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Specialty*: Organic Chemistry*
Option*: Phytochemistry*

TITLE

Chemical study of *Euphorbia guyoniana and Launaea resedifolia* followed by Study of Reactivity of γ-alkylidene Butenolides

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إهـــــــــــــــداء

اهدي هذا العمل إلى روح الفقيد والأخ الفاضل المرحوم الأستاذ الدكتور احمد عبد الإله احمد الذي استقبلنا في مخبره لعدة مرات وكان له الدور البارز في إنجاز هذه البحوث راجيا من الله أن يتغمده برحمته الواسعة.

Table of Contents

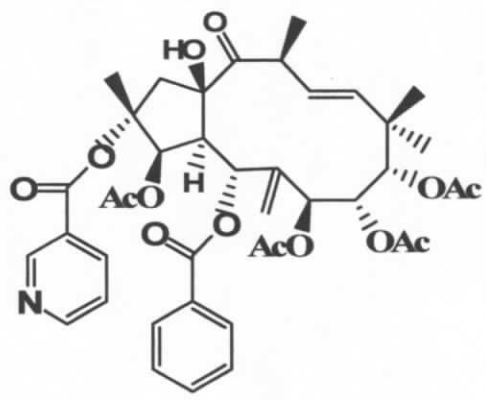
Summary

Herbal systems of medicine have become increasingly popular in recent years. A recent study demonstrated that about 34% of the general population used one or the other system at least once a year.

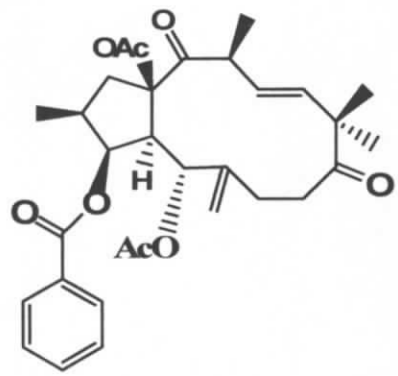
In light of growing interest in herbal drugs, chemical study of medicinal plants becomes primarily important. The standardized herbal extracts are considered to be more scientific than crude drugs. Our intention through the present study was to take part in the assessment of our botanical patrimony which remains till now less explored.

The first part of this thesis deals with a chemical study of two major medicinal plants: ***Euphorbia guyoniana*** **and** ***Launaea resedifolia.***

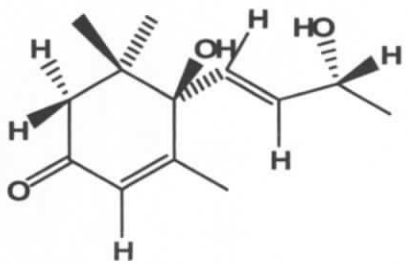
For *E. guyoniana,* the terpenoids content study was mainly targeted through the extraction, purification and identification leading to two new jadrophanes diterpenoids named as guyonianin A and B and vomifoliol whose skeletons were identified through a series of spectral data including mass spectroscopy, 1D and 2D NMR.



Guyonianin A

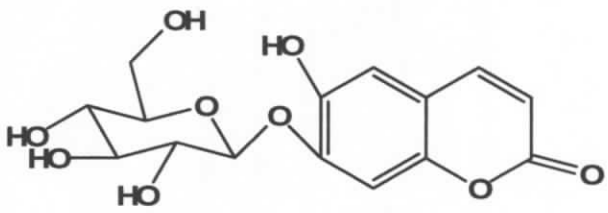


Guyonianin B

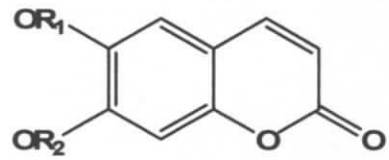


Vomifoliol

As far as *Launaea resedifolia* is concerned, the coumarin content was investigated and the results revealed the presence of four coumarins, namely Cichoriin, Esculetin, Scopoletin and isoscopoletin, extracted for the first time from this species.



Cichoriin



Esculetin R_1=H R_2=H

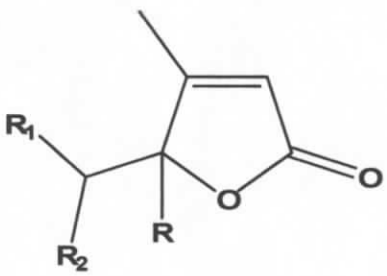
Scopoletin R_1=Me R_2=H

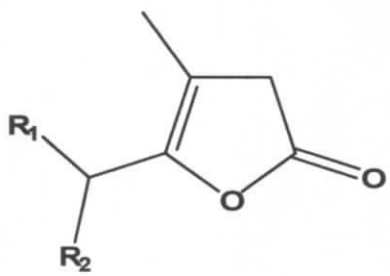
Isoscopoletin R_1=H R_2=Me

The second part of this work deals with the study of the reactivity of alkylidene butenolides by carrying out the 1,6 addition using some organocopper reagents.

The butenolides and their analogues represent a wide range of natural occurring compounds of medical and biological importance.

The study gave rise to a series of new 1,6-cuprate addition products that need to be deepened through the balancing with other reagents towards the synthesis of biological active compounds.





R= H, OH

R_1= Me or nBu

R_2= nBu, nHex or Methoxymethyl

Declaration

'I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.'

Noureddine Gherraf
2006

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I would like to thank my supervisor, Pr. Rhouati Salah, for his guidance and wisdom during my years of research. Pr. Rhouati Salah was always willing to listen and offer suggestions about my research project. I thank him as well for his continuous interest and tireless encouragement at all stages of this work.

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The last but not the least to thank are all those who have contributed directly or indirectly in the success of my academic career throughout my scholar pathway.

Publications

1- ***isolation of Coumarins and Coumarin glucoside from Launaea resedifolia Noureddine Gherraf, Ashraf A. El-Bassuony, Ammar Zellagui, Salah Rhouati, Ahmed. A. Ahmed, Med Ridha Ouahrani. Asian journal of chemistry, 2006, 18(3), 2348-2352.***

2-Guyonianin A and B, Two Polyester Diterpenes from Algerian Euphorbia guyoniana. Ahmed A. Ahmed, Noureddine Gherraf, Ashraf A. El-Bassuony, Salah Rhouati, Mahmoud H. Gad, Shinji Ohta and Toshifumi Hirata. Natural Product Communications, 2006, 1(4), 273-279.

Glossary of Abbreviations

Br: broad

NMR: nuclear Magnetic Resonance

COSY: Correlation Spectroscopy

S: singlet

d: doublet

dd: doublet of doublet

ddd: doublet of doublet of doublet

t: triplet

q: quartlet

m: multiplet

DEPT: distortionless enhancement by polarization transfer

1D: one dimension

2D: two dimensions

et al: Et alia (and others)

HMBC: heteronuclear multiple bond correlation

HMQC: heteronuclear multiple quantum coherence

NOESY: Nuclear Overhauser Enhancement Spectroscopy

NOE: Nuclear Overhauser Effect

HRMS: High resolution mass spectroscopy

CIMS: chemical ionization mass spectrographs

J: Coupling constant

TLC: thin layer chromatography

ml: milliliter

m p: melting point

m/z: mass to charge ratio

HRFABMS: high resolution fast atom bombardment mass spectrometry

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

Chapter One

General

1.1. Foreword

The vegetable world comprises three main groups of plants: Superior, Intermediary, and Inferior. These encompass bacteria, microscopic algae, mushrooms, ferns, brushes, and trees, among others. Their identification is a task of specialists and the limit between the vegetal and animal world is not clear. To simplify matters, plants are considered such as those recognized by ordinary people. Subjects about medicinal properties of vegetables normally seem to treat differently herbs and medicinal plants. However, herbs are seed producing annual, biennial, or perennial plants that do not develop a persistent woody tissue. Perhaps because herbs have such an important historical and tradition in healing, sometimes they are treated as a special category of plants i.e., those particularly valued for their medicinal, savory or aromatic qualities.[1]

1.2. Historical background

Medicinal plants are significant source of synthetic and herbal drugs. Medicinal plants have been used for the treatment of diseases since antiquity. India and China have been on the forefront when we talk about history of herbal drugs. The traditional systems of medicines viz. Ayurveda, Siddha, Unani, Western Herbal Medicine, Traditional Chinese Medicine, and Homeopathy have roots in medicinal herbs. Herbal medicine has produced number of distinguished researchers and due to its accessibility to traditions it is still practiced even by lay practitioners. Ayurveda, the ancient healing system of India, flourished in the Vedic era in India. According to historical facts, the classical texts of Ayurveda, Charaka Samhita and Sushruta Samhita were written around 1000B.C. The Ayurvedic Materia Medica includes 600 medicinal plants along with therapeutics. Herbs like turmeric, fenugreek, ginger, garlic, and holy basil are integral part of Ayurvedic formulations. The formulations incorporate single herb or more than two herbs (polyherbal formulations). The history of Traditional Chinese Medicine is glorious and they have preserved the herbal system beautifully. It originated about 3000 years ago and is a popular science in western countries. Some of the medicinal herbs mentioned in Chinese medicine are common with Ayurveda. Traditional Chinese medicine favors the use of medicinal herbs in natural form rather than extraction. The herbal

drugs have different history in Europe and America and they have produced healers like Culpeper. The use of tinctures in Homeopathy is based on medicinal herbs. [1-3]

Before the availability of synthetic drugs, man was completely dependent on medicinal herbs for prevention from and treatment of diseases. The use of the medicinal herbs for curing disease has been documented in the history of all civilizations. The drugs were used in crude forms like expressed juice, powder, decoction or infusion. Although the formulations mentioned in ancient texts are difficult to understand in terms of scientific parameters, but some of them are reputed for their curative values. Ancient healers, developed formulations based on medicinal herbs, were probably not aware about the chemical composition of the herbs. But the advancement they made despite the non-availability of scientific procedures is astonishing. The work on Terminalia chebula (myrobalan) mentioned in Charaka Samhita is quite authentical and modern studies have revealed that the purgative activity mentioned in Ayurveda is justified by the isolation of chebulic acid, the active constituent of myrobalan.[1]

1.3. Introduction

Herbal Medicine sometimes referred to as Herbalism or Botanical Medicine, is the use of herbs for their therapeutic or medicinal value. An herb is a plant or plant part valued for its medicinal, aromatic, or savory qualities. Herb plants produce and contain a variety of chemical substances that act upon the body.

Herbal medicine is the oldest form of healthcare known to mankind. Herbs had been used by all peoples throughout history. It was an integral part of the development of modern civilization. Primitive man observed and appreciated the great diversity of plants available to him. The plants provided food, clothing, shelter, and medicine. Much of the medicinal use of plants seems to have been developed through observations of wild animals, and by trial and error. As time went on, each tribe added the medicinal power of herbs in their area to its knowledgebase. They methodically collected information on herbs and developed well-defined herbal pharmacopoeias. Well into the 20th century much of the pharmacopoeia of scientific medicine was derived from the herbal lore of native peoples. Many drugs commonly used today are of herbal origin. Indeed, about 25 percent of the prescription drugs dispensed in the world contain at least one active ingredient derived from plant material. Some are made from plant extracts; others are synthesized to mimic a natural plant compound.

The World Health Organization (WHO) estimates that 4 billion people, 80 percent of the world population, presently use herbal medicine for some aspect of primary health care.

Herbal medicine is a major component in all indigenous peoples' traditional medicine and a common element in Ayurvedic, homeopathic, naturopathic, traditional oriental, and Native American Indian medicine. WHO notes that of 119 plant-derived pharmaceutical medicines, about 74 percent are used in modern medicine in ways that correlated directly with their traditional uses as plant medicines by native cultures. Major pharmaceutical companies are currently conducting extensive research on plant materials gathered from the rain forests and other places for their potential medicinal value. [4]

Substances derived from the plants remain the basis for a large proportion of the commercial medications used today for the treatment of heart disease, high blood pressure, pain, asthma, and other problems. For example, ephedra is an herb used in Traditional Chinese Medicine for more than two thousand years to treat asthma and other respiratory problems. Ephedrine, the active ingredient in ephedra, is used in the commercial pharmaceutical preparations for the relief of asthma symptoms and other respiratory problems. It helps the patient to breathe more easily. [5]

Interest in the world had been growing in the recent years from the reported success stories from the use of herbs. Medicinal herb is considered to be a chemical factory as it contains multitude of chemical compounds like alkaloids, coumarins, glycosides, saponins, resins, oleoresins, sesquiterpene lactones, steroids and oils (essential and fixed). Some rare compounds like furanocoumarins, hydroxycoumarins, napthoquinones, acylphloroglucinols, and sterones are also distributed in the plant kingdom. The active constituents are usually secondary metabolites, derived from biosynthetic pathways present within the plant tissue. Allicin, a sulphur compound, present in garlic (Allium sativum) is considered to be the active constituent. It is produced from alliin by an enzymatic reaction in response to injury. Allicin due to its noxious smell protects garlic from attack of pests also. Thus an active constituent has therapeutic as well as protective activity. The formulations used in ancient texts are based on plant in natural form. They do not believe in extracting the active constituent from the plant. According to experts, some significant virtues of the plant are lost during extraction. According to one estimate nearly 70 % of the synthetic drugs are derived from medicinal herbs. With introduction of sophisticated techniques, the scientists started exploring the plant flora for active constituents. In 1803, Sertuner isolated a crystalline alkaloid, morphine from opium poppy (Papaver somniferum) which still remains a priced drug in medicine as analgesic. Sertuner's research unearthed the mode of action of herbal remedies. Later on the antitussive alkaloid, codeine was isolated and it proved the fact that a medicinal herb can exert different pharmacological activities due to the presence of number of constituents. Later

on drugs like atropine, arecoline, muscarine, and hyoscine were purified for medicinal applications. Drugs like vinblastine, vincristine, reserpine, digoxin are reputed drugs for the treatment of cancer and heart ailments.4 Recently silymarin (hepatoprotective), taxol (anti-cancer), and Artemisinin (antimalarial) have figured high in pharmaceutical industry because of high therapeutic activity. Hypericin (antiviral) and hyperforin (antidepressant) have great reputation as research based medicinal agents. The chemistry of medicinal herbs is very complex. Not all the constituents present in the plant have therapeutic activity, some are poisonous e.g. pyrrolizidine and tropane alkaloids. Phytochemistry deals with study of chemical composition of the plant material (Phyto refers to plant). Plants are used in various forms varying from powders to extracts. Powder represents the drug in ground form and these types of preparations are considered to be crude. The Pharmacopoeia mentions standardized vegetable powders for therapeutic application. Herbal systems of medicine have become increasingly popular in recent years. A recent study from America demonstrated that about 34% of the general population used one or the other system at least once a year. In India 76% of patients visiting the general medicine OPD of a tertiary care hospital use alternative therapies. In light of growing demand of herbal drugs, the quality control and assurance is primarily important. The standardized herbal extracts are considered to be more scientific than crude drugs. [5-7]

Algerian flora is becoming of great interest in nowadays due to many aspects. In one hand Algerian people is still attached to herbal medicine overall in the southern part and in the other hand some of Algerian plants are endemic and hence they are considered as a powerful source and a rich material for interesting research scopes, things that incited many research groups to make great strides in developing this side of chemistry.

This thesis is an attempt to assess the chemical value of two important and potential medicinal plants of our rich desert flora: Euphorbia guyoniana and Launaea resedifolia. A good deal of attention has been paid to provide accurate information.

1.4. Major Classes of Natural Products

1.4.1. Alkaloids

An alkaloid is a nitrogenous organic molecule that has a pharmacological effect on humans and animals. The name derives from the word alkaline; originally, the term was used to describe any nitrogen-containing base (an amine in modern terms). Alkaloids are found as secondary metabolites in plants (e.g., in potatoes and tomatoes), animals (e.g., in shellfish)

and fungi, and can be extracted from their sources by treatment with acids (usually hydrochloric acid or sulfuric acid, though organic acids such as maleic acid and citric acid are sometimes used). Usually alkaloids are derivatives of amino acids. Even though many alkaloids are poisonous (such as strychnine or coniine), some are used in medicine as analgesics (pain relievers) or anaesthetics, particularly morphine and codeine. Most alkaloids have a very bitter taste.[8-10]

1.4.2. Flavonoids

The term flavonoid refers to a class of plant secondary metabolites based around a phenylbenzopyrone structure. Their skeleton can be represented as the C_6 - C_3 - C_6 system. Flavonoids are most commonly known for their antioxidant activity. Flavonoids are also commonly referred to as bioflavonoids in the media – these terms are equivalent and interchangeable, since all flavonoids are biological in origin.[9-11]

1.4.2.1. Biological Effects

Flavonoids are widely distributed in plants fulfilling many functions including producing yellow or red/blue pigmentation in flowers and protection from attack by microbes and insects. The widespread distribution of flavonoids, their variety and their relatively low toxicity compared to other active plant compounds (for instance alkaloids) mean that many animals, including humans, ingest significant quantities in their diet. Flavonoids have been found in high concentrations in butterflies and moths sequestered from dietary intake at the larval stage and then stored in adult tissues.[10]

Flavonoids have been referred to as "nature's biological response modifiers" because of strong experimental evidence of their ability to modify the body's reaction to allergens, viruses, and carcinogens. They show anti-allergic, anti-inflammatory, anti-microbial and anti-cancer activity. In addition, flavonoids act as powerful antioxidants, protecting against oxidative and free radical damage.[10]

Consumers and food manufacturers have become interested in flavonoids for their medicinal properties, especially their potential role in the prevention of cancers and cardiovascular disease. The beneficial effects of fruit, vegetables, and tea or even red wine have been attributed to flavonoid compounds rather than to known nutrients and vitamins.

1.4.2.2. Availability through microorganisms:[11]

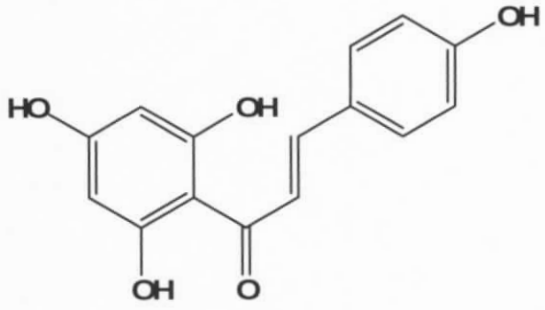
A number of recent research articles have demonstrated the efficent production of flavonoid molecules from recombinant microorganisms. Such an approach opens the possibility of readily producing these compounds using renewable feedstocks and thus increasing the availability of rare flavonoid molecules for human and animal feed through dietary supplements.

1.4.2.3. Subgroups:

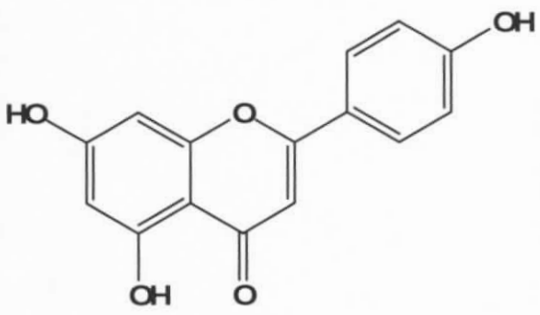
Over 5000 naturally occurring flavonoids have been characterized from various plants. They have been classified according to their chemical structure, and are usually subdivided into 6 subgroups:

Examples of the 6 major subgroups are:

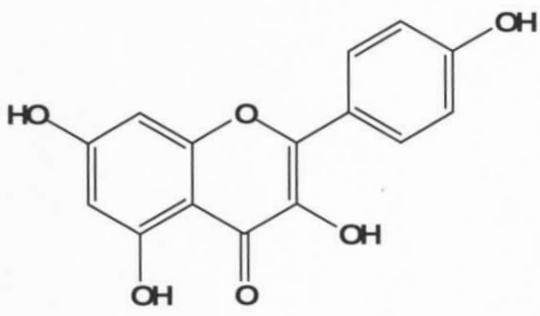
a. Chalcones: The important chalcones are naringenin and phloridzin. They are found in a number of plant families including the Compositae.



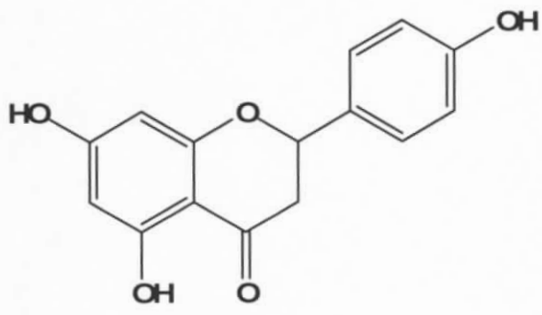
b. Flavones: (generally in herbaceous families, e.g. Labiatae, Umbelliferae, Compositae). Apigenin (Apium graveolens, Petroselinum crispum), Luteolin (Equisetum arvense)



c. Flavonols : (generally in woody angiosperms), Quercitol (Ruta graveolens, Fagopyrum esculentum, Sambucus nigra), Kaempferol (Sambucus nigra, Cassia senna, Equisetum arvense, Lamium album, Polygonum bistorta). Myricetin.

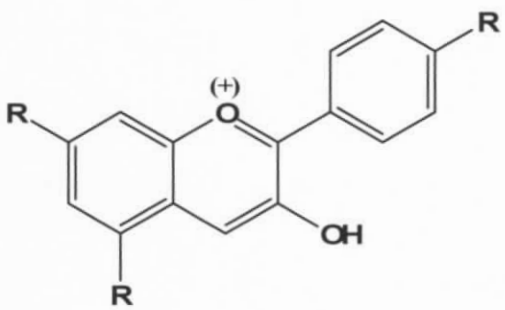


d. Flavanones: Good sources of flavanones are citrus fruit.



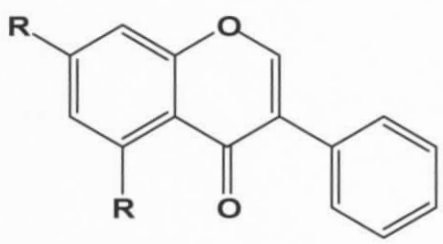
The major dietary flavanones are hesperetin, naringenin and eriodictyol.

e. Anthocyanidins: The anthocyanidins constitute a large family of differently colored compounds and occur in countless mixtures in practically all parts of higher plants. They are of great economic importance as fruit pigments and thus are used to color fruit juices, wine, and some beverages.



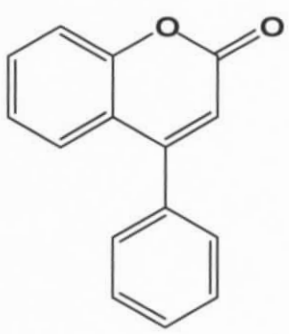
The anthocyanidins in Hydrangea, colors it red in acid soil and blue in alkali soil.

f. Isoflavonoids: In contrast to most other flavonoids, isoflavonoids have a rather limited taxonomic distribution, mainly within the Leguminosae. The isoflavonoids are all colorless. Clinical research has demonstrated isoflavones to be effective in menstrual diseases. They have antioxidant activity also.



Most of these (flavanones, flavones, flavonols, and anthocyanidins) bear ring B in position 2 of the heterocyclic ring. In isoflavonoids, ring B occupies position 3.

A group of benzopyrone -2 and 4 (chromone) derivatives with ring B in position 4 (4-phenyl-coumarins = Neoflavonoids is shown below.



1.4.3. Coumarins:

1.4.3.1. Nomenclature

Coumarins owe their class name to 'coumarou', the vernacular name of the tonka bean (*Dipteryx odorata* Willd., Fabaceae), from which coumarin itself was isolated in 1820. [12]

Coumarins belong to a group of compounds known as the benzopyrones, all of which consist of a benzene ring joined to a pyrone. Coumarin and the other members of the coumarin family are benzo-α-pyrones, while the other main members of the benzopyrone group – the flavonoids –contain the γ-pyrone group. [13] Coumarins may also be found in nature in combination with sugars, as glycosides. Coumarins generally have, in addition, an oxygen atom, often as a hydroxy group at position7, as in umbelliferone. Often further hydroxy or metoxy groups are present, as in fraxetin isolated from the bark of ash. Osthol was islated from the roots of Augelica archangolica.

1.4.3.2. Classes: [14]

The coumarins can be roughly categorized as follows:

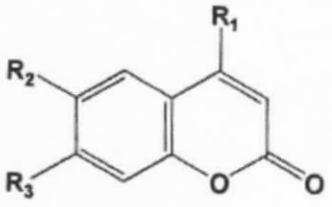
a. Simple Coumarins– these are the hydroxylated, alkoxylated and alkylated derivatives of the parent compound, coumarin, along with their glycosides.

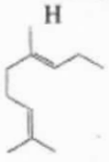
b. Furanocoumarins – these compounds consist of a five-membered furan ring attached to the coumarin nucleus, divided to linear and angular types with substituents at one or both of the remaining benzenoid positions.

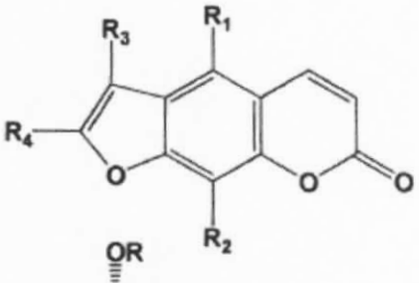
c. Pyranocoumarins – members of this group are analogous to the furanocoumarins, but contain a six-membered ring.

d. Coumarins Substituted in the Pyrone Ring.

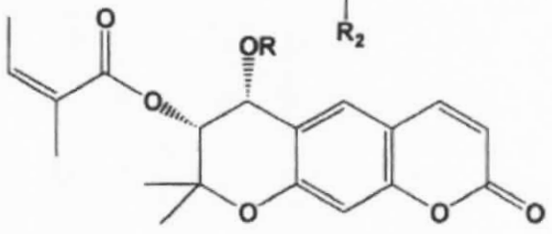
It has been shown that these simple compounds are derived in the plant from the cinnamic acid as a glucoside which cyclizes to give a coumarin.

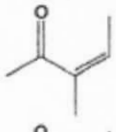
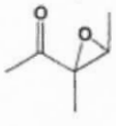


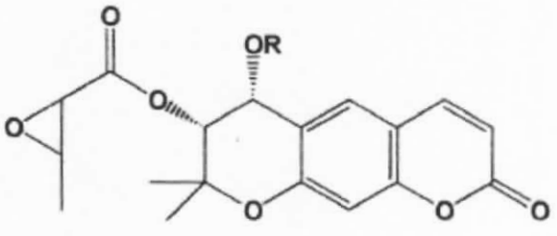
	R_1	R_2	R_3
Coumarin	H	H	H
Herniarin	H	H	O(
Methyl-umbelliferone	CH_3	H	O
Scopoletin	H	OCH_3	O
Umbelliferone	H	H	O
Ostruthin	H		O



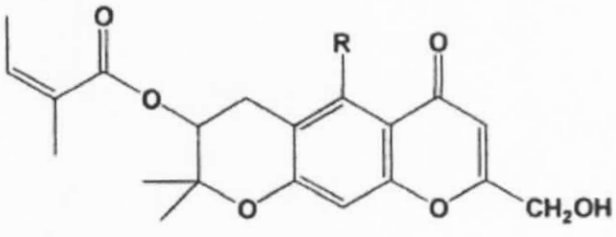
	R_1	R_2	R_3	R_4
Bergapten	OCH_3	H	H	H
Isopimpinellin	OCH_3	OCH_3	H	H
Peucedanin	H	H	OCH_3	CH(
Psoralen	H	H	H	H
Xanthotoxin	H	OCH_3	H	H



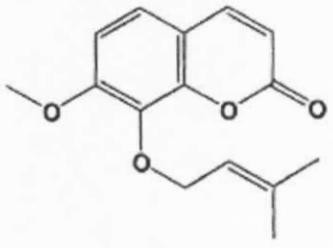
	R
Xanthalin	
Peuarenarin	



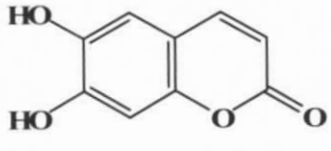
Peuarenin "



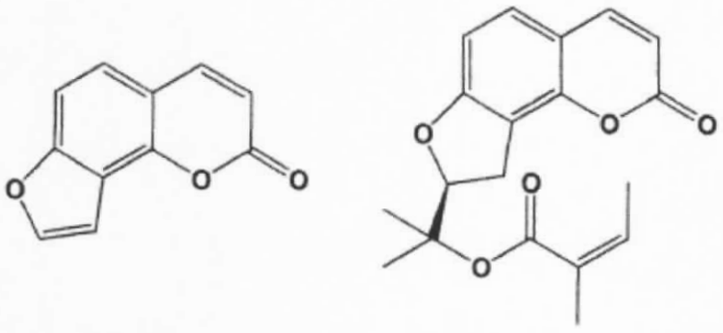
	R
Ledebouviellol	OH
2-Methylchromone derivative of ledebouviellol	OCH_3



Osthol



Esculetin



Angelicin Columbianadin

Chemical Structures of Some Coumarin Compounds

The primary site of synthesis of coumarins is suggested to be the young, actively growing leaves, with stems and roots playing a comparatively minor role.[14] However, one should not forget the possibility of species and compound variation, for example furanocoumarins in *Pastinaca sativa* are formed in the fruits where they also accumulate, and furanocoumarins in *Angelica archangelica* are formed in the leaves with the exception of osthenol, a simple coumarin, which is probably formed in the roots.

1.4.3.3. Botanical Aspects

Coumarins are found free or as heterosides in many dicotyledonous families, including the Apiaceae, Asteraceae, Fabiaceae, Moraceae, Rosaceae, Rubiaceae, Rutaceae, and Solanaceae.[15] Many monocotyledonous plants, especially the Gramineae and orchids, also contain large amounts of coumarins. Although mainly synthesized in the leaves, coumarins occur at the highest levels in the fruits, followed by the roots and stems. In addition, seasonal changes and environmental conditions may affect the occurrence in various parts of the plant. The distribution of biologically active coumarins in a wide range of plants seems to correlate with their ability to act as phytoalexins, *i.e.* they are formed as a response to traumatic injury, during the wilting process, by plant diseases or through drying, they accumulate on the surface of the leaves, fruits and seeds, and they inhibit the growth and sporulation of fungal plant pathogens and act as repellents against beetles and other terrestrial invertebrates.[15] Coumarins are leached from the roots of some plants, such as wild *Avena*, into the soil, where they provide a defence tool against hostile micro-organisms.

Coumarins are also active in plant metabolism, taking part in growth regulation.[15] In particular furanocoumarins are known to inhibit root tip growth and seem to induce

membrane disturbances, and their excretion on seed surfaces might be a means to delay germination.

1.4.3.4. Biological Effects of Plant Coumarins

Coumarins have a variety of bioactivities including anticoagulant, estrogenic, dermal photosensitising, antimicrobial, vasodilator, molluscacidal, antithelmintic, sedative and hypnotic.

Analgesic and hypothermic activity [16]

Anti-inflammatory activity, *in vitro*, *in vivo*[17]

Antifungal activity [18]

Antimalarial activity, *in vitro*, *in vivo*[19]

Antimicrobial activity [20]

Antitumor-promoting activity, *in vitro* [21]

Antiviral activity, *in vitro* [22]

Inhibition of blood coagulation [23]

Ability of absorbing UV light (used for skin diseases) [24]

1.4.4. Essential Oils

Monoterpenes together with sesquiterpenes and diterpenes form the majority of essential oils and are distributed in more than 2, 000 plant species belonging to some 60 families (Rutaceae; Myrtaceae; Umbellifereae; Labiatae; Compositae; Pinaceae). They are distributed in all plant parts: flowers (Bergamot); leaves (Citronella, Laurel); roots (Vetiver); rhizome (Ginger); wood (Sandalwood); bark (Cinnamon tree); fruit and seeds (Nutmeg).

1.4.5. Terpenes: [11, 12]

Terpenes history spans various civilizations. As they are largely found in essential oils, they were used in the Ancient Egypt for various religions aims. Camphor was introduced in Europe from the East by the Arabs around the 11th century.
The process of obtaining plant essential oils by fatty extraction was known by the early middle Ages. In the 12th century, Arnaud de Villanosa described distillation of oils from rosemary and sage. He made an "*oleum mirabile*" from oils of turpentine and rosemary. Analysis of oils of turpentine was made in 1818 by JJ Houston de la Billardière. Dumas determined the structure in 1866 and proposed the name terpene, derived from turpentine,

instead of camphor for crystalline oxygenated substances extracted from essential oils. In 1887 Wallach proposed an isoprene rule to distinguish the monoterpenes and the sesquiterpenes. The structure of camphor was established by Bredt in 1893, that of pinene by Wagner in 1894 and that of citral by Tiemann in 1895. β-carotene was isolated in 1837 by Wackenrodder from carrots, and in 1907 its correct molecular form was determined by Willstätter.

The period since 1945 has seen an extensive explosion in natural product chemistry due to the advent of chromatographic and spectroscopic techniques. Mevalonic acid was Shown in 1956 to be a biosynthetic precursor of cholesterol and later, its incorporation into a number of terpenoids has been demonstrated. Actually, an increasing number of terpenoids are described in the plant kingdom and many of them were shown to have important biological activities. Thus, several sesquiterpenes and diterpenes have antibiotic properties, some sesquiterpenes and diterpenes are insect and plant hormones, respectively.

At the last account there were some 11,000 structurally determined naturally occurring compounds: of these approximately 4,000 are primarily terpenoids in their biogenetic origin.

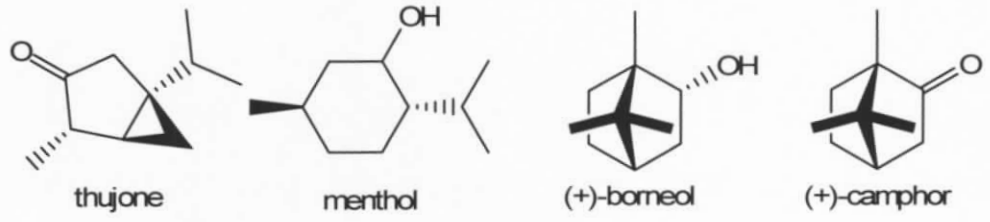
The terpenes have been classically identified through the recognition of an "isoprene" pattern in their skeletons. It is the number of these significant C5 units in the compound that has given rise to a simple primary classification system. The organization of the isoprenyl carbon skeleton within each primary class then gives rise to the various secondary classes. These are a little more arbitrary being selected skeletons which represent several naturally occurring compounds. Thus the terpenes have been classified primarily on their carbon number (C10, C15, etc.) and then on their carbon skeleton.

	Terpenes	Isoprene units	Carbon atoms
1	Monoterpenes	2	10
2	Sesquiterpenes	3	15
3	Diterpenes	4	20
4	Sesterpenes	5	25
5	Triterpenes	6	30
6	Carotenoids	8	40
7	Rubber	> 100	> 500

1.4.5.1. Monoterpenes: [25]

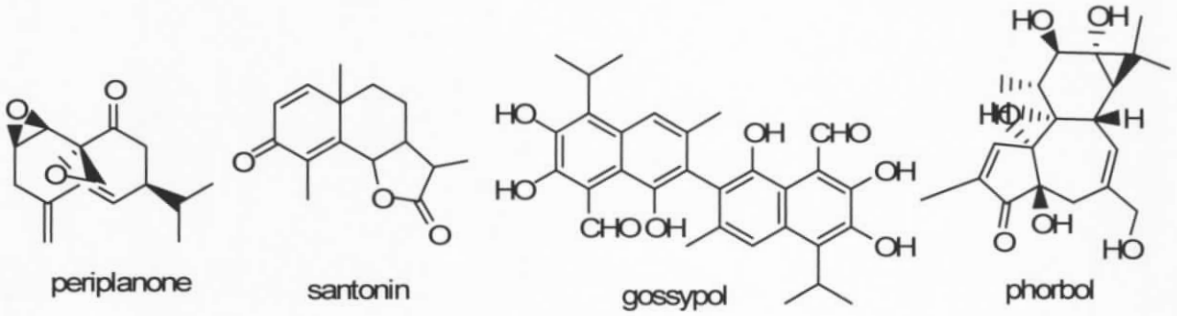
Monoterpenes contain two units of isoprene. Their contents in the plants vary with the family, the age, and the organ being treated. They exist mainly in Rutaceae, Lamiaceae and Myraceae.

Menthol, a monoterpene (10 carbons) isolated from various mints, is a topical pain reliever and antipuretic (relieves itching). Plants in the mint family have been used for medicinal purposes since before 2000 BC, but menthol was not isolated until 1771. Thujone, another monoterpene, is the toxic agent found in Artemisia absinthium (wormwood) from which the liqueur, absinthe, is made. Borneol and camphor are two common monoterpenes. Borneol, derived from pine oil, is used as a disinfectant and deodorant. Camphor is used as a counterirritant, anesthetic, expectorant, and antipruritic, among many other uses.



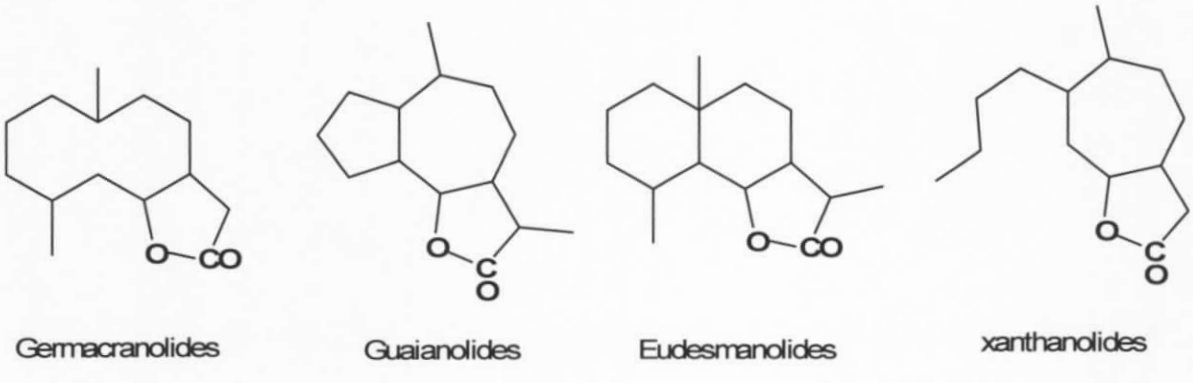
1.4.5.2. Sesquiterpenes

Sesquiterpenes are biogenetically derived from farensyl pyrophosphate and in structure may be linear, monocyclic, or bicyclic. They constitute a very large group of secondary metabolites, some having been shown to be stress compounds formed as a result of disease or injury. PeriplanoneB a sesquiterpene (15 carbons), is the female sex attractant of a species of cockroach. Another sesquiterpene, santonin, is also found in wormwood and is a photosensitizer. Gossypol is a dimeric sesquiterpene isolated from the seeds of cotton plants. It has been used clinically in China as a male contraceptive.



1.4.5.3. Sesquiterpene Lactones

Over 500 compounds of this group are known; they are particularly characteristics of the Compositae but do occur sporadically in other families. Not only have they proved to be of interest from chemical and chemotaxonomic viewpoints, but also possess many antitumor, anti-leukaemic, cytotoxic and antimicrobial activities. They can be responsible for skin allergies in humans and they can also act as insect feeding deterrents. Chemically the compounds can be classified according to their carboxylic skeletons; thus, from the germacranolides can be derived the guaianolides, pseudoguaianolides, eudesmanolides, eremophilanolides, xanthanolides, etc….



A structural feature of all these compounds, which appears to be associated with much of the biological activity, is the α,β-unsaturated-γ-lactone.

1.4.5.4. Diterpenes

Diterpenes occur in all plant families and consist of compounds having a C20 skeleton. There are about 2500 known diterpenes that belong to 20 major structural types. Plant hormones Gibberellins and phytol occurring as a sidechain on chlorophyll are diterpenic derivatives. The biosynthesis occurs in plastids and interestingly mixtures of monoterpenes and diterpenes are the major constituents of plant resins. In a similar manner to monoterpenes, diterpenes arise from metabolism of geranyl geranyl pyrophosphate (GGPP). Acyclic diterpenes, other than phytol, are not commonly accumulated, although small amounts do occur in a number of plants. Some of these compounds are kairomones and pheromonal substances for insects. Macrocyclic diterpenes are commonly isolated from gymnosperms. Examples are cembrene and its relatives. Among plants, the taxanes occur only in the gymnospermous family Taxaceae. Furthermore, diterpenes are also the major constituents of resins (Primaric acid from Pinus species). Complex derivatives of macrocyclic precursors, the co-carcinogenic diterpenes, occur in two plant families, the Euphorbiaceae and the Thymelaeaceae. Many of these compounds are extremely caustic. They are not carcinogenic, but when an animal is exposed to co-carcinogens and later to carcinogens, the activity of the latter is enhanced. The caustic properties and co-carcinogenicity are not directly linked. Diterpenes have limited therapeutical importance and are used in certain sedatives (coughs) as well as in antispasmodics and antoxiolytics.

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a-Diterpenic Plants of Potential Interest

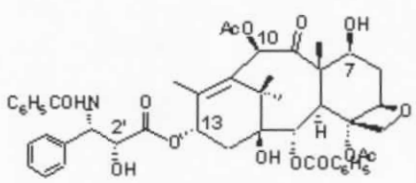
• (Taxus baccata L.):

Taxol:

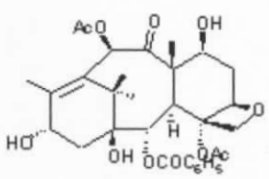
One of the most well known medicinally valuable terpenes is the diterpene, taxol. Taxol was first isolated from the bark of the Pacific yew, Taxus brevifolia, in the early 1960's, but it was not until the late 1980's that its value as an anticancer drug was determined. It acts to stabilize the mitotic apparatus in cells, causing them to act as normal cells rather than undergo rapid proliferation as they do in cancer.

There has been a great deal of interest in taxol from the standpoint of understanding what pieces of the compound are required for activity. These structure-activity relationships have been determined by isolating or synthesizing homologues and derivatives of taxol and testing these compounds for their anti-cancer activity in various cell culture and in vivo screens. If the side chain ester was removed to give baccatin III, activity was lost. If different N-acyl groups were present on the side chain, activity was maintained. If the 2' - OH on the side chain was converted to another group, activity was reduced unless the group could be hydrolyzed in vivo. The stereochemistry at C - 7 has no effect on the activity, nor is C – 10 acylation critical. The oxetane ring must be present.

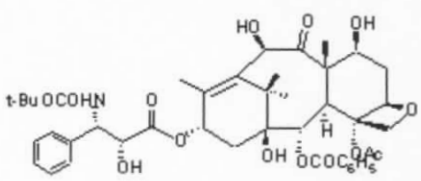
Since one of the major problems with taxol, as with many other natural products used as drugs, is solubility in aqueous systems, much effort has been devoted to finding a more soluble form. Taxotère (docetaxel) was prepared by the French firm, Rhone-Poulenc, and has similar activity to taxol (paclitaxel), but slightly better solubility. Other researchers have tried to add a group to the 2' – OH, which would increase the solubility and then be removed in vivo. These are mostly esters with a salt incorporated to increase the water solubility. Other investigators have modified the C – 13 side chain ester and added functionality at C-14 to increase the oral bioavailability. These modified taxoids are still at early stages of testing, but illustrate the principles of development of secondgeneration drugs.



taxol



baccatin III



taxotere

b. Acyclic and Related Diterpenoids

Geranylgeraniol and some oxygenated derivatives have been obtained [26] from the brown alga *Bifurcaria bifurcata*. Miriamin **1** has been identified [27] as a defensive diterpenoid produced by the eggs of a land slug of the *Arion* species. It has been shown to provide antifeedant protective action against predation by various species of beetle. The meroterpenoid chrysochlamic acid **2** from *Chrysochlamys ulei* has been reported [28] to inhibit DNA polymerase β. The antifungal agent, methoxybifuracerenone **3**, which was previously reported as a constituent of *Cystoseira amentacea*, has been isolated [29] from *C. tamariscifolia*.

c. Bicyclic Diterpenoids

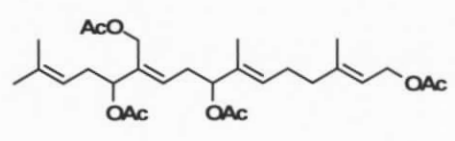
- Labdanes

The dinorlabdane **4** has been found [30] in Copaiba oil. The triene, juniperexcelsic acid **5**, has been shown[31] to be a cytotoxic constituent of the berries of *Juniperus excelsa*. The furanolabdadienoic acid **6** was amongst the diterpenoid constituents of *Baccharis pingraea*.[32] Further investigations of *Vitex rotundifolia* have afforded[33] the spiro-ether **7**. Labdanes have continued to be obtained from *Croton* species including *Croton oblongifolius*.[34] Crotonadiol **8** was isolated [35] from the stems of *C. zambesicus*. The highly oxygenated 6,7-secolabdane, 2β-hydroxysaudinolide **9**, was obtained [36] from *Clutia richardiana*. A number of bis-diterpenoids have been reported including moldenin **10** from *Moldenhawera nutans*.[37] Further studies on the excoecarins from the wood of *Excoecaria agalocha* have been reported.[38]

Studies on the partial synthesis of labdanes have included the synthesis of limonidilactone **11** from zamuranic acid.[39]

- Clerodanes

The full ^{1}H and ^{13}C NMR assignments for stephalic acid **12** have been reported.[40] Conyzalactone **13** has been obtained [41] from *Conyza blinii*. Examination of the Mexican plant *Onoseris alata* has afforded[42] some derivatives of **14**. Further investigations of *Teucrium polium*, which has been used in Turkish folk medicine for the treatment of stomach complaints, has yielded [43] teululinA **15**. ClerodendrinI **16**, which is a feeding stimulant for the turnip sawfly, has been isolated [44] from *Clerodendron trichotomum*. The insect antifeedant activity of scutecyprol B, obtained from *Scutelaria rubicunda* and of some other compounds derived by modification of fruticolone and scutelagin B, has been examined.[45,46]



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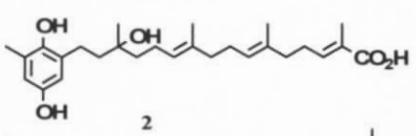

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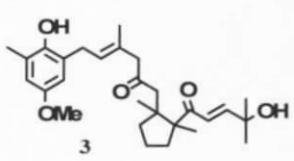

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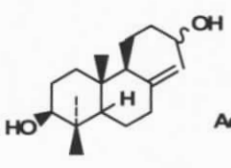

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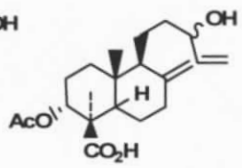

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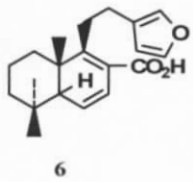

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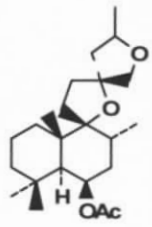

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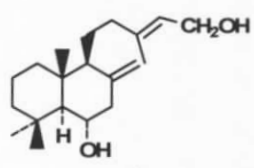

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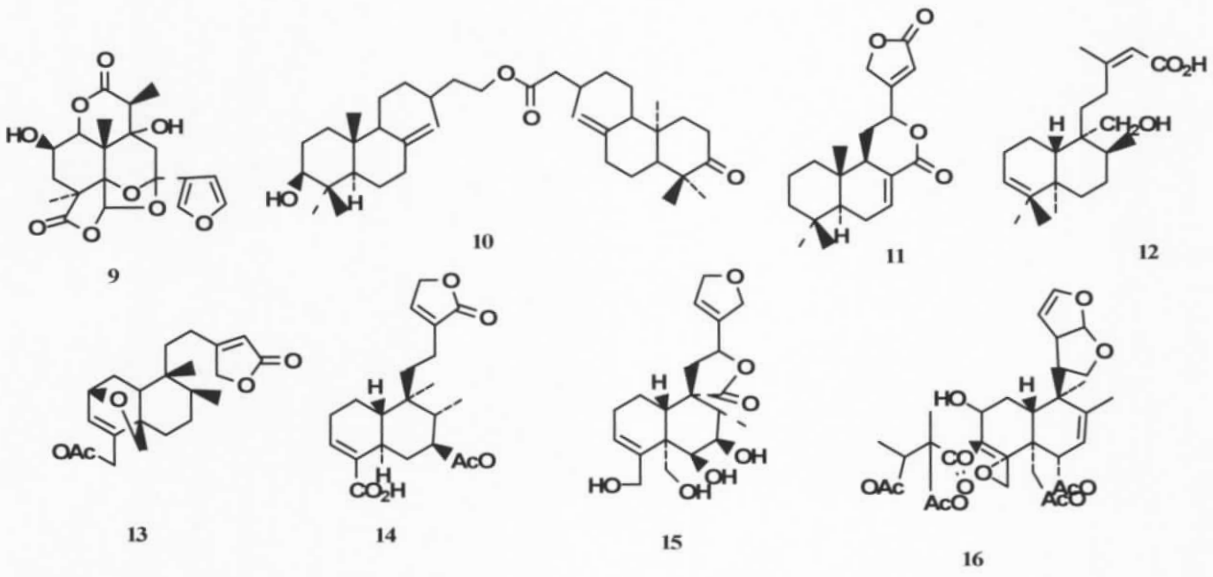
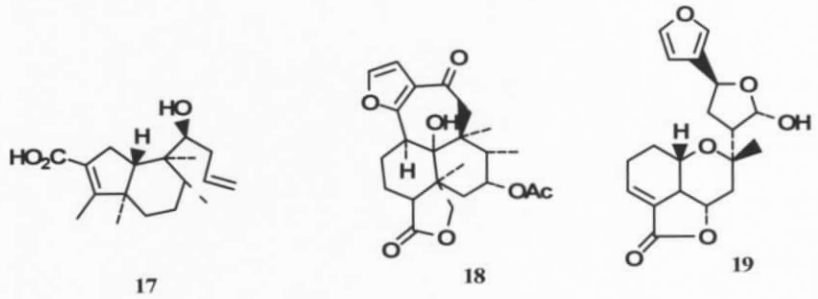


9 10 11 12

13 14 15 16

A rearranged (4→2)-*abeo*-clerodane **17** has been obtained [47] from *Aristolochia chamissonis*. The *cis* languidulane carbon skeleton of salvimexicanolide **18**, isolated from *Salvia mexicana*, may be derived from a clerodane.[48] JamesoniellideH **19** is a seco-clerodane which was obtained [49] from axenic cultures of the liverwort *Jamesoniella autumnalis*. Other *cis* clerodanes were isolated from the liverwort, *Scapania nemorea*.

The photochemical transformation of clerodanes including fruticolone has been examined.[49] The structures of the products has led to the suggestion that some clerodanes may be photochemical artefacts. The photoxidation of the furan ring of hardwickiic acid to form a butenolide has been used in the clarification of the structure of some clerodanes.

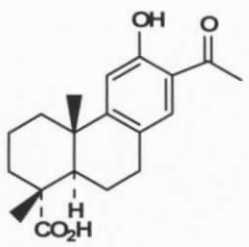


17 18 19

d. Tricyclic Diterpenoids

11α-Hydroxyabietadiene has been obtained [50] from *Cryptomeria japonica* (sugi). The structure **20** has been assigned [51] to gaultheric acid which was isolated from the roots of

Gaultheria yunnanensis. A study [52] of the immunosuppressive constituents of *Tripterygium wilfordii* led to the isolation of triptobenzene L **21** whilst the cyclic peroxide **22** was obtained [53] from the heartwood.



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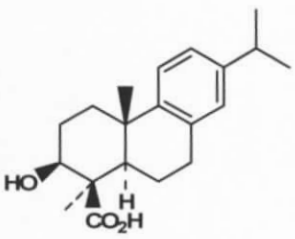

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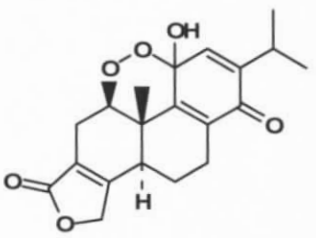
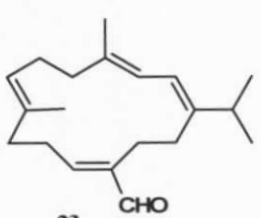


22

e. Macrocyclic Diterpenoids and their Cyclization Products

Further investigation of *Croton oblongifolius* has led[54] to the isolation of neocrotocembranal **23**. The number of cembranes that have been obtained from marine organisms continues to rise. Cembranes that have been described include sartol acetate B **24** from a *Sarcophyton* species,[55] brassicolide **25** from the coral, *Nephthea brassica*,[56]sethukarailin **26** from *Sinularia maxima*,[57]and further cembranolides from *Pseudopterogorgia bipinnata*.[58]



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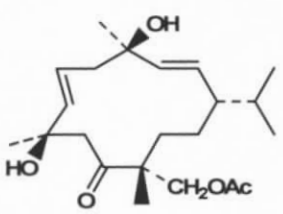

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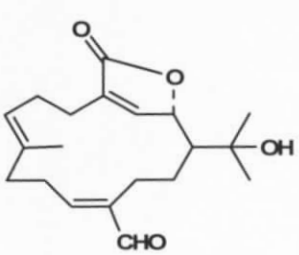

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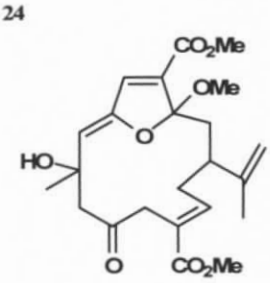
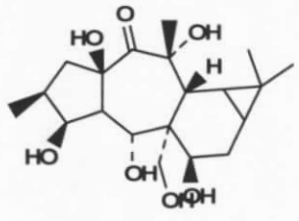


26

Investigations of the latex of the Euphorbiaceae have continued to yield diterpenes with the lathyrane, jatrophane, and phorbol skeleta. These include euforboetol **28** which was isolated as its 3,5,17-triacetate from the irritant latex of a Portugese collection of *Euphorbia boetica*,[59] some further jatrophanes from *E. peplus*,[60] ingol esters from *E. lactea*,[61] lathyranes from *E. lathyris*,[62] and tumour promoting ingenol esters (milliamines) from *E. leuconeura*.[63] The latter is a succulent plant which is sometimes used as an indoor decorative plant. Maprouneacin **29** is a daphnane with antihyperglycemic activity which was isolated [64] from *Maprounea africana*.



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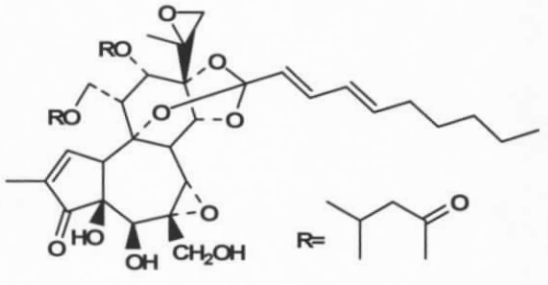


29

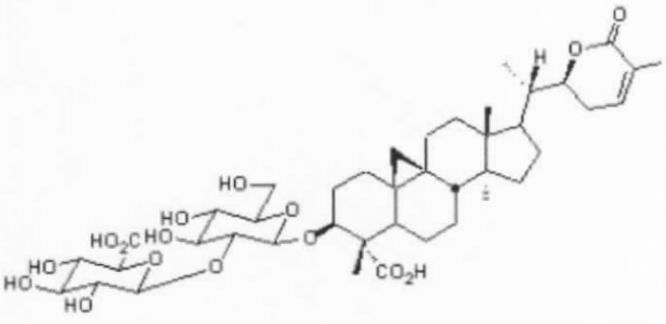
There are in excess of 1000 monoterpenes, more than 7000 sesquiterpenes and more than 3000 diterpenes.[65, 66]

1.4.5.5. Triterpenes and Steroids

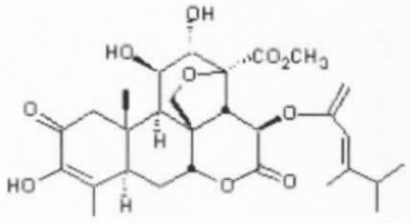
Triterpenes contain 30 carbons, derived essentially from coupling of two sesquiterpene precursors. Many of these compounds occur in plants as glycosides, often called saponins (molecules made up of sugars linked to steroids or tripterpenes) due to their ability to make aqueous solutions appear foamy. Arbruside E, for example, comes from a plant called *Arbrus precatorius* which has been used as an abortifacient and purgative. Arbruside E, however, appears to be relatively non-toxic, and is 30-100 times sweeter than sucrose, making it a potential sugar substitute. Triterpenes of the quassinoid class, such as bruceantin, have been shown to have significant antineoplastic activity in animal systems and have been investigated for the treatment of cancers.

Steroids are modified triterpenes. They are probably most familiar from their role as hormones, *i.e.,* androgens such as testosterone and estrogens such as progesterone. Steroids,

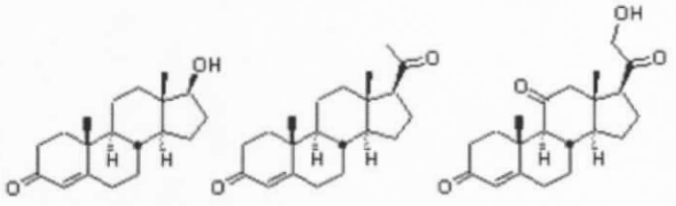
such as cortisone, are most often used as anti-inflammatory agents, but many have other uses such as in birth control pills. Prior to 1943, most steroids were obtained from natural sources.



Arbruside E



bruceantin



testosterone progesterone cortisone

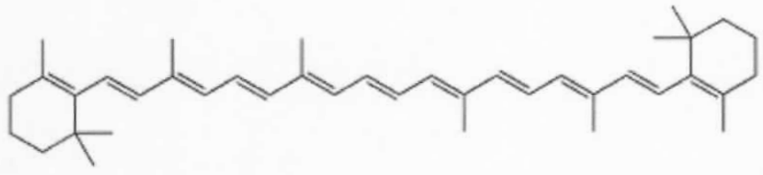
For example, progesterone could only be isolated in quantities of 20 mg from 625 kg of pig ovaries. The large numbers of commercially and medicinally valuable steroids available today have been made possible by the semi-synthetic preparation of progesterone from diosgenin.

1.4.5.6. Tetraterpenes

Important among these are the C40 yellow or orange-red Carotenoid pigments, of which about 180 have been reported. Carotene was isolated from carrots as early as 1831. Between 1913 and 1915, the existence of a fat-soluble growth factor, now known as Vitamin A, was proved by feeding experiments to be present in materials such as butter or cod-liver oil.

Carotenes $C_{40}H_{56}$:

Carotenes in association with chlorophyll participate in photosynthesis, but also occur in other plant organs as the carrot.



β-carotenoid

They have vitamin A activity. The colors of the red tomato and the orange are due to the carotenoids lycopene and citraurin, respectively. Because the carotenes are non-toxic, they are used as colorants in the formulation of tablets and in the food industry. Some carotenoids are oxygenated derivatives.

The carotenoids are probably the widely distributed group of colorants in nature. In addition to the natural carotenoids, many others have been synthesized. Both types are generally more expensive than the synthetic azodyes. The colors possible are also limited, generally to yellows and oranges. Carotenoid colors tend to be relatively stable, in that they retain their coloring ability throughout a normal shelf life, but do degrade through oxidation. Loss of color as they degrade can be offset by increasing the concentration used. Carotenoids are not corrosive and are not usually affected by reducing agents such as ascorbic acid.

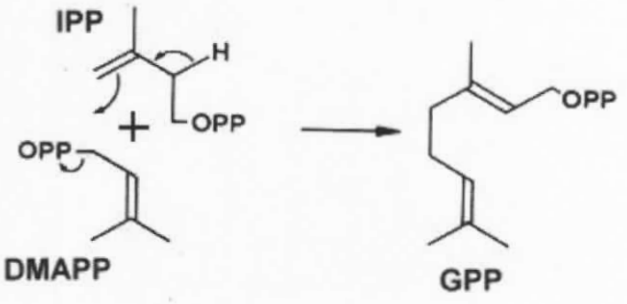
1.4.5.7. Polyterpenes $[C_5H_8]_n$

Polyterpenes are composed of many isoprene units. Common examples, both having macromolecules of molecular weight over 100 000, are found in indiarubber and guttapercha. Doubtless, the rubber-like substances of many other plants have similar composition. Chemically, pure rubber is cis-1,4-polyisoprene $(C_5H_8)n$, although in the natural state other materials are present. Its occurrence is confined to the dicotyledons, and the one important commercial source is Hevea brasiliensis. Gutta-percha is trans-1,4-polyisoprene, and chile, obtained from Achras sapota, contains a mixture of low molecular weight cis- and transpolyisoprenes.

No biological function for polyisoprenes has yet been discovered.

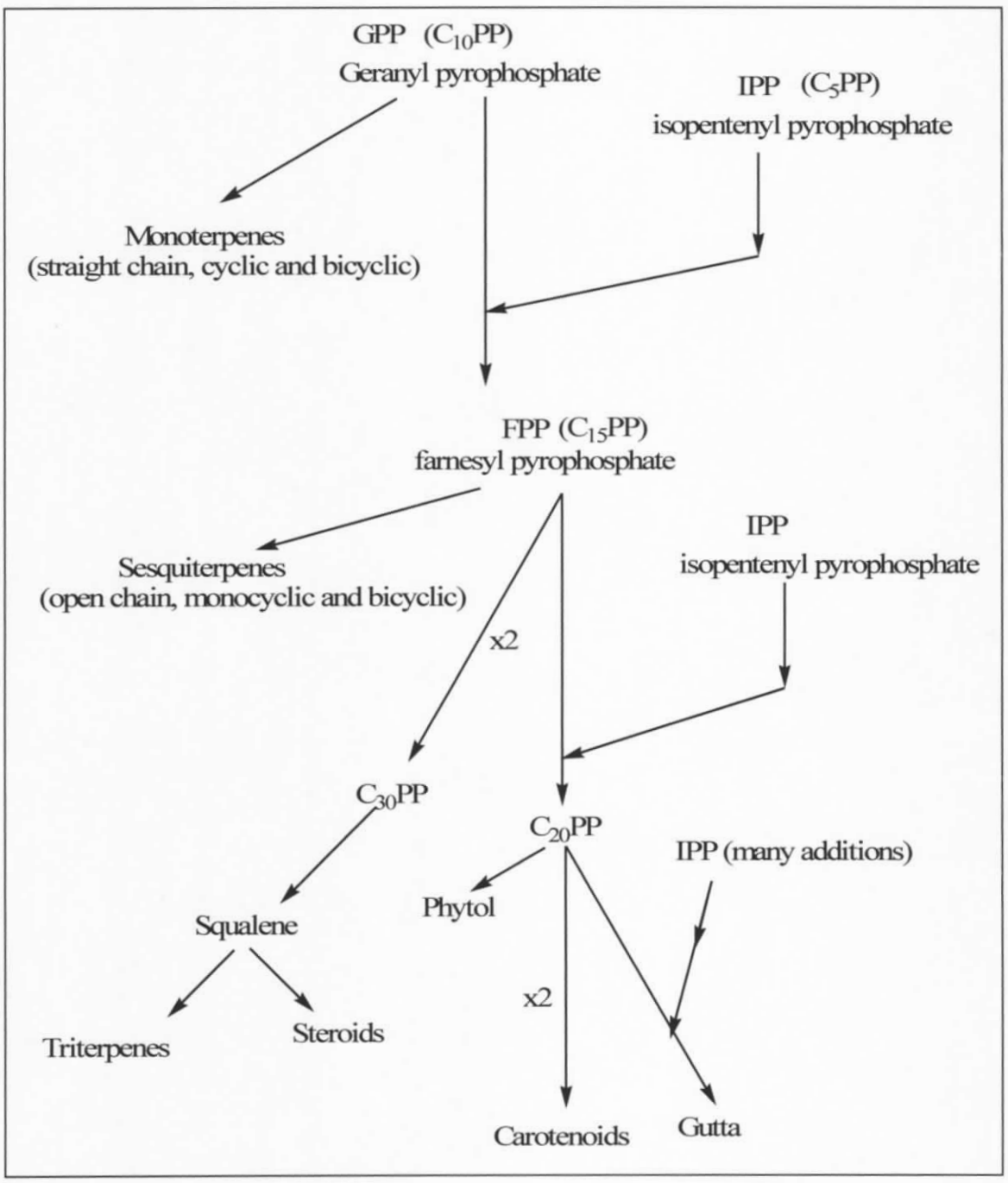
1.4.5.8. Terpenes Biosynthesis

Terpenoids are extraordinarily diverse but they all originate through the condensation of the universal phosphorylated derivative of hemiterpene, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) giving geranyl pyrophosphate (GPP).



In higher plants, IPP is derived from the classic mevalonic acid pathway in the cytosol but from the methylerythritol phosphate pathway in plastids. It is generally accepted that the cytosolic pool of IPP serves as a precursor of sesquiterpenes and triterpenes, whereas the plastid pool of IPP provides the precursors of mono-, di- and tetraterpenes. [66] Some exceptions have been described showing that interactions between the two biosynthetic pathways may exist. [67]

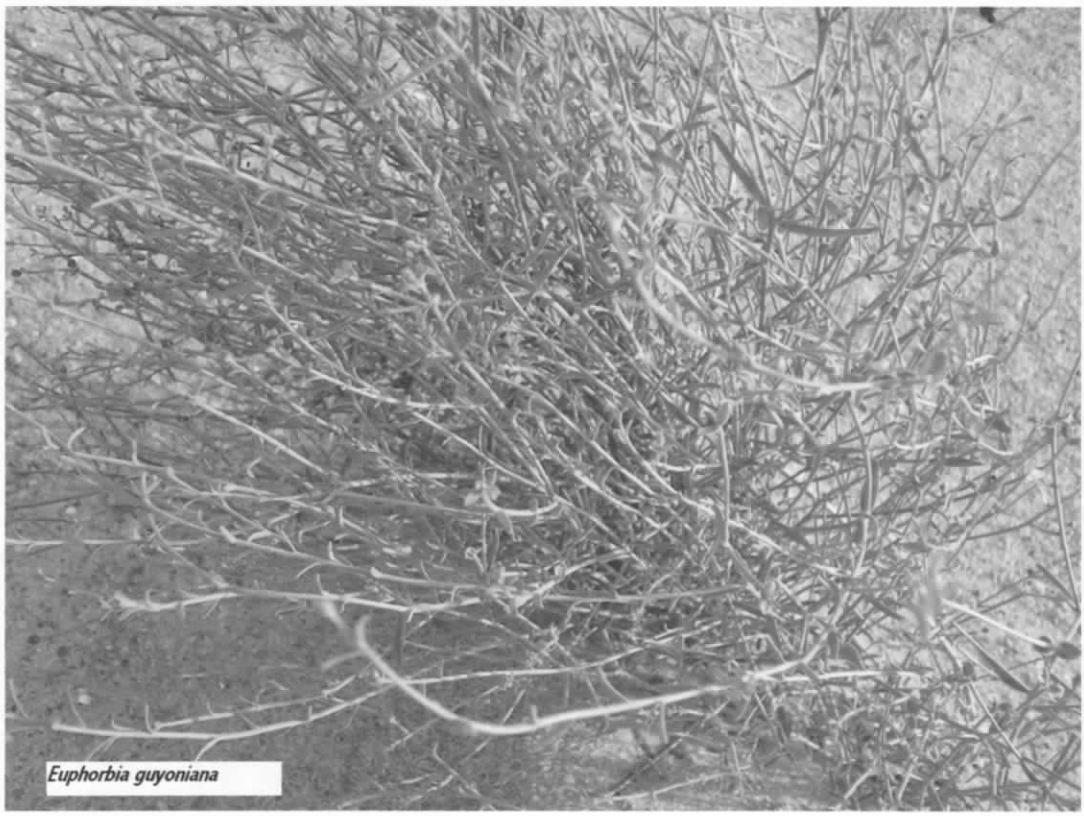
Biosynthesis of Terpenes



Chapter Two

Plant Description and Medical Use

2.1. *Euphorbia guyoniana*



2.1.1. Family Description:

The Spurge family (Euphorbiaceae) [68-70] is a large family of flowering plants with 240 genera and around 6,000 species. Most are herbs, but some, especially in the tropics, are also shrubs or trees. Some are succulent and resemble cacti.

This family occurs mainly in the tropics, with the majority of the species in the Indo-Malayan region and tropical America a good second. There is a large variety in tropical Africa, but it is not as abundant or varied as in the two tropical regions. However, *Euphorbia* also has many species in non-tropical areas such as the Mediterranean, the Middle East, South Africa, and southern USA. The leaves are alternate, seldom opposite, with stipules. They are mainly simple, but where compound, are always palmate, never pinnate. Stipules may be reduced to hairs, glands, or spines.

The radially symmetrical flowers are unisexual, with the male and the female flowers usually occurring on the same plant. As can be expected from such a large family, there is a wide variety in the structure of the flowers. They can be monoecious or dioecious. The stamens (the male organs) can number from 1 to 10 (or even more). The female flowers are hypogynous, that is, with a superior ovary.

The genera, *Euphorbia* and *Chamaesyce*, show a highly specialized form of inflorescence called a **cyathium**. This is usually a small cup-like involucre consisting of peripheral horseshoe-shaped nectaries surrounding a ring of male flowers, each a single stamen. In the middle of the cyathium stands a female flower: a single pistil with branched stigmas. This whole arrangement resembles a single flower.

The fruit is usually a schizocarp, sometimes a drupe. A typical schizocarp is the **regma**, a capsular fruit with three or more cells, each of which splits open at maturity into separate parts and then breaks away explosively, scattering the small seeds.

Many members of the euphorbia family, including the genus ***Euphorbia***, contain a poisonous milky-latex sap. The toxin is a mixture of diterpene esters, and contact with the skin may cause inflammation and a blistering rash.

2.1.2. *Euphorbia guyoniana:*

Euphorbia guyoniana presents dressed, nonfleshy stems and alternate leaves. The seeds are without caruncle, and provided with grey longitudinal ribs; round cyathe glands, without point. It is a powerful plant, from 3 to 10 dm with dressed, and branched out stems, narrow

leaves, often absent on the flowered branches. It is encountered in the dunes and sandy rocks in all the predesertic area of the septentrional Sahara.

2.1.3. Classification:

Euphorbia guyoniana

Kingdom	*Plantae* – Plants
Subkingdom	*Tracheobionta* – Vascular plants
Superdivision	*Spermatophyta* – Seed plants
Division	*Magnoliophyta* – Flowering plants
Class	*Magnoliopsida* – Dicotyledons
Subclass	*Rosidae* –
Order	*Euphorbiales* –
Family	*Euphorbiaceae* – Spurge family
Genus	*Euphorbia* L. – spurge
Species	*Euphorbia guyoniana*

2.1.4. *Euphorbia* Reported Medical Activities:

A variety of inconclusive reports on the therapeutic potential effects of the sap of these plants have been published along with reports of tumor promotion and skin and ocular irritation. The most intensively studied species of this group is *Euphorbia pilulifera* L.

A recent report describes selective cytotoxicity of a number of tiglilane diterpene esters from the latex of *Euphorbia poisonii*, a highly toxic plant found in Northern Nigeria, which is used as a garden pesticide. One of these compounds has been reported to have a selective cytotoxicity for the human kidney carcinoma cell line A-498 more than 10,000 times greater than that of Adriamycin .[71]

There are isolated reports of anti-cancer activity of various *Euphorbia* preparations[71] On the other hand, compounds present in at least one *Euphorbia* species were reported to be carcinogenic [72] one species has a skin-irritant and tumourpromoting effect [73]and another species reduces EBV-specific cellular immunity in patients with Burkitt's lymphoma. [74]

The crude latex of Crown-of-Thorns (*Euphorbia milii* var. *hislopii*) is a potent plant molluscicide and a promising alternative to the synthetic molluscicides used in schistosomiasis control.[75]

Euphorbia tirucalli has been used for many purposes: [76-80]

Africa

for parasites, sexual impotence, snakebite, syphilis, tumors.

Asia

for broken bones, hemorrhoids, pain, swellings, ulceration.

Brazil

for abscess, asthma, bacterial infections, cancer, constipation, fungal infections, rheumatism, scorpion bite, snakebite, spasms, syphilis, tumor, viruses, warts, and as an expectorant, and irritant.

Dutch Indies

for bone aches, hemorrhoids, leprosy, nose ulcers, paralysis, thorns.

India

for abscess, asthma, colic, constipation, cough, earache, gastralgia, neuralgia, rheumatism, syphilis, toothache, warts.

Peru

for abscesses, asthma, cancer, colic, cough, earache, neuralgia, rheumatism, stomachache, toothache.

Euphorbia hirta has traditionally been used in Asia to treat bronchitic asthma and laryngeal spasm, though in modern herbalism it is more used in the treatment of intestinal amoebic dysentery. It should not be used without expert guidance, however, since large doses cause gastro-intestinal irritation, nausea and vomiting.[81] The plant is anodyne, antipruritic, carminative, depurative, diuretic, febrifuge, galactogogue, purgative and vermifuge.The aerial parts of the plant are harvested when in flower during the summer and can be dried for later use.[82] The stem, taken internally, is famed as a treatment for asthma, bronchitis, and various other lung complaints. [82-84] The herb relaxes the bronchioles but apparently depresses the heart and general respiration.[84] It is usually used in combination with other anti-asthma herbs such as Grindelia camporum and Lobelia inflata. It is also used to treat intestinal amoebic dysentery.[85] The whole plant is decocted and used in the treatment of athlete's foot, dysentery, enteritis and skin conditions[82]. It has been used in the treatment of syphilis.[86] The sap is applied to warts in order to destroy them. [82, 84] The treatment needs to be repeated 2-3 times a day over a period of several weeks to be fully effective.

Euphorbia corollata is used by Native Americans for many medical purposes including, treating skin infections externally, and gonorrhea internally, it should probably be avoided as the plant is a powerful purgative and the juice may irritate the skin.[87]

Euphorbia quadrangularis pax arial parts are used for general body weakness and skin desease [88].

Euphorbia abyssinica

In Central Africa, the plant has been used as a caustic on skin lesions [89].

Euphorbia acaulis

The plant is irritant and the latex has been used for its mild irritant effect in the treatment of chronic eczema [90].

