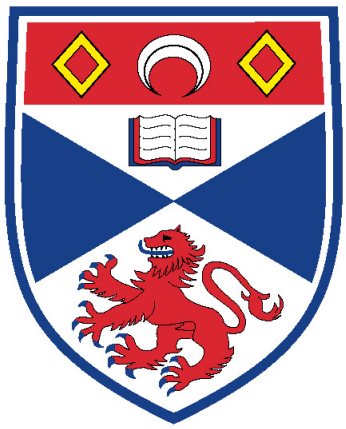
Studies on the synthesis of dicaffeoylquinic acid conjugates



University
of
St Andrews

School of Chemistry and
Centre for Biomolecular Sciences

Kolawole Saki Raheem

May 2011

Thesis submitted to the University of St Andrews in application for the degree of Doctor of Philosophy

Supervisor: Dr Nigel P. Botting

STUDIES ON THE SYNTHESIS OF DICAFFEOYLQUINIC ACID CONJUGATES

Kolawole Saki Raheem

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews

2011

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To my father,
Thanks for your love and support

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Abbreviations

Ac_2O	Acetic anhydride
BF_3-OEt_2	Boron trifluoride diethyl etherate
BnBr	Benzyl bromide
bw	Body weight
CA	Caffeic acid
CCl_3CN	Trichloroacetonitrile
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
COSY	Correlation Spectroscopy
Cs_2CO_3	Cesium carbonate
CQA	Caffeoylquinic Acid
DAHP	3-Deoxy-D-arabino-heptulosoni acid 7-phosphate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEIPS	Diethylisopropylsilyl
DHQ	Dehydroquinic acid
DCQA	Diccafeoylquinic acid
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
Bu_2SnO	Dibutyltin oxide
eq	Equivalents(s)
EI	Electron Impact
ESI	Electrospray Ionisation
Et_3N	Triethylamine
EtOAc	Ethyl acetate
et al.	*Et alia* (Latin), and others
FA	Ferulic acid
FQA	Feruloylquinic acid
GC/MS	Gas Chromatography/mass Spectrometry
h	Hours
HF-pyridine	Hydrogen fluoride pyridine complex
HIV	Human Immunodeficiency Virus
HMBC	Heteronuclear Multiple Bond Connectivity
HSQC	Heteronuclear Single Quantum Coherence
HPLC	High Performance Liquid Chromatography
HBV	Human Hepatitis B virus
Hz	Hertz
IR	Infrared
J	Coupling constant (Hz)
KCN	Potassium cyanide
K_2CO_3	Potassium carbonate
Kg	Kilogram
LDL	Low Density Lipoprotein
LiOH	Lithium Hydroxide
Lit.	Literature
i-Pr3Si	*tri*-Isopropylsilyl

iv	Intravenous
µg	Microgram
MeOH	Methanol
MHz	Megaherz
ml	Millilitre
mmol	Millimole
mol	Mole(s)
mp	Melting point
m/z	Mass over charge ratio (mass spectrometry)
NAD	Nicotinamide Adenine Dinucleotide
NaH	Sodium hydride
NaOH	Sodium hydroxide
NMR	Nuclear Magnetic Resonance
Pd	Palladium
Pd/C	Palladium on carbon
$Pd(OH)_2$	Palladium hydroxide
PEP	Phosphoenopyruvate
ppm	Parts per million
p-TsOH	*para*-Toluenesulfonic acid
p-CoQA	*p*-Coumaric acid
R_f	Retention factor
SHR	Spontaneously Hypertensive Rat
RSV	Respiratory Syncytial Virus
rt	Room temperature
TBS	*tert*-Butyldimethylsilyl
Bu_4NI	Tetrabutylammonium iodide
TBAF	Tetrabutylammonium fluoride
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TIPS	*tri*-Isopropylsilyl
TMB	Tetramethoxybutane
TsCl	Tosyl chloride
UDP	Uridine 5'-diphosphate
UDPGT	UDP-Glucuronosyltransferase

Abstract

Dicaffeoylquinic acid (DCQA) is a natural polyphenolic compound widely distributed in plants such as coffee beans, which possesses a range of pharmacological activities. Herein, is reported studies undertaken towards the first total synthesis of 3,5-DCQA conjugates. Two synthetic routes were investigated. The first route involves a seven step sequence beginning from quinic acid. The overall yield *via* this synthetic approach was 30%. The key steps involved in the sequence were a regioselective benzylation of the C-3-hydroxyl group followed by silyl protection of the C-1 and C-4 hydroxyl groups. Deprotection of the benzyl group by hydrogenolysis and opening of the lactone afforded the 3,5-diol. Esterification of the 3,5-diol with 3,4-*tert*-butyldimethylsilyl caffeoyl chloride afforded the di-ester. Removal of the protecting groups afforded 3,5-DCQA. The second route involved selective protection of the C-3-hydroxyl group with silyl followed by benzylation of the C-1 and C-3 hydroxyl groups. Saponification of the lactone ring followed by benzylation of the carboxylic acid gave the benzyl ester. Silyl deprotection afforded the 3,5-diol. The 3,5-diol was subsequently esterified by refluxing in toluene with commercially available Meldrum's acid. In the final step, the synthesis of 3,5-DCQA was achieved by a Knoevenagel condensation of 3,4-dihydroxybenzaldehyde and a malonate ester of quinic acid. An efficient method for the synthesis of possible metabolites of quinic acid conjugates was also described. This protocol employs *N*-(4-methoxyphenyl)-trifluoroacetimidate glucuronyl as the donor. The key reaction in this sequence was the coupling of *N*-(4-methoxyphenyl)-trifluoroacetimidate glucuronyl with 4-hydroxy-3-methoxy-benzaldehyde.

Contents

Chapter One

1.0 Introduction

1.1 Caffeoylquinic Acid Chemistry and Natural Occurrence

1.1.1 Discovery

Caffeoylquinic acid (CQA) derivatives were first reported in 1837. 3-Caffeoylquinic acid (3-CQA) **1**, initially known as chlorogenic acid, was the first to be reported. The trivial name chlorogenic acid was first introduced in 1846. (Figure 1).[1] Eliel and Ramirez have indicated an alternative nomenclature.[2] However, through this thesis the historic nomeclature was used as shown in Figure 1, numbering anticlockwise from carbon 1.

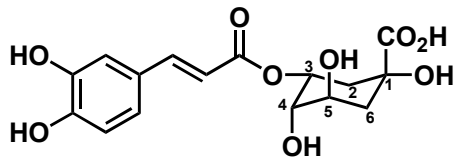

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Figure 1. Chemical *structure of 3-CQA **1**.*[1]

CQA derivatives are formed naturally by esterification of hydroxycinnamic acids, caffeic acid **2** ferulic acid, **3**, and *p*-coumaric acid **4** (*p*-CoQA), with quinic acid **5** (Figure 2).[3, 4]

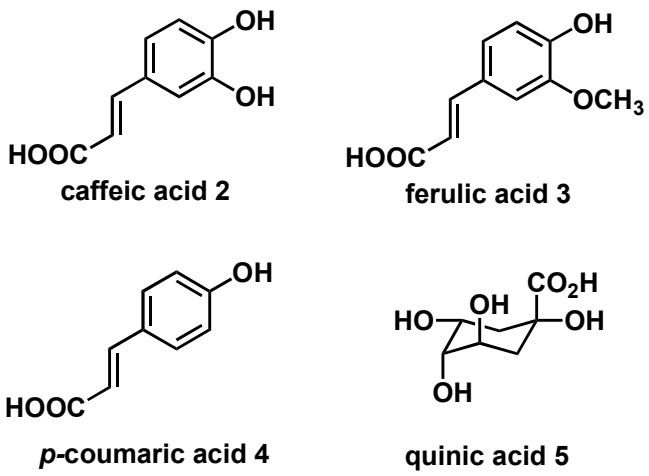
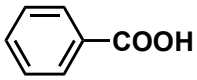
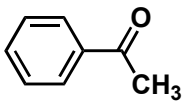
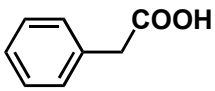
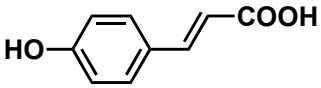
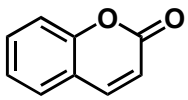
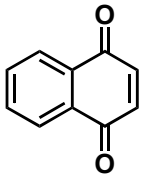
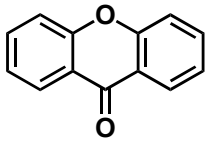
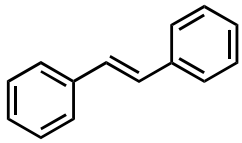
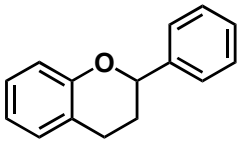


Figure 2 *Chemical structures of caffeic acid* ***2,*** *ferulic acid* ***3****, p-coumaric acid* ***4*** *and quinic acid* ***5***.[3]

CQA derivatives are a class of natural polyphenolic (e.g. polyphenolic Table 1) compounds widely distributed in plants[4] such as *Tanacetum parthenium,*[5] sweetpotato leaf,[6] *Eleutherococcus senticosus,*[7] *Chrysanthemum coronarium L*,[8] *Phyllostachys edulis,*[9] *potato,*[10] *sweet potato*[11, 12] and *Ipomoea batatas L.*[13] CQA derivatives are also found in olives, fruits, vegetables,[14] and coffee beans.[15, 16] The most abundant natural source are coffee beans, which contain more than eighteen caffeoyl derivatives that are not acylated at the C-1 position.[3]

***Table 1**. Basic structural skeletons of phenolic and polyphenolic compounds.*[17]

Skeleton	Classification	Basic structure
C_6-C_1	Benzoic acid	
C_6-C_2	Acetophenones	
C_6-C_2	Phenylacetic acid	
C_6-C_3	Hydroxycinnamic acid	
C_6-C_3	Coumarins	
C_6-C_4	Naphthoquinones	
C_6-C_1-C_6	Xanthones	
C_6-C_1-C_6	Stilbenes	
C_6-C_3-C_6	Flavonoids	

CQA derivatives can be subdivided by the identity, number and position of the acyl residues.[18, 19] The following subgroups are known:

1.1.2 Mono-ester

3-CQA **1** is a mono-ester of caffeic acid **2**, which is the only commercially available compound. 5-CQA **6** and 4-CQA **7** are synonymous with neochlorogenic acid and cryptogenic acid and the two names are often used interchangeably. 4-*O*-Feruloylquinic acid **7** (FQA), 3-FQA **9** and 5-FQA **10** are monoferuloylquinic acids. The structures of some of the CQA and FQA are shown in Figure 3.[20]

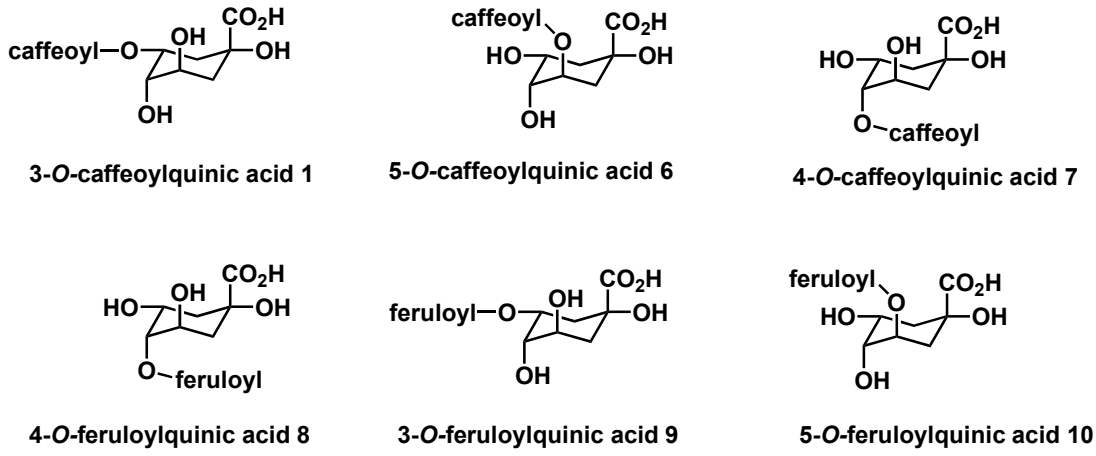
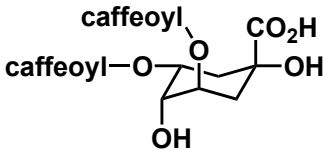


Figure 3. *Structure of CQA and FQA derivatives.*[20]

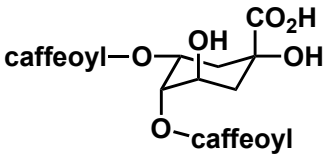
1.1.3 Di-esters

Three di-esters, 3,5-dicaffeoylquinic acid **11** (DCQA), 3,4-DCQA **12** and 4,5-DCQA **13**, have been isolated from plants. Methyl esters of 3,5-DCQA **11** and 4,5-DCQA **13** have been also found to occur naturally in plants. 3,5-DCQA **11** and 4,5-DCQA **13** can be formed from 3-CQA **1** because most of

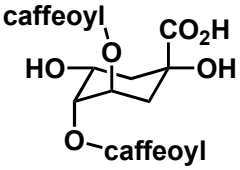
the CQAs have a caffeoyl group at C_3-OH.[20] 4,5-DCQA **13** is more abundant in nature than 3,5-DCQA **11**. 1,3-DCQA **15** is the least common of all the DCQAs with the caffeoyl group attached to the tertiary alcohol (C_1-OH). In 2005 Kim *et al.*[21] reported the first isolation of 1,3-DCQA **15**. The most common moiety of DCQA is the caffeoyl, however other phenulpropanoids such as 1,3-FQA **16** exist (Figure 4). The mixed di-esters of caffeic acid **2** ferulic acid **3**, e.g 3-*O*-caffeoyl-4-*O*-feruloylquinic acid **17** 3-*O*-caffeoyl-*5*-*O*-feruloylquinic acid **18**, and 4-*O*-caffeoyl-*O*-feruloylquinic acid **19** can be found in robusta coffee.[21, 22]



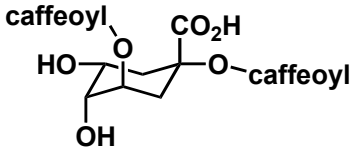
3,5-di-*O*-caffeoylquinic acid 11



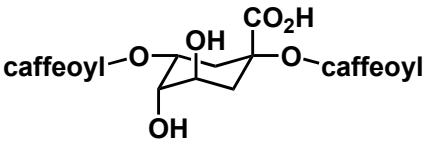
3,4-di-*O*-caffeoylquinic acid 12



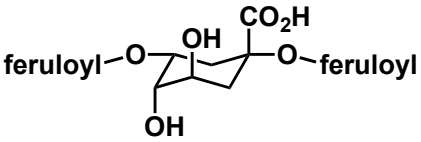
4,5-di-*O*-caffeoylquinic acid 13



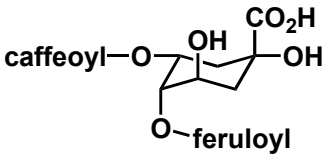
1,5-di-*O*-caffeoylquinic acid 14



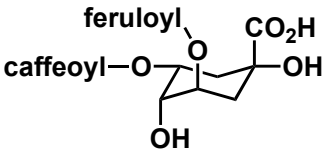
1,3-di-*O*-caffeoylquinic acid 15



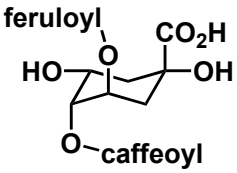
1,3-di-*O*-feruloylquinic acid 16



3-*O*-caffeoyl-4-*O*-feruloyquinic acid 17



3-*O*-caffeoyl-5-*O*-feruloyquinic acid 18



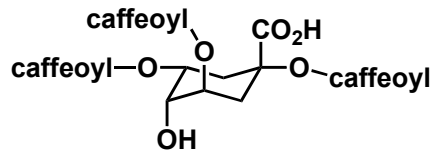
4-*O*-caffeoyl-5-*O*-feruloyquinic acid 19

Figure 4. *Structure of di-esters.*[20]

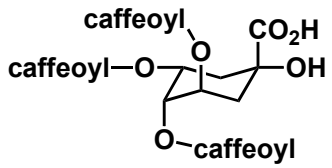
1.1.4 Tri and Tetra-esters

Tri- and *tetra*-caffeoylquinic acid (*tri*-CQAs and *tetra*-CQAs) are less common in nature than CQAs and DCQAs. 1,3,4-tri-CQA **20** has one *tert*-hydroxyl and two *sec*-hydroxyls of the quinic acid esterified, and in 3,4,5 *tri*-CQA **21**, every

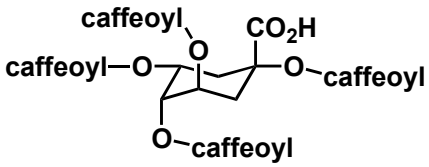
secondary hydroxyl group is coupled with a caffeoyl moiety. 1,3,4,5-*tri*-CQA **22** has one *tert*-hydroxyl and three *sec*-hydroxyl groups of the quinic acid esterified (Figure 5).[20]



1,3,4-tri-*O*-caffeoylquinic acid 20



3,4,5-tri-*O*-caffeoylquinic acid 21



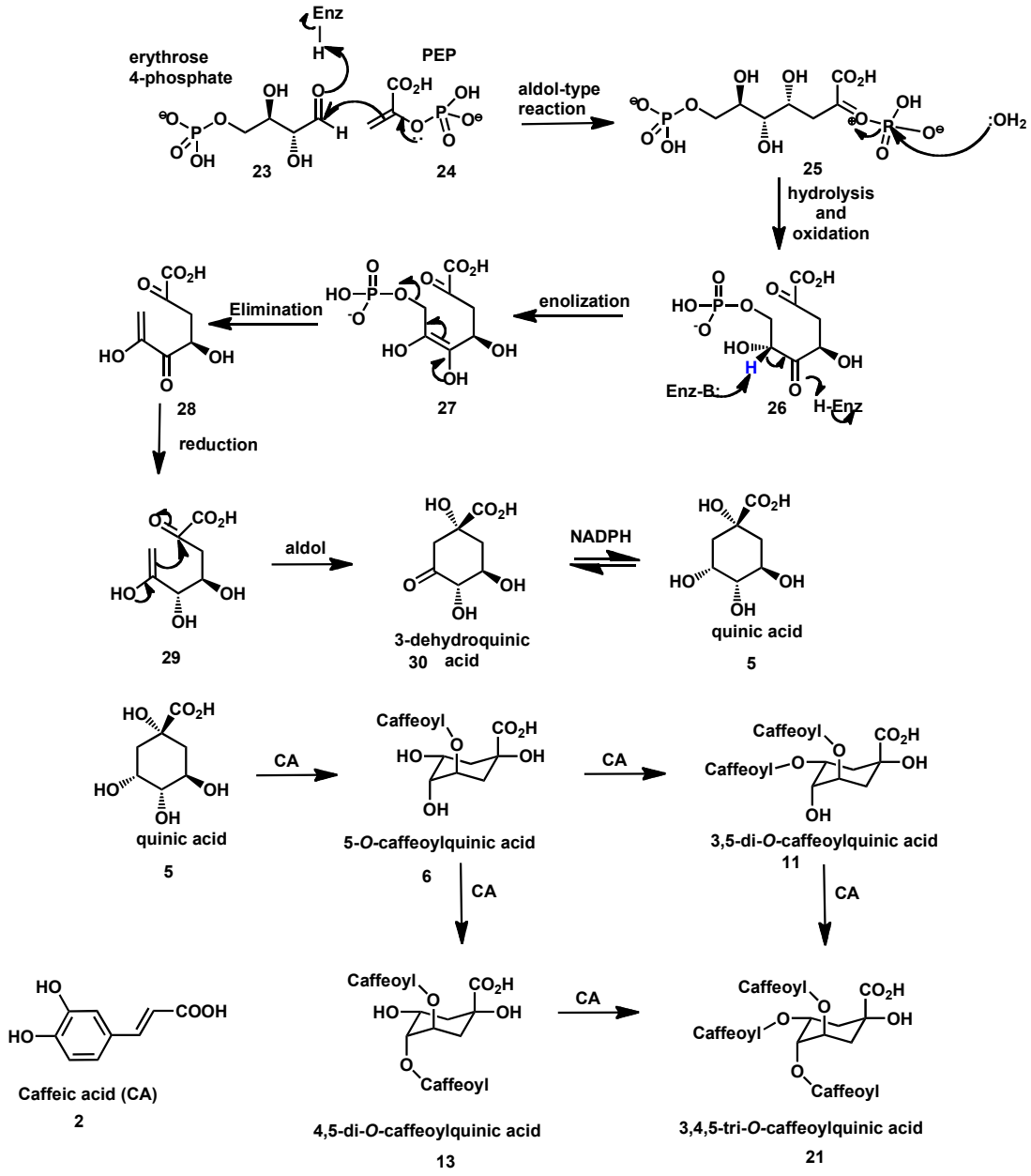
1,3,4,5-tetra-*O*-caffeoylquinic acid 22

Figure 5. *Structure of tris-CQAs and tetra-CQAs derivatives.* [20]

1.2 Caffeoylquinic Acid Biosynthesis

CQA derivatives are biosynthesised *via* the shikimic acid pathway (Scheme 1). Quinic acid **5** is the reduction product of 3-dehydroquinic acid **30**. The proposed biosynthesis of CQA starts with the coupling of phosphoenopyruvate (PEP) **24** and D-erythrose-4-phosphate **23** to give 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DAHP) **25**. Hydrolysis of the phosphate releases the C_7 α-keto-acid **26**. Removal of the hydrogen at C-6 could be problematic since it is not at all acidic. In this case, the hydroxyl group at C-5 is initially oxidised to a ketone (NAD^+ oxidation) and increased acidity of the C-6 proton promotes an *E1cB* elimination followed by an intramolecular cyclisation. Reduction of the cyclised product, 3-dehydroquinic acid **30**, leads to quinic acid **5**.[23-29] In the final steps, esterification of the

caffeic acid moiety on various hydroxyl groups of quinic acid gives *mono-, di-, tri-,* and *tetra-* CQA derivatives (Scheme 1).[20]



Scheme 1. *Proposed biosynthesis of CQA derivatives.*[20]

1.3 Caffeoylquinic acid in foods & beverages

1.3.1 Coffee

The origin of the coffee crop can be traced back to the Ethiopian highlands (today Yemen) as early as 14th century. Moreover, the Arabic textbook the *Encyclopedia of Islam* suggests that coffee was used as a beverage in 14th Century, and spread to the Middle Eastern countries in the 15th Century and across the Arabian Sea to India.[30, 31]

The coffee plant belongs to the family Rubiaceae and genus *Coffea*. Coffee is one of the world's most popular beverages,[32-34] and comprises about 1% of the overall value of world trade. It is the second most important trade commodity in the world after oil.[35] In 2004-2005 the total world coffee production was 6.9 million tons, valued at 11.2 billion US dollars.[32, 36] It has been reported that 100 million people work in the industry, growing, processing and marketing coffee, and that the crop is being grown by 25-30 million coffee farmers across 68 countries.[30]

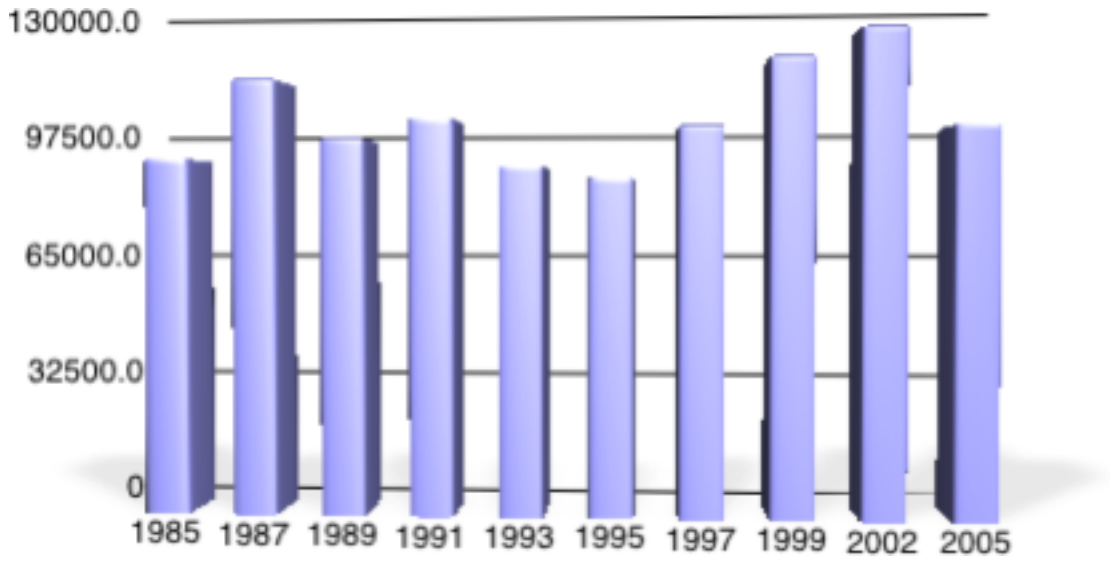


Figure 6. *Total world coffee production, 1985-2005 (60 kg bags x 1000).*[30]

In the last 150 years coffee production has grown significantly. The market price of coffee is rising due to increased demand in developed countries. In the past, increase in price was attributed to either natural disasters or political influence. In 1963, the United Nations established the International Coffee Organization, which represents both exporting and importing countries, and aims to provide price stabilisation. The 2007 International Coffee Agreement unites 77 member countries (45 producers and 32 importers). The Agreement is an instrument to facilitate international coffee trade, to provide a legal framework for inter-governmental cooperation, and is particularly focused on the needs of the least developed member-countries and small scale producers.[30, 37, 38]

About 70% of the world's coffee production comes from 25 million small-scale farmers. Therefore, fluctuations in market prices have a strong impact on the economies of the least developed countries and strongly affect the revenue of millions of small-scale producers in Latin America, Africa and

Asia. Since the value of the world retail trade increased from 30 to 70 billion US dollars (1993-2003), and the earnings of coffee-exporting countries fell from 12 to 5.5 billion US dollars at the same time, it is important to provide a sustainable international coffee market.[36, 37]

Two main types of coffee trees have great commercial importance, *C. arabica* which accounts for 90% of the world market and *C. canephora* (also know as robusta coffee) accounting for 10%.[17, 34, 39-42] *C. arabica* coffee is favoured by consumers due to its more subtle flavour which tends to be less bitter.[18, 35]

According to Clifford *et al.*[43] the most important source of caffeoyl derivatives are green coffee beans which contain about 6-10% 3-CQA **1** on a dry weight basis.[43, 44] 3-CQA **1** is the most abundant caffeoyl derivative found in green beans accounting for 50% of the total weight, alongside 4-CQA **7**, 1,3-FQA **15** and 3,4-DCQA **12**, 3,5-DCQA **11** and 4,5-DCQA **13**.[1] In 2006, Clifford *et al.* found many minor mono-acyl and diacyl 3-CQA derivatives in green coffee beans, this also included *p*-coumaric acid **4** and caffeic acid **2** and a series of amino acid conjugates.[43] Tests have also shown that robusta coffee has a greater content of 3-CQA 1 than arabica.[45, 46]

1.3.1.1 Coffee Field Processing

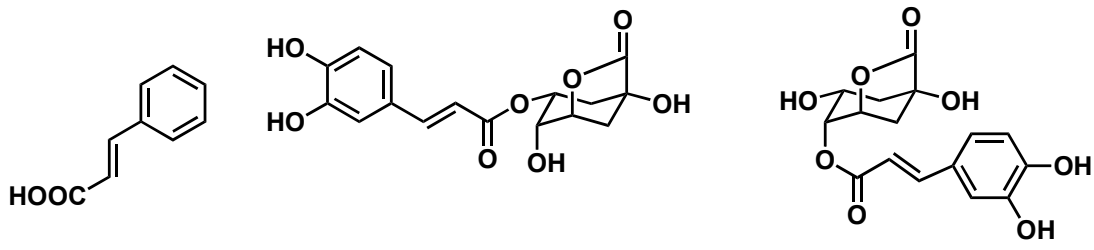
After harvesting, coffee berries can be processed in two different ways: dry- or wet-processes. The dry process, also known as the natural method, involves drying the whole fruit. The coffee berries are sorted and cleaned,

then dried in the sun for up to 4 weeks until they reach a maximum moisture content of 12.5%. This is a key stage of the process and determines the final quality of the coffee. Next, the dried fruit is hulled and the seeds (beans) are ready for grading and packing as green coffee. Most of the robusta coffees are processed by the dry-method and these are also known as unwashed robusta.[45, 47, 48] This method is also used for 90% of arabica coffee in dry regions with low humidity such as Brazil, Ethiopia, Haiti and Ecuador.[45]

The wet-process is known as the "washed method". Shortly after harvesting the coffee, cherries are sorted and cleaned and the outer layers of the fruit are removed by pulping. In the next step, the beans undergo a fermentation process (24-36 h) in which the remaining mucilage is removed by natural enzymes. In the final stage the coffee berries are hulled and go through sorting and grading processes. The wet-process yields mild coffee and is used for arabica coffee. This type of coffee, also known as washed arabica, has the best quality and the highest price.[45, 47, 48]

Next, coffee beans are roasted at air temperatures as high as 230 ºC for a few minutes, or at 180 ºC for up to 20 minutes. During this roasting process, up to 8-10% of the 3-CQA **1** is transformed.[49] A study conducted by Clifford showed that coffee beverages are the major dietary source of 3-CQA.[50] In fact, in the early stages of the roasting process, when there is still plenty of water, isomerisation *via* acyl migration occurs followed by some hydrolysis, releasing cinnamic acid **31** and quinic acid **5**. In the later stages the free

quinic acid **5** isomerises and lactonises to form 3-*O*-caffeoyl-1-quinide **32** and 4-*O*-caffeoyl-1-quinide **33** (Figure 7).[51, 52]

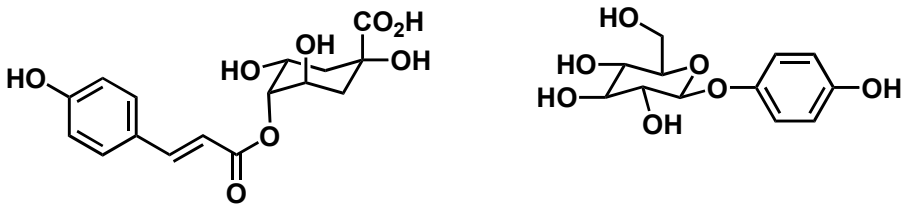


cinnamic acid 31 **3-caffeoyl-1,5-quinide 32** **4-caffeoyl-1,5-quinide 33**

Figure 7. *Structure of CQA derivatives in coffee beverage.*[52]

1.3.2 Fruits

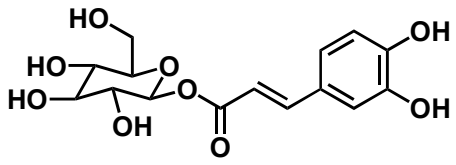
CQs derivatives have also been found in apples and pears.[53] A study conducted by Galvis-Sanchez *et al.*[54] showed that the total phenolic content in pears is between 1235 and 2500 mg/kg in peel and 28-81 mg/kg in flesh. The phenolic composition of pears is similar to that of apples with both containing 3-CQA **1**, and 4-*O*-*p*-CoQA **34**.[55] However, the main difference is that pears contain 1-hydroxyphenyl-4-*O*-glucoside **35** and apples dihydrochalcones (Figure 8).[20]



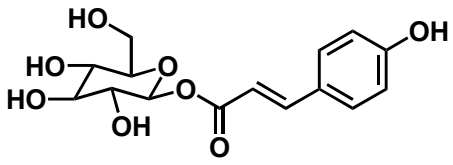
4-O-*p*-Coumaroylquinic acid 34 **1-hydroxyphenyl-4-*O*-glucoside 35**

Figure 8. Phenolic composition of pears.[17]

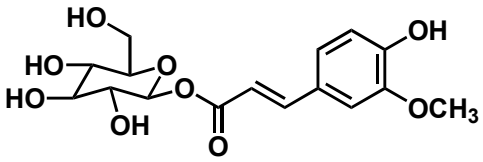
According to Spanos *et al.*[56] apples contain 62-385 mg/kg of 3-CQA **1**, up to 40 mg/kg 4-*O*-*p*-CoQA and some amounts of caffeoylglucose **36**, *p*-coumaroylglucose **37** and feruloylglucose **38** (Figure 9).



caffeoylglucose 36



***p*-coumaroylglucose 37**



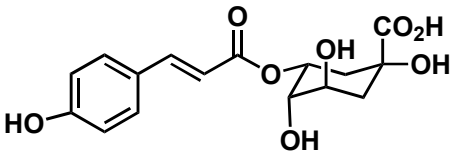
feruloylglucose 38

Figure 9. *Structure of caffeoylglucose **36**, p-coumaroglucose **37**, and feruloylglucose **38**.*[17]

Stone fruits contain 3-CQA **1** and 4-*O*-*p*-CoQA **34** in about 150-600 mg/kg and 3-200 mg/kg, respectively, at least in cherries found mainly adjacent to the peel. Levels of 3-CQA **1** were 3 to 4 times greater than 5-CQA **6** in peach and apricot juice.[1]

1.3.3 Vegetables

Vegetables contain a variety of caffeoyl derivatives e.g. 3-CQA **1** and 5-CQA **5**, 3 4-*O*-*p*-CoQA **39**, 3-CQA **1** and 3,5-DCQA **11** (Figure 10). A study by Alasalvar *et al.*[57] showed that 3-CQA **1** can be found in orange, purple, yellow and white carrots, with the levels of 3-CQA **1** in purple carrots being 10-fold higher than that amount present in the other varieties.[57]



3-O-*p*-coumaroylquinic acid 39

***Figure 10**. Phenolic composition in vegetables*.[17]

In 1983, Winter *et al.*[23] found 3-CQA **1**, 3-*O*-*p*-CoQA **39** and 3-FCQA **21** in the leafy Brassicas (kale, cabbage and brussels sprouts) at levels of 6-120 mg/kg, 104 mg/kg and up to 37 mg/kg respectively along with different amounts of the 4- and 5-isomers. Winter *et al.*[23] also reported a greater amount of sugar derivatives with feruloylglucose **38** dominating with levels up to 350 mg/kg in kale in red cabbage and radish, cinnamoyl esters of anthocyanins.[17]

1.3.4 Cider and Beer

Cider is one of the most popular alcoholic beverages in developed countries and is produced by yeast fermentation of apples (*Malus domestica*).[17] A study conducted in England showed that cider contains 44 mg/L of phenolic compounds.[58] Furthermore, the study revealed that the major components were 5-CQA **1** and procyanidins, (+)- catechin **40**, (-)-epicatechin **41**, the dihydrochalcones phloretin-2'-*O*-glucoside (phloridzin) **42**, and phloretin-2'-*O*-(2''-*O*-xylosyl)-glucoside **43**, hydroxycinnamates (Figure 11).[17]

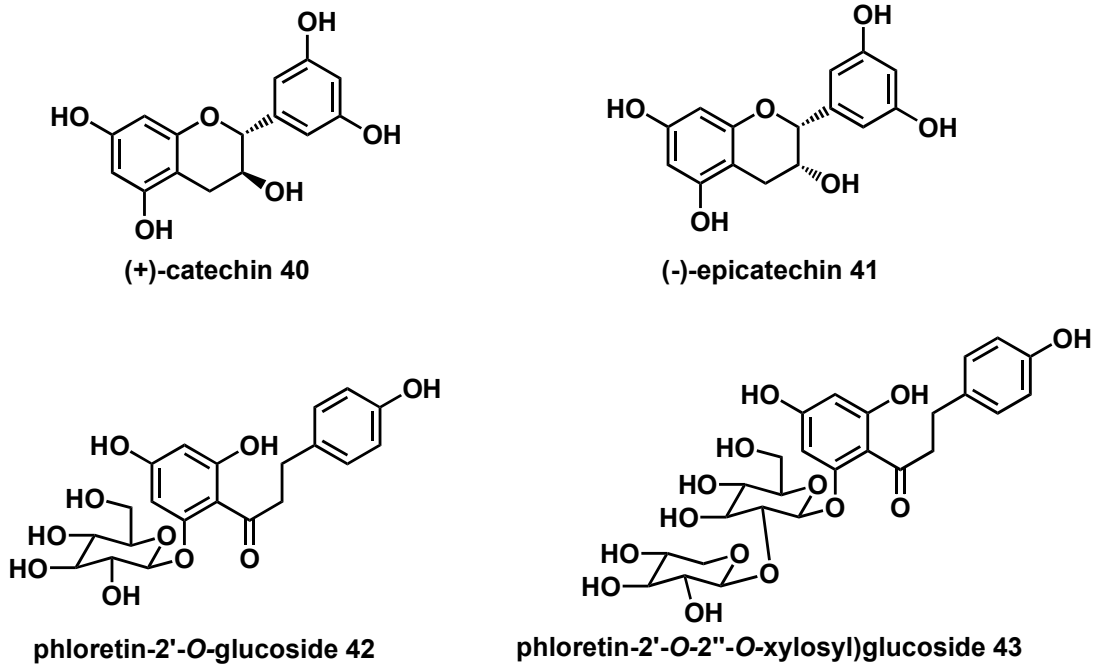


Figure 11. *Phenolic composition of cider.*[17]

Beer is another popular alcoholic beverage made from malted grains, barley (*Hordeum vulgae*), hops (*Humulus lupulus*), yeast (*Saccharomyces spp*) and water. In fact, beer contains a variety of phenolic and polyphenolic compounds. Flavan-3-ols **44** can be found in both hops and malt. These include monomers, for example (+)-catechin **40**, and (-)-epicatechin **41**, and the dimers procyanidin B1 **46**, and procyanidin B3 **47**. 3,4-dihydroxybenzoic acid (protocatechuic acid) **45**, caffeic acid **2**, and ferulic acid **3** are found in malt.[17]

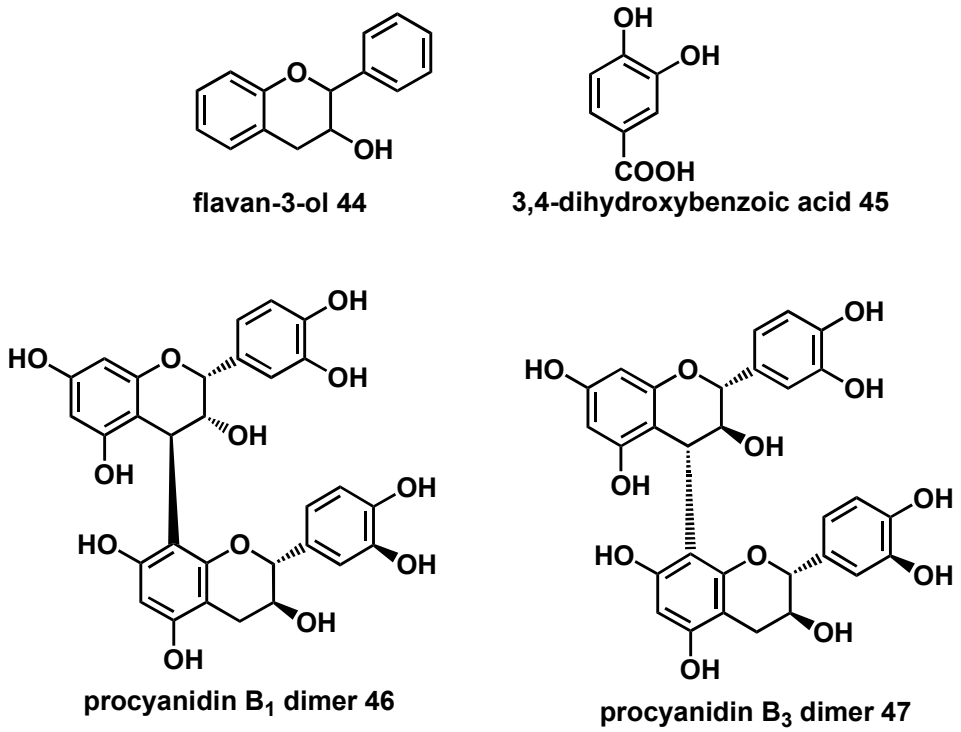


Figure 12. *Flavonols composition of beer.*[17]

1.4 Pharmacological effects of caffeoylquinic acid derivatives

CQA derivatives possess a wide range of pharmacological properties, including antiviral, antioxidant, antibacterial, and antihistaminic activities.[59] According to Saito *et al.*[60] their activity increases in proportion to the number of caffeoyl residues.

1.4.1 Antiviral effect of caffeoylquinic acid derivatives

CQA derivatives have been recognised as one of the most promising class of human immunodeficiency virus (HIV) integrase inhibitors.[61-65] Epidemiological study shows that HIV infects an estimated 33 million people globally and poses a significant healthcare challenge. In 1996 Robinson *et*

al.[66] reported selective inhibitory effect of DCQA derivatives for HIV-1 integrase. However, 3-CQA showed no anti-HIV activity.[63, 67]

Experiments conducted by Wang *et al.*[68] have shown that CQA derivatives act against the human hepatitis B virus (HBV), which is the major epidemiological agent of acute and chronic hepatitis. HBV carriers can develop cirrhosis and hepatocellular carcinoma. Wang *et al*.[68] used the HepG2.2.15 cell line to assess the antiviral activity of CQA derivatives. The results showed that 3-CQA **1** inhibited HBV replication in a dose-dependent manner *in vitro* and also *in vivo.*[68] However, the mechanism of action of 3-CQA **1** against HBV replication is still unknown.

In 2005 Ojwang *et al.*[69] reported that CQA can inhibit respiratory syncytial virus (RSV). RSV is the leading cause of severe lower respiratory tract infections in infants and children under 2 years of age. Statistical data had revealed that RSV is responsible for 40-50% of hospitalisations for bronchitis in the United States and 25% of pediatric hospitalisations for pneumonia.[69] The virus is an important factor in the development of otitis media infections and hyper-reactive airway disease in later life.[69] Epidemiological studies have revealed the impact of RSV mortality in the United States, showing 17,000 people died from RSV infection in 2005, with 80% of these deaths occurring in people over the age of 65. At present no vaccine is available for prophylactic use to prevent RSV infections. The only drug available for the treatment of the RSV infection is ribavirin, which is a nucleotide analogue. However, experimental studies have shown that ribavirin is teratogenic.[69]

Ojqang *et al.*[69] have demonstrated that 3,5-DCQA **11** can inhibit RSV *in vivo* and *in vitro*. This study showed that 3,5-DCQA **11** is a highly selective and potent inhibitor of RSV replication in tissue culture with activity against both the A and B subgroups of RSV. In a rat model, 3,5-DCQA **11** reduced the viral titre in the lungs of RSV-infected rats. The results from both *in vitro* and *in vivo* studies using 3,5-DCQA **11** demonstrated powerful antiviral activity against RSV, which was considered to be more effective than ribavirin. However, the mechanism of action of 3,5-DCQA **11** against RSV is still unclear.[69]

1.4.2 Antibacterial effect of caffeoylquinic acid derivatives

A study conducted in 2010 confirmed that *Streprococcus mutans*, a gram-positive bacteria that causes dental problems in humans, can be inhibited by CQA derivatives.[70] In this study it was found that 3-CQA **1** inhibits the growth of *S. mutans*, with a minimum inhibitory concentration of 0.8 mg/mL. Another study by Almeida *et al.*[71] showed antibacterial effects of CQA derivatives against *Enterobacterial* and *S. mutans.* Recently, Lee *et al* [72] have shown an anti-candidal effect of CQA derivatives in septic arthritis caused by *Candida albican* in mice.

1.4.3 Antioxidant effects of caffeoylquinic acid derivatives

Experimental studies have shown that oxidised low density lipoprotein (LDL) is a risk factor for developing cardiovascular disease because of its role in atherosclerosis. A study by Gordon *et al.*[73] has demonstrated that 3-CQA **1** can inhibit oxidative modification of LDL. It is well known that oxidation

processes promote a change in LDL particle structure, and oxidised LDL is taken up by the scavenger receptors of macrophages and not from normal LDL receptors. Oxidised LDL particles also initiate the expression of adhesion molecules, growth factors and cytokines, which are important factors in the progression of atherosclerosis.[74]

An in *vitro* study by Tanaka *et al.*[75] showed that 3-CQA **1** can decrease the incidence of chemical carcinogenesis in the colon and liver in animal models. The activity of 3-CQA **1** against chemical carcinogenesis can be related to its anti-oxidative and anti-inflammatory properties. Another study on the A549 human lung cancer cell line by Feng *et al.*[76] showed that 3-CQA **1** can up-regulate cellular antioxidant enzymes.

1.4.4 Antihypertensive effects of caffeoylquinic acid derivatives

Numerous studies have revealed the hypotensive effects of CQA derivatives. In experiments conducted by Woodiwiss *et al.*[77] a single injection of 3-CQA **1** (30-600 mg/kg) reduced blood pressure in spontaneously hypertensive (SHR) rats. Also, when a diet containing 0.5% 3-CQA **1** was administrated to rats for a period of 8 weeks, the development of hypertension was inhibited. In another study by Kagawa *et al.* [78] a single oral ingestion (50-200 mg/kg) of 3-CQA **1**, using SHR rats decreased blood pressure. Furthermore, the study revealed that the metabolites of 3-CQA **1** induced anti-hypertensive activities. The effect of chlorogenic acid as a anti-hypertensive agent has also been studied in humans. Watanabe *et al.*[79] 3-CQA **1** showed anti-hypertensive

effects against mildly hypertensive subjects, whose blood pressure dropped significantly.

Recent studies have shown the neuroprotective effect of 3,5-DCQA **11**. Kim *et al.*[80] described the anticarcinogenic effect of 3,5-DCQA **11** on hydrogen peroxide induced SH-SY5Y human neuroblastoma cytotoxicity.

In a study by Cho *et al.*[81] 3-CQA **1** an anti-obesity effect against high-fat diet obese mice was observed. In this study, Cho *et al.*[81] demonstrated that 3-CQA **1** can reduce body weight by 16%.

1.5 Metabolism of Caffeoylquinic Acid Derivatives

The mechanism and site of absorption of CQA derivatives are still debated and remain unconfirmed. However, several theories have been published.

Camarasa *et al.*[82] Choudhury *et al.*[83] Azuma *et al.*[16] Booth *et al.*[84] and Bourne *et al.*[85] reported the presence of caffeic acid **2** in the plasma of rats after dosing of 3-CQA **1**. In fact, Camarasa *et al.*[82] shows the presence of caffeic acid **2** in the plasma of rats and rabbits after dosing of 3-CQA **1** at 40 or 120 mg/kg bw and 10 mg/kg bw respectively. In rats the half-life of absorption was 4 min and the half-life for plasma clearance was just over 3 h. In rabbits given 10 mg/kg bw, a maximal plasma level of ~1 μg/ml was achieved within 30 min and declined steadily to about half that value over 4h,

whereas rats given 100 mg/kg bw achieved a plasma level of 85 μg/ml within 30 min.[86]

However, Gonthier *et al.*[87] Cremin *et al.*[88] Olthof *et al.*[89] and Rechner *et al.*[90] the reported the presence of both intact CQA and a variety of metabolites in the urine and plasma of rats. The detection of intact chlorogenic acid in the rodent urine indicated that it has been absorbed in its native form. In fact, Olthof *et al.*[89] recover 33% of chlorogenic acid in a gut using ileostommized volunteers. The Author, speculate that the low recovery of chlorogenic acid in urine can be explained by its hydrolysis in the body.

The proposed metabolic pathway of 3-CQA **1** is shown below (Figure 13). There is evidence that 3-CQA is not absorbed in the proximal part of the gut, but that it reaches, the large intestine where it is hydrolysed to caffeic acid **2** and quinic acid **5** by microflora, which exhibit esterase activities. Quinic acid **5** is further metabolised into hippuric acid **49**, which is formed by aromatisation of quinic acid **5** into benzoic acid **48** by the microflora and subsequent conjugation with glycine in the liver and kidney.[83, 87, 91-93] Caffeic acid **3** can also be metabolised into ferulic acid **3**, isoferulic acid **50,** 3,4-dihydroxyphenylpropionic acid **52**, and *m*-coumaric acid **51**. The hydroxylated derivatives of phenylpropionic, benzoic acid **48** and hippuric acid **49** derive from the metabolism of caffeic acid **2** by the gut microflora. 3-Hydroxyphenylpropionic acid **53** is further dehydroxylated to give the 3-hydroxybenzoic acid **54**. Conjugation of benzoic acid **48** with glycine leads to the formation of 3-hydroxylhippuric acid **55** and hippuric acid **49**. [83, 84, 87, 91, 92]

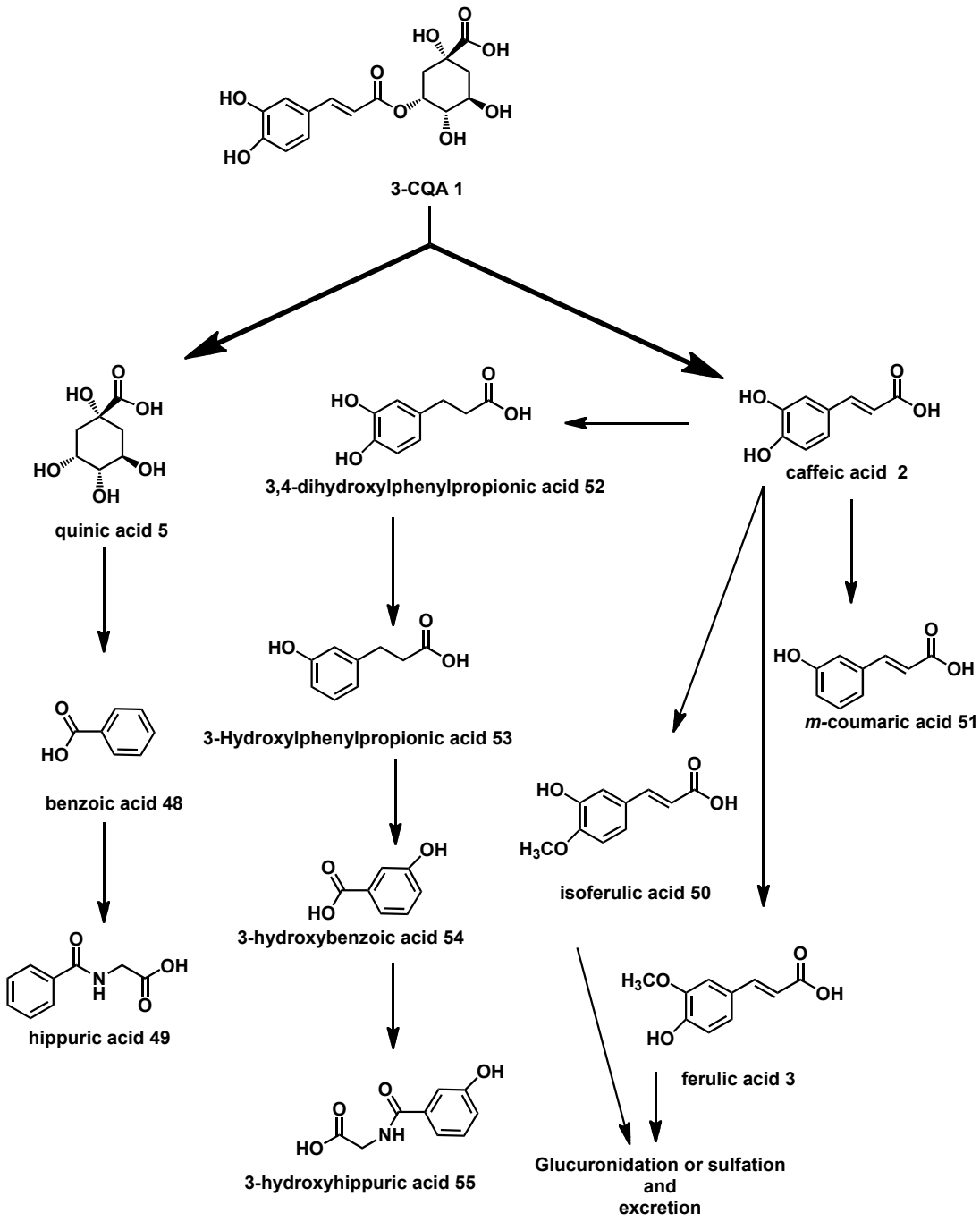


Figure 13. Proposed metabolic pathway of 3-CQA **1**.[87, 90]

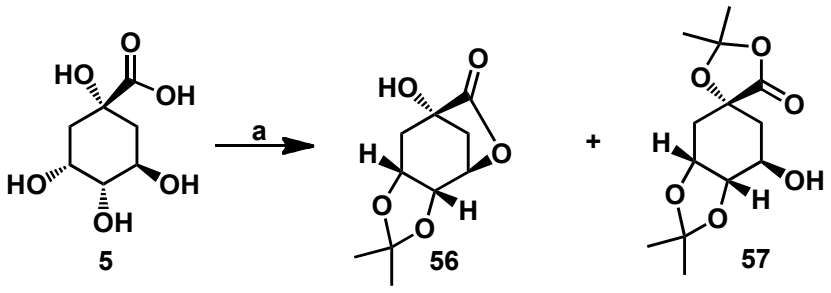
1.6 Previous synthesis of Caffeoylquinic acid Derivatives

In 1964, Haslam *et al.*[94] reported the first regioselective synthesis of 5-CQA **6** and 1-CQA **60**. 1-CQA **60** was synthesised from the acetone quinide **56** and

di-*O*-ethylcarbonate-protected caffeoyl chloride. However, neither the conditions used or the yields obtained for each stage in the protocol were reported in detail. 5-CQA **6** was obtained in six steps from **5** in a 5% overall yield.[94] Numerous reports have since appeared regarding the synthesis of CQAs.

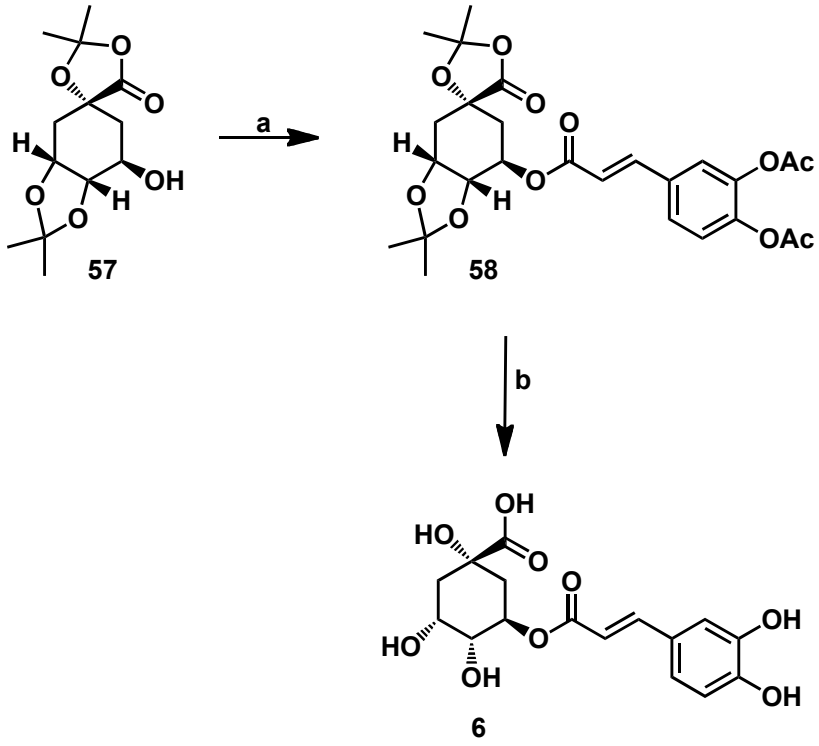
1.6.2 Synthesis of 1-, 4-, and 5-caffeoylquinic acids

In 2001, Sefkow *et al.*[95, 96] reported the total synthesis of 1-, 3-, 4-, and 5-CQAs starting from quinic acid **5**. The reaction of quinic acid **5** with 2,2-dimethoxypropane, *p*-toluenesulfonic acid monohydrate in acetone under reflux, afforded two products **56** and **57** with **56** being formed as the major product in a 82% and **57** the minor in an 8% yield (Scheme 2). Sefkow *et al.*[94] utilised this particular protecting group because it could be easily removed in the final steps of the synthesis in the present of ester. The unexpected synthesis of **57** paved the way for a synthesis of 5-CQA **6** because the C-4 hydroxyl group is left unprotected, and it could therefore be used in the coupling reaction to provide the 5-CQA **6**. In fact, an attempt to improved the yield of **57** without success.



