.[12,13] Dokli *et al*.[14] reported the syntheses of 3-, 4- and 5-feruloylquinic acids utilizing similar method to Sefkow's with minor modifications on the protected quinic acids.

From our previous report,[15] a different pathway in the synthesis of 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, was investigated and discussed in Chapter 3. This technique employed Sefkow and Dokli et al. methods with a great success. In this Chapter, however, a new synthetic strategy in selective construction of chlorogenic acid and its isomers using caffeic acid vinyl ester would be discussed.

The use of vinyl ester as an activated form of carboxylic acid to react with alcohol is particularly interesting since this transesterification reaction is irreversible,[16-18] proceeding only in one direction towards products. The products are a new ester and a vinyl alcohol molecule that quickly transforms into acetaldehyde. The schematic reaction is shown in Scheme 5.1.



Scheme 5.1 Process in a transesterification using vinyl ester

Transesterification reactions of caffeic acid vinyl ester with protected quinic acids were assisted by the presence of lanthanum(III) nitrate monohydrate as catalyst. La(III) complexes have been recognized as harmless and colorless substances and have been proved to be effective catalysts for transesterification of carboxylic esters with alcohols by Okano, Neverov, Mei, and Hatano et al.[19-22] Hatano's report, in particular, presented that lanthanum(III) nitrate alkoxide has

been *in situ* generated and promoting this complex to be highly active and nearly neutral transesterification catalyst.[22] They disclosed that employing $La(NO_3)_3 \cdot H_2O$ as catalyst and $(n\text{-Oct})_3P$ as additive in 1:2 mol ratio in the reaction of dimethyl carbonate with 1-ethenyl-1-cyclohexanol achieved the desired product in 99% yield.

A reaction between vinyl cinnamic esters and protected quinic acids are similar to Hatano's prototype reaction. Considering this similarity, it is assumed that the use of $La(NO_3)_3 \cdot H_2O$ as catalyst and $(n\text{-Oct})_3P$ as additive would also work for transesterification of vinyl cinnamic esters reacted with protected quinic acids. The transesterification products would be protected CQAs, and the corresponding CQAs (chlorogenic acid and its isomers) would be achieved after the removal of all the protecting groups using low concentration of hydrochloric acid.

5.2 Experimental

5.2.1 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 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 ^1H and ^{13}C NMR spectra were performed in

JEOL NMR of JNM-LA 400 and ECA500 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.

5.2.2 Synthesis of (1*S*,3*R*,4*R*,5*R*)-1-[3-(3,4-di-*O*-*tert*-butyldimethylsiloxy) caffeoyl-1,3-quinic acid lactone)] (45)

Lanthanum nitrate monohydrate (43 mg, 0.12 mmol) and tri-*n*-octylphosphine (91 mg, 0.24 mmol) were added into 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 **12** (254 mg, 1.19 mmol) and vinyl ester caffeate **41** (515 mg, 1.19 mmol) were added and then stirred at reflux temperature for 48 h. 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 **45**, 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.

5.2.3 Preparation of 1-CQA (10)

As much as 209 mg (0.34 mmol) of compound **45** 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 **45** (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 **10** (Figue 5.2), 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).

5.2.4 Attempted synthesis of protected ester 5-CQA (46)

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 **16** (320 mg, 1.3 mmol) and vinyl ester caffeate **41** (565 mg, 1.3 mmol) were added and then stirred at reflux temperature for 48 h. 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, **45** instead of **46**, Figure 5.3, 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 **45**. 5-CQA was also attempted to achieve, however, the resulted product was 1-CQA (**10**).

5.2.5 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] (47)

Lanthanum nitrate monohydrate (37 mg, 0.10 mmol) and tri-*n*-octylphosphine (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 **14** (288 mg, 1.0 mmol) and vinyl ester caffeate (435 mg, 1.0 mmol) were added and then stirred at reflux temperature for 48 h. 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 **47** 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.

5.2.6 Synthesis of 4-CQA (9)

As much as 213 mg (0.40 mmol) of protected 4-CQA (**47**) 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 **9**, 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).