Euphorbia candelabrum

The sap is very irritating to the human eye, producing intense pain and temporary blindness.[89]

Euphorbia caput medusae

The latex is said to be highly acrid and irritant. [89]

Euphorbia esculenta

This plant and also *Euphorbia hamata* Sweet is used as cattle fodder suggesting that they are not strongly irritant.[89]

Euphorbia gaudichaudii

This species is among spurges that can cause an acute dermatitis on contact with their sap or latex. [91]

Euphorbia genistoides

This species is irritant to the skin of sheep. [89]

Euphorbia gorgonis

The latex is applied as an aid to the removal of warts and other skin eruptions. It is also used as a styptic. [89]

Euphorbia grandidens

The latex of this thorny succulent species is thought to be irritant and possibly capable of causing blindness. [89]

Euphorbia grantii

The plant is a powerful purgative. [89]

Euphorbia heterophylla

The latex of the plant is used as an antidote for the irritation produced by other species of Euphorbia .[89]

Euphorbia venenata

This thorny succulent species can produce severe inflammation of the mucosae. [89]

Euphorbia virosa

The latex of this species is said to be irritant and virulently poisonous. [89]

Euphorbia abyssinica

This plant is considered poisonous and has been used for homicidal purposes. In central Africa the latex is used as a purgative and as a caustic on skin lesions. On the other hand neither the latex nor the watery extract from it is toxic to guinea pigs when given by mouth.[89]

Euphorbia antisyphilitica

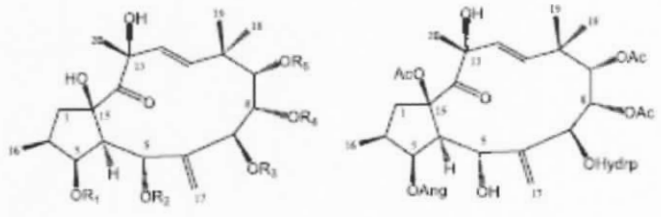
A wax called Candelila is made from this *Euphorbia.* It is used in leather polishes and for waterproofing certain products. Mixed with rubber it is used for insulation, dental mouldings and is also used in sealing wax, metal lacquers, paint removers, and lithographic colors. Mixed in paraffin it is used to make candles. It is not surprising therefore that the latex can cause skin problems.[92]

Euphorbia cooperi

The latex is so irritant that a slight smear on the face or tender skin produces a blister within a short period. The latex is irritant to the eye and may result in blindness. If a person stands close to a bleeding plant, inhalation of the air from the neighborhood produces a burning sensation in the throat. Some Africans use the latex to poison fish. Apparently the fish rise, paralyzed but still breathing. They can then easily be caught and eaten with impunity. [92]

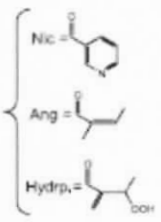
2.1.5. Chemical Review of *Euphorbia*

Gabriella Corea *et al* (2005) isolated twelve new 13 *a*-OH jatrophane diterpenes from *Euphorbia amygdaloides L.*[93]

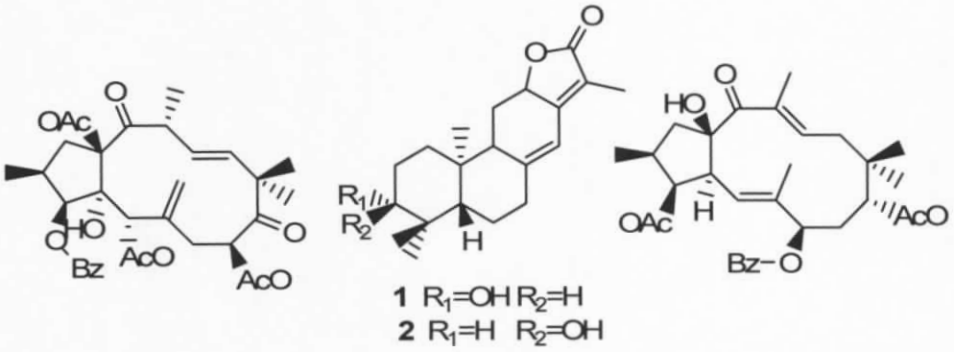


6

	R_1	R_2	R_3	R_4	R_5
1	Ac	Ac	Ang	Ang	Nic
2	Ang	H	Ang	Ac	Nic
3	Hydrp.	H	Ang	Ac	Nic
4	Ang	H	Ang	Ac	Ac
5	Ang	H	Hydrp.	Ac	Ac
7	Ang	Ac	H	Hydrp.	Ac
8	Hydrp	Ac	H	Ang	Ac
9	Ac	Hydrp.	H	Ang	Ac
10	Hydrp.	Ac	Ang	H	Ac
11	Ac	Hydrp	Ang	H	Ac
12	Ang	Ac	Hydrp.	H	Ac



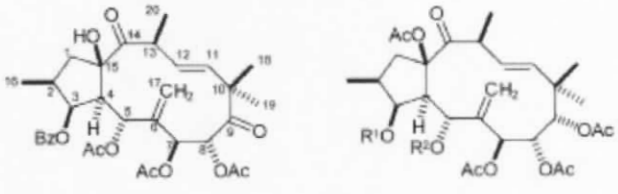
Claudia Valente, *et al* (2004) investigated a new jatrophane diterpene, pubescenol (**1**), known *ent*-abietane lactones, helioscopinolide A (**2**) and B (**3**), and taraxerone, 24-methylenecycloartanol, and vanillin have been isolated from *Euphorbia pubescens*.[94]



1 R_1=OH R_2=H
2 R_1=H R_2=OH

1 **2** **3**

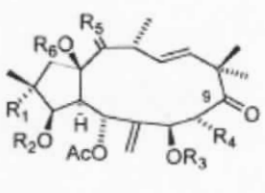
Judit Hohmann, *et al* (2003) isolated from the dried aerial parts of *Euphorbia mongolica* three new acylated polyhydroxy diterpenoids based on the jatrophane framework.[95]



1

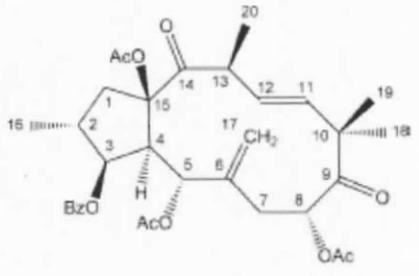
	R^1	R^2
2	Bz	Ac
3	Ac	Bz

G. Appendino, *et al* (2002) studied the aerial parts of *Euphorbia hyberna* subsp. *insularis* from Sardinia which are found to contain large amounts of macrocyclic diterpenoids of the jatrophane type .[96]



	R_1	R_2	R_3	R_4	R_5	R_6
1a	H	Bz	Ac	H	βH, α-OAc	H
1b	H	Bz	Ac	O*i*Bu	βH, α-OAc	H
1c	H	Bz	Ac	OAc	βH, α-OAc	H
1d	H	Bz	Ac	OH	βH, α-OH	H
1e	H	Bz	Ac	OAc	βH, α-OH	H
1f	OAc	Ac	Ac	H	= O	Ac
1g	ONic	Ac	Ac	OAc	= O	Ac
1h	OAc	Ac	i-Bu	OAc	=O	Ac

Ana Margarida V.D. Ferreira, *et al* (2002) isolated a new diterpene tetraester, from the jatrophane family, and two new diterpene triesters, with a lathyrane skeleton, from the chloroform extract of the roots of *Euphorbia hyberna L.*[97]



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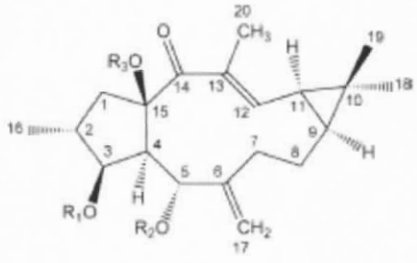
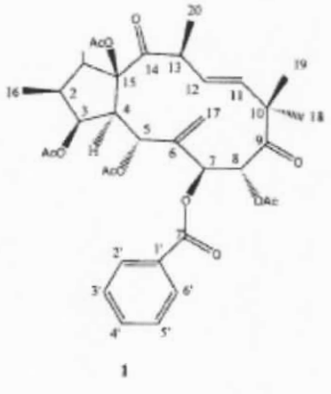


	R_1	R_2	R_3
2	Bz	Ac	Ac
3	Ac	Ac	Ac

Li Gen Liu and Ren Xiang Tan (2001) reported the isolation of five new (**1-5**) and one known (**6**) jatrophane diterpenoid esters from the ethanol extract of the whole herb of *Euphorbia turczaninowii.* [98]



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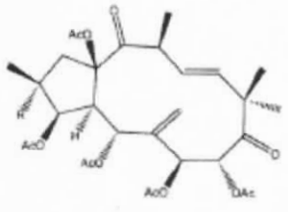
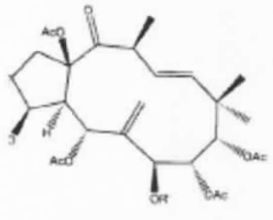
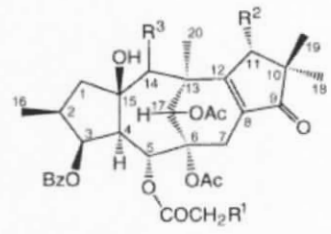


2 R = H
6 R = OBz

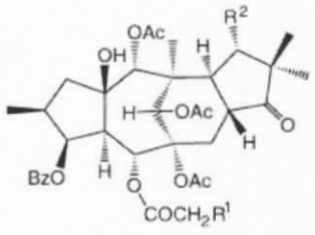


3 R = OAc R' = Bz
4 R = H R' = Bz
5 R = OBz R' = OAc

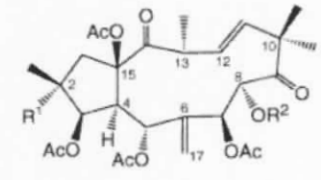
Samir A.M. Abdelgaleil *et al* (2001) isolated two segatane diterpenoids containing a bicyclic [4,3,1] ring system, together with 11 known diterpenoids, four segatanes, five jatrophanes and two paralianes, from the aerial parts of *Euphorbia paralias.*[99]



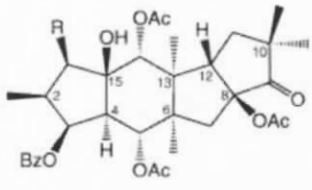
	1	2
R^1	H	OAc
R^2	OAc	H
R^3	β-OAc	α-OAc



	3	4	5	6
R^1	H	OAc	OAc	OH
R^2	OAc	H	OAc	H

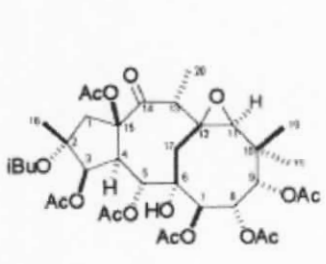


	7	8	9	10	11
R^1	OAc	OAc	H	OAc	OAc
R^2	iBu	Ang	iBu	MeBu	Bz

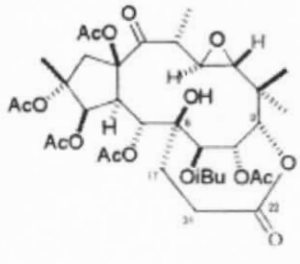


	12	13
R	OAc	H

Judit Hohmann, *et al* (2001) isolated two new diterpenes (**1** and **2**) from a dichloromethane extract of fresh, whole plants of *Euphorbia salicifolia*: salicifoline (**1**) is the first representative of a new type of tricyclic diterpenes involving a novel 5-8-8 fused ring system, and salicinolide (**2**) is a bishomoditerpene lactone based on the jatrophane skeleton.[100]

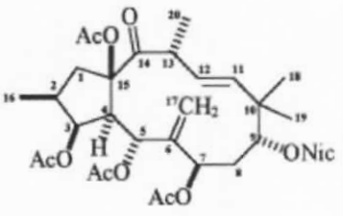


1

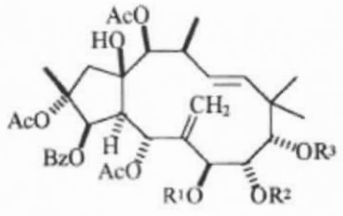


2

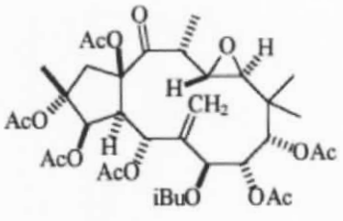
J. Hohmann, *et al* (1999) reported that the pro-inflammatory active extract of *Euphorbia peplus* afforded new diterpene polyester (1) based on the jatrophane skeleton together with the known compounds **2-5**. The irritant activities of some jatrophane diterpenes **(2, 3 and 6-9)** were also investigated. [101]



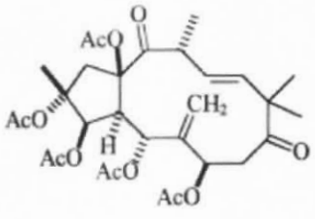
1



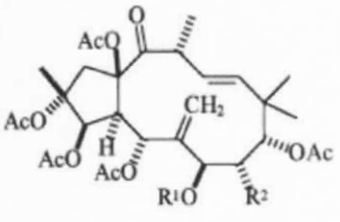
	R^1	R^2	R^3
2	iBu	H	Nic
3	Ac	Ac	Ac
4	iBu	H	Ac
5	Ac	H	Nic



6

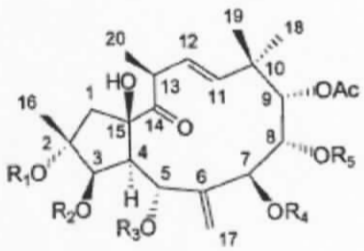


7

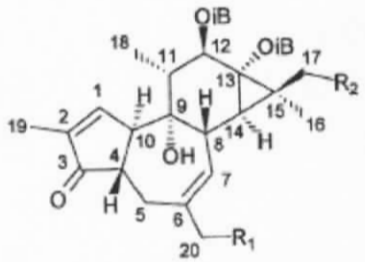


	R^1	R^2
8	Ac	H
9	iBu	OAc

J. Alberto Marco, *et al* (1999) reported that the latex of *Euphorbia obtusifolia* yielded twelve new diterpene polyesters. Seven of them displayed the jatrophane framework and five were 4-deoxyphorbol esters. A further isolated tigliane diterpene, a derivative of 4-epi-4-deoxyphorbol, was most likely an artifact of the isolation procedure.[102]



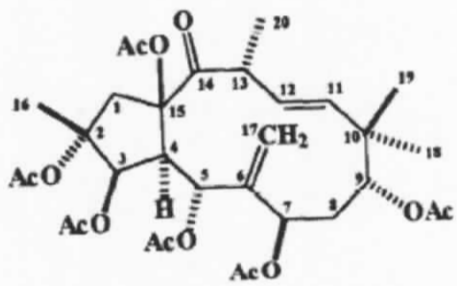
	R_1	R_2	R_3	R_4	R_5
1	MB	H	MB	Ac	Ac
2	iB	H	MB	Ac	Ac
3	Nic	H	MB	Ac	Ac
4	MB	H	MB	iB	Ac
5	Ac	H	MB	iB	Ac
6	MB	MB	H	Ac	Bz
7	MB	MB	H	iB	Ac



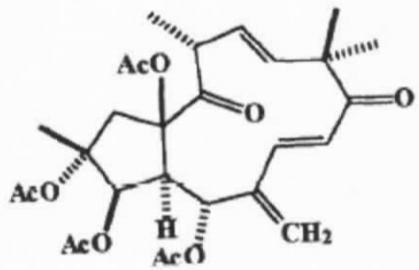
	R_1	R_2
8	H	H
9	OH	H
10	OH	OAc
11	H	OAc
12	OAc	H
13	(4-*epi*-**9**)	

MB = 2-methylbutyrate
iB = isobutyrate
Bz = benzoate
Nic = nicotinate

GABOR GUNTHER, *et al* (1998) isolated -two new jatrophane diterpenoids, esulatin D and E, from the dichloromethane extract of the whole, undried plant of *Euphorbia esula.*[103]

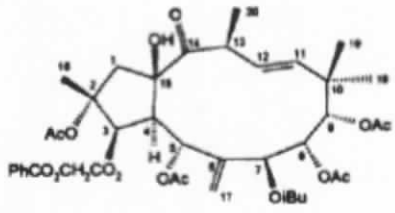


1

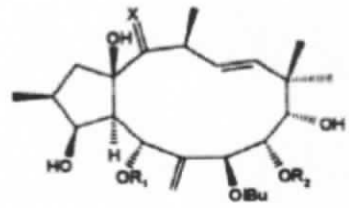


2

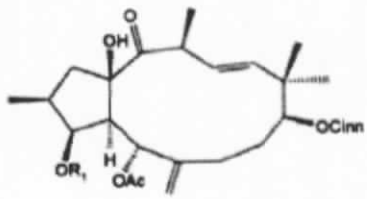
J. JAKUPOVIC, *et al* (1998) reported the isolation of numerous new diterpenes including several with new skeletons from *Euphorbia segetalis.*[104]



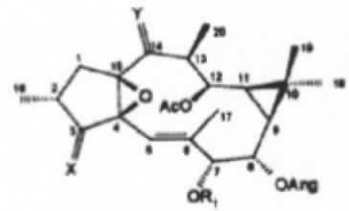
1



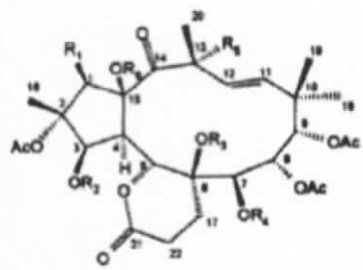
	2	3	4	5
R_1	Mebu	iBu	Mebu	iBu
R_2	Mebu	iBu	Mebu	Mebu
X	β-OAc,H	O	O	O



	6	7
R_1	Bz	Cinn

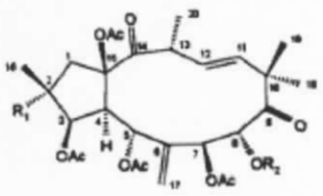


	8	8a	8b
R_1	Ac	Ac	H
X	O	β-OH,H	β-OH,H
Y	O	α-OH,H	α-OH,H

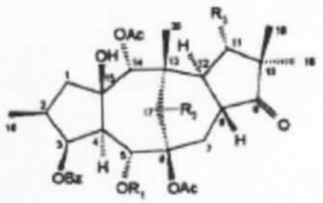


	9	10	11	12	13	14	15	16
R_1	H	H	H	H	H	OAc	H	OAc
R_2	Ac	Ac	H	Ac	H	Ac	Ac	Ac
R_3	Bz	Ac	Ac	Bz	iBu	Ac	Ac	Ac
R_4	iBu	iBu	iBu	Pro	iBu	iBu	iBu	iBu
R_5	H	H	H	H	H	H	OH	OH
R_6	Ac	Ac	Ac	Ac	Ac	H	Ac	H

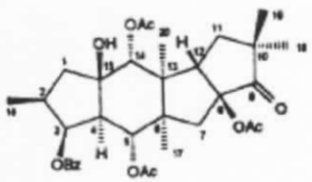
J. JAKUPOVIC, *et al* (1998) reported that chemical investigation of *Euphorbia paralias* from Spain afforded 13 diterpenes of different structural types.[105]



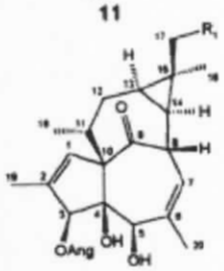
	1	2	3	4	5	6
R_1	OAc	OAc	OAc	OAc	OAc	H
R_2	Bz	iBu	Mebu	Ang	Ac	iBu



	7	8	9	10
R_1	AcOAc	Ac	AcOAc	AcOAc
R_2	H	OAc	OAc	OAc
R_3	OAc	OAc	OAc	H



11



	12	13
R_1	H	OAng

2.2. *Launaea resedifolia*

2.2.1. Family Description:

The family Asteraceae or, alternatively, family Compositae, known as the aster, daisy or sunflower family, is a taxon of dicotyledonous flowering plants. The family name is derived from the genus Aster and refers to the star-shaped flower head of its members, typified well by the daisy. The Asteraceae is the second largest family in the Division Magnoliophyta, with some 1,100 genera and over 20,000 recognized species. Only the orchid family (Orchidaceae) is larger, with about 25,000 described species.[106-108]

Plants belonging to the Asteraceae share all the following characteristics.[109] None of these traits, taken separately, can be considered synapomorphic.

Inflorescence: a capitulum or flower head.

Syngenesious anthers, i.e. with the stamens fused together at their edges by the anthers, forming a tube.

Ovary with basal arrangement of the ovules.

Ovules one per ovary.

Pappus (a tuft of hairs on a fruit).

The fruit is an achene.

The most common characteristic of all these plants is an inflorescence or flower head; a densely packed cluster of many small, individual flowers, usually called florets (meaning "small flowers").

Plants in the family Asteraceae typically have one or both of two kinds of florets. The outer perimeter of a flower head like that of a sunflower is composed of florets possessing a long strap-like petal, termed a ligule; these are the ray florets. The inner portion of the flower head (or disc) is composed of small flowers with tubular corollas; these are the disc florets. The composition of asteraceous inflorescences varies from all ray flowers (like dandelions, genus Taraxacum) to all disc flowers (like pineapple weeds).

The composite nature of the inflorescences of these plants led early taxonomists to call this family the Compositae. Although the rules governing naming conventions for plant families state that the name should come from the type genus, in this case Aster and thus Asteraceae. However, the long prevailing name Compositae is also authorized as an alternative family name.[110]

The numerous genera are divided into about 13 tribes. Only one of these, Lactuceae, is considered distinct enough to be a subfamily (subfamily Cichorioideae); the remainer, which are mostly overlapping, are put in the subfamily Asteroideae .[111]

2.2.2. *Launaea resedifolia*:

Biennal or perrenial herbs or spiny drarf shrubs. Stems solitary or few, freely and dichotomously branched. Leaves mostly basal. Capitula few or numerous. Involcral bracts in several rows, imbricate, with scarious margins. Receptacle without scales. All florets hermaphrodite, yellow ligules, often with an olive stripe, cylindrilcal achenes or slightly compressed. ribbed, not beaked; pappus in several rows, of simple hairs.

2.2.3. Classification.

Up to the Kingdom

Kingdom Plantae -- Plants

Subkingdom Tracheobionta -- Vascular plants

Superdivision Spermatophyta -- Seed plants

Division Magnoliophyta -- Flowering plants

Class Magnoliopsida -- Dicotyledons

Subclass Asteridae

Order Asterales

Family Asteraceae -- Aster family

Genus Launaea

Species resedifolia

2.2.4. Medical Use

Plants belonging to the family have received important uses in folk medicine as for examples:

Drug preparations of the flavonoids-rich *Helichrysum arenarium* have been used in folk medicine as an anti-chloretic and as remedy of liver diseases. The artichoke *Cynara scolumus* has enjoyed a large reputation in folk medicine, the property of liver protection were ascribed to the extract of leaves.[112]

Marticaria chemomilla, is one of the oldest pharmaceutical plants, aqueous and alcoholic extracts have been used internally and externally for their anti inflammatory and wound healy activity.[112]

Ainbrosia maritima, used as antispasmodic, diuretic, to promote elimination of renal calculi, molluscicidal activity for the control of bilharziasis and is proved to have lethal effect on snails. [113]

Xanthium spinosum is used for treatment of diabetes, intermittent fever, rabies and as stimulant to the secretion of saliva and urine. [114]

In traditional hawaiian folk medicine, the herbe of *Bidens campylontheca*, has been used in the treatment of generaldebility of the body, throat and stomach troubles, for stimulating appetite and treating sever cases of asthma, while *Bidens andicola*, used in peruvian folk medicine is an anthirumatic, a decoction of the whole plantis claimed to be effective when taken orally as a conyraceptive. On the other hand, leaves of bidens pilosa used as treatment for rheumatism, sor eyes, abdominal troubles, ulcers, swollen glands and toothache.[115-117]

Both fresh and dried leaf preparations of *Banacetum parthenium* used as herbal remedy for the control of arthritis and migraine.[118]

Inula britanica used in Chinese traditional medicine for treatment of bronchitis and other inflammations while *inula grantioides* is recommended for treatment of asthma. On the other hand *inula salsploides* is used for treatment of dysentery and inflammatory diseases.[119]

Launaea nudicaulis was reported to increase the secretion of the milk and is also taken during constipation. Leaves are applied to children in fever. [120]

Launaea nudicaulis* and *Launaea resedifolia are reported to have insecticidal and cytotoxic activities. [121]

Launaea fallax is reported to have activity on Leucorrhoea. [122]

Launaea procumbens extracts are reported to have antimicrobial activities. [123]

Launaea acaulis is used as nutritive, diuretic, stomachic and blood purifier.

It is also used as as antidote for poisoning. Leaves and roots are given in leprosy and leucorrhoea. [124]

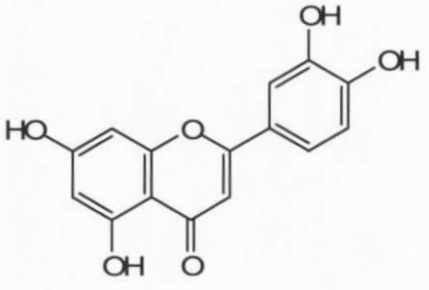
The latex; the stems and leaves, and the roots of ***Launaea arborescens*** are used for diabetes.[125]

Hot water extracts of the leaves of ***Launaea cornuta*** and the roots of Cissampelos pareira are used to treat epilepsy. [126]

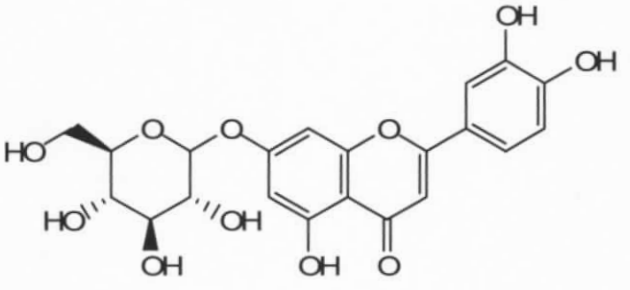
Launaea residifolia whole plant is reported to be febrifuge and lactagogue. [127]

2.2.5. Chemical Review of *Launaea*

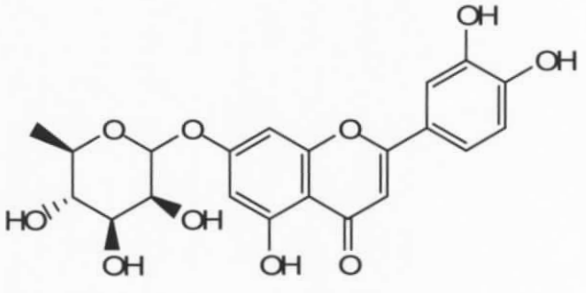
Giner, Rosa Maria, *et al* (1992) isolated eight phenolic compounds from the MeOH extract of the aerial parts of *Launaea arborescens*. The compounds isolated were luteolin, luteolin-7-O-glucoside, luteolin-7-O-rhamnoside, apigenin-7-O-glucoside, esculetin, its 7-glucoside (cichoriin), ferulic acid, and methylcaffeoate. HPLC-DAD analyses of the MeOH extract of *L. acanthoclada* and *L. resedifolia* showed all the compounds already identified in *L. arborescens*. These three species are chem. similar and the differences between them are only quantitative. In all cases, the major compound is cichoriin and the rest of the phenolic constituents are found in smaller amounts.[130]



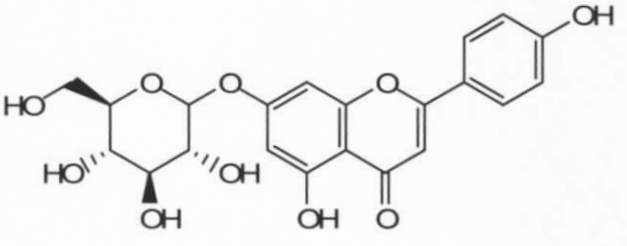
luteolin



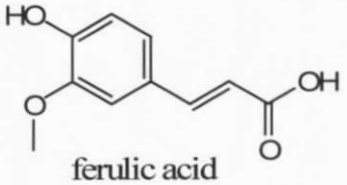
luteolin-7-O-glucoside



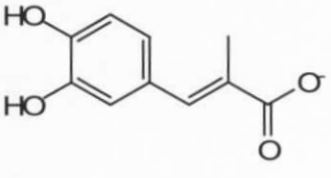
luteolin-7-O-rhamnoside



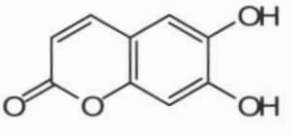
apigenin-7-O-glucoside



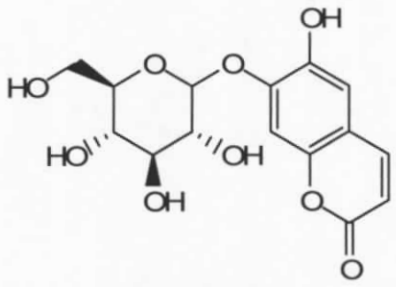
ferulic acid



methylcaffeoate



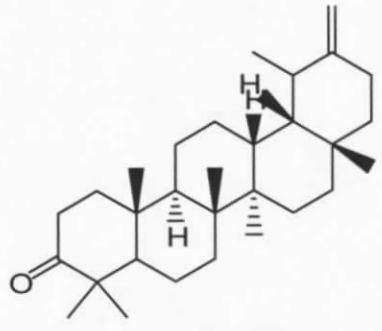
esculetin



cichoriin

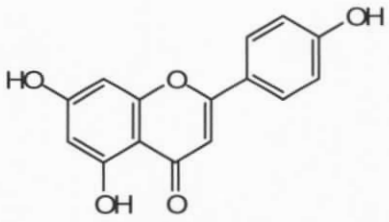
Abd El-Fattah. H, et *al* (1990) isolated from *Launaea* resedifolia (Asteraceae), the triterpenes α-amyrin, moretenol and lupeol, their acetate derivatives as well as their esters with a complex series of long chain fatty acids were obtained. In addition, the steroid Δ7-stigmastenol and its 3-O-glucoside were isolated.[131]

Gupta, M. M, *et al* (1989) isolated taraxasteryl acetate (0.02%), taraxasterone (0.003), taraxasterol (0.012), stigmasterol (0.003), Et palmitate (0.2), Et stearate (0.08), hexacosanol (0.2), octacosanol (0.008), and octacosanoic acid (0.006) *Launaea asplenifolia*. The presence of flavonoids in *Launaea procumbens* and their absence in *Launaea asplenifolia* will serve as marker for the distinction between these two closely related species. [132]

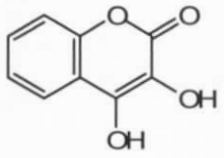


taraxasterone

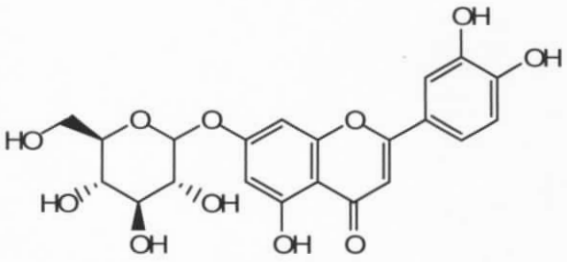
Saleh, M. R. I, *et al* (1988) isolated apigenin, dihydroxycoumarin, luteolin-7-O-glucoside, and apigenin-5-O-diglucoside from *Launaea resedifolia* grown in Egypt. [133]



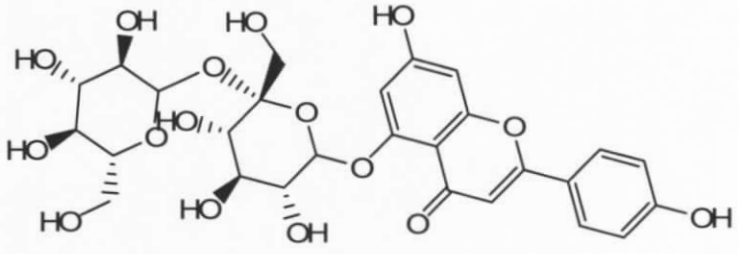
Apigenin



dihydroxycoumarin

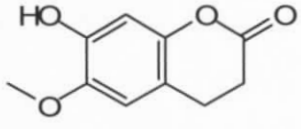


luteolin-7-O-glucoside



apigenin-5-O-diglucoside

Sarg, T. M, *et al* (1987) reported that column chromatography fractionation of the EtOAc extract of *Launaea spinosa* afforded 3, 4-dihydroscopoletin, esculetin, cichoriin, and luteolin 7-O-glucoside. The first compound is a new natural product. Column chromatography of the chloroform extract over silica gel afforded stigmasterol, **β**-sitosterol, friedelin, lupeol, and **β**-sitosterol glucoside. [134]



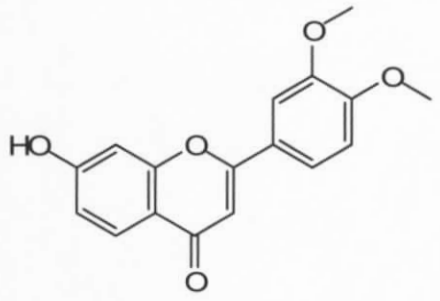
3,4-dihydroscopoletin

Sarg, T. M, *et al* (1986) isolated three phenolic compounds: esculetin, cichoriin and luteolin 7-O-glucoside for the first time from *Launaea nudicaulis*.[135]

Abdel Salam, N. A, *et al* (1986) carried out a phytochemical study of *Launaea tenuiloba* that resulted in isolation of three sesquiterpene lactones of guaianolide type lactucin, 8-deoxylactucin, and its 11**β**,13-dihydro derivative known as jacquilenlin, two coumarins (cichoriin and esculetin), and three flavone glycosides (luteolin 7-glucoside, apigenin 7-glucoside, and apigenin 7-diglucoside). [136]

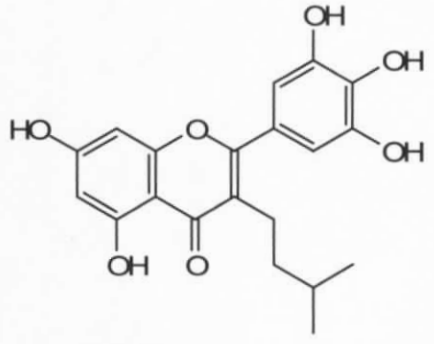
Gupta, D. R.; Dhiman, R. P.; Ahmed, Bahar (1985) reported that the extraction of the small herb *Launaea asplenifolia* with various solvents yielded 9 compounds which were

identified as octacosanoic acid, lupeol, 7-hydroxy-3',4'-dimethoxyflavone, apigenin, luteolin, apigenin-7-O-glucoside, vitexin, luteolin-7-O-glucoside, and delphinidin. [137]



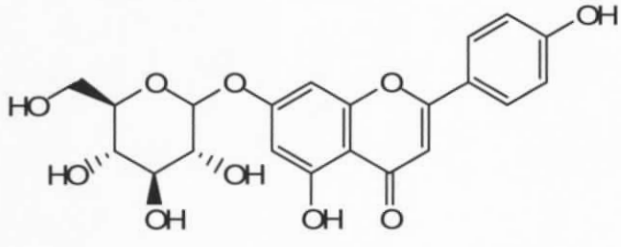
7-hydroxy-3',4'-dimethoxyflavone

Gupta, D. R. and Ahmed, Bahar (1985) isolated a new flavone, asplenetin (I), from *Launaea asplenifolia* and was characterized as 5,7,3',4',5'-pentahydroxy-3-(3-methylbutyl)flavone. Its glycoside, asplenetin 5-O-neohesperidoside, is also reported.[138]



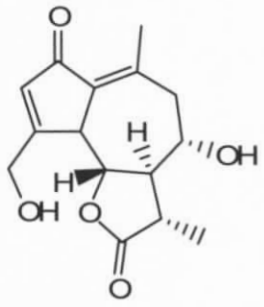
5,7,3',4',5'-pentahydroxy-3-(3-methylbutyl)flavone

Mansour, Ragaa M. A., *et al* (1983) reported that apigenin 7-glucoside and 7-gentiobioside, and luteolin 7-glucoside, 7-gentiobioside, 7-rutinoside, 7,3'-diglucoside, 7,4'-diglucoside, and 7-gentiobioside-4'-glucoside were isolated from *Launaea nudicaulis* and detected in *L. capitata*, *L. cassiniana*, *L. resedifolia*, *L. spinosa*, and *L. tenuiloba*. The 7'-glucosides were the major glycosides in all 6 species.[139]



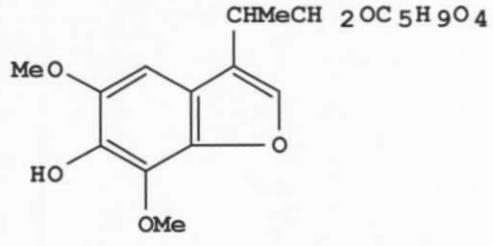
Apigenin 7-glucoside

Sarg, T. M., *et al* (1982) reported that the roots of *Launaea mucronata* afforded, in addition. to lactucin, lactucin 8-O-acetate, and the corresponding dihydro derivative., 11β,13-dihydrolactucin. [140]



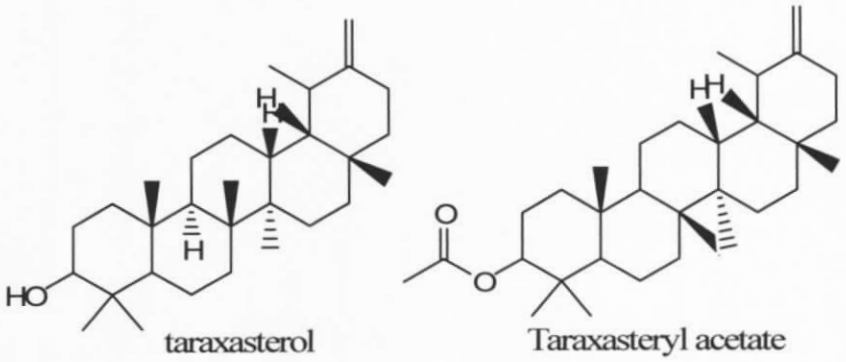
11β,13-dihydrolactucin

Sharma, Sushma, *et al* (1980) reported that the dried, powdered leaves of *Launaea. nudicaulis* (Compositae), extracted with 95% EtOH, yielded a $C_{18}H_{16}O_5$ glycoside (I) comprised of D-(+)-xylose and a $C_{13}H_{16}O_5$ moiety as the aglycon.. [128]



I

Prabhu, K. R.; Venkateswarlu, V. (1969) found that the leaves and roots of *Launaea pinnatifida* contain taraxasterol and taraxasteryl acetate.[129]



taraxasterol Taraxasteryl acetate

Chapter Three

Results and Discussion

3.1. *Euphorbia guyoniana*

3.1.1. Phytoscreening of *Euphorbia guyoniana*

The different parts of *Euphorbia guyoniana* were subjected to many phytochemical tests to reveal the following results.

Table 1: Results of phytoscreening tests

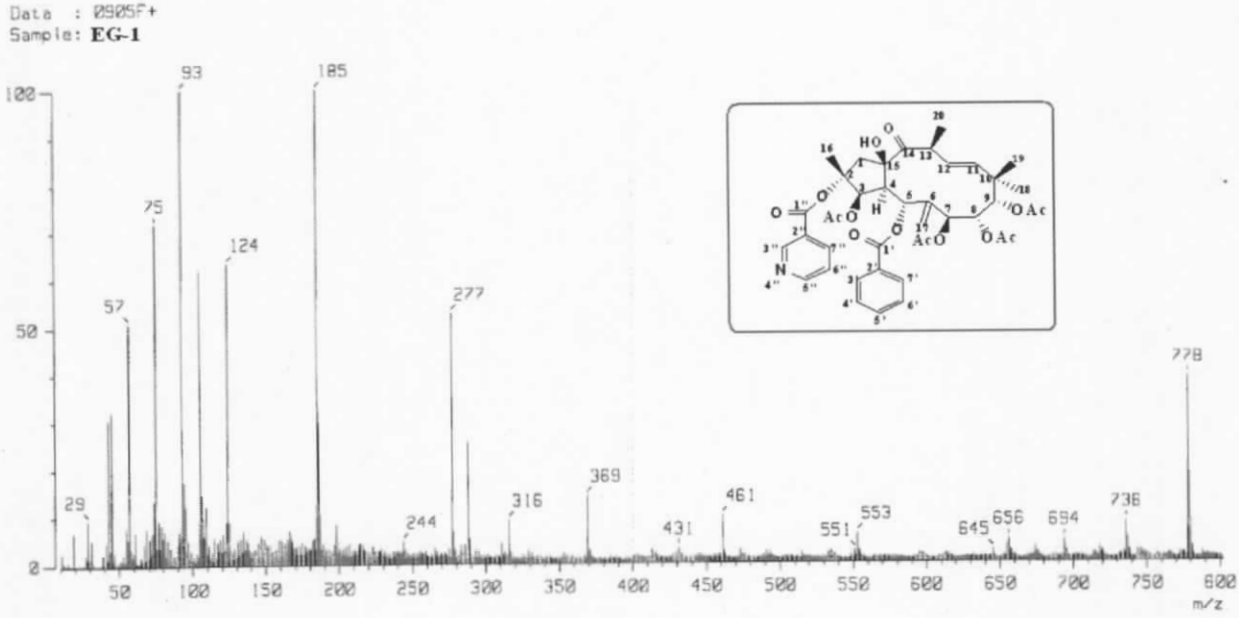
organ / active principal	Roots	Stems	Leaves	Flowers	Seeds
Steam distillation	-	+	+	+	+
Flavonoids	+	+	+	+	+
Alkaloids	-	-	-	-	-
Tannins	+	+	+	+	+
Saponins	+	+	+	+	-
Sterols and Triterpenes	+	+	+	+	+
Coumarins	+	+	+	+	+

The tests reveal the presence of many important chemical families and hence consolidate our choice of study.

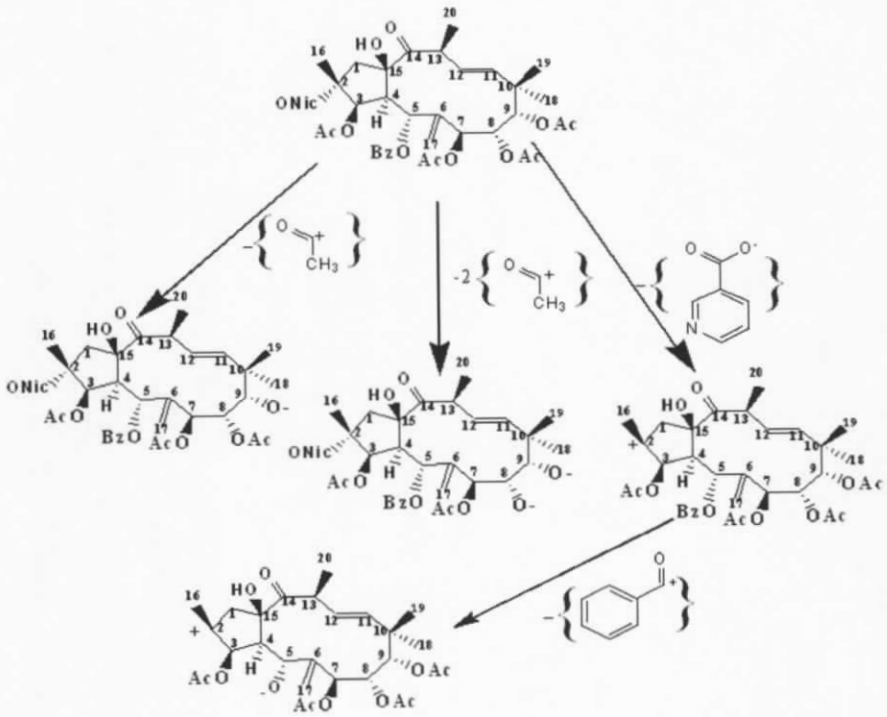
3.1.2. Compound EG-1

The mass spectrum (spectrum 1) exhibits the molecular peak at *m/z* (%) = 778 $[M + H]^+$ (45), other fragments at 736 $[M + H - AcO]^+$ (10), 694 $[M + H - 2AcO]^+$ (5) on the basis of positive HRFABMS.

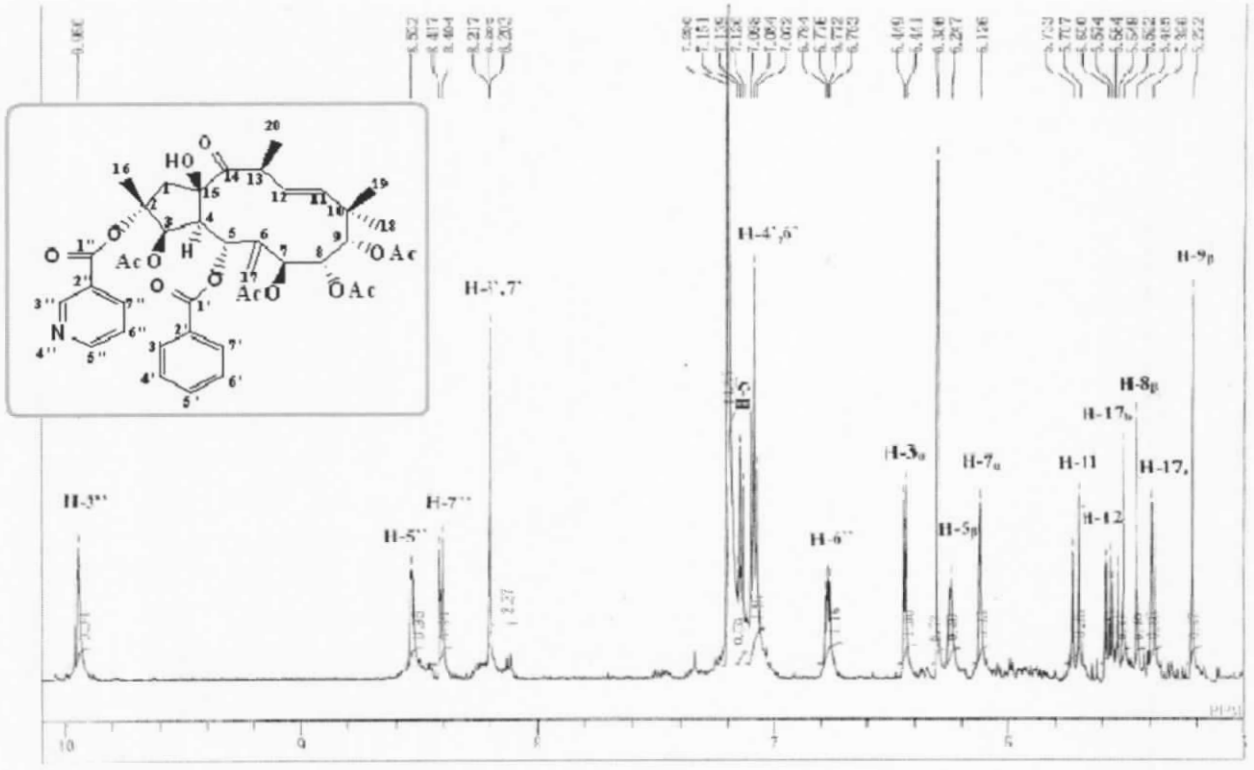
The molecular formula was established as $C_{41}H_{47}NO_{14}$ resulting in 19 insaturations.



Spectrum1 : positive HRFABMS of EG-1



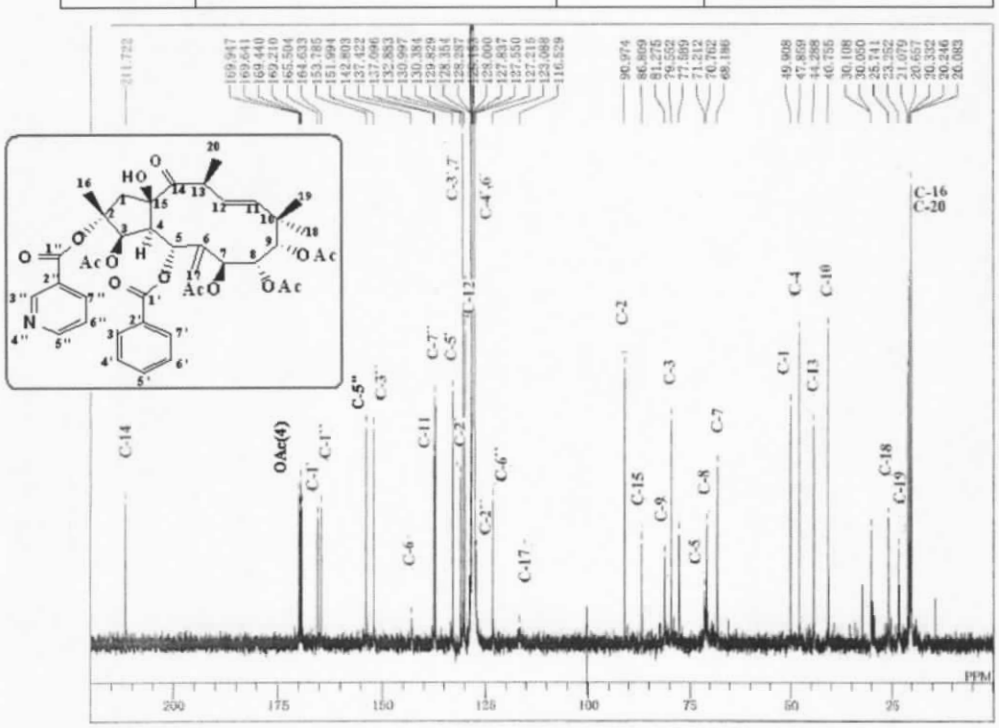
The ^{1}**H** and ^{13}**C** NMR data of **EG-1** (spectra 2 and 3, Table 2 and 3) reveale the presence of one nicotinate group [δ_H 9.95 br d (1H), 8.53br d (1H), 6.77 dd (1H), 8.41 dt (1H); δ_C 164.6 (CO), 127.2 (=C=), 152.0 (CH), 153.8 (CH), 123.1 (CH), 137.1 (CH)], one benzoate group [δ_H 8.21 dd (2H), 7.08 td (2H), 7.14 tt (1H), δ_C 165.5 (CO), 131.0, 130.4 (2×CH), 128.4 (2×CH), 132.9 (CH)] .



Spectrum 2: ^{1}H NMR of compound EG-1 (5-10ppm)

Table2: ^{1}H NMR Spectral Data of EG-1(600MHz, benzene-*d6*)

Proton	δ_H(*J* in Hz)	Proton	δ_H(*J* in Hz)
1β	2.34 (d, 16.1)	19	1.21 (s)
1α	3.35 (d, 16.1)	20	1.06 (d, 7.1)
3α	6.45 (d, 5.0)	15-OH	4.54 (br s)
4α	4.05 (dd, 5.5,5.0)	3', 7'	8.21 (dd, 7.6, 1.5)
5β	6.25 (d, 5.5)	4', 6'	7.08 (td, 7.6, 1.5)
7α	6.13 (br s)	5'	7.14 (tt, 7.6, 1.5)
8β	5.47 (br s)	3"	9.95 (brd, 2.0)
9β	5.22 (br s)	5"	8.53 (br d, 4.5)
11	5.72 (d, 15.6)	6"	6.77 (dd, 8.1, 4.5)
12	5.57 (dd, 15.6, 9.6)	7"	8.41 (dt, 8.1, 2.0)
13α	3.69 (dq, 9.6, 7.1)	3-OAc	1.69(s)
16	1.85 (s)	7-OAc	1.67 (s)
17a	5.40 (br s)	8-OAc	1.85 (s)
17b	5.52 (br s)	9-OAc	1.97 (s)
18	0.78 (s)		



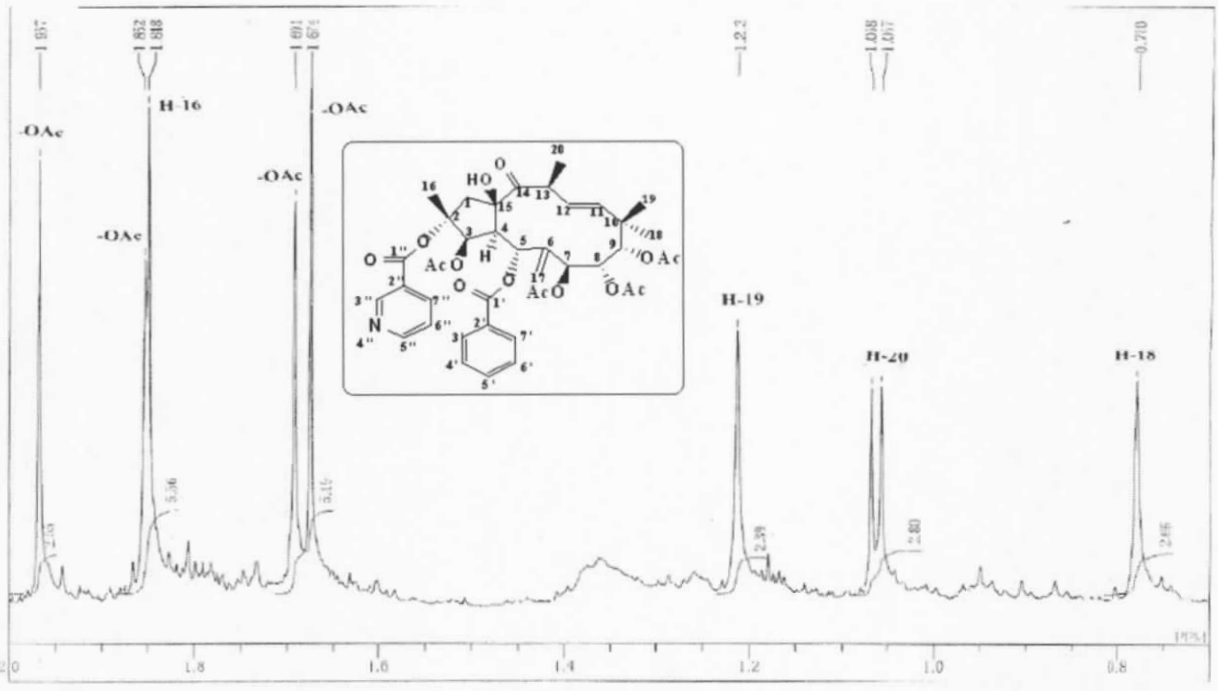
Spectrum 3: ^{13}C NMR of compound EG-1

Table 3: ^{13}C NMR Spectral Data of EG-1(150MHz, benzene-*d6*)

Carbon	δ_C	Carbon	δ_C
1	49.9 (t)	19	23.3 (q)
2	91.0 (s)	20	20.1 (q)
3	79.6 (d)	1'	165.5 (s)
4	47.9 (d)	2'	131.0 (s)
5	71.2 (d)	3', 7'	130.4 (d)
6	142.8 (s)	4', 6'	128.4 (d)
7	68.2 (d)	5'	132.9 (d)
8	70.8 (d)	1"	164.6 (s)
9	81.3 (d)	2"	127.2 (s)
10	40.8 (s)	3"	152.0 (d)
11	137.4 (d)	5"	153.8 (d)
12	129.8 (d)	6"	123.1 (d)
13	44.3 (d)	7"	137.1 (d)
14	211.7 (s)	3-OAc	169.9 (s) 21.1 (q)
15	86.8 (s)	7-OAc	169.6 (s) 20.2 (q)
16	20.1 (q)	8-OAc	169.4 (s) 20.7 (q)
17	116.5 (t)	9-OAc	169.2(s) 20.3 (q)
18	25.7 (q)		

Multiplicity was determined by DEPT experiments; s= quaternary, d= methine, t= methylene, q= methyl.

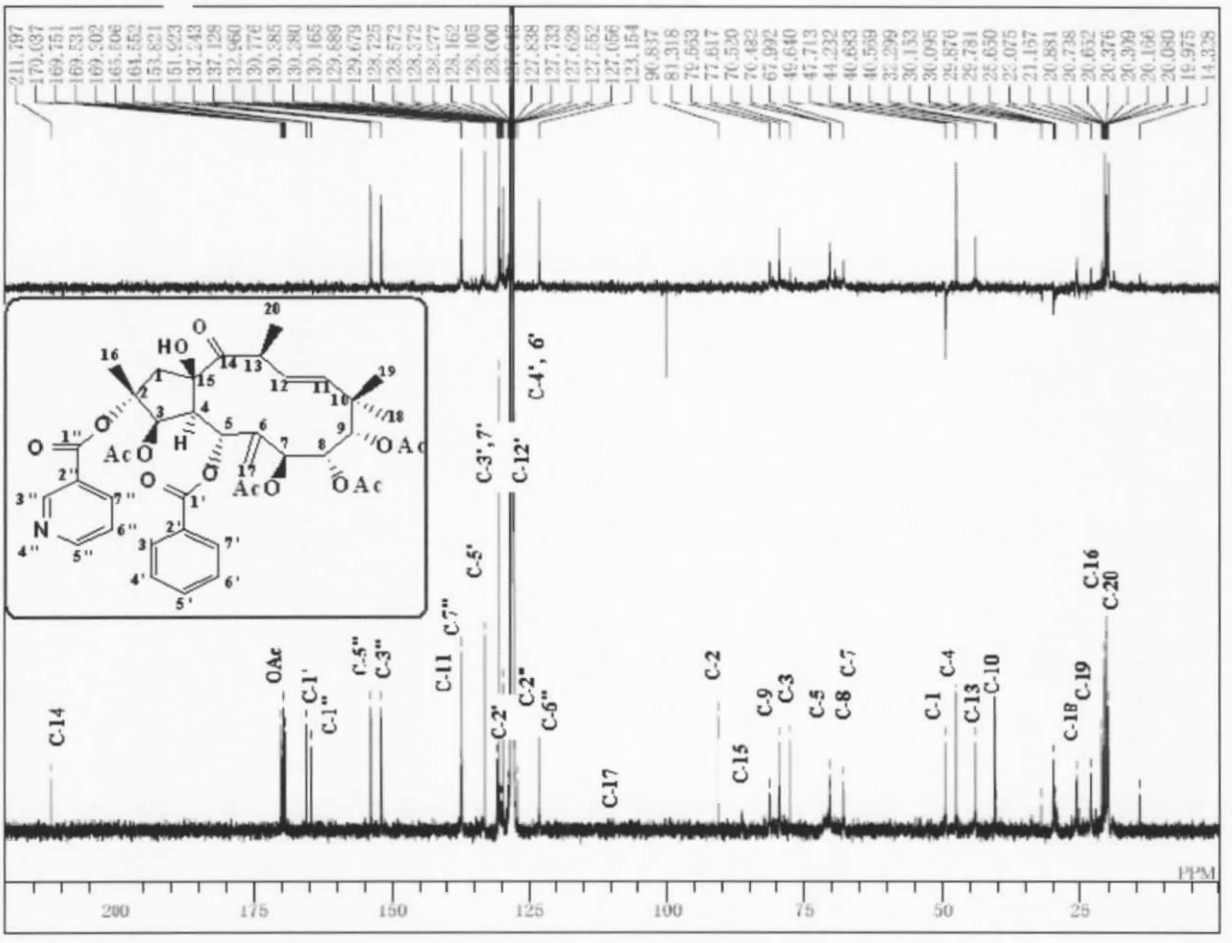
Four acetate groups [δ_H 1.67, 1.97, 1.85, 1.69; δ_C 169.2, 169.4, 169.6, 169.9 (CO) and 20.2, 20.3, 20.7, 21.1 (CH_3)] (spectra 3 and 4).



Spectrum 4: ^{1}H NMR of compound EG-1 (0-2ppm)

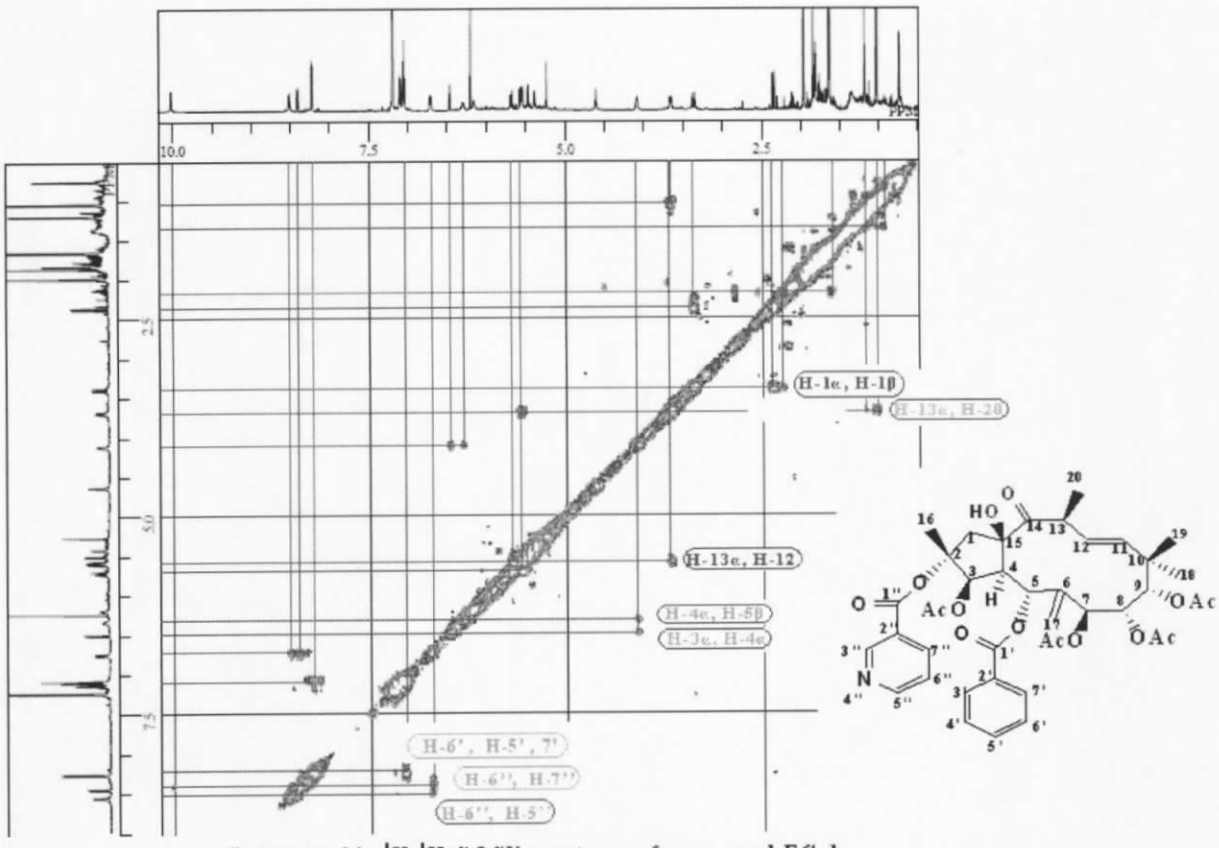
Additionally, its ^{1}H NMR (spectrum 4) exhibited three tertiary methyl groups [δ_H 1.85, 1.21, 0.78], and one secondary methyl group (δ_H 1.06). The parent diterpene skeleton and its structural fragments were established from a series of NMR experiments.

The ^{13}C NMR (spectrum 3) and DEPT (spectrum 5) spectral data of **EG-1** revealed the presence of twenty carbon signals: five quaternary carbons, nine methines, two methylenes, and four methyl groups.

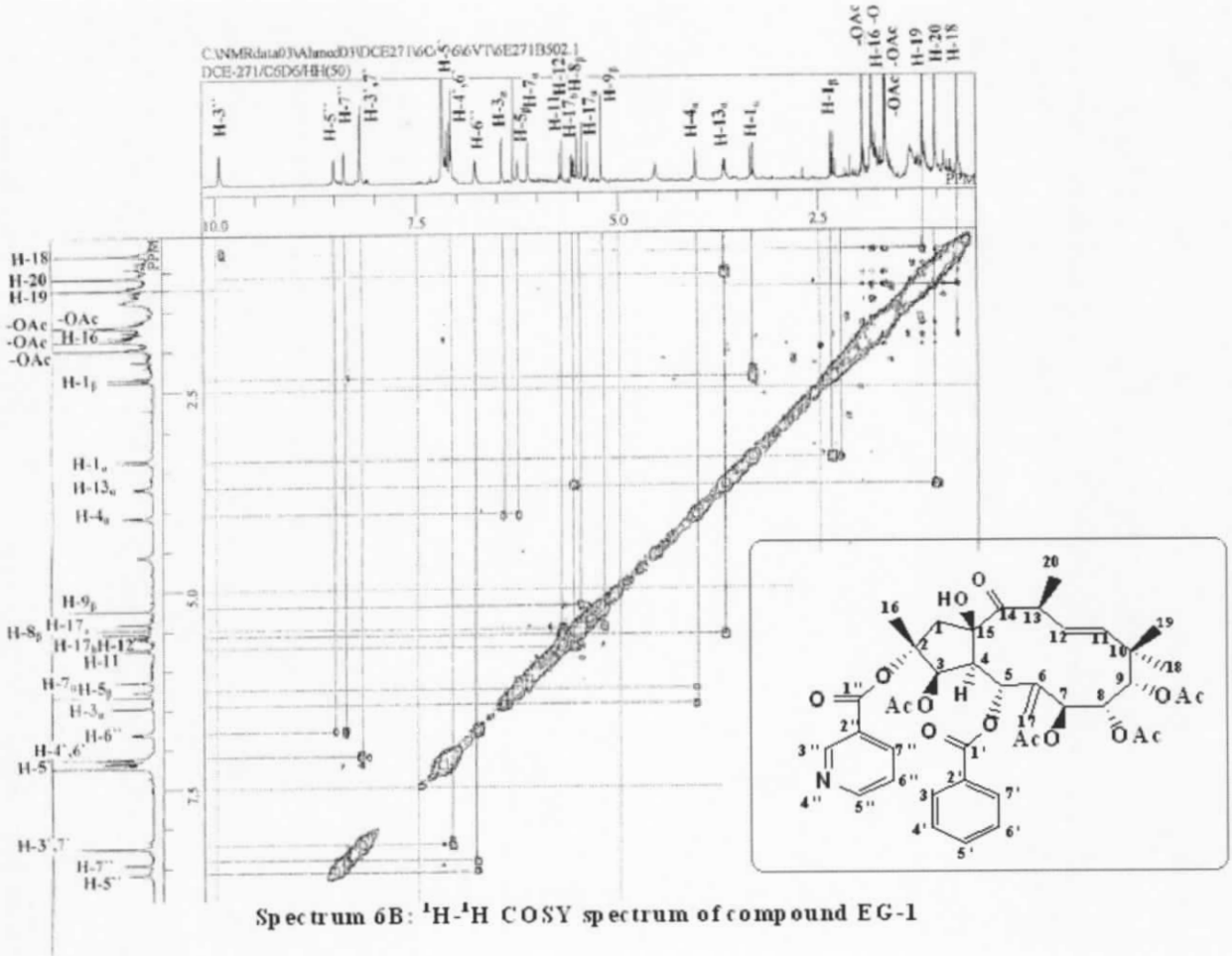


Spectrum 5: DEPT spectrum of compound EG-1

In a ^{1}H-^{1}H COSY experiment (spectra 6A and 6B), the signal at δ_H 5.57 (dd, J = 15.6, 9.6 Hz, H-12) was correlated with two signals at δ_H 5.72 (d, J = 15.6 Hz, H-11) and 3.69 (dq, J = 9.6, 7.1 Hz H-13), suggesting the presence of a *trans*-CH=CHCH(CH_3)- moiety; the signal at δ_H 5.47 (br s, H-8) showed a weak correlation with two signals at δ_H 6.13 (br s, H-7) and 5.22 (br s, H-9), indicating the presence of a -CH(O)-CH(O) -CH(O)- moiety; and the signal at δ_H 4.05 (dd, J = 5.5, 5.0 Hz, H-4) was correlated with two signals at δ_H 6.25 (d, J = 5.5 Hz, H-5) and 6.45 (d, J = 5.0 Hz, H-3), which suggested the presence of a -CH(O)-CH-CH(O)- moiety. The other $_1H$ NMR spectral features included an AB system at δ_H 3.35 (d, J = 16.1, H-1a) and 2.34 (d, J = 16.1, H-1b), and two olefinic protons at δ_H 5.40 and 5.52.

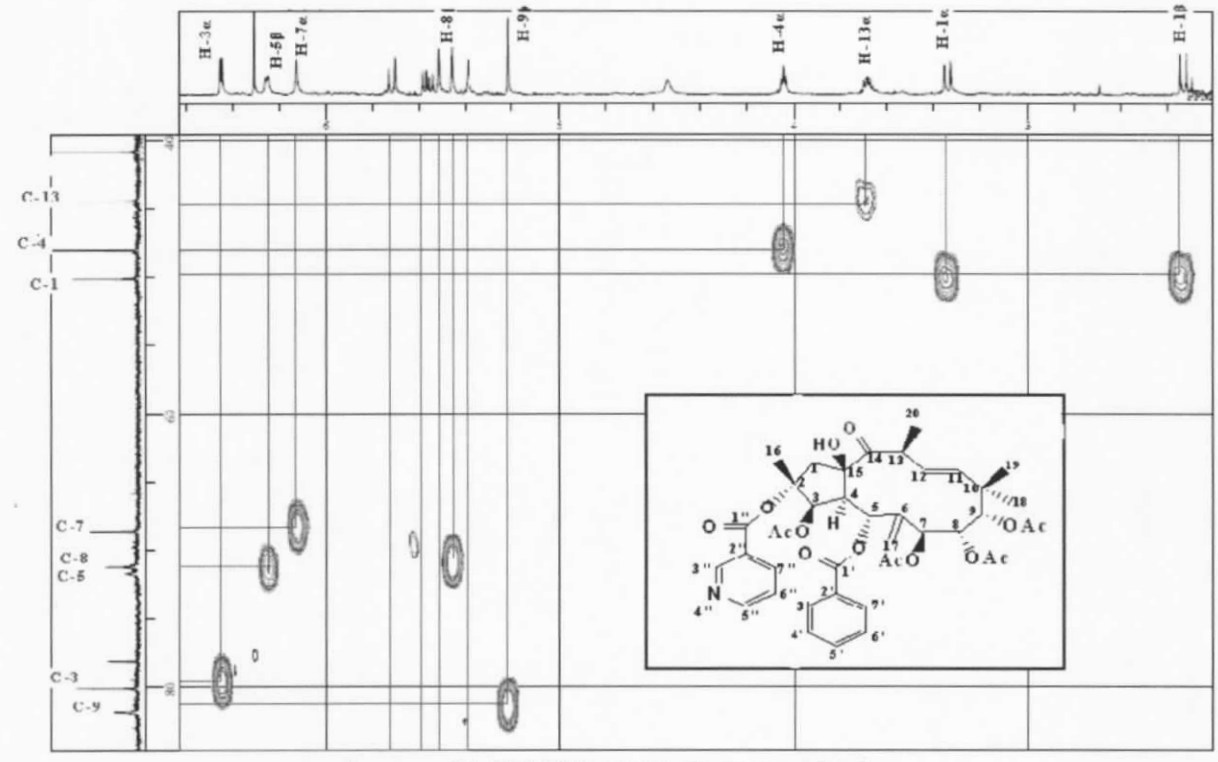


Spectrum 6A: ^{1}H-^{1}H COSY spectrum of compound EG-1

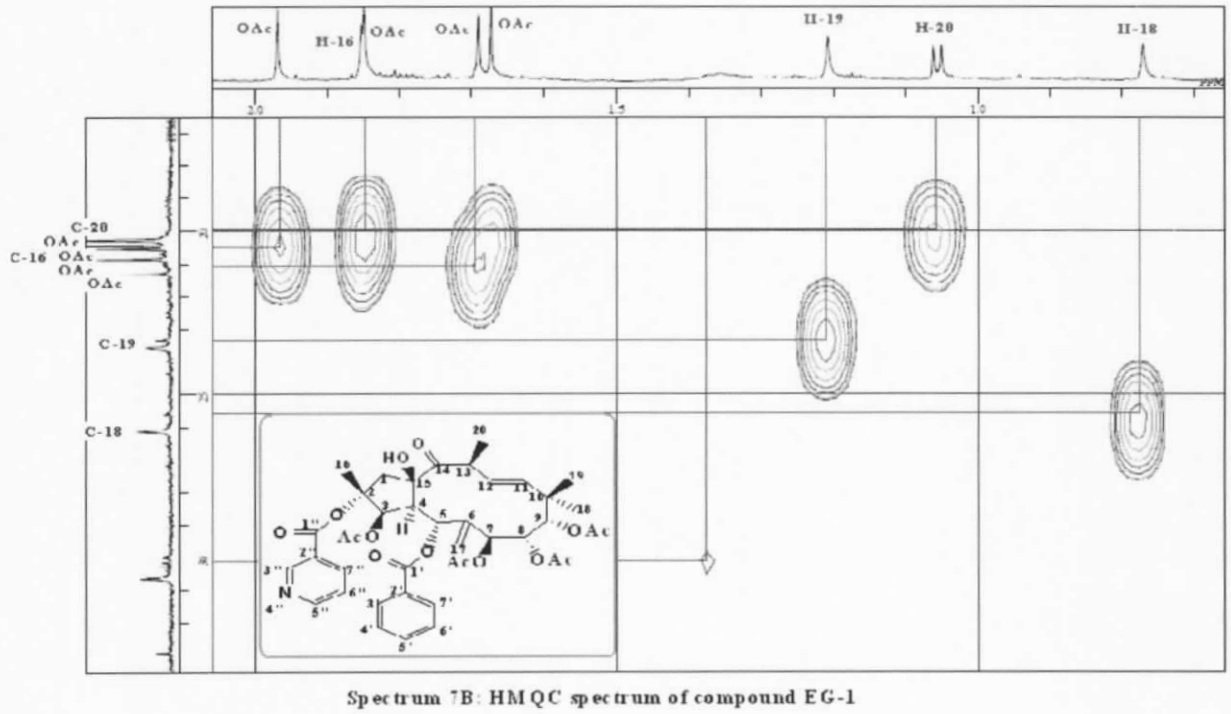


Spectrum 6B: ^{1}H-^{1}H COSY spectrum of compound EG-1

The HMQC analysis show clearly the correlations between ($H1_\beta$, $H1_\alpha$ and C1), ($H4_\alpha$ and C4), ($H7_\alpha$, C7), ($H9_\beta$, C9), ($H3_\alpha$, C3), as well as between the acetates' methyls and their corresponding carbons (spectra 7A and 7 B).

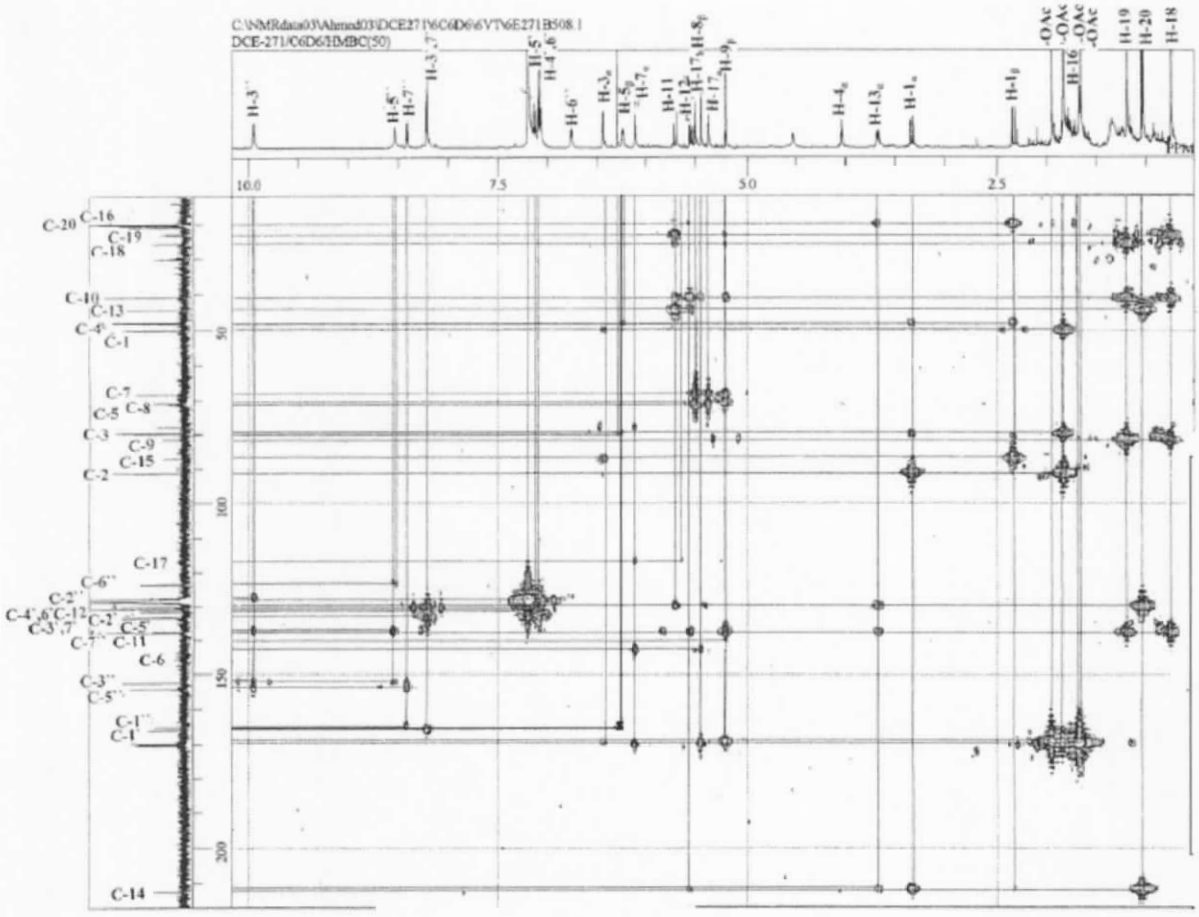


Spectrum 7A: HMQC spectrum of compound EG-1



Spectrum 7B: HMQC spectrum of compound EG-1

The connectivities of the partial moieties and the positions of the acetate groups were established by HMBC analysis. In this experiment, H-1β (δ_H 2.34) was correlated with C-15, C-14, C-3, C-4 and C-16, whereas H-1α (δ_H 3.35) exhibited correlations with C-2, C-3, C-4 and C-14 (spectrum 8A, table 4).

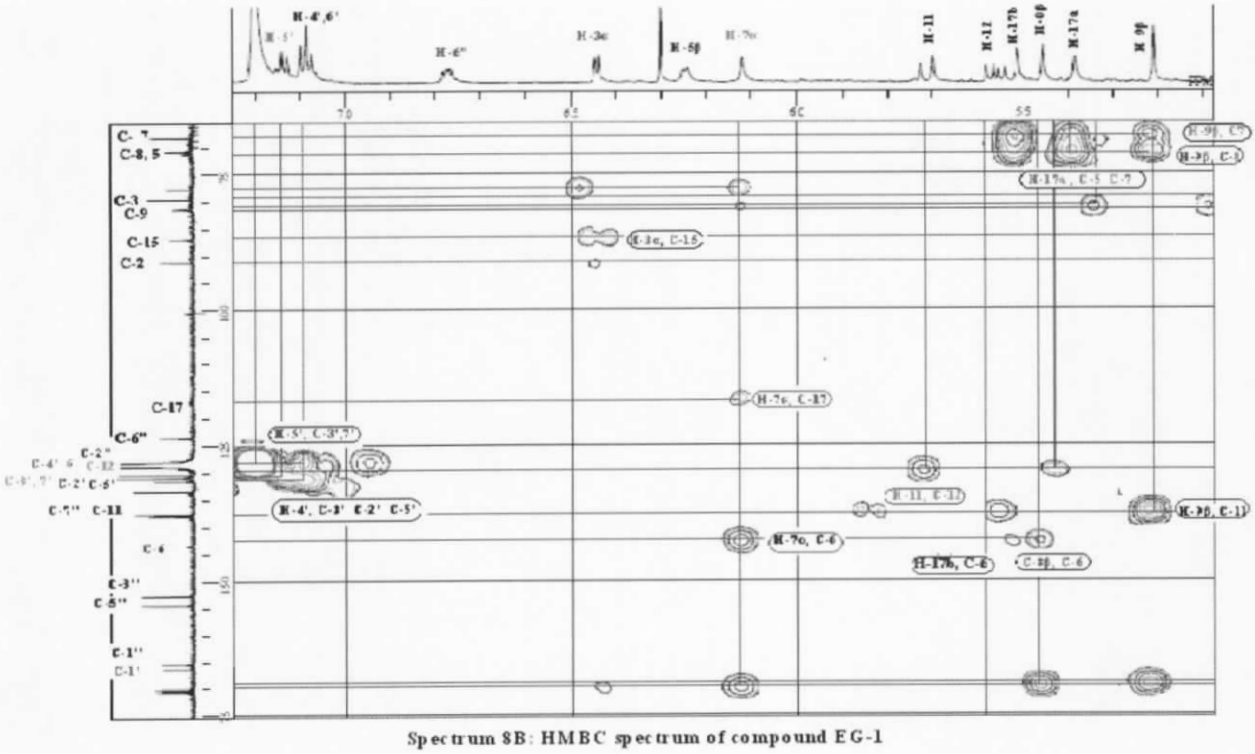


Spectrum 8A: HMBC of EG-1

Table 4: HMBC Spectral Data of EG-1

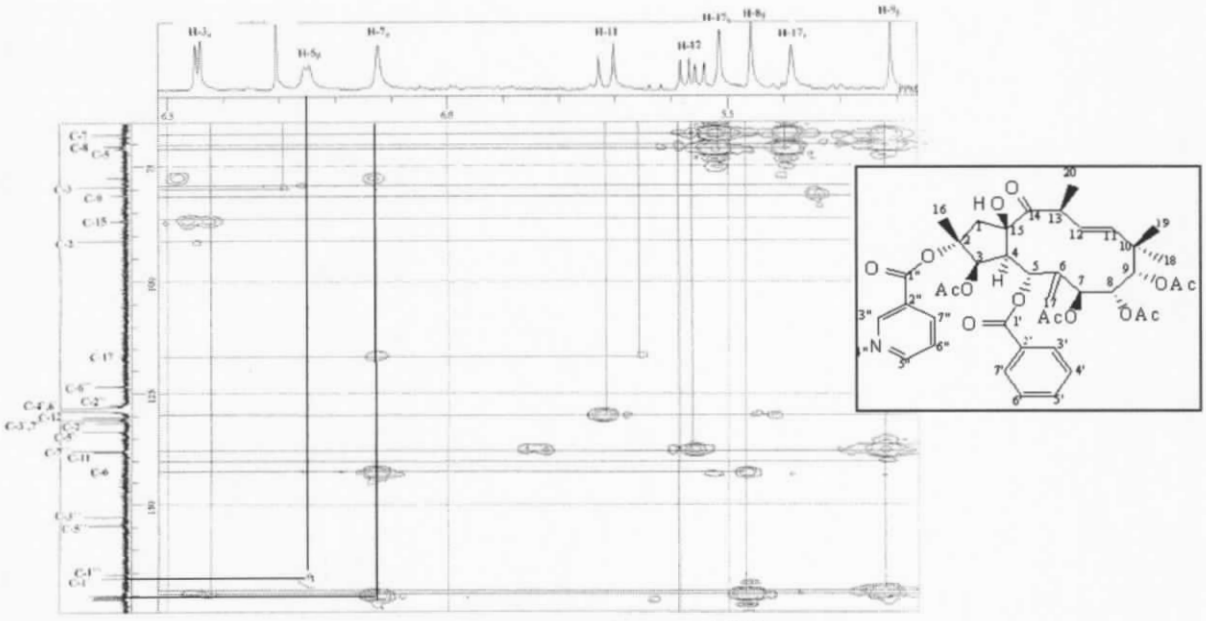
Protons	HMBC	Protons	HMBC
1β	C-3, C-4,C-14, C-15, C-16	17b	C-5, C-6, C-7
1α	C-2, C-3, C-4, C-14	18	C-11, C-10, C-9, C-19
3α	C-1, C-2, C-15	19	C-11, C-10, C-9, C-18
5β	C-3, C-4, C-1“	20	C-12, C-13, C-14
7α	C-6, C-17, C=O (7-OAc)	3', 7'	C-1', C-5', C-7'
8β	C-6, C-10, C=O (8-OAc)	4', 6'	C-2', C-6'
9β	C-7, C-8, C-10, C-11, C-18 C-19, C=O (9-OAc)	5'	C-3', C-7'
11	C-10, C-12, C-13, C-18,C-19	3”	C-2”, C-7”, C-5”
12	C-10, C-11, C-13, C-14	5”	C-6”, C-7”, C-3”
13α	C-11, C-12, C-14, C-20	6”	
16	C-1, C-2, C-3	7”	C-1”, C-3”, C-5”
17a	C-5, C-7		

Other significant HMBC correlations were between δ_H 6.25 (H-5) and C-3 and C-4; H-17a, b (δ_H 5.40, 5.52) and C-5, C-6 and C-7; H-9 (δ_H 5.22) and C-7, C-8, C-10, C-11, C-18 and C-19(spectrum 8B).



Spectrum 8B: HMBC spectrum of compound EG-1

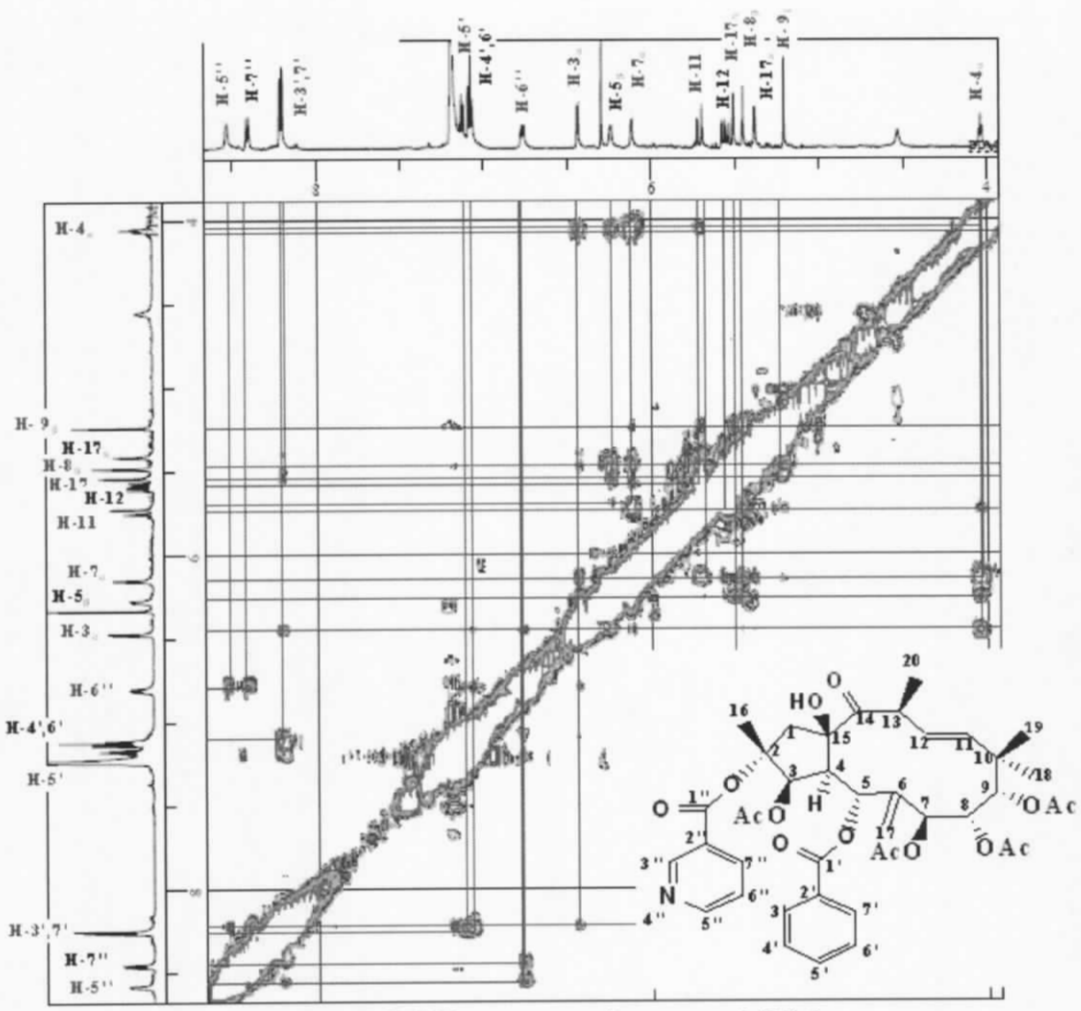
The placement of the benzoate group at C-5 was determined from the correlation of H5 with benzoate (δ_c 165.5, C1') (spectrum8C), besides the NOE effects between the two H-5 (δ_H 6.25) and the carbonyl carbon of the exomethylene protons (δ_H 5.52, 5.40, H-17a,b) and H-3',7'. The placement of the nicotinate at C-2 was determined from the NOE effects between H-3 (δ_H 6.45) and H-6" (δ_H 6.77) (spectrum9A, table 5).



