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Synthèse de dérivés et analogues des acides dicinnamoyl quiniques nouvelle et évaluation de leur activité insecticide

Synthesis of new dicinnamoyl quinic acid derivatives and analogs and the evaluation of their potential as biopesticides

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Abbreviations

Ac	Acetyl
AChE	Acetylcholinesterase
AIBN	Azobisisobutyronitrile
ATP	Adenosine triphosphate
BBA	Butane 2,3-bisacetal
CAL-A	*Candida Antarctica* lipase A
CDI	1,1'-Carbonyldiimidazole
COSY	Correlation spectroscopy
CQA	Hydroxycinnamoylquinic acid
CSA	Camphorsulfonic acid
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDT	Dichlorodiphenyltrichloroethane

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DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dimethoxypropane
DMSO	Dimethyl sulfoxide
EPA	Environmental Protection Agency
FAO	Food and Agriculture Organization
HMBC	Heteronuclear multiple-bond correlation
HPLC	High Performance Liquid Chromatography
HSQC	Heteronuclear single-quantum correlation spectroscopy
IPM	Integrated pest management
LC_{50}	Lethal Concentration causing 50% death
LT50	Median Lethal Time
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
SEM	[(Trimethylsilyl)ethoxy]methyl
TBS	*Tert*-butyldimethylsilyl
TBAF	*Tetra-n*-butylammonium fluoride

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TBME	*Tert*-butylmethyl ether
TBDPS	*Tert*-butyldiphenylsilyl
TCDI	1,1'-Thiocarbonyl-diimidazole
TFA	Trifluoroacetic acid
TMAH	*Tetra*methylammonium hydroxide
TMB	*Tetra*methoxy butane
TMS	Trimethylsilyl
TMSOTf	Trimetylsilyl trifluoromethanesulfonate
TLC	Thin layer chromatography
p-TsOH	*p*-Toluenesulfonic acid

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Abstract

The use of conventional pesticides, especially the synthetic chemical pesticides, has greatly reduced the crop losses and gained a commercial success. However, the excessive use of pesticides lacking toxic specificity has caused a series of environmental and public health problems. The research interest toward new naturally-occurring biopesticides with novel modes of actions aims at a better balance between the efficiency of pesticide and reducing possible harms to environment and humans. Botanicals are an important source of biopesticides. Cinnamoyl quinic acids (CQA), isolated from various plants and shown to exhibit *in vivo* and *in vitro* a wide spectrum of biological activities, have attracted the attention with potential as biopesticides based on the patented toxicity of 3,5-di-*O*-caffeoylquinic acid against the larvae of *Myzus persicae*. The investigation of the insecticidal activity of CQA including their mode of action and the study of some structure-activity relationships could benefit from the synthesis of different CQA derivatives and analogs. A series of natural CQA derivatives natural 3,4- and 4,5-dicinnmamoylquinic acid derivatives but also analogs like 4-deoxy-3,5-dicinnamoylquinic acids were so synthesized. Seven targeted 4-deoxy CQA analogs were subjected to insecticidal assays, and two compounds were found to exhibit higher insecticidal activities than natural 3,5-dicaffeoylquinic acid. As perspectives to this work, confirming the activity of the synthesized compounds on other aphid species of agronomic importance could be performed. Furthermore, other collaborations could be established with biologists dedicated to measure other bioactivities of the synthesized compounds or use them as tools to investigate various biological pathways.

Key Words: Crop protection; Biopesticide; Cinnamoylquinic acid (CQA); 4-Deoxy CQA analogs; 3,4- and 4,5-DiCQA derivatives; Insecticidal assays.

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Résumé

L'utilisation de pesticides conventionnels, en particulier les pesticides chimiques de synthèse, a considérablement réduit les pertes de récoltes et a connu un succès commercial. Cependant, l'utilisation excessive de pesticides chimiques qui manquent de toxicité spécifique a provoqué une série de problèmes environnementaux et de santé publique. L'intérêt de la recherche vers de nouveaux biopesticides naturels avec de nouveaux modes d'actions vise à un meilleur équilibre entre l'efficacité des pesticides et la réduction des méfaits possibles pour l'environnement et les humains. Les plantes sont une source importante de biopesticides. Les acides chlorogéniques (CQA), isolés à partir de diverses plantes et présentent *in vivo* et *in vitro* un large spectre d'activités biologiques, ont attiré l'attention avec un potentiel comme biopesticides basé sur la toxicité brevetée de l'acide 3,5-di-*O*-caféoylquinique contre les larves de *Myzus persicae*. L'étude des propriété insecticides notamment la mode d'action et l'étude de certaines relations structure-activité pourrait bénéficier de la synthèse de différents dérivés et analogues de CQA. Des analogues des acides 4-désoxy-3,5-dicinnamoy quiniques et 3,4- et 4,5-dicinnamoylquiniques naturels ont été synthétisés. Sept analogues dans la série 4-désoxy ont été soumis à des essais insecticides et deux composés présentent une activité insecticide plus élevée que l'acide 3,5-dicaféoylquinique naturel. Comme perspectives à ce travail, confirmer l'activité des composés synthétisés sur d'autres espèces de pucerons d'importance agronomique pourrait être réalisé. De plus, d'autres collaborations avec des biologistes pourraient être établies afin d'évaluer d'autres activités des composés synthétisés ou les utiliser comme outils pour étudier des mécanismes de biosynthése.

Mots clés: Protection des cultures; Biopesticides; Acids chlorogéniques; Analogues 4-désoxy; Dérivés 3,4- et 4,5-diCQA; Essais insecticides.

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Chapter 1 State of the art

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1.1 Crop protection

1.1.1 A brief history

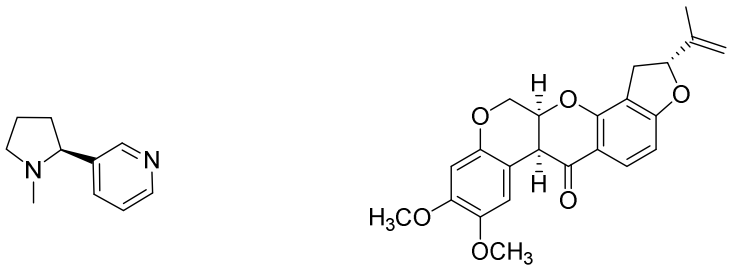
The global population is currently 7 billion people and is predicted to grow to over 9 billion by 2050.[1] And with the economic advances in developing countries, more high quality food, which means more consumption of meat and dairy food and increasing use of grains for livestock feed, are supposed to be present in their daily food consumption. Both these two facts exert great pressure to the crop production with limited suitable land and restricted water availability. Thus, a more sustainable crop production is urgently needed.

Productivity of crops has been threatened by the universal incidence of pests since the dawn of agriculture. In consequence, crop protection measures have been developed to prevent or reduce the crop losses caused by harmful organisms including weeds, insects and pathogens.

In the early times, manual work such as hand weeding and hand-picking of insect larvae were the only options for the pest control. Sumerians and Chinese firstly developed sulphur compounds as pesticides.[2] A survey of the Shengnong Ben Tsao Jing era (25–220 A.D.) showed that 267 plant species were known to have pesticidal activity.[3] Later on, the use of beneficial insects to control other insect pests was mentioned by Linnaeus as early as 1752.[4] Inorganic chemicals including copper, sulphur and organic mercury were also used to control plant diseases.[5] For example, Bordeaux mixture ("Bouillie bordelaise"), a mixture of copper sulfate ($CuSO_4$) and slaked lime ($Ca(OH)_2$), was invented in late 19th century to control powdery and downy mildew.

In the early 20th century, four kinds of natural compounds including nicotine and alkaloids, rotenone and rotenoids, *pyrethrum* and pyrethrins and vegetables oils were commonly used pesticides.[6] However, the use of these compounds was disadvantaged by their nonspecific toxicity (nicotine) or instability (*pyrethrum*).[6]

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Nicotine

1

Rotenone

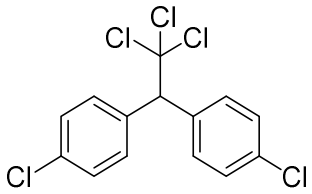
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Figure 1 Structures of nicotine and rotenone

A rapid emergence of pesticide exploitation started during the Second World War with the introduction of synthetic pesticides such as organochlorides, carbamates and organophosphates. These synthetic chemicals were effective, low-costly, easy to use and thus have gained a great popularity. In consequence, these discoveries gave rise to a new era of pest management for crop protection.

However, the wide use of these synthetic pesticides has caused a series of environmental and health problems which brought about the movements towards more environmentally friendly crop protection methods emerged in the 1960s. The story of DDT (dichlorodiphenyltrichloroethane) was a representative example for these changes. DDT's insecticidal action was discovered by the Swiss chemist Paul Hermann Müller in 1939. DDT was made available for use as an agricultural insecticide and its production and use duly increased. Müller was awarded the Nobel Prize in Physiology or Medicine “for his discovery of the high efficiency of DDT as a contact poison against several arthropods” in 1948. The great success of DDT in pest control stimulated the development of other synthetic pesticides. In 1962, Rachel Carson’s book “Silent Spring” was published, DDT was shown to cause cancer and threaten wildlife, particularly birds. Subsequently the manufacture and use of DDT were banned or severely restricted in many countries during the period 1970 to 2000.

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3

Figure 2 Structure of DDT

Since the environmental movements in the 1960s, researchers began to find alternative methods called integrated pest management (IPM).[7] According to the definition of FAO (Food and Agriculture Organization), IPM means "the careful consideration of all available pest control techniques and subsequent integration of appropriate measures that discourage the development of pest populations and keep pesticides and other interventions to levels that are economically justified and reduce or minimize risks to human health and the environment. IPM emphasizes the growth of a healthy crop with the least possible disruption to agro-ecosystems and encourages natural pest control mechanisms." IPM assumes that low levels of pests are tolerable and thus eradication is not necessarily a goal or even desirable in some cases because the elimination of a pest may also result in the loss of the beneficial predators or parasites that need the pest in order to survive. However, IPM has rarely been used as substitute to strategies using pesticides, and the latter were often the best choice to handle with pest outbreaks.[7]

The advent of new naturally-occuring biopesticides with novel modes of action offers the opportunity to protect crops with better selectivity towards the targeted pest and reduced impact on environment and public health. The development of these biopesticides has in many cases been inspired by the identification of the working mechanisms of natural pesticides. Based on a series of closely related compounds, the structure-activity relationships can be identified and then help the researchers to design new biopesticides betting for improved pesticide activity and reduced environmental risk.

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There exist also other techniques for pest control such as the use of genetic engineering[8,9] and sex pheromone attractants.[10] Our work, however, focuses on conventional pesticides and biopesticides.

For the perspectives, the trend toward reduced-risk biopesticides will likely continue and thus keep on reducing the load of xenobiotic chemicals in the environment. Practical levels of pest control could be maintained, or even increased, so that agriculture can meet its challenge of supplying enough food within existing limited resources of land, water, and other resources to a world population expected to exceed 9 billion by 2050.

The development, mode of action, pros and cons of common used pesticides will be discussed in next section.

1.1.2 Mainly used pesticides

Pesticides are defined as "chemical substances used to prevent, destroy, repel or mitigate any pest ranging from insects (i.e., insecticides), rodents (i.e., rodenticides) and weeds (herbicides) to microorganisms (i.e., algicides, fungicides or bactericides)".[11]

Pesticides may be classified in a number of ways by their chemical nature (inorganic and organic pesticides), their target pest species (fungicides, herbicides, insecticides, pesticides *et al*.) or by how they enter the target organism or where they act (contact toxicants, stomach toxicants, systemic toxicants *et al*.).[12] We have been interested in organic pesticides, the vast majority of which are synthetic pesticides, some of which are natural pesticides, and a few of which are synthetic natural-derived pesticides.[13]

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1.1.2.1 Synthetic pesticides

The use of synthetic pesticides became widespread after World War II. These pesticides were found to increase farm yield far beyond pre-World War II levels.[14] The main classes of synthetic pesticides consist of organochlorines, organophosphates and carbamates.

1.1.2.1.1 Organochlorines

Organochlorine pesticides are chlorinated hydrocarbons used extensively from the 1940s through the 1960s in agriculture and mosquito control. Representative compounds in this group include DDT, methoxychlor, lindane, dieldrin, toxaphene *et al*. Based on different sites of toxic action or mechanisms, organochlorine pesticides can be divided into DDT-like pesticides (e.g. DDT, methoxychlor in **Figure 3**) and chlorinated alicyclic pesticides (e.g. lindane, dieldrin and toxaphene in **Figure 3**).[15]

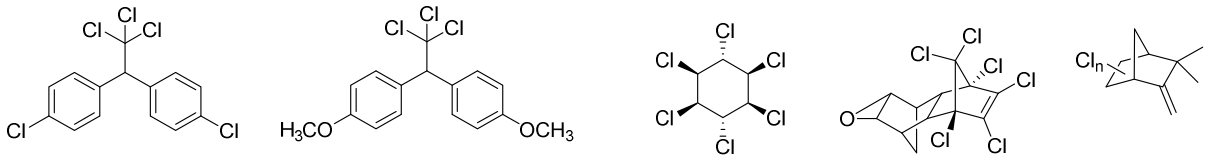


Figure 3 Representative compounds of organochlorine pesticides

The organochlorine pesticides attack the sensory organs of insects and their mechanisms differ slightly. For example, DDT exerts its toxic action by preventing the deactivation or closing of sodium gate of the axon after activation. The hyperexcitability of the nerve results in repetitive discharges in the neuron.[16] For chlorinated alicyclic

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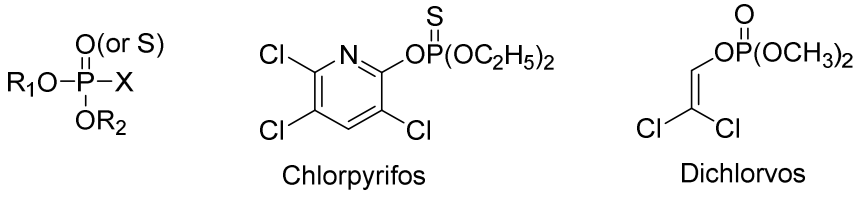
pesticides, the mechanism is the pesticide binding with γ-aminobutyric acid chloride ionophore complex, which inhibites chloride flow into the nerve and results in hyperexcitability.[17]

These organochlorine pesticides have a broad spectrum of pesticide activities, low acute toxicity to mammals and are inexpensive.[18] However, they are very resistant to degradation and, therefore, persist and accumulate in the environment.[15] Their nonspecific toxicity in the nervous system affects also animals and humans, and has caused a lot of environmental and health problems.[19, 20]

1.1.2.1.2 Organophosphates

Organophosphates are primarily triesters of phosphoric acid $P(O)(OH)_3$ and phosphorothioic acid $P(S)(OH)_3$. They are characterized by their ability or that of their metabolites to inhibit the enzyme acetylcholinesterase (AChE) that deactivates the neurotransmitter acetylcholine.[21] That's the main mechanism by which the organophosphorous pesticides exert their toxicity.[22]

The general structure of organophosphates can be illustrated in **Figure 4**, in which X is the "leaving group" that is displaced when organophosphates bind to AChE, R_1 and R_2 are alkyl, aryl, alkylthio or alkylamino groups.



Chlorpyrifos

Dichlorvos

8 **9** **10**

Figure 4 General structure of organophosphates and two examples

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Organophosphorus pesticides degrade rapidly by hydrolysis on exposure to sunlight, air, and soil. Therefore, their use does not cause the problems of bioaccumulation and food chain transfer. Their biodegradable property made them an attractive alternative to the persistent organochloride pesticides.[23] However, these organophosphorus pesticides generally lack selectivity and are toxic to nearly all animals including humans.[18, 24]

1.1.2.1.3 Carbamates

Carbamates are organic compounds derived from carbamic acid (NH_2COOH). The representative compounds in this group are aldicarb , carbofuran, carbaryl, fenobucarb and oxamyl *etc*.

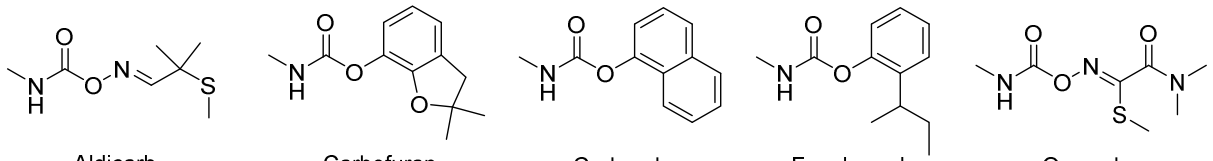


Figure 5 Representative compounds of carbamate pesticides

Carbamates are the third major group of synthetic pesticides developed after organochlorine and organophosphorus pesticides. These insecticides kill insects by a similar mechanism to that of organophosphate pesticides. But inactivating the enzyme acetylcholinesterase by carbamates is reversible and, therefore, carbamates are much safer than organophosphates.[18]

These carbamate pesticides are generally biodegradable and have lower environmental effect than organochlorine pesticides. Nevertheless, some carbamates

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(e.g., aldicarb, oxamyl) have caused severe poisoning in humans and domestic animals.[18]

In general, synthetic pesticides are quite controversial due to their combined characterizations of a wide spectrum of pesticide activities, low cost and their potential harmful effects to environment and public health, which were barely known before their use. As a contrast, many natural compounds have found a use in crop protection. The natural pesticides currently used will be discussed in the next section.

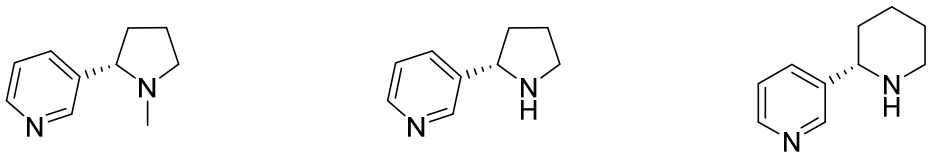
1.1.2.2 Natural pesticides

Although synthetic pesticides are favored by pesticide industry for having greatly reduced the cost and increased the efficiency of pest control, there is a growing requirement for "greener" pesticides. The use of natural pesticides often meets this need. There are a number of currently market available natural pesticides. The representative examples are nicotinoids, neem-based products, spinosads, rotenone and pyrethrum.

1.1.2.2.1 Nicotinoids

Nicotine is the main bioactive component of the tobacco plant *Nicotiana tabacum* and *Nicotiana rustica*.[25] Nicotine was used to control a wide range of pests including aphids, thrips and whitefly.[26] Other nicotinoids such as nornicotine and anabasine are also naturally occurring pesticides.[18]

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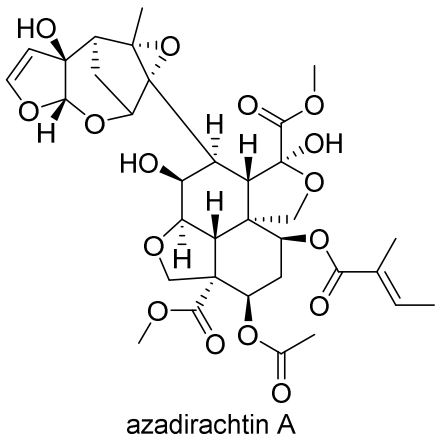
Nicotine **1** Nornicotine **16** Anabasine **17**

Figure 6 Structures of three nicotinoid pesticides

These nicotinoid pesticides affect the nervous system of insects by binding to the cholinergic acetylcholine nicotinic receptor and cause a sustaining firing of this neuroreceptor.[26,27] However, nicotine is very toxic to humans by inhalation and by skin contact and to birds, fish and other aquatic organisms.[26] The lethal oral dose for humans was stated to be 40–60 mg.[26]

1.1.2.2.2 Neem based products

The neem-based pesticides were extracted from the seeds of the Indian neem tree, *Azadirachta indica*. The major active constituent is azadirachtin A.[28]



azadirachtin A

18

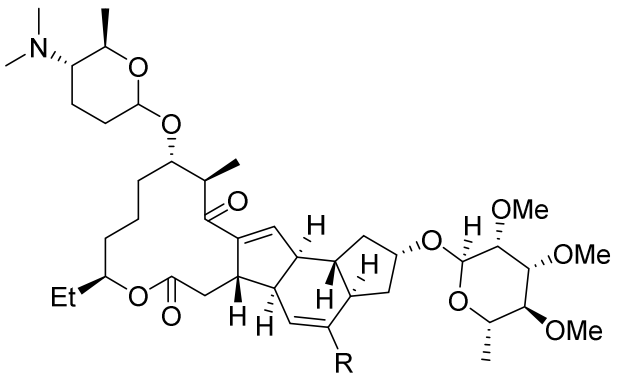
Figure 7 Structure of azadirachtin A

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Well known as a potent antifeedant to many insects, azadirachtin blocks the synthesis and release of molting hormones and leads to incomplete ecdysis in immature insects and sterility in adult female insects.[28] Azadirachtin-based products such as Agroneem® and Trilogy® are used to control a wide spectrum of insects and fungal infections.[13]

1.1.2.2.3 Spinosads

Spinosad was originally isolated from the fermentation of the soil Actinomycete, *Saccharopolyspora spinose*. The major active constituents are spinosyn A and D.[26]



19 spinosyn A, R = H **20** spinosyn D, R = Me

Figure 8 Structure of the major active constituent from soil actinomycete, *Saccharopolyspora spinose*

The mode of action of spinosad is the activation of nicotinic acetylcholine receptors leading to disruption of acetylcholine neurotransmission,[29] and secondary effects on γ-amino-butyric acid neurotransmission leading to hyperexcitation and disruption of the nervous system of insects.[29,30]

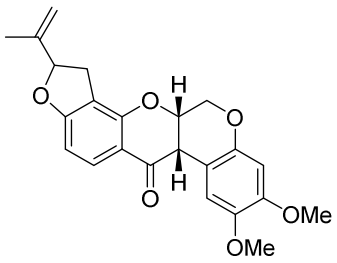
Spinosad has a very low mammalian toxicity and is non-toxic to birds but slightly to moderately toxic to fish.[26] For example, even the highest observed daily dosage for a

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spinosad-treated hamster was below the LC50 for rats (> 5000 mg/kg rat oral).[31] Besides, spinosad is degradable by photolysis on soil surface and by soil microorganisms below the soil surface.[26,32] Spinosad products are sold as concentrated aqueous formulations under several trade names[26,33] such as Conserve®, Entrust® and SpinTor® and are quickly becoming a main choice for not only conventional farmers but also organic farmers.[13]

1.1.2.2.4 Rotenone

Rotenone was mainly obtained from plant species *Derris*, *Lonchocarpus* and *Tephrosia*.



Rotenone
21

Figure 9 Structure of rotenone, a major constituent in rotenone pesticides

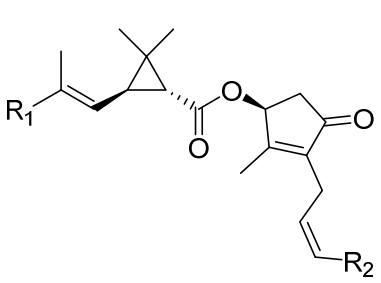
For the mode of action, rotenone works as an inhibitor of the electron-transport chain for respiration of insects and as a selective pesticide with contact and stomach action.[26,34]

Rotenone is used to control a wide spectrum of arthropod pests. However, rotenone is highly toxic to mammals (with the estimated lethal dose for humans being 300–500 mg kg^{-1}) and fish.[26]

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1.1.2.2.5 Pyrethrum

Pyrethrum refers to a mixture extracted from flowers of *Chrysanthemum cinerariaefolium* and *Cynomorium coccineum*. The mixture contains at least six pyrethrin esters.



22 Pyrethrin I R_1 = Me, R_2 = Et

23 Pyrethrin II R_1 = COOMe, R_2 = Et

24 Cinerin I R_1 = Me, R_2 = Me

25 Cinerin II R_1 = COOMe, R_2 = Me

26 Jasmolin I R_1 = Me, R_2 = Et

27 Jasmolin II R_1 = COOMe, R_2 = Et

Figure 10 Structures of six pyrethrin esters.

For the mode of action, pyrethrins have been shown to activate the voltage-sensitive sodium channels in insect nervous systems leading to death.[26]

Pyrethrins are especially valuable pesticides due to their rapid paralysis of flying insects and that their toxic action is inactivated on exposure to light.[18] They are recommended to control a wide range of insects and mites on fruit, vegetables and field crops.[26] Pyrethrins have moderate toxicity to mammals, low toxicity to birds but high toxicity to fish and honey bees.[26,35]

In general, the use of pesticides for crop protection has greatly helped to reduce the crop losses. However, the intensive use of pesticides, especially the synthetic pesticides, has also led to a lot of environmental and health problems. A number of pesticides such as DDT were withdrawn and banned in many countries.[36] Combined with the rapidly developed resistance and consumers' concern about the safety of pesticide residue in

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food, the need for alternative tactics aiming at more sustainable crop protection is increasingly urgent. The use of biopesticides will probably meet these requirements. In the next section, the focus of the discussion was on biopesticides.

1.1.3 The advent of biopesticides?

According to U.S. Environmental Protection Agency (EPA), biopesticides are defined as "certain types of pesticides derived from such natural materials as animals, plants, bacteria, and certain minerals".[37]

Biopesticides have been researched and promoted as new tools for crop protection for many years. The desirable qualities of biopesticides include a natural occurring origin, a target specificity, a reduced toxicity to nontarget organisms, a reduced persistence in the environment, a low mammalian toxicity.[38] These desirable qualities of biopesticides are also their advantages as an important competitor or replacer for conventional pesticides.

Despite the increasing interest in biopesticides for crop control, the market for biopesticide products still represents a small percentage (only 3% of the global annual market for pesticides in 2014).[38,39] Several reasons exist for the current low penetration of biopesticides into the pesticide market. Among these are factors such as low efficacy, narrow range of target species, inconsistent field performance, high cost, short self-life and difficulties in production.[39,40] These disadvantages are, however, offset by their distinct advantages compared with conventional chemical pesticides.[40] Another factor driving the research of biopesticides is their good suitability in integrated pest management (IPM) programs.[39]

Many commercialized biopesticides have good specificity and target a single major pest. Contans®, originating from fungus *Coniothyrium minitans*, attacks solely the

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pathogen genus *Sclerotinia spp*.[41] Bioshield™, based on the bacterium *Serratia entomophila*, targets only a single grass grub insect.[42] The narrow range of toxicity of highly-specific biopesticides makes it difficult for them to share a bigger percentage of the market.

A major group of commercially available biopesticide products are these derived from the bacterium *Bacillus thuringiensis* (Bt).[39,40] Their successful penetration into the market may attribute to the ability to kill a range of invertebrate pest species.[39] The mode of action for *Bacillus thuringiensis*-based pesticides is to produce a protein crystal (the Bt δ-endotoxin) during bacterial spore formation leading lysis of gut cells of insects. The produced δ-endotoxin is safe to vertebrates, humans, beneficial organisms and the environments.[43]

A narrow definition of biopesticide includes only these products originating from microorganisms.[39] The reason for that may be that a majority of the currently commercialized biopesticides are microorganism-based.[40] But in a broader definition of biopesticide, botanical compounds and semiochemicals (e.g. pheromones) should also be encompassed.[39] The commercialized neem-based products and pyrethrum mentioned above can be considered as biopesticides in the broader definition. But another botanical compound nicotine is not regarded as “bio” since it is as toxic and hazardous as many synthetic pesticides.[6]

The discoveries of botanical compounds used as pesticides rely on two parallel methods: (1) Isolation and identification of active molecules from the traditional used plants and extracts for crop protection. That is the case for nicotine extracted from tobacco.[25] (2) A wide screening of series of plants exhibiting better self-protecting resistance to some pest species followed by analysis of plant extracts and biological tests in order to discover the active molecules. The focus in this thesis concerns a series of botanical compounds belonging to the family of hydroxycinnamoylquinic acids (CQA). The discovery of pesticide activities of CQA falls in the second category.

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1.2 Hydroxycinnamoylquinic acids (CQA)

1.2.1 CQA and derivatives as new biopesticide?

Hydroxycinnamoylquinic acids (CQA) are series of compounds exhibiting various bioactivities such as antioxidant, antibacterial, anticancer, antiviral *etc*.[44,45,46,47] However, the pesticide activities of CQA have been rarely studied and with discordant results. Although some authors have established a correlation between di-*O*-caffeoylquinic acid (di-*O*-CaQA) from lettuce root and its resistance to an aphid (*Pemphigus bursarius*), they have never shown direct face-to-face biological activities as pesticides.[48]

A patent, co filled by a team from INSA-Lyon-BF2I and INRA-Avignon, has recently related a method to prepare 3,5-di-*O*-caffeoylquinic acid and other derivatives from non-tuberous roots, and its use for fighting against aphids.[49] A correlation was made between concentration in CQA and disease susceptibility or insect infestation susceptibility of peach trees (*Prunus persica*).

The peach tree, which adapts to the Mediterranean climate, is mainly cultivated in China, North America (California), South America (Chili and Argentina) and in Europe (Spain, Italy, France and Greece). It represents an undeniable economic interest for the meridional regions. However, the peach tree is the target of numerous animal or microbes derived pest attacks. A particularly preoccupant attack is that of the green aphid, *Myzus persicae*. This biting and sucking insect is particularly harmful, not only by direct damage it causes but also because it is a potential vector of *Plum Pox Virus*, the causative agent of Sharka disease that causes deformations and discolorations of fruits, making them unmarketable. The infected trees must be cut down with no curative control available.

So it is necessary to find new treatments to fight effectively but respectful way of the environment against aphids, including green peach aphid (*Myzus persicae*).

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Reduced levels of infection to some green peach aphids, *Myzus persicae*, appeared in plants showing higher concentrations of CQA. Some plant species thus seem to develop resistance mechanisms and an insecticide activity was detected for some CQA isomers.[49]

The mechanism of toxicity against *Myzus persicae* is however still to be discovered and the enzymes involved in this biosynthetic pathway are very interesting targets for new non-toxic insecticides as the shikimic pathway is absent in mammals.[49] In addition, the migration of caffeoyl group between vicinal hydroxyl groups was observed during test or even natural conditions leading from a pure isomeric product to a mixture of isomers (**Figure 11**). This phenomenon makes it difficult to achieve unambiguous conclusions about the activities of each isomer.

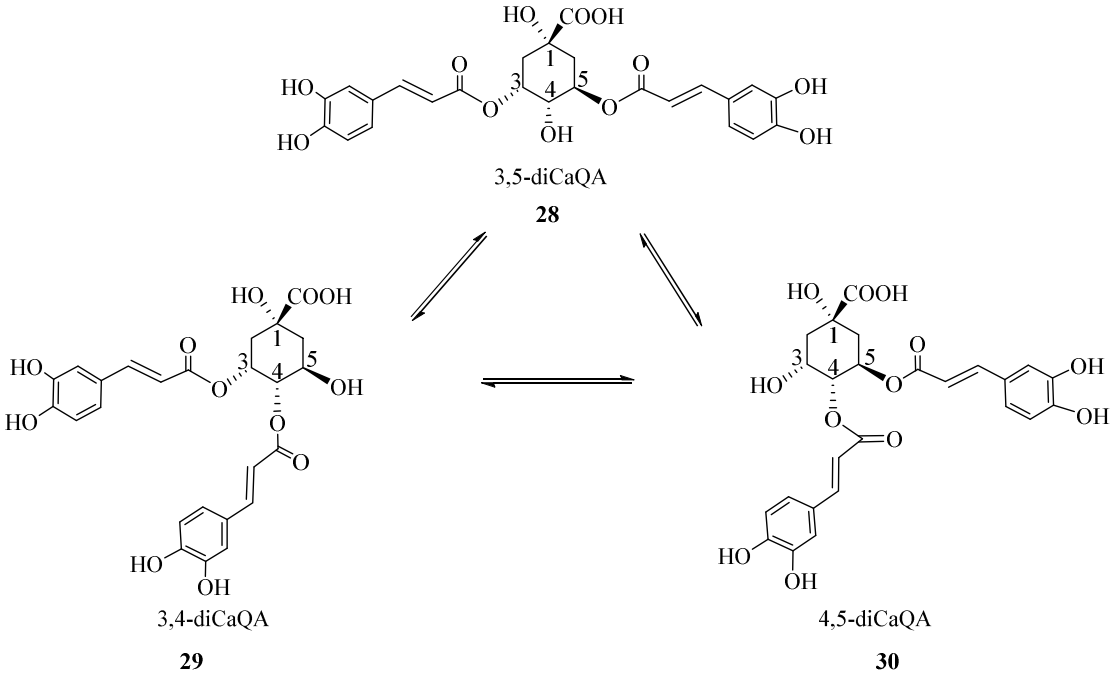


Figure 11 The migration of caffeoyl group at vicinal hydroxyl groups

A better understanding of the metabolism of di-*O*-caffeoylquinic acids will need some standard samples as tools to further investigate their action on aphids. This is the

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purpose of this thesis through a synthetic chemistry program designed to prepare various CQA derivatives and analogs and test their pesticide activities under the collaboration with the biologists from INSA-Lyon-BF2I (Biologie Fonctionnelle Insectes et Interaction). In the section below, the literatures on CQA including its classification, biological activities, synthetic methodologies and the stabilities of CQA molecules are reviewed.

1.2.2 Definition and classification

Hydroxycinnamoylquinic acids (CQA) (**Figure 12**) are constituted by a quinic acid core and different hydroxycinnamic acids groups.

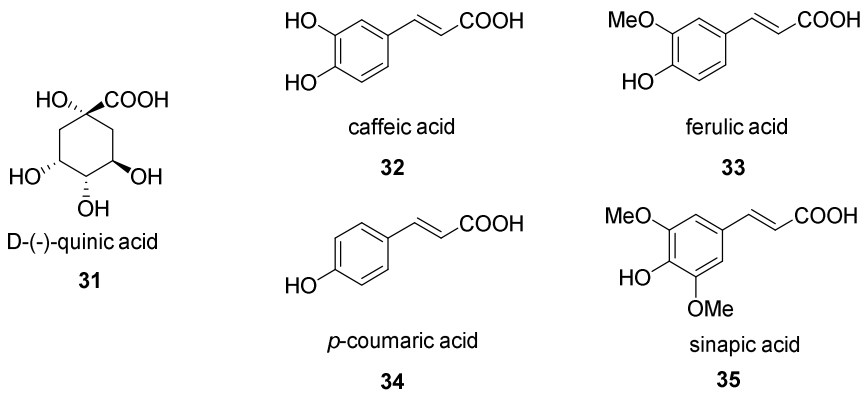


Figure 12 Structures of D-(-)-quinic acid and examples of hydroxycinnamic acids

It should be carefully noted that there exist different numbering systems of the quinic acid ring.[50] Using the preferred IUPAC recommended numbering[51] as illustrated in **Figure 13**, the commonest individual CQA is 5-*O*-caffeoylquinic acid (5-*O*-CaQA). It is still often called chlorogenic acid[52,53] or 3-*O*-caffeoylquinic acid[53] (preIUPAC numbering), but the use of both terms should be discouraged. In some reports,[54,55,56]

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chlorogenic acids refer to a series of compounds which in this thesis are called hydroxycinnamoylquinic acids (CQA).



Figure 13 IUPAC and preIUPAC numbering systems for CQA taking 5-*O*-caffeoylquinic acid as an example on its main conformation

More than 70 different species of CQA have now been identified from different sources.[57] These classic CQA may be subdivided by the identity, number and position of the acyl residues. The following subgroups are known:

(1) the relatively widespread mono-esters of caffeic acid (caffeoylquinic acids (CaQA)), *p*-coumaric acid (*p*-coumaroylquinic acids (*p*CoQA)) and ferulic acid (feruloylquinic acids (FQA)). Presentative examples are given below in **Figure 14**.

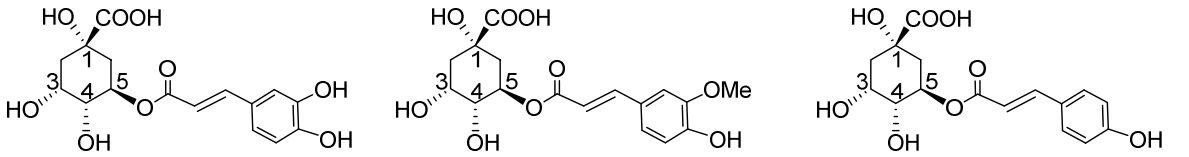
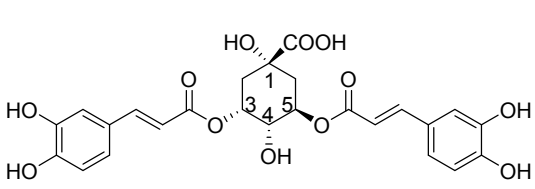


Figure 14 Three 5-*O*-hydroxycinnamoylquinic acids

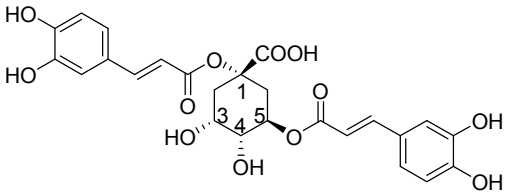
(2) homodiesters (di-*O*-CQA), homotriesters (tri-*O*-CQA) and the single tetra-ester of caffeic acid (tetra-*O*-CaQA).[58,59]

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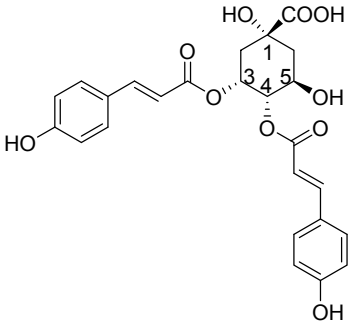
3,5-di-*O*-caffeoylquinic acid (3,5-di-*O*-CaQA)

28



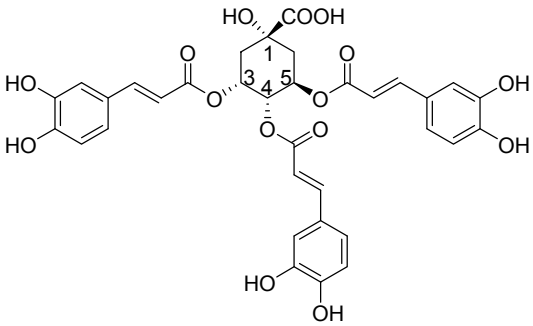
1,5-di-*O*-caffeoylquinic acid (1,5-di-*O*-CaQA)

39



3,4-di-*O*-*p*-coumaroylquinic acid (3,4-di-*O*-*p*CoQA)

40

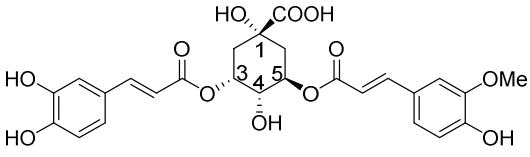


3,4,5-tri-*O*-caffeoylquinic acid (3,4,5-tri-*O*-CaQA)

41

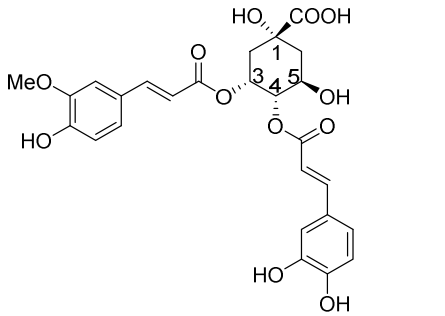
Figure 15 CQA homodiesters and homotriesters

(3) heterodiesters[60,61] and heterotriesters.[62]



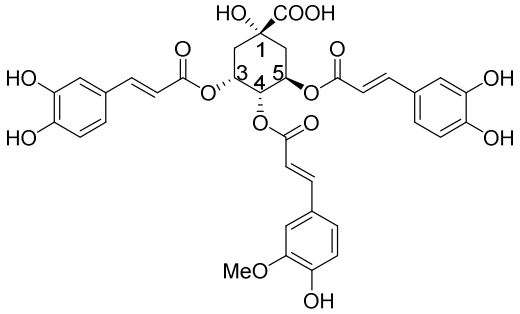
3-*O*-caffeoyl-5-*O*-feruloylquinic acid (3-*O*-Ca-5-*O*-FQA)

42



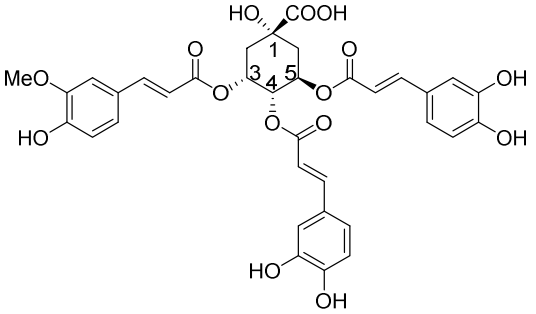
3-*O*-feruloyl-4-*O*-caffeoylquinic acid (3-*O*-F-4-*O*-CaQA)

43



3,5-*O*-dicaffeoyl-4-*O*-feruloylquinic acid (3,5-*O*-diCa-4-*O*-FQA)

44



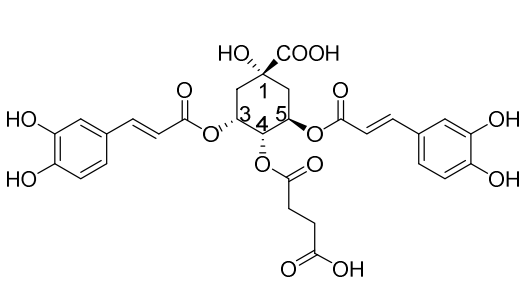
3-*O*-feruloyl-4,5-*O*-dicaffeoylquinic acid (3-*O*-F-4,5-*O*-diCaQA)

45

Figure 16 CQA heterodiesters and heterotriesters

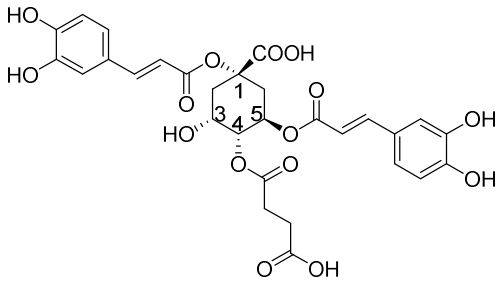
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(4) derivatives involving various permutations of residue of caffeic acid with residue of aliphatic acid[63,64] or aliphatic chain.[65]



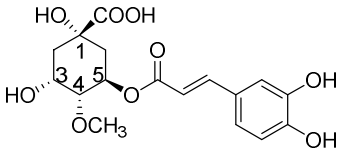
3,5-*O*-dicaffeoyl-4-*O*-succinylquinic acid (3,5-*O*-diCa-4-*O*-SuQA)

46



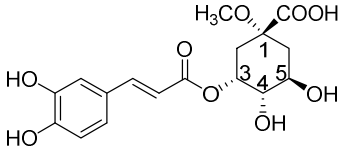
1,5-*O*-dicaffeoyl-4-*O*-succinylquinic acid (1,5-*O*-diCa-4-*O*-SuQA)

47



4-*O*-methyl-5-*O*-caffeoylquinic acid (4-*O*-Me-5-*O*-CaQA)

48



1-*O*-methyl-3-*O*-caffeoylquinic acid (1-*O*-Me-3-*O*-CaQA)

49

Figure 17 CQA derivatives bearing non-cinnamoyl substitutes

1.2.3 Isolation and diverse biological activities

CQA have been isolated in various plants such as coffee species, various fruits and vegetables, oilseeds such as soya bean and sunflower and also from medicinal plants.[66,67,68,69,70]

The reported methods for isolation, purification, identification and characterization of CQA include nuclear magnetic resonance spectroscopy,[71] infrared spectrometry,[72] liquid chromatography,[73,74] gas chromatography,[75] and chemiluminescence.[76]

A series of *Coffea* genetic resources have been reported to contain CQA at significant levels.[77] It has been suggested that CQA consumed by regular coffee drinkers have correlation with some therapeutic effects such as lower risks of symptomatic gallstone disease and liver cirrhosis.[78,79]

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Fruits and vegetables are another source, in which CQA are the most important and predominant phenolic molecules. Möller and Herrmann studied the CQA content in stone and pome fruits.[70] In fresh plum, three monocaffeoylesters 3-*O*-caffeoylquinic acid (3-*O*-CaQA), 4-*O*-caffeoylquinic acid (4-*O*-CaQA), and 5-*O*-caffeoylquinic acid (5-*O*-CaQA) were identified. In cherries, 3-*O*-caffeoylquinic acid (3-*O*-CaQA) and 3-*O*-*p*-coumaroylquinic acid (3-*O*-*p*CoQA) were identified as the major constituents of CQA, 5-*O*-caffeoylquinic acid (5-*O*-CaQA) and 4-*O*-caffeoylquinic acid (4-*O*-CaQA) were also found in minor quantities. In addition, 3-*O*-caffeoylquinic acid (3-*O*-CaQA) and 5-*O*-caffeoylquinic acid (5-*O*-CaQA) were predominant in apricots and peaches. Apples and pears contained 5-*O*-caffeoylquinic acid (5-*O*-CaQA) in a predominant quantity.

Besides, three CQA derivatives including 3-*O*-(3'-methylcaffeoyl) quinic acid, 4-methoxy-5-*O*-caffeoylquinic acid, 1-methoxy-3-*O*-caffeoylquinic acid have been isolated from the leaves of bamboo *Phyllostachys edulis*.[68] A total number of nine CQA were identified and quantified from fourteen medicinal plants by Marques.[80]

CQA and derivatives isolated from natural sources were investigated in a very large number of publications with respect to a variety of biological activities (see **Figure 18**).

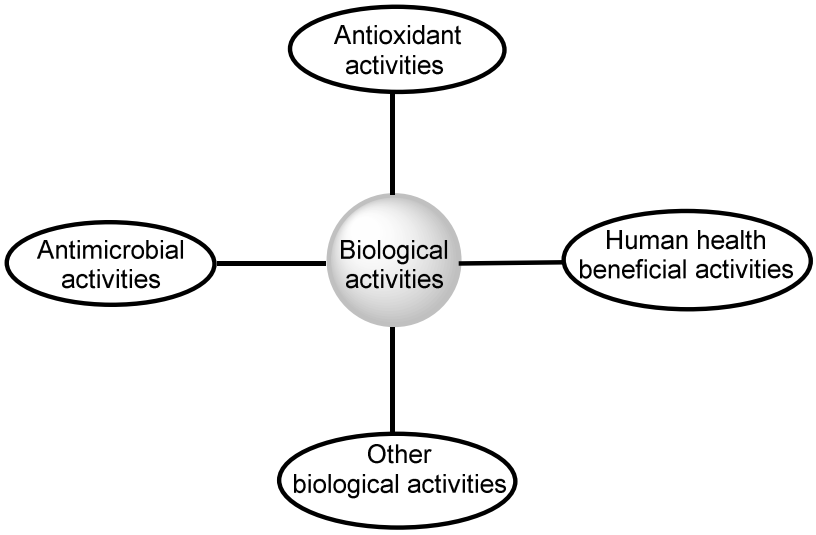


Figure 18 Scope of biological activities of CQA

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From the best of our knowledge, the biological activities of CQA can be divided into 3 categories: (1) antioxidant activities,[44,81] (2) inhibition of human chronic diseases or other health beneficial activities,[82,83,84] and (3) antimicrobial activities including antifungal, antibacterial, and antiviral.[45,46,47] Other biological effects of CQA such as the effect of on the sleep–wakefulness cycle in rats were also investigated.[85]

The antioxidant activities of CQA arise from the hydroxycinnamic acid moiety resulting from their ability of inhibiting the formation of reactive radical species or scavenging them. Hydroxycinnamates readily form a resonance-stabilized phenoxy radical, which account for their antioxidant activities, due to both the phenolic moiety and extended unsaturated side-chain conjugation.

In an environment with reactive radicals, the contact of radicals with phenol readily results in the abstract of a hydrogen atom from the phenol to form a phenoxy radical. This radical is highly stabilized due to the formation of different resonance forms in which the unpaired electron may be present not only on the oxygen but also through the entire molecule. The unsaturated side chain provides additional resonance stability. Different resonance forms are illustrated below in **Figure 19** taking ferulic acid as an example.

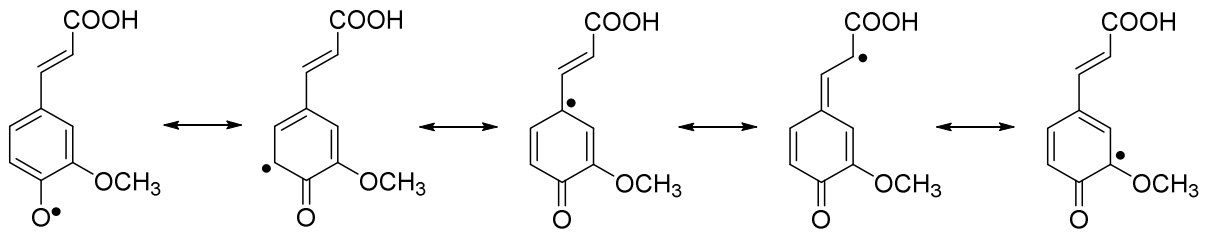


Figure 19 Resonance stabilization of ferulic acid radical

As a consequence of the resonance stabilization, the phenoxy radical generates easily and lacks reactivity to initiate or propagate a radical chain reaction. Therefore, a

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collision and condensation of the phenoxy radical with another radical is its most probable fate.[44]

The presence of a second phenolic hydroxyl group, e.g. in caffeic acid, enhances the radical-scavenging ability. In caffeic acid, the donation of a hydrogen atom from the phenolic hydroxyl group generates a stable phenoxy radical which can readily give out another hydrogen atom resulting in the formation of quinone. The formed quinone provides additional stability.

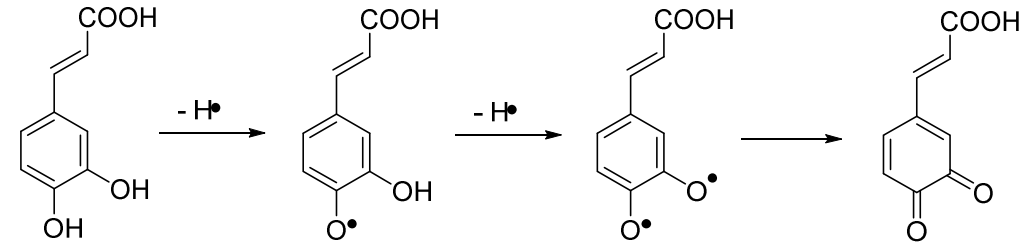


Figure 20 Formation of quinone from caffeic acid

Ferulic acid can be considered as the derivative of *p*-coumaric acid by methoxylation at a *ortho* position of the phenolic hydroxyl group. The methoxylation destabilizes the phenoxy radical to some extent, and slightly impairs the antioxidant potential of ferulic acid.

Both the enhancing effect of a second phenolic hydroxyl group in caffeic acid and impairing effect of a methoxyl group in ferulic acid on the stability of phenoxy radicals account for that the order of antioxidant activities of these three hydroxycinnamic acids is caffeic acid > *p*-coumaric acid > ferulic acid. This order was observed in Guptas' study of the role of phenolics as antioxidant for the clarified butter Ghee.[81]

Due to the antioxidant activities of CQA, their uses are suggested in pharmaceuticals, foodstuffs, feed additives, and cosmetics. CQA such as 5-*O*-

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caffeoylquinic acid is marketed under the trade name Svetol® in Norway and the United Kingdom as a food active ingredient used in coffee, chewing gum, and mints.

Furthermore, CQA may play a beneficial role in the prevention of certain oxidative diseases.[86,87,88,89,90] In particular, 5-*O*-caffeoylquinic acid has been reported to exert inhibitory effects on carcinogenesis in the large intestine, liver, tongue, and a protective action on oxidative stress *in vivo*. Other research has examined the protective effects of 5-*O*-caffeoylquinic acid against oxidative damage.[91] In addition, 5-*O*-caffeoylquinic acid and caffeic acid are antioxidants *in vitro* and might therefore contribute to the prevention of cardiovascular disease[92] and type 2 diabetes mellitus.[93]

Additional non-antioxidant mechanisms have also been suggested for their role in inhibition of chronic diseases.[82,83,84] For example, evidence from *in vitro* and *in vivo* studies suggests that the prevention of β-amyloid fibril deposition by ferulic acid may be independent of its antioxidant activities.[94,95] Furthermore, anti-hypertensive effects of dietary ferulic acid may be mediated through significant decreases in angiotensin-1-converting enzyme activities in stroke-prone spontaneously hypertensive rats.[96,97,98] In addition, ferulic acid prevents the production of thromboxane A2 and stimulates the production of NO in animal models.[99,100,101] 5-*O*-Caffeoylquinic acid and 5-*O*-*p*-coumaroylquinic acid significantly inhibit intestinal absorption of glucose and increases gut hormone GLP-1[102,103] suggesting a potential preventative role against type 2 diabetes.[82,104] 5-*O*-Caffeoylquininic acid exerts anti-inflammatory effects through lipopolysaccharide-induced cyclooxygenase-2 expression,[105] and was also observed to have beneficial effects on cardiovascular diseases via suppressing P-selectin expression on platelets.[106]

CQA were also claimed to have antimicrobial activities including antifungal,[45,107] antibacterial,[46,108] and antiviral[47,109] effects with relatively low toxicity and side effects.

From the aforementioned isolation and biological activities of CQA, most of these research concerns monohydroxycinnamoylquinic acid (monoCQA). Other diesters

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(homo and hetero), triesters and tetraesters were also isolated but poorly further studied no matter their biological activities or synthesis.

As a contrast to the reported various biological activities, however, the pesticide activities of CQA have been rarely studied. The aforementioned patent[49] related 3,5-di-*O*-Caffeoylquinic acid and other derivatives with disease susceptibility or insect infestation susceptibility of peach trees (*Prunus persica*). Further pesticide activity research needs the synthesis of CQA derivatives and analogs. In the next section, a summary of existing methods and procedures for the synthesis of CQA derivatives and analogs will be discussed.

1.2.4 Synthesis of CQA derivatives and analogs

The retrosynthetic analysis of CQA mainly relies on the coupling of a quinic acid core and different hydroxycinnamic acid moieties. The quinic acid part, bearing four hydroxyl groups and one carboxylic group, needs a tedious protection and deprotection process before being used in a specific reaction at desired positions. The chemical insights in D-(-)-quinic acid would deepen our understanding of these kinds of compounds and give us the information needed for the modification of the quinic acid core during our synthesis for CQA derivative and analog targets.

D-(-)-Quinic acid ((1*R*,3*R*,4*R*,5*R*)-1,3,4,5-tetrahydroxycyclohexane-l-carboxylic acid) occurs widely in both plants and microorganisms.[110] Being easily isolated in a state of very high enantiomeric purity from natural sources through simple processes, it is commercially available (cas number 77-95-2). In fact, chemists have long been aware of the potential advantages of using natural chiral building blocks as starting materials in organic chemical synthesis. The application of D-(-)-quinic acid as a chiral template in natural product synthesis have been rapidly growing.

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Barco *et al.*[110] and Mulzer *et al.*[111] have discussed the use of D-(-)-quinic acid as a chiral scaffold in the synthesis of natural products. D-(-)-Quinic acid itself and its transformations (quinide, quinide ketals and acetals) provided a series of synthetic routes to introduce new stereogenic centers in more complex structures and culminated in the synthesis of different classes of natural products.

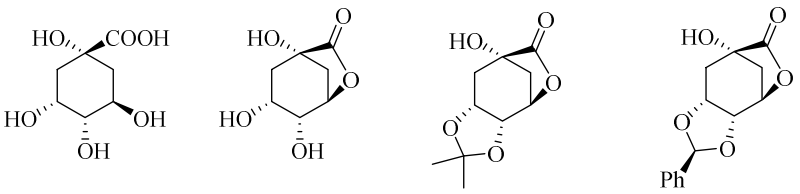


Figure 21 Structures of D-(-)-quinic acid and different quinide, ketals or acetals

Based on the two reported reviews[110,111] about the use of D-(-)-quinic acid as the starting material in synthesis, the possible transformations from D-(-)-quinic acid are summarized in **Figure 22**.

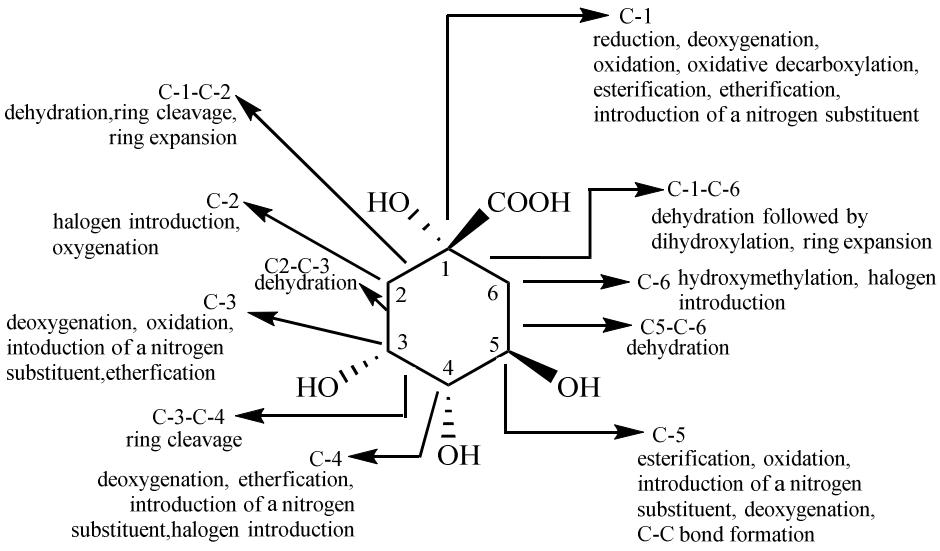


Figure 22 A summary of possible modifications in D-(-)-quinic acid molecule

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From **Figure 22**, the wide utility of D-(-)-quinic acid in synthesis is self-evident due to the presence of possible reaction centers throughout the whole molecule. On the other hand, that increases spontaneously the difficulties of using D-(-)-quinic acid for a specific reaction, in which a complex protection and deprotection process is generally required. The difficulties also reside in the chemical synthesis for our targeted CQA derivatives and analogs.

The reports concerning the synthesis of CQA derivatives and analogs are rather limited compared to the great number of publications of their various biological activities. To the best of our knowledge of the literatures concerned with the synthesis of CQA derivatives and analogs, the reported synthesis procedures used mainly 3 kinds of methodologies: (1) esterification of properly-protected quinic acid unit with suitable protected hydroxycinnamic acid moiety followed by deprotection reactions; (2) enzymatic esterification reactions; (3) a process by first transferring the quinic acid core into malonic esters and later formation of the cinnamoyl moiety with Knoevenagel condensation.

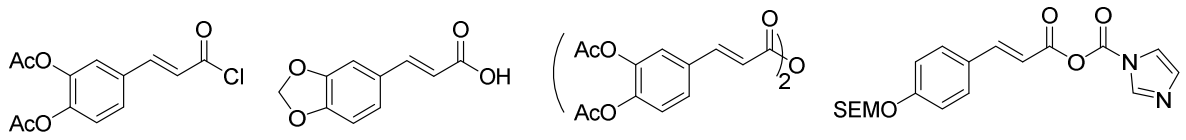
1.2.4.1 Esterification of a quinic acid moiety with a hydroxycinnamic acid moiety

The most commonly used coupling method is the esterification of an appropriately-protected quinic acid moiety with an appropriately-protected hydroxycinnamic acid moiety, the latter is normally activated as acid chloride, anhydride or imidazolide or is used directly as carboxylic acid.

The protected acid chloride is the most widely used one for the coupling reactions with the quinic acid moiety, and in most cases, the phenols were protected as acetate.[52,53,112,113] Other protected hydroxycinnamoyl chlorides will also be illustrated later in the following review of synthetic methodologies for CQA derivatives and

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analogs. In addition, the protected carboxylic acids,[114] the protected anhydrides[115] and the protected imidazolide[116] played also the role of a cinnamoyl-group-donor.



54 55 56 57

Figure 23 Examples of protected hydroxycinnamic acid unit for coupling

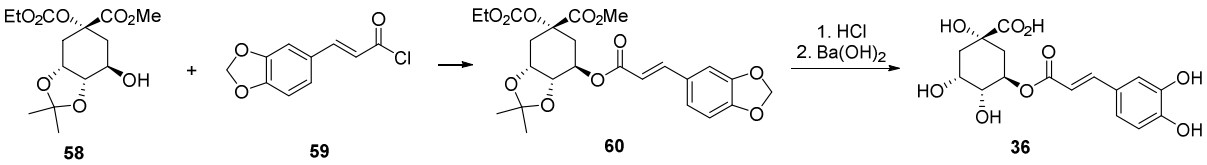
The key coupling reactions were accomplished under different conditions providing esters, and, after deprotection, the final CQA were obtained. More details are given in the next section firstly about the synthesis of monohydroxycinnamoylquinic acids (monoCQA) then about the synthesis of dihydroxycinnamoylquinic acids (diCQA) and the trihydroxycinnamoylquinic acids (triCQA) and other derivatives.

1.2.4.1.1 Synthesis of monoCQA and derivatives

The synthesis of different 1-*O*-, 3-*O*-, 4-*O*- and 5-*O*-monoCQA and derivatives were reported. Among them, 5-*O*-monoCQA, as the most abundant CQA in natural sources, was the most studied.

As early as in 1955, Panizzi *et al.*[117] reported the synthesis of 5-*O*-caffeoylquinic acid **36** (named chlorogenic acid in the literature) in a route shown in **Scheme 1**. A key intermediate **58** was made from quinic acid in 4 steps, then the target 5-*O*-caffeoylquinic acid was obtained by esterification of the unsubstituted hydroxyl group at position 5 with 3,4-oxomethylenedioxycinnamoyl chloride **59** providing ester **60**, followed by removal of the isopropylidene group in acid and hydrolysis of the carbonate, ethoxycarbonyl, and methyl ester groups with barium hydroxide.

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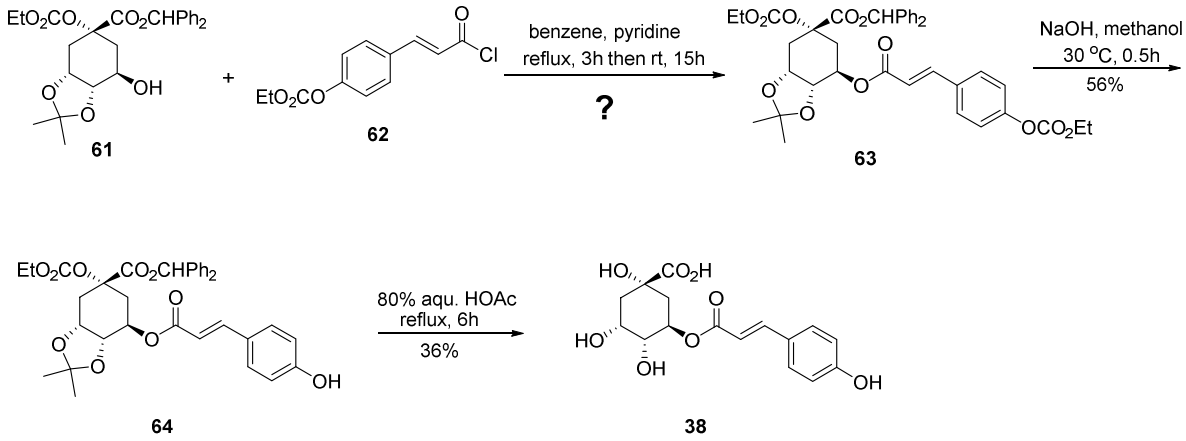


Scheme 1 Synthesis of 5-*O*-caffeoylquinic acid

It is the first report about the synthesis of 5-*O*-caffeoylquinic acid. However, no detailed protocols or yields were given. In 2001, Sefkow cited this literature[52] commenting that the overall yield in seven steps from quinic acid was low (<5%). This method required several protecting steps and a sequential hydrolysis of protecting groups first in acidic condition then in basic condition. Basic hydrolysis in the last step should be avoided since hydroxycinnamoylquinic acids are sensitive to oxidation in basic conditions. The final basic hydrolysis may impair to some extent the final product and contribute to the low yield.

In 1961, E. Haslam *et al.*[118] reported the synthesis of 5-*O*-*p*-coumaroylquinic acid (named 3-*O*-*p*-coumaroylquinic acid in the literature using the preIUPAC numbering system) **38** (**Scheme 2**) in modifying Panizzi's method. It was sought in particular to protect the carboxylic group of quinic acid with diphenylmethyl group which can be removed in acidic conditions. 5-*O*-*p*-Coumaroylquinic acid was prepared by esterification of the unsubstituted hydroxyl group at position 5 in the ester **61** with 4-*O*-ethoxycinnamoyl chloride **62** providing ester **63** (There exist data errors in the literature, based on which the yield of ester **63** from ester **61** was calculated as 139%) followed by removal of the phenolic ethoxy group by hydrolysis with NaOH solution in methanol giving **64** and the protecting groups for carboxylic acid, 1-hydroxyl and isopropylidene group in 80% aqueous acetic acid solution.

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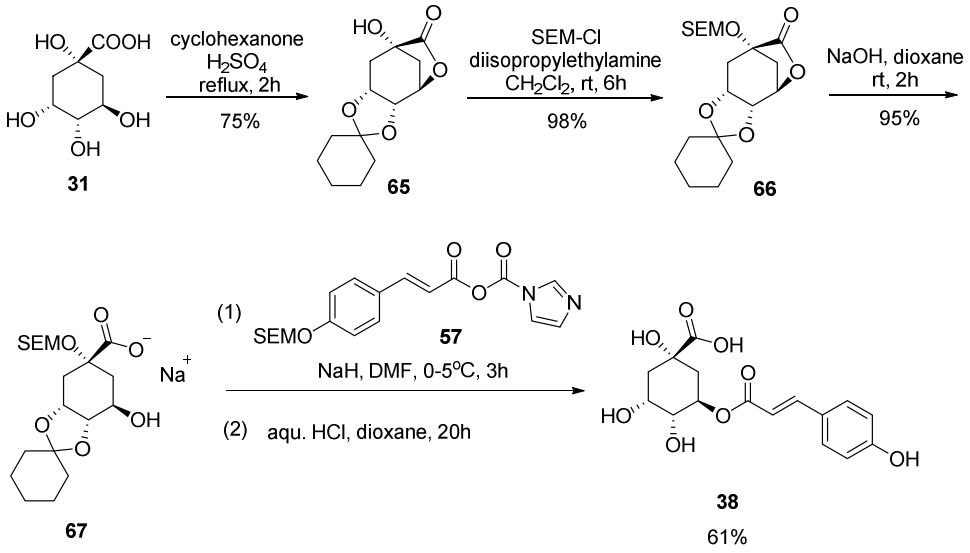


Scheme 2 Synthesis of 5-*O*-*p*-coumaroylquinic acid

In this procedure, a protecting process and a two-step deprotection manipulation were still needed. Although the deprotection process was modified to avoid the possible losses of the final product as in Panizzi's procedure using basic hydrolysis in the final step (**Scheme 1**), the yield for the two-step deprotection process was only 20%. No overall yield can be calculated since that the yield of ester **61** from quinic acid was not given and due to the presence of data errors.

In 1997, the synthesis of a series of CQA derivatives including 5-*O*-*p*-coumaroylquinic acid **38** was reported by Hemmerle *et al.*[116] From quinic acid, 3,4-*O*-cyclohexylidene lactone **65** was synthesized in refluxing cyclohexanone with H_2SO_4. After protection of the hydroxyl group of **65** at position 1 with [(trimethylsilyl)ethoxy]methyl chloride (SEM-Cl) and hydrolysis of lactone moiety with NaOH, a key intermediate sodium salt **67** was obtained. The coupling of sodium salt **67** with imidazolide **57** followed by an acidic hydrolysis of all protecting groups gave the final product 5-*O*-*p*-coumaroylquinic acid **38** (61% two-step yield).

