Efficient synthesis of chlorogenic acid and its regioisomers

Abstract

Efficient synthesis of chlorogenic acid and its regioisomers

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Summary

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 $La(NO_3)_3.H_2O$ 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.

1. Background and Research Overview

Chlorogenic acid, as an individual compound, also known as 5-caffeoylquinic acid (5-CQA) probably the most widespread of all monoesters formed between caffeic and quinic acids and considered to be a storage form of cinnamic acid derivatives. As a group, chlorogenic acids (CQAs) are referred to a related family of esters of hydroxycinnamic acids, which are one of the most abundant 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. Originally, these compounds occur naturally that have important roles to protect plants against pathogenic diseases and to protect them from intensive radiation exposure. Owing to their essential protective biological functions, these substances are widely distributed, almost in all plants including food groups, fruits, fruit juices, grains, vegetables and legumes. Coffee products and apple are among those sources constituting high percentage of CQAs.

Regarding their antioxidant and other biological effects, convenient methods of CQAs have been explored for practical synthesis. As a result, numerous scientific papers have been published on the chemical and enzymatic synthetic methods. Among these methods, Sefkow 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 of Sefkow's method is really hard to trace.

This study was conducted to investigate new efficient methods for synthesis of chlorogenic acid and its regioisomers of caffeoylquinic acids (CQAs). Structures of chlorogenic acid and its regioisomers are depicted in Figure 1.1. Basically processes involved were reactions between regioselectively protected quinic acids with phenolic hydroxyl protected as well as carbonyl activated caffeic acid derivatives. The esterification reactions of the protected quinic acids were performed in the basis of two approaches; first, condensation reactions using diacetylcaffeoyl chloride and second, transesterification reactions using TBS-protected vinyl caffeate. And the schematic pathway of the synthesis of chlorogenic acid **1** and its regioisomers **2**, **3**, and **4** is shown in Figure 1.2.

2. Protection of Quininic Acid and Caffeic Acid

Since quinic acid **6** possesses four hydroxyl groups, Figure 2.1, a non-protected quinic acid if reacted with caffeic acid **5** will lead to the formation of regioisomer mixtures. Therefore regioselective protection of the hydroxyl groups of quinic acid was necessary to yield chlorogenic acid and its regioisomers. And the subject for selective protections was selected based on which site of hydroxyl group intended to react with caffeic acid to result in particular caffeoylquinic acids. Schematic protection of hydroxyl groups of quinic acid is shown in Figure 2.2.

To provide suitable reagent for the synthesis of 1-caffeoylquinic acid (1-CQA), protection of quinic acid **6** was performed in refluxed ethyl acetate using 2,2-dimethoxypropane in the presence of *p*-TsOH resulting in 3,4,5-protected lactone **7**.

This resulted compound was then treated with $NaOCH_3$ in methanol to give 3,4-protected quinic acid **8** for the synthesis of 5-CQA (chlorogenic acid). Moreover, protections of quinic acid for the starting materials of 4- and 3-CQAs syntheses were performed similarly using TBS-protecting group with temperature alterations. Commencing with the conversion of quinic acid to lactone **9** by refluxing it in a mixture of toluene and DMF with *p*-TsOH, then the resulted lactone was treated with TBSCl at low temperature to afford 3,5-protected quinic acid **10** for synthesis of 4-CQA and at higher temperature to achieve 4,5-protected quinic acid **11** for preparation of 3-CQA.

Caffeic acid **5**, Figure 2.1, possesses phenolic hydroxyl groups and a carboxyl group. The presence of phenolic hydroxyl groups tends to inhibit the esterification reaction. Then protection of the phenolic hydroxyl groups and activation of the carbonyl group are necessary. Protection of phenolic hydroxyl group was conducted by reacting caffeic acid with acetic anhydride in the presence of DMAP as catalyst to afford diacetylcaffeic acid **12** and activation of the carbonyl group of this protected caffeic acid was performed by treating it with oxalyl chloride to afford a diacetylcaffeoyl chloride **13**, as shown in Figure 2.3.

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

The reactions of diacetylcaffeoyl chloride with regioselectively protected quinic acids in the presence of DMAP afforded the protected esters of chlorogenic acid and its isomers. Cleavage of all protecting groups using low concentration of HCl gave the corresponding chlorogenic acid and its regioisomers. Reactions of diacetylcaffeoyl chloride with regioselectively protected quinic acids are shown in Figure 3.1.