Spectrum 8C: HMBC spectrum of compound EG-1

Table5: NOESY Spectral Data of EG-1

Protons	NOESY	Protons	NOESY
1β	H-16	13α	H1α, H-4, H-11
1α	H-4 , H-13, H-16, H-20	16	H-1β, H-1α
3α	H-3', H-3", H-4, H-6", H-16	17a	H-3',7'
4α	H-3, H-1α, H-7, H-11, H-13	17b	H-5, H-3',7'
5β	H-8, H-17 b, H-19	18	H-9, H-11, H-19,9
7α	H-4, H-11	19	H-5, H-8, H-9, H-12, H-18
8β	H-5, H-9, H-19	20	H-1α, H-12
9β	H-8, H-18, H-19	3', 7'	H-3, H-17a, 17b
11	H-4 , H-7, H-18, H-13	6"	H-3
12	H-19, H-20	9-OAc	H-18



Spectrum 9A: NOESY spectrum of compound EG-1

Moreover, the four acetyl carbonyl carbons showed correlation with their acetoxymethine protons in the HMBC experiment (spectrum 8B). The HMBC correlations are exhibited in figure 1

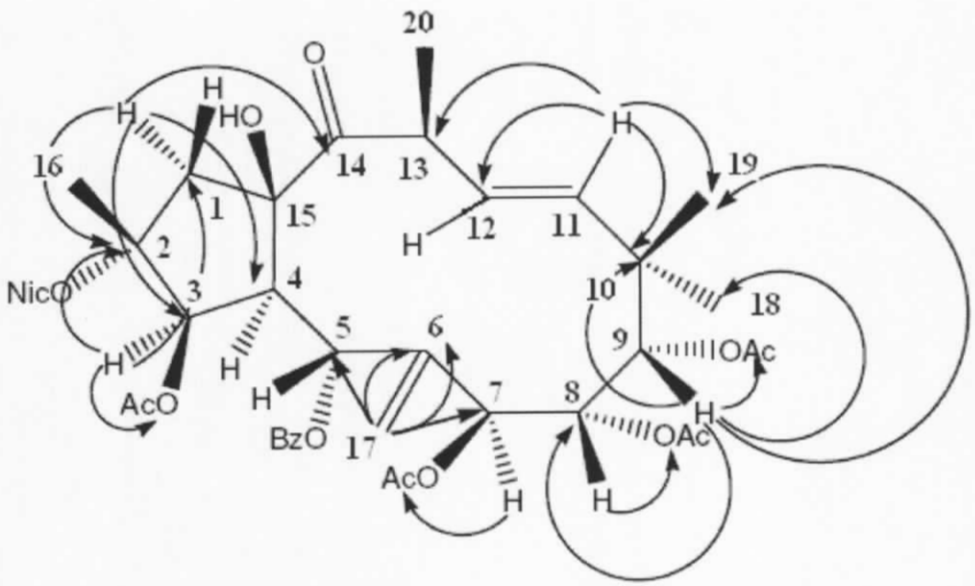
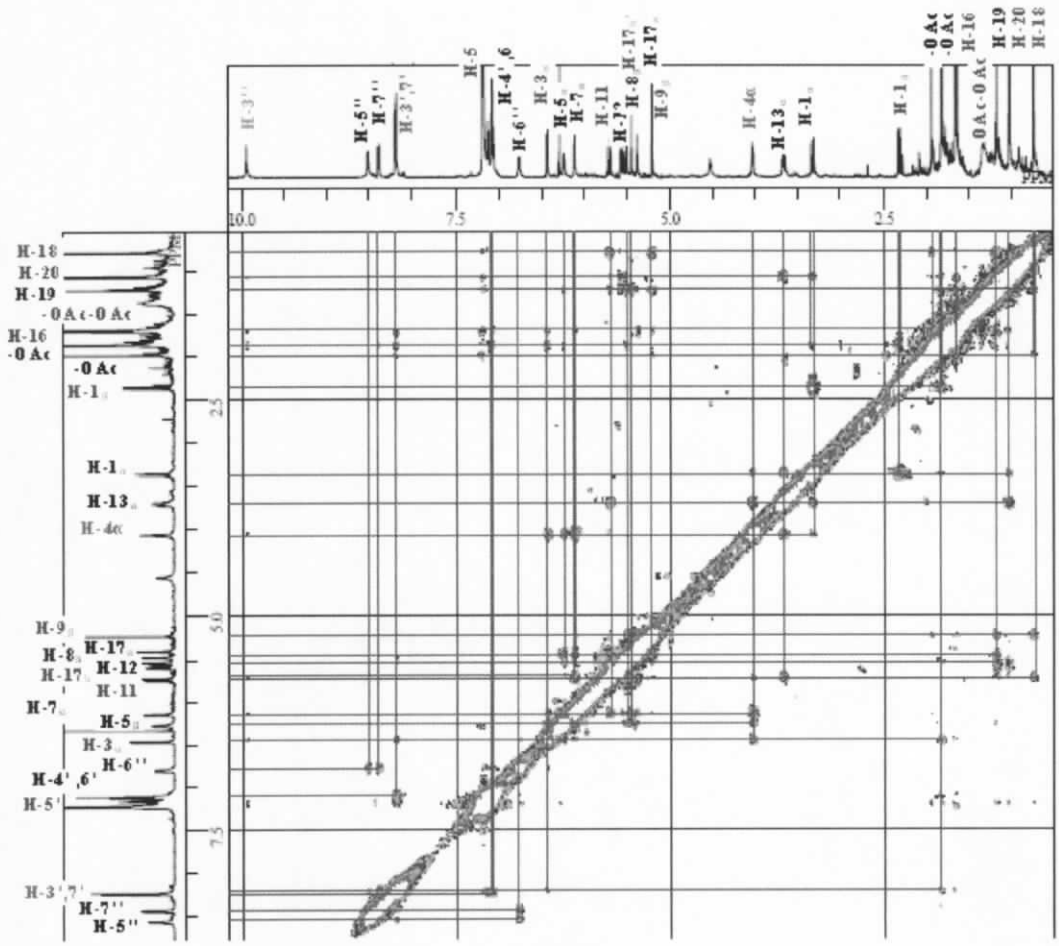


Fig 1: Selected HMBC correlations of EG-1

The relative stereochemistry of compound **EG-1** was studied through the analysis of the coupling constants and NOESY spectrum (spectrum 9B, Figure 2).



Spectrum 9B: NOESY spectrum of compound EG-1

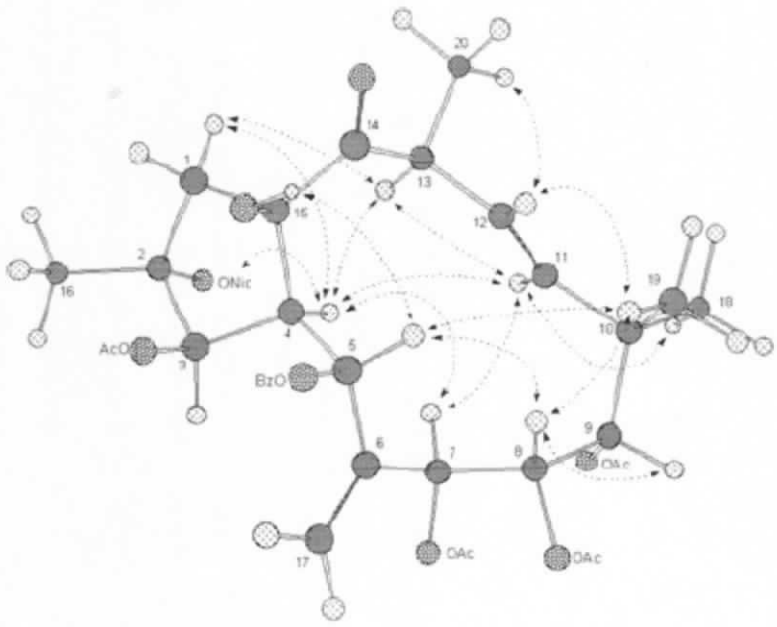


Fig 2: Selected NOE correlations of compound EG-1

H-4 was used as a convenient reference point; NOE cross-peaks of H-4 with H-1 (δ_H 3.35), H-3, H-7, H-13, and H-3" suggested an a α orientation for those protons and the nicotinate group. The presence of NOEs between H- 5/H-8, H-5/15-OH, H-8/H-19, H-8/H-9, H-12/H-19, and H-12/H-20 suggested β-orientation of H-5, H-8, H-9, H-12, 15-OH, H-19, and H-20. These NOE interactions and the relatively small ^3J4–5 value (5.5 Hz) are diagnostic for an *exo*-type conformation of the jatropane core.

EG-1 was given the name of **Guyonianin A**

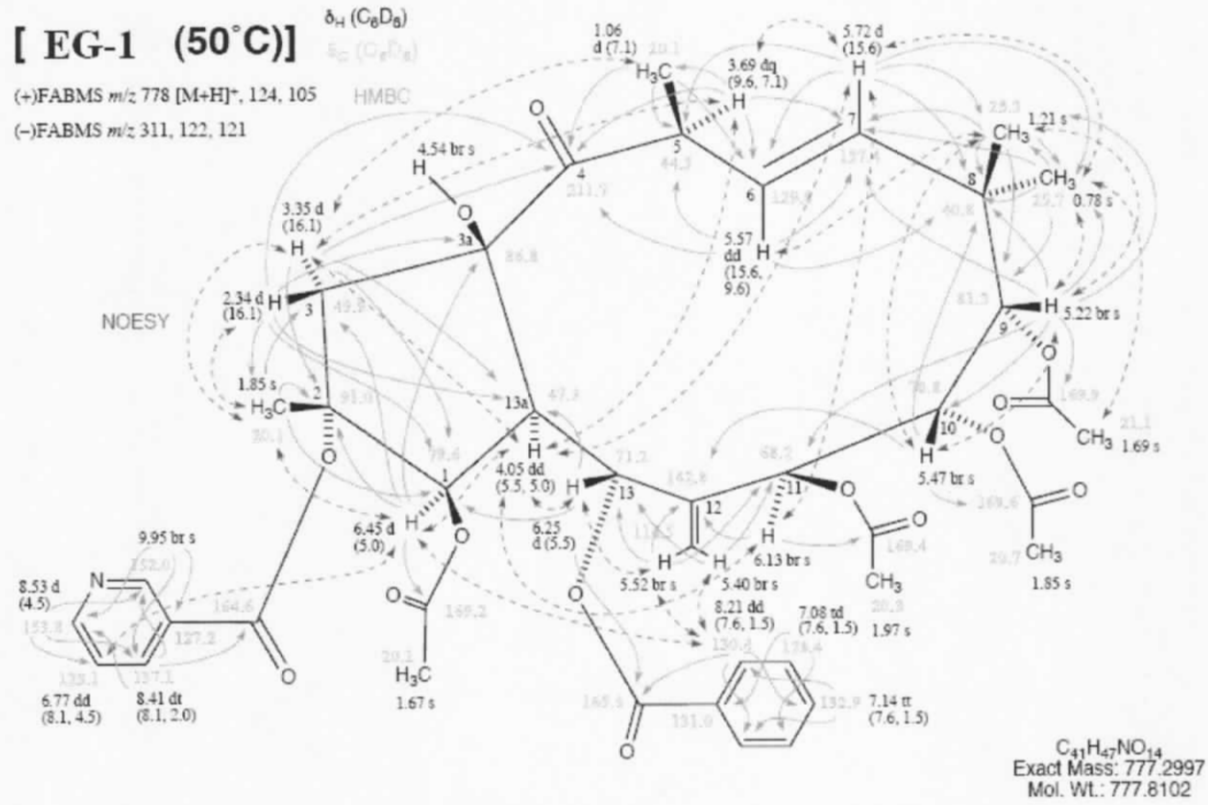
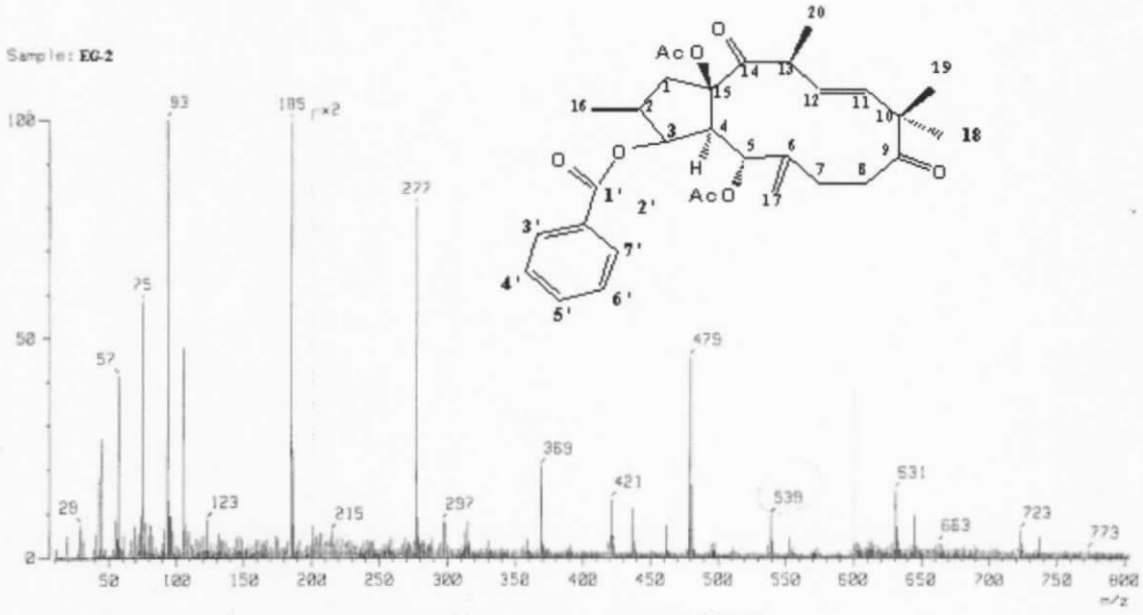


Fig 3: EG-1

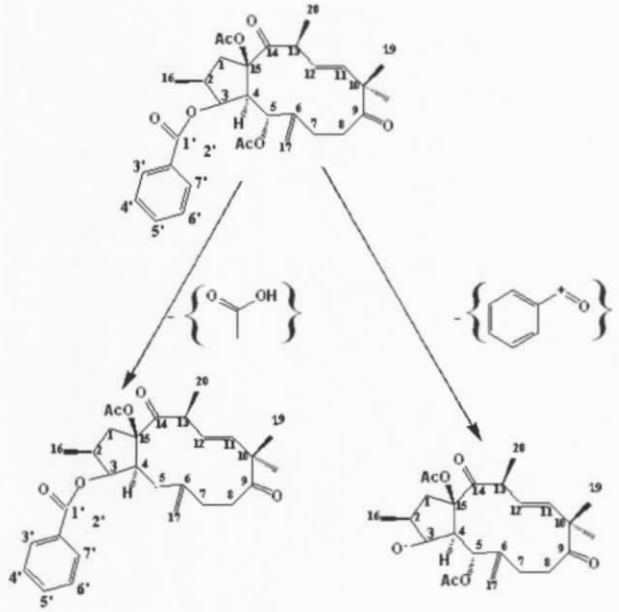
3.1.3. Compound EG-2

The mass spectrum (spectrum 10) exhibits the molecular peak at *m/z* (%) = 539 $[M + H]^+$ (12), other fragments at $[M + H - AcOH]^+$ (55), 434 $[M + H - benzoate]^+$(15) on the basis of positive HRFABMS.

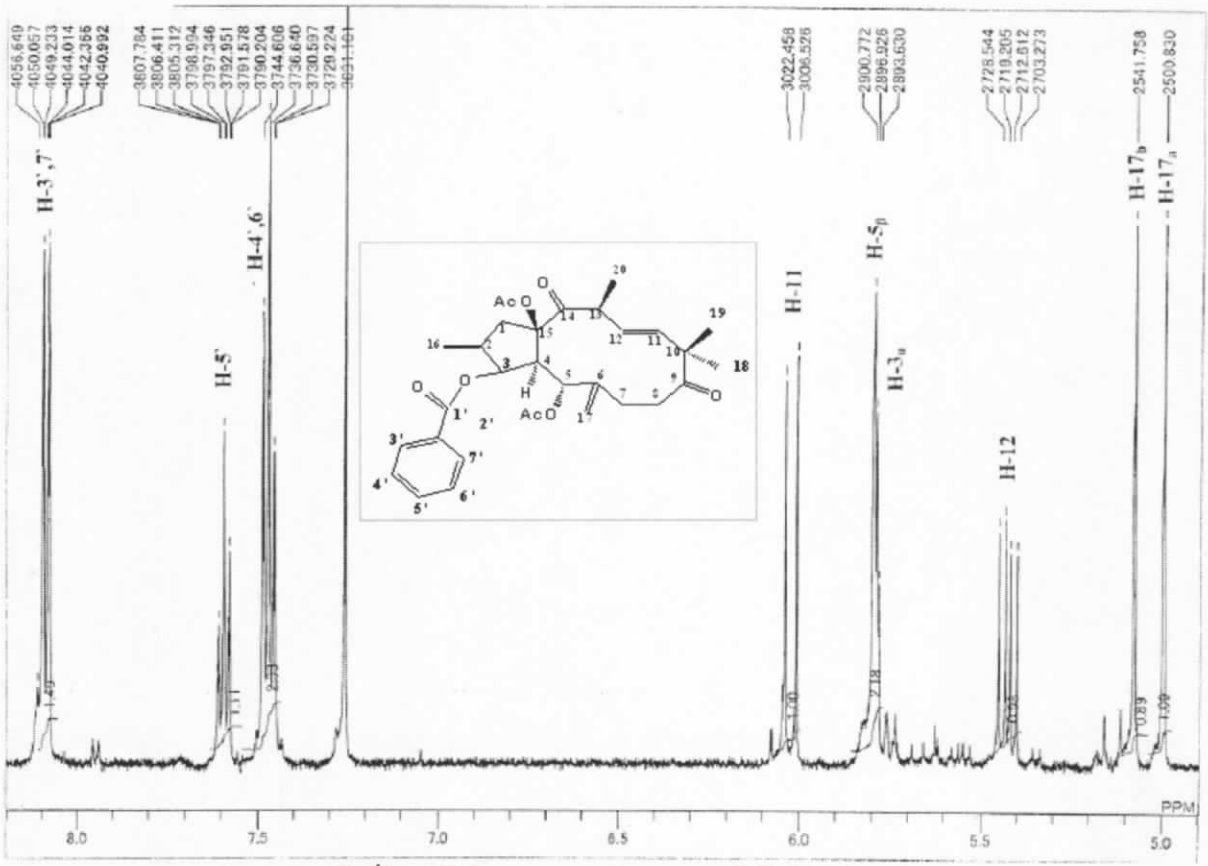
The molecular formula was established as $C_{31}H_{38}O_8$ resulting in 13 insaturations.



Spectrum 10: Mass spectrum of compound EG-2



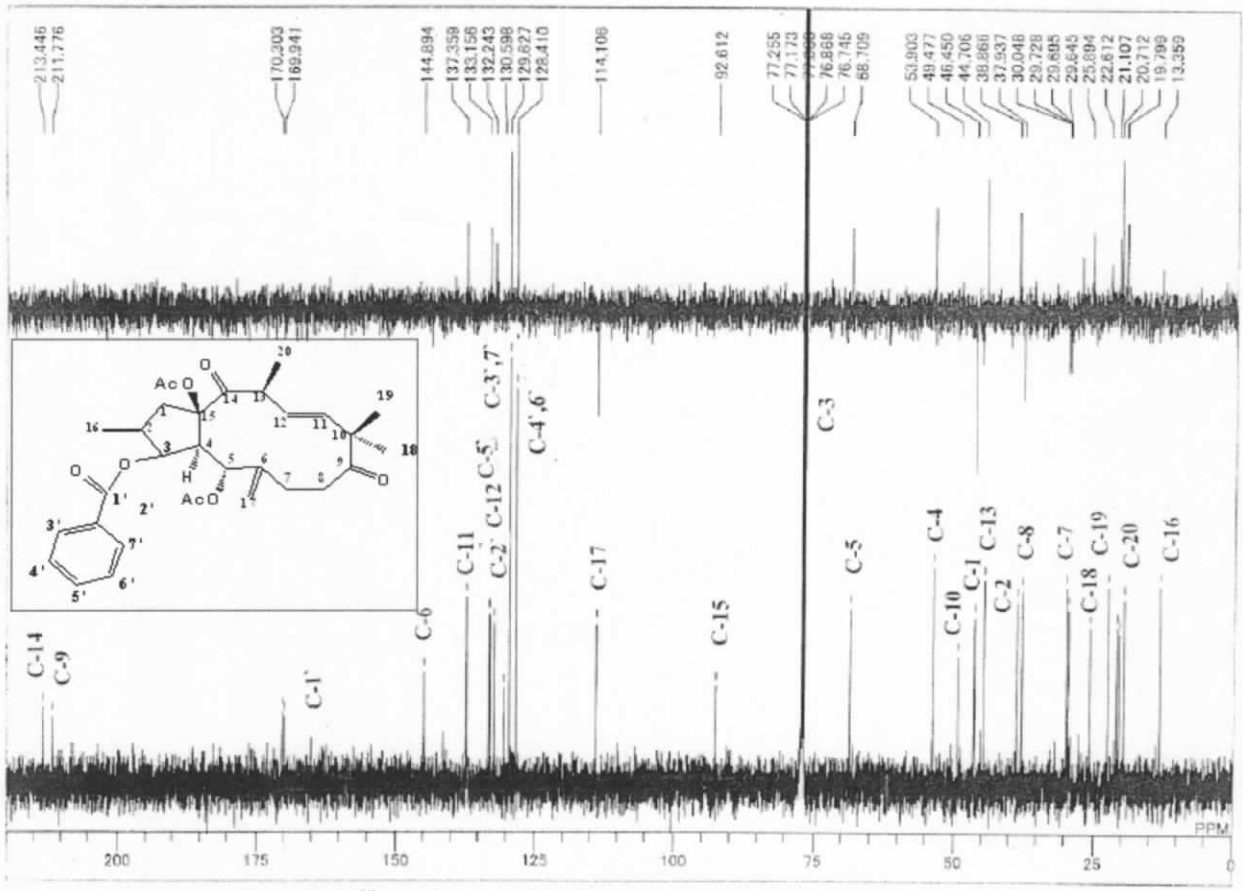
The ^1H and ^{13}C NMR spectra of EG-2 exhibited signals for one benzoate group; H-3',7' appeared as a double doublet at δ_H 8.09 (2H, J = 7.1, 1.4 Hz, δ_C 129.6); H-4',6' at δ_H 7.47 (2H, t, J = 7.1 Hz, δ_C 128.4); H-5' at δ_H 7.60 (1H, tt, J = 7.1, 1.4 Hz, δ_C 133.2); and the carbonyl carbon appeared at δ_C 165.1 (spectra 11, 12 and tables 6, 7)



Spectrum 11: ^{1}H NMR spectrum of compound EG-2(5-8ppm)

Table 6: ^{1}H NMR Spectral Data of EG-2(600MHz, benzene-*d6*)

Protons	δ_H(*J* in Hz)	Protons	δ_H(*J* in Hz)
1β	1.80 (dd, 14.3, 12.9)	13α	3.59 (dd, 9.1, 6.3)
1α	3.08 (dd, 14.3, 7.4)	16	0.96 (d, 6.6)
2α	2.25 (m)	17a	5.00 (br s)
3α	5.79 (t, 3.3)	17b	5.08 (br s)
4α	2.17 (m)	18	1.18 (s)
5β	5.80 (br s)	19	1.19 (s)
7α	2.36 (ddd, 13.7, 9.3, 9.3)	20	1.17 (d, 6.3)
7β	1.81(m)	3', 7'	8.09 (dd, 7.1, 1.4)
8α	2.20 (m)	4', 6'	7.47 (t, 7.1)
8β	2.87 (ddd, 13.5, 9.1, 3.3)	5'	7.60 (tt, 7.1, 1.4)
11	6.03 (d, 15.9)	5-OAc	1.55 (s)
12	5.34 (dd, 15.9, 9.6)	15-Ac	2.19 (s)



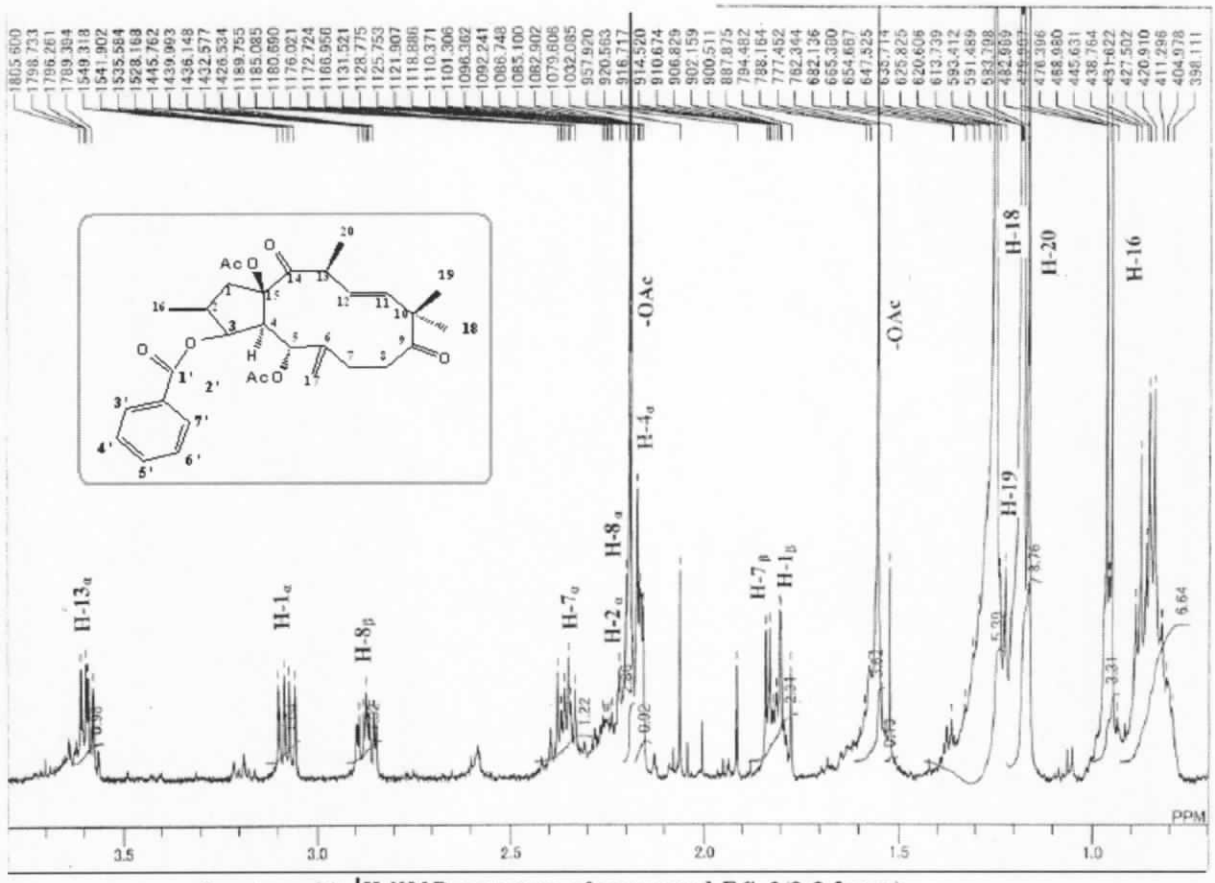
Spectrum 12: ^{13}C NMR and DEPT spectra of compound EG-2

Table 7: ^{13}C NMR Spectral Data of EG-2(150MHz, benzene-*d6*)

Carbons	δ_C	Carbons	δ_C
1	46.5 (t)	14	213.4 (s)
2	38.9 (d)	15	92.6 (s)
3	76.9 (d)	16	13.4 (q)
4	53.9 (d)	17	114.1 (t)
5	68.7 (d)	18	25.9 (q)
6	144.9 (s)	19	22.6 (q)
7	30.0 (t)	20	19.8 (q)
7	1.81 (m)	1'	165.1 (s)
8	37.9 (t)	2'	130.6 (s)
9	211.8 (s)	3', 7'	129.6 (d)
10	49.5 (s)	4', 6'	128.4 (d)
11	137.4 (d)	5'	133.2 (d)
12	132.2 (d)	5-OAc	169.9 (s) 20.7 (q)
13	44.7 (d)	15-Ac	170.3 (s) 21.1 (q)

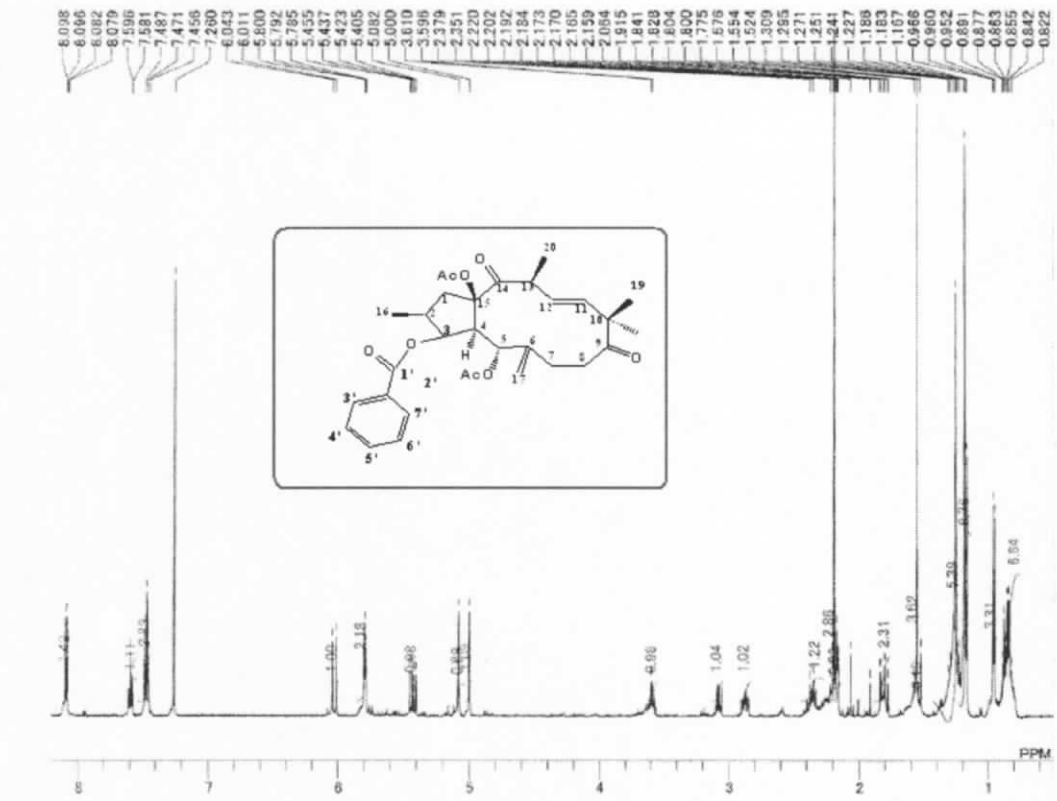
Multiplicity was determined by DEPT experiments; s= quaternary, d= methine, t= methylene, q= methyl.

Furthermore, two acetate groups were detected at δ_H 1.55 (δ_C 169.9, 20.7) and 2.19 (δ_C 170.3, 21.1).

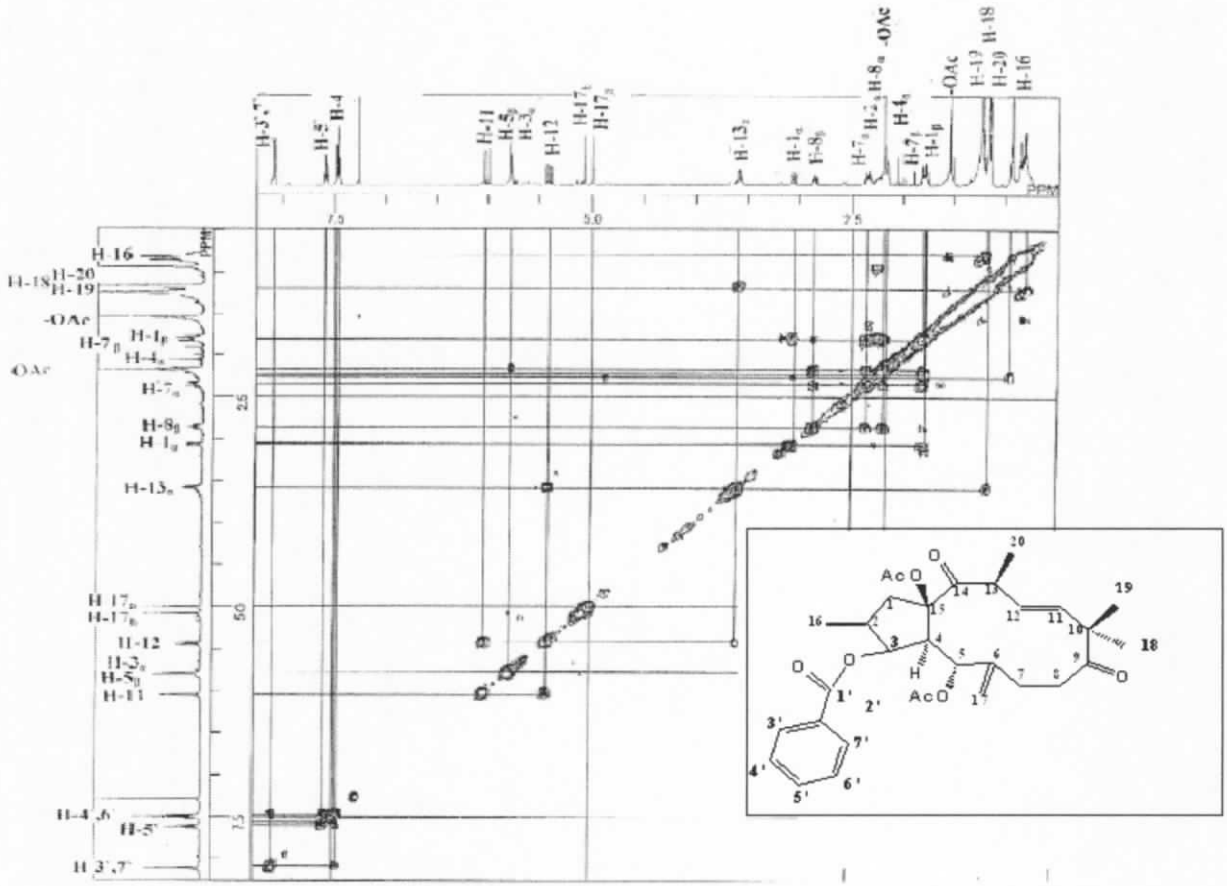


Spectrum 13: ^{1}H NMR spectrum of compound EG-2(0-3.5ppm)

The parent skeleton was considered to be a diterpene from the presence of twenty carbons in the ^{13}C NMR spectrum and DEPT experiments (spectrum 12). Comparison of the 1D and 2D spectral data of EG-1 with those of EG-2 revealed the presence of a *trans*-CH=CH-CH(CH3)- moiety; H-11 appeared at δ_H 6.03 (1H, d, J = 15.9 Hz); H-12 at δ_H 5.43 (1H, dd, J = 15.9, 9.6 Hz); and H-13 at δ_H 3.59 (1H, dd, J = 9.6, 6.3 Hz). The ^{1}H NMR and ^{1}H-^{1}H COSY spectral data were consistent with the presence of an exomethylene group, -CH2-CH2-, and –CH(O)-CHCH(O)-CH(CH3)-CH2- moieties.

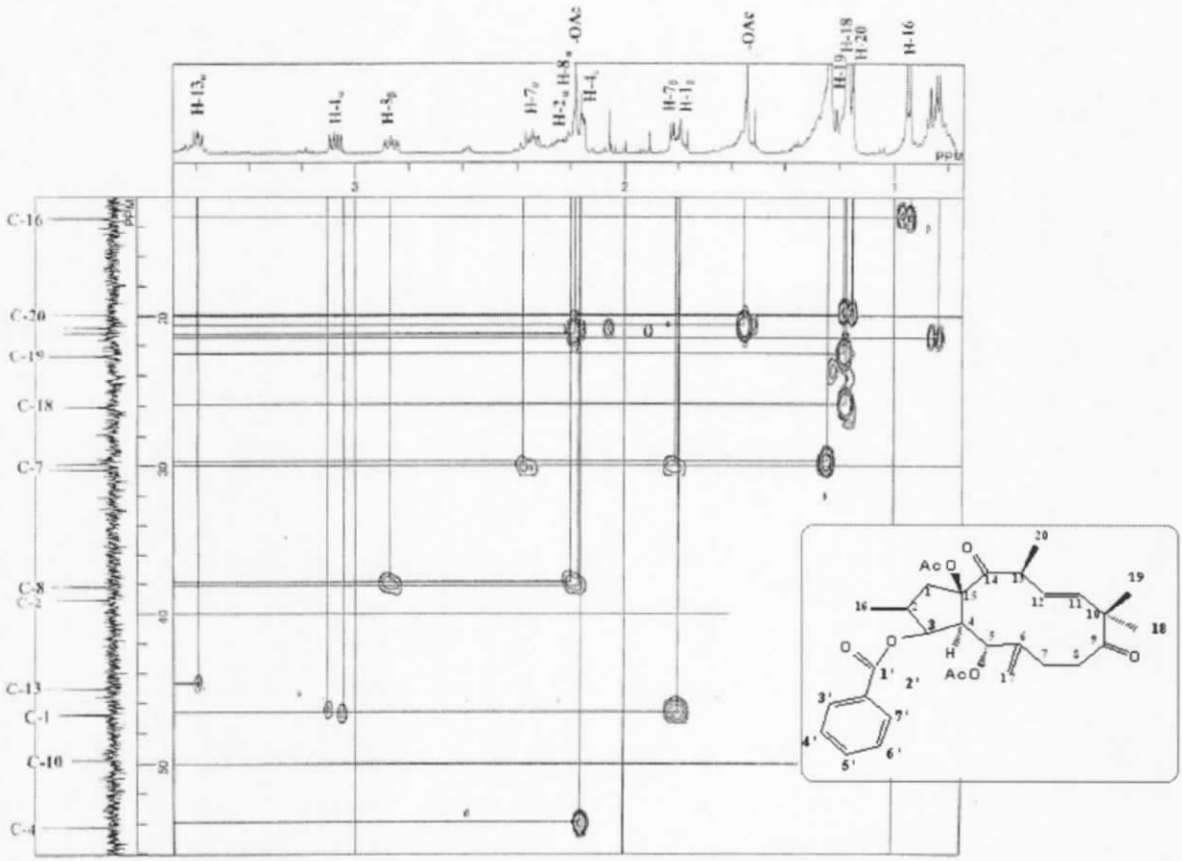


Spectrum 14: ^{1}H NMR spectrum of compound EG-2

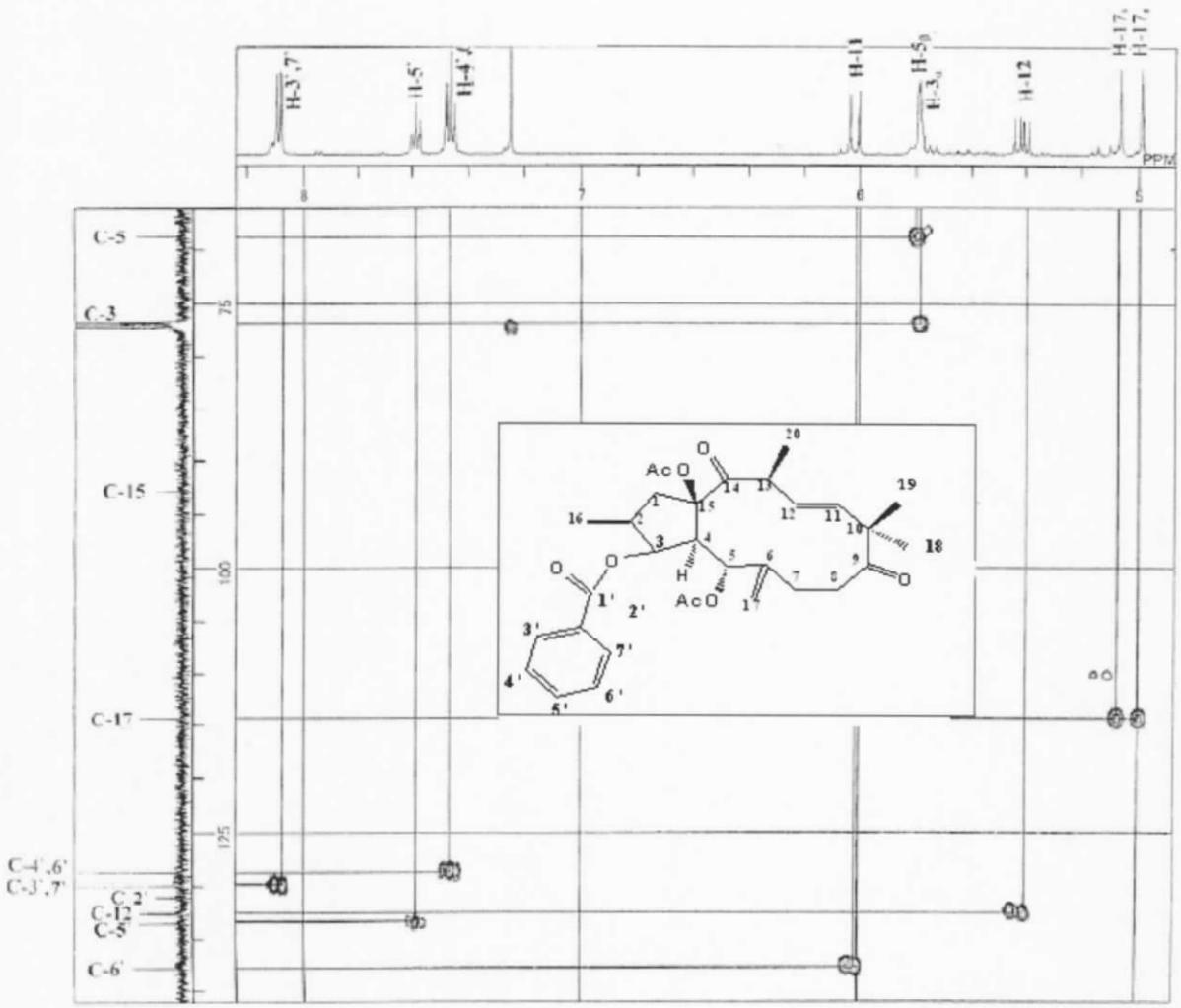


Spectrum 15: ^{1}H-^{1}H COSY spectrum of compound EG-2

Methyl groups were distinguishable into two tertiary groups (δ_H 1.19 and 1.18), and two secondary groups (δ_H 0.96 and 1.17). Furthermore, ^{13}C NMR and DEPT spectral data of EG-2 (spectrum 12) indicated the presence of two ketones at δ_C 211.8 and 213.4. The correlations between protons and their corresponding carbons were determined from HMQC analysis (spectra 16A and 16B).



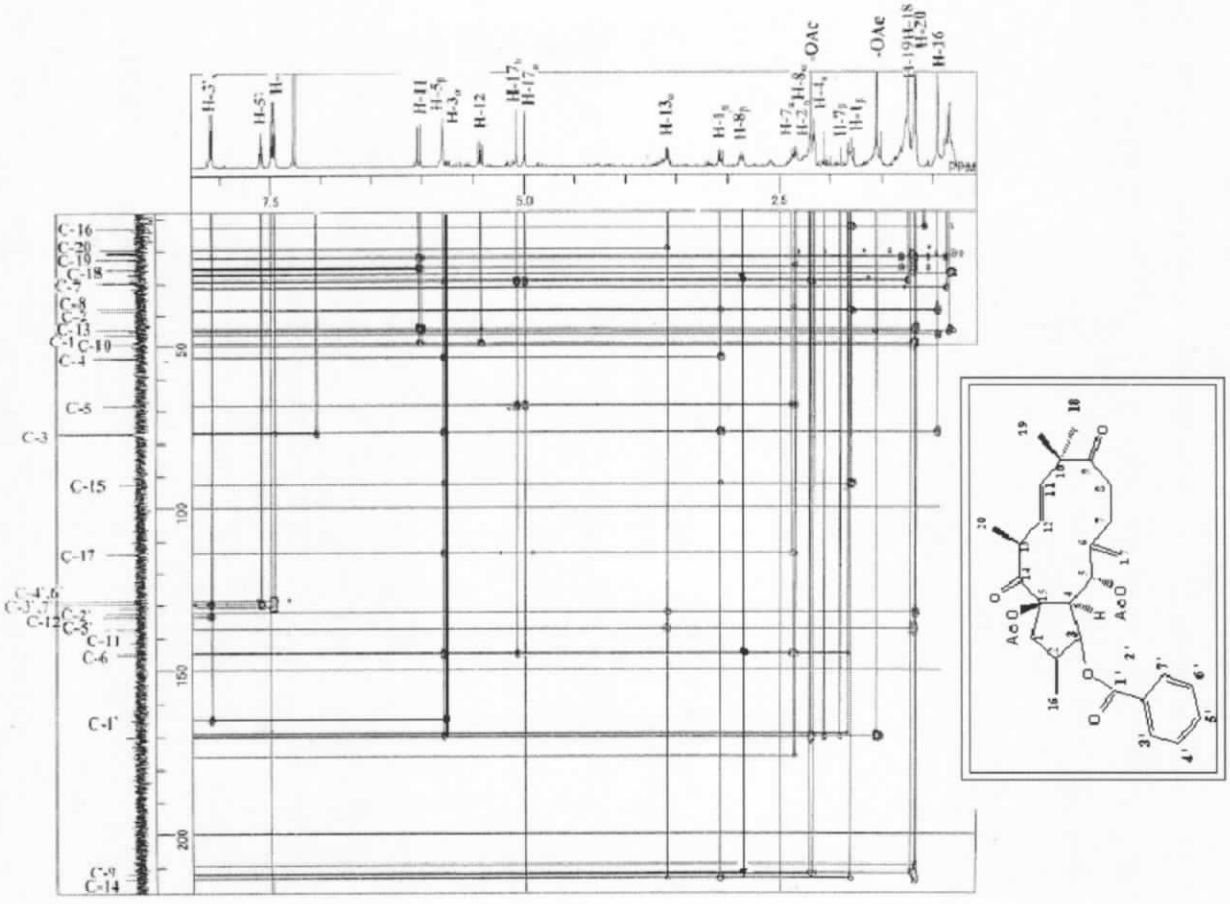
Spectrum 16A: HMQC spectrum of compound EG-2



Spectrum 16B : HMQC spectrum of compound EG-2

The connectivity between partial structures and the positions of the acyl groups were determined from HMBC analysis (spectrum 17, Table 8).

In this experiment, C-H correlations were observed between the protons of the exomethylene group at δ_H 5.00 and 5.08 (H-17a and H-17b) and the carbon signals at δ_C 144.9 (C-6), 30.0 (C-7) and 68.7 (C-5); between the proton signal at δ_H 2.87 (H-8β) and the carbon signals at δ_C 144.9 (C-6), and 30.0 (C-7) and the carbonyl signal at δ_C 211.8 (C-9).



Spectrum 17: HMBC spectrum of compound EG-2

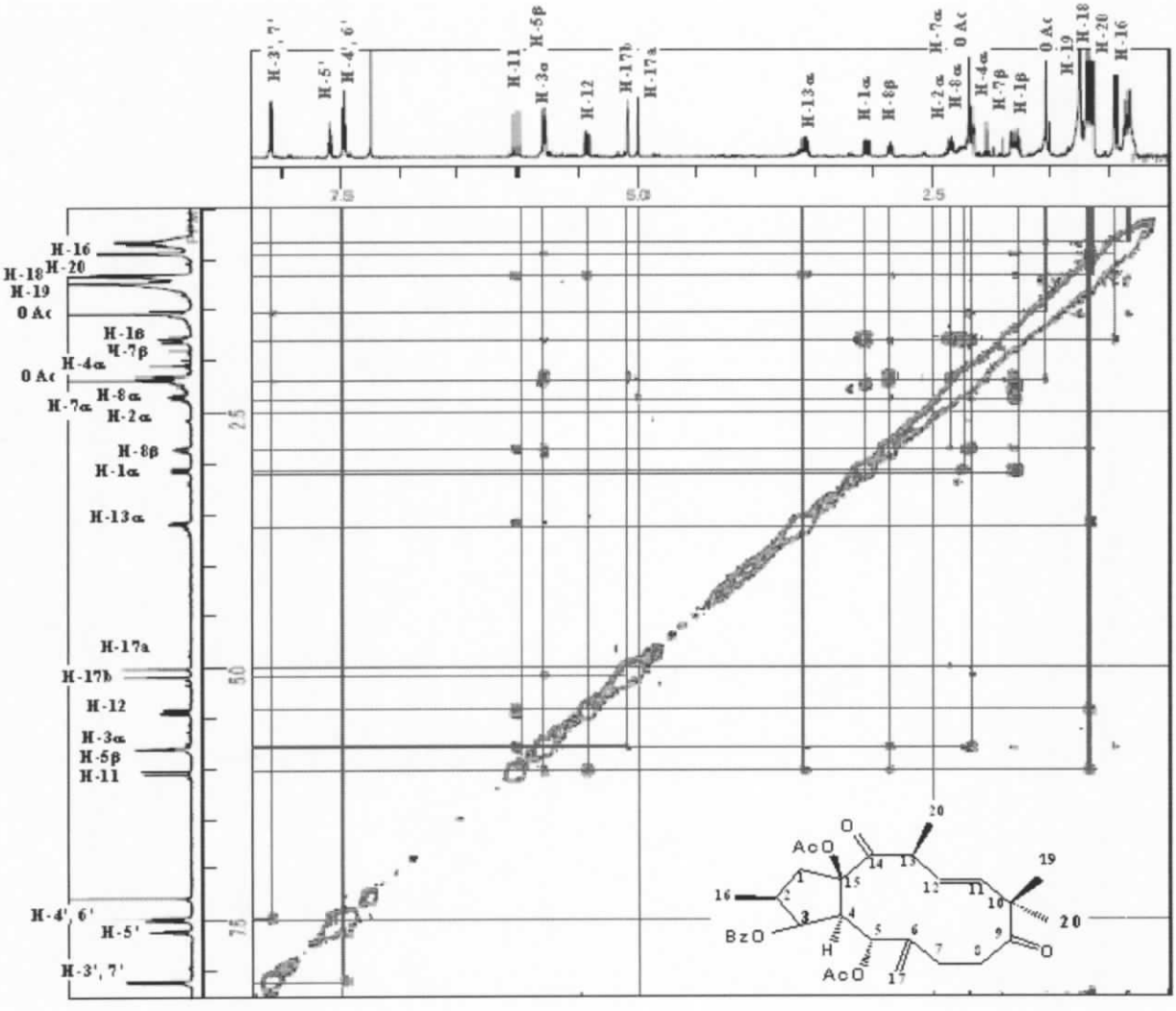
Table 8: HMBC Spectral Data of EG-2

Protons	HMBC	Protons	HMBC
1α	C-2, C-3, C-4, C-14, C-15	17a	C-6, C-7
3α	C-1, C-1', C-15	17b	C-5, C-6
4α	C-6, C-14, C-3	18	C-9, C-10, C-11, C-19
5 β	C-3, C-4, C-6, C-17, 5-OAc	19	C-9, C-10, C-11, C-18
7α	C-5, C-6, C-8, C-17	20	C-12, C-13, C-14
8 β	C-6, C-7, C-9	3', 7'	C-1', C-5'
11	C-10, C-13, C-18, C-19	4', 6'	C-2'
12	C-10, C-13, C-20	5'	C-3', C-7'
13α	C-11, C-12, C-14, C-20	5-OAc	C=O (5-OAc)
16	C-1, C-2, C-3	15-Ac	C=O (15-OAc)

The placement of the benzoate group at C-3 was suggested from the correlation between

H-3, (δ_H 5.79) and the carbonyl carbon at δ_C 165.1. The remaining two acetate groups must be at C-5 and C-15, where H-5 (δ_H 5.80) exhibited correlation with the carbonyl carbon at δ_C 169.9. The unusual high field chemical shift of the acetate group at C-5 (δ_H 1.55) was due to the anisotropic shielding effect of the benzoate moiety at C-3.

The relative configuration was investigated by means of NOESY measurements. The observed NOE correlations between H3/H-17b, H-4/H-11, H-4/H17b, H-7α/H-17a, and H-11/H-13 supported the α-orientation of all protons. The NOE correlations between H-1β/H-16, H-5/H-7β, H-5/H-8β,15-OAc/ H-20, 15-OAc/H-3,7 indicated the β-orientation of these protons (spectrum 18, Table 9).



Spectrum 18: NOESY spectrum of compound EG-2

Table 9: NOESY Spectral Data of EG-2

Protons	NOESY	Protons	NOESY
1β	H-16	12	H-20
1α	H-2	13α	H-5, H-11
2α	H-1	16	H-1 β, H-3
3α	H-4, H-16, H-17b	17a	H-7α
4α	H-5, H-11, H-17b	17b	H-3, H-4, H-5
5 β	H-4, H-7 β, H-8 β, H-13, H-17b	20	H-12
7α	H-17b	3', 7'	5-OAc, 15-OAc
7 β	H-5	5-OAc	H-3', H-7'
8 β	H-5, H-11	15-Ac	H-3', H-7'
11	H-4, H-5, H-8, H-13		

The selected HMBC and NOESY correlations are shown in figures 3 and 4 respectively.

EG-2 was given the name of **Guyonianin B**

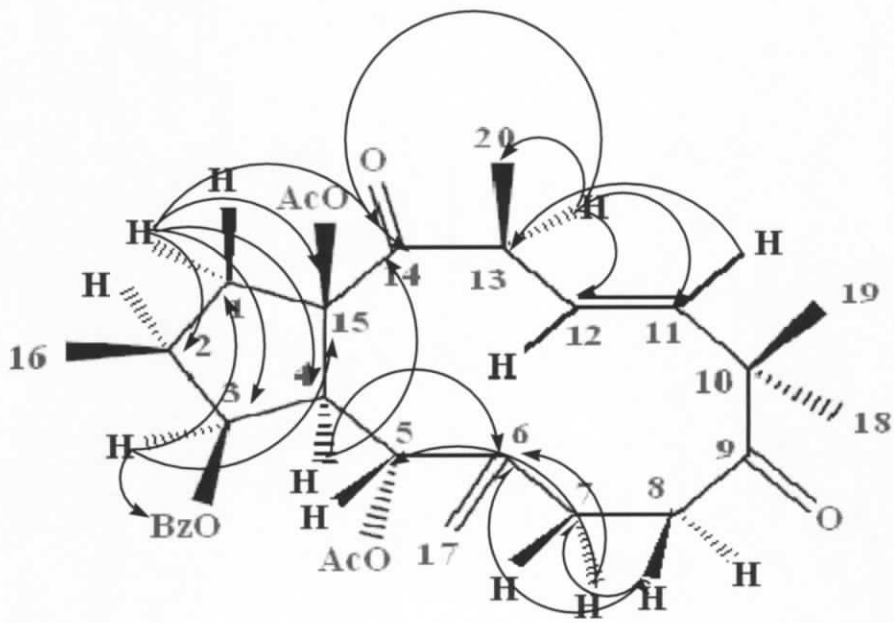


Fig 4: Selected HMBC correlations of compound EG-2

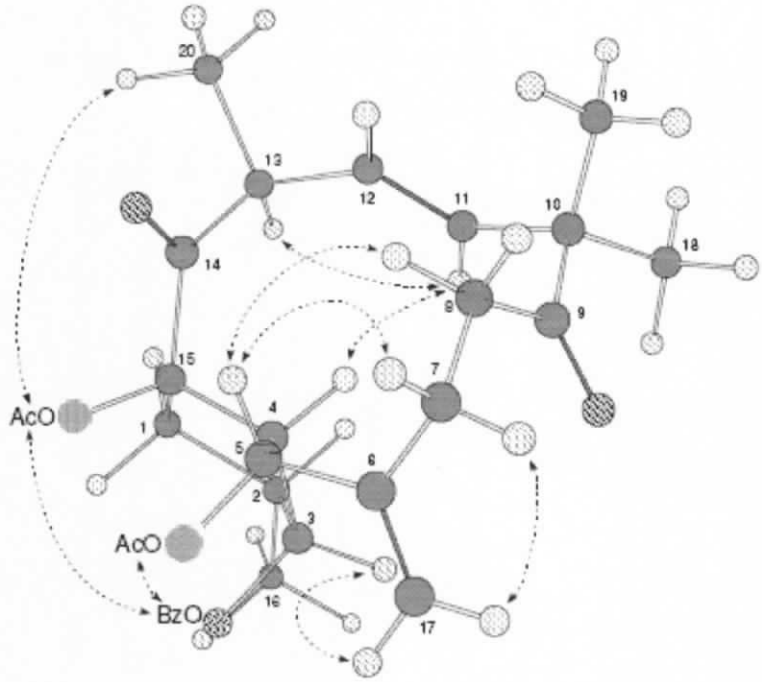
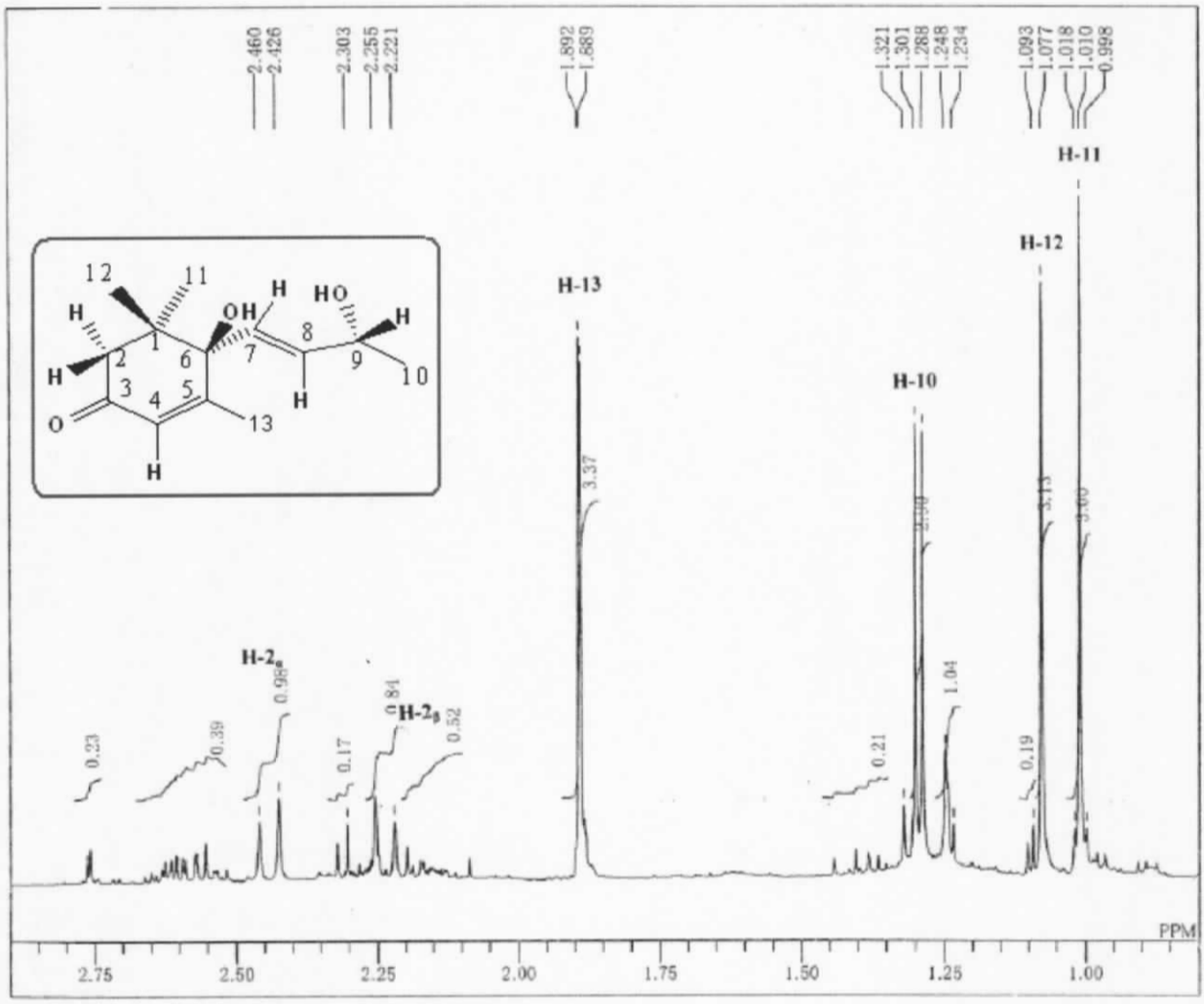


Fig 5: Selected NOE correlations of compound EG-2

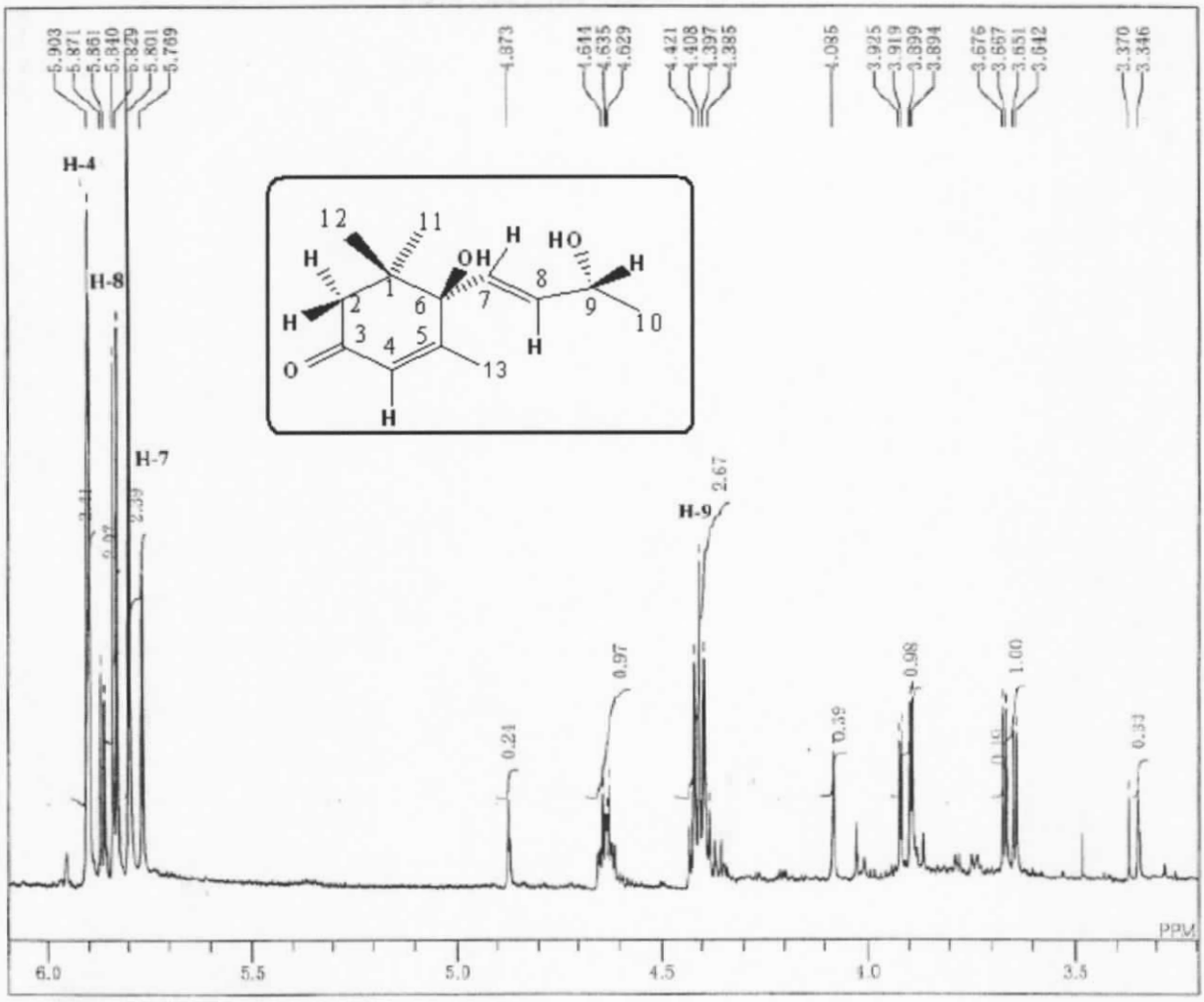
3.1.4. Compound EG-3

Compound EG-3 was determined to be vomifoliol (or blumenol A) through the comparison of its spectral data with those given in the literature.[141,142] The mass spectrum of this compound was in full agreement with the proposed structures. The IR band at 1650 cm−1 suggested the presence of an enone system. The 1H NMR spectrum showed two tertiary methyls at δ 1.08 (3H, s, H-12) and 1.01 (3H, s, H-11), a secondary methyl at δ 1.29 (3H, d, *J*= 6.6 Hz, H-10), a methyl attached to an olefinic carbon at δ 1.89 (3H, d, *J*= 1.2 Hz, H-13), an isolated methylene group α to CO at δ 2.44 (1H, d, *J* = 17.1 Hz, H-2α) and 2.24 (1H, d, *J* = 17.1 Hz, H-2β), and an oxymethine proton at δ 4.41(m, H-9).(spectra 19 and 20)

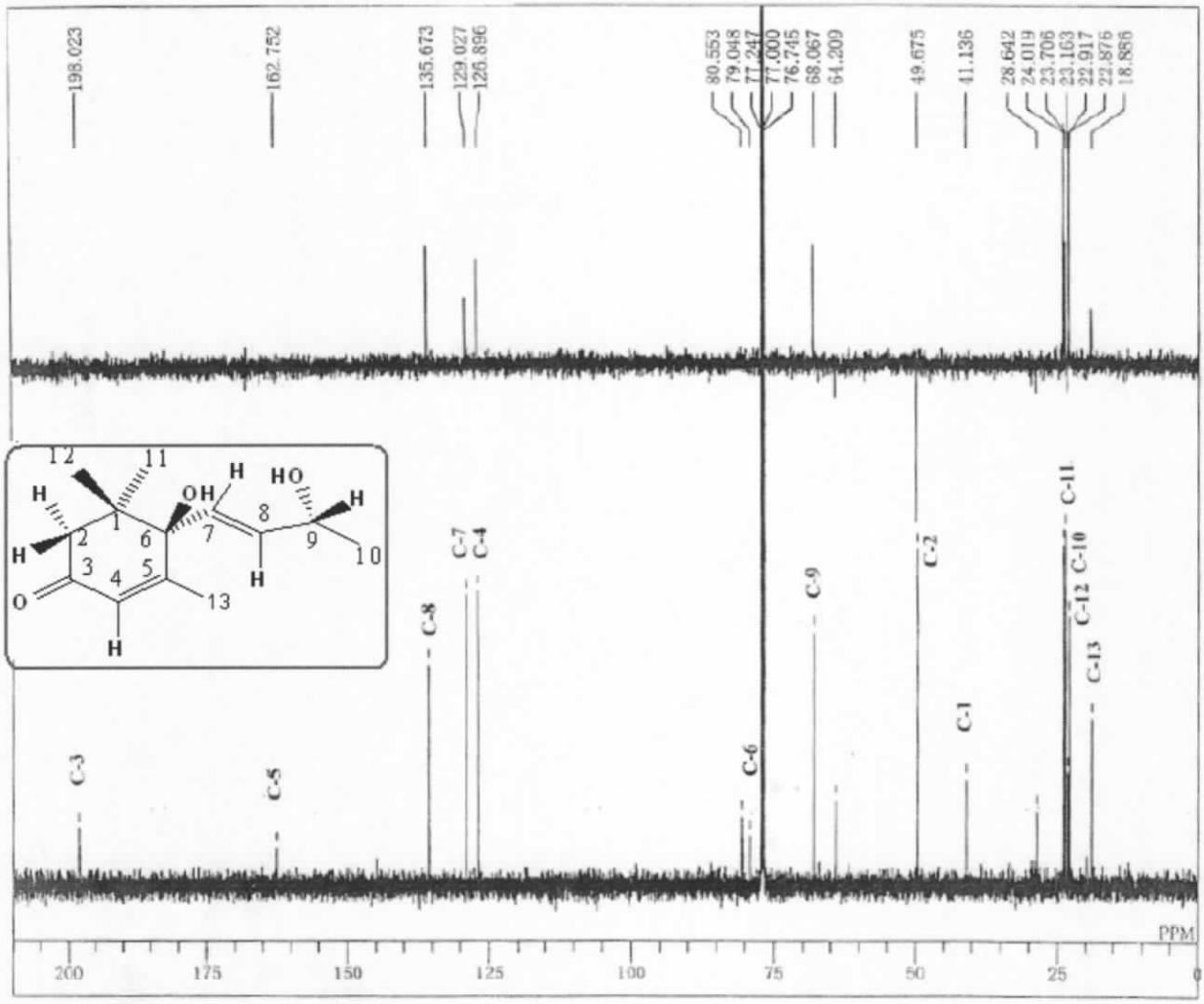


Spectrum 19A: ^{1}H NMR spectrum of compound EG-3

The instauration on the side chain was followed by ^{1}H and ^{13}C NMR resonances at δ 5.85 (dd, *J*= 5.4 and 15.6 Hz, H-8, δ_C 135.7) and 5.79 (d, *J*= 15.6 Hz, H-7, δ_C 129.0).

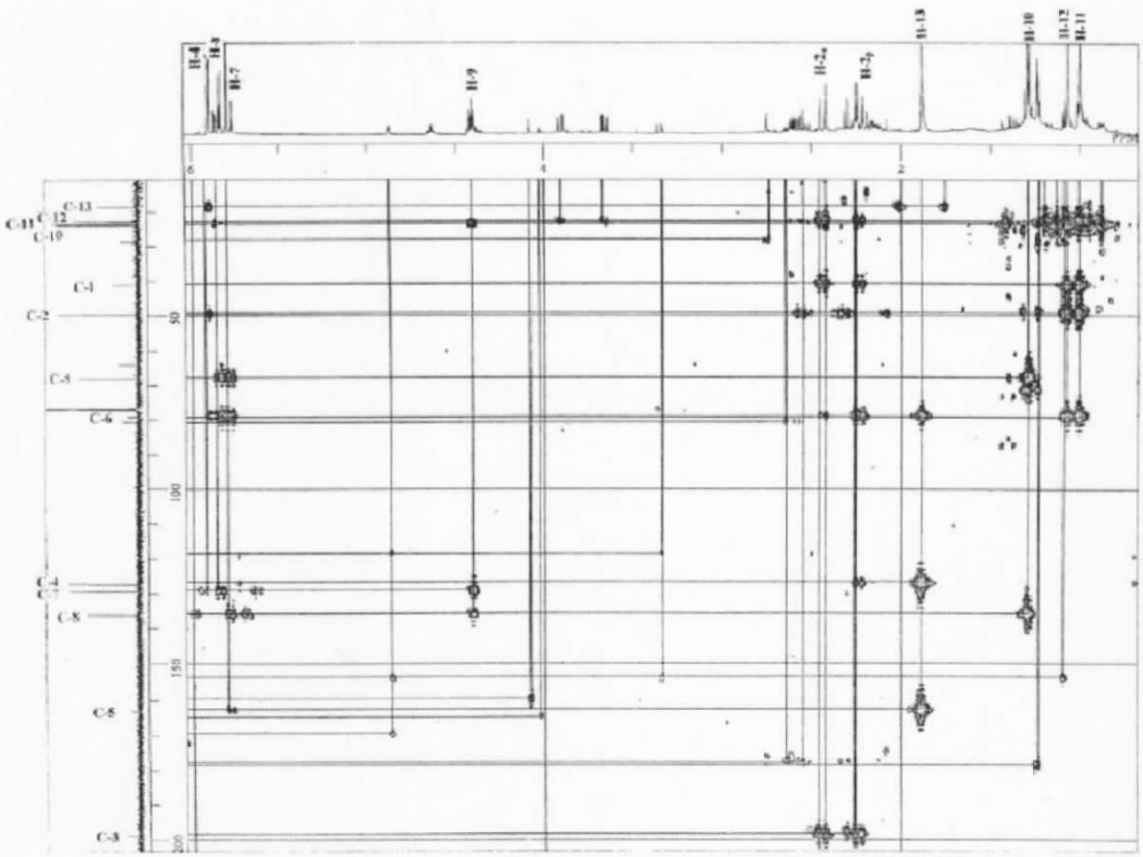


Spectrum 19B: ^{1}H NMR spectrum of compound EG-3



Spectrum 20: ^{13}C NMR and DEPT spectra of compound EG-3

The use of 2D NMR experiments has permitted the confirmation its structure. The cyclohexenone structure was confirmed by the observation in the HMBC spectrum of correlations between the AB system H2αβ (δ 2.44, δ 2.24, *J*1=*J*2=17.1Hz) and C3 (δ 198.0), C6 (δ 79.0) and C4 (δ 126.9). The location of the two high field methyl groups CH_3-11 and CH_3-12 at C1 was ascertained by the detection of the H2α,β-C11 and H2α,β-C12 correlations. The position of the side chain on C6 of the cyclohexenone ring is confirmed by the observation in the HMBC spectrum of the H7-C6 correlation.



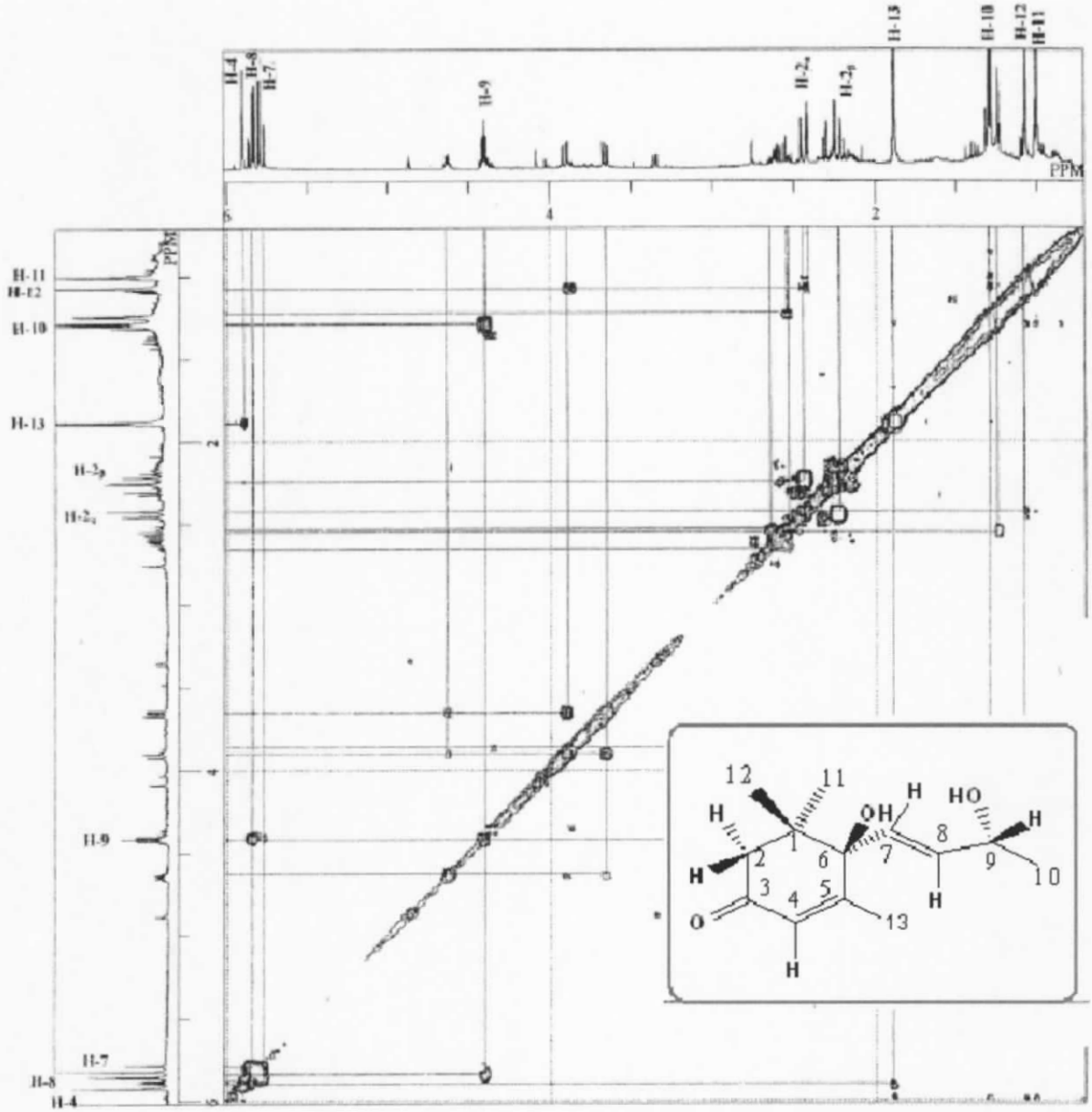
Spectrum 21: HMBC spectrum of compound EG-3

Table 10: ^{1}H and ^{13}C NMR (500 and 125 MHz in $CDCl_3$, 22.3 ^{o}C) of EG.3

Protons	δ_H(*J* in Hz)	Carbons*	HMBC
1		41.1 (s)	
2α	2.44(d, 17.1)	49.7 (t)	C1, C3, C6, C11, C12
2β	2.24(d, 17.1)		C1, C3, C4, C6, C11, C12
3		198.0 (s)	
4	5.90(br.q, 1.2)	126.9 (d)	C2, C6, C13
5		162.8 (d)	
6		79.0 (s)	
7	5.79(d, 15.6)	129.0 (d)	C6,C8,C9
8	5.85(dd, 15.6, 5.4)	135.7 (d)	C6,C7,C9,C10
9	4.41(quin, 5.9)	68.1 (d)	C7,C8,C10
10	1.29(d, 6.6)	23.7 (q)	C8,C9
11	1.01(s)	24.0 (q)	C1, C2, C6, C12
12	1.08(s)	22.9 (q)	C1, C2, C6, C11
13	1.89(d, 1.2)	18.9 (q)	C4,C5,C6

Multiplicity was determined by DEPT experiments; s= quaternary, d= methine, t= methylene, q= methyl.

The COSY spectrum revealing correlations between the olefinic signal H7 (δ 5.79) with the other olefinic proton H8 (δ 5.85) which in turn had a cross peak with H9 (δ 4.41) permitted us to confirm the structure of this side chain.



Spectrum 22: ^{1}H-^{1}H COSY spectrum of compound EG-3

Table11: ^{1}H and ^{13}C NMR (500 and 125 MHz in $CDCl_3$, 22.3 ^{o}C) of EG.3

Protons	δ_H(*J* in Hz)	Carbons*	HMBC
1		41.1 (s)	
2α	2.44(d, 17.1)	49.7 (t)	C1, C3, C6, C11, C12
2β	2.24(d, 17.1)		C1, C3, C4, C6, C11, C12
3		198.0 (s)	
4	5.90(br.q, 1.2)	126.9 (d)	C2, C6, C13
5		162.8 (d)	
6		79.0 (s)	
7	5.79(d, 15.6)	129.0 (d)	C6,C8,C9
8	5.85(dd, 15.6, 5.4)	135.7 (d)	C6,C7,C9,C10
9	4.41(quin, 5.9)	68.1 (d)	C7,C8,C10
10	1.29(d, 6.6)	23.7 (q)	C8,C9
11	1.01(s)	24.0 (q)	C1, C2, C6, C12
12	1.08(s)	22.9 (q)	C1, C2, C6, C11
13	1.89(d, 1.2)	18.9 (q)	C4,C5,C6

***Multiplicity was determined by DEPT experiments; s= quaternary, d= methine, t= methylene, q= methyl.**

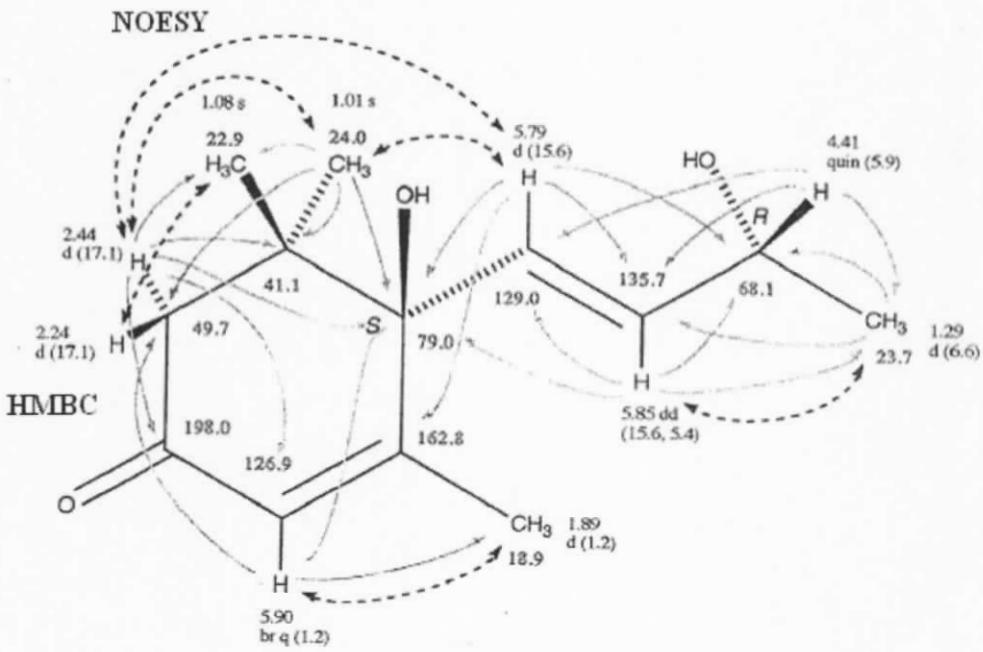


Fig 6. Selected NOESY and HMBC correlations of compound EG-3

3.2. *Launaea resedifolia*

3.2.1. Phytoscreening of *Launaea resedifolia*

The different parts of *Launaea resedifolia* were subjected to many phytochemical tests to reveal the following results.