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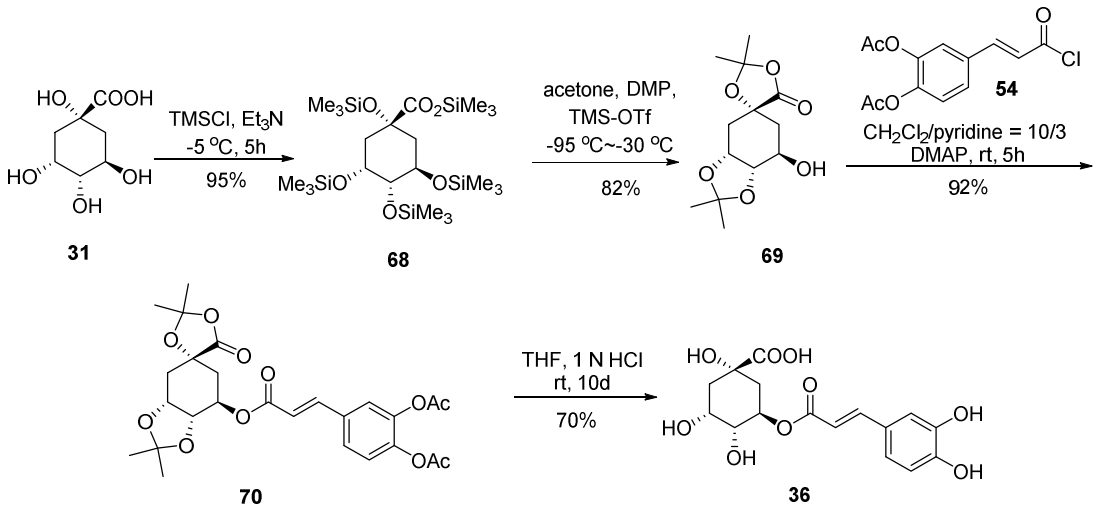
Scheme 3 Synthesis of 5-*O*-*p*-coumaroylquinic acid

The synthesis was fulfilled in 5 steps from quinic acid and the overall yield was 42%. Using the key intermediate sodium salt, the carboxylic acid was regenerated after the coupling reaction by acidification to pH 4 with 1N potassium hydrogen sulfate aqueous solution. That avoids the protection of carboxylic group before the coupling reaction.

In 2001, Sefkow's group also reported the synthesis of monohydroxycinnamoylquinic acids (monoCQA).[52,53] Firstly, an efficient synthesis of 5-*O*-caffeoylquinic acid **36** (referred under the preIUPAC numbering as 3-*O*-caffeoylquinic acid in the literature) was reported.[52] First, silylation of quinic acid with trimethylsilyl chloride (TMSCl) afforded the pentasilyl derivative **68** in 95% yield. After an optimization of both the kinetic acetalization conditions and the workup procedure, the best yield (82%) for bisacetonide **69** was obtained by treatment of silyl ether **68** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) at -95 °C for 2 hours then -30 °C for 24 hours. Esterification of **69** with 1.5 equivalents of caffeoyl chloride **54**, which was obtained by acylation of caffeic acid with Ac_2O in pyridine and chlorination with 2

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equivalents of oxalyl chloride, was realized in a solvent system CH_2Cl_2/pyridine with the catalysis of DMAP, giving the ester **70** in 92% yield. Cleavage of all protecting groups was achieved with 1N aqueous HCl containing 15% THF after 10 days at room temperature and the 5-*O*-caffeoylquinic acid **36** was isolated in 70% yield.



Scheme 4 Synthesis of 5-*O*-caffeoylquinic acid

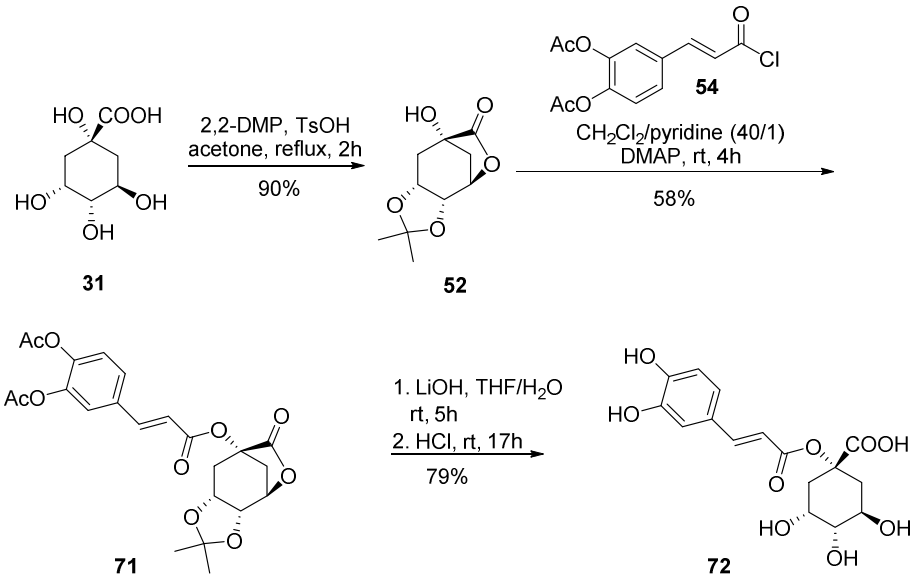
Thus, 5-*O*-caffeoylquinic acid **36** was synthesized in only 4 steps from quinic acid **31** with an overall yield of 51%. The preparation of the intermediate **69** by a kinetic acetalization protocol in 78% yield from quinic acid was the key step for the improvement in overall yield. However, an ultralow temperature was needed for the synthesis of the intermediate **69**. The deprotection step under acidic conditions needed a quite long reaction time (10 days).

Sefkow *et al*. also reported the synthesis of 3 other monocaffeoylquinic acids including 1-*O*-caffeoylquinic acid **72** (**Scheme 5**), 4-*O*-caffeoylquinic acid **75** (**Scheme 6**), and 3-*O*-caffeoylquinic acid **79** (**Scheme 7**).[53]

Obtained from quinic acid **31**, the intermediate quinide **52** with unprotected hydroxyl group at position 1 was prepared, then the esterification was conducted with

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acid chloride **54** in the CH_2Cl_2/pyridine/DMAP system but with a different volume ratio of CH_2Cl_2/pyridine (40/1), providing the ester **71** in 58% yield. Hydrolysis of the protecting groups was accomplished in a two-step sequence. All labile esters were cleaved using LiOH in a degassed H_2O/THF solution under an inert gas, and removal of the acetal group was then achieved after acidification of the reaction mixture with 2 M HCl, 1-*O*-caffeoylquinic acid **72** was obtained in 79% yield (41% from quinic acid **31**, **Scheme 5**). The yield of 1-*O*-caffeoylquinic acid **72** was less than 20% when the hydrolysis was performed entirely under acidic conditions (1 M HCl). What is worthy of being mentioned is that the solution turned deep brown after addition of the base LiOH if the solution H_2O/THF was not carefully degassed, indicating that the liberated catechol had been oxidized to some extent.

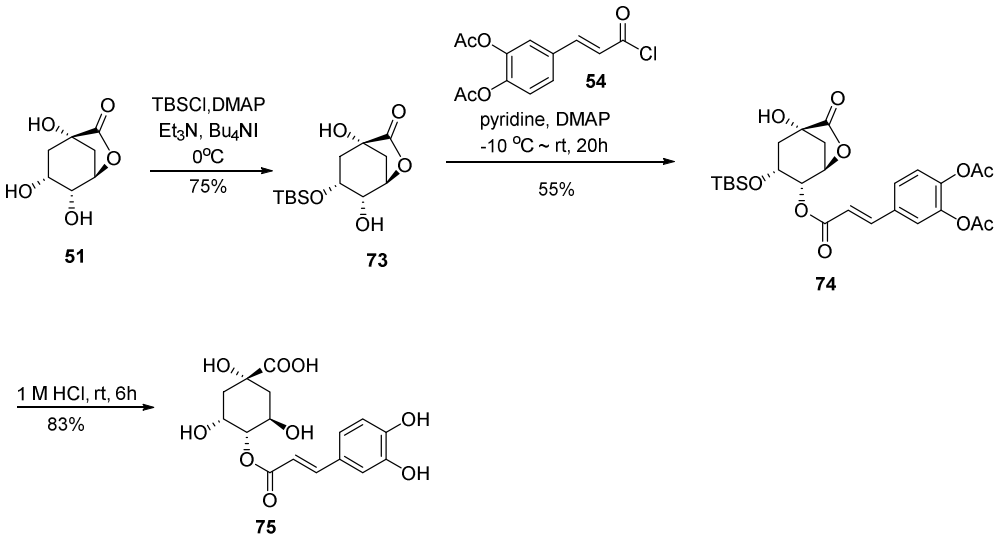


Scheme 5 Synthesis of 1-*O*-caffeoylquinic acid

The synthesis of 3-*O*-caffeoylquinic acid **75** is illustrated in **Scheme 6**. Differentiation of the secondary hydroxyl groups at positions C-4 and C-5 of quinide **51**[119] was effectively achieved with TBSCl at a low temperature, providing silyl ether **73**[119] in over 75% yield. Esterification of **73** with 1.2 equivalents of acid chloride in

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pyridine provided ester **74** in 55% yield, indicating the esterification of 1-hydroxyl was more difficult due to a bigger steric hindrance. It was mentioned that no esterification was observed when the reaction was performed in CH_2Cl_2 even with several equivalents of pyridine. Hydrolysis of all protecting groups was accomplished with 1M HCl at room temperature, and 4-*O*-caffeoylquinic acid **75** was obtained in 83% yield (36% from quinic acid **31**, **Scheme 6**). When the sequential basic and acid procedure (used for synthesis of 1-*O*-caffeoylquinic acid in **Scheme 5**) was performed, however, the cleavage of all esters was observed.

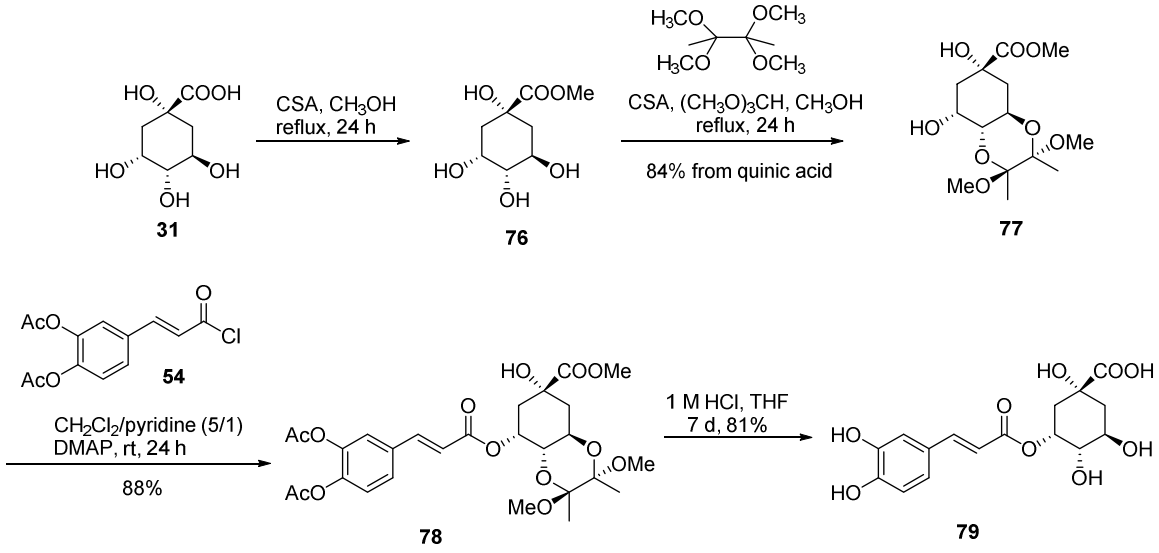


Scheme 6 Synthesis of 4-*O*-caffeoylquinic acid

For the synthesis of 3-*O*-caffeoylquinic acid **79** (referred to 5-*O*-caffeoylquinic acid with preIUPAC numbering in the literature, **Scheme 7**), a strategy involving *trans*-acetal **77**[120] was developed. Quinic acid **31** was converted into methylquinate **76** using (±)-10-camphorsulfonic acid (CSA) in refluxing methanol. Selective protection of the C-3 and C-4 vicinal diequatorial hydroxyls with 2,2,3,3-tetramethoxybutane in the presence of CSA and trimethyl orthoformate resulted in butane 2,3-bisacetal (BBA) protected methyl quinate **77** in 84% yield from quinic acid. Selective esterification of the 5-hydroxyl was accomplished with 1.2 equivalents of acid chloride **54** using the

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CH_2Cl_2/pyridine/DMAP system providing ester **78** in 88% yield, then the removal of all protecting groups was achieved with 1M HCl and the 3-*O*-caffeoylquinic acid **79** was afforded in 81% yield (60% from quinic acid **31**) containing small amounts of 4-*O*-caffeoylquinic acid as indicated by ^{1}H NMR.



Scheme 7 Synthesis of 3-*O*-caffeoylquinic acid

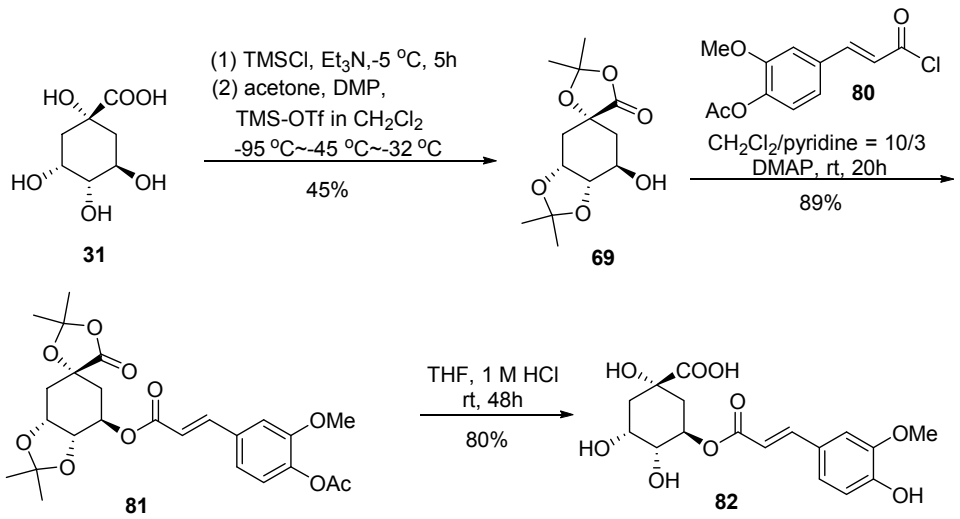
Thus, Sefkow's group has shown the synthesis of four different monoCaQA including 1-, 3-, 4- and 5-*O*-caffeoylquinic acid in 3 to 5 steps in fair to good overall yields from quinic acid. The conditions and yields for coupling reactions varied from each other depending on different substrates.

Besides, the synthesis of other monohydroxycinnamoylquinic acids (monoCQA) including 3-, 4-, 5-*O*-feruloylquinic acids, 5-*O*-feruloylquinic acid methyl ester, 1-*O*-(3,4-dimethoxycinnamoyl)quinic acid and 1-methoxy-5-*O*-caffeoylquinic acid were also reported.

In 2006, T. Hofmann *et al*. studied the decomposition of roast coffee beverage and provided the synthetic procedures for 5-*O*-feruloylquinic acid **82** (**Scheme 8**).[121] The same intermediate **69** as used by Sefkow for 5-*O*-caffeoylquinic acid was prepared in a

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two-step 45% yield from quinic acid by using Sefkow's synthetic strategy with modifications shown in **Scheme 8**. The esterification of **69** with acetyl protected feruloyl chloride **80** gave the ester **81** in 89% yield, the cleavage of all protecting groups was accomplished in THF/HCl and the 5-*O*-feruloylquinic acid **82** was obtained in 80% yield.



Scheme 8 Synthesis of 5-*O*-feruloylquinic acid

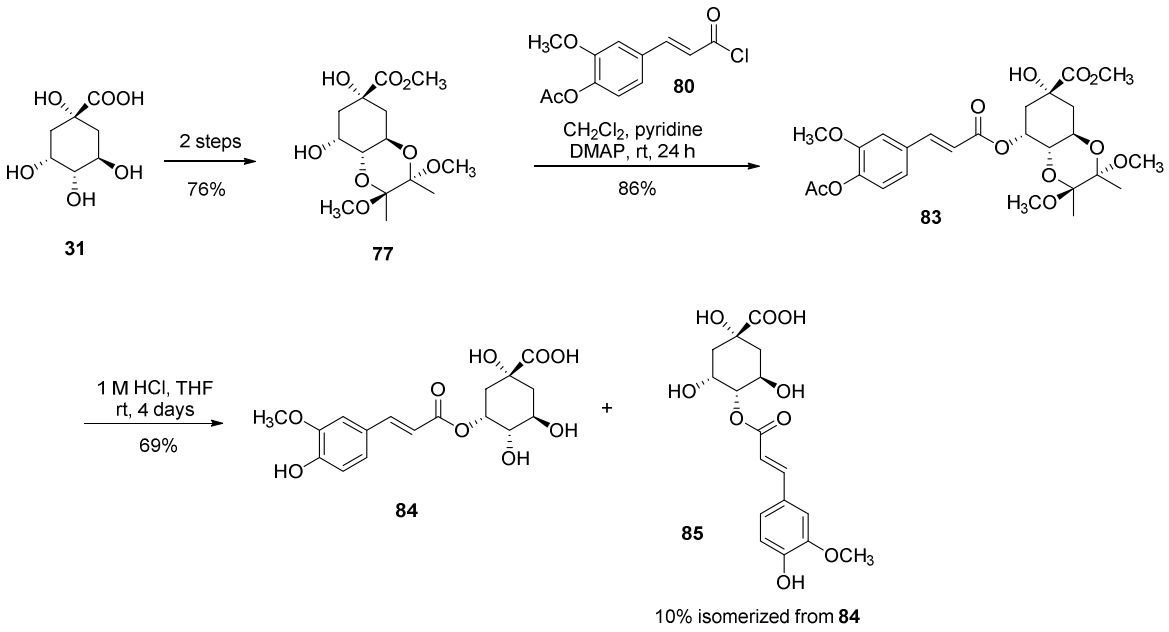
Hofmann barely modified Sefkow's protocol (TMS-OTf was added as solution in CH_2Cl_2 at -95 °C then the mixture was stirred for 2 hours at -45 °C and kept at -32 °C for 24 hours) and admitted a poorer yield of intermediate bisacetonide **69** than Sefkow (45% vs 81%) as this intermediate must be sensitive and unstable.

In 2013, Dokli *et al*. reported the synthesis of 3-, 4-, and 5-*O*-feruloylquinic acids (**84**, **85** and **82**, preIUPAC numbering was used in this literature) applying Sefkow's procedures with a few modifications in overall yields of 45%, 15% and 33%, respectively.[54]

The synthesis of 3-*O*-feruloylquinic acid **84** was illustrated in **Scheme 9**. The synthesis route for 3-*O*-feruloylquinic acid was based on Sefkow's strategy for the

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synthesis of 3-*O*-caffeoylquinic acid, the same intermediate **77**, the same coupling and deprotection conditions were applied. The migration of cinnamoyl group from C-3 to C-4 (up to 10%) leading to a mixture of isomers was also observed after deprotection but pure 3-*O*-feruloylquinic acid **84** was obtained in 69% yield after twice recrystallization from THF/diisopropyl ether. A lower overall yield was obtained for 3-*O*-feruloylquinic acid (45%) **84** by Dokli compared to the yield for 3-*O*-caffeoylquinic acid **79** (60%) by Sefkow.

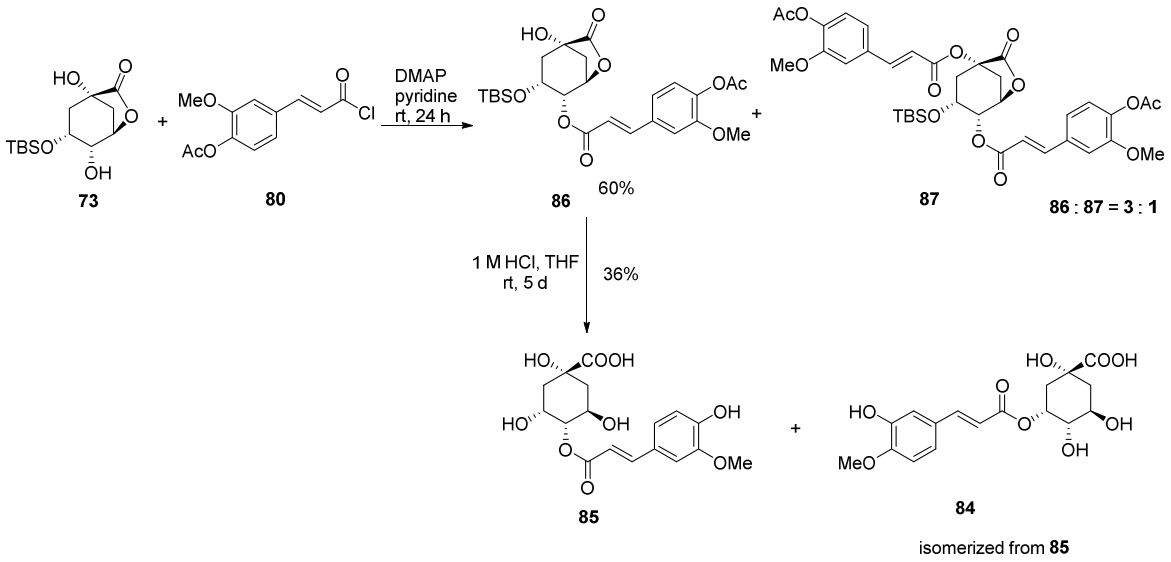


Scheme 9 Synthesis of 3-*O*-feruloylquinic acid

For the synthesis of 4-*O*-feruloylquinic acid, the same intermediate quinide **73** as used by Sefkow was prepared. In contrast with the esterification of quinide **73** with acetyl protected caffeoyl chloride by Sefkow (as mentioned above, pyridine/DMAP system was used, and no conversion of quinide **73** was observed in CH_2Cl_2/pyridine/DMAP system), esterification of quinide **73** with 1.5 equivalents of acetyl protected feruloyl chloride **80** in CH_2Cl_2/pyridine/DMAP system after 4 days at room temperature resulted in 90% conversion and resulted in a mixture of 4-

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monoesterificated **86** and 1,4-diesterificated **87** product in a molar ratio of **86**: **87** = 1.5:1. Better results were obtained when the reaction proceeded in pyridine/DMAP system with 1.8 equivalents of acid chloride **80** at room temperature. After 24 hours, the conversion was 100%, and the molar ratio of products was **86**:**87** = 3:1. Pure **86** was isolated after chromatography in 60% yield. All protecting groups were, as above, removed using 1 M aqueous HCl in THF (4:1) at room temperature. However, they observed that under the given reaction conditions, acyl migration from the 4-hydroxy to the 3-hydroxy occurred to some extent to give 3-*O*-feruloylquinic acid **84** as a side product. This made the purification and isolation of pure 4-*O*-feruloylquinic acid **85** by recrystallization difficult because 4-*O*-feruloylquinic acid **85** was found to be more soluble than 3-*O*-feruloylquinic acid **84** in all of the tested mixtures of solvents. The longer reaction time required for the full conversion (8 days) resulted in more acyl migration product **84** (20%). This problem was solved by stopping the reaction at 90% conversion (5 days), followed by column chromatography in order to remove 3-*O*-feruloylquinic acid **84** (up to 5%), and then recrystallization from a mixture of THF/diisopropyl ether to afford pure 4-*O*-feruloylquinic acid **85** in 36% yield (**Scheme 10**).

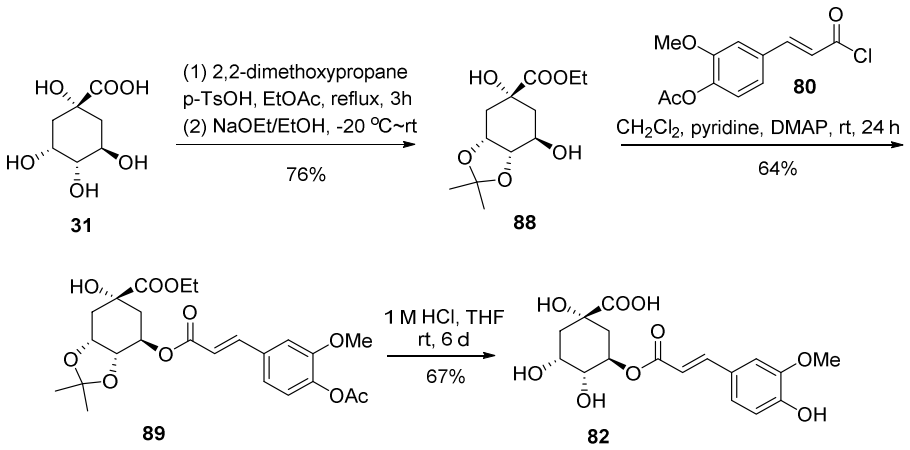


Scheme 10 Synthesis of 4-*O*-feruloylquinic acid

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Compared to Sefkow's synthetic procedure for 4-*O*-caffeoylquinic acid, a lower overall yield of 4-*O*-feruloylquinic acid was obtained. That may be due to two reasons, first, the acetyl protected feruloyl chloride was added at room temperature (Sefkow did at -10 °C) leading to the generation of disubstituted product **87** (disubstituted product was not observed by Sefkow); a bigger loss of the pure product caused by the migration of feruloyl group was observed during purification (no migration of caffeoyl group was mentioned by Sefkow).

For the synthesis of 5-*O*-feruloylquinic acid **82**, a different intermediate ester **88** from the one used by Sefkow for getting 5-*O*-caffeoylquinic acid was prepared 2 steps from quinic acid in 76% yield. Esterification of ester **88** with acetyl protected feruloyl chloride **80** in the DCM/pyridine/DMAP system gave compound **89** in 64% yield. All of the protecting groups were removed using 1 M aqueous HCl in THF (4:1) at room temperature for 6 days to afford 5-*O*-feruloylquinic acid **82** in 67% yield (**Scheme 11**) after two recrystallizations.



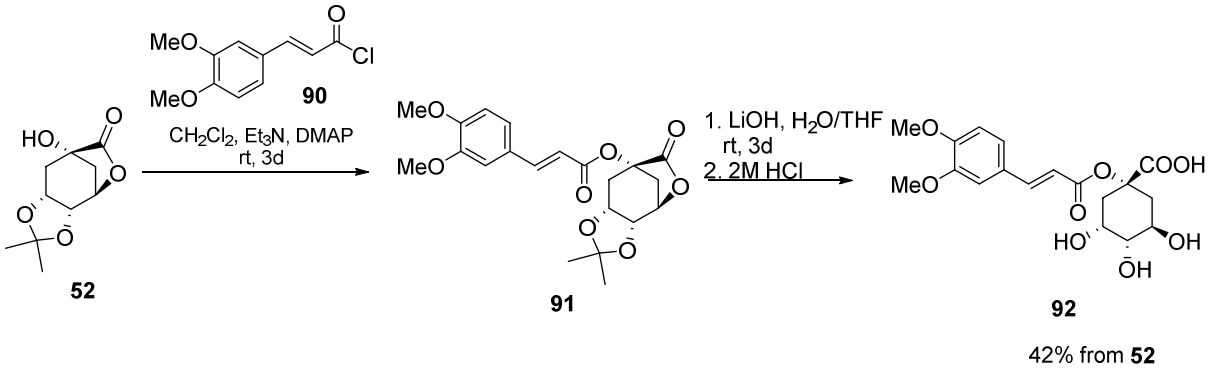
Scheme 11 Synthesis of 5-*O*-feruloylquinic acid

No migration of feruloyl group was mentioned. Also, in Sefkow's literature for the synthesis of 5-*O*-caffeoylquinic acid, no migration of caffeoyl group was observed after

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deprotection. The combined results indicate that 5-*O*-substituted ester is more stable than 3-*O*-substituted ester and 4-*O*-substituted ester. Compared to Sefkow's procedure, a lower overall yield was obtained, but the protocol for the synthesis of the key intermediate **88** was manipulatively easier since Sefkow's kinetic synthesis of intermediate **69** needs an ultralow temperature (-95 °C).

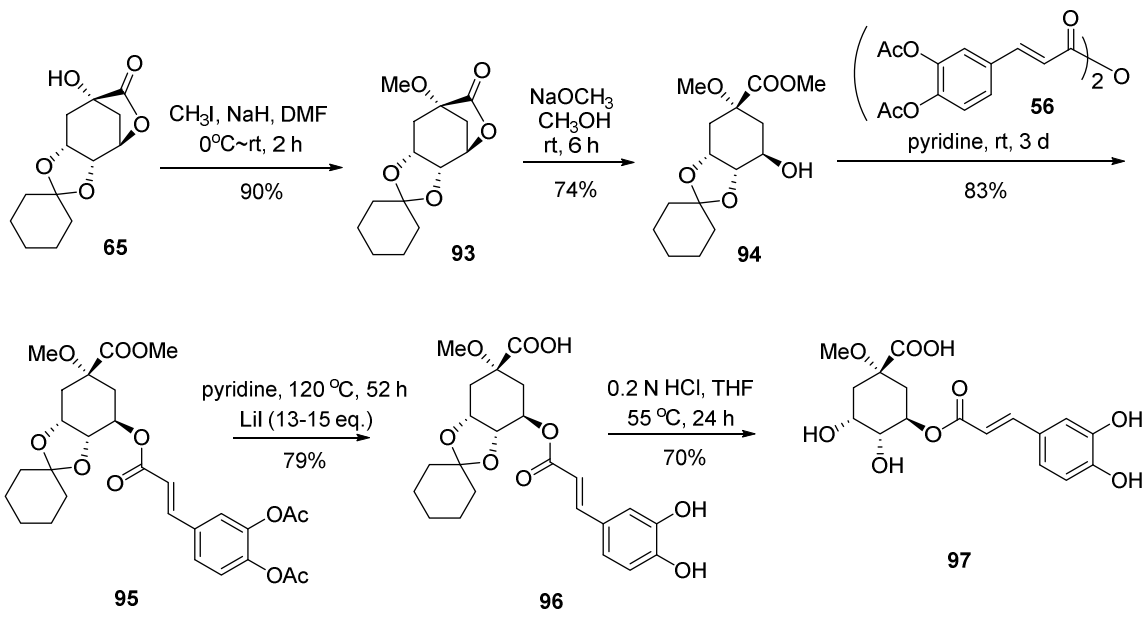
In 2006, M. Clifford[122] provided a synthetic route for 1-*O*-(3,4-dimethoxycinnamoyl) quinic acid **92** (**Scheme 12**) using the same intermediate quinide **52** as used by Sefkow for the synthesis of 1-*O*-caffeoylquinic acid (**Scheme 5**). What is different from Sefkow's standard condition is the change of the base from pyridine to Et_3N. The esterification of quinide **52** with 3,4-dimethoxycinnamoyl chloride **90** provided ester **91** as a crude product, which was directly conducted to the deprotection with LiOH in H_2O/THF for 3 days then being quenched by 2M HCl to afford the final product 1-*O*-(3,4-dimethoxycinnamoyl)quinic acid **92** in 42% yield from quinide **52**.



Scheme 12 Synthesis of 1-*O*-(3,4-dimethoxycinnamoyl)quinic acid

In 2014, W. Zeller reported the synthesis of 1-*O*-methyl-5-*O*-caffeoylquinic acid **97**,[115] for the reassignment of its structure and that of its isomer 5-*O*-caffeoylquinic acid methyl ester, which was mistaken as 1-*O*-methyl-5-*O*-caffeoylquinic acid **97** in the paper working on the extracts from *Phyllostachys edulis* leaves.[68]

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Scheme 13 Synthesis of 1-*O*-methyl-5-*O*-caffeoylquinic acid

Starting from quinic acid **31**, lactone **65** was obtained in 75% yield.[116] After methylation at OH-1 and lactone opening, the intermediate **94** was obtained. The caffeoyl moiety was introduced through acylation of the hydroxyl group at position 5 with caffeic acid anhydride tetraacetate **56**, a reagent developed specifically for construction of caffeoyl-containing compounds, and afforded the fully protected target compound **95** in 83% yield. The methyl ester functionality was cleaved with lithium iodide in pyridine[114] which also resulted in concomitant loss of the caffeoyl acetate protecting groups to give the intermediate ketal **96** in 79% yield. Completion of the synthesis of 1-*O*-methyl-5-*O*-caffeoylquinic acid **97** was achieved after treatment of ketal **96** with aqueous HCl in THF (**Scheme 13**).

The overall yield of 1-*O*-methyl-5-*O*-caffeoylquinic acid from quinic acid was 23%. The introduction of a new cinnmaoyl group donor anhydride **56** was an important innovative point for the coupling reaction.

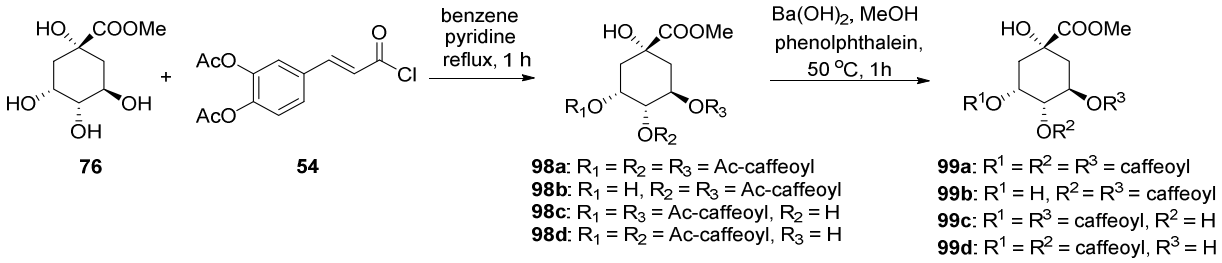
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1.2.4.1.2 Synthesis of diCQA,triCQA and other derivatives

Compared to monoCQA, much less reports concern the synthesis of CQA and derivatives with two or more cinnamoyl groups, and the first synthetic work was reported only 15 years ago.

In 2001, Kadota *et al.* reported the synthesis of three methyl di-*O*-caffeoylquinates, methyl 3,4,5-tri-*O*-caffeoylquinate (**Scheme 14**) and 3,4-di-*O*-caffeoylquinic acid (**Scheme 15**) and their antihepatotoxic and antiproliferative activities were evaluated.[112]

The esterification of methyl quinate **76** with acid chloride **54** was achieved in benzene/pyridine under reflux for 1 hour and provided a mixture of **98a**-**98d**. In the presence of 3 equivalents of acid chloride **54** at 50 °C, only **98b** and **98c** were obtained in low yields (7.3% and 2.2%, respectively). As the reaction temperature was raised to 80 °C, **98a**, **98b**, **98c** and **98d** were obtained with the yields of 10.4%, 17.2%, 6.1% and 14.1%. While the use of 5 equivalents of acid chloride **54** gave **98a** selectively in 25.7% yield. The di- and tri-*O*-esters **98a**-**98d** were deprotected with 0.5 N $Ba(OH)_2$ in MeOH[123] to give the methyl quinates **99a**-**99d** (82% yield for **99a**, 65% for **99b** and **99c**, 85% for **99d**).



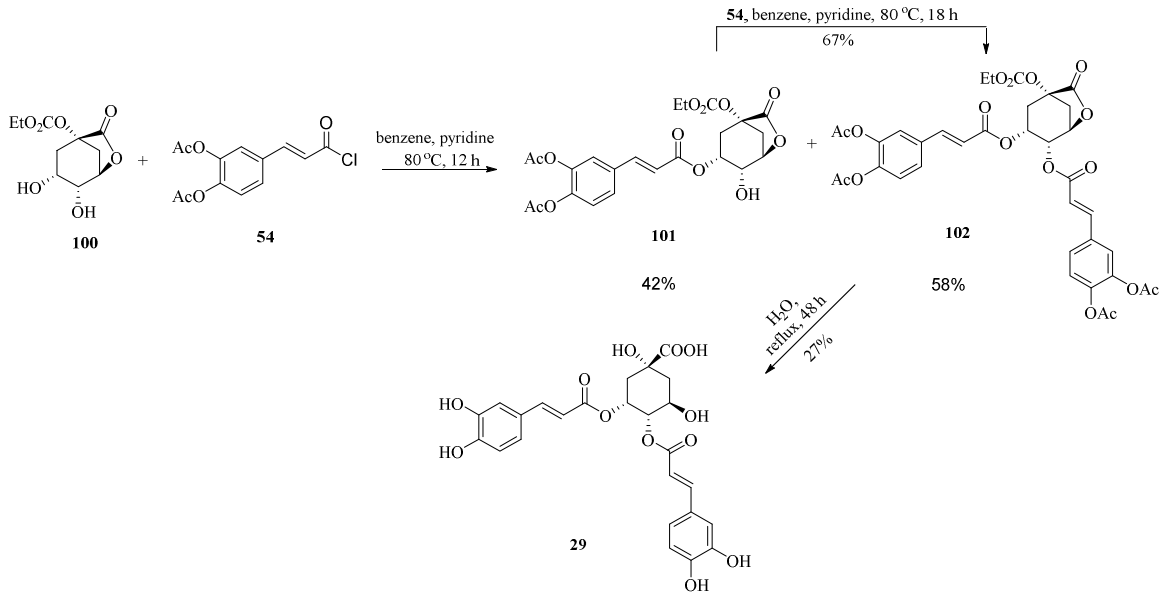
Scheme 14 Synthesis of di- and tri-*O*-caffeoyl methyl quinates 99a-99d

It is the first report about the synthesis of di- and tri-*O*-caffeoylquinic acid methyl esters. The one-pot synthesis based on the random coupling of methyl quinate **76** and

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acid chloride **54** provided three different diesters and one triester but in low yields due to the lack of specificity. The purification of reaction crude was subjected to reversed-phase preparative TLC, which should have been difficult although the authors did not mention it.

Compound 3,4-di-*O*-caffeoylquinic acid **29** was synthesized (**Scheme 15**) from quinide **100**[123] through esterification with 5 equivalents of acid chloride **54**, giving a monoester **101** and diester **102** in 42% and 58% yield. The former monoester **101** was subsequently converted to the diester **102** with 5 equivalents of acid chloride **54** in 67% yield, then diester **102** was hydrolyzed into **29** in 27% yield with H_2O under reflux for 48 hours.



Scheme 15 Synthesis of 3,4-di-*O*-caffeoylquinic acid

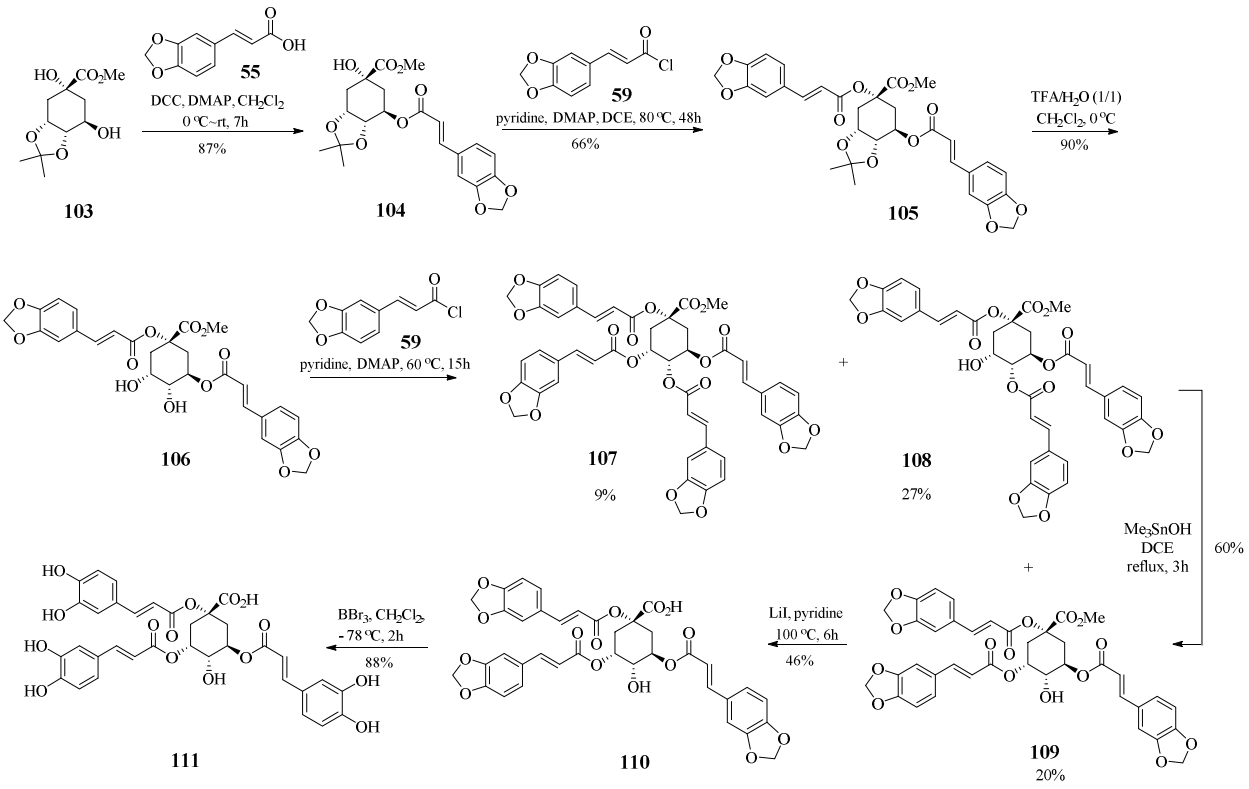
It is the first report about the synthesis of 3,4-di-*O*-caffeoylquinic acid. But this strategy suffers from a low yield and low atom-economy. Even with 5 equivalents of acid chloride, there still existed 42% monoester **101**, and the conversion of monoester **101** to diester **102** needed another 5 equivalents of acid chloride. The deprotection step was performed in water under reflux without any acidic or basic catalysis and provided

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a low yield (27%). However, we can question about the yields for the coupling step and the deprotection conditions were doubtful: (1) the total yield of monoester **101** and diester **102** adds up to 100%, which was unreasonable and never seen in other literatures on CQA synthesis; (2) the deprotection step was carried out without any catalyst but only in refluxing water, that's the only case reported.

In 2009, Brummond *et al*. reported the synthesis of 1,3,5-tri-*O*-caffeoylquinic acid **111**,[114] which was found as a potent Ribonuclease H inhibitor and anti-HIV agent.[124] The synthetic route is illustrated in **Scheme 16**. They began with the formation of diol **103** from quinic acid **31** in 50% yield in 2 steps using a previously developed protocol.[125,126] Diol **103** was then transformed into the 5-substituted compound **104** *via* DCC-catalyzed coupling with 1.5 equivalents of 3,4-(methylenedioxy)cinnamic acid **55** in 87% yield and then the compound **105** with 2.5 equivalents of acid chloride **59** in DCE/pyridine/DMAP system in 66% yield. Removal of the acetonide protecting group of **105** was accomplished in 90% yield with TFA/H_2O (1/1) to give diol **106**, which was then reacted with 1.1 equivalents of acid chloride **59** in pyridine/DMAP system at 60 °C to give a mixture of tetrasubstituted ester **107**, 1,4,5-trisubstituted ester **108** and 1,3,5-trisubstituted ester **109** in 9%, 27% and 20% yield, respectively. It was found that reacting the undesired 1,4,5-triester **108** with Me_3SnOH in refluxing DCE resulted in a migration of cinnamoyl group from C-4 to C-3, giving the desired 1,3,5-triester **109** in 60% yield. The saponification of the methyl ester was accomplished by refluxing **109** in pyridine with excess LiI to give the analogous acid **110** in 46% yield.[127] The carboxylic acid **110** was then reacted with excess BBr_3 at –78 °C to give the final product **111** in 88% yield. Attempts to remove the methylene acetal protecting group first and then to saponify the methyl ester to the acid gave very low yields of the natural product, which was attributed to the poor stability of the liberated catechol moieties.

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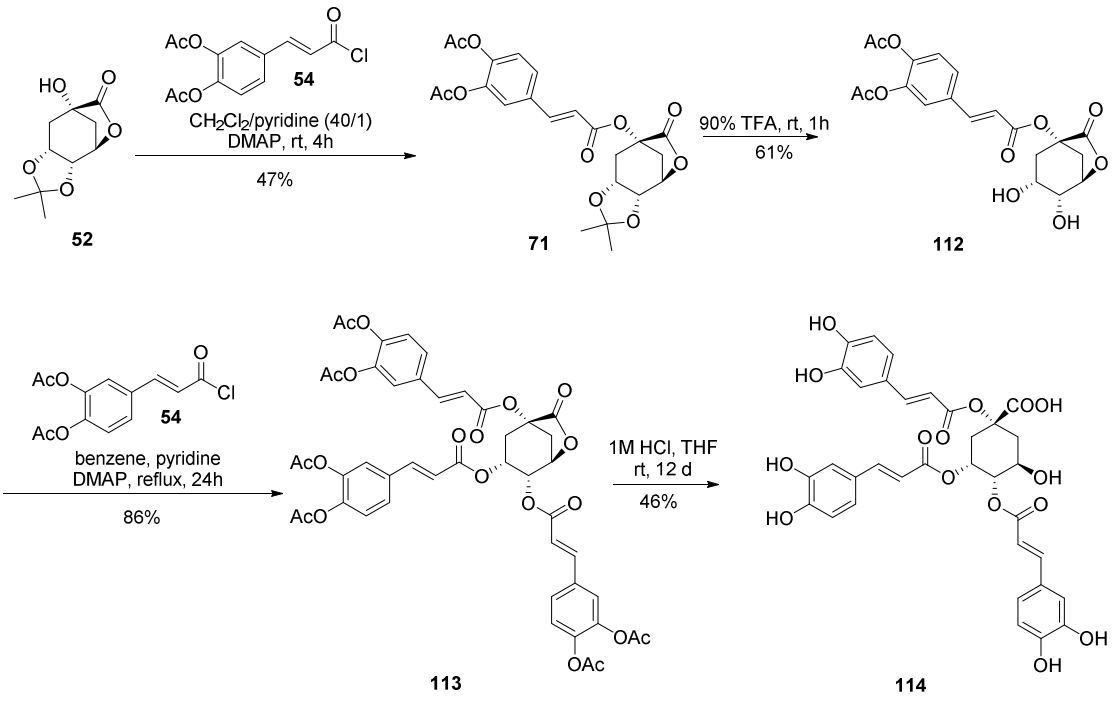
Scheme 16 Synthesis of 1,3,5-tri-*O*-caffeoylquinic acid

This is the first report on the synthesis of 1,3,5-tri-*O*-caffeoylquinic acid. In this strategy, a tedious protection and deprotection process was needed. The final product was afforded in 8 steps from quinic acid in a low overall yield (< 4%). In addition, two different caffeoyl group donors (acid and acid chloride) were used for the coupling reactions. The conditions for the first, second and third coupling varied from each other. For the deprotection of methylenedioxy group, an ultralow temperature was needed. All these disadvantages make this strategy low efficient and manipulatively difficult.

In 2011, Shigemori *et al*. reported the synthesis of 1,3,4-tri-*O*-caffeoylquinic acid (named 1,4,5-tri-*O*-caffeoylquinic acid in the literature using preIUPAC numbering) **114** (**Scheme 17**), 3,4-di-*O*-caffeoylquinic acid (named 4,5-di-*O*-caffeoylquinic acid in the literature using preIUPAC numbering) **29** (**Scheme 18**) and 3,4,5-tri-*O*-caffeoylquinic acid **41** (**Scheme 19**).[113]

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Quinide **52** reacted with acid chloride **54** in DCM/pyridine/DMAP system to afford ester **71** in 47% yield.[53] The acetonide group of **71** was cleaved with 90% TFA to give in 61% yield diol **112**, which was then heated with 5 equivalents of acid chloride **54** in benzene/pyridine/DMAP system under reflux for 24 h to afford triester **113** in 86% yield. Hydrolysis of all protecting groups was achieved with 1M HCl at room temperature for 12 days to obtain 1,3,4-tri-*O*-caffeoylquinic acid **114** in 46% yield.

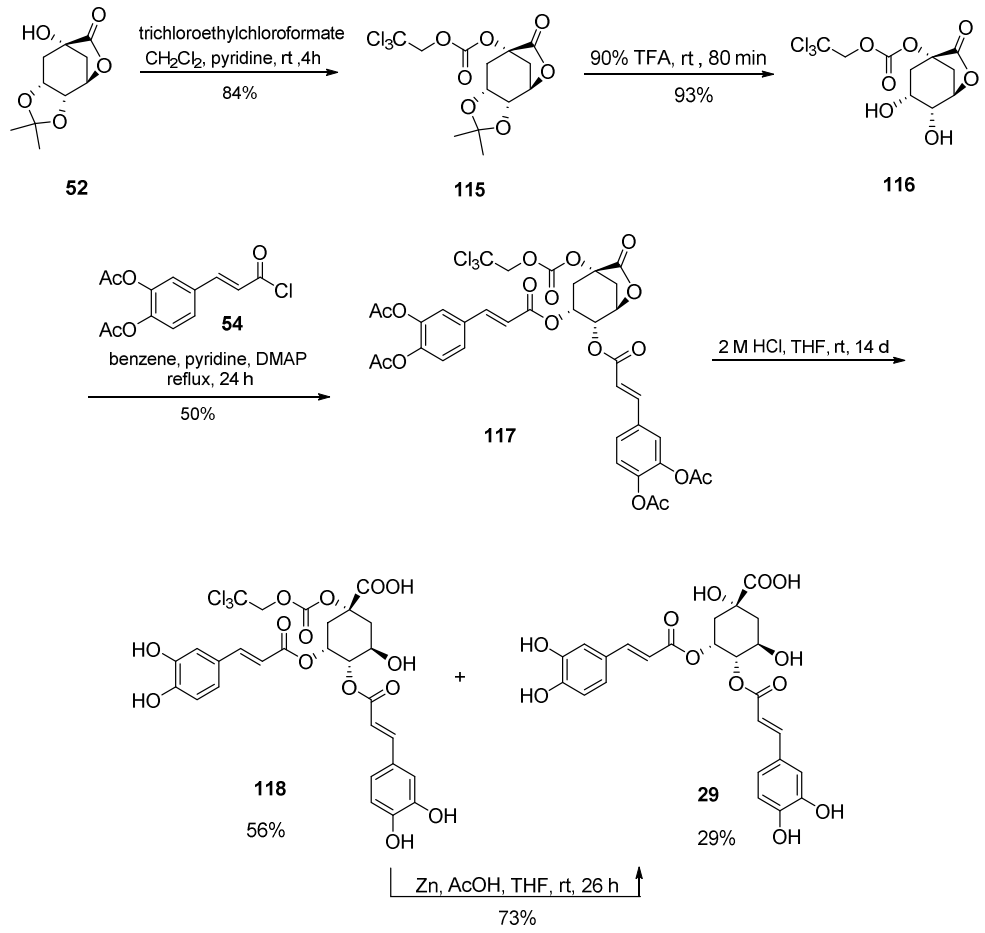


Scheme 17 Synthesis of 1,3,4-tri-*O*-caffeoylquinic acid

This is the first report about the synthesis of 1,3,4-tri-*O*-caffeoylquinic acid. The overall four-step yield from quinide **52** was only 11%. The one-pot diesterification at positions 3 and 4 of compound **112** needed 5 equivalents of acid chloride, which was poor atom-economic. The deprotection under acidic conditions needed a quite long time (12 days), that increases the risk of the generation of byproducts and therefore contributes to the low yield.

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The synthesis of 3,4-di-*O*-caffeoylquinic acid **29** by Shigemori *et al*. is illustrated in **Scheme 18**. With a purpose to improve the yield of **29** first synthesized by Kadota *et al*.(**Scheme 15**),[112] Shigemori *et al*. changed the protecting group for hydroxyl group at position 1 to trichloroethylethoxy carbonate group that could be specifically cleaved with zinc and AcOH.[121] Then the acetonide group of quinide **115** was removed by 90% TFA to afford in 93% yield diol **116**, which was heated with 4 equivalents of acid chloride **54** in benzene/pyridine/DMAP system under reflux for 24 hours to afford di-*O*-ester **117** in 50% yield. Cleavages of acetyl groups and lactone moiety by 2 M HCl at room temperature gave the incompletely deprotected compound **118** and 3,4-di-*O*-caffeoylquinic acid **29** in 56% and 29% yield, respectively. Finally, the carbonate group of **118** was removed with zinc powder and AcOH to obtain **29** in 73% yield.

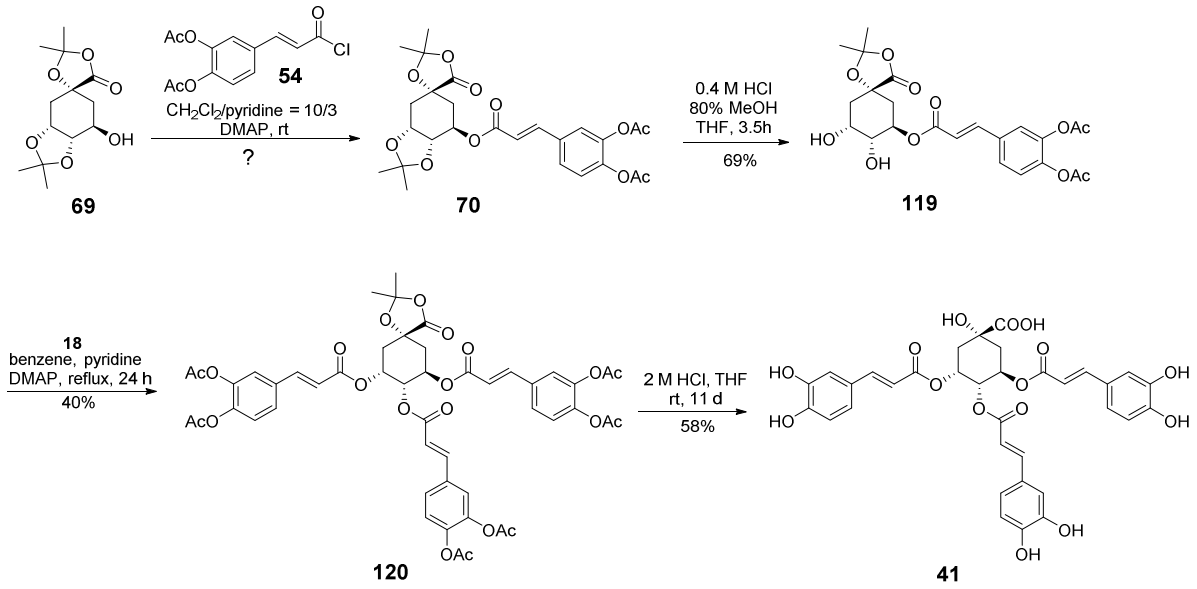


Scheme 18 The synthesis of 3,4-di-*O*-caffeoylquinic acid

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Compared with Kadota's strategy (**Scheme 15**), Shigemori *et al*. improved the yield of deprotection step by the introduction of trichloroethylethoxy carbonate group to protect hydroxyl group at position 1. However, four equivalents of acid chloride was needed for disubstitution of diol **116**, and the reaction time of deprotection step under acidic conditions was quite long (14 days).

The synthesis of 3,4,5-tri-*O*-caffeoylquinic acid **41** by Shigemori *et al*. is illustrated in **Scheme 19**. Bisacetonide **69** was obtained starting from quinic acid by Sefkow's kinetic synthetic protocol.[52] Then bisacetonide **69** was reacted with acid chloride **54** under Sefkow's standard conditions providing ester **70** (no yield was given).[52] The acetonide group of 5-*O*-substituted ester **70** was removed with 0.4 M HCl in 80% MeOH and THF to afford in 69% yield diol **119**, which was heated with 4 equivalents of acid chloride **54** in benzene/pyridine/DMAP under reflux for 24 hours to give triester **120** in 40% yield. Hydrolysis of the acetonide and acetyl groups was achieved with 2 M HCl at room temperature for 11 days to obtain 3,4,5-tri-*O*-caffeoylquinic acid **41** in 58% yield.



Scheme 19 The synthesis of 3,4,5-tri-*O*-caffeoylquinic acid

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This is the first report about the synthesis of 3,4,5-tri-*O*-caffeoylquinic acid. Again, this strategy still suffers to a low atom-economy due to the excessive use of acid chloride (4 equivalents) for 3,4-biscoupling providing only 40% product and a long reaction time for deprotection (11 days).

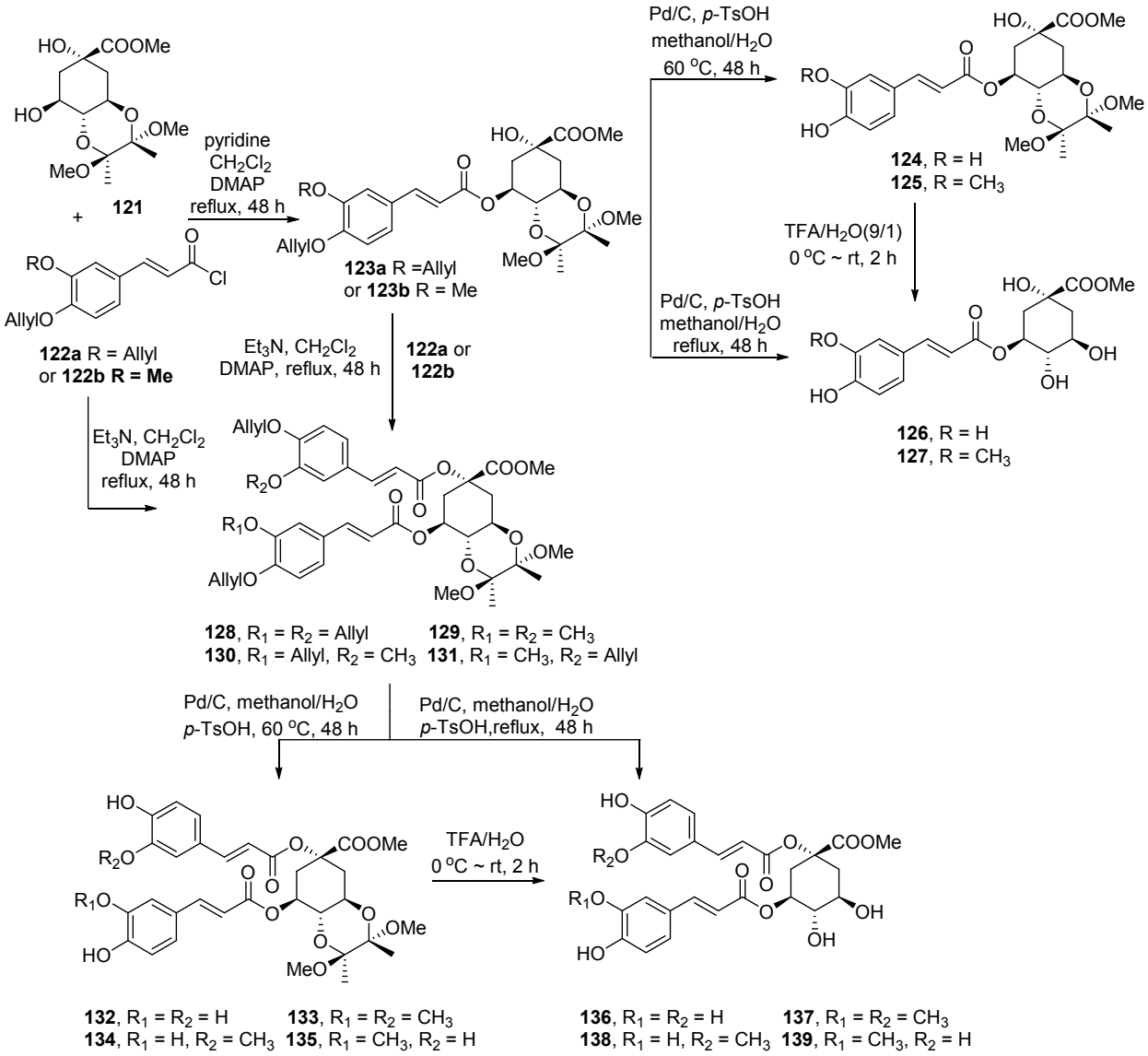
In 2012, N. Kuhnert *et al*. reported the synthesis of six caffeoyl- and/or feruloyl-*muco*-quinic acids derivatives (**126**, **127**, **136-139**) in good yields in 5 steps from quinic acid (**Scheme 20**).[128]

As mentioned above, acetyl groups have been mostly commonly used for phenolic OH protection, however, this was found to be problematic and unreliable, since both acid or base induced deprotection[129]leads to incomplete or non-selective removal of the acetate groups with competing hydrolysis of the cinnamic quinic acid ester bonds. Instead, they introduced allyl group for the protection of phenolic hydroxyl groups.

An esterification of methyl TMB-*muco*-quinate **121** with acid chloride **122a** (allyl protected caffeoyl chloride) or **122b** (allyl protected feruloyl chloride) was performed in DCM at reflux temperature for 48 hours in the presence of an organic base. For the monoacylation, pyridine and 1.5 equivalents of acid chlorides were used and for the hetero and homo diacylation, triethylamine and 1.5 and 3 equivalents of acid chlorides were used, respectively (**Scheme 20**). Deprotection of the allyl ether and the TMB group was achieved in one step in the presence of Pd/C catalyst, *p*-toluenesulfonic acid (*p*-TsOH), and aqueous methanol (90%) as the solvent.[130] When the temperature of the reaction was not higher than 60 °C, only deprotection of the allyl ether group was observed, while at reflux temperature both groups were deprotected. For compounds **123a** and **123b**, acylation at temperature of 60 °C followed by TFA treatment were performed to yield compounds **126** and **127**. Additionally, they obtained a series of disubstituted *muco*-quinic acid derivatives. Using NEt_3 as a base, diacylation was observed to give, after deallylation, the two caffeoyl and feruloyl homodiesters **136** and

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137. Using a sequential esterification reaction with different acid chlorides, and after deprotection, the two heterodiesters **138** and **139** could be obtained as well.



Scheme 20 Synthesis of several caffeoyl- or feruloyl-*muco*- methylquinates

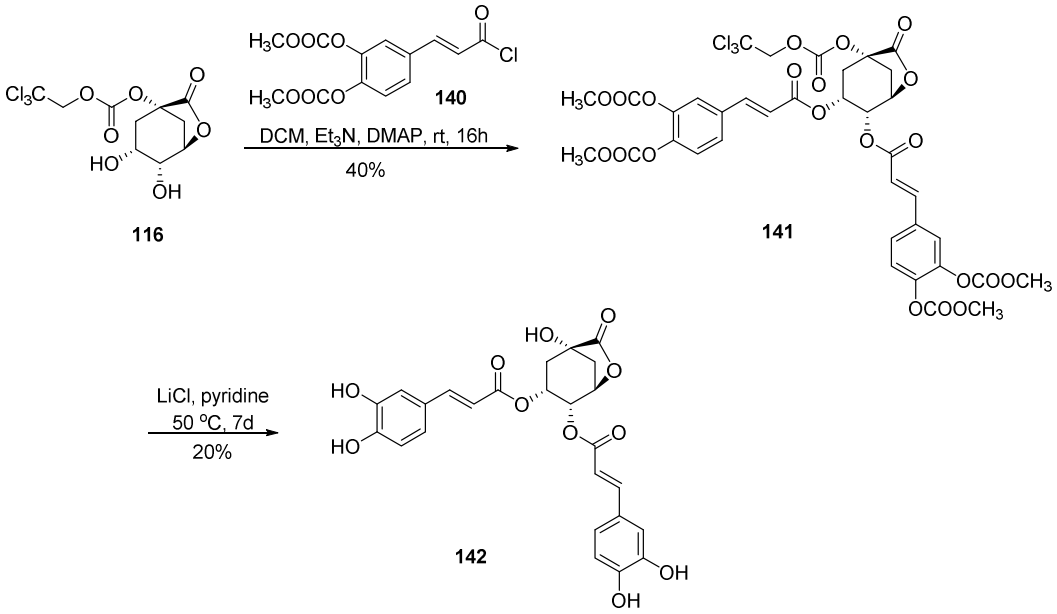
It's the first report about the synthesis of heterodiester derivatives of CQA bearing two different hydroxycinnamoyl groups. And a new protecting group allyl group for phenols was introduced. The conditions of esterification reactions highly depend on the

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substrates. For monoesterificaion at position 3, pyridine was the base used, but for diesterification or the second esterification at position 1, base Et_3N was needed.

In addition, the patent invented by Huynh-ba[131] introduced also the synthesis of 1- and 5-*O*-mono- and 3,4-*O*-disubstituted CQA derivatives including quinide derivatives. These compounds were prepared also by reacting a protected a hydroxycinnamic acid derivative with a quinic acid derivative and by using the same or similar coupling and deprotection conditions as mentioned above, with some modifications on the protecting groups for phenols or carboxylic acid.

More recently in 2014[55] and 2015,[132] Sinisi *et al*. reported the synthesis of several mono-, di- and tri-*O*-3,4-dimethoxycinnamoyl-1,5-γ-quinides or 3,4-*O*-dicaffeoyl-1,5-γ-quinide by utilizing the same track of thoughts.



Scheme 21 Synthesis of 3,4-*O*-dicaffeoyl-1,5-γ-quinide

For example, the acylation of quinide **116** with 4.87 equivalents of 3,4-*O*-dimethoxycarbonyl caffeoyl chloride **140** under DCM/Et_3N/DMAP system at room temperature for 16 hours provided the 3,4-diacylated quinide **141** in 40% yield. The

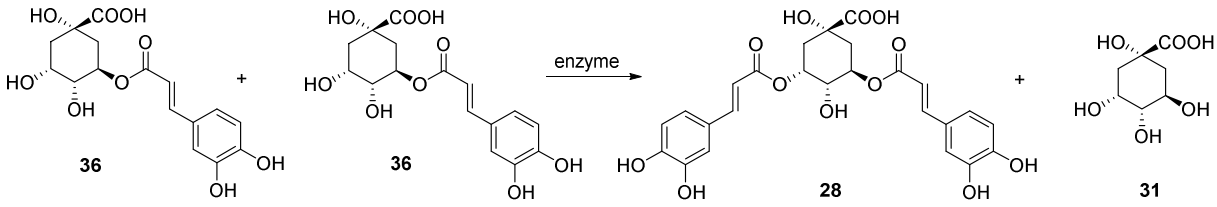
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cleavage of carbonate groups was achieved with LiCl in pyridine at reflux for 7 days providing 3,4-*O*-dicaffeoyl-1,5-γ-quinide **142** in 20% yield. The authors mentioned that the coupling reaction under DCM/pyridine system[133] always afforded a mixture of monoesters and only a small amount of diester **141** was obtained. The use of basic solvent pyridine and a long reaction time at reflux may contribute to the low yield of the deprotection reaction.

1.2.4.2 Enzymatic esterification

As seen above, chemical synthesis of CQA is difficult due to phenolic acids being heat-sensitive and susceptible to oxidation under certain pH conditions[134] and the need for several protection and deprotection process. This is why some enzymatic alternatives were investigated.

In 1985, Kondo *et al*. found that enzymes present in sweet potato root were able to catalyze the conversion of 5-*O*-caffeoylquinic acid **36** to 3,5-di-*O*-caffeoylquinic acid **28**.[135]



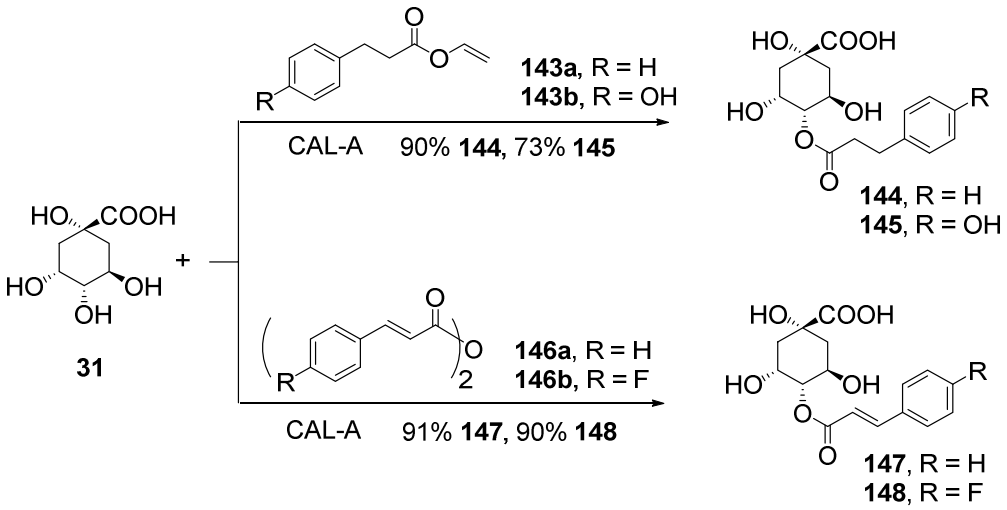
Scheme 22 Proposed enzymatic reaction for production of 3,5-di-*O*-caffeoylquinic acid

A reaction mixture consisting of 5-*O*-caffeoylquinic acid **36**, magnesium chloride, phosphate (pH 6.4) and enzyme was incubated at 30 °C. The final reaction mixture contained **36**, **28** and **31**. Consequently, it was expected that one molecule of quinic acid **31** was produced with production of one molecule of 3,5-di-*O*-caffeoylquinic acid **28** as

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proposed in **Scheme 22**. However, it was not a strict mechanism due to the lack of both the comparison with constant groups and data for molar ratio of each compounds.

