Synthesis of fluorinated benzophenones and phenylcoumarins

Submitted in fulfillment of the academic requirements for the degree of

Doctor of Philosophy

School of Chemistry and Physics

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By

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Abstract

The aim of this project was to develop methods for the preparation of fluorine analogues of natural products. The incorporation of fluorine into bioactive organic compounds enhances bioactivity and the replacement of either a hydrogen atom or oxygen atom with fluorine atom is sterically favoured since their atomic sizes are similar. Three classes of fluorine-containing compounds were synthesized, i.e. prenylated benzophenones, geranylated benzophenones and 4-phenylcoumarins.

Prenylated benzophenones are compounds with interesting activities such as anticancer, anti-inflammation, anti-HIV, cholesterol regulatory, cytotoxic and antimicrobial activity. Fluorine-containing prenylated benzophenones were prepared by an improved synthetic route which includes the application of Friedel-Crafts acylation and electrophilic aromatic substitution reactions. The analogues of benzophenones that were synthesized in this study include monoprenylated, diprenylated, triprenylated and tetraprenylated benzophenones with a fluorine substituent in either the *ortho*-, *meta*- or *para*-position of the benzene ring. Among the analogues of benzophenones synthesized were (3-fluorophenyl)[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (monoprenylated), (3-fluorophenyl)[2,4,6-trihydroxy-3,5-bis(3-methyl-2-butenyl)phenyl]methanone (diprenylated), (3-fluorophenyl)[2,4,6-tris(3-methylbut-2-enyloxy)phenyl]methanone (triprenylated) and (3-fluorophenyl)[2-hydroxy-3,5-bis(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (tetraprenylated). Similar types of 4-fluoro analogues of benzophenones were synthesized which includes *C*- and *O*-prenylated benzophenones. Geranylated benzophenones were also synthesized in this study including monogeranylated, digeranylated, trigeranylated and tetrageranylated benzophenones. The prenylation reaction of a 2-fluorobenzophenone using prenyl bromide and DBU was not successful, but when K_2CO_3 was used instead of DBU, the reaction was successful.

Coumarins belong to a class of phenolic compounds characterized by a benzene ring fused to a pyrone ring. Many coumarins exhibit biological activities such as antibacterial, anti-inflammatory, anti-oxidant, anticoagulant, anti-tumour, hepatoprotective, anti-carcinogenic, anti-viral and anti-thrombotic activities. In this study, fluorinated 4-phenylcoumarins (fluorine-substituted neoflavones) were synthesized by the Pechmann reaction. Fluorine-substituted 4-aryl β-ketoesters were successfully synthesized by a newly developed method

and subjected to Pechmann reactions using resorcinol and phloroglucinol as starting materials to form 7-hydroxyneoflavones and 5,7-dihydroxyneoflavones, respectively.

Some of the synthesized fluorinated prenylated benzophenones and fluorinated neoflavones were assayed for HIV activity at a concentration of 10 $\mu g.mL^{-1}$ but did not show any activity at this concentration.

Thesis declaration

I hereby certify that this research is as a result of my own investigation, which has not already been accepted in substance for any degree and is not submitted in candidature for any other degree.

Signed…….……. Date…….

Vuyisa Mzozoyana

I hereby certify that this statement is correct.

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January 2015

Plagiarism declaration

I, Vuyisa Mzozoyana declare that:

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Acknowledgements

‘Sengiyabaleka ngiya enqabeni yami’ “Baba, Mama, nin’eniKhanyayo ngiyabonga” ‘Ngokubonga ngikukhonze ngakhokonk’okwami’.

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Abbreviations

°C	Degrees Celsius
^{13}C NMR	Carbon nuclear magnetic resonance
^{1}H NMR	Proton Nuclear magnetic resonance
BuLi	Butyllithium
$CDCl_3$	Deuterated chloroform
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
DEPT	Distortionless enhancement polarization transfer
DMAP	4-(*N*,*N*-Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dt	Doublet of triplets
EtOAc	Ethyl acetate
h	Hour (s)
HCl	Hydrochloric acid
HIV	Human immunodeficiency virus
HMBC	Heteronuclear multiple quantum coherence
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
IR	Infrared

J	Coupling (spectral)
K_2CO_3	Potassium carbonate
$LiAlH_4$	Lithium aluminium hydride
m	Multiplets
m/z	Mass-to-charge ratio
MeI	Iodomethane
$MgSO_4$	Magnesium sulfate
MHz	Megahertz
min	Minute (s)
mmol	Millimole (s)
MOM	Methoxymethyl
Mp	Melting point
NMR	Nuclear magnetic resonance spectroscopy
OMe	Methoxy
Ph	Phenyl
p-TsOH	*p*-Toluenesulfonic acid
s	Singlet
TB	Tuberculosis
td	Triplet of doublets
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
tt	Triplet of triplet

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CHAPTER 1. INTRODUCTION

1.1 Microbes as cause of infectious diseases

Microbes can be defined as tiny living organisms that efficiently reproduce and spread quickly. Microbes are too small to be seen by the naked eye which makes them difficult to control. They are abundant on earth and they live everywhere, in air, water, rock and soil. Microbes can survive harsh conditions such as living under freezing conditions, at high temperatures, aerobic and anaerobic conditions. Microbes belong to one of four major groups:

1. Fungi, e.g. *Candida albicans*, which causes some yeast infections.
2. Bacteria, e.g. *Staphylococcus aureus*, which causes some staph infections.
3. Viruses, e.g. *Hemophilus influenzae*, which causes flu
4. Parasites, e.g. *Plasmodium falciparum*, which causes malaria.

Infectious diseases have been a major challenge to human survival as they remain among the top causes of death and disability globally.[1] Infectious diseases were not known to be caused by microbes until the development of a better microscopic magnification by van Leeuwenhoek in 1670's, who was the first to identify bacteria. Thereafter, there had been a number of suspicions of infectious diseases (e.g. smallpox) that could not be proven to be associated with microbes at that time. More than a century later, Bassi managed to prove that some diseases (infectious diseases) were caused by microorganisms.[2] A decade later in 1876, Koch isolated *Bacillus anthracis* (first bacterium isolation).[2] Identification of infectious diseases and isolation of microbes has been ongoing.

1.2 Antibiotics

1.2.1 Definition of antibiotics

Antimicrobials including antibiotics are chemical compounds that kill or inhibit the growth of microorganisms by different kinds of action. Antibiotics used to be defined as chemical compounds produced by microorganisms that have the ability to kill or inhibit the growth of the other microorganisms even in small concentrations.[3] Hutter[4] and coworkers defined antibiotics as the products of secondary metabolites with an incidental action on growth processes even in high dilution.

Antimicrobial agents from different chemical classes may have the same mode of action, e.g. penicillin and cephalosporin both inhibit the synthesis of bacterial cell wall. Antimicrobials can affect the metabolism, RNA, DNA; can affect respiratory electron transport chain and thus depriving the cell of the energy currency (ATP); can inhibit the cell wall synthesis and cell membrane synthesis, thus affect its permeability. In this research, however, antimicrobials are classified on the basis of their chemical structure as well as their bioactivities.[3]

Due to the steady increase in the rate of bacterial drug-resistance and the lack of new effective antimicrobial drugs appearing from pharmaceutical development worldwide,[5] there is a need to identify new targets for antimicrobial action and strategies to overcome antimicrobial resistance.

1.2.2 Discovery of antibiotics

Since the discovery of antimicrobial agents, there has been a substantial reduction in the threat posed by infectious diseases. The history of antibiotic agents started in 1907, when Ehrlich successfully developed the first example of a purely synthetic antimicrobial drug, the "magic bullet", Salvarsan (**1.1**) (Figure 1.1), an arsenic containing drug.[6] Although it was not active against a wide range of bacterial infections, it did show activity against the protozoal disease sleeping sickness, and the spirochaete disease of syphilis. The drug was used until 1945 when penicillin came into the market. In 1928, Alexander Fleming discovered the effect of penicillin (**1.2**) as an antimicrobial agent from fungus *Penicillium notatum*, but it was not known that it could be used as a therapeutic agent. Penicillin was not used as a therapeutic agent until 1940s, when Florey and Chain managed to isolate penicillin under mild conditions and was used to treat bacterial infections during the Second World War.[7] While Fleming was working on penicillin in the 1930s, Gerhard Domagk, a German doctor, publicized the discovery of a synthetic sulfur-containing compound (Prontosil) with antibacterial properties. Prontosil (**1.3**) is a member of the sulfonamides or sulfa drugs and is the first of a long series of synthetic antibiotics.[8] Prontosil was used to combat urinary tract infections, pneumonia and other conditions. Sulfa drugs are now used as effective antibiotics for the treatment of a wide range of infectious conditions.

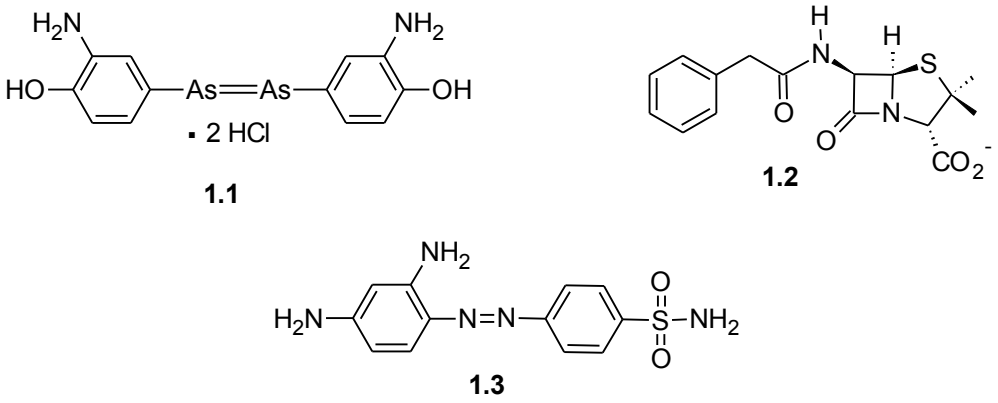


Figure 1.1: Structure of salvarsan, penicillin and prontosil.

The discovery of penicillin drew attention to nature as a source of biologically active agents. As a result, microorganisms were investigated as a source of useful pharmaceutical compounds. Many new antibiotics were then discovered, including sulfonamides, *β*-lactams, aminoglycosides, chloramphenicol, cephalosporins, tetracyclines, macrolides, lincosamides, streptogramins, glycopeptides, rifamycin, nitroimidazole, quinolone and trimethoprim (1968) (Table 1.1).[9] More than thirty years later, oxazolidinones, lipopeptides and glycylcylinones were introduced. The search for new and more effective antimicrobials has been successful since the discovery of penicillin and more than 350 antimicrobial drugs have reached the market.

Table 1.1: History of antibacterial drug introduction and approval.

Year Introduced	Class of Drugs
1935	Sulfonamides
1941	*β*-Lactams
1944	Aminoglycosides
1949	Chloramphenicol
1950	Tetracyclines
1952	Macrolides, Lincosamides, Streptogramins
1956	Glycopepdides
1957	Rifamycins
1959	Nitromidiazoles
1962	Quinolones
1968	Trimethoprim
2000	Oxazolidinones
2003	Lipopeptides

1.3 Resistance to antimicrobial agents

The battle of treating microbial infections has been increasingly complicated by the ability of microbes to develop resistance to the existing antimicrobial drugs. The development of resistance to antimicrobial drugs starts almost as soon as the drug is deployed. Antimicrobial agent resistance is the ability for microbes to grow in the presence of the drug that would normally kill or inhibit their growth. Ever since antimicrobial resistance emerged, there has been pressure to develop more antimicrobial drugs with a broad spectrum of activity, high level of efficacy, and that are environmentally friendly.[10]

The emergence of antimicrobial drug resistance is as a result of both natural causes and societal pressure. Resistance due to natural causes arises from random genetic mutation that microbes can undergo. The societal pressure is associated with both overuse and misuse of antimicrobial drugs in both human medicine and agriculture. This can be due to the lack of instruction, carelessness or ignorance of humans. Due to these factors, the number of infections by the bacteria that are resistant to at least one of the drugs that are commonly used for treatment has gone up to about 70%. It is also documented that some of these microbes are resistant to all recommended antimicrobial drugs and can only be treated with potentially toxic drugs.[11]

1.3.1 Mechanisms of antibacterial agent resistance

Bacteria may develop resistance to antibacterial agents through a variety of mechanisms. Antibiotic resistance occurs when a microorganism's cellular physiology and the structure of the microorganism changes due to alterations in its usual genetic makeup leading to the protection of the bacteria from the action of an antibiotic drug, and the mechanism is called microbial resistance.[12,13] There are four main ways in which microorganisms may acquire the ability to resist the effect of antimicrobial agents (Figure 1.2):

- Extrusion of the antibiotic agent (active efflux) before it can damage the microorganism.
- Alteration in the drug target for antibiotic action: mutations in the target, production of alternative targets or protection of the target, thus leading to the ineffectiveness of the drug.

- Inactivation of the antibiotic drug. This is where the microorganism produces drug-inactivating enzymes that chemically modify the drug and make it ineffective.
- Changed access: alteration in the bacterial outer membrane, making it hard for a drug to bind to the exterior of the microorganism.

Microbes have increased their resistant ability to antimicrobials to an extent that they may acquire more than one resistant mechanism for one class of antibiotics (Table 1.2). For example, sulfonamides and trimethoprim may either bypass their metabolic inhibition-reaction or be made insufficient for their target sites due to the overproduction of antibiotic target sites by microbes.

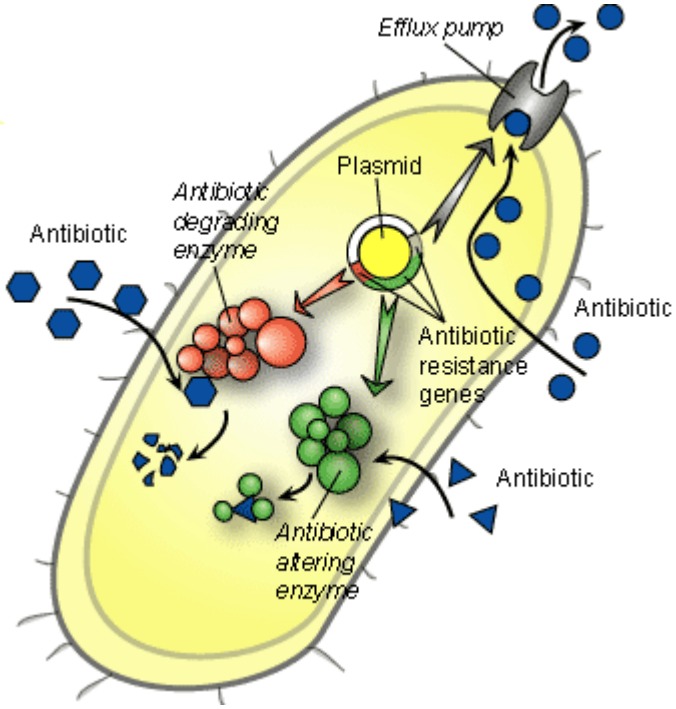


Figure 1.2: Mechanisms of antibiotic resistance in bacteria.[14]

Generally bacteria are frequently referred to as being resistant to antibiotics, but the biochemical meaning of resistance is rarely considered. Even the bacteria that are referred to be the most resistant can be killed by sufficiently high concentration of antibiotics. However, high doses of antibiotics cannot always be used because it may exceed the level that the human body can tolerate. For example, most strains of *Streptococcus pneumonia* are inhibited by a minimum concentration of 0.01 mg/L of benzylpenicillin which the body can manage, whereas for *Escherichia coli* a minimum of 60 mg/L is required, which

exceeds the level the human body can tolerate. This resistance is called 'clinical resistance'.[15]

Microorganisms may develop resistance to a certain antimicrobial drug as soon as it is applied. This can be due to the above-mentioned mechanisms resulting from genetic mutations, the acquisition of resistance genes from the other microorganisms *via* gene transfer or the combination of both phenomena. Antimicrobial resistance in bacteria may be an inherent trait of an organism that renders it naturally resistant or be acquired by means of mutation in its own DNA or acquisition of resistance-conferring DNA from another source.[12]

Table 1.2: Some modes of resistance to some antibiotics.[14]

Antibiotic	**Mode of resistance**
Chloramphenicol	Reduced uptake into cell
Tetracycline	Active efflux from the cell
β-Lactams, Erythromycin, Lincomycin	Eliminates or reduces binding of antibiotic to cell target
β-lactams, Aminoglycosides, Chloramphenicol	Enzymatic cleavage or modification to inactivate antibiotic molecule
Sulfonamides, Trimethoprim	Metabolic bypass of inhibited reaction
Sulfonamides, Trimethoprim	Overproduction of antibiotic target (titration)

Resistance of some bacteria to antibiotics may be inherent. For example, bacteria may lack the target site for the antibacterial molecule or a transportation system for antibacterial drug for an active efflux mechanism which is inherited for generations. Gram-negative bacteria have cell wall that is covered with an outer membrane that establishes a permeability barrier against some antimicrobial drugs.[16]

Mutational resistance is a spontaneous event that occurs regardless of whether an antimicrobial is present or not. Mutational resistance in bacteria occurs when a strain changes its DNA bases, which leads to the change in RNA and in turn to the change in the proteins produced. Chromosomal mutations can lead to a change in cell proteins that is responsible for the structure of the site of action of the antimicrobial.[12] A bacterium

acquiring such a mutation is at a huge advantage as it withstands the antimicrobials while the susceptible cells are being killed.

The strive to develop new antibiotics has never stops due to the ability of microbes to develop resistance to existing antibiotics.[17]

1.4 Fluorine in pharmaceuticals

Halogen-containing compounds are limited in nature, especially fluorinated natural products. However, the introduction of fluorine into a biologically active compound imparts a variety of properties such as enhanced binding interaction, metabolic stability, reaction selectivity and changes in physical and chemical properties. No fluorine-containing drug had been developed before 1957. Since then, over 150 fluorine-containing drugs have come onto the market, accounting for about 20% of all pharmaceuticals.[18] The increasing prevalence and success of fluorine-containing pharmaceuticals has stimulated further interest into the synthesis of such compounds. There is a limited number of fluorination methods available. This is because of the dangers of using fluorine gas usually associated with these chemical reactions.[19]

It has been reported that fluorinated pharmaceuticals are among the top-selling drugs on the market and these include Prozac® (anti-depressant drug), Lipitor® (cholesterol-lowering drug), Ciprobay® (antibacterial drug) and Xeloda® (anti-cancer agent) as shown in figure 1.3.[19] It was further reported that the introduction of fluorine or fluoroalkyl groups into these compounds had improved their binding affinity and the inhibitory ability. Kirk *et al*.[20] and Hagmann[21] reviewed the different ways of incorporating fluorine and/or fluoroalkyl groups into organic molecules.

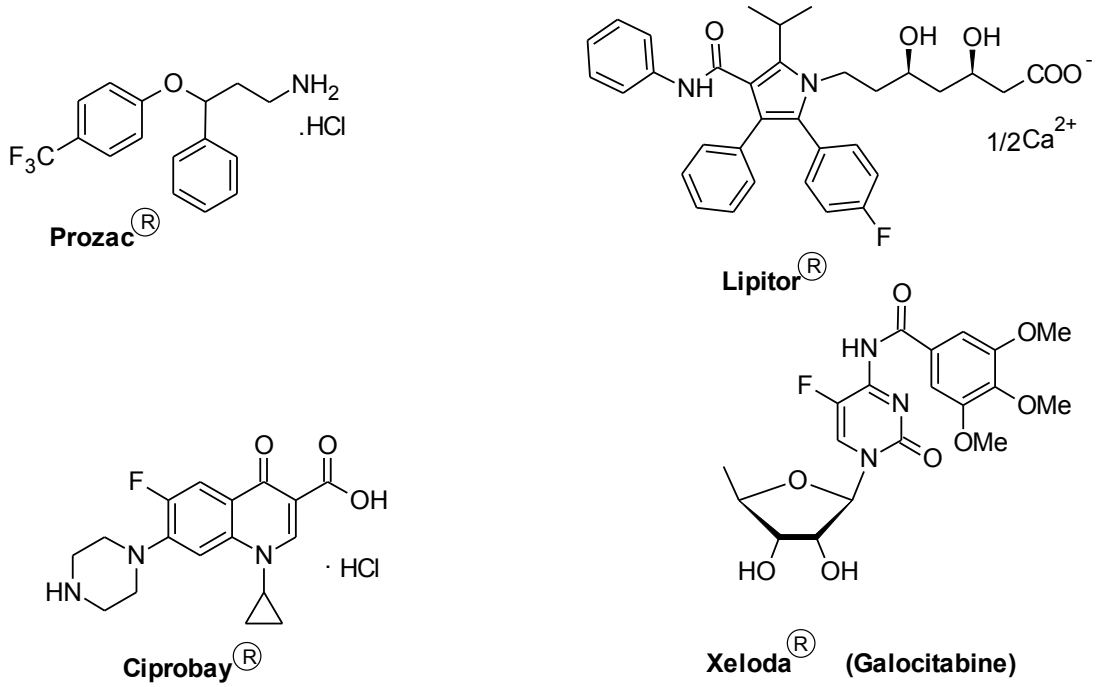


Figure 1.3: Some examples of top-selling fluorinated pharmaceuticals.

Due to the shortage of drugs on the market, it is crucial that new biologically active compounds including fluorinated ones are developed. An overview of fluorine in organic compounds will be given in Chapter 2.

1.5 Prenylated/geranylated benzophenones

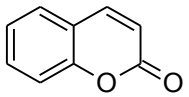
Prenylated benzophenones and geranylated benzophenones are natural products with interesting biological activities. Those activities include anticancer, anti-HIV, cholesterol regulatory, cytotoxic, anti-inflammatory and antimicrobial activity. The benzophenone class (Figure 1.4) is one of the big classes of organic compounds and often serve as precursors for synthesis. In this context, the focus will be on the prenylated and geranylated benzophenones which are naturally occurring and have been reported from various plant species.[22, 23]

Figure 1.4: General structure of benzophenone.

Among prenylated benzophenones, the position or/and the number of the prenyl groups may affect the biological activity of the compounds. Some details about prenylated benzophenones will be covered in Chapter 3.

1.6 Coumarins

Coumarins constitute an important class of naturally occurring compounds. The first coumarin was isolated from the tonka bean (*Dipteryx odorata*) by Vogel and Guibourt in 1820. To date, more than 1300 coumarins have been identified from natural sources.[22,24] Many more have been synthesized *via* numerous methods including the Pechmann condensation,[25] Perkin reaction,[26] Knoevenagel condensation,[27] Reformatsky reaction,[28] Wittig reaction[29] and Baylis-Hillman reaction.[30] In addition, coumarins have been reported to possess antibacterial,[31] anti-inflammatory,[32] anti-oxidant,[33] anticoagulant[34], anti-tumor[35], hepatoprotective, anti-carcinogenic, anti-viral and anti-thrombotic activities.[36]



Coumarin

Figure 1.5: General structure of coumarin.

Coumarins are characterized by a benzene ring fused with a pyrone ring as shown in figure 1.5 and are structurally diverse and can be roughly classified into five major groups depending on the position of the substituent/s (explained in Chapter 4). The type and position of the substituent/s in the coumarin structure have huge impact on the biological activities, physical and chemical properties.

1.7 Aims of the project

Our research group specializes in Natural Product Chemistry. In one of the projects on phytochemistry of South African *Hypericum* species, bioactive prenylated benzophenones and pyrones have been isolated.[37] Incorporating fluorine into these structures might change the activities of the compounds.

In this research, the aim was to develop methods to prepare fluorine-containing prenylated benzophenones and 4-phenylcoumarins (Figure 1.6). Although some prenylated and

geranylated benzophenones have been synthesized in the laboratory, none of them contain fluorine.

The main objectives of this investigation were:

- To develop methods for the synthesis of fluorine-containing analogues of prenylated and geranylated benzophenones.
- To improve the methods for synthesizing fluorinated 4-phenylcoumarins.
- To establish the biological activity of the synthesized compounds.

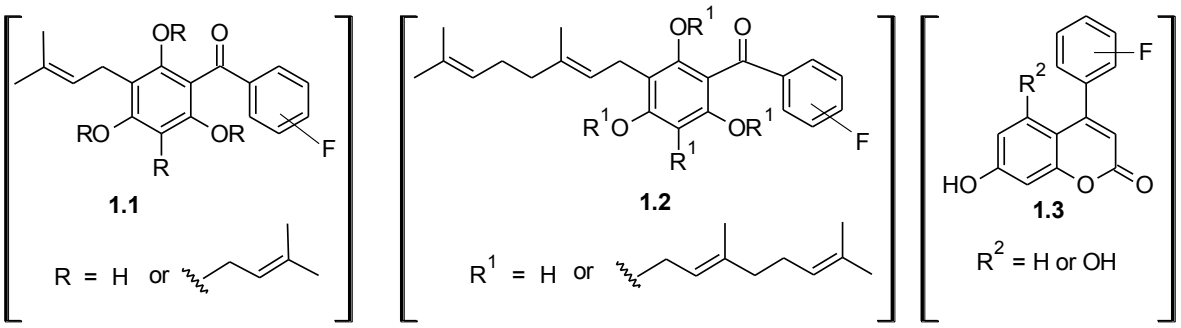


Figure 1.6: Compounds proposed to be synthesized.

1.8 Structure of this Thesis

This thesis consists of five chapters including this chapter, Chapter 1 (introductory chapter). Chapter 2 explores the nature of fluorine and its effect on organic molecules. Chapter 3 examines the synthesis of fluorinated prenylated benzophenones. It also reviews bioactive prenylated benzophenones and their synthesis. Chapter 4 covers the synthesis of 4-phenylcoumarins. This chapter also reviews the biological activities of 4-phenylcoumarins as well as the synthetic methods that have been used to synthesize 4-arylcoumarins. Chapter 5 is a short conclusion chapter.

CHAPTER 2. AN OVERVIEW OF FLUORINE IN ORGANIC COMPOUNDS

2.1 Background on fluorine and fluorinated compounds

Many of the current pharmaceuticals on the international market are fluorinated compounds. Fluorine is the 13th most abundant element in earth's crust. South Africa is the third largest producer of fluorspar (CaF_2, the mineral that is the main source of fluorine) in the world. Elemental fluorine was first isolated by Moissan in 1886 and is an extremely dangerous yellow-green gas.[20] Fluorine is the most electronegative element in the periodic table leading to high polarization of the C–F covalent bond which results in the shortening of the bond length and an increase in the bond strength, as shown in Table 2.1. Replacing hydrogen with fluorine in organic molecules has a small steric effect since their van der Waals radii are not too different (Table 2.1).[38] In a C-F bond, the fluorine atom has three lone pairs, which are electrostatically held tightly to the nucleus and, therefore, are non-reactive.

Table 2.1: Properties of some selected elements and when bonded to carbon.[39, 40]

	H	F	O	N	C	Cl	Br
Van der Waals radius (Å)	1.20	1.47	1.52	1.55	1.70	1.75	1.85
Pauling electronegativity	2.1	4.0	3.5	3.0	2.5	3.2	2.8
Length of single bond to carbon (Å)	1.09	1.40	1.43	1.47	1.52	1.77	1.97
Strength of bond to carbon (kcal.mol^{-1})	98	105	84	70	83	77	66

The electron pull by fluorine in a C-F bond of an organic compound has a large electronic effect on the neighbouring atoms. For example, the electron-withdrawing ability of fluorine increases the acidity of organic acids as shown by the pK_a values in Table 2.2. The substitution of the first hydrogen with fluorine changes the pK_a value by 2.2, for the

second and the third substitution the change in the pK_a values is 1.4 and 1.0, respectively. The pK_a values for the chlorinated analogues indicate that the pulling effect of chlorine is less pronounced than that of fluorine.[41]

Table 2.2: Acidity of acetic acid and its fluorinated and chlorinated analogues.[41]

Acid	pKa at 25 °C
CH_3COOH	4.8
CH_2FCOOH	2.6
$CH_2ClCOOH$	2.9
CHF_2COOH	1.2
$CHCl_2COOH$	1.3
CF_3COOH	0.2
CCl_3COOH	0.6

The incorporation of a fluorine atom into a molecule enhances the acidity of the hydrogens bonded to the same carbon as fluorine. The nature of the highly polarized C-F bond results in the presence of a low-energy σ* antibonding orbital located behind the carbon atom in the plane of C-F bond. This vacant σ* antibonding orbital can accept the electron density from the neighboring σ-bonds, π-bonds or lone pairs (hyperconjugation effect). This effect increases the acidity of the protons on the adjacent carbons.[39, 42]

2.2 Naturally occurring fluoroorganic compounds

More than 4000 halogenated natural products have been isolated but less than 1% of these are fluorinated natural products. The rarity of the naturally occurring fluoroorganic compounds is in contrast to the high abundance of fluorine in the earth's crust.[43] The main reason for this phenomenon is that fluorine exists predominantly in insoluble forms such as calcium fluorspar (CaF_2), cryolite (Na_3AlF_6) and fluorapatite [$Ca_5(PO_4)_3F$], which hinder the uptake of this element by bioorganisms.[20] Fluorine has a very high redox potential and its ionic form is highly hydrated, making it a very poor nucleophile and therefore inhibits C–F bond formation in nature.[44]

To the best of my knowledge, only 30 naturally occurring fluoroorganic compounds have been identified. Fluoroacetic acid (**2.1**) was the first naturally occurring fluoroorganic compound to be isolated (Figure 2.1). It was first extracted in 1943 by Marais from the South African "gifblaar shrub" (*Dichapetalum cymosum*),[45] a plant that is known to be highly toxic to cattle and sheep in South Africa.[46] Fluoroacetic acid can be a good mimic of acetic acid which has a crucial role in the Krebs cycle (cellular metabolism). Fluoroacetate combines with coenzyme A (CoA) to form fluoroacetyl-CoA which reacts with citrate synthase to form fluorocitrate. Fluorocitrate binds irreversibly to aconitase, thus halting the Krebs cycle which results in the accumulation of citrate in the blood, thereby depriving the cells of energy.[47]

The antibiotic nucleocidin (**2.2**) was first isolated in 1957 from the bacterial culture *Streptomyces calvus*.[48] The structure of **2.2** was elucidated in 1968 and was confirmed by total synthesis.[49] Fluorothreonine (**2.3**) is an amino acid derivative that was isolated from *Streptomyces cattleya* in 1986. This bacterium also produces fluoroacetate and the antibiotic thienamycin.[50] 5-Fluorouracil analogue **2.4** was extracted from a marine sponge *Phakellia fusca* by a Chinese research group in 2003 and it was found to be active against cancer cells. 10-Fluorodecanoic acid (**2.5**), 18-fluorooleic acid (**2.6**) and several other fluorinated fatty acids were extracted from the seeds of the Sierra Leone shrub *Dichapetalum toxicarium*.[51, 52]

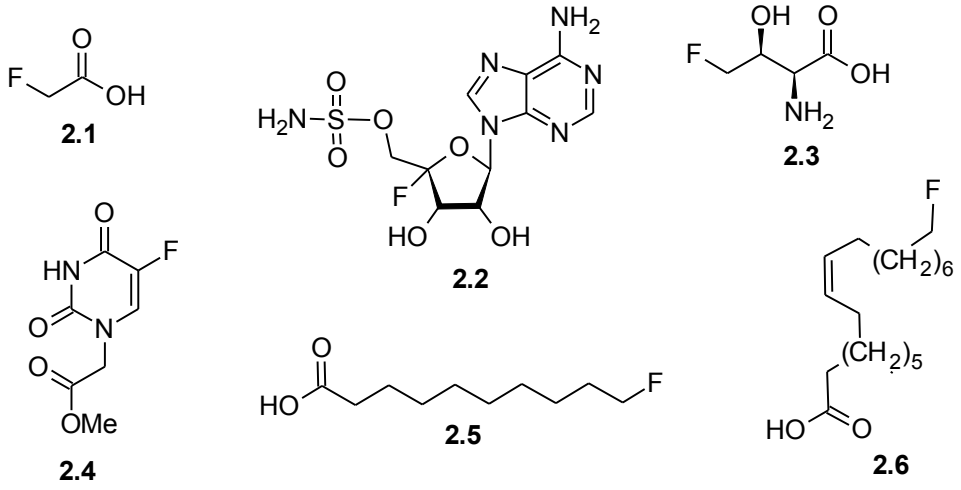
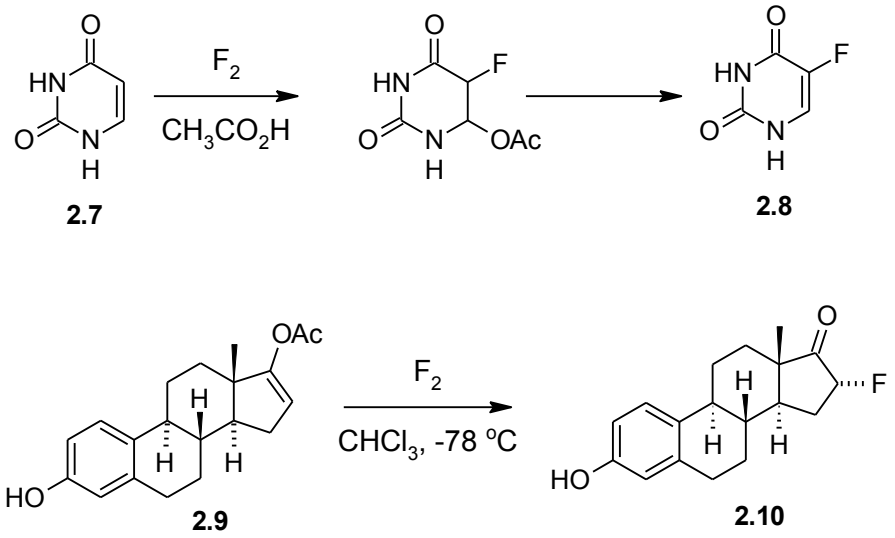


Figure 2.1: Some examples of naturally occurring fluoroorganic compounds.

2.3 Fluorination of organic compounds

Synthetic methods in fluoroorganic chemistry have made massive progress since Borodin reported the first synthesis of a fluoroorganic compound in 1863[53] and Swarts published the fluorination of polychloroalkenes in 1892 using mercury fluoride, zinc fluoride or antimony trifluoride.[54] The scope of fluorination reactions with elemental fluorine started to expand in 1960s when elemental fluorine was diluted with inert gases such as argon or nitrogen and the process was commercialized.[55] Fluorination of uracil (**2.7**) using elemental fluorine in an inert gas to form 5-fluorouracil (**2.8**) is one of the earliest examples of the use of F_2:N_2 gas mixture (Scheme 2.1). Another typical example is fluorination of the enol acetate steroid **2.9** to form **2.10**.

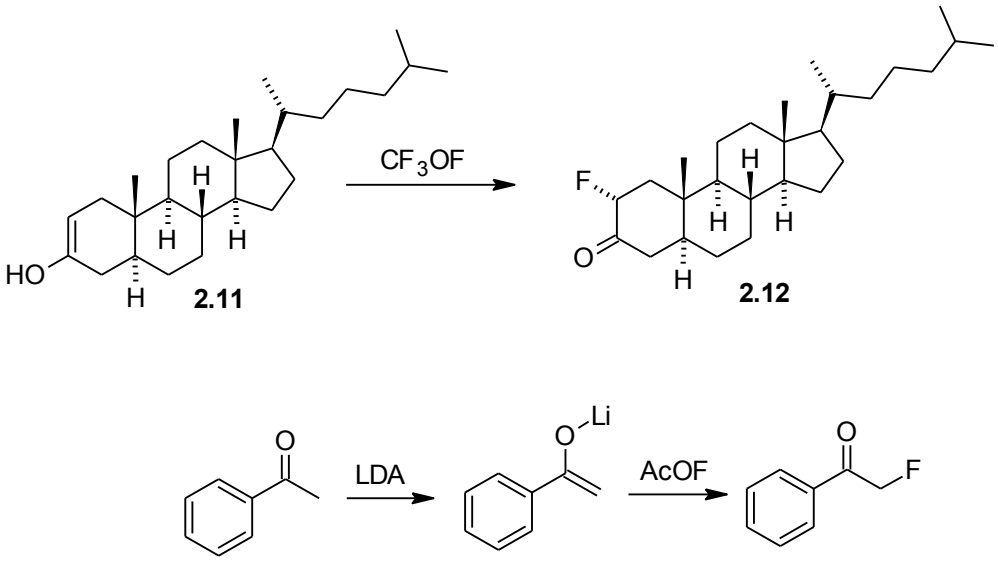


Scheme 2.1: Synthesis of 5-fluorouracil (**2.8**)[56] and *α*-fluoroketone steroid (**2.10**).[57]

2.3.1 Electrophilic fluorination of organic compounds

The success of fluorination with elemental fluorine resulted in the development of electrophilic fluorination, in which a nucleophile attacks electrophilic fluorine of the fluorinating agent.[55] Fluoroxytrifluoromethane is one of the early reagents and was developed by Barton in 1968 in his research on fluorination of biologically active compounds such as steroids,[58] as illustrated in Scheme 2.2 (CF_3OF was used to fluorinate **2.11** to form α-fluorocholestane **2.12**). Acetyl hypofluorite (CH_3COOF) was developed by Rozen in 1981[59] and has been used in many fluorination reactions such as the fluorination of lithium enolates[60] (Scheme 2.2) and aromatic fluorination. The success of this reagent in

electrophilic fluorination resulted in the introduction of other electrophilic fluorinating agents such as xenon difluoride, perchloryl fluoride and many more, but most of these are strong oxidizing agents which may result in a lack of selectivity.[55]



Scheme 2.2: Examples of *O*-F electrophilic fluorination reactions.

Subsequently, electrophilic fluorinating reagents that are relatively stable and convenient to handle have been developed and are now commercially available (Figure 2.2). Those reagents containing a *N*-F moiety such as *N*-fluoropyridinium triflate (**2.13**) were developed by Umemoto,[61,62] *N*-fluorobenzenesulfonimide (NFSI) (**2.14**) were developed by Differding,[63] Selectfluor® or F-TEDA-BF_4 (**2.15**) were synthesized by Banks and co-workers,[64] and many more. There have been extensive developments on these fluorinating agents such as an increase in their fluorinating ability, selectivity and stability. That is achieved by varying the substituents of the structure, e.g. the fluorinating ability of **2.13** increases with a decrease in electron density at the N^+-F site, which is accomplished by replacing the aromatic protons with electron-withdrawing groups.

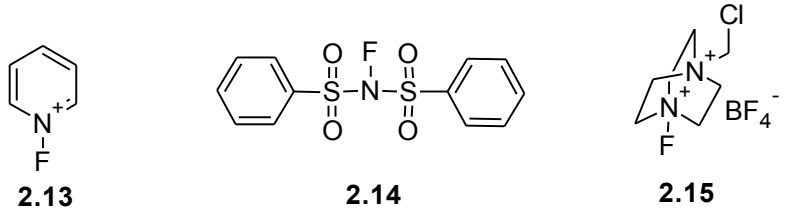
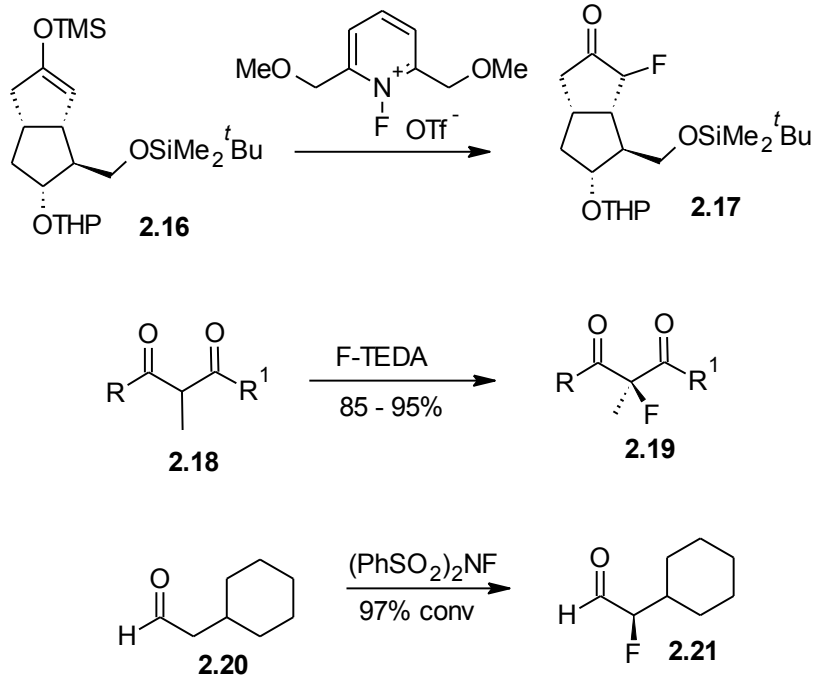


Figure 2.2: Examples of *N*-F electrophilic fluorinating agents.

These fluorinating reagents have become very popular with various applications, including fluorination of aromatic rings, carbon-metal bonds, steroids, carbanions, nucleosides, enol esters and other related substrates. For example, fluorination of the enol Corey lactone prostaglandin intermediate **2.16** with an activated analogue of **2.13** yielded **2.17** (Scheme 2.3).[20] Methodologies for introduction of fluorine have improved to a stage where enantioselective fluorination is possible. These fluorinating reagents have been modified to react under mild conditions to minimize loss of chirality. The first enantioselective reaction of Selectfluor® was reported by Togni, the reaction of *β*-keto ester **2.18** in the presence of **2.15** and transition metal catalyst to yield **2.19**.[65, 66] NFSI (**2.14**) has recently been reported to efficiently and selectively fluorinate the aldehyde **2.20** to form α-fluoroaldehyde **2.21**.[67]



Scheme 2.3: Examples of *N*-F electrophilic fluorination reactions.

2.3.2 Nucleophilic fluorination of organic compounds

Fluorination of organic compounds does not rely only on electrophilic fluorination but can also be done by nucleophilic fluorination. Fluoride is regarded as a poor nucleophile since it strongly solvates in protic solvents and forms tight ion pairs in most aprotic solvents. Hydrogen fluoride (HF) is one of the nucleophilic fluorinating agents that have been widely used in organofluorination. However, HF is corrosive and highly reactive, and thus hard to handle and has poor selectivity. These problems were overcome by the introduction

of amines, e.g. pyridiniumpoly(hydrogen fluoride) (PPHF), which generally reduces the nucleophilicity. An example of the application of PPHF is the opening of an epoxide ring (Scheme 2.4) to form a fluorinated analogue of shikimic acid (**2.22**).[68]

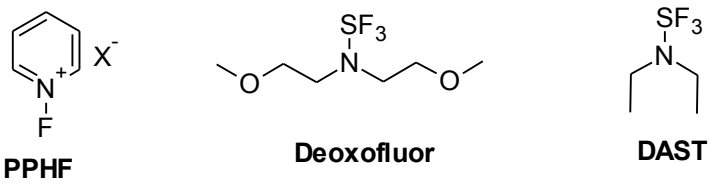
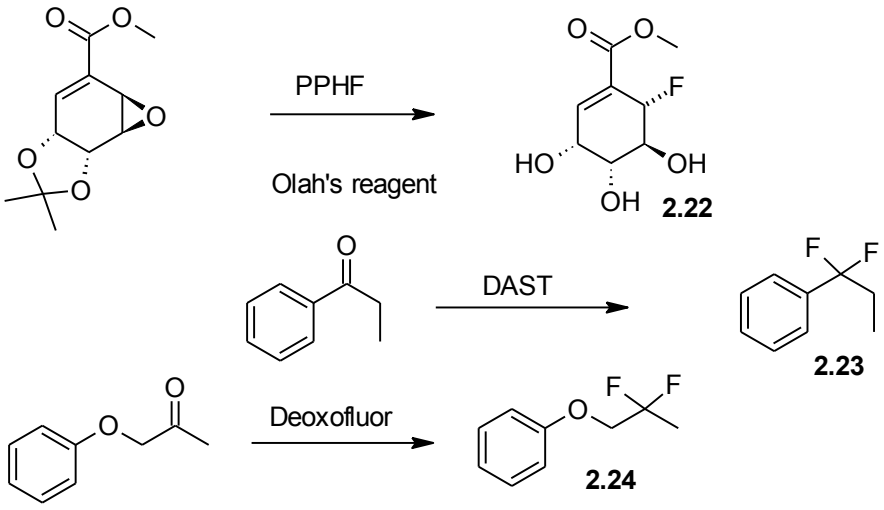


Figure 2.3: Examples of nucleophilic fluorinating agents.

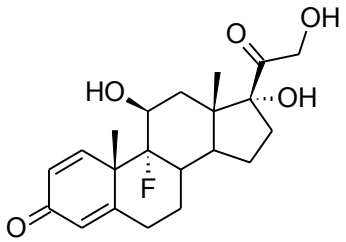
Until the 1970s, the fluorinating agents used were extremely reactive which limited the widespread use of organofluorination in ordinary laboratory equipment. In 1975 Middleton reported the first preparation of diethylaminosulfur trifluoride (DAST) which has been proven to be a valuable versatile fluorinating reagent.[69] This breakthrough led to the introduction of other fluorinating reagents that are selective, stable and compatible with laboratory equipment. Among those reagents was bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor®) which was reported by Lat in the late 1990s.[70,71] These reagents are commercially available and are reported to fluorinate organic compounds such as ketones, aldehydes and alcohols selectively.[19] DAST and Deoxofluor® react with ketones to form difluoroalkyl compounds (**2.23** and **2.24**) as illustrated in Scheme 2.4.[72] The development of these user-friendly fluorinating reagents (electrophilic and nucleophilic) resulted in an increase in the number organofluorinations reported.



Scheme 2.4: Examples of *N*-F electrophilic fluorination reactions.

2.4 Fluorine-containing drugs

Incorporation of fluorine into bioactive organocompounds has a profound impact on improving the biological activities. The journey of developing fluorine-containing drugs started in 1954 when Fried and Sabo reported the improvement of the therapeutic index of cortisol (an anti-inflammatory drug) by the incorporation of fluorine in the 9α position (Figure 2.4).[73] Since then, more than 150 fluorinated drugs have come onto the market and those compounds constitute 20% of all drugs on the market.[21] Of the top 30 best-selling pharmaceutical drugs (2008 US sales), 10 contain at least one fluorine atom.[74]



9α-Fluorocortisone

Figure 2.4: The first fluorinated pharmaceutical developed.

2.4.1 Best-selling fluorinated pharmaceutical products

Fluorine-containing drugs are among the best selling drugs in the pharmaceutical industry (Figure 2.5). Among all pharmaceutical products on the market worldwide, Lipitor® has the biggest sales. It holds the most prominent position in the blockbuster league with sales of more than 5.9 billion dollars in 2011.[74] Lipitor® (Atorvastatin) belongs to the 'statin' class of drugs and is prescribed to lower the amount of biosynthetic cholesterol. Advair Discus® (also called fluticasone propionate) is an anti-inflammatory steroidal drug used to treat various conditions (inflammation associated with psoriasis and dermatosis), depending on how it is administered.[75] It is at fourth position relative to all pharmaceuticals and the second relative to the fluorinated drugs with sales of 3.6 billion dollars per year. Prevacid® (lansoprazole) is currently at the fifth position relative to all pharmaceuticals and the third relative to the fluorinated drugs with 3.3 billion dollars per year. It is the most successful drug in the class of antacids.[76] Lexapro® (Escitaloppram, Cipralex) is the most important drug for treating anxiety and depression.[77] This drug is currently sitting at position 11 of all drugs and fourth relative to fluorinated drugs with 2.4

billion dollars sales. The fifth drug in the fluorinated drug's league is Crestor® (rosuvastatin) with 1.7 billion dollars sales per year and is in the 17th position relative to all pharmaceutical drugs.[78]

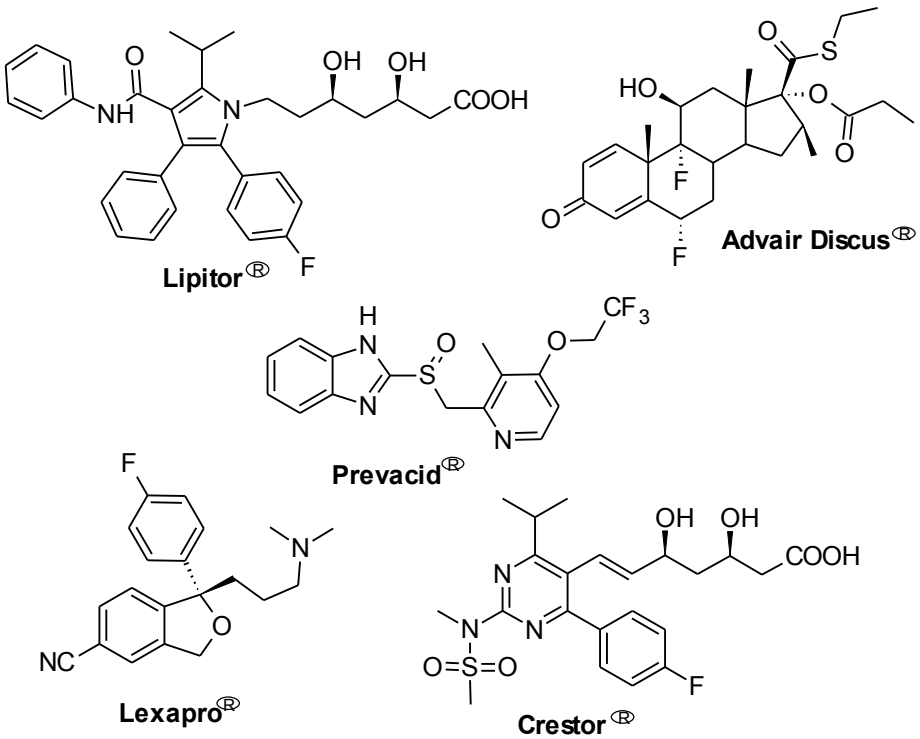


Figure 2.5: The top 5 of the best-selling fluorinated pharmaceutical in USA in 2011.

2.4.2 Some fluorinated drugs

2.4.2.1 Cholesterol regulators

There are numerous cholesterol-lowering drugs that have reached the market. Some of them are fluorine-containing compounds such as Lipitor® (**2.25**) and Lescol® (**2.26**) (Figure 2.6). Both Lipitor® and Lescol® belong to the drug class known as statins and they lower the level of cholesterol in the blood which prevents hypercholesterolemia and related diseases. These cholesterol lowering agents act through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme found in liver tissues that are responsible for the production of cholesterol in the body.[79, 80]

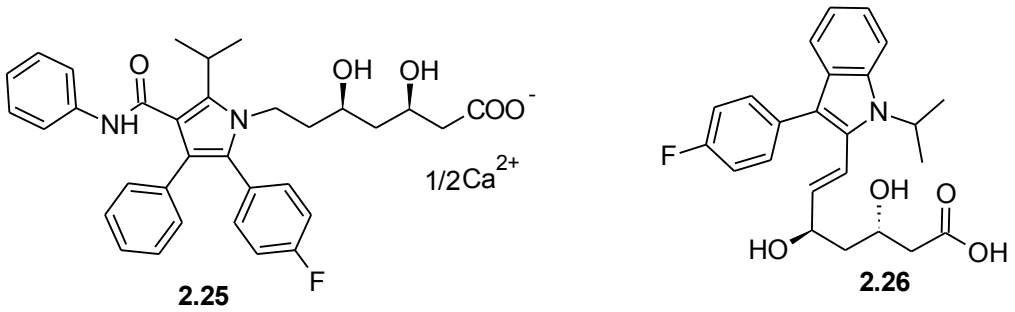


Figure 2.6: Chemical structure of Lipitor® (**2.25**) and Lescol® (**2.26**).

2.4.2.2 Anticancer agents

Cancer has always been a major public health problem in both developed and developing countries.[81] Galocitabine® (**2.27**) and Gemcitabine® (**2.28**) are among the top anticancer drugs that are in the market (Figure 2.7).[20] These drugs bind to the ribonucleotide reductase (RNR) and inactivate this RNR irreversibly.[82] This enzyme is responsible for the synthesis of deoxyribonucleotides which is required for DNA replication and repair.

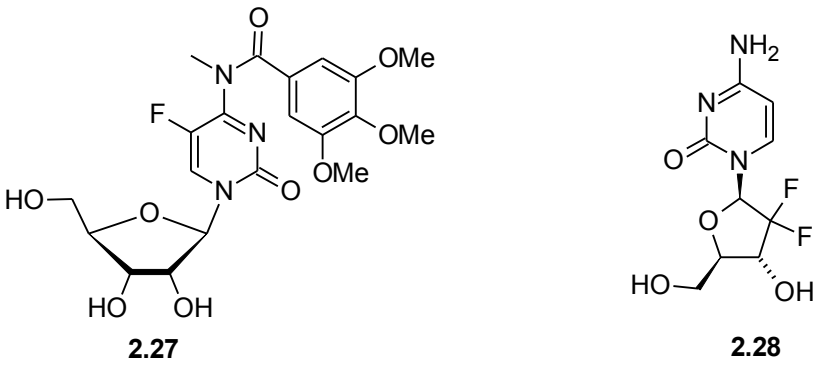


Figure 2.7: Chemical structure of Galocitabine® (**2.27**) and Gemcitabine® (**2.28**).

2.4.2.3 Antimicrobial agents (DNA inhibitors)

Quinolones are among the most important drugs in the anti-infective chemotherapy field. A variety of quinolone derivatives have been introduced into the market since 1962 and each derivative has its own biological activity,[83] which resulted in a significant improvement in antimicrobial activity and spectrum. The introduction of norfloxacin, fluoroquinolones resulted in a drastic change in the landscape of antibacterial chemotherapy.[84] Although fluoroquinolones are reported to have clinically important

activity against Gram-positive bacterial pathogens, their activity is relatively moderate. In addition, due to the extensive use of fluoroquinolones, some pathogens became resistant. Due to this resistance phenomenon, new quinolones to enhance the antibacterial activity of this class, including gatifloxacin (**2.29**), gemifloxacin (**2.30**), sitafloxacin (**2.31**), moxifloxacin (**2.32**) and BMS-284756 (T-3811) (**2.33**) were introduced (Figure 2.8).[85]

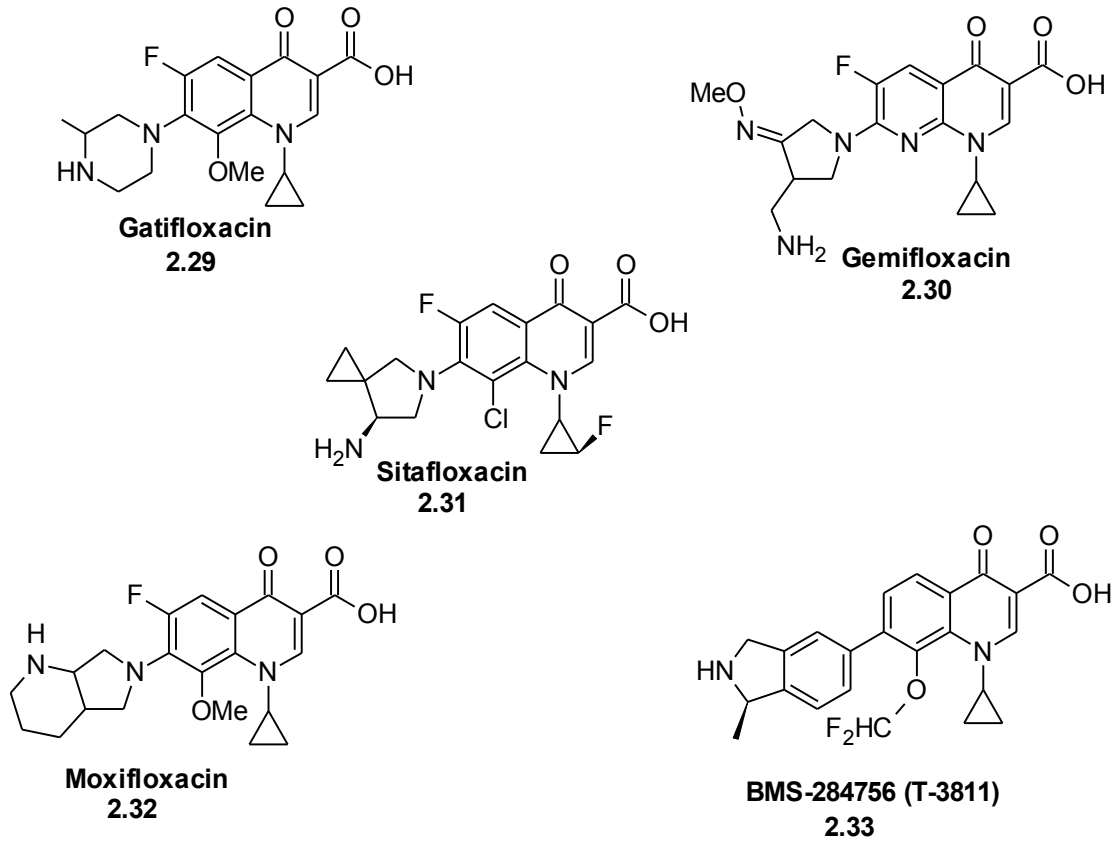


Figure 2.8: Examples of fluorinated quinolones with antimicrobial activities.

The target of quinolones in microbial cells are the bacterial topoisomerase IV and DNA gyrase, enzymes responsible for regulation of super coiling and decatenation of bacteria DNA.[86] Before the introduction of quinolones, there were other compounds used in chemotherapy such as nalidixic acid with similar activity but they had a limited activity and poor systemic distribution, and were used mainly for Gram-negative urinary tract infections. Fluoroquinolones (norfloxacin, ciprofloxacin and ofloxacin) were introduced as a next generation of quinolones with an enhanced activity against Gram-negative bacteria which actively act on DNA topoisomerase. Moxifloxacin and levofloxacin are new fluoroquinolones with highly improved activity against many Gram-positive and Gram-negative bacteria. Since levofloxacin and moxifloxacin are effective against chlamydia,

legionella and mycoplasma are therefore used for treatment of atypical pneumonia. Ciprofloxacin is widely used mainly for upper tract urinary infections and exacerbations of chronic bronchitis, both in hospital and ambulatory settings.

2.5 Summary

This review clearly shows that the incorporation of fluorine into bioactive organic compounds enhances bioactivity. This is due to the special nature of fluorine which imparts a variety of properties to certain medicines such as the enhancement of binding interactions, metabolic stability and selectivity, thus increase their bioactivities. It is also shown that the replacement of either a hydrogen atom or oxygen atom with fluorine atom is sterically favored since their atomic sizes are similar. Natural products have always been a good source for bioactive compounds. This study aims to synthesize a library of compounds consisting of fluorinated natural products therapy combining the potential for bioactivity of these classes of compounds.

CHAPTER 3. PRENYLATED BENZOPHENONES

3.1 Introduction

Benzophenones form a big class of organic compounds. The benzophenone structure is characterized by two benzene rings linked by a carbonyl carbon (Figure 3.1). Each ring may have different substituents and that gives the uniqueness to each compound. This study will narrow its focus to prenylated benzophenones.

Prenylated benzophenones are mostly naturally occurring compounds and have shown interesting biological activities. Although these compounds have been synthesized previously, fluorine-containing prenylated benzophenones have not been reported. This study aims to develop methods for the synthesis of fluorine-containing prenylated benzophenones. In the next two Sections the biological activities and synthesis of prenylated benzophenones are reviewed. The results obtained in our synthesis of fluorine-containing prenylated benzophenones are discussed in Section 3.4 and the last Section covers the experimental procedures for all the successful reactions.

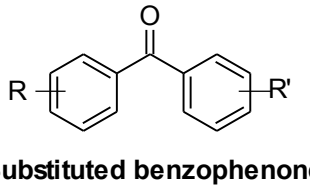


Figure 3.1: General structure of substituted benzophenone.

3.2 Bioactive prenylated/geranylated benzophenones

Prenylated benzophenones and geranylated benzophenones are a group of compounds that have various biological activities such as anticancer, anti-inflammation, anti-HIV, cholesterol regulatory, cytotoxic and antimicrobial activity.[37] Most prenylated and geranylated benzophenones that are reported in the literature were isolated from plants.

3.2.1 Anticancer activity

Cancer has always been a major public health problem in both developed and developing countries and it remains among the leading causes of death worldwide.[81] There are

anticancer agents that are on the market such as galocitabine®,[20] but the death rate caused by cancer has been increasing. In 2012 alone, more than 8 million deaths due to cancer were reported and the most common causes of cancers are liver, lung, colorectal, stomach and breast cancers.[87]

Natural products have been the most successful leads for the development of new chemotherapeutic agents.[88] Among the prenylated compounds that have the potential for treating cancer are garciniaphenone (**3.1**) and 7-epiclusianone (**3.2**), isolated from the fruits of *Rheedia brasiliensis* (Figure 3.2).[89]

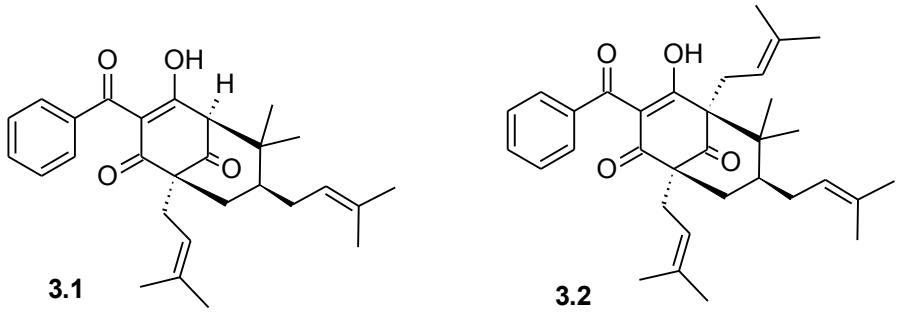


Figure 3.2: Chemical structure of garciniaphenone (**3.1**) and 7-epiclusianone (**3.2**).

These prenylated benzophenones showed antiproliferative activity on human cancer cells, including the drug-resistant breast (NCI-ADR), kidney (786-0), melanoma (UACC-62), lung/non-small cells (NCI460), ovarian (OVCAR 03), prostate (PC03), breast (MCF-7), lung (NCI-460) and tongue (CRL-1624 and CRL-1623) cancer cells. Both garciniaphenone (**3.1**) and 7-epiclusianone (**3.2**) have shown a multiple proliferation inhibitory effects *in vitro*.[89]

3.2.2 Anti-inflammatory activity

Steroidal and non-steroidal anti-inflammatory drugs are well known and commonly used drugs for reducing or eliminating pain and many of these drugs such as glucocorticoids alleviate inflammation by binding to glucocorticoid receptors.[90] Non-steroidal anti-inflammatory drugs (NSAIDs) reduce pain by preventing the synthesis of prostaglandins which create inflammation. NSAIDs counteract the cyclooxygenase (COX) enzyme stopping it from synthesizing prostaglandins. NSAIDs containing a carboxy group in their chemical structures such as salicylic acid and aspirin® are reported to inhibit both COX-1

and COX-2 non-selectively.[91] These drugs are also known to have analgesic and antipyretic (fever-reducing) activities.

Prenylated benzophenone derivatives have shown anti-inflammation activity.[92] Guttiferones O (**3.3**) and P (**3.4**) were isolated from *Garcinia solomonensis* and are inhibitors of mitogen-activated protein kinase-2 (MAPKAPK-2) (Figure 3.3). This enzyme (MAPKAPK-2) is a member of the MAPK family of protein kinases, which is phosphorylated and activated by p38 in retort to stress, cytokines and chemotactic factors. This activity is known to play an important role in regulating cellular activities such as gene expression, differentiation, mitosis and cell survival, which could be useful in the treatment of inflammatory diseases.[93]

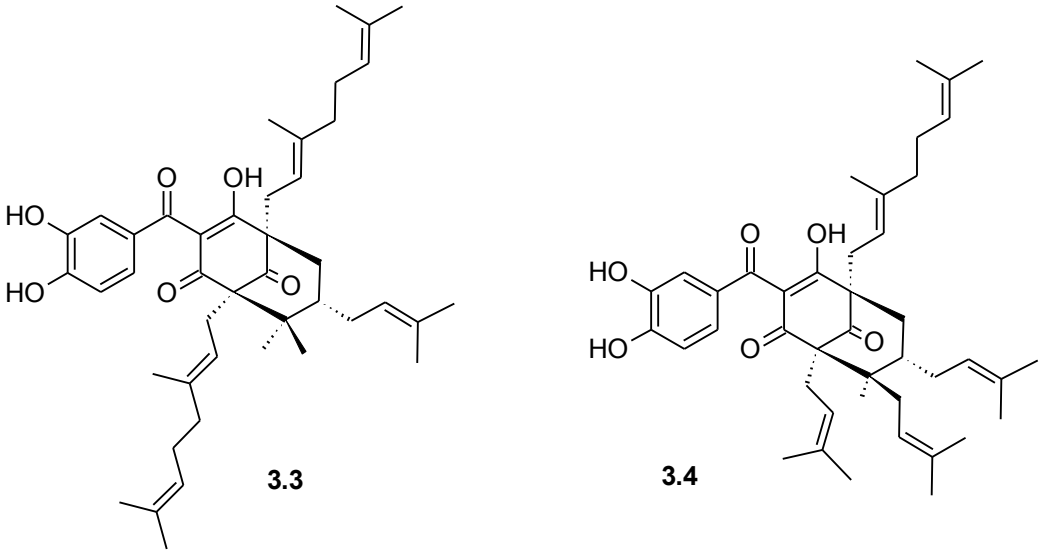
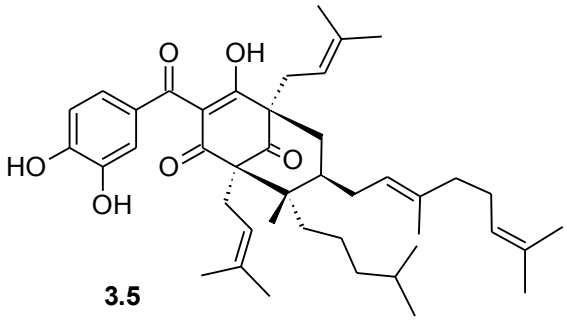


Figure 3.3: Chemical structure of guttiferones O (**3.3**) and P (**3.4**).[23]

3.2.3 Cholesterol regulator

The liver has X-receptors which are powerful tools in the human body to regulate cholesterol. Liver X receptors (LXR) are members of a superfamily of nuclear hormone receptors and are implicated in cholesterol homeostasis.[94,95] Oxysterols have been identified as endogenous ligands for these receptors.[96-98] Liver X receptors chelate with the retinoid X receptors (RXRs) to form heterodimers, to regulate the quantity of genes involved in cholesterol and fatty acid metabolism.[99]

There are cholesterol-lowering drugs that have reached the market. One of them is a fluorinated compound, Lipitor®. As a result of the demand of the cholesterol-lowering drugs on the market, a number of potential cholesterol-lowering prenylated compounds have been reported, such as guttiferone I (**3.5**). This polyprenylated benzophenone **3.5** was isolated from *Garcinia humilis* and has shown activity against LXR ligand binding sites (Figure 3.4).[100]



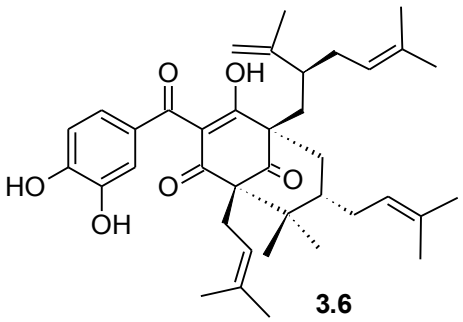
3.5

Figure 3.4: Chemical structure of guttiferone I.

3.2.4 Anti-HIV activity

It has been 30 years since the establishment of the human immunodeficiency virus (HIV) as the causative agent of the acquired immunodeficiency syndrome (AIDS).[101, 102] Millions of deaths caused by AIDS are reported annually which pose an ongoing threat to humans. Despite the impressive research on AIDS worldwide, the fight is not yet over because no drug has thus far been discovered which can cure the AIDS disease completely. However, there are drugs that inhibit human immunodeficiency virus (anti-HIV drugs) on the market. 3'-Azido-3'-deoxythymidine (AZT)[103] was the first anti-HIV drug approved by the Food and Drug Administration (FDA) and is still the most useful therapeutic agent.[104,105] There are other important anti-HIV drugs that are used especially in cases of AZT-resistance such as zalcitabine, didanosine and stavudine.[106,107,108]

Natural products that have shown anti-HIV activity include the prenylated benzophenones, guttiferones A-E which were isolated from three different genera, *Garcinia*, *Symphonia* and *Clusia*.[109] Polyprenylated benzophenones, guttiferone F (**3.6**) isolated from *Allanblackia stuhlmannii*[110] and vismiaphenone D (**3.7**) extracted from *Vismia cayennensis*,[111] were reported to exhibit anti-HIV activity (Figure 3.5).



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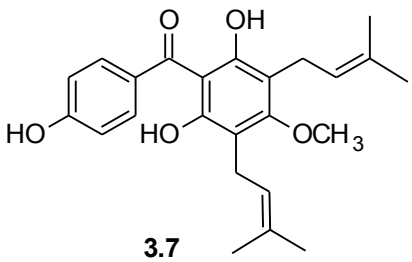


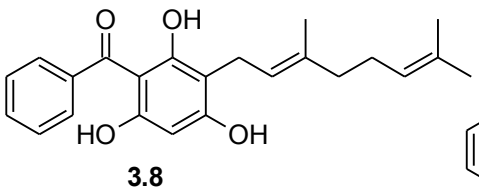
3.7

Figure 3.5: Chemical structure of guttiferone F (**3.6**) and vismiaphenone D (**3.7**).

3.2.5 Antimicrobial and cytotoxic activity

Microbial organisms pose a huge threat to human beings, and have led to the deaths of millions of people. As a result, a number of antimicrobial drugs have been discovered, for example imipenem and penicillin. Both imipenem and penicillin belong to the *β*-lactam class of antimicrobial agents, which are widely used because of their high effectiveness, minimal side effects, low cost and easy delivery.

Ever since antimicrobial agents were discovered, there has been an ongoing effort to develop more drugs with a broad spectrum antimicrobial activity, high level of efficacy, and that are environmentally friendly. In addition, micro-organisms develop resistance since they mutate rapidly and so the antimicrobials that are currently in use often have to be replaced. Prenylated benzophenones such as 3-geranyl-2,4,6-trihydroxybenzophenone (**3.8**) and 4-geranyloxy-2,6-dihydroxybenzophenone (**3.9**) have potential for the treatment of microbial infections (Figure 3.6). Compound **3.9** was isolated from the ethanol extract of *Tovomita longifolia*[112] and has shown antimicrobial and cytotoxic activity.[113] Compound **3.8** was isolated from the chloroform extract of the same plant, but was also extracted from other plant species such as *Hypericum roeperianum*[37] and *Garcinia vieillardii.*[114,115]



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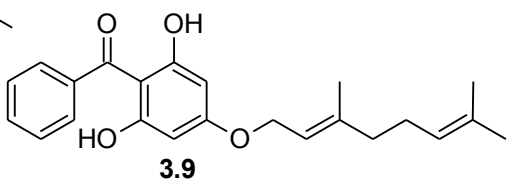


3.9

Figure 3.6: Chemical structure of 3-geranyl-2,4,6-trihydroxybenzophenone (**3.8**) and 4-geranyloxy-2,6-dihydroxybenzophenone (**3.9**).

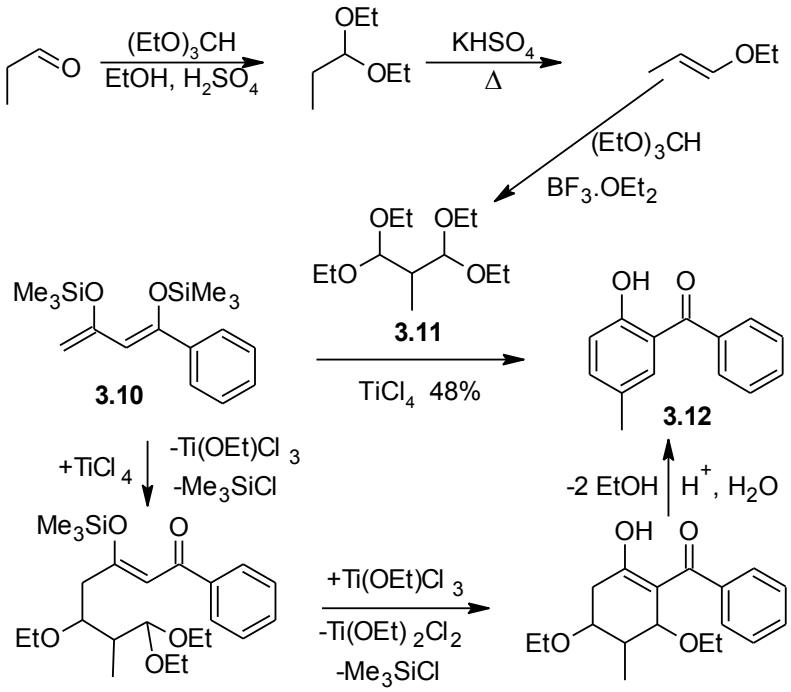
From the short review above it is clear that many prenylated/geranylated benzophenones exhibit biological activities.

3.3 A brief review of the synthesis of prenylated/geranylated benzophenones

Most of the prenylated benzophenones reported in the literature have been isolated from plants and limited synthetic routes towards the synthesis of these compounds have been reported in the literature. Amongst the few synthetic routes found in the literature, the key reactions include acylation, *C*-prenylation and *O*-prenylation reactions. The most popular acylation is the Friedel-Crafts acylation reaction. In this project, the Friedel-Crafts reaction was applied to synthesize benzophenones. However, there are other reactions routes to prepare benzophenones reported in the literature. These reactions have been conducted under different conditions including different catalysts and solvents and some examples of these reactions are shown in detail below. In the subsequent Sections Friedel-Crafts acylation reactions, *C*- and *O*-prenylation reactions and the synthesis of prenylated acylphloroglucinols are reviewed.

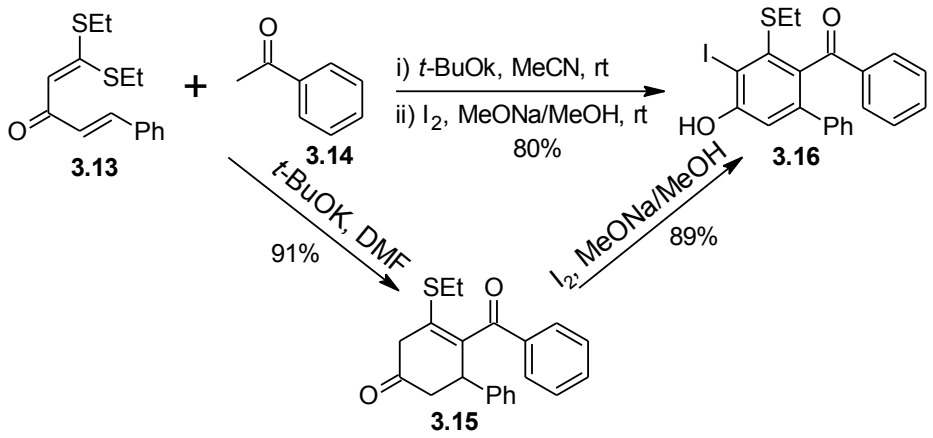
3.3.1 General methods to synthesize benzophenones

Benzophenones are important intermediates for the preparation of fine chemicals such as agrochemicals, pharmaceuticals and fragrances. This Section will show different synthetic routes (that do not involve Friedel-Crafts acylation) to synthesize benzophenones. One of these synthetic routes is the formal [3+3] cyclization of 1,3-bis(silyl enol ether) **3.10** with 2-methyl-1,1,3,3-tetraethoxypropane (**3.11**) to form 5-methyl-2-hydroxy benzophenone (**3.12**) as reported by Langer *et al*.[116] They firstly synthesized **3.11** by a three-step reaction from propanal as shown in Scheme 3.1. The $TiCl_4$-mediated condensation of bis(acetal) **3.11** with **3.10** (readily prepared from benzoylacetone) afforded **3.12**.



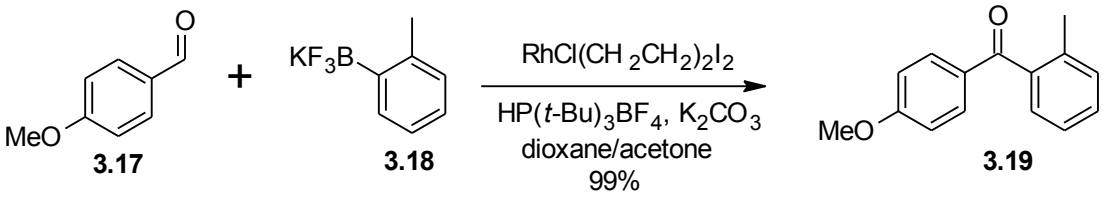
Scheme 3.1: Synthesis of 2-hydroxy-5-methylbenzophenone (**3.12**).[116]

Wang *et al*.[117] reported the synthesis of multi-substituted benzophenones by a regiospecific [5C+1C] annulation reaction of α-alkenoyl ketene *S,S*-acetal **3.13** with acetophenone (**3.14**) (Scheme 3.2). They developed two routes to synthesize **3.16**, one is a direct synthesis of benzophenone and the other one is *via* the formation of cyclohexenone **3.15**. This reaction starts with the Michael addition of the enol anion of acetophenone, followed by the intramolecular Michael addition to form **3.15**. Cyclohexenone **3.15** was treated with iodine and sodium methoxide in methanol to form **3.16**.



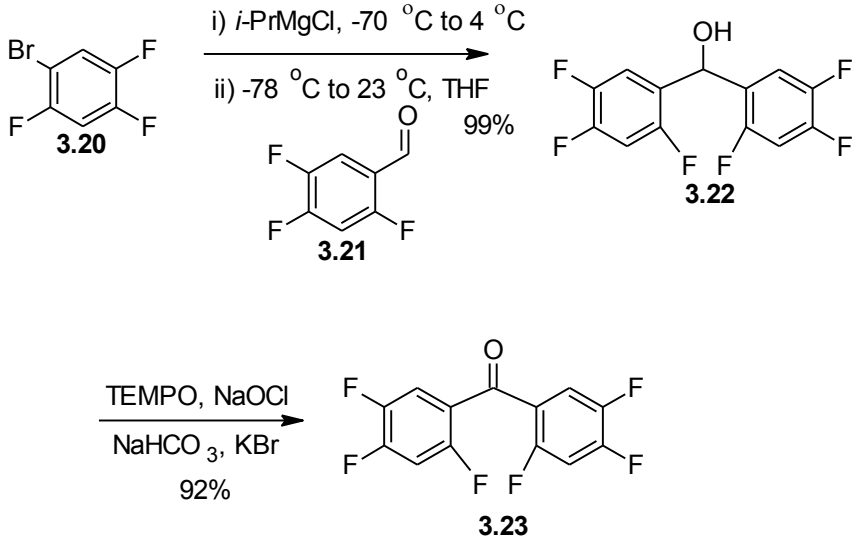
Scheme 3.2: Synthesis of 2-(ethylthio)-4-hydroxy-3-iodo-6-phenylbenzophenone (**3.16**).[117]

Rhodium catalysts were also used to synthesize benzophenones. Darses *et al*.[118] reported the synthesis of benzophenone **3.19** from aryl aldehyde **3.17** and potassium benzyltrifluoroborate (**3.18**) (Scheme 3.3). They used a stable form of the phosphonium salt of tri-*t*-butylphosphane-rhodium catalyst system in a dioxane-acetone solvent system to achieve maximum yields.



Scheme 3.3: Synthesis of (4-methoxyphenyl)(1-methyphenyl)methanone (**3.19**).

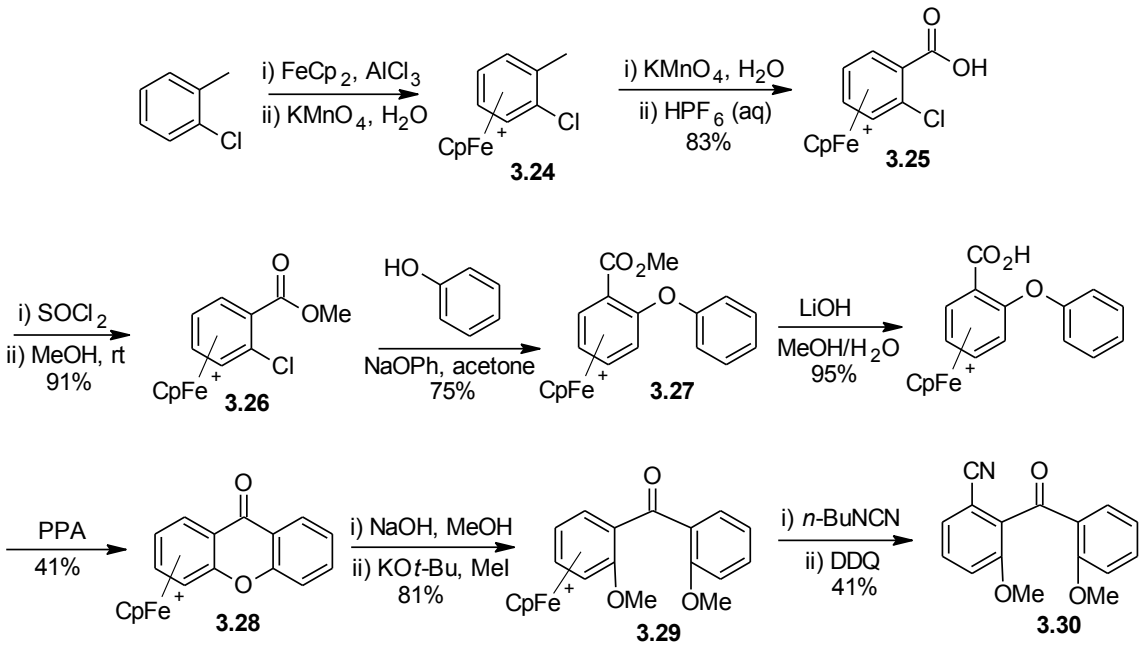
Peterson *et al*.[119] have synthesized a hexafluorobenzophenone (**3.23**) from 1-bromo-2,4,5-trifluorobenzene (**3.20**) and 2,4,5-trifluorobenzaldehyde (**3.21**) by a Grignard reaction as shown in Scheme 3.4. The Grignard derivative of **3.20** was reacted with a benzaldehyde to afford the corresponding benzyl alcohol **3.22**. Oxidation of the benzyl alcohol with TEMPO and sodium hypochlorite[120] produced bis(2,4,5-trifluorophenyl)methanone (**3.23**).



