Synthesis of Chlorogenic Acids & Chlorogenic Acid Lactones

by

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Doctor of Philosophy in Chemistry

Approved Dissertation Committee

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Abstract

The chlorogenic acids are a family of esters formed between certain trans-cinnamic acids and quinic acid. Chlorogenic acids are among the most abundant polyphenols, which are naturally occurring in plants, with various biological activities beneficial to human health. Chlorogenic acids are secondary metabolites that are found in plants. As a group they generally contain several subgroups and usually several isomers within each subgroup. The development of methods for the synthesis of existing chlorogenic acids and new series of chlorogenic acids were developed in this thesis in order to have the compounds available as analytical standards, for confirmation of previous and future LC/MS work, and most importantly for individual biological testing in various assays.

The target compounds were obtained with two strategies 1.selective synthesis using appropriate protecting groups strategies, 2.nonselective synthesis producing mixtures of isomers. The general strategy, which was applied through out the thesis in order to synthesise the target compounds was, as follows;

- Preparation of acid chlorides of cinnamic acids
- Preparation of protected quinic acid derivatives
- Acylation
- Deprotection

A series of mono-acyl chlorogenic acids and esters, in particular of those substituted in the 1-, 3-, 4- and 5- positions of the quinic acid with coumaroyl, feruloyl, caffeoyl and dimethoxy cinnamoyl and cinnamoyl substituents, have been successfully synthesised. As intermediates in these syntheses a series of quinide esters, potential metabolites and degradation products of naturally occurring chlorogenic acids have also been obtained. The first examples of di-acyl chlorogenic acids, have been successfully synthesised. A general protection and deprotection strategy for the synthesis of chlorogenic acids has been established. Poly-acyl chlorogenic acids starting from quinic acid and quinic acid lactones also have been established. The right conditions for the synthesis of certain type of chlorogenic acids and esters have been established in this work.
“Imagination is more important than knowledge”

Albert Einstein (1879-1955)
Acknowledgements

I would like to thank Prof. Nikolai Kuhnert for giving me the opportunity to work in this project and for everything he has done during my seven years study.

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I would like to thank all my family for their unlimited love and support which has been only the impulse to achieve my goals, especially for believing in me always and forever. I would also like to thank “my little brother” Cihangir for being the most cheerful part of my life.

Finally, I have to say 'thank-you' to all my friends wherever they are.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>Acetic anhydride</td>
</tr>
<tr>
<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>MeCN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>CGA</td>
<td>Chlorogenic acids</td>
</tr>
<tr>
<td>CHCl$_3$</td>
<td>Chloroform</td>
</tr>
<tr>
<td>(COCl)$_2$</td>
<td>Oxalyl chloride</td>
</tr>
<tr>
<td>CoQA</td>
<td>$p$-coumaroylquinic</td>
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<tr>
<td>CQA</td>
<td>Caffeoylquinic acid</td>
</tr>
<tr>
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<td>Cinnamoyl chloride</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
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<tr>
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<td>Dimethylformamide</td>
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<tr>
<td>DMP</td>
<td>Dimethoxypropane</td>
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<tr>
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<td>Dimethyl sulfoxide</td>
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<tr>
<td>Et$_3$N</td>
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</tr>
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</tr>
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<td>Ethanol</td>
</tr>
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<td>FT</td>
<td>Fourier transform</td>
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<td>IR</td>
<td>infrared</td>
</tr>
<tr>
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<td>Iodine</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin-layer chromatography</td>
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<tr>
<td>TMS-Cl</td>
<td>Trimethylsilyl chloride</td>
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<td>TMSOTf</td>
<td>trimethylsilyl trifluoromethanesulfonate</td>
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<td>TrocCl</td>
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</tr>
<tr>
<td>PE</td>
<td>Petroleum ether</td>
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<tr>
<td>PTSA</td>
<td>p-toluenesulfonic acid</td>
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### Abbreviations for NMR

<table>
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<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>COSY</td>
<td>$^1$H-$^1$H Correlation spectroscopy</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear Multiple Quantum Coherence (heteronuclear correlation spectroscopy)</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond correlation</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>bs</td>
<td>broad signal</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
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<td>doublet</td>
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<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
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### Abbreviations for MS

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<th>Description</th>
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<tbody>
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<td>MS</td>
<td>Mass Spectrometry</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionization</td>
</tr>
<tr>
<td>EI</td>
<td>electron ionization</td>
</tr>
<tr>
<td>m/z</td>
<td>mass-to-charge ratio</td>
</tr>
<tr>
<td>M+</td>
<td>parent molecular ion</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid Chromatography Mass Spectroscopy</td>
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</table>
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BACKGROUND

Chapter 1
Phenolic Phytochemicals
Phenolic phytochemicals are secondary metabolites of plant origin, which constitute one of the most abundant groups of natural products and form an important part of both human and animal diets. These phenolic metabolites function to protect the plants against biological and environmental stresses and therefore are synthesized in response to pathogenic attack such as fungal or bacterial infection or to high energy radiation exposure such as prolonged UV exposure. Because of their important protective biological functions, phenolic phytochemicals are ubiquitous in all plants and therefore find their place in almost all food groups. Common fruits such as apples, cranberries, grapes, raspberries, and strawberries and their beverages such as red wine, apple and orange juice are rich sources of phenolic phytochemicals. In addition to fruit, vegetables such as cabbage and onion, and food grains such as sorghum, millet, barley, peas, and other legumes are also described as important sources of phenolic phytochemicals.

The classification of the numerous different types of phenolic phytochemicals is based on their ring structure and the number of carbon atoms substituting the ring and linking them together (Table 1). Metabolic processing of phenolic phytochemicals in plants for their final biological function has led to chemical variations in basic phenolic structure. The structural variation ranges from simple molecules, for example the phenolic acids with a single ring structure (Figure 1), through to biphenyls and flavanoids having 2-3 phenolic rings (Figure 1). Another abundant group of phenolic phytochemicals in fruits and vegetables often referred to as polyphenols, contain 12-16 phenolic groups.

These polyphenols are classified as condensed proanthocyanidins, tannins, which include galloyl and hexahydroxydiphenoyl (or ellagoyl) esters and their derivatives, and phlorotannins (Figure 1). Flavanoids such as quercetin constitute the largest group of phenolic phytochemicals and are widespread in fruit. Structural variations within the rings resulting in an alteration in the degree of hydroxylation, methylation, isoprenylation, dimerization and glycosylation (producing O- or C-glycosides), subdivide the flavonoids into several families: flavonols, flavones, flavanols, isoflavones, anthocyanidins and others. To increase the solubility and to target the phenolic phytochemicals to specific parts of the plant and to prevent enzymatic and chemical degradation, phenolic phytochemicals are often found as glycosides esterified with sugars and other chemical components such as quinic acid through the hydroxyl groups.
of the phenolic ring. All the phenolic phytochemicals are derived from a common biosynthetic pathway, incorporating precursors from both the shikimate and/or the acetate-malonate pathways (Figure 2).\textsuperscript{9,10}

Table 1: The major classes of phenolic compounds in plants

<table>
<thead>
<tr>
<th>Number of carbon atoms</th>
<th>Basic skeleton</th>
<th>Class</th>
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<td>6</td>
<td>C₆</td>
<td>Simple phenols</td>
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<td></td>
<td></td>
<td>Benzoquinones</td>
</tr>
<tr>
<td>7</td>
<td>C₆C₁</td>
<td>Phenolic acids</td>
</tr>
<tr>
<td>8</td>
<td>C₆C₂</td>
<td>Acyldepsipeptides</td>
</tr>
<tr>
<td>9</td>
<td>C₆C₃</td>
<td>Tyrosine derivatives</td>
</tr>
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<td>C₆C₄</td>
<td>Phenylacetic acids</td>
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<td>Phenylpropanes</td>
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<tr>
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<td>C₆C₅</td>
<td>Heterocyclic acids</td>
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<tr>
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<td>C₆C₆</td>
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</tr>
<tr>
<td>15</td>
<td>C₆C₇</td>
<td>Isochromones</td>
</tr>
<tr>
<td>18</td>
<td>C₆C₈</td>
<td>Chalcones</td>
</tr>
<tr>
<td>30</td>
<td>C₆C₉</td>
<td>Flavonoids</td>
</tr>
<tr>
<td>N</td>
<td>C₆C₊</td>
<td>Isocoumarins</td>
</tr>
<tr>
<td></td>
<td>C₆C₆C₇</td>
<td>Flavones</td>
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<tr>
<td></td>
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<td>Flavonoids</td>
</tr>
<tr>
<td></td>
<td>C₆C₆C₉</td>
<td>Flavonoids</td>
</tr>
</tbody>
</table>

\textsuperscript{9,10}Figure 1: Common simple phenol, bioflavonoids, flavonoids and tannins in plants

\textsuperscript{9,10}Figure 2: Biosynthesis of phenolic phytochemicals.
Types of polyphenols
Hydroxybenzoic acids and hydroxycinnamic acids are abundant in foods and may account for about one third of the phenolic compounds in the human diet. These compounds are found as esters, which are either soluble and accumulate in vacuoles, or insoluble as cell-wall components. The most frequently encountered hydroxycinnamic acids are caffeic acid and ferulic acids. The former is found in many fruits such as apple, plum, tomato, and grape. Ferulic acid is linked through ester bonds to hemicellulose of the cell wall and is found in many food sources. Derivatives of hydroxycinnamic acids are found in almost every plant. Those of interest include chlorogenic acid (a caffeoyl ester of quinic acid) and curcumin. Chlorogenic acids are present in many fruits and vegetables especially in coffee (about 7% of dried beans) and the key substrates for the enzymatic oxidation which leads to browning, particularly in apples and pears. Curcumin, which contains two ferulic acid moieties linked by a methylene, with a β-diketone structure in a highly conjugated system, is the major yellow pigment in turmeric and mustard. It is used widely as a food preservative and yellow coloring agent for foods, drugs, and cosmetics.

Flavonoids are the largest class of phenolic compounds and more than 5000 compounds have been described. They are mainly classified into flavones, flavanols (catechins), isoflavones, flavonols, flavanones, and anthocyanins. All are structurally related to the parent compound, flavone (2-phenylbenzopyrone).

Flavanols are the most ubiquitous flavonoids in foods, and the main representatives are quercetin and kaempferol. The richest sources are onions, curly kale, leek, broccoli and blueberries. Red vine and tea also contain flavanols. These compounds are present in glycosylated forms. The associated sugar moiety is very often glucose or rhamnose, but other sugars may also be involved (eg, galactose, arabinose, xylose, glucuronic acid.) Fruit often contains between 5 to 10 different flavanol glycosides.¹¹

Flavones are much less common than flavanols in fruit and vegetables. The only important edible source of flavones identified to date parsley and celery. The skin of citrus fruit contains large quantities of polymethoxylated flavones; tangeretin, nobiletin, and sinensetein (essential oil of mandarin).¹²
Flavanones are found in tomatoes and certain aromatic plants such as mint, but they are in high concentrations only in citrus fruit. The main aglycones are naringenin in grapefruit, hesperetin in oranges, and eriodictiol in lemons. Flavanones are generally glycosylated by a disaccharide at position 7 either a neohesperidose, which imparts a bitter taste (such as naringin in grapefruit), or a rutinose, which is flavourless.

Isoflavones are flavonoids with structural similarities to estrogens. Although they are not steroids, they have hydroxyl groups in position 7 and 4 in a configuration analogous to that of the hydroxyls in the estradiol molecule. They contain three main molecules; genistein, daidzin and glycitein, generally in a concentration ratio of 1:2:0.2.\(^{13}\)

Flavanols exist in both the monomer form (catechins) and the polymer form (proanthocyanidins). Catechins are found in many types of fruits; apricots, green tea, chocolate are the richest source of catechins.\(^{14}\)

Proanthocyanidins, which are also known as condensed tannins, are dimers, oligomers, and polymers of catechins that are bound together by links between C4 and C8 (or C6). Through the formation of complexes with salivary proteins, condensed tannins are responsible for the astringent character of fruit (grapes, peaches, kakis, apples, pears, berries, etc) and beverages (wine, cider, tea, beer, etc) and for the bitterness of chocolate.\(^{15}\)

Anthocyanins are pigments dissolved in the vacuolar sap of the epidermal tissues of flowers and fruit, to which they impart a pink, red, blue, or purple colour. In human diet, anthocyanidins are found in red wine, certain varieties of cereals, and certain leafy and root vegetables (aubergines, cabbage, beans, onions, radishes), but they are most abundant in fruit. Cyanidin is the most common anthocyanidin in foods.\(^{16}\)

Lignans are formed of two phenylpropane units. The richest dietary source is linseed, which contains secoisolariciresinol and low quantities of matariresinol. Other cereals, grains, fruit, and certain vegetables also contain traces of these same lignans, but concentrations in linseed are \(\approx 1000\) times as high as concentrations in these other food sources. Most lignans appear to pass through the intestinal tract as fiber.\(^{17}\)
Stilbenes contain two phenyl compounds connected by a 2-carbon methylene bridge. They occur in nature in a rather restricted distribution. Most stilbenes in plants act as antifungal phytoalexins, compounds that are usually synthesized only in response to infection or injury. One of these, resveratrol for which anticarcinogenic effects have been shown during screening of medical plants and which has been extensively studied, is found in low quantities in wine. Some of the chemical structures of polyphenols are shown Figure 3 below.

Figure 3: Chemical structures of polyphenols
Phenolic acids

**Hydroxybenzoic acids**

Hydroxybenzoic acids have a general structure of C6-C1 derived directly from benzoic acid (Figure 4) Variations in the structures of individual hydroxybenzoic acids lie in the hydroxylations and methylations of the aromatic ring.\(^{19}\) Four acids occur commonly: p-hydroxybenzoic, vanillic, syringic, and protocatechuic acid. They may be present in soluble form conjugated with sugars or organic acids as well as bound to cell wall fractions, e.g. lignin.\(^{20,21}\) A common hydroxybenzoic acid is salicylic acid (2-hydroxybenzoate). Gallic acid (Figure 4a) is a trihydroxyl derivative which participates in the formation of hydrolysable gallotannins.\(^{22,23}\) Its dimeric condensation product (hexahydroxydiphenic acid) and related lactone, ellagic acid (Figure 4b), are common plant metabolites. Ellagic acid is usually present in ellagitannins as esters of the diphenic acid analogue with glucose.\(^{24}\)

![Figure 4: Chemical structures of (a) hydroxybenzoic acids: p-hydroxybenzoic acid, R\(^1\)=H, R\(^2\)=H; gallic acid, R\(^1\)=OH, R\(^2\)=OH, and (b) ellagic acid.](image)

**Hydroxycinnamic acids**

The four most widely distributed hydroxycinnamic acids in fruits are p-coumaric, caffeic and ferulic acids (Figure 5).\(^{25}\) Hydroxycinnamic acids usually occur in various conjugated forms, the free forms being artefacts from chemical or enzymatic hydrolysis during tissue extraction. The conjugated forms are esters of hydroxyacids such as quinic, shikimic and tartaric acid, as well as their sugar derivatives.\(^{26}\)

![Figure 5: Chemical structure of three common hydroxycinnamic acids: p-coumaric acid, R\(^1\)=H; caffeic acid, R\(^1\)=OH; ferulic acid, R\(^1\)=OCH\(_3\).](image)
Biosynthesis of phenolic compounds in plants

Phenolics display a wide variety of structures, ranging from simple moieties containing a single hydroxylated aromatic ring to highly complex polymeric substances.27,28 The biosynthetic pathways of phenolic compounds in plants are well established.29 The biosynthetic pathways of some flavonols and phenolic acids are shown in Figure 6. The biosynthesis and accumulation of secondary compounds can be an endogenously controlled process during developmental differentiation or it can be regulated by exogenous factors such as light, temperature and wounding. Phenylalanine, produced in plants via the shikimate pathway, is a common precursor for most phenolic compounds in higher plants (Figure 6). Similarly, hydroxycinnamic acids, and particularly their coenzyme A esters, are common structural elements of phenolic compounds, such as cinnamate esters and amides, lignin, flavonoids and condensed tannins30 (Figure 6). The phenylalanine/hydroxycinnamate pathway is defined as general phenylpropanoid metabolism. It includes reactions leading from L-phenylalanine to the hydroxycinnamates and their activated forms. The enzymes catalysing the individual steps in general phenylpropanoid metabolism are phenylalanine ammonialyase (PAL), cinnamic acid 4-hydroxylase (CA4H), and hydroxycinnamate: coenzyme A ligase (C4L). These three steps are necessary for the biosynthesis of phenolic compounds. A growing body of evidence indicates that phenylpropanoid and flavonoid pathways are catalysed by several membrane-associated multienzyme complexes.31
Figure 6: Biosynthesis of hydroxycinnamic acids, hydroxybenzoic acids and flavonoids. Solid arrows represent well-characterised reactions catalysed by single enzymes. Dashed lines represent transformations that require multiple enzymes that are less characterised, or vary among plant species. Enzymes: CA4H, cinnamic acid 4-hydroxylase; CHS, chalcone synthase; 4CL, 4-coumarate: coenzyme A ligase; PAL, phenylalanine ammonialyase.
Biological activity of Polyphenols

Polyphenols are receiving increasing interest from consumers and food manufacturers for several reasons. Epidemiological studies have suggested associations between the consumption of polyphenol-rich foods or beverages and the prevention of diseases. Fruit and vegetable consumption prevents cancers.\textsuperscript{32} It may also prevent stroke,\textsuperscript{33} whereas wine consumption might prevent coronary heart disease.\textsuperscript{34,35} The consumption of tea may protect against cancers\textsuperscript{36} and coronary heart diseases,\textsuperscript{37} and that of soy may protect against breast cancer and osteoporosis.\textsuperscript{38} A second reason is linked to the fundamental chemical nature of polyphenols. Polyphenols are reducing agents, and together with other dietary reducing agents, such as vitamin C, vitamin E and carotenoids, they protect the body’s tissues against oxidative stress. Commonly referred to as antioxidants, they may prevent various diseases associated with oxidative stress, such as cancers, cardiovascular diseases, inflammation and others. Last, polyphenols are the most abundant antioxidants in our diets. Metabolism of polyphenols occurs via a common pathway in our diet (Figure 7).\textsuperscript{39} The aglycones can be absorbed from the small intestine. However most of the polyphenols are present in food as esters, glycosides or polymers that can not be absorbed in the native form. These substances must be hydrolyzed by intestinal enzymes or by the colonic microflora before they can be absorbed.

![Diagram](image)

**Figure 7:** Possible routes for consumed polyphenols in humans.\textsuperscript{39}
Once absorbed, polyphenols are subjected to human phase II metabolism (the conjugation): this process, that mainly includes *methylation*, *sulfation*, and *glucuronidation*, represents a metabolic detoxication process, common to many xenobiotics, that restricts their potential toxic effects and facilitates their biliary and urinary elimination by increasing their hydrophilicity.\(^{40}\)

Catechol-\(O\)-methyl transferase (COMPT) catalyzes the transfer of a methyl group from S-adenosyl-L-methionine to polyphenols such as quercetin, luteolin, caffeic acid, catechins and cyaniding.\(^{41}\) COMPT activity is highest in the liver and the kidneys, although it is present in a number of tissues.\(^{42}\)

Phenil-Sulfotransferases (P-PST) catalyze (the transfer of a sulphate moiety from 3’-phosphoadenosine-5’-phosphosulfate to a hydroxyl group on various substrates, among which are polyphenols. The sulfation occurs mainly in the liver, but the position of sulfation for polyphenols have not been clearly identified yet.\(^{43}\)

UDP-glucuronosyltransferases (UDPGT) are membrane-bound enzymes located in the endoplasmic reticulum in many tissues, which catalyze the transfer of a glucuronic acid from UDP-glucuronic acid to polyphenols as well as to steroids, bile acids and many dietary constituents. Glucuronidation occurs in the intestine and in the liver.\(^{44,45}\)

Circulating polyphenols in plasma are conjugated derivatives that are extensively bound to albumin. Polyphenols are able to penetrate tissues, particularly those in which they are metabolized, such as intestine and liver.\(^{46}\)

**Functions of phenolic acids in plants**

Phenolics are great importance as cell-wall support materials. They form an integral part of the cell-wall structure, mainly in the form of polymeric materials such as lignins. Lignins are, after cellulose, the second most abundant organic structures on earth. A most significant function of the phenolic phytochemicals is their contribution to flower and fruit colours. This is an important for attracting insects and birds to the plant for pollination and seed dispersal. Phenolics may influence the competition among plants, a phenomenon called ‘allelopathy’. Besides the well-known volatile
terpenoids, toxic water-soluble phenolics, such as simple phenols, hydroxybenzoic acids and hydroxycinnamic acids may serve as allelopathic compounds.\textsuperscript{47}

An important function of phenolic acids is their action in plant defence mechanisms.\textsuperscript{48} Stress conditions such as excessive UV light, wounding or infection induces the biosynthesis of phenolic compounds. Thus, environmental factors may have a significant contribution to the content of acids in plants. Phenolics may accumulate as inducible low-molecular-weight compounds, called ‘plytoalexins’, as a result of microbial attack. Plytoalexins are post-infectional, i.e. although they might already be present at low concentrations in the plant, they rapidly accumulate upon attack. In contrast, the pre-infectional toxins are constitutive compounds. They are present in healthy tissue at concentrations high enough for defence, either a free toxins or in conjugated forms from which they are released after attack. Among the phenolic phytoalexins and toxins, hydrocoumarins and hydroxycinnamic acids are of major importance.\textsuperscript{49}

**Polyphenol content in food and dietary intake**

The structural diversity of dietary polyphenols is not limited to differences in the structure of the carbon skeleton and in the oxidation state of the heterocycle of flavonoids. It is further complicated by varying patterns of hydroxylation of the phenolic rings, by glycosylation of most flavonoids, by acylation with phenolic acids and by the existence of stereoisomers, among others. The structural diversity of polyphenols makes the estimation of their content in food difficult. The content of various classes of polyphenols in some foods and beverages commonly consumed in Western diets was presented in Table 2. Polyphenols are not evenly distributed in plant tissues, and food fractionation during processing may result in a loss or enrichment of some phenolic compounds. For a number of reasons, including structural diversity, lack of standardized analytical methods and variation of content in a particular foodstuff, it is extremely difficult to estimate the average daily intake of polyphenols. Most authors refer to the data published 25 years ago by Kühnau.\textsuperscript{50} However, most recently reliable data on polyphenol intake have been complied and can be found on the website polyphenol explorer.
Two different approaches are used to estimate polyphenols: a) specific compounds such as chlorogenic acid in potato or coffee, quercetin in onions or catechins in tea are estimated individually by chromatographic techniques or b) total phenols are estimated by reduction of the Folin-Ciocalteu reagent. Values obtained by the first method are usually lower than those estimated by the Folin assay. One reason is that some polyphenols in a given food source may escape determination by chromatography. These can be unknown compounds, compounds present as traces that were not considered in the characterization of food sources, or compounds that are not resolved by chromatography, such as proanthocyanidin polymers and oxidized polyphenols as in apple, wine, tea or beer. A second reason is that other reducing agents may be present in food. Ascorbic acid also reduces the Folin reagent. For example, the ascorbic acid content of potato, tomato, onion, apple and orange juice (17, 24, 8, 12 and 54 mg/100 g fresh weight, respectively) would account for 40 and 46% of the estimated total phenols in potato and tomato but for only 6 and 4% in polyphenol-rich onion and apple.

Environmental factors have a major effect on polyphenol content. These factors may be pedoclimatic (soil type, sun exposure, rainfall) or agronomic (culture in greenhouses or fields, biological culture, hydroponic culture, fruit yield per tree, etc). Exposure to light has a considerable effect on most flavonoids. The degree of ripeness considerably affects the concentrations and proportions of the various polyphenols. In general, phenolic acid concentrations decrease during ripening, whereas anthocyanin concentrations increase. Many polyphenols, especially phenolic acids, are directly involved in the response of plants to different types of stress: they contribute to healing by lignification of damaged areas, they possess antimicrobial properties, and their concentrations may increase after infection.

Storage may also affect the content of polyphenols that are easily oxidized. Oxidation reactions result in the formation of more or less polymerized substances, which lead to changes in the quality of foods, particularly in color and organoleptic characteristics. Such changes may be beneficial (as is the case with black tea) or undesirable (browning of fruit) to consumer acceptability. Therefore, storage may cause loss of phenolic acids.
Table 2: Bioavailability of Polyphenols

<table>
<thead>
<tr>
<th>Polyphenol</th>
<th>Source (serving size)</th>
<th>By wt or vol (mg/kg fresh wt or mg/L)</th>
<th>By serving (mg/serving)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxybenzoic acids (2, 6)</td>
<td>Blackberry (100 g)</td>
<td>80-270</td>
<td>8-27</td>
</tr>
<tr>
<td>Protocatechuic acid</td>
<td>Raspberry (100 g)</td>
<td>60-100</td>
<td>6-10</td>
</tr>
<tr>
<td>Gallic acid</td>
<td>Black currant (100 g)</td>
<td>40-130</td>
<td>4-13</td>
</tr>
<tr>
<td>p-Hydroxybenzoic acid</td>
<td>Strawberry (200 g)</td>
<td>20-90</td>
<td>4-18</td>
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<td>Hydroxycinnamic acids (2, 5–7)</td>
<td>Blueberry (100 g)</td>
<td>2000–2200</td>
<td>200–220</td>
</tr>
<tr>
<td>Caffeic acid</td>
<td>Kiwi (100 g)</td>
<td>600-1000</td>
<td>60-100</td>
</tr>
<tr>
<td>Chlorogenic acid</td>
<td>Cherry (200 g)</td>
<td>180–1150</td>
<td>36-230</td>
</tr>
<tr>
<td>Coumaric acid</td>
<td>Plum (200 g)</td>
<td>140–1150</td>
<td>28-230</td>
</tr>
<tr>
<td>Ferulic acid</td>
<td>A ubergine (200 g)</td>
<td>600–660</td>
<td>120–132</td>
</tr>
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<td>Sinapic acid</td>
<td>Apple (200 g)</td>
<td>50–600</td>
<td>10–120</td>
</tr>
<tr>
<td>Artichoke (100 g)</td>
<td>Pear (200 g)</td>
<td>15–600</td>
<td>3–120</td>
</tr>
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<td>Potato (200 g)</td>
<td>Coffee (200 mL)</td>
<td>10–500</td>
<td>2–100</td>
</tr>
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<td>Corn flour (75 g)</td>
<td>Yellow onion (100 g)</td>
<td>350–1200</td>
<td>35–120</td>
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<tr>
<td>Anthocyanins (8–10)</td>
<td>Myricetin (200 g)</td>
<td>15–200</td>
<td>3–40</td>
</tr>
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<td>Cyanidin</td>
<td>Broccoli (200 g)</td>
<td>40–100</td>
<td>8–20</td>
</tr>
<tr>
<td>Pelargonidin</td>
<td>Blueberry (100 g)</td>
<td>30–160</td>
<td>3–16</td>
</tr>
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<td>Peonidin</td>
<td>Black grape (200 g)</td>
<td>30–70</td>
<td>3–7</td>
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<td>Delphinidin</td>
<td>Cherry (200 g)</td>
<td>350–4500</td>
<td>70–900</td>
</tr>
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<td>Malvidin</td>
<td>Rhubarb (100 g)</td>
<td>2000</td>
<td>200</td>
</tr>
<tr>
<td>Strawberry (200 g)</td>
<td>Red wine (100 mL)</td>
<td>200–350</td>
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<td>Red wine (100 mL)</td>
<td>Plum (200 g)</td>
<td>20–250</td>
<td>4–50</td>
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<tr>
<td>Red cabbage (200 g)</td>
<td>Tomato (200 g)</td>
<td>2–15</td>
<td>0.4–3</td>
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<tr>
<td>Yellow onion (100 g)</td>
<td>Black tea infusion (200 mL)</td>
<td>30–45</td>
<td>6–9</td>
</tr>
<tr>
<td>Anthocyanins (11–12, 14, 18)</td>
<td>Green tea infusion (200 mL)</td>
<td>20–35</td>
<td>4–7</td>
</tr>
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<td>Flavones</td>
<td>Parsley (5 g)</td>
<td>240–1850</td>
<td>1.2–9.2</td>
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<td>Apigenin</td>
<td>Celery (200 g)</td>
<td>20–140</td>
<td>4–28</td>
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<td>Luteolin</td>
<td>Capsicum pepper (100 g)</td>
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<td>0.5–1</td>
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<td>Flavanones (19–21)</td>
<td>Orange juice (200 mL)</td>
<td>215–685</td>
<td>40–140</td>
</tr>
<tr>
<td>Hesperetin</td>
<td>Grapefruit juice (200 mL)</td>
<td>100–650</td>
<td>20–130</td>
</tr>
<tr>
<td>Naringenin</td>
<td>Lemon juice(200 mL)</td>
<td>50–300</td>
<td>10–60</td>
</tr>
<tr>
<td>Isoflavones (22–25)</td>
<td>Soy flour (75 g)</td>
<td>800–1800</td>
<td>60–135</td>
</tr>
<tr>
<td>Daidzein</td>
<td>Soybeans, boiled (200 g)</td>
<td>200–900</td>
<td>40–180</td>
</tr>
<tr>
<td>Genistein</td>
<td>Miso (100 g)</td>
<td>250–900</td>
<td>25–90</td>
</tr>
<tr>
<td>Glycitein</td>
<td>Tofu (100 g)</td>
<td>80–700</td>
<td>8–70</td>
</tr>
<tr>
<td>Soy milk (200 mL)</td>
<td>30–175</td>
<td>6–35</td>
<td></td>
</tr>
<tr>
<td>Monomeric flavanols (6, 17, 26, 27)</td>
<td>Chocolate (50 g)</td>
<td>460–610</td>
<td>23–30</td>
</tr>
<tr>
<td>Epicatechin</td>
<td>Catechin Beans (200 g)</td>
<td>350–550</td>
<td>70–110</td>
</tr>
<tr>
<td>Monomeric flavanols (6, 17, 26, 27)</td>
<td>Chocolate (50 g)</td>
<td>460–610</td>
<td>23–30</td>
</tr>
<tr>
<td>Epicatechin</td>
<td>Apricot (200 g)</td>
<td>100–250</td>
<td>20–50</td>
</tr>
<tr>
<td>Cherry (200 g)</td>
<td>Grape (200 g)</td>
<td>50–220</td>
<td>10–44</td>
</tr>
<tr>
<td>Grape (200 g)</td>
<td>Peach (200 g)</td>
<td>50–140</td>
<td>10–28</td>
</tr>
<tr>
<td>Apple (200 g)</td>
<td>Green tea (200 mL)</td>
<td>100–800</td>
<td>20–160</td>
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<td>Black tea (200 mL)</td>
<td>Red wine (100 mL)</td>
<td>60–500</td>
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<tr>
<td>Red wine (100 mL)</td>
<td>80–300</td>
<td>8–30</td>
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</tr>
</tbody>
</table>
THE CHLOROGENIC ACIDS

Esters formed between hydroxycinnamates and quinic acid represent a major family of plant phenolics. Chlorogenic acid (5-CQA) is the most widespread of all monoesters formed between caffeic and quinic acids (CQA).\textsuperscript{57} It is commonly considered to be a storage form of cinnamic acid derivatives and has been suggested to be an intermediate in the lignin pathway.\textsuperscript{58}

Classically, chlorogenic acids (CGA) are a family of esters formed between certain \textit{trans}-cinnamic acids and quinic acid (1L-1(OH),3,4/5-tetrahydroxycyclohexane carboxylic acid) which has axial hydroxyls on carbons 1 and 3, and equatorial hydroxyls on carbons 4 and 5.

Using the preferred IUPAC numbering,\textsuperscript{59} the commonest individual chlorogenic acid is 5-\textit{O}-caffeoylquinic acid (5-CQA). It is the only one commercially available and is still often called chlorogenic acid, although this term should be discouraged.

![Figure 8: (-) Quinic acid](image)

![Figure 9: Chlorogenic acid](image)
These well known CGAs may be subdivided by the identity, number and position of the acyl residues.

Besides cinnamate derivatives, esters of gallic acid are commonly found in natural sources.

Quinic acid forms esters using all four OH groups.

The following subgroups of esters have been described in the literature;

- the relatively widespread mono-esters of caffeic acid, ie caffeoylquinic acids (CQA), p-coumaroylquinic acids (pCoQA) and feruloyl quinic acids (FQA);
- di-esters, tri-esters and the single tetra-ester of caffeic acid, ie diCQA, triCQA and tetraCQA, of the homo type (all esters the same).
• mixed di-esters of caffeic and ferulic acid, ie caffeoyl-feruloylquinic acids (CFQA) which are characteristic of robusta coffee or caffeic and sinapic acid, ie caffeoylsinapoylquinic acids (CSiQA) (hetero type, different ester residues).
• mixed esters involving various permutations of between one and three residues of caffeic acid with one or two residues of a dibasic aliphatic acid (eg glutaric, oxalic, succinic acid)(Figure: 10i, 10ii, 10iii).

![Figure 10](image)

This list of well known CGA can be extended to include the galloyl conjugates of quinic acid and the cinnamoyl conjugates of quinic acid derivatives such as shikimic acid (Figure:11i) and muco-quinic acid (Figure:11i) which differs from the isomer described above by having an equatorial hydroxyl on carbon 3.

![Figure 11](image)

**Natural occurrence of chlorogenic acids and dietary intake**

Hydroxycinnamic acid compounds are widely distributed in the plant kingdom. They usually exist as esters of organic acid or glycosides or are bound to protein and other cell wall polymers. Only a small number of them exist as free acids in nature. The occurrence of such compounds in food significantly affects stability, color, flavor, nutritional value, and other food qualities.
Hydroxycinnamic acids such as caffeic, ferulic, sinapic and \( p \)-coumaric acids are present in a large variety of fruits and vegetables including blueberries, grapes, apples, cereal brans, broccoli, spinach and lettuce (Figure 12).

![Structure of five most common hydroxycinnamates](image)

**Figure 12**: Structure of five most common hydroxycinnamates. The hydroxy cinnamates all have a single phenolic ring structure and differ in their side chain.

The important source of cinnamates reviewed by Clifford\(^{63} \) and divided into two categories i) a particular cinnamate (independent of the conjugate type and extent of hydrolysis in the gastrointestinal tract) and ii) a particular conjugate (Table 3).

<table>
<thead>
<tr>
<th>Class of compound</th>
<th>Main dietary source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(i) Cinnamates</strong></td>
<td></td>
</tr>
<tr>
<td>Caffeic acid</td>
<td>Coffee beverage, blueberries, apples, ciders</td>
</tr>
<tr>
<td>( p )-Coumaric acid</td>
<td>Spinach, sugar beet, cereal brans</td>
</tr>
<tr>
<td>Ferulic acid</td>
<td>Coffee, citrus juices, sugar beet fibre, cereal brans</td>
</tr>
<tr>
<td>Sinapic acid</td>
<td>Broccoli, kale, other leafy brassicas, citrus juices</td>
</tr>
<tr>
<td><strong>(ii) Conjugates</strong></td>
<td></td>
</tr>
<tr>
<td>Caffeoylquinic acids</td>
<td>Coffee beverage, blueberries, apples, ciders</td>
</tr>
<tr>
<td>( p )-Coumaroylquinic acids</td>
<td>Sweet cherries</td>
</tr>
<tr>
<td>Feruloylquinic acids</td>
<td>Coffee</td>
</tr>
<tr>
<td>Tartaric conjugates</td>
<td>Spinach, lettuce, grapes, wines</td>
</tr>
<tr>
<td>Malic conjugates</td>
<td>Lettuce, spinach, possibly legumes</td>
</tr>
<tr>
<td>Rosmarinic acid</td>
<td>Culinary herbs, mixed herbs, possibly stuffings</td>
</tr>
<tr>
<td>Cell wall conjugates</td>
<td>Spinach, sugar beet fibre, cereal brans.</td>
</tr>
</tbody>
</table>

**Table 3**: Important source(s) of (i) individual cinnamates (regardless of conjugate type) and (ii) each major class of conjugate.
Other cinnamate conjugates

Cinnamic acids may be conjugated to many molecules other than quinic acid and its close relatives. This second category includes:

1. esters of other hydroxy acids; particularly α-hydroxyhydrocaffeic, malic and tartaric but including galactaric, glucaric, gluconic, hydroxycitric, methoxyalderic, phenylpyruvic and tartronic
2. amides of amino compounds including aromatic amino acids, choline, anthranilic acids and diamines
3. esters of polysaccharides, simple sugars, sugar alcohols including glycerol and myo-inositol, and glycosides including those of anthocyanins, flavonols and diterpenes
4. esters of lipids including alkanols, alkandiois, hydroxy-fatty acids and sterols
5. glycosides.

Caffeic acid is the most predominant phenolic acid in sunflower seeds and greatly affects the solubility of plant protein. Chlorogenic acid and caffeic acid were found in potatoes, and their concentrations in the peel are higher than the concentrations in the flesh inside of the potatoes. These phenolic compounds are responsible for enzymatic browning and act as antioxidants in potatoes. It is well-known that chlorogenic acid makes up 5-10% of the weight of coffee beans and plays a significant role in coffee color and aroma formation. Ferulic acid occurs widely in grain foods and vegetables, and it is one of the major antioxidant constituents in beer. The occurrence of ferulic acid in orange juice is responsible for the off-flavor formation during storage. In rosemary and sage, two of the most important spices in meat processing, rosmarinic acid one of the principle antioxidative constituents.

Coffee beans are one of the richest dietary sources of CGA. During the roasting there is a progressive destruction and transformation of CGA with some 8-10% being lost every 1% loss of dry matter into domestic brew and commercial soluble coffee providers. It was found that a 200 ml cup of roast and ground coffee might supply from 20 mg CGA (weak brew, very dark roast) up to 675 mg CGA (strong brew, very pale roast robusta). It was also reported that some of the CGA lactones were present in coffee. The tea leaf the major dietary source of theogallin and it is accompanied by
small amounts of \( p \)-coumaroyl quinic acid and caffeoyl quinic acid. These substances are not substrates for tea polyphenol oxidase and appear to survive fermentation and can thus be found in black tea as well as green tea. There are no data for their contents in tea brew, but 10-50 gkg\(^{-1}\) has been reported for green and black tea leaf.\(^{75,76}\)

Matè is traditional South African beverage which is rich in caffeoyl quinic acid and di caffeoyl quinic acid. There have been few studies of the brew consumption but green mate material bought and brewed in Europe provided 107-133 mg CGA per approximately 200 ml of di caffeoyl quinic acid.\(^{77}\)

Apples are one of most studied pome fruits. The CGA compounds are found at similar concentrations in the isolated flesh and skin (30-60 mgkg\(^{-1}\)) but are absent from the seeds and pomace. Whole apple contains 62-385 gkg\(^{-1}\) 5-CGA, up to 40 mgkg\(^{-1}\) \( p \)-coumaroyl quinic acid and smaller amounts of caffeoyl-, \( p \)-coumaroyl- and ferruloyl-glucoses (up to 6, 6 and 9 mgkg\(^{-1}\), respectively). According to researchers, pears and pear juices are similar in consumption with some 60-280 mgkg\(^{-1}\) 5-CGA in whole fruit and up to 240 mgkg\(^{-1}\) in juice.\(^{78-83}\) Stone fruits contain 5-CGA and \( p \)-coumaroyl quinic acid in the range 150-600 mgkg\(^{-1}\) and 3-200 mgkg\(^{-1}\) respectively. Cherries and plums are rich in \( p \)-coumaroyl quinic acid compared with peaches and apricots.\(^{84}\)

Only a few quantitative data are available for berry fruits in the literature. Blueberries contain 0.5-2 gkg\(^{-1}\) Blackcurrants supply some 140 mgkg\(^{-1}\) of total conjugates. Blackberries provide some 70 mgkg\(^{-1}\) CGA. Raspberries, strawberries, redburrants and gooseberries are poor sources by comparison with berries mentioned before.\(^{85-87}\) Citrus fruits contain rare conjugates of glutaric (feruloyl, \( p \)-coumaroyl and diferuloyl) and galactaric acids and some associated lactones. All of these occur mainly in the peel (170-250, 27-62, 55-67 mgkg\(^{-1}\) in oranges, grapefruit and lemon respectively).\(^{88-89}\) The 3-caffeoyl quinic acid, 3-\( p \)-coumaroyl quinic acid and 3-feruloyl quinic acid have been reported in the leafy Brassica (kale, cabbage and Brussels sprouts) at level up to 6-120 mgkg\(^{-1}\), 104 mgkg\(^{-1}\) and 37 mgkg\(^{-1}\) respectively. Significant amounts of sugar derivatives have also been reported with feruloyl glucose and sinapoyl glucose dominating in kale and other leafy vegetables.\(^{80,86,87,94-97}\)

Amounts of cinnamates in certain food and beverages are presented in (Table 4).
Table 4: Amount of chlorogenic acids in foods and beverages

<table>
<thead>
<tr>
<th>Source</th>
<th>Amount</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coffee</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roast coffee</td>
<td>20-675 mg200ml⁻¹</td>
<td>74</td>
</tr>
<tr>
<td><strong>Tea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black tea</td>
<td>10-50 g/kg⁻¹</td>
<td>75, 76</td>
</tr>
<tr>
<td><strong>Mate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mate</td>
<td>107-133 mg200ml⁻¹</td>
<td>77</td>
</tr>
<tr>
<td><strong>Pome fruits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apple</td>
<td>62-385 mgkg⁻¹</td>
<td>78, 79, 80</td>
</tr>
<tr>
<td>Pear</td>
<td>60-280 mgkg⁻¹</td>
<td>81, 82, 83</td>
</tr>
<tr>
<td><strong>Stone fruits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cherries, apricot</td>
<td>150-600 mgkg⁻¹</td>
<td>84</td>
</tr>
<tr>
<td><strong>Berry fruits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blueberries</td>
<td>0.5-2 gkg⁻¹</td>
<td>85</td>
</tr>
<tr>
<td>Blackcurrants</td>
<td>140 mgkg⁻¹</td>
<td>86</td>
</tr>
<tr>
<td>Blackberries</td>
<td>70 mgkg⁻¹</td>
<td>87</td>
</tr>
<tr>
<td>Raspberries</td>
<td>20-30 mgkg⁻¹</td>
<td>85-87</td>
</tr>
<tr>
<td>Strawberries</td>
<td>20-30 mgkg⁻¹</td>
<td>85-87</td>
</tr>
<tr>
<td>Redcurrant</td>
<td>20-30 mgkg⁻¹</td>
<td>85-87</td>
</tr>
<tr>
<td>Gooseberries</td>
<td>20-30 mgkg⁻¹</td>
<td>85-87</td>
</tr>
<tr>
<td><strong>Citrus fruits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oranges</td>
<td>170-250 mgkg⁻¹</td>
<td>88, 89</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>27-62 mgkg⁻¹</td>
<td>88, 89</td>
</tr>
<tr>
<td>Lemon</td>
<td>55-67 mgkg⁻¹</td>
<td>88, 89</td>
</tr>
<tr>
<td><strong>Grapes and wines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grape juice</td>
<td>10-430 ml⁻¹</td>
<td>90</td>
</tr>
<tr>
<td>American wine</td>
<td>9-116 ml⁻¹</td>
<td>91</td>
</tr>
<tr>
<td><strong>Other fruits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pine apple</td>
<td>3 ml⁻¹</td>
<td>92</td>
</tr>
<tr>
<td>Kiwi</td>
<td>11 ml⁻¹</td>
<td>93</td>
</tr>
<tr>
<td><strong>Brassica vegetables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kale</td>
<td>6-120 mgkg⁻¹</td>
<td>94, 95</td>
</tr>
<tr>
<td>Cabbage</td>
<td>104 mgkg⁻¹</td>
<td>86, 87</td>
</tr>
<tr>
<td>Brussells sprouts</td>
<td>37 mgkg⁻¹</td>
<td>86, 87</td>
</tr>
<tr>
<td>Broccoli</td>
<td>60 ml⁻¹</td>
<td>96</td>
</tr>
<tr>
<td>Cauliflower</td>
<td>20 mgkg⁻¹</td>
<td>80</td>
</tr>
<tr>
<td>Radish</td>
<td>240-500 mgkg⁻¹</td>
<td>97</td>
</tr>
<tr>
<td><strong>Chenopodiaceae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinach</td>
<td>200 mgkg⁻¹</td>
<td>98</td>
</tr>
<tr>
<td><strong>Asteraceae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lettuce</td>
<td>50-120 mgkg⁻¹</td>
<td>99</td>
</tr>
<tr>
<td>Endive</td>
<td>200-500 mgkg⁻¹</td>
<td>83</td>
</tr>
<tr>
<td>Chicory</td>
<td>20 mgkg⁻¹</td>
<td>83</td>
</tr>
<tr>
<td><strong>Solanaceae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potato</td>
<td>500-1200 mgkg⁻¹</td>
<td>100</td>
</tr>
<tr>
<td>Aubergines</td>
<td>600 mgkg⁻¹</td>
<td>83</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>10-80 mgkg⁻¹</td>
<td>101</td>
</tr>
<tr>
<td><strong>Apiaceae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrot</td>
<td>20-120 mgkg⁻¹</td>
<td>102</td>
</tr>
<tr>
<td><strong>Cereals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barley bran</td>
<td>50 mgkg⁻¹</td>
<td>103</td>
</tr>
<tr>
<td>Rice</td>
<td>12 gkg⁻¹</td>
<td>104</td>
</tr>
</tbody>
</table>
**Cinnamate transformation products**

There is little information on cinnamate transformation during food preparation and processing. It has been established that cinnamic acids may be released from conjugates by hydrolysis and subsequently decarboxylated either by heat\(^{105}\) or microorganisms yielding various alkylphenols. Possibly the first to be recognised was the grape reaction product (GRP) 2-S-glutathionylcaftaric acid and 2,5-di-S-glutathionylcaftaric acid formed from caftaric acid (caffeoyl tartaric acid) during wine making.\(^{106,107}\) Red wine contains adducts formed by the interaction of anthocyanins with vinyl phenol from \(p\)-coumarate decarboxylation\(^{108}\) and caffeic acid released during coffee roasting is partially converted to tetrahydroxy-phenylindans.\(^{109}\) Hydrolysis of CGA during coffee roasting also releases the quinic acid residue (\textit{vide supra}) which is then converted to the full theoretical complement of quinic acid and quinic lactone (quinide) diastereoisomers.\(^{110}\) Unhydrolysed CQA and FQA can be converted similarly to the corresponding 1,5- lactones or quinides\(^{111}\) and possibly other diastereoisomers, either of the lactones or the original acids, might also be formed.

**Analytical methods for determination of chlorogenic acids**

Chlorogenic acid has attracted continuous attention since it was first detected in coffee by Robiquet and Boutron in 1837.\(^{112}\) It is extremely widely distributed among higher plants and in some cases is found in surprisingly high concentrations. An additional reason for the sustained interest is that a great many closely related intramolecular esters of hydroxy acids and aromatic acids have been discovered and that this group of substances has a vast diversity of effects on biological reactions in vitro. In 1821 caffeine was isolated by the French chemist Pierre Jean Robiquet and demonstrated to be the compound responsible for the stimulating effects of coffee. The problem with isolating caffeine from coffee was that there were other substances that must be separated from the caffeine. When isolating caffeine from coffee, the primary impurities were tannins, glucose, and chlorogenic acid (5-CQA). The tannins and 5-CQA are acidic, and they can be converted to the salts. Chlorogenic acid itself is generally isolated from coffee as the caffeine complex of the potassium salt.\(^{113}\)
Scientists such as Lampadius (1832), Robiquet and Bouteron (1837), suspected the presence and identity of volatile acids by smell and by simple intuition.\textsuperscript{114} The early isolation and identification of non-volatile crystalline members such as quinic acid was facilitated by their crystallization.\textsuperscript{115} Freudenberg in 1920 reported that the enzyme tannase hydrolysed chlorogenic acid to equimolar quantities of caffeic and quinic acid.\textsuperscript{116} In 1932 Fischer and Dangschat concluded that chlorogenic acid was 3-caffeoylquinic acid.\textsuperscript{117} Under current IUPAC recommendations it is now designated 5-caffeoylquinic acid.\textsuperscript{118} In 1950 Barnes announced that 5-CQA was not the only component in the chlorogenic acid fraction, by the isolation from coffee beans of a fraction called isochlorogenic acid. Barnes et al. were of the opinion that isochlorogenic acid is isomeric with chlorogenic acid and that the caffeoyl group is substituted on the 5-OH group of quinic acid.\textsuperscript{119} Thus Bean and Corse point out that an enhancement of conductance of a chlorogenic acid isomer in boric acid solution can be due to either the presence of vicinal hydroxyls or to alpha hydroxyl carboxylic acid groups.\textsuperscript{120} Williams showed that the chlorogenic acid and other cinnamic acid derivatives give two spots due to the separation of the cis- and trans-isomers.\textsuperscript{121} Paper chromatography of quinic acid has also led to the appearance of multiple spots, attributable, in part at least, to the formation of the 3-1actone.\textsuperscript{122} The observation by Butler and Siegelman that caffeic acid (3,4-dihydroxycinnamic acid) is partially oxidized to esculetin during paper chromatography points to another possible source of artifact formation.\textsuperscript{123} Cellulose columns,\textsuperscript{124} thin layer chromatography\textsuperscript{125} and electrophoresis\textsuperscript{126} have also been employed. Ion exchange chromatography on the conventional polystyrene resins is unsuited for the fractionation of chlorogenic acids because of poor recoveries. Apparently the phenolic moiety is very strongly bound to the resin, and a certain amount of irreversible adsorption occurs. These shortcomings can probably be overcome by the use of modified cellulose ion exchange materials, e.g., diethylaminoethylcellulose and carboxymethylcellulose. Silica gel columns are particularly well adapted for work with chlorogenic acids. Using dilute aqueous sulfuric acid as the stationary phase and a chloroform-butanol mixture, in which the butanol content was increased stepwise, Sondheimer separated the chlorogenic acids into four distinct bands.\textsuperscript{127} This procedure has yielded quantitative information on the distribution patterns of the chlorogenic acids in different plants, and has also been
used in the isolation of chlorogenic acid and related compounds from unroasted coffee beans.\textsuperscript{128} A refinement of this method, employing a linear solvent gradient with cyclohexane, t-butyl alcohol and chloroform, has been described by Hanson and Zucker.\textsuperscript{129} Zucker found out that there is danger of rearrangements because of trans-esterifications during the isolation of the chlorogenic acids and this seems to be more likely to occur with bases than under acidic conditions.