Scheme 2. *Synthesis of quinide acetal **56** and bisacetonide **57** from quinic acid **5**. Reagents and conditions: a) $MeC(OMe)_2$, p-TsOH, acetone, reflux, 2 h, 92% and 8%.*

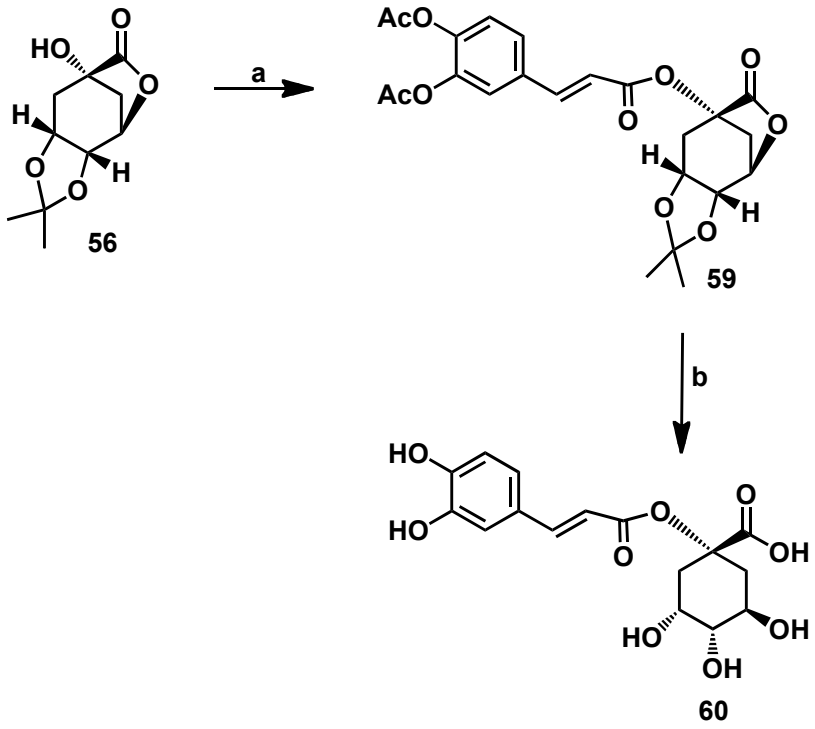
Esterification of **57** utilising 1.5 eq of di-*O*-acetylcaffeoyl chloride in CH_2Cl_2 at room temperature for 5 h afforded the ester **58** in a 92% yield. Global deprotection in the final step of the synthesis was achieved with 1 N aqueous HCl in 15% THF for 10 days to afford 5-CQA **6** in a 91% yield (Scheme 3). When 2 N aqueous HCl was used, esterification of caffeic ester **58** was observed.



Scheme 3. Synthesis[96] of 5-CQA, *Reagents and conditions: **a**) DMAP, CH_2Cl_2, di-O-acetylcaffeoyl chloride, pyridine, room temperature, 5 h, 91%. **b**) i) LiOH, THF-H_2O, ii) 2 N HCl, room temperature, 5 h, 79% over two steps.*

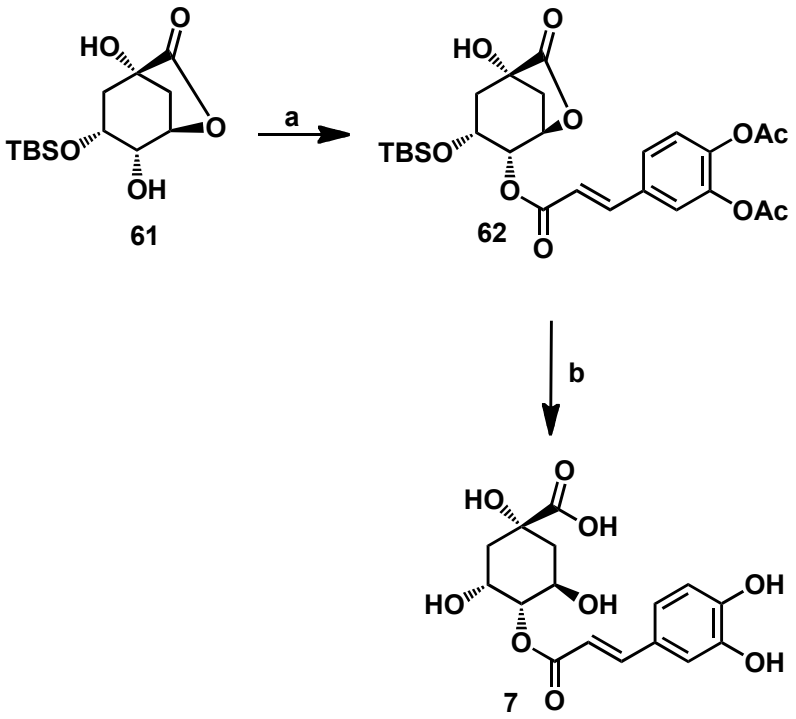
In the synthesis of 1-CQA **60**, acetone quinide **56** was reacted with the di-*O*-acetylcaffeoyl chloride to afford the ester **59** in a 58% yield (Scheme 2). Hydrolysis of **59** was achieved in two-steps with the lactone and acetate

protecting groups being cleaved using LiOH in THF-H_2O, while the removal of the acetal group was then accomplished using 2 N HCl, affording 1-CQA **60** in a 79% yield (Scheme 4).



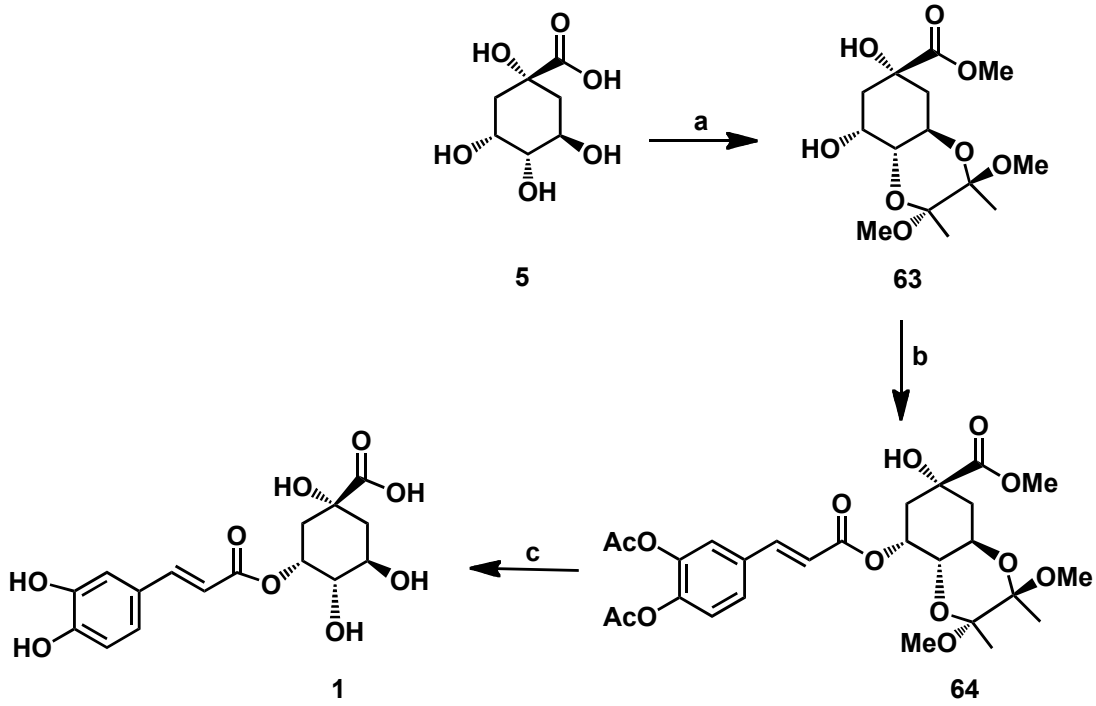
***Scheme 4**. Synthesis [96] of 1-CQA **60**. Reagents and conditions: **a**) di-O-acetylcaffeoyl chloride, pyridine, room temperature, 4 h, 58%; **b**) i) LiOH, THF-H_2O, ii) 2 M HCl, room temperature, 5 h, 79% over two steps.*

In a study conducted by Manthey *et al.*[97] differentiation of the secondary hydroxyl groups at C-4 and C-5 of the quinide was successfully achieved with *tert*-butyldimethylsilyl (TBS) chloride, yielding the silyl ether **61** in a 75% yield. Esterification of **61** utilising 1.2 eq of di-*O*-acetylcaffeoyl chloride in pyridine afforded the ester **62** in 55% yield. Global deprotection was accomplished with 1 N HCl at room temperature, affording 4-CQA **7** in an 83% yield (Scheme 5).



***Scheme 5**. Synthesis [96] of 4-CQA **7**. Reagents and conditions: **a**) di-O-acetylcaffeoyl chloride, pyridine, room temperature, 17 h, 55%; **b**) 1N HCl, room temperature, 6 days, 83%.*

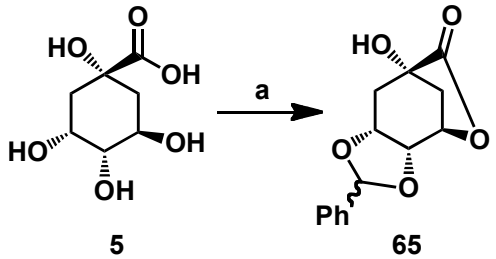
Protection of the C-3 and C-4 vicinal diequatorial hydroxyls was achieved using 2,2,3,3,-tetramethoxybutane (TMB). Selective esterification of the hydroxyl group at the C-5 was then carried out utilising 1.2 eq of di-*O*-acetylcaffeoyl chloride under standard conditions affording the ester **64** in an 88% yield. No esterification was observed at the C-1 hydroxyl group due to the steric effect. Global deprotection was accomplished with 1 N HCl to afford 3-CQA **1** in an 81% yield (Scheme 6). Hydrolysis of ester **64** was also observed in this reaction as described above.



***Scheme 6**. Synthesis [96] of 3-CQA **1** from quinic acid **5**. Reagents and conditions: **a**) i) Dowex 50 H^+, MeOH, refluxed, 15 h, ii) 2,2,3,3,-tetramethoxybutane, camphosulforic acid, reflux, 22 h, 81% **b**) di-O-acetylcaffeoyl chloride, pyridine, room temperature, 24 h, 88%; **c**)1N HCl, room temperature, 7 days, 81%.*

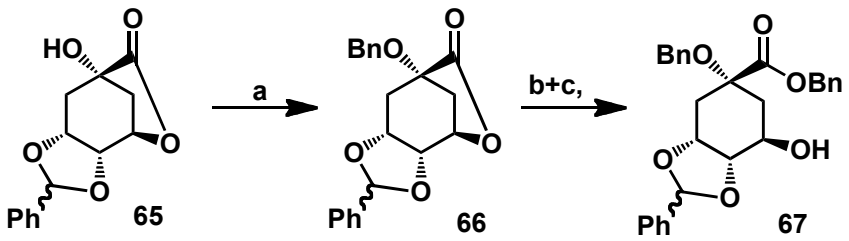
1.6.2 Synthesis of 5-O-feruloylquinic acid

In 2008 Smarrito *et al.*[98] reported the total synthesis of 5-feruloylquinic acid **10**. 5-*O*-feruloylquinic acid **10** was synthesised from commercially available quinic acid **5**. Compound **65** was obtained by reacting **5** with benzaldehyde and *p*-TsOH in toluene under reflux for 16 h to afford **65** in a 92% yield (Scheme 7).



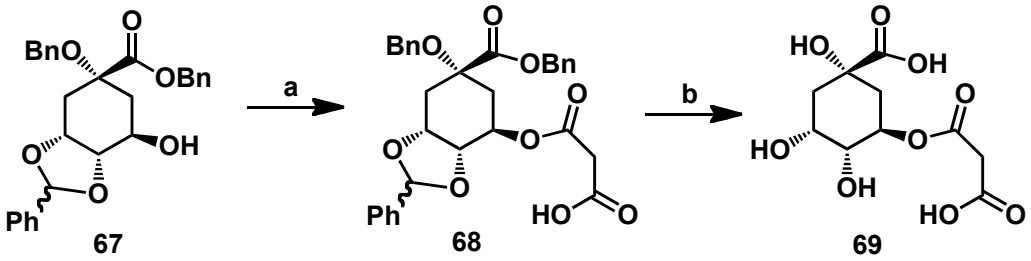
***Scheme 7**. Reagents and conditions: a) PhCHO, p-TsOH, toluene, reflux, 16 h, 92%.*

The C-1 hydroxyl group was benzylated using NaH and benzyl bromide in DMF to afford **66** in an 87% yield (Scheme 5). Hydrolysis of **66** was achieved with NaOH in THF-H_2O at room temperature. This was followed by benzylation of the resulting carboxylate using Cs_2CO_3 and benzyl bromide to afford the benzyl ester **67** in an excellent 94% yield (Scheme 8).



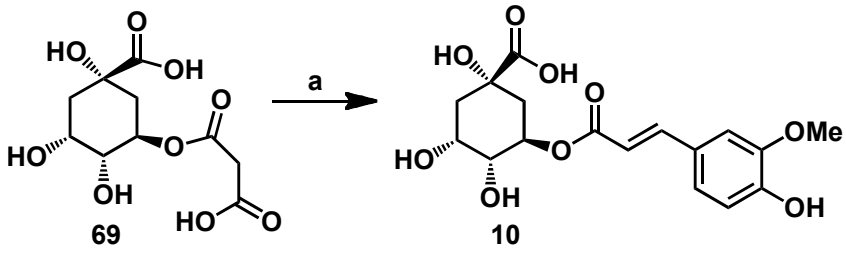
***Scheme 8**. Reagents and conditions: a) NaH, DMF, 0 °C, 30 min then BnBr, DMF, room temperature, 12 h, 87%; **b**) NaOH, THF-H_2O, room temperature, 40 min, quant; **c**) Cs_2CO_3, MeOH-H_2O, room temperature, 20 min then BnBr, DMF, room temperature, 8 h, **67**, 94%.*

The secondary hydroxyl group was esterified utilising Meldrum's acid, to afford the malonate **68** in a 92% yield. Deprotection of the benzyl groups was achieved with Pd/C 5%, in MeOH/H_2O to affording **69** in a 70% (Scheme 9).



***Scheme 9.** Reagents and conditions: **a**) Meldrum's acid, toluene, reflux, 3 h 30 min, 92%. **b**)H_2, Pd/C 5%, MeOH-H_2O, room temperature, 40 h, 70%.*

In the final step of the synthesis Smarrito *et al.*[98] employed the Knoevenagel condensation reaction utilising DMAP, vanillin and malonate **67** affording the target 5-*O*-feruloylquinic acid **10** in a moderate 40% yield (Scheme 10). The advantage of this methodology is that the aldehyde and quinic acid fragment are not required to be protected in the final step of the synthesis.



***Scheme 10**. Reagents and conditions: a) vanillin, DMAP, piperidine, DMF, room temperature, 7 days, **9** 40%.*

1.7 Aim of Research

The aim of this project was to obtain, by chemical synthesis, the potential human metabolites of 3,5-DCQA **11**. These compounds will be used as standards in order: i) to make other derivatives; ii) identify the potential human circulating forms of 3,5-DCQA **11** and iii) assess biological activity.

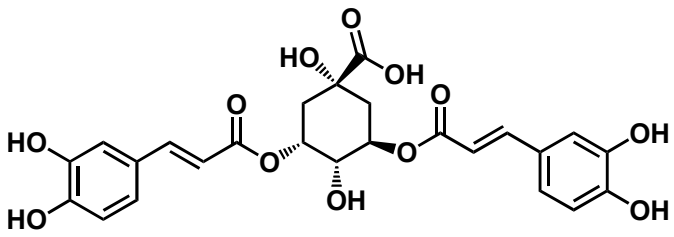


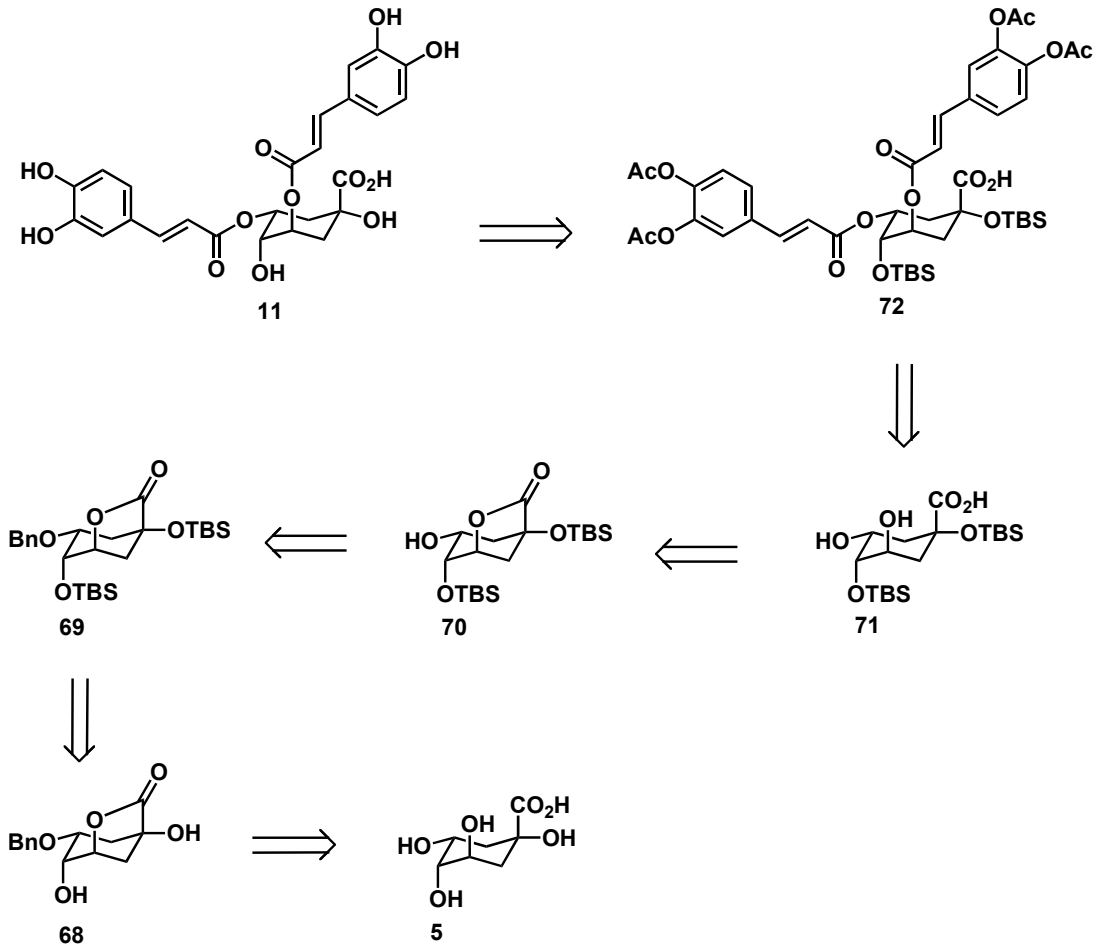
***Figure 14.** Structure of 3,5 DCQA **11**.*

As outlined previously 3,5-DCQA **11** is one of the constituents of coffee and artichokes extracts.[15] However, the metabolic pathway of this product in humans has never been studied in detail, although it is believed that caffeoylquinic esters in general, are cleaved into caffeic acid **3**, which is further metabolised.

However, recent studies have suggested through appropriate testing, that 3-CQA **1** could actually be absorbed intact, and that conjugated forms of 3-CQA **1** circulate in the plasma. The exact nature of the conjugates is uncertain in the absence of a fully characterised standard compounds hence it is likely that a similar situation occurs in the case of 3,5-DCQA **11**.

1.8 Retrosynthetic Analysis

The general approach to the synthesis of 3,5-DCQA **11** is illustrated, in retrosynthetic format, in Scheme 8. 3,5-DCQA **11** could be derived from advance intermediate **72** through a straightforward sequence of deprotections. It was envisaged that intermediate **72** could be formed in a single operation through an esterification reaction between **71** and caffeoyl chloride. Cleavage of the ester linkage in **72** could provide compound **71** as a potential precursor. Saponification of the lactone ring in **70** could secure intermediate **71**. Compound **69** could be formed from **68** using TBS ether protection, and diol **68** could be derived in two steps through a straightforward sequence of reaction from quinic acid **5**.

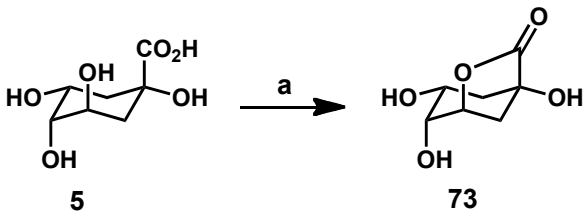


***Scheme 8**. Retrosynthetic approach to 3,5-DCQA.*

Chapter Two

2.1 Synthesis of 3,5-O-dicaffeoylquinic acid *via esterification*

In line with our synthetic plan, the synthesis of 3,5-DCQA **11** began with the preparation of quinide **73** (Scheme 9) a compound used previously as a key intermediate in number of syntheses of quinic acid derivatives.[99] Cyclisation of quinic acid **5** to the lactone **73** was achieved using *p*-toluenesulfonic acid monohydrate in a 1:5 mixture of DMF/toluene, according to the method of Kaila *et al*.[99] This afforded lactone **73** in excellent yield (Scheme 9). The structure of lactone **73** was confirmed by analysis of the ^{1}H NMR spectrum, which was found to be in close agreement with the literature data.[99] Further confirmation was provided by mass spectral analysis, which gave a signal at 174 Daltons, corresponding to the expected molar ion of $[M+H]^{+}$ $C_7H_{10}O_5$.

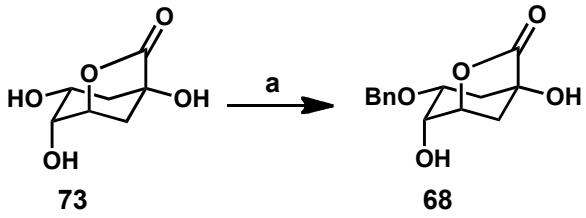


5 **73**

Scheme 9*. Reagents and conditions:* ***a)*** *p-TsOH, toluene, DMF, reflux, 12 h, Dean-Stark, 99%.*

Regioselective *O*-benzylation of the C-3 hydroxyl group was achieved by treatment of lactone **73** with dibutyltin oxide and benzyl bromide in toluene and DMF to afford diol **68** in a good 68% yield (Scheme 10). This yield was improved by the application of the conditions reported by Desai *et al*.[100] The use of dibutyltin oxide, tetrabutylammonium iodide and benzyl bromide in

refluxing acetonitrile afforded diol **68** in much improved 90% yield (Scheme 10).



73 **68**

***Scheme 10**. Reagents and conditions: **a)** Bu_2SnO, Bu_4NI, CH_3CN, BnBr, reflux, 12 h, 90%.*

Elegant studies on the regioselective dibutylstannylation of polyols, such as carbohydrates, and their subsequent acylation or alkylation based on the nucleophilic enhancement of the oxygen atoms have been reported by David and Hanessian.[101, 102] Bu_2SnO was employed in a catalytic fashion to form the dibutylstannylene acetal under neutral conditions. The regioselective *O*-benzylation can be rationalised based on the stannylene structure. The two oxygen atoms of the diol are differentiated in the stannylene, one being in an equatorial position, and the other one in an apical position in a trigonal bipyramid centered on the tin atom.[101-103] The apical oxygen of the stannane complex is more reactive than the equatorial and reacts preferentially with the benzyl bromide (Figure 15).

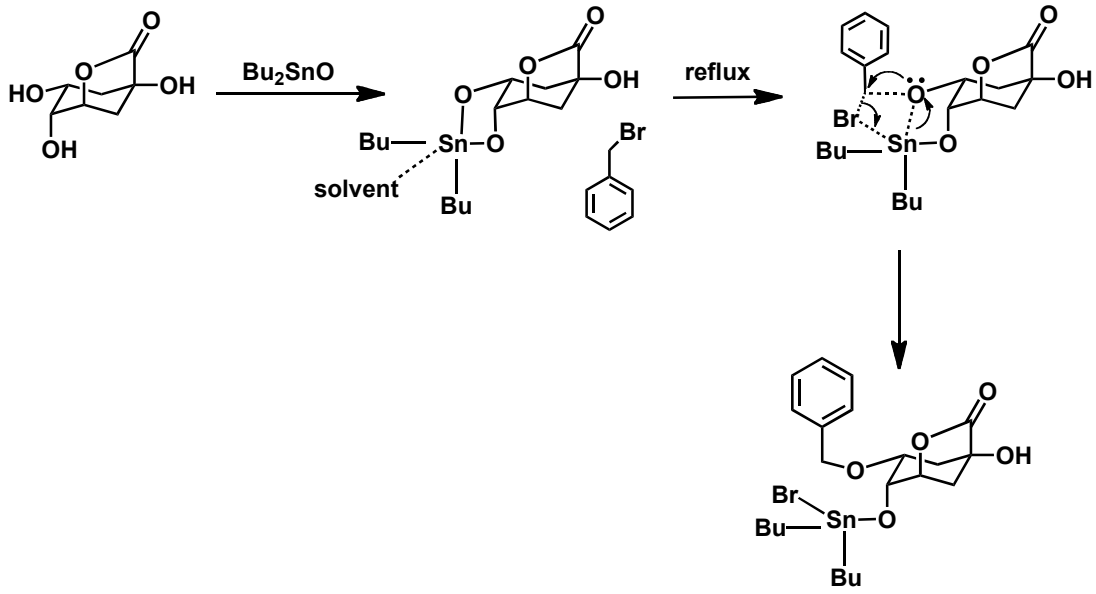


***Figure 15**. Proposed mechanism of the regioselective benzylation of the C-3 hydroxyl group using Bu_2SnO.*

The exact structure assignment was based on a literature study.[103] The ^1H NMR spectrum displayed the requisite resonances. In particular, the aromatic protons appeared as a multiplet between δ 7.31-7.20 ppm. The benzylic protons appeared as an AB system at δ 4.54-4.44 ppm, with a geminal coupling constant of 12.0 Hz. The hydroxyl groups C-1 and C-4 appeared as a singlet at δ 5.93 ppm and as doublet at 5.21 ppm respectively. The methine protons H-5, H-4 and H-3 appeared as an apparent triplet at δ 4.60 ppm (*J* = 5.4, Hz), multiplets at δ 4.14-4.09 ppm and doublet of doublet of doublet at δ 4.19 ppm (*J* = 4.7, 4.7, 4.5 Hz). The methylene protons H-2 and H-6 appeared as an apparent doublet at δ 2.26 ppm (*J* = 11.2 Hz), multiplets at δ 2.16-1.20 ppm, δ 1.98-1.94 ppm and as an apparent triplet at δ 1.72 ppm (*J* = 11.6 Hz) (Figure 16). The mass spectrum gave a signal at 263 corresponding to the molecular ion $[M+H]^+$ expected for $C_{14}H_{16}O_5$.

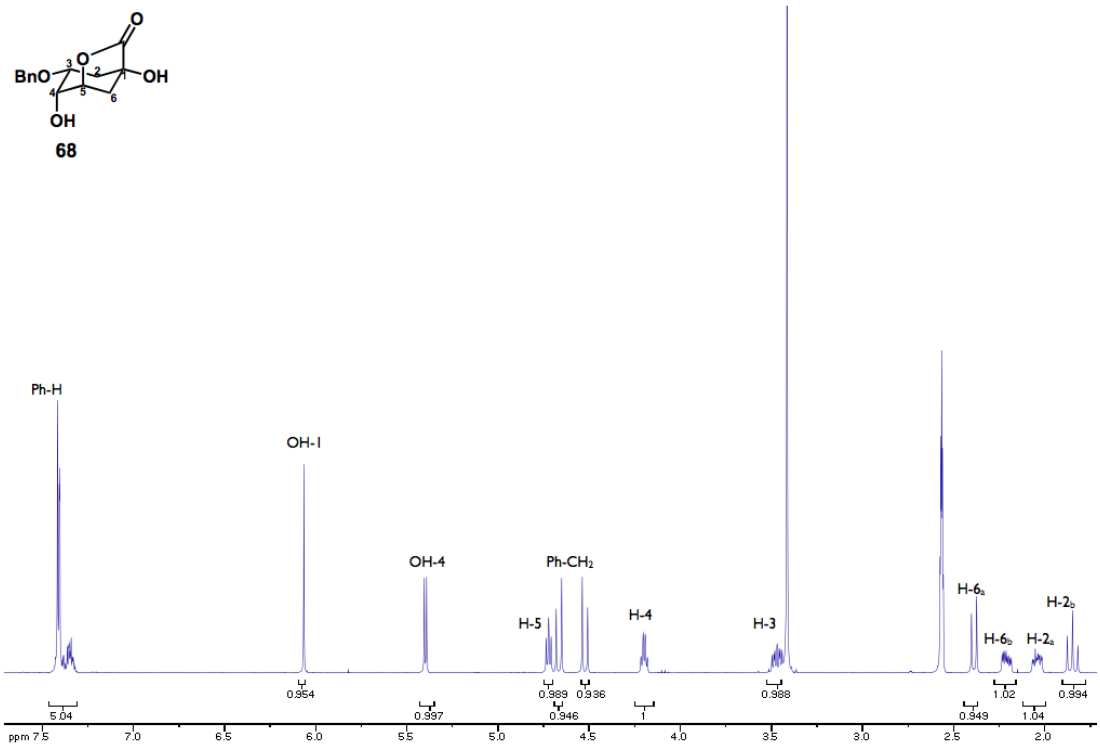
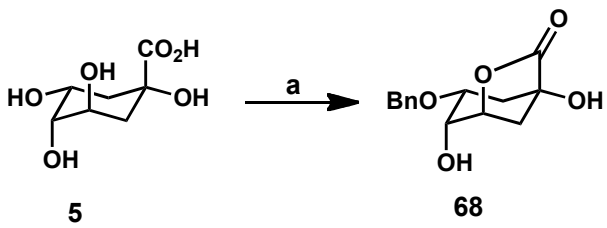


Figure 16. *^{1}H NMR spectrum of **68** in DMSO-d_6.*

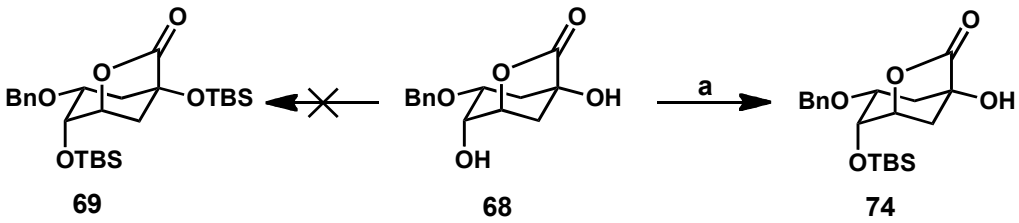
The synthesis of diol **68** has previously been reported by Hanessian *et al.*[104] using a one-pot strategy. This protocol began with quinic acid **5** and *p*-toluenenesulfonic acid in DMF/toluene (1:1) as solvent, followed by the addition of dibutyltin oxide and benzyl bromide to the crude intermediate (Scheme 11).



Scheme 11. *Reagents and conditions:* ***a)*** *p-TsOH, toluene, DMF, Bu_2SnO, BnBr, reflux, 6 h, 30%.*

However, in our hands, this method afforded diol **68** in a poor 30% yield compared with the 81% obtained in the original report.[104] The two step method described above was the method of choice because it gave 90% yield in comparison with 81% yield reported by Hanessian *et al.*[104] over one step.

The next goal was the *O*-silylation of the 1- and 4-hydroxyl groups as *tert*-butyldimethylsilyl (TBS) ether. Initial reaction of diol **68** was attempted with imidazole in DMF at 0 ºC, followed by addition of TBS chloride. The mixture was then stirred at 0 ºC for 30 min and 1 h at room temperature.[105] The reaction was monitored by TLC, which indicated the formation of one less polar product as well as unreacted starting materials. Alcohol **74** was isolated in 70% yield after column chromatography (Scheme 12) as the only product.



***Scheme 12**. Reagents and conditions: **a)** Imidazole, TBS-Cl, DMF, 0 ºC for 30 min and then 1 h at room temperature, 70%.*

The ^{1}H NMR spectrum of the isolated product showed diagnostic resonances at δ 0.78 ppm due to the *t*-butyl group at δ 0.00 and δ at -0.02 ppm due to the methyl groups of the TBS group. On close analysis of the spectrum it was clear that only one hydroxyl group had been protected. Mono-protection was

confirmed by the observation of a signal at 379 Daltons in the mass spectrum, corresponding to $C_{20}H_{30}O_5Si$. This was judged to be the C-4 hydroxyl group due to the absence of 4-OH signal in the ^1H NMR spectrum at δ 5.32 ppm, implying that the product was the alcohol **74** rather than the desired bis-TBS lactone **69** (Figure 17). The selectivity is entirely consistant with tertiary hydroxyl group at C-1 is more sterically hindered and less reactive than the secondary 4-OH hydroxyl group.

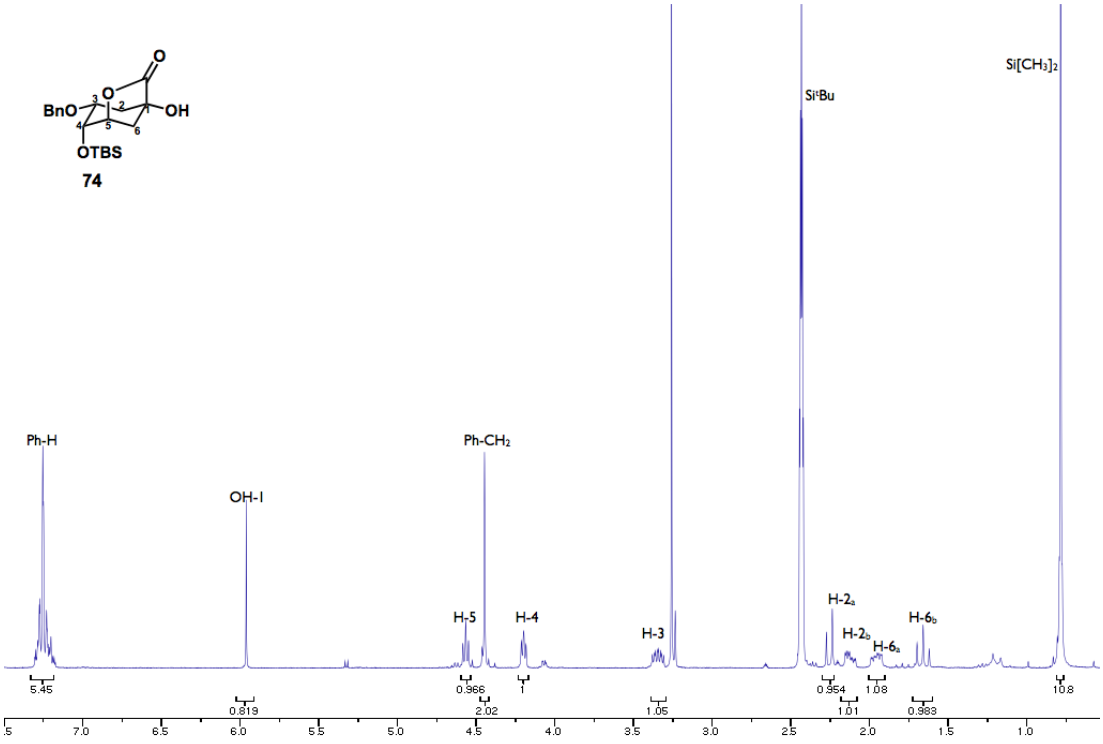
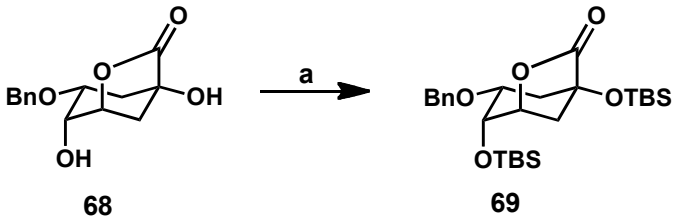


Figure 17. *^1H NMR spectrum of **74** in DMSO-d_6.*

A further attempt at protection of the 1- and 4- hydroxyl groups employed adaptations of literature methods,[105] using 3 equivalents of TBS chloride, but they was unsuccessful. However, a larger excess of both TBS chloride (6 eq) and imidazole (4 eq) and a higher reaction temperature of 100 ºC as well as the inclusion of DMAP (0.01 eq) as a catalyst was successful. DMAP was not

used in the previous literature (Scheme 13). This reaction proceeded smoothly affording the desired *bis*-TBS ether **69** in 86% yield following purification by column chromatography. The structure of **69** was confirmed by ^{1}H NMR spectroscopy (Figure 18) and mass spectral analysis, which gave a signal at 515 Daltons, corresponding to the sodium adduct $[M+Na]^{+}$



68 **69**

Scheme 13*. Reagents and conditions:* ***a)*** *Imidazole, TBS chloride, DMAP, DMF, 100 ºC, 12 h, 86%.*

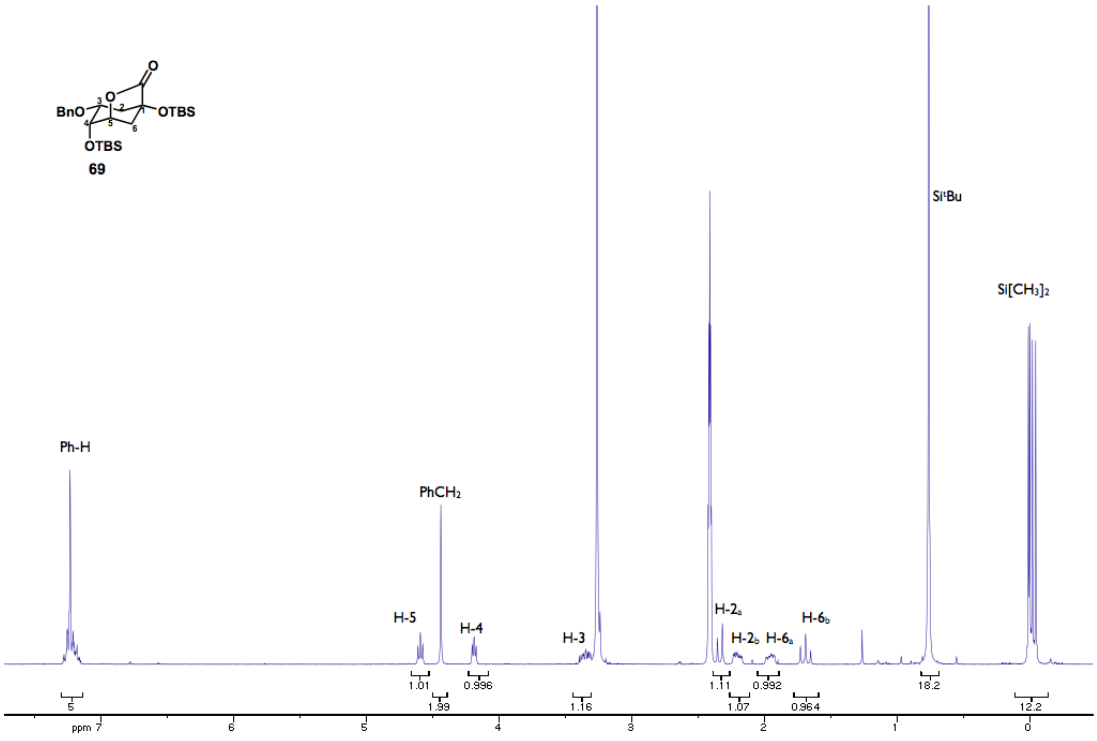
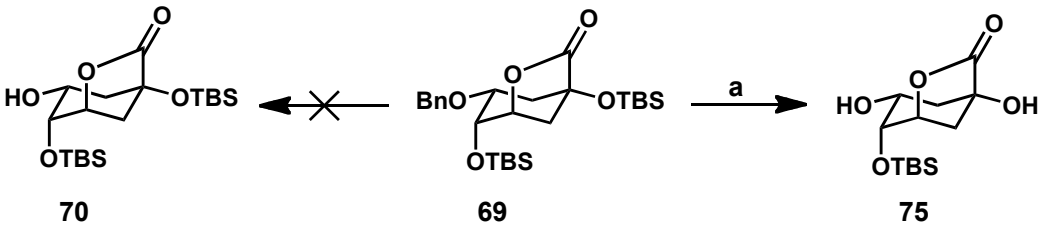


Figure 18. *^{1}H NMR spectrum of* ***69*** *in DMSO-d_6.*

Following the protection of the 1- and 4-hydroxyl groups to give ether **69**, several unsuccessful attempts were made at hydrogenolysis of the benzyl protecting group using various palladium catalysts (Scheme 14).



70 **69** **75**

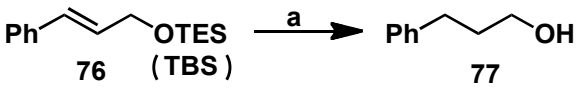
Scheme 14*. Reagents and conditions:* ***a)*** *H_2, 10% Pd/C or Pd/$(OH)_2$, MeOH, EtOAc, or THF, room temperature*

In all cases an unexpected cleavage of the TBS group at the C-1 position was observed giving compound **75** (Table 2). The ^{1}H NMR spectrum had diagnostic resonances at δ 0.78 ppm due to the *t*-butyl group and at δ 0.00 and δ -0.02 ppm. The integrals indicated the presence of only one hydroxyl group, which appears to be that at C-4 due to the absence of 4-OH signal in the ^{1}H NMR spectrum. The structure was supported by mass analysis which gave a molecular ion of *m/z* 288 Daltons. It was concluded that the cleavage reaction of TBS with 5% and 10% Pd/C was promoted by the acid contamination in the 5% or 10% Pd/C catalysts. The results are shown in Table 2.

***Table 2**. Cleavage of the TBS ether **69** in the presence of Pd catalyst and hydrogen.*

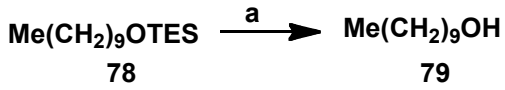
Entry	Pd	Solvent	Temp	Time (h)	Product	Yield %
1	5% Pd/C	MeOH	r.t	12 h	**75**	95%
2	5% Pd/C	MeOH	r.t	1 h	**69**	no reaction
3	5% Pd/C	EtOAc	r.t	12 h	**75**	95%
4	5% Pd/C	THF	r.t	12 h	**75**	95%
5	10% Pd/C	MeOH	r.t	12 h	**75**	95%
6	10% Pd/C	EtOAc	r.t	12 h	**75**	95%
7	10% Pd/C	THF	r.t	12 h	**75**	95%
8	$Pd/(OH)_2$	MeOH	r.t	12 h	**75**	95%
9	$Pd/(OH)_2$	EtOAc	r.t	12 h	**75**	95%
10	$Pd/(OH)_2$	THF	r.t	12 h	**75**	95%

Unexpected cleavage of silyl protected alcohols such as TBS and DEIPS ethers under various hydrogenolysis conditions has been previously reported.[106-108] In 2004 Ikawa *et al.*[106] reported the cleavage of TBS and TES ethers under hydrogenation conditions using 10% Pd/C in MeOH at room temperature (Scheme 15).



***Scheme 15**. Reagents and conditions: **a)** H_2, 10% Pd/C, MeOH, room temperature, 12 h.*[106]

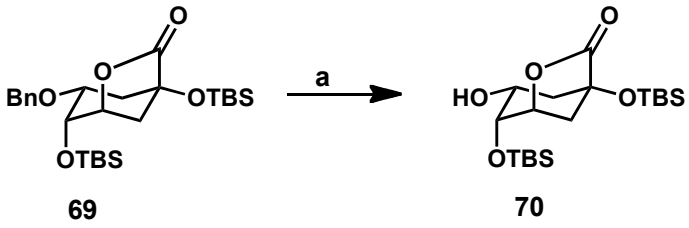
In a separate reported by Prunet *et al*.[107] the cleavage of a TES ether using 10% Pd/C in MeOH or 95% EtOH at room temperature in the absence of a hydrogen atmosphere was also reported (Scheme 16).



Scheme 16. *Reagents and conditions: a) without H_2, 10% Pd/C, MeOH or EtOH, room temperature, 12 h.*[107]

These observations are in agreement with our findings. Palladium chloride in concentrated hydrochloric acid solution is generally used for the preparation of Pd/C catalysts. The palladium chloride is absorbed on to heavy metal free activated charcoal and reduced using a suitable reductant. It may therefore be contaminated by a trace amount of retained hydrochloric acid, and/or residual palladium chloride due to incomplete reduction during the production process, even after washing with distilled water.[106]

To counter this problem, it was decided to use palladium black in MeOH at room temperature under a hydrogen atmosphere for 36 h. Under these new conditions the desired alcohol **70** was achieved in quantitative yield. This reaction proved to be clean and no further purification of the alcohol **70** was required. The ^{1}H NMR spectrum of alcohol **70** displayed the expected resonances (Figure 19). The absence of the aromatic protons at δ 7.26-7.15 ppm was indicative of cleavage of the benzyl ether. The TBS groups appeared as singlets at δ 0.77 ppm, 0.76 ppm due to the *t*-butyl groups and δ 0.02, 0.00, -0.00, -0.02 ppm due to the methyl groups. An absorption in the infrared spectrum at 3300 cm^{-1} was indicative of the alcohol functionality and mass spectral analysis gave a signal at 403 Daltons, corresponding to the molecular ion $[M+H]^+$ expected for $C_{19}H_{38}O_5Si_2$ (Scheme 17).



69 **70**

Scheme 17*. Reagents and conditions:* ***a)*** *H_2, Pd/black, MeOH, room temperature, 36 h, 99%.*

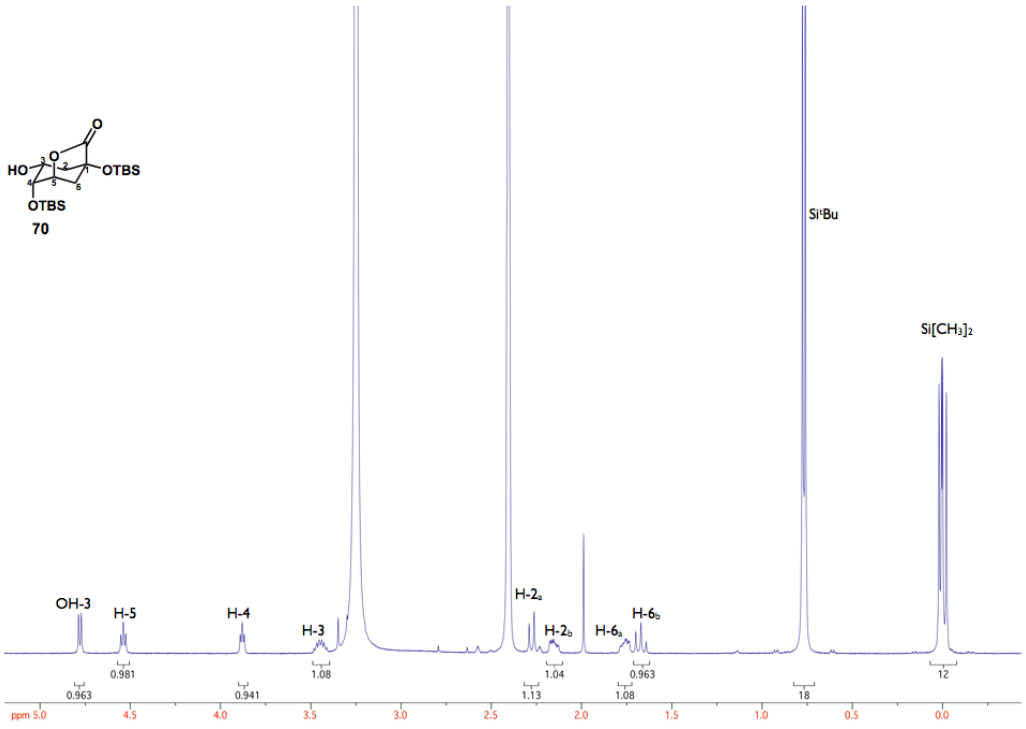
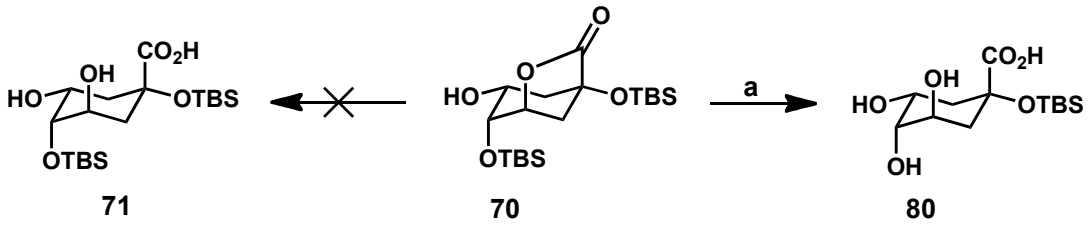


Figure 19. *^{1}H NMR spectrum of alcohol* ***70*** *in DMSO-d_6.*

The next step in the proposed synthesis was ring opening of the lactone. Hydrolysis of the lactone **70** with a catalytic amount of LiOH in THF/H_2O at room temperature was exploved. However, this led to the removal of the TBS group at C-4. Further attempts towards lactone ring opening without the cleavage of the TBS group at C-4 position, were carried out as shown in Table 3. Replacing LiOH with NaOH, as well as decreasing the reaction

temperature and duration of the reaction all failed to give the desired product (Table 3).



***Scheme 18**. Reagents and conditions: **a)** Table 2*

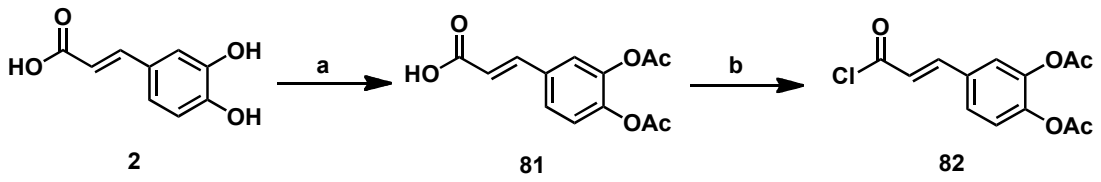
***Table 3.** Hydrolysis of lactone **70** using LiOH and NaOH at various temp and time.*

Entry	Reagent	Solvent	Temp	Time (h)	Product	Yield %
1	LiOH (1.1 eq)	THF/H_2O	0 °C	0.5 h	**70+80**	89%+11%
2	LiOH (1.1 eq)	THF/H_2O	0 °C	1 h	**70+80**	67%+33%
5	LiOH(1.1 eq)	THF/H_2O	r.t	6 h	**80**	68%
7	LiOH (2.1 eq)	THF/H_2O	r.t	24 h	**80**	99%
8	NaOH (1.1 eq)	THF/H_2O	0 °C	1 h	**70+80**	60+40%
9	NaOH (2.1 eq)	THF/H_2O	r.t	6 h	**80**	76%
10	NaOH (2.1 eq)	THF/H_2O	r.t	24 h	**80**	92%

The ^{1}H NMR spectrum of the hydrolysis product showed the presence of only one silyl protecting group with diagnostic resonances at δ 0.83 ppm (9H) for the *t*-butyl group, and δ 0.00 and 0.03 ppm for to the methyl groups. Further confirmation came *via* HRMS (ES^-) 305.1420 for $C_{13}H_{25}O_6Si$ indicating the presence of only one silyl group.

With triol **80** in hand, the possibility of the coupling reaction with diacetyl caffeoyl chloride **82** was investigated to determine which hydroxyl groups would react.[95] Diacetyl caffeoyl chloride **82** was obtained from caffeic acid **2** in two steps. Acetylation of caffeic acid **2** with Ac_2O and DMAP, in pyridine

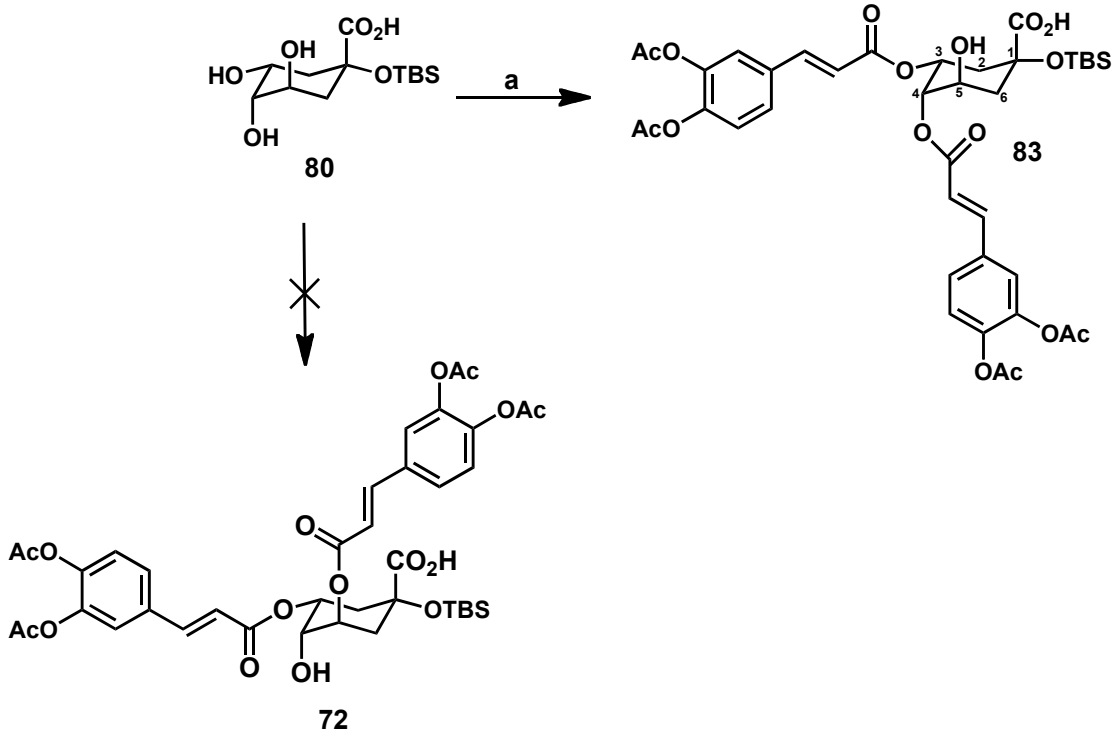
afforded **81** in a 95% yield. Reaction of **81** with 2 eq. of oxalyl chloride provided the diacetyl caffeoyl chloride **82** in an excellent 98% yield (Scheme 19).[95]



2 **81** **82**

Scheme 19*. Reagents and conditions:* ***a****) DMAP, pyridine, acetic anhydride, DMF, 0 ºC, 1 h, 95 %,* ***b****) oxalyl chloride, -5 ºC, 3 h room temperature, 98%.*

Treatment of triol **80** with diacetyl caffeoyl chloride **82** (2.2 eq) in the presence of DMAP at room temperature[95, 96] gave the 3,4-dicaffeoyl ester **83** and not the desired 3,5-dicaffeoyl ester **72** (Scheme 20).



80 **83** **72**

***Scheme 20**. Reagents and conditions: a) DMAP, diacetyl caffeoyl chloride, 12 h, room temperature. 63%.*

The axial 5-hydroxyl group is more sterically hindered, at C-1 and less likely to react, owing to the proximity of the carboxylated group also in an the axial orientation.

The ^{1}H NMR spectrum of **83** was found to be in close agreement with a previous literature report.[109] The alkene protons appear as a doublet at δ 6.66 ppm and δ 6.54 ppm. COSY NMR analysis shows strong coupling between the methine proton at δ 3.85 ppm and the H-3, H-5, respectively. This methine proton was assigned to H-4 because only this proton can show homonuclear coupling with H-3 and H-5 and not to H-2 and H-4 respectively. More evidence came from the observation that OH-C showed connectivity to C-5 or C-3, whereas it was not connected to C-4 (Figure 21). This assignment was further confirmed by HSQC (Figure 22).