Scheme 3.4: Synthesis of bis(2,4,5-trifluorophenyl)methanone (**3.23**).[119]

Storm and Andersson[121] reported the synthesis of unsymmetrically substituted-benzophenone **3.30** by using an intermediate iron complex (Scheme 3.5). Their first and key step was to synthesize η^6-2-chlorotoluene-η^5-cyclopentadienyl iron (**3.24**) which was oxidized in an aqueous solution of potassium permanganate to form a carboxylic acid-iron

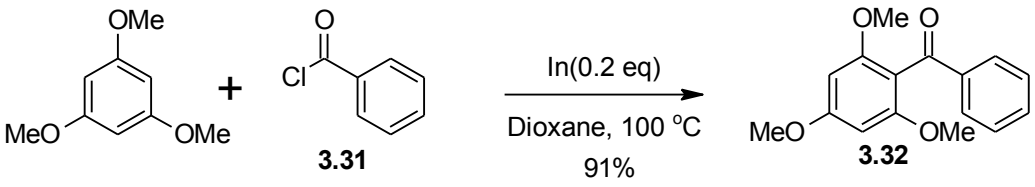
complex **3.25**. This acid was then converted into the methyl ester-iron complex **3.26**, which underwent a nucleophilic aromatic substitution by a phenol nucleophile to form diaryl ether **3.27**. The ester functionality of **3.27** was hydrolyzed to a carboxylic acid before it was subjected to an intramolecular Friedel-Crafts acylation to yield a xanthone complex **3.28**. After a ring opening of **3.28** with an oxygen nucleophile, the benzophenone complex **3.29** was obtained and with a cyanide nucleophilic substitution in the presence of DDQ, the unsymmetrically substituted benzophenone **3.30** was obtained.



Scheme 3.5: Synthesis of 3-methoxy-2-(2-methoxybenzoyl)benzonitrile (**3.30**).[121]

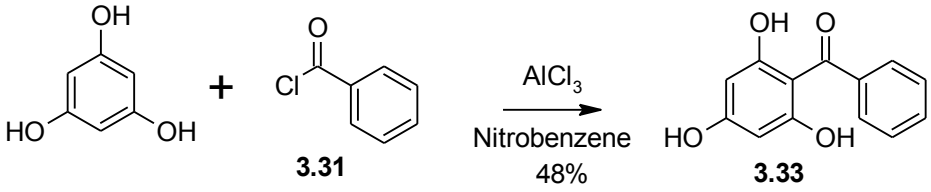
3.3.2 Friedel-Crafts acylation reactions to synthesize benzophenones

The Friedel-Crafts acylation reaction is the conventional reaction to synthesize aromatic ketones. This reaction takes place between aromatic compounds and acid chlorides in the presence of strong Lewis acids such as $TiCl_4$, $AlCl_3$, $SnCl_4$ or $FeCl_3$.[122,123] However, Jong and co-workers reported a Friedel-Crafts acylation reaction that proceeds in the absence of Lewis acids.[124] In their reactions, indium metal was used as a catalyst instead of a Lewis acid, and the reaction was run either neat or in dioxane as a solvent (Scheme 3.6). In the reaction between 1,3,5-trimethoxybenzene and benzoyl chloride (**3.31**), they reported a 91% yield of 2,4,6-trimethoxybenzophenone (**3.32**).



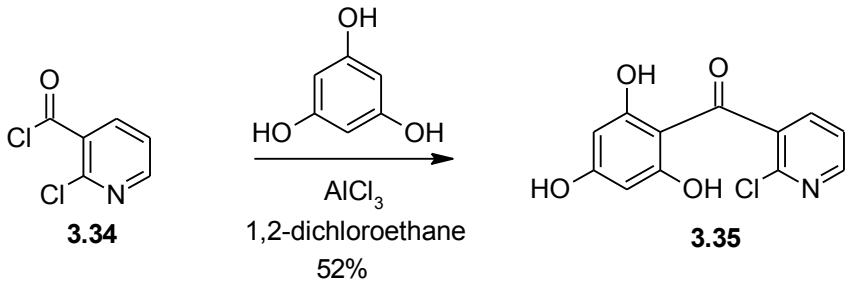
Scheme 3.6: Friedel-Crafts acylation in the absence of a Lewis acid.

Synthesis of 2,4,6-trihydroxybenzophenone (**3.33**) is another example of the application of a Friedel-Crafts acylation reaction, whereby phloroglucinol reacts with benzoyl chloride (Scheme 3.7).[125] This reaction was performed in the presence of $AlCl_3$ in nitrobenzene and gave a 48% yield.



Scheme 3.7: Synthesis of 2,4,6-trihydroxybenzophenone (**3.33**).

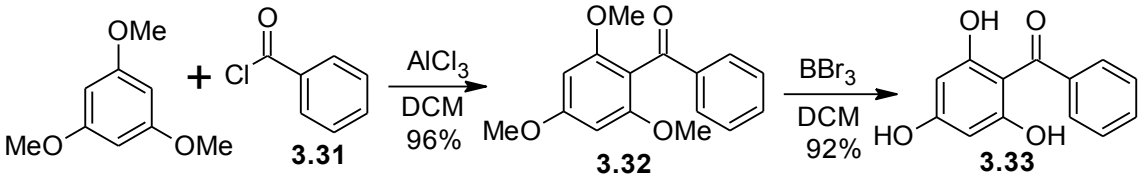
These acylation reactions are also applicable to the heterocyclic acid chlorides such as 2-chloronicotinoyl chloride (**3.34**) as reported by Marakos *et al*. (Scheme 3.8).[126] This acid chloride **3.34** reacted with phloroglucinol in 1,2-dichloroethane in the presence of $AlCl_3$ (Scheme 3.8) to afford nicotinoyl phloroglucinol (**3.35**).



Scheme 3.8: Synthesis of nicotinoylphloroglucinol (**3.35**).

Mondal *et al*.[127] reported the synthesis of 2,4,6-trihydroxybenzophenone (**3.33**) in two successful steps (Scheme 3.9). The first step was the Friedel-Crafts acylation of 1,3,5-trimethoxybenzene with benzoyl chloride (**3.31**) in the presence of $AlCl_3$ in DCM. The resulting 2,4,6-trimethoxybenzophenone (**3.32**) was subjected to the demethylation

reaction in a BBr_3-mediated reaction. Both these reactions were run under dry conditions to achieve the optimum yields.



Scheme 3.9: Synthesis of 2,4,6-trihydroxybenzophenone (**3.33**).[127]

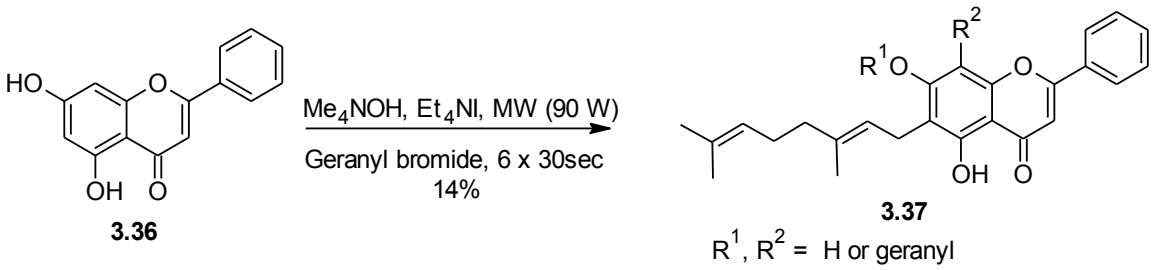
3.3.3 Prenylation reactions

The presence of a prenyl group affects the bioactivity of a compound as it influences the physicochemical properties such as lipophilicity and three-dimensional properties. These properties eventually control the interaction with the biological targets. The biological activities can be achieved depending on the length and the position of the prenyl group. For example, some relationship between presence, the length and the position of the prenyl group and the biological activity such as antitumor,[128] anti-inflammation,[129] PKC modulation[130] and human lymphocyte proliferation[131] have been observed. There are many bioactive prenylated compounds that are reported in the literature, most of them were isolated from living organisms. In this Section, however, we will focus on the synthesis of prenylated compounds as our main interest is on the prenylation of organic compounds. Normally, the prenylation of organic compounds takes place on carbon (*C*-prenylation) or oxygen (*O*-prenylation).

3.3.3.1 C-prenylation reactions

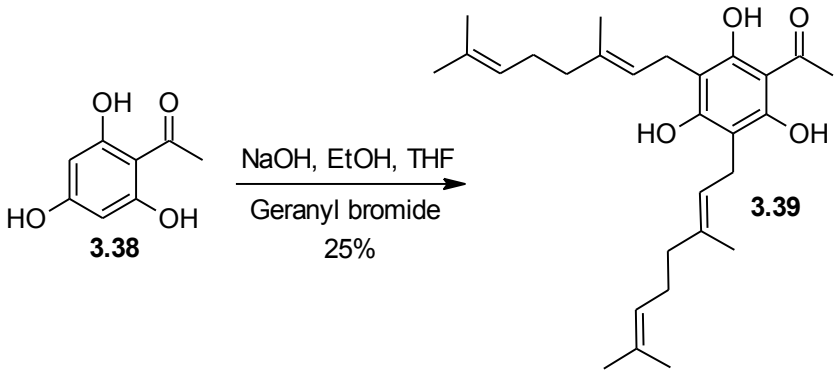
C-Prenylation reactions refer to reactions where the prenyl group is incorporated in the organic compound on a carbon atom. This implies the formation of a carbon-carbon bond. Normally, these reactions take place between aromatic compounds and halogenated prenyls and are therefore electrophilic aromatic substitution reactions. Barron *et al.*[132] reported the alkylation of flavonols with the use of microwave radiation. Basabe *et al.*[133] have applied the same conditions to prenylate chrysin (**3.36**) to afford a prenylated derivative of chrysin (**3.37**) (Scheme 3.10). They optimized their yield by using 10 equiv. of tetramethylammonium hydroxide and 6 successive 30 s microwave irradiations (90 W). This prenylation reaction had a poor selectivity as it yielded only 15% of **3.37**, the rest of

the products were diprenylated and triprenylated chrysin, as shown by R^1 and R^2 in structure **3.37**.



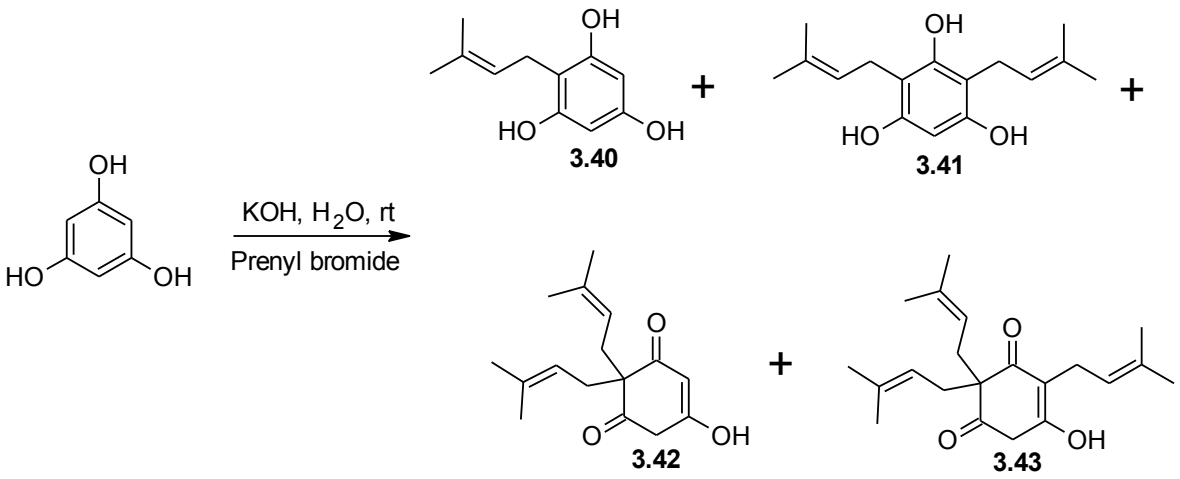
Scheme 3.10: Synthesis of 6-*C*-geranylchrysin (**3.37**).

Basabe *et al*.[133] also reported the synthesis of 3-geranyl-2,4,6-trihydroxyacetophenone and 3,5-digeranyl-2,4,6-trihydroxyacetophenone (**3.39**) by the prenylation of the acetophenone **3.38** (Scheme 3.11). This reaction was run in a NaOH medium with 0.5 equiv. of geranyl bromide to achieve monogeranylation and bigeranylation of acetophenone.



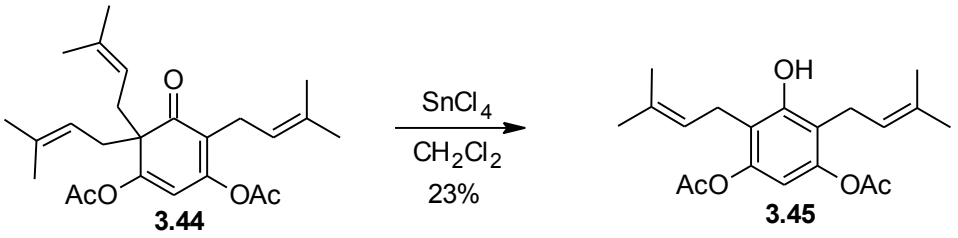
Scheme 3.11: Synthesis of 3,5-digeranyl-2,4,6-trihydroxyacetophenone (**3.39**).

C-prenylation reactions are not restricted to the use of organic solvents as Nuhant *et al*.[134] reported the synthesis of polyprenylated phloroglucinol by regioselective prenylation in an aqueous medium (Scheme 3.12). When the prenylation reaction was run in a potassium hydroxide medium, monoprenylated **3.40**, diprenylated **3.41** and **3.42** and triprenylated phloroglucinol **3.43** were formed.



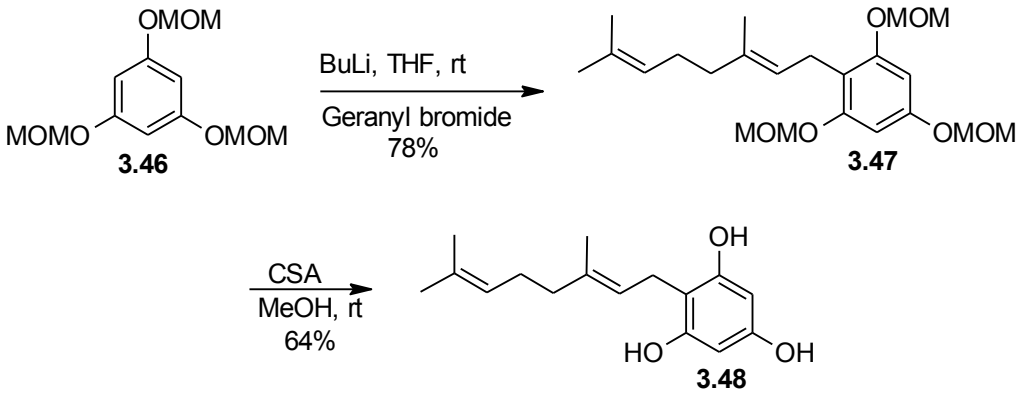
Scheme 3.12: Prenylation of phloroglucinol in aqueous medium.

The formation of the *gem*-substituted phloroglucinols **3.42** and **3.43** resulted in the loss of the aromaticity of the ring. The aromaticity of the bis(enol acetate) **3.44** was reinstated by a tin(IV) chloride-mediated deprenylation reaction to form a biprenylated phloroglucinol (**3.45**) (Scheme 3.13).[134]



Scheme 3.13: Synthesis of 3,5-diacetoxy-2,6-bis(3-methylbut-2-enyl)phenol (**3.45**).

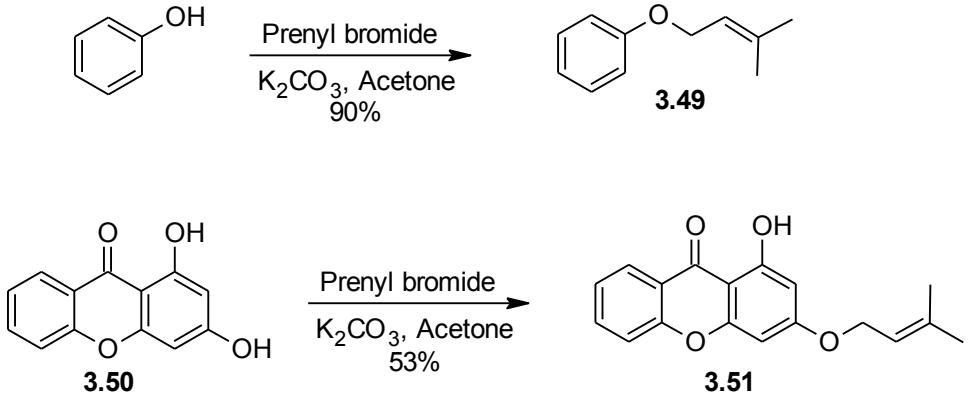
The yield of a monoprenylated phloroglucinol was increased by the use of the classic *ortho*-lithiation method. Firstly, tris-MOM ether **3.46** was synthesized from phloroglucinol which was then prenylated in the presence of butyl lithium in THF to afford **3.47**. The cleavage of the MOM ether with CSA in methanol resulted in the formation of geranyl phloroglucinol **3.48**.



Scheme 3.14: Synthesis of 2-(3,7-dimethylocta-2,6-dienyl)benzene-1,3,5-triol (**3.48**).

3.3.3.2 O-prenylation reactions

O-Prenylation reactions involve the use of a base. The most commonly used base in these reactions is potassium carbonate in acetone (Scheme 3.15). But other bases such as tetramethylammonium hydroxide (Scheme 3.10) and potassium hydroxide are also used. The selective prenylation of a phenol and a dihydroxyxanthone (**3.50**) in a K_2CO_3-mediated reaction was reported to successfully produce corresponding monoprenylated compound **3.49** and **3.51**.[135,136]

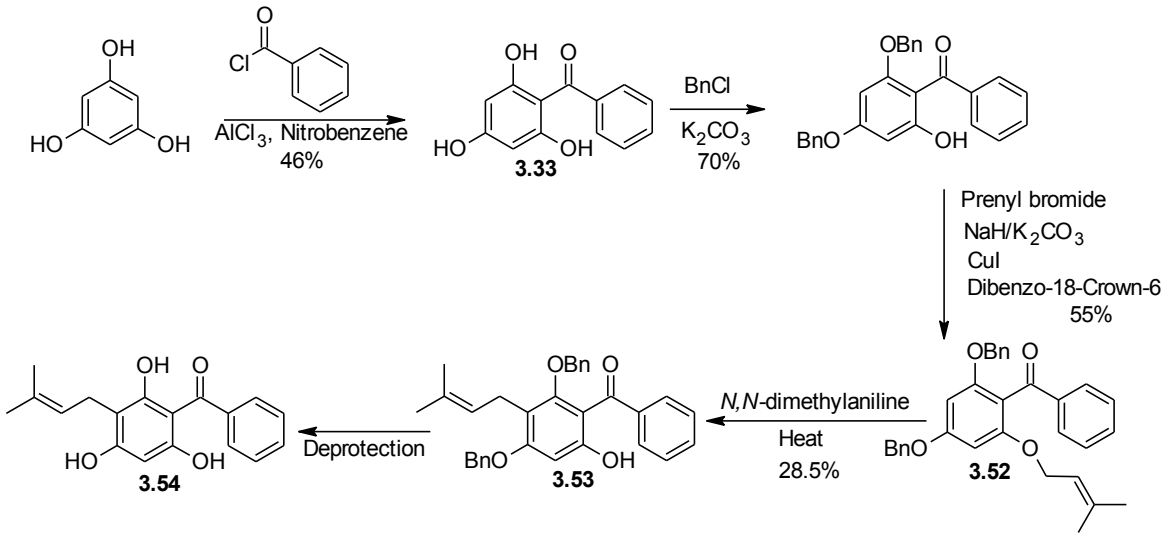


Scheme 3.15: Oxyprenylation reactions using K_2CO_3.

3.3.4 Synthesis of prenylated acylphloroglucinols

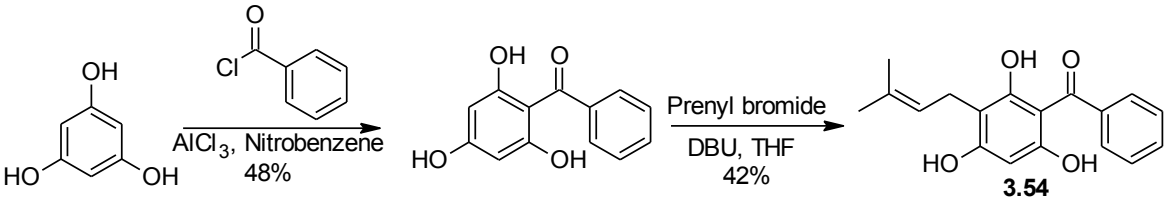
Smith[37] reported the synthesis of prenylated benzophenone **3.54** by Friedel-Crafts acylation of phloroglucinol followed by a *C*-prenylation (Scheme 3.16). She started her synthesis with the benzoylation of phloroglucinol, followed by the selective protection of

benzoyl phloroglucinol (**3.33**). Prenylation of the protected benzophenone in the presence of K_2CO_3, CuI and dibenzo-18-crown-6 formed the *O*-prenylated benzophenone **3.52**, which underwent a Claisen/Cope rearrangement when heated in *N,N*-dimethylaniline to form the *C*-prenylated benzophenone **3.53**. Compound **3.53** was subjected to a deprotection reaction to yield 2,4,6-trihydroxy-3-prenylbenzophenone (**3.54**).



Scheme 3.16: Synthesis of 2,4,6-trihydroxy-3-prenylbenzophenone (**3.54**).[37]

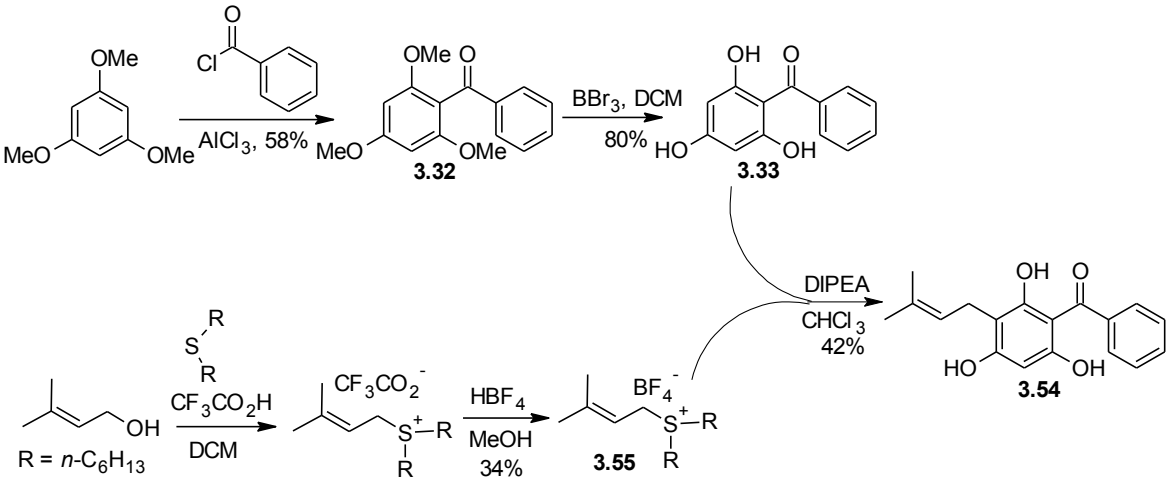
Lee *et al*.[125] also reported the synthesis of 2,4,6-trihydroxy-3-prenylbenzophenone (**3.54**) from phloroglucinol (Scheme 3.17). They synthesized benzoyl phloroglucinol from the benzoylation of phloroglucinol in the presence of aluminium trichloride. DBU was used as a base in the prenylation reaction to afford **3.54** (42% yield).



Scheme 3.17: Synthesis of 2,4,6-trihydroxy-3-prenylbenzophenone (**3.54**).[125]

Delpech *et al*.[137] reported the synthesis of 2,4,6-trihydroxy-3-prenylbenzophenone (**3.54**) by prenylation with the prenyl sulfonium salt. Trimethoxybenzophenone **3.32** was synthesized from the benzoylation of trimethoxybenzene. Demethylation of **3.32** with boron tribromide resulted in the formation of trihydroxybenzophenone **3.33**. Prenyl sulfonium salt (**3.55**) was prepared by sulfonation of prenol in presence of the

trifluoroacetic acid followed by anion exchange with tetrafluoroboric acid. Lastly, the trihydroxybenzophenone was prenylated with the prenyl sulfonium salt in the presence of *N,N*-diisopropylethylamine to afford the prenylated benzophenone **3.54**.



Scheme 3.18: Use of sulfonium salt of prenol in the synthesis of prenylated benzophenone (**3.54**).[137]

The review above has shown that prenylated benzophenones are natural compounds and exhibit biological activities such as anticancer, anti-inflammatory, anti-HIV and antimicrobial activity. It also showed reactions for the synthesis of benzophenones, the most popular reaction being Friedel-Crafts acylation. Prenylation reactions (*O*-prenylation and *C*-prenylation) were also explored but these reactions often result in the formation of more than one product.

3.4 Results and discussion

3.4.1 Introduction

The aim of this research was to develop methods for the synthesis of fluorine-substituted benzophenones. The structures of the targeted benzophenones were based on bioactive benzophenones isolated from plants of the *Hypericum* family, *viz*. geranyl-2,4,6-trihydroxybenzophenone (**3.8**), 4-geranyloxy-2,6-dihydroxybenzophenone (**3.9**) and vismiaphenone D (**3.7**) (Figure 3.7). Benzophenone **3.8** was isolated from *Hypericum roeperianum*[37] and *Garcinia vieillardii* and exhibits inhibitory effect against *Mycobacterium smegmatis* (IC_{50} = 50 μg/mL) and other microbes.[114,115] Compound **3.9**

was isolated from *Tovomita longifolia*[112] and has a higher activity against *Staphylococcus aureus* and *Mycobacterium smegmatis* (IC_{50} = 12.5 µg/mL), and is also cytotoxic to human cancer cells such as SF-268 (IC_{50} = 2.0 µg/mL), H-460 (IC_{50} = 4.4 µg/mL), and MCF-7 (IC_{50} = 4.8 µg/mL).[113] The diprenylated benzophenone, vismiaphenone D (**3.7**) was extracted from *Vismia cayennensis* and was reported to exhibit HIV-inhibitory activity in the NCI primary screen.[111]

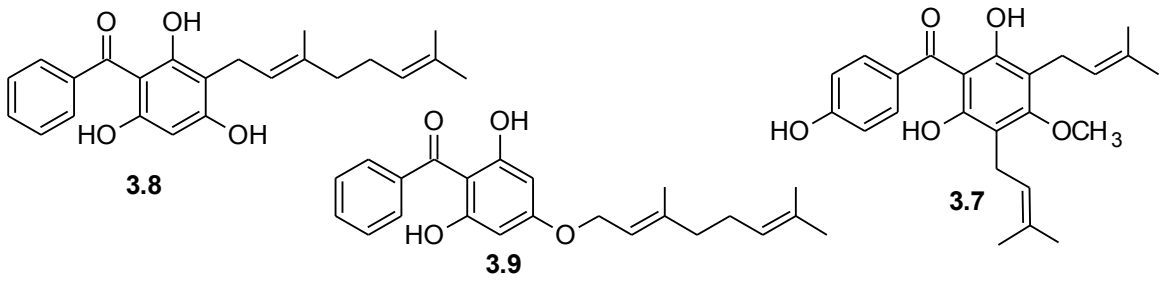


Figure 3.7: Some examples of biologically active prenylated benzophenones.

We envisaged synthesizing a library of compounds based on the structure in Figure 3.8. Although a number of acylated phloroglucinols have been synthesized, the synthesis of fluorinated derivatives have never been attempted.

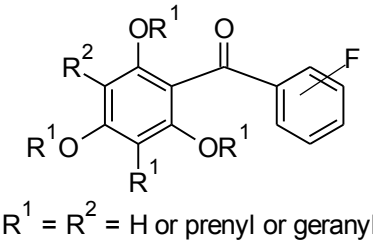
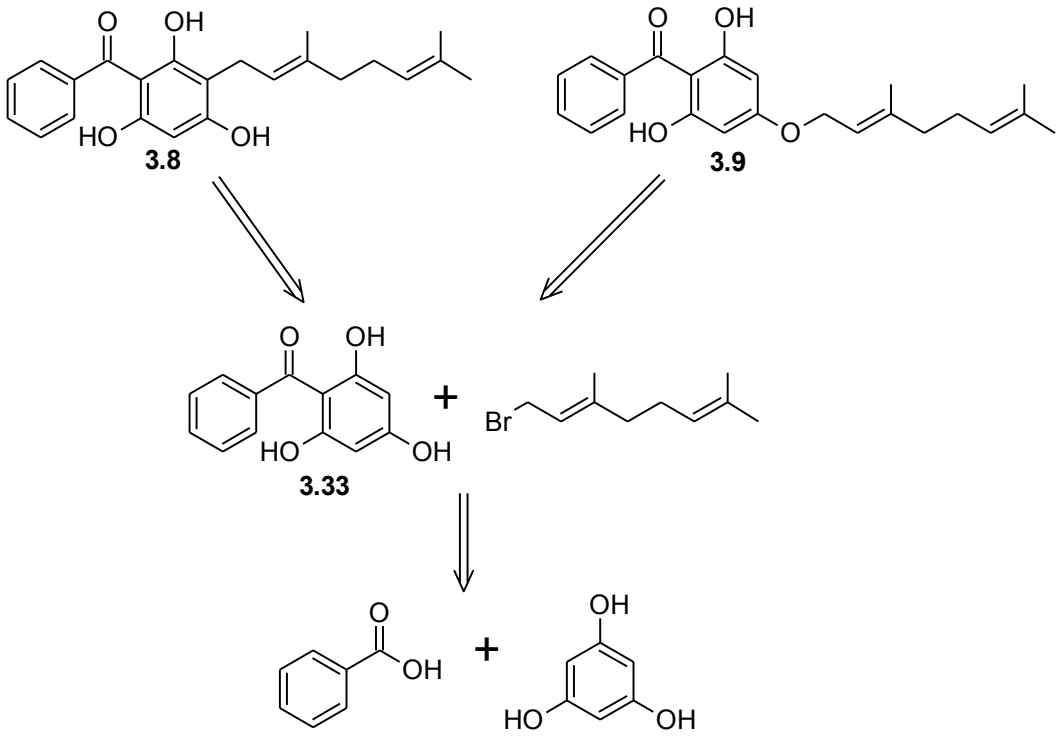


Figure 3.8: Proposed benzophenone derivatives to be synthesized.

3.4.1.1 Retrosynthetic analysis



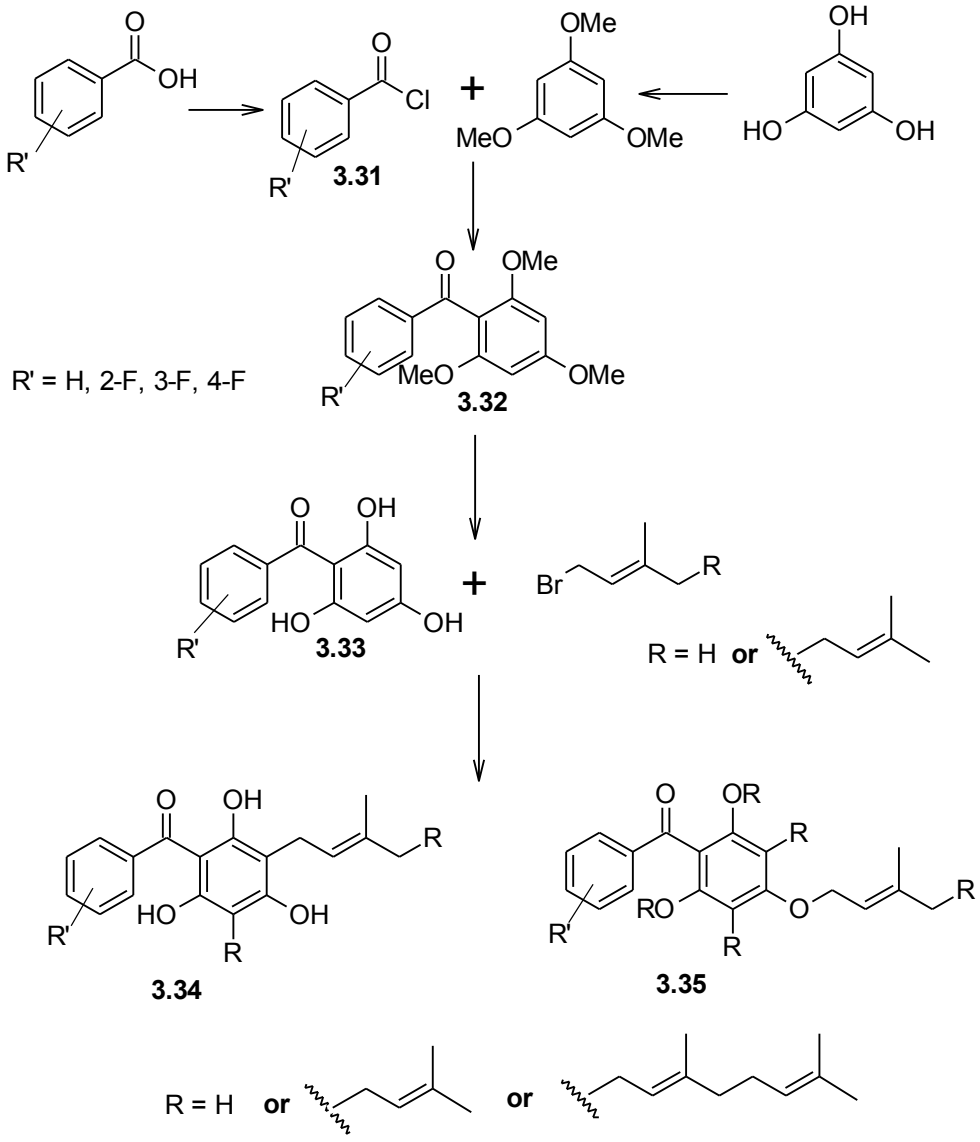
Scheme 3.19: Retrosynthesis of prenylated benzophenone.

The retrosynthetic analysis in Scheme 3.19 outlines the synthetic approach for the preparation of the prenylated benzophenones. It was envisaged that the benzophenones (**3.33**) could be formed by the acylation of phloroglucinol. The hydroxy groups on the aromatic ring are *ortho* directing and the C-C prenylation of benzophenone by electrophilic aromatic substitution is feasible to form *C*-prenylated benzophenones such as **3.8**. On the other hand, benzophenones **3.33** could be *O*-prenylated to form *O*-prenylated benzophenones such as **3.9**.

3.4.1.2 Synthetic route to prenylated benzophenones

In Scheme 3.20, the proposed syntheses of benzophenones containing fluorine and/or prenyl substituent are outlined. The first step of this synthesis is the methylation of phloroglucinol to form 1,3,5-trimethoxybenzene. The second reaction is a Friedel-Crafts acylation reaction whereby 1,3,5-trimethoxybenzene is reacted with a fluorinated benzoyl chloride to form a fluorinated phenyl(2,4,6-trimethoxyphenyl)methanone **3.32**. Phenyl(2,4,6-trimethoxyphenyl)methanone is demethylated to form fluorinated benzoyl

phloroglucinol **3.33**, which is prenylated by electrophilic aromatic substitution to yield *C*-prenylated benzophenones **3.34** and/or *O*-prenylated benzophenones **3.35**.

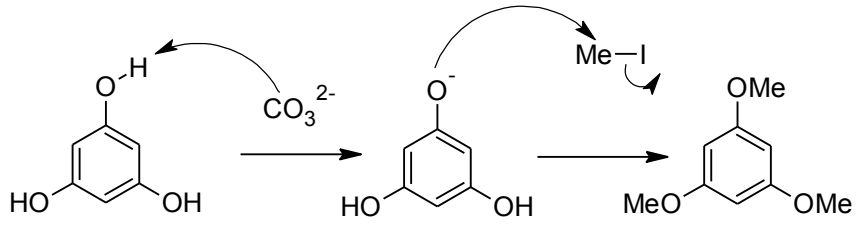


Scheme 3.20: General scheme for the synthesis of fluorinated prenylated benzophenones.

3.4.2 Synthesis of 1,3,5-trimethoxybenzene

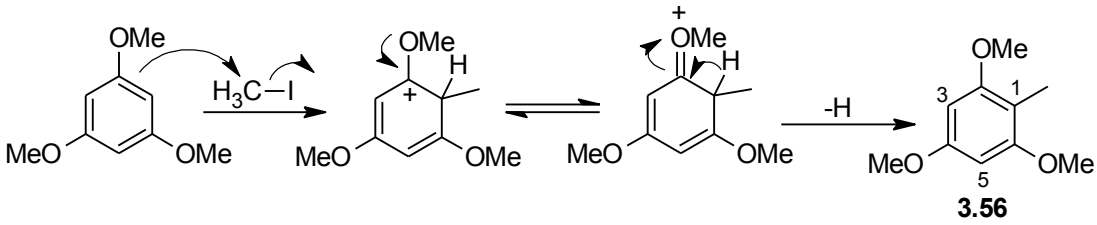
A key step in the synthesis of the required compounds is the preparation of an acylated phloroglucinol. Phloroglucinol is an electron-rich aromatic compound and Friedel-Crafts reactions result in a mixture of *O*-acylated, *C*-acylated and polyacylated products. Therefore, it was desired to use the methylated derivative of phloroglucinol as starting material for the acylation step, similar to the approach of Delpech *et al*.[137] Methylation of

phloroglucinol resulted not only in the required product (93%) (Scheme 3.21), but a side product **3.56** (7%) was also formed (Scheme 3.22).



Scheme 3.21: Mechanism for the synthesis of 1,3,5-trimethoxybenzene.

The mechanism for the conversion of phloroglucinol into 1,3,5-trimethoxybenzene (Scheme 3.21) is a S_N2 reaction where the base removes the hydroxy proton of phloroglucinol to form a nucleophile. Nucleophilic attack on the carbon of the iodomethane results in the formation of 1,3,5-trimethoxybenzene. 1,3,5-Trimethoxybenzene is electron rich and it can react with excess iodomethane to form 1,3,5-trimethoxy-2-methylbenzene (**3.56**) (Scheme 3.22). The electron-rich benzene ring attacks on the partially positive carbon of iodomethane to form an arenium ion intermediate which immediately releases a proton to form compound **3.56**.



Scheme 3.22: Mechanism for the synthesis of 1,3,5-trimethoxy-2-methylbenzene (**3.56**).

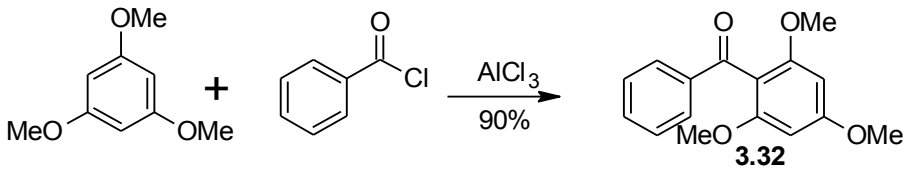
The structure of 1,3,5-trimethoxybenzene and **3.56** was confirmed by NMR and IR spectrometry and HRMS. In the ^{1}H NMR spectrum of 1,3,5-trimethoxybenzene only two singlet peaks (δ_H 6.08 and δ_H 3.78 with a relative integration of 1:3) were observed. The ^{13}C NMR spectrum of 1,3,5-trimethoxybenzene showed three peaks, an upfield peak at δ_C 55.4 due to the methoxy carbons, and aromatic carbons at δ_C 93.1 and δ_C 161.7. HRMS confirmed the molecular formula of the compound.

The structure of 1,3,5-trimethoxy-2-methylbenzene was verified by the ^{1}H NMR spectrum in which the methyl protons appear as a singlet at δ_H 2.00. The ^{13}C NMR spectrum also confirmed the structure by the presence of a methyl carbon at δ_C 7.8, C-1 at δ_C 106.9, C-2

and C-6 at δ_C 158.8 and C-4 at δ_C 160.0. HRMS also confirmed the molecular formula by showing a good agreement between the observed mass and the calculated mass.

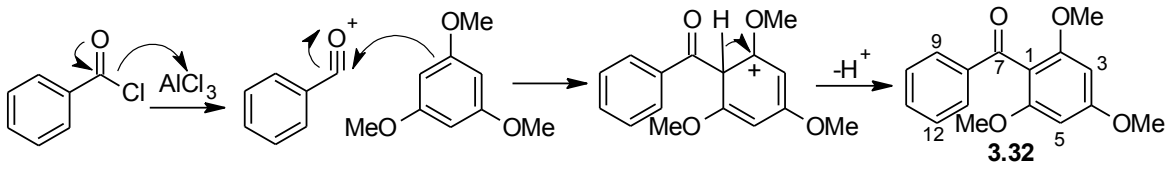
3.4.3 Synthesis of phenyl(2,4,6-trimethoxyphenyl)methanone (3.32)

The second step of the reaction sequence was the Friedel-Crafts acylation reaction. This is an electrophilic aromatic substitution whereby an aromatic hydrogen of 1,3,5-trimethoxybenzene is replaced with an acyl group in the presence of the Lewis acid. This reaction was carried out in dichloromethane with aluminum trichloride ($AlCl_3$) to give **3.32** as colourless crystals in a yield of 90% (Scheme 3.23).



Scheme 3.23: Synthesis of phenyl(2,4,6-trimethoxyphenyl)methanone **(3.32)**.

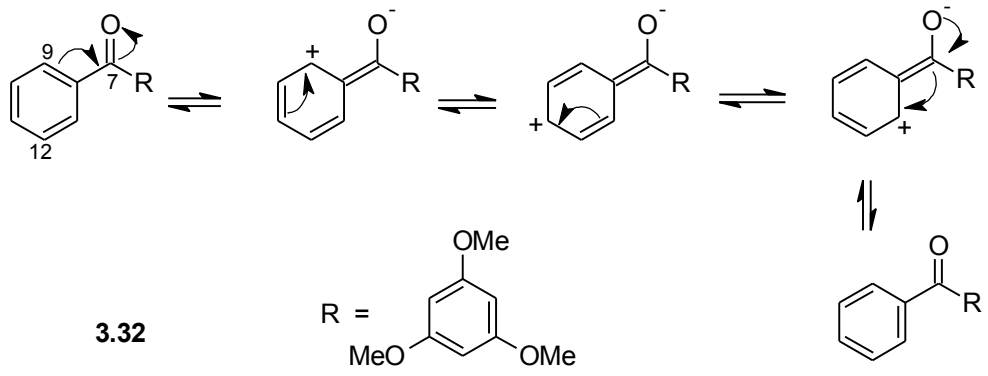
The carbonyl group of benzoyl chloride was activated with aluminium trichloride which extracts chlorine leaving a highly electrophilic acylium ion. As a result, it is attacked by a nucleophile (1,3,5-trimethoxybenzene) giving an arenium ion intermediate as shown in Scheme 3.24. This arenium ion is stabilized through resonance with the lone pairs of electrons of the methoxy groups. Deprotonation of the arenium ion results in the formation of phenyl(2,4,6-trimethoxyphenyl)methanone **(3.32)**.



Scheme 3.24: Proposed mechanism for the formation of phenyl(2,4,6-trimethoxyphenyl) methanone **(3.32)**.

The structure of phenyl(2,4,6-trimethoxyphenyl)methanone **(3.32)**, as well as phenyl(2,4,6-trimethoxy-3-methylphenyl)methanone **(3.57)**, were verified by standard techniques, including NMR, IR and HRMS.

The ^{1}H NMR spectrum of 3.32 (Plate 1) reveals that the *ortho* and the *para* protons of the phenyl ring are more deshielded (δ_H 7.82 and δ_H 7.50, respectively) than the meta protons (δ_H 7.39). This can be attributed to resonance interaction between the carbonyl groups and the aromatic ring (Scheme 3.25). In addition, the *ortho* protons experience a great negative inductive effect than the *para* protons from the carbonyl group and as a result H-9 and H-13 resonate further downfield than H-11. The protons on the methoxy substituted ring are shielded and resonate relatively upfield, due to the electron donating ability of the methoxy groups.



Scheme 3.25: Resonance forms for phenyl(2,4,6-trimethoxyphenyl)methanone **(3.32)**.

The ^{13}C NMR spectrum of **3.32** (Plate 1) revealed a ketone carbonyl peak at δ_C 195.2, also confirmed by the HMBC and DEPT-135 spectra. Two quaternary carbon peaks at δ_C 159.0 and δ_C 162.7 were assigned to the aromatic carbons bonded to the methoxy groups (C-2, C-4 and C-6). It also showed all the remaining aromatic carbons in the aromatic region (δ_C 128-133) including the quaternary carbons (C-1 and C-8 at δ_C 111.3 and δ_C 138.5, respectively). The methoxy carbons appeared upfield at δ_C 55.7 and δ_C 56.1 and with the use of an HSQC spectrum and taking into account the relative intensity of the signals in the ^{13}C spectrum, they were assigned as 4-OCH_3 and 2,6-OCH_3, respectively.

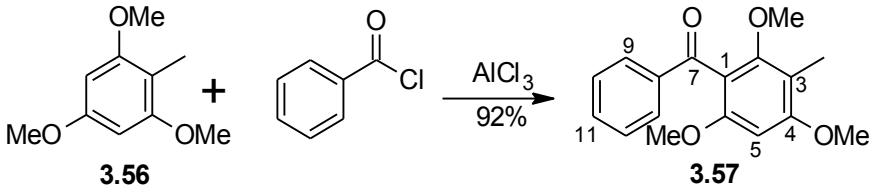
The elucidation of the structure of phenyl(2,4,6-trimethoxyphenyl)methanone was also confirmed by the appearance of a strong carbonyl band at 1660 cm^{-1} in the IR spectrum. The aromatic and alkyl C-H bond stretching appeared at 3053 cm^{-1} and 2949 cm^{-1}, respectively.

The structure of phenyl(2,4,6-trimethoxyphenyl)methanone was also confirmed by the high-resolution mass spectrum (HRMS) which shows good agreement between the

calculated mass for the sodium adduct of 295.0946 ($C_{16}H_{16}O_4Na$) and a pseudo-molecular ion peak at *m/z* 295.0945 $[M+Na]^+$.

3.4.4 Synthesis of phenyl(2,4,6-trimethoxy-3-methylphenyl)methanone (3.57)

Phenyl(2,4,6-trimethoxy-3-methylphenyl)methanone **(3.57)** was synthesized using the Friedel-Crafts acylation reaction (Scheme 3.26). The reaction mechanism is similar to the one shown in Scheme 3.23 except for the use of 1,3,5-trimethoxy-2-methylbenzene **(3.56)**.



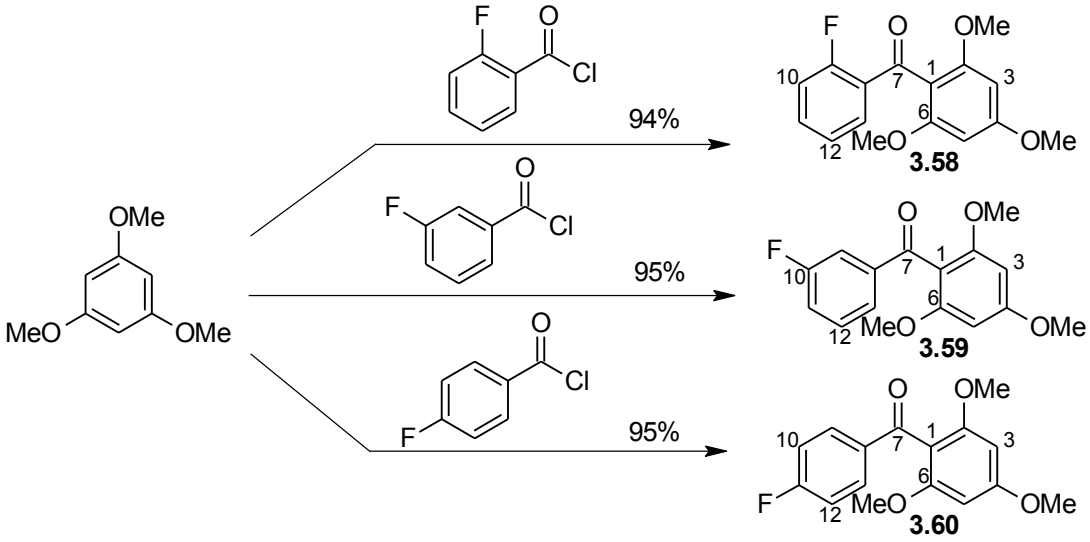
Scheme 3.26: Reaction for the formation of phenyl(2,4,6-trimethoxy-3-methylphenyl) methanone **(3.57)**.

The ^1H and ^{13}C NMR spectra of phenyl(2,4,6-trimethoxy-3-methylphenyl)methanone **(3.57)** revealed the peaks that are similar to those of **3.32** except for additional upfield peaks (Plate 2). One of the new peaks is due to the methyl group (3-CH_3) which appears further upfield at δ_H 2.11 in the ^1H NMR spectrum and integrates for three protons. An HSQC spectrum revealed that this methyl group correlates with the upfield peak in the ^{13}C NMR spectrum at δ_C 8.4. The methoxy groups (2-OCH_3 and 6-OCH_3) are no longer in the same environment and as a result they resonate with different frequencies, δ_H 3.62 and δ_H 3.72 in the ^1H NMR spectrum and at δ_C 62.0 and δ_C 56.0 in the ^{13}C NMR spectrum, respectively. The DEPT-135, HSQC, HMBC, IR and mass spectra were also carried out to confirm the structure.

3.4.5 Synthesis of fluorinated phenyl(2,4,6-trimethoxyphenyl) methanone (3.58-3.60)

Since the application of the Friedel-Crafts acylation reaction (reaction of 1,3,5-trimethoxybenzene with benzoyl chloride) in the second step of the reaction sequence was successful, the same reaction was then performed with the fluorinated benzoyl chlorides as shown in Scheme 3.27. The same reaction conditions were used and distinct colour

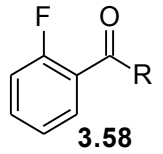
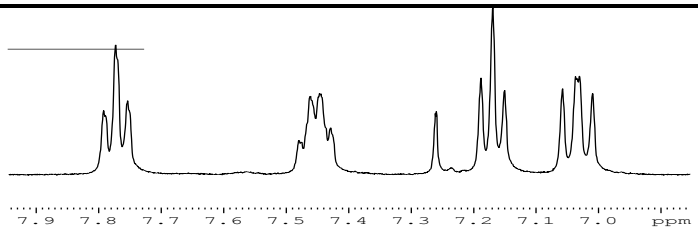
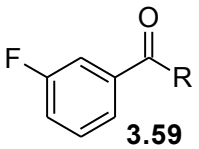
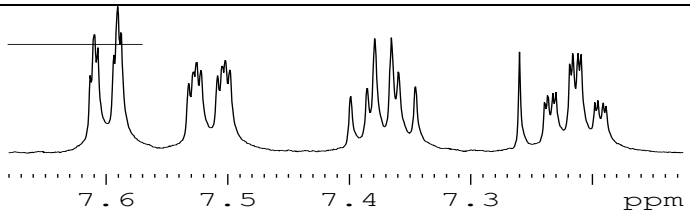
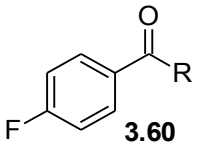
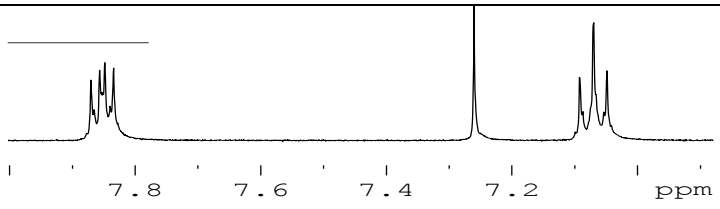
changes were observed during the reaction. The reaction of 2-fluorobenzoyl chloride was the first to be conducted.



Scheme 3.27: Reaction of 1,3,5-trimethoxybenzene with fluorinated benzoyl chloride.

The formation of (2-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone **(3.58)** was successful as confirmed by the ^{1}H NMR spectrum (Plate 3). The methoxy protons are more shielded and as a result they resonate upfield, 2,6-OCH_3 and 4-OCH_3 appearing at δ_H 3.67 and δ_H 3.83, respectively. The methoxy groups are electron donating which causes the aromatic protons (H-3 and H-5) to resonate upfield (δ_H 6.12) relative to the protons in the monofluorinated aromatic ring. The *ortho* (H-13) and *para* (H-11) are the most deshielded protons (δ_H 7.75 and δ_H 7.43, respectively) in the ring because of the mesomeric effect caused by the carbonyl group (as shown in Scheme 3.25). In addition to the mesomeric effect, H-13 experiences a greater negative inductive effect from the carbonyl group than H-11 as a result H-13 is shifted further downfield. The *meta* protons (H-10 and H-12) were the most shielded protons in the fluorinated benzene ring, at δ_H 7.01 and δ_H 7.15, respectively. Coupling was observed in the spectra in Table 3.1 and the coupling constants are given in Table 3.2.

Table 3.1: Aromatic region of the ^{1}H NMR spectra of the fluorinated benzophenones.

Chemical structure	Aromatic region of the ^{1}H NMR spectra
 **3.58**	
 **3.59**	
 **3.60**	

The ^{13}C NMR spectrum of (2-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (Plate 3) also supports the structure with a carbonyl carbon peak at δ_C 190.7. As a result of the high electronegativity of fluorine, the fluorine-containing carbon (C-9) resonates downfield at δ_C 160.4 relative to C-13 which resonates at δ_C 131.4 ($\Delta\delta$ = 30 ppm). The carbon peaks in this ring were all split due to coupling to the fluorine. The magnitude of the ^{19}F,^{13}C coupling constants depend on the number of bonds between the fluorine and the carbon, for example the *ipso* carbon (C-9) has ^{1}J = 256.5 Hz (one-bond coupling with fluorine). The *J*-values decrease as the number of bonds increase as shown in Table 3.2.

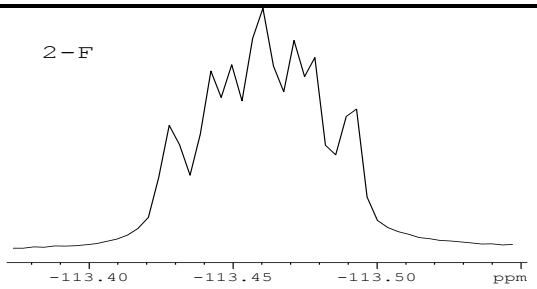
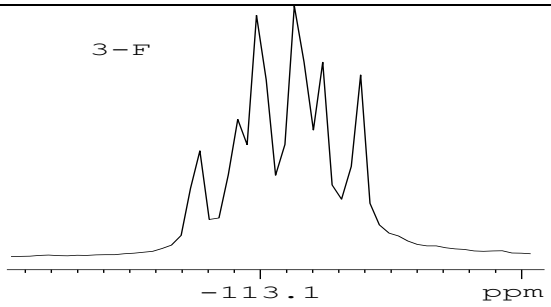
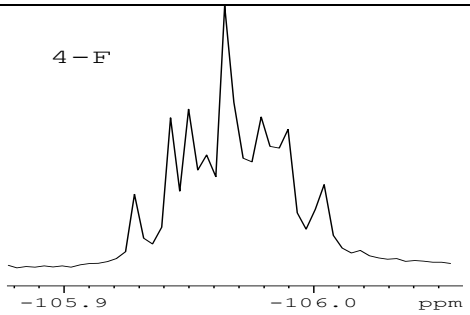
The structure of (2-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone **(3.58)** was also confirmed by the high-resolution mass data which shows a good agreement between the calculated mass for the sodium adduct of 313.0852 ($C_{16}H_{15}O_4FNa$) and an observed molecular ion peak at *m/z* 313.0849 $[M+Na]^+$.

Table 3.2: ^{1}H and ^{13}C NMR data for the fluorinated aromatic rings of **3.58**, **3.59** and **3.60**.

Compound No:	Protons and carbons of the fluorinated aromatic rings					
	H-8/C-8	H-9/C-9	H-10/C-10	H-11/C-11	H-12/C-12	H-13/C-13
3.58	…… δ_C 127.9 d, J =9.5	…… δ_C 161.7 d, J = 256.5	δ_H 7.01 dd J = 11.4,8.5 …… δ_C 116.3 d, J = 22.8	δ_H 7.43 m …… δ_C 133.8 d, J = 9.1	δ_H 7.15 t J = 7.7 …… δ_C 123.8 d, J = 3.9	δ_H 7.75 dd J = 7.7, 7.6 …… δ_C 131.4 d, J = 1.4
3.59	…… δ_C 140.6 d, J = 6.2	δ_H 7.51 dt J = 9.3, 1.8 …… δ_C 115.9 d, J = 22.4	…… δ_C 162.8 d, J = 246.6	δ_H 7.37 m …… δ_C 119.7 d, J = 21.5	δ_H 7.21 td J = 8.2, 2.8 …… δ_C 129.8 d, J = 7.5	δ_H 7.60 dt J = 8.2, 1.8 …… δ_C 125.1 d, J = 2.8
3.60	…… δ_C 134.9 s	δ_H 7.85 dd J = 8.6, 5.7 …… δ_C 132.0 d, J = 9.4	δ_H 7.07 dd J = 9.2, 8.6 …… δ_C 115.3 d, J = 22.0	…… δ_C 165.8 d, J=154.8	δ_H 7.07 dd J = 9.2, 8.6 …… δ_C 115.3 d, J = 22.0	δ_H 7.85 dd J = 8.6, 5.7 …… δ_C 132.0 d, J = 9.4

The Friedel-Crafts acylation was also applied to synthesize (3-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone **(3.59)** and (4-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone **(3.60)** where 3-fluorobenzoyl chloride and 4-fluorobenzoyl chloride were used, respectively, to react with 1,3,5-trimethoxybenzene. These reactions were highly successful and gave good yields of up to 95% as shown in Table 3.4. The ^{1}H NMR spectra of these benzophenone derivatives showed interesting proton splittings as a result of the position of the fluorine (shown in Table 3.1). In general, the coupling constant for ^{1}H to the neighboring ^{19}F is always bigger than the coupling constant between ^{1}H and the neighboring ^{1}H on the related position. For example, for the 2-fluoro substituted derivative **(3.58)**, the *ortho* coupling constants (J values) for H-10 to 9-F and H-11 are 11.4 Hz and 8.5 Hz, respectively as shown in Table 3.2.

Table 3.3: Splitting observed in the ^{19}F NMR spectra due to ^{1}H, ^{19}F coupling.

Compound	^{19}F NMR Spectrum
3.58	
3.59	
3.60	

The ^{19}F NMR spectra were run for all the fluorinated benzophenones to verify the position of fluorine in each structure. Because of its ability to couple with the neighboring carbons, the splitting varies from the *ortho*, *meta* and *para* substituted fluorine as shown in Table 3.3.

Table 3.4: Percentage yields and physical properties of the synthesized benzophenones.

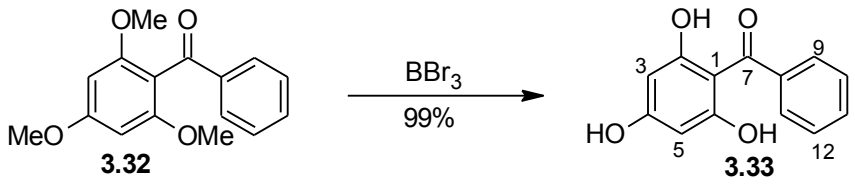
	3.32	**3.57**	**3.58**	**3.59**	**3.60**
Yield	90%	92%	94%	95%	95%
Melting point	112-114 °C	95-96 °C	127-129 °C	107-109 °C	155-157 °C
Appearance	Colourless crystals	Colourless crystals	Colourless crystals	Colourless crystals	Colourless crystals

All the synthesized fluorinated benzophenones were fully characterized by other techniques such as IR, HRMS and melting points. Their IR spectra look similar to that of phenyl(2,4,6-trimethoxyphenyl)methanone **(3.32)** as they all show strong carbonyl peaks within a carbonyl range (1600 - 1700 cm^{-1}). The melting point for the *para*-substituted benzophenone **(3.60)** was the highest (155 °C - 157 °C), followed by the *ortho*-substituted fluorine derivative **3.58** (127 °C - 129 °C).

The results discussed above show that the Friedel-Crafts reaction can be applied for the acylation of phloroglucinol derivatives to form benzophenones as it gave good yields (90% - 95%). $AlCl_3$ has also proved to be a good Lewis acid for this type of acylation reaction. All benzophenone derivatives were obtained as colourless crystals.

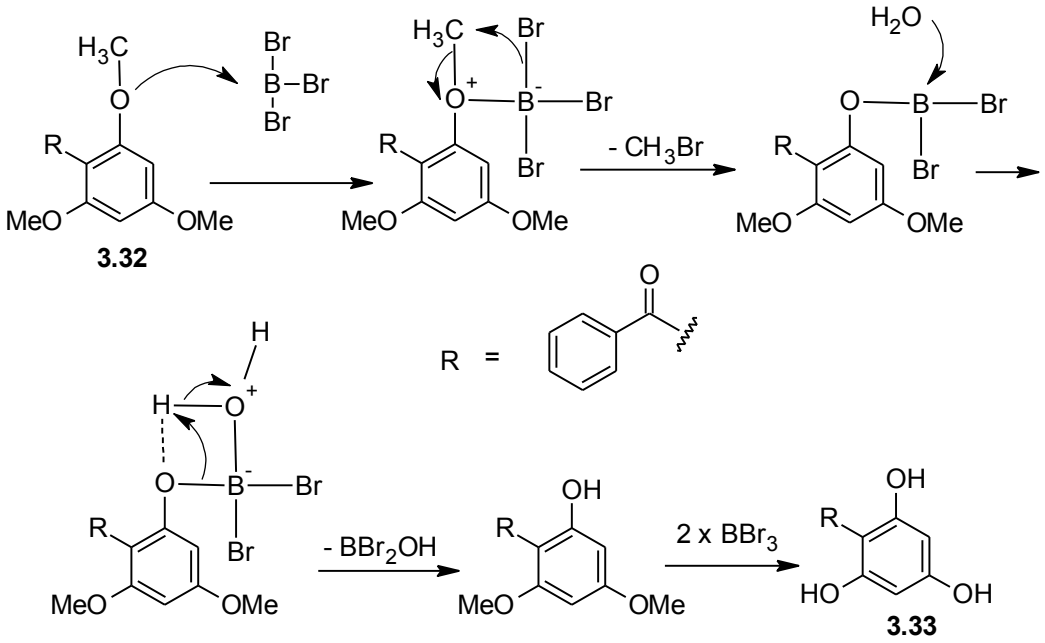
3.4.6 Synthesis of phenyl(2,4,6-trihydroxyphenyl)methanone (3.33)

The third step was the demethylation of the methoxy groups of the aromatic ring using a strong Lewis acid (boron tribromide, BBr_3).[138,139] BBr_3 has been used to cleave ethers and acetals that cannot be deprotected by the use of a normal acid.[140] This use of BBr_3 for aryl deprotection in this research was preferred over the other methods because the reaction proceeds under mild conditions. This reaction was carried out in dichloromethane at -78 °C with 5 equivalents of BBr_3 added quickly to the solution of **3.32** (Scheme 3.28). The reaction was stirred at room temperature for 24 h, resulting in a complete demethylation. When the reaction was run for 10 h, the TLC showed some spots with higher R_f values which may be due to partially demethylated products. After isolation, NMR analysis revealed the existence of some methoxy peaks in the structure. With longer reaction time, the yield of these side products was decreased. After monitoring a few reactions, it was found that the average time to complete the reaction was 24 h and yields up to 99% were observed.



Scheme 3.28: Reaction for the formation of phenyl(2,4,6-trihydroxyphenyl)methanone (**3.33**).

The mechanism of demethylation of phenyl(2,4,6-trimethoxyphenyl)methanone (**3.32**) to form **3.33** is outlined in Scheme 3.29. The lone pair of the methoxy oxygen attacks the electrophilic boron atom in BBr_3 to form an unstable zwitterion. The release of methyl bromide results in the formation of the dibromo(organo)borane which undergoes hydrolysis to form an unstable intermediate which cleaves off dibromo(hydroxy)borane to yield phenyl(2,4,6-trihydroxyphenyl)methanone (**3.33**).



Scheme 3.29: Proposed mechanism for the formation of phenyl(2,4,6-trihydroxyphenyl) methanone **(3.33)**.

The formation of the desired product was confirmed by NMR, IR and mass spectrometry. The ^{1}H NMR spectrum of **3.33** revealed the disappearance of the methoxy proton peaks and the appearance of hydroxy proton peaks resonating downfield (shown in Plate 6). The *ortho* hydroxy protons are more deshielded, as they resonate at δ_H 10.08 and integrate for two protons, than the *para*-OH which resonate at δ_H 9.82 and integrates for one proton. The monosubstituted aromatic protons (H-9, H-10, H-11, H-12 and H-13) resonate between δ_H 7.42 and δ_H 7.63. The phloroglucinol protons (H-3 and H-5) appear as a singlet at δ_H 5.84 which integrates for two protons.

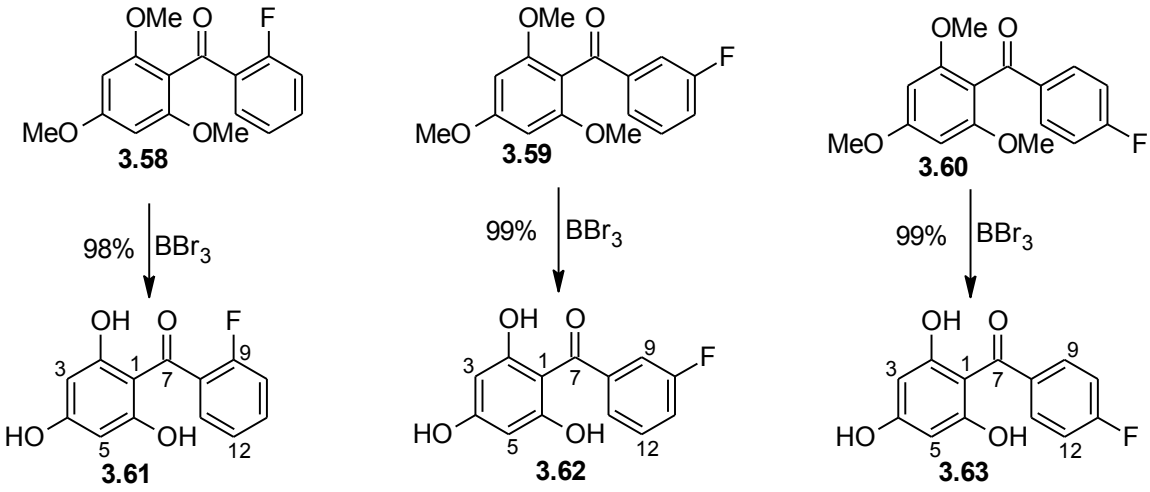
With the support of DEPT-135, HSQC and HMBC spectra, the peaks in the ^{13}C NMR spectrum were assigned. The absence of methoxy carbon peaks is evidence of the success of the demethylation reaction. C-3 and C-5 is the most shielded carbon and appeared at δ_C 94.8 (Plate 6). The quaternary carbons adjacent to the carbonyl C-1 and C-8 resonate at δ_C

106.0 and δ_C 140.2, respectively. The monosubstituted aromatic carbons resonate within a range of δ_C 128-133 which is within the aromatic region.

The structure of phenyl(2,4,6-trihydroxyphenyl)methanone **(3.33)** was also confirmed by HRMS. The IR spectrum showed a strong carbonyl band at 1625 cm^{-1} and a broad band for the phenol (O-H stretch) at 3621 cm^{-1}.

3.4.7 Synthesis of fluorinated phenyl(2,4,6-trihydroxyphenyl) methanone (3.61 - 3.63)

The demethylation reaction with BBr_3 was also applied to **3.58 - 3.60** to produce **3.61 - 3.63** successfully as shown in Scheme 3.30. The success of these reactions was confirmed by NMR, IR and mass spectra. The ^1H NMR spectra of these compounds revealed that the methoxy proton signals were absent and the appearance of the hydroxy proton signals resonating downfield as shown in Plates 7, 8 and 9. In the ^{13}C NMR spectra, the methoxy carbon signals were no longer evident in the upfield region.

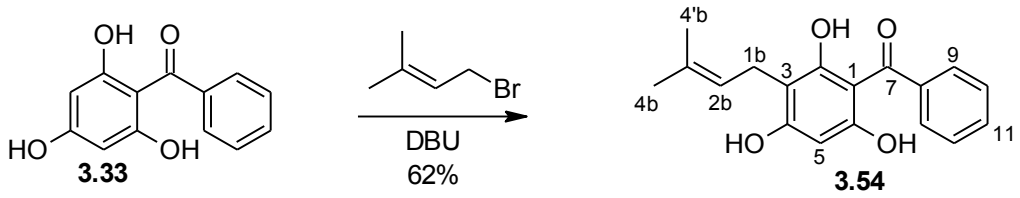


Scheme 3.30: Demethylation reactions to form fluorinated benzophenones.

Demethylation of trimethoxybenzophenone derivatives (**3.32**, **3.58**, **3.59** and **3.60**) with BBr_3 was successful with yields of about 98%. These results confirm that BBr_3 is a good demethylating agent for the methyl ether system.

3.4.8 C-Prenylation reactions

3.4.8.1 Synthesis of phenyl[2,4,6-trihydroxy-3-(3-methyl-2-butenyl) phenyl]methanone (3.54)

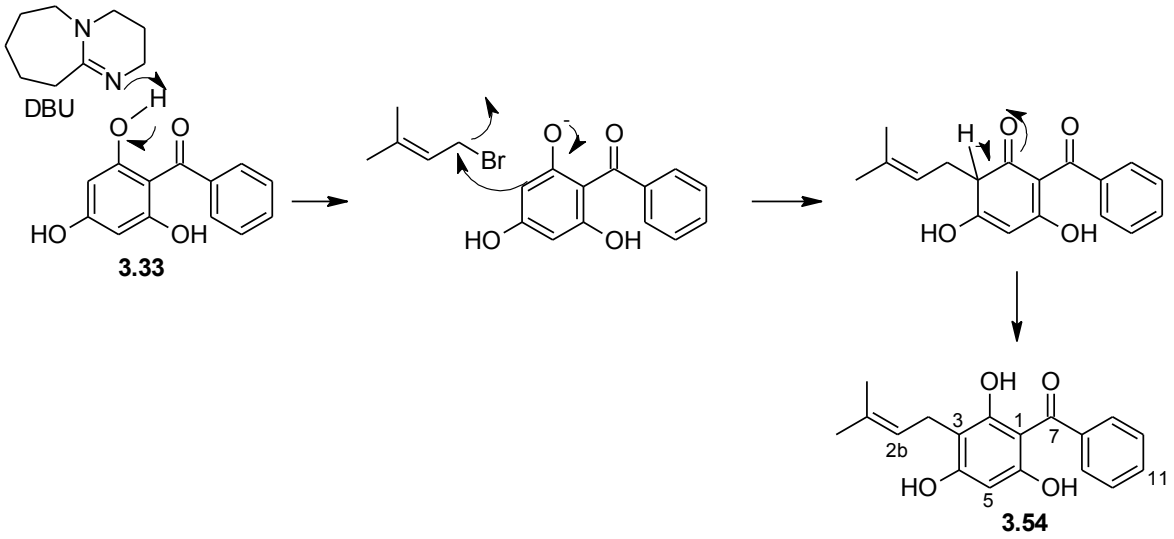


Scheme 3.31: Synthesis of phenyl[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl] methanone (**3.54**).

Method A

The last step of the reaction consists of two types of prenylation, *C*- and *O*-prenylation. The method for the *C*-prenylation of benzophenones was an adaption of the method of Lee *et al*.[125] (method A). During this electrophilic aromatic substitution, an aromatic proton is replaced by a prenyl group by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 3.31). This prenylation method was preferred over the other methods (discussed in the previous Sections) because it gives better yields and does not require harsh conditions. These reactions took place in THF at room temperature.

DBU is a mild base which extracts an acidic phenolic proton from benzophenone **3.33** to form a phenolate ion intermediate which reacts freely with prenyl bromide *via* an S_N2 mechanism and re-aromatize to form the prenylated benzophenone **3.54** (Scheme 3.32).



Scheme 3.32: Proposed mechanism for the formation of phenyl[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (**3.54**).

NMR, IR and mass spectrometry were the key techniques used to confirm the structure of the product of the prenylation reaction. The ^{1}H NMR spectrum of **3.54** revealed two upfield methyl peaks at δ_H 1.76 (doublet, J = 1.1 Hz) and δ_H 1.80 (singlet), corresponding to the *cis*-allylic methyl-protons (H-4'b) and *trans*-allylic protons (H-4b), respectively (Plate 10). A doublet peak, integrating for two hydrogens, appears at δ_H 3.36 (J = 7.0 Hz) and was assigned to H-1b. A vinylic proton peak (H-2b) appeared as a multiplet at δ_H 5.26. The replacement of aromatic hydrogen (H-3) with a prenyl group was also confirmed by the decrease of the integral from two to one proton as well as the upfield shift of the peak from δ_H 5.84 to δ_H 5.26. This shift is due to the addition of an electron-donating group to the aromatic ring which shields the aromatic proton. The aromatic protons of the monosubstituted ring appeared at δ_H 7.64 (H-9,13), δ_H 7.51 (H-10,12) and δ_H 7.58 (H-11).

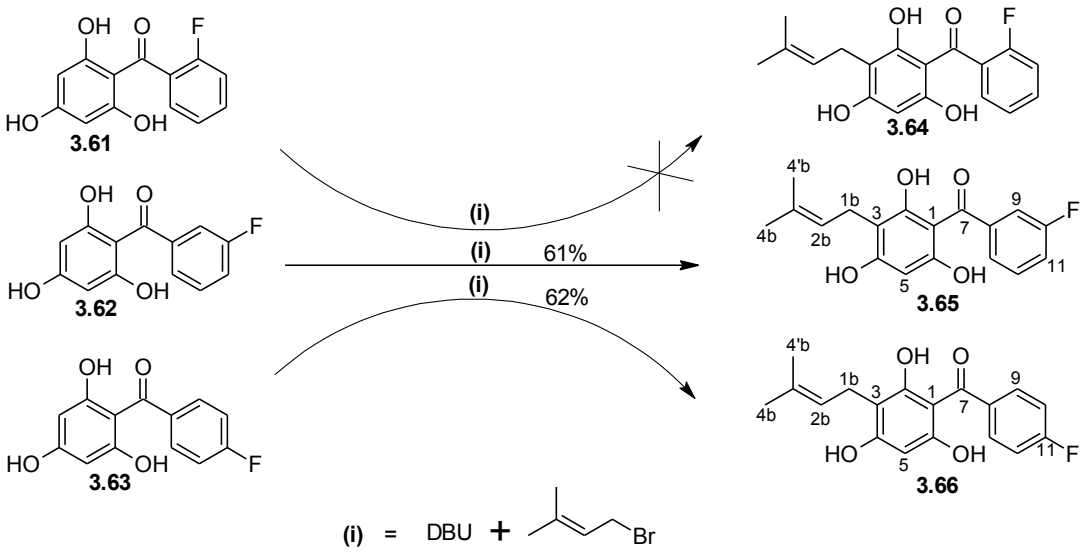
DEPT-135, HSQC and HMBC spectra were used for the assignment of ^{13}C NMR peaks. In the ^{13}C NMR spectrum (Plate 10) of **3.54** the prenyl carbons resonate upfield which is in agreement with the ^{1}H NMR spectrum. The terminal allylic carbons, C-4b and C-4'b resonate at δ_C 17.9 and δ_C 25.8, respectively, whereas the olefinic carbons (C-2b and C-3b) resonate at δ_C 121.6 and δ_C 135.4, respectively. The peak appearing downfield at δ_C 197.7 was assigned for the carbonyl carbon (C-7). The quaternary carbon (C-8) and hydroxy carbons (C-2, C-4 and C-6) were deshielded and appeared downfield at δ_C 140.0, δ_C 160.8, δ_C 162.6 and δ_C 159.4, respectively.

The IR spectrum confirmed the presence of the carbonyl group as shown by a strong band at 1625 cm^{-1} and the presence of hydroxy groups (O-H stretch band that appeared at 3621 cm^{-1}). The structure of **3.54** was also confirmed by the high-resolution mass data which shows good agreement between the calculated mass of 297.1127 ($C_{18}H_{17}O_4$) and a molecular ion peak at *m/z* 297.1130 $[M-H]^-$.

3.4.8.2 Synthesis of fluorinated monoprenylated benzophenones (3.64-3.66)

Method A

After the prenylation of **3.33** was successfully performed, it was applied to the fluorinated benzophenones (**3.61 - 3.63**) as well. However, the reaction was not successful with the 2-fluorobenzophenone **3.61** as shown in Scheme 3.33, with no product being observed. The reason for the difference in reactivity between 2-fluorobenzophenone and 3- and 4-fluorobenzophenone is not clear to us. It might be that there is an interaction of the fluorine and the phenolate which reduces the nucleophilicity of the aromatic ring (Figure 3.9). However, computational studies will be needed to shed light on this problem.



Scheme 3.33: Prenylation reactions to form fluorinated prenylated benzophenones.

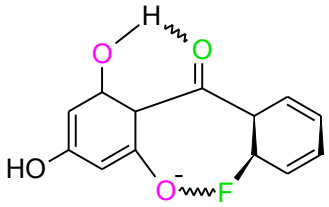


Figure 3.9: Intramolecular hydrogen bonding of 2-fluorobenzophenones (**3.61**).

Due to this hydrogen bonding, these *ortho* hydroxy groups contribute less of an inductive and mesomeric effect to the ring, which reduce the acidity of the hydroxy protons. Hence, DBU was no longer a strong enough base to abstract the hydroxy protons. However, the prenylation of 3-fluoro and 4-fluoro analogues was successful and NMR (Plate 11 and 12), IR and mass spectra confirmed the structures of the products.

3.4.8.3 Synthesis of diprenylated benzophenones (3.67, 3.68 and 3.69)

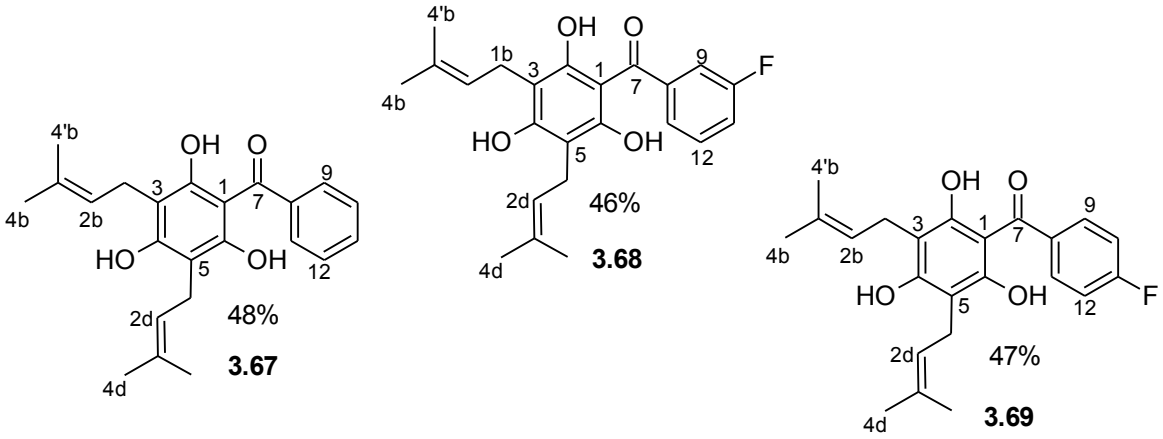


Figure 3.10: Chemical structures of diprenylated benzophenones (**3.67**, **3.68** and **3.69**).