Titration experiments and infrared absorption spectra of isochlorogenic acid have failed to support the claim for a mobile equilibrium between an open acid form and a lactone. Also, evidence has become available that isochlorogenic acid, as purified by the procedure of Barnes et al., is still heterogeneous and can be subdivided by chromatographic techniques into several fractions.\textsuperscript{130}

Hanson reported optical rotatory dispersion (ORD) data for quinic acid and CiQA, but the complex curves were not interpreted.\textsuperscript{131} Gaffield reported and discussed ORD data for quinic acid, quinide and several derivatives. The conformational implications were consistent with the available NMR data.\textsuperscript{132} Mass spectra for 3-CQA, 4-CQA, 5-CQA and 1,5-diCQA have been published by Bombardelli and König and Sturm.\textsuperscript{133,134} NMR spectra of quinic acid and many derivatives including some lactones and chlorogenic acids were reported extensively by Corse and his colleagues.\textsuperscript{135,136,137} UV spectra of various chlorogenic acids was reported by several authors.\textsuperscript{138,139} Gas chromatograph method for chlorogenic acids was published by Kung, Müller and Herman.\textsuperscript{140,141}

Hanson and Zucker applied low pressure column chromatography to the separation of chlorogenic acids. They used cyclohexane-chloroform (10:90) and t-butylalcohol-chloroform (10:30).\textsuperscript{142} The earliest chlorogenic acid analyses by HPLC were published by Court, Rees and Theaker. Van der Stegen and Van Duijn achieved a separation of twelve chlorogenic and two cinnamic acids.\textsuperscript{143,144,145} Later on this system with minor variations was widely adopted.\textsuperscript{146,147,148,149} Engelhardt et al. developed an HPLC method that allowed the determination of mono and dicafeoylquinic acids along with corresponding lactones and ferruloylquinic acids, in roasted coffee in one chromatographic run. The elution order was verified by isolation of individual compounds by preparative HPLC, chromatography of the fractions on the analytical HPLC system, NMR spectroscopy and thermospray LC-MS.\textsuperscript{150}
Clifford has reported a new rapid isocratic reversed phase system for routine work which will resolve nine characterized chlorogenic acids, three cinnamic acid and caffeine.\textsuperscript{151} The fragmentation behaviour of eighteen chlorogenic acids that are not substituted at position 1 has been investigated using LC-MS\textsuperscript{4}.\textsuperscript{152} Clifford \textit{et al.}\textsuperscript{153} also investigated the fragmentation behaviour of all six dicafeoylquinic acid by using LC-MS\textsuperscript{4}, the hierarchial key was proposed to facilitate this process.

**Functions of hydroxycinnamic acids in plants**

Due to their antioxidant and antibiotic properties, hydroxycinnamoylquinic acids are involved in numerous biological plant functions such as pest and disease resistance.\textsuperscript{154, 155}

Mono and di caffeoylquinic acids are involved in insect resistance in different cultivated species.\textsuperscript{156, 157} Chlorogenic acid also appears to be involved in the response to different abiotic stresses.\textsuperscript{158} Caffeoylquinic acids are potent antioxidants that are synthesized in response to oxidative stresses, and act particularly against lipid peroxidation.\textsuperscript{159, 160} Hydroxycinnamoylquinic acids are involved in a broad range of stress responses. Like other phenolics, they are accumulated inside vacuoles or in the apoplast during leaf ageing, and their biosynthesis apparently occurs within chloroplasts since the last enzyme that catalyses their biosynthesis is described as chloroplastic.\textsuperscript{161}

Hydroxycinnamic acids also have the potential to link with cell wall proteins via tyrosine or cysteine residues.\textsuperscript{162, 163} Covalently-bound hydroxycinnamates have been implicated in reducing the digestibility of cell walls through restricting the accessibility of carbohydrases.\textsuperscript{164} Monomeric and dimeric hydroxycinnamates may act as nucleation sites for lignification in grasses.\textsuperscript{165, 166} There is circumstantial evidence that ferulate dehydrodimers are involved in cell-cell adhesion.\textsuperscript{167} Using model compounds it has been demonstrated that ferulic acid has the potential to cross-link polysaccharides and lignin through covalent ester-ether bridges.\textsuperscript{168} It was demonstrated that ferulic acid can be transferred from feruloyl-CoA to a polysaccharide, implicating a feruloyl-CoA-oligosaccharide feruloyltransferase.\textsuperscript{169} Chlorogenic acid is a secondary metabolite synthesized in many plants. Chlorogenic
acid is implicated in free radical scavenging, inhibition of lipid peroxidation, enzymatic browning of fruits and vegetables, antifungal activity, and host-plant resistance against insects.

**Biosynthesis of chlorogenic acids in plants**

Three distinct pathways have been proposed for the synthesis of CGA: (1) the trans-esterification of caffeoyl-CoA and quinic acid via hydroxycinnamoyl-CoA:quinate hydroxycinnamoyl transferase (HQT) activity; (2) the hydroxylation of p-coumaroyl quinate to CGA; and (3) the hydroxylation of p-coumaroyl shikimate to caffeoyl shikimic acid, which is then converted to caffeoyl-CoA, a substrate of hydroxycinnamoyl-CoA:shikimate hydroxycinnamoyl transferase HCT. The order of events can vary among plant systems, but previous studies have suggested the pathway shown in Figure 13.

The formation of hydroxycinnamic acids (caffeic, ferulic, 5-hydroxyferulic and sinapic acids) from p-coumaric acid requires two types of reactions: hydroxylation and methylation. The introduction of a second hydroxyl group into p-coumaric acid to give caffeic acid is catalysed by monophenol mono-oxygenases, a well-known group of plant enzymes. Methylation of caffeic acid leads to the formation of ferulic acid which, together with p-coumaric acid, are the precursors of lignins. The methylation is catalysed by an O-methyltransferase. Caffeic acid is the substrate for rare 5-hydroxyferulic acid, which yields sinapic acid as a result of O-methylation. The formation of hydroxycinnamic acid derivatives requires the formation of hydroxycinnamate-CoAs (e.g. p-coumaroyl-CoA) catalysed by hydroxycinnamoyl-CoA ligases or by the action of O-glycosyl transferases. The hydroxycinnamate-CoA enters various specific phenylpropanoid reactions, such as condensations with malonyl-CoA leading to flavonoids or NADPH-dependent reductions leading to lignins. Moreover, hydroxycinnamate-CoA species can conjugate with organic acids. In the biosynthesis of sugar derivatives of hydroxycinnamic acids, the transfer of glucose from uridine diphosphoglucose to hydroxycinnamic acid is catalysed by glucosyl transferase.
Figure 13: A simplified diagram of enzymes and major products in the synthesis of chlorogenic acid in plants. The product names appear between the arrows. Enzymes involved in this pathway are PAL:, phenylalanine ammonia lyase; C4H, cinnamate 4-hydroxylase; 4CL, 4-hydroxycinnamoyl-CoA ligase; HCT, hydroxycinnamoyl-CoA shikimate/quinate hydroxycinnamoyl transferase; HQT, hydroxycinnamoyl CoA quinate hydroxycinnamoyl transferase; C3’H, p-coumaroyl ester 3’-hydroxylase.
Chlorogenic acid is a product of the phenylpropanoid biochemical pathway and the first step in the phenylpropanoid pathway involves the deamination of phenylalanine to cinnamate via the enzyme phenylalanine ammonia lyase (PAL). Phenylalanine ammonia lyase RNA levels respond to several regulatory signals, and were reported to be a main factor affecting CGA levels in transgenic systems. Synthesis of CGA from cinnamate requires four enzymes to complete two hydroxylations on the aromatic ring and a conjugation of the hydroxycinnamate and quinate moieties: cinnamate-4-hydroxylase (C4H), 4-coumaroyl-CoA ligase (4CL), coumaroyl-CoA:quinate hydroxycinnamoyl-transferase (HQT), and coumarate/coumaroylquininate-3-hydroxylase (C3H).\textsuperscript{182,183}

**Metabolism of chlorogenic acids and health**

Dietary polyphenols when tested in animals or humans affect various physiologic and physiopathologic processes, but the exact nature of the active compounds is still unknown. Knowledge concerning the absorption of chlorogenic acid in humans is essential to evaluate possible health effects in vivo because the absorbed fraction of chlorogenic acid will enter into the blood circulation and thus can induce biological effects in the blood circulation. Furthermore, the fraction that is not absorbed will enter into the colon where it might have biological effects.

Like other dietary polyphenols, chlorogenic acids are an antioxidant. In vitro, it scavenges radicals generated in the aqueous phase,\textsuperscript{184,185} increases the resistance of LDL to lipid peroxidation\textsuperscript{186,187,188} and inhibits DNA damage.\textsuperscript{189,190} In vivo, when added to the diet, it inhibits chemically induced carcinogenesis of the large intestine, liver and tongue in rats and hamsters.\textsuperscript{191,192,193,194}

Caffeic acid and chlorogenic acids have antioxidant properties, illustrated by their ability to scavenge various free radicals when tested in vitro.\textsuperscript{195,196,197,198,199} In vivo, when ingested with the diet, caffeic acid and chlorogenic acid increase the plasma antioxidant capacity, the concentrations of endogenous antioxidants such as vitamin E and the \textit{ex vivo} resistance of lipoproteins to oxidation.\textsuperscript{200,201,202} Chlorogenic acids also are able to reverse the pro-oxidant effects of drugs such as paraquat.\textsuperscript{203} Chlorogenic
acid and caffeic acid have been reported to prevent different cancers and CVD in several experimental studies on animal models.\textsuperscript{204,205,206,207,208} The biological properties of hydroxycinnamic acids depend on their absorption in the gut and on their metabolism. The absorption of caffeic acid in the small intestine has been well characterized in both experimental animals and in man,\textsuperscript{209,210,211} but the bioavailability of chlorogenic acid is more controversial. In some studies, chlorogenic acid has been detected in urine with a recovery varying from 0·3\% to 2·3\%, suggesting absorption without structural modification.\textsuperscript{212,213} Other authors have failed to detect chlorogenic acid in the plasma of both rats and man after its ingestion as a pure compound or in coffee.\textsuperscript{214,215,216} Caffeic acid and its O-methylated metabolites are commonly found in plasma and urine after ingestion of chlorogenic acid in rats and man, showing that chlorogenic acid is hydrolysed in the body.\textsuperscript{217,218} Such a reaction could either take place in the gut mucosa or arise from catalysis by the gut microflora. No esterase activity able to hydrolyse chlorogenic acid could be detected in human tissues (intestinal mucosa, liver) or biological fluids (plasma, gastric juice, duodenal fluid) in rats or man.\textsuperscript{219,220,221,222,223} On the other hand, microflora in the large intestine possess esterase activity towards chlorogenic acid.\textsuperscript{224,225} These results suggest that caffeic acid found in plasma originates from the hydrolysis of chlorogenic acid in the colon.

**Mechanisms of absorption**

The absorption of caffeic acid esterified with quinic acid (chlorogenic acid) was less than that of caffeic acid itself. It is possible that chlorogenic acid and caffeic acid are absorbed through different absorption mechanisms. There are two possible mechanisms for the absorption of chlorogenic acid in humans. The first mechanism might involve absorption of chlorogenic acid as an intact molecule as indicated by the presence of traces of chlorogenic acid in urine after ingestion of chlorogenic.\textsuperscript{226} The second mechanism might involve hydrolysis of chlorogenic acid in the stomach and/or small intestine into caffeic acid and quinic acid before absorption. The caffeic acid moiety and the quinic acid moiety are subsequently absorbed.\textsuperscript{227,228} The general pathway of chlorogenic acid metabolism in rats is shown in Figure 14.
Figure 14: General pathway of chlorogenic acids metabolism in rats. Bold arrows indicate reactions carried out by the gut microflora.

The other metabolites formed from chlorogenic acid were similar to those observed after caffeic acid intake and thus derive from the metabolism of the caffeic acid moiety. Caffeic acid is the direct product of chlorogenic acid hydrolysis, and ferulic and isoferulic acids are tissular metabolites formed by methylation of caffeic
acid.\textsuperscript{229,230} \textit{m}-Coumaric acid and hydroxylated derivatives of phenylpropionic, benzoic and hippuric acids derive from the metabolism of caffeic acid by the microflora. \textit{m}-Coumaric acid is formed by dehydroxylation, and 3,4-dihydroxyphenylpropionic and 3-hydroxyphenyl-propionic acids by hydrogenation and dehydroxylation.\textsuperscript{231,232,233} Their microbial origin was clearly established by suppression of their formation in rats treated with antibiotics\textsuperscript{234,235} and in germ-free rats.\textsuperscript{236,237,238} 3-hydroxyphenylpropionic acid is further dehydroxylated in part by the microflora and \(\beta\)-oxidized in tissue to form benzoic acid or directly \(\beta\)-oxidized once absorbed, yielding 3-hydroxybenzoic acid.\textsuperscript{239,240,241,242,243} Subsequent tissular conjugation of benzoic acid metabolites with glycine leads to the formation of 3-hydroxyhippuric and hippuric acids.\textsuperscript{244}

**Chemical synthesis of chlorogenic acids**

The selective syntheses of chlorogenic acids are fairly complex, although the individual steps which are summarised in the literature are relatively simple. All methods described in the literature involved condensing an acid chloride with a derivative of quinic acid. Subsequently the condensation products are hydrolysed with acid, and the resulting chlorogenic acids are isolated either directly, or after purification by means of column chromatography or CCD. Protection is required to prevent unwanted reactions, such as self-condensation of the acid chloride. Protection is required on aromatic hydroxyl groups in the acyl chloride, the quinic acid carboxyl group and usually one or more of the quinic acid hydroxyl groups. Ideally the protecting groups should be easily removed in dilute acid since the CGA are particularly unstable in base.

Quinide was synthesised from quinic acid by Wolinski \textit{et al.}\textsuperscript{245} The quinic acid was heated at 230º C for 90 min in an open flask. The resulting orange/brown glassy solid was recrystallised from absolute ethanol to give (-) quinide in 24% yield.

Most research groups have protected hydroxyl groups, where present, by preparing ethoxycarbonyl derivatives by the method of Son.\textsuperscript{246} This protection can be removed by treatment with hydrazine hydrate in methanol, preferably before removing the protection on the esterified hydroxyl groups in the quinic acid residue to minimise
acyl migration and saponification of the ultimate CGA.\textsuperscript{247} Haslam \textit{et al.}\textsuperscript{248} preferred benzoylation with removal by palladium-charcoal hydrogenation for the oxidation sensitive CQA. The protected aromatic acids can be converted to acyl chlorides by treatment with sulphonyl chloride.\textsuperscript{247}

**Protection of Quinic acid**

Different protection processes for selective hydroxyl groups were suggested by different authors in literature. Some of the protection process for specific hydroxyl groups as summarised below.

**Carboxy protection**

Protection of the carboxy group was suggested by de Pooter \textit{et al.} as esterification with diazodiphenylmethane and has been widely used by other authors.\textsuperscript{247}

**Protection of hydroxyl groups**

1) for 1-acyl CGA: One-step protection can be achieved by boiling quinic acid in acetone in the presence of p-toluenesulphonic acid (TsOH).\textsuperscript{247} During the reaction the solvent was continuously dried by means of molecular sieves. The 3,4-isopropyledene can be used without isolation. The C-1 hydroxy group of the quinide is in the accessible equatorial conformation.

2) for 5-acyl CGA: It was reported that the 3,4-isopropyledenequinide may be converted to the free acid by boiling with NaHCO\textsubscript{3}. The C-1 carboxy group should be protected, as previously described, prior to esterifying the equatorial C-5 hydroxy group using mild conditions.\textsuperscript{249}

3) for 3-acyl and 4-acyl CGA: The specific synthesis of 3-acyl and 4-acyl CGA is available in the literature. Mixtures of 3-acyl CGA and 4-acyl CGA have been prepared as separated chromatographically. Scarpati \textit{et al.}\textsuperscript{250} used an excess of quinide in the synthesis of CQA whereas Zane and Wender\textsuperscript{251} used 1-ethoxycarbonyl quinide in the synthesis of FQA. A more convenient method might be the isomerisation of the appropriate 5-acyl CGA.
4) for 1-substituted diacyl CGA: de Pooter et al.\textsuperscript{249} suggest that 1,3-diacyl CGA will be the easily synthesised member of this CGA subgroup. The use of quinide would permit access to the equatorial hydroxy groups at C-1 and C-3 while limiting access to the axial hydroxyl group at C-4. Even if 1,4-diacylation occurs, a high yield of the 1,3-diacyl CGA might still be achieved since it has been reported that 1,4-diCQA rapidly isomerises to 1,3-diCQA.\textsuperscript{252} Scarpati et al.\textsuperscript{250} reported a synthesis of 1,5-diCQA. Adapting their method slightly to take account of the papers by de Pooter et al. indicates that diphenylmethyl-3, 4-isopropyledene quinate would be a suitable precursor.

For the synthesis of 1,4-diCQA, Panizzi and Scarpata\textsuperscript{252} blocked the C-3 equatorial hydroxy group of quinide with dihydropyran. This reaction carried out in tetrahydrofuran, gave a mixture with a poor yield of the desired quinic acid derivative Alberti et al.\textsuperscript{253} reported that 1,3,4-triCQA could be selectively saponified using barium hydroxide to yield 1, 4-diCQA. Another approach would be controlled isomerisation of 1, 5-diCQA.

5) for 3,4-diacyl CGA: Quinide, prepared by heating quinic acid dioxan containing dry hydrochloric acid as described as Panizzi et al.\textsuperscript{254} is a suitable precursor. A simpler method might be quinic acid at 230º C for 9 min as described by Wolinsky et al.\textsuperscript{255}

6) for poly-acyl CGA: Alberti et al.\textsuperscript{253} prepared 1,3,4-triCQA from quinide, and Haslam et al.\textsuperscript{256} prepared 3,4,5-triCQA from 1-benzyl-diphenylmethylquinate and used diphenylmethylquininate in the preparation of 1,3,4-tetraCQA.
Reported Synthesis of chlorogenic acids in literature

**Synthesis of 5-caffeoylquinic acid**

The first efficient synthesis of 1-caffeoylquinic acid was published by Panizzi.\textsuperscript{264} Chlorogenic acid was synthesized by condensation of caffeoyl chloride with the methyl ester of 1-carboethoxy-4,5-acetonequinide by the successive action of \( \text{Ba(OH)}_2 \) and \( \text{CH}_2\text{N}_2 \). The protector groups present in the condensation product are removed by processes of mild controlled hydrolysis at room temperature, first in acid, then in alkaline solution \( \text{Ba(OH)}_2 \) and 1-carboethoxy-4,5-acetonequinide were processed to give 1-carbethoxy-4,5-acetonequinic acid, thick white prisms which were very soluble in cold \( \text{H}_2\text{O} \), MeOH, EtOH, slightly soluble in cold AcOEt and very little soluble in \( \text{C}_6\text{H}_6 \).

The methyl ester of 1-carbethoxy-4,5-acetonequinic acid, prepared with \( \text{CH}_2\text{N}_2 \) as a colourless viscous oil. Caffeoyl chloride and methyl ester of 1-carbethoxy-4,5-acetonequinic acid gave the methyl ester of 1-carbethoxy-3-caffeoylquinic acid, white, microcrystalline solid. \( \text{Ba(OH)}_2 \) with 1-carbethoxy-3-caffeoylquinic acid gives 3-caffeoylquinic acid. (Later on under IUPAC recommendations this was called 5-caffeoylquinic acid). The product was purified by column chromatography using 40% BuOH, 10% AcOH, and 50% H2O by volume. 5-caffeoylquinic acid was obtained as small white thin needles. Reaction was achieved in seven steps and overall yield was very low (5%). Haslam at al achieved to synthesise the same compound from six steps.

**1-O-p-coumaroylquinic acid**

Haslam at al.\textsuperscript{257} was obtained 1-O-p-coumaroylquinic acid by refluxing 1-O-(O-acetyl-p-coumaroyl)-4,5-O-isopropyledenequinide in acetone and 3 N hydrochloric acid (1:1 by volume) for 2.5 hours.
**1-O-caffeoylquinic acid**
Rúveda\(^{258}\) obtained 1-O-caffeoylquinic acid by heating 1-O-caffeoylquininide in 0.1 N HCl at 100º C for 15 min.

**1-O-galloylquinic acid**
Haslam et al.\(^{259}\) obtained 1-O-galloylquinic acid, by heating aqueous 1-O-galloylquinide at 100º C for 40 hours.

**Synthesis of 3-O-cinnamoyl and 3-O-p-coumaroylquinic**
Levy and Zucker\(^{260}\) proved that 3-O-cinnamoyl and 3-O-p-coumaroylquinic acids are intermediates in the biosynthesis of chlorogenic acid. 1-O-Cinnamoylquinic acid was previously obtained by Josephson\(^{261}\) who treated (2) with HCl in aqueous acetone and isolated 1-O-cinnamoyl-quinide together with a small quantity of (5) as shown in Figure 15. Lactone opening under acidic conditions has been employed as the final step in the synthesis of the corresponding caffeoyl, p-coumaroyl, and galloyl compounds.

![Figure 15: Synthesis of 1-O-cinnamoylquinic acid](image-url)
1-O-Cinnamoylquinic acid

1-O-Cinnamoylquinic acid (5) was synthesised by Hanson\textsuperscript{262} as shown in Figure 15. The isopropyledene group was removed from the acid (4) either by leaving a solution of the acid at room temperature overnight or by heating a solution for 3 hours at 100º C. The yield in this step was essentially quantitative. In control experiments the O-cinnamoylquinic acid believed to be the 3- and 5- isomers. Recrystallisation of the product from ethyl acetate-ethanol gave short prisms of 1-O-Cinnamoylquinic acid (5).

3-O-Cinnamoylquinic acid

Attempts to prepare 1-O-Ethoxycarbonyl-4,5-O-isopropylidenequinic acid (7) was described by Panizzi were unsuccessful, Haslam\textsuperscript{263} also reported an improved preparation of this compound. 3-O-Cinnamoylquinic acid (10) was again synthesised by Hanson\textsuperscript{262} as shown in Figure 16. The route was developed by Haslam et al\textsuperscript{263} for the preparation of 3-O-p-coumaroylquinic acid and subsequently employed to synthesise the corresponding galloyl compound. Scarpati et al.\textsuperscript{264} in their earlier study of the synthesis of chlorogenic acid employed a methyl group, rather than the acid-labile diphenylmethyl group, to block the carboxyl function. The conditions required to remove the protecting groups from (9) were investigated with the aid of the analytical silica gel column. 1-O-Ethoxycarbonyl-4,5-O-isopropylidenequinic acid (7) was synthesized in 85 \% yield the same way as Josephson.\textsuperscript{261} Then diphenylmethyl 3-O-Cinnamoyl-1-O-ethoxycarbonyl-4,5-O-isopropylidenequinate (9) was prepared by reacting Diphenylmethyl 1-O-ethoxycarbonyl-4,5-O-isopropylidenequinate (8) in pyridine with cinnamoyl chloride and chloroform. Reaction mixture was left at 25º C for 2 days and than refluxed for 2 hours with 3 ml methanol. Recrystallisation of the crude product from alcohol-acetone and benzene-petroleum ether gave the fine needles of (9).

When (9) was heated in 50 \% acetic acid at 100º C for 2 hours, the major product was 3-O-cinnamoylquinic acid (10). Hanson found out that when methyl 3-O-isopropylidenequininate was heated (with CH\textsubscript{3} in place of Ph\textsubscript{2}HC-) at 100º C in 50 \% acetic acid for 2,3 or 5 hours, only the isopropylidene group was removed.
Figure 16: Synthesis of 3-O-cinnamoylquinic acid

4- and 5-O-Cinnamoylquinic acid

A mixture of the four possible mono O-cinnamoylquinic acids was obtained by treating 1-O-cinnamoylquinide (11) in dioxane with 1 equiv of aqueous barium hydroxide at 40°C for 15 minutes. The reaction mixture was then concentrated to one-third of its volume, sufficient 5N sulfuric acid was added to precipitate all of barium, and the suspension was further concentrated to give a sticky gum (Figure 17). The mixture of compounds was separated with analytical column which was introduced by Hanson and Zucker,265 800 ml of acid-equilibrated cyclohexane-chloroform (10:90 by volume).
Figure 17: The action of barium hydroxide on 1-O-cinnamoylquinide

**Synthesis of 1-, 4- and 5-O-p-coumaroylquinic acid**

Haslam *et al.*\(^{266}\) obtained 4- and 5-O-p-coumaroylquinic acids by the condensation of O-acetyl p-coumaroyl chloride with an equimolar proportion of 1-O-ethoxycarbonyl quinide (15: \(R^4=R^5=, R^1=\text{ethoxycarbonyl}\)) as shown in Figure 18. The intractable mixture of esters which resulted was treated directly with acetic acid to hydrolyse the lactone and ethoxycarbonyl groups and then with ammonia at 0º C to remove the acetyl group. Alternatively, hydolysis of the mixed ester condensation product gave a product identified by titration which was 5-O-p-coumaroyl-1-O-ethoxycarbonylquinic acid (14; \(R^1=\text{ethoxycarbonyl}, R^2=R^3=R^4=H, R^5=p\)-coumaroyl), and which on hydrolysis with water or acetic acid gave 5-O-P-coumaroylquinic acid. Selective hydrolysis of the di-ester (15; \(R^1=\text{ethoxycarbonyl}, R^4=R^5=p\)-coumaroyl) gave poor yields of both 4- and 5-O-p-coumaroyl quinic acid. 1,3,4,5-tetra GQA was prepared by using diphenylmethyl and 4-5-O-isopropyledeene protection.
First step was to prepare 1-O-(O-Acetyl-p-coumaroyl)-4,5-O-isopropylidenequinide which was obtained by recation O-acetyl-p-coumaroyl chloride and 4,5-O-isopropylidenequinide in benzene containing pyridine refluxed for 5 hours. 1-O-(O-acetyl-p-coumaroyl)-4, 5-O-isopropylidenequinide was then dissolved in acetone containing 3N HCl and refluxed for half an hour to produce 1-O-p-coumaroylquinic acid.

1-O-p-coumaroylquinic acid was used to prepare 5-O-p-coumaroylquinic acid. A solution of 1-O-p-coumaroylquinic acid in acetone containing dry HCl was slowly stirred at room temperature for 2 days, barium carbonate was added and stirred for further 3 days to prepare 1-O-p-coumaroyl-4,5-isopropylidenequinide. A solution of O-acetyl-p-coumaroyl chloride and 1-O-ethoxycarbonylquinide in benzene containing pyridine was refluxed for 3 hours to prepare 5-O-p-coumaroyl-1-O-ethoxycarbonylquinic acid (14: R^1=ethoxycarbonyl, R^2=R^3=R^4=H, R^5=caffeoyl). This was then refluxed for 4 hours in water to give 5-O-p-coumaroylquinic acid. Haslam has to set up several step reactions in order to reach the final compound therefore the overall yield for the final product was very low (3%).

Haslam also introduced an alternative way to synthesise 4- and 5-O-p-coumaroyl quinic acids although yield was low. To a solution of 1-O-ethoxycarbonylquinide in chloroform containing pyridine a solution of O-acetyl-p-coumaroyl chloride in chloroform was added during 1 hour. The mixture was left at room temperature for 15 hours and diluted with additional of 200 ml chloroform. Paper chromatography showed that the two isomers were present and they separated by extraction and crystallisation. Treatment of 1-O-ethoxycarbonylquinide with 3,4-diacetoxycinnaoyl

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**Figure 18:** Structures for synthesis of 1-, 4- and 5-O-p-coumaroylquinic acid
chloride gave a mixture of esters which after a treatment with acid gave 5-O-caffeoyl-
1-O-ethoxycarbonylquinic acid (14; R1: ethoxycarbonyl, R2=R3=R4=H, R5=caffeoyl). Hydrolysis of the later with water and isolation of the products gave 5-O-
caffeoylquinic acid.

3-O-o-Coumaroyl, 3-O-Feruloyl and 3-O-Sinapyl –D-(−) quinic acid

3-O-o-coumaroyl (20), 3-O-feruloyl (21) and 3-O-sinapyl –D-(−) quinic acid (22) were synthesised by de Pooter et al.267 as shown in Figure 19. In the first step 4,5-O-
isopropyledenequinide (A) was transformed into 4,5-O-isopropyledenequinic acid. This compound was then immediately, without further purification, treated with diphenyl diazomethane, resulting in the formation of diphenylmethyl 4,5-O-
isopropyledenequininate (B). Then (B) was condensed with O-methoxycarbonyl-o-
coumaroyl chloride (16), O-ethoxycarbonyl ferulyl chloride (17) or O-
ethoxycarbonylsinapyl chloride (18), affording the corresponding protected intermediates (19). Subsequently, these intermediates were first treated with hydrazine hydrate (for removal of the protecting group), and then with a mixture of acetic acid-
formic acid-water at 100º C. After purification, 3-O-o-coumaroyl (20), 3-O-feruloyl
(21) and 3-O-sinapyl-D-(−)-quinic acid (22) were isolated as crystalline substance. Under current IUPAC recommendations these compounds now called as 5-O-o-
coumaroyl, 5-O-feruloyl and 5-O-sinapyl-D-(−)-quinic acids.

Pooter et al. demonstrated that wasn’t necessary to protect the axial C-1 hydroxy group of quinic acid, provided that mild conditions are employed during the subsequent esterification step, has eliminated a troublesome, destructive protection of the C-1 hydroxyl group. If this observation is generally applicable to all axial hydroxyl groups in quinic acid derivatives, then the ideal quinic acid derivatives to used to in synthesis are those in which the hydroxyl groups to be esterified is equatorial and all others are axial. In quinic acid the axial hydroxyl groups are C-1 and C-3 but at C-4 in the easily prepared quinide and its derivatives.
**Figure 19:** Synthesis of 3-O-o-Coumaroyl, 3-O-Feruloyl and 3-O-Sinapylquinic acid (Under new IUPAC recommendations 3-O-o-Coumaroyl, 3-O-Feruloyl and 3-O-Sinapylquinic acid designated to 5-O-o-Coumaroyl, 5-O-Feruloyl and 5-O-Sinapylquinic acid)
Synthesis of 1-, 4-, 5-Caffeoylquinic acid with different approach

Sefkow et al.\textsuperscript{268} introduced a short and efficient regioselective synthesis by kinetic acetalisation. All quinic acid derivatives were prepared by esterification of suitable caffeic and quinic acid derivatives. Di-acetyl caffeoyl chloride 27 was used as the acylating agent. Esterifications followed by a two step hydrolysis of all protecting groups. In this approach a protected quinic acid derive, bisacetonide 25, was used, which was gained as the main product from the kinetic acetalization of the penta silylterivate 24 of (-)-quinic acid 23. For this acetalization a reagent mixture of acetone, 2,2-dimethoxypropane (DMP) and trimethylsilyl trifluoromethanesulfonate (58:17:18) was given to the penta silylderivate 24 at -95°C and stirred for 2 h at this temperature. After stirring for 3 h at -80°C the protected quinide 26 and bisacetonide 25 was obtained in a ratio of 6:74 Figure 20 in 82 % yield.

![Figure 20: Kinetic acetalisation of quinic acid](image)

Esterification of the bisacetonide 25 was achieved with 1.5 equivalents of the diacetylcaffeic acid chloride 27 with 4-(dimethylamino)-pyridine (DMAP) and pyridine in dichlormethane at 0°C with a reaction time of 5 h Figure 21.

![Figure 21: Esterification of the bisacetonide 25 with the acid chloride 27](image)
Cleavage of all protecting groups was achieved with 1 N aqueous HCl containing 15 % THF. Hydrolysis of the protecting groups was complete after stirring for 10 days at room temperature. The 5-caffeoyl quinic acid 29 was isolated in 91 % yield Figure 22.

![Figure 22: Cleavage of the protecting groups for 5-caffeoyl quinic acid](image)

**Synthesis of 1-caffeoyl quinic acid**

In a publication of 1964 by Weiss, 1-caffeoyl quinic acid 31 was synthesised from the by-product of the kinetic acetalysation, the protected quinide 26. The caffeic acid chloride was di-ethylcarbonate protected, but no yield and no conditions were described in detail. Also in this synthesis the by-product of the kinetic acetalysation, the protected quinide 26 was used as quinic acid derivate in the esterification step. According to Rohloff et al., the ratio of the protected quinide 26 and bisacetonide 25 was changed to 92:8 by using conditions for a thermodynamic acetalization of (-)-quinic acid 23. This acetalization was accomplished by refluxing (-)-quinic acid 23, p-toluensulfonic acid, 2,2 dimethoxy propane (DMP) and acetone for 2 h in 90 % yield Figure 23.

![Figure 23: Thermodynamic acetalisation of quinic acid](image)
Esterification of the protected quinide 26 was realized with 1.5 equivalents of the diacetyl caffeic acid chloride 27 with 4-(dimethylamino)pyridine (DMAP) and pyridine in dichloromethane at room temperature and a reaction time of 4h Figure 24.

**Figure 24:** Esterification of the protected quinide with the acid chloride

In this case, hydrolysis of the protecting groups was carried out in a two step process. All labile ester were cleaved with an equimolar amount of LiOH in a degassed water / THF solution. The removal of the acetal group was then achieved by acidification of the reaction mixture with 2M HCl. The 1-caffeoyl-quinic acid 30 was obtained with a yield of 97 % Figure 25.

**Figure 25:** Cleavage of the protecting groups for 1-caffeoyl quinic acid
Synthesis of 4-caffeoyl quinic acid

The starting material for the synthesis of the 4-isomer of the caffeoyl-quinic acid was the \( \gamma \)-quinide 32. The problem in this route is the protection of the hydroxyl groups at position 1 and 3 by an acetalization with 2,2,3,3,-tetramethoxybutane (TMB), because it does not react with vicinal cis-diols Figure 26.

\[
\begin{array}{c}
\text{32} \\
\text{HO} \\
\text{HO} \\
\text{OH} \\
\end{array} \xrightarrow{TMB, H^+} \begin{array}{c}
\text{33} \\
\text{MeO} \\
\text{OH} \\
\text{MeO} \\
\end{array} \\
\text{or} \begin{array}{c}
\text{34} \\
\text{MeO} \\
\text{OH} \\
\text{MeO} \\
\end{array}
\]

Figure 26: Synthesis of acetics 33 and 34

Abel et al.\textsuperscript{271} demonstrated the differentiation of the two secondary hydroxyl groups at position 4 and 5 of the quinide cyclohexyl ring by an esterification with tert. butyl dimethyl silyl chloride (TBS-Cl) providing silyl ether 35 in 75 % yield. In this silyl ether two sterically hindered hydroxyl groups are available for an esterification with 1.2 equivalents of the diacetyl caffeic acid chloride 27, but the reaction only occurred on position 4 of the quinide ring in 55 % yield. Again, the Hydrolysis of all protecting groups was accomplished with 1 M HCl at room temperature by stirring for 6 days and 4-Caffeoyl-quinic acid 37 was obtained in 83% yield Figure 27.

\[
\begin{array}{c}
\text{35} \\
\text{HO} \\
\text{HO} \\
\text{OH} \\
\end{array} \xrightarrow{\text{Pyridine}} \begin{array}{c}
\text{36} \\
\text{OAc} \\
\text{OAc} \\
\end{array} \xrightarrow{1 \text{ M HCl}} \begin{array}{c}
\text{37} \\
\text{OH} \\
\text{OH} \\
\end{array}
\]

Figure 27: Synthesis of 4-caffeoyl quinic acid
Synthesis of 3-caffeoyl-quinic acid

Montchamp et al.\textsuperscript{272} protected (-)-quinic acid \textsuperscript{23} at position 4 and 5 of the acid cyclohexyl ring by refluxing with Dowex 50 H+ in Methanol for 15 h. After filtration of the acid catalyst, 2,2,3,3-tetramethoxybutane and 10-camphorsulfonic acid was added and the mixture was refluxed for another 22 h. The obtained trans-acetal \textsuperscript{38} was esterificated by Sefkow et al. without any further protection of the remaining hydroxyl group at position 1 of the cyclohexane ring with 1.5 equivalents of the diacetyl caffeic acid chloride. Ester \textsuperscript{39} was obtained in 88 \% yield. Hydrolysis of the protecting groups was again achieved with 1 M HCl in 81 \% yield of 3-caffeoyl-quinic acid (\textsuperscript{40}) Figure \textsuperscript{28}.

Figure \textsuperscript{28}: Synthesis of 3-caffeoyl quinic acid
Chlorogenic acid composition and coffee

Despite the large distribution of some CGA in the plant kingdom, green coffee is known as one of the main food sources of CGA. Coffee contains hundreds of biologically active compounds. The most abundant water-soluble constituents of coffee include phenolic polymers (8 g/100 g), polysaccharides (6 g/100g), chlorogenic acid (4 g/100 g), minerals (3 g/100 g), organic acids (0.5 g/100 g), sugars (0.3 g/100 g) and lipids (0.2 g/100 g).\textsuperscript{273}

CGA, which are present in high concentrations in green coffee seeds (up to 14 %), have a marked influence in determining coffee quality and play an important role in the formation of coffee flavor.\textsuperscript{274}

The main groups of CGA found in green coffee beans are: caffeoylquinic acids (CQA), with 3 isomers (3-, 4- and 5-CQA); dicaffeoylquinic acids (diCQA), with 3 isomers (3,4-diCQA; 3,5-diCQA; 4,5-diCQA); feruloylquinic acids (FQA), with 3 isomers (3-, 4- and 5- FQA); p-coumaroylquinic acids (pCoQA), with 3 isomers (3-, 4- and 5- pCoQA), and six mixed diesters of caffeoylferuloyl-quinic acids (CFAQ).\textsuperscript{275}

Table 5 presents the contents of the three main groups of CGA in samples of green coffee beans, obtained by chromatographic analytical methods. Considering the nine main isomers of CGA: 5-CQA; 4-CQA and 3-CQA; 3,5-diCQA, 4,5-diCQA and 3,4-diCQA, 5-FQA, 4-FQA and 3-FQA, in order of abundance in green coffee beans, 5-CQA alone is responsible for about 56-62 % of total CGA. Considering that 4-isomers usually equal or slightly exceed 3-isomers, 3-CQA and 4-CQA account for up to 10% each of total CGA. DiCQA isomers account for about 15-20% of total CGA in green coffee beans and FQA isomers, for 5-13% of total CGA. p-CoQA isomers, CFQA isomers and the newly identified diferuloylquinic acids and dimetoxycinnamoylquinic acid derivatives account together for the remaining percentage.\textsuperscript{276,277}
Table 5: Chlorogenic acids content in green coffee beans, expressed in g%, dry matter.

<table>
<thead>
<tr>
<th>Samples</th>
<th>CQA</th>
<th>FQA</th>
<th>diCQA</th>
<th>Total CGA</th>
<th>References</th>
</tr>
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<td>0.87</td>
<td>6.88</td>
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<td>5.62</td>
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<td>0.34</td>
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<td>0.53</td>
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<td>C. arabica (Angola)</td>
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<td>0.79</td>
<td>1.39</td>
<td>7.85</td>
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<td>C. arabica cv. Bourbon (Brazil)</td>
<td>4.2</td>
<td>0.28</td>
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<td>5.25</td>
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<td>C. arabica cv. Longberry (Ethiopia)</td>
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<td>0.29</td>
<td>0.84</td>
<td>5.73</td>
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<td>1.43</td>
<td>2.31</td>
<td>11.3</td>
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<td>C. canephora var. Robusta (Uganda)</td>
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<td>0.47</td>
<td>1.34</td>
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<td>Timor hybrid (C. arabica x C. canephora)</td>
<td>4.71</td>
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<td>5.62</td>
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<tr>
<td>Catimor (Timor hybrid x C. arabica)</td>
<td>5.51</td>
<td>0.35</td>
<td>0.45</td>
<td>6.31</td>
<td>279</td>
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<td>C. liberica cv. Dewevrei</td>
<td>5.39</td>
<td>0.48</td>
<td>1.1</td>
<td>6.97</td>
<td>280</td>
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</table>

CGA are found in the surface of coffee seeds, in association with the cuticular wax, and in the cytoplasm adjacent to the cell walls of the endosperm parenchyma, but there seem to be no reports whether the distribution of CGA differ in these two locations. According to Zeller and Saleeb, part of the cell wall CGA may be associated with caffeine, as a 1:1 or 2:1 molar complex. Although CGA are mostly found in the coffee seeds, they have also been found in the leaves and in the coffee pulp. Total CGA content of green coffee beans may vary according to genetics – species and cultivar, degree of maturation and, less importantly, agricultural practices, climate and soil. The diversity of methodology employed in the analysis of CGA is another important factor in establishing levels, since there may be a certain discrepancy between results obtained by high resolution chromatographic methods and those obtained by less sophisticated methods.
In general, the values described in the literature for total CGA in regular green coffee beans, on dry matter basis (dm), may vary from 4 to 8.4 % for *Coffea arabica*, and from 7 to 14.4 % for *Coffea canephora*, with some hybrids presenting intermediate levels. Not only total CGA content, but the CGA composition of coffee beans also varies considerably during fruit maturation. Considering variations between species and cultivars, a sigmoidal increase in total CQA, mostly in parallel with the total dry matter gain, is initially observed with maturation. The ratio CQA/diCQA appears to increase with maturation until ripeness of the fruit, probably due to hydrolysis of diCQA into mono esters. At a certain stage before ripeness, CQA content starts to drop, according to, due to oxidation. From this point on, an inverse association between the levels of CQA and coffee fruits maturation is observed. Recently, Farah et al. reported a reduction not only in CQA levels, but also in FQA and diCQA levels, at this last stage of maturation. The authors reported a total of 8.7 % of CGA (dm) for immature *C. arabica* seeds (from dark green fruits), while seeds of over-ripened fruits presented levels as low as 1.3 %. Montavón et al. suggested that unripe seeds are more sensitive towards oxidation than ripe seeds and that the lower sensitivity of ripe seeds occurs because the defense mechanisms against oxidative stress become more efficient during maturation.

### Changes during the Roasting

In addition to their relevance for plant physiology and for a potential use in the pharmacology field, CGA take part in the generation of colour, flavor and aroma of coffee during roasting. Due to their thermal instability, CGA may be almost completely degraded into phenol derivatives when submitted to intense roasting conditions. During roasting, part of CGA is isomerized, part is transformed into quinolactones due to dehydration and formation of an intramolecular bond, and part is hydrolyzed and degraded into low molecular weight compounds.

Drastic roasting conditions may produce losses of up to 95% of CGA, with 8-10% being lost for every 1% loss of dry matter. Total CGA content in commercial roasted coffee ranges from about 0.5 to 7 %, depending on the type of processing,
roasting degree, blend and analytical conditions. CGA contents in light to medium roasted coffees still stand out when compared to most food sources of CGA.\textsuperscript{300} While coffee abstainers may typically ingest less than 100 mg of CGA/day, modest and heavy coffee drinkers intake may range from 0.1 to 2g.\textsuperscript{301} In relation to changes in CGA individual subgroups and isomers during roasting, at the beginning of the roasting process, isomerization of CGA occurs. The levels of the substitutes of the 5-position of the quinic acid decrease substantially while those of the substitutes in the 3- and 4- positions increase in some cases to almost double their original levels. According to Leloup \textit{et al.},\textsuperscript{302} at this roasting stage, diCQA may be partially hydrolysed into monoesters and cafeic acid, which may be again hydrolysed, decarboxylated and degraded to a range of simple phenols. Chlorogenic acid lactones formation occurs after 6 to 7\% of weight loss.\textsuperscript{303} About 7\% of CGA in regular Arabica coffee and 5.5\% in Robusta coffee seem to be transformed into 1,5-γ-quinolactones during the roasting process. Average lactones levels of 210 and 100 mg\% (dm) were reported for commercial regular ground coffee.\textsuperscript{304} The content of total CGA lactones increases until about 14\% weight loss, i.e., light medium roast, reaching average levels of 398 and 424 mg\% (dm) for Arabica and Robusta coffees, respectively, and decreasing gradually thereafter.\textsuperscript{305}
RESULTS AND DISCUSSION

Chapter 3
Aims and objectives

As described chlorogenic acids are an integral and important part of the human diet. This class of compounds is ubiquitous in dietary material and responsible for a large variety of known health benefits and possibly for a series of health benefits not established to date. The project aims at making a first step in addressing the importance of chlorogenic acids in the human diet. An attempt has been made to synthesise as many as possible regioisomeric mono-acyl, di-acyl and poly-acyl chlorogenic acids of the homo di-acyl type and the hetero di-acyl type.

Ideally one or more complete series of mono-acyl and di-acyl chlorogenic acids aimed to be synthesised.

The compounds are required for the following purpose:

1. As reference standards for future analysis of chlorogenic acid containing food material.
2. As reference standards for verifying LC-MS\textsuperscript{a} based hierarchical scheme for the identification of chlorogenic acids
3. To have as many as reference material available for systematic biological testing and screening of dietary chlorogenic acids in the future.
4. As reference standards to be able to study reactivity of chlorogenic acids in food processing in the future.

Furthermore with the analytical reference material in hand, the compounds should be mapped against naturally occurring chlorogenic acids using LC-MS methods.
General synthetic procedure:

The first chemical synthesis of chlorogenic acid (5-CQA) was reported by Panizzi et al. 45 years ago\textsuperscript{306}. The natural product was prepared in seven steps from quinic acid but the overall yield was low (<5%). The major disadvantage of their synthesis was the formation of a quinide acetal with the 2-3 hydroxyl groups unprotected. The synthesis required several protecting group manipulations and acidic and basic hydrolysis as the final steps\textsuperscript{307}. Basic hydrolysis, in particular, is to be avoided because chlorogenic acids are very sensitive to oxidation in basic solutions.

Regioselective synthesis of caffeoyl quinic acids (1-caffeoylquinic acid and 5-caffeoylquinic acid) were reported by C. Weisser in 1964 and by Nagels at all in 1980.\textsuperscript{308, 309} A further synthetic route yielding mono-esters of caffeic acid (1-, 4-, and 5-Caffeoylquinic acid) was reported by Sefkow.\textsuperscript{310} The efficient synthesis of chlorogenic acids was achieved in principally two steps from quinic acid. All such methods involve condensing an acid chloride with a derivative of quinic acid. General acylation procedures are used in the synthesis of chlorogenic acids. Protection is required to prevent unwanted reactions, such as self-condensation of acid chloride.

As a protecting group strategy three orthogonal protecting groups were chosen, which are acid labile, base labile and labile to metal reducing agents. Firstly, appropriately protected derivatives of cinnamic acids were obtained, which were in a second step reacted with appropriately protected quinic acid derivatives. Overall deprotection resulted in the chlorogenic acid derivatives.

Synthesis was achieved by using acid-labile protecting group and Troc protecting group gives good overall yields (57-95%). Protection is required on aromatic hydroxyl group(s) in the acyl chloride, the quinic acid carboxy group and usually one or more of the quinic acid hydroxyl groups.

Cleavage of acid labeled protecting groups of esters is achieved with 2N aqueous HCl containing THF. Hydrolysis of protecting groups was completed after 24 hours at room temperature. Cleavage of Troc group followed treatment with zinc in acetic acid. Elimination of Troc protecting groups was completed after 72 hours.

Treatment of the ester, thus produced, with LiOH in a degassed THF/HCl solution completed chlorogenic acid synthesis.
Preparation of acid chlorides of cinnamic acids:

For the synthesis of cinnamic acid chlorides as mentioned by Sefkow was adopted. The cinnamic acid derivatives caffeic, ferulic and coumaric acids were reacted with Ac$_2$O in pyridine in the presence of 5% 4-(dimethylamino)pyridine (DMAP, Steglich catalyst) as a nucleophilic acylation catalyst. The acetate protected compounds were obtained in good yield (91-94%) as white powder. Further reaction with oxalyl chloride, DMF in DCM, produced the acid chlorides (81-87%) as water sensitive solids in good yields. All spectroscopic datas were in full agreement with the structures. Similarly the acid chloride of 3, 4-dimethoxycinnamic acid was obtained in 93 % yield as a yellow powder.

Synthesis of diacetyl caffeic acid chloride, (41)

Scheme 1: Synthesis of diacetyl caffeic acid chloride (41)

As it was described by Sefkow diacetyl caffeic acid chloride (41) was obtained in 92% yield by esterification of caffeic acid with two equivalents of acetic anhydride in pyridine. 5% of 4-(dimethylamino)-pyridine (DMAP, Steglich catalyst) used as catalyst in the synthesis.

Synthesis of acetyl ferulic acid chloride (42), Acetyl p-coumaric acid chloride, (43), and 3, 4-dimethoxycinnamic acid chloride, (44) achieved similar way by using sufficient amount of acetic anhydride as shown in the Scheme 2, Scheme 3, Scheme 4.
The $^1$H-NMR spectrum for compound (41) shows two methyl groups at 2.28 ppm and 2.29 ppm as singlet with three proton intensity. These protons were assigned to H-12 and H-13. Two olefinic protons as two doublets appeared at 6.57 ppm and 7.73 ppm and assigned to H-2 and H-3 due to $^1$H-$^1$H-COSY and their chemical shift. Each has
coupling constant around 16 Hz, which indicates that the pair of proton was \textit{trans} to each other. Three aromatic protons of aromatic group appeared at 7.28 ppm, 7.40 ppm and 7.41 ppm as one singlet and two doublets respectively.

