SYNTHESIS AND CHARACTERIZATION OF 2-ARYLIDENE-4-ARYL-BUT-3-EN-4-OLIDES

Islamabad

A Dissertation submitted to the Department of Chemistry, Quaid-i-Azam University, Islamabad, in partial fulfillment of the requirements for the degree of

Master of Philosophy

in

Organic Chemistry

by

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Islamabad
2007

CERTIFICATE

This is to certify that this dissertation titled " Synthesis and characterization of 2-Arylidene-4-aryl-but-3-en-4-olides" submitted by **Sajid Ali** is accepted in its present form by the Department of Chemistry, Quaid-i-Azam University, Islamabad, as satisfying the dissertation requirement for the degree of **Master of Philosophy** in **Organic Chemistry**.

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بسم الله الرحمن الرحيم
In the Name of Allah,
the Beneficent, the Merciful.

Dedicated To

My Parents

Who make me to pursue my dreams

Allah will exalt those who believe among you and those who have knowledge to high ranks.

(The Holy Quran)

CONTENTS

Spectra

ACKNOWLEDGEMENTS

All praises be to **Allah Almighty** who bestowed us with the heart to feel and brain to think; so that we know, what we don't. Indeed He is the Best Knower, the Wisest. Peace and blessings of Allah be upon His dearest **Holy Prophet (PBUH)** who is a real role model for the mankind.

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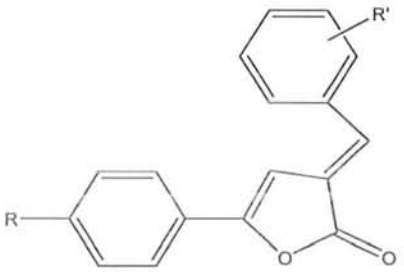
Sahibzada Sajid Ali

Butenolides and their derivatives are known to possess a wide range of biological activities. In the present work two series of butenolides were synthesized pertaining to 26 compounds in total. These consist of seventeen compounds of A-series ie 2-arylidene-4-(4-ethoxy phenyl)but-3-en-4-olides and nine compounds of B-series ie 2-arylidene-4-(4-bromo phenyl)but-3-en-4-olides. These compounds were synthesized by condensing 3-(4-substituted benzoyl)propionic acid with appropriate aromatic aldehydes in the presence of triethyl amine in acetic anhydride. These compounds were purified by using recrystallization and were characterized completely on the basis of their physical and spectral data (IR, ^{1}H, ^{13}C NMR, Mass) as well as elemental analysis results. The general structure of the synthesized compounds and their names are as follows:



A-Series 2-Arylidene-4-(4-ethoxy phenyl)but-3-en-4-olides

B-Series 2-Arylidene-4-(4-bromo phenyl)but-3-en-4-olides

A-Series:

BO2C 2-(2-Chlorobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide

BO4C 2-(4-Chlorobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide

BO3B 2-(3-Bromobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide

BO4B 2-(4-Bromobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide

BO2F 2-(2-Florobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide

BO3F 2-(3-Florobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide

BO4F 2-(4-Florobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide

BO2M	2-(2-Methoxybenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide
BO3M	2-(3-Methoxybenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide
BO4E	2-(4-Ethoxybenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide
BO2H	2-(2-Hydroxybenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide
BO3H	2-(3-Hydroxybenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide
BO4H	2-(4-Hydroxybenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide
BO2N	2-(2-Nitrobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide
BO3N	2-(3-Nitrobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide
BO4N	2-(4-Nitrobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide
BO4T	2-(4-Methylbenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide

B-Series:

BBO2C	2-(2-Chlorobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide
BBO4C	2-(4-Chlorobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide
BBO3B	2-(3-Bromobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide
BBO4F	2-(4-Florobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide
BBO3M	2-(3-Methoxybenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide
BBO2H	2-(2-Hydroxybenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide
BBO3N	2-(3-Nitrobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide
BBO4N	2-(4-Nitrobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide
BBO4T	2-(4-Methylbenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide

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CHAPTER #1

INTRODUCTION

Chapter - 1

INTRODUCTION

Organic synthesis has a long history that can be traced back to ancient times, although it was not recognized as such, due to lack of scientific knowledge. As a science, arguably the synthesis of urea by Wöhler in the year 1828 is the beginning of organic synthesis. This synthesis was followed by other milestones such as synthesis of acetic acid (Kolbe, 1885), glucose (Fisher, 1890), α-terpineols (Perkin, 1904), camphor (Komppa, 1903), torpinone (Robinson, 1917), quinine (Woodward, 1944), and many other natural products (K.C. Nicolaou et al. 2000).[1] Today, organic synthesis can be broadly divided into two main parts: target oriented (total synthesis) and method oriented. The target oriented molecule can be a natural product or a designed molecule.

The organic chemist is free to imagine and design unlimited numbers of new molecules never seen before either in nature or in the laboratory. This molecular design process is often guided by the particular interests of the chemist and can be aided by molecular modeling studies. These designed molecules can be of theoretical, physical, material science or biological interest. Undoubtedly, the most fertile area of molecular design for the organic chemist is that of biologically interesting molecules. Frequently the designed molecule are based on the structures of bioactive natural products (natural product analogue) or a completely imagined molecule targeted towards a specific biological action. Today molecular design, chemical synthesis and the biological evaluation is a powerful multidisciplinary approach to drug discovery and development. For this reason it has been a great challenge for a synthetic chemist to synthesize analogues of natural products.

From the last twenty years there has been a lot of work directed towards the heterocyclic groups as special substituents in biologically active molecules. Natural and synthetic compounds bearing heterocyclic functionality are endowed with large spectrum of biological properties ranging from enzyme inhibitions to insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor and antiviral activities (J. Salaun et al. 1995).[2]

Organic synthesis is the preparation of the desired compound from readily available materials. Synthesis is one of the major areas of organic chemistry. A synthesis

may be a simple one-step reaction, or it may involve many steps and incorporate a subtle strategy for assembling the correct carbon skeleton with all the functional groups in the right positions.

The organic synthesis involves the development of new synthetic methodology and asymmetric processes and their application to the synthesis of natural products, enzyme inhibitors and related compounds of biological, pharmaceutical, polymers and agrochemical research interest.

1.1 Butenolides

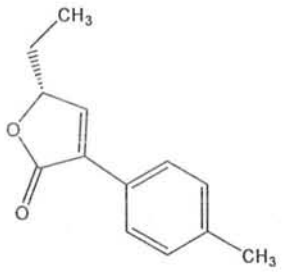
Butenolides consist of unsaturated γ-lactone rings which are also known as 2, 3 and 2, 5-dihydrofuran-2-ones. They have natural as well as synthetic source and are known to possess interesting biological activities. They are valuable synthetic intermediates and key structural subunits of a variety of natural products. They are typical products of a polyketide biochemical synthesis pathway.

1.2 Significance of Butenolides

Butenolides and their derivatives are known to possess interesting biological properties which include anti-inflammatory, analgesic, antimicrobial, antitumor, cardiotonic, anticonvulsant etc (A. Husain et al. 2005).[3]

The butenolide system as present in many cardiac glycosides shows strong oral cardiotonic activity. Physiological activity of the natural lactones is ever known since santonin was used as an important anthelmintic and ascaricidal agent (A. Husain et al. 2005).[4]

Molecules possessing the 2(5H)-furanone moiety, a frequently found substructure in natural products and biologically active compounds, have received considerable attention in the contexts of plant protection, anti-fungal, antibacterial, and anti-inflammatory agents. Especially interesting in this regard are incrustoporin (1) and rofecoxib (2) (Vioxx^{R}), which exhibit potent fungicidal and selective COX-II inhibitory activity, respectively (Y.S. Song et al. 2006).[5]



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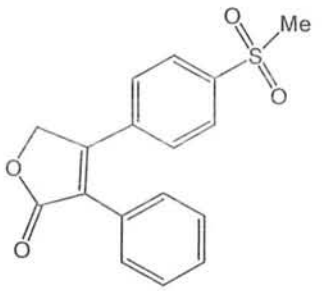
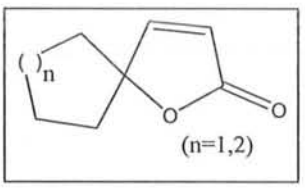


(2)

Among the plethora of heterocyclic subunits present in biologically active natural or synthetic products, spirobutenolides occupy a central position. In addition, the unusually high number of molecules displaying useful biological activities and embodying the basic structure of (a) further illustrates the unique properties of this class of compounds. Representative examples including manmade molecules, such as the remarkably active acaricides and insecticides spiromesifen **(3)**, spirodiclofen **(4)** and the spirocyclic neuropeptide Y antagonist and naturally occurring substances, such as spirofragilide **(5)** or the recently isolated lambertellol A **(6)**, are shown below (N. Malulide et al. 2006).[6]



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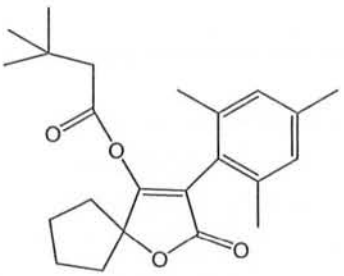

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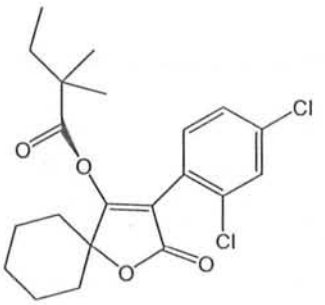

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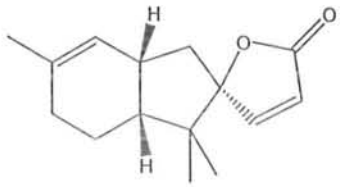

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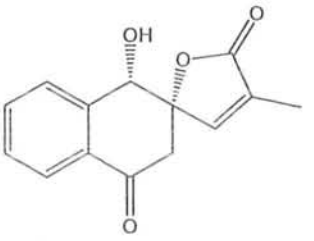
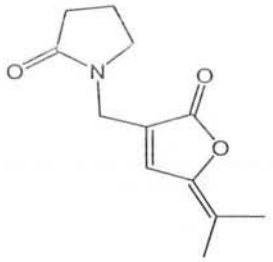


(6)

Uncinine (7) is a novel butenolide alkaloid, isolated from *Artabotrys uncinatus*, a plant used as a traditional folk medicine in Taiwan in the treatment of nasopharyngeal carcinoma. Its structural features, namely the combination of the γ-alkylidene butenolide and pyrrolidinone fragments, promise potentially interesting biological activity. Firstly, the presence of the pyrrolidin-2-one moiety is a characteristic of piracetam-derived cognitive enhancers and, secondly, γ-alkylidene butenolides themselves display a wide array of biological activities. The most simple compound of this class, protoanemonin (8), possesses antimicrobial and antifungal activities. In an in vitro assay, uncinine displayed potentially promising cytotoxicity against the Hep G_2 cell line (H. Fakova et al. 2005).[7]



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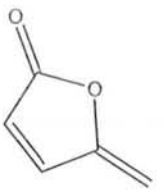
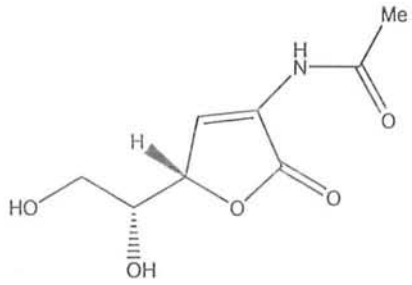


(8)

Isotetronic acids and butenolides are of great pharmacological relevance and occur in a number of natural products: for example, (+)-leptosphaerin **(9)** represents a metabolite of the marine ascomycete *Leptoshaeria oraemaris* and compound WF-3681 **(10)** represents an aldose reductase inhibitor produced by *Chaetomella raphigera* (R. Dede et al. 2005).[8]



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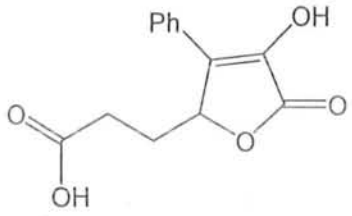
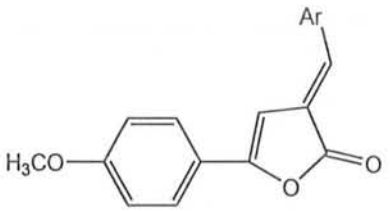


(10)

There are a number of biologically active γ-alkylidene butenolides for example asparagamine A is an alkaloid from *Asparagus racemosus*, which reveals potent antioxytocin activity, and lissoclinolide from *Lissoclinum patella* exihibits activity against the Gram-negative bacterium *Escherichia coli*. Recently the total synthesis of xerulinic acid, an intensely yellow pigment from the fungus *Xerula melanotricha*, that suppresses the biosynthesis of cholesterol through inhibition of HMG-CoA was repoted. Synthesis of halogenated γ-alkylidene-butenolide based natural product analogues with quorum sensing antagonist activities has also been explored (J. Zhang et al 2005).[9]

A. Husain et al. 2005, have reported the antibacterial and anti-inflammatory activities of 2-arylidene-4-(4-methoxy phenyl) but-3-en-4-olides **(11)** [3] and antimicrobial and anti-inflammatory activities of 2-arylidene-4-(4-phenoxy phenyl) but-3-en-4-olides **(12)**.[4]



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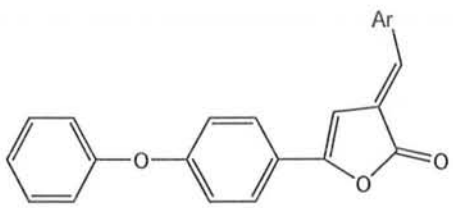
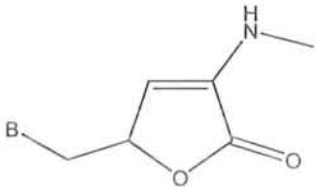


(12)

The biological importance of unsaturated lactones ie butenolides is well known: they have been used to prepare peptide analogues or HIV-1 protease inhibitors; protoanemonin **(8)**, its analogues and its derivatives **(13a-c)** possess antiviral, antibiotic and anticancer acivity, as well as 4-(1-alkynyl)-substituted 2-(5H)-furanones (U. Chiacchio et al. 2004).[10]

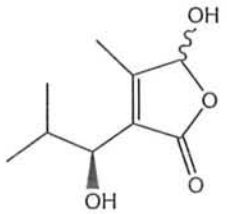
(8)



	B
a	Thymine
b	N-acetylcytosine
c	5-florouracil

(13a-c)

The reinvestigation of the strain *Streptomyces antibioticus* TU 99 using HPLC with photoconductivity detection, led to the discovery of four new metabolites, the substituted butenolides **(14-17)**. These butenolides showed in preliminary tests an antibiotic activity against *pseudomonas* as well weak inhibition of the chitinase from *Serratia marcescens* (G. Grossmann et al. 2003).[11]



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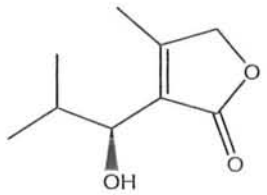

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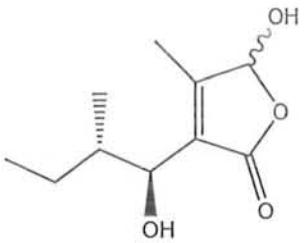

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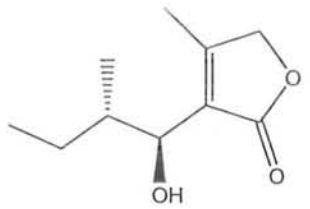
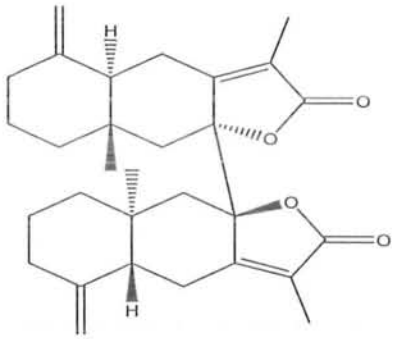


(17)

Biatractylolide **(18)** and biepiasterolide **(19)** both containing butenolide moieties are novel bisesquiterpenoids recently isolated from the Chinese medical plant *Atractylodes macrocephala*. Biologically, biatractylolide has shown powerful negative inotropic and chronotropic effects, making it a potential blood pressure lowering agent (S.K. Bagal et al. 2003).[12]



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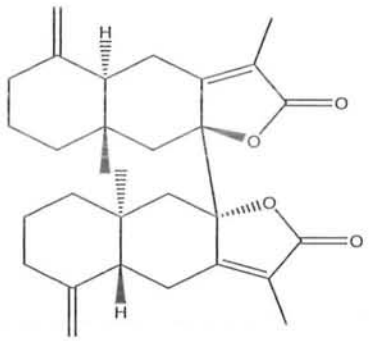
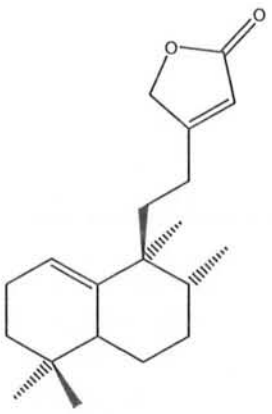


(19)

Annonaceae plants are a rich source of bioactive substances such as acetogenins. The occurrence of the natural diterpenes possessing hydroxy butenolides units has been reported frequently in plants of the genera *Polyalthia*, *Acritopappus*, *Premna* and *Cyathocalux* (Annonaceae).It is interesting to note that many species of these genera are widely used in folk medicine, and that some natural diterpene hydroxyl butenolides show significant biological activity such as antifeedant, antimicrobial, and cytotoxic activities. In 1955, Hara and Co-workers reported the isolation of a great number of clerodanes and ent-halimanes from *polyalthia langifolia*, among them the first three natural ent-halimanolides known until now are **(20)**, **(21)**, and **(22)**. These compounds are the first ent-halimane diterpenes which have been isolated from Annonaceae plants (I.S. Marcos et al. 2003).[13]



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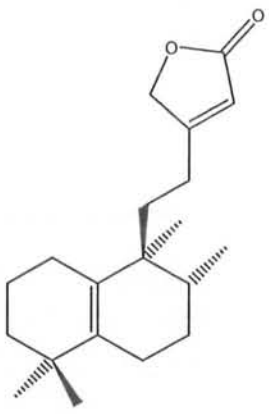

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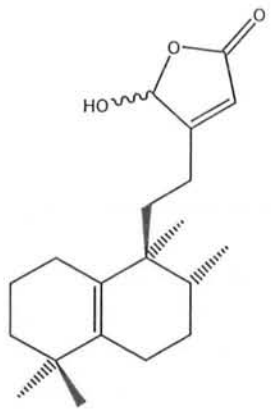
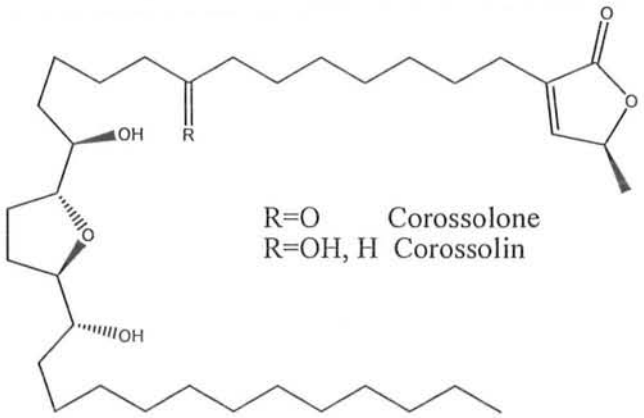


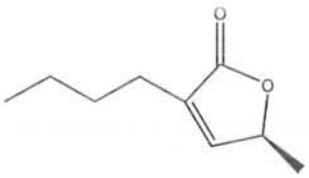
(22)

Annonaceous acetogenins are the most famous representative member of butenolides family. Usually the butenolide segment of annocaceous acetogenins is a typical 3-substituted -5-(S)-methyl-2-(5H)-furanone, which is now believed to be one of the essential subunits for the cytotoxicity of these acetogenins (**23**) (corossolone and corossolin are examples). Other known butenolides also have interesting properties, for example (**24**) is a metabolite from *Streptomyses griseas*, and (**25**) and (**26**) were recently isolated from leaves of *Hortonia* (family Monimiaceae). Both butenolides (**25**) and (**26**) exhibited mosquito larvicidal activity (Y.T. He et al. 2002).[14]

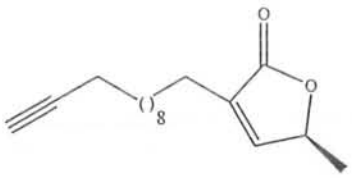


R=O Corossolone
R=OH, H Corossolin

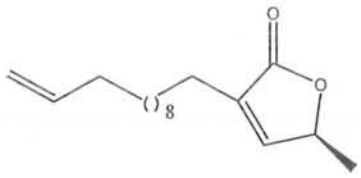
(**23**)



(**24**)

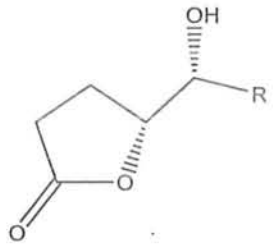


(**25**)



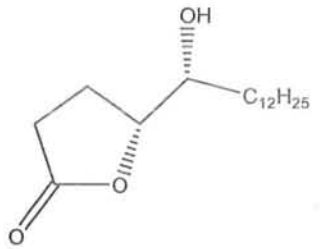
(**26**)

Chiral hydroxyl lactones occupy an important position as bio-active molecules and useful synthetic intermediates in total synthesis. One such group of hydroxyl lactones comprises the 5-hydroxyalkyl butan-4-olides (**27**). These are widely found in nature and show diverse biological properties. One example is (-)muricatacin (**28**). It was isolated from the seeds of *Annona muricata* L.(annonaceae) commonly known as sour soap or guanabana and is grown commercially as a fruit crop through out the tropical regions of the world. Muricatacin was shown to be cytotoxic towards human tumor cells (M. Chandrasekhar et al. 2002).[15]