Method B

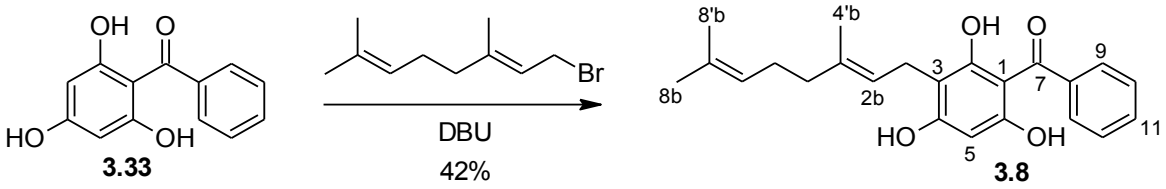
When the prenylation reaction was given more time in the presence of DBU (1.5 eq) and prenyl bromide (2.2 eq) (as in method A), diprenylation was observed. This reaction was run at 35 °C for 48 h for optimum yields (46-48%) (Figure 3.10). The rest of the reaction mixture consists of monoprenylated product and non-reacted starting material. The NMR and mass spectra results for these compounds were analysed to confirm their structure.

The ^{1}H NMR spectra of these compounds revealed the absence of C-3 and C-5, the aromatic protons of the hydroxy-substituted ring. The prenyl protons appeared upfield with

their integration double that of the monoprenylated compounds (**3.54**, **3.65** and **3.66**). The aromatic protons of the fluorine/ hydrogen-substituted ring were not disturbed and their resonances were similar to those of the monoprenylated benzophenones (**3.54**, **3.65** and **3.66**).

DEPT-135 spectra confirmed that C-3 and C-5 were quaternary carbon which proved that the aromatic protons were indeed substituted by the prenyl groups. HSQC and HMBC spectra showed that C-3 and C-5 had no protons bonded to them. The resonances of these carbons (C-3 and C-5) were shifted downfield from δ_C 96 to δ_C 106, showing the quaternary nature of these carbons. The carbonyl carbons, fluorine and hydroxy substituted carbons appeared downfield in the ^{13}C NMR spectra (Plates 13, 14 and 15).

3.4.8.4 Synthesis of phenyl[3-(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]methanone (3.8)



Scheme 3.34: Geranylation reactions to form geranylated benzophenones.

Method C

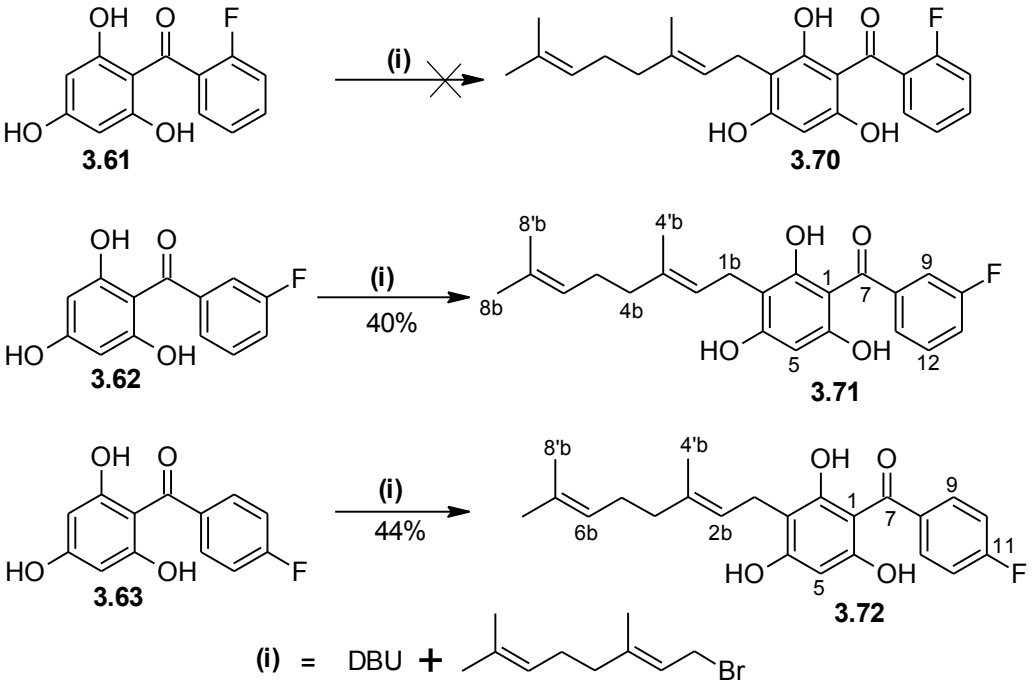
The reaction conditions in this method are the same as in method A but with geranyl bromide replacing prenyl bromide. This reaction was run at 35 °C for 24 h to give a yield of 40%-44% (Scheme 3.34). After purification, the product was obtained as an orange semi-solid.

The ^{1}H NMR spectrum of **3.8** showed the disappearance of one of the aromatic protons (H-3) of the geranylated ring leaving only one aromatic proton (H-5) on this ring. The appearance of the geranyl protons confirms the incorporation of geranyl. Geranyl protons including the terminal allylic protons (H-4'b, H-8b and H-8'b), non-terminal allylic protons (H-1b, H-4b and H-5b) and olefinic protons (H-2b and H-6b) are shown in the ^{1}H NMR spectrum (Plate 16). The DEPT-135, HSQC and HMBC spectra were used to assign the signals in the ^{13}C NMR spectrum.

The IR spectrum confirmed the existence of the carbonyl group as shown by a strong band at 1656 cm^{-1}, while an aromatic C-H stretch band at 3073 $cm^{-1}$and O-H stretch bands at 3533 cm^{-1} were apparent. The structure of **3.8** was also confirmed by HRMS which shows a good agreement between the calculated mass of 389.1729 ($C_{23}H_{26}O_4$ Na) and a pseudo-molecular ion peak at *m/z* 389.1721 $[M+Na]^+$.

3.4.8.5 Synthesis of fluorinated monogeranylated benzophenones (3.70, 3.71 and 3.72)

The geranylation of fluorinated benzophenones **3.62** and **3.63** was successful (Scheme 3.35). As was found with the prenylation reactions, the geranylation of the *O*-fluorinated benzophenone **3.61** was unsuccessful. The structures of the products of these reactions were confirmed by NMR, IR and mass spectrometry. ^{1}H NMR and ^{13}C NMR spectra revealed the presence of all components of each structure such as geranyl resonances and also for both aromatic rings (Plate 17 and 18). The IR spectra revealed the presence of the carbonyl groups (bands at 1662 cm^{-1} and 1657 cm^{-1}) for **3.71** and **3.72**, respectively.



Scheme 3.35: Geranylation of fluorinated benzophenones.

3.4.8.6 Synthesis of fluorinated digeranylated benzophenone (3.73 and 3.74)

Method D

The double geranylation reactions to yield **3.73** and **3.74** involved an adaptation of method B (Figure 3.11). These reactions were run for 48 h in THF in the presence of DBU (1.5 eq) and geranyl bromide (2.2 eq) which yielded the desired products. The NMR, IR and mass spectra were used to confirm the structures of the products. ^{1}H NMR spectra (Plate 19 and Plate 20) revealed the absence of the aromatic proton peaks (H-3 and H-5) of the hydroxy substituted aromatic ring which proved that the substitution took place in C-3 and C-5. The appearance of the geranyl protons resonating upfield confirmed the incorporation of the geranyl group. ^{13}C NMR spectra revealed the presence of the geranyl carbons, carbonyl carbon and aromatic carbons peaks, confirming the structures.

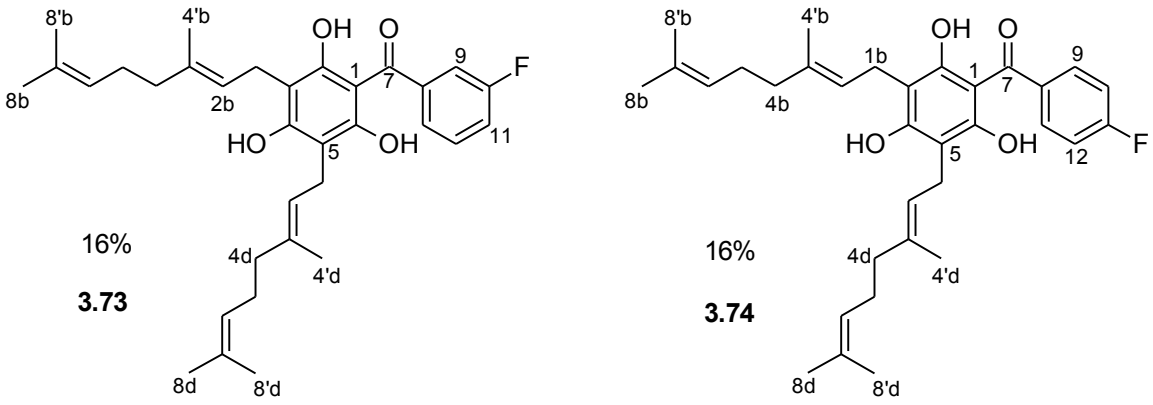


Figure 3.11: Chemical structure of digeranylated benzophenones (**3.73** and **3.74**).

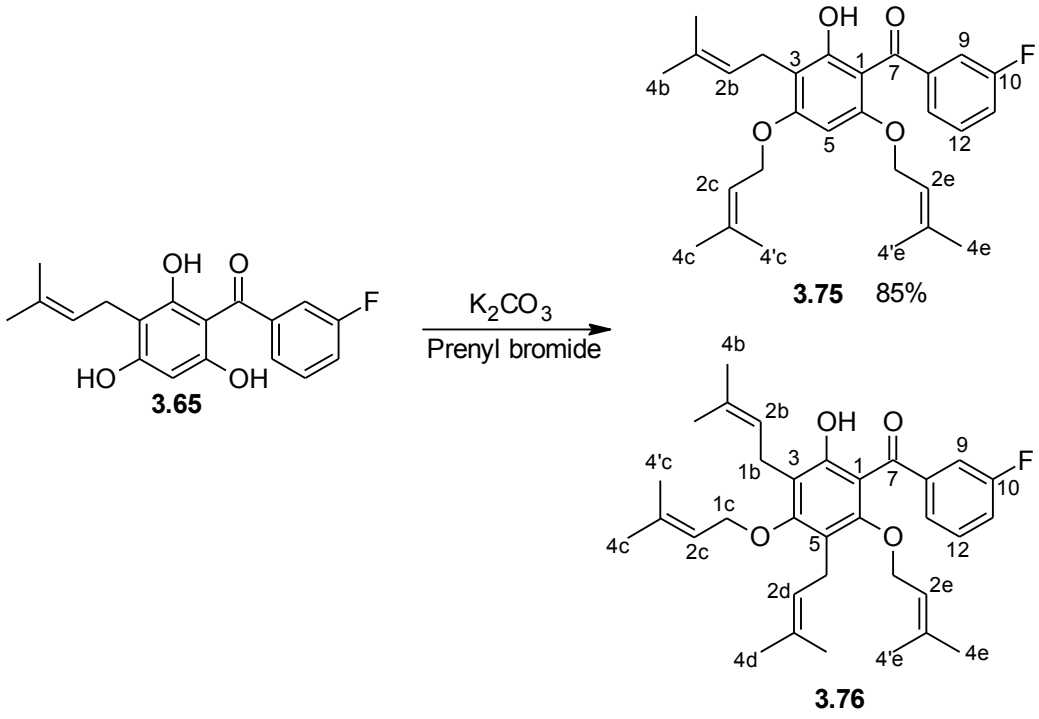
The results above show that DBU is a good base to be used for *C*-prenylation and *C*-geranylation reactions of trihydroxybenzophenones. DBU can selectively monoprenylate or diprenylate benzophenones depending on the reaction time (diprenylation reactions need longer reaction time). According to the results, the monoprenylation is favored with more than 60% yields whereas, for diprenylation, the yield is less than 48%.

3.4.9 O-prenylation reactions

3.4.9.1 O-prenylation of C-prenylated benzophenones

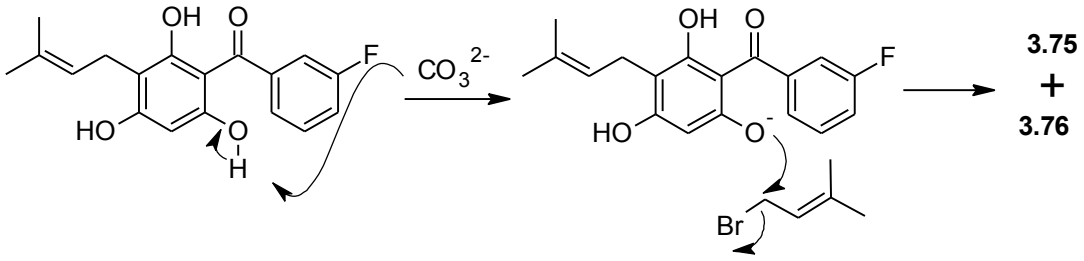
Method E

The observations on the DBU-mediated reactions showed that the use of DBU restricts the prenylation to *C*-prenylation only. A harder base (K_2CO_3) was used to obtain *O*-prenylated benzophenones.[136,144] These reactions were performed under reflux in acetone in the presence of the K_2CO_3 (4 eq) and prenyl bromide (3 eq) for 5 h (Scheme 3.36). Two products, (3-fluorophenyl)[2-hydroxy-3-(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (**3.75**) and (3-fluorophenyl)[2-hydroxy-3,5-bis(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (**3.76**), were obtained in this reaction and their NMR spectra are shown on Plate 21 and Plate 22, respectively. Compound **3.75** was the major product of this reaction and was obtained in 85% yield (relative yield) whereas **3.76** was formed in 15% yield. When this reaction was run in other solvents such as THF and DMF, the yield was not good (less than 58% for **3.75**).



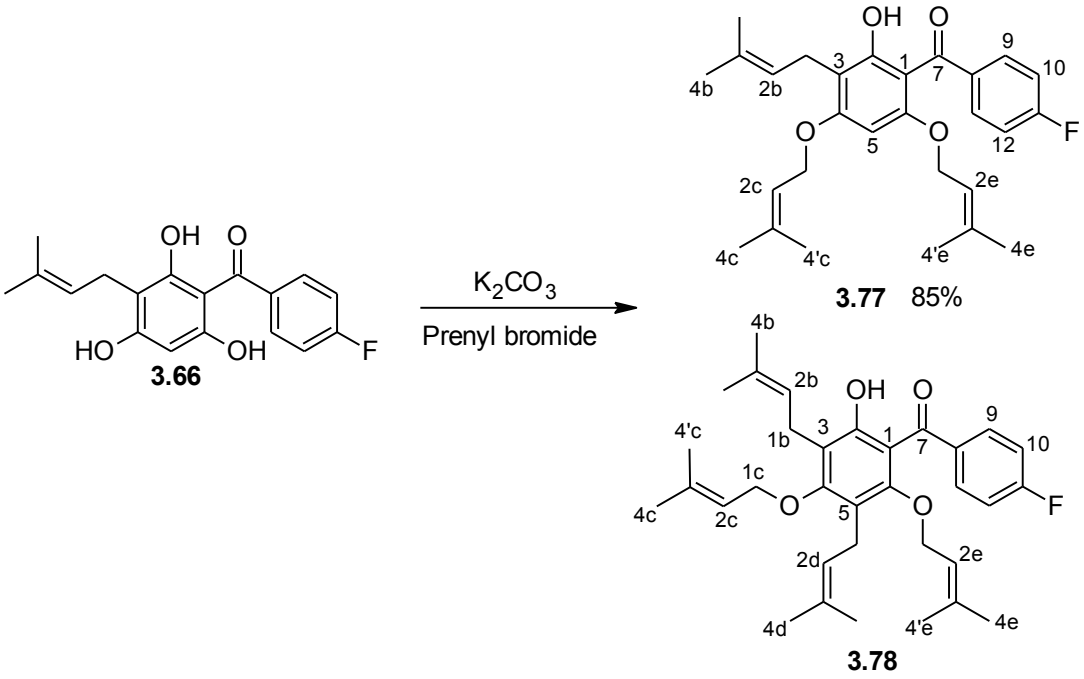
Scheme 3.36: *O*-prenylation of monoprenylated 3-fluorobenzophenone.

The base abstracts the hydroxy proton of the prenylated benzophenone to form a phenolate ion intermediate as shown in Scheme 3.37. This then acts as a nucleophile substituting the bromine in prenyl bromide resulting in the formation of **3.75** and **3.76**.



Scheme 3.37: Proposed mechanism for *O*-prenylation of monoprenylated benzophenone.

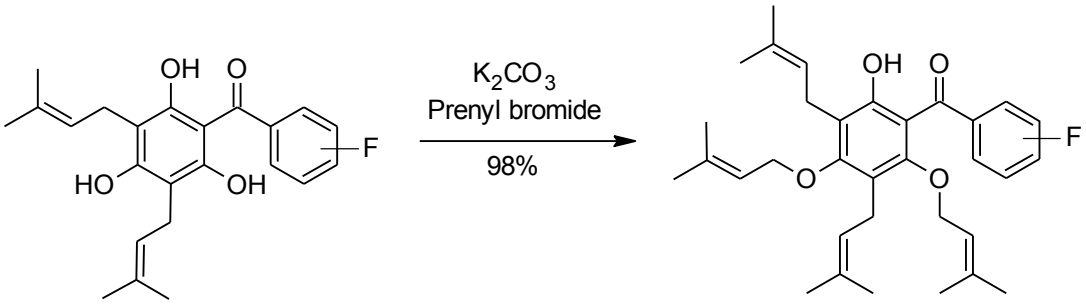
After the *O*-prenylation reaction was optimized, it was applied to a *para*-fluorinated benzophenone. Two products **3.77** and **3.78** were formed in this reaction (Scheme 3.38). The NMR spectra for compound **3.77** and **3.78** are shown on Plate 25 and Plate 26, respectively. The IR and mass data were also in agreement with the assigned structures.



Scheme 3.38: *O*-Prenylation of 4-fluorinated monoprenylated benzophenone.

Method F

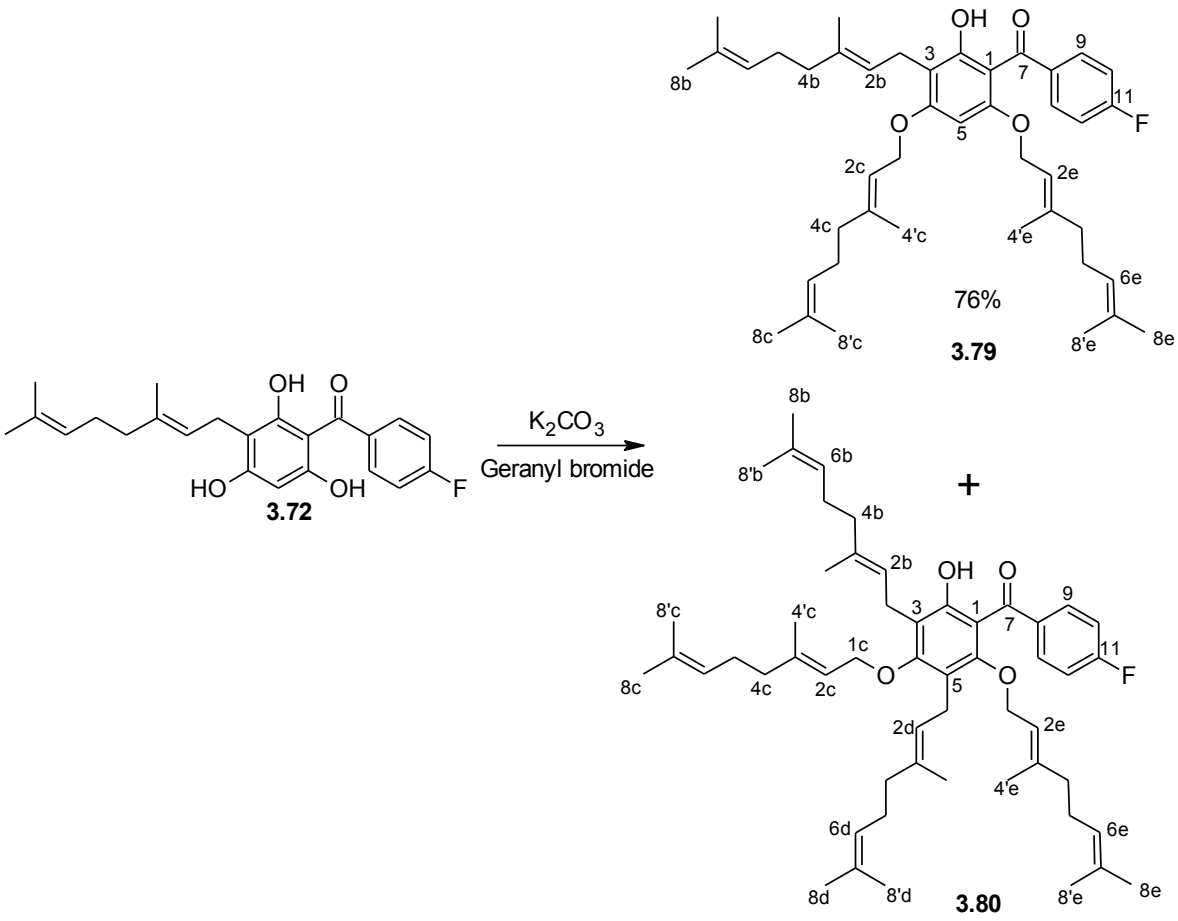
The yield of **3.76** and **3.78** could be improved by subjecting biprenylated benzophenones (**3.68** and **3.69**) to the *O*-prenylation reaction (Scheme 3.39). This reaction was run in the presence of the base (K_2CO_3, 2.2 eq) and prenyl bromide (2.1 eq) in refluxing acetone for 2 hours to give a quantitative conversion. This method was the best route to synthesize this kind of polyprenylated benzophenone. NMR, IR and MS were used to confirm the structures of **3.76** and **3.78**. This alkylation reaction (method F) was also applied to bigeranylated benzophenone **3.74** which afforded polygeranylated benzophenone **3.80**.



Scheme 3.39: *O*-prenylation of fluorinated diprenylated-benzophenone.

3.4.9.2 O-geranylation of C-geranylated benzophenones

The *O*-alkylation reaction was not only restricted to prenyl groups but was extended to geranyl groups.[145,146] Method E was adapted to synthesize multi-geranylated benzophenone (4-fluorophenyl)[2-hydroxy-3-(3,7-dimethylocta-2,6-dienyl)-4,6-bis(3,7-dimethylocta-2,6-dienyloxy)phenyl]methanone (**3.79**) and (4-fluorophenyl)[2-hydroxy-3,5-bis(3,7-dimethylocta-2,6-dienyl)-4,6-bis(3,7-dimethylocta-2,6-dienyloxy)phenyl] methanone (**3.80**) as shown in Scheme 3.40. The ratio of products **3.79** : **3.80** was found to be 6 : 1. NMR, IR and MS analysis confirmed the structures of these compounds. The NMR spectra for **3.79** and **3.80** are shown on Plate 29 and Plate 30, respectively.

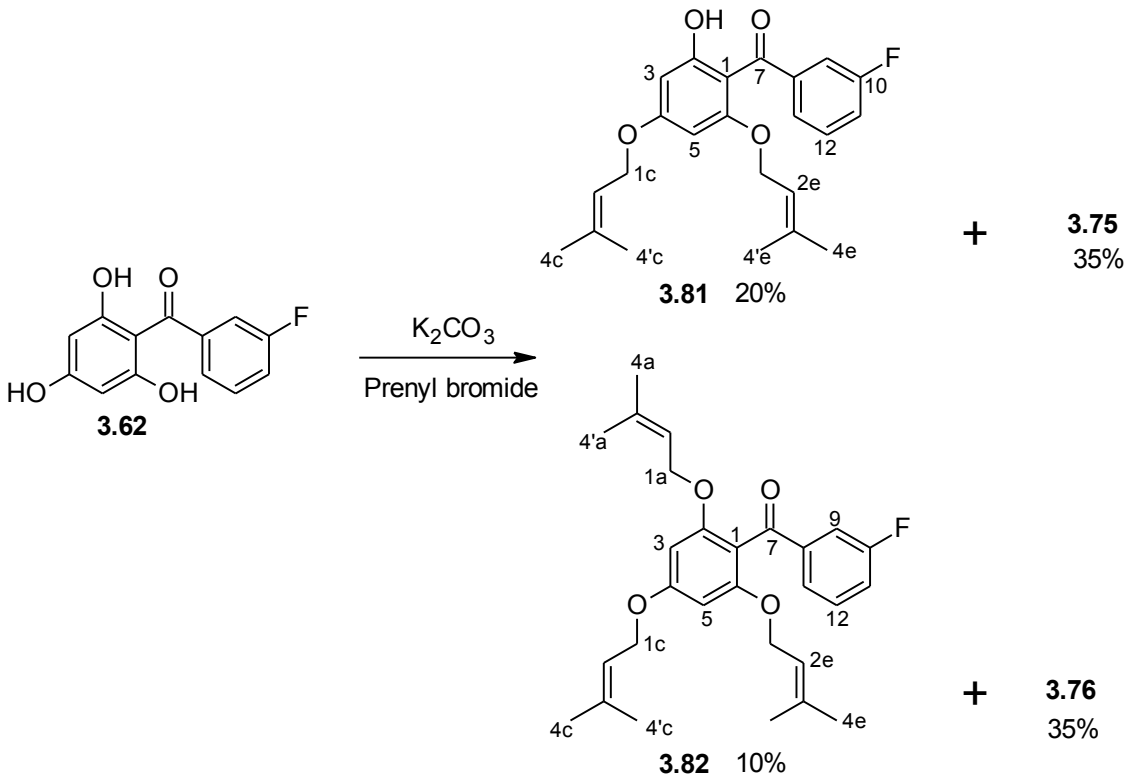


Scheme 3.40: *O*-geranylation of monogeranylated 4-fluorobenzophenone.

3.4.9.3 Polyprenylation of benzophenones

Method G

The prenylation reaction was also applied to non-prenylated benzophenones to explore the mechanism of the carbonate base in these kinds of reactions. When (3-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone was subjected to this type of prenylation reaction, four prenylated benzophenones were isolated. A mixture of (3-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (**3.62**) and prenyl bromide (4 eq) was refluxed in acetone in the presence of K_2CO_3 (4 eq) for 6 hours. After purification, it was found that two of these products (**3.75** and **3.76**) had already been synthesized by method E and method F. The other two products were the *O*-prenylated benzophenones, (3-fluorophenyl)[2-hydroxy-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (**3.81**) and (3-fluorophenyl)[2,4,6-tris(3-methylbut-2-enyloxy)phenyl]methanone (**3.82**) as shown in Scheme 3.41.



Scheme 3.41: Prenylation of *meta*-fluorinated benzophenone.

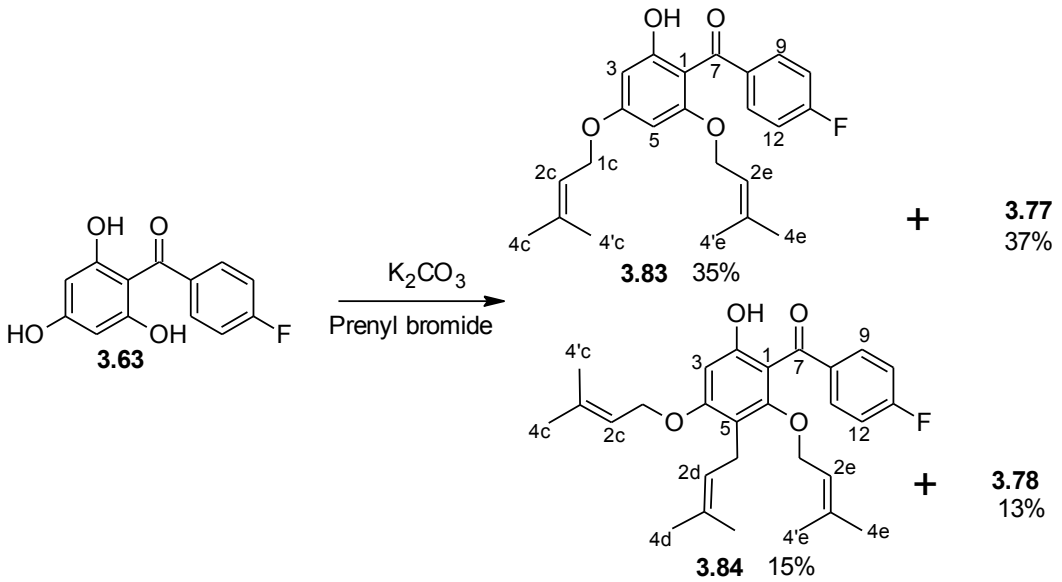
The results showed that every proton of the hydroxy-substituted ring of benzophenone can be substituted by prenyl in the presence of K_2CO_3. This reaction favoured **3.75** and **3.76** as each of them was produced in 35% yield, whereas the yields of **3.81** and **3.82** were only 20% and 10%, respectively. The yield of **3.82** was the smallest as was expected, because of the hydrogen bonding that exists between the *ortho*-hydroxy hydrogen and the carbonyl oxygen as explained in Section 3.4.8.2, and hence, this hydroxy is less reactive.

The ^{1}H NMR spectrum of **3.81** showed two sets of non-equivalent prenyl protons, for example, the allylic protons H-1c resonate at δ_H 4.58 and H-1e resonates at δ_H 4.20. The 2-OH peak appeared downfield at δ_H 12.37. The aromatic protons of the hydroxy substituted ring, H-3 and H-5, are no longer in the same environment and resonate as doublets at δ_H 5.94 and δ_H 6.17, respectively. With the help of COSY, DEPT-135, HSQC and HMBC NMR spectra, the carbon signals in ^{13}C NMR spectrum were assigned (Plate 23). The related compound (**3.83**) was synthesized from the *para*-fluorinated benzophenone as shown in Scheme 3.42. The NMR spectrum of **3.83** is shown in Plate 27.

No hydroxy peaks were observed in the ^{1}H NMR spectrum of **3.82** (Plate 24). Also, in the ^{1}H NMR spectrum, three prenyl groups were observed, two of which are in the same

environment. For example, the olefinic protons of the prenyl groups, H-2a resonates at δ_H 5.20 and integrates for 2H whereas H-2c resonates at δ_H 5.53 and integrates for 1H. The appearance of an aromatic peak in the ^{1}H NMR spectrum which integrates for two protons showed that only *O*-prenylation occurred.

When these reaction conditions (method G) were applied to the *para*-fluorinated benzophenone (**3.63**), the products **3.77**, **3.78**, **3.83** and **3.84** were produced in relative yields of 37%, 13%, 35% and 15%, respectively.



Scheme 3.42: Prenylation of *para*-fluorinated benzophenone.

The ^{1}H NMR spectrum of **3.84** was found to be similar to that of **3.77** since they both are triprenylated, two *O*-prenylation on the same position (4-**O** and 6-**O**) for both and one *C*-prenylation on different positions (C-3 for **3.77** and C-5 for **3.84**). The structure of **3.77** was also confirmed by X-ray crystallography (Figure 3.12) which confirms the positions of the prenyl groups. An aromatic proton of the hydroxy substituted ring of **3.84** (H-3) appeared as a singlet at δ_H 6.38 as opposed to H-5 of **3.77** which resonate at δ_H 5.95. The protons of the *C*-substituted prenyl of **3.84** were found to be more deshielded than those of **3.77**, for example the allylic protons of **3.84** (H-1b) resonate at δ_H 4.01 while those of **3.77** (H-1d) resonate at δ_H 3.33, H-2b resonate at δ_H 5.33, while H-2d resonate at δ_H 5.26.

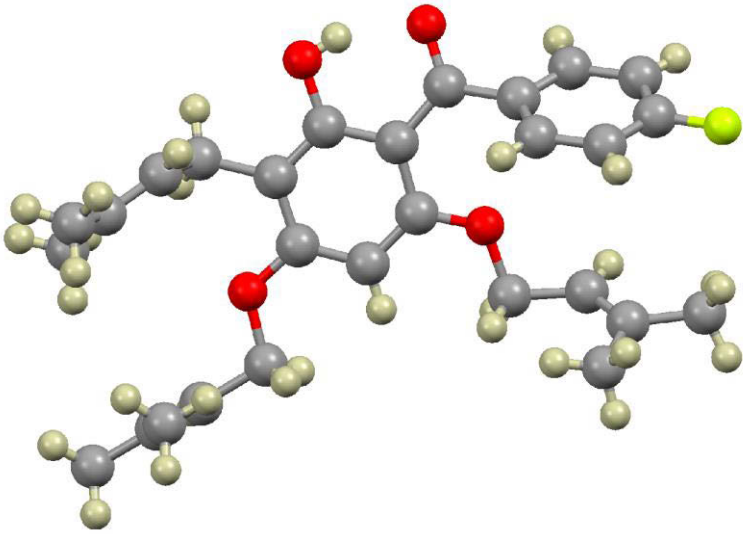
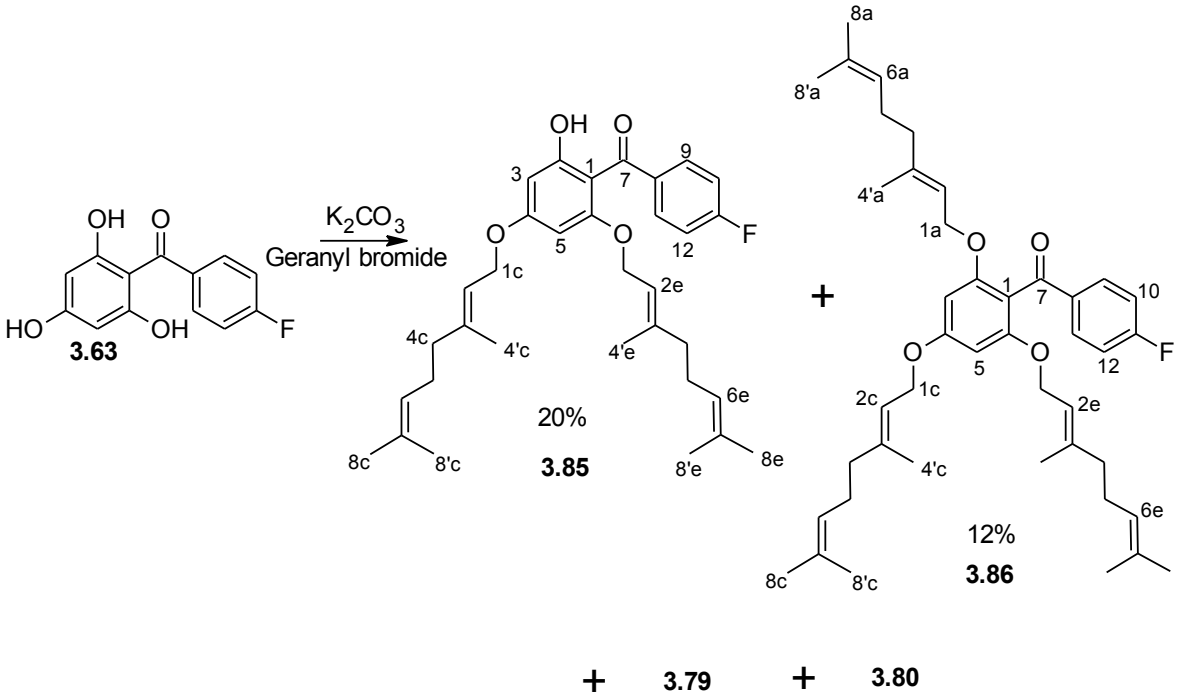


Figure 3.12: Crystal structure of (4-fluorophenyl)[2-hydroxy-3-(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (**3.77**)

3.4.9.4 Polygeranylation of benzophenones

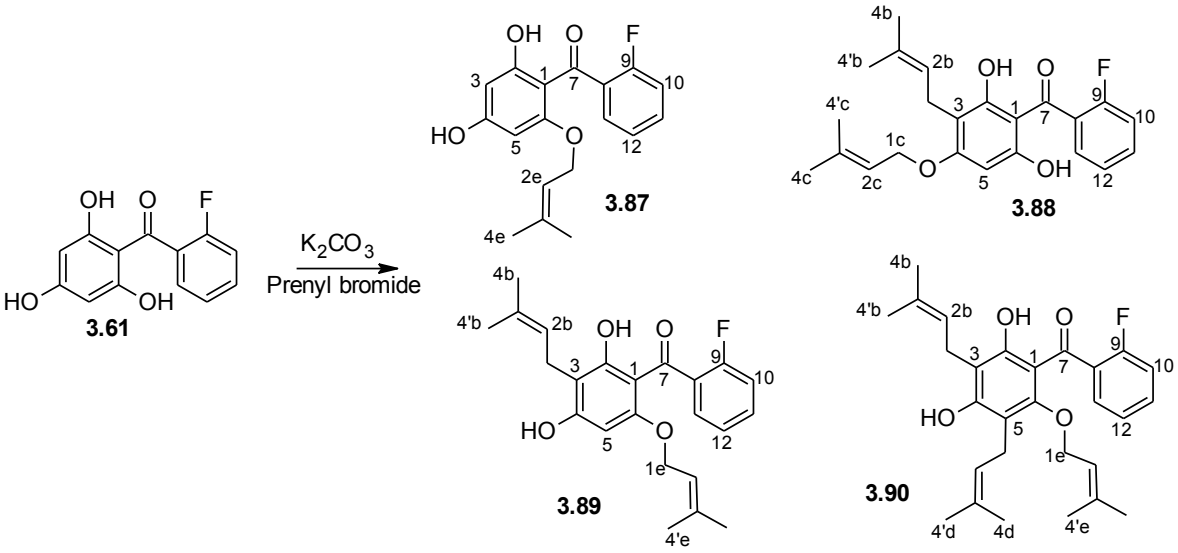
The alkylation reaction of *para*-fluorinated benzophenone (as per method G) was repeated but with geranyl bromide instead of prenyl bromide. This reaction afforded both *O*-geranylated benzophenones (**3.85** and **3.86**) and benzophenones with a combined *O* and *C*-geranyl groups (**3.79** and **3.80**). NMR, IR and MS were used to confirm the structures of these compounds.



Scheme 3.43: Geranylation of *para*-fluorinated benzophenone.

3.4.9.5 Prenylation of (2-fluorophenyl)(2,4,6-trihydroxyphenyl) methanone

As it was explained in Section 3.4.8.2 and Figure 3.9, (2-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (**3.61**) could not be *C*-prenylated with DBU as a base, unlike the other benzophenones. The use of K_2CO_3 as base as in method G as shown in Scheme 3.44 was attempted. After the reaction was completed, four new spots were observed by TLC. The mixture was separated by chromatography and the compounds analyzed by NMR, IR and mass spectrometry. The NMR spectra of these spots (**3.87**, **3.88**, **3.89** and **3.90**) clearly showed that the prenyl group was indeed incorporated in the benzophenone structure.



Scheme 3.44: Prenylation of (2-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone.

The products obtained in this reaction were different from those obtained from the 3-fluoro and 4-fluorobenzophenones. The ^{1}H NMR spectrum of (2-fluorophenyl)[2,4-dihydroxy-6-(3-methylbut-2-enyloxy)phenyl]methanone (**3.87**) revealed that only one prenyl group was incorporated and that was through the *ortho*-oxygen atom. The aromatic protons H-3 and H-5 appeared as doublets at δ_H 6.37 at δ_H 6.45, respectively. The ^{13}C NMR spectrum of **3.87** revealed that C-3 resonates at δ_C 97.6 and C-5 at δ_C 93.4, while the hydroxy-substituted carbons C-2 and C-4 resonate at δ_C 163.5 and at δ_C 157.7, respectively (Plate 33).

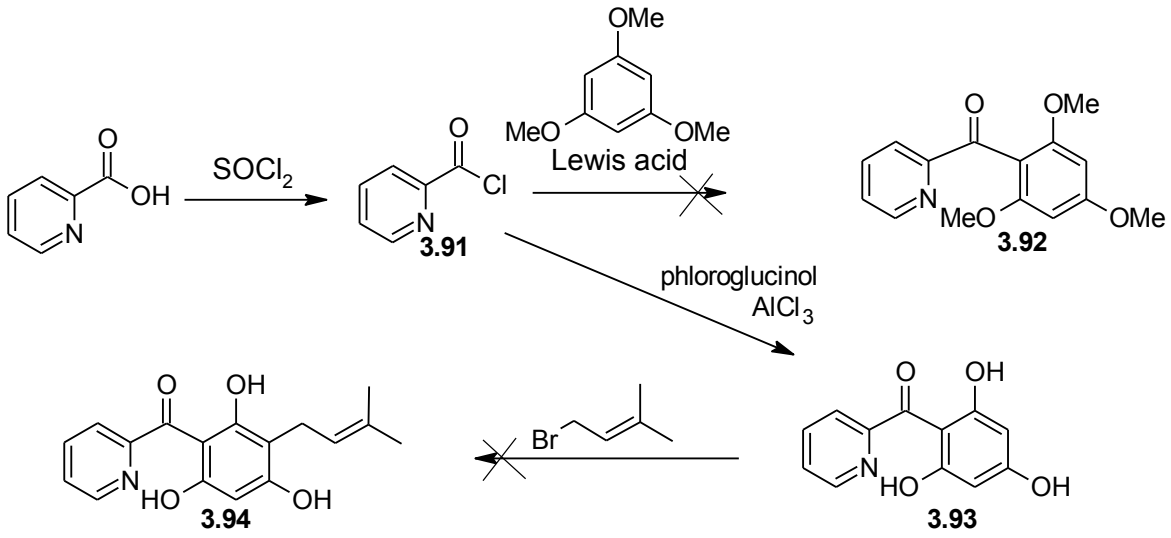
The diprenylated benzophenones (2-fluorophenyl)[2,6-dihydroxy-3-(3-methylbut-2-enyl)-4-(3-methylbut-2-enyloxy)phenyl]methanone (**3.88**) and (2-fluorophenyl)[2,6-dihydroxy-5-(3-methylbut-2-enyl)-4-(3-methylbut-2-enyloxy)phenyl]methanone (**3.89**) were also produced in this reaction. The elucidation of the structures of these compounds was not so easy, as they appeared similar in most analytical aspects such mass, IR and UV spectra. Their molecular formulae are the same, which made it impossible to differentiate them using mass spectrometry. Their NMR spectra showed the same number of protons and carbons but fortunately, the chemical shifts of some protons and carbons were different, and this difference was used to elucidate their structure. The ^{1}H NMR spectra of these compounds revealed that the aromatic protons (H-3 of **3.89** and H-5 of **3.88**) were not

resonating in the same region, H-3 is relatively more shielded than H-5 as they resonate at δ_H 6.40 and δ_H 6.45, respectively.

K_2CO_3 was used to achieve the *O*-prenylation of the benzophenones, but prenylation with this base was found to be nonselective as it also does the *C*-prenylation. Protection of some acidic protons in the structure is necessary when using K_2CO_3 in order to maximize the yield of the desired product.

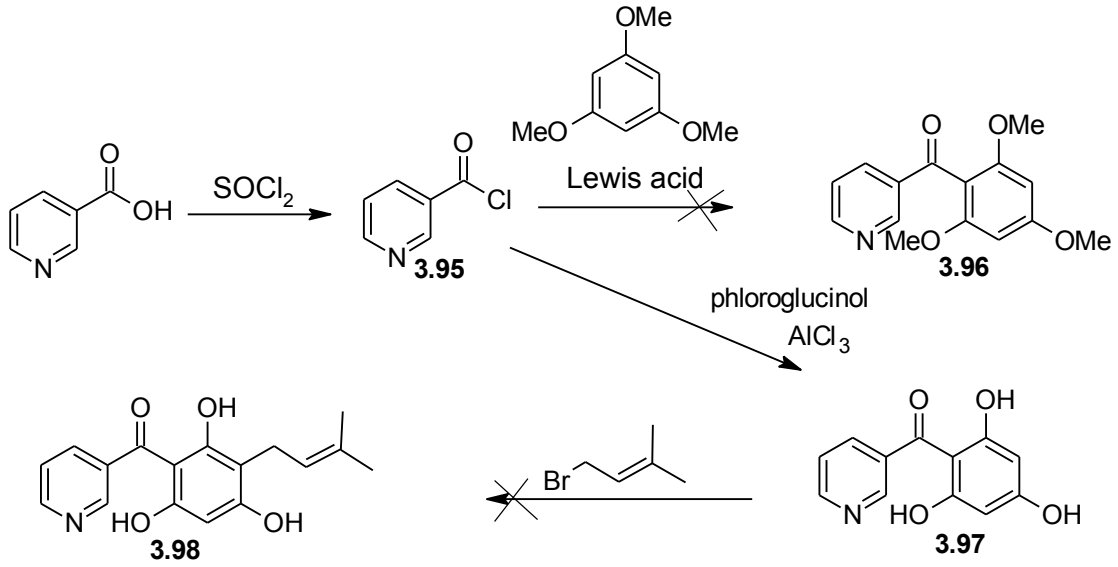
3.4.10 Attempted synthesis of prenylated pyridinoyl phloroglucinol

Having successfully synthesized prenylated benzophenones, we decided to explore nitrogen-containing analogues such as prenylated pyridinoyl phloroglucinol. The aim of this reaction was also to confirm the impact of hydrogen bonding on the prenylation step of this synthesis as shown below. The *ortho* and *meta N*-substituted pyridinoyl substituents were selected for this reaction.[147] Due to the cost of pyridinoyl chloride, picolinoyl chloride (**3.91**) and nicotinoyl chloride (**3.95**) were synthesized from the corresponding carboxylic acids by treatment with thionyl chloride ($SOCl_2$) as shown in Schemes 3.45 and 3.46.[148,149] The acyl chloride is more reactive than the corresponding carboxylic acid in the following Friedel-Crafts reaction.



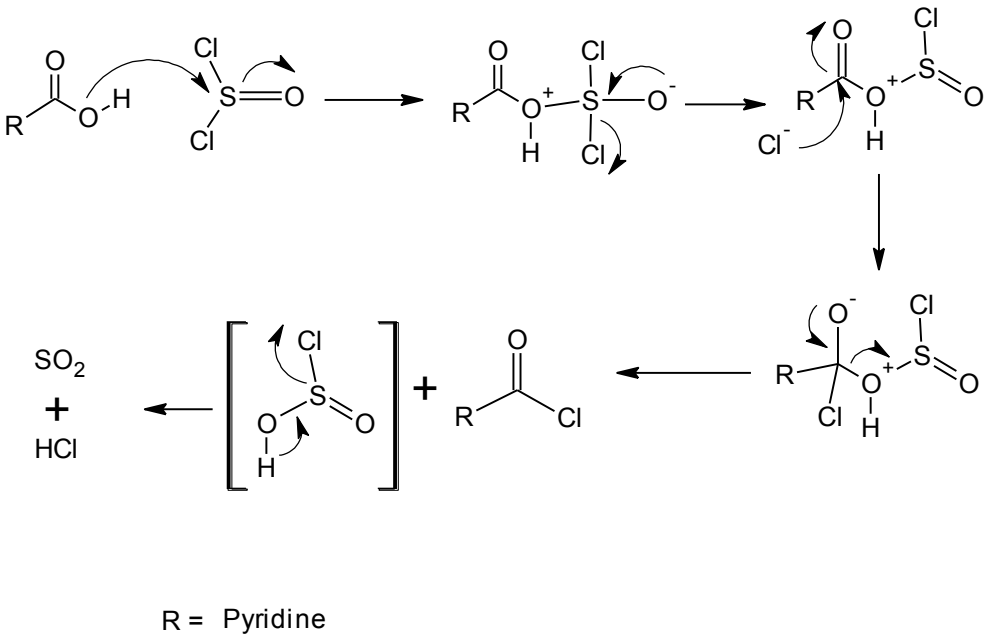
Scheme 3.45: Attempted synthesis of (pyridine-2-yl)[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (**3.94**).

The first step of this reaction was the formation of the acyl chloride. The lone pair of electrons of oxygen attacks the thionyl group of $SOCl_2$ to form a protonated acyl chlorosulfite intermediate as shown in Scheme 3.47. This highly unstable intermediate releases acyl chloride (product) with SO_2 and HCl as by-products. The acyl chloride was purified by distillation and used immediately for the following step of the reaction as it is moisture sensitive.



Scheme 3.46: Attempted synthesis of (pyridine-3-yl)[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (**3.98**).

The second step of this reaction involves the Friedel-Crafts acylation reaction as described in the previous Sections. This reaction was first tried with 1,3,5-trimethoxybenzene but the reaction was unsuccessful. When tried with phloroglucinol in the presence of $AlCl_3$, the pyridinoyl phloroglucinols, **3.93** and **3.97** were obtained. Surprisingly, the yield of **3.97** was one third that of **3.93** and this can be explained in terms of the reactivity of pyridinoyl chloride (see below).



Scheme 3.47: Mechanism for the preparation of acyl chloride.

The last step of this synthesis involved prenylation. (Pyridin-3-yl)(2,4,6-trihydroxyphenyl)methanone (**3.93**) was subjected to the reaction in the presence of DBU, but this reaction was unsuccessful. This compound forms an intramolecular hydrogen bond between the *ortho* hydroxy proton and carbonyl oxygen which is enhanced by the inductive effect caused by the nitrogen (Figure 3.13). This results in the reduction of the acidity of the hydroxy protons, so the protons cannot be easily abstracted by the base (DBU).

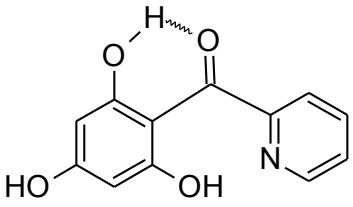


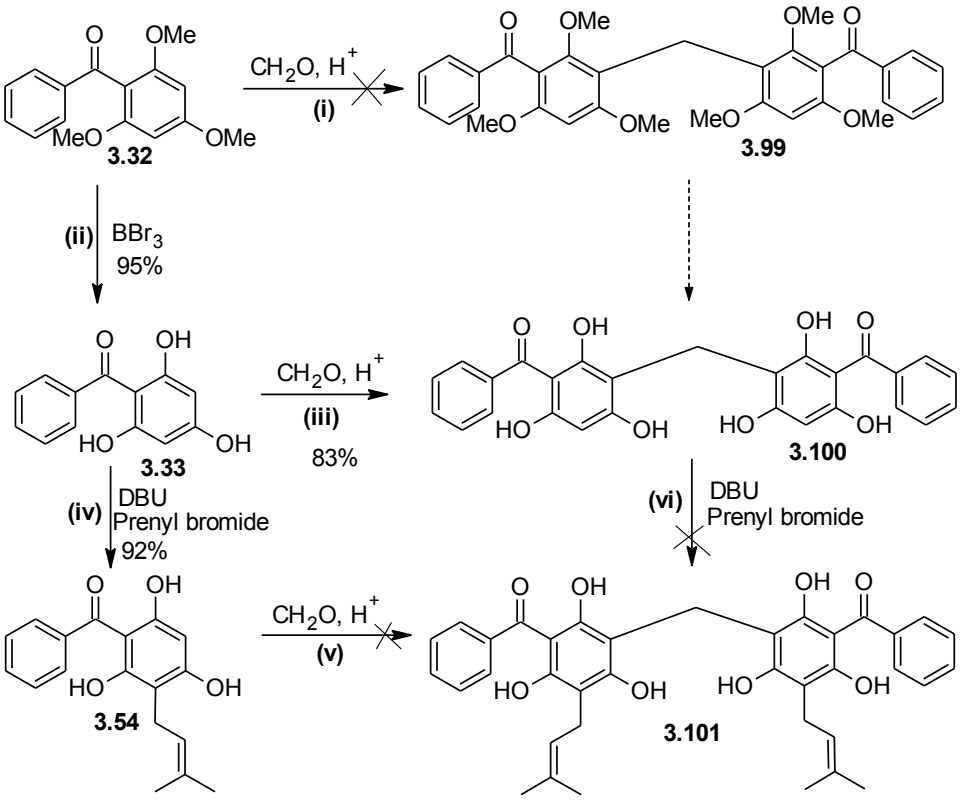
Figure 3.13: Intramolecular hydrogen bonding of 2-pyridinoyl phloroglucinol (**3.93**).

$AlCl_3$ was not good enough to activate nicotinoyl chloride (**3.95**) in the acylation reaction and as a result, nicotinoyl phloroglucinol (**3.97**) was produced in very low yield. In future, one might need to alter the reaction conditions to improve the yields of **3.97** as well as **3.93**. One would also need to use K_2CO_3 or other stronger bases instead of DBU for the

prenylation of **3.93** to overcome the intramolecular hydrogen bonding that exist in the structure of **3.93** as shown in Figure 3.13.

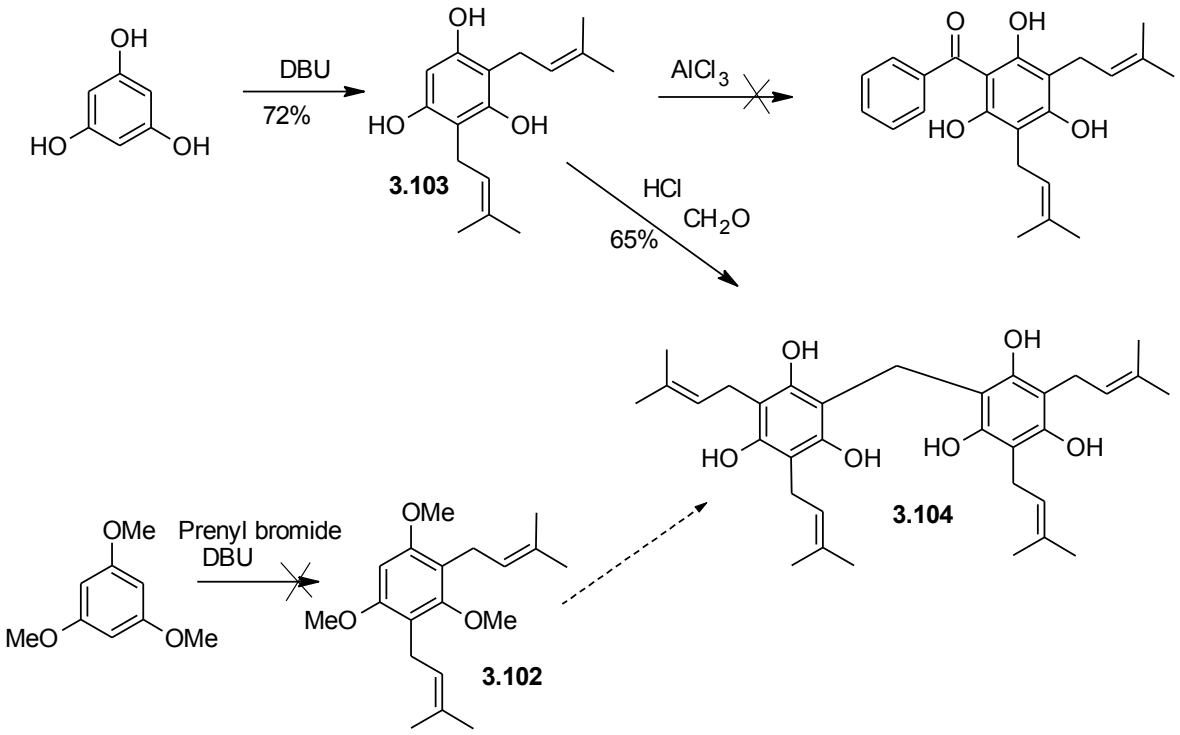
3.4.11 Synthesis of dimeric prenylated compounds

Dimeric phloroglucinols are reported to have interesting biological activities such as anticancer,[150] anti-HIV,[151, 152] antiproliferative and antiplasmodial[153] activity. We then attempted to synthesize this type of compounds. The prenylated benzophenone **3.54** was reacted with paraformaldehyde in the presence of a range of catalysts such as HCl, p-TsCl, $POCl_3$ and toluic acid in various solvents, aiming to form dimeric prenylated-benzophenone **3.101** as shown in Scheme 3.48, but the reaction was unsuccessful. Failing with this route, the same reaction was tried with trimethoxybenzophenone (**3.32**) under the same conditions but it was also unsuccessful. Reaction with the trihydroxybenzophenone **3.33** gave a good yield of 95%. The next step was to prenylate this dimeric benzophenone (**3.100**) under the previously-used conditions (DBU in THF), but the reaction failed. This reaction was reported to work at 750 W microwave power, but we did not have this facility.[150]



Scheme 3.48: Attempted synthesis of dimeric prenylated benzophenone (**3.101**).

This synthesis was also attempted with the system that did not have an electron-withdrawing group on the phloroglucinol ring. As a result, dimeric prenylated phloroglucinol **3.104** was targeted to explore the impact of the electron-withdrawing group on the system (Scheme 3.49).



Scheme 3.49: Synthesis of dimeric prenylated-phloroglucinol (**3.104**).

In the first attempt, the prenylation of 1,3,5-trimethoxybenzene using DBU as base did not give a product (Scheme 3.49). When the same reaction was applied to phloroglucinol, it was successful and a good yield (72%) of biprenylated trihydroxybenzene (**3.103**) was obtained. Two equivalents of compound **3.103** was reacted with 1 equivalent of paraformaldehyde in the presence of acid catalyst. After running this reaction for 10 min under 100 W power in a microwave, a new spot was observed on the TLC which was the desired product (**3.104**). The success of this reaction (formation of **3.104**) clearly shows that the presence of the electron-withdrawing group in the trihydroxybenzene ring does reduce the nucleophilicity of the ring. As a result, the formation of **3.101** needed a microwave of more than 750 W as oppose to the formation of **3.104** which required only 100 W power.

3.5 Activity of benzophenones

Benzophenones (**3.75**, **3.77**, **3.81**, **3.83**, **3.87**, **3.88**, **3.89** and **3.90**) were subjected to an *in vitro* cell-base HIV assay in the MINTEK laboratories at a concentration of 10 $\mu g.mL^{-1}$, but none of these showed any activity. The concentration of 10 $\mu g.mL^{-1}$ is a vigorous level to consider for activity, but activity at this level is needed for drug discovery. Many of the compounds reported in the literature to have anti-HIV activity have IC_{50} at much higher concentrations. Antimicrobial and cytotoxic activities of cell lines are currently under investigation.

3.6 Conclusion

One of the aims of this project was to synthesize fluorine-containing prenylated benzophenones. Friedel-Crafts acylation and electrophilic aromatic substitution reactions were the key reactions of this synthesis to achieve these fluorinated prenylated benzophenones. Friedel-Crafts acylation reactions were conducted under $AlCl_3$-mediated conditions to form a benzophenone scaffold (trihydroxybenzophenones) which were then prenylated *via* carbon or oxygen at the last step of the reaction using DBU and K_2CO_3.

3.7 Experimental Procedure

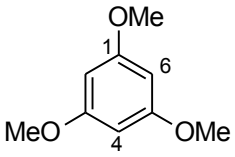
3.7.1 General Experimental Procedure

Unless otherwise stated, all reagents (including solvents) were purchased from the chemical suppliers Aldrich, Fluka and Merck (the chemical suppliers). For all moisture-sensitive reactions, the glassware was thoroughly dried in an oven at ca. 140 °C for 12 h prior to use, and anhydrous solvents were used under inert conditions. Qualitative thin-layer chromatography (TLC) was used to monitor reactions and to determine the purity of compounds. TLC plates (Merck Kieselgel 60_{254} aluminum backed) were bought ready for use. Visualization of the TLC plates was achieved using an iodine tank and/or fluorescence on exposure to short wavelength ultraviolet light (254 nm). For purification, centrifugal chromatography was conducted on a Harrison Research Chromatotron model 7924T on glass plates coated with Merck silica gel (particle size 0.040 - 0.063 mm), 1 - 4 mm thick. Column chromatography was conducted using Merck Kieselgel 60 (230-400 mesh). Preparative scale TLC plates were prepared using Merck Kieselgel 60_{254} which was coated

onto 20 x 20 cm glass plates. Silica gel (200 g) was homogeneously suspended in 500 mL of water to make up two TLC plates with thickness of 2 mm (silica gel). These plates were kept in a draft-free area overnight at room temperature and were subsequently activated overnight at 120 ºC.

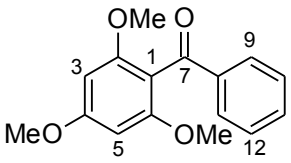
Melting points (Mp) were determined using a Stuart melting point apparatus with open-ended capillary tubes and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz UltraShield spectrometer at frequencies of 399.995 MHz and 100.4296 MHz for proton (^{1}H) and carbon (^{13}C), respectively. Chemical shifts (δ) are reported in parts per millions (ppm) and coupling constants (*J* values) were measured in hertz (Hz). In all spectra, the residual proton solvent resonance was used as an internal reference. The spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), dt (doublet of triplets), t (triplet), td (triplets of doublet) q (quartet), br (broad), or m (multiplet). Infrared (IR) spectra were recorded on a Perkin Elmer spectrometer (FTIR Spectrum 100) as neat solid or liquid samples (the samples were put on the IR machine lens). High-resolution mass spectrometry (HRMS) was performed on a Waters LCT Premier time-of-flight mass spectrometer.

3.7.2 Synthesis of 1,3,5-trimethoxybenzene



A mixture of phloroglucinol (1.0 g, 7.93 mmol), iodomethane (5.0g, 35.2 mmol), and anhydrous K_2CO_3 (4.9 g, 35.2 mmol) in acetone (70 mL) was refluxed for 6 h. The resulting mixture was cooled to room temperature and filtered through celite. The solvent was removed *in vacuo*. The crude mixture was purified by silica gel column chromatography with 10%, 30% and 50% EtOAc in hexanes as eluent. The solvent was removed under reduced pressure to yield a colourless solid (1.36 g, 7.93 mmol, 100%). After recrystallization (Hexanes-EtOAc, 1:1), 1,3,5-trimethoxybenzene was obtained as colourless crystals, mp 53-54 ºC, TLC R_f 0.16 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 3.75 (9H, s, 1,3,5-OCH_3), 6.08 (3H, s, H-2,4,6). ^{13}C NMR (100 MHz, $CDCl_3$) 55.4 (1,3,5-OCH_3), 93.1 (C-2,4,6), 161.7 (C-1,3,5).

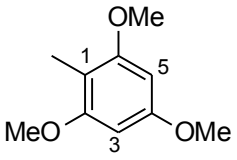
3.7.3 Synthesis of phenyl(2,4,6-trimethoxyphenyl)methanone (3.32)



3.32

Benzoyl chloride (0.190 g, 0.2 mL, 1.35 mmol) was added dropwise to an ice-cooled stirred mixture of $AlCl_3$ (0.180 g, 1.35 mmol) in DCM (20 mL). After being stirred at 0 ºC for 1 h, the reaction mixture was added slowly to a solution of 1,3,5-trimethoxybenzene (0.227 g, 1.35 mmol) in DCM (15 mL) at 0 ºC. The reaction mixture was allowed to reach room temperature and stirred for a further 12 h. An ice-cooled 6 M HCl (20 mL) was poured slowly into the reaction mixture and DCM (20 mL) was also added into the mixture. The organic layer was separated and washed with saturated $NaHCO_3$ solution (15 mL), water (20 mL) and brine (15 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The resulting product was purified by silica gel column chromatography (hexanes-EtOAc, 7:3) to give **3.32** as a white solid (0.331 g, 1.21 mmol, 90%). After recrystallization (Hexanes-EtOAc, 1:9), **3.32** was obtained as colourless crystals, mp 113-115 ºC (lit.[127] 113-114 °C), TLC R_f 0.15 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 3.66 (6H, s, 2,6-OCH_3), 3.84 (3H, s, 4-OCH_3), 6.16 (2H, s, H-3,5), 7.39 (2H, t, *J*= 7.9 Hz, H-10,12), 7.50 (1H, tt, *J* = 7.9, 1.3 Hz, H-11), 7.82 (2H, dd, *J* = 7.9, 1.3 Hz, H-9,13). ^{13}C NMR (100 MHz, $CDCl_3$) 55.7 (4-OCH_3), 56.1 (2,6-OCH_3), 91.0 (C-3,5), 111.3 (C-1), 128.5 (C-10,12), 129.6 (C-9,13), 133.1 (C-11), 138.5 (C-8), 159.0 (C-2,6), 162.7 (C-4), 195.2 (C-7). [Plate 1]. HRMS (ESI^+): Found $[M+Na]^+$ 295.0945, Calc. for $C_{16}H_{16}NaO_4$ 295.0946. IR (neat) ν_{max} (cm^{-1}) 3053, 2949, 1660, 1599, 1583, 1453, 1123.

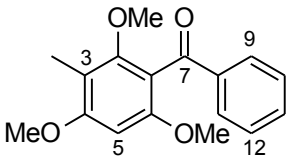
3.7.4 Synthesis of 1,3,5-trimethoxy-2-methylbenzene (3.56)



A mixture of phloroglucinol (1.0 g, 7.93 mmol), iodomethane (5.5 mL, 35.2 mmol), and anhydrous K_2CO_3 (12 g, 35.2 mmol) in acetone (70 mL) was refluxed for 12 h. The resulting mixture was cooled to room temperature, and filtered through celite. The solvent

was removed *in vacuo*. The crude product was purified by silica gel column chromatography with 30% EtOAc in hexanes as eluent. The solvent was removed under reduced pressure to yield **3.56** as a colourless amorphous solid (0.9 g, 4.84 mmol, 61%), TLC R_f 0.17 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 2.00 (3H, s, CH_3), 3.78 (9H, s, 2,4,6-OCH_3), 6.12 (2H, s, H-3,5). ^{13}C NMR (100 MHz, $CDCl_3$) 7.8 (CH_3), 55.8 (2,4,6-OCH_3), 90.7 (C-3,5), 106.9 (C-1), 158.8 (C-2,6), 160.0 (C-4).

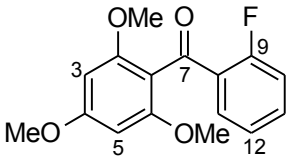
3.7.5 Synthesis of phenyl(2,4,6-trimethoxy-3-methylphenyl)methanone (3.57)



3.57

Benzoyl chloride (0.190 g, 0.2 mL, 1.35 mmol) was added dropwise to an ice-cold stirred mixture of $AlCl_3$ (0.180 g, 1.35 mmol) in DCM (20 mL). After being stirred at 0 ºC for 1 h, the reaction mixture was added slowly to a solution of 1,3,5-trimethoxy-2-methylbenzene (0.246 g, 1.35 mmol) in DCM (15 mL) at 0 ºC. The reaction mixture was allowed to attain room temperature and stirred for a further 12 h. An ice-cooled 6 M HCl (20 mL) was poured slowly into the reaction mixture and DCM (20 mL) was also added into the mixture. The organic layer was washed with saturated $NaHCO_3$ solution (15 mL), water (20 mL) and brine (15 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The resulting mixture was purified by silica gel column chromatography (Hexanes-EtOAc, 3:7) to yield the product as a white solid (0.356 g, 1.24 mmol, 92%). After recrystallization (Hexanes-EtOAc, 1:9), **3.57** was obtained as colourless crystals, mp 95-96 ºC, TLC R_f 0.16 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 2.11 (3H, s, CH_3), 3.62 (3H, s, 2-OCH_3) 3.72 (3H, s, 6-OCH_3), 3.91 (3H, s, 4-OCH_3), 6.34 (1H, s, H-5), 7.43 (2H, dd, J = 8.0, 7.6, H-10,12), 7.55 (1H, tt, J = 7.6, 1.3, H-11), 7.86 (2H, dd, J = 8.0, 1.3, H-9,13). ^{13}C NMR (100 MHz, $CDCl_3$) 8.4 (CH_3), 55.7 (4-OCH_3), 56.0 (6-OCH_3), 62.0 (2-OCH_3), 91.4 (C-5), 112.2 (C-1), 115.9 (C-3), 128.3 (C-10,12), 129.4 (C-9,13), 132.9 (C-11), 138.3 (C-8), 156 (C-6), 157.0 (C-2), 160.1 (C-4), 195.3 (C-7). [Plate 2]. HRMS (ESI+): Found $[M+Na]^+$ 309.1103, Calc. for $C_{17}H_{18}NaO_4$ 309.1103. IR (neat) ν_{max} (cm^{-1}) 3051, 2940, 1655, 1599, 1583, 1450, 1112.

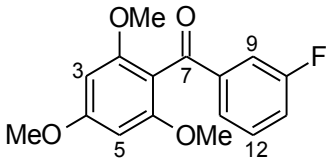
3.7.6 Synthesis of (2-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (3.58)



3.58

2-Fluorobenzoyl chloride (0.715 g, 4.51 mmol) was added dropwise to an ice-cold stirred mixture of $AlCl_3$ (0.670 g, 5.03 mmol) in DCM (15 mL). After being stirred at 0 ºC for 1 h, the reaction mixture was added slowly to a solution of 1,3,5-trimethoxybenzene (0.759 g, 4.51 mmol) in DCM (15 mL) at 0 ºC. The reaction mixture was allowed to reach room temperature and stirred for a further 12 h. An ice-cooled 6 M HCl (20 mL) was poured slowly into the reaction mixture and DCM (20 mL) was also added into the mixture. The organic layer was washed with saturated $NaHCO_3$ solution (15 mL), water (20 mL) and brine (15 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The resulting mixture was purified by silica gel column chromatography (Hexanes-EtOAc, 3:7) to yield the product as a white solid (1.23 g, 4.24 mmol, 94%). After recrystallization (Hexanes-EtOAc, 1:9), **3.58** was obtained as colourless crystals, mp 127-129 ºC, TLC R_f 0.21 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 3.67 (6H, s, 2,6-OCH_3), 3.83 (3H, s, 4-OCH_3), 6.12 (2H, s, H-3,5), 7.01 (1H, dd, J = 11.4, 8.5, H-10), 7.15 (1H, t, J = 7.7, H-12), 7.43 (1H, m, H-11), 7.75 (1H, dd, J = 7.7, 7.6, H-13). ^{13}C NMR(100 MHz, $CDCl_3$) 55.4 (4-OCH_3), 55.9 (2,6-OCH_3), 90.8 (C-3,5), 113.1 (C-1), 116.3 (d, J = 22.8, C-10), 123.8 (d, J = 2.9,C-12), 127.9 (d, J = 9.5,C-8), 131.4 (d, J = 1.4,C-13), 133.8 (d, J = 9.1, C-11), 159.1 (C-2,6), 161.7 (d, J = 256.5, C-9), 162.7 (C-4), 190.7 (C-7). [Plate 3]. HRMS (ESI$^+$): Found $[M+Na]^+$ 313.0849,Calc. for $C_{16}H_{15}FNaO_4$ 313.0852.IR (neat) ν_{max} (cm^{-1}) 3010, 2949, 1651, 1603, 1583, 1451, 1122.

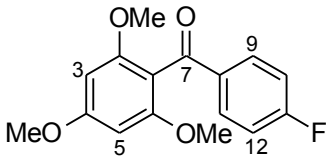
3.7.7 Synthesis of (3-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (3.59)



3.59

3-Fluorobenzoyl chloride (0.715 g, 4.51 mmol) was added dropwise to an ice-cooled stirred mixture of $AlCl_3$ (0.670 g, 5.03 mmol) in DCM (15 mL). After being stirred at 0 ºC for 1 h, the reaction mixture was added slowly to a solution of 1,3,5-trimethoxybenzene (0.759 g, 4.51 mmol) in DCM (15 mL) at 0 ºC. The reaction mixture was allowed to attain room temperature and stirred for a further 12 h. An ice-cooled 6 M HCl (20 mL) was poured slowly into the reaction mixture and DCM (20 mL) was also added into the mixture. The organic layer was washed with saturated $NaHCO_3$ solution (15 mL), water (20 mL) and brine (15 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The resulting mixture was purified by silica gel column chromatography (Hexanes-EtOAc, 3:7) to yield the product as a white solid (1.24 g, 4.28 mmol, 95%). After recrystallization (Hexanes-EtOAc, 1:9), **3.59** was obtained as colourless crystals, mp 107-109 °C, TLC R_f 0.22 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 3.69 (6H, s, 2,6-OCH_3), 3.86 (3H, s, 4-OCH_3), 6.17 (2H, s, H-3,5), 7.21 (1H, td, *J* = 8.2, 2.8, H-12), 7.37 (1H, m, H-11), 7.51 (1H, dt, *J* = 9.3, 1.8, H-9), 7.60 (1H, dt, *J* = 8.2, 1.8, H-13). ^{13}C NMR(100 MHz, $CDCl_3$) 55.5 (4-OCH_3), 55.8 (2,6-OCH_3), 90.8 (C-3,5), 110.4 (C-1), 115.9 (d, *J* = 22.4, C-9), 119.7 (d, *J* = 21.5, C-11), 125.1 (d, *J* = 2.8, C-13), 129.8 (d, *J* = 7.5, C-12), 140.6 (d, *J*= 6.2, C-8), 158.9 (C-2,6), 162.7 (C-4), 162.8 (d, *J* = 246.6, C-10), 193.6 (C-7). [Plate 4]. HRMS (ESI^+): Found $[M+Na]^+$ 313.0849, Calc. for $C_{16}H_{15}FNaO_4$ 313.0852.IR (neat) ν_{max} (cm^{-1}) 2947, 2841, 1676, 1583, 1267.

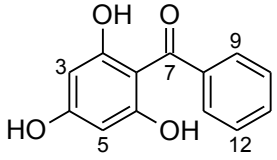
3.7.8 Synthesis of (4-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (3.60)



3.60

4-Fluorobenzoyl chloride (0.715 g, 4.51 mmol) was added dropwise to an ice-cooled stirred mixture of $AlCl_3$ (0.670 g, 5.03 mmol) in DCM (15 mL). After being stirred at 0 ºC for 1 h, the reaction mixture was added slowly to a solution of 1,3,5-trimethoxybenzene (0.759 g, 4.51 mmol) in DCM (15 mL) at 0 ºC. The reaction mixture was allowed to attain room temperature and stirred for a further 12 h. An ice-cooled 6 M HCl (20 mL) was poured slowly into the reaction mixture and DCM (20 mL) was also added into the mixture. The organic layer was washed with saturated $NaHCO_3$ solution (15 mL), water (20 mL) and brine (15 mL) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The resulting mixture was purified by silica gel column chromatography (Hexanes-EtOAc, 3:7) to yield the product as a white solid (1.24 g, 4.28 mmol, 95%). After recrystallization (1:9 Hexanes-EtOAc), **3.60** was obtained as colourless crystals, mp 155-157 ºC, TLC R_f 0.22 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 3.69 (6H, s, 2,6-OCH_3), 3.86 (3H, s, 4-OCH_3), 6.17 (2H, s, H-3,5), 7.07 (2H, dd, J = 9.2, 8.6, H-10,12), 7.85 (2H, dd, J = 8.6,5.7, H-9,13). ^{13}C NMR(100 MHz, $CDCl_3$) 55.5 (4-OCH_3), 55.8 (2,6-OCH_3), 90.8 (C-3,5), 110.7 (C-1), 115.3 (d, J = 22.0, C-10,12), 132.0 (d, J = 9.4, C-9,13), 134.9 (C-8), 158.7 (C-2,6), 162.6 (C-4), 165.8 (d, J = 254.8, C-11), 193.3 (C-7). [Plate 5]. HRMS (ESI$^+$): Found $[M+Na]^+$ 313.0849, Calc. for $C_{16}H_{15}FNaO_4$ 313.0852. IR (neat) ν_{max} (cm^{-1}) 3001, 2943, 1658, 1593, 1504, 1272.

3.7.9 Synthesis of phenyl(2,4,6-trihydroxyphenyl)methanone (3.33)

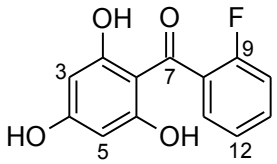


3.33

To a stirred solution of phenyl(2,4,6-trimethoxyphenyl)methanone (500 mg, 1.84 mmol) in DCM (30 mL) at -78 ºC was added boron tribromide (1 mL). The temperature of the

reaction mixture was allowed to reach the room temperature slowly. After being stirred for 30 h at room temperature, the reaction mixture was cooled to 0 ºC and quenched with water. DCM (15 mL) was added into a stirred mixture. A clear liquid was decanted off the mixture and the residue was washed with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The resulting yellow product was purified by silica gel column chromatography with 40% EtOAc in hexanes as eluent and **3.33** was obtained as a light yellow crystalline solid (419 mg, 1.82 mmol, 99%), mp 168-170ºC (lit.[125,127] 168-170 °C), TLC R_f 0.52 (Hexanes-EtOAc, 1:1). ^{1}H NMR (400 MHz, DMSO-d_6) 5.84 (2H, s, H-3,5), 7.43 (2H, t, *J*= 7.9, H-10,12), 7.53 (1H, tt, *J* = 7.9, 1.3, H-11), 7.62 (2H, dd, *J*= 7.9, 1.3, H-9,13), 9.82 (1H, bs, 4-OH), 10.08 (2H, bs, 2,6-OH). ^{13}C NMR (100 MHz, DMSO-d_6) 94.8 (C-3,5), 106.0 (C-1), 128.6 (C-10,12), 128.9 (C-9,13), 132.1 (C-11), 140.2 (C-8), 159.8 (C-2,6), 162.3 (C-4), 196.9 (C-7). [Plate 6]. HRMS (ESI$^-$) : Found $[M-H]^-$ 229.0497, Calc. for $C_{13}H_9O_4$ 229.0501. IR (neat) ν_{max} (cm^{-1}): 3621, 1625, 1598, 1543, 1319.

3.7.10 Synthesis of (2-fluorophenyl)(2,4,6-trihydroxyphenyl) methanone (3.61)

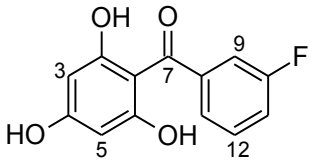


3.61

To a stirred solution of (2-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (2.1 g, 7.23 mmol) in DCM (45 mL) at -78 ºC was added boron tribromide (3.1 mL). The temperature of the reaction mixture was allowed to reach the room temperature slowly. After being stirred for 30 h at room temperature, the reaction mixture was cooled to 0 ºC and quenched with water. DCM (20 mL) was added into a stirred mixture. A clear liquid was decanted off the mixture and the residue was washed with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The resulting yellow product was purified by silica gel column chromatography with 40% EtOAc in hexanes as eluent and **3.61** was obtained as a yellow crystalline solid (1.76 g, 7.08 mmol, 98%), mp 125-128 ºC, TLC R_f 0.49 (Hexanes-EtOAc, 1:1). ^{1}H NMR (400 MHz, DMSO-d_6) 5.78 (2H, s, H-3,5), 7.15-7.25 (2H, m, H-10,12), 7.38 (1H, t, *J*= 7.5 H-11), 7.46 (1H, m, H-13), 10.52 (1H, bs, 4-OH), 11.47 (2H, bs, 2,6-OH). ^{13}C NMR (100 MHz, DMSO-d_6) 94.7 (C-3,5),

105.0 (C-1), 115.5 (d, J = 21.4, C-10), 124.5 (d, J = 8.3, C-13), 128.9 (d, J = 3.5, C-12), 131.5 (d, J = 16.2, C-8), 131.7 (d, J = 8.3, C-11), 158.8 (d, J = 248.0, C-9), 163.9 (C-2,6), 166.1 (C-4), 193.9 (C-7). [Plate 7]. HRMS (ESI$^-$): Found $[M-H]^-$ 247.0405, Calc. for $C_{13}H_8FO_4$ 247.0407. IR (neat) ν_{max} (cm^{-1}): 3598, 1627, 1596, 1514, 1309.

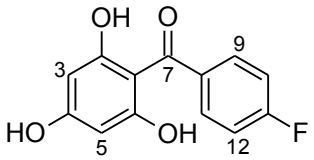
3.7.11 Synthesis of (3-fluorophenyl)(2,4,6-trihydroxyphenyl) methanone (3.62)



3.62

To a stirred solution of (3-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (2.1 g, 7.23 mmol) in DCM (45 mL) at -78 ºC was added boron tribromide (3.1 mL). The temperature of the reaction mixture was allowed to reach the room temperature slowly. After being stirred for 30 h at room temperature, the reaction mixture was cooled to 0 ºC and quenched with water. DCM (20 mL) was added into a stirred mixture. A clear liquid was decanted off the mixture and the residue was washed with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The resulting yellow product was purified by silica gel column chromatography with 40% EtOAc in hexanes as eluent and **3.62** was obtained as a yellow crystalline solid (1.78 g, 7.16 mmol, 99%), mp 172-174ºC, TLC R_f 0.49 (Hexanes-EtOAc, 1:1). ^{1}H NMR (400 MHz, DMSO-d_6) 5.84 (2H, s, H-3,5), 7.29-7.53 (4H, m, H-9,11,12,13), 9.92 (1H, bs, 4-OH), 10.22 (2H, bs, 2,6-OH). ^{13}C NMR (100 MHz, DMSO-d_6) 94.7 (C-3,5), 105.4 (C-1), 114.9 (d, J = 22.0, C-9), 118.8 (d, J = 21.4, C-11), 124.9 (d, J = 2.6, C-13), 130.6 (d, J = 7.9, C-12), 142.9 (d, J = 6.5, C-8), 160.0 (C-2,6), 162.3 (d, J= 244.0, C-10), 162.7 (C-4), 195.3 (C-7). [Plate 8]. HRMS (ESI$^-$) : Found $[M-H]^-$ 247.0406, Calc. for $C_{13}H_8FO_4$ 247.0407. IR (neat) ν_{max} (cm^{-1}): 3419, 1635, 1596, 1513, 1300.