5.2.7 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 (48)

Lanthanum nitrate monohydrate (37 mg, 0.10 mmol) and tri-*n*-octylphosphine (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 **18** (288 mg, 1.0 mmol) and vinyl ester caffeate (435 mg, 1.0 mmol) were added and then stirred at reflux temperature for 48 h. 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 **48**, 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_3Si), 0.18 (s, 3H, CH_3Si), 0.21 (s, 6H, $(CH_3)_2$-Si), 0.22 (s, 6H, $(CH_3)_2$-Si), 0.95 (s, 9H, $(CH_3)_3C$), 0.98 (s, 9H, $(CH_3)_3C$), 0.99 (s, 9H, $(CH_3)_3C$), 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.

5.2.8 Synthesis of 3-CQA (11)

As much as 213 mg (0.4 mmol) of protected 3-CQA (**48**) 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 **48**, 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).

5.3 Results and discussion

5.3.1 Preparation of diTBS vinyl caffeate

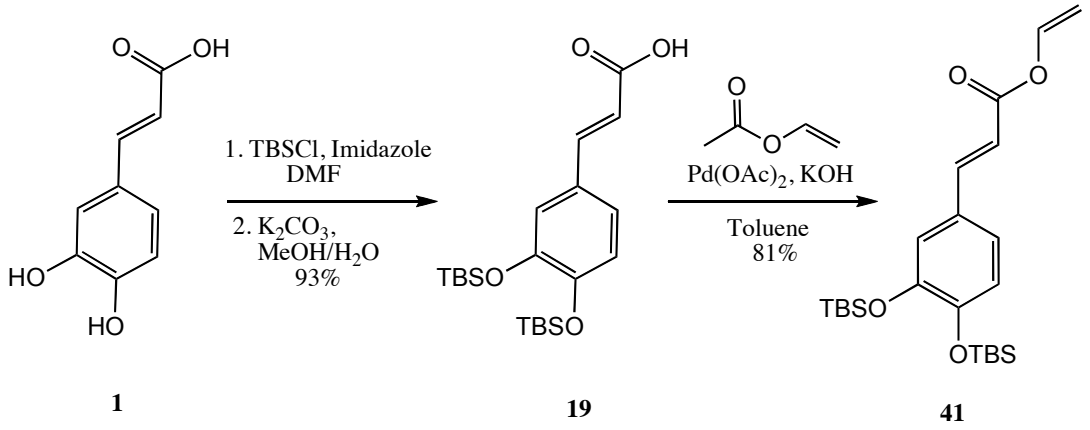


Figure 5.1 Synthesis of 3,4-di-*tert*-butyldimethylsiloxyvinylcinnamate (**41**) from caffeic acid (**1**) via ditbs-cinnamic acid (**19**)

Vinyl caffeate ester **41** used in this work was prepared, as depicted in Figure 5.1, 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 93% of acid **19,** based on known procedure.[23] The resulted acid was then reacted with vinyl acetate in the presence of palladium acetate as catalyst in basic condition to yield new compound, **41**, (81%) as a handful starting material 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 at 1713 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 **19** to vinyl ester **41**. HRMS result concluded that **41** was achieved and completely isolated, showing an agreement result of the calculated data with the figure found from HRMS analysis.