In 2003,[136] *Candida antarctica* lipase A. (CAL-A) was used by V. Gotor *et al*. for the first direct synthesis of 4-*O*-cinnamoyl derivatives of quinic (**Scheme 23**) and shikimic acids.



Scheme 23 CAL-A catalyzed synthesis of 4-*O*-cinnamoylquinic acid derivatives

Four cinnamate ester derivatives of quinic acid (**144**, **145**, **147** and **148**) were effectively synthesized from quinic acid **31** and acyl donors such as vinyl hydrocinnamate **143a**, vinyl *p*-hydroxyphenylpropionate **143b**, cinnamic anhydride **146a** and *p*-fluorocinnamic anhydride **146b** by direct transesterification using CAL-A (**Scheme 23**) in *tert*-butylmethyl ether (TBME) at 40 ºC. The reactions with the acyl donners proceeded satisfactorily giving good to excellent isolated yields (90% for **144**, 73% for **145**, 91% for **147**, 90% for **148**) of the targeted compounds. For the acylation with **143b**, the rate of esterification was lower than the rate of esterification with **143a**, indicating the inhibitory effect of the *p*-hydroxy substituent in the activity of the lipase.

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The enzymatic synthesis is advantaged by no requirement for the tedious protection-deprotection process, facile manipulation and high regioselectivity for acylation. The discovery of other enzymes which could be used for CQA synthesis remains to be explored. That would be, if possible, a great breakup for the synthetic research for CQA.

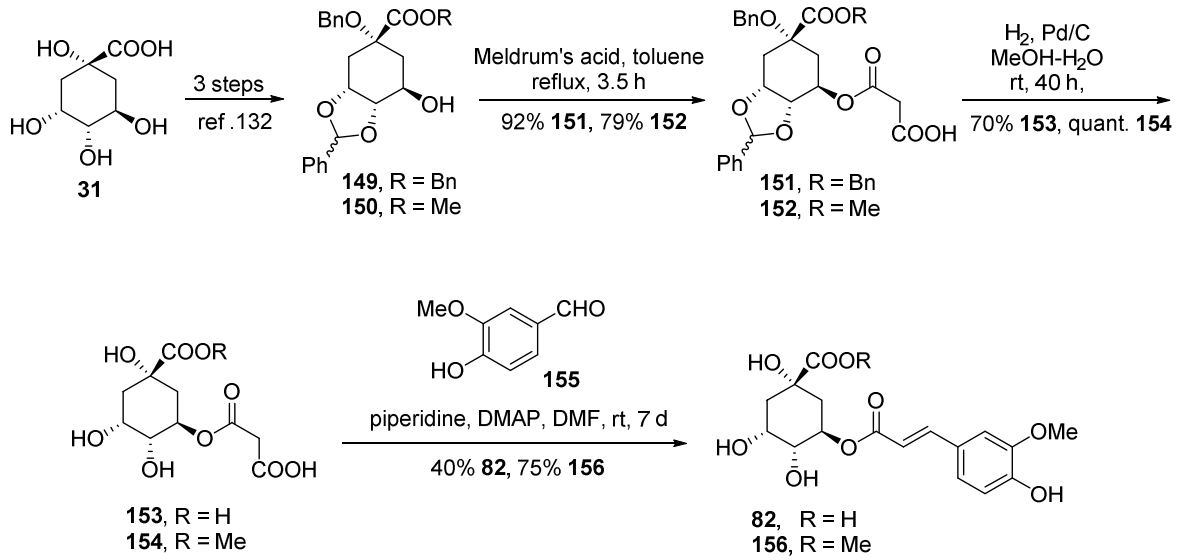
1.2.4.3 Knoevenagel condensation

As summarized above (1.2.4.1), the most commonly used regioselective esterification protocol requires suitable protection of both precursors, and the final deprotection step could be delicate. D. Barron *et al*. introduced a different route for CQA synthesis applying a Knoevenagel condensation reaction in the formation of the cinnmaoyl moiety.[137,138]

In 2008, starting from quinic acid **31** and vanillin **155**, the syntheses of 5-*O*-feruloylquinic acid **82** and 5-*O*-feruloyquinic acid methyl ester **156** were achieved in 19% and 44% overall yields, respectively.[137]

Following the reported procedure,[139] compounds **149** and **150** were obtained in yields of 75% from quinic acid **31**. The hydroxyl group at position 5 of compounds **149** and **150** was then esterified by refluxing in toluene with commercially available 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid),[140] to lead to the corresponding esters **151** and **152** in 92% and 79% yields, respectively. Removal of all protective groups was then performed in one step using hydrogenative conditions (Pd/C 5%, MeOH/H_2O), to give the monofunctionalized quinic acid **153** and methyl ester **154** (70% and quantitative, respectively). Finally, the piperidine-catalyzed Knoevenagel condensation was achieved on vanillin **155** with esters **153** and **154**, using the mild conditions developed by List *et al*. (rt, 7 days).[141] This afforded 5-*O*-feruloyquinic acid **82** (40%) and 5-*O*-feruloylquinic acid methyl ester **156** (75%).

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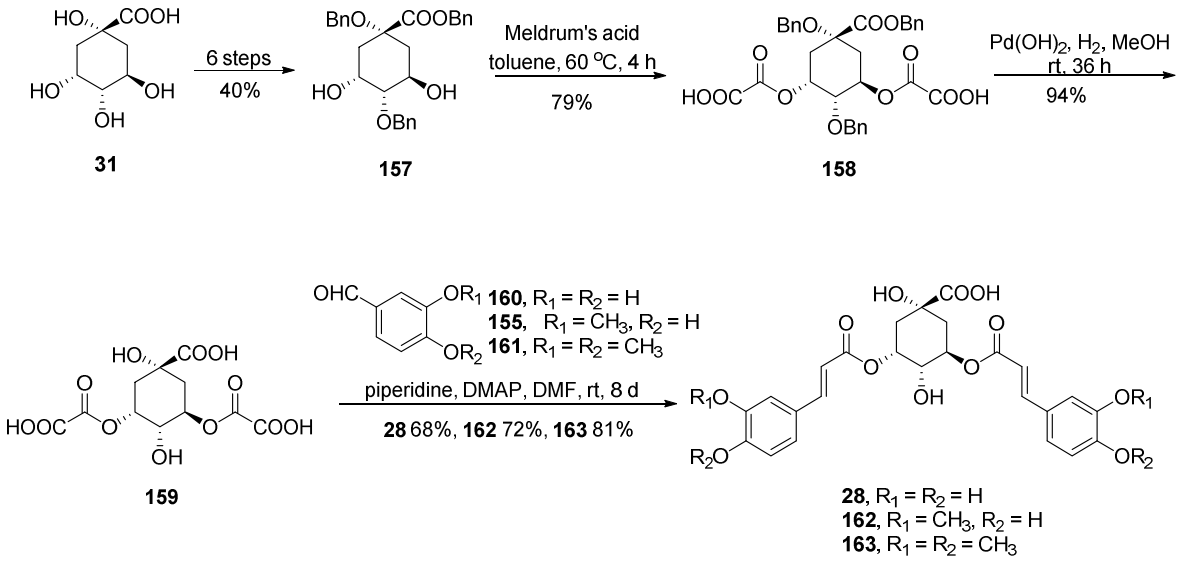


Scheme 24 Synthesis of 5-*O*-feruloylquinic acid 82 and methyl ester 156

In 2011, the Knoevenagel condensation methodology was applied to achieve the first synthesis of 3,5-di-*O*-caffeoylquinic acid **28**, 3,5-di-*O*-feruloylquinic acid **162** and 3,5-di-*O*-(3,4-methoxycinnamyl)quinic acid **163** (**Scheme 25**).[138]

Starting from quinic acid **31**, six steps were needed for the preparation of diol **157** with free hydroxyl groups at positons 3 and 5 in 40% yield. Diol **157** was then subjected to a double acylation by treatment with 2.2 equivalents of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) in toluene at 60 °C to give diester **158** in 79% yield.[140] Cleavage of the benzyl protecting groups was achieved in 94% yield by hydrogenolysis [$Pd(OH)_2$, MeOH] to give the deprotected diester **159** as the immediate precursor to three diCQA. The final step of the syntheses involved a double Knoevenagel condensation without any protecting groups. Accordingly, treatment of **159** with aldehydes **160**, **155** and **161**, DMAP and piperidine in anhydrous DMF afforded the target compounds in moderate to good yields 3,5-di-*O*-caffeoylquinic acid **28** (68%), 3,5-di-*O*-feruloylquinic acid **162** (72%) and 3,5-di-*O*-(3,4-methoxycinnamyl)quinic acid **163** yield (81%).

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Scheme 25 Synthesis of 3,5-di-*O*-caffeoylquinic acid 28, 3,5-di-*O*-feruloylquinic acid 162 and 3,5-di-*O*-(3,4-methoxycinnamyl)quinic acid 163

The new strategy for CQA synthesis applying Knoevenagel condensation reaction developed by D. Barron *et al*. is advantaged by no requirement for protection of aldehyde or quinic acid fragment for the final step and no need for deprotection step eliminating any additional reaction on the sensitive CQA skeleton. However, a tedious protection process, especially for 3,5-diesters, was needed to avoid possible acylation reactions of hydroxyl groups with Meldrum's acid at undesired positions. In addition, this synthetic route suffers from a long reaction time (8 days) for the last Knoevenagel condensation and the difficulties for purification due to the presence of one to three carboxylic groups in the molecules **153**, **154** and **159**.

Up to now, the reported strategies for the synthesis of CQA and derivatives were summarized as above. Different CQA and derivatives were synthesized including 1-, 3-, 4-, and 5-monoCQA; 3,4- and 3,5-diCQA (but the synthesis of 4,5-diCQA was never reported); 1,3,5-, 1,3,4- and 3,4,5-triCQA. The chemical synthetic routes, no matter the commonly used esterification of protected quinic acid moiety with protected

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hydroxycinnamic acid moiety, or the Knoevenagel condensation involved procedure, require a tedious protection and deprotection process making the synthesis manipulatively difficult and the overall yields rather low. The enzymatic synthesis of CQA is advantaged by high regiospecificity and high yields but disadvantaged by a narrow applicability of substrates and that only two enzymes are currently available for CQA synthesis. A screening of possible active enzymes for regiospecific synthesis of CQA may be a research hotpot in the future.

One important property of CQA molecules is the easy migration of cinnamoyl groups between different hydroxyl groups. For example, as mentioned above, for the synthesis of 3-, and 4-*O*-caffeoyl and feruloylquinic acids, the migration of caffeoyl groups and feruloyl groups occurred after deprotection.[53,54] This character of CQA molecules not only increases the difficulties for the synthesis and purification but also makes it difficult to achieve unambiguous conclusions about their biological activities. Thus, it is of great interest to us to discuss and get a better understanding of the stability of CQA molecules. In next section, our attention will be focused on the discussion of the relative stabilities of different CQA molecules, the migration of cinnamoyl groups including the discussion of possible mechanisms and the isomerization under different conditions.

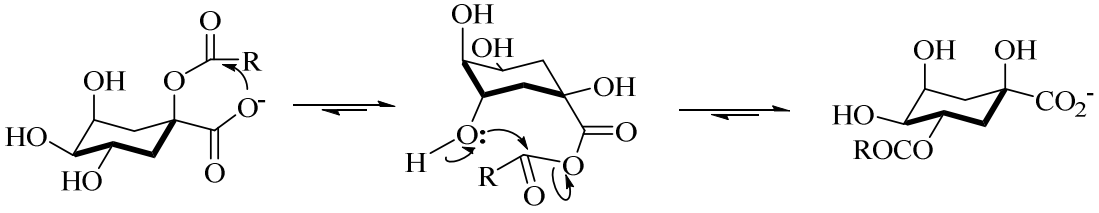
1.2.5 Stability of CQA molecules

CQA molecules suffer from a poor stability due to not only the instability of unprotected catechol groups but also the easy migration of cinnamoyl group between the hydroxyl groups at different positions.

As early as in 1964, Haslam *et al.* described the migration of *p*-coumaroyl group from the hydroxyl group at position 1 to the hydroxyl group at position 5 and between hydroxyl groups at positions 3, 4 and 5 on heating in $NaHCO_3$ solution and a mechanism

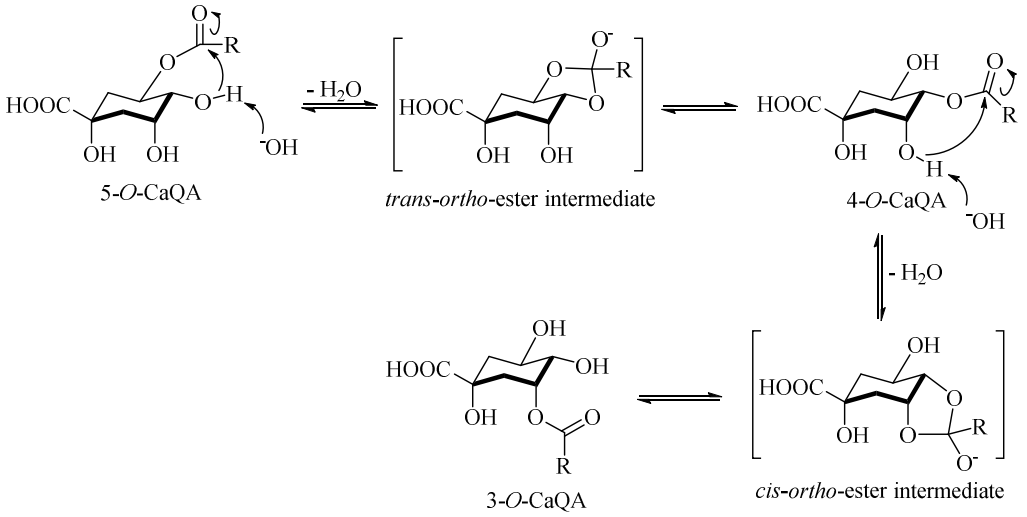
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for these rearrangement was discussed.[142] A suggested mechanism for the rearrangement from 1-*O*-*p*-coumaroylquinic acid to 5-*O*-*p*-coumaroylquinic acid was shown in **Scheme 26**.



Scheme 26 Proposed migration mechanism from 1-OH to 5-OH under basic conditions

In addition, on heating (90 ºC) in $NaHCO_3$ solution, facile migration of the *p*-coumaroyl group was observed in 3-, 4-, and 5-*O*-*p*-coumaroylquinic acid.[142] Migration of the acyl group in these cases was thought therefore to proceed in a stepwise fashion (3↔4↔5) and probably via the formation of the *trans*- or *cis*-*ortho*-ester intermediates as shown in **Scheme 27**.



Scheme 27 Mechanism of the acyl migration through *ortho*-ester intermediates

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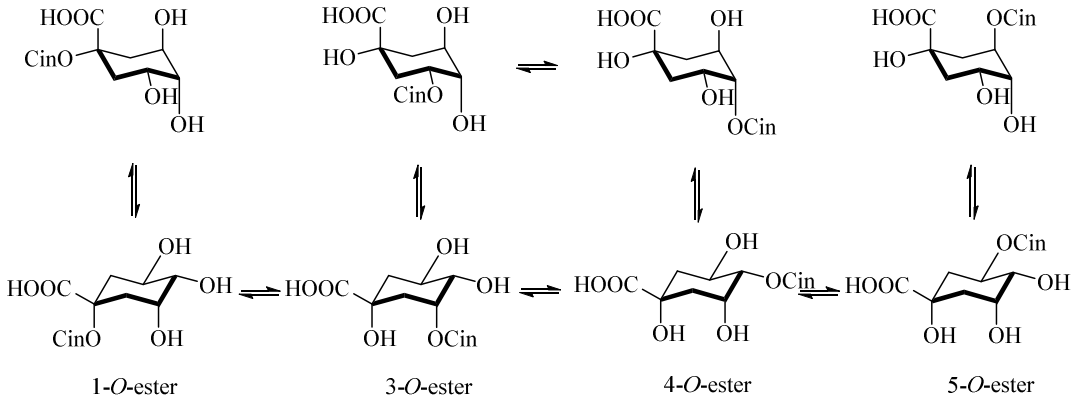
In 1964, Scarpati and Esposito[143] reported that a caffeoyl group does not migrate from the 1-position to an appreciable extent under the alkaline conditions as illustrated by Haslam *et al.* Rapid migration between the 3-, 4-, and 5-positions does, however, take place. Deulofeu and his associates also reported that the rate of alkali-catalyzed migration from the 1-position is relatively slow.[144]

In 1965, K. Hanson[123] discussed the migration between the 4 hydroxyl groups. The results of experiments with [U-^{14}C] quinic acid[145] established that the base-catalyzed migration of cinnamoyl groups of the CQA molecules is an intramolecular process. Three lines of evidence established that migrations occur in the sequence 1↔3↔4↔5. It is unlikely that a 1→5 migration (proposed by Haslam *et al*.[142]), by way of a cinnamic-quinic mixed anhydride (**Scheme 26**), contributes importantly to the migration process.

First, to get to know whether the isomerization caused by migration of acyl groups is an intermolecular process or intramolecular one, 1-*O*-cinnamoylquinide was treated with barium hydroxide in the presence of [U-^{14}C] quinic acid. No detectable radioactivity appeared in the several ester fractions, and all of the recovered activity was associated with the quinic acid fraction. Free quinic acid is thus not an intermediate and, since there is no reason why trace quantities of di-*O*-cinnamoylquinic acids should act as intermediates, the base-catalyzed process is intramolecular.

Then, the probability of two possible routes (1→3 or 1→5) for the migration from hydroxyl group at position 1 was discussed theoretically and evaluated by some well-designed experiments. Two routes (1→3 or 1→5) for the migration of the cinnamoyl group from the 1-position may be considered. The simplest hypothesis is to suppose that migration of the cinnamoyl group takes place in the sequence 1↔3↔4↔5(**Scheme 28**).

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Scheme 28 Possible migration of cinnamoyl group in the sequence 1↔3↔4↔5

If the several isomers exist in aqueous solution primarily as a mixture of two possible chair conformations in dynamic equilibrium,[146] then migration of the cinnamoyl group between the 1- and 3-positions, and also between the 4- and 5-positions, can take place only when the carboxyl group is equatorial. In all probability, the COOH-equatorial conformation is the more favored conformation in aqueous solution.

Theoretically stereochemical inspection into CQA molecules reveals that an *ortho*-ester bridge can be formed between the 1- and 3-positions, but only with distortion of bond angles. In the strainless ring (chair form) shown in formula B (**Figure 24**, R = styryl) the ionized oxygen of the *ortho* ester and the C-5 hydrogen are almost in the same position, which is impossible. In formula A, the strainless ring is in the chair conformation, and the ionized oxygen is 1.6 Å from the C-2 hydrogen, *i.e.*, the van der Waals' radii overlap by about 1.0 Å. The extent to which the radii overlap may be reduced by flattening and twisting the cyclohexane ring. The formation of *ortho* ester five-membered rings between the 3,4- and 4,5-positions of quinic acid also tends to deform the cyclohexane ring but to a smaller extent (less strain is involved in bridging cis-hydroxyl groups on a five-membered ring). Stereochemically, therefore, 1↔3 and 3↔4↔5 migrations are similar, but it is impossible to predict relative migration rates.

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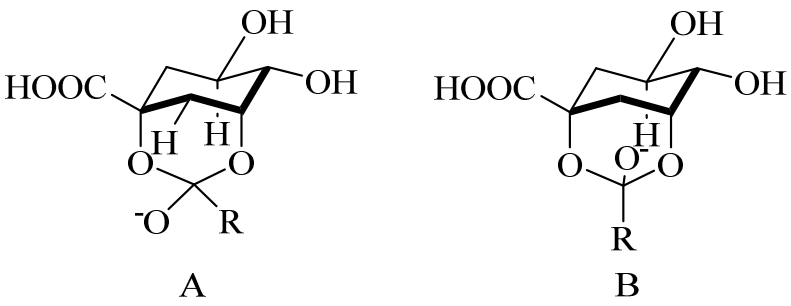


Figure 24 Structures of *ortho*-ester ions as intermediates in the 1↔3 migration

In order to distinguish experimentally between the 2 hypotheses (1→3 or 1→5), three studies were carried out:[123] (1) studies of migration when the carboxyl is methylated, which indicated that the rate of migration from the 1-position appeared to be somewhat faster for the methyl ester than the free acid; (2) studies of migration when the 3,4-hydroxyl groups are blocked by an isopropylidene group, after which no 5-*O*-cinnamoylquinic acid was observed; (3) studies of the rates of migration in buffered solutions (pH 6-10), which was designed to avoid the possible influence of introduction of an isopropylidene or a methyl group on the equilibrium between the 2 chair conformations of quinic acid and therefore on migration rates. Hanson detected that the rate of migration from or to the 1-position was very slow compared to the rates of 3↔4↔5 migration, which was entirely reasonable on steric grounds. The difference in the 1→3 and 3→1 rates may be interpreted in terms of a difference in the standard energies of the 2 isomers. The equilibrium would strongly favor the 3-isomer. Under conditions where the 3-, 4-, and 5-isomers were far from equilibrium, the amounts of these isomers from the 1-isomer were 3->4->5-. This result would be expected if the migration sequence is 1→3→4→5 and the rates of 3↔4↔5 migration are approximately equal. The rate of migration from the 1-position, like the rates of 3↔4↔5 migration, is pH dependent. If attack by the carboxylate ion on the C-1 substituent were rate-determining step, the rate of migration from 1-position would be pH independent.

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In conclusion, the mechanism of the 1→5 migration (proposed by Haslam *et al.*[142]), by way of a cinnamic-quinic mixed anhydride, is not improbable. As a contrast, the 1→3 migration way has a higher possibility.

In 1989, Clifford's group reported a simultaneous isomerization of 5-*O*-caffeoylquinic acid (5-*O*-CaQA) and four diCaQA with tetramethylammonium hydroxide (TMAH).[147] Each CQA substituent was checked by analytical HPLC.

Their studies showed that several interdependent reactions occurred when 5-*O*-caffeoylquinic acid was treated with TMAH. The main products were 3-*O*-caffeoylquinic acid, 4-*O*-caffeoylquinic acid, 5-*O*-caffeoylquinic acid and methyl caffeate. When mild conditions are employed (15s at 20 °C, 5 min at 0 °C) 5-*O*-CaQA remained the dominant product. With slightly harsher conditions (5 min, 20 °C) 3-*O*-CaQA, 4-*O*-CaQA, 5-*O*-CaQA and methyl caffeate are present in similar quantities, while forcing conditions (1 h 20 °C, 5 min 38 °C) produce methyl caffeate as the major product. Once the four products have been formed in similar quantities these ratios are maintained, but total yield declines due to instability in base.

Four of the six possible di-*O*-CaQA isomers (1,3-, 3,4-, 3,5- and 4,5-di-*O*-CaQA) from coffee beans were similarly examined. The di-*O*-CaQA isomers differed significantly in their susceptibility to acyl migration. 1,3-di-*O*-CaQA was the most resistant. Even after 10 minutes treatment of 1,3-di-*O*-CaQA at 20 °C, only the second most resistant isomer, 3,4-di-*O*-CaQA, was observed. The three di-*O*-CaQA isomers produced qualitatively identical mixtures but 3,5-di-*O*-CaQA and 4,5-di-*O*-CaQA were noticeably more susceptible to isomerization than 3,4-di-*O*-CaQA. It was proved impossible to detect either 1,4- or 1,5-di-*O*-CaQA in any of the reaction mixtures.

By integrating these results with those obtained for the mono-*O*-CaQA isomers, it appeared that CaQA bearing axial substituents (1 and/or 3) in the main chair conformation are rather more resistant to acyl migration and/or transesterification than

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those bearing equatorial substituents (4 and/or 5), with the axial-equatorial 3,4-di-*O*-CaQA and 3,5-di-*O*-CaQA being intermediate.

In 2001, J. Slanina reported a new and facile preparation of 1,3-di-*O*-caffeoylquinic acid (1,3-di-*O*-CaQA) from a fraction of the leaves *Cynara cardunculus* rich in 1,5-di-*O*-caffeoylquinic acid (1,5-di-*O*-CaQA).[148] The dried leaves of *Cynara cardunculus* were extracted with methanol. After treatment, the fraction rich in 1,5-di-*O*-CaQA was dissolved in water, made alkaline with dilute aqueous ammonia until the yellow colour of phenoxide was observed and the solution kept at 100 °C for 2 h. Under these conditions 1,5-di-*O*-CaQA was smoothly converted to the significantly more polar 1,3-di-*O*-CaQA. The reaction mixture was then acidified to pH 4 and extracted twice with diethyl ether. The organic layer contained unreacted 1,5-di-*O*-CaQA and compounds with similar polarity as 1,5-di-*O*-CaQA, whereas 1,3-di-*O*-CaQA, owing to its higher polarity, remained in the aqueous phase. Compound 1,3-di-*O*-CaQA was obtained after concentration and recrystallization.

In 2010, the thermal stability of 3-*O*-CaQA (named 5-*O*-CaQA in the literature using preIUPAC numbering system) was investigated by A. Dawidowicz *et al.*[149] During heating with water, under both reflux and higher pressure, as many as 9 compounds (CQA derivatives and their reaction products with water) were observed by LC-MS from 3-*O*-CaQA. The amount of each formed component depended on the heating time and temperature. Later in 2011[150], the same author reported the influence of pH on the thermal stability of 5-*O*-CaQA (the recommended IUPAC name) in aqueous solutions. It has been found by LC-MS that as many as 14 compounds (CQA derivatives and their reaction products with water) were formed from 5-*O*-CaQA. The amount of each formed component depends on the heating time and pH. The results proved not only the isomerization but also other transformations such as esterification, hydrolysis, and reaction with water of CQA molecules during the water extraction or under certain pH conditions. These products can be mistakenly treated as new components, or can result in erroneous quantitative estimations of plant compositions.

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In 2014, Kuhnert studied the acyl migration in mono- and di-*O*-caffeoylquinic acids under aqueous basic, aqueous acidic and dry roasting conditions.[151] Under all three conditions, acyl migration was observed, however only dominating as a pathway under aqueous basic conditions. Under aqueous acidic and dry roasting conditions acyl migration products were in contrast observed as minor products.

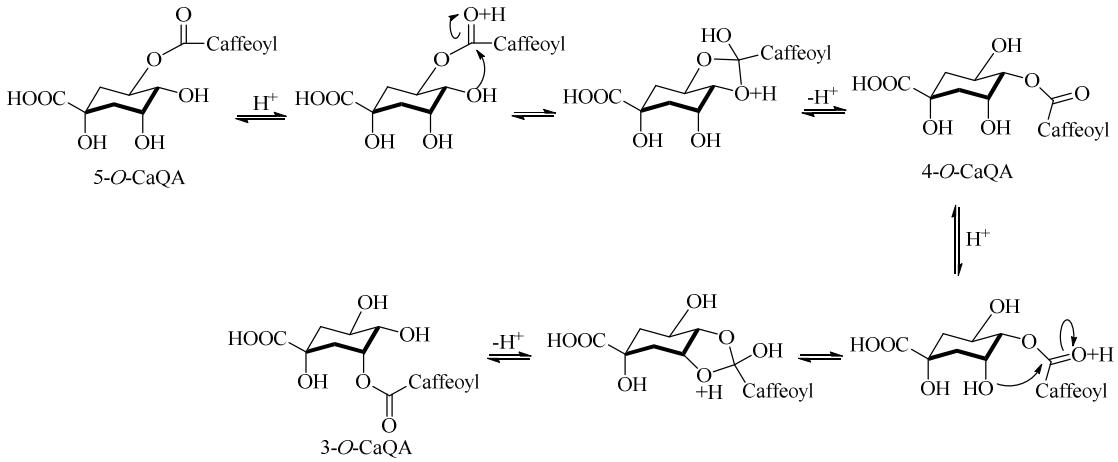
Recently, Xiao *et al*. investigated the thermal stability of 3-*O*-CaQA, 4-*O*-CaQA, 5-*O*-CaQA, 3,4-di-*O*-CaQA, 3,5-di-*O*-CaQA and 4,5-di-*O*-CaQA in water by heating an aqueous solution of each compound in the boiling water for 0-6 hours.[152]

Three mono-*O*-CaQAs have different degradation rates. The order of transformation extent is 4-*O*-CaQA > 3-*O*-CaQA > 5-*O*-CaQA at any time during heated for 6 h in the boiling water bath. Therefore, the order of thermal stability is 5-*O*-CaQA > 3-*O*-CaQA > 4-*O*-CaQA for mono-*O*-CaQAs. It could be concluded that the order of the stability is 5 > 3 > 4 in terms of the hydrolysis of the caffeoyl ester under the condition of heating each compound aqueous solution in the boiling water bath. When the mono-*O*-CaQAs were treated with aqueous tetramethylammonium hydroxide (pH 12) at room temperature, the order of the stability is 5 > 4 > 3 in terms of the hydrolysis of the caffeoyl ester.[151] When the mono-*O*-CaQAs were heated at 180 °C for 12 min, only 4-*O*-CaQA was detected the transformation products.[151] It could be presumed that 4-*O*-CaQA is the most susceptible compound under the heated conditions in the aqueous solution. But 3-*O*-CaQA is the most susceptible compound under the basic conditions.[151] According to the literature, 5-*O*-CaQA is the most abundant CQA in some traditional Chinese medicines, such as *Lonicera japonica* Thumb., *Lonicera macranthoides* Hand.Mazz, *Lonicera hypoglauca* Miq., *Lonicera confusa* DC. and *Lonicera fulvotomentosa* Hsu et S.C. Cheng.[153] All these phenomena might be related to the higher stability of 5-*O*-CaQA.

For di-*O*-CQA, the order of thermal stability is 4,5-*O*-di-CaQA > 3,5-*O*-di-CaQA > 3,4-*O*-diCaQA during heated in the boiling water bath. Compared the transformation extent of mono-*O*-CaQAs and di-*O*-CaQAs, it is deduced that mono-*O*-CaQAs are more

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stable than di-*O*-CaQAs under heating condition. It could be concluded that the mechanism of 5-*O*-CQA ⇋ 4-*O*CQA ⇋ 3-*O*-CQA is acyl migration, and the representative mechanism is displayed in **Scheme 29**. The mechanism of 4,5-*O*-di-CaQA ⇋ 3,5-*O*-di-CaQA ⇋ 3,4-*O*-di-CaQA is similar to that of mono-*O*-CaQAs.



Scheme 29 Mechanism of the acyl migration in boiling water bath

The easy migration of cinnamoyl groups in CQA molecules causes troubles for chemists and biologists in their research. However, this aptitude of CQA molecules can also give benefits. For example, as mentioned above in Brummond's synthesis of 1,3,5-tri-*O*-caffeoylquinic acid (**Scheme 16**),[114] the migration of cinnamoyl group with Me_3SnOH in refluxing 1,2-dichloroethane lead the undesired 1,4,5-triester into the desired 1,3,5-triester. Slanina's facile preparation of 1,3-di-*O*-caffeoylquinic acid from 1,5-di-*O*-caffeoylquinic acid was based on the migration of caffeoyl group from position from position 5 to position 3 and that these two diesters have different polarity and, therefore, different solubilities in aqueous or organic solvents.[148]

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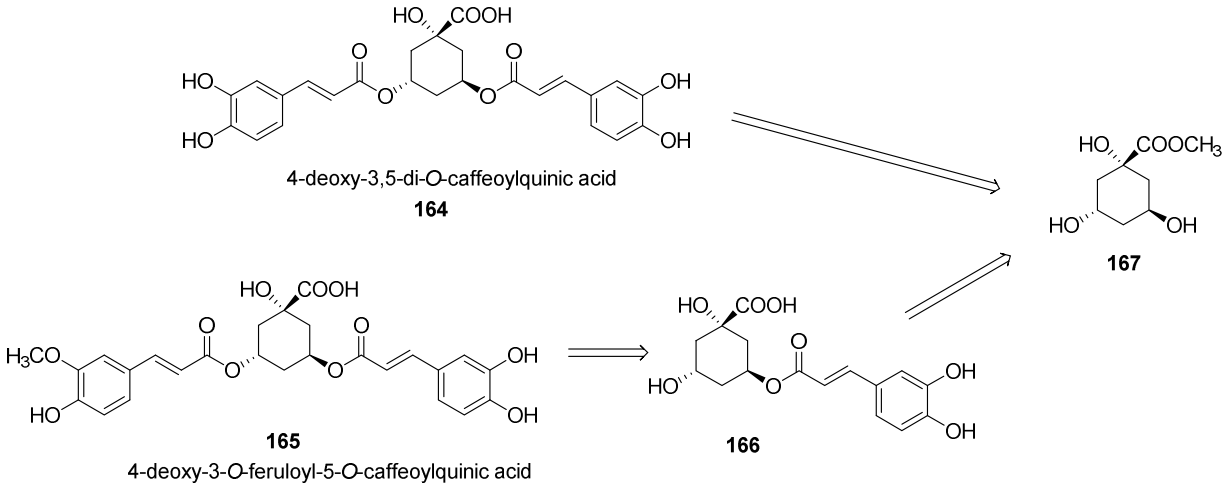
1.3 Conclusions

The use of conventional pesticides, especially the synthetic chemical pesticides, has greatly reduced the crop losses and gained a commercial success. However, the excessive use of chemical pesticides lacking toxic specificity has caused a series of environmental and public health problems. The research and commercialization trend toward new eco-friendly biopesticides with novel modes of actions will aim at finding a better balance between the efficiency of pesticide and reducing possible harms to environment and humans. Botanicals are an important source of biopesticides. CQA, isolated from various plants and found to exhibit *in vivo* and *in vitro* a wide spectrum of biological activities, have attracted our attention with potential as biopesticides. The investigation of the toxicity of CQA including the working mechanism and structure-activity relationships requires the preparation of different CQA derivatives and analogs. The existing chemical synthetic methodologies needs a tedious protection and deprotection process, which is manipulatively difficult and give unsatisfactory overall yields. The alternative enzymatic synthesis relies on the discovery of more enzymes appropriate for CQA synthesis. In addition, as an important drawback of CQA molecules, the migration of cinnamoyl groups between hydroxyl groups at different positions increased the difficulties for their synthesis and purification and to draw conclusions about the biological activity of each isomer.

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1.4 Thesis project

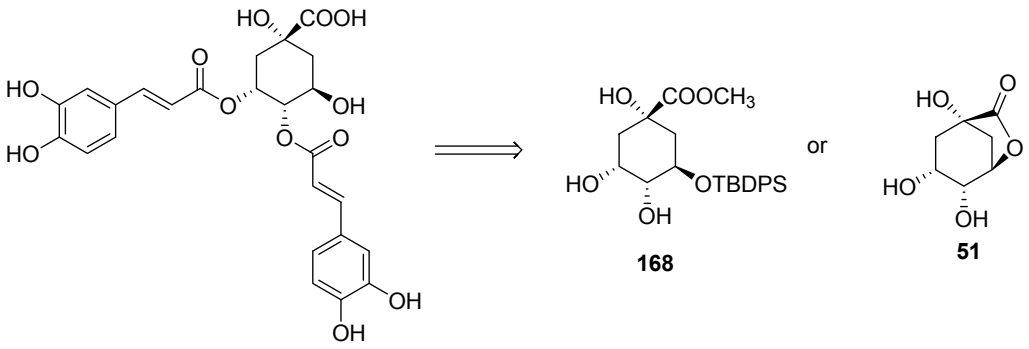
With purposes of getting insight into the pharmacophoric centers of CQA molecules, into the mode of action of the insecticidal activities of CQA, into the structure-toxicity relationships and, furthermore, help to design new compounds with potential higher activities, a serious of CQA derivatives and analogs were synthesized. Firstly, in order to address the problems of isomerization between 3,5-, 3,4- and 4,5-di-*O*-CaQA under bioassay conditions[49] or even basic conditions,[151] we speculated that the 4-deoxy CQA derivatives would prevent the easy migration of cinnamoyl groups. Our retrosynthetic analysis was inspired by both the methodologies of CQA synthesis and the reported possible modifications on quinic acid core. As illustrated in **Scheme 30**, the synthesis of 4-deoxy-3,5-diester (both homodiesters and heterodiesters) was based on a key intermediate triol **167**.



Scheme 30 Retrosynthetic analysis for 4-deoxy-3,5-di-*O*-homo or heterocinnamoylquinic acid

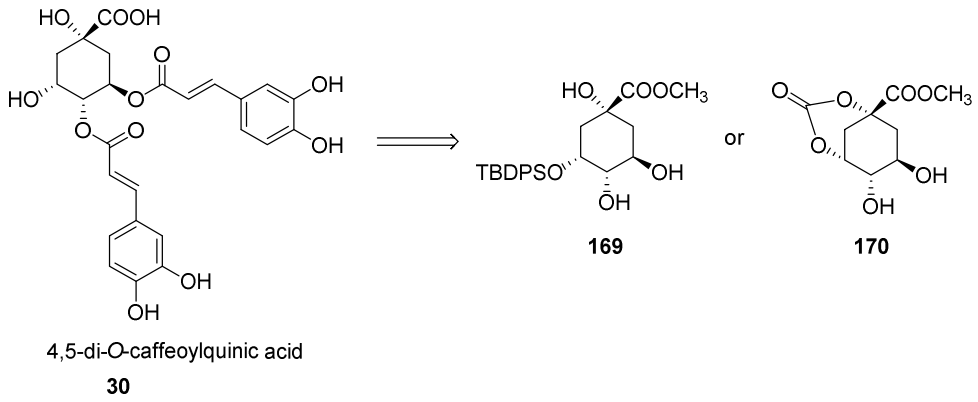
In parallel, we also synthesized natural 3,4-di-*O*-esters and 4,5-di-*O*-esters. For the attempts towards 3,4-di-*O*-CQA, two precursors including 5-*O*-TBDPS substituted intermediate triol **168** and quinide **51** were prepared and investigated.

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Scheme 31 Retrosynthetic analysis for 3,4-di-*O*-caffeoylquinic acid

For 4,5-di-*O*-CQA, two intermediates including 3-*O*-TBDPS substituted intermediate triol **169** and a carbonate diol **170** were prepared and investigated.



Scheme 32 Retrosynthetic analysis for 4,5-di-*O*-caffeoylquinic acid

The following chapters will focus on the results and discussions of this thesis.

(a) In chapter 2, the details about 4-deoxy-3,5-di-*O*-CQA derivatives including the synthesis of intermediate triol **167**, the optimization of coupling conditions, the

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choice of deprotection protocols, the characterization of new compounds, and the results of insecticidal tests would be given.

(b) In Chapter 3, the investigations towards 3,4- and 4,5-di-*O*-CQA involve also the preparation of intermediates, the optimization of coupling reactions, the assays to find appropriate deprotection procedures, and the characterization of new compounds.

(c) In Chapter 4, the experimental section, the detailed experimental procedures and the characterization of all new compounds studied will be given.

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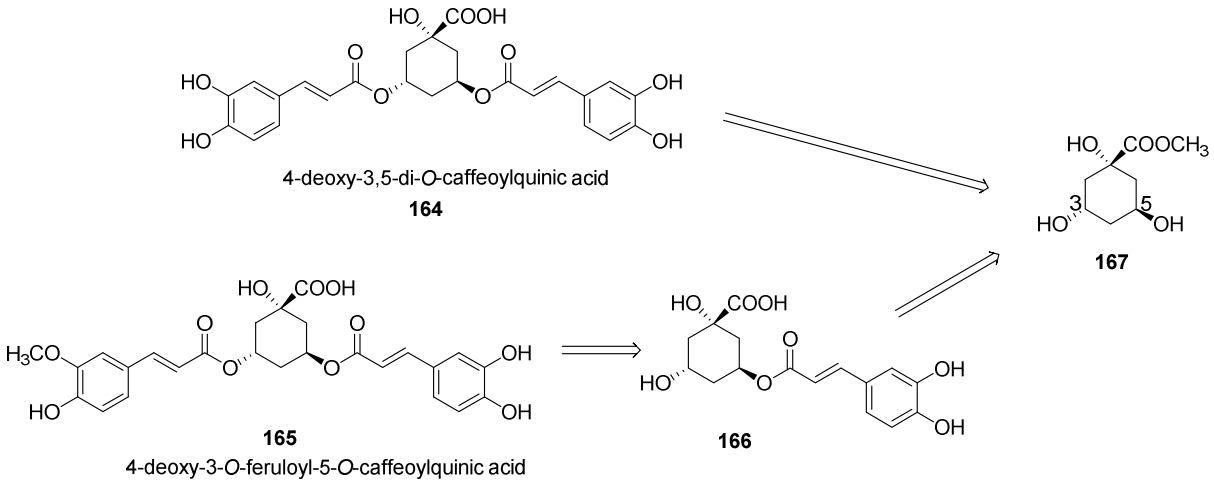
Chapter 2 Synthesis of CQA analogs based on a 4-deoxy intermediate

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2.1 Introduction

The retrosynthetic analysis of 4-deoxy-3,5-di-*O*-homo or heterocinnamoylquinic acids deduces a new key intermediate 4-deoxy methyl quinate **167**.



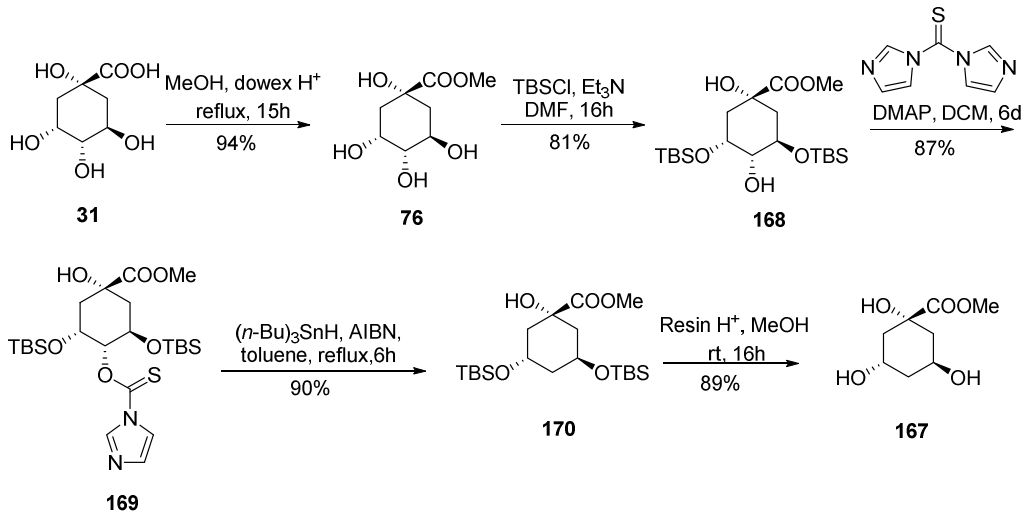
Scheme 30 Retrosynthetic analysis for 4-deoxy-3,5-di-*O*-homo or heterocinnamoylquinic acids

In this part, our attention was focused on the synthesis of 4-deoxy CQA analogs including both homodiesters and heterodiesters. First, a screening of coupling reactions from a new triol **167** will be reported. Then, both homodiesters and heterodiesters were obtained *via* bis coupling reactions or two-step coupling reactions with different cinnamoyl chlorides followed by the deprotection reactions providing the final 4-deoxy CQA analogs. The bioassays of selected compounds will also be introduced.

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2.2 Preparation of 4-deoxy methyl quinate

The synthesis of 4-deoxy methyl quinate **167** was based on the preparation of a known intermediate **170**.[154,155,156]



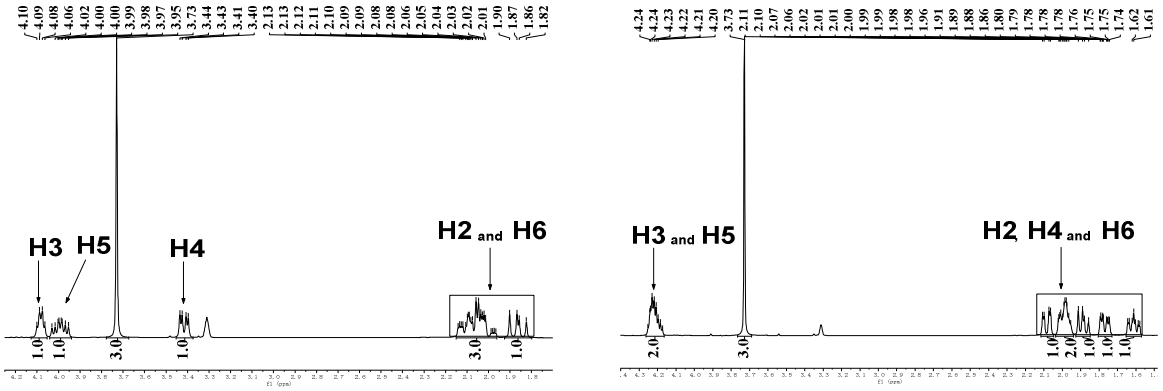
Scheme 33 Synthesis of a key intermediate 4-deoxy triol 167

First, the methyl esterification of quinic acid **31** gave methyl quinate **76** in 94% yield after recrystallization in methanol/petroleum ether. The protection of hydroxyl groups at positions 3 and 5 was fulfilled by regioselective bis silylation of methyl quinate **76** with 2.5 equivalents of *tert*-butyldimethylsilyl chloride (TBSCl) with Et_3N in DMF providing silyl ether **168** in 81% yield. For the reduction of hydroxyl group at position 4, Barton-McCombie's procedure for the free radical deoxygenation of secondary alcohols was applied.[157] Silyl ether **168** was firstly converted into the thioimidazolide **169** in 87% yield with 1.6 equivalents of 1,1'-thiocarbonyl-diimidazole (TCDI) and DMAP (10 %) in CH_2Cl_2 at high concentration for 6 days. The following free radical deoxygenation with tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) gave the 4-deoxy silyl ether **170** in 90% yield. Acidic

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hydrolysis into **167** was performed in the presence of a heterogeneous H^+ resin in methanol with an isolated 89% yield (**Scheme 33**). Thus, the new key intermediate 4-deoxy methyl quinate **167** was prepared in 53% yield in 5 steps from quinic acid **31**. Lucie Grand and Thomas Pouleriguen first prepared the intermediate **167**, which was scaled up to grams in my hands for following coupling reactions.

The triol **167** was fully characterized. The comparison of the ^{1}H NMR (in MeOD) of the initial methyl quinate **76**[158] bearing the hydroxyl group at position 4 and that of the 4-deoxy methyl quinate **167** is shown in **Figure 25**.



a ^{1}H NMR of methyl quinate **76** in MeOD **b** ^{1}H NMR of 4-deoxy methyl quinate **167** in MeOD

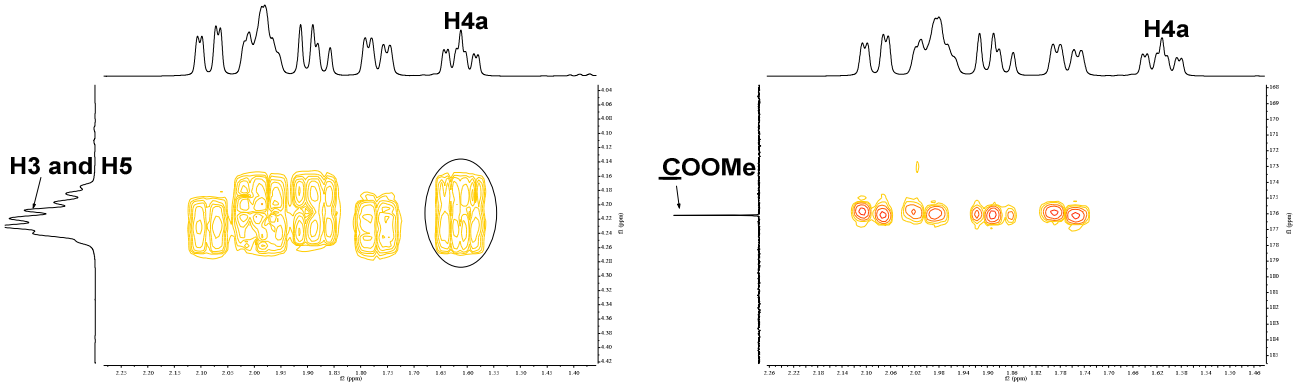
Figure 25

In the high-field region, the assignment of methylene proton signals for methyl quinate **76** is blurred due to the severe signal overlap within a narrow spectral region (1.6-2.2 ppm) and the multiple spin coupling. The same difficulties exist for the assignment of methylene protons of 4-deoxy methyl quinate **167**. Nevertheless, the value of integration for methylene protons has changed from 4 to 6, indicating the generation of a new methylene. In addition, the signals for secondary protons at positions 3 and 5 of methyl quinate **76** in **Figure 25a** were "combined" to an overlapped

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multiplet signal at 4.16-4.24 ppm in **Figure 25b**. The signal for secondary proton H4 at 3.42 ppm in **Figure 25a** has disappeared in **Figure 25b**.

With the help of 2D ^{1}H-^{1}H COSY (**Figure 26a**) and ^{1}H-^{13}C HMBC NMR (**Figure 26b**), the assignment of only one methylene proton H4a (the ddd signal at 1.60 ppm) was achieved, which is supported by the observation of its interactions with both secondary protons H3 and H5 in ^{1}H-^{1}H COSY, the lack of correlation signal with the ester carbon in ^{1}H-^{13}C HMBC, and the coupling constants ^{2}J 12.7 Hz, $^{3}J_{\text{H4a-H5a or H3a}}$ 9.2 Hz, $^{3}J_{\text{H4a-H5e or H3e}}$ 3.0 Hz.



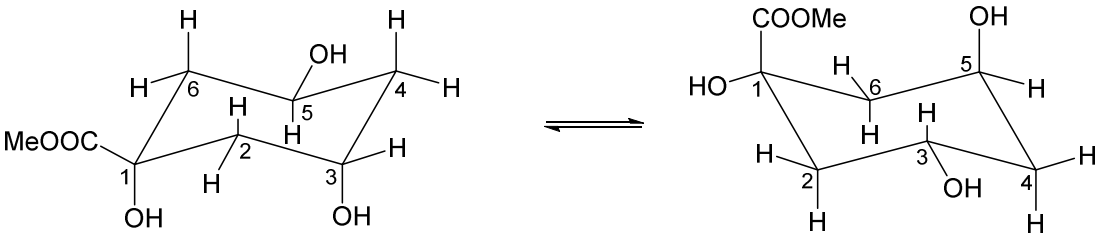
a ^{1}H-^{1}H COSY of **167** in MeOD

b ^{1}H-^{13}C HMBC of **167** in MeOD

Figure 26

In addition, the large *trans*-diaxial coupling constant of H4a (9.2 Hz) points to preferred chair conformations (as shown in **Scheme 34**). The structure makes the interaction possible between the signals assigned to H3 and H5. So it is difficult to conclude on a predominant conformer. We can note that previous structure on methyl quinate proved that the conformer featuring an equatorial carboxylic methyl ester group is favored.

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Scheme 34 The interconvertible chair conformations of 167

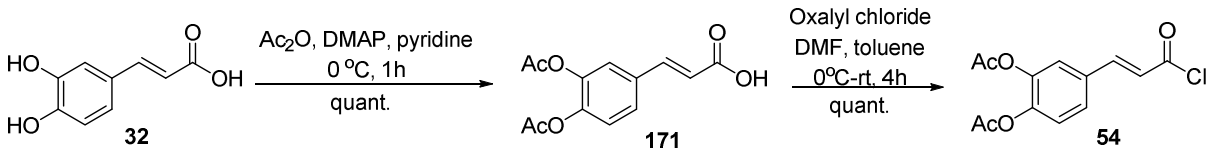
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2.3 Synthesis of 4-deoxy-3,5-homodicinnamoyl methyl ester and quinic acid analogs and bioassays

2.3.1 Screening of coupling conditions

As seen in Chapter 1, the coupling conditions with protected cinnamoyl chloride vary greatly for different substrates. The reported solvent systems include benzene/pyridine,[118,112,113] DCM/pyridine,[52,53,121,54] pyridine,[53,114] DCM/Et_3N,[122] and DCE/pyridine.[114] Besides, the coupling conditions vary in different temperatures (from -10 °C,[53] room temperature[52,53,122], 60 °C[114] to reflux in benzene/pyridine[118,113]) and reaction time (from 4 hours[53] to 3 days[122]), and DMAP was used as a catalyst in some coupling reactions[52,53,114] but not in others.[118,112]

Lucie Grand worked on the preliminary screening of the reported coupling conditions of triol **167** with acetylated caffeoyl chloride **54**, which was prepared two steps from caffeic acid with known procedures.[52]



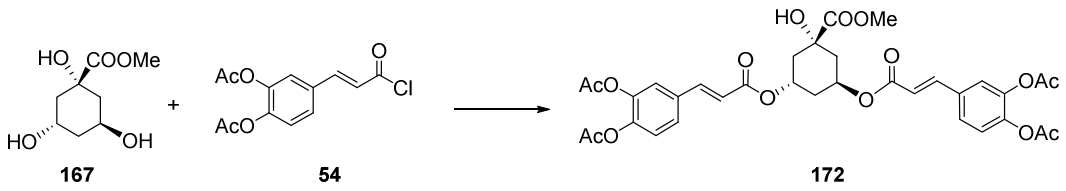
Scheme 35 Preparation of acetylated caffeoyl chloride 54

With 3 equivalents of acid chloride **54** in pyridine at room temperature for 4 days (entry 1), the complete conversion of triol **167** was observed but diester **172** was isolated in less than 7% yield (mixed with uncharacterized impurities). When the reaction was performed in a more diluted solution (0.05 M) and at a higher temperature (40 °C), 5 equivalents of acid chloride was needed for the total conversion of triol **167**, which

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resulted into a more complex reaction crude and no pure diester **172** was obtained (entry 2). The use of DCE/pyridine/DMAP system at room temperature did not afford pure diester **172** (entry 3). In DCM/pyridine/DMAP system at room temperature, 6 equivalents of acid chloride and 7 days were needed for a complete conversion of triol **167**, but only 40% yield of diester **172** was obtained (entry 4). The result of coupling reaction using DCM/pyridine system with DMAP at room temperature (entry 4) was, unfortunately, not reproducible in repeated experiments.

Table 1 Preliminary screening of coupling conditions from 4-deoxy methyl quinate 167



167 **54** **172**

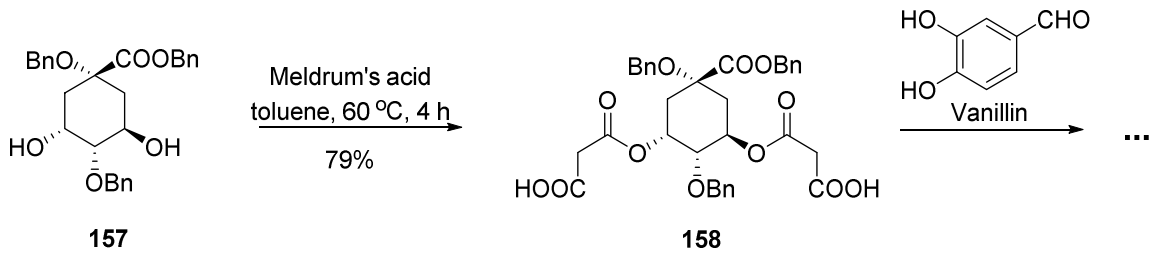
Entry	Molar equiv. of **54**	Catalyst[a]	Solvent	Concentration (M)	Temp.	Time	Yield[b]
1	3	DMAP	Pyridine	0.7	rt	4 d	<7%
2	5	DMAP	Pyridine	0.05	40°C	5 h	nd[c]
3	4	DMAP	DCE/Pyridine	0.15	rt	2 d	nd[d]
4	6	DMAP	DCM/Pyridine	0.05	rt	7 d	40%

[a] DMAP (20%); [b] Isolated yield of **172**; [c] A monoester was detected but not quantified; [d] No pure product was obtained.

The unsatisfactory results of the preliminary screening of coupling conditions with acid chloride encouraged us to investigate other procedures. Barron's methodology[137,138] involving a Knoevenagel condensation was tested on the key intermediate **167**. The free

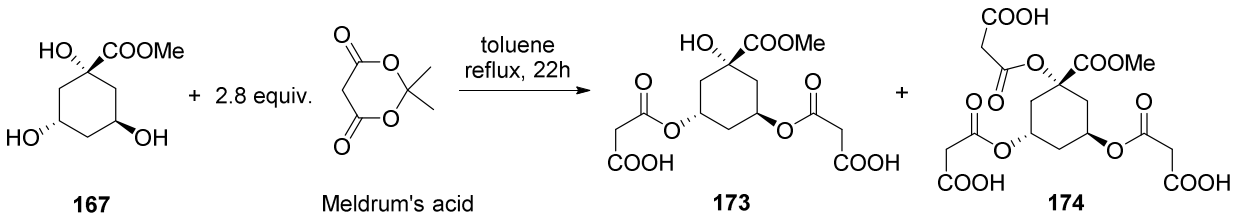
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hydroxyl groups need to be converted into malonyl derivatives with Meldrum's acid. For example in Barron's report for the synthesis of 3,5-di-*O*-caffeoylquinic acid, diol **157** was converted into **158** before the Knoevenagel condensation with vanillin (**Scheme 36**).[138]



Scheme 36 Reported esterification of diol 157 with Meldrum's acid

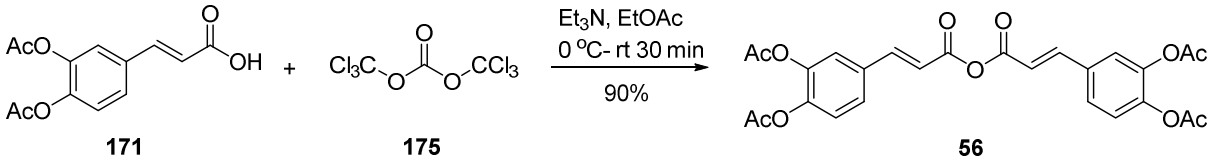
The esterification of 4-deoxy methyl quinate **167** with Meldrum's acid in our hands turned to be unsatisfactory. The reaction was performed in toluene at reflux for 22 hours, the generation of diester **173** and triester **174** was detected by mass analysis of the crude indicating the lack of esterification selectivity of free hydroxyl groups. The purification of the crude was difficult due to the high polarity of malonyl derivatives bearing carboxylic groups and no pure products (diester **173** or triester **174**) were isolated. Thus, this methodology was abandoned and our efforts were then focused on the investigation of other methodologies.



Scheme 37 Esterification of triol 167 with Meldrum's acid

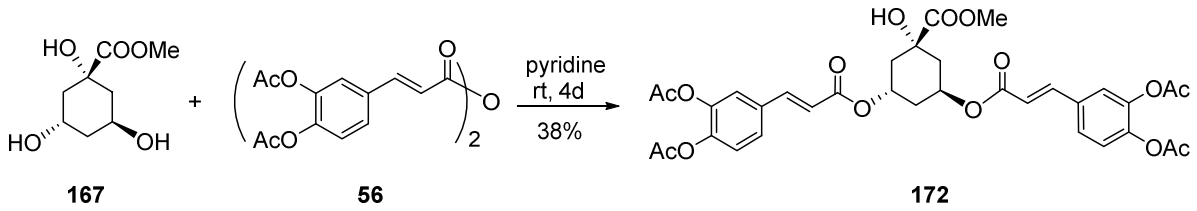
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Another caffeoyl-donor anhydride **56** was also prepared with known procedures.[159,115] This anhydride is stable at room temperature for at least 3 months without any noticeable degradation (^{1}H NMR).[159]



Scheme 38 Preparation of caffeic acid anhydride tetraacetate 56

Using anhydride **56**[159,115] in pyridine at room temperature for 4 days, diester **172** was isolated in only 38% yield. Analysis of the crude mixtures concluded to an incomplete conversion of triol **167** and single esterification of a secondary alcohol.



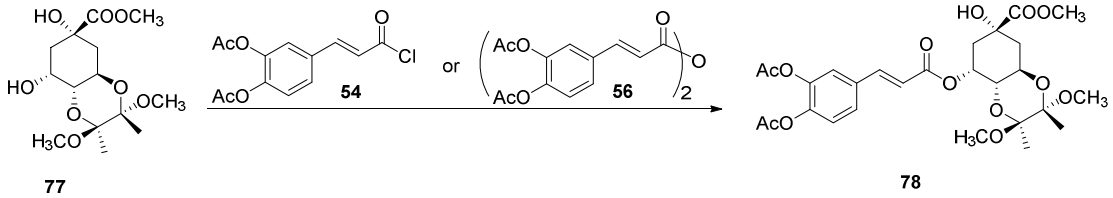
Scheme 39 Esterification of triol 167 with anhydride 56

In order to reproduce the results reported in the literature,[53] the intermediate **77** was synthesized in one step from quinic acid in 80% yield with trimethyl orthoformate, 2,3-butanedione and camphorsulfonic acid in refluxing methanol.[160,161] In Sefkow's procedure for the synthesis of 3-*O*-caffeoylquinic acid,[53] compound **77** was converted into ester **78** in 88% yield with 1.2 equivalents of acid chloride **54** in DCM/pyridine/DMAP system at room temperature after 24 hours. The same reaction in

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our hands (Table 2, entry 1), however, gave different results. Little conversion of starting material **77** was observed after 80 hours (Table 2, entry 1).

Table 2 The screening of coupling conditions with 77



Entry	Acylation agent (Molar equiv.)	Catalyst[a]	Solvent	Conc. (M)	Temp.	Time	Yield[b]
1	**54** (1.5)	DMAP	DCM/Pyridine[c]	0.2	rt	80 h	nd[f]
2	**56** (1.3)		Pyridine	0.17	rt	60 h	nd[f]
3	**54** (1.5)	DMAP	DCM/Et_3N[d]	0.05	0 °C~rt	3 h	56%
4	**54** (2.2)		DMF/Pyridine[e]	0.4	45 °C	1 h	83%

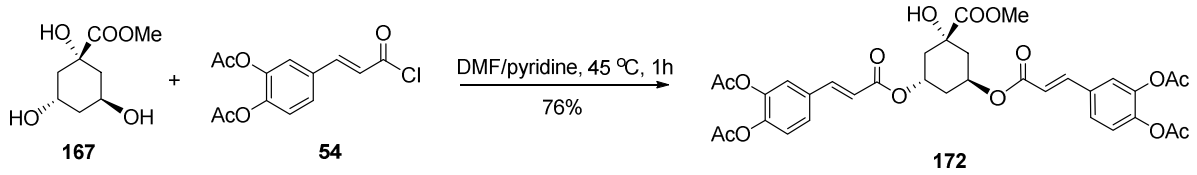
[a] DMAP (20%); [b] Isolated yield of **78**; [c] DCM/pyridine (v:v) = 5/1; [d] DCM/Et_3N (v:v) = 20/1; [e] DMF/pyridine (v:v) = 3/2; [f] Little conversion of **77** was observed and no pure product was obtained.

The intermediate **77** was then reacted with 1.3 equivalents of anhydride **56** at room temperature, after 60 hours stirring, little conversion of starting material **77** was observed (Table 2, entry 2). When the DCM/Et_3N/DMAP system was applied (Table 2, entry 3), ester **78** was isolated in 56% yield after 3 hours (1.5 equivalents of acid chloride **54** was added by portions at 0 °C and the reaction mixture was allowed to warm to room temperature). Another solvent system DMF/pyridine[162] was first introduced for the

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synthesis of CQA derivatives. As illustrated in entry 4, compound **77** was converted into ester **78** in 83% yield with 2.2 equivalents of acid chloride **54** in DMF/pyridine after 1 hour stirring at 45 °C. Then we decided to study the coupling reactions from triol **167** using the new DMF/pyridine solvent system.

The coupling reactions of triol **167** with 3 equivalents of acid chloride **54** was then performed in DMF/pyridine at 45 °C for 1h, the diester **172** was isolated in 76% yield.

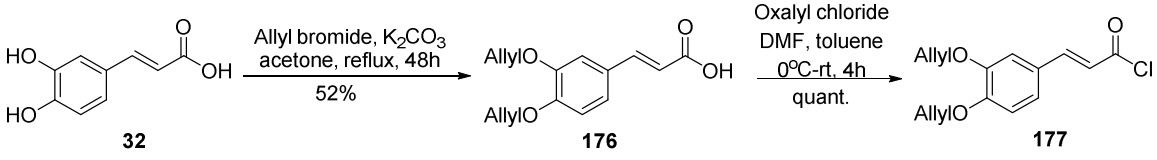


Scheme 40 Coupling of triol 167 with acid chloride 54 under DMF/pyridine system

2.3.2 Synthesis of 4-deoxy-3,5-di-*O*-homoesters

In order to prepare various 4-deoxy-3,5-di-*O*-cinnamoylquinic acid derivatives, triol **167** was reacted with different acid chlorides including acetyl protected caffeoyl chloride **54**, feruloyl chloride **178**, *p*-coumaroyl chloride **179** and *o*-coumaroyl chloride **180** and allyl protected caffeoyl chloride **177**.

The allyl protected caffeoyl chloride **177** was prepared[128] since both acid or base induced removal of acetate groups sometimes leads to incomplete or non-selective deprotection with competing hydrolysis of the cinnamate quinic acid ester bonds.[163,164]



Scheme 41 Preparation of allyl protected caffeoyl chloride 177

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The acetyl protected feruloyl chloride **178**, *p*-coumaroyl chloride **179** and *o*-coumaroyl chloride **180** were prepared using the same methods as mentioned above for the synthesis of acetyl protected caffeoyl chloride **54**.

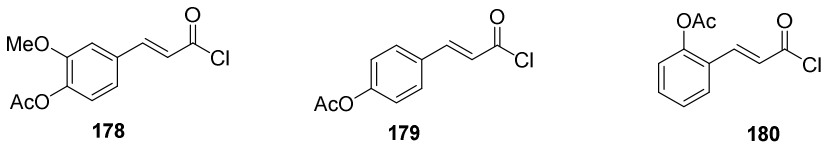


Figure 27 Structures of three acetyl protected cinnamoyl chlorides

Then, the diesterification reactions of 4-deoxy methyl quinate **167** with 3 equivalents of different protected cinnamoyl chlorides were performed first in DMF/pyridine at 45 °C (see **Table 3**) then at 0 °C to room temperature (see **Table 4**, entries 1-3), the conventional DCM/pyridine/DMAP system was also used at a low temperature (0 °C or -18 °C to room temperature). Corresponding 4-deoxy-3,5-di-*O*-caffeoylesters **172** and **181**, 4-deoxy-3,5-di-*O*-feruloylester **182**, 4-deoxy-3,5-di-*O*-*p*-coumaroylester **183**, and 4-deoxy-3,5-di-*O*-*o*-coumaroylester **184** were obtained in fair to good yields.

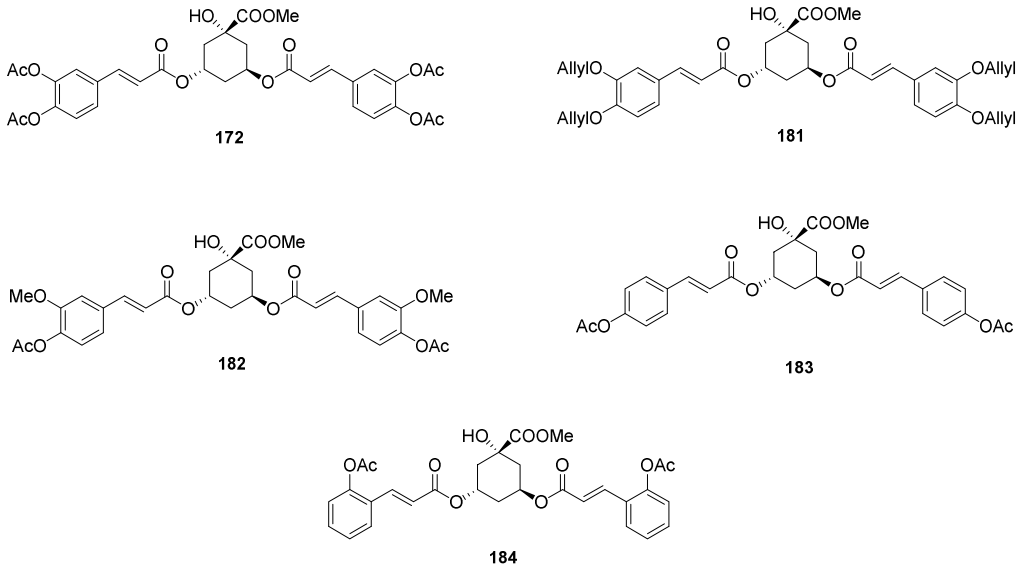


Figure 28 Structures of five 4-deoxy-3,5-di-*O*-cinnamoylquinic acid analogs

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First, the coupling reactions were performed with 3 equivalents of acid chlorides under DMF/pyridine system at 45 °C (as shown in **Table 3**), the reactions were completed within 1 hour (1h 30 in entry 2) providing corresponding diesters in fair to good yields (55% - 82%).