![Figure 31: $^1$H$^{13}$C-HMQC spectrum of diacetyl caffeic acid chloride, (41)](image)

$^{13}$C-NMR spectrum was in line with the $^1$H-NMR spectrum of caffeoyl chloride \textit{(41)}. Two methyl groups appeared at 20.67 ppm and 20.72 ppm as it was expected. Two carbons of olefinic group signals appeared at 118.67 ppm and 141.21 ppm. These carbons were assigned to C-2 and C-3 respectively. Three aromatic carbons which have hydrogen attached to it appeared at 123.47, 124.08 and 127.50 ppm and were assigned to C-9, C-6 and C-5. Another carbon which hasn’t got any hydrogen attached to it occurred at 132.26 ppm and assigned to C-4. The other two aromatic carbons which are next to carboxyl groups appeared at 144.62 and 145.96. These carbons were assigned to C-7 and C-8. One of the three sets of carboxyl carbons, the one next to the chlorine atom occurred at 165.91 ppm and is assigned C-1. The other two carboxyl carbons which are next to an oxygen atom appeared at 167.82 and 168.14 ppm and they were assigned to C-10 and C-11.

The Infrared data shows absorption of groups at 1758 (C=O), 1689, 1630 ($C_{Ar}=C_{Ar}$), 1208 (C-O) as expected.
Figure 32: Infrared spectrum of diacetyl caffeic acid chloride, (41)

Scheme 2: Synthesis of acetyl ferulic acid chloride (42)

Scheme 3: Acetyl p-coumaric acid chloride, (43)

Scheme 4: 3, 4-dimethoxycinnamic acid chloride, (44)
Preparation of protected quinic acid derivatives:

**Figure 33:** Structure of starting materials

**Synthesis of 1L-1(OH), 3, 4/5-Tetrahydroxycyclohexanecarboxylic acid (Quinide), (51)-p178**

**Scheme 5:** Synthesis of Quinide (51)
Quinide was synthesized by heating quinic acid at 220°C for one hour in the absence of solvent. The product was purified by recrystallisation from EtOH. Quinide was obtained in 30% yield by this quinic acid lactonisation.

![Figure 34: $^1$H NMR of Quinide, (51)](image)

All spectroscopic data ($^1$H-NMR, $^{13}$C-NMR, IR and elemental analysis) are in full agreement with the proposed structure. The $^1$H-NMR spectrum shows two triplets and one doublet of doublet of doublet at 4.91, 4.16 and 3.87 ppm corresponding to the three protons HCO next to an oxygen atom. Furthermore four signals at 2.48, 2.42, 2.13 and 1.94 ppm correspond to the four non-equivalent protons of the two sets of CH$_2$ groups. Because of chemical shift considerations the most downfield proton at 4.91 was assigned to H-5, the proton next to the lactone functionality. From the $^1$H–$^1$H-COSY spectrum the signal at 4.16 ppm can be identified as H-4 due to crosspeaks to H-5. The multiplet at 3.87 ppm was consequently assigned as H-3. A cross peak from H-3 to the signals at 2.13 and 1.94 ppm shows that these two signals correspond to the H-2 CH$_2$ moiety confirmed by their crosspeak. The two H-6 protons are identified at 2.48 and 2.42 ppm. Interestingly a further crosspeak is evident in the $^1$H–$^1$H-COSY spectrum between the two signals at 2.42 ppm and 2.13 ppm due to a $^4$J$_{HCCCH}$ long range W-coupling. This automatically identifies the two signals as the two equatorial protons, since such a W-coupling can only occur between two equatorial protons.
Moreover it is worth noting that the H-6-CH$_2$ protons are unexpectedly shifted downfield if compared to the H-2 CH$_2$ protons. The coupling constants in the quinide...
are as expected due to the Karplus relationship which describes the dependence between $^3J_{HCCH}$ coupling constants and the dihedral angle between the two coupling protons. Values of $^3J_{HCCH}$ coupling constants between two equatorial protons are observed between 4 and 5.5 Hz (e.g. H-4 and H-5 or H-5 and H-6$_{eq}$). The values of $^3J_{HCCH}$ between equatorial and axial protons are found to be very small due to a dihedral angle close to $90^\circ$. Finally the values of $^3J_{HCCH}$ between two axial protons are found to be very large (e.g. 11.7 Hz for the coupling pair H-3 and H-2$_{ax}$) because of a dihedral angle close to $180^\circ$.

![Figure 37: $^1$H$^{13}$C-HMQC of Quinide, (51)](image)

The stereochemical relationship between all protons was also confirmed by $^1$H-$^1$H-NOESY spectroscopy. Most characteristically the two axial protons H-6$_{ax}$ and H-2$_{ax}$ show a strong NOE effect between them. All further NOE effects observed are in full agreement with the structure. The $^{13}$C-NMR shows seven signals as expected. The carbonyl carbon is found at 179.77 ppm as expected, and C-1 and C-5 are to be found at 72.51 and 77.46 ppm respectively. The $^1$H$^{13}$C-HMQC spectrum allows unambiguous identification and assignment of C-4 at 66.79 ppm, C-3 at 64.96 ppm, C-6 at 37.74 ppm and C-2 at 36.35 ppm. The infrared spectrum shows absorptions for the carbonyl ester and the OH groups as expected. The mass spectrum shows the molecular ion and a series of fragment ions corresponding to dehydrated fragments of the quinic acid ester (lactone).
Synthesis of 3, 4-isopropyldene quinide (Quinide acetal), (45)-p183

Scheme 6: Quinide acetal formed by common acetalisation

The quinide acetal was produced by thermodynamic acetalisation of quinic acid. The acetalisation was accomplished by refluxing quinic acid, p-toluenesulfonic acid, 2,2-dimethoxy propane (DMP) and acetone for 2 hours providing the shown compound in 76-90 % yield. The crystals were suitable for single crystal X-ray diffraction and could be obtained from EtOAc-PE (25:4) solvent combination. The compound was first described and synthesized by Sefkow. The crystal data and structure of the product are given below and have not been reported in the literature yet. The structure was solved by Dr. M. Dickman in the laboratory of Prof. U. Kortz.

Figure 38: Crystal structure of the quinide acetal
Table 6: Crystal data and structure refinement for 3, 4-O-Isopropylidene quinide

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<th>3, 4-O-Isopropylidene quinide</th>
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<tbody>
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<td>C(<em>{10})H(</em>{14})O(_{5})</td>
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<td>Formula weight</td>
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<td>Temperature</td>
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<td>a = 5.6079(5) Å</td>
<td>α = 90°</td>
</tr>
<tr>
<td>b = 9.3722(9) Å</td>
<td>β = 90°</td>
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<tr>
<td>c = 18.9411(18) Å</td>
<td>γ = 90°</td>
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<td>Z</td>
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<tr>
<td>Density (calculated)</td>
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<td>Absorption correction</td>
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<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F(^2)</td>
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<td>Goodness-of-fit on F(^2)</td>
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<td>Final R indices [I&gt;2sigma(I)]</td>
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<tr>
<td>R indices (all data)</td>
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<tr>
<td>Largest diff. peak and hole</td>
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Table 7: Bond lengths [Å] for 3, 4-O-Isopropylidene quinide

<table>
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<th>Bond</th>
<th>Bond lengths [Å]</th>
<th>Bond</th>
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<td>C(6)-H(6A)</td>
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<td>C(4)-C(5)</td>
<td>1.514(3)</td>
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Table 8: Bond angles [°] for 3, 4-O-Isopropylidene quinide

<table>
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<th>Bond</th>
<th>Bond angles [°]</th>
<th>Bond</th>
<th>Bond angles [°]</th>
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<td>O(1)-C(1)-C(6)</td>
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<td>C(1)-C(6)-H(6B)</td>
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<td>H(6A)-C(6)-H(6B)</td>
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<td>C(6)-C(1)-C(7)</td>
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<td>O(2)-C(7)-O(3)</td>
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<td>C(6)-C(1)-C(2)</td>
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Table 8 continued

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The $^1$H-NMR of 3,4-Isopropylidene quinide (45) shows two singlets for the methyl protons of isopropylidene moiety at 1.30 and 1.49 ppm with three proton intensity. Three peaks at 4.28, 4.47 and 4.69 ppm correspond to the O-CH on the cyclohexane ring. Following the $^1$H$^1$H-COSY spectrum crosspeaks and chemical shift, the 4.69 ppm signal was assigned to H-5, and the other two multiplet signals at 4.28 and 4.47 ppm were assigned to H-4 and H-3 protons. Two non-equivalent protons of H-6 appeared at 2.34 and 2.59 ppm. Other two non-equivalent protons which belong to H-2 CH$_2$ protons can be assigned to the signals at 2.16 and 2.30 ppm as a doublet of doublet and multiplet.

$^1$H$^1$H-COSY and $^{13}$C-NMR spectra confirmed the assignments of the $^1$H-NMR spectrum for the 3, 4-isopropylidene quinide (45).
Figure 39: \textsuperscript{1}H-NMR spectrum of 3, 4-O-Isopropylidene quinide, (45)

![H-NMR spectrum](image)

Figure 40: \textsuperscript{13}C-NMR spectrum of 3, 4-O-Isopropylidene quinide, (45)

![C-NMR spectrum](image)

The carbonyl carbon found at 179.04 ppm was assigned to C-7. The signal at 109.86 ppm which has no proton attached to it was assigned to acetal carbon C-8. The quinide carbons were found at 34.36, 38.20, 71.58, 71.63, 72.16 and 75.91 ppm and
assigned to C-2, C-6, C-3, C-4, C-5 and C-1 carbons respectively. Two methyl carbons were found at 24.37, 27.04 ppm and were assigned to C-9 and C-10. The IR spectrum shows the characteristic lactone peak at 1777 cm$^{-1}$ as it was expected.

\textbf{Figure 41:} $^1$H$^{13}$C-HMQC spectrum of 3, 4-O-Isopropylidene quinide, (45)

\textbf{Figure 42:} Infrared spectrum of spectrum of 3, 4-O-Isopropylidene quinide, (45)
**Synthesis of 3, 4-O-Isopropylidene quinic acid, (46)-p184**

Scheme 7: Synthesis of 3, 4-O-Isopropylidene quinic acid, (46)

The 3, 4-isopropylidene-quinide and a mixture of degassed THF/ water was treated with 1.1 equivalent LiOH/ H₂O at room temperature. The solution was stirred for 24 hours at room temperature, and acidified by using 2M HCl solution. After work up, the combination of solvents were removed under reduced pressure to give the title compound 46 as a white powder in 93% yield.

Figure 43: $^1$H-NMR spectrum of 3, 4-O-Isopropylidene quinic acid, (46)
The $^1$H-NMR spectrum shows that the data is in full agreement with the proposed structure. The $^1$H-NMR spectrum shows six methylene protons as two multiplets and two doublet of doublets. The multiplets found at 1.71 and 1.72 ppm each one of them with one proton intensity and were assigned to 6-H$_{ax}$ and 6-H$_{eq}$ protons respectively. Another set of methylene protons were found at 1.95 and 2.11 ppm as two doublet of doublets, and were assigned to 2-H$_{ax}$ with coupling constant $J$ 16-1.6 Hz and 2-H$_{eq}$ with coupling constant between $J$ 10.8-5.2 Hz. Two typical protons of quinic acid which are attached to oxygen atoms occurred at 3.88 ppm as a multiplet and 4.41 ppm as a doublet of doublets, and were assigned to H-4 and H-3 protons due to $^1$H-$^1$H-COSY spectrum crosspeaks. The last proton of cyclohexane ring was found at 3.91 ppm as multiplet and assigned to H-5 proton following chemical shift and $^1$H-$^1$H-COSY spectrum crosspeaks.

**Figure 44:** $^1$H-$^1$H-COSY spectrum of 3, 4-O-Isopropylidene quinic acid, (46)
The $^{13}$C-NMR spectrum was in harmony with the $^1$H-NMR spectrum of the 3,4-Isopropylidene quinic acid. Two methyl carbons of the acetal group were found at 25.07 and 27.53 ppm and assigned to C-9 and C-10 carbons. The two methylene carbons of the cyclohexane ring appeared at 34.50 and 39.02 ppm. These two carbons were assigned to C-6 and C-2 respectively. The other three carbon signals were found at 68.09, 74.14 and 75.24 and assigned to C-5, C-3 and C-4 carbons by a combination of $^1$H-$^1$H-COSY and HMQC analysis. Typically the C-1 carbon was found at 79.78 ppm followed by the acetal carbon which hasn’t got any hydrogen attached to it at 109.32 ppm and assigned to C-8. And last, carboxylic acid carbon C-7 found was found at 181.98 ppm. The IR spectrum shows absorption for carboxylic acid broad peak at 1602 cm$^{-1}$. 

Figure 45: $^{13}$C-NMR spectrum of 3, 4-O-isopropylidene quinic acid, (46)
Figure 46: $^1$H$^{13}$C-HMQC spectrum of 3, 4-O-isopropylidene quinic acid, (46)

Figure 47: IR spectrum of 3, 4-O-isopropylidene quinic acid, (46)
Synthesis of 1-(β, β, β-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide, (47)-p185

Scheme 8: Synthesis of 1-(β, β, β-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide

2,2,2- Trocchloroethanol and derivatives have found wide application as protecting groups that are easily removed by zinc reduction under a variety of conditions. Further protection of the hydroxyl group in the first position in the quinide acetal was achieved using Troc-Cl, and pyridine in DCM at room temperature for twelve hours. The 1- Troc protected quinide was obtained as white powder with a yield of 96%. The spectroscopic data are in agreement with the proposed structure of this novel compound (47).

Figure 48: $^1$H-NMR spectrum of 1-(β, β, β-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide, (47)
Identification of the product was supported by $^1$H-NMR spectra. The $^1$H-NMR spectrum shows that the two methyl protons of acetyl group at 1.30 and 1.46 ppm with three proton intensity and assigned to H-12 and H-13 protons. Furthermore four signals at 2.38, 2.51, 2.64 and 3.02 ppm correspond to the four non-equivalent protons of the two sets of CH$_2$ groups. The most highfield peak of CH$_2$ occurred as doublet of doublet at 2.38 ppm and was assigned to 2-H$_{ax}$, then another pear of the same methylene group which was occurred at 2.51 ppm as multiplet was assigned to 2-H$_{eq}$.

The non-equivalent protons of another methylene group at 2.64 ppm as doublet with the 11.4 Hz coupling constant were assigned to 6-H$_{eq}$ and then the multiplet at 3.02 ppm assigned to 6-H$_{ax}$. The two diastereotopic protons of the Troc group which are identical to each other appeared as two doublets at 4.71 and 4.80 ppm.; both protons have coupling constant around 12 Hz, typical of a $^2$J$_{HCH}$ coupling. The $^1$H-NMR spectrum shows two doublet of doublet and one doublet of doublet of doublet at 4.31, 4.52 and 4.76 ppm, corresponding to the three protons HCO next to an oxygen atom. Because of the chemical shift considerations the most downfield proton at 4.76 ppm was assigned to H-5, the proton next to the lactone functionality. From the $^1$H-$^1$H-COSY spectrum the signal at 4.31 ppm, which occurred as doublet of doublet, identified as H-4 due to crosspeaks to H-5. The doublet of doublet of doublets at 4.52 ppm was assigned to H-3 proton.

Figure 49: $^{13}$C-NMR spectrum of 1-(β, β, β-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide, (47)
The $^{13}$C-NMR shows thirteen signals, which are consistent with the $^1$H-NMR spectrum. The very first two signals at 24.36 and 28.14 ppm are methyl carbons which correspond to C-12 and C-13. The two methylene carbons occurred at 34.48 ppm and 38.63 ppm was assigned to C-2 and C-6. The typical carbons of quinide found at 66.73, 68.21 and 72.30 ppm was assigned to C-3, C-4 and C-5. The two Troc group carbons found at 74.65 and 93.45 ppm. The signal at 74.65 ppm assigned to CH$_2$ carbon of the Troc group and the signal at 93.45 ppm was assigned to another carbon of Troc group, which is adjacent to chlorine atoms therefore due to the electronegative effect of the chlorine group this carbon occurred in downfield compared to the methylene carbon of the Troc group.

The typical C-1 quinide carbon was found at 82.39 ppm. The quaternary acetal which hasn’t got any hydrogen attached to it appeared at 109.14 ppm and assigned to C-11. Two peaks of the carbonyl group were found downfield at 152.38 and 170.78 ppm. Due to electronegative effect the peak at 152.38 ppm was assigned to C-8 carbon and the peak at 170.78 ppm was assigned to C-7 carbons. The Infrared spectrum shows absorptions for the carbonyl ester at 1807, 1767 cm$^{-1}$.

Figure 50: $^1$H$^{13}$C-HMQC spectrum of 1-(β, β, β-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide, (47)
**Figure 51:** IR spectrum of 1-(\(\beta, \beta, \beta\)-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide, (47)

**Synthesis of 1-(\(\beta, \beta, \beta\)-trichloroethoxycarbonyl) quinide, (48)-p186**

**Scheme 9:** Synthesis of 1-(\(\beta, \beta, \beta\)-trichloroethoxycarbonyl) quinide, (48)

Cleavage of all acetal protecting groups was generally achieved by using THF/2N HCl solution at room temperature in twenty four hours. But, hydrolysis of Troc protected quinide could not be achieved in the same manner. After unsuccessful evaluation of acetal deprotection protocols in the literature, Troc quinide was treated with I\(_2\)/MeOH at 45°C for seventy-two hours and the acetal protecting group was then successfully removed as shown in **Scheme 9** above. Later on the Troc protecting group was removed successfully giving a yield of 92%, by treating Troc quinide with Zn powder in acetic acid. Although the attachment of Troc is novel, liberation of the 3
and 4-OH groups were achieved by deprotection using the usual I$_2$ in MeOH to give this unsynthesized and undescribed diol with a yield of 78%.\textsuperscript{315} Purification of the compound was achieved from toluene by recrystallisation. It was found that when the reaction scale increased synthetic problems with low yields and decreased purity of the product were observed.

\textbf{Figure 52:} $^1$H-NMR spectrum of 1-(β, β, β-trichloroethoxycarbonyl) quinide, (48)

All spectroscopic data ($^1$H-NMR, $^{13}$C-NMR, IR and elemental analysis) are in full agreement with proposed structure. The $^1$H-NMR spectrum shows four typical methylene proton signals at 1.85, 2.16, 2.46 and 2.74 ppm. The signal at 1.85 ppm occurred as doublet of doublet with large coupling constant and assigned as 2-H$_{ax}$. The 6-H$_{eq}$ occurred as a doublet with a weak coupling constant (J 3.6) compared to the axial per of H-6 proton at 2.16 ppm. The crosspeaks on $^1$H-$^1$H-COSY spectrum allow to be assigned the signals at 2.46 and 2.74 ppm as 2-H$_{eq}$ and 6-H$_{ax}$. The three protons of quinide were identified with the $^1$H-$^1$H-COSY and chemical shift concern. The two doublet of doublet at 3.52 ppm and 4.18 ppm were assigned to H-4 and H-5 protons. The other signal at 4.11 ppm was evidence of the H-5 proton which was identified due to crosspeaks at $^1$H-$^1$H-COSY spectrum. The two identical protons of the Troc group with similar coupling constant (J 12 and J 11.6) showed two doublet at 4.72 and 4.79 ppm each one of them with one proton intensity.
Figure 53: $^{13}$C-NMR spectrum of 1-(β, β, β-trichloroethoxycarbonyl) quinide, (48)

The $^{13}$C-NMR shows that acetal protecting group was removed successfully and the spectrum shows ten signals as expected. As before carbons which belong to CH$_2$ groups of quinide occurred in the typical range 33.95 and 38.62 ppm and were assigned to the C-2 and C-6 carbons. The other carbons of quinide were found at 66.38, 68.36 and 75.24 ppm and assigned to the C-3, C-4 and C-5 by $^1$H-$^1$H-COSY and HMQC spectrums. Another quinide were carbon in the first position which is attached to two oxygen atom found at 83.59 ppm was assigned to C-1. Two carbons of the Troc protecting group were found at 77.44 and 94.40 ppm as expected and the signal downfield assigned to the carbon which is adjacent to chlorine atom due to chemical shift caused by electronegative effects and then the signal at 77.44 ppm was assigned to C-9 as usual. The carbonyl carbons were appeared in the typical region and the peak at 152.24 ppm was assigned to C-8. The peak occurred in most downfiled at 171.07 ppm assigned to C-7 since it is the peak which is in the most electronegative environment.

The infrared spectrum showed a very broad peak at 3441 cm$^{-1}$ in the range of hydroxyl group then sharp peaks at 1750 and 1636 cm$^{-1}$ therefore full spectroscopic data was in full agreement with the structure of the title compound.
Results and discussion

Chapter 3

Figure 54: $^1$H$^{13}$C-HMQC spectrum of 1-(β, β, β-trichloroethoxycarbonyl) quinide, (48)

Figure 55: IR spectrum of 1-(β, β, β-trichloroethoxycarbonyl) quinide, (48)
Synthesis of bisacetonide, (49)-p187

![Scheme 10: Synthesis of bisacetonide, (49)](image)

The synthesis of bisacetonide from quinic acid was published by Sefkow in 1999. He found that quinic acid could be subjected to conditions of kinetic acetalisation. Reaction of quinic acid with 5.28 equivalent of TMS-Cl and 5 equivalent of Et$_3$N afforded the penta silyl ether, which was without isolation reacted with dimethoxypropane in the presence of the Lewis acidic TMS-OTf at low temperature (-15 ºC). As a product the bisacetonide was obtained, which contains a free 5-OH group. The method was first time reported in the literature by Sefkow but, the crystal structure of the compound hasn’t been reported in the literature yet. The spectroscopic data were in agreement with the structure. When alcohols undergo reaction with TMS-Cl it forms trimethylsilyl ethers and these groups can be used as protecting groups. Therefore, TMS-Cl was used to form trimethylsilyl ethers, which are intermediate product of the reaction. Further more, treating the reaction mixture with TMS-OTf produced chemoselective protection of quinic acid.

![Figure 56: Crystal structure of bisacetonide](image)
The bisacetonide was synthesised by following the method which was described by Sefkow. However, the crystal form of the title product was achieved by using PE/EtOAc solvent combination. The crystal structure of the compound hasn’t been reported in the literature yet. The crystal structure of the title product as is shown in Figure 56.

**Table 9: Crystal data and structure refinement for bisacetonide**

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Table 10: Bond lengths [Å] for bisacetonide

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Table 11: Bond angles [°] for bisacetonide

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Symmetry transformations used to generate equivalent atoms
Examination of $^1$H-NMR spectra shows that the peaks at 1.25, 1.34, 1.58 and 1.59 ppm are belong to four methyl protons of the bisacetonide. Each peak has three proton intensity and they were assigned to H-10, H-11, H-12 and H-13 protons. Two non-equivalent protons of cyclohexane ring appeared at 1.91 and 2.09 ppm and they were both assigned to 6-H$_{ax}$ and 6-H$_{eq}$. Another two non-equivalent protons occurred at 2.20 ppm which was assigned to 2-H$_{ax}$ and at 2.27 ppm which was assigned to 2-H$_{eq}$ in accordance with $^1$H$^1$H-COSY spectrum cross peaks and chemical shift. All the non-equivalent protons occurred as doublet of doublet with typical constant values $J$ between 3.6-15.5 Hz. Also three peaks at 3.99, 4.01 and 4.66 ppm corresponds to three characteristic protons of the cyclohexane ring. The peak at 3.99 ppm was assigned to H-4, 4.01 ppm was assigned to H-5 and the 4.66 ppm was assigned to H-3 on the basis of $^1$H$^1$H-COSY spectrum and electronegative effect.

**Figure 57:** $^1$H-NMR spectrum of bisacetonide, (49)
Figure 58: $^{13}$C-NMR spectrum of bisacetonide, (49)

$^{13}$C-NMR shows nineteen signals as it was expected. Four methyl protons which are characteristic for the acetonide moiety occurred at 25.36, 25.62, 28.64 and 28.84 ppm and were assigned to C-10, C-11, C-12 and C-13. The signals of methylene carbons were found at 35.08 and 37.38 ppm and assigned to C-6 and C-2 carbons. The other three carbons of cyclohexane ring which has one proton attached to each, are found at 67.36, 71.79 and 76.78 ppm and assigned to C-5, C-3 and C-4 carbons on the basis of chemical shift. Another peak was observed at 78.45 ppm and assigned to C-1 due to electronegativity consideration effect. The two carbons which belong to two acetal groups were found at 109.08 and 111.57 ppm and assigned to C-8 and C-9 carbons. The carbonyl carbon found at 176.21 ppm assigned as C-7. The IR spectrum of bisacetonide also showed the typical peak at 1788 cm$^{-1}$ as expected.
**Figure 59:** $^1$H$^{13}$C-HMQC spectrum of bisacetonide, (49)

**Figure 60:** IR spectrum of bisacetonide, (49)
General synthetic route for efficient synthesis of chlorogenic acids and derivatives (hydroxycinnamoyl quinic acids)

The first efficient method for synthesis of chlorogenic acids was published by M. Sefkow in 2001. 1-, 4- and 5-Caffeoylquinic acid were successfully synthesised by the Sefkow group. However, no synthetic methods for the synthesis of dietary relevant 1-cafeoyl and mono acyl derivatives, with substituents other than cafeoyl diacyl quinic acids have ever been reported and for the topic of the following section. All possible regioisomeric homo diacyl and hetero diacyl quinic acids are shown in Scheme 11 and Scheme 12 below.

The variety of compounds depends on subtituents; for an instance when the reactions focused on caffeic acid considering combinations with other four substituents there are six homo and twelve hetero isomers that possibly could be synthesised. The possible structure of compounds as shown below;

![Scheme 11: Structures of six possible homo isomers of di-acyl chlorogenic acids](image)

Scheme 11: Structures of six possible homo isomers of di-acyl chlorogenic acids
Scheme 12: Structures of twelve possible hetero isomers of di-acyl chlorogenic acids
Results and discussion

Chapter 3

Synthesis of (1S, 3R, 4R, 5R)-1-cinnamoyl-3, 4-isopropylidene-quinide, (52)-p188

Scheme 13: Synthesis of (1S, 3R, 4R, 5R)-1-cinnamoyl-3, 4-isopropylidene-quinide

The synthesised compound was obtained in a 70% yield by acylation of quinide acetal with 1.1 equivalent cinnamoylchloride by using 5% DMAP as catalyst in dichloromethane and triethylamine solution.

Figure 61: ¹H-NMR of (1S, 3R, 4R, 5R)-1-cinnamoyl-3, 4-isopropylidene-quinide

Examination of ¹H-NMR spectra shows that the peaks at 4.82, 4.57 and 4.35 ppm correspond to the three protons of the quinide. Following the ¹H¹H-COSY spectrum crosspeaks and chemical shift, the signal at 4.82 ppm assigned to H-5. Two multiplet signals at 4.57 and 4.35 ppm were assigned to H-3 and H-4. Two non equivalent protons of H-6 appeared at 3.12 and 2.64 ppm. Other non-equivalent protons which
belong to H-2 CH$_2$ protons can be assigned to the signals at 2.53 and 2.43 ppm as a multiplet and a doublet. The $^1$H-NMR and $^1$H$^1$HCOSY spectrum confirmed that C=CH olefinic protons at 7.74 and 6.45 ppm with coupling constant of 16 Hz each indicating that both pairs of protons were trans to each other. Two methyl groups appeared at 1.54 ppm and 1.34 ppm as singlets with three proton intensity. Equivalent protons of aromatic group appeared around 7.26-7.44 ppm as multiplet as expected.

![Figure 62: $^{13}$C-NMR spectrum of 52](image)

The $^{13}$C-NMR shows nineteen signals as expected. The carbonyl carbons at 173.77 ppm assigned as C-7 and another peak at 165.22 ppm assigned to C-11. A combination of $^1$H$^1$H-COSY and HMQC shows that the signals at 146.97 ppm and 117.32 ppm were belong to another pair of C=CH olefinic protons which are assigned to C-13 and C-12. Aromatic group carbons appeared as six signals between 128.52 ppm and 134.25 ppm. The signal at 110.22 ppm with small intensity may be assigned to one of the acetal group carbons C-8 which hasn’t got any proton attached to it. C-1 and C-5 were identified at 76.43 ppm and 75.65 ppm. Significant protons of quinide C-4, C-3, C-6, C-2 were seen at 72.74, 71.46, 35.92 and 30.96 ppm, respectively. Two of the methyl carbons which are part of the acetyl group were found at 24.58 and 27.23 ppm and assigned to C-9 and C-10.
The IR spectrum showed peak for a carbonyl ester as expected. The mass spectrum shows the molecular ion and fragment ions corresponding to structure of compound.

The same method was applied for the synthesis of (1S, 3R, 4R, 5R)-1-(3,4-dimethoxycinnamoyl)-3,4-isopropylidene-quinide, (1S, 3R, 4R, 5R)-1-caffeoyl-3,4-isopropylidene-quinide, (1S, 3R, 4R, 5R)-1-feruloyl-3,4-isopropylidene-quinide, (1S,
3R, 4R, 5R)-1-coumaroyl-3, 4-isopropylidene-quinide. All the reactions successfully produced the desired compounds in very good yields (70-90%).

Synthesis of (1R, 3R, 4S, 5R)-1-cinnamoylquinic acid, (59)-p195

Scheme 14: Synthesis of (1R, 3R, 4S, 5R)-1-cinnamoyl-quinic acid

The synthesized product was obtained with a yield of 40 % by treating (1S, 3R, 4R, 5R)-1-cinnamoyl-3, 4-isopropylidene-quinide with 2N HCl/ THF solution at room temperature. Complete hydrolysis of the acetal group was achieved in 24 hours.

Figure 65: $^1$H-NMR of (1R, 3R, 4S, 5R)-1-cinnamoylquinic acid, (59)

The $^1$H-NMR spectrum shows that the reaction was achieved successfully. All the peaks are present as expected. The peaks at 7.75 and 6.61 ppm are two doublets and are assignable as olefinic protons. An aromatic group appeared between 7.47-7.67
Results and discussion

From the $^1$H$^1$H-COSY spectrum the signal at 3.60 ppm was identified as H-4 due to crosspeaks to H-5 and H-3. Due to chemical shift and $^1$H$^1$H-COSY spectroscopy the signals at 4.25 and 4.11 ppm were assigned to H-3 and H-5 protons. The H-5 appeared as multiplet and H-3 identified as doublet of triplet. The two non-equivalent protons of CH$_2$ groups were identified by considering chemical shifts and $^1$H$^1$H-COSY spectrum as with others. The signals at 2.26 and 2.57 ppm were assigned as two non-equivalent protons of H-2. The signals at 2.53 and 1.95 ppm were assigned to H-6 protons. According to Karplus relationship coupling constants (J=15 and J=3.5 Hz) the signal at 2.26 indicates that H is an axial position and gain the doublet of doublet at 1.95 ppm with large coupling constant indicates that the signal an axial position as well.

![Figure 66: $^1$H$^1$H-COSY spectrum of 59](image)

The $^{13}$C-NMR spectrum was in agreement with $^1$H-NMR spectrum. Sixteen signals observed with $^{13}$C-NMR as was expected. The signal at 175.95 ppm can be assigned as carboxyl group and the signal at 168.19 ppm can be identified as a carbonyl group which belongs to the ester group at C-8. Two olefinic carbons were found at 147.26 and 117.60 ppm due to HMQC spectrum. Six aromatic carbons gave signals between 128.62 and 134.19 ppm. The small signal at 134.19 ppm indicates that it was belongs to C-11 which hasn’t got any hydrogen adjacent to it. The C-1 carbon with no hydrogen was found at 81.56 ppm with very small intensity. The signal at 74.71 ppm
was assigned to C-4 due to consistency between HMQC and $^1$H$^1$H-COSY spectrum. Two other signals at 68.88 and 66.37 ppm were identified as C-3 and C-5. The two signals in the aliphatic range of $^{13}$C-NMR spectrum at 38.73 and 34.61 ppm were assigned to C-2 and C-6. Infrared spectroscopy shows absorption for the acid and OH groups as expected. Mass spectrum shows the molecular ion and fragment ions corresponds the compound structure. Since the compound has some impurity, elemental analyses showed that C and H values below the specifications.

Figure 67: $^{13}$C-NMR spectrum of 59

Figure 68: $^1$H$^1$C-HMQC spectrum of 59
Results and discussion

Chapter 3

Synthesis of (1R, 3R, 4S, 5R)-1-(3, 4-dimethoxycinnamoyl)-3,4-isopropylidene-quinic acid, (58)-p194

Scheme 15: Synthesis of (1R, 3R, 4S, 5R)-1-(3, 4-dimethoxy-cinnamoyl)-3, 4-isopropylidene-quinic acid.

The synthesized (1R, 3R, 4S, 5R)-1-(3, 4-dimethoxycinnamoyl)-3, 4-isopropylidene-quinic acid was obtained with a yield of 90% by treating (1S, 3R, 4R, 5R)-1-(3, 4-dimethoxycinnamoyl)-3, 4-isopropylidene-quinic acid with LiOH in a degassed H₂O/THF (3ml/5ml) solution at room temperature for seventeen hours.

Figure 69: ¹H-NMR of (1S, 3R, 4R, 5R)-1-(3, 4-dimethoxycinnamoyl)-3, 4-isopropylidene-quinic, (58)
$^1$H-NMR revealed two aromatic protons appearing as doublets at 7.24 and 7.23 ppm respectively. One proton of the aromatic group H-12 appeared as a singlet at 7.03 ppm. Sets of olefinic protons were identified at 7.67 and 6.43 ppm. The signal at 7.67 ppm was assigned to H-10 and the signal at 6.43 ppm was assigned to H-9 due to $^1$H$^1$H-COSY and electronegative effects. Coupling constants of these two protons ($J=12.5$ Hz) indicate that both pairs of proton were trans to each other. Two methoxy groups, at 3.91 and 3.90 ppm appeared as two singlets with three proton intensity. The triplet at 4.59 ppm was assigned to H-3 following the $^1$H$^1$H-COSY spectrum and the coupling constant of $J 4.5$ Hz which showed that the proton was equatorial position according to Karplus equation. Another two single protons of quinic acid skeleton H-5 and H-4 were identified at 4.12 and 4.08 ppm as multiplets. Non-equivalent protons of two CH$_2$ groups appeared up field as usual. In accordance with the $^1$H$^1$H-COSY spectrum the signals at 2.77 and 2.38 ppm were assigned to H-2 protons. The doublet at 2.77 ppm was identified as H-2$_{eq}$ due to the coupling constant (J16.5 Hz). The signal at 2.40 ppm was a multiplet and therefore coupling constant for H-2$_{eq}$H-3$_{eq}$ could not be detected. Two other signals at 2.38 and 1.84 ppm identified as H-6 non-equivalent protons as indicated by $^1$H$^1$H-COSY spectroscopy. Two methyl group protons appeared in aliphatic region of spectrum at 1.48 and 1.37 ppm with three proton intensity as expected.
Comparison of the $^1$H-NMR spectrum of 58 with the $^1$H-NMR spectrum of 53 showed that the two spectra compare to each other quite well, the only the difference found being that with the acid form, the peaks slightly shifted to the up field which is consistent with the structures.

![Figure 71: $^1$H$^1$H-COSY spectrum of 58](image1)

![Figure 72: $^1$H$^1$C-HMQC spectrum of 58](image2)
The $^{13}$C-NMR spectrum of 58 supported these assignments in addition to carbonyl carbons at 177.85 ppm and 167.73 ppm. Two carbons of olefinic group signals appeared at 145.82 and 123.29 ppm. Three aromatic carbons with no hydrogen attached appeared at 150.55, 148.39 and 127.40 ppm. Another three protons of the aromatic group were identified at 115.91, 111.72 and 110.33 ppm. These signal assignments were confirmed by HMQC spectrum. The signal at 82.11 ppm was assigned to C-1. Three CH carbons of quinic acid were found at 79.80, 73.98 and 68.33 ppm. While the signal at 79.80 ppm was assigned to C-4, and two other signals were assigned to C-3 and C-5, C-2 was found at 37.49 ppm and C-6 was identified at 31.15 ppm. While two methyl carbons of acetyl group were assigned at 27.68 and 25.13 ppm and another carbon of acetyl group with no hydrogen attached was found at 109.46 ppm. Two methoxy groups appeared at 55.79 and 55.73 ppm.

The Infrared spectrum shows absorption of ester and other groups as expected. The protonated molecular ion at $m/z$: 422 suggested the molecular formula C$_{21}$H$_{26}$O$_9$ (M=422) which is in agreement with the product 58.

**Synthesis of (1R, 3R, 4S, 5R)-1-(3, 4-dimethoxycinnamoyl)-quinic acid, (60)-p196**

![Scheme 16: Synthesis of (1R, 3R, 4S, 5R)-1-(3, 4-dimethoxycinnamoyl)-quinic acid](image)

The product was obtained with a yield of 84% by treating (1S, 3R, 4R, 5R)-1-(3, 4-dimethoxycinnamoyl)-3, 4-isopropylidene-quinide with 2N HCl and THF solution at room temperature and hydrolysis of the acetal group achieved in three days.
Figure 73: $^1$H-NMR of $(1R, 3R, 4S, 5R)$-1-(3, 4-dimethoxycinnamoyl)-quinic acid

$^1$H-NMR shows two aromatic protons of aromatic group appeared as doublets at 7.04 ppm and 6.86 ppm respectively. One proton of aromatic group H-12 appeared as a singlet at 6.99 ppm. The sets of olefinic protons were identified at 7.53 and 6.33 ppm. The signal at 7.53 ppm was assigned to H-10 and the signal at 6.33 ppm was assigned to H-9 due to $^1$H$^1$H-COSY and electronegative effect. The coupling constants of these two protons $J=15.9$ Hz indicates that both pairs of proton were trans to each other. Two methoxy groups, at 3.86 and 3.82 ppm appeared as two singlets with three proton intensity. The triplet at 4.26 ppm was assigned to H-3 following the $^1$H$^1$H-COSY spectrum. The coupling constant $J=3.65$ Hz showed that the proton was in an equatorial position according to Karplus equation. Another two single protons of quinic acid skeleton H-5 and H-4 were identified at 4.14 and 3.61 ppm as a multiplet and a triplet. The non-equivalent protons of two CH$_2$ groups appeared up field as expected. Due to the $^1$H$^1$H-COSY spectrum the signal at 2.55 and 2.26 ppm were assigned to H-2 protons. The doublet at 2.55 ppm was identified as H-2$_{eq}$ due to dihedral angle close to 90° and a coupling constant was found as $J=4.84$ Hz. The other two signals at 2.50 and 1.96 ppm identified as H-6 non-equivalent protons due to $^1$H$^1$H-COSY spectrum.
As we observed from the $^1$H-NMR spectrum two peaks for methyl protons doesn’t appear anymore. Comparing the $^1$H-NMR spectrum of 60 with the $^1$H NMR spectrum of 58 showed that the two spectra are consistent with each other apart from the two methyl protons disappearance. The $^{13}$C-NMR spectrum of 60 supported these assignments in addition to carbonyl carbons at 175.26 ppm and 168.08 ppm. Two carbons of olefinic group signals appeared at 147.02 and 123.61 ppm. Three aromatic carbons which haven’t got any hydrogen attached to it appeared at 150.63, 148.12 and 127.02 ppm and were assigned as C-OMe, C-OMe and C$_{Ar}$. Another three protons of aromatic group were identified at 114.48, 111.35 and 110.03 ppm. The signal assignments were confirmed by $^1$H$^{13}$C-HMQC spectrum and $^1$H$^1$H-COSY spectrum. The signal at 77.99 ppm was assigned to C-1. Three carbons of quinic acid were found at 74.44, 68.59 and 66.13 ppm. While the signal at 74.44 ppm was assigned to C-4, another two signals 68.59 and 66.13 ppm were assigned to C-3 and C-5. The C-2 was found at 38.46 ppm and C-6 was identified at 34.30 ppm. Two methoxy carbons appeared at 55.65 and 55.50 ppm.
The Infrared spectrum shows absorption of ester and other groups as expected. The protonated molecular ion at \( m/z: 382 \) suggested the molecular formula \( C_{18}H_{22}O_9 \) which is in agreement with the product (60).

**Figure 75: \(^1\)H\(^{13}\)C-HMQC spectrum of 60**

**Syntesis of 5- acetyl p-coumaroyl bisacetonide, (66)-p202**

The 5- acetyl p-coumaroyl bisacetonide was obtained in by condensation of bisacetonide (49) with 1.1 equivalent acetyl p-coumaric acid chloride by using 5 %
DMAP in DCM and pyridine solution. The reaction reached completion in twelve hours to give the corresponding ester as colourless solid.

**Figure 76:** $^1$H-NMR spectrum of 5-acetyl p-coumaroyl bisacetonide, (66)

The $^1$H-NMR spectrum shows that the reaction was achieved successfully. All the peaks are present as it was expected. The singlets found at 1.23, 1.42 and 1.58 ppm were assigned to four methyl protons of two acetal peaks. The peaks at 1.23 and 1.42 ppm with three proton intensity assigned to H-9 and H-10. The next peak at 1.58 ppm occurred with six proton intensity and assigned to H-12 and H-13 protons. As before two non equivalent protons of CH$_2$ groups were identified by considering chemical shifts and $^1$H$^1$H-COSY spectrum. The multiplet at 2.01 ppm and doublet of doublet at 2.13 ppm were assigned to 6-H$_{ax}$ and 2-H$_{ax}$ due to large coupling constants and the cross peaks at $^1$H$^1$H-COSY spectrum. The other pair of non equivalent protons of CH$_2$ groups were found at 2.17 ppm and 2.21 ppm with smaller coupling constants ($J$ 3.2 and $J$ 4.1). According to Karplus relationship coupling constants the triplet at 2.17 ppm was assigned to 6-H$_{eq}$ and then the doublet was assigned to 2-H$_{eq}$ respectively due to small coupling constants. The three protons of the methoxy group occurred at 2.29 ppm with three signal intensity as expected. From the $^1$H$^1$H-COSY spectrum the signal at 3.96 ppm was identified as H-4 due to crosspeaks to H-5 and H-3. Due to
chemical shift and $^1$H-$^1$H-COSY spectrum the signals at 4.02 and 4.47 ppm were assigned to H-3 and H-5 protons. H-3 appeared as multiplet and H-5 as doublet of doublet ($J$ 10.1 and 4.6). The peaks at 6.41 and 7.73 ppm were assigned as peaks of olefinic protons. These peaks assigned to H-15 and H-16 respectively due to chemicals shift considerations. Two identical protons of coumaroyl moiety were identified at 7.12 and 7.55 ppm as two doublets with the same coupling constant ($J$ 8.7 Hz).

![Figure 77: $^{13}$C-NMR spectrum of 5- acetyl p-coumaroyl bisacetonide, (66)](image)

The $^{13}$C-NMR spectrum was in an agreement with $^1$H-NMR spectrum. Twenty four signals were observed as expected. The signal at 21.03 ppm was assigned to the acetal methyl carbon of coumaroyl moiety C-24. The four carbons of two acetonide were found at 25.47, 27.96, 28.37 and 28.48 ppm. These carbons were assigned to C-9, C-10, C-12 and C-13 carbons. Two non equivalent carbons of quinic acid signals found at 35.02 and 39.75 ppm and were assigned to C-6 and C-2. The three typical carbons of quinic acid moiety which has hydrogen attached to each carbon found at 66.97, 72.03 and 77.49 ppm and each one of them assigned to C-5, C-3 and C-4 carbons due to HMQC spectrum. The C-1 carbon next to carboxyl group occurred at 77.82 ppm.
with small signal intensity since there is no hydrogen attached to it. The two carbons of acetal group which haven’t got any other atom attached to it were found at 108.61 and 110.64 ppm and both assigned to C-8 at C-11. The two carbons of coumaroyl moiety occurred at 119.09 and 143.20 ppm. The five carbons of aromatic group occurred at 122.07, 122.27 129.01 and 132.17 ppm. The first signal at 122.07 ppm found with two signal intensity and due to HMQC spectrum this signal were assigned to C-19 and C-21. The other three signals were assigned as C-22, C-18 and C-17. The last carbons of aromatic group which are adjacent to oxygen atom occurred at 151.85 ppm and were assigned to C-20. Two carbonyl signals found at 168.37 and 168.98 ppm which were assigned to C-14 and C-24. The last carbon occurred at 175.17 ppm which was assigned to C-7. Infrared spectrum shows all the data is in agreement with rest of the spectroscopic evidence.

Figure 78: $^1$H$^{13}$C-HMQC spectrum of 5- acetyl $p$-coumaroyl bisacetonide, (66)
Figure 79: IR spectrum of 5- acetyl p-coumaroyl bisacetonide, (66)

Synthesis of 5-O-p-coumaroylquinic acid, (71)-p207

Scheme 18: Synthesis of 5- o- p-coumaroylquinic acid, (71)

5- coumaroyl -bisacetonide treated with a solution of one part THF to two parts HCl solution at room temperature. Hydrolysis of the acetal groups was achieved after twenty four hours as before. The same reaction steps were used as before for the synthesis of 5-O-p-caffeoylquinic acid (69) and the same reaction was performed for the synthesis of Synthesis of 5-ferolyl-quinic acid (70), Synthesis of 5-cinnamoyl-quinic acid (73) and for the Synthesis of 5-(3,4-dimethoxycinnamoyl)- quinic acid (72). All the spectroscopic data were in line for the five products. As an example 5-O- p-coumaroylquinic acid spectral data are analysed below.
After comparing the $^1$H-NMR spectrum of 5-acetyl $p$-coumaroyl bisacetonide (66) and 5-O-$p$-coumaroylquinic acid (71) spectral data shows that all the protecting groups were removed successfully. The characteristic signals for the methyl groups disappeared from all the spectral data and the ester was converted to acid. As before two non-equivalent protons of CH$_2$ groups were identified by considering chemical shifts and $^1$H$^1$H-COSY spectrum. The signals at 1.66 and 1.81 ppm were assigned to non-equivalent two protons of H-6. The signal at 1.69 and 1.82 ppm were assigned to non-equivalent two protons of H-2. According to the Karplus relationship, for coupling constants, the signals at 1.66 and 1.69 indicates that these two protons belong to 6-H$_{ax}$ and 2-H$_{ax}$ respectively due to large coupling constants. The other signals at 1.81 and 1.82 ppm were assigned to 6-H$_{eq}$ and 2-H$_{eq}$ form the $^1$H$^1$H-COSY spectrum. From the $^1$H$^1$H-COSY spectrum the signal at 3.21 ppm identified as H-4 due to crosspeaks to H-5 and H-3. Due to chemical shift and the $^1$H$^1$H-COSY spectrum the signals at 3.71 and 3.84 ppm were assigned to H-3 and H-5 protons. H-3 appeared as doublet of doublet of doublets, and H-5 as quintet. The identical peaks at 6.22 and 7.45 ppm were assigned to olefinic protons H-9 and H-10. The four affordable protons of coumaroyl moiety were found at 6.74 and 7.48 ppm with two proton intensity. The signals of the two protons were overlapping on top of each other.
Figure 81: $^1$H-$^1$H-COSY spectrum of 5-O-p-coumaroylquinic acid, (71)

Figure 82: $^{13}$C-NMR spectrum of 5-O-p-coumaroylquinic acid, (71)

The $^{13}$C-NMR spectrum was in agreement with $^1$H-NMR spectrum. Again spectrum showed that all the protecting groups were removed successfully. Two non
equivalent methylene carbons of quinic acid were found at 39.51 and 39.72 ppm and were assigned to C-6 and C-2. The three typical CHO carbons of quinic acid carbons which have one hydrogen attached each were found at 63.68, 66.05 and 72.04 ppm and each one of them was assigned to C-3, C-4 and C-5 carbons respectively due to HMQC spectrum. C-1 carbon next to carboxyl group occurred at 76.41 ppm with low signal intensity. The two carbons of olefinic caffeoyl moiety occurred at 115.79 and 142.85 ppm. The first four carbons of the aromatic group occurred at 116.9 and 127.62 ppm. Each signal occurred with two carbon intensity and they were assigned to C-13, C-15, C-12 and C-16. These signals proved that $^{13}$C-NMR spectrum was in agreement with $^1$H-NMR spectrum. Another two carbons of aromatic group occurred at 130.60 ppm and 169.13 ppm. The signal at 130.60 ppm which was adjacent to hydroxyl group assigned to C-11 and the other signal at 169.13 ppm was assigned to C-14 with no hydrogen attached to it. Another set of carbonyl carbons found at 168.49 and 176.11 ppm were assigned to C-8 and C-7 respectively. The Infrared spectrum confirmed the assigned peaks $^1$H-NMR spectrum and $^1$H$^1$H-COSY spectrum.

Figure 83: $^1$H$^{13}$C-HMQC spectrum of 5-O-$p$-coumaroylquinic acid, (71)
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Figure 84: IR spectrum of 5-O-<i>p</i>-coumaroylquinic acid, (71)

**Synthesis of (1S, 3R, 4R, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-4-dimethoxycinnamoyl quinide, (75)-p211**

![Scheme 19](image)

**Scheme 19**: Synthesis of (1S, 3R, 4R, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-4-dimethoxycinnamoyl quinide, (75)

To a solution of Troc-quinide and DMAP in dichloromethane were added 3,4-dimethoxycinnamic acid chloride in pyridine. The reaction solution was stirred for 12 hours at room temperature and reaction was worked up by diluting with
dichloromethane, washing with 2M HCl, NaHCO$_3$ solution and brine. The organic solvent was removed under reduced pressure to give title compound (75) as a slightly yellow powder in a 94% yield. Interestingly only a single regioisomer was observed in this reaction.

Careful analysis of spectroscopic data (below) allows assignment of the product on the 4-caffeoyl regioisomer. It appear as if the axial OH group is earlier deprotected by pyridine has a high reactivity towards the acyl chloride.