As can be seen from Figure 3.1, the processes to synthesize CQAs were identical. For example, in Figure 3.1 (a), lactone **7** was reacted with diacetylcaffeoylquinic acid in the presence of DMAP as catalyst to afford an intermediate ester **14** in good yield. After treating **14** with low concentration of HCl, 1-CQA was afforded. Other regioisomers were afforded by following the same procedure, as it is shown in Figure 3.1 (b), (c) and (d).

4. Synthesis of Vinyl Esters

Besides diacetylcaffeoyl chloride, vinyl caffeate was another caffeic acid derivative that has been applied in this investigation. Apart from its function as the activating agent of the carbonyl group of caffeic acid, this substance is much more stable compound than its corresponding acid chloride. The syntheses of vinyl esters, such as vinyl caffeate and vinyl coumarate, were found in literatures. However, the methods applied were merely relying on mercury catalysts and it is widely known that mercury compounds in any oxidation state are high risk to environments and human health. For this reason, we used Pd(II) acetate as the catalyst in transvinylation reactions.

To examine the performance of Pd(II) acetate as a potential replacement for Hg(II) catalysts in transvinylation reactions of caffeic acid derivatives with vinyl acetate, cinnamic acid **18** was used as the model compound for this reaction, as shown in Figure 4.1. And in fact, reaction of cinnamic acid with vinyl acetate proceeded well to afford vinyl cinnamate **19** in the presence of Pd(II) acetate. Even better yields were achieved when some additives, such as H_2SO_4 and KOH added in the reaction. Based on the excellent result of cinnamic acid transvinylation, Pd(II) acetate as catalyst was then used to synthesize vinyl

esters of several caffeic acid derivatives. The results of transvinylation reactions are presented in Figure 4.2. The process of making vinyl ester for transesterification reactions in this work began with treating the caffeic acid with TBSCl in DMF in the presence of imidazole to afford TBS-protected caffeic acid **29**. Then this protected caffeic acid was reacted with vinyl acetate using Pd(II) acetate as catalyst instead of using conventional Hg(II) catalyst to obtain the TBS-protected vinyl caffeate **30**. Other transvinylation results, such as diacetyl-protected vinyl caffeate **33** and dibenzyl-protected vinyl caffeate **35** have also been obtained in good yields.

5. Synthesis of Caffeoylquinic Acids via Transesterification of Vinyl Caffeate

Transesterifications of the TBS-protected vinyl caffeate **30** with protected quinic acids in the presence of $La(NO_3)_3 \cdot H_2O$ as catalyst and $(n\text{-Oct})_3P$ as additive were performed at refluxed toluene for 48 h. The resulted protected esters were hydrolyzed using low concentration of HCl to yield the corresponding caffeoylquinic acids. The reactions were shown in Figure 5.1. The synthesis of 1-, 3-, and 4-CQAs proceeded well. However, the synthesis of 5-CQA employing the same protected quinic acid as for the condensation reaction in the subtitle 3, did not work. Instead of protected ester of 5-CQA, protected ester of 1-CQA **36** was obtained. This could happen because there was an intramolecular trasesterification occurred in compound **8** transforming to be **7** prior to reaction with **30**. And this is an interesting fact to take into account and therefore in future, to be able to afford 5-CQA using transesterification with vinyl ester, protected quinic acid possessing ester in its structure should be avoided to prevent the intramolecular transesterification.

6. Conclusion

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

Vinyl esters used in this study were synthesized using a transvinylation reaction of vinyl acetate with TBS-protected caffeic acid in the presence of Pd(II) acetate as catalyst. This catalyst showed great performances and it is a newly safer and efficient catalyst capable of replacing the common highly risk to environment and human health of Hg(II) catalysts. Further studies aimed at expanding the scope of these reactions to prepare the other bioactive CQA derivatives are in progress.