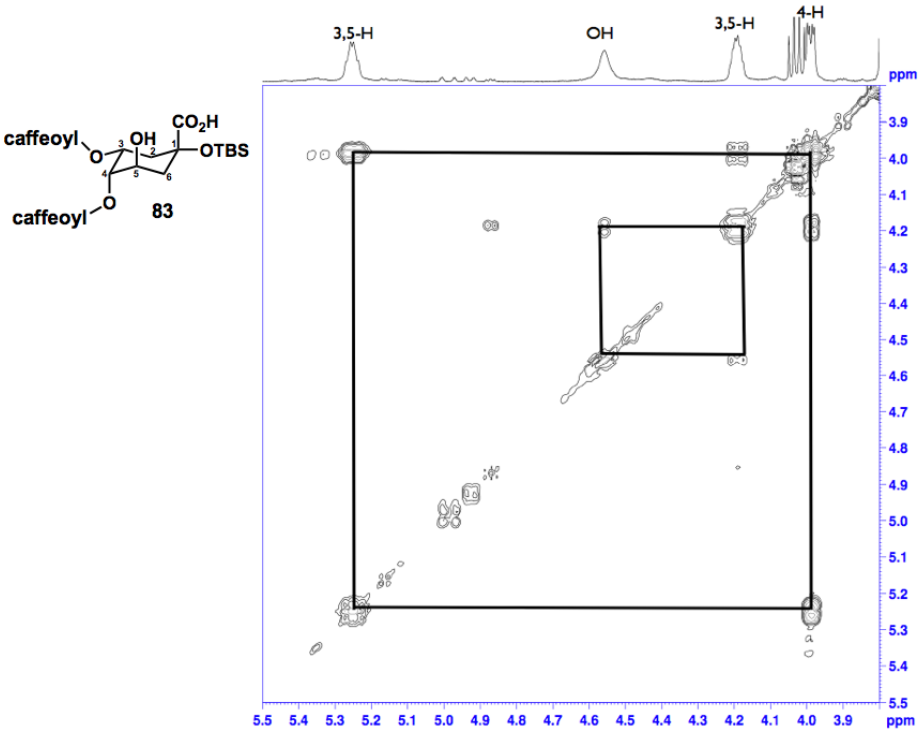


Figure 21. *^{1}H -^{1}H COSY spectrum of 3,4 dicaffeoyl ester **83** in DMSO-d_6.*

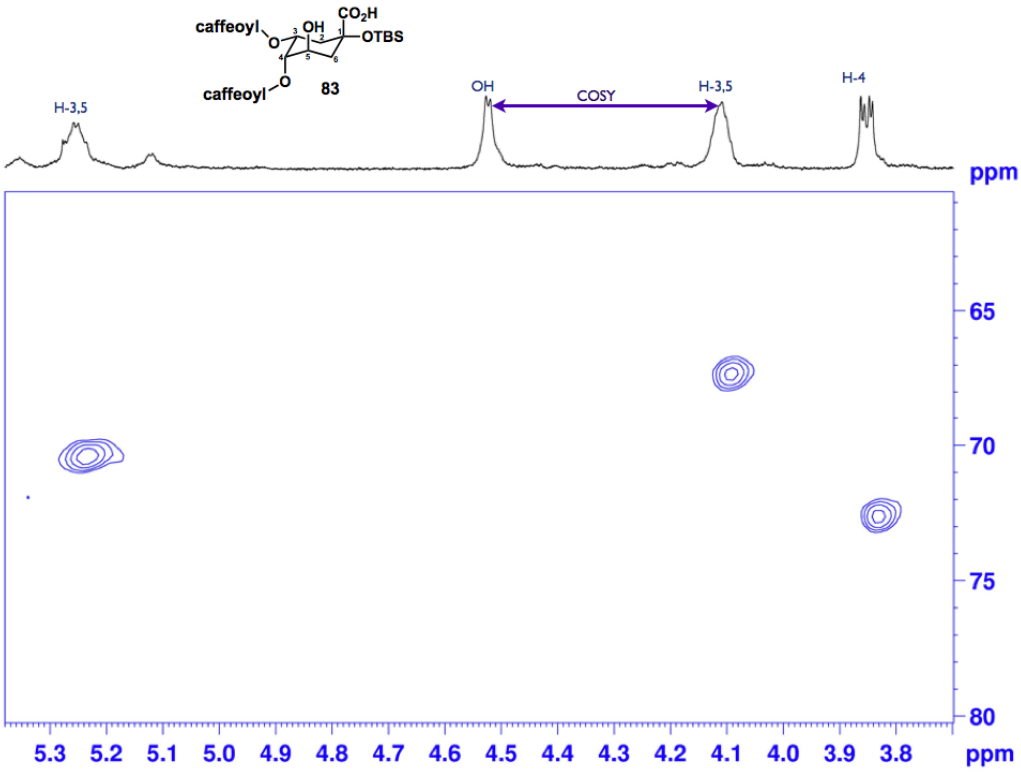
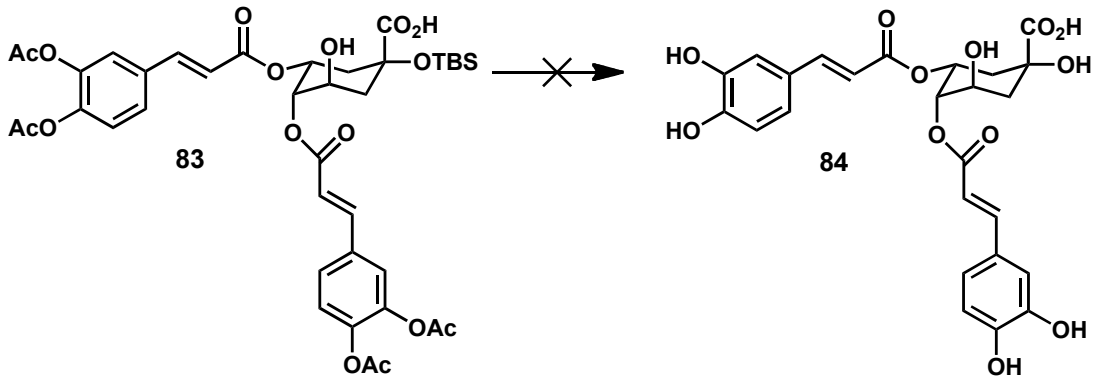


Figure 22. *^{1}H -^{13}C-HSQC spectrum of 3,4 dicaffeoyl ester **83** in DMSO-d_6.*

Various efforts to remove the protecting groups of coupled product **83** were unsuccessful (Scheme 21).



***Scheme 21**. Reagent and conditions: a) Table 4.*

Using 0.5 N HCl in THF for 5 days, no reaction was observed when monitoring the reaction by TLC. Increasing the reaction time to 10 days at the same concentration had no effect on the observed outcome. Increasing the concentration of HCl from 0.5 N to 1 N HCl had a significant effect on the reaction (Table 4). Analysis the ^{1}H NMR spectrum of this product after isolation and purification by column chromatography indicated the cleavage of both ester groups.

***Table 4.** Attempted cleavage of the protecting group using HCl.*

Entry	HCl	Days	Temp	Product
1	0.5 N	5 days	r.t	no reaction
2	0.5 N	10 days	r.t	no reaction
3	1 N	10 days	r.t	hydrolysis
4	2 N	1 days	r.t	no reaction
5	2 N	5 days	r.t	no reaction

2.2 An Alternative to the TBS ether Protecting Group.

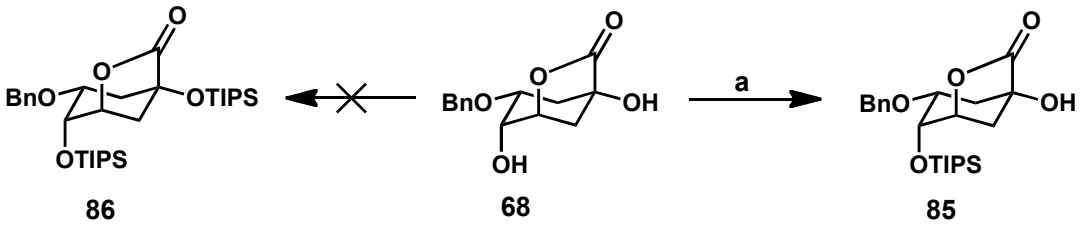
In the preceding sections the initial unsuccessful efforts to synthesise 3,5-DCAQ **11** using the TBS ether protecting group were discussed. This necessitated the shift to an alternative silyl protecting group. The triisopropylsilyl (TIPS) ether protecting group was chosen because it was believed that the bulkier TIPS silyl ether group would have greater stability towards acid and base hydrolysis. Table 5 shows the half-lives for cleavage of the two silyl ethers.[110]

Table 5. *Half-lives in the cleavage of silyl ethers.*[110]

Protecting Groups Si	Acid[a]	Base[b]	Fluoride[c]
t-BuMe_2Si	4 min	26 h	76 min
i-Pr_3Si	100 min	44 h	137 min

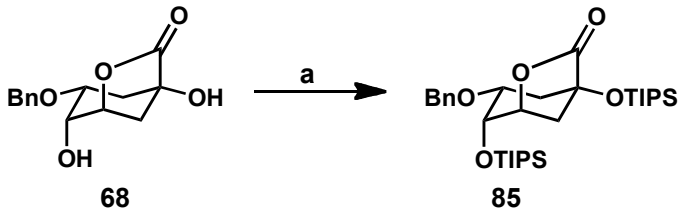
[a] 1% HCl/95% EtOH, 22.5 °C; [b] 5% NaOH/ 95% EtOH, 90 °C; [c] 2 equiv TBAF/ THF 22.5 °C

The initial steps of the synthesis were as before. The protection of diol **68** was then investigated using 2,6-lutidine in DMF at 0 ºC with *i*Pr_3SiOTf as the source the silyl group.[111] The mixture was stirred at room temperature for 6 h. Under these conditions protection of only the 4-hydroxyl group was observed (Scheme 22).



***Scheme 22**. Reagents and conditions: **a)** iPr$_3$SiOTf, 2,6 Lutidine, DMF, 0 ºC to room temperature, 89%.*

However, increasing the reaction temperature to 70 ºC with 4.1 equiv of *i*Pr$_3$SiOTf and increasing the reaction time to 8 h afforded the *bis*-TIPS ether **85** in a good (78%) yield (Scheme 23).



***Scheme 23**. Reagents and conditions: **a)** iPr$_3$SiOTf, 2,6 lutidine, DMF, room temperature to 70 ºC, 78%.*

The structure of *bis*-TIPS ether **85** was initially confirmed by ^{1}H NMR spectroscopy (Figure 23). This showed the absence of both hydroxyl groups at δ 6.06 ppm and δ 5.40 ppm respectively. The methine protons H-5 and H-4 appeared as an apparent triplet at δ 4.60 ppm (*J* = 5.4, Hz) and δ 4.22 ppm (*J* = 4.4, Hz) respectively. H-3 appeared as a multiplet between δ 3.37-3.32 ppm. The methylene H-2 appeared as an apparent doublet at δ 2.41 ppm (*J* = 11.3 Hz) and a multiplet at δ 2.23-2.16 ppm. H-6 appeared as a multiplet at δ 1.98-1.92 ppm and as an apparent triplet at δ 1.72 ppm (*J* = 11.0 Hz). The TIPS ether protecting groups appeared as multiplets at δ 0.93-0.90 ppm

(42H). An accurate mass measurement displayed a signal at 599 Daltons, corresponding to that expected for the sodium adduct $[M+Na]^+$ $C_{31}H_{60}O_2Si_4Na$.

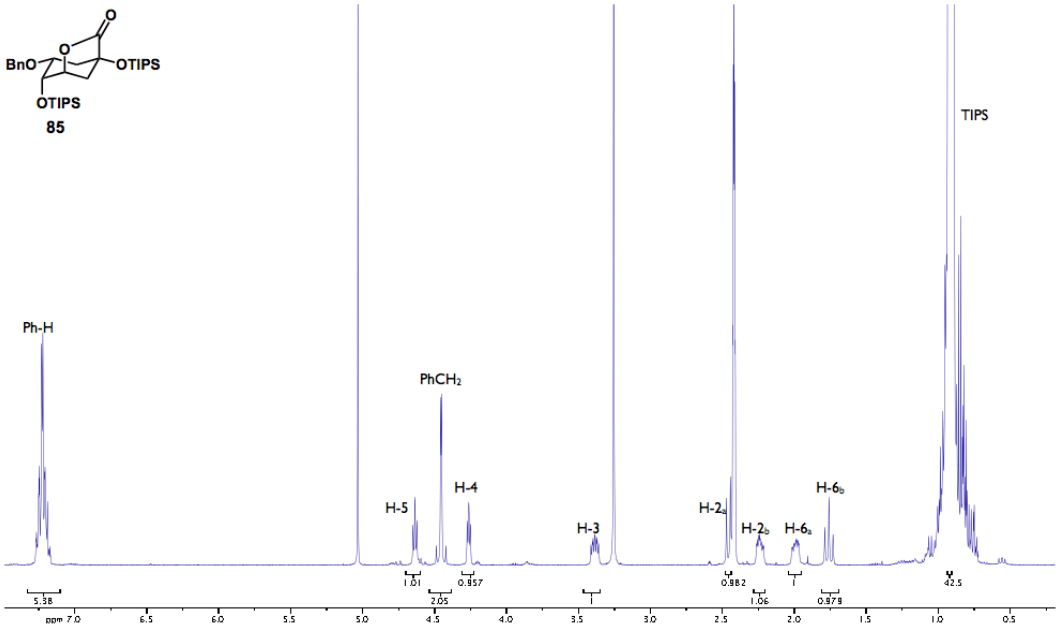
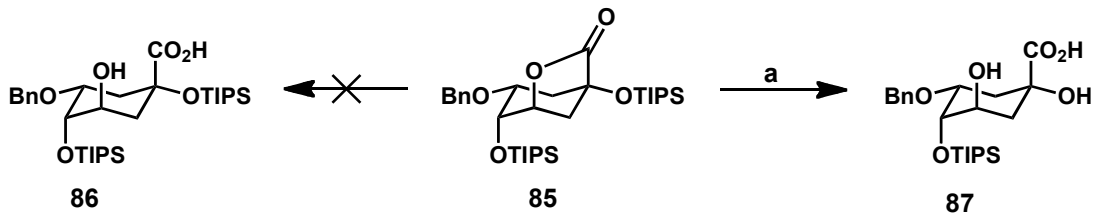


Figure 21. *^{1}H NMR spectrum of **85** in DMSO-d_6.*

Next came the crucial step involving the opening of the lactone ring without the concomitant cleavage of the TIPS ether groups at the C-1 and C-4 positions. Using LiOH in THF-H_2O at room temperature for 45 min, it was observed that the TIPS at the C-4 position was retained intact while the TIPS group at the C-1 position was cleaved (Scheme 24).



***Scheme 24**. Reagents and conditions: **a)** Table 6.*

This is in contrast to the original conditions, which utilised the TBS protecting group (previously) where the TBS ether group at the C-1 position was retained while the TBS group at the C-4 position was cleaved. Several further attempts to open the lactone ring without the cleavage of the TIPS group at the C-1 position were conducted. The result of which are summarised below (Table 6). Replacing LiOH with NaOH as well as decreasing the reaction temperature and increasing the time failed to give the desired product (Table 6).

***Table 6.** Hydrolysis of lactone **85** using LiOH and NaOH at various temp and time.*

Entry	Reagent	Solvent	Temp	Time (h)	Product	Yield %
1	LiOH (1.1 eq)	THF/H_2O	0 °C	0.5 h	**85+87**	93%+7%
2	LiOH (1.1 eq)	THF/H_2O	0 °C	1 h	**85+87**	72%+28%
3	LiOH (1.1 eq)	THF/H_2O	r.t	6 h	**87**	65
7	LiOH (1.1 eq)	THF/H_2O	r.t	24 h	**87**	99%
8	NaOH (1.1 eq)	THF/H_2O	0 °C	1 h	**85+87**	92%+8%
9	NaOH (1.1 eq)	THF/H_2O	r.t	6 h	**87**	67%
10	NaOH (2.1 eq)	THF/H_2O	r.t	24 h	**87**	99%

The structure of diol **87** was confirmed by NMR spectroscopy (Figure 22). The ^{1}H NMR of spectrum of the diol **87** displayed the appropriate resonances. In particular, the aromatic protons appeared as a multiplet between δ 7.42-7.29 ppm (5H). The benzylic proton appeared as an AB

system at δ 4.62-4.51 ppm, with a coupling constant of 12.2 Hz. The methine H-4 and H-5 appeared as a series of multiplets between δ 4.03-3.99 ppm and 3.87-3.80 ppm. The methine H-3 appeared as doublets of triplets at δ 3.90, which coupling constant of 11.1 and 2.8 Hz respectively. The methylene H-2 and H-6 appeared as multiplets at δ 2.44-2.40 ppm, δ 2.37-2.31 ppm, and δ 1.98-1.82 ppm, respectively. The TIPS ether protecting group appeared as multiplets at δ 1.04-1.00 ppm.

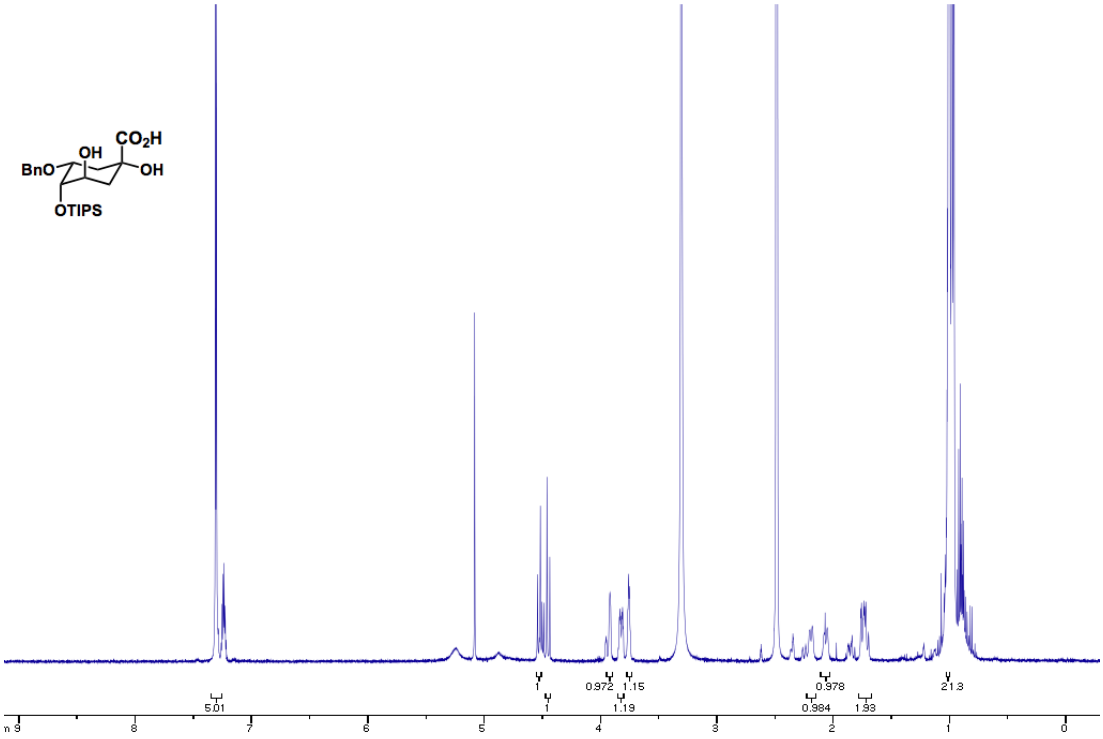


Figure 22. *^{1}H NMR spectrum of diol **87** in DMSO-d_6.*

The 2 dimensional (2D) 1H, ^{29}Si correlation experiment further revealed that the remaining silyl protecting group was at the C-4 position and also confirmed that only one silyl protecting group was present (Figure 23).

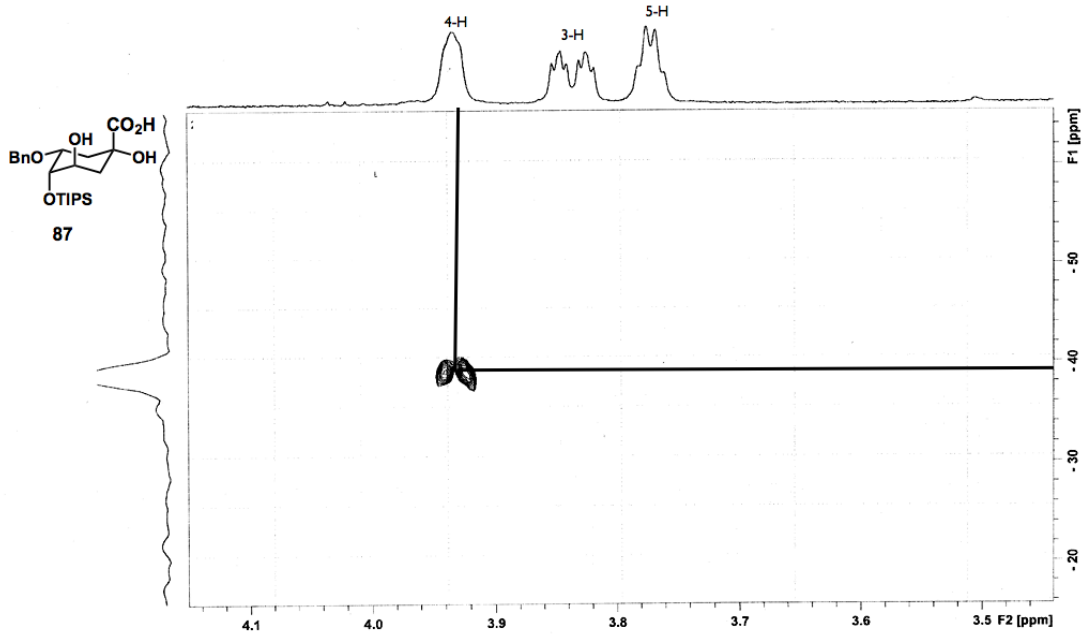
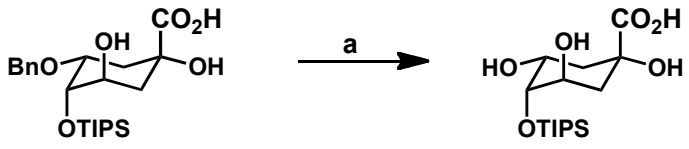


Figure 23. *^{1}H-^{29}Si correlation experiment.*

It was speculated that the TIPS ether group at the C-1 position was cleaved due to the greater relief of steric strain. It was also believed that the coupling of the caffeoyl chloride to the C-3 and C-5 positions could be efficiently carried out with no protection of the C-1 hydroxyl group due to the steric effects hindering reaction at this position.

Therefore, next goal was the selective deprotection of the benzyl protecting group on the 3-hydroxyl group without cleavage of the TIPS group at the C-4 position. This was achieved using 10% Pd/C in EtOH at 60 ºC under a hydrogen atmosphere for 36 h. Under these conditions the triol **88** was obtained in 82% yield (Scheme 26).

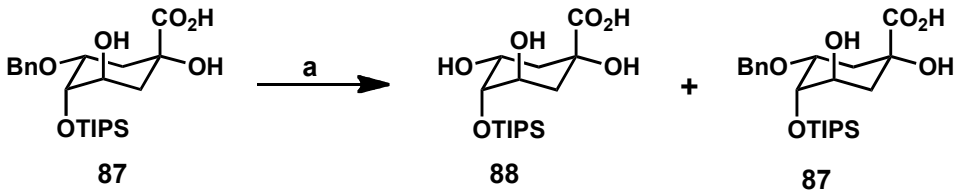


87 88

***Scheme 26**. Reagents and conditions: **a)** H_2, 10% Pd/C, EtOH, 60 ºC, 82%.*

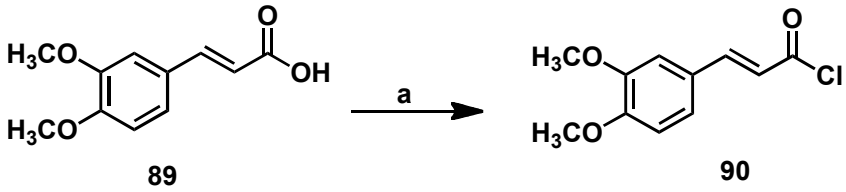
The ^{1}H NMR of the isolated triol **88** showed the absence of aromatic protons between δ 7.31-7.29 ppm and the benzylic protons at δ 4.52-4.44 ppm. The methine protons at H-3, H-5 and H-4 appeared as multiplets between δ 4.08-3.92 ppm, and δ 3.72-3.59 ppm. The remaining signals, which can be attributed to the methylene groups appear as a multiplet between δ 1.87-1.51 ppm (4H), and the protons at δ 1.03-101 ppm (21H) pertain to the TIPS ether protecting group. The structure was supported by mass spectrometry which gave a molecular ion of *m/z* 347 indicating the absence of the benzyl protecting group.

However, when this protocol was attempted using 10% Pd/C in EtOH at room temperature for 36 h, incomplete conversion of diol **87** to the desired product triol **88** was observed. Only a poor 8% yield of the desired product triol **88** was observed with the remaining 92% being unreacted starting material **87** (Scheme 27).



***Scheme 27**. Reagents and conditions: **a)** H_2, 10% Pd/C, EtOH, room temperature, 36 h, 8% (**88**), 92% (**87**)*

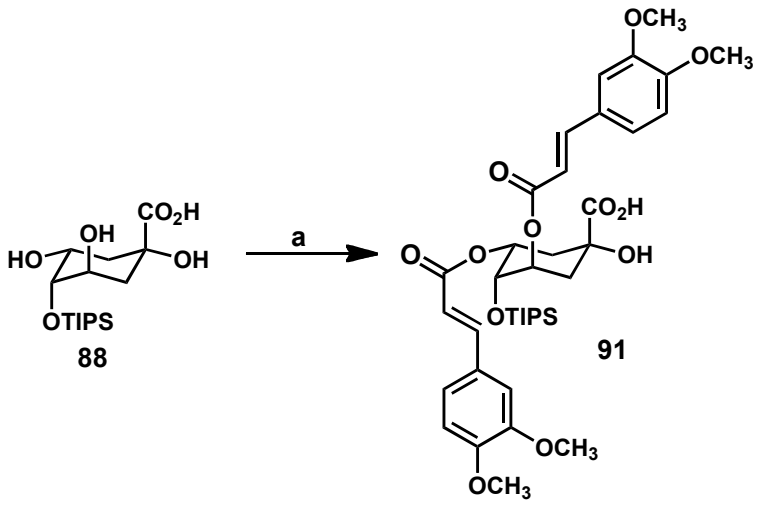
With triol **88** in hand, the next task was to introduce the caffeoyl groups at the C-3 and C-5 positions. This was achieved by adopting the methodology reported by Sefkow *et al*.[95, 96] It was first decided to use 3,4-dimethoxycinnamic acid to investigate the coupling at the C-3 and C-5 positions, because the tetramethylated product would be easier to handle and purify. Simple deprotection of just one silyl group at the C-4 position would then give one of the target molecules. The required 3,4,dimethoxycinnamyl chloride **90** was obtained from 3,4,-dimethoxycinnamic acid **89** using oxalyl chloride in toluene and a catalytic amount of DMF affording **90** in 92% yield (Scheme 28).



***Scheme 28.** Reagents and conditions: **a)** toluene, cat. DMF, oxalyl chloride, -5 ºC to room temperature, 3 h, 92%*

Treatment of triol **88** with DMAP (0.01 eq) and 3,4,dimethoxycinnamyl chloride **90** (2.2 eq) in pyridine at room temperature for 12 h afforded the 3,5-

coupled product **91** in an excellent 92% yield after column chromatography (Scheme 29).



***Scheme 29**. Reagents and conditions: **a)** DMAP, 3,4-dimethoxycinnamoyl chloride, pyridine, CH_2Cl_2, room temperature, 12 h, 92%.*

The vinyl protons appeared as two doublets at δ 7.56 and 6.69 ppm. These downfield signals were deemed to be consistent with the β-protons of an α,β-unsaturated carbonyl system, with the large reciprocal coupling of 16.0 Hz. Tables 7 and 8 show ^{1}H NMR analysis of the quinic acid moiety and the caffeoyl moiety.

Table 7. *^{1}H NMR data for the quinic acid moiety of **91**.*

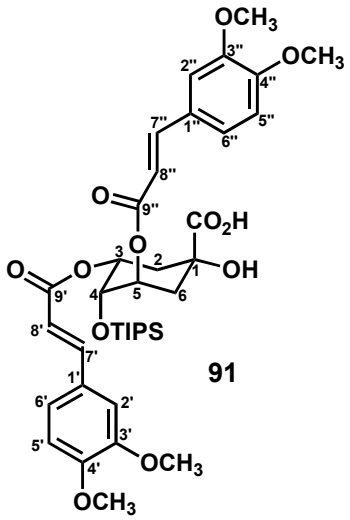
signal	assignment	shift[a] ppm	multi-plicity[b]	Hz[c]
3 or 5	axial	5.34 - 5.24	m	-
3 or 5	axial	4.19 - 4.09	m	-
4	equatorial	3.94 - 3.88	m	-
6	axial/equatorial	2.40 - 2.32	m	-
2	axial/equatorial	2.00 - 1.93	m	-

[a] In ppm, relative to DMSO-d_6 at 2.50; [b] m =multiplet, [c] Hz coupling constants.

Table 8. *^{1}H NMR data for the caffeoyl moiety of* ***91****.*

signal	assignment	shift[a] ppm	multi-plicity[b]	Hz[c]
7’	-	7.56	d	16.0
7”	-	7.48	d	16.0
2’	-	7.32	s	-
2”	-	7.26	s	-
5’	-	7.18	d	8.6
5”	-	7.18	d	8.6
6’	-	6.98	dd	8.6, 1.6
6”	-	6.96	dd	8.6,1.6
8’	-	6.49	d	16.0
8”	-	6.40	d	16.0
-OCH_3	-	3.80	s	-
-OCH_3	-	3.78	s	-

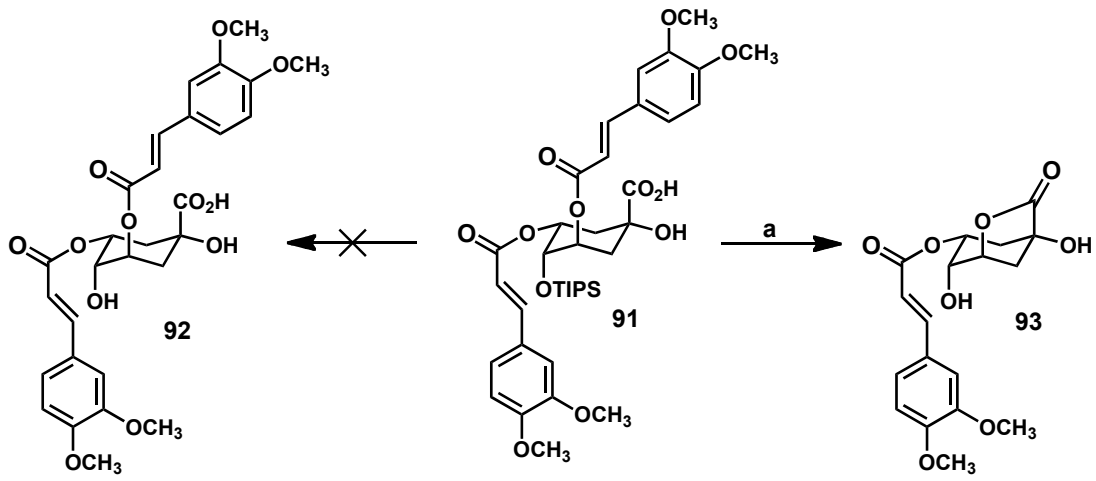
[a] In ppm, relative to DMSO-d_6 at 2.50; [b] s= singlet, d = doublet, [c] Hz coupling constants.



91

The next step, *O*-desilylation of the TIPS ether protecting group proved to be problematic. Treatment of TIPS-ether **91** with TBAF in THF under various reaction conditions failed to produce the desired product **92** (Scheme 30), but

instead gave the lactone **93**, as was confirmed by mass spectroscopetry which gave a molecular ion of *m/z* 364.

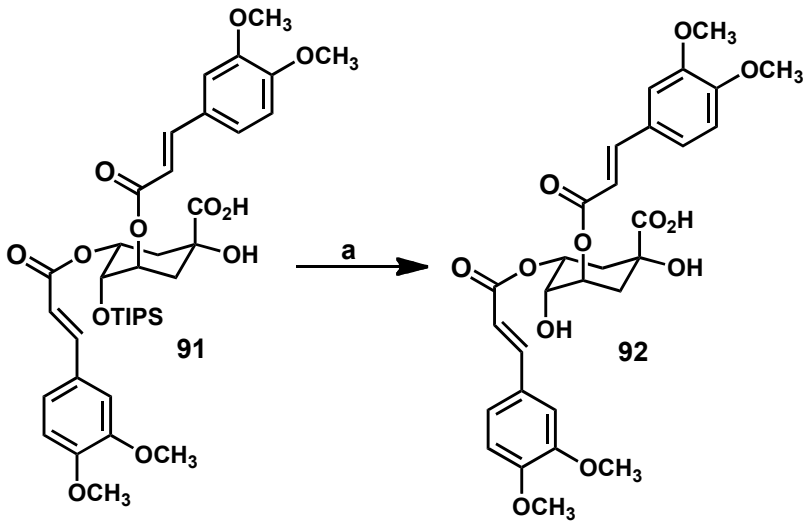


***Scheme 30**. Reagents and conditions: **a)** Table 9*

***Table 9.** Cleavage of the silyl protecting group at various temp and time.*

Entry	Reagent	Temp	Time (h)	Product	Yield %
1	TBAF/THF	r.t	3 h	**93**	66%
2	TBAF/THF	r.t	1 h	**93**	57%
3	TBAF/THF	0 °C	0.5 h	**93**	35%
4	TBAF/THF	0 °C	1 h	**93**	48%

The best conditions for this deprotection involved the treatment of **91** with HF-pyridine in THF at 0 ºC and allowing the resultant reaction mixture to warm up to room temperature overnight.[112] The desired product **92** was exclusively obtained in an excellent 98% yield following column chromatography (Scheme 31).



***Scheme 31**. Reagents and conditions: **a)** HF-pyr, THF, 0 ºC to room temperature, 12 h, 98%.*

The structure of this compound **92** was initially confirmed by its ^{1}H NMR spectrum, which showed the absence of the silyl protecting group and the presence of an additional hydroxyl group at δ 4.95 ppm. The vinyl protons appeared as doublets at δ 7.38, 7.37, 6.33 and 6.27 (Figure 24).

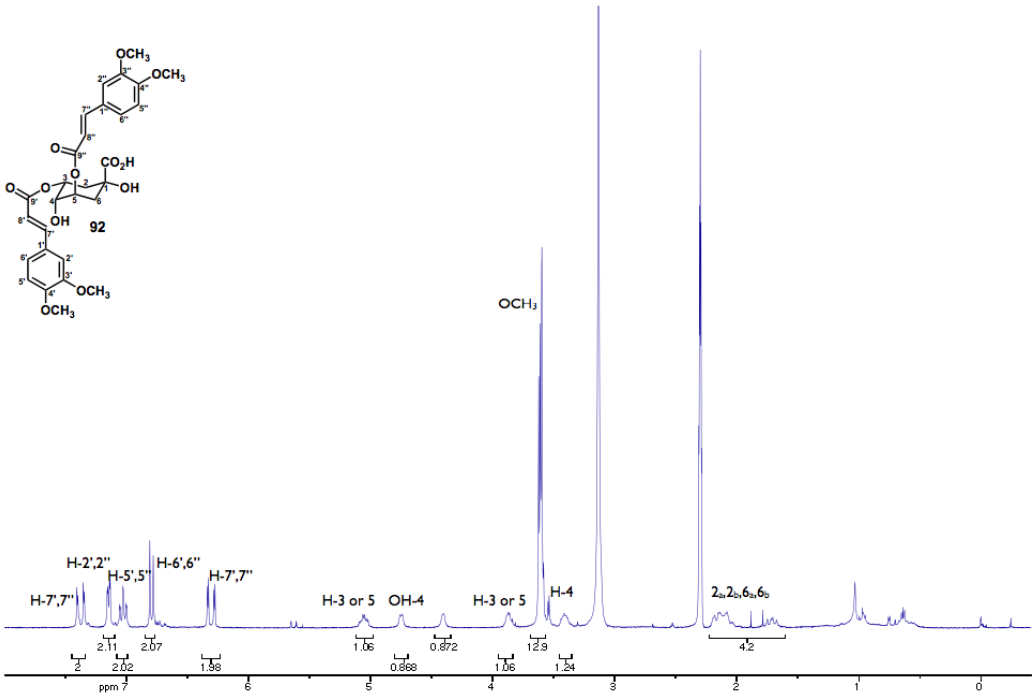


Figure 24. *^{1}H NMR spectrum of **92** in DMSO-d_6.*

The infrared spectrum of **92** displayed an absorption at 3054 cm^{-1} and 1707 cm^{-1}, consistent with the presence of a hydroxyl group and a carbonyl group, respectively. The mass spectrum gave a signal at 595 Daltons, corresponding to the sodium adduct $[M+Na]^+$ expected for $C_{29}H_{32}O_{12}Na$.

The purity of compound **92** was determined by reverse phase HPLC in methanol and H_2O (70:30) (using a Kingsorb 5u C_{18} column) giving a single peak with a retention time of 8.30 min (Figure 25).

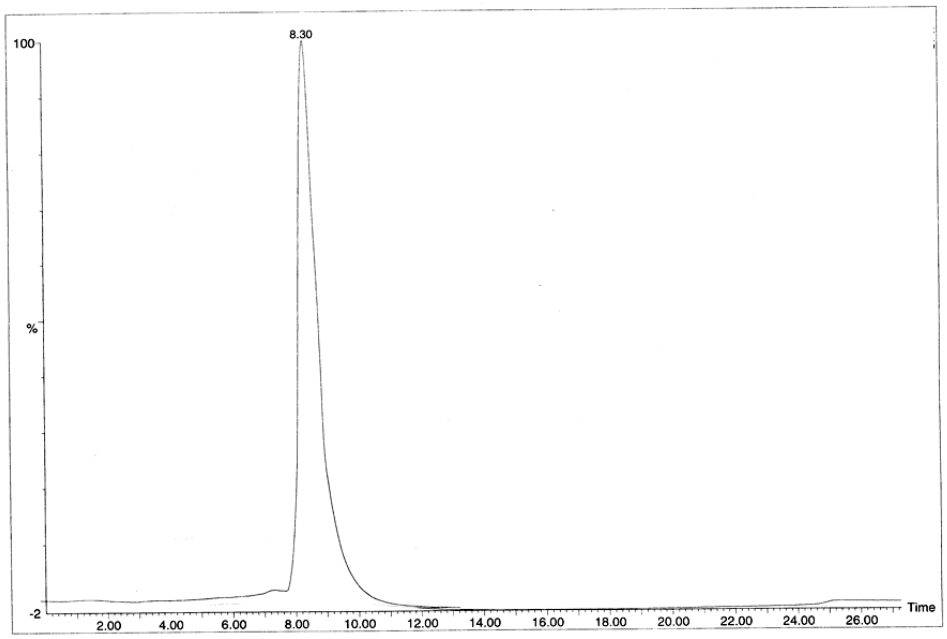
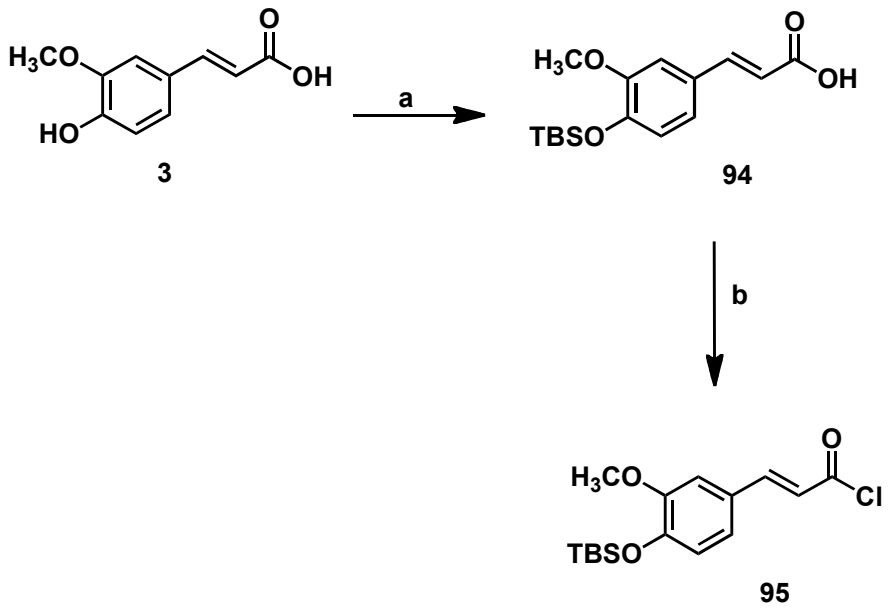


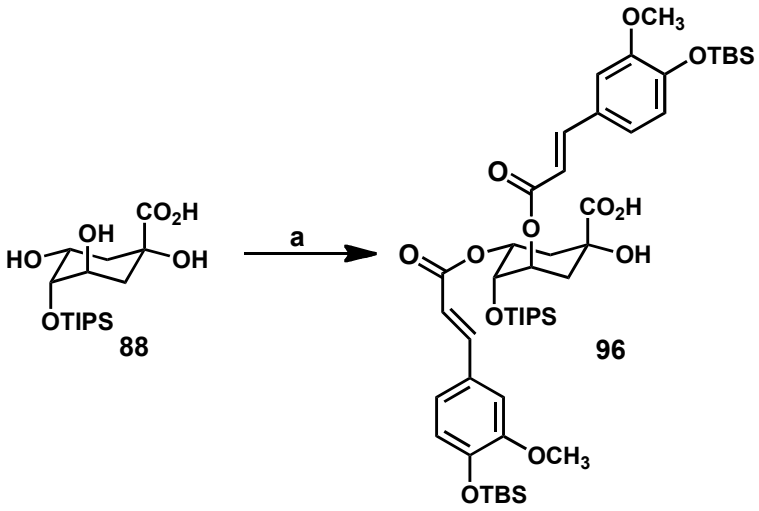
Figure 25. Reverse phase HPLC of compound **92** after initial purification.

With compound **92** in hand, investigation of the synthesis of 3,5-FQA **96** was then conducted. The synthesis of 3,5-FQA **96** was expected to be more difficult than that of **92** due to the increased polarity of the compound. As a starting point for the synthesis it was decided to use the TBS ether protecting group for the protection of the ferulic acid **3** because it would be an advantage to cleaved all the protecting group in the final step of the synthesis using HF-pyridine. *O*-Silylation of ferulic acid **3** with TBS and imidazole in anhydrous DMF gave silyl ether **93** in 96% yield. Treatment of **93** with oxalyl chloride and catalytic amount of DMF at room temperature afforded **94** in 78% yield (Scheme 32).



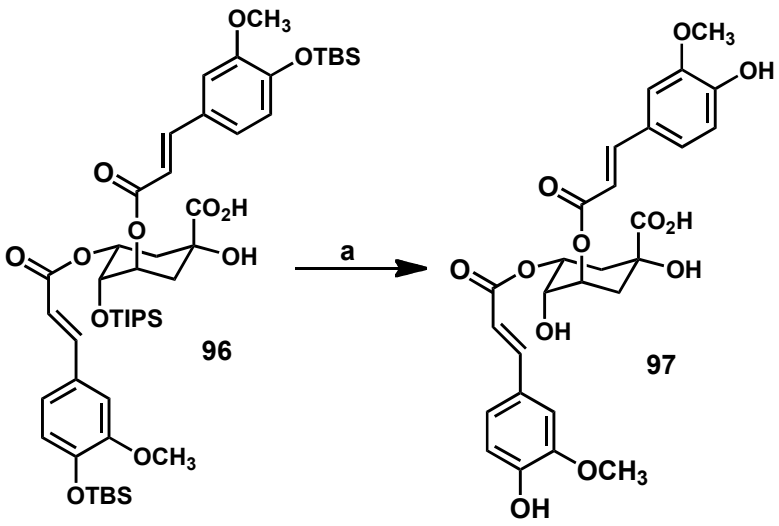
***Scheme 32**. Reagents and conditions: **a)** imidazole, anhydrous DMF, TBS chloride, 96 ºC, 3 h, 90%; **b)** toluene, cat. DMF, oxalyl chloride, -5 ºC to room temperature, 3 h, 78%.*

Treatment of triol **88** with **95** (2.2 eq), under the conditions used for the previous coupling, afforded **96** in 88% yield following column chromatography (Scheme 33).



***Scheme 23**. Reagents and conditions: **a)** DMAP, **95**, pyridine, CH_2Cl_2, room temperature, 12 h, 88%.*

Global deprotection of the silyl protecting groups was accomplished as described previously affording the target 3,5-FQA **97** in an excellent 91% yield (Scheme 34).



***Scheme 34**. Reagents and conditions: **a)** HF-pyr, THF, 0 ºC to room temperature, 12 h, 91%.*

This represents the first efficient synthesis of the 3,5-FQA **97**. The structure of 3,5-FQA **97** was initially confirmed by ^{1}H NMR spectroscopy. The H-3 or 5 and H-3 or 5 of the quinic acid moiety appeared as doublet of doublet of doublet at δ 5.24 ppm (*J* = 3.5, 3.5, 4.1 Hz) and as a complex multiplet between δ 4.10-4.07 ppm. The H-4, H-2 and H-6 appear as multiplets at between δ 3.64-3.58 ppm, δ 2.38-2.23 ppm and 1.98-187 ppm respectively (Figure 26).

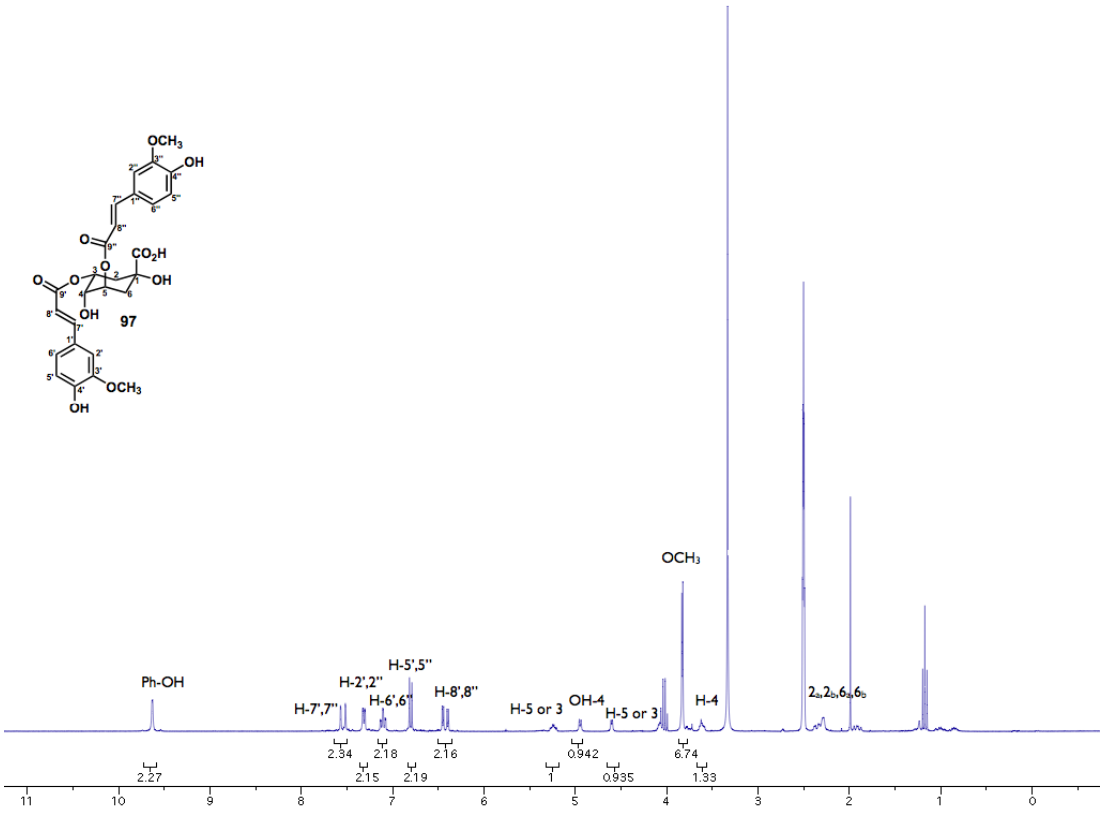


Figure 26. *^{1}HNMR spectrum of 3,5-FQA **97** in DMSO-d_6.*

The 2D 1H, 1H COSY of the caffeoyl moiety of 3,5-FQA **97**, (Figure 27) showed the presence of the (*E*)-double bonds at δ 7.54, 7.53, 6.45, and 6.39 with a large reciprocal coupling constant of 16.0 Hz. The H-2'/2''appear as 2 doublets at δ 7.32/7.30 ppm, with coupling constants of 1.8 Hz. The H-6'/6'' appears as 2 × doublets of doublet at δ 7.08/6.80, with coupling constants of 8.1 and 1.8 Hz respectively. The H-5'/5'' signals also coincide with each other appearing as a doublet at δ 6.80 ppm, with a coupling constant of 8.1 Hz. The OCH_3 of the caffeoyl moiety appear as singlets at 3.83 ppm and 3.82 ppm. The hydroxyl group on the caffeoyl moiety appear as a singlets at δ 9.63 ppm and 9.62 ppm respectively. The infrared spectrum of 3,5-FQA **97** was found to contain a broad absorption band at 3460 cm^{-1}, and further absorptions at 1696 and 1783 cm^{-1}, which are indicative of the alcohol

functionality and the carbonyl groups. The mass spectrum gave a signal at 543 Daltons, corresponding to the molecular ion $[M-H]^-$ expected for $C_{27}H_{27}O_{12}$ *m/z* = 543 $[M-H]^-$. An accurate mass measurement confirmed the expected molecular formula of $C_{27}H_{27}O_{12}$.

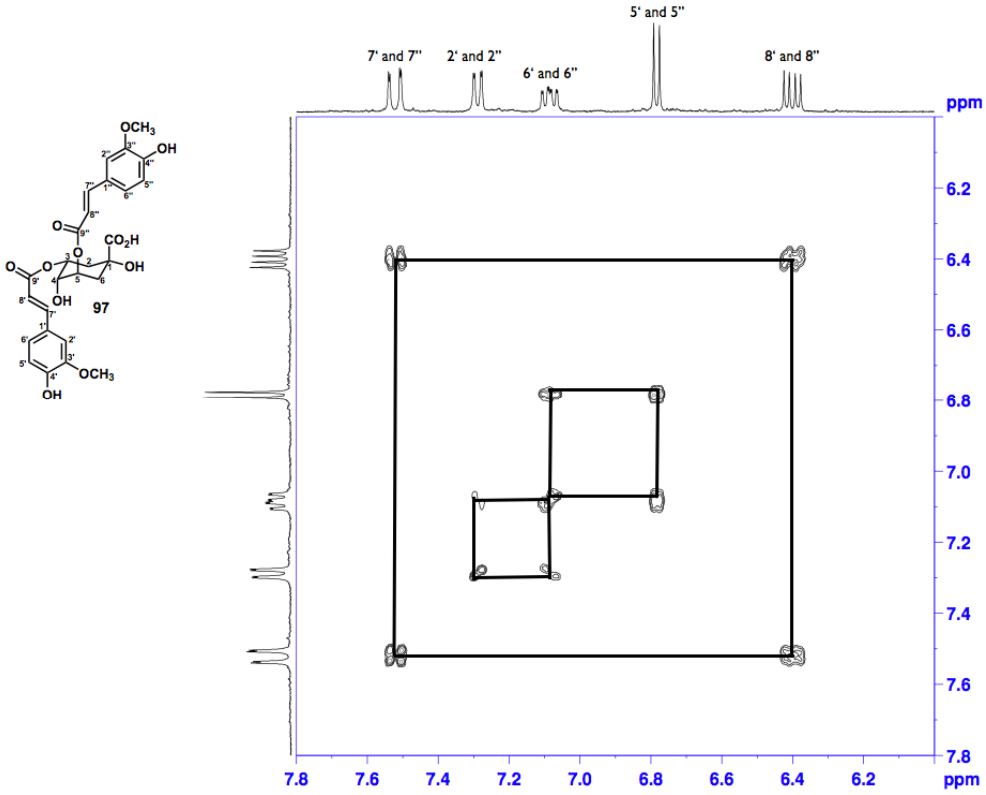


Figure 27. *2D ^1H, ^1H-COSY spectrum of caffeoyl moiety of 3,5-FQA* ***97****.*

With 500 milligrams of crude product in hand, the purification of 3,5-FQA **97** was embarked upon by reverse phase HPLC on a Kingsorb 5µ C_{18} column eluting with methanol and H_2O (80:20). This gave a chromatograph with a single peak in the UV trace (254 nm) with a retention time of 3.87 min (Figure 28).

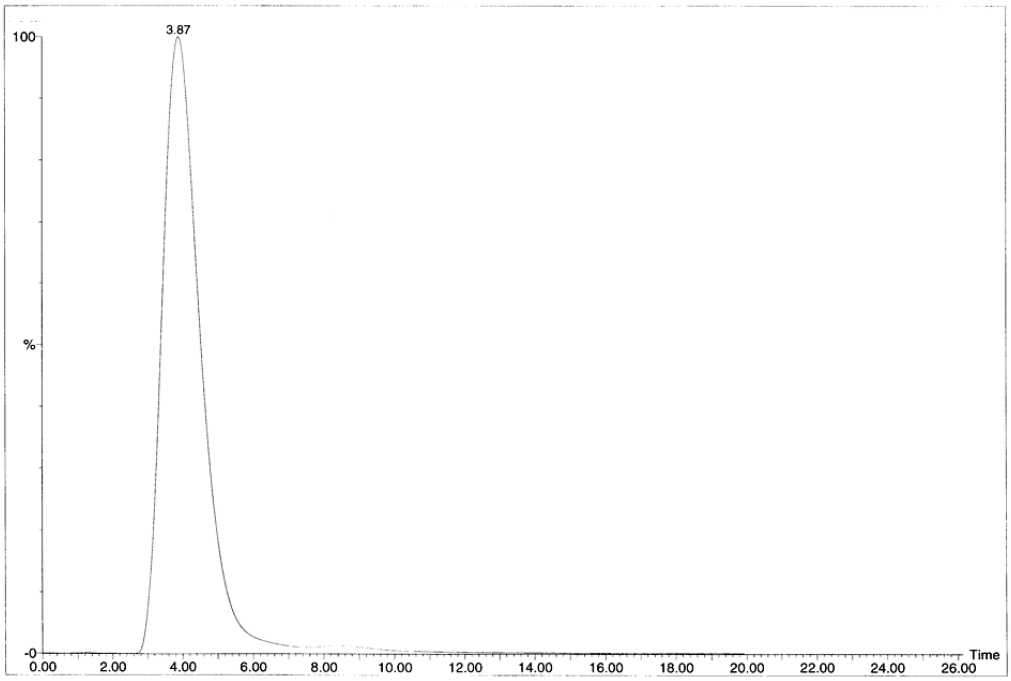
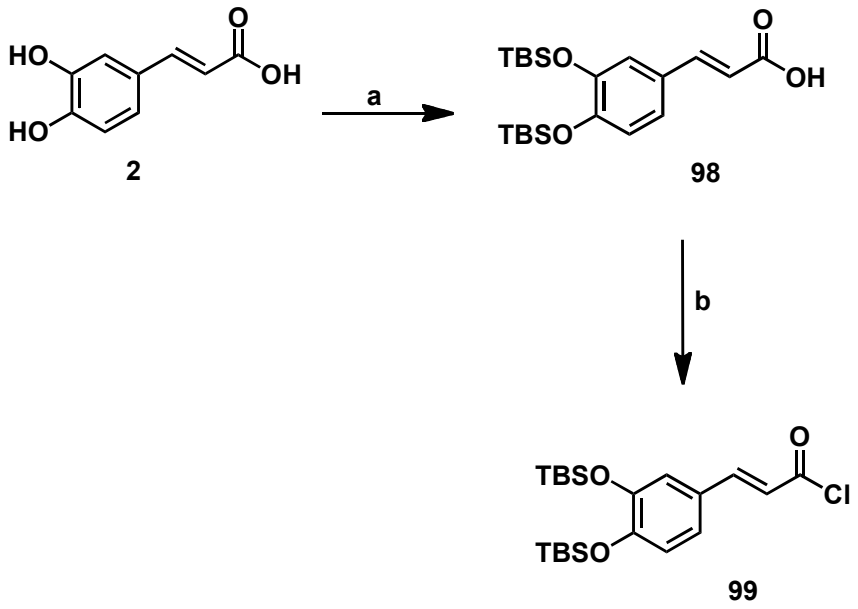


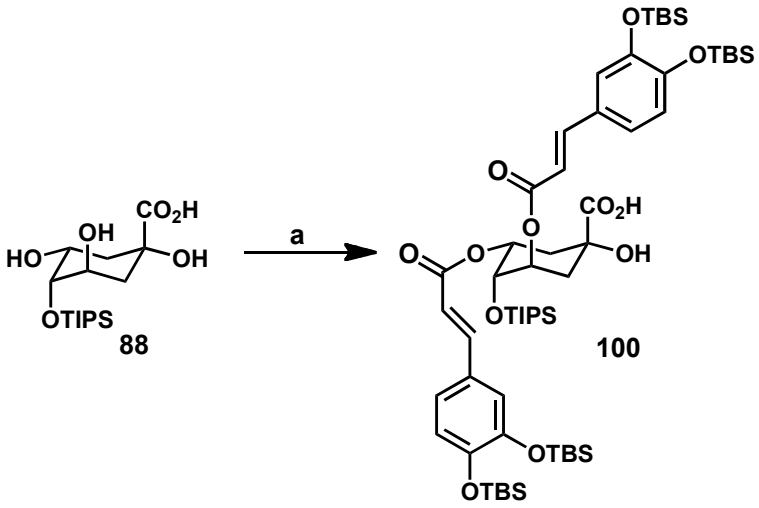
Figure 28. *Reverse phase HPLC of compound 3,5-FCQA* ***97*** *after initial purification.*

With the first two compounds 3,5-(3,4-dimethoxycinnamyl)quinic acid **92** and 3,5-FQA **97** in hand, the synthesis of 3,5-DCQA **11** was then investigated. It was assumed that the synthesis of 3,5-DCQA **11** would be more problematic due to its higher polarity relative to 3,5-(3,4-dimethoxycinnamyl)quinic acid **92** and 3,5-FQA **97.** A suitably protected caffeoyl chloride **99** was prepared from caffeic acid **2**. In this case, it was also decided to use TBS ether for the protection of caffeic acid **2** because all the protecting groups could be removed in one step using HF-pyridine. *O*-Silylation of caffeic acid **2** with TBS chloride and imidazole in anhydrous DMF as solvent afforded *bis*-TBS ether **98** in an excellent 94% yield. Treatment of 3,4-*tert*-butyldimethylsilyl caffeic acid **98** with 2 equivalents of oxalyl chloride afforded the desired 3,4,-*tert*-butyldimethylsilyl caffeoyl chloride **99** in a good 86% yield (Scheme 35).