Table 12: Results of phytoscreening tests

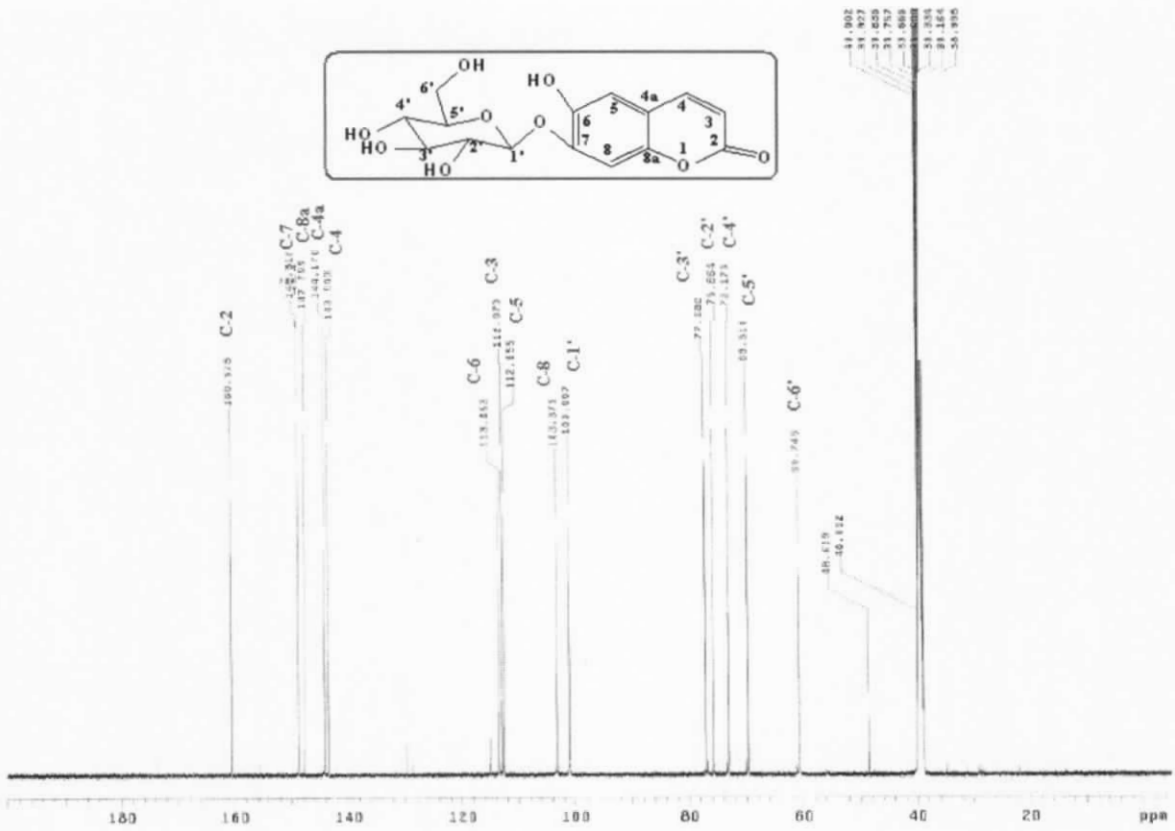
organ / active principle	Roots	Stems	Leaves	Flowers	Seeds
Steam distillation	+	+	+	+	+
Flavonoids	+	+	+	+	+
Alkaloids	-	-	-	-	-
Tannins	+	+	+	+	+
Saponins	+	+	+	+	-
Sterols and Triterpenes	+	+	+	+	+
Coumarins	+	+	+	+	+

It is worth mentioning that the plant contains many important chemical families and hence we have opted for the study of coumarins.

3.2.2. Compound LR-1

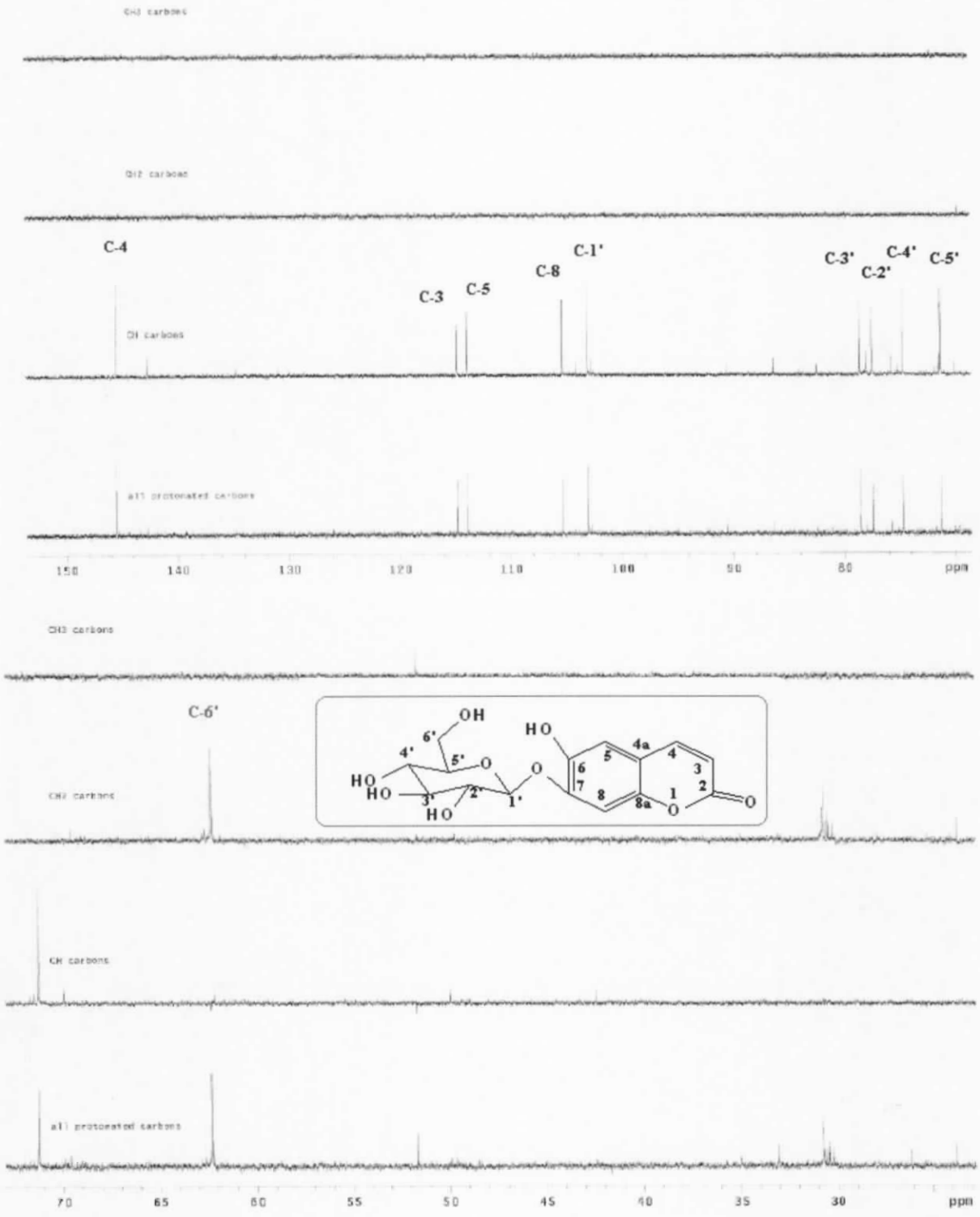
Colorless oil, CIMS showed a molecular ion peak $[M+1]^+$ at *m/z* 341 in according with the molecular formula $C_{15}H_{16}O_9$.

The ^{13}C-NMR spectrum of compound I displayed fifteen carbon signals.



Spectrum 23: ^{13}C NMR spectrum of compound LR-1

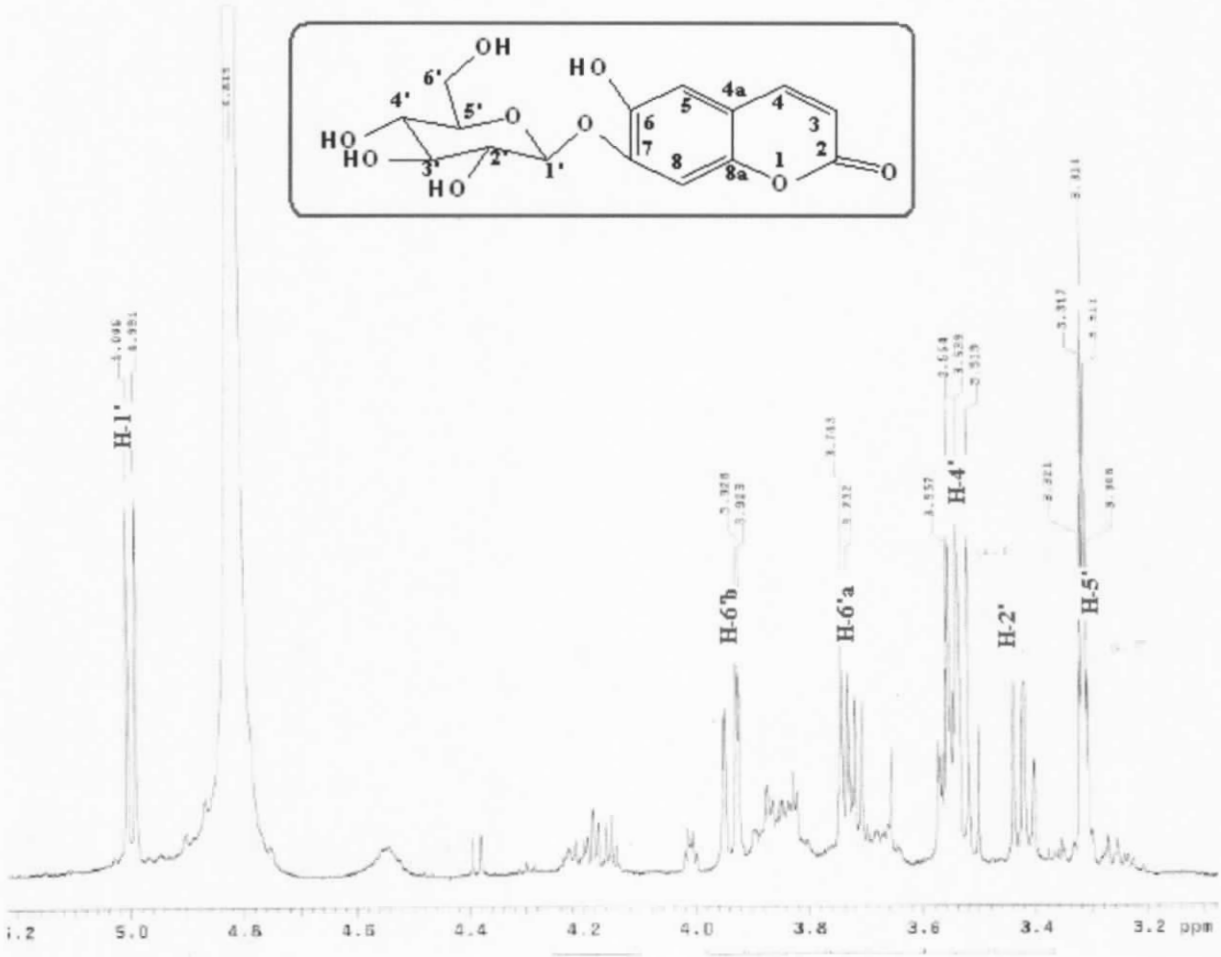
DEPT experiments indicated these signals as: one carbonyl carbon at δ_C 160.57 (s, C-2), one methylene carbon at δ_C 60.74 (t, C-6`); nine methine carbons at $\delta_C$ 143.59 (d, C-4), 112.97 (d, C-3), 112.65 (d, C-5), 103.37 (d, C-8), 100.99 (d, C-1`), 77.28(d, C-3`), 75.86 (d, C-2`), 73.17 (d, C-4`) and 69.81 (d, C-5`) and four quaternary carbons at δ_C 148.81 (s, C-7), 147.79 (s, C-8_a), 144.17 (s, C-4_a) and 113.45 (s, C-6).



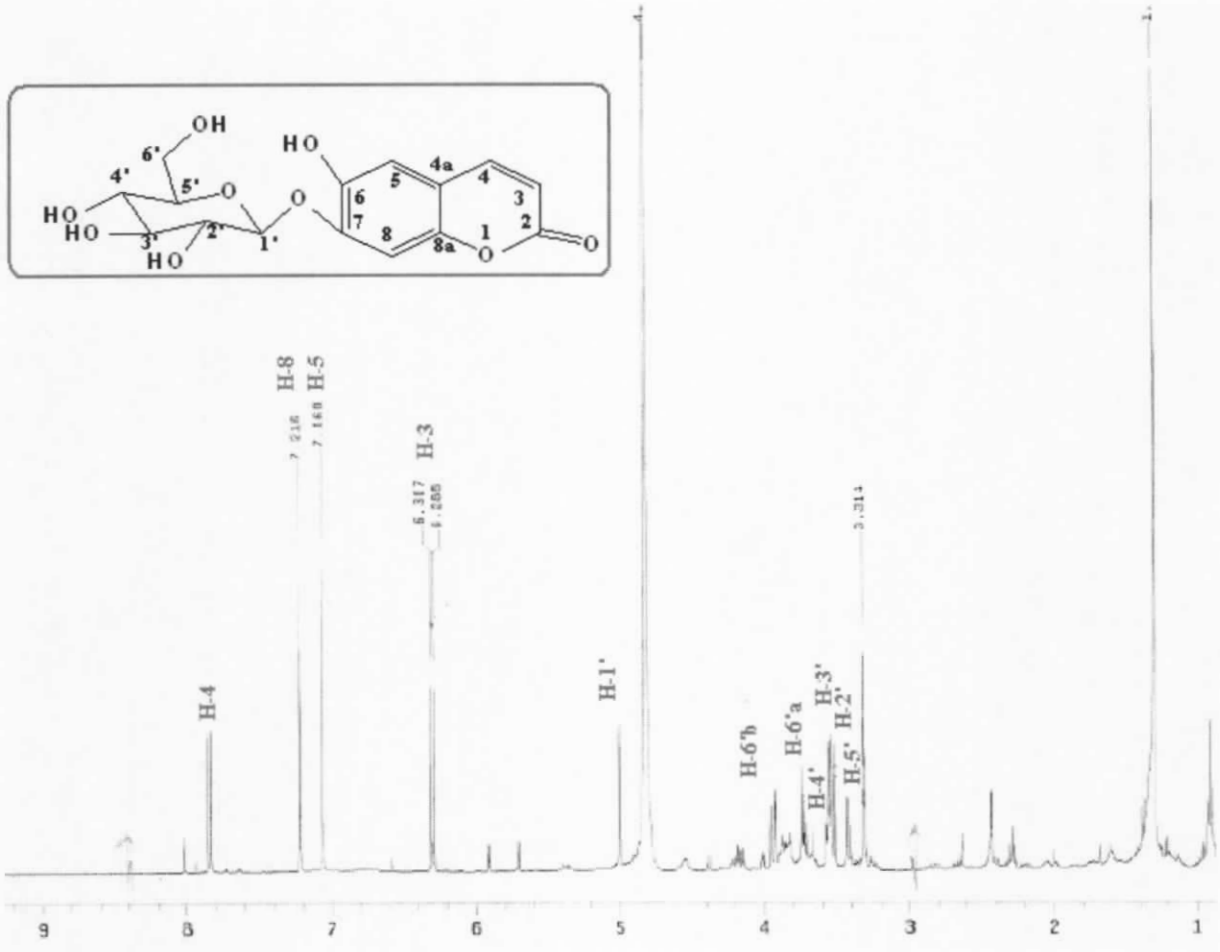
Spectra 24: DEPT spectra of compound LR-1

The ^{1}H-NMR spectrum showed characteristic signals of glucose moiety, whereas, the methylene protons H-6'$_a$ and H-6'$_b$ appeared as two double doublets at δ_H 3.93 (J = 12.0, 3.0 Hz) and 3.72 (J = 12.0, 3.0 Hz). The anomeric proton H-1' appeared downfield as doublet

signal at δ_H 4.96 (J = 7.5 Hz), the other methine protons H-2`, H-3`, H-4` and H-5` appeared at δ_H 3.54 (dd, J = 7.5, 8.5 Hz), 3.50 (dd, J = 8.5, 9.0 Hz), 3.41(dd, J = 9.0, 9.0 Hz) and 3.51 (ddd, J = 3.0, 5.0, 9.0 Hz), respectively.

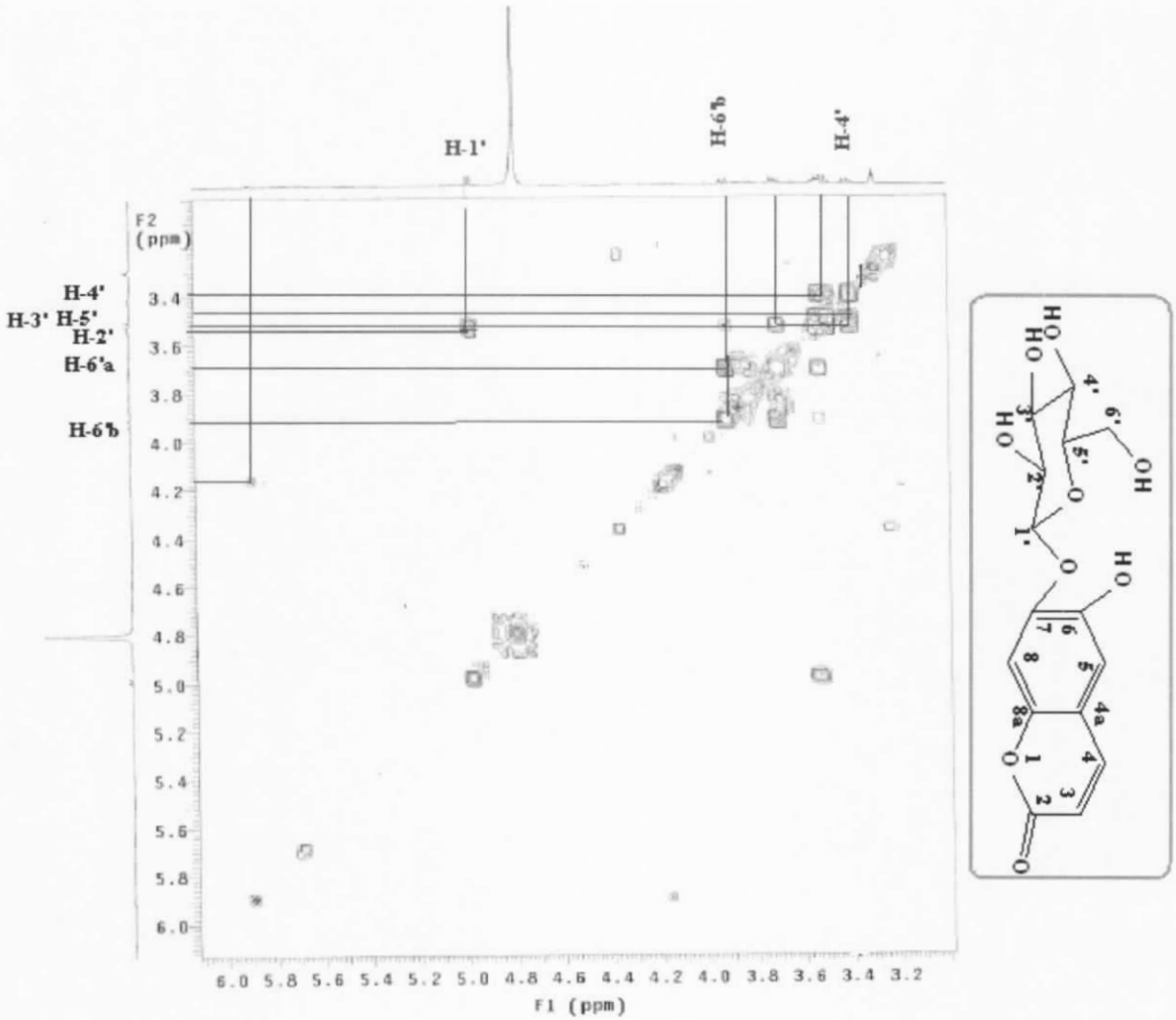


Spectrum 25A: ^{1}H NMR spectrum of compound LR-1



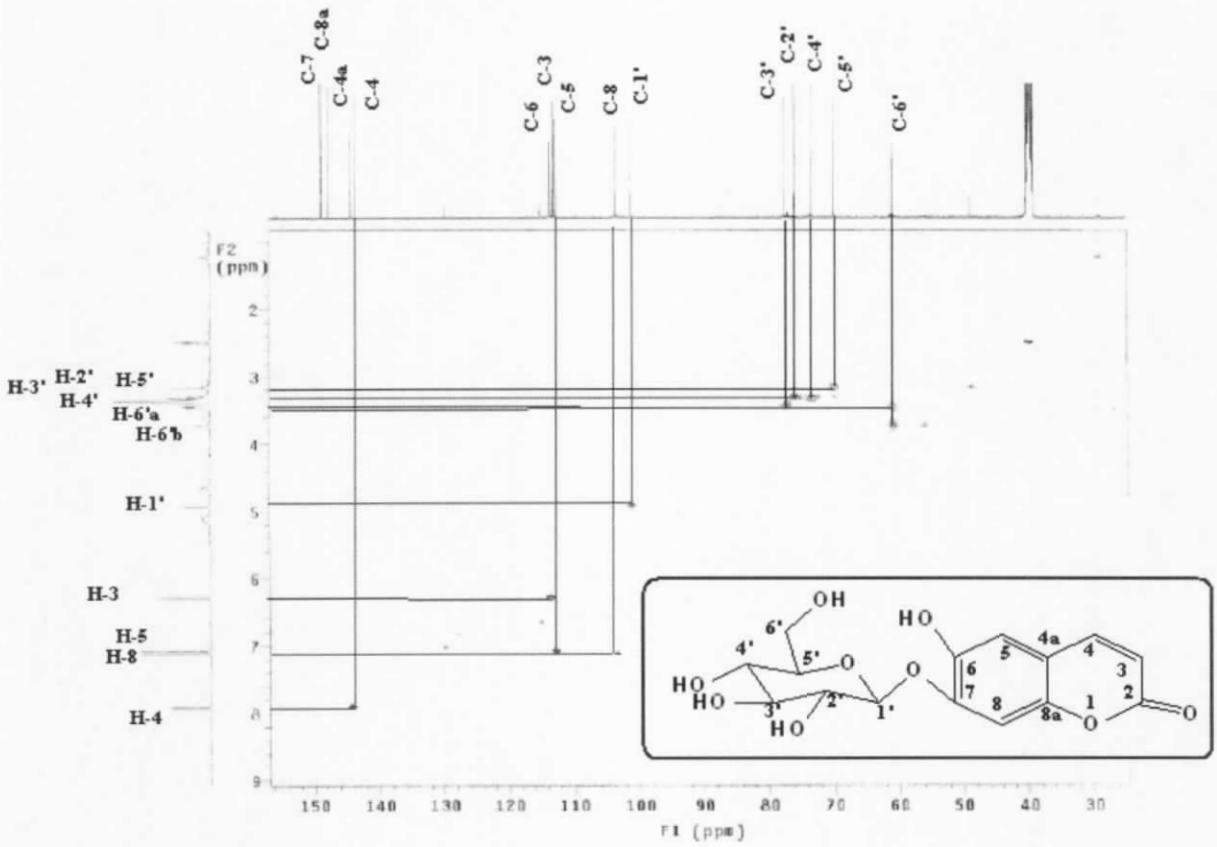
Spectrum 24B: ^{1}H NMR spectrum of compound LR-1

The coumarin moiety exhibited characteristic signals as a doublet at δ_H 7.81 (H-4, J = 9.5 Hz), which correlated in ^{1}H-^{1}H COSY with doublet at δ_H 6.27 (H-3, J = 9.5 Hz). The two singlet signals appeared at δ_H 7.20 and 7.03 were assigned for H-8 and H-5, respectively. All proton and carbon signals were assigned by ^{1}H-^{1}H and ^{1}H-^{13}C COSY.



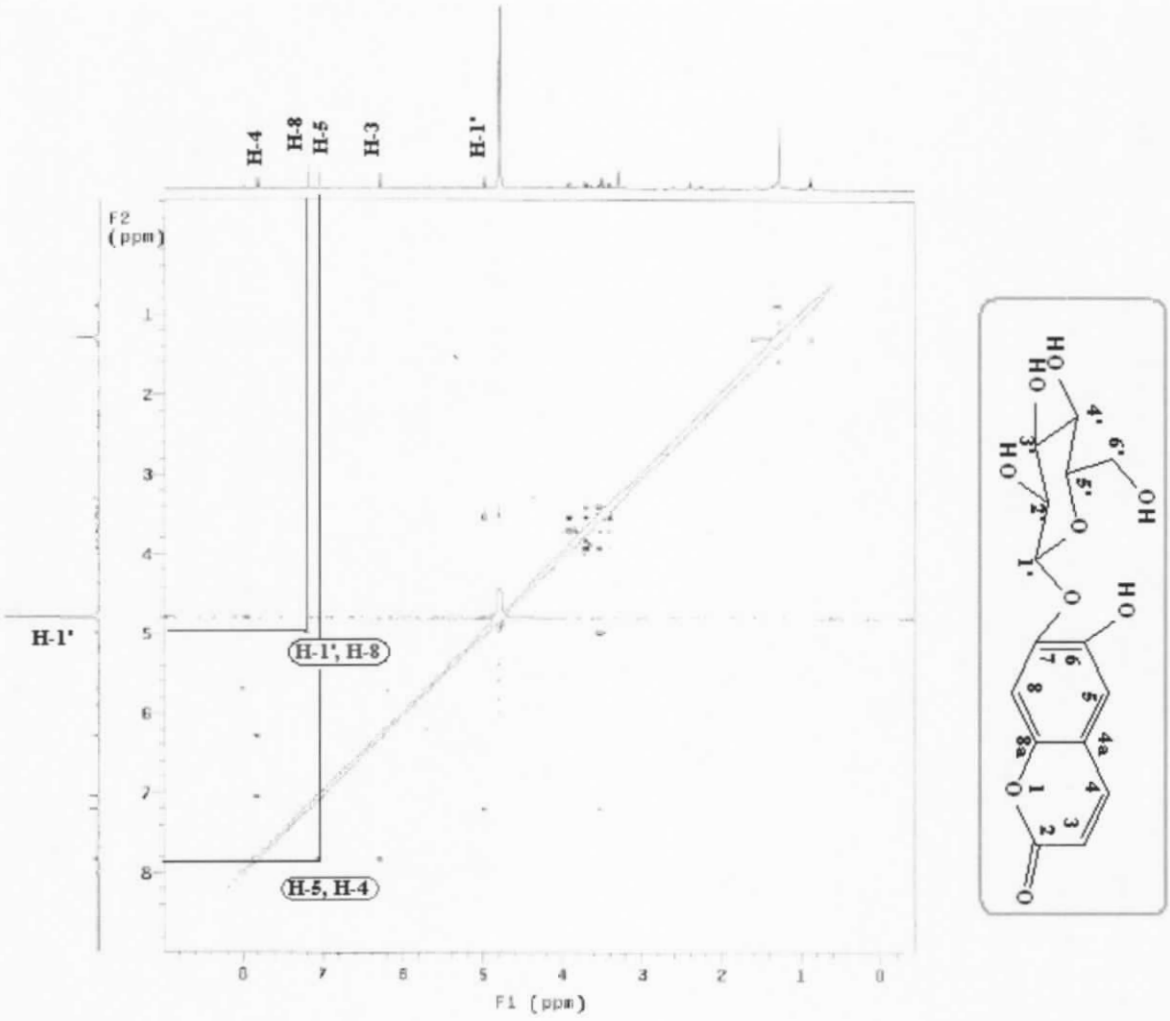
Spectrum 26: ^{1}H- ^{1}H NMR spectrum of compound LR-1

In the ^{1}H-^{13}C COSY, the signal at δ_H 4.96 (H-1`) showed correlation with the carbon signal at $\delta_C$ 101.0 (C-1`). The two double doublet signals at δ_H 3.93 and 3.72 correlated with carbon signal at δ_C 60.74 (C-6`).



Spectrum 27: HMQC spectrum of compound LR-1

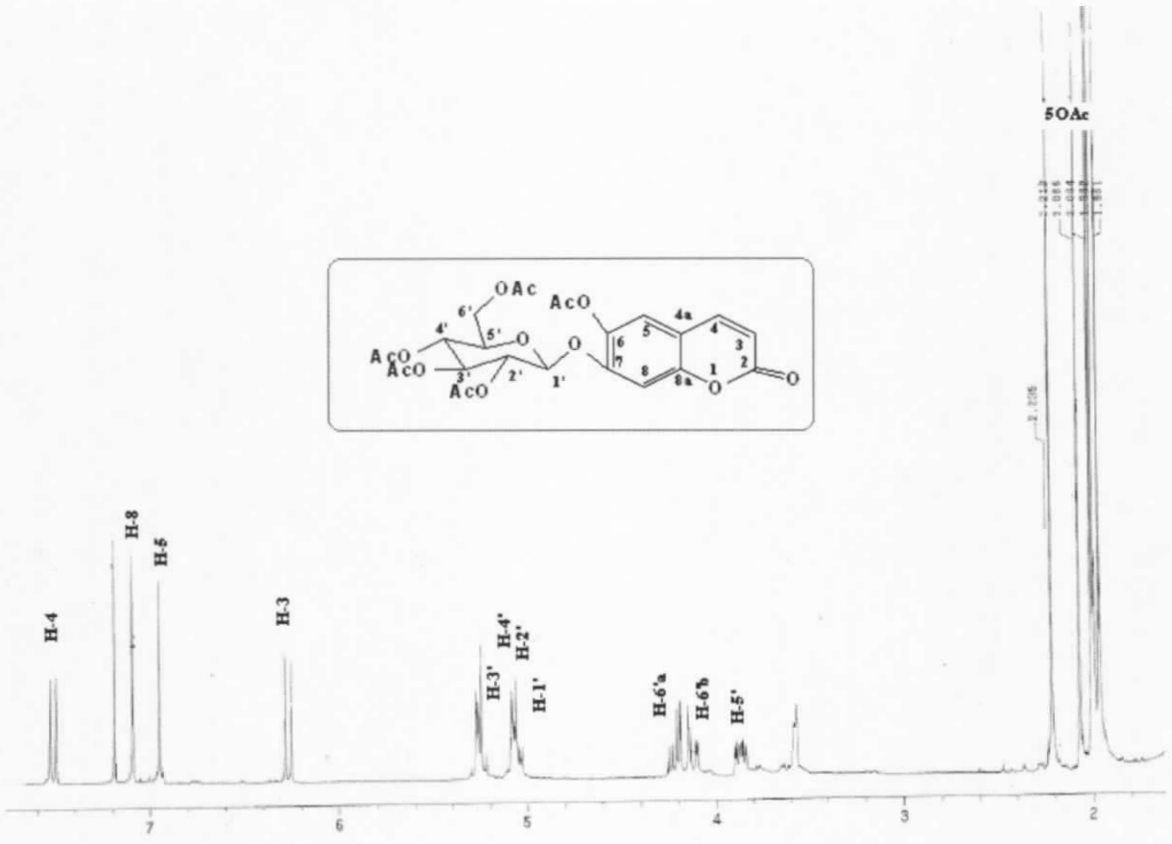
The presence of sugar moiety in position 7 was proved by NOE spectrum which showed correlation between doublet at δ_H 7.81 (H-4) and the two signals at δ_H 7.03 (H-5) and doublet at δ_H 6.27 (H-3) and correlation between singlet at δ_H 7.20 (H-8) and the doublet at δ_H 4.96 (H-1`).



Spectrum 28: NOE spectrum of compound LR-1

Therefore, compound **LR-1** was identified as Cichoriin. [144]

Acetylation of a portion of compound LR-1 gives the acetylated derivative **LR-1a**. HRCIMS provides a molecular ion peak $[M+1]^+$ at *m/z* 551 corresponding to $C_{25}H_{26}O_{14}$. The ^{1}H-NMR spectrum revealed the five acetyl signals at δ_H 2.04, 2.07, 2.08, 2.14 and 2.29.

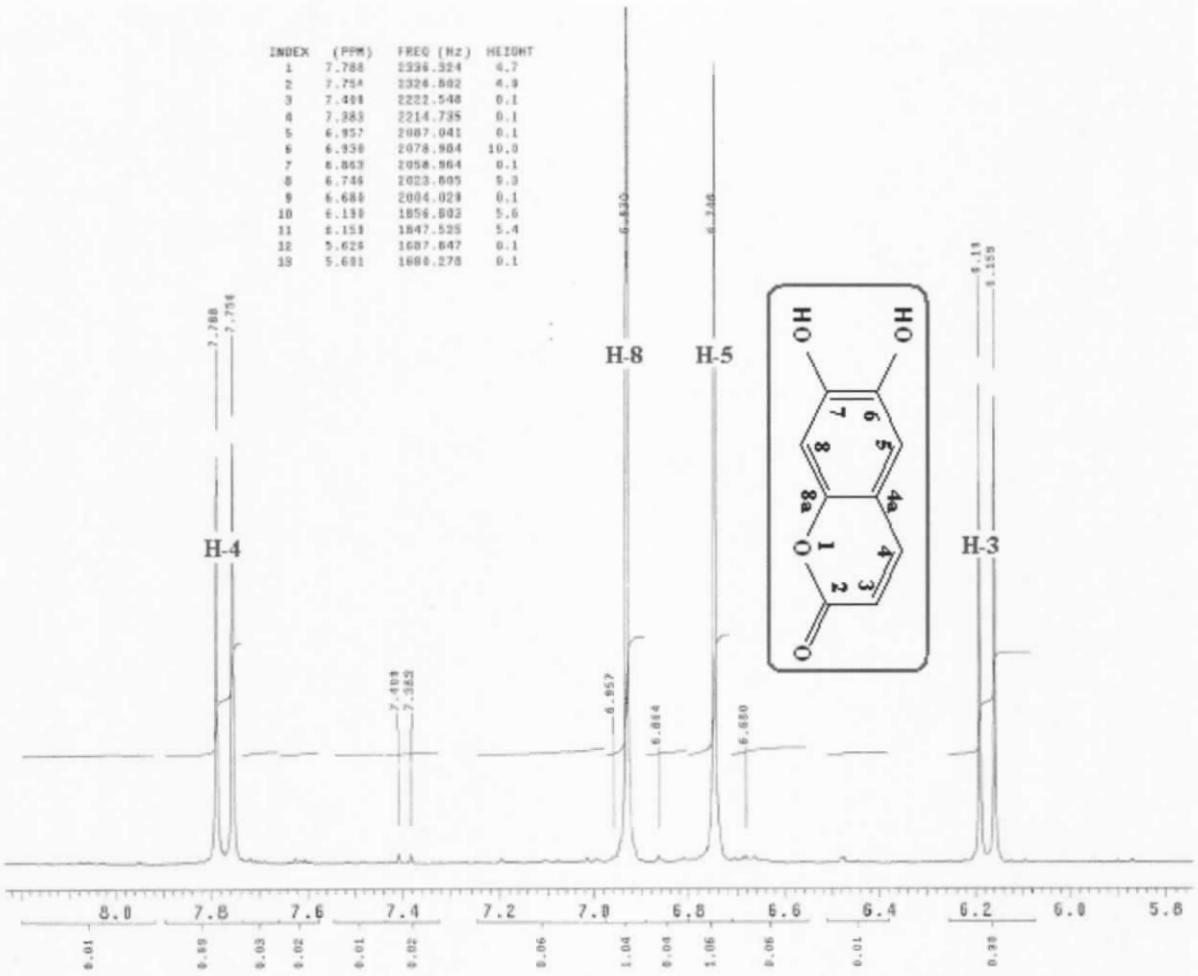


Spectrum 29: ^{1}H NMR spectrum of compound LR-1a

The protons of the sugar and coumarin moieties were given in table 13.

3.2.3. Compound LR-2

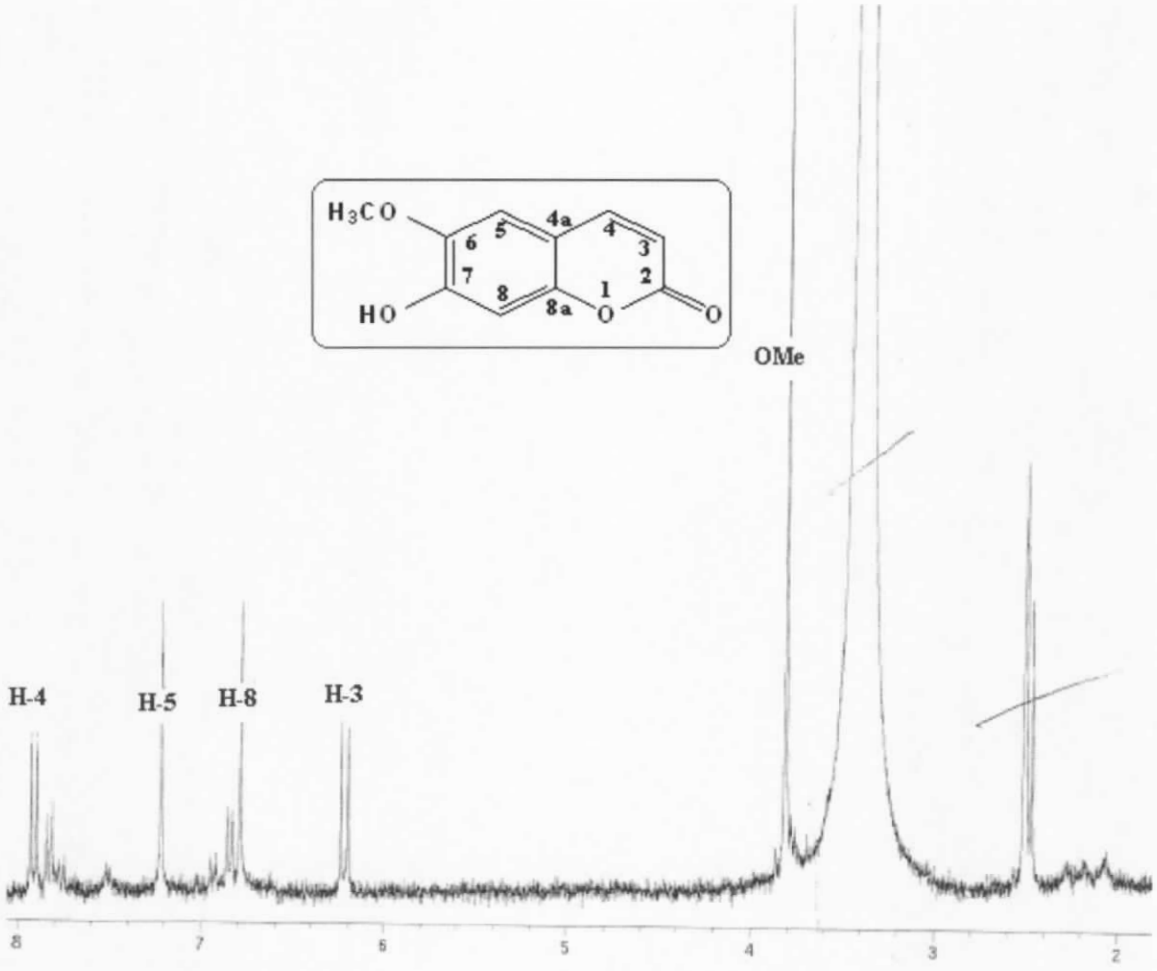
The HRCIMS of compound LR-2 showed the molecular ion peak $[M+1]^+$ at *m/z* 179 in accord with the molecular formula $C_9H_6O_4$. ^{1}H-NMR spectrum of II showed presence of two singlet signals at δ_H 6.93 (H-8) and 6.74 (H-5) and the two doublets at δ_H 7.75 (H-4, J = 9.5 Hz) and 6.15 (H-3, J = 9.5 Hz). Therefore compound LR-2 was identified as esculetin.



Spectrum 30: ^{1}H NMR spectrum of compound LR-2

3.2.4. Compound LR-3

The IR spectrum of LR-3 displayed absorption bonds characteristic of carbonyl group (1700 cm^{-1}, C=O). The HRCIMS showed the molecular ion peak $[M+1]^+$ at *m/z* 193 in accord with the molecular formula $C_{10}H_8O_4$. The ^{1}H-NMR spectrum of compound LR-3 revealed the presence of two doublets at δ_H 7.90 (H-4, J = 6.0 Hz) and 6.25 (H-3, J = 6.0 Hz). The two singlet signals appeared at δ_H 6.80 and 7.25 were assigned for the two protons H-5 and H-8, respectively. The difference between compound LR-2 and LR-3 was the presence of singlet signal at δ_H 3.85, which assigned for a methoxy group. Therefore, compound LR-3 was identified as scopoletin.



Spectrum 31: ^{1}H NMR spectrum of compound LR-3

3.2.5. Compound LR-4

The ^{1}H-NMR spectrum of compound LR-4 was close to compound LR-3. The difference in the chemical shifts of the signals suggested that compound LR-4 was isomer of compound LR-3 (isoscopoletin), H-8 of compound LR-3 appeared as singlet at δ_H 7.25, whereas, H-8 of compound LR-4 appeared as singlet at δ_H 6.93. Also, few differences in the chemical shifts for H-5, H-3 and H-4 were observed, table 13. The HRCIMS revealed a molecular ion peak $[M+1]^+$ at *m/z* 193 which corresponds to the molecular formula $C_{10}H_8O_4$.

Table 13: ^{1}H NMR (500 MHz in CD_3OD) of *L. resedifolia* coumarins

Protons	LR-1	LR-1a	LR-2	LR-3	LR-4
3	6.27 (d, 9.5)	6.37	6.15	6.25	6.30
4	7.81 (d, 9.5)	7.65	7.75	7.90	7.65
5	7.03 (s)	7.05	6.74	6.80	6.86
8	7.20 (s)	7.20	6.93	7.25	6.93
1`	4.96 (d, 7.5)	5.15			
2`	3.54 (dd, 7.5, 8.5)	5.35			
3`	3.50 (dd, 8.5, 9.0)	5.37			
4`	3.41 (dd, 9.0, 9.0)	5.36			
5`	3.51 (ddd, 3.0, 5.0, 9.0)	3.95			
6`	3.93 (dd, 12.0, 3.0)	4.35			
	3.72 (dd, 12.0, 3.0)	4.22			
OMe				3.85 (s)	4.00 (s)

+ OAc, 2.04, 2.07, 2.08, 2.14 and 2.29.

Chapter Four
Experimental

4.1- Euphorbia guyoniana

4.1.1- Material and techniques

Optical rotations were measured in $CHCl_3$ with a Perkin-Elemer 2435 polarimeter. IR spectra were recorded on a JASCO FT/IR-5300 spectrometer. NMR spectra were obtained with a JEOL ECA600 spectrometer (600 MHz for 1H, 150 MHz for 13C). NMR chemical shifts were referenced to solvent peaks: δ_H 7.26 (residual $CHCl_3$) and δ_C 77.0 for $CDCl_3$. FABMS were recorded on a JEOL SX102A mass spectrometer. HPLC was performed in the reverse phase using a Knauer instrument, pump type 64, detector: different refractometer (Knauer system), column: RP-8, 250×25 mm (Knauer system), and flow rate = 17 mL/min, elution with MeOH-H2O, mixtures.

-Adsorbents:

1- Silica gel (70-230 mesh, E-Merck) for columm chromatography.
2- Sephadex LH-20 (Sigma) for column chromatography.
3- Precoated silica gel plates (GF254, E-Merck) for TLC.

-Spray reagent:

The developed chromatograms were sprayed with vanillin-sulfuric acid reagent :
0.5g of vanillin was dissolved in 100 ml sulfuric acid-methanol (4:1). Then the sprayed plates were heated up to 110°C until the spots become with maximum color intensity.

4.1.2. Plant material: The aerial parts of *Euphorbia guyoniana* Boiss et Reut. were collected from Ouargla, Algeria in March 2003, and were identified by Dr A. Chahma, Department of Agriculture, Faculty of Science, University of Ouargla, Algeria. A voucher specimen was deposited in the Chemistry Department, University of Mentouri- Constantine, Algeria under the code EG-10019.

4.1.3. Phytochemical Screening of the Aerial Parts of *Euphorbia guyoniana*

The aerial parts of *Euphorbia guyoniana* were subjected to different phytochemical screening tests. [143]

10 grams of the powdered material was extracted with petroleum ether over night and then the ether extract is filtered, concentrated and subject to the following tests:

4.1.3.1. Volatile oils: 10 to 20ml of ether extract is out in a flask and evaporated till dryness, a good smell of the residue reveals the presence of volatile oils.

4.1.3.2. Sterols and Triterpenes: 10ml of the ether extract is evaporated till dryness and the residue is dissolved in 0.5 ml of anhydrous acetic acid then in 0.5 ml of chloroform. 1 ml of concentrated sulfuric acid is added to the organic layer, the apparition of a red brown or violet ring in the zone of contact of the two liquids reveals the presence of sterols and Triterpenes.

4.1.3.3. Alkaloids: 10 ml of the ether extract is dried and the residue is dissolved in 1.5 ml of 2% hydrochloric acid then one or two drops of Mayer reagent is added, the apparition of a white precipitate reveals the presence of alkaloids.

4.3.4. Flavonoids: 3 ml of the ether extract is dried and dissolved in 2 ml of methanol 50% in a warm bath then 5 drops of HCl is added with a small piece of magnesium, the apparition of a red or orange color reveals the presence of flavonoids.

4.1.3.5. Coumarins: 3 ml of the ether extract is dried and the residue is well dissolved in 2 ml of distillated water and made alkaline by adding 0.5 ml of ammonia 10%, the apparition of fluorescence under UV reveals the presence of coumarins and their derivatives.

4.1.3.6. Tanins: 1 ml of the alcoholic extract of the powdered material is died and dissolved in a bit of ferric chloride solution, the apparition of a green or dark blue color reveals the presence of tannins.

4.1.3.7. Saponins: 2 g of dried material is boiled with 80 ml of distillated water then it is filtered and cooled before being stirred, the apparition of foam reveals the presence of saponins.

4.1.4. Extraction and isolation: The air-dried and powdered plant (850 g) was extracted exhaustively with CH_2Cl_2-MeOH (1:1) at room temperature. The solvent was distilled under reduced pressure, furnishing a gummy residue (15 g). The residue was submitted to flash column chromatography, and eluted with *n*-hexane, CH_2Cl_2 and MeOH, increasing the degree of polarity. The *n*-hexane- CH_2Cl_2 (25:75) fraction was pre-fractionated by CC on Sephadex LH-20 (6×120 cm) and eluted with *n*-hexane- CH_2Cl_2- MeOH (6: 4: 1) to give a complex mixture. This was purified by HPLC (MeOH-H_2O, 70: 30, R_t = 5.6 and 6.0 min) to yield compounds EG-1 (20 mg), EG-2 (15mg) and EG-3 (22 mg).

4.1.5. Compound EG-1

Yellowish powder.

$[\alpha]^{25}_{D}$: –172° (*c* 1.0, CH_3OH).

IR (oil film): 3450, 1738, and 1724 cm-1.

^{1}H NMR of Compound EG-1 (600 MHz, C_6D_6)

δ_H=2.34 (d, *J*=16.1Hz, H-1$_\beta$), 3.35 (d, *J*=16.1Hz, H-1$_\alpha$), 6.45 (d, *J*=5.0 Hz, H-3$_\alpha$), 4.05 (dd, *J*=5.5 Hz, 5.0, H-4$_\alpha$), 6.25 (d, *J*=5.5 Hz, H-5$_\beta$), 6.13 (br s, H-7$_\alpha$), 5.47 (br s, H-8$_\beta$), 5.22 (br s, H-9$_\beta$), 5.72 (d, *J*=15.6 Hz, H-11), 5.57 (dd, *J*=15.6 Hz, 9.6 Hz, H-12), 3.69 (dq, *J*= 9.6 Hz, 7.1 Hz, H-13$_\alpha$), 1.85 (s, H-16) 5.40 (br s, H-17a), 5.52 (br s, H-17b), 0.78 (s, H-18), 1.21 (s, H-19), 1.06 (d, *J*=7.1 Hz, H-20), 8.21 (dd, *J*= 7.6 Hz, 1.5 Hz, H3', 7'), 7.08 (td, *J*=7.6 Hz, 1.5 Hz, H-4', 6'), 7.14 (tt, *J*=7.6 Hz, 1.5 Hz, H-5'), 9.95 (b d, *J*= 2.0 Hz, H-3"), 8.53 (br d, *J*=4.5 Hz, H-5"), 6.77 (dd, *J*= 8.1 Hz, 4.5 Hz, H-6"), 8.41 (dt, *J*=8.1 Hz, 2.0 Hz, H-7"), 1.69 (s, H-3-OAc), 1.67 (s, H-7-OAc), 1.85 (s, H-8-OAc), 1.97 (s, H-9-OAc).

^{13}C NMR of Compound EG-1 (150MHz, C_6D_6)

δ_C=49.9 (C-1), 91.0 (C-2), 79.6 (C-3), 47.9 (C-4), 71.2 (C-5), 142.8 (C-6), 68.2 (C-7), 70.8 (C-8), 81.3 (C-9), 40.8 (C-10), 137.4 (C-11), 129.8 (C-12), 44.3 (C-13), 211.7 (C-14), 86.8 (C-15), 20.1 (C-16), 116.5 (C-17), 25.7 (C-18), 23.3 (C-19), 20.1 (C-20), 165.5 (C-1'), 131.0 (C-2'), 130.4 (C-3') 128.4 (C-4', C-6'), 132.9 (C-5'), 164.6 (C-1"), 127.2 (C-2"), 152.0 (C-3"), 153.8 (C-5"), 123.1 (C-6"), 137.1 (C-7"), [169.9 (C=O), 21.1 (CH_3)], [169.6 (C=O), 20.2 (CH_3)], [169.4 (C=O), 20.7 (CH_3)], [169.2 (C=O), 20.3 (CH_3)].

FAB-MS (positive): *m/z* (%) = 778 $[M + H]^+$ (45), 736 $[M + H - AcO]^+$ (10), 694 $[M + H - 2AcO]^+$ (5).

HR-FAB-MS (positive): *m/z* $[M + H]^+$ calculated for $C_{41}H_{48}O_{14}N$: 778.308; found: 778.307.

4.1.6. Compound EG-2

Greenish oil. $[\alpha]^{25}_{D}$: –90o (*c* 0.1, $CHCl_3$).

IR (oil film): 1738 and 1727 cm-1.

FAB-MS (positive): *m/z* (%) = 539 $[M + H]^+$ (12), 479 $[M + H - AcOH]^+$ (55), 434 [M + H - benzoate]$^+$(15).

HR-FAB-MS (positive): *m/z* $[M + H]^+$ calculated for $C_{31}H_{39}O_8$: 539.265; found 539.264.

^{1}H NMR of Compound EG-2 (600 MHz, C_6D_6)

δ_H =1.80 (dd, 14.3, 12.9, H-1β), 3.08 (dd, 14.3, 7.4, H-1α), 2.25 (m, H-2α), 5.79 (t, 3.3,H-3α), 2.17 (m, H-4α), 5.80 (br s, H-5β), 2.36 (ddd, 13.7, 9.3, 9.3, H-7α), 1.81 (m, H-7β), 2.20 (m, H-8α), 2.87 (ddd, 13.5, 9.1, 3.3, H-8β), 6.03 (d, 15.9, H-11), 5.34 (dd, 15.9, 9.6, H-12), 3.59 (dd, 9.1, 6.3, H-13α), 0.96 (d, 6.6, H-16), 5.00 (br s, H-17a), 5.08 (br s, H-17b), 1.18 (s, H-18), 1.19 (s, H-19), 1.17 (d, 6.3, H-20), 8.09 (dd, 7.1, 1.4, H-3', 7'), 7.47 (t, 7.1, H-4', 6'), 7.60 (tt, 7.1, 1.4, H-5'), 1.55 (s, H-5-OAc), 2.19 (s, H-15-OAc).

^{13}C NMR of Compound EG-2 (150MHz, C_6D_6)

δ_C =46.5(C-1), 38.9(C-2), 76.9(C-3), 53.9(C-4), 68.7(C-5), 144.9(C6), 30.0(C-7), 37.9(C-8), 211.8(C-9), 49.5(C-10), 137.4(C-11), 132.2(C-12), 44.7(C-13), 213.4(C1-4), 92.6(C-15), 13.4(C-16), 114.1(C-17), 25.9(C-18), 22.6(C-19), 19.8(C-20), 165.1(C-1'), 130.6(C-2'), 129.6(C-3', 7'), 128.4(C-4', 6'), 133.2(C-5'), [169.9 (C=O), 20.7 (CH_3), 5-OAc], [170.3 (C=O), 21.1 (CH_3), 15-OAc].

4.1.7. Compound EG-3

$[\alpha]^{25}_D$ + 231 (*c* 0.97, $CHCl_3$)

IR ($CHCl_3$) cm−1:

3388, 2922, 1713, 1650 (enone), 1059 (*trans*-disubstituted double bond), 749

^{1}H NMR of Compound EG-3 (500 MHz, $CDCl_3$)

δ_H=2.44(d, 17.1, H-2α), 2.24(d, 17.1, H-2β), 5.90(br.q, 1.2,H-4), 5.79(d, 15.6, H-7), 5.85(dd, 15.6, 5.4, H-8), 4.41(quin, 5.9, H-9), 1.29(d, 6.6, H-10), 1.01(s, H-11), 1.08(s, H-12), 1.89(d, 1.2, H-13).

^{13}C NMR of Compound EG-3 (125 MHz, $CDCl_3$)

δ_C=41.1(C-1), 49.7(C-2), 198.0(C-3), 126.9(C-4), 162.8(C-5), 79.0(C-6), 129.0(C-7), 135.7(C-8), 68.1(C-9), 23.7(C-10), 24.0(C-11), 22.9(C-12), 18.9(C-13).

4.2. *Launaea resedifolia*

4.2.1. Materials and Techniques:

IR spectra were obtained in a Perkin-Elmer 1000 FT-IR instruments, KBr pellets. The NMR spectra were recorded on Bruker AC 500 [500 MHz (^{1}H) and 125, MHz (^{13}C)] spectrometer. Chemical shifts were recorded in δ (ppm) using TMS as internal standard. EIMS were obtained at 70 eV using a VG-ZAB-E instrument. Column chromatography (CC) was performed using silica gel 60 (Merck, 0.063-0.2 mm). TLC analyses were performed with silica gel (Merck, Kieselgel). Spots were visualized by UV (λ_{max} 259 and 360 mm). HPLC was carried out in the reverse phase on knauer pump 64 and different refractometer (column: RP-8, 250x25 mm, flow = 17 ml/min, elution with MeOH-H_2O, mixtures, refractive index.

4.2.2. Plant material

Aerial parts of *L. resedifolia*, were collected in March 2002 from 25 km north of Ouargla, Algeria, during flowering period. A voucher specimen was deposited at the herbarium of chemistry department, faculty of sciences, Constantine University; under the code number SR 101, Algeria

4.2.3. Phytochemical Screening of the Aerial Parts of *L. resedifolia:*

The aerial parts of *Launaea resedifolia* were subjected to different phytochemical screening tests.

10 grams of the powdered material was extracted with petroleum ether over night and then the ether extract is filtered, concentrated and subject to the following tests:

4.2.3.1. Volatile oils: 10 to 20ml of ether extract is out in a flask and evaporated till dryness, a good smell of the residue reveals the presence of volatile oils.

4.2.3.2. Sterols and Triterpenes: 10ml of the ether extract is evaporated till dryness and the residue is dissolved in 0.5 ml of anhydrous acetic acid then in 0.5 ml of chloroform. 1 ml of concentrated sulfuric acid is added to the organic layer, the apparition of a red brown or violet ring in the zone of contact of the two liquids reveals the presence of sterols and Triterpenes.

4.2.3.3. Alkaloids: 10 ml of the ether extract is dried and the residue is dissolved in 1.5 ml of 2% hydrochloric acid then one or two drops of Mayer reagent is added, the apparition of a white precipitate reveals the presence of alkaloids.

4.2.3.4. Flavonoids: 3 ml of the ether extract is dried and dissolved in 2 ml of methanol 50% in a warm bath then 5 drops of HCl is added with a small piece of magnesium, the apparition of a red or orange color reveals the presence of flavonoids.

4.2.3.5. Coumarins: 3 ml of the ether extract is dried and the residue is well dissolved in 2 ml of distillated water and made alkaline by adding 0.5 ml of ammonia 10%, the apparition of fluorescence under UV reveals the presence of coumarins and their derivatives.

4.2.3.6. Tanins: 1 ml of the alcoholic extract of the powdered material is died and dissolved in a bit of ferric chloride solution, the apparition of a green or dark blue color reveals the presence of tannins.

4.2.3.7. Saponosides: 2 g of dried material is boiled with 80 ml of distillated water then it is filtered and cooled before being stirred, the apparition of foam reveals the presence of saponosides.

4.2.4. Extraction and Isolation

The aerial parts of *L. resedifolia* (1 Kg) were dried, powdered, and extracted with methylene chloride-methanol (1:1) at room temperature. The solvent was distilled under reduced pressure furnishing a residue (10 g). The residue was submitted to flash column chromatography, being eluted with *n*-hexane, methylene chloride, and methanol, in increasing polarity. The extracts were prefractionated by CC (6 x120 cm) on silica gel eluting with *n*-hexane followed by a gradient of *n*-hexane-CH_2Cl_2 up to 100% CH_2Cl_2 and CH_2Cl_2-MeOH up to 15% MeOH. The fractions were further purified by CC (2x40 cm); a Sephadex LH-20 eluted with *n*-hexane-CH_2Cl_2-MeOH (6:4:1) giving a complex mixture. The mixture was purified by HPLC (MeOH-H_2O, 65:35, R_t = 5.6 and 6.0 min) to yield compounds LR-1, LR-2, LR-3, and LR-4.

4.2.5. Compound LR-1

^{1}H NMR of Compound LR-1(Cichoriin) (125 MHz, CD_3OD)

δ_H=6.27 (d, 9.5, H-3), 7.81 (d, 9.5, H-4), 7.03 (s, H-5), 7.20 (s, H-8), 4.96 (d, 7.5, H-1`), 3.54 (dd, 7.5, 8.5, H-2`), 3.50 (dd, 8.5, 9.0, H-3`), 3.41 (dd, 9.0, 9.0, H-4`), 3.51 (ddd, 3.0, 5.0, 9.0, H-5`), 3.93 (dd, 12.0, 3.0, H-6`), 3.72 (dd, 12.0, 3.0, H-6`).

^{13}C NMR of Compound LR-1(Cichoriin) (500 MHz, CD_3OD)

δ_C 160.57 (s, C-2), 112.97 (d, C-3), 143.59 (d, C-4), 144.17 (s, C-4_a), 112.65 (d, C-5), 113.45 (s, C-6), δ_C 148.81 (s, C-7), 103.37 (d, C-8), 147.79 (s, C-8_a), 100.99 (d, C-1`), 75.86 (d, C-2`), 77.28(d, C-3`), 73.17 (d, C-4`), 69.81 (d, C-5`), 60.74 (t, C-6`).

4.2.6. Compound LR-2

^{1}H NMR of Compound LR-2 (125 MHz, CD_3OD)

δ_H=6.15 (d, 9.5, H-3), 7.75(d, 9.5, H-4), 6.74(s, H-5), 6.93(s, H-8)

4.2.7. Compound LR-3

^{1}H NMR of Compound LR-3 (125 MHz, CD_3OD)

δ_H=6.25 (d, 9.5, H-3), 7.90(d, 9.5, H-4), 6.80(s, H-5), 7.25(s, H-8), 3.85(s, OMe)

4.2.8. Compound LR-4

^{1}H NMR of Compound LR-4 (125 MHz, CD_3OD)

δ_H=6.30 (d, 9.5, H-3), 7.65(d, 9.5, H-4), 6.86(s, H-5), 6.93(s, H-8), 4.00(s, OMe)

Conclusion

Natural products are not just accidents or products of convenience of nature. More than likely they are a natural expression of the increase in complexity of organisms. Interest in natural sources to provide treatments for pain, palliatives, or curatives for a variety of maladies or recreational use reaches back to the earliest points of history.

The World Health Organization estimates that approximately 80 percent of the world's population relies primarily on traditional medicines as sources for their primary health care

We have aimed in the present study at emphasizing the chemical and medicinal value of a part of our natural patrimony which is not well appraised.

Euphorbia guyoniana investigation led to the isolation of two new jatrophane diterpenoids.

The peculiar importance of pattern of the present set of jatrophane compounds expands considerably the library for this class of compounds, whose interest resides on their activity in reducing multidrug resistance associated to antitumor therapy. In this regard, preliminary tests are being undertaken.

On the other hand, the study of *Launaea resedifolia* led to four known coumarins extracted for the first time from this species.

Our first objective to be achieved subsequently is to carry out all biological tests of the isolated compounds and attempt to establish a structure–activity relationship.

It is worth mentioning that our desert region involves considerable number of herbs not yet explored in spite of their wide use in folk medicine and hence we do recommend to pursue the study and to make up a platform of all endemic plants.

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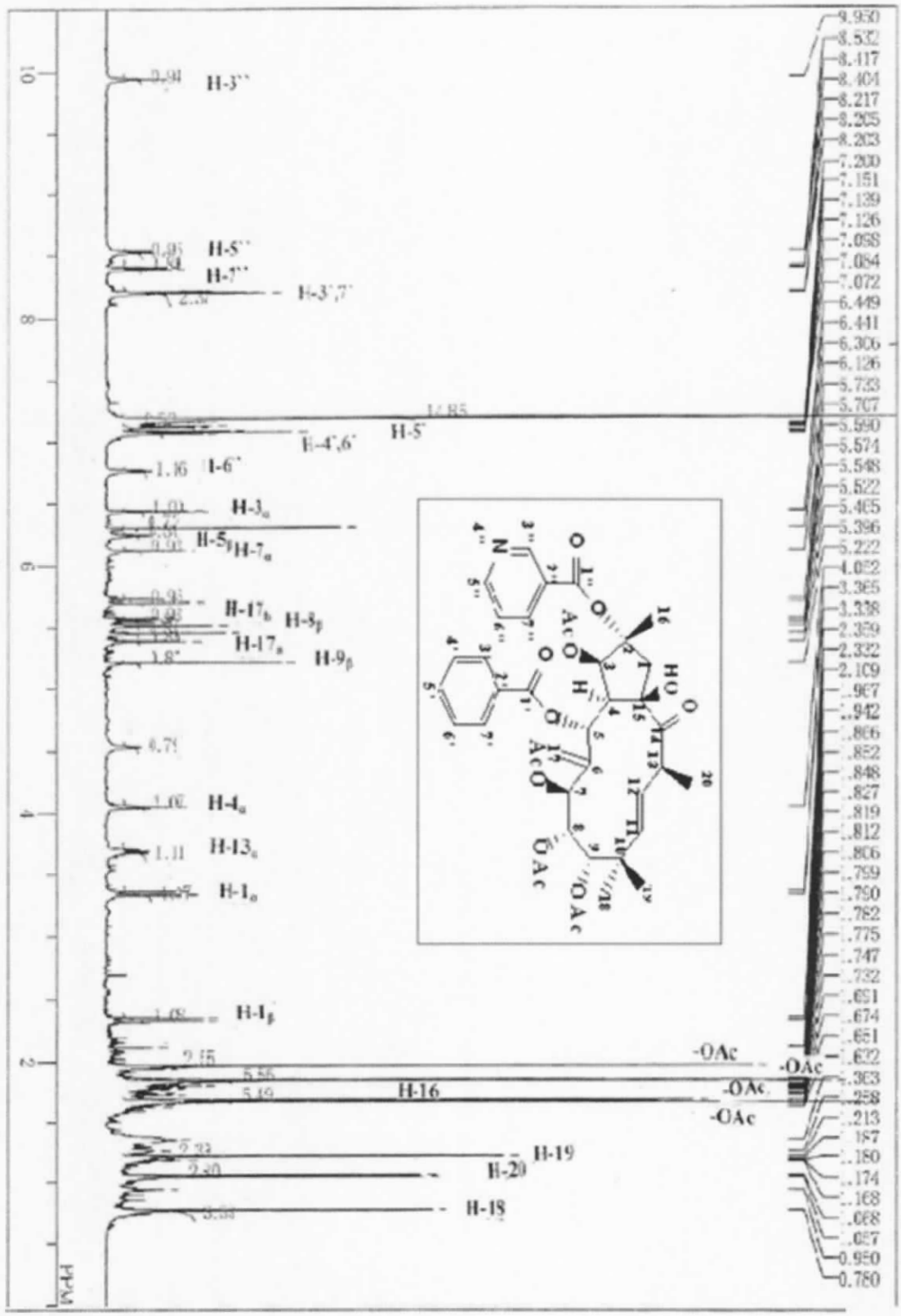
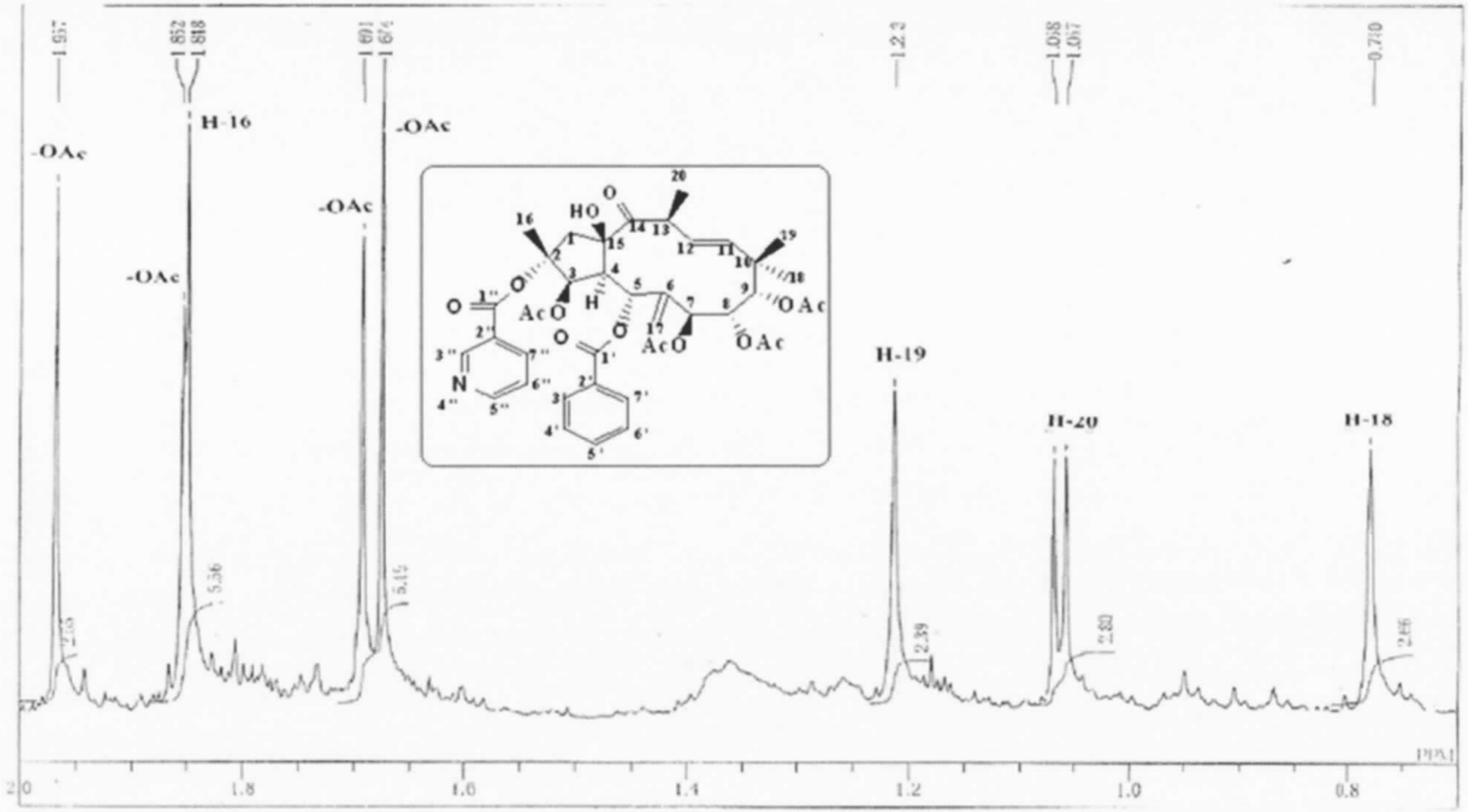
Annex 1

EG-1



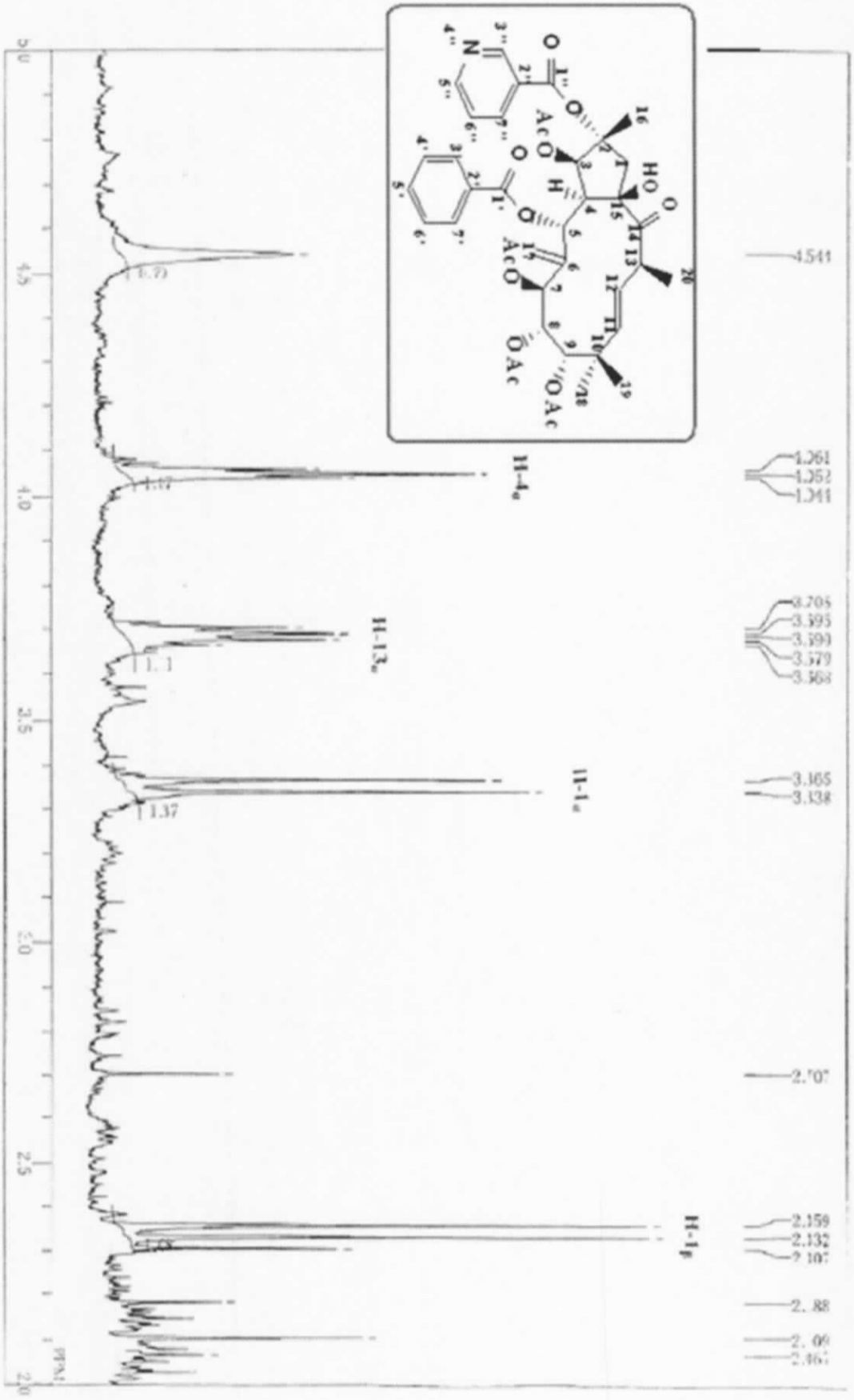
¹H NMR of compound EG-1



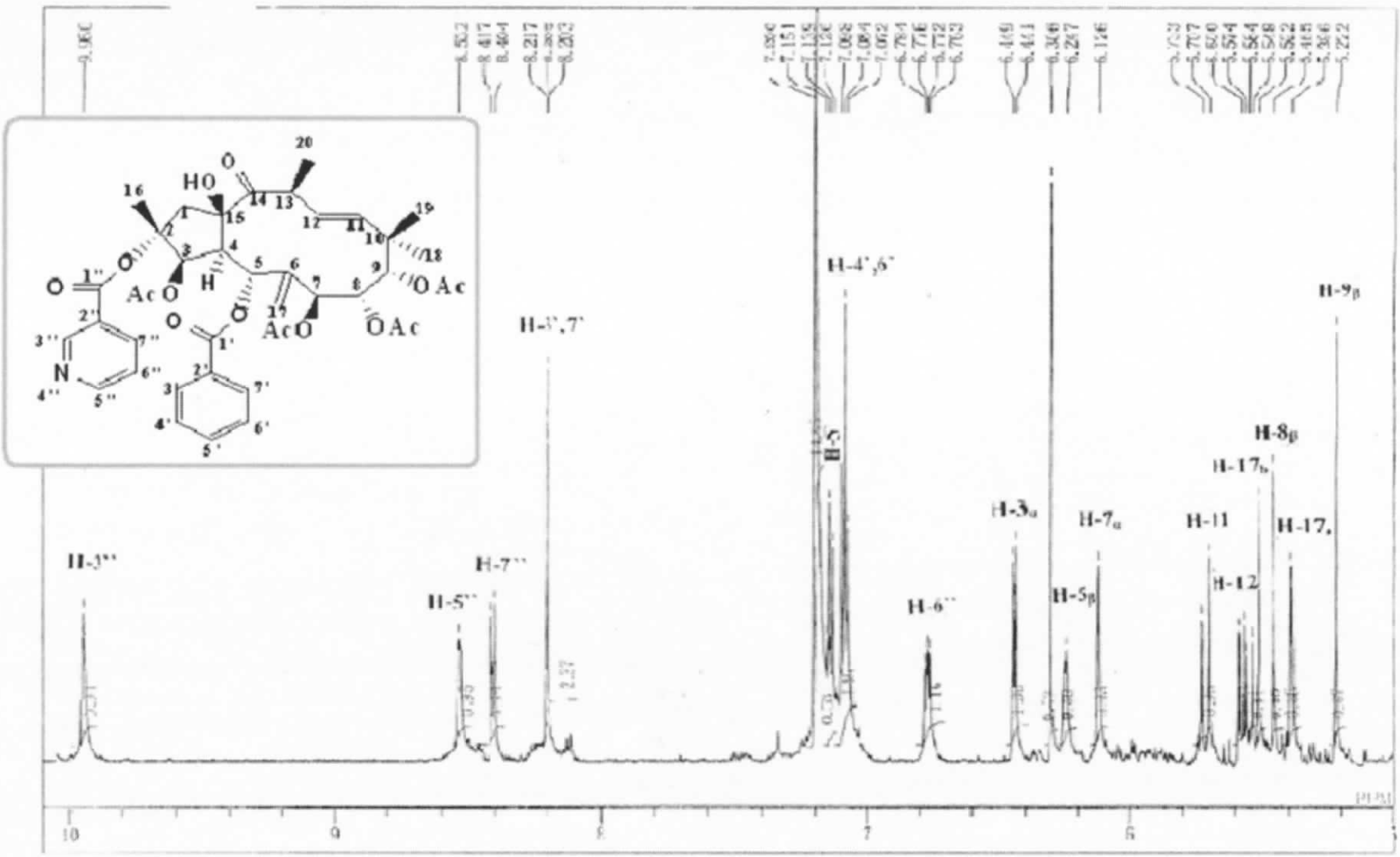
^{1}H NMR of compound EG-1 (0-2ppm)

Part 1

Part 1

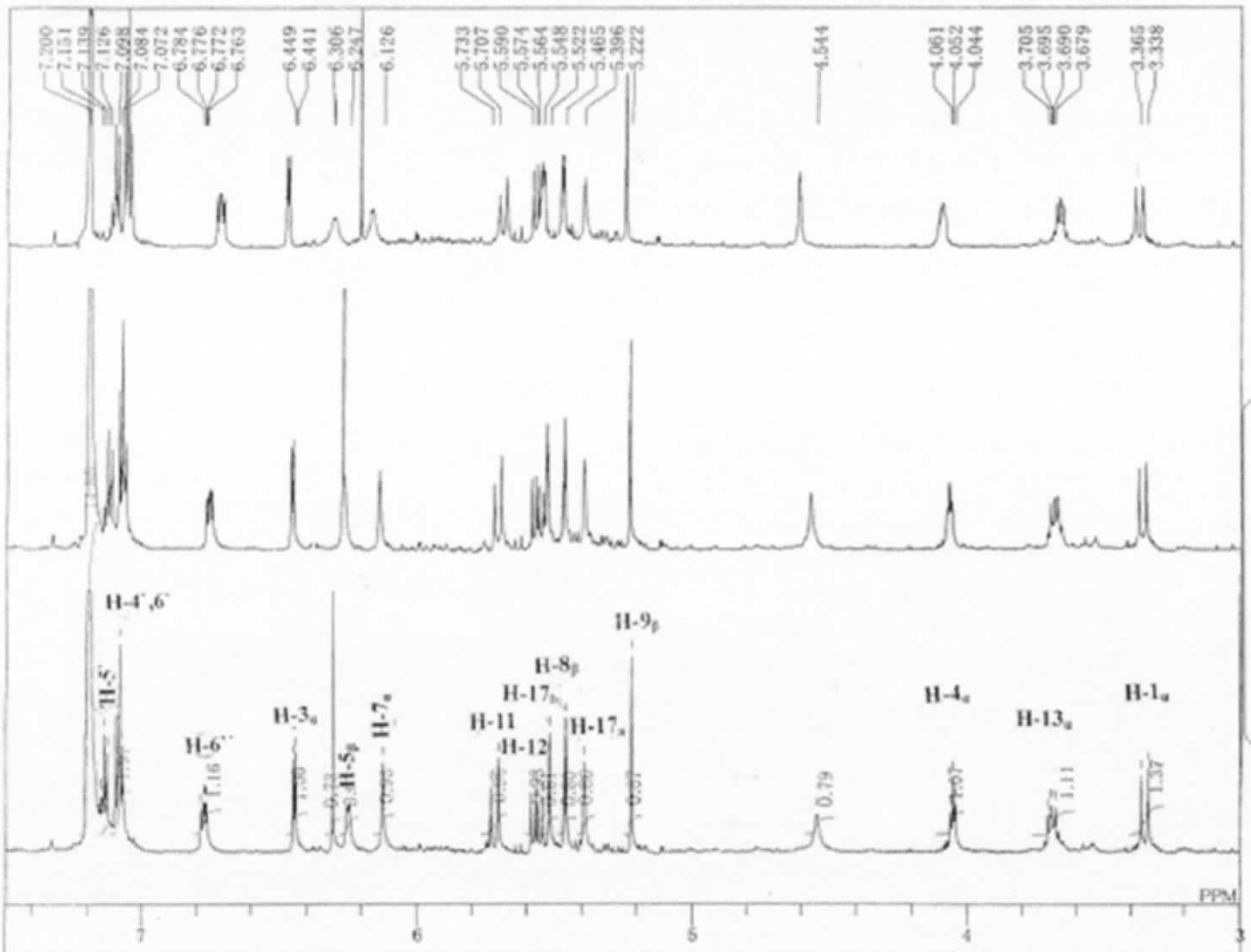


^{1}H NMR of compound EG-1 (2-5 ppm)

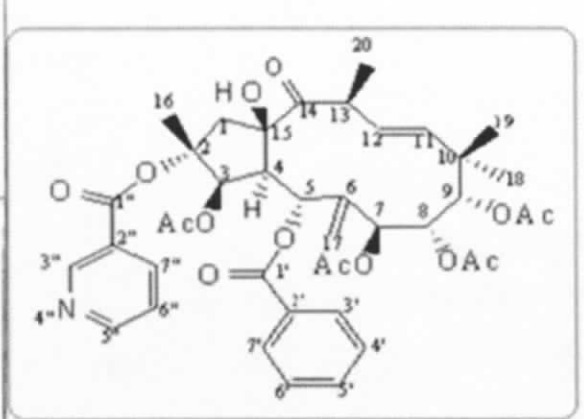


^{1}H NMR of compound EG-1 (5-10ppm)