Table 3 Diesterification of 4-deoxy methyl quinate 167 under DMF/pyridine system at 45 °C

Entry	Acylating agent (molar equiv.)	Solvent[a]	Conc. (M)	Temp. (°C)	Time	Product	Yield[b]
1	**54**(3)	DMF/Pyridine	0.4	45	1h	**172**	76%
2	**177**(3)	DMF/Pyridine	0.4	45	1h30	**181**	59%
3	**178**(3)	DMF/Pyridine	0.4	45	1h	**182**	55%
4	**179**(3)	DMF/Pyridine	0.4	45	1h	**183**	82%[c]
5	**180**(3)	DMF/Pyridine	0.4	45	1h	**184**	62%

[a] DMF/pyridine (v:v) = 3/2; [c] Isolated yields; [c] A triester was isolated in 7% yield.

Then we decided to carry out the coupling reactions at low temperatures betting for better yields of 4-deoxy-3,5-di-*O*-caffeoylesters **172**, 4-deoxy-3,5-di-*O*-feruloylester **182**, and 4-deoxy-3,5-di-*O*-*p*-coumaroylester **183**. When the reactions were performed at 0 °C to room temperature, complete conversions of triol **167** were observed within four hours, and better or comparable yields of these three diestes were obtained (**Table 4**, entries 1-3). As mentioned above (in **Table 1**, entry 4), the use of classical DCM/Pyridine/DMAP system, in which reactions are usually reported at room[52,132,55,54] or higher temperature,[113,112,128] gave unrepeatable results in our hands. However, when

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the reaction was started at a lower temperature (- 18 °C or 0 °C), the diesterification reactions of triol **167** proceeded well in DCM/pyridine/DMAP system and corresponding diesters **172**, **182**, and **183** were isolated in 92%, 69%, and 64% yields, respectively (**Table 4**, entries 4-6). In all cases, an easier purification could be gained when these conditions were started at a lower temperature (- 18 °C or 0 °C).

Table 4 Diesterification of 4-deoxy methyl quinate 167 at low temperatures

Entry	Acylating agent (molar equiv.)	Catalyst[a]	Solvent[b]	Conc.(M)	Temp.	Time	Product	Yield[c]
1	**54**(3)		DMF/Pyridine	0.4	0°C to rt	4h	**172**	90%
2	**178**(3)		DMF/Pyridine	0.4	0°C to rt	4h	**182**	69%
3	**179**(3)		DMF/Pyridine	0.4	0°C to rt	4h	**183**	75%
4	**54**(3)	DMAP	DCM/Pyridine	0.1	-18°C to rt	4h	**172**	92%
5	**178**(3)	DMAP	DCM/Pyridine	0.1	-18°C to rt	4h	**182**	69%
6	**179**(3)	DMAP	DCM/Pyridine	0.1	0°C to rt	4h	**183**	<64%[d]

[a] DMAP (20%); [b] DMF/pyridine (v:v) = 3/2, and DCM/pyridine (v:v) = 5/1; [c] Isolated yields; [d] Product was contaminated with polar caffeic acid derivative.

These five homodiesters (**172** and **181-184**) were fully characterized. Taking 4-deoxy-3,5-di-*O*-feruloylester **182** as an example, the ^{1}H (**Figure 29**) and ^{13}C NMR spectra (**Figure 30**) in $CDCl_3$ demonstrate the formation of two ester groups. For the ^{1}H NMR spectrum (400M Hz, $CDCl_3$, 297 K), in the high-field region (1.7-2.4 ppm), the value of integration shows 12 protons including six protons of two acetyl groups (two

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OCOC$\underline{H}_3$) and six protons of three methylenes (three C$\underline{H}_2$ at positions 2, 4 and 6) on quinic aicd scaffold. The three signals at 3.85, 3.84, and 3.76 ppm belong to the three methoxy groups (two phenolic methoxyls PhOC$\underline{H}_3$ and one methyl ester $CO_2C\underline{H}_3$). The multiplet signals for two secondary protons at positons 3 and 5 locate in the region 5.46-5.60 ppm indicating the esterification reaction occurred at two hydroxyl groups at positions 3 and 5 rather than at the tertiary OH-1. If the diesterification had occurred to the hydroxyl groups at positions 1,3 or 1,5, the signals of secondary protons at positions 3 and 5 would have been split into two separate signals rather than overlapped together. The signals in the low-field region (6.3-7.7 ppm) correspond to the ten unsaturated protons (five for each cinnamoyl unit) including six aromatic protons and four double-bond protons.

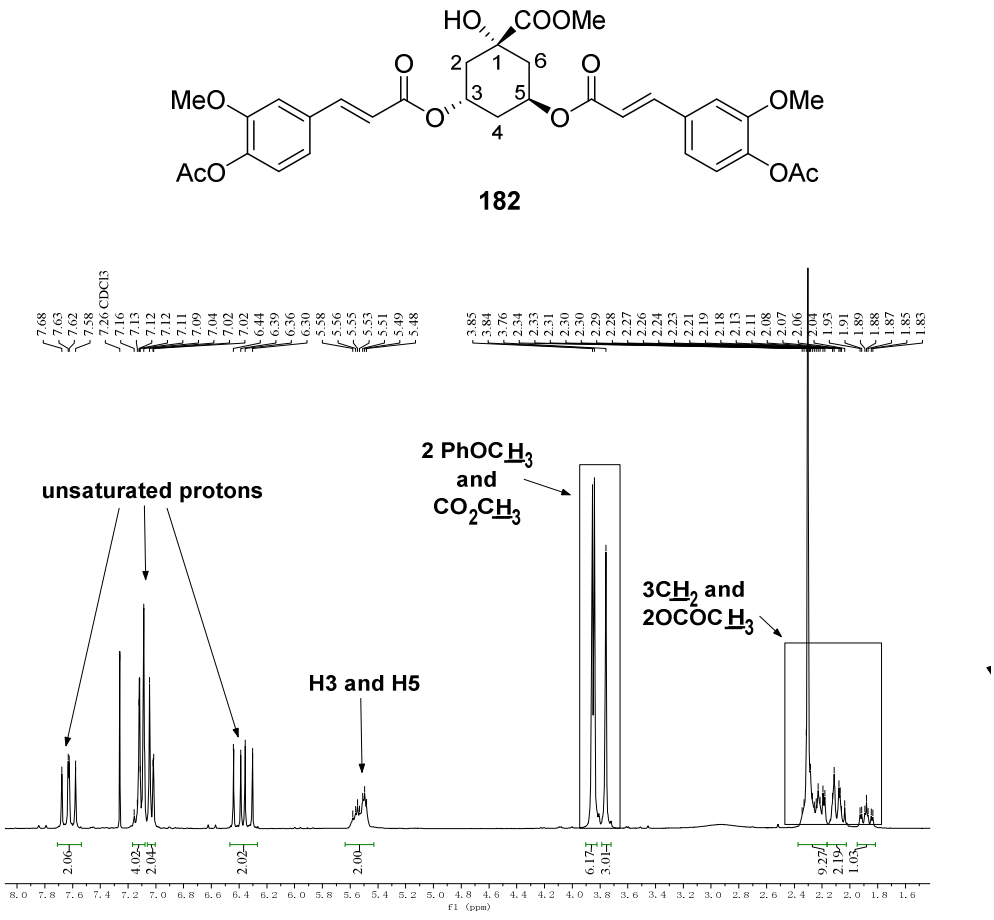


Figure 29 ^{1}H NMR (in $CDCl_3$) of diester 182

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In addition, the number and chemical shifts of ^{13}C peaks (100M Hz, $CDCl_3$, 297 K) match with the expected structure of diester **182**. The three peaks at 166.1, 165.8, and 175.0 ppm correspond to the three ester carbonyl groups including one methyl ester group and two newly-formed ester groups during the coupling reaction. The signals in the region 111.2-151.4 ppm belong to the unsaturated carbons of cinnamic acid moiety. The signals in the region 74.8-20.7 ppm correspond to the saturated carbons of methyl ($\underline{C}H_3$), methylene ($\underline{C}H_2$) and methyne ($\underline{C}H$) groups and tertiary carbon ($\underline{C}$).

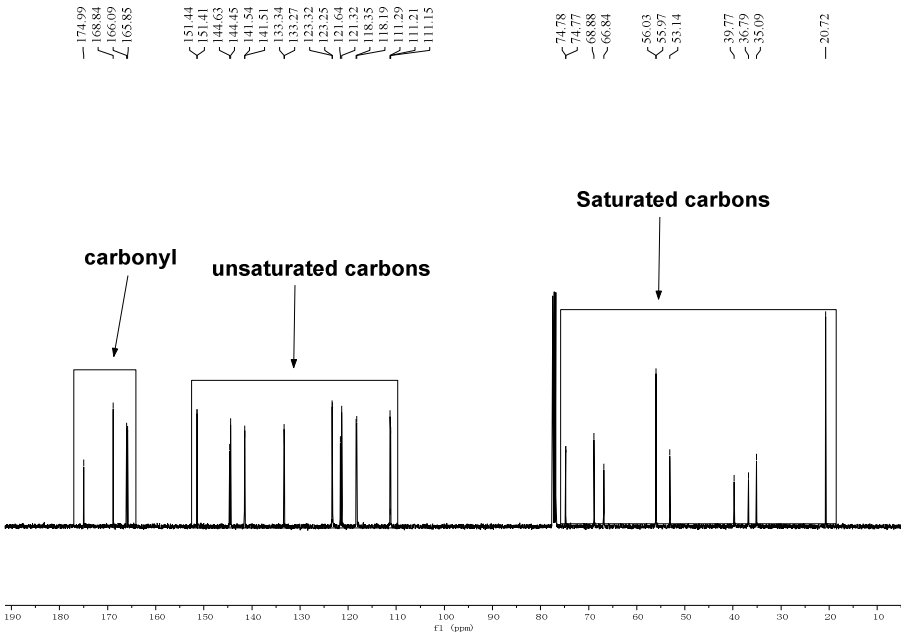


Figure 30 ^{13}C NMR (in $CDCl_3$) of diester 182

The full assignment of all NMR signals was achieved with the help of 2D NMR including COSY (^1H-^1H), HSQC (^1H-^{13}C) and HMBC (^1H-^{13}C). For example, a ddd signal in ^1H NMR at 1.88 ppm can be identified as the signal for the axial proton at C-4 based not only on its ^1H-^1H COSY signals with both H3 and H5 but also its coupling constants of 13.6 Hz ($^2J_{H4a\text{-}H4e}$), 10.4 Hz ($^3J_{H4a\text{-}H3a\text{ or }5a}$) and 3.4 Hz ($^3J_{H4a\text{-}H3e\text{ or }5e}$) (**Figure 31**). However, the assignment of other methylene protons and the differentiation of two secondary protons at C-3 and C-5 cannot be done due to the severe overlap in ^1H NMR spectrum and close chemical shifts in ^{13}C NMR spectrum.

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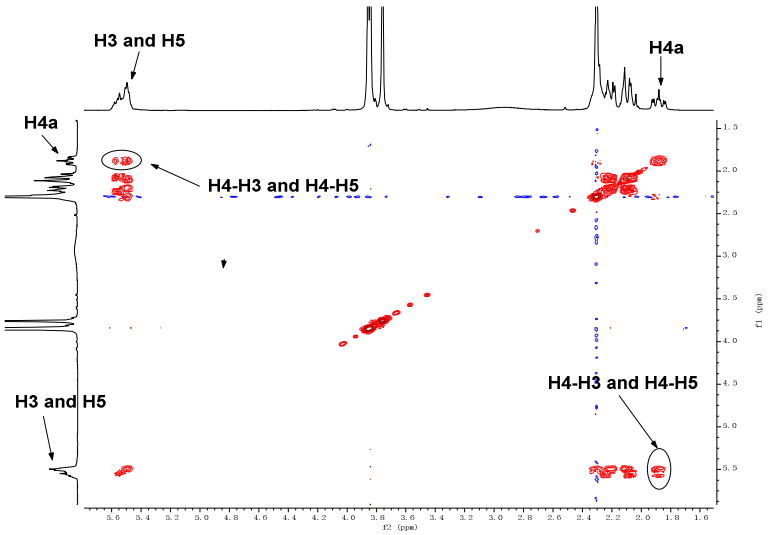


Figure 31 Partial ^{1}H-^{1}H COSY NMR (in $CDCl_3$) of diester 182

The differentiation of close signals from the two phenolic methoxyls and one carboxylic methyl ester was achieved with the help of the ^{1}H-^{13}C HMBC NMR. In **Figure 32**, are highlighted in ovals the interaction between carbonyl carbon ($\underline{C}OOCH_3$, 175.0 ppm) and methyl ester protons ($COOC\underline{H}_3$, 3.76 ppm), and the interaction between phenolic methoxy protons ($PhOC\underline{H}_3$, 3.85 and 3.84 ppm) and the connected aromatic carbon (aromatic C_q, 151.4 ppm).

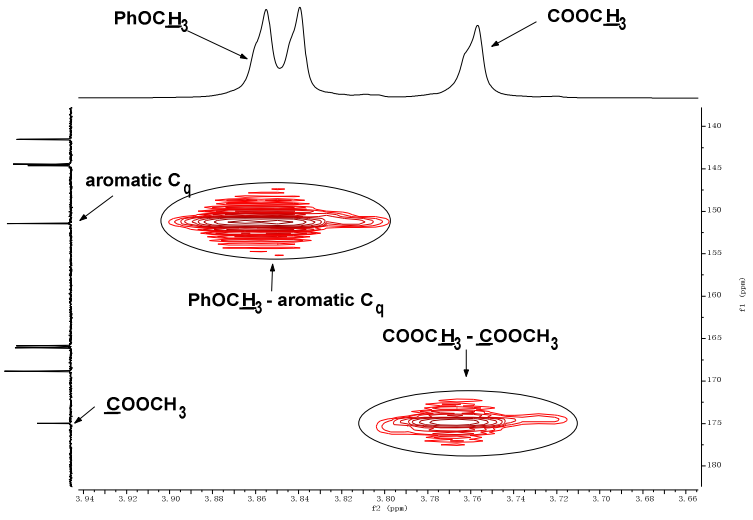


Figure 32 Partial ^{1}H-^{13}C HMBC NMR (in $CDCl_3$) of diester 182

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The carbon-carbon double bond protons (7.69-7.57 ppm and 5.45-6.29 ppm) exhibit different interactions with the aromatic carbons (labelled in ovals in **Figure 33**) in ^{1}H-^{13}C HMBC NMR, which helps to confirm the assignment of alkene protons.

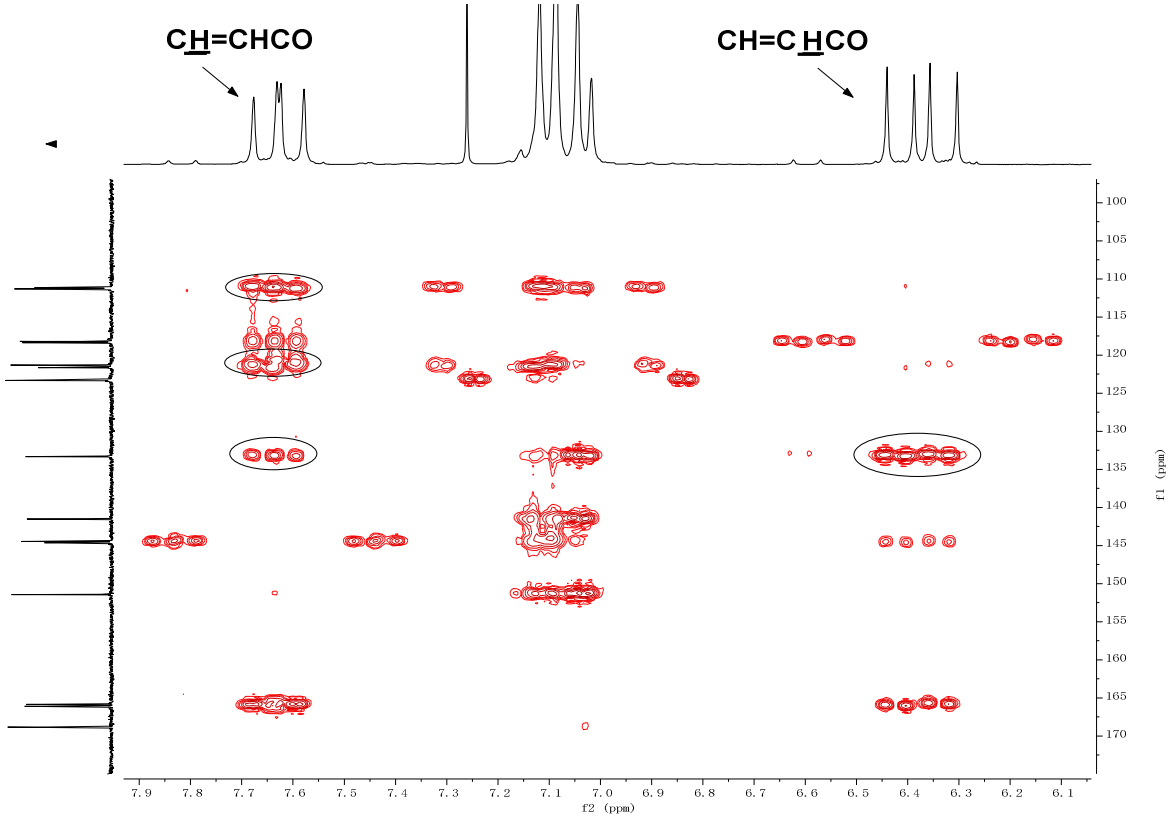


Figure 33 Partial ^{1}H-^{13}C HSQC NMR (in $CDCl_3$) of diester 182

With the help of HSQC (^{1}H-^{13}C) NMR shown in **Figure 34**, the assignment of other ^{13}C NMR signals was accomplished. In ^{13}C NMR, the signal at 20.7 ppm was attributed to the methyl group carbon of acetyl group ($OCO\underline{C}H_3$); the signal at 35.1 ppm belongs to the carbon at position 4; the signals at 36.8 and 39.8 ppm belong to the carbons at position 2 and/or 6; the signal at 53.1 ppm belongs to the methyl ester carbon ($COO\underline{C}H_3$); the signal at 56.0 ppm belongs to the phenolic methyl ether group carbon ($PhO\underline{C}H_3$); the signals at 66.8 and 68.9 ppm belong to the carbons at position 3 and/or 5; the signal at 74.8 ppm belongs to the carbon at position 1; the signals at 118.2 and 118.3 ppm

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belong to the double bond carbon connected with an carbonyl group (CH=CHCO); the signals at 144.4 and 144.6 ppm belong to the double bond carbon connected with an benzene ring (CH=CHCO). The aromatic carbons were identified as aromatic CH showing interaction in HSQC (^{1}H-^{13}C) NMR spectrum or as aromatic C_q showing no interaction in HSQC (^{1}H-^{13}C) NMR spectrum.

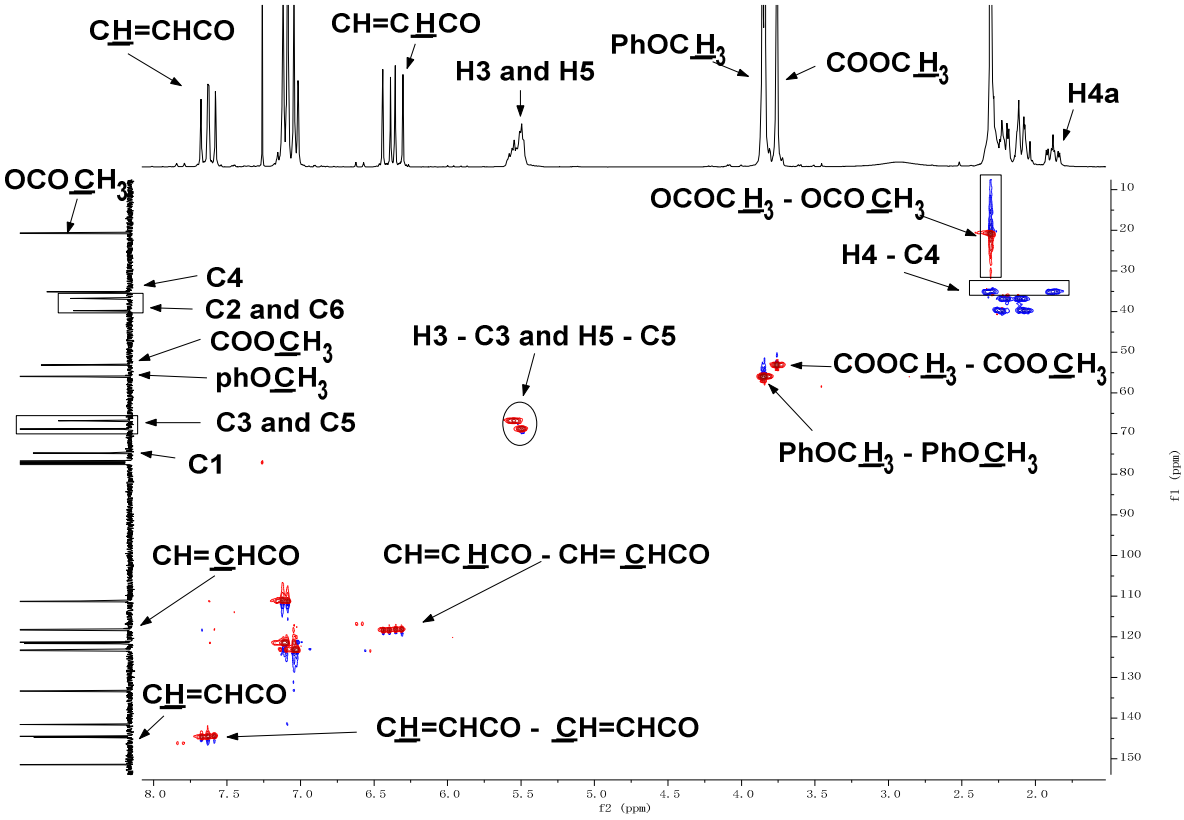


Figure 34 Partial ^{1}H-^{13}C HSQC NMR (in $CDCl_3$) of diester 182

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2.3.3 Deprotection to target compounds

2.3.3.1 Selective deprotection towards methyl ester analogs

As important derivatives of hydroxycinnamoyl quinic acid (CQA), CQA methyl esters were also isolated from different natural resources and have shown various biological activities.[112,165,166,167,168] For example, in 2012, 3,5-di-*O*-caffeoyl quinic acid methyl ester (or named methyl 3,5-di-*O*-caffeoyl quinate as in the literature) was isolated from *Kalopanax pictus* leaves by M. Wang *et al*. and has been shown to exert free radical scavenging activity, ferric reducing power activity, and to inhibit hydrogen peroxide (H_2O_2)-induced human embryonic kidney 293 cell death *in vitro* and lipid peroxidation.[167] In 2006, six caffeoyl quinic acid derivatives including 3,4-di-*O*-caffeoyl quinic acid methyl ester **185**, 3,5-di-*O*-caffeoylquinic acid methyl ester **186**, and 4,5-di-*O*-caffeoylquinic acid methyl ester **187** were isolated from the roots of *Dipsacus asper* Wall and their antioxidant activities were tested indicating an important role to play in preventing the development of atherosclerotic disease.[165] So the synthesis of CQA methyl ester analogs is also of great interest to us.

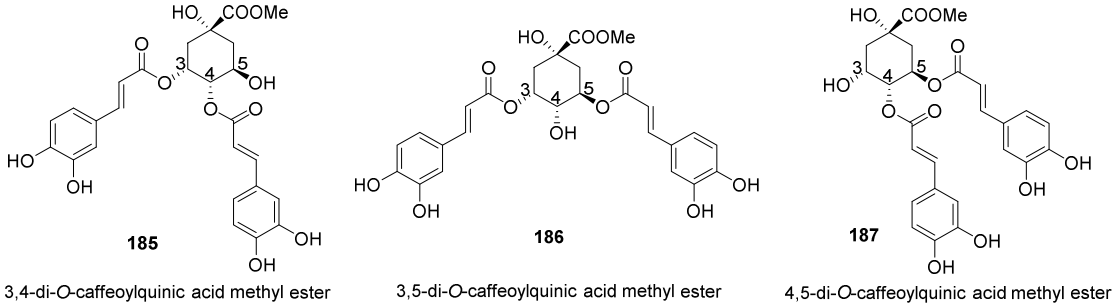
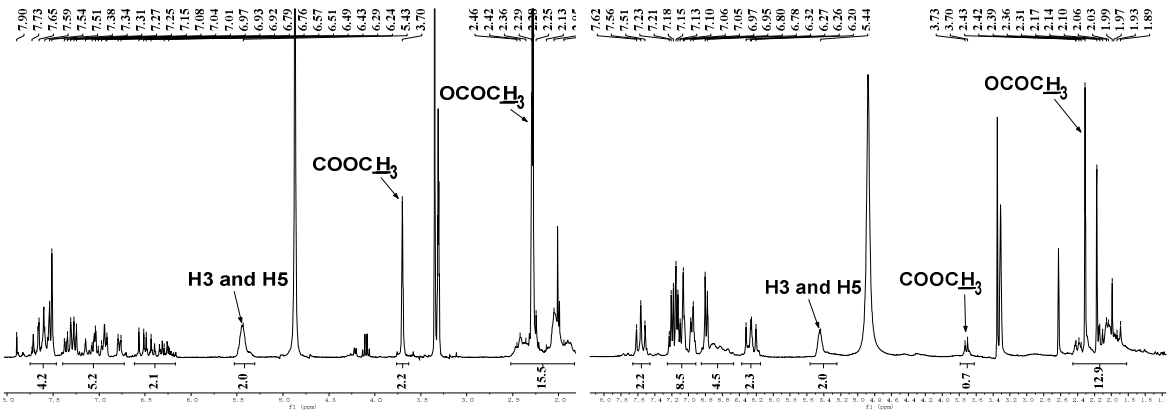


Figure 35 Structures of three methyl di-*O*-caffeoyl quinates isolated from the roots of *Dipsacus asper* Wall

In order to get 4-deoxy CQA methyl ester analogs, diester **172** was firstly treated with reported acidic conditions (i.e., aqueous HCl, in THF at room temperature[52,53,113] or in refluxing acetone[159,169]).

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However, after 12 days in 1 M HCl in THF, a complex mixture of diester **172** and other unknown compounds was obtained. The analysis of ^{1}H NMR (in MeOD) of the reaction crude concluded to a complex mixture with partial cleavage of methyl ester group but that the acetyl groups remained nearly untouched (see **Figure 36a**). When diester **172** was treated with 3M HCl in reflux acetone for 3 hours, the ^{1}H NMR analysis of the resulting reaction crude (see **Figure 36b**) indicates similar results (partial cleavage of methyl ester was observed but acetyl groups still remained.).



a ^{1}H NMR (in MeOD) of the crude from treating **172** with 1 M HCl in THF at rt for 12 days

b ^{1}H NMR (in MeOD) of the crude from treating **172** with 3 M HCl in refluxing acetone for 3 hours

Figure 36

The hydrolysis of the aromatic acetates of synthesized 4-deoxy-3,5-*O*-diesters **172**, **182**, **183**, and **184** was then successfully performed with sodium acetate in refluxing ethanol/water[170] and/or with a mild method reported recently using hydrazine acetate in DMF at room temperature.[171] Four corresponding CQA methyl ester analogs were obtained including 4-deoxy-3,5-di-*O*-caffeoylquinic acid methyl ester **188**, 4-deoxy-3,5-di-*O*-feruloylquinic acid methyl ester **189**, 4-deoxy-3,5-di-*O*-*p*-coumaroylquinic acid methyl ester **190**, and 4-deoxy-3,5-di-*O*-*o*-coumaroylquinic acid methyl ester **191**.

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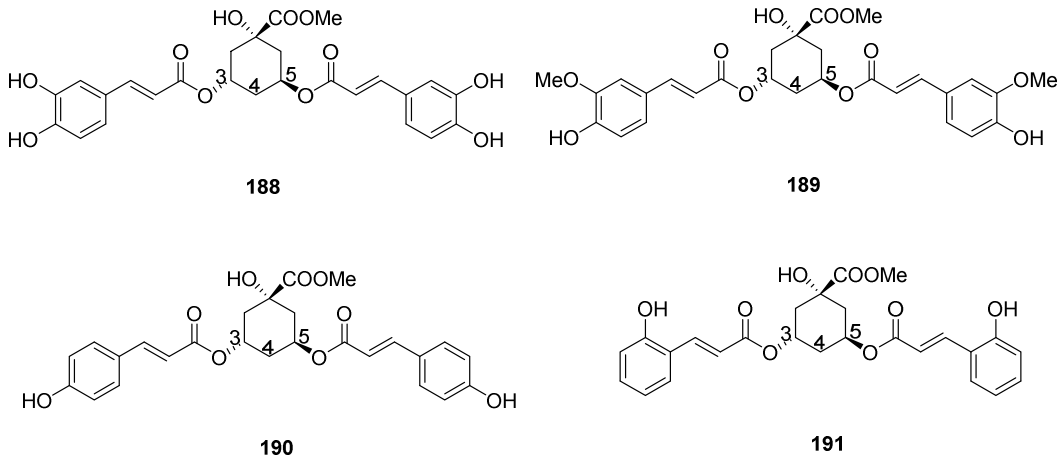


Figure 37 Structures of four 4-deoxy CQA methyl ester analogs

The results of deprotection reactions using sodium acetate in refluxing ethanol/water are summarized in **Table 5**. For diester **172**, the deprotection reaction with sodium acetate in ethanol/water at reflux in 4 hours provided 4-deoxy-3,5-di-*O*-caffeoylquinic acid methyl ester **188** in 61% isolated yield (entry 1). However, for the other cinnamoyl conjugates, the deprotection reactions turned out to be incomplete under these conditions (entries 2-4).

Table 5 Hydrolysis of aromatic acetates with sodium acetate

Entry	Starting materials	Conditions	Products	Yields[a]
1	**172**	20 equiv. NaOAc, EtOH/H_2O, 0.1 M, reflux, 4 h	**188**	61%
2	**182**	20 equiv. NaOAc, EtOH/H_2O, 0.1 M, reflux, 4 h	**189**	nd[b,c]
3	**183**	20 equiv. NaOAc, EtOH/H_2O, 0.1 M, reflux, 4 h	**190**	50%[c]
4	**184**	20 equiv. NaOAc, EtOH/H_2O, 0.1 M, reflux, 4 h	**191**	33%[c]

[a] Isolated yields. [b] No pure product was obtained. [c] The hydrolysis of acetate was incomplete

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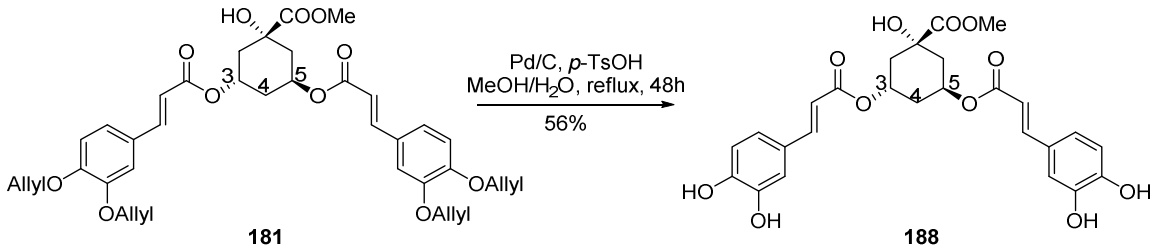
With hydrazine acetate in DMF at room temperature in 1 hour,[171] the selective removal of acetates groups proceeded well and all the methyl ester derivatives could be obtained with very good isolated yields (89-91%, **Table 6**).

Table 6 Hydrolysis of aromatic acetates with hydrazine acetate

Entry	Starting materials	Conditions	Products	Yields[a]
1	**172**	4.5 equiv. N_2H_4·HOAc, DMF, 0.2 M, rt, 1 h	**188**	89%
2	**182**	4.5 equiv. N_2H_4·HOAc, DMF, 0.2 M, rt, 1 h	**189**	89%
3	**183**	4.5 equiv. N_2H_4·HOAc, DMF, 0.2 M, rt, 1 h	**190**	91%
4	**184**	4.5 equiv. N_2H_4·HOAc, DMF, 0.2 M, rt, 1 h	**191**	89%

[a] Isolated yields.

The removal of aromatic allyl ethers from diester **181** was then performed using Pd/C in the presence of *p*-TsOH in MeOH/H_2O at reflux for 48 hours providing 4-deoxy-3,5-di-*O*-caffeoylquinic acid methyl ester **188** but in a disappointing yield inferior to 56%.



Scheme 42 Deprotection of allyl groups of diester 181

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These four 4-deoxy-3,5-di-*O*-cinnamoylquinic acid methyl esters **188-191** were also fully characterized. Taking 4-deoxy-3,5-di-*O*-caffeoylquinic acid methyl ester **188** as an example, the ^{1}H NMR spectrum (in MeOD) is shown in **Figure 38**: the complete removal of aromatic acetate groups is clearly displayed in the region 1.7-2.5 ppm; The labile aliphatic ester groups remained untouched since we can see the signals of two caffeoyl groups and the overlapped signal of secondary protons H3 and H5.

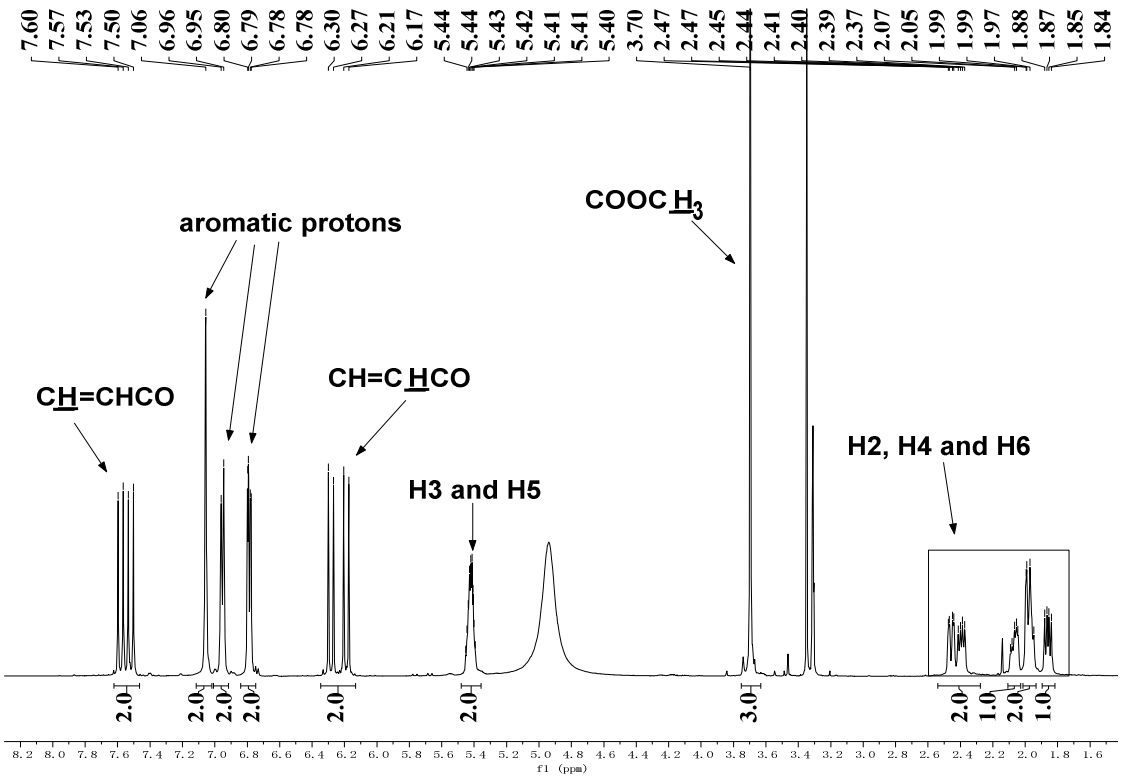


Figure 38 ^{1}H NMR (in MeOD) of 188

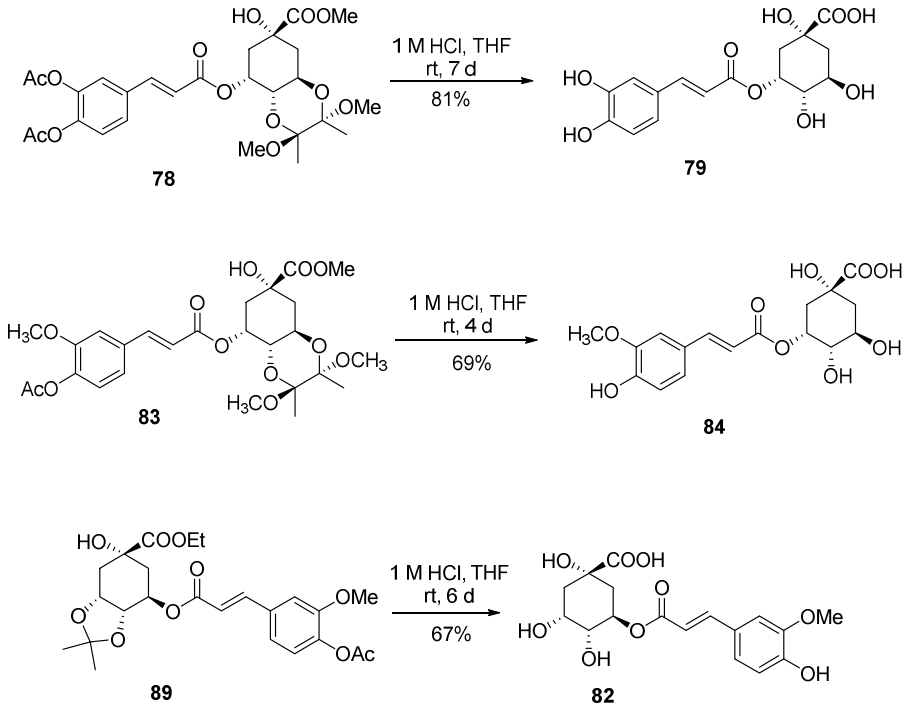
2.3.3.2 Total deprotection to carboxylic acid targets

The deprotection of all protecting groups for both the carboxylic acid and aromatic hydroxyl groups was explored betting for a better solubility in water of the carboxylic

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acid analogs during bioassays and to identify the pharmacophoric importance of the carboxylic acid moiety.

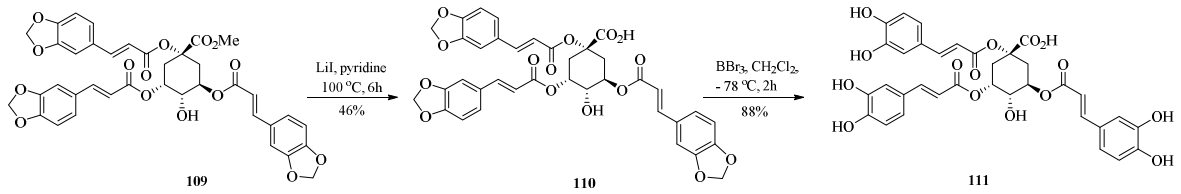
The most commonly used acidic conditions for a total deprotection used aqueous HCl in THF. For example, the methyl ester or ethyl ester, the acetates for aromatic hydroxyl groups and other aliphatic hydroxyl protecting groups of esters **78**, **83**, **89** were all removed in one step using acidic conditions (1 M HCl, THF, rt, 4-7 days) in satisfactory or good yields (67-81%).[53,54]



Scheme 43 Selected reported total deprotection in acidic conditions

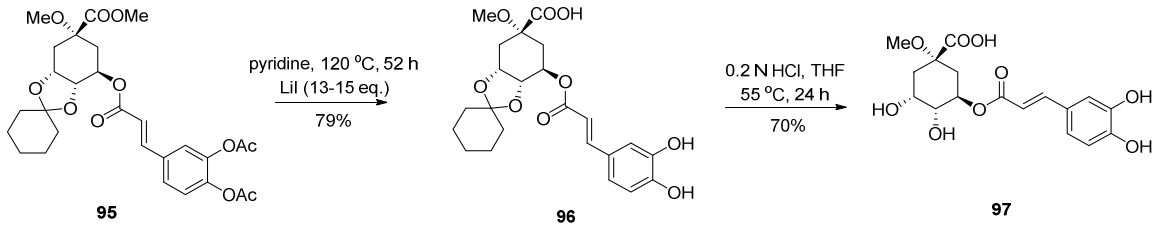
K. Brummond *et al*. proposed a two-step deprotection procedure.[114] The cleavage of the methyl ester of **109** was first accomplished in pyridine at reflux with excess LiI, then the methylene acetal group for aromatic hydroxyl groups were removed with excess BBr_3 at –78 °C.

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Scheme 44 Two-step total deprotection of ester 51

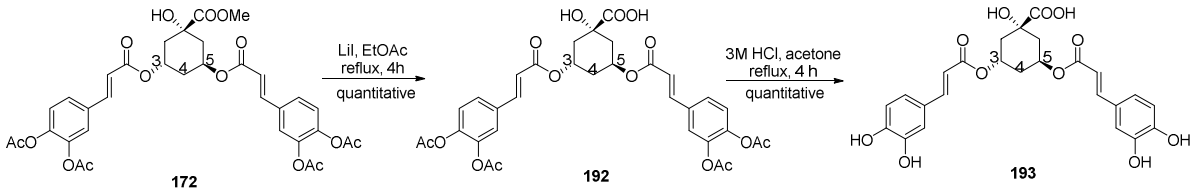
Furthermore, W. Zeller even reported that the methyl ester functionality of ester **95** was cleaved with lithium iodide in pyridine which also resulted in concomitant loss of the caffeoyl acetate protecting groups providing carboxylic acid **96** in 79% yield.[55]



Scheme 45 Two-step total deprotection of ester 95

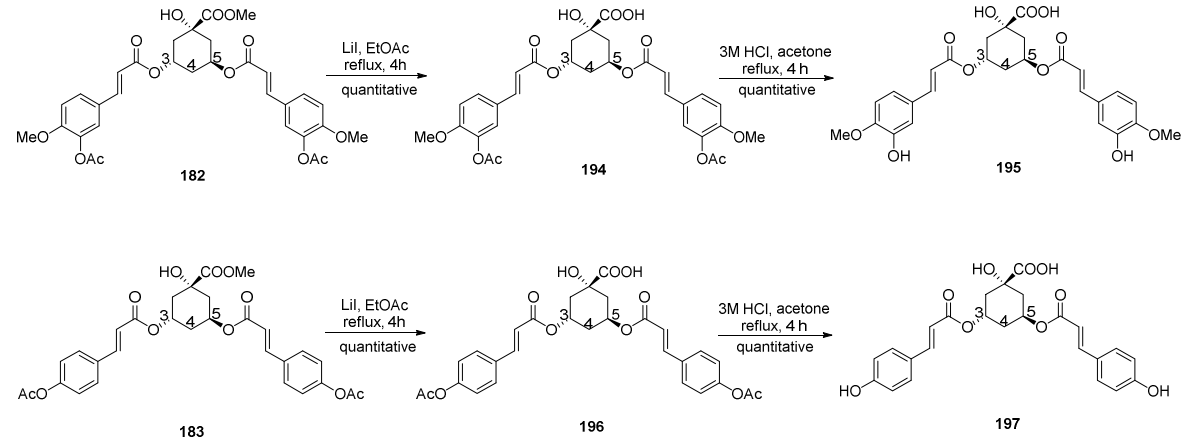
Our attention was thus turned to a two-step procedure since the one-step acidic deprotection conditions of diester **172** resulted in complex mixtures as shown above in **Figure 36**. First, diester **172** was treated with 11 equivalents of LiI at reflux in pyridine for 12 hours, but resulted in a complex mixture. When the solvent was changed from pyridine to ethyl acetate,[172] the removal of methyl ester was achieved without breaking the acetate groups or any aliphatic esters. And a resulting crude (**192**) was quantitatively obtained with adequate purity for full characterization and for the next deprotection step. Then by acidic hydrolysis of **192** with 3 M HCl in acetone under reflux for 4 hours, the final product 4-deoxy-3,5-di-*O*-caffeoylquinic acid **193** was obtained quantitatively.

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Scheme 46 Two-step total deprotection of diester 172

The two-step procedure was also applied in the total deprotection of protected diesters **182** and **183** to quantitatively give corresponding 4-deoxy-3,5-di-*O*-feruloylquinic acid **195** and 4-deoxy-3,5-di-*O*-*p*-coumaroylquinic acid **197**. A more diluted solution with more equivalents of LiI and a shorter reaction time could improve the purity of the resulting crudes, and LiI should be a fresh reagent to avoid oxidative effect of I_2 on the catechol group.

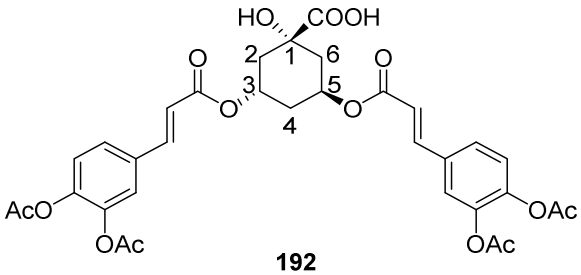


Scheme 47 Two-step total deprotection of diesters 182 and 183

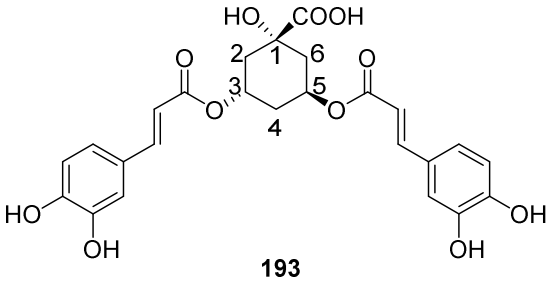
These selectively deprotected carboxylic acids **192**, **194**, **196** and totally deprotected targets **193**, **195**, **197** were fully characterized. Taking the compounds **192** and **193** as examples, in **Figure 39a**: the peak of carboxylic methyl ester has disappeared indicating the complete removal of methyl ester group; acetate groups remained untouched (2.19-2.44 ppm) in the first deprotection step. Next, in **Figure 39b**: in the

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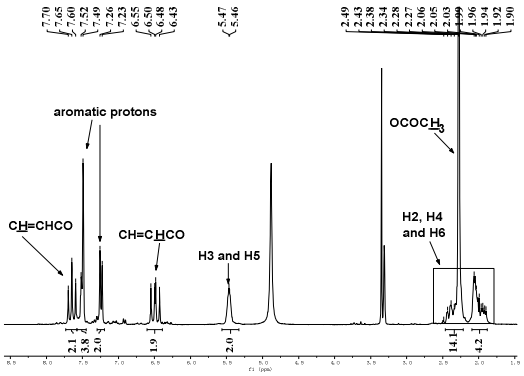
region 2.19-2.44 ppm, the signals of acetate groups have disappeared proving the complete cleavage of acetate groups. The labile aliphatic ester groups remained untouched during the two-step deprotection process. It is still difficult to distinguish secondary protons H3 and H5, and methylene protons H2, H4, and H6 due to the severe signal overlap.



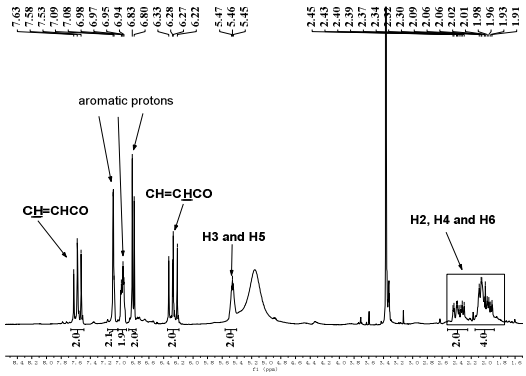
192



193



a ^{1}H NMR (in MeOD) of **192**

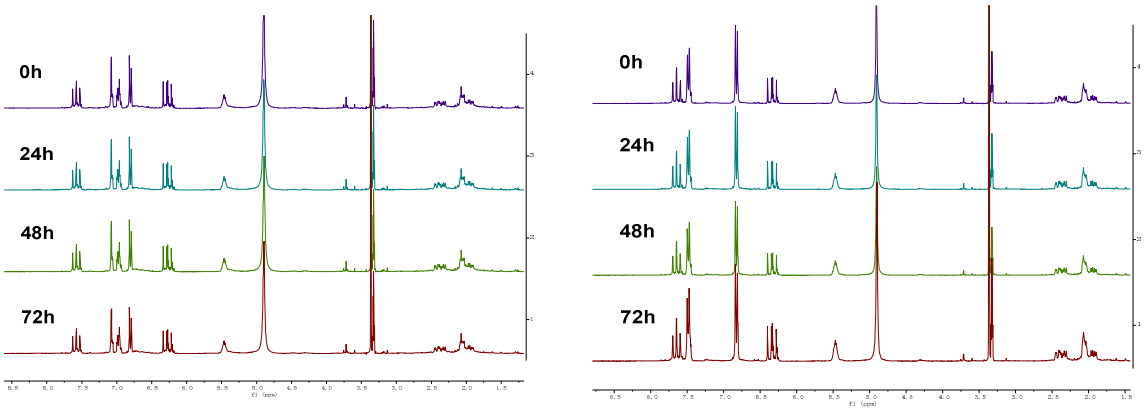


b ^{1}H NMR (in MeOD) of **193**

Figure 39

The ^{1}H NMR (CD_3OD) spectra of **193** and **197** at different time intervals confirmed the stability of these compounds at least over 72 hours compared to 3,5-di-*O*-caffeoylquinic acid.[173]

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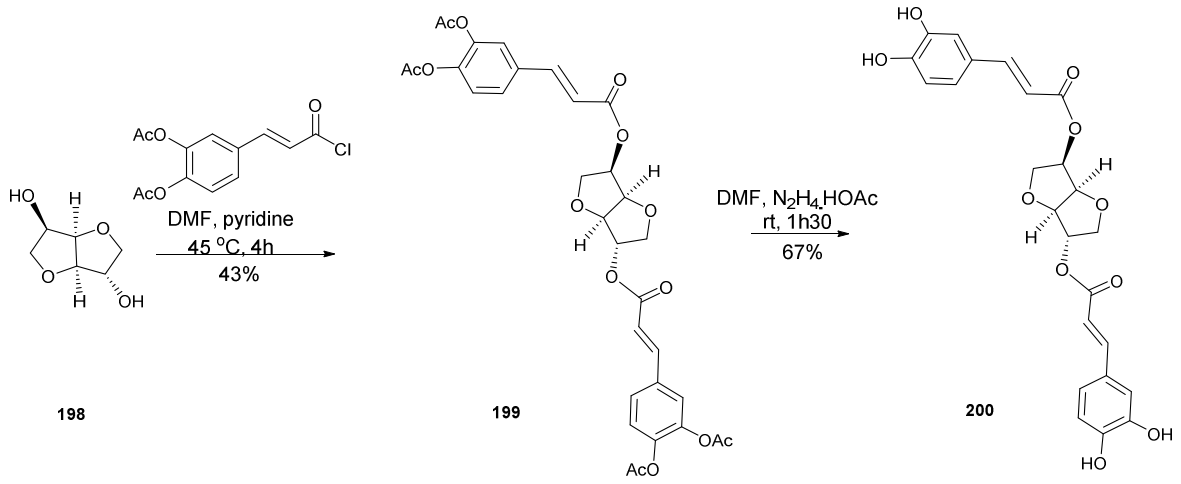


^{1}H NMR of **193** in MeOD over 72 h ^{1}H NMR of **197** in MeOD over 72 h

Figure 40 ^{1}H NMR of 193 and 197 in MeOD at different time intervals

Thus, starting from quinic acid **31**, a first series of targeted compounds was synthesized including four methyl ester analogs and three carboxylic acid analogs in 7 and 8 steps, respectively.

In another project of our lab, a dicaffeoyl derivative **200** with an isosorbide core **198** replacing the 4-deoxy quinic acid had also been prepared by Lucie Grand using a similar coupling-deprotection process in 29% yield from isosorbide **198** (see **Scheme 48**).



Scheme 48 Synthesis of 200

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The compound **200**, readily available, was also included in bioassays with the seven 4-deoxy CQA analogs (4-deoxy-3,5-di-*O*-caffeoylquinic acid methyl ester **188**, 4-deoxy-3,5-di-*O*-feruloylquinic acid methyl ester **189**, 4-deoxy-3,5-di-*O*-*p*-coumaroylquinic acid methyl ester **190**, and 4-deoxy-3,5-di-*O*-*o*-coumaroylquinic acid methyl ester **191**, 4-deoxy-3,5-di-*O*-caffeoylquinic acid **193**, 4-deoxy-3,5-di-*O*-feruloylquinic acid **195**, and 4-deoxy-3,5-di-*O*-*p*-coumaroylquinic acid **197**) for comparison. Preparative HPLC before bioassays confirmed the high purity of the different samples.

2.3.4 Insecticidal bioassays

Compounds **188**, **189**, **190**, **191**, **193**, **195**, **197** and **200** were incorporated in culture media during nymphal development of the pea aphid *Acyrthosiphon pisum*. This specialist and model aphid species (*A. pisum*) was shown to be highly sensitive to the natural compound 3,5-di-*O*-caffeoylquinic acid **108**,[49] and was therefore selected as control for toxicity and growth-inhibition bioassays. These biological tests have been performed by biologists Pedro da Silva and Yvan Rahbé and their team in the lab INRA BF2I (INSA Lyon, Biologie Fonctionnelle Insectes et Interaction)

Bioassays were scored for mortality data, summarized as median lethal time 50% (LT50) resulting from a survival analysis (i.e. the median time necessary for killing 50% of the insect population). Dose 500 µM gave the most discriminating analysis, and we will only discuss this dose level. Toxicity (mortality) features of the most active compounds **193**, **197, 108, 191, 195**, **188** are summarized in **Figure 41** according to decreasing activities from **193** to **188**. The LT50 for 3 other compounds **189**, **190**, and **200** surpass 20 days and were not included in **Figure 41**.

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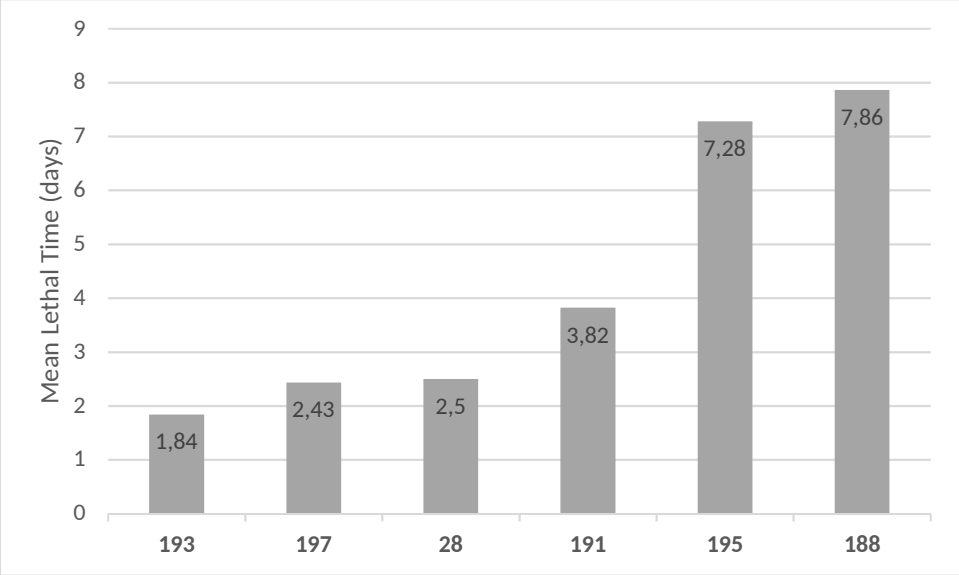
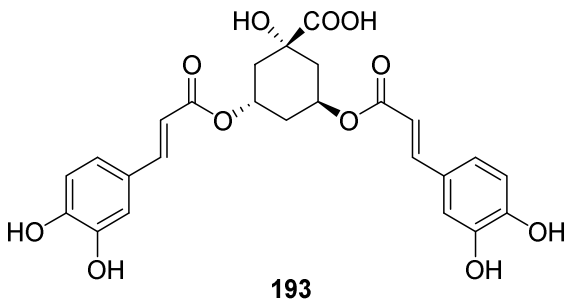
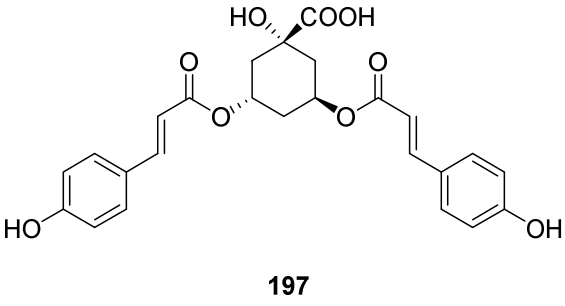


Figure 41 Survival analysis LT50 mean values per active compound

Growth inhibition was measured by weighing and was analysed by a set of two one-way Anova. These growth inhibition analyses mainly underline the activity of two new molecules, **193** and **197**, superior or close to the natural product **108**. According to the results of both toxicity and growth-inhibition bioassays, one might rank the global toxicity index of compounds as: **193** > **197** > **108** ≈ **191** > **195** ≥ **188** > **190** ≈ **189** > **200**.



193



197

Figure 42 Structures of 4-deoxy CQA analogs 193 and 197

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2.4 Synthesis towards 4-deoxy-3,5-heterodicinnamooyl quinic acid analogs

2.4.1 Introduction

Mixed di-esters (or heterodiesters) are an important subgroup of CQA including diesters of caffeic and ferulic acid (caffeoylferuloylquinic acids (CaFQA)) as found in robusta coffee (Coffea *canephora*, Rubiaceae)[60,61,174] and sweet potato from China,[175] caffeic and sinapic acid (caffeoylsinapoylquinic acids (CaSiQA)) as found in *Gardenia jasminoides* (Rubiaceae),[176,177] caffeic and *p*-coumaric acid (caffeoyl*p*-coumaroylquinic acids (Ca*p*CoQA)) plus *p*-coumaric and ferulic acid (*p*-coumaroylferuloylquinic acids (*p*CoFQA)) as found in green coffee beans.[178]

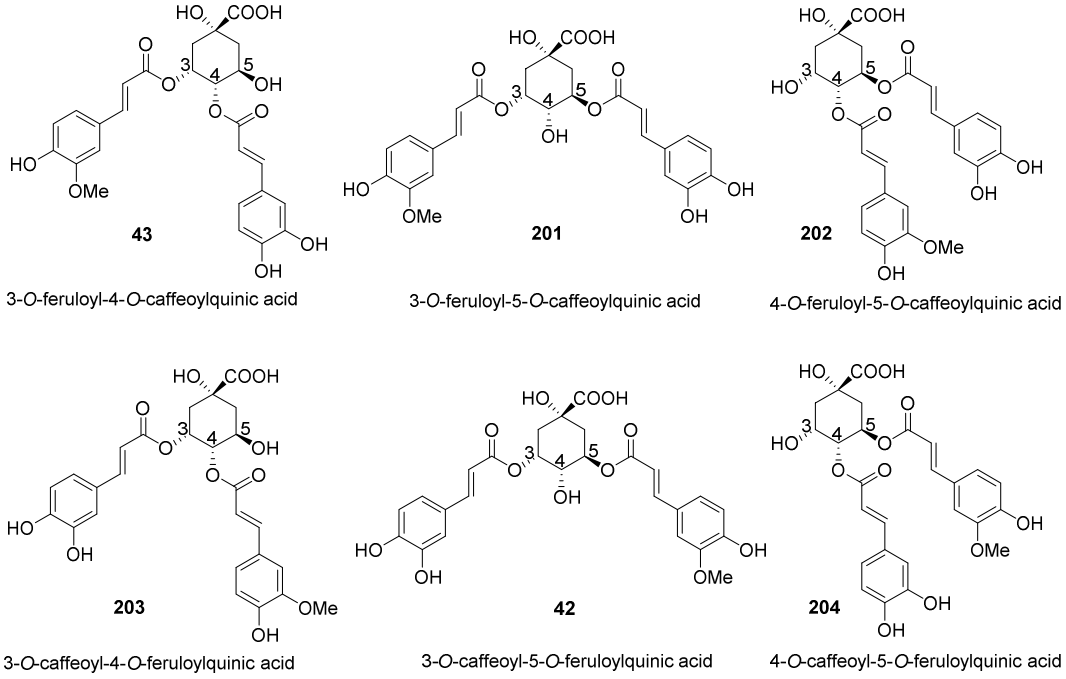
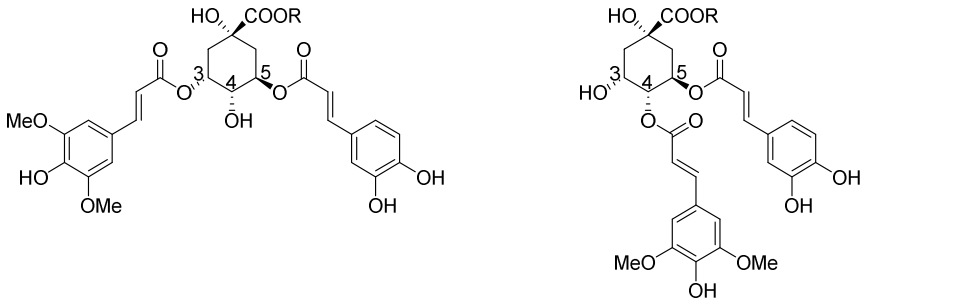


Figure 43 Structures of six caffeoylferuloylquinic acids isolated from sweet potato (*Ipomea batatas*)[175]

In addition, methyl or ethyl ester derivatives of heterodiesters were also isolated from *Gardeniae jasminoides*.[179]

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205 R = methyl, methyl 3-*O*-sinapoyl-5-*O*-caffeoylquinate
206 R = ethyl, ethyl 3-*O*-sinapoyl-5-*O*-caffeoylquinate
207 R = methyl, methyl 4-*O*-sinapoyl-5-*O*-caffeoylquinate
208 R = ethyl, ethyl 4-*O*-sinapoyl-5-*O*-caffeoylquinate

Figure 44 Structures of four methyl or ethyl heterodicinnamoyl quinates from *Gardeniae jasminoides*

To the best of our knowledge, the heterodiesters were isolated from different natural resources in small amounts and the only example of such heterodiesters was described by N. Kuhnert synthesizing two caffeoyl-feruloyl-*muco*-quinic acid derivatives.[128] In our goal to prepare a small library of diCQA analogs, we decided to investigate the possibility of a two-step coupling procedure with 4-deoxy methyl quinate **167** to access various heterodiesters.

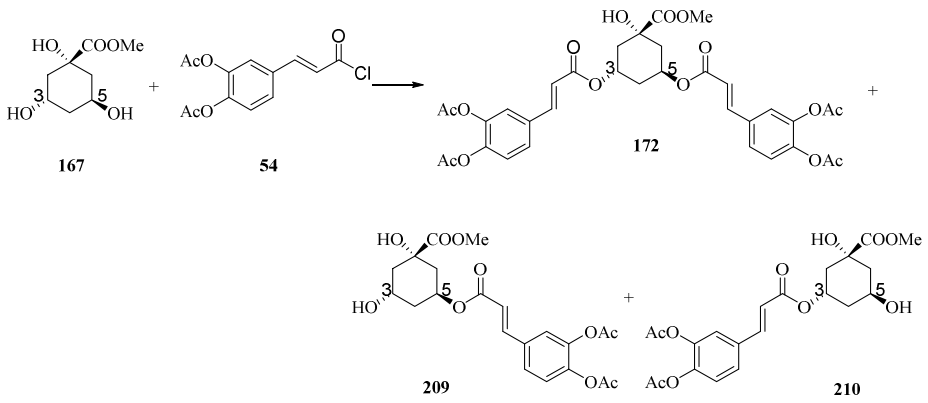
2.4.2 Synthesis of monoesters

2.4.2.1 An optimization process

First we had to study the monoesterification. The coupling reactions of triol **167** with 1.1-1.8 equivalents of acid chloride **54** were carried out wishing for a good acylation selectivity between the two secondary hydroxyl groups at positions 3 and 5 or, at least, the possibility to obtain two monoesters as regioisomers. The results of an optimization by reacting 4-deoxy methyl quinate **167** with protected caffeoyl chloride **54** are shown in **Table 7**.

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Table 7 Optimization for the synthesis of monoesters



Entry	Molar equiv. of **54**	Catalyst	Solvent[a]	Temp. (°C)	Time	Yields[b] **172**	**209**	**210**	Conversion
1	1.1		DMF/pyridine	45	0.5 h	3%	15%	<17%[c]	<35%
2	1.1		DMF/pyridine	45	12 h	4%	14%	<14%[c]	<32%
3	1.2		DMF/pyridine	45	4 h	<11%[d]	19%	<26%[c]	<56%
4	1.5		DMF/pyridine	45	4 h	<16%[d]	25%	<24%[c]	<65%
5	1.5		DMF/pyridine	0-rt	4 h	25%	24%	25%	74%
6	1.5	DMAP[f]	DCM/pyridine	0-rt	4 h	8%	39%	12%	59%
7	1.5	DMAP[f]	DCM/pyridine	-18-rt	4 h	11%	37%	13%	61%
8	1.8		DMF/pyridine	45	3 d		nd[e]		--

[a] DMF/pyridine = 3/2, 0.4 M; DCM/pyridine = 5/1, 0.1 M. [b] isolated yields, [c] mixed with **209** or other impurities, [d] mixed with unknown impurities, [e] no pure product obtained. [f] 20% DMAP

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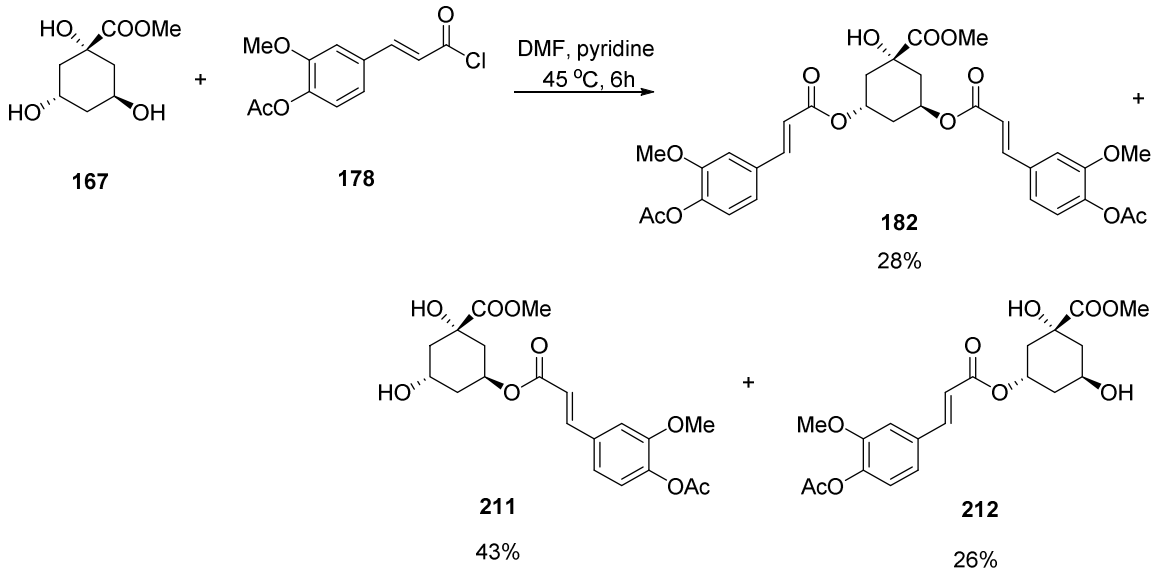
Less than 35% conversion of triol **167** was observed with 1.1 equivalent of acid chloride **54** (entry 1) in DMF/pyridine at 45 °C after 30 minutes providing two monoesters **209** and **210** in 15% and 17% yield, and homodiester **172** in 3% yield. The isolation of pure monoester **210** was difficult due to its similar polarity to **209**. Aiming at producing more monoesters, a balance between the amounts of acid chloride **54** and the limited formation of diester **172** should be found. A longer reaction time (12 hours) did not help to improve the conversion of starting material **167** with 1.1 equivalent of acid chloride (entry 2). The conversion of triol **167** was improved along with the increase use of acid chloride **54**, but good yields for monoesters were never obtained (entries 3 and 4). A lower temperature (0 °C - rt) made the purification less difficult, but no improvement in the yields of monoesters was observed (entries 5 vs 4). When triol **167** was reacted with 1.8 equivalent of chloride for 3 days, the reaction mixture was complex and no pure product was isolated (entry 8). Then another mixed solvent DCM/pyridine with catalyst DMAP was tested for the mono-coupling. The reaction was started at 0 °C (entry 6) or -18 °C (entry 7) and warmed slowly to room temperature. Under these conditions, the purification was less difficult, a better selectivity between the two secondary hydroxyl groups at positions 3 and 5 was observed (about 3:1). During the optimization process, the conversion of triol **167** has never surpassed 75%, but the residual triol **167** could be got back after chromatography purification.