7. Figures

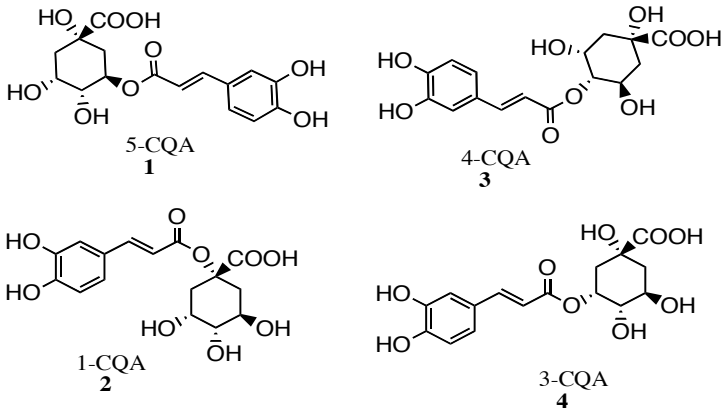


Figure 1.1 Chemical structure of chlorogenic acid (5-CQA: **1**) and its regioisomers **2 - 4**

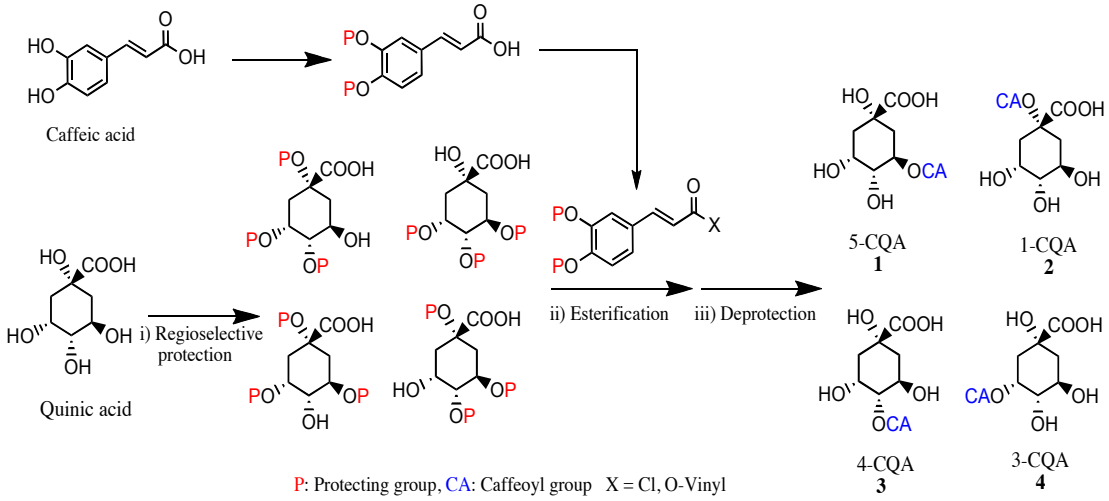
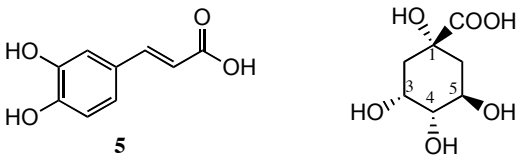