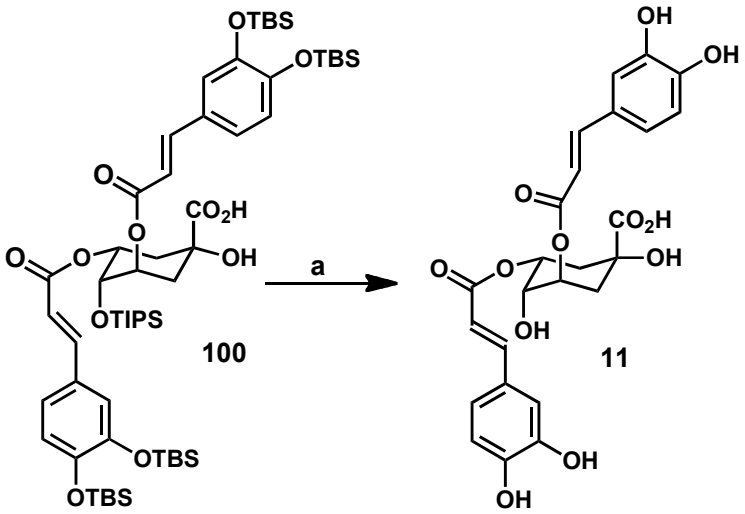
***Scheme 35**. Reagents and conditions: **a)** imidazole, anhydrous DMF, TBS chloride, 70 ºC, 3 h, 94%; **b)** toluene, cat. DMF, oxalyl chloride, -5 ºC to room temperature, 3 h, 86%.*

Treatment of triol **88** with DMAP and 3,4-*tert*-butyldimethylsilyl chloride **99** (2.2 eq) in pyridine at room temperature for 12 h afforded the adduct **100** in excellent 63% yield (Scheme 36).



***Scheme 36**. Reagents and conditions: **a)** DMAP, **99**, pyridine, CH_2Cl_2, room temperature, 12 h, 63%*

Cleavage of all protecting groups of adduct **100** was achieved by initial treatment with HF-pyridine using THF as solvent at 0 °C, allowing the resultant mixture to warm up to room temperature overnight, affording 3,5-DCQA **11** in an excellent 92% yield following isolation and purification by column chromatography (Scheme 37).



***Scheme 37**. Reagents and conditions: **a)** HF-pyr, THF, 0 ºC to room temperature, 12 h, 92%.*

Comparison of the spectral data obtained for the synthesised 3,5-DCQA **11** with that from a previous report was undertaken,[113] the results of which are presented below (Table 9).

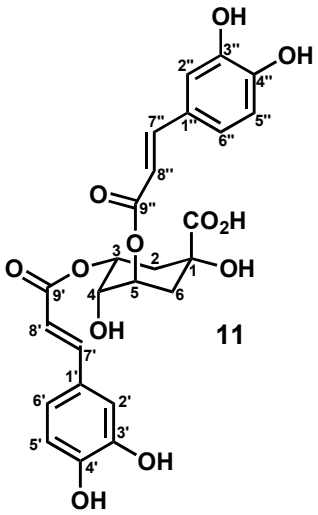


***Table 9**. [1]H and [13]C NMR data comparison of the natural and synthetic 3,5-DCQA **11**.*

	Natural		**Synthetic**	
Position	δ $^{1}H^{a}$	δ $^{13}C^{a}$	δ $^{1}H^{a}$	δ $^{13}C^{a}$
Ph-OH	-	-	9.59	-
Ph-OH	-	-	9.16	-
7’	7.48	144.2	7.47	146.0
7’’	7.46	144.2	7.46	146.0
2’	7.05	114.3	7.04	115.2
2’’	7.03	114.3	7.05	115.2
6’	7.00	120.9	7.00	121.7
6’’	6.97	120.9	6.99	121.8
5’	6.76	115.4	6.77	116.4
5’’	6.76	115.4	6.77	116.4
8’	6.22	114.4	6.20	114.6

	Natural		Synthetic	
8''	6.22	114.4	6.19	114.6
5 or 3	5.27	71.1	5.25	70.3
1-OH	-	-	4.95	-
4-OH	-	-	4.59	-
5 or 3	5.16	72.5	5.12	71.2
4	3.72	69.9	3.65	67.8
2_{ax}	2.11	35.9	2.37-2.26	34.5
2_{eq}	1.76	35.9	2.37-2.26	34.5
6_{ax}	1.94	38.8	1.95-1.88	36.1
6_{eq}	1.81	38.8	1.95-1.88	36.1

[a] In ppm, relative to DMSO-d_6.

No significant differences were identified between the ^{1}H NMR spectra of the natural and the synthetic 3,5-DCQA **11** (Figure 29). Differences of between 0.02 to -0.03 ppm were observed between the ^{1}H NMR spectra of the natural and synthetic 3,5-DCQA **11**.

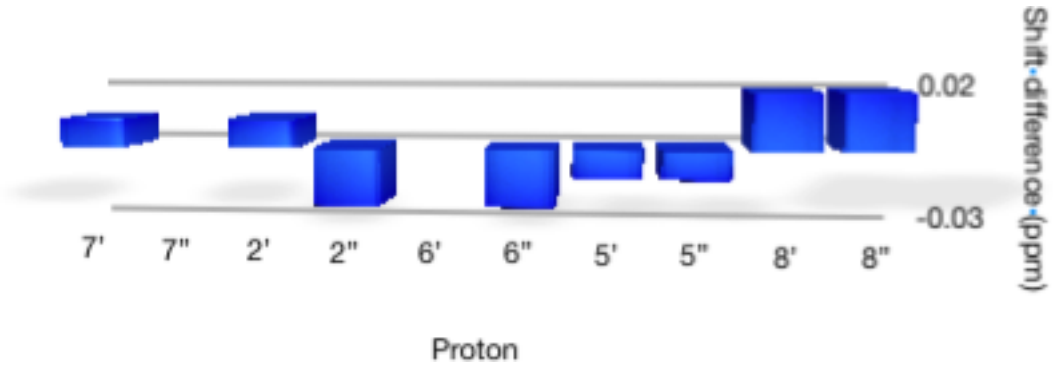


Figure 29. *^{1}H NMR chemical shift differences (ppm) natural and synthetic 3,5-DCQA **11**.*

The ^{13}C NMR spectra of the synthetic product was similar to the natural. The differences in the ^{13}C spectra for the natural and the synthetic forms of 3,5-DCQA **11** were between 0.2 to -1.8 ppm (Figure 30).

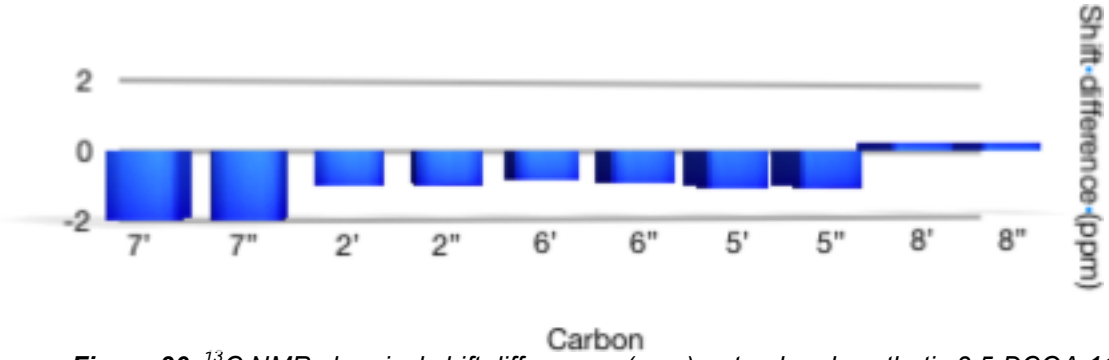


Figure 30. *^{13}C NMR chemical shift differences (ppm) natural and synthetic 3,5-DCQA **11**.*

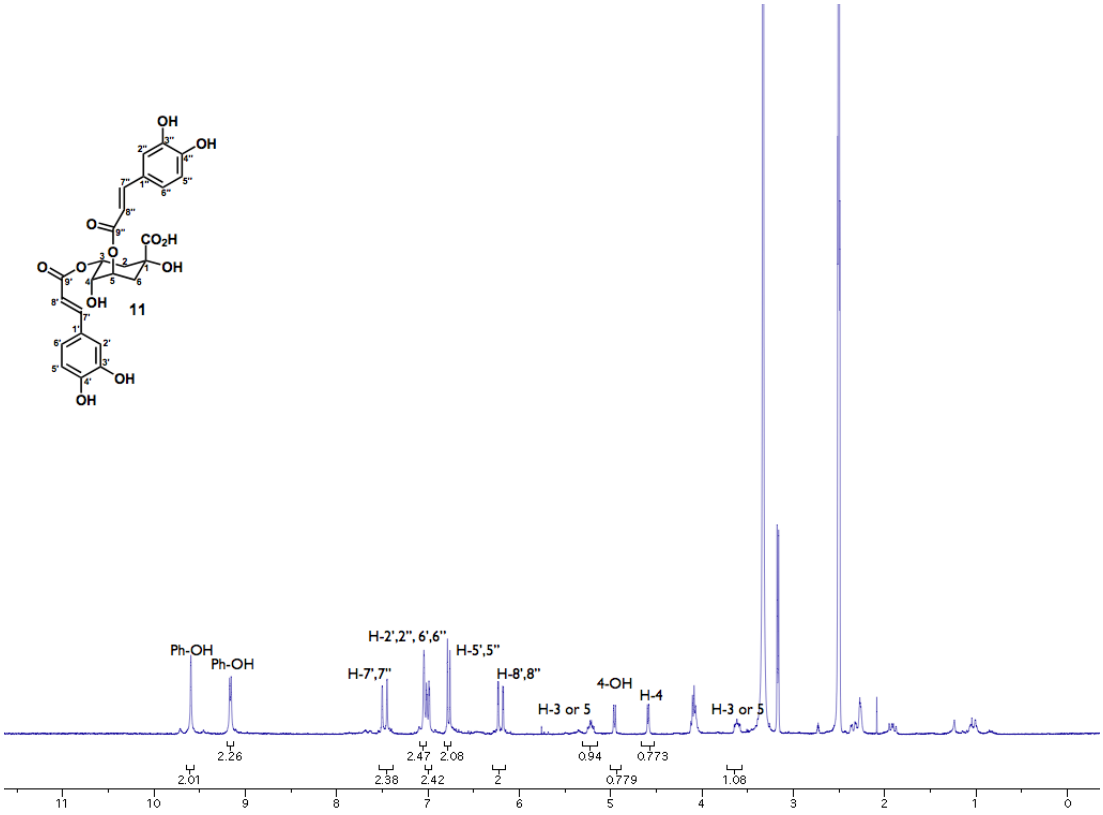


Figure 31. *^{1}H NMR spectrum of 3,5-DCQA **11** in DMSO-d_6.*

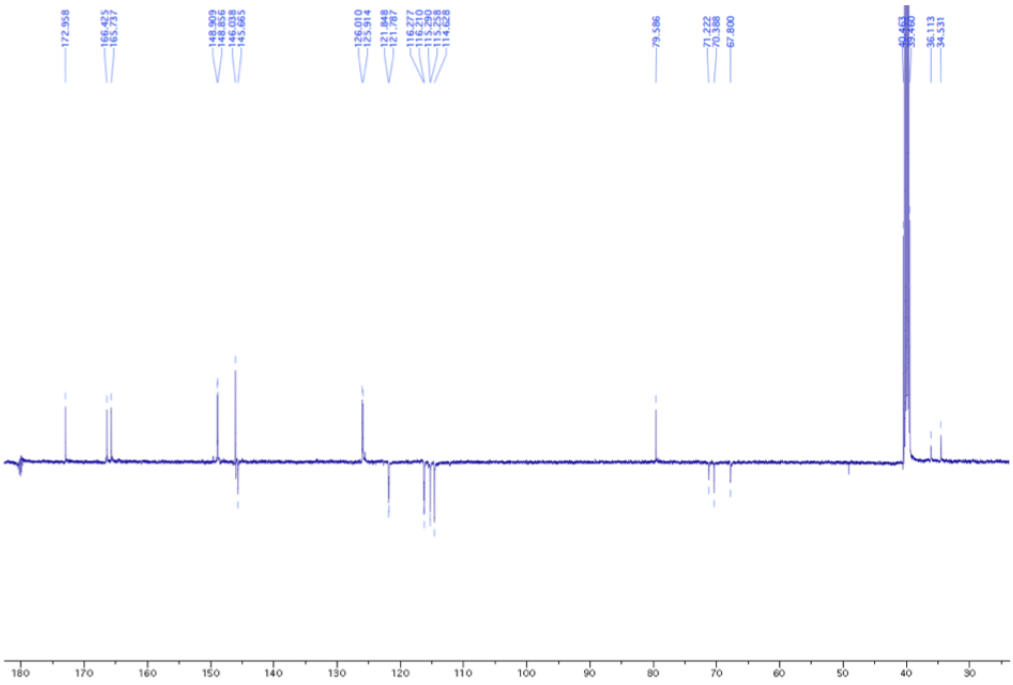


Figure 32. *^{13}C NMR spectrum of **11** in DMSO-d_6.*

The infrared spectrum contained a broad absorption band at 3019 cm^{-1}, and absorptions at 1717 cm^{-1}, indicative of the alcohol functionality and carbonyl groups. The mass spectrum gave a signal at 515 corresponding to the molecular ion $[M-H]^-$ expected for $C_{25}H_{23}O_{12}$ *m/z* = 515 $[M-H]^-$. An accurate mass measurement confirmed the expected 515.1190 molecular formula of $C_{23}H_{25}O_{12}$.

The purity of compound 3,5-DCQA **11** was determined by reverse phase HPLC using a Kingsorb 5µ C_{18} column eluting with methanol and H_2O (80:20), displaying a single peak in the UV (254nm) with a retention time of 9.30 min (Figure 33).

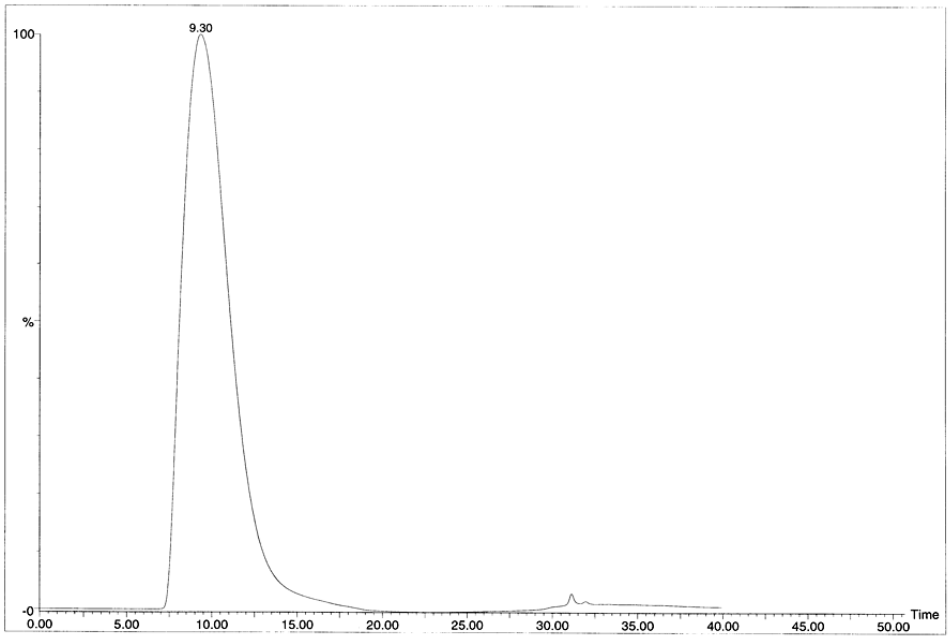


Figure 33. *Reverse phase HPLC of compound 3,5-DCQA* ***11*** *after initial purification.*

Conclusion

A novel synthetic protocol for the synthesis of 3,5-DCQA **11** and its derivatives was developed the details of which were discussed. The strategy employed quinic acid as a reagent for the formation of these types of compounds. In the original approach the quinide **73** was assembled followed by the regioselective benzylation of the 3-hydroxyl group on **73**. Compound **68** was fully protected utilising the TBS ether protecting group which afforded **69**. Hydrogenolysis of the benzyl ether was eventually achieved with Pd/black after several attempts affording alcohol **70**. However, in an unexpected reaction the silyl protecting group at the C-4 position underwent nucleophilic attack during the lactone hydrolysis step resulting in the cleavage of the silyl ether protecting group at the C-4 position to give compound triol **80**. Coupling of triol **80** with diacetyl caffeoyl chloride afforded the undesired product **93**.

An alternative protocol was developed utilising an alternative protecting group strategy for the synthesis of 3,5-DCQA **11** and its derivatives. Quinide **68** was protected using the TIPS protecting group affording **85**. Hydrolysis of the lactone ring of **85**, however lead to the cleavage of the silyl protecting group at the C-1 position. Debenzylation of **85** was achieved using Pd/C. In the last few steps of the synthesis triol **88** was coupled with 3-methoxyl-4-*O*-*tert*-butyldimethylsilyloxycinnamyl chloride **95**, 3,4-*tert*-butyldimethylsilyl caffeoyl chloride **99** and 3,4 dimethoxycinnamyl chloride **90** followed by cleaved of the silyl protecting groups. The target compounds 3,5-DCQA **11**,

3,5-FQA **97**, and 3,5-(3,4-dimethoxycinnamyl)quinic acid **92** were achieved over 7 steps in 30%, 36%, and 38% yield respectively.

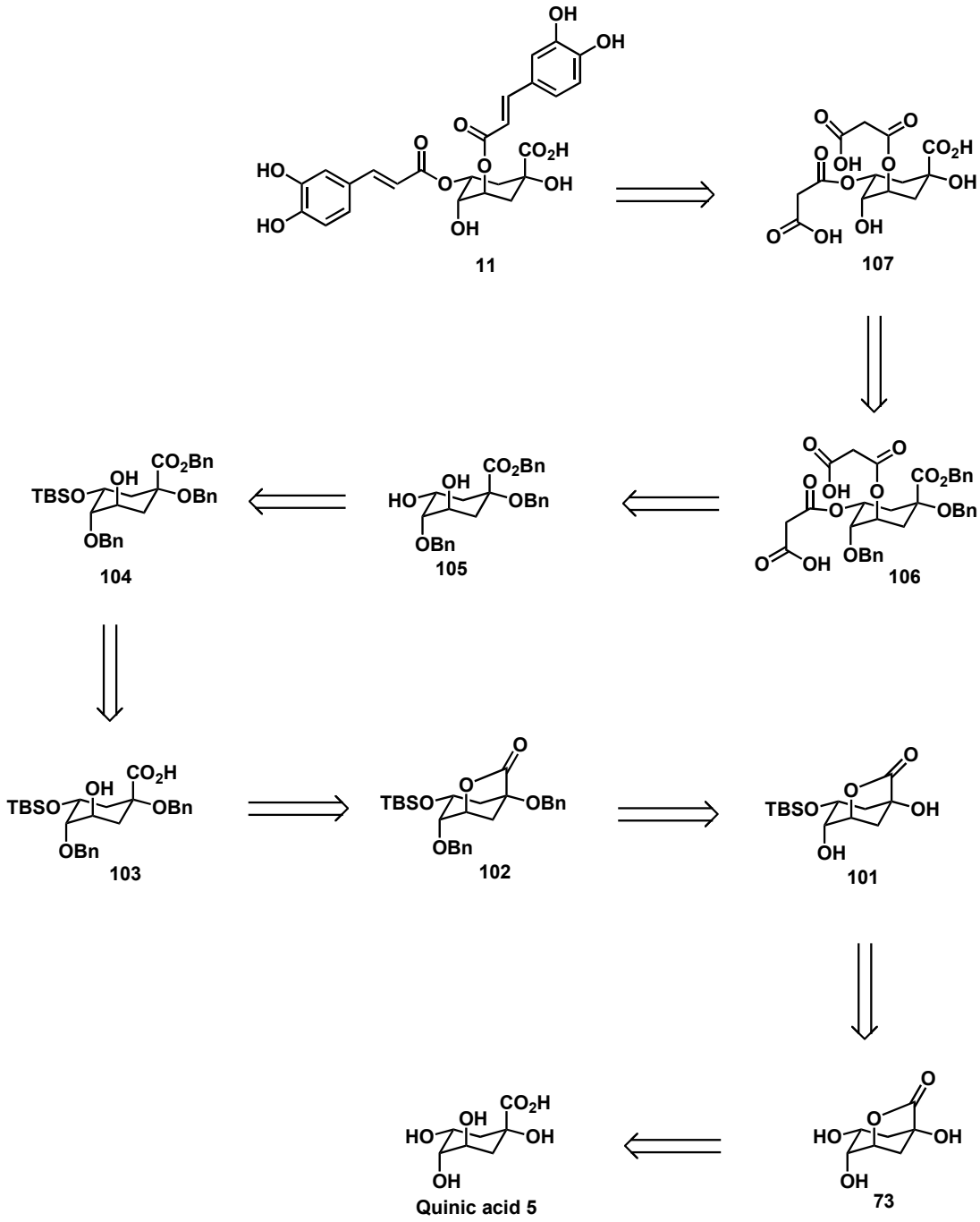
Chapter Three

3.0 Synthesis of 3,5-O-dicaffeoylquinic acid via Knoevenagel condensation

In Chapter 2, the synthesis of 3,5-DCQA **11** was described by final esterification of a suitably protected quinic acid with 3,4-*O*-*tert*-butyldimethylsilyl caffeoyl chloride. However, an alternative approach towards the synthesis of 3,5-DCQA **11** was also investigated.

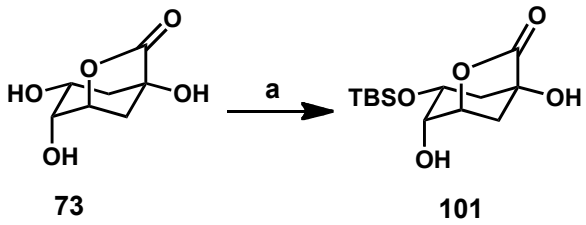
3.1 Retrosynthetic Analysis

The general features of a second synthesis of 3,5-DCQA **11** are outlined in Scheme 38. The target compound 3,5-DCQA **11** could be formed *via* condensation of the aldehyde with malonate **106** using the Knoevenagel methodology developed by Smarrito *et al.*[98] Advantageously, the condensation reaction does not require protection of the aldehyde or the dimalonyl quinic acid derivative **106**, in contrast with the esterification methodology described in section 2.1, where the quinic acid fragment **88** had to be fully protected until the last step of the synthesis. Compound **106** can be derived in one step from intermediate **105**. The fully protected **105** could be fashioned from diol **104** through a coupling reaction with Meldrum's acid. The diol **104** can be obtained through cleavage of the silyl ether of **103**. Benzylation of the carboxylic acid of **102** result in the formation of intermediate **103**. Alcohol **102** could be obtained from hydrolysis of **101**. Intermediate **101**, can be derived in 3 steps from quinide **73**. Compound **73** can be prepared from quinic acid **5**.



Scheme 38. *Retrosynthetic analysis for 3,5-DCQA* ***11****.*

To begin, quinide **73** was selectively protected at the equatorial hydroxyl group (C-3) using a TBS ether according to the method of Glebocka *et al*.[105] The TBS protecting group was chosen because it was deemed robust enough to protect the 3-hydroxyl group of quinide **73** through several functional group manipulations. Thus, **73** was treated with imidazole in DMF at 0 °C, followed by addition of TBS chloride. The mixture was stirred at 0 °C for 30 min and then 1 h at room temperature to afford the protected diol **101** in an excellent 83% yield after purification (Scheme 39). The structure of **101** was conclusively confirmed by detailed analysis of the ^{1}H NMR spectrum, which was found to be in close agreement with the original literature data.[105] Further confirmation was provided by mass spectral analysis, which gave a signal at 287 Daltons, corresponding to the molecular ion of expected for $C_{13}H_{24}O_5Si$.

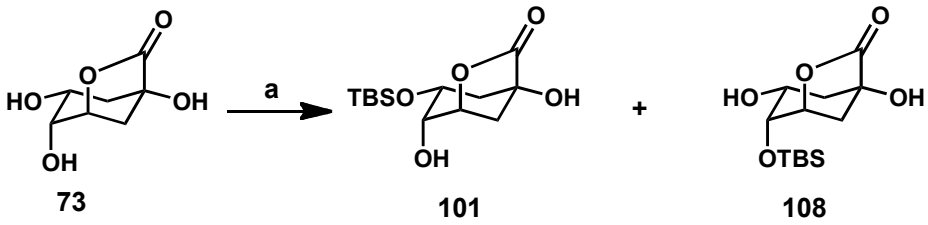


73 **101**

Scheme 39*. Reagents and conditions:* ***a)*** *imidazole, DMF, TBS chloride, 0 °C for 30 min and 1 h at room temperature, 83%.*

At this point a discussion on the selectivity of the equatorial hydroxyl over axial hydroxyl groups is pertinent. It was theorised that the low reaction temperature and the short reaction time led to the selective formation of **101**, as the equatorial secondary hydroxyl group at C-3 is less hindered than the axial secondary hydroxyl group at C-4. However, when the reaction was

carried out at room temperature, we observed a mixture of TBS mono-protection at 3- and 4-positions in a 50:50 ratio (Scheme 40). The 2D ^{1}H, ^{29}Si correlation experiment shows the present of two silyl groups, one at C-3 and the other at C-4 position (Figure 34).



73 101 108

Scheme 40. *Reagents and conditions:* ***a)*** *imidazole, DMF, TBS chloride, room temperature ,1h, 50% (**101**), 50% (**108**).*

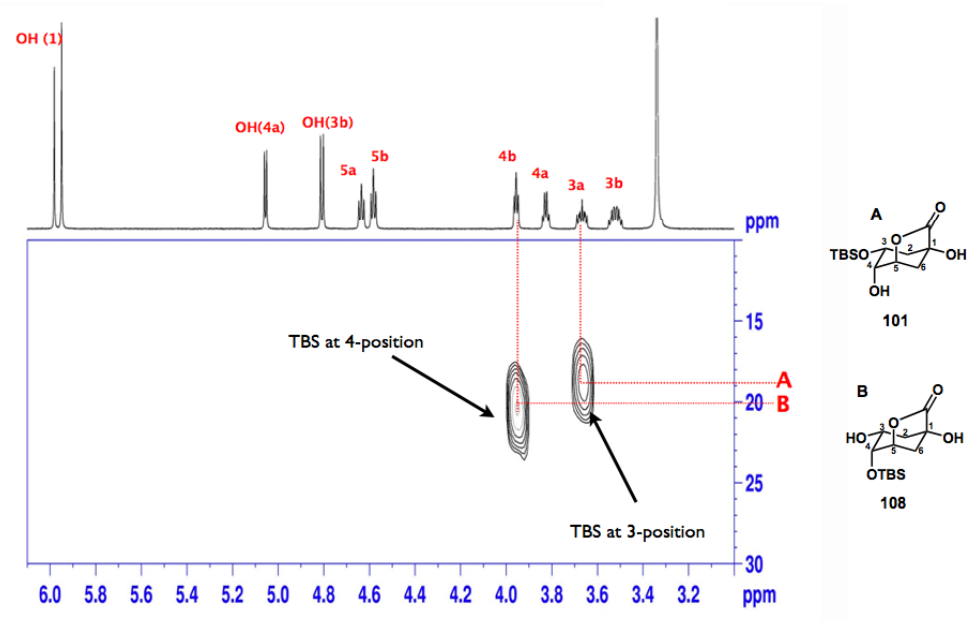
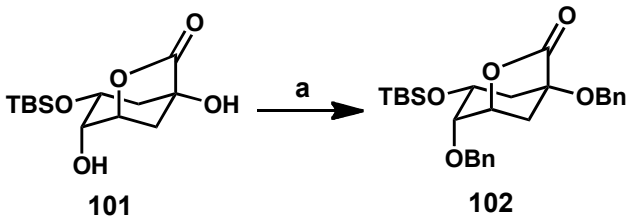


Figure 34. *^{1}H, ^{29}Si-HMBC*

The regioselective *O*-silylation of the equatorial hydroxyl group of **73** has also been described by Manthey *et al.*[97] using TBS chloride in DMF containing tetrabutylammonium iodide and triethylamine at 0 °C for 6 h. Under these

conditions the observed a mixture of TBS protection at the 3- and 4- position in a 97:3 ratio.

The next goal was the *O*-benzylation of both the 1- and 4-hydroxyl groups (Scheme 41). In the event, exposure of diol **101** to a cold solution (0 °C) of sodium hydride in DMF, followed by addition of benzyl bromide afforded lactone **102** in 30% yield after column chromatography.[99] The low yield in this reaction probably reflects the difficulties in the protection of the hindered tertiary hydroxyl group at C-1.[97]



101 **102**

Scheme 41*. Reagents and conditions:* ***a)*** *DMF, NaH, BnBr, 0 °C for 30 min and 21 h at 60 °C, 60%.*

After extensive experimental work, It was observed that the best conditions for the protection of the 1- and 4- hydroxyl groups involved warming the reaction up to 60 °C for 12 h as shown in Table 10. Under these conditions, the desired lactone **102** was obtained in 60% yield.

Table 10. *Reaction conditions for the dibenzylation of diol **101**.*

Entry	Reagent	Solvent	Temp	Time (h)	Product	Yield %
1	NaH/BnBr	DMF	r.t	3 h	**102**	15%
2	NaH/BnBr	DMF	r.t	6 h	**102**	18%
3	NaH/BnBr	DMF	r.t	12 h	**102**	31%
4	NaH/BnBr	DMF	60 °C	3 h	**102**	40%
5	NaH/BnBr	DMF	60 °C	12 h	**102**	60%

The ^{1}H NMR spectrum of **102** displays the appropriate resonances (Figure 35). Notably, the aromatic protons appear as a multiplet at between δ 7.33-7.14 ppm. The benzylic protons for 4-OCH_2Ph and 1-OCH_2Ph appear as an AB system patterns at δ 4.74-4.37 ppm and δ 4.49-4.45 ppm, respectively, with geminal coupling constants around 11.0 to 12.0 Hz. (Figure 36). An accurate mass measurement gave a signal at 491.2230 Daltons, corresponding to the sodium adduct $[M+Na]^+$ for $C_{27}H_{36}O_5SiNa$.

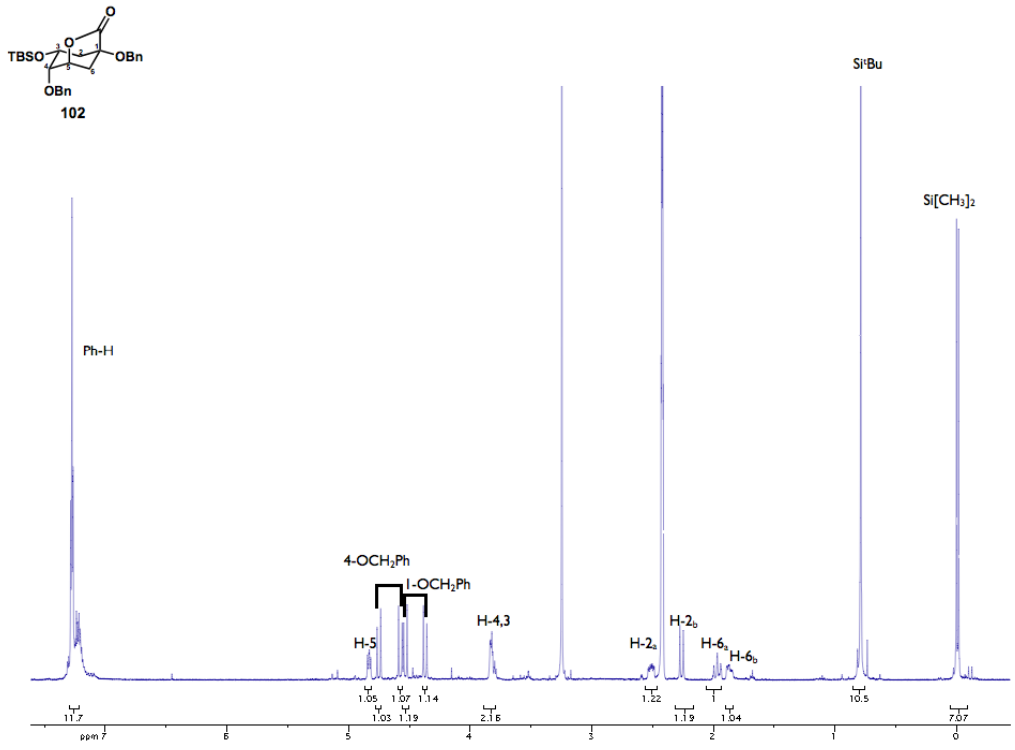
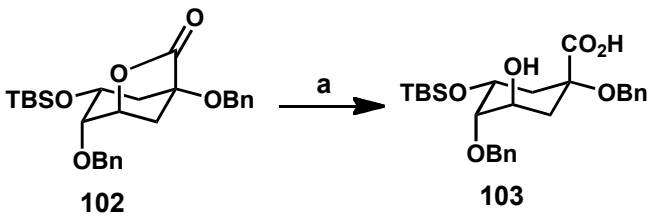


Figure 35. *^{1}H NMR spectrum of **102** in DMSO-d_6.*

Benzylation was followed by base catalysed hydrolysis of the lactone **102** in THF/H_2O at room temperature for 12 h, which afforded the desired product **103** in 90% yield (Scheme 42).



Scheme 42. *Reagents and conditions*: **a)** NaOH, THF-H_2O, room temperature, 12 h, 90%.

The ^{1}H NMR spectrum of compound **103** showed some differences when compared with that for lactone **102**. The benzylic protons of 1-OCH_2Ph were shifted downfield to 4.38-4.28 ppm, (J = 11.0 Hz) (Figure 36).

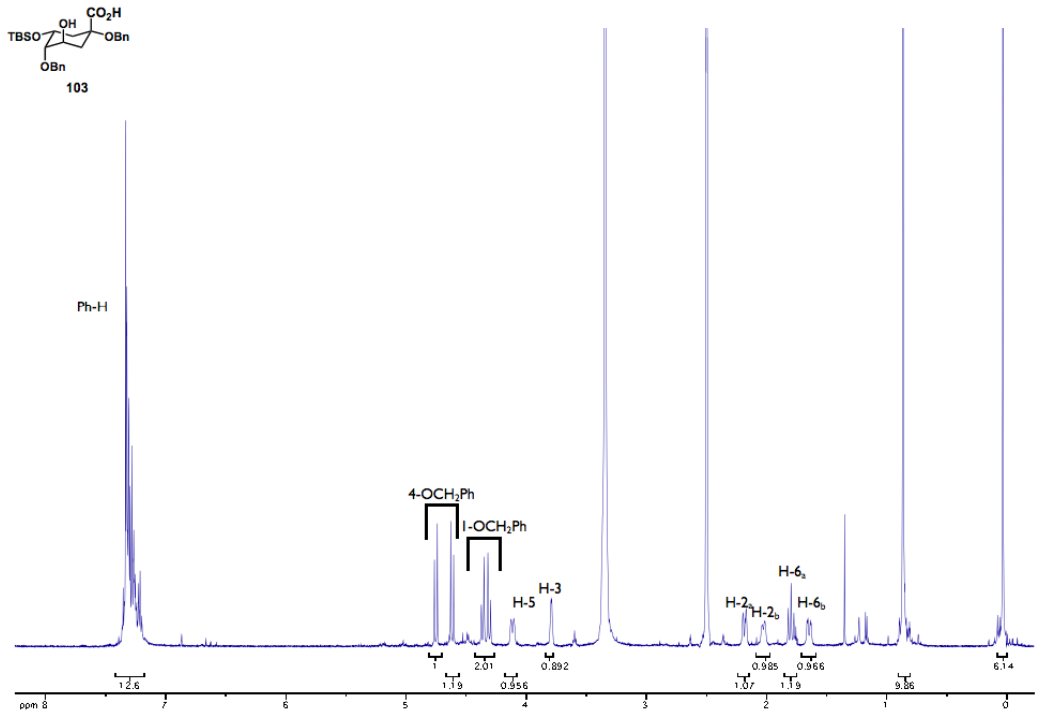


Figure 36. *^{1}H NMR spectrum of **103** in DMSO-d_6.*

The H-4 proton is not apparent in the ^{1}H NMR due to overlap with the H_2O signal from DMSO-d_6. In this case a 2D NMR experiment was carried out to determine the position of the H-4. The position of this proton is clearly seen from the HSQC experiment, around 3.44 ppm (Figure 37). The infrared spectrum also shows the presence of the OH group at 3495 cm^{-1}. Further confirmation came *via* High Resolution MS, which gave a signal at 485.2359 Daltons, corresponding to the molecular ion expected for $C_{27}H_{37}O_6$.

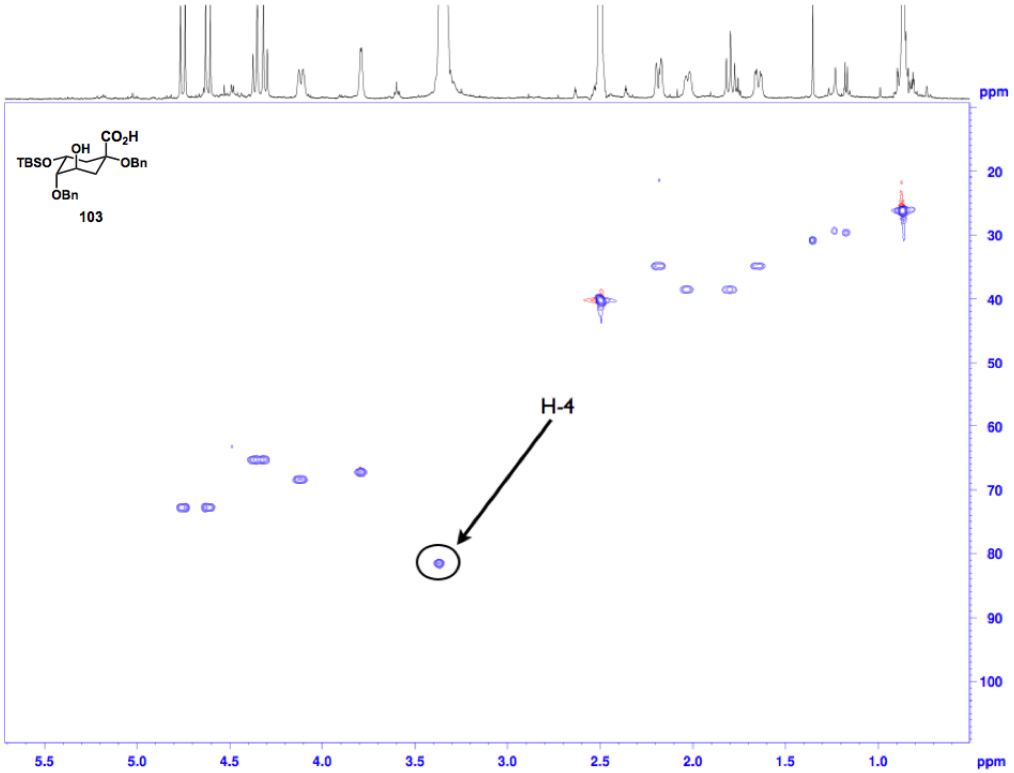
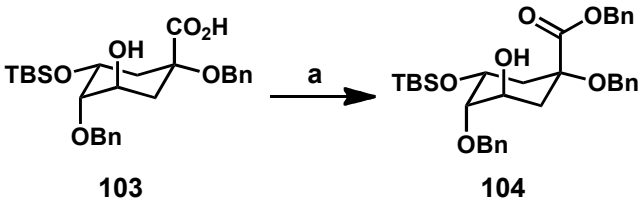


Figure 37. *HSQC spectrum of compound **103**.*

Selective benzylation of the carboxylic acid **103** was achieved utilising the method of Montchamp *et al.*[114] Compound **103** was treated with Cs_2CO_3 (0.5 eq) in MeOH-H_2O at room temperature for 10 min. The solvent was then evaporated followed by the addition of benzyl bromide in DMF at 0 °C for 1 h before being allowed to warm up to room temperature stirring for a further 10 h. This gave alcohol **104** in an excellent 95% yield (Scheme 43).



103 **104**

***Scheme 43**. Reagents and conditions: **a)** Cs_2CO_3, MeOH-H_2O, room temperature, then BnBr, DMF, 1 h, 0 °C then room temperature, 12h, 95%.*

The ^{1}H NMR spectrum of **104** displayed the expected resonances (Figure 38). Notably, the new AB system at δ 5.21-4.98 ppm which can be attributed to the benzyl ester 1-CO_2CH_2Ph, with a geminal coupling constant around 12.0 Hz. The two remaining AB systems at δ 4.70-4.58 and 4.46-4.04 ppm are from the benzyl ethers, at the 4- and 1-positions, respectively. The infrared spectrum contained a broad band at 3421 cm^{-1} and absorption at 1654 cm^{-1} indicative of both the alcohol and carbonyl groups, respectively. An accurate mass measurement displayed a signal at 599.2797 Daltons corresponding to that expected for the sodium adduct $C_{34}H_{44}O_6SiNa$.

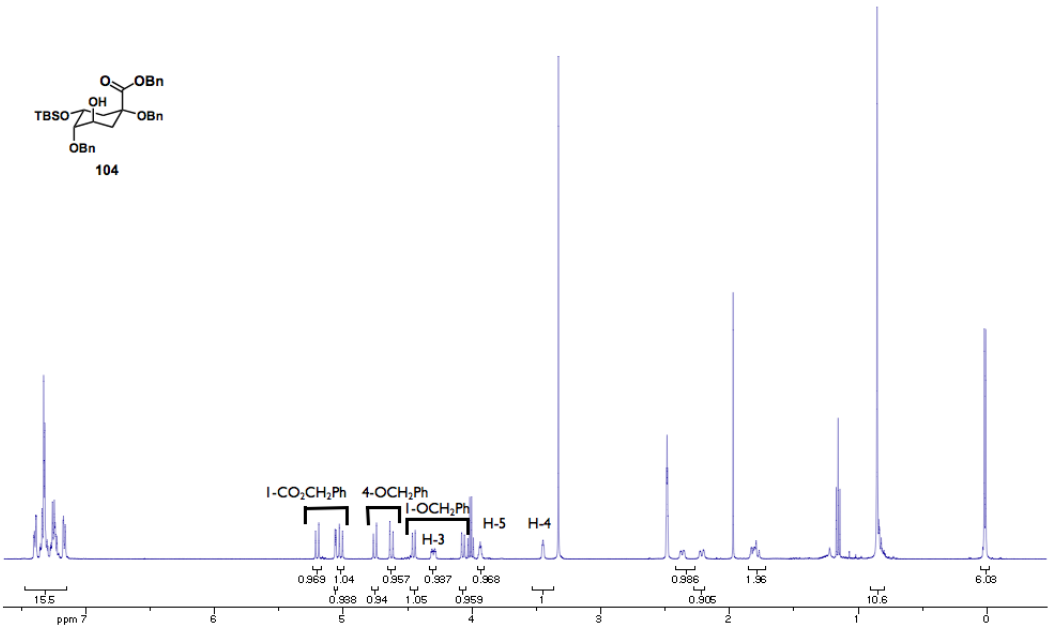
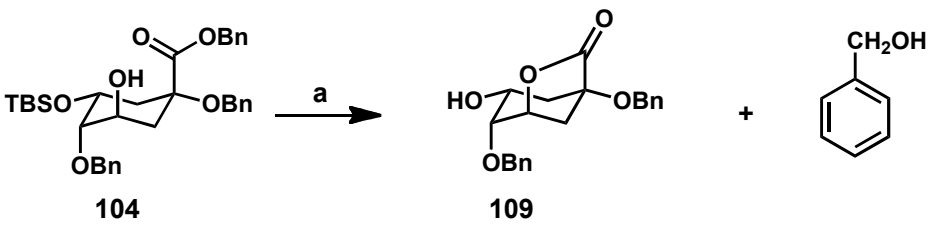


***Figure 38**. ^{1}H NMR spectrum of **104** in DMSO-d_6.*

Having served its purpose, the TBS ether protecting group at C-3 position was then removed. Reaction of alcohol **104** with TBAF in THF resulted in cleavage of the TBS ether, but also the unexpected formation of the quinide

lactone **109** (Scheme 44). The ^{1}H NMR spectrum of **109** clearly shows the loss of the AB system for benzyl ester (Figure 39).



104 **109**

***Scheme 44**. Reagents and conditions: **a)** TBAF, THF, room temperature, 6 h, 88%.*

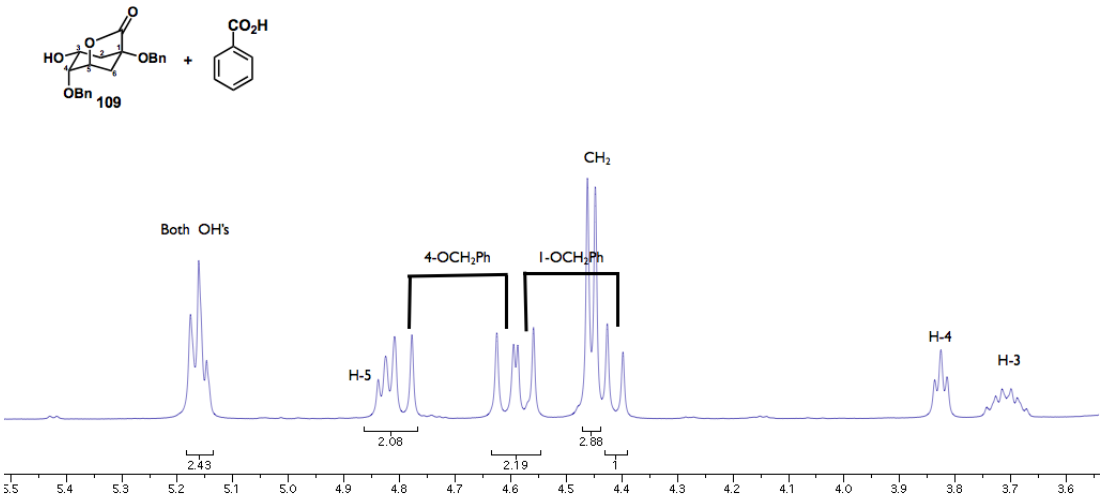


***Figure 39**. ^{1}H NMR spectrum of **109** in DMSO-d_6.*

The HSQC spectrum shows that the multiplet at 5.13-5.18 ppm, is made up of two protons, which do not correlate with any carbon atom and must therefore be due to the hydroxyl groups (2 × OH) (Figure 40).

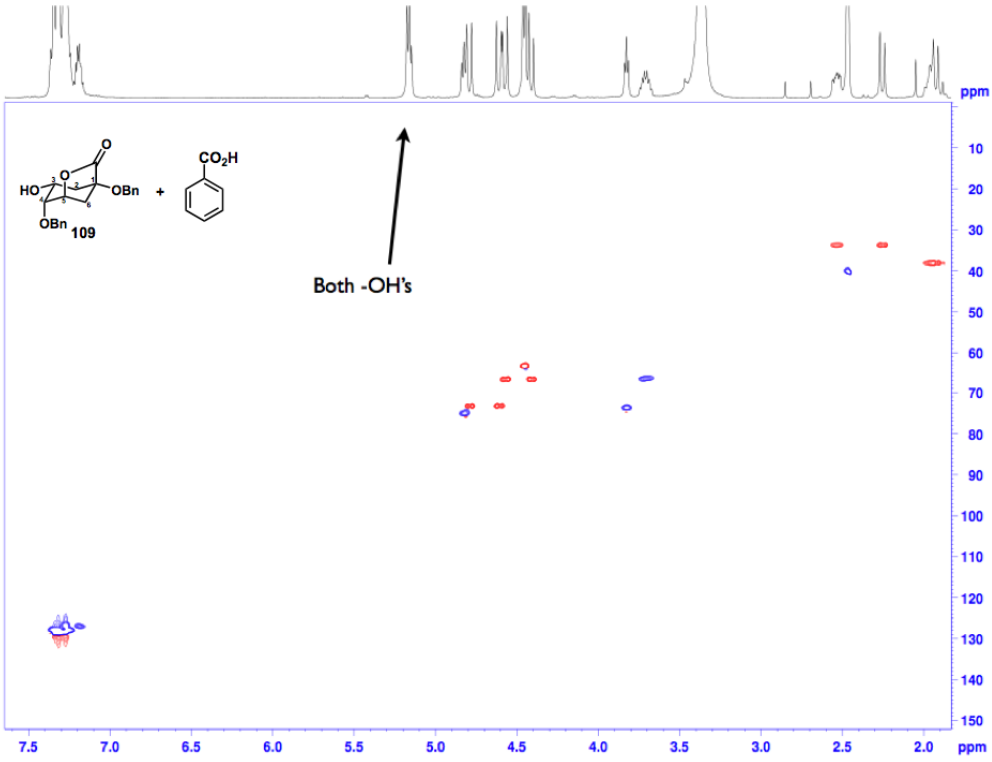


***Figure 40**. HSQC spectrum of compound **109**.*

The COSY NMR experiment showed that one of the OH groups couples with the doublet CH_2 at 4.45 ppm. This suggests the presence of a free benzyl alcohol (Figure 41). Further confirmation was provided by mass spectral analysis, which gave a signal at 354 Daltons, corresponding to the molecular ion of expected for $C_{21}H_{22}O_5$.

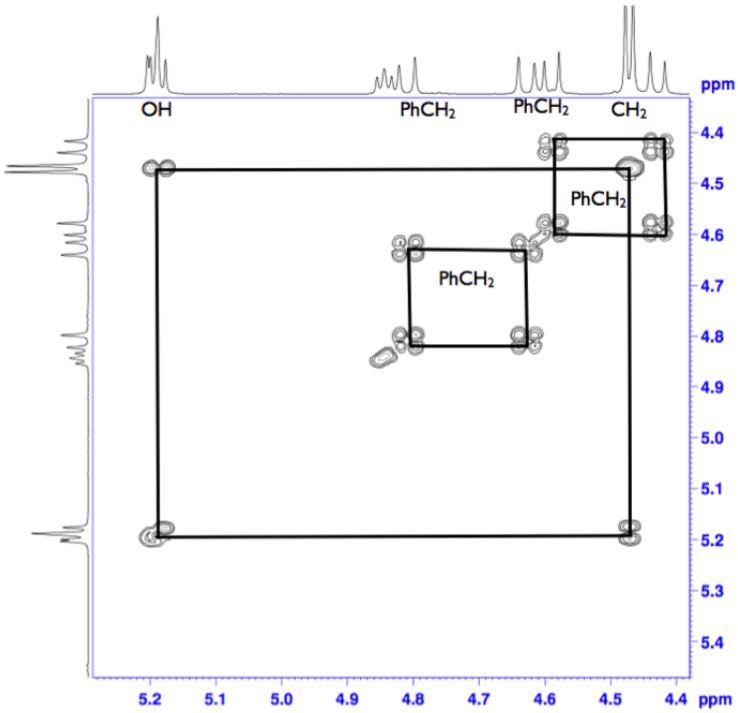


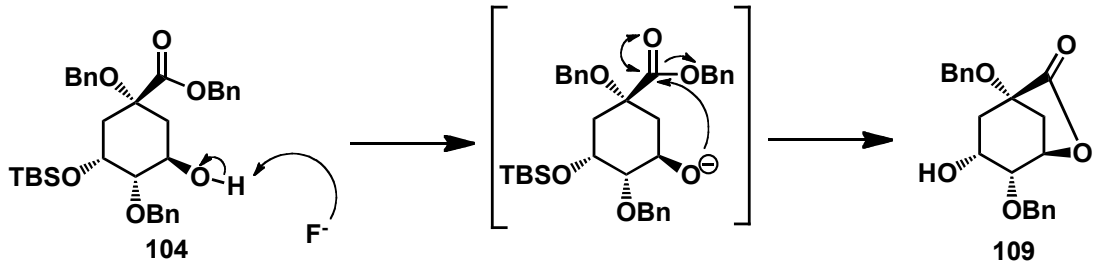
***Figure 41**. COSY spectrum of lactone **109**.*

Several attempts were made to cleave the TBS protecting group without the formation of the lactone ring, the results of which are shown below (Table 11).

***Table 11.** Attempt for the synthesis of diol **105**.*

Entry	Reagent	Temp	Time (h)	Product	Yield %
1	TBAF	r.t	6	**109**	87%
2	TBAF	r.t	3	**109**	69%
3	TBAF	r.t	1	**105+109**	58%+42%
4	TBAF	r.t	0.5	**105+109**	91%+9%
5	TBAF	0 °C	0.5	**105+109**	91%+9%
6	TBAF	0 °C	1	**105+109**	69%+31%
7	TBAF	0 °C	3	**109**	55%

In all cases, both lactone **109** and unreacted starting material were isolated. Decreasing the reaction temperature to 0 °C and reducing the duration of the reaction gave lactone **109** and starting material. A proposed mechanism for this reaction is shown below (Scheme 45). Compound **104** is particularly base-sensitive and cyclises quickly to form the lactone in the presence of fluoride (F^-). The hydroxyl group is deprotonated by fluoride ion followed by intramolecular attack at the carbonyl to form the lactone.

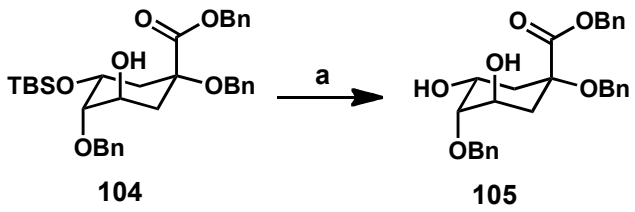


Scheme 45. *Proposed mechanism of the lactone formation.*

The strategy for resolving this problem was based upon treatment of alcohol **104** with TFA in THF at 0 °C before allowing the reaction warm up to room temperature and then stirring at this temperature for a further 12 h. This methodology was utlised by White *et al.*[115] in the synthesis of *cis*-9,10-dehydroepothilone D. The White group removed two TBS ether protecting groups using trifluoroacetic acid in CH_2Cl_2 at 0 °C for 8 h in the presence of base sensitive protecting groups.[115]

In the event, reaction of alcohol **104** with trifluoracetic acid[115] or HF-pyridine[112] in THF at 0 °C before warming to room temperature and stirring

for 12 h successfully furnished compound **105** a good in 89% yield, setting the stage for the endgame of the synthesis (Scheme 46).



***Scheme 46**. Reagents and conditions: **a)** TFA or HF-pyridine, THF, 0 °C to room temperature, 89%, 83%.*

1D and 2D NMR experiments were carried out to confirm the structure of diol **105**. The ^{1}H NMR spectrum of **105** displayed the appropriate resonances (Figure 42). The TBS ether protecting group at δ 0.83, 0.00 and -0.01 was absent but all the benzyl groups were still observed. The position of the methine proton H-4 was again not apparent from the ^{1}H NMR spectrum due to overlap with the H_2O signal from the DMSO-d_6 solvent as shown perviously for lactone **109**. The HSQC NMR experiment revealed the presence of H-4 at around δ 3.48 ppm (Figure 43). Further confirmation was provided by mass spectral analysis, which gave a signal at 485 Daltons corresponding to the sodium adduct ion expected for $C_{28}H_{30}O_6Na$.