2.4.2.2 Synthesis of feruloyl and *p*-coumaroylmonoesters

After having proved the availability of two caffeoylmonoesters by the coupling reaction of triol **167** with acetyl protected caffeoyl chloride **54**, four other monoesters were obtained by mono-coupling reactions of triol **167** with acetyl protected feruloyl chloride **178** and acetyl protected *p*-coumaroyl chloride **179**.

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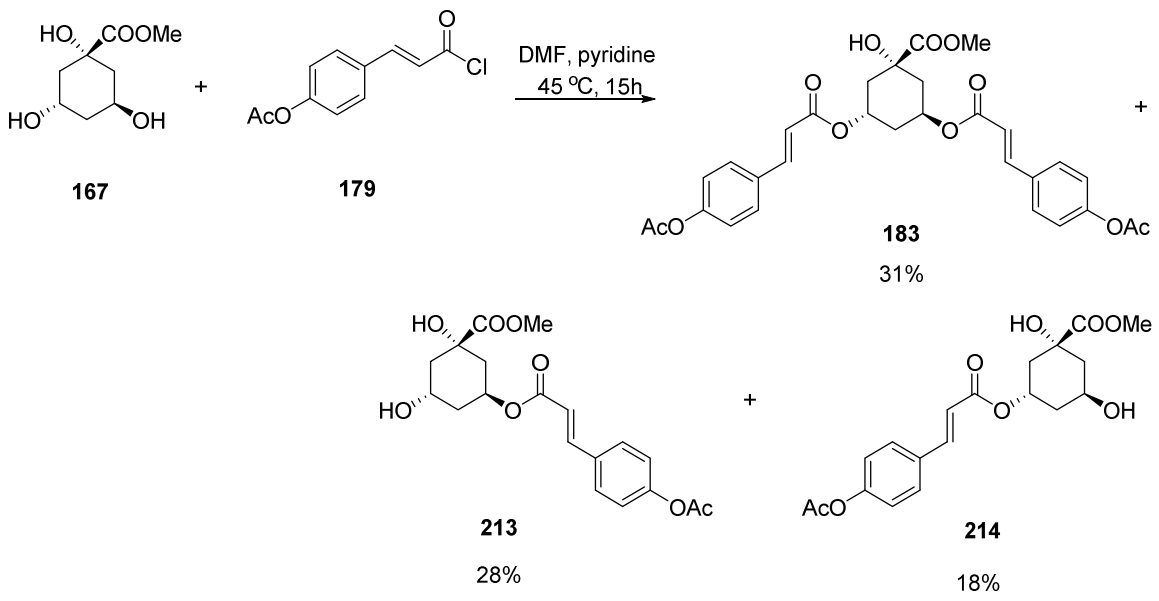
In contrast with the mono-coupling reactions with caffeoyl chloride **54**, the mono-coupling reaction with 1.5 equivalents of feruloyl chloride **178** proceeded well in DMF/pyridine at 45 °C, however, the conversion of triol **167** was still incomplete. A combined 69% yield of two monoesters **211** and **212** together with 28% yield of diester **182** were obtained. Compared with caffeoylmonoesters, a better selectivity between two secondary hydroxyl groups and better yields for monoesters were observed under these conditions.



Scheme 49 Synthesis of feruloyl monoesters

The mono-coupling reaction of triol **167** with 1.5 equivalents of *p*-coumaroyl chloride **179** in DMF/pyridine at 45 °C for 15 hours provided *p*-coumaroyl diester **183** in 31% yield, *p*-coumaroyl monoesters **213** in 28% and **214** in 18% yield.

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Scheme 50 Synthesis of *p*-coumaroyl monoesters

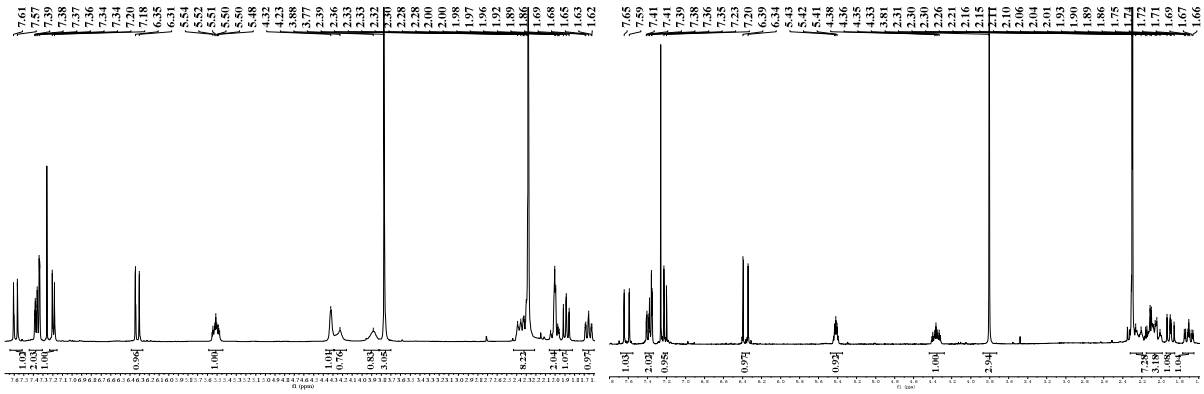
Thus, six monoesters were obtained in our hands with good purity including 5-*O*-caffeoylmonoester **209**, 3-*O*-caffeoylmonoester **210**, 5-*O*-feruloylmonoester **211**, 3-*O*-feruloylmonoester **212**, 5-*O*-*p*-coumaroylmonoester **213**, and 3-*O*-*p*-coumaroylmonoester **214**. Then we focused on the second coupling reactions by reacting these monoesters with another different acid chloride as cinnamoyl group donor.

2.4.2.3 Confirmation of mono-acylation positions

In the monoesterification reactions, two regioisomers were obtained. The high purity of each sample allowed us to identify each of them. The confirmation of the mono-acylation positions was achieved by the analysis of their NMR spectra (in $CDCl_3$).

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First, the possibility of acylation at position 1 was excluded. In **Figure 45a** and **b**, both the ^{1}H NMR spectra of caffeoyl monoesters **209** and **210** show two multiplets of secondary protons at 5.5 ppm and 4.3 ppm. If the acylation had occurred at position 1, the signals of these two secondary protons at positions 3 and 5 should have been close to each other or even overlapped together as in the case of triol **167**. So the monosubstitution occurred at C-3 or C-5 position. The ^{1}H NMR spectra of monoesters **209** and **210** (**Figure 45a** and **b**) resemble each other especially in the high-field region (1.6-2.4 ppm) and the low-field region (6.3-7.7 ppm). And the peaks for secondary protons at C-3 and C-5 showed very close chemical shifts (5.53 ppm vs 5.42 ppm and 4.36 ppm vs 4.32 ppm). The similarities of the ^{1}H NMR exist also for the two feruloyl (**211** and **212**) and two *p*-coumaroyl monoesters (**213** and **214**).

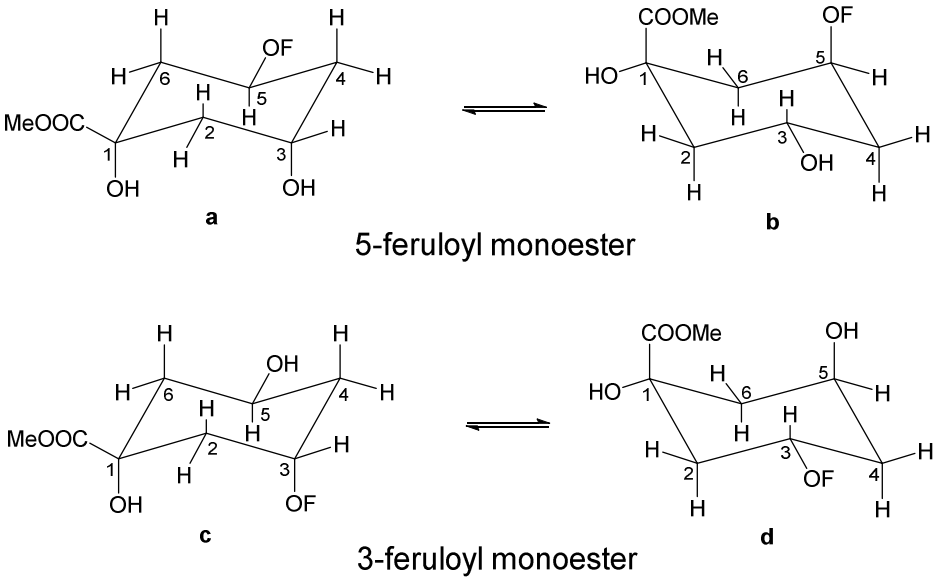


a ^{1}H NMR of **209** in $CDCl_3$ **b** ^{1}H NMR of **210** in $CDCl_3$

Figure 45

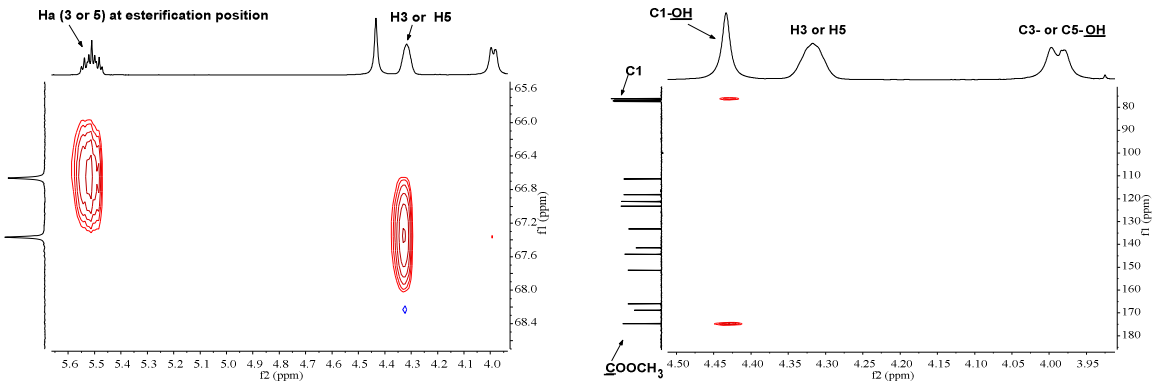
The key for the differentiation of the two isomers was based on the more favored chair conformations, which are supported by the observation of the large *trans*-diaxial coupling constant of H4a (e.g., ^{3}J 11.5 Hz for monoester **211** and ^{3}J 10.3 Hz for monoester **212**). The possible chair conformations of 5- and 3-feruloyl monoesters are as depicted in **Scheme 50**.

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Scheme 50 Chair conformations of 5- and 3-feruloyl monoesters 211 and 212

First, based on the ^{1}H-^{13}C HSQC of monoester **211**, the tt signal at 5.51 ppm with coupling constants ^{3}J 11.2 Hz and ^{3}J 4.4 Hz is identified as the secondary proton at the esterification position; the multiplet at 4.35 – 4.28 ppm is identified as another secondary proton at the position with free hydroxyl group. Then, based on the ^{1}H-^{13}C HMBC, the signal at 4.43 ppm is identified as hydroxyl group at position 1; the signal at 4.00 ppm is identified as the hydroxyl group at position 3 or 5.



a ^{1}H-^{13}C HSQC ($CDCl_3$) of **211** **b** ^{1}H-^{13}C HMBC ($CDCl_3$) of **211**

Figure 46

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In ^{1}H-^{1}H NOESY, the two hydroxyl groups exhibit interactions with each other (labelled in squares) indicating the *cis* positions of these two hydroxyl groups, which is consistent with 5-feruloyl monoester (see **Figure 47**). Thus, the acylation position of monoester **211** was confirmed to be at position 5 and monoester **212** at position 3. In addition, the secondary Haxial at 5.51 ppm exhibits interactions (labelled in ovals) with these two hydroxyl groups providing additional proof for the acylation position and that the conformation (**Scheme 50a**) with an equatorial carboxylic group is more likely to be the predominant one for monoester **211** in $CDCl_3$. In the same way, the acylation positions of caffeoyl and *p*-coumaroyl monoesters were also confirmed.

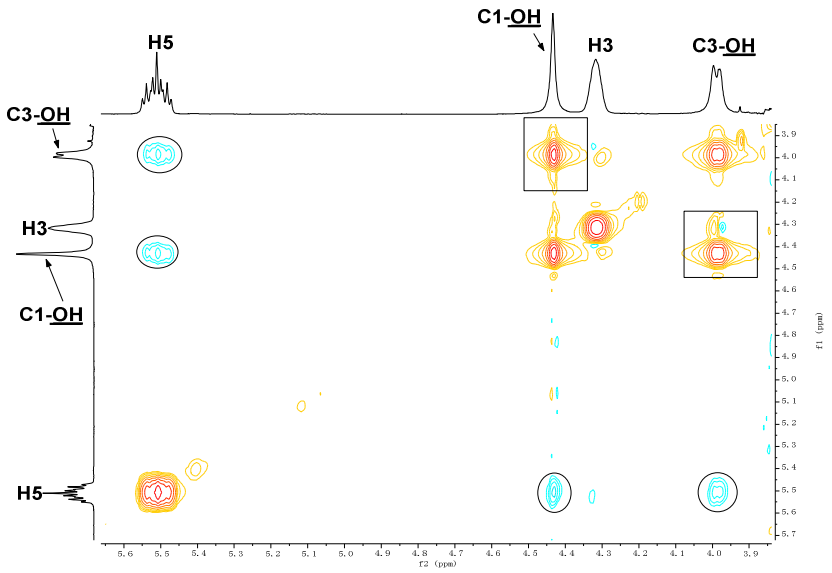


Figure 47 ^{1}H-^{1}H NOESY (in $CDCl_3$) of 211

2.4.3 Synthesis of heterodiesters

A total number of six different heterodiesters were obtained including 3-*O*-feruloyl-5-*O*-caffeoyldiester **215** (F-Ca), 3-*O*-*o*-coumaroyl-5-*O*-caffeoyldiester **216** (*o*Co-Ca), 3-*O*-*p*-coumaroyl-5-*O*-caffeoyldiester **217** (*p*Co-Ca), 3-*O*-*p*-coumaroyl-5-*O*-

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feruloyldiester **218** (*p*Co-F), 3-*O*-feruloyl-5-*O*-*p*-coumaroyl diester **219** (F-*p*Co), and 3-*O*-caffeoyl-5-*O*-*p*-coumaroyl diester **220** (Ca-*p*Co).

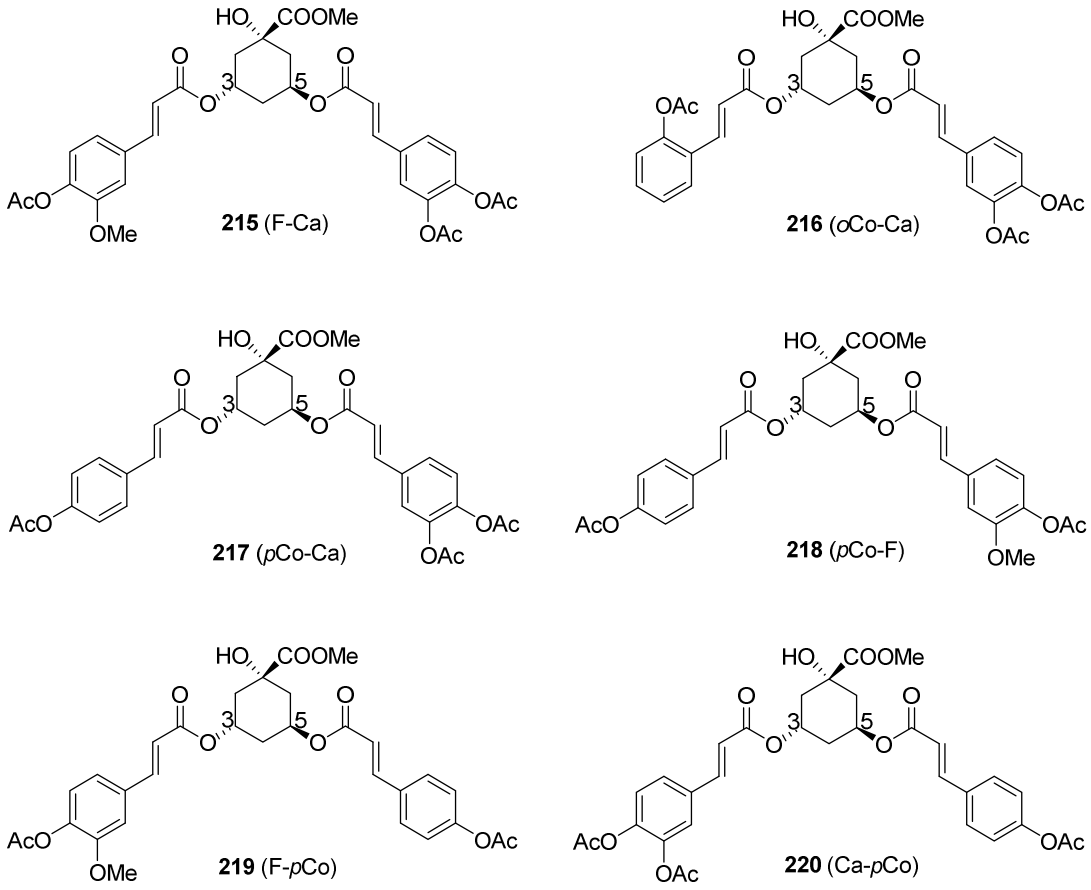


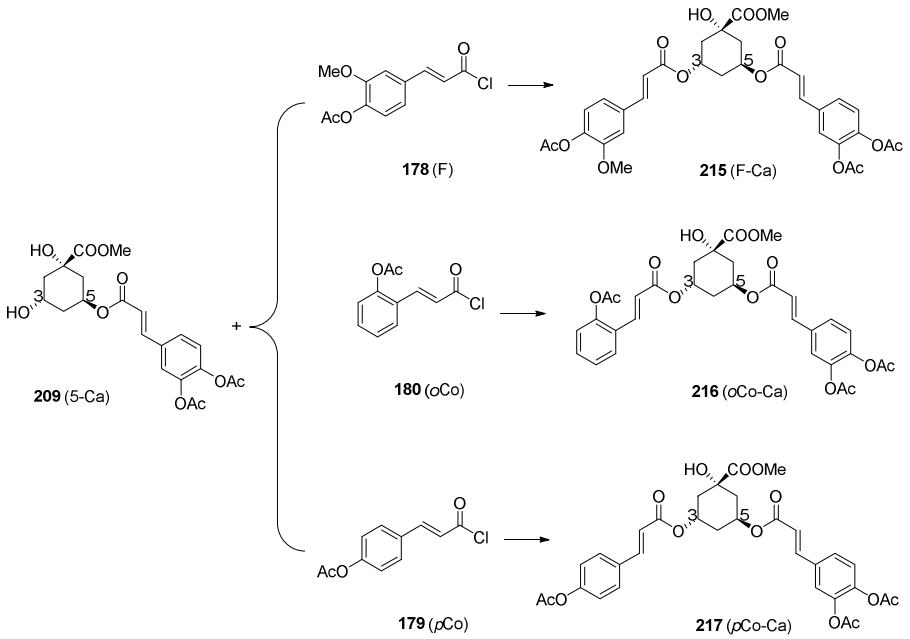
Figure 48 Structures of six 3,5-heterodiesters

The coupling reactions of monoesters with a different acid chloride turned out to be difficult and complex.

Firstly, 5-*O*-caffeoylester **209** (5-Ca) was reacted with protected feruloyl chloride **178** (F), *p*-coumaroyl chloride **179** (*p*Co) and *o*-coumaroyl chloride **180** (*o*Co) to make different heterodiesters (see **Table 8**).

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Table 8 Synthesis of heterodiesters from monoester 209



Entry	Starting material (code)	Acid chloride (code) (M equiv.)	Solvent[a]	Temp. (°C)	Time (h)	Products (code)	Results[b]
1	**209** (5-Ca)	**178** (F) (1.2)	DMF/pyridine	45	0.5	**215** (F-Ca)	54%[c]
2	**209** (5-Ca)	**178** (F) (1.2)	DMF/pyridine	45	3	**215** (F-Ca)	41%[c]
3	**209** (5-Ca)	**178** (F) (1.5)	DMF/pyridine	45	0.5	**215** (F-Ca)	62%[d]
4	**209** (5-Ca)	**178** (F) (1.5)	DMF/pyridine	0 - rt	4	**215** (F-Ca)	62%
5	**209** (5-Ca)	**178** (F) (1.5)	DCM/pyridine	0 - rt	4	**215** (F-Ca)	54%
6	**209** (5-Ca)	**180** (*o*Co) (1.2)	DMF/pyridine	45	3	**216** (*o*Co-Ca)	39%[c]
7	**209** (5-Ca)	**179** (*p*Co) (2)	DMF/pyridine	45	4	**217** (*p*Co-Ca)	62%[c]

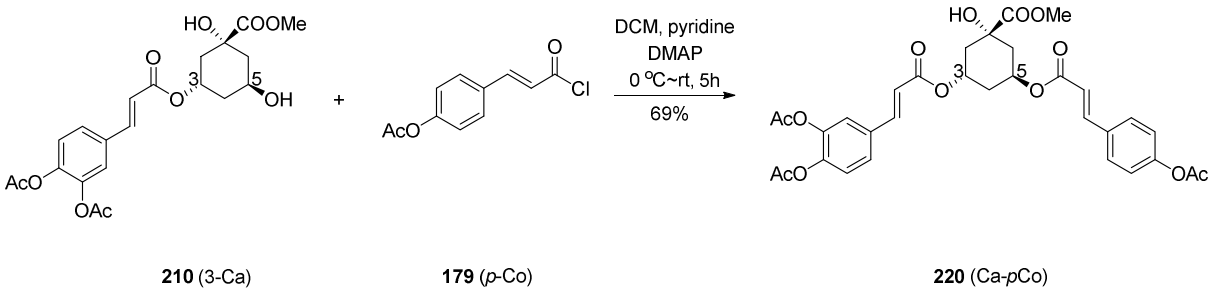
[a] DMF/pyridine (v:v) = 3/2, 0.4 M; DCM/pyridine (v:v) = 5/1, 0.1 M, with 20% DMAP. [b] Isolated yields. [c] Incomplete conversion. [d] A triester was isolated in 9% yield.

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An incomplete conversion of 5-*O*-caffeoylester **209** (5-Ca) was observed using 1.2 equivalents of feruloyl chloride **178** (F) at 45 °C in DMF/pyridine in 0.5 h (entry 1) providing 3-*O*-feruloyl-5-*O*-caffeoyldiester **215** (F-Ca) in 54% yield. A longer reaction time (3 hours, entry 2) using 1.2 equivalents of acid chloride did not improve the ratio of conversion of the starting monoester but made the reaction more complex and decrease the isolated yield from 54% to 41% (entries 2 vs 1). With 1.5 equivalents of feruloyl chloride **178** (F), a complete conversion of 5-*O*-caffeoylester **209** (5-Ca) was confirmed by TLC and the 3-*O*-feruloyl-5-*O*-caffeoyldiester **215** (F-Ca) and a triester were isolated with yields of 62% and 9%, respectively (entry 3). The coupling reaction conducted in a lower temperature (0 °C to room temperature, entry 4) did not give a better yield of 3-*O*-feruloyl-5-*O*-caffeoyldieser **215** (F-Ca) (entries 4 vs 3). The DCM/pyridine/DMAP system was also used at 0 °C to room temperature providing 3-*O*-feruloyl-5-*O*-caffeoyldieser **215** (F-Ca) in 54% yield (entry 5). When *o*-coumaroyl chloride **180** (*o*Co) and *p*-coumaroyl chloride **179** (*p*Co) were used as the acylation reagent of 5-*O*-caffeoylester **209** (5-Ca) in DMF/pyridine at 45 °C, corresponding 3-*O*-*o*-coumaroyl-5-*O*-caffeoyldiester **216** (*o*Co-Ca) and 3-*O*-*p*-coumaroyl-5-*O*-caffeoyldiester **217** (*p*Co-Ca) were obtained respectively in 39% and 62% yields (entries 4 and 5).

The coupling reactions from 3-*O*-caffeoylester **210** (3-Ca) were also performed. With 2.1 equivalents of protected feruloyl chloride **178** (F) in DMF/pyridine at 45 °C for 8h, an incomplete conversion of the starting monoester was observed and no pure product was obtained from the resulted complex mixture. When 1.8 equivalents of *p*-coumaroyl chloride **179** (*p*Co) was used at 0 °C to room temperature for 5h, the conversion of starting monoester was still incomplete but the 3-*O*-caffeoyl-5-*O*-*p*-coumaroyl diester **220** (Ca-*p*Co) was isolated in 69% yield.

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210 (3-Ca) **179** (*p*-Co) **220** (Ca-*p*Co)

Scheme 51 Coupling of monoester 210 with *p*-coumaroyl chloride

As mentioned in Chapter 1, 4-deoxy-3,5-di-*O*-caffeoylquinic acid **193** and 4-deoxy-3,5-di-*O*-*p*-coumaoylquinic acid **197** have shown better insecticidal activities than natural 3,5-di-*O*-Caffeoylquinic acid. The 3-*O*-caffeoyl-5-*O*-*p*-coumaroyl diester **220** could be subjected to deprotection reactions and the bioassays of the corresponding 4-deoxy-3-*O*-caffeoyl-5-*O*-*p*-coumaroylquinic acid could be performed in the future.

The coupling reactions using 5-*O*-feruloylester **211** (5-F) as substrate (**Table 9**) turned out to be the most complex. Again, a complete conversion of 5-*O*-feruloylester **211** (5-F) has never been observed even with a large excess of acid chloride (10.4 equivalents of caffeoyl chloride **54** (entry 1) and *o*-coumaroyl chloride **180** (entry 2), 8 equivalents for *p*-coumaroyl chloride **179** (entry 3) and a long reaction time. The purification was difficult attributed to a complicated reaction mixture, and only pure 3-*O*-*p*-coumaroyl-5-*O*-feruloyldiester **218** (*p*Co-F) was isolated in 43% yield (entry 3).

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Table 9 Synthesis of heterodiesters from 5-feruloylmonoester 211

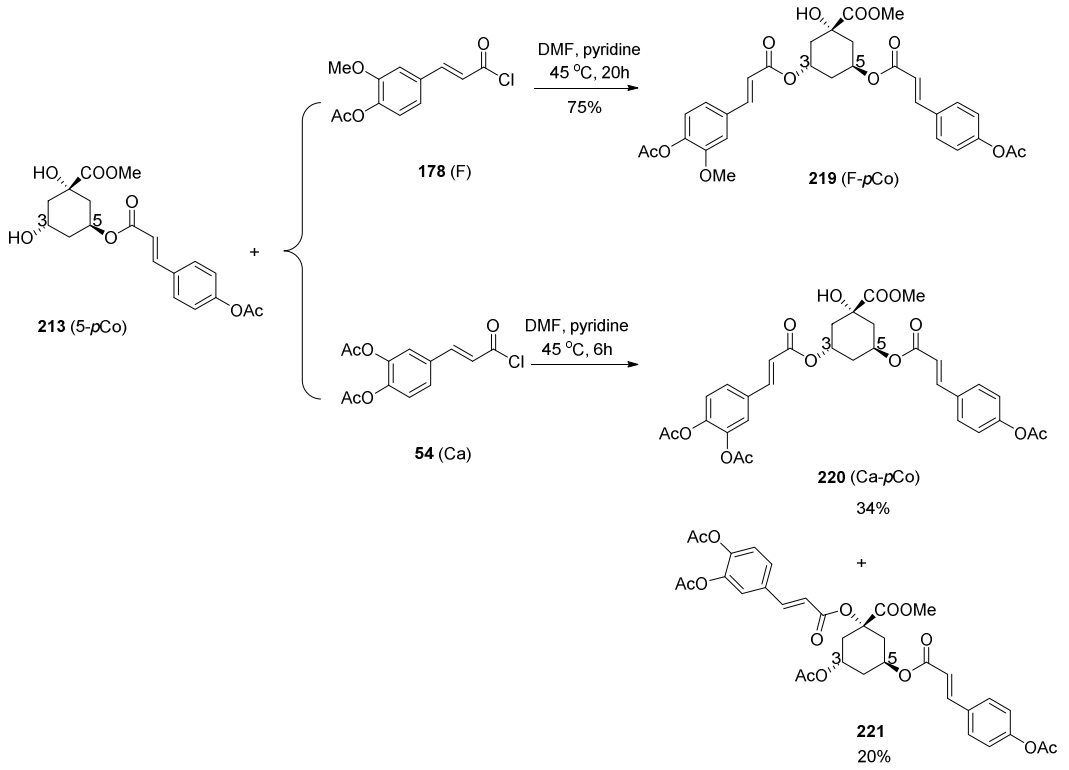
Entry	Starting material (code)	Acid chloride (code) (M equiv.)	Solvent[a]	Temp. (°C)	T. (h)	Products (code)	Results[b]
1	**211** (5-F)	**54** (Ca) (10.4)	DMF/pyridine	45	22	--	nd[c,d]
2	**211** (5-F)	**180** (*o*Co) (10.4)	DMF/pyridine	45	22	--	nd[c,d]
3	**211** (5-F)	**179** (*p*Co) (8)	DMF/pyridine	45	30	**218** (*p*Co-F)	43%[c]

[a] DMF/pyridine (v:v) = 3/2, 0.4 M. [b] Isolated yield. [c] Incomplete conversion. [d] No pure product was obtained.

When 5-*O*-*p*-coumaroylester **213** (5-*p*Co) was used as the substrate for the second coupling, two other heterodiesters including 3-*O*-feruloyl-5-*O*-*p*-coumaroyldiester **219** (F-*p*Co) and 3-*O*-caffeoyl-5-*O*-*p*-coumaroyldiester **220** (Ca-*p*Co) were obtained in 75% and 34% yields. Another new compound 1-*O*-caffeoyl-3-*O*-acetyl-5-*O*-*p*-coumaroyltriester **221** was also isolated in 20% yield resulting from the reaction of 5-*O*-*p*-coumaroylester **213** (5-*p*Co) with caffeoyl chloride **54**. The structure of compound **221** demonstrates that a transesterification reaction occurred between the hydroxyl group at position 3 and the acetyl aromatic ester, which should have resulted into the generation of free phenol group, a high reactive functional group with a potential to make more chaos. In addition, the acylation of the tertiary hydroxyl at C-1 was also available under these conditions. The information given by compound **221** may help to explain the complexity of the reaction system.

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Table 10 Synthesis of heterodiesters from 5-*p*-coumaroylmonoester 213



Entry	Starting material (code)	Acid chloride (code) (M equiv.)	Solvent[a]	Temp. (°C)	T. (h)	Products (code)	Results[b]
1	**213** (5-*p*Co)	**178** (F) (2.5)	DMF/pyridine	45	20	**219** (F-*p*Co)	75%[c]
2	**213** (5-*p*Co)	**54** (Ca) (2.5)	DMF/pyridine	45	6	**220** (Ca-*p*Co)	34%[c,d]

[a] DMF/pyridine (v:v) = 3/2, 0.4 M. [b] Isolated yields. [c] Incomplete conversion. [d] Compound **221** was isolated in 20% yield.

All these six heterodiesters were fully characterized. A test confirming the stability of 5-*O*-caffeoylester **209** and 3-*O*-caffeoylester **210** in DMF/pyridine system at 45 °C

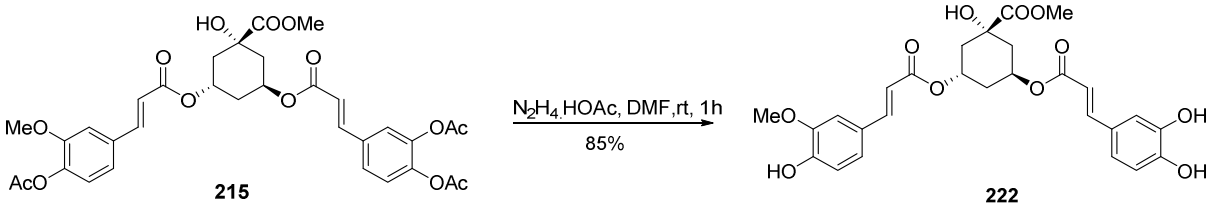
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for 1 hour and in DCM/pyridine/DMAP at 0 °C to room temperature for 4 hours were performed without any addition of acid chloride. The NMR analysis of the resulting crudes demonstrates that no migration of cinnamoyl group had occurred during the second coupling under these conditions.

2.4.4 Deprotection reactions

Among these six heterodiesters, 3-*O*-feruloyl-5-*O*-caffeoyldiester **215**, available in large amount, could be submitted to deprotection procedures to get the targeted methyl ester analog **222** and carboxylic acid analog **224**.

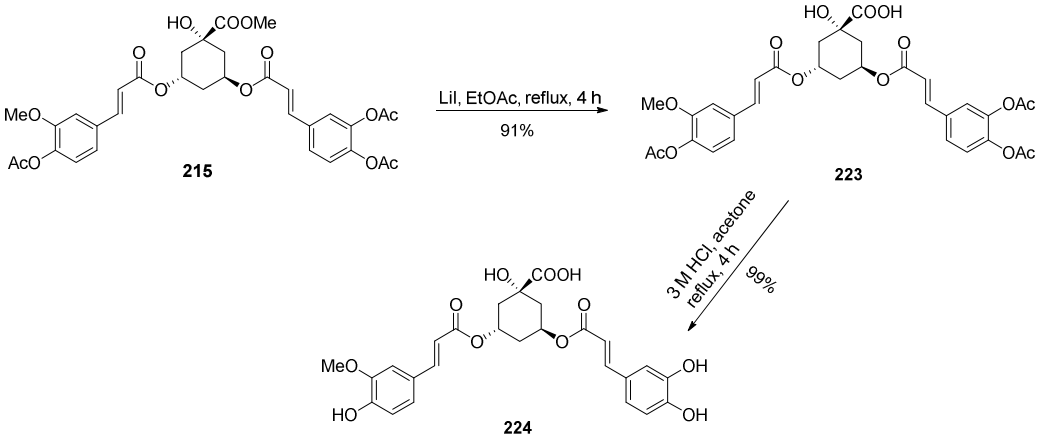
First, a selective deprotection of acetate groups of **215** with hydrazine acetate in DMF at room temperature in 1 hour provided 4-deoxy-3-*O*-feruloyl-5-*O*-caffeoylquinic acid methyl ester **222** in 85% yield (**Scheme 52**).



Scheme 52 Selective deprotection of 3-*O*-feruloyl-5-*O*-caffeoyldiester 215

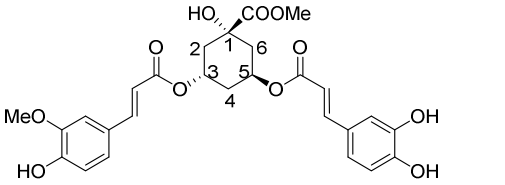
Then 3-*O*-feruloyl-5-*O*-caffeoyldiester **215** was subjected to a two-step total deprotection procedure first with excessive LiI in refluxing ethyl acetate for 4 hours providing acid **223** then with 3 M HCl in refluxing acetone for 4 hours giving 3-*O*-feruloyl-4-deoxy-5-*O*-caffeoylquinic acid **224** in overall 90% yield (**Scheme 53**).

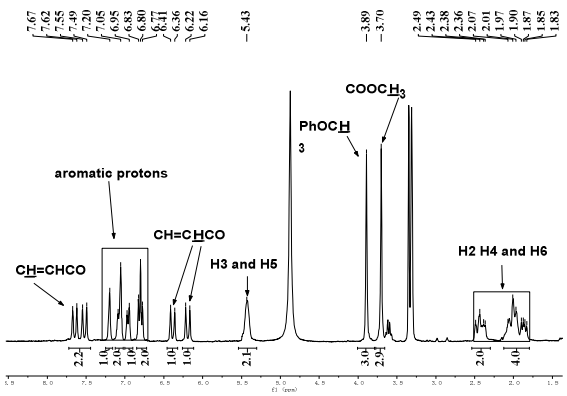
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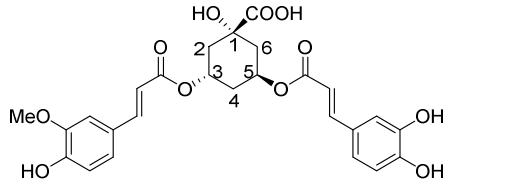
Scheme 53 Total deprotection of 3-*O*-feruloyl-5-*O*-caffeoyldiester 215

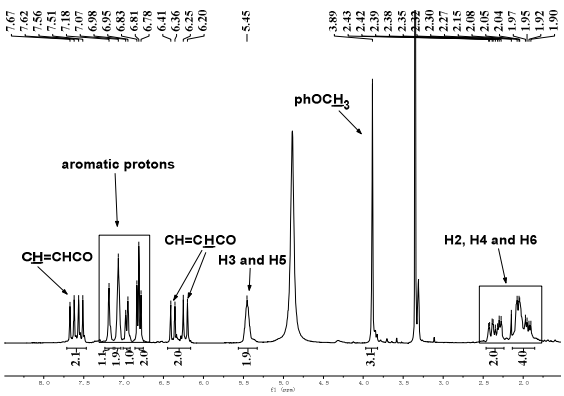
These two final products **222** and **224** were fully characterized. In **Figure 49a**, acetyl groups were completely removed; in **Figure 49b**, both methyl ester group and acetyl groups were removed. The ^{1}H NMR spectra of these two compounds almost coincide with each other except the signal of methyl ester group of **222**.





a ^{1}H NMR (in MeOD) of **222**





b ^{1}H NMR (in MeOD) of **224**

Figure 49

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2.5 Conclusions

For the synthesis of 4-deoxy-3,5-*O*-dicinnamoylquinic acid and methyl esters, a new intermediate named 4-deoxy methyl quinate was obtained in 53% yield in 5 steps from quinic on the multi-gram scale. Since the reported chemical synthetic procedures vary greatly for different substrates, a screening of coupling reactions was first performed. As a result, two kinds of conditions using DMF/pyridine or DCM/pyridine/DMAP were found appropriate for coupling reactions of 4-deoxy methyl quinate with different protected cinnamoyl chlorides. Five homodiesters including two caffeoyldiesters (acetyl protected and allyl protected), one feruloyldiester, one *p*-coumaroyldiester, and one *o*-coumaroyldiester were obtained *via* bis coupling reactions of 4-deoxy methyl quinate with different cinnamoyl chlorides with repeatable yields. Then by selective deprotection of phenol protecting groups of these five homodiesters, four 4-deoxy-3,5-di-*O*-cinnamoylquinic acid methyl esters were prepared; by a two-step total deprotection of both methyl ester and acetate groups, three 4-deoxy-3,5-di-O-cinnamoylquinic acids were obtained. These compounds exhibit better stability than natural compounds in terms of blocking the migration of cinnamoyl groups. These seven targeted 4-deoxy CQA analogs were subjected to insecticidal bioassays, and two compounds 4-deoxy-3,5-di-*O*-caffeoylquinic acid and 4-deoxy-3,5-di-*O*-*p*-coumaroylquinic acid were found to exhibit higher insecticidal activities than natural 3,5-di-*O*-caffeoylquinic acid. At the same time, six heterodiesters were also prepared by a two-step sequential coupling of 4-deoxy methyl quinate with different cinnamoyl chlorides in two steps. Although the complete conversion of starting 4-deoxy methyl quinate has never been observed with less than 2 equivalents of acid chlorides, six monoesters were obtained and their substitution on secondary positions were confirmed by NMR analysis. The second-step coupling reactions of these monoesters turned out to be very complex but six heterodiesters bearing different cinnamoyl groups at positions 3 and 5 were obtained. A byproduct 1-O-caffeoyl-3-O-acetyl-5-O-p-coumaroyltriester

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was isolated, which indicates the occurrence of transesterification reactions and acylation at the tertiary hydroxyl group (position 1). Nevertheless, six 3,5-*O*-heterodiesters were obtained in our hands. Among them, the maximum scaled 3-*O*-feruloyl-5-*O*-caffeoyldiester was subjected to both a selective deprotection and a two-step total deprotection to provide targeted 3-*O*-feruloyl-4-deoxy-5-*O*-caffeoylquinic methyl ester and acid. In general, a synthetic route was developed in our lab to get new 4-deoxy dihydroxycinnamoylquinic acid and methyl ester analogs *via* 8 or 7 steps from D-quinic acid. As perspectives to this work, the same insecticidal activity of heterodiesters could be conducted. More specific bioassays, such as behaviour-oriented short-term bioassays, may be realized. Confirming the activity of the synthesized compounds on other aphid species of agronomic importance could also be performed. Furthermore, expected collaborations could be established with other biologists dedicated to measure other bioactivities of the synthesized compounds or use them as tools to investigate various biological pathways.

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Chapter 3 Towards natural 3,4- and 4,5-di-*O*-CQA derivatives

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3.1 Introduction

Dicinnamoylquinic acids (DCQA) are a class of natural polyphenolic compounds isolated from a wide spectrum of natural resources such as *Isertia pittieri*,[180] *Eleutherococcus senticosus*,[181] *Ilex brevicuspis*,[182] sweet potato leaf,[183] fennel (*Foeniculum vulgare*),[184] Conyza filaginoides,[185] green coffee beans[178] *etc*. and have shown a range of biological activities including antiviral,[186] antioxidant,[187] anti-inflammatory,[188] antimutagenicity,[183] neuroprotective effect[189] *etc*.

It was suggested in some reports that the number of cinnamoyl groups is important for the biological activities of CQA.[113,183,185] For example, 3,4-di-*O*-caffeoylquinic acid showed stronger tyrosinase inhibitory activity than 4-*O*-caffeoylquinic acid and 5-*O*-caffeoylquinic acid;[185] 3,4,5-tri-*O*-caffeoylquinic acid was found to exhibit higher accelerating activity on ATP production than 4,5-di-*O*-caffeoylquinic acid.[113]

The study of the working mechanism, the structure-activity relationship, the metabolism *in vivo* of CQA needs the preparation of fully characterized standard compounds. However, the reports on the synthesis of DCQA are rather limited, to the best of our knowledge, only two examples concerned the synthesis of 3,4-di-*O*-caffeoylquinic acid[112,113] and one for 3,5-di-*O*-cinnamoylquinic acids.[138] The synthesis of 4,5-di-*O*-cinnamoylquinic acids has never been reported.

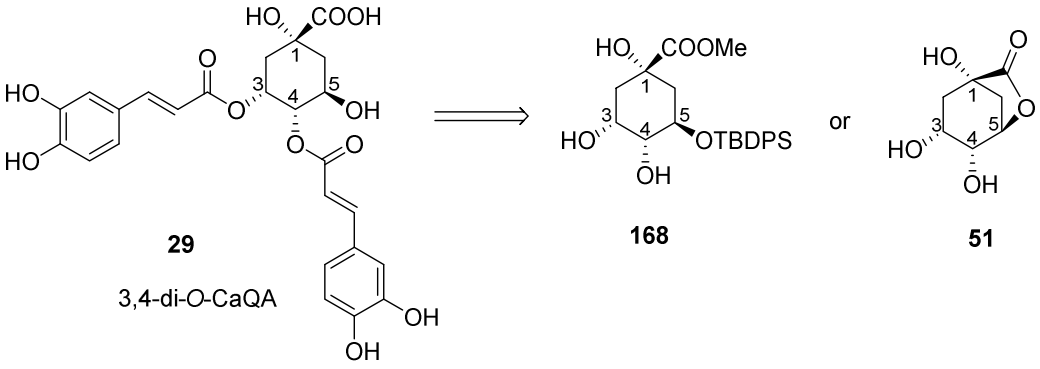
In order to get various 3,4- and 4,5-diCQA (homo or heterodiesters), four compounds including 5-*O*-TBDPS substituted intermediate triol **168** and quinide **51** as precursors for 3,4-diCQA, and 3-*O*-TBDPS substituted intermediate triol **169** and a carbonate diol **170** as precursors for 4,5-diCQA were prepared and their coupling reactions were investigated.

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3.2 Towards 3,4-di-*O*-CQA derivatives

3.2.1 Preparation of two triol intermediates

Our retrosynthetic analysis for 3,4-di-*O*-CQA derivatives was demonstrated in **Scheme 31**. The carboxylic acid group and OH-5 were protected respectively as methyl ester and silyl ether in a new triol **168**. The widely used quinide **51** with a locked conformation were also used for bis 3,4-coupling. The tertiary hydroxyl at C-1 was supposed to be less reactive than the 2 hydroxyl groups at C-3 and C-4 and thus to be not touched in coupling reactions unless with a large excessive equivalents of acid chloride and under specific conditions. The different coupling reaction activities of triol **168** and quinide **51** would provide useful information about the effect of the molecule conformation on the reactivity of free hydroxyl groups.

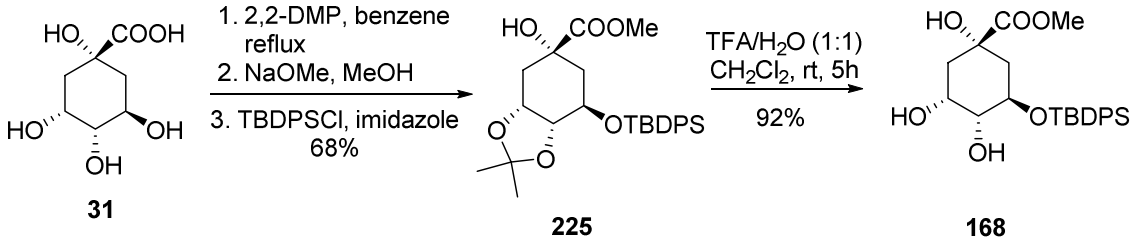


Scheme 31 (seen also in Chapter 1) Retrosynthetic analysis of 3,4-di-*O*-CaQA

As demonstrated in **Scheme 54**, the synthesis of new triol **168** was based on the preparation of a known compound **225**.[190] Quinic acid **31** was converted to the corresponding lactone acetonide, followed by the lactone ring-opening reaction to give the methyl ester, and then the protection of the free alcohol with TBDPSCl afforded protected acetonide **225** in a three-step 68% yield. Removal of the acetonide protecting

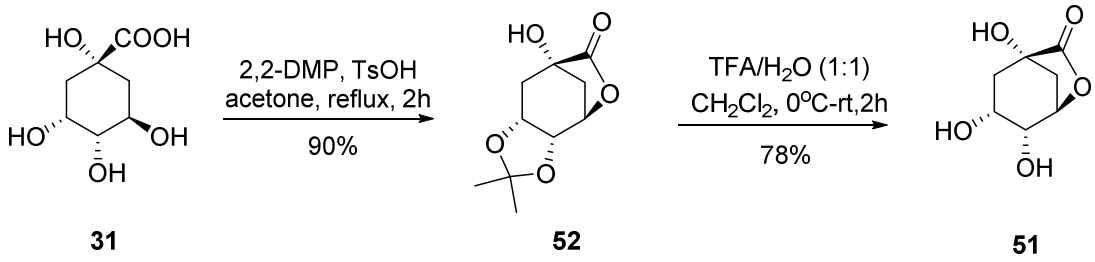
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group was accomplished in 92% yield with TFA/H_2O (1/1) in CH_2Cl_2 to give a new silylated triol **168**,[114] which was fully characterized and then used for coupling reactions.



Scheme 54 Synthesis of triol 168

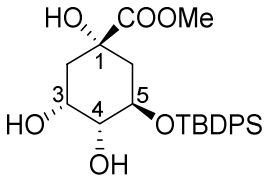
For the synthesis of quinide **51**, quinic acid **31** was first converted to **52** with 2,2-dimethoxypropane with TsOH in refluxing acetone in 90% yield.[53] The acetonide protecting group was removed with TFA/H_2O (1/1) in CH_2Cl_2 to give quinide **51** in 78% yield.[114]



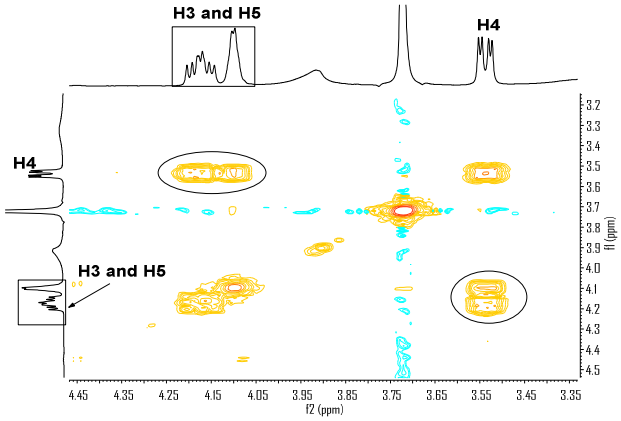
Scheme 55 Synthesis of quinide 51

The assignment of the structure of triol **168** was achieved by the analysis of its NMR spectra. Frist, the dd signal at 3.54 ppm is identified as H4 since it correlates with both secondary protons H3 and H5 in ^1H-^1H COSY (**Figure 50b**).

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168

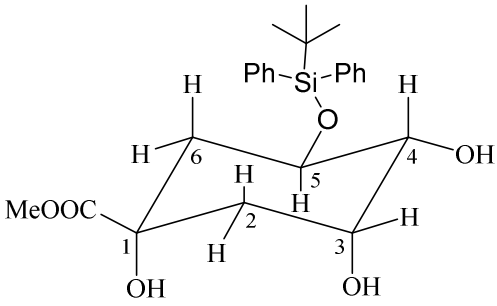


a Structure of triol **168**

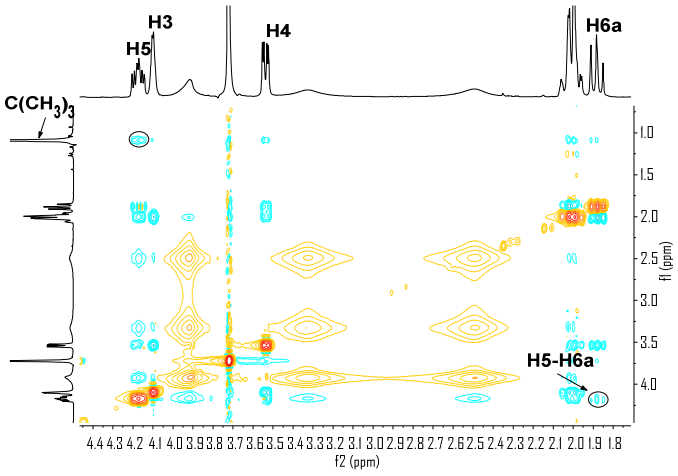
b ^{1}H-^{1}H COSY (in $CDCl_3$) of triol **168**

Figure 50

The assignment of secondary protons H3 and H5 relies on the analysis of ^{1}H-^{1}H NOESY spectrum.



168



a The more favored conformation of triol **168**

b ^{1}H-^{1}H NOESY (in $CDCl_3$) spectrum of triol **168**

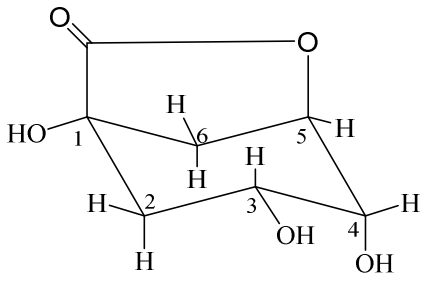
Figure 51

As shown in **Figure 51b**, the nine methyl protons of TBDPS group exhibit a stronger coupling signal with the ddd signal at 4.17 ppm than the multiplet at 4.13-4.07

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ppm indicating the former is H5 and the latter is H3. The coupling constants of H5 ($^3J_{H5\text{-}H6a}$ 10.6 Hz, $^3J_{H5\text{-}H4}$ 10.0 Hz and $^3J_{H5\text{-}H6e}$ 4.7 Hz) and H4 ($^3J_{H4\text{-}H5}$ 9.0 Hz, $^3J_{H4\text{-}H3}$ 3.2 Hz) match with a preferred chair conformation with an equatorial carboxylic ester as depicted in **Figure 51a**. The dd signal at 1.88 ppm is identified as H6a showing the interaction signal with H5 and coupling constants $^2J_{H6a\text{-}H6e}$ 13.2 Hz and $^3J_{H6a\text{-}H5}$ 10.9 Hz.

In contrast, the quinide **51** presents a locked conformation due to the bicyclic lactone. So, the three secondary protons at positions 3, 4, and 5 of quinide **51** were axial, equatorial, and equatorial, which are all in contrary with those of triol **168**.



51

Figure 52 The locked conformation of quinide 51

3.2.2 Coupling from triol 168

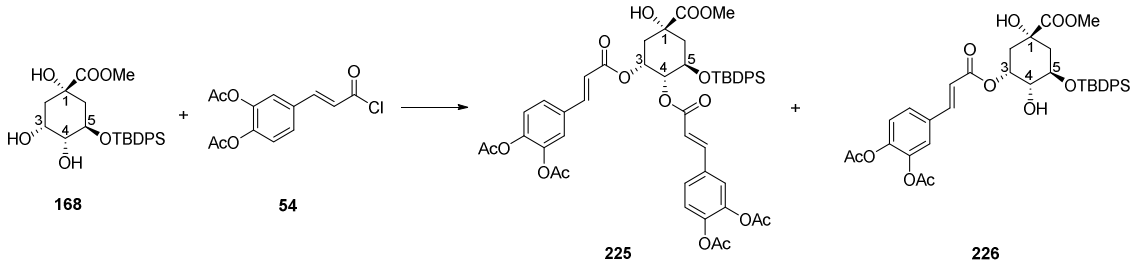
3.2.2.1 Coupling with caffeoyl chloride

Lucie Grand made the first attempts for a screening of reported coupling conditions, but this work gave unrepeatable results. The screening of coupling conditions with 4-deoxy methyl quinate in Chapter 2 opened new perspectives for CQA synthesis.

The coupling reactions of triol **168** with acetyl protected caffeoyl chloride **54** were performed in three kinds of conditions including pyridine/DMAP, DCM/pyridine/DMAP, and DMF/pyridine (see **Table 11**).

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Table 11 The coupling reactions of 168 with acetyl protected caffeoyl chloride 54



Entry	Molar equiv. of 54	Catalyst[a]	Solvent[b]	Con.	Temp.	Time	Yields[c] 225	Yields[c] 226
1	4	DMAP	pyridine	0.1M	70 °C	30h	15%	7%
2	4	DMAP	pyridine	0.1M	40 °C	5h		38%
3	2	DMAP	pyridine	0.3M	rt	4h		51%
4	3	DMAP	DCM/pyridine	0.1M	-18 °C-rt	4h	52%	
5	3		DMF/pyridine	0.4M	-18 °C-rt	4h	nd[d]	
6	1.5	DMAP	DCM/pyridine	0.1M	-18 °C-rt	4h		86%
7	1.5		DMF/pyridine	0.4M	-18 °C-rt	3h	nd[d]	

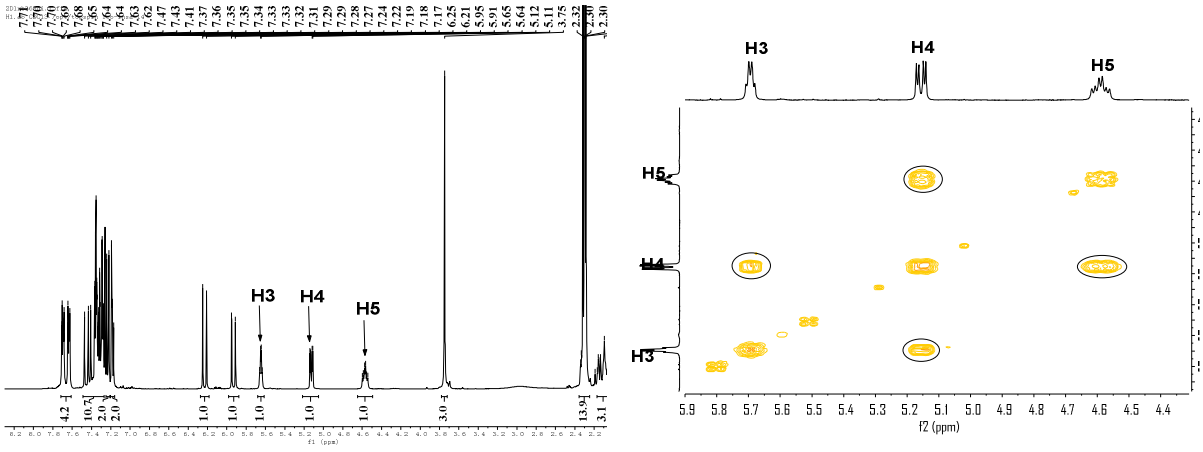
[a] 20% DMAP. [b] DCM/pyridine (v:v) = 5/1, DMF/pyridine (v:v) =3/2. [c] Isolated yields. [d] Difficult purification and no pure product was obtained.

In pyridine/DMAP system, when triol **168** was reacted with 4 equivalents of caffeoyl chloride **54** at 70 °C for 30 hours, diester **225** and monoester **226** were isolated in 15% and 7% yields (entry 1). When the coupling reactions were performed at lower temperatures (40 °C in entry 2, room temperature in entry 3) with 4 (entry 2) or 2 equivalents (entry 3) of caffeoyl chloride **54**, only pure monoester **226** was isolated in

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rather low yields (38% in entry 2, and 51% in entry 3). The procedure using DCM/pyridine/DMAP system (entries 4 and 6) proceeded well for both the bis- (entry 4) and mono-coupling (entry 6). The bis-coupling reaction of triol **168** with 3 equivalents of caffeoyl chloride **54** was performed at -18 ºC to room temperature in DCM/pyridine with DMAP providing diester **225** in a moderate 52% yield (entry 4). When 1.5 equivalents of caffeoyl chloride **54** was used under the same conditions, monoester **226** was obtained in a good 86% yield. In DMF/pyridine system, both the bis-coupling reaction with 3 equivalents of caffeoyl chloride **54** (entry 5) and the mono-coupling reaction with 1.5 equivalents of caffeoyl chloride **54** (entry 7) resulted into complex mixtures, from which no pure products were isolated. So the DCM/pyridine/DMAP system was an effective method for the coupling reactions of triol **168** with caffeoyl chloride **54**. The diester **225** and monoester **226** were then fully characterized.

The confirmation of the acylation positions of the diester **225** and the monoester **226** was achieved by the analysis of their NMR spectra.



a ^{1}H NMR (in $CDCl_3$) of diester **225** **b** ^{1}H-^{1}H COSY NMR (in $CDCl_3$) of diester **225**

Figure 53

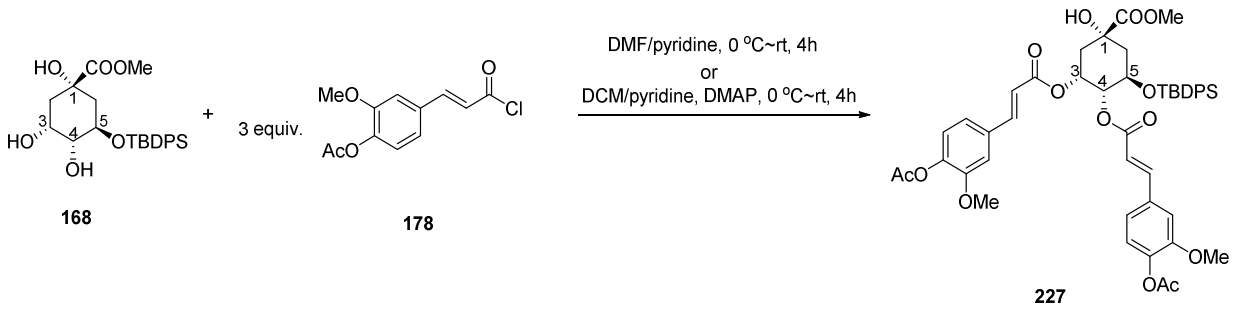
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In Figure **53a**, the value of integration shows the formation of two ester groups. Compared with triol **168**, the signals for H3 and H4 of diester **225** have been shifted to a lower field region indicating the diesterification was at positions 3 and 4. In Figure **53b**, the ^{1}H-^{1}H COSY NMR helps to distinguish H3 and H4. Then the diester **225** is confirmed to be 3,4-*O*-dicaffeoylester. In the same way, the monoester **226** is confirmed to be 3-*O*-caffeoylester. In addition, the coupling constants of the H3, H4 and H5 of both diester **225** and monoester **226** indicate that their favored conformation is with the carboxylic ester in equatorial position (in $CDCl_3$).

3.2.2.2 Coupling with ferulic and *p*-coumaroyl chloride

The triol **168** was also reacted with acetyl protected feruloyl chloride **178** and *p*-coumaroyl chloride **179** to prepare corresponding feruloyl and *p*-coumaroylesters.

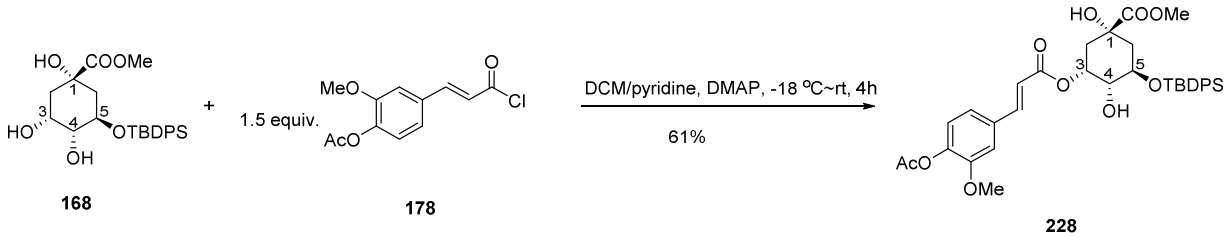
The bis-coupling reactions of triol **168** with 3 equivalents of feruloyl chloride **178** in both DMF/pyridine and in DMC/pyridine/DMAP systems resulted into complex mixtures, from which the isolation of pure products was difficult. The pure diester **227** was obtained after purification by three times chromatography with eluent systems EtOAc/pentane, Et_2O/DCM and Et_2O/pentane but no yield could be calculated. The diester **227** was confirmed to be the 3,4-*O*-diferuloylester by the analysis of its NMR spectra.



Scheme 56 Diesterification of triol 168 with feruloyl chloride 178

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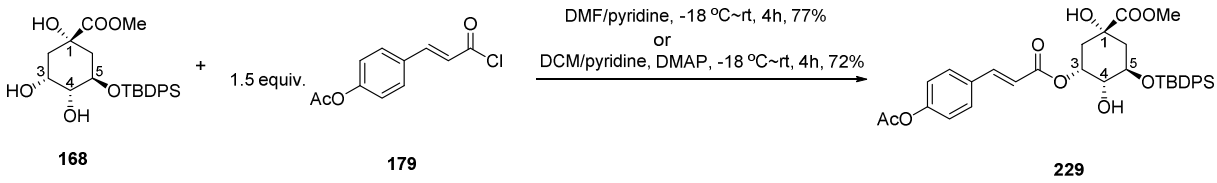
When triol **168** was reacted with 1.5 equivalents of feruloyl chloride **178** in DCM/pyridine/DMAP system, the resulting crude was complex and twice chromatography sequentially with different eluent systems EtOAc/pentane and Et_2O/pentane was necessary to obtain the pure monoester **228** in 61% yield. The monoester **228** was confirmed to be the 3-*O*-feruloylester by the analysis of its NMR.



Scheme 57 Monoesterification of triol 168 with feruloyl chloride 178

The bis-coupling reaction of triol **168** with 3 equivalents of *p*-coumaroyl chloride **179** under DCM/pyridine/DMAP system at -18 °C to room temperature resulted in a complex mixture and, unfortunately, no pure *p*-coumaroyldiester was isolated.

The mono-coupling reactions of triol **168** with 1.5 equivalents of *p*-coumaroyl chloride **179** were performed under both DCM/pyridine/DMAP and DMF/pyridine systems at low temperatures giving *p*-coumaroylester **229** in 72% and 77% yield respectively as shown in Scheme **58**. The monoester **229** was confirmed to be the 3-*O*-*p*-coumaroylester by the analysis of its NMR.



Scheme 58 Monoesterification of triol 168 with *p*-coumaroyl chloride 179

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Thus, by the coupling reactions of triol **168** with protected caffeoyl chloride **54**, feruloyl chloride **178**, and *p*-coumaroyl chloride **179**, two homodiesters including 3,4-di-*O*-caffeoylester **225** and 3,4-di-*O*-feruloylester **227** and three monoesters including 3-*O*-caffeoylester **226**, 3-*O*-feruloylester **228**, and 3-*O*-*p*-coumaroylester **229** were synthesized. The more favored conformation of triol **168** and these five esters is always with an equatorial carboxylic ester (in $CDCl_3$). In addition, these monoesters can be reacted with a different cinnamoyl chloride to make different heterodiesters in the future.

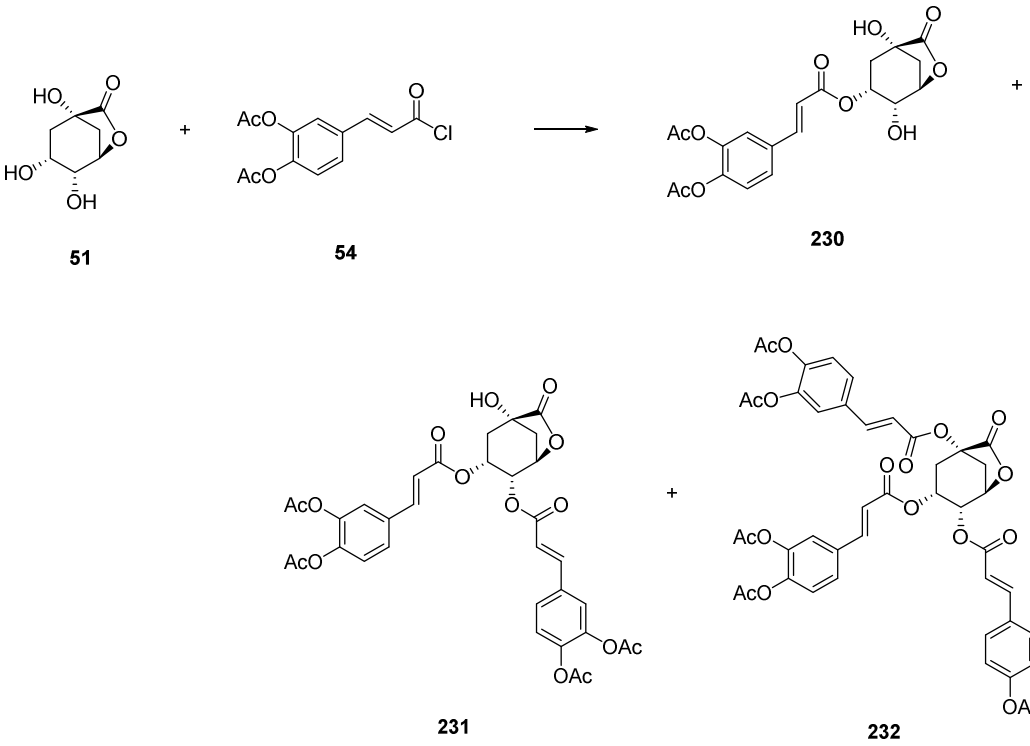
3.2.3 Coupling from quinide 51

3.2.3.1 Diesterification

The results of the bis-coupling reactions aiming at corresponding 3,4-di-*O*-caffeoyldiester by acylation of quinide **51** with protected caffeoyl chloride **54** were summarized in **Table 12**. When the reactions were carried out with excessive acid chloride **54** (2.5 or 4 equivalents) at 45 ^oC in DMF/pyridine (entries 1 and 2), no pure products were isolated from the resulted complex reaction mixtures. Then the reaction was performed with 3 equivalents of acid chloride at 0 ^oC to room temperature in DMF/pyridine (entry 3), the resulting mixture was complex and impure diester **231** and triester **169** were obtained. With less equivalents of acid chloride **54** and a more diluted solvent system, a complex mixture was obtained and only impure diester **231** and triester **169** were obtained in lower yields (entry 4). When the reaction was started at a lower temperature (-18 ^oC, entry 5) in DMF/pyridine, diester **231** was isolated in 31% yield. The coupling reaction using DCM/pyridine/DMAP system was also performed at -18 ^oC to room temperature with 3 equivalents of acid chloride but afforded only the monoester **230** in 10% yield (entry 6).