Figure 1.2 Synthetic pathway of chlorogenic acid and regioisomers



5 **6**

Figure 2.1 Chemical structure of caffeic acid **5** and quinic acid **6**

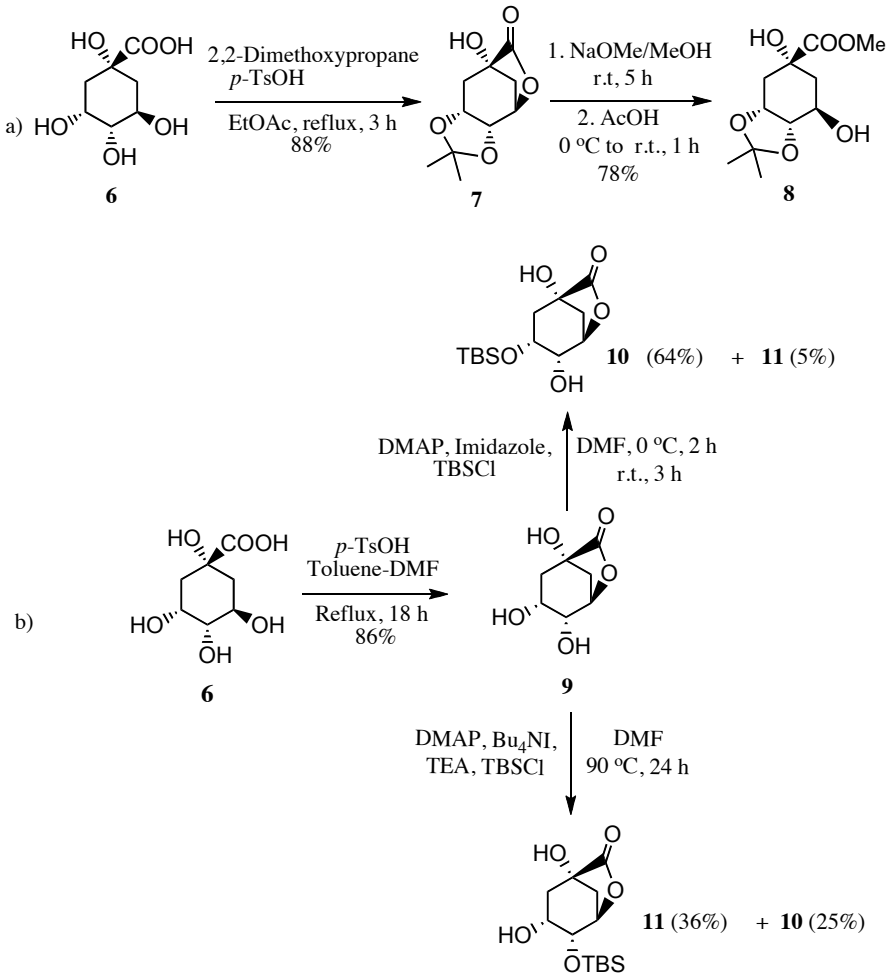
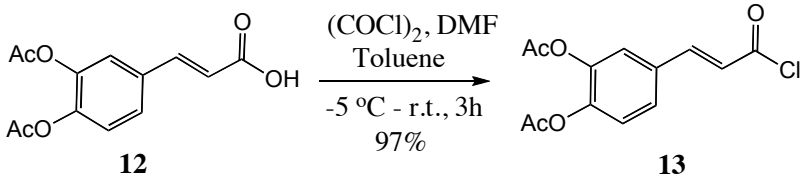


Figure 2.2 Protection of quinic acid for synthesis 1-CQA **7**, 5-CQA **8**, 4-CQA **10**, and 3-CQA **11**



12 **13**

Figure 2.3 Activation of carbonyl group of diacetylcaffeic acid **12** to produce acid chloride **13**