5.3.2 Synthesis of 1-CQA (10) and 5-CQA (3)

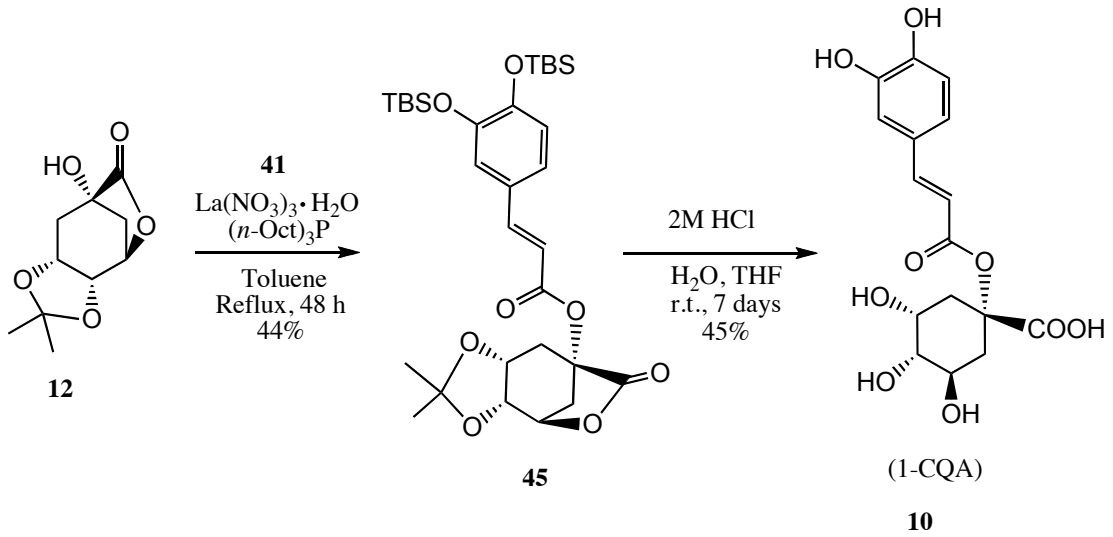


Figure 5.2 Synthesis route of 1-CQA (**10**) via protected ester **45**

Synthesis of 1-CQA is shown Figure 5.2. Lactone **12** has only one hydroxyl group located at the required site to undergo an esterification reaction with TBS-protected vinyl caffeate (**41**) producing protected 1-CQA (**45**). Reaction was performed at refluxed toluene in the presence of $La(NO_3)_3{\cdot}H_2O/(n\text{-Oct})_3P$ as catalyst, attaining 52% yield from compound **12**. The formation of compound **45**

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.[24] From the proton NMR spectrum, all protons/signals attributed to compound **45** 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 **45**. 1-CQA (**10**) 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 **45**.

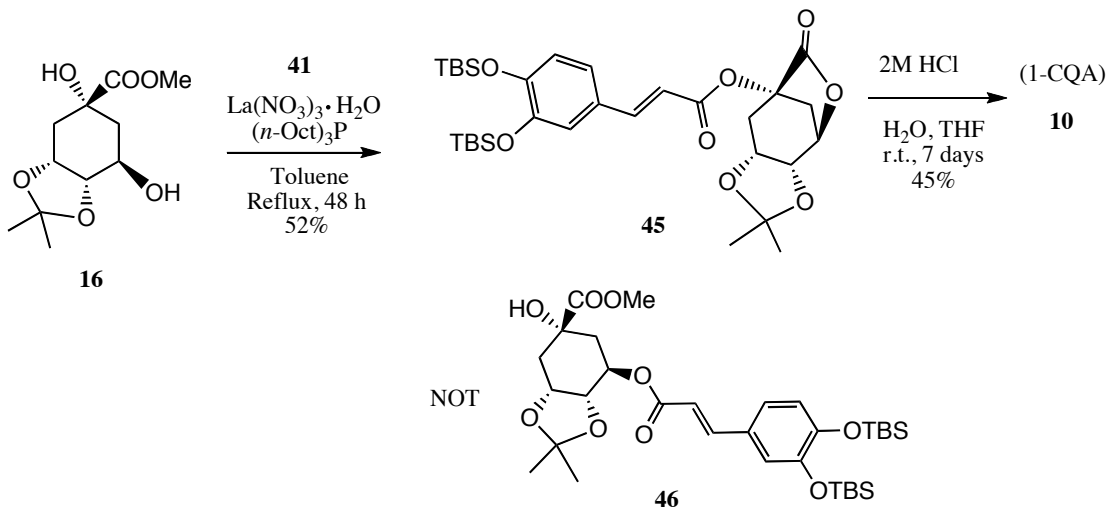


Figure 5.3 Attempt to synthesize 5-CQA via intermediate ester **46**

Attempt to synthesize 5-CQA is depicted in Figure 5.3. Protected quinic acid (**16**) was reacted with (**41**) at the same condition applied for making 1-CQA, previously. Interestingly, the resulted product was not compound **46**, as