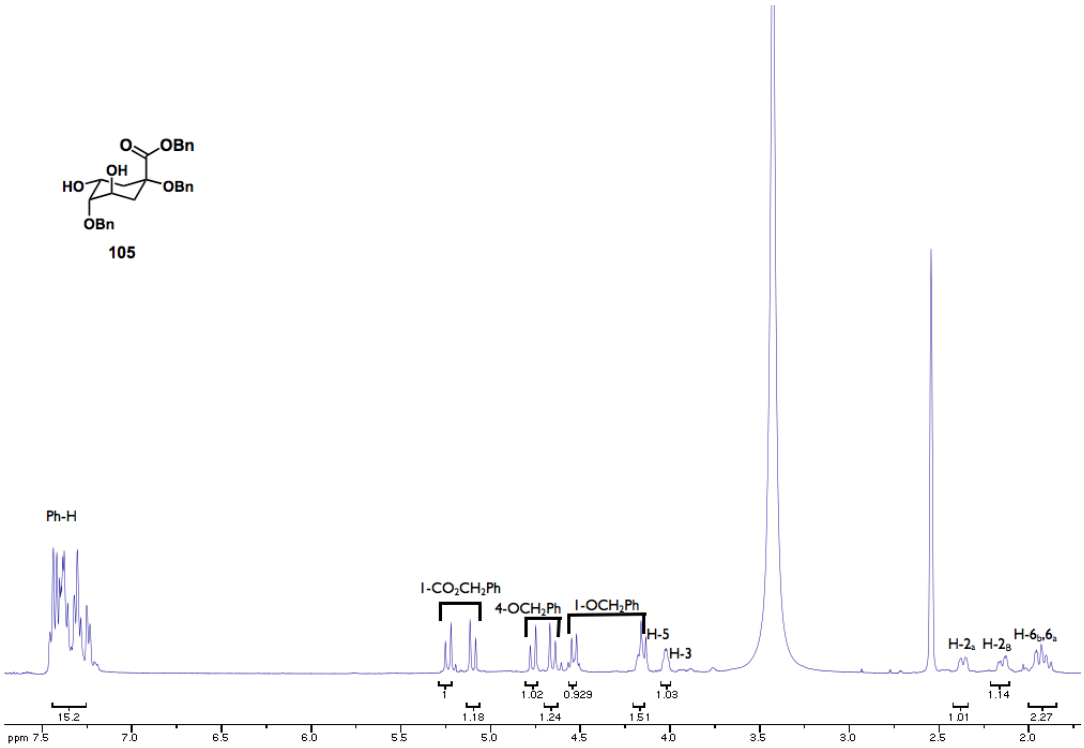


Figure 42. *^{1}H NMR spectrum of diol **105** in DMSO-d_6.*

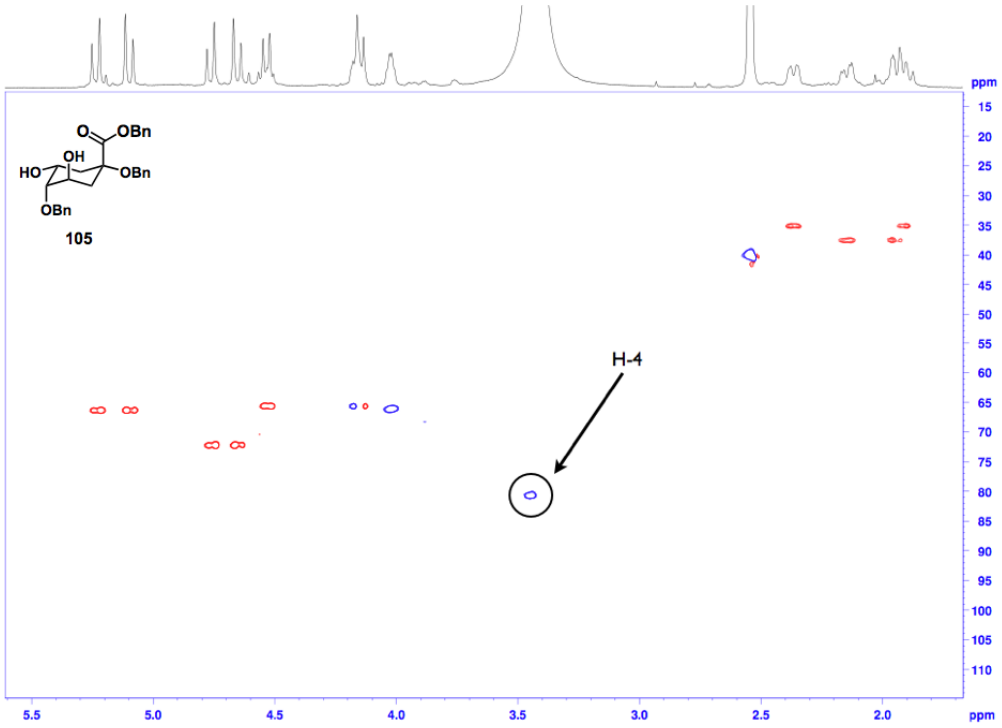
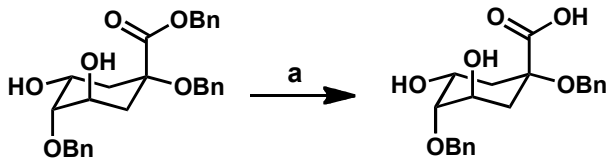


Figure 43. *HSQC spectrum of compound diol **105**.*

A critical stage in the synthesis was thus reached. The next task was coupling of the diol **105** with Meldrum's acid, employing the methodology of List *et al.*[116] The diol **105** was treated with 2.1 eq of Meldrum's acid in toluene under reflux for 3 h.[117] However, under these conditions the desired product was not obtained. Instead compound **110** was isolated in 73% yield (Scheme 56) with ^{1}H NMR spectrum showing the loss of the benzyl ester at 5.24-5.09 ppm (Figure 44). Further confirmation was provided by mass spectral analysis, which gave a signal at 372 Daltons, corresponding to the molecular ion of expected for $C_{21}H_{24}O_6$.



105 **110**

***Scheme 47**. Reagents and conditions: **a)** Meldrum's acid, toluene reflux, 3 h,THF, 73%.*

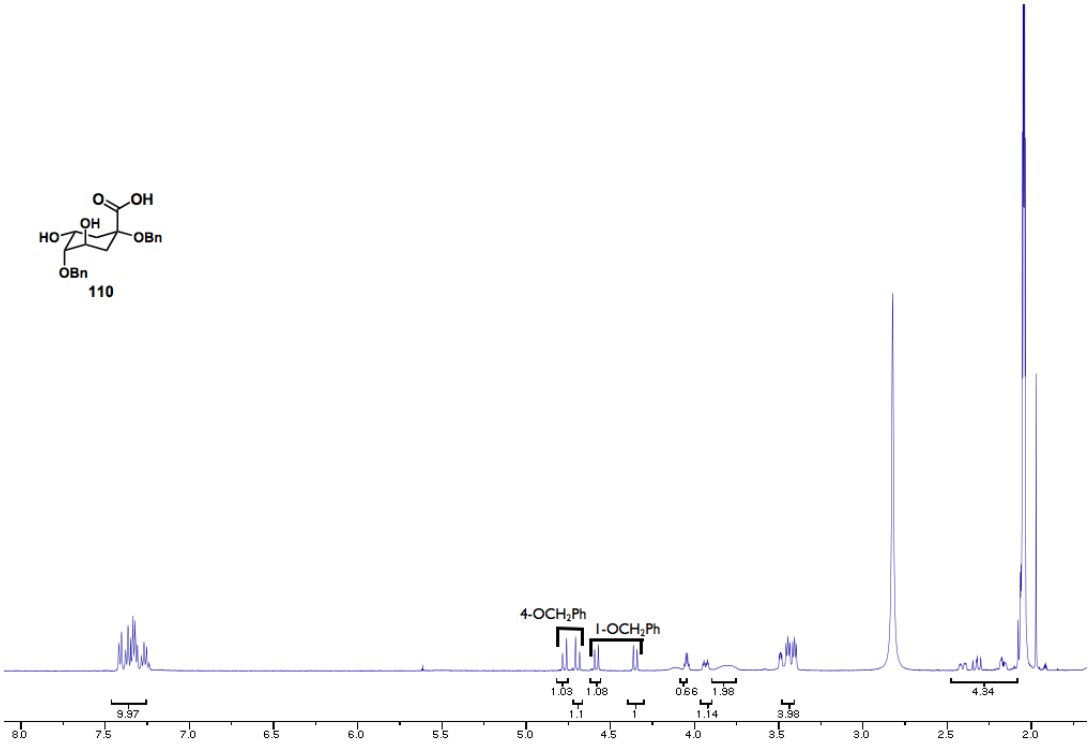
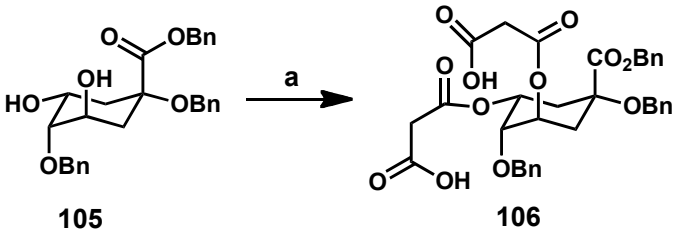


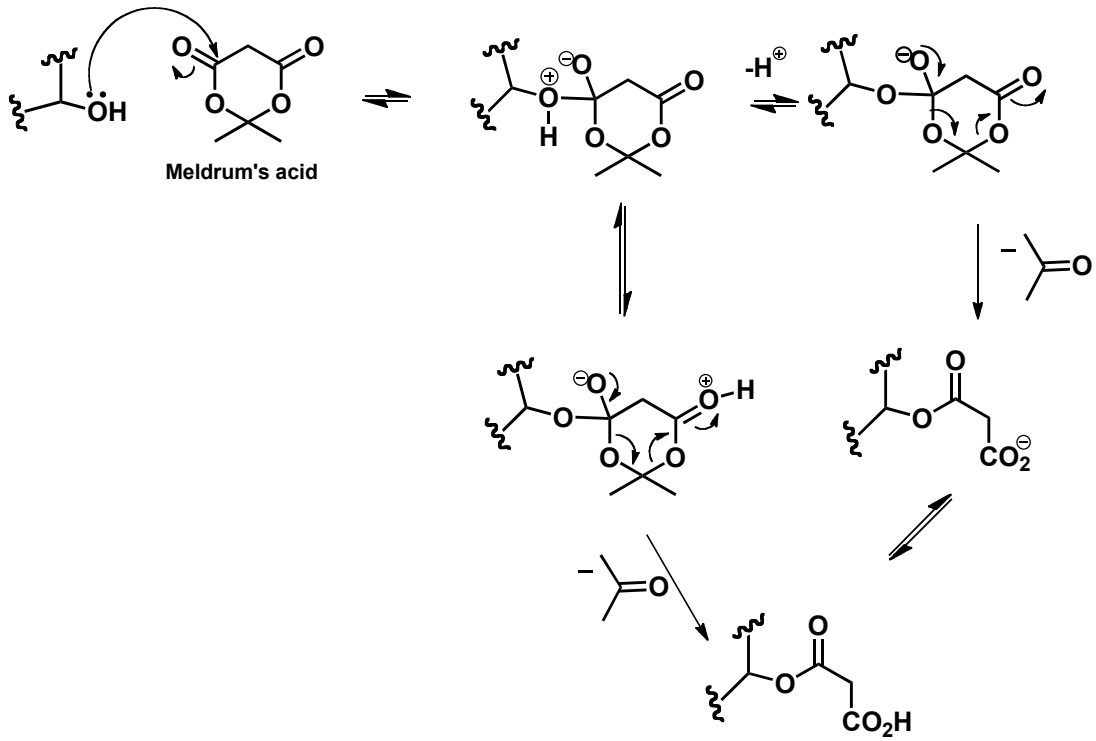
Figure 44. *^{1}H NMR spectrum of **110** in acetone-d_6.*

The experimental conditions were then altered to attempt to obtain the desired product and the results are shown below in Table 12. Treatment of diol **105** with Meldrum's acid in toluene at room temperature for 6 or 12 h, failed to produce the desired product. However, changing the temperature from room temperature to 60 °C afforded the malonate **106** in a good 79% yield with retention of all the benzyl protecting groups (Scheme 48).



Scheme 48. *Reagents and conditions:* ***a)*** *Meldrum's acid, 4 h, 60 °C, 79%.*

The mechanism for reaction of Meldrum's acid with diol **105** is shown on Scheme 49.



***Scheme 49**. Mechanism of reaction of Meldrum's acid with the diol **106**.*

In the ^{1}H NMR spectrum the methylene groups of the malonates were impossible to see due to the overlap with H_2O signal from the DMSO-d_6 (Figure 45). Attempts to dissolve this compound in different solvents ($CDCl_3$, acetone-d_6, methanol-d_4, and acetonitrile-d_3) were unsuccessful.

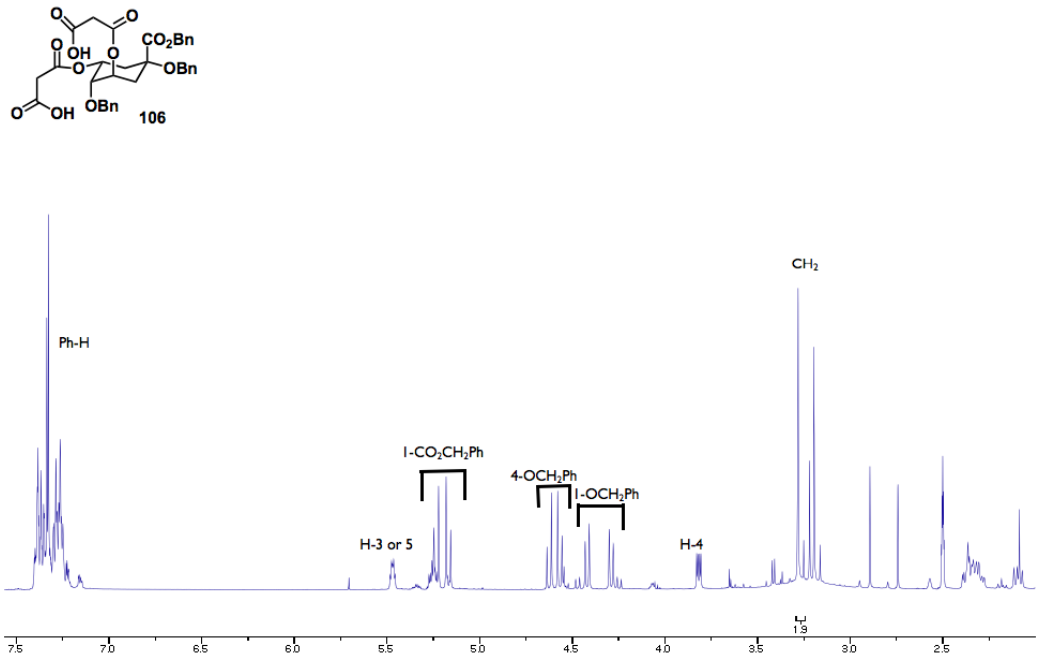


Figure 45. *^{1}H NMR spectrum of adduct **106** in DMSO-d_6.*

The 2D NMR experiments, in particular the HSQC experiment, showed the presence of a CH_2 (Figure 46). Further confirmation was provided by mass spectral analysis, which gave a signal at 657 Daltons, corresponding to the molecular ion of expected for $C_{34}H_{34}O_{12}$.

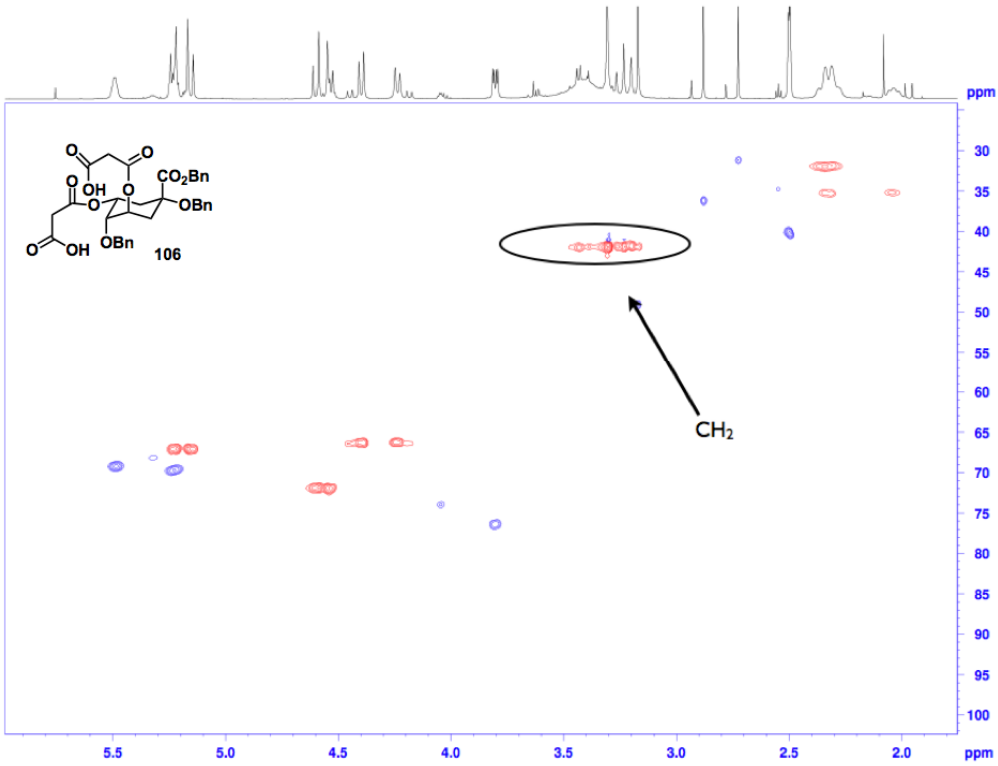


***Figure 46**. HSQC spectrum of **106**.*

The HMBC experiments showed two carbonyls at around 168 and 166 ppm which showed connectivity with the CH_2 groups of the dimalonate. The resonance with the lower chemical shift shows connectivity with the H-3 or H-5 (Figure 47).

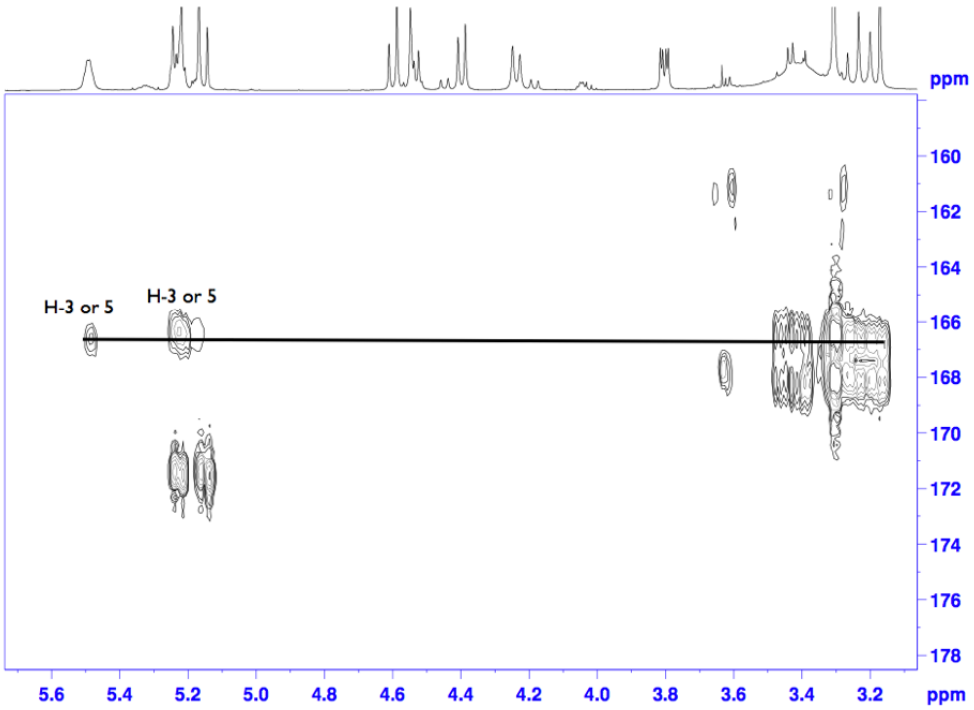


Figure 47. *HMBC spectrum of adduct* ***106***.

1D NMR experiments at 330 K were also conducted, in order to visualise the CH_2 more clearly (Figure 48). The CH_2 signal of the malonate appeared at δ 3.23-318 ppm (AB system, J = 16.0 Hz).

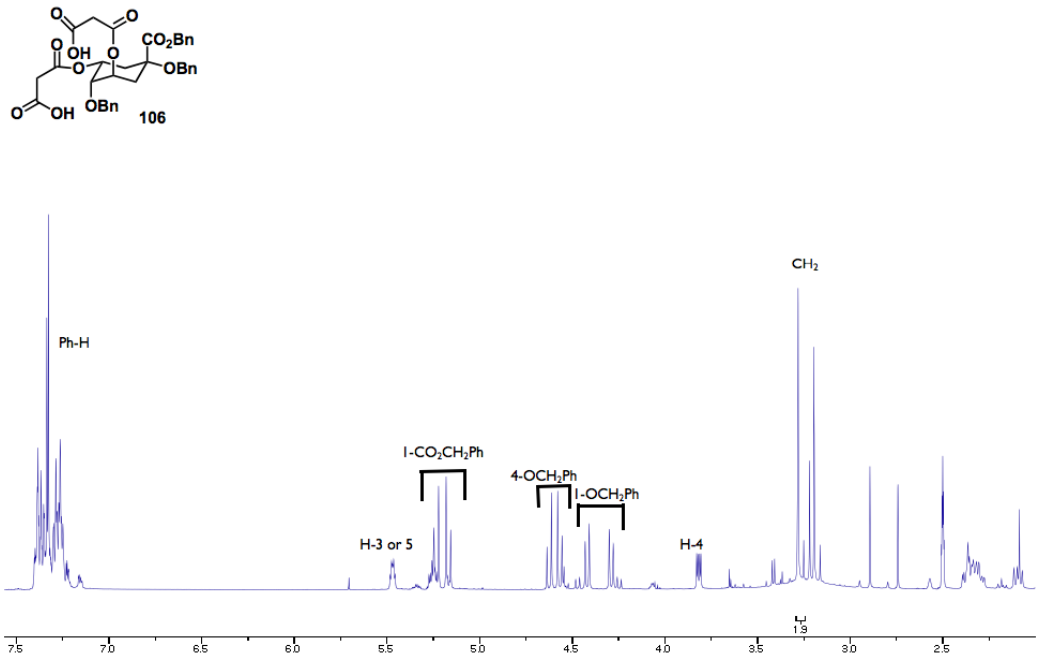
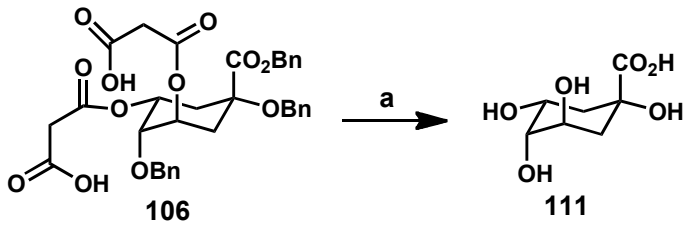


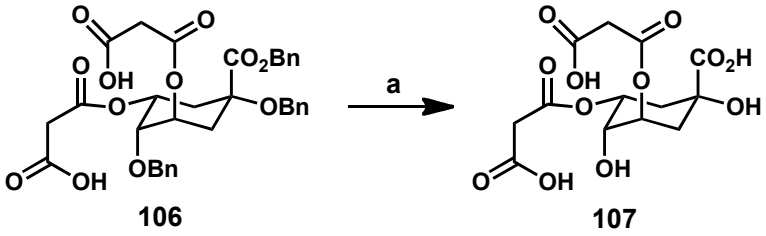
Figure 48. *^{1}H NMR spectrum of **106** in DMSO-d_6 at 330K.*

The next step was cleavage of all three benzyl groups. Initial 10% Pd/C-catalysed hydrogenolysis failed to produce the desired product. The starting material was fully recovered. Increasing the reaction temperature to 60 °C resulted in addition to removal of the benzyl groups, hydrolysis of both malonate esters (Scheme 50). It was believed that the hydrolysis of the malonate esters occurred because of acid contamination in the palladium catalyst.



***Scheme 50**. Reagents and conditions: **a)** Pd/C, EtOH, 60 °C, 12 h, quantitative yield.*

To avoid this problem, it was decided to use $Pd(OH)_2$ in EtOH at room temperature under a hydrogen atmosphere for 36 h. Under these experimental conditions the desired diol **107** was successfully obtained in quantitative yield (Scheme 51)

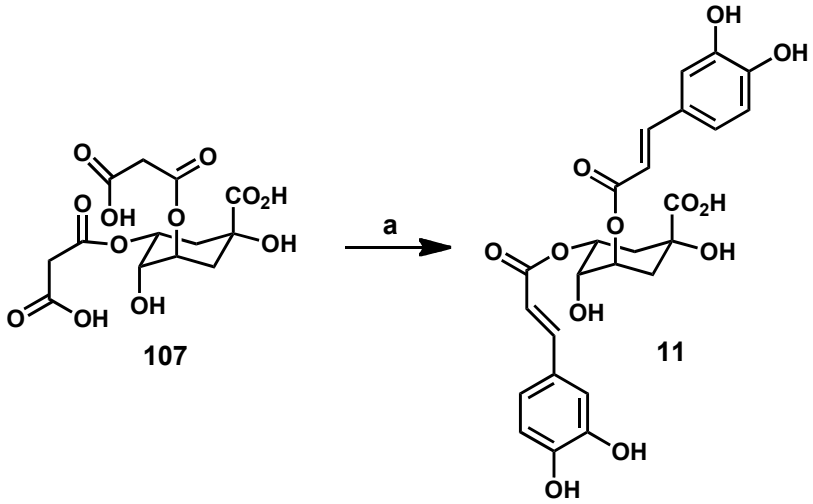


***Scheme 51**. Reagents and conditions: **a)** $Pd(OH)_2$, EtOH, room temperature, 36 h, quantitative yield.*

The ^1H NMR spectrum confirmed the structure of diol **107**, *via* the absence of all the signals due to the benzyl protecting groups. Further confirmation was provided by mass spectral analysis, which gave a signal at 387.0541 Daltons, corresponding to the molecular ion expected for $C_{13}H_{16}O_{12}$.

In the final step of the synthesis, the List *et al.*[116] protocol was adapted. Treatment of diester **107** with DMAP, 3,4-dihydroxybenzaldehyde and a catalytic amount of piperidine in anhydrous DMF at room temperature for 8 days afforded the desired 3,5-DCQA **11** in 68% yield (Scheme 52). Spectral

data were identical to those reported for 3,5-DCQA **11** in chapter two, which were identical to previous literature data.



***Scheme 52**. Reagents and conditions: **a)** 3,4-dihydroxybenzaldehyde, DMAP, piperidine, room temperature, 8 days, DMF, 68%.*

Conclusion

The development of a novel protocol for the synthesis of 3,5-DCQA **11** was described. Using this protocol the synthesis of 3,5-DCQA **11** was achieved in a 20% overall yield over eight steps. While this is fewer synthetic steps and poorer overall yield than the synthesis in Chapter 2 it is the preferred one. Only two of the eight steps require column chromatography, all other steps can be used without further purification. The previous seven steps synthesis requires extensive purification at each step. As such the eight step process is preferred as material can be accessed more quickly. Additionaly the reagents used are less toxic and in particular the use of tin is no longer required. In the final step of the synthesis, following the deprotection of the dimalonyl quinic acid derivative **107**, the (*E*)-double bond was formed by condensation of the aldehyde with malonate. Advantageously this condensation reaction did not require protection of the phenol and or the dimalonyl quinic acid derivative

107. This was in contrast with the previous methodology, which required the protection of the quinic fragment until the final step of the synthesis. Using this approach the purification of the target molecule was easier in comparison with the methodology described in Chapter 2. This methodology could be applied in the future to the synthesis of unsymmetrical derivatives of 3,5-DCQA **11**.

Chapter Four

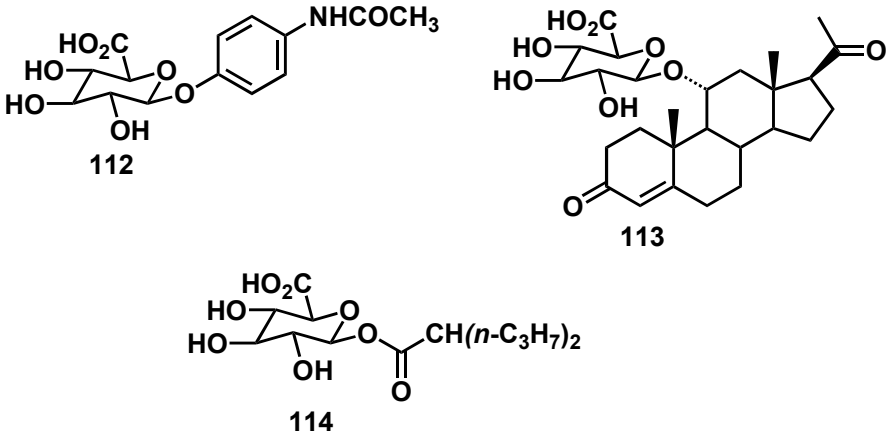
4.0 Synthesis of possible metabolites of quinic acid conjugates

4.1 Introduction

It was decided to investigate the synthesis of compound **132** because there is evidence that such molecules are metabolised by glucuronidation. [118]

Glucuronidation is a major phase II pathway for drug metabolism,[118, 119] where it is common in the metabolism of a range of endo- and xenobiotics. After gluruconic acid conjugation, the substances become more hydrophilic and are more easily excreted from the body.[120]

O-Glucuronides can be divided into three classes by their aglycone groups: i) aryl (paracetamol glucuronide **112**), ii) alkyl (11β-hydroxyprogesterone glucuronide **113** and iii) acyl (valproic acid glucuronide **114**).[121] They are generally the β-anomers

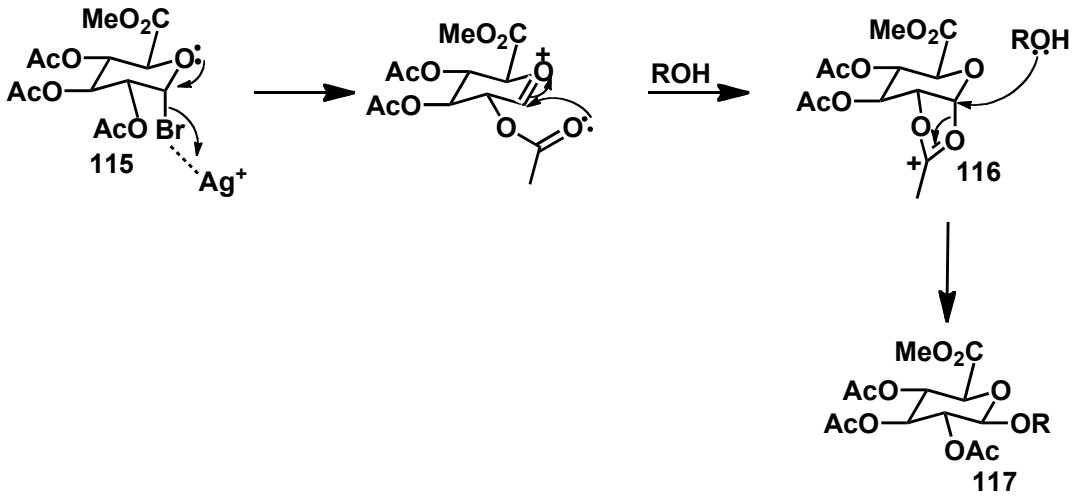


In fact, some of the same synthetic methods may be used for both aryl and alkyl glucuronides, and both of these exhibit good chemical stability.[121, 122]

4.2 Chemical synthesis of Glucuronides

4.2.1 The Knoenings-Knorr method

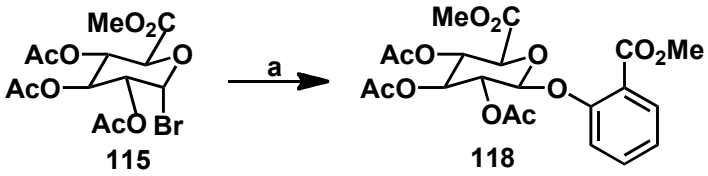
One of the most traditional method for the synthesis of glucuronide, is the Knoenigs-Knorr method. The Knoenigs-Knorr method uses 1α-bromo sugar **115** as donor in the synthesis of a wide range of alkyl and aryl glucuronides.[123] The mechanism involves elimination of AgBr followed by the formation of a 1,2-acyloxonium ion **116** by the participation of the adjacent acetyl group. The alcohol nucleophile attack from the *β*-face to give the *β*-*O*-glucuronide **117** (Scheme 53).



***Scheme 53**. The Koenigs-Knorr reaction.*[123]

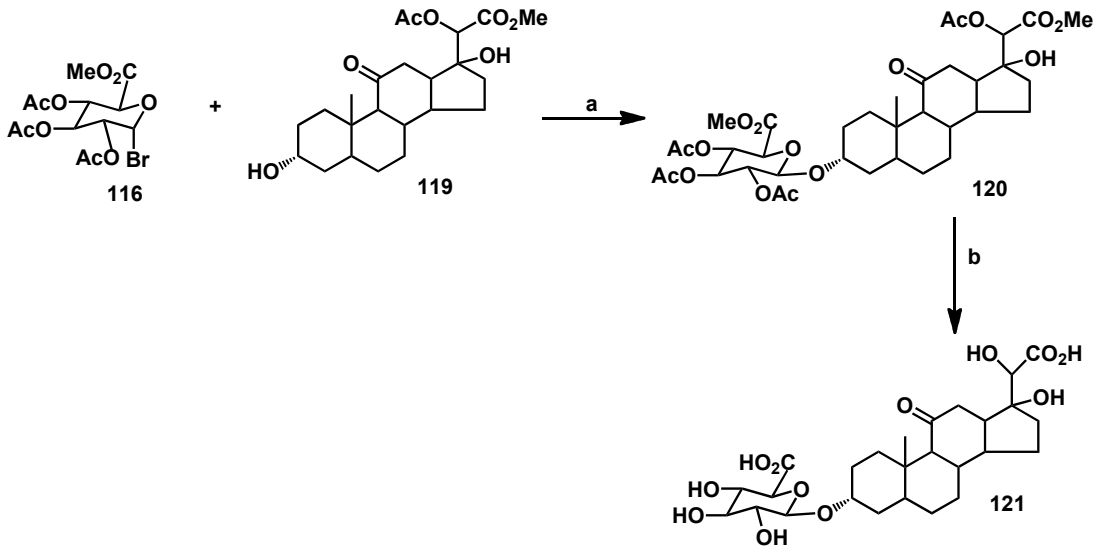
The acetyl groups can be removed by a selection of methods, such as MeONa/MeOH,[124] KCN/EtOH,[125] K_2CO_3/MeOH,[126] and Et_3N/MeOH.[127]

In 1956 Lunsford *et al.*[128] described the synthesis of *O*-carboxyphenyl *β*-D-glucopyranosiduronic acid **118** using 1*α*-bromo sugar **115** and silver oxide (Scheme 54).



***Scheme 54**. Reagents & Conditions: **a**) methyl salicylate, isoquinoline, silver oxide, 0 °C, 20 min, 57%.*[128]

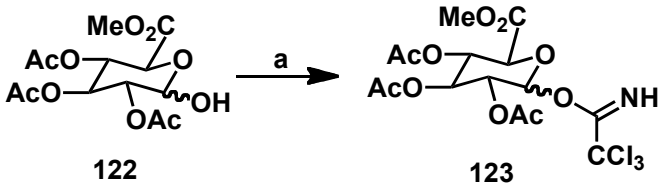
Hosoda *et al.*[129] described the synthesis of 20*β*-cortolonic acid 3-glucuronides **121** using the Koenigs Knorr methodology (Scheme 55).



***Scheme 55**. Reagents & Conditions: **a**) toluene, silver carbonate, room temperature, 20 h, 57%. **b**) potassium hydroxide, MeOH, room temperature, 3h.*[129]

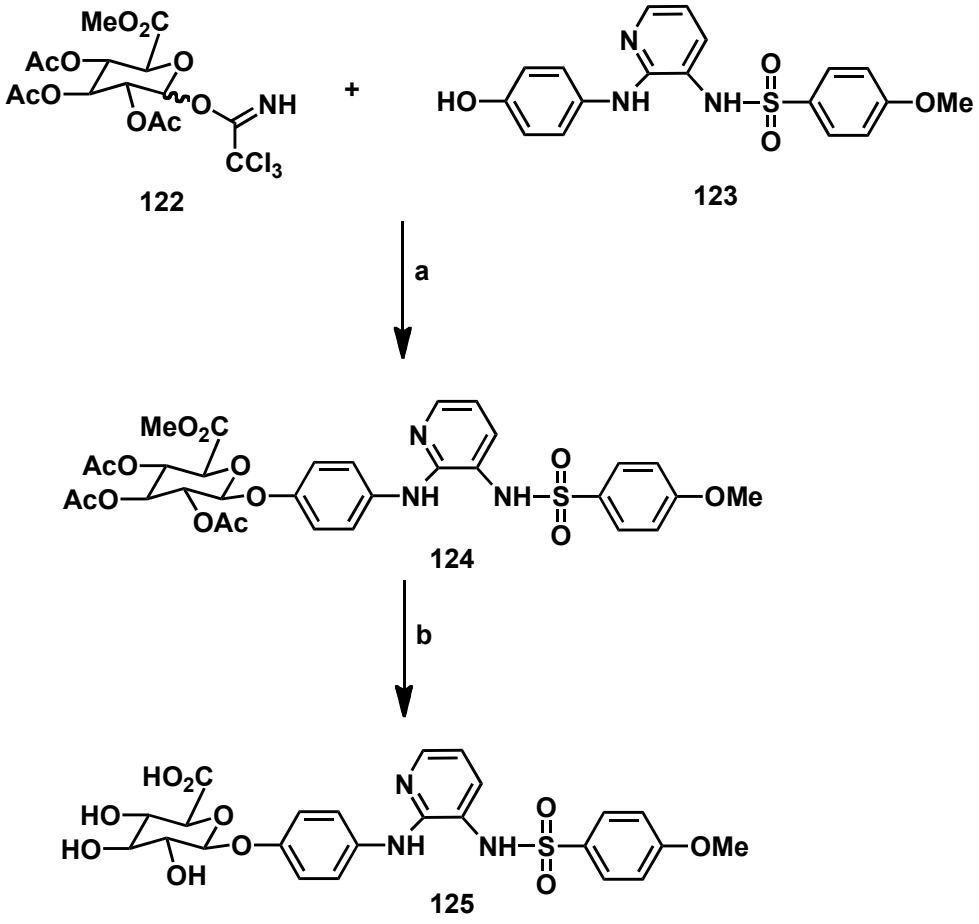
4.2.2 Trichloroacetimidate method (Schmidt)

Schmidt's pioneering studies on glycosidation using trichloroacetimidates have led to an increase in their application to glucuronidation.[130] The relatively mild catalysis required and very high *β*-stereoselectivity make **123** an attractive intermediate. Glucuronyl trichloroacetimidates can be prepared using a variety of methods. In fact, both the *α*-and *β*-anomers of the glucuronyl trichloroacetimidates can be prepared in pure form depending on which base is used for the deprotonation of the hemiacetal **123**. In 1984 Grundler and Schmidt[131] showed the synthesis of both *α*-and *β*-anomers of glycosyl trichloroacetimidates. The α anomer (axial) can be obtained using NaH, CCl_3CN in CH_2Cl_2 at room temperature,[132] while the *β*-anomer (equatorial) can be achieved using a weak base K_2CO_3 and Cl_3CCN at room temperature.[133]



***Scheme 56**. Reagents & Conditions: **a**) Cl_3CCN, base.*[120]

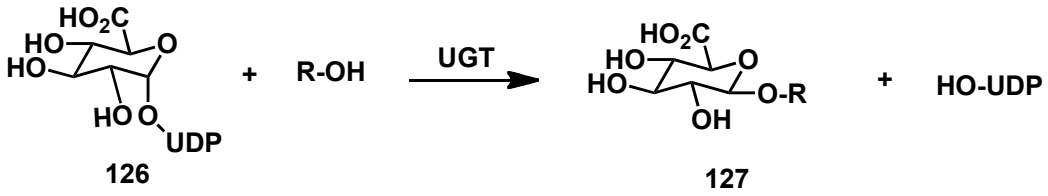
In 2007, Engstrom *et al.*[134] described the synthesis of a glucuronide metabolite of ABT-751 **125** employing the Schmidt trichloroacetimidate methodology (Scheme 57) in the presence of BF_3-Et_2O. ABT-751 **125** is used in the treatment of pediatric neuroblastoma.



***Scheme 57**. Reagents & Conditions: **a**) $BF_3.Et_2O$, CH_2Cl_2, room temperature, **b**) LiOH-H_2O, MeOH, room temperature.*[134]

Glucuronides can also be synthesised by enzymatic methods. Enzymes that are involved in the glucuronidation of xenobiotics are known as UDP-glucuronosyltransferases (UDPGTs). UDPGTs are transmembrane proteins located in the endoplasmic reticulum of cells from a number of tissues especially the liver.[121] The families of UDPGTs play an important role in the metabolism of a variety of endogenous and various food chemicals.[121]

The proposed mechanism involved in the glucuronidation of substance (ROH) is illustrated in Scheme 58. The enzymatic glucuronidation reaction is believed to be a S_N2 reaction where the aglycone substrate (ROH) attacks the UDPG **126**.[121] The reaction inversion an inversion of configuration, thus converts the glucuronic acid from the α- to the β-anomer **127**.

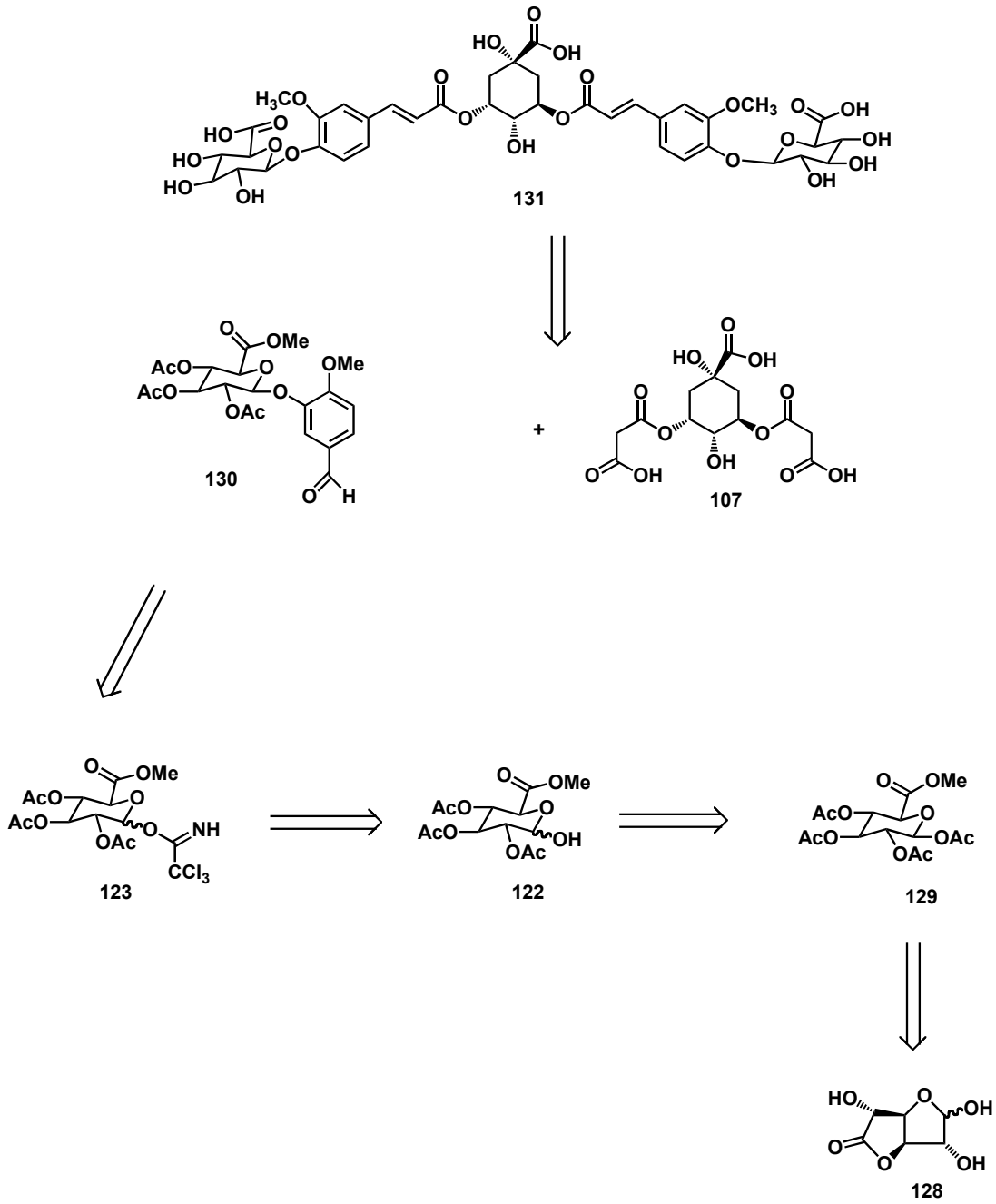


***Scheme 58**. Glucuronidation of compound ROH. The UGT-catalysed reaction produces β-D -glucuronides from α-anomeric UDP and aglycone substrate.*

4.3 Retrosynthetic Analysis

The strategy adopted for the synthesis of **131** involved the coupling of sugar **130** with **107** for which the Knoevenagel condensation methodology could be employed. It was decided to employ Schmidt trichloroacetimidate glycosidation methodology to assemble a glucuronidated vanillin derivative. The Schmidt methodology has been successfully employed to make a number of phenol glucuronides. The aldehyde could then be attached to the

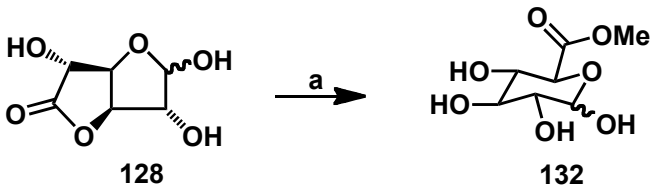
3,5-dimalonyl derivative of quinic acid **130**, prepared previously, *via* the Knoevenagel condensation reaction. The glucuronyl trichloroacetimidate **123**, would be assembled stepwise from D-glucurono-6,3-lactone **128** in 3 steps (Scheme 59).



Scheme 59. *Retrosynthetic analysis for compound* ***131****.*

4.2 Synthesis of Glucuronyl Donor

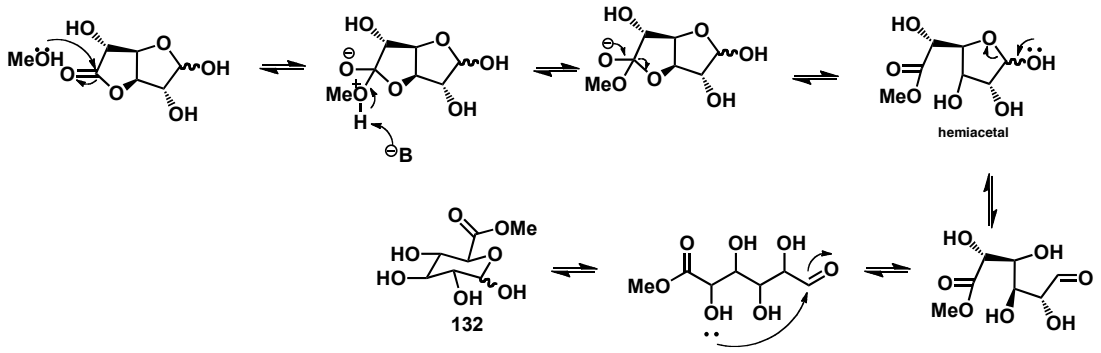
The sugar **132** was synthesised utilising the method of Nakajima *et al*.[135] A catalytic amount of sodium hydroxide was dissolved in methanol followed by treatment with D-glucurono-6,3-lactone **128**. Further portions of sodium hydroxide were added to achieve a pH of 8-9 and the reaction stirred at room temperature for 1 h affording **132** as a viscous oil (Scheme 60).



128 **132**

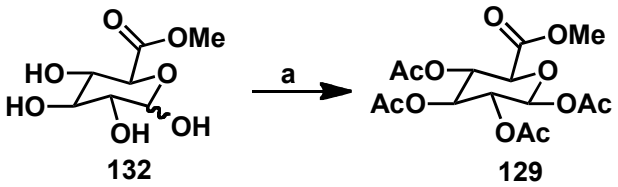
Scheme 60. *Reagents & conditions:* ***a****) NaOH, MeOH,room temperature,1h.*

The mechanism for the lactone hydrolysis under basic condition is shown in Scheme 60. The reaction was initiated by the nucleophilic attack of methanol on the carbonyl of the lactone. The tetrahedral intermediate formed quickly collapses back to a carbonyl centre *via* the opening of the five member ring, generating a free hydroxyl group. Finally, the aldehyde for the ribofuranose ring, which is in equilibrium with its hemiacetal form, undergoes alternative ring closing with the free OH group, that forms farvourable pyranose six-membered ring structure **132**.



Scheme 61. *Mechanism of lactone hydrolysis.*

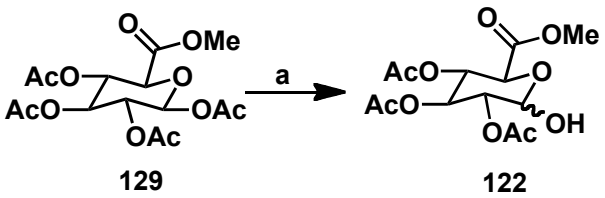
Acetylation of crude **132** with acetic anhydride and pyridine at 30 °C for 16 h resulted in the formation of compound **129** in quantitative yield over two steps (Scheme 62).[136] The ^{13}C and ^{1}H NMR spectral data showed that **129** contained one anomeric ^{13}C at δ 91.3 (C-1) that correlated to the proton signal at δ 6.42 (1H, d, *J* = 7.7 Hz, H-1) indicating the presence of one sugar unit in the beta form.



Scheme 62. *Reagents & conditions:* ***a****) acetic anhydride, pyridine, 30 °C, 16 h, quant.*

With a substantial quantity of **129** in hand, attention was focused on the selective deacylation of the acetyl group, using ethylenediamine in THF at room temperature.[137] Extensive monitoring of the reaction by TLC showed one product after 2 h, which was more polar than the starting material (Scheme 63). Purification by column chromatography afforded the 2,3,4,6-*O*-protected sugar as a mixture of α-and β-anomers (1:1.4). The ^{13}C NMR

spectroscopic data revealed the presence of only three acetyl carbons between 20.9 ppm and 21.0 ppm respectively.



129 **122**

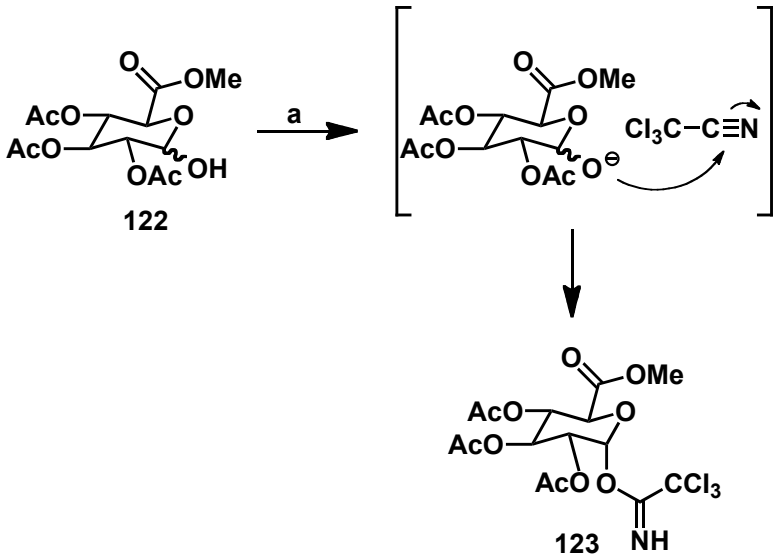
Scheme 63. *Reagents & conditions:* ***a****) ethylenediamine, THF, room temperature 2 h, quant.*

Under these conditions, the reaction could not be run at room temperature for more than 2 h, because the fully deacylated product compound was obtained from compound **129** (Table 12). An alternative procedure by Zhang *et al.*[137] used ethylenediamine in a mixture with acetic acid to overcome this problem.

Table 12*. Selective deacylation of anomeric center*

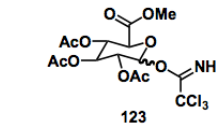
Entry	Ethylenediamine	Solvent	Time (h)	Temperature	Product	Yield %
1	1.1 eq	THF	1	r.t	**129 + 122**	41%+69%
2	1.1 eq	THF	2	r.t	**122**	99%
3	1.1 eq	THF	8	r.t	**132**	95%

The resulting hemiacetal **122** was then used for the preparation of the glucuronyl trichloroacetimidate. Treatment of hemiacetal **122** with DBU in CH_2CI_2 led to the anomeric oxyanion, which added across the nitrile bond of trichloroacetonitrile affording the desired glucuronyl trichloroacetimidate donor **123** (Scheme 64).



Scheme 64. *Reagents & conditions:* ***a****) DBU, Cl_3CCN, CH_2Cl_2, 0 °C to room temperature, 2 h, 93%.*

The ^{1}H NMR spectrum of the glucuronyl trichloroacetimidate donor **123** displayed the appropriate resonances (Figure 49). The appearance of an NH proton singlet at δ 8.74 ppm confirmed the formation of the glucuronyl trichloroacetimidate donor **123**. The anomeric proton H-1 appeared as a doublet, with a small coupling constant of *J* = 3.5 Hz. The coupling constant of *J* = 3.5 Hz is indicative of an axial-equatorial coupling between H-1 and H-2 which suggests that only the alpha anomer was formed. The anomeric proton appears at δ 5.59 ppm due to the electron withdrawing glucuronyl trichloroacetylimidoyl group. The protons on H-3 and H-4 appear as triplets at δ 5.64 ppm and 5.28 ppm with coupling constants of 10.1 Hz. The H-2 proton appears as a doublet of doublets at 5.16 ppm with a coupling constants of 3.5 Hz and 10.1 Hz. The H-5 proton appears as a doublet at δ 4.51 ppm with a coupling constant of 10.1 Hz. The remaining protons are attributed to the methyl ester (3.76, s, 3H) and acetyl-CH_3 (2.08, 2.07, 2.04).



123

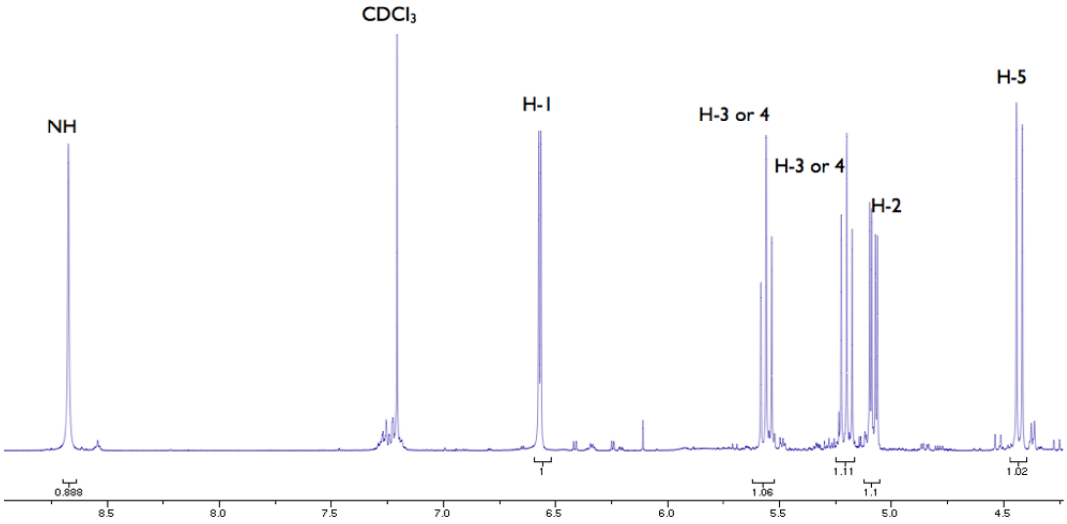
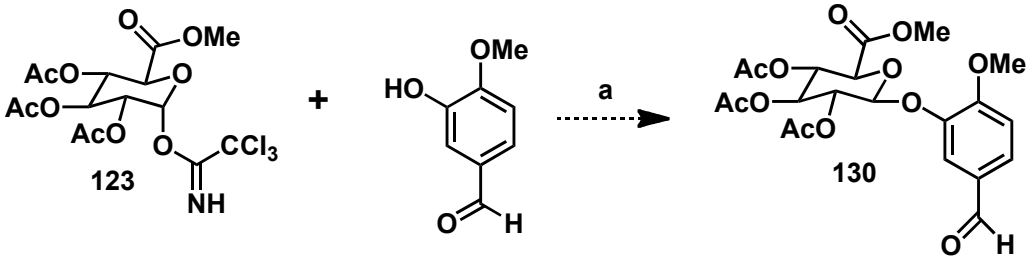


Figure 49. *^{1}H NMR spectrum of **123** glucuronyl trichloroacetimidate donor in $CDCl_3$.*

With the glucuronyl trichloroacetimidate donor **123** in hand, it was assumed that vanillin could be coupled to **123** under suitable acidic conditions. However, treatment of a cooled (-50 °C) solution of **122** and vanillin in dry CH_2Cl_2, containing pre-activated 4 Å molecular sieves, with boron trifluoride etherate, failed to give the desired product **130** (Scheme 65).



Scheme 65. *Reagents & conditions:* ***a****) CH_2Cl_2, BF_3-Et_2O, 0 °C to room temperature,* 4 Å molecular sieves *2 h.*

Unfortunately, all further attempts to couple **123** with vanillin also failed to generate the desired product. The results of these studies are summarised in Table 13. In entries 1 and 2, the reaction temperature was increased from -50 °C to 0 °C, while for entries 3-5, the reaction temperature and reaction time were increased. In entries 6 and 7 both the reaction temperature as well as the quantity of the BF_3-Et_2O were increased.