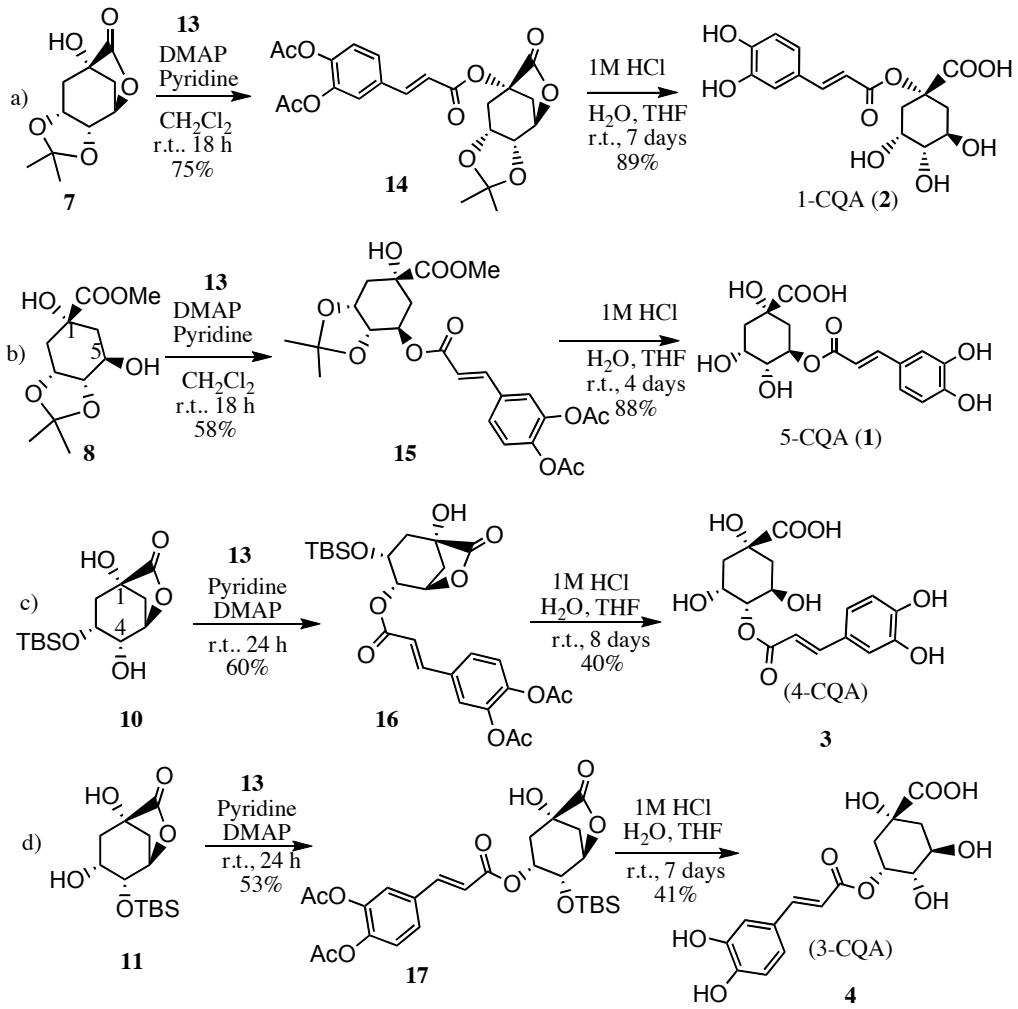
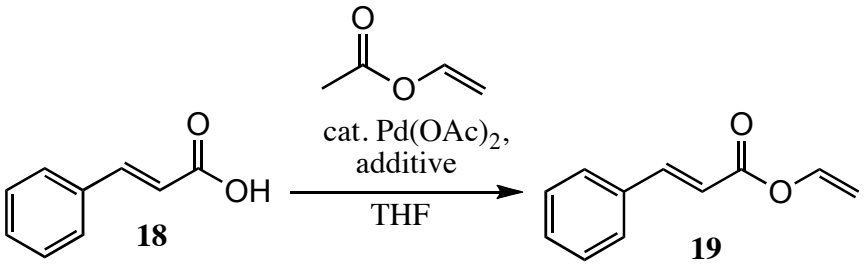


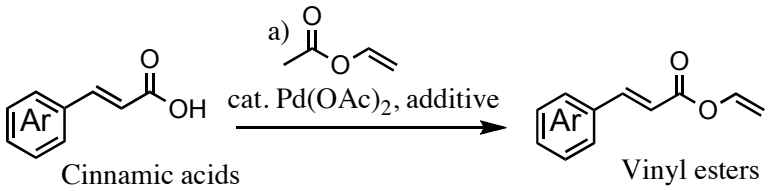
Figure 3.1 The schematic esterification of protected quinic acids with diacetylcaffeoyl chloride **13** to afford chlorogenic acid and regioisomers