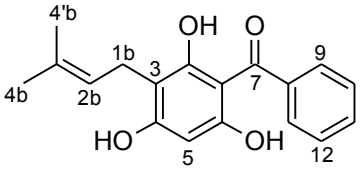
3.7.12 Synthesis of (4-fluorophenyl)(2,4,6-trihydroxyphenyl) methanone (3.63)



3.63

To a stirred solution of (4-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (2.1 g, 7.23 mmol) in DCM (45 mL) at -78 ºC was added boron tribromide (3.1 mL). The temperature of the reaction mixture was allowed to reach room temperature slowly. After being stirred for 30 h at room temperature, the reaction mixture was cooled to 0 ºC and quenched with water. DCM (20 mL) was added into a stirred mixture. A clear liquid was decanted off the mixture and the residue was washed with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The resulting yellow product was purified by silica gel column chromatography with 40% EtOAc in hexanes as eluent and **3.63** was obtained as a yellow crystalline solid (1.78 g, 7.16 mmol, 99%), mp 166-168 ºC, TLC R_f 0.49 (Hexanes-EtOAc, 1:1). ^{1}H NMR (400 MHz, DMSO-d_6) 5.85 (2H, s, H-3,5), 7.26 (2H, m, H-10,12),7.69 (2H, m, H-9,13), 9.82 (1H, bs, 4-OH), 10.04 (2H, bs, 2,6-OH). ^{13}C NMR (100 MHz, DMSO-d_6) 94.9 (C-3,5), 106.0 (C-1), 115.4 (d, J = 22.0, C-10,12), 131.7 (d, J = 9.3, C-9,13), 136.8 (d, J = 2.7, C-8), 159.6 (C-2,6), 162.3 (C-4), 164.7 (d, J = 249.7, C-11), 195.3 (C-7) [Plate 9]. HRMS (ESI$^-$): Found $[M-H]^-$ 247.0409, Calc. for $C_{13}H_8FO_4$ 247.0407. IR (neat) ν_{max} (cm^{-1}): 3556, 1641, 1595, 1506, 1288.

3.7.13 Synthesis of phenyl[2,4,6-trihydroxy-3-(3-methyl-2-butenyl) phenyl]methanone (3.54)

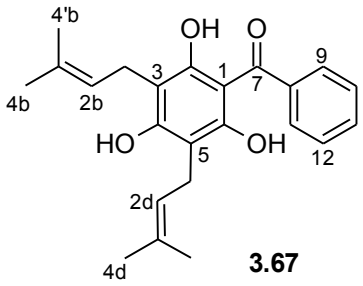


3.54

To a mixture of phenyl(2,4,6-trihydroxyphenyl)methanone (0.276 g, 1.2 mmol) and DBU (0.183 g, 1.2 mmol) in dry THF (15 mL) was added prenyl bromide (0.179 g, 1.2 mmol) in small increments. The mixture was stirred at room temperature for 24 h. After addition of 2

M HCl (30 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (4 x 20 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography (Hexanes-EtOAc, 3:7), **3.54** was obtained as a light orange semisolid (0.222 g, 0.744 mmol, 62%); TLC R_f 0.44 (Hexanes-EtOAc, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) 1.76 (3H, d, *J* = 1.1, H-4'b), 1.80 (3H, s, H-4b), 3.36 (2H, d, *J* = 7.0, H-1b), 5.26 (1H, m, H-2b), 5.93 (2H, s, H-5, 4-OH), 6.15 (1H, bs, 2-OH), 7.51 (2H, dd, *J* = 8.1, 7.5, H-10,12), 7.58 (1H, tt, *J* = 7.5,1.5, H-11), 7.64 (2H, dd, *J* = 8.1,1.5, H-9,13), 10.29 (1H, bs, 6-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.9 (C-4b), 21.7 (C-1b), 25.8 (C-4'b), 96.2 (C-5), 104.6 (C-1), 106.6 (C-3), 121.6 (C-2b), 127.8 (C-9,13), 129.2 (C-10,12), 132.2 (C-11), 135.4 (C-3b), 140.0 (C-8), 159.4 (C-6), 160.8 (C-2), 162.6 (C-4), 197.7 (C-7). [Plate 10]. HRMS (ESI$^-$): Found $[M-H]^-$ 297.1130, Calc. for $C_{18}H_{17}O_4$ 297.1127. IR (neat) ν_{max} (cm^{-1}): 3523, 3023, 2953, 1652, 1594, 1577, 1420, 1111.

3.7.14 Synthesis of phenyl[2,4,6-trihydroxy-3,5-bis(3-methyl-2-butenyl)phenyl]methanone (3.67)

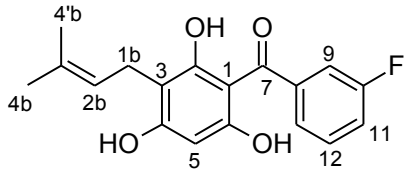


3.67

To a mixture of phenyl(2,4,6-trihydroxyphenyl)methanone (0.276 g, 1.2 mmol) and DBU (0.366 g, 2.4 mmol) in dry THF (15 mL) was added prenyl bromide (0.358 g, 2.4 mmol) in small increments. The mixture was stirred at room temperature for 48 h. After addition of 2 M HCl (30 mL) to the mixture, it was stirred for a further 15 min and extracted with EtOAc (4 x 20 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography (Hexanes-EtOAc, 2:8), **3.67** was obtained as a light orange semisolid (0.211 g, 0.576 mmol, 48%); TLC R_f 0.85 (Hexanes-EtOAc, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) 1.74 (6H, d, *J* = 1.1, H-4'b,4'd), 1.79 (6H, s, H-4b,4d), 3.34 (4H, d, *J* = 7.1, H-1b,1d), 5.22 (2H, m, H-2b,2d), 6.35 (1H, bs, 4-OH), 7.50 (2H, dd, *J* = 8.0, 7.7, H-10,12), 7.57 (1H, tt, *J* = 7.7, 1.5, H-11), 7.64 (2H, dd, *J* = 8.0, 1.5, H-9,13), 8.91

(2H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.6 (C-4b,4d), 21.8 (C-1b,1d), 26.0 (C-4'b,4'd), 104.6 (C-1), 106.3 (C-3,5), 121.9 (C-2b,2d),127.8 (C-9,13), 129.2 (C-10,12), 132.2 (C-11), 135.4 (C-3b,3d), 140.0 (C-8), 157.5 (C-2,6), 161.0 (C-4), 198.0 (C-7). [Plate 13]. HRMS (ESI^+): Found $[M+Na]^+$ 389.1723, Calc. for $C_{23}H_{26}NaO_4$ 389.1729. IR (neat) ν_{max} (cm^{-1}): 3512, 3023, 2942, 1632, 1586, 1566, 1443, 1121.

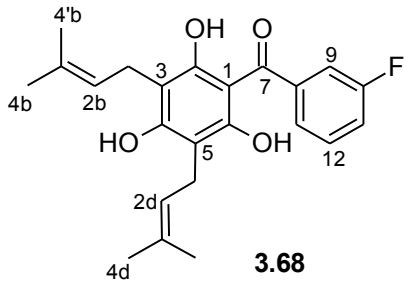
3.7.15 Synthesis of (3-fluorophenyl)[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (3.65)



3.65

To a mixture of (3-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (0.298 g, 1.2 mmol) and DBU (0.183 g, 1.2 mmol) in dry THF (15 mL) was added prenyl bromide (0.179 g, 1.2 mmol) in small increments. The mixture was stirred at room temperature for 24 h. After addition of 2 M HCl (30 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (4 x 20 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography using 30% EtOAc in hexanes, **3.65** was obtained as a light orange semisolid (0.231 g, 0.732 mmol, 61%); TLC R_f 0.43 (Hexanes-EtOAc, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) 1.76 (3H, d, *J*= 1.1, H-4'b), 1.80 (3H, s, H-4b), 3.36 (2H, d, *J* = 7.1, H-1b), 5.25 (1H, m, H-2b), 5.91 (1H, s, H-5), 7.24 (1H, t, *J* = 8.1, H-12), 7.32 (1H, m, H-11), 7.38-7.48 (2H, m, H-9,13), 10.16 (1H, bs, 6-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.9 (C-4b), 21.7 (C-1b), 25.8 (C-4'b), 96.2 (C-5), 104.5 (C-1), 106.5 (C-3), 115.1 (d, *J* = 22.9, C-9), 118.7 (d, *J* = 21.1, C-11), 121.3 (C-2b), 130.4 (d, *J* = 7.6, C-13), 130.4 (d, *J* = 7.6, C-12), 135.9 (C-3b), 142.5 (d, *J* = 6.6, C-8), 159.2 (C-6), 160.9 (C-2), 162.5 (C-4), 162.6 (d, *J* = 249.2, C-10), 196.6 (C-7). [Plate 11]. HRMS (ESI^+): Found $[M+Na]^+$ 339.1003, Calc. for $C_{18}H_{17}FNaO_4$ 339.1009. IR (neat) ν_{max} (cm^{-1}): 3507, 3061, 2925, 1663, 1594, 1572, 1446, 1112.

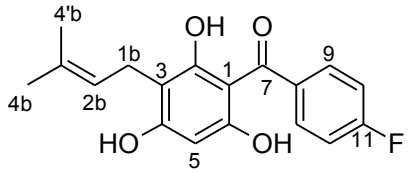
3.7.16 Synthesis of (3-fluorophenyl)[2,4,6-trihydroxy-3,5-bis(3-methyl-2-butenyl)phenyl]methanone (3.68)



3.68

To a mixture of (3-phenyl)(2,4,6-trihydroxyphenyl)methanone (0.298 g, 1.2 mmol) and DBU (0.366 g, 2.4 mmol) in dry THF (15 mL) was added prenyl bromide (0.358 g, 2.4 mmol) in small increments. The mixture was stirred at room temperature for 48 h. After addition of 2 M HCl (30 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (4 x 20 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography (Hexanes-EtOAc, 3:7), **3.68** was obtained as a light orange semisolid (0.212 g, 0.552 mmol, 46%); TLC R_f 0.85 (Hexanes-EtOAc, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) 1.75 (6H, d, *J* = 1.1, H-4'b,4'd), 1.79 (6H, s, H-4b,4d), 3.35 (4H, d, *J* = 7.1, H-1b,1d), 5.22 (2H, m, H-2b,2d), 6.38 (1H, bs, 4-OH), 7.22 (1H, t, *J* = 8.1 H-12), 7.31 (1H, m, H-11), 7.38-7.47 (2H, m, H-9,13), 8.83 (2H, bs, 2,6-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.6 (C-4b,4d), 21.8 (C-1b,1d), 26.1 (C-4'b,4'd), 104.6 (C-1), 106.1 (C-3,5), 115.2 (d, *J* = 22.9, C-9), 118.6 (d, *J* = 21.1, C-11), 121.6 (C-2b,2d), 123.6 (d, *J* = 3.0, C-13), 130.3 (d, *J* = 7.4, C-12), 135.8 (C-3b,3d), 142.9 (d, *J* = 6.5, C-6), 157.7 (C-2,6), 160.9 (C-4), 162.5 (d, *J* = 247.9, C-10), 197.0 (C-7). [Plate 14]. HRMS (ESI$^+$): Found $[M+Na]^+$ 407.1634, Calc. for $C_{23}H_{25}FNaO_4$ 407.1635. IR (neat) ν_{max} (cm^{-1}): 3524, 3035, 2941, 1653, 1587, 1577, 1431, 1142.

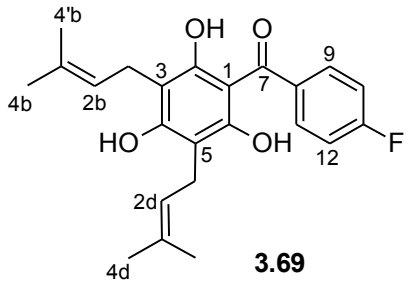
3.7.17 Synthesis of (4-fluorophenyl)[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (3.66)



3.66

To a mixture of (4-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (0.298 g, 1.2 mmol) and DBU (0.183 g, 1.2 mmol) in dry THF (15 mL) was added prenyl bromide (0.179 g, 1.2 mmol) in small increments. The mixture was stirred at room temperature for 24 h. After addition of 2 M HCl (30 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (4 x 20 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography (Hexanes-EtOAc, 3:7), **3.66** was obtained as a light orange semisolid (0.235 g, 0.744 mmol, 62%); TLC R_f 0.43 (Hexanes-EtOAc, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) 1.76 (3H, d, J = 1.1, H-4'b), 1.80 (3H, s, H-4b), 3.36 (2H, d, J = 7.1, H-1b), 5.25 (1H, m, H-2b), 5.92 (1H, s, H-5), 6.22 (1H, bs, 4-OH), 7.14 (2H, m, H-10,12), 6.50 (1H, bs, 2-OH), 7.67 (2H, m, H-9,13), 10.03 (1H, bs, 6-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.9 (C-4b), 21.7 (C-1b), 25.8 (C-4'b), 96.1 (C-5), 104.6 (C-1), 106.5 (C-3), 115.8 (d, J = 21.9, C-10,12), 121.4 (C-2b), 130.9 (d, J = 9.0, C-9,13), 135.7 (C-3b), 136.4 (d, J = 3.1, C-8), 160.0 (C-6), 160.6 (C-2), 162.2 (C-4), 165.0 (d, J = 253.6, C-11), 196.6 (C-7). [Plate 12]. HRMS (ESI^-): Found $[M-H]^-$ 315.1035, Calc. for $C_{18}H_{16}FO_4$ 315.1033. IR (neat) ν_{max} (cm^{-1}): 3559, 3055, 2952, 1663, 1596, 1587, 1450, 1143.

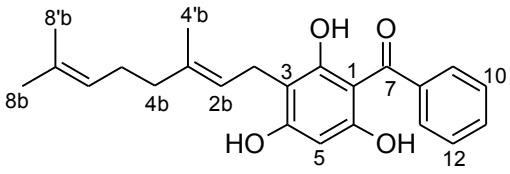
3.7.18 Synthesis of (4-fluorophenyl)[2,4,6-trihydroxy-3,5-bis(3-methyl-2-butenyl)phenyl]methanone (3.69)



3.69

To a mixture of (4-phenyl)(2,4,6-trihydroxyphenyl)methanone (0.298 g, 1.2 mmol) and DBU (0.366 g, 2.4 mmol) in dry THF (15 mL) was added prenyl bromide (0.358 g, 2.4 mmol) in small increments. The mixture was stirred at room temperature for 48 h. After addition of 2 M HCl (30 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (4 x 20 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography (Hexanes-EtOAc, 2:8), **3.69** was obtained as a light orange semisolid (0.217 g, 0.564 mmol, 47%); TLC R_f 0.85 (Hexanes-EtOAc, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) 1.75 (6H, d, *J* = 1.1, H-4'b,4'd), 1.79 (6H, s, H-4b,4d), 3.35 (4H, d, *J* = 7.1, H-1b,1d), 5.22 (2H, m, H-2b,2d), 6.34 (1H, bs, 4-OH), 7.14 (2H, m, H-10,12), 7.67 (2H, m, H-9,13), 8.75 (2H, bs, 2,6-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.9 (C-4b,4d), 21.9 (C-1b,1d), 25.8 (C-4'b,4'd), 104.7 (C-1), 106.1 (C-3,5), 115.7 (d, *J* = 21.9, C-10,12), 121.6 (C-2b,2d), 130.9 (d, *J* = 9.0, C-9,13), 135.6 (C-3b,3d), 136.7 (d, *J* = 3.1, C-8), 157.4 (C-2,6), 160.6 (C-4), 164.9 (d, *J* = 253.6, C-11), 196.9 (C-7). [Plate 15]. HRMS (ESI$^-$): Found $[M-H]^-$ 383.1653, Calc. for $C_{23}H_{24}O_4F$ 383.1659. IR (neat) ν_{max} (cm^{-1}): 3552, 3046, 2945, 1663, 1596, 1574, 1441, 1145.

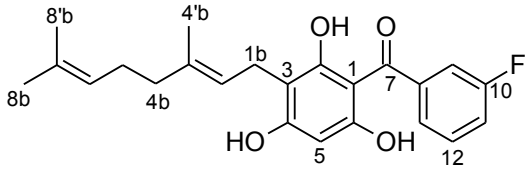
3.7.19 Synthesis of phenyl[3-(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]methanone (3.8)



3.8

To a mixture of phenyl(2,4,6-trihydroxyphenyl)methanone (0.276 g, 1.2 mmol) and DBU (0.183 g, 1.2 mmol) in dry THF (15 mL) was added geranyl bromide (0.261 g, 1.2 mmol) in small increments. The mixture was stirred at room temperature for 24 h. After addition of 2 M HCl (30 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (4 x 20 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography (Hexanes-EtOAc, 2:8), **3.8** was obtained as a light orange semisolid (0.181 g, 0.51 mmol, 42%); TLC R_f 0.46 (Hexanes-EtOAc, 2:8). ^{1}H NMR (400 MHz, $CDCl_3$) 1.59 (3H, d, *J* = 1.1, H-8'b), 1.66 (3H, s, H-8b), 1.79 (3H, s, H-4'b), 2.02-2.16 (4H, m, H-4b,5b), 3.37 (2H, d, *J* = 7.0, H-1b), 5.05 (1H, t, *J* = 6.6, H-6b), 5.27 (1H, t, *J* = 6.8, H-2b), 5.93 (1H, s, H-5), 6.27 (1H, bs, 4-OH), 7.47-7.66 (5H, m, H-9,10,11,12,13), 10.28 (1H, bs, 6-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 16.2 (C-4'b), 17.7 (C-8'b), 21.7 (C-1b), 25.7 (C-8b), 26.3 (C-5b), 39.7 (C-4b), 96.3 (C-5), 104.6 (C-1), 106.5 (C-3), 121.5 (C-2b), 123.7 (C-6b), 127.8 (C-9,13), 129.1 (C-10,12), 123.1 (C-7b), 132.2 (C-11), 139.3 (C-3b), 140.1 (C-8), 159.4 (C-6), 160.8 (C-2), 162.6 (C-4), 197.8 (C-7). [Plate 16]. HRMS (ESI$^+$): Found $[M+Na]^+$ 389.1721, Calc. for $C_{23}H_{26}NaO_4$ 389.1729. IR (neat) ν_{max} (cm^{-1}): 3533, 3073, 2943, 1656, 1595, 1569, 1444, 1161.

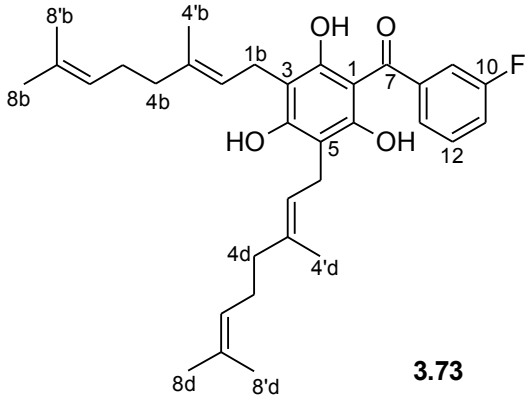
3.7.20 Synthesis of (3-fluorophenyl)[3-(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]methanone (3.71)



3.71

To a mixture of (3-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (0.276 g, 1.2 mmol) and DBU (0.183 g, 1.2 mmol) in dry THF (15 mL) was added geranyl bromide (0.261 g, 1.2 mmol) in small increments. The mixture was stirred at room temperature for 24 h. After addition of 2 M HCl (30 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (4 x 20 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography (Hexanes-EtOAc, 2:8), **3.71** was obtained as a light orange semisolid (0.18 g, 0.458 mmol, 40%); TLC R_f 0.45 (Hexanes-EtOAc, 2:8). ^{1}H NMR (400 MHz, $CDCl_3$) 1.58 (3H, s,H-8'b), 1.65 (3H, s, H-8b), 1.79 (3H, s, H-4'b), 2.02-2.16 (4H, m, H-4b,5b), 3.38 (2H, d, J = 7.2, H-1b), 5.04 (1H, t, J = 6.8, H-6b), 5.26 (1H, t, J = 6.9, H-2b), 5.92 (1H, s, H-5), 6.24 (1H, bs, 4-OH), 7.23 (1H, t, J = 8.2 H-12), 7.32 (1H, m, H-11), 7.38-7.48 (2H, m, H-9,13), 7.54 (1H, bs, 2-OH), 10.13 (1H, bs, 6-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 16.2 (C-4'b), 17.7 (C-8'b), 21.7 (C-1b), 25.6 (C-8b), 26.2 (C-5b), 39.7 (C-4b), 96.2 (C-5), 104.5 (C-1), 106.4 (C-3), 115.1 (d, J = 22.8, C-9), 118.7 (d, J = 21.2, C-11), 121.2 (C-2b), 123.5 (d, J = 3.0, C-13), 123.6 (C-6b), 130.3 (d, J = 7.9, C-12), 130.5 (C-7b), 139.9 (C-3b), 142.6 (d, J = 6.6, C-8), 159.3 (C-6), 160.9 (C-2), 162.7 (C-4), 162.6 (d, J = 248.6, C-10), 197.8 (C-7). [Plate 17]. HRMS (ESI$^+$): Found $[M+Na]^+$ 407.1632, Calc. for $C_{23}H_{25}FNaO_4$ 407.1635. IR (neat) ν_{max} (cm^{-1}): 3561, 3059, 2947, 1662, 1598, 1575, 1457, 1133.

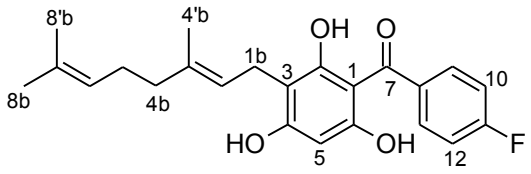
3.7.21 Synthesis of (3-fluorophenyl)[3,5-bis(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]methanone (3.73)



3.73

To a mixture of (3-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (0.276 g, 1.2 mmol) and DBU (0.183 g, 1.2 mmol) in dry THF (15 mL) was added geranyl bromide (0.522 g, 2.4 mmol) in small increments. The mixture was stirred at room temperature for 48 h. After addition of 2 M HCl (30 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (4 x 20 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography (Hexanes-EtOAc, 2:8), **3.73** was obtained as a light orange oil (0.120 g, 0.192 mmol, 16%); TLC R_f 0.88 (Hexanes-EtOAc, 2:8). ^{1}H NMR (400 MHz, $CDCl_3$) 1.58 (6H, s, H-8'b,8'd), 1.64 (6H, s, H-8b,8d), 1.78 (6H, s, H-4'b,4'd), 2.03-2.15 (8H, m, H-4b,4d,5b,5d), 3.37 (4H, d, J = 6.9, H-1b,1d), 5.03 (2H, t, J = 6.8, H-6b,6d), 5.23 (2H, t, J = 6.9, H-2b,2d), 6.42 (1H, bs, 4-OH), 7.20 (1H, m, H-12), 7.31 (1H, m, H-11), 7.38-7.48 (2H, m, H-9,13), 8.86 (2H, bs, 2,6-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 16.2 (C-4'b,4'd), 17.7 (C-8'b,8'd), 21.8 (C-1b,1d), 25.6 (C-8b,8d), 26.2 (C-5b,5d), 39.7 (C-4b,4d), 104.6 (C-1), 106.0 (C-3,5), 115.1 (d, J = 22.8, C-9), 118.4 (d, J = 21.1, C-11), 121.5 (C-2b,2d), 123.6 (d, J = 3.0, C-13), 123.6 (C-6b,6d), 130.0 (d, J = 7.9, C-12), 132.1 (C-7b,7d), 139.7 (C-3b,3d), 143.1 (d, J = 6.6, C-8), 157.8 (C-2,6), 160.9 (C-4), 162.5 (d, J = 247.8, C-10), 197.2 (C-7). [Plate 19]. HRMS (ESI$^+$): Found $[M+Na]^+$ 543.2895, Calc. for $C_{33}H_{41}FNaO_4$ 543.2887. IR (neat) ν_{max} (cm^{-1}): 3543, 3046, 2936, 1657, 1594, 1586, 1455, 1145.

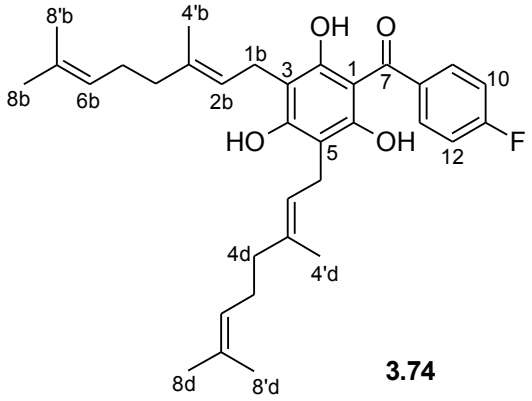
3.7.22 Synthesis of (4-fluorophenyl)[3-(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]methanone (3.72)



3.72

To a mixture of (4-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (0.276 g, 1.2 mmol) and DBU (0.183 g, 1.2 mmol) in dry THF (15 mL) was added geranyl bromide (0.261 g, 1.2 mmol) in small increments. The mixture was stirred at room temperature for 24 h. After addition of 2 M HCl (30 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (4 x 20 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography (Hexanes-EtOAc, 2:8), **3.72** was obtained as a light orange semisolid (0.202 g, 0.528 mmol, 44%). TLC R_f 0.45 (Hexanes-EtOAc, 2:8). ^{1}H NMR (400 MHz, $CDCl_3$) 1.59 (3H, s, H-8'b), 1.65 (3H, s, H-8b), 1.79 (3H, s, H-4'b), 2.03-2.14 (4H, m, H-4b,5b), 3.38 (2H, d, *J* = 7.1, H-1b), 5.04 (1H, t, *J* = 6.9, H-6b), 5.26 (1H, t, *J* = 7.0, H-2b), 5.92 (1H, s, H-5), 6.26 (1H, bs, 4-OH), 7.14 (2H, m, H-10,12), 7.57 (1H, bs, 2-OH), 7.67 (2H, m, H-9,13), 10.00 (1H, bs, 6-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 16.3 (C-4'b), 17.7 (C-8'b), 21.7 (C-1b), 25.6 (C-8b), 26.3 (C-5b), 39.7 (C-4b), 96.2 (C-5), 104.6 (C-1), 106.4 (C-3), 115.7 (d, *J* = 21.9, C-10,12), 121.3 (C-2b), 122.1 (C-6b), 130.9 (d, *J* = 9.0, C-9,13), 132.1 (C-7b), 136.4 (d, *J* = 3.4, C-8), 139.6 (C-3b), 159.0 (C-6), 160.6 (C-2), 162.3 (C-4), 165.0 (d, *J* = 253.8, C-11), 196.7 (C-7). [Plate 18]. HRMS (ESI$^+$): Found $[M+Na]^+$ 407.1632, Calc. for $C_{23}H_{25}FNaO_4$ 407.1635. IR (neat) ν_{max} (cm^{-1}): 3548, 3062, 2946, 1662, 1595, 1572, 1451, 1141.

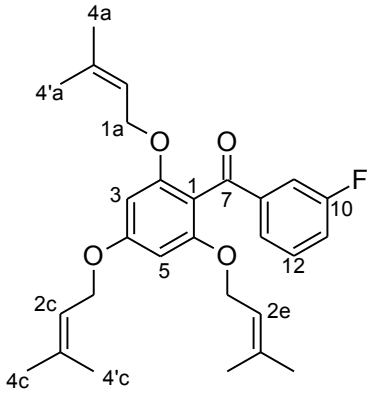
3.7.23 Synthesis of (4-fluorophenyl)[3,5-bis(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]methanone (3.74)



3.74

To a mixture of (4-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (0.276 g, 1.2 mmol) and geranyl bromide (0.522 g, 2.4 mmol) in dry THF (15 mL) was added DBU (0.183 g, 1.2 mmol) in small increments. The mixture was stirred at room temperature for 48 h. After addition of 2 M HCl (30 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (4 x 20 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent *in vacuo* resulted in a light orange product. After purification by silica gel column chromatography (Hexanes-EtOAc, 2:8), **3.74** was obtained as a light orange oil (0.120 g, 0.192 mmol, 16%), TLC R_f 0.88 (Hexanes-EtOAc, 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) 1.58 (6H, s, H-8'b,8'd), 1.64 (6H, s, H-8b,8d), 1.78 (6H, s, H-4'b,4'b), 2.03-2.15 (8H, m, H-4b,4d,5b,5d), 3.37 (4H, d, *J* = 7.2, H-1b,1d), 5.03 (2H, t, *J* = 6.9, H-6b,6d), 5.23 (2H, t, *J* = 7.2, H-2b,2d), 6.37 (1H, bs, 4-OH), 7.11 (2H, m, H-10,12), 7.67 (2H, m, H-9,13), 8.78 (2H, bs, 2,6-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 16.2 (C-4'b,4'd), 17.7 (C-8'b,8'd), 21.8 (C-1b,1d), 25.6 (C-8b,8d), 26.3 (C-5b,5d), 39.7 (C-4b,4d), 104.7 (C-1), 106.0 (C-3,5), 115.5 (d, *J* = 21.9, C-10,12), 121.6 (C-2b,2d), 123.6 (C-6b,6d), 131.0 (d, *J* = 8.9, C-9,13), 132.1 (C-7b,7d), 136.9 (d, *J* = 3.2, C-8), 139.5 (C-3b,3d), 157.5 (C-2,6), 160.6 (C-4), 164.9 (d, *J* = 252.5, C-11), 197.1 (C-7). [Plate 20]. HRMS (ESI$^+$): Found $[M+Na]^+$ 543.2895, Calc. for $C_{33}H_{41}FNaO_4$ 543.2887. IR (neat) ν_{max} (cm^{-1}): 3549, 3041, 2929, 1652, 1584, 1589, 1456, 1149.

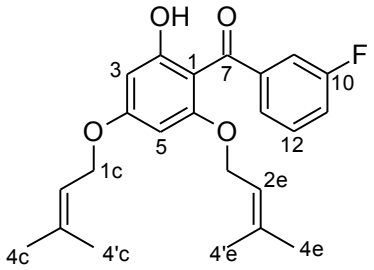
3.7.24 Synthesis of (3-fluorophenyl)[2,4,6-tris(3-methylbut-2-enyloxy)phenyl]methanone (3.82)



3.82

A mixture of (3-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (0.20 g, 0.81 mmol), prenyl bromide (0.48 g) and K_2CO_3 (0.44 g) in dry acetone (10 mL) was refluxed for 6 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:4) to obtain **3.82** (36 mg, 10%) as a light orange semisolid, TLC R_f 0.61 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.57 (6H, s, H-4a,4e), 1.67 (6H, s, H-4'a,4'e), 1.79 (3H, s, H-4c), 1.84 (3H, s, H-4'c), 4.42 (4H, d, *J* = 6.7, H-1a,1e), 4.55 (2H, d, *J* = 6.8, H-1c), 5.20 (2H, t, *J* = 6.7, H-2a,2e), 5.53 (1H, t, *J* = 6.8, H-2c), 6.19 (2H, s, H-3,5), 7.21 (1H, t, *J* = 7.8, H-11), 7.37 (1H, m, H-12), 7.51 (1H, d, *J* = 9.5, H-9), 7.61 (1H, d, *J* = 7.8, H-13). ^{13}C NMR (100 MHz, $CDCl_3$) 18.1 (C-4a,4e), 18.2 (C-4c), 25.6 (C-4'a,4'e), 25.8 (C-4'c), 64.9 (C-1c), 65.6 (C-1a,1e), 92.9 (C-3,5), 111.5 (C-1), 115.9 (d, *J* = 22.1, C-9), 119.3 (d, *J* = 21.3, C-11), 119.3 (C-2c), 119.5 (C-2a,2e), 125.0 (d, *J* = 2.2, C-13), 129.6 (d, *J* = 7.6, C-12), 137.5 (C-3a,3e), 138.6 (C-3c), 141.1 (d, *J* = 6.2, C-8), 158.2 (C-2,6), 161.6 (C-4), 162.7 (d, *J* = 253.0, C-10), 193.7 (C-7). [Plate 24]. HRMS (ESI^+): Found $[M+Na]^+$ 475.2267, Calc. for $C_{28}H_{33}FNaO_4$ 475.2261.

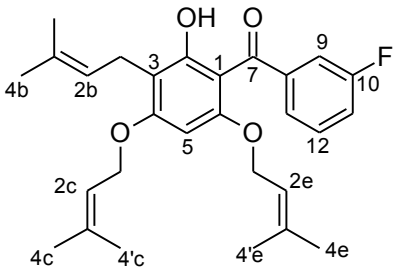
3.7.25 Synthesis of (3-fluorophenyl)[2-hydroxy-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (3.81)



3.81

A mixture of (3-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (0.2 g), prenyl bromide (0.48 g) and K_2CO_3 (0.44 g) in dry acetone (10 mL) was refluxed for 6h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. The organic layer was dried over $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:4) to obtain **3.81** (62 mg, 20%) as a cream white semisolid, TLC R_f 0.70 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.54 (3H, s, H-4e), 1.62 (3H, s, H-4'e), 1.78 (3H, s, H-4c), 1.83 (3H, s, H-4'c), 4.20 (2H, d, *J* = 6.8, H-1e), 4.58 (2H, d, *J* = 6.8, H-1c), 4.73 (1H, t, *J* = 6.8, H-2e), 5.50 (1H, t, *J* = 6.8, H-2c), 5.94 (1H, d, *J* = 2.3, H-3), 6.17 (1H, d, *J* = 2.3, H-5), 7.10-7.18 (2H, m, H-9,11), 7.27 (1H, d, *J* = 7.8, H-13), 7.33 (1H, m, H-12), 12.37 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.9 (C-4e), 18.2 (C-4c), 25.5 (C-4'e), 25.8 (C-4'c), 65.0 (C-1e), 65.2 (C-1c), 92.5 (C-3), 94.1 (C-5), 105.4 (C-1), 114.3 (d, *J* = 22.7, C-9), 116.8 (d, *J* = 21.7, C-11), 118.0 (C-2e), 118.6 (C-2c), 122.8 (d, *J* = 3.0, C-13), 129.2 (d, *J* = 7.6, C-12), 137.8 (C-3e), 139.3 (C-3c), 144.5 (d, *J* = 7.1, C-8), 161.4 (C-6), 162.1 (d, *J* = 244.0, C-10), 166.2 (C-4), 166.4 (C-2), 198.0 (d, *J* = 1.9, C-7). [Plate 23]. HRMS (ESI$^+$): Found $[M+Na]^+$ 407.1642, Calc. for $C_{23}H_{25}FNaO_4$ 407.1635.

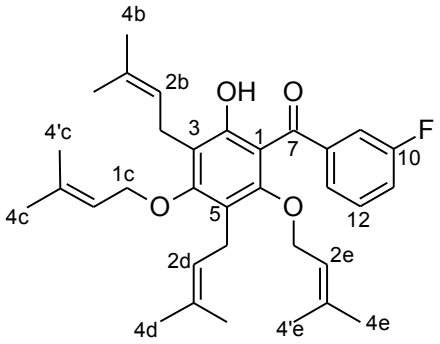
3.7.26 Synthesis of (3-fluorophenyl)[2-hydroxy-3-(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (3.75)



3.75

A mixture of (3-fluorophenyl)[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (0.1 g, 0.32 mmol), prenyl bromide (0.14 g) and K_2CO_3 (0.17 g) in dry acetone (10 mL) was refluxed for 5 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. The organic layer was dried over $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (hexanes-EtOAc, 1:4) to obtain **3.75** (0.12 g, 85%) as light yellow crystals, mp 108-109 °C, TLC R_f 0.82 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.56 (3H, s, H-4e), 1.63 (3H, s, H-4'e), 1.70 (3H, s, H-4b), 1.77 (3H, s, H-4c), 1.79 (3H, s, H-4'b), 1.83 (3H, s, H-4'c), 3.33 (2H, d, *J* = 7.1, H-1b), 4.21 (2H, d, *J* = 6.7, H-1e), 4.60 (2H, d, *J* = 6.7, H-1c), 4.74 (1H, t, *J* = 6.7, H-2e), 5.26 (1H, t, *J* = 7.1, H-2b), 5.49 (1H, t, *J* = 6.8, H-2c), 5.94 (1H, s, H-3), 7.09-7.19 (2H, m, H-9,11), 7.27 (1H, d, *J* = 7.8, H-13), 7.33 (1H, m, H-12), 12.21 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.7 (C-4e), 17.9 (C-4b), 18.3 (C-4c), 21.6 (C-1b), 25.6 (C-4'e), 25.7 (C-4'b), 25.8 (C-4'c), 65.0 (C-1c), 65.2 (C-1e), 88.7 (C-3), 105.4 (C-1), 110.1 (C-5), 114.3 (d, *J* = 23.3, C-9), 116.5 (d, *J* = 21.2, C-11), 118.3 (C-2e), 119.4 (C-2c), 122.6 (C-2b), 122.9 (d, *J* = 2.8, C-13), 129.2 (d, *J* = 8.0, C-12), 131.3 (C-3b), 137.6 (C-3e), 138.1 (C-3c), 144.9 (d, *J* = 7.1, C-8), 160.0 (C-6), 162.3 (d, *J* = 245.5, C-10), 162.4 (C-2), 163.5 (C-4), 198.3 (d, *J* = 1.9, C-7). [Plate 21]. HRMS (ESI$^+$): Found $[M+Na]^+$ 475.2262, Calc. for $C_{28}H_{33}FNaO_4$ 475.2261.

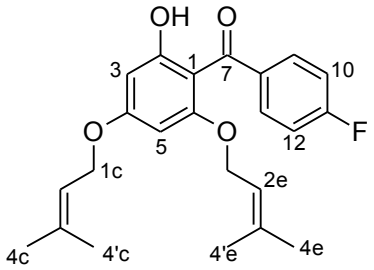
3.7.27 Synthesis of (3-fluorophenyl)[2-hydroxy-3,5-bis(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (3.76)



3.76

A mixture of (3-fluorophenyl)[2,4,6-trihydroxy-3,5-bis(3-methyl-2-butenyl)phenyl] methanone (0.10 g), prenyl bromide (77 mg) and K_2CO_3 (90 mg) in dry acetone (10 mL) was refluxed for 2 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:4) to obtain **3.76** (0.13 g, 98%) as a light orange semisolid, TLC R_f 0.90 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.36 (3H, s, H-4e), 1.59 (3H, s, H-4'e), 1.69 (3H, s, H-4b), 1.71 (6H, s, H-4c,4'b), 1.73 (3H, s, H-4d), 1.79 (3H, s, H-4'd), 1.82 (3H, s, H-4'c), 3.31 (2H, d, *J* = 6.4, H-1b), 3.42 (2H, d, *J* = 6.4, H-1d), 3.96 (2H, d, *J* = 7.0, H-1e), 4.39 (2H, d, *J* = 7.0, H-1c), 4.70 (1H, t, *J* = 7.0, H-2e), 5.16 (1H, t, *J* = 6.4, H-2b), 5.27 (1H, t, *J* = 6.4, H-2d), 5.58 (1H, t, *J* = 7.0, H-2c), 7.23 (1H, dd, *J* = 9.5, 7.8, H-11), 7.39 (1H, m, H-12), 7.42 (1H, d, *J* = 9.5, H-9), 7.51 (1H, d, *J* = 7.8, H-13), 10.88 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.7 (C-4e), 17.9 (C-4d), 17.9 (C-4b), 18.0 (C-4c), 23.3 (C-1d), 23.4 (C-1b), 25.6 (C-4'e), 25.6 (C-4'b), 25.7 (C-4'd), 25.8 (C-4'c), 71.3 (C-1c), 72.7 (C-1e), 110.0 (C-1), 112.0 (C-5), 116.3 (d, *J* = 22.8, C-9), 118.8 (d, *J* = 21.3, C-11), 119.5 (C-2e), 120.4 (C-2c), 121.2 (C-3), 122.8 (C-2d), 124.0 (C-2b), 125.3 (d, *J* = 2.4, C-13), 129.2 (d, *J* = 7.6, C-12), 131.3 (C-3b), 132.1 (C-3d), 137.5 (C-3e), 137.5 (C-3c), 141.9 (d, *J* = 6.6, C-8), 156.7 (C-6), 169.3 (C-2), 162.1 (d, *J* = 248.3, C-10), 162.5 (C-4), 198.1 (C-7). [Plate 22]. HRMS (ESI$^+$): Found $[M+Na]^+$ 543.2882, Calc. for $C_{33}H_{41}FNaO_4$ 543.2887.

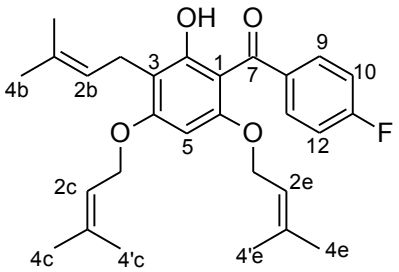
3.7.28 Synthesis of (4-fluorophenyl)[6-hydroxy-2,4-bis(3-methylbut-2-enyloxy)phenyl]methanone (3.83)



3.83

A mixture of (4-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (0.20 g), prenyl bromide (0.48 g) and K_2CO_3 (0.44 g) in dry acetone (10 mL) was refluxed for 6 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:4) to obtain **3.83** (62 mg, 20%) as cream white crystals, mp 86-90 °C, TLC R_f 0.71 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.53 (3H, s, H-4e), 1.62 (3H, s, H-4'e), 1.77 (3H, s, H-4c), 1.83 (3H, s, H-4'c), 4.21 (2H, d, *J* = 6.7, H-1e), 4.56 (2H, d, *J* = 6.7, H-1c), 4.75 (1H, t, *J* = 6.7, H-2e), 5.49 (1H, t, *J* = 6.7, H-2c), 5.94 (1H, d, *J* = 2.4, H-3), 6.18 (1H, d, *J* = 2.4, H-5), 7.04 (2H, m, H-10,12), 7.51 (2H, m, H-9,13), 12.19 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.9 (C-4e), 18.2 (C-4c), 25.5 (C-4'e), 25.8 (C-4'c), 65.0 (C-1e), 65.2 (C-1c), 92.5 (C-3), 94.2 (C-5), 105.6 (C-1), 114.4(d, *J* = 21.9, C-10,12), 118.2 (C-2e), 118.7 (C-2c), 130.0 (d, *J* = 9.1, C-9,13), 137.6 (C-3e), 138.4 (d, *J* = 3.0, C-8), 139.3 (C-3c), 161.1 (C-6), 164.2 (d, *J* = 250.0, C-11), 165.8 (C-4), 166.0 (C-2), 198.0 (C-7). [Plate 27]. HRMS (ESI$^+$): Found $[M+Na]^+$ 407.1640, Calc. for $C_{23}H_{25}FNaO_4$ 407.1635.

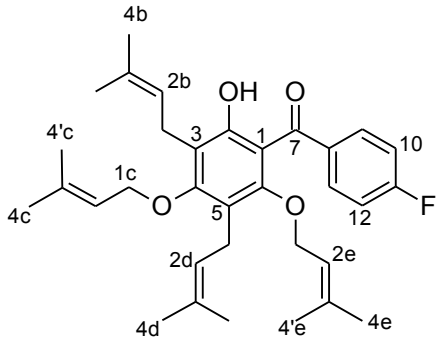
3.7.29 Synthesis of (4-fluorophenyl)[2-hydroxy-3-(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (3.77)



3.77

A mixture of (4-fluorophenyl)[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (0.1 g), prenyl bromide (0.14 g) and K_2CO_3 (0.17 g) in dry acetone (10 mL) was refluxed for 5 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:4) to obtain **3.77** (0.12 g, 85%) as light yellow crystals, mp 114-115 °C, TLC R_f 0.67 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.56 (3H, s, H-4e), 1.64 (3H, s, H-4'e), 1.70 (3H, s, H-4b), 1.77 (3H, s, H-4c), 1.79 (3H, s, H-4'b), 1.83 (3H, s, H-4'c), 3.33 (2H, d, *J* = 7.2, H-1b), 4.22 (2H, d, *J* = 6.6, H-1e), 4.60 (2H, d, *J* = 6.7, H-1c), 4.77 (1H, t, *J* = 6.6, H-2e), 5.26 (1H, t, *J* = 7.2, H-2b), 5.49 (1H, t, *J* = 6.7, H-2c), 5.95 (1H, s, H-3), 7.04 (2H, m, H-10,12), 7.53 (2H, m, H-9,13), 12.08 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.7 (C-4e), 17.9 (C-4b), 18.3 (C-4c), 21.6 (C-1b), 25.5(C-4'e), 25.7 (C-4'b), 25.8 (C-4'c), 65.1 (C-1c), 65.2 (C-1e), 88.9 (C-3), 105.7 (C-1), 110.2 (C-5), 114.4 (d, *J* = 21.9, C-10,12), 118.6 (C-2e), 119.5 (C-2c), 122.7 (C-2b), 130.0 (d, *J* = 9.1, C-9,13), 131.2 (C-3b), 137.4 (C-3e), 138.0 (C-3c), 138.7 (d, *J* = 3.0, C-8), 159.7 (C-6), 162.0 (C-2), 163.1 (C-4), 164.1 (d, *J* = 263.9, C-11), 198.3 (C-7). [Plate 25]. HRMS (ESI$^+$): Found $[M+Na]^+$ 475.2263, Calc. for $C_{28}H_{33}FNaO_4$ 475.2261.

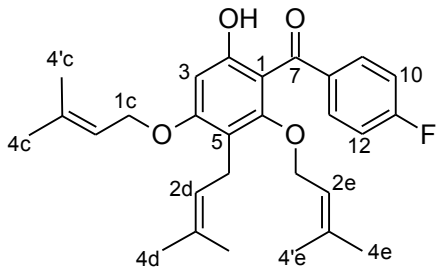
3.7.30 Synthesis of (4-fluorophenyl)[2-hydroxy-3,5-bis(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (3.78)



3.78

A mixture of (4-fluorophenyl)[2,4,6-trihydroxy-3,5-bis(3-methyl-2-butenyl)phenyl] methanone (0.1 g), prenyl bromide (77 mg) and K_2CO_3 (90 mg) in dry acetone (10 mL) was refluxed for 2 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:4) to obtain **3.78** (0.13 g, 98%) as a light orange semisolid, TLC R_f 0.90 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.35 (3H, s, H-4e), 1.58 (3H, s, H-4'e), 1.67-1.74 (12H, m, H-4b,4c,4'b,4d), 1.79 (3H, s, H-4'd), 1.82 (3H, s, H-4'c), 3.31 (2H, d, *J* = 6.3, H-1b), 3.41 (2H, d, *J* = 6.6, H-1d), 3.94 (2H, d, *J* = 7.0, H-1e), 4.38 (2H, d, *J* = 6.9, H-1c), 4.70 (1H, t, *J* = 7.0, H-2e), 5.15 (1H, t, *J* = 6.3, H-2b), 5.27 (1H, t, *J* = 6.6, H-2d), 5.58 (1H, t, *J* = 6.9, H-2c), 7.10 (2H, m, H-10,12), 7.78 (2H, m, H-9,13), 10.81 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.7 (C-4e), 17.9 (C-4d), 17.9 (C-4b), 18.0 (C-4c), 23.3 (C-1d), 23.4 (C-1b), 25.6 (C-4'e), 25.6 (C-4'b), 25.7 (C-4'd), 25.8 (C-4'c), 71.3 (C-1c), 72.5 (C-1e), 112.0 (C-1), 114.7 (d, *J* = 22.0, C-10,12), 119.4 (C-2e), 119.5 (C-2c), 120.4 (C-3), 121.1 (C-5), 122.9 (C-2d), 124.1 (C-2b), 131.2 (C-3b), 132.0 (C-3d), 132.3 (d, *J* = 9.0,C-9,13), 135.7 (d, *J* = 3.0, C-8), 137.5 (C-3e), 137.6 (C-3c), 156.5 (C-6), 159.1 (C-2), 162.1 (C-4), 165.2 (d, *J* = 255.0, C-11), 197.9 (C-7). [Plate 26]. HRMS (ESI$^+$): Found $[M+Na]^+$ 543.2884, Calc. for $C_{33}H_{41}FNaO_4$ 543.2887.

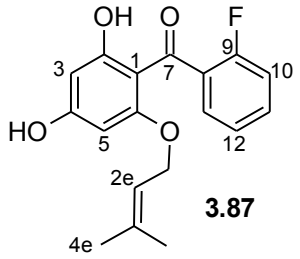
3.7.31 Synthesis of (4-fluorophenyl)[6-hydroxy-3-(3-methylbut-2-enyl)-2,4-bis(3-methylbut-2-enyloxy)phenyl]methanone (3.84)



3.84

A mixture of (4-fluorophenyl)[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (0.10 g), prenyl bromide (0.14 g) and K_2CO_3 (0.17 g) in dry acetone (10 mL) was refluxed for 5 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. A combined organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:4) to obtain **3.84** (21 mg, 15%) as a light orange semisolid, TLC R_f 0.43 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.59 (6H, s, H-4e,4d), 1.67 (3H, s, H-4'd), 1.68 (3H, s, H-4'e), 1.79 (3H, s, H-4c), 1.83 (3H, s, H-4'c), 3.39-4.46 (4H, m, H-1e,1d), 4.64 (2H, d, *J* = 6.6, H-1c), 5.18 (1H, t, *J* = 6.5, H-2e), 5.33 (1H, t, *J* = 7.3, H-2d), 5.53 (1H, t, *J* = 6.6, H-2c), 6.38 (1H, s, H-3), 7.04 (2H, m, H-10,12), 7.83 (2H, m, H-9,13). ^{13}C NMR (100 MHz, $CDCl_3$) 17.9 (C-4d), 18.1 (C-4e), 18.4 (C-4c), 25.6 (C-4'e), 25.7 (C-4'd), 25.8 (C-4'c), 66.0 (C-1e), 66.6 (C-1c), 71.7 (C-1d), 95.7 (C-5), 99.5 (C-1), 115.4 (d, *J* = 22.2, C-10,12), 118.0 (C-3), 119.1 (C-2e), 119.1 (C-2c), 119.5 (C-2d), 132.1 (d, *J* = 9.6, C-9,13), 134.6 (d, *J* = 3.0, C-8), 138.0 (C-3e), 138.5 (C-3c), 139.1 (C-3d), 155.1 (C-6), 156.5 (C-2), 157.6 (C-4), 165.8 (d, *J* = 254.4, C-11), 192.4 (C-7). [Plate 28]. HRMS (ESI^+): Found $[M+Na]^+$ 475.2265, Calc. for $C_{28}H_{33}FNaO_4$ 475.2261.

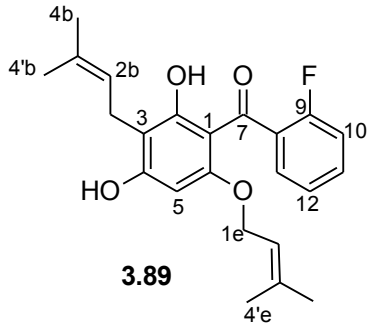
3.7.32 Synthesis of (2-fluorophenyl)[2,4-dihydroxy-6-(3-methylbut-2-enyloxy)phenyl]methanone (3.87)



3.87

A mixture of (2-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (2.0 g), prenyl bromide (1.3 g) and K_2CO_3 (1.3 g) in dry acetone (15 mL) was refluxed for 1 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. A combined organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:4) to give a light yellow solid product (1.8 g, 65%). After recrystallization (1:9 Hexanes-EtOAc), **3.87** was obtained as light yellow crystals, mp 138-139 °C. TLC R_f 0.61 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.78 (3H, s, H-4e), 1.83 (3H, s, H-4'e), 4.62 (2H, d, *J* = 6.8, H-1e), 5.51 (1H, t, *J* = 6.8, H-2e), 6.37 (1H, d, *J* = 2.2, H-3), 6.45 (1H, d, *J* = 2.2, H-5), 7.38 (1H, t, *J* = 7.6, H-12), 7.44 (1H, dd, *J* = 8.5, 7.6, H-10), 7.72 (1H, t, *J* = 7.6, H-11), 8.62 (1H, d, *J* = 7.6, H-13), 12.86 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 18.3 (C-4e), 25.8 (C-4'e), 65.5 (C-1e), 93.5 (C-5), 97.6 (C-3), 103.6 (C-1), 117.6 (C-10), 118.5 (C-2e), 120.4(C-8), 123.9 (C-12), 125.9 (C-13), 134.9 (C-11), 139.4 (C-3e), 157.7 (C-6), 157.7 (C-9), 163.5 (C-2), 166.1 (C-4), 181.5 (C-7). [Plate 33]. HRMS (ESI$^+$): Found $[M+Na]^+$ 317.3141, Calc. for $C_{18}H_{18}FNaO_4$ 317.3161.

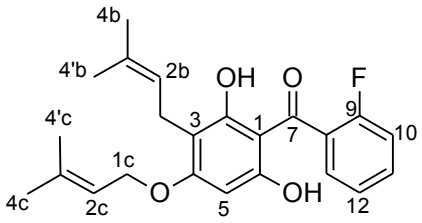
3.7.33 Synthesis of (2-fluorophenyl)[2,4-dihydroxy-3-(3-methylbut-2-enyl)-6-(3-methylbut-2-enyloxy)phenyl]methanone (3.89)



3.89

A mixture of (2-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (2.0 g), prenyl bromide (2.6 g) and K_2CO_3 (2.8 g) in dry acetone (15 mL) was refluxed for 3 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. A combined organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:4) to give a light yellow solid product (1.2 g, 38%). After recrystallization (Hexanes-EtOAc, 1:9), **3.89** was obtained as a light yellow crystals, mp 98-100 °C, TLC R_f 0.70 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.68 (3H, s, H-4b), 1.77 (3H, s, H-4e), 1.82 (3H, s, H-4'e), 1.87 (3H, s, H-4'b), 3.51 (2H, d, *J* = 7.4, H-1b), 4.63 (2H, d, *J* = 6.5, H-1e), 5.24 (1H, t, *J* = 7.4, H-2b), 5.50 (1H, t, *J* = 6.5, H-2e), 6.40 (1H, s, H-5), 7.37 (1H, t, *J* = 7.6, H-12), 7.46 (1H, dd, *J* = 8.3, 7.6, H-10), 7.71 (1H, t, *J* = 7.6, H-11), 8.25 (1H, d, *J* = 7.6, H-13), 12.96 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.8 (C-4'b), 18.3 (C-4e), 21.7 (C-1b), 25.7 (C-4b), 25.8 (C-4'e), 65.5 (C-1e), 95.1 (C-5), 103.6 (C-1), 117.6 (C-10), 119.0 (C-2e), 120.4 (C-8), 122.2 (C-2b), 123.7 (C-12), 125.8 (C-13), 131.5 (C-3b), 134.8 (C-11), 138.5 (C-3e), 154.1 (C-4), 156.2 (C-9), 161.9 (C-2), 163.7 (C-6), 181.5 (C-7). [Plate 35]. HRMS (ESI$^+$): Found $[M+Na]^+$ 407.1633, Calc. for $C_{23}H_{25}FNaO_4$ 407.1635.

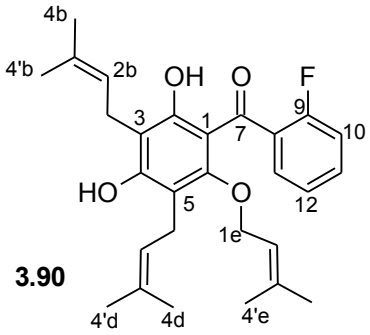
3.7.34 Synthesis of (2-fluorophenyl)[2,6-dihydroxy-3-(3-methylbut-2-enyl)-4-(3-methylbut-2-enyloxy)phenyl]methanone (3.88)



3.88

A mixture of (2-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (2.0 g), prenyl bromide (2.6 g) and K_2CO_3 (2.8 g) in dry acetone (15 mL) was refluxed for 3 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. A combined organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:4) to give a light yellow solid product (1.9 g, 60%). After recrystallization (Hexanes-EtOAc, 1:9), **3.88** was obtained as light yellow crystals, mp 122-123 °C, TLC R_f 0.74 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.70 (3H, s, H-4b), 1.79 (3H, s, H-4c), 1.81 (3H, s, H-4'b), 1.84 (3H, s, H-4'c), 3.39 (2H, d, *J* = 7.2, H-1b), 4.65 (2H, d, *J* = 6.6, H-1c), 5.27 (1H, t, *J* = 7.2, H-2b), 5.53 (1H, t, *J* = 6.6, H-2c), 6.45 (1H, s,H-5), 7.37 (1H, t, *J* = 7.6, H-12), 7.43 (1H, dd, *J* = 8.5, *J* = 7.6, H-10), 7.70 (1H, t, *J* = 7.6, H-11), 8.27 (1H, d, *J* = 7.6, H-13), 12.92 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.8 (C-4'b), 18.3 (C-4c), 21.4(C-1b), 25.7 (C-4d), 25.8 (C-4'c), 65.6 (C-1c), 90.7 (C-5), 103.7 (C-1), 112.2 (C-3), 117.4 (C-10), 119.0 (C-2c), 120.8 (C-8), 122.1(C-2b), 123.8 (C-12), 125.9 (C-13), 131.7 (C-3b), 134.6 (C-11), 138.5 (C-3c), 155.9 (C-9), 156.3 (C-6), 159.7 (C-2), 163.8 (C-4), 180.7 (C-7). [Plate 34]. HRMS (ESI^+): Found $[M+Na]^+$ 407.1630, Calc. for $C_{23}H_{25}FNaO_4$ 407.1635.

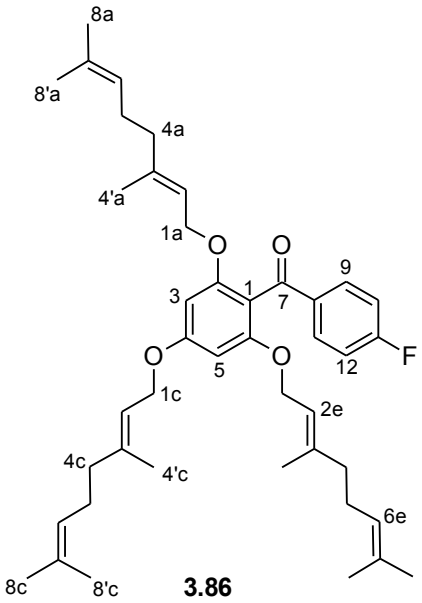
3.7.35 Synthesis of (2-fluorophenyl)[2,4-dihydroxy-3,5-bis(3-methylbut-2-enyl)-6-(3-methylbut-2-enyloxy)phenyl]methanone (3.90)



3.90

A mixture of (2-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (2.0 g), prenyl bromide (4.8 g) and K_2CO_3 (4.5 g) in dry acetone (15 mL) was refluxed for 6 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. A combined organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was reduced *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:4) and **3.90** was obtained as a light yellow amorphous solid (2.5 g, 68%), TLC R_f 0.83 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.71 (9H, m, H-4b,4e,4d), 1.81 (3H, s, H-4'b), 1.82 (3H, s, H-4e'), 1.89 (3H, s, H-4'd), 3.45 (2H, d, *J* = 6.6, H-1b), 3.57 (2H, d, *J* = 6.8, H-1d), 4.65 (2H, d, *J* = 7.0, H-1e), 5.25 (1H, t, *J* = 6.8, H-2d), 5.28 (1H, t, *J* = 6.6, H-2b), 5.61 (1H, t, *J* = 6.6, H-2e), 7.37 (1H, t, *J* = 7.6, H-12), 7.47 (1H, dd, *J* = 8.5, 7.6, H-10), 7.72 (1H, t, *J* = 7.6, H-11), 8.28 (1H, d, *J* = 7.6, H-13), 12.96 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 17.9 (C-4d), 18.0 (C-4b), 18.1 (C-4e), 22.8 (C-1d), 23.0 (C-1b), 25.7 (C-4'b), 25.7 (C-4'd), 25.8 (C-4'e), 71.8 (C-1e), 106.1 (C-1), 113.4 (C-5), 117.5 (C-3), 117.7 (C-10), 120.2 (C-2e), 120.4 (C-8), 122.7 (C-2b), 122.9 (C-2d), 123.8 (C-12), 125.9 (C-13), 131.7 (C-3b), 132.0 (C-3d), 135.0 (C-11), 137.9 (C-3e), 153.2 (C-9), 156.2 (C-6), 159.0 (C-2), 162.9 (C-4), 181.8 (C-7). [Plate 36]. HRMS (ESI^+): Found $[M+Na]^+$ 475.4267, Calc. for $C_{28}H_{33}FNaO_4$ 475.4261.

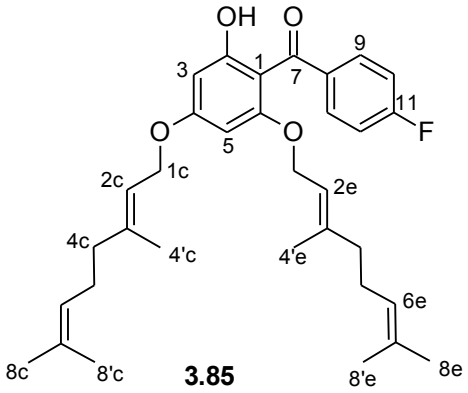
3.7.36 Synthesis of (4-fluorophenyl)[2,4,6-tris(3,7-dimethylocta-2,6-dienyloxy)phenyl]methanone (3.86)



3.86

A mixture of (4-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (1.0 g), geranyl bromide (3.5 g) and K_2CO_3 (2.2 g) in dry acetone (10 mL) was refluxed for 6 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc (3 x 20 mL). A combined organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was removed under reduced pressure, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:9), and **3.86** was obtained as a light orange oil (0.32 g, 12%), TLC R_f 0.57 (Hexanes-EtOAc, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$) 1.58 (6H, s, H-4'a,4'e), 1.58 (6H, s, H-8a,8e), 1.64 (3H, s, H-8c), 1.66 (6H, s, H-8'a,8'e), 1.70 (3H, s, H-8'c), 1.78 (3H, s, H-4'c), 1.81-1.90 (8H, m, H-4a,4e,5a,5e), 1.98-2.06 (4H, m, H-4c,5c), 4.45 (4H, d, *J* = 6.3, H-1a,1e), 4.57 (2H, d, *J* = 6.6, H-1c), 5.03 (2H, t, *J* = 6.2, H-6a,6e), 5.13 (1H, t, *J* = 6.1, H-6c), 5.21 (2H, t, *J* = 6.3, H-2a,2e), 5.52 (1H, t, *J* = 6.6, H-2c), 6.19 (2H, s, H-3,5), 7.06 (2H, m, H-10,12), 7.85 (2H, m, H-9,13). ^{13}C NMR (100 MHz, $CDCl_3$) 16.5 (C-4'c), 16.7 (C-4'a,4'e), 17.6 (C-8a,8e), 17.7 (C-8c), 25.6 (C-8'a,8'e), 25.7 (C-8'c), 26.2 (C-5a,5e), 26.3 (C-5c), 39.4 (C-4a,4e), 39.6 (C-4c), 65.0 (C-1c), 65.7 (C-1a,1e), 92.9 (C-3,5), 110.3 (C-1), 114.1 (d, *J* = 21.6, C-10,12), 119.1 (C-2c), 119.4 (C-2a,2e), 123.7 (C-6a,6e), 123.7 (C-6c), 131.7 (C-7a,7e), 131.9 (C-7c), 131.9 (d, *J* = 9.4, C-9,13), 135.3 (d, *J* = 2.7, C-8), 140.5 (C-3a,3e), 141.6 (C-3c), 158.0 (C-2,6), 161.5 (C-4), 166.2 (d, *J* = 253.3, C-11), 193.5 (C-7). [Plate 32]. HRMS (ESI$^+$): Found $[M+Na]^+$ 679.4142, Calc. for $C_{43}H_{57}FNaO_4$ 679.4139.

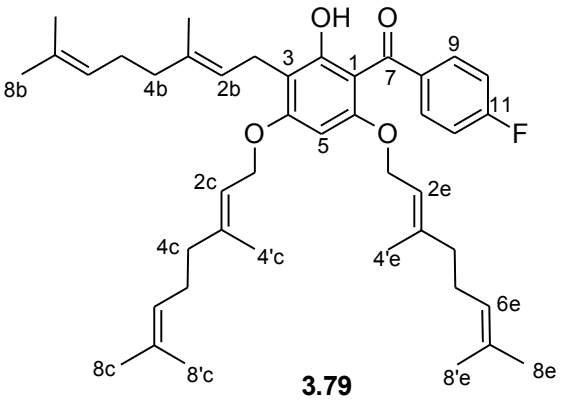
3.7.37 Synthesis of (4-fluorophenyl)[2-hydroxy-4,6-bis(3,7-dimethylocta-2,6-dienyloxy)phenyl]methanone (3.85)



3.85

A mixture of (4-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (1.0 g), geranyl bromide (3.5 g) and K_2CO_3 (2.2 g) in dry acetone (10 mL) was refluxed for 6 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc (3 x 20 mL). A combined organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was removed under reduced pressure, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:9), and **3.85** was obtained as a light orange oil (0.42 g, 20%), TLC R_f 0.63 (Hexanes-EtOAc, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (3H, s, H-4'e), 1.61 (3H, s, H-8e), 1.63 (3H, s, H-8c), 1.70 (3H, s, H-8'e), 1.70 (3H, s, H-8'c), 1.77 (3H, s, H-4'c), 1.85-2.05 (4H, m, H-4e,5e), 2.07-2.20 (4H, m, H-4c,5c), 4.25 (2H, d, *J* = 6.4, H-1e), 4.60 (2H, d, *J* = 6.6, H-1c), 4.76 (1H, t, *J* = 6.5, H-2e), 5.04 (2H, t, *J* = 6.9, H-6e), 5.12 (1H, t, *J* = 6.5, H-6c), 5.50 (1H, t, *J* = 6.6, H-2c), 5.95 (1H, s, H-3), 6.17 (1H, s, H-5), 7.04 (2H, m, H-10,12), 7.54 (2H, m, H-9,13), 10.18 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 16.6 (C-4'e), 16.7 (C-4'c), 17.6 (C-8e), 17.7 (C-8c), 25.7 (C-8'e), 25.7 (C-8'c), 26.1 (C-5e), 26.3 (C-5c), 39.2 (C-4e), 39.5 (C-4c), 65.2 (C-1e), 65.3 (C-1c), 92.6 (C-3), 94.2 (C-5), 105.6 (C-1), 114.5 (d, *J* = 21.3, C-10,12), 117.8 (C-2e), 118.4 (C-2c), 123.7 (C-6e), 123.7 (C-6c), 130.1 (d, *J* = 9.1, C-9,13), 131.8 (C-7e), 131.9 (C-7c), 138.4 (d, *J* = 3.5, C-8), 140.8 (C-3e), 142.3 (C-3c), 161.1 (C-6), 164.4 (d, *J* = 250.0, C-11), 168.5 (C-2), 166.0 (C-4), 198.0 (C-7). [Plate 31]. HRMS (ESI$^+$): Found $[M+Na]^+$ 543.2878, Calc. for $C_{33}H_{41}FNaO_4$ 543.2887.

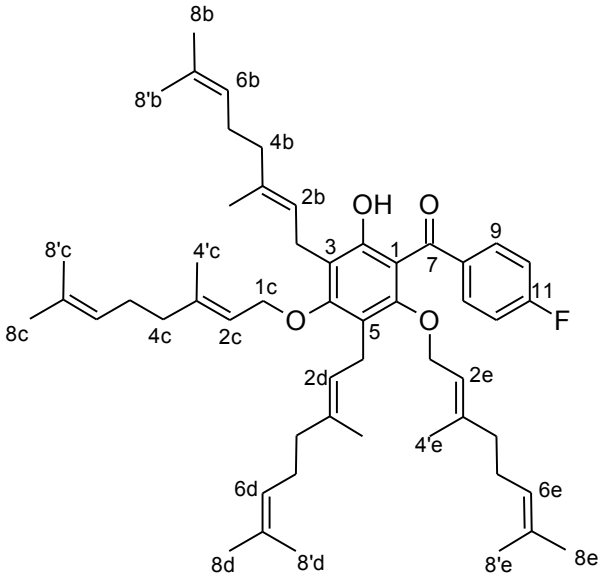
3.7.38 Synthesis of (4-fluorophenyl)[2-hydroxy-3-(3,7-dimethylocta-2,6-dienyl)-4,6-bis(3,7-dimethylocta-2,6-dienyloxy)phenyl]methanone (3.79)



3.79

A mixture of (4-fluorophenyl)[2,4,6-trihydroxy-3-(3,7-dimethylocta-2,6-dienyl)phenyl] methanone (1.0 g), geranyl bromide (1.7 g) and K_2CO_3 (1.4 g) in dry acetone (10 mL) was refluxed for 5 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc. A combined organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was removed *in vacuo*, the crude was purified by column chromatography (Hexanes-EtOAc, 1:9) to obtain 1.3 g (76%) of **3.79** as a light orange semisolid, TLC R_f 0.78 (Hexanes-EtOAc, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$) 1.57 (3H, s, H-4'e), 1.60 (3H, s, H-8b), 1.61 (3H, s, H-8e), 1.63 (3H, s, H-8c), 1.67 (3H, s, H-8'b), 1.70 (3H, s, H-8'e), 1.70 (3H, s, H-8'c), 1.76 (3H, s, H-4'c), 1.79 (3H, s, H-4'b), 1.87-2.05 (4H, m, H-4e,5e), 2.04-2.20 (8H, m, H-4c,4b,5c,5b), 3.35 (2H, d, *J* = 7.1, H-1b), 4.25 (2H, d, *J* = 6.4, H-1e), 4.62 (2H, d, *J* = 6.4, H-1c), 4.76 (1H, t, *J* = 6.4, H-2e), 5.05 (2H, t, *J* = 7.2, H-6e), 5.08-5.17 (2H, m, H-6c,6b), 5.27 (1H, t, *J* = 7.1, H-2b), 5.50 (1H, t, *J* = 6.5, H-2c), 5.96 (1H, s, H-3), 7.04 (2H, m, H-10,12), 7.55 (2H, m, H-9,13), 12.00 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 16.1(C-4'b), 16.6 (C-4'e), 16.7 (C-4'c), 17.6 (C-8e), 17.6 (C-8c), 17.7 (C-8b), 21.6 (C-1b), 25.6 (C-8'e), 25.6 (C-8'b), 25.6 (C-8'c), 26.2 (C-5e), 26.3 (C-5c), 26.8 (C-5b), 39.3 (C-4e), 39.5 (C-4c), 39.9 (C-4b), 65.2 (C-1e), 65.3 (C-1c), 88.9 (C-3), 105.7 (C-1), 110.2 (C-5), 114.4 (d, *J* = 21.6, C-10,12), 118.2 (C-2e), 119.3 (C-2c), 122.5 (C-2b), 123.7 (C-6e), 123.7 (C-6c), 124.5 (C-6b), 130.1 (d, *J* = 8.5, C-9,13), 131.1 (C-7b), 131.8 (C-7e), 131.9 (C-7c), 134.7 (C-3b), 138.7 (d, *J* = 3.0, C-8), 140.6 (C-3e), 141.3 (C-3c), 159.7 (C-6), 162.0 (C-2), 163.2 (C-4), 164.2 (d, *J* = 251.9, C-11), 198.3 (C-7). [Plate 29]. HRMS (ESI$^+$): Found $[M+Na]^+$ 679.4142, Calc. for $C_{43}H_{57}FNaO_4$ 679.4141.

3.7.39 Synthesis of (4-fluorophenyl)[2-hydroxy-3,5-bis(3,7-dimethylocta-2,6-dienyl)-4,6-bis(3,7-dimethylocta-2,6-dienyloxy) phenyl]methanone (3.80)

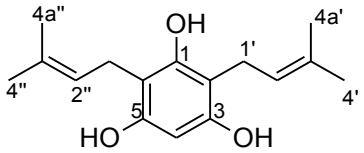


3.80

A mixture of (4-fluorophenyl)[2,4,6-trihydroxy-3,5-bis(3,7-dimethylocta-2,6-dienyl)phenyl]methanone (1.0 g), geranyl bromide (0.90 g) and K_2CO_3 (0.66 g) in dry acetone (10 mL) was refluxed for 2 h. The mixture was allowed to cool before being filtered through a sintered funnel. The filtrate was washed with a minimal amount of water and extracted with EtOAc (3 x 20 mL). A combined organic layer was dried over anhydrous $MgSO_4$. After the solvent of the mixture was removed *in vacuo*, the mixture was purified by column chromatography (Hexanes-EtOAc, 1:9) to give 1.3 g (88%) of **3.80** as a light yellow semisolid, TLC R_f 0.87 (Hexanes-EtOAc, 1:10). ^{1}H NMR (400 MHz, $CDCl_3$) 1.35 (3H, s, H-4'e), 1.59 (6H, s, H-8d,8b), 1.60 (3H, s, H-8e), 1.64 (3H, s, H-8c), 1.65 (6H, s, H-8'd,8'b), 1.69 (3H, s, H-8'e), 1.69 (3H, s, H-8'c), 1.72 (3H, s, H-4'c), 1.72 (3H, s, H-4'b), 1.79 (3H, s, H-4'd), 1.82-1.90 (4H, m, H-4e,5e), 1.92-2.20 (12H, m, H-4b,4c,4d,5b,5c,5d), 3.33 (2H, d, *J* = 6.2, H-1b), 3.43 (2H, d, *J* = 6.3, H-1d), 3.97 (2H, d, *J* = 6.9, H-1e), 4.41 (2H, d, *J* = 6.6, H-1c), 4.70 (1H, t, *J* = 6.9, H-2e), 5.02 (2H, t, *J* = 7.0, H-6e), 5.05-5.11 (2H, m, H-6d,6b), 5.11-5.22 (2H, m, H-6c,2b), 5.29 (1H, t, *J* = 6.4, H-2d), 5.59 (1H, t, *J* = 6.7, H-2c), 7.09 (2H, m, H-10,12), 7.78 (2H, m, H-9,13), 10.84 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) 16.2 (C-4'd), 16.3 (C-4'b), 16.4 (C-4'e), 16.6 (C-4'c), 17.6 (C-8e), 17.6 (C-8c), 17.6 (C-8b), 17.7 (C-8d), 23.3 (C-1b), 23.4 (C-1d), 25.6 (C-8'e), 25.6 (C-8'c), 25.7 (C-8'b), 26.2 (C-5e), 26.1 (C-5e), 26.4 (C-5c), 26.7 (C-5b), 26.7 (C-

5d), 39.4 (C-4e), 39.6 (C-4c), 39.7 (C-4b), 39.7 (C-4d), 71.3 (C-1e), 72.6 (C-1c), 112.0 (C-1), 114.7 (d, *J* = 21.9, C-10,12), 119.0 (C-2e), 119.5 (C-2c), 120.2 (C-3), 121.1 (C-5), 122.8 (C-2d), 123.8 (C-6e), 123.9 (C-6c), 124.0 (C-2b), 124.3 (C-6d), 124.3 (C-6b), 131.2 (C-7b), 131.3 (C-7d), 131.7 (C-7e), 131.8 (C-7c), 132.4 (d, *J* = 9.0, C-9,13), 134.8 (C-3b), 135.6 (C-3d), 135.7 (d, *J* = 3.0, C-8), 140.7 (C-3e), 140.8 (C-3c), 156.6 (C-6), 159.2 (C-2), 162.2 (C-4), 165.3 (d, *J* = 251.9, C-11), 197.9 (C-7). [Plate 30]. HRMS (ESI^+): Found $[M+Na]^+$ 815.5397, Calc. for $C_{53}H_{73}FNaO_4$ 815.5391.

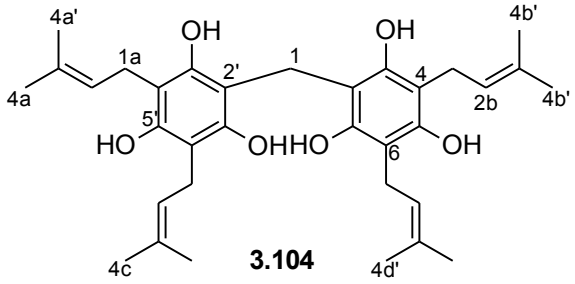
3.7.40 Synthesis of 2,4-bis(3-methyl-2-butenyl)-1,3,5-benzenetriol (3.103)



3.103

To a mixture of phloroglucinol (1.0 g, 7.93 mmol) and prenyl bromide (2.36 g, 15.86 mmol) in dry THF (50 mL) was added DBU (2.42 g, 15.86 mmol) in small increments. The mixture was stirred at room temperature for 6 h. After addition of 2 M HCl (20 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (4 x 30 mL), washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The crude was purified by silica gel column chromatography (Hexanes-EtOAc 1:9) and **3.103** was obtained as a deep orange oil (1.5 g, 5.71 mmol, 72%), TLC R_f 0.63 (Hexanes-EtOAc, 1:9). ^1H NMR (400 MHz, $CDCl_3$) 1.74 (6H, s, H-4',4"), 1.81 (6H, s, H-4a',4a"), 3.34 (4H, d, *J* = 7.1, H-1',1"), 5.24 (2H, m, H-2',2"), 5.97 (1H, s, H-6). ^{13}C NMR (400 MHz, $CDCl_3$) 17.8 (C-4a',4a"), 22.4 (C-1',1"), 25.7 (C-4',4"), 96.2 (C-4), 106.5 (C-2), 122.4 (C-2',2"), 134.8 (C-3',3"), 152.9 (C-3,5), 154.1 (C-1). IR (neat) ν_{max} (cm^{-1}): 3412, 2916, 1572, 1574, 1423, 1135.

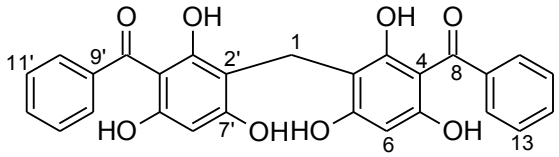
3.7.41 *Synthesis of 2,2'-methylene bis[2,4-bis(3-methyl-2-butenyl)-1,3,5-benzenetriol] (3.104)*



3.104

To a stirred mixture of 2,4-bis(3-methyl-2-butenyl)-1,3,5-benzenetriol (0.05 g, 0.19 mmol) and paraformaldehyde (3 mg, 0.1 mmol) in THF (3 mL) was added a mixture of 4 M HCl in diethyl ether (2.0 mL). The mixture was heated in a microwave oven (100 W power, 100 Psi pressure, 50 ºC) for 10 min. After addition of 2 M HCl (5 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (3 x 10 mL), washed with brine (6 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent under vacuum resulted in an orange crude product which was purified by silica gel column chromatography (Hexanes-EtOAc, 2:8) giving **3.104** as a light orange viscous liquid (0.06 g, 0.12 mmol, 65%), TLC R_f 0.58 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 1.61 (12H, s, H-4a,4b,4c,4d), 1.66 (12H, s, H-4a',4b',4c',4d'), 2.36-2.55 (8H, m, H-1a,1b,1c,1d), 3.39 (2H, s, H-1), 4.91 (4H, m, H-2a,2b,2c,2d). ^{13}C NMR (100 MHz, $CDCl_3$) 17.9 (C-4a',4b',4c',4d'), 27.8 (C-4a,4b,4c,4d), 33.5 (C-1a,1b,1c,1d), 67.5 (C-2,2'), 117.8 (C-2a,2b,2c,2d), 134.8 (C-4,4',6,6'), 136.1 (C-3a,3b,3c,3d), 203.9 (C-3,3',7,7'), 207.3 (C-5,5'). IR (neat) ν_{max} (cm^{-1}): 3511, 2941, 1589, 1580, 1400, 1115.

3.7.42 *Synthesis of methylene bis(3-benzoyl-2,4,6-trihydroxybenzene) (3.100)*

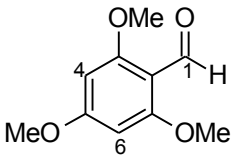


3.100

A mixture of phenyl(2,4,6-trihydroxyphenyl)methanone (0.2 g, 0.87 mmol) and para-formaldehyde (0.026 g, 0.87 mmol) was stirred in toluene (10 mL) at room temperature for 2 min. A mixture of 2M HCl (5 mL) in diethyl ether (5 mL) was added to the reaction

mixture and was stirred at room temperature for a further 18 h. After addition of 2 M HCl (10 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (3 x 20 mL), washed with brine (10 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent under vacuum resulted in a yellow crude product which was purified by silica gel column chromatography (Hexanes-EtOAc, 3:7) giving **3.100** as a yellow solid (0.34 g, 0.722 mmol, 83%), mp 249-252 ºC, TLC R_f 0.41 (Hexanes-EtOAc, 3:7). ^{1}H NMR (400 MHz, DMSO-d_6) 3.62 (2H, s, H-1), 6.01 (2H, s, H-6,6'), 7.44 (4H, t, *J* = 7.6, H-11,11',13,13'), 7.54 (2H, t, *J* = 7.6, H-12,12'), 7.63 (4H, d, *J* = 7.6, H-10,10',14,14'), 9.70 (2H, s, 7,7'-OH), 10.14 (2H, bs, 3,3'-OH), 10.58 (2H, bs, 5,5'-OH). ^{13}C NMR (100 MHz, DMSO-d_6) 16.4 (C-1), 95.2 (C-6,6'), 105.8 (C-2,2'), 107.2 (C-4,4'), 128.5 (C-11,11',13,13'), 128.9 (C-10,10',14,14'), 132.3 (C-12,12'), 140.1 (C-9,9'), 156.8 (C-5,5'), 157.3 (C-3,3'), 157.7 (C-7,7'), 196.9 (C-8,8'). IR (neat) ν_{max} (cm^{-1}): 3620, 1637, 1588, 1551, 1320.