expected. Based on proton NMR spectrum, the product was compound **45**, this was also supported by the IR spectrum. It seems that at high temperature, lactone **16**, which is an ester underwent an intramolecular transesterification between the methoxy group with hydroxyl group at carbon number 5 of the compound rather than an intermolecular transesterification with **41**. It may occur by the help of catalyst, $La(NO_3)_3 \cdot H_2O$, being used in this experiment. As acid catalyst, lanthanum (III) nitrate functions like *p*-TsOH,[25] as for the formation of **17** from **2** (Figure 2.3, Chapter 2). It could also be boosted by the involvement of $(n\text{-Oct})_3P$ to generate an acid-base catalyst of lanthanum alkoxide.[26] Hence, this process led to the formation of lactone **12**, which then reacted with vinyl caffeate to form ester **45** (protected 1-CQA) and the possible route to this process is presented in Figure 5.4. To obtain 5-CQA, the alternative protected quinic acid that does not possess ester-protecting groups is suggested.

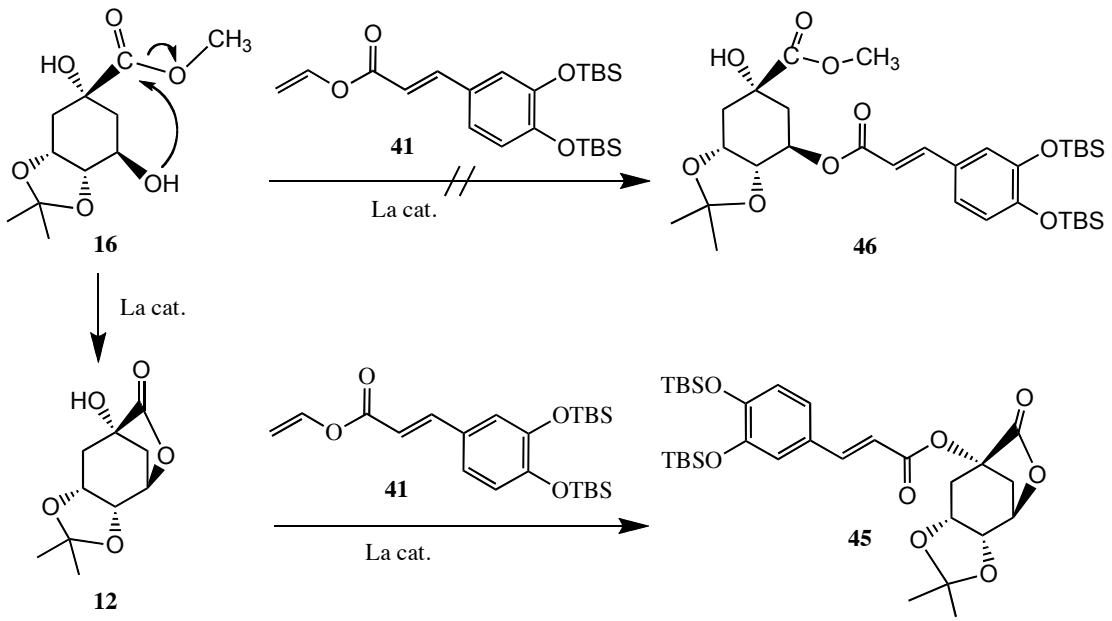


Figure 5.4 Possible reaction route to provide protected-1CQA (**45**) via intramolecular transesterification

5.3.3 Synthesis of 4-CQA (9)

Lactone **14** was used in the synthesis of protected 4-CQA by reacting it with compound **41** to give 46% yield of the desired compound **47**. The confirmation that compound **47** had been obtained was examined from its IR and NMR spectra as well as HRMS data. As for compound **45**, peak at 915 cm^{-1} was also unidentified in the product, proofing that transesterification had proceeded, and 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.