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Table 12 The coupling reactions of quinide 51 for diester 231



51 54 230 231 232

Entry	Molar equiv. of 54	Catalyst[a]	Solvent[b]	Con.	Temp.	Time	Yields[c] 230	231	232
1	2.5		DMF/pyridine	0.4M	45 °C	1.5h		nd[d]	
2	4		DMF/pyridine	0.4M	45 °C	1.5h		nd[d]	
3	3		DMF/pyridine	0.4M	0 °C-rt	4h		<26%[e]	<27%[e]
4	2.2		DMF/pyridine	0.1M	0 °C-rt	4h		<16%[e]	<3%[e]
5	3		DMF/pyridine	0.4M	-18 °C-rt	4h		31%	
6	3	DMAP	DCM/pyridine	0.1M	-18 °C-rt	4h	10%		

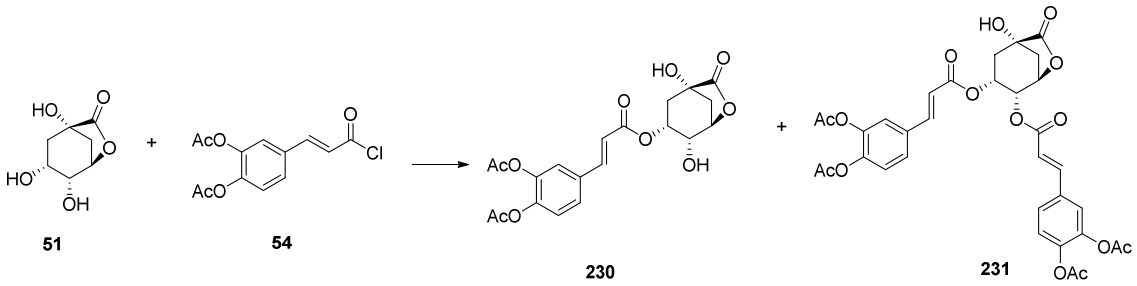
[a] 20% DMAP [b] DCM/pyridine (v:v) = 5/1, DMF/pyridine (v:v) = 3/2 [c] Isolated yields. [d] difficult purification and no pure product obtained. [e] mixed with impurities uncharacterized

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3.2.3.2 Monoesterification

The monoesterification reactions of quinide **51** aiming at an optimized yield of monoester **230** with caffeoyl chloride **54** were summarized in **Table 13**.

Table 13 The coupling reactions of quinide 51 for monodiester 230



Entry	Molar equiv. of 54	Catalyst[a]	Solvent[b]	Con.	Temp.	Time	Yields[c] 230	Yields[c] 231
1	1.5		DMF/pyridine	0.4M	0 °C-rt	4h	62%	<14%[d]
2	1.3		DMF/pyridine	0.4M	0 °C-rt	4h	nd[e]	
3	1.5	DMAP	DCM/pyridine	0.1M	-18 °C-rt	4h	nd[e]	

[a] 20% DMAP [b] DCM/pyridine (v:v) = 5/1, DMF/pyridine (v:v) = 3/2 [c] Isolated yields. [d] Mixed with DMF. [e] Difficult purification and a mixture of two different monoesters were obtained.

When the reaction was performed in DMF/pyridine with 1.5 equivalents of caffeoyl chloride **54** at 0 °C to room temperature for 4 hours (entry 1), the monoester **230** was isolated in 62% yield (with diester **231** in less than 14% yield). Betting for a better yield

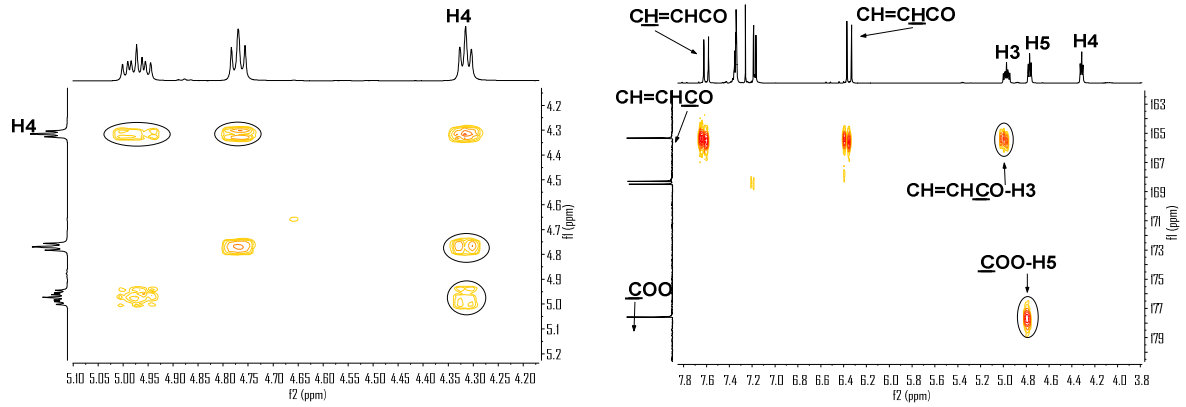
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of monoester **230** by lessening the generation of undesired diester **231**, 1.3 equivalents of acid chloride was used, (entry 2) but only a mixture of two different monoesters was obtained. The coupling reaction using DCM/pyridine/DMAP system at -18 °C to room temperature (entry 3) resulted in a complex mixture and, again, only a mixture of two different monoesters was obtained. So the best conditions we could obtain for getting monoester **230** were in DMF/pyridine system with a low starting temperature (0 °C) affording a 62% yield. For the perspectives, the feruloyl and *p*-coumaroylester may be prepared in similar conditions and these monoesters could be scaled up and subjected to the coupling reactions with a different cinnamoyl acid chloride to afford different heterodiesters.

3.2.3.3 Confirmation of the acylation positions

The confirmation of the acylation positions of both monoester **230** and diester **231** was achieved by the analysis of their NMR spectra. Taking the monoester **230** as an example, in the ^{1}H-^{1}H COSY spectrum (**Figure 54a**), the dd signal at 4.32 ppm is identified as the signal for H4 since it exhibits the interaction signals with both secondary protons H3 and H5. In ^{1}H-^{13}C HMBC NMR spectrum of monoester **230**, the dd multiplet at 4.77 ppm exhibits interaction signal with lactone carbonyl carbon (C<u>O</u>O) and is identified as H5; the ddd multiplet at 4.97 ppm shows interaction signals with the carbonyl carbon (CH=CHC<u>O</u>) in cinnamoyl moiety (**Figure 54b**) and, therefore, is identified as H3. Thus, the monoesterification was confirmed to be at position 3. In addition, the ddd splitting and coupling constants of H3 ($^{3}J_{H3\text{-}H2a}$ 11.3 Hz, $^{3}J_{H3\text{-}H4}$ 7.0 Hz and $^{3}J_{H3\text{-}H2e}$ 4.3 Hz) are consistent with the locked conformation. The diesterification was confirmed to be at positions 3 and 4 by the analysis of their NMR.

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a ^{1}H-^{1}H COSY (in $CDCl_3$) of monoester **230** **b** ^{1}H-^{13}C HMBC (in $CDCl_3$) of monoester **230**

Figure 54

In general, two 3,4-di-*O*-cinnamoylesters and three 3-*O*-cinnamoylesters were obtained in fair to good yields by the coupling reactions of triol **168**; the 3-*O*-caffeoylquinide ester and 3,4-di-*O*-caffeoylquinide ester were also prepared from quinide **51**. In monoesterification reactions of 5-*O*-silylated triol **168**, the 3-*O*-cinnamoylesters were the only monoesters obtained in good yields (61% - 86%) indicating the steric effect of the large TBDPS group may play an important role in determining the relative reactivity of the two hydroxyl groups at positions 3 and 4 in DCM/pyridine/DMAP system. The monoesterification of quinide **51** in DMF/pyridine system also occurred at position 3 (62% yield) confirming that the equatorial OH group at position 3 is more reactive than the axial OH group at positon 4. In addition, the DCM/pyridine/DMAP system functioned better than DMF/pyridine system for the coupling (bis and mono) from triol **168** whereas the contrary is the case for quinide **51**. The rather low yield (31%) of diesters from quinide **51** indicates that the locked 4-axial OH group is more difficult to touch than 4-axial OH group of triol **168**. For the perspectives, a more complete optimization of coupling conditions of both triol **168** and quinide **51** could be performed; more 3,4-homo and heterodiesters could be obtained and subjected to deprotection reactions to get the targeted 3,4-di-*O*-cinnamoylquinic acids.

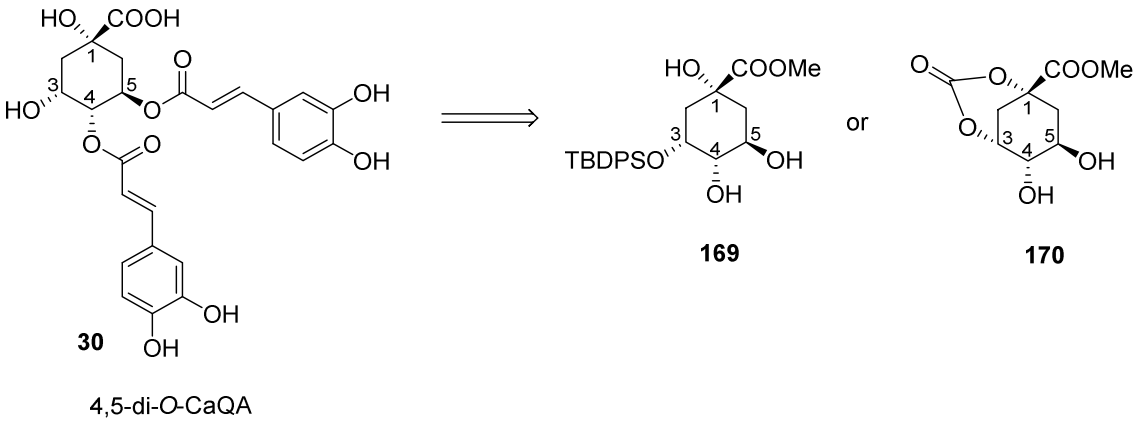
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3.3 Towards 4,5-di-*O*-CQA derivatives

3.3.1 Preparation of two intermediates

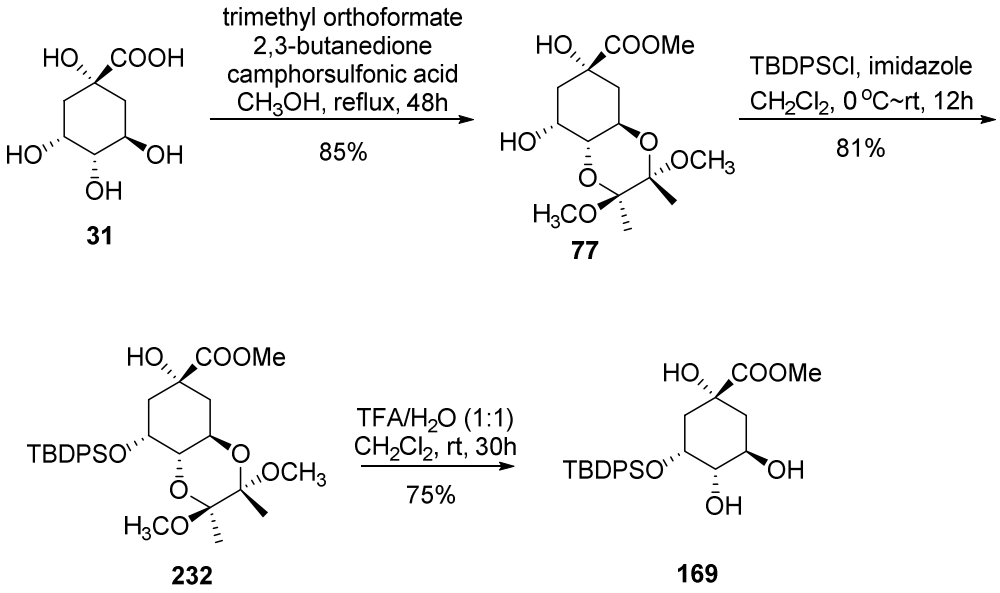
Our retrosynthetic analysis for 4,5-di-*O*-CQA derivatives was demonstrated in **Scheme 32**. The carboxylic acid group and OH-3 were protected respectively as methyl ester and silyl ether in a new triol **169**. In addition, a new carbonate intermediate **170** with a locked conformation was also prepared in order to investigate the effect of the molecule conformation on the reactivity of the free hydroxyl groups.



Scheme 32 (seen also in Chapter 1) Retrosynthetic analysis of 4,5-di-*O*-CaQA

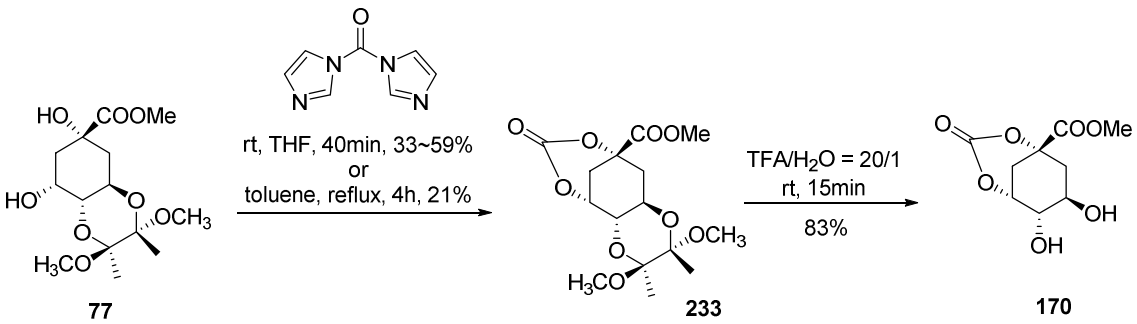
As demonstrated in **Scheme 59**, quinic acid **31** was converted to the *trans*-ketal **77** in 85% yield according to a reported procedure.[128] Then the protection of the free alcohol at position 3 was performed with TBDPSCl providing compound **232** in 81% yield. Selective removal of the *trans*-ketal group was accomplished in 75% yield with TFA/H_2O (1/1) in CH_2Cl_2 to give a new triol **169** (52% from quinic acid).[114] The new triol **169** was then fully characterized.

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Scheme 59 Synthesis of triol 169

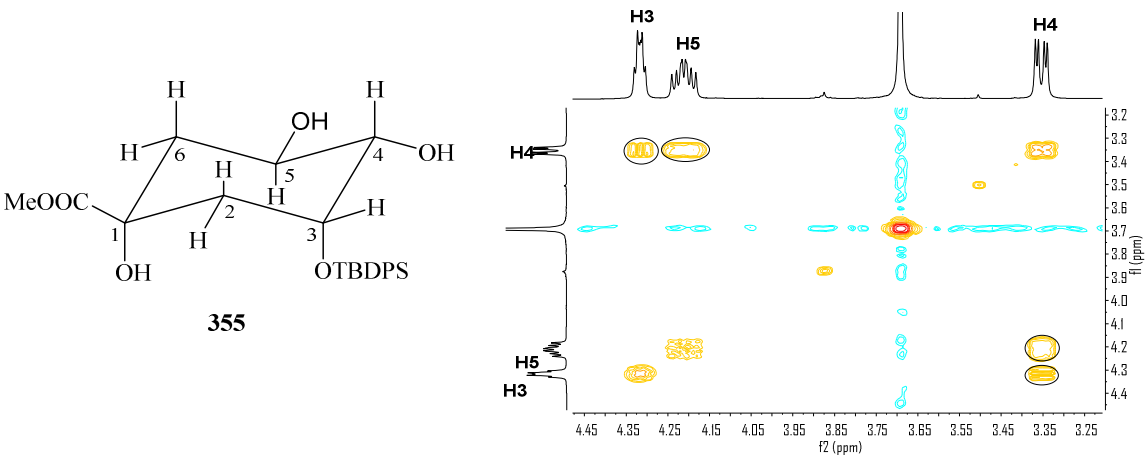
The *trans*-ketal **77** was converted into carbonate **233** with 1,1-carbonyldiimidazole (CDI) under two reported conditions (in THF at room temperature or in toluene at reflux) for the formation of carbonate at 1,3-*cis*-diol group.[191] The carbonation of *trans*-ketal **77** under these conditions gave the carbonate in rather low and unreproducible yields but in enough amount to carry out the coupling reactions. The cleavage of the *trans*-ketal group was accomplished in 83% yield in TFA/H_2O (20/1) to give a new 1,3-carbonate-4,5-diol **170.**[192] The new diol **170** was also fully characterized.



Scheme 60 Synthesis of 1,3-carbonate-4,5-diol 170

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The assignment of the structure of triol **169** was completed by the analysis its NMR spectra. In ^{1}H-^{1}H COSY (**Figure 55b**), the dd signal at 3.35 ppm is identified as the signal for H4 since it exhibits the interaction signals with both secondary protons H3 and H5. In addition, the coupling constants of H4 are $^{3}J_{H4\text{-}H5}$ 8.6 Hz, $^{3}J_{H4\text{-}H3}$ 2.9 Hz indicating that H4 is axial in $CDCl_3$ as depicted below in **Figure 55a**. Then the ddd signal at 4.22 ppm is identified as H5, the coupling constants of which are $^{3}J_{H5\text{-}H6a}$ 9.8 Hz, $^{3}J_{H5\text{-}H4a}$ 8.8 Hz and $^{3}J_{H5\text{-}H6e}$ 4.5 Hz providing additional proof that the preferred conformation of triol **169** in $CDCl_3$ is with H5 axial and so an equatorial carboxylic ester. The *trans*-diaxial coupling constant in a perfect chair conformation is usually more than 10 Hz, the large TBDPS group at axial position should have changed to some extent the chair conformation of triol **169** in $CDCl_3$.



a Structure of triol **169** on its favored conformation

b ^{1}H-^{1}H COSY (in $CDCl_3$) of triol **169**

Figure 55

The carbonate **170** presents a locked conformation due to the bicyclic carbonate as depicted in **Figure 56**. The coupling constant $^{3}J_{H4\text{-}H5}$ is meseared as 7.2 Hz in MeOD

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indicating the six-membered ring of quinic acid core is somewhat twisted from a perfect boat conformation.

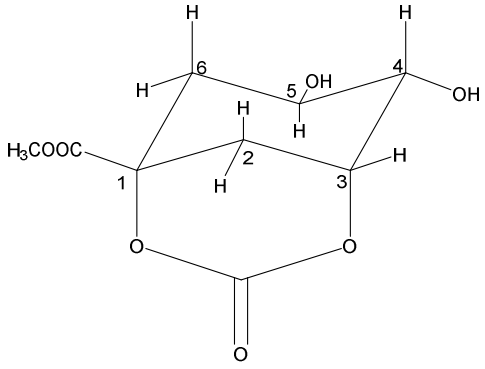


Figure 56 Locked conformation of 1,3-carbonate-4,5-diol 170

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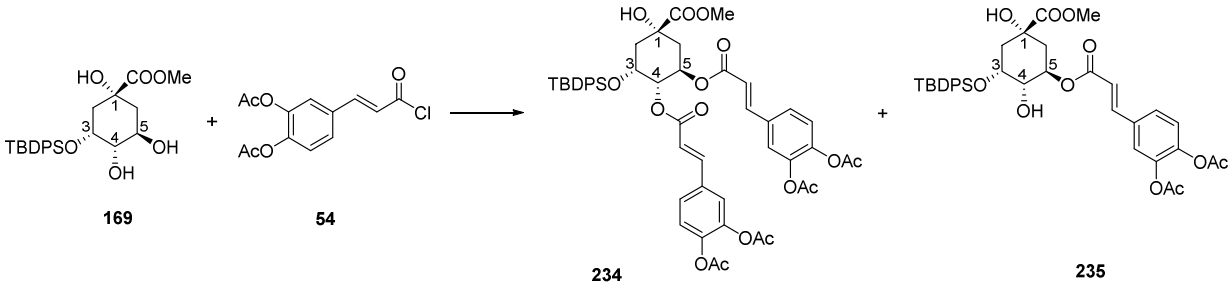
3.3.2 Coupling from triol 169

3.3.2.1 Screening of coupling conditions

A screening of coupling conditions for triol **169** with acetyl protected caffeoyl chloride **54** was performed as summarized in **Table 14**. First, for the di-coupling of triol **169**, the DMF/pyridine system was used at 45 °C with different ratios of DMF/pyridine (entries 1-3). The ratio DMF/pyridine = 3/2 (entry 1) gave a better yield than the ratio DMF/pyridine = 4/1 (entry 2) and 1/4 (entry 3). However, the yield of diester **234** (34%) was unsatisfactory due to a resulted complex mixture. When the coupling was performed in a more diluted solution (0.1 M, entry 4), diester **234** and monoester **235** were obtained in 18% and 19% yield, respectively. An increase in the use of acid chloride **54** (4 equivalents) resulted in a more complex mixture and gave a comparable 37% yield (entries 5 vs 1). When the di-coupling reaction was performed in DMF/pyridine at room temperature, the yield of diester **234** was improved to 53% (entry 6). When DMAP was introduced as a catalyst to the DMF/pyridine system at room temperature, however, the diester **234** was isolated in a lower 29% yield (entry 7). When the bis-coupling reaction of triol **169** with 3 equivalents of acid chloride **54** was performed at 0 °C to room temperature, a better 64% yield (entries 8 vs 6 vs 1) was obtained. When a lower starting temperature (-18 °C) was used (entry 9), the solubility decreased and a more diluted solution (0.1 M) was needed, and the diester **234** was isolated in a 49% yield. The DCM/pyridine/DMAP system was also used for the bis-coupling of triol **169** with 3 equivalents of acid chloride **54**, which was performed at -18 °C to room temperature (entry 10), a 60% yield of diester **234** was obtained. When the DCM/pyridine/DMAP system was used for the mono-coupling of triol **169** with 1.5 equivalents of acid chloride **54**, an excellent 85% yield of monoester **235** was obtained. From these results discussed above, for the synthesis of diester **234**, DMF/pyridine system (0.4 M) at 0 °C to room temperature and DCM/pyridine/DMAP system (0.1 M) at -18 °C to room temperature gave the best yields (64% and 60%), the latter functioned well also for the mono-coupling of triol **169** and gave an excellent 85% yield of monoester **235**.

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Table 14 The coupling reactions of triol 169 with caffeoyl chloride 54



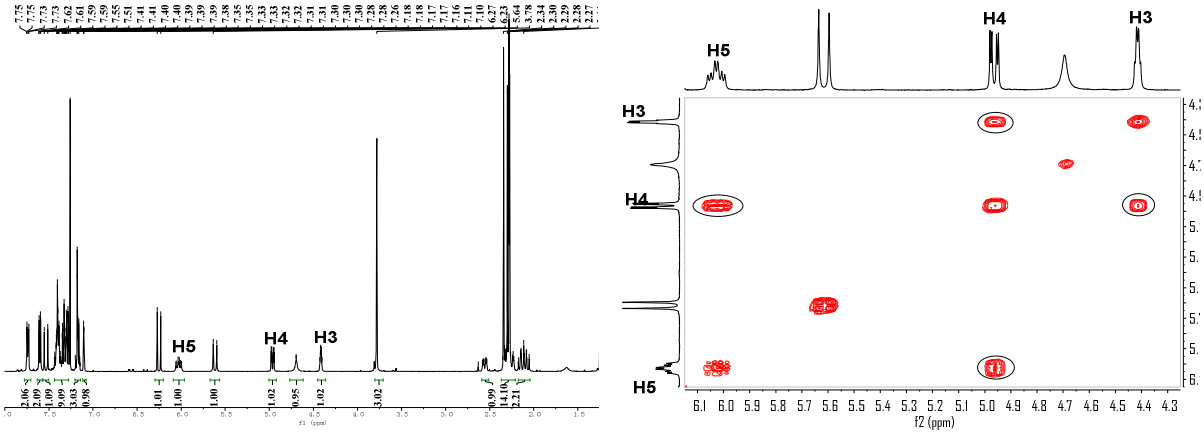
169 **54** **234** **235**

Entry	Molar equiv. of 54	Catalyst[a]	Solvent (v:v)	Con.	Temp.	Time	Yields[b] 234	235
1	3		DMF/pyridine (3/2)	0.4M	45 °C	1h	34%	
2	3		DMF/pyridine (4/1)	0.4M	45 °C	1h	32%	
3	3		DMF/pyridine (1/4)	0.4M	45 °C	1h	20%	
4	3		DMF/pyridine (3/2)	0.1M	45 °C	6h	18%	19%
5	4		DMF/pyridine (3/2)	0.4M	45 °C	1h	37%	
6	3		DMF/pyridine (3/2)	0.4M	rt	7h	53%	
7	3	DMAP	DMF/pyridine (3/2)	0.4M	rt	7h	29%	
8	3		DMF/pyridine (3/2)	0.4M	0 °C-rt	4h	64%	
9	3		DMF/pyridine (3/2)	0.1M	-18 °C-rt	7h	49%	
10	3	DMAP	DCM/pyridine (5/1)	0.1M	-18 °C-rt	3h	60%[c]	
11	1.5	DMAP	DCM/pyridine (5/1)	0.1M	-18 °C-rt	3h		85%

[a] 20% DMAP [b] Isolated yields. [c] A triester was isolated in 4% yield.

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The confirmation of the acylation positions of the diester **234** and the monoester **235** was achieved by the analysis of their NMR spectra. In **Figure 57a**, the value of integration shows the formation of two ester groups. Compared with triol **169**, the signals for H4 and H5 of diester **234** have shifted to a lower field region indicating the diesterification was at positions 4 and 5. In **Figure 57b**, the ^{1}H-^{1}H COSY NMR helps to distinguish H4 and H5. Then the diester **234** is confirmed to be 4,5-*O*-dicaffeoylester. The monoester **235** is confirmed to be 5-*O*-caffeoylester. In addition, the coupling constants of the H3, H4 and H5 of both diester **234** and monoester **235** show that their more favored conformation is still with an equatorial carboxylic ester (in $CDCl_3$).



a ^{1}H NMR (in $CDCl_3$) of diester **234** **b** ^{1}H-^{1}H COSY NMR (in $CDCl_3$) of diester **234**

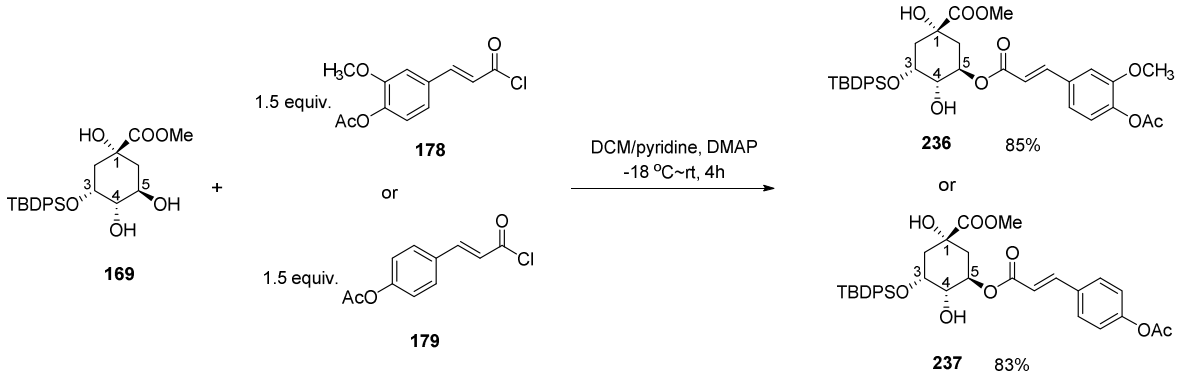
Figure 57

3.3.2.2 Coupling with ferulic and *p*-coumaroyl chloride

Then triol **169** was reacted with feruloyl chloride **178** and *p*-coumaroyl chloride **179**. The monoesterification reactions of triol **169** with 1.5 equivalents of feruloyl chloride **178** or *p*-coumaroyl chloride **179** were performed under DCM/pyridine/DMAP system giving feruloylmonoester **236** in 85% yield and *p*-coumaroylmonoester **237** in

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83% yield, respectively. The acylation position of these two monoesters **236 and 237** was confirmed to be at 5 by the analysis of its NMR spectra. The diesterification reaction of triol **169** with 3 equivalents of *p*-coumaroyl chloride **179** under DMF/pyridine system at 0 ^{o}C to room temperature in 4 hours resulted in a complex mixture and, unfortunately, no pure *p*-coumaroyldiester was isolated.



Scheme 61 Monoesterification of triol 169 with feruloyl chloride 178 or *p*-coumaroyl chloride 179

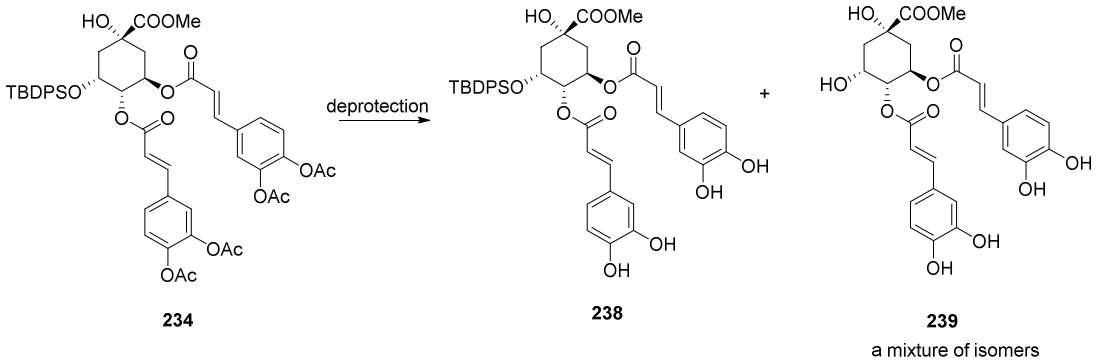
Thus, by the coupling reactions of triol **169**, 4,5-di-*O*-caffeoylester **234** and 5-*O*-caffeoylester **235**, 5-*O*-feruloylester **236** and 5-*O*-*p*-coumaroylester **237** were synthesized. For the perspectives, the coupling reactions of triol **169** to prepare 4,5-di-*O*-*p*-coumaroylester under DCM/pyridine/DMAP system and 4,5-di-*O*-feruloylester and 5-*O*-feruloylester under appropriate conditions could be performed. Furthermore, and coupling reactions of monoesters with a different cinnamoyl chloride to make different heterodiesters could also be carried out.

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3.3.3 Deprotection reactions

In order to remove the silyl group and acetate groups of 3-*O*-TBDPS-4,5-*O*-diester **234**, a screening of deprotection conditions was performed as summarized in **Table 15**.

Table 15 Deprotection of diester 234 to methyl ester derivatives



234 **238** **239**
a mixture of isomers

Entry	Conditions	Results
1	HF·pyridine in THF, rt, 4 d	A complex mixture
2	HF in CH_3CN, 50 °C, 3 h	A complex mixture
3	TBAF in THF, rt, 30 min	A complex mixture
4	1.25 M methanolic HCl, rt, 24 h	A complex mixture
5	TfOH·SiO_2 in CH_3CN, 0 °C, 2 h	A complex mixture
6	NH_4F in methanol, 60 °C, 40 min	13% **238** and 27% **239** (a mixture of isomers 10:1)
7	NH_4F in methanol, 60 °C, 5 h	59% **239** (a mixture of isomers 3:2)
8	NH_4F in methanol, 0 °C-rt, 60 h	59% **239** (a mixture of isomers 1:1)
9	NH_4F in THF/H_2O, 0-55 °C, 48 h	A complex mixture
10	NH_4F in CH_3CN/H_2O, 0-55 °C, 48 h	A complex mixture

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The deprotection reactions under HF·pyridine (entry 1),[193] HF in CH_3CN (entry 2),[194] TBAF in THF (entry 3),[195,196] methanolic HCl (entry 4)[197,198] or $TfOH·SiO_2$ (entry 5)[199] all resulted in complex mixtures and no pure product could be isolated. When the deprotection reaction was performed with NH_4F in methanol at 60 °C for 40 min, the 3-*O*-TBDPS-4,5-di-*O*-caffeoylquinic acid methyl ester **238** and a mixture of two di-*O*-caffeoylquinic acid methyl esters were isolated in 13% and 27% yield (entry 6). The monitoring of the reaction by TLC showed that the phenol acetate groups were removed prior to the silyl group. In order to accomplish the cleavage of the silyl group, the reactions were carried out with NH_4F in methanol at 60 °C for 5 hours (entry 7) or at 0 °C to room temperature for 60 hours (entry 8), but only mixtures of isomers were isolated in 59% yield (entries 7 and 8). The ratios of isomers (entries 6, 7 and 8) were calculated based on the ^1H NMR as shown in **Figure 58** but the positions of two caffeoyl groups could not be given. It seems that a longer reaction time in these conditions has led the isomerization to a larger extent. In order to investigate the effect of the solvent on the ratio of the two isomers, the deprotection reactions were also performed with NH_4F in THF/H_2O (entry 9) or CH_3CN/H_2O (entry 10), but the resulting mixtures were too complex to get any clear NMR spectra.

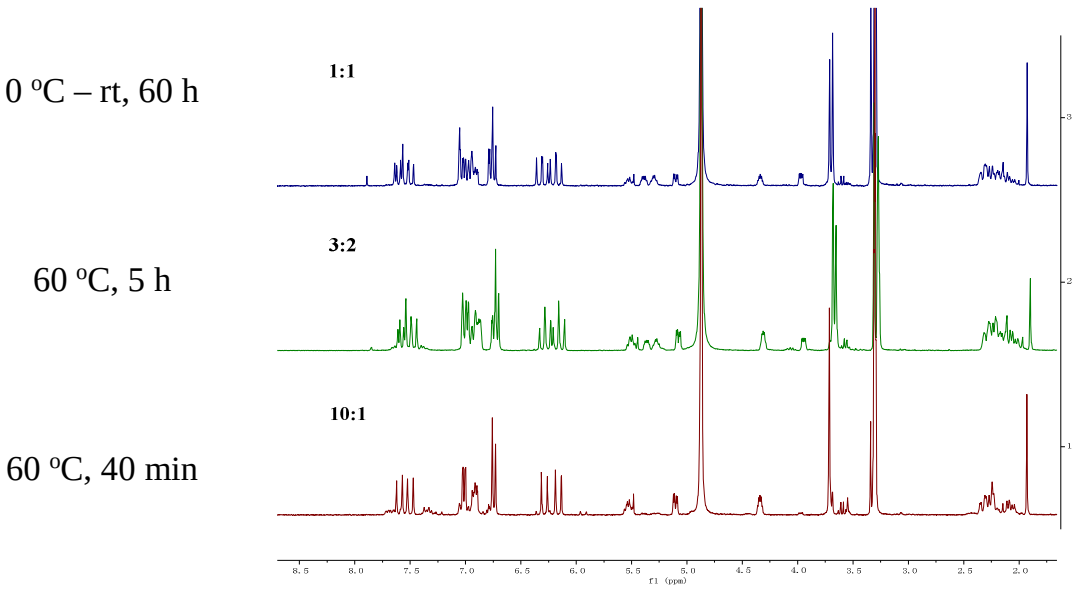
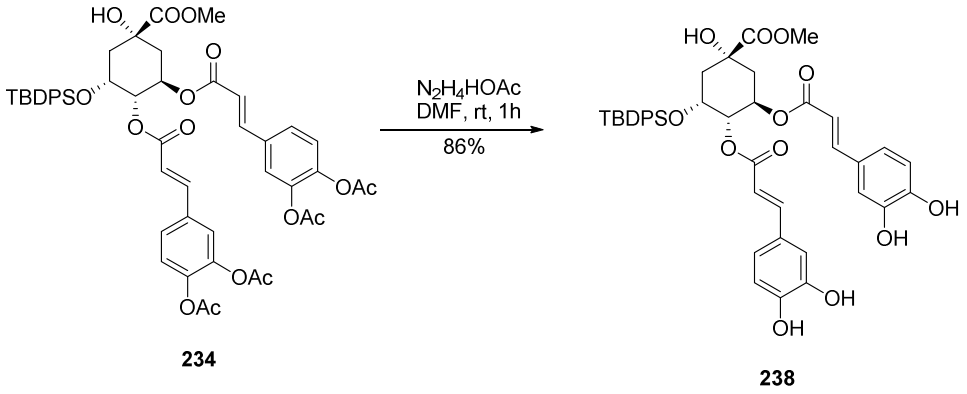


Figure 58 ^1H NMR (in MeOD) of mixtures of two di-*O*-caffeoylquinic acid methyl ester isomers

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A two-step deprotection procedure was also performed to remove first the acetate groups and then silyl group. The acetate groups of diester **234** was removed with hydrazine acetate in DMF at room temperature in 1 hour providing 3-*O*-TBDPS-4,5-di-*O*-caffeoylquinic acid methyl ester **238** in 86% yield.

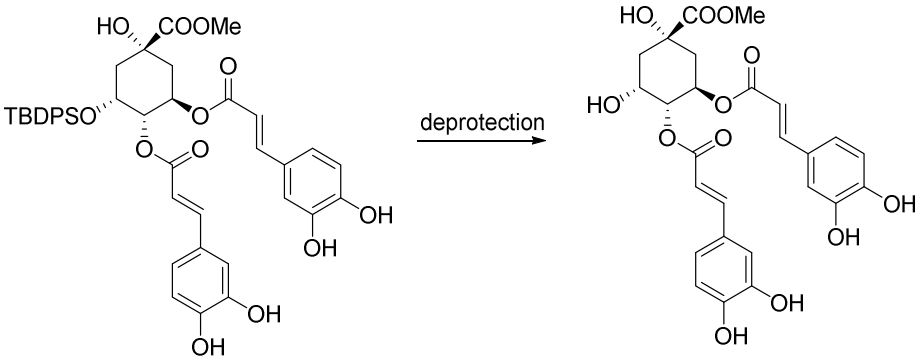


Scheme 62 Deprotection of the acetate groups of diester 234

Then the pure 3-*O*-TBDPS-4,5-di-*O*-caffeoylquinic acid methyl ester **238** was subjected to the deprotection reactions for removing the silyl group as summarized in **Table 16**.

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Table 16 Removal of TBDPS silyl group of ester 238



238 **239**

a mixture of isomers

Entry	Conditions	Results
1	HF·pyridine in THF, 0 °C-rt, 5 h	A complex mixture
2	HF in CH_3CN, 0 °C-rt, 3 h	A complex mixture
3	TBAF in THF, 0 °C, 15 min	A complex mixture
4	1.25 M methanolic HCl, 0 °C-rt, 5 h	45% **239** (a mixture of isomers 6:1)
5	1.25 M methanolic HCl, 0 °C-rt, 10 h	43% **239** (a mixture of isomers 3:1)

The deprotection of silyl group with HF·pyridine (entry 1),[193] HF in CH_3CN (entry 2),[194] and TBAF in THF (entry 3)[195,196] were, again, inefficient. In contrast, the removal of TBDPS silyl group of ester **238** was accomplished with 1.25 M methanolic HCl[197,198] at 0 °C to room temperature in 5 hours providing a mixture of isomers in 45% yield. (entry 4). It was also observed that a longer reaction time (10 hours, entry 5) has led the isomerization to a larger extent (entries 5 vs 4) as shown in **Figure 59**.

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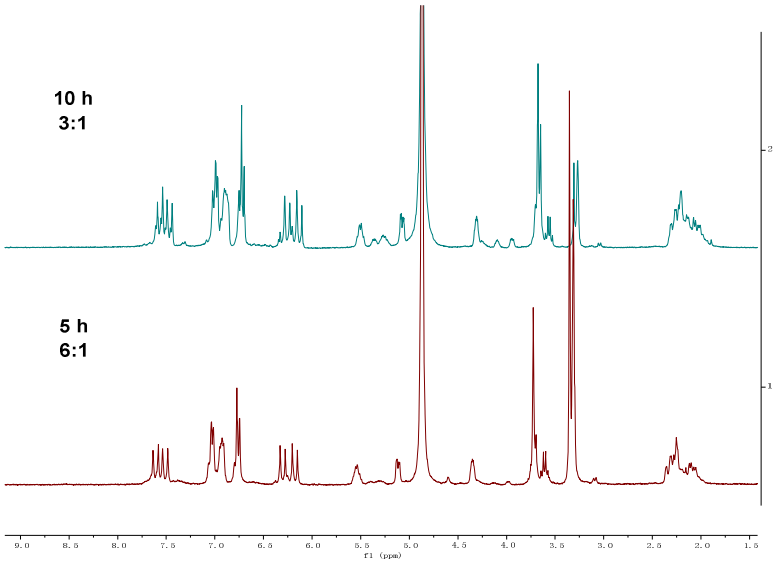
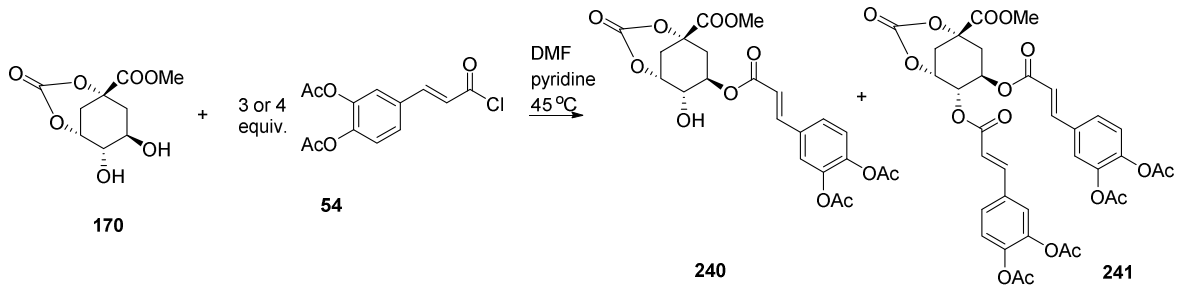


Figure 59 ^{1}H NMR (in MeOD) of mixtures of two di-*O*-caffeoylquinic acid methyl ester isomers

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3.3.4 Coupling from 1,3-carbonate-4,5-diol 170

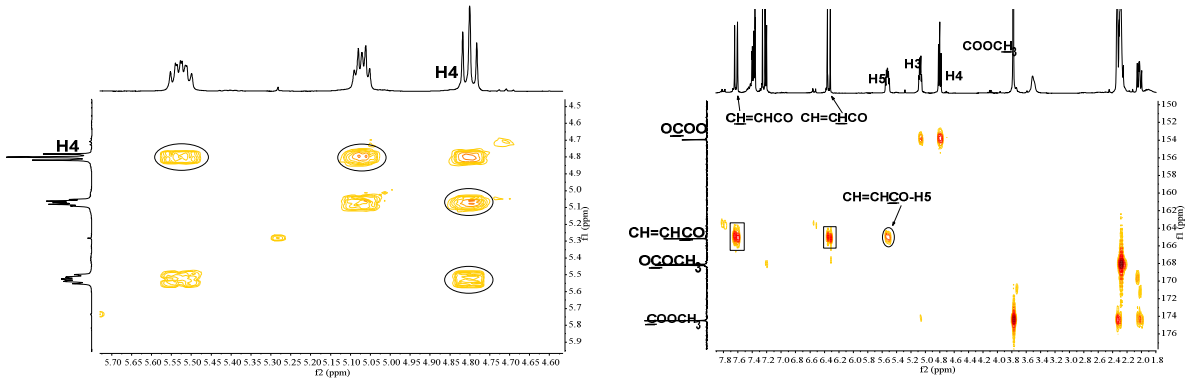
The compound 1,3-carbonate-4,5-diol **170** was subjected to the coupling reactions in DMF/pyridine at 45 °C with an excess of caffeoyl chloride **54**. When 3 equivalents of acid chloride **54** were used, the reaction was completed in 30 min, and monoester **240** and diester **241** were isolated respectively in 76% yield and less than 17% yield (impure product), respectively. Betting for a better yield of diester **241**, diol **170** was then reacted with 4 equivalents of acid chloride **54** in DMF/pyridine at 45 °C for 3 hours. However, the monoester **240** was still the main product and isolated in 71% yield and the diester **241** was obtained in less than 20% yield as an impure product.



Scheme 63 Coupling reactions of diol 170 with caffeoyl chloride 54

The confirmation of acylation position of monoester **240** was achieved by the analysis of its NMR spectra. In ^{1}H-^{1}H COSY NMR spectrum of monoester **240**, the dd signal at 4.80 ppm is identified as H4 since it exhibits interactions with both the other two secondary protons (**Figure 60a**). In ^{1}H-^{13}C HMBC NMR spectrum (**Figure 60b**) of monoester **240**, the signal at 165.2 ppm in ^{13}C NMR spectrum belongs to the carbonyl carbon in caffeoyl moiety (CH=CHCO) since it correlates with two protons in double bond (highlighted in squares). Furthermore, the carbonyl carbon in caffeoyl moiety (CH=CHCO) has no interaction signal with H4 but a ddd signal at 5.53 ppm indicating the esterification was at OH-5 (highlighted in ovals). So the monoester **240** is the 5-*O*-caffeoylester as depicted above in **Scheme 63**.

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a l ^{1}H-^{1}H COSY (in $CDCl_3$) of monoester **240**

b ^{1}H-^{13}C HMBC (in $CDCl_3$) of monoester **240**

Figure 60

In general, a study of coupling conditions of triol **169** with protected caffeoyl chloride **54** was performed and the 4,5-di-*O*-caffeoylester **234**, 5-*O*-caffeoyl and *p*-coumaroylesters (**235** and **237**) were obtained in fair to good yields; the coupling reactions of carbonate **170** provided the 5-*O*-caffeoylester **240** as the main product even with a large excessive equivalents of acid chloride. Both the DMF/pyridine and DCM/pyridine/DMAP system at low temperature worked well for the diesterification of triol **169** and the latter is appropriate for its monoesterification. A screening of deprotection conditions was carried out with 4,5-di-*O*-caffeoylester **234**, among them, two procedures (with NH_4F or two-step with hydrazine acetate and then methanolic HCl) afforded the deprotected products but as mixtures of isomers which could be separated by preparative-HPLC in the future. In addition, more 4,5-homo and also heterodiesters could be obtained in the future and subjected to deprotection reactions to get the targeted 4,5-di-*O*-cinnamoylquinic acids.

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3.4 Conclusions

For the synthesis of natural 3,4- and 4,5-di-*O*-cinnamoylquinic acid and derivatives, four intermediates including 5-*O*-TBDPS-1,3,4-triol **168**, quinide **51**, 3-*O*-TBDPS-1,4,5-triol **169** and 1,3-carbonate-4,5-diol **170** were prepared from quinic acid. Consequently, the coupling of triol **168** afforded two 3,4-di-*O*-cinnamoylesters including 3,4-di-*O*-caffeoylester **225** and 3,4-di-*O*-feruloylester **227** and three 3-*O*-cinnamoylesters including 3-*O*-caffeoylester **226**, 3-*O*-feruloylester **228**, and 3-*O*-*p*-coumaroylester **229**; the coupling of quinide **51** provided the 3-*O*-caffeoylquinide ester **230** and 3,4-di-*O*-caffeoylquinide **231**; the coupling of triol **169** afforded the 4,5-di-*O*-caffeoylester **234**, 5-*O*-caffeoyl, feruloyl and *p*-coumaroylesters (**235**, **236** and **237**); the coupling of carbonate **170** provided the 5-*O*-caffeoylester **240**. An optimization of deprotection conditions of 4,5-di-*O*-caffeoylester **234** for corresponding CQA methyl ester derivatives was performed, and two procedures (with NH_4F or two-step with hydrazine acetate and then methanolic HCl) afforded the deprotected products but as mixtures of two isomers. In the future, a more complete optimization of both coupling and deprotection conditions could be done and different homo or heterodicinnmaoylquinic acid derivatives could be prepared.

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General Conclusions

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Hydroxycinnamoylquinic acids (CQA), as an important class of polyphenols, have been isolated from various plants and shown to possess a range of biological activities. It has drawn our interest to evaluate the potential of CQA as biopesticides and the investigation of their toxicity mechanism and structure-activity relationships, which would benefit from the preparation of a library of CQA derivatives and analogs.

However, the natural CQA molecules suffer from a poor stability, the migration of cinnamoyl groups between hydroxyl groups in assay or even natural conditions often result in a mixture of regioisomers, which makes it difficult to draw unambiguous conclusions about the biological activity of each isomer. In this thesis, two series of diCQA derivatives and analogs including 4-deoxy-3,5-diCQA analogs aiming at the prevention of isomerization and natural 3,4- or 4,5-diCQA derivatives were synthesized. The insecticidal assays of selected compounds were also performed.

First, for the synthesis of 4-deoxy-3,5- diCQA analogs, a new intermediate named 4-deoxy methyl quinate was obtained in 53% yield in 5 steps from quinic acid on the multi-gram scale. A screening of coupling reactions was then performed providing two kinds of conditions appropriate for the coupling of our substrates using DMF/pyridine or DCM/pyridine/DMAP in repeatable and reproducible yields. A series of homo or heterodiesters were obtained *via* bis coupling or a two-step sequential coupling from 4-deoxy methyl quinate with different cinnamoyl chlorides. The selective or total deprotection of these diesters afforded 4-deoxy-3,5-di-*O*-cinnamoylquinic methyl esters or acids. These CQA analogs were found to exhibit better stability as expected than natural compounds in terms of blocking the migration of cinnamoyl groups. Among them, seven 4-deoxy CQA analogs were subjected to insecticidal bioassays, and two compounds 4-deoxy-3,5-di-*O*-caffeoylquinic acid and 4-deoxy-3,5-di-*O*-*p*-coumaroylquinic acid were found produce higher insecticidal activities than natural 3,5-di-*O*-caffeoylquinic acid.

Then, for the synthesis of natural 3,4- and 4,5-diCQA derivatives, four precursors including a 5-*O*-TBDPS-1,3,4-triol, a 1,5-γ-quinide, a 3-*O*-TBDPS-1,4,5-triol and a 1,3-

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carbonate-4,5-diol were prepared from quinic acid. Consequently, the bis- or mono-coupling from these four intermediates with different protected cinnamoyl chlorides under DMF/pyridine or DCM/pyridine/DMAP system afforded a small library of CQA homodiesters and monoesters. A screening of deprotection conditions of 3-*O*-TBDPS-4,5-di-*O*-caffeoylester for corresponding CQA methyl ester derivatives was performed, and two procedures (with NH_4F or two-step with hydrazine acetate and then methanolic HCl) provided the targeted products but as mixtures of two isomers. It has also been observed that a longer reaction time would lead the isomerization to a larger extent.

In general, a synthetic route was developed to get new 4-deoxy-3,5-*O*-dihydroxycinnamoylquinic acid and methyl ester analogs *via* 8 or 7 steps from $_D$-quinic acid; a series of natural 3,4- or 4,5-*O*-dihydroxycinnamoylquinic acid derivatives were also prepared.

As perspectives to this work, expected collaborations could be established with other biologists dedicated to evaluate other bioactivities of these 4-deoxy CQA analogs; a larger library of natural 3,4- or 4,5-CQA derivatives could be constructed to serve as standard samples or as tools to investigate the working mechanism, the structure-activity relationship and the metabolism *in vivo* of CQA molecules.

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Chapter 4 Experimental Section

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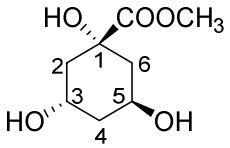
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General

Reagents and solvents were supplied by Aldrich, Acros, Lancaster, Alfa Aesar, Fluka or TCI and purchased at the highest commercial quality to be used withort further purification. NMR spectra were recorded on a Bruker 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz), Bruker 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz), or Bruker 500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) spectrometers, at 2151-298K, using $CDCl_3$, CD_3OD and DMSO-d_6 or D_2O as solvents. The chemical shifts (d ppm) are referenced to the solvent residual peak and corpling constants (Hz) are reported in the standard fashion. The following abbreviations are used to explain the multiplicities: s = singlet, d = dorblet, t = triplet, q = quartet, quint. = quintuplet, sext. = sextuplet, hept. = heptuplet, m = multiplet, br = broad. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a Thermo Finnigan LCQ Advantage mass. High-resolution mass spectra (HRMS) were recorded on a Finnigan Mat 151xL mass spectrometer using electrospray. Analytical thin-layer chromatography was carried out on silica gel Merck 60 D254 (0.25 mm). Flash chromatography was performed on Merck Si 60 silica gel (40–63 μm). Infra-red (IR) spectra were recorded with a IRAffinity-1 Shimadzu spectrometer using Attenuated Total Reflectance (ATRMiracle), and the wavenumbers are expressed in cm^{-1}. Optical rotations were measured on a Perkin Elmer 241 or Jasco P1010 polarimeter with a 10 cm cell (concentration c expressed as g/100 mL). Melting points were measured using Büchi apparatus B-540. Preparative HPLC was performed on Agilent equipment with a column Phenomenex C18: Jupiter® 5μm; 300 Å, LC Column 250 x 4.6mm, flow 1ml/min; Mobile phase 0 - 2min: 80% H_2O UHQ + TFA (A) / 20% CH_3CN + TFA (B); 22min: 40 % A / 60% B; 30min: 100% B; 33min: 80% A/ 20% B. Samples were dissolved in MeOH (6mL) and 10μg were injected per sample. All data for hydroxycinnamoyl quinic acids or related derivatives presented in this paper use the recommended IUPAC numbering system.

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Methyl (3S,5S)-1,3,5-trihydroxycyclohexanecarboxylate or methyl 4-deoxy quinate 167



167

The disilylated compound **170** (106.7 mg, 0.25 mmol) was stirred in MeOH (2mL) with Amberlyst®A15 (H^+ form) at room temperature for 24h. After filtration and evaporation, the crude product was purified by flash chromatography (pentane/ethyl acetate 50/50 then ethyl acetate/methanol 90/10) to provide **167** (colorless oil then white solid on standing, 42.7 mg, 89%).

$[\alpha]_D^{25}$ - 3.7 (*C* 1.06, CH_3OH).

IR 3350, 2951, 2930, 2855, 1173, 1730, 1661, 1435, 1371, 1281, 1240, 1134, 1057, 1016 cm^{-1}.

^1H NMR (400 MHz, 297K, CD_3OD) d (ppm) = 4.24-4.16 (m, 2H, H_{3e} and H_{5a}), 3.73 (s, 3H, OMe), 2.08 (dd, 1H, ^2J 13.8 Hz, $^3J_{H_5/H_6}$ 3.3 Hz, H_6 or H_2), 2.00 (m, 2H, H_2 or H_6 and H_4), 1.88 (dd, 1H, ^2J 12.8 Hz, $^3J_{H_2/H_3}$ 9.1 Hz, H_2 or H_6), 1.77 (dd, 1H, ^2J 13.8 Hz, ^3J 4.8 Hz, H_6 or H_2), 1.60 (ddd, 1H, ^2J 12.7 Hz, $^3J_{H_{4a}/H_{5a\text{ or }3a}}$ 9.2 Hz, $^3J_{H_{4a}/H_{3e\text{ or }H5e}}$ 3.0 Hz, H_{4a}).

^{13}C NMR (CD_3OD, 297K, 100MHz) d (ppm) = 176.1 (COOMe), 76.8 (C_1), 67.8 (C_5 or C_3), 64.0 (C_3 or C_5), 52.8 (OMe), 43.8 (C_2 or C_6), 42.0 (C_4), 40.3 (C_6 or C_2).

MS-ESI m/z $[M+Na]^+$ 213.1; HRMS-ESI m/z $[M+Na]^+$ calcd for $C_8H_{14}NaO_5$ 213.0733; found 213.0733.

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General procedures for the synthesis of homodiesters from 4-deoxy methyl quinate

Procedure A:

To a solution of triol **167** in DMF / pyridine (v/v 3/2, c = 0.4M) under nitrogen was added the acetylated cinnamoyl chloride (3 equiv.) The mixture was stirred at 45°C until completion, in general after 1h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography on silica using the appropriate eluent.

Procedure B:

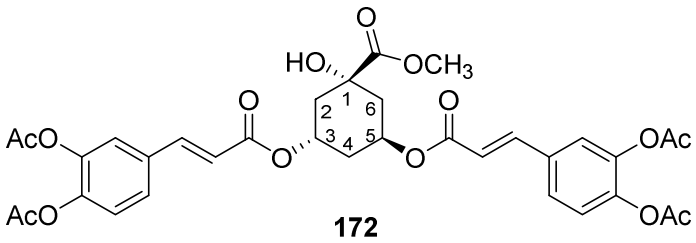
To a solution of triol **167** in DMF / pyridine (v/v 3/2, c = 0.4M) under nitrogen was added the acetylated cinnamoyl chloride (3 equiv.) The mixture was stirred at 0°C until completion, in general after 4h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography on silica using the appropriate eluent.

Procedure C:

To a solution of triol **167** in dichloromethane / pyridine (v/v 5/1, c = 0.1M) under nitrogen was added the acetylated cinnamoyl chloride (3 equiv.) and DMAP (20%).The mixture was stirred at -18°C to room temperature until completion, in general after 4h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography on silica using the appropriate eluent.

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Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 172



172

Synthesized according to the general procedure B using diacetylated caffeoyl chloride and methyl 4-deoxy quinate **167** (105 mg, 0.553 mmol). **172** was obtained as a white solid (348 mg, yield: 92%) after purification by flash chromatography on silica using DCM/Et_2O 12/1 to 6/1.

$[\alpha]_D^{25}$ = -46.9 (c 1.215, CH_2Cl_2).

m.p. = 92.8-94.1°C.

IR(ATR) 2943, 2832, 1775, 1742, 1713, 1639, 1504, 1449, 1427, 1371, 1321, 1242, 1205, 1180, 1147, 1132, 1111, 1022 cm^{-1}.

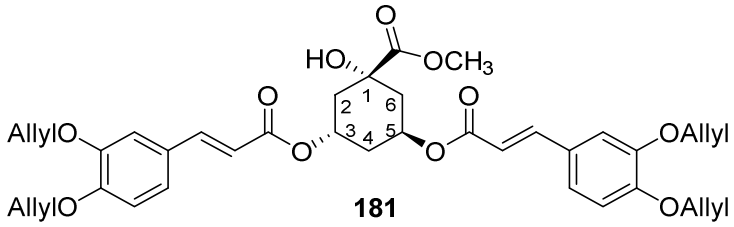
^{1}H NMR ($CDCl_3$, 298K, 500MHz) d (ppm) = 7.63 and 7.58 (2d, 2H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.39 and 7.38 (2dd, 2H, J_{ortho} 8.4Hz, J_{meta} 1.9 Hz, 2x$H_{6'}$), 7.35 and 7.34 (2d, 2H, J_{meta} 1.9 Hz, 2x$H_{2'}$), 7.20 (d, 2H, J_{ortho} 8.4 Hz, 2x$H_{5'}$), 6.40 and 6.32 (2d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.51 (ddd, 1H, ^2J 13.8 Hz, ^3J 9.8 Hz, ^3J 3.9 Hz, $H_{3\ or\ 5ax}$), 5.46 (ddd, 1H, ^3J=^3J 7.8 Hz, ^3J 3.9 Hz, $H_{3e\ or\ 5e}$), 3.76 (s, 1H, OH_1), 3.74 (s, 3H, COOMe), 2.28, 2.271 and 2.268 (3s, 12H, $OCOCH_3$), 2.32 (m, 1H, H_4), 2.23-2.18 (m, 2H, H_2 and H_6), 2.08-2.00 (m, 2H, H_2 and H_6), 1.87 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.3 Hz, ^3J 3.45 Hz, H_{4a}).

^{13}C NMR ($CDCl_3$, 298K, 125 MHz) d (ppm) = 175.0, 168.1(2) and 168.0(2) (4x$OCOCH_3$), 165.8 and 165.5 (2xCOO), 143.59 and 143.57 (C_q), 143.3 and 143.2 (<u>C</u>H=CHCO) , 142.5 and 142.4 (C_q), 133.2 and 133.1(C_q), 126.5 and 126.4 ($C_{6'}$), 124.0 and 123.9 ($C_{5'}$), 122.9 and 122.8 ($C_{2'}$), 119.4 and 119.2 (CH=<u>C</u>HCO), 74.7 (C_1) , 68.9 (C_3 or C_5), 66.9 (C_5 or C_3), 53.1 (OMe), 39.7 (C_2 or C_6), 36.7 (C_2 or C_6), 35.0 (C_4), 20.7(2), 20.62 and 20.60 (4x OCO<u>C</u>H_3).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{34}H_{34}NaO_{15}$ 705.1790; found 705.1780.

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Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-di-(prop-2-en-1-yloxy)phenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 181



181

Synthesized according to the general procedure A using diallylated caffeoyl chloride and triol **167 (**102 mg, 0.537 mmol). Purification by flash chromatography on silica using petroleum ether/EtOAc 50/50, providing the triester (51 mg, 10%) and diester **181** (214 mg, 59%) as white solid.

$[\alpha]_D^{25}$ - 140.8 (*C* 0.86, CH_2Cl_2).

m.p. 89-91°C.

IR(ATR) 2922, 2827, 1706, 1631, 1597, 1510, 1456, 1423, 1362, 1335, 1304, 1246, 1223, 1165, 1134, 1090, 1067 cm^{-1}.

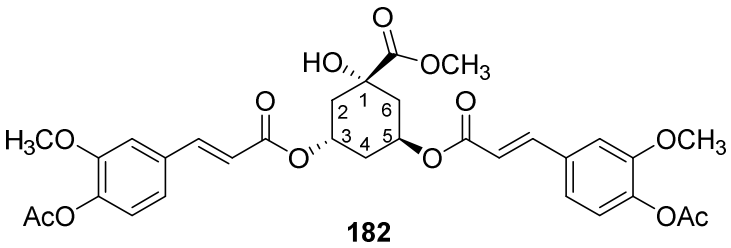
^{1}H NMR ($CDCl_3$, 298K, 300MHz) d (ppm) = 7.63 and 7.58 (2d, 2H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.08 (m, 4H, CH_{Ar}), 6.87 (m, 2H, CH_{Ar}), 6.31 and 6.23 (2d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 6.07 (m, 4H, CH_2=C<u>H</u>CH_2O), 5.60-5.50 (m, 2H, H_3 and H_5), 5.42-5.39 (m, 2H, C<u>H</u>$_2$anti=CHCH_2O), 5.30 (m, 4H, C<u>H</u>$_2$syn =CHCH_2O), 4.64 (m, 8H, CH_2=CHC<u>H</u>$_2$O), 2.32 (m, 1H, H_2 or H_4 or H_6), 2.24-2.02 (m, 4H, H_2 or H_4 or H_6), 1.86 (ddd, 1H, *J* 13.7 Hz, *J* 10.4 Hz, *J* 3.4 Hz, H_2 or H_4 or H_6).

^{13}C NMR ($CDCl_3$, 296K, 75 MHz) d (ppm) = 175.1 (COOMe), 166.5 and 166.3 (OCO), 150.8 (2xC_q), 148.7 (2xC_q), 145.4 and 145.1(<u>C</u>H=CHCO), 133.2 133.1, 133.05 and 133.01 (4xCH_2=<u>C</u>HCH_2O), 127.64, 127.57 (2xCq), 123.2 and 122.9 (2xCHAr), 118.15, 118.11, 118.1, 118.07 (4x<u>C</u>H_2=CHCH_2O), 115.88 and 115.84 (CH=<u>C</u>HCO), 113.50, 113.44, 112.7 and 112.5 (4xCH_{Ar}), 75.0 (C_1), 70.1, 70.0, and 69.8(2) (4xCH_2=CH<u>C</u>H_2O), 68.8 and 66.6 (C_3 and C_5), 53.2(OMe), 40.0, 36.9 and 35.2 (C_2, C_4 and C_6).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{38}H_{42}NaO_{11}$ 697.2619; found 697.2615.

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Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 182



182

Synthesized according to the general procedure C using acetylated feruloyl chloride and methyl 4-deoxy quinate **167** (117 mg, 0.616 mmol). **182** was obtained as a white solid (266 mg, yield: 69%) after purification by flash chromatography on silica using DCM/Et_2O 10/1.

$[\alpha]_D^{25}$ = - 74.5 (c 1.05, CH_2Cl_2).

m.p. 90-92°C.

IR(ATR) 1765, 1709, 1638, 1508, 1464, 1418, 1369, 1298, 1263, 1215, 1198, 1153, 1123, 1033, 1011 cm^{-1}.

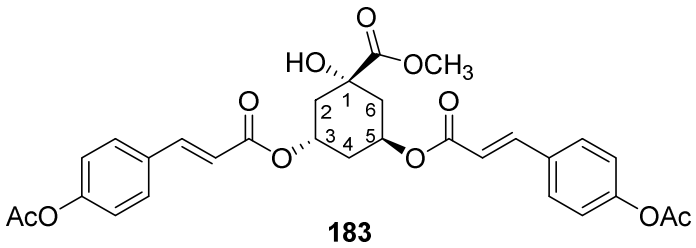
^{1}H NMR ($CDCl_3$, 296K, 400MHz) d (ppm) = 7.65 and 7.60 (2d, 2H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.12-7.02 (m, 6H, CH_{Ar}), 6.41 and 6.33 (2d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.55 and 5.49 (2m, ^3J 9.3 Hz, ^3J 3.3 Hz, H_5 and H_3), 3.85 and 3.84 (2s, 2x3H, 2xOMe), 3.76 (s, 3H, COOMe), 2.30(s, 6H, 2xOAc), 2.28 (m, 1H, H_{4e}), 2.22-2.18 and 2.11-2.04(m, 2x2H, 2xH_6 and 2xH_2), 1.88 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.4 Hz, ^3J 3.4 Hz, H_4).

^{13}C NMR ($CDCl_3$, 296 K, 100 MHz) d (ppm) = 175.0 (COOMe), 168.8 (2xO<u>C</u>OCH_3), 166.1 and 165.8 (COO), 151.4 (2xC_q), 144.6 and 144.4 (<u>C</u>H=CHCO), 141.54 and 141.51 (C_q), 133.34 and 133.30 (C_q), 123.33 and 123.25(CHAr), 121.6 and 121.3 (CHAr), 118.3 and 118.2 (CH=<u>C</u>HCO), 111.3 and 111.1 (CH_{Ar}), 74.8 (C_1), 68.9 (C_3 or C_5), 66.8 (C_5 or C_3), 56.0(2xOMe), 53.1 (COO<u>Me</u>), 39.8 and 36.8 (C_6 and C_2), 35.1 (C_4), 20.7 (2xOCO<u>C</u>H_3).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{32}H_{34}NaO_{13}$ 649.1892; found 649.1865.

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Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 183



183

Synthesized according to the general procedure A using acetylated *para*-cormaroyl chloride and methyl 4-deoxy quinate **167** (58mg, 0.172 mmol). **183** was obtained as a white solid (142 mg, yield: 82%) after purification by flash chromatography on silica using DCM/Et_2O 10/1.

$[\alpha]_D^{25}$ -79.4 (*C* 0.83, CH_2Cl_2).

m.p. 86-88°C.

IR(ATR) 1765, 1736, 1709, 1638, 1601, 1506, 1418, 1369, 1312, 1265, 1202, 1163, 1140, 1086, 1063, 1011 cm^{-1}.

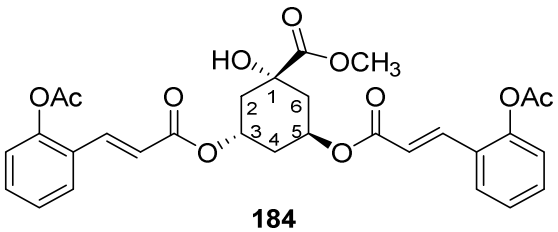
^1H NMR ($CDCl_3$, 295K, 400MHz) d (ppm) = 7.67 and 7.62 (2d, 2H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.52 and 7.50 (2d, 4H, J_{ortho} 8.5 Hz, $H_{2'}$), 7.10 (2d, 4H, J_{ortho} 8.5 Hz, $H_{3'}$), 6.41 and 6.33 (2d, 2H, ^3J 16.0 Hz, CH=<u>C</u>HCO), 5.53 and 5.48 (2 m, 2H, ^3J 4.0 Hz, H_3 and H_5), 3.74 (s, 3H, COOMe), 2.27 (s, 6H, OAc), 2.24 (m, 1H, H_4), 2.23-2.19 (m, 2H, H_2 and H_6), 2.11-2.06 (m, 2H, H_2 and H_6), 1.88 (ddd, 1H, ^2J 13.0 Hz, ^3J 10.2 Hz, ^3J 3.5 Hz, H_4).