![Figure 85: $^1$H-NMR spectrum of 75](image)

Examination of $^1$H NMR spectrum of the compound shows that the peaks at 1.86, 2.19, 2.48 and 2.76 ppm were belongs to CH$_2$ groups of the quinide. The two non-equivalent protons of H-6 appeared as doublet of doublets at 2.19 ppm and a doublet of doublet of doublets at 2.76 ppm. Other non-equivalent protons which belong to H-2 CH$_2$ protons occurred at 1.86 and 2.48 ppm as two doublets of doublets. The doublet of doublet with small coupling constant ($J=9.2$ and $J=3.2$ Hz) at 3.54 ppm assigned to H-5 due to it’s crosspeaks to H-4 and H-3, protons which were found in $^1$H-$^1$H-COSY spectrum. Two methoxy protons were found in the typical range of the methyl protons at 3.84 and 3.90 ppm. Each signal showed that three proton intensity and were assigned to H-20 and H-21 protons. The other two peaks occurred at 4.13 and 4.21 ppm as one quintet one triplet. The triplet at 4.21 ppm, due to small coupling constant and correlation identified in $^1$H-$^1$H-COSY spectrum showed that this signal was H-4.
Then the other signal at 4.13 ppm assigned to H-3 due to crosspeaks at \( ^1\text{H}^1\text{H}-\text{COSY} \) spectrum. The two identical CH\(_2\) protons of Troc group were found at 4.73 and 4.78 ppm. The calculation of the coupling constants (\( J = 11.9 \text{ Hz} \)) proved that these two protons were identical. Another identical CH=CH protons were found at 6.28 ppm and 7.68 ppm as two doublets with very large coupling constant (\( J = 16 \text{ Hz} \)). These two protons identified as CH=CH protons of caffeoyl moiety and were assigned to H-12 and H-13. Three set of aromatic protons occurred as two doublets and one doublet of doublet at 6.85, 7.05 and 7.06 ppm. The signals were assigned to H-15, H-18 and H-19 respectively due to chemical shift.

![Figure 86: \(^{13}\text{C}-\text{NMR} \) spectrum of 75](image)

The \(^{13}\text{C}-\text{NMR} \) showed twenty one signals as expected. Two CH\(_2\) carbons were found at 33.90 and 38.59 ppm, these two signals were assigned to C-2 and C-6 due to crosspeak in \(^1\text{H}^1\text{H}-\text{COSY} \) spectrum and HMQC spectrum. Due to highfield shift of C-4 in \(^{13}\text{C}-\text{NMR} \) and \(^1\text{H}-\text{NMR} \) the compound was assigned as the 4-acylated isomer. The two methoxy carbons were found at 55.99 and 56.07 ppm. The significant protons of quinide C-3, C-4, C-5 were seen at 66.69, 68.46 and 76.79 ppm respectively. These peaks were identified clearly due to HMQC spectrum of the compound. The peak at 83.56 ppm was identified as C-1 carbon. Another peak at 94.42 with small intensity and the results of HMQC spectrum proved that this peak was belong to C-10 carbon which is adjacent to chlorine atom in the Troc protecting group.
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Combination of $^1$H-$^1$H-COSY and HMQC shows that the signals at 115.07 ppm and 146.83 ppm belong to a pair of CH=CH olefinic protons which are assigned to C-12 and C-13. The aromatic group carbons appeared at 109.87, 111.13, 127.18 ppm and these signal are assigned to C-15, C-19, C-14. The other two aromatic signals at 149.34 and 151.56 ppm, shifted because of which has oxygen next to them were assigned to C-16 and C-17. Three carbonyl carbons found at 151.56, 152.22 and 170.97 ppm. These peaks were assigned to C-7, C-8 and C-11 due to crosspeaks at HMQC spectrum. IR spectrum shows absorptions for carbonyl ester as expected. The mass spectrum shows the molecular ion and fragment ions corresponding to structure of compound. The same method was applied for the synthesis of (1S, 3R, 4R, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-4-cinnamoyl quinidine, (74), (1S,3R,4R,5R)-1-(β, β, β-trichloroethoxycarbonyl)-4-acetylferuloyl quinidine, (76) (1S,3R,4R,5R)-1-(β, β, β-trichloroethoxycarbonyl)-4-acetyl p-coumaroyl quinidine, (77), (1S,3R,4R,5R)-1-(β, β, β-trichloroethoxycarbonyl)-4-diacetylcaffeoyl quinidine, (78). All the reactions successfully produced the desired compounds in very good yields. The synthesised compounds are shown below.

**Scheme 20:** Synthesis of (1S, 3R, 4R, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-4-cinnamoyl quinidine, (74)

**Scheme 21:** Synthesis of (1S,3R,4R,5R)-1-(β, β, β-trichloroethoxycarbonyl)-4-acetylferuloyl quinidine, (76)
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Scheme 22: Synthesis of (1S,3R,4R,5R)-1-(β, β-trichloroethoxycarbonyl)-4-acetyl p-coumaroyl quinide, (77)

Scheme 23: Synthesis of (1S,3R,4R,5R)-1-(β, β-trichloroethoxycarbonyl)-4-diacetylcaffeoyl quinide, (78)

Figure 87: \(^1\text{H}\)\(^{13}\text{C}\)-HMOC spectrum of 75
Optimization of the mono substituted chlorogenic acids and esters:

There are two possible substitutions for the mono-acyl chlorogenic acids (esters). Since there is only one substituent, the acyl group can either attach an axial or equatorial position. It was described in the literature that the cyclohexanes are more stable if the substituents are in the equatorial position. Also, according to the experimental data, the acylation of a hydroxyl group produces a paramagnetic (downfield) shift of about 1.2-1.4 ppm of the hydrogen attached to the carbon has the acyloxy group. These chemical shifts were clearly seen in the NMR spectrums of the each compound.

The experimental results proved the assumption that since all the acylation reactions were performed at room temperature; protecting groups, nature of solvent and the possibility of inter- or intramolecular acyl migration are the most important factors in the control of diastereoselectivity in these reactions which are presented in this work.
The experimental data proved that the type of organic base also plays an important role especially, in the synthesis of mono acyl chlorogenic acids (esters) as well as producing di-substituted chlorogenic acids or esters.

It was concluded that for the di-substituted chlorogenic acids or esters; triethylamine being a stronger base (pKa ~ 10) and perhaps it can deprotonate one of the axial hydroxyl groups, whose acidity is higher than that of normal alcohols due to very strong intramolecular hydrogen bond. Therefore, the substitution may occur at axial H-4 proton as well as equatorial H-3 proton or H-1 proton. Therefore, triethylamine was preferred for the synthesis of the di-acyl and poly-acyl substituted chlorogenic acids or esters. Whereas, pyridine is a weak organic base (pKa ~ 7) and it can not deprotonate the C-4 hydroxyl group. Hence, the reactivity of pyridine among the three hydroxyl groups is determined by the relative nucleophilicity and steric factors. Therefore, based on outcome of the experimental data pyridine is the most appropriate solvent for the mono substituted chlorogenic acids or esters.

Interestingly, $^1$H-NMR spectrum of the Troc protected mono substituted chlorogenic acid derivatives for example; (1$S$, 3$R$, 4$R$, 5$R$)-1-(β, β, β-trichloroethoxycarbonyl)-4-dimethoxycinnamoyl quinide (75), showed that the substitution was occurred at H-4 axial proton instead of H-3 equatorial proton which is generally most preferred. Presumably, dielectric behaviour of the Troc protecting group and steric hindrance caused by a large protecting group allowed 3,4-dimethoxychloride to attach to the least preferred axial H-4 proton.

The same results were observed in the synthesis of (1$S$, 3$R$, 4$R$, 5$R$)-1-(β, β, β-trichloroethoxycarbonyl)-4-cinnamoyl quinide, (74), (1$S$,3$R$,4$R$,5$R$)-1-(β, β, β-trichloroethoxycarbonyl)-4-acetylferuloyl quinide, (76) (1$S$,3$R$,4$R$,5$R$)-1-(β, β, β-trichloroethoxycarbonyl)-4-acetyl p-coumaroyl quinide, (77), (1$S$,3$R$,4$R$,5$R$)-1-(β, β, β-trichloroethoxycarbonyl)-4-diacetylcaffeoyl quinide, (78).
Synthesis of (1S, 3R, 4R, 5R)-3-diacetylcaffeoyl quinide, (79)-p215, (80)-p216

![Chemical structure](image)

**Figure 89:** Step 1 - (79), (80)

![Chemical structure](image)

**Figure 90:** Step 2 - (79), (80)

Synthesis of (1S, 3R, 4R, 5R)-3-diacetyl caffeoyl quinide was obtained in two steps. First of all acylation of Troc protected quinide (79) was achieved by reacting Troc quinide with 2.2 equivalent of diacetyl caffeic acid chloride in dichloromethane and triethylamine solution. Reaction was stirred for eighteen hours then worked up by treating with dichloromethane, and washing with 2M HCl, NaHCO₃ solution and brine. After removal of solvents, a mixture of compounds was obtained as yellow solid. Purification of the product with chloroform-acetone (8:2) provided the (1S, 3R, 4R, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-3-diacetylcaffeoyl quinide (79) in 44% yield.

Then zinc powder used as reagent to cleave off the Troc protecting group. Reaction performed in acetic acid solution and completed in 48 hours and product was obtained in 31%. Comparison of the spectra showed that the two diastereopic protons of the Troc group disappeared from all the spectra. The same reaction was repeated by replacing caffeoyl chloride with ferruloyl chloride, coumaroyl chloride,
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dimethoxycinnamoyl chloride and cinnamoyl chloride. All the reaction achieved successfully resulting (1S, 3R, 4R, 5R)-3-acetylferuloyl quinide, (81), (1S, 3R, 4R, 5R)-3-acetyl p-coumaroyl quinide, (82), (1S, 3R, 4R, 5R)-3-dimethoxycinnamoyl quinide, (83) and (1S, 3R, 4R, 5R)-3-cinnamoyl quinide, (84) final products which are shown below.

Scheme 24: Synthesis of (1S, 3R, 4R, 5R)-3-acetylferuloyl quinide, (81)

Scheme 25: Synthesis of (1S, 3R, 4R, 5R)-3-acetyl p-coumaroyl quinide, (82)

Scheme 26: Synthesis of (1S, 3R, 4R, 5R)-3-dimethoxycinnamoyl quinide, (83)
Scheme 27: Synthesis of (1S, 3R, 4R, 5R)-3-cinnamoyl quinide, (84)

Figure 91: $^1$H-NMR spectrum of (1S, 3R, 4R, 5R)-3-diacetylcaffeoyl quinide, (80)

$^1$H-NMR confirmed that the product was produced successfully. The two typical methyl protons were found at 2.28 and 2.29 ppm with three proton intensity each. The signals at 2.07, 2.30, 2.33 and 2.63 ppm correspond to 2-H$_{ax}$, 6-H$_{eq}$, 6-H$_{ax}$ and 2-H$_{eq}$ due to crosspeaks in the $^1$H$^1$H-COSY spectrum. The three quinide protons were found at 4.35, 4.81 and 4.99 ppm. The first peak at 4.35 occurred as triplet and it was assigned to H-4 which was identified from the $^1$H$^1$H-COSY spectrum. The other triplet at 4.81 ppm was assigned to H-5 and the quintet was assigned to H-3 based on crosspeaks from the $^1$H$^1$H-COSY spectrum. The two olefinic protons of caffeoyl
groups found at 7.24 and 7.64 ppm which were assigned to H-9 and H-10 protons due to chemical shift. Both signals showed large coupling constant (J= 16 Hz) which showed that both protons were trans to each other. The three aromatic protons were found at 7.24, 7.35 and 7.37 ppm. These peaks were occurred as two doublets and one doublet of doublets and were assigned to H-12, H-15 and H-16 respectively due to \(^1\)H\(^1\)H-COSY spectrum and HMQC spectrum.

\(^{13}\)C-NMR was in agreement with the assignments of the \(^1\)H-NMR spectrum. Two methyl groups which are belong to caffeoyl moiety was observed as overlapping two signals at 20.82 ppm assigned to C-19 and C-20. Two CH\(_2\) appeared at 30.93 and 35.82 ppm. Typical quinide carbons were found at 71.36, 72.66 and 75.62 ppm. Due to \(^1\)H\(^1\)H-COSY and HMQC spectrum the signal at 71.36 ppm as signed to C-4, the signal at 72.66 ppm C-3 and the signal at 75.62 ppm assigned to C-5. C-1 carbon found at 78.76 ppm with small signal intensity. The two identical olefinic carbons of caffoyl moiety were found at 116.14 ppm and 142.54 ppm. Due to chemical shifht which caused by electronegative effect the signal at 116.14 ppm assigned to C-9 and the signal at 142.54 ppm assigned to C-10. Another six set of signals occurred at 122.19, 123.84, 126.45, 131.27, 143.22 and 145.11 ppm. The first three peaks were assigned to C-12, C-15 and C-16 which each has one hydrogen atom attached to it. Then the other signal at 131.27 ppm assigned to C-11 which has very small signal intensity compare to other aromatic carbons. Then C-13 and C-14 found at 143.22 and 145.11 ppm which are next to the acetyl group of caffeoyl moiety. The four carbonyl functional groups were identified at 166.92, 168.78, 168.94 and 170.22 ppm and these were assigned to C-8, C-17, C-18 and C-7 carbons. Infrared spectra of the compound showed the relevant signals as it was expected.
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Figure 92: $^1$H-NMR spectrum of (79)

Figure 93: $^{13}$C-NMR spectrum of (79)
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Figure 94: $^1$H$^{13}$C-HMOC spectrum of (79)

Figure 95: IR spectrum of (79)
To verify the regiochemical assignments:

In case of mono substituted chlorogenic acids or esters, if the starting material is quinide itself without any protecting groups, there are three different possibilities for the acylation of the hydroxyl groups which are attached at C-1, C-3 or C-4 carbons.

After collecting the column fractions for nonselective synthesis, it was observed that the mono substituted chlorogenic acid esters were always at the third position of the quinide moiety. It was concluded that the addition to the free hydroxyl group at C-1 was very difficult or impossible because of the steric hindrance which was caused by carbonyl function. In fact there is no other free hydroxyl available for the acylation of the compound then the substituent could attach to the hydroxyl at C-1. Moreover, more acidic hydroxyl groups expected to be less nucleophilic than basic hydroxyl groups. Therefore, for the nonselective synthesis starting from quinide (51) in the presence of triethylamine without any protecting group allowed acylation to occur at the third position of the quinide moiety as it was observed in the synthesis of the (1S, 3R, 4R, 5R)-3-acetylferuloyl quinide, (81), (1S, 3R, 4R, 5R)-3-acetyl p-coumaroyl quinide, (82), (1S, 3R, 4R, 5R)-3-dimethoxycinnamoyl quinide, (83) and (1S, 3R, 4R, 5R)-3-cinnamoyl quinide, (84). The signals and the chemical shifts which were occurred on the $^1$H-NMR spectrum of the compounds (81), (82), (83) and (84) proved that the assumption was correct.

As an example, the chemical shift assignments of the $^1$H-NMR spectrum for the (1S, 3R, 4R, 5R)-3-acetylferuloyl quinide, (81), showed that the acylation of hydroxyl groups produces a paramagnetic shift of about 1.16 ppm of the hydrogen attached to the carbon having the acyloxy group. As expected the proton at H-3 was shifted to downfield ($\delta = 3.87$ ppm to $\delta = 5.03$ ppm). However, it was observed that the acylation of the hydroxyl group at the third position of the quinide moiety leads paramagnetic SCS effect of the direct neighbouring protons. The comparison of the $^1$H-NMR spectrum for the (1S, 3R, 4R, 5R)-3-acetylferuloyl quinide, (81) and quinide (51) showed that H-2 and H-4 protons were moved to the downfiled of the spectrum about +0.17 ppm and +0.20 ppm respectively. It was also observed that the esterification of acyl chlorides with quinide also leads to paramagnetic shift of the olefinic protons CH=CH as well as H-3 proton.
**Synthesis of (1S, 3R, 4R, 5R)-1-(β,β,β-trichloroethoxycarbonyl)-3, 4-di-(3, 4-dimethoxycinnamoyl)-quinide: (86)-p222**

![Scheme 28: Synthesis of (1S, 3R, 4R, 5R)-1-(β,β,β-trichloroethoxycarbonyl)-3, 4-di-(3, 4-dimethoxycinnamoyl)-quinide](image.png)

The synthesized di-(3, 4-dimethoxycinnamoyl)-quinide compound (86) was obtained with a yield of 57.4% by acylation of Troc protected quinide with 2.2 equivalent 3, 4-dimethoxycinnamoyl chloride by using 5% DMAP in DCM and Et3N solution. The product was purified by recrystallisation from EtOH.

![Figure 96: 1H-NMR spectrum of (86)](image.png)
The identification of the product was supported by the $^1$H-NMR spectrum of the compound. First, four sets of signals were found at 2.47, 2.56, 2.75 and 3.21 ppm. Due to $^1$H$^1$H-COSY spectrum and concerning chemical shifts the peaks at 2.47 ppm were assigned to 2-H$_{ax}$ and the peak at 2.75 ppm assigned to 2-H$_{eq}$. The other two non-equivalent protons of a CH$_2$ group were found at 2.56 and 3.21 ppm. These peaks assigned to 6-H$_{eq}$ and 6-H$_{ax}$ protons. The four methoxy group of dimethoxycinnamic acid moiety occurred at 3.21, 3.81, 3.89 and 3.91. All of these four peaks appeared as singlets and every one of them occurred with three proton intensity. Further more two signals at 4.75 and 4.85 ppm were assigned to the CH$_2$ groups of Troc group. Each peak had large coupling constant 12 Hz. Due to Karplus equation along with $^1$H$^1$H-COSY spectral data proved that these two peaks were trans to each other. The three protons of the quinide moiety were found at 5.03, 5.38 and 5.72 ppm was assigned. The peak at 5.72 ppm assigned to H-4 after carefully analysing the $^1$H$^1$H-COSY spectrum. Once the H-4 proton was identified the other protons were identified due to chemical shift and the crosspeak in the $^1$H$^1$H-COSY. As a result the multiplet at 5.38 ppm was assigned to H-3 and the quintet with small coupling constant (J= 5.5 Hz) assigned to H-5 proton. The other two sets of protons identified at 6.31, 6.38, 7.58 and 7.68 ppm. Due to chemical shifts and the crosspeaks in the $^1$H$^1$H-COSY spectrum the first two peaks at 6.31 and 6.38 were assigned to H-12 and H-23 then the other pear at 7.58 and 7.68 ppm were identified as H-13 and H-14. At last the aromatic protons were found between 6.78 and 7.03 ppm as multiplets.

The $^{13}$C-NMR shows consistent signals with $^1$H-NMR spectrum. The two CH$_2$ carbons were found at 33.99 and 34.06 ppm. The signal at 33.99 ppm assigned to C-2 and the other signal at 34.06 ppm assigned to C-6. The for methoxy protons were occurred at 56.05, 56.20, 56.27 and 56.32 ppm and assigned to C-20, C-21, C-31 and C-32 carbons respectively. The three protons of quinide were appeared at 64.95, 65.96 and 74.02 ppm. Due to crosspeaks at HMQC spectrum these peaks were assigned to C-4, C-3 and C-5 carbons. The CH$_2$ carbons of Troc protecting group was occurred at 77.50 ppm assigned to C-9. Another carbon atom of quinide which is next to carbonyl group was found at 79.03 ppm and assigned to C-1. This peak was followed by another Troc protecting group carbon which is adjacent to chlorine atom. This carbon was occurred at 94.13 ppm with very small intensity and assigned to C-10. The four pear of C=CH protons were found at 114.07, 114.40, 146.50 and 1147.11...
The first two peaks assigned to C-12 and C-23 due to crosspeaks at $^1$H$^1$H-COSY spectrum then the other peak at 146.50 and 1147.11 ppm assigned to C-13 and C-24. The four carbons of each aromatic group were found around 109.90, 110.02, 111.20, 111.30, 123.14, 123.46, 127.02 and 127.22 ppm. The peaks were assigned to C-15, C-26, C-18, C-29, C-19, C-30, C-14 and C-25 carbons. The other set of peaks at 149.42, 149.59, 151.65 and 151.99 ppm were the peaks which are adjacent to oxygen atoms. These peaks assigned C-16, C-17, C-27 and C-28. The peak at 152.14 ppm assigned to C-8 carbonyl carbon the it followed by the peaks at 165.36 ppm which was assigned to C-11 then the other peak at 165.64 ppm which was assigned to C-22. The last peak in very down filed found at 170.31 ppm and assigned to C-7.

![Figure 97: $^{13}$C-NMR spectrum of (86)](image)

The infrared spectrum shows absorptions for the carbonyl ester and the aromatic groups as expected. The mass spectrum shows the molecular ion and a series of fragment ions corresponding to dehydrated fragments of the title compound 86.
The same reaction was repeated by replacing dimethoxycinnamoyl chloride with caffeoyl chloride and cinnamoyl chloride. All the reactions were achieved successfully resulting in \((1S, 3R, 4R, 5R)-1-(\beta, \beta, \beta\text{-trichloroethoxycarbonyl})-3,4\text{-bis-(diacetylcaffeoyl)}\) quinide, \((85)\), \((1S,3R,4R,5R)-1-\) \((\beta,\beta,\beta\text{-trichloroethoxycarbonyl})-3, 4\text{-di-cinnamoyl quinide, (87) as final products shown below.}\)
**Scheme 29:** Synthesis of (1S, 3R, 4R, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-3,4-bis-(diacetylcaffeoyl) quinide, (85)

**Scheme 30:** Synthesis of (1S,3R,4R,5R) 1- (β,β,β-trichloroethoxycarbonyl)-3, 4-dicinnamoyl quinide, (87)

**Synthesis of (1S, 3R, 4R, 5R)-3, 4-di-(3, 4-dimethoxycinnamoyl)-quinide: (88)-p224**

**Scheme 31:** Synthesis of (1S, 3R, 4R, 5R)-3, 4-di-(3, 4-dimethoxycinnamoyl)-quinide
The synthesized di-(3, 4-dimethoxycinnamoyl)-quinide product was obtained with a yield of 80% by removal of the Troc group. Zinc powder was used as reagent to cleave the Troc group. The two diastereopic protons of the Troc group form two doublets at 4.8 ppm and 4.7 ppm not apparent in the $^1$H-NMR spectrum of the product. The reactions with feruloyl chloride and caffeoyl chloride required column chromatography which was performed with chloroform-acetone (8:2) to give the title products.

![Figure 99: $^1$H-NMR spectrum of 88](image)

The $^1$H-NMR spectrum of the compound proved that the product was pure. First four sets of signals found at 2.27, 2.38, 2.52 and 2.64 ppm. Due to $^1$H$^1$H-COSY spectrum and concerning chemical shifts the peaks at 2.27 ppm assigned to 2-H$_{ax}$ and the doublet at 2.64 ppm assigned to 2-H$_{eq}$. The other two non-equivalent protons of CH$_2$ group were found at 2.38 and 2.52 ppm. These peaks assigned to 6-H$_{eq}$ and 6-H$_{ax}$ protons. The four methoxy group of dimethoxycinnamic acid moiety occurred at 3.82, 3.88, 3.92 and 3.93. All of these four peaks appeared as singlet and every one of them occurred with three proton intensity. Comparison of 90a $^1$H-NMR spectrum with the current spectra showed that two signals at 4.75 and 4.85 ppm which were belong to CH$_2$ groups of Troc group were completely disappeared from the $^1$H-NMR spectra. The three protons of quinide moiety were found at 4.95, 5.29 and 5.69 ppm. The doublet of doublet at 5.69 ppm assigned to H-4 after analysing the $^1$H$^1$H-COSY
spectrum. Once H-4 proton identified the other protons were identified due to chemical shift and the crosspeak at the $^1$H$^1$H-COSY. As a result the multiplet at 5.29 ppm assigned to H-3 and the triplet with small coupling constant ($J = 5.5$ Hz) assigned to H-5 proton. The other two sets of protons identified at 6.21, 6.38, 7.58 and 7.68 ppm as before. Due to chemical shifts and the crosspeaks at $^1$H$^1$H-COSY spectrum the first two peaks at 6.21 and 6.38 assigned to H-9 and H-18 then the other peak at 7.58 and 7.68 ppm identified as H-10 and H-19. All of these for signals occurred as doublets with very large coupling constant ($J=15.5-16$ Hz) and this proved the protons were in axial position and trans to each other. At last the aromatic protons found between 6.72 and 6.88 ppm as multiplet.
The $^{13}$C-NMR shows consistent signals with $^1$H-NMR spectrum. The two CH$_2$ carbons were found at 37.11 and 37.69 ppm. The signal at 37.11 ppm assigned to C-2 and the other signal at 37.69 ppm assigned to C-6. The for methoxy protons were occurred at 56.03, 56.19, 56.27 and 56.28 ppm as the previous spectra and assigned to C-13, C-14, C-26 and C-27 carbons respectively. The three protons of quinide were
appeared at 64.84, 66.44 and 72.34 ppm. Due to crosspeaks at HMQC spectrum these peaks were assigned to C-4, C-3 and C-5 carbons. The CH$_2$ carbons of Troc protecting group was again disappeared at 77.50 ppm. Another carbon atom of quinide which is next to carbonyl group was found at 74.29 ppm and assigned to C-1. The four pear of C=CH protons were found at 114.30, 114.66, 146.31 and 146.91 ppm. The first two pear assigned to C-9 and C-18 due to crosspeaks at $^1$H$^1$H-COSY spectrum then the other pear at 146.31 and 146.91 ppm assigned to C-10 and C-19. The four carbons of each aromatic group were found around 110.02, 110.05, 111.19, 111.32, 123.11, 123.38, 127.08 and 127.27 ppm. The peaks were assigned to C-12, C-21, C-15, C-24, C-16, C-25, C-11 and C-20 carbons. The other set of peaks at 149.39, 149.59, 151.58 and 151.91 ppm were the peaks which are adjacent to oxygen atoms. These peaks assigned C-13, C-14, C-22 and C-23. The peak at 165.72 ppm assigned to C-8 carbonyl carbon the it followed by the peaks at 165.86 ppm which was assigned to C-17 then the last peak at 176.33 ppm assigned to C-7. The infrared spectrum shows absorptions for the carbonyl ester and the aromatic groups as expected. The mass spectrum shows the molecular ion and a series of fragment ions corresponding to dehydrated fragments of the title compound 88. The same reaction was repeated by replacing dimethoxycinnamoyl chloride with caffeoyl chloride and feruloyl chloride and cinnamoyl chloride. All the reactions were achieved successfully resulting (1S,3R,4R,5R)-3,4-bis-(diacetylcaffeoyl) quinide, (90), (1S,3R,4R,5R)-3,4-di-(acetylferuloyl) quinide, (89), as final products shown below.

**Scheme 32**: Synthesis of (1S,3R,4R,5R)-3,4-bis-(diacetylcaffeoyl) quinide, (90)
Results and discussion

Scheme 33: Synthesis of (1S,3R,4R,5R)-3,4-di-(acetylferuloyl) quinide, (89)

Attempted synthesis of (1S,3R,4R,5R)-1,3-di-(acetylferuloyl) quinide, (92)-p228

Scheme 34: Synthesis of (1S,3R,4R,5R)-1,3-di-(acetylferuloyl) quinide

Using quinide (51) as a nucleophile it seemed interesting to investigate where any selectivity could be observed in an acylation reaction with two equivalents of acyl chloride. Hence quinide (51) was reacted with two equivalent acetyl ferulic acid chloride using triethylamine and N, N-(dimethylamino) pyridine to give a much of the compound. A major product (1S,3R,4R,5R)-1,3-di-(acetylferuloyl) quinide was observed in a 82% yield. Although not of satisfactory purity the identity of the product was achieved from the spectral data.

The result is rather intriguing since in a previous example acylation occurred selectively in position 4 of the quinic acid. Presumably, the absence of Troc group in position 1 makes HO-C-3 more acceptable resulting in selective C-3 acylation followed by C-1 acylation.
The $^1$H-NMR spectrum was consistent with the experimental results. The two non-equivalent protons of H-2 were found at 2.03 ppm and 2.48 ppm. The both signal were occurred as multiplet. Then the other peak appeared at 2.06 ppm and 2.68 ppm which were assigned to non-equivalent protons of H-6. The two acetyl of feruloyl moiety were occurred as one singlet at 2.32 ppm with six proton intensity which assigned to H-30 and H-31 protons. Two methoxy protons of feruloyl moiety again appeared as two singlets at 3.85 ppm and 3.86 ppm with three proton intensity each. The three typical protons of quinide moiety were occurred at 4.37, 4.84 and 5.06 ppm. Due to $^1$H-$^1$H-COSY spectrum the triplet at 4.37 ppm identified as H-4. Then the crosspeaks at $^1$H-$^1$H-COSY spectrum allowed to distinguish between H-5 and H-3 protons. According the crosspeaks at $^1$H-$^1$H-COSY spectrum the triplet at 4.84 ppm identified as H-5 and then the quintet at 5.06 ppm assigned to H-3. The four protons which were belong to two pears of C=CH protons identified as doublets with very large coupling constants (J=16 Hz). The large coupling constants proved that these protons were in axial positions to each other. These signals found at 6.36, 6.42, 7.58 and 7.69 ppm and were assigned to H-9, H-18, H-10 and H-19 protons. Aromatic protons were occurred between 7.07 and 7.25 ppm as usual.
Results and discussion

Figure 103: $^{13}$C-NMR spectrum of (1$S$,3$R$,4$R$,5$R$)-1,3-di-(acetylferuloyl) quinide

$^{13}$C-NMR was shows consistent signals as $^1$H-NMR spectrum. The two methoxy carbon found as overlapped on top each other as the $^1$H-NMR spectrum of the title compound. The two CH$_2$ carbons occurred at 36.44 and 36.54 ppm. These signals were assigned to C-2 and C-6. Another two carbons occurred at 56.01 and 56.03 ppm and were found that they were belongs to C-26 and C-27. The quinide moiety protons were found at 64.22, 66.29 and 72.03 ppm and assigned to C-4, C-3 and C-5 carbons due to crosspeaks at HMQC spectrum and $^1$H $^1$H-COSY spectrums. Another carbon of quinide moiety found at 77.41 ppm and assigned to C-1 due to chemical shifts. The four carbons of CH$_2$ groups which are part of the feruloyl moiety occurred at 116.88, 116.93, 141.93 and 141.95 ppm and these peaks were assigned to C-9, C-18, C-10 and C-19 respectively. Another set of signals occurred at 111.49, 111.58, 121.58, 121.65, 123.42, 123.48, 133.08 and 133.59 ppm. These signals assigned to C-12, C-21, C-15, C-24, C-16, C-25, C-11 and C-20. The last two pairs of aromatic carbons occurred at 145.86, 146.30, 151.54 and 151.58 ppm. These protons were assigned to C-13, C-22, C-14 and C-23. The four carbonyl carbons identified slightly in down field at 165.03, 165.20, 168.85, 170.58 and 177.40 ppm. Due to HMQC spectra and chemical shifts these signals assigned to C-8, C-17, C-28, C-28, C-29 and C-7.
Infrared spectrum showed expected absorptions for carbonyl carbons and other groups. The same reactions repeated caffeoyl chloride, coumaroyl chloride, dimethoxycinnamoyl chloride and cinnamoyl chloride. All the reactions were achieved successfully and resulted following (1S,3R,4R,5R)-1,3-bis-(diacetylcaffeoyl) quinide (91), (1S,3R,4R,5R)-1,3-di-(acetyl p-coumaroyl) quinide (93), (1S,3R,4R,5R)-1,3-bis-(dimethoxycinnamoyl) quinide (94) and (1S,3R,4R,5R)-1,3-di-cinnamoyl quinide (95) as final product shown below.

Scheme 35: Synthesis of (1S,3R,4R,5R)-1,3-bis-(diacetylcaffeoyl) quinide, (91)

Scheme 36: Synthesis of (1S,3R,4R,5R)-1,3-di-(acetyl p-coumaroyl) quinide, (93)
Scheme 37: Synthesis of (1S,3R,4R,5R)-1,3-bis-(dimethoxycinnamoyl) quinide, (94)

Scheme 38: Synthesis of (1S,3R,4R,5R)-1,3-di-cinnamoyl quinide, (95)
Figure 104: $^1$H$^{13}$C-HMQC spectrum of (1S,3R,4R,5R)-1,3-di-(acetylferuloyl)quinide

Figure 105: IR spectrum of (1S,3R,4R,5R)-1,3-di-(acetylferuloyl) quinide
**Synthesis of (1S,3R,4R,5R)-1,4-di-cinnamoyl quinide, (96)-p232**

**Scheme 39:** Synthesis of (1S,3R,4R,5R)-1,4-di-cinnamoyl quinide, (96)

To quinide (51) and N, N-(dimethylamino)pyridine in dichloromethane was added triethylamine followed by the addition of cinnamic acid chloride. The reaction mixture was stirred for sixteen hours at room temperature and worked up as other reactions. This crude product was purified by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to afford the title compound (1S,3R,4R,5R)-1,4-di-cinnamoyl quinide as a white powder in a 75.9%.

**Figure 106:** $^1$H-NMR spectrum of (1S,3R,4R,5R)-1,4-di-cinnamoyl quinide,

$^1$H-NMR spectrum shows that the compound was synthesised successfully. The peaks at 2.09 and 2.16 ppm found to be belong to CH$_2$ protons. The first triplet assigned to 2-H$_{ax}$ due to large coupling constant. The other peak of 2.16 ppm occurred as
multiplet and assigned to 2-\textit{H}_{eq} due to crosspeaks at $^1\text{H}^1\text{H}$-COSY spectrum. The other CH$_2$ peaks at 2.18 and 2.51 ppm were assigned to 6-\textit{H}_{ax} and 6-\textit{H}_{ax}. The three protons of quinide moiety were found at 4.10, 5.06 and 5.41 ppm. The crosspeaks at $^1\text{H}^1\text{H}$-COSY spectrum enable to identify the peak at 5.41 ppm as H-4. The other protons were identified due to cross peaks to H-4. The peak at 5.06 ppm was assigned to H-5 and the other signal at 5.41 ppm was assigned to H-4 proton. After checking the chemical shift sequence and carefully analysing the $^1\text{H}$-NMR spectrum and $^1\text{H}^1\text{H}$-COSY spectrum signals showed that one of the cinnamoyl moiety was next to the H-4 proton. The two pair of doublets at 6.43 ppm and 6.47 ppm identified as CH=CH protons. These signals appeared to be \textit{trans} to their partner. These signals assigned to H-9 and H-18 protons. The other pair of CH=CH protons occurred at 7.74 and 7.25 ppm and assigned to H-10 and H-19 protons due to chemical shifts and large coupling constants (J=16 Hz). The ten aromatic protons occurred between 7.40-7.54 ppm.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{1H-1H-COSY_spectrum.png}
\caption{$^1\text{H}^1\text{H}$-COSY spectrum of (1S,3\textit{R},4\textit{R},5\textit{R})-1,4-di-cinnamoyl quinide}
\end{figure}
The $^{13}\text{C}$-NMR showed similar peaks which were in harmony with $^1\text{H}$-NMR spectrum. The first two signals at 36.42 and 36.54 ppm assigned to C-2 and C-6 carbons as before. Then the quinide carbons occurred at 64.24, 68.76 and 72.12 ppm which were assigned to C-3, C-4 and C-5 carbons respectively. The small peak at 76.10 ppm assigned to C-1. The four olefinic carbons occurred at 116.70, 117.23, 146.68 and 147.14 ppm. These carbons were assigned to C-9, C-18, C-10 and C-19 due to HMQC assignments. The eight aromatic carbons occurred at 128.33, 128.44, 129.05 and 129.09 ppm as four signals and each one of the with two carbon intensity. By analysing the $^{13}\text{C}$-NMR and HMQC spectrum these peaks were assigned to C-12, C-16, C-21, C-25, C-13, C-15, C-22 and C-24 carbons. The other two aromatic carbons found at 130.82 and 130.91 ppm assigned to C-14 and C-23. The last pair of aromatic carbons which hasn’t got any hydrogen attached to them identified at 134.01 and 134.13 ppm and assigned to C-11 and C-20 carbons. The two carbonyl carbons which are belong to cinnamoyl carbonyl functional groups occurred at 165.39 ppm. The intensity of the signal and the HMQC spectrum showed that this signals were C-8 and C-17. At last quinide carbonyl C-7 found at 171.61 ppm due to HMQC spectrum of the compound. Infrared spectrum of the compound showed the relevant signals. The strong signal at 1786 cm$^{-1}$ belong to C=O functional group and also $C_{\text{Ar}-C_{\text{Ar}}}$ at 1632 cm$^{-1}$ proved the identification of the compound.
Results and discussion

Figure 109: $^1$H$^{13}$C-HMQC spectrum of (1S,3R,4R,5R)-1,4-di-cinnamoyl quinide

Figure 110: IR spectrum of (1S,3R,4R,5R)-1,4-di-cinnamoyl quinide
Synthesis of (1S,3R,4R,5R)-1-cinnamoyl-3-(acetyl p-coumaroyl) quinide,

Due to previously observed regioselectivity quinide acylation a sequential acylation sequence was attempted in which y was added after x. Again a reversal of selectivity was observed in this case with selective acylation at C-4 rather than C-3 as in the previous example. It can only be concluded that acylation reactions are regioselective. However, selectivity could be depend on substituent and therefore could be vice versa?. A major product was isolated by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to afford the title compound (1S,3R,4R,5R)-1-cinnamoyl-3-(p-coumaroyl acetyl) quinide as a white powder in a 31.15% yield.

Figure 111: $^1$H-NMR spectrum of (1S,3R,4R,5R)-1-cinnamoyl-3-(acetyl p-coumaroyl) quinide
The $^1$H-NMR spectrum of the compound proved that the product was synthesized successfully. First four sets of signals found at 2.27, 2.30, 2.32 and 2.70 ppm. Due to $^1$H$^1$H-COSY spectrum and chemical shifts the peaks at 2.27 ppm was assigned to 2-H$_{ax}$ and the multiplet at 2.32 ppm assigned to 2-H$_{eq}$. The other two non-equivalent protons of CH$_2$ group were found at 2.30 and 2.70 ppm. These peaks were assigned to 6-H$_{ax}$ and 6-H$_{eq}$ protons. The singlet at 2.29 ppm identified as acetyl proton with three proton intensity and assigned to H-27. The three protons of quinide moiety were found at 4.40, 4.86 and 5.07 ppm. The triplet at 4.40 ppm assigned to H-4 after analysing the $^1$H$^1$H-COSY spectrum. Once H-4 proton was identified the other protons were identified due to chemical shift and the crosspeak in the $^1$H$^1$H-COSY spectrum. As a result the quintet at 5.07 ppm was assigned to H-3 and the triplet at 4.86 ppm assigned to H-5 proton. The other two sets of olefinic protons were identified at 6.38, 6.43, 7.70 and 7.74 ppm as before. Due to chemical shifts and the crosspeaks at $^1$H$^1$H-COSY spectrum the first two peaks at 6.38 and 6.43 were assigned to H-9 and H-18 then the other pair at 7.70 and 7.74 ppm identified as H-10 and H-19. All of these four signals occurred as doublets with coupling constant between J=8-16 Hz. At last the aromatic protons showed multiplet between 7.04 and 7.56 ppm as it was expected.

Figure 112: $^{13}$C-NMR spectrum of (1S,3R,4R,5R)-1-cinnamoyl-3-(acetyl $p$-coumaroyl) quinide
The $^{13}$C-NMR shows consistent signals with $^1$H-NMR spectrum. The first signal at 21.26 ppm assigned to acetyl carbon C-27. The two CH$_2$ carbons were found at 36.46 and 36.51 ppm. The signal at 36.46 ppm assigned to C-2 and the other signal at 36.51 ppm assigned to C-6. The three protons of quinide were appeared at 64.21, 68.79 and 72.12 ppm. Due to crosspeaks at HMQC spectrum these peaks were assigned to C-4, C-3 and C-5 carbons. The typical carbon atom of quinide which is next to carbonyl group was found at 76.12 ppm and assigned to C-1. The four pear of C=CH protons were found at 116.75, 117.46, 145.88 and 146.62 ppm. The first two pear assigned to C-9 and C-18 due to crosspeaks at $^1$H$^1$H-COSY spectrum then the other pear at 145.88 and 146.62 ppm assigned to C-10 and C-19. The eight carbons of aromatic groups which has hydrogen attached to it were found around 122.30, 128.33, 128.93, 129.04, 129.09, 129.58, 130.80 and 130.90 ppm. The other two carbons with small intensity at 131.87 and 134.01 ppm assigned to single carbon atoms of aromatic group C-11 and C-20. The two signals at 152.49 and 165.43 ppm identified as C-23 and C-8 which are adjacent to oxygen atoms. The last set of peaks at 165.43, 169.24, 171.30 and 177.55 ppm assigned to C-8, C-17, C-26 and C-7 carbons respectively due to chemical shifts. The infrared spectrum shows strong signals for the two carbonyl esters at 1765 cm$^{-1}$ and 1684 cm$^{-1}$. Also strong signal at 1633 cm$^{-1}$ for the aromatic groups as it was expected.

![Figure 113: $^1$H$^{13}$C-HMQC spectrum of (1S,3R,4R,5R)-1-cinnamoyl-3-(acetyl p-coumaroyl) quinide](image)
How to distinguish between the constitutional isomers:

The combination of the NMR spectrometric data which was based on $^1$H-NMR, $^{13}$C-NMR, $^1$H-$^1$H-COSY, HMBC and HSQC techniques as well as careful consideration of substituent chemical shifts (SCS) contain a lot of information for the assignment of the correct constitutional isomers. During experimental process it was observed that the assigned proton shifts are valuable tools in the analysis of quinic acid, quinic acid esters and their isomers. It was also observed that the acylation of a hydroxyl groups produces a paramagnetic (downfield) shift of about 1.20-1.4 ppm of the according to the electronegativity of the substituent.

As an instance of the theory; the $^1$H-NMR spectrum of the (1S,3R,4R,5R)-1,3-di-(acetylferuloyl) quinide (92) exhibited the signals for the two feruloyl moieties and quinide moiety. After careful consideration of the $^1$H-NMR spectrum of the (92) in comparison with $^1$H-NMR spectrum of the quinide (51) showed that there was only one single significantly deshielded proton signal (H-3 $\delta=5.06$ ppm) because of the ester linkage. The same affect was observed with all the other compounds throughout.
the thesis. After checking all the spectrometric results which was presented in this work, it was concluded that if the second feruloyl moiety was attached to the hydroxyl at C-4 then the H-4 proton would have been shifted to the downfield as it observed with H-3. Therefore, one of the feruloyl substituent must have been attached to the C-1 of the quinide moiety. HMBC experiments also showed that the hydroxyl groups at C-1 and C-3 were esterified by ferulic acid, because of the cross peaks arising from the carbonyls of the ferulic acids (δ= 165.07, δ= 165.20 ppm). Also, the signals at $^{13}$C-NMR spectra showed that the paramagnetic shift of the C-1 and C-3 (δ= 77.41, δ= 66.29 ppm), compared to the quinic acid esters which substituted at other positions, confirmed that the assignment was correct.

Another interesting conclusion was observed in the synthesis of the (1S,3R,4R,5R)-1,4-di-cinnamoyl quinide, (96). The same chemical shift differences were observed on the NMR spectral data as it was mentioned above and the assignment of the peaks along with spectral data confirmed that the compound was 1,4-di-cinnamoyl quinide instead of 1,3-di-cinnamoyl quinide. However, since the both type of compounds 1,3 and 1,4-diacyl substituted chlorogenic acid esters were obtained after the column chromatography, it was observed that the 1,3-disubstituted chlorogenic acid ester was formed first and collected then it was followed by 1,4-disubstituted chlorogenic acid ester. The ratio of 1,3-disubstituted chlorogenic acid ester to 1,4-disubstituted chlorogenic acid ester found as 1:3. This was simply because, in a regioselective reaction there are possible constitutional isomers, but, more of some formed than others. This conclusion was discovered at very late stage of the project. Therefore fraction collection for all the 1,4-di substituted chlorogenic acids couldn’t be achieved before the end of the project.

The structures of the following compounds (1S,3R,4R,5R)-1,3-bis-(diacetylcaffeoyl) quinide (91), (1S,3R,4R,5R)-1,3-di-(acetyl p-coumaroyl) quinide (93), (1S,3R,4R,5R)-1,3-bis-(dimethoxycinnamoyl) quinide (94) and (1S,3R,4R,5R)-1,3-di-cinnamoyl quinide (95), (1S,3R,4R,5R)-1,4-di-cinnamoyl quinide (96) and (1S,3R,4R,5R)-1-cinnamoyl-3-(acetyl p- coumaroyl) quinide (97) were solved the same way, as mentioned above.
Quinide tri-acetate, (98)-p234

Scheme 41: Synthesis of quinide tri-acetate, (98)

The solution of quinide (51) and N, N-(dimethylamino) pyridine, acetic anhydride and pyridine was stirred for 1 hour at 0° C and then poured into crushed ice. The aqueous phase was acidified with 2M HCl and stirred for an additional hour. The reaction mixture was extracted with EtOAc and purified by recrystallisation with CDCl₃ to give the Quinide tri-acetate (98) as pale orange powder in 84%.

Figure 115: $^1$H-NMR spectrum of (1S, 3R, 4R, 5R)-1, 3, 4-tri-acetate-quinide

The $^1$H-NMR spectrum of quinide tri-acetate (98) shows three singlet for the acetyl groups at 2.01, 2.14 and 2.15 ppm. Each signal shows three proton intensity and these signals assigned to H-11, H-12 and H-13. Another four signals found at 2.12 ppm, 2.29 ppm, 2.56 ppm and 3.09 ppm. The first two sets of CH₂ protons identified at 2.12 and 2.29 ppm. The first doublet assigned to 2-Hₚ due to crosspeaks between other protons of CH₂ groups. Further down the doublet of doublet at 2.29 ppm assigned to
2-\text{H}_{\text{eq}}\text{ then followed by } 6-\text{H}_{\text{eq}}\text{ at 2.56 ppm and } 6-\text{H}_{\text{ax}}\text{ at 3.09 ppm. The quinide protons found at 4.85, 5.17 and 5.47 ppm. By analyzing } ^{1}\text{H}^{1}\text{H-COSY spectrum of the product the doublet of doublet at 5.47 ppm identified } H-4\text{ due to crosspeaks to } H-5\text{ and } H-3\text{ protons. Due to chemical shift considerations the triplet at 4.85 ppm assigned to } H-5 \text{ and the multiplet at 5.17 ppm assigned to } H-3.\text{ }^{13}\text{C-NMR showed consistent signal with } ^{1}\text{H-NMR spectrum. The acetyl carbons } C-11, C-12, C-13 \text{ found at 21.10, 21.16 and 21.30 ppm. } ^{13}\text{C-NMR spectrum along with } ^{1}\text{H}^{1}\text{H-COSY spectrum and } ^{1}\text{H}^{13}\text{C-HMQC spectrum allowed identification and assignments of quinide carbons. The signals at 33.76 ppm, 34.20 ppm, 65.04 ppm, 65.87 ppm, 71.68 ppm, assigned to } C-2, C-6, C-3, C-4, C-5 \text{ and } C-1. \text{ The following signals found at 169.30 ppm, 169.35 ppm, 171.52 ppm and 171.29 ppm. Due to chemical shift and the cross peaks at HMQC spectrum this signals assigned to } C-8, C-9, C-10 \text{ and } C-7. \text{ Infrared spectrum shows strong signals for carbonayl esters at 1800, 1755 cm}^{-1} \text{ (C=O) and the mass spectrum shows the molecular ion and fragment ions corresponding to structure of the compound.} 

\begin{figure}
\centering
\includegraphics[width=\textwidth]{13C-NMR_spectrum_of_98.png}
\caption{\textbf{13C-NMR spectrum of 98}}
\end{figure}
Figure 117: $^1\text{H}^1\text{H}$-COSY spectrum of 98

**Synthesis of (1S, 3R, 4R, 5R)-1, 3, 4-tri-cinnamoyl quinide, (99)-p235**

(Attempt of tetra-acyl quinic acid)

Scheme 42: Synthesis of (1S, 3R, 4R, 5R)-1, 3, 4-tri-cinnamoyl quinide
The first naturally occurring tetra acyl quinic acid was recently reported. For this reason the synthesis of this claimed of compound is of interest. Quinic acid was reacted with an excess of cinnamoyl chloride to give surprisingly a tri acyl quinide. The title compound was obtained in 80-90% yield by acylation of quinic acid with four equivalent cinnamoyl chloride by using 5% N, N-(dimethylamino) pyridine in dichloromethane and triethylamine. The reaction mixture was stirred for 18 hours at room temperature and worked up by using dichloromethane and 2M HCl. The residue was purified by recrystallisation from EtOH to give the title compound.

An attempt was made to directly acylate quinic acid using cinnamoyl chloride. It was expected that the three secondary OH groups would react preferably to yield 3, 4, 5 – tri acyl quinic acid derivatives. Surprisingly, 1,3,4-tri cinnamoyl quinide was isolated as the major product. The reaction mixture was then refluxed at 100 ºC for 5 days and purified by recrystallisation from EtOH to get the desired product but, spectrometric data was the same as the previous product (1S, 3R, 4R, 5R)-1, 3, 4-tri-cinnamoyl quinide.

Mechanistically this observation can be explained by assuming the formation of a mixed anhydride species (I) formed from quinic acid and cinnamic acid. This anhydride can in an invert chain conformation (II) form a quinide leaving the remaining the OH’s available for further acylation as shown below.