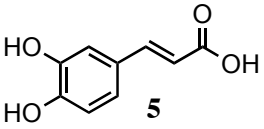
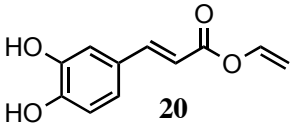
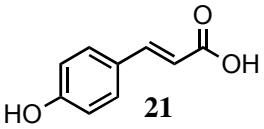
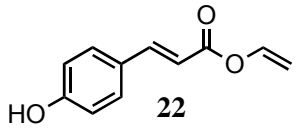
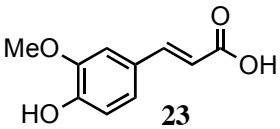
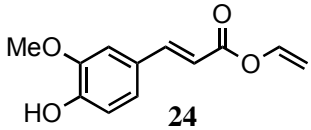
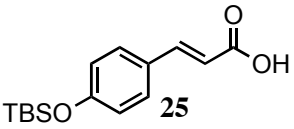
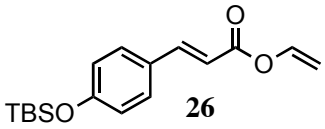
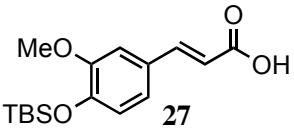
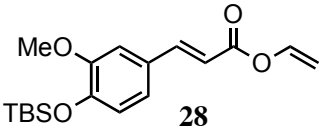
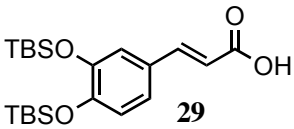
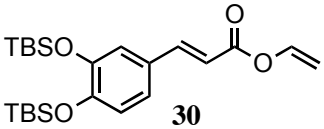
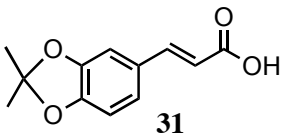
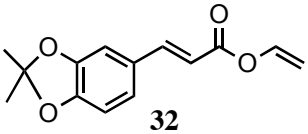
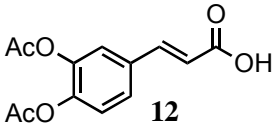
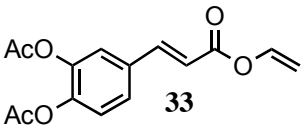
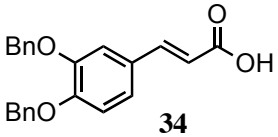
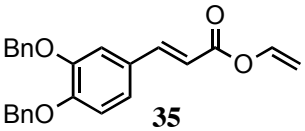


Entry	Additive	Yield[a] (%)
1	-	66
2	*p*-TsOH	67
3	$BF_3.OEt_2$	68
4	H_2SO_4	95[b]
5	Pyridine	No reaction
6	K_2CO_3	94
7	KOH	96[b]

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

Figure 4.1 Transvinylation of cinnamic acid in the presence of Pd(II) acetate catalyst and various additive



Entry	Cinnamic acids	Additive	Vinyl esters	Yield (%)
1	 **5**	H_2SO_4	 **20**	21
2	 **21**	H_2SO_4	 **22**	35
3	 **23**	H_2SO_4	 **24**	16
4	 **25**	KOH	 **26**	70
5	 **27**	KOH	 **28**	50
6	 **29**	KOH	 **30**	81
7	 **31**	KOH	 **32**	84
8	 **12**	H_2SO_4	 **33**	84
9	 **34**	KOH	 **35**	64