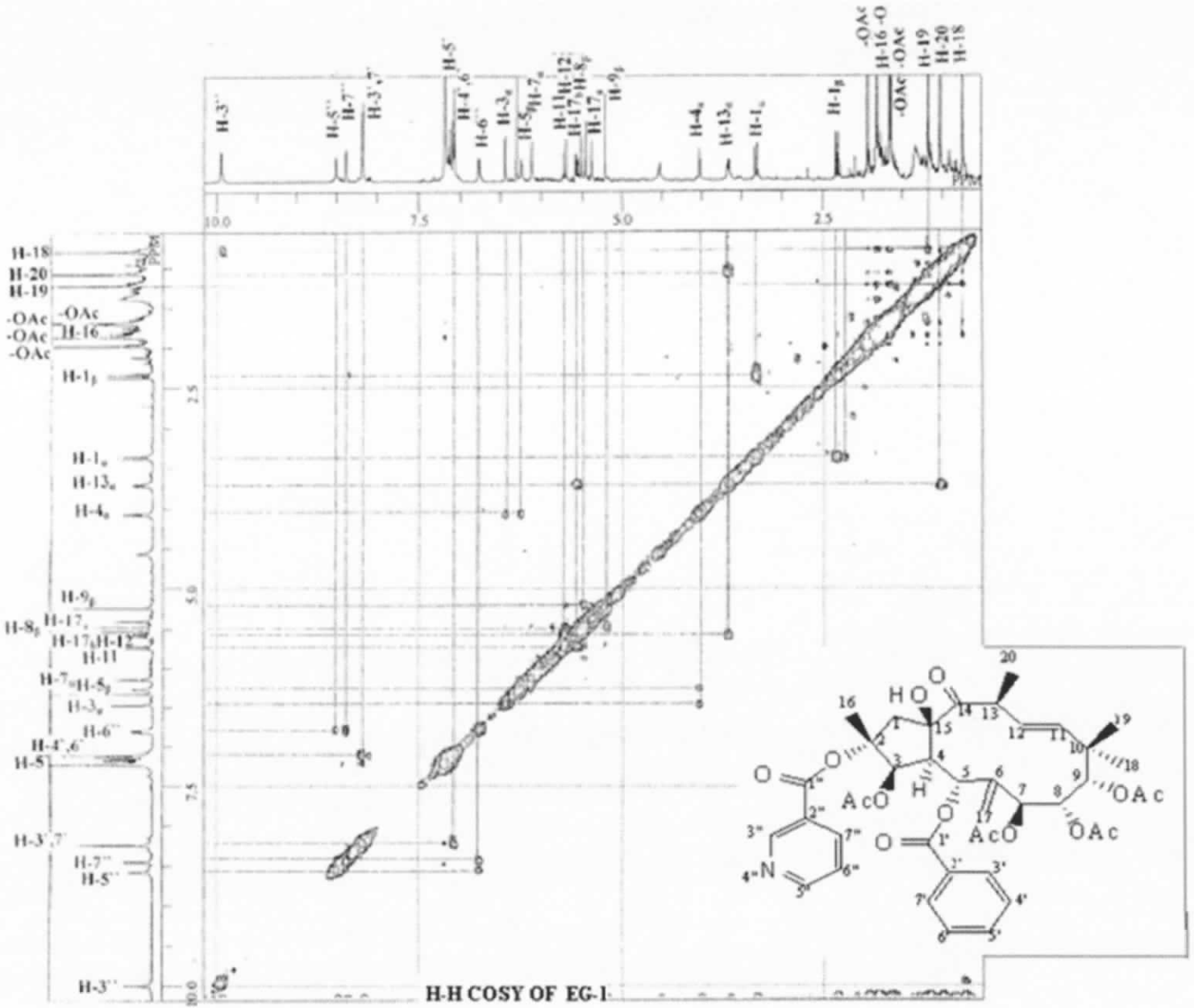
Part 1



^{1}H NMR of compound EG-1

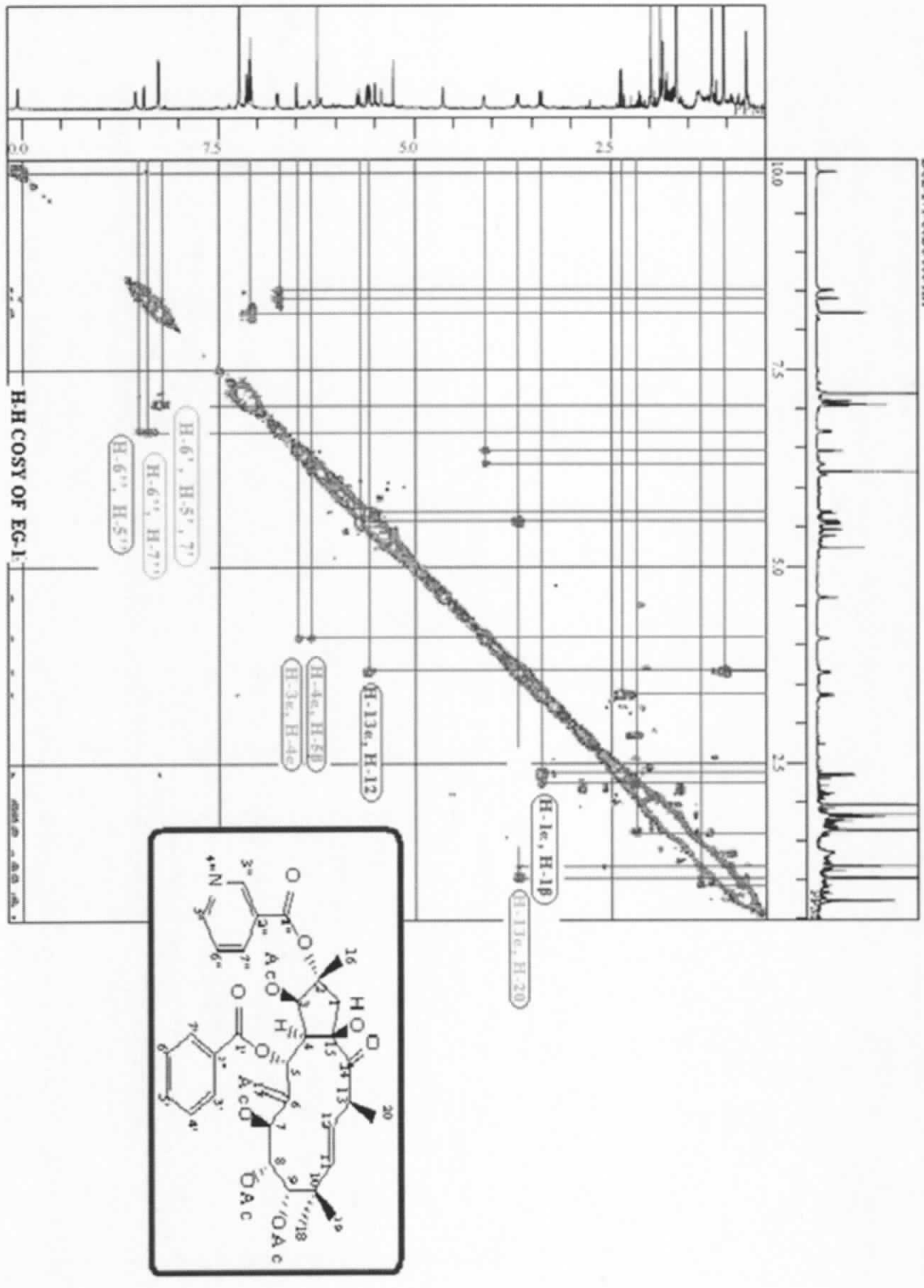


Part 1

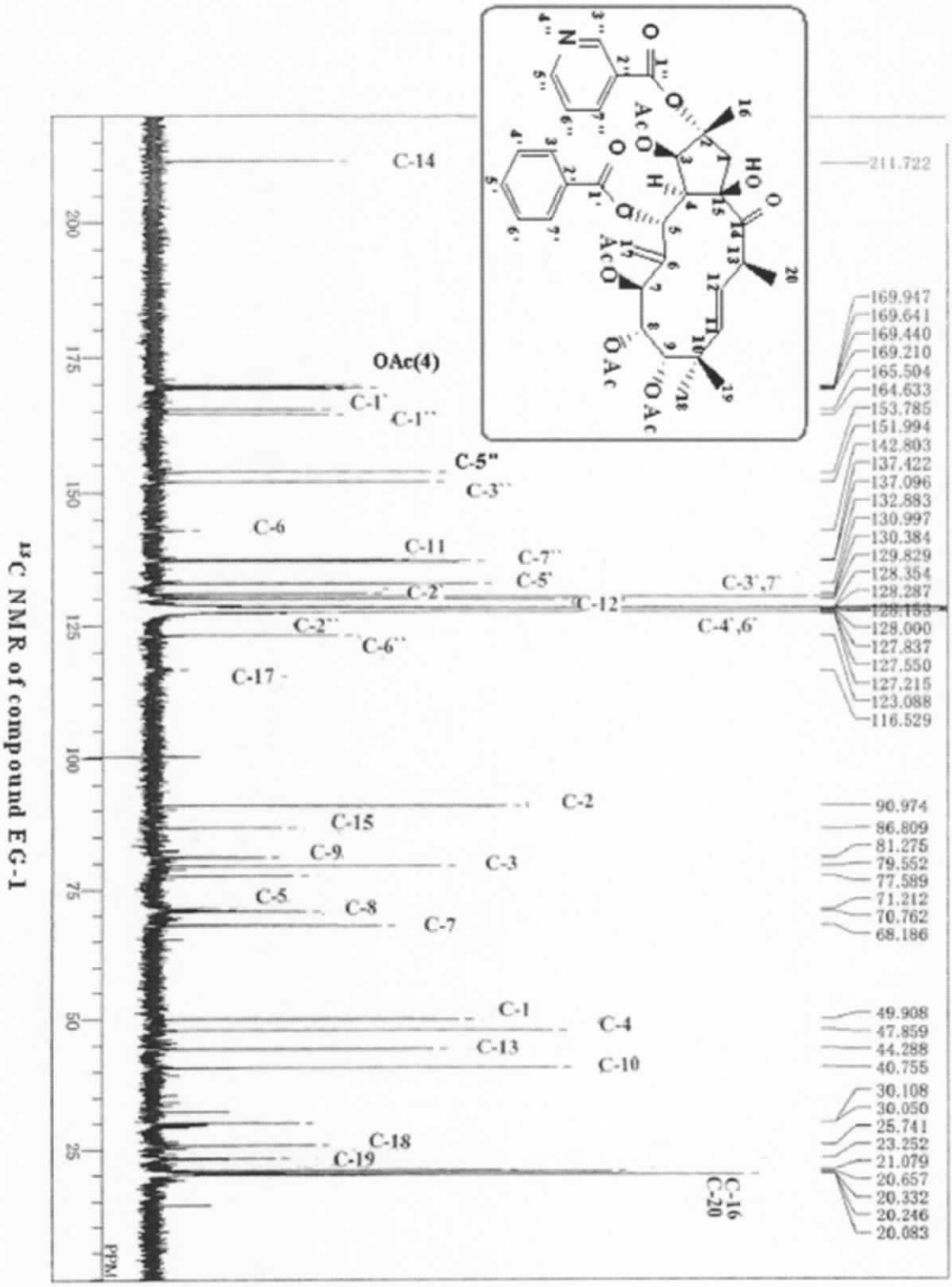

H-3''
H-5''
H-7''
H-3',7'
H-5'
H-4',6'
H-6''
H-3α
H-5β
H-7α
H-11
H-12
H-17α
H-8β
H-17β
H-9β
H-4α
H-13α
H-1α
H-1β
-OAc
H-16
-OAc
-OAc
H-19
H-20
H-18
10.0
7.5
5.0
2.5
H-18
H-20
H-19
-OAc
-OAc
-OAc
H-16
H-1β
H-1α
H-13α
H-4α
H-9β
H-8β
H-17α
H-17β
H-12
H-11
H-7α
H-5β
H-3α
H-6''
H-4',6'
H-5'
H-3',7'
H-7''
H-5''
H-3''
2.5
5.0
7.5
10.0
HO
O
20
16
19
18
OAc
OAc
AcO
AcO
N
H-H COSY OF EG-1

Part 1

Part 1

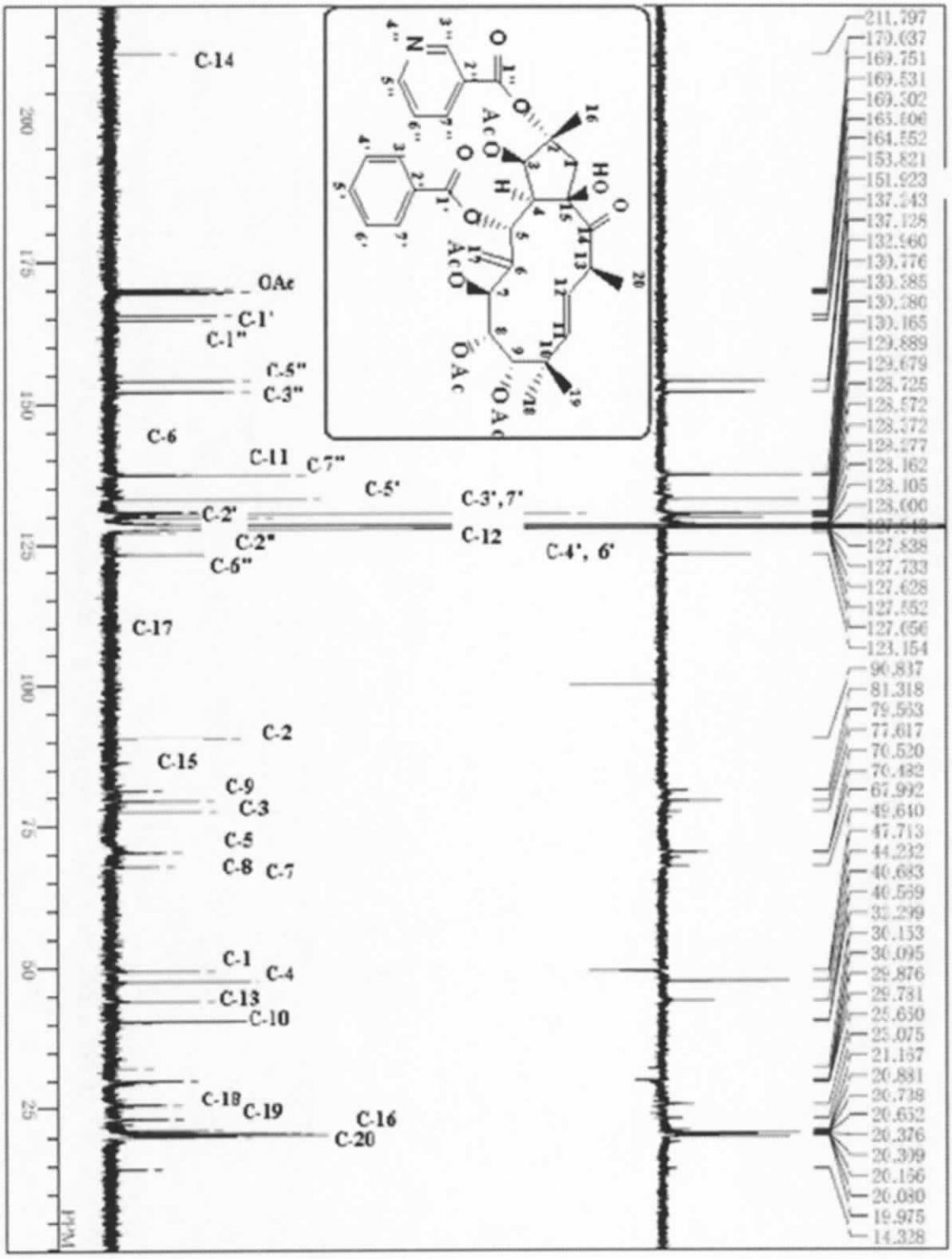

H-H COSY OF EG-1
H-6'', H-5''
H-6'', H-7''
H-6', H-5', 7'
H-3e', H-4e'
H-4e', H-5β
H-13e', H-12
H-1e, H-1β
H-11e', H-20

Part 1

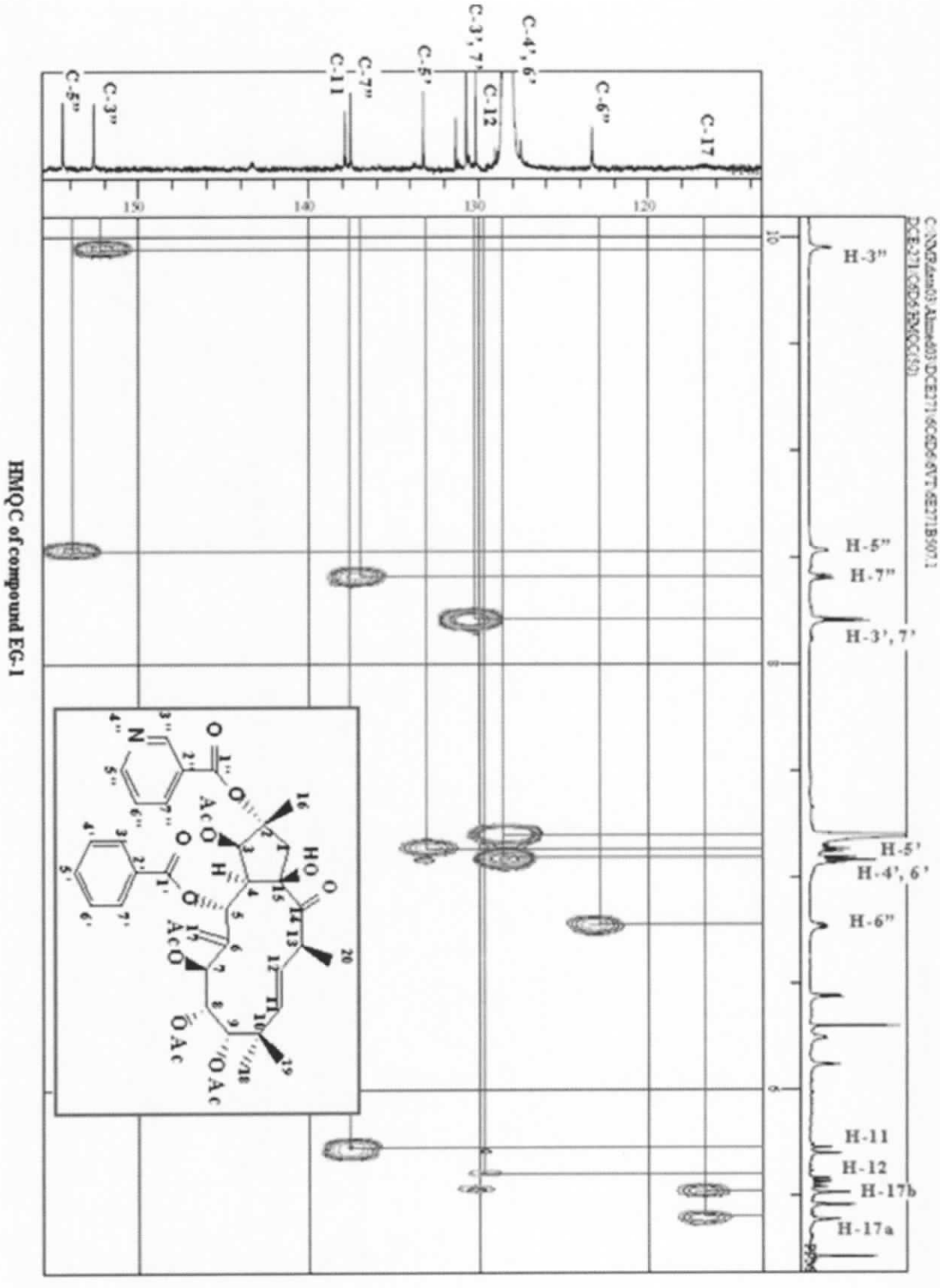


^{13}C NMR of compound EG-1

Part 1

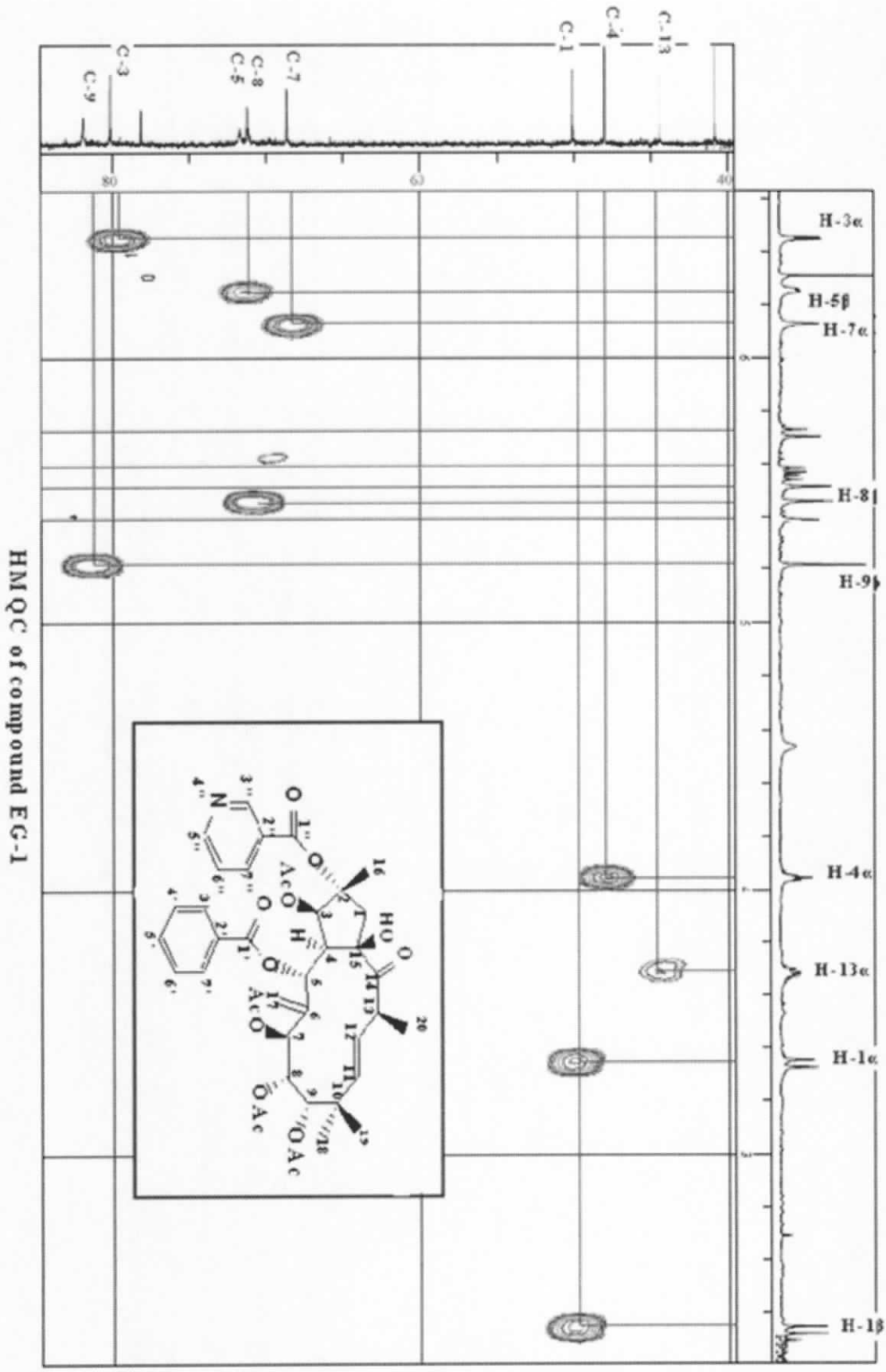

DEPT spectrum of compound EG-1
C-14
OAc
C-1'
C-1"
C-5"
C-3"
C-6
C-11
C-7"
C-5'
C-3',7'
C-2'
C-12
C-2"
C-6"
C-4', 6'
C-17
C-2
C-15
C-9
C-3
C-5
C-8
C-7
C-1
C-4
C-13
C-10
C-18
C-19
C-16
C-20
211.797
179.037
169.751
169.531
169.302
165.606
164.552
153.821
151.923
137.243
137.125
132.560
130.776
130.585
130.380
130.165
129.889
129.679
128.725
128.572
128.372
128.277
128.162
128.105
128.000
127.838
127.733
127.628
127.552
127.656
123.154
90.837
81.318
79.553
77.617
70.520
70.482
67.992
49.640
47.713
44.232
40.683
40.569
32.299
30.133
30.095
29.876
29.781
25.630
25.075
21.167
20.881
20.738
20.652
20.376
20.309
20.156
20.080
19.975
14.328

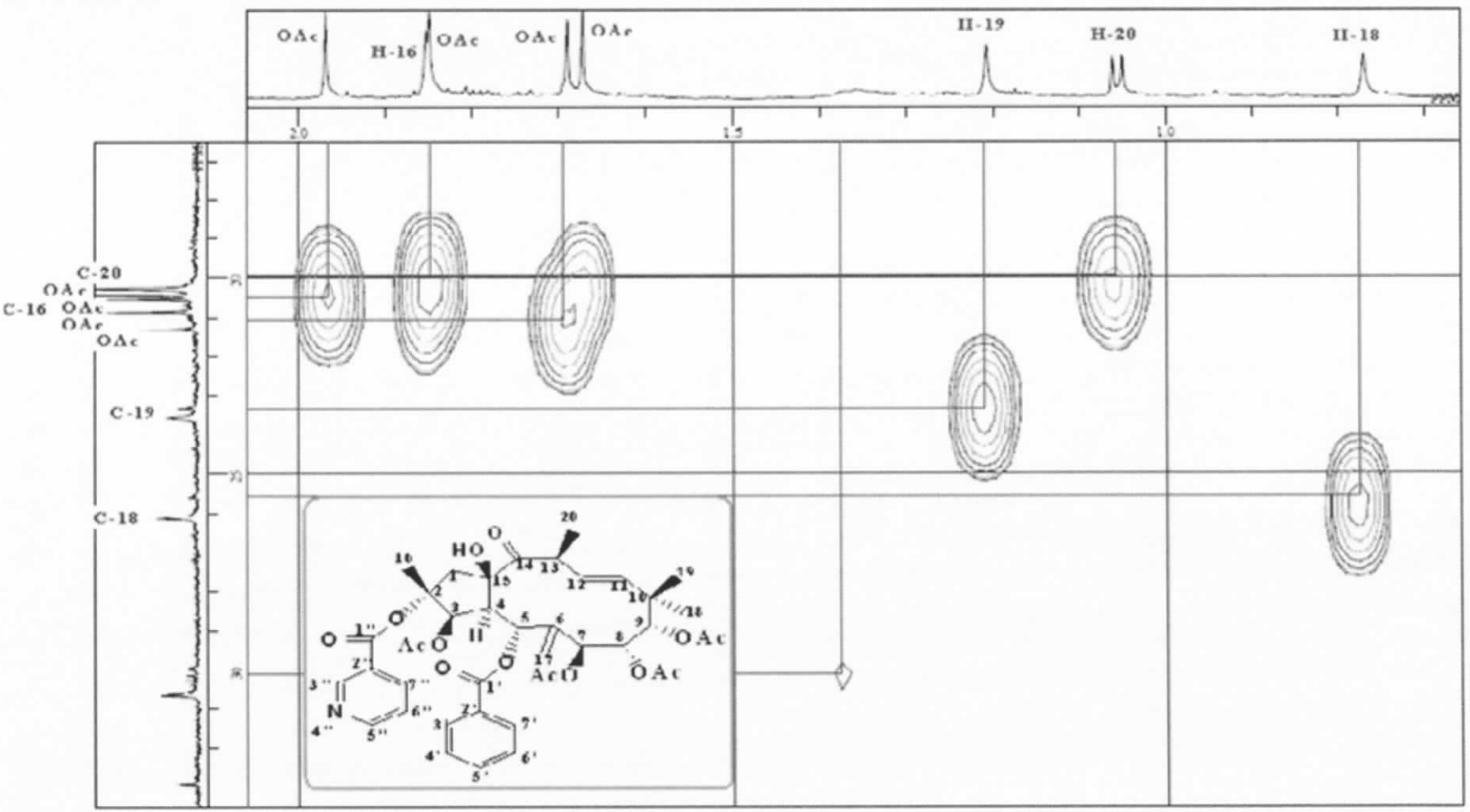
Part 1



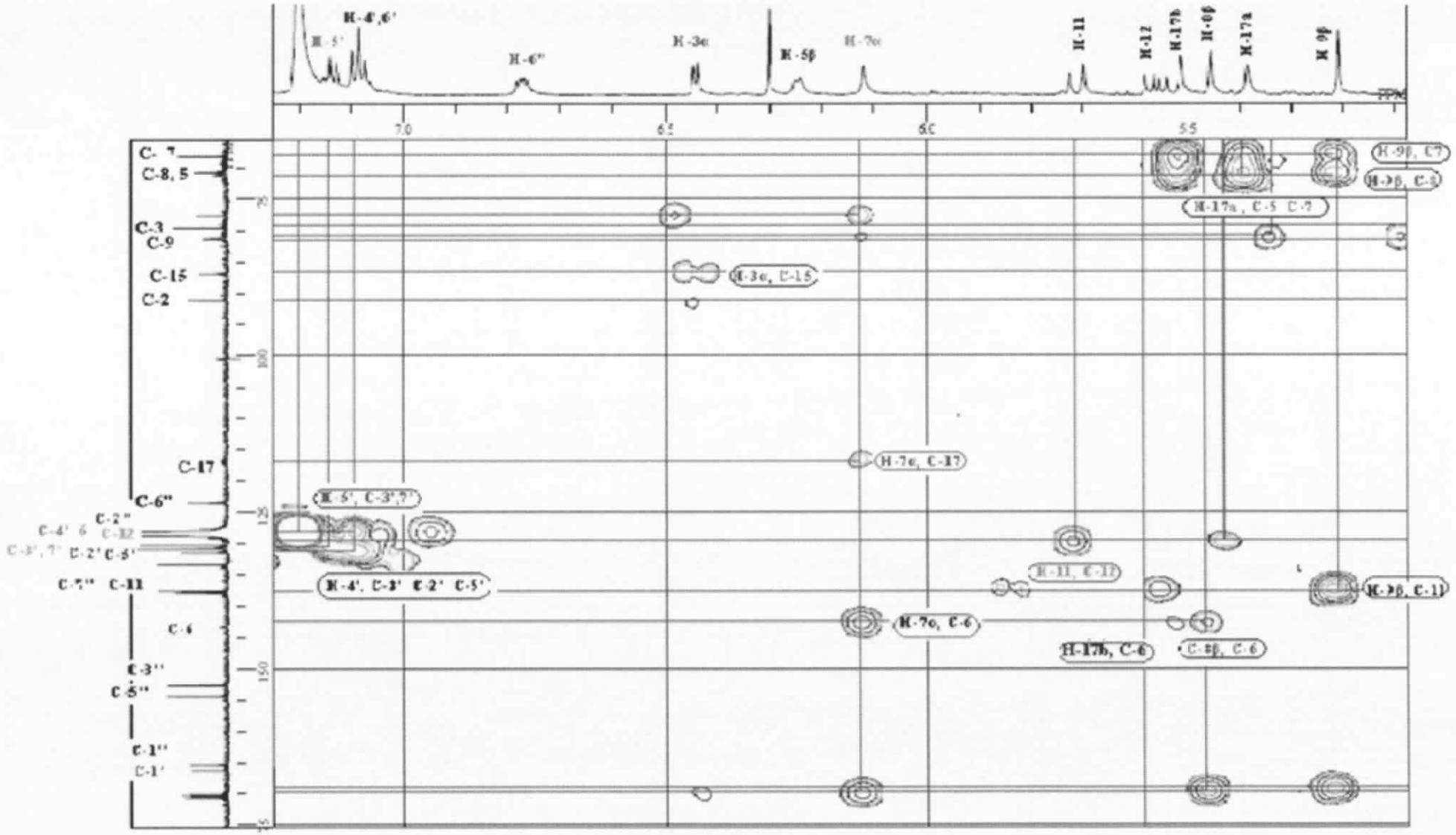
HMQC of compound EG-1

Part 1


HMQC of compound EG-1
C-9
C-3
C-5
C-8
C-7
C-1
C-4
C-13
80
60
40
H-3α
H-5β
H-7α
H-8β
H-9β
H-4α
H-13α
H-1α
H-1β
AcO
HO
OAc
OAc

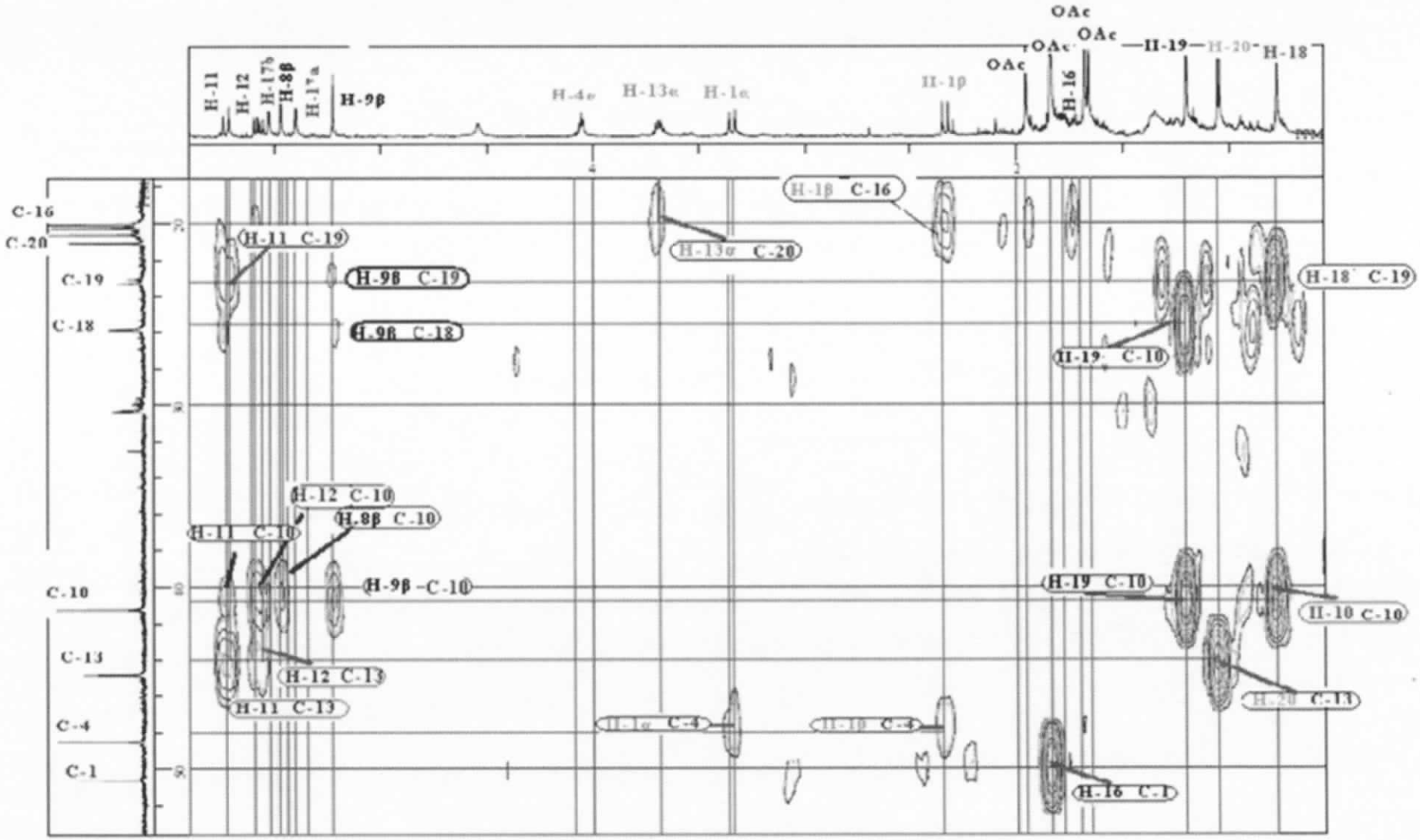


HMQC of compound EG-1



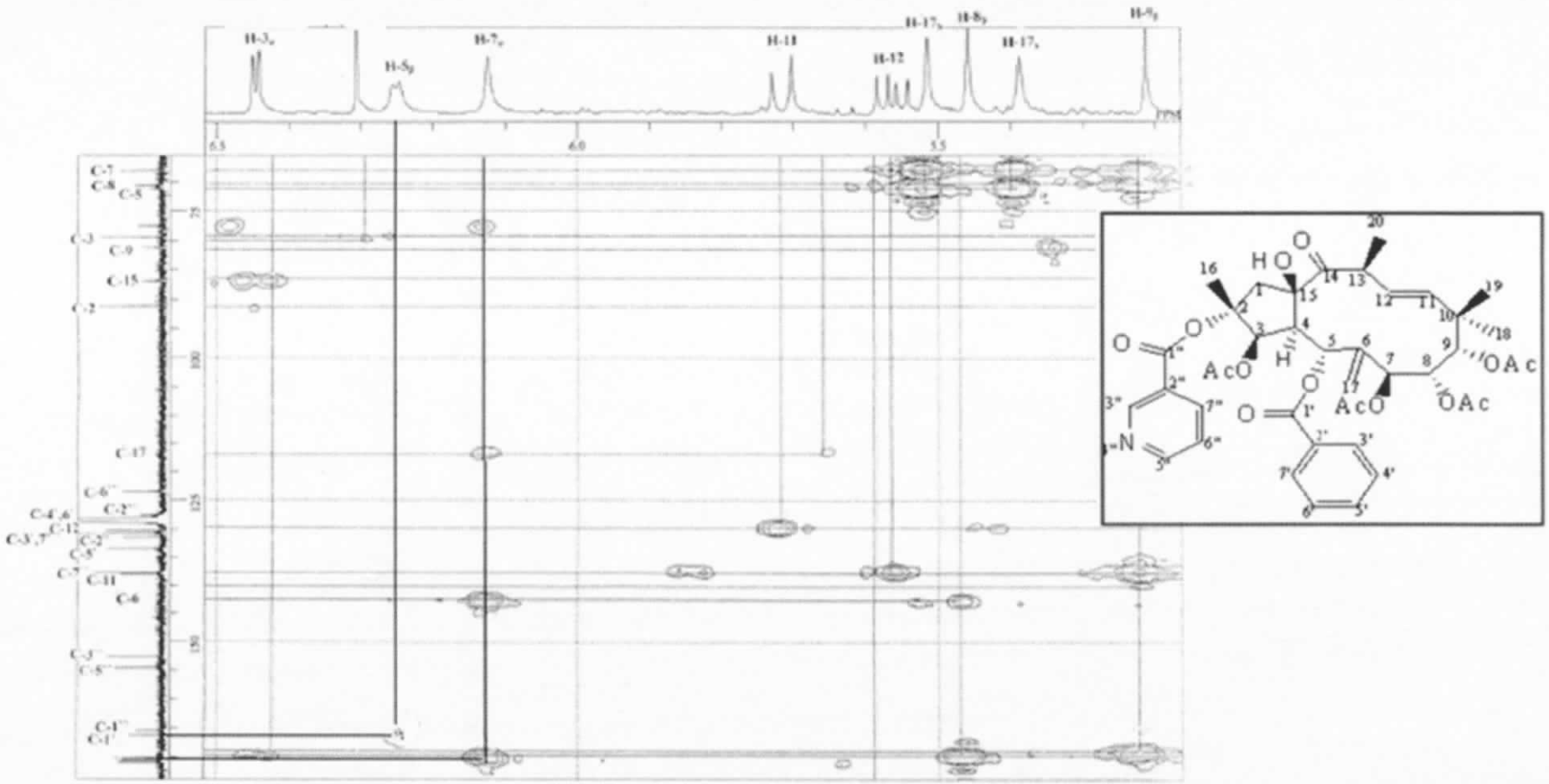
HMBC of compound EG-1

Part 1



HMBC compound EG-1

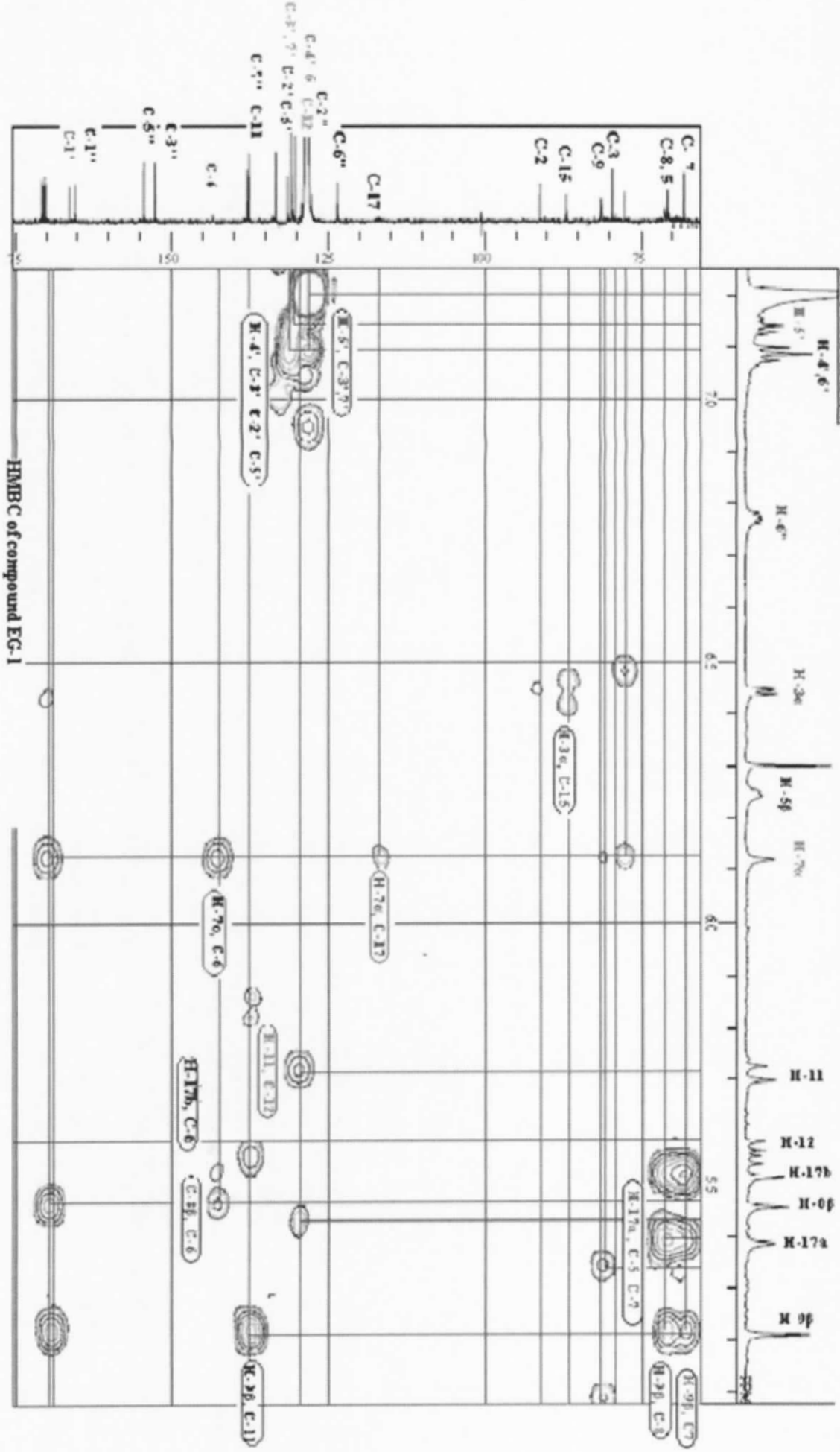
Part 1



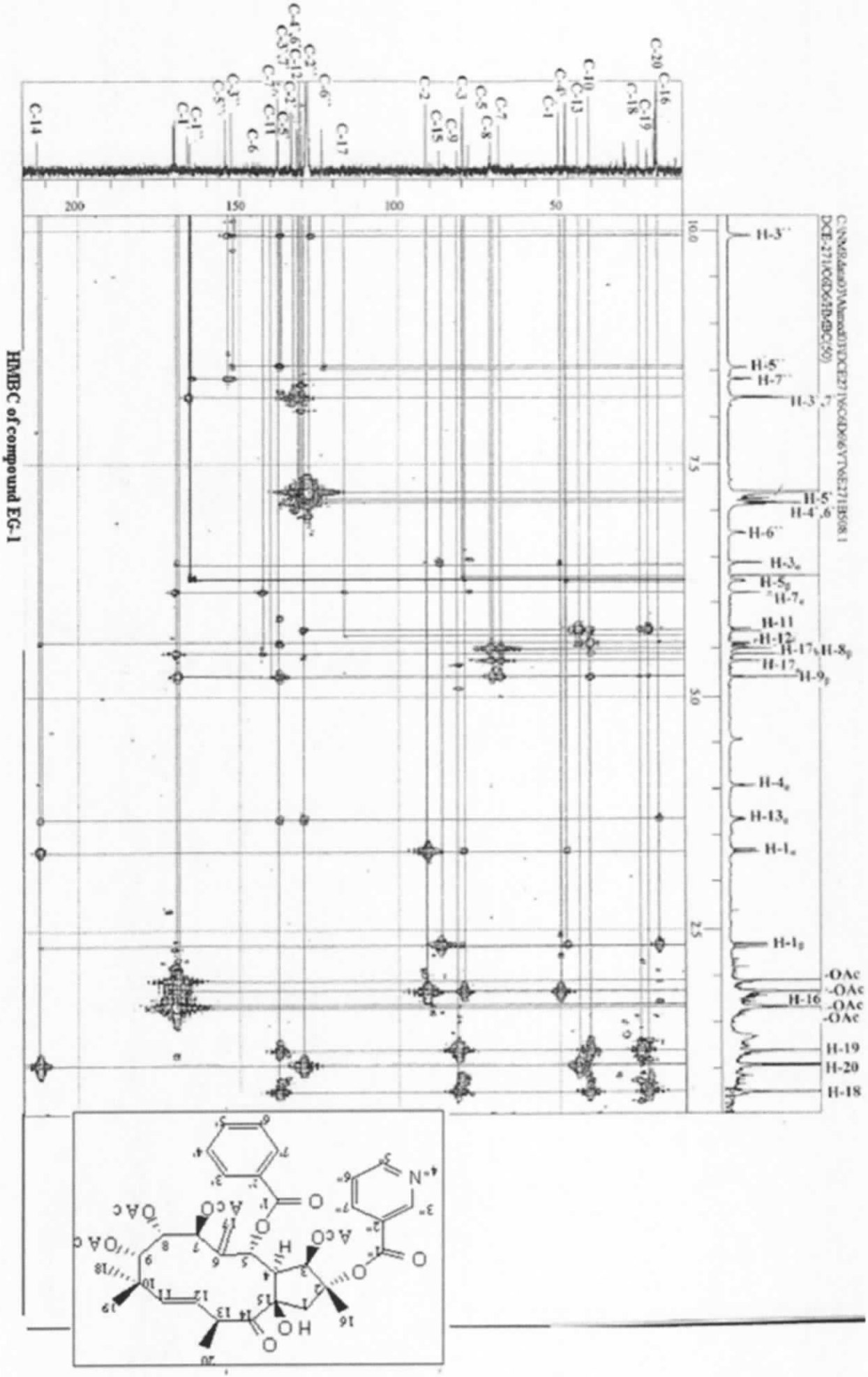
HMBC of compound EG-1

Part 1

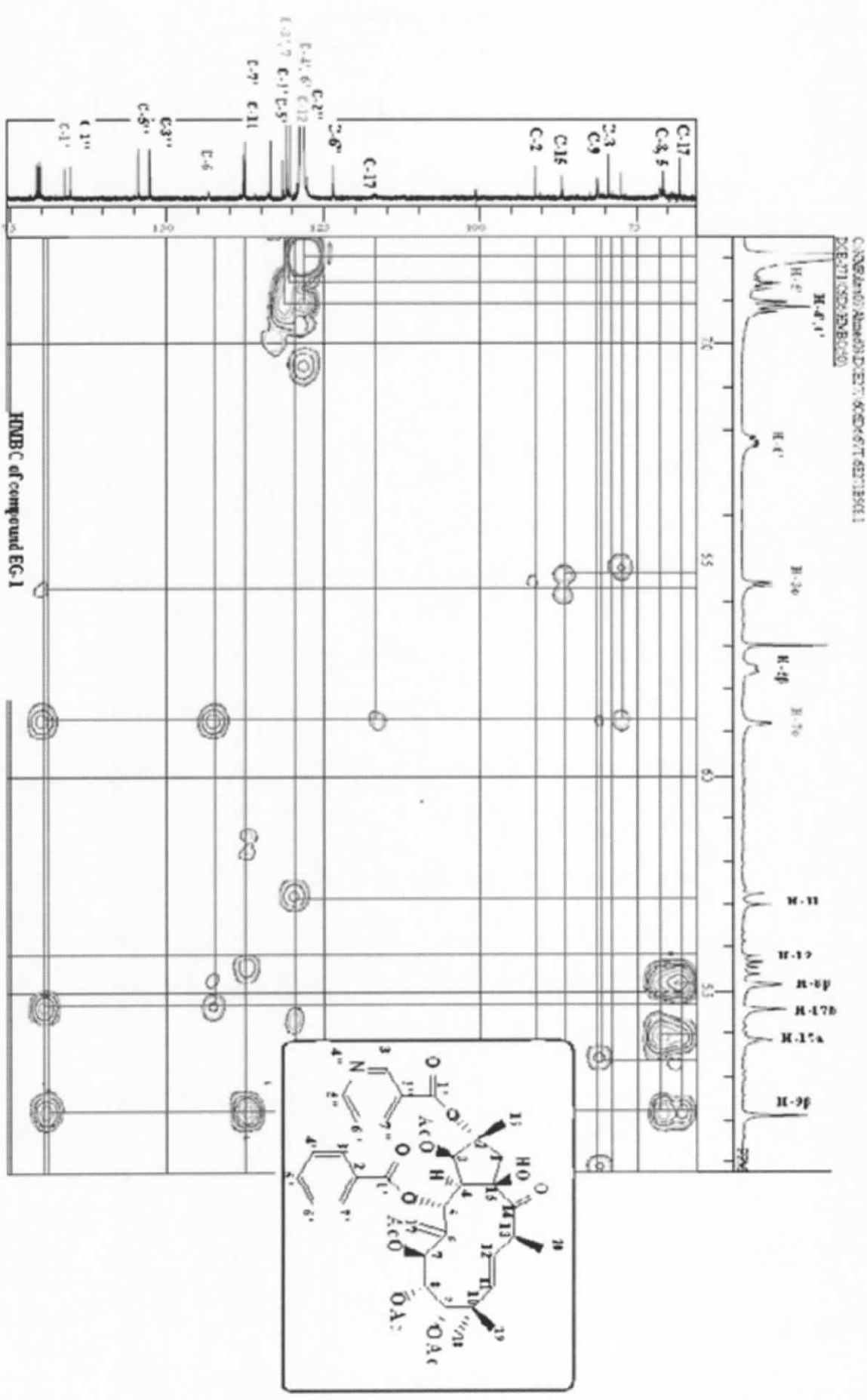
Part 1


HMBC of compound EG-1
H-4', 6'
H-6''
H-3α
H-5β
H-7α
H-11
H-12
H-17b
H-9β
H-17a
H-9β
H-5', C-3''
H-4', C-3'', C-2', C-5'
H-3α, C-15
H-7α, C-17
H-7α, C-6
H-11, C-12
H-17b, C-6
H-17a, C-5, C-7
H-9β, C-8
H-9β, C-7
H-9β, C-1'

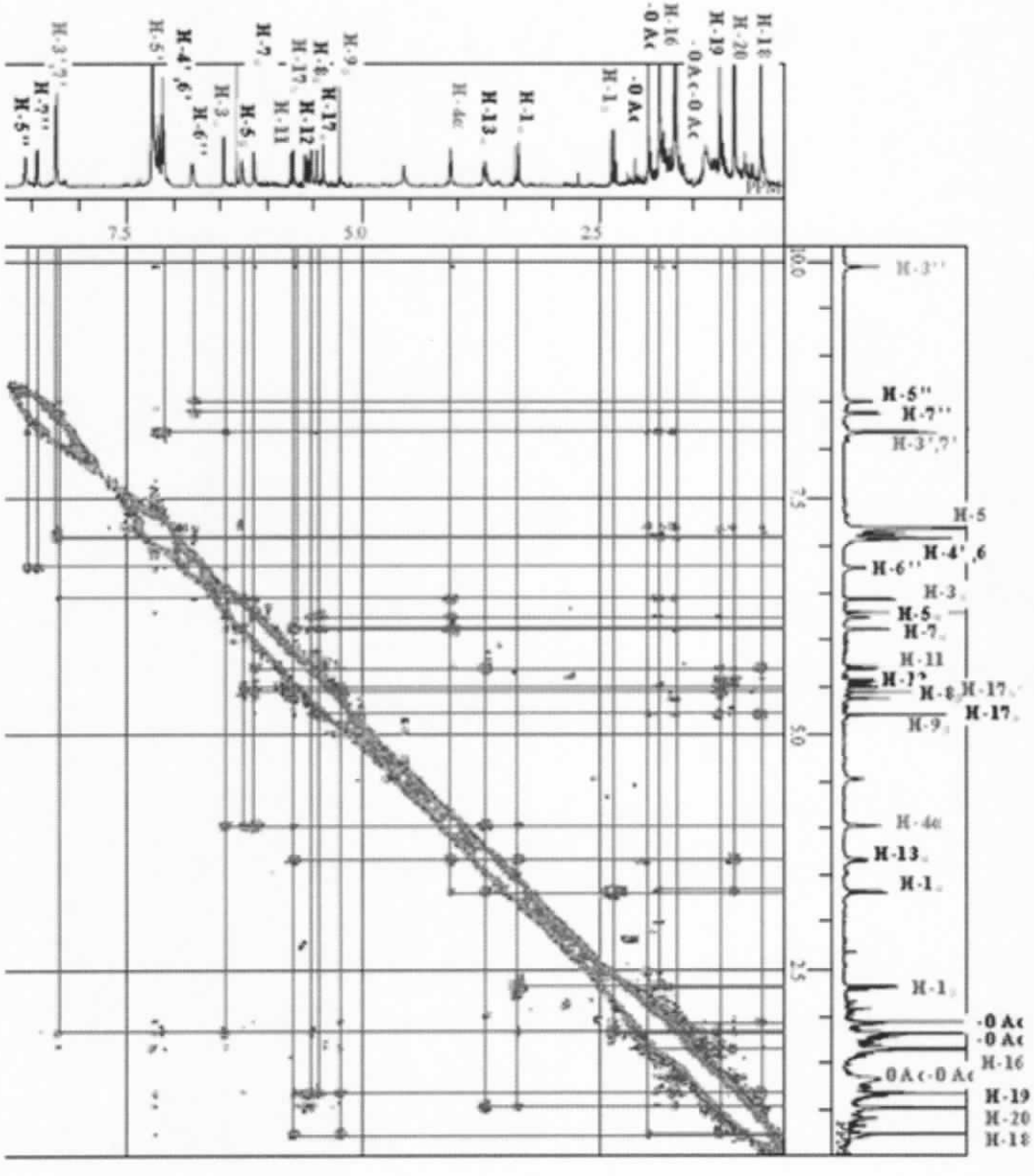
Part 1


HMBC of compound EG-1
C-14
C-1''
C-5''
C-3''
C-6
C-11
C-12
C-2''
C-6''
C-17
C-2
C-15
C-9
C-3
C-5
C-8
C-7
C-1
C-4
C-10
C-13
C-18
C-19
C-20
C-16
200
150
100
50
10.0
7.5
5.0
2.5
H-3''
H-5''
H-7''
H-3'
H-5'
H-4',6'
H-6''
H-3α
H-5β
H-7α
H-11
H-12
H-17b
H-8β
H-17a
H-9β
H-4α
H-13α
H-1α
H-1β
-OAc
-OAc
-OAc
-OAc
H-16
H-19
H-20
H-18

Part 1



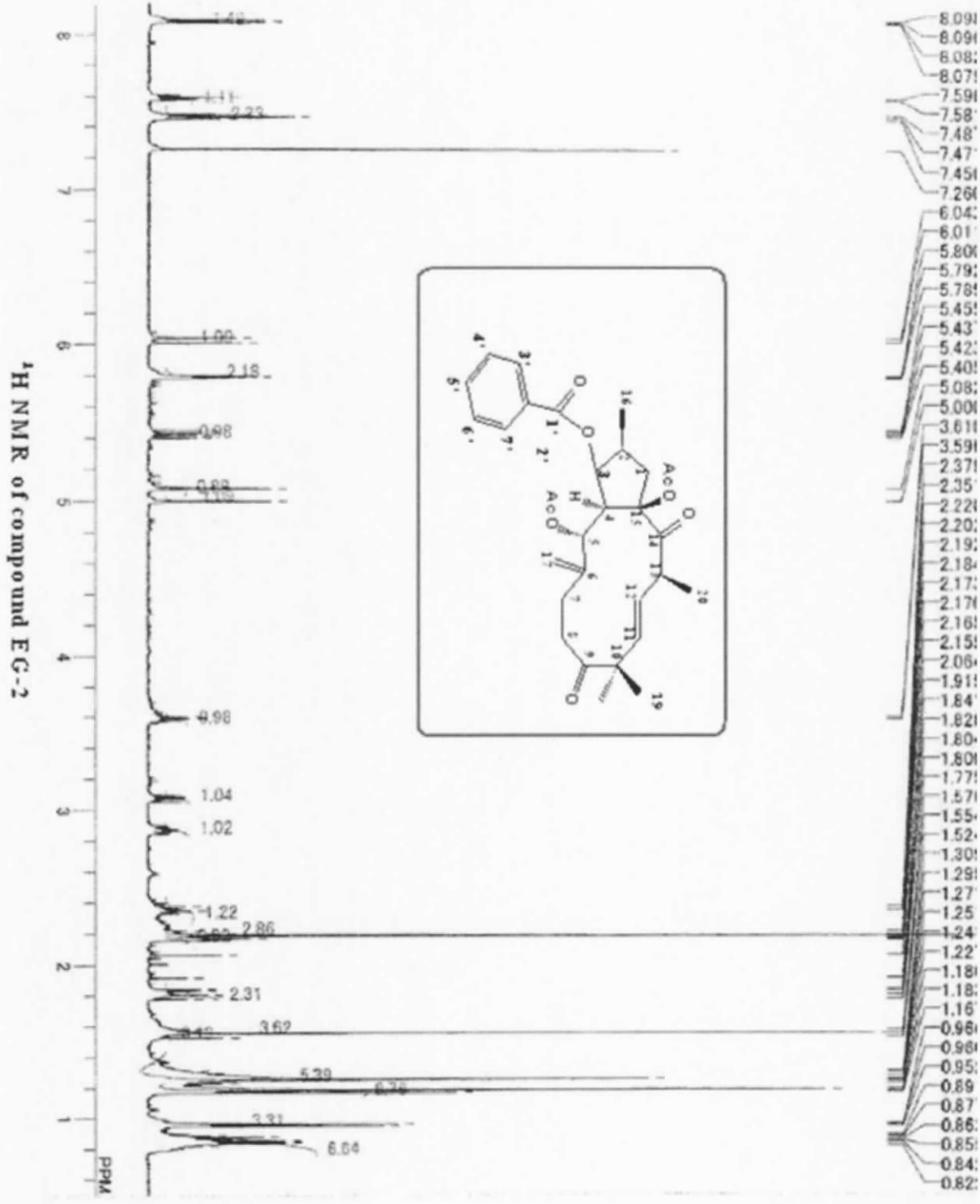
Part 1



NOESY spectrum of compound EG-1

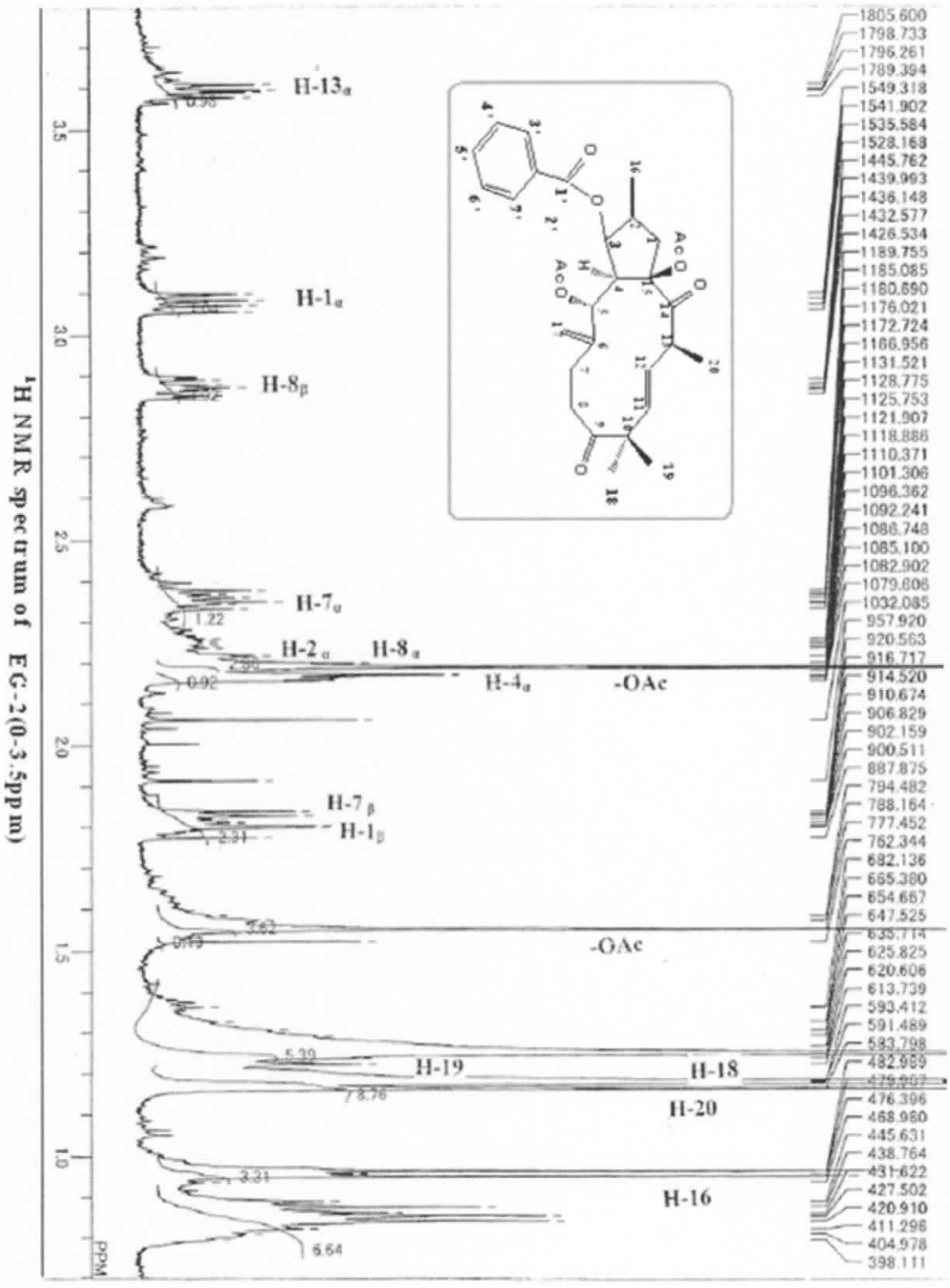
Part 1

EG-2



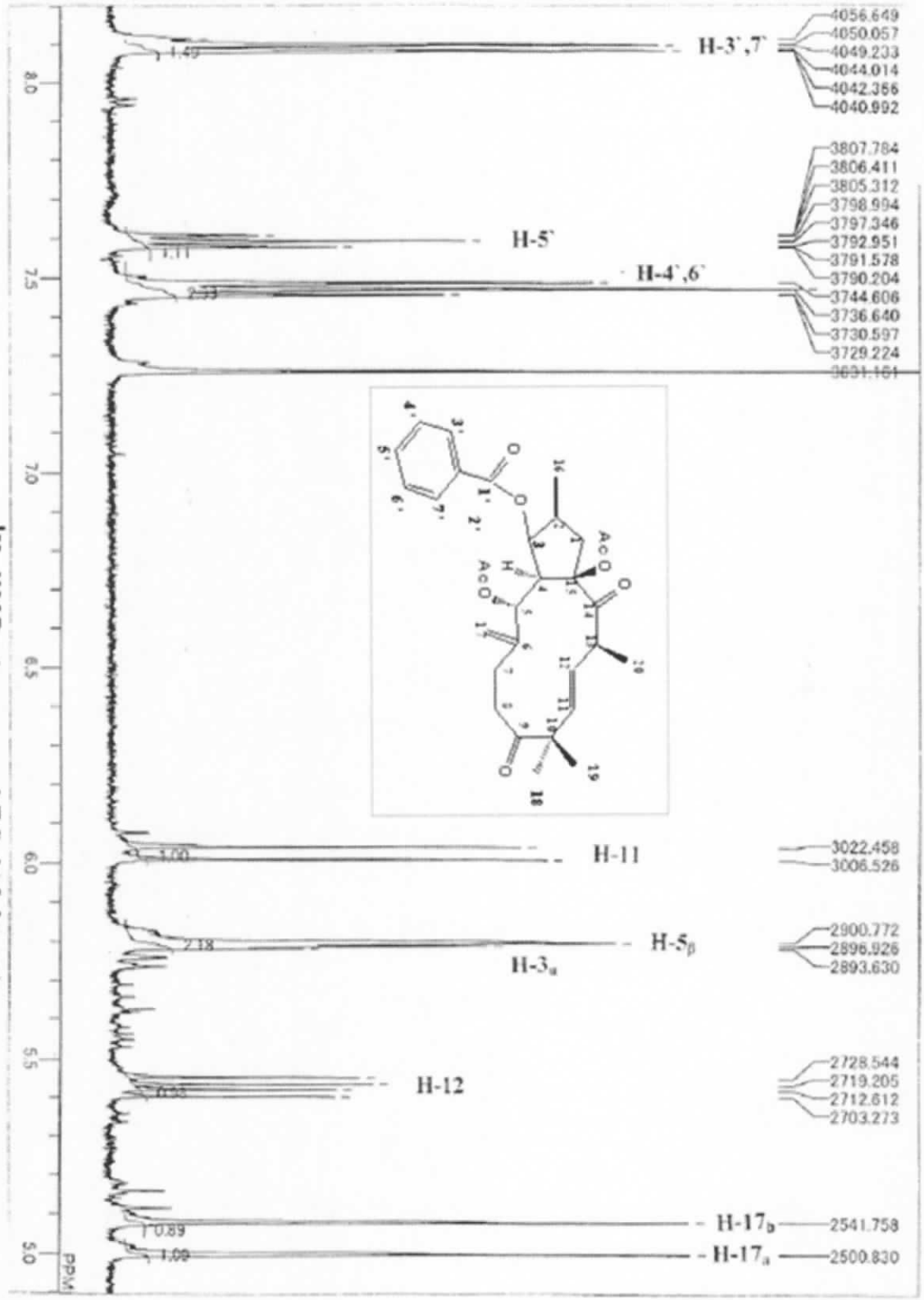
^{1}H NMR of compound EG-2

Part 1



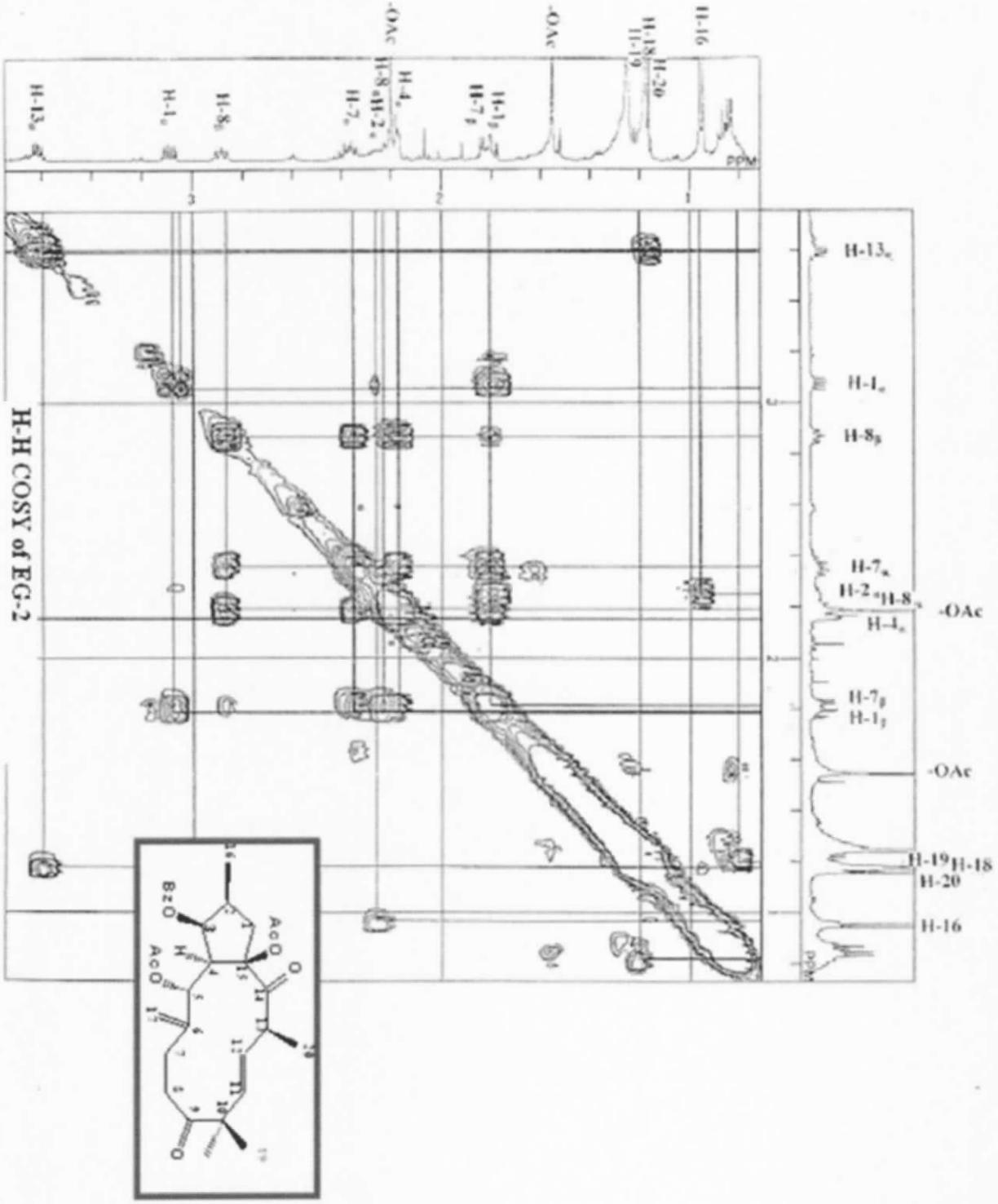
^{1}H NMR spectrum of EG-2(0-3.5ppm)

Part 1



^{1}H NMR of compound EG-2(5-8ppm)

Part 1


H-H COSY of EG-2
H-13α
H-1α
H-8β
H-7α
H-8α*H-2α*
H-4α
H-7β
H-1β
-OAc
-OAc
H-18
H-19
H-20
H-16
PPM
H-13α
H-1α
H-8β
H-7α
H-2α*H-8α*
-OAc
H-4α
H-7β
H-1β
-OAc
H-19
H-18
H-20
H-16
BzO
AcO
AcO
O
O

Part 1

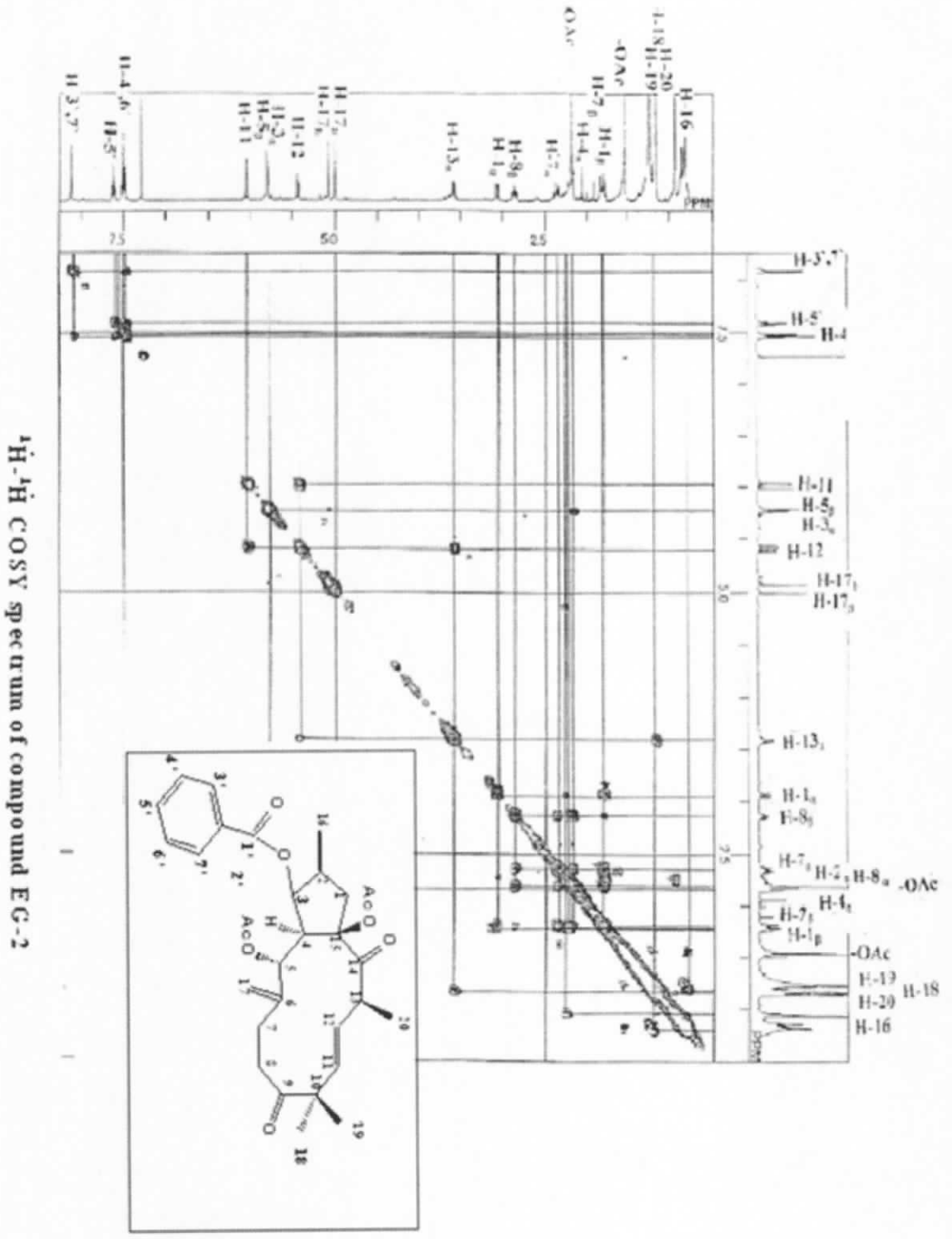
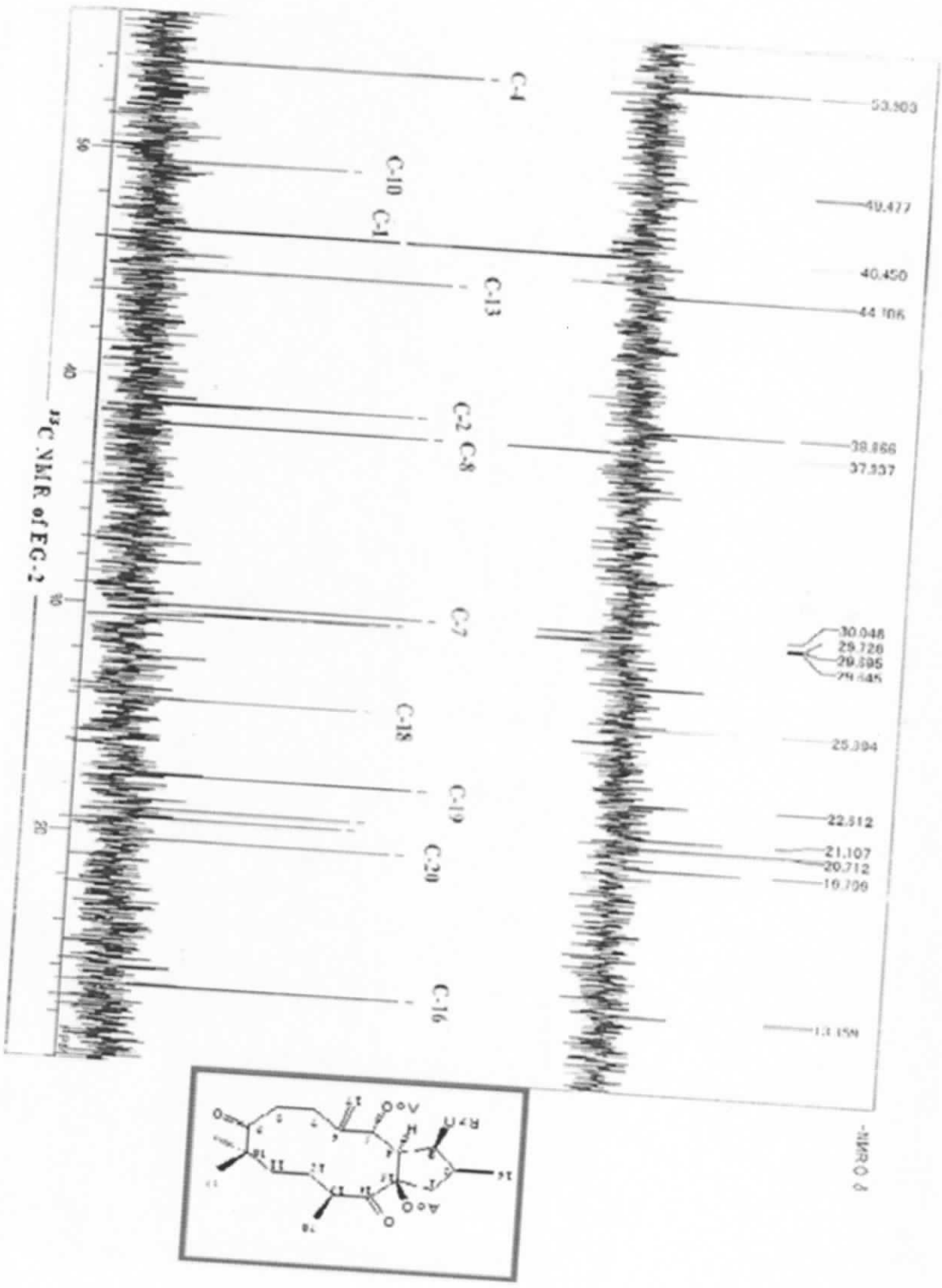
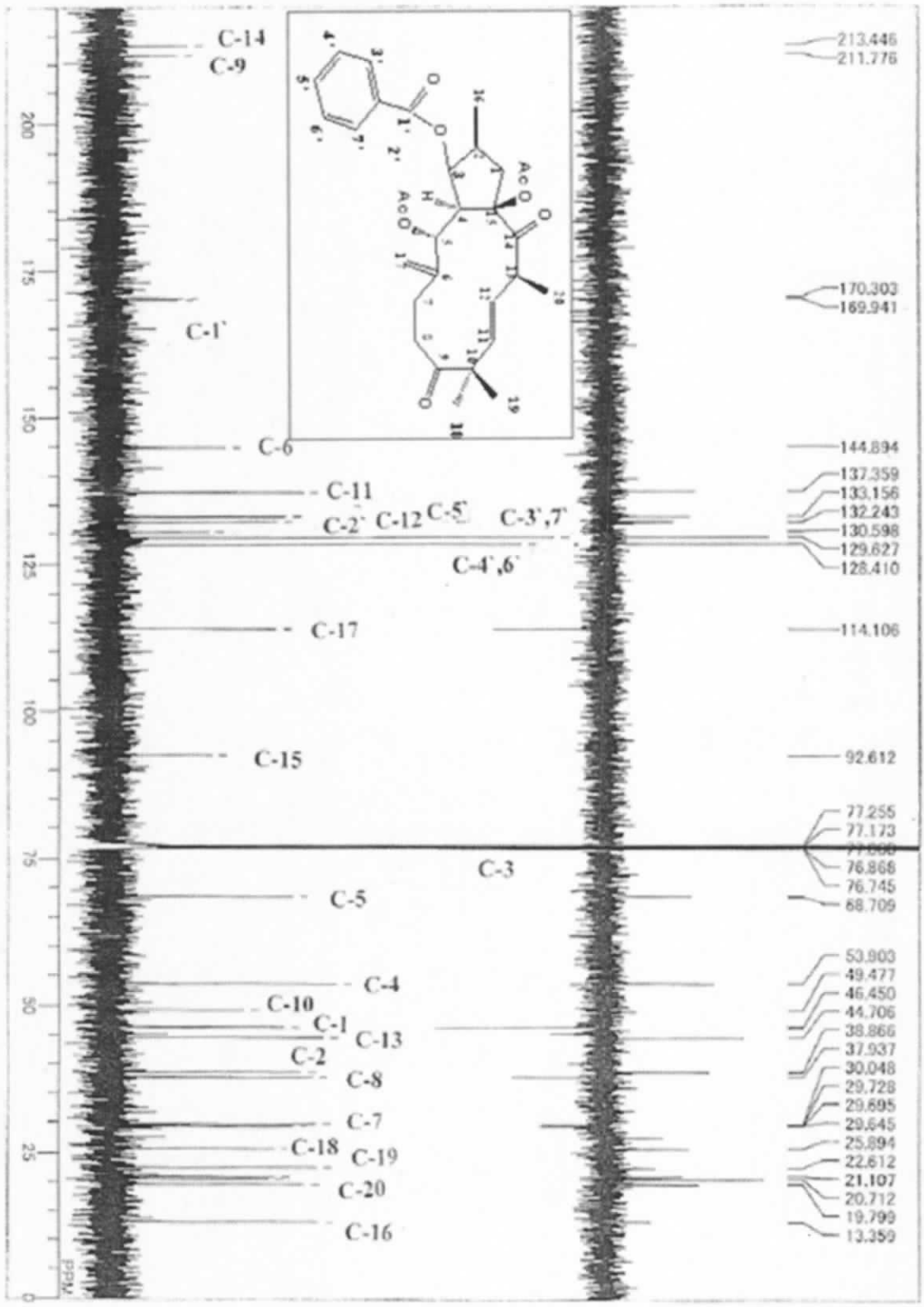
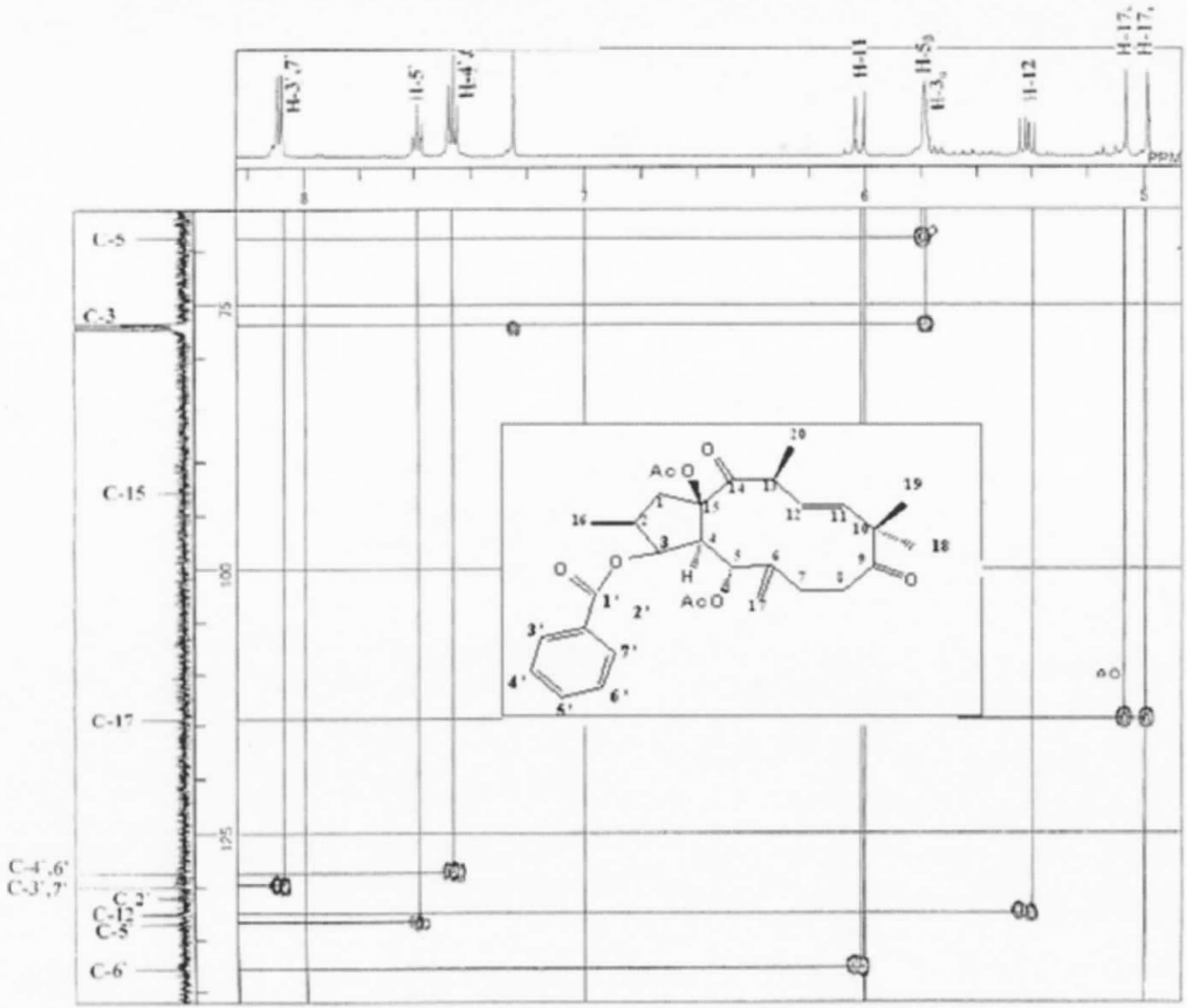