Scheme 43: Possible synthetic route for the title compound (99)
Results and discussion

Figure 118: $^1$H-NMR of (1$S$, 3$R$, 4$R$, 5$R$)-1, 3, 4-tri-O-cinnamoyl-quinide

$^1$H-NMR spectrum confirmed that the product was (1$S$, 3$R$, 4$R$, 5$R$)-1, 3, 4-tri-O-cinnamoyl-quinide. The four non-equivalent protons of CH$_2$ group were found at 2.56, 2.82, 3.11 and 3.20 ppm. The first doublet of doublet at 2.56 ppm assigned to 2-H$_{ax}$ because of the large coupling constant ($J$ 15.4 and 11.4 Hz) due to Karplus relationship. The second peak occurred as doublet at 2.82 ppm and assigned to 6-H$_{eq}$ due to crosspeaks on $^1$H$^1$H-COSY spectrum. Then another doublet of doublet at 3.11 ppm and the multiplet at 3.20 ppm identified as 2-H$_{eq}$ and 6-H$_{ax}$ due to crosspeaks in relationship with $^1$H$^1$H-COSY spectrum. The quinide protons showed peaks at 5.03 ppm, 5.39 ppm and 5.73 ppm. The peak at 5.73 ppm occurred as triplet and was assigned to H-4 due to crosspeaks to H-3 and H-5 protons after analysing the $^1$H$^1$H-COSY spectrum. Then the doublet of doublet of doublet at 5.39 ppm identified as H-3 due to chemical shifts and large coupling constant. The last protons of quinide moiety H-5 occurred in downfield as triplet at 5.03 ppm with smaller coupling constant ($J$ 5.5 Hz) in comparison to H-3 proton. The three sets of olefinic doublets were found at 6.36, 6.46, 6.55, 7.74, 7.75 and 7.78 ppm with large coupling constants $J$ 15 -16 Hz. These protons were assigned to H-9, H-18, H-27, H-10, H-19 and H-28 protons due to crosspeaks at $^1$H$^1$H-COSY and $^1$H$^{13}$C-HMQC spectrum. The aromatic protons occurred between 7.40-7.55 ppm as it was expected.
The $^{13}$C-NMR spectrum shows consistent signals with $^1$H-NMR spectrum. The first two signals of the spectrum occurred at 34.12 ppm and 34.55 ppm with similar intensity assigned to C-2 and C-6. These signals followed by quinide protons at 65.19, 66.20 and 74.12 ppm identified as C-4, C-3 and C-4 carbons due to $^1$H$^{13}$C-HMQC spectrum. The slightly smaller signal at 74.43 ppm assigned to C-1. The first set of aromatic carbons were found at 116.48, 116.59, 116.81 ppm then the second part occurred at 128.13, 128.35, 128.44, 128.85, 128.95, 129.05, 130.19, 130.66, 130.82, 130.94 and 131.01 ppm. The last parts of aromatic carbons which have no proton attached to it were found at 133.98, 134.02 and 134.23 ppm. These signals were assigned to C-11, C-20 and C-29. The six olefinic carbons occurred in two different regions as well. The first set of signals occurred at 117.04, 117.28 and 117.46 ppm and assigned to C-9, C-18 and C-27 due to crosspeaks at $^1$H$^{13}$C-HMQC. Then the second sets of olefinic carbons occurred at 133.98, 134.02 and 134.23 ppm. These carbons assigned to C-11, C-20 and C-9 respectively. At lasts carbonyl carbons occurred at very last part of the spectrum 165.21, 165.39, 165.60 and 171.77 ppm. The first three signals showed similar intensity and due to chemical shift assigned to C-8, C-17 and C-26 carbons. Then the last signal at 171.77 ppm identified as C-7 due to $^1$H$^{13}$C-HMQC spectrum.
Infrared spectrum shows expected absorptions for carbonyl esters 1804, 1763, 1717 cm\(^{-1}\) and other groups. The mass spectrum shows signals for molecular ion and fragment ions which is consistent with the molecular structure of 99. The protonated molecular ion at \(m/z\) 564 suggested the molecular formula C\(_{34}\)H\(_{28}\)O\(_8\) which is in agreement with the spectrometric data of the title compound.

Similarly, the same reaction was repeated with other reactants and resulted (1\(S\), 3\(R\), 4\(R\), 5\(R\))-1, 3, 4-tri-(dimethoxycinnamoyl) quinide, (100); (1\(S\), 3\(R\), 4\(R\), 5\(R\))-1, 3, 4-tri-(acetyl \(p\)-coumaroyl) quinide, (101); (1\(S\), 3\(R\), 4\(R\), 5\(R\))-1, 3, 4-tri-(acetylferuloyl) quinide, (102); (1\(S\), 3\(R\), 4\(R\), 5\(R\))-1, 3, 4-tri-(diacetylcaffeoyl) quinide, (103) as pure products between 55-95% yield as shown below.

**Scheme 44:** Synthesis of (1\(S\), 3\(R\), 4\(R\), 5\(R\))-1, 3, 4-tri-(dimethoxycinnamoyl) quinide, (100)

**Scheme 45:** Synthesis of (1\(S\), 3\(R\), 4\(R\), 5\(R\))-1, 3, 4-tri-(acetyl \(p\)-coumaroyl) quinide, (101)
**Scheme 46:** Synthesis of (1S, 3R, 4R, 5R)-1, 3, 4-tri-(acetylferuloyl) quinide, (102)

**Scheme 47:** Synthesis of (1S, 3R, 4R, 5R)-1, 3, 4-tri-(diacetylcaffeoyl) quinide, (103)
Figure 120: $^1$H$^{13}$C-HMQC spectrum of (1$S$, 3$R$, 4$R$, 5$R$)-1, 3, 4-tri-cinnamoyl quinide

Figure 121: IR spectrum of (1$S$, 3$R$, 4$R$, 5$R$)-1, 3, 4-tri-cinnamoyl quinide
Results and discussion  

Synthesis of (1S, 3R, 4R, 5R)-1, 3, 4-tri-(acetyl p-coumaroyl) quinide, (106)-p242

Scheme 48: Synthesis of (1S, 3R, 4R, 5R)-1, 3, 4-tri-(acetyl p-coumaroyl) quinide

Figure 122: $^1$H-NMR spectrum of (1S, 3R, 4R, 5R)-1, 3, 4-tri-(acetyl p-coumaroyl) quinide

The identification of product is supported by the $^1$H-NMR spectrum where that the data is in full agreement with the proposed structure. The $^1$H-NMR spectrum shows two singlets at the beginning of the spectra and these protons were assigned to H-38, H-39 and H-40 acetal groups of coumaroyl moiety. The first peak occurred with three proton intensity which was assigned to H-38. Then the second peak occurred with six proton intensity which was identified as H-39 and H-40. The four signal at 2.53, 2.54, 2.77 and 3.18 ppm corresponding to the four non-equivalent protons of the two sets of...
CH₂ groups. The cross peak from H-3 to the signals at 2.53 ppm and 2.54 ppm showed these two signals correspond to the H-2 CH₂ moiety confirmed by their cross peaks and these two peaks were assigned to 2-Hₐₓ and 2-Hₑₒₗ. The two H-6 protons were identified at 2.77 and 3.18 ppm. Due to chemical shift, coupling constant and cross peaks to H-5 and H-3 protons these peaks were identified as 6-Hₑₒₗ and 6-Hₐₓ.

The ¹H-NMR spectrum shows two triplets and one quintet at 5.01, 5.37 and 5.71 ppm. Consequent upon chemical shift considerations the most downfield proton occurred as triplet at 5.01 ppm was assigned to H-5, the next to the lactone functionality. From the ¹H¹H-COSY spectrum the signal at 5.71 ppm was identified as H-4 due to crosspeaks to H-5 and H-3. After analysing ¹H¹H-COSY and ¹H¹³C-HMQC spectra the quintet at 5.37 ppm was assigned to H-3. Consequently the ¹H-NMR spectrum shows six doublets with large coupling constants $J 16$ Hz. These doublets were identified as olefinic protons of coumaroyl moiety. The first sets of olefinic protons found at 6.26, 6.44 and 6.45 ppm then the second set found at 7.56, 7.59 and 7.63 ppm. These olefinic protons of CH₂ groups assigned to H-9, H-18, H-27, H-10, H-19 and H-28 respectively due to cross peaks at ¹H-NMR spectrum and chemical shift considerations. Finally the aromatic protons found between 7.04 and 7.53 ppm as multiplets.

![13C-NMR spectrum of (1S, 3R, 4R, 5R)-1, 3, 4-tri-(acetyl p-coumaroyl) quinide](image)

**Figure 123:** ¹³C-NMR spectrum of (1S, 3R, 4R, 5R)-1, 3, 4-tri-(acetyl p-coumaroyl) quinide
$^{13}$C-NMR spectrum signals were consistent with the $^1$H-NMR spectrum. The $^{13}$C-NMR spectrum showed that some of the signals were overlapped due to the same kind of chemical shifts. The first peak at 21.21 ppm with three carbon intensity identified as C-38, C-39 and C-40. Then this signal followed by quinide carbons. The peak at 33.97 and 34.51 ppm identified as C-2 and C-6 due to cross peaks at $^1$H$^1$H-COSY and $^1$H$^{13}$C-HMQC spectrums. Another four signals of quinide carbons found at 66.15, 66.19, 76.05 and these signals were assigned to C-4, C-3 and C-5. The first carbons of quinide moiety C-1 occurred in downfield 77.12 ppm compare to other carbons of quinide with smaller signal intensity. The six sets of olefinic carbons in the region as it was expected. The first olefinic carbons occurred at 116.66, 116.88, 116.97 ppm and assigned to C-9, C-18 and C-27. These signals followed by overlapping twelve carbons of aromatic group. The signals occurred at 122.24, 122.35, 122.41, 129.45, 129.59 and 129.72 ppm assigned to C-13, C-15, C-22, C-24, C-31, C-33, C-12, C-16, C-21, C-25, C-30 and C-34. The next set of carbons occurred at 131.70, 131.71 and 131.75 ppm. This group identified as carbons of aromatic group which hasn’t got any hydrogen adjacent to it. These signals assigned to C-11, C-20, C-29 due to cross peaks at $^1$H$^{13}$C-HMQC spectrum. The second set of olefinic carbons occurred just after aromatic carbons where it was expected before. The signal at 145.13, 145.80 and 145.90 ppm assigned to C-10, C-19 and C-28 carbons due to chemical shift consideration and the cross peaks which was observed at $^1$H$^1$H-COSY and $^1$H$^{13}$C-HMQC spectrum. The first set of carbonyl carbons found at 152.41, 152.62 and 152.70 ppm and this signals assigned to C-8, C-17 and C-26. Then the other three carbonyl carbons occurred at 164.91, 165.23 ppm. By looking at the signal intensity and the cross peaks at $^1$H$^{13}$C-HMQC spectrum the signal at 164.91 ppm identified as overlapping two carbonyl carbons C-14 and C-23. Then the signal at 165.23 ppm with one carbon intensity assigned to C-32. The very last part of carbonyl carbons of coumaroyl moiety was occurred at 169.14 ppm with three carbon intensity and assigned to C-35, C-36 and C-37. The carbonyl carbon of quinide moiety occurred at the end of the spectrum at 171.32 ppm and assigned to C-7.

The infrared spectrum showed consistent signals at 1806, 1765, 1721 cm$^{-1}$ (C=O), 1635 (C$_{Ar}$=C$_{Ar}$), 1267, 1243, 1156, 1077 cm$^{-1}$ (C-O) as the other spectral data.
Figure 124: $^1$H$^1$C-HMQC spectrum of (1S, 3R, 4R, 5R)-1, 3, 4-tri-(acetyl $p$-coumaroyl) quinide

Figure 125: IR spectrum of (1S, 3R, 4R, 5R)-1, 3, 4-tri-(acetyl $p$-coumaroyl) quinide
Results and discussion

_Synthesis of (1R, 3R, 4S, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-3,4,5-tri-(acetylferuloyl) quinic acid, (109)-p245_

![Scheme 49](image)

The result of the experiment was rather unexpected. In comparison to the previous compound, the product was expected to be a di-substituted Troc protected quinide as a major product. The spots of 3-acyl Troc protected quinic acid observed in more less the same place as triacyl quinide. It was presumed that the Troc protected quinide was gone under a reaction with column solvent (chloroform-acetone). It’s known that the hydrogen atom in chloroform is capable of hydrogen bonding to a suitable electron-donor molecule. Also, hydrogen bond of acetone lies in the plane of the three carbons of acetone along with hybridized lone pairs of oxygen and act as electron donor. Presumably dielectric behaviour of Troc allows the ester chain to open and form the title compound with access amount of acid chloride.

The examination of $^1$H-NMR spectrum shows that the data is in full agreement with the proposed structure. As a result of $^1$H$^1$H-COSY spectrum first non equivalent protons of the CH$_2$ group occurred at 2.27 ppm as multiplet and assigned to 6-H$_{ax}$. This signal followed by acetyl protons of the feruloyl moiety. The signal at 2.29 ppm identified as overlapping singlet with nine proton intensity and assigned to H-44, H-45 and H-46 protons. The non equivalent CH$_2$ protons occurred as one multiplet and two doublet of doublet at 2.31, 2.59 and 2.83 ppm. These signals assigned to 2-H$_{ax}$, 6-H$_{eq}$, 2-H$_{eq}$ due to cross peaks at $^1$H$^1$H-COSY spectrum.
Three methoxy protons of feruloyl moiety occurred at 3.71, 3.82 and 3.87 ppm. Each protons of methoxy group showed three protons intensity and assigned to H-38, H-39 and H-40. The signals at 4.72 and 4.80 ppm were assigned to CH$_2$ protons of Troc protecting group. Two identical protons appeared as two doublets coupling constant of 11.9 Hz. Due to Karplus relationship, coupling constant indicates that these two protons were *trans* to each other. The quinide protons observed at 5.34, 5.80 and 5.81 ppm. The doublet of doublet at 5.34 ppm assigned to H-4 due to cross peaks at $^1$H$^1$H-COSY spectrum. Then the two multiplets at 5.80 ppm and 5.81 ppm were assigned to H-5 and H-3 after analysing $^1$H$^1$H-COSY and $^1$H$^{13}$C-HMQC spectrums. The $^1$H-NMR spectrum shows six doublets at 6.29, 6.32, 6.47, 7.58, 7.62 and 7.65 ppm with large coupling constants between $J$ 10.5- 16 Hz. The first three peaks 6.29, 6.32, 6.47 ppm were assigned to H-12, H-21 and H-30. These signals were followed by multiplet at 6.96-7.14 ppm which was assigned to aromatic protons. The second set of olefinic protons occurred again as doublets just after aromatic group protons as it was expected. The signals at 7.58, 7.62 and 7.65 ppm were assigned to H-13, H-22 and H-31.
Figure 127: $^{13}$C-NMR $^1$H-NMR spectrum of $(1R, 3R, 4S, 5R)$-1-(β, β, β-trichloroethoxy carbonyl)-3,4,5-tri-(acetylferuloyl) quinic acid.

The $^{13}$C-NMR shows forty six signals which corresponding the proposed structure of the compound. Very first signal occurred as overlapping at 27.10 ppm with three carbon intensity. These signals were assigned to C-44, C-45 and C-46. Then the two CH$_2$ carbons occurred at 32.30 ppm and 36.84 ppm which were assigned to C-6 and C-2 due to cross peaks on $^1$H$^1$H-COSY and $^1$H$^{13}$C-HMQC spectrums. Three carbons of methoxy groups occurred 55.92, 56.02 and 56.14 ppm which are assigned to C-38, C-39 and C-40. The three carbons of quinide moiety were occurred at 66.73, 67.90 and 74.20 ppm. Due to cross peaks at $^1$H$^{13}$C-HMQC spectrum these peaks were assigned C-5, C-3 and C-4. The quinide carbons followed by CH$_2$ carbons of Troc protecting group at 76.83 ppm and assigned to C-9. The signal with small intensity at 82.11 ppm assigned to C-1 due to chemical shift considerations and $^1$H$^{13}$C-HMQC spectrum. Another Troc carbon which is adjacent to three chlorine of Troc protecting group was found as very small intensity at 94.24 ppm and assigned to C-10. Further down of the spectrum aromatic carbons were observed at 111.22, 111.35 and 111.43 ppm and these peaks were identified as C-15, C-24 and C-33 due to cross peaks at $^1$H$^{13}$C-HMQC spectrum. The first set of olefinic carbons with similar signal intensity found at 117.32, 117.44 and 117.64 ppm which were assigned to C-12, C-21 and C-30. Another six typical aromatic carbons occurred 121.52, 121.60, 123.32, 123.32,
123.34, 123.37 ppm and identified as C-18, C-27, C-36, C-19, C-28, C-37. Further down the three aromatic carbons which hasn’t got and other atom adjacent to it found at 132.32, 133.04, 133.34 ppm and assigned to C-14, C-23 and C-32. After checking $^1$H$^{13}$C-HMQC spectrum these signals followed by another three signals with slightly smaller intensity at 141.74, 141.77 and 141.80 ppm. These signals identified as other set of olefinic carbons and assigned to C-13, C-22 and C-31. The last carbons of aromatic group which are adjacent to oxygen atoms were found at 145.35, 145.42, 145.50, 151.45, 151.51 and 151.60 ppm. The first three signals at 145.35, 145.42, 145.50 ppm identified as C-17, C-26 and C-35 which are next to the acetayl group of feruloyl moiety. Then the 151.45, 151.51 and151.60 ppm identified as C-16, C-28 and C-34 which are next to the methoxy group of feruloyl moiety. The carbonyl carbons occurred at the very last part of the spectrum and identified concerning chemical shift and $^1$H$^{13}$C-HMQC spectrum. The first carbonayl carbons found at 152.41, 165.70, 165.76, 165.81 ppm and assigned to 152.41 ppm carbo nyl of Troc protecting group C-8, carbonayl group of Feruloyl moieties C-11, C-20 and C-29. Then these peaks followed by one big singlet at 168.74 ppm with three carbon intensity which proved that three signals were overlapping and identified as carbonyls of acetayl group of feruloyl moiety C-41, C-42 and C-43. The last signal at 169.95 assigned to C-7 as before. The infrared spectrum shows strong signals at 2845 cm$^{-1}$ (COOH), 1764, 1719 cm$^{-1}$ (C=O), 1636 cm$^{-1}$ ($\text{C}_{\text{Ar}}=\text{C}_{\text{Ar}}$), 1259, 1198, 1123, 1088, 1033 cm$^{-1}$ (C-O) which are consistent with other spectrums of the compound.
Figure 128: $^1$H$^{13}$C-HMQC spectrum of (1R, 3R, 4S, 5R)-1-(β, β, β-trichloroethoxy carbonyl) -3,4,5-tri-(acetylferuloyl) quinic acid.

Figure 129: IR spectrum of (1R, 3R, 4S, 5R)-1-(β, β, β-trichloroethoxy carbonyl) -3,4,5-tri-(acetylferuloyl) quinic acid.
Synthesis of (1R, 3R, 4S, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-3,4,5-tri-(acetyl p-coumaroyl) quinic acid, (110)-p246

Scheme 50: Synthesis of (1R, 3R, 4S, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-3,4,5-tri-(acetyl p-coumaroyl) quinic acid

The synthesised (1R, 3R, 4S, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-3,4,5-tri-(acetyl p-coumaroyl) quinic acid was obtained 14.2% by acylation of the Troc protected quinide with two equivalent acetyl p-coumaric acid chloride 5 N,N-(dimethylamino)pyridine in dichloromethane and triethylamine solution. After reaction worked up and solvents were removed the crude product was purified by using flash chromatography (chloroform-acetone) to provide title compound.

Figure 130: $^1$H-NMR spectrum (1R, 3R, 4S, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-3,4,5-tri-(acetyl p-coumaroyl) quinic acid.
The $^1$H-NMR spectrum shows that the reaction was achieved successfully. The non equivalent protons of the two $\text{CH}_2$ group occurred at the beginning of the spectra. The doublet of doublet at 2.12 ppm with large coupling constant $J$ 14.9-12 Hz assigned to 6-$\text{H}_{\text{ax}}$. This signal followed by multiplet at 2.18 ppm and assigned to 2-$\text{H}_{\text{ax}}$ due to cross peaks at $^1$H$^1$H-COSY spectrum. The singlet at 2.29 ppm identified as overlapping protons of the coumaroyl moiety. The singlet showed three protons intensity and was assigned to H-41, H-42 and H-43. Another non equivalent protons of $\text{CH}_2$ group occurred as two doublet of doublet. These two signals assigned to 6-$\text{H}_{\text{eq}}$ and 2-$\text{H}_{\text{eq}}$. The first part of $\text{CH}_2$ protons of Troc protecting group were identified at 4.57 and 4.78 ppm. The both protons found to be identical two doublets with large coupling constant 11.9 Hz. Due to Karplus relationship, coupling constant indicates that these two protons were trans to each other. The quinide protons observed at 5.31, 5.78 and 5.80 ppm. The doublet of doublet at 5.31 ppm assigned to H-4 due to cross peaks at $^1$H$^1$H-COSY spectrum. Then the two multiplets at 5.78 ppm and 5.80 ppm were assigned to H-5 and H-3 after analysing cross peaks of $^1$H$^1$H-COSY and $^1$H$^{13}$C-HMQC spectrums. The $^1$H-NMR spectrum shows six doublets at 6.29, 6.32, 6.47, 7.58, 7.62 and 7.65 ppm with large coupling constants between $J$ 10.5- 16 Hz. The first three peaks 6.29, 6.32, 6.47 ppm were assigned to H-12, H-21 and H-30. These signals were followed by multiplet at 6.96-7.14 ppm which was assigned to aromatic protons. The second set of olefinic protons occurred again as three doublets just after aromatic group protons between 7.02- 7.50 ppm. The signals at 7.57, 7.58 and 7.59 ppm were assigned to H-13, H-22 and H-31.
The $^{13}$C-NMR spectrum of the compound showed consistent peaks with $^1$H-NMR spectrum. The first two signals found at 21.19 and 21.22 ppm and identified as acetayl carbons of coumaroyl moiety. The first signal at 21.19 ppm showed two carbons intensity which proved that two signals were overlapping. The two CH$_2$ carbons occurred at 32.40 ppm and 36.71 ppm which were assigned to C-6 and C-2 due to cross peaks on $^1$H-$^1$H-COSY and $^1$H-$^{13}$C-HMQC spectrums. These signals followed by the three carbons of quinide moiety which were occurred at 66.73, 67.92 and 71.83 ppm. Due to cross peaks at $^1$H-$^{13}$C-HMQC spectrum these peaks were assigned C-5, C-3 and C-4 carbons. The quinide carbons followed by CH$_2$ carbon of Troc protecting group at 76.80 ppm and assigned to C-9. The signal at 82.11 ppm with small intensity assigned to C-1 due to chemical shift. Another Troc carbon which is adjacent to three chlorine of Troc protecting group was found at 94.24 ppm and assigned to C-10. The first set of olefinic carbons with similar signal intensity found at 117.10, 117.33 and 117.66 ppm which were assigned to C-12, C-21 and C-30. The fifteen typical aromatic carbons occurred 121.17, 122.25, 129.51, 129.58, 131.85 and 132.06 ppm. Some of these signal appeared to be overlapping. The signal at 121.17 ppm occurred with three carbons intensity and assigned to C-16, C-25 and C-34. The next peak at
122.25 ppm assigned to C-18, C-27 and C-36. The other aromatic group peak found at 129.51 ppm and assigned to C-15, C-25 and C-34. Similarly the peak at 129.58 ppm assigned to C-19, C-28 and C-37. Further down of the $^{13}$C-NMR spectrum another two peak found to be belong to aromatic carbons. The first one occurred at 131.85 ppm with one proton intensity and assigned to C-14 then the second peak occurred at 132.06 ppm as overlapping two carbon and assigned to C-23 and C-32. The last carbons of aromatic group which are adjacent to oxygen atoms were found at 144.88, 144.94 ppm, 145.09 ppm and the signal assigned to as C-17, C-26 and C-35 due to chemical shift considerations and $^1$H$^{13}$C-HMQC spectrum. The carbonyl carbons occurred at down field of the $^{13}$C-NMR spectrum. The first carbonayl carbons found at 152.43, 165.67, 165.77, 165.84 ppm and assigned to C-8, C-11, C-20 and C-29. Then these peaks followed by a singlet at 169.13 ppm with three carbon intensity which proved that three signals were overlapping. Due to cross peaks at $^1$H$^{13}$C-HMQC spectrum these carbons identified as carbonyls of acetyl group of coumaroyl moiety C-38, C-39 and C-40. The signal at 169.97 assigned to C-7 as other spectral data. The infrared spectrum shows strong signals at 2957 cm$^{-1}$(COOH), 1765, 1718 cm$^{-1}$ (C=O), 1636 cm$^{-1}$ (C$_{Ar}$=C$_{Ar}$), 1205, 1165, 1107 cm$^{-1}$ (C-O) as it was expected.

![Figure 132: $^1$H$^{13}$C-HMQC spectrum of (1R, 3R, 4S, 5R)-1-(β, β', β'-trichloroethoxy carbonyl)-3,4,5-tri-(acetyl p-coumaroyl) quinic acid](image-url)
Figure 133: IR spectrum of (1R, 3R, 4S, 5R)-1-((\(\beta\), \(\beta\), \(\beta\)-trichloroethoxy carbonyl)-3,4,5-tri-(acetyl \(p\)-coumaroyl) quinic acid

**Attempt for the cleavage of acetal protecting groups**

Cleavage of acid labelled protecting groups of esters is achieved with 2N aqueous HCl containing THF for the 3, 4-isopropylidene quinide and bisacetonide.

Sefkow\(^{310}\) achieved cleavage of protecting groups in two steps; LiOH in degassed water/THF, then followed by acidification of the reaction with 2 M HCl. Also, cleavage of all protecting groups of bisacetonide was achieved with 1N aqueous HCl and 15% THF was published by Hemmerle.\(^{316}\) It was reported that when 2N HCl was used, saponification was observed (15%). Also when the reaction was treated with 0.5 N HCl deprotection was very slow. Sefkow’s group managed to complete the deprotection in 10 days.
After several attempts it was observed that the Sefkow’s method didn’t give any result for the reactions. Experiments were set up by using different combinations of Sefkow’s published data. Initially the reaction mixtures were treated with LiOH/THF/water (1:2) and this solvent combination was seemed to be suitable to open the lactone chain as shown in the example below. Afterwards, reactions were treated with 2M HCl for 2 days and deprotection of acetal was achieved. This reaction again was tried with different solvent combinations until the right solvent combination was found and finally stirring the reaction mixture with THF (5 ml) and HCl (10ml) 24 hours at room temperature gave the best result for the removal of the acetal group.

Orthogonal protection strategy used for the deprotection of acetal group in the presence of Troc protecting group from the 1-(β, β, β-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide. After stepwise cleavage of acetal group followed by mono-substitution or some cases di-substation of acyl chloride to the Troc protected quinide moiety. The reaction conditions for the removal of acetal protecting group in the absence of Troc protecting group was already obtained in the previous reactions. Unfortunately, quite a large number of reactions simply by changing the amount of solvent and reaction time didn’t give the same results as before.

Acetal group form the 1-(β, β, β-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide wasn’t achieved by applying the same method as it was shown above. The same reaction was set with several different solvent combinations such as: 1 ml THF/2ml 2M HCl for 5 days; 2.5 ml THF/1ml 2M HCl /5 ml water for 10 days; 4 ml THF/20ml 2M HCl 6 days; 2 ml acetic acid/ 4 ml water 40 hours; 2 ml acetic acid/ 10 ml water 3 days; 4ml TFA/ 4 ml water 12 hours; 6 ml TFA/ 20 ml water 33 hours; 2 ml TFA/ 20 ml water 33 hours……etc. and none of these experiment showed the removal of acetal protecting group.

It was observed that the cleavage of the acetal group was influenced by the Troc protected group. The conclusion drawn from the experimental results showed that the structure of the protecting groups and the type of solvent were the most important factors to optimize the reaction conditions. Hence, in order to achieve the deprotection reaction for the acetal protecting group in the presence of Troc protecting group alternative solvent system and different reaction temperatures used.
Alternatively, 1-((\beta,\beta,\beta\text{-})trichloroethoxycarbonyl)-3,4-O-isopropylidene quinide was treated as it was described in the literature\textsuperscript{311,312,313,314,315} with 30 ml of 1\% I\textsubscript{2} in Methanol at 45\(^\circ\)C in oil bath for four days to remove the acetal group completely from the 1-((\beta,\beta,\beta\text{-})trichloroethoxycarbonyl)-3,4-O-isopropylidene quinide. This new reaction conditions gave very good results in small scale. Surprisingly, when reaction scale was increased (from 1\text{gr} to 7\text{gr}) results were disappointing. Once again different ratio of the solvents and different temperatures were tried but, reactions didn’t work as before. Therefore, acetal group removal succeeded when amount of starting material was up to 2 grams.
CONCLUSION

Chapter 4
Conclusions

A series of mono-acyl chlorogenic acids, in particular substituted in the 1-, 3-, 4- and 5- position of the quinic acid with coumaroyl, feruloyl, caffeoyl and dimethoxy cinnamoyl substituents have been successfully synthesized. The improvement of the existing Sefkow’s acylation method allowed for some of the first synthesis of chlorogenic acids to be established. As intermediates in these synthesis a series of quinide esters, potential metabolites and degradation products of naturally occurring chlorogenic acids have also been obtained. The first examples of di-acyl chlorogenic acids and poly-acyl chlorogenic acids have been successfully synthesized. A general protection and deprotection strategy for the synthesis of chlorogenic acids has been established. The list of the synthesised compounds in this thesis and applied methods for each type of the synthesis in general is mentioned in the following paragraphs. During the experimental work it was observed that chlorogenic acids are sensitive to air and less stable than ester forms. Keeping in mind that the reference materials should be available for future work of the project, chain opening reactions in THF/H₂O solution wasn’t performed for every product.

Acid chlorides

The method for synthesis of acid chlorides di-acetyl caffeic acid chloride, acetyl ferulic acid chloride, acetyl p-coumaric acid chloride was available in the literature. Cinnamoyl chloride is the only commercially available acyl chloride, which was used for synthesis. The 3, 4-dimethoxycinnamic acid chloride (44) is a new type of acyl chloride which is also prepared for the synthesis. The list of the acyl chlorides which were synthesised is shown below;

![Acid chlorides](image_url)
Starting materials

Quinide (1L-1 (OH), 3, 4,5-Tetrahydroxycyclohexane carboxylic acid) (51) made available by converting quinic acid to quince acid lactone. This product was then used as starting materials for most of the reactions.

The method which was used for the synthesis of 3, 4-O-Isopropylidene quinide (45) was established by John C. Rohloff in 1998. The same method used to make 3, 4-O-Isopropylidene quinide (415) in order to use for further synthesis. As a new approach 3, 4-O-Isopropylidene quinic acid, (46) was synthesised by applying 3, 4-O-Isopropylidene quinide (415) in THF/H2O and LiOH suspension at room temperature which was again used for some of the synthesis. Troc protection and removal of protecting group was described by Thomas B. Winholdz and David B.R. Johnson in 1967. The same method was applied for producing Troc protected quinide 1-(β, β, β-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide, (47). After removal of acetal group from the structure 1-(β, β, β-trichloroethoxycarbonyl) quinide, (48) was obtained. This compound was used for the synthesis of mono-acetyl, di acetyl and poly-acetyl chlorogenic acid and lactone synthesis. The Troc protected quinide at first position has not been reported in the literature yet. First synthesis of bisacetonide in order to make derivates of chlorogenic acids was published by M. Sefkow and his group in 2001. M. Sefkow’s published method was slightly improved by using different quantities and compound was optimised as white crystals at the end of the reaction.

![Synthesised starting materials](image-url)

**Figure 134:** Synthesised starting materials
Mono-acyl chlorogenic acids

Mono-acyl chlorogenic acids synthesis achieved in four different ways by using 3, 4-O-Isopropylidene quinide, Troc protected quinide, bisacetonide and quinide as starting materials. The products produced from 3, 4-O-Isopropylidene quinide were all pure after the reactions and didn’t require any purification. The products which are synthesised from Troc protecting quinide and quinide needed further purification which was performed by flash chromatography using chloroform /acetone mixture. It was reported that the hydrogen atom in chloroform is capable of hydrogen bonding to a suitable electron donor molecule. Therefore this combination (chloroform /acetone) wouldn’t be a good solvent choice. Surprisingly, it gave very sufficient results for the synthesis of chlorogenic acids purifications.

The products produced from 3, 4-O-Isopropylidene quinide at -1 position

The synthesised compounds were obtained by acylation of quinide acetal with 1.1 equivalent cinnamoyl chloride by using DMAP in dichloromethane and N, N, N-Triethylamine solution. These esters were stirred in THF/ H₂O solution to provide corresponding mono-acyl chlorogenic acids. The list of the products synthesised from 3, 4-O-Isopropylidene quinide (45) as shown below;

Part I:

![Synthesised mono-acyl chlorogenic acid lactones leading mono-acyl chlorogenic acids](image)

**Figure 135:** Synthesised mono-acyl chlorogenic acid lactones leading mono-acyl chlorogenic acids
Part II:

Figure 136: Synthesised mono-acyl chlorogenic acids

The products produced from quinide at -3 position
The same acylation method was used to make the chlorogenic acids esters at 3-position starting from quinide. Purification of all the products completed by using column chromatography (chloroform-acetone 8:2) which was enable to get the pure chlorogenic acid lactones products. These products weren’t treated with typical THF/H₂O solution to form acids because of the reason mentioned at the beginning.

Figure 137: Synthesised mono-acyl chlorogenic acid lactones at 3rd position
The products produced from 1-(β, β, β-trichloroethoxycarbonyl) quinide

The acylation method which was established by Sefkow and his group was also applied to synthesis of Troc protected quinide derivatives. The only the difference between acylating acetal protected quinide and Troc protected quinide reactions was the starting materials. The same principle of the method was applied to both type of reactions. The Troc protecting group hasn’t removed from all of the synthesised compounds. But, the way to remove the Troc protection by using zinc powder was already established in the literature. In this thesis it was proven (by the reaction 80 and 88) that the same method works without any problem during the synthesis of the chlorogenic acids. Therefore, for some of the compounds removal of the Troc protection was left out but at least the way to make the pure compounds available was established. The list of the products synthesised from 1-(β, β, β-trichloroethoxycarbonyl) quinide, (48) as shown below;

Figure 138: Troc protected chlorogenic acid lactones
The products produced from bisacetonide at -5 position

Here again, Sefkow’s method was used for the synthesised products which were produced from bisacetonide. Sefkow and his group had already prepared 5-CQA. The same method was developed slightly different quantities and reactions provided 5-diacetylfaffeoyl bisacetonide, 5-acetylferuloyl bisacetonide, 5-acetyl p-coumaroyl bisacetonide, 5-dimethoxycinnamoyl bisacetonide, 5-cinnamoyl bisacetonide as pure compounds in very good yields.

![Chemical structures of synthesised chlorogenic acids at 5th position](image)

**Figure 139:** Synthesised chlorogenic acids at 5th position
Di-acyl chlorogenic acids

Di-acyl chlorogenic acid esters synthesised from two different starting materials. The first type of synthesis achieved by using Troc quinide (48) and provided 3, 4-di-acyl chlorogenic acid esters. In the second type of synthesis quinide used as starting material to provide 1,2-di-acyl chlorogenic acid esters. Sefkow’s acylation method used for both type of the synthesis with small differences in the reaction conditions. Both reactions required purification and flash chromatography from (chloroform-acetone) provided the compounds shown below. Troc protection removed only from one of the products (88) to demonstrate the reprotaction of protecting group which made 3,4-di-acyl esters available. Then the next step would be treating the ester with THF/H$_2$O solution as usual to make 3, 4-di-acyl chlorogenic acids. Previous reactions proved that these type of reactions are working for chlorogenic acids. Therefore, these steps left out to concentrate on new synthesis. The synthesised compounds for both type as shown below;

*The products produced from Troc quinide at -3,-4 position*

![Synthesised di-acyl chlorogenic acid lactones](image)

*Figure 140: Synthesised di-acyl chlorogenic acid lactones*
Conclusions

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The products produced from quinide and 3, 4-O-Isopropylidene quinic acid at -1,-3 position

-Homo:

Figure 141: Synthesised chlorogenic acid lactones at 1- and 3- positions

-Homo 1, 4-di-acyl and Hetero 1, 3-di-acyl position:

Figure 142: Synthesised chlorogenic acid lactones at 1- and 2- positions
Poly-acyl chlorogenic acids and esters
The same acylation method with different quantities staring from quinic acid and quinide was provided the selection of poly-acyl chlorogenic acid esters at -1,-2 and -3 positions. Some of the compounds obtain after column chromatography by using the same solvent combination as the other reactions. Again, the synthesised compounds could be converted to acids to form chlorgenic acids at -1,-2 and -3 positions but, because of the stability reasons this step was left for future in order to use the compounds as reference material when it’s needed. Also Troc protecting group wasn’t removed from the -3, -4, -5 substituted chlorgenic acids.

Figure 143: Synthesised Poly-acyl chlorogenic acid lactones
Figure 144: Synthesised Troc protected poly-acyl chlorogenic acids
EXPERIMENTAL

Chapter 5
General Experimental

All chemicals were purchased from either Aldrich or ACROS Chemical Companies. \(^1\)H-NMR and \(^{13}\)C- NMR spectra were recorded on a Bruker Avance DRX-500 MHz and Jeol ECX 400 MHz spectrometer, which were also used for \(^1\)H-\(^1\)H-COSY and \(^1\)H\(^{13}\)C-HMQC experiments. Standard Bruker 2-D and Jeol Delta software were used for spectral processing. All chemical shifts are quoted as \(\delta\) values in ppm relative to TMS (\(\delta_H = 0\) ppm; \(\delta_C = 0\) ppm), CDCl\(_3\) (\(\delta_H = 7.26\) ppm; \(\delta_C = 77.23\) ppm), DMSO (\(\delta_H = 2.50\) ppm; \(\delta_C = 39.50\) ppm), and D\(_2\)O (\(\delta_H = 4.81\) ppm). Coupling constants (\(J\)) are reported in Hz. Peak assignments in the proton NMR spectra abbreviated as follows; s = singlet, d = doublet, dd = doublet of doublet, t = triplet and m = multiplet.

Infrared spectra were recorded on a Perkin-Elmer 200 spectrometer and FT-IR spectrometer Nicolet Avatar 370. Samples were analysed Nujol mulls and KBr plates, absorptions (\(\nu_{\text{max}}\)) are reported in cm\(^{-1}\). Microanalysis was carried out using a Leeman CE 440 automatic elemental analyser.

The mass spectra (\(m/z\)) were recorded at a Thermo Quest Finnigan MAT 95 XL spectrometer in CI mode, Bruker microTOFQ instrument using an ESI source and a Bruker HCT ultra ion mass spectrometer. X-ray crystallography was carried out using Bruker Kappa single-crystal X-ray diffractometer. Melting points were determined with a Yanaco MP-500 D melting point apparatus.

Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F\(_{254}\) silica 0.25 mm pre-coated, commercially available plates. The silica for the column chromatography was performed using Fluka silica gel pore size 33-70\(\mu\)m and Merck Kieselgel 60 F\(_{254}\) silica.

Elemental analysis was carried out by Judith Peters, University of Surrey. Mass spectra (\(m/z\)) and accurate mass were carried out by Richard Chaundy, University of Surrey and Anja Mueller, Jacobs University Bremen. X-ray crystallography was carried out by Dr. Michael H. Dickman, Jacobs University Bremen.
Synthesis of starting materials

**Quinide (1L-1 (OH), 3, 4,5-Tetrahydroxycyclohexane carboxyclic acid), (51)-p58**

Quinic acid (5.000 g, 26.018mmol) was heated for one hour at 220 °C. The brownish crude product was recrystallised from ethanol up to five times to yield the title compound quinide (51) as a white powder (1.360 g, 30%). Rf 0.73 [acetonitrile]; mp: 150°C; \( \nu_{\text{max}} \) (Nujol)/cm\(^{-1}\): 3461, 3325, 3248 (OH), 1794 (C=O), 1140, 1083, 1056 (C-O); \( \delta \)H (500 MHz, D\(_2\)O): 1.94 (1 H, t, J 11.7, 2-H\(_{eq}\)), 2.13 (1 H, m, 2-H\(_{ax}\)), 2.42 (1 H, m, 6-H\(_{ax}\)), 2.48 (1 H, d, J 11.8, 6-H\(_{eq}\)), 3.87 (1 H, dd, J 5.6, 3.8 and 2, 3-H), 4.16 (1 H, d, J 4.5, 4-H), 4.91 (1 H, t, J 5.4, 5-H); \( \delta \)C (125 MHz, D\(_2\)O): 36.5 (C-2), 37.7 (C-6), 64.96 (C-3), 66.79 (C-4), 72.51 (C-1), 77.46 (C-5), 179.78 (C-7); MS, m/z 175 [M+H], 157 [M-OH], 139 [M-H\(_2\)O]; CHN: ( C\(_7\)H\(_{10}\)O\(_5\) 174 g/mol requires: C, 48.27%; H, 5.73%, Found: C, 48.85%; H, 5.73%.
Diacetyl caffeic acid chloride, (41) -p54

To a solution of caffeic acid (3.600 g, 19.980 mmol) and DMAP (0.060 g, 0.500 mmol) in pyridine (10 ml), was added acetic anhydride was (4.7 ml, 50 mmol) at 0 °C. The reaction mixture was stirred for 4 hours and then poured onto crushed ice. The aqueous phase was acidified with 2M HCl (50 ml) and extracted with EtOAc/THF (3:1). The combined organic extracts were dried over MgSO₄, filtered and the solvents were removed under reduced pressure. The residue was washed with petroleum ether and evaporated under reduced pressure to give diacetyl caffeic acid (4.850 g, 91.85%) as a colourless powder. This product (4.850 g, 18.355 mmol) was suspended in toluene (100 ml) containing five drops of DMF. Oxalyl chloride (3.29 ml, 37.65 mmol) was added at -5 °C and stirred for 2 hours. The reaction mixture was stirred additional 15 hours at room temperature, filtered and the solvent was removed under vacuum to give the title compound 41 as a slightly yellow powder (4.600 g, 81%). Rf 0.38 [chloroform: acetone (8:2)]; ν_max (KBr)/cm⁻¹: 1758 (C=O), 1689, 1630 (Cᴬ=Cᴬ), 1208 (C-O); δ_H (400 MHz, CDCl₃): 2.28 (3 H, s, 12-H), 2.29 (3 H, s, 13-H), 6.57 (1 H, d, J 16, 2-H), 7.28 (1 H, s, 9-H), 7.40 (1 H, d, J 2.3, 6-H), 7.41 (1 H, d, J 2.3, 5-H), 7.73 (1 H, d, J 16, 3-H); δ_C (125 MHz, CDCl₃): 20.67 (C-12), 20.72 (C-13), 118.67 (C-2), 123.47 (C-3), 120.8 (C-6), 127.50 (C-5), 132.26 (C-4), 141.21 (C-7), 145.96 (C-8), 165.91 (C-1), 167.82 (C-10), 168.14 (C-11).
Acetyl ferulic acid chloride, (42)

To a solution of ferulic acid (5.000 g, 25.749 mmol) and DMAP (0.077 g, 0.643 mmol) in pyridine (10 ml) was acetic anhydride added (2.35 ml, 25 mmol) at 0°C. The reaction mixture was stirred for 4 hours and then poured onto crushed ice. The aqueous phase was acidified with 2M HCl (50 ml) and extracted with EtOAc/THF (3:1). The combined organic extracts were dried over MgSO₄, filtered and the solvents were removed under reduced pressure. The residue was washed with petroleum ether and evaporated under reduced pressure to give acetyl ferulic acid (5.750 g, 94.54%) as a colourless powder. This product (5.550 g, 23.495 mmol) was suspended in toluene (100 ml) containing five drops of DMF. Oxalyl chloride (4.36 ml, 50 mmol) was added at -5°C and stirred for 2 hours. The reaction mixture was stirred additional 15 hours at room temperature, filtered and the solvent was removed under vacuum to give the title compound 42 as a pale yellow powder (5.830 g, 95.8%). Rf 0.32 [chloroform: acetone (8:2)]; ν max (KBr)/cm⁻¹: 1762 (C=O), 1639 (C₆H₅=CH=O), 1218 (C-O); δ H (400 MHz, CDCl₃): 2.16 (3 H, s, 11-H), 3.71 (3 H, s, 12-H), 6.20 (1 H, d, J 16, 2-H), 6.95-6.97 (1 H, m, Ph-H), 7.44 (1 H, d, J 16, 3-H); δ C (125 MHz, CDCl₃): 20.63 (C-11), 55.91 (C-12), 111.19 (C-2), 119.21 (C-9), 121.12 (C-6), 123.16 (C-5), 133.56 (C-4), 141.25 (C-3), 143.73 (C-7), 151.35 (C-8), 168.48 (C-1), 168.70 (C-10).
**Acetyl \( p \)-coumaric acid chloride, (43)**

To a solution of \( p \)-coumaric acid (5.000 g, 30.458 mmol) and DMAP (0.091 g, 0.761 mmol) in pyridine (10 ml) was acetic anhydride added (2.35 ml, 25 mmol) at 0 °C. The reaction mixture was stirred for 4 hours and then poured onto crushed ice. The aqueous phase was acidified with 2M HCl (5 0 ml) and extracted with EtOAc/THF (3:1). The combined organic extracts were dried over MgSO₄, filtered and the solvents were removed under reduced pressure. The residue was washed with petroleum ether and evaporated under reduced pressure to give acetyl \( p \)-coumaric acid (5.800 g, 92.35%) as a colourless powder. This product (5.800 g, 28.129 mmol) was suspended in toluene (100 ml) containing five drops of DMF. Oxalyl chloride (5.048 ml, 57.70 mmol) was added at -5 °C and stirred for 2 hours. The reaction mixture was stirred additional 15 hours at room temperature, filtered and the solvent was removed under vacuum to give the title compound 43 as a white powder (6.000 g, 87%). Rf 0.38 [chloroform: acetone (8:2)]; \( \nu_{\text{max}} \) (KBr)/cm⁻¹: 1773 (C=O), 1653 (Cₓ=Cₓ), 1026 (C-O); \( \delta_{\text{H}} \) (400 MHz, CDCl₃): 2.26 (3 H, s, 11-H), 6.35 (1 H, d, J 16, 2-H), 7.06-7.50 (1 H, m, Ph-H), 7.51 (1 H, d, J 16, 3-H); \( \delta_{\text{C}} \) (125 MHz, CDCl₃): 21.02 (C-11), 119.79 (C-2), 122.06 (C-6, C-8), 128.98 (C-5, C-9), 132.15 (C-4), 143.15 (C-3), 151.84 (C-7), 168.27 (C-1), 168.95 (C-10).
3, 4-dimethoxycinnamic acid chloride, (44)

3, 4-dimethoxycinnamic acid (5.000 g, 24.014 mmol) was suspended in toluene (100 ml) containing five drops of DMF. Oxalyl chloride (4.31 ml, 49.26 mmol) was added at -5 °C and stirred for 2 hours. The reaction mixture was stirred additional 15 hours at room temperature, filtered and the solvent was removed under vacuum to give the title compound 44 as a bright yellow powder (5.090 g, 93.56%). Rf 0.45 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 1682 (C=O), 1626 (C=O), 1141 (C-O); δH (400 MHz, CDCl3): 3.93 (3 H, s, 10-H), 3.97 (3 H, s, 11-H), 6.48 (1 H, d, J 16, 2-H), 6.88 (1 H, d, J 8.4, 9-H), 7.05 (1 H, d, J 2, 6-H), 7.17 (1 H, dd, J 8.2 and 1.6, 5-H), 7.29 (1 H, d, J 16, 3-H); δC (125 MHz, CDCl3): 55.99 (C-10), 56.08 (C-11), 109.87 (C-9), 111.13 (C-6), 114.82 (C-2), 123.19 (C-5), 127.13 (C-4), 147.05 (C-3), 149.37 (C-8), 151.78 (C-7), 171.92 (C-1).
3, 4-O-Isopropylidene quinide, (45)-p62

A mixture of (1R, 3R, 4R, 5R)-(-)-quinic acid (20.000 g, 104.074 mmol), p-toluenesulfonic acid monohydrate (0.200 g, 1.050 mmol), 2, 2-dimethoxypropane (3.800 g, 364.900 mmol) and acetone (80 ml) was refluxed for 2 hours. The reaction mixture was cooled to 50 ºC and neutralised by the addition of 21% sodium ethoxide in denatured ethanol (0.340 g, 1.050 mmol). Most of the ethanol was removed under rotary evaporator and gummy residue was dissolved by dissolved in EtOAc (120 ml). This mixture was washed with water (30 ml) and extracted with EtOAc (15 ml). The organic layers were combined and washed with 5% aqueous sodium bicarbonate (13.500 g, 8.00 mmol). The solvents was removed under rotary evaporator and gummy residue was dissolved by colourless needles. Rf 0.42 [chloroform: acetone (8:2)]; δ\text{H} (400 MHz, CDCl$_3$): 1.30 (3 H, s, 9-H), 1.49 (3 H, s, 10-H), 2.16 (1 H, dd, J 14.6 and 2.8, 2-H$_{ax}$), 2.30 (1 H, m, 2-H$_{eq}$), 2.34 (1 H, m, 6-H$_{ax}$), 2.59 (1 H, d, J 11.9, 6-H$_{eq}$), 4.28 (1 H, dd, J 3.6 and 2.3, 4-H), 4.47 (1 H, ddd, J 9.6, 8.8 and 2.8, 3-H), 4.69 (1 H, d, J 5.9 and 2.3, 5-H); δ\text{C} (125 MHz, CDCl$_3$): 24.37 (C-9), 27.04 (C-10), 34.36 (C-2), 38.20 (C-6), 71.58 (C-3), 71.63 (C-4), 72.16 (C-5), 75.91 (C-1), 109.86 (C-8), 179.04 (C-7).
To a solution of 3, 4-isopropylidene-quinide (2.270 g, 10.596 mmol) in a mixture of degassed THF (10 ml) and water (3 ml) was treated with LiOH (0.279 g, 11.656 mol) in 2ml H₂O at room temperature. The solution was stirred for 24 hours at room temperature, acidified by using 2M HCl (10 ml) solution and extracted with DCM (50 ml). The organic layer was dried with MgSO₄ and filtered. The solvent was removed under reduced pressure to give the title compound 46 as a white powder (2.300 g, 93%). Rf 0.36 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3454 (OH), 1602 (COOH), 1421, 1383 (CH₃), 1219, 1049 (C-O); δH (400 MHz, D₂O):1.25 (3 H, s, 9-H), 1.40 (3 H, s, 10-H), 1.71 (1 H, m, 6-Hax), 1.72 (1 H, m, 6-Heq), 1.95 (1 H, dd, J 16 and 1.6, 2-Hax), 2.11 (1 H, dd, J 10.8 and 5.2, 2-Heq), 3.88 (1 H, m, 4-H), 3.91 (1 H, m, 5-H), 4.41 (1 H, ddd, J 7.3, 4.6 and 2.7, 3-H); δC (125 MHz, D₂O): 25.07 (C-9), 27.53 (C-10), 34.50 (C-6), 39.02 (C-2), 68.09 (C-5), 74.14 (C-3), 75.24 (C-4), 79.78 (C-1), 109.32 (C-8), 181.98 (C-7).
1-(β, β, β-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide, (47)-p72