^{13}C NMR ($CDCl_3$, 295K, 100 MHz) d (ppm) = 174.9 (<u>C</u>OOMe), 169.2 (2xO<u>C</u>OCH_3), 166.1 and 165.8 (COO), 152.2 and 152.1 (C_q), 144.1 and 144.0 (<u>C</u>H=CHCO), 132.1 and 132.0 (2xCH_{Ar}), 129.4 and 129.3 (2xCH_{Ar}), 122.2 and 122.1 (C_q), 118.3 and 118.1 (CH=<u>C</u>HCO), 74.7 (C_1), 68.8 and 66.8 (C_3 and C_5), 53.0 (OMe), 39.7 and 36.8 (C_2 and C_6) 35.0 (C_4) 21.1 (2xCH_3).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{30}H_{30}NaO_{11}$ 589.1680; found 589.1655.

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Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(2-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 184



184

Synthesized according to the general procedure A using acetylated *o*-coumaroyl chloride and methyl 4-deoxy quinate **167** (82 mg, 0.432 mmol). Purification by flash chromatography (DCM/Et_2O 10/1) afforded **184** as a white solid (152 mg, yield: 62%)

$[\alpha]_D^{25}$ - 50.0 (*C* 1.12, CH_2Cl_2).

m.p. 87-90°C.

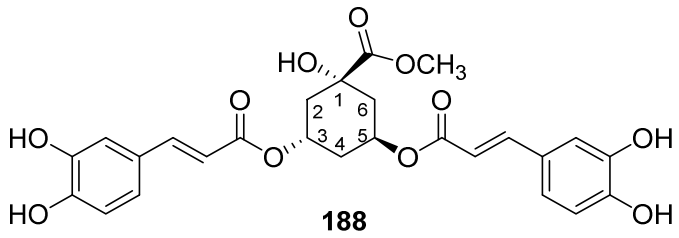
IR(ATR) 1763, 1711, 1638, 1483, 1454, 1437, 1371, 1315, 1265, 1198, 1179, 1140, 1094, 1063, 1009 cm^{-1}.

^1H NMR ($CDCl_3$, 296K, 300MHz) d (ppm) = 7.81 and 7.73 (2d, 2H, *J* 16.1 Hz, C<u>H</u>=CHCO), 7.63 (dd, 2H, *J* 7.9 Hz, H ortho), 7.40 (dd, 2H, *J* 7.40 Hz, H meta OAc), 7.25 (dd, 2H, *J* 7.6 Hz, H para OAc), 7.11 (d, 3H, J 8.1 Hz, H orthoOAc), 6.46 and 6.40 (2d, 2H, *J* 16.1 Hz, CH=C<u>H</u>CO), 5.53 (m, 2H, H_3 and H_5), 3.75 (s, 3H, COOMe), 2.40 and 2.38 (2s, 2x3H, 2xOAc), 2.29-2.19 (m, 3H, H_4, H_2 and H_6), 2.13-2.02 (m, 2H, H_2 and H_6) 1.90 (ddd, 1H, ^2J 13.5 Hz, ^3J 10.0 Hz, ^3J 3.4 Hz, H_4); ^{13}C NMR ($CDCl_3$, 2151K, 100 MHz) d (ppm) = 175.0 (COOMe), 169.45 and 169.40 (O<u>C</u>OCH_3), 165.8 and 165.6 (COO), 149.4(2xC_q), 138.56 and 138.50 (<u>C</u>H=CHCO), 131.34 and 131.30 ($C_{4'}$), 127.6 and 127.5 ($C_{6'}$), 127.1 and 127.0 (C_q), 126.44 and 126.41($C_{5'}$), 123.26 and 123.20 ($C_{3'}$), 120.2 and 120.1 (CH=<u>C</u>HCO), 74.6 (C_1), 68.8 (C_3 or C_5), 67.0 (C_5 or C_3), 53.2 (COO<u>Me</u>), 39.7 and 36.9 (C_6 and C_2), 35.1 (C_4), 21.0 (2x OCO<u>C</u>H_3).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{30}H_{30}NaO_{11}$ 589.1680; found 589.1669.

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Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 188



188

To a solution of **172** (116 mg, 0.170 mmol) in DMF (0.9 mL) was added hydrazine acetate (71 mg, 0.64 mmol). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc (50 mL), washed with brine (3x30 mL) then the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (CH_2Cl_2/ CH_3OH = 40/1) to provide **188** as a colorless oil (78 mg, 89%).

$[\alpha]_D^{25}$ - 167.0 (*C* 0.64, CH_3OH).

IR(ATR) 3323, 3304, 3285, 3275, 2949, 2835, 1680, 1630, 1599, 1516, 1443, 1373, 1256, 1159, 1140, 1119, 1067, 1016 cm^{-1}.

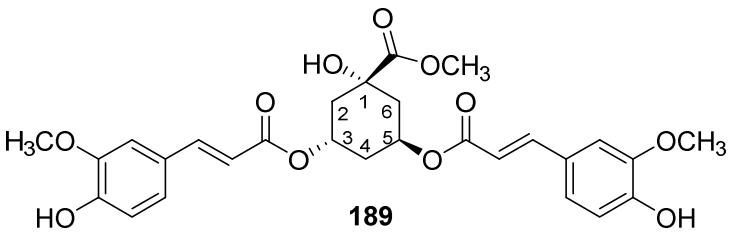
^1H NMR (CD_3OD, 298K, 500 MHz) d ppm = 7.58 and 7.52 (d, 2H, ^3J 15.8 Hz, C<u>H</u>=CHCO), 7.06 (bs, 2H, Ar-$H_{2'}$), 6.151 (dt, 2H, J_{ortho} = 8.1, J_{meta} 2.3 Hz, Ar-$H_{6'}$), 6.80 (dd, 2H, J_{ortho} 8,2 Hz, J_{meta} 2,7 Hz, Ar-$H_{5'}$), 6.28 and 6.19 (d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.42 (m, 2H, H_3 and H_5), 3.70 (s, 3H, OMe), 2.46 (dd, 1H, ^2J 13.4 Hz, ^3J 3.5 Hz, H_2 or H_6), 2.39 (dd, 1H, ^2J 13.6 Hz, ^3J 6.9 Hz, H_2 or H_6), 2.06 (m, 1H, H_4), 1.97 (m, 2H, H_4 and H_2 or H_6), 1.86 (dd, 1H, ^2J 13.4 Hz, ^3J 7.7 Hz, H_2 or H_6).

^{13}C NMR (CD_3OD, 298K, 125 MHz) d (ppm) = 175.7 (COOMe), 168.5 (OCO), 168.0 (OCO), 149.6 (C_q), 149.5 (C_q), 147.2 and 147.0 (<u>C</u>H=CHCO), 146.8 (C_q), 146.7(C_q), 127.7 (C_q), 127.6 (C_q), 123.04 and 123.00 ($C_{6'}$), 116.53 and 116.50 ($C_{5'}$), 115.4 and 115.1 (OCOCH=<u>C</u>H), 115.09 and 115.00 ($C_{2'}$), 75.0 (C_1), 69.5 and 69.0 (C_3 and C_5), 53.0(OMe), 39.7, 39.3 and 35.9 (3xCH_2, C_2, C_6 and C_4).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{26}H_{26}NaO_{11}$ 537.1367; found 537.1351.

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Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)- 3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 189



189

To a solution of **181** (65 mg, 0.104 mmol) in DMF (0.45 mL) was added hydrazine acetate (43 mg, 0.47 mmol). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc (50 mL), washed with brine (3x30 mL) then the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (CH_2Cl_2/ CH_3OH = 40/1) to provide **189** as a colorless oil (50 mg, 89%).

$[\alpha]_D^{25}$ - 170.0 (*C* 0.93, CH_3OH).

IR(ATR) 3516, 3057, 2957, 2941, 1701, 1631, 1593, 1512, 1462, 1454, 1429, 1377, 1263, 1207, 1157, 1138, 1032, 1009 cm^{-1}.

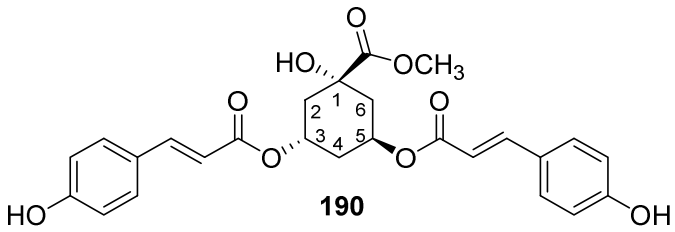
^1H NMR (CD_3OD, 400 MHz) d ppm = 7.63 and 7.57 (d, 2H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.12 (bs, 2H, Ar-H), 7.07 (dd, 2H, J_{ortho} 8,2 Hz, J_{meta} 2,7 Hz, Ar-H), 6.81 (dd, 2H, J_{ortho} 8,2 Hz, J_{meta} 2,2 Hz, Ar-H), 6.38 and 6.29 (d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.432 (m, 2H, H_3 and H_5), 3.88 (s, 6H, 2x OMe), 3.70 (s, 3H, COOMe), 2.45 (dd, 1H, ^2J 13.6 Hz, ^3J 4.1 Hz, H_2 or H_6), 2.38 (dd, 1H, ^2J 13.6 Hz, ^{3}J 7.2 Hz, H_2 or H_6), 2.14-1.97 (m, 3H, 2x H_4 and H_2 or H_6), 1.88 (dd, 1H, ^2J 13.6 Hz, ^3J 7.5 Hz, H_2 or H_6).

^{13}C NMR (CD_3OD, 100 MHz) d (ppm) = 175.7 ((COOMe), 168.4 and 168.0 (OCO), 150.7, 150.6, 149.4, 149.3 ($C_{q\,Ar}$), 147.1 and 147.0 (<u>C</u>H=CHCO), 127.7 and 127.5 ($C_{q\,Ar}$), 124.2 and 124.1 (CH_{Ar}), 116.5 and 116.4 (CH_{Ar}), 115.7 and 115.4 (OCOCH=<u>C</u>H), 111.6 (CH_{Ar}), 75.0 (C_1), 69.5 and 69.0 (C_5 or C_3), 56.4(2) (2xOCH_3), 53.0 (COO<u>Me</u>), 39.8 and 39.2 (C_2 or C_6), 35.9 (C_4).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{28}H_{30}NaO_{11}$ 565.1680; found 565.1662.

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Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 190



190

To a solution of **183** (80 mg, 0.14 mmol) in DMF (0.6 mL) was added hydrazine acetate (59 mg, 0.64 mmol). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc (50 mL), washed with brine (3x30 mL) then the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (CH_2Cl_2/ CH_3OH = 40/1) to provide **190** as a colorless oil (62 mg, 91%).

$[\alpha]_D^{25}$ - 174.7 (*C* 0.95, CH_3OH).

IR(ATR) 3325, 3308, 3279, 3267, 2947, 2832, 1688, 1632, 1603, 1587, 1514, 1441, 1371, 1325, 1307, 1254, 1202, 1165, 1144, 1103, 1065, 1018 cm^{-1}.

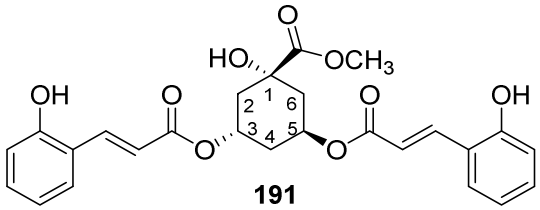
^{1}H NMR (CD_3OD, 400 MHz) d (ppm) = 7.65 and 7.59 (2d, 2H, ^3J 15.9 Hz, 2x C<u>H</u>=CHCO), 7.47 (d, 4H, J_{ortho} 8.6 Hz, Ar-H), 6.81 (dd, 4H, J_{ortho} 8.6 Hz, J_{meta} 1.8 Hz Ar-H), 6.34 and 6.26 (d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.43 (m, 2H, H_3 and H_5), 3.69 (s, 3H, OMe), 2.46 (dd, 1H, ^2J 13.4 Hz, ^3J 4.1 Hz, H_2, H_4 or H_6), 2.40 (dd, 1H, ^2J 13.7 Hz, ^{3}J 7.0 Hz, H_2, H_4 or H_6), 2.10-1.151 (m, 3H, H_2, H_4 or H_6), 1.87 (dd, 1H, ^2J 13.4 Hz, ^{3}J 7.6 Hz H_2, H_4 or H_6).

^{13}C NMR (CD_3OD, 100 MHz) d (ppm) = 175.7 (COOMe), 168.5(OCO), 168.0(OCO), 161.4 (C_q), 161.3 (C_q), 146.8 and 146.7 (2x<u>C</u>H=CHCO), 131.23 and 131.20 (2x2xCH), 127.2 and 127.0 (2xC_q), 116.9, 116.8 (2x2 CH), 115.5 and 115.1 (2x OCOCH=<u>C</u>H), 75.0 (C_1), 69.5, 69.0 (<u>C</u>$_3$ and C_5), 53.0 (OMe), 39.8, 39.3 and 35.9 (3xCH_2, C_2, C_6 and C_4).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{26}H_{26}NaO_9$ 505.1469; found 505.1452.

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Methyl (3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(2-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 191



191

To a solution of **184** (118 mg, 0.21 mmol) in DMF (0.9 mL) was added hydrazine acetate (88 mg, 0.96 mmol). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc (50 mL), washed with brine (3x30 mL) then the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (CH_2Cl_2/ CH_3OH = 40/1) to provide **191** as a colorless oil (89 mg, 89%).

$[\alpha]_D^{25}$ - 104.3 (*C* 1.00, CH_3OH).

IR(ATR) 3337, 3298, 3283, 3256, 2945, 2835, 1688, 1626, 1603, 1499, 1458, 1369, 1317, 1294, 1254, 1169, 1146, 1113, 1067, 1018 cm^{-1}.

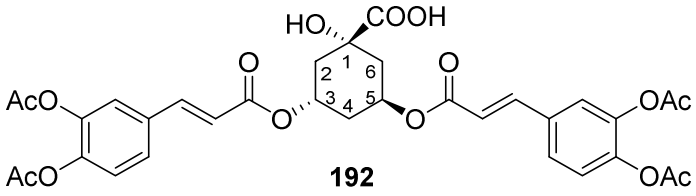
^1H NMR (CD_3OD, 400 MHz) d ppm = contaminated with chloroform at 7.90 ppm, 8.00 and 7.91 (2d, 2H, ^3J 16.1 Hz, C<u>H</u>=CHCO), 7.48 (pseudo t, 2H, J_{ortho} 8,2 Hz Ar-H), 7.21 (pseudot, 2H, J_{ortho} 7.4 Hz Ar-H), 6.84 (m, 4H, Ar-H), 6.63 and 6.58 (d, 2H, ^3J 16.1 Hz, CH=C<u>H</u>CO), 5.45 (m, 2H, H_3 and H_5), 3.72 (s, 3H, OMe), 2.49 (dd, 1H, ^2J 13.4 Hz, ^3J 3.6 Hz, H_2, H_4 or H_6), 2.43 (dd, 1H, ^2J 13.8 Hz, ^{3}J 6.8 Hz, H_2, H_4 or H_6), 2.15-2.09 (m, 1H, H_2, H_4 or H_6), 2.00-1.96 (m, 2H, H_2, H_4 or H_6), 1.86 (dd, 1H, ^2J 13.3 Hz, ^3J 7.9 Hz, H_2, H_4 or H_6).

^{13}C NMR (CD_3OD, 100 MHz) d (ppm) = contaminated with chloroform at 79.4 ppm; 175.7 (COOMe), 168.8(OCO), 168.4(OCO), 158.5 and 158.3 (2xC_q), 142.9 and 142.5 (2x<u>C</u>H=CHCO), 132.7, 132.6, 130.6, 130.2 (4xCH_{Ar}), 122.6, 122.5 (2xC_q), 120.8 (2xCH_{Ar}), 118.6, 118.5 (2x OCOCH=<u>C</u>H), 117.0 (2xCH_{Ar}), 79.4, 75.0 (C_1), 69.5, 69.1 (C_3 and C_5), 53.0 (OMe), 39.8, 39.4 and 35.9 (3xCH_2, C_2, C_6 and C_4).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{26}H_{26}NaO_9$ 505.1469; found 505.1448.

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(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylic acid 192



192

LiI (287 mg, 2.14 mmol) was added to a solution of **172** (146 mg, 0.214 mmol) in EtOAc (1.5 mL) then the mixture was heated under reflux 5h. After cooling down to room temperature, the mixture was diluted with EtOAc (30 mL), washed with 1M HCl (2x10 mL) and extracted with EtOAc (3x30 mL). The organic layer was dried over $MgSO_4$, concentrated to give the crude **192** (128 mg, crude yield: 90%), pure enough for characterization and used directly in the following step.

$[\alpha]_D^{26}$: - 94.8 (*C* 1.03, CH_3OH).

IR(ATR) 3370, 2941, 2833, 1769, 1707, 1638, 1504, 1369, 1240, 1201, 1174, 1143, 1109, 1012 cm^{-1}.

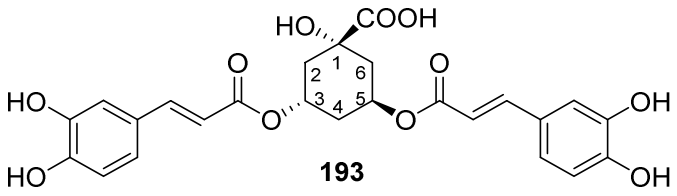
^1H NMR (CD_3OD, 298K, 400 MHz) d ppm = 7.67 and 7.62 (2d, 2H, *J* 16.0 Hz, C<u>H</u>=CHCO), 7.50 (m, 2H, $H_{6'}$), 7.49 (m, 2H, $H_{2'}$), 7.24 (d, 2H, J_{ortho} 8.2 Hz, H_5'), 6.52 and 6.46 (2d, 2H, *J* 16.0 Hz, CH=C<u>H</u>CO), 5.46 (m, 2H, H_3 and H_5), 2.44-2.19 (m, 14H) and 2.06-1.90 (m, 4H, 3xCH_2 and 4x$OCOCH_3$).

^{13}C NMR (CD_3OD, 298K, 100 MHz) d (ppm) = 177.3 (COOH), 169.8 and 169.7 (4x O<u>C</u>OCH_3), 167.5 and 167.2 (2xOCO), 145.2 and 145.1 (2xC_q), 144.5 and 144.4 (2x<u>C</u>H=CHCO), 144.0 (2xC_q), 134.60 and 134.56 (2xC_q), 127.7 and 127.6 (2x$C_{6'}$), 125.13 and 125.11 (2x$C_{5'}$), 124.14 and 124.09 ($C_{2'}$), 120.45 and 120.13 (2x CH=<u>C</u>HCO), 75.0 (C_1), 70.2, 69.2 (C_3 and C_5), 39.9, 38.7, 35.9 (C_2, C_4, C_6), 20.5 (4XOCO<u>C</u>H_3).

HRMS-ESI m/z $[M+H]^+$ calcd for $C_{33}H_{33}O_{15}$ 669.1814; found 669.1801.

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(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylic acid 193



193

To a solution of **192** (208 mg) in acetone (4 mL) was added 3M HCl aqueous solution (2.0 mL) and the mixture was refluxed for 5h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated to give the crude quantitatively as a pale solid **193** (190 mg).

$[\alpha]_D^{25}$ - 42.7 (*C* 0.82, CH_3OH).

IR(ATR) 3345, 3210, 1687, 1603, 1523, 1445, 1362, 1279, 1182, 1138, 1119 cm^{-1}.

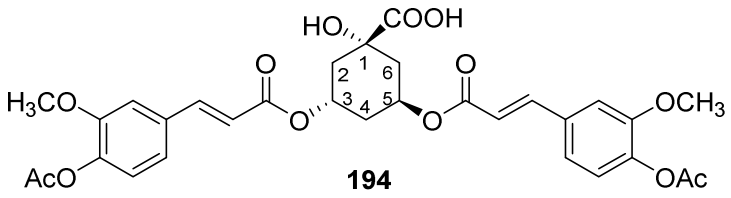
^1H NMR (CD_3OD, 400 MHz, 295K) d (ppm) = 7.65 and 7.60 (2d, 2H, *J* 16.0 Hz, C<u>H</u>=CHCO), 7.45 (m, 4H, ArH), 6.81 (m, 4H, ArH), 6.34 and 6.27 (2d, 2H, *J* 16.0 Hz, CH=C<u>H</u>CO), 5.45 (m, 2H, H_3 and H_5), 2.41 (dd, 1H, ^2J 14.0 Hz, ^3J 3.8 Hz, H_2, H_4 or H_6), 2.32 (dd, 1H, ^2J 13.3 Hz, ^3J 8.2 Hz, H_2, H_4 or H_6), 2.06 (m, 3H, H_2, H_4 or H_6), 1.93 (dd, 1H, ^2J 13.8 Hz, ^3J 6.5 Hz, H_2, H_4 or H_6).

^{13}C NMR (CD_3OD, 100 MHz, 297K) d (ppm) = 177.4 (COOH), 171.0 (2xC_q), 168.5 and 168.3 (2xOCO), 161.12 and 161.07 (2xCq), 146.7 and 146.7 (2x<u>C</u>H=CHCO), 131.2, 131.1 (2xCH_{Ar}), 127.1 (2xC_q), 116.8 (4xCHAr), 115.5, 115.1 (2x CH=<u>C</u>HCO), 75.1 (C_1), 69.9, 68.7 (C_3 and C_5), 39.9, 38.6, 35.9 (C_2, C_4, C_6).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{25}H_{24}NaO_{11}$ 523.1211; found 523.1204.

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(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylic acid 194



194

LiI (54 mg, 2.27 mmol) was added to a solution of **182** (142 mg, 0.2274 mmol) in EtOAc (8.0 mL) then the mixture was heated under reflux 6h. After cooling down to room temperature, the mixture was diluted with EtOAc (25 mL), washed with 3M HCl (5 mL) and extracted with EtOAc (3x30 mL). The organic layer was dried over $MgSO_4$, concentrated to give the crude **194** (quantitative crude yield), pure enough for characterization and used directly in the following step.

$[\alpha]_D^{25}$ - 97.5 (*C* 0.96, CH_3OH).

IR(ATR) 3466, 2941, 2833, 1763, 1705, 1599, 1508, 1464, 1454, 1418, 1369, 1256, 1215, 1177, 1152, 1063, 1020 cm^{-1}.

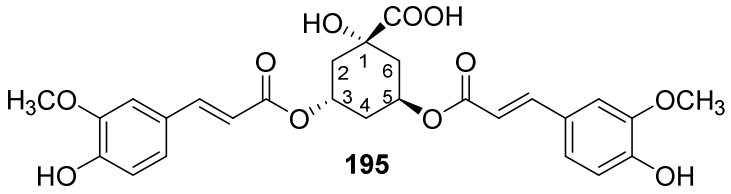
^1H NMR ($CDCl_3$, 400 MHz) d (ppm) = 7.66 and 7.61 (2d, 2H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.13-7.03 (2m, 6H, Ar-H), 6.41 and 6.34 (2d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.50 (m, 2H, H_3 and H_5), 3.87 and 3.85 (2s, 2x3H, 2xOMe), 2.33-1.83 (m, 12H, H_2, H_4, H_6 and 2x$OCOCH_3$).

^{13}C NMR ($CDCl_3$, 100 MHz) d (ppm) = 176.7 (COOH), 169.04 and 169.02 (2xO<u>C</u>OCH_3), 166.1 and 166.0 (2xCOO), 151.53 and 151.50 (2xC_q), 145.3, 144.8 (2x<u>C</u>H=CHCO), 141.7, 141.6 (2xC_q), 133.3, 133.2 (2xC_q), 123.4 (2xCH_{Ar}), 121.8, 121.4 (2x CH=<u>C</u>HCO), 118.1, 117.9 (2xCH_{Ar}), 111.4, 111.3(2xCH_{Ar}), 75.2(C_1), 69.4, 66.5 (C_3 and C_5), 56.1, 56.0 (2xOMe), 39.3, 36.5, 34.9 (C_2, C_4, C_6), 20.8 (2xOCO<u>C</u>H_3).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{31}H_{32}NaO_{13}$ 635.1735; found 635.1706.

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(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylic acid 195



195

To a solution of **194** (176 mg) in acetone (3.0 mL) was added 3M HCl aqueous solution (1.5 mL) and the mixture was refluxed for 4h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated then dissolved in MeOH/H_2O (30/40 mL) and washed with pentane (2x15 mL). After concentration, the crude was obtained as a pale solid **195** (150 mg, quantitative yield).

$[\alpha]_D^{25}$ - 94.4 (*C* 0.67, CH_3OH).

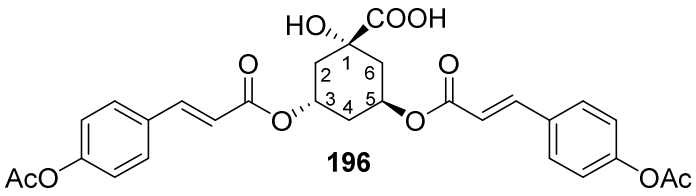
IR(ATR) 3356, 3277, 1684, 1632, 1605, 1514, 1443, 1327, 1261, 1204, 1171, 1138, 1007 cm^{-1}.

^1H NMR (CD_3OD, 300 MHz, 297K) d (ppm) = 7.65 and 7.60 (2d, 2H, *J* 15.9 Hz, C<u>H</u>=CHCO), 7.17 (m, 2H, ArH), 7.07 (m, 2H, ArH), 6.83 (d, 2H, J_{ortho} 8.1 Hz, ArH), 6.39 and 6.32 (2d, 2H, *J* 15.9 Hz, CH=C<u>H</u>CO), 5.47 (m, 2H, H_3 and H_5), 3.89 (s, 6H, 2xOMe), 2.42 (dd, 1H, ^2J 13.9 Hz, ^3J 4.0 Hz, H_2, H_4 or H_6), 2.34 (dd, 1H, ^2J 13.4 Hz, ^3J 8.2 Hz, H_2, H_4 or H_6), 2.00 (m, 4H, H_2, H_4 or H_6).

^{13}C NMR (CD_3OD, 75 MHz, 297K) d (ppm) = 177.4 (COOH), 170.9 (2xC_q), 168.5 and 168.2 (2xOCO), 150.44, 150.38 (2xC_q), 146.9 and 146.8 (2x<u>C</u>H=CHCO), 127.74 and 127.68 (2xC_q), 124.1, 124.0, 123.9, 116.4, 115.8, 115.5 (6x CH_{Ar}), 111.7 and 111.6 (2x CH=<u>C</u>HCO), 75.1 (C_1), 69.9, 68.7 (C_3 and C_5), 56.43 and 56.41 (2xOMe), 40.0, 38.7, 36.0 (C_2, C_4, C_6).

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(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylic acid 196



196

LiI (250 mg, 1.87 mmol) was added to a solution of **183** (105 mg, 0.186 mmol) in EtOAc (6.0 mL) then the mixture was heated under reflux 6h. After cooling down to room temperature, the mixture was diluted with EtOAc (25 mL), washed with 3M HCl (5 mL) and extracted with EtOAc (3x30 mL). The organic layer was dried over $MgSO_4$, concentrated to give the crude **196** (quantitative crude yield), pure enough for characterization and used directly in the following step.

$[\alpha]_D^{25}$ - 111.9 (*C* 1.03, CH_3OH).

IR(ATR) 3447, 1729, 2961, 1765, 1707, 1601, 1585, 1506, 1418, 1369, 1312, 1265, 1202, 1163, 1136, 1057, 1009 cm^{-1}.

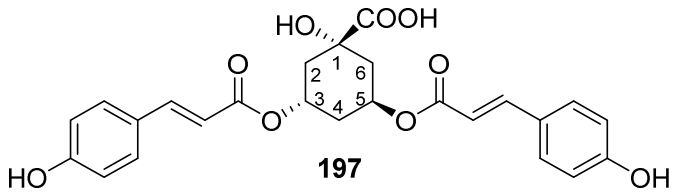
^1H NMR ($CDCl_3$, 298K, 400 MHz) d ppm = 7.68 and 7.62 (2d, 2H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.52 (dd, 4H, J_{ortho} 8,6 Hz, J_{ortho} 6.8 Hz, Ar-H), 7.11 (dd, 4H, J_{ortho} 8,6 Hz, J_{meta} 2.0 Hz, Ar-H), 6.41 and 6.34 (2d, 2H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.49 (m, 2H, H_3 and H_5), 2.36-2.02 and 1.86 (2m, 11 and 1H, H_2, H_4, H_6 and 2x$OCOCH_3$).

^{13}C NMR ($CDCl_3$, 298K, 100 MHz) d (ppm) = 177.0 (COOH), 169.41 and 169.39 (2xO<u>C</u>OCH_3), 166.2, 166.1 (2xCOO), 152.4, 152.3 (2xC_q), 144.9, 144.4 (2x<u>C</u>H=CHCO), 132.04, 132.0 (2xC_q), 129.6, 129.5 (4xCH_{Ar}), 122.3 (4xCH_{Ar}), 118.0, 117.9 (2x CH=<u>C</u>HCO), 75.2 (C_1), 69.4, 66.6 (C_3 and C_5), 39.3, 36.5, 34.9 (C_2, C_4 and C_6), 21.3 (2x $OCOCH_3$).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{29}H_{28}NaO_{11}$ 575.1524; found 575.1503.

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(3S,5S) 1-hydroxy-3,5 bis[[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylic acid 197



197

To a solution of **196** (196 mg) in acetone (4.0 mL) was added 3M HCl aqueous solution (2.0 mL) and the mixture was refluxed for 5h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated, dissolved in MeOH/H_2O (20/50 mL) and washed with pentane (2x15 mL). After concentration, the crude quantitatively as a pale solid **197** (165 mg).

$[\alpha]_D^{25}$ - 72.6 (*C* 0.71, CH_3OH).

IR (ATR) 3406, 2976, 2947, 1692, 1593, 1514, 1456, 1429, 1375, 1269, 1209, 1177, 1161, 1138, 1032 cm^{-1}.

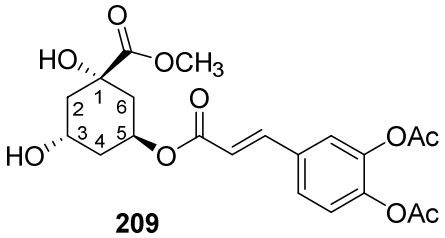
^1H NMR (CD_3OD, 400 MHz, 295K) d (ppm) = 7.59 and 7.54 (2d, 2H, *J* 16.0 Hz, C<u>H</u>=CHCO), 7.08 (m, 4H, ArH), 6.97-6.92 (m, 4H, ArH), 6.81 (m, 2H, ArH), 6.29 and 6.23 (2d, 2H, *J* 16.0 Hz, CH=C<u>H</u>CO), 5.44 (m, 2H, H_3 and H_5), 2.40 (dd, 1H, ^2J 13.9 Hz, ^3J 4.3 Hz, H_2, H_4 or H_6), 2.32 (dd, 1H, ^2J 13.4 Hz, ^3J 8.2 Hz, H_2, H_4 or H_6), 1.96 (m, 4H, H_2, H_4 or H_6).

^{13}C NMR (CD_3OD, 100 MHz, 297K) d (ppm) = 177.4 (COOH), 171.0 (2xC_q), 168.6 and 168.5 (2xOCO), 149.4, 149.3 (2xC_q), 147.1 and 146.9 (2x<u>C</u>H=CHCO), 127.74 and 127.68 (2xC_q), 123.1, 123.0, 116.5, 116.4 (x2), 115.4, .115.2, 115.11, 115.09, 115.0 (8x CH_{Ar} +2x CH=<u>C</u>HCO), 75.0 (C_1), 69.9, 68.7 (C_3 and C_5), 39.9, 38.6, 35.9 (C_2, C_4, C_6).

HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{25}H_{24}NaO_9$ 491.1313; found 491.1300.

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Methyl (3S,5S) 1,3-dihydroxy-5-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 209



209

To a solution of triol **167** (102 mg, 0.537 mmol) in DCM (4.5 mL) and pyridine (0.9 mL) with DMAP (13 mg, 0.107 mmol) under nitrogen was added the acetylated caffeoyl chloride (227mg, 0.806 mmol). The mixture was stirred at -18°C to room temperature until completion after 4h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O / DCM = 1/10 to 1/4) providing diester **172** (40 mg, 11%), monoester **209** (86 mg, 37%) and monoester **210** (30 mg, 13%) as white solids.

$[\alpha]_D^{25}$: + 6.5 (*C* 1.215, CH_2Cl_2).

IR(ATR) 1770, 1736, 1711, 1639, 1504, 1425, 1371, 1263, 1242, 1205, 1177, 1145, 1111, 1049, 1010 cm^{-1}.

^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ (ppm) 7.59 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.44 – 7.31 (m, 2H, H_{Ar}), 7.19 (d, 1H, J_{ortho} 8.3 Hz, H_{Ar}), 6.33 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.53 (tt, ^3J 11.4 Hz, ^3J 4.4 Hz, 1H, H_5), 4.32 (s, 1H, H_3), 4.23 (s, 1H, O<u>H</u>$_1$ or O<u>H</u>$_3$), 3.88 (s, 1H, O<u>H</u>$_1$ or O<u>H</u>$_3$), 3.77 (s, 3H, COOC<u>H</u>$_3$), 2.43 – 2.21 (m, 8H, H_4, H_6 and 2xOCOC<u>H</u>$_3$), 2.07 – 1.151 (m, 2H, 2xH_2), 1.151 – 1.82 (m, 1H, H_6), 1.71 – 1.60 (m, 1H, H_4).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ (ppm) = 174.9 (<u>C</u>OOCH$_3$), 168.2 and 168.1 (2xO<u>C</u>OCH$_3$), 165.9 (CH=CH<u>C</u>O), 143.6 ($C_{q\,Ar}$), 143.1 (<u>C</u>H=CHCO), 142.5 ($C_{q\,Ar}$), 133.3 ($C_{q\,Ar}$), 126.5 (CH_{Ar}), 124.0 (CH_{Ar}),

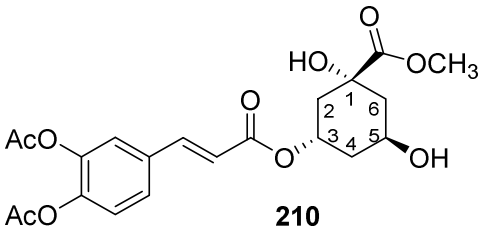
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122.8 (CH_{Ar}), 119.3 (CH=CHCO), 76.3 (C_1), 67.5 (C_3), 66.8 (C_5), 53.2 ($COOCH_3$), 39.7 (C_6), 38.1 (C_4), 38.0 (C_2), 20.71 and 20.66 ($OCOCH_3$).

HRMS (ESI): calcd for $C_{21}H_{24}O_{10}$ [M + Na^+]: 459.1262, found: 459.1251.

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Methyl (3S,5S) 1,5-dihydroxy-3-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 210



210

$[\alpha]_D^{25}$: + 24.7 (*C* 0.925, CH_2Cl_2).

IR(ATR) 1773, 1732, 1707, 1639, 1504, 1425, 1371, 1319, 1265, 1244, 1206, 1179, 1134, 1111, 1080, 1012 cm^{-1}.

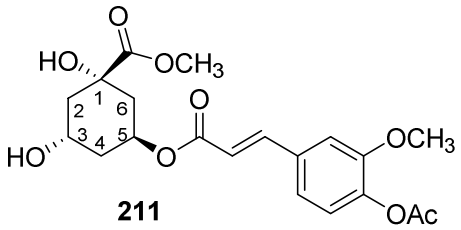
^1H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.60 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.41 – 7.32 (m, 2H, H_{Ar}), 7.20 (d, 1H, *J*ortho 8.3 Hz, H_{Ar}), 6.36 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.40 (p, 1H, ^3J 3.9 Hz, H_3), 4.40 – 4.29 (m, 1H, H_5), 3.78 (s, 3H, COOC<u>H</u>$_3$), 2.29 and 2.28 (2s, 6H, 2xOCOC<u>H</u>$_3$), 2.24 – 2.16 (m, 1H, H_4), 2.15 – 1.97 (m, 3H, 2xH_2 and H_6), 1.89 (dd, 1H, ^2J 12.9 Hz, ^3J 10.0 Hz, H_{6a}), 1.69 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.2 Hz, ^3J 3.3 Hz, H_{4a}).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.8 (<u>C</u>OOCH$_3$), 168.2 and 168.1 (O<u>C</u>OCH$_3$), 165.9 (CH=CH<u>C</u>O), 143.6 ($C_{q\,Ar}$), 143.3 (<u>C</u>H=CHCO), 142.5 ($C_{q\,Ar}$), 133.3 ($C_{q\,Ar}$), 126.6 (CH_{Ar}), 124.0 (CH_{Ar}), 122.9 (CH_{Ar}), 119.5 (CH=<u>C</u>HCO), 75.1 (C_1), 69.5 (C_3), 63.3 (C_5), 53.2 (COO<u>C</u>H$_3$), 42.98 (C_6), 38.35 (C_4), 37.02 (C_2), 20.75 and 20.70 (OCO<u>C</u>H$_3$).

HRMS (ESI): calcd for $C_{21}H_{24}O_{10}$ [M + Na^+]: 459.1262, found: 459.1253.

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Methyl (3S,5S) 1,3-dihydroxy-5-[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 211



211

To a solution of triol **167** (205 mg, 1.079 mmol) in DMF (1.6 mL) and pyridine (1.1 mL) under nitrogen was added the acetylated feruloyl chloride (418mg, 1.639 mmol). The mixture was stirred at 45 °C for 6h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc / petroleum ether = 1/1 to 3/1) providing diester **182** (187 mg, 28%), monoester **211** (164 mg, 43%) and monoester **212** (99mg, 26%) as white solids.

$[\alpha]_D^{25}$: - 5.8 (*C* 0.885, CH_2Cl_2).

IR(ATR) 2934, 1763, 1736, 1707, 1638, 1601, 1508, 1456, 1418, 1369, 1258, 1238, 1213, 1196, 1172, 1153, 1123, 1049, 1031, 1010 cm^{-1}.

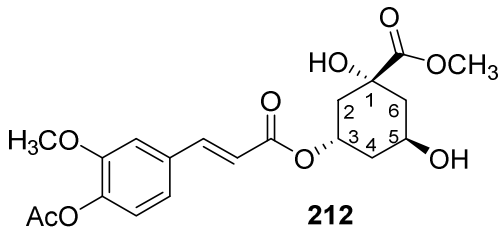
^1H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.58 (d, 1H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.11 – 7.05 (m, 2H, H_{Ar}), 7.00 (d, 1H, J_{ortho} 8.6 Hz, H_{Ar}), 6.31 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.51 (tt, 1H, ^3J 11.2 Hz, ^3J 4.4 Hz, H_5), 4.43 (s, 1H, O<u>H</u>$_1$), 4.35 – 4.28 (m, 1H, H_3), 4.05 – 3.94 (m, 1H, O<u>H</u>$_3$), 3.81 (s, 3H, COOC<u>H</u>$_3$), 3.74 (s, 3H, PhOC<u>H</u>$_3$), 2.40 – 2.24 (m, 2H, H_4 and H_6), 2.28 (s, 3H, OCOC<u>H</u>$_3$), 2.05 – 1.94 (m, 2H, 2xH_2), 1.89 (dd, 1H, ^2J 12.6 Hz, ^3J 11.2 Hz, H_{6a}), 1.65 (ddd, 1H, ^2J 12.7 Hz, ^3J 11.5 Hz, ^3J 3.0 Hz, H_{4a}).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 174.7 (<u>C</u>OOCH$_3$), 168.8 (O<u>C</u>OCH$_3$), 166.0 (CH=CH<u>C</u>O), 151.4 ($C_{q\,Ar}$), 144.3 (<u>C</u>H=CHCO), 141.4 ($C_{q\,Ar}$), 133.3 ($C_{q\,Ar}$), 123.2 (CH_{Ar}), 121.2 (CH_{Ar}), 118.3 (CH=<u>C</u>HCO), 111.3 (CH_{Ar}), 76.3 (C_1), 67.4 (C_3), 66.7 (C_5), 55.9 (PhO<u>C</u>H$_3$), 53.0 (COO<u>C</u>H$_3$), 39.7 (C_6), 38.0 (C_4), 38.0 (C_2), 20.6 (OCO<u>C</u>H$_3$).

HRMS (ESI): calcd for $C_{20}H_{24}O_9$ [M + Na^+]: 431.1313, found: 431.1332.

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Methyl (3S,5S) 1,5-dihydroxy-3-[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 212



212

$[\alpha]_D^{25}$: + 3.3 (*C* 0.805, CH_3OH)

IR(ATR) 3443, 2951, 2926, 1763, 1732, 1705, 1634, 1599, 1510, 1454, 1418, 1369, 1258, 1215, 1176, 1155, 1143, 1082, 1012 cm^{-1}.

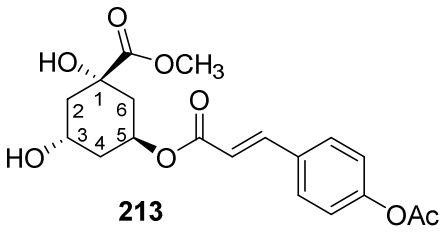
^1H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.64 (d, 1H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.16 – 7.09 (m, 2H, H_{Ar}), 7.08 – 7.02 (m, 1H, H_{Ar}), 6.37 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.44 (p, 1H, ^3J 3.9 Hz, H_3), 4.38 (tt, 1H, ^3J 10.2 Hz, ^3J 4.1 Hz, H_5), 3.87 (s, 3H, PhOC<u>H</u>$_3$), 3.82 (s, 3H, COOC<u>H</u>$_3$), 2.35 (s, 3H, OCOC<u>H</u>$_3$), 2.30 – 2.23 (m, 1H, H_4), 2.18 – 2.09 (m, 2H, H_2 and H_6), 2.08 – 2.02 (m, 1H, H_2), 1.90 (dd, 1H, ^2J 12.9 Hz, ^3J 10.1 Hz, H_{6a}), 1.71 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.3 Hz, ^3J 3.4 Hz, H_{4a}).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.8 (<u>C</u>OOCH$_3$), 168.9 (O<u>C</u>OCH$_3$), 166.1 (CH=CH<u>C</u>O), 151.5 ($C_{q\,Ar}$), 144.7 (<u>C</u>H=CHCO), 141.6 ($C_{q\,Ar}$), 133.4 ($C_{q\,Ar}$), 123.4 (CH_{Ar}), 121.6 (CH_{Ar}), 118.4 (CH=<u>C</u>HCO), 111.3 (CH_{Ar}), 76.2 (C_1), 69.5 (C_3), 63.5 (C_5), 56.1 (PhO<u>C</u>H$_3$), 53.4 (COO<u>C</u>H$_3$), 43.1 (C_6), 38.5 (C_4), 37.1 (C_2), 20.8 (OCO<u>C</u>H$_3$).

HRMS (ESI): calcd for $C_{20}H_{24}O_9$ [M + Na^+]: 431.1313, found: 431.1298.

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Methyl (3S,5S) 1,3-dihydroxy-5-[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 213



213

To a solution of triol **167** (168 mg, 0.884 mmol) in DMF (1.3 mL) and pyridine (0.151 mL) under nitrogen was added the acetylated *p*-coumaroyl chloride (298 mg, 1.33 mmol). The mixture was stirred at 45 °C for 15h. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc / petroleum ether = 1/1 to 3/1) providing diester **183** (154 mg, 31%), monoester **213** (93 mg, 28%) and monoester **214** (59 mg, 18%) as white solids.

$[\alpha]_D^{25}$: + 3.6 (*C* 1.03, CH_2Cl_2).

IR(ATR) 1765, 1736, 1709, 1638, 1506, 1435, 1418, 1369, 1265, 1202, 1165, 1144, 1011 cm^{-1}.

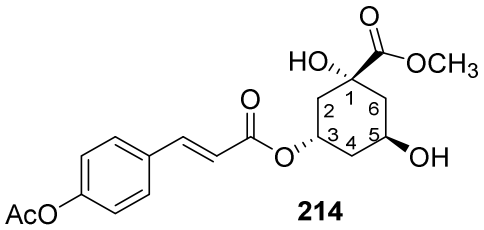
^1H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.62 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.50 (2s, 2H, H_{Ar}), 7.09 (2s, 2H, H_{Ar}), 6.33 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.52 (tt, 1H, ^2J 11.3 Hz, ^3J 4.4 Hz, H_5), 4.33 (p, 1H, ^3J 3.3 Hz, H_3), 3.84 (s, 1H, O<u>H</u>), 3.77 (s, 3H, COOC<u>H</u>$_3$), 2.44 – 2.34 (m, 2H, H_4 and H_6), 2.28, (s, 3H, OCOC<u>H</u>$_3$), 2.04 – 1.85 (m, 3H, 2xH_2 and H_6), 1.74 – 1.60 (m, 1H, H_4).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 174.9 (<u>C</u>OOCH$_3$), 169.3 (O<u>C</u>OCH$_3$), 166.1 (CH=CH<u>C</u>O), 152.2 ($C_{q\ Ar}$), 144.0 (<u>C</u>H=CHCO), 132.1 ($C_{q\ Ar}$), 129.3 (CH_{Ar}), 122.2 (CH_{Ar}), 118.3 (CH=<u>C</u>HCO), 76.3 (C_1), 67.5 (C_3), 66.6 (C_5), 53.2 (COO<u>C</u>H$_3$), 39.8 (C_6), 38.2 (C_4), 38.0 (C_2), 21.2 (OCO<u>C</u>H$_3$).

HRMS (ESI): calcd for $C_{19}H_{22}O_8$ [M + Na^+]: 401.1207, found: 401.1196.

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Methyl (3S,5S) 1,5-dihydroxy-3-[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 214



214

$[\alpha]_D^{25}$: + 27.8 (*C* 0.965, CH_2Cl_2).

IR(ATR) 3406, 3323, 2947, 2932, 1759, 1724, 1680, 1634, 1601, 1508, 1446, 1418, 1366, 1306, 1281, 1203, 1167, 1132, 1086, 1026, 1011 cm^{-1}.

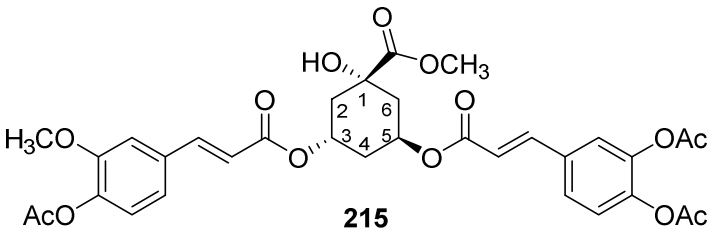
^1H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.65 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.53 (2s, 2H, H_{Ar}), 7.13 – 7.10 (m, 2H, H_{Ar}), 6.37 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.42 (p, 1H, ^3J 3.9 Hz, H_3), 4.36 (tt, 1H, ^3J 10.1 Hz, ^3J 4.0 Hz, H_5), 3.80 (s, 3H, COOC<u>H</u>$_3$), 2.30 (s, 3H, OCOC<u>H</u>$_3$), 2.26 – 2.20 (m, 1H, H_4), 2.16 – 2.08 (m, 2H, H_2 and H_6), 2.03 (m, 1H, H_2), 1.90 (dd, 1H, ^2J 13.0 Hz, ^3J 9.9 Hz, H_{6a}), 1.71 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.2 Hz, ^3J 3.4 Hz, H_4).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.8 (<u>C</u>OOCH$_3$), 169.3 (O<u>C</u>OCH$_3$), 166.2 (CH=CH<u>C</u>O), 152.2 ($C_{q\ Ar}$), 144.2 (<u>C</u>H=CHCO), 132.1 ($C_{q\ Ar}$), 129.4 (CH_{Ar}), 122.2 (CH_{Ar}), 118.4 (CH=<u>C</u>HCO), 75.12 (C_1), 69.5 (C_3), 63.4 (C_5), 53.3 (C_8), 43.1 (C_6), 38.4 (C_4), 37.1 (C_2), 21.3 (OCO<u>C</u>H$_3$).

HRMS (ESI): calcd for $C_{19}H_{22}O_8$ [M + Na^+]: 401.1207, found: 401.1197.

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Methyl (3S,5S) 1-hydroxy-3-[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]-5-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 215



215

To a solution of 5-caffeoylmonoester **209** (220 mg, 0.505 mmol) in DMF (0.9 mL) and pyridine (0.6 mL) under nitrogen was added the acetylated feruloyl chloride (193 mg, 0.757 mmol). The mixture was stirred at 0 °C to room temperature for 4h. Methanol (1 mL) was added (stirring 15 min), the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl, saturated $NaHCO_3$ solution then brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O / DCM = 1/15 to 1/6) providing heterodiester **215** (204 mg, 62%), as a white solid.

Mp: 80 - 82 °C.

$[\alpha]_D^{25}$: - 83.5 (*C* 1.035, CH_2Cl_2).

IR(ATR) 1767, 1709, 1639, 1506, 1420, 1371, 1319, 1263, 1203, 1176, 1153, 1141, 1122, 1063, 1034, 1011 cm^{-1}.

^1H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.64 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.58 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.43 – 7.31 (m, 2H, H_{Ar}), 7.20 (d, 1H, J_{ortho} = 8.4 Hz, H_{Ar}), 7.14 – 7.07 (m, 2H, H_{Ar}), 7.06 – 6.99 (m, 1H, H_{Ar}), 6.41 (d, 1H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 6.32 (d, 1H, ^3J 16.1 Hz, CH=C<u>H</u>CO), 5.59 – 5.43 (m, 2H, H_3 and H_5), 3.85 (s, 3H, PhOC<u>H</u>$_3$), 3.75 (s, 3H, COOC<u>H</u>$_3$), 3.30 (s, 1H, O<u>H</u>), 2.30, 2.28, and 2.27 (3s, 9H, 3x OCOC<u>H</u>$_3$), 2.35 – 2.16 (m, 3H, H_4, H_2 and H_6), 2.16 – 2.02 (m, 2H, H_6 and H_2), 1.86 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.4, ^3J 3.5 Hz, H_4).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.0 (<u>C</u>OOCH$_3$), 168.8, 168.1 and 168.0 (O<u>C</u>OCH$_3$), 166.1 and 165.6 (CH=CH<u>C</u>O), 151.4 ($C_{q\ Ar}$), 144.6 (<u>C</u>H=CHCO), 143.6 ($C_{q\ Ar}$), 143.2 (<u>C</u>H=CHCO), 142.5, 141.5, 133.3 and 133.1 ($C_{q\ Ar}$), 126.4, 124.0, 123.5, 123.2, 122.8 and 121.6 (CH_{Ar}), 119.2 and 118.4

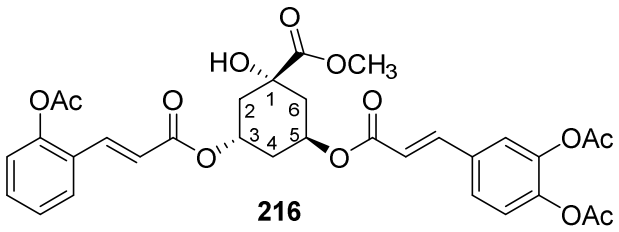
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(CH=CHCO), 111.2 (CH_{Ar}), 74.7 (C_1), 68.9 (C_5 or C_3), 66.9 (C_5 or C_3), 56.0 ($PhOCH_3$), 53.1 ($COOCH_3$), 39.7 (C_6 or C_2), 36.7 (C_6 or C_2), 35.0 (C_4), 20.68 and 20.63 ($OCOCH_3$).

HRMS (ESI): calcd for $C_{33}H_{34}O_{14}$ [M + Na^+]: 677.1841, found: 677.1830.

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Methyl (3S,5S) 1-hydroxy-3-[[(2E)-3-(2-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]-5-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 216



216

To a solution of 5-caffeoylmonoester **209** (34 mg, 0.078 mmol) in DMF (0.11 mL) and pyridine (0.078 mL) under nitrogen was added the acetylated *o*-coumaroyl chloride (21 mg, 0.094 mmol). The mixture was stirred at 45 °C for 3h. Methanol (1 mL) was added (stirring 15 min), the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl, saturated $NaHCO_3$ solution then brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc / Pentane = 1/1 to 3/1) providing heterodiester **216** (19 mg, 39%) as a white solid.

Mp: 85 - 87 °C.

$[\alpha]_D^{25}$: - 47.5 (*C* 0.84, CH2Cl2).

IR(ATR) 1771, 1732, 1711, 1510, 1423, 1371, 1317, 1265, 1204, 1179, 1142, 1113, 1094, 1011 cm^{-1}.

^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.82 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.66 (dd, 1H, J_{ortho} 7.8 Hz, J_{meta} 1.6 Hz, H_{Ar}), 7.60 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.48 – 7.32 (m, 3H, H_{Ar}), 7.31 – 7.20 (m, 2H, H_{Ar}), 7.12 (dd, 1H, J_{ortho} 8.2 Hz, J_{meta} 1.2 Hz, H_{Ar}), 6.47 (d, 1H, ^3J 16.1 Hz, CH=C<u>H</u>CO), 6.34 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.59 – 5.47 (m, 2H, H_3 and H_5), 3.78 (s, 3H, COOC<u>H</u>$_3$), 2.41, 2,31, and 2.30 (3s, 9H, 3xOCOC<u>H</u>$_3$), 2.36 – 2.14 (m, 3H, H_2, H_4 and H_6), 2.12 – 2.02 (m, 2H, H_2 or H_4 or H_6), 1.92 – 1.83 (m, 1H, H_2 or H_4 or H_6).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.2 (<u>C</u>OOCH$_3$), 169.5, 168.2, and 168.1 (O<u>C</u>OCH3), 165.9 and 165.6 (CH=CH<u>C</u>O), 149.5 ($C_{q\ Ar}$), 143.7 ($C_{q\ Ar}$), 143.2 (<u>C</u>H=CHCO), 142.6 ($C_{q\ Ar}$), 138.7 (<u>C</u>H=CHCO), 133.3 ($C_{q\ Ar}$), 131.3 (CH_{Ar}), 127.6 (CH_{Ar}), 127.2 ($C_{q\ Ar}$), 126.5 (CH_{Ar}), 126.5 (CH_{Ar}), 124.1

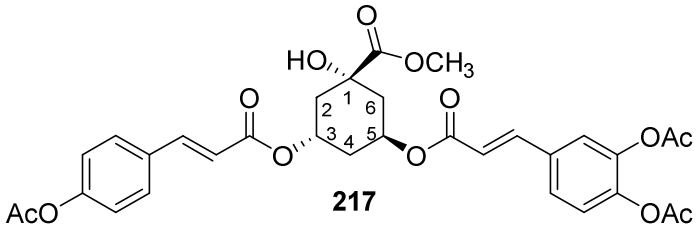
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(CH_{Ar}), 123.2 (CH_{Ar}), 122.9 (CH_{Ar}), 120.2 and 119.3 (CH=<u>C</u>HCO), 74.8 (C_1), 68.9 (C_5 or C_3), 66.9 (C_5 or C_3), 53.3 (COO<u>C</u>H_3), 39.9 (C_6 or C_2), 36.8 (C_6 or C_2), 35.2 (C_4), 21.01, 20.80 and 20.76 (OCO<u>C</u>H_3).

HRMS (ESI): calcd for $C_{32}H_{32}O_{13}$ [M + H^+]: 625.1916, found: 625.1899.

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Methyl (3S,5S) 1-hydroxy-3-[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]-5-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 217



217

To a solution of 5-caffeoylmonoester **209** (48 mg, 0.11 mmol) in DMF (0.22 mL) and pyridine (0.15 mL) under nitrogen was added the acetylated *p*-coumaroyl chloride (49 mg, 0.22 mmol). The mixture was stirred at 45 °C for 4h. Methanol (1 mL) was added (stirring 15 min), the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl, saturated $NaHCO_3$ solution then brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/ Pentane = 1/1 to 2/1) providing heterodiester **217** (43 mg, 62%) as a white solid.

Mp: 87 - 89 °C.

$[\alpha]_D^{25}$: - 67.5 (*C* 1.05, CH_2Cl_2).

IR(ATR) 1767, 1734, 1709, 1638, 1504, 1418, 1369, 1312, 1265, 1242, 1204, 1167, 1140, 1111, 1063, 1011 cm^{-1}.

^1H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.68 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.59 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.58 – 7.52 (m, 2H, H_{Ar}), 7.44 – 7.32 (m, 2H, H_{Ar}), 7.21 (d, 1H, J_{ortho} 8.4 Hz, H_{Ar}), 7.11 (2s, 2H, H_{Ar}), 6.42 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 6.33 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.59 – 5.45 (m, 2H, H_3 and H_5), 3.77 (s, 3H, COOC<u>H</u>$_3$), 2.34 – 2.16 (m, 12H, 3xOCOC<u>H</u>$_3$, H_4, H_6 and H_2), 2.14 – 2.03 (m, 2H, H_6 and H_2), 1.87 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.3 Hz, ^3J 3.4 Hz, H_4).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ 175.1 (<u>C</u>OOCH$_3$), 169.2, 168.2 and 168.1 (O<u>C</u>OCH$_3$), 166.1 and 165.6 (CH=CH<u>C</u>O), 152.2 ($C_{q\,Ar}$), 144.3 (<u>C</u>H=CHCO), 143.6 ($C_{q\,Ar}$), 143.2 (<u>C</u>H=CHCO), 142.5 ($C_{q\,Ar}$), 133.2 ($C_{q\,Ar}$), 132.2 ($C_{q\,Ar}$), 129.4 (CH_{Ar}), 126.5 (CH_{Ar}), 124.1 (CH_{Ar}), 122.9 (CH_{Ar}), 122.2 (CH_{Ar}), 119.2

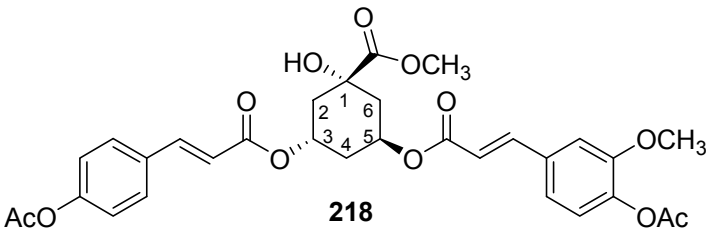
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and 118.3 (CH=CHCO), 74.8 (C_1), 68.9 (C_5 or C_3), 67.0 (C_5 or C_3), 53.2 (C_8), 39.8 (C_6 or C_2), 36.8 (C_6 or C_2), 35.1 (C_4), 21.24, 20.75 and 20.71 ($OCOCH_3$).

HRMS (ESI): calcd for $C_{31}H_{32}O_{12}$ [M + Na^+]: 647.1735, found: 647.1707.

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Methyl (3S,5S) 1-hydroxy-3-[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]-5-[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 218



218

To a solution of 5-feruloylmonoester **211** (57 mg, 0.14 mmol) in DMF (0.3 mL) and pyridine (0.2 mL) under nitrogen was added the acetylated *p*-coumaroyl chloride (251 mg, 1.18 mmol). The mixture was stirred at 45 °C for 30h. Methanol (1 mL) was added (stirring 15 min), the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl, saturated $NaHCO_3$ solution then brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/ Pentane = 1/1 to 2/1) providing heterodiester **218** (36 mg, 43%) as a white solid.

Mp: 86 - 87 °C.

$[\alpha]_D^{25}$: -74.7 (*C* 0.95, CH_2Cl_2).

IR(ATR) 1765, 1732, 1709, 1638, 1601, 1506, 1418, 1369, 1312, 1265, 1240, 1200, 1165, 1155, 1138, 1088, 1063, 1034, 1011 cm^{-1}.

^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.69 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.62 (d, 1H, ^3J 16.1 Hz, C<u>H</u>=CHCO), 7.59 – 7.52 (m, 2H, H_{Ar}), 7.18 – 7.09 (m, 4H, H_{Ar}), 7.06 – 7.02 (m, 1H, H_{Ar}), 6.42 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 6.34 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.60 – 5.46 (m, 2H, H_3 and H_5), 3.86 (s, 3H, PhOC<u>H</u>$_3$), 3.77 (s, 3H, COOC<u>H</u>$_3$), 2.32 and 2.30 (2s, 6H, 2xOCOC<u>H</u>$_3$), 2.37 – 2.18 (m, 3H, , H_4, H_6 and H_2), 2.14 – 2.04 (m, 2H, H_6 and H_2), 1.89 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.3 Hz, ^3J 3.4 Hz, H_4).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.0 (<u>C</u>OOCH$_3$), 169.2 and 168.9 (O<u>C</u>OCH$_3$), 166.2 and 165.9 (CH=CH<u>C</u>O), 152.2 ($C_{q\ Ar}$), 151.5 ($C_{q\ Ar}$), 144.5 and 144,3 (<u>C</u>H=CHCO), 141.6 ($C_{q\ Ar}$), 133.3 ($C_{q\ Ar}$), 132.2 ($C_{q\ Ar}$), 129.5 (CH_{Ar}), 123.4 (CH_{Ar}), 122.2 (CH_{Ar}), 121.4 (CH_{Ar}), 118.4 and 118.3 (CH=<u>C</u>HCO),

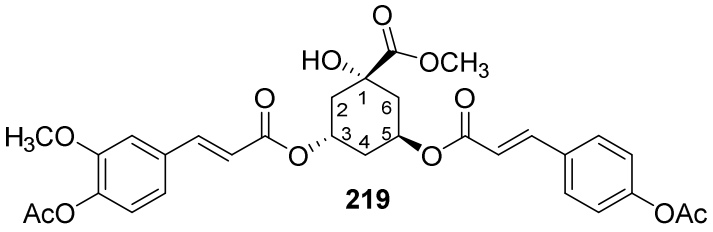
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111.3 (CH_{Ar}), 74.8 ($COO\underline{C}H_3$), 68.9 (C_5 or C_3), 66.9 (C_5 or C_3), 56.0 ($PhO\underline{C}H_3$), 53.2 ($COO\underline{C}H_3$), 39.9 (C_6 or C_2), 36.8 (C_6 or C_2), 35.1 (C_4), 21.3 and 20.8 ($OCO\underline{C}H_3$).

HRMS (ESI): calcd for $C_{31}H_{32}O_{12}$ [M + Na^+]: 619.1786, found: 619.1777.

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Methyl (3S,5S) 1-hydroxy-3-[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]-5-[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 219



219

To a solution of 5-*p*-coumaroylmonoester **213** (62 mg, 0.164 mmol) in DMF (0.3 mL) and pyridine (0.2 mL) under nitrogen was added the acetylated feruloyl chloride (105 mg, 0.246 mmol). The mixture was stirred at 45 °C for 20h. Methanol (1 mL) was added (stirring 15 min), the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl, saturated $NaHCO_3$ solution then brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/ Pentane = 1/2 to 1/1) providing heterodiester **219** (73 mg, 75%) as a white solid.

Mp: 87 - 89 °C.

$[\alpha]_D^{25}$: - 79.7 (*C* 1.035, CH_2Cl_2).

IR(ATR) 1762, 1736, 1705, 1636, 1601, 1506, 1418, 1369, 1312, 1256, 1198, 1159, 1125, 1086, 1065, 1030, 1009 cm^{-1}.

^1H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.65 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.63 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.55 – 7.47 (m, 2H, H_{Ar}), 7.15 – 7.07 (m, 4H, H_{Ar}), 7.03 (d, 1H, J_{ortho} 8.0 Hz, H_{Ar}), 6.41 (d, 1H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 6.34 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.53 (m, 2H, H_3 and H_5), 3.85 (s, 3H, PhOC<u>H</u>$_3$), 3.76 (s, 3H, COOC<u>H</u>$_3$), 2.30 and 2.29 (2s, 6H, 2xOCOC<u>H</u>$_3$), 2.35 – 2.17 (m, 3H, H_4, H_6 and H_2), 2.14 – 2.02 (m, 2H, H_6 and H_2), 1.88 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.3 Hz, ^3J 3.5 Hz, H_{4a}).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.1 (<u>C</u>OOCH$_3$), 169.3 and 168.9 (O<u>C</u>OCH$_3$), 166.2 and 166.0 (CH=CH<u>C</u>O), 152.3 ($C_{q\ Ar}$), 151.5 ($C_{q\ Ar}$), 144.7 and 144.1 (<u>C</u>H=CHCO), 141.6 ($C_{q\ Ar}$), 133.4 ($C_{q\ Ar}$), 132.1 ($C_{q\ Ar}$), 129.4 (CH_{Ar}), 123.3 (CH_{Ar}), 122.3 (CH_{Ar}), 121.7 (CH_{Ar}), 118.5 and 118.2 (CH=<u>C</u>HCO),

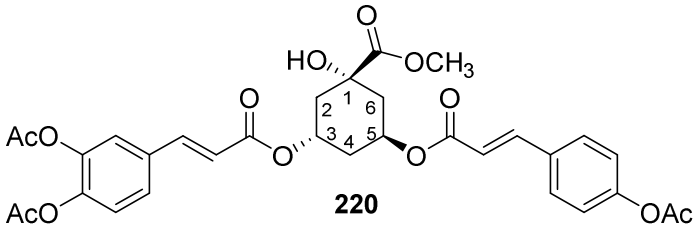
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111.2 (CH_{Ar}), 74.9 (C_1), 69.0 (C_5 or C_3), 66.9 (C_5 or C_3), 56.1 ($PhO\underline{C}H_3$), 53.2 ($COO\underline{C}H_3$), 39.9 (C_6 or C_2), 36.9 (C_6 or C_2), 35.2 (C_4), 21.3 and 20.8 ($OCO\underline{C}H_3$).

HRMS (ESI): calcd for $C_{31}H_{32}O_{12}$ [M + H^+]: 597.1967, found: 597.1944.

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Methyl (3S,5S) 1-hydroxy-3-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]-5-[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 220



220

To a solution of 3-caffeoylmonoester **210** (75 mg, 0.172 mmol) in DCM (1.8 mL) and pyridine (0.36 mL) with DMAP (4 mg, 0.033 mmol) under nitrogen was added the acetylated *p*-coumaroyl chloride (71 mg, 0.316 mmol). The mixture was stirred at 0 °C to room temperature for 5h. Methanol (1 mL) was added (stirring 15 min), the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl, saturated $NaHCO_3$ solution then brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/ Pentane = 1/2 to 1/1) providing heterodiester **220** (74 mg, 69%) as a white solid.

Mp: 87 - 89 °C.

$[\alpha]_D^{25}$: -75.0 (*C* 1.04, CH_2Cl_2).

IR(ATR) 1767, 1738, 1707, 1638, 1504, 1418, 1369, 1317, 1254, 1200, 1165, 1144, 1109, 1065, 1011 cm^{-1}.