FIG. 2 ^1H-^1H COSY spectrum of compound EG-2

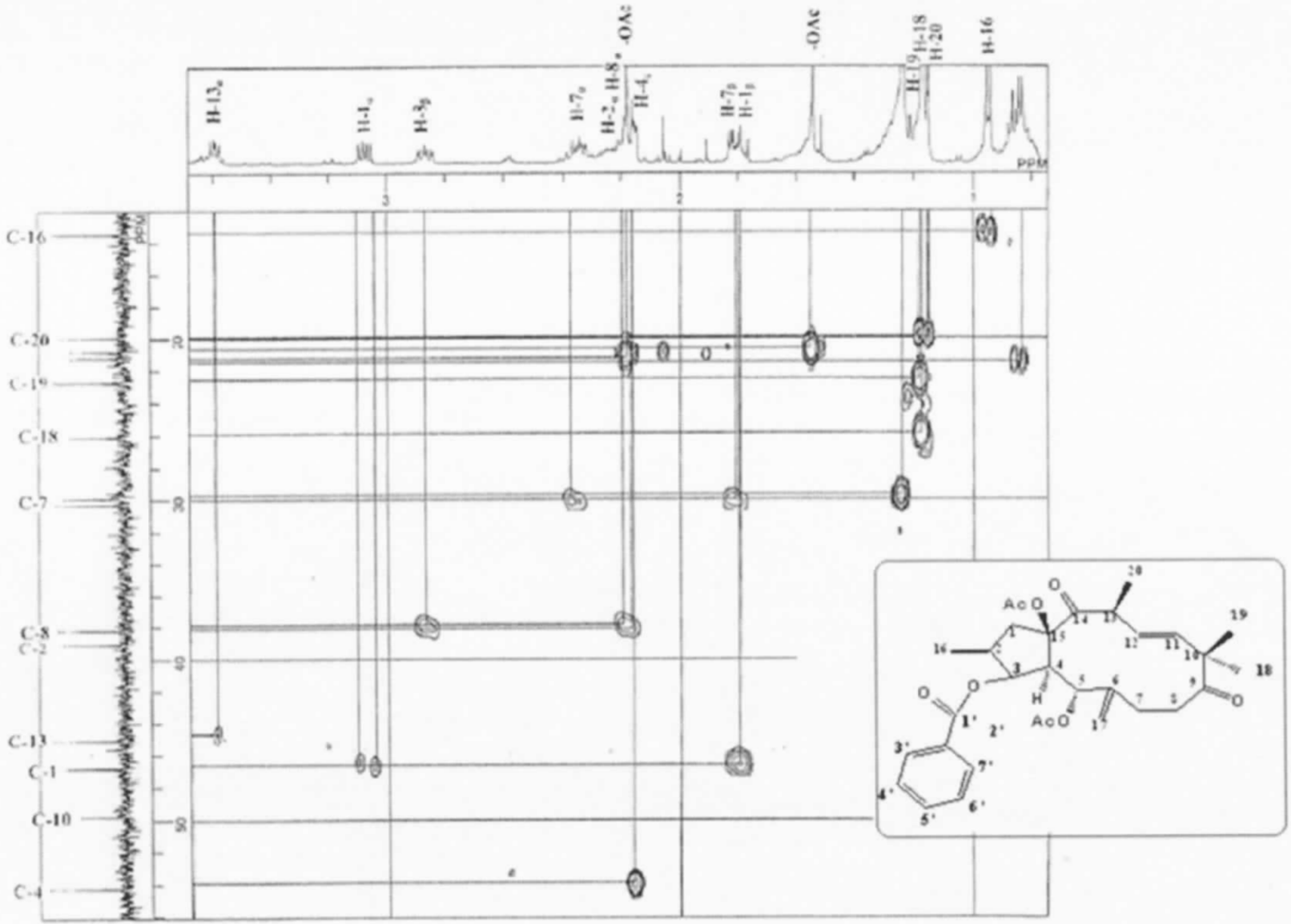

13C NMR of EG-2
C-4
C-10
C-1
C-13
C-2
C-8
C-7
C-18
C-19
C-20
C-16
53.303
49.477
40.450
38.866
37.337
30.048
29.728
29.395
25.394
22.512
21.107
20.712
16.709
13.159
80
40
20



^{13}C NMR and DEPT spectra of compound EG-2

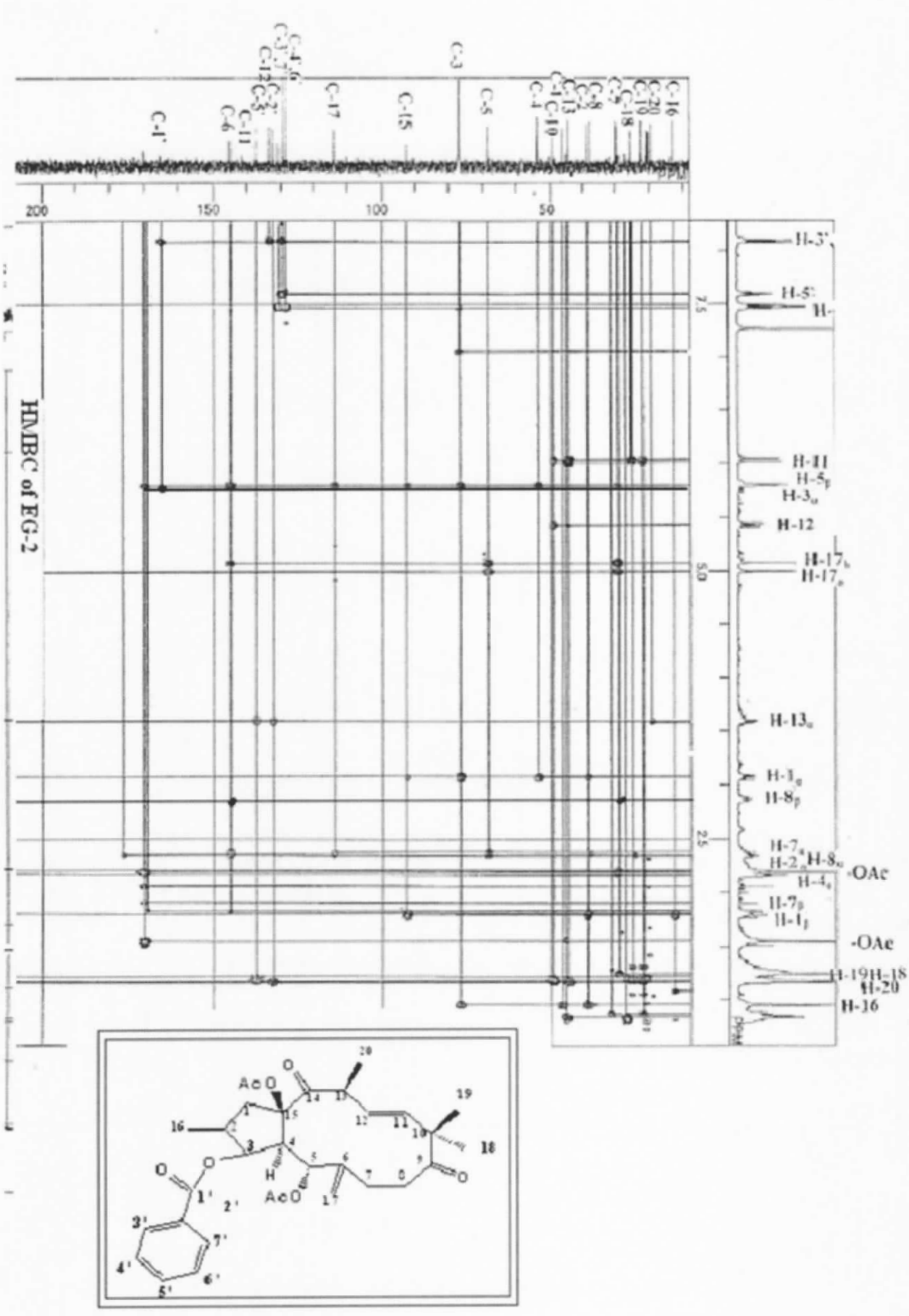


HMQC spectrum of compound EG-2

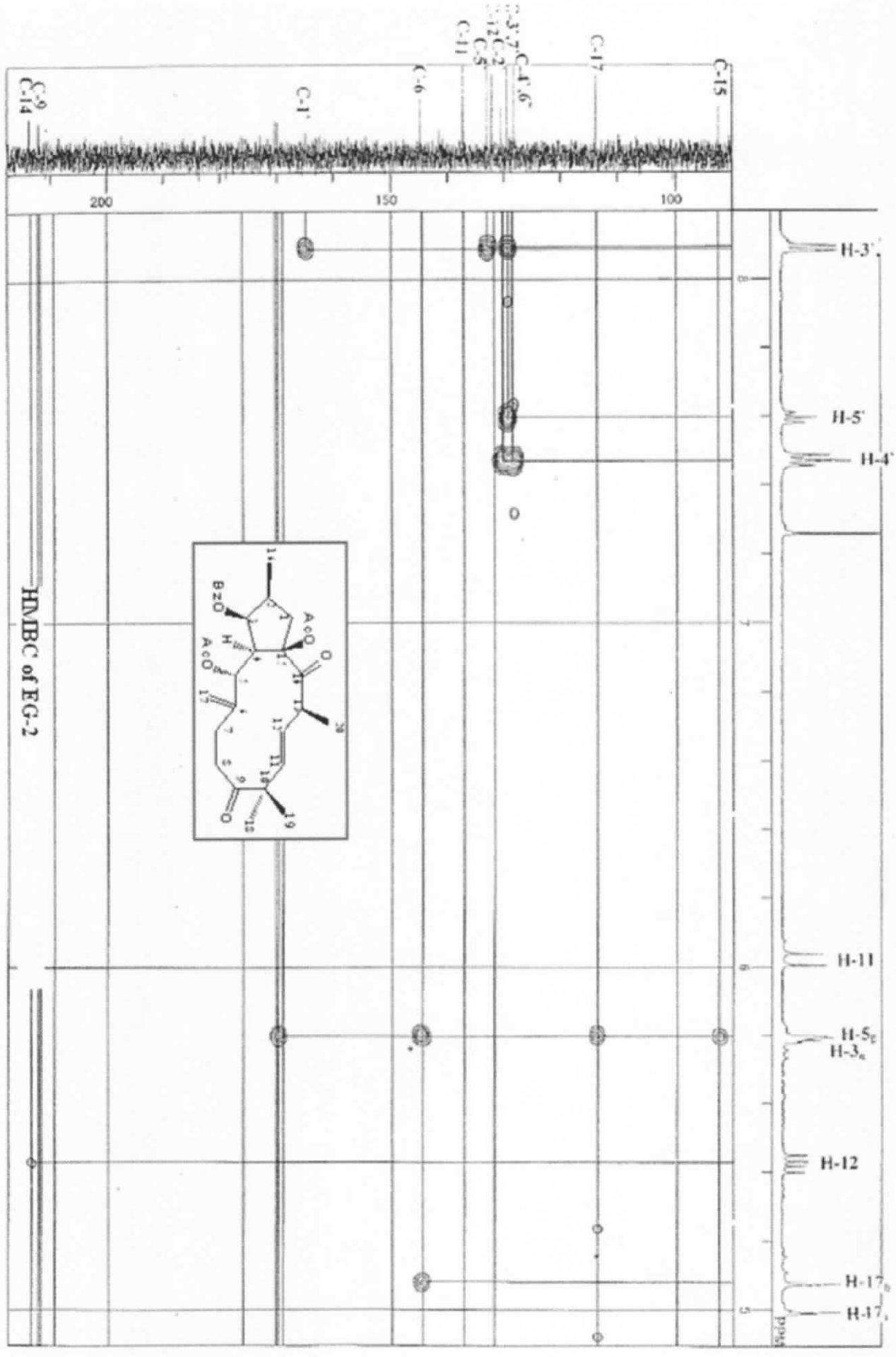


HMQC spectrum of compound EG-2

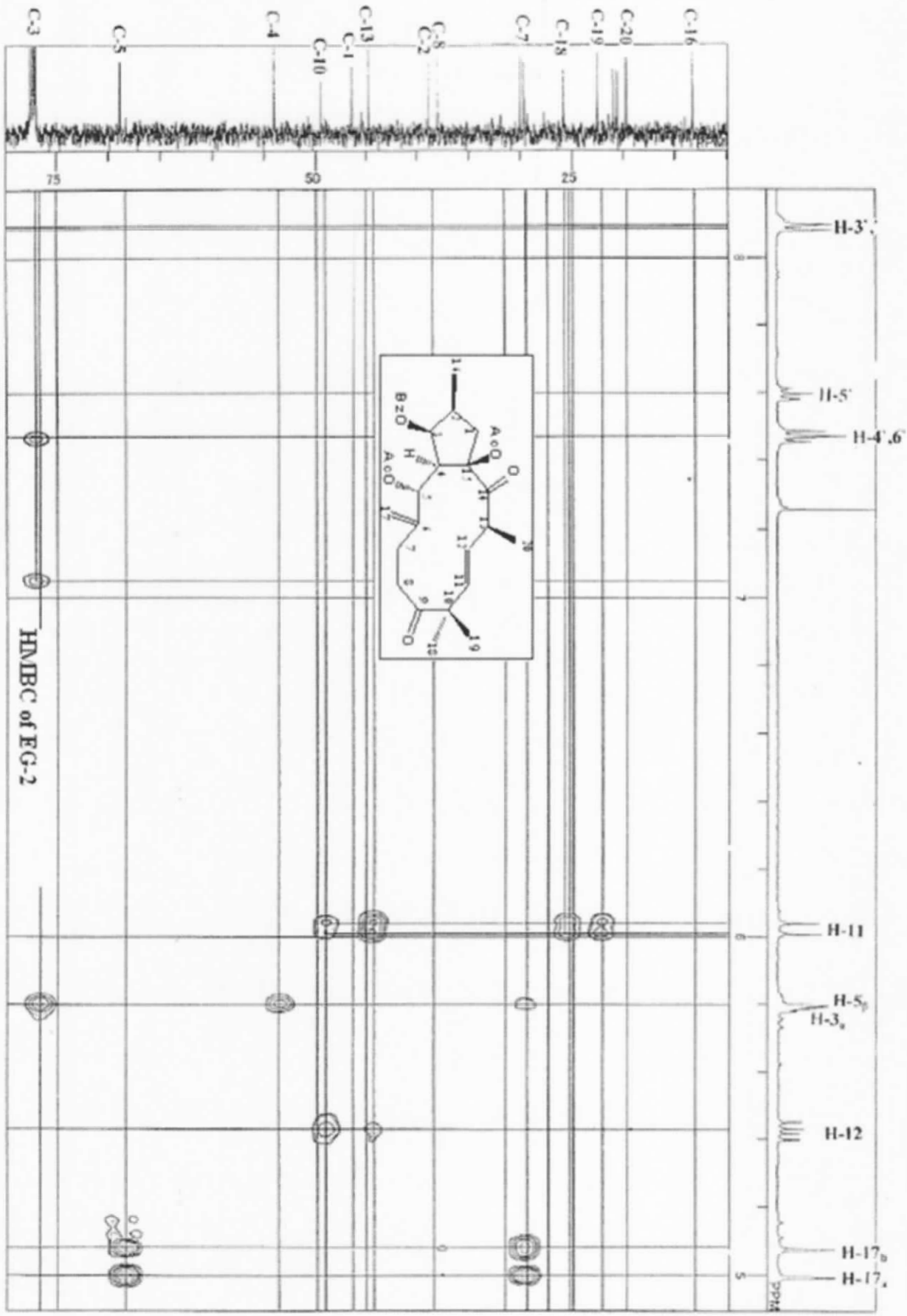
Part 1


HMBC of EG-2
C-1'
C-6
C-11
C-12
C-3'
C-17
C-15
C-3
C-5
C-4
C-19
C-13
C-9
C-8
C-18
C-20
C-10
C-16
200
150
100
50
H-3'
H-5'
H-11
H-5β
H-3α
H-12
H-17b
H-17a
H-13a
H-1α
H-8β
H-7α
H-2α
H-8α
-OAc
H-4α
H-7β
H-1β
-OAc
H-19
H-18
H-20
H-16
7.5
5.0
2.5
AcO
AcO
O
H
16
18
19
20
1'
2'
3'
4'
5'
6'
7'

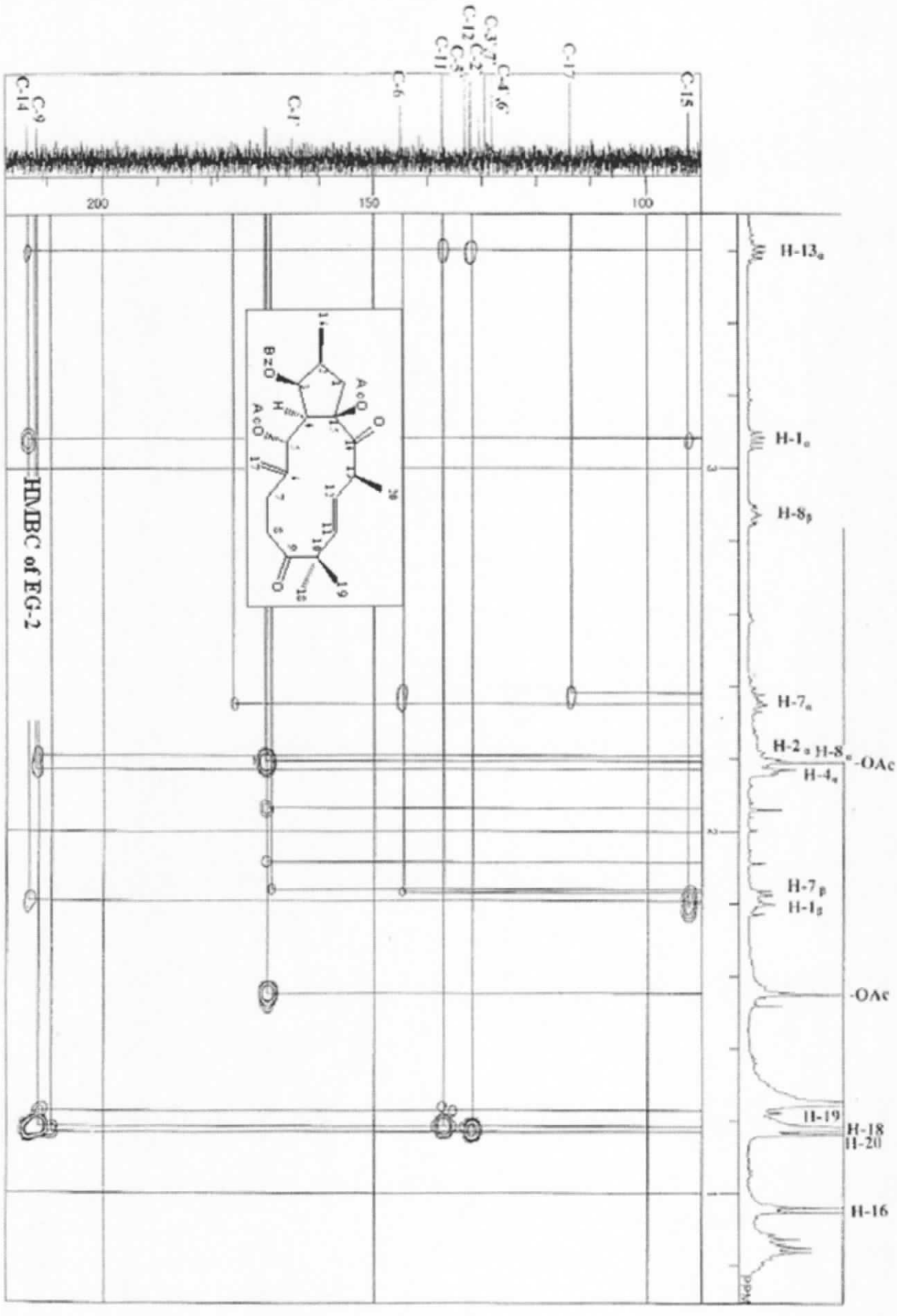
Part 1


C-14
C-9
C-1'
C-6
C-11
C-5
C-12
C-2
C-3',7'
C-4',6'
C-17
C-15
200
150
100
H-3'
H-5'
H-4'
H-11
H-5β
H-3α
H-12
H-17b
H-17a
8
7
6
5
ppm
HMBC of EG-2
BzO
AcO
AcO
O
O
O
O
H
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20

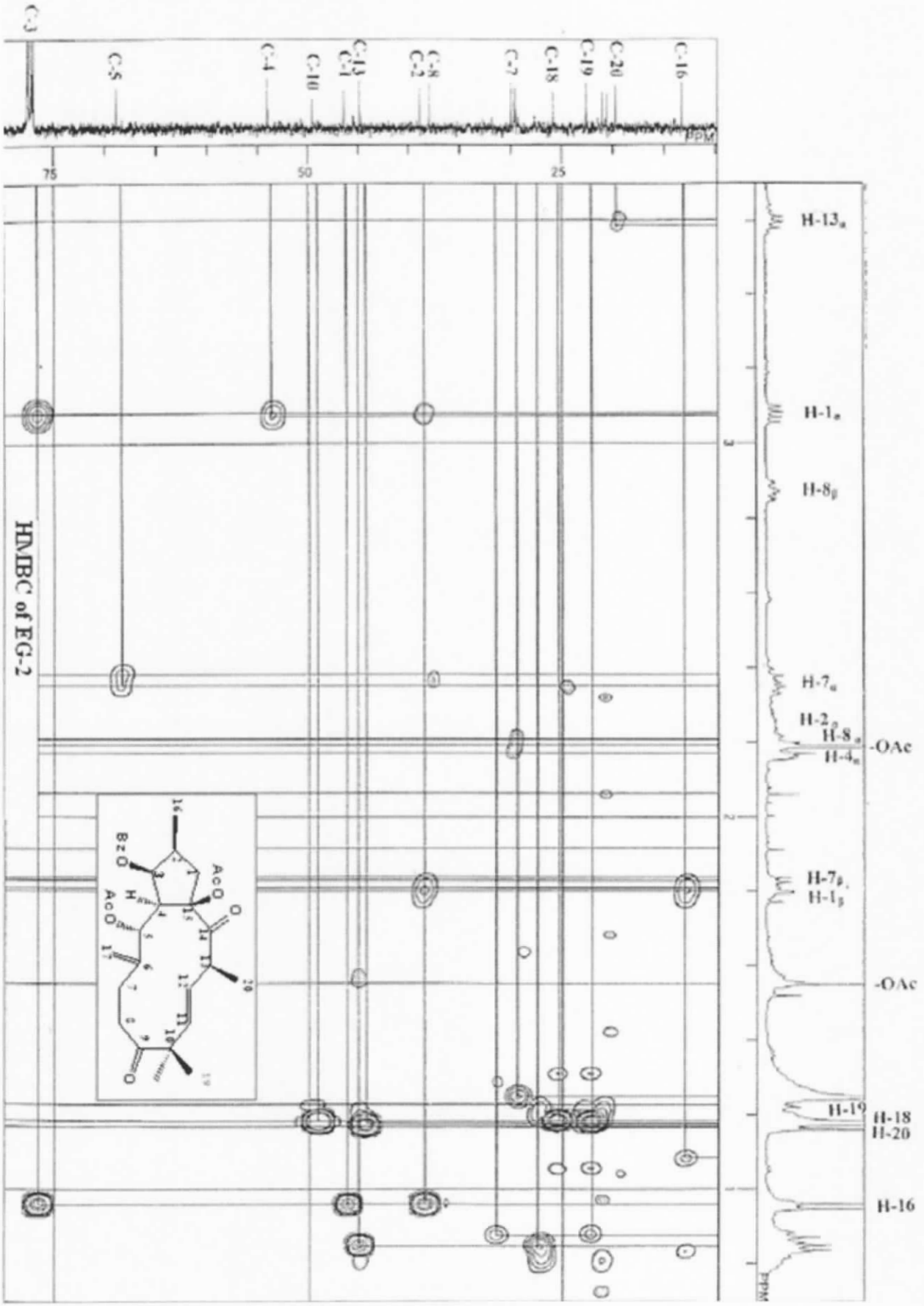
Part 1


C-3
C-5
C-4
C-10
C-13
C-1
C-8
C-2
C-7
C-18
C-19
C-20
C-16
75
50
25
H-3'
H-5'
H-4',6'
H-11
H-5β
H-3α
H-12
H-17b
H-17a
HMBC of EG-2

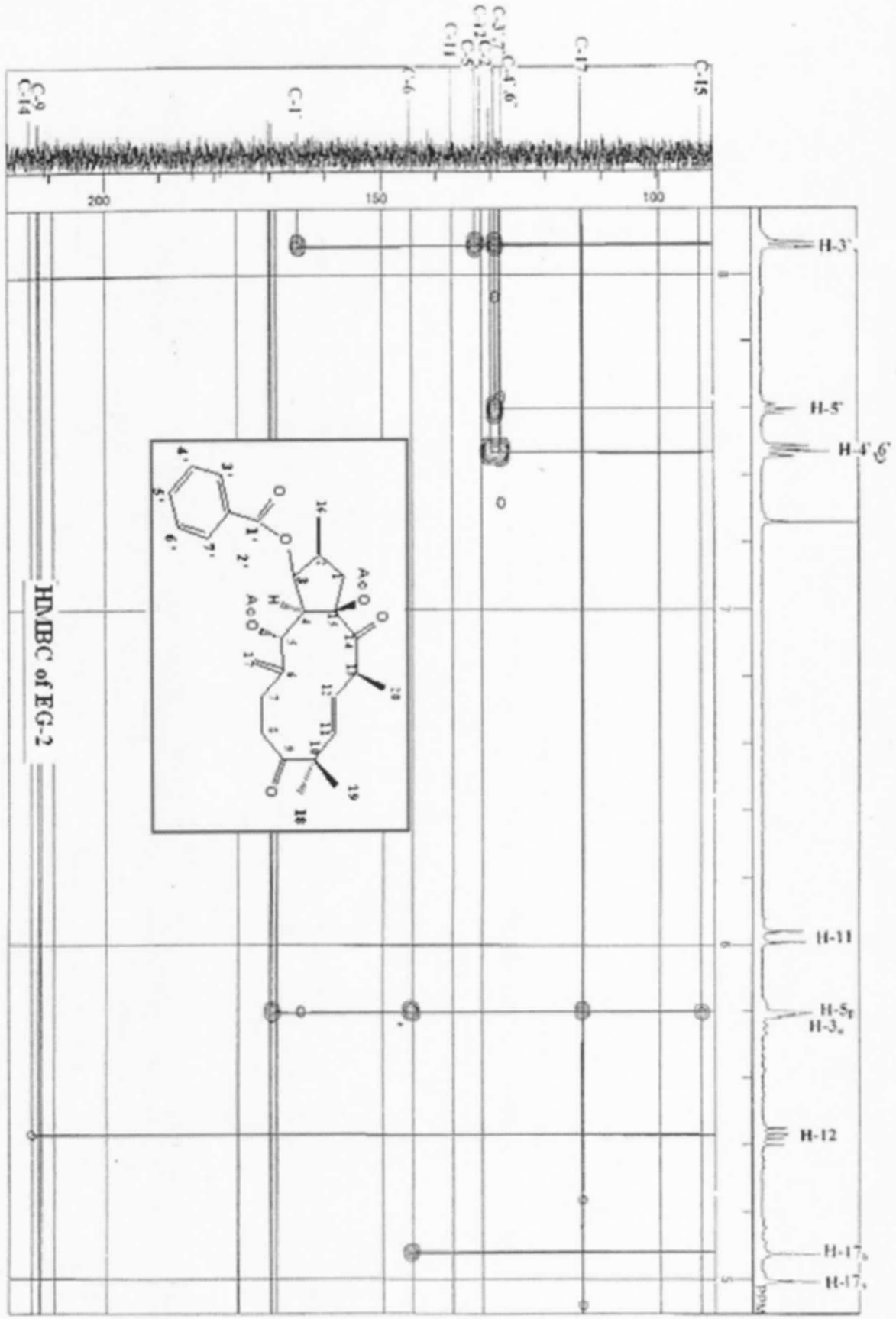
Part 1


HMBC of EG-2
C-14
C-9
C-1'
C-6
C-11
C-12
C-2'
C-3',7'
C-4',6'
C-17
C-15
200
150
100
H-13a
H-1a
H-8β
H-7a
H-2a H-8a
-OAc
H-4a
H-7β
H-1β
-OAc
H-19
H-18
H-20
H-16
BzO
AcO
AcO
3
2
1
PPM

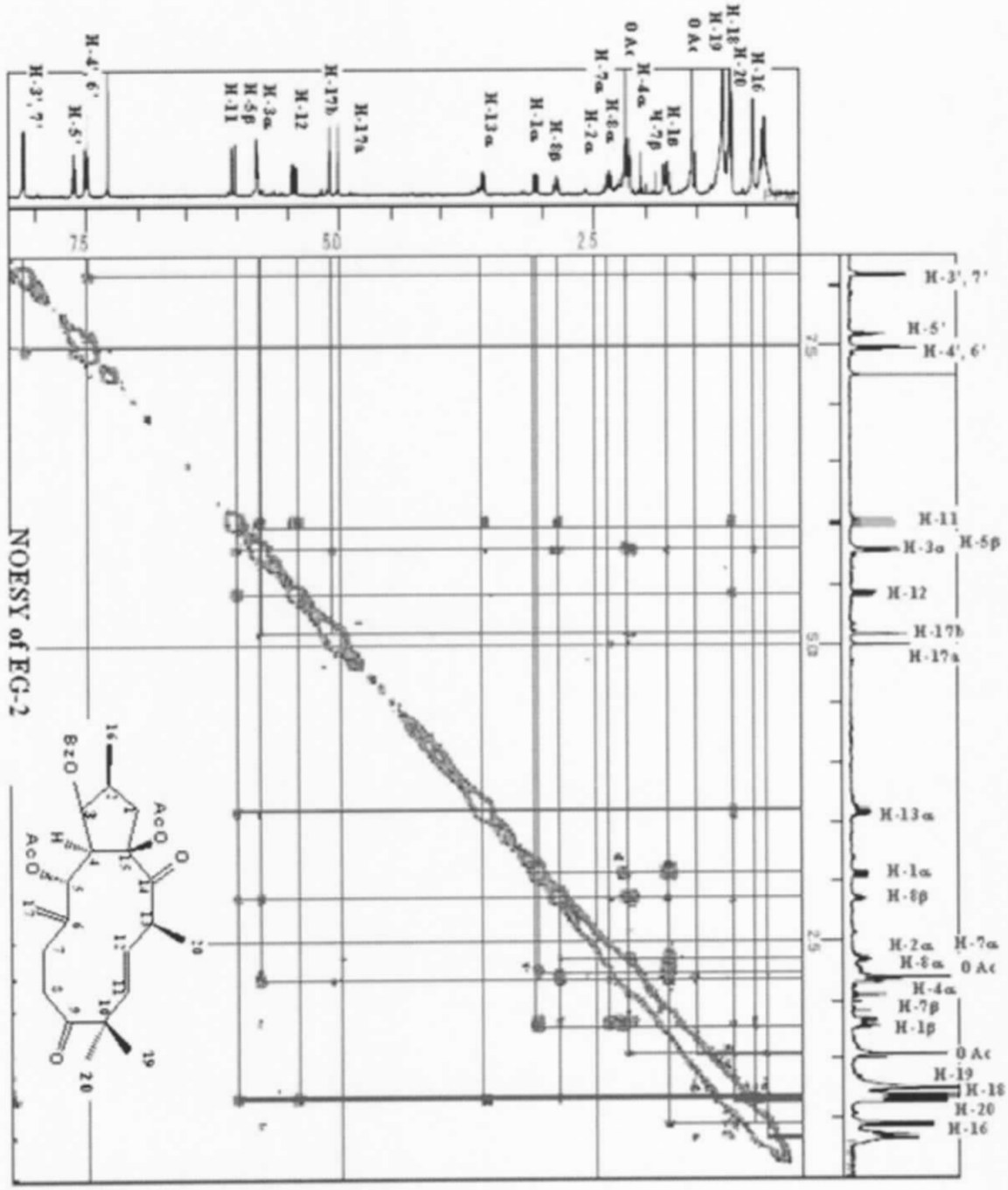
Part 1


HMBC of EG-2
C-3
C-5
C-4
C-10
C-13
C-1
C-8
C-2
C-7
C-18
C-19
C-20
C-16
ppm
75
50
25
H-13a
H-1a
H-8β
H-7a
H-2β
H-8a
H-4a
-OAc
H-7β
H-1β
-OAc
H-19
H-18
H-20
H-16
ppm
BzO
AcO
AcO

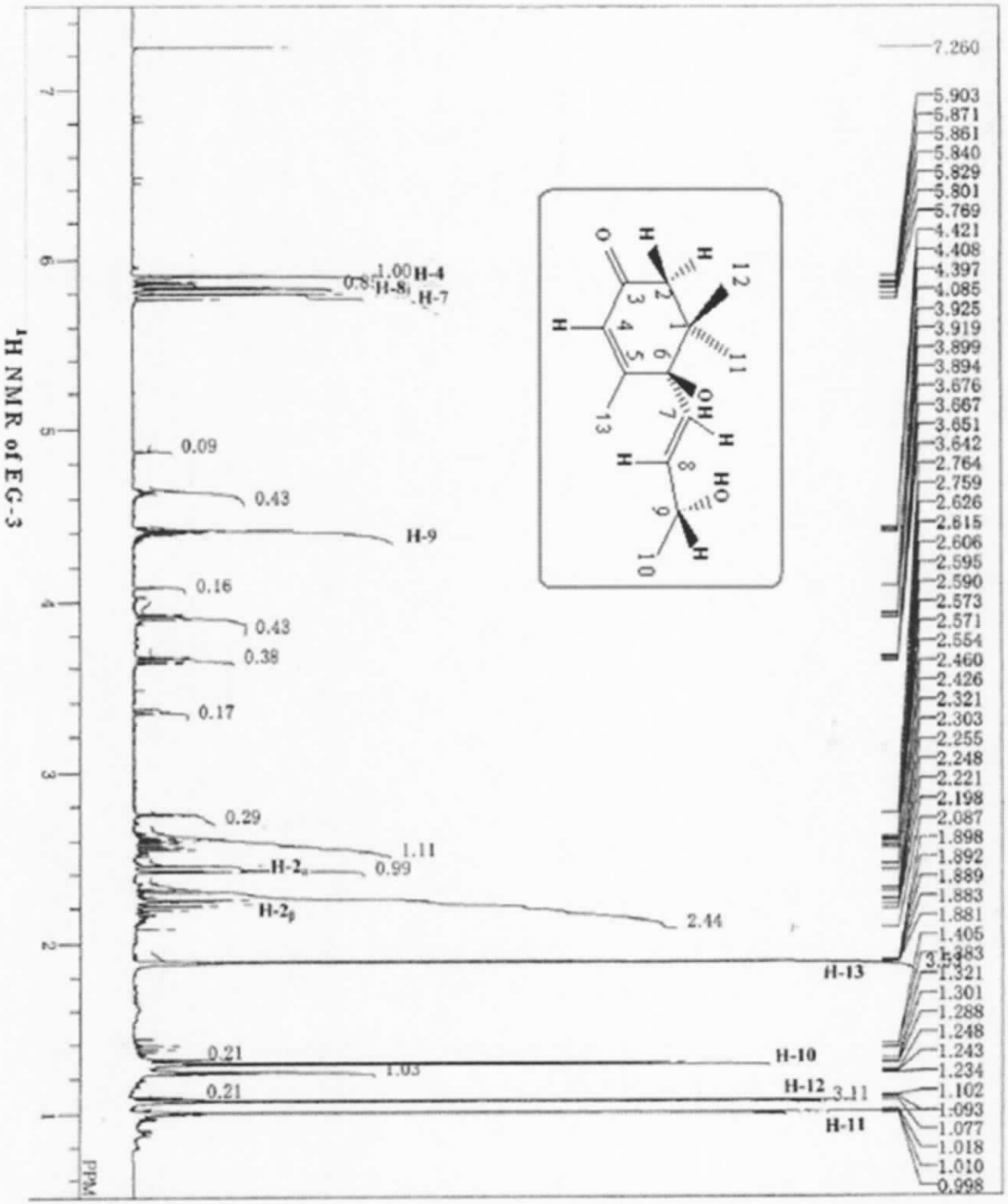
Part 1


C-9
C-14
C-1'
C-7
C-11
C-17
C-15
200
150
100
H-3'
H-5'
H-4',6'
H-11
H-5β
H-3α
H-12
H-17b
H-17a
HMBC of EG-2

Part 1


NOESY of EG-2
H-3', 7'
H-5'
H-4', 6'
H-11
H-5β
H-3α
H-12
H-17b
H-17a
H-13α
H-1α
H-8β
H-2α
H-7α
H-8α
0 Ac
H-4α
H-7β
H-1β
0 Ac
H-19
H-18
H-20
H-16
BzO
AcO
AcO
O
O
16
19
20

EG-3


^{1}H NMR of EG-3
PPM
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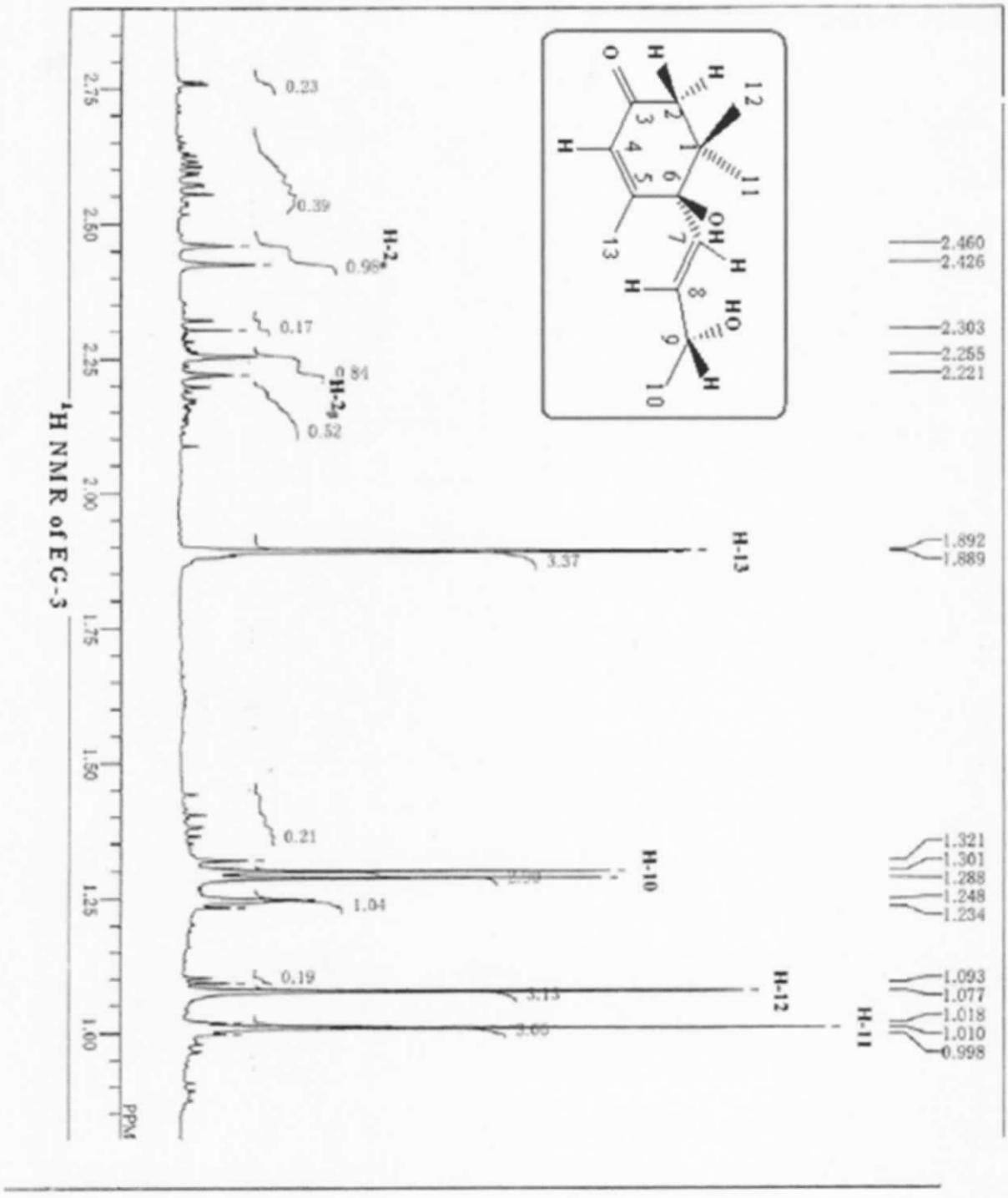
5.871
5.861
5.840
5.829
5.801
5.769
4.421
4.408
4.397
4.085
3.925
3.919
3.899
3.894
3.676
3.667
3.651
3.642
2.764
2.759
2.626
2.615
2.606
2.595
2.590
2.573
2.571
2.554
2.460
2.426
2.321
2.303
2.255
2.248
2.221
2.198
2.087
1.898
1.892
1.889
1.883
1.881
1.405
1.321
1.301
1.288
1.248
1.243
1.234
1.102
1.093
1.077
1.018
1.010
0.998
1.00 H-4
0.8 H-8
H-7
0.09
0.43
H-9
0.16
0.43
0.38
0.17
0.29
1.11
H-2α
0.99
H-2β
2.44
H-13
0.21
1.03
H-10
0.21
H-12
3.11
H-11
O
H
H
12
2
3
1
H
4
5
6
11
OH
7
13
H
8
HO
9
10
H

Part 1


^{1}H NMR of EG-3
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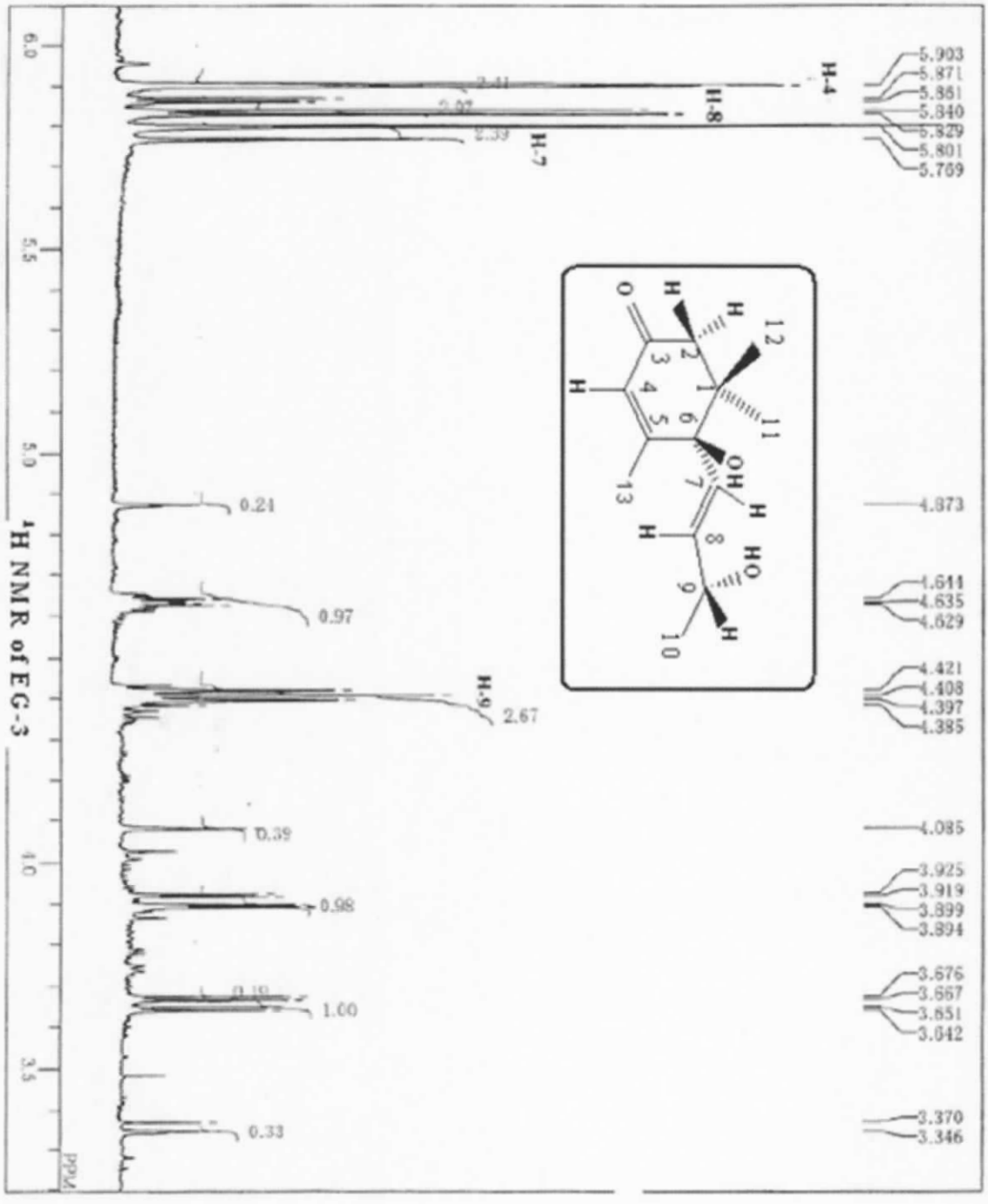
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.23
0.39
H-2a
0.98
0.17
0.84
H-2b
0.52
3.37
H-13
0.21
H-10
1.04
0.19
H-12
3.13
3.00
H-11
2.460
2.426
2.303
2.255
2.221
1.892
1.889
1.321
1.301
1.288
1.248
1.234
1.093
1.077
1.018
1.010
0.998
O
H
H
12
2
1
11
3
4
5
6
H
OH
H
7
13
H
8
HO
9
H
10

Part 1


¹H NMR of EG-3
H-4
H-8
H-7
H-6
5.903
5.871
5.861
5.840
5.829
5.801
5.769
4.873
4.611
4.635
4.629
4.421
4.408
4.397
4.385
4.085
3.925
3.919
3.899
3.894
3.676
3.667
3.651
3.642
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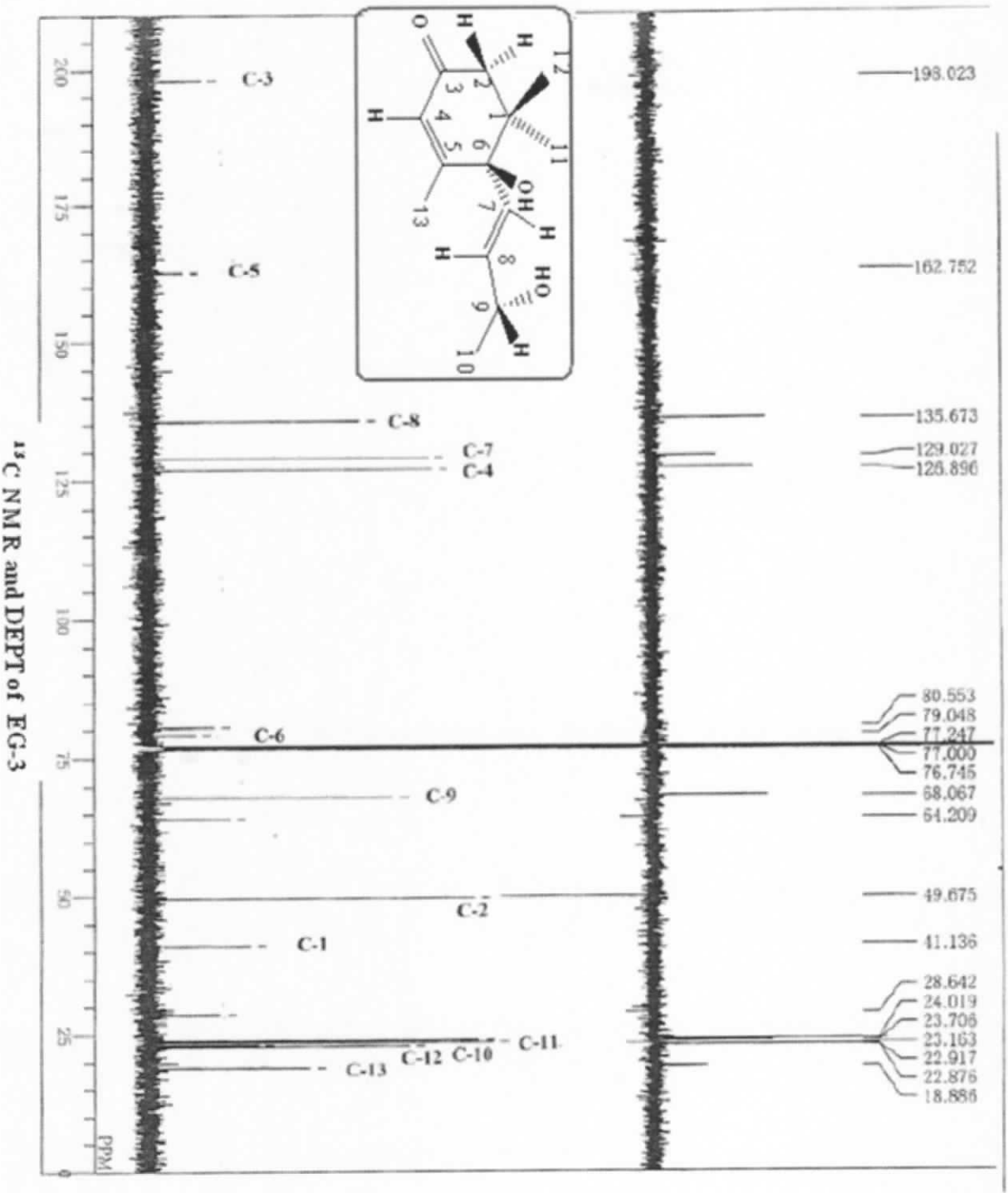
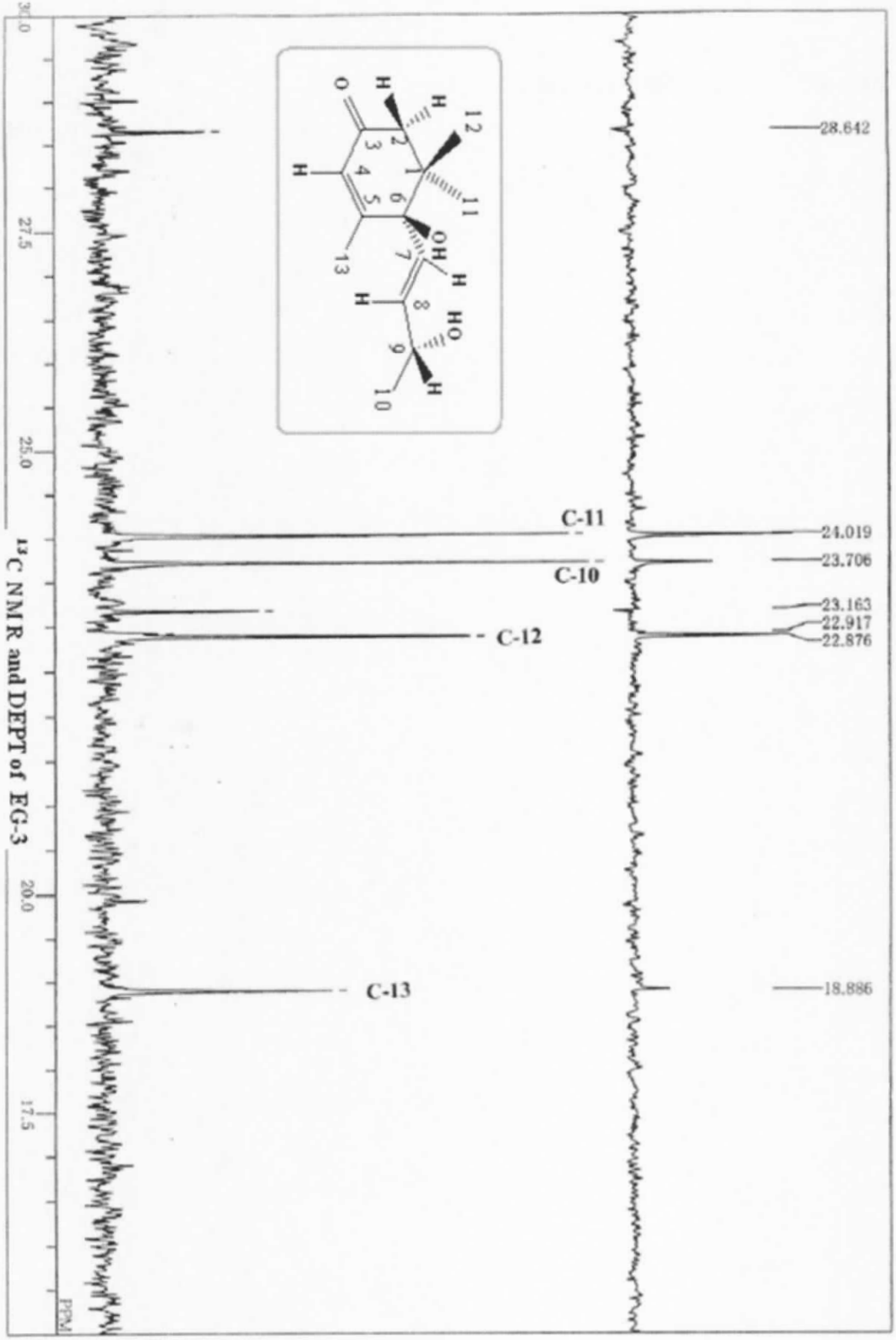
0.21
0.97
2.67
0.39
0.98
1.00
0.33
OH
HO
ppm

Part 1



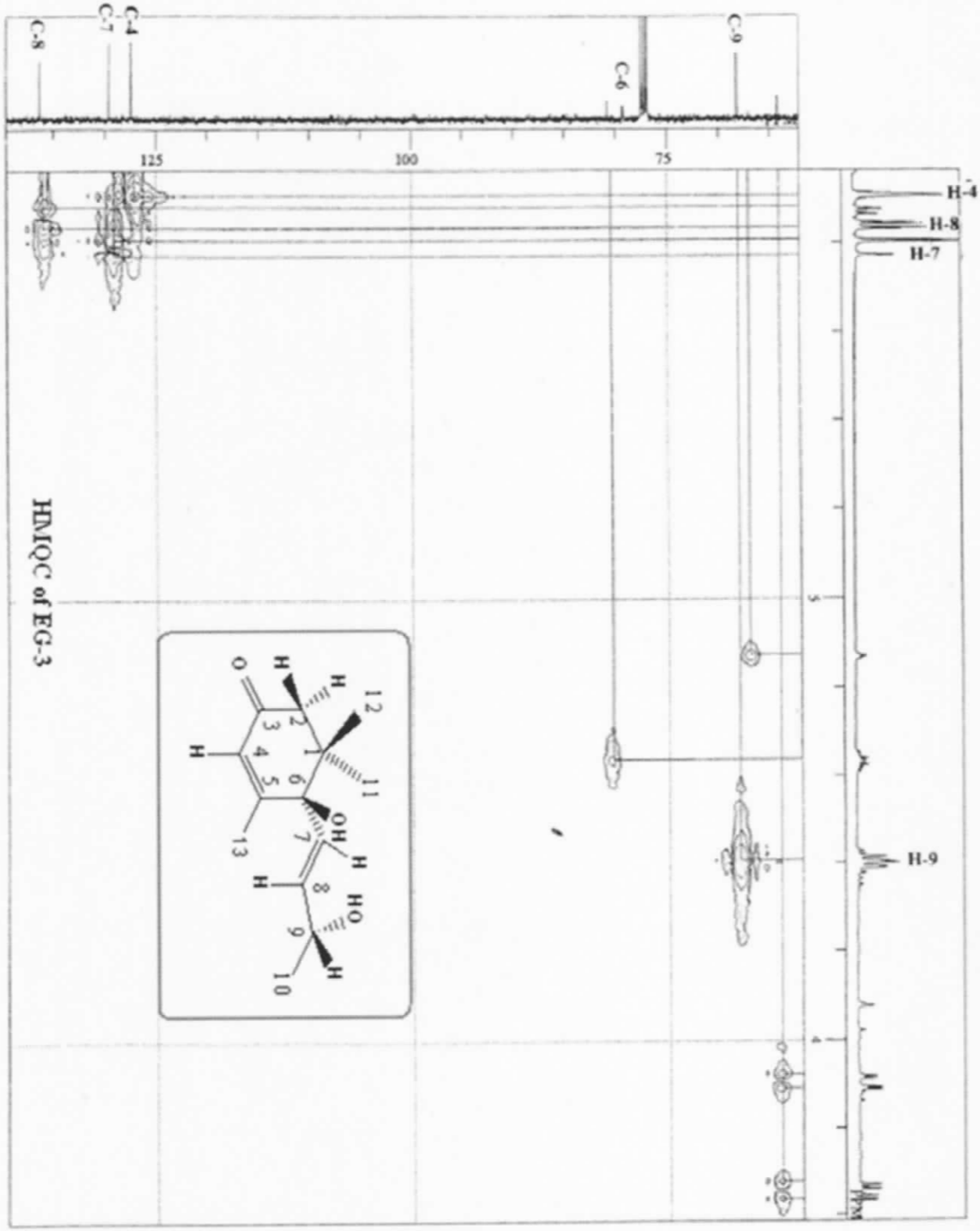
^{13}C NMR and DEPT of EG-3

Part 1

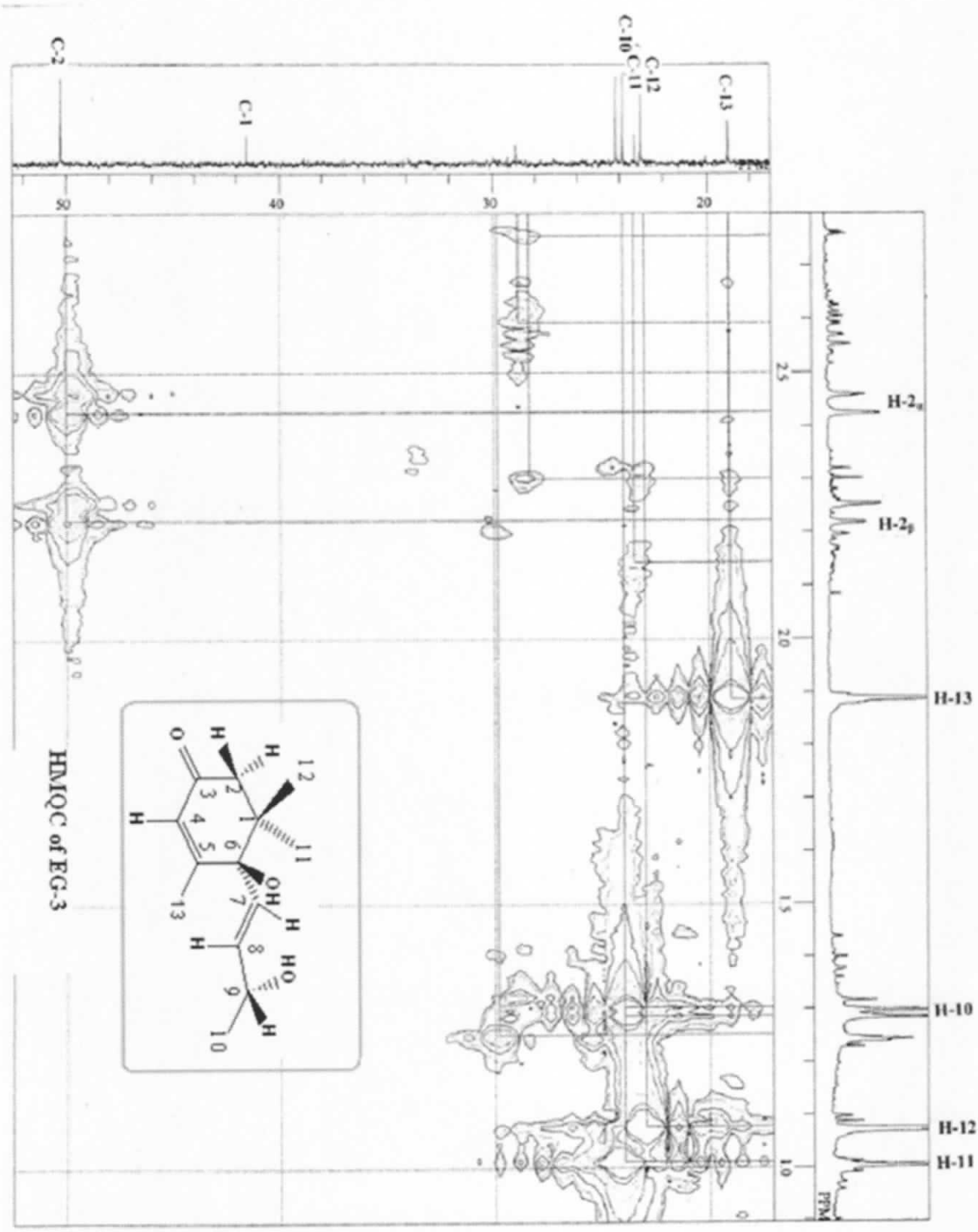


^{13}C NMR and DEPT of EG-3

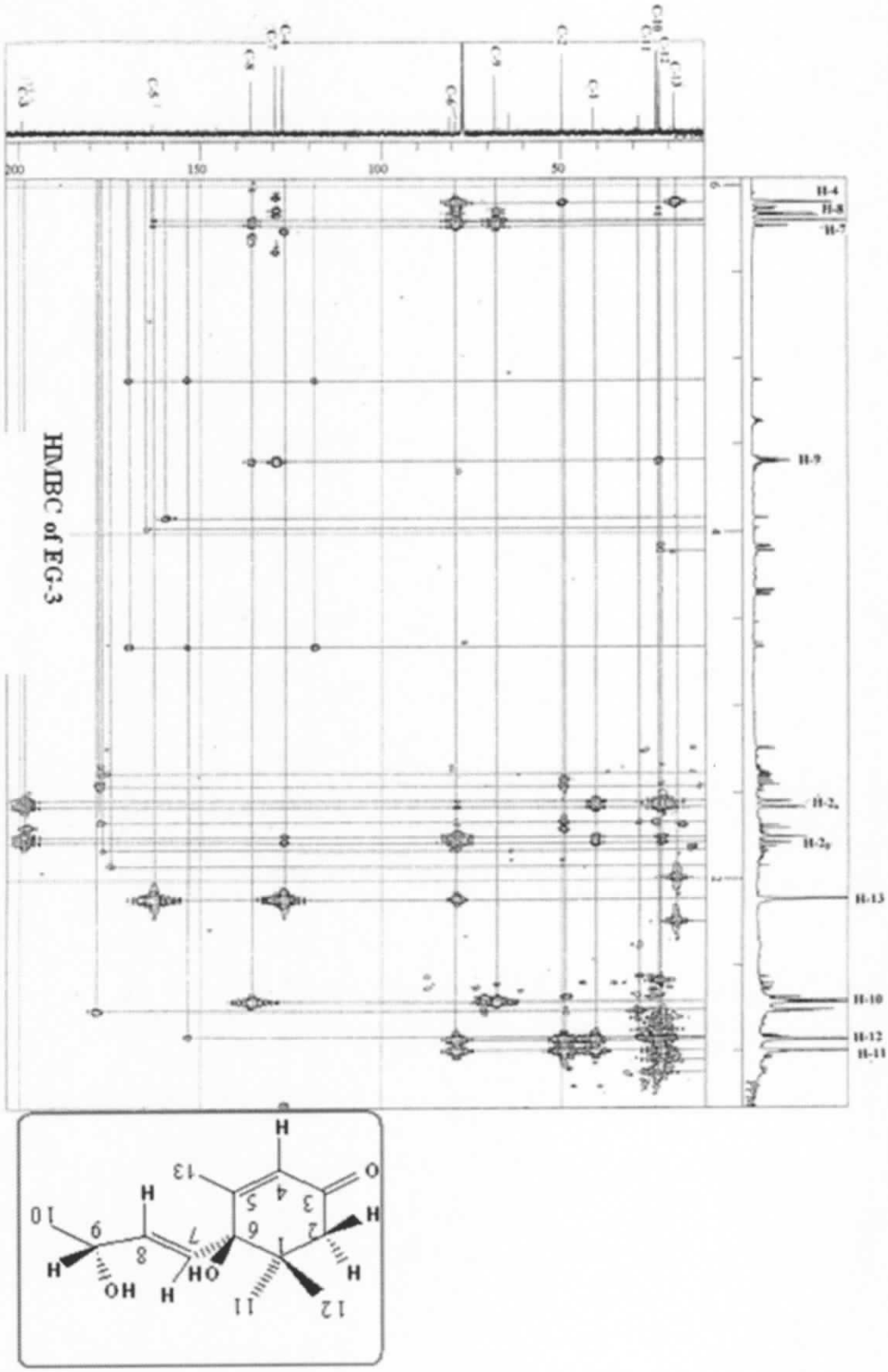
Part 1



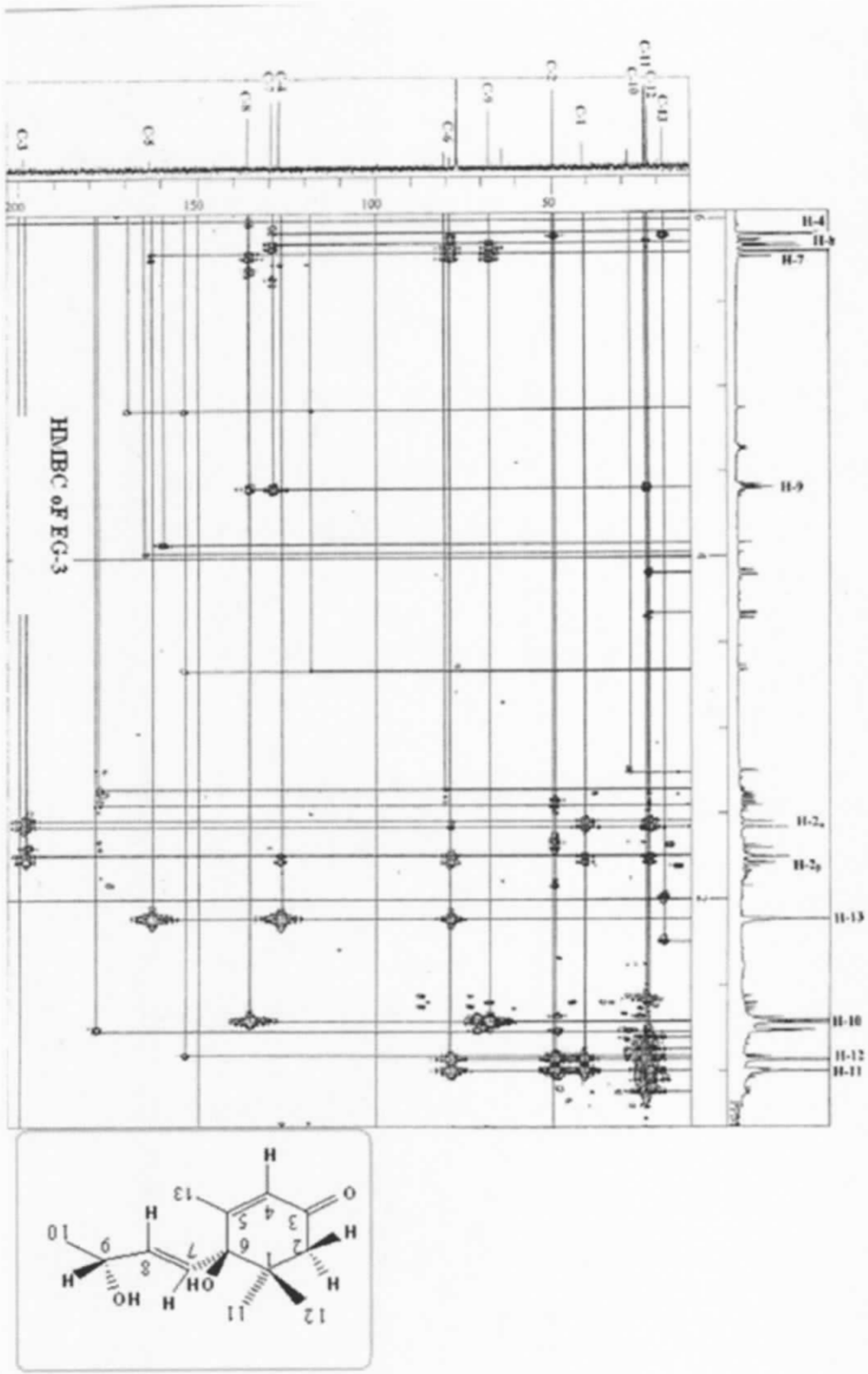
Part 1


C-2
C-1
C-10
C-11
C-12
C-13
50
40
30
20
25
20
15
10
PPM
H-2α
H-2β
H-13
H-10
H-12
H-11
HMQC of EG-3
O
H
H
H
OH
H
HO
H
1
2
3
4
5
6
7
8
9
10
11
12
13

Part 1



Part 1

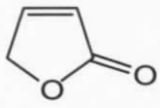


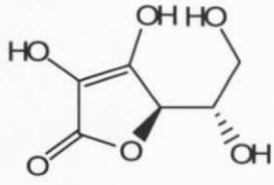
Part Two

Chapter One
Butenolides

1.1. Definition

Butenolides are a class of lactones with a four-carbon heterocyclic ring structure. They are sometimes considered oxidized derivatives of furan. The simplest butenolide is 2-furanone, which is a common component of larger natural products and is sometimes referred to as simply "butenolide". A common biochemically important butenolide is ascorbic acid (vitamin C). Butenolide derivatives are produced by some plants on exposure to high temperatures due to brush fires; these compounds can trigger seed germination in plants whose reproduction is fire-dependent.[1,2]



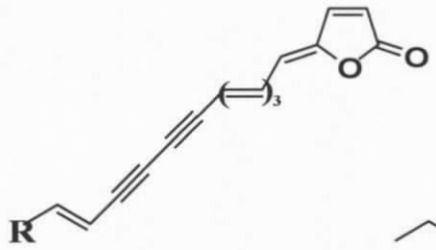


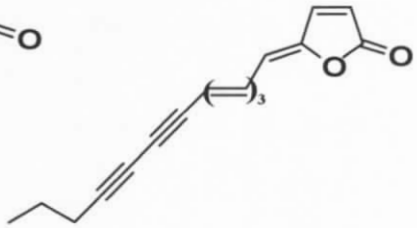
2-furanone ascorbic acid

The term butenolide describing the buteno or crotono lactones has been used for the first time in 1898by Klobb [3]. Prior to that, the butenolides were named crotonolactones. It was only in 1970's when the furanone nomenclature was adopted to name such compounds.

The butenolides [4,5] and their analogues represent a wide range of natural occurring compounds of medical and biological importance, in the last decades, a great number of compounds of different structures overall the (Z) or (E) γ-alkylidenebutenolides have been isolated from natural sources and many of them exhibit important biological activities such as the inhibition of cholesterol biosynthesis observed with xeruline, xerulinique acid and dihydroxeruline.[6]

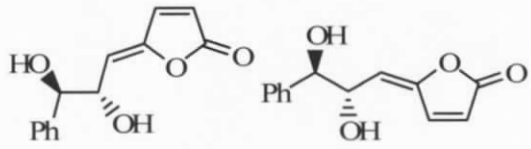
The goniobutenolides A and B [5,7-12] and the nostoclides [13,14] display cytotoxic activities.

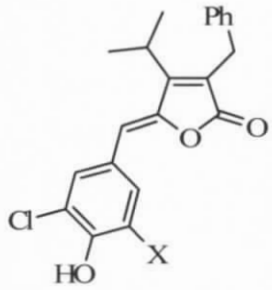




Xeruline: R=Me **dihydroxeruline**

Xerulinic acid: R=COOH

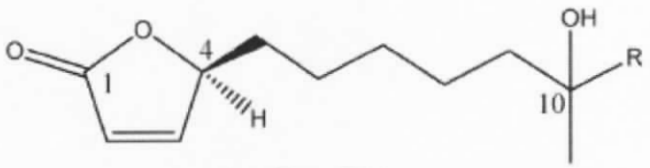




Goniobutenolide A and B **Nostoclide I: X=Cl, and II: X=H**

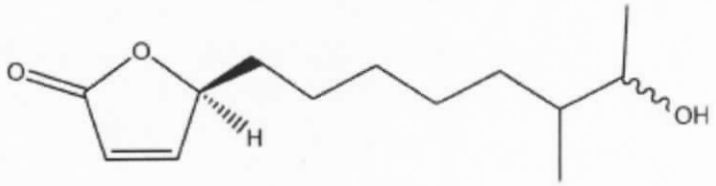
1.2. Butenolides with Significant Activities:

Crude extracts from bacteria strain 11014, identified as Streptoverticillium luteoverticillatum, exhibited cytotoxicity against the mouse tsFT210 cancer cell line. Further studies on the active constituents of this bacterium led to the isolation of four butenolides by bioassay-guided fractionation. Their structures were determined to be (4S)-4, 10-dihydroxy-10-methyl-undec-2-en-1, 4-olide (1), (4S)-4, 10-dihydroxy-10-methyl-dodec-2-en-1, 4-olide (2), and two diastereomeric (4S)-4, 11-dihydroxy-10-methyl-dodec-2-en-1, 4-olides (3/4).[15]



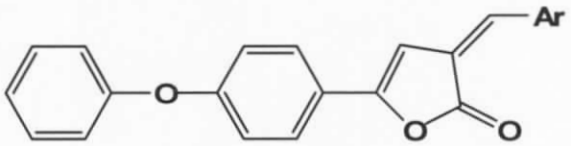
1 $R = CH_3$

2 $R = CH_2CH_3$



3, 4

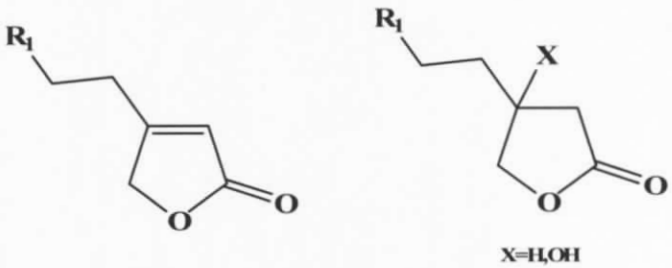
It has been reported that the butenolide system in cardiac glycoside shows cardiotonic activity.[16] The synthetic derivatives containing butenolide system reported to posess antiviral [17,18] antimicrobial [19] antimalarial[20] and anticancer[21] activities. The butenolides are also reported to have protein tyrosine phosphates (CDC 25) inhibitory and endogenous feeding suppressant activities.[22,23] Recently Husain *et al* reported a series of butenolides with anti-inflammatory potential.[24]



Chemical structure and anti-inflammatory potential of structurally similar 2-Arylidene-4-(4-phenoxy -phenyl) but-3-en-4-olides.[24]

The butenolides include the litseabutenolide, 3- epi-litsenolide D2, cis-listenolide D1, 4-hydroxy-2-methylbut-2-enolide, and hydroxydihydrobovolide were reported to have to inhibit HIV-1 replication.[25]

Other butenolide-based model compounds are reported to have antifeedant activities.[26]



Gholam Hossein Hakimelahi *et al* reported the inhibitory activity in vivo against animal tumour systems and in vitro against cells derived from human carcinoma of the nasopharynx (KB) of some Purine-containing butenolides.[27]

1.3. Synthesis of Butenolides

The majority of natural butenolides are (Z)-γ-alkyl (or aryl) idene-*5H*-furane-2-ones.

The different approaches to carry out the syntheses of butenolides lead generally to (Z) configuration, nevertheless a few stereoselective methods leading to (E) configuration were developed recently.

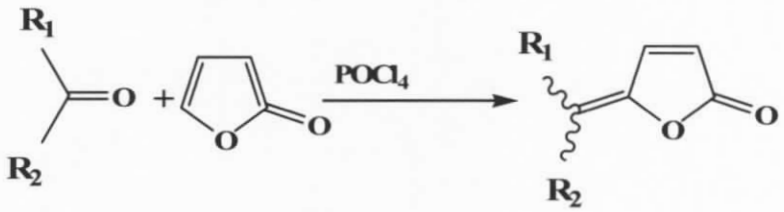
Rao [4,28] and more recently Neghishi[29] have reviewed the different methods of synthesis of butenolides that can be grouped in three categories:

1- Alkylidenation of 5-ring heterocyclic compounds.
2- From 4-oxo-acids and 4-hydroxyacids.
3- From propiolic acid and 4-enoic acid derivatives

An example of each category is illustrated below

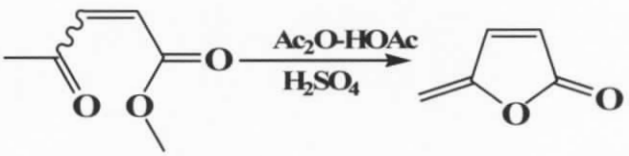
Category 1:

Synthesis from a butenolide [30-37]



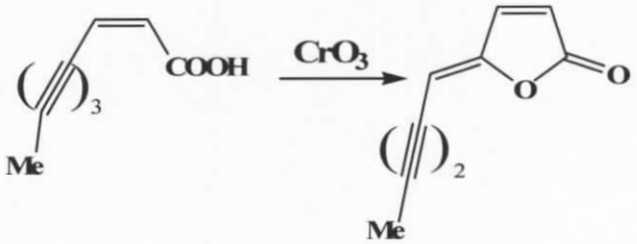
Category 2:

Synthesis via keto-acids[38-40]

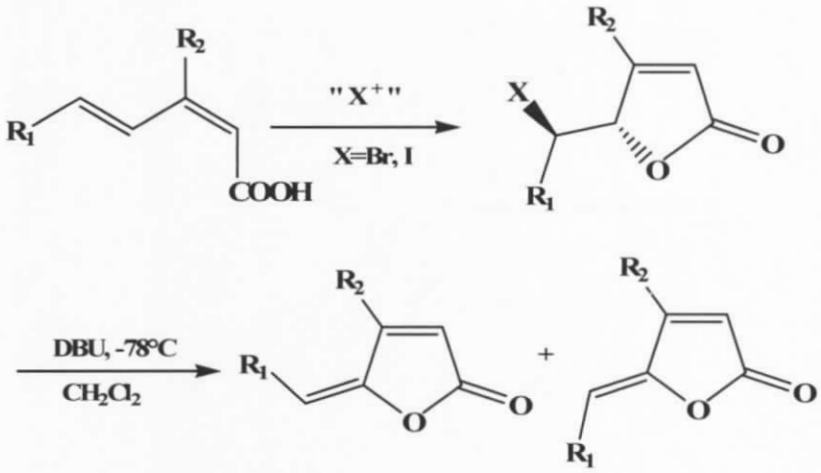


Category 3:

Synthesis via propiolic acid derivatives:[41]

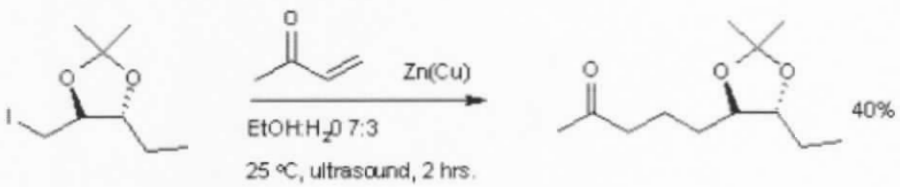


Recently J.L. Parrain et *al* reported a stereoselective synthesis of alkylidene butenolides from (2*Z*,4*E*)-dienoic acids by a sequence involving halocyclisation and elimination reactions. Selectivity was found to be highly dependent on the nature of the substituents.[42]

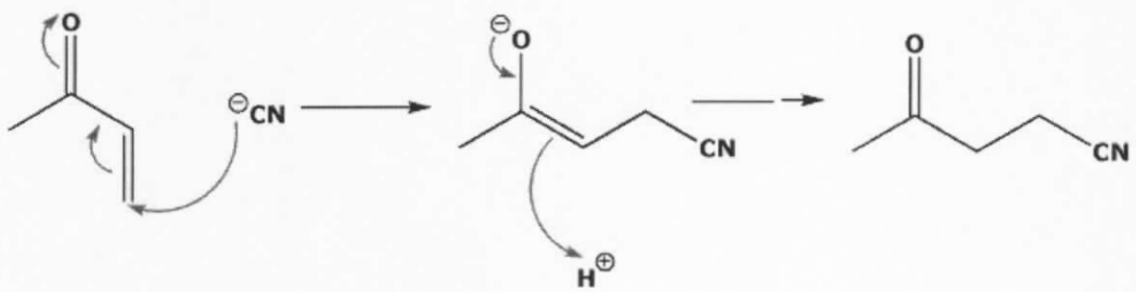


1.4. Conjugate Addition

Conjugate addition is effective in the formation of new carbon to carbon bonds with the aid of organometallic reagents such as the organo zinc iodide reaction with methylvinylketone .[43]



When a C=C bond is next to an oxo (or other double bond =R which can form a negatively charged R) group, a nucleophile can attack at the C=C instead of the C=O via. a *conjugate addition*. The mechanism follows two steps: addition followed by protonation.