To a suspension of 3, 4-O-isopropylidene-quinide 45 (7.000 g, 32.676 mmol) and trichloroethyl chloroformate (4.40 ml, 32.676 mmol) in dichloromethane (50 ml) was added pyridine (10 ml) at room temperature. The reaction mixture was stirred for 12 hours at room temperature and worked up by diluting with Dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give the 1- (β, β, β-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide (47) as a white solid (11.300 g, 88.76%). Rf 0.81 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 1807,1767 (C=O), 1437, 1380 (CH₃), 1204, 1078 (C-O), 837 (C-Cl); δH (400 MHz, CDCl₃): 1.30 (3 H, s, 12-H), 1.46 (3 H, s, 13-H), 2.38 (1 H, dd, J 14.6 and 2.8, 2-Hax), 2.51 (1 H, m, 2-Heq), 2.64 (1 H, d, J 11.4, 6-Heq), 3.02 (1 H, m, 6-Hax), 4.31 (1 H, dd, J 5.5 and 1.2, 4-H), 4.52 (1 H, ddd, J 9.6, 7.7 and 2.7, 3-H), 4.71 (1 H, d, J 11.9, 9-H), 4.76 (1 H, dd, J 6.4 and 2.7, 5-H), 4.80 (1 H, d, J 11.9, 9-H³); δC (125 MHz, CDCl₃): 24.36 (C-12), 28.14 (C-13), 34.48 (C-2), 38.63 (C-6), 66.73 (C-3), 68.21 (C-4), 72.30 (C-5), 74.65 (C-9), 82.39 (C-1), 93.45 (C-10), 109.14 (C-11), 152.38 (C-8), 170.78 (C-7).
**1-(β, β, β-trichloroethoxycarbonyl) quinide, (48)-p75**

1-(β, β, β-trichloroethoxycarbonyl)-3, 4-O-isopropylidene quinide 47 (2.000 g, 5.133 mmol) followed by 30 ml of 1% Iodine in methanol. This solution was replaced in oil bath at 45 °C and stirred for 96 hours. The reaction mixture was quenched with 80 ml of saturated sodium thiosulphate and extracted with EtOAc (3x50 ml). The organic layers were combined, dried with MgSO$_4$, filtered and the solvents were removed by reduced pressure to give slightly yellow liquid. This crude product was recrystallised by toluene to give the title compound as pale yellow powder (1.400 g, 78%). Rf 0.43 [chloroform: acetone (8:2)]; $\nu_{\text{max}}$(KBr)/cm$^{-1}$: 3441 (OH), 1750, 1636 (C=O), 1289, 1108, 1058 (C-O), 818 (C-Cl);

$\delta_H$ (400 MHz, D$_2$O): 1.85 (1 H, dd, J 12 and 2.8, 2-H$_{ax}$), 2.16 (1 H, d, J 3.6, 6-H$_{eq}$), 2.46 (1 H, ddd, J 14, 6.8 and 3.2, 2-H$_{eq}$), 2.74 (1 H, ddd, J 15.6, 6.8 and 3.6, 6-H$_{ax}$), 3.52 (1 H, dd, J 9.2 and 3.2, 4-H), 4.11 (1 H, m, 3-H), 4.18 (1 H, dd, J 7.6 and 3.2, 5-H), 4.72 (1 H, d, J 12, 9-H), 4.79 (1 H, d, J 11.6, 9-H$^1$); $\delta_C$ (125 MHz, D$_2$O): 33.95 (C-2), 38.62 (C-6), 66.38 (C-3), 68.36 (C-4), 75.24 (C-5), 77.44 (C-9), 83.59 (C-1), 94.40 (C-10), 152.24 (C-8), 171.07 (C-7).
Bisacetonide, (49)-p79

Quinic acid (5.000 g, 26.018 mmol) dried for 4 hours at 40 °C. To a suspension of dried quinic acid in dichloromethane (50 ml) was added triethylamine (20 ml, 145 mmol) at -15 °C. The reaction mixture turned clear within a few minutes and trimethylsilyl chloride (17.5 ml, 137.5 mmol) was added at that temperature. A white precipitate was immediately formed. The suspension was stirred for 12 h while the temperature was maintained below 0 °C. Pentane (200 ml) was added and the precipitate was filtered off. The filter cake was washed with hot pentane (5x100 ml). The solvents were removed under reduced pressure. The residue was redissolved in pentane (200 ml) and any remaining ammonium salt was filtered off. Pentane was removed under rotary evaporator to give a total of silyl ether as a yellow liquid (10.140 g, 18.334 mmol). This was kept in a fridge at -22 °C for two days. A solution of silyl ether (10.140 g, 18.334 mmol) in acetone (50 ml) and DMP (50 ml) was cooled to -70 °C and a solution of TMS-OTf (0.3 ml, 1.7 mmol) in dichloromethane (3 ml) was added drop wise. The reaction mixture was stirred for 4 hours while warming to -45 °C. The yellow solution was kept at -22 °C for 2 days, re-cooled to -70 °C and added to a saturated NaHCO₃ solution (200 ml), whereupon the colour faded. The aqueous layer was extracted with EtOAc (3x80 ml). The combined organic extracts were dried over MgSO₄, filtered and the solvents were removed under reduced pressure. The residue was recrystallised from EtOAc to give bisacetonide (49) as colourless crystals (3.800 g, 53.64%). Rf 0.52 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3447 (OH), 1788 (C=O), 1381 (CH₃), 1275, 1220, 1056 (C-O); δH (400 MHz, CDCl₃): 1.25 (3 H, s, 10-H), 1.34 (3 H, s, 11-H), 1.58 (3 H, s, 12-H), 1.59 (3 H, s 13-H), 1.91 (1 H, dd, J 13.7 and 9.1, 6-Hax), 2.09 (1 H, dd, J 14.6 and 3.6, 6-Heq), 2.20 (1 H, dd, J 15.1 and 4.2, 2-Hax), 2.27 (1 H, dd, J 15.5 and 4.6, 2-Heq), 3.99 (1 H, m, 4-H), 4.01 (1 H, m, 5-H), 4.66 (1 H, dd, J 10.1 and 4.6, 3-H); δC (125 MHz, CDCl₃): 25.36 (C-10), 28.62 (C-11), 28.64 (C-12), 28.84 (C-13), 35.08 (C-6), 37.38 (C-2), 67.36 (C-5), 71.79 (C-3), 76.78 (C-4), 78.45 (C-1), 109.08 (C-8), 111.57 (C-9), 176.21 (C-7); MS, m/z (ESI): 271.1189 [M⁺ - C₁₃H₂₀O₆ requires 271.1187].
(1S, 3R, 4R, 5R)-1-cinnamoyl-3, 4-isopropylidene quinide, (52)-p88

To a suspension of 3,4-isopropylidene-quinide (0.500 g, 2.33 mmol) and N,N-(dimethylamino) pyridine (0.0142 g, 2.57 mmol) in dichloromethane (10 ml) was added triethylamine (0.358 ml) followed by the addition of cinnamic acid chloride (0.428 g, 2.57 mmol). The reaction mixture was stirred for 17 hours at room temperature and worked up by diluting with dichloromethane (100 ml) and washing with 2M HCl (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give the title compound (52) as a white solid (0.520 g, 70%). Rf 0.42 [ethyl acetate: petrol ether (2:3)]; mp 175 °C; v_max (Nujol)/cm⁻¹: 1711, 1705 (C=O), 1640 (C=Ar=Ar), 1461, 1376 (CH₃), 1173, 1073 (C=O); δ_H (500 MHz, CDCl₃): 1.34 (3 H, s, 9-Me), 1.54 (3 H, s, 10-Me), 2.43 (1 H, dd, J 11.5 and 3, 2-Hₐx), 2.53 (1H, m, 2-H_eq), 2.64 (1 H, d, J 11.5, 6-H_eq), 3.12 (1 H, m, 6-H_eq), 4.35 (1 H, m, 4-H), 4.57 (1 H, m, 3-H), 4.82 (1 H, dd, J 6.5 and 2, 5-H), 6.45 (1 H, d, J 16, 12-H), 7.26-7.44 (5 H, m, Ph-H), 7.74 (1 H, d, J 16, 13-H); δ_C (125 MHz, CDCl₃): 24.58 (C-9), 27.23 (C-10), 30.96 (C-2), 35.92 (C-6), 71.46 (C-3), 72.74 (C-4), 75.65 (C-5), 76.43 (C-1), 110.22 (C-8), 117.23 (C-12), 128.52 (C-15), 128.82 (C-16), 129.32 (C-17), 129.85 (C-18), 130.98 (C-19), 134.25 (C-14), 146.97 (C-13), 165.22 (C-11), 173.77 (C-7); MS, m/z (Cl): 344 [M⁺], 345 [M+H], 329 [M-CH₃]; CHN: (C₁₉H₂₀O₆) 344 g/mol requires: C, 66.2%; H, 5.82%. Found: C, 66.94%; H, 5.82%. 
To a suspension of 3,4-isopropylidene-quinide (0.50 g, 2.33 mmol) and N,N-
(dimethylamino) pyridine (0.014 g, 0.116 mmol) in dichloromethane (10 ml) was
added triethylamine (0.320 ml) followed by the addition of 3, 4-dimethoxycinnamic
acid chloride (0.529 g, 2.330 mmol). The reaction mixture was stirred for 17 hours at
room temperature and worked up by diluting with dichloromethane (100 ml) and
washing with 2M HCl (10 ml). The organic layer was dried over MgSO4 and the
solvent was removed under reduced pressure to give the title compound (53) as a
white solid (0.850g, 90%). Rf 0.62 [ethyl acetate: petrol ether (2:3)]; mp 130 °C; νmax
(Nujol)/cm⁻¹: 1774, 1683 (C=O), 1625 (Cₓ=Cₓ), 1462, 1377 (CH₃), 1074, 1141 (C-
O); δH (500 MHz, CDCl₃): 1.34 (3 H, s, 9-H), 1.54 (3 H, s, 10-H), 2.45 (1 H, dd, J 14
and 3, 2-Hax), 2.54 (1 H, m, 2-H eq), 2.63 (1 H, d, J 11.5, 6-H eq), 3.12 (1 H, m, 6-Hax),
3.91 (3 H, s, 20-H), 3.92 (3 H, s, 21-H), 4.34 (1 H, dd, J 6.5 and 2, 4-H), 4.57 (1 H, m,
3-H), 4.82 (1 H, ddd, J 8.5, 6.5 and 2, 5-H), 6.31 (1 H, d, J 15.5, 12-H), 6.87 (1 H, d, J
8.5, 15Ph-H), 7.04 (1 H, d, J 6.5 and 2, 19Ph-H), 7.10 (1 H, d, J 6.5 and 2, 19Ph-H), 7.15
(1 H, d, J 16, 13-H); δC (125 MHz, CDCl₃): 24.56 (C-9), 27.21 (C-10), 31.03 (C-2),
35.91 (C-6), 56.12 (C-20), 56.19 (C-21), 71.41 (C-3), 72.71 (C-4), 75.62 (C-5), 77.48
(C-1), 109.89 (C-8), 110.20 (C-15), 111.28 (C-18), 114.61 (C-12), 123.22 (C-19),
127.22 (C-14), 146.85 (C-13), 149.47 (C-16), 151.75 (C-17), 165.42 (C-11), 173.85
(C-7); MS, m/z (CI): 404 [M⁺], 405 [M+H]; CHN: (C₂₁H₂₆O₉) 422 g/mol requires: C,
59.71%; H, 6.16%; Found: C, 55.71%; H, 6.01%.
(1S, 3R, 4R, 5R)-1-diacetylcaffeoyl-3, 4-isopropyli dene quinide, (54)

To a suspension of 3,4-isopropyli dene-quinide (0.200 g, 0.934 mmol) and N,N-(dimethylamino)pyridine (0.0057 g, 0.0467 mmol) in dichloromethane (10 ml) was added pyridine (4 ml) followed by the addition of diacetyl caffeic acid chloride (0.290 g, 1.028 mmol). The reaction mixture was stirred for 15 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give the title compound (54) as a white solid (0.310 g, 72%). Rf 0.59 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 1790, 1785, 1775 (C=O), 1653 (C₁₀=C₁₅), 1381, 1384 (CH₃), 1054, 1026 (C-O); δH (400 MHz, CDCl₃): 1.35 (3 H, s, 9-H), 1.50 (3 H, s, 10-H), 2.17 (1 H, dd, J 14.4 and 2.7, 2-Hax), 2.28 (3 H, s, 22-H), 2.29 (3 H, s, 23-H), 2.30 (1 H, ddd, J 14.5, 7.9 and 2, 2-Heq), 2.31 (1 H, d, J 11.5, 6-Heq), 2.65 (1 H, dd, J 11.5 and 6, 6-Hax), 4.19 (1 H, dd, J 8.2 and 4.4, 4-H), 4.41 (1 H, q, J 3.7, 3-H), 4.63 (1 H, ddd, J 9.7, 8 and 3.2, 5-H), 6.15 (1 H, d, J 16, 12-H), 7.20 (1 H, d, J 8.4, 15-H), 7.30 (1 H, d, J 1.7, 18-H), 7.40 (1 H, dd, J 8.4 and 1.9, 19-H), 7.63 (1 H, d, J 16, 13-H); δC (125 MHz, CDCl₃): 21.11 (C-22), 21.57 (C-23), 24.81 (C-9), 27.37 (C-10), 34.66 (C-2), 39.81 (C-6), 71.11 (C-3), 71.47 (C-4), 74.84 (C-5), 80.38 (C-1), 110.14 (C-8), 115.14 (C-12), 116.25 (C-15), 117.47 (C-18), 119.24 (C-19), 132.92 (C-14), 142.04 (C-17), 142.65 (C-18), 146.24 (C-13), 165.10 (C-11), 169.16 (C-20), 169.66 (C-21), 173.57 (C-7); MS, m/z (ESI): 459.1300 [M⁺ - C₂₃H₂₂O₁₀ requires 459.1297]
To a suspension of 3,4-isopropyldiene-quinine (0.200 g, 0.934 mmol) and N,N-(dimethylamino)pyridine (0.0057 g, 0.0467 mmol) in dichloromethane (10 ml) was added pyridine (4 ml) followed by the addition of acetyl ferulic acid chloride (0.261 g, 1.028 mmol). The reaction mixture was stirred for 15 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give the title compound (55) as a white solid (0.350 g, 86.63%). Rf 0.50 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 1792, 1789, 1780 (C=O), 1658 (C₉=C₈), 1464, 1469 (CH₃), 1028, 1013 (C-O); δH (400 MHz, CDCl₃): 1.37 (3 H, s, 9-H), 1.51 (3 H, s, 10-H), 2.15 (1 H, dd, J 12 and 2.4, 2-Hax), 2.31 (1 H, m, 6-Hax), 2.32 (3 H, s, 22-H), 2.35 (1 H, m, 6-Heq), 2.62 (1 H, d, J 12, 2-Heq), 3.86 (1 H, s, 20-H), 4.20 (3 H, dd, J 16 and 6, 4-H), 4.43 (1 H, q, J 1.6, 3-H), 4.62 (1 H, dd, J 9.2 and 3.2, 5-H), 6.37 (1 H, d, J 16, 12-H), 7.05 (1 H, d, J 7.6, 18-H), 7.12 (1 H, d, J 3.2, 15-H), 7.15 (1 H, dd, J 8.4 and 3.4, 19-H), 7.70 (1 H, d, J 16, 13-H); δC (125 MHz, CDCl₃): 20.93 (C-22), 24.81 (C-9), 27.94 (C-10), 39.63 (C-2), 39.84 (C-6), 56.51 (C-20), 71.10 (C-3), 71.43 (C-4), 72.15 (C-5), 74.82 (C-1), 109.36 (C-8), 112.36 (C-12), 120.05 (C-18), 121.87 (C-15), 123.77 (C-19), 133.45 (C-14), 141.25 (C-17), 143.87 (C-13), 151.75 (C-16), 168.05 (C-11), 169.02 (C-21), 178.68 (C-7).
(1S, 3R, 4R, 5R)-1-acetyl p-coumaroyl-3, 4-isopropylidene quinide, (56)

To a suspension of 3,4-isopropylidene-quinide (0.200 g, 0.934 mmol) and N,N-(dimethylamino) pyridine (0.0057 g, 0.0467 mmol) in dichloromethane (10 ml) was added pyridine (4 ml) followed by the addition of acetyl p-coumaric acid chloride (0.230 g, 1.028 mmol). The reaction mixture was stirred for 15 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give the title compound (56) as a white solid (0.280 g, 74.46%). Rf 0.46 [chloroform: acetone (8:2)]; νₘₐₓ (KBr)/cm⁻¹: 1789, 1759, 1751 (C=O), 1658 (C₈=C₉), 1471, 1457 (CH₃), 1054, 1027, 1001 (C-O); δ_H (400 MHz, CDCl₃): 1.21 (3 H, s, 9-H), 1.39 (3 H, s, 10-H), 1.84 (1 H, dd, J 11.6 and 3.2, 2-Hₓₓ), 2.18 (1 H, m, 6-Hₓₓ), 2.24 (1 H, m, 6-Hₑₑₑₑ), 2.29 (1 H, s, 21-H), 2.31 (1 H, d, J 11.6, 2-Hₑₑₑₑ), 4.20 (1 H, t, J 4.4, 4-H), 4.42 (1 H, q, J 1.6, 3-H), 4.62 (1 H, t, J 6, 5-H), 6.45 (1 H, d, J 16, 12-H), 7.15 (2 H, d, J 8.4, 16-H, 18-H), 7.53 (1 H, d, J 16, 13-H), 7.70 (2 H, d, J 8.8, 15-H, 19-H); δ_C (125 MHz, CDCl₃): 24.81 (C-9), 27.38 (C-10), 39.69 (C-2), 39.84 (C-6), 71.10 (C-3), 71.47 (C-4), 72.15 (C-5), 74.82 (C-1), 109.23 (C-8), 119.82 (C-12), 122.89 (C-16, C-18), 129.96 (C-15, C-19), 132.35 (C-14), 143.49 (C-13), 152.31 (C-17), 168.05 (C-11), 169.60 (C-21), 178.48 (C-7).
A solution of quinic acid lactone 52 (0.500 g, 1.45 mmol) in a mixture of degassed THF (5 ml) and water (3 ml) was treated with LiOH (0.037 g, 1.59 mmol) at room temperature. The brownish solution was stirred for 17 hours at room temperature. The solution was extracted with dichloromethane (50 ml) and dried with MgSO₄. The solvent was removed under reduced pressure to give the title compound 57 as a white powder (0.155 g, 29.4%). Rf 0.51 [chloroform: acetone (10:1)]; mp 165 °C; ν_max (Nujol)/cm⁻¹: 2924 (COOH), 2854 (C-H), 1802, 1791 (C=O), 1641 (C≡C=O), 1463, 1381 (CH₃), 1156, 1074 (C-O); δ_H (500 MHz, CDCl₃): 1.38 (3 H, s, 18-H), 1.52 (3 H, s, 19-H), 1.66 (1 H, dd, J 12.8 and 2.3, 6-H_a), 1.69 (1 H, dd, J 15.4 and 3.8, 2-H_a), 1.82 (1 H, m, 6-H_q), 2.03 (1 H, dd, J 11.5 and 1.9, 2-H_q), 3.71 (1 H, dd, J 10.2 and 2.8, 4-H), 3.83 (1 H, m, 5-H), 3.94 (1 H, q, J 4.2, 3-H), 6.94 (1 H, d, J 16, 9-H), 7.37-7.62 (5 H, m, Ph-H), 7.64 (1 H, d, J 16, 10-H); δ_C (125 MHz, CDCl₃): 21.38 (C-18), 21.39 (C-19), 34.61 (C-6), 38.73 (C-2), 65.42 (C-5), 66.16 (C-3), 72.38 (C-4), 79.35 (C-1), 115.27 (C-9), 127.43, 127.55, 128.32, 128.34, 128.47, 131.22 (C-12, C13, C-14, C15, C16, C-11), 143.12 (C-10), 168.05 (C-8), 171.28 (C-7); MS, m/z (Cl): 304 [M⁺], 305 [M+H]; CHN: (C₁₆H₁₆O₆) 304 g/mol requires: C, 63.15%; H, 5.26%; Found: C, 60.83%; H, 5.65%.
A solution of quinic acid lactone 53 (0.200 g, 0.50 mmol) in a mixture of degassed THF (5 ml) and water (3 ml) was treated with LiOH (0.013 g, 0.55 mmol) at room temperature. The brownish solution was stirred for 17 hours at room temperature. The solution was extracted with dichloromethane (50 ml) and dried with MgSO₄. The solvent was removed under reduced pressure to give the title compound 58 as a white powder (0.190 g, 90.9%). Rf 0.23 [chloroform: acetone (10:1)]; mp 135 °C; ν<sub>max</sub> (Nujol)/cm<sup>-1</sup>: 2924 (COOH), 2854 (C-H), 1798, 1712 (C=O), 1629, 1599 (C<sub>Ar</sub>=C<sub>Ar</sub>), 1463, 1377 (CH₃), 1157, 1076 (C-O); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>): 1.37 (3H, s, 18-H), 1.48 (3H, s, 19-H), 1.84 (1H, dd, J13.5 and 12, 6-H<sub>ax</sub>), 2.35 (1H, m, 2-H<sub>ax</sub>), 2.40 (1H, m, 6-H<sub:eq</sub>), 2.77 (1H, dd, J12.5 and 11.4, 2-H<sub:eq</sub>), 3.87 (3H, s, 20-H), 3.88 (3H, s, 21-H), 4.06 (1H, m, 4-H), 4.12 (1H, m, 5-H), 4.59 (1H, ddd, J4.5, 9.5 and 11.5, 3-H), 6.43 (1H, d, J16, 9-H), 7.03 (1H, d, J9, 12-H), 7.23 (1H, d, J2, 15-H), 7.24 (1H, d, J2, 16-H), 7.67 (1H, d, J16, 10-H); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>): 25.13 (C-18), 27.68 (C-19), 31.16 (C-6), 37.49 (C-2), 55.73 (C-20), 55.79 (C-21), 68.33 (C-5), 73.98 (C-3), 74.80 (C-4), 82.11 (C-1), 109.46 (C-17), 110.33 (C-12), 111.72 (C-15), 115.98 (C-16), 123.29 (C-9), 123.40 (C-11), 145.82 (C-10), 148.39 (C-13), 150.55 (C-14), 167.33 (C-8), 177.85 (C-7); MS, m/z (Cl): 422 [M⁺], 405 [M-H₂O]; CHN: (C<sub>21</sub>H<sub>24</sub>O<sub>8</sub> 422 g/mol requires: C, 62.37%; H, 5.94%), Found: C, 55.43%; H, 6.00%.
(1R, 3R, 4S, 5R)-1-cinnamoylquinic acid, (59)-p91

To a solution of quinic acid lactone 52 (0.400 g, 1.160 mmol) was dissolved in THF (8 ml) and treated with LiOH (0.028 g, 1.16 mmol in 4ml H2O) at room temperature. The solution was stirred for 2 days at room temperature, acidified by using 2M HCl (10 ml) solution and extracted with dichloromethane (50 ml). The organic layer was dried with MgSO4 and filtered. The solvent was removed under reduced pressure to give the title compound 59 as a pale yellow powder (0.150 g, 40.1%). Rf 0.40 [chloroform: acetone (10:1)]; mp 164 °C; νmax (Nujol)/cm⁻¹: 3407 (OH), 2954 (COOH), 2854 (C-H), 1792, 1694 (C=O), 1636 (C=O), 1062, 1031 (C-O); δH (500 MHz, D2O): 1.95 (1 H, dd, J 11 and 1.95, 6-Hαα), 2.26 (1 H, dd, J 15 and 3.5, 2-Hαα), 2.53 (1 H, m, 6-Hαβ), 2.57 (1 H, m, 2-Hαβ), 3.60 (1 H, dd, J 9.5 and 3.5, 4-H), 4.11 (1 H, m, 5-H), 4.25 (1 H, dt, J 15.5 and 3.5, 3-H), 6.61 (1 H, d, J 16, 9-H), 7.67-7.47 (5 H, m, Ph-H), 7.75 (1 H, d, J 16, 10-H); δC (125 MHz, D2O): 34.61 (C-6), 38.73 (C-2), 66.37 (C-5), 68.88 (C-3), 74.71 (C-4), 81.56 (C-1), 117.60 (C-9), 128.62, 128.72, 129.39, 131.14, 131.32 (C-12, C13, C-14, C-15, C-16), 134.19 (C-11), 147.26 (C-10), 168.19 (C-8), 175.95 (C-7); MS, m/z (CI): 322 [M⁺], 323 [M+H], 131 [M-C8H10O]; CHN: (C16H18O7) 322 g/mol requires: C, 59.62%; H, 5.59%; Found: C, 60.83%; H, 5.65%.
(1R, 3R, 4S, 5R)-1-dimethoxycinnamoylquinic acid, (60)-p97

To a solution of quinic acid lactone 53 (0.200 g, 0.50 mmol) was dissolved in THF (8 ml) and treated with LiOH (0.012 g, 0.50 mmol in 4ml H2O) at room temperature. The solution was stirred for 3 days at room temperature, acidified by using 2M HCl (10 ml) solution and extracted with dichloromethane (50 ml). The organic layer was dried with MgSO4 and filtered. The solvent was removed under reduced pressure to give the title compound 60 as a pale yellow powder (0.158 g, 84%). Rf 0.38 [chloroform: acetone (10:1)]; mp 150 ºC; νmax (Nujol)/cm⁻¹: 3368 (OH), 2954 (COOH), 2854 (C-H), 1797, 1712 (C=O), 1628 (C=O=O=CAr), 1156, 1075 (C-O); δH (500 MHz, D2O): 1.97 (1 H, dd, J 13.7 and 10.9, 6-Hαα), 2.29 (1 H, dd, J 15.5 and 3.4, 2-Hαa), 2.50 (1 H, ddd, J 13.7, 4.4 and 3.4, 6-Heq), 2.59 (1 H, dt, J 12.8 and 3.4, 2-Heq), 3.63 (1 H, dd, J 9.2 and 3.4, 4-H), 3.86 (3 H, s, 17-H), 3.88 (3 H, s, 18-H), 4.16 (1 H, ddd, J 10.9, 9.2 and 4.4, 5-H), 4.27 (1 H, q, J 3.4, 3-H), 6.43 (1 H, d, J 15.9, 9-H), 6.49 (1 H, d, J 8.3, 12-H), 7.18 (1 H, d, J 1.9, 15-H), 7.20 (1 H, dd, J 8.3 and 1.9, 16-H), 7.63 (1 H, d, J 15.9, 10-H); δC (125 MHz, D2O): 34.3 (C-6), 38.51 (C-2), 55.64 (C-17), 55.75 (C-18), 66.13 (C-5), 68.12 (C-3), 74.46 (C-4), 80.93 (C-1), 110.26 (C-12), 111.57 (C-15), 114.77 (C-9), 123.65 (C-16), 127.19 (C-11), 146.93 (C-10), 148.26 (C-13), 150.69 (C-14), 168.16 (C-8), 175.53 (C-7); MS, m/z (Cl): 382 [M⁺], 365 [M-OH]; CHN: (C18H22O9) 382 g/mol requires: C, 56.5%; H; 5.75%; Found: C, 47.71%; H, 5.37%.
(1R, 3R, 4S, 5R)-1-caffeoylquinic acid, (61)

To a solution of quinic acid lactone 54 (0.100 g, 0.217 mmol) in a mixture of degassed THF (3 ml) and 2M HCl (3 ml) was treated with LiOH (0.0052 g, 0.217 mmol in 3 ml H$_2$O) at room temperature. The solution was stirred for 24 hours at room temperature, acidified by using 2M HCl (10 ml) solution and extracted with dichloromethane (50 ml). The organic layer was dried with MgSO$_4$ and filtered. The solvent was removed under reduced pressure to give the title compound 61 as a pale yellow powder (0.045 g, 58.44% yield). Rf 0.44 [chloroform: acetone (8:2)]; $\nu_{\max }$ (KBr)/cm$^{-1}$: 3428 (OH), 2971 (COOH), 1785, 1710 (C=O), 1654, 1631 ($\Delta\alpha_{C-\alpha}$), 1057, 1029, 1009 (C=O); $\delta_H$ (400 MHz, DMSO): 1.66 (1 H, dd, J 12.8 and 9.6, 6-H$_{ax}$), 1.69 (1 H, dd, J 13.7 and 4.12, 2-H$_{eq}$), 1.81 (1 H, ddd, J 12.8, 4.17 and 2.2, 6-H$_{eq}$), 1.84 (1 H, m, 2-H$_{eq}$), 3.21 (1 H, dd, J 9.4 and 2.8, 4-H), 3.72 (1 H, ddd, J 13.4, 8.7 and 4.2, 5-H), 3.84 (1 H, q, J 2.8, 3-H), 6.15 (1 H, d, J 16, 9-H), 6.75 (1 H, d, J 8.7, 12-H), 6.88 (1 H, d, J 7.8, 15-H), 6.91 (1 H, d, J 8.24, 16-H), 7.37 (1 H, d, J 16, 10-H); $\delta_C$ (125 MHz, DMSO): 39.50 (C-6), 39.92 (C-2), 67.16 (C-5), 69.58 (C-3), 74.91 (C-4), 75.12 (C-1), 115.14 (C-12), 115.58 (C-9), 116.36 (C-15), 123.70 (C-16), 126.16 (C-11), 142.52 (C-10), 147.01 (C-13), 148.67 (C-14), 168.43 (C-8), 176.11 (C-7); MS, $m/z$ (ESI): 437.1079 [$M^+$ - C$_{20}$H$_{12}$O$_{11}$ requires 437.1089]
To a solution of quinic acid lactone 55 (0.100 g, 0.231 mmol) in a mixture of degassed THF (3 ml) and 2M HCl (3 ml) was treated with LiOH (0.0055 g, 0.231 mmol) in 3ml H₂O at room temperature. The solution was stirred for 24 hours at room temperature, acidified by using 2M HCl (10 ml) solution and extracted with dichloromethane (50 ml). The organic layer was dried with MgSO₄ and filtered. The solvent was removed under reduced pressure to give the title compound 62 as a white powder (0.062 g, 72.85% yield). Rf 0.52 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3434 (OH), 2932 (COOH), 1695, 1687 (C=O), 1612, 1594 (C₆H₅=C₆H₅), 1060, 1017 (C-O); δH (400 MHz, DMSO): 1.60 (1 H, m, 6-Hax), 1.68 (1 H, m, 2-Hax), 1.73 (1 H, ddd, J 12.8, 9.8 and 3.2, 6-Heq), 1.80 (1 H, dd, J 9.5 and 3.2, 2-Heq), 3.22 (1 H, dd, J 10.4 and 3.6, 4-H), 3.68 (1 H, m, 5-H), 3.74 (1 H, q, J 3.6, 3-H), 3.85 (3 H, s, 17-H), 6.30 (1 H, d, J 16, 9-H), 6.75 (1 H, d, J 8.28, 12-H), 7.03 (1 H, d, J 1.83, 15-H), 7.16 (1 H, ddd, J 8.9 and 1.9, 16-H), 7.40 (1 H, d, J 16, 10-H); δC (125 MHz, DMSO): 39.28 (C-6), 39.83 (C-2), 56.18 (C-17), 65.74 (C-5), 67.11 (C-3), 69.62 (C-4), 75.01 (C-1), 111.58 (C-12), 115.59 (C-9), 116.07 (C-15), 123.29 (C-16), 126.25 (C-11), 145.17 (C-10), 148.41 (C-14), 149.50 (C-13), 168.66 (C-8), 176.16 (C-7); MS, m/z (ESI): 409.1144 [M⁺ - C₁₉H₂₂O₁₀ requires 409.1140]
(1R, 3R, 4S, 5R)-1-p-coumaroylquinic acid, (63)

To a solution of quinic acid lactone 56 (0.100 g, 0.248 mmol) in a mixture of degassed THF (3 ml) and 2M HCl (3 ml) was treated with LiOH (0.059 g, 0.248 mmol) in 3ml H2O at room temperature. The solution was stirred for 24 hours at room temperature, acidified by using 2M HCl (10 ml) solution and extracted with dichloromethane (50 ml). The organic layer was dried with MgSO4 and filtered. The solvent was removed under reduced pressure to give the title compound 63 as a white powder (0.073 g, 87%). Rf 0.45 [chloroform: acetone (8:2)]; \nu_{\text{max}} (KBr)/cm\textsuperscript{-1}: 3426 (OH), 2976 (COOH), 2836 (C-H), 1788, 1764 (C=O), 1661, 1605 (C=\text{Ar}=C=\text{Ar}), 1075, 1029, 1009 (C-O); \delta_{\text{H}} (400 MHz, DMSO): 1.62 (1 H, dd, J 12.4 and 1.9, 6-H\text{ax}), 1.76 (1 H, dd, J 13.7 and 4.1, 2-H\text{ax}), 1.77 (1 H, m, 6-H\text{eq}), 1.79 (1 H, m, 2-H\text{eq}), 3.17 (1 H, dd, J 10.3 and 3.2, 4-H), 3.70 (1 H, ddd, J 10.9, 4.2 and 2.6, 5-H), 3.83 (1 H, q, J 3.2, 3-H), 6.21 (1 H, d, J 16, 9-H), 6.63 (2 H, d, J 8.7, 13-H, 15-H), 7.37 (2 H, d, J 16, 12-H, 16-H), 7.41 (1 H, d, J 7.8, 10-H); \delta_{\text{C}} (125 MHz, DMSO): 39.33 (C-6), 39.75 (C-2), 67.07 (C-5), 69.59 (C-3), 75.07 (C-4), 76.43 (C-1), 115.67 (C-9), 116.34 (C-13, C-15), 127.95 (C-12, C-16), 130.53 (C-11), 141.78 (C-10), 160.12 (C-14), 168.50 (C-8), 176.05 (C-7); MS, m/z (ESI): 379.1033 [M\textsuperscript{+} - C\textsubscript{18}H\textsubscript{20}O\textsubscript{9} requires 379.1035]
5- diacetylcaffeoyl bisacetonide, (64)

To a solution of bisacetonide (0.200 g, 0.734 mmol) and DMAP (0.0045 g, 0.0368 mmol) in dichloromethane (10 ml) were added pyridine (4 ml) and diacetyl caffeic acid chloride (0.228 g, 0.808 mmol) at room temperature. The reaction mixture was stirred for 12 hours at room temperature. The reaction solution was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic phase was dried with MgSO₄, filtered and the solvent was removed on a rotary evaporator to afford the title compound 64 as yellow solid (0.305 g, 80.26%). Rf 0.89 [chloroform: acetone (8:2)]; νₘₐₓ (KBr/cm⁻¹): 1778 (C=O), 1652 (C₆H₅=C₆H₅), 1436, 1374 (CH₃), 1246, 1062, 1026 (C-O); δH (400 MHz, CDCl₃): 1.34 (3 H, s, 9-H), 1.49 (3 H, s, 10-H), 1.58 (3 H, s, 12-H), 1.59 (3 H, s, 13-H), 1.91 (1 H, m, 6-Hax), 2.14 (1 H, ddd, J 13.5, 2.3 and 1.8, 2-Hax), 2.25 (1 H, t, J 4.1, 6-Heq), 2.26 (1 H, d, J 4.1, 2-Heq), 2.27 (3 H, s, 25-H), 2.28 (3 H, s, 26-H), 4.01 (1 H, m, 4-H), 4.08 (1 H, m, 3-H), 4.48 (1 H, dd, J 14.2 and 4.5, 5-H), 6.40 (1 H, d, J 16, 15-H), 7.13 (1 H, d, J 8.7, 18-H), 7.21 (1 H, dd, J 8.2, 21-H), 7.39 (1 H, d, J 8.2 and 1.8, 22-H), 7.62 (1 H, d, J 16, 16-H); δC (125 MHz, CDCl₃): 20.30 (C-25), 21.10 (C-26), 25.70 (C-9), 26.50 (C-10), 27.40 (C-12), 27.90 (C-13), 34.30 (C-6), 35.02 (C-2), 63.64 (C-5), 64.72 (C-3), 74.31 (C-4), 80.71 (C-1), 109.53 (C-8), 114.65 (C-11), 116.23 (C-15), 122.95 (C-18), 123.88 (C-21), 126.43 (C-22), 131.24 (C-17), 142.55 (C-16), 143.28 (C-19), 145.17 (C-20), 166.54 (C-14), 168.29 (C-23), 168.34 (C-24), 173.91 (C-7).
To a solution of bisacetonide (0.200 g, 0.734 mmol) and DMAP (0.0045 g, 0.0368 mmol) in dichloromethane (10 ml) were added pyridine (4 ml) and acetyl ferulic acid chloride (0.205 g, 0.808 mmol) at room temperature. The reaction mixture was stirred for 12 hours at room temperature. The reaction solution was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic phase was dried with MgSO₄, filtered and the solvent was removed on a rotary evaporator to afford the title compound 65 as pale yellow solid (0.323 g, 87.50%). Rf 0.78 [chloroform: acetone (8:2)]; νₘₐₓ (KBr/cm⁻¹): 1769, 1767 (C=O), 1641 (Cₓ=ₓCₓ), 1420, 1373 (CH₃), 1280, 1169, 1026 (C-O); δₓ (400 MHz, CDCl₃): 1.10 (3 H, s, 9-H), 1.27 (3 H, s, 10-H), 1.35 (6 H, s, 12-H), 1.82 (1 H, m, 13-H), 1.88 (1 H, m, 6-Hₓₓ), 1.91 (1 H, m, 2-Hₓₓ), 1.97 (1 H, d, J 1.97, 6-Hₓ), 2.08 (3 H, s, 2-Hₓ), 2.36 (6 H, s, 25-H), 3.84 (3 H, s, 23-H), 4.02 (1 H, m, 4-H), 4.03 (1 H, m, 3-H), 4.58 (1 H, d, J 9.6 and 5.1, 5-H), 6.14 (1 H, d, J 16, 15-H), 6.88 (1 H, d, J 10.9, 18-H), 7.30 (1 H, d, J 8.7, 21-H), 7.38 (1 H, d, J 15.3, 22-H), 7.65 (1 H, d, J 16, 16-H); δₓ (125 MHz, CDCl₃): 20.08 (C-25), 25.47 (C-9), 27.96 (C-10), 28.37 (C-12, C-13), 35.02 (C-6), 39.06 (C-2), 56.80 (C-23), 66.95 (C-3), 72.02 (C-5), 79.25 (C-4), 80.18 (C-1), 108.61 (C-8), 110.63 (C-11), 119.09 (C-15), 122.06 (C-18, C-21), 129.10 (C-22), 132.17 (C-17), 148.18 (C-20), 151.85 (C-19), 168.35 (C-14), 168.98 (C-24), 175.15 (C-7).
5- acetyl p-coumaroyl bisacetonide, (66)-p100

To a solution of bisacetonide (0.200 g, 0.734 mmol) and DMAP (0.0045 g, 0.0368 mmol) in dichloromethane (10 ml) were added pyridine (4 ml) and acetyl p-coumaric acid chloride (0.181 g, 0.808 mmol) at room temperature. The reaction mixture was stirred for 12 hours at room temperature. The reaction solution was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic phase was dried with MgSO4, filtered and the solvent was removed on a rotary evaporator to afford the title compound 66 as colourless solid (0.300 g, 88.75%).

Rf 0.81 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹:1781, 1741 (C=O), 1653 (CAr=CAr), 1424, 1373 (CH₃), 1207, 1168, 1050 (C-O); δH (400 MHz, CDCl₃): 1.23 (3 H, s, 9-H), 1.42 (3 H, s, 10-H), 1.58 (6 H, s, 12-H, 13-H), 2.01 (1 H, m, 6-Hax), 2.13 (1 H, dd, J 13.4 and 4.21, 2-Hax), 2.17 (1 H, t, J 3.2, 6-Heq), 2.21 (1 H, d, J 4.1, 2-Heq), 2.29 (3 H, s, 24-H), 3.96 (1 H, m, 4-H), 4.02 (1 H, m, 3-H), 4.47 (1 H, dd, J 10.1 and 4.6, 5-H), 6.41 (1 H, d, J 16, 15-H), 7.12 (2 H, d, J 8.7, 19-H, 21-H), 7.55 (2 H, d, J 8.7, 18-H, 22-H), 7.73 (1 H, d, J 16, 16-H); δC (125 MHz, CDCl₃): 21.03 (C-24), 25.47 (C-9), 27.96 (C-10), 28.37 (C-12), 28.48 (C-13), 35.02 (C-6), 39.75 (C-2), 66.97 (C-3), 72.03 (C-5), 77.49 (C-4), 77.82 (C-1), 108.61 (C-8), 110.64 (C-11), 119.09 (C-15), 122.07 (C-19, C-21), 122.27 (C-22), 129.01 (C-18), 132.17 (C-17), 143.20 (C-16), 151.85 (C-20), 168.37 (C-14), 168.98 (C-23), 175.17 (C-7).
5-dimethoxycinnamoyl bisacetonide, (67)

To a solution of bisacetonide (0.200 g, 0.7345 mmol) and DMAP (0.0045 g, 0.0368 mmol) in dichloromethane (10 ml) were added pyridine (4 ml) and 3,4-dimethoxycinnamic acid chloride (0.183 g, 0.808 mmol) at room temperature. The reaction mixture was stirred for 12 hours at room temperature. The reaction solution was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic phase was dried with MgSO₄, filtered and the solvent was removed on a rotary evaporator to afford the title compound 67 as pale pink solid (0.280 g, 82.35%). Rf 0.78 [chloroform: acetone (8:2)]; νₓ max (KBr)/cm⁻¹: 1781 (C=O), 1653 (C₅=C₅), 1462, 1420 (CH₃), 1262, 1142, 1026 (C-O); δH (400 MHz, CDCl₃): 1.25 (3 H, s, 9-H), 1.50 (3 H, s, 10-H), 1.59 (6 H, s, 12-H, 13-H), 2.04 (1 H, m, 6-Hₜx), 2.15 (1 H, d, J 11.5, 2-Hₜx), 2.21 (1 H, d, J 5.4, 6-Hₜq), 2.25 (1 H, m, 2-Hₜq), 3.45 (6 H, s, 23-H, 24-H), 3.46 (1 H, m, 4-H), 3.97 (1 H, m, 3-H), 4.42 (1 H, dd, J 10.2 and 5.4, 5-H), 6.29 (1 H, d, J 16, 15-H), 6.88 (1 H, d, J 8.3, 18-H), 7.07 (1 H, d, J 1.8, 21-H), 7.10 (1 H, dd, J 8.3 and 1.9, 22-H), 7.58 (1 H, d, J 16, 16-H); δC (125 MHz, CDCl₃): 25.46 (C-9), 27.05 (C-10), 28.34 (C-12), 28.46 (C-13), 39.57 (C-6), 39.98 (C-2), 55.78 (C-23), 55.84 (C-24), 66.89 (C-3), 77.02 (C-5), 77.22 (C-4), 77.86 (C-1), 108.54 (C-18), 111.08 (C-21), 116.58 (C-15), 122.38 (C-22), 127.43 (C-17), 144.25 (C-16), 149.05 (C-19), 150.02 (C-20), 168.67 (C-14), 175.07 (C-7).
5-cinnamoyl bisacetonide, (68)

To a solution of bisacetonide (0.200 g, 0.734 mmol) and DMAP (0.0045 g, 0.0368 mmol) in dichloromethane (10 ml) were added pyridine (4 ml) and cinnamic acid chloride (0.134 g, 0.808 mmol) at room temperature. The reaction mixture was stirred for 12 hours at room temperature. The reaction solution was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic phase was dried with MgSO₄, filtered and the solvent was removed on a rotary evaporator to afford the title compound 288 as colourless solid (0.256 g, 86.77%). Rf 0.82 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 1783, 1736 (C=O), 1636 (C₆=C₆), 1451, 1381 (CH₃), 1277, 1058, 1026 (C-O); δH (400 MHz, CDCl₃): 1.63 (1 H, s, J 10.9 and 2.3, 9-H), 1.64 (1 H, s, 10-H), 1.66 (1 H, s, 12-H), 1.67 (1 H, s, 13-H), 1.89 (1 H, dd, J 10.2 and 3.6, 6-Hax), 2.10 (1 H, m, 2-Hax), 2.17 (1 H, m, 6-Hsq), 2.29 (1 H, d, J 4.6, 2-Hsq), 3.50 (1 H, dd, J 10.2 and 3.6, 4-H), 4.03 (1 H, m, 3-H), 4.22 (1 H, dd, J 12.8, 9.2 and 3.6, 5-H), 6.45 (1 H, d, J 16, 15-H), 7.22-7.47 (5 H, m, Ph-H), 7.70 (1 H, d, J 16, 16-H); δC (125 MHz, CDCl₃): 25.47 (C-9), 27.96 (C-10), 28.52 (C-12), 28.59 (C-13), 37.98 (C-6), 39.80 (C-2), 66.70 (C-3), 67.31 (C-5), 72.02 (C-4), 80.32 (C-1), 108.90 (C-Ph), 110.90 (C-Ph), 111.70 (C-Ph), 118.69 (C-15), 128.07 (C-Ph), 128.89 (C-Ph), 134.52 (C-17), 145.52 (C-16), 169.07 (C-14), 175.62 (C-7).
5-O-caffeoylquinic acid, (69)-p104

5-diacetyl caffeoyl-bisacetone 64 (0.100 g, 0.192 mmol) in a mixture of degassed THF (5 ml) and 2M HCl (10 ml) was stirred for 24 hours at room temperature. The solvent was removed under reduced pressure to give the title compound 69 as a yellowish powder (0.047 g, 69%). Rf 0.65 [chloroform: acetone (8:2)]; \( \nu_{\text{max}} \) (KBr/cm\(^{-1} \)): 3425 (OH), 1773 (C=O), 1653 (C\(_\text{Ar}=\text{C}_{\text{Ar}} \)), 1213, 1050, 1026 (C-O); \( \delta_{\text{H}} \) (400 MHz, DMSO): 1.67 (1 H, dd, J 12.82 and 2.3, 6-H\(_{\text{ax}} \)), 1.73 (1 H, dd, J 14.9 and 3.2, 2-H\(_{\text{ax}} \)), 1.83 (1 H, ddd, J 13.5, 4.6 and 3.2, 6-H\(_{\text{eq}} \)), 1.87 (1 H, dt, J 14.9 and 3.2, 2-H\(_{\text{eq}} \)), 3.19 (1 H, dd, J 8.7 and 2.8, 4-H), 3.72 (1 H, ddd, J 12.4, 8.3 and 4.2, 3-H), 3.84 (1 H, q, J 5.7, 5-H), 6.10 (1 H, d, J 15.9, 9-H), 6.73 (1 H, d, J 8.2, 12-H), 6.91 (1 H, d, J 8.2, 15-H), 6.94 (1 H, s, 16-H), 7.36 (1 H, d, J 16, 10-H); \( \delta_{\text{C}} \) (125 MHz, DMSO): 35.61 (C-6), 37.83 (C-2), 68.74 (C-3), 69.57 (C-5), 71.66 (C-4), 79.69 (C-1), 115.72 (C-9), 122.61 (C-12), 122.93 (C-15), 123.15 (C-16), 132.82 (C-11), 142.47 (C-13), 145.23 (C-14), 166.85 (C-8), 177.37 (C-7).
5-O-feruloylquinic acid, (70)-p104

5-acetyl feruloyl-bisacetonide 65 (0.100 g, 0.203 mmol) in a mixture of degassed THF (5 ml) and 2M HCl (10 ml) was stirred for 24 hours at room temperature. The solvent was removed under reduced pressure to give the title compound 70 as a yellowish powder (0.057 g, 76%). Rf 0.59 [chloroform: acetone (8:2)]; \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\): 3430 (OH), 1757 (C=O), 1653 (C\(_{\text{A}}\)=C\(_{\text{A}}\)), 1177, 1051, 1027 (C-O); \( \delta_{\text{H}} \) (400 MHz, DMSO): 1.67 (1 H, dd, J 13.8 and 3.7, 6-H\(_{\text{ax}}\)), 1.69 (1 H, dd, J 7.8 and 1.9, 2-H\(_{\text{ax}}\)), 1.82 (1 H, m, 6-H\(_{\text{eq}}\)), 1.84 (1 H, d, J 3.7, 2-H\(_{\text{eq}}\)), 3.21 (1 H, dd, J 10.6 and 2.4, 4-H), 3.74 (1 H, m, 3-H), 3.85 (1 H, q, J 3.2, 5-H), 6.55 (1 H, d, J 16, 9-H), 7.07 (1 H, d, J 8.3, 12-H), 7.27 (1 H, dd, J 8.3 and 1.9, 15-H), 7.43 (1 H, d, J 1.9, 16-H), 7.53 (1 H, d, J 16, 10-H); \( \delta_{\text{C}} \) (125 MHz, DMSO): 39.40 (C-6), 39.82 (C-2), 56.53 (C-17), 66.06 (C-3), 67.20 (C-5), 74.93 (C-4), 75.13 (C-1), 112.60 (C-9), 120.06 (C-12), 121.08 (C-15), 123.72 (C-16), 133.78 (C-11), 142.58 (C-10), 143.83 (C-14), 151.66 (C-13), 168.62 (C-8), 176.09 (C-7).
5-O-p-coumaroylquinic acid, (71)-p104