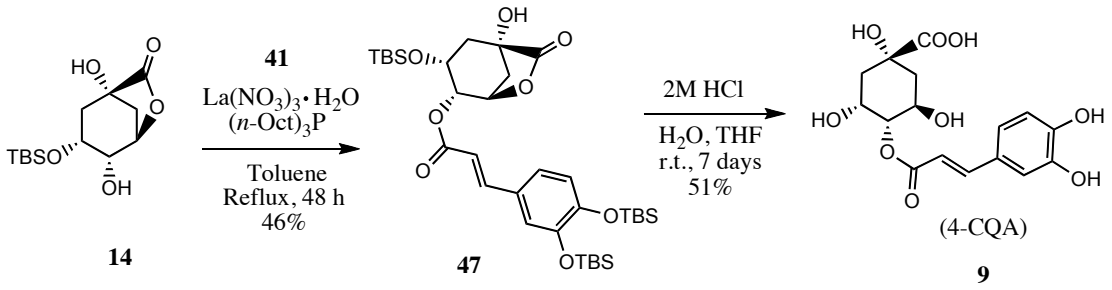


Figure 5.5 Synthesis route of making 4-CQA via intermediate ester **47**

Also the peak at 1463 cm^{-1} represented CH_2 scissoring for cyclohexane.[24] A typical broad peak at 3442 is assigned for OH absorption. All protons/signals attributed to compound **47** are clearly presented in the experimental section (Section 5.2.8). So do the 13 carbon NMR signals. The m/z found from HRMS analysis is consistent with calculation result. 4-CQA (**9**) was attained (51% yield) from purification over column chromatograph after which compound **47** was stirred with 2 M HCl for 7 days.

5.3.4 Synthesis of 3-CQA (11)

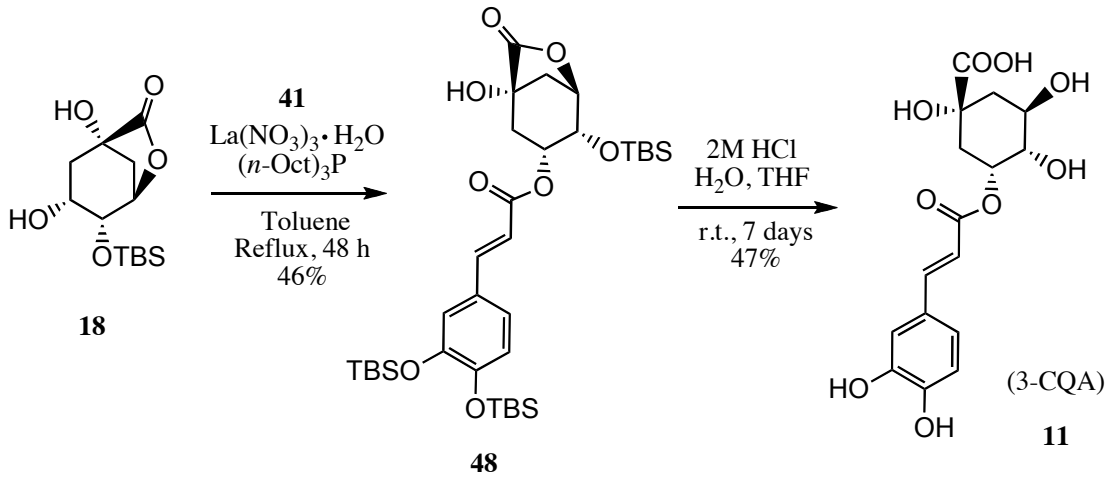


Figure 5.6 Synthesis route of making 3-CQA (**11**) via intermediate ester **48**

Employing an identical procedure to the synthesis of compound **47**, except using lactone **18** instead of **14**, the desired product **48** (protected 3-CQA) was achieved in 43% yield. Spectrophotometry data analysis supported the formation of **48**. 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.[24] Also the peak at 1463 cm^{-1} representing CH_2 scissoring for cyclohexane was also found as well as a broad peak at 3441 for OH absorption was found. All protons/signals attributed to compound **48** are clearly presented in the experimental section (section 5.2.11). The m/z found from HRMS analysis is consistent with calculation result. This ester was hydrolyzed with 2 M HCl for 7 days followed by purification over column chromatograph attaining the unprotected ester of compound **11** with 47% yield.