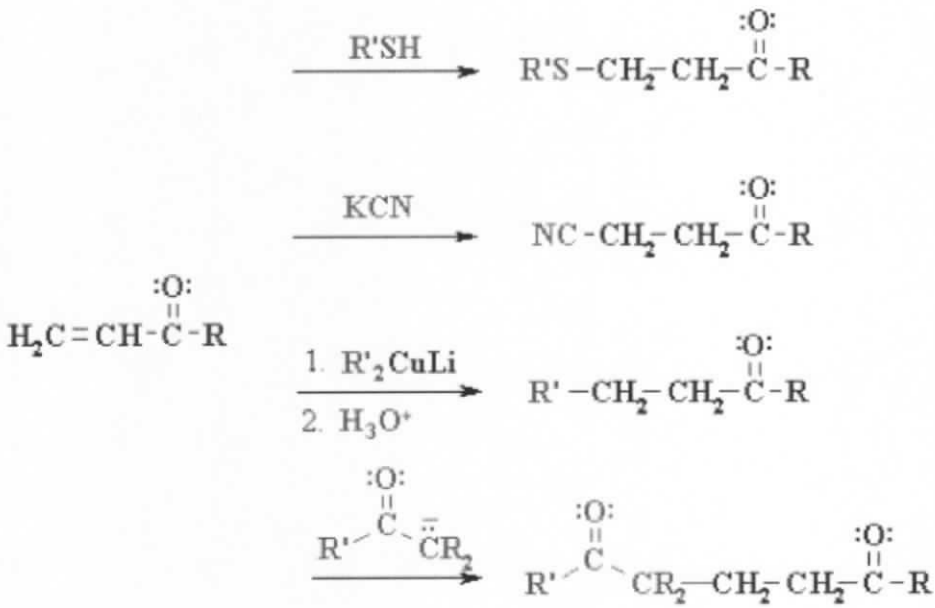


The π-system in these reagents is conjugated, and so reacts differently to the way in which the

isolated functional groups would. Addition to the C=C is termed '1,4-addition', addition to the C=O is termed '1,2-addition'.

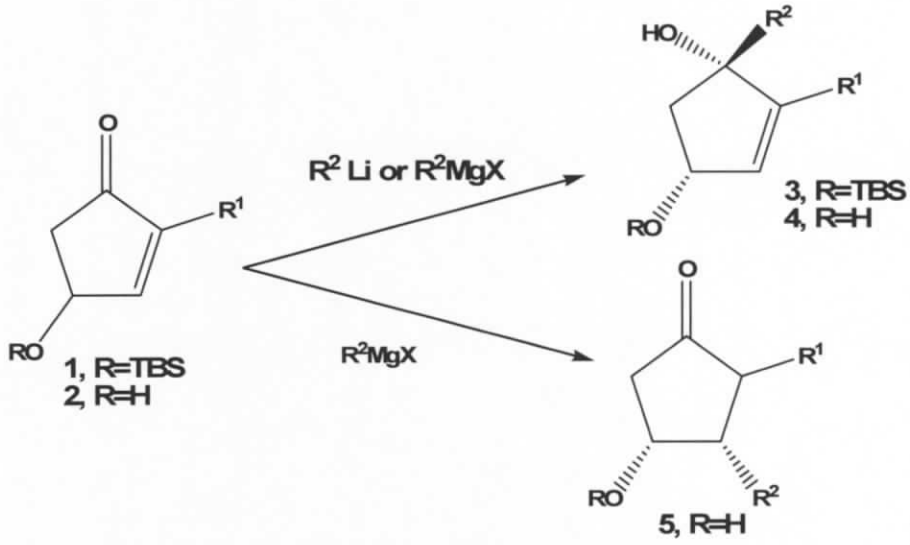
Conjugate Addition reactions [44]

- **Conjugate** or 1,4-addition tends to occur with nucleophiles that are weaker bases. Examples: thiols **RSH**, cyanide ion $^{-}$**CN**, organocopper reagents **R_2CuLi**, and enolates.
- **Direct** or 1,2-addition tends to occur with nucleophiles that are stronger bases. Examples: Organolithiums **RLi**, lithium aluminium hydride, **$LiAlH_4$** and Grignard reagents, **RMgX**.
- The product of conjugate addition is usually more stable (*i.e.* the thermodynamic product) as it still contains the strong **C=O** bond.



1.4.1. Nucleophilic Addition with Different Catalysts

Reaction of Cyclopentenones (1) with Organolithium or Grignard Reagents through 1,2 or 1,4 addition have been reported [44] in details giving rise to 2,3-disubstituted 3,5-*syn*-dihydroxycyclopentenes (2) and 3,4-*syn*-4,5-*anti*-3-hydroxycyclopentanones (3) with different yiels as shown in the table below:



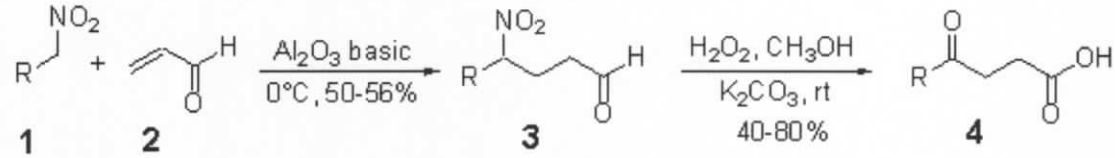
h

Reaction of cyclopentenones 1 and 2 withOrganolithium and grignard Reagents

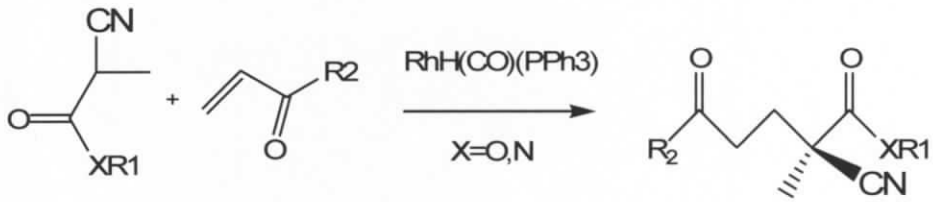
compound	R^1	R^2M	(%)
1	Ph	MeLi	70 of 3
1	Ph	MeMgI	90 of 3
1	Ph	PhLi	90 of 3
1	Me	PhLi	50 of 3
1	Me	PhMgBr	75 of 3
2	Ph	MeMgI	60 of 5 90:10 of (5,4)
2	Ph	EtMgI	65 of 5 95:05 of (5,4)
2	Ph	PhMgBr	70 of 5 95:05 of (5,4)
2	Ph	*p*-F-C_6H_5-MgBr	65 of 5 95:05 of (5,4)
2	Me	MeMgI	65 of 5 90:10 of (5,4)
2	Ph	MeLi	65 of 5 0:100 of (5,4)
2	Me	MeLi	70 of 5 0:100 of (5,4)

Conjugate addition of nitroalkanes to enones and enoates provides a rapid entry to the corresponding γ-nitro carbonyl derivatives that can undergo a Nef reaction giving 1,4-dicarbonyl compounds. This procedure represents one of the most exploited methods to prepare such difunctionalized derivatives that find a number of applications in the synthesis of important target molecules. The Michael addition of nitroalkanes to electron-poor olefins can be realized using basic catalysts that operate in heterogeneous systems can be employed profitably to carry out a conjugate addition. Basic alumina is a formidable promoter of such nucleophilic additions that can be accomplished even in solvent-less condition. Reaction of

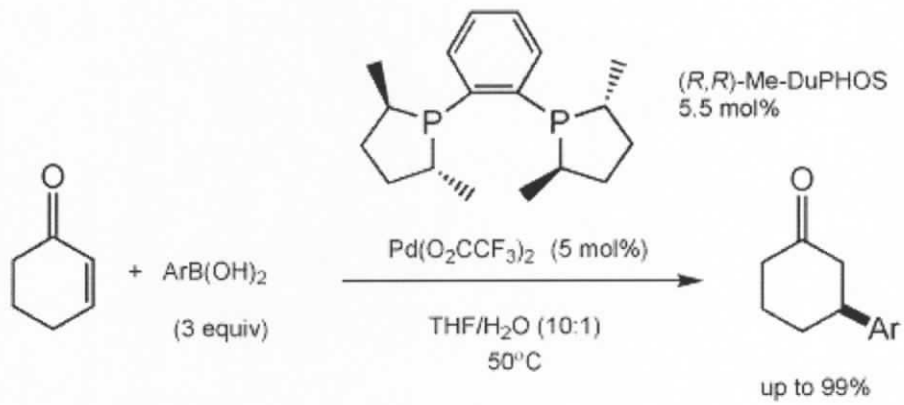
nitroalkanes **1** with acrolein **2** allows a rapid formation of the adduct **3** that upon oxidative Nef reaction leads to the corresponding 4-oxoalkanoic acid derivative **4**.[45]



Ito and co-workers reported the rhodium catalysed Michael addition of α-cyanocarboxylates to vinyl ketones [46]

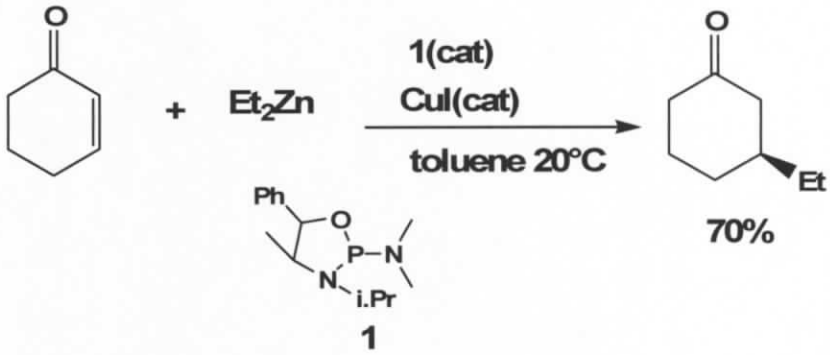


- F.Gini et al reported palladium-catalyzed enantioselective conjugate addition of arylboronic acids.[47]



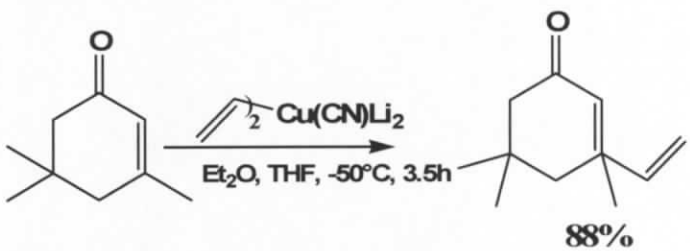
Ti(O*i*-Pr)$_4$ was used as catalyst in the addition of hydrogen cyanide to several aromatic and aliphatic aldehydes. [48]

Alexakis and co-workers reported the first example of copper catalysed enantioselective conjugate addition of diethylzinc to 2-cyclohexenone[49]. The use of 10 mol% of CuI and 20 mol% of trivalent phosphorous ligand resulted in an enantioselectivity of 32%. Under the same conditions chalcone gave racemic material.



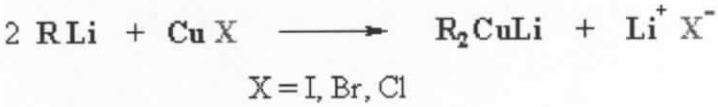
1

Lipshutz et al reported the addition of higher order divinylcyanocuprate to isophorne. [50]



Organolithium cuprates, **R_2CuLi** are particularly useful for conjugate additions to α,β–unsaturated aldehydes and ketones due to their safety, low cost and handling easiness.

Lithium dialkylcuprates are formed from organolithium compounds

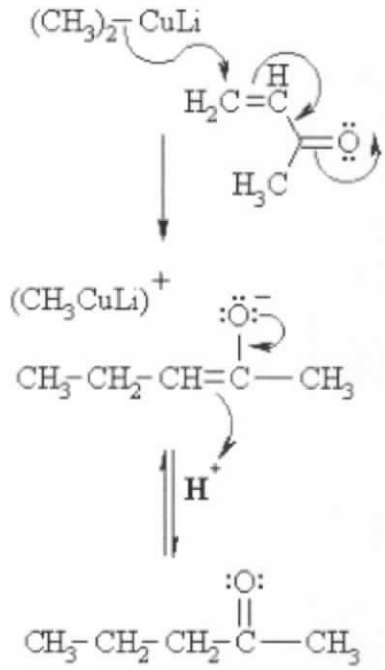


It should be remembered that enolates, organometallic compounds are a source of nucleophilic **C** systems. So it is "useful" to impose ionic character on organometallics *e.g.* **RMgX** is equivalent to **R^- Mg2+ X^-** or **R_2CuLi** is equivalent to **$(R^-)_2$ Cu+ Li+**

1.4.2. Mecanism of the organocuprate addition [51]

Step1:

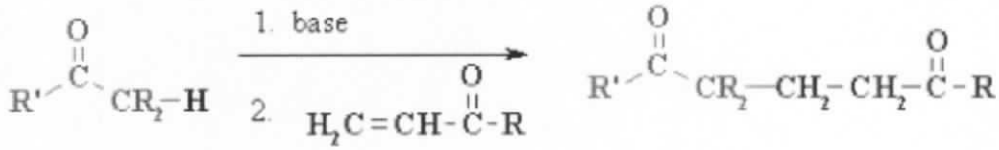
The nucleophilic **C** in the cuprate attacks the conjugated ketone at the electrophilic alkene **C** in a nucleophilic addition type process with the electrons being pushed through to the electronegative **O**, giving an intermediate enolate.



Step2:

On acidic work-up, the enolate is protonated at the α-**C** creating the more favourable carbonyl group.

1.4.3. The Michael Addition reaction

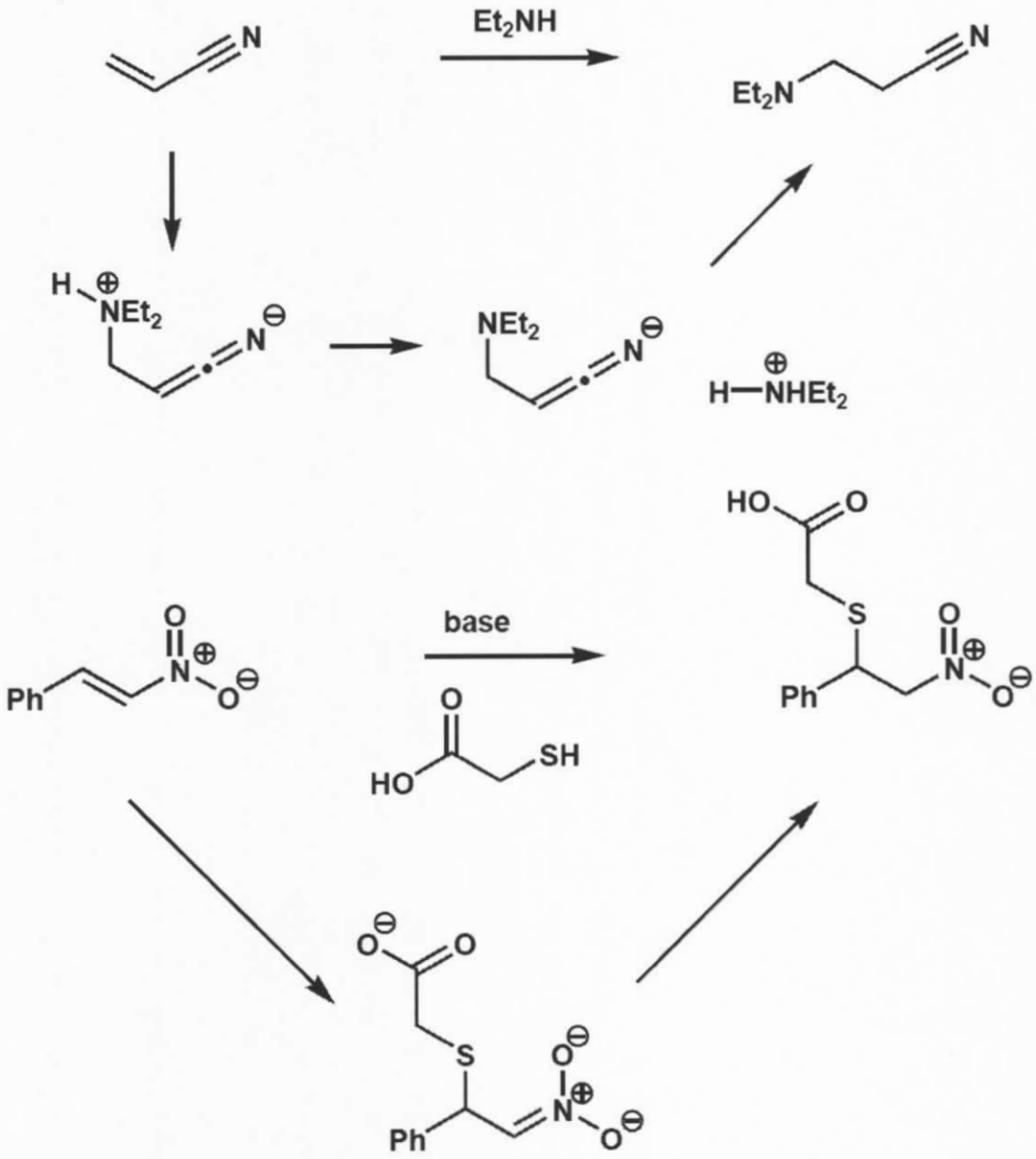


Reaction type: Conjugate addition

Summary

- Reagents: commonly bases such as NaOH or KOH.
- The first step is the formation of the enolate.
- Enolates tend to react with α,β-unsaturated ketones via conjugate addition.
- A conjugate addition with a carbanion nucleophile is known as the *Michael reaction* or *Michael addition.*

Conjugate addition is not limited to α,β-unsaturated carbonyl compounds. Any group which can readily stabilize a negative charge can be used. Examples are as follows:

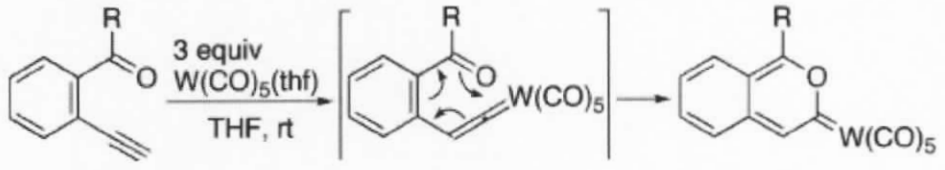


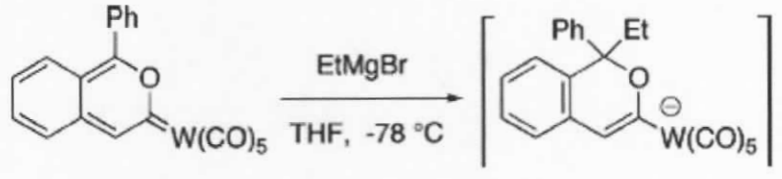
1.5. 1,6-Addition Review

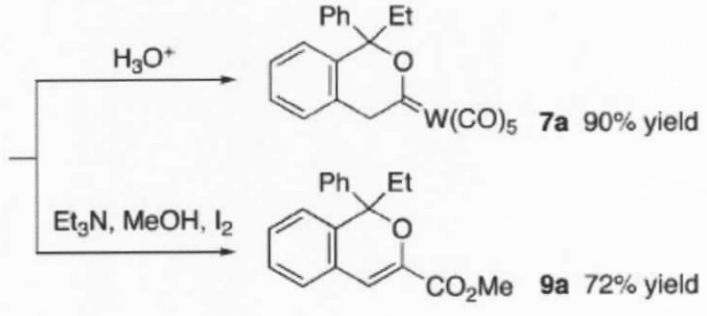
The conjugate addition of organocuprate reagents to α,β-unsaturated carbonyl compounds belongs to the basic carbon- carbon forming reactions.[52] Among the different classes of Michael additions, the 1,4-addition to enones, enoates, and acetylenic esters is still the most noted, but recent developments expand the reaction to 1,6-, 1,8-, 1,10-, and 1,12-additions to Michael acceptors that bear a conjugated system of double and triple bonds.[53]

1.5.1. Preparation of isochromene carboxylates

A concise method for the preparation of isochromene carboxylates has been developed by the regioselective 1,6-addition of various nucleophiles such as Grignard reagents, alkoxide, and cyanide onto enzopyranylidenetungsten(0) complexes, followed by iodine oxidation of the addition intermediates.[54]



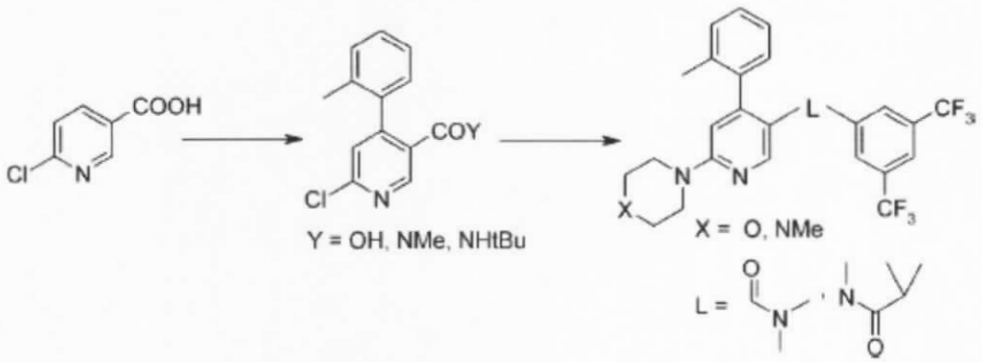




1.5.2. Synthesis of two novel classes of NK1 receptor antagonists

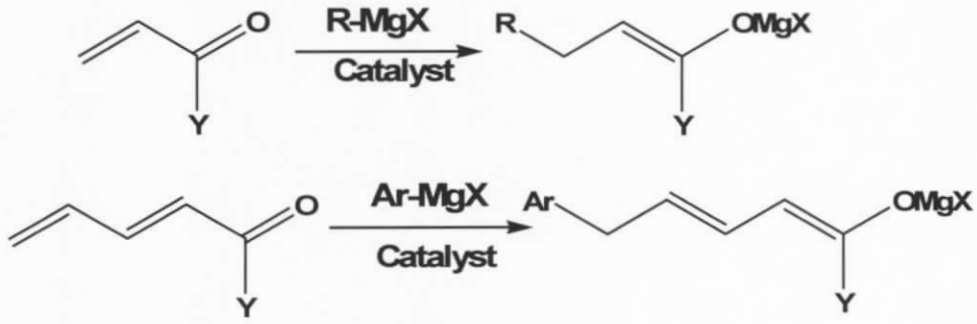
Fabienne Hoffmann-Emery, *et al* developed a new efficient synthesis of two novel classes of NK1 receptor antagonists, among them befetupitant and netupitant, starting from 6-

chloronicotinic acid. The introduction of the *o*-tolyl substituent at C(4) of the pyridine ring was achieved by a one-pot selective 1,4-Grignard addition/oxidation sequence to 6-chloronicotinic acid or a derivative of it. The scope of this addition/oxidation sequence was examined. It was also shown that the carboxylic function can be converted to a methyl amino group by a Hofmann rearrangement followed by reduction. Furthermore, a new high-yielding synthesis of 2-(3,5-bistrifluoromethylphenyl)- 2-methyl propionic acid based on the carbonylation of the tertiary alcohol obtained by Grignard addition of 3,5-bis(trifluoromethyl)bromobenzene to acetone was established.[55]

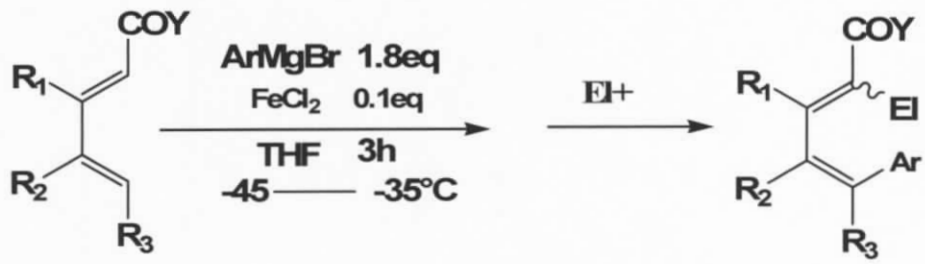


1.5.3. Iron-catalyzed 1,6-addition of aryl Grignard reagents to 2,4-dienoates and -dienamides

K. Fukuhara, *et al* reported that 1,6-Addition of aryl Grignard reagents to 2,4-dienoates or -dienamides was nicely catalyzed by iron salt to give 5-aryl-3-enoates or the corresponding amides in a highly regio- and stereoselective manner.[56]



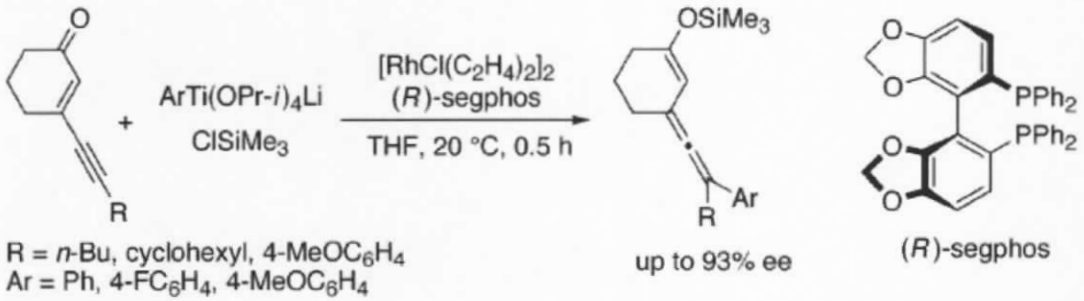
1,4- and 1,6-addition of Grignard reagent.



Iron-catalyzed 1,6-addition of aryl Grignard reagents

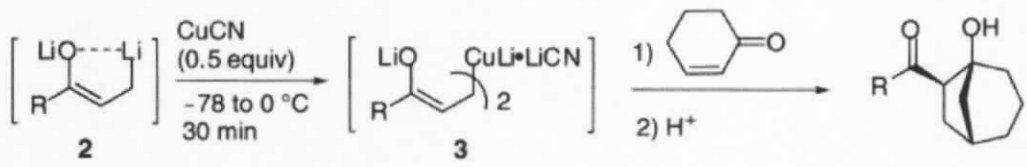
1.5.4. Addition of Aryltitanate

Tamio Hayashi, *et al* (2004) reported that the addition of aryltitanate reagents ArTi(OPr-*i*)4Li to 3-alkynyl-2-en-1-ones in the presence of chlorotrimethylsilane and a rhodium-(*R*)-segphos as a catalyst proceeded in a 1,6-fashion to give a high yield of axially chiral allenylalkenyl silyl enol ethers with up to 93% .[57]

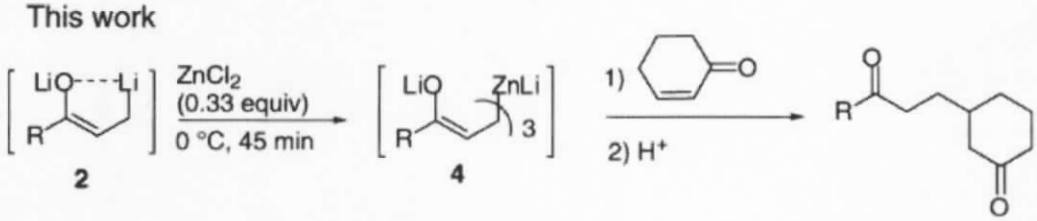


1.5.5. Conjugate Addition of Organozincates

Ilhyong Ryu, *et al* (2000) examined the conjugate addition of organozincates derived from ketone α,β-dianions to enones. Good yields of unsymmetrical 1,6-diketones were obtained by this reaction. A mixed zincate consisting of the dianion and methyllithium in a 2:1 ratio gave results which were comparable to those of an unmixed dianion zincate.[58]



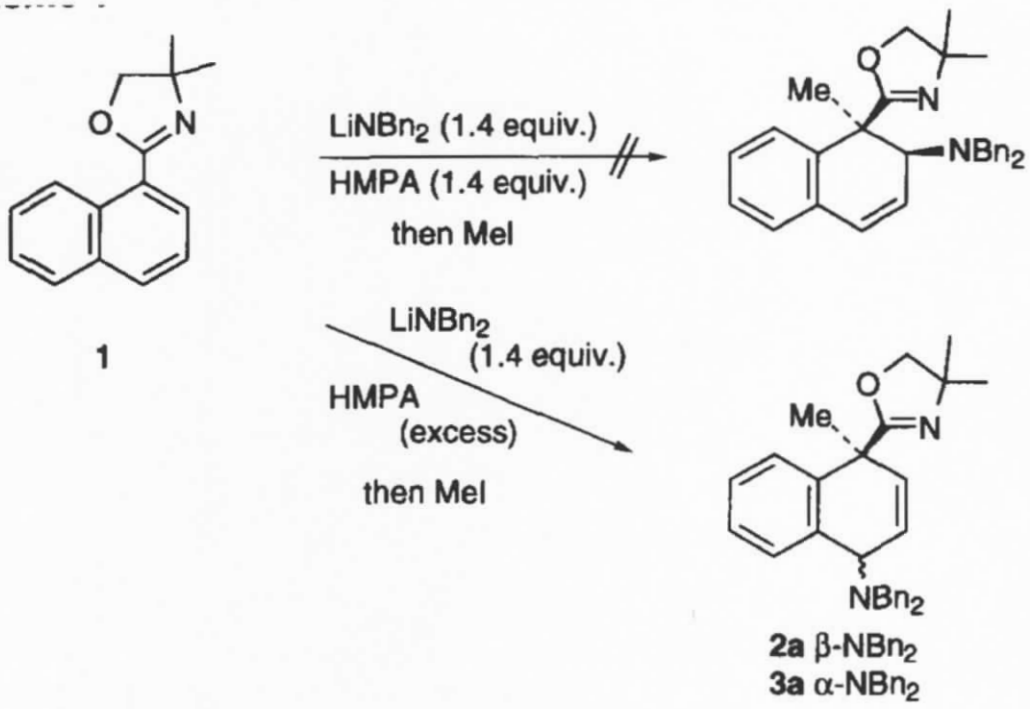
This work



1.5.6. Novel 1,6-amino Addition Reaction to the Naphthalene

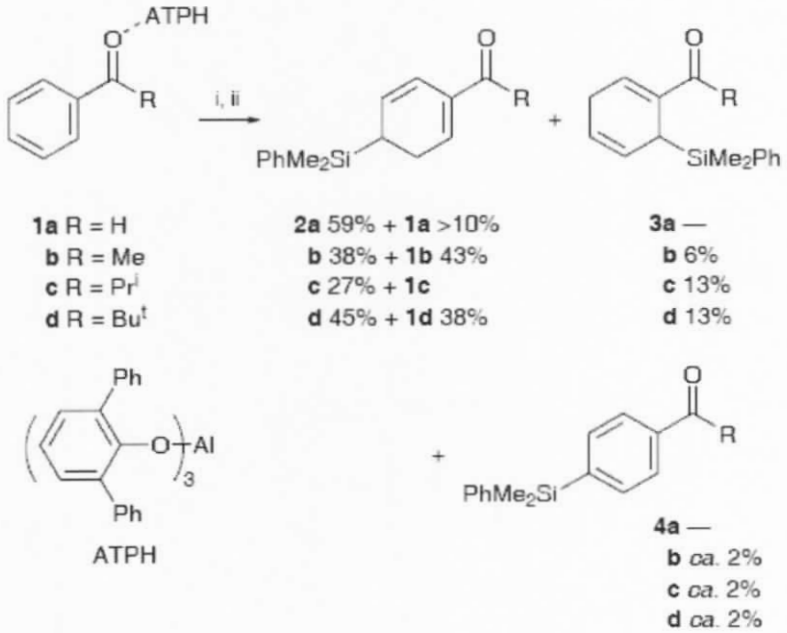
The novel 1,6-amino addition reaction to the naphthalene ring system followed by the electrophilic alkylation is presented. The detailed mechanistic studies suggest the existence of two equilibrations that result in the 1,4-amino addition reaction and the 1,6-amino addition reaction. The stability and bulkiness of lithium amide play a key role in directing the course of the reaction. The transformation of the 1,6-amino adducts to other useful compounds is

concisely demonstrated. The methodology provides a remote-controlled diastereoselective synthesis of δ-amino acid derivatives.[59]



1.5.7. 1,6-addition of silyllithium reagents to aromatic carbonyl substrates

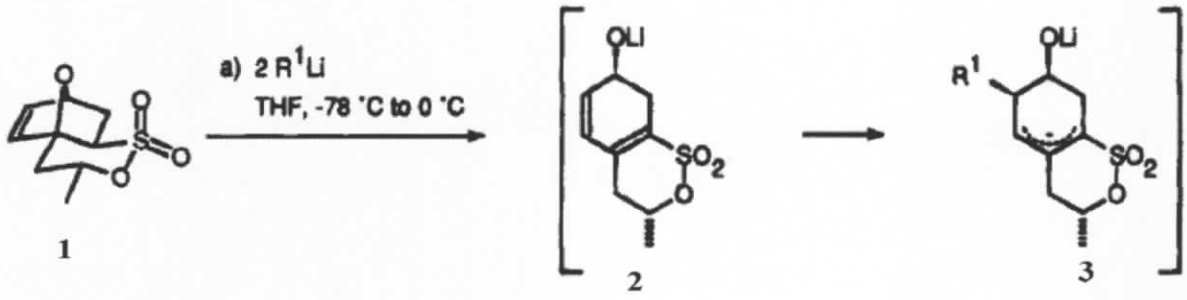
Susumu Saito, *et al* (1997), reported that conjugate 1,6-addition of silyllithium reagents to aromatic carbonyl substrates in the presence of the carbonyl protector aluminium tris(2,6-diphenylphenoxide) (ATPH) gives allylsilanes.[60]



Reagents: i, $PhMe_2SiLi$; ii, HCl, H_2O

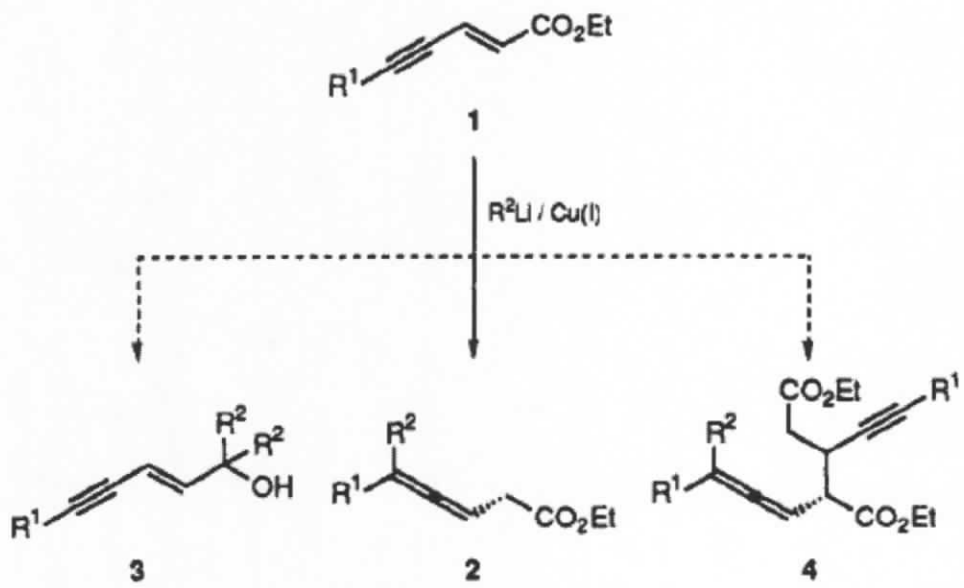
1.5.8. l,6-addition leading to alkylated products

Peter Metz, *et al* (1994) investigated the reaction of organolithium reagents with **1** in order to achieve a tandem elimination/l,6-addition leading to alkylated products. When sultone **1** was treated with 2 equiv of an alkyllithium species in THF, the desired alkylation was accomplished. Using only 1 equiv of R_1Li, the dienol corresponding to **2** was isolated after aqueous workup. The facility of the 1,6-addition depends on the nature of R'. Whereas n-butyllithium rapidly added to **2** at -78 °C already, a comparably fast reaction of methyllithium was only observed after raising the temperature to 0 °C.[61]



1.5.9. 1,6-addition of organometallic reagents to 2-en-4-ynoates

Andreas Haubrich, *et al* (1993) developed a catalytic method for the 1,6-addition of organometallic reagents to 2-en-4-ynoates (1) in order to open a more efficient access to 8-allenic carbonyl compounds (2). [62]



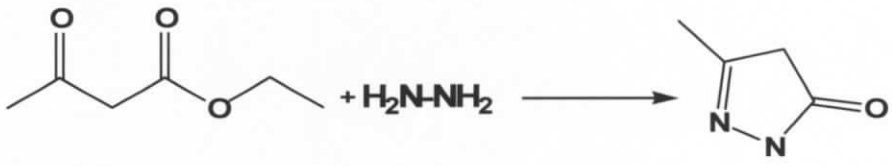
Chapter Two

Results and Discussion

2.1. Preparation of Lactones

The preparation of lactones involve a number of steps starting by the synthesis of 3-methyl-5-oxo-2-pyrazoline **[1]** from ethylacetoacetate and hydrazine as shown in reaction 1

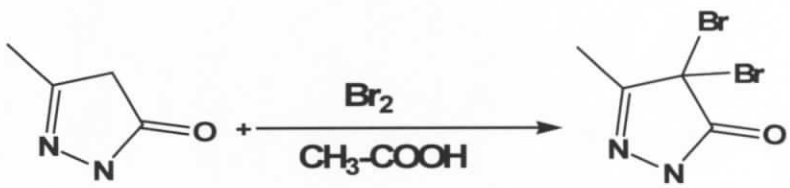
Reaction 1



[1]

The reaction of **[1]** with bromine and acetic acid leads to 4,4-dibromo-3-methyl-5-oxo-2-pyrazoline **[2]**

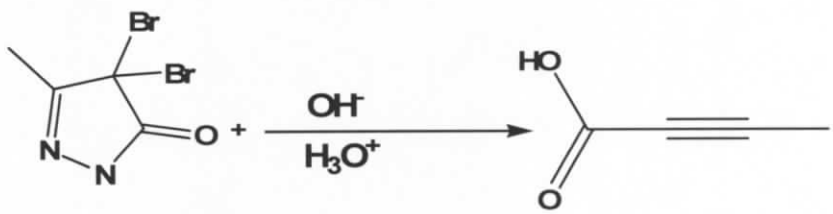
Reaction 2



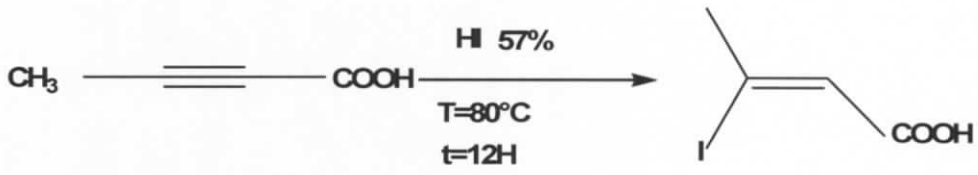
[2]

Tetrolic acid **[3]** is prepared by the reaction of **[2]** with a basic solution and then acidified as shown in reaction **3.**

Reaction 3



Stereoselective synthesis of β-iodide-α,β-unsaturated acids have been developed previously in the laboratory. Hence, the addition of iodohydric acid on the propiolic acid derivatives gives rise toβ-iodide-α,β-unsaturated acid **[4]** of Z configuration under specific conditions.



[4]

We have been interested in the preparation of some alkylidene butenolides using the method previously developed in our laboratory. In fact the method deals with the cyclization of β-iodide-α,β-unsaturated acids using an alkyne derivative with the presence of potassium carbonate and copper iodide.

General reaction

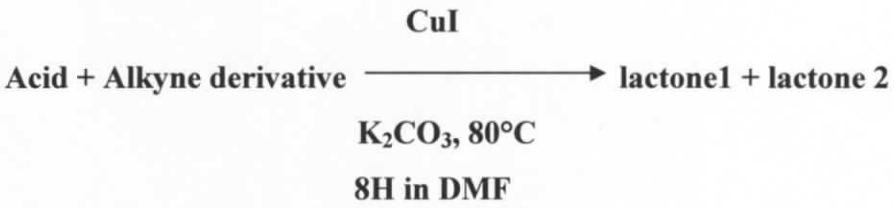
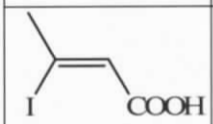
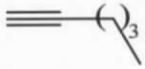
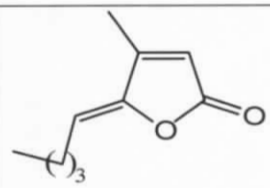
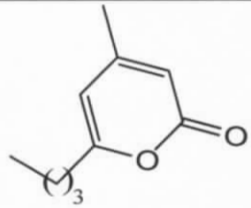
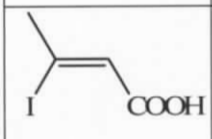
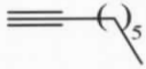
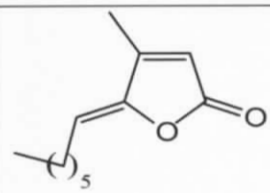
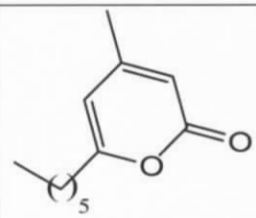
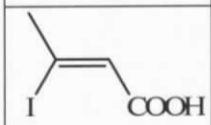
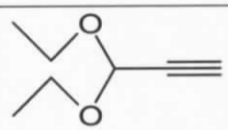
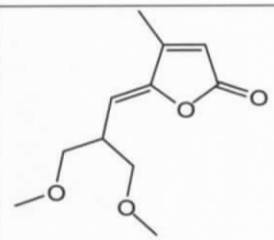
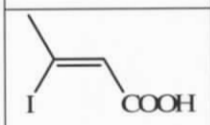
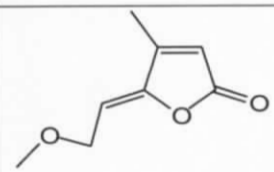
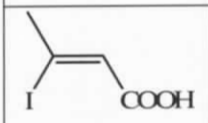
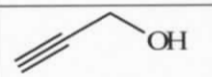
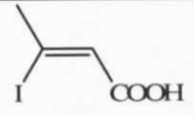
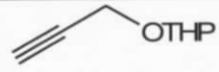


Table 14: Results of lactonization

acid	alkyne	Lactone1	Lactone2	yield
				**83% (57:43)**
				**84% (62:38)**
			**None**	**53%**
			**None**	**60%**
		**None**	**None**	
		**None**	**None**	

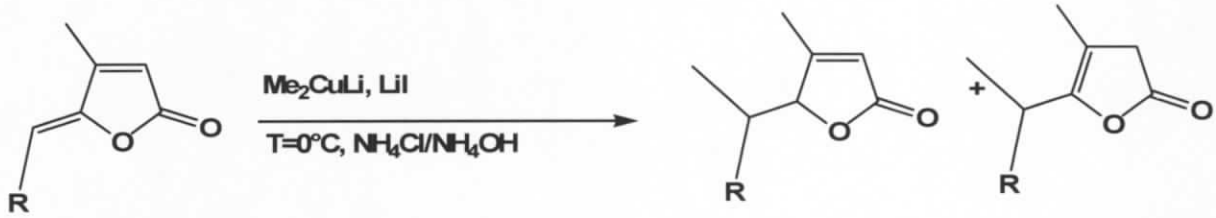
Reactions with hexyne and octyne gave rise to two isomers: a furanone and a pyranone contrarily to the remaining alkynes which gave only the corresponding furanone.

There are no cyclization products with propargyl alcohol and 2-(prop-2-ynyloxy)-tetrahydro-2H-pyran.

2.2. Addition of cuprates

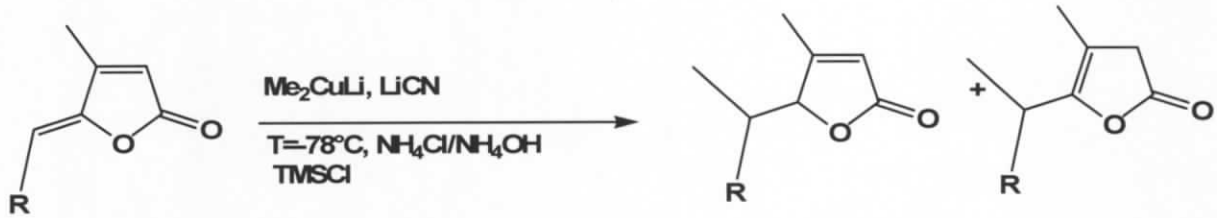
Once the lactones were in hand the next step consist of carrying out the cuprate addition using copper iodide.

For the cuprate addition, the prescribed method is to add the methyllithium on copper iodide in anhydrous ether at –5°C and then the lactone is added dropwise via canola before being quenched with NH_4Cl/NH_4OH (90/10) at 0°C and warmed till rt, nevertheless this method reveals the presence of two isomers when R is an alkyl as shown blow



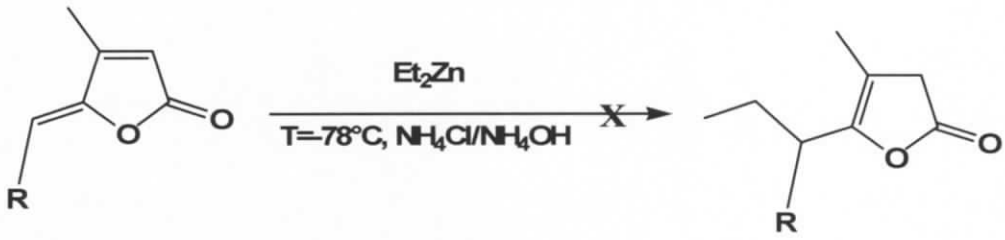
R= alkyl **yield 46%(42:58)**

To improve the total output, the idea was to replace the copper iodide by other copper salts such as copper cyanide but there was almost no enhancement even by adding TMSCl as accelerator.

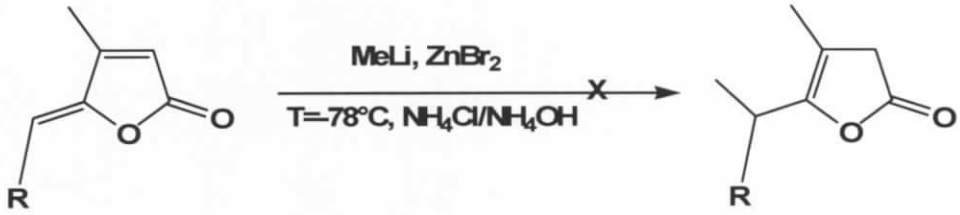


Yield <50%

Another attempt to find out the best method to undertake the conjugate addition was the use of diethylzinc rather than copper reagent but the reaction did not take place.

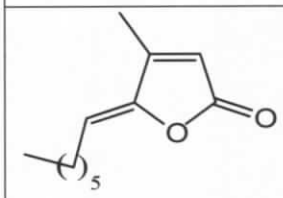
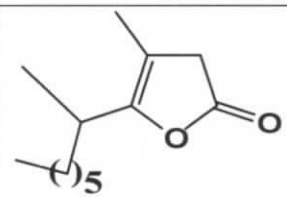
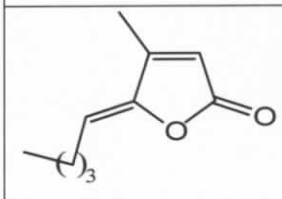
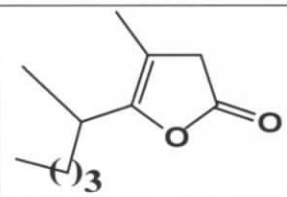
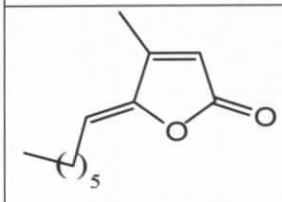
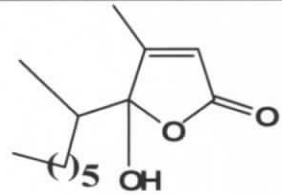
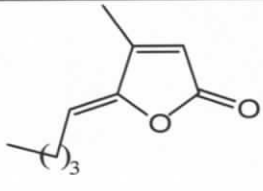
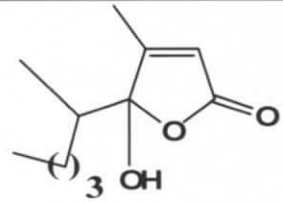


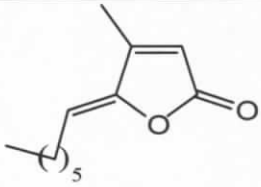
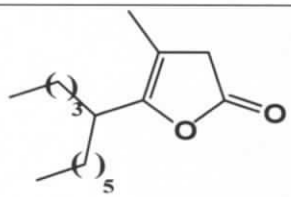
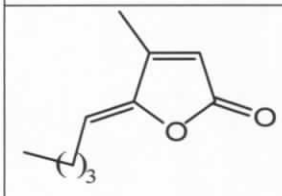
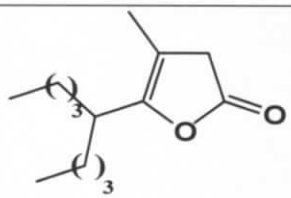
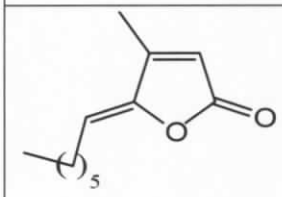
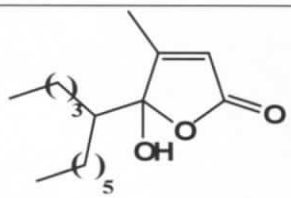
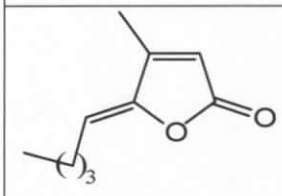
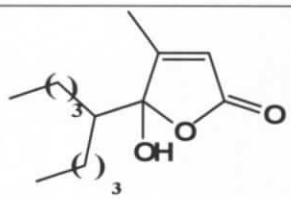
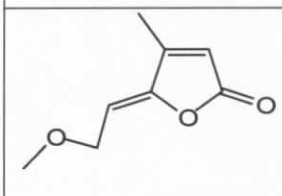
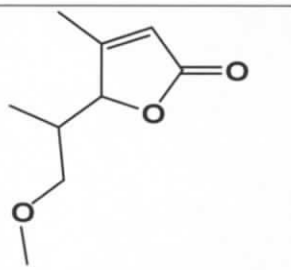
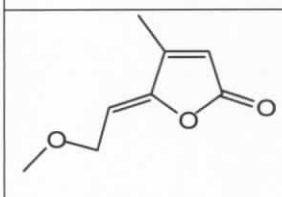
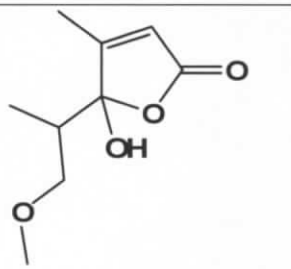
The copper iodide has been replaced by zinc bromide to check the validity of such substitution in the progress of the addition being studied but the reaction did not work.



When we quenched the reaction of cupration at -80°C instead of 0°C, surprisingly the reaction gave only one isomer with appreciable yield.

Table15: Results of Cuprate Addition:

lactone	reagent	quench	product	yield
	**Me_2Li Cu, LiI, 1 Hour at 0°C**	**NH_4Cl and NH_4OH (90:10) -80°C**		93
	**Me_2Li Cu, LiI, 1 Hour at 0°C**	**NH_4Cl and NH_4OH (90:10) -80°C**		86
	**Me_2Li Cu, LiI, 1 Hour at 0°C**	**O_2 , (NH_4Cl, NH_4OH)(90:10) -80°C**		95
	**Me_2Li Cu, LiI, 1 Hour at 0°C**	**O_2 , NH_4Cl and NH_4OH (90:10) -80°C**		52

	**Bu_2LiCu, LiI, 1 Hour at -50°C**	**NH_4Cl and NH_4OH (90:10) -80°C**		65
	**Bu_2LiCu, LiI, 1 Hour at -50°C**	**NH_4Cl and NH_4OH (90:10) -80°C**		82
	**Bu_2LiCu, LiI, 1 Hour at -50°C**	**O_2 , NH_4Cl and NH_4OH (90:10) at -80°C**		78
	**Bu_2LiCu, LiI, 1 Hour at -50°C**	**O_2 , NH_4Cl and NH_4OH (90:10) -80°C**		69
	**Me_2Li Cu, LiI, 1 Hour at 0°C**	**NH_4Cl and NH_4OH (90:10) -80°C**		74
	**Me_2Li Cu, LiI, 1 Hour at 0°C**	**O_2 , NH_4Cl and NH_4OH (90:10) -80°C**		46

Chapter Three
Experimental

3.1. Material and Techniques

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Bruker AC 200 and AC 300 spectrometer. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuterochloroform ($CDCl_3$) at ambient temperature unless otherwise specified. For ^1H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ 7.26) was used as the internal reference. ^1H NMR data are recorded as follows: chemical shift (δ), multiplicity (defined as: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sex = sextet, sept = septet, non = nonatet, m = multiplet, bs = broad singlet, app. = apparent), relative integral, coupling constant(s) *J* (Hz), assignment. For proton-decoupled ^{13}C NMR spectra recorded in $CDCl_3$, the central peak (δ 77.16) of the $CDCl_3$ triplet was used as the internal reference and the data are given as chemical shift (δ). The assignments of signals observed in various NMR spectra were occasionally assisted by heteronuclear (^1H-^{13}C) correlation spectroscopy (HETCOR or HMQC).

Mass spectra were recorded on one of the following instruments using either electron impact (EI), (70 eV) Hewlett Packard 5989A with quadripolar analysor over colonne HP1 25M x 0.25MM DF = 0.2UM, or ***electrospray (ESI)*** where the sample s dissolved in 500 μL of dichloromethane and diluted to 1/1000 in a solution of methanol with 3mM of ammonium acetate.

Conditions: - ESI+ (ISV : 5000 V; OR : 50V)

- flow rate : 5 μL/min
- gas flow rate: 0.6 L/min

Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 F254 plates (Merck) and the plates were visualised under a 254 nm UV lamp and/or by treatment with either anisaldehyde dip (*p*-Anisaldehyde, 9.2 mL; H_2SO_4, 12.5 mL; AcOH, 3.75 mL; EtOH, 338 mL) or potassium permanganate dip ($KMnO_4$, 3 g; K_2CO_3, 20 g; 5% NaOH, 5 mL; H_2O, 300 mL), followed by heating with a heat gun. Flash chromatography was conducted using silica gel 60 (mesh size 0.040-0.063 mm) as the stationary phase and the analytical reagent (AR) solvents indicated.

Many starting materials and reagents were available from Chemical Companies (Sigma-Aldrich, Alfa Aesar, Agros, fluka…) and were used as supplied, or dried and distilled using standard procedures. Triethylamine (Et_3N) was distilled from calcium hydride under argon prior to use . Reactions employing air and/or moisture-sensitive reagents and intermediates were performed under an atmosphere of argon (unless otherwise specified) in well-dried flasks. Anhydrous reagents were handled under argon using standard techniques.

Room temperature (rt) varied between 19-25°C. Concentration *in vacuo* refers to the use of a rotary evaporator with the water bath temperature generally not exceeding 45°C.

Tetrahydrofuran (THF), diethyl ether (Et_2O) were dried using sodium metal wire and then distilled, as required, from sodium-benzophenone ketyl under argon. *N,N*-dimethylformamide (DMF) was distilled and stored on molecular sieve. Other solvents were distilled from calcium hydride under argon as required. All other solvents used for reactions/extractions were distilled prior to use.

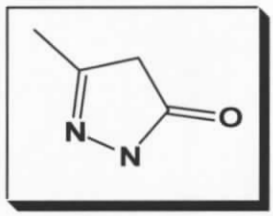
Used Abreviations:

- THF Tetrahydrofuran
- DMF *N,N*-dimethylformamide
- E Diethyl Ether
- PE Petroleum Ether
- TLC Thin layer chromatography
- eq equivalent
- TEA Triethylamine

3.2. Experimental Procedures

3.2.1. Preparation 3-methyl-5-oxo-2-pyrazoline [1]

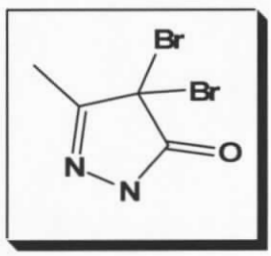
To a stirred solution of ethylacetoacetate (260g, 2moles) in 440ml of ethanol, was added dropwise hydrate hydrazine (100g, 2 moles) in 120ml of ethanol. After 2 hours at room temperature, the solution is cooled to 0°C, filtered, and washed with ethanol to give 177 g of compound **[1] (yield 90%, mp =222 °C)**. Spectral data were identical to those reported in the literature.



[1]

3.2.2. Preparation of 4,4-dibromo-3-methyl-5-oxo-2-pyrazoline [2]

To a stirred solution of 3-methyl-5-oxo-2-pyrazoline **(** 60 g, 0.61 mole) mixed with 240 ml of acetic acid, was added dropwise (96 g, 0.6 mole) of bromine in 60 ml of acetic acid, followed by 150 ml of water then another (96 g, 0.6 mole) of bromine in 60 ml of acetic acid was added dropwise. The solution was stirred at rt overnight before adding 3l of water. The crystals were filtered, washed with water and dried at rt. we obtained the titled compound **[2]** (yield 80%), suitable for use without further purification. Spectral data were identical to those reported in the literature.

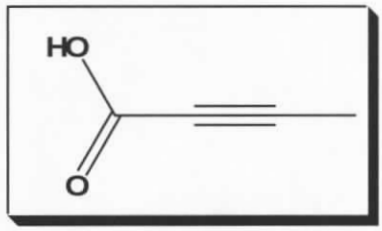


[2]

3.2.3. Preparation of but-2-yonic acid (tetrolic acid) [3]

To a stirred solution of soda (4l, 10%) cooled at -5°C ,was added dropwise a solution of 4-4-dibromo-3-methyl-5-oxo-2-pyralozine (256g , 1 mole) in 120 ml of diethyl ether , the temperature should not exceed 0°C for 1 hour and another hour at rt, the aqueous phase was

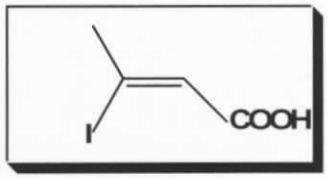
acidified at cold (T<5°C) with concentrated HCl and the extraction was carried with diethyl ether(150ml x 3). The dried (MgSO4) organic extracts were filtered and concentrated *in vacuo* to yield a residue which was refluxed in hexane before being crystallized to tetrolic acid **(3)** (yield 85%). Spectral data were identical to those reported in the literature.



[3]

3.2.4. Preparation of β-iodide,α-β-unsaturated acid [4]

To a stirred solution of tetrolic acid in diethyl ether (10 g, 0.12 mole), was added dropwise a solution of HI 57% (35g, 20.4 ml). The mixture was put under reflux at 80°C for 12 hours, after cooling, 100 ml of diethyl ether was added together with 40 ml of saturated solution of $Na_2S_2O_3$ and the mixture was shacked until the disappearance of the red color. The extraction was then carried out three times with diethyl ether. The dried (MgSO4) organic extracts were filtered and concentrated *in vacuo* to yield a colorless residue which was dissolved in a mixture of petroleum ether/ diethyl ether (85/15) before being crystallized to yield compound **[4].**



[4]

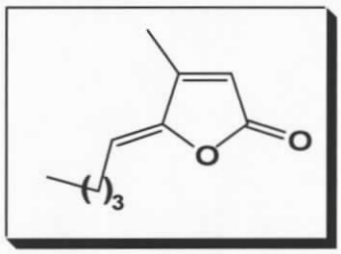
3.2.5. Preparation of lactones

3.2.5.1. General procedure for the preparation of lactones

Under a nitrogen atmosphere the β iodide acid was added to a stirred solution of calcium carbonate (2eq) in DMF, the resulting mixture was cooled down to –80°C for 10 minutes and then warmed up to room temperature, then the alkyne (1,5 eq) and the copper iodide (0.2 eq) were added respectively under nitrogen flux. After heating to 80°C and stirring overnight the solution was cooled to rt and quenched with saturated aqueous solution of NH_4Cl before

being extracted three times with AcOEt. The combined organic layers were washed with saturated brine, dried over anhydrous $MgSO_4$ and then concentrated in vacuo. The residual oils were purified by flash chromatography using an eluent system of petroleum ether/ether (1:1) to give the corresponding lactones.

a. Compound [5] (Z)-4-methyl-5-pentylidenefuran-2(5H)-one



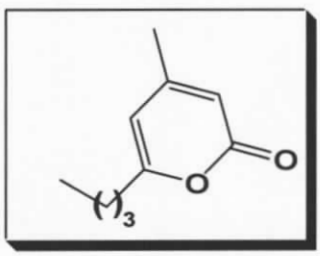
[5]

RMN ^{1}H (300 MHz, $CDCl_3$): δ=0.91 (t, *J*=6.99Hz, 3H), 1.43(m, 4H), 2.13(s, 3H), 2.36(m, 2H), 5.30(t, *J*=7.93, 1H), 5.89(s, 1H).

RMN ^{13}C (75 MHz, $CDCl_3$)

δ=11.61(1C), 13.70(1C), 22.29(1C), 25.83(1C), 31.02(1C), 113.24(1C), 115.79(1C), 150.65(1C), 154.71(1C), 169.53(1C).

b. Compound [6] 6-butyl-4-methyl-2H-pyran-2-one

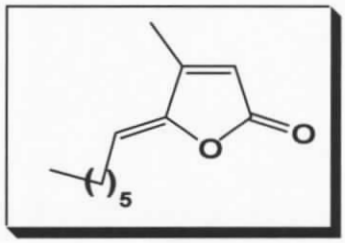


[6]

RMN ^{1}H (300 MHz, $CDCl_3$): δ=0.92 (t, *J*=7.17 Hz, 3H), 1.34(m, 2H), 1.62(m, 2H), 2.11(s, 3H), 2.44(t, *J*=7.55 Hz, 2H), 5.82(s, 1H), 5.93(s, 1H).

RMN ^{13}C (75 MHz, $CDCl_3$)

c. Compound [7] (Z)-5-heptylidene-4-methylfuran-2(5H)-one



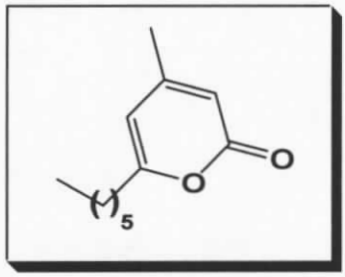
[7]

RMN ^{1}H (300 MHz, $CDCl_3$): δ=0.84 (t, *J*=6.80 Hz, 3H), 1.25 (m, 6H), 1.43 (m, 2H), 2.10(s, 3H), 2.31 (q, *J*=7.37 Hz, 2H), 5.27 (t, *J*=7.74Hz, 1H), 5.84(s, 1H).

RMN ^{13}C (75 MHz, $CDCl_3$)

δ=11.72(1C), 14.06(1C), 22.57(1C), 26.26(1C), 29.01(2C), 31.59(1C), 113.37(1C), 115.96(1C), 150.74(1C), 154.69(1C), 169.62(1C) .

d. Compound [8] 6-hexyl-4-methyl-2H-pyran-2-one



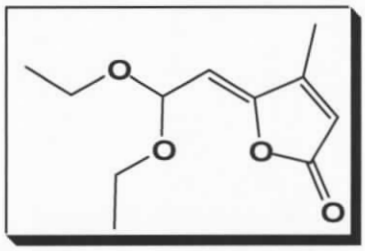
[8]

RMN ^{1}H (300 MHz, $CDCl_3$): δ=0.84 (t, *J*=6.66 Hz, 3H), 1.30(m, 6H), 1.64(m, 2H), 2.12(s, 3H), 2.44(t, *J*=7.69 Hz, 2H), 5.83(s, 1H), 5.94(s, 1H).

RMN ^{13}C (75 MHz, $CDCl_3$)

δ=14.14(1C), 21.56(1C), 22.60(1C), 26.95(1C), 28.78(1C), 31.56(1C), 33.78(1C), 105.79(1C), 110.70(1C), 156.34(1C), 163.51(1C), 165.15(1C).

e. Compound [9] (Z)-5-(2,2-diethoxyethylidene)-4-methylfuran-2(5H)-one



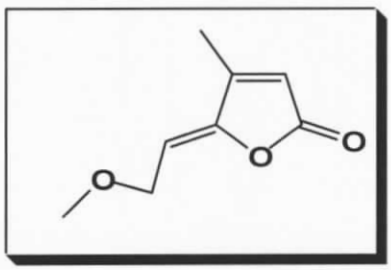
[9]

RMN ^{1}H (300 MHz, $CDCl_3$): δ=1.23 (t, *J*=6.99 Hz, 6H), 2.14(s, 3H), 3.56 (m, 2H), 3.72 (m, 2H), 5.35(d, *J*=7.74 Hz, 1H), 5.44(d, *J*=7.74 Hz, 1H), 5.99(s, 1H).

RMN ^{13}C (75 MHz, $CDCl_3$)

δ=11.90(1C), 15.32(2C), 62.69(2C), 96.99(1C), 107.95(1C), 117.98(1C), 151.49(1C), 155.27(1C), 168.61(1C).

f. Compound [10] (Z)-5-(2-methoxyethylidene)-4-methylfuran-2(5H)-one



[10]

RMN ^{1}H (300 MHz, $CDCl_3$): δ=2.16(s, 3H), 3.39 (s, 3H), 4.29(d, *J*=6.80 Hz, 2H), 5.41(t, *J*=6.80 Hz, 1H), 5.98(s, 1H).

RMN ^{13}C (75 MHz, $CDCl_3$)

δ=12.16(1C), 58.96(1C), 66.87(1C), 108.30(1C), 117.81(1C), 150.63(1C), 154.74(1C), 169.48(1C).

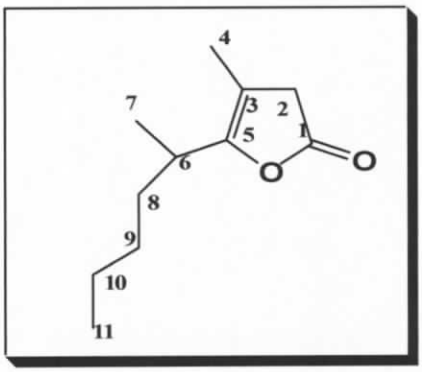
3.2.6. 1,6-cuprate addition

3.2.6.1. General procedure for the preparation of compounds

1-Under a nitrogen atmosphere, metyllithium (1,6 M in diethyl ether , 3 eq) was added drop wise to a stirred solution of copper iodide in anhydrous EtO_2 at –5°C, after the solution became clear the lactone diluted with anhydrous EtO_2 or THF was added via canola and the mixture was set at 0°C for 1 hour, the mixture was, then, cooled to –80°C and quenched with aqueous saturated solution of NH_4Cl and NH_4OH (90:10) and let to warm up to r.t. After extracting three times with AcOEt, the combined organic layers were washed with saturated brine, dried over anhydrous $MgSO_4$ and then concentrated in vacuo. The residual oils were purified by flash chromatography using an appropriate eluent system of petroleum ether/ether.
For compounds with hydroxide group the same procedure is prescribed except that the mixture was bubbled with pure oxygen before being quenched.

2-Under a nitrogen atmosphere, n-butyllithium (2.5 M in hexane, 3 eq) was added drop wise to a stirred solution of copper iodide in anhydrous EtO_2 at –78°C, after one hour of stirring, the lactone diluted with anhydrous EtO_2 or THF was added at –50°C via canola and the mixture was set for 1 hour, the mixture was, then, cooled to –80°C and quenched with aqueous solution of NH_4Cl and NH_4OH (90:10) and let to warm up to rt After extracting three times with AcOEt, the combined organic layers were washed with saturated brine, dried over anhydrous $MgSO_4$ and then concentrated in vacuo. The residual oils were purified by flash chromatography using an appropriate eluent system of petroleum ether/ether.
For compounds with hydroxide group the same procedure is prescribed except that the mixture was bubbled with pure oxygen before being quenched.

a. Compound [11] 5-(hexan-2-yl)-4-methylfuran-2(3H)-one



RMN ^{1}H (300 MHz, $CDCl_3$)

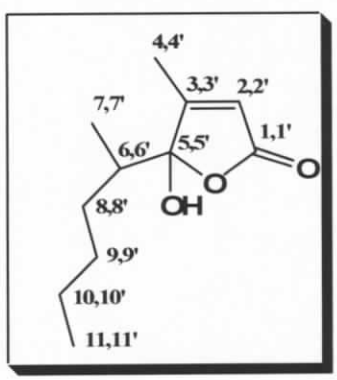
δ=0.87(t, 3H, H11), 1.11(d, *J*=6.99Hz, 3H, H7), 1.26-1.60(m, 6H, H8-H10), 1.71(s, 3H, H4) 2.27(m, 1H, H6), 3.10(s, 2H, H2).

RMN ^{13}C (75 MHz, $CDCl_3$)

δ=10.82(1C, C7), 14.16(1C, C11), 18.32(1C, C4), 22.68(1C, C10), 29.93(1C, C9), 30.77(1C, C6), 33.75(1C, C8), 38.23(1C, C2), 106.90(1C, C3), 153.29(1C, C5), 176.71(1C, C1).

-ESI+: 200 $[M+NH_4]^+$

b. Compound [12] 5-(hexan-2-yl)-5-hydroxy-4-methylfuran-2(5H)-one



RMN ^{1}H (300 MHz, $CDCl_3$)

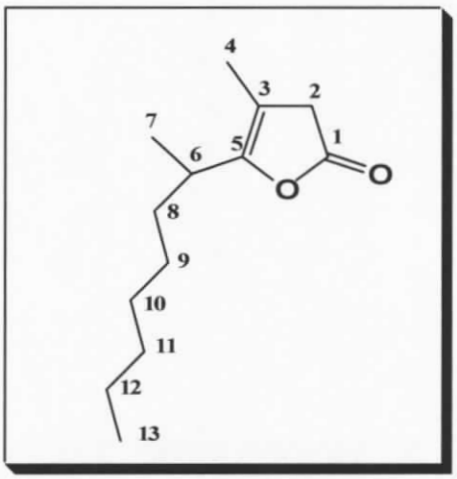
δ=0.76(d, *J*=6.61, 3H, H7), 0.88(t, 3H, H11), 1.11(d, *J*=6.61, 3H, H7'), 1.24-1.42(m, 6H, H8-10), 1.89 (m, 1H, H6) , 2.02(s, 3H, H4), 4.08 (bs, 1H, OH), 5.71(s, 1H, H2)

RMN ^{13}C (75 MHz, $CDCl_3$)

δ=12.33(1C, C7), 13.01(1C, C11), 13.12(1C, C11'), 13.38(1C, C7'), 14.15(2C, C4, C4') 22.80(1C, C10), 22.97(1C, C10'), 29.07(1C, C8) 29.55(1C, C8') 29.89(2C, C9, C9'), 37.88(1C, C6) 37.99(1C, C6') 110.50(1C, C2, C2'), 118.06(1C, C5), 118.28(1C, C5'), 167.85(1C, C3), 168.07(1C, C3'), 171.58(C, C1), 171.66(1C, C1').

-ESI+: 216 $[M+NH_4]^+$

c. Compound [13] 4-methyl-5-(octan-2-yl)furan-2(3H)-one

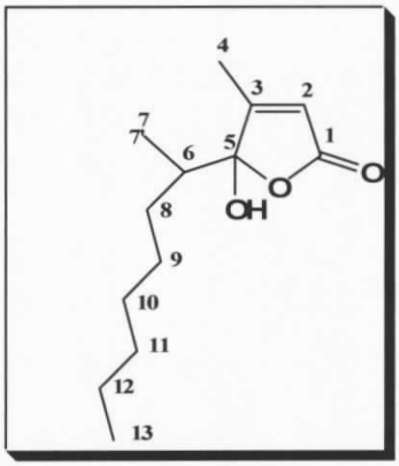


RMN ^1H (300 MHz, $CDCl_3$) δ=0.85 (t, 3H, H13), 1,08(, d, *J*=6.99Hz, 3H, H7), 1.22(m, 8H, H9-H12), 1.37-1.49(m, 2H, H8), 1.69(s, 3H, H4), 2.54(m, 1H, H6), 3.08(s, 2H, H2).

RMN ^{13}C (75 MHz, $CDCl_3$) δ=10.76(1C, C13), 14.12(1C, C7), 18.25(1C, C4), 22.69 (1C, C12), 27.63(1C, C9), 29.21(1C, C7), 30.71(1C, C6), 31.86(1C, C11), 33.99(1C, C8), 38.16(1C, C2), 106.87(1C, C3), 153.22(1C, C5), 176.61(1C, C1).

-ESI+: 228 $[M+NH_4]^+$

d. Compound: [14] 5-hydroxy-4-methyl-5-(octan-2-yl) furan-2(5H)-one



RMN ^{1}H (300 MHz, $CDCl_3$)

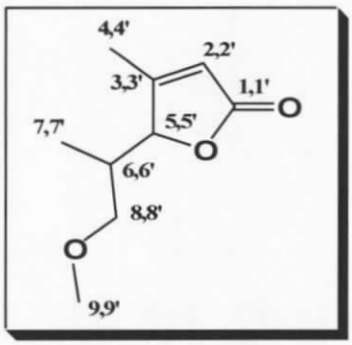
δ=0.87 (t, 3H, H13), 0.77 (d, *J*=6.8Hz, 3H, H7), 1.12 (d, *J*=6.8Hz, 3H, H7'), 1.29(m,10H, H8-H12) , 1.92(m, 1H, H6), 2.03(s, 3H, H4), 3.45(bs, 1H, OH), 5.79(s, 1H, H2).

RMN ^{13}C (75 MHz, $CDCl_3$)

δ=13.09,13.30(1C, C7, 7'), 13.08(1C, C13), 14.14(1C, C4) 22.70(1C, C12), 27.27(1C, C8), 29.40(1C, C9) 30.15(1C, C10), 31.86(1C, C11) 37.96(1C, C6), 110.73(1C, C2), 116.09(1C, C5), 168.11(1C, C3), 171.84(1C, C1).

-ESI+: 244 $[M+NH_4]^+$

e. Compound [15] 5-(1-methoxypropan-2-yl)-4-methylfuran-2(5H)-one



RMN ^{1}H (300 MHz, $CDCl_3$) :

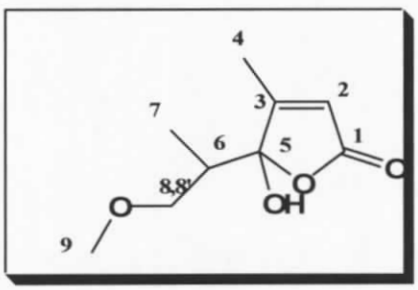
δ=0.63(d, *J*=7Hz, 3H, H7), 1.09(d, *J*=7Hz,3H, H7'), 2.01(s, 3H, H4), 2.08(s, 3H, H4'), 2.18(m, 1H, H6), 2.33(m, 1H, H6'), 3.15(m, 2H,H8), 3.18(s,3H,H9), 3.36(s,1H, H9'), 3.44(m, 2H, H8'), 4,82(s, 1H, H5), 5.11(s, 1H, H5'), 5.75(s, 1H, H2), 5.82(s, 1H, H2').

RMN ^{13}C (75 MHz, $CDCl_3$):

δ=8.16(1C, C7), 13.90 (1C, C7'), 14.68(1C, C4), 35.00(1C,C6), 35.75(1C, C6'), 58.76(1C, C9), 59.04(1C,C9'), 72.24(1C,C8), 74.41(1C, C8'),83.82(1C,C5), 86.82(1C, C5'), 116.49(1C, C2), 117.62(1C, C2'), 168.25(1C, C3), 169.17(1C, C3'), 173.63(2C, C1,C1').

-ESI+: 188 $[M+NH_4]^+$

f. Compound [16] 5-hydroxy-5-(1-methoxypropan-2-yl)-4-methylfuran-2(5H)-one



RMN ^{1}H (300 MHz, $CDCl_3$)

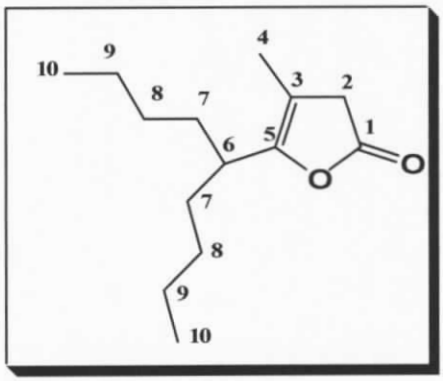
δ=0.64(d, *J*=7.04Hz, 3H, H7), 2.01(s, 3H, H4), 2.37(m, 1H, H6), 3.42(s, 3H, H9), 3.57(dd, *J*=3.97, 9.22, 1H, H8), 3.83(dd, *J*=9.22, 11.00, 1H, H8'), 6.70(s, 1H, H2).

RMN ^{13}C (75 MHz, $CDCl_3$)

δ=11.09(1C, C7), 12.64(1C, C4), 36.85(1C, C6), 59.40(1C, C9), 75.71(1C, C8), 110.24(1C, C5), 118.88(1C, C2), 165.78(1C, C3), 171.09(1C, C1).

-ESI+: 204 $[M+NH_4]^+$

g. Compound: [17]_4-methyl-5-(nonan-5-yl) furan-2(3H)-one



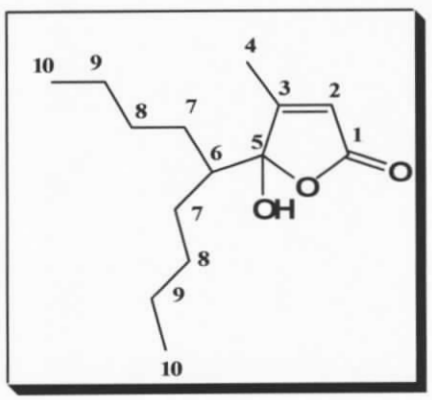
RMN ^1H (300 MHz, $CDCl_3$) δ=0.85 (t, 6H, H10), 1,23-1.49 (m, 12H, H7-9), 1.70(s, 3H, H4), 2.39(m, 1H, H6), 3.11(s, 2H, H2).

RMN ^{13}C (75 MHz, $CDCl_3$)

10.86(1C, C14) 14.14(2C, C10), 22.69(2C, C9), 29.89(2C,C7), 32.33(2C, C8), 36.48(1C, C6), 38.09(1C, C2), 108.56(1C, C3), 151.91(1C, C5), 176.72(1C,C1).

-ESI+: 242 $[M+NH_4]^+$

h. Compound: [18]_5-hydroxy-4-methyl-5-(nonan-5-yl) furan-2(5H)-one

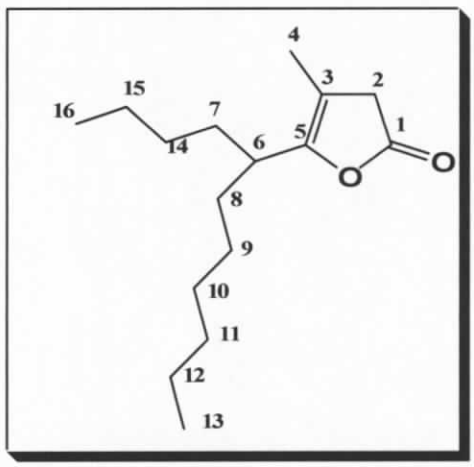


RMN ^{1}H (300 MHz, $CDCl_3$) δ=0.88(m, 6H, H10), 1.28(m, 12H, H7-9), 1.76(m, 1H, H6), 2.02(s, 3H, H4), 5.75(s, 1H, H2).

RMN ^{13}C (75 MHz, $CDCl_3$) δ=13.30(1C, C4), 14.11 (2C, C10), 23.15(2C, C9), 28.41(2C, C7), 30,28 (2C, C8), 42.66(1C, C6), 110.50(1C,C4), 119.11(1C,C2), 168.39(1C, C3), 171.86(1C,C1).

-ESI+: 258 $[M+NH_4]^+$

i. Compound [19]4-methyl-5-(undecan-5-yl)furan-2(3H)-one



RMN ^{1}H (300 MHz, $CDCl_3$):

δ=0.85 (m, 6H, H13+H16), 1,23- 1.49 (m, 16H, H 7,8,9,10,11,12,14,15), 1.70(s, 3H, H4,), 2.38(m, 1H, H6), 3.12(s, 2H, H2).

RMN ^{13}C (75 MHz, $CDCl_3$)

δ=10.91(1C, C4), 14.17(2C, C13, C16), 22.73(2C, C12, C15), 27.67(1C, C9) 29.32(1C, C14), 29.92(1C, C10), 31.94(1C, C9), 32.36(1C, C8), 32.63(1C, C11), 36.52(1C, C6), 38.13(1C, C2), 108.57(1C, C3), 151.98(1C, C5), 176.76(1C, C1).

-ESI+: 270 $[M+NH_4]^+$

Conclusion

Butenolides are often generated in fungi, bacteria, and gorgonians. The ring system of butenolides constitutes the central skeleton of a series of natural oxygenated heterocycles and is widely present in secondary metabolites which show interesting physiological activities, such as anti-tumor activity and antibiotic activity against Pseudomonas aeruhinosa**.** Besides their biological features, butenolides are useful intermediates in organic synthesis; starting with such compounds, peptide analogues or HIV-1 protease inhibitors have, for example, been prepared.

In this work we have undertaken the study of reactivity of some butenolides through the 1,6-addition pathway using high order organocopper reagents. A set of addition products has been established using methyllithium and butyllithium.

To our knowledge this work has not been conducted before.

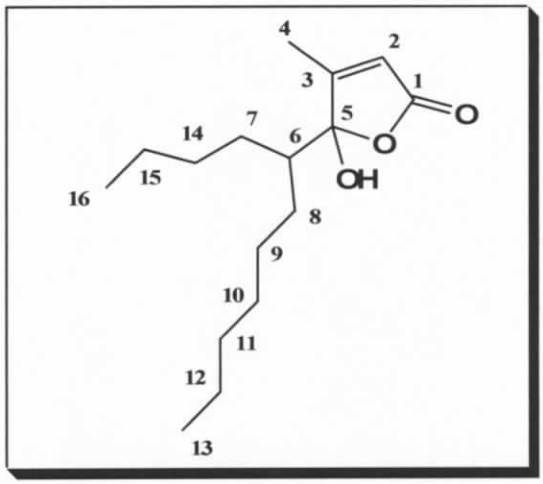
New compounds have been synthesized.