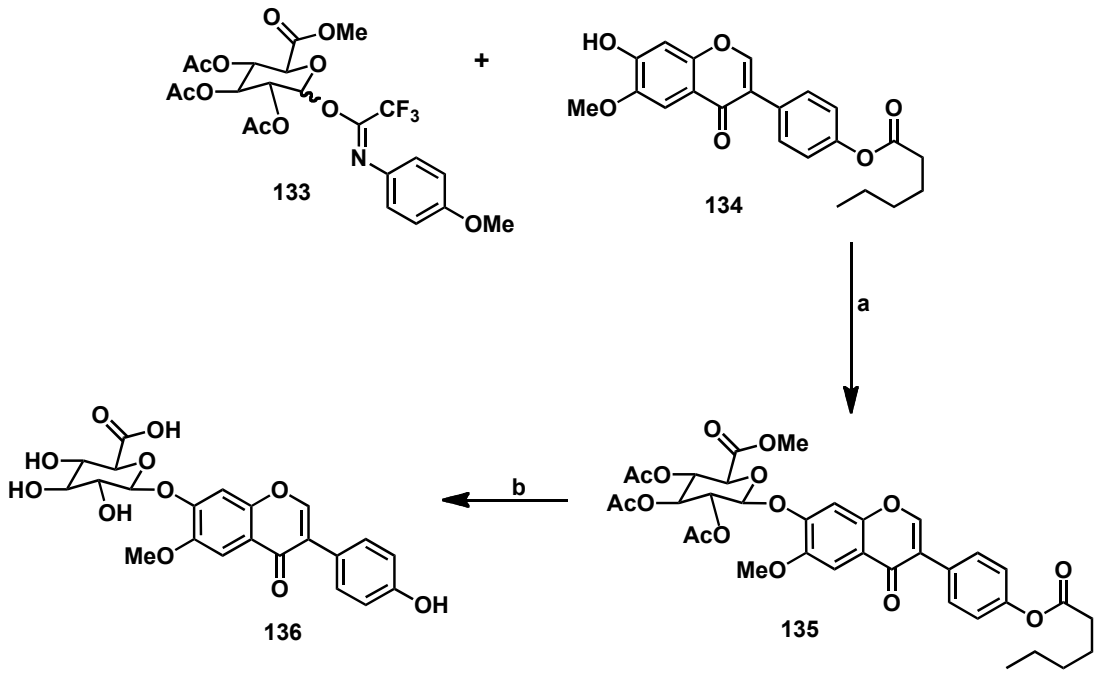
Table 13. *Summary of studies conducted towards the synthesis of* ***133***.

Entry	BF_3•Et_2O (eq)	Temperature	Time	Results
1	0.1 eq	-50 ℃	6 h	no reaction
2	0.1 eq	0 ℃	6 h	no reaction
3	0.1 eq	r.t	12 h	no reaction
4	0.1 eq	r.t	24 h	no reaction
5	0.1 eq	r.t	36 h	no reaction
6	0.5 eq	r.t	12 h	no reaction
7	1.0 eq	r.t	24 h	no reaction

Attempts to resolve this problem were then focused on the Lewis acid catalyst used in the reaction. Unfortunately, a switch to TMSOTf also failed to afford the desired product **130**.

To overcome the poor reactivity of trichloroacetimidate donor **123**. It was decided to utilised the *N*-(4-methoxylphenyl)trifluoroacetimidate donor **133** methodology developed by Yu *et al.*[138] and used previously in house.[139, 140] Former projects within the Botting group accomplished the synthesis of various isoflavone glucuronides using methyl 2,3,4-triacetyl-D-

glucopyranosidunoryl 1-(*N*-4-methoxy-phenyl)-trifluoroacetimidate donor **133** (Scheme 66).[139, 140]

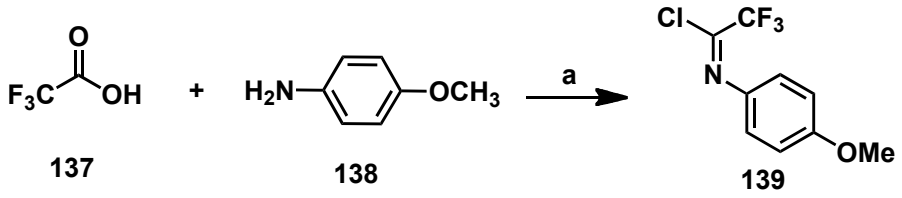


Scheme 66. *Reagents & conditions:* ***a****) CH_2Cl_2, $BF_3.Et_2O$, room temperature,* 4 Å molecular sieves, *6 h, 78%* ***b)*** *K_2CO_3, acetone, H_2O, MeOH-THF, 40 °C, 5 h, room temperature, 90%.*[139, 140]

This new strategy commenced with the synthesis of the methyl 2,3,4-triacetyl-D-glucopyranosidunoryl 1-(*N*-4-methoxy-phenyl)-trifluoroacetimidate **133**, which was prepared from *N*-4-methoxyphenyltrifluoroacetimidoyl chloride **139**.

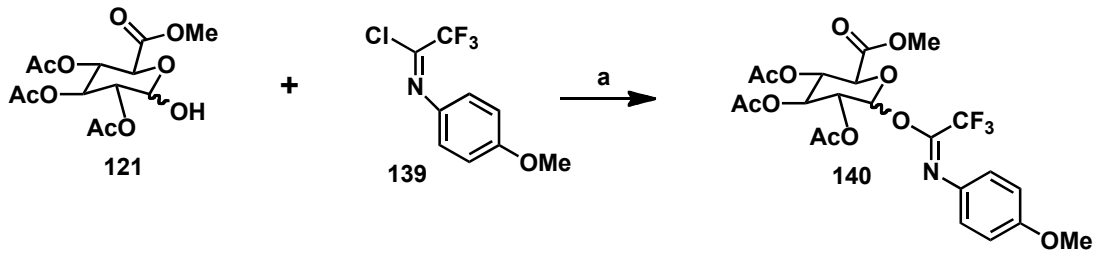
The *N*-4-methoxyphenyltrifluoroacetimidoyl chloride **139** was itself prepared by the reaction of trifluoroacetic acid **137** with 4-methoxyaniline **138**, triphenylphosphine, triethylamine and carbon tetrachloride (Scheme 67). The structure of **139** was confirmed by analysis of the ^{1}H NMR spectrum, which

was found to be in close agreement with the literature data.[141] Further confirmation was provided by mass spectral analysis, which gave a signal at 238 Daltons, corresponding to the expected molecular ion $[M+H]^+$ for $C_4H_5N_3O_3F_5$.



***Scheme 67**. Reagents & conditions: **a**) Ph_3P, Et_3N, CCl_4, reflux, 3 h 91%.*[141]

Treatment of **121** with *N*-4-methoxyphenyltrifluoroacetimidoyl chloride **139** in the presence of K_2CO_3 in acetone and H_2O at room temperature gave compound **140** as a mixture of α and β-anomers (1.22:1) in an excellent 76% yield (Scheme 68).



***Scheme 68.** Reagents & conditions: **a**) K_2CO_3, acetone, H_2O, room temperature 3 h, 76%.*

The ^{1}H NMR spectrum of the glucuronyl trifluoroacetimidate donor **140** displayed the appropriate resonances, which were also in close agreement with the data reported by Al-Maharik and Botting[140] (Figure 50). The aromatic proton appears as multiplet between δ 6.72-6.85 ppm. The anomeric protons H^{α}-1 and H^{β}-1 appear as broad singlets at δ 6.46 and 5.85 ppm, respectively.

The H-2 proton appears as a doublet of doublets at δ 5.14 ppm with coupling constants of *J* = 10.2 and *J* = 3.9 Hz. Other resonances between δ 5.21 and 5.34 ppm (3H, s), 4.42 ppm, 3.73 ppm, 3.76 ppm, 3.77 ppm, (12H, s), 2.016 ppm, 2.02 ppm, 2.03 ppm, 2.05 ppm (18H, s) were attributed to the sugar moiety and the methoxy group of the aromatic ring.

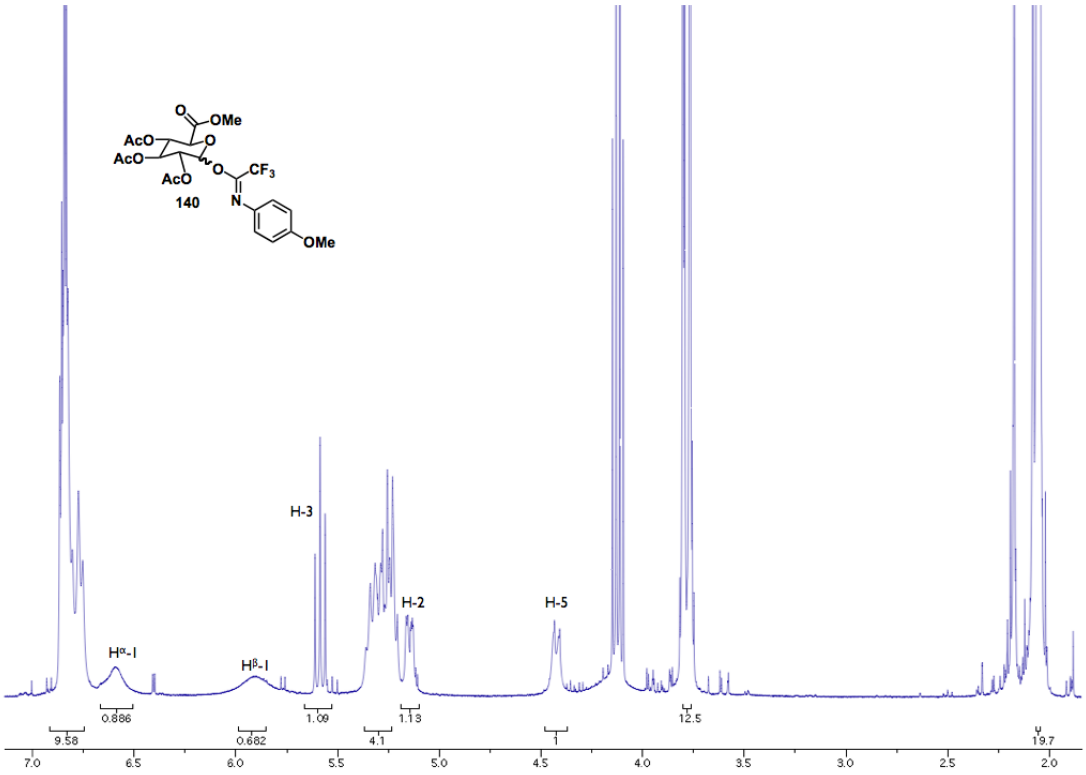
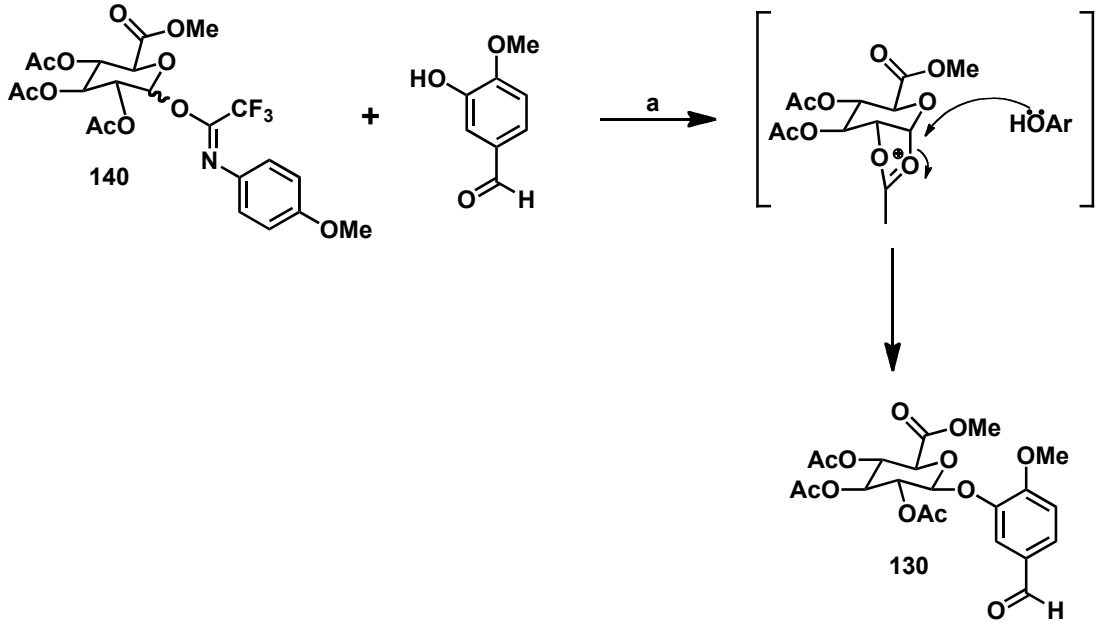


Figure 50. *^{1}H NMR spectrum of glucuronyl trichloroacetimidate **140** in $CDCl_3$.*

However, it was observed that the glucuronyl trifluoroacetimidate **140** was unstable at room temperature and was therefore kept at -78 °C. With donor **140** in hand the next step was the synthesis of **130**. Treatment of vanillin with the glucuronyl trifluoroacetimidate **140** donor in dry CH_2Cl_2 containing pre-dried 4Å molecular sieves and $BF_3{-}Et_2O$ at room temperature for 6 h afforded the desired coupling product **130** in an excellent yield 81% (Scheme 69). It is believed that the boron trifluoride initiated cleavage of the anomeric

trichloroacetimidate on **140** afforded the transient acetoxonium ion, which in turn subsequently reacted with the phenol group in a stereoselective fashion. In fact, the configuration of the anomeric carbon in **140** is not important to the stereochemical outcome of the glycosidation step because both anomers of **140** couple streoselectively with the phenol to give the exclusively the β-glucuronide **130**.



***Scheme 69**. Reagents & conditions: **a**) CH_2Cl_2, $BF_3.Et_2O$ 0 °C to room temperature,* 4 Å molecular sieves, *6 h, 81%.*

The ^{1}H NMR spectrum of **130** displayed the appropriate resonances (Figure 51). The appearance of a singlet at δ 9.89 ppm confirmed the presence of the aldehyde. The aromatic protons appeared as a doublet at δ 7.54 ppm (*J* = 8.1 Hz), a doublet of doublets at δ 7.52 ppm (*J* = 8.1, 1.8 Hz) and a doublet at δ 7.39 ppm (*J* = 8.1 Hz). The anomeric proton H-1 appeared as a doublet at 5.61 ppm with a large coupling constant *J* = 7.7 Hz. This coupling constant implied an axial-axial coupling between H-1 and H-2 which suggested that

only the β-anomer had been formed. The proton at H-3 appeared as a triplets at δ 5.48 ppm (*J* = 10.1 Hz) while those on H-2 and H-4 appeared as multiplets at between δ 5.31 and δ 5.22 ppm. The proton at H-5 appeared as a doublet at δ 4.51 ppm (*J* = 10.1 Hz). The H-5 proton appeared as a doublet at δ 4.60 ppm (*J* = 10.1 Hz).

The remaining protons are attributed to the methyl ester (3.39, s, 3H), methoxy (3.92, s, 3H) and acetyl (2.03, 2.01, 2.00). The ^{13}C NMR spectral data also showed that **130** contained one anomeric carbon at δ 99.6 ppm (C-1) that correlated to the proton signals at δ 5.61 (1H, d, *J* = 7.7 Hz), indicating the presence of one sugar unit in the β-form. An accurate mass measurement displayed a signal at 491.1165 Daltons corresponding to that expected for the sodium adduct $C_{21}H_{24}O_{12}Na$.

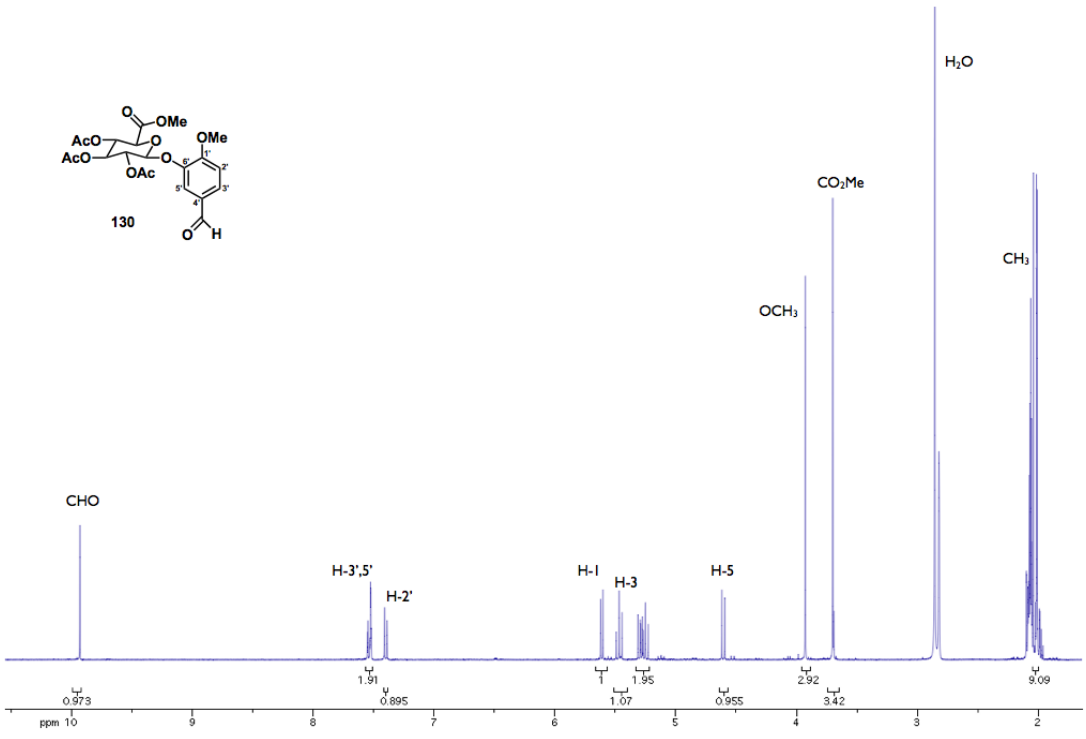
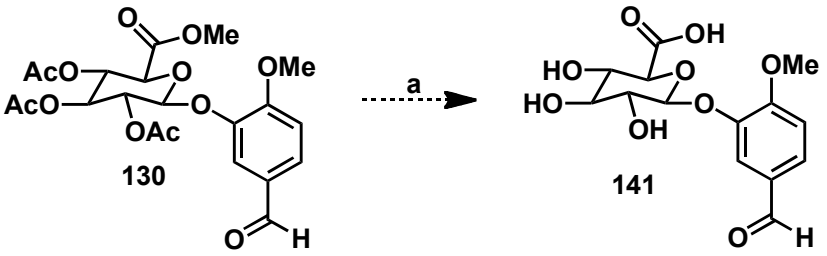


Figure 51 ^{1}H NMR spectrum of **130** in Acetone-d_6.

A key stage in the synthesis was thus achieved and attention was then turned to the deprotection of the acetyl protecting groups. An initial attempt involving treatment of **130** with K_2CO_3 in mixture of MeOH-THF and H_2O at 40 °C for 5 h failed to give the desired product **141** (Scheme 70).



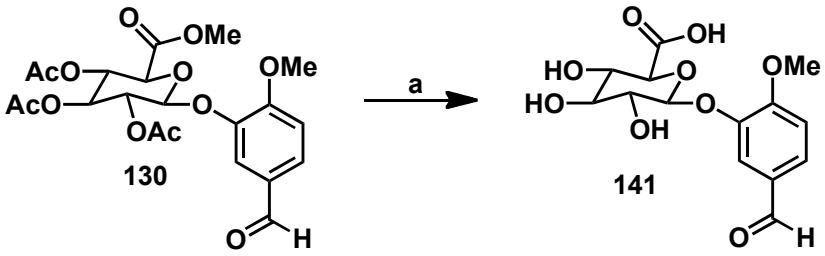
***Scheme 70**. Reagents & conditions: **a**) K_2CO_3, MeOH-THF, H_2O, 40 °C 5 h.*

Under these conditions, the acetyl protecting groups were only partially removed. A summary of the various conditions attempted during the optimisation of the conditions for the deprotection of the acetyl groups are shown below (Table 12). Treatment of **130** with 3 equivalents of K_2CO_3 in MeOH-THF and H_2O at room temperature for 5 h failed to furnish compound **141** (Entry 1). Increasing the temperature from room temperature to 40 °C also failed to give the desired product (Entry 2 and 3). Similarly, increasing the temperature and time of the reaction from 5 h to 3 days (Entry 4) and increasing the amount of K_2CO_3 used from 3 to 6 equivalents also failed (Entry 5).

Table 12. *Reaction conditions for the deprotection of acetyl groups.*

Entry	K_2CO_3	Solvent	Temperature	Time	Product
1	3 eq	MeOH-THF	r.t	5 h	partial deacetylation
2	3 eq	MeOH-THF	40 °C	5 h	partial deacetylation
3	3 eq	MeOH-THF	40 °C	24 h	partial deacetylation
4	3 eq	MeOH-THF	40 °C	3 days	partial deacetylation
5	6 eq	MeOH-THF	40 °C	6 days	partial deacetylation

After extensive experimental work, it was found that the best conditions for the deprotection involved treatment of **130** with LiOH in MeOH-H_2O (50:50) at room temperature for 48 h (Scheme 71).[142] Under these conditions the desired product was obtained in 71% yield.



Scheme 71. *Reagents & conditions:* ***a****) LiOH, MeOH-H_2O, room temperature, 48 h, 71%.*

The structure of **141** was confirmed by ^1H NMR spectroscopy, which showed the absence of methoxy ester at δ 3.92 ppm (s, 3H), and acetyl groups at δ 2.03 ppm, 2.01 ppm, 2.00 ppm (Figure 52). An accurate mass measurement displayed a signal at 327.0716 Daltons, corresponding to that expected for $C_{14}H_{16}O_9$.

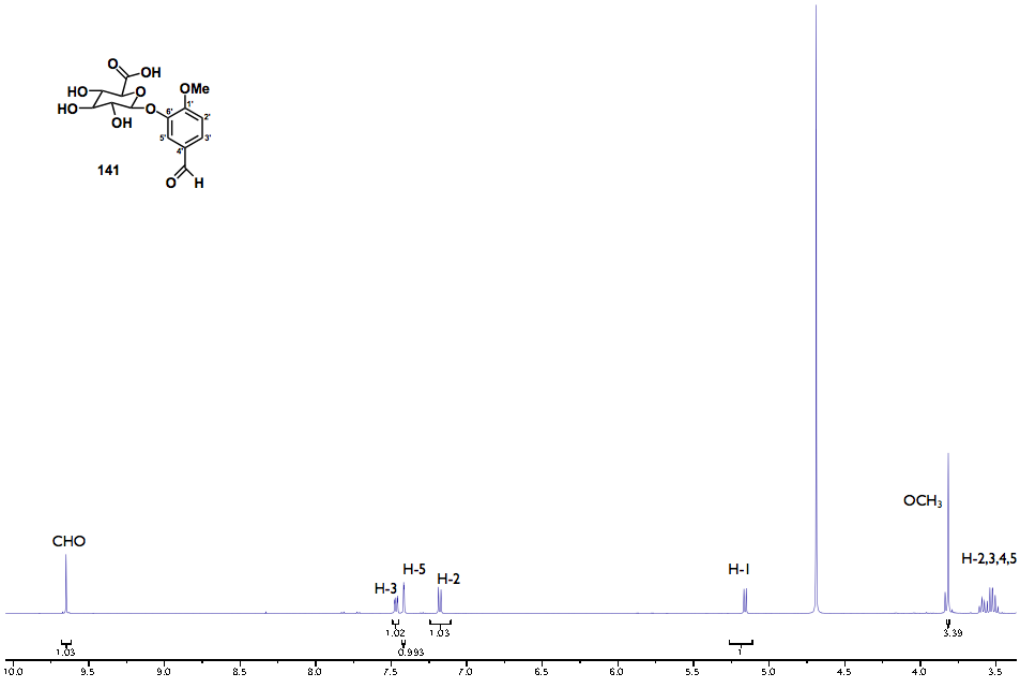
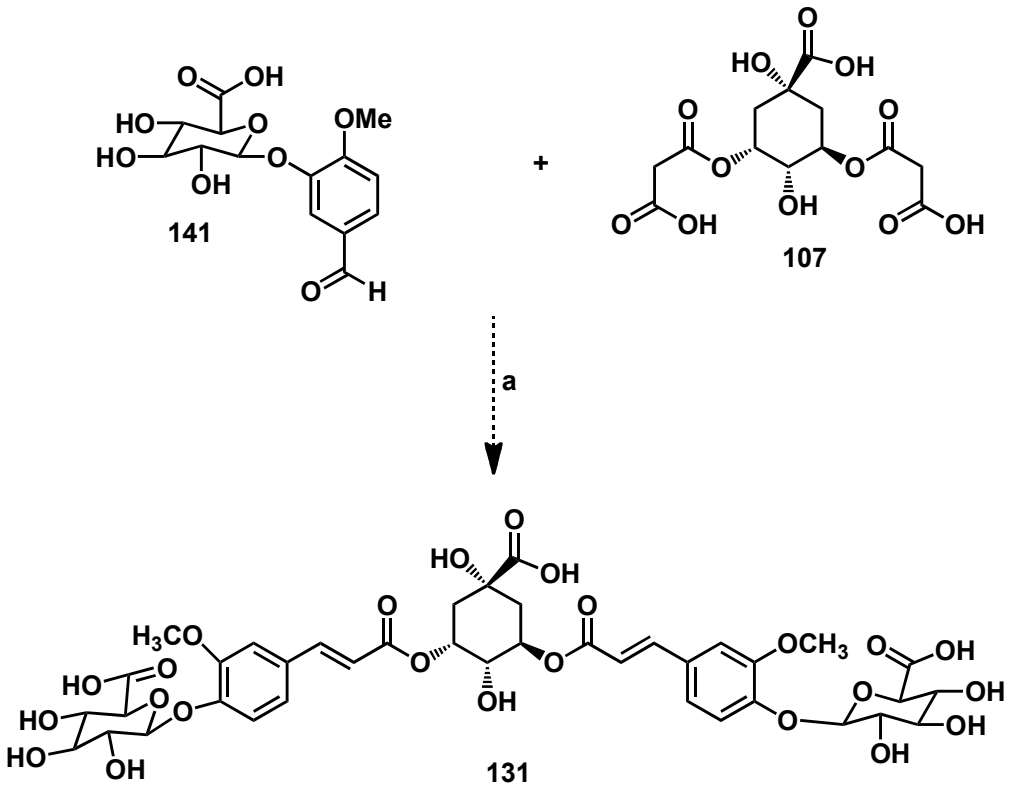


Figure 52. *^{1}H NMR spectrum of **141** in D_2O.*

In the final step of the synthesis, treatment of **141** with **107** in the present of DMAP and a catalytic amount of piperidine in anhydrous DMF at room temperature for 8 days failed to give the desired product **131** (Scheme 72).[116]

Scheme 72. *Reagents and conditions:* ***a)*** *DMAP, piperidine, room temperature, 8 days, DMF.*

In an attempt to further investigate the feasibility of this coupling reaction, a study was carried out with model substrate **142**, which resembles the dimalonate functionality of **106**. This was treated with **141** under the same conditions. However, no coupling products were observed after 8 days of reaction (Scheme 73).



Scheme 73**. Reagents and conditions:* ***a) *DMAP, piperidine, room temperature, 8 days, DMF.*

A probable explanation for this failed reaction was due to the formation of anionic species for both substrates. The glucuronic acid moiety of **141**, will become deprotonated and will exist as the glucuronate anion, while the dimalonic acids **107** and **142** will also become deprotonated, and probably exist as dimalonate species, under the basic reaction conditions.

Since the two substrates exist as anions in the reaction mixture, the negative charges they carry will cause them to repel and avoid coming into proximity of each other, therefore hindering any reaction.

When the reaction was attempted with a crude mixture of partially deprotected product, coupling product was observed by MS and NMR. Thus, the failure may be attributed to the free carbonxylic acid on **141**. Unfortunately the reaction gave an inseparable mixture of coupling products.

Conclusion

A novel synthetic strategy was developed and applied towards the synthesis of 3,5-FQA glucuronyl. The synthesis of glucuronyl trichloroacetimidate **123** was accomplished over 3 steps. However, the coupling of glucuronyl trichloacetimidate **123** with vanillin proved to be more difficult than originally anticipated. The coupling reaction was achieved using a coupling protocol developed within the Botting group for the synthesis of isoflavone glucuronides. This new strategy employed glucuronyl trifluoroacetimidate **140** as the donor. The glucuronyl trifluoroacetimidate **140** was coupled with vanillin in a stereoselective fashion affording compound **130**. Cleavage of the protecting groups from **130** was achieved after several attempts with LiOH in H_2O-MeOH for 36 h. In the final step of the synthesis a Knoevenagel condensation reaction of **141** and a dimalonate ester of quinic acid **107** failed to give the target compound **131**.

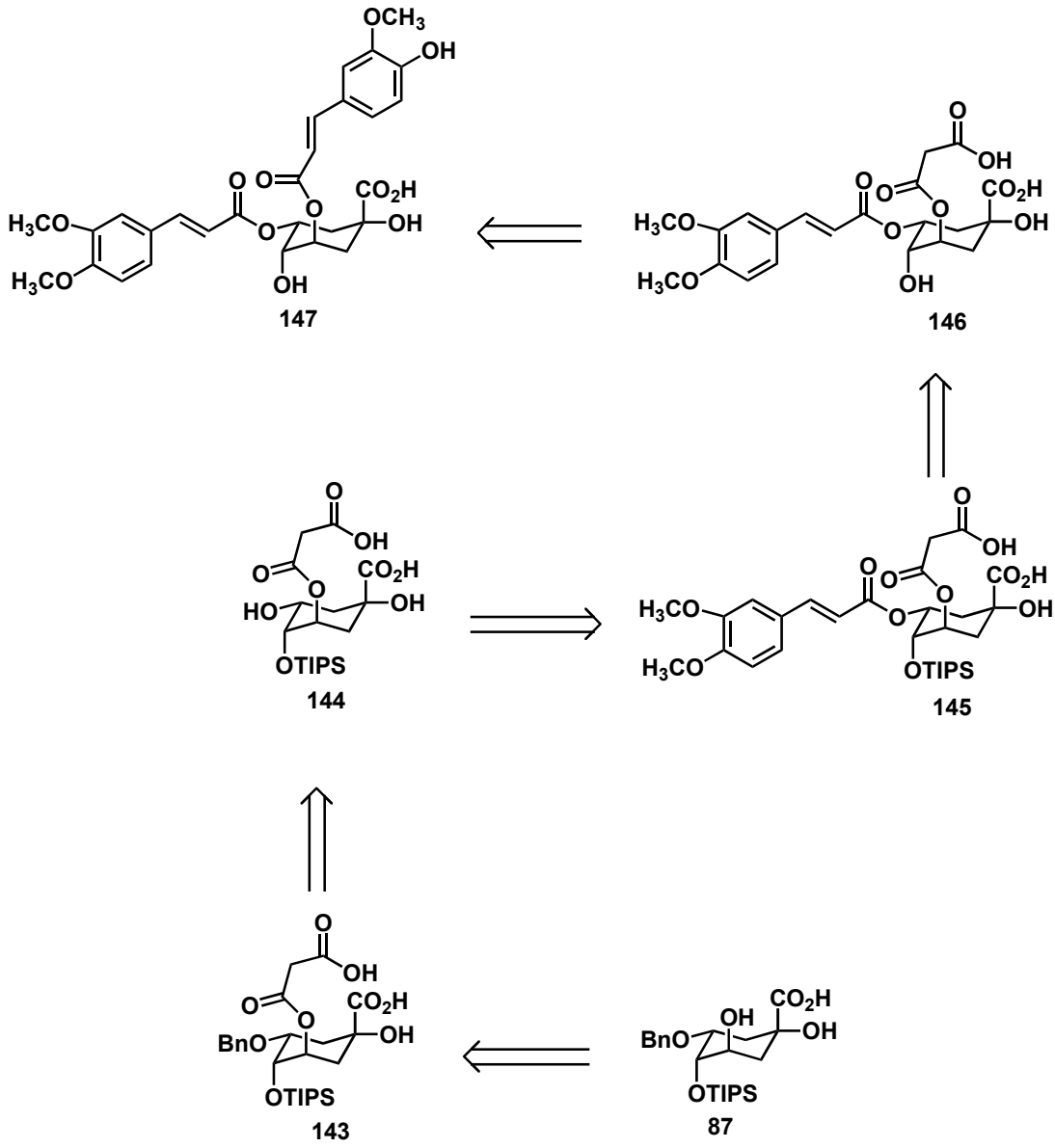
Chapter Five

5.0 Attempted synthesis of unsymmetrical quinic acid conjugates

In this chapter the studies undertaken in an attempt to synthesise unsymmetrical quinic acid conjugates are described. The synthesis of these unsymmetrical quinic acid conjugates are based on the previously developed methodology described in chapters 2 and 3.

5.1 Retrosynthetic Analysis

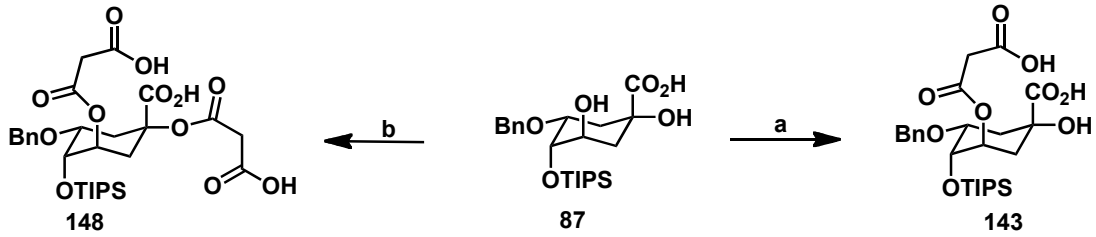
A proposed strategy for the synthesis of an unsymmetrical quinic acid conjugate is depicted below (Scheme 74), which would have a dimethoxycinnamyl ester at C-5 and a ferulyl ester at C-3. It was envisioned that the protected quinic acid **87** could be reacted with Meldrum's acid to afford the intermediate **143**. Cleavage of the benzyl ether by hydrogenolysis would then leave the 3-hydroxyl group free for reaction. At this point a cinnamyl group could be attached *via* a simple esterification reaction. Removal of the TIPS group would then be followed by Knoevenagel condensation with vanillin to attach a ferulyl group at C-5.



Scheme 74. *Retrosynthetic analysis of unsymmetrical quinic acid conjugates.*

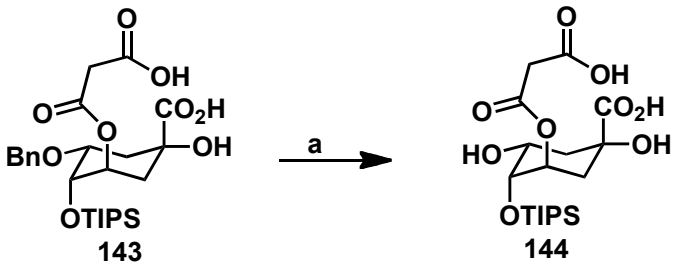
5.1 Synthesis of unsymmetrical quinic acid conjugates

The first step of the synthesis involved the refluxing of diol **87** in toluene with 1.1 eq of Meldrum's acid for 3 hours.[117] Under these conditions the desired product **143** was obtained in a moderate 45% yield (Scheme 74). The structure of the malonate **143** was confirmed by both ^{1}H NMR and mass spectrometry (*m/z* 524 corresponding to the molecular ion $[M+H]^+$ expected for $C_{26}H_{40}O_9Si$). When, the amount of Meldrum's acid was increased to 2.0 eq, this afforded the fully protected compound **148** (Scheme 75).



***Scheme 75**. Reagents & conditions: **a**) Meldrum's acid (1.1 eq), toluene, 3 h, reflux, 45% **b**) Meldrum's acid (2.0 eq), toluene, 3 h, reflux, 89%.*

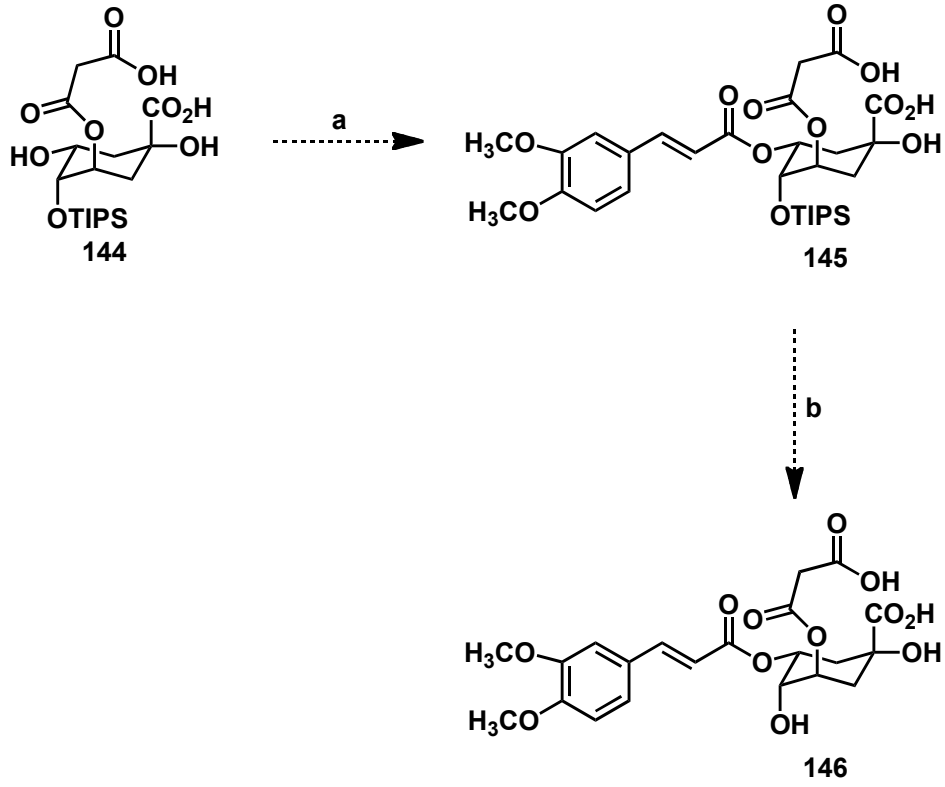
With malonate **143** in hand, the next step was the cleavage of the benzyl protecting group at the 3-position. This was achieved by hydrogenolysis using 10% Pd/C in EtOH at room temperature for 58 hours. These conditions afforded the desired product **144** in an excellent 98% yield (Scheme 76).



***Scheme 76**. Reagents & conditions: **a**) 10% Pd/C, EtOH, room temperature, 48 h, 60%.*

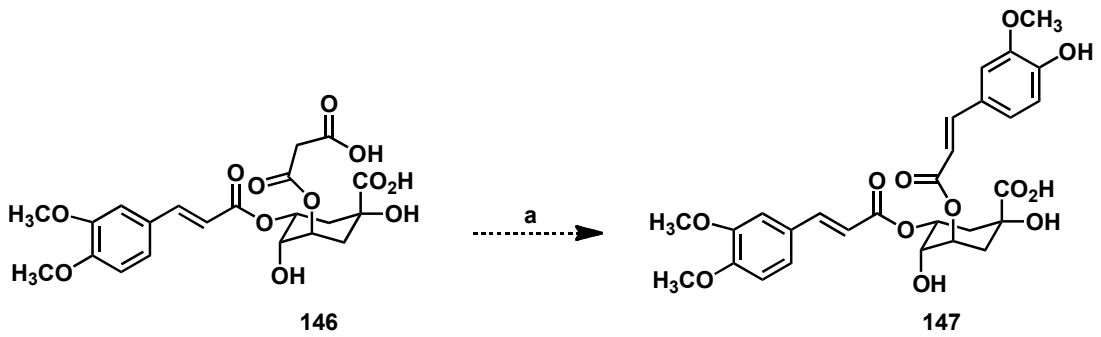
The structure of compound **144** was confirmed once again by both ^{1}H NMR spectroscopy and mass spectrometry (*m/z* 434 corresponding to the molecular ion $[M+H]^{+}$ expected for $C_{19}H_{34}O_9Si$).

Completion of the synthetic sequence to give **147** would require the coupling of **144** with 3,4-dimethoxycinnamyl chloride **90** to give **145** followed by the cleavage of the silyl protecting group (Scheme 77).



Scheme 77. ***Proposed final stages in the synthesis of 146****. Proposed Reagents and conditions:* ***a)*** *DMAP, 3,4-dimethoxycinnamoyl chloride, pyridine, CH_2Cl_2, room temperature, 12 h;* ***b****) HF-pyr, THF, 0 ºC to room temperature, 12 h.*

It was envisioned that the final step of the synthesis could be achieved by the Knoevenagel condensation of **146** and vanillin to afford the target compound **147** (Scheme 78).



Scheme 78. ***Proposed final stages in the synthesis of 147****. Proposed Reagents and conditions:* ***a)*** *3,4-dihydroxybenzaldehyde, DMAP, piperidine, room temperature, DMF.*

Conclusion

An attempt was made to synthesise unsymmetrical conjugates of 3,5-DCQ utilising the methodology previously developed and described in Chapters 2 and 3. The strategy is based on the late stage Knoevenagel condensation reaction between the advanced of intermediate **146** and vanillin. Some progress has so far been made, however due to the time constrains the last steps of the synthesis are yet to be completed.

Chapter Six

Conclusion and Future work

In conclusion, novel synthetic methodologies for the synthesis of 3,5-DCQA and its derivatives were developed. Two distinct synthetic protocols were developed both of which utilise quinide **73** as a starting point. In the original protocol, (a 7 step sequence beginning with quinic acid **2**), the key steps involved are the regioselective benzylation of the C-3-hydroxyl group followed by silyl protection of the 1- and 4- hydroxyl groups. Deprotection of the benzyl group by hydrogenolysis and opening of the lactone ring provided the 3,5 diol. In the final steps of the synthesis 3,5-DCQA derivatives were prepared by selective esterification of the secondary hydroxyl groups followed by removal of the silyl protecting groups.

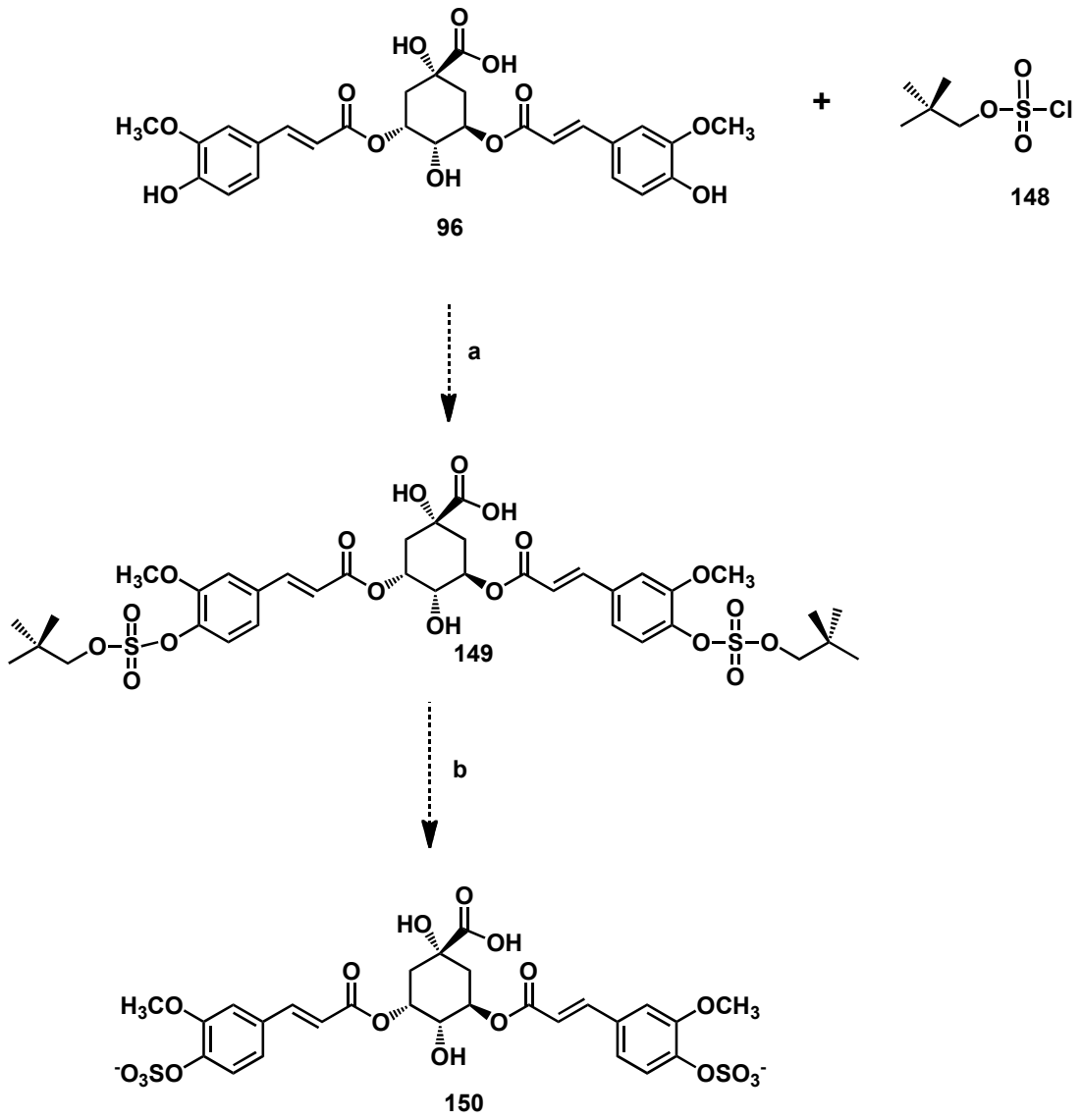
In the alternative route, (an 8 step sequence begining with quinic acid **2**), the key step is the late stage Knoevenagel condensation between vanillin and a malonate ester of quinic acid **107**. Using this protocol, the target molecule was obtained directly without protection of the quinic acid fragment **107**.

In chapter four the synthesis of compound **131** was described. The synthesis of advanced intermediate **130** was achieved in 6 steps starting from **128**. The key intermediate **140** was prepared in a 5 step sequence starting from *D*-glucurono-6,3-lactone **128**. The second intermediate, malonate **107**, was prepared by esterification of the quinic fragment with Meldrum's acid. In the

final step of the synthesis a Knoevenagel condensation reaction of **141** and a malonate ester of quinic acid **107** failed to give the target compound **131**.

In the final Chapter, an attempt to adapt the methodologies developed in Chapters 2 and 3 to the synthesis of unsymmetrical quinic acid conjugate was described. The key intermediate in this sequence was the malonate **144**, which could then be coupled to 3,4-dimethoxycinnamyl chloride **90** thus in turn allowing the synthesis of the unsymmetrical quinic acid conjugates **147** to be completed

In future it is envisaged that these methodologies could be applied to the synthesis of various unsymmetrical quinic acid conjugates or for the synthesis of potential human metabolites. A possible approach to the synthesis of sulfated conjugates is depicted below, (Scheme 78).



Scheme 78. ***Proposed synthesis of 150***. *Proposed Reagents and conditions:* ***a)*** *NaHMDS, THF, -15 °C, 20 min.* ***b)*** *sodium azide, DMF, 70 °C, 12 h.*

Experimental Procedures

General Procedures

Proton (^{1}H), carbon (^{13}C) and fluorine (^{19}F) NMR spectra were recorded on a Bruker Avance 300 spectrometer operating at 300.1 MHz for ^{1}H, 75.5 MHz for ^{13}C and 282 MHz for ^{19}F, Bruker Avance II 400 operating at 400.1 MHz for ^{1}H and 100 MHz for ^{13}C and Bruker Avance 500 operating at 499.90 MHz for ^{1}H, 125.71 MHz for ^{13}C and 470.26 for ^{19}F. Chemical shifts were recorded at δ values in parts per million (ppm). Spectra were acquired in $CDCl_3$, DMSO-d_6, CD_3OD, acetone-d_6 or deuterium oxide at ambient temperature unless otherwise specified. For ^{1}H and ^{13}C NMR spectra recorded in $CDCl_3$, DMSO-d_6, CD_3OD and deuterium oxide, the peak due to residual $CDCl_3$ (7.27 ppm for ^{1}H, 77.00 ppm for ^{13}C), DMSO-d_6 (2.5 ppm for ^{1}H, 39.5 ppm for ^{13}C), CD_3OD (3.31, 4.79 ppm for ^{1}H, 49 ppm for ^{13}C) or water (4.72 ppm for ^{1}H) was used as the internal reference. ^{1}H NMR data are reported as follows: chemical shift (δ), relative integral, multiplicity (defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet), coupling constant(s) *J* (Hz), assignment. The assignments of signals observed in various NMR spectra were assisted by conducting homonuclear (^{1}H-^{1}H) correlation spectroscopy (COSY), heteronuclear (^{1}H-^{13}C) correlation spectroscopy (HMQC) and long-range heteronuclear (^{1}H-^{13}C) correlation spectroscopy (HMBC) experiments.

HRMS and LRMS (High and Low resolution Electrospray mass spectrometry) was recorded on a water micromass, LCT to Time of Flight mass spectrometer, coupled to a water 2975 hplc. Chemical ionisation (CI) was

recorded on a waters micromass GCT Time of Flight mass spectrometer. The parent ion (M^+, $[M+H]^+$ or $[M+Na]^+$) is quoted, followed by significant fragments with relative intensities.

Infrared spectra were recorded on a Perkin-Elmer GX FT-IR spectrometer with the absorptions recorded in wavenumbers (cm^{-1}). The bands associated with C-H stretching frequencies (2960-2850 cm^{-1}) were ubiquitous and have been omitted. Samples were analyzed as thin films on NaCl discs.

Optical rotations were measured with a Perkin-Elmer model 341 polarimeter, referenced to the sodium D line (589 nm) at 20 °C, using the spectroscopic grade solvents specified and at the concentration (*c, g*/100 mL) indicated. The measurements were carried out in a cell with a 1 dm path length.

Melting points were recorded on a Gallenkamp hot-stage apparatus, and are uncorrected.

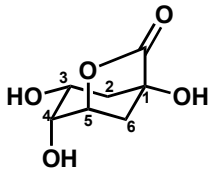
Analytical thin layer chromatography (tlc) was conducted on Merck pre-coated (25 μm) silical gel $60F_{254}$ plates or on aluminium-backed 0.2 mm thick silical gel 60 F_{254} plates (Merck) and the plates were visualized under a 254 nm UV lamp and/or by treatment with either anisaldehyde dip or alkaline potassium permangate dip, followed by heating with a heat gun. The retention factor (R_f) quoted is rounded to the nearest 0.01. Flash chromatography was conducted using silica gel $60F_{254}$ as the stationary phase and the solvent indicated.

Reagent and solvents were purified by standard means. Methanol was distilled from calcium hydride in a recycling still under nitrogen.[143] Dichloromethane (DCM), toluene, tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by passage through two coloumns of alumina using a MBRAUN (SPS-800) solvent purification system. Anhydrous DMF was purchased from Aldrich UK and dried by distillation from 4 Å molecular sieves under a nitrogen atmosphere. All reagents and starting materials were used as purchased from Aldrich UK, Acros UK or Alfa Aesar UK, except where otherwise stated in the experimental procedures.

Reactions employing air and/or moisture-sensitive reagents were performed under an atmosphere of nitrogen (unless otherwise specified) in flame-dried apparatus. Anhydrous reagents were handled under nitrogen using standard techniques.

Room temperature varied between 19-25 °C. “Removed at reduced pressure” refers to the use of a rotary evaporator with the water bath temperature generally not exceeding 40 °C.

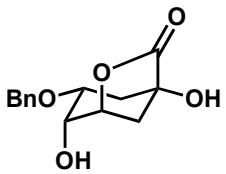
Quinide(73)[97, 99]



73

A mixture of quinic acid **5** (10 g, 52 mmol) and *p*-toluenesulfonic acid monohydrate (0.99 g, 5.2 mmol) in DMF (25 mL) and toluene (90 mL) was heated under reflux with azeotropic removal of water (Dean-Stark apparatus). After 12 h the solution was cooled to room temperature. The solvent was removed under reduced pressure to give a solid, which was then heated under reflux in ethyl acetate (100 mL) for 4 h and the solution was cooled to room temperature. The solvent was then removed under reduced pressure to give quinide **73** as a colorless solid (9 g, 99%); m.p. 182-183 °C; (lit.,[97] 184-185 °C); R_f 0.2 (petroleum ether:EtOAc, 80:20); ν_{max}(film)/cm^{-1} 3349, 1790; δ_H (300 MHz, DMSO-d_6) 5.98 (1H, s, 1-OH), 5.32 (1H, d, *J* = 4.4 Hz, 4-OH), 4.91 (1H, d, *J* = 7.0 Hz, 3-OH), 4.68 (1H, apparent d, *J* = 5.4, Hz, 5-H), 3.88 (1H, ddd, *J* = 4.7, 4.7, 4.5 Hz, 4-H), 3.61-3.50 (1H, m, 3-H), 2.33 (1H, apparent d, *J* = 11.2 Hz, 6_a-H), 2.21-2.14 (1H, m, 6_b-H), 1.95-1.98 (1H, m, 2_a-H), 1.76 (1H, apparent t, *J* = 11.6 Hz, 2_b-H); *m/z* (ES$^+$) 174 [(M+H)$^+$, 100%]. The data were in good agreement with the literature value.[97, 99]

(1*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-1,4-dihydroxy-6-oxabicyclo[3.2.1]octan-7-one (68).[104]

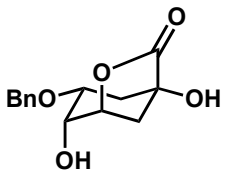


68

Method 1:

A stirred solution of quinide **73** (1.8 g, 10 mmol) and Bu_2SnO (3.1 g, 12 mmol) in toluene (10 mL) was heated under reflux with azeotropic removal of water (Dean-Stark apparatus). After 4 h, the solution was cooled to room temperature before benzyl bromide (2 mL, 16.8 mmol) and DMF (5 mL) were added. The reaction mixture was heated under reflux for 6 h. The solvents were removed under reduced pressure. Flash column chromatography on silica eluting with petroleum ether:EtOAc (80:20) gave **68** as a colorless solid (0.82 g, 30%); m.p. 154-155 °C (lit.,[104] 153-154 °C); R_f 0.5 (petroleum ether:EtOAc, 80:20); $[\alpha]_D$ -50 (*c* 0.33, $CHCl_3$) (lit., [104] -48, c 0.33, $CHCl_3$); ν_{max}(film)/cm^{-1} 3423, 1773, 1628; δ_H (300 MHz, DMSO-d_6) 7.31-7.20 (5H, m, Ar-H), 5.93 (1H, s, 1-OH), 5.21 (1H, d, *J* = 5.0 Hz, 4-OH), 4.60 (1H, apparent t, *J* = 5.4, Hz, 5-H), 4.54-4.40 (2H, AB system, *J* = 12.0 Hz, $PhCH_2$), 4.19 (1H, ddd, *J* = 4.7, 4.7, 4.5, 4-H), 3.42-3.36 (1H, m, 3-H), 2.26 (1H, apparent d, *J* = 11.2 Hz, 6_a-H), 2.16-1.20 (1H, m, 6_b-H), 1.98-1.94 (1H, m, 2_a-H), 1.72 (1H, apparent t, *J* = 11.6 Hz, 2_b-H); *m/z* (ES^-) 263 [$(M-H)^-$, 100%]. The data were in good agreement with the literature value. [104]

(1*S*,3*R*,4*R*,5*R*)-3-(benzyloxy)-1,4-dihydroxy-6-oxabicyclo[3.2.1]octan-7-one (68).[100]

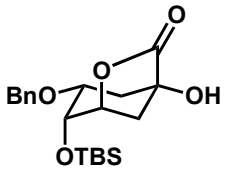


68

Method 2:

A mixture of quinide **73** (10.0 g, 57.3 mmol), Bu_2SnO (15.5 g, 62.2 mmol), tetrabutylammonium iodide (20.0 g, 54.2 mmol) and benzyl bromide (30.0 g, 175.4 mmol) in acetonitrile (100 mL) was stirred under reflux with removal of water *via* Soxhlet apparatus filled with 3 Å molecular sieves. After 12 h the solution was concentrated at reduced pressure. The residue was then suspended in water (80 mL) and extracted with ethyl acetate (250 mL). The organic fractions were combined, stirred with saturated $NaHCO_3$ solution (30 mL), filtered over Celite, then washed with brine (30 mL) and dried over Na_2SO_4. The solvents were removed under reduced pressure. Flash column chromatography on silica eluting with petroleum ether/EtOAc (80:20) gave **68** as a colorless solid (13.8 g, 91%). The data were in good agreement with the literature value. [104]

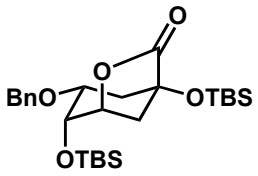
3-*O*-Benzyl-*4*-*O*-*tert*-butyldimethylsilyl quinide (74).