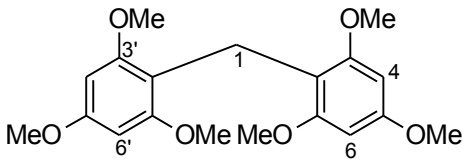
3.7.43 Synthesis of 2,4,6-trimethoxybenzaldehyde (3.105)



3.105

N,N-Dimethylformamide (1.00 mL, 12.8 mmol) was cooled to 0 °C and freshly distilled $POCl_3$ (1.2 mL, 12.8 mmol) was added. The faint orange solution was stirred vigorously for approximately 5 min until the mixture solidified. Distilled acetonitrile (10 mL) was added until the white solid dissolved. The reaction mixture was stirred for a further 30 min at room temperature. A solution of 1,3,5-trimethoxybenzene (1.6 g, 12.8 mmol) in acetonitrile (10 mL) was added to the reaction mixture and stirred under reflux for 15 h. After the mixture was cooled to room temperature, a solution of methanol-water (2:1, 10 mL) was added for imine hydrolysis and was stirred for 45 min. The resulting product was purified by silica gel column chromatography with 25% EtOAc in hexanes as eluent to obtain **3.105** as a cream crystalline solid (1.3 g, 54%), mp 122-124 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) 3.84 (3H, s, 5-OCH_3), 3.85 (6H, s, 3,7-OCH_3), 6.04 (2H, s, H-4,6), 10.32 (1H, s, H-1). ^{13}C NMR (100 MHz, $CDCl_3$) 55.7 (5-OCH_3), 56.2 (3,7-OCH_3), 90.5 (C-4,6), 109.1 (C-2), 164.3 (C-3,7), 166.4 (C-5), 187.9 (C-1). IR (neat) ν_{max} (cm^{-1}): 2920, 2796, 1662, 1596, 1575, 1131.

3.7.44 Synthesis of methylene bis(2,4,6-trimethoxybenzene) (3.99)



3.99

A mixture of 1,3,5-trimethoxybenzene (0.63 g, 5.0 mmol) and para-formaldehyde (0.15 g, 5.0 mmol) in toluene was stirred at room temperature for 2 h. 2 M HCl in diethyl ether (8.0 mL) was then added dropwise to the mixture and stirred for a further 48 h. After addition of 2 M HCl (10 mL), the mixture was stirred for a further 15 min and extracted with EtOAc (3 x 15 mL), washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The removal of the solvent under vacuum resulted in a yellow crude product. The crude product was purified by silica gel column chromatography (Hexanes-EtOAc, 3:7) giving **3.99** as colourless-white crystalline solid (1.7 g, 95%), TLC R_f 0.62 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 3.73 (12H, s, 3,3',7,7'-OCH_3), 3.78 (6H, s, 5,5'-OCH_3), 3.87 (2H, s, H-1), 6.12 (4H, s, H-4,4'6,6'). ^{13}C NMR (100 MHz, $CDCl_3$) 16.7 (C-1), 55.2 (5,5'-OCH_3), 56.1 (3,3',7,7'-OCH_3), 91.3 (C-2,2'), 112.1 (C-4,4',6,6'), 158.7 (C-5,5'), 159.3 (C-3,3',7,7'). IR (neat)ν_{max} (cm^{-1}): 3002, 2958, 1593, 1327.

CHAPTER 4. 4-PHENYLCOUMARINS

4.1 Introduction

Coumarins are a class of phenolic compounds characterized by a benzene ring fused to a pyrone ring (**4.1**) and are structurally diverse. They can roughly be classified into five major groups (Figure 4.1), simple coumarins (**4.2**), pyranocoumarins (**4.3**), furocoumarins (**4.4**), pyrone-substituted coumarins (**4.5**) and dimeric coumarins (**4.6**).[154] Coumarins with substituents on the benzene ring are named 'simple' coumarins. The second group of coumarins, pyranocoumarins, contains a linear- or an angular-fused six-membered oxygen heterocyclic ring. Furocoumarins are compounds with the coumarin moiety fused to a five-membered furan ring. Pyrone-substituted coumarins have substituents on the pyrone ring, at either position 3 or 4. The last group are dimeric coumarins which are characterized by two or more coumarin units linked together.

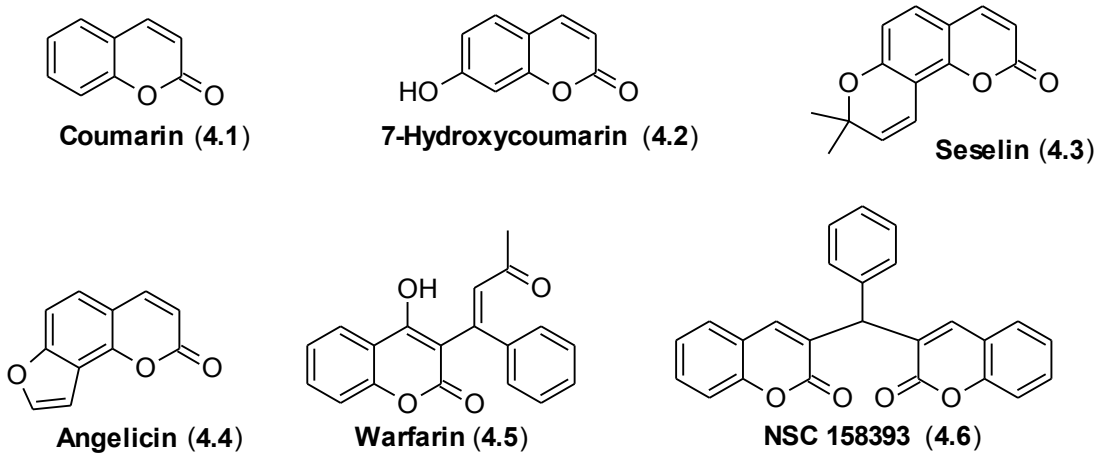
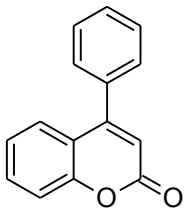


Figure 4.1: Examples of the different classes of coumarin.

Coumarins constitute one of the big classes of naturally occurring compounds. The first coumarin was isolated from tonka bean (*Dipteryx odorata*) by Vogel and Guibourt in 1820. Due to their sweet smell, they have been used to make perfumes since 1882. Since then, there has been an increase in the number of isolated coumarins that were reported. Presently, more than 1300 coumarins were identified from natural sources.[22, 24] Sweet woodruff (*Galium odoratum*), mullein (*Verbascum spp.*), sweet grass (*Hierochloe odorata*), vanilla grass (*Anthoxanthum odoratum*), cassia cinnamon (*Cinnamomum cassia*), deertongue (*Dichanthelium clandestinum*) and sweet-clover (*Melilotus ssp.*) were found to have high concentration of coumarins.[155] These compounds play an important role in the

physiology and biochemistry of the plant as they act as enzyme inhibitors, antioxidants and precursors of toxic substances.[156] They also are involved in the processes of plant photosynthesis, respiration, the action of plant growth hormones and growth regulator as well as defense against infections.[157]

Coumarins have been reported to play a vital role as food and cosmetics constituents,[158] dye-sensitized solar cells[159] and cigarettes additives.[160] In addition, coumarins possess antibacterial,[31] anti-inflammatory,[32] anti-oxidant,[33] anticoagulant,[34] anti-tumor,[35] hepatoprotective, anti-carcinogenic, anti-viral and anti-thrombotic activities.[36] The variety of uses of these compounds resulted in an increase in demand for large quantities of coumarins. Due to an insufficient natural supply of these organic compounds, numerous methods for their synthesis have been developed, including using the Pechmann condensation,[161] Stille coupling reaction, Knoevenagel condensation,[27] Heck coupling reaction, Perkin reaction,[26] Kostanecki reaction, Baylis-Hillman reaction,[30] Michael reaction, Suzuki-Miyaura cross-coupling reaction, Negishi cross-coupling reaction and Wittig reaction.[29]



Neoflavone

Figure 4.2: Skeletal structure of 4-phenylcoumarin (neoflavone).

This chapter will focus on the natural sources, synthesis and biological activities of 4-phenylcoumarins (neoflavones). The first neoflavone was isolated from *Calophyllum inophyllum* seeds in 1951 and its structure was established in 1957. Several other 4-phenylcoumarins were isolated from plants of the *Mammea* and *Dalbergia* genera in the 1960's, and since then neoflavones were recognized as a new group of natural compounds. Neoflavones have been isolated from more than 58 plant species of the Clusiaceae, Thelypteridaceae, Rubiaceae, Rutaceae, Fabaceae, Asteraceae, and Passifloraceae families.

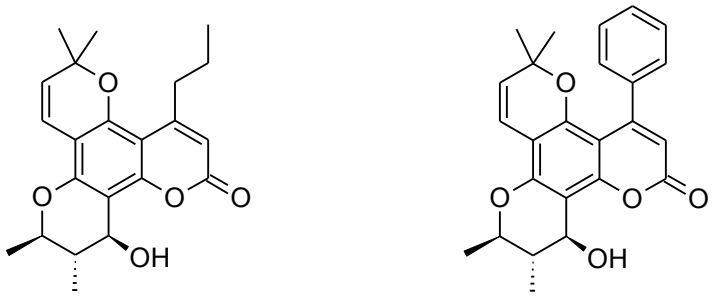
The aim of this investigation was to develop and improve the methods for the preparation of substituted 4-arylcoumarins. The chapter starts by giving an overview on naturally occurring coumarins followed by an overview of the biological activities of 4-

phenylcoumarins and a summary of different synthetic methods for the synthesis of 4-phenylcoumarins. The results obtained in the synthesis of 4-phenylcoumarins are discussed in the second-last Section of this chapter. The last Section gives detailed experimental procedures for all the successful syntheses.

4.2 Naturally occurring coumarins

After the isolation of the first coumarin in 1820, a large number of coumarins have been reported. For example, (+)-calanolide A (**4.7**) was first isolated from a Malaysian plant *Calophyllum lanigerum*[162] and was identified as a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) with potent activity against HIV-1 (Figure 4.3).[162,163] To meet the demand for **4.7** for preclinical and clinical research, a total synthesis of this tetracyclic coumarin was developed.[164]

(+)-Inophyllum B (**4.8**) was also reported to be a highly active inhibitor of HIV-reverse transcriptase. This pentacyclic coumarin was isolated by Patil *et al*. from *Calophyllum inophyllum*.[165] Shortly after **4.8** was isolated, its total synthesis was developed to increase the availability of the compound.[166]



(+)-calanolide A (4.7) **(+)-inophyllum B (4.8)**

Figure 4.3: Structure of (+)-calanolide A (**4.7**) and (+)-inophyllum B (**4.8**).

Cruz *et al*. reported the isolation of 4-arylcoumarins **4.9** and **4.10** from the stem of *Kielmeyera reticulate*, a wild shrub belonging to Guttiferae (Clusiaceae) (Figure 4.4).[167]

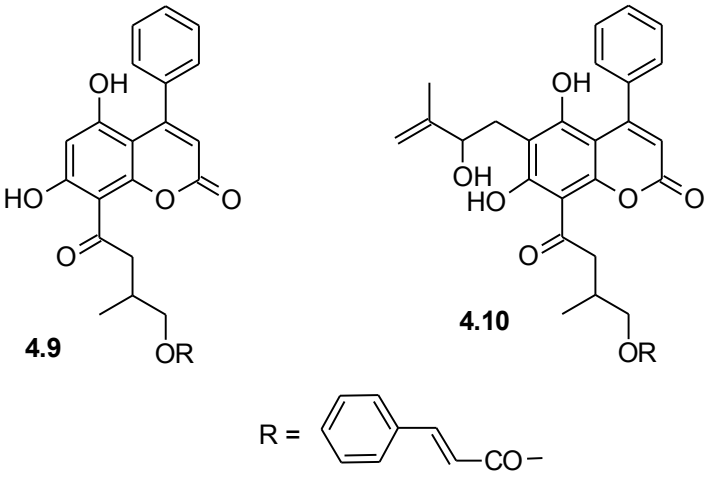


Figure 4.4: Naturally occurring 5,7-dihydroxy-4-phenylcoumarins from *Kielmeyera reticulate*.

5,7-Dimethoxy-4-*p*-methoxyphenylcoumarin (**4.11**) and 5,7-dimethoxy-4-phenylcoumarin (**4.12**) were isolated from a microorganism *Streptomyces aureofaciens* CMUAc130, which was isolated from the root tissues of *Zingiber officinale* Rosc. (Zingiberaceae) (Figure 4.5).[168] These 4-phenylcoumarins tested active against phytopathogenic fungi. These secondary metabolites are very useful to plants as they protect plants against attacks by pests and fungi.

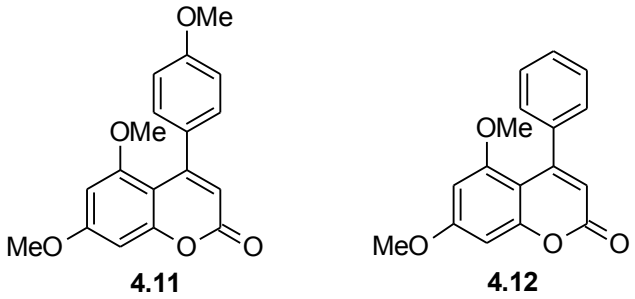


Figure 4.5: Naturally occurring 4-phenylcoumarins from *Streptomyces aureofaciens*.

Mata *et al*. isolated 5-[β-D-xylopyranosyl-(1→6)-β-D-glucopyranosyloxy]-7,3',4'-trihydroxy-4-phenylcoumarin (**4.13**) from the stem bark of *Exostema caribaeum* (Figure 4.6). This compound was found to be less toxic relative to the other 4-phenylcoumarins isolated from the same plant even at a concentration as high as 5 g/kg.[169]

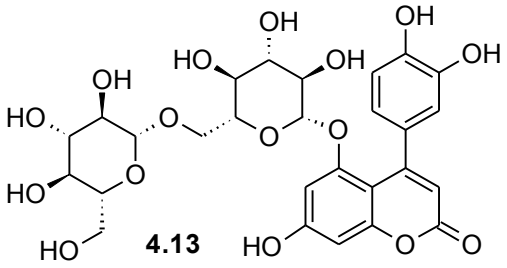


Figure 4.6: Naturally occurring 4-arylcoumarin from *Exostema caribaeum*.

Yu *et al*. reported the extraction of 4-phenylcoumarin-7-*O*-*β*-D-glucopyranoside (**4.14**) and 7-hydroxy-4-phenylcoumarin-5-*O*-*β*-D-glucopyranoside (**4.15**) from *Polygonum multiflorum* (Figure 4.7). **4.14** and **4.15** were biosynthesized using transgenic hairy roots of *P. multiflorum* from 7-hydroxy-4-phenylcoumarin and 5,7-dihydroxy-4-phenylcoumarin (substrates), respectively.[170]

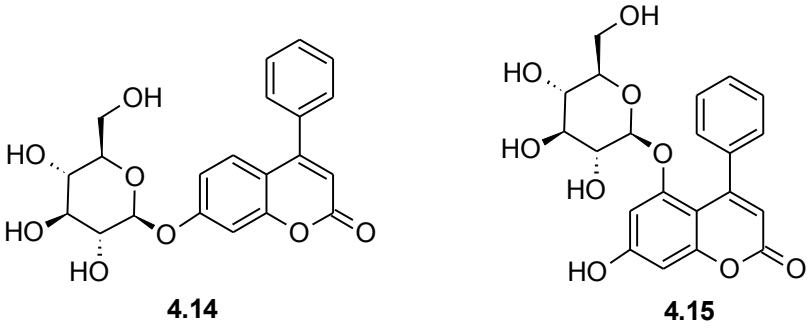


Figure 4.7: 4-Phenylcoumarins from *Polygonum multiflorum*.

4.3 Biologically active 4-arylcoumarins

The structure of coumarins is extremely variable, which influences their biological activities. Neoflavones (4-phenylcoumarins) have been reported to exhibit several biological activities such as anti-HIV, antibacterial, antimalarial, antitumor, antimicrobial, anti-diabetic, antiprotozoal and cytotoxicity.[171, 172]

4.3.1 Anti-HIV 4-arylcoumarins

The human immunodeficiency virus type 1 (HIV-1) belongs to a subfamily of retroviruses (*Lenti virinae*) which causes the acquired immunodeficiency syndrome (AIDS). Currently, there are four HIV-1 protease inhibitors that have been approved for the treatment of AIDS, namely, nelfinavir, saquinavir, indinavir and ritonavir.[173, 174]

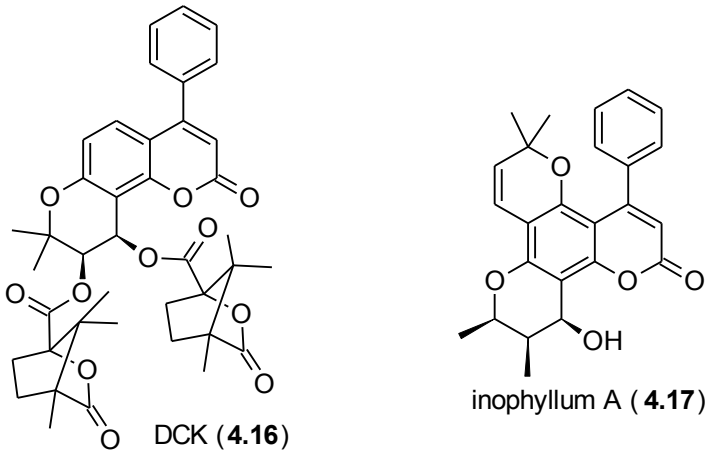


Figure 4.8: Structure of HIV-1 inhibitors.

Lee *et al*. reported the synthesis of 3',4'-di-*O*-(*S*)-(-)-camphanoyl-4-phenyl-(+)-*cis*-khellactone (DCK) (**4.16**) which was prompted by the isolation of the suksdorfin from *Lomatium uksdorfii*. DCK (**4.16**) and derivatives tested positive towards the inhibition of HIV-1 replication. The mode of action of these khellactones was proven not to involve inhibition of HIV reverse transcriptase (RT), which makes it possible for them to be used in combination with RT inhibitors.[175]

Inophyllum A (**4.17**) is one of the 4-phenylcoumarins isolated from *Calophyllum* genus (Guttiferae) and it has been reported that it strongly inhibited the *in vitro* replication and cytopathicity of HIV-1.[175]

4.3.2 Antimicrobial 4-arylcoumarins

Microbes are the main causes of infectious diseases. For example, tuberculosis (TB) is one of the infectious diseases caused by the bacillus *Mycobacterium tuberculosis* (Mtb). According to the World Health Organization, this disease is estimated to have infected one-third of the world´s population and caused 1.7 million deaths in 2009.[176]

Hung *et al*.[177] reported the synthesis of potentially anti-tubercular 4-arylcoumarins, one of which is 5,7-dimethyl-6-phenyl-4-phenylcoumarin (**4.18**) (Figure 4.9). This class of compounds was reported to target the fatty acyl ACP synthetase activity of the FadD32 enzyme which is essential for Mtb survival because it plays a crucial role in the biosynthesis of the unique branched fatty acids (mycolic acids) that make up the Mtb cell wall.[178-180] Chin *et al*.[181] reported the synthesis of 6-benzoyl-5,7-hydroxy-4-phenylcoumarin (**4.19**) which showed good antibacterial activity against *Staphylococcus aureus*.

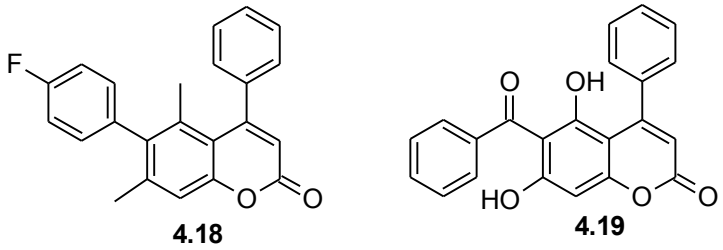


Figure 4.9: 4-Arylcoumarins with anti-tubercular (**4.18**) and antibacterial (**4.19**) activities.

4.3.3 Antimalarial and anticancer 4-arylcoumarins

Malaria is one of the most important parasitic diseases which causes more than one million deaths per year. This disease is a worldwide threat and mostly affects children in Sub-Saharan countries.[182] 4-(3,4-Dimethoxyphenyl)-6,7-dimethoxycoumarin (**4.20**) showed a strong antiprotozoal activity against multidrug-resistant strains of *Plasmodium falciparum* and *Leishmania donovani* and was synthesized by a Suzuki-Miyaura cross-coupling reaction (Figure 4.10).[183] This 4-phenylcoumarin and derivatives were found to strongly inhibit the proliferation of parasites. Compound **4.20** also showed anticancer activity.

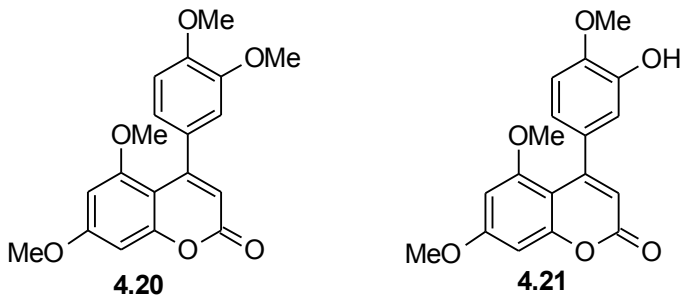


Figure 4.10: Structures for the derivatives of neoflavone.

Cancer is a class of diseases characterized by abnormal cell growth. Cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called tumors. There are over 100 different types of cancer that have been identified and each is classified by the type of cells or tissues that are initially affected.[184] According to the World Health Organization, in 2012, about 14.1 million new cases of cancer occurred and about 8.2 million deaths or 14.6% of all human deaths globally were caused by cancer.[185]

Beletskaya *et al*.[186] and Bailly *et al*.[187] reported the synthesis of 4-(3-hydroxy-4-methoxyphenyl)-6,7-dimethoxycoumarin (**4.21**) by a Suzuki-Miyaura cross-coupling reaction. This 4-arylcoumarin was found to be an antimitotic agent that inhibits tubulin assembly for the treatment of cancer.

4.4 Synthetic routes for 4-arylcoumarins

The variety of the biological uses of coumarins and an insufficient supply from natural sources led to the development of synthetic routes for coumarins of which most involve the lactone ring closure. Numerous methods have been developed for the synthesis of coumarins, including the Pechmann condensation, Perkin reaction, Knoevenagel condensation, Reformatsky reaction, Wittig reaction and Baylis-Hillman reaction.

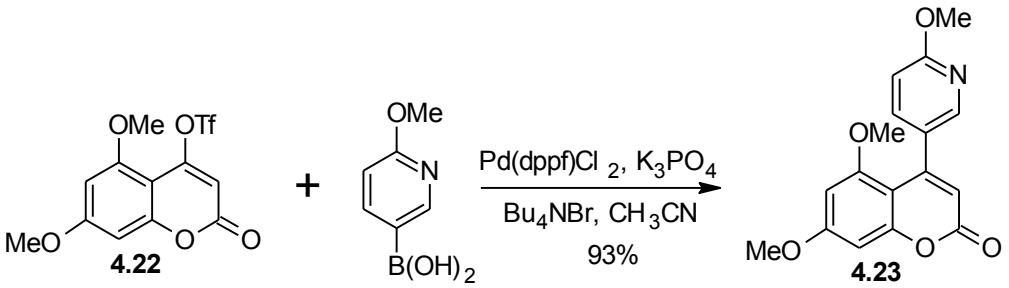
4.4.1 Transition metal-catalyzed reactions

Transition metal-catalyzed reactions have become one of the popular reactions to prepare 4-phenylcoumarins. These reactions are based on the palladium-catalyzed Suzuki coupling, Negishi coupling or Stille coupling reactions with the use of organometallic reagents (such as organoboron,[188] organotin,[189] organozinc,[190] organobismuth[191]or organoindium[192]) and phenyl electrophilic reagents (aryl halogen, triflate, phosphonate or tosylate). These reactions have been used for the successful C–C bond formation in the past decades and have been used to synthesize 4-arylcoumarins by direct coupling or pyrone ring closing reactions.

4.4.1.1 Transition metals in direct coupling

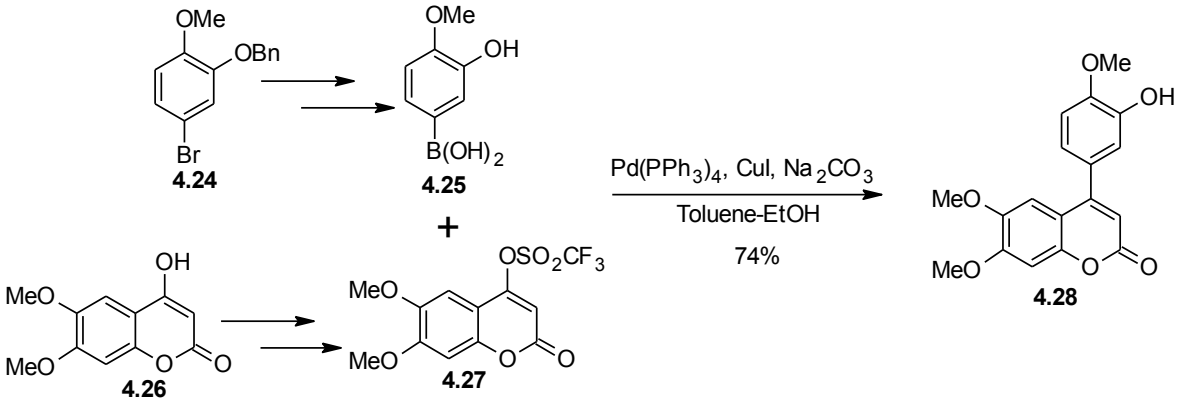
4.4.1.1.1 Suzuki-Miyaura cross-coupling reaction

Beletskaya *et al.*[186] have reported the synthesis of polymethoxylated 4-heterophenylcoumarins **4.23** by a Suzuki-Miyaura cross-coupling reaction. They treated 4-trifluoromethyl-sulfonyloxycoumarins (**4.22**) with 4-methoxypyridin-3-ylboronic acid under Suzuki-Miyaura cross-coupling conditions as shown in Scheme 4.1. These 4-pyridinylcoumarins are cytotoxic to cancer cells.



Scheme 4.1: Synthesis of 5,7-dimethoxy-4-(4-methoxypyridin-3-yl)coumarin (**4.23**).

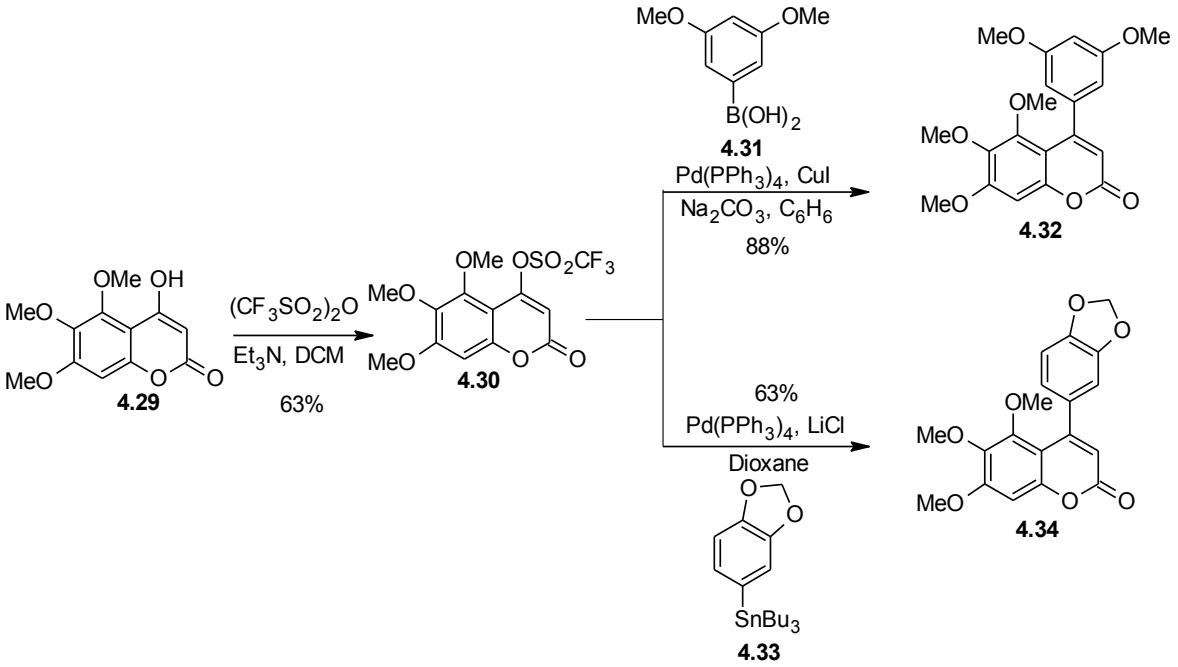
Peyrot *et al.*[193] have applied the Suzuki-Miyaura cross-coupling reaction in the synthesis of polymethoxylated neoflavone **4.28** (Scheme 4.2). Debenzylation and boronation of bromobenzene **4.24** afforded 3-hydroxy-4-methoxyphenylboronic acid (**4.25**) which was reacted with 4-trifluoromethylsulfonyloxycoumarin (**4.27**) (prepared from 4-hydroxycoumarin, **4.26**) under Suzuki-Miyaura cross-coupling conditions to yield trimethoxyneoflavone (**4.28**). This 4-phenylcoumarin was found to exhibit antiproliferative activity.



Scheme 4.2: Synthesis of 6,7-dimethoxy-4-(3-hydroxy-4-methoxyphenyl)coumarin (**4.28**).

4.4.1.1.2 Stille coupling reaction

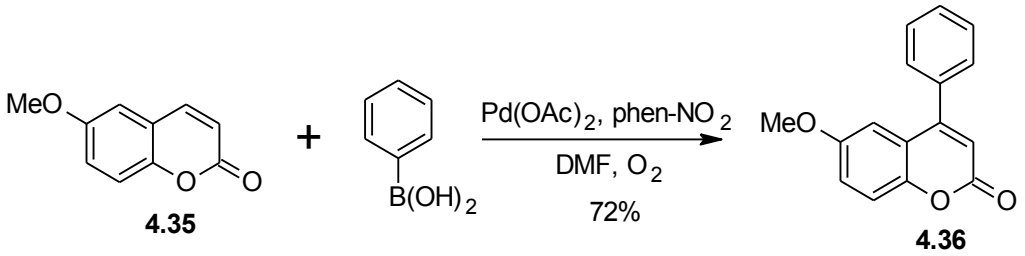
Bailly and coworkers[187] have synthesized 5,6,7-trimethoxy-4-(3,5-dimethoxyphenyl) coumarin (**4.32**) by a Suzuki-Miyaura cross-coupling reaction and 5,6,7-trimethoxy-4-(3',4'-methylenedioxyphenyl)coumarin (**4.34**) by a Stille coupling reaction (Scheme 4.3). The Suzuki reaction was achieved by C-4 arylation of a trifluorosulfonyl-activated coumarin (**4.30**) with 3,5-dimethoxyphenylboronic acid (**4.31**) under palladium-copper catalysis. The Stille reaction of **4.30** and tributyl-3,4-methylenedioxyphenyltin was catalyzed by a palladium-lithium catalyst. Cytotoxicity studies of these polymethoxylated neoflavones indicated a potent activity against a CEM leukemia cell line.



Scheme 4.3: Synthesis of 4-arylcoumaris by the Suzuki and Stille reactions.

4.4.1.1.3 Heck coupling reaction

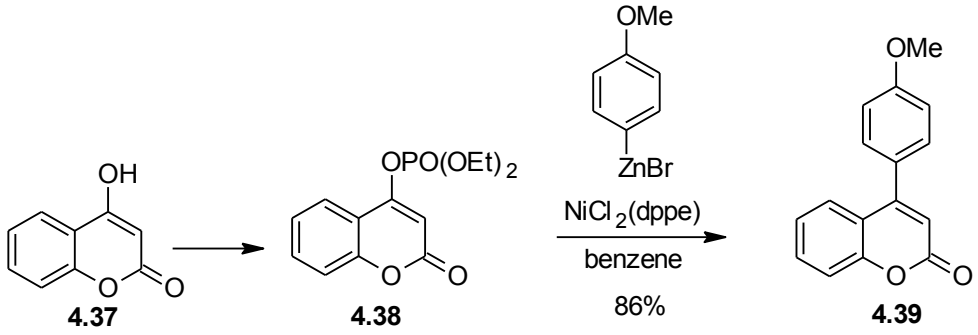
The palladium-catalyzed oxidative Heck coupling reaction has been used for the direct synthesis of 6-methoxy-4-phenylcoumarin (**4.36**) (Scheme 4.4).[194] A coumarin proton (at C-4) was oxidatively displaced by a phenyl group in a palladium-catalyzed reaction in the presence of oxygen gas.



Scheme 4.4: Synthesis of 6-methoxy-4-phenylcoumarin (**4.36**) by the Heck reaction.

4.4.1.1.4 Negishi cross-coupling reaction

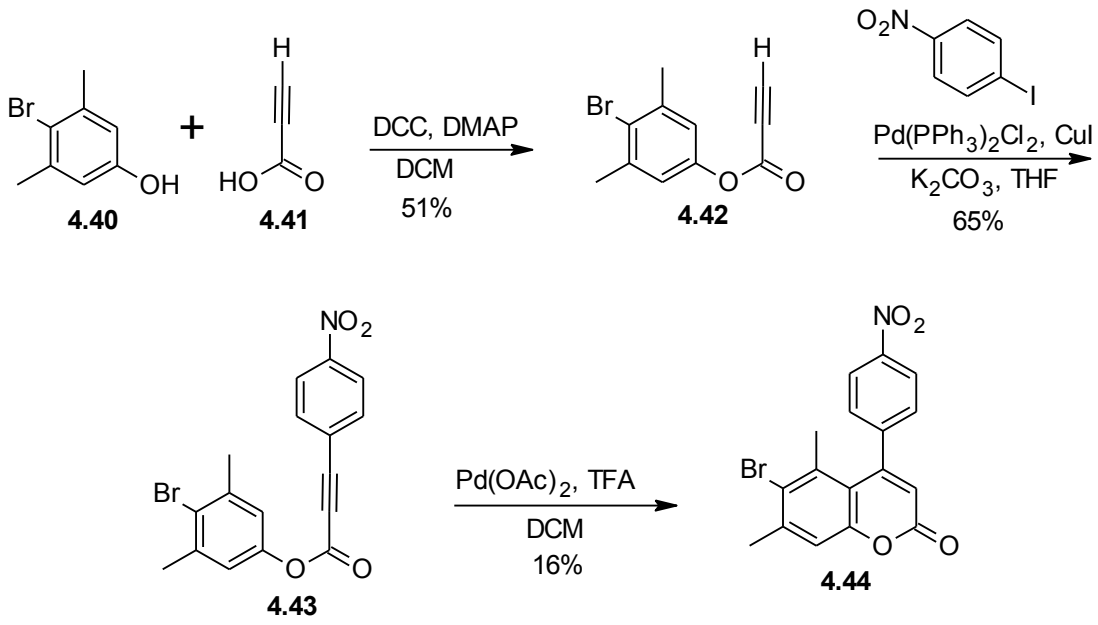
Yang and Wu[195] have reported the synthesis of 4-(4-methoxyphenyl)coumarin (**4.39**) by the Negishi cross-coupling reaction with the use of a nickel catalyst (Scheme 4.5). They activated 4-hydroxycoumarin (**4.37**) by forming a vinylic phosphate coumarin **4.38** which was then reacted with methoxyphenylzinc bromide under nickel-mediated conditions to yield coumarin **4.39**.



Scheme 4.5: Synthesis of 4-(4-methoxyphenyl)coumarin (**4.39**) *via* Negishi reaction.

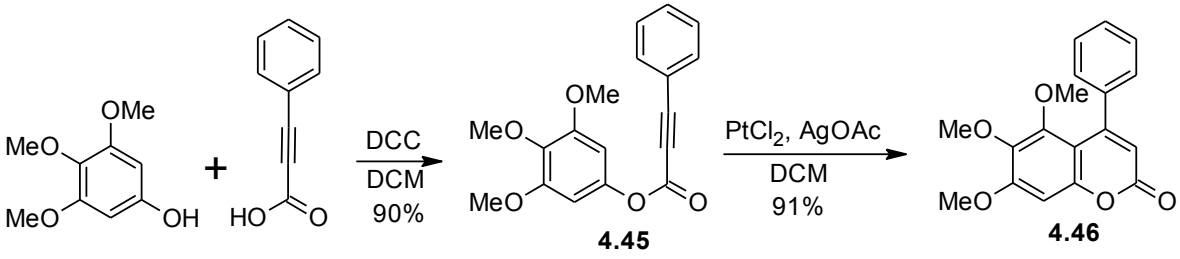
4.4.1.2 Transition metals in pyrone ring closure

The Sonogashira coupling reaction is one of the most widely used methods for the coupling of vinyl or aryl halides with terminal alkynes to form conjugated enynes or aryl alkynes. Hung and coworkers[177] have applied the Sonogashira reaction to couple an aryl iodide to the terminal alkyne ester **4.42**, which was prepared by the esterification of a trisubstituted phenol **4.40** with an acetylenic carboxylic acid **4.41**, to form an alkyne ester intermediate **4.43** (Scheme 4.6). The intramolecular cyclization of **4.43** in the presence of a palladium catalyst afforded the substituted neoflavone **4.44**.



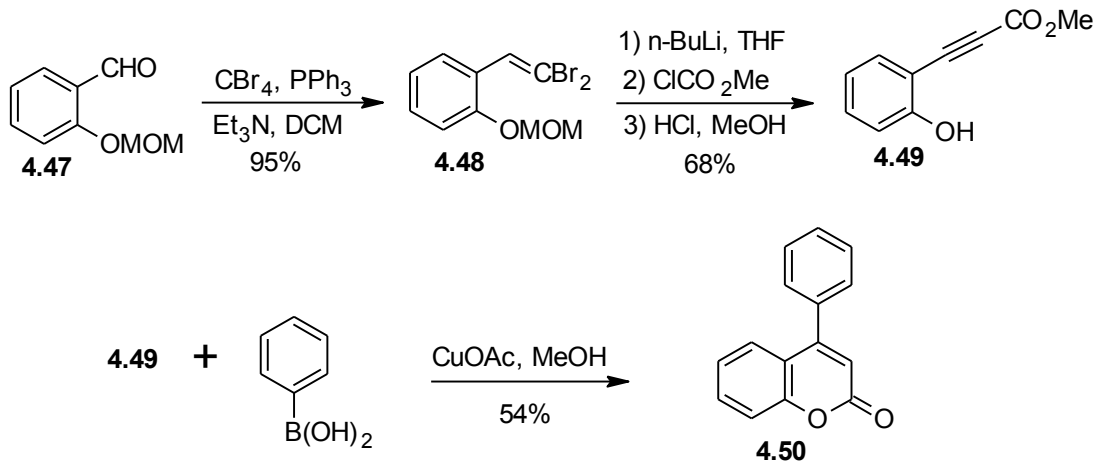
Scheme 4.6: Synthesis of polysubstituted 4-arylcoumarin (**4.44**) by Pd catalysis.

Fujiwara *et al*.[196] have reported the synthesis of trimethoxyneoflavone **4.46** by pyrone ring closure (Scheme 4.7). They firstly prepared trimethoxyphenyl phenylpropiolate (**4.45**) by the esterification of phenylpropiolic acid and trimethoxyphenol in the presence of *N,N′*-dicyclohexylcarbodiimide. Compound **4.45** undergoes an intramolecular ring cyclization when treated with platinum-silver coupled catalyst.



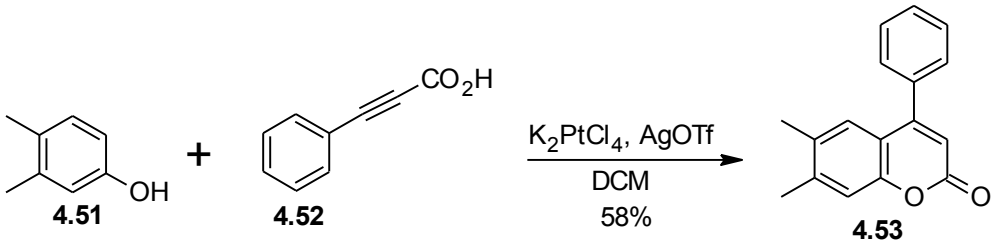
Scheme 4.7: Synthesis of trimethoxy-4-arylcoumarin **4.46** under Pt-catalyzed conditions.

Yamamoto and Kirai[197] reported the synthesis of 4-phenylcoumarin **4.50** by copper-catalyzed hydroarylation (Scheme 4.8). The treatment of MOM-protected salicylaldehyde (**4.47**) with CBr_4, Et_3N and PPh_3 afforded dibromoalkene **4.48** which was treated with butyllithium and then with acid to form methyl phenylpropiolate (**4.49**). Compound **4.49** was treated with a copper catalyst in the presence of phenylboronic acid to form neoflavone **4.50**.



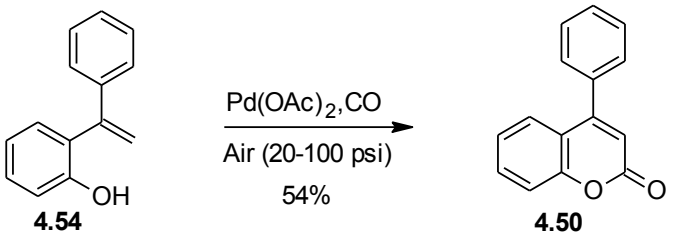
Scheme 4.8: Cu-catalyzed hydroarylation reaction to form neoflavone (**4.50**).

Kitamura and Oyamada[198] have reported the use of platinum and silver catalysts to form 6,7-dimethyl-4-arylcoumarin (**4.53**) *via* hydroarylation of phenylpropiolic acid (**4.52**) with 3,4-dimethylphenol (**4.51**) (Scheme 4.9). They also used platinum and TFA in their cyclisation reactions which were run at room temperature to get the expected results.



Scheme 4.9: Pt-Ag couple-catalyzed hydroarylation reaction.

Alper *et al.*[199] have synthesized neoflavone (**4.50**) *via* palladium-catalyzed oxidative cyclocarbonylation of vinylphenol **4.54** (Scheme 4.10). This oxidative carbonylation reaction is an intramolecular reaction which involves the connection of two components through a carbonyl group. This reaction was run at low CO/air pressures at 110 °C. 1,4-Benzoquinone was also used as a substitute for air in the presence of Pd catalyst to form the same coumarin.

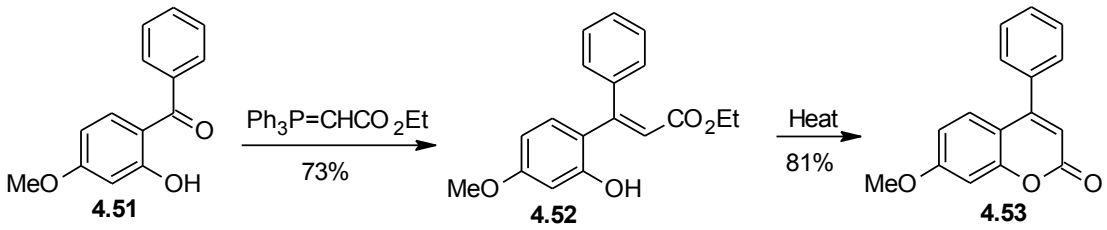


Scheme 4.10: Pd-catalyzed oxidative cyclocarbonylation reaction.

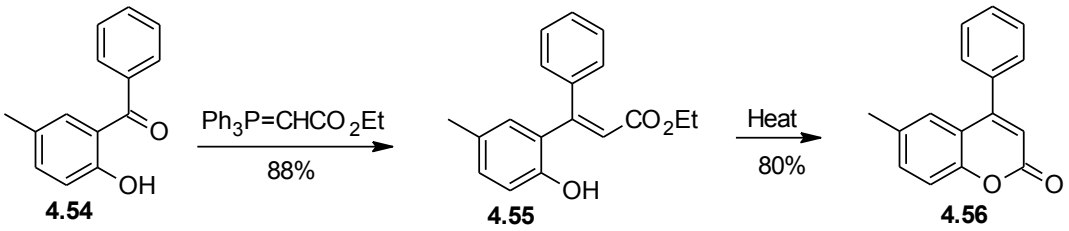
4.4.2 Wittig reaction

The Wittig reaction has also been applied to the synthesis of 4-phenylcoumarin derivatives. This approach involves reaction of an aromatic ketone with a triphenyl phosphonium ylide. This reaction, discovered in 1954 by Georg Wittig, is widely used in organic synthesis for the synthesis of alkenes.[200, 201]

Bissel and coworkers[202] have developed a synthesis for 7-methoxy-4-arylcoumarin (**4.53**) *via* the Wittig reaction, i.e. the reaction between 2-hydroxy-4-methoxybenzophenone (**4.51**) and ethyl 2-(triphenylphosphoranylidene)acetate (Scheme 4.11). Similar reactions were applied by Gallagher *et al.*[203] and Chen *et al.*[204] to synthesize 6-methyl-4-arylcoumarin (**4.56**) from the reaction of 2-hydroxy-5-methylbenzophenone (**4.54**) and ethyl 2-(triphenylphosphoranylidene)acetate (Scheme 4.12).



Scheme 4.11: Synthesis of 7-methoxy-4-arylcoumarin (**4.53**).

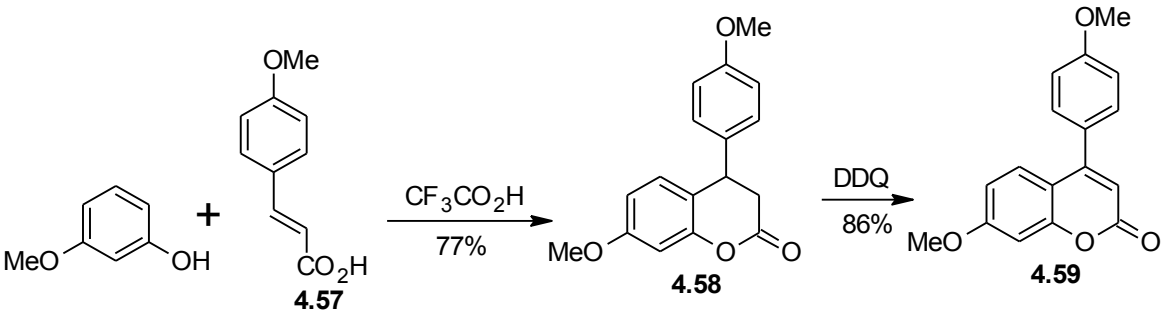


Scheme 4.12: Synthesis of 6-methyl-4-arylcoumarin (**4.56**).

4.4.3 Michael reaction

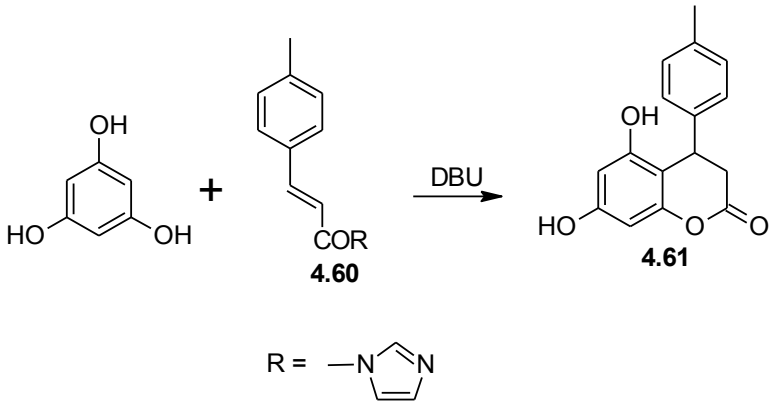
The Michael addition is a conjugate addition reaction which involves the nucleophilic addition of a nucleophile (normally carbanion) to an *α,β*-unsaturated carbonyl compound. This reaction is one of the most used reactions for the formation of C–C bonds under mild conditions.[205]

Rizzi *et al*.[206] have reported a novel, mild procedure for the synthesis of 7-methoxy-4-(4-methoxyphenyl)coumarin (**4.59**) by a Michael-type reaction (Scheme 4.13). They condensed *m*-methoxyphenol with cinnamic acid (**4.57**) in the presence of trifluoroacetic acid at room temperature to form a 4-phenylcoumarin intermediate (**4.58**) which was oxidized with DDQ to afford 4-arylcoumarin **4.59**.



Scheme 4.13: Synthesis of 7-methoxy-4-(4-methoxyphenyl)coumarin (**4.59**).

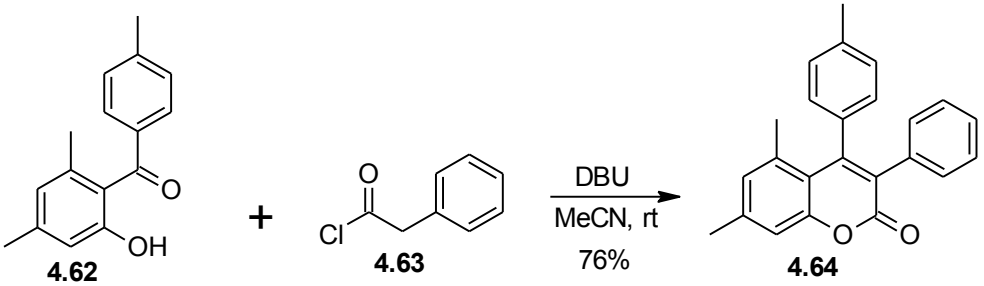
Speranza *et al*.[207] on the other hand, have reported a synthetic procedure for 4-aryl-3,4-dihydrocoumarin (**4.61**) by a Michael reaction of phloroglucinol with *p*-substituted *N*-cinnamoylazole **4.60** in the presence of DBU (Scheme 4.14).



Scheme 4.14: Synthesis of 4-aryl-3,4-dihydrocoumarin (**4.61**).

4.4.4 Kostanecki reaction

In the Kostanecki acylation, a 4-phenylcoumarin is formed by acylation of an *O*-hydroxyaryl ketone with an acid chloride followed by an intramolecular aldol condensation cyclization. Lee and coworkers[208] have reported the synthesis of a 4-arylcoumarin **4.64** by the Kostanecki reaction of trimethylated 2-hydroxybenzophenone (**4.62**) with phenylacetyl chloride (**4.63**) in the presence of DBU (Scheme 4.15).

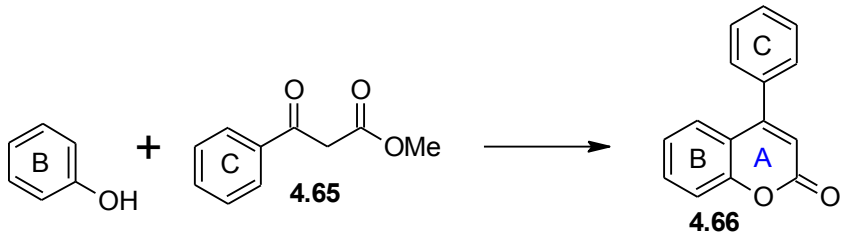


Scheme 4.15: Synthesis of 5,7-dimethyl-3-phenyl-4-(4-methylphenyl)coumarin (**4.64**).

4.4.5 Pechmann reaction

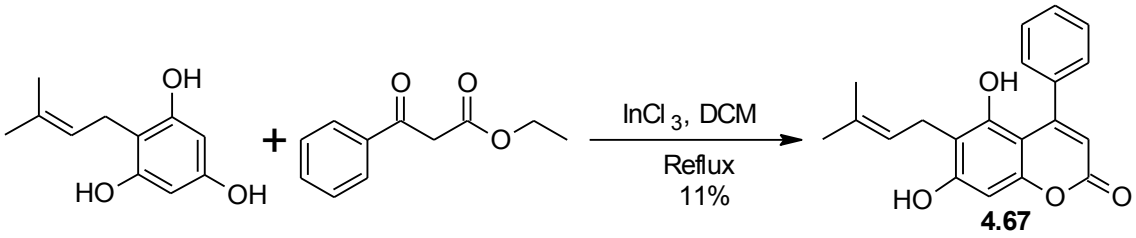
The Pechmann condensation is one of the most commonly used procedures for the preparation of 4-phenylcoumarins and derivatives. This method involves the reaction of a *β*-ketoester with phenol in the presence of a homogeneous acidic catalyst (sulfuric, hydrochloric,[209] phosphoric or trifluoroacetic acid[210] and a Lewis acid such as iron(III) chloride, titanium chloride,[211] aluminium chloride,[212] tin(IV) chloride and zinc chloride[213]) or a heterogeneous catalyst (cation exchange resins, Nafion-H, zeolite-HBEA and other solid acids).[214] Lately, microwave irradiation,[215] ionic liquids[216] and ultrasound[217] have also been applied to this reaction.

Until now, the Pechmann reaction for the synthesis of 4-arylcoumarins (**4.66**) has been limited to unsubstituted phenyl C-rings (Scheme 4.16), partly because the substituted phenyl-*β*-ketoesters (**4.65**) are not readily available. 4-Arylcoumarins that are substituted on the C-ring have been synthesized but hardly any have been synthesized by the Pechmann reaction. Most of these substituted coumarins have been made by transition metal-catalyzed reactions and other reactions such as the Michael reaction as shown in the previous Sections.



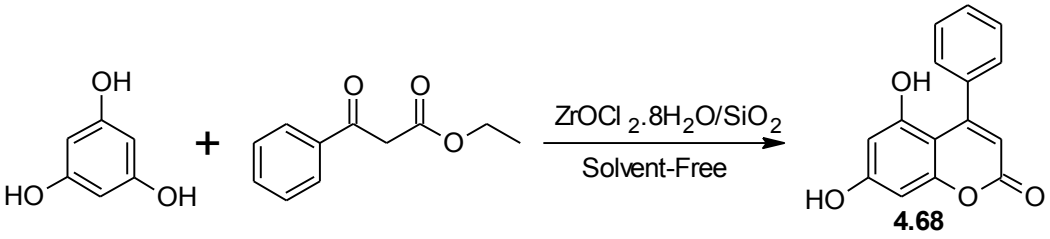
Scheme 4.16: General Pechmann reaction to synthesize 4-arylcoumarin (**4.66**).

Guilet *et al*.[218] reported the synthesis of 5,7-dihydroxy-6-prenyl-4-phenylcoumarin (**4.67**) by the Pechmann condensation catalyzed by indium(III) chloride (Scheme 4.17). They obtained their product by refluxing prenylated phloroglucinol and ethyl benzoylacetate in DCM for 2 h.



Scheme 4.17: Indium (III) chloride catalyzed reaction.

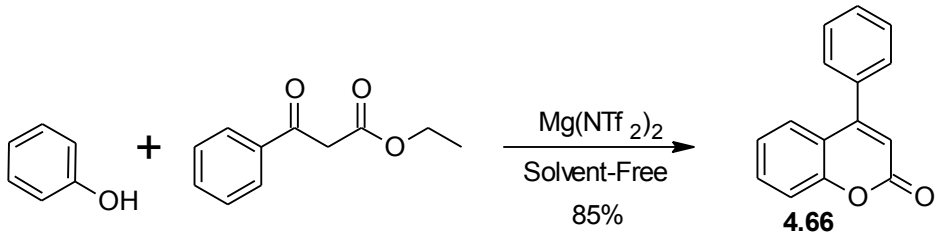
Karami and co-workers[219] synthesized 5,7-dihydroxy-4-phenylcoumarin (**4.68**) from the reaction of ethyl benzoylacetate with phloroglucinol in the presence of $ZrOCl_2.8H_2O/SiO_2$ (Scheme 4.18). Their reaction was run in a solvent-free environment at 90 °C.



Scheme 4.18: Solvent-free reaction in the presence of $ZrOCl_2.8H_2O/SiO_2$.

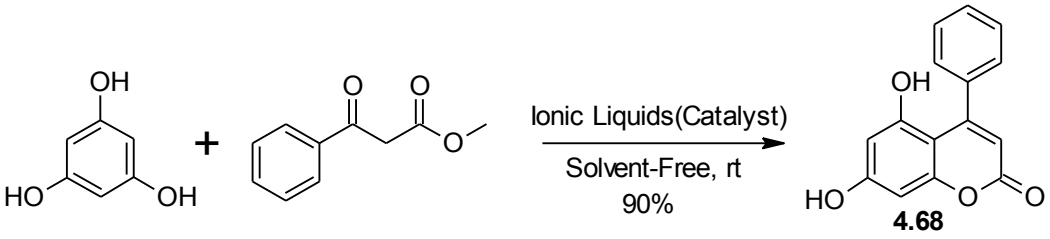
Wang *et al*.[220] reported the synthesis of neoflavone **4.66** by reacting phenol with ethyl benzoylacetate in the presence of magnesium bis(trifluoromethane)sulfonamide (Scheme 4.19). This Pechmann reaction was run under solvent-free conditions to get a maximum

yield of 87% as opposed to a reaction in solvent which gave a lower yield (between 50% and 74%).



Scheme 4.19: Synthesis of neoflavone **4.66**.

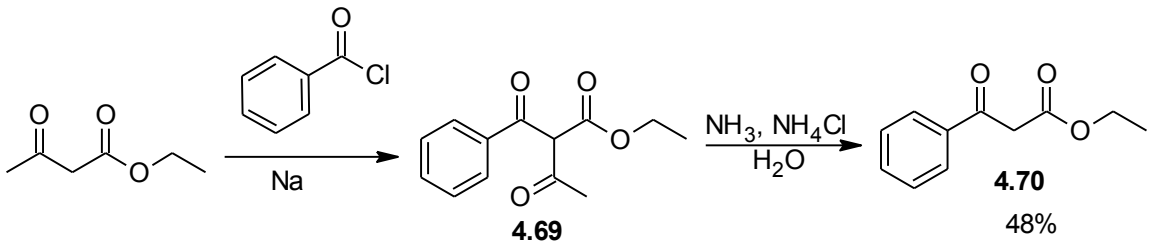
Ionic liquids have been used as alternative solvents for reactions as well as catalyst for various reactions. The use of ionic liquids has gained more attention as a result of green chemistry. Shaterian and Aghakhanizadeh[221] have used ionic liquids in their synthesis of 5,7-dihydroxyneoflavone (**4.68**) (Scheme 4.20). They reacted phloroglucinol with the *β*-ketoester under solvent-free conditions, at room temperature, in the presence of Brønsted acid ionic liquids such as 2-pyrrolidonium hydrogen sulfate, *N*-methyl-2-pyrrolidonium hydrogen sulfate, and *N*-methyl-2-pyrrolidonium hydrogen phosphate.



Scheme 4.20: Pechmann reaction with ionic liquid catalyst.

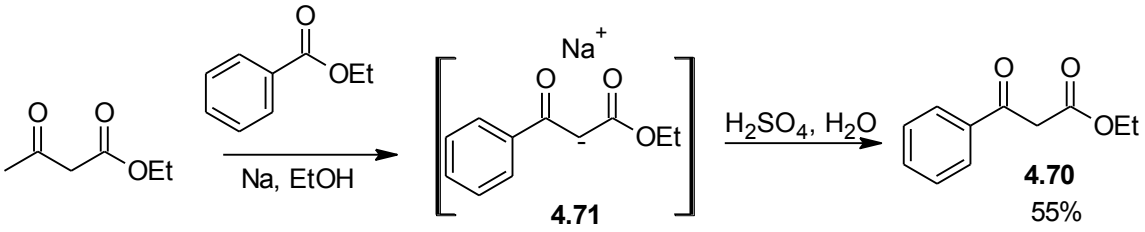
4.4.5.1 Synthesis of β-ketoesters

β-Ketoesters are known to be important intermediates in the synthesis of ceramides, degradable polymers and antibiotics (e.g. coumarins, quinolones, etc.).[222] Shriner and coworkers[223] have synthesized ethyl benzoylacetate (**4.70**) by the acylation of ethyl acetoacetate at C-2 in the presence of sodium to form ethyl benzoylacetoacetate (**4.69**) which was further hydrolyzed in the presence of ammonia and ammonium chloride to yield *β*-ketoester **4.70** as shown in Scheme 4.21.



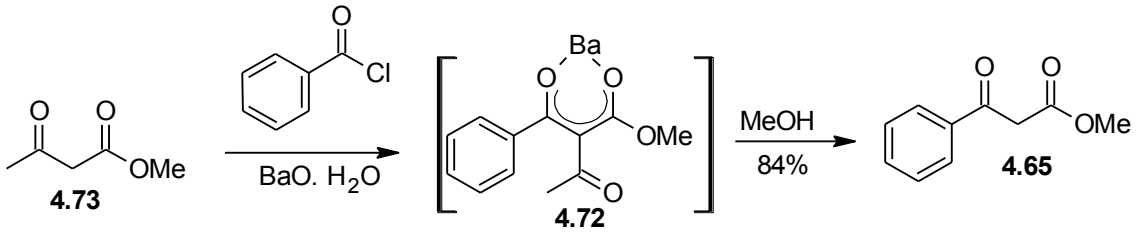
Scheme 4.21: Synthesis of ethyl benzoylacetate (**4.70**) from benzoyl chloride.

McElvain and Weber[224] have reported the synthesis of ethyl benzoylacetate (**4.70**) by acylating ethyl acetoacetate with ethyl benzoate under sodium-mediated conditions to form the sodium enolate **4.71** (Scheme 4.22). This enolate was treated with aqueous sulfuric acid and heated to 140 °C for 6 h to afford ethyl benzoylacetate (**4.70**).



Scheme 4.22: Synthesis of ethyl benzoylacetate (**4.70**) from ethyl benzoate.

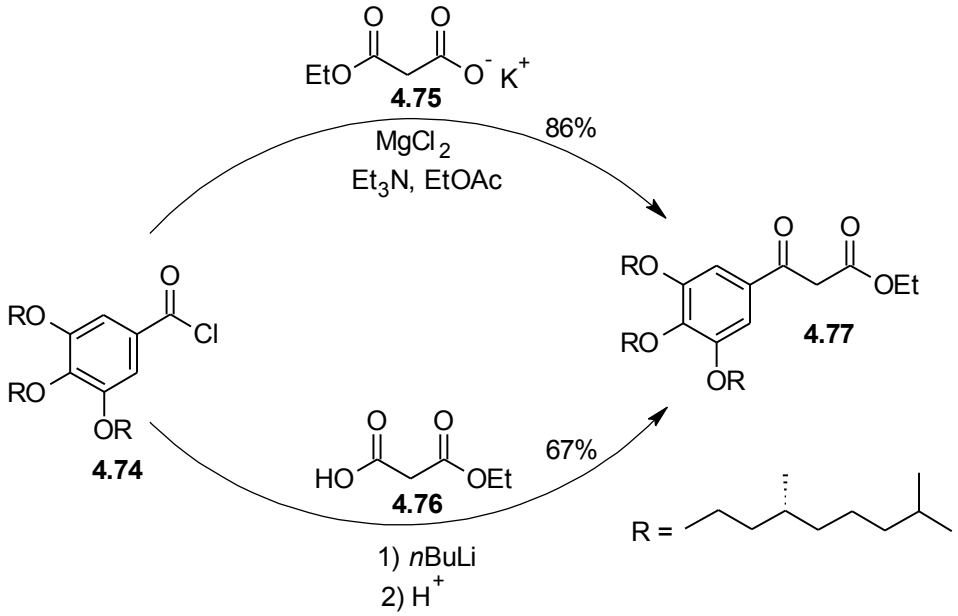
Yuasa and Tsuruta[225] have reported the synthesis of methyl benzoylacetate (**4.65**) using barium oxide as catalyst (Scheme 4.23). They acylated methyl acetoacetate (**4.73**) reacted with benzoyl chloride in the presence of BaO catalyst to form an enolate-barium complex **4.72** which was hydrolyzed in methanol to yield methyl benzoylacetate.



Scheme 4.23: Synthesis of methyl benzoylacetate (**4.65**) using BaO.

Sijbesma *et al.*[226] have reported the synthesis of ethyl 3,4,5-tris((*S*)-3,7-dimethyloctyloxy) benzoylacetate (**4.77**) from ethyl malonate (**4.76**) or/and potassium monoethyl malonate (**4.75**). One of their reactions was the acylation of ethyl malonate with acid chloride **4.74** in

the presence of butyllithium to form *β*-ketoester (**4.77**). The other reaction started by forming potassium-malonate salt (**4.75**) from diethyl malonate, which was then acylated with an acid chloride in the presence of $MgCl_2$, EtOAc and Et_3N to afford *β*-ketoester **4.77**.



Scheme 4.24: Synthesis of ethyl 3,4,5-tris((*S*)-3,7-dimethyloctyloxy) benzoylacetate (**4.77**).

It is shown in the review above that coumarins are natural compounds and that many are biological active. The first neoflavone was isolated from *Calophyllum inophyllum* seeds in 1951 and since then several synthetic methods for neoflavones have been developed.

4.5 Results and discussion for 4-arylcoumarins

4.5.1 Introduction

The Pechmann reaction (Section 4.4.5) is a general reaction used for the preparation of 4-substituted coumarins. However, this reaction has received very little attention in the synthesis of 4-arylcoumarins with substituents on the phenyl ring, most likely because of problems encountered in the preparation of the *β*-ketoesters. Most substituted 4-arylcoumarins have been prepared by palladium-catalysed reactions such as the Suzuki reaction (Section 4.4.1.1.1).

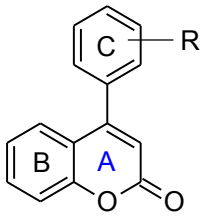
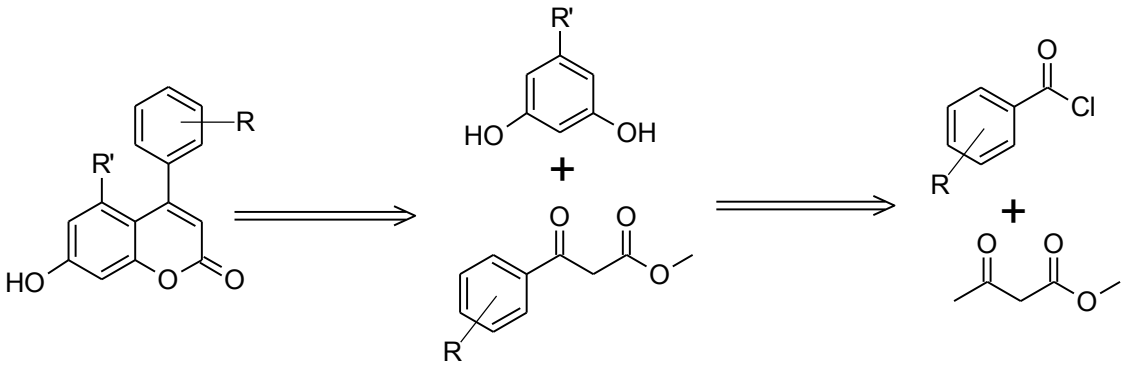


Figure 4.11: Structure of a ring-C substituted neoflavone.

Our aim was to find new or better methods for synthesizing substituted 4-phenylcoumarins. In this report, we present a new palladium-free method for constructing *β*-keto esters containing a fluorine-substituted phenyl ring. This has enabled us to successfully synthesize ring-C fluorinated neoflavones by the Pechmann reaction.

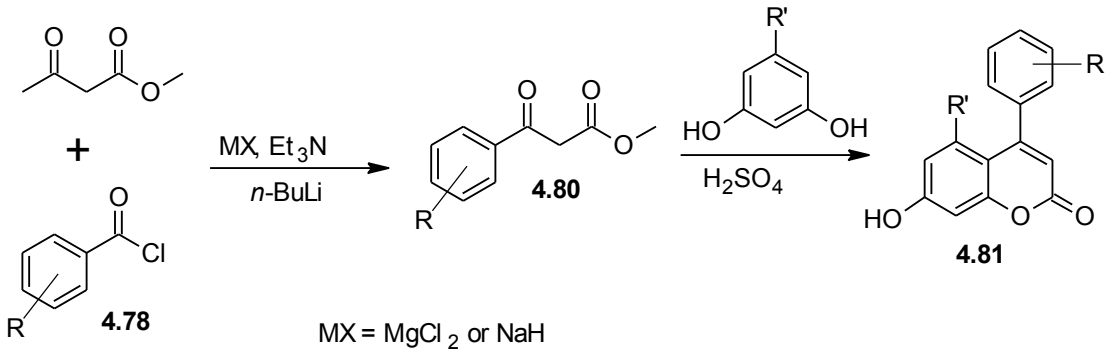
4.5.1.1 Retrosynthetic Analysis



Scheme 4.25: Retrosynthetic analysis for 4-phenylcoumarins.

The retrosynthetic analysis of the target coumarin is based on the condensation of a *β*-ketoester with a phenolic compound by the Pechmann reaction. The formation of the aryl-substituted *β*-ketoester can be achieved by a benzoylation-deacylation reaction of methyl acetoacetate.

4.5.1.2 *Synthetic route for fluorinated 4-phenylcoumarins*



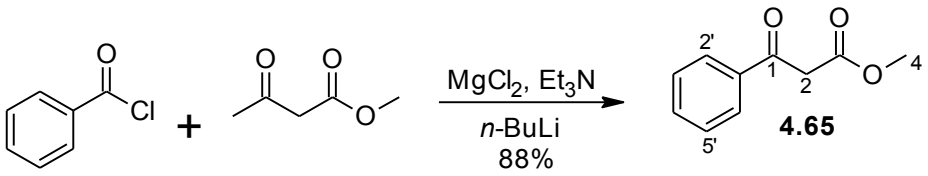
Scheme 4.26: Synthetic scheme of fluorinated 4-phenylcoumarins.

Scheme 4.26 outlines our approach to synthesize fluorinated 4-phenylcoumarins (**4.81**). The key step in this synthesis was the development of an effective procedure for the synthesis of fluorinated methyl benzoylacetates (**4.80**). The final step of this synthesis was the application of the Pechmann reaction to yield 4-arylcoumarins (**4.81**).

4.5.2 *Synthesis of β-keto ester*

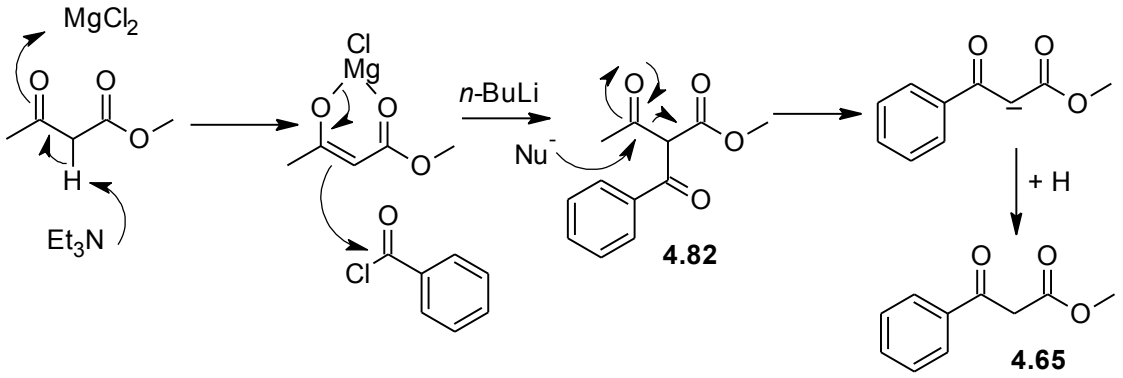
4.5.2.1 *Synthesis of methyl benzoylacetate (4.65)*

The first step of the reaction was to synthesize a substituted *β*-keto ester. This was accomplished *via* a novel reaction using readily available reagents and mild condition. Methyl acetoacetate was treated with $MgCl_2$ (or NaH), Et_3N and *n*-BuLi in DCM (or THF) and then with benzoyl chloride to yield methyl benzoylacetate (**4.65**). After a series of trials of different combinations to optimize the yield, a combination of $MgCl_2$, Et_3N and *n*-BuLi in DCM was found to give the optimum yield (88%). The use of NaH in DCM gave an average yield of 52%. THF was also found not to favour this reaction as the yields were lower than that of the DCM reactions.



Scheme 4.27: Synthesis of methyl benzoylacetate (**4.65**).

This reaction is an acylation-deacylation reaction which takes place under mild conditions (0 °C to 25 °C). In combination of $MgCl_2$, Et_3N behaves as a much stronger base and is more effective in enolizing a β-keto ester than Et_3N on its own. This combination has been used in a number of interesting reactions, as was summarised by Anwar.[227] The proposed mechanism for acylation-deacylation reaction is shown in Scheme 4.28. Methyl acetoacetate was treated with $MgCl_2$ to form a six membered-ring magnesium complex which makes the α-protons (CH_2) of methyl acetoacetate even more acidic. The removal of an acidic proton with the weak base (Et_3N) results in the formation of an enolate magnesium-complex chloride salt. This in turn reacts with the acid chloride to form a diketoester **4.82**. The intermediate **4.82** contains three carbonyl groups (an acetyl, a benzoyl and an ester carbonyl). These three carbonyls differ in reactivity towards a nucleophile, with the acetyl carbonyl being the most reactive. As a result, the nucleophile attacks the acetyl carbonyl causing **4.82** to deacetylate to afford methyl benzoylacetate (**4.65**) in a high yield.



Scheme 4.28: Proposed mechanism for acylation-deacylation reaction.

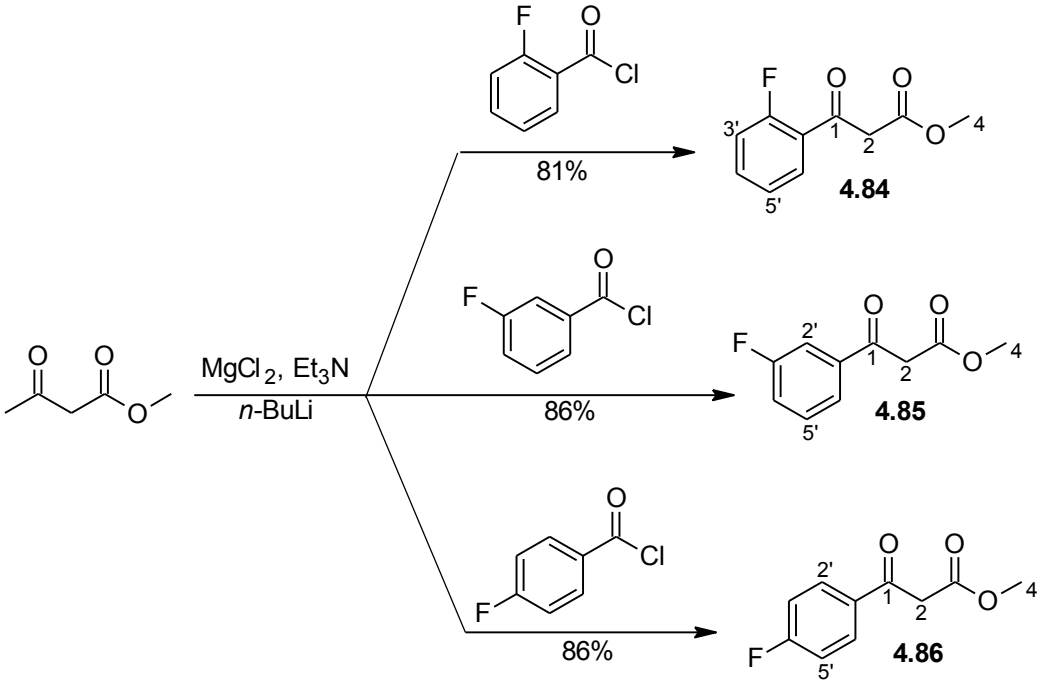
The success of the reaction to form methyl benzoylacetate was confirmed by the absence of the methyl acyl proton peak in the ^1H spectrum (Plate 37). The acetyl group had been replaced by a benzoyl group. The phenyl protons were evident at δ_H 7.50 (t), δ_H 7.62 (t) and δ_H 7.97 (d). The *ortho* protons on the phenyl ring are deshielded by the anisotropic effect of the carbonyl and as a result, they appeared further downfield (δ_H 7.97). Two singlets upfield at δ_H 3.77 (3H) and δ_H 4.03 (2H) were assigned to the methoxy and α-protons, respectively.

The ^{13}C NMR spectrum revealed eight signals which correlate with the expected number of carbon peaks. Two singlets, assigned to the ketone carbonyl carbon and ester carbonyl

carbon, occur at δ_C 192.4 and δ_C 167.9. A quaternary singlet appeared downfield (δ_C 136.0) relative to the other aromatic carbons. With the aid of DEPT-135 and HSQC spectra, the α-carbon (C-2) was assigned to the signal at δ_C 45.7. This NMR data is in agreement with published data.[225]

4.5.2.2 Synthesis of fluorinated methyl benzoylacetates (4.84, 4.85 and 4.86)

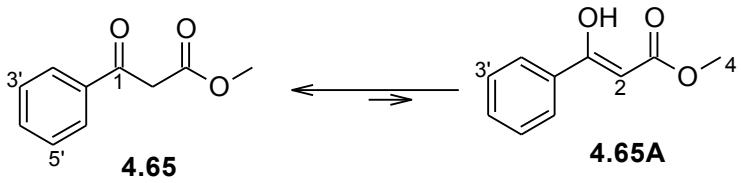
Methyl 2-fluorobenzoylacetate (**4.84**), methyl 3-fluorobenzoylacetate (**4.85**) and methyl 4-fluorobenzoylacetate (**4.86**) were also synthesized in a similar manner to the synthesis of **4.65** (Section 4.5.2.1) using 2-fluorobenzoyl chloride, 3-fluorobenzoyl chloride and 4-fluorobenzoyl chloride, respectively (Scheme 4.29).



Scheme 4.29: Synthesis of fluorinated methyl benzoylacetates (**4.84, 4.85 and 4.86**).

The products were characterized by NMR (Plate 38, 39, and 40). The ^{13}C-NMR spectra revealed that all the aromatic ^{13}C signals are split into doublets due to coupling with ^{19}F. The ^{13}C,^{19}F coupling constant of the *ipso* carbon is quite large ($J \sim 250$ Hz), but for the rest of the aromatic carbons, the *J*-values decrease with the increase in the number of bonds to the fluorine, for example, the *ortho* carbons, C-2' and C-4', for **4.85** J = 21.4 Hz and 22.5 Hz, respectively. The *meta*- and *para*- carbons of the same compound have coupling constants of 7.5 Hz and 2.0 Hz, respectively.

The ^{1}H NMR spectra for these fluorinated β-keto esters revealed that the $^{1}H,^{19}F$ coupling constants are always greater than that of ^{1}H, ^{1}H coupling constants for protons located in the same position. For example, in the ^{1}H NMR spectrum of **4.84**, the *ortho* $^{1}H,^{19}F$ coupling constant ($^{3}J_{H\text{-}3',F}$ = 12.1 Hz) of H-3'-to-fluorine is significantly larger than the ^{1}H, ^{1}H coupling constant of the same proton (H-3') to the *ortho* proton (H-4') ($^{3}J_{H\text{-}3',H\text{-}4'}$ = 8.5 Hz). The ^{1}H NMR spectrum of **4.85** showed $^{3}J_{H\text{-}4',F}$ = 9.1 Hz and $^{3}J_{H\text{-}4',H\text{-}5'}$ = 8.0 Hz which are the coupling constants of H-4' with ^{19}F and H-4' with H-5', respectively.



Scheme 4.30: Keto-enol tautomerism of methyl benzoylacetate.

The NMR spectra for all β-keto esters synthesized suggest that these organic molecules exist as a mixture of keto-enol tautomers (Scheme 4.30). The keto form (**4.65**) is more favourable than the enol form (**4.65A**). For example, **4.65** and **4.86** exist at a keto-enol ratio of 6:1 as shown by the peak integrals (Table 4.1). The 2-fluoro (**4.84**) and 3-fluoro (**4.85**) β-keto ester derivatives have keto-enol ratios that are more than 50% less than that of **4.65** and **4.86**.

Table 4.1: Keto-enol ratio from methoxy protons of β-keto esters.