5-acetyl p-coumaroyl-bisacetonide 66 (0.100 g, 0.217 mmol) in a mixture of degassed THF (5 ml) and 2M HCl (10 ml) was stirred for 24 hours at room temperature. The solvent was removed under reduced pressure to give the title compound 71 as a white powder (0.048 g, 65.4%). Rf 0.62 [chloroform: acetone (8:2)]; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$: 3429 (OH), 1789 (C=O), 1658 (C$_{\text{Ar}}$=C$_{\text{Ar}}$), 1250,1062, 1027 (C-O); $\delta$$_{\text{H}}$ (400 MHz, DMSO):1.66 (1 H, dd, $J$ 12.9 and 3.1, 6-H$_{\text{ax}}$), 1.69 (1 H, dd, $J$ 8.3 and 2.4, 2-H$_{\text{eq}}$), 1.81 (1 H, m, 6-H$_{\text{eq}}$), 1.82 (1 H, d, $J$ 9.6, 2-H$_{\text{eq}}$), 3.21 (1 H, ddd, $J$ 10.5, 9.4 and 4.6, 4-H), 3.71 (1 H, ddd, $J$ 12.3, 8.4 and 5.1, 3-H), 3.84 (1 H, q, $J$ 3.9, 5-H), 6.22 (1 H, d, $J$ 15.6, 9-H), 6.74 (2 H, d, $J$ 8.7, 13-H, 15-H), 7.45 (2 H, d, $J$ 11.5, 10-H), 7.48 (1 H, d, $J$ 15.7, 12-H, 16-H); $\delta$$_{\text{C}}$ (125 MHz, DMSO): 39.51 (C-6), 39.72 (C-2), 65.68 (C-3), 66.05 (C-4), 72.04 (C-5), 76.41 (C-1), 115.79 (C-9), 116.29 (C-13, C-15), 127.62 (C-12, C-16), 130.60 (C-11), 142.85 (C-10), 169.13 (C-14), 168.49 (C-8), 176.11 (C-7).
5-O-dimethoxycinnamoylquinic acid, (72)-p104

5-dimethoxycinnamoyl-bisacetonide 67 (0.100 g, 0.216 mmol) in a mixture of degassed THF (5 ml) and 2M HCl (10 ml) was stirred for 24 hours at room temperature. The solvent was removed under reduced pressure to give the title compound 72 as a white powder (0.065g, 78%). Rf 0.71 [chloroform: acetone (8:2)]; νmax (KBr)/cm\(^{-1}\): 3428 (OH), 1777 (C=O), 1653 (C\(_\text{Ar}==\text{C}_{\text{Ar}}\)), 1258, 1052, 1027 (C-O); δ\(_H\) (400 MHz, DMSO): 1.89 (1 H, m, 6-H\(_{\text{ax}}\)), 1.92 (1 H, m, 2-H\(_{\text{ax}}\)), 2.04 (1 H, d, J 12.9, 6-H\(_{\text{eq}}\)), 2.06 (1 H, d, J 5.04, 2-H\(_{\text{eq}}\)), 3.12 (1 H, m, 4-H), 3.18 (1 H, m, 3-H), 3.88 (6 H, s, 17-H, 18-H), 4.26 (1 H, t, 4.2, 5-H), 6.37 (1 H, d, J 15.9, 9-H), 6.91 (1 H, d, J 8.3, 12-H), 7.14 (1 H, d, J 8.3, 15-H), 7.26 (1 H, s, 16-H), 7.45 (1 H, d, J 16, 10-H); δ\(_C\) (125 MHz, DMSO): 34.77 (C-6), 39.84 (C-2), 56.12 (C-17), 56.22 (C-18), 66.62 (C-3), 72.70 (C-5), 73.87 (C-4), 80.04 (C-10), 110.73 (C-12), 112.06 (C-15), 117.22 (C-9), 123.10 (C-16), 127.58 (C-11), 144.60 (C-10), 151.24 (C-13), 151.30 (C-14), 168.40 (C-8), 174.76 (C-7).
5-O-cinnamoylquinic acid, (73)-p104

5-cinnamoyl-bisacetonide 68 (0.100 g, 0.248 mmol) in a mixture of degassed THF (5 ml) and 2M HCl (10 ml) was stirred for 24 hours at room temperature. The solvent was removed under reduced pressure to give the title compound 73 as a white powder (0.050 g, 62.5%). Rf 0.66 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3429 (OH), 1782 (C=O), 1654 (C=\(\text{Ar}\)=C=\(\text{Ar}\)), 1208, 1054, 1027 (C-O); δH (400 MHz, DMSO): 1.57 (1 H, m, 6-H\text{ax}), 1.60 (1 H, m, 2-H\text{ax}), 1.82 (1 H, dd, J 9.6 and 5.2, 6-H\text{eq}), 2.06 (1 H, d, J 16.4 and 2.8, 2-H\text{eq}), 3.70 (1 H, m, 4-H), 3.78 (1 H, m, 3-H), 4.26 (1 H, t, J 4.8, 5-H), 6.47 (1 H, d, J 16, 9-H), 7.31-7.47 (5 H, m, Ph-H), 7.53 (1 H, d, J 16, 10-H); δC (125 MHz, DMSO): 34.95 (C-6), 39.41 (C-2), 66.72 (C-3), 72.70 (C-5), 78.94 (C-4), 80.05 (C-1), 108.11 (C-Ph), 110.72 (C-Ph), 119.74 (C-9), 128.71 (C-Ph), 129.42 (C-Ph), 130.73 (C-Ph), 134.76 (C-11), 144.45 (C-10), 168.08 (C-8), 174.92 (C-7).
(1S, 3R, 4R, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-4-cinnamoyl quinide, (74)-p111

To a solution of Troc-quinide (0.100 g, 0.286 mmol) and DMAP (0.0104 g, 0.085 mmol) in dichloromethane (10 ml) were added cinnamic acid chloride (0.052 g, 0.314 mmol) in pyridine (15 ml). The reaction solution was stirred for 12 hours at room temperature. The reaction was worked up by diluting with DCM (50 ml), washing with 2M HCl (10 ml), NaHCO₃ (10 ml) solution and brine (15 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give title compound (74) as a slightly yellow powder (0.097 g, 70.7%). Rf 0.31 [chloroform: acetone (8:2)]; \textit{v} \textsubscript{max} (KBr)/cm⁻¹: 3428 (OH), 1752,1748 (C=O), 1649 (C\textsubscript{Ar}=C\textsubscript{Ar}), 1206, 1199, 1063 (C-O), 824, 809 (C-Cl); \textit{δ} \textsubscript{H} (400 MHz, CDCl₃): 1.88 (1 H, dd, J 13.4 and 3.3, 2-H\textsubscript{ax}), 2.16 (1 H, dd, J 12.8 and 3.2, 6-H\textsubscript{eq}), 2.38 (1 H, dd, J 15.4 and 3.3, 2-H\textsubscript{eq}), 2.76 (1 H, ddd, J 15.9, 7.2 and 3.4, 6-H\textsubscript{ax}), 4.14 (1 H, dd, J 9.8 and 4.6, 5-H), 4.19 (1 H, q, J 4.2, 3-H), 4.33 (1 H, t, J 4.2, 4-H), 4.74 (1 H, d, J 11.6, 9-H), 4.78 (1 H, d, J 11.6, 9-H\textsuperscript{1}), 6.42 (1 H, d, J 16, 12-H), 7.39-7.50 (5 H, m, Ph-H), 7.74 (1 H, d, J 16, 13-H); \textit{δ} \textsubscript{C} (125 MHz, CDCl₃): 33.96 (C-2), 38.90 (C-6), 66.74 (C-3), 68.46 (C-4), 75.53 (C-5), 83.03 (C-9), 83.56 (C-1), 94.40 (C-10), 117.46 (C-12), 128.41 (C-15, C-19), 129.03 (C-16, C-18), 130.74 (C-17), 134.20 (C-14), 145.29 (C-13), 166.63 (C-11), 171.37 (C-7).
(1S, 3R, 4R, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-4-dimethoxycinnamoyl quinide, (75)-p108

To a solution of Troc-quinide (0.100 g, 0.286 mmol) and DMAP (0.0104 g, 0.0858 mmol) in dichloromethane (10 ml) were added 3,4-dimethoxycinnamic acid chloride (0.071 g, 0.314 mmol) in pyridine (15 ml). The reaction solution was stirred for 12 hours at room temperature. The reaction was worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ (10 ml) solution and brine (15 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give title compound (75) as a slightly yellow powder (0.145 g, 94%). Rf 0.23 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3433 (OH), 1749,1700, 1681 (C=O), 1626 (C₆=C₆), 1295, 1269, 1149 (C-O), 838, 816 (C-Cl); δH (400 MHz, CDCl₃): 1.86 (1 H, dd, J 14.2 and 3.2, 2-Hax), 2.19 (1 H, dd, J 13.4 and 3.6, 6-Heq), 2.48 (1 H, dd, J 15.5 and 3.6, 2-Heq), 2.76 (1 H, ddd, J 16, 6.4 and 3.2, 6-Hax), 3.54 (1 H, dd, J 9.2 and 3.2, 5-H), 3.90 (3 H, s, 20-H), 3.91 (3 H, s, 21-H), 4.13 (1 H, q, J 4.4, 3-H), 4.21 (1 H, t, J 4.2, 4-H), 4.73 (1 H, d, J 11.9, 9-H), 4.78 (1 H, d, J 11.9, 9-H¹), 6.28 (1 H, d, J 16, 12-H), 6.85 (1 H, d, J 8, 15-H), 7.05 (1 H, d, J 2, 18-H), 7.06 (1 H, dd, J 8 and 2, 19-H), 7.68 (1 H, d, J 16, 13-H), δC (125 MHz, CDCl₃): 33.90 (C-2), 38.59 (C-6), 55.99 (C-20), 56.07 (C-21), 66.69 (C-3), 68.46 (C-4), 76.79 (C-5), 77.42 (C-9), 83.56 (C-1), 94.42 (C-10), 109.87 (C-15), 111.13 (C-19), 115.07 (C-12), 127.18 (C-14), 146.83 (C-13), 149.34 (C-16), 151.56 (C-17), 152.22 (C-8), 170.97 (C-11), 171.88 (C-7).
(1S,3R,4R,5R)-1-(β, β, β-trichloroethoxycarbonyl)-4-acetylferuloyl quinide, (76)-p111

To a solution of Troc-quinide (0.100 g, 0.286 mmol) and DMAP (0.0104 g, 0.0858 mmol) in dichloromethane (10 ml) were added acetyl ferulic acid chloride (0.080 g, 0.314 mmol) in pyridine (15 ml). The reaction solution was stirred for 12 hours at room temperature. The reaction was worked up by diluting with DCM (50 ml), washing with 2M HCl (10 ml), NaHCO$_3$ (10 ml) solution and brine (15 ml). The organic layer was dried over MgSO$_4$ and the solvent was removed under reduced pressure to give title compound (76) as a slightly yellow powder (0.134 g, 82.7%). Rf 0.36 [chloroform: acetone (8:2)]; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$: 3421 (OH), 1798, 1762, 1695 (C=O), 1658 (C$_{Ar}$=C$_{Ar}$), 1217, 1195, 1011 (C-O), 828, 763 (C-Cl); $\delta$H (400 MHz, CDCl$_3$): 1.88 (1 H, dd, J 14 and 3.2, 2-H$_{ax}$), 2.20 (1 H, dd, J 15.6 and 3.6, 6-H$_{eq}$), 2.32 (1 H, s, 21-H), 2.51 (1 H, ddd, J 13.6, 7.2 and 3.2, 2-H$_{eq}$), 2.77 (1 H, ddd, J 15.6, 8.8 and 3.6, 6-H$_{ax}$), 3.53 (1 H, dd, J 8.8 and 3.2, 5-H), 3.86 (1 H, s, 22-H), 4.14 (1 H, q, J 4.8, 3-H), 4.20 (1 H, dd, J 7.2 and 3.6, 4-H), 4.74 (1 H, d, J 11.6, 9-H), 4.81 (1 H, d, J 12.8, 9-H$^1$), 6.42 (1 H, d, J 16, 12-H), 6.98 (1 H, d, J 17.6, 15-H), 7.06 (1 H, d, J 2, 18-H), 7.34 (1 H, dd, J 7.8 and 2, 19-H), 7.73 (1 H, d, J 16, 13-H); $\delta$C (125 MHz, CDCl$_3$): 21.36 (C-21), 23.15 (C-2), 39.73 (C-6), 66.01 (C-3), 71.53 (C-4), 76.06 (C-5), 77.12 (C-9), 80.69 (C-1), 100.31 (C-10), 111.75 (C-15), 119.22 (C-12), 121.04 (C-18), 123.13 (C-19), 133.49 (C-14), 143.63 (C-13), 151.30 (C-16), 168.42 (C-8), 168.63 (C-20), 176.86 (C-7).
To a solution of Troc-quinide (0.100 g, 0.286 mmol) and DMAP (0.0104 g, 0.0858 mmol) in dichloromethane (10 ml) were added acetyl p-coumaric acid chloride (0.070 g, 0.314 mmol) in pyridine (15 ml). The reaction solution was stirred for 12 hours at room temperature. The reaction was worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ (10 ml) solution and brine (15 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give title compound (77) as a slightly yellow powder (0.131 g, 86.2%). Rf 0.47 [chloroform: acetone (8:2)]; νₑₛₑ (KBr)/cm⁻¹: 3431 (OH), 1789, 1765 (C=O), 1653 (C₆H₅=CH₂), 1206, 1169, 1058 (C-O), 825, 763 (C-Cl); δH (400 MHz, CDCl₃): 1.87 (1 H, dd, J 13.8 and 10.9, 2-Hax), 2.19 (1 H, dd, J 15.6 and 3.6, 6-Hax), 2.30 (1 H, s, 21-H), 2.50 (1 H, ddd, J 13.7, 4.1 and 3.2, 2-Heq), 2.77 (1 H, dd, J 15.7 and 3.2, 6-Heq), 3.52 (1 H, dd, J 8.7 and 3.2, 5-H), 4.20 (1 H, q, J 4.8, 3-H), 4.38 (1 H, dd, J 6.9 and 3.6, 4-H), 4.74 (1 H, d, J 11.9, 9-H), 4.78 (1 H, d, J 11.9, 9-H¹), 6.38 (1 H, d, J 15.6, 12-H), 7.12 (2 H, d, J 8.2, 16-H, 18-H), 7.56 (2 H, d, J 8.7, 15-H, 19-H), 7.75 (1 H, d, J 16, 13-H); δC (125 MHz, CDCl₃): 20.96 (C-21), 33.73 (C-2), 39.50 (C-6), 65.87 (C-3), 72.30 (C-4), 75.34 (C-5), 77.31 (C-9), 80.79 (C-1), 100.09 (C-10), 119.06 (C-12), 122.03 (C-16, C-18), 128.92 (C-15, C-19), 132.07 (C-14), 143.04 (C-13), 151.79 (C-17), 168.42 (C-11), 168.86 (C-20), 176.75 (C-7).
To a solution of Troc-quinide (0.100 g, 0.286 mmol) and DMAP (0.0104 g, 0.0858 mmol) in dichloromethane (10 ml) were added diacetyl caffeic acid chloride (0.314 mol, 0.088 g) in pyridine (15 ml). The reaction solution was stirred for 12 hours at room temperature. The reaction was worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ (10 ml) solution and brine (15 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give title compound (78) as a white powder (0.126 g, 74%). Rf 0.38 [chloroform: acetone (8:2)]; v max (KBr)/cm⁻¹: 3430 (OH), 1814, 1753, 1695 (C=O), 1645 (C=O=C), 1242, 1201, 1053 (C-O), 833, 768 (C-Cl); δ H (400 MHz, CDCl₃): 2.28 (6 H, s, 22-H, 23-H), 2.30 (1 H, t, J 12, 2-H₉), 2.34 (1 H, m, 6-H₉), 2.76 (1 H, d, J 11.6, 6-H₉), 3.05 (1 H, m, 2-H₉), 3.46 (1 H, t, J 4.8, 5-H), 4.78 (1 H, d, J 11.6, 9-H), 4.82 (1 H, d, J 11.6, 9-H), 4.92 (1 H, t, J 5.2, 3-H), 5.07 (1 H, q, J 4.4, 4-H), 6.34 (1 H, d, J 16, 12-H), 7.14 (1 H, d, J 8.4, 15-H), 7.34 (1 H, d, J 1.8, 18-H), 7.37 (1 H, d, J 8.5, 19-H), 7.77 (1 H, d, J 16, 13-H); δ C (125 MHz, CDCl₃): 20.71 (C-22), 20.89 (C-23), 33.20 (C-2), 33.60 (C-6), 64.16 (C-3), 68.25 (C-4), 76.82 (C-5), 77.13 (C-9), 77.45 (C-1), 94.02 (C-10), 117.65 (C-12), 122.98 (C-15), 124.17 (C-18), 126.95 (C-19), 132.80 (C-14), 142.57 (C-13), 143.92 (C-16), 144.59 (C-17), 164.90 (C-8), 168.26 (C-20), 169.89 (C-21), 170.93 (C-7); MS, m/z (ESI): 594.9998 [M⁺ - C₂₃H₂₁O₁₂Cl₃ requires 594.9998].
(1S, 3R, 4R, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-3-diacetylcaffeoyl quinide, (79)-p114

To a solution of Troc-quinide (0.500 g, 1.430 mmol) and DMAP (0.0087 g, 0.0715 mmol) in dichloromethane (10 ml) were added diacetyl caffeic acid chloride (3.147 mmol, 0.889 g) in triethylamine (1 ml). The reaction solution was stirred for 18 hours at room temperature. The reaction was worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO$_3$ (10 ml) solution and brine (15 ml). The organic layer was dried over MgSO$_4$ and the solvent was removed under reduced pressure to yield a slightly yellow solid. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to give the title product (1S, 3R, 4R, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-3-diacetylcaffeoyl quinide (79) was recovered as white powder (0.374 g, 44%). Rf 0.52 [chloroform: acetone (8:2)]; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$: 3502 (OH), 1807, 1769, 1718 (C=O), 1639 (C$_{\text{Ar}}$=C$_{\text{Ar}}$), 1243, 1209, 1180 (C-O), 829, 779 (C-Cl); $\delta_H$ (400 MHz, CDCl$_3$): 2.29 (3 H, s, 22-H), 2.30 (3 H, s, 23-H), 2.36 (1 H, t, $J_{11.7}$, 2-H$_{ax}$), 2.39 (1 H, m, 6-H$_{eq}$), 2.75 (1 H, d, $J_{11.4}$, 2-H$_{eq}$), 3.04 (1 H, m, 6-H$_{ax}$), 4.36 (1 H, t, $J_{4.1}$, 4-H), 4.70 (1 H, d, $J_{11.91}$, 9-H), 4.77 (1 H, d, $J_{11.91}$, 9-H$^1$), 4.83 (1 H, t, $J_{5.5}$, 5-H), 5.03 (1 H, q, $J_{2.7}$, 3-H), 6.36 (1 H, d, $J_{16}$, 12-H), 7.16 (1 H, d, $J_{8.5}$, 15-H), 7.32 (1 H, d, $J_{1.9}$, 18-H), 7.35 (1 H, dd, $J_{8.5}$ and 1.9, 19-H), 7.63 (1 H, d, $J_{16.13}$-H), 7.67 (1 H, d, $J_{16.13}$-H); $\delta_C$ (125 MHz, CDCl$_3$): 20.70 (C-22), 20.88 (C-23), 32.61 (C-2), 33.16 (C-6), 64.07 (C-4), 68.50 (C-3), 76.07 (C-5), 77.49 (C-9), 79.05 (C-1), 117.65 (C-12), 122.97 (C-15), 124.16 (C-18), 126.79 (C-19), 132.68 (C-14), 142.52 (C-13), 144.46 (C-16), 145.04 (C-17), 151.43 (C-8), 165.05 (C-11), 168.33 (C-20), 168.39 (C-21), 171.09 (C-7).
Troc quinide (258-2) (0.300 g, 0.503 mmol) was dissolved in glacial acetic acid (2 ml) and zinc powder (0.493 g, 7.553 mmol) added to the solution. The reaction mixture was stirred for 12 hours at room temperature and diluted by the addition of extra glacial acetic acid (5 ml). The mixture was stirred for additional 36 hours at room temperature. The obtained slightly suspension was filtered and the filtrate was diluted in water which caused the white participate. The mixture was extracted with chloroform (3x30 ml) whereas the white solid was dissolved. The combined organic phases were washed with water (3x30 ml) dried over MgSO₄ and the solvent was evaporated to give the title compound (80) as a white powder (0.065 g, 31%). Rf 0.13 [chloroform: acetone (8:2)]; ν<sub>max</sub> (KBr)/cm<sup>-1</sup>: 3428 (OH), 1718 (C=O), 1653 (C<sub>Ar</sub>=C<sub>Ar</sub>), 1261, 1050, 1026 (C-O); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 2.07 (1 H, s, 2-H<sub>ax</sub>), 2.28 (3 H, t, J 11.5, 19-H<sub>ax</sub>), 2.29 (3 H, s, 20-H), 2.30 (1 H, m, 6-H<sub>eq</sub>), 2.33 (1 H, m, 6-H<sub>ax</sub>), 2.63 (1 H, d, J 11.4, 2-H<sub>eq</sub>), 4.35 (1 H, t, J 4.1, 4-H), 4.81 (1 H, t, J 5.3, 5-H), 4.99 (1 H, q, J 4.6, 3-H), 6.37 (1 H, d, J 16, 9-H), 7.24 (1 H, d, J 8.1, 12-H), 7.35 (1 H, d, J 1.6, 15-H), 7.37 (1 H, dd, J 8.2 and 1.9, 16-H), 7.64 (1 H, d, J 16, 10-H); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>): 20.82 (C-19, C-20), 30.93 (C-2), 35.82 (C-6), 71.36 (C-4), 72.66 (C-3), 75.62 (C-5), 78.76 (C-1), 116.14 (C-9), 122.19 (C-12), 123.84 (C-15), 126.45 (C-16), 131.27 (C-11), 142.54 (C-10), 143.22 (C-13), 145.11 (C-14), 166.92 (C-8), 168.78 (C-17), 168.94 (C-18), 170.22 (C-7); MS, m/z (ESI): 419.0981[M<sup>+</sup> - C<sub>20</sub>H<sub>20</sub>O<sub>10</sub>] requires 419.0984}
(1S, 3R, 4R, 5R)-3-acetylferuloyl quinide, (81)-p115

To a solution of quinide (0.500 g, 2.871 mmol) and N,N-(dimethylamino)pyridine (0.017 g, 0.143 mmol) in dichloromethane (10 ml) was added triethylamine (1 ml) followed by the addition of acetyl ferulic acid chloride (1.607 g, 6.316 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to give the title compound of compound (1S, 3R, 4R, 5R)-3-acetylferuloyl quinide (81) as a yellow powder (0.430 g, 38%). Rf 0.16 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3454 (OH), 1787, 1785, 1710 (C=O), 1636 (C₆H₅-C₆H₅), 1260, 1197, 1115, 1088 (C-O); δH (400 MHz, CDCl₃): 2.19 (1 H, d, J 11.4, 2-Hax), 2.23 (1 H, m, 2-Heq), 2.29 (3 H, s, 19-H), 2.31 (1 H, m, 6-Hax), 2.68 (1 H, d, J 11.9, 6-Heq), 3.83 (3 H, s, 17-H), 4.36 (1 H, t, J 4.6, 4-H), 4.81 (1 H, t, J 5.5, 5-H), 5.03 (1 H, q, J 4.3, 3-H), 6.39 (1 H, d, J 16, 9-H), 7.05-7.25 (3 H, m, Ph-H), 7.68 (1 H, d, J 16, 10-H); δC (125 MHz, CDCl₃): 20.72 (C-19), 36.44 (C-2), 36.66 (C-6), 56.02 (C-17), 64.17 (C-4), 68.84 (C-3), 72.10 (C-5), 77.42 (C-1), 111.50 (C-12), 116.97 (C-9), 121.49 (C-15), 123.47 (C-16), 132.96 (C-11), 141.90 (C-10), 145.83 (C-14), 151.56 (C-13), 165.28 (C-8), 168.93 (C-18), 177.42 (C-7).
To a solution of quinide (0.500 g, 2.871 mmol) and N,N-(dimethylamino)pyridine (0.0175 g, 0.143 mmol) in dichloromethane (10 ml) was added triethylamine (1 ml) followed by the addition of acetyl p-coumaric acid chloride (1.418 g, 6.316 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to give the title compound (1S, 3R, 4R, 5R)-3-acetyl p-coumaroyl quinide (82) as a white powder (0.245 g, 23.55%). Rf 0.14 [chloroform: acetone (8:2)]; νmax (KBr/cm⁻¹: 3458 (OH), 1718, 1708 (C=O), 1636 (C₆H₅=C₆H₅), 1207, 1166, 1089 (C-O); δH (400 MHz, CDCl₃): 2.02 (1H, dd, J 11.4 and 2.8, 2-Hax), 2.16 (1H, m, 2-Heq), 2.29 (3H, s, 18-H), 2.31 (1H, m, 6-Hax), 2.64 (1H, d, J 11.4, 6-Heq), 4.35 (1H, t, J 4.6, 4-H), 4.80 (1H, t, J 5.5, 5-H), 5.01 (1H, q, J 4.1, 3-H), 6.29 (1H, d, J 16, 9-H), 7.08-7.21 (5H, m, Ph-H), 7.68 (1H, d, J 16, 10-H); δC (125 MHz, CDCl₃): 21.21 (C-18), 36.31 (C-2), 36.44 (C-6), 64.05 (C-4), 68.93 (C-3), 72.17 (C-5), 77.12 (C-1), 117.03 (C-9), 122.29 (C-13), 122.35 (C-15), 129.51 (C-12), 129.52 (C-16), 131.76 (C-11), 145.32 (C-10), 152.48 (C-14), 165.52 (C-8), 169.42 (C-17), 177.64 (C-7).
To a solution of quinide (0.500 g, 2.871 mmol) and N,N-(dimethylamino)pyridine (0.0175 g, 0.143 mmol) in dichloromethane (10 ml) was added triethylamine (1 ml) followed by the addition of 3,4-dimethoxycinnamic acid chloride (1.430 g, 6.316 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to give the title compound (1S, 3R, 4R, 5R)-3-dimethoxycinnamoyl quinide (83) as a yellow powder (0.310 g, 29.6%). Rf 0.08 [chloroform: acetone (8:2)]; ν max(KBr)/cm⁻¹: 3438 (OH), 1786, 1715 (C=O), 1637 (C₆=C₆), 1266, 1178, 1140 (C-O); δ H (400 MHz, CDCl₃): 2.16 (1 H, dd, J 12 and 3.6, 2-Hex), 2.20 (1 H, m, 2-Heq), 2.37 (1 H, m, 6-Hax), 2.69 (1 H, d, J 11.6, 6-Heq), 3.87 (3 H, s, 17-H), 3.91 (3 H, s, 18-H), 4.39 (1 H, t, J 4.8, 4-H), 4.85 (1 H, t, J 5.2, 5-H), 5.07 (1 H, q, J 4.4, 3-H), 6.28 (1 H, d, J 16, 9-H), 6.86 (1 H, d, J 8, 12-H), 7.04 (1 H, d, J 6.4 and 1.6, 15-H), 7.10 (1 H, dd, J 5.6 and 1.2, 16-H), 7.68 (1 H, d, J 16,10-H); δ C (125 MHz, CDCl₃): 36.86 (C-2), 37.15 (C-6), 55.99 (C-17), 56.08 (C-18), 66.41 (C-4), 66.73 (C-3), 69.77 (C-5), 81.30 (C-1), 109.85 (C-12), 111.12 (C-15), 114.83 (C-9), 123.20 (C-16), 127.12 (C-11), 145.83 (C-10), 149.36 (C-13), 151.91 (C-14), 165.34 (C-8), 171.95 (C-7).
To a solution of quinide (0.500 g, 2.871 mmol) and N,N-(dimethylamino)pyridine (0.0175 g, 0.143 mmol) in dichloromethane (10 ml) was added triethylamine (1 ml) followed by the addition of cinnamic acid chloride (1.052 g, 6.316 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to give the target compound (84) as a white powder (0.394 g, 45.2%). Rf 0.11 [chloroform: acetone (8:2)]; ν_max (KBr)/cm⁻¹: 3422 (OH), 1714, 1687 (C=O), 1635 (C₅=CN), 1216, 1049, 1026 (C-O); δ_H (400 MHz, CDCl₃): 1.85 (1 H, m, 2-H), 1.87 (1 H, m, 6-H), 2.03 (1 H, m, 2-H), 2.08 (1 H, dd, J 8.8 and 4, 6-H), 4.08 (1 H, t, J 5.4, 4-H), 4.18 (1 H, q, J 3.2, 5-H), 4.68 (1 H, dd, J 7.8 and 3.6, 3-H), 6.37 (1 H, d, J 16, 9-H), 7.35-7.50 (5 H, m, Ph-H), 7.51 (1 H, d, J 6.5, 10-H); δ_C (125 MHz, CDCl₃): 38.45 (C-2), 38.85 (C-6), 64.83 (C-4), 67.62 (C-3), 73.45 (C-5), 77.98 (C-1), 118.45 (C-9), 128.56 (C-12, C-16), 129.53 (C-13, C-15), 131.59 (C-14), 134.10 (C-11), 145.59 (C-10), 169.33 (C-8), 174.99 (C-7).
To a solution of Troc-quinide (0.500 g, 1.430 mmol) and DMAP (0.0087 g, 0.0715 mmol) in dichloromethane (10 ml) were added diacetyl caffeic acid chloride (3.147 mmol, 0.889 g) in triethylamine (1 ml). The reaction solution was stirred for 18 hours at room temperature. The reaction was worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO$_3$ (10 ml) solution and brine (15 ml). The organic layer was dried over MgSO$_4$ and the solvent was removed under reduced pressure to yield a slightly yellow solid. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to give the title compound (1S, 3R, 4R, 5R)-1-($\beta$, $\beta$, $\beta$-trichloroethoxycarbonyl)-3,4-bis-(diacetylcaffeoyl) quinide (85) was recovered as a yellowish powder (0.081 g, 6.8 %). $R_f$ 0.84 [chloroform: acetone (8:2)]; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$: 1809, 1770, 1724 (C=O), 1638 (C$_{Ar}$=C$_{Ar}$), 1242, 1180, 1036 (C-O), 830, 737 (C-Cl); $\delta_{\text{H}}$ (400 MHz, CDCl$_3$): 2.26 (6 H, s, 22-H, 35-H), 2.29 (6 H, s, 23-H, 36-H), 2.46 (1 H, t, $J_{11.4}$, 2-H$_{ax}$), 2.54 (1 H, m, 6-H$_{eq}$), 2.71 (1 H, d, $J_{11.4}$, 2-H$_{eq}$), 3.21 (1 H, m, 6-H$_{ax}$), 4.75 (1 H, d, J 12, 9-H), 4.82 (1 H, d, J 12, 9-H$^1$), 5.01 (1 H, t, J 5.5, 5-H), 5.35 (1 H, q, J 4.6, 3-H), 5.69 (1 H, t, J 4.1, 4-H), 6.26 (1 H, d, J 16, 12-H), 6.43 (1 H, d, J 16, 25-H), 7.16-7.41 (6 H, m, Ph-H), 7.58 (1 H, d, J 16, 13-H), 7.66 (1 H, d, J 16, 26-H); $\delta_{C}$ (125 MHz, CDCl$_3$): 20.72 (C-22, C-35), 20.81 (C-23, C-36), 33.71 (C-2), 33.81 (C-6), 64.94 (C-4), 66.01 (C-3), 73.72 (C-5), 76.93 (C-9), 78.74 (C-1), 93.99 (C-10), 117.46 (C-12), 117.64 (C-25), 122.82 (C-15), 122.98 (C-28), 123.76 (C-18), 124.69 (C-31), 126.80 (C-19), 126.95 (C-32), 132.63 (C-14), 132.85 (C-27), 142.53 (C-16), 142.63 (C-29), 144.59 (C-17), 144.65 (C-30), 145.18 (C-13), 145.32 (C-26), 151.49 (C-8), 164.68 (C-11), 164.85 (C-24), 167.99 (C-20, C-33), 168.15 (C-21, C-34), 170.10 (C-7); MS, $m/z$ (ESI): 841.0529 [M$^+$ - C$_{36}$H$_{31}$O$_{17}$Cl$_3$ requires 841.0527]
To a solution of Troc-quinide (0.500 g, 1.430 mmol) and DMAP (0.008 g, 0.0715 mmol) in dichloromethane (10 ml) were added 3,4-dimethoxycinnamic acid chloride (0.712 g, 3.147 mmol) in triethylamine (0.43 ml). The reaction solution was stirred for 17 hours at room temperature. Dichloromethane (60 ml) and 2M HCl (10 ml) were added to solution and the organic layer was separated. The organic layer was then dried over MgSO\(_4\) and filtered. The solvent was removed under reduced pressure. The residue was purified by recrystallisation from EtOH to give the title product (86) as a white powder (0.600 g, 57.4%). Rf 0.76 [ethyl acetate: petrol ether (2:3)]; mp: 140°C; \(\nu_{\text{max}}\) (Nujol)/cm\(^{-1}\): 1812, 1767, 1711 (C=O), 1652 (C\(_{Ar}\)=C\(_{Ar}\)), 1238, 1137, 1020 (C-O), 721 (C-Cl); \(\delta_{\text{H}}\) (500 MHz, CDCl\(_3\)): 2.47 (1 H, t, \(J=11.5\), 2-H\(_{ax}\)), 2.56 (1 H, m, 6-H\(_{eq}\)), 2.75 (1 H, q, \(J=11.5\), 2-H\(_{eq}\)), 3.21 (1 H, m, 6-H\(_{eq}\)), 3.81 (3 H, s, 20-H), 3.89 (3 H, s, 21-H), 3.91 (3 H, s, 31-H), 3.93 (3 H, s, 32-H), 4.75 (1 H, d, \(J=9\), 9-H), 4.85 (1 H, d, \(J=12\), 9-H\(_1\)), 5.03 (1 H, q, \(J=5.5\), 5-H), 5.38 (1 H, m, 3-H), 5.72 (1 H, dd, \(J=9.5\) and 4.5, 4-H), 6.31 (1 H, d, \(J=15.5\), 12-H), 6.38 (1 H, d, \(J=15.5\), 23-H), 6.78-7.03 (6 H, m, Ph-H), 7.58 (1 H, d, \(J=16\), 13-H), 7.68 (1 H, d, \(J=16\), 14-H); \(\delta_{\text{C}}\) (125 MHz, CDCl\(_3\)): 33.99 (C-2), 34.06 (C-6), 56.05 (C-20), 56.20 (C-21), 56.27 (C-31), 56.32 (C-32), 64.95 (C-4), 65.96 (C-3), 74.02 (C-5), 77.50 (C-9), 79.03 (C-1), 94.13 (C-10), 109.90 (C-15), 110.02 (C-26), 111.20 (C-18), 111.30 (C-29), 114.07 (C-12), 114.40 (C-23), 123.14 (C-19), 123.46 (C-30), 127.02 (C-14), 127.22 (C-25), 146.50 (C-13), 147.11 (C-24), 149.42 (C-16), 149.59 (C-17), 151.65 (C-27), 151.99 (C-28), 152.14 (C-8), 165.36 (C-11), 165.64 (C-22), 170.31 (C-7); MS, \(m/z\) (CI): [M\(^+\)] 728/730/732/734; CHN: (C\(_{32}\)H\(_{31}\)O\(_{13}\)Cl\(_3\) 729.5 g/mol requires: C, 52.64%; H, 4.25%), Found: C, 52.96%; H, 4.17%.
(1S,3R,4R,5R) 1- (β,β,β-trichloroethoxycarbonyl)-3, 4-di-cinnamoyl quinide, (87)-p123

To a solution of Troc-quinide (0.500 g, 1.430 mmol) and DMAP (0.0087 g, 0.0715 mmol) in dichloromethane (10 ml) were added cinnamoyl chloride (0.524 g, 3.147 mmol) in triethylamine (0.430 ml). The reaction solution was stirred for 15 hours at room temperature. Dichloromethane (60 ml) and 2M HCl (10 ml) were added to solution and the organic layer was separated. The organic layer was then dried over MgSO₄ and filtered. The solvent was removed under reduced pressure. The residue was purified by recrystallisation from EtOH to give the title product (87) as a white powder (0.690 g, 79.12%). Rf 0.55 [ethyl acetate: petrol ether (2:3)]; mp: 183°C; νmax (Nujol)/cm⁻¹: 1806, 1771, 1710 (C=O), 1630 (C₆=C₆), 1461, 1376 (CH₃), 1264, 1239, 1213 (C-O), 732 (C-Cl); δH (500 MHz, CDCl₃): 2.48 (1 H, t, J 12, 2-Hax), 2.58 (1 H, m, 6-Heq), 2.73 (1 H, d, J 11.5, 2-Heq), 3.23 (1 H, m, 6-Hax), 4.75 (1 H, d, J 12, 9-H), 4.85 (1 H, d, J 12, 9-H1), 5.05 (1 H, q, J 6, 5-H), 5.39 (1 H, m, 3-H), 5.72 (1 H, dd, J 4.5 and 9.5, 4-H), 6.34 (1 H, d, J 16, 12-H), 6.52 (1 H, d, J 15.5, 21-H), 7.54-7.30 (10 H, m, Ph-H), 7.65 (1 H, d, J 16, 13-H), 7.74 (1 H, d, J 16, 22-H); δC (125 MHz, CDCl₃): 33.81 (C-2), 33.97 (C-6), 65.04 (C-4), 66.05 (C-3), 73.92 (C-5), 77.48 (C-9), 78.94 (C1), 94.12 (C-10), 116.51 (C-12), 116.75 (C-21), 128.46 (C-15), 128.49 (C-19), 128.53 (C-25), 128.56 (C-28), 129.09 (C-16), 129.26 (C-18), 130.63 (C-25), 130.75 (C-27), 130.84 (C-17), 131.21 (C-20), 134.03 (C-14), 134.19 (C-23), 146.61 (C-13), 147.25 (C-22), 151.65 (C-8), 165.12 (C-11), 165.39 (C-21), 170.76 (C-7); MS, m/z (CI): [M+]+ 608/610/612/614, [M-Cl] 575/577/579; CHN: (C₂₅H₂₃O₉Cl₃ 609.5 g/mol requires: C, 55.13%; H, 3.78%), Found: C, 56.17%; H, 3.81%.
(1S,3R,4R,5R)-3, 4-bis-(dimethoxycinnamoyl) quinide, (88)-p124

Quinic acid lactone 90a (0.200 g, 0.274 mmol) was dissolved in glacial acetic acid (3 ml) and zinc powder (0.268 g, 4.112 mmol) added to the solution. The reaction mixture was stirred for 12 hours at room temperature and diluted by the addition of extra glacial acetic acid (6 ml). The mixture was stirred for additional 36 hours at room temperature. The obtained slightly suspension was filtered and the filtrate was diluted in water which caused the white participate. The mixture was extracted with chloroform (3x30 ml) whereas the white solid was dissolved. The combined organic phases were washed with water (3x30 ml) dried over MgSO₄ and the solvent was evaporated to give the title compound (88) as a white powder (0.120 g, 80%). Rf 0.28 [chloroform: acetone (10:1)]; mp: 113°C; ν_max (Nujol)/cm⁻¹: 3430 (OH), 2854 (COOH), 1732 (C=O), 1631 (C₆=CH₂), 1269, 1139 (C-O); δ_H (500 MHz, CDCl₃): 2.27 (1 H, t, J 5, 2-H₉), 2.38 (1 H, m, 6-H₁₀), 2.52 (1 H, m, 6-H₉), 2.64 (1 H, d, J 12, 2-H₉), 3.82 (3 H, s, 24-H), 3.88 (3 H, s, 25-H), 3.92 (3 H, s, 26-H), 3.93 (3 H, s, 27-H), 4.95 (1 H, t, J 5.5, 5-H), 5.29 (1 H, m, 3-H), 5.69 (1 H, dd, J 9 and 4.5, 4-H), 6.21 (1 H, d, J 16, 9-H), 6.38 (1 H, d, J 15.5, 18-H), 6.72-6.88 (6 H, m, Ph-H), 7.58 (1 H, d, J 15.5, 10-H), 7.68 (1 H, d, J 16.19-H); δ_C (125 MHz, CDCl₃): 37.11 (C-2), 37.69 (C-6), 56.03 (C-13), 56.19 (C-14), 56.26 (C-26), 56.28 (C-27), 64.84 (C-4), 66.44 (C-3), 72.34 (C-5), 74.29 (C-1), 110.02 (C-12), 110.05 (C-21), 111.19 (C-15), 111.32 (C-24), 114.30 (C-9), 114.66 (C-18), 123.11 (C-16), 123.38 (C-25), 127.08 (C-11), 127.27 (C-20), 146.31 (C-10), 146.91 (C-19), 149.39 (C-13), 149.59 (C-14), 151.58 (C-22), 151.91 (C-23), 165.72 (C-8), 165.86 (C-17), 176.33 (C-7); MS, m/z (CI): 553 [M⁺], 554 [M+H]; CHN: (C₂₀H₃₀O₁₁) 554 g/mol requires: C, 62.8%; H, 5.41%, Found: C, 53.05%; H, 4.57%.
To a solution of Troc-quinide (0.200 g, 0.572 mmol) and DMAP (0.003 g, 0.0287 mmol) in dichloromethane (10 ml) were added acetyl ferulic acid chloride (0.320 g, 1.258 mmol) in triethylamine (1 ml). The reaction solution was stirred for 16 hours at room temperature. The reaction was worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ (10 ml) solution and brine (15 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to yield a slightly yellow solid. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to give the title product (1S,3R,4R,5R)-3,4-di-(acetylferuloyl) quinide (89) was recovered as a yellow powder (0.120 g, 34.5 %). Rf 0.72 [chloroform: acetone (8:2)]; \nu_{\text{max}}\ (\text{KBr})/\text{cm}^{-1}: 3473\ (\text{OH}), 1764, 1718\ (\text{C=O}), 1636\ (\text{C}_{\text{Ar}}=\text{C}_{\text{Ar}}), 1258, 1198, 1153\ (\text{C-O}); \delta_H\ (400\ \text{MHz, CDCl}_3): 2.01\ (1\ \text{H, dd, } J = 13.6\ \text{and } 9.8,\ 2-\text{H}_{\text{ax}}), 2.29\ (6\ \text{H, s, } 28-\text{H, 29-H}), 2.46\ (1\ \text{H, d, } J = 14.8, 6-\text{H}_{\text{ax}}), 2.54\ (1\ \text{H, dd, } J = 14.4\ \text{and } 3.2,\ 2-\text{H}_{\text{eq}}), 2.99\ (1\ \text{H, dd, } J = 8.4\ \text{and } 3.2,\ 6-\text{H}_{\text{eq}}), 3.85\ (3\ \text{H, s, } 30-\text{H}), 3.86\ (3\ \text{H, s, } 31-\text{H}), 5.02\ (1\ \text{H, dd, } J = 11.6\ \text{and } 2.3,\ 5-\text{H}), 5.28\ (1\ \text{H, dd, } J = 9.6\ \text{and } 2.3,\ 4-\text{H}), 5.52\ (1\ \text{H, q, } J = 5.1, 3-\text{H}), 6.27\ (1\ \text{H, d, } J = 16, 9-\text{H}), 6.41\ (1\ \text{H, d, } J = 16, 18-\text{H}), 7.03-7.13\ (6\ \text{H, m, Ph-H}), 7.50\ (1\ \text{H, d, } J = 16, 10-\text{H}), 7.62\ (1\ \text{H, d, } J = 16, 19-\text{H}); \delta_C\ (125\ \text{MHz, CDCl}_3): 20.71\ (C-28, C-29), 29.87\ (C-2), 37.45\ (C-6), 53.71\ (C-30), 55.79\ (C-31), 67.07\ (C-3), 73.38\ (C-4), 75.15\ (C-5), 80.87\ (C-1), 111.43\ (C-12), 111.49\ (C-21), 116.70\ (C-9), 116.82\ (C-18), 122.55\ (C-15), 121.73\ (C-24), 123.40\ (C-16), 123.41\ (C-25), 132.94\ (C-11), 133.01\ (C-20), 141.84\ (C-10), 141.97\ (C-19), 145.81\ (C-14), 146.04\ (C-23), 151.52\ (C-13, C-22), 165.32\ (C-8), 166.05\ (C-17), 167.87\ (C-20, C-27), 168.79\ (C-7).
(1S,3R,4R,5R)-3,4-bis-(diacetylcaffeoyl) quinide, (90)-p128

To a solution of quinide (0.500 g, 2.871 mmol) and N,N-(dimethylamino)pyridine (0.0175 g, 0.143 mmol) in dichloromethane (10 ml) was added triethylamine (1 ml) followed by the addition of diacetyl caffeic acid chloride (1.784 g, 6.316 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to give the title compound (1S,3R,4R,5R)-3,4-bis-(diacetylcaffeoyl) quinide (90) as a yellow powder (0.083 g, 4.3%). Rf 0.88 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3460 (OH), 1763 (C=O), 1635 (C=O=C), 1258, 1198, 1152 (C-O); δH (400 MHz, CDCl₃): 2.14 (1 H, dd, J 14.2 and 10.1, 2-Hax), 2.30 (6 H, s, 30-H, 31-H), 2.31 (6H, s, 32-H, 33-H), 2.46 (1 H, d, J 15.1, 6-Hax), 2.55 (1 H, dd, J 11.9 and 4.9, 2-Heq), 2.98 (1 H, m, 6-Heq), 3.04 (1 H, t, J 5.9, 5-H), 5.28 (1 H, dd, J 12.4 and 5.3, 4-H), 5.52 (1 H, q, J 5.5, 3-H), 6.27 (1 H, d, J 16, 9-H), 6.38 (1 H, d, J 16, 18-H), 7.03-7.11 (1 H, m, Ph-H), 7.51 (1 H, d, J 15.9, 10-H), 7.64 (1 H, d, J 16, 19-H); δC (125 MHz, CDCl₃): 20.69 (C-30, C-31, C-32, C-33), 36.85 (C-2), 39.12 (C-6), 63.45 (C-3), 64.57 (C-4), 76.12 (C-5), 81.03 (C-1), 116.52 (C-12, C-21), 117.12 (C-9, C-18), 121.45 (C-15), 121.56 (C-24), 123.32 (C-16), 123.48 (C-25), 131.03 (C-11), 131.15 (C-20), 142.34 (C-10), 142.81 (C-19), 149.21 (C-13), 149.38 (C-14), 151.15 (C-21), 151.18 (C-23), 164.42 (C-8, C-17), 168.14 (C-26), 168.22 (C-27), 168.39 (C-28), 168.45 (C-29), 173.20 (C-7).
To a solution of quinide (0.500 g, 2.871 mmol) and N,N-(dimethylamino)pyridine (0.017 g, 0.143 mmol) in dichloromethane (10 ml) was added triethylamine (1 ml) followed by the addition of diacetyl caffeic acid chloride (1.784 g, 6.316 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to give the title compound (1S,3R,4R,5R)-1,3-bis-(diacetylcaffeoyl) quinide (91) (0.138 g, 7.21). Rf 0.22 [chloroform: acetone (8:2)];νmax (KBr)/cm⁻¹:3433 (OH), 1788, 1763 (C=O), 1638 (C₈=C₆), 1260, 1197, 1209 (C-O); δH (400 MHz, CDCl₃): 2.16 (1 H, m, 2-Hax), 2.29 (6 H, s, 30-H, 31-H), 2.30 (6 H, s, 32-H, 33-H), 2.42 (1 H, m, 6-Hax), 2.47 (1 H, m, 2-Heq), 2.64 (1 H, d, J 11.9, 6-Heq), 4.34 (1 H, t, J 4.6, 4-H), 4.78 (1 H, t, J 5.1, 5-H), 5.01 (1 H, q, J 4.1, 3-H), 6.39 (1 H, d, J 16, 9-H), 6.47 (1 H, d, J 16, 18-H), 7.18-7.38 (6 H, m, Ph-H), 7.52 (1 H, d, J 16, 10-H), 7.53 (1 H, d, J 16, 19-H); δC (125 MHz, CDCl₃): 20.70 (C-30, C-31), 20.73 (C-32, C-33), 36.33 (C-2), 36.34 (C-6), 64.06 (C-4), 68.97 (C-3), 72.13 (C-5), 77.17 (C-1), 118.05 (C-9), 118.93 (C-18), 122.86 (C-12), 123.05 (C-21), 124.09 (C-15), 124.16 (C-24), 126.75 (C-16), 126.77 (C-25), 132.87 (C-11), 133.02 (C-20), 142.33 (C-10), 142.55 (C-19), 142.26 (C-13), 145.32 (C-14), 145.33 (C-22), 145.54 (C-23), 163.51 (C-8), 165.52 (C-17), 168.14 (C-26), 169.17 (C-27), 169.87 (C-28), 169.88 (C-29), 176.57 (C-7).
To a solution of quinide (0.100 g, 0.574 mmol) and N,N-(dimethylamino)pyridine (0.003 g, 0.0287 mmol) in dichloromethane (5 ml) was added triethylamine (0.5 ml) followed by the addition of acetyl ferulic acid chloride (0.321 g, 1.263 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with Dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give the compound. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to afford to title compound (1S,3R,4R,5R)-1,3-di-(acetylfuruloyl) quinide (92) as a white powder (0.287 g, 82%). Rf 0.18 [chloroform: acetone (8:2)]; νₘₐₓ (KBr)/cm⁻¹: 3427 (OH), 1717 (C=O), 1641 (C₅-C₅), 1209, 1062, 1027 (C-O); δH (400 MHz, CDCl₃): 2.03 (1 H, m, 2-Hax), 2.06 (1 H, m, 6-Hax), 2.32 (6 H, s, 30-H, 31-H), 2.48 (1 H, m, 2-Heq), 2.68 (1 H, d, J 11.9, 6-Heq), 3.85 (3 H, s, 26-H), 3.86 (3 H, s, 27-H), 4.37 (1 H, t, J 4.8, 4-H), 4.84 (1 H, t, J 5.5, 5-H), 5.06 (1 H, q, J 4.2, 3-H), 6.36 (1 H, d, J 16, 9-H), 6.42 (1 H, d, J 16, 18-H), 7.07-7.25 (6 H, m, Ph-H), 7.58 (1 H, d, J 16, 10-H), 7.69 (1 H, d, J 16, 19-H); δC (125 MHz, CDCl₃): 20.72 (C-30, C-31), 36.44 (C-2), 36.54 (C-6), 56.01 (C-26), 56.03 (C-27), 64.22 (C-4), 66.29 (C-3), 72.03 (C-5), 77.41 (C-1), 111.49(C-12), 111.58 (C-21), 116.88 (C-9), 116.93 (C-18), 121.58 (C-15), 121.65 (C-24), 123.42 (C-16), 123.48 (C-25), 133.08 (C-11), 133.59 (C-20), 141.93 (C-10), 141.95 (C-19), 145.86 (C-13), 146.30 (C-22), 151.54 (C-14), 151.58 (C-23), 165.03 (C-8), 165.20 (C-17), 168.85 (C-28), 170.58 (C-29), 177.40 (C-7).
(1S,3R,4R,5R)-1,3-di-(acetyl p-coumaroyl) quinide, (93)-131