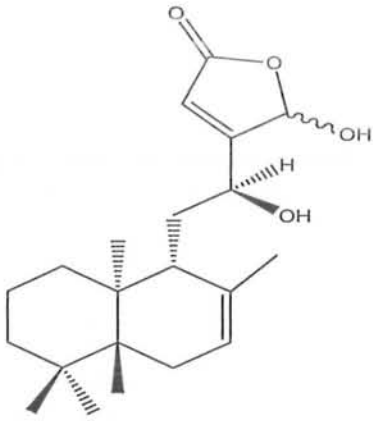
R = CH_3, C_4H_9, C_5H_{11} etc

(27)



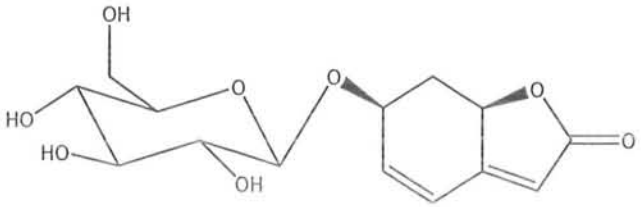
(28)

Labdane diterpenoids are among the most common types of diterpenes isolated from higher plants. The interest of this class of compounds (containing butenolide moiety) resides in their significant antimutagenic, antibacterial, and antifungal activities. As an example (12S,16E)-12,16-dihydroxy-ent-labda-7,13-dien-15,16-olide **(29)** has been recently isolated from *Alomira myriadenia* (Asteraceae). This compound shows significant cytotoxic activity against human oral epidermoid carcinoma and against colon cancer (M.C. de la Torre et al. 2002).[16]

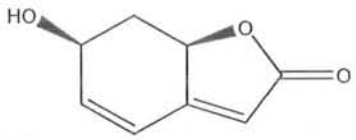


(29)

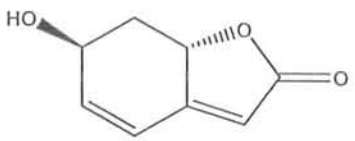
(-)-Phyllanthurinolactone **(30)**, the leaf closing factor of a large tamarind tree (*Tamarindus indica* L.), has its aglycone (-)-menisdaurilide **(31)**, which is one of several cyclohexanoids isolated form *Sinumenium acutum* containing a butenolides moiety; others include (-) aquilegiolide **(32)** and (-)-dihydromenisdaurilide **(33)** (M. Honzumi et al. 2002).[17]



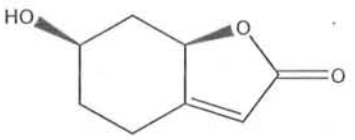
(30)



(31)

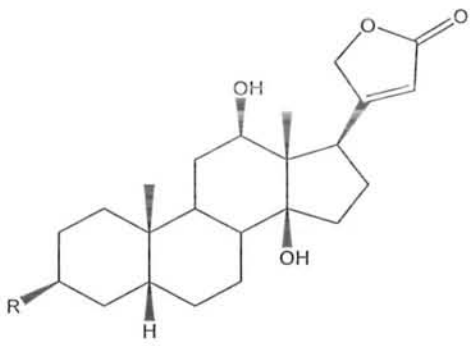


(32)

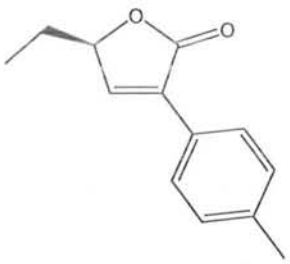


(33)

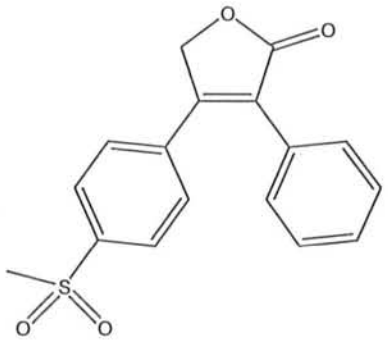
Butenolides also known as 2(5H)-furanones, are ubiquitious chemical moieties found in many natural products. They are typical products of a pokyketide biochmical synthesis pathway. Examples are the cardiotonic digitoxines **(34)** from *Digitaliz* sp. and the antifungal (-)-incrustoporine **(35)**. Rofecoxib **(36)** is a recently launched NSAID (Non Steroidal Anti-Inflammatory Drug) with a butenolide core structure and is efficacious in treating rheumatoid arthritis (B. Beck et al. 2001).[18]



(34)

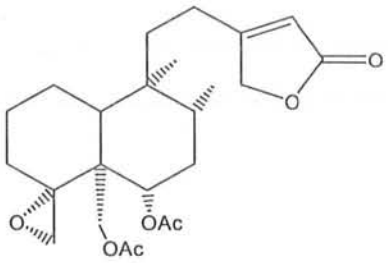


(35)

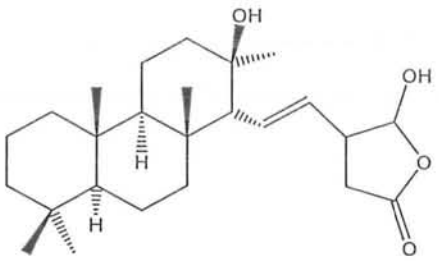


(36)

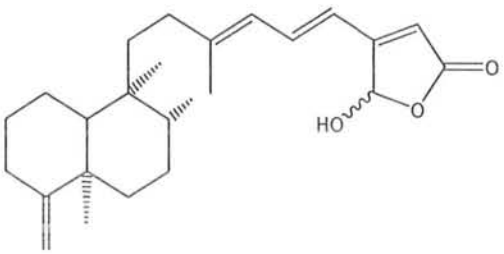
Strong biological activities have been reported for mono or polycyclic molecules, diterpenes or sesterterpenes, that possess a five-membered oxygenated ring with different functionalities. Ajugarin **(37)**, a neoclerodane with a butenolide, is an antifeedant, aplyolide **(38)** has anti-inflammatory activities, polauolide **(39)** (an unsaturated hemiacetal) has antimicrobial properties and dysidiolide **(40)** is the first naturally derived inhibitor of the cdc25A protein phophatase (I.S. Marcos et al. 2000).[19]



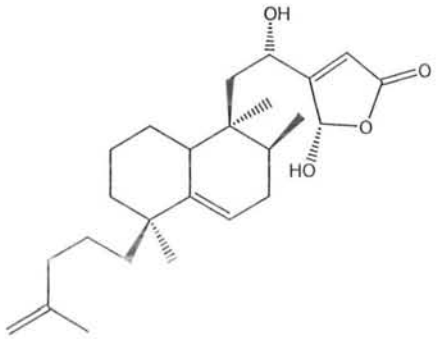
(37)



(38)

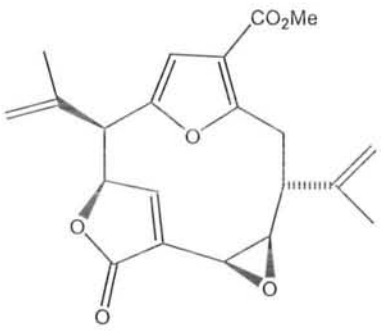


(39)

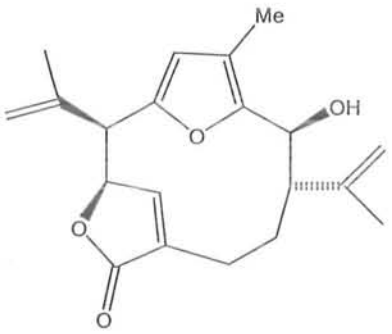


(40)

Octocorals of the genus *pseudopterogorgia* produce, among other metabolites, diterpenoids of the rare pseudopterane family. Several of these possess significant biological activity. Thus pseudopterolide **(41)**, the first member of the family exhibits potent cytotoxicity, and kallolide A **(42)**, is an anti-inflammatory agent with activity comparable to that of indomethacin (J.A. Marshall et al. 1998).[20]

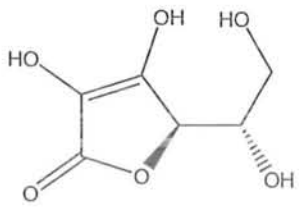


(41)

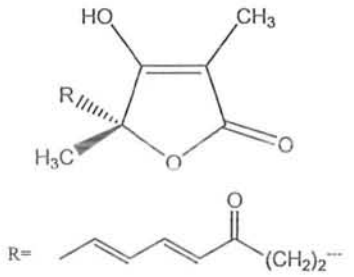


(42)

Tetronic acids comprise a subclass of β-hydroxy butenolides, perhaps the best known of which is Ascorbic acid **(43)** (Vitamin C). Many tertronic acids and their derivatives possess interesting biological properties like antibiotic, insecticidal, and herbicidal etc. Vertinolide **(44)** a new mycotoxin is a highly branched tetronic acid isolated from *Verticillium intertextum* (J.E. Wrobel et al. 1983).[21]

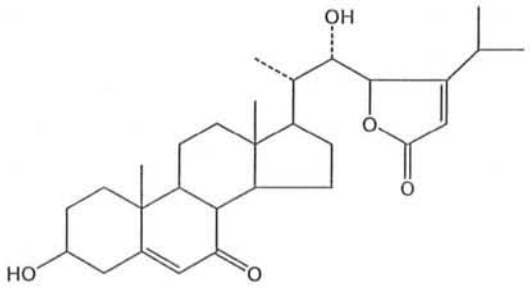


(43)



(44)

Antheridiol **(45)** is a hormonal substance which is secreted by female strains of the aquatic fungus, *Achlya* and which acts on male strains causing the formation of antheridial hyphae or male sex organs (T.C. McMorris et al. 1974).[22]



(45)

1.3 Aim of Research:

In view of the extensive literature survey, it was revealed that butenolides belong to a very important class of heterocyclic compounds that exhibit a vast variety of biological properties such as antibacterial, antifungal, anti-inflammatory, anticancer, anti HIV, cardiotonic, anticonvulsant, analgesic, acaricidal, insecticidal, and mosquito larvicidal activities etc. Furthermore, literature survey has also revealed that amongst the methods reported for the synthesis of butenolides, the method involving the condensation reaction of 3-(4-substituted benzoyl) propionic acid with benzaldehydes is probably the most convenient and high yielding. The present study is therefore devoted to the synthesis of butenolides from 3-(4-substituted benzoyl) propionic acid and variably substituted benzaldehydes. This study was carried out in the quest to synthesize butenolides, not synthesized earlier, that may have new and/or enhanced biological properties.

CHAPTER #2

SYNTHETIC METHODS

Chapter - 2
SYNTHETIC METHODS

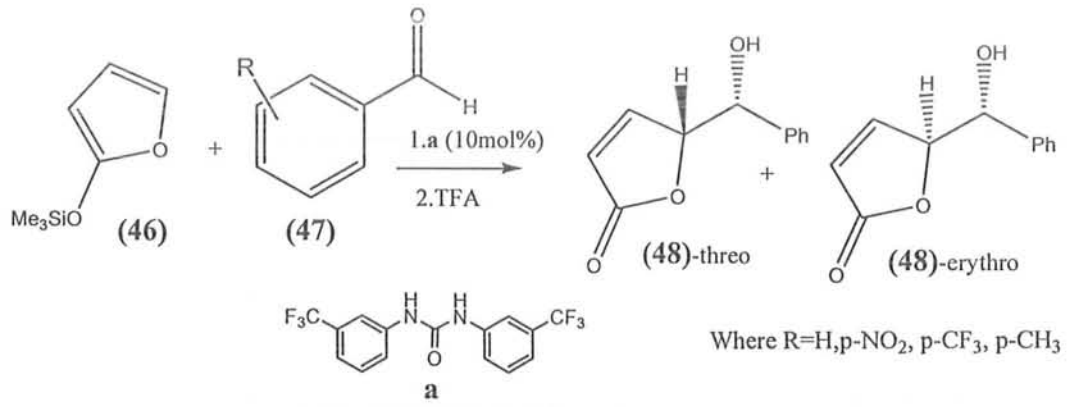
A number of synthetic methods are being developed and reported each year for the synthesis of butenolides.

2.1 Methods Used for the Synthesis of Butenolides

Following are different methods used for the synthesis of butenolides.

2.1.1 Organocatalytic addition of trimethyl siloxy furan to carbonyl compounds

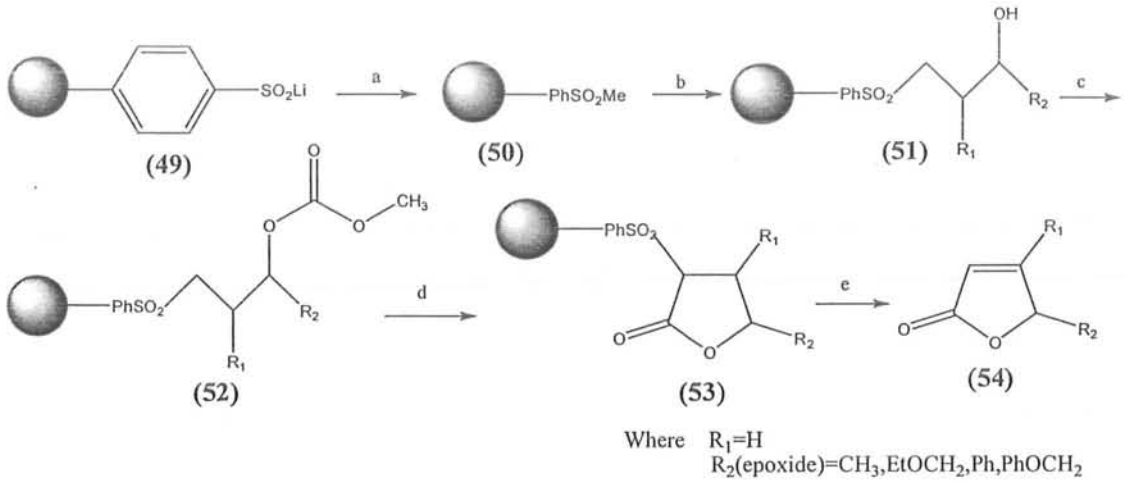
M.D. Rosa et al. 2006, [23] have reported a very attractive method for the synthesis of butenolides substituted at γ-positions by a chain bearing hydroxyl groups. In this 2-trimethyl siloyloxy fruan (TMSOF) **(46)** was reacted with different aromatic aldehydes in the presence of urea derivative **(a)** as catalyst at room temperature to give butenolide (48).



2.1.2 Solid phase synthesis of substituted butenolides

S.R. Sheng et al. 2006, [24] have reported sulfone linker strategy for convenient, traceless, solid phase synthesis of substituted butenolides. The procedure for the synthesis of target compounds from, polystyrene/1% divinyl benzene lithiophenylsulphinate **(49)** includes(a) sulphinate S-alkylation to give **(50)**, (b) the sulpehnyl anion alkylation with an epoxide giving **(51)**, (c) the acylation of the resulting γ-hydroxy sulphone giving **(52)**, (d) the intramolecular acylation cyclization of the α-

sulphonylcarbanion to give (53), and (e) traceless product release by desulphonation to give butenolides (54).

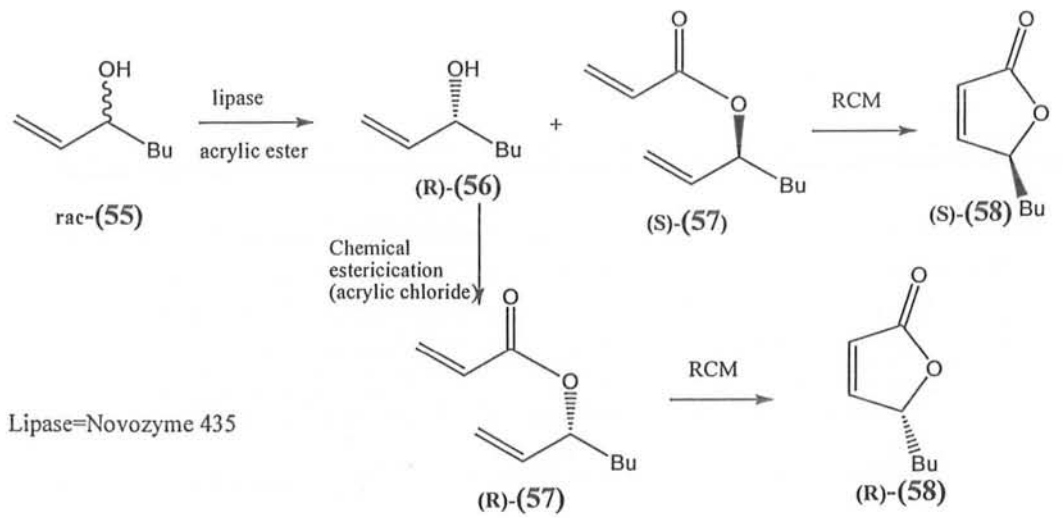


Where R_1=H
R_2(epoxide)=CH_3,$EtOCH_2$,Ph,$PhOCH_2$

Reagents and Conditions: (a) MeI, THF/DMF (2/1), 80 °C, 15 h (b) (i) $CH_3S(O)CH_2Li$, THF,rt, 0.5h (ii) epoxide, THF, rt, 2h (c) $ClCO_2CH_3$, pyridine, 0 °C, 1h (d) LDA,THF, -78 °C,1h, 0 °C, 2h, then rt, 1h (e) Et_3N, CH_2Cl_2, rt,10h(LDA=Lithium diisopropyl amide)

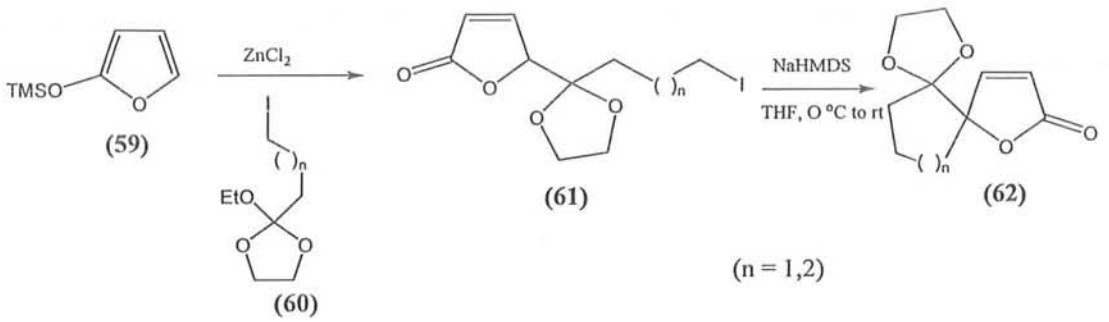
2.1.3 Chemoenzymatic synthesis of optically active γ-alkyl-γ-butenolide

M. Fujii et al. 2006, [25] have reported chemoenzymatic synthesis of optically active γ-alkyl-γ-butenolide. They reported a facile chemoenzymatic synthesis of (58) from commercially available racemic hept-1-en-3-ol (55) by the combination of lipase catalyzed transesterification and ring closing metathesis (RCM) by Grubbs'catalyst.



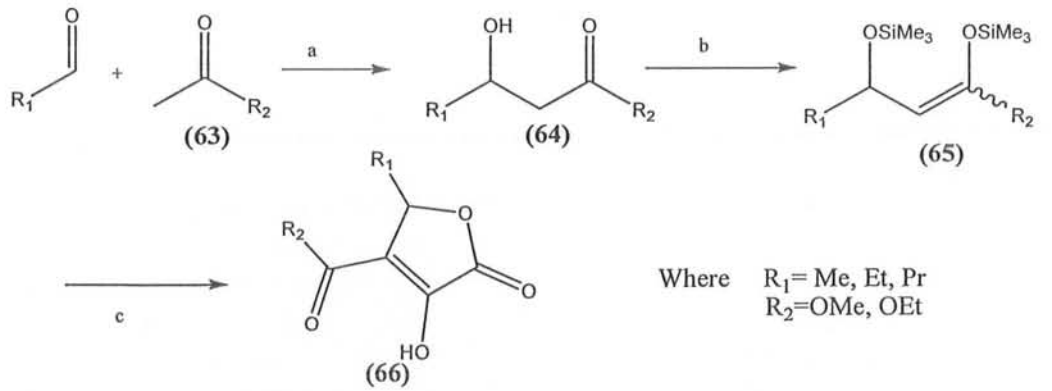
2.1.4 A two step synthesis of functionalized spirocylclic butenolides

N. Maulide and I.E. Marko, 2006, [6] have reported a very good method for the synthesis of spirocyclic butenolides as shown in the following scheme. In this scheme **(61)** is first produced in high yield through the $ZnCl_2$-promoted condensation of trimethyl silyl oxy furan **(59)** with ortho ester **(60)**, which upon treatment with base resulted in the formation of spirocylclic compounds **(62)**.



2.1.5 Synthesis of isotetronic acid by cyclization of 1,3-bis(trimethy-silyloxy)alk-1-enes with oxalyl chloride:

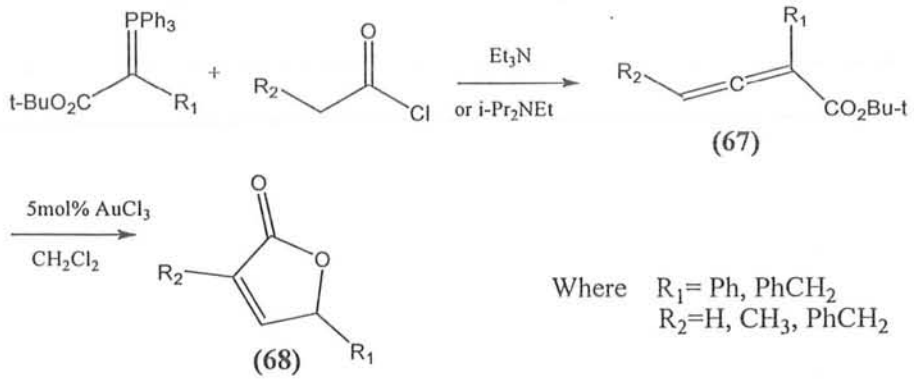
R. Dede et al. 2005, [8] have reported a convenient one pot synthesis of isotetronic acids **(66)** by cyclization of 1,3-bis(trimethylsilyloxy)alk-1-enes **(65)** with oxalyl chloride. The 1,3-bis(trimethyl siloxy)alk-1-enes **(65)** were prepared by generation of the dianions of the 3-hydroxy alkanoates **(64)** with trimetyhl chlorosilane, which are available by aldol reaction of ethyl and methyl acetate **(63)** with corresponding aldehydes.



Reagents and Conditions: (a) LDA, THF, 5 min, -78 °C (b) i) LDA, THF,1h, -78 °C, ii)Me_3SiCl, -78-20 °C, 24h (c) $(COCl)_2$,-78-20 °C, 18h.

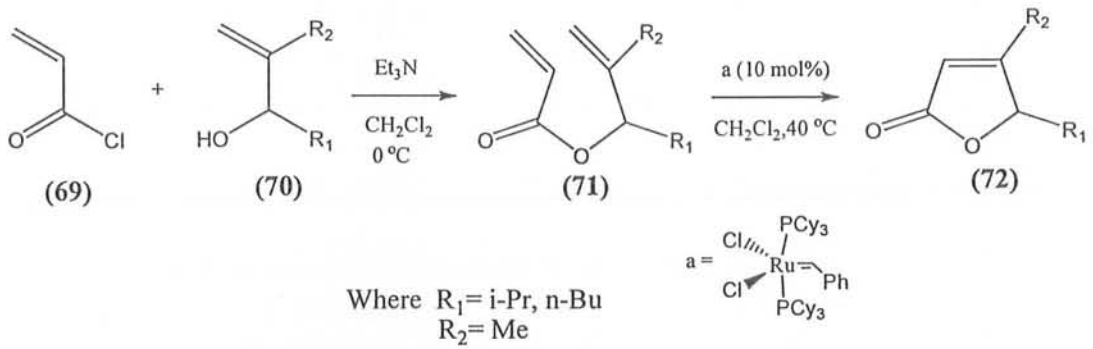
2.1.6 General synthesis of 2,4-functionalized butenolides

J.E. Kang et al. 2005, [26] have presented an attractive method for the synthesis of 2,4-disubstututed γ-butenlides. They have shown synthesis of 2,4 functionalized butenolides (68) by gold (III) catalyzed cyclization of tert-butyl allenoates (67) which can be obtained by wittig olefination of ketene i.e.



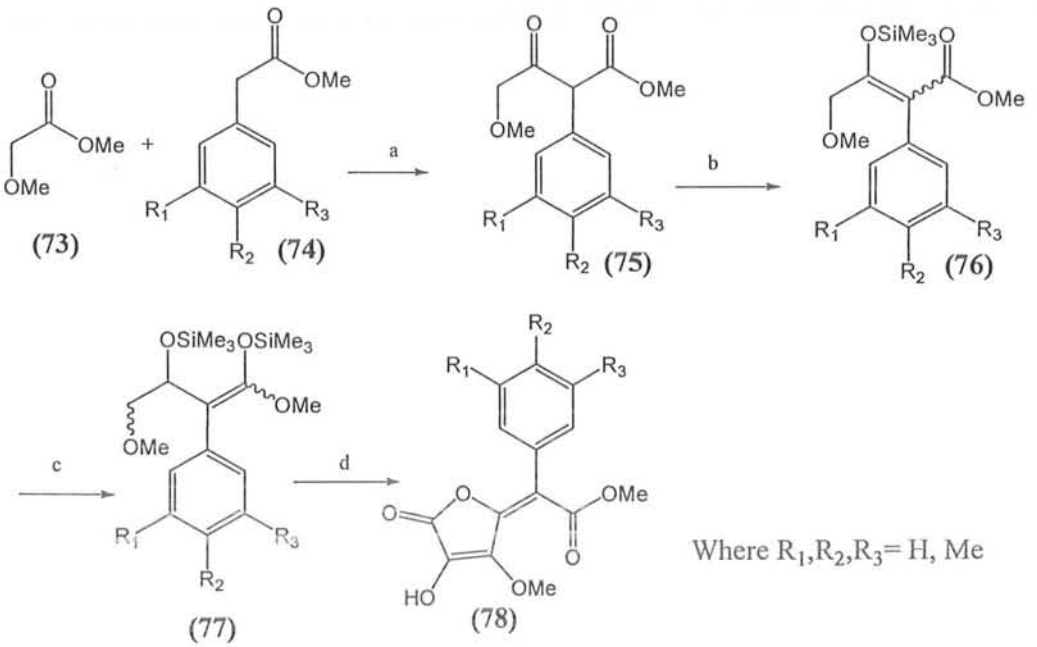
2.1.7 Synthesis of 4,5-disubstituted butenolides by ring closing metathesis

M. Bassetti et al. 2005, [27] have reported the synthesis of 4,5-disubstituted butenolides (71) by ring closure metathesis reaction (RCM) of methallyl acrylate esters (72) in the presence of commercially available first generation Grubb's catalyst (a). The starting methallyl acrylate esters have been prepared by the reaction of secondary allyl alcohol (70) with acryloyl chloride (69).



2.1.8 Synthesis of γ-alkylidene butenolides

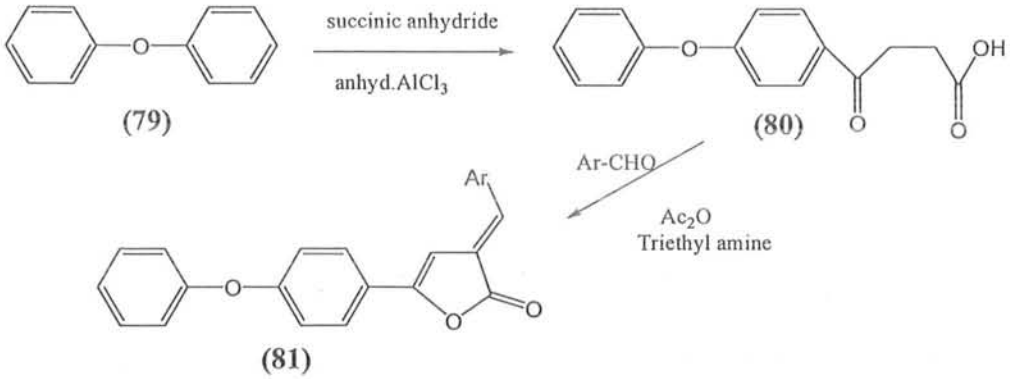
Z. Ahmad and P. Langer, 2005, [28] have reported synthesis of γ-alkylidene butenolides. This consists of the reaction of methyl methoxy acetate (73) with the arylacetic ester (74) affording formation of β-keto esters (75). The reaction of (75) with NEt_3/Me_3SiCl gave the silyl enol ethers (76) which were then transformed into 1,3-bissilylenol ethers (77). The TMSOTf catalyzed cyclization of (77) with oxalyl chloride afforded the γ-alkylidene butenolide (78).



Reagents and Conditions: (a) i) LDA, THF ii) -78-20 °C (b) Me_3SiCl,NEt_3, toluene, 20 °C (c) i)LDA, THF, -78 °C, ii)Me_3SiCl, -78-20 °C (d) oxalyl chloride, Me_3SiOTf, CH_2Cl_2,-78-20 °C

2.1.9 Synthesis of 2-Arylidene-4-(4-phenoxy phenyl) but-3-en-4-olides

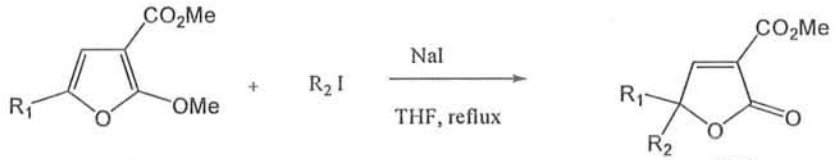
A. Husain et al. 2005, [4] have reported synthesis of 2-Arylidene-4-(4-phenoxy phenyl) but-3-en-4-olides. They first synthesized 3-(4-phenoxy benzoyl) propionic acid **(80)** by reaction of succinic anhydride with di-phenyl ether **(79)** in the presence of anhydrous $AlCl_3$ in dry nitrobenzene which was then condensed with different aromatic aldehydes in the presence of triethyl amine to give target butenolides **(81)**.



(79) (80) (81)

2.1.10 An efficient synthesis of butenolides

S. Ma et al. 2005, [29] have reported an efficient I⁻-catalyzed methyl-oxygen bond cleavage in 2-methoxy furans **(82)**. The subsequent C-C bond formation by reaction with organic halides occurred at the 5-position to afford substituted butenolide **(83)**.

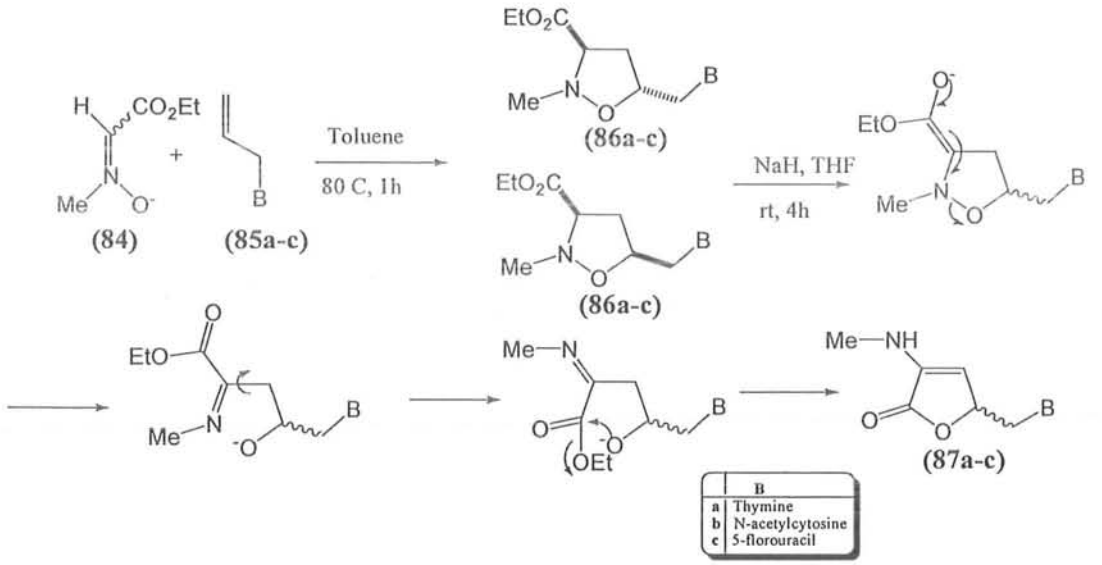


(82) (83)

Where R_1= Ph, C_4H_9, Bn
R_2= MeI, CH_2=CH-CH_2I

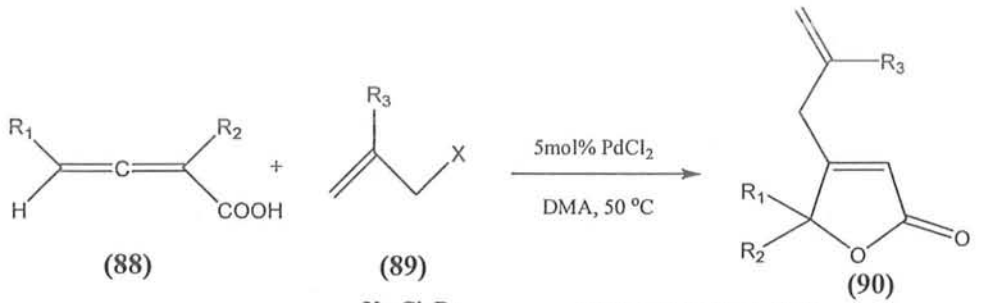
2.1.11 Synthesis of pyrimidine-containing 3-aminobutenlides

U. Chiacchio et al. 2004, [10] have recently reported a versatile entry to functionalized 2-(5H) furanones through a new rearrangement pattern of the isoxazolidine **(86a-c)**, easily accessible by 1,3-dipolar cycloaddition of nitrone **(84)** with suitable alkenes, here allyl nucleobases **(85a-c)**. The reaction consists of a basic treatment of isoxazolidine **(86a-c)** with NaH at room temperature to give lactones **(87a-c)**.



2.1.12 Pd-Catalyzed coupling cyclization of 2, 3 Allenoic acids with Allyl halides

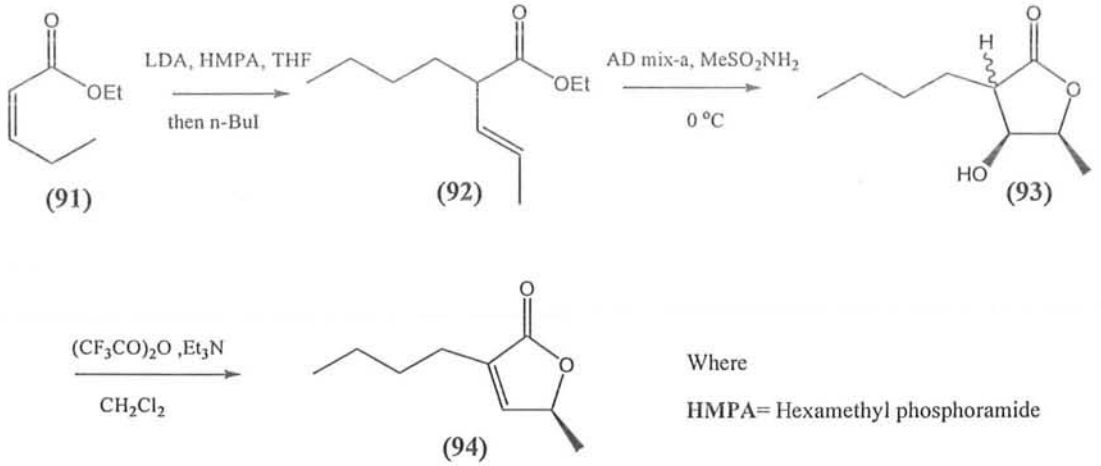
S. Ma and Z. Yu, 2003, [30] have successfully developed a two step protocol for the synthesis of the β-allylic-substituted butenolides. They prepared β-allylic-substituted butenolides **(90)** by the Pd (II)-catalyzed coupling cyclization of 2,3-allenoic acids **(88)** with allylic halides **(89)**.



2.1.13 Sharpless AD strategy towards the γ-methyl butenolide unit of Acetogenins

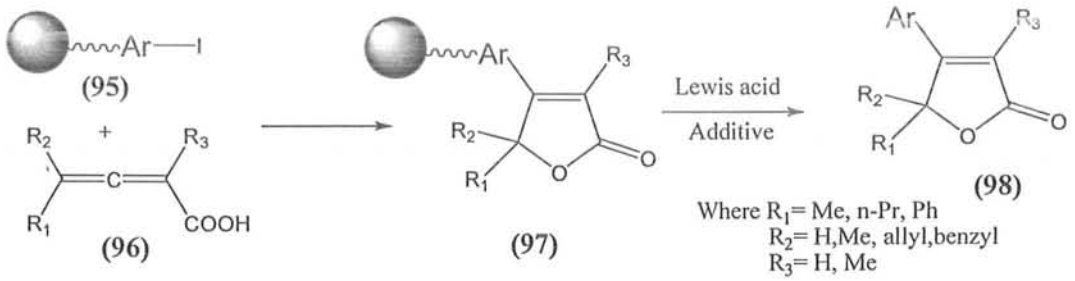
Y-Tao He et al. 2002, [14] have devised a strategy towards the synthesis of α-γ-di-substituted butenolides. As shown in the following scheme, cis-pent-2-enoic acid ethyl ester **(91)** was treated with LDA and then coupled to n-butyl iodide (n-BuI) at -70 to -40 °C for 6h to give only the 3-E-product **(92)** in good yield. Asymmetric dihydroxylation of the enyne **(92)** with AD-mix-α gave mixture of diasteriomers of β hydroxy lactone

(93), dehydration of which with trifloroacetic acid anhydride and triethyl amine afforded (94).



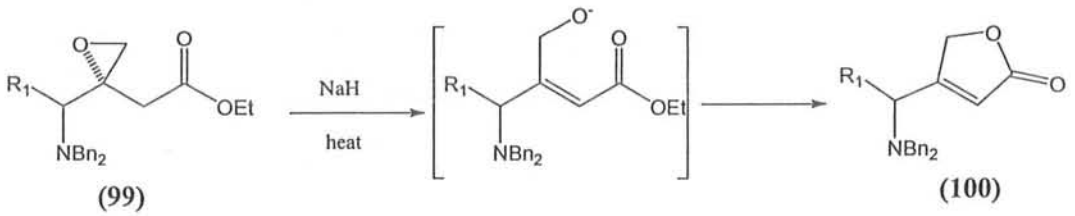
2.1.14 Solid phase parallel synthesis of butenolides

S. Ma et al. 2002, [31] devised strategies for the synthesis of combinatorial libraries of butenolides. They attached an organic halide to a polymeric chain to get (95), upon its treatment with an excess amount of 2,3-allenoic acids (96), the reaction afforded polymer supported butenolides (97) which were then detached giving butenolide (98).



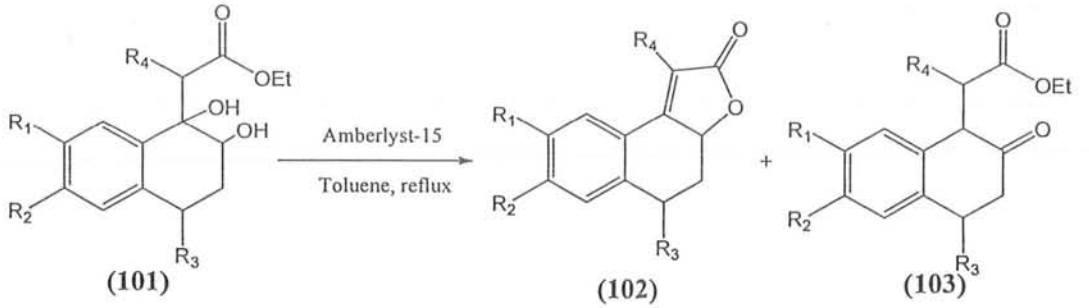
2.1.15 Synthesis of chiral amino γ-butenolides

J.M. Concellon et al. 2002, [32] have reported synthesis of chiral amino γ-butenolides. When epoxy ester (99) with out α-substituent were treated with a base such as NaH, α,β-unsaturated lactones (100) were produced in high yield.



2.1.16 Conversion of β,γ-dihydroxy esters into butenolides

S.P. Chavan and C.A. Govande, 2002, [33] have reported an efficient entry to butenolides synthesis via the corresponding diols **(101)** involving an intramolecular cyclization using solid catalyst Amberlyst-15. Use of excess catalyst/substrate ratio resulted in the formation of butenolide **(102)** in good yield.

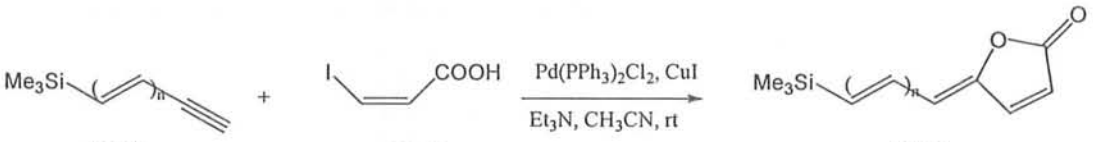


(101) **(102)** **(103)**

Where R_1= H , Me
R_2= H, OMe
R_3= H, Me
R_4= H, Me ,Et

2.1.17 An efficient stereoselective approach to silylated polyunsaturated γ-alkylidene butenolides

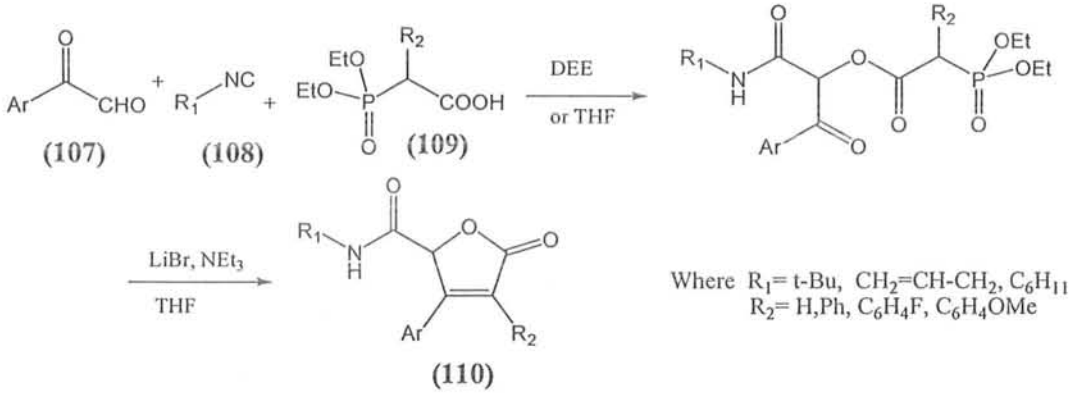
V. Fiandanese and Co-workers, 2001, [34] have reported this method. In this method the cross coupling reaction between enyne **(104)** and iodoacid **(105)** was performed at room temperature in the presence of Pd catalyst in acetonitrile as solvent leading directly to butenolides **(106)**.



(104) (n=1,2) **(105)** **(106)**

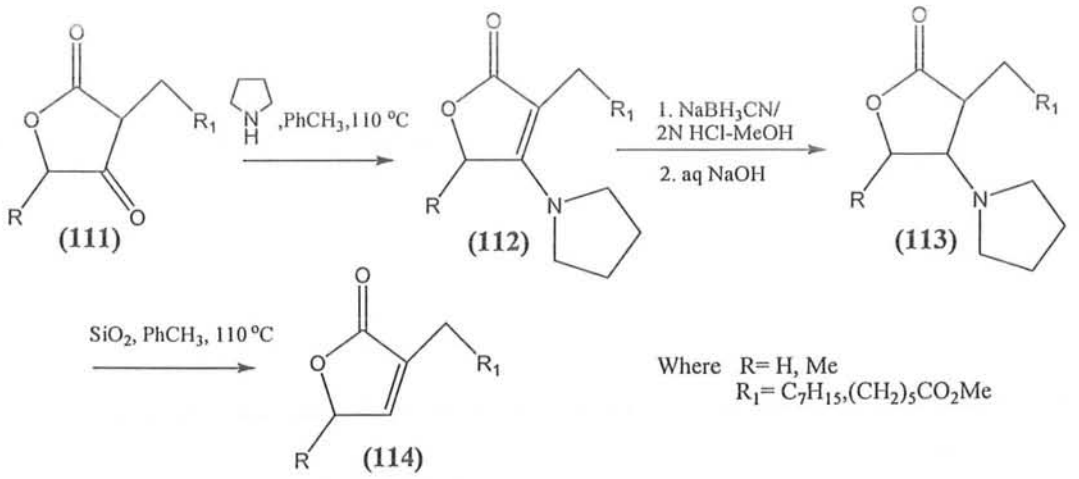
2.1.18 A Novel three component butenolide synthesis

B. Beck et al. 2001, [18] have reported a new multi component reaction (MCR) of aryl glycoxals **(107)**, isocyanides **(108)**, and α-substituted diethyl carboxylicmethan phosphonates **(109)** producing butenolides **(110)**. The total transformation is a combination of the Passerini three component reaction followed by intramolecular wittig type reaction.



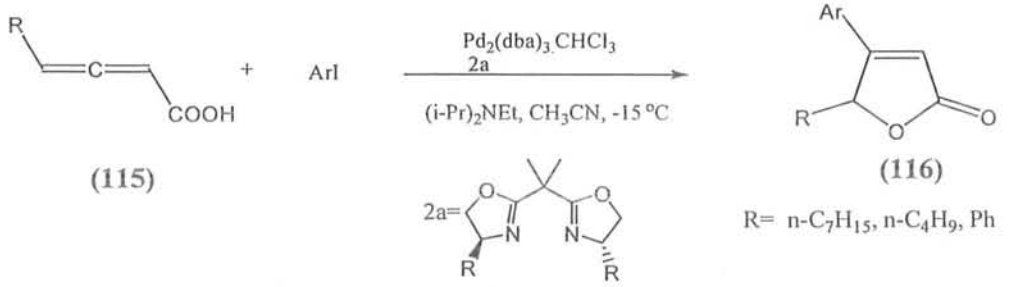
2.1.19 A new efficient synthesis of alkyl substituted Δ^2- butenolides

F.S. Pashkovsky et al. 2001, [35] have reported a new three step route to 2-alkyl substituted Δ^2- butenolides from the readily available 3-alkyl tetronic acids. Thus boiling of 3-alkyl tetronic acids **(111)** with pyrrolidine in toluene results in the formation of corresponding enaminolactones **(112)**. Reduction of the conjugated double bond in enaminolactones with sodium cyano borohydride in methonolic 2N HCl solution followed by treatment with NaOH give amino lactones **(113)** which on reflux in toluene in the presence of silica gel undergo a retro Micheal elimination of the pyrrolidine moiety to give Δ^2- butenolides **(114)**.



2.1.20 Enatioselective synthesis of β-aryl butenolides

S. Ma et al. 2001, [36] have reported enatioselecive synthesis of β-aryl butenolides **(116)** via palladium(0) catalyzed asymmetric coupling cyclization reaction of 2,3-allenoic acids **(115)** with aryl iodides.

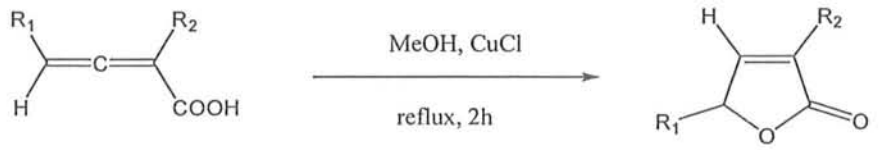


(115) (116)

R= n-C_7H_{15}, n-C_4H_9, Ph

2.1.21 A cost effective synthesis of β-unsubstituted butenolides

S. Ma et al. 2001, [37] have reported CuCl-catalyzed cycloisomerization reaction of 2,3 allenoic acids **(117)** to β-unsubstituted butenolides **(118)**. i.e.

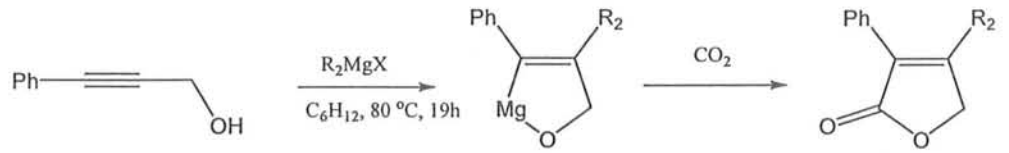


(117) **(118)**

Where R_1= Ph, napthyl, C_3H_7
R_2= CH_3, n-C_3H_7, $PhCH_2$

2.1.22 Direct synthetic route to furanones

P. Forgione, et al. 2000, [38] have devised direct synthetic route to furanones. In this the butenolide was synthesized by Mg mediated carbomettalation of propargyl alcohol **(119)** with phenyl magnesium chloride to form the chelate **(120)** followed by exposure to CO_2 giving butenolide **(121)**.

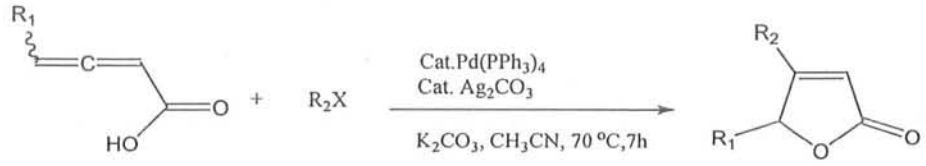


(119) **(120)** **(121)**

Where R_2= Ph

2.1.23 An efficient synthesis of butenolides

S. Ma and Z. Shi, 1998, [39] have reported a very efficient method for the synthesis of butenolides. In this method they synthesized butenolides **(123)** by Pd (0) /Ag+-cocatalyzed cyclization of 1,2-Allenoic carboxylic acids **(122)** with Aryl halides.

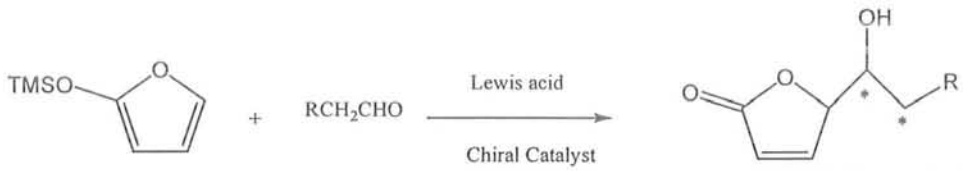


(122) **(123)**

Where R_1= n-C_4H_9, nC_7H_{15}
R_2= Ph, C_6H_4I,C_6H_4Br

2.1.24 Highly enatioselective 1,2 addition of 2-(trimethylsiloyloxy) furan to aldehydes

M. Szlosek et al. 1998, [40] reported the first enatioselective addition of trimethyl siloxy furan **(124)** on chiral aldehydes to form the expected butenolides **(125)** in highly enatiomerically pure form.



(124)

(125)

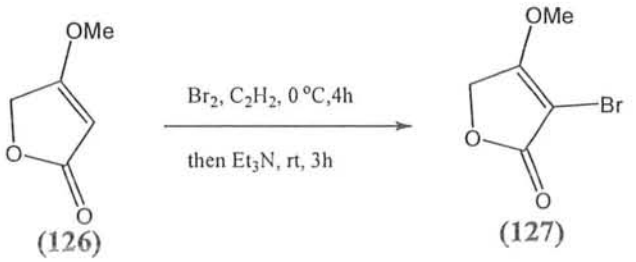
R= C_5H_{11}, $C_{11}H_{23}$
Lewis acid= $TiCl_4$, $SnCl_4$

2.2 Reactions of Butenolides

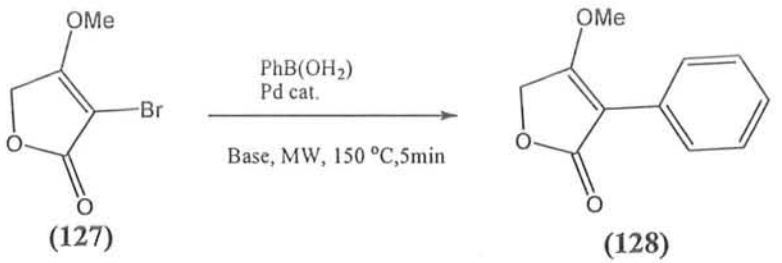
Numerous reactions of butenolides have been reported in literature. Some of the important reactions of butenolides are shown below.

2.2.1 Suzuki-Miyaura reactions of 3-brome-4-methoxy-2-(5H) furanones with aryl boronic acids

Y.S. Song et al. 2006, [5] have reported Suzuki-Miyaura reaction of 3-brome-4-methoxy-2-(5H) furanones **(127)** with aryl boronic acids under microwave irradiation conditions which serves as a general and highly efficient method for the synthesis of 3-aryl-4-methoxy-2-(5H)-furanones **(128)**. The starting 3-bromo-4-methoxy-2-(5H)-furanones **(127)** was prepared via sequential bromination and base mediated elimination reactions of commercially available 4-methoxy-2-(5H)furanones **(126)**.



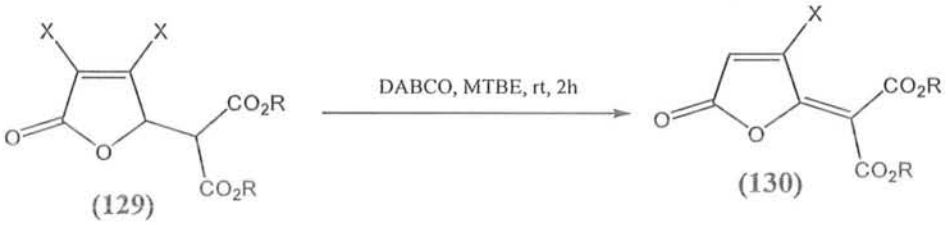
(126) (127)



(127) (128)

2.2.2 Conversion of mucohalic acid to γ-Alkylidene butenolides

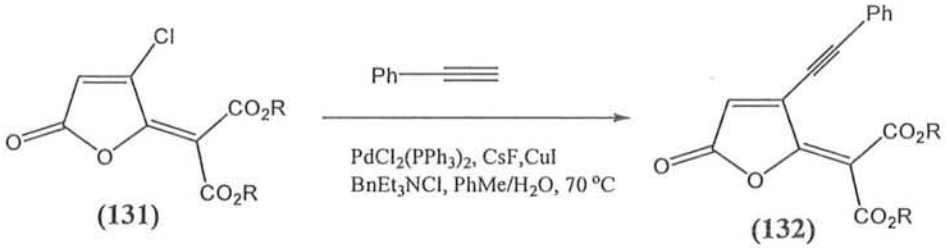
J. Zhang et al. 2005, [9] have reported formation of a series of β-halo-γ-alkylidene butenolides **(130)** by the reaction of **(129)** with base, DABCO (1,4-diazabicyclo octane) in tert. methyl butyl ether (MTBE).



(129) (130)

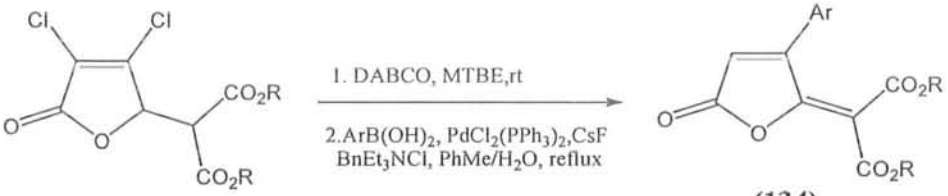
Where X= Cl, Br
R= Me, Et, i-Pr, Bn

These novel β-halo-γ-alkylidene butenolides **(131)** turned out to be useful building blocks for Pd catalyzed C-C bond formation reactions.



(131) **(132)**

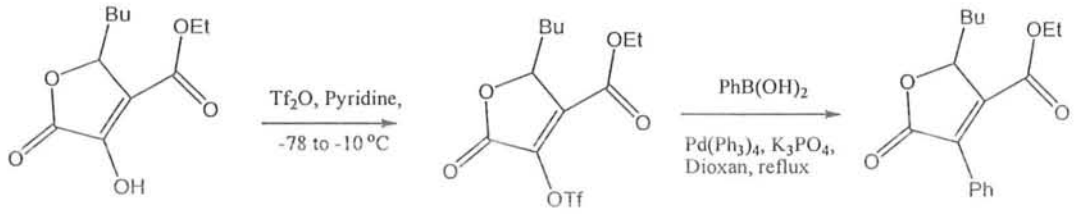
Similarly Suzuki coupling with an aryl boronic acid worked with out using any ligand or harsh conditions.



(133) **(134)**

2.2.3 Conversion of isotetronic acid into butenolide

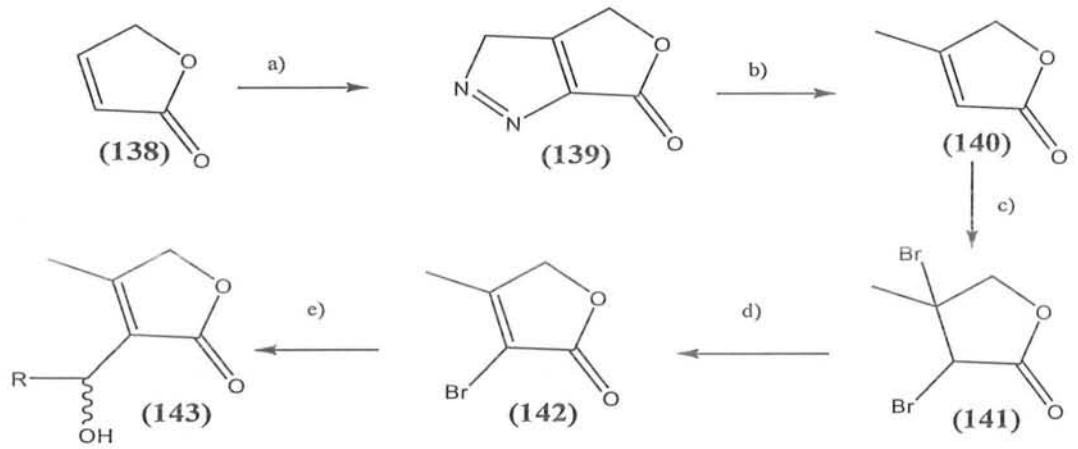
R. Dede et al. 2005, [8] have reported this reaction. In this reaction the hydroxyl group of isotetronic acid was successfully functionalized by transition metal catalyzed cross coupling reaction. For example **(135)** was transformed into enol triflate **(136)**. The Suzuki reaction of **(136)** with phenyl boronic acid afforded **(137)**.



(135) (136) (137)

2.2.4 Conversion of furanone into various derivatives

G.Grossmann et al. 2003, [11] have reported conversions of furanones into variours derivatives. Cycloaddition of diazomethane to the commercially available furanone **(138)** followed by elimination of nitrogen gave the methylated furanone **(140)** which was then transformed to **(141)** and sequentially to **(142)** by a bromination debromination process. Halogen metal exchange with tert-butyl lithium gave a nucleophile which now could be added to suitable aldehydes giving **(143)**.



Where R= i-pr, 2-methylbutyl

Reagents and Conditions: (a) Et_2O, diazomethane, rt, (b) Dioxane, 130 °C. (c) CH_2Cl_2, Br_2, 40 °C (d) CH_2Cl_2, sym-collidine, rt (e) THF/pentane/Et_2O, t-BuLi,2-methyl propanal -120 °C

CHAPTER #3

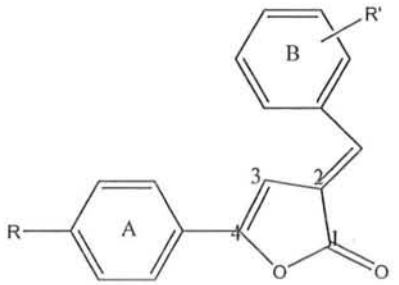
EXPERIMENTAL, RESULTS AND DISCUSSION

Chapter - 3

EXPERIMENTAL, RESULTS AND DISCUSSION

3.1 Plan of Work

This chapter describes the methods, experimental procedures and instrumentation used for the synthesis of the following two series of butenolides. These series are based on the reactions between substituted benzenes with succinic anhydride and finally the condensation reaction with variably substituted benzaldehydes. As such, there are two elements of diversity present in the target compounds, that is ring A, and ring B based on substituents present in substituted benzene and benzaldehydes respectively.



R = OC_2H_5, Br
R' = Cl, Br, OC_2H_5, OH, NO_2, CH_3

A-Series 2-Arylidene-4-(4-ethoxy phenyl)but-3-en-4-olides

B-Series 2-Arylidene-4-(4-bromo phenyl)but-3-en-4-olides

Complete stepwise synthesis, mechanism and general protocols are discussed here in detail.

3.2 Experimental

3.2.1 Substrates and Reagents

The following substrates and reagents were used:

1) Ethoxy benzene
2) Bromo benzene
3) Succinic anhydride
4) Anhydrous Aluminium chloride
5) 2 and 4-Chlorobenzaldehyde
6) 3 and 4-Bromobenzaldehyde
7) 2,3 and 4-Florobenzaldehyde

8) 2 and 3-Methoxybenzaldehyde
9) 4-Ethoxybenzaldehyde
10) 2,3 and 4-Hydroxybenzaldehyde
11) 2,3 and 4-Nitrobenzaldehyde
12) 4-Tolualdehyde
13) Acetic anhydride
14) Triethyl amine

The above cited chemicals were purchased from Sigma Aldrich (Germany). The liquid reagents were distilled at their boiling points and the purity of the solid reagents was determined by recording their melting points. No further purification was required for solid compounds. Sulphuric acid, hydrochloric acid and formic acid were purchased from Fluka (Switzerland).

3.2.2 Drying of Solvents

All the solvents were used after necessary purification and drying according to the standard procedures. The dried solvents were stored over molecular sieves (4°A). A brief account of purification procedures employed for drying the solvents is as follows.

Chloroform

Chloroform was treated with excess amount of water then dried over by using 200 gm/L of $CaCl_2$ and then distilled at 61°C.

Methanol

250 gm of calcium oxide dried in an oven at 120°C, was introduced into a round bottom flask containing one liter of methanol. It was refluxed for 6 hours and then distilled at 65°C.

Toluene

Commercial toluene may contain methyl thiophene, b.p. 112-113°C, which cannot be removed by simple distillation. Toluene was therefore purified by shaking it with conc. H_2SO_4, then washing the acidic layer with water, 10% sodium carbonate solution, again with water and finally dried with anhydrous $CaCl_2$. After filtration, toluene was distilled through an efficient fractionating column, the fraction, b.p. 110.5°C was collected. By this procedure dry toluene was obtained by storing it over Na wire.

Ethyl acetate

In one liter of ethyl acetate, 50 ml of acetic anhydride and 10~15 drops of conc. H_2SO_4 was added and refluxed for 5 hours. It was fractionated and treated with 25 gm of anhydrous potassium carbonate. This mixture was filtered and distilled over 40 gm of CaH_2 at 77 °C.

Pet-ether

A R grade pet-ether (40-60°C) was used.

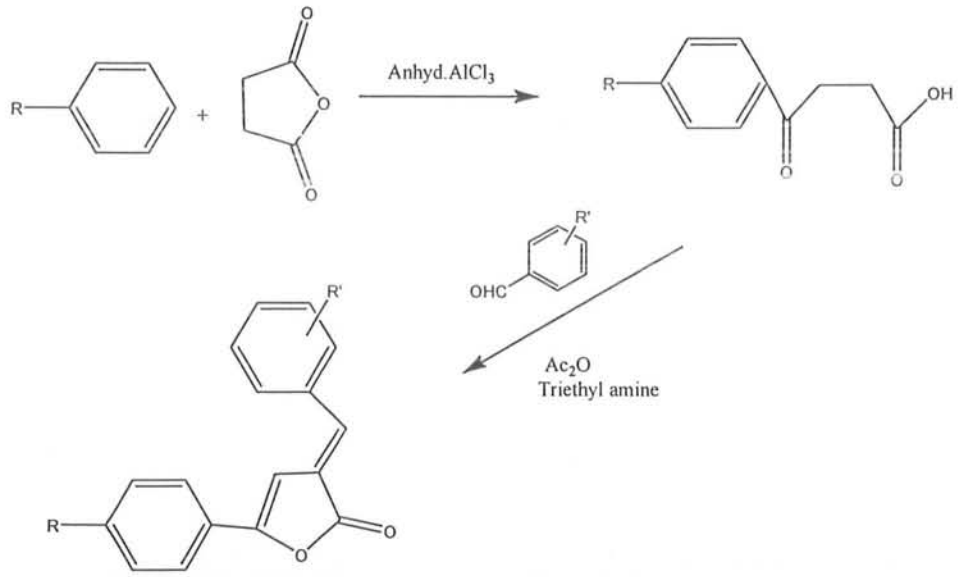
3.3 Instrumentation

R_f values were calculated by using pre-coated silica gel aluminum backed plates Kiesel gel 60 F_{254} Merck (Germany), using toluene: ethyl acetate: formic acid (5:4:1) as developing solvents. Melting points of the compounds were determined in open capillaries using Gallenkamp melting point apparatus and are un-corrected. The FTIR spectra were recorded on Bio-Rad Merlin spectrophotometer using KBr discs. The ^1H and ^{13}C NMR spectra were recorded on Bruker (300 MHz) AM-250 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on Agilent GCMS model (5973 MSD). Purity of each compound was monitored by thin layer chromatography and the purification of the synthesized compounds was achieved by recrystallization.

3.4 General Synthetic Strategy

In view of the immense pharmacological and physiological importance of butenolides, the present work was undertaken to synthesize this class of heterocycles, which afforded us to diversify the substituents in the aromatic rings provided by starting substituted benzenes and different benzaldehydes. The general applicability of this procedure is apparent, as it is found to be tolerant of a wide range of substitution patterns on the butenolide moiety and a variety of butenolide derivatives were obtained in moderate to good yields. The synthetic strategy for the target compounds is outlined in scheme 3.1. The methodology employed for the synthesis of butenolides is that reported by A. Husain et al. 2005[4] (scheme 2.1.9).

To the best of our knowledge, this study is a first attempt to synthesize these target butenolides which may possess substantial biological activities, and providing promising new templates for further discovery of potent inhibitors targeting a number of microbes, fungi and bacteria.



Series	R	R'
A-Series	OC_2H_5	Cl, Br, F, OCH_3, OC_2H_5, OH,NO_2,CH_3
B-Series	Br	Cl, Br, F, OCH_3, OC_2H_5, OH,NO_2,CH_3

Scheme. 3.1: General methodology for the synthesis of butenolides.

3.5 Proposed Mechanism for the Synthesis of Butenolides

The step-wise proposed mechanism of the reactions involved in the synthesis of butenolides is as follows:

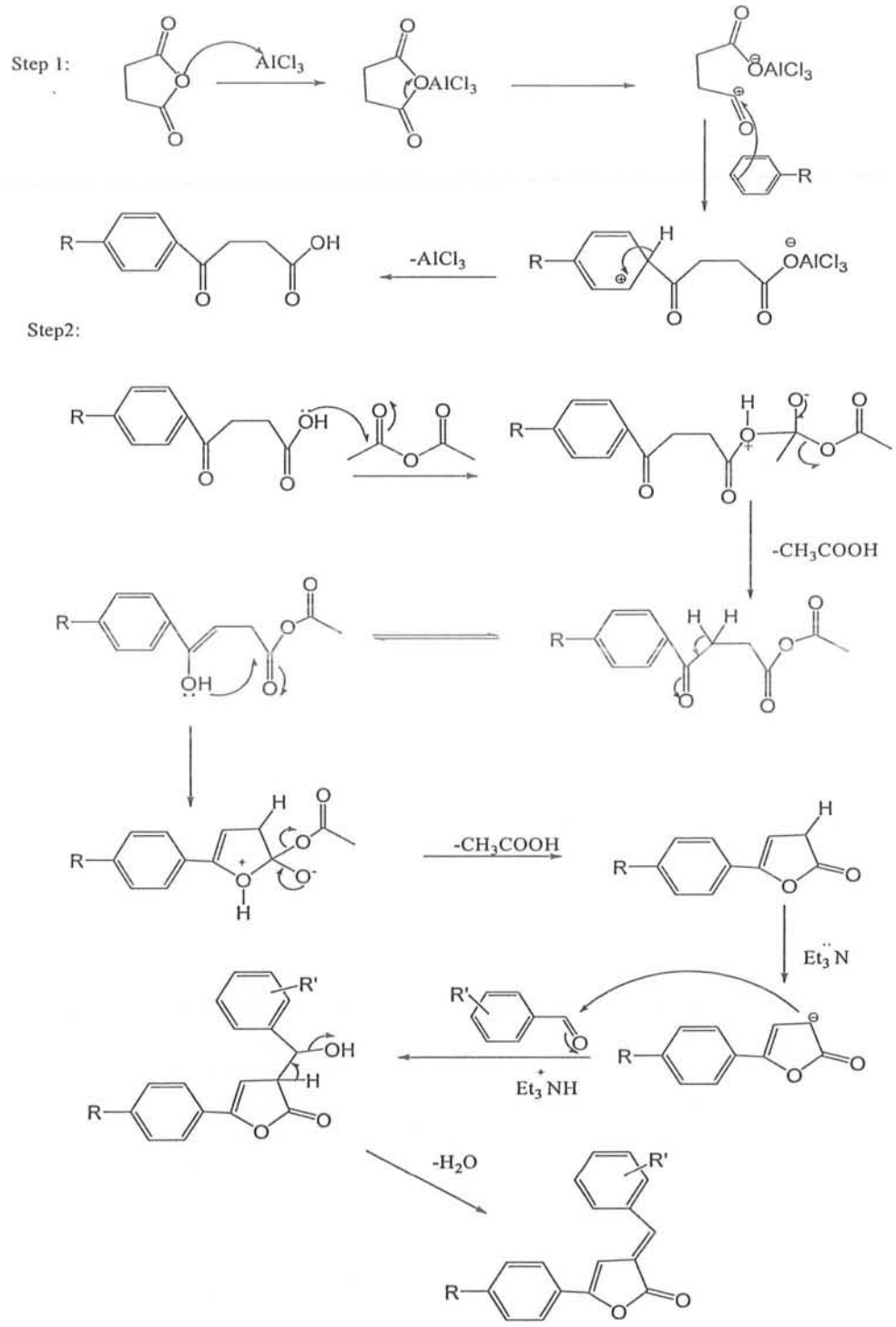


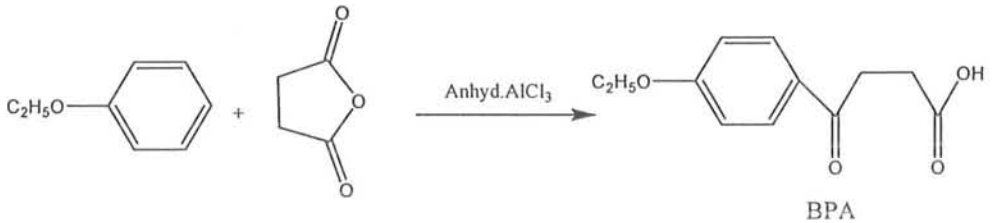
Fig. 3.1: Proposed mechanism involved in the synthesis of butenolides.

3.6 Results and Discussion

3.6.1 Synthesis of A-Series Butenolides

A total of 17 new compounds in this series were prepared as outlined in scheme 3.1. 2-Arylidene-4-(4-ethoxy phenyl)but-3-en-4-olides were synthesized from 3-(4-ethoxy benzoyl) propionic acid (BPA) by reacting with benzaldehydes in the presence of triethyl amine in acetic anhydride. The required 3-(4-ethoxy benzoyl) propionic acid (BPA) was prepared by condensing ethoxy benzene with succinic anhydride in the presence of anhydrous aluminium chloride following Friedal Craft's acylation reaction conditions. One of the representative compounds from A-series has been described here in detail. Complete physical data and structural elucidation of representative molecule is discussed. The same is applicable to the rest of the compounds of this series, and physical and spectral data about them are presented in tabulated form.

3.6.1.1 Synthesis of 3-(4-Ethoxy benzoyl) propionic acid (BPA):



BPA

Succinic anhydride (2g, 0.02 mol) was condensed in the presence of anhyrdrous aluminium chloride (6g, 0.044 mol) with phenetole (15 ml). The reaction mixture was refluxed for 4h. After completion of the reaction, excess solvent (phenetole) was removed by steam distillation. The resultant solid product was purified by dissolving it in sodium hydroxide solution (5% w/v), filtering followed by addition of hydrochloric acid. The solid mass so obtained was filtered, washed with cold water, dried and crystallized from methanol to give 3-(4-ethoxy benzoyl) propionic acid (BPA).

3-(4-ethoxy benzoyl) propionic acid (BPA) was obtained as white crystals with (65%) yield and was recrystallized using methanol. The molecular formula and molecular weight of the compound (BPA) was found to be $C_{12}H_{14}O_4$ and 222 respectively. The FTIR spectrum showed stretching frequencies at 1244, 1040 cm^{-1}, 1677 cm^{-1}, 1709 cm^{-1}, and 2979 cm^{-1} which are characteristics of C – O, C = O (ketone), C = O (acid), and O – H, respectively. (Table 3.1).

Table 3.1: FTIR data of compound BPA.

Compd.	C – O (cm^{-1})	C = O (cm^{-1})	C = C (Ar) (cm^{-1})	O – H (cm^{-1})
BPA	1244,1040	1677 (ketone), 1709 (Acid)	1570	2979

The elemental analysis of BPA shows good agreement between the calculated and found values which show the formation of this product and is shown below:

Table 3.2: CHN analysis of BPA($C_{12}H_{14}O_4$).

Analysis	%C	%H	%N
Calculated	64.85	6.35	----
Found	64.08	6.25	----

The ^{1}H NMR spectrum of 3-(4-Ethoxy benzoyl) propionic acid (BPA) showed a triplet at δ 1.46 ppm for the methyl protons at position 1 with coupling constant J =6.9 Hz. The methylene protons at position 2 showed quartet at δ 4.12 ppm, with J =6.9 Hz. The aromatic protons at position 2′ and 6′ showed a doublet of doublet at δ 6.94 ppm by coupling with ortho and meta protons respectively which is evident by J values at 9 and 2.7 Hz. Similarly the protons at position 3′ and 5′ also showed doublet of doublet at δ 7.97 ppm with ortho and meta coupling, J values being 9.6 and 3.0 Hz. The methylene protons at 2″ and 3″ gave triplet each at δ 3.29 and 2.81 ppm respectively with coupling constant J =6.6 Hz. The carboxyl proton at 5″ gave singlet at δ 11.1 ppm. The δ values, multiplicity and J values of all protons of BPA are tabulated in table 3.3.

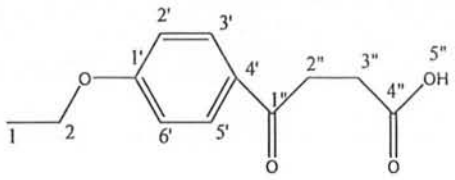


Table 3.3: ^{1}H NMR spectral data of compound BPA ($CDCl_3$, 300 MHz).

Type of Proton	^{1}H (δ ppm)	Multiplicity	J(Hz)
1	1.46	3H, t	6.9
2	4.12	2H, q	6.9
2′, 6′	6.94	2H, dd	9, 2.7
3′, 5′	7.97	2H, dd	9, 2.7
2″	3.29	2H, t	6.6
3″	2.81	2H, t	6.6
5″	11.1	1H, s	–

In the ^{13}C NMR spectrum of 3-(4-ethoxy benzoyl) propionic acid (BPA), a peak is observed at δ 14.69 ppm for the carbon at position 1. Similarly carbon at position 2 gave a peak at δ 63.79 ppm. The aromatic carbon at position 1′ gave a peak at δ 163.11 ppm. The aromatic carbons at positions 2′ and 6′ gave peak at δ 114 ppm. Similarly the carbons of aromatic ring at position 3′ and 5′ gave peak at δ 130.36 and that at position 4′ at δ 129.25 ppm. The other carbons at positions 1″, 2″, 3″and 4″ gave peaks at δ 196.5, 32.79, 28.4 and 178.36 ppm respectively. The δ values of all carbons of BPA are tabulated in table 3.4.

Table 3.4: ^{13}C NMR spectral data of compound BPA ($CDCl_3$, 75 MHz).

Carbon #	^{13}C (δ ppm)	Carbon #	^{13}C (δ ppm)
1	14.69	4′	129.25
2	63.79	1″	196.5
1′	163.11	2″	32.79
2′ 6′	114	3″	28.4
3′ 5′	130.36	4″	178.36

The mass spectrum of BPA showed molecular ion peak at m/z 222 in reasonable intensity (15%) which is in good agreement with the molecular weight of the compound. The base peak appears at m/z 149 by loss of $C_3H_5O_2$ from the molecular ion. The base peak by loss of CO give peak at m/z 121 in good intensity (51%). This can further loss C_2H_5O to give peak at m/z 76 which on further loss of C_2H_2 give peak at m/z 50.The ion at m/z 121 can also loss C_2H_4 by McLafferty rearrangement to give peak at m/z 93 which on successive loss of CO and C_2H_2 give peaks at m/z 65 and 39 respectively. The complete fragmentation pattern of BPA is given in fig 3.3.

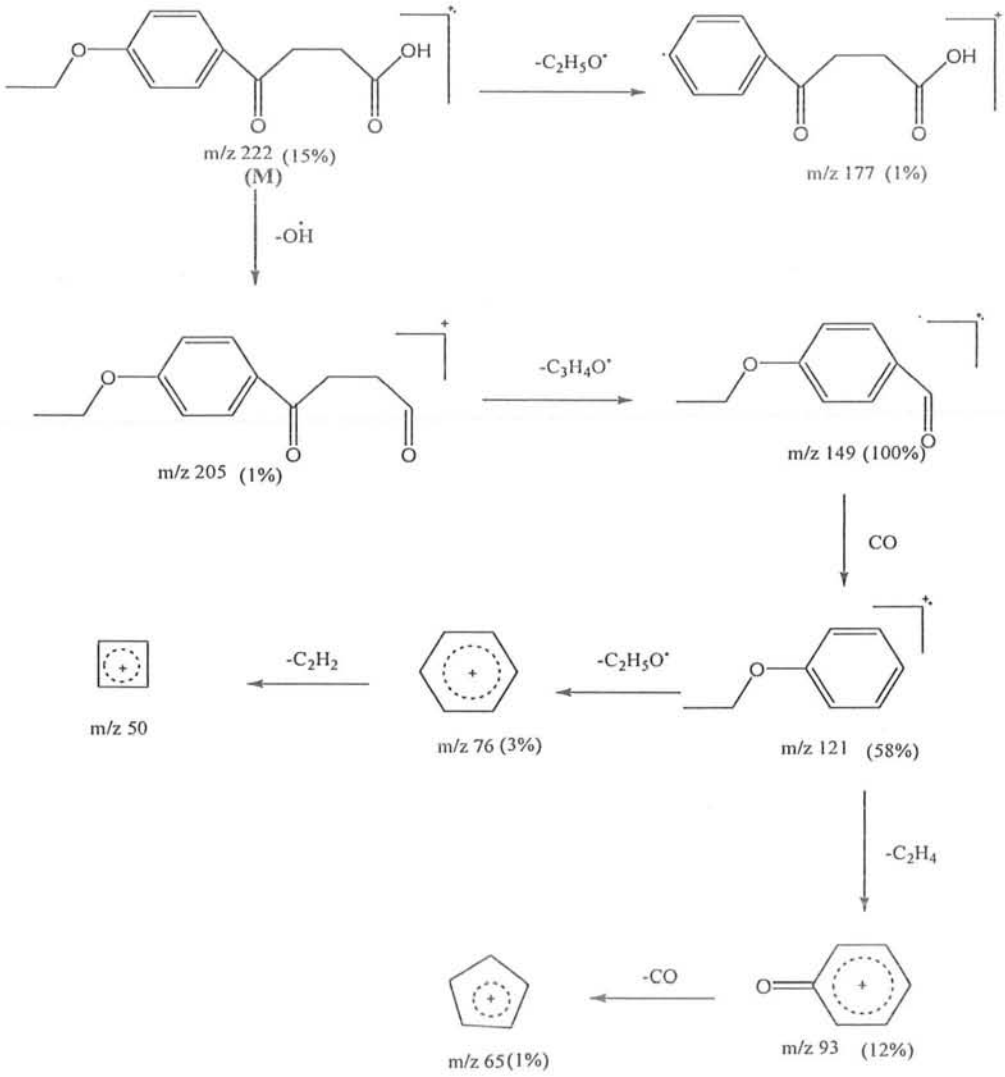
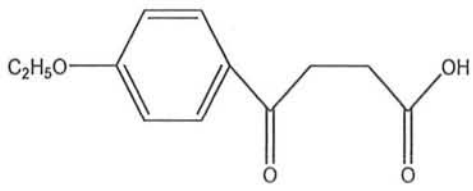


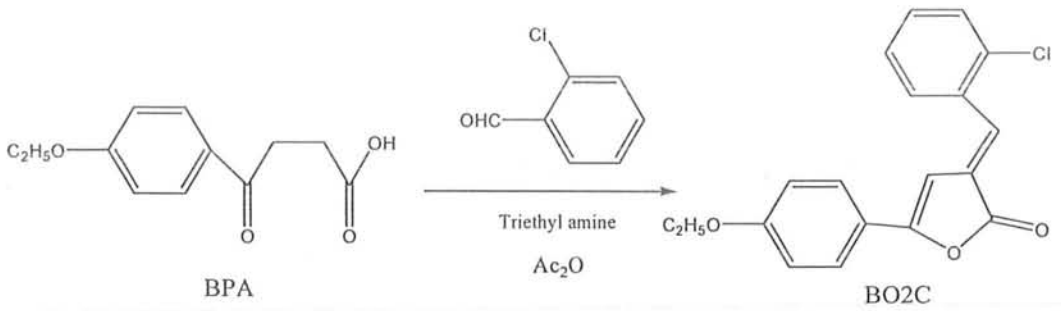
Fig 3.2: Mass fragmentation of BPA.

On the basis of interpretation of IR, ^{1}H, ^{13}C NMR, mass spectral data and physical constants, the structure of (BPA) was determined as 3-(4-Ethoxy benzoyl) propionic acid :



3-(4-Ethoxy benzoyl) propionic acid

3.6.1.2 Synthesis of 2-(2-Chlorobenzylidene)-4-(4-ethoxyphenyl)but-3-en-4-olide (BO2C):



BPA BO2C

To a solution of 3-(4-ethoxy benzoyl) propionic acid (0.5g, 0.002 mol) and 2-chlorobenzaldehyde (0.22ml, 0.002 mol) in acetic anhydride (5 ml) was added triethyl amine (3-4 drops) and reaction mixture was refluxed for 4h under anhydrous conditions. After completion of reaction, the mixture was poured onto crushed ice and a yellow colored solid mass, which separated out, was filtered, washed, dried and crystallized from methanol: chloroform mixture (1:1) to give butenolide (BO2C).

2-(2-Chlorobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide (BO2C) was obtained as yellow fluffy solid with 65% yield which was recrystallized by methanol: chloroform (1:1). The molecular formula and molecular weight of the compound (BO2C) is $C_{19}H_{15}ClO_3$ and 326 respectively. The FTIR spectrum showed stretching frequencies at 1245, 1043 cm^{-1}, 1186 cm^{-1}, 1508 cm^{-1} and 1120 cm^{-1} which are characteristics of C – O, C = O, C = C (Ar), C – Cl respectively. (Table 3.5).

Table 3.5: FTIR data of compound BO2C.

Compd.	C – O (cm^{-1})	C = O (cm^{-1})	C = C(Ar) (cm^{-1})	C – Cl (cm^{-1})
BO2C	1245,1043	1786	1508 cm^{-1}	1120

The CHN analysis of BO2C shows good agreement between the calculated and found values which show the formation of this product and is shown below:

Table 3.6: CHN analysis of BO2C ($C_{19}H_{15}ClO_3$)

Analysis	%C	%H	%N
Calculated	69.84	4.63	----
Found	70.10	4.52	----

The ^{1}H-NMR spectrum of 2-(2-Chlorobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide (BO2C) showed two characteristic singlets at δ 6.69 and 7.28 ppm, which could be assigned to the lactone ring β-H and the olefinic hydrogen of the arylidene substituent respectively. A triplet is observed at δ 1.46 ppm for the methyl hydrogens at position 1 while a quartet at δ 4.10 ppm for the methylene hydrogens at position 2 with J value being 6.9 Hz. A doublet of doublet at 6.96 ppm is observed for aromatic protons at 2′ and 6′ due to ortho and meta coupling as shown by J values 8.7 and 3 Hz while a multiplet at δ 7.70 ppm is observed for aromatic protons at positions 3′, 5′ and 6″. A multiplet at δ 7.32-7.41 ppm is observed for aromatic protons at 4″ and 5″. A doublet of doublet at δ 7.49 ppm is observed for aromatic proton at 3″ due to ortho and meta coupling with J values being 6.6 and 2.4 Hz. The δ values, multiplicity and J values of all protons of BO2C are tabulated in table 3.7.

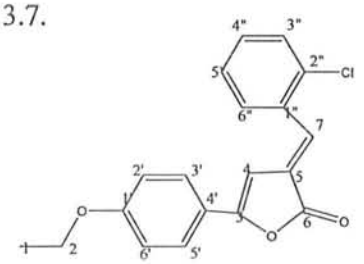


Table 3.7: ^{1}H NMR spectral data of compound BO2C ($CDCl_3$, 300 MHz).

Type of Proton	^{1}H (δ ppm)	Multiplicity	J(Hz)
1	1.46	3H, t	6.9
2	4.10	2H, q	6.9
4	6.69	1H, s	--
7	7.28	1H, s	--
2′ 6′	6.96	2H,dd	8.7,3
3′ 5′	7.68-7.73	2H, m	--
3″	7.49	1H, dd	6.6,2.4
4″	7.32-7.41	1H, m	--
5″	7.32-7.41	1H, m	--
6″	7.68-7.73	1H, m	--

In the ^{13}C NMR spectrum of 2-(2-Chlorobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide (BO2C) a characteristic peak at δ 97.44 ppm is observed for the lactone ring β C at position 4 and a peak at δ 135.51 for the olefinic C at position 7. A peak at δ 14.74 ppm is observed for the carbon at position 1. Similarly C at position 2 gave a peak at δ 63.74 ppm. Carbons at position 5, 6 gave peak at δ 97.44 and 135.51 ppm respectively. The aromatic C at 1′ gave peak at δ 161.13 ppm. Similarly the aromatic carbons at positions 2′, 6′and 3′, 5′ gave peaks at δ 114.89 and 127.22 respectively. The aromatic C at postion 4′, gave peak at δ 120.26 ppm. The arylidene ring carbons gave peaks in close range i.e. δ 129-133 ppm. The δ values of all carbons of BO2C are tabulated in table 3.8.

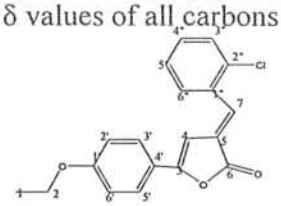


Table 3.8: ^{13}C NMR spectral data of compound BO2C ($CDCl_3$, 75 MHz).

Carbon #	^{13}C (δ ppm)	Carbon #	^{13}C (δ ppm)
1	14.74	3′, 5′	127.22
2	63.74	4′	120.26
3	151.87	1″	133.74
4	97.44	2″	130.66
5	130.66	3″	129.60
6	168.97	4″	129.76
7	135.51	5″	127.65
1′	161.13	6″	129.60
2′, 6′	114.89	------	------

The mass spectrum of BO2C showed characteristic isotopic peaks for chlorine. The molecular ion peak appears in reasonable intensities (52%) at m/z 326 which are found in good agreement with molecular weight of the compound. The molecular ion on loss of chlorine gave the base peak at m/z 291.This base fragment ion can further loss CO to give peak at 203 which subsequently loses C_9H_6 and CO, to give peak at m/z 149 and 121 in good intensity. It can further loss C_2H_4 by McLafferty rearrangement to give peak at m/z 93 which on successive loss of CO and C_2H_2 give peaks at m/z 65 and 39 respectively. The base peak at m/z 291 can also lose C_2H_4 by McLafferty rearrangement to give peak at m/z 263 which on further loss of CO give peak at m/z 235. The complete mass fragmentation pattern of BO2C is given in fig 3.4.

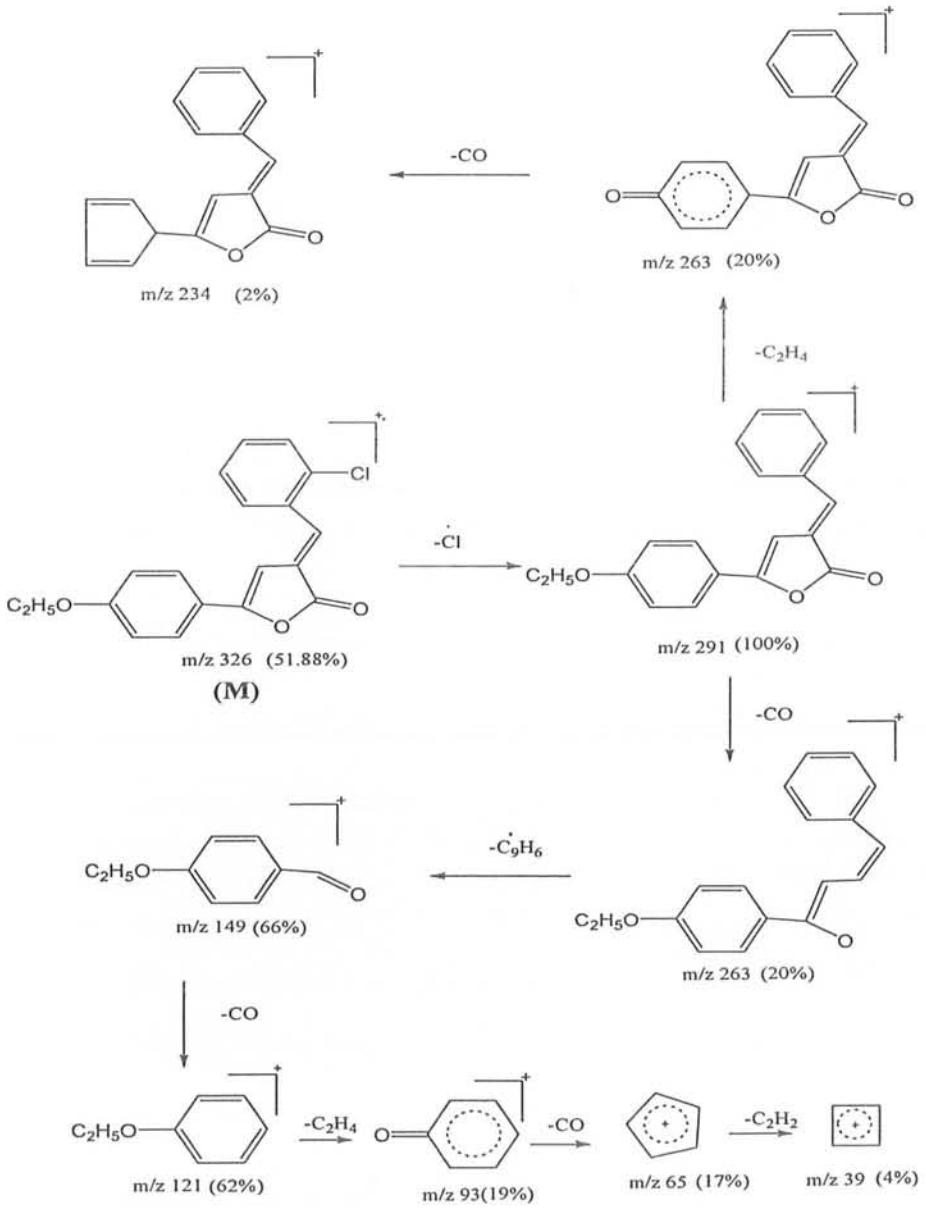
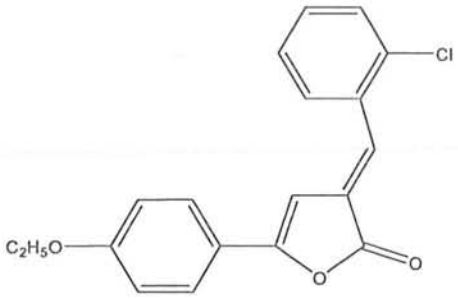


Fig 3.3: Mass fragmentation pattern of BO2C.

On the basis of interpretation of IR, ^{1}H, ^{13}C NMR, mass spectral data and physical constants, the structure of (BO2C) was determined as 2-(2-Chlorobenzylidene)-4-(4-ethoxy phenyl)but-3-en-4-olide :



2-(2-Chlorobenzylidene)-4-(4-ethoxy phenyl)
but-3-en-4-olide

3.6.1.3 Synthesis of other A-Series Butenolides:

The synthetic procedure used for the synthesis of BO2C was also used for the synthesis of other members of the A-series of butenolides. Molar ratios, physical data, FTIR, ^{1}H, ^{13}C NMR and EIMS data for these compounds are tabulated in Table 3.9-3.15.

Table 3.9: Molar Ratios of A-series compounds.

Compd.	Benzoyl propionic acid	Substituted benzaldehyde	Yield	Solvent for Recrystallization
BO4C	0.5 g (0.002 mol)	0.28 g (0.002 mol)	0.35 g (50%)	Methanol: Chloroform
BO3B	0.5 g (0.002 mol)	0.23 ml (0.002 mol)	0.6 g (70%)	Methanol: Chloroform
BO4B	0.5 g (0.002 mol)	0.37 g (0.002 mol)	0.6 g (70%)	Methanol: Chloroform
BO2F	0.5 g (0.002 mol)	0.21 ml (0.002 mol)	0.5 g (72%)	Methanol: Chloroform
BO3F	0.5 g (0.002 mol)	0.211 ml (0.002 mol)	0.48 g (70%)	Methanol: Chloroform
BO4F	0.5 g (0.002 mol)	0.214 ml (0.002 mol)	0.45 g (69%)	Methanol: Chloroform
BO2M	0.5 g (0.002 mol)	0.27 g (0.002 mol)	0.4g (60%)	Methanol: Chloroform
BO3M	0.5 g (0.002 mol)	0.24 ml (0.002 mol)	0.45 g (65%)	Methanol: Chloroform
BO4E	0.5 g (0.002 mol)	0.27 ml (0.002 mol)	0.4 g (50%)	Methanol: Chloroform
BO2H	0.5 g (0.002 mol)	0.21 ml (0.002 mol)	0.45 g (68%)	Methanol: Chloroform
BO3H	0.5 g (0.002 mol))	0.24 g (0.002 mol)	0.4 g (65%)	Methanol: Chloroform
BO4H	0.5 g (0.002 mol)	0.24 g (0.002 mol)	0.4 g (65%)	Methanol: Chloroform
BO2N	0.5 g (0.002 mol)	0.30 g (0.002 mol)	0.5 g (68%)	Methanol: Chloroform
BO3N	0.5 g (0.002 mol)	0.30 g (0.002 mol)	0.56 g (72%)	Methanol: Chloroform
BO4N	0.5 g (0.002 mol)	0.30 g (0.002 mol)	0.6 g (75%)	Methanol: Chloroform
BO4T	0.5 g (0.002 mol)	0.23 ml (0.002 mol)	0.4 g (60%)	Methanol: Chloroform

Table 3.10: Physical data of A-series compounds.

Comp.	Molecular Formula	Molecular Weight	m.p. (°C)	R_f^* Values x 100	Solubility
BO4C	$C_{19}H_{15}ClO_3$	326.5	205-206	70	$CHCl_3$
BO3B	$C_{19}H_{15}BrO_3$	371	166-167	68	$CHCl_3$
BO4B	$C_{19}H_{15}BrO_3$	371	208-209	70	$CHCl_3$
BO2F	$C_{19}H_{15}FO_3$	310	146-147	62	$CHCl_3$
BO3F	$C_{19}H_{15}FO_3$	310	169-170	64	$CHCl_3$
BO4F	$C_{19}H_{15}FO_3$	310	161-162	65	$CHCl_3$
BO2M	$C_{20}H_{18}O_4$	322	137-138	60	$CHCl_3$
BO3M	$C_{20}H_{18}O_4$	322	124-125	64	$CHCl_3$
BO4E	$C_{21}H_{20}O_4$	336	181-182	63	$CHCl_3$
BO2H	$C_{19}H_{16}O_4$	308	142-143	70	$CHCl_3$
BO3H	$C_{19}H_{16}O_4$	308	137-138	72	$CHCl_3$
BO4H	$C_{19}H_{16}O_4$	308	190-191	70	$CHCl_3$
BO2N	$C_{19}H_{15}NO_5$	337	189-190	76	$CHCl_3$
BO3N	$C_{19}H_{15}NO_5$	337	175-176	74	$CHCl_3$
BO4N	$C_{19}H_{15}NO_5$	337	252-253	72	$CHCl_3$
BO4T	$C_{20}H_{18}O_3$	306	164-165	68	$CHCl_3$

* Solvent for R_f values = Pet. ether : ethyl acetate (4:1)

Table 3.11: FTIR data of A-series butenolides

Compd.	C–O (cm^{-1})	C=O (cm^{-1})	C=C (Ar) (cm^{-1})	C–X (cm^{-1})
BO4C	1255, 1050	1759	1508	1092 (C-Cl)
BO3B	1262, 1044	1761	1504	1069 (C-Br)
BO4B	1078, 1256	1758	1509	923(C-Br)
BO2F	1043,1265	1786	1506	1117 (C-F)
BO3F	1043, 1257	1785	1508	1117 (C-F)
BO4F	1049, 1258	1758	1507	1113 (C-F)
BO2M	1244	1778	1504	1115 (C-OMe)
BO3M	1250	1759	1507	1175 (C-OMe)
BO4E	1167	1752	1506	1250 (C-OEt)
BO2H	1258	1762	1506	3100 (O-H)
BO3H	1256	1785	1511	3068 (O-H)
BO4H	1256	1758	1505	3053 (O-H)
BO2N	1263	1775	1522	1522,1341 (C-N)
BO3N	1249	1758	1528	1561, 1350 (C-N)
BO4N	1249	1763	1507	1563, 1339 (C-N)
BO4T	1254	1759	1506	1395 ($C-CH_3$)

Table 3.12: ^{1}H NMR spectral data of A series compounds $CDCl_3$, 300 MHz.

Protons	Spectral data	BO4C	BO3B	BO4B	BO2F	BO3F	BO4F	BO2M	BO3M
1	^{1}H-δppm Multiplicity J(Hz)	1.47 t 6.9	1.47 t 6.9	1.47 t 6.9	1.46 t 6.9	1.46 t 6.9	1.46 t 6.9	1.46 t 6.9	1.46 t 6.9
2	^{1}H-δppm Multiplicity J(Hz)	4.11 q 6.9	4.11 q 6.9	4.11 q 6.9	4.11 q 6.9	4.11 q 6.9	4.11 q 6.8	4.10 q 6.9	4.11 q 6.9
4	^{1}H-δppm Multiplicity J(Hz)	6.76 s --	6.75 s --	6.76 s ---	6.74 s ---	6.77 s ----	6.76 s ---	6.76 s ---	6.80 s ---
7	^{1}H-δppm Multiplicity J(Hz)	7.28 s ---	7.25 s ---	7.72 s ---	7.54 s ---	7.12 s ---	7.33 s ---	7.67 s ---	7.14 s ---
2′ 6′	^{1}H-δppm Multiplicity J(Hz)	6.98 dd 9,2.7	6.97 dd 8.7,3	6.97 dd 9,3	6.97 dd 9,2.1	6.97 dd 8.7,3	6.97 dd 8.7,1.8	6.95 dd 9,1.8	6.97 dd 9,2.1
3′ 5′	^{1}H-δppm Multiplicity J(Hz)	7.44 dd 8.4,2.7	7.53 dd 9, 2.8	7.49 dd 8.4,2.8	7.74- 7.66 m ---	7.48- 7.28 m	7.71 dd 9,2.1	7.72- 7.66 m ---	7.71 dd 9,2.1
2″	^{1}H-δppm Multiplicity J(Hz)	7.72 dd 7.3,2.4	7.35- 7.45 m ----	7.28 dd 8.8,2.1	----	7.72 dd 4,2.4	7.63 ddd 5.4,1.8	7.14- 7.25 m ----	7.42- 7.34 m ---
3″	^{1}H-δppm Multiplicity J(Hz)	7.57 dd 8.4,2.7	-----	7.60 dd 8.4,3	7.45- 7.37 m ---	----	7.17 ddd 8.7,2.1	---	----
4″	^{1}H-δppm Multiplicity J(Hz)	---	7.35- 7.45 m ---	----	7.74- 7.66 m ---	7.48- 7.28 m	----	7.43- 7.38 m ----	7.42- 7.34 m ---
5″	^{1}H-δppm Multiplicit J(Hz)	7.57 dd 8.4,2.7	7.32 dd 8.8,3	7.60 dd 8.4,3	7.26- 7.13 m ---	7.48- 7.28 m	7.17 ddd 8.7,2.1	7.08- 7.03 m ---	7.24 dd 7.5,0.6
6″	^{1}H-δppm Multiplicity J(Hz)	7.72 dd 9,2.7	7.24 m ---	7.28 dd 8.8,2.1	7.74- 7.66 m ---	7.48- 7.28 m	7.63 ddd 5.4,1.8	7.72- 7.66 m ---	7.42- 7.34 m ---
X-H	^{1}H-δppm Multiplicity J(Hz)	----	----	----	----	----	----	3.91 s ---	3.89 s ---

Contd. table.....3.12

Protons	Spectral data	BO4E	BO2H	BO3H	BO4H	BO2N	BO3N	BO4N	BO4T
1	^{1}H-δppm Multiplicity J(Hz)	1.49-1.44 m(6H) ---	1.46 t 6.9	1.46 t 6.9	1.46 t 6.9	1.46 t 6.9	1.47 t 6.8	1.48 t 6.9	1.46 t 6.9
2	^{1}H-δppm Multiplicity J(Hz)	4.07-4.15 m(4H) ----	4.11 q 6.9	4.11 q 6.9	4.11 q 6.9	4.10 q 6.9	4.12 q 6.8	4.12 q 6.9	4.11 q 6.9
4	^{1}H-δppm Multiplicity J(Hz)	6.80 s ---	6.73 s ---	6.77 s ---	6.78 s ---	6.52 s ---	6.80 s ---	6.81 s ---	6.81 s ---
7	^{1}H-δppm Multiplicity J(Hz)	7.34 s ---	6.95 s ---	7.33 s ---	7.74 s ---	8.15 s ---	8.48 s ---	7.34 s ---	7.36 s ---
2′ 6′	^{1}H-δppm Multiplicity J(Hz)	6.94-7.00 m ---	7.19 dd 6.6,2.2	6.36 dd 8.7,3	7.21 dd 8.7,2.1	6.96 dd 9,2.7	7.19 dd 9,3	7.00 dd 8.7,2	6.96 dd 9,2.1
3′ 5′	^{1}H-δppm Multiplicity J(Hz)	7.70 dd 9,2.1	7.75 dd 6,1.5	7.72 dd 9,2.1	7.71 dd 9,2.1	7.56-7.62 m ---	7.63-7.91 m ---	7.75 dd 6.7,2.7	7.71 dd 9,2.1
2″	^{1}H-δppm Multiplicity J(Hz)	7.58-7.61 m ----	----	6.97 dd 9,2.1	7.65 dd 8.7,2.4	----	8.24 dd 7,3	7.78 dd 6.8,2.7	7.54 dd 8.1,2.7
3″	^{1}H-δppm Multiplicity J(Hz)	6.94-7.00 m ---	6.96 dd 9,3	----	6.97 dd 9,2.1	8.18 dd 7.8,2.4	----	8.33 dd 9,3	7.27-7.29 m ----
4″	^{1}H-δppm Multiplicity J(Hz)	----	7.33-7.48 m	7.13-7.16 m	---	7.66-7.75 m	7.63-7.91 m	----	----
5″	^{1}H-δppm Multiplicity J(Hz)	6.94-7.00 m ---	7.33-7.48 m ---	7.48 dd 7.8,2.3	6.97 dd 9,2.1	7.66-7.75 m ---	7.63-7.91 m ---	8.33 dd 9,3	7.27-7.29 m ----
6″	^{1}H-δppm Multiplicity J(Hz)	7.58-7.61 m ----	7.70 dd 9,2.1	7.13-7.16 m	7.65 dd 8.7,2.4	7.66-7.75 m	7.63-7.91 m ---	7.78 dd 6.8,2.7	7.54 dd 8.1,2.7
X-H	//	----	2.39 s	2.38 s	2.36 s	----	----	----	2.43 s

Table 3.13: ^{13}C NMR spectral data of A series compounds.

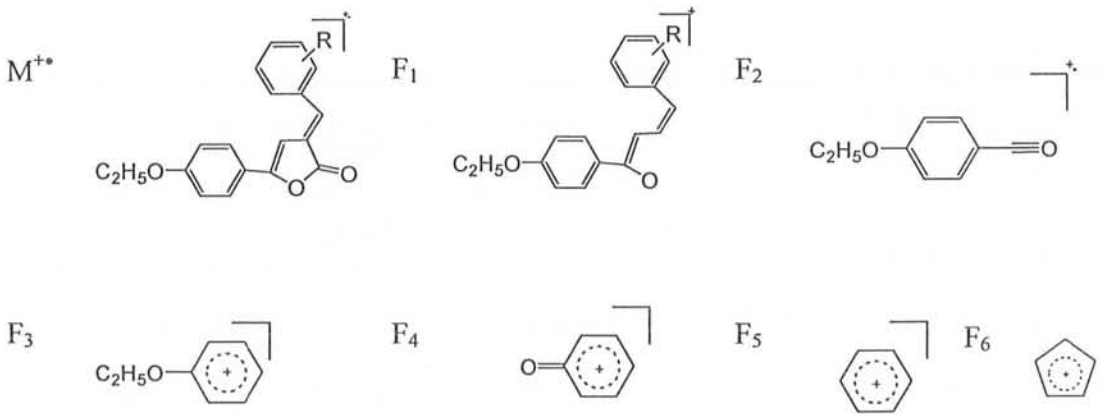
carbon No.	^{13}C-δ(ppm), Compounds							
	BO4C	BO3B	BO4B	BO2F	BO3F	BO4F	BO2M	BO3M
1	14.74	14.74	14.75	14.73	14.73	14.74	14.76	14.74
2	63.74	63.75	63.75	63.73	63.74	63.72	63.69	63.71
3	157.49	157.89	156.20	157.20	157.80	157.22	156.40	151.09
4	97.57	97.48	97.61	98.00	97.55	97.48	98.17	97.94
5	129	128.48	130.05	129.86	130.53	131.70	129.39	130.05
6	169.5	169.28	167.40	169.21	169.36	169.64	169.80	169.68
7	135.83	137.43	139.60	131.55	137.51	132.42	131.60	136.66
1′	161.10	161.20	156.70	157.48	161.30	161.38	158.56	159.89
2′ 6′	114.91	114.91	114.90	114.89	114.92	114.88	114.82	115.38
3′ 5′	127.20	127.32	127.21	127.16	127.27	125.26	125.22	125.91
4′	120.30	123.15	119.87	120.34	120.21	120.39	124.61	122.50
1″	132.07	132.59	134.27	123.60	131.90	131.88	117.25	133.70
2″	126.01	130.52	131.22	161.12	115.50	127.10	160.79	116.60
3″	126.01	120.17	132.33	116.20	164.61	116.34	111.07	160.96
4″	133.88	132.26	122.30	129.83	116.73	165.10	129.25	114.87
5″	126.01	130.51	123.60	124.53	131.91	116.34	120.73	127.11
6″	127.8	126.71	125.68	127.21	125.95	127.10	126.93	120.45
X-C	----	----	----	----	----	----	55.60	55.41

Contd. table.....3.13

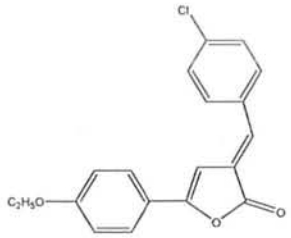
carbon No.	^{13}C-δ (ppm), Compounds							
	BO4E	BO2H	BO3H	BO4H	BO2N	BO3N	BO4N	BO4T
1	14.76	14.73	14.74	14.74	14.71	14.72	14.70	14.76
2	63.70	63.73	64.73	63.72	63.76	63.80	63.70	63.70
3	155.93	149.67	151.04	157.25	146.2	148.71	146.2	156.50
4	97.98	97.80	97.69	97.65	96.90	97.03	97.20	98.04
5	134.08	129.40	130.02	127.12	130.5	130.10	130.5	130.07
6	170.22	169.19	169.39	169.50	168.40	168.89	168.39	169.97
7	131.96	130.85	136.85	133.14	137.60	137.01	137.50	140.65
1′	160.66	157.61	157.56	151.63	160.70	161.53	161.70	160.81
2′ 6′	115.08	114.90	120.31	114.89	114.91	114.99	114.3	114.84
3′ 5′	128	127.20	127.24	125.69	127.35	127.56	127	126.99
4′	123.04	126.78	126.57	122.35	122	123.75	122	120.62
1″	126.85	123.22	132.37	131.09	130.99	135.49	141.3	132.66
2″	128	161.09	114.89	132.56	158.10	119.84	127.3	124.65
3″	114.82	120.30	161.09	120.41	121	158.94	121	129.85
4″	160.60	128.39	122.48	161	129.83	128	158.60	134.13
5″	114.82	126.38	127.46	120.41	134.8	129.66	121	129.85
6″	128	127.42	122.99	132.56	128.63	132.5	127.3	124.65
X-C	---	----	----	----	----	----	----	21.64

Table 3.14: EIMS data of A series compounds.

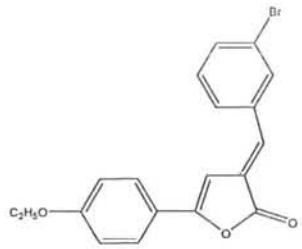
Compd.	Peaks (m/z, %)						
	$M^{+\bullet}$	F_1	F_2	F_3	F_4	F_5	F_6
BO4C	326(100)	298(8)	149(80)	121(75)	93(14)	76(3)	65(11)
BO3B	370(73)	342(4)	149(95)	121(100)	93(19)	76(5)	65(17)
BO4B	370(100)	342(10)	149(80)	121(75)	93(15)	76(5)	65(10)
BO2F	310(100)	282(8)	149(65)	121(70)	93(15)	76(3)	65(11)
BO3F	310(100)	282(8)	149(71)	121(80)	93(20)	76(3)	65(15)
BO4F	310(100)	282(10)	149(67)	121(66)	93(20)	76(3)	65(11)
BO2M	322(100)	294(5)	149(88)	121(66)	93(19)	76(6)	65(15)
BO3M	322(81)	294(5)	149(100)	121(65)	93(14)	76(5)	65(11)
BO4E	336(100)	308(19)	149(76)	121(52)	93(15)	76(4)	65(10)
BO2H	308(100)	280(10)	149(55)	121(65)	93(15)	76(5)	65(10)
BO3H	308(46)	280(7)	149(100)	121(75)	93(20)	76(6)	65(15)
BO4H	308(100)	280(8)	149(60)	121(52)	93(13)	76(3)	65(12)
BO2N	337(38)	309(10)	149(100)	121(89)	93(29)	76(10)	65(24)
BO3N	337(100)	309(8)	149(90)	121(52)	93(20)	76(5)	65(15)
BO4N	337(100)	309(10)	149(52)	121(95)	93(20)	76(5)	65(5)
BO4T	306(100)	278(10)	149(85)	121(57)	93(15)	76(3)	65(11)



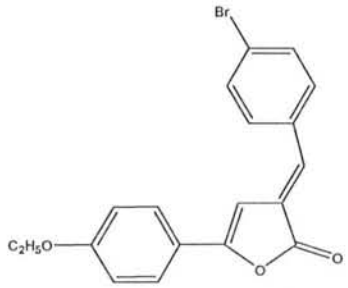
As a result of interpretation of physical and spectral data, the structures of A-series butenolides were elucidated and are given below:



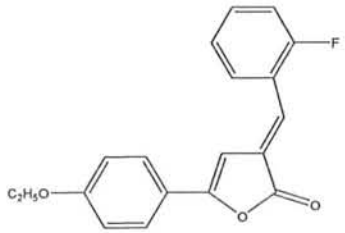
2-(4-Chlorobenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO4C)**



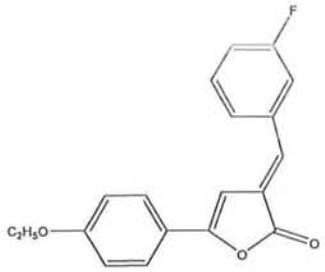
2-(3-Bromobenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO3B)**



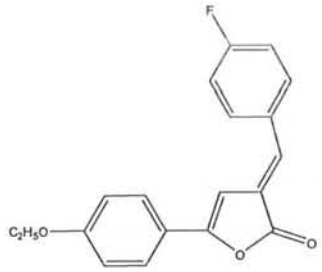
2-(4-Bromobenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO4B)**



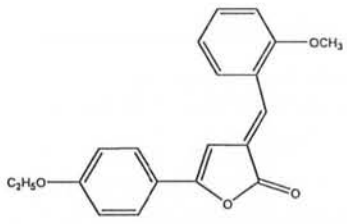
2-(2-Flororobenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO2F)**



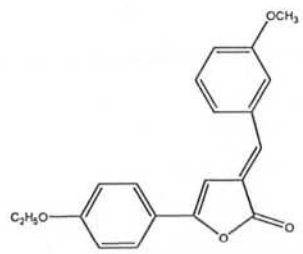
2-(3-Florobenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO3F)**



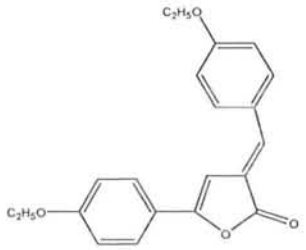
2-(4-Florobenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO4F)**



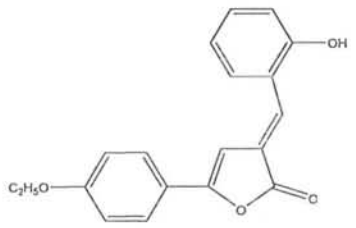
2-(2-Methoxybenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO2M)**



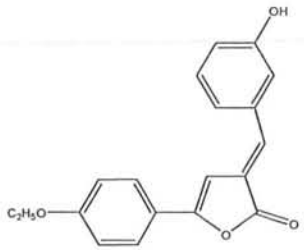
2-(3-Methoxybenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO3M)**



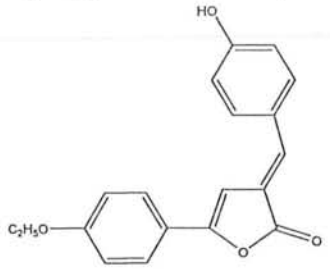
2-(4-Ethoxybenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO4E)**



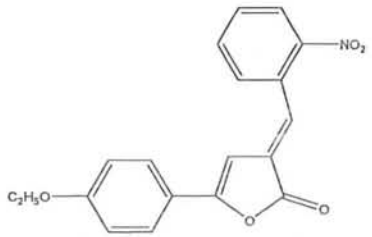
2-(2-Hydroxybenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO2H)**



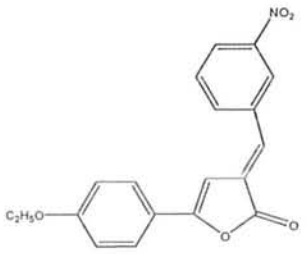
2-(3-Hydroybenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO3H)**



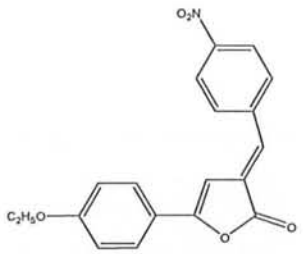
2-(4-Hydroxybenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO4H)**



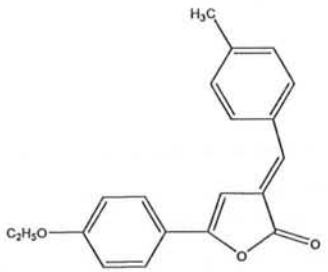
2-(2-Nitrobenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO2N)**



2-(3-Nitrobenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO3N)**



2-(4-Nitrobenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO4N)**

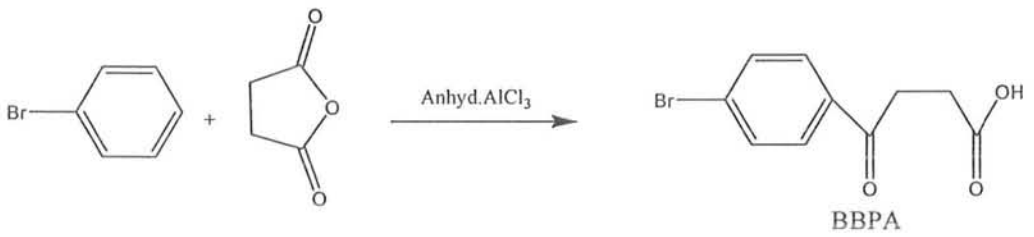


2-(4-Methylbenzylidene)-4-(4-ethoxy phenyl)but3-en-4-olide **(BO4T)**

3.6.2 Synthesis of B-Series Butenolides

Overall 9 new compounds were prepared following scheme as outlined in scheme fig 3.1. 2-Arylidene-4-(4-bromo phenyl)but-3-en-4-olides were synthesized from 3-(4-Bromo benzoyl) propionic acid (BBPA) by reacting with aromatic aldehydes in the presence of triethyl amine in acetic anhydride. The required 3-(4-Bromo benzoyl) propionic acid (BBPA) was prepared by condensing bromo benzene with succinic anhydride in the presence of anhydrous aluminium chloride following Friedal Craft's acylation reaction conditions. One of the representative compounds from B-series has been described here in detail. Complete physical data and structural elucidation of representative molecule is discussed. The same is applicable to the rest of the compounds of this series, and physical and spectral data about them are presented in tabulated form.

3.6.2.1 Synthesis of 3-(4-Bromo benzoyl) propionic acid (BBPA):



BBPA

Succinic anhydride (2g, 0.02 mol) was condensed in presence of anhyrdrous aluminium chloride (6g, 0.044 mol) with bromobenzene (15 ml). The reaction mixture was refluxed for 4h.After completion of the reaction excess solvent (bromobenzene) was removed by steam distillation. The resultant solid product was purified by dissolving it in sodium hydroxide solution (5% w/v), filtering followed by addition of hydrochloric acid. The solid mass so obtained was filtered, washed with cold water, dried and crystallized from methanol to give 3-(4-bromo benzoyl) propionic acid(BBPA).

3-(4-bromo benzoyl) propionic acid (BBPA) was obtained as white crystals with (75%) yield and was recrystallized by methanol. The molecular formula and molecular weight of the compound (BBPA) was found to be $C_{10}H_9BrO_3$ and 256 respectively. The FTIR spectrum showed stretching frequencies at 1674 cm^{-1}, 1700 cm^{-1}, 1072 cm^{-1}, 1584 cm^{-1}, and 3059 cm^{-1} which are characteristics of C = O (ketone), C = O (Acid), C – Br, C = C(Ar) and O – H, respectively. (Table 3.15).

Table 3.15: FTIR data of compound BBPA.

Compd.	C = O (cm^{-1})	C – Br (cm^{-1})	C = C(Ar) (cm^{-1})	O – H (cm^{-1})
BBPA	1674 (ketone), 1700 (Acid)	1072	1584	3059

The elemental analysis of BBPA shows good agreement between the calculated and found values which show the formation of this product and is as shown below:

Table 3.16: CHN analysis of BBPA($C_{12}H_{14}O_4$).

Analysis	%C	%H	%N
Calculated	46.72	3.53	----
Found	47.72	3.49	----

The ^{1}H NMR spectrum of 3-(4-Bromo benzoyl) propionic acid (BBPA) showed doublet of doublet at δ = 7.64 ppm for the aromatic protons at position 2′ and 6′ by coupling with ortho and meta protons respectively which is evident by J values 8.4 and 1.8 Hz. Similarly the aromatic protons at positions 3′ and 5′ also showed doublet of doublet at δ 7.86 ppm with ortho and meta coupling, J values being 8.7 and 2.1 Hz. The methylene protons at 2″and 3″ gave triplet each at δ 3.29 ppm and 2.81 ppm respectively with coupling constant 6.6 and 6.3 Hz respectively. The carboxyl proton at 5″ position gave singlet at δ 11.3 ppm. The δ values, multiplicity and J values of all protons of BBPA are tabulated in table 3.17.

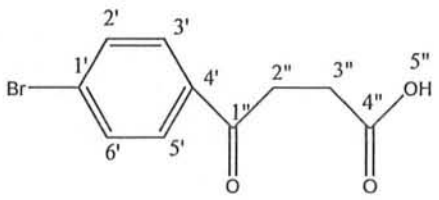


Table 3.17: ^{1}H NMR spectral data of compound BBPA ($CDCl_3$, 300 MHz).

Type of Proton	^{1}H (δ ppm)	Multiplicity	J(Hz)
2′ 6′	7.64	2H, dd	8.4,1.8
3′ 5′	7.86	2H, dd	8.7,2.1
2″	3.29	2H, t	6.6
3″	2.83	2H, t	6.3
5″	11.3	1H, s	–

In the ^{13}C NMR spectrum of 3-(4-Bromo benzoyl)propionic acid (BBPA), aromatic carbon at position 1′ gave a peak at δ 128.58 ppm. The aromatic carbons at positions 2′ and 6′ gave peak at δ 132.00 ppm. Similarly the carbons of aromatic ring at positions 3′ and 5′ gave peak at δ 129.58 ppm and that at position 4′ gave peak at δ 135.07 ppm. The other carbons at positions 1″, 2″, 3″and 4″ gave peaks at δ 196.83, 33.10, 27.87 and 178.35 ppm respectively. The δ values of all carbons of BPA are tabulated in table 3.18.

Table 3.18: ^{13}C NMR spectral data of compound BBPA ($CDCl_3$, 75 MHz).

Carbon #	^{13}C (δ ppm)	Carbon #	^{13}C (δ ppm)
1′	128.58	1″	196.83
2′ 6′	132.00	2″	33.10
3′ 5′	129.58	3″	27.87
4′	135.07	4″	178.35

The mass spectrum of BBPA showed molecular ion peak at m/z 256 in reasonable intensity (7%) which is in good agreement with the molecular weight of the

compound. The base peak appears at m/z 183 by loss of $C_3H_5O_2$ from the molecular ion. The base peak by loss of CO give peak at m/z 155 in good intensity (29%). This can further loss Br to give peak at m/z 76 which on further loss of C_2H_2 give peak at m/z 50. The ion at m/z 155 can also loss C_2H_2 to give peak at m/z 129 which on further loss of C_2H_2 give peaks at m/z 103. The complete fragmentation pattern of BBPA is given in fig 3.5.

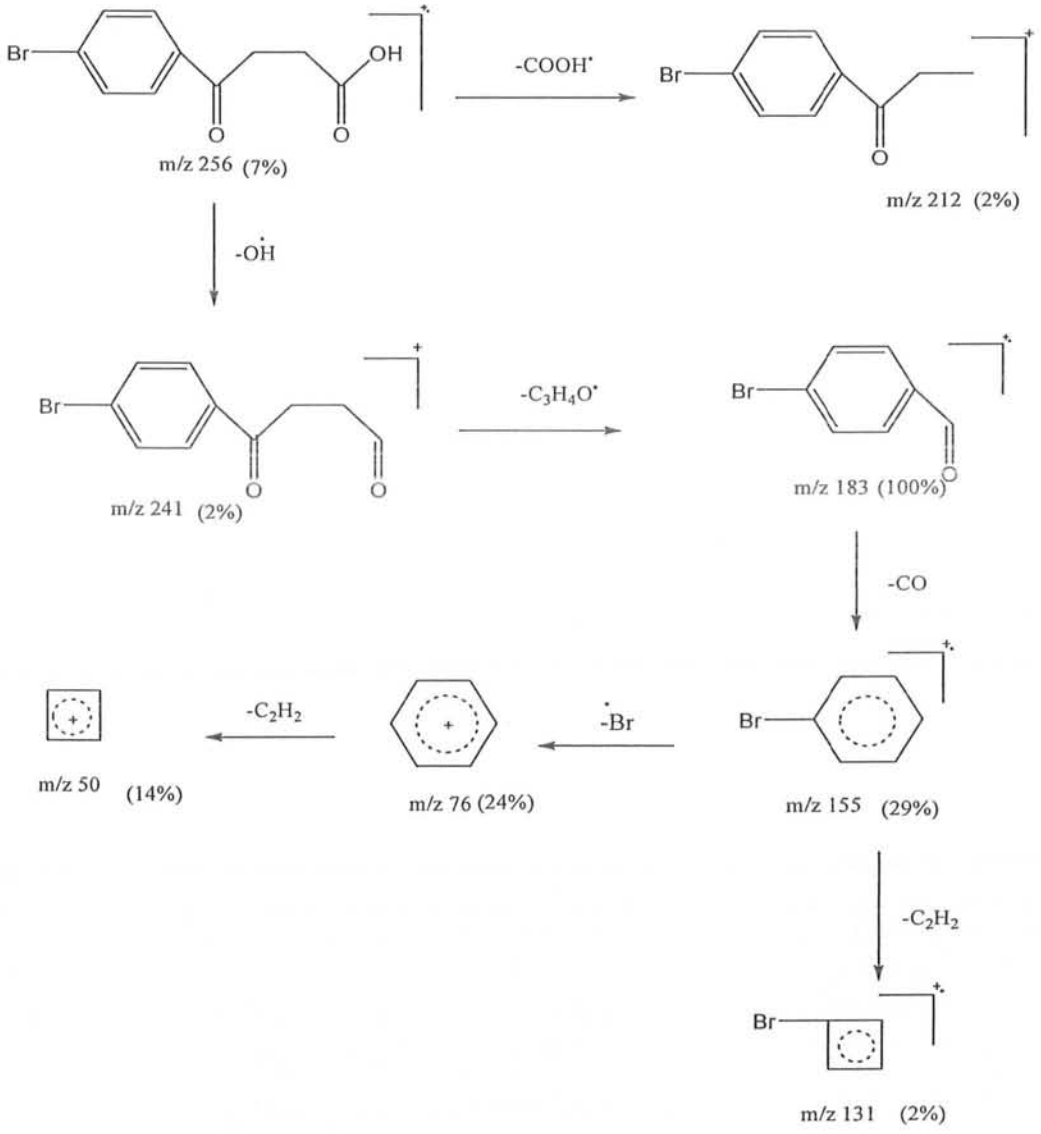
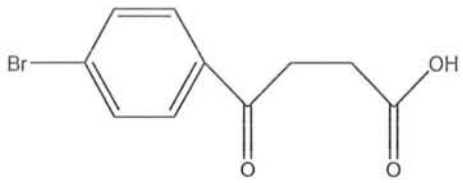


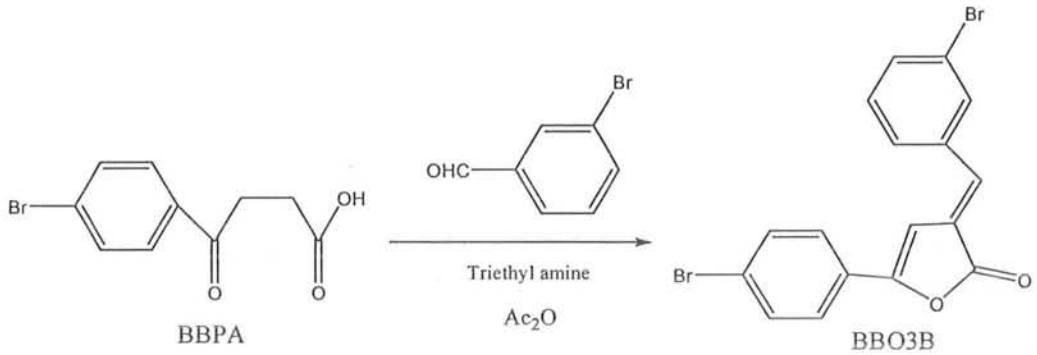
Fig 3.4: Mass fragmentation of BBPA.

On the basis of interpretation of IR, ^{1}H, ^{13}C NMR, mass spectral data and physical constants, the structure of (BBPA) was determined as 3-(4-bromo benzoyl) propionic acid :



3-(4-bromo benzoyl)propionic acid

3.6.2.2 Synthesis of 2-(3-Bromobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide (BBO3B):



To a solution of 3-(4-Bromo benzoyl)propionic acid (0.5g, 0.002 mol) and 3-bromobenzaldehyde (0.35g, 0.002 mol) in acetic anhydride (5 ml) was added triethyl amine (3-4 drops) and reaction mixture was refluxed for 4h under anhydrous conditions. After completion of reaction, the mixture was poured onto crushed ice and a colored solid mass, which separated out, was filtered, washed dried and crystallized from methanol: chloroform mixture (1:1) to give butenolide (BBO3B).

2-(3-Bromobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide (BBO3B) was obtained as yellow fluffy solid with (65%) yield and was recrystallized by methanol: chloroform (1:1). The molecular formula and molecular weight of the compound (BBO3B) was found to be $C_{17}H_{10}Br_2O_2$ and 404 respectively. The FTIR spectrum showed stretching frequencies at 1763 cm^{-1}, 1335 cm^{-1}, 1590 cm^{-1}, and 1071, 999 cm^{-1} which are characteristics of C = O, C – O, C = C(Ar), and C – Br respectively. (Table 3.19).

Table 3.19: FTIR data of compound BBO3B.

Compd.	C = O (cm^{-1})	C – O (cm^{-1})	C = C(Ar) (cm^{-1})	C – Br (cm^{-1})
BBO3B	1763	1335	1590	1071,999

The CHN analysis of BBO3B shows good agreement between the calculated and found values which show the formation of this product and is shown below:

Table 3.20: CHN analysis of BBO3B ($C_{17}H_{10}Br_2O_2$)

Analysis	%C	%H	%N
Calculated	50.28	2.48	----
Found	49.20	2.80	----

The ^{1}H-NMR spectrum of 2-(3-Bromobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide (BBO3B) showed two characteristic singlets at δ 6.91 and 7.76 ppm, which could be assigned to the lactone ring β-H and the olefinic hydrogen of the arylidene substituent respectively. A doublet of doublet at δ 7.37 ppm is observed for aromatic protons at 3′ and 5′ due to ortho and meta coupling as shown by J values 8.8 and 3 Hz while a multiplet in the range δ =7.54-7.67 ppm is observed for aromatic protons at positions 2′, 6′ , 2″, 4″ and 6″. A doublet of doublet at δ 7.34 ppm is observed for aromatic proton at 5″ due to ortho and meta coupling with J values being 7.8 and 1.2 Hz. The δ values, multiplicity and J values of all protons of BBO3B are tabulated in table 3.21.

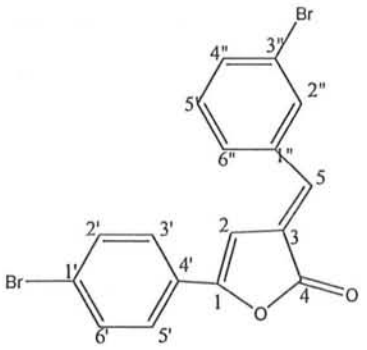


Table 3.21: ^{1}H NMR spectral data of compound BBO3B ($CDCl_3$, 300 MHz).

Type of Proton	^{1}H (δ ppm)	Multiplicity	J(Hz)
2	6.91	1H, s	---
5	7.76	1H, s	---
2′ 6′	7.54-7.67	2H,m	---
3′ 5′	7.37	2H, dd	8.8,3
2″	7.54-7.67	1H,dd	6.2,2.1
4″	7.54-7.67	1H, m	--
5″	7.34	1H, dd	7.8,1.2
6″	7.54-7.67	1H, m	--

In the ^{13}C NMR spectrum of 2-(3-Bromobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide (BBO3B), a characteristic peak at δ 99.92 ppm is observed for the lactone ring β-C at position 2 and a peak at δ 168.61 ppm for the olefinic C at position 5. A peak at δ 156.77 ppm is observed for the carbon at position 1. Similarly C at position 3 and 4 gave peak at δ 130.64 and 168.61 ppm respectively. The aromatic C at 1′ gave peak at δ 123.27 ppm. Similarly the aromatic carbons at positions 2′, 6′and 3′, 5′ gave peaks at δ 132.27 and 126.91 ppm respectively. The aromatic C at position 4′ gave peak at δ 128.65 ppm. The arylidene ring carbons gave peaks in close range i.e. δ 125-133 ppm. The δ values of all carbons of BBO3B are tabulated in table 3.22.

Table 3.22: ^{13}C NMR spectral data of compound BBO3B ($CDCl_3$, 75 MHz).

Carbon #	^{13}C (δ ppm)	Carbon #	^{13}C (δ ppm)
1	156.77	4′	128.65
2	99.92	1″	133.91
3	130.64	2″	125.27
4	168.61	3″	126.35
5	137.02	4″	132.43
1′	123.27	5″	126.35
2′ 6′	132.27	6″	125.27
3′ 5′	126.91	------	------

The mass spectrum of BBO3B showed characteristic isotopic peaks for bromine. The molecular ion peak appears at reasonable intensities (54%) at m/z 404 which is found in good agreement with molecular weight of the compound. The molecular ion on loss of bromine gave the peak at m/z 325.This fragment ion can further loss CO to give peak at m/z 297 which subsequently loses C_9H_6 to give base peak at m/z 183 which on loss of CO give peak at m/z 155 in good intensity (29%). It can further loss bromine to give peak at m/z 76 which on further loss of C_2H_2 give peaks at m/z 50. The peak at m/z 297 can also lose oxygen to give peak at m/z 281 which on further loss of bromine give peak at m/z 205 in good intensity (48%). The complete fragmentation pattern of BBO3B is given in fig 3.6.

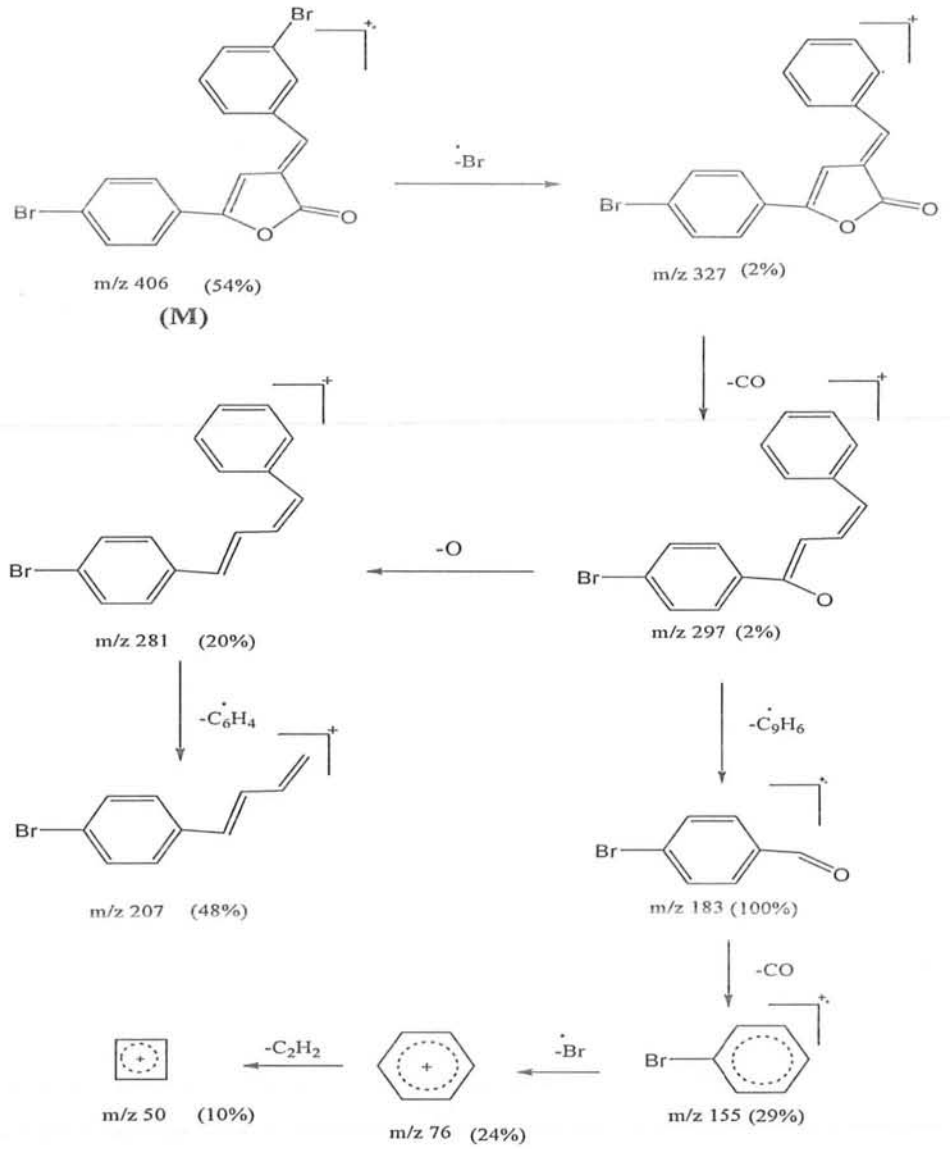
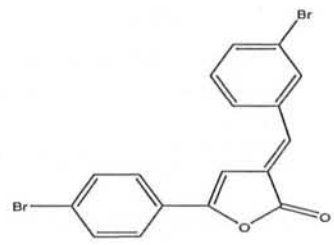


Fig 3.5: Mass fragmentation pattern of BBO3B.

On the basis of interpretation of IR, ^{1}H, ^{13}C NMR, mass spectral data and physical constants, the structure of (BBO3B) was determined as 2-(3-Bromobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide :



2-(3-Bromobenzylidene)-4-(4-bromo phenyl)but-3-en-4-olide

3.6.2.3 Synthesis of other B-Series Butenolides:

The synthetic procedure used for the synthesis of BBO3B was also used for the synthesis of other members of the B-series of Butenolides. The molar ratios, physical data, FTIR, ^{1}H, ^{13}C NMR and EIMS data for these compounds are tabulated in Table 3.23-3.28.

Table 3.23: Molar ratios of B-series compounds.

Compd.	Benzoyle propionic acid	Substituted benzaldehyde	Yield	Solvent for Recrystallization (1:1)
BBO2C	0.5 g (0.002 mol)	0.213 ml (0.002 mol)	0.55g (70%)	Methanol: Chloroform
BBO4C	0.5 g (0.002 mol)	0.266 g (0.002 mol)	0.4g (50%)	Methanol: Chloroform
BBO4F	0.5 g (0.002 mol)	0.203 ml (0.002 mol)	0.42g (50%)	Methanol: Chloroform
BBO3M	0.5 g (0.002 mol)	0.230 ml (0.002 mol)	0.45g (50%)	Methanol: Chloroform
BBO2H	0.5 g (0.002 mol))	0.202 ml (0.002 mol)	0.49g (60%)	Methanol: Chloroform
BBO3N	0.5 g (0.002 mol)	0.286 g (0.002 mol)	0.56g (65%)	Methanol: Chloroform
BBO4N	0.5 g (0.002 mol)	0.286 g (0.002 mol)	0.6g (70%)	Methanol: Chloroform
BBO4T	0.5 g (0.002 mol)	0.223 ml (0.002 mol)	0.48g (60%)	Methanol: Chloroform

Table 3.24: Physical data of B-series compounds.

Compd.	Mol. Formula	Mol. Wt.	m.p. °C	R_f-Values x 100	Soluble
BBO2C	$C_{17}H_{10}BrClO_2$	360	234-235	70	$CHCl_3$
BBO4C	$C_{17}H_{10}BrClO_2$	360	272-273	75	$CHCl_3$
BBO4F	$C_{17}H_{10}BrFO_2$	344	143-244	68	$CHCl_3$
BBO3M	$C_{18}H_{13}BrO_3$	356	180-181	70	$CHCl_3$
BBO2H	$C_{17}H_{11}BrO_3$	342	175-176	68	$CHCl_3$
BBO3N	$C_{17}H_{10}BrNO_4$	371	224-225	70	$CHCl_3$
BBO4N	$C_{17}H_{10}BrNO_4$	371	277-278	70	$CHCl_3$
BBO4T	$C_{18}H_{13}BrO_2$	340	261-262	75	$CHCl_3$

* Solvent for R_f values = Pet. ether : ethyl acetate (4:1)

Table 3.25: FTIR data of B-series compounds.

Comp.	C=O (cm^{-1})	C=C(Ar) (cm^{-1})	C–Br (cm^{-1})	C–X (cm^{-1})
BBO2C	1775	1584	1069	998(C-Cl)
BBO4C	1756	1585	1092	998(C-Cl)
BBO4F	1757	1585	1070	996 (C-F)
BBO3M	1754	1589	1069	997(C-OCH_3)
BBO2H	1762	1582	1070	3140 (C-OH)
BBO3N	1784	1585	1067	1517, 1358 (C-N)
BBO4N	1761	1600	1073	1520, 1344 (C-N)
BBO4T	1755	1584	1067	1402(C-CH_3)

Table 3.26: ^{1}H NMR spectral data of B series compounds $CDCl_3$, 300 MHz.

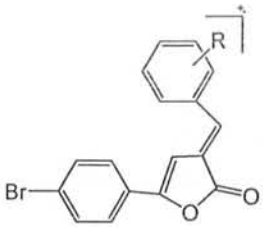
Protons	Spectral data	BBO2C	BBO4C	BBO4F	BBO3M	BBO2H	BBO3N	BBO4N	BBO4T
2	^{1}H-δppm Multiplicity J(Hz)	6.87 s ----	6.89 s ---	6.90 s ---	6.94 s ---	6.87 s ---	6.92 s ---	6.90 s ---	6.91 s ---
5	^{1}H-δppm Multiplicity J(Hz)	7.86 s --	7.59 s ---	7.59 s ---	7.60 s ---	7.52 s ---	7.70 s ---	7.73 s ---	7.59 s ---
2′, 6′	^{1}H-δppm Multiplicity J(Hz)	7.38 dd 8.8,3	7.38 dd 8.8,2.4	7.38 dd 9,3	7.58-7.66 m ---	7.73 dd 9,2.1	7.38 dd 8.8,3	7.38 dd 8.7,3	7.38 dd 8.8,3
3′, 5′	^{1}H-δppm Multiplicity J(Hz)	7.19 dd 8.8,3	7.19 dd 9,2.1	7.19 dd 8.8,2.4	7.42 dd 8.3,2.1	7.47 dd 8.8,2.9	7.19 dd 8.8,3	7.19 dd 9,3	7.18- 7.19 m ---
2″	^{1}H-δppm Multiplicity J(Hz)	---	7.22- 7.24 m ---	7.28 dd 7,3	6.99-7.02 m ---	----	8.23 dd 7.7,2.4	7.56 dd 8.7,2.4	7.18- 7.19 m ---
3″	^{1}H-δppm Multiplicity J(Hz)	7.22 dd 9,2.1	7.22- 7.24 m ---	6.92 dd 7.2,3	----	7.20 dd 6.8,2.6	----	8.14 dd 6.6,2.4	7.01 dd 6.7,2.4
4″	^{1}H-δppm Multiplicity J(Hz)	7.08 m ---	----	----	6.99-7.02 m ---	7.58- 7.65 m ---	8.07 dd 8.7,2.4	----	----
5″	^{1}H-δppm Multiplicity J(Hz)	7.09 m ---	7.22- 7.24 m ---	6.92 dd 7.6,2.9	7.42 dd 9,2.1	7.58- 7.65 m ---	7.47- 7.69 m ---	8.14 dd 8.6,2.4	7.01 dd 7.9,2.4
6″	^{1}H-δppm Multiplicity J(Hz)	7.24 dd 8,2.3	7.22- 7.24 m ---	7.28 dd 9,2.1	7.25 dd 8.2,2.7	7.35- 7.40 m ----	7.47- 7.69 m ---	7.56 dd 7,2.4	7.18- 7.19 m ---
X-H	-----	---	----	----	3.89 s	2.40 s	---	----	2.35

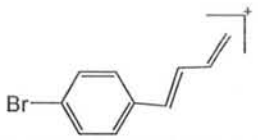
Table 3.27: ^{13}C NMR spectral data of B-series compounds ($CDCl_3$, 75 MHz)

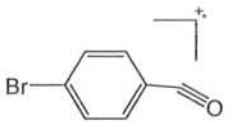
carbon No.	^{13}C-δ(ppm), Compounds							
	BBO2C	BBO4C	BBO4F	BBO3M	BBO2H	BBO3N	BBO4N	BBO4T
1	146.2	156.77	156.77	155.95	149.82	149.82	149.82	149.82
2	99.27	99.92	99.92	100.41	100.27	100.27	100.27	100.27
3	129.60	130.64	130.64	130.19	129.48	129.48	129.48	128.50
4	167.35	167.4	169.50	169.04	169	169	169	169.8
5	137	139.6	137.02	136.28	132.24	139.6	139.6	139.6
1′	122.3	122.3	123.27	122.62	123.35	123.35	123.35	122.35
2′ 6′	132.27	132.27	132.27	132.20	129	129	129	129
3′ 5′	126.91	126.91	126.91	126.80	126.85	126.85	126.85	126.85
4′	128.65	128.65	128.65	126.95	128.07	128.07	128.07	128.07
1″	132	132	135.8	136	126.48	135.49	141.3	128
2″	131.2	133.87	124	115.67	156.48	119.84	127.3	126.3
3″	125.50	128.8	128.14	159.94	125.10	158.94	121	129
4″	133.87	131.2	162.14	124.89	131.41	128	147.6	137.6
5″	124.90	128.8	115.4	132	121.3	129.66	121	129
6″	127.8	127.8	128	125.45	127.8	132.5	127.3	126.3
X-C	--	--	--	55.45	--	--	--	24.3

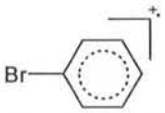
Table 3.28: EIMS data of B series compounds.

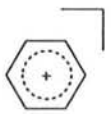
Compd.	$M^{+\bullet}$	Peaks (m/z, %)				
		F_1	F_2	F_3	F_4	F_5
BBO2C	362(50)	205(15)	183(100)	155(28)	103(15)	76(25)
BBO4C	362(100)	205(20)	183(85)	155(30)	103(20)	76(20)
BBO4F	346(100)	205(15)	183(68)	155(30)	103(19)	76(22)
BBO3M	358(38)	205(10)	183(100)	155(25)	103(20)	76(23)
BBO2H	344(100)	205(15)	183(80)	155(38)	103(15)	76(33)
BBO3N	373(100)	205(16)	183(45)	155(30)	103(16)	76(20)
BBO4N	373(100)	205(18)	183(35)	155(75)	103(20)	76(30)
BBO4T	342(100)	205(15)	183(85)	155(35)	103(20)	76(26)

$M^{+\bullet}$ 

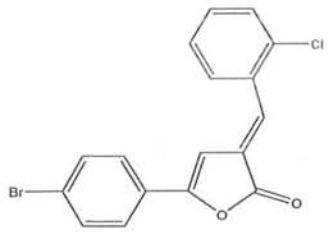
F_1 

F_2 

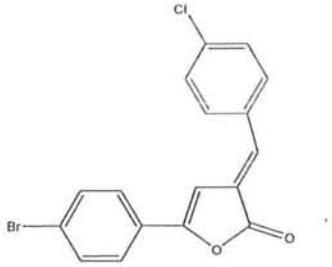
F_3 

F_5 

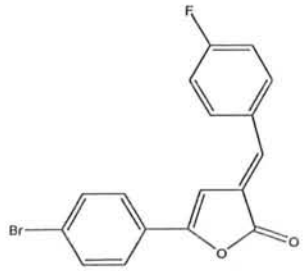
The interpretation of the physical and spectral data of the compounds elucidated the following structures for the B-series of butenolides:



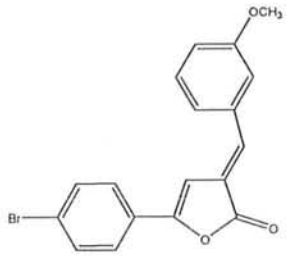
2-(2-Chlorobenzylidene)-4-(4-bromo phenyl)but3-en-4-olide **(BBO2C)**



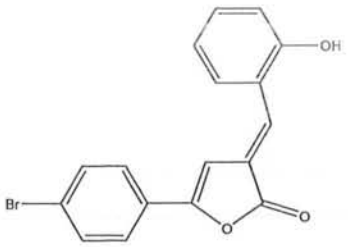
2-(4-Chlorobenzylidene)-4-(4-bromo phenyl)but3-en-4-olide **(BBO4C)**



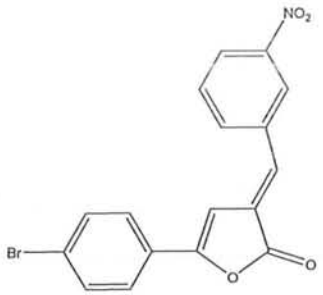
2-(4-Florobenzylidene)-4-(4-bromo phenyl)but3-en-4-olide **(BBO4F)**



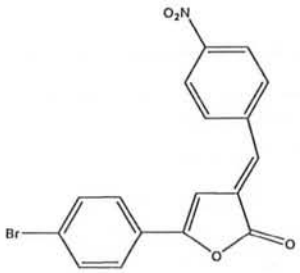
2-(3-Methoxybenzylidene)-4-(4-bromo phenyl)but3-en-4-olide **(BBO3M)**



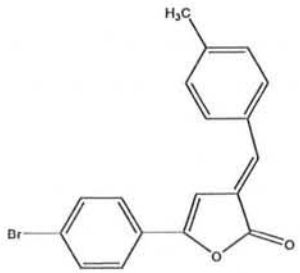
2-(2-Hydroxybenzylidene)-4-(4-bromo phenyl)but3-en-4-olide **(BBO2H)**



2-(3-Nitrobenzylidene)-4-(4-bromo phenyl)but3-en-4-olide **(BBO3N)**



2-(4-Nitrobenzylidene)-4-(4-bromo phenyl)but3-en-4-olide **(BBO4N)**



2-(4-Methylbenzylidene)-4-(4-bromo phenyl)but3-en-4-olide **(BBO4T)**

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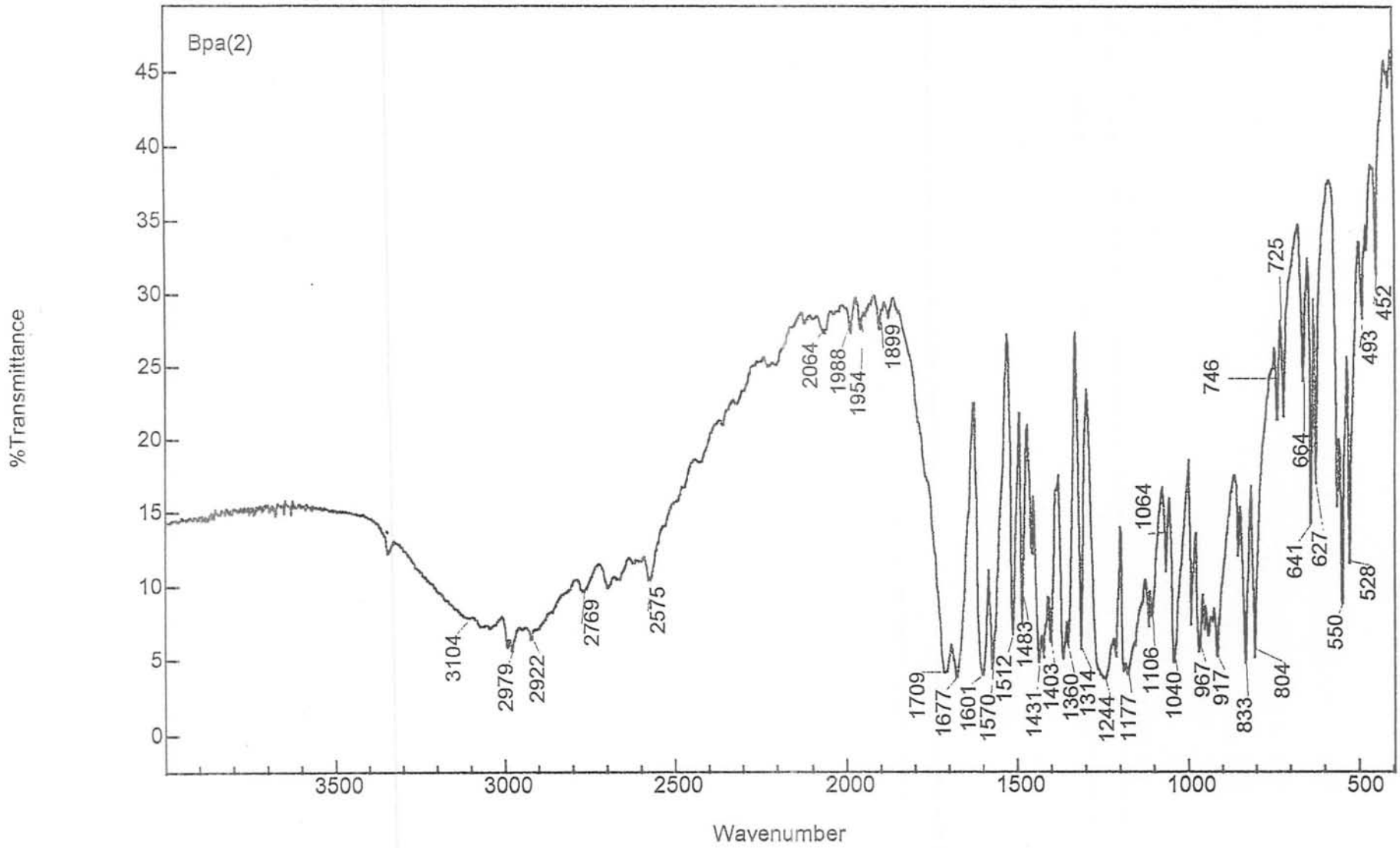