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

Figure 4.2 Transvinylation of protected caffeic acid derivatives

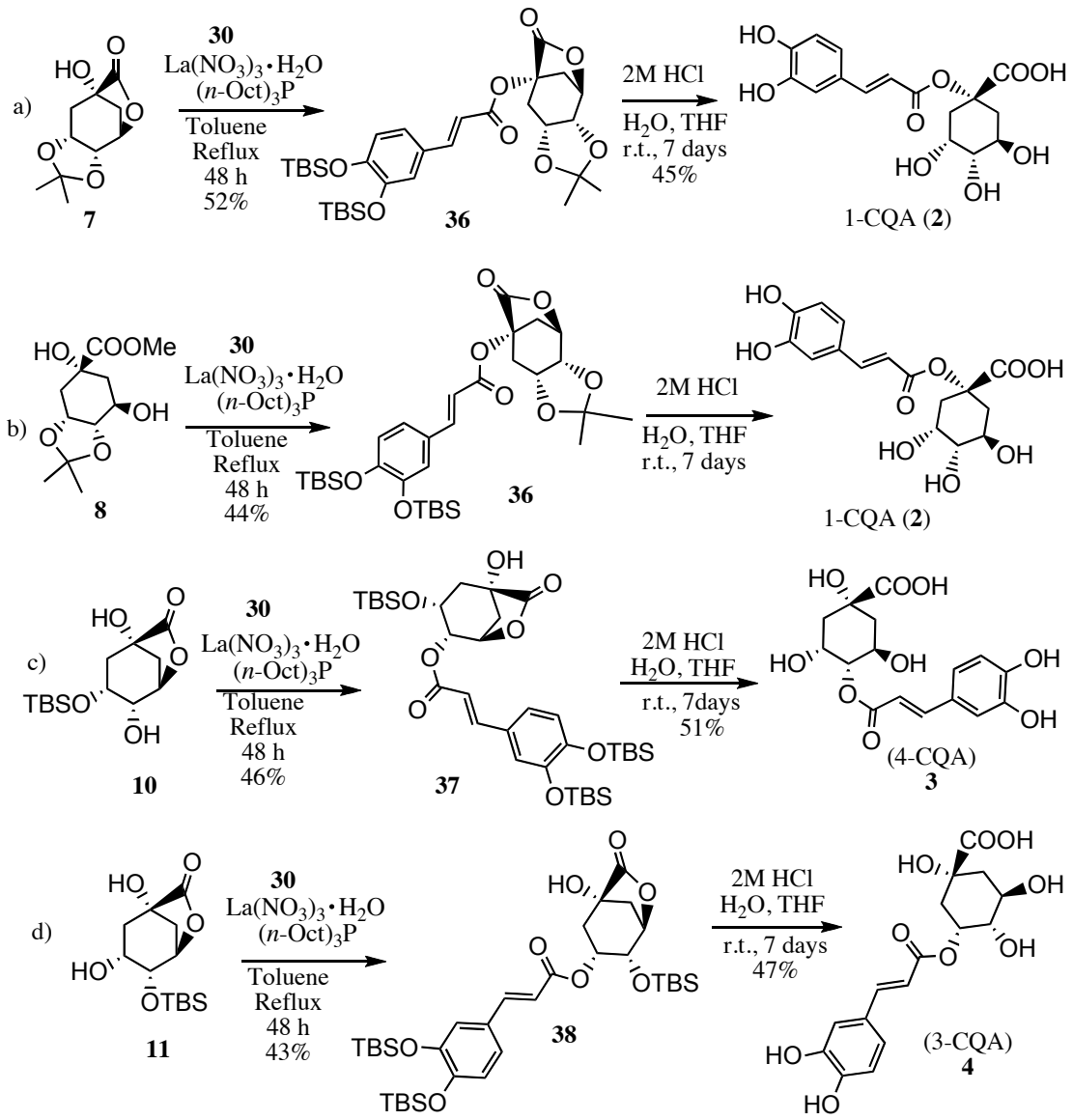


Figure 5.1 Transesterification of protected quinic acid with diTBS-protected vinyl caffeate to obtain regioisomers of chlorogenic acid

平成２８年　８月　４日

学位論文審査報告書（甲）

１．学位論文題目（外国語の場合は和訳を付けること。）

Efficient synthesis of chlorogenic acid and its regioisomers

クロロゲン酸およびその位置異性体の選択的合成法の開発に関する研究

２．論文提出者　(1) 所　　属　物質科学　専攻

(2) 氏（ふり）　名（がな）　La Ode Kadidae（らおでかでぃだえ）

３．審査結果の要旨（600～650 字）

提出された学位論文に対して，各審査委員が個別に予備審査を実施するとともに，平成 28 年 8 月 4 日に開催された口頭発表および質疑応答の結果を踏まえて，同日に論文審査委員会を開催して協議を行った。その結果，以下の様に判定した。

クロロゲン酸は，脂肪を消費しやすくするポリフェノールとして缶飲料に高濃度に含まれるなど近年注目を集める化学物質であるが，その位置異性体を含め簡便な合成法はあまり知られていない。本論文では，活性化したカフェ酸と位置選択的に水酸基を保護したキナ酸とのエステル化反応による，クロロゲン酸およびその位置異性体の効率良い合成法を明らかにしている。カフェ酸の活性化では，フェノール性水酸基を保護した後に酸塩化物またはビニルエステルへと変換しているが，ビニルエステル合成において Pd 触媒が効果的であることを見出し，Hg 触媒を用いる従来法に比べクリーンな合成法の開発に成功した。一方，キナ酸の 4 つの水酸基およびカルボキシル基を巧みに位置選択的に保護し，これら各種保護体とカフェ酸塩化物との反応によりクロロゲン酸類の選択的な生成に成功した。また，La 触媒存在下カフェ酸ビニルを用いたエステル交換反応によるクロロゲン酸類の新規合成法を確立した。以上，本研究の成果は，天然材料からの抽出が比較的困難なケイ皮酸誘導体の大量合成を可能にするだけでなく，その他の生理活性物質の合成にも応用可能で有機合成化学的に意義深い。よって本論文は博士(学術)の学位に値するものと判断した。

４．審査結果　(1) 判　　定（いずれかに○印）　(合　格)　・　不合格

(2) 授与学位　博　士（学　術）