To a solution of quinide (0.100 g, 0.574 mmol) and DMAP (0.003 g, 0.0287 mmol) in dichloromethane (10 ml) were added acetyl p-coumaric acid chloride (0.193 g, 0.861 mmol) in pyridine (15 ml). The reaction solution was stirred for 12 hours at room temperature. The reaction mixture was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give the compound (93) as a white powder (0.260 g, 82.27%). Rf 0.16 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3436 (OH), 1788, 1765, 1699 (C=O), 1634 (C₆H₅-C₆H₅), 1205, 1118, 1054 (C-O); δH (400 MHz, CDCl₃): 2.16 (1 H, t, J 11.9, 2-Hax), 2.17 (1 H, m, 6-Hax), 2.22 (1 H, m, 2-Heq), 2.27 (6 H, s, 28-H, 29-H), 2.62 (1 H, d, J 11.6, 6-Heq), 4.37 (1 H, t, J 4.8, 4-H), 4.75 (1 H, t, J 5.6, 5-H), 5.01 (1 H, q, J 4.4, 3-H), 6.47 (2 H, d, J 16, 9-H, 18-H), 7.15-7.64 (8 H, m, Ph-H), 7.68 (2 H, d, J 16, 10-H, 19-H); δC (125 MHz, CDCl₃): 20.45 (C-28, C-29), 38.45 (C-2), 38.66 (C-6), 62.15 (C-4), 68.03 (C-3), 70.64 (C-5), 76.32 (C-1), 116.89 (C-9), 118.03 (C-18), 121.01 (C-13, C-22), 121.11 (C-15, C-24), 127.90 (C-12, C-21), 128.02 (C-16, C-25), 130.17 (C-11), 131.04 (C-20), 142.02 (C-10), 142.82 (C-20), 150.76 (C-14), 151.03 (C-23), 164.36 (C-8), 167.15 (C-26), 167.84 (C-27), 176.39 (C-7).
To a solution of quinide (0.100 g, 0.574 mmol) and DMAP (0.003 g, 0.0287 mmol) in dichloromethane (10 ml) were added 3,4-dimethoxycinnamic acid chloride (0.195 g, 0.861 mmol) in pyridine (15 ml). The reaction solution was stirred for 12 hours at room temperature. The reaction mixture was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give the compound (94) as a yellow powder (0.206 g, 64.7%). Rf 0.13 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3430 (OH), 1788, 1716, 1699 (C=O), 1633 (C₆H₅=C₆H₅), 1262, 1058, 1027 (C-O); δH (400 MHz, CDCl₃): 2.21 (1 H, t, J 14.7, 2-H(ax)), 2.28 (1 H, m, 6-H(ax)), 2.34 (1 H, m, 2-H(eq)), 2.65 (1 H, d, J 11.6, 6-H(eq)), 3.91 (6 H, s, 26-H, 27-H), 3.92 (6 H, s, 28-H, 29-H), 4.38 (1 H, t, J 4.4, 4-H), 4.94 (1 H, t, J 5.6, 5-H), 5.04 (1 H, q, J 2.4, 3-H), 6.32 (1 H, d, J 16, 9-H), 6.45 (1 H, d, J 16, 18-H), 6.95-7.13 (6 H, m, Ph-H), 7.62 (1 H, d, J 15.7, 10-H), 7.74 (1 H, d, J 15.9, 19-H); δC (125 MHz, CDCl₃): 38.47 (C-2), 38.68 (C-6), 54.69 (C-26, C-27), 54.76 (C-28, C-29), 62.24 (C-4), 67.77 (C-3), 70.65 (C-5), 81.08 (C-1), 114.54 (C-12, C-21), 115.98 (C-9, C-18), 120.30 (C-15), 121.47 (C-24), 127.29 (C-16), 127.53 (C-25), 132.03 (C-11), 132.34 (C-20), 149.17 (C-10), 149.80 (C-18), 153.95 (C-13), 154.01 (C-14), 155.73 (C-22), 156.04 (C-23), 170.69 (C-8), 173.61 (C-7).
To a solution of quinide (0.200 g, 1.148 mmol) and DMAP (0.007 g, 0.0574 mmol) in dichloromethane (10 ml) were added cinnamic acid chloride (0.287 g, 1.722 mmol) in pyridine (15 ml). The reaction solution was stirred for 12 hours at room temperature. The reaction mixture was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give the title compound (95) as a white powder (0.350 g, 70.3%). Rf 0.19 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3420 (OH), 1789, 1706 (C=O), 1636 (C₆H₅=CH₅), 1282, 1204, 1173 (C-O); δH (400 MHz, CDCl₃): 2.19 (1 H, t, J = 11.91, 2-H₉ax), 2.26 (1 H, m, 6-H₈ax), 2.35 (1 H, m, 2-H₉eq), 2.70 (1 H, d, J = 11.91, 6-H₈eq), 4.41 (1 H, t, J = 4.58, 4-H), 4.85 (1 H, t, J = 5.50, 5-H), 5.06 (1 H, q, J = 4.12, 3-H), 6.42 (1 H, d, J = 16.9, 9-H), 6.43 (1 H, d, J = 16.9, 18-H), 7.39-7.53 (10 H, m, Ph-H), 7.71 (1 H, d, J = 16.9, 10-H), 7.75 (1 H, d, J = 16.9, 19-H); δC (125 MHz, CDCl₃): 36.45 (C-2), 36.54 (C-6), 64.24 (C-4), 68.76 (C-3), 72.12 (C-5), 76.77 (C-1), 116.70 (C-9), 117.23 (C-18), 128.33 (C-12, C-16), 128.44 (C-21, C-25), 129.05 (C-13, C-15), 129.09 (C-22, C-24), 130.82 (C-14), 130.91 (C-23), 134.01 (C-11), 134.13 (C-20), 146.68 (C-10), 147.14 (C-19), 171.61 (C-7).
(1S,3R,4R,5R)-1,4-di-cinnamoyl quinide, (96)

To a solution of quinide (0.100 g, 0.574 mmol) and N,N-(dimethylamino)pyridine (0.003 g, 0.0287 mmol) in dichloromethane (5 ml) was added triethylamine (0.5 ml) followed by the addition of cinnamic acid chloride (0.210 g, 1.263 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to afford the title compound (1S,3R,4R,5R)-1,4-di-cinnamoyl quinide (96) as a white powder (0.189 g, 75.9%). Rf 0.14 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3447 (OH), 1786 (C=O), 1632 (C₆H₅=C₆H₅), 1287, 1171 (C-O); δH (400 MHz, CDCl₃): 2.09 (1 H, t, J 12.4, 2-Heq), 2.16 (1 H, m, 2-Heq), 2.18 (1 H, m, 6-Hax), 2.51 (1 H, d, J 11.9, 6-Heq), 4.10 (1 H, q, J 4.3, 3-H), 5.06 (1 H, t, J 5.5, 5-H), 5.41 (1 H, t, J 4.5, 4-H), 6.43 (1 H, d, J 16, 9-H), 6.47 (1 H, d, J 16, 18-H), 7.40-7.54 (10 H, m, Ph-H), 7.74 (1 H, d, J 16, 10-H), 7.25 (1 H, d, J 16, 19-H); δC (125 MHz, CDCl₃): 36.45 (C-2), 36.54 (C-6), 64.24 (C-3), 68.76 (C-4), 72.12 (C-5), 76.10 (C-1), 116.70 (C-9), 117.23 (C-18), 128.33 (C-12, C-16), 128.44 (C-21, C-25), 129.05 (C-13, C-15), 129.09 (C-22, C-24), 130.82 (C-14), 130.91 (C-23), 134.01 (C-11), 134.13 (C-20), 146.68 (C-10), 147.14 (C-19), 165.39 (C-8, C-17), 171.61 (C-7).
To a solution of quinide (0.200 g, 1.148 mmol) and N,N-(dimethylamino)pyridine (0.007 g, 0.05742 mmol) in dichloromethane (10 ml) was added pyridine (15 ml) followed by the addition of cinnamic acid chloride (0.191 g, 1.148 mmol) and acetyl p-coumaric acid chloride (0.257 g, 1.1484 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to give the title compound (1S,3R,4R,5R)-1-cinnamoyl-3-(acetyl p-coumaroyl) quinide (97) as a white powder (0.176 g, 31.15%).

Rf 0.16 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 3454 (OH), 1785, 1684 (C=O), 1633 (C₅=CH₂), 1206, 1167, 1017 (C-O); δH (400 MHz, CDCl₃): 2.27 (1 H, m, 2-H₆), 2.29 (3 H, s, 27-H), 2.30 (1 H, m, 6-H₆), 2.32 (1 H, m, 2-H₆), 2.70 (1 H, d, J 11.6, 6-H₆), 4.40 (1 H, t, J 4.8, 4-H), 4.86 (1 H, t, J 5.6, 5-H), 5.07 (1 H, q, J 4.4, 3-H), 6.38 (1 H, d, J 16, 9-H), 6.43 (1 H, d, J 13.6, 18-H), 7.04-7.56 (9 H, m, Ph-H), 7.70 (1 H, d, J 8, 10-H), 7.74 (1 H, d, J 8, 19-H); δC (125 MHz, CDCl₃): 21.26 (C-27), 36.46 (C-2), 36.51 (C-6), 64.21 (C-4), 68.79 (C-3), 72.12 (C-5), 76.12 (C-1), 116.75 (C-9), 117.46 (C-18), 122.30 (C-Ph), 128.33 (C-Ph), 128.93 (C-Ph), 129.04 (C-Ph), 129.09 (C-Ph), 129.58 (C-Ph), 130.80 (C-Ph), 130.90 (C-Ph), 131.87 (C-11), 134.01 (C-20), 145.88 (C-10), 146.62 (C-19), 152.49 (C-23), 165.43 (C-8), 169.24 (C-17), 171.30 (C-26), 177.55 (C-7).
Quinide tri-acetate, (98)-p141

To a solution of quinide 60 (0.100 g, 0.574 mmol) and N,N-(dimethylamino)pyridine (0.003 g, 0.0028 mmol) in pyridine (0.2 ml) was added acetic anhydride (0.2 ml) at 0°C. The reaction mixture was stirred for 1 hour and then poured onto 150 ml crushed ice. The aqueous phase was acidified with 10 ml 2M HCl and stirred for an additional hour. The reaction mixture was extracted with EtOAc (50 ml). The organic phase was dried over MgSO₄ filtered and the solvent was removed under reduced pressure purified by recrystallisation with CDCl₃ to give the title compound (98) as pale orange powder (0.145 g, 84%). Rf 0.22 [chloroform: acetonitrile (10:1)]; mp: 98°C; νₘₐₓ (Nujol)/cm⁻¹:1800, 1755 (C=O), 1463, 1377 (CH₃), 1057 (C-O); δₜ (500 MHz, CDCl₃): 2.01 (3 H, s, 11-H), 2.12 (1 H, d, J 5.5, 2-Hₐₙ), 2.14 (3 H, s, 12-H), 2.15 (3 H, s, 13-H), 2.29 (1 H, dd, J 10.5 and 2.3, 2-Hₑₐ), 2.56 (1 H, d, J 11.5, 6-Hₑₐ), 3.09 (1 H, m, 6-Hₐₙ), 4.85 (1 H, t, J 5, 5-H), 5.17 (1 H, m, 3-H), 5.47 (1 H, dd, J 8.5 and 1.5, 4-H); δₜ (125 MHz, CDCl₃): 21.10 (C-11), 21.16 (C-12), 21.30 (C-13), 33.76 (C-2), 34.20 (C-6), 65.04 (C-3), 65.87 (C-4), 71.68 (C-5), 76.38 (C-1), 169.30 (C-8), 169.35 (C-9), 171.52 (C-10), 171.29 (C-7); MS, m/z (Cl): 300 [M⁺], 301 [M+H]; CHN: (C₁₃H₁₆O₇) 300 g/mol requires: C, 52%; H; 5.3%, Found: C, 50.2%; H, 5.3%.
(1S, 3R, 4R, 5R)-1, 3, 4-tri-cinnamoyl quinide, (99)

To a suspension of quinic acid (0.200 g, 1.0407 mmol) and N,N-(dimethylamino)pyridine (0.006 g, 0.052 mmol) in dichloromethane (6 ml) were added triethylamine (0.6 ml) and cinnamoyl chloride (0.693 g, 4.163 mmol) at room temperature. The reaction mixture was stirred for 18 hours at room temperature. The reaction solution was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic phase was dried with MgSO4, filtered and the solvent was removed under reduced pressure. The residue was purified by recrystallisation from EtOH to give the title compound (1S, 3R, 4R, 5R)-1, 3, 4-tri-cinnamoyl quinide (99) as white powder (0.550 g, 93.61%). Rf 0.60 [ethyl acetate: petrol ether (2:3)]; mp 180 °C; νmax (KBr)/cm⁻¹: 1804, 1763, 1717 (C=O), 1635 (C=C=C), 1258, 1216, 1198, 1123 (C-O); δH (400 MHz, CDCl3): 2.56 (1 H, dd, J 15.4 and 11.4, 2-Hα), 2.82 (1 H, d, J 11.9, 6-Hα), 3.11 (1 H, dd, J 14.6 and 7.3, 2-Hα), 3.20 (1 H, m, 6-Hα), 5.03 (1 H, t, J 5.5, 5-H), 5.39 (1 H, ddd, J 11.4, 10.9 and 4.1, 3-H), 5.73 (1 H, t, J 4.6, 4-H), 6.36 (1 H, d, J 16, 9-H), 6.46 (1 H, d, J 15.6, 18-H), 6.55 (1 H, d, J 16, 27-H), 7.40-7.55 (15 H, m, Ph-H), 7.74 (1 H, d, J 16, 10-H), 7.75 (1 H, d, J 5.5, 19-H), 7.78 (1 H, d, J 16, 28-H); δc (125 MHz, CDCl3): 34.12 (C-2), 34.55 (C-6), 65.19 (C-4), 66.20 (C-3), 74.12 (C-5), 77.43 (C-1), 116.48 (C-Ph), 116.59 (C-Ph), 116.81 (C-Ph), 117.04 (C-9), 117.28 (C-18), 117.46 (C-27), 128.13 (C-Ph), 128.35 (C-Ph), 128.44 (C-Ph), 128.85 (C-Ph), 128.95 (C-Ph), 129.05 (C-Ph), 129.09 (C-Ph), 130.19 (C-Ph), 130.66 (C-Ph), 130.82 (C-Ph), 130.94 (C-Ph), 131.01 (C-Ph), 133.98 (C-11), 134.02 (C-20), 134.23 (C-29), 146.95 (C-10), 147.10 (C-19), 147.14 (C-28), 165.21 (C-8), 165.39 (C-17), 165.60 (C-26), 171.77 (C-7); m/z (CI): 564 [M⁺], 565 [M+H]; CHN: (C₃₄H₂₈O₈) 565 g/mol requires: C, 72.34%; H, 4.96%). Found: C, 68.87%; H, 6.01%.
To a suspension of quinic acid (0.500 g, 2.600 mmol) and N,N-(dimethylamino)pyridine (0.015 g, 1.3 mmol) in dichloromethane (10 ml) were added triethylamine (1.4 ml) and 3, 4 dimethoxycinnamoyl chloride (2.357 g, 10.407 mmol) at room temperature. The reaction mixture was stirred for 12 hours at room temperature then refluxed for 5 days at 100°C. The reaction solution was extracted with dichloromethane (2x50 ml) and 2M HCl (20 ml). The organic phase was dried with MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by recrystallisation from EtOH to give the title compound (100) as a slightly yellow powder (1.900 g, 95%). Rf 0.75 [ethyl acetate: petrol ether (2:3)]; mp: 125 °C; νₘₐₓ (Nujol)/cm⁻¹: 1763 (C=O), 1655 (C₆H₅=C₆H₅), 1260, 1200, 1124, 1032 (C-O); δH (500 MHz, CDCl₃): 1.81 (1 H, m, 2-Hₐ), 1.95 (1 H, dd, J 11.5 and 1.9, 6-Heq), 2.47 (1 H, d, J 12.5, 2-Heq), 2.75 (1 H, m, 6-Hₐ), 3.83 (6 H, s, 35-H, 36-H), 3.84 (6 H, s, 37-H, 38-H), 3.89 (6 H, s, 39-H, 40-H), 4.42 (1 H, m, 5-H), 5.01 (1 H, m, 3-H), 5.56 (1 H, t, J 3.5, 4-H), 6.33 (1 H, d, J 16, 9-H), 6.51 (1 H, d, J 16, 18-H), 6.57 (1 H, d, J 16, 27-H), 7.31-7.45 (9 H, m, Ph-H), 5.51 (1 H, d, J 15.5, 10-H), 7.57 (1 H, d, J 15.5, 19-H), 7.60 (1 H, d, J 15.5, 28-H); δC (125 MHz, CDCl₃): 39.72 (C-2), 39.74 (C-6), 56.01 (C-35), 56.10 (C-36), 56.16 (C-37), 56.22 (C-38), 56.26 (C-39), 56.36 (C-40), 63.20 (C-4), 63.90 (C-3), 69.22 (C-5), 79.77 (C-1), 110.95 (C-12), 111.07 (C-21), 111.20 (C-30), 111.61 (C-15), 112.22 (C-24), 112.28 (C-33), 116.25 (C-9), 116.28 (C-18), 166.60 (C-27), 123.30 (C-16), 123.40 (C-25), 123.65 (C-34), 127.42 (C-11), 127.83 (C-20), 127.92 (C-29), 144.82 (C-10), 144.49 (C-19), 145.77 (C-28), 149.02 (C-13), 149.37 (C-14), 149.66 (C-22), 151.46 (C-23), 151.67 (C-31), 151.70 (C-32), 166.15 (C-8), 166.58 (C-17), 166.69 (C-26), 172.69 (C-7); MS, m/z (Cl): 744 [M⁺], 745 [M+H⁺], 544 [M-C₄H₉O₃]; CHN: (C₄₀H₄₀O₄₄) 744 g/mol requires: C, 64.52%; H, 5.38%. Found: C, 63.83%; H, 5.48%.
(1S, 3R, 4R, 5R)-1,3,4-tri-(acetyl p-coumaroyl) quinide, (101)

To a suspension of quinic acid (0.200 g, 1.0407 mmol) and N,N-(dimethylamino)pyridine (0.006 g, 0.052 mmol) in dichloromethane (6 ml) were added triethylamine (0.6 ml) and acetyl p-coumaroyl chloride (0.934 g, 4.163 mmol) at room temperature. The reaction mixture was stirred for 18 hours at room temperature. The reaction solution was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic phase was dried with MgSO₄, filtered and the solvent was removed under reduced pressure to give the title compound (1S, 3R, 4R, 5R)-1,3,4-tri-(acetyl p-coumaroyl) quinide (101) as white powder (0.560 g, 73%). Rf 0.88 [chloroform: acetone (8:2)]; νₓ max (KBr)/cm⁻¹: 1785 (C=O), 1631 (C₉=C₈), 1158 (C-O); δ_H (400 MHz, CDCl₃): 2.29 (9 H, s, 38-H, 39-H, 40-H), 2.31 (1 H, m, 2-Hax), 2.55 (1 H, d, J 11.4, 6-Heq), 2.78 (1 H, d, J 11.6, 2-Heq), 3.11 (1 H, m, 6-Hax), 5.02 (1 H, t, J 5.2, 5-H), 5.38 (1 H, m, 3-H), 5.77 (1 H, t, J 4.4, 4-H), 6.26 (1 H, d, J 16, 9-H), 6.40 (1 H, d, J 16, 18-H), 6.45 (1 H, d, J 16, 27-H), 7.14-7.56 (12 H, m, Ph-H), 7.59 (1 H, d, J 16, 10-H), 7.67 (1 H, d, J 16, 19-H), 7.78 (1 H, d, J 16, 28-H); δ_C (125 MHz, CDCl₃): 21.06 (C-38), 21.21 (C-39), 21.29 (C-40), 35.83 (C-2), 35.95 (C-6), 64.72 (C-4), 65.16 (C-3), 71.84 (C-5), 117.28 (C-9), 117.36 (C-18), 117.42 (C-27), 122.30 (C-13, C-15), 122.38 (C-22, C-24), 122.47 (C-31, C-33), 129.26 (C-12, C-16), 129.58 (C-21, C-25), 129.73 (C-30, C-34), 131.82 (C-11), 132.33 (C-20), 133.57 (C-29), 145.74 (C-10), 145.80 (C-19), 145.98 (C-28), 150.88 (C-14), 151.24 (C-23), 152.55 (C-32), 165.02 (C-8), 165.56 (C-17), 165.84 (C-20), 168.90 (C-35), 169.19 (C-36), 169.24 (C-37), 171.16 (C-7).
To a suspension of quinic acid (0.200 g, 1.0407 mmol) and N,N-(dimethylamino)pyridine (0.006 g, 0.052 mmol) in dichloromethane (6 ml) were added triethylamine (0.6 ml) and acetyl ferulic acid chloride (1.059 g, 4.163 mmol) at room temperature. The reaction mixture was stirred for 18 hours at room temperature. The reaction solution was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic phase was dried with MgSO4, filtered and the solvent was removed under reduced pressure to give the title compound (1S, 3R, 4R, 5R)-1, 3, 4-tri-(acetylfuruloyl) quinide (102) as yellow solid (0.810 g, 94%). Rf 0.85 [chboroform: acetone (8:2)]; \( \nu_{\text{max}} \) (KBr)/cm\(^{-1} \): 1803, 1715 (C=O), 1631 (C\( _{\text{ar}} \)=C\( _{\text{ar}} \)), 1204, 1163, 1055 (C-O); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)): 2.32 (9 H, s, 38-H, 39-H, 40-H), 2.50 (1 H, m, 2-H\(_{\text{ax}} \)), 2.57 (1 H, t, J 11.9, 6-H\(_{\text{eq}} \)), 2.60 (1 H, d, J 11.4, 2-H\(_{\text{eq}} \)), 2.88 (1 H, dd, J 14.6 and 7.3, 6-H\(_{\text{ax}} \)), 3.85 (9 H, s, 41-H, 42-H, 43-H), 4.93 (1 H, t, J 5.5, 5-H), 5.38 (1 H, m, 3-H), 5.72 (1 H, t, J 4.5, 4-H), 6.25 (1 H, d, J 16, 9-H), 6.36 (1 H, d, J 15.5, 18-H), 6.49 (1 H, d, J 15.5, 27-H), 7.07 7.25 (9 H, m, Ph-H), 7.70 (1 H, d, J 16, 10-H), 7.74 (1 H, d, J 15.5, 18-H), 7.81 (1 H, d, J 15.5, 28-H); \( \delta_{\text{C}} \) (125 MHz, CDCl\(_3\)): 20.72 (C-39, C-40, C-41), 33.63 (C-2), 34.39 (C-6), 55.83 (C-41), 56.02 (C-42), 56.17 (C-43), 63.83 (C-4), 65.72 (C-3), 76.77 (C-5), 77.44 (C-1), 111.26 (C-12), 111.58 (C-21), 111.64 (C-30), 116.35 (C-9), 116.36 (C-18), 117.40 (C-27), 121.65 (C-15), 121.77 (C-24), 121.79 (C-33), 121.82 (C-16), 122.34 (C-25), 123.42 (C-34), 132.72 (C-11), 132.85 (C-20), 133.08 (C-29), 141.23 (C-10), 141.39 (C-19), 141.44 (C-28), 146.08 (C-14), 146.28 (C-23), 146.42 (C-32), 151.52 (C-13), 151.55 (C-22), 151.58 (C-31), 168.43 (C-8), 168.48 (C-17), 168.52 (C-26), 168.57 (C-35), 168.81 (C-36), 161.88 (C-37), 171.18 (C-7).
(1S, 3R, 4R, 5R)-1, 3, 4-tri-(diacetylcaffeoyl) quinide, (103)

To a suspension of quinic acid (0.200 g, 1.0407 mmol) and N,N-(dimethylamino)pyridine (0.006 g, 0.052 mmol) in dichloromethane (6 ml) were added triethylamine (0.6 ml) and diacetyl caffeic acid chloride (1.175 g, 4.163 mmol) at room temperature. The reaction mixture was stirred for 18 hours at room temperature. The reaction solution was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic phase was dried with MgSO4, filtered and the solvent was removed under reduced pressure to give the title compound (1S, 3R, 4R, 5R)-1, 3, 4-tri-(diacetylcaffeoyl) quinide (103) as white powder (0.530 g, 55.6%). Rf 0.92 [chloroform: acetone (8:2)]; ν<sub>max</sub> (KBr)/cm<sup>-1</sup>: 1796 (C=O), 1653 (C<sub>AR</sub>=C<sub>AR</sub>), 1211, 1209, 1158 (C-O); δ<sub>HI</sub> (400 MHz, CDCl<sub>3</sub>): 2.30 (18 H, s, 41-H, 42-H, 43-H, 44-H, 45-H, 46-H), 2.51 (1 H, m, 2-H<sub>ax</sub>), 2.75 (1 H, d, J 11.6, 6-H<sub>eq</sub>), 3.10 (1 H, d, J 11.9, 2-H<sub>eq</sub>), 3.20 (1 H, m, 6-H<sub>ax</sub>), 5.01 (1 H, t, J 5.3, 5-H), 5.26 (1 H, m, 3-H), 5.69 (1 H, t, J 4.2, 4-H), 6.15 (1 H, d, J 16, 9-H), 6.39 (1 H, d, J 15.3, 18-H), 6.43 (1 H, d, J 15.3, 27-H), 7.20-7.40 (9 H, m, Ph-H), 7.65 (1 H, d, J 16, 10-H), 7.70 (1 H, d, J 15.9, 19-H), 7.79 (1 H, d, J 15.9, 28-H); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>): 20.72 (C-41, C-42, C-43, C-44, C-45, C-46), 34.71 (C-2), 36.35 (C-6), 65.42 (C-4), 65.63 (C-3), 72.78 (C-5), 77.92 (C-1), 110.82 (C-12), 110.96 (C-21), 111.21 (C-30), 114.67 (C-9), 114.94 (C-18), 115.22 (C-27), 122.34 (C-16), 123.51 (C-25), 127.65 (C-34), 131.24 (C-11), 131.44 (C-20), 132.85 (C-29), 142.76 (C-10), 143.32 (C-19), 143.94 (C-28), 145.41 (C-14), 145.82 (C-23), 146.37 (C-32), 146.86 (C-13), 147.23 (C-22), 147.92 (C-31), 166.21 (C-8), 166.44 (C-17), 166.65 (C-20), 168.13 (C-35, C-36), 168.34 (C-37, C-38), 168.69 (C-39, C-40), 177.18 (C-7); MS, m/z (ESI): 935.2001 [M+ - C<sub>46</sub>H<sub>40</sub>O<sub>20</sub> and C<sub>46</sub>H<sub>40</sub>O<sub>20</sub>Na requires 935.2005].
(1S, 3R, 4R, 5R)-1, 3, 4-tri-cinnamoyl quinide, (104)

To a solution of quinide (0.200 g, 1.150 mmol) and N,N-(dimethylamino)pyridine (0.007 g, 0.0575 mmol) in dichloromethane (5 ml) was added triethylamine (0.64 ml) followed by the addition of cinnamic acid chloride (0.765 g, 4.600 mmol). The reaction mixture was stirred for 12 hours at room temperature under a nitrogen atmosphere. Dichloromethane (2x30 ml) and 10 ml 2M HCl were added to solution and the organic layer was separated. The organic layer was then dried over MgSO₄ and filtered. The solvent was removed under reduced pressure. The residue was purified by recrystallisation from EtOH to give the title product (1S, 3R, 4R, 5R)-1, 3, 4-tri-cinnamoyl quinide (104) as a white powder (0.200 g, 31%). Rf 0.60 [ethyl acetate: petrol ether (2:3)]; mp 180 °C; νmax (Nujol)/cm⁻¹: 2854 (C-H), 1795 (C=O), 1634 (C₆H₅=CH), 1190, 1173, 1083 (C-O); δH (500 MHz, CDCl₃): 2.53 (1 H, m, 2-Hax), 2.58 (1 H, d, J 11.5, 2-Heq), 3.20 (1 H, m, 6-Hax), 3.23 (1 H, m, 6-Heq), 5.02 (1 H, t, J 5.4, 5-H), 5.39 (1 H, m, 3-H), 5.73 (1H, t, J 4.3, 4-H), 6.35 (1 H, d, J 15.9, 9-H), 6.48 (1 H, d, J 16, 18-H), 6.52 (1 H, d, J 16, 27-H), 7.33-7.42 (15 H, m, Ph-H), 7.54 (1 H, d, J 14.5, 10-H), 7.72 (1 H, d, J 15.5, 19-H), 7.76 (1 H, d, J 16, 28-H); δC (125 MHz, CDCl₃): 34.16 (C-2), 34.71 (C-6), 65.33 (C-4), 66.32 (C-3), 74.14 (C-5), 80.32 (C-1), 116.75 (C-9), 116.92 (C-18), 116.97 (C-27), 128.24 (C-Ph), 128.27 (C-Ph), 128.46 (C-Ph), 128.58 (C-Ph), 129.10 (C-Ph), 129.24 (C-Ph), 130.80 (C-Ph), 131.10 (C-Ph), 131.15 (C-Ph), 134.12 (C-11), 134.18 (C-20), 134.27 (C-29), 146.43 (C-10), 147.09 (C-19), 147.24 (C-28), 165.22 (C-8), 165.53 (C-17), 165.60 (C-26), 171.52 (C-7); MS, m/z (Cl): 564 [M⁺], 565 [M+H]; CHN: (C₃₄H₃₈O₈ 565 g/mol requires: C, 72.34%; H, 4.96%). Found: C, 48.87%; H, 6.01%.
(1S, 3R, 4R, 5R)-1, 3, 4-tri-(dimethoxycinnamoyl) quinide, (105)

To a solution of quinide (0.500 g, 2.871 mmol) and N,N-(dimethylamino)pyridine (0.002 g, 0.140 mmol) in dichloromethane (5 ml) was added triethylamine (1.4 ml) followed by the addition of 3,4-dimethoxycinnamic acid chloride (2.275 g, 10.048 mmol). The reaction mixture was stirred for 12 hours at room temperature under a nitrogen atmosphere. Dichloromethane (2x30 ml) and 2M HCl (20 ml) were added to solution and the organic layer was separated. The organic layer was then dried over MgSO\(_4\) and filtered. The solvent was removed under reduced pressure. The residue was purified by recrystallisation from EtOH to give the title compound (105) as a slightly yellow powder (1.780 g, 84%). Rf 0.75 [ethyl acetate: petrol ether (2:3)]; mp 125 °C; IR\(_{\text{vmax}}\) (Nujol)/cm\(^{-1}\): 2840 (C-H), 1758, 1756, 1713 (C=O), 1627, 1599 (C\(_{\text{ar}}\)=C\(_{\text{ar}}\)), 1267, 1243, 1156, 1077 (C-O); \(\delta\)\(_{\text{H}}\) (500 MHz, CDCl\(_3\)): 2.52 (1 H, m, 2-H\(_{\text{ax}}\)), 2.65 (1 H, t, J 11.5, 6-H\(_{\text{ax}}\)), 2.89 (1 H, d, J 11.5, 2-H\(_{\text{eq}}\)), 3.14 (1 H, m, 2-H\(_{\text{ax}}\)), 3.80 (3 H, s, 35-H), 3.88 (3 H, s, 36-H), 3.90 (3 H, s, 37-H), 3.91 (3 H, s, 38-H), 3.92 (1 H, s, 39-H), 3.96 (1 H s, 40-H), 5.02 (1 H, t, J 5, 5-H), 5.38 (1 H, m, 3-H), 5.73 (1 H, t, J 4.5, 4-H), 6.22 (1 H, d, J 16, 9-H), 6.36 (1 H, d, J 16, 18-H), 6.42 (1 H, d, J 15.5, 27-H), 6.79-7.28 (9 H, m, Ph-H), 7.13 (1 H, d, J 16, 10-H), 7.58 (1 H, d, J 16, 19-H), 7.70 (1 H, d, J 15.5, 28-H); \(\delta\)\(_{\text{C}}\) (125 MHz, CDCl\(_3\)): 34.12 (C-2), 34.98 (C-6), 56.03 (C-35), 56.19 (C-36), 56.21 (C-37), 56.23 (C-38), 56.24 (C-39), 56.16 (C-40), 65.17 (C-4), 66.25 (C-3), 74.24 (C-5), 76.67 (C-1), 109.82 (C-12), 109.94 (C-21), 110.03 (C-30), 111.22 (C-15), 111.28 (C-24), 111.29 (C-33), 114.32 (C-9), 114.50 (C-18), 114.63 (C-27), 123.09 (C-16), 123.49 (C-25), 123.51 (C-34), 127.11 (C-11), 127.15 (C-20), 127.27 (C-29), 146.28 (C-10), 146.93 (C-19), 147.13 (C-28), 149.41 (C-13), 149.54 (C-14), 149.59 (C-22), 151.20 (C-23), 151.59 (C-31), 151.89 (C-32), 165.42 (C-8), 165.54 (C-17), 165.78 (C-26), 171.74 (C-7); MS, \(m/z\) (Cl): 744 [M\(^{+}\)]
To a solution of quinide (0.100 g, 0.574 mmol) and N,N-(dimethylamino)pyridine (0.003 g, 0.0287 mmol) in dichloromethane (6 ml) was added triethylamine (0.6 ml) followed by the addition of acetyl \textit{p}-coumaric acid chloride (0.451 g, 2.010 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO\textsubscript{3} solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO\textsubscript{4} and the solvent was removed under reduced pressure and residue was purified by recrystallisation from EtOH to give the title compound (1\textit{S}, 3\textit{R}, 4\textit{R}, 5\textit{R})-1, 3, 4-tri-(acetyl \textit{p}-coumaroyl) quinide (106) as a white powder (0.395 g, 93%). Rf 0.91 [chloroform: acetone (8:2)]; \(\nu\)\textsubscript{max} (KBr)/cm\textsuperscript{-1}: 1806, 1765, 1721 (C=O), 1635 (C\textsubscript{Ar}=C\textsubscript{Ar}), 1267, 1243, 1156, 1077 (C-O); \(\delta\textsubscript{H} (400 MHz, CDCl\textsubscript{3})\): 2.29 (3 H, s, 38-H), 2.30 (3 H, s, 39-H), 2.31 (3 H, s, 40-H), 2.55 (1 H, m, 2-H\textsubscript{ax}), 2.58 (1 H, dd, \(J\) 11.2 and 2.9, 6-H\textsubscript{eq}), 2.78 (1 H, d, \(J\) 11.6, 2-H\textsubscript{eq}), 3.13 (1 H, m, 6-H\textsubscript{ax}), 5.02 (1 H, t, \(J\) 4.8, 5-H), 5.38 (1 H, m, 3-H), 5.72 (1 H, t, \(J\) 4.4, 4-H), 6.26 (1 H, d, \(J\) 16, 9-H), 6.38 (1 H, d, \(J\) 16, 18-H), 6.44 (1 H, d, \(J\) 16, 27-H), 7.05-7.43 (12 H, m, Ph-H), 7.54 (1 H, d, \(J\) 15.3, 10-H), 7.56 (1 H, d, \(J\) 15.9, 19-H), 7.83 (1 H, d, \(J\) 15.3, 28-H); \(\delta\textsubscript{C} (125 MHz, CDCl\textsubscript{3})\): 21.12 (C-38), 21.24 (C-39), 21.28 (C-40), 34.62 (C-2), 35.86 (C-6), 66.21 (C-4), 66.86 (C-3), 72.66 (C-5), 78.92 (C-1), 112.43 (C-13, C-15), 112.85 (C-22, C-24), 113.37 (C-31, C-33), 114.81 (C-9), 115.17 (C-18), 115.64 (C-27), 122.31 (C-12, C-16), 122.39 (C-21, C-25), 122.53 (C-30, C-34), 131.82 (C-11), 132.35 (C-20),
132.93 (C-29), 144.84 (C-10), 145.15 (C-19), 145.47 (C-28), 151.24 (C-14), 151.52 (C-23), 151.85 (C-32), 166.46 (C-8), 166.71 (C-17), 166.97 (C-26), 169.11 (C-35), 169.23 (C-36), 169.45 (C-37), 171.83 (C-7); MS, m/z (ESI): 761.1743 [M⁺ - C₄₀H₃₄O₁₄ and C₄₀H₃₄O₁₄ Na requires 761.1841].

(1S, 3R, 4R, 5R)-1, 3, 4-tri-(acetylferuloyl) quinide, (107)

To a solution of quinide (0.100 g, 0.574 mmol) and N,N-(dimethylamino)pyridine (0.003 g, 0.0287 mmol) in dichloromethane (6 ml) was added triethylamine (0.6 ml) followed by the addition of acetyl ferulic acid chloride (0.511 g, 2.010 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2 M HCl (10 ml), NaHCO₃ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give the title compound (1S, 3R, 4R, 5R)-1, 3, 4-tri-(acetylferuloyl) quinide (107) as a pale yellow powder (0.445 g, 93.6%). Rf 0.84 [chloroform: acetone (8:2)]; νmax (KBr)/cm⁻¹: 1802, 1763, 1717 (C=O), 1636 (C₆=C₆), 1258, 1198, 1153, 1052 (C-O); δH (400 MHz, CDCl₃): 2.29 (3 H, s, 38-H), 2.32 (3 H, s, 39-H), 2.34 (3 H, s, 40-H), 2.57 (1 H, m, 2-Hax), 2.60 (1 H, dd, J 12 and 2.8, 6-Heq), 2.86 (1 H, d, J 11.2, 2-Heq), 3.15 (1 H, m, 6-Hax), 3.63 (1 H, s, 41-H), 3.75 (1 H, s, 42-H), 3.82 (1 H, s, 43-H), 5.01 (1 H, t, J 5.6, 5-H), 5.39 (1 H, m, 3-H), 5.73 (1 H, t, J 4.4, 4-H), 6.29 (1 H, d, J 16, 9-H), 6.42 (1 H, d, J 16, 18-H), 6.45 (1 H, d, J 16, 27-H), 6.99-7.25 (9 H, m, Ph-H), 7.56 (1 H, d, J 16, 10-H), 7.66 (1 H, d, J 15.5, 19-H), 7.70 (1 H, d, J 15.5, 28-H); δC (125 MHz, CDCl₃): 20.49 (C-38), 20.72 (C-39), 20.93 (C-40), 33.74 (C-2), 33.76 (C-6), 55.52 (C-41), 56.05 (C-42), 56.06 (C-43), 64.57 (C-4), 66.01 (C-3), 76.77 (C-5), 89.09 (C-1), 110.0 (C-12), 111.40 (C-21), 111.72 (C-30), 116.74 (C-9), 116.86 (C-18), 116.98 (C-27), 121.34 (C-15), 121.68
(C-24), 121.95 (C-33), 123.34 (C-16), 123.18 (C-25), 123.47 (C-34), 132.92 (C-11), 133.09 (C-20), 133.25 (C-29), 141.51 (C-10), 141.81 (C-19), 141.94 (C-28), 141.61 (C-14), 146.12 (C-23), 147.30 (C-32), 151.51 (C-13), 151.67 (C-22), 151.73 (C-31), 164.97 (C-8), 165.06 (C-17), 166.73 (C-26), 168.60 (C-35), 168.65 (C-36), 168.74 (C-37), 172.62 (C-7); MS, m/z (ESI): 851.2160 [M$^+$ - C$_{43}$H$_{40}$O$_{17}$ and C$_{43}$H$_{40}$O$_{17}$ Na requires 851.2158].

**(1S, 3R, 4R, 5R)-1, 3, 4-tri-(diacetylcaffeoyl) quinide, (108)**

To a solution of quinide (0.100 g, 0.574 mmol) and N,N-(dimethylamino)pyridine (0.003 g, 0.0287 mmol) in dichloromethane (6 ml) was added triethylamine (0.6 ml) followed by the addition of diacetyl caffeic acid chloride (0.511 g, 2.010 mmol). The reaction mixture was stirred for 16 hours at room temperature and worked up by diluting with dichloromethane (50 ml), washing with 2M HCl (10 ml), NaHCO$_3$ solution (10 ml) and brine (10 ml). The organic layer was dried over MgSO$_4$ and the solvent was removed under reduced pressure to give the title compound (1S, 3R, 4R, 5R)-1, 3, 4-tri-(diacetylcaffeoyl) quinide (108) as a yellow powder (0.490 g, 93%). Rf 0.89 [chloroform: acetone (8:2)]; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$: 1804, 1772, 1719 (C=O), 1637 (C$_A$=C$_A$), 1206, 1189, 1110, 1049 (C-O); $\delta_{H}$ (400 MHz, CDCl$_3$): 2.29 (6 H, s, 41-H, 42-H), 2.30 (6 H, s, 43-H, 44-H), 2.31 (6 H, s, 45-H, 46-H), 2.47 (1 H, m, 2-H$_{ax}$), 2.78 (1 H, d, J 11.6, 6-H$_{eq}$), 2.92 (1 H, dd, J 12.4 and 2.8, 2-H$_{eq}$), 3.10 (1 H, m, 6-H$_{ax}$), 5.08 (1 H, t, J 4.8, 5-H), 5.37 (1 H, m, 3-H), 5.69 (1 H, t, J 4.4, 4-H), 6.29 (1 H, d, J 16, 9-H), 6.39 (1 H, d, J 16, 18-H), 6.43 (1 H, d, J 16, 27-H), 7.22-7.42 (9 H, m, Ph-H), 7.66 (1 H, d, J 16, 10-H), 7.70 (1 H, d, J 15.9, 19-H), 7.79 (1 H, d, J 16, 28-H); $\delta_{C}$ (125 MHz, CDCl$_3$): 20.72 (C-41, C-42), 20.73 (C-43, C-44), 20.74 (C-45, C-46),
36.47 (C-2), 36.93 (C-6), 63.46 (C-4), 63.81 (C-3), 75.75 (C-5), 77.47 (C-1), 109.65 (C-12), 109.82 (C-21), 110.01 (C-30), 115.74 (C-9), 116.34 (C-18), 116.52 (C-27), 119.23 (C-15), 119.34 (C-24), 119.81 (C-33), 122.84 (C-16), 124.65 (C-25), 125.24 (C-34), 132.63 (C-11), 133.46 (C-20), 133.93 (C-29), 144.64 (C-10), 145.15 (C-19), 145.82 (C-28), 146.23 (C-13), 146.45 (C-22), 146.93 (C-31), 148.63 (C-14) 149.26 (C-23), 149.54 (C-32), 162.22 (C-8), 162.51 (C-17), 162.65 (C-26), 167.92 (C-35), 168.16 (C-37), 168.34 (C-39), 168.77 (C-36), 168.98 (C-38), 169.14 (C-40), 173.26 (C-7); MS, m/z (ESI): 935.2005 [M+ - C_{46}H_{40}O_{20} and C_{45}H_{40}O_{20} Na requires 935.2005]

(1R, 3R, 4S, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-3,4,5-tri-(acetylferuloyl) quinic acid, (109)-154

To a solution of Troc-quinide (0.300 g, 0.858 mmol) and DMAP (0.052 g, 0.429 mmol) in dichloromethane (5 ml) were added acetyl ferulic acid chloride (0.436 g, 1.716 mmol) in triethylamine (0.5 ml). The reaction solution was stirred for 16 hours at room temperature. The reaction solution was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic phase was dried with MgSO4, filtered and the solvent was removed under reduced pressure. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to afford (1R, 3R, 4S, 5R)-1-(β, β, β-trichloroethoxycarbonyl)-3,4,5-tri-
(acetylferuloyl) quinic acid (109) (0.085 g, 9.7%). Rf 0.91 [chloroform: acetone (8:2)]; $\nu_{\text{max}}$ (KBr)/cm$^{-1}$: 3510 (OH), 2958 (COOH), 2845 (C-H), 1764, 1719 (C=O), 1636 (C$_\text{Ar}$=C$_\text{Ar}$), 1259, 1198, 1123, 1088, 1033 (C-O); $\delta_H$ (400 MHz, CDCl$_3$): 2.27 (1 H, m, 6-H$_{\text{ax}}$), 2.29 (9 H, s, 44-H, 45-H, 46-H), 2.31 (1 H, m, 2-H$_{\text{ax}}$), 2.59 (1 H, dd, $J$ 12.8 and 2.4, 6-H$_{\text{eq}}$), 2.83 (1 H, dd, $J$ 14 and 2.4, 2-H$_{\text{eq}}$), 3.71 (3 H, s, 38-H), 3.82 (3 H, s, 39-H), 3.87 (3 H, s, 40-H), 4.72 (1 H, d, $J$ 11.9, 9-H), 4.80 (1 H, d, $J$ 11.9, 9-H$^1$), 5.34 (1 H, dd, $J$ 9.6 and 3.2, 4-H), 5.80 (1 H, m, 5-H), 5.81 (1 H, m, 3-H), 6.29 (1 H, d, $J$ 10.5, 12-H), 6.32 (1 H, d, $J$ 10.5, 21-H), 6.47 (1 H, d, $J$ 16, 30-H), 6.96-7.14 (9 H, m, Ph-H), 7.58 (1 H, d, $J$ 16, 13-H), 7.62 (1 H, d, $J$ 15.5, 22-H), 7.65 (1 H, d, $J$ 16, 31-H); $\delta_C$ (125 MHz, CDCl$_3$): 27.10 (C-44, C-45, C-46), 32.30 (C-6), 36.84 (C-2), 55.92 (C-38), 56.02 (C-39), 56.14 (C-40), 66.73 (C-5), 67.90 (C-3), 74.20 (C-4), 76.83 (C-9), 82.11 (C-1), 94.24 (C-10), 111.22 (C-15), 111.35 (C-24), 111.43 (C-33), 117.32 (C-12), 117.44 (C-21), 117.63 (C-30), 121.52 (C-18), 121.60 (C-27), 121.93 (C-36), 123.32 (C-19), 123.34 (C-28), 123.37 (C-37), 132.32 (C-14), 133.04 (C-23), 133.34 (C-32), 141.74 (C-13), 141.77 (C-22), 141.80 (C-31), 145.35 (C-17), 145.42 (C-26), 145.50 (C-35), 151.45 (C-16), 151.51 (C-28), 151.60 (C-34), 152.41 (C-8), 165.70 (C-11), 165.76 (C-20), 165.81 (C-29), 168.74 (C-41, C-42, C-43), 169.95 (C-7).

$\text{(1R, 3R, 4S, 5R)-1-}(\beta, \beta, \beta\text{-trichloroethoxycarbonyl})-3,4,5\text{-tri-(acetyl p-coumaroyl) quinic acid, (110)-p159}$
To a solution of Troc-quinide (0.300 g, 0.858 mmol) and DMAP (0.052 g, 0.429 mmol) in dichloromethane (5 ml) were added acetyl p-coumaric acid chloride (0.385 g, 1.716 mmol) in triethylamine (0.5 ml). The reaction solution was stirred for 16 hours at room temperature. The reaction solution was extracted with dichloromethane (50 ml) and 2M HCl (10 ml). The organic phase was dried with MgSO4, filtered and the solvent was removed under reduced pressure. The purification of compound carried out by flash chromatography on silica gel eluting with chloroform-acetone (8:2) to afford (1R, 3R, 4S, 5R)-1-(\(\beta\), \(\beta\), \(\beta\)-trichloroethoxycarbonyl)-3,4,5-tri-(acetyl p-coumaroyl) quinic acid (110) (0.113 g, 14.2%). Rf 0.88 [chloroform:acetone (8:2)]; \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\): 3481 (OH), 2957 (COOH), 1765, 1718 (C=O), 1636 (C\(_{Ar}=C_{Ar}\)), 1205, 1165, 1107 (C-O); \(\delta\)\(_{H}\) (400 MHz, CDCl\(_3\)): 2.12 (1 H, dd, \(J\) 14.9 and 12, 6-H\(_{ax}\)), 2.18 (1 H, m, 2-H\(_{ax}\)), 2.29 (9 H, s, 41-H, 42-H, 43-H), 2.57 (1 H, dd, \(J\) 12.8 and 4.2, 6-H\(_{eq}\)), 2.88 (1 H, dd, \(J\) 13.5 and 4.2, 2-H\(_{eq}\)), 4.57 (1 H, d, \(J\) 11.9, 9-H), 4.78 \(J\) (1 H, d, \(J\) 11.9, 9-H), 5.31 (1 H, dd, \(J\) 9.4 and 2.8, 4-H), 5.78 (1 H, m, 5-H), 5.80 (1 H, m, 3-H), 6.26 (1 H, d, \(J\) 8.8, 12-H), 6.28 (1 H, d, \(J\) 8.8, 21-H), 6.44 (1 H, d, \(J\) 16, 30-H), 7.02-7.50 (12 H, m, Ph-H), 7.57 (1 H, d, \(J\) 16, 13-H), 7.58 (1 H, d, \(J\) 15.9, 22-H), 7.59 (1 H, d, \(J\) 16, 31-H); \(\delta\)\(_{C}\) (125 MHz, CDCl\(_3\)): 21.19 (C-42, C-43), 21.22 (C-41), 32.40 (C-6), 36.71 (C-2), 66.73 (C-5), 67.92 (C-3), 71.83 (C-4), 76.80 (C-9), 81.14 (C-1), 94.24 (C-10), 117.10 (C-12), 117.33 (C-21), 117.66 (C-30), 122.17 (C-Ph), 122.25 (C-Ph), 129.51 (C-Ph), 129.58 (C-Ph), 131.85 (C-Ph), 132.06 (C-Ph), 144.88 (C-17), 144.94 (C-26), 145.09 (C-35), 152.43 (C-8), 165.67 (C-11), 165.77 (C-20), 165.84 (C-29), 169.13 (C-38, C-39, C-40), 169.97 (C-7).
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Chapter 6
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