The different steps involved in the reactions are simple and economic.

The subsequent separations of compounds are easy and do not involve any special equipments apart from the ordinary column chromatography.

The results are promoting and we do recommend pursuing the study using other reactants and performing the biological activities of the new compounds.

j. Compound [20] 5-hydroxy-4-methyl-5-(undecan-5-yl)furan-2(5H)-one



RMN ^{1}H (300 MHz, $CDCl_3$)

δ=0.87(6H, m, H16, H13), 1.26(m,16H, H8-13, H7-15) , 1.78(m, 1H, H6), 2.04(s, 3H, H4), 5.77(s, 1H, H2).

RMN ^{13}C (75MHz, $CDCl_3$)

δ=13.33, 14.20 (2C), 22.76(2C), 23.22, 28.68, 34.58, 29.85, 31.83(2C), 42.74, 118.20 120.54, 168.19, 171.64.

-ESI+: 286$[M+NH_4]^+$

Conclusion

Butenolides are often generated in fungi, bacteria, and gorgonians. The ring system of butenolides constitutes the central skeleton of a series of natural oxygenated heterocycles and is widely present in secondary metabolites which show interesting physiological activities, such as anti-tumor activity and antibiotic activity against Pseudomonas aeruhinosa. Besides their biological features, butenolides are useful intermediates in organic synthesis; starting with such compounds, peptide analogues or HIV-1 protease inhibitors have, for example, been prepared.

In this work we have undertaken the study of reactivity of some butenolides through the 1,6-addition pathway using high order organocopper reagents. A set of addition products has been established using methyllithium and butyllithium.

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The results are promoting and we do recommend pursuing the study using other reactants and performing the biological activities of the new compounds.

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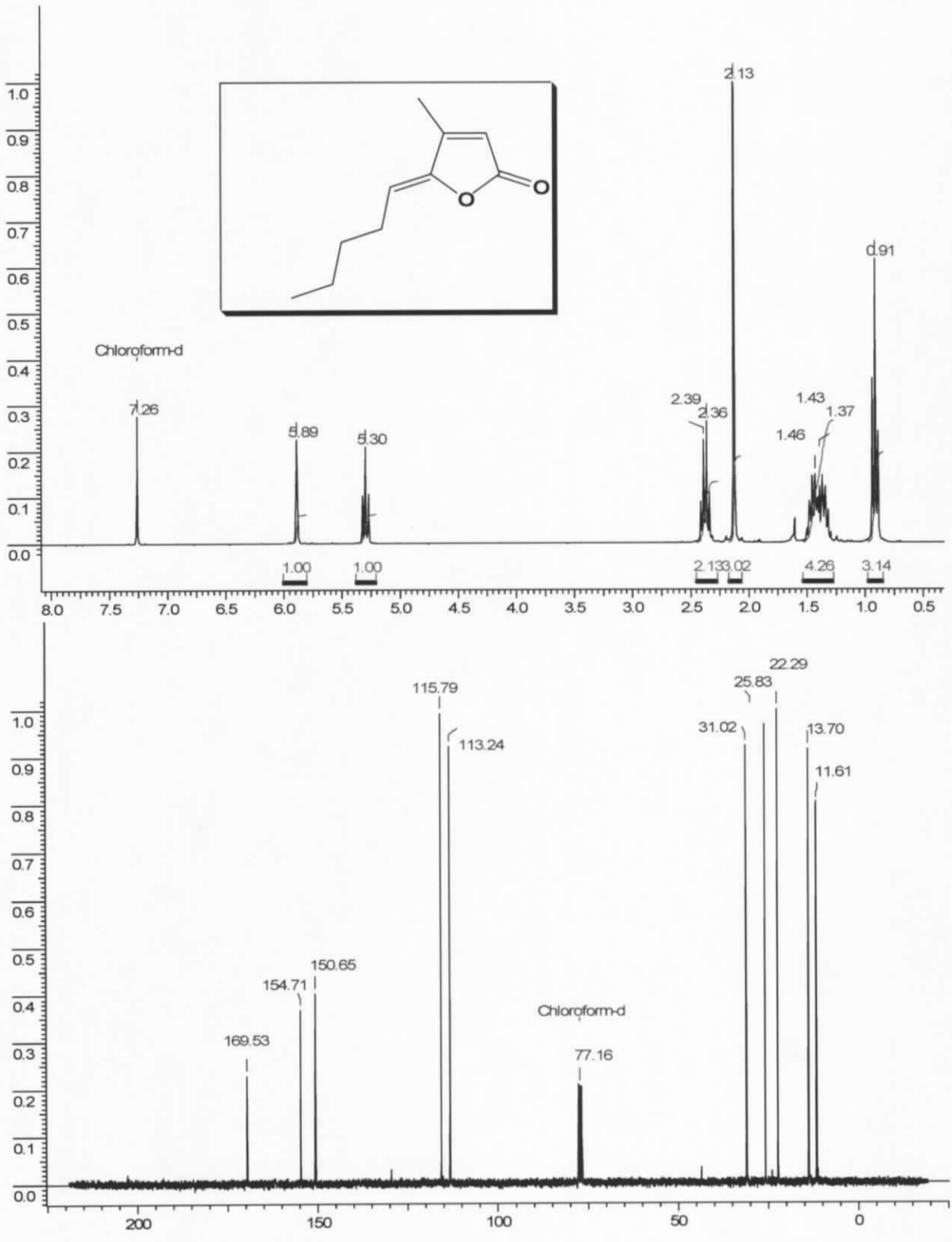
Annex 2

Part II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5.89
5.30
2.39
2.36
2.13
1.46
1.43
1.37
0.91
1.00
1.00
2.13
3.02
4.26
3.14
115.79
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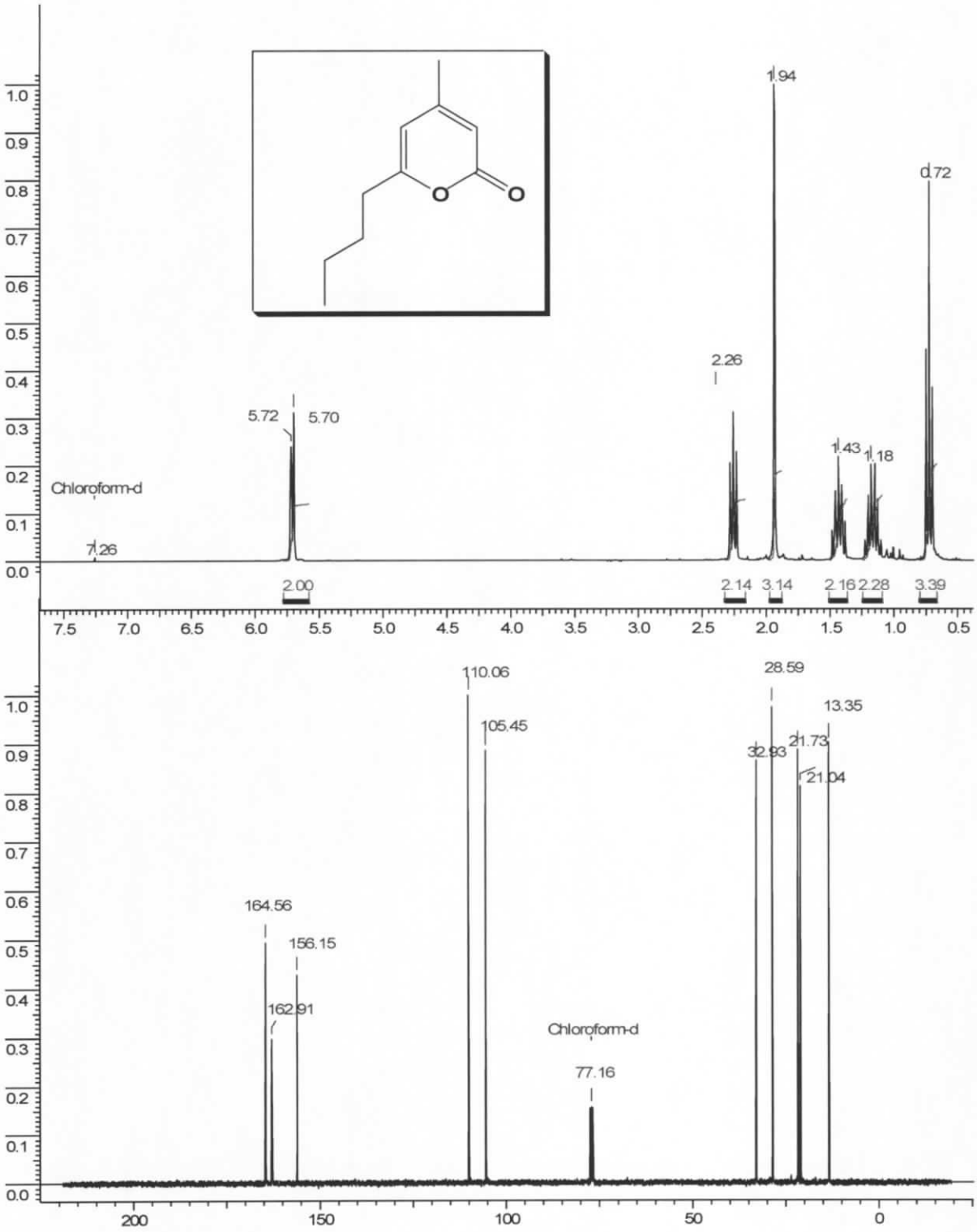
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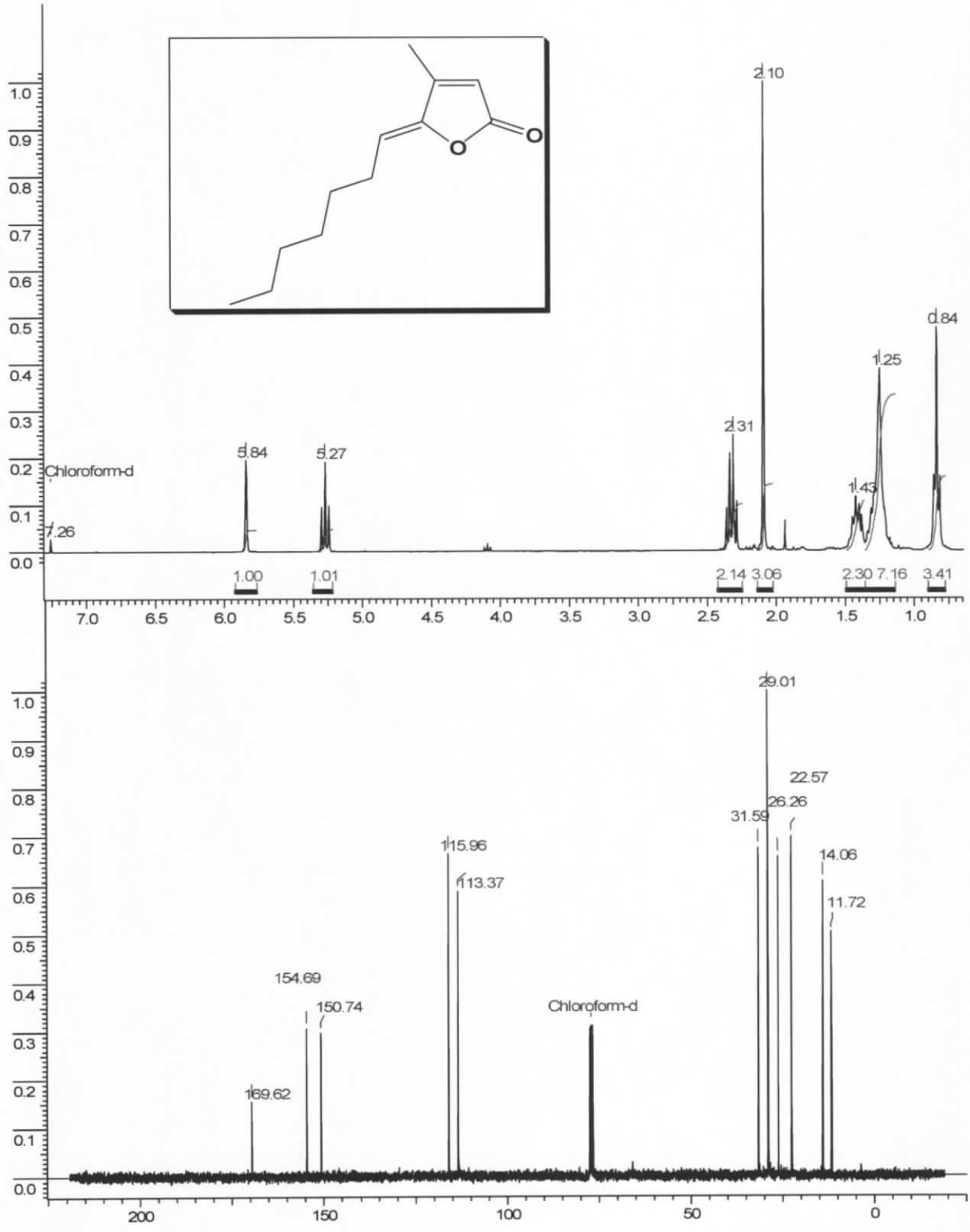
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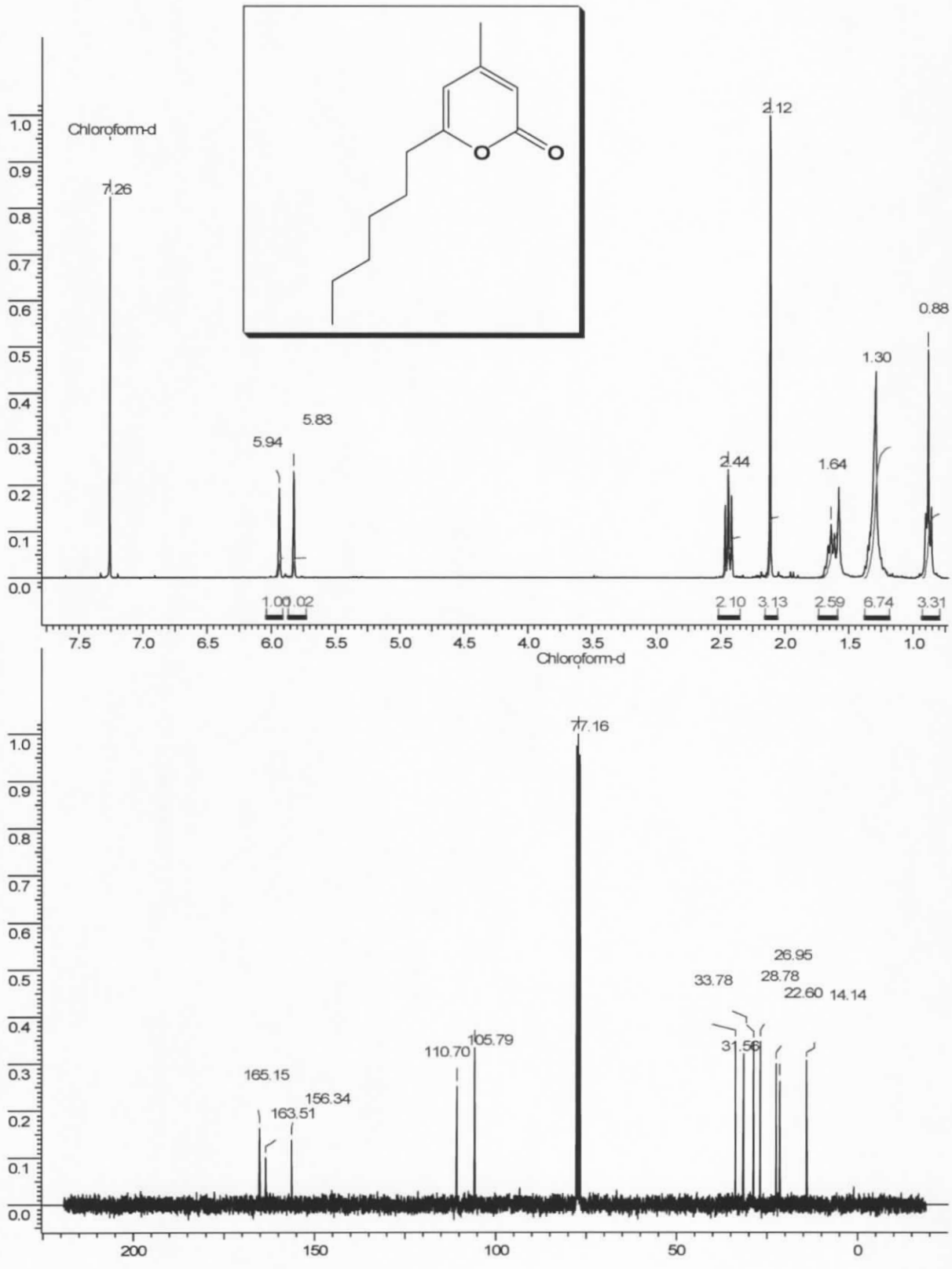
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Chloroform-d
77.16
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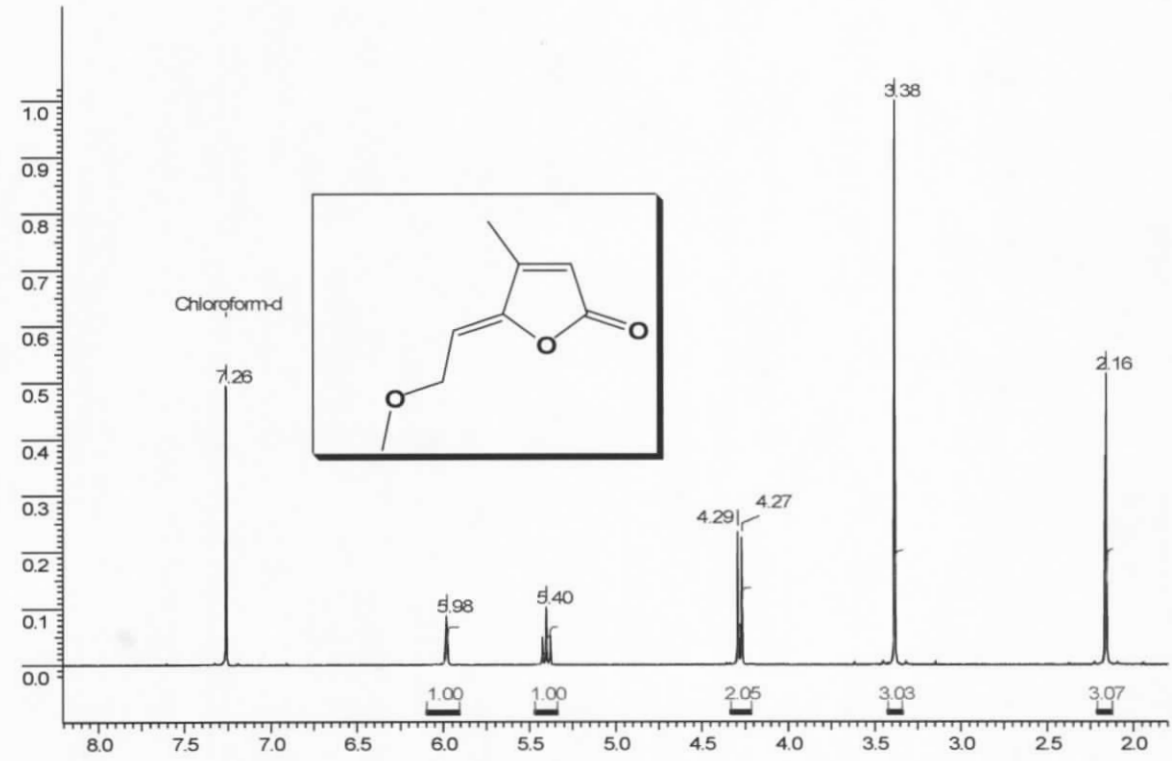
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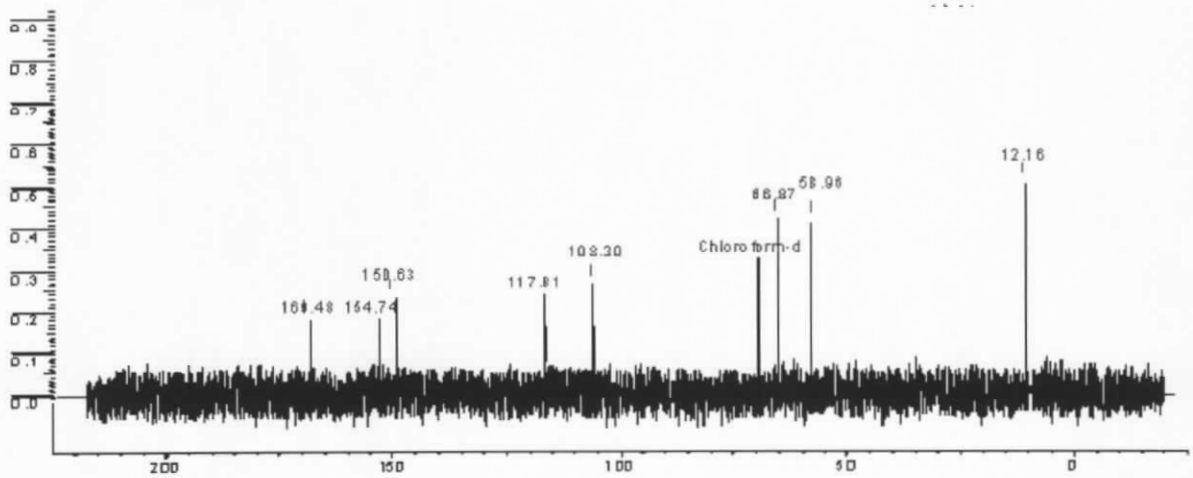
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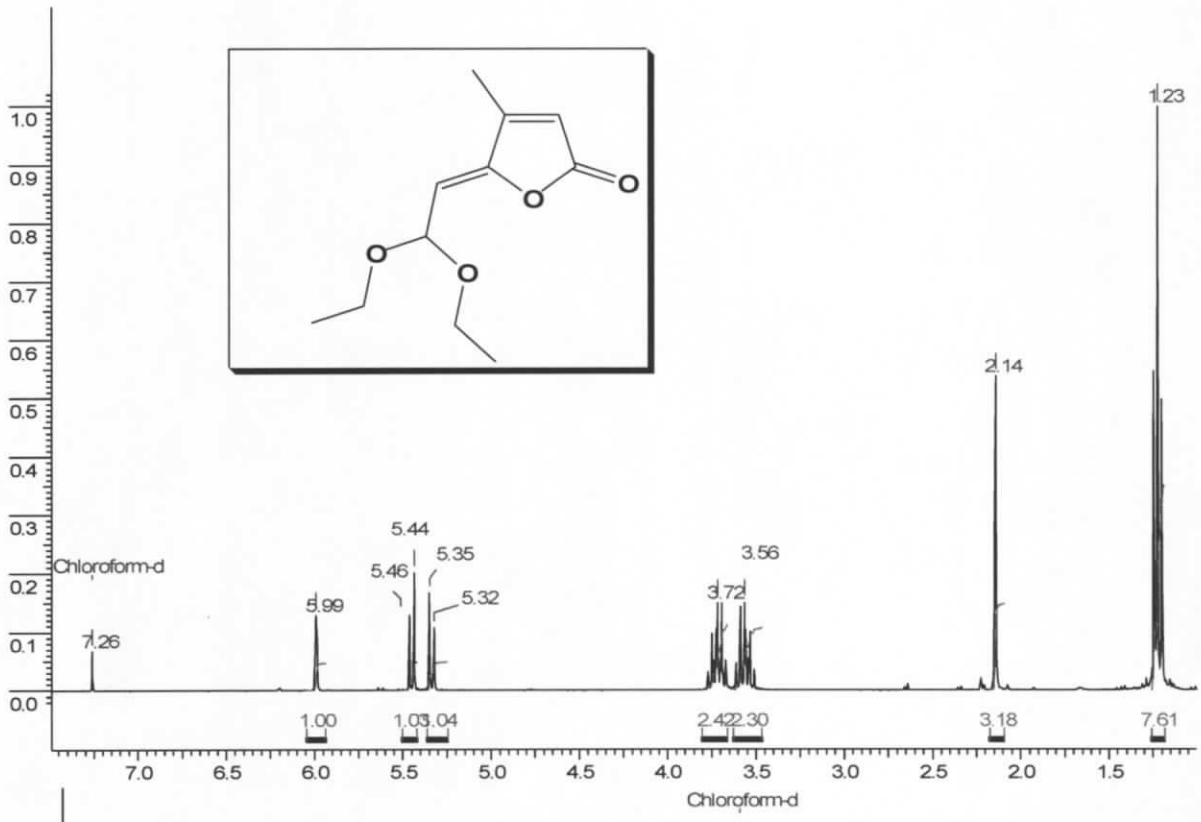
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3.04
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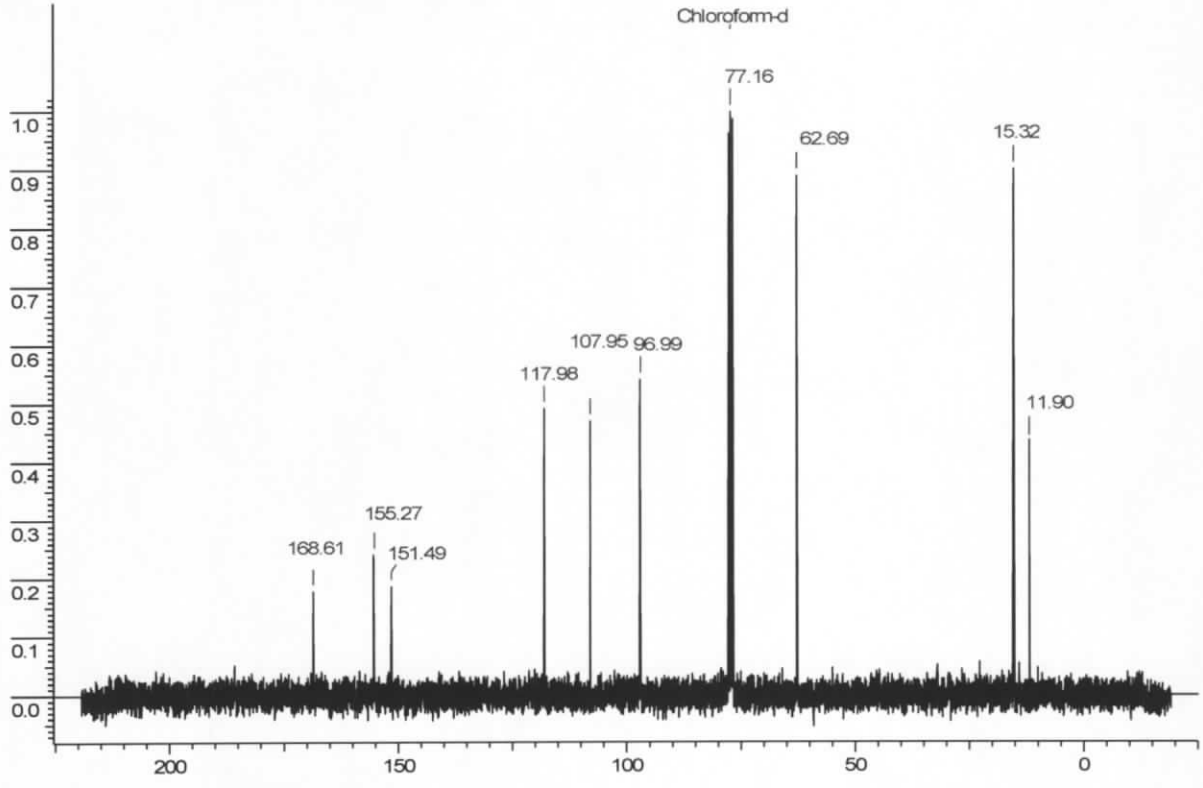
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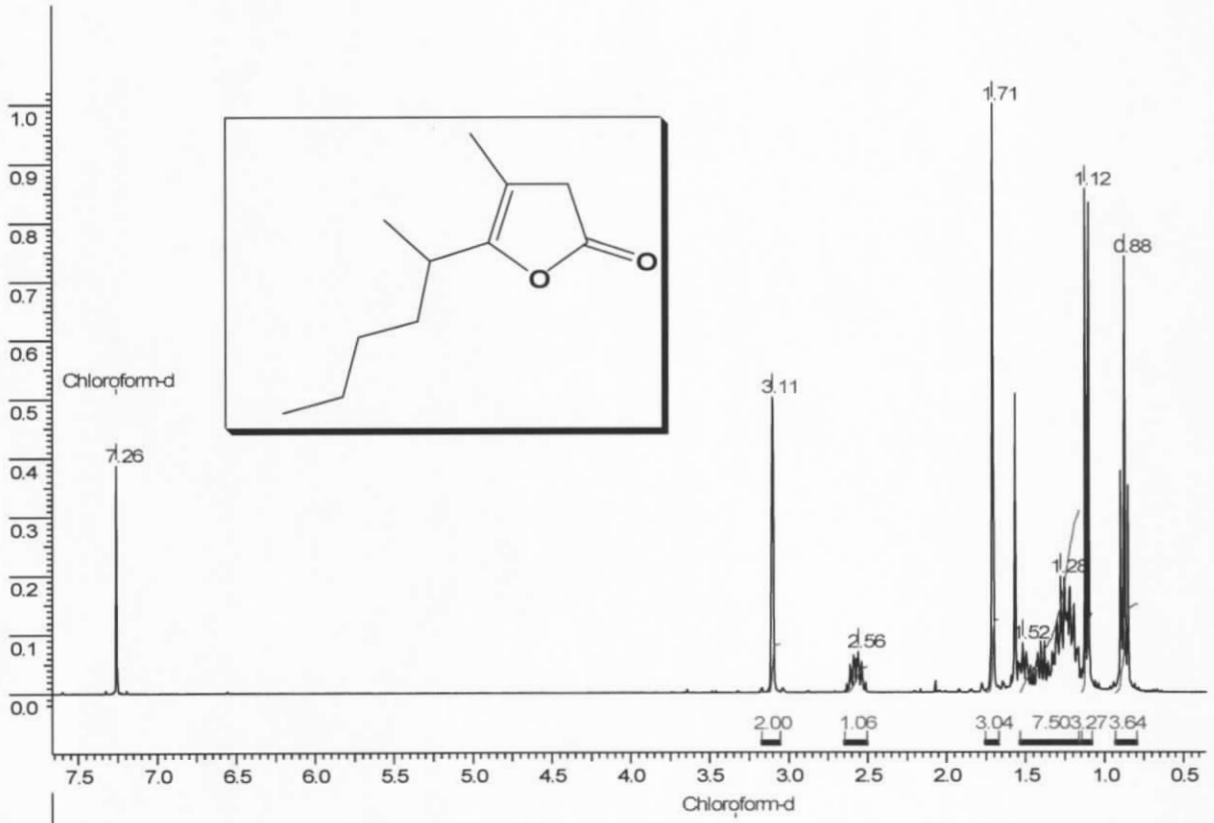
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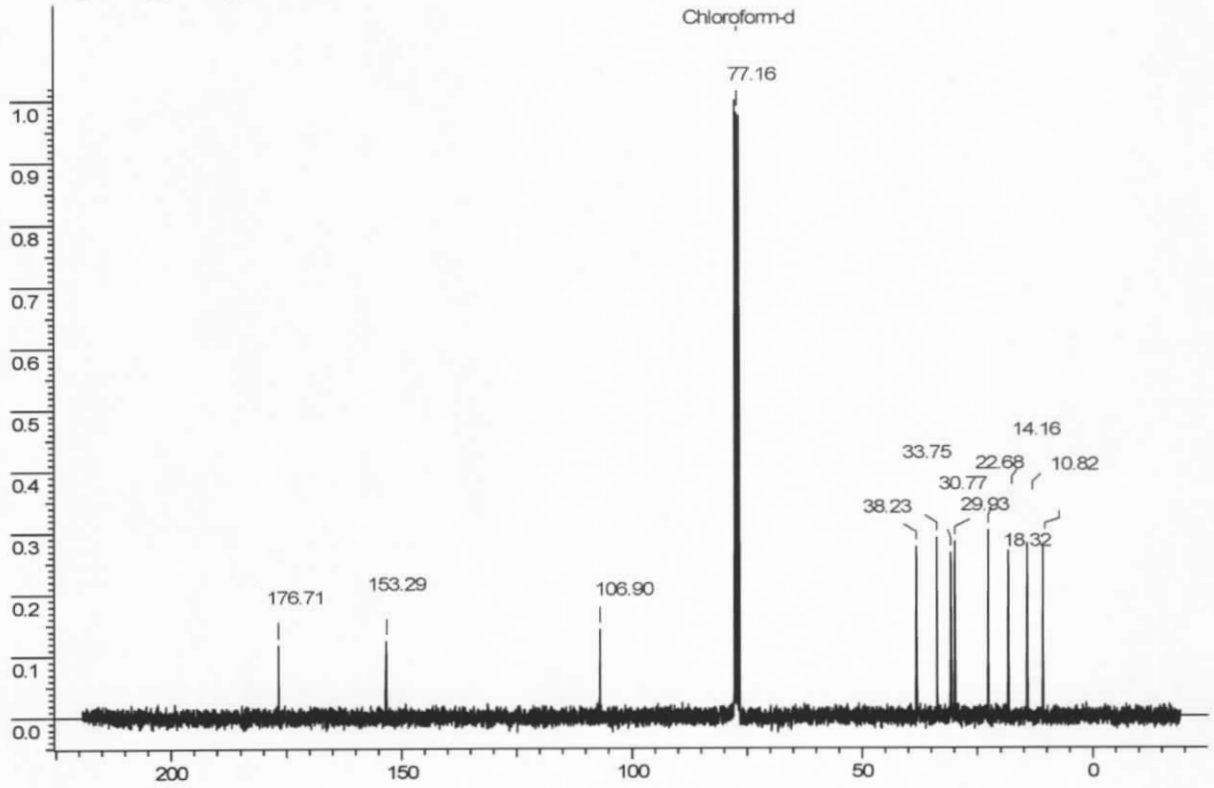
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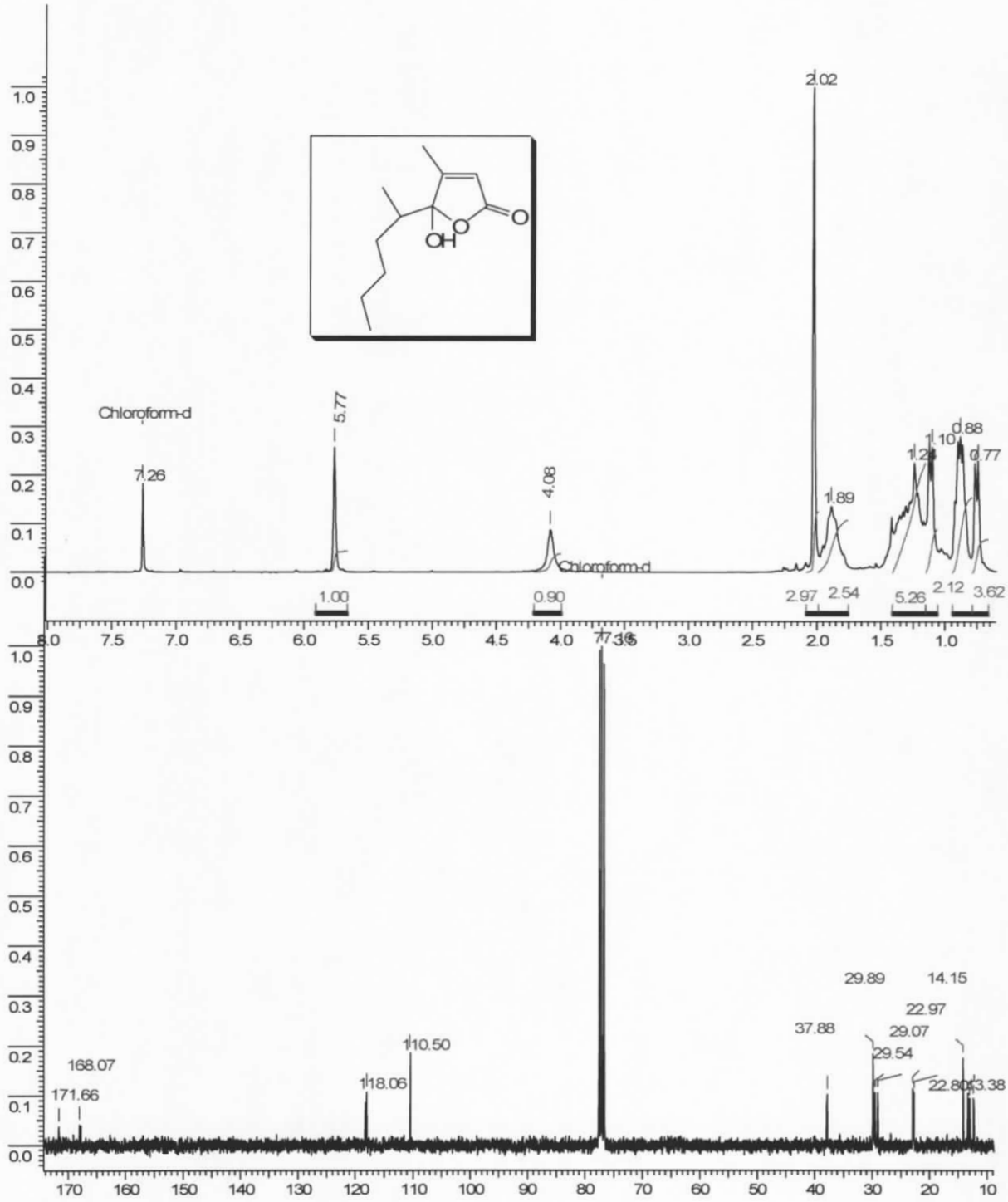
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0.90
2.97
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2.12
3.62
168.07
171.66
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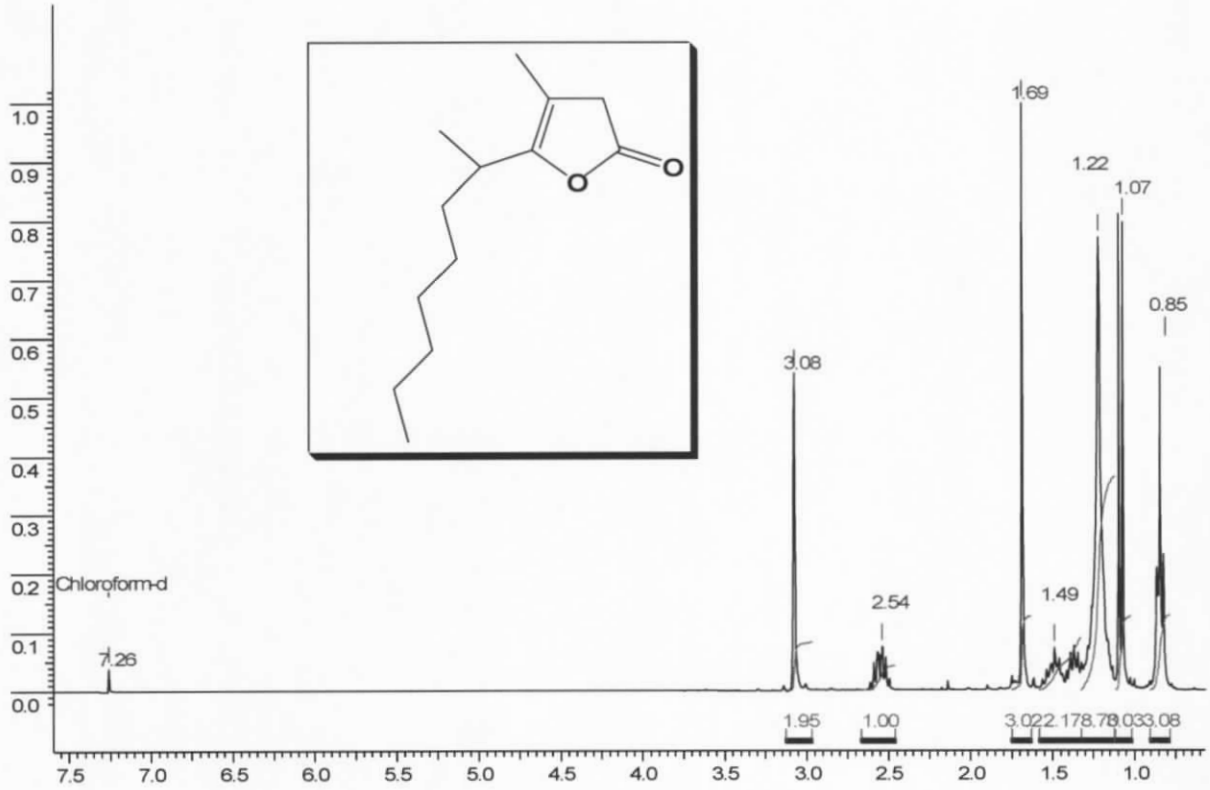
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Chloroform-d
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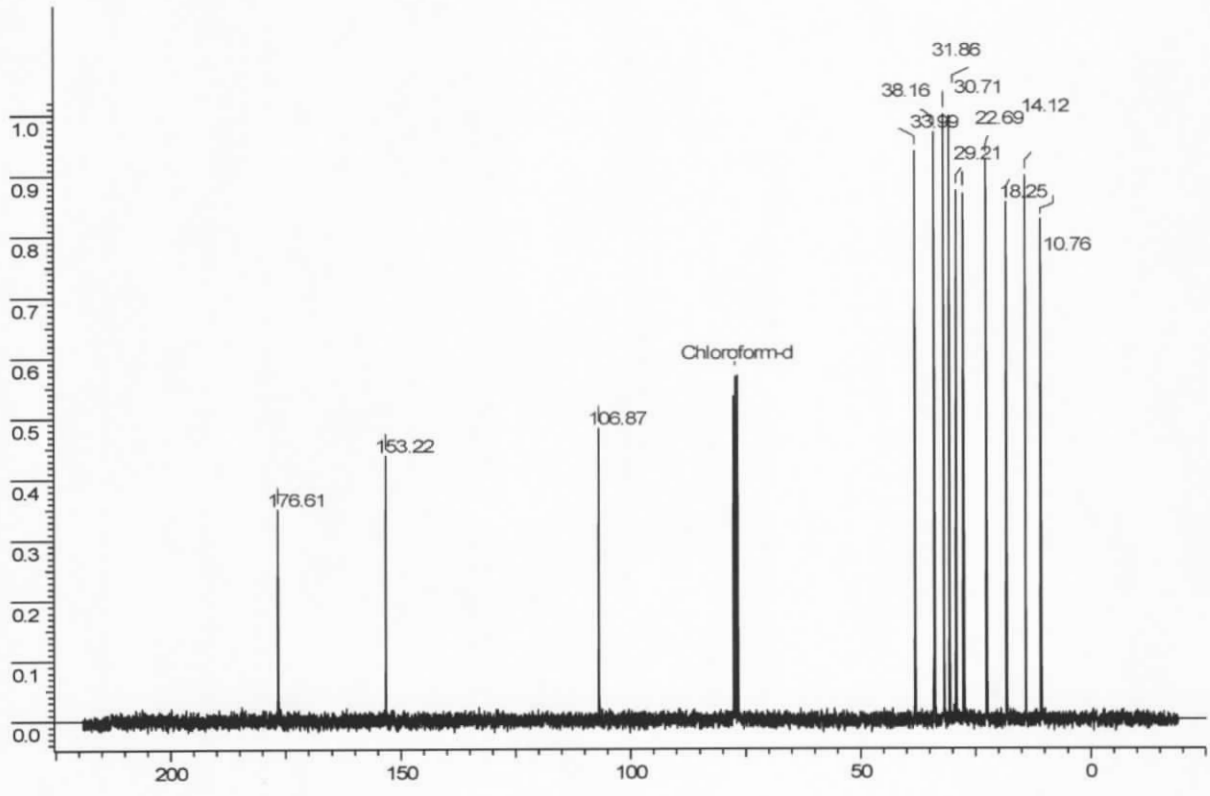
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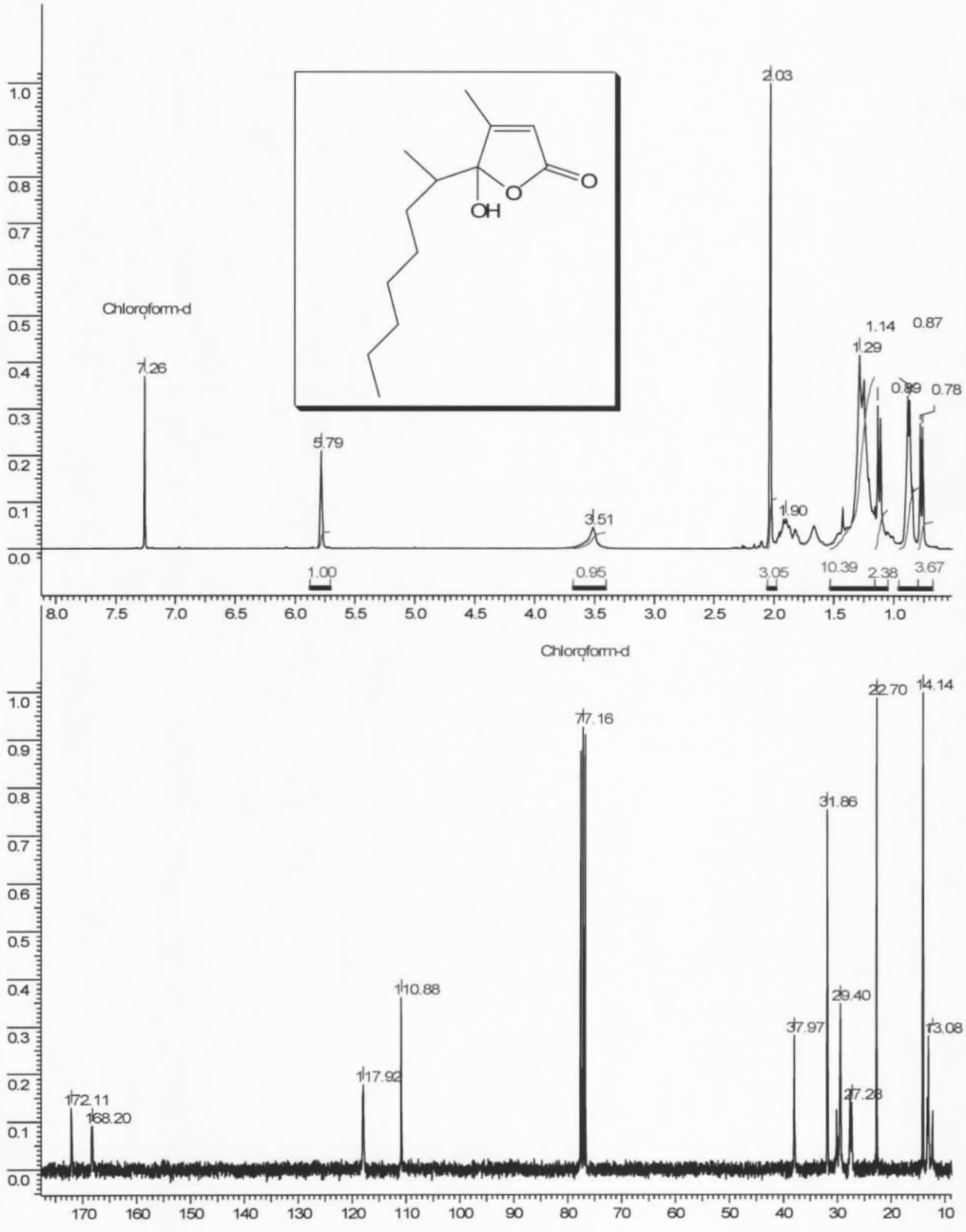
Part II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0.89
0.78
1.00
0.95
3.05
10.39
2.38
3.67
OH
O
O

Chloroform-d
172.11
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110.88
77.16
37.97
31.86
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27.28
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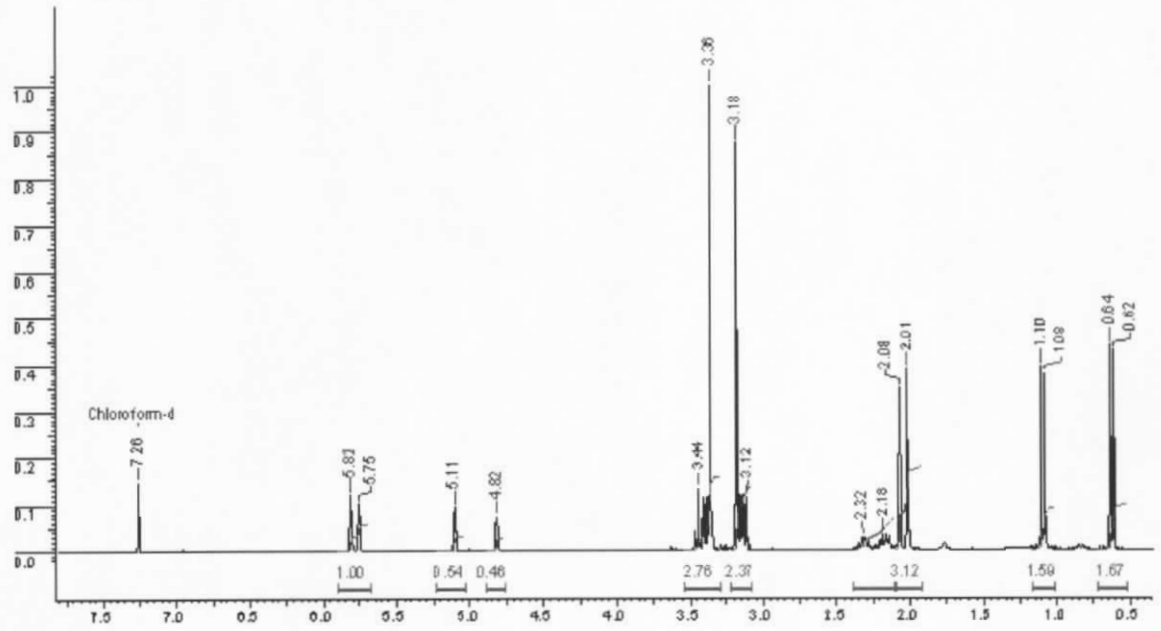
13.08

Part II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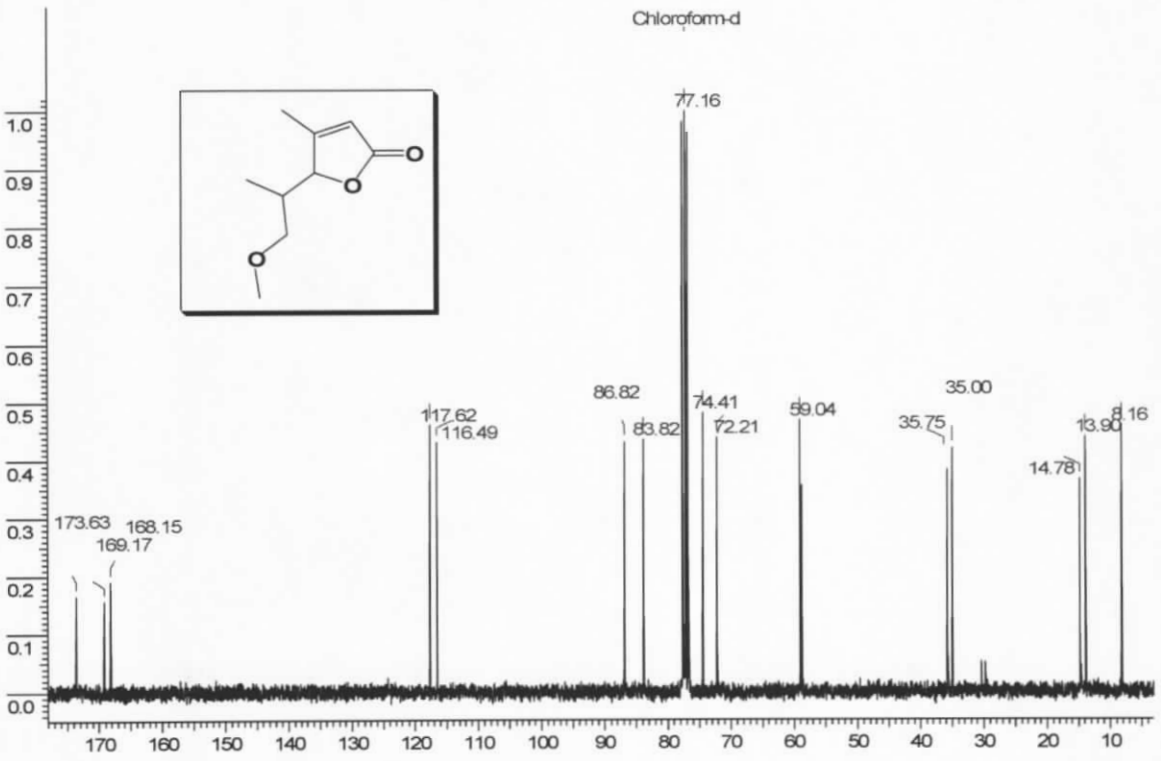
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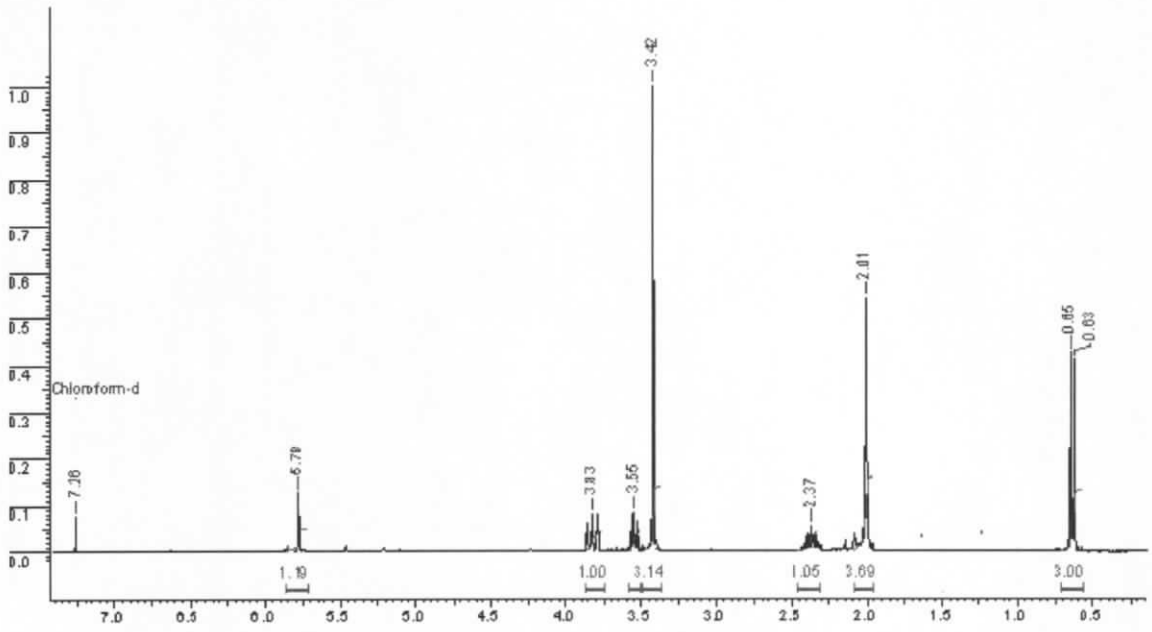
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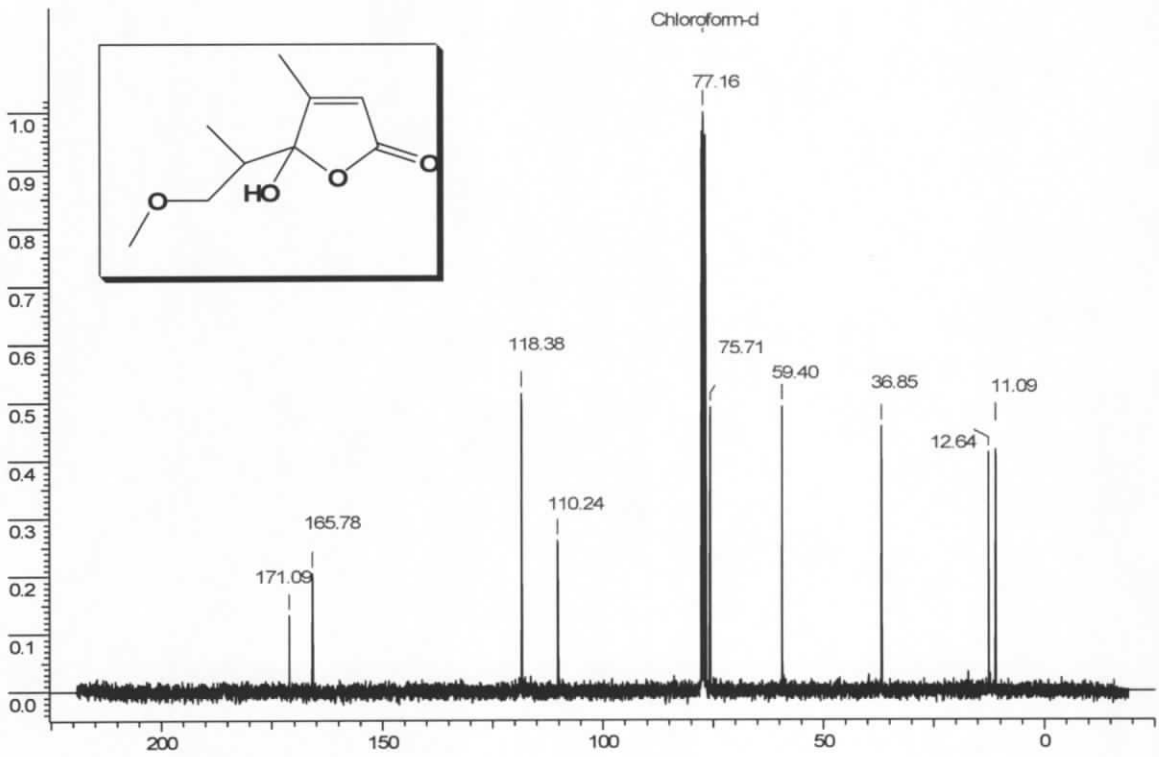
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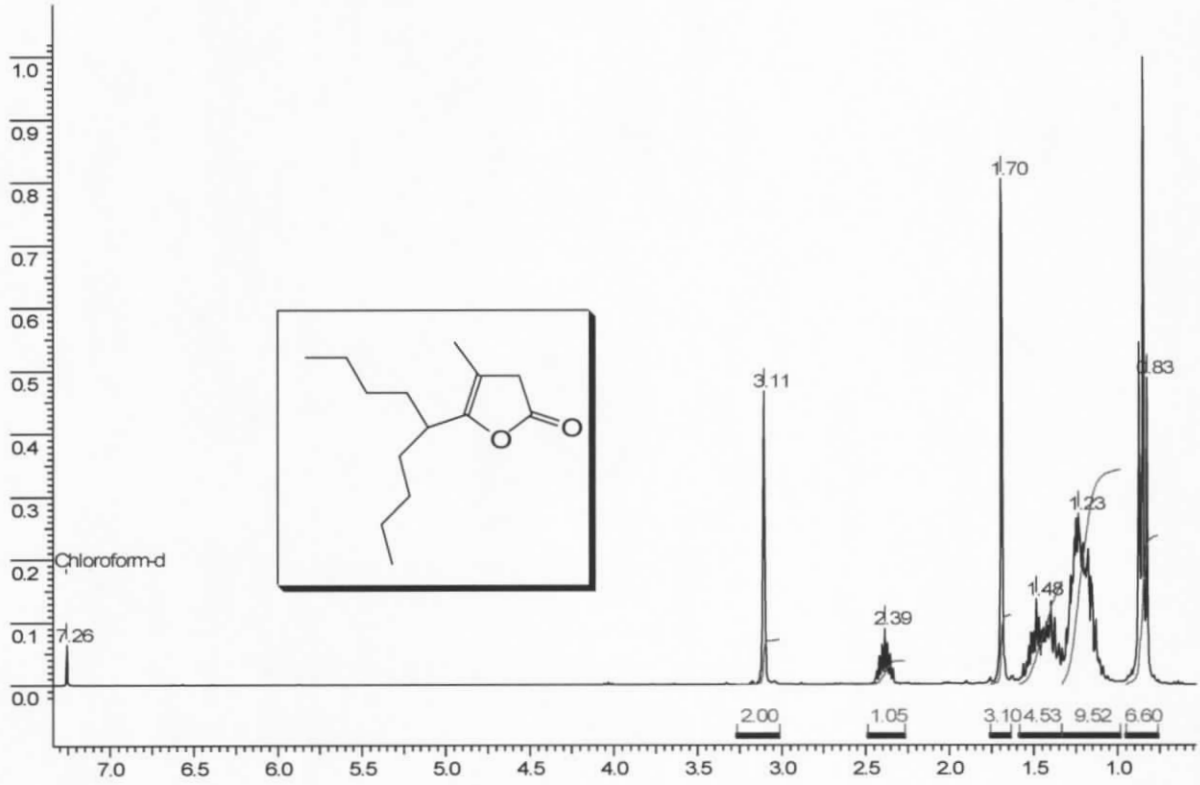
HO
O
O
O

Part II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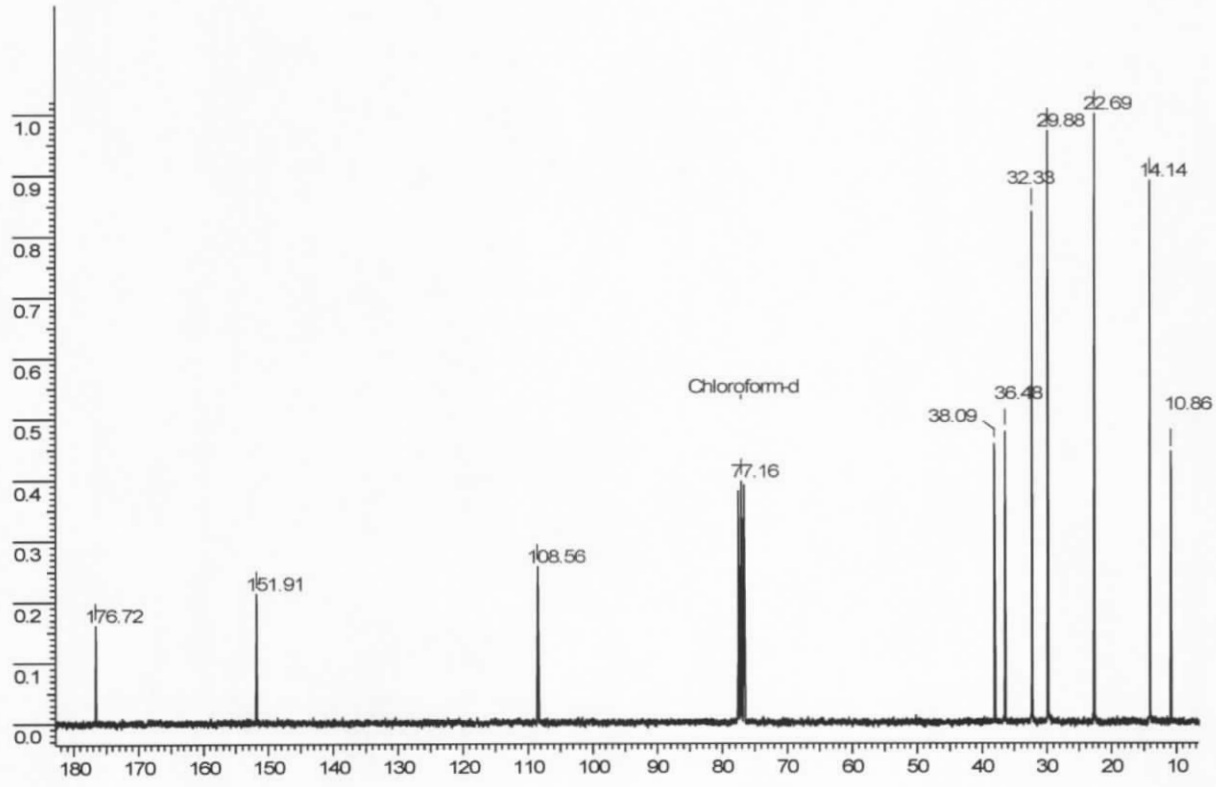
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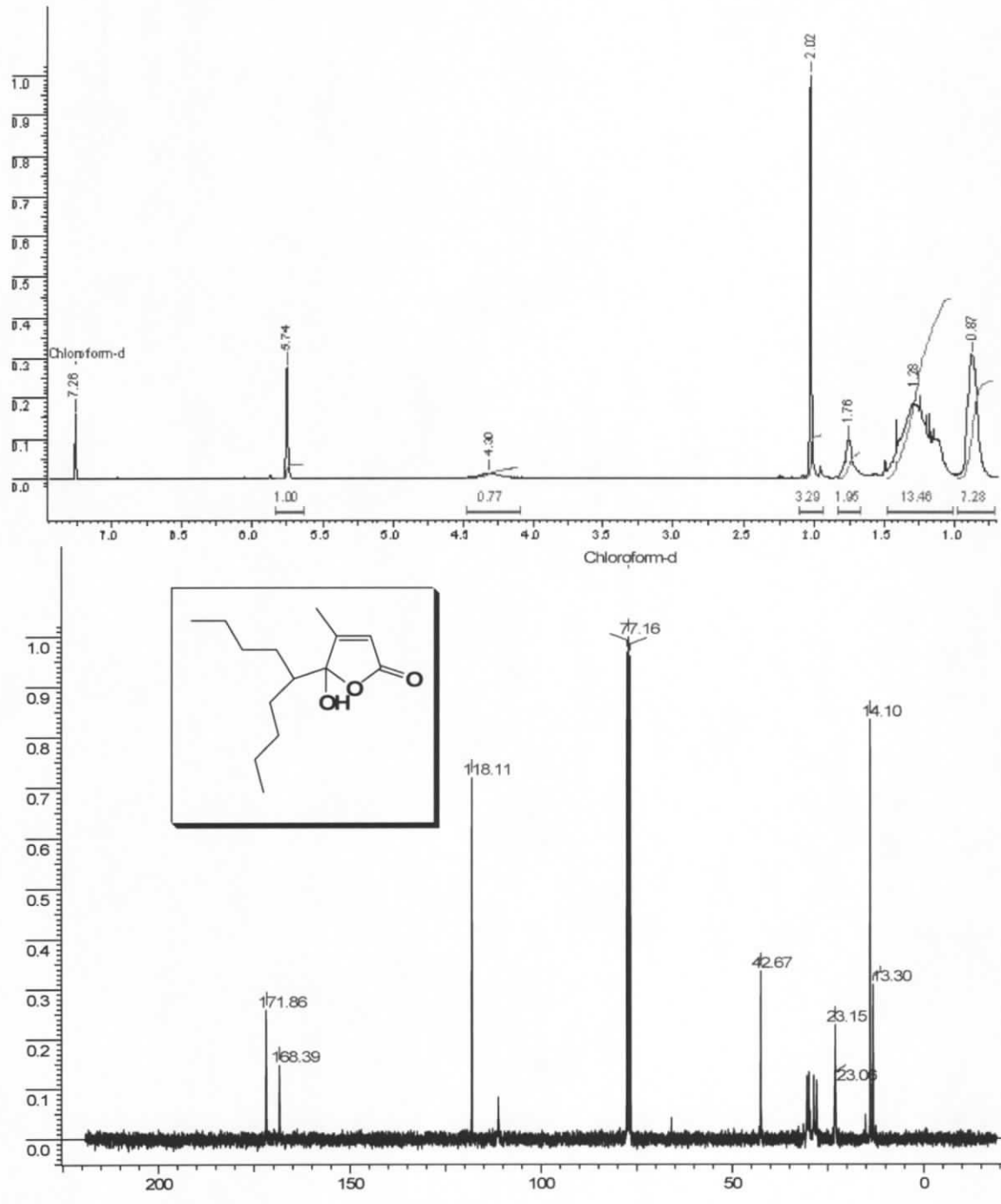
Part II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Chloroform-d
OH
O
O
77.16
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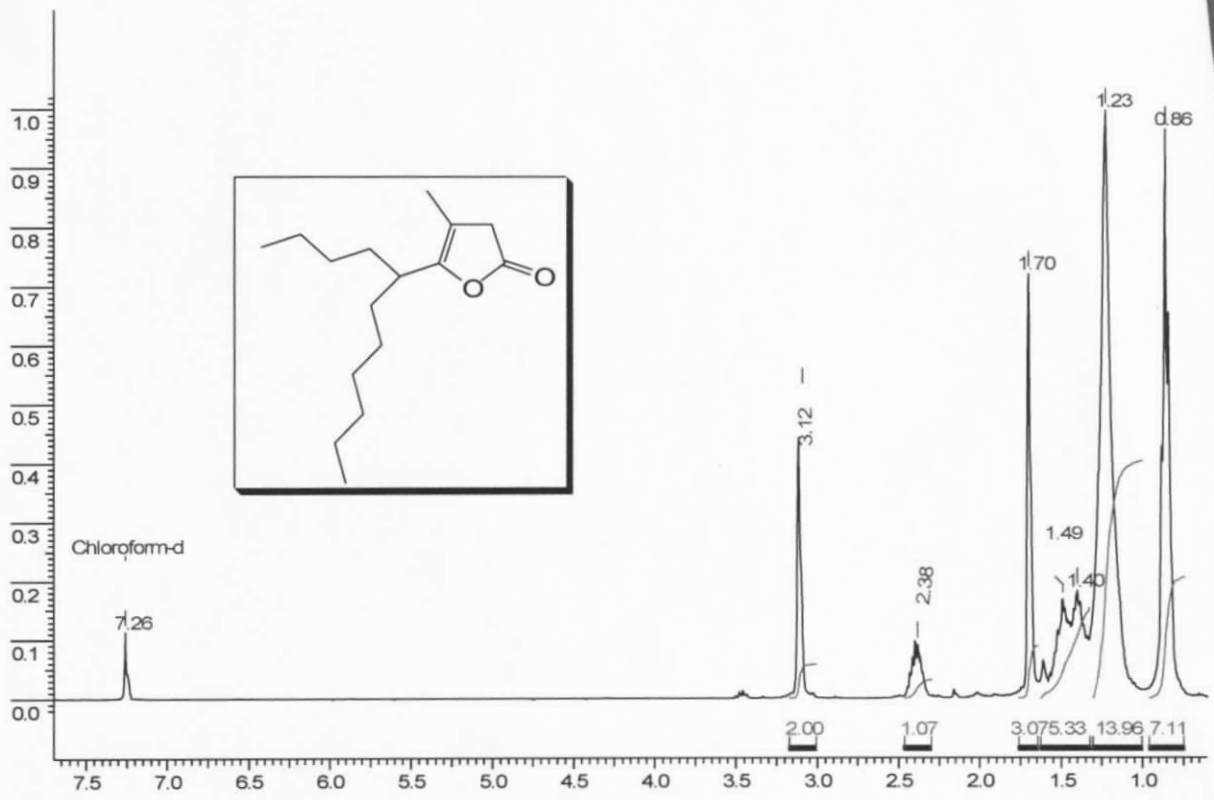
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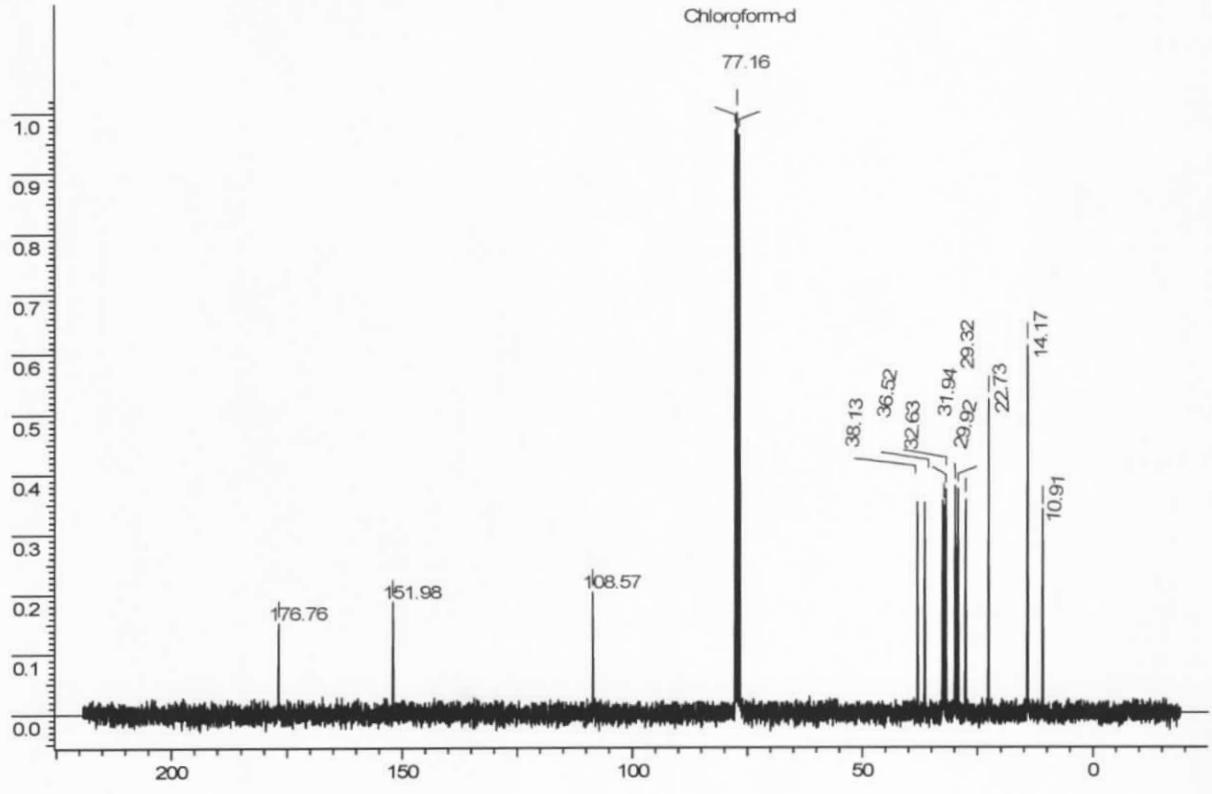
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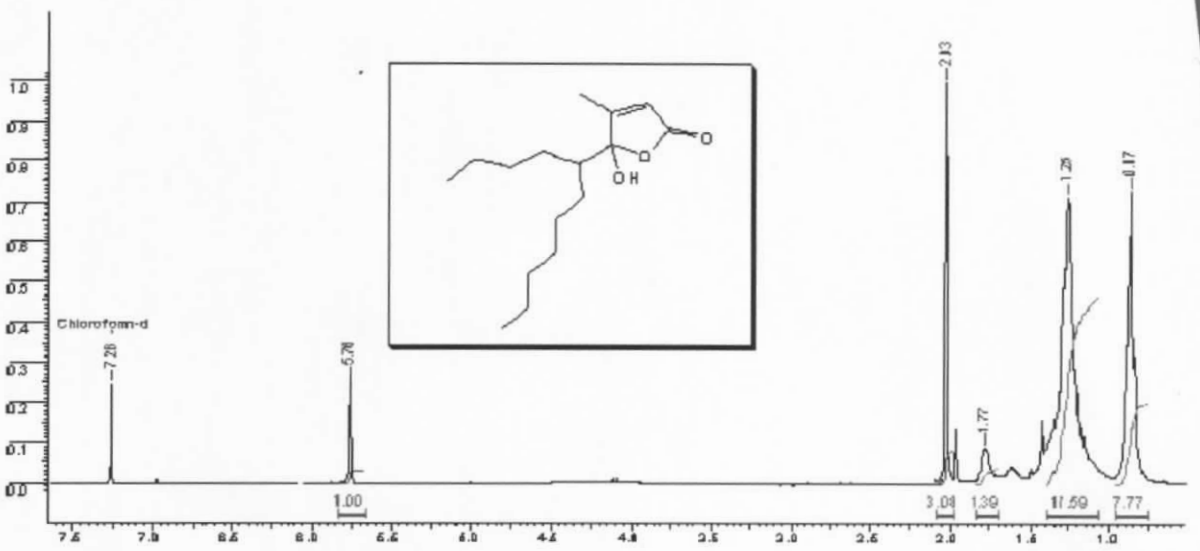
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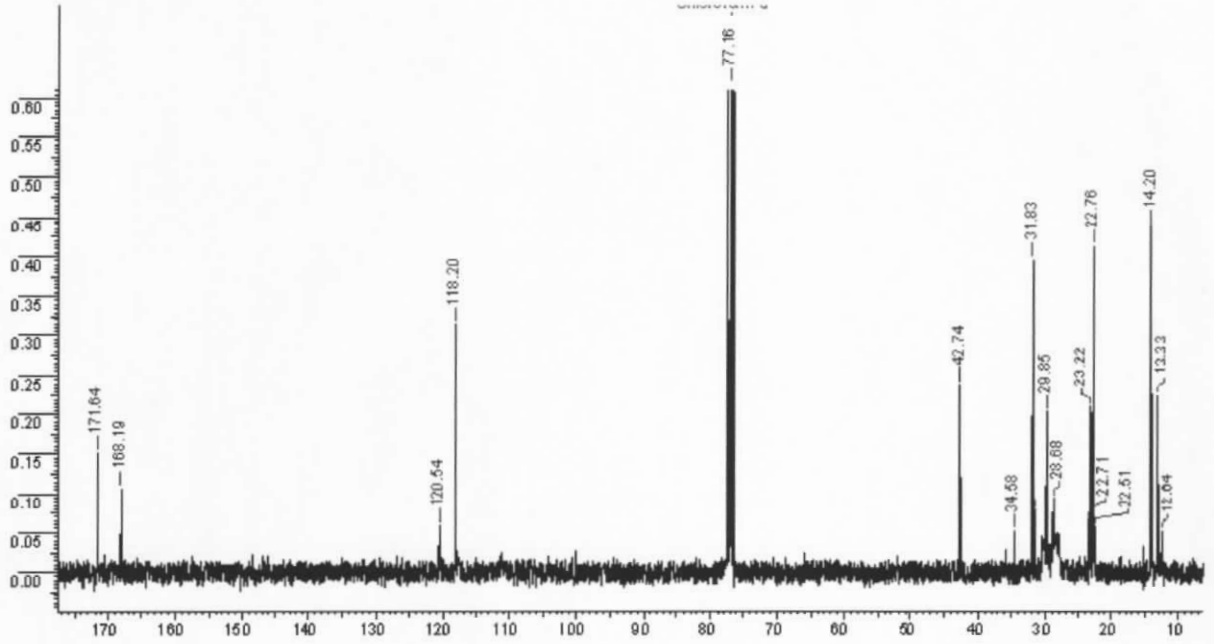
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22.51
12.76
14.20
12.33
12.04

ملخص

تعتبر الطبيعة مصدرا هاما من حيث الغذاء و الدواء و قد ازداد اهتمام الباحثين في السنوات الأخيرة بالأعشاب الطبية حيث أصبحت تمثل مصدرا أساسيا في العلاجات الشعبية وقد بينت دراسات حديثة أن نسبة كبيرة من شعوب العالم تستعمل الطب البديل في علاج الكثير من الأمراض المستعصية و من المعروف أن إنتاج الأدوية من مصادر طبيعية أصعب من مثيلاتها المصنعة لكن رغم هذا فان الكثير من الهيئات العالمية تشجع إنشاء أقسام الأدوية الطبيعية.و قد اعتمدت منظمة الصحة العالمية في برامجها العلاجية ضرورة الاهتمام بالعلاج التقليدي الذي يعتمد أساسا على النباتات الطبية المتداولة في الطب الشعبي أين تساهم العلوم الحديثة في تقنينها و اكتشاف مركبات جديدة تسمح بإنتاج أدوية نافعة.

و لكون الطب الشعبي في الجزائر لا يزال يحضى بالاهتمام و الممارسة و لأن مجال الدراسة في الجزائر لا يزال بكرا فاننا ارتأينا أن نغوص في هذه الدراسة البحثية المتعلقة بنباتين من النباتات الصحراوية .

و قد تمكنا من استخراج بعض المركبات الجديدة من نبات المسمى اللبينة ***Euphorbia guyoniana***.

كما فصلنا مركبات معروفة لكن تستخرج لأول مرة من النبات المسمى العضيض ***Launaea resedifolia***

أما في المرحلة الثانية من البحث فقد قمنا بدراسة الفاعلية لبعض البيتونولايدات و ذلك باستعمال تفاعل الإضافة 1,6 عن طريق المفاعلات العضوية النحاسية و تمكنا من خلالها من الحصول على مجموعة من المركبات الجديدة التي تحتاج إلى مواصلة البحث مستقبلا بإضافة مفاعلات أخرى و اختبارها بيولوجيا.

Résumé

L'utilisation des herbes dans la médecine est devenue de plus en plus populaire ces dernières années. Une étude récente a démontré qu'environ 34% de la population mondiale a employé des plantes comme remèdes au moins une fois par an.

A la lumière de l'intérêt croissant envers la médicine traditionnelle, l'étude chimique des plantes médicinales devient principalement importante. Les extraits de herbes normalisés sont considérés comme plus scientifiques que les drogues brutes. Notre objective par la présente étude est de participer à l'évaluation de notre patrimoine botanique qui demeure jusqu'à maintenant peu exploré.

La première partie de cette thèse concerne une étude chimique de deux plantes médicinales principales : *Euphorbia guyoniana* et *Launaea resedifolia.*

Pour *l'E. guyoniana*, l'étude des terpènes a été principalement visée par l'extraction, la purification et l'identification menant à deux nouveaux diterpenes de type jatrophane (guyonianin A et B) et vomifoliol dont les squelettes ont été identifiés par une série de données spectrales comprenant la spectroscopie de masse, le RMN 1D et le 2D.

En ce qui concerne *Launaea resedifolia*, les coumarines ont été étudiés et les résultats ont indiqué la présence de quatre coumarins, à savoir cichoriin, esculetin, scopoletin et isoscopoletin, extraits pour la première fois à partir du cette espèce.

La deuxième partie de cette thèse concerne l'étude de la réactivité de quelques alkylidene butenolides en effectuant l'addition 1.6 des organocuprates. Les butenolides et leurs analogues représentent une famille chimique d'importance médicale et biologique. L'étude a décelé une série de nouveaux produits qui pourront être sujets à d'autres types de réactions aussi bien à des tests biologiques.