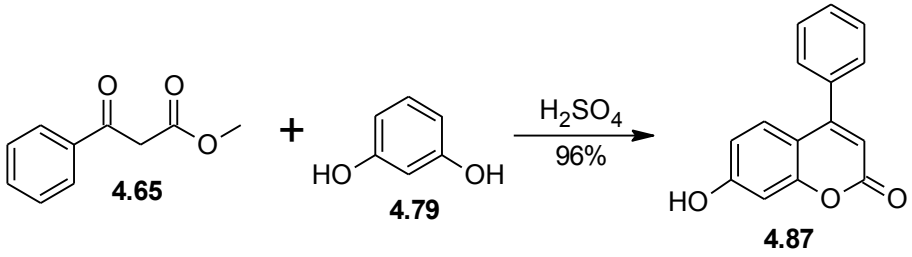
Compound	Tautomeric form	Integration of methoxy protons	Integral ratio (keto : enol)
4.65	Ketone	3.0331	6.0:1.0
	Enol	0.5077	
4.84	Ketone	3.0465	2.7:1.0
	Enol	1.1174	
4.85	Ketone	3.0000	2.9:1.0
	Enol	1.0260	
4.86	Ketone	3.0000	6.0:1.0
	Enol	0.4978	

4.5.3 Pechmann reaction

The Pechmann reaction is commonly used to synthesize coumarins. This involves cyclization of a *β*-keto ester with phenol in the presence of a catalyst. The second step of our reaction involves the application of the Pechmann reaction to synthesize fluorinated 4-phenylcoumarins (neoflavones).

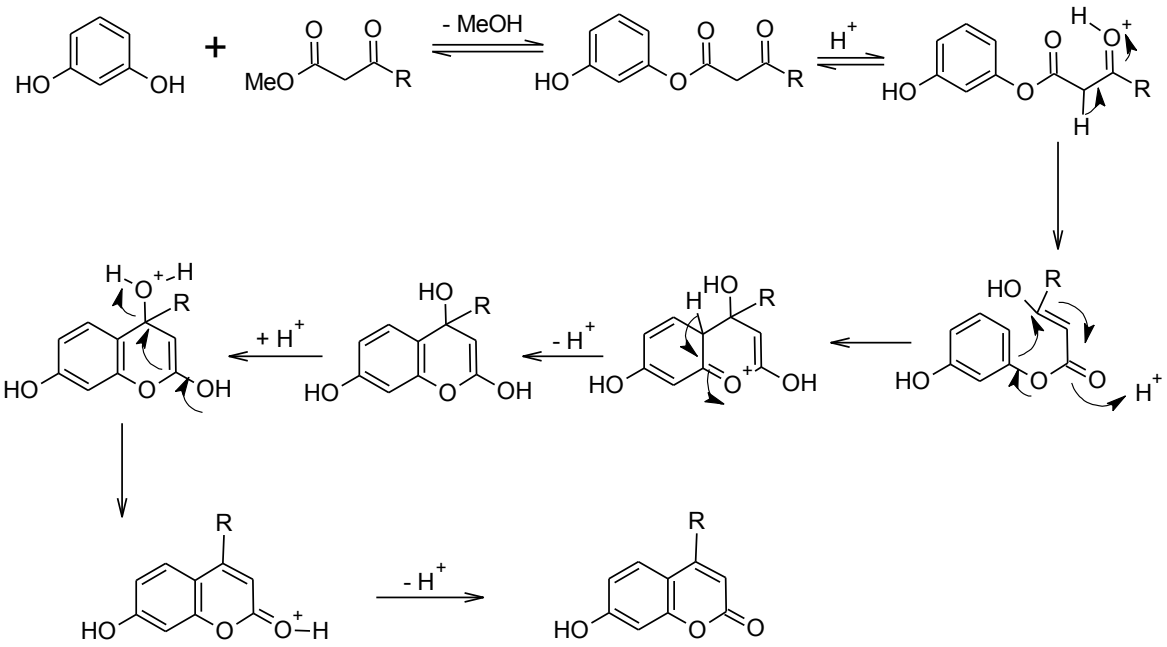
4.5.3.1 Synthesis of 7-hydroxy-4-phenylcoumarin (4.87)

7-Hydroxy-4-phenylcoumarin (**4.87**) was synthesized by the Pechmann reaction. The treatment of methyl benzoylacetate (**4.65**) and resorcinol (**4.79**) with H_2SO_4 at 35 °C produced **4.87** in a yield of 96% (Scheme 4.31). The product **4.87** was isolated as a yellow solid and its structure was verified by NMR, mass spectrometry and the melting point which agree with the literature.[228]



Scheme 4.31: Synthesis of 7-hydroxy-4-phenylcoumarin (**4.87**).

A mechanism for the Pechmann reaction is proposed in Scheme 4.32. The acid catalyses the transesterification process to form a reactive *β*-keto ester which readily converts to the enol tautomer. An intramolecular Michael addition forms the coumarin skeleton. Subsequent acid-induced dehydration and dehydrogenation lead to the coumarin.

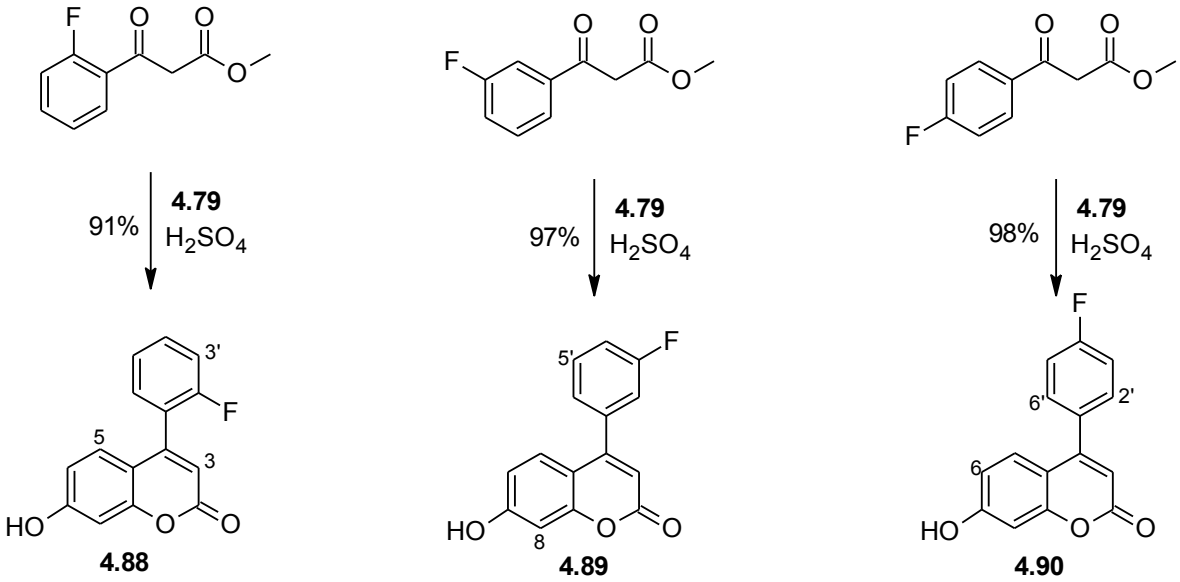


Scheme 4.32: A proposed mechanism for the Pechmann reaction.

The structure of **4.87** was confirmed by the ^{1}H NMR spectrum which revealed an olefinic α-proton peak (H-3) as a singlet at δ_H 6.41 and three proton peaks of the phenolic aromatic ring (H-6, H-8 and H-5) resonating at δ_H 6.78, δ_H 6.80 and δ_H 7.27, respectively (Plate 41). H-6 appeared as doublet of doublets due to *ortho*- and *meta*-coupling with H-5 (J = 8.7 Hz) and H-8 (J = 2.4 Hz), respectively. H-8 appeared as a doublet due to *meta*-coupling with H-6 (J = 2.4 Hz) and H-5 with *ortho*-coupling to H-6 (J = 8.7 Hz). This coupling pattern was confirmed by the COSY spectrum which showed a correlation between H-5 and H-6, and further correlation between H-6 and H-8. Two multiplets (for the phenyl moiety) which integrate to two protons (δ_H 7.50) and three protons (δ_H 7.55) were assigned to the *ortho* protons (H-2', H-6') and *meta* and *para* protons (H-3', H-4', H-5'), respectively. A broad hydroxy proton peak appeared downfield at δ_H 10.64.

The ^{13}C NMR spectrum also confirmed the structure **4.87** by showing the expected thirteen signals (Plate 41). HSQC, HMBC and DEPT-135 NMR spectra were used to assign each of these thirteen peaks. The phenolic and carbonyl carbons were most deshielded as they resonate at δ_C 161.9 and δ_C 160.6, respectively. The non-protonated aromatic carbons (H-8a, H-4 and H-1') were also deshielded as they appeared downfield at δ_C 156.0, δ_C 155.9 and δ_C 135.7, respectively. The rest of the aromatic carbons were assigned based on the HSQC NMR spectra.

4.5.3.2 *Synthesis of fluorinated 7-hydroxy-4-phenylcoumarins (4.88, 4.89 and 4.90)*

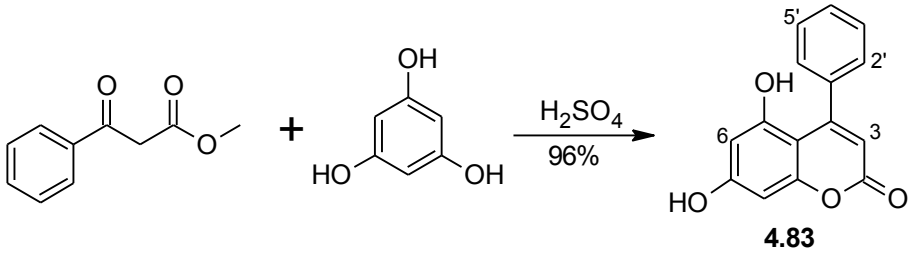


Scheme 4.33: Synthesis of fluorinated 4-arylcoumarins (**4.88, 4.89 and 4.90**).

Having successfully synthesized 4-arylcoumarin (**4.87**) by the Pechmann condensation, the reaction was also applied in the synthesis of fluorinated 4-phenylcoumarins (Scheme 4.33). Resorcinol (**4.79**) was reacted with *ortho*-, *meta*- and *para*-fluorinated aryl *β*-keto esters to yield the corresponding fluorinated 4-phenylcoumarins, (**4.88**, **4.89** and **4.90**), respectively. The reaction conditions for these reactions were similar to that for the synthesis of **4.87** and fluorinated coumarins (**4.88, 4.89 and 4.90**) were obtained in good yields (91% - 98%). The chemical structures of the fluorinated coumarins were confirmed by NMR spectroscopy (Plate 42, 43 and 44) and mass spectrometry.

4.5.3.3 *Synthesis of 5,7-dihydroxy-4-phenylcoumarin (4.83)*

The synthesis of coumarins by the Pechmann condensation was also investigated with phloroglucinol instead of resorcinol (**4.79**) as a starting material. The reaction of the 3-phenyl *β*-keto ester with phloroglucinol in acid medium afforded 5,7-dihydroxy-4-phenylcoumarin (**4.83**) in good yield. The structure of **4.83** was confirmed by NMR spectroscopy, mass spectrometry and melting point.



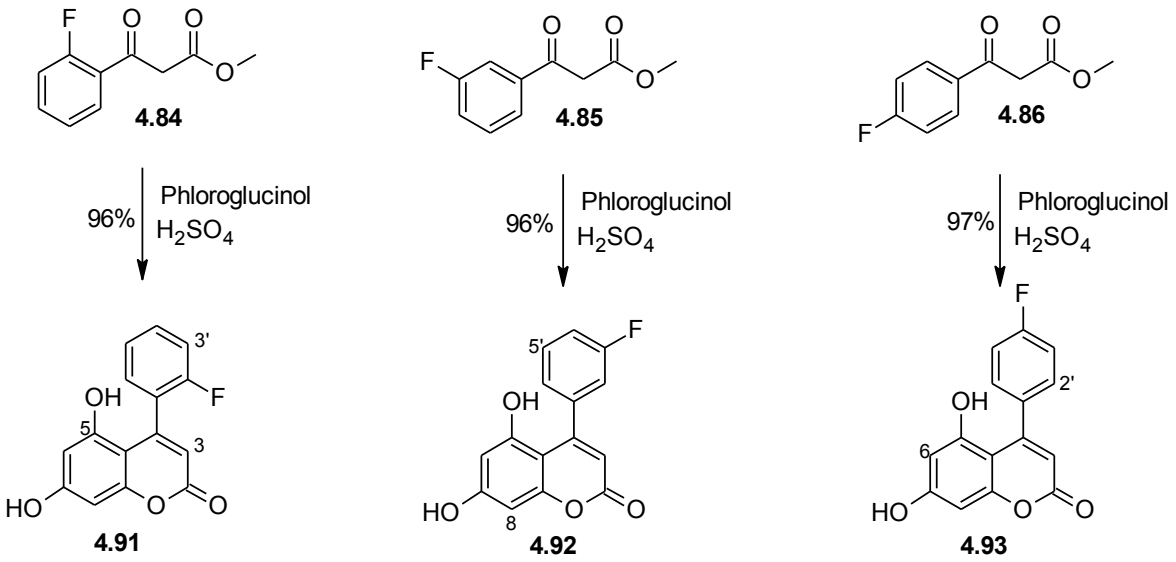
4.83

Scheme 4.34: Synthesis of 5,7-dihydroxy-4-phenylcoumarin (**4.83**).

The structure of **4.83** was characterized by the presence of two deshielded singlet peaks at δ_H 10.10 and δ_H 10.38 in the ^{1}H NMR spectrum (Plate 45) assigned to 7-OH and 5-OH, respectively. The aromatic protons of the phenyl group are more deshielded than the aromatic protons of the coumarin ring (H-6 and H-8) as they resonate at δ_H 7.30-7.38 while H-6 and H-8 appear at δ_H 6.16 and δ_H 6.26, respectively. The ^{13}C NMR spectrum also confirmed the structure of **4.83** by showing thirteen carbon peaks. Two phenolic carbons (C-5 and C-7) and a carbonyl carbon resonate at δ_C 157.6, δ_C 162.2 and δ_C 160.4, respectively. The spectrum also showed the presence of four non-protonated carbons (C-1', C-4, C-4a and C-8a).

4.5.3.4 Synthesis of fluorinated 5,7-dihydroxy-4-phenylcoumarins (4.91, 4.92 and 4.93)

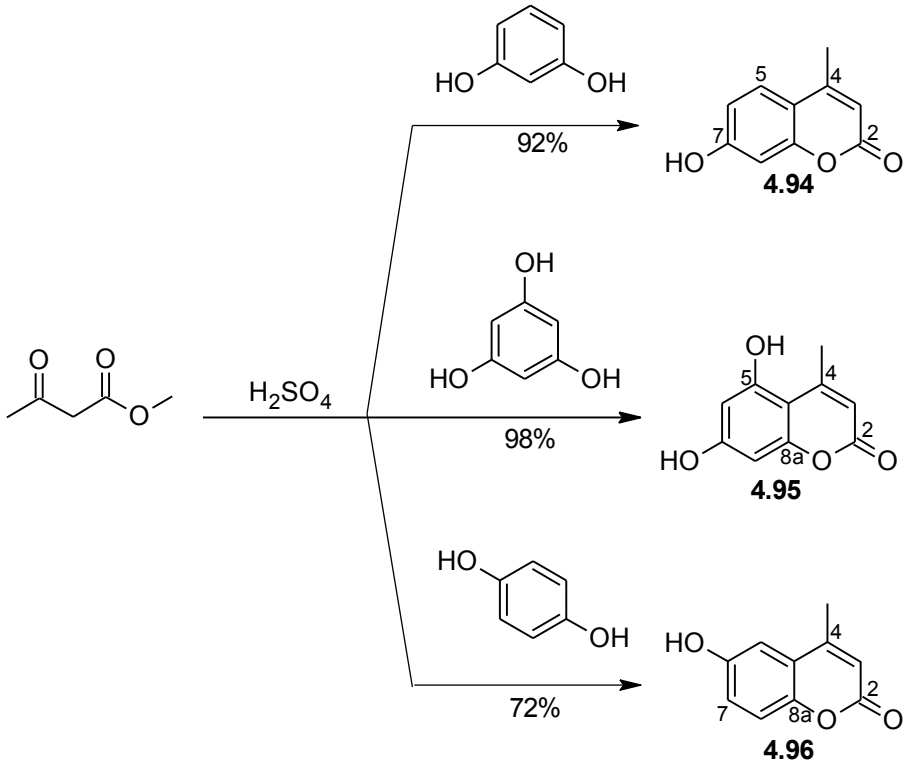
Fluorinated 5,7-dihydroxy-4-phenylcoumarins (**4.91, 4.92 and 4.93**) were also synthesized by the same manner as **4.83**. *Ortho*-, *meta*- and *para*-fluorinated 4-aryl *β*-keto esters (**4.84**, **4.85** and **4.86**, respectively) were used in this reaction to yield the corresponding fluorinated 5,7-dihydroxy-4-phenylcoumarins as shown in Scheme 4.35. The formation of these compounds was confirmed by NMR spectroscopy (Plates 46, 47 and 48) and mass spectrometry.



Scheme 4.35: Synthesis of fluorinated dihydroxy-4-arylcoumarins (**4.91, 4.92 and 4.93**).

4.5.3.5 Synthesis of 4-methylcoumarins

4-Methylcoumarins (**4.94**, **4.95** and **4.96**) were also synthesized by Pechmann condensation. Methyl acetoacetate was reacted with resorcinol, phloroglucinol and 4-hydroxyphenol separately to yield 7-hydroxy-4-methylcoumarin (**4.94**), 5,7-dihydroxy-4-methylcoumarin (**4.95**) and 6-hydroxy-4-methylcoumarin (**4.96**), respectively. These acid-mediated reactions were run at low temperatures (less than 50 °C, except for the reaction of 4-hydroxyphenol) to yield 4-methylcoumarins and their structures were confirmed by NMR, mass spectra and melting points.



Scheme 4.36: Synthesis of 4-methylcoumarins by Pechmann reaction.

The 4-methylcoumarins were characterized by the presence of an allylic methyl resonance (C**H**$_3$) in the upfield region (δ_H 2.35 – 2.48) in their ^{1}H NMR spectra (Plates 49, 50 and 51). This allylic peak appears as a doublet due to long-range coupling with the vinylic proton (3-H) with an average coupling constant of 1.1 Hz. The vinylic proton also appeared as a doublet at about δ_H 6. ^{13}C NMR revealed ten carbon peaks which correspond to the number of carbons in the structure. The carbonyl and phenolic carbons were deshielded as they appeared downfield followed by the non-protonated carbons. The structures of these compounds were also confirmed by mass spectrometry.

4.6 Activity of coumarins

Coumarins (**4.83**, **4.87**, **4.88**, **4.89**, **4.90**, **4.91**, **4.92** and **4.93**) were subjected to an *in vitro* cell-base HIV assay in the MINTEK laboratories at a concentration of 10 µg.mL^{-1}, but none of these showed any activity. The concentration of 10 µg.mL^{-1} is too low to consider for activity, but we are arranging to repeat the tests at higher concentrations. Antimicrobial and cytotoxic activities of cell lines are currently under investigation.

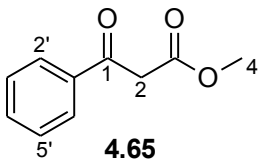
4.7 Conclusion

The objective of this study was to investigate the application of the Pechmann reaction in the synthesis of 4-phenylcoumarins (neoflavones) with substituents in the 4-phenyl ring. Fluorine-substituted 4-aryl *β*-ketoesters (the precursors for the fluorine-substituted neoflavones) were synthesized by a new method which gave good yields (81%-88%). Fluorine-substituted neoflavones were successfully synthesized by the Pechmann reaction for the first time (reaction of fluorinated *β*-ketoesters with different phenols) and were isolated in good yields of more than 91%.

4.8 Experimental Procedure

General experimental procedures are given in Section 3.7.1.

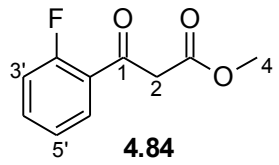
4.8.1 Synthesis of methyl benzoylacetate (4.65)



4.65

To a stirred mixture of $MgCl_2$ (2.0 g, 21 mmol) and Et_3N (2.1 g, 21 mmol) in dry DCM (15 mL) at room temperature, methyl acetoacetate, (2.0 g, 17 mmol) was added slowly. The mixture was stirred for 30 min before the temperature was reduced to 0 °C. *n*-BuLi (20 mL of a 1.6 M in hexane, 32 mmol) was added slowly into the mixture and the mixture was stirred for a further 30 min. Benzoyl chloride (2.4 g, 17 mmol) was added dropwise into the mixture and the mixture was stirred for 15 min. The reaction mixture was allowed to reach room temperature and was stirred overnight. To the reaction was added 5 M HCl (8 mL) and distilled water (10 mL) and the mixture was extracted with DCM (3 x 30 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The resulting yellow product was purified by silica gel column chromatography with 10% EtOAc in hexanes as eluent and **4.65** was obtained as a light orange viscous liquid (2.6 g, 88%), TLC R_f 0.45 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 3.77 (3H, s, H-4), 4.03 (2H, s, H-2), 7.50 (2H, t, *J* = 7.8, H-3',5'), 7.62 (1H, t, *J* = 7.8, H-4'), 7.97 (2H, d, *J* = 7.8, H-2',6'). ^{13}C NMR (100 MHz, $CDCl_3$) 45.7 (C-2), 52.5 (C-4), 128.5 (C-2',6'), 128.8 (C-3',5'), 133.8 (C-4'), 136.0 (C-1'), 167.9 (C-3), 192.4 (C-1). [Plate 37].

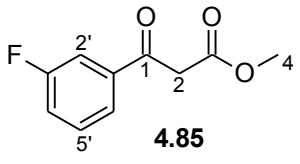
4.8.2 Synthesis of methyl 2-fluorobenzoylacetate (4.84)



4.84

To a stirred mixture of $MgCl_2$ (2.0 g, 21 mmol) and Et_3N (2.1 g, 21 mmol) in dry DCM (15 mL) at room temperature, methyl acetoacetate (2.0 g, 17 mmol) was added slowly. The mixture was stirred for 30 min before the temperature was reduced to 0 °C. *n*-BuLi (20 mL of a 1.6 M in hexane, 32 mmol) was added slowly into the mixture and the mixture was stirred for a further 30 min. 2-Fluorobenzoyl chloride (2.7 g, 17 mmol) was added dropwise into the mixture and the mixture was stirred for 15 min. The reaction mixture was allowed to reach room temperature and was stirred overnight. To the reaction was added 5 M HCl (8 mL) and distilled water (10 mL) and the mixture was extracted with DCM (3 x 30 mL).The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The resulting yellow product was purified by silica gel column chromatography with 10% EtOAc in hexanes as eluent and **4.84** was obtained as a light orange viscous liquid (2.7 g, 81%), TLC R_f 0.50 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 3.76 (3H, s, H-4), 4.01 (2H, s, H-2), 7.15 (1H, ddd, *J* = 12.1, 8.5, 1.0, H-3'), 7.26 (1H, t, *J* = 7.5, H-5'), 7.57 (1H, m, H-4'), 7.95 (2H, td, *J* = 7.6, 1.9, H-6'). ^{13}C NMR (100 MHz, $CDCl_3$) 49.6 (d, *J* = 8.1, C-2), 52.3 (C-4), 116.7 (d, *J* = 24.1, C-3'), 124.7 (d, *J* = 2.9, C-6'), 129.3 (d, *J* = 21.7, C-1'), 131.0 (d, *J* = 2.3, C-5'), 135.5 (d, *J* = 9.6, C-4'), 162.2 (d, *J* = 254.3, C-2'), 167.8 (d, *J* = 3.0, C-3), 190.1 (d, *J* = 3.7, C-1). [Plate 38].

4.8.3 Synthesis of methyl 3-fluorobenzoylacetate (4.85)

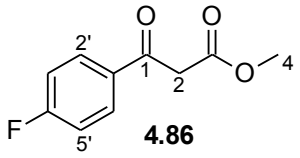


4.85

To a stirred mixture of $MgCl_2$ (2.0 g, 21 mmol) and Et_3N (2.1 g, 21 mmol) in dry DCM (15 mL) at room temperature, methyl acetoacetate (2.0 g, 17 mmol) was added slowly. The mixture was stirred for 30 min before the temperature was reduced to 0 °C. *n*-BuLi (20 mL of a 1.6 M in hexane, 32 mmol) was added slowly into the mixture and the mixture was stirred for a further 30 min. 3-Fluorobenzoyl chloride (2.7 g, 17 mmol) was added

dropwise into the mixture and the mixture was stirred for 15 min. The reaction mixture was allowed to reach room temperature and was stirred overnight. To the reaction was added 5 M HCl (8 mL) and distilled water (10 mL) and the mixture was extracted with DCM (3 x 30 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The resulting yellow product was purified by silica gel column chromatography with 10% EtOAc in hexanes as eluent and **4.85** was obtained as a light orange viscous liquid (2.9 g, 86%), TLC R_f 0.48 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 3.77 (3H, s, H-4), 4.00 (2H, s, H-2), 7.31 (1H, dddd, *J* = 8.5, 8.0, 2.5, 1.0, H-4'), 7.48 (1H, m, H-5'), 7.46 (1H, ddd, *J* = 9.3, 2.5, 1.0, H-2'), 7.73 (1H, dt, *J* = 7.7, 1.0, H-6'). ^{13}C NMR (100 MHz, $CDCl_3$) 45.7 (C-2), 52.5 (C-4), 115.2 (d, *J* = 22.5, C-4'), 120.8 (d, *J* = 21.4, C-2'), 124.3 (d, *J* = 2.0, C-6'), 130.5 (d, *J* = 7.5, C-5'), 138.0 (d, *J* = 6.6, C-1'), 162.8 (d, *J* = 246.3, C-3'), 167.5 (C-3), 191.1 (C-1). [Plate 39].

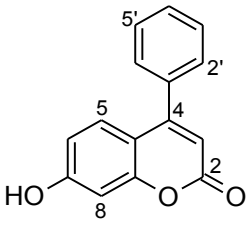
4.8.4 Synthesis of methyl 4-fluorobenzoylacetate (4.86)



4.86

To a stirred mixture of $MgCl_2$ (2.0 g, 21 mmol) and Et_3N (2.1 g, 21 mmol) in dry DCM (15 mL) at room temperature, methyl acetoacetate (2.0 g, 17 mmol) was added slowly. The mixture was stirred for 30 min before the temperature was reduced to 0 °C. *n*-BuLi (20 mL of a 1.6 M in hexane, 32 mmol) was added slowly into the mixture and the mixture was stirred for a further 30 min. 4-Fluorobenzoyl chloride (2.7 g, 17 mmol) was added dropwise into the mixture which was stirred for 15 min. The reaction mixture was allowed to reach room temperature and was stirred overnight. To the reaction was added 5 M HCl (8 mL) and distilled water (10 mL) and the mixture was extracted with DCM (3 x 30 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The resulting yellow product was purified by silica gel column chromatography with 10% EtOAc in hexanes as eluent and **4.86** was obtained as a light orange viscous liquid (2.9 g, 86%), TLC R_f 0.48 (Hexanes-EtOAc, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) 3.76 (3H, s, H-4), 3.98 (2H, s, H-2), 7.16 (2H, m, H-3',5'), 7.98 (2H, m, H-2',6'). ^{13}C NMR (100 MHz, $CDCl_3$) 45.6 (C-2), 52.5 (C-4), 116.0 (d, *J* = 22.0, C-3',5'), 131.3 (d, *J* = 9.6, C-2', 6'), 132.5 (d, *J* = 3.0, C-1'), 166.1 (d, *J* = 243.1, C-4'), 167.7 (C-3), 190.7 (C-1). [Plate 40].

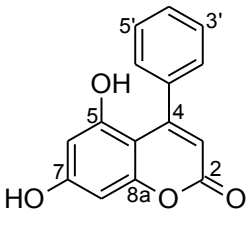
4.8.5 Synthesis of 7-hydroxy-4-phenylcoumarin (4.87)



4.87

To a mixture of resorcinol (2.0 g, 18 mmol) and methyl benzoylacetate (3.2 g, 18 mmol) was added conc. H_2SO_4 (8 mL, 75%). The temperature of the stirred mixture was increased to 35 °C. After stirring for 5 h, the mixture was poured into crushed ice and neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue was washed with plenty of water. The resulting product was purified by silica gel column chromatography with 70% EtOAc in hexanes as eluent and **4.87** was obtained as a yellow solid (4.1 g, 96%), mp 247-249 °C (lit.[228] 247-248 ºC), TLC R_f 0.48 (Hexanes-EtOAc, 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) 6.14 (1H, s, H-3), 6.78 (1H, dd, *J* = 8.7, 2.4, H-6), 6.80 (1H, d, *J* = 2.4, H-8), 7.27 (1H, d, *J* = 8.7, H-5), 7.50 (2H, m, H-2',6'), 7.55 (3H, m, H-3',4',5'), 10.64 (1H, s, OH). ^{13}C NMR (100 MHz, DMSO-d_6) 103.2 (C-8), 110.8 (C-3), 111.2 (C-6), 113.7 (C-4a), 128.6 (C-5), 128.8 (C-2',6'), 129.0 (C-4'), 129.3 (C-3',5'), 135.7 (C-1'), 155.9 (C-4), 156.0 (C-8a), 160.6 (C-2), 161.9 (C-7). [Plate 41]. HRMS (ESI$^+$): Found $[M+Na]^+$ 261.0531, Calc. for $C_{15}H_{10}NaO_3$ 261.0528.

4.8.6 Synthesis of 5,7-dihydroxy-4-phenylcoumarin (4.83)

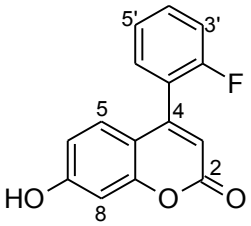


4.83

To a mixture of phloroglucinol (2.3 g, 18 mmol) and methyl benzoylacetate (3.2 g, 18 mmol) was added conc. H_2SO_4 (8 mL, 75%). The temperature of a stirred mixture was increased to 35 °C. After stirring for 5 h, the mixture was poured into crushed ice and neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue was washed with plenty of water. The resulting product was purified by silica gel column

chromatography with 70% EtOAc in hexanes as eluent and **4.83** was obtained as a light orange solid (4.4 g, 96%), mp 240-242 °C (lit.[220] 241-242 ºC), TLC R_f 0.48 (Hexanes-EtOAc, 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) 5.73 (1H, s, H-3), 6.16 (1H, d, *J* = 2.3, H-6), 6.26 (1H, d, *J* = 2.3, H-8), 7.30-7.34 (2H, m, H-2',6'), 7.35-7.38 (3H, m, H-3',4',5'), 10.10 (1H, s, 7-OH), 10.38 (1H, s, 5-OH). ^{13}C NMR (100 MHz, DMSO-d_6) 95.1 (C-8), 99.6 (C-6), 101.1 (C-4a), 110.6 (C-3), 127.7 (C-2',6'), 127.8 (C-3',5'), 128.2 (C-4'), 140.0 (C-1'), 156.5 (C-4), 157.2 (C-8a), 157.6 (C-5), 160.4 (C-2), 162.2 (C-7). [Plate 45]. HRMS (ESI$^+$): Found $[M+Na]^+$ 277.0480, Calc. for $C_{15}H_{10}NaO_4$ 277.0477.

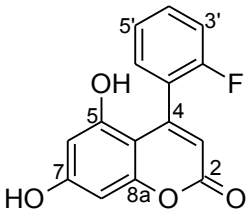
4.8.7 Synthesis of 7-hydroxy-4-(2-fluorophenyl)coumarin (4.88)



4.88

To a mixture of resorcinol (2.0 g, 18 mmol) and methyl 2-fluorobenzoylacetate (3.5 g, 18 mmol) was added conc. H_2SO_4 (8 mL, 75%). The temperature of a stirred mixture was increased to 35 °C. After stirring for 5 h, the mixture was poured into crushed ice and neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue was washed with plenty of water. The resulting product was purified by silica gel column chromatography with 70% EtOAc in hexanes as eluent and **4.88** was obtained as a light yellow solid (4.2 g, 91%), mp 204-207 °C, TLC R_f 0.45 (Hexanes-EtOAc, 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) 6.24 (1H, s, H-3), 6.77 (1H, dd, *J* = 8.6, 2.4, H-6), 6.81 (1H, d, *J* = 2.4, H-8), 7.03 (1H, dd, *J* = 8.6, 2.6, H-5), 7.37-7.45 (2H, m, H-3',6'), 7.50 (1H, td, *J* = 7.5, 1.8, H-5'), 7.61 (1H, m, H-4'), 10.67 (1H, s, OH). ^{13}C NMR (100 MHz, DMSO-d_6) 102.6 (C-8), 110.7 (C-4a), 112.1 (C-3), 113.4 (C-6), 116.1 (d, *J* = 21.3, C-3'), 122.7 (d, *J* = 15.3, C-1'), 125.2 (d, *J* = 3.6, C-6'), 127.9 (d, *J* = 1.6, C-5), 130.8 (d, *J* = 2.9, C-5'), 132.0 (d, *J* = 8.2, C-4'), 150.3 (C-4), 155.2 (C-8a), 158.6 (d, *J* = 248.6, C-2'), 160.0 (C-2), 161.6 (C-7). [Plate 42]. HRMS (ESI$^+$): Found $[M+Na]^+$ 279.0437, Calc. for $C_{15}H_9FNaO_3$ 279.0433.

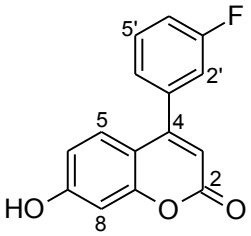
4.8.8 Synthesis of 5,7-dihydroxy-4-(2-fluorophenyl)coumarin (4.91)



4.91

To a mixture of phloroglucinol (2.3 g, 18 mmol) and methyl 2-fluorobenzoylacetate (3.5 g, 18 mmol) was added conc. H_2SO_4 (8 mL, 75%). The temperature of a stirred mixture was increased to 35 °C. After stirring for 5 h, the mixture was poured into crushed ice and neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue was washed with plenty of water. The resulting product was purified by silica gel column chromatography with 70% EtOAc in hexanes as eluent and **4.91** was obtained as an orange solid (4.7 g, 96%), mp 168-171 °C, TLC R_f 0.42 (Hexanes-EtOAc, 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) 5.84 (1H, s, H-3), 6.14 (1H, d, *J* = 2.3, H-6), 6.26 (1H, d, *J* = 2.3, H-8), 7.16-7.24 (2H, m, H-3',6'), 7.35 (1H, td, *J* = 7.6, 1.9, H-5'), 7.42 (1H, m, H-4'), 10.19 (1H, s, 7-OH). ^{13}C NMR (100 MHz, DMSO-d_6) 95.0 (C-8), 99.5 (C-6), 101.4 (C-4a), 111.1 (C-3), 114.9 (d, *J* = 21.1, C-3'), 124.3 (d, *J* = 3.3, C-6'), 128.1 (d, *J* = 16.0, C-1'), 129.6 (d, *J* = 3.5, C-5'), 130.6 (d, *J* = 8.2, C-4'), 150.5 (C-4), 156.8 (C-8a), 157.6 (C-5), 159.2 (d, *J* = 245.9, C-2'), 160.2 (C-2), 162.3 (C-7). [Plate 46]. HRMS (ESI$^+$): Found $[M+Na]^+$ 295.0391, Calc. for $C_{15}H_9FNaO_4$ 295.0383.

4.8.9 Synthesis of 7-hydroxy-4-(3-fluorophenyl)coumarin (4.89)

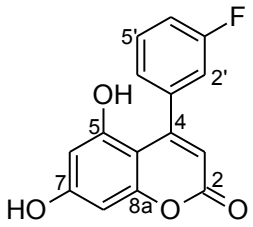


4.89

To a mixture of resorcinol (2.0 g, 18 mmol) and methyl 3-fluorobenzoylacetate (3.5 g, 18 mmol) was added conc. H_2SO_4 (8 mL, 75%). The temperature of a stirred mixture was increased to 35 °C. After stirring for 5 h, the mixture was poured into crushed ice and neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue

was washed with plenty of water. The resulting product was purified by silica gel column chromatography with 70% EtOAc in hexanes as eluent and **4.89** was obtained as a yellow solid (4.5 g, 97%), mp 208-211 °C, TLC R_f 0.45 (Hexanes-EtOAc, 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) 6.19 (1H, s, H-3), 6.79 (1H, dd, *J* = 8.6, 2.4, H-6), 6.81 (1H, d, *J* = 2.4, H-8), 7.26 (1H, d, *J* = 8.6, H-5), 7.35 (1H, dt, *J* = 7.7, 1.1, H-6'), 7.36-7.42 (2H, m, H-2',4'), 7.60 (1H, m, H-5'), 10.66 (1H, s, OH). ^{13}C NMR (100 MHz, DMSO-d_6) 102.8 (C-8), 110.5 (C-6), 110.9 (C-3), 113.4 (C-4a), 115.6 (d, *J* = 22.6, C-4'), 116.5 (d, *J* = 20.4, C-2'), 124.7 (d, *J* = 2.9, C-6'), 128.1 (C-5), 131.0 (d, *J* = 8.1, C-5'), 137.4 (d, *J* = 8.0, C-1'), 154.1 (d, *J* = 2.3, C-4), 155.6 (C-8a), 160.1 (C-2), 161.6 (C-7), 162.2 (d, *J* = 245.2, C-3'). [Plate 43]. HRMS (ESI$^+$): Found $[M+Na]^+$ 279.0435, Calc. for $C_{15}H_9FNaO_3$ 279.0433.

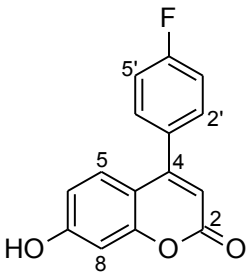
4.8.10 Synthesis of 5,7-dihydroxy-4-(3-fluorophenyl)coumarin (4.92)



4.92

To a mixture of phloroglucinol (2.3 g, 18 mmol) and methyl 3-fluorobenzoylacetate (3.5 g, 18 mmol) was added conc. H_2SO_4 (8 mL, 75%). The temperature of a stirred mixture was increased to 35 °C. After stirring for 5 h, the mixture was poured into crushed ice and neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue was washed with plenty of water. The resulting product was purified by silica gel column chromatography with 70% EtOAc in hexanes as eluent and **4.92** was obtained as a light brown solid (4.7 g, 96%), mp 267-269 °C, TLC R_f 0.44 (Hexanes-EtOAc, 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) 5.79 (1H, s, H-3), 6.16 (1H, d, *J* = 2.3, H-6), 6.27 (1H, d, *J* = 2.3, H-8), 7.14-7.23 (3H, m, H-3',4',6'), 7.40 (1H, m, H-5'), 10.18 (1H, s, 7-OH), 10.42 (1H, s, 5-OH). ^{13}C NMR (100 MHz, DMSO-d_6) 95.2 (C-8), 99.6 (C-6), 100.9 (C-4a), 110.7 (C-3), 114.9 (d, *J* = 20.8, C-2'), 115.1 (d, *J* = 22.9, C-4'), 124.0 (d, *J* = 2.8, C-6'), 129.8 (d, *J* = 8.7, C-5'), 142.2 (d, *J* = 8.2, H-1'), 154.9 (d, *J* = 1.6, H-4), 157.1 (C-8a), 157.4 (C-5), 160.2 (C-2), 161.7 (d, *J* = 242.2, C-3'), 162.3 (C-7). [Plate 47]. HRMS (ESI$^+$): Found $[M+Na]^+$ 295.0388, Calc. for $C_{15}H_9FNaO_4$ 295.0383.

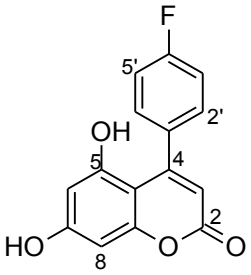
4.8.11 Synthesis of 7-hydroxy-4-(4-fluorophenyl)coumarin(4.90)



4.90

To a mixture of resorcinol (2.0 g, 18 mmol) and methyl 4-fluorobenzoylacetate (3.5 g, 18 mmol) was added conc. H_2SO_4 (8 mL, 75%). The temperature of a stirred mixture was increased to 35 °C. After stirring for 5 h, the mixture was poured into crushed ice and neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue was washed with plenty of water. The resulting product was purified by silica gel column chromatography with 70% EtOAc in hexanes as eluent and **4.90** was obtained as a light orange solid (4.5 g, 98%), mp 279-283 °C, TLC R_f 0.46 (Hexanes-EtOAc, 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) 6.13 (1H, s, H-3), 6.76 (1H, dd, *J* = 8.7, 2.4, H-6), 6.78 (1H, d, *J* = 2.4, H-8), 7.25 (1H, d, *J* = 8.7, H-5), 7.38 (2H, m, H-3',5'), 7.57 (2H, m, H-2',6'). ^{13}C NMR (100 MHz, DMSO-d_6) 103.2 (C-8), 110.8 (C-3), 110.9 (C-6), 113.9 (C-4a), 116.3 (d, *J* = 22.1, C-3',5'), 123.5 (C-5), 131.2 (d, *J* = 8.2, C-2',6'), 132.0 (d, *J* = 2.9, C-1'), 154.9 (C-4), 156.0 (C-8a), 160.6 (C-2), 161.1 (d, *J* = 245.8, C-4'), 162.0 (C-7). [Plate 44]. HRMS (ESI$^+$): Found $[M+Na]^+$ 279.0434, Calc. for $C_{15}H_9FNaO_3$ 279.0433.

4.8.12 Synthesis of 5,7-dihydroxy-4-(4-fluorophenyl)coumarin (4.93)

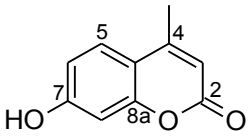


4.93

To a mixture of phloroglucinol (2.3 g, 18 mmol) and methyl 4-fluorobenzoylacetate (3.5 g, 18 mmol) was added conc. H_2SO_4 (8 mL, 75%). The temperature of a stirred mixture was increased to 35 °C. After stirring for 5 h, the mixture was poured into crushed ice and

neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue was washed with plenty of water. The resulting product was purified by silica gel column chromatography with 70% EtOAc in hexanes as eluent and **4.93** was obtained as a light brown solid (4.7 g, 97%), mp 266-266 °C, TLC R_f 0.45 (Hexanes-EtOAc, 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) 5.76 (1H, s, H-3), 6.16 (1H, d, *J* = 2.3, H-6), 6.26 (1H, d, *J* = 2.3, H-8), 7.18 (2H, m, H-3',5'), 7.37 (2H, m, H-2',6'), 10.18 (1H, s, 7-OH), 10.44 (1H, s, 5-OH). ^{13}C NMR (100 MHz, DMSO-d_6) 95.2 (C-8), 99.6 (C-6), 101.0 (C-4a), 110.8 (C-3), 114.6 (d, *J* = 22.1, C-3',5'), 130.1 (d, *J* = 8.6, C-2',6'), 136.2 (d, *J* = 2.8, C-1'), 155.4 (C-4), 157.2 (C-8a), 157.5 (C-5), 160.3 (C-2), 162.2 (C-7), 162.4 (d, *J* = 243.5, C-4'). [Plate 48]. HRMS (ESI$^+$): Found $[M+Na]^+$ 295.0386, Calc. for $C_{15}H_9FNaO_4$ 295.0383.

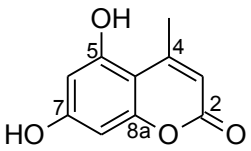
4.8.13 Synthesis of 7-hydroxy-4-methylcoumarin (4.94)



4.94

To a mixture of resorcinol (4.0 g, 36 mmol) and ethyl acetoacetate (4.7 g, 36 mmol) was added conc. H_2SO_4 (10 mL, 75%). The temperature of a stirred mixture was increased to 50 °C. After stirring for 2 h, the mixture was poured into crushed ice and neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue was washed with plenty of water. The resulting product was purified by silica gel column chromatography with 70% EtOAc in hexanes as eluent and **4.94** was obtained as a light yellow solid (5.8 g, 92%), mp 184-186 °C (lit.[229] 182-184 ºC), TLC R_f 0.46 (Hexanes-EtOAc, 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) 2.35 (3H, d, *J* = 1.1, CH_3), 6.10 (1H, d, *J* = 1.1, H-3), 6.69 (1H, d, *J* = 2.3, H-8), 6.79 (1H, dd, *J* = 8.6, 2.3, H-6), 7.57 (1H, d, *J* = 8.6, H-5). ^{13}C NMR (100 MHz, DMSO-d_6) 18.3 (CH_3), 102.4 (C-8), 110.4 (C-3), 112.2 (C-6), 113.1 (C-4a), 126.8 (C-5), 153.8 (C-4), 155.1 (C-8a), 160.6 (C-2), 161.4 (C-7). [Plate 49]. HRMS (ESI$^+$): Found $[M+Na]^+$ 199.0368, Calc. for $C_{10}H_8NaO_3$ 199.0371.

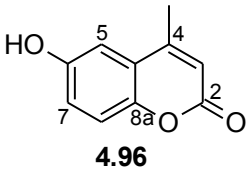
4.8.14 Synthesis of 5,7-dihydroxy-4-methylcoumarin (4.95)



4.95

To a mixture of phloroglucinol (4.5 g, 36 mmol) and ethyl acetoacetate (4.7 g, 36 mmol) was added conc. H_2SO_4 (10 mL, 75%). The temperature of a stirred mixture was increased to 50 °C. After stirring for 3 h, the mixture was poured into crushed ice and neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue was washed with plenty of water. The resulting product was purified by silica gel column chromatography with 70% EtOAc in hexanes as eluent and **4.95** was obtained as a cream-white solid (6.8 g, 98%), mp 290-293 °C (lit.[230] 286-288 ºC), TLC R_f 0.38 (Hexanes-EtOAc, 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) 2.48 (3H, d, *J* = 1.1, CH_3), 5.83 (1H, d, *J* = 1.1, H-3), 6.16 (1H, d, *J* = 2.3, H-6), 6.25 (1H, d, *J* = 2.3, H-8), 10.36 (1H, bs, 7-OH), 10.47 (1H, bs, 5-OH). ^{13}C NMR (100 MHz, DMSO-d_6) 23.9 (CH_3), 95.0 (C-8), 99.6 (C-3), 102.6 (C-4a), 109.3 (C-6), 155.5 (C-4), 156.9 (C-8a), 158.4 (C-5), 160.6 (C-2), 161.5 (C-7). [Plate 51]. HRMS (ESI$^+$): Found $[M+Na]^+$ 215.0321, Calc. for $C_{10}H_8NaO_4$ 215.0320.

4.8.15 Synthesis of 6-hydroxy-4-methylcoumarin (4.96)



4.96

To a mixture of 4-hydroxyphenol (4.0 g, 36 mmol) and ethyl acetoacetate (4.7 g, 36 mmol) was added conc. H_2SO_4 (10 mL, 75%). The temperature of a stirred mixture was increased to 95 °C. After stirring for 2 h, the mixture was poured into crushed ice and neutralized with a NaOH solution. The mixture was filtered under vacuum and the residue was washed with plenty of water. The resulting product was purified by silica gel column chromatography with 70% EtOAc in hexanes as eluent and **4.96** was obtained as a grey solid (4.6 g, 72%), mp 222-225 °C, TLC R_f 0.40 (Hexanes-EtOAc, 3:2). ^{1}H NMR (400 MHz, DMSO-d_6) 2.37 (3H, d, *J* = 1.2, CH_3), 6.34 (1H, d, *J* = 1.2, H-3), 7.02 (1H, d, *J* = 2.7, H-5), 7.04 (1H, dd, *J* = 9.6, 2.7, H-7), 7.23 (1H, d, *J* = 9.6, H-8), 9.76 (1H, s, 4-OH).

^{13}C NMR (100 MHz, DMSO-d_6) 18.5 (CH_3), 110.0 (C-4a), 110.1 (C-5), 114.9 (C-3), 117.8 (C-8), 120.2 (C-7), 146.7 (C-8a), 153.3 (C-4), 154.4 (C-6), 160.5 (C-2). [Plate 50]. HRMS (ESI^+): Found $[M+Na]^+$ 199.0372, Calc. for $C_{10}H_8NaO_3$ 199.0371.

CHAPTER 5. CONCLUSION

The aim of this research was to develop methods to prepare fluorine-containing natural products. A library of fluorine-containing prenylated benzophenones and fluorine-substituted 4-phenylcoumarins were successfully synthesized in this research.

The structures of the targeted benzophenones that were synthesized were based on bioactive benzophenones isolated from South African *Hypericum* species, *viz*. geranyl-2,4,6-trihydroxybenzophenone (**3.8**). Friedel-Crafts acylation and electrophilic aromatic substitution reactions were the key reactions in this synthesis to achieve the targeted fluorinated prenylated benzophenones and 27 prenylated benzophenones were successfully synthesized in this study. The compounds prepared include four monoprenyl-, seven diprenyl-, five triprenyl-, two tetraprenyl-, three monogeranyl-, three digeranyl-, two trigeranyl- and one tetrageranyl benzophenone.

The Friedel-Crafts acylation of phloroglucinol is a reaction with low selectivity and thus protection of the hydroxy groups was essential to obtain the acylated product in high yield. The reactivities of benzoyl chloride and 2-, 3- of 4-fluorobenzoyl chloride in the Friedel-Crafts reactions were similar and almost quantitative yields were observed. In the prenylation step, the 2-fluorobenzophenone derivative was less reactive than the other substrates and this is most likely a result of increased electron-withdrawing effect the 2-fluoro derivative on the adjacent aromatic ring.

In general *C*-prenylation of the benzophenones was obtained with DBU as a base, whereas the use of K_2CO_3 as a base resulted in *O*-prenylation.

Fluorine-substituted 4-phenylcoumarins were synthesized by the application of the Pechmann reaction (a palladium-free method). In the first step of this reaction, fluorine-substituted 4-aryl *β*-ketoesters (the precursors) were synthesized by a new method which

gave good yields. Fluorine-substituted neoflavones were successfully synthesized by the Pechmann reaction using fluorine-substituted 4-aryl β-ketoesters. A total of 11 coumarins (four monohydroxy- and four dihydroxy- neoflavones and three 4-methylcoumarins) were synthesized by our newly developed method.

Some of the benzophenones (**3.75**, **3.77**, **3.81**, **3.83**, **3.87**, **3.88**, **3.89** and **3.90**) and coumarins (**4.83**, **4.87**, **4.88**, **4.89**, **4.90**, **4.91**, **4.92** and **4.93**) were assayed for HIV activity in the MINTEK laboratories at a concentration of 10 $\mu g.mL^{-1}$ but none of them show any activity at this concentration. Antimicrobial and cytotoxic activities of the compounds are currently under investigation.

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Appendix

Plate 1. ^{1}H and ^{13}C NMR spectra of phenyl(2,4,6-trimethoxyphenyl)methanone (**3.32**).

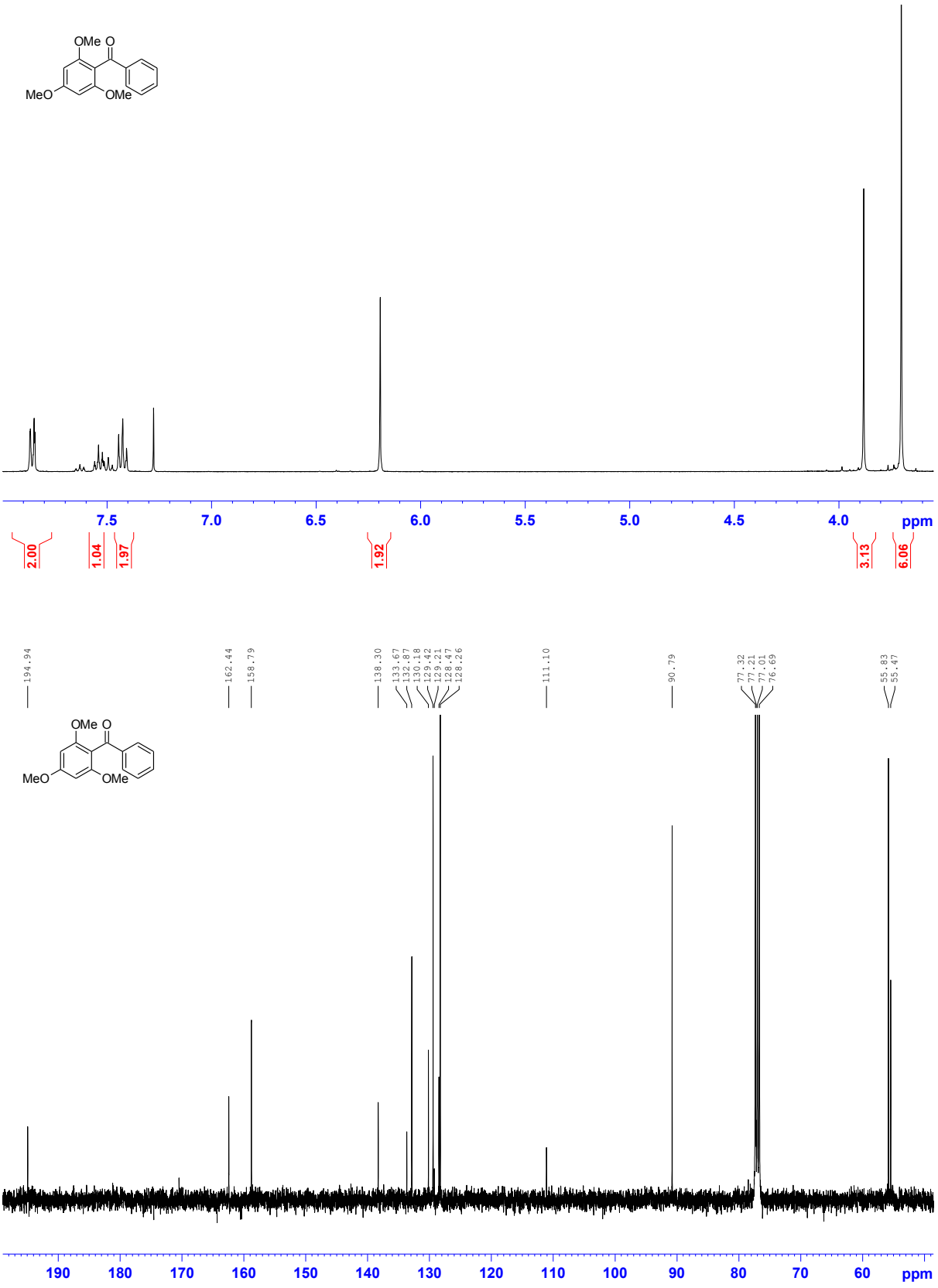

Plate 2. ^{1}H and ^{13}C NMR spectra of phenyl(2,4,6-trimethoxy-3-methylphenyl)methanone (**3.57**).

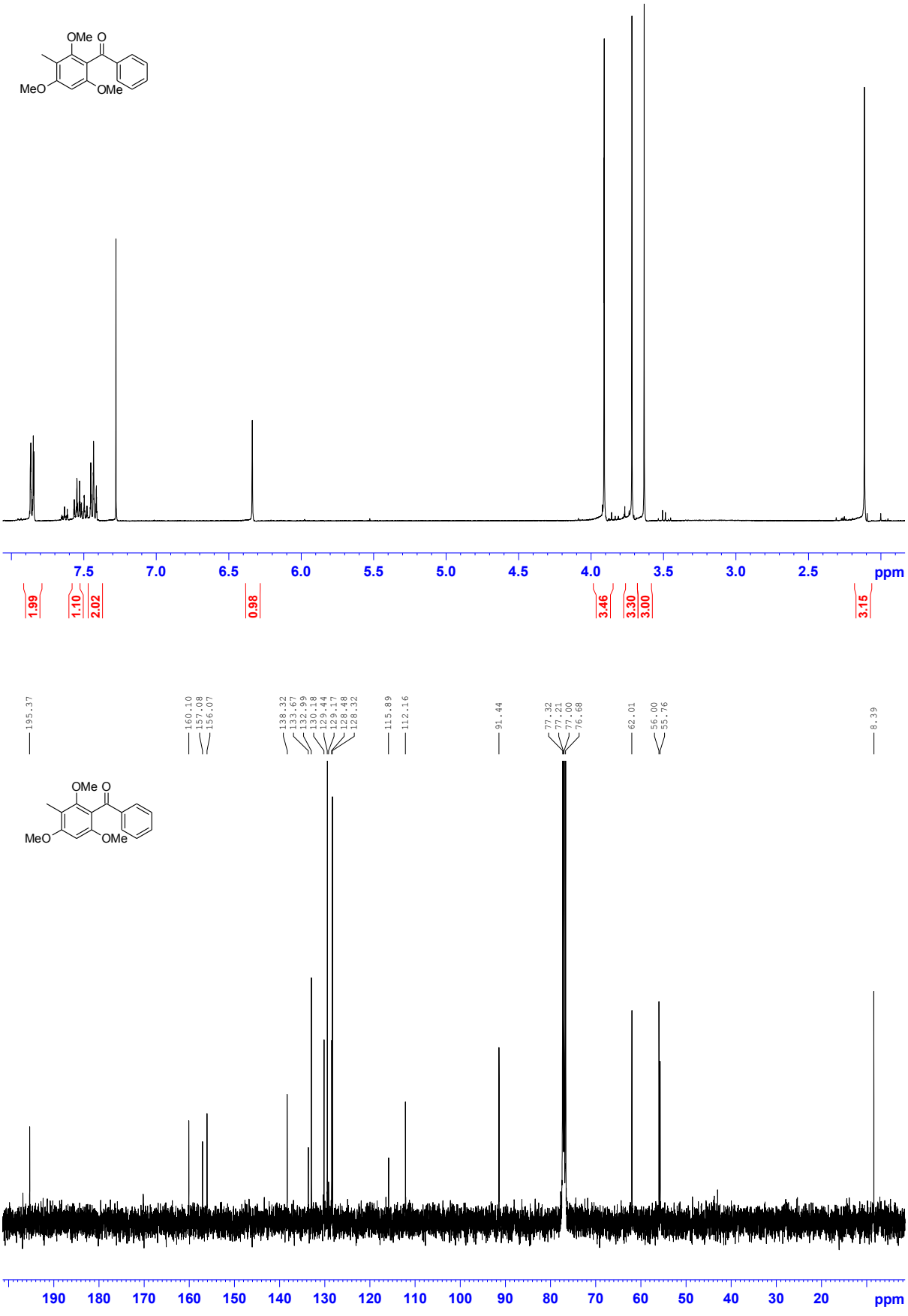

Plate 3. ^{1}H and ^{13}C NMR spectra of (2-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (**3.58**).

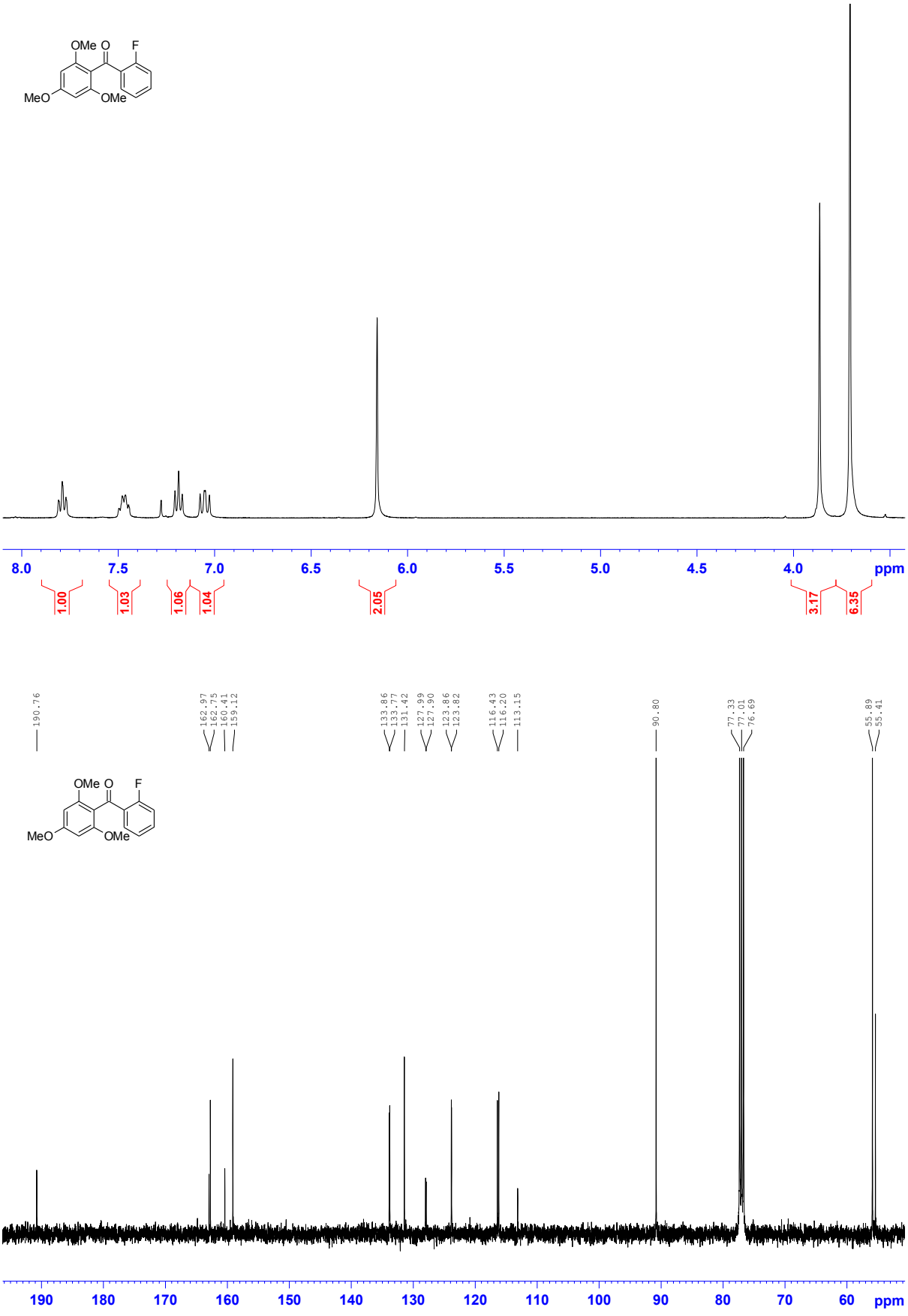

Plate 4. ^{1}H and ^{13}C NMR spectra of (3-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (**3.59**).

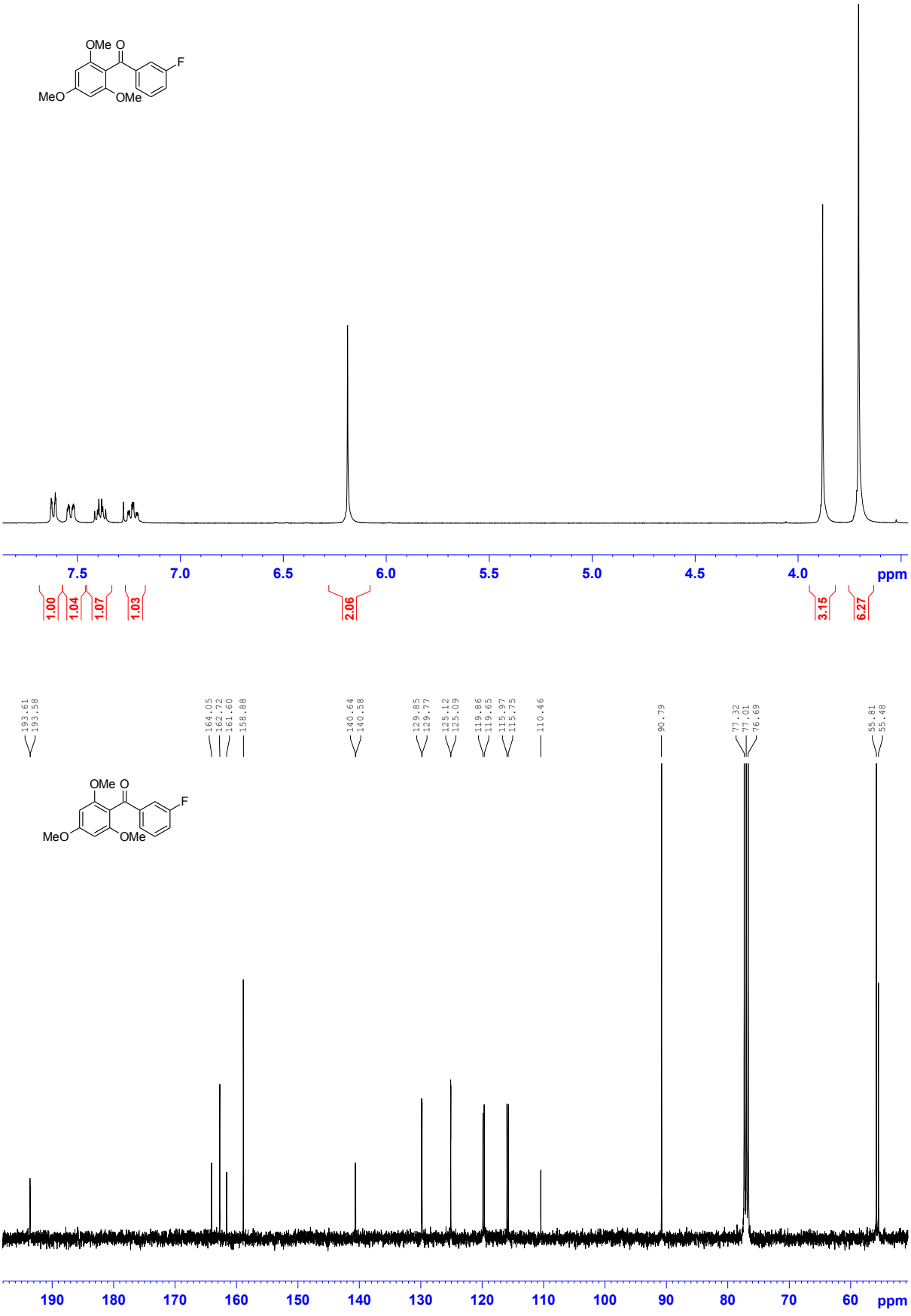

Plate 5. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)(2,4,6-trimethoxyphenyl)methanone (**3.60**).

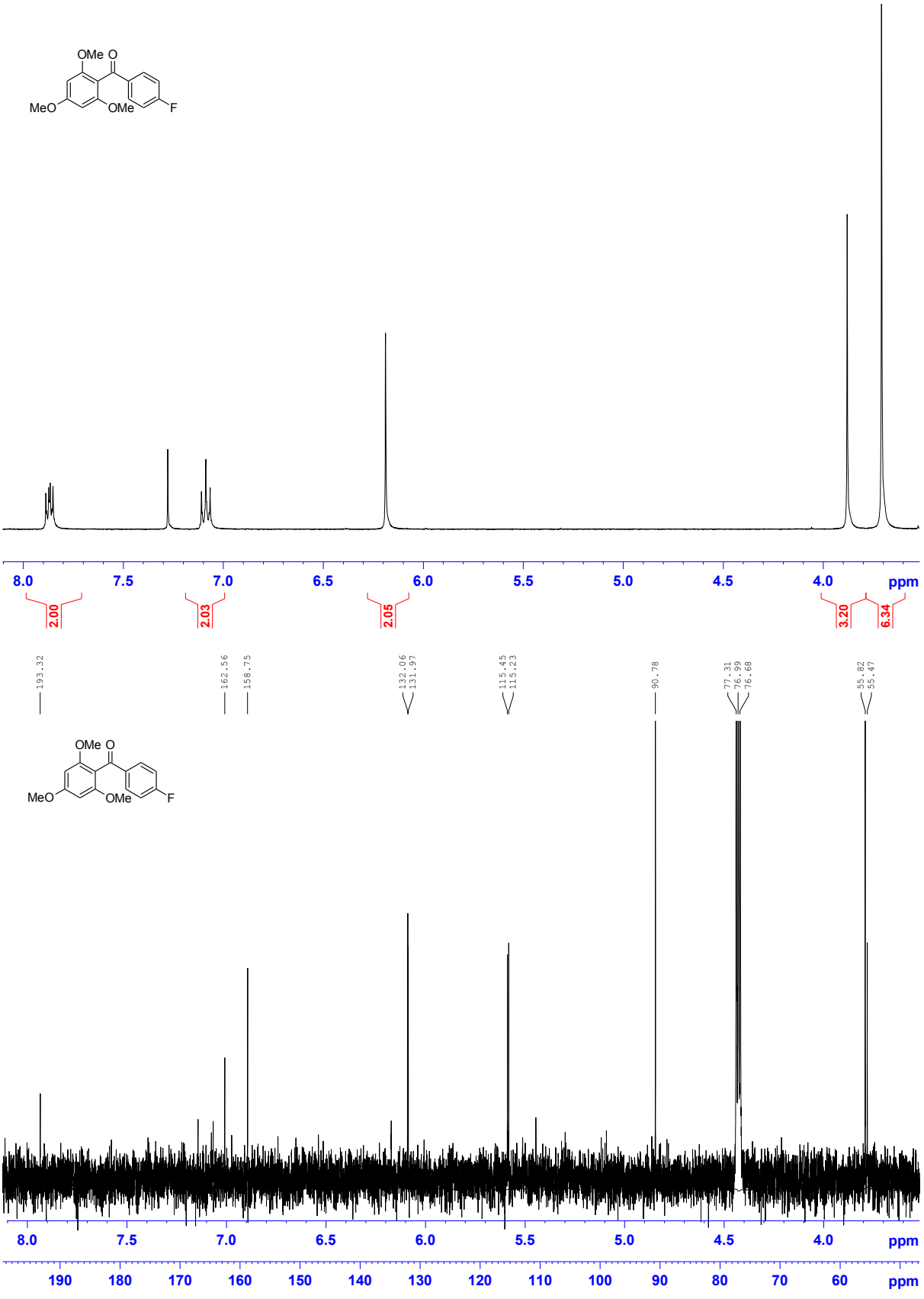

Plate 6. ^{1}H and ^{13}C NMR spectra of phenyl(2,4,6-trihydroxyphenyl)methanone (**3.33**).

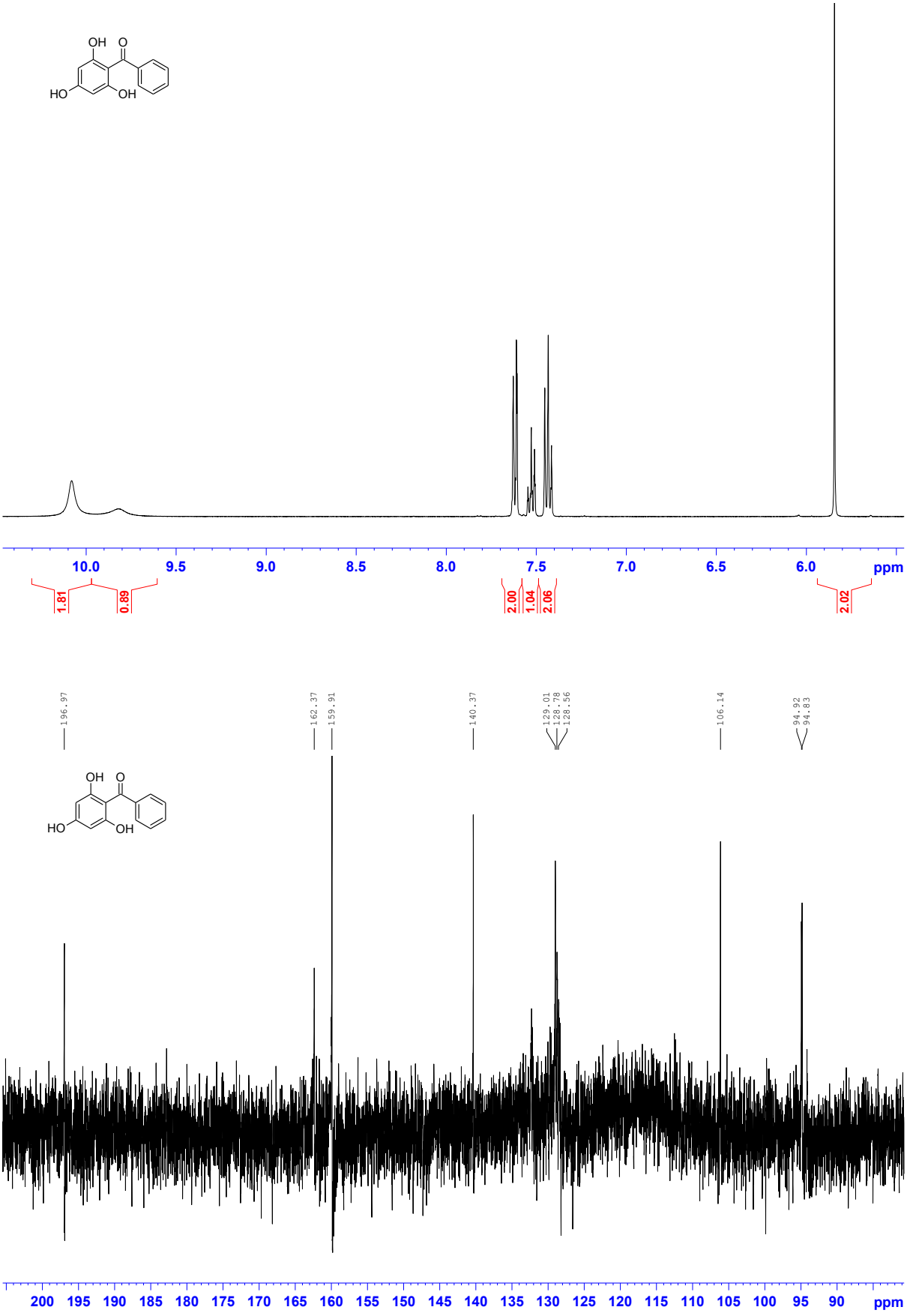

Plate 7. ^{1}H and ^{13}C NMR spectra of (2-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (**3.61**).

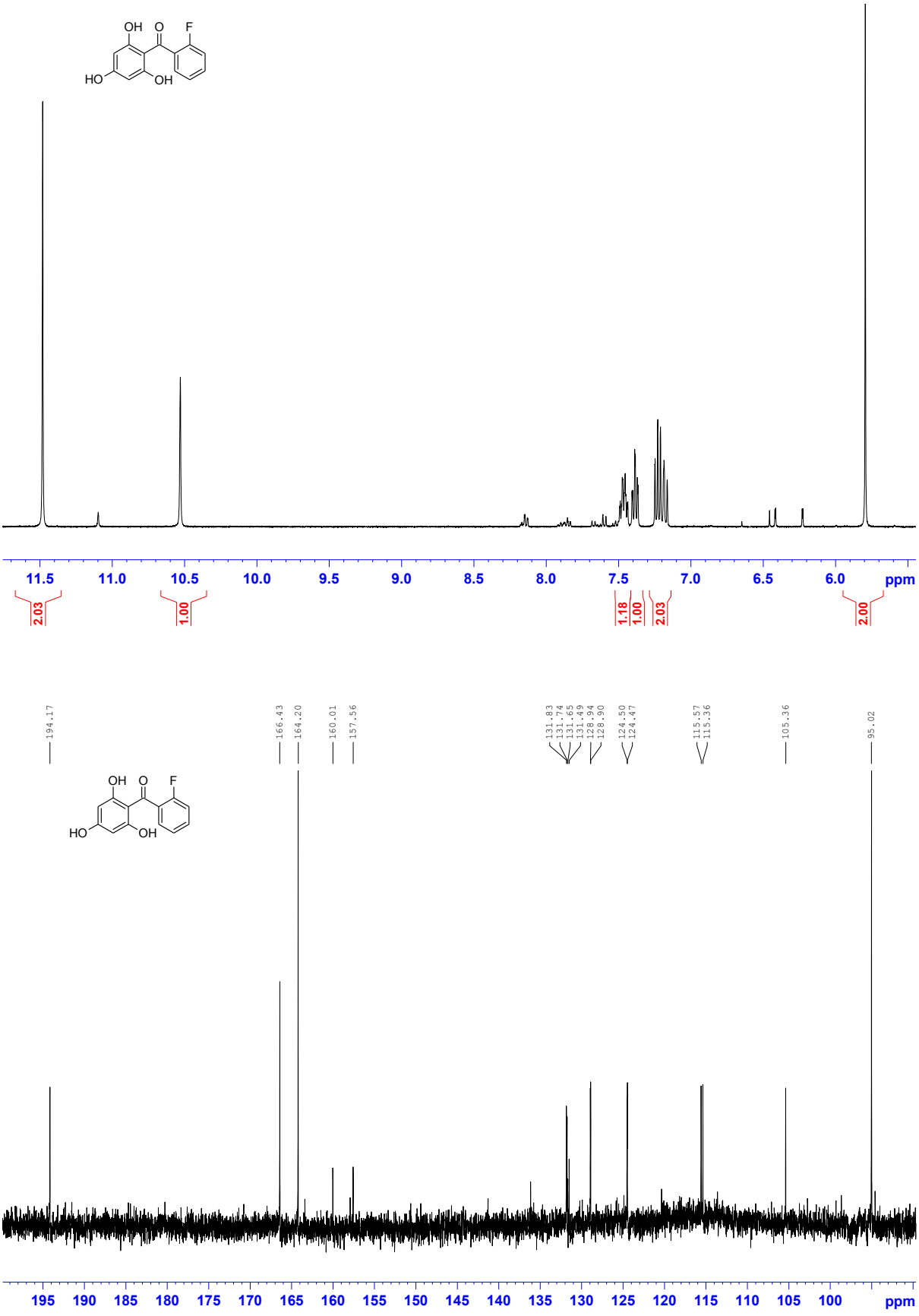

Plate 8. ^{1}H and ^{13}C NMR spectra of (3-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (**3.62**).

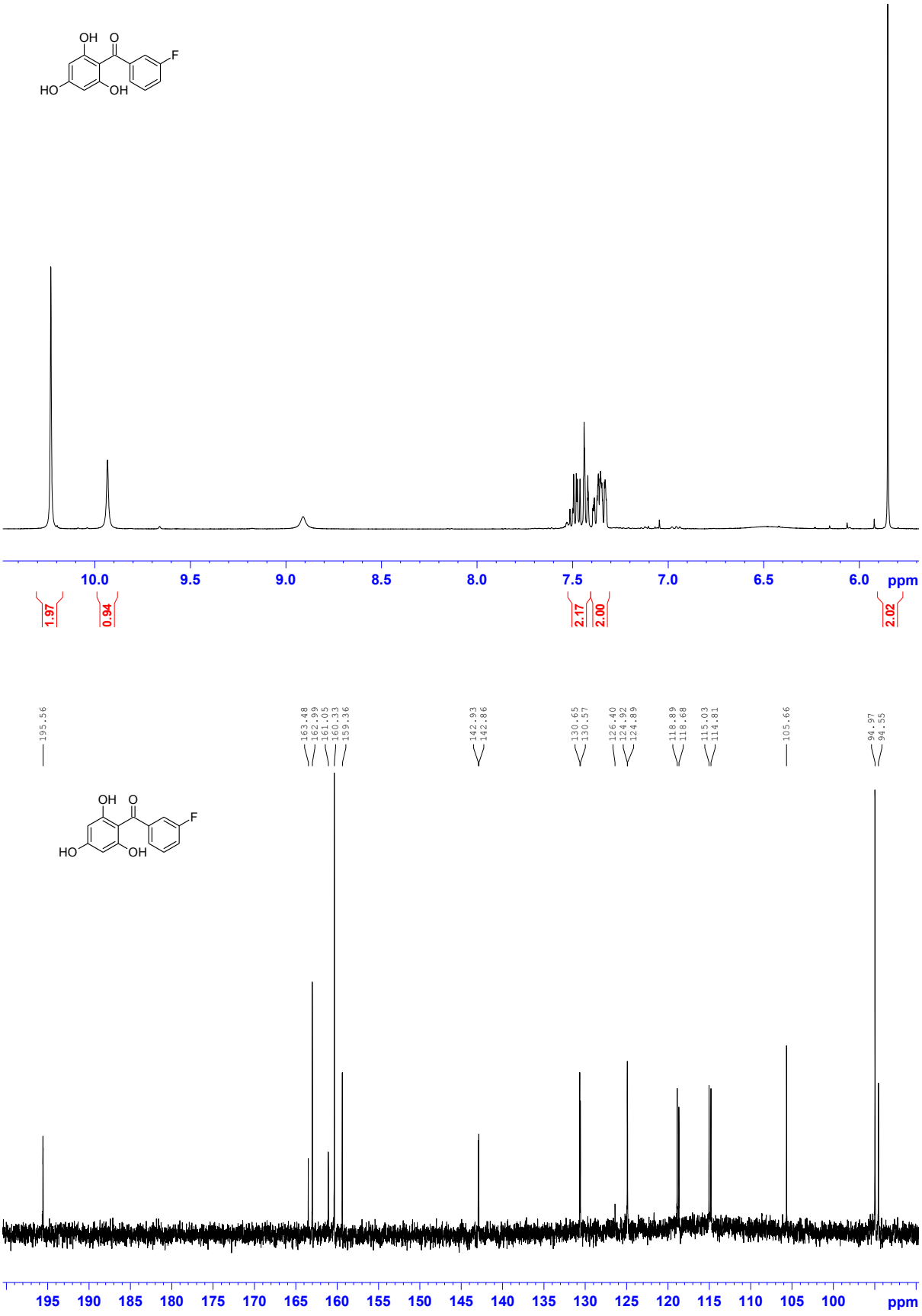

Plate 9. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)(2,4,6-trihydroxyphenyl)methanone (**3.63**).