74

To a stirred solution of **73** (5.0 g, 18.9 mmol) and imidazole (5.0 g, 76.0 mmol), in anhydrous DMF (30 mL) was added *tert*-butyldimethylsilyl chloride (18.0 g, 118.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and 1 h at room temperature, poured into water (100 mL) and extracted with ethyl acetate (40 mL) and diethyl ether (40 mL). The organic layer was washed several times with water (3 × 100 mL), dried over Na_2SO_4 and the solvents removed under reduced pressure to give a solid residue. The residue was purified by flash chromatography on silica eluting with petroleum ether:EtOAc (70:30) to give **74** as a colorless solid (5.5 g, 76%). m.p. 100-103 °C; R_f 0.66 (petroleum ether/ EtOAc, 70:30); $[\alpha]_D$ -38.0 (c 0.33, $CHCl_3$) ν_{max}(film)/cm^{-1} 3422, 3056, 1791, 1463; δ_H (300 MHz, DMSO-d_6) 7.30-7.20 (5H, m, Ar-H), 5.96 (1H, s, 1-OH), 4.56 (1H, apparent t, *J* = 5.4, Hz, 5-H), 4.44 (2H, s, $PhCH_2$), 4.19 (1H, apparent t, *J* = 4.5, Hz, 4-H), 3.38-3.30 (1H, m, 5-H), 2.23 (1H, apparent d, *J* = 11.2 Hz, 6_a-H), 2.15-2.08 (1H, m, 6_b-H), 1.99-1.91 (1H, m, 2_a-H), 1.65 (1H, apparent t, *J* = 11.2 Hz, 2_b-H), 0.78 (9H, s, Si^{t}Bu), 0.00, -0.02 (6H, 2 × s, Si[CH_3]$_2$); δ_c (75.4 MHz, DMSO-d_6) 177.0 (C=O), 138.2 (2 x C-Ar), 128.1 (2 x C-Ar), 127.4 (2 x C-Ar), 75.3 (C-1), 73.0 (C-3), 71.4 (C-4), 64.1 (C-5), 64.9 ($PhCH_2$), 36.7 (C-6), 36.2 (C-2), 25.6 (Si^{t}Bu), 17.7 (Si^{t}Bu), -4.6 (Si[CH_3]$_2$), -4.9 (Si[CH_3]$_2$); *m/z* (CI^+) 379 [$(M+H)^+$, 100%]; HRMS (CI^+) [Found: $(M+H)^+$, 379.1941, $C_{20}H_{30}O_5Si$ requires 379.1941].

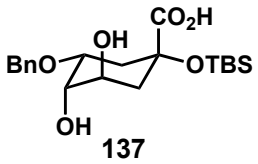
3-*O*-Benzyl-1,4-*O*-di-*tert*-butyldimethylsilyl quinide (69).[144]



69

To a stirred solution of **68** (5.0 g, 18.9 mmol), imidazole (8.0 g, 66.0 mmol) and DMAP (5.0 g, 38.0 mmol) in anhydrous DMF (30 mL) was added TBS chloride (18.0 g, 119.4 mmol) at room temperature. The mixture was stirred at 100 °C for 12 h, poured into water (10 mL) and extracted with ethyl acetate (80 ml) and diethyl ether (80 mL). The organic layer was washed with water (3 x 100 mL), dried over Na_2SO_4 and the solvents removed under reduced pressure to give a solid residue. The residue was purified by flash chromatography eluting with EtOAc: petroleum ether (40:60) to afford the desired product **69** as an oil (8.1 g, 86%); R_f 0.68 (petroleum ether:EtOAc, 90:10); $[\alpha]_D$ -13.0 (*c* 1.4, $CHCl_3$) , (lit.,[144] $[\alpha]_D$ -14.0, c 1.4, $CHCl_3$); δ_H (300 MHz, DMSO-d_6) 7.26-7.15 (5H, m, Ar-H), 4.58 (1H, apparent t, *J* = 5.4, Hz, 3-H), 4.42 (2H, s, $PhCH_2$), 4.18 (1H, apparent t, *J* = 4.5, Hz, 4-H), 3.39-3.31 (1H, m, 5-H), 2.32 (1H, apparent d, *J* = 11.4 Hz, 6_a-H), 2.22-2.17 (1H, m, 6_b-H), 1.98-1.92 (1H, m, 2_a-H), 1.72 (1H, apparent t, *J* = 11.2 Hz, 2_b-H), 0.76 (18H, s, Si^{t}Bu), 0.01, 0.00, -0.02, -0.04 (12H, 4 × s, 2 × Si$[CH_3]_2$); *m/z* (ES^+) 515 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 515.2625, $C_{26}H_{44}O_5NaSi_2$ requires 515.2624]. The data were in good agreement with the literature value. [144]

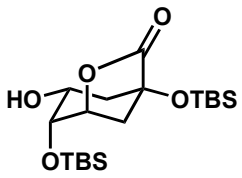
3-*O*-Benzyl-1-*O*-*tert*-butyldimethylsilyl quinic acid (137).



137

A solution of **69** (7.80 g, 15.9 mmol) in THF/H_2O (120:60 100 mL) was treated with LiOH (0.5 g, 20.8 mmol) at room temperature for 45 min. The mixture was taken up into water (80 mL) and extracted with EtOAc (180 mL). The organic layer was dried over Na_2SO_4, and the solvent removed under reduced pressure. Flash column chromatography of the residue (CH_2Cl_2:MeOH, 90:10) gave **137** as a colorless solid (5.8 g, 92%) m.p. 238-240 °C; R_f 0.20 (CH_2Cl_2 : MeOH, 90:10); $[\alpha]_D$ -38.6 (*c* 0.5, MeOH); ν_{max}(film)/cm^{-1} 3100, 1680; δ_H (300 MHz, DMSO-d_6) 7.35-7.19 (5H, m, Ar-H), 4.44 (2H, s, $PhCH_2$), 3.95-3.89 (1H, m, 5-H), 3.81-3.77 (1H, m, 3-H), 3.55-3.50 (1H, m, 4-H), 1.97-180 (3H, m, 6_a-H, 6_b-H,and 2_a-H), 1.63 (1H, d, *J* = 13.6 Hz, 2_b-H), 0.83 (9H, s, Si^{t}Bu), 0.00, -0.03 (6H, 2 × s, Si[CH_3]$_2$); δ_c (75.4 MHz, DMSO-d_6) 178.9 (C=O), 139.0 (2 × C-Ar), 127.9 (2 × C-Ar), 127.0 (2 × C-Ar), 74.0 (C-4), 72.4 (C-1), 71.9 (C-5), 69.7 (C-3), 69.6 ($PhCH_2$), 35.6 (C-6), 35.4 (C-2), 25.7 (Si^{t}Bu), 17.8 (Si^{t}Bu), -4.5 (Si[CH_3]$_2$), -5.1 (Si[CH_3]$_2$); *m/z* (ES^-) 395 [$(M-H)^-$, 100%)]; HRMS (ES^-) [Found: $(M-H)^-$, 395.1901, $C_{19}H_{35}O_3Si_3$ required 395.1894].

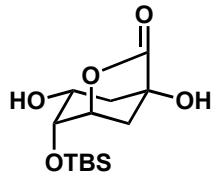
1,4-*O*-Di-*tert*-butyldimethylsilyl quinide (70).[144]



70

A suspension of the disilyl ether **69** (8.0 g, 16.2 mmol) and palladium black (0.3 g, 2.8 mmol) in ethanol (50 mL) was stirred under a hydrogen atmosphere at room temperature for 48 h. The mixture was filtered over Celite, and the residue was washed with ethanol (30 mL). The filtrate and washings were evaporated under reduced pressure to yield alcohol **70** (6.5 g, 99%) as colorless needles; m.p. 106-107 °C (lit., [144] 107-108 °C); R_f 0.45 (petroleum ether:EtOAc, 90:10); δ_H (300 MHz, DMSO-d_6) 4.78 (1H, d, J = 6.0 Hz, 3-OH), 4.53 (1H, apparent t, J = 5.4, Hz, 5-H), 3.87 (1H, apparent t, J = 4.7, Hz, 4-H), 3.50-3.40 (1H, m, 3-H), 2.28 (1H, apparent d, J = 11.1 Hz, 6_a-H), 2.18-2.12 (1H, m, 6_b-H), 1.79-1.72 (1H, m, 2_a-H), 1.66 (1H, apparent t, J = 11.2 Hz, 2_b-H), 0.77 (9H, s, Si^{t}Bu), 0.76 (9H, s, Si^{t}Bu), 0.02, 0.00, -0.00, -0.02 (12H, 4 × s, 2 × Si[CH_3]$_2$); *m/z* (CI^+) 403 [$(M+H)^+$, 100%]. The data were in good agreement with the literature value. [144]

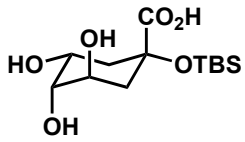
1-*tert*-Butyldimethylsilyl quinide (75).



75

A suspension of the disilyl ether **70** (8.0 g, 16.2 mmol) and 5% Pd/C (0.3 g, 2.8 mmol) in ethanol (50 mL) was stirred under a hydrogen atmosphere at room temperature for 48 h. The mixture was filtered over Celite, and the residue was washed with ethanol (30 mL). The filtrate and washings were evaporated under reduced pressure to yield alcohol **75** (6.5 g, 99%) as an oil; R_f 0.25 (CH_2Cl_2:MeOH, 90:10); $[\alpha]_D$ -1.5 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3440, 1439; δ_H (300 MHz, DMSO-d_6) 4.76 (1H, d, *J* = 6.0 Hz, 3-OH), 4.50 (1H, apparent t, *J* = 5.4 5-H), 3.86 (1H, ddd, *J* = 4.7, 4.7, 4.5, Hz, 4-H), 3.52-3.40 (1H, m, 3-H), 2.26 (1H, apparent d, *J* = 11.1 Hz, 6_a-H), 2.16-2.11 (1H, m, 6_b-H), 1.79-1.72 (1H, m, 2_a-H), 1.65 (1H, apparent t, *J* = 11.2 Hz, 2_b-H), 0.76 (9H, s, Si^{t}Bu), -0.00, -0.02 (6H, 2 × s Si[CH_3]$_2$); δ_c (75.4 MHz, DMSO-d_6) 75.8 (C-1), 75.6 (C-4), 71.4 (C-5), 66.9 (C-3), 38.6 (C-6), 37.3 (C-2), 25.8 (Si^{t}Bu), 25.7 (Si^{t}Bu), -3.0 (Si[CH_3]$_2$) -4.4 (Si[CH_3]$_2$); *m/z* (ES^+) 289 [$(M+H)^+$, 100%]; HRMS (ES^+) [Found: $(M+H)^+$, 289.1391, $C_{14}H_{24}O_5Si$, required 289.1393].

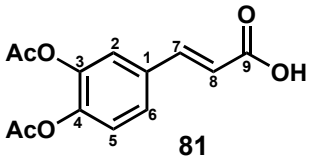
1-*O-tert*-Butyldimethylsilyl quinic acid (80).



80

A solution of **75** (6.5 g, 16.1 mmol) in THF/H_2O (120:60 180 mL) was treated with LiOH (1.0 g, 41.0 mmol) was stirred at room temperature for 45 min. The mixture was taken up into water (50 mL) and then extracted with EtOAc (180 mL) and dried over Na_2SO_4. The solvents were removed under reduced pressure. Flash column chromatography of the residue (EtOAc:petroleum ether, 40:60) gave **80** as a white solid (4.1 g, 83%); m.p. 85-90 °C; R_f 0.42 (CH_2CI_2:MeOH, 90:10); $[\alpha]_D$ +2.5 (*c* 0.86, MeOH); ν_{max}(film)/cm^{-1} 3439, 1638; δ_H (300 MHz, DMSO-d_6) 4.08-4.05 (1H, m, 5-H), 3.96-3.91 (1H, m, 3-H), 3.52-3.48 (1H, m, 4-H), 1.75-1.69 (1H, m, 6_a), 1.61 (1H, apparent t, *J* = 11.2 Hz, 2_a-H), 151-1.44 (1H, m, 6_b and 2_b-H), 0.84, 0.82 (9H, 2 × s, Si^{t}Bu), 0.03, 0.02 (6H, s, Si $[CH_3]_2$); δ_c (75.4 MHz, DMSO-d_6) 75.5 (C-1), 75.0 (C-4), 70.1 (C-5), 66.6 (C-3), 40.4 (C-6), 36.9 (C-2), 25.7 (Si^{t}Bu), 25.6 (Si^{t}Bu), -3.2 (Si $[CH_3]_2$) -4.4 (Si $[CH_3]_2$); *m/z* (ES^-) 305 [$(M-H)^-$, 100%], HRMS (ES^-) [Found: $(M-H)^-$, 305.1420, $C_{13}H_{25}O_6Si$ required 305.1424].

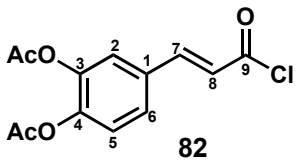
Di-*O*-acetylcaffeic acid (81). [95]



81

To a solution of caffeic acid **2** (7.20 g, 40 mmol) and DMAP (0.12 g, 1 mmol) in pyridine (20 mL) was added acetic anhydride (9.4mL, 0.1 mol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and then poured onto crushed ice. The aqueous phase was acidified with HCl (2N, pH ≈ 2) and extracted with EtOAc/THF (3:1, 3 × 80 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. Trituration of the residue with light petroleum containing a small amount of EtOAc afforded di-*O*-acetylcaffeic acid **81** as a colorless powder (10.0 g, 95%); m.p. 189-190 °C (lit.,[95] 190-191 °C); δ_H (300 MHz, acetone-d_6) 7.42 (1H, d, *J* = 16.0 Hz, 7-H), 7.49 (1H, d, *J* = 1.8 Hz, 2-H), 7.36 (1H, dd, *J* = 8.4, 1.8 Hz, 6-H), 7.07 (1H, d, *J* = 8.4 Hz, 5-H), 6.29 (1H, d, *J* = 16.0 Hz, 8-H), 2.29 (3H, s, CH_3), 2.28 (3H, s, CH_3). The data were in good agreement with the literature value. [95]

Di-*O*-acetylcaffeoyl chloride (82). [95]

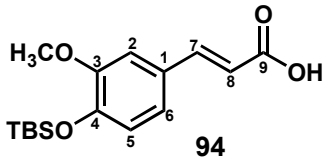


82

To a solution of **81 (**10.4 g, 39 mmol) in toluene (200 mL) containing five drops of DMF, was added oxalyl chloride (7.0 mL) at -5 °C. After stirring for 3 h at room temperature, all starting material had dissolved resulting in a pale-

brown solution. Toluene and unreacted oxalyl chloride were removed under reduced pressure. The residual brownish product was recrystallised from toluene to afford the di-*O*-acetylcaffeoyl chloride **82** as a pale yellow powder (10.4 g, 93%). m.p. 78-80 °C (lit., [95] 78-80 °C); δ_H (300 MHz, $CDCl_3$) 7.77 (1H, d, *J* = 16.0 Hz, 7-H), 7.46 (1H, d, *J* = 1.8 Hz, 2-H), 7.43 (1H, dd, *J* = 8.4 Hz, 1.8 Hz, 6-H), 7.28 (1H, d, *J* = 8.4 Hz, 5-H), 6.49 (1H, *J* = 16.0 Hz, 8-H), 2.32 (3H, s, CH_3), 2.31 (3H, s, CH_3). The data were in good agreement with the literature value. [95]

3-Methoxy-4-*O*-*tert*-butyldimethylsilyloxycinnamic acid (94).[145, 146]

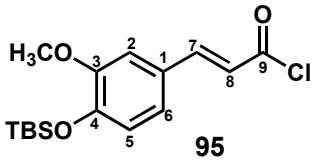


94

To a stirred solution of ferulic acid **3** (1.0 g, 5.1 mmol), and imidazole (0.7 g, 10.3 mmol) in anhydrous DMF (15 mL) was added TBS chloride (1.0 g, 6.6 mmol) at room temperature. The mixture was stirred at 70 °C for 3 h, poured into water (50 mL) and extracted with diethyl ether (80 mL). The organic layer was washed several times with water (100 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a solid residue. The resultant residue was purified by flash chromatography on silica eluting with petroleum ether:EtOAc (60:40) to give 3-methoxyl-4-*O*-*tert*-butyldimethylsilyloxycinnamic acid **94** as a colorless solid (1.5 g, 94%); m.p 118-120 °C; R_f: 0.4 (petroleum ether: EtOAc, 60:40); δ_H (300 MHz, acetone-d_6) 7.42 (1H, d, *J* = 15.5 Hz, 7-H), 7.16 (1H, d, *J* = 1.2 Hz, 2-H), 6.96 (1H, dd, *J* = 8.4, 1.2 Hz, 6-H), 6.72 (1H, d, *J* = 8.4 Hz, 5-H), 6.57 (1H, d, *J* = 15.5 Hz, 8-H), 3.32 (3H, s, CH_3), 0.81 (9H, s, Si^{t}Bu), 0.00, -0.01 (6H, 2 × s, Si $[CH_3]_2$);

m/z (ES^+) 331 [$(M+H)^+$, 100%]. The data were in good agreement with the literature value. [145, 146]

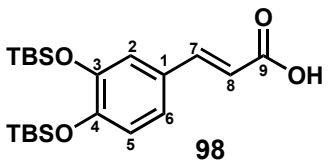
3-Methoxy-4-*O-tert*-butyldimethylsilyloxycinnamyl chloride (95). [145, 146]



95

To a solution of **94** (1.0 g, 3.2 mmol), in toluene (50 mL) containing five drops of DMF, was added oxalyl chloride (0.6 mL, 7.9 mmol) at -5 °C. After stirring for 3 h at room temperature, all starting material had dissolved resulting in a pale-brown solution. Toluene and unreacted oxalyl chloride were removed under reduced pressure to yield 3-methoxy-4-*O-tert*-butyldimethylsilyloxycinnamyl chloride **95** as an oil (0.85 g, 80%), which was used without further purification; δ_H (300 MHz, acetone-d_6) 7.64 (1H, d, *J* = 16.0 Hz, 7-H), 7.31 (1H, dd, *J* = 8.4, 1.2 Hz, 6-H), 7.12 (1H, d, *J* = 1.2 Hz, 2-H), 6.77 (1H, d, *J* = 8.4 Hz, 5-H), 6.58. (1H, d, *J* = 16.0 Hz, 8-H), 3.72 (3H, s, CH_3), 0.80 (9H, s, Si^{t}Bu), 0.00, -0.02 (6H, 2 × s, Si $[CH_3]_2$); *m/z* (ES^-) 325 [$(M-H)^-$, 100%], HRMS (ES^-) [Found: $(M-H)^-$, 325.1105, $C_{16}H_{23}ClO_3Si$ required 325.1106]. The data were in good agreement with the literature value. [145, 146]

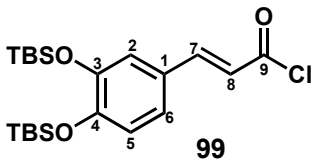
3,4-*tert*-Butyldimethylsilyl caffeic acid (98).[147]



98

To a stirred solution of caffeic acid **2** (5.0 g, 27.7 mmol), and imidazole (5.0 g, 72.6 mmol) in anhydrous DMF (60 mL) was added TBS chloride (8.5 g, 56.6 mmol) at room temperature. The mixture was stirred at 70 °C for 3 h, poured into water (100 mL) and extracted with diethyl ether (250 mL). The organic layer was washed several times with water (200 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a solid residue. The resultant residue was purified by flash chromatography on silica eluting with petroleum ether:EtOAc (90:10) to give **98** as colorless solid (8.0 g, 70%); m.p 151-154 °C, (lit.,[147] 152-155 °C); R_f: 0.23 (petroleum ether:EtOAc, 90:10); δ_H (300 MHz, $CDCl_3$) 7.28 (1H, d, *J* = 15.5 Hz, 7-H), 6.80 (1H, d, *J* = 1.2 Hz, 2-H), 6.78 (1H, dd, *J* = 8.4, 1.2 Hz, 6-H), 6.60 (1H, d, *J* = 8.4 Hz, 5-H), 5.99 (1H, d, *J* = 15.5 Hz, 8-H), 0.11 (18H, 2 × s, Si^{t}Bu), 0.00, -0.00 (12H, 2 × s, 2 × Si $[CH_3]_2$); *m/z* (ES^+) 431 [$(M+Na)^+$, 100%]. The data were in good agreement with the literature value. [147]

3,4-*tert*-Butyldimethylsilyl caffeoyl chloride (99). [147]

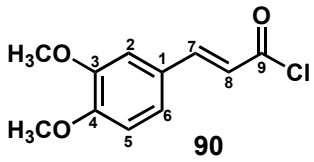


99

To a solution of **98** (8.0 g, 19.6 mmol), in toluene (200 mL) containing five drops of DMF, was added oxalyl chloride (1.69 mL, 19.7 mmol) at -5 °C. After stirring for 3 h at room temperature, all starting material had dissolved resulting in a pale-brown solution. Toluene and unreacted oxalyl chloride were removed under reduced pressure to yield 3,4-*tert*-butyldimethyllsilyl caffeoyl chloride **99** as an oil (7.5 g, 90%), which was used without further

purification; δ_H (300 MHz, $CDCl_3$) 7.74 (1H, d, *J* = 15.5 Hz, 7-H), 7.11 (1H, dd, *J* = 8.4, 2.0 Hz, 6-H), 6.89 (1H, d, *J* = 2.0 Hz, 2-H), 6.45 (1H, d, *J* = 8.4 Hz, 5-H), 5.99 (1H, d, *J* = 15.5 Hz, 8-H), 1.03, 1.01 (18H, 2 × s, Si^tBu), 0.26, 0.25 (12H, 2 × s, 2 × Si $[CH_3]_2$); *m/z* (ES^+) 427 [$(M+H)^+$, 100%]. The data were in good agreement with the literature value. [147]

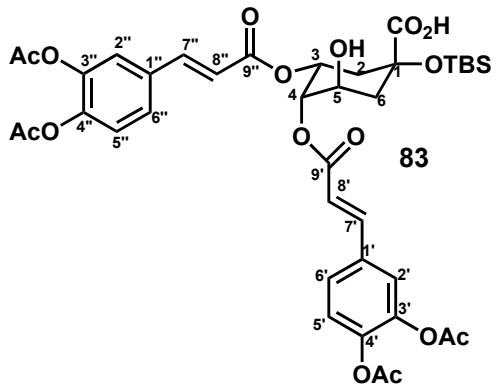
3,4-Dimethoxycinnamyl chloride (90).[148]



90

To a solution of 3,4-dimethoxylcinnamic acid **89** (10 g, 48.0 mmol), in toluene (50 mL) containing five drops of DMF, was added oxalyl chloride (5.4 mL, 63.0 mmol) at -5 °C. After stirring for 3 h at room temperature, all starting material had dissolved resulting in a pale-brown solution. Toluene and unreacted oxalyl chloride were removed under reduced pressure to yield 3,4 dimethoxycinnamyl chloride **90** as an oil (10.1 g, 92%), which was used without further purification; δ_H (300 MHz, DMSO-d_6) 7.51 (1H, d, *J* = 16.0 Hz, 7-H), 7.30 (1H, dd, *J* = 8.4, 1.8 Hz, 6-H), 7.19 (1H, d, *J* = 1.8 Hz, 2-H), 6.96 (1H, d, *J* = 8.4 Hz, 5-H), 6.44 (1H, d, *J* = 16.0 Hz, 8-H), 3.79 (3H, s, CH_3), 3.78 (3H, s, CH_3); δ_C (75.4 MHz, DMSO-d_6) 167.8 (C=O), 150.7 (Ar), 148.9 (Ar), 144.0 (C=C), 127.0 (Ar), 122.6 (Ar), 116.6 (C=C), 111.4 (Ar), 110.2 (Ar), 55.5 (CH_3), 55.5 (CH_3). The data were in good agreement with the literature value. [148]

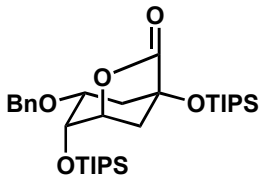
1-*O*-*tert*-Butyldimethylsilyl-3,4-di-*O*-acetylcaffeoylquinic acid (83).



DMAP (0.02 g, 0.16 mmol), and di-*O*-acetylcaffeoyl chloride **82** (0.5 g, 2.2 mmol) were added at room temperature to a solution of triol **80** (0.2 g, 0.4 mmol) in pyridine (2 mL) and CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 12 h and was then quenched by slow addition of aqueous HCl solution (1N, 8 mL). The aqueous organic phases were dried with $MgSO_4$ and the solvents removed under reduced pressure. The resultant residue was purified by flash chromatography eluting with EtOAc:petroleum ether (40:60) to give **83** as a colorless crystals (0.32 g, 62%); m.p. 128-131 °C; R_f: 0.24 (petroleum ether: EtOAC, 60:40); $[\alpha]_D$ +40 (*c* 0.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3460, 1650; δ_H (300 MHz, DMSO-d_6) 7.73 (1H, d, *J* = 1.8 Hz, 2'-H), 7.68 (1H, d, *J* = 1.8 Hz, 2''-H), 7.66 (1H, dd, *J* = 8.1, 1.8 Hz, 6'-H), 7.64-7.63 (1H, m, 6''-H), 7.33 (1H, d *J* = 8.1 Hz, 5'-H), 7.31 (1H, d *J* = 8.1 Hz, 5''-H), 6.66 (1H, d, *J* = 16.0 Hz, 7',7''- H), 6.54 (1H, d, *J* = 16.0 Hz, 8' and 8''- H), 5.28-5.23 (1H, m, 5-H), 4.53-4.50 (1H, m, 3-H), 4.13 (1H, br, 5-OH), 3.85 (1H, dd, *J* = 7.3, 3.0 Hz, 4-H), 2.30, 2.29, 2.28, 2.27 (12H, 4 × s, OCH_3), 2.26-2.22 (2H, m, 2_a and 2_b-H), 2.19-2.07 (2H, m, 6_b and 6_b-H), 0.84 (9H, s, Si^{t}Bu), 0.09, 0.06 (6H, 2 × s, Si $[CH_3]_2$). δ_c (75.4 MHz, DMSO-d_6) 170.9 (C=O), 165.2 (C-9', C-9''), 145.2 (C-4', C-4''), 143.1 (C-7', C-7''), 142.8

(C-3', C-3''), 128.4 (C-1',C-1''), 127.1 (C-6', 6''), 124.5 (C-5', 5''), 123.4 (C-2', 2''), 119.5 (C-8', 8''), 80.0 (C-1), 72.0 (C-5), 70.3 (C-3), 67.1 (C-4), 34.7 (C-6), 34.6 (C-2); 27.9 (Si^tBu), 21.2 (Si^tBu), 18.1 (OCH_3), -4.5 (Si $[CH_3]_2$); *m/z* (ES^+) 821 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 821.2453, $C_{39}H_{46}O_{16}NaSi$ requires 821.2454].

3-*O*-Benzyl-1,4-*O*-ditriisopropylsilyl quinide (85).

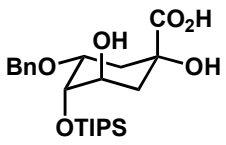


85

To a stirred solution of **68** (4.0 g, 15.1 mmol) and 2,6-lutidine (4.3 mL, 37.3 mmol) in DMF (50 mL) at 0 °C was added TIPSOTf (8.0 mL, 39.2 mmol) and the mixture was heated at 70 °C. After 17 h, the reaction was quenched with methanol at 0 °C, diluted with diethyl ether (100 mL) and washed with water (200 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and the solvents removed under reduced pressure. Flash column chromatography of the residue (petroluem ether:EtOAc, 90:10) gave the desired product **85** as a colorless solid (6.8 g, 78%); m.p 58-60 °C; R_f 0.26 (petroleum ether); $[\alpha]_D$ -42 (*c* 0.33, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2944, 1463; δ_H (300 MHz, DMSO-d_6) 7.23-7.15 (5H, m, Ar-H), 4.60 (1H, apparent t, *J* = 5.4, Hz, 3-H), 4.43-4.39 (2H, AB system, *J* = 12.2 Hz, $PhCH_2$), 4.22 (1H, apparent t, *J* = 4.4, Hz, 4-H), 3.37-3.32 (1H, m, 5-H), 2.41 (1H, apparent d, *J* = 11.3 Hz, 6_a-H), 2.23-2.16 (1H, m, 6_b-H), 1.98-1.92 (1H, m, 2_a-H), 1.72 (1H, apparent t, *J* = 11.2 Hz, 2_b-H), 0.90 (42H, s, iPr_3Si); δ_c (75.4 MHz, DMSO-d_6)

175.3 (C=O), 138.1 (C-Ar), 128.0 (2 × C-Ar), 127.6 (C-Ar), 127.4 (2 × C-Ar), 75.1 (C-1), 73.5 (C-3), 73.4 (C-5), 70.6 (CH_2Ph), 65.7 (C-4), 37.1 (C-6), 37.0 (C-2), 17.7 ($i$$Pr_3Si$), 12.3 ($i$$Pr_3Si$), 12.0 ($i$$Pr_3Si$), 11.8 ($i$$Pr_3Si$); m/z (ES^+) 599 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 599.3568, $C_{32}H_{56}O_5Si_2Na$ requires 599.3568].

3-*O*-Benzyl-4-*O*-triisopropylsilyl quinic acid (87).

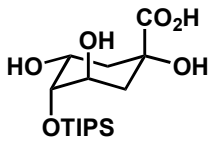


87

A solution of **85** (6.8 g, 11.8 mmol) in THF/H_2O (120:60, 180mL) was treated with LiOH (0.4 g, 16.7 mmol) and the mixture was stirred at room temperature for 45 min. The reaction mixture was taken up into water (80 mL) and then extracted with EtOAc (100 mL). The combined organic layers were dried over $MgSO_4$ and the solvents removed under reduced pressure. Flash column chromatography of the residue (CH_2Cl_2/MeOH, 80:20) gave the desired product **87** as a colorless solid (4.85 g, 94%); m.p. 198-200 °C; R_f 0.23 (CH_2Cl_2:MeOH, 80:20); $[\alpha]_D$ -21 (c 1.0, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2944, 1215, 1123; δ_H (300 MHz, DMSO-d_6) 7.42-7.29 (5H, m, Ar-H), 4.62-4.51 (2H, AB system, J = 12.2 Hz, $PhCH_2$), 4.03-3.99 (1H, m, 4-H), 3.90 (1H, dt, J = 11.1, 2.8 Hz, 3-H), 3.87-3.80 (1H, m, 5-H), 2.44-2.40 (1H, m, 6_a,-H), 2.37-2.31 (1H, m, 2_a-H) 1.98-1.82 (2H, m, 6_b and 2_b-H), 1.014-1.00 (21H, m, $i$$Pr_3Si$); δ_c (75.46 MHz, DMSO-d_6) 175.7 (C=O), 139.2 (Ar), 127.8 (2 × C-Ar), 127.6 (C-Ar), 127.4 (2 × C-Ar), 80.9 (C-1), 74.7 (C-3), 72.2 (C-4), 70.3

($PhCH_2$), 69.3 (C-5), 37.7 (C-6), 34.5 (C-2), 18.1 ($i$$Pr_3Si$), 12.0 ($i$$Pr_3Si$); *m*/*z* ($ES^-$) 437 [$(M-H)^-$, 100%]; HRMS ($ES^-$) [Found: $(M-H)^-$, 437.2359, $C_{23}H_{38}O_6Si$ requires 437.2359].

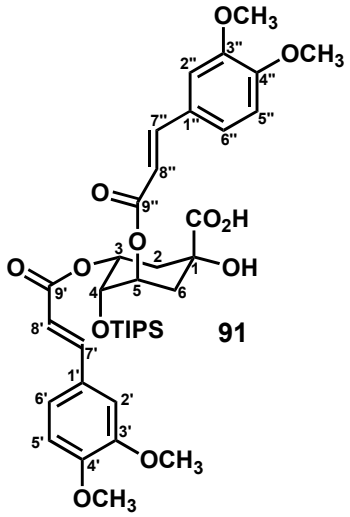
4-*O*-Triisopropylsilyl quinic acid (88).



88

A suspension of silyl ether **87** (1.01 g, 3.20 mmol) and 10% Pd/C (0.01 g, 0.09 mmol) in ethanol (30 mL) was stirred under a hydrogen atmosphere at 120 °C for 36 h. The mixture was filtered over Celite and the residue was washed with ethanol (30 mL). The filtrate and washings were evaporated under reduced pressure. Flash column chromatography of the residue (CH_2Cl_2:MeOH, 70:30) gave the desired product **88** as a colorless solid (0.66 g, 82%); m.p. 239-242 °C; R_f 0.23 (CH_2Cl_2:MeOH, 70:30); $[\alpha]_D$ -32 (*c* 1.0, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3019, 1216; δ_H (300 MHz, DMSO-d_6) 4.15 (1H, d, *J* = 5.0 Hz, 3-OH), 4.00-3.96 (1H, m, 3-H), 3.72-3.68 (1H, m, 5-H), 3.61-3.56 (1H, m, 4-H), 1.80-1.68 (2H, m, 6_a-H and 6_b-H), 1.54-1.50 (2H, m, 2_a-H and 2_b-H) 1.03-1.01 (21H, m, $i$$Pr_3Si$); δ_c (75.4 MHz, DMSO-d_6) 74.4 (C-1), 73.1 (C-5), 72.9 (C-3), 69.0 (C-4), 31.6 (C-6), 30.6 (C-2), 18.0 ($i$$Pr_3Si$), 17.9 ($i$$Pr_3Si$); *m*/*z* ($ES^-$) 347 [$(M-H)^-$, 100%]; HRMS ($ES^-$) [Found: $(M-H)^-$, 347.1891, $C_{16}H_{31}O_6Si$ requires 347.1890].

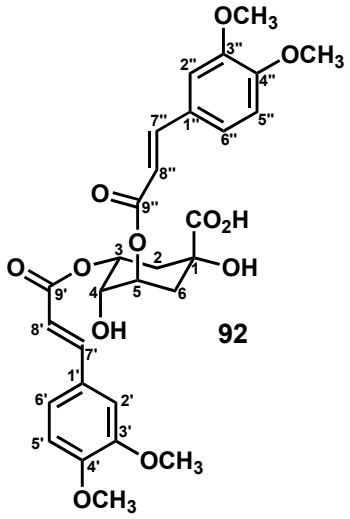
3,5-Di-*O*-dimethoxycinnamoyl-4-*O*-triisopropylsilylquinic acid (91).



To a solution of **88** (0.58 g, 1.6 mmol) and DMAP (0.05 g, 0.4 mmol), in CH_2Cl_2 (30 mL) were added pyridine (2 mL) and 3,4 dimethoxycinnamyl chloride **90** (1.0 g, 4.7 mmol) at room temperature. The mixture was stirred at room temperature for 12 h and was then quenched by the slow addition of aqueous HCl solution (1N, 10 mL). The organic phases were dried with $MgSO_4$ and the solvents removed under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2:MeOH (90:10) to give **91** as a solid (0.87 g, 72%); m.p. 109-115 °C; R_f 0.25 (CH_2Cl_2:MeOH, 90:10); $[\alpha]_D$ +31 (*c* 0.30, MeOH); ν_{max}(film)/cm^{-1} 3054, 2305, 1717, 1421, 1263; δ_H (500 MHz, DMSO-d_6) 7.56 (1H, d, *J* = 16.0 Hz, 7'-H), 7.48 (1H, d, *J* = 16.0 Hz, 7''-H), 7.32 (1H, s, 2'-H), 7.26 (1H, s, 2''-H), 7.18 (2H, d, *J* = 8.6 Hz, 5' and 5''-H), 6.98 (1H, d, *J* = 8.6 Hz, 6'-H), 6.96 (1H, d, *J* = 8.6 Hz, 6''-H), 6.49 (1H, d, *J* = 16.0 Hz, 8'-H), 6.40 (1H, d, *J* = 16.0 Hz, 8''-H), 5.34-5.24 (1H, m, 5 or 3-H), 4.19-4.09 (1H, m, 3 or 5-H), 3.94-3.88 (1H, m, 4-H), 3.80 (3H, s, CH_3), 3.78 (3H, s, CH_3), 3.79 (6H, s, CH_3), 2.40-2.32 (2H, m, 6_a and 6_b-H), 2.00-1.93 (2H, m, 2_a and 2_b-H), 1.03-1.01 (21, m, *i*Pr$_3$Si); δ_c (75.4 MHz,

DMSO-d_6) 165.3 (C-9', C-9''), 151.0 (C-4', C-4''), 148.9 (C-7', C-7''), 145.0 (C-3', C-3''), 127.0 (C-1'), 126.7 (C-1''), 122.7 (C-6'), 122.6 (C-6''), 115.2 (C-5'), 111.5 (C-5''), 111.3 (C-2'), 110.3 (C-2''), 110.1 (C-8'), 110.0 (C-8''), 71.7 (C-1), 70.1 (C-5), 66.9 (C-3), 64.7 (C-4), 55.5 (CH_3), 34.2 (C-6), 29.3 (C-2), 17.9 (iPr$_3$Si), 11.9 (iPr$_3$Si); m/z (ES^-) 727 [$(M-H)^-$, 100%]; HRMS (ES^-) [Found: $(M-H)^-$, 727.3154, $C_{37}H_{55}O_9Si_3$ requires 727.3157].

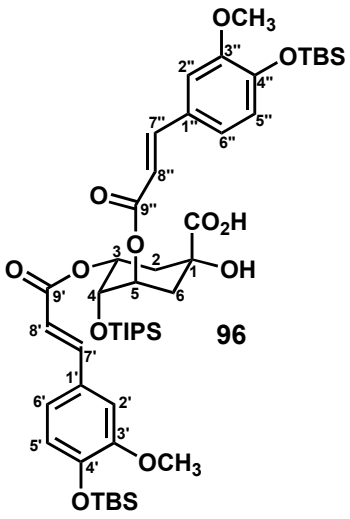
3,5-(3,4-Dimethoxycinnamyl)quinic acid (92)



To a stirred solution of **91** (0.12 g, 0.10 mmol) in THF (8 mL) in a polypropylene vessel at 0 °C was added HF•py (0.9 mL) dropwise. After 16 h at room temperature, the reaction mixture was recooled to 0 °C and a further aliquot of HF•py (1.2 mL) was added. Stirring was continued at room temperature for another 8 h. The mixture was then partitioned between aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (6 x 30 mL). The organic phases were dried with $MgSO_4$ and the solvents removed under reduced pressure. Flash chromatography MeOH/CH_2Cl_2 (20:80) gave **92** as a solid (0.087 g, 92%); m.p 110-115 °C; R_f: 0.25 (MeOH/CH_2Cl_2 20:80); $[\alpha]_D$ +52 (*c* 0.18,

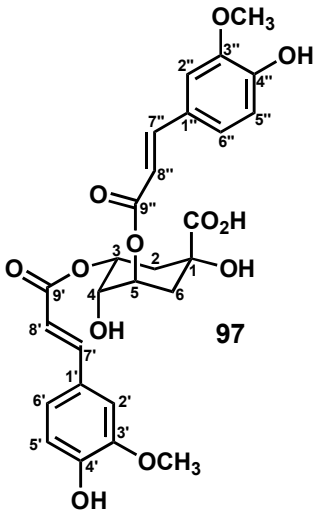
MeOH); ν_{max}(thin film)/cm^{-1} 3054, 1707, 1631, 1263; δ_H (500 MHz, DMSO-d_6) 7.38 (1H, d, *J* = 16.0 Hz, 7'-H), 7.37 (1H, d, *J* = 16.0 Hz, 7''-H), 7.15 (1H, d, *J* = 1.8 Hz, 2'-H), 7.13 (1H, d, *J* = 1.8 Hz, 2''-H), 7.04 (1H, dd, *J* = 8.1, 1.8 Hz, 6'-H), 7.01 (1H, dd, *J* = 8.1, 1.8 Hz, 6''-H), 6.82 (2H, d, *J* = 8.1, 5',5''-H), 6.33 (1H, d, *J* = 16.0 Hz, 8'-H), 6.27 (1H, d, *J* = 16.0 Hz, 8''-H), 5.09-5.01 (1H, m, 5 or 3-H), 4.70 (1H, d, *J* = 4.4 Hz, 1-OH), 3.91-3.82 (1H, m, 3 or 5-H), 3,62 (3H, s, CH_3), 3.61 (3H, s, CH_3), 3.59 (6H, s, CH_3), 3.43-3.37 (1H, m, 4-H), 2.02-2.07 (2H, m, 6_a and 6_b-H), 1.75-1.67 (2H, m, 2_a and 2_b-H); δ_c (75.4 MHz, DMSO-d_6) 173.0 (C-7), 166.4 (C-9'), 165.8 (C-9''), 151.4 (C-4', C-4''), 149.4 (C-7', C-7''), 145.4 (C-3'), 145.1 (C-3''), 127.3 (C-1', C-1''), 123.6 (C-6'), 123.4 (C-6''), 116.2 (C-2'), 112.0 (C-2''), 110.7 (C-8'), 110.5 (C-8'), 79.9 (C-1), 71.5 (C-5), 70.5 (C-3), 68.0 (C-4), 56.0 (CH_3), 36.3 (C-6), 34.5 (C-2); *m/z* (ES^+) 595 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 595.1791, $C_{29}H_{32}O_{12}Na$ requires 595.1793].

3,5-Bis(((E)-3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)acryloyl)oxy)-1-hydroxy-4-((triisopropylsilyl)oxy)cyclohexanecarboxylic acid (95).



To a solution of **88** (0.40 g, 1.1 mmol) and DMAP (0.05 g, 0.40 mmol), in CH_2Cl_2 (10 mL) were added pyridine (2 mL) and 3-methoxy-4-*O*-*tert*-butyldimethylsilyloxycinnamyl chloride **95** (1.5 g, 4.9 mmol) at room temperature. The mixture was stirred at room temperature for 12 h and was then quenched by the slow addition of 1N aqueous HCl solution (40 mL). The organic phases were dried with $MgSO_4$ and the solvents removed under reduced pressure. The residue was purified by flash chromatography eluting with petroleum ether/ EtOAc (40:60) to give **96** as a solid (0.85 g, 79%); R_f 0.14 (petroleum ether/EtOAc , 40:60); m.p. 87-89 °C; $[\alpha]_D$ +38 (*c* 1.0, MeOH); δ_H (300 MHz, DMSO-d_6) 7.58 (1H, d, *J* = 16.0 Hz, 7'-H), 7.56 (1H, d, *J* = 16.0 Hz, 7''-H), 7.31 (1H, s, 2'-H), 7.30 (1H, s, 2''-H), 7.14 (2H, d, *J* = 8.6 Hz, 5', 5''-H), 6.86 (1H, d, *J* = 8.6 Hz, 6'-H), 6.84 (1H, d, *J* = 8.6 Hz, 6''-H), 6.42 (1H, d, *J* = 16.0 Hz, 8'-H), 6.35 (1H, d, *J* = 16 Hz, 8''-H), 5.57-5.40 (1H, m, 5 or 3-H), 4.38-4.30 (1H, m, 3 or 5-H), 4.27-4.20 (1H, m, 4-H), 3.87 (3H, s, CH_3), 3.86 (3H, s, CH_3), 2.43-2.30 (2H, m, 6_a and 6_b-H), 2.20-2.07 (2H, m, 2_a and 2_b-H), , 1.03-1.01 (21, m, *i*Pr_3Si), 0.78 (18H, s, Si^{t}Bu), -0.01, 0.00, -0.02, 0.04 (12H, 4 × s, 2 × $Si[CH_3]_2$) δ_C (75.46, DMSO-d_6) 164.6 (C-9'), 164.5 (C-9''), 151.2 (C-4'), 151.1 (C-4''), 149.8 (C-7'), 149.4 (C-7''), 147.9 (C-3'), 141.5 (C-3''), 133.4 (C-1', C-1''), 133.1 (C-6'), 132.7 (C-6''), 125.3 (C-5', 5''), 115.5 (C-2', 2''), 111.3 (C-8', 8''), 87.0 (C-1), 81.9 (C-5), 72.9 (C-3), 61.5 (C-4), 58.5 (CH_3), 55.6 (CH_3), 25.7 (C-6), 25.5 (C-2), 17.9 (Si^{t}Bu), 17.8 (*i*PrSi), 11.9 (*i*PrSi), -3.2 ($Si[CH_3]_2$), -3.3 ($Si[CH_3]_2$); *m/z* (ES^-) 927 [$(M-H)^-$, 100%]; HRMS (ES^-) [Found: $(M-H)^-$, 927.4571, $C_{47}H_{79}O_9Si_5$ requires 927.4568].

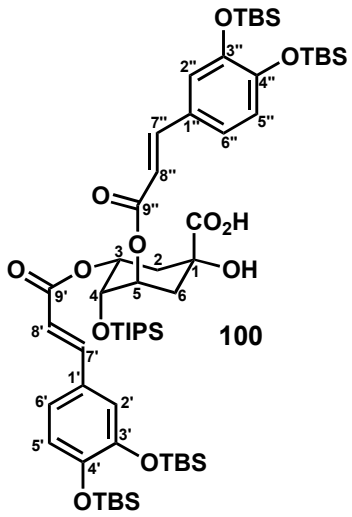
3,5-Di-*O*-feruloycinnamic acid (97).



To a stirred solution of **96** (0.04 g, 0.04 mmol) in THF (2 mL) in a polypropylene vessel at 0 °C was added HF•py (0.12 mL) dropwise. After 16 h at room temperature, the reaction mixture was re-cooled to 0 °C and a further aliquot to HF•py (0.6 mL) was added. Stirring was continued at room temperature for another 8 h. The mixture was then partitioned between aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (4 × 10 mL). The organic phases were dried with $MgSO_4$ and the solvents removed under reduced pressure. Flash chromatography MeOH:CH_2Cl_2 (80:20) gave **97** as a yellow solid (0.021 g, 89%); m.p 148-150 °C; R_f 0.26 (CH_2Cl_2:MeOH, 80:20); $[\alpha]_D$ +39 (*c* 0.5, MeOH); ν_{max}(film)/cm^{-1} 3460, 1592, 1513, 1270, 1158; δ_H (500 MHz, DMSO-d_6) 9.63 (1H, s, Ph-OH), 9.62 (1H, s, Ph-OH), 7.54 (1H, d, *J* = 16.0 Hz, 7'-H), 7.53 (1H, d, *J* = 16.0 Hz, 7''-H), 7.32 (1H, d, *J* = 1.8 Hz, 2'-H), 7.30 (1H, d, *J* = 1.8 Hz, 2''-H), 7.11 (1H, dd, *J* = 8.1, 1.8 Hz, 6'-H), 7.08 (1H, dd, *J* = 8.1, 1.8 Hz, 6''-H), 6.80 (2H, d, *J* = 8.1 Hz, 5',5''-H), 6.45 (1H, d, *J* = 16.0 Hz, 8'-H), 6.39 (1H, d, *J* = 16.0 Hz, 8''-H), 5.24 (1H, ddd, *J* = 3.5, 3.5, 4.1 Hz, 5 or 3-H), 4.95 (1H, d, *J* = 4.4 Hz, 4-OH), 4.10-4.07 (1H, m, 3 or 5-H), 3.83

(3H, s, CH_3), 3.82 (3H, s, CH_3) 3.64-3.58 (1H, m, 4-H), 2.38-2.25 (3H, m, 2_a-H 2_b-H and 6_a-H), 1.95-1.87 (1H, m, 6_b-H); δ_c (75.4 MHz, DMSO-d_6) 172.5 (C=O), 166.0 (C-9'), 165.4 (C-9''), 149.3 (C-4'), 149.2 (C-4''), 147.9 (C-7'), 147.8 (C-7''), 145.4 (C-3'), 145.0 (C-3''), 125.5 (C-1', C-1''), 123.3 (C-6'), 123.1 (C-6''), 115.4 (C-5', C-5''), 114.6 (C-2', C-2''), 111.1 (C-8'), 110.8 (C-8''), 79.1 (C-1), 70.9 (C-5), 69.8 (C-3), 67.4 (C-4), 55.6 (CH_3), 35.7 (C-6), 34.0 (C-2); *m/z* (ES^-) 543 [$(M-H)^-$], 100%]; HRMS (ES^-) [Found: $(M-H)^-$, 543.1500, $C_{27}H_{27}O_{12}$ requires 543.1503].

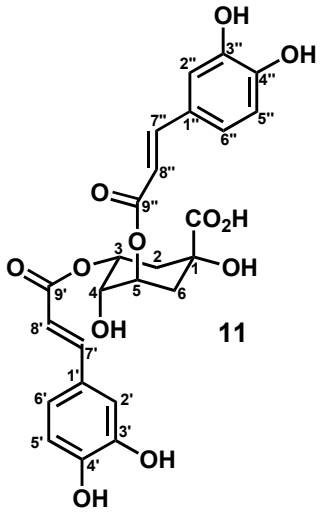
3,5-Di-O-ditert-butyldimethylsilyl-4-O-triisopropylsilylquinic acid (100).



To a solution of **88** (0.58 g, 1.6 mmol) and DMAP (0.05 g, 0.4 mmol), in CH_2Cl_2 (40 mL) were added pyridine (4 mL) and 3,4-*tert*-butyldimethylsilyl caffeoyl chloride **99** (2.5 g, 5.8 mmol) at room temperature. The mixture was stirred at room temperature for 12 h and was then quenched by the slow addition of 1N aqueous HCl solution (20 mL). The aqueous organic phases were dried with $MgSO_4$ and the solvents removed under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2:MeOH

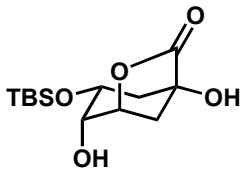
(90:10) to give **100** as a solid (1.19 g, 63%); m.p. 99-100 °C; $[\alpha]_D$ +28 (*c* 1.0, MeOH); δ_H (300 MHz, DMSO-d_6) 7.47 (1H, d, *J* = 16.0 Hz, 7'-H), 7.48 (1H, d, *J* = 16.0 Hz, 7''-H), 7.07 (1H, dd, *J* = 8.1, 1.9 Hz. 6'-H), 7.03 (1H, dd, *J* = 8.1, 1.9 Hz. 6''-H), 6.99 (1H, d, *J* = 8.1, Hz, 5'-H), 6.96 (1H, d, *J* = 8.1, Hz, 5''-H), 6.69 (1H, d, *J* = 1.8 Hz, 2'-H), 6.67 (1H, d, *J* = 1.8 Hz, 2''-H), 6.31 (1H, d, *J* = 16.0 Hz, 8'-H), 6.26 (1H, d, *J* = 16.0 Hz, 8''-H), 5.19-5.15 (1H, m, 5 or 3-H), 4.92-4.88 (1H, m, 3 or 5-H), 3.96-3.90 (1H, m, 4-H), 2.47-2.42 (2H, m, 2_a-H and 2_b-H), 2,14-2.08 (2H, m, 6_a-H and 6_b-H), 0.85 (21, s, *i*Pr_3Si), 0.75, 0.76 (36H, 2 × s, 4 × Si^{t}Bu),0.01, -0.00, 0.02, -0.03, -0.02, -0.01 (24H, 6 × s, 4 × Si $[CH_3]_2$); δ_c (75.4 MHz, DMSO-d_6) 172.3 (C=O), 165.4 (C-9'), 165.3 (C-9''), 149.4 (C-4', C-4''), 147.9 (C-7'), 147.8 (C-7''), 146.7 (C-3'), 145.4 (C-3''), 127.8 (C-1'), 125.4 (C-1''), 123.5 (C-6'), 122.9 (C-6''), 115.6 (C-5'), 115.6 (C-5''), 144.1 (C-2', C-2''), 111.2 (C-8'), 111.1 (C-8''), 79.0 (C-1), 78.9 (C-5), 70.1 (C-3), 55.6 (C-4), 34.2 (C-6), 33.1 (C-2), 25.4 (Si^{t}Bu), 17.9 (*i*Pr_3Si), 11.8 (*i*Pr_3Si), -3.2 (Si $[CH_3]_2$) -4.6 (Si $[CH_3]_2$); *m/z* (ES^-) 1127 [$(M-H)^-$, 100%]; HRMS (ES^-) [Found: $(M-H)^-$,1127.6014, $C_{54}H_{103}O_{13}Si_6$ requires 1127.6001].

3,5-Di-O-dicaffeoylquinic acid (11)



To a stirred solution of **100** (0.12 g, 0.10 mmol) in THF (8 mL) in a polypropylene vessel at 0 °C was added HF•py (0.9 mL) dropwise. After 16 h at room temperature, the reaction mixture was re-cooled to 0 °C and a further aliquot of HF•py (1.2 mL) was added. Stirring was continued at room temperature for another 8 h. The mixture was then partitioned between saturated $NaHCO_3$ (20 mL) and CH_2Cl_2 (6 x 30 mL). The organic phases were dried with $MgSO_4$ and the solvents removed under reduced pressure. Flash chromatography MeOH:CH_2Cl_2 (30:70) gave **11** as a solid (0.051 g, 93%); m.p 163-169 °C; R_f 0.13 (MeOH:CH_2Cl_2, 30:70); $[\alpha]_D$ +76 (*c* 0.1, MeOH); ν_{max}(film)/cm^{-1} 3019, 1717, 1216, 770; δ_H (500 MHz, DMSO-d_6) 9.59 (2H, s, Ph-OH), 9.16 (2H, s, Ph-OH), 7.47 (1H, d, *J* = 16.0 Hz, 7'-H), 7.46 (1H, d, *J* = 16.0 Hz, 7''-H), 7.04 (1H, d, *J* = 1.8 Hz, 2'-H), 7.05 (1H, d, *J* = 1.8 Hz, 2''-H), 7.00 (1H, dd, *J* = 8.1, 1.8 Hz, 6'-H), 6.99 (1H, dd, *J* = 8.1, 1.8 Hz, 6''-H), 6.77 (2H, d, *J* = 8.1 Hz, 5',5''-H), 6.20 (1H, d, *J* = 16.0 Hz, 8'-H), 6.19 (1H, d, *J* = 16.0 Hz, 8''-H), 5.25 (1H, td, *J* = 8.4, 3.9 Hz, 5 or 3-H), 4.95 (1H, s, 1-OH), 4.59 (1H, d, *J* = 4.3 Hz, 4-OH), 4.12-4.10 (1H, m, 5 or 3-H), 3.65-3.58 (1H, m, 4-H), 2.37-2.26 (3H, m, 2_a, 2_b and 6_a-H), 1.95-1.88 (1H, m, 6_b-H); δ_c (75.4 MHz, DMSO-d_6) 172.9 (C-7), 166.4 (C-9'), 165.7 (C-9''), 148.9 (C-4'), 148.8 (C-4''), 146.0 (C-7', C-7''), 145.9 (C-3'), 145.6 (C-3''), 126.0 (C-1'), 125.9 (C-1''), 121.8 (C-6'). 121.7 (C-6''), 116.2 (C-5', C-5''), 115.2 (C-2', C-2''), 114.6 (C-8', C-8''), 79.5 (C-1), 71.2 (C-5), 70.3 (C-3), 67.8 (C-4), 36.1 (C-6), 34.5 (C-2); *m/z* (ES$^-$) 515 [(M-H)$^-$, 100%]; HRMS (ES$^-$) [Found: (M-H)$^-$, 515.1190, $C_{25}H_{23}O_{12}$ requires 515.1190]. The data were in good agreement with the literature value.[113]

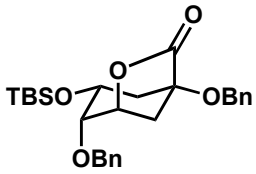
1-*O*-*tert*-Butyldimethylsilyl quinide (101). [105]



101

To a stirred solution of quinide **73** (1.80 g, 10.34 mmol) and imidazole (2.63 g, 38.2 mmol) in anhydrous DMF (14 mL) was added TBS chloride (1.80 g, 11.9 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min, 1 h at room temperature, and then poured into water (50 mL) and extracted with ethyl acetate (50 ml) and diethyl ether (40 mL). The organic layer was washed several times with water (3 × 100 mL), dried over Na_2SO_4 and the solvents removed under reduced pressure to give a solid residue, which was purified by flash chromatography eluting with EtOAc: petroleum ether (40:60) to afford the desired product 1-*O*-t*ert*-butyldimethylsilyl quinide **101** as a solid (2.5 g, 83%); m.p 90-95 °C (lit., [105] 90-94 °C); R_f 0.35 (petroleum ether/EtOAc, 90:10); $[\alpha]_D$ -42 (c 1.0, $CHCl_3$), (lit., [105] - 44 (c 1.0, $CHCl_3$)); ν_{max}(film)/cm^{-1} 3422, 1773, 1638; δ_H (300 MHz, DMSO-d_6) 5.92 (1H, s, 1-OH), 4.99 (1H, d, *J* = 5.0 Hz, 4-OH), 4.60 (1H, apparent t, *J* = 5.4, Hz, 3-H), 3.79-3.72 (1H, m 4-H), 3.65-3.59 (1H, m, 5-H), 2.25 (1H, apparent d, *J* = 11.2 Hz, 6_a-H), 2.102.03 (1H, m, 6_b-H), 1.83-1.71 (2H, m, 2-H and 2_b-H), 0.81 (9H, s, Si^tBu), 0.00, -0.01 (6H, 2 × s, $Si[CH_3]_2$); *m/z* (ES^-) 287 [$(M-H)^-$,100%]. The data were in good agreement with the literature value. [105]

3-*O*-*tert*-Butyldimethylsilyl-1,4-*O*-dibenzyl quinide(102).