5.4 Conclusions

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 was developed. 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. Moreover, in the future, to make 5-CQA through transesterification reaction of vinyl caffeate with protected quinic acid is suggested to employ a protected quinic acid without having an ester in its structure to avoid an intramolecular transesterification.

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CHAPTER 6

General Conclusions

This study was presenting efficient synthesis of chlorogenic acid and its regioisomers. Basically, the process involved was an esterification reaction between quinic acids and caffeic acids. However, due to the presence of hydroxyl groups in both quinic acid and caffeic acid, the common direct esterification of the two reagents was less efficient. Under these circumstances, there are two approaches that have been conducted to improve the reactions' yields. First, hydroxyl groups on both quinic and cinnamic acids were protected when required. Next, two methods of esterification were employed, the first was an acylation of protected quinic acids and the second was a transesterification of vinyl esters with protected quinic acids. These processes were described in details in Chapter 2, chapter 3, chapter 4, and chapter 5.

In chapter 2, hydroxyl groups of quinic acid were successfully regioselectively protected. To provide a suitable reagent for synthesizing 1-CQA, protection of quinic acid was performed using 2,2-dimethoxy propane resulting in a desired compound, **12**, while the starting material for synthesizing 5-CQA (chlorogenic acid), suitable protected quinic acid was achieved by treating compound **12** with sodium methoxide to afford the desired compound **16**. Moreover, protection of quinic acids to provide the starting materials for 4- and 3-CQA were performed in a similar fashion using *tert*-butyldimethylchlorosilane, achieving compound **14** for making 4-CQA and **18** for 3-CQA.

In Chapter 3, a series of CQAs has been synthesized via esterification of diacetylcaffeoyl chloride with protected QAs. With this method, not only mono-CQAs were achieved as main products, but some byproducts of diesters were also detected. This chapter is especially providing a new approach of 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.

In Chapter 4, palladium(II) acetate showed a mutual combination with additives, such as H_2SO_4 and KOH to catalyze the reactions of transvinylation replacing the function of highly health-risk of mercury(II) catalysts. The use of Pd(II) acetate was proceeding very well with very good performances to mostly all the hydrocinnamic acid derivatives used in the experiments. So, the reaction employing Pd(II) acetate is a newly safety and efficient method capable of replacing Hg(II) catalyst in transvinylation reactions.

In Chapter 5, a new method for efficient synthesis of CQAs is described. Transesterification reactions of TBS-protected vinyl caffeate with regioselectively protected quinic acids, performed in the presence of lanthanum(III) acetate as catalyst combined with $(n\text{-Oct})_3P$ as additive proceeded quite well to give the desired CQAs.

Acknowledgment

The present work was carried out under supervision of Associate Professor Mitsunori Honda as the principal supervisor and Professor Ko-Ki Kunimoto as co-Supervisor, to whom I am sincerely grateful for their encouraging guidance, constructive advice and patiently help when needed throughout the study.

I would also like to thank to Professor Masahito Segi, Professor Yutaka Ukaji, and Professor Hajime Maeda for being constructive examiners by asking some fundamental questions and giving suggestions to improve the quality of this dissertation. Furthermore, I would like to thank all my lab members, especially to Akira Usami, Tomoya Koyama and Takuma Matsui. Even though, language sometimes was a big barrier to communicate among us, heart and mind connections surpassed all the hindrances. Your help when asked for made this work progress smoothly.

Next, I would like to express my gratitude to the Department of Research and Higher Education of the Republic of Indonesia providing financial support during my precious time in Kanazawa.

Last but not least, I would like to thank my parents and family who always being supportive during my study. Special thank to my wife Wa Ode Fitriati because of this work you have become a single fighter of taking care of our children and also thank to all my children Wa Ode Fathimah Nurul Haq, Novella Permata Adelaide and La Ode Titan Dafit Alkautsar for being the catalyst to complete this study.