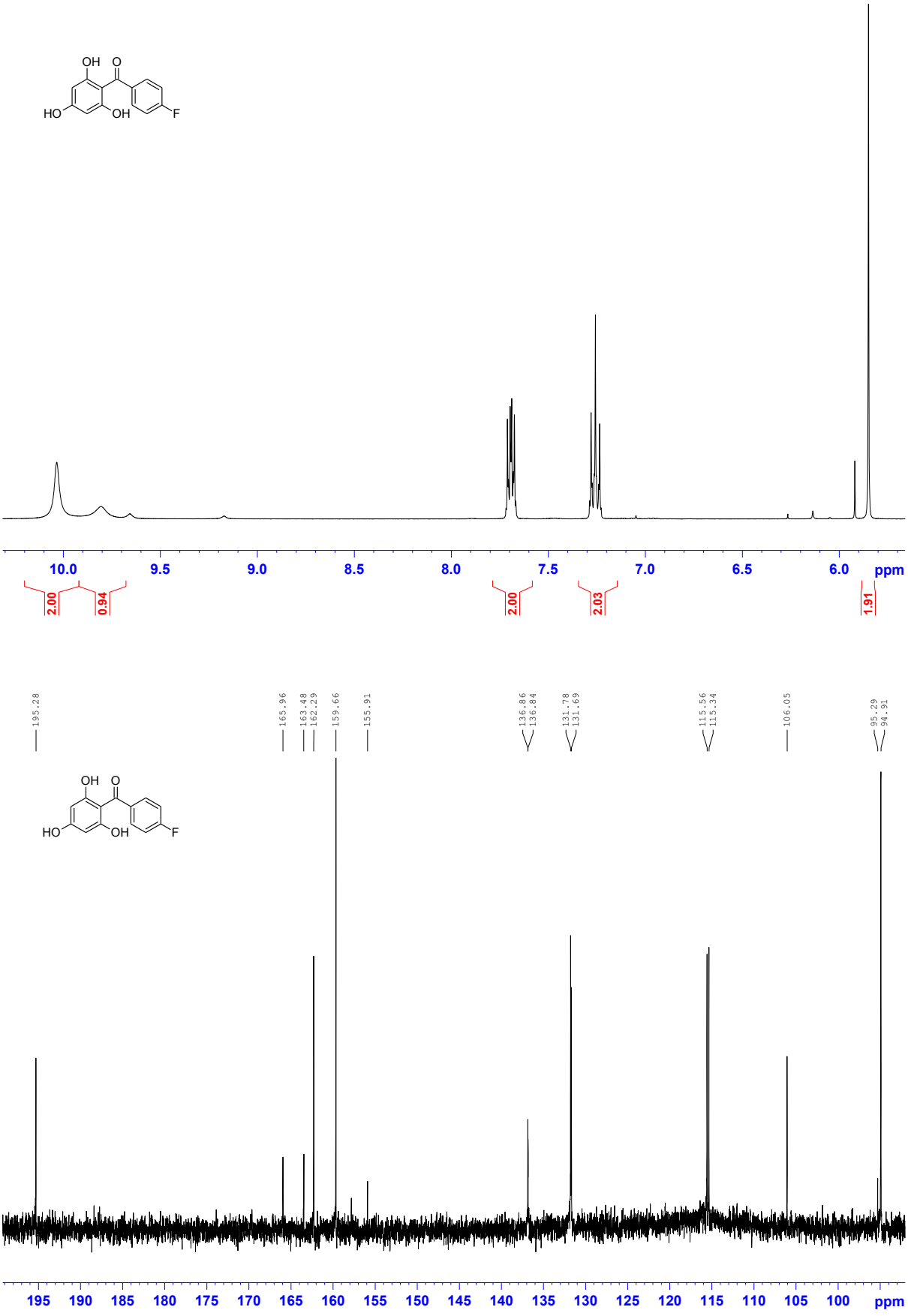

Plate 10. ^{1}H and ^{13}C NMR spectra of phenyl[2,4,6-trihydroxy-3-(3-methyl-2-butenyl) phenyl]methanone (**3.54**).

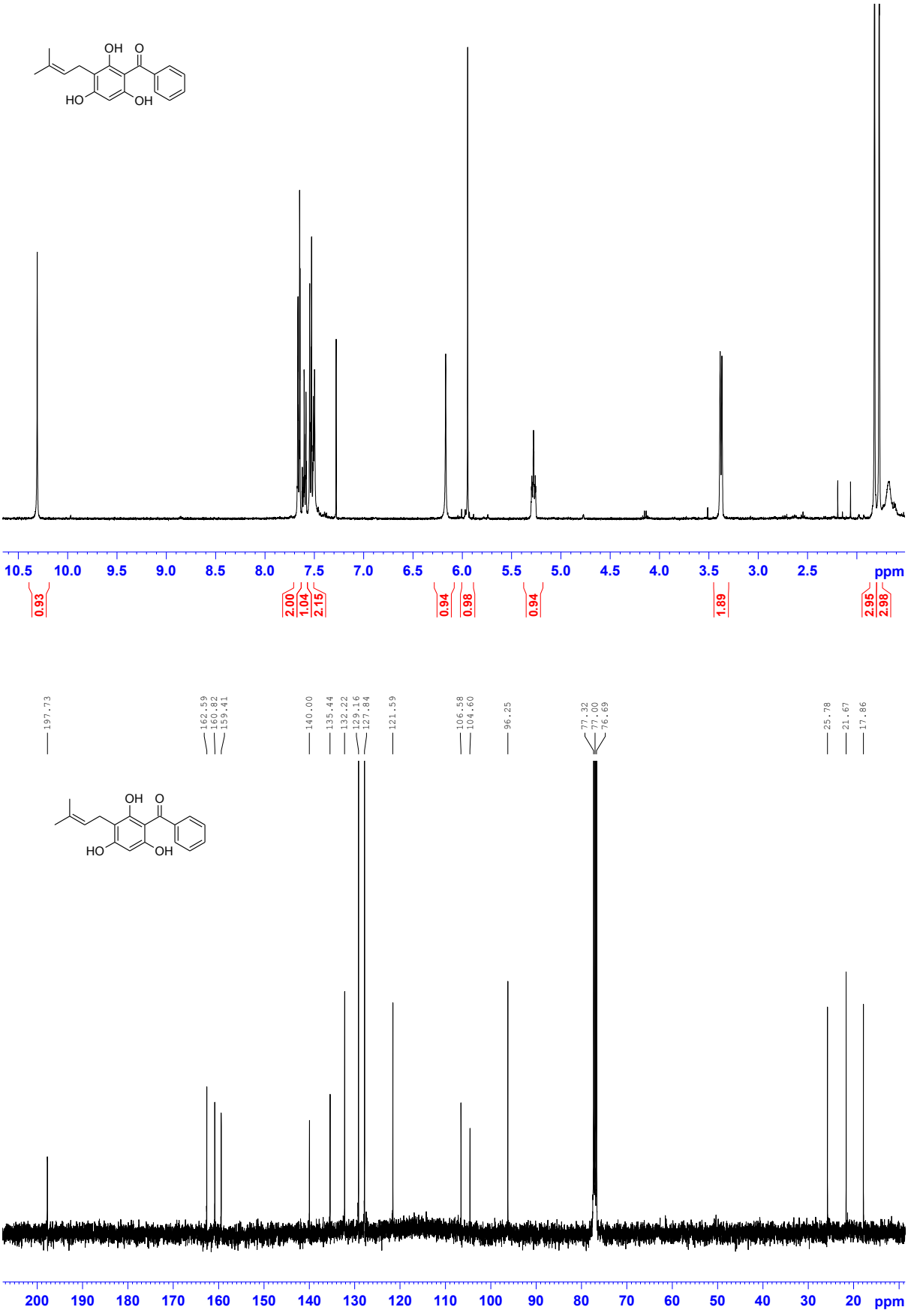

Plate 11. ^{1}H and ^{13}C NMR spectra of (3-fluorophenyl)[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (**3.65**).

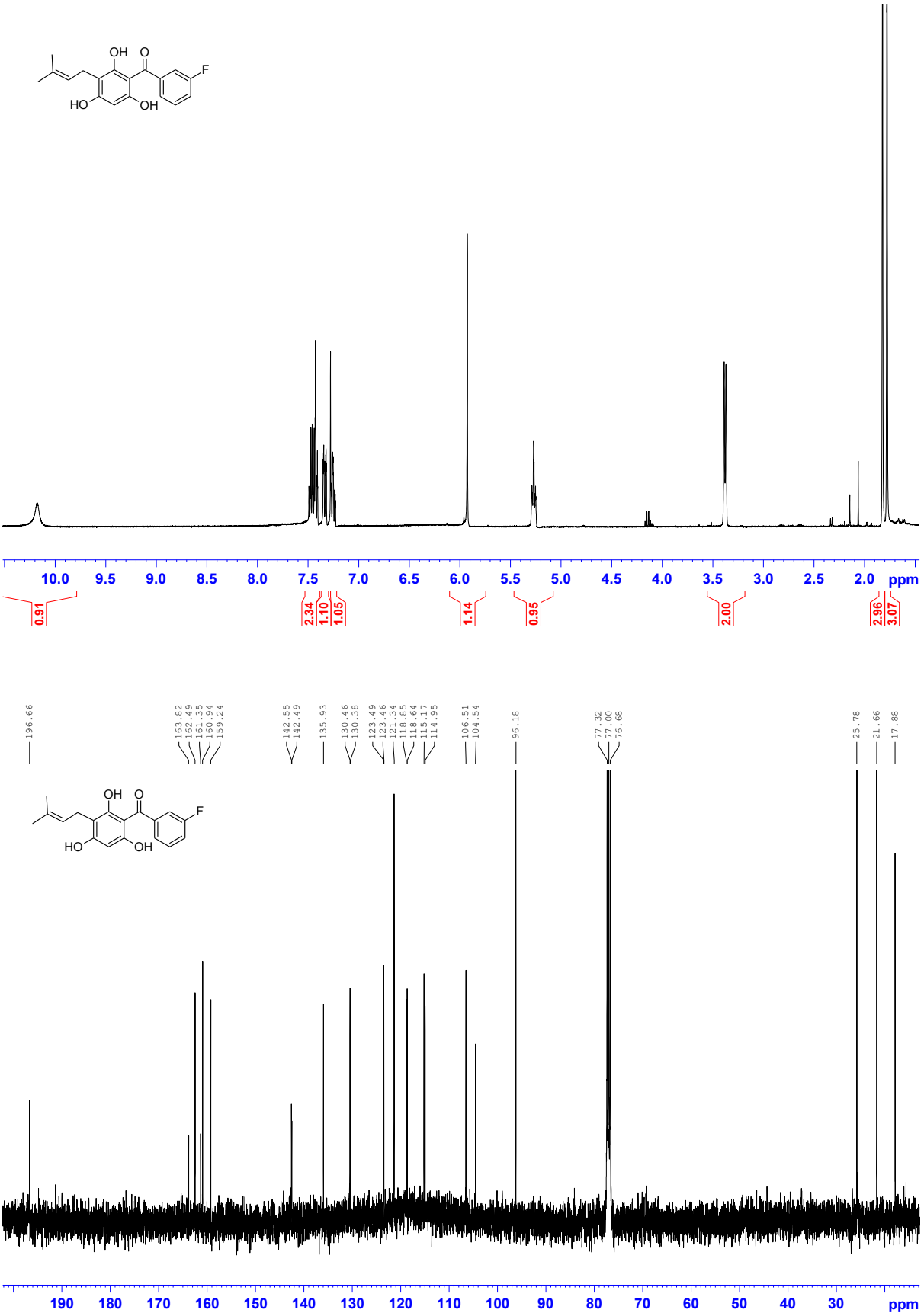

Plate 12. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)[2,4,6-trihydroxy-3-(3-methyl-2-butenyl)phenyl]methanone (**3.66**).

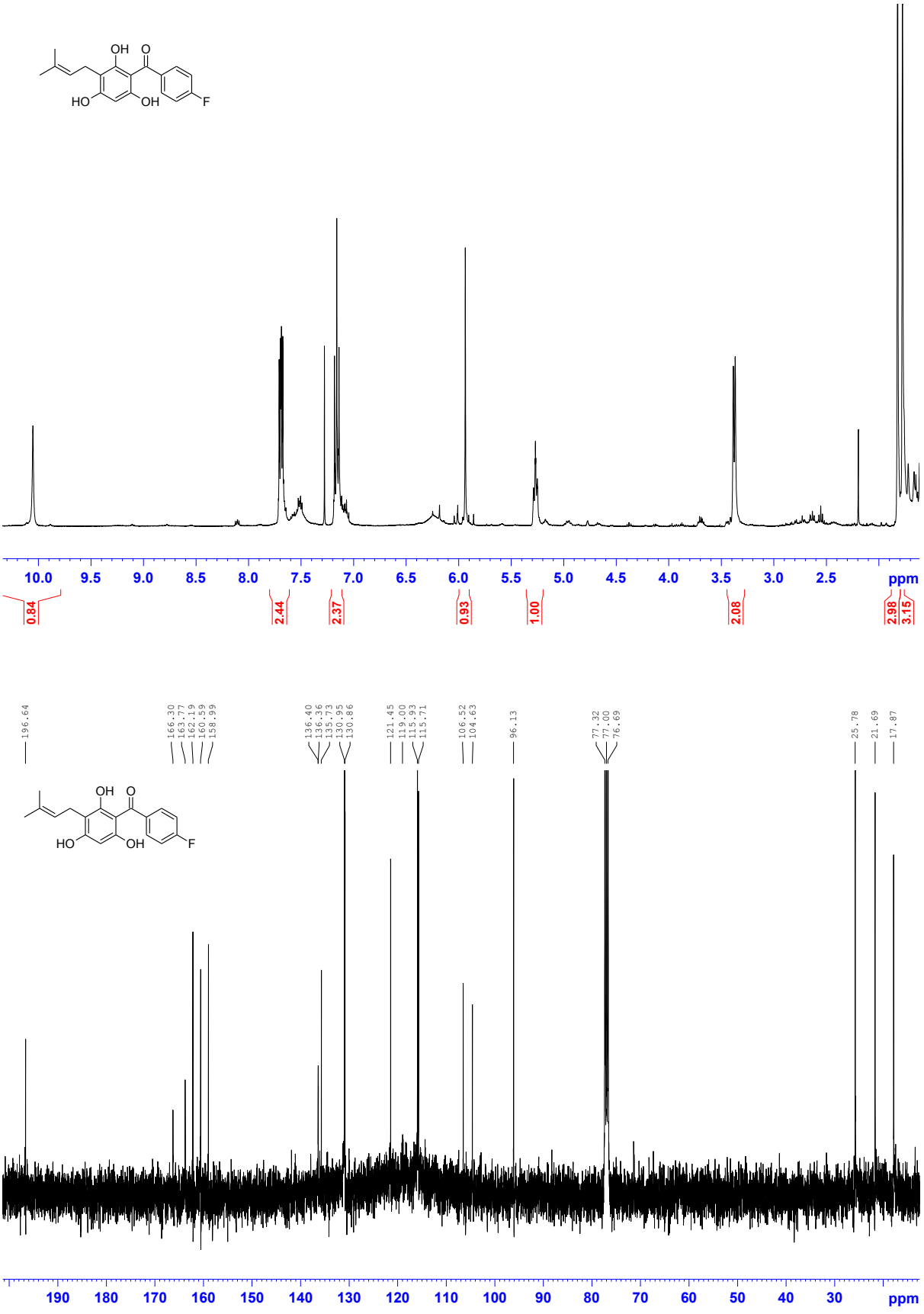

Plate 13. ^{1}H and ^{13}C NMR spectra of phenyl[2,4,6-trihydroxy-3,5-bis(3-methyl-2-butenyl)phenyl]methanone (**3.67**).

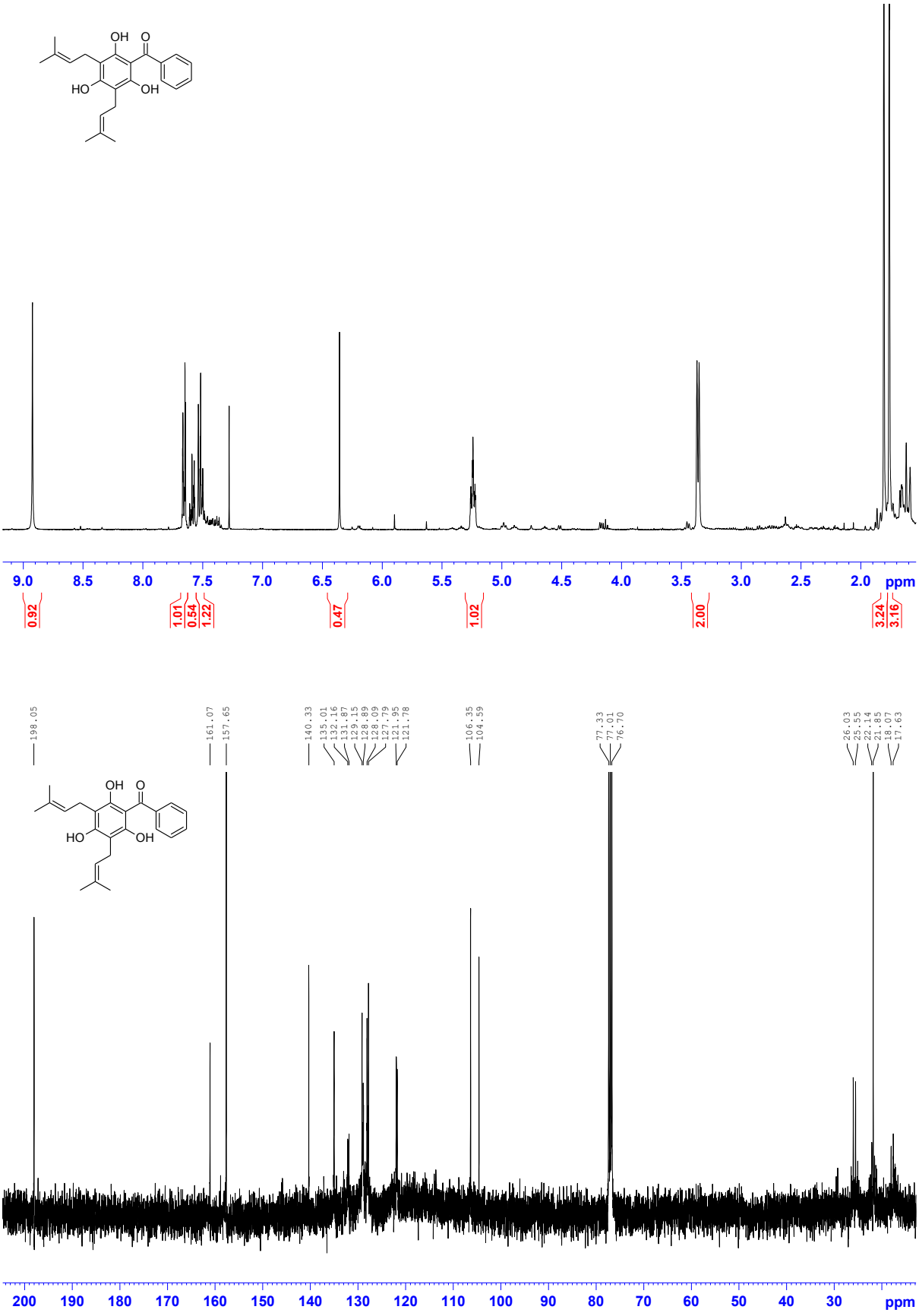

Plate 14. ^{1}H and ^{13}C NMR spectra of (3-fluorophenyl)[2,4,6-trihydroxy-3,5-bis(3-methyl-2-butenyl)phenyl]methanone (**3.68**).

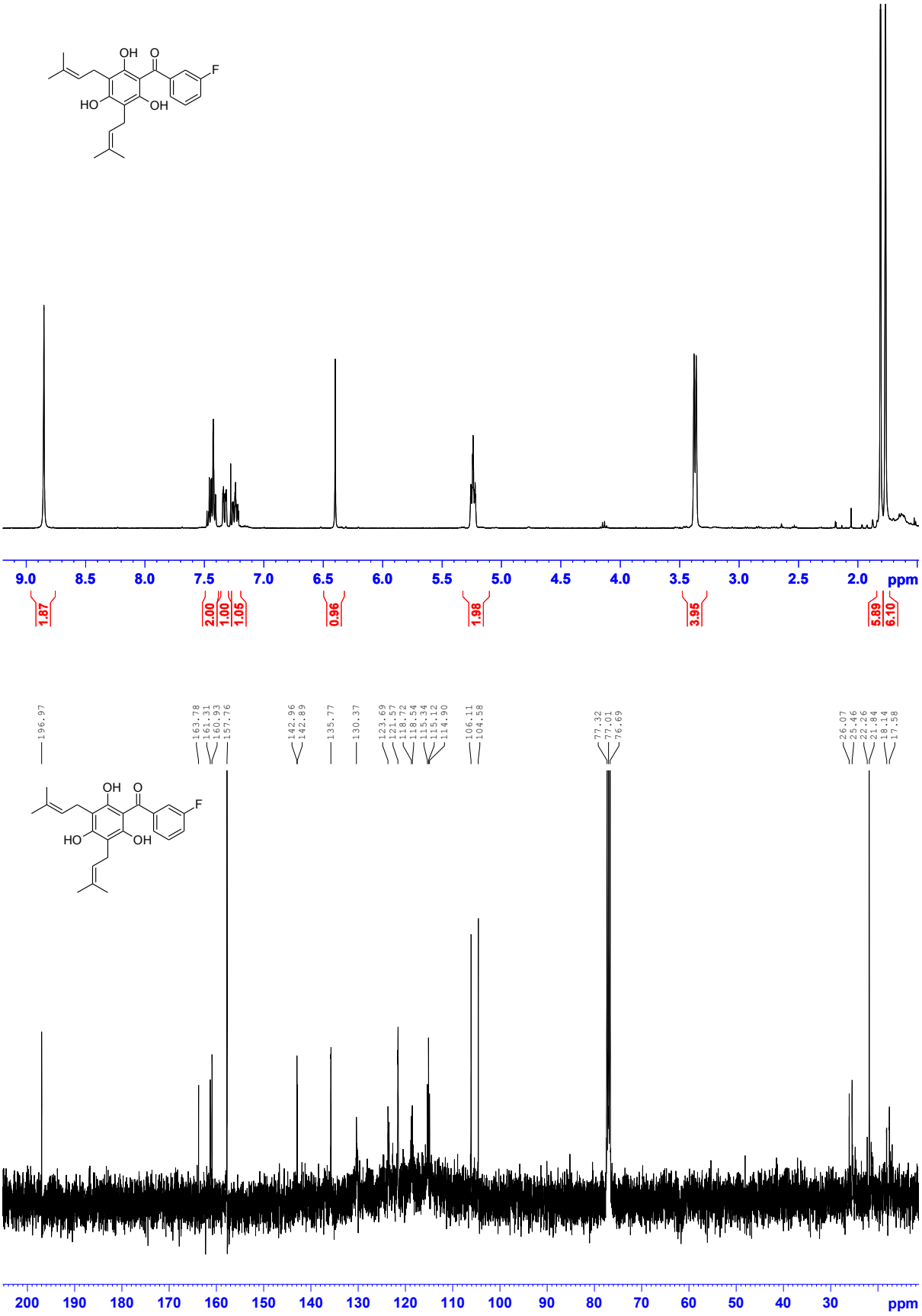

Plate 15. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)[2,4,6-trihydroxy-3,5-bis(3-methyl-2-butenyl)phenyl]methanone (**3.69**).

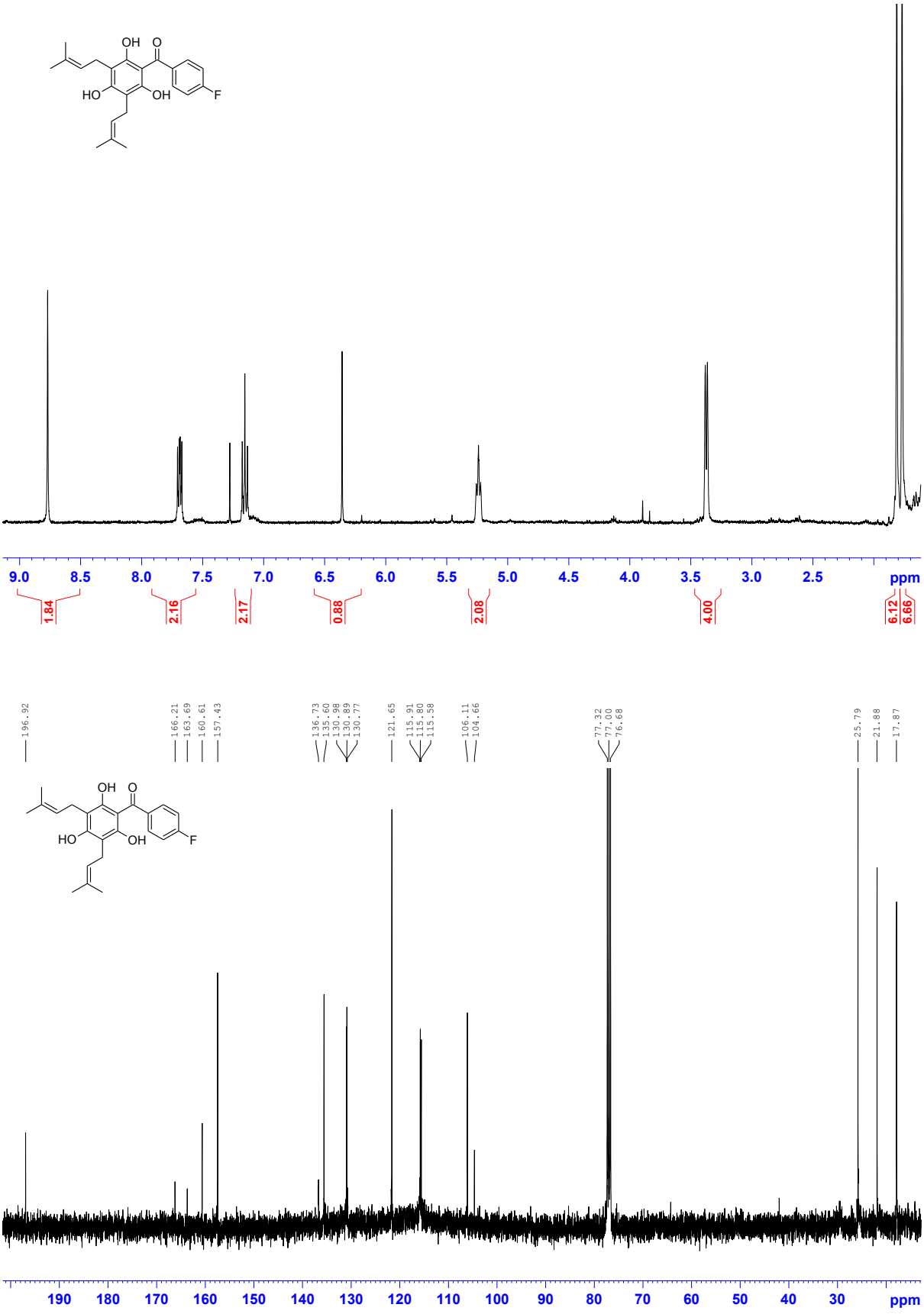

Plate 16. ^{1}H and ^{13}C NMR spectra of phenyl[3-(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]methanone (**3.8**).

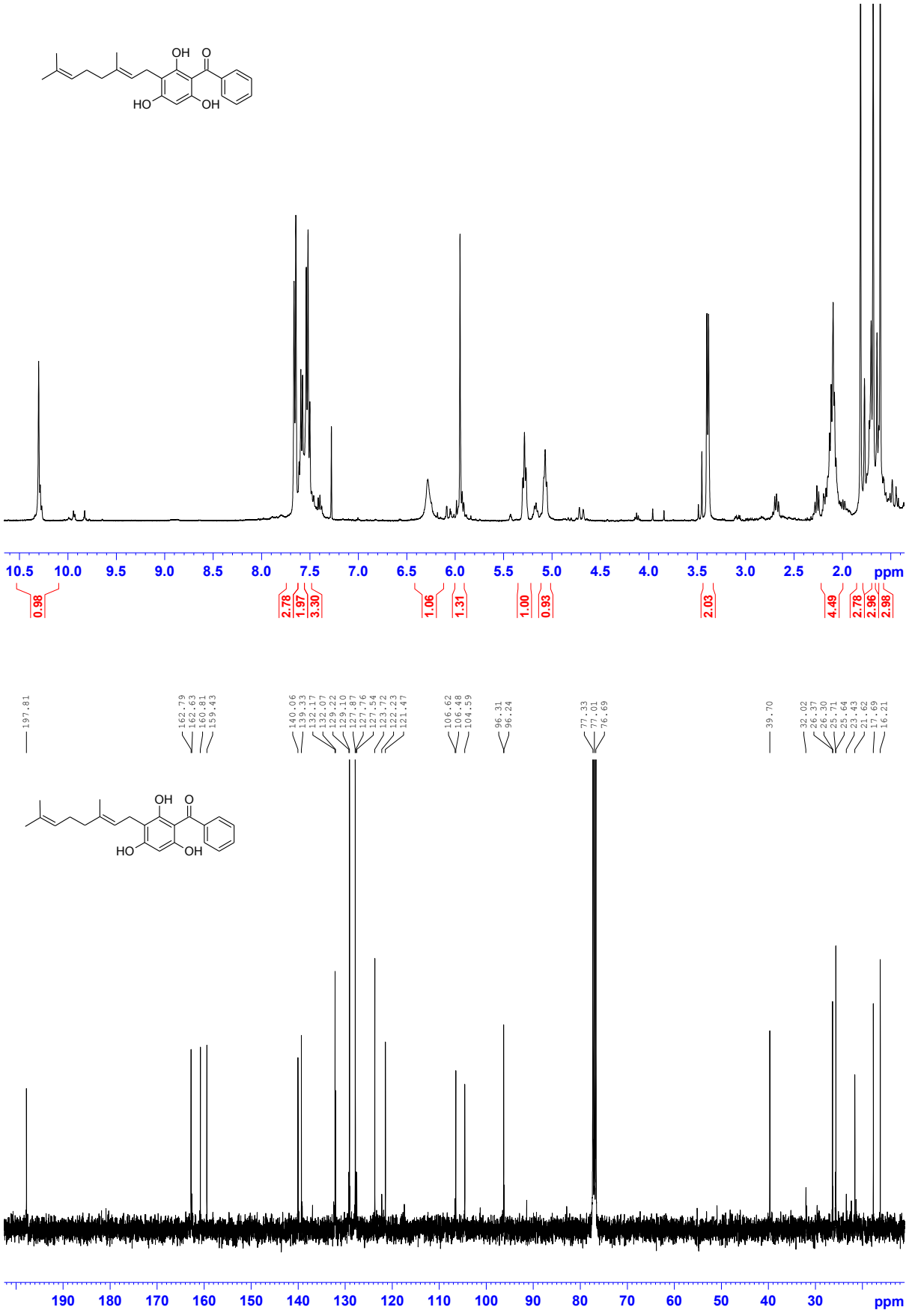

Plate 17. ^{1}H and ^{13}C NMR spectra of (3-fluorophenyl)[3-(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]methanone (**3.71**).

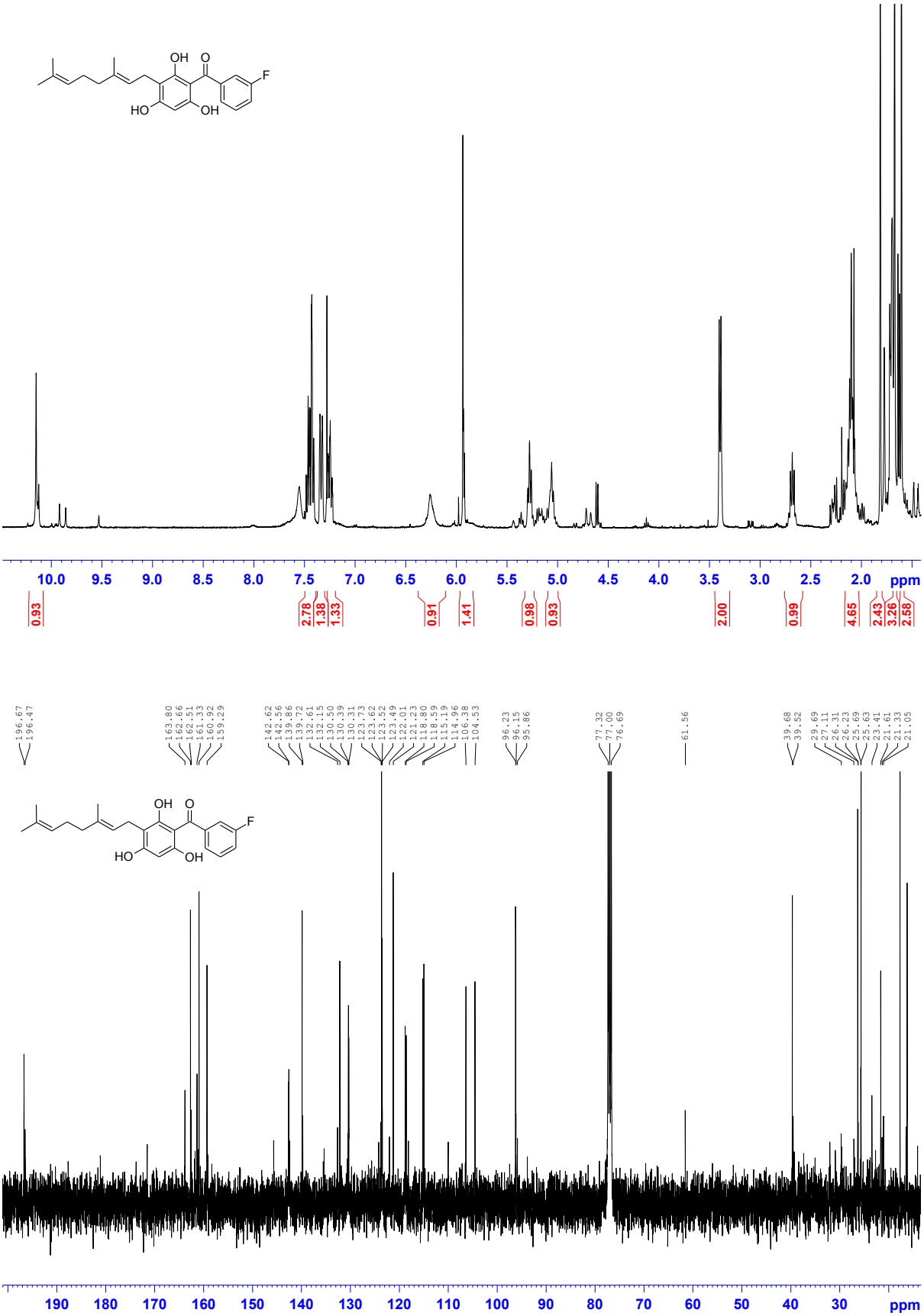

Plate 18. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)[3-(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]methanone (**3.72**).

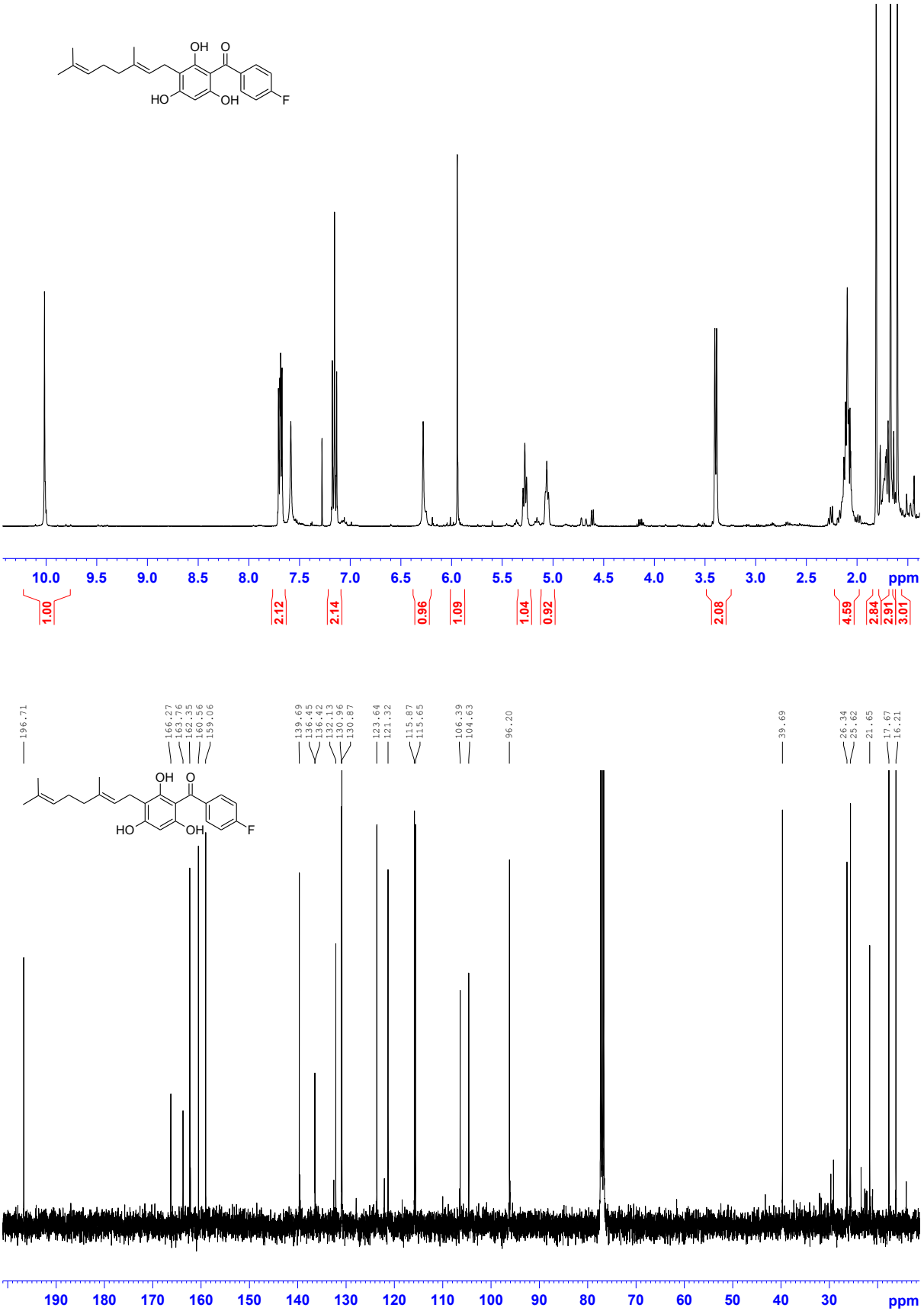

Plate 19. ^{1}H and ^{13}C NMR spectra of (3-fluorophenyl)[3,5-bis(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]methanone (**3.73**).

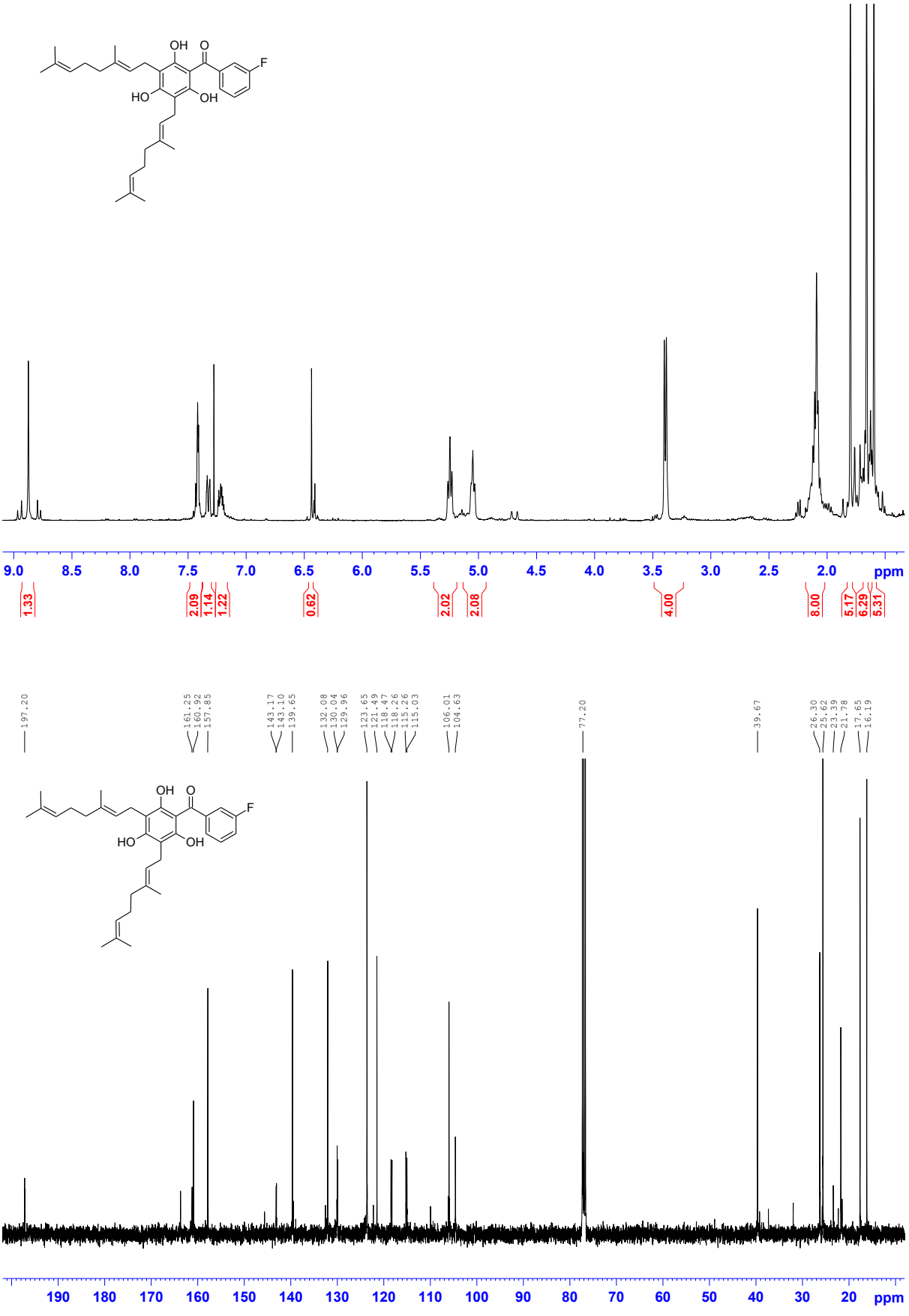

Plate 20. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)[3,5-bis(3,7-dimethyl-2,6-octadienyl)-2,4,6-trihydroxyphenyl]methanone (**3.74**).

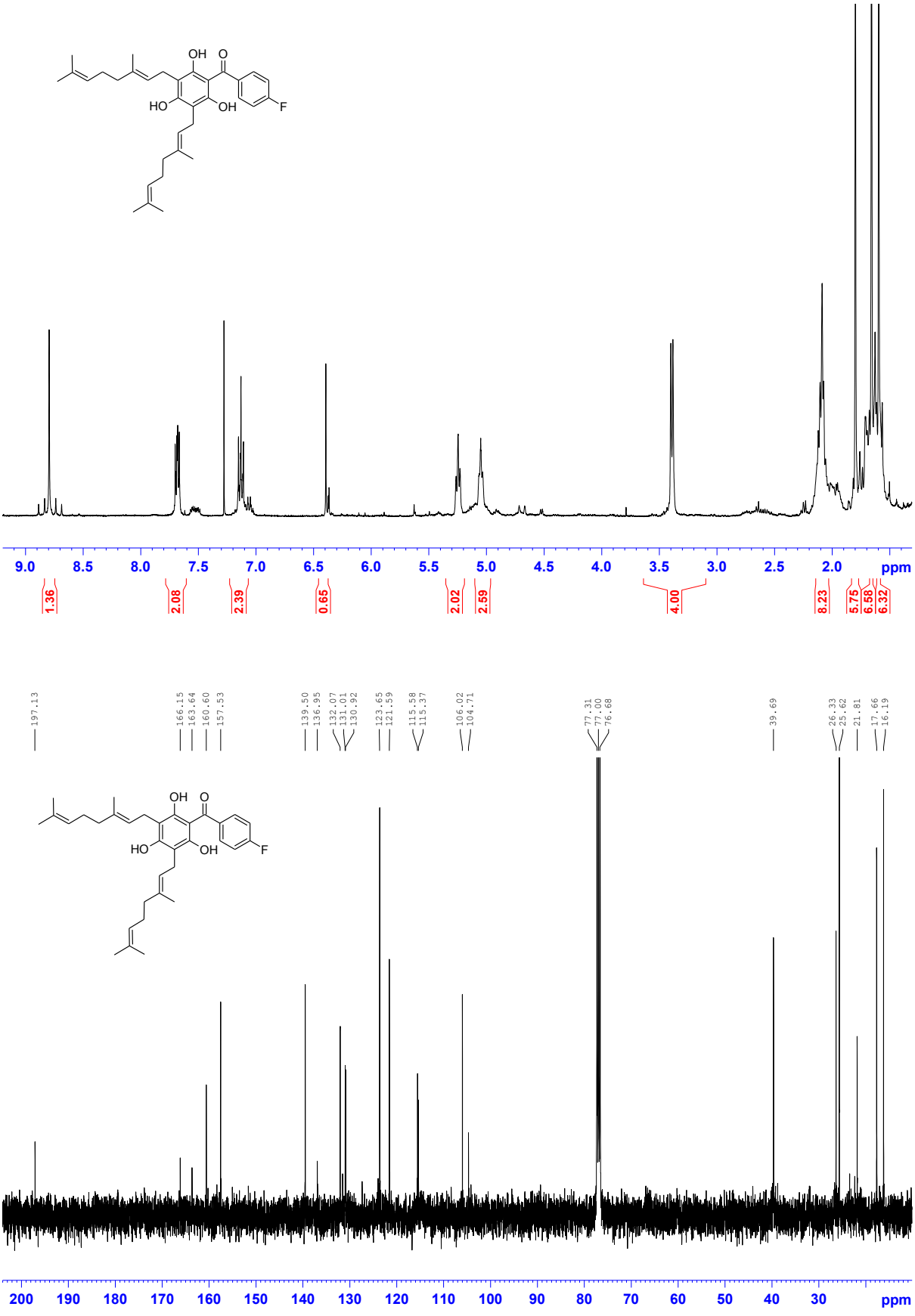

Plate 21. ^{1}H and ^{13}C NMR spectra of (3-fluorophenyl)[2-hydroxy-3-(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (**3.75**).

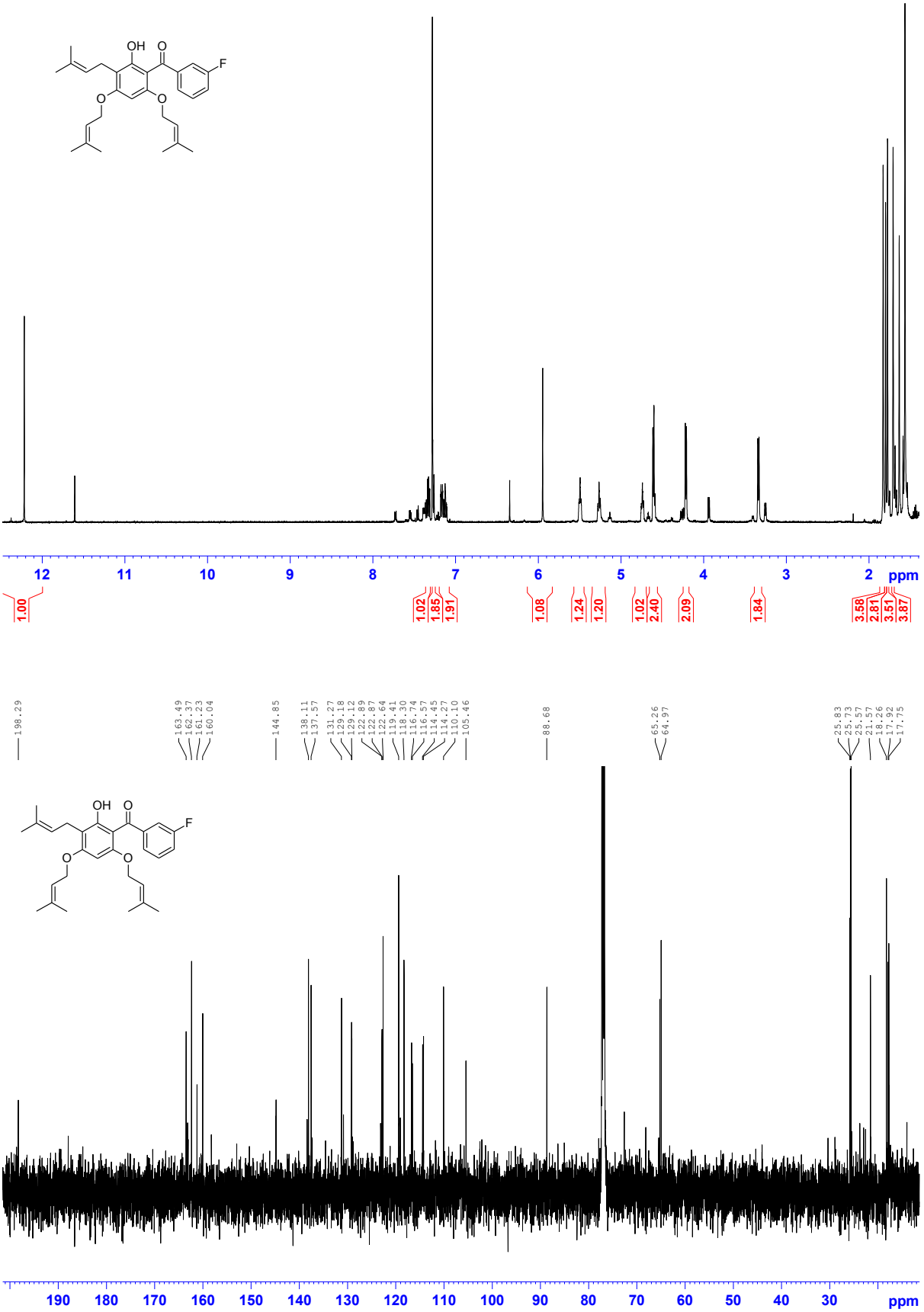

Plate 22. ^{1}H and ^{13}C NMR spectra of (3-fluorophenyl)[2-hydroxy-3,5-bis(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (**3.76**).

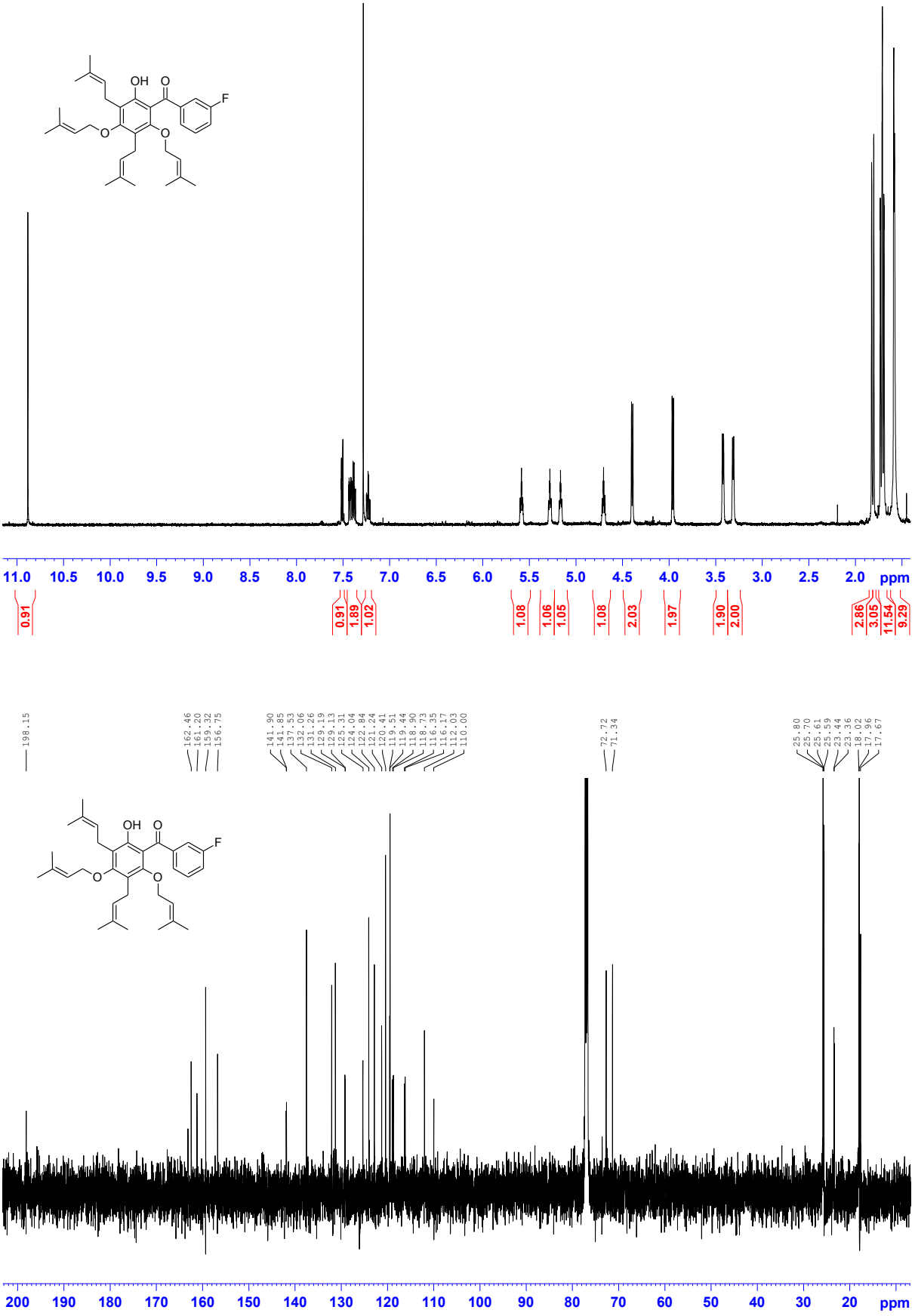

Plate 23. ^{1}H and ^{13}C NMR spectra of (3-fluorophenyl)[2-hydroxy-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (**3.81**).

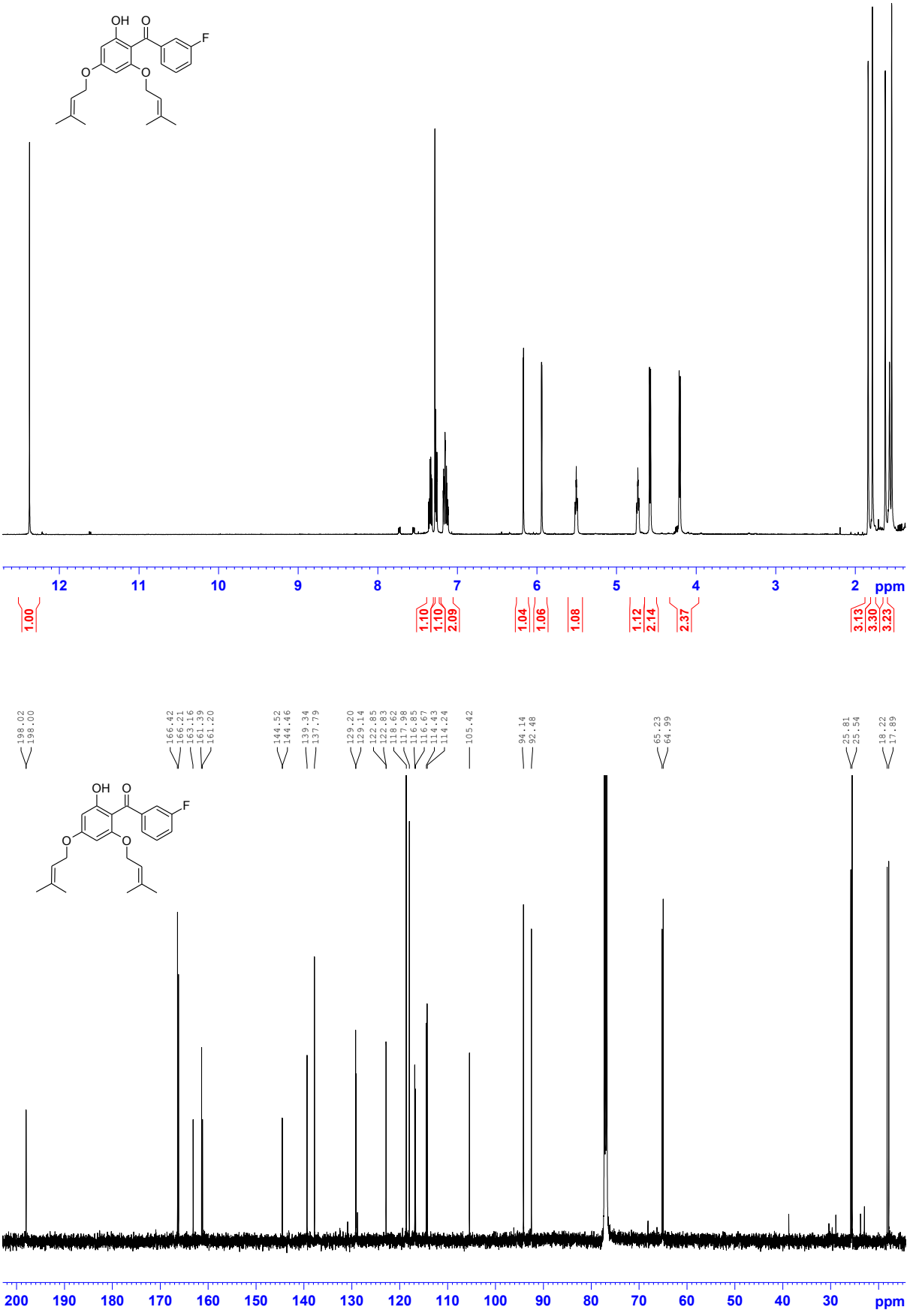

Plate 24. ^{1}H and ^{13}C NMR spectra of (3-fluorophenyl)[2,4,6-tris(3-methylbut-2-enyloxy)phenyl]methanone (**3.82**).

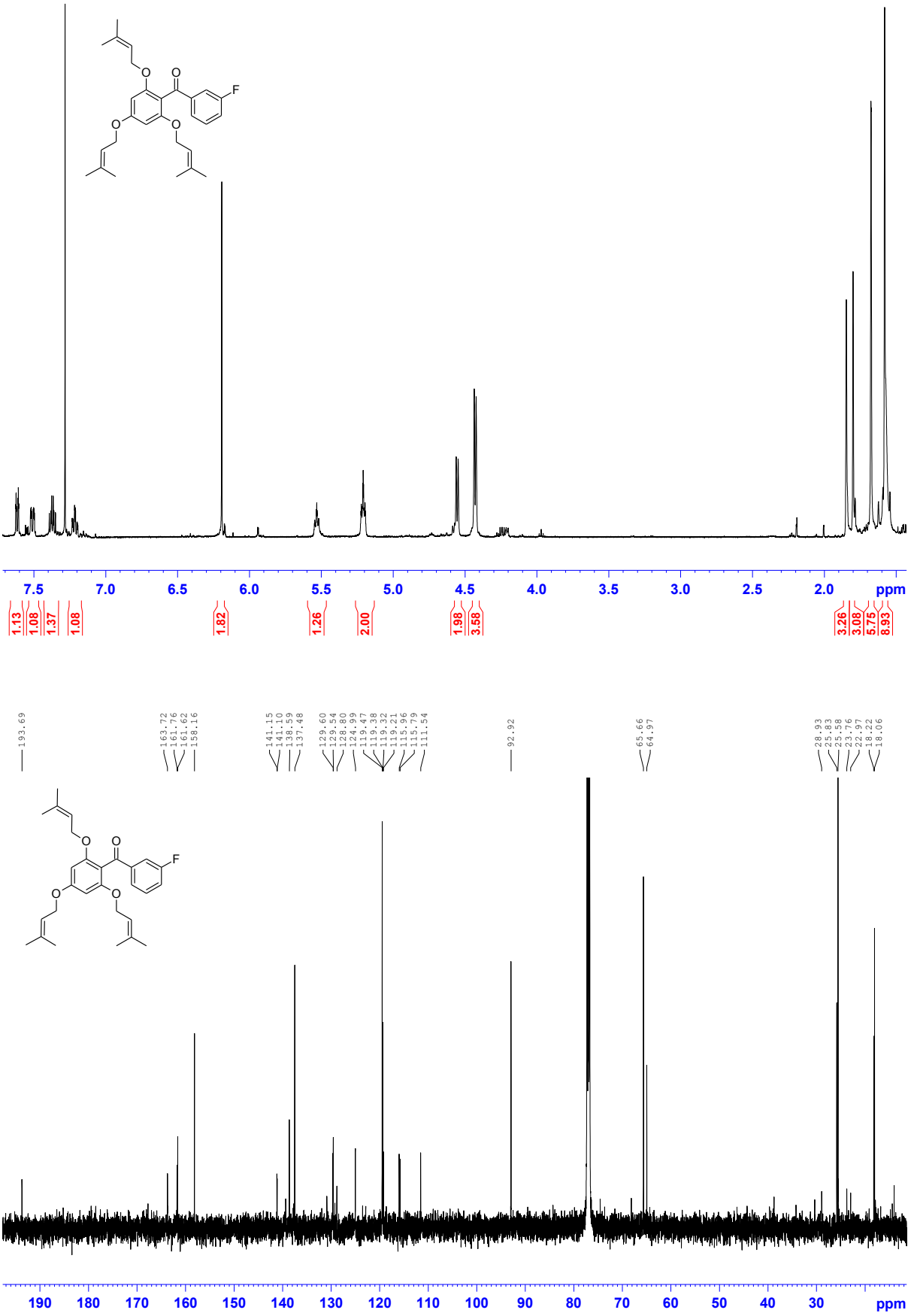

Plate 25. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)[2-hydroxy-3-(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (**3.77**).

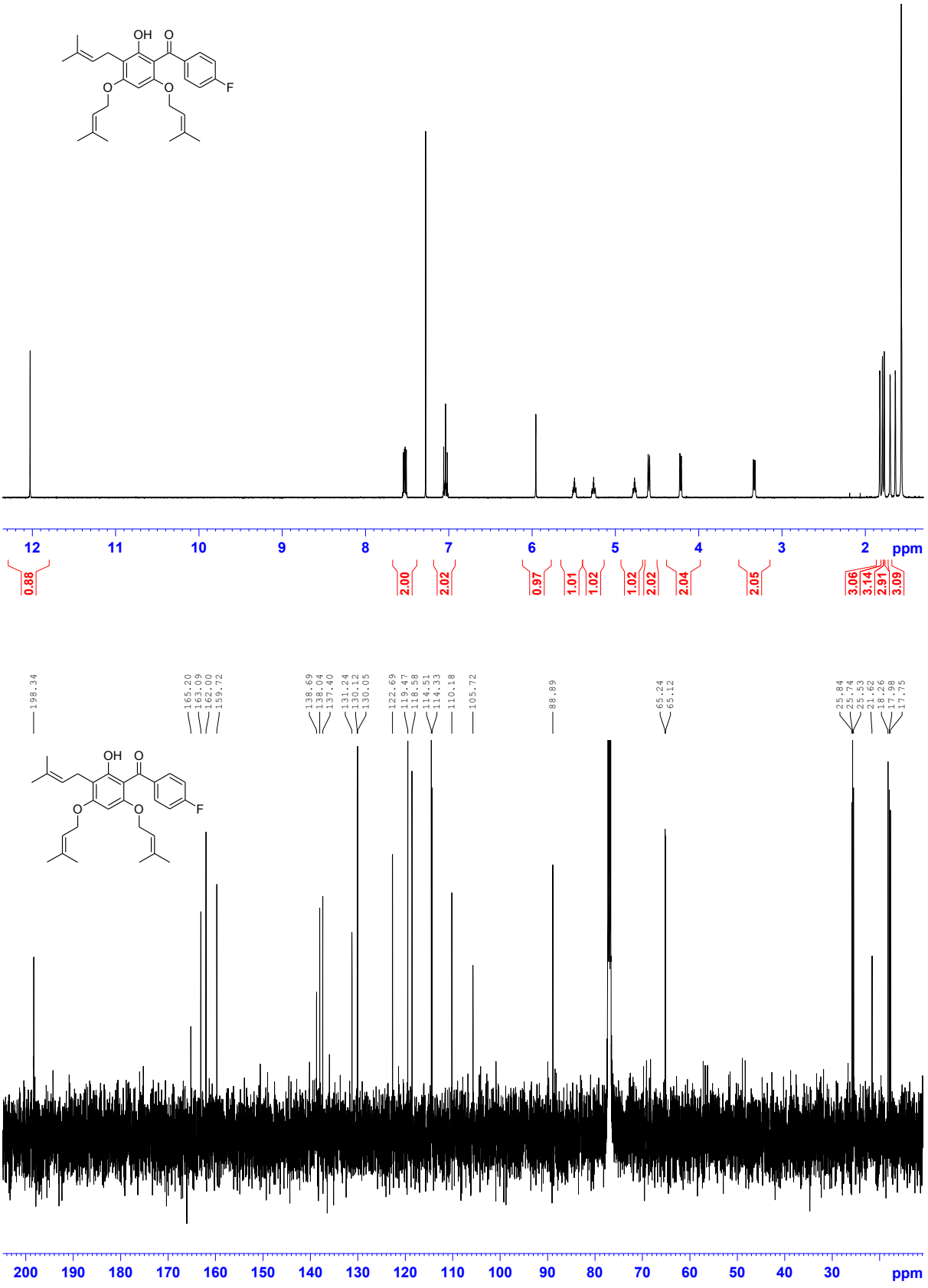

Plate 26. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)[2-hydroxy-3,5-bis(3-methylbut-2-enyl)-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (**3.78**).

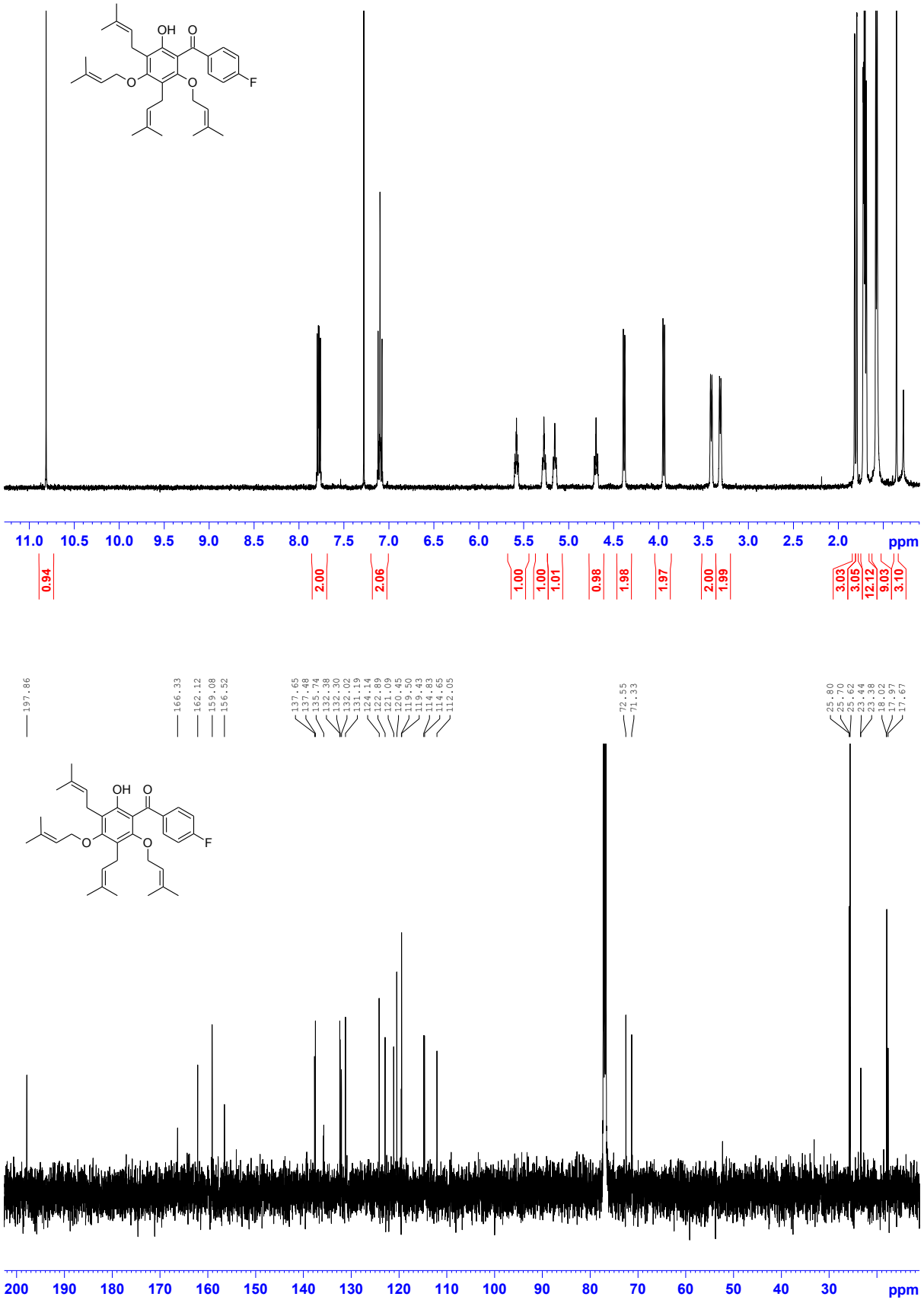

Plate 27. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)[2-hydroxy-4,6-bis(3-methylbut-2-enyloxy)phenyl]methanone (**3.83**).

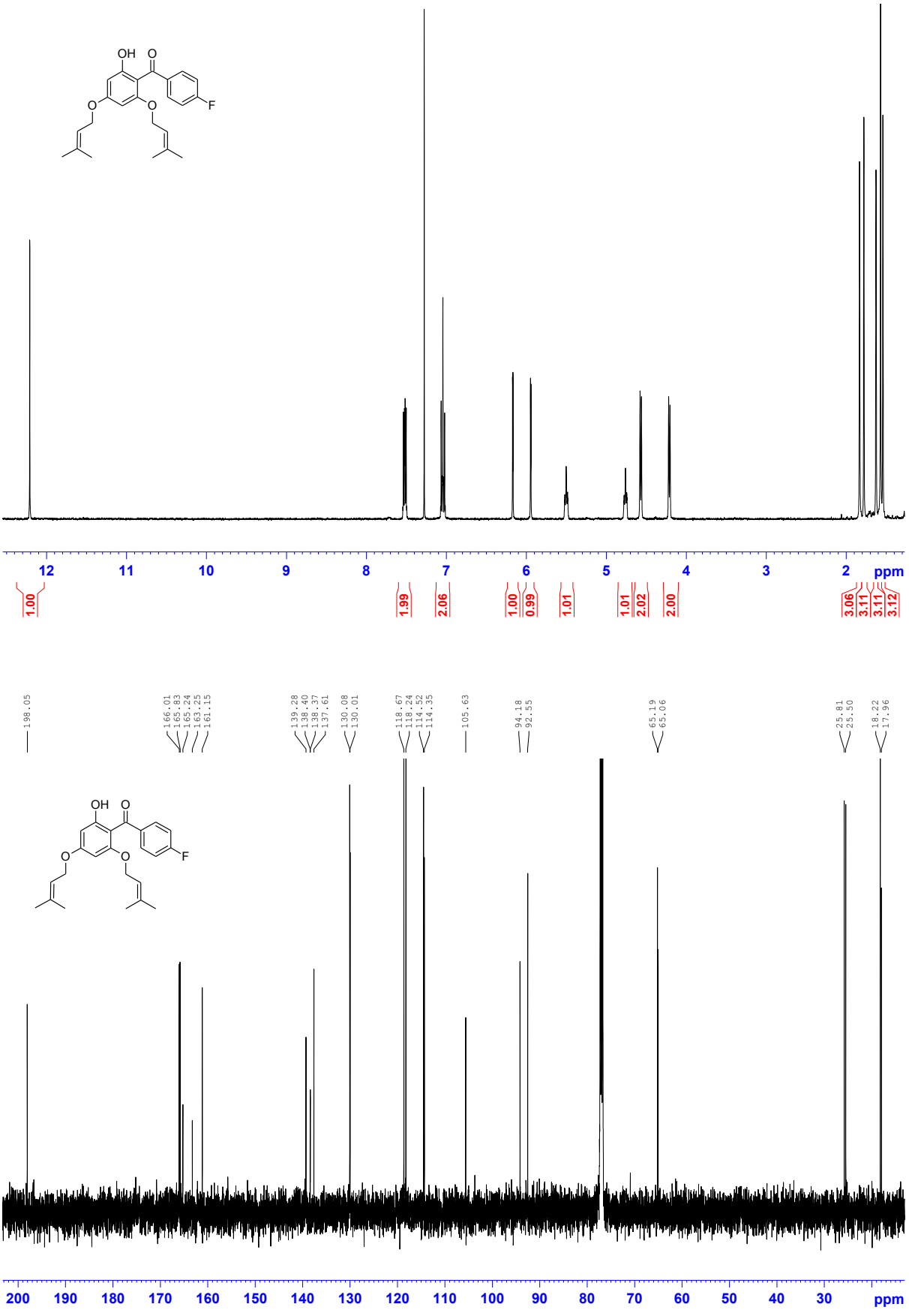

Plate 28. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)[6-hydroxy-3-(3-methylbut-2-enyl)-2,4-bis(3-methylbut-2-enyloxy)phenyl]methanone (**3.84**).

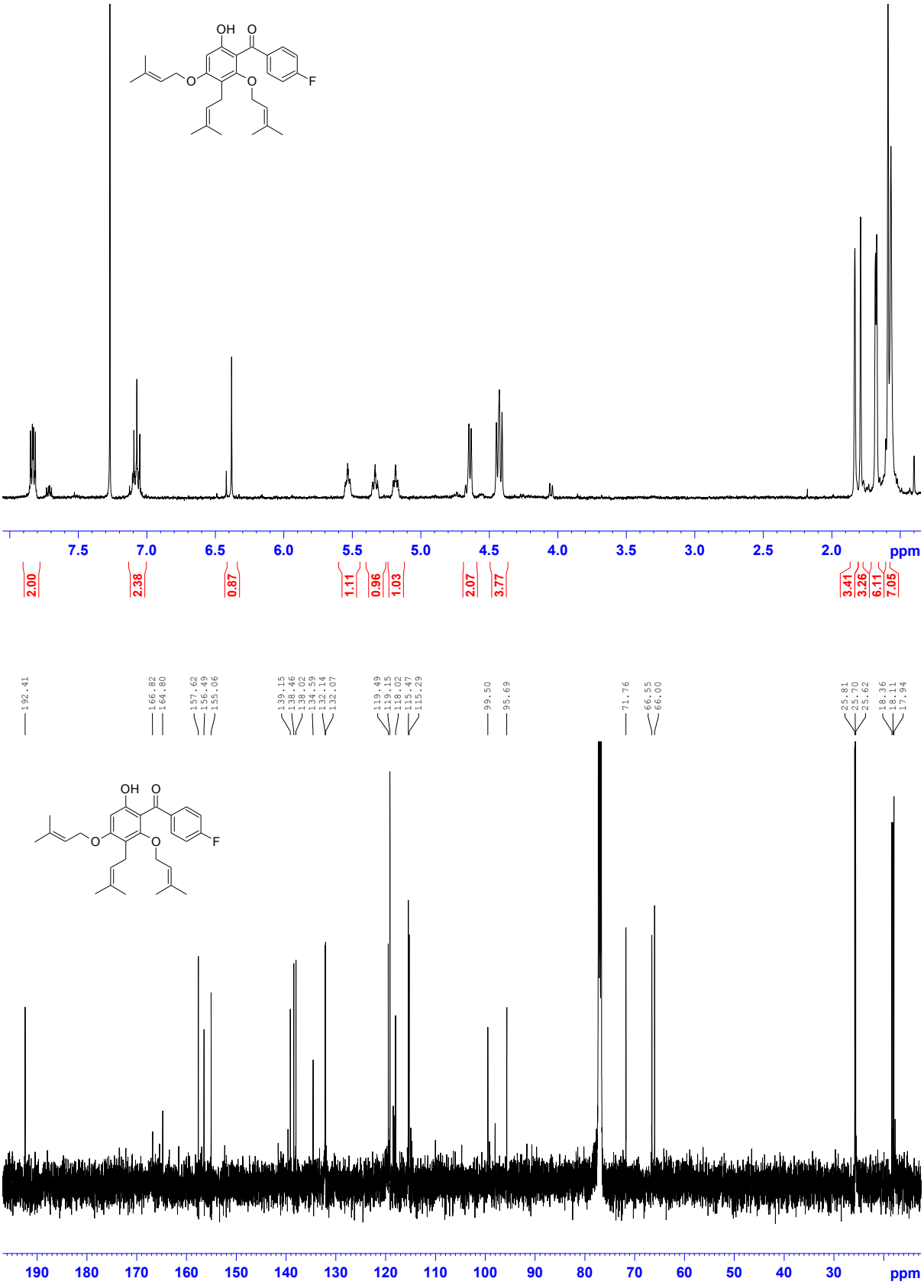

Plate 29. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)[2-hydroxy-3-(3,7-dimethylocta-2,6-dienyl)-4,6-bis(3,7-dimethylocta-2,6-dienyloxy)phenyl]methanone (**3.79**).

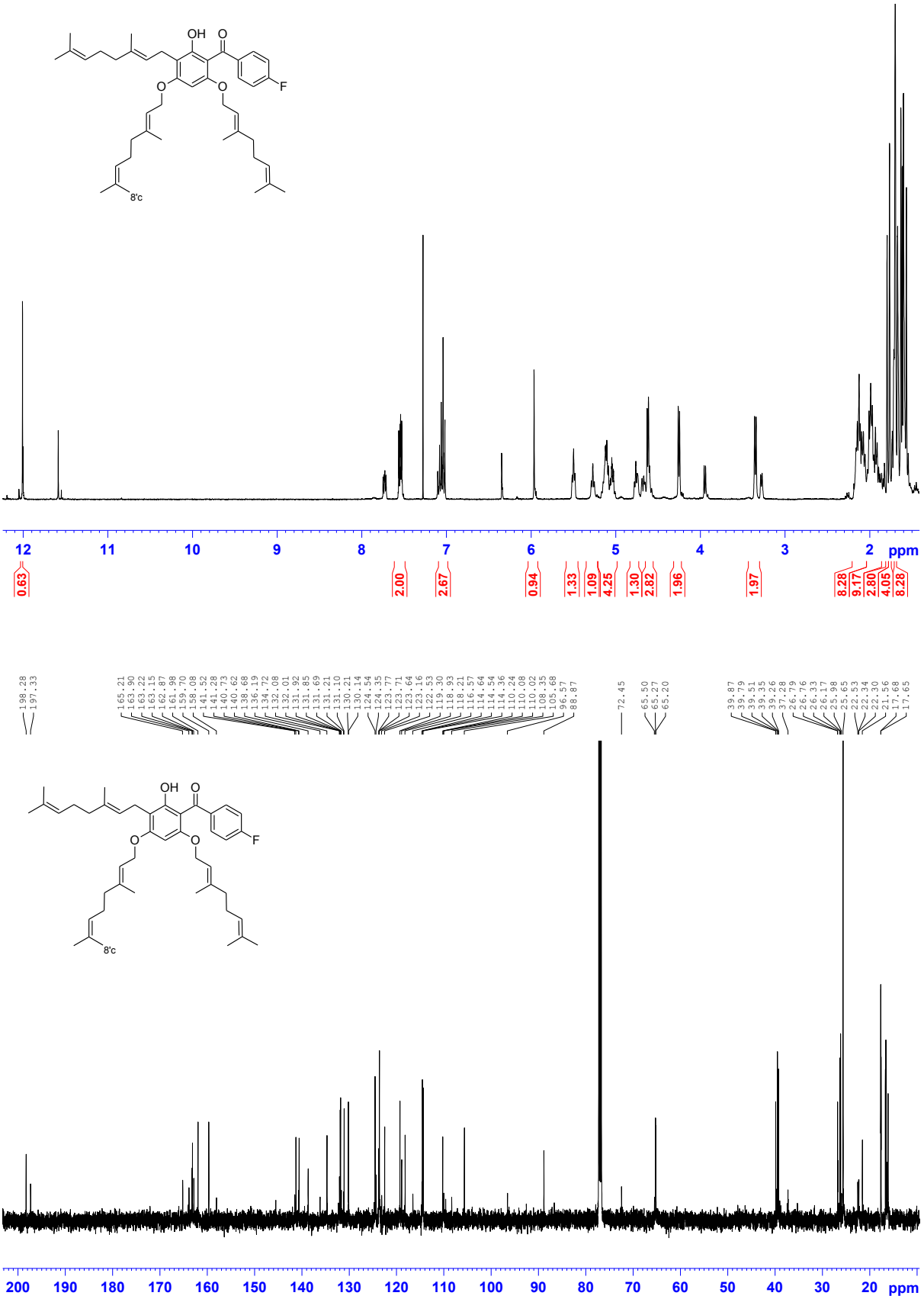

Plate 30. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)[2-hydroxy-3,5-bis(3,7-dimethylocta-2,6-dienyl)-4,6-bis(3,7-dimethylocta-2,6-dienyloxy)phenyl]methanone (**3.80**).