^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.58 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.57 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.47 (2s, 2H, H_{Ar}), 7.36 – 7.30 (m, 2H, H_{Ar}), 7.15 (d, 1H, J_{ortho} = 8.4 Hz, H_{Ar}), 7.05 (2s, 2H, H_{Ar}), 6.34 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 6.28 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.52 – 5.39 (m, 2H, H_3 and H_5), 3.71 (s, 3H, COOC<u>H</u>$_3$), 2.24, 2.24, and 2.23 (3s, 9H, 3xOCOC<u>H</u>$_3$), 2.25 – 2.13 (m, 3H, H_4, H_6 and H_2), 2.14 – 2.03 (m, 2H, H_6 and H_2), 1.82 (ddd, 1H, ^2J 13.6 Hz, ^3J 10.3 Hz, ^3J 3.4 Hz, H_{4a}).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.1 (<u>C</u>OOCH$_3$), 169.3, 168.2 and 168.1 (O<u>C</u>OCH$_3$), 165.9 (CH=CH<u>C</u>O), 152.2 ($C_{q\,Ar}$), 144.1 (<u>C</u>H=CHCO), 143.6 ($C_{q\,Ar}$), 143.4 (<u>C</u>H=CHCO), 142.5 ($C_{q\,Ar}$), 133.3

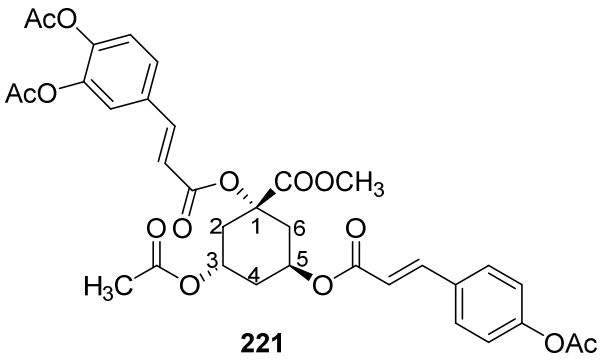
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($C_{q\ Ar}$), 132.1 ($C_{q\ Ar}$), 129.4 (CH_{Ar}), 126.6 (CH_{Ar}), 124.0 (CH_{Ar}), 123.0 (CH_{Ar}), 122.3 (CH_{Ar}), 119.4 and 118.2 (CH=<u>C</u>HCO), 74.8 (C_1), 69.0 (C_5 or C_3), 66.9 (C_5 or C_3), 53.2 (COO<u>C</u>H_3), 39.9 (C_6 or C_2), 36.8 (C_6 or C_2), 35.1 (C_4), 21.3, 20.8 and 20.7 (OCO<u>C</u>H_3).

HRMS (ESI): calcd for $C_{31}H_{32}O_{12}$ [M + Na^+]: 647.1735, found: 647.1704.

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Methyl (3S,5S) 1-hydroxy-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]-3-acetoxy-5-[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylate 221



221

$[\alpha]_D^{25}$: - 19.8 (*C* 0.35, CH_2Cl_2).

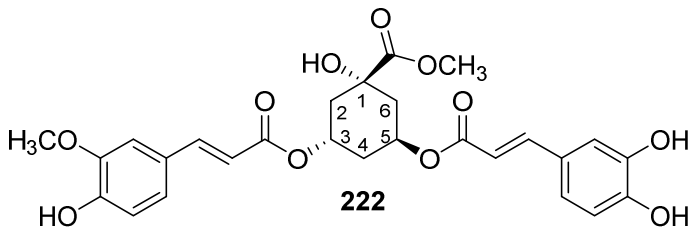
IR(ATR) 2953, 2928, 1765, 1732, 1709, 1634, 1601, 1505, 1431, 1370, 1312, 1246, 1200, 1163, 1111, 1065, 1013 cm^{-1}.

^1H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.69 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCOOC$_1$), 7.63 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCOOC$_5$), 7.53 (d, 2H, J_{ortho} 8.6 Hz, H_{Ar}), 7.42 (dd, 1H, J_{ortho} 8.4 Hz, J_{meta} 2.0 Hz, H_{Ar}), 7.38 (d, 1H, J_{meta} 2.0 Hz, H_{Ar}), 7.23 (d, 1H, J_{ortho} 8.4 Hz, H_{Ar}), 7.15 – 7.07 (m, 2H, H_{Ar}), 6.39 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>COOC$_1$), 6.33 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>COOC$_5$), 5.47 (tt, 1H, ^3J 9.9 Hz, ^3J 4.0 Hz, H_5), 5.36 (p, 1H, ^3J 3.9 Hz, H_3), 3.77 (s, 3H, COOC<u>H</u>$_3$), 2.31, 2.31, and 2.30 (3s, 9H, 3xOCOC<u>H</u>$_3$), 2.34 – 2.10 (m, 3H, H_2, H_4, and H_6), 2.09 (s, 3H, C<u>H</u>$_3$COO), 2.08 – 2.01 (m, 2H, H_2 and H_6), 1.82 (ddd, 1H, ^2J 13.7 Hz, ^3J 10.2 Hz, ^3J 3.5 Hz, H_4).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.1 (<u>C</u>OOCH$_3$), 171.0 (CH=CH<u>C</u>OOC$_1$), 170.7 (CH$_3$<u>C</u>OO), 169.4, 168.3, and 168.2 (O<u>C</u>OCH$_3$), 166.0 (CH=CH<u>C</u>OOC$_5$), 152.4 ($C_{q\ Ar}$), 144.9 (<u>C</u>H=CHCOOC$_1$), 144.2 (<u>C</u>H=CHCOOC$_5$), 144.0 ($C_{q\ Ar}$), 142.7 ($C_{q\ Ar}$), 133.2 ($C_{q\ Ar}$), 132.2 ($C_{q\ Ar}$), 129.5 (CH_{Ar}), 126.9 (CH_{Ar}), 124.2 (CH_{Ar}), 123.2 (CH_{Ar}), 122.4 (CH_{Ar}), 118.8 (CH=<u>C</u>HCOOC$_1$), 118.3 (CH=<u>C</u>HCOOC$_5$), 74.9 (C_1), 69.0 (C_3), 66.9 (C_5), 53.3 (COO<u>C</u>H$_3$), 40.0 (C_6), 36.7 (C_2), 35.1 (C_4), 21.6 (<u>C</u>H$_3$COO), 21.4, 20.9, and 20.85 (OCO<u>C</u>H$_3$).

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Methyl (3S,5S) 1-hydroxy-3-[[(2E)- 3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]-5-[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexanecarboxylate 222



222

To a solution of heterodiester **215** (38 mg, 0.058 mmol) in DMF (0.4 mL) was added hydrazine acetate (27 mg, 0.243 mmol). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc (50 mL), washed with brine (30 mL x 3) then the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (CH_2Cl_2/ CH_3OH = 30/1) to provide **222** as a colorless oil (26 mg, 85%).

$[\alpha]_D^{25}$: - 119.4 (*C* 0.955, CH_3OH).

IR(ATR) 3343, 3312, 2943, 2833, 1690, 1629, 1597, 1514, 1447, 1433, 1381, 1254, 1159, 1128, 1020 cm^{-1}.

^1H NMR (400 MHz, 298K, MeOD) δ = 7.65 (d, 1H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.52 (d, 1H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.20 (d, 1H, J_{meta} 1.9 Hz, H_{Ar}), 7.11 – 7.01 (m, 2H, H_{Ar}), 6.96 (dd, 1H, J_{ortho} 8.3 Hz, J_{meta} 2.0 Hz, H_{Ar}), 6.80 (2s, 2H, H_{Ar}), 6.40 (d, 1H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 6.19 (d, 1H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.50 – 5.35 (m, 2H, H_3 and H_5), 3.89 (s, 3H, PhOC<u>H</u>$_3$), 3.70 (s, 3H, COOC<u>H</u>$_3$), 2.47 (dd, 1H, ^2J 13.5 Hz, ^3J 4.2 Hz, H_2 or H_4 or H_6), 2.40 (dd, 1H, ^2J 13.5 Hz, ^3J 6.8 Hz, H_2 or H_4 or H_6), 2.12 – 2.03 (m, 1H, H_2 or H_4 or H_6), 2.03 – 1.92 (m, 2H, H_2 or H_4 or H_6), 1.86 (dd, 1H, ^2J 13.4 Hz, ^3J 7.6 Hz, H_2 or H_4 or H_6).

^{13}C NMR (100 MHz, 298K, MeOD) δ = 175.7 (<u>C</u>OOCH$_3$), 168.5 and 168.0 (CH=CH<u>C</u>O), 150.6 ($C_{q\,Ar}$), 149.7 ($C_{q\,Ar}$), 149.3 ($C_{q\,Ar}$), 147.2 and 146.9 (<u>C</u>H=CHCO), 146.8 ($C_{q\,Ar}$), 127.7 ($C_{q\,Ar}$), 127.6 ($C_{q\,Ar}$), 124.1 (CH_{Ar}), 123.0 (CH_{Ar}), 116.5 (CH_{Ar}), 116.4 (CH_{Ar}), 115.7 (CH=<u>C</u>HCO), 115.1 (CH_{Ar}), 115.0

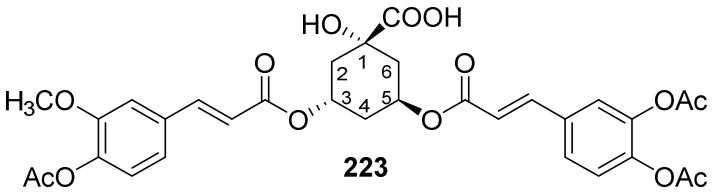
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(CH=CHCO), 111.6 (CH_{Ar}), 75.0 (C_1), 69.5 (C_5 or C_3), 69.0 (C_5 or C_3), 56.4 ($PhOCH_3$), 53.0 ($COOCH_3$), 39.8 (C_2 or C_4 or C_6), 39.3 (C_2 or C_4 or C_6), 35.9 (C_2 or C_4 or C_6).

HRMS (ESI): calcd for $C_{27}H_{28}O_{11}$ [M + Na^+]: 551.1524, found: 551.1503.

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(3S,5S) 1-hydroxy-3-[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]-5-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylic acid 223



223

LiI (652 mg, 4.86 mmol) was added to a solution of **215** (146 mg, 0.214 mmol) in EtOAc (2.5 mL) then the mixture was heated under reflux 2h. After cooling down to room temperature, the mixture was diluted with EtOAc (30 mL), washed with 1M HCl (2x10 mL) and extracted with EtOAc (3x30 mL). The organic layer was dried over $MgSO_4$, concentrated to give the crude **223** (180 mg, 91% yield) pure enough for characterization and used directly in the following step.

$[\alpha]_D^{26}$: - 106.8 (*C* 0.99, CH_3OH).

IR(ATR) 3356, 3337, 2941, 2833, 1765, 1707, 1636, 1601, 1508, 1420, 1371, 1258, 1159, 1177, 1148, 1018 cm^{-1}.

^1H NMR (400 MHz, 298K, MeOD) δ = 7.66 (d, 2H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.59 (d, 2H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.49 – 7.43 (m, 2H, H_{Ar}), 7.29 – 7.12 (m, 3H, H_{Ar}), 7.03 (d, 1H, J_{ortho} 8.1 Hz, H_{Ar}), 6.52 (d, 2H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 6.43 (d, 2H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.53 – 5.40 (m, 2H, H_3 and H_5), 3.80 (s, 3H, PhOC<u>H</u>$_3$), 2.41 (dd, 1H, ^2J 13.7 Hz, ^3J 3.8 Hz, H_2 or H_4 or H_6), 2.36 – 2.20 (m, 1H, H_2 or H_4 or H_6), 2.27, 2.26, and 2.26 (3s, 9H, 3xOCOCH_3), 2.11 – 2.00 (m, 3H, H_2 or H_4 or H_6), 1.94 (dd, 1H, ^2J 13.7 Hz, ^3J 6.4 Hz, H_2 or H_4 or H_6).

^{13}C NMR (100 MHz, 298K, MeOD) δ = 177.3 (<u>C</u>OOCH$_3$), 170.4, 169.8, and 169.7 (O<u>C</u>OCH$_3$), 167.7 (<u>C</u>H=CHCO), 167.2 (<u>C</u>H=CHCO), 152.8 ($C_{q\,Ar}$), 145.6 (<u>C</u>H=CHCO), 145.1 ($C_{q\,Ar}$), 144.4 (<u>C</u>H=CHCO), 143.9 ($C_{q\,Ar}$), 142.8 ($C_{q\,Ar}$), 134.7 ($C_{q\,Ar}$), 134.5($C_{q\,Ar}$), 127.7 (CH_{Ar}), 125.1 (CH_{Ar}), 124.2 (CH_{Ar}), 124.1 (CH_{Ar}), 122.4 (CH_{Ar}), 120.1 (CH=<u>C</u>HCO), 119.5 (CH=<u>C</u>HCO), 112.6 (CH_{Ar}), 75.0 (C_1), 70.1 (C_3 or C_5),

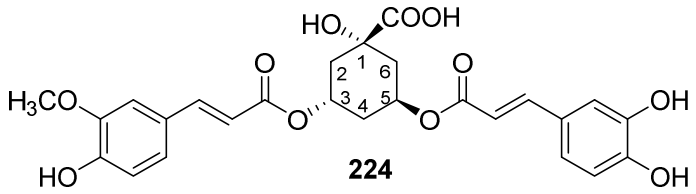
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69.1 (C_3 or C_5), 56.5 ($PhO\underline{C}H_3$), 39.9 (C_2 or C_4 or C_6), 38.7 (C_2 or C_4 or C_6), 35.89 (C_2 or C_4 or C_6), 20.8, 20.7, and 20.50 ($OCO\underline{C}H_3$).

HRMS (ESI): calcd for $C_{32}H_{32}O_{14}$ [M + Na^+]: 663.1684, found: 663.1678.

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(3S,5S) 1-hydroxy-3-[[(2E)-3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]-5-[[(2E)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexanecarboxylic acid 224



224

To a solution of **223** (80 mg) in acetone (1.2 mL) was added 3M HCl aqueous solution (0.5 mL) and the mixture was refluxed for 4h. After completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc (30 mL) and washed with brine (20 mL). The organic layer was concentrated to give the crude quantitatively as a pale solid **224** (64 mg).

$[\alpha]_D^{25}$: - 77.6 (*C* 0.975, CH_3OH).

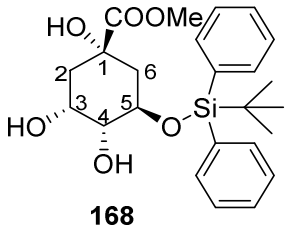
^{1}H NMR (400 MHz, 298K, MeOD) δ = 7.65 (d, 1H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.54 (d, 1H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.18 (d, 1H, J_{ortho} 8.2 Hz, H_{Ar}), 7.09 – 7.04 (m, 2H, H_{Ar}), 6.96 (d, 1H, J_{ortho} 8.2 Hz, H_{Ar}), 6.84 – 6.78 (m, 2H, H_{Ar}), 6.39 (d, 1H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 6.23 (d, 1H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.52 – 5.39 (m, 2H, H_3 and H_5), 3.89 (s, 3H, COOC<u>H</u>$_3$), 2.40 (dd, 1H, ^2J 13.9 Hz, ^3J 3.8 Hz, H_2 or H_4 or H_6), 2.35 – 2.26 (m, 1H, H_2 or H_4 or H_6), 2.11 – 1.89 (m, 4H, H_2 or H_4 or H_6).

^{13}C NMR (100 MHz, 298K, MeOD) δ = 177.4 (<u>C</u>OOH), 168.5 (CH=CH<u>C</u>O), 168.3 (CH=CH<u>C</u>O), 150.4 ($C_{q\ Ar}$), 149.5 ($C_{q\ Ar}$), 149.3 ($C_{q\ Ar}$), 147.1 (<u>C</u>H=CHCO), 146.9 (<u>C</u>H=CHCO), 146.7 ($C_{q\ Ar}$), 127.8 ($C_{q\ Ar}$), 127.7 ($C_{q\ Ar}$), 124.1 (CH_{Ar}), 123.1 (CH_{Ar}), 116.5 (CH_{Ar}), 116.4 (CH_{Ar}), 115.9 (CH=<u>C</u>HCO), 115.20 (CH=<u>C</u>HCO), 115.2 (CH_{Ar}), 111.6 (CH_{Ar}), 75.1 (C_1), 70.0 (C_3 or C_5), 68.7 (C_3 or C_5), 56.4 (PhO<u>C</u>H$_3$), 40.0, 38.7 and 36.0 (C_2 or C_4 or C_6).

HRMS (ESI): calcd for $C_{26}H_{26}O_{11}$ [M + Na^+]: 537.1367, found: 537.1366.

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Methyl (1S,3R,4R,5R)-5-[(tert-butyldiphenylsilyl)oxy]-1,3,4-trihydroxy cyclohexane-1-carboxylate 168



168

To a solution of acetonide **225** (3.705 g, 7.655 mmol) in DCM (80 mL) was added 3 mL of a mixed solution of trifluoroacetic acid / H_2O (1:1, v:v). The mixture was stirred at room temperature for 5h. The resulting mixture was washed with saturated $NaHCO_3$ solution then brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc/ Pentane = 1/2 to 1/1) providing triol **168** (3.122 g, 92%) as a white sticky solid.

$[\alpha]_D^{22}$: - 39.6 (*C* 1.15, CH_2Cl_2).

^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.78 – 7.63 (m, 4H, H_{Ar}), 7.47 – 7.33 (m, 6H, H_{Ar}), 4.17 (ddd, 1H, ^3J 10.6 Hz, ^3J 10.0 Hz, ^3J 4.7 Hz, H_5), 4.13 – 4.07 (m, 1H, H_3), 3.93 (s, 1H, OH), 3.72 (s, 3H, $COOCH_3$), 3.54 (dd, 1H, ^3J 9.0 Hz, ^3J 3.2 Hz, H_4), 3.41 (s, 1H, OH), 2.49 (s, 1H, OH), 2.08 – 1.93 (m, 3H, 2xH_2 and H_6), 1.88 (dd, 1H, ^2J 13.2 Hz, ^3J 10.9 Hz, H_{6a}), 1.09 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 174.7 ($\underline{C}OOCH_3$), 135.9 (CH_{Ar}), 133.8 ($C_{q\ Ar}$), 133.7 ($C_{q\ Ar}$), 129.88 (CH_{Ar}), 129.86 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 76.37 (C_4), 75.9 (C_1), 70.4 (C_3), 69.7 (C_5), 53.0 ($COO\underline{C}H_3$), 42.0 (C_6), 37.0 (C_2), 27.0 ($C(\underline{C}H_3)_3$), 19.4 ($\underline{C}(CH_3)_3$).

HRMS (ESI): calcd for $C_{24}H_{32}O_6Si$ [M + Na^+]: 467.1860, found: 467.1869.

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General procedures for bis- or mono-coupling from triol 168, quinide 51 or triol 169

Procedure D: (taking triol 168 as an example)

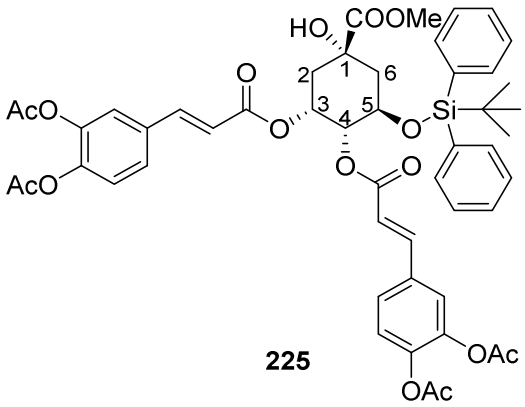
To a solution of triol **168** in DMF / pyridine (v/v 3/2, c = 0.4M) under nitrogen was added the acetylated cinnamoyl chloride (3 equiv. for di-coupling; 1.5 equiv. for mono-coupling) The mixture was stirred at 0 °C or -18 °C to room temperature until completion. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography on silica using the appropriate eluent.

Procedure E:

To a solution of triol **168** in dichloromethane / pyridine (v/v 5/1, c = 0.1M) under nitrogen was added the acetylated cinnamoyl chloride (3 equiv. for di-coupling; 1.5 equiv. for mono-coupling) and DMAP (20%).The mixture was stirred at 0 °C or -18 °C to room temperature until completion. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography on silica using the appropriate eluent.

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Methyl (1S,3R,4R,5R)-5-[(tert-butyldiphenylsilyl)oxy]-1-hydroxy-3,4-bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexane-1-carboxylate 225



225

Synthesized according to the general procedure E (-18 °C to rt, 4h) using acetylated caffeoyl chloride (424 mg, 1.5 mmol) and triol **168** (222 mg, 0.5 mmol). Diester **225** was obtained as a white solid (242 mg, yield: 52%) after purification by flash chromatography on silica using EtOAc/ Pentane = 1/3 to 1/1.

$[\alpha]_D^{25}$: - 57.1 (*C* 1.27, CH_2Cl_2).

^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.72 – 7.61 (m, 4H, H_{Ar}), 7.44 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.39 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.36 – 7.27 (m, 9H, H_{Ar}), 7.23 (d, 2H, J_{ortho} = 8.4 Hz, H_{Ar}), 7.20 – 7.16 (m, 2H, H_{Ar}), 6.23 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.93 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=C<u>H</u>CO), 5.65 (q, 1H, ^3J 3.7 Hz, H_3), 5.13 (dd, 1H, ^3J 8.9 Hz, ^3J 3.2 Hz, H_4), 4.57 (td, 1H, ^3J 9.1 Hz, ^3J 4.4 Hz, H_5), 3.75 (s, 3H, COOC<u>H</u>$_3$), 2.35 – 2.32 (m, 1H, H_2), 2.32, 2.30, 2.30 and 2.29 (4s, 12H, 4xOCOC<u>H</u>$_3$), 2.17 – 2.04 (m, 3H, 2xH_6 and H_2), 1.04 (s, 9H, C(C<u>H</u>$_3$)$_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.0 (<u>C</u>OOCH$_3$), 168.11 168.10, and 168.02 (O<u>C</u>OCH$_3$), 165.7 (CH=CH<u>C</u>O), 165.3 (CH=CH<u>C</u>O), 143.6 ($C_{q\,Ar}$), 143.5 ($C_{q\,Ar}$), 143.4 (<u>C</u>H=CHCO), 143.0 (<u>C</u>H=CHCO), 142.4 ($C_{q\,Ar}$), 142.4 ($C_{q\,Ar}$), 136.0 (CH_{Ar}), 135.9 (CH_{Ar}), 133.6 ($C_{q\,Ar}$), 133.5 ($C_{q\,Ar}$), 133.20 ($C_{q\,Ar}$), 133.15 ($C_{q\,Ar}$), 129.8 (CH_{Ar}), 129.7 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 126.63 (CH_{Ar}), 126.58 (CH_{Ar}), 123.92 (CH_{Ar}), 123.85 (CH_{Ar}), 122.9 (CH_{Ar}), 122.7 (CH_{Ar}), 119.0 (CH=<u>C</u>HCO), 118.7 (CH=<u>C</u>HCO), 75.0 (C_1),

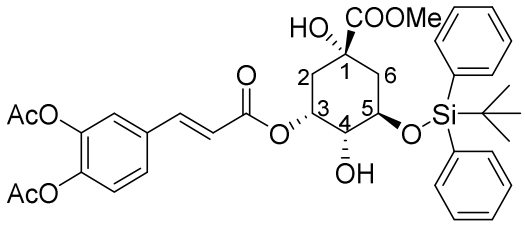
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74.3 (C_4), 69.1 (C_3), 66.7 (C_5), 53.2 ($COO\underline{C}H_3$), 42.2 (C_6), 35.7 (C_2), 26.9 ($C(\underline{C}H_3)_3$), 20.7 and 20.6 ($OCO\underline{C}H_3$), 19.2 ($\underline{C}(CH_3)_3$).

HRMS (ESI): calcd for $C_{50}H_{52}O_{16}Si$ [M + H^+]: 937.3097, found: 937.3091.

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Methyl (1S,3R,4R,5R)-5-[(tert-butyldiphenylsilyl)oxy]-1,4-dihydroxy-3-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexane-1-carboxylate 226



226

Synthesized according to the general procedure E (-18 °C to rt, 4h) using acetylated caffeoyl chloride (212 mg, 0.75 mmol) and triol **168** (222 mg, 0.5 mmol). Monoester **226** was obtained as a white solid (297 mg, yield: 86%) after purification by flash chromatography on silica using EtOAc/ Pentane = 1/3 to 1/1.

$[\alpha]_D^{25}$: + 8.7 (*C* 1.15, CH_2Cl_2).

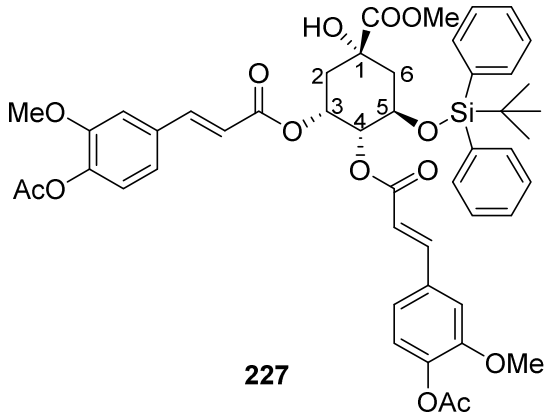
^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.73 – 7.66 (m, 4H, H_{Ar}), 7.48 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.42 – 7.32 (m, 7H, H_{Ar}), 7.30 (d, 1H, J_{meta} 2.0 Hz, H_{Ar}), 7.23 (d, 1H, J_{ortho} 8.3 Hz, H_{Ar}), 6.25 (d, 1H, ^3J 16.0 Hz, CH=CHCO), 5.50 (dt, 1H, ^3J 5.1 Hz, ^3J 3.4 Hz, H_3), 4.30 (td, 1H, ^3J 8.6 Hz, ^3J 4.4 Hz, H_5), 3.76 – 3.74 (m, 1H, H_4), 3.73 (s, 3H, COOC<u>H</u>$_3$), 2.82 (s, 1H, OH), 2.32 and 2.31 (2s, 6H, 2xOCOCH_3) 2.21 – 2.08 (m, 2H, H_2), 2.04 – 1.94 (m, 2H, H_6), 1.09 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.1 (<u>C</u>OOCH_3), 168.2 and 168.1 (O<u>C</u>OCH_3), 165.8 (CH=CH<u>C</u>O), 143.6 (Cq Ar), 143.3 (<u>C</u>H=CHCO), 142.5 (Cq Ar), 136.00 (CH_{Ar}), 135.94 (CH_{Ar}), 133.6 (Cq Ar), 133.5 (Cq Ar), 133.3 (Cq Ar), 130.03 (CH_{Ar}), 129.97 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 126.5 (CH_{Ar}), 124.0 (CH_{Ar}), 122.9 (CH_{Ar}), 119.3 (CH=<u>C</u>HCO), 74.5 (C_1), 73.9 (C_4), 71.2 (C_3), 69.8 (C_5), 53.1 (COOCH_3), 41.2 (C_6), 35.3(C_2), 27.1 (C(<u>C</u>H_3)$_3$), 20.8 and 20.7 (OCO<u>C</u>H_3), 19.4 (<u>C</u>(CH_3)$_3$).

HRMS (ESI): calcd for $C_{37}H_{42}O_{11}Si$ [M + Na^+]: 713.2389, found: 713.2411.

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Methyl (1S,3R,4R,5R)-5-[(tert-butyldiphenylsilyl)oxy]-1-hydroxy-3,4-bis[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexane-1-carboxylate 227



227

Synthesized according to the general procedure D (0 °C to rt, 4h) or E (0 °C to rt, 4h) using acetylated feruloyl chloride and triol **168**. Diester **227** was obtained as a white solid (no exact yield can be given) after purification by three times flash chromatography on silica using EtOAc/ Pentane = 1/4 to 1/1 then Et_2O/DCM = 1/30 to 1/10 then Et_2O/Pentane = 3/1 to 5/1.

$[\alpha]_D^{25}$: - 74.1 (*C* 1.06, CH_2Cl_2).

^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.73 – 7.63 (m, 4H, H_{Ar}), 7.49 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.42 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.38 – 7.27 (m, 6H, H_{Ar}), 7.08 – 6.92 (m, 6H, H_{Ar}), 6.25 (d, 1H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 6.00 (d, 1H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.69 (q, 1H, ^3J 3.7 Hz, H_3), 5.16 (dd, 1H, ^3J 8.8 Hz, ^3J 3.2 Hz, H_4), 4.59 (td, 1H, ^3J 9.1 Hz, ^3J 4.3 Hz, H_5), 3.85 (s, 3H, $OCOCH_3$), 3.79 (s, 3H, $OCOCH_3$), 3.76 (s, 3H, $COOC\underline{H}_3$), 2.96 (s, 1H, OH), 2.38 – 2.34 (m, 1H, H_2), 2.33 and 2.32 (2s, 6H, 2x$OCOCH_3$), 2.17 – 2.04 (m, 3H, H_2 and 2xH_6), 1.04 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.0 (<u>C</u>$OOCH_3$), 168.9 (O<u>C</u>OCH_3), 165.9 (CH=CH<u>C</u>OOC_4), 165.7 (CH=CH<u>C</u>OOC_3), 151.5 ($C_{q\,Ar}$), 151.4 ($C_{q\,Ar}$), 144.7 (<u>C</u>H=CHCOOC_3), 144.3 (<u>C</u>H=CHCOOC_4), 141.6 and 141.5 ($C_{q\,Ar}$), 136.1 and 136.0 (CH_{Ar}), 133.7 and 133.3 ($C_{q\,Ar}$), 129.9, 129.7, 127.7, 127.6, 123.3, 123.25, 121.5 and 121.3 (CH_{Ar}), 118.1 (CH=<u>C</u>HCOOC_3), 117.9 (CH=<u>C</u>HCOOC_4), 111.5 (CH_{Ar}),

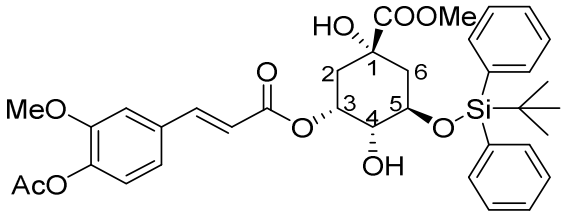
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111.4 (CH_{Ar}), 74.9 (C_1), 74.4 (C_4), 69.2 (C_3), 66.8 (C_5), 56.1 ($PhOCH_3$), 56.0 ($PhOCH_3$), 53.3 (C_8), 42.2 (C_6), 35.8 (C_2), 26.9 ($C(CH_3)_3$), 20.8 ($OCOCH_3$), 19.3 ($C(CH_3)_3$).

HRMS (ESI): calcd for $C_{48}H_{52}O_{14}Si$ [M + Na^+]: 903.3019, found: 903.3007.

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Methyl (1S,3R,4R,5R)-5-[(tert-butyldiphenylsilyl)oxy]-1,4-dihydroxy-3-[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexane-1-carboxylate 228



228

Synthesized according to the general procedure E (-18 °C to rt, 5h) using acetylated feruloyl chloride (191 mg, 0.75 mmol) and triol **168** (222 mg, 0.5 mmol). Monoester **228** was obtained as a white solid (204 mg, yield: 61%) after purification by twice flash chromatography on silica using EtOAc/ Pentane = 1/3 to 1/1 then Et_2O/Pentane = 2/1 to 5/1.

$[\alpha]_D^{25}$: + 15.2 (*C* 0.94, CH_2Cl_2).

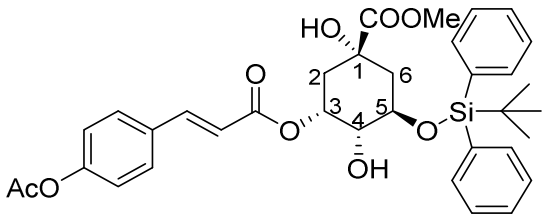
^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.74 – 7.67 (m, 4H, H_{Ar}), 7.52 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.41 – 7.33 (m, 6H, H_{Ar}), 7.06 (s, 3H, H_{Ar}), 6.27 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.53 (dt, 1H, ^3J 5.0 Hz, ^3J 3.6 Hz, H_3), 4.32 (td, 1H, ^3J 8.5, ^3J 4.3 Hz, H_5), 3.86 (s, 3H, PhOC<u>H</u>$_3$), 3.79 – 3.71 (m, 1H, H_4), 3.73 (s, 3H, COOC<u>H</u>$_3$) 2.87 (s, 1H, OH), 2.33 (s, 3H, OCOC<u>H</u>$_3$), 2.20 (dd, 1H, ^2J 14.5 Hz, ^3J 3.8 Hz, H_2), 2.13 – 1.96 (m, 3H, H_2 and 2xH_6), 1.09 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.1 (<u>C</u>OOCH$_3$), 168.9 (O<u>C</u>OCH$_3$), 166.0 (CH=CH<u>C</u>O), 151.4 ($C_{q\,Ar}$), 144.6 (<u>C</u>H=CHCO), 141.5 ($C_{q\,Ar}$), 136.0 (CH_{Ar}), 135.9 (CH_{Ar}), 133.6 ($C_{q\,Ar}$), 133.55 ($C_{q\,Ar}$), 133.4 ($C_{q\,Ar}$), 130.0 (CH_{Ar}), 129.9 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 123.3 (CH_{Ar}), 121.5 (CH_{Ar}), 118.3 (CH=<u>C</u>HCO), 111.3 (CH_{Ar}), 74.5 (C_1), 73.8 (C_4), 71.1 (C_3), 69.9 (C_5), 56.0 (PhO<u>C</u>H$_3$), 53.1 (COO<u>C</u>H$_3$), 41.1 (C_6), 35.3 (C_2), 27.1 (C(<u>C</u>H$_3$)$_3$), 20.8 (OCO<u>C</u>H$_3$), 19.4 ((<u>C</u>(CH_3)$_3$).

HRMS (ESI): calcd for $C_{36}H_{42}O_{10}Si$ [M + Na^+]: 685.2439, found: 685.2447.

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Methyl (1S,3R,4R,5R)-5-[(tert-butyldiphenylsilyl)oxy]-1,4-dihydroxy-3-[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]cyclohexane-1-carboxylate 229



229

Synthesized according to the general procedure D (-18 °C to 0 °C, 4h) using acetylated *p*-coumaroyl chloride (91 mg, 0.405 mmol) and triol **168** (120 mg, 0.27 mmol). Monoester **229** was obtained as a white solid (131 mg, yield: 77%) after purification by flash chromatography on silica using Et_2O/Pentane = 1/1 to 2/1.

$[\alpha]_D^{25}$: + 10.5 (*C* 1.05, CH_2Cl_2).

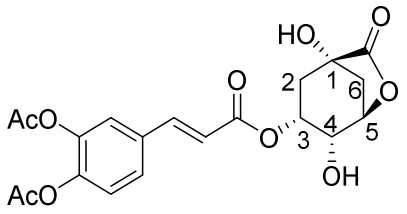
^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.74 – 7.67 (m, 4H, H_{Ar}), 7.54 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.48 (d, 2H, J_{ortho} 8.4 Hz, H_{Ar}), 7.41 – 7.34 (m, 6H, H_{Ar}), 7.13 (d, 2H, J_{ortho} 8.5 Hz, H_{Ar}), 6.27 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.52 (dt, 1H, ^3J 5.3 Hz, ^3J 2.6 Hz, H_3), 4.31 (td, 1H, ^3J 8.4 Hz, ^3J 4.3 Hz, H_5), 3.75 (dd, 1H, ^3J 7.9 Hz, ^3J 3.2 Hz, H_4), 3.72 (s, 3H, COOC<u>H</u>$_3$), 2.31 (s, 3H, OCOC<u>H</u>$_3$), 2.23 – 2.17 (m, 1H, H_2), 2.13 – 1.97 (m, 3H, H_2 and 2xH_6), 1.10 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 175.0 (<u>C</u>OOCH$_3$), 169.2 (O<u>C</u>OCH$_3$), 166.0 (CH=CH<u>C</u>O), 152.1 ($C_{q\ Ar}$), 144.1 (<u>C</u>H=CHCO), 136.0 (CH_{Ar}), 135.9 (CH_{Ar}), 133.6 ($C_{q\ Ar}$), 133.5 ($C_{q\ Ar}$), 132.1 ($C_{q\ Ar}$), 130.0 (CH_{Ar}), 129.9 (CH_{Ar}), 129.3 (CH_{Ar}), 127.84 (CH_{Ar}), 127.82 (CH_{Ar}), 127.7 (CH_{Ar}), 122.1 (CH_{Ar}), 118.2 (CH=<u>C</u>HCO), 74.4 (C_1), 73.7 (C_4), 71.1 (C_3), 69.8 (C_5), 53.0 (COO<u>C</u>H$_3$), 41.0 (C_6), 35.2 (C_2), 27.1 (C(<u>C</u>H$_3$)$_3$), 21.2 (OCO<u>C</u>H$_3$), 19.3 (<u>C</u>(CH_3)$_3$).

HRMS (ESI): calcd for $C_{35}H_{40}O_9Si$ [M + Na^+]: 655.2334, found: 655.2315.

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(1S,3R,4R,5R)-1,4-dihydroxy-3-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexane-1,5-γ-lactone 230



230

Synthesized according to the general procedure D (0 °C to rt, 4h) using acetylated caffeoyl chloride (107 mg, 0.38 mmol) and quinide **51** (44 mg, 0.25 mmol). Diester **230** was obtained as a white solid (65 mg, yield: 62%) after purification by flash chromatography on silica using DCM/CH_3OH = 100/1 to 10/1.

$[\alpha]_D^{25}$: + 5.3 (*C* 1.02, CH_3OH).

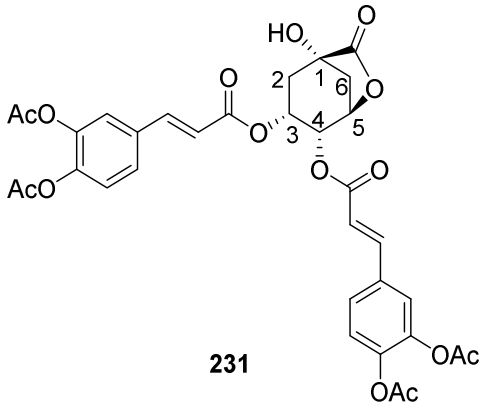
^1H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.60 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.38 – 7.32 (m, 2H, H_{Ar}), 7.18 (d, 1H, J_{ortho} 8.9 Hz, H_{Ar}), 6.35 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 4.97 (ddd, 1H, ^3J 11.3 Hz, ^3J 7.0 Hz, ^3J 4.3 Hz, H_3), 4.77 (t, 1H, ^3J 5.4 Hz, H_5), 4.32 (t, 1H, ^3J 4.6 Hz, H_4), 2.63 (d, 1H, ^2J 11.7 Hz, H_6), 2.36 – 2.26 (m, 1H, H_6), 2.28 (2s, 6H, 2xOCOC<u>H</u>$_3$) 2.23 – 2.12 (m, 2H, H_2).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 177.6 (<u>C</u>OO), 168.5 and 168.3 (O<u>C</u>OCH$_3$), 165.3 (CH=CH<u>C</u>O), 144.3 (<u>C</u>H=CHCO), 143.8 ($C_{q\,Ar}$), 142.5 ($C_{q\,Ar}$), 132.9 ($C_{q\,Ar}$), 126.7 (CH_{Ar}), 124.1 (CH_{Ar}), 123.0 (CH_{Ar}), 118.2 (CH=<u>C</u>HCO), 76.2 (C_5), 72.2 (C_1), 69.1 (C_3), 63.9 (C_4), 36.4 (C_2 or C_6), 36.2 (C_2 or C_6), 20.75 and 20.74 (OCO<u>C</u>H$_3$).

HRMS (ESI): calcd for $C_{20}H_{20}O_{10}$ [M + Na^+]: 443.0949, found: 443.01512.

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(1S,3R,4R,5R)-1-hydroxy-3,4-bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexane-1,5-γ-lactone 231



231

Synthesized according to the general procedure D (-18 °C to rt, 4h) using acetylated caffeoyl chloride (214 mg, 0.75 mmol) and quinide **51** (44 mg, 0.25 mmol). Diester **231** was obtained as a white solid (52 mg, yield: 31%) after purification by flash chromatography on silica using DCM/CH_3OH = 100/1 to 20/1.

$[\alpha]_D^{25}$: + 250.7 (*C* 1.15, CH_2Cl_2).

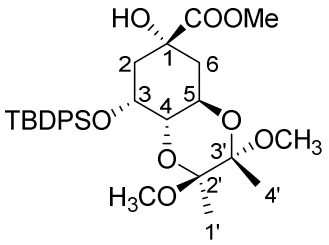
^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.66 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.57 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.43 – 7.38 (m, 2H, H_{Ar}), 7.33 – 7.28 (m, 2H, H_{Ar}), 7.25 – 7.22 (m, 1H, H_{Ar}), 7.16 (d, 1H, J_{ortho} 8.5 Hz, H_{Ar}), 6.45 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 6.27 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.66 (t, 1H, ^3J 4.8 Hz, H_4), 5.32 – 5.22 (m, 1H, H_3), 4.91 (t, 1H, ^3J 5.3 Hz, H_5), 2.59 (d, ^2J 12.0 Hz, 1H, H_6), 2.49 (ddd, 1H, ^2J 11.4 Hz, ^3J 5.4 Hz, ^3J 2.1 Hz, H_6), 2.34 – 2.23 (m, 2H, H_2), 2.30, 2.30, 2.27, and 2.26 (4s, 12H, 4xOCOCH_3).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 176.8 (<u>C</u>OO), 168.24, 168.21, 168.08 and 168.07 (O<u>C</u>OCH$_3$), 165.01 and 164.151 (CH=CH<u>C</u>O), 144.9 and 144.3 (<u>C</u>H=CHCO), 144.1 ($C_{q\ Ar}$), 143.8 ($C_{q\ Ar}$), 142.6 ($C_{q\ Ar}$), 142.5 ($C_{q\ Ar}$), 132.9 ($C_{q\ Ar}$), 132.7 ($C_{q\ Ar}$), 127.0 (CH_{Ar}), 126.8 (CH_{Ar}), 124.2 (CH_{Ar}), 124.1 (CH_{Ar}), 123.0 (CH_{Ar}), 122.9 (CH_{Ar}), 118.0 (CH=<u>C</u>HCO), 117.7 (CH=<u>C</u>HCO), 73.9 (C_5), 72.1 (C_1), 66.5 (C_3), 64.8 (C_4), 37.5 (C_2 or C_6), 36.85 (C_2 or C_6), 20.76, 20.75, 20.73 and 20.68 (OCO<u>C</u>H$_3$).

HRMS (ESI): calcd for $C_{33}H_{30}O_{15}$ [M + Na^+]: 689.1477, found: 689.1453.

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Methyl (2'S,3'S)-3-*O*-(tert-butyldiphenylsilyl)-4-*O*,5-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-quinate 232



232

To a mixture of *tans*-ketal **77** (1.10 g, 3.44 mmol) and imidazole (702 mg, 10.32 mmol) in DCM (9 mL) under nitrogen was added dropwise *tert*-butyl(chloro)diphenylsilane (TBDPSCl, 1.135g, 4.13 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. Then the reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and diluted with DCM (20 mL), the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (EtOAc/Pentane = 1/15 to 1/6) to provide **232** as a white solid (1.562 g, 81%).

$[\alpha]_D^{25}$: + 50.7 (*C* 1.08, CH_2Cl_2).

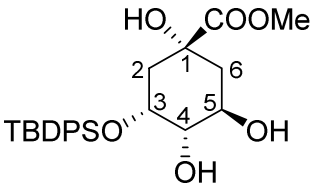
^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.79 (d, 2H, J_{ortho} 6.9 Hz, H_{Ar}), 7.71 – 7.65 (m, 2H, H_{Ar}), 7.45 – 7.31 (m, 6H, H_{Ar}), 4.78 (s, 1H, OH), 4.49 (ddd, 1H, ^3J 12.0 Hz, ^3J 10.0 Hz, ^3J 4.7 Hz, H_5), 4.23 (q, 1H, ^3J 2.9 Hz, H_3), 3.74 (s, 3H, $COOCH_3$), 3.39 (dd, 1H, ^3J 10.1 Hz, ^3J 2.7 Hz, H_4), 3.32 (s, 3H, $C_{3'}OCH_3$), 3.01 (s, 3H, $C_{2'}OCH_3$), 2.24 (ddd, 1H, ^2J 12.8 Hz, ^3J 4.5 Hz, ^3J 2.8 Hz, H_{6e}), 2.07 (dt, 1H, ^2J 14.9 Hz, ^3J 3 .1 Hz, H_2), 1.91 (dd, 1H, ^2J 14.8 Hz, ^3J 2.5 Hz, H_2), 1.84 (dd, 1H, $^2J = {}^3J$ 12.5 Hz, H_{6a}), 1.26 (s, 3H, $H_{4'}$), 1.12 (s, 12H, $H_{1'}$ and $C(CH_3)_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 173.7 ($\underline{C}OOCH_3$), 136.8 (CH_{Ar}), 136.3 (CH_{Ar}), 133.1 ($C_{q\ Ar}$), 132.5 (CH_{Ar}), 130.0 ($C_{q\ Ar}$), 129.7 ($C_{q\ Ar}$), 127.7 ($C_{q\ Ar}$), 127.2 ($C_{q\ Ar}$), 100.0 ($C_{2'}$), 99.5 ($C_{3'}$), 76.2 (C_1), 72.7 (C_4), 71.4 (C_3), 62.7 (C_5), 52.7 (C_8), 47.8 ($C_{3'}O\underline{C}H_3$), 47.6 ($C_{2'}O\underline{C}H_3$), 39.4 (C_6), 38.0 (C_2), 27.1 ($C(\underline{C}H_3)_3$), 19.4 ($\underline{C}(CH_3)_3$), 17.9 ($C_{3'}\underline{C}H_3$), 17.5 ($C_{2'}\underline{C}H_3$).

HRMS (ESI): calcd for $C_{30}H_{42}O_8Si$ [M + Na^+]: 581.2541, found: 581.2540.

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Methyl (1R,3R,4S,5R)-3-((tert-butyldiphenylsilyl)oxy)-1,4,5-trihydroxy cyclohexane-1-carboxylate 169



169

To a solution of **232** (200 mg, 0.367 mmol) in DCM (10 mL) was added 50% aqueous TFA (v:v 1:1, 1 mL). The mixture was stirred at room temperature for 16 hours, then was treated with saturated aqueous $NaHCO_3$ solution (10 mL) and diluted with DCM (20 mL), the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (EtOAc/Pentane = 1/3 to 1/1) to provide **169** as a sticky white solid (123 mg, 75%).

$[\alpha]_D^{25}$: - 14.1 (*C* 1.165, CH_2Cl_2).

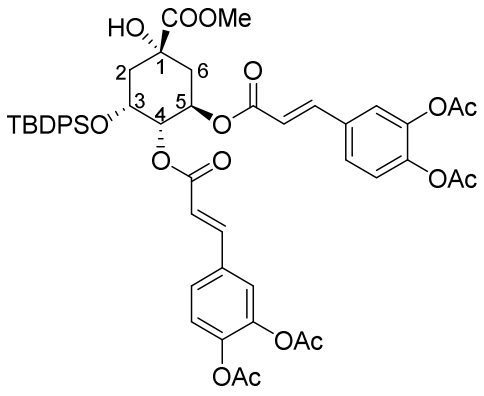
^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.73 – 7.66 (m, 4H, H_{Ar}), 7.49 – 7.35 (m, 6H, H_{Ar}), 4.32 (dt, 1H, ^3J 4.5 Hz, ^3J 3.0 Hz, H_3), 4.22 (ddd, 1H, ^3J 9.8 Hz, ^3J 8.8 Hz, ^3J 4.5 Hz, H_5), 3.69 (s, 3H, COOC$\underline{H}_3$), 3.35 (dd, 1H, ^3J 8.6 Hz, ^3J 2.9 Hz, H_4), 2.28 (ddd, 1H, ^2J 13.2 Hz, ^3J 4.4 Hz, ^3J 2.4 Hz, H_{6e}), 2.08 – 2.00 (m, 1H, H_2), 1.89 (dd, 1H, ^2J 14.5 Hz, ^3J 3.0 Hz, H_2), 1.80 (dd, 1H, ^2J 13.3 Hz, ^3J 10.1 Hz, H_{6a}), 1.11 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 174.5 ($\underline{C}OOCH_3$), 136.1 (CH_{Ar}), 132.6 ($C_{q\ Ar}$), 132.5($C_{q\ Ar}$), 130.3 (CH_{Ar}), 128.0 (CH_{Ar}), 75.9 (C_4), 75.6 (C_1), 72.2 (C_3), 67.5 (C_5), 52.8 (COO$\underline{C}H_3$), 41.0 (C_6), 37.7 (C_2), 27.1 ($C(\underline{C}H_3)_3$), 19.4 ($\underline{C}(CH_3)_3$).

HRMS (ESI): calcd for $C_{24}H_{32}O_6Si$ [M + Na^+]: 467.1860, found: 467.1843.

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Methyl (1S,3R,4R,5R)-3-[(tert-butyldiphenylsilyl)oxy]-1-hydroxy-4,5-bis[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexane-1-carboxylate 234



234

Synthesized according to the general procedure D (0 °C to rt, 4h) using acetylated caffeoyl chloride (424 mg, 1.5 mmol) and triol **169** (222 mg, 0.5 mmol). Diester **234** was obtained as a white solid (301 mg, yield: 64%) after purification by flash chromatography on silica using Acetone/ Pentane = 1/4 to 1/2.

$[\alpha]_D^{25}$: - 5.0 (*C* 1.18, CH_2Cl_2).

^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.76 – 7.72 (m, 2H, H_{Ar}), 7.63 – 7.58 (m, 2H, H_{Ar}), 7.53 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.44 – 7.27 (m, 9H, H_{Ar} and C<u>H</u>=CHCO), 7.20 – 7.09 (m, 4H, H_{Ar}), 6.25 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 6.02 (dt, 1H, ^3J 10.8 Hz, ^3J 5.4 Hz, H_5), 5.62 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 4.96 (dd, 1H, ^3J 10.1 Hz, ^3J 2.8 Hz, H_4), 4.69 (s, 1H, O<u>H</u>), 4.41 (q, 1H, ^3J 2.8 Hz, H_3), 3.78 (s, 3H, $COOCH_3$), 2.56 (ddd, 1H, ^2J 12.9 Hz, ^3J 4.5 Hz, ^3J 2.5 Hz, H_{6e}), 2.34, 2.30, 2.28 and 2.27 (4s, 12H, 4xOCO<u>C</u>H_3), 2.36 – 2.21 (m, 1H, H_2), 2.18 – 2.04 (m, 2H, H_2 and H_{6a}), 1.12 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 173.5 (<u>C</u>$OOCH_3$), 168.14, 168.12, 168.08 and 168.02 (O<u>C</u>OCH_3), 165.5 and 165.4 (CH=CH<u>C</u>O), 143.72, 143.66, 143.61 and 143.56 (<u>C</u>H=CHCO and CH_{Ar}), 142.47 and 142.44 ($C_{q\ Ar}$), 136.6 and 136.2 (CH_{Ar}), 133.2 and 133.1 ($C_{q\ Ar}$), 132.4 ($C_{q\ Ar}$), 131.6 ($C_{q\ Ar}$), 130.5 and 130.0 (CH_{Ar}), 128.1 (CH_{Ar}), 127.8 (CH_{Ar}), 126.8 (CH_{Ar}), 126.7 (CH_{Ar}), 124.0 (CH_{Ar}), 123.9 (CH_{Ar}), 123.0 (CH_{Ar}), 122.9 (CH_{Ar}), 118.8 and 118.3 (CH=<u>C</u>HCO), 75.7 (C_1), 74.8 (C_4), 71.5 (C_3), 67.2

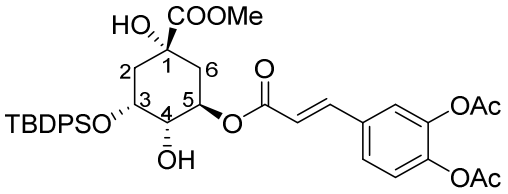
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(C_5), 53.0 (COO<u>C</u>H_3), 40.1 (C_6), 37.9 (C_2), 27.1 (C(<u>C</u>H_3)$_3$), 20.81, 20.77, 20.73 and 20.71 (OCO<u>C</u>H_3), 19.5 (<u>C</u>(CH_3)$_3$).

HRMS (ESI): calcd for $C_{50}H_{52}O_{16}Si$ [M + Na^+]: 959.2917, found: 959.2889.

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Methyl (1S,3R,4R,5R)-3-[(tert-butyldiphenylsilyl)oxy]-1,4-dihydroxy-5-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexane-1-carboxylate 235



235

Synthesized according to the general procedure E (-18 °C to rt, 4h) using acetylated caffeoyl chloride (212 mg, 0.75 mmol) and triol **169** (222 mg, 0.5 mmol). Monoester **235** was obtained as a white solid (292 mg, yield: 85%) after purification by flash chromatography on silica using Acetone/ Pentane = 1/4 to 1/2.

$[\alpha]_D^{25}$: + 14.4 (*C* 1.255, CH_2Cl_2).

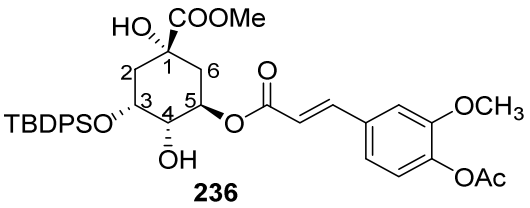
^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.76 – 7.69 (m, 4H, H_{Ar}), 7.54 (d, 1H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.48 – 7.29 (m, 9H, H_{Ar}), 7.22 (d, 1H, J_{ortho} 8.3 Hz, H_{Ar}), 6.28 (d, 1H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 5.57 (td, 1H, ^3J 8.9 Hz, ^3J 4.3 Hz, H_5), 4.38 (dt, 1H, ^3J 5.1 HZ, ^3J 3.4 Hz, H_3), 3.99 (s, 1H, O<u>H</u>), 3.67 (s, 3H, $COOCH_3$), 3.60 – 3.52 (m, 1H, H_4), 2.38 – 2.32 (m, 1H, H_6), 2.31 and 2.30 (2s, 6H, 2x$OCOCH_3$) 2.11 – 2.01 (m, 3H, H_6 and $2H_2$), 1.14 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 173.8 (<u>C</u>$OOCH_3$), 168.13 and 168.07 (O<u>C</u>OCH_3), 166.3 (CH=CH<u>C</u>O), 143.7 (<u>C</u>H=CHCO), 143.6 ($C_{q\ Ar}$), 142.5 ($C_{q\ Ar}$), 136.3 (CH_{Ar}), 136.1 (CH_{Ar}), 133.2 ($C_{q\ Ar}$), 132.7 ($C_{q\ Ar}$), 132.5 ($C_{q\ Ar}$), 130.28 (CH_{Ar}), 130.25 (CH_{Ar}), 128.0 (CH_{Ar}), 127.97 (CH_{Ar}), 126.5 (CH_{Ar}), 124.1 (CH_{Ar}), 122.9 (CH_{Ar}), 118.83 (CH=<u>C</u>HCO), 75.1 (C_1), 73.5 (C_4), 72.4 (C_3), 70.4 (C_5), 52.8 (COO<u>C</u>H_3), 38.6 (C_6), 37.2 (C_2), 27.2 (C(<u>C</u>H_3)$_3$), 20.77 and 20.72 (OCO<u>C</u>H_3), 19.34(<u>C</u>$(CH_3)_3$).

HRMS (ESI): calcd for $C_{37}H_{42}O_{11}Si$ [M + Na^+]: 713.2389, found: 713.2402.

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Methyl (1S,3R,4R,5R)-3-[(tert-butyldiphenylsilyl)oxy]-1,4-dihydroxy-5-[[(2E)-3-(3-acetoxy,4-methoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexane-1-carboxylate 236



236

Synthesized according to the general procedure E (-18 °C to rt, 4h) using acetylated feruloyl chloride (96 mg, 0.375 mmol) and triol **169** (111 mg, 0.25 mmol). Monoester **236** was obtained as a white solid (141 mg, yield: 85%) after purification by flash chromatography on silica using EtOAc/ Pentane = 1/3 to 2/3.

$[\alpha]_D^{25}$: + 25.3 (*C* 0.96, CH_2Cl_2).

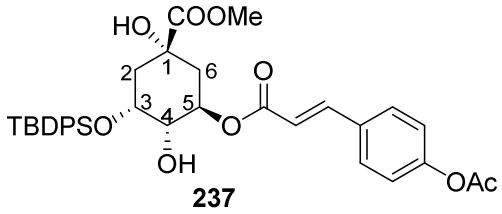
^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.77 – 7.70 (m, 4H, H_{Ar}), 7.58 (d, 1H, ^3J 15.9 Hz, C<u>H</u>=CHCO), 7.48 – 7.38 (m, 6H, H_{Ar}), 7.10 – 7.03 (m, 3H, H_{Ar}), 6.30 (d, 1H, ^3J 15.9 Hz, CH=C<u>H</u>CO), 5.60 (td, 1H, ^3J 9.2 Hz, ^3J 4.3 Hz, H_5), 4.42 – 4.36 (m, 1H, H_3), 4.04 (s, 1H, OH), 3.85 (s, 3H, $PhOCH_3$), 3.68 (s, 3H, $COOCH_3$), 3.56 (dd, 1H, ^3J 8.6 Hz, ^3J 3.0 Hz, H_4), 2.40 – 2.32 (m, 1H, H_6), 2.32 (s, 3H, $OCOCH_3$), 2.11 – 1.98 (m, 3H, H_6 and 2xH_2), 1.15 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 173.8 (<u>C</u>$OOCH_3$), 168.9 (O<u>C</u>OCH_3), 166.6 (CH=CH<u>C</u>O), 151.5 ($C_{q\ Ar}$), 144.8 (<u>C</u>H=CHCO), 141.6 ($C_{q\ Ar}$), 136.3 (CH_{Ar}), 136.1 (CH_{Ar}), 133.3 ($C_{q\ Ar}$), 132.7 ($C_{q\ Ar}$), 132.4 ($C_{q\ Ar}$), 130.3 (CH_{Ar}), 130.2 (CH_{Ar}), 128.03 (CH_{Ar}), 127.97 (CH_{Ar}), 123.4 (CH_{Ar}), 121.4(CH_{Ar}), 117.9 (CH=<u>C</u>HCO), 111.3 (CH_{Ar}), 75.2 (C_1), 73.7 (C_4), 72.6 (C_3), 70.3 (C_5), 56.0 ($PhO\underline{C}H_3$), 52.8 ($COO\underline{C}H_3$), 38.7 (C_6), 37.2 (C_2), 27.1 ($C(\underline{C}H_3)_3$), 20.8 ($OCO\underline{C}H_3$), 19.4 (<u>C</u>$(CH_3)_3$).

HRMS (ESI): calcd for $C_{36}H_{42}O_{10}Si$ [M + Na^+]: 685.2439, found: 685.2412.

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Methyl (1S,3R,4R,5R)-3-[(tert-butyldiphenylsilyl)oxy]-1,4-dihydroxy-5-[[(2E)-3-(4-acetoxyphenyl)-1-oxo-2-propen-1-yl]oxy] cyclohexane-1-carboxylate 237



237

Synthesized according to the general procedure E (-18 °C to 0 °C, 4h) using acetylated *p*-coumaroyl chloride (118 mg, 0.526 mmol) and triol **169** (156 mg, 0.351 mmol). Monoester **237** was obtained as a white solid (184 mg, yield: 83%) after purification by flash chromatography on silica using Acetone/ Pentane = 1/6 to 1/3.

$[\alpha]_D^{25}$: + 19.4 (*C* 1.05, CH_2Cl_2).

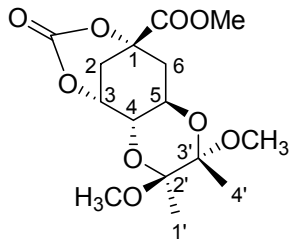
^{1}H NMR (400 MHz,298K, $CDCl_3$) δ = 7.77 – 7.71 (m, 4H, H_{Ar}), 7.56 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.49 (d, 2H, J_{ortho} 8.5 Hz, H_{Ar}), 7.45 – 7.36 (m, 6H, H_{Ar}), 7.12 (d, 2H, J_{ortho} 8.5 Hz, H_{Ar}), 6.28 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.56 (td, 1H, ^3J 8.3 Hz, ^3J 4.1 Hz, H_5), 4.39 (q, 1H, ^3J 4.5 Hz, H_3), 4.03 (s, 1H, OH), 3.65 (s, 3H, COOC<u>H</u>$_3$), 3.58 (dd, 1H, ^3J 7.8 Hz, ^3J 2.3 Hz, H_4), 2.38 – 2.26 (m, 1H, H_6), 2.29 (s, 3H, OCOC<u>H</u>$_3$), 2.17 – 1.97 (m, 3H, 2xH_2 and H_6), 1.14 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 173.8 (<u>C</u>OOCH$_3$), 169.2 (O<u>C</u>OCH$_3$), 166.4 (CH=CH<u>C</u>O), 152.2 ($C_{q\ Ar}$), 144.3 (<u>C</u>H=CHCO), 136.2 (CH_{Ar}), 136.0 (CH_{Ar}), 132.8 ($C_{q\ Ar}$), 132.5 ($C_{q\ Ar}$), 131.9 ($C_{q\ Ar}$), 130.2 (CH_{Ar}), 130.1 (CH_{Ar}), 129.3 (CH_{Ar}), 127.9 (CH_{Ar}), 127.9 (CH_{Ar}), 122.2 (CH_{Ar}), 117.7 (CH=<u>C</u>HCO), 74.9 (C_1), 73.1 (C_4), 72.1 (C_3), 70.3 (C_5), 52.7 (COO<u>C</u>H$_3$), 38.2 (C_6), 37.1 (C_2), 27.1 (C(<u>C</u>H$_3$)$_3$), 21.2 (OCO<u>C</u>H$_3$), 19.3 (<u>C</u>(CH_3)$_3$).

HRMS (ESI): calcd for $C_{35}H_{40}O_9Si$ [M + Na^+]: 655.2334, found: 655.2329.

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Methyl (2'S,3'S)-1,3-dioxan-4-*O*,5-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-quinate 233



233

To a solution of **77** (320 mg, 1 mmol) in THF (20 mL) was added 1,1-carbonyldiimidazole (CDI, 266 mg, 1.64 mmol) and NaH (168 mg, 60% in mineral oil, 4.2 mmol), the mixture was stirred under nitrogen for 25 min. Then the reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (20 mL), the organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography (Et_2O/DCM = 1/8) to provide **233** as a white solid (182 mg, 53%).

$[\alpha]_D^{25}$: + 66.6 (*C* 0.98, CH_2Cl_2).

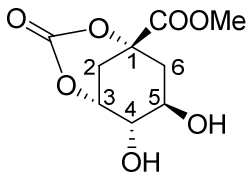
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 = (dt, 1H, ^3J 4.6 Hz, ^3J 1.7 Hz, H_3), 4.05 (ddd, 1H, ^3J 12.0 Hz, ^3J 9.9 Hz, ^3J 5.5 Hz, H_5), 3.83 (s, 3H, $COOCH_3$), 3.77 – 3.70 (m, 1H, H_4), 3.24 (s, 3H, $C_{2'}OCH_3$), 3.20 (s, 3H, $C_{3'}OCH_3$), 2.51 (ddd, 1H, ^2J 13.6 Hz, ^3J 5.5 Hz, ^3J 2.8 Hz, H_{6e}), 2.44 (ddd, 1H, ^2J 14.5 Hz, ^3J 4.6 Hz, ^3J 2.8 Hz, H_{2a}), 2.25 (dd, 1H, ^2J 14.5 Hz, ^3J 1.6 Hz, H_{2e}), 2.03 (dd, 1H, ^2J 13.6 Hz, ^3J 12.0 Hz, H_{6a}), 1.32 (s, 3H, $C_{1'}$), 1.27 (s, 3H, $C_{4'}$).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 168.4 ($\underline{C}OOCH_3$), 146.7 (O$\underline{C}$OO), 101.1 ($C_{2'}$), 100.4 ($C_{3'}$), 81.7 (C_1), 75.7 (C_3), 72.1 (C_4), 63.1 (C_5), 53.6 (COO$\underline{C}H_3$), 48.3 ($C_{2'}O\underline{C}H_3$), 48.2 ($C_{3'}O\underline{C}H_3$), 36.6 (C_6), 30.7 (C_2), 17.8 ($C_{4'}$), 17.7 ($C_{1'}$).

HRMS (ESI): calcd for $C_{15}H_{22}O_9$ [M + Na^+]: 369.1156, found: 369.1153.

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Methyl (1R,3R, 4R, 5S)-4,5-dihydroxy-1,3-dioxan-1-carboxylate 170



170

The mixture of **233** (270 mg, 0.78 mmol) in TFA/H_2O (20:1, 0.8 mL) was stirred at room temperature for 15 min. The resulting mixture was concentrated purified by flash chromatography (EtOAc/CH_3OH = 25/1) to provide **170** as a colorless oil (150 mg, 83%).

$[\alpha]_D^{22}$: -21.0 (*C* 1.015, CH_3OH).

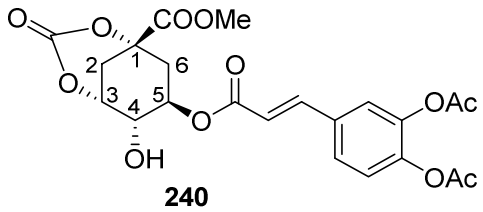
^{1}H NMR (400 MHz, 298K, MeOD) δ = 5.05 (ddd, 1H, ^3J 7.3 Hz, ^3J 5.1 Hz, ^3J 3.3 Hz, H_3), 4.57 (t, 1H, ^3J 7.2 Hz, H_4), 4.17 (ddd, 1H, ^3J 11.7 Hz, ^3J 7.2 Hz, ^3J 4.8 Hz, H_5), 3.76 (s, 3H, $COOCH_3$), 2.38 – 2.20 (m, 2H, H_2), 2.05 (ddd, 1H, ^2J 13.7 Hz, ^3J 4.8 Hz, ^3J 2.0 Hz, H_{6e}), 1.87 (dd, 1H, ^2J 13.7 Hz, ^3J 11.2 Hz, H_{6a}).

^{13}C NMR (100 MHz, 298K, MeOD) δ = 176.1 ($\underline{C}OOCH_3$), 156.8 (O$\underline{C}$OO), 82.3 (C_4), 77.6 (C_3), 74.1 (C_1), 67.6 (C_5), 53.1 (COO$\underline{C}H_3$), 39.4 (C_6), 34.6 (C_2).

HRMS (ESI): calcd for $C_9H_{12}O_7$ [M + Na^+]: 255.0475, found: 255.0472.

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Methyl (1R,3R, 4R, 5S)-4-hydroxy-5-[[(2E)-3-(3,4-diacetoxyphenyl)-1-oxo-2-propen-1-yl]oxy]-1,3-dioxan-1-carboxylate 240



240

To a solution of diol **170** (39 mg, 0.168 mmol) in DMF (0.26 mL) and pyridine (0.17 mL) under nitrogen was added the acetylated caffeoyl chloride (142 mg, 0.504 mmol) The mixture was stirred at 45 °C for 30 min. Methanol was added and after 15min under stirring, the resulting mixture was concentrated, diluted with EtOAc, washed with 1M HCl then with a saturated $NaHCO_3$ solution then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (Et_2O/DCM = 1:15 to 1:4) providing the monoester **240** as a white solid (43 mg, 65%).

$[\alpha]_D^{25}$: - 35.4 (*C* 1.15, CH_2Cl_2).

^{1}H NMR (400 MHz, 298K, $CDCl_3$) δ = 7.63 (d, 1H, ^3J 16.0 Hz, C<u>H</u>=CHCO), 7.43 – 7.33 (m, 2H, H_{Ar}), 7.21 (d, 1H, J_{ortho} 8.3 Hz, H_{Ar}), 6.34 (d, 1H, ^3J 16.0 Hz, CH=C<u>H</u>CO), 5.53 (ddd, 1H, ^3J 9.7 Hz, ^3J 6.5 Hz, ^3J 5.0 Hz, H_5), 5.07 (dt, 1H, ^3J 7.8 Hz, ^3J 4.0 Hz, H_3), 4.80 (t, 1H, ^3J 7.1 Hz, H_4), 3.78 (s, 3H, COOC<u>H</u>$_3$), 3.51 (s, 1H, OH), 2.36 – 2.25 (m, 3H, 2xH_2 and H_6), 2.09 – 1.98 (m, 1H, H_6).

^{13}C NMR (100 MHz, 298K, $CDCl_3$) δ = 174.5 (<u>C</u>OOCH$_3$), 168.2 and 168.1 (O<u>C</u>OCH$_3$), 165.2 (CH=CH<u>C</u>O), 154.0 ($C_{q\,Ar}$), 144.4 (<u>C</u>H=CHCO), 143.9 ($C_{q\,Ar}$), 142.5 ($C_{q\,Ar}$), 132.9 ($C_{q\,Ar}$), 126.7 (CH_{Ar}), 124.1 (CH_{Ar}), 123.0 (CH_{Ar}), 118.1 (CH=<u>C</u>HCO), 76.2 (C_4), 74.8 (C_3), 72.2 (C_1), 69.3 (C_5), 53.6 (COO<u>C</u>H$_3$), 35.8 (C_6), 34.0 (C_2), 20.73 and 20.69 (OCO<u>C</u>H$_3$).

HRMS (ESI): calcd for $C_{22}H_{22}O_{12}$ [M + Na^+]: 501.1003, found: 501.0994.

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