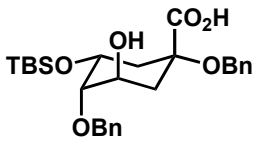


102

To a stirred solution of **101** (0.6 g, 2.08 mmol) in DMF (16 mL) at 0 °C was added NaH (0.32 g, 4.5 mmol, 60% dispersion in mineral oil). The reaction was stirred at 0 °C for 30 min. Benzyl bromide (1.2 mL, 8.7 mmol) was then added and the reaction left in the ice bath for 30 min. The ice bath was then removed and the reaction stirred at room temperature for 1 h, then at 60 °C for 12 h. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with EtOAc (80 mL). The organic layer was washed several times with water (2 × 100 mL), dried over Na_2SO_4 and the solvents removed under reduced pressure. The resultant residue was purified by flash chromatography eluting with hexanes:EtOAc gave pure product **102** as an oil (0.59 g, 60%). R_f 0.27 (petroleum ether:EtOAc, 90:10); $[\alpha]_D$ -6.9 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2032, 2930, 1793, 1603, 1454; δ_H (300 MHz, DMSO-d_6) 7.33-7.14 (10H, m, Ar-H), 4.84-4.80 (1H, m, 5-H), 4.74-4.37 (2H, AB system, *J* = 11.0 Hz, 4-OCH_2Ph), 4.49-4.45 (2H, AB system, *J* = 12.0 Hz, 1-OCH_2Ph), 3.82-3.77 (2H, m, 4,3-H), 2.51(1H, ddd, *J* = 2.7, 6.2, 11.2 Hz, 6_a-H), 2.26 (1H, apparent d, *J* = 11.2 Hz, 6_b-H), 2.00-1.93 (1H, m, 2_a-H), 1.90-1.84 (1H, m 2_b-H), 0.78 (9H, s, Si^tBu), 0.00, -0.01 (6H, 2 × s, $Si[CH_3]_2$); δ_c (75.4 MHz, DMSO-d_6) 174.6 (C=O), 138.4 (C-Ar), 137.9 (C-Ar), 128.2 (2 × C-Ar), 128.1 (2 × C-Ar), 127.6 (2 × C-Ar), 127.5 (2 × C-Ar), 127.3 (2 × C-Ar), 77.4 (C-4), 74.4 (C-1), 73.0 (C-3), 68.2 (C-5), 66.3 ($PhCH_2$), 59.7

($PhCH_2$), 37.9 (C-6), 33.0 (C-2), 25.6 (Si^tBu), 20.7 (Si^tBu), 17.7 ($Si[CH_3]_2$), -4.91($Si[CH_3]_2$), -5.0 ($Si[CH_3]_2$); *m/z* (ES^+) 491 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 491.2230, $C_{27}H_{36}O_5SiNa$ requires 491.2235].

3-*O*-*tert*-Butyldimethylsilyl-1,4-*O*-dibenzyl quinic acid (103).

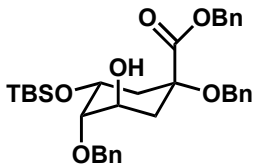


103

A solution of **102** (0.6 g, 2.08 mmol) in THF/H_2O (12:8, 20 mL) was treated with NaOH (0.2 g, 5 mmol) and the mixture was stirred at room temperature for 45 min. The residue was taken up into water (20 mL), extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and the solvents removed under reduced pressure to give a solid residue. The residue was purified by flash chromatography eluting with EtOAc: petroleum ether (40:60) to give **103** as a colorless solid (0.6 g, 96%); m.p 78-83 °C; R_f 0.23 (CH_2Cl_2:MeOH, 90:10); $[\alpha]_D$ -7.4 (*c* 0.35, MeOH); ν_{max}(film)/cm^{-1} 3495, 1607, 1065; δ_H (500 MHz, DMSO-d_6) 7.33-7.15 (10H, m, Ar), 4.78-4.59 (2H, AB, *J* = 12.0 Hz, 4-OCH_2Ph), 4.38-4.28 (2H, AB system, *J* = 11.0 Hz, 1-OCH_2Ph), 4.10-4.07 (1H, m, 5-H), 3.80-3.77 (1H,m, 3-H), 3.33-3.31 (1H, m, 4-H), 2.17-2.13 (1H, m, 6_a-H), 2.01-1.98 (1H, m, 2_a-H), 1.63 (1H, dd *J* = 3.9, 13.3 Hz, 6_b-H), 0.86-0.80 (1H, m, 2_b-H), 0.83 (9H, s, Si^tBu) 0.00, -0.01 (6H, 2 × s, $Si[CH_3]_2$); δ_c (75.46 MHz, DMSO-d_6) 175.6 (C=O), 139.1 (C-Ar), 138.8 (C -Ar), 128.2 (2 × C-Ar), 128.1 (2 × C-Ar), 127.5 (2 × C-Ar), 127.4 (2 × C-Ar), 127.3 (2 × C-Ar), 81.7 (C-4), 80.1 (C-1), 73.0 ($PhCH_2$), 68.6 (C-5),

67.2 (C-3), 65.1 ($PhCH_2$), 38.7 (C-6), 34.6 (C-2), 25.6 (Si^tBu), 17.7 (Si^tBu), -4.9 ($Si[CH_3]_2$), -5.0 ($Si[CH_3]_2$); *m*/*z* (ES^-) 485 [$(M-H)^-$, 100%]; HRMS (ES^-) [Found: $(M-H)^-$, 485.2359, $C_{27}H_{37}O_6Si$ requires 485.2363].

Benzyl-3-*O*-*tert*-butyldimethylsilyl-benzyl-1,4-*O*-benzylquinate (104).

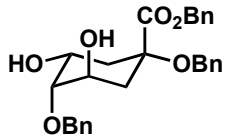


104

A solution of **103** (0.9 g, 1.80 mmol) in aqueous methanol (90%) was titrated with a solution of Cs_2CO_3 (0.3 g, 0.5 mmol) to pH 7. The solvent was evaporated at reduced pressure and then co-evaporated with toluene (2 × 10 mL). The cesium salt thus obtained was suspended in anhydrous DMF (10 mL), cooled to 0 °C, and treated with benzyl bromide (1.75 mL). After 1 h stirring, the solution was allowed to warm to room temperature and stirring was continued for a further 10 h before the solvent was removed under reduced pressure The residue was taken up into water (10 mL) and then extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and the solvents removed under reduced pressure. Flash column chromatography of the residue (petroleum ether:EtOAc, 80:20) gave the desired product **104** as an oil (1.02 g, 95%); R_f 0.45 (petroleum ether:EtOAc, 80:20); $[\alpha]_D$ -34 (*c* 0.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 3421, 1654 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.40-7.15 (15H, m, Ar), 5.21-4.98 (2H, AB system, *J* = 12.2 Hz, 1-CO_2CH_2Ph), 5.04 (1H, d, *J* = 3.5 Hz, 5-OH), 4.76-4.58 (2H, d, *J* = 12.2 Hz, 4-OCH_2Ph), 4.46-4.04 (2H, d, *J* = 12.2 Hz, 1-OCH_2Ph), 4.28 (1H,

dt, *J* = 10.5, 3.4 Hz, 3-H), 3.92 (1H, dt, *J* = 6.9, 3.4 Hz, 5-H), 3.46-3.43 (1H, m, 4-H), 2.38-2.32 (1H, m, 2_a-H), 2.23-2.17 (1H, m, 6_a-H), 1.83-1.80 (1H, m, 2_b-H), 1.80-1.75 (1H, m, 6_b-H) 0.84 (9H, s, Si^{t}Bu) 0.00, -0.00 (6H, 2 x s, Si[CH_3] $_2$); δ_c (75.46 MHz, DMSO-d_6) 171.7 (C=O), 139.1 (C-Ar), 138.0 (C-Ar), 136.0 (C-Ar), 128.3 (2 × C-Ar), 128.2 (2 × C-Ar), 128.1 (2 × C-Ar), 128.0 (2 × C-Ar), 127.6 (C-Ar), 127.3 (2 × C-Ar), 127.2 (2 × Ar), 127.1 (2 × C-Ar), 79.7 (C-4) 79.2 (C-1), 72.7 ($PhCH_2$), 68.3 (C-3), 66.9 (C-5), 66.3 ($PhCH_2$), 65.1 ($PhCH_2$) 36.4 (C-6), 35.8 (C-2), 25.7 (Si^{t}Bu), 17.7 (Si^{t}Bu), 14.0 (Si[CH_3] $_2$), -4.81 (Si[CH_3] $_2$), -4.97 (Si[CH_3] $_2$); *m*/*z* (ES^+) 599 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 599.2797, $C_{34}H_{44}O_6SiNa$ requires 599.2796].

Benzyl 1,4-di-O-benzylquinate (105).

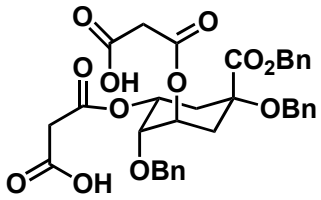


105

To a stirred solution of **104** (0.2 g, 0.34 mmol) in THF was added TFA (0.06 mL, 0.87 mmol) at 0 °C. The mixture was allowed to warm slowly to room temperature over 12 h, poured into water (5 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was dried over Na_2SO_4 and the solvents removed under reduced pressure. Flash column chromatography of the residue (petroluem ether:EtOAc, 80:20) gave the desired product **105** as an oil (0.15 g, 93%); R_f 0.1 (petroleum ether:EtOAc, 80:20); $[\alpha]_D$ -6.0 (c 1.4, $CHCl_3$); V_{max} (thin firm)$^{cm-1}$ 3351, 1687; δ_H (500 MHz, DMSO-d_6) 7.46-7.20 (15H, m, Ar), 5.24-5.09 (2H, AB system, *J* = 12.4 Hz, 1-CO_2CH_2Ph), 4.78-4.62 (2H, AB system, *J* = 12.2 Hz, 4-OCH_2Ph), 4.35-4.11 (2H, AB system, *J*

= 12.2 Hz, 1-OCH_2Ph), 4.19-4.17 (1H, m, 3-H), 4.04-3.90 (1H, m, 5-H), 3.48-3.42 (1H, m, 2_a-H), 2.38-2.34 (1H, m, 2_a-H), 2.17-2.09 (1H, m, 6_b-H), 1.98-1.86 (2H, m, 2_a-H and 6_b-H); δ_c (75.4 MHz, DMSO-d_6) 171.8 (C=O), 139.3 (C-Ar), 138.1 (C-Ar), 136.0 (C-Ar), 128.3 (2 x C-Ar), 128.0 (2 x C-Ar), 128.0 (C-Ar), 127.9 (2 × C-Ar), 127.7 (2 × C-Ar), 127.3 (2 × C-Ar), 127.2 (2 × C-Ar),127.1 (2 × C-Ar), 80.6 (C-4), 80.2 (C-1), 71.8 ($PhCH_2$), 66.3 ($PhCH_2$), 66.0 (C-5), 65.7 (C-3), 65.6 ($PhCH_2$), 37.6 (C-6), 35.1 (C-2); *m*/*z* (ES^+) 485 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 485.1940, $C_{28}H_{30}O_6Na$ requires 485.1946].

2,5-Bis(benzyloxy)-5(benzyloxy)carbonyl)cyclohexane-1,3-diyl)bis(oxy)bis(3-oxopropanoic acid) (106).

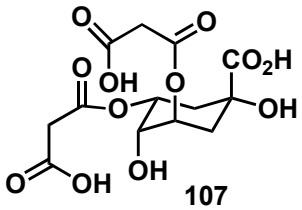


106

To a solution of diol **105** (1.66 g, 3.59 mmol) in anhydrous toluene (100 mL), Meldrum's acid (1.4 g, 9.9 mmol) was added at room temperature. The mixture was heated at 60 °C for 5 h, poured into water (40 mL), extracted with CH_2Cl_2 (80 mL) and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure to give an oily residue, which was purified by flash chromatography on silica eluting with CH_2Cl_2:MeOH (80:20) to give **106** as an oil (1.81 g, 79%); R_f 0.20 (CH_2Cl_2:MeOH, 70:30); $[\alpha]_D$ -15.6 (c 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 1724; δ_H (300 MHz, DMSO-d_6) 7.40-7.22 (15H, m, Ar), 5.48-5.45 (1H, m, 3 or 5-H), 5.27-5.23 (1H, m, 5 or 3-H),

5.22-5.16 (2H, AB system, *J* = 12.2 Hz, 1-CO_2CH_2Ph), 4.62-4.56 (2H, AB system, *J* = 12.2 Hz, 4-OCH_2Ph), 4.41-4.29 (2H, AB system, *J* = 12.2 Hz, 1-OCH_2Ph), 3.81 (1H, dd, *J* = 8.0, 3.4 Hz, 4-H), 3.28 (2H, s, CH_2), 3.19 (2H, s, CH_2), 3.23-3.18 (4H, AB system, *J* = 16.0 Hz, CH_2) 2.29-2.27 (3H, m, 6_a,6_b and 2_a-H), 2.09 (1H, q, *J* = 7.1 Hz, 2_b-H); δ_C (75.4 MHz, DMSO-d_6) 171.1 (C=O), 167.7 (C=O), 167.6 (C=O), 166.3 (C=O), 166.0 (C=O), 138.2 (C-Ar) 137.7 (C-Ar), 135.5 (C-Ar), 128.4 (2 × C-Ar), 128.2 (2 × C-Ar), 128.1 (2 × C-Ar), 128.0 (2 × C-Ar), 127.9 (2 × C-Ar), 127.6 (C-Ar), 127.5 (2 × C-Ar), 127.4 (2 × C-Ar), 77.4 (C-4), 74.4 (C-1), 73.2 ($PhCH_2$), 69.2 (C-5), 68.2 (C-3), 67.8 ($PhCH_2$), 66.2 ($PhCH_2$), 43.4 (CH_2), 43.3 (CH_2), 36.2 (C-6), 33.2 (C-2); *m/z* (ES^+) 657 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 657.1948, $C_{34}H_{34}O_{12}Na$ requires 657.1951].

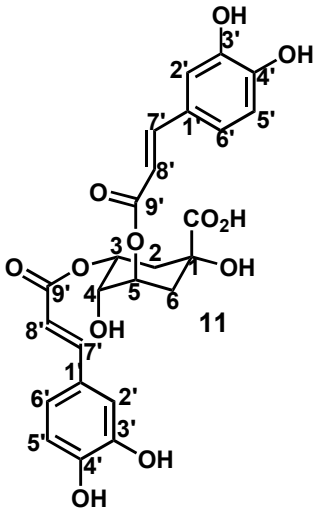
5-Carboxy-2,5-dihydroxycyclohexane-1,3-diyl)bis(oxy)bis(3-oxopropanoic acid (107).



A suspension of **106** (1.2 g, 1.89 mmol) and 10% $Pd(OH)_2$ (0.05 g, 0.47 mmol) in ethanol (60 mL) was stirred under a hydrogen atmosphere at room temperature for 36 h. The mixture was filtered over Celite, and the residue was washed with ethanol. The filtrate and washings were evaporated under reduced pressure to yield **107** as an oil (0.66 g, 94%); $[\alpha]_D$ -34 (*c* 0.5, $CHCl_3$); R_f: 0.23 (EtOAc:H_2O:MeOH, 8:1:1); ν_{max}(film)/cm^{-1} 3304, 1690; δ_H(300 MHz,

DMSO-d_6) 5.27 (1H, br, OH), 5.07-5.01 (2H, m, 3 and 5-H), 3.71 (1H, dd, *J* = 8.0, 3.4 Hz, 4-H), 3.46-3.41 (4H, AB system, *J* = 16.0 Hz, CH_2), 2.11-1.88 (4H, m, 6_a-H, 6_b-H 2_a-H and 2_b-H); δ_C (75.4 MHz, DMSO-d_6) 174.4 (C=O), 168.1 (C=O), 167.8 (C=O), 166.6 (C=O), 166.1 (C=O), 72.4 (C-1), 71.6 (C-4), 67.9 (C-5), 66.1 (C-3), 55.9 (CH_2), 37.0 (C-6), 35.6 (C-2); *m/z* (ES^+) 387 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found $M+Na)^+$, 387.0541, $C_{13}H_{16}O_{12}Na$, requires 387.0541.

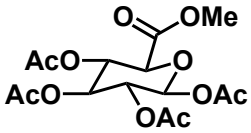
3,5-Di-O-dicaffeoylquinic acid (11).



11

To a solution of quinic acid derivative **107** (0.11 g, 0.31 mmol), 3,4-dihydroxybenzaldehyde (0.1 g, 0.72 mmol) in anhydrous DMF (5 mL), DMAP (10 mg, 0.08 mmol) piperidine (90 µL, cat) was added at room temperature. The solution was then stirred for 9 days and then concentrated under reduced pressure. The resultant residue was purified by flash chromatography on silica eluting with CH_2Cl_2:MeOH (70:30) to give 3,5-DCQA**11** as a yellow solid (0.11 g, 73%). Spectral data were identical to those reported previously.

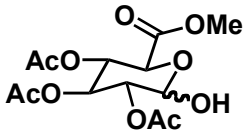
Methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate (129). [149]



129

Sodium hydroxide (0.06 g, 1.5 mmol), was dissolved in methanol (160 mL) and *D*-glucurono-6,3-lactone **128** (21.42 g, 121.6 mmol) was added. Further sodium hydroxide was added (0.1 g) to achieve pH 8-9 and the reaction mixture was stirred at room temperature for 1 h. The mixture was then concentrated at reduced pressure to leave a viscous oil. Acetic anhydride (50 mL) was added and the resulting mixture was stirred at approximately 30 °C for 2 h. Acetic anhydride (70 mL) in pyridine (50 mL) was added slowly enough to maintain the temperature under 40 °C. The reaction mixture was left stirring at 4 °C for 16 h. Concentration at reduced pressure yielded the crude product which was washed with diethyl ether (100 mL) to leave the desired product **129** (45 g, 98%) as a light brown solid; m.p. 176-177 °C (lit., [149] 178 °C); δ_H (400 MHz, $CDCl_3$), 6.42 (1H, d, *J* = 7.7 Hz, H-1), 5.35-5.21 (2H, m, H-2 and H-3), 5.17-5.11 (1H, m, H-4), 4.18 (1H, d, *J* = 9.4, H-5), 3.75 (3H, s, OCH_3), 2.12, 2.04, 2.03, 2.03 (12H, 4 × s, CH_3); δ_C (100 MHz, $CDCl_3$) 169.9 ($COCH_3$), 169.4 ($COCH_3$), 169.1 ($COCH_3$), 168.6 ($COCH_3$), 166.8 (CO_2Me), 91.3 (C-1), 73.0 (C-5), 71.8 (C-4), 70.6 (C-3), 68.9 (C-2), 53.0 (OCH_3), 207, 20.5, 20.4, 20.3 (4 × CH_3C). The data were in good agreement with the literature value.[150]

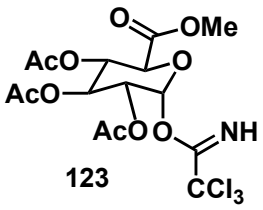
Methyl 2,3,4-tri-*O*-acetyl-α/β-D-glucopyranuronate (122).[151]



122

To a solution of **129** (20.0 g, 59.8 mmol) in THF (100 mL), ethylenediamine (5.0 mL, 83.3 mmol) was added at room temperature. The mixture was stirred at room temperature for 3 h, poured into water (80 mL) and extracted with EtOAc (250 mL) and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure to give an oily residue, which was purified by flash chromatography on silica eluting with petroleum ether: EtOAc (40:60) to give **122** as an oil (17.7 g, 99%); m.p 114-116 °C (lit.,[152] 116 °C); δ_H (400 MHz, $CDCl_3$) 5.62-5.52 (1H, m, 3-H), 5.22-5.12 (1H, m, 4-H), 4.90 (1H, dd, *J* = 3.7, 10.0 Hz, H-2), 4.59 (1H, d, *J* = 10.0 Hz, H-1^{β}), 4.43 (1H, s, br, H-1^{α}), 3.74 (3H, s, OCH_3), 2.08, 2.04, 2.03 (9H, 3 × s, CH_3); δ_C (100 MHz, $CDCl_3$) 170.2 ($COCH_3$), 170.1 ($COCH_3$), 169.7 ($COCH_3$), 168.5 ($COCH_3$), 95.4 (C-1^{β}), 90.2 (C-1^{α}), 72.8 (C-3^{β}), 72.5 9 (C-3^{α}), 72.1 (C-5^{β}), 71.6 (C-5^{α}), 70.8 (C-2^{β}), 69.5 (C-2^{α}), 69.1 (C-4^{β}), 67.9 (C-4^{α}), 53.0 and 52.9 (OCH_3), 21.0, 21.9, 20.8, 20.7, 20.6, 20.5 (6 × CH_3C). The data were in good agreement with the literature value.[152]

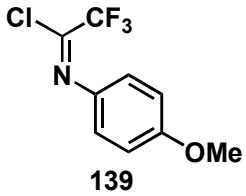
Methyl 2,3,4-tri-*O*-acetyl-1-*O*-(trichloroacetylimidoyl)-α-D-glucopyranuronate (123).[153]



123

To a stirred solution of **122** (0.49 g, 1.47 mmol) in anhydrous DCM (20 mL) were added trichloroacetonitrile (5.5 mL, 54. 90 mmol) and DBU (0.04 mL). The reaction mixture was then stirred for 2 h at room temperature. The solvent was removed under reduced pressure to give an oily residue, which was purified by flash chromatography on silica eluting with petroleum ether:EtOAc, 60:40) yielding **123** a yellow solid (0.65 g, 93%); m.p 106-107 °C, (lit.,[132] 108 °C) δ_H(400 MHz, $CDCl_3$) 8.74 (1H, s, NH), 6.65 (1H, d, *J* = 3.6 Hz, H-1), 5.64 (1H, t, *J* = 10.1 Hz, H-3 or H-4), 5.28 (1H, t, *J* = 10.1 Hz, H-3 or H-4), 5.16 (1H, dd, *J* = 3.6 Hz, *J* = 10.1 Hz, H-2), 4.51 (1H, d, *J* = 10.1 Hz, H-5), 3.76 (3H, s, OCH_3), 2.08, 2.07, 204 (9H, 3 x s, CH_3); δ_C (100 MHz, $CDCl_3$) 169.7 ($COCH_3$), 169.5 ($COCH_3$), 167.1 ($COCH_3$), 160.6 (CO_2Me), 92.6 (C-1), 70.5 (C-5), 69.5 (C-4), 69.0 (C-3), 68.9 (C-2), 53.0 (OCH_3), 207, 20.5, 20.4 (3 × CH_3C). The data were in good agreement with the literature value.[132]

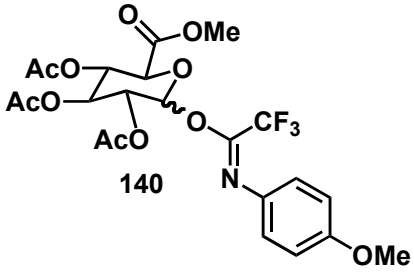
Methyl 2, *N*-(*p*-anisyl)-2,2,2-trifluoroacetimidoyl chloride (139).[141]



139

To a stirred solution of Ph_3P (34.5 g, 132 mmol) were added Et_3N (7.3 mL, 53 mmol), CCl_4 (21.1 mL, 220 mmol), and TFA (3.4 mL, 44 mmol). After the solution was stirred for about 10 min at 0 °C, *p*-anisidine (6.48 g, 53 mmol) dissolved in CCl_4 (21.1 mL, 220 mmol) was added. The mixture was then heated under reflux for 3 h. The solvents were removed under reduced pressure, and the residue was diluted with hexane (100 mL) and filtered. The filtrate was concentrated under reduced pressure, and the residue was distilled to afford **139** as a yellow oil (11.4 g, 91%); Bp: 97-98 °C (105 MMHg); δ_H(400 MHz, $CDCl_3$) 7.33-7.29 (2H, m, Ar-H), 6.97-6.93 (2H, m, Ar-H), 3.83 (3H, s, OCH_3); HRMS (ES^+) [Found: $(M+H)^+$, 238.0251, $C_4H_5N_3O_3F_5$ requires 238.0250]. The data were in good agreement with the literature value.[141]

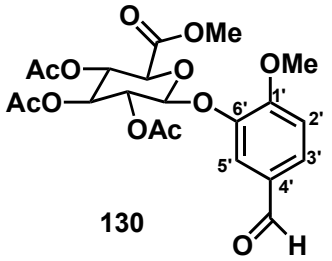
2,3,4-Tri-*O*-acetyl-D-glycopyranosiduronyl2,2,2-trifluoro-*N*-(*p*-methoxyphenyl)acetamidate (140).[140]



140

N-(*p*-Methoxyphenyl)acetimidoyl chloride (0.4 g, 1.6 mmol) was slowly added to a suspension of sugar hemiacetal **121** (0.5 g, 1.5 mmol) and K_2CO_3 (0.45 g, 3.2 mmol) in wet acetone (50 mL) at room temperature. After 3 h stirring at room temperature the solid was filtered off, and the solvent was evaporated off under reduced pressure. The residue was subjected to flash chromatography by using petroleum ether:EtOAc (60:40) to obtain **140** as a yellow viscous oil (0.61 g, 76%), δ_H (400 MHz, $CDCl_3$) 6.87-6.75 (8H, m, Ph-H), 6.58 (1H, s, br, 1-H^{α}), 5.87 (1H, s, br, 1-H^{β}), 5.58 (1H, t, *J* = 9.9 Hz, H-3), 5.36-5.21 (3H, m), 5.14 (1H, dd, *J* = 3.6 Hz, *J* = 10.1 Hz, H-2), 4.42 (1H, d, *J* = 10.1 Hz, H-5), 3.77, 3.76, 3.73 (12 H, 3 x s, 2 CO_2CH_3, 2 OCH_3), 2.053, 2.019, 2.016 (18H, 5 x s, 6 CH_3C); *m/z* (ES^+) 558 [$(M+Na)^+$, 100%]. The data were in good agreement with the literature value.[140]

2-(5-Formyl-2-methoxyphenoxy)-6-(methoxycarbonyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (130).

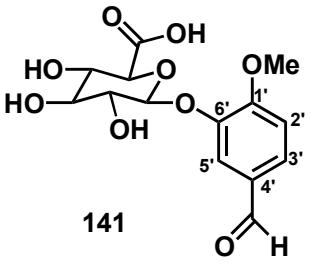


130

A mixture of **140** (3.94 g, 7.36 mmol), vanillin (1.3 g, 8.4 mmol), freshly dried molecular sieves (0.8 g) in dry dichloromethane (100 mL), and $BF_3 \cdot Et_2O$ (0.13 mL, 1.0 mmol) was stirred under nitrogen at room temperature. After 6 h, the solids were removed by filtration through a pad of Celite, and the filtrate was concentrated at reduced pressure. The residue was purified by flash chromatography with petroleum ether:EtOAc (60:40) to give **130** as a

brown solid (2.8 g, 81%); m.p. 59-60 °C; R_f 0.3 (petroleum ether:EtOAc, 40:60); $[\alpha]_D$ -54.6 (*c* 0.5, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1755, 1686; δ_H (400 MHz, acetone-d_6) 9.93 (1H, s, CHO), 7.54 (1H, dd, *J* = 1.8, 8.0 Hz, 3'-H), 7.52 (1H, d, *J* = 1.8 Hz 5'-H), 7.39 (1H, d, *J* = 8.0 Hz, 2'-H), 5.61 (1H, d, *J* = 7.7, 1-H), 5.48 (1H, t, *J* = 10.1 Hz, 3-H), 5.31-5.22 (2H, m, 4 and 2-H), 4.60 (1H, d, *J* = 10.1 Hz, 5-H), 3.92 (3H, s, OCH_3), 3.69 (3H, s, CO_2Me), 2.03, 201, 2.00 (9H, 3 × s, 9 CH_3); δ_C (100 MHz, $CDCl_3$) 190.9 (CHO), 170.1 (C=O), 169.3 (C=O), 169.2 (C=O), 166.8 (C=O), 151.0 (C-Ar), 150.8 (C-Ar), 133.0 (C-Ar), 125.5 (C-Ar), 118.7 (C-Ar), 110.6 (C-Ar), 99.6 (C-1), 72.7 (C-3), 71.5 (C-5), 70.9 (C-2), 69.0 (C-4), 53.0 (CH_3C), 20.66 (CH_3C), 20.64 (CH_3C), 20.55 (CH_3C); *m/z* (ES^+) 491 [$(M+Na)^+$, 100%); HRMS (ES^+) [Found: $(M+Na)^+$, 491.1165, $C_{21}H_{24}O_{12}Na$ requires 491.1150].

6-(5-Formyl-2-methoxyphenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid (141).

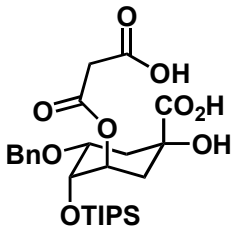


141

A solution of LiOH (0.16 g, 6.7 mmol) in MeOH-H_2O (10:10 mL) was added to **130** (0.5 g, 1.0 mmol), and the mixture was stirred at 0 °C for 22 h. The solution was then diluted with H_2O, and the pH was adjusted to 4.0 with Amberlite IR 200 (H^+). The resin was removed by filtration, the solution was

neutralised to pH 7.2 with diluted NaOH, and the solvent was evaporated off under reduced pressure. The residue was then purified by flash chromatography (EtOAc:MeOH:H_2O, 7:2:1) to give **141** as a brown solid (0.08 g, 71%); m.p. 88-89 °C; R_f 0.22 (EtOAc:MeOH:H_2O, 7:2:1); $[\alpha]_D$ -10.2 (c 0.4, H_2O); ν_{max}(thin film)/cm^{-1} 3334, 2344; δ_H (400 MHz, D_2O) 9.65 (1H, s, CHO), 7.46 (1H, dd, *J* = 1.8, 8.0 Hz, 3'-H), 7.41 (1H, d, *J* = 8.0 Hz, 5'-H), 7.17 (1H, d, *J* = 8.0 Hz, 2'-H), 5.15 (1H, d, *J* = 7.7, 1-H), 3.81 (3H, s, OCH_3), 3.61-3.49 (4H, m, 2,3,4,5-H); δ_C (100 MHz, D_2O) 194.6 (CHO), 151.1 (C-Ar), 148.9 (C-Ar), 131.0 (C-Ar), 126.8 (C-Ar), 114.9 (C-Ar), 111.2 (C-Ar), 99.4 (C-1), 76.3 (C-3), 75.1 (C-5), 72.5 (C-2), 71.5 (C-4), 55.8 (OCH_3); *m/z* (ES^-) 327 [$(M-H)^-$, 100%); HRMS (ES^-) [Found: $(M-H)^-$, 327.0716, $C_{14}H_{15}O_9$ requires 327.0716].

3-(Benzyloxy)-5-(2-carboxyacetoxy)-1-hydroxy-4-((triisopropylsilyl)oxy)cyclohexanecarboxylic acid (143).

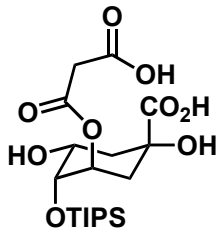


143

To a solution of **87** (1.00 g, 2.2 mmol) in anhydrous toluene (100 mL), Meldrum's acid (0.4 g, 2.7 mmol) was added at room temperature. The mixture was heated at 60 °C for 5 h, poured into water (40 mL), extracted with CH_2Cl_2 (80 mL) and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure to give a solid residue, which was purified by flash chromatography on silica eluting with CH_2Cl_2:MeOH

(90:10) to give **143** as a white solid (0.6 g, 50%); m.p 260-261 °C; R_f: 0.2 (CH_2Cl_2:MeOH, 85:15); $[\alpha]_D$ -3.4 (c 0.5, $CHCl_3$); δ_H (300 MHz, DMSO-d_6) 7.46-7.15 (5H, m, Ar), 5.00-4.81 (1H, m, 4-H), 4.69 (2H, AB system, J = 12.2 Hz, $PhCH_2$), 4.06-3.82 (2H, m, 3 and 5-H), 3.56-3.53 (2H, AB system, J = 16.0 Hz, CH_2), 2.36-2.08 (2H, m ,6_a-H and 6_b-H), 1.94-1.59 (2H, m, 2_a H and 2_b-H), 1.00 (21H, s, iPr$_3$Si); δ_c (75.4 MHz, DMSO-d_6) 175.0 (C=O), 167.7 (C=O), 132.2 (Ar), 127.9 (2 × C-Ar), 127.3(2 × C-Ar), 127.1 (C-Ar), 76.9 (C-4), 73.9 (C-1), 71.2 (C-3) 70.3 (C-5), 63.5 ($PhCH_2$), 55.3 (CH_2) 38.0 (C-6), 37.6 (C-2), 17.9 (iPr$_3$Si), 11.9 (iPr$_3$Si); m/z (ES^+) 547 [$(M+H)^+$, 100%]; HRMS (ES^+) [Found: $(M+H)^+$, 547.2339, $C_{26}H_{40}O_9SiNa$ requires 547.2330].

3-(2-Carboxyacetoxy)-1,5-dihydroxy-4-((triisopropylsilyl)oxy)cyclohexanecarboxylic acid (144).



144

A suspension of the **143** (0.8 g, 1.5 mmol) and 10% $Pd(OH)_2$ (0.06 g, 0.4 mmol) in ethanol (40 mL) was stirred under a hydrogen atmosphere at room temperature for 36 h. The mixture was filtered over Celite and the residue was washed with ethanol. The filtrate and washings were evaporated under reduced pressure to yield **144** as an oil (0.67 g, 96%); R_f:0.15 (CH_2Cl_2:MeOH, 80:20); $[\alpha]_D$ -9.3 (*c* 0.3, $CHCl_3$); δ_H (300 MHz, DMSO-d_6) 4.99-4.79 (1H, m, 4-H), 4.04-3.80 (2H, m, 3 and 5-H), 3.56-3.52 (2H, AB system, J = 16.0 Hz, CH_2), 2.35-2.07 (2H, m ,6_a and 6_b-H), 1.93-1.58 (2H, m,

2_a-H and 2_b-H), 1.01 (21H, s, *i*Pr_3Si); δ_c (75.4 MHz, DMSO-d_6) 175.0 9C=O), 167.7 (C=O), 76.9 (C-4), 73.9 (C-1), 71.4 (C-3) 70.2 (C-5), 55.9 (CH_2) 38.2 (C-6), 37.5 (C-2), 17.8 (*i*Pr_3Si), 11.7 (*i*Pr_3Si); *m*/*z* (ES^+) 457 [$(M+Na)^+$, 100%]; HRMS (ES^+) [Found: $(M+Na)^+$, 457.1870, $C_{19}H_{34}O_9SiNa$ requires 457.1866].

References

1. M. N. Clifford, *J. Sci. Food Agric.*, 1999, **79**, 362-372.
2. E. L. Eliel and M. B. Ramizer, *Tetrahedron: Asymmetry*, 1997, **8**, 3551-3554.
3. M. N. Clifford, S. Marks, S. Knight and N. Kuhnert, *J. Agric. Food Chem.*, 2006, **54**, 4095-4101.
4. M. N. Clifford, *J. Sci. Food Agric*, 2000, **80**, 1033-1043.
5. C. Wu, F. Chen, X. Wang, H.-J. Kim, G.-Q. He, V. Haley-Zitlin and G. Huang, *Food Chem.*, 2006, **96**, 220-227.
6. Yoshimoto. M, Yahara. S, Okuno. S, Islam. Md-S, Ishiguro. K and Yamakawa. O, *Biosci. Biotechnol. Biochem.*, 2002, **66**, 2336-2341.
7. A. Tolonen, T. Joutsamo, S. Mattlla, T. Kämäräinen and J. Jalonen, *Phytochem. Analysis*, 2002, **13**, 316-328.
8. Y. Chuda, H. Ono, M. Ohnishi-Kameyama, T. Nagata and T. Tsushida, *J. Agric. Food Chem.*, 1996, **44**, 2037-2039.
9. M.-H. Kweon, H.-J. Hwang and H.-C. Sung, *J. Agric. Food Chem.*, 2001, **49**, 4646-4655.
10. Y. Narita and K. Inouye, *Food Chem.*, 2011, **127**, 1532-1539.
11. M. S. Islam, M. Yoshimoto, S. Yahara, S. Okuno, K. Ishiguro and O. Yamakawa, *J. Agric. Food Chem.*, 2002, **50**, 3718-3722.
12. M. Takenaka, X. Yan, H. Ono, M. Yoshida, T. Nagata and T. Nakanishi, *J. Agric. Food Chem.*, 2002, **51**, 793-796.
13. R. Kurata, M. Adachi, O. Yamakawa and M. Yoshimoto, *J. Agric. Food Chem.*, 2006, **55**, 185-190.
14. M. Nardini, E. Cirillo, F. Natella and C. Scaccini, *J. Agric. Food Chem.*, 2002, **50**, 5735-5741.
15. M. N. Clifford, *Phytochemistry*, 1986, **25**, 1767-1769.
16. K. Azuma, K. Ippoushi, M. Nakayama, H. Ito, H. Higashio and J. Terao, *J. Agric. Food Chem.*, 2000, **48**, 5496-5500.
17. A. Crozier, I. B. Jaganath and M. N. Clifford, *Nat. Prod. Rep.*, 2009, **26**, 1001-1043.
18. R. C. Alves, S. Casal, M. R. Alves and M. B. Oliveira, *Food Chem.*, 2009, **114**, 295-299.
19. M. Lepelley, G. Cheminade, N. Tremillon, A. Simkin, V. Caillet and J. McCarthy, *Plant Sci.*, 2007, **172**, 978-996.
20. H.-J. Park, *Arch. Pharm. Res.*, 2010, **33**, 1703-1720.
21. H. J. Kim and Y. S. Lee, *Plant Med.*, 2005, **71**, 871-876.
22. H. Iwahashi, H. Morishita, N. Osaka and R. Kido, *Phytochemistry*, 1985, **24**, 630-632.
23. M. Winter and K. Herrmann, *J. Agric. Food Chem.*, 1986, **34**, 616-620.
24. C. Abell, in *Comrehensive Natural Products Chemisty*, Elsevier, 1999, vol. 1, pp. 573-607.
25. J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic Chemistry*, Oxford University Press, 2001.
26. A. Barco, S. Benetti, C. D. Risi, P. Marchetti, G. P. Pollini and V. Zanirato, *Tetrahedron: Asymmetry*, 1997, **8**, 3515-3545.

27. K. M. Herrmann and L. M. Weaver, *Ann. Rev. Plant Physiol. Plant Mol. Biol*, 1999, **50**, 473-503.
28. A. R. Knaggs, *Nat. Prod. Rep.*, 2003, **20**, 119-136.
29. N. P. Botting, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 1397-1398.
30. J. M. Waller, M. Bigger and R. J. Hillocks, *Coffee pests, disease & their management*, 1st edn., CABI, 2007.
31. I. Flament, *Coffee flavor chemistry*, Wiley-Blackwell, Chichester, 2001.
32. D. Perrone, A. Farah, C. M. Donangelo, T. De Paulis and P. R. Martin, *Food Chem.*, 2008, **106**, 859-867.
33. J.-K. Moon, H. S. Yoo and T. Shibamoto, *J. Agric. Food Chem.*, 2009, **57**, 5365-5369.
34. R. M. El-Abassy, P. Donfack and A. Materny, *Food Chem.*, 2011, **126**, 1443-1448.
35. D. H. S. G. Barbosa, R. M. Souza and H. D. Vieira, *Crop Prot.*, 2010, **29**, 175-177.
36. K. Fujioka and T. Shibamoto, *Food Chem.*, 2008, **106**, 217-221.
37. J. L. Cidell and H. C. Alberts, *Geoforum*, 2006, **37**, 999-1007.
38. A. Mehta and J.-P. Chavas, *J. Dev. Econ.*, 2008, **85**, 282-311.
39. C. Bertrand, M. Noirot, S. Doulbeau, A. De Kochko, S. Hamon and C. Campa, *Plant Sci.*, 2003, **165**, 1355-1361.
40. M. G. Ferruzzi, *Physiol. Behav.*, 2010, **100**, 33-41.
41. J. M. C. Mondego, R. O. Vidal, M. F. Carazzolle, E. K. Tokuda, L. P. Parizzi, G. G. L. Costa, L. F. P. Pereira, A. C. Andrade, C. A. Colombo, L. G. E. Vieira and G. A. G. Pereira, *BMC Plant Biology*, 2011, **11**, 30.
42. C. F. Silva, R. F. Schwan, À. q. Sousa Dias and A. E. Wheals, *Int. J. Food Microbiol.*, 2000, **60**, 251-260.
43. M. N. Clifford, S. Knight, B. Surucu and N. Kuhnert, *J. Agric. Food Chem.*, 2006, **54**, 1957-1969.
44. K. Schrader, A. Kiehne, U. H. Engelhardt and H. Gerhard Maier, *J. Sci. Food Agric*, 1996, **71**, 392-398.
45. R. J. Clarke, *Coffee* Elsevier Applied Science, London, 1987.
46. C. L. Ky, J. Louarn, S. Dussert, B. Guyot, S. Hamon and M. Noirot, *Food Chem.*, 2001, **75**, 223-230.
47. G. S. Duarte, A. A. Pereira and A. Farah, *Food Chem.*, 2010, **118**, 851-855.
48. O. Gonzalez-Rios, M. L. Suarez-Quiroz, R. Boulanger, M. Barel, B. Guyot, J.-P. Guiraud and S. Schorr-Galindo, *J. Food Compos. Anal.*, 2007, **20**, 289-296.
49. O. Gonzalez-Rios, M. L. Suarez-Quiroz, R. Boulanger, M. Barel, B. Guyot, J.-P. Guiraud and S. Schorr-Galindo, *J. Food Compos. Anal.*, 2007, **20**, 297-307.
50. M. N. Clifford, *Coffee: botany, biochemistry, and production of beans and beverage*, 1st edn., Springer, 1985.
51. R. H. Stadler, D. H. Welti, A. A. Stampfli and L. B. Fay, *J. Agric. Food Chem.*, 1996, **44**, 898-905.
52. A. Farah, T. De Paulis, D. P. Moreira, L. C. Trugo and P. R. Martin, *J. Agric. Food Chem.*, 2006, **54**, 374-381.

53. Y. Konishi and S. Kobayashi, *J. Agric. Food Chem.*, 2004, **52**, 2518-2526.
54. A. C. Galvis Sánchez, A. Gil-Izquierdo and M. I. Gil, *J. Sci. Food Agric.*, 2003, **83**, 995-1003.
55. A. Farah, T. De Paulis, L. C. Trugo and P. R. Martin, *J. Agric. Food Chem.*, 2005, **53**, 1505-1513.
56. G. A. Spanos and R. E. Wrolstad, *J. Agric. Food Chem.*, 1992, **40**, 1478-1487.
57. C. Alasalvar, J. M. Grigor, D. Zhang, P. C. Quantick and F. Shahidi, *J. Agric. Food Chem.*, 2001, **49**, 1410-1416.
58. S. C. Marks, W. Mullen and A. Crozier, *J. Agric. Food Chem.*, 2007, **55**, 8723-8730.
59. X. Zhang, H. Huang, T. Yang, Y. Ye, J. Shan, Z. Yin and L. Luo, *Injury*, 2010, **41**, 746-752.
60. S. Saito, S. Kurakane, M. Seki, E. Takai, T. Kasai and J. Kawabata, *Bioorg. Med. Chem.*, 2005, **13**, 4191-4199.
61. B. Yang, Z. Meng, J. Dong, L. Yan, L. Zou, Z. Tang and G. Dou, *Drug Metabol. Dispo.*, 2005, **33**, 930-936.
62. B. McDougall, P. J. King, B. W. Wu, Z. Hostomsky, M. G. Reinecke and W. E. Robinson Jr, *Antimicrob. Agents Ch.*, 1998, **42**, 140-146.
63. K. Zhu, M. L. Cordeiro, J. Atienza, W. E. Robinson Jr and S. A. Chow, *J. Virol.*, 1999, **73**, 3309-3316.
64. J. Slanina, E. T·borsk·, H. Bochor·kov·, I. Slaninov·, O. Humpa, W. E. Robinson Jr and K. H. Schram, *Tetrahedron Lett.*, 2001, **42**, 3383-3385.
65. P. J. King, G. Ma, W. Miao, Q. Jia, B. R. McDougall, M. G. Reinecke, C. Cornell, J. Kuan, T. R. Kim and W. E. Robinson, *J. Med. Chem.*, 1999, **42**, 497-509.
66. W. E. Robinson Jr, M. G. Reinecke, S. Abdel-Malek and S. A. Chow, *Proc. Natl. Acad. Sci. USA*, 1996, **93**, 6326-6331.
67. H. Tamura, T. Akioka, K. Ueno, T. Chujyo, K.-i. Okazaki, P. J. King and W. E. Robinson, *Mol. Nutr. Food Res.*, 2006, **50**, 396-400.
68. G.-F. Wang, L.-P. Shi, Y.-D. Ren, Q.-F. Liu, H.-F. Liu, R.-J. Zhang, Z. Li, F.-H. Zhu, P.-L. He, W. Tang, P.-Z. Tao, C. Li, W.-M. Zhao and J.-P. Zuo, *Antivir. Res.*, 2009, **83**, 186-190.
69. J. O. Ojwang, Y.-H. Wang, P. R. Wyde, N. H. Fischer, W. Schuehly, J. R. Appleman, S. Hinds and C. D. Shimasaki, *Antivir. Res.*, 2005, **68**, 163-172.
70. A. G. Antonio, R. S. Moraes, D. Perrone, L. C. Maia, K. N. Santos, N. L. P. Lurio and A. Farah, *Food Chem.*, 2010, **118**, 782-788.
71. A. A. P. Almeida, A. Farah, D. A. M. Silva, E. A. Nunan and M. B. A. Gloria, *J. Agric. Food Chem.*, 2006, **54**, 8738-8743.
72. J.-H. Lee, J. H. Park, Y. S. Kim and Y. Han, *Int. Immunopharmacol.*, 2008, **8**, 1681-1685.
73. M. H. Gordon and K. Wishart, *J. Agric. Food Chem.*, 2010, **58**, 5828-5833.
74. G. K. Hansson, *N. Engl. J. Med.*, 2005, **352**, 1685-1695.

75. T. Tanaka, T. Kojima, T. Kawamori, A. Wang, M. Suzui, K. Okamoto and H. Mori, *Carcinogenesis*, 1993, **14**, 1321-1325.
76. R. Feng, Y. Lu, L. L. Browman, Y. Qian, V. Castranova and M. Ding, *J. Biol. Chem.*, 2005, **280**, 27888-27895.
77. A. J. Woodiwiss, B. Nkeh, N. J. Samani, D. Badenhorst, M. Maseko, A. D. Tiago, G. P. Candy, E. Libhaber, P. Sareli, R. Brooksbank and G. R. Norton, *J. Hypertens.*, 2006, **24**, 1065-1073.
78. D. Kagawa, A. Suzuki, R. Ochiai, I. Tokimitsu and I. Saito, *Hypertens. Res.*, 2002, **25**, 99-107.
79. T. Watanabe, Y. Arai, Y. Mitsui, T. Kusaura, W. Okawa, Y. Kajihara and I. Saito, *Clin. Exp. Hypertens.*, 2006, **28**, 439-449.
80. S.-S. Kim, R.-Y. Park, H.-J. Jeon, Y.-S. Kwon and W. Chun, *Phytother. Res.*, 2005, **19**, 243-245.
81. A.-S. Cho, S.-M. Jeon, M.-J. Kim, J. Yeo, K.-I. Seo, M.-S. Choi and M.-K. Lee, *Food Chem. Toxicol.*, 2010, **48**, 937-943.
82. J. Camarasa, E. Escubedo and T. Adzet, *J. Pharmaceut. Biomed. Anal.*, 1988, **6**, 503-510.
83. R. Choudhury, S. K. Srai, E. Debnam and C. A. Rice-Evans, *Free Radical Bio. Med.*, 1999, **27**, 278-286.
84. A. Booth, H., O. H. Emerson, T. Jones and F. DeEds, *J. Biol. Chem*, 1957, **229**, 51-59.
85. L. C. Bourne and C. Rice-Evans, *Free Radic. Res*, 1998, **28**, 429-438.
86. Y.-S. Uang, F.-L. Kang and K.-Y. Hsu, *J. Chrom. B: Biomed. Appl.*, 1995, **673**, 43-49.
87. M.-P. Gonthier, M.-V. Verny, C. Besson, C. Remesy and A. Scalbert, *J. Nutr.*, 2003, **133**, 1853-1859.
88. P. Cremin, S. Kasim-Karakas and A. L. Waterhouse, *J. Agric. Food Chem.*, 2001, **49**, 1747-1750.
89. M. R. Olthof, C. H. Hollman, C. Peter and M. B. Katan, *J. Nutr.*, 2001, **131**, 66-71.
90. A. R. Rechner, J. P. E. Spencer, G. Kuhnle, U. Hahn and C. A. Rice-Evans, *Free Radic. Bio. Med.*, 2001, **30**, 1213-1222.
91. G. W. Plumb, M. T. Garcia-Conesa, P. A. Kroon, M. Rhodes, S. Ridley and G. Williamson, *J. Sci. Food Agric.*, 1999, **79**, 390-392.
92. D. Couteau, A. L. McCartney, G. R. Gibson, G. Williamson and C. B. Faulds, *J. Appl. Microbiol.*, 2001, **90**, 873-881.
93. R. Fumeaux, C. Menozzi-Smarrito, A. Stalmach, C. Munari, K. Kraehenbuehl, H. Steiling, A. Crozier, G. Williamson and D. Barron, *Org. Biomol. Chem*, 2010, **8**, 5199-5211.
94. E. Haslam, G. K. Makinson, M. O. Naumann and J. Cunningham, *J. Am. Chem. Soc.*, 1964, 2137-2146.
95. M. Sefkow, *Eur. J. Org. Chem.*, 2001, 1137-1141.
96. M. Sefkow, A. Kelling and U. Schilde, *Eur. J. Org. Chem.*, 2001, 2735-2742.
97. M. K. Manthey, C. Gonzalez-Bello and C. Abell, *J. Chem. Soc., Perkin Trans. 1*, 1997, 625-628.
98. C. M. Smarrito, C. Munari, F. Robert and D. Barron, *J. Org. Biomol. Chem.*, 2008, **6**, 986-987.

99. N. Kaila, W. S. Somers, B. E. Thomas, P. Thakker, K. Janz, S. DeBernardo, S. Tam, W. J. Moore, R. Yang, W. Wrona, P. W. Bedard, D. Crommie, J. C. Keith, D. H. H. Tsao, J. C. Alvarez, H. Ni, E. Marchese, J. T. Patton, J. L. Magnani and R. T. Camphausen, *J. Med. Chem.*, 2005, **48**, 4346-4357.
100. T. Desai, J. Gigg, R. Gigg and S. Payne, *Carbohydr. Res.*, 1992, **225**, 209-228.
101. S. David, in *Preparative carbohydrate chemistry*, ed. S. Hannesian, Marcel Dekker, New York, First Edition edn., 1997, pp. 69-83.
102. S. David and S. Hanessian, *Tetrahedron*, 1985, **41**, 643-663.
103. J. D. Elliott, M. Hetmanski, R. J. Stoodley and M. N. Palfreyman, *J. Chem. Soc. Perkin Trans 1*, 1981, 1782-1789.
104. S. Hanessian, J. Pan, A. Carnell, H. Bouchard and L. Lesage, *J. Org. Chem.*, 1997, **62**, 465-473.
105. A. Glebocka, R. R. Sicinski, L. A. Plum, M. Clagett-Dame and H. F. DeLuca, *J. Med. Chem.*, 2006, **49**, 2909-2920.
106. T. Ikawa, H. Sajiki and K. Hirota, *Tetrahedron*, 2004, **60**, 6189-6195.
107. D. Rotulo-Sims and J. Prunet, *Org. Lett.*, 2002, **4**, 4701-4704.
108. K. Toshima, K. Yanagawa, S. Mukaiyama and K. Tatsuta, *Tetrahedron Lett.*, 1990, **31**, 6697-6698.
109. C.-B. Cui, S. K. Jeong, S. O. Lee, I.-J. Kang and S. S. Lim, *J. Korean Soc. Appl. Biol. Chem*, 2009, **52**, 655-662.
110. R. F. Cunico and L. Bedell, *J. Org. Chem.*, 1980, **45**, 4797-4798.
111. I. Kadota and Y. Yamamoto, *J. Org. Chem.*, 1998, **63**, 6597-6606.
112. D. A. Evans, J. R. Gage and J. L. Leighton, *J. Am. Chem. Soc*, 1992, **114**, 9434-9453.
113. A. Carnat, A. Heitz, D. Fraisse, A.-P. Carnat and J.-L. Lamaison, *Fitoterapia*, 2000, **71**, 587-589.
114. J.-L. Montchamp, J. Peng and J. W. Frost, *J. Org. Chem.*, 1994, **59**, 6999-7007.
115. J. D. White, R. G. Carter, K. F. Sundermann and M. Wartmann, *J. Am. Chem. Soc.*, 2001, **123**, 5407-5413.
116. B. List, A. Doehring, M. T. Hechavarria Fonseca, A. Job and R. Rios Torres, *Tetrahedron*, 2006, **62**, 476-482.
117. Y. Ryu and A. I. Scott, *Tetrahedron Lett.*, 2003, **44**, 7499-7502.
118. G. J. Mulder, *J. Annu. Rev. Pharmacol. Toxicol.*, 1992, **32**, 25-49.
119. K. M. Engstrom, J. F. Daanen, S. Wagaw and A. O. Stewart, *J. Org. Chem.*, 2006, **71**, 8378-8383.
120. S. M. Wilkinson, C. W. Liew, J. P. Mackay, H. M. Salleh, S. G. Withers and M. D. McLeod, *Org. Lett.*, 2008, **10**, 1585-1588.
121. A. V. Stachulski and G. N. Jenkins, *Nat. Prod. Repor.*, 1998, **15**, 173-186.
122. J. A. Perrie, J. R. Harding, D. W. Holt, A. Johnston, P. Meath and A. V. Stachulski, *Org. Lett.*, 2005, **7**, 2591-2594.
123. W. Knoenigs and E. Knorr, *Ber. Dtcsh. Chem. Ges.*, 1901, **34**, 957-981.
124. P. Lewis, S. Kaltia and K. Wahala, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2481-2484.

125. K. Mori and M. Sasaki, *Tetrahedron Lett.*, 1979, **20**, 1329-1332.
126. J. J. Plattner, R. D. Gless and H. Rapoport, *J. Am. Chem. Soc.*, 1972, **94**, 8613-8615.
127. F. Cinger and R. R. Schmidt, *Synlett.*, 1993, 168-170.
128. C. D. Lunsford and R. S. Murphey, *J. Org. Chem.*, 1956, **21**, 580-582.
129. H. Hosoda, H. Yokohama and T. Tambara, *Chem. Pharm. Bull.*, 1984, **32**, 1359-1364.
130. R. R. Schmidt and W. Kinzy, *Adv. Carbohydr. Chem. Biochem*, 1994, **50**, 21-123.
131. G. Grundler and R. R. Schmidt, *Liebigs. Ann. Chem*, 1984, 1826-1847.
132. B. Fischer, A. Nudelman, M. Ruse, J. Herzig, H. E. Gottlieb and E. Keinan, *J. Org. Chem.*, 1984, **49**, 4988-4993.
133. R. T. Brown, F. Scheinmann and A. V. Stachulski, *J. Chem. Res., (S).* 1997, 370-371.
134. K. M. Engstrom, R. F. Henry and I. Marsden, *Tetrahedron Lett.*, 2007, **48**, 1359-1362.
135. R. Nakajima, M. Ono, S. Aiso and H. Akita, *Chem. Pharm. Bull.*, 2005, **53**, 684-687.
136. G. N. Bollenback, J. W. Long, D. G. Benjamin and J. A. Lindquist, *J. Am. Chem. Soc.*, 1955, **77**, 3310-3315.
137. J. Zhang and P. Kovac, *J. Carbohydr. Chem.* , 1990, **18**, 461-469.
138. B. Yu and H. Tao, *Tetrahedron Lett.*, 2001, **42**, 2405-2407.
139. N. Al-Maharik and N. P. Botting, *Tetrahedron Lett.*, 2006, **47**, 8703-8706.
140. N. Al-Maharik and N. P. Botting, *Eur. J. Org. Chem.*, 2008, 5622-5629.
141. K. Tamura, H. Mizukami, K. Maeda, H. Watanabe and K. Uneyama, *J. Org. Chem.*, 1993, **58**, 32-35.
142. A. G. Pearson, M. J. Kiefel, V. Ferro and M. v. Itzstein, *Carbohydr Res.*, 2005, **340**, 2077-2085.
143. D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd edn., Pergamon Press, Oxford, 1988.
144. C. Sanchez-Sixto, V. F. V. Prazeres, L. Castedo, H. Lamb, A. R. Hawkins and C. Gonzalez-Bello, *J. Med. Chem.*, 2005, **48**, 4871-4881.
145. S. A. Snyder and F. Kontes, *J. Am. Chem. Soc.*, 2009, **131**, 1745-1752.
146. F. Fache, N. Suzan and O. Piva, *Tetrahedron*, 2005, **61**, 5261-5266.
147. D. E. Bogucki and J. L. Charlton, *Can. J. Chem.*, 1997, **75**, 1783-1794.
148. S. E. Drewes, A. J. Hall, R. A. Learmonth and U. J. Upfold, *Phytochemistry*, 1984, **23**, 1313-1316.
149. R. Kumar, U. Ramachandran, K. Srinivasan, P. Ramarao, S. Raichur and R. Chakrabarti, *Bioorg. Med. Chem.*, 2005, **13**, 4279-4290.