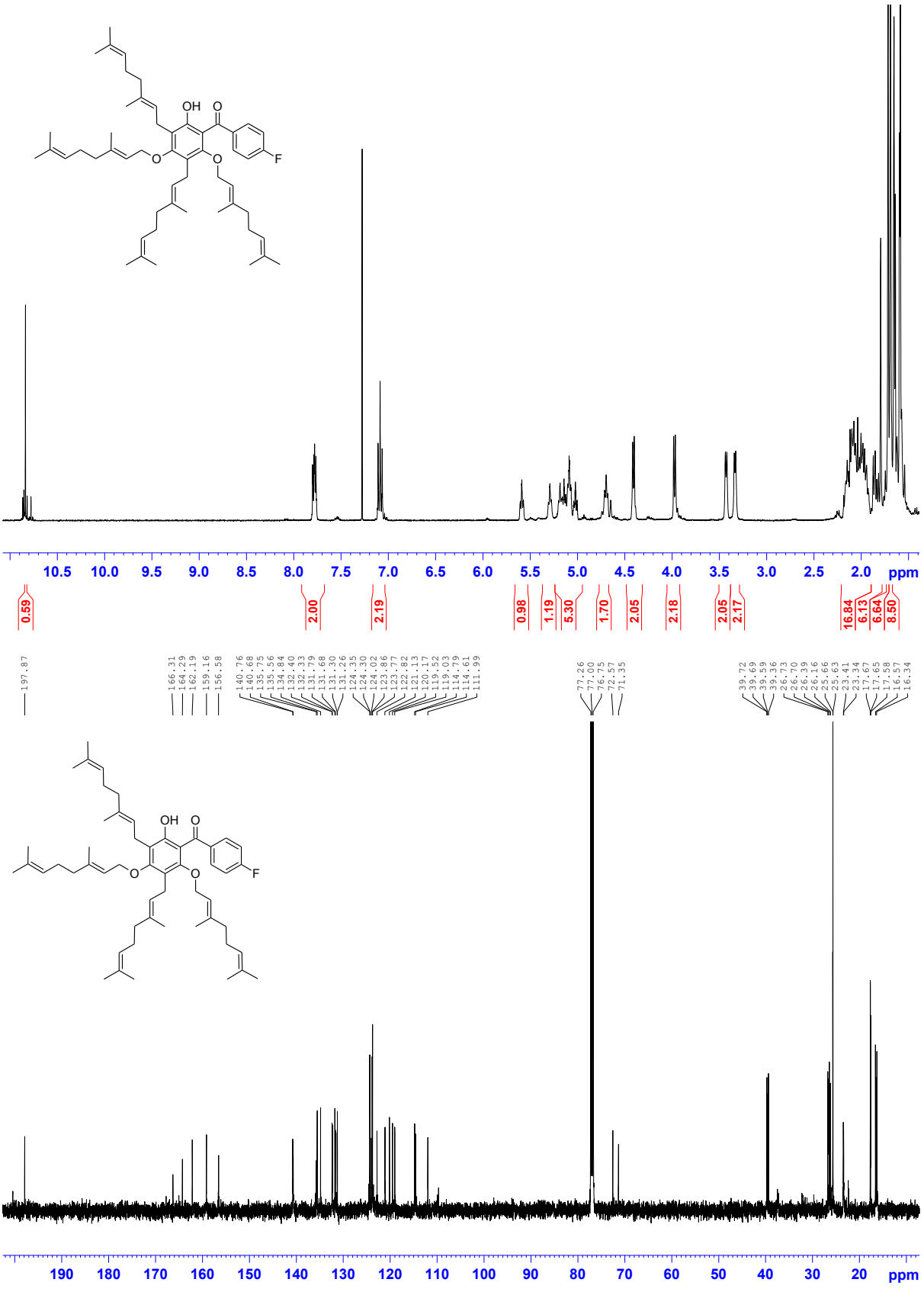

Plate 31. ^{1}H NMR spectra of (4-fluorophenyl)[2-hydroxy-4,6-bis(3,7-dimethylocta-2,6-dienyloxy)phenyl]methanone (**3.85**).

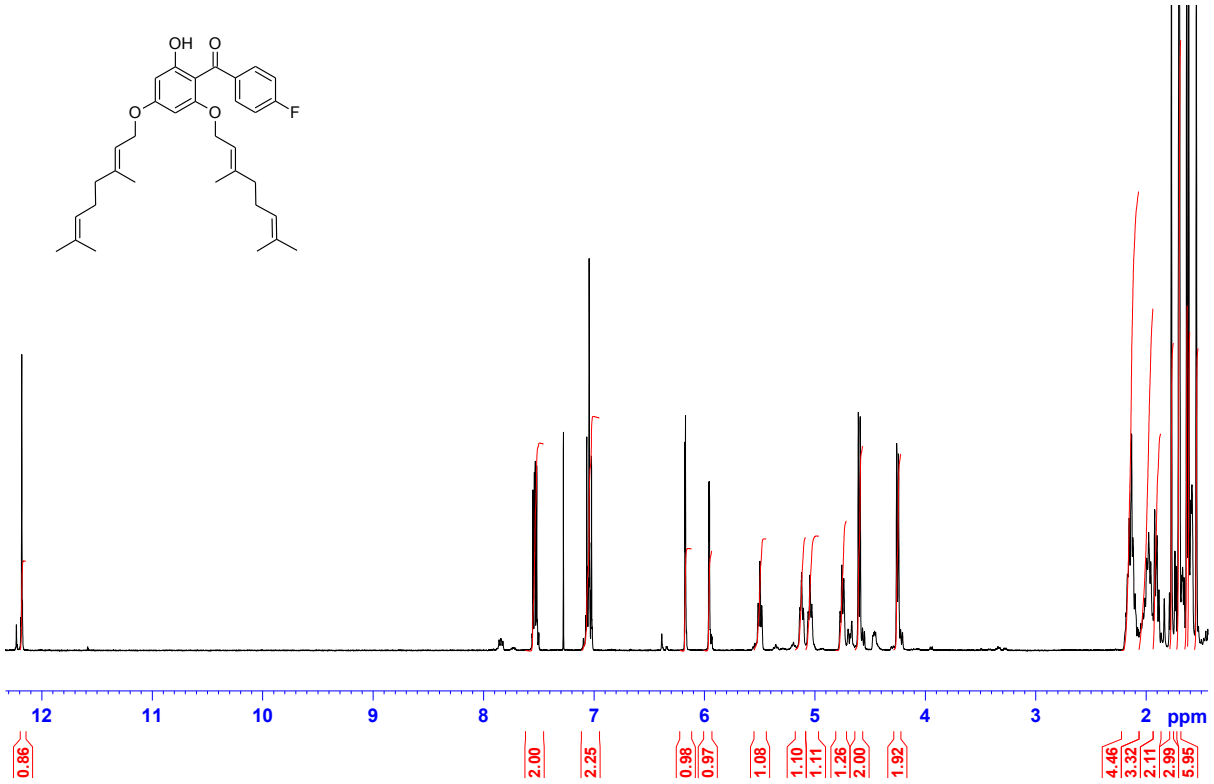

Plate 32. ^{1}H and ^{13}C NMR spectra of (4-fluorophenyl)[2,4,6-tris(3,7-dimethylocta-2,6-dienyloxy)phenyl]methanone (**3.86**).

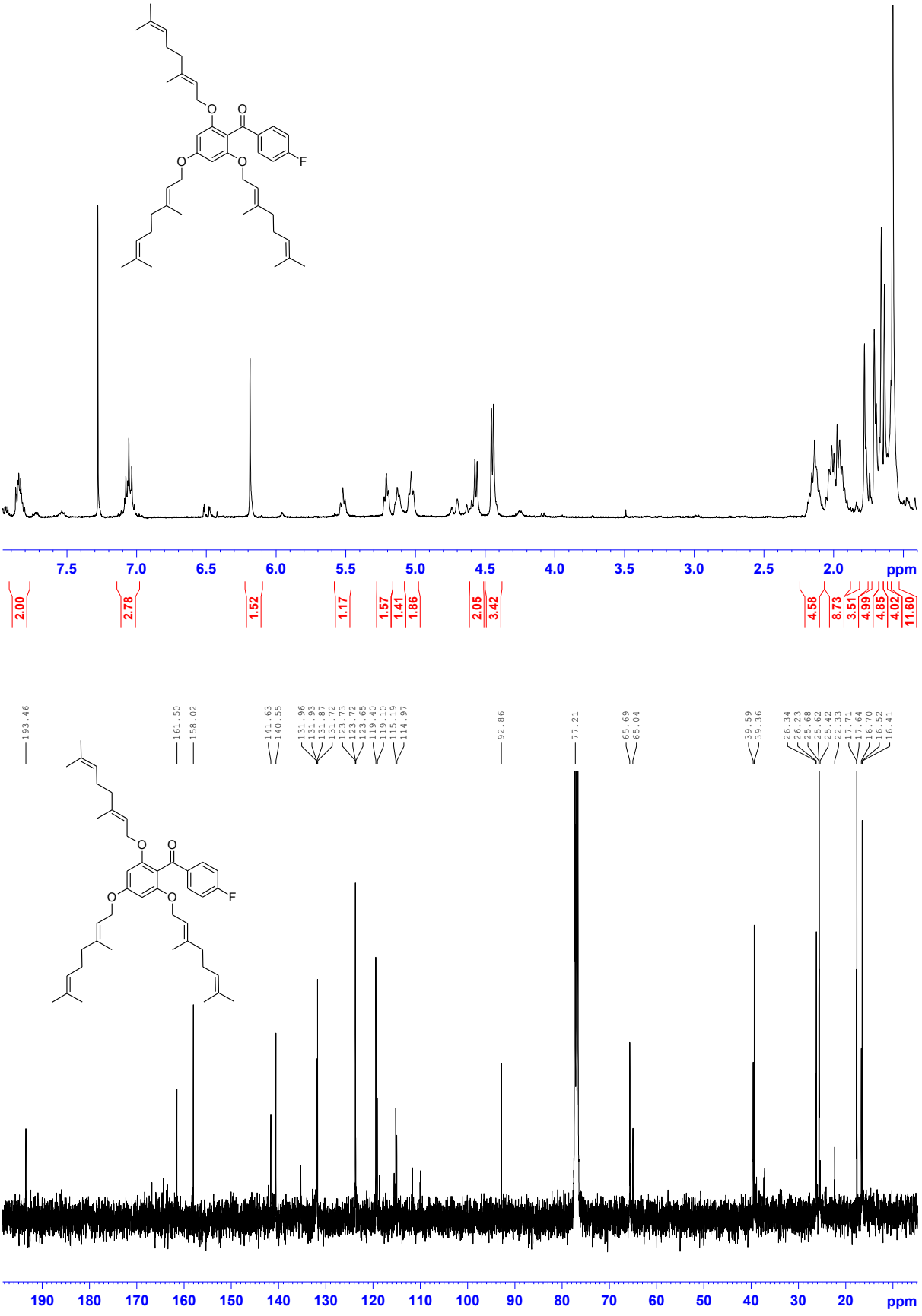

Plate 33. ^{1}H and ^{13}C NMR spectra of (2-fluorophenyl)[2,4-dihydroxy-6-(3-methylbut-2-enyloxy)phenyl]methanone (**3.87**).

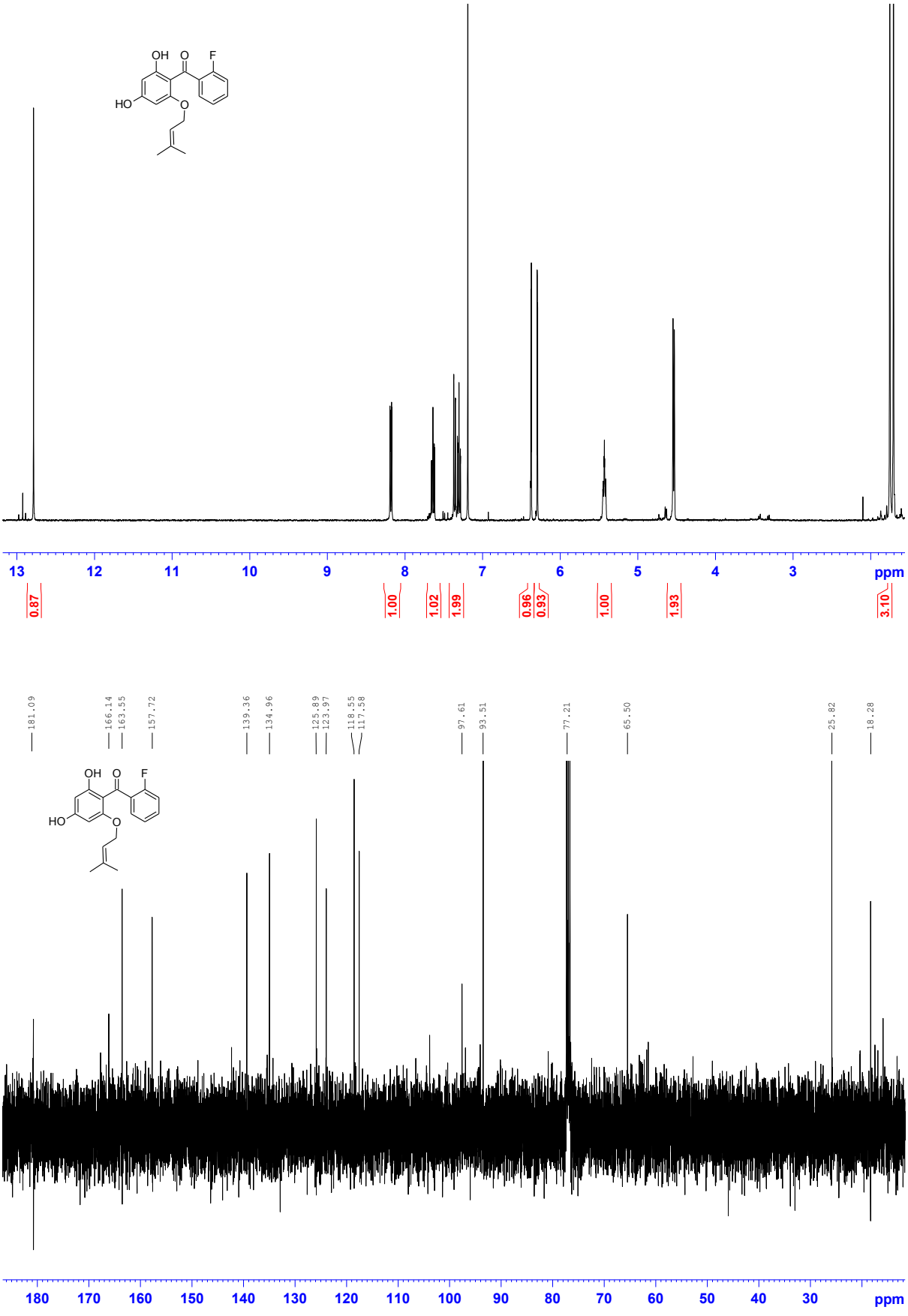

Plate 34. ^{1}H and ^{13}C NMR spectra of (2-fluorophenyl)[2,6-dihydroxy-3-(3-methylbut-2-enyl)-4-(3-methylbut-2-enyloxy)phenyl]methanone (**3.88**).

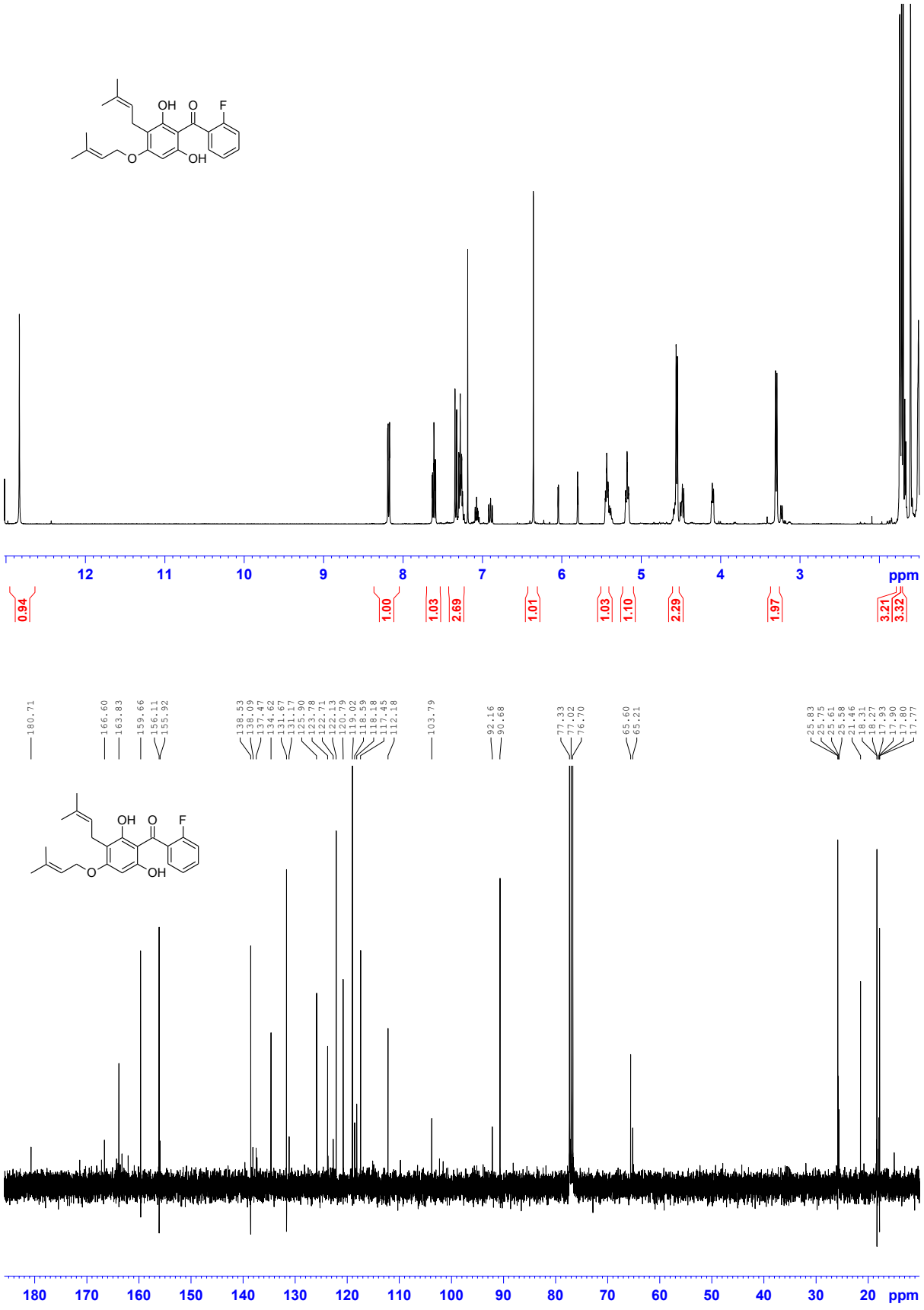

Plate 35. ^{1}H and ^{13}C NMR spectra of (2-fluorophenyl)[2,6-dihydroxy-3-(3-methylbut-2-enyl)-4-(3-methylbut-2-enyloxy)phenyl]methanone (**3.89**).

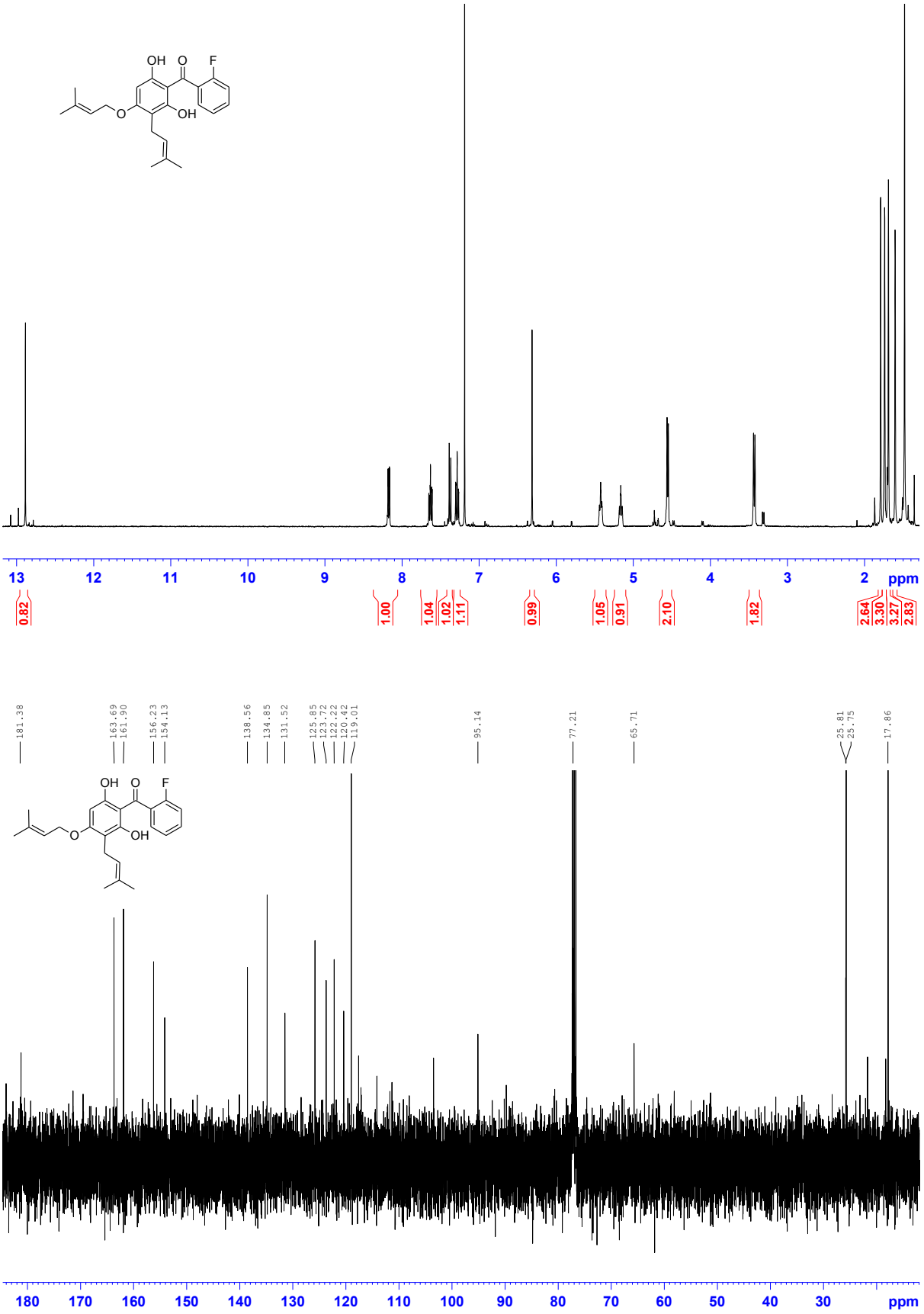

Plate 36. ^{1}H and ^{13}C NMR spectra of (2-fluorophenyl)[2,4-dihydroxy-3,5-bis(3-methylbut-2-enyl)-6-(3-methylbut-2-enyloxy)phenyl]methanone (**3.90**).

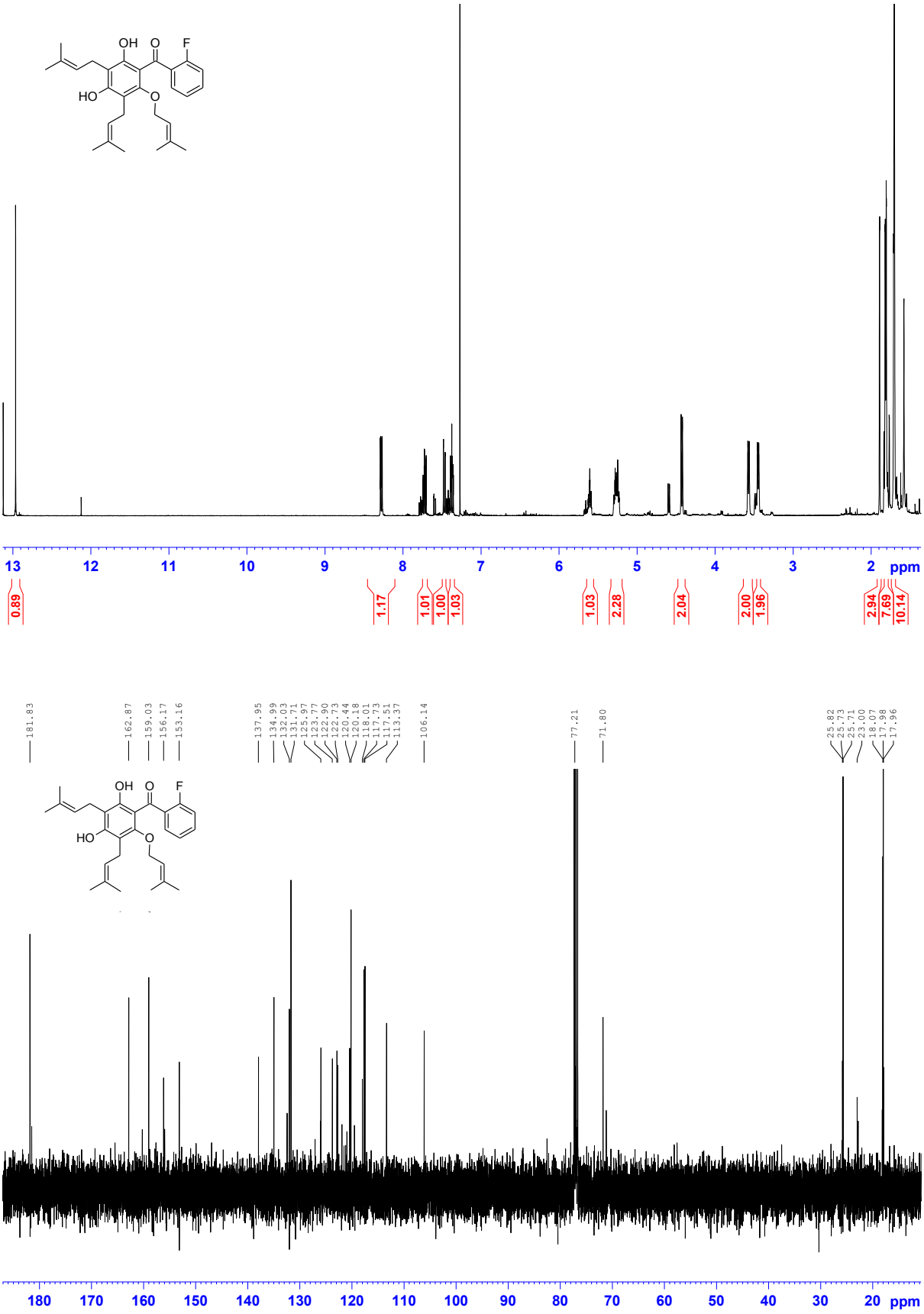

Plate 37. ^{1}H and ^{13}C NMR spectra of methyl benzoylacetate (**4.65**).

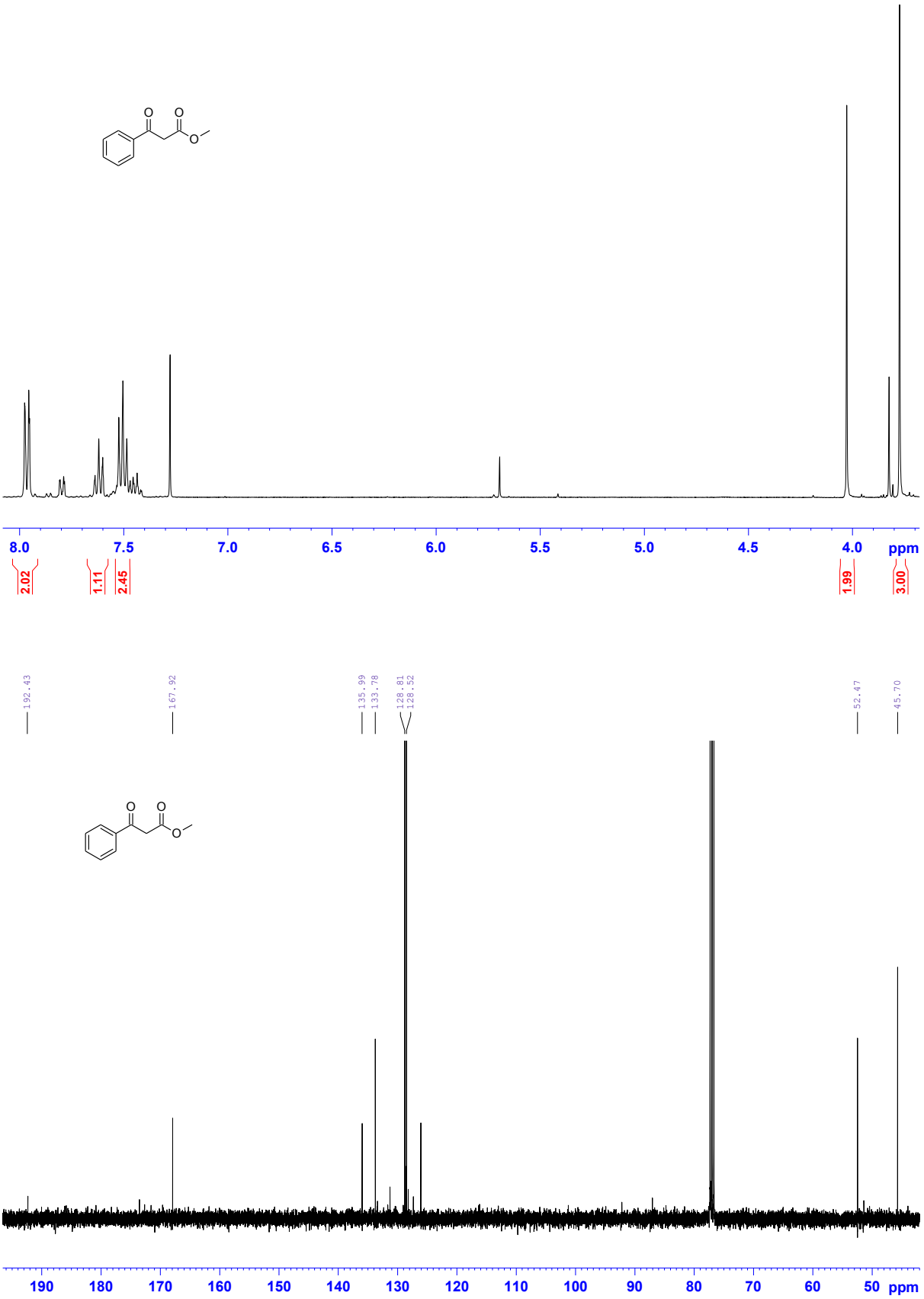

Plate 38. ^{1}H and ^{13}C NMR spectra of methyl 2-fluorobenzoylacetate (**4.84**).

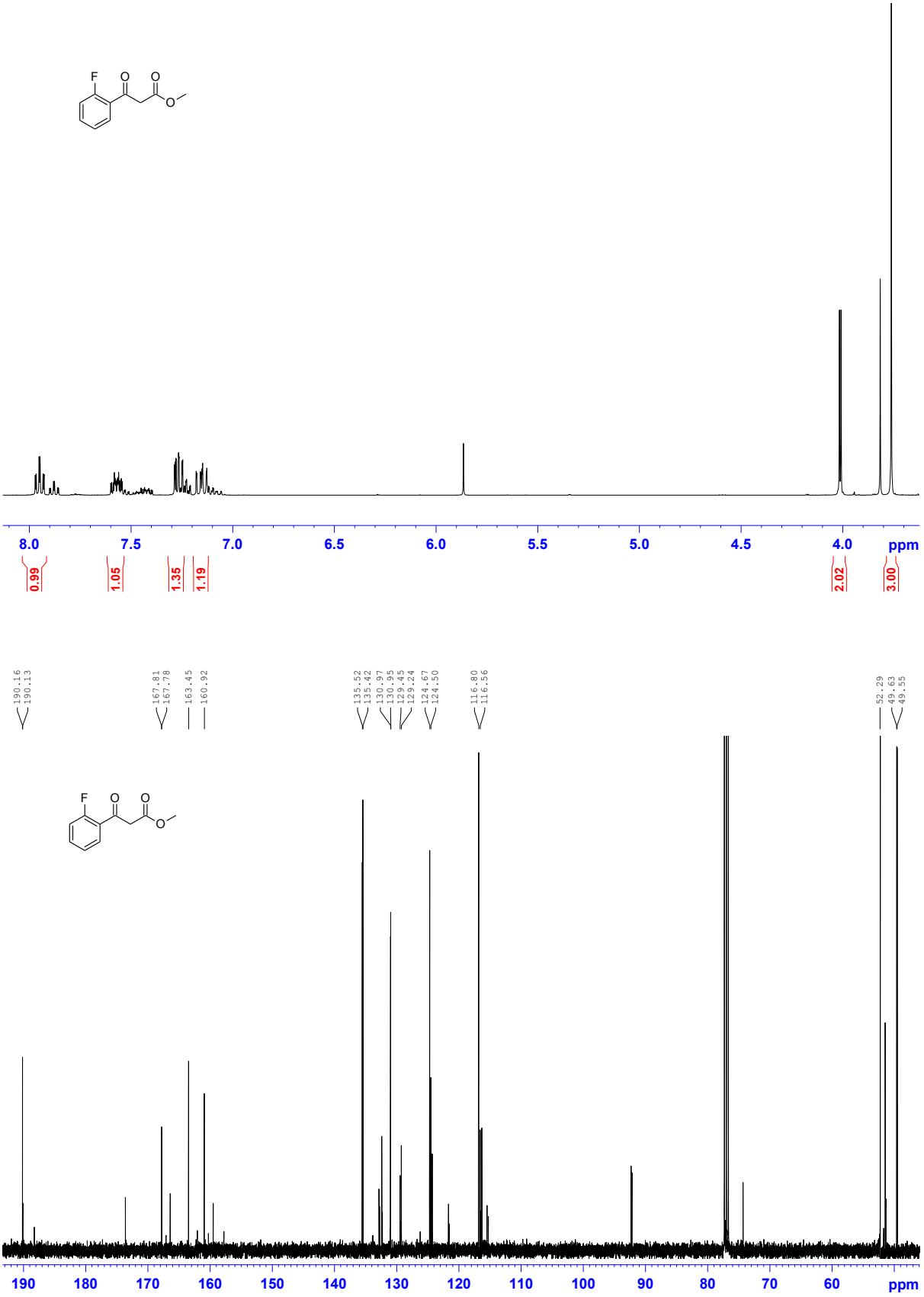

Plate 39. ^{1}H and ^{13}C NMR spectra of methyl 3-fluorobenzoylacetate (**4.85**).

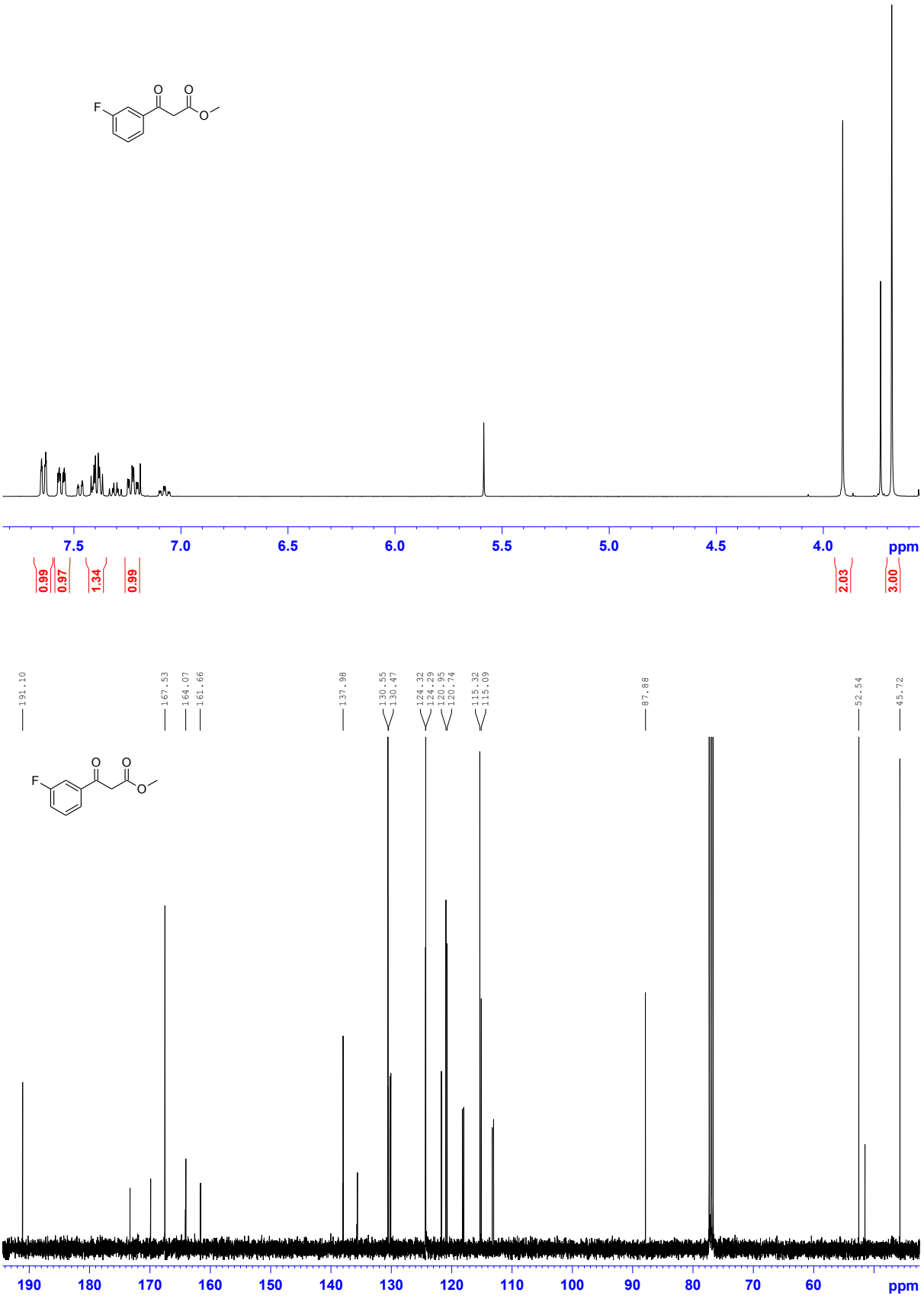

Plate 40. ^{1}H and ^{13}C NMR spectra of methyl 4-fluorobenzoylacetate (**4.86**).

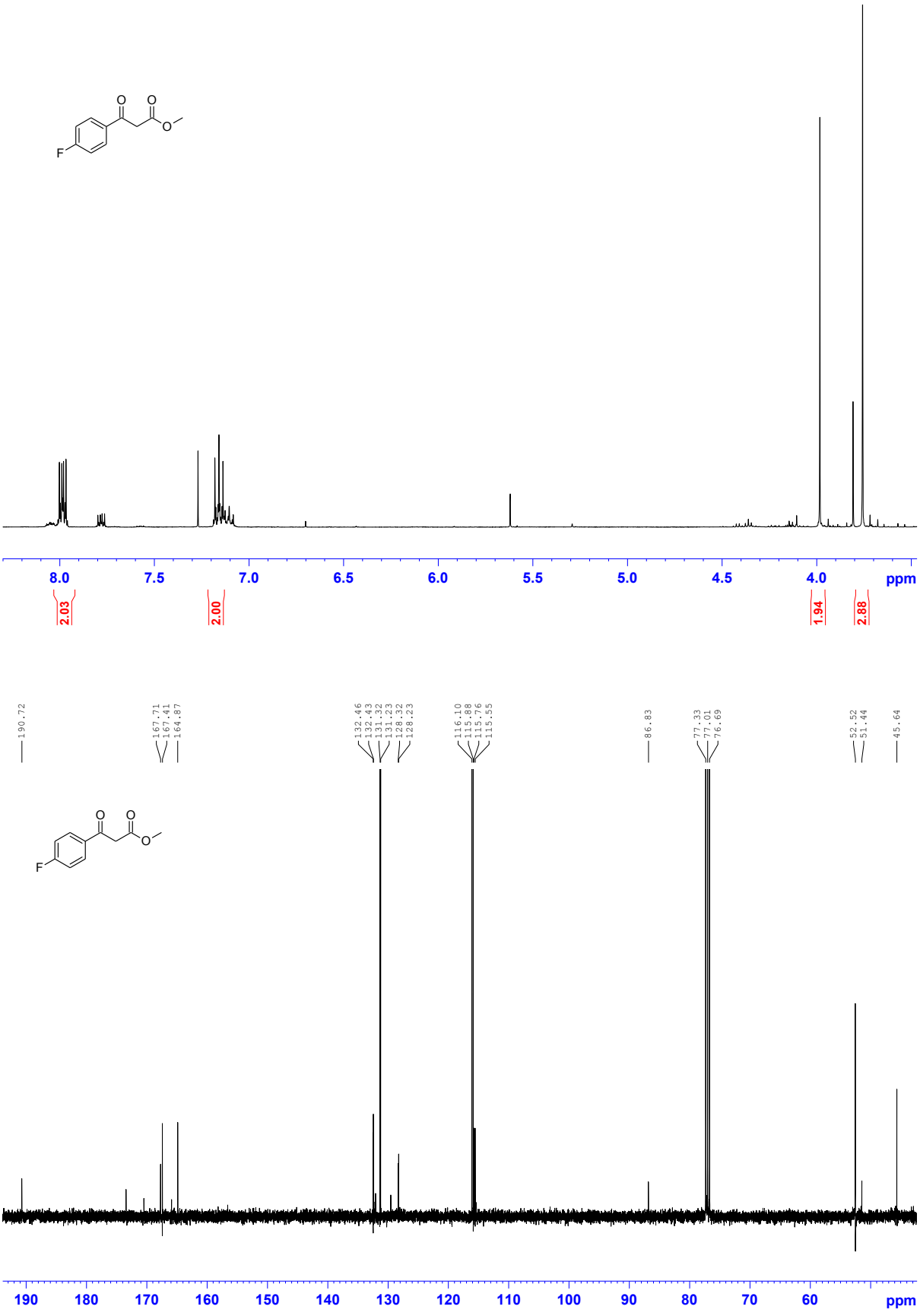

Plate 41. ^{1}H and ^{13}C NMR spectra of 7-hydroxy-4-phenylcoumarin (**4.87**).

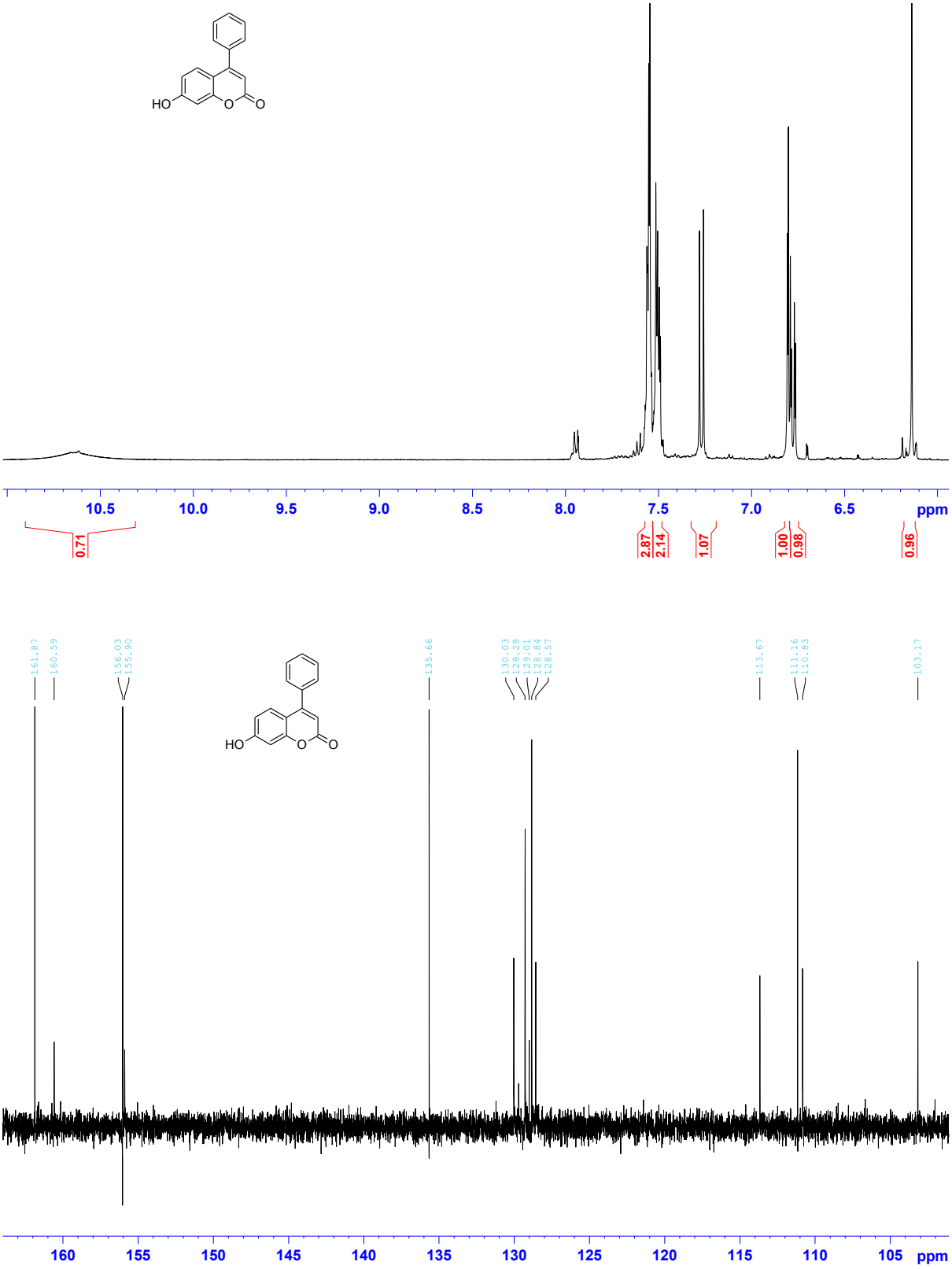

Plate 42. ^{1}H and ^{13}C NMR spectra of 7-hydroxy-4-(2-fluorophenyl)coumarin (**4.88**).

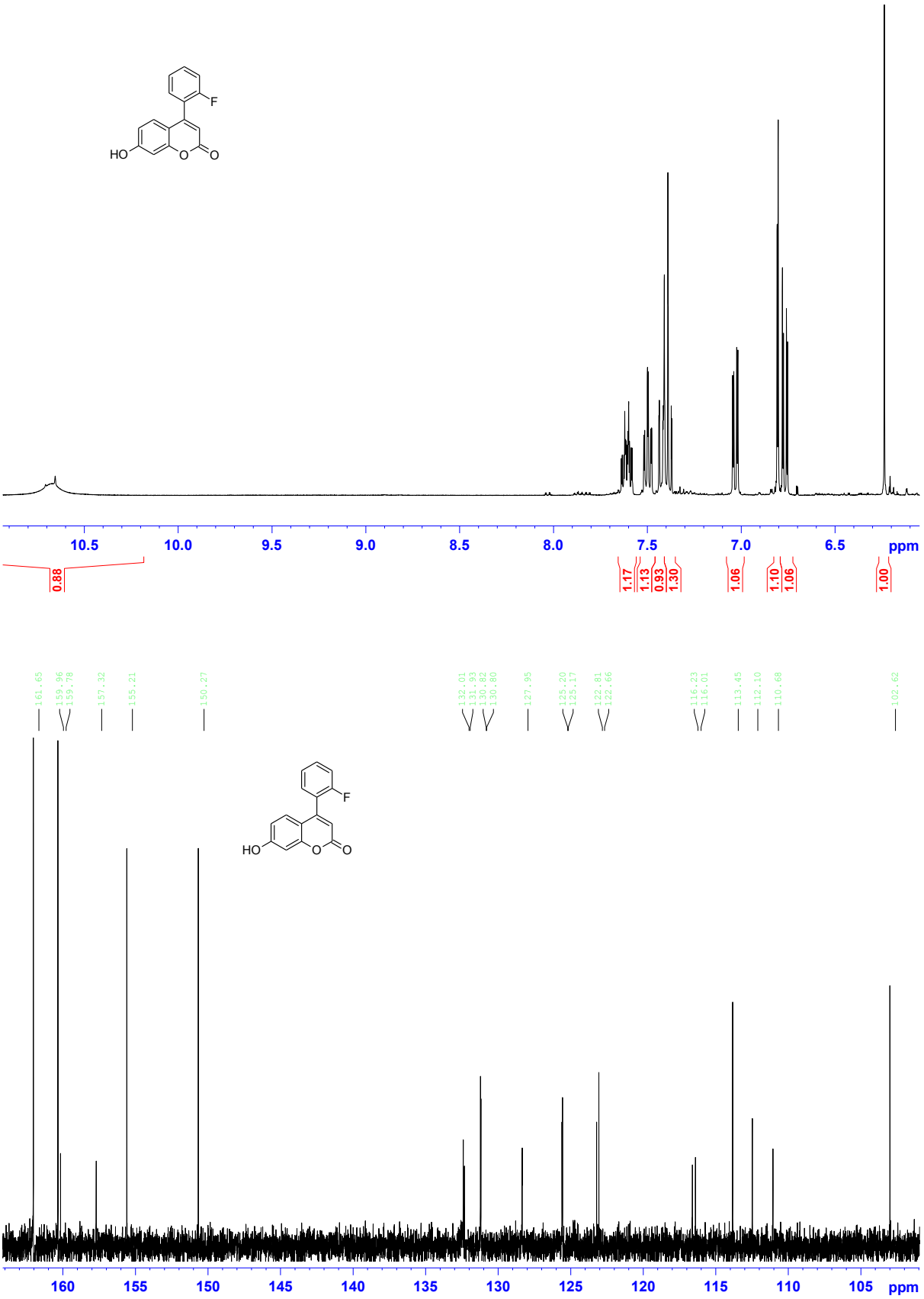

Plate 43. ^{1}H and ^{13}C NMR spectra of 7-hydroxy-4-(3-fluorophenyl)coumarin (**4.89**).

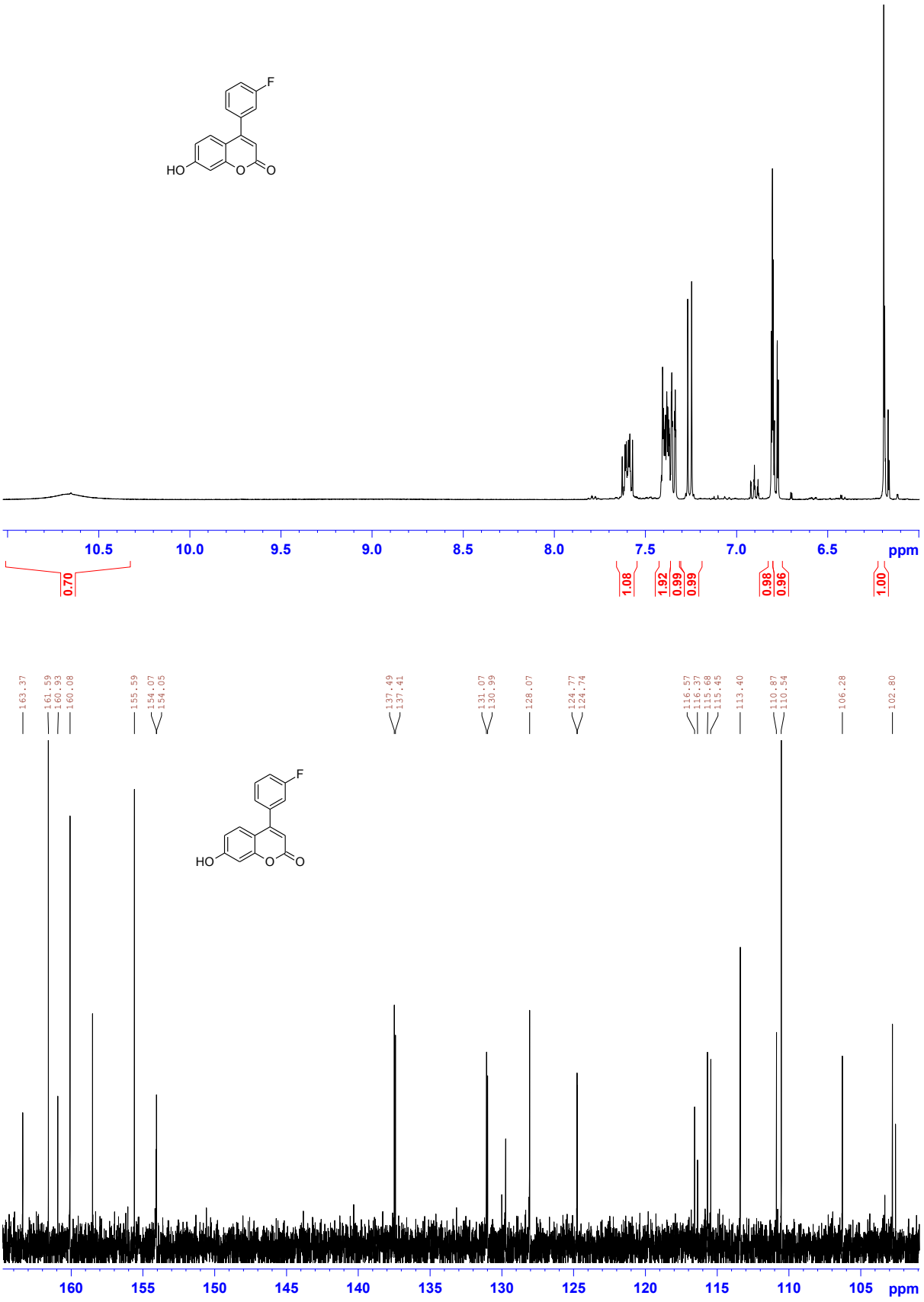

Plate 44. ^{1}H and ^{13}C NMR spectra of 7-hydroxy-4-(4-fluorophenyl)coumarin(**4.90**).

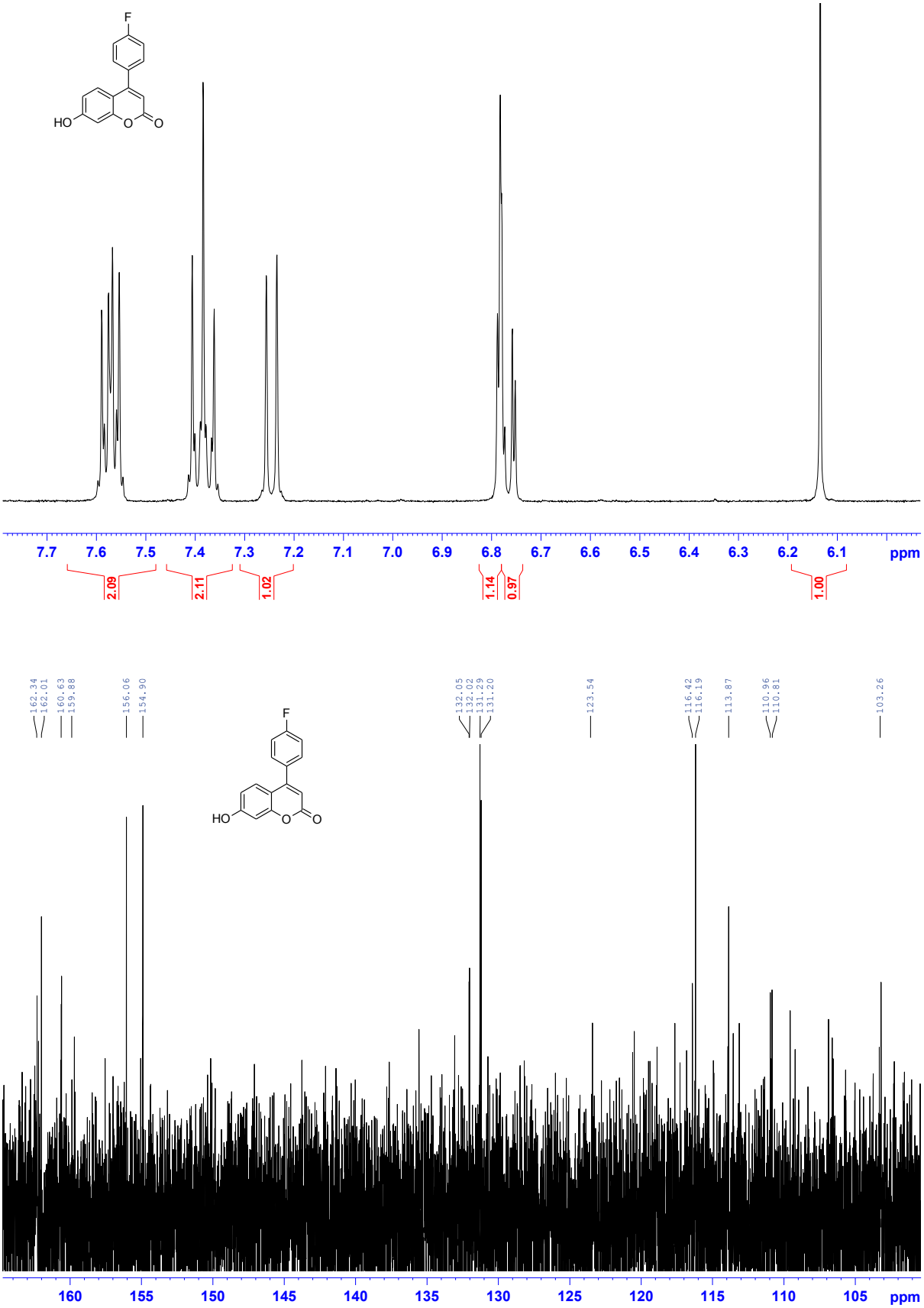

Plate 45. ^{1}H and ^{13}C NMR spectra of 5,7-dihydroxy-4-phenylcoumarin (**4.83**).

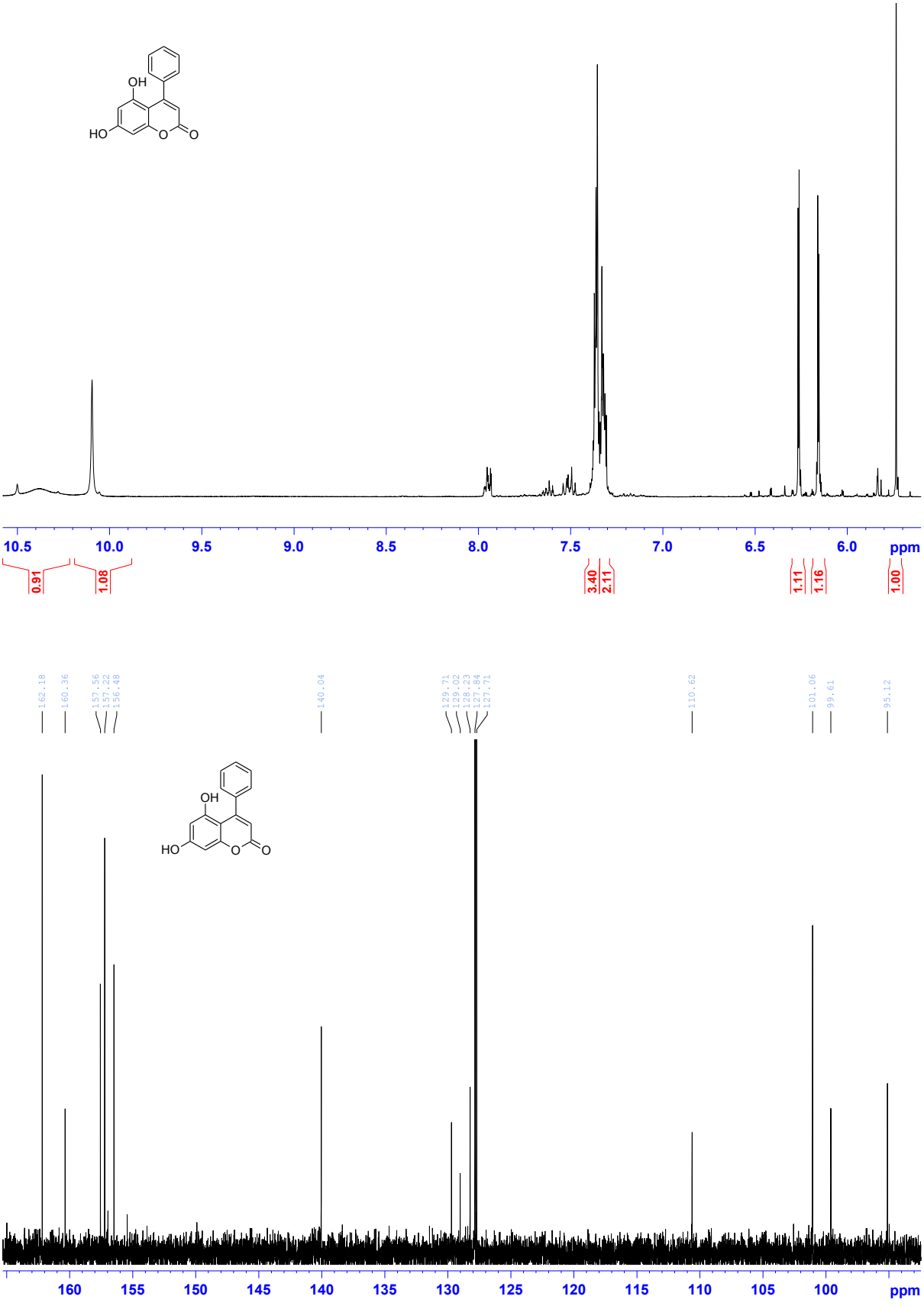

Plate 46. ^{1}H and ^{13}C NMR spectra of 5,7-dihydroxy-4-(2-fluorophenyl)coumarin (**4.91**).

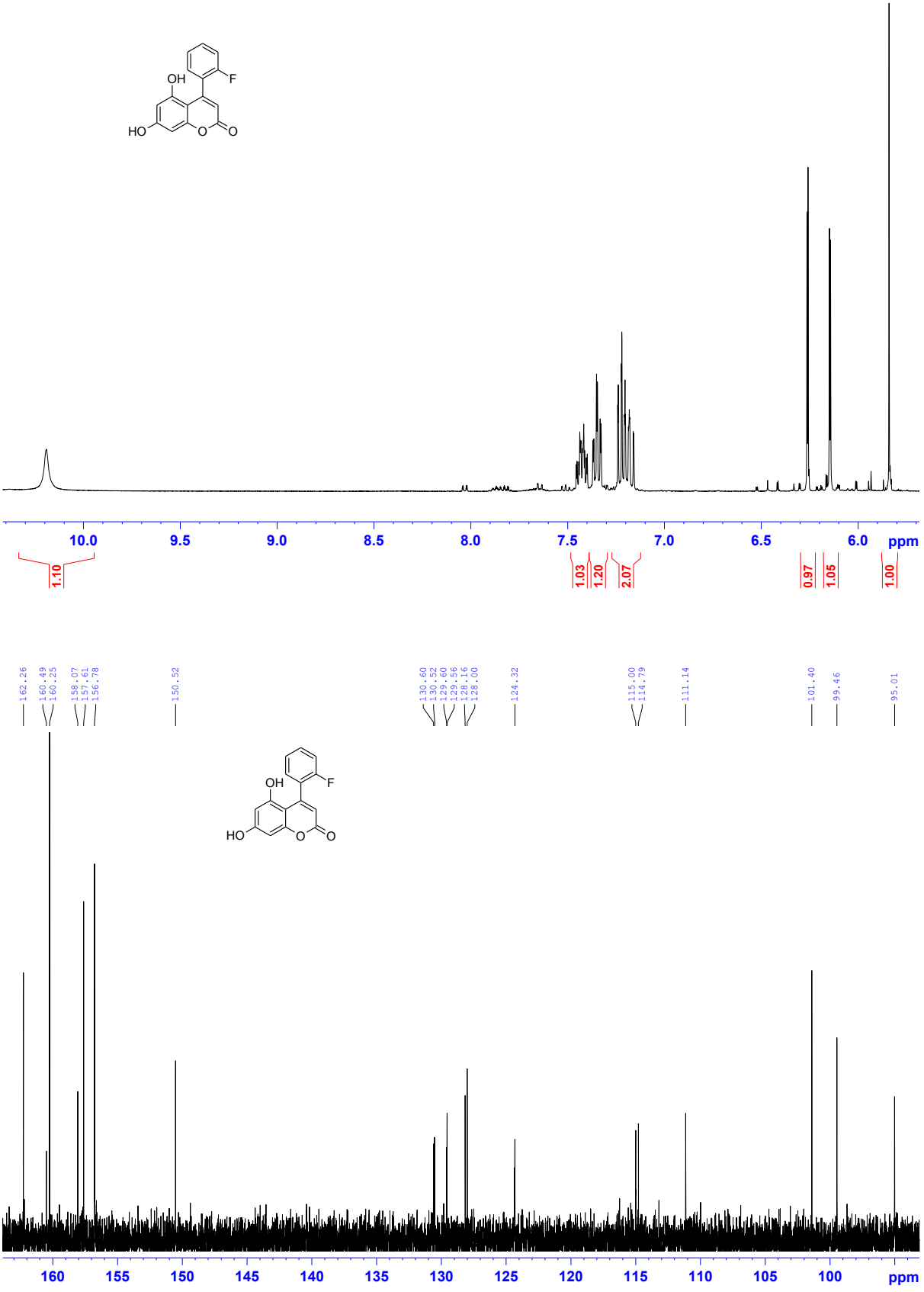

Plate 47. ^{1}H and ^{13}C NMR spectra of 5,7-dihydroxy-4-(3-fluorophenyl)coumarin (**4.92**).

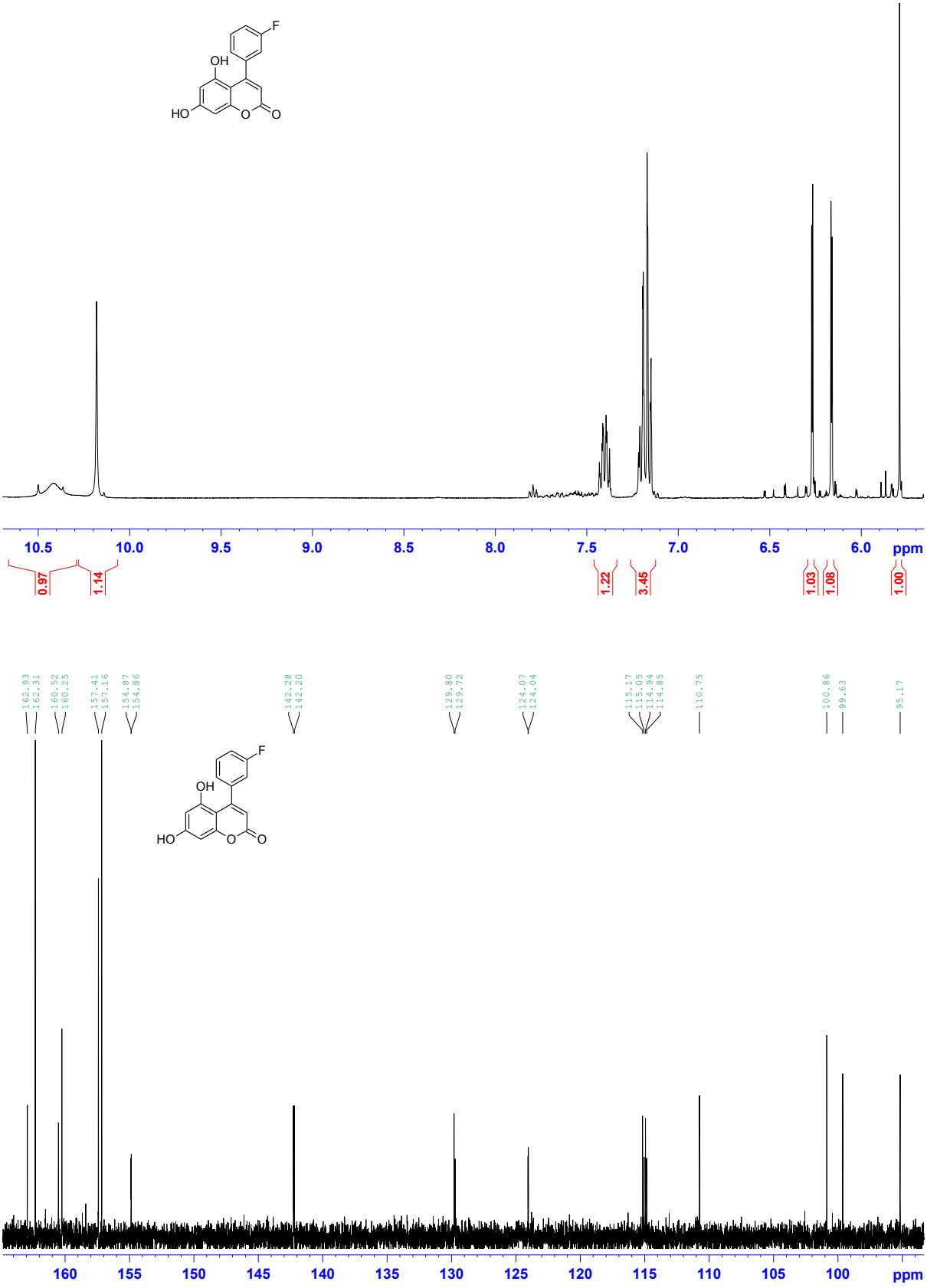

Plate 48. ^{1}H and ^{13}C NMR spectra of 5,7-dihydroxy-4-(4-fluorophenyl)coumarin (**4.93**).

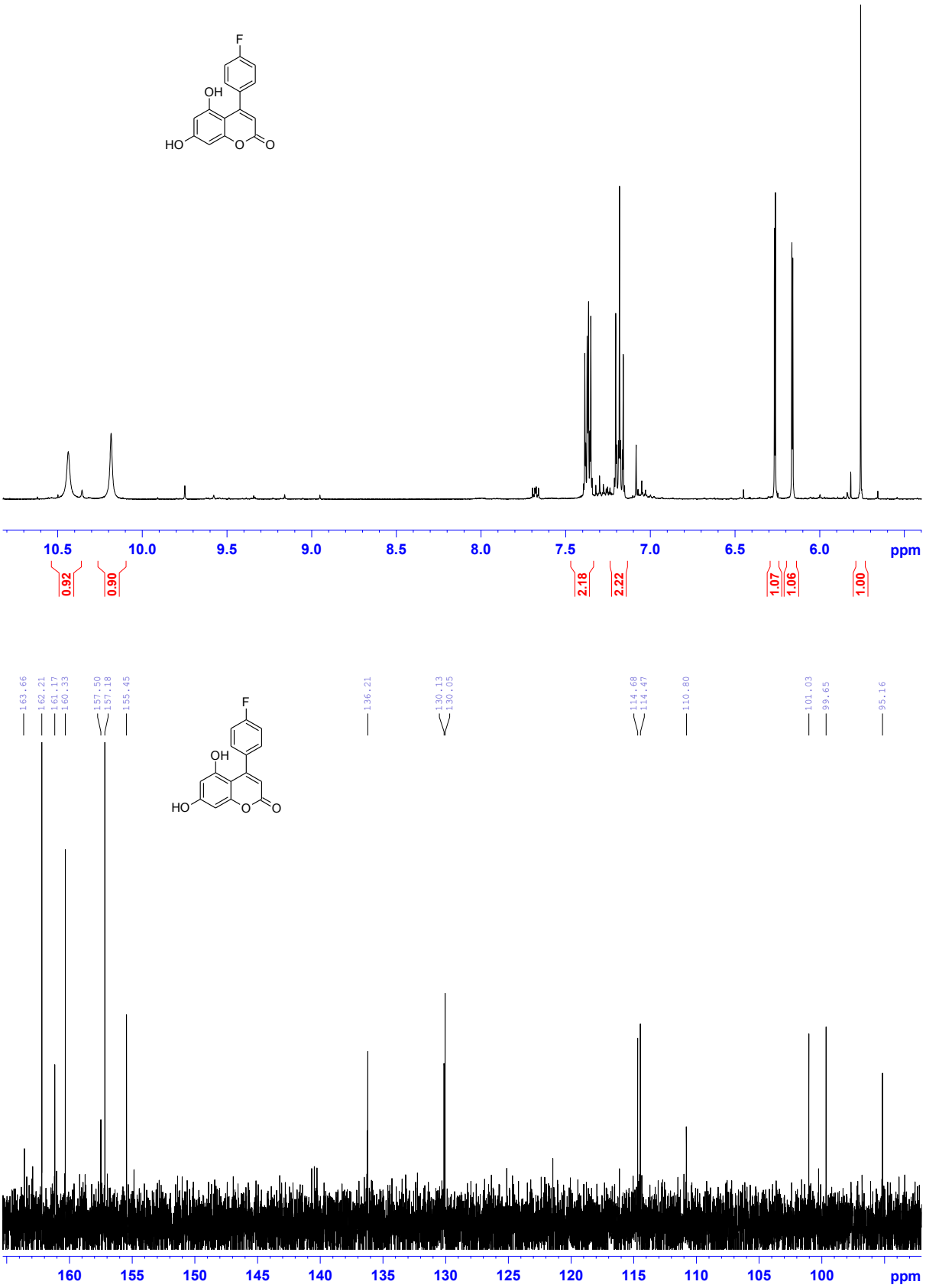

Plate 49. ^{1}H and ^{13}C NMR spectra of 7-hydroxy-4-methylcoumarin (**4.94**).

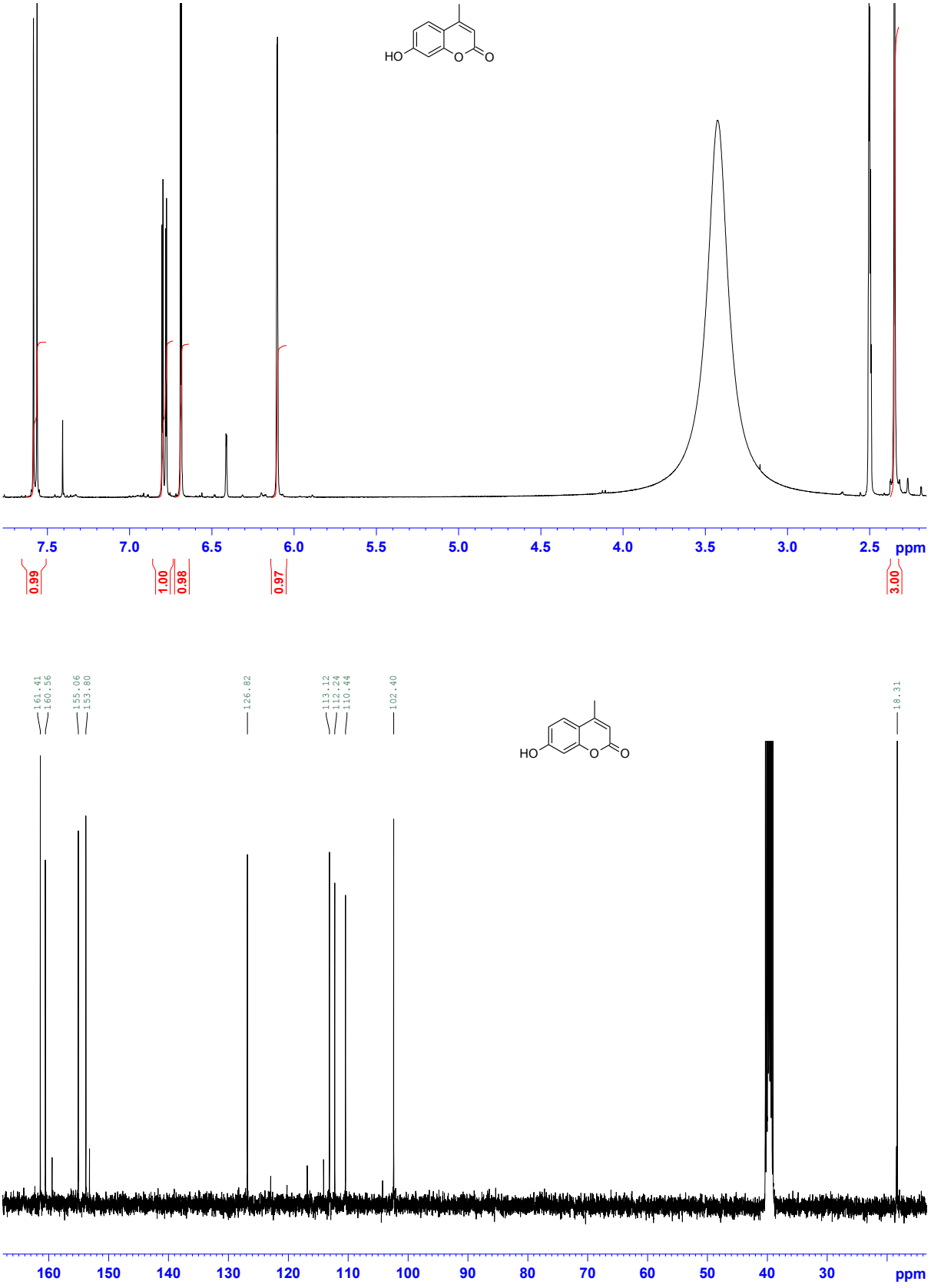

Plate 50. ^{1}H and ^{13}C NMR spectra of 6-hydroxy-4-methylcoumarin (**4.96**).

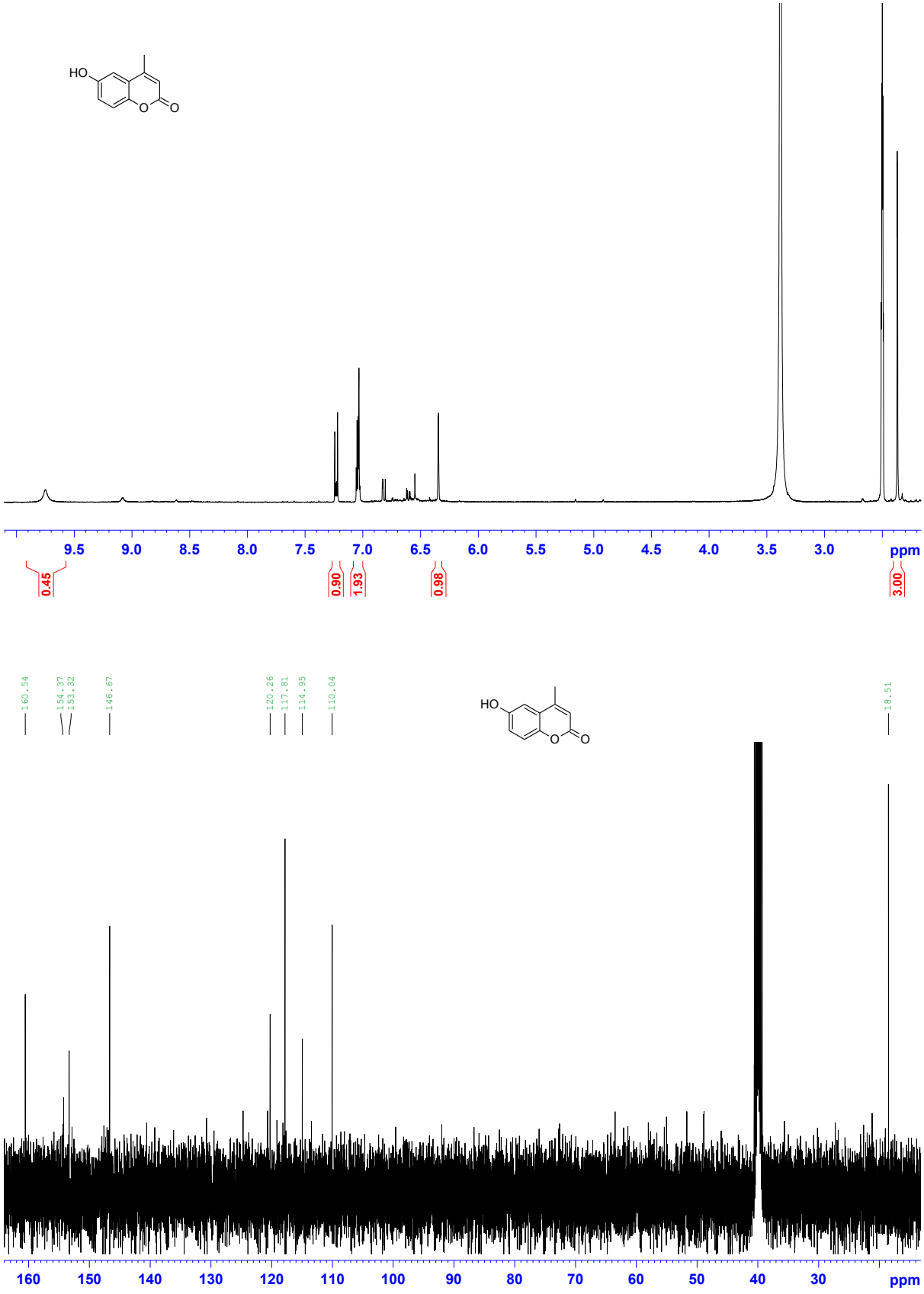

Plate 51. ^{1}H and ^{13}C NMR spectra of 5,7-dihydroxy-4-methylcoumarin (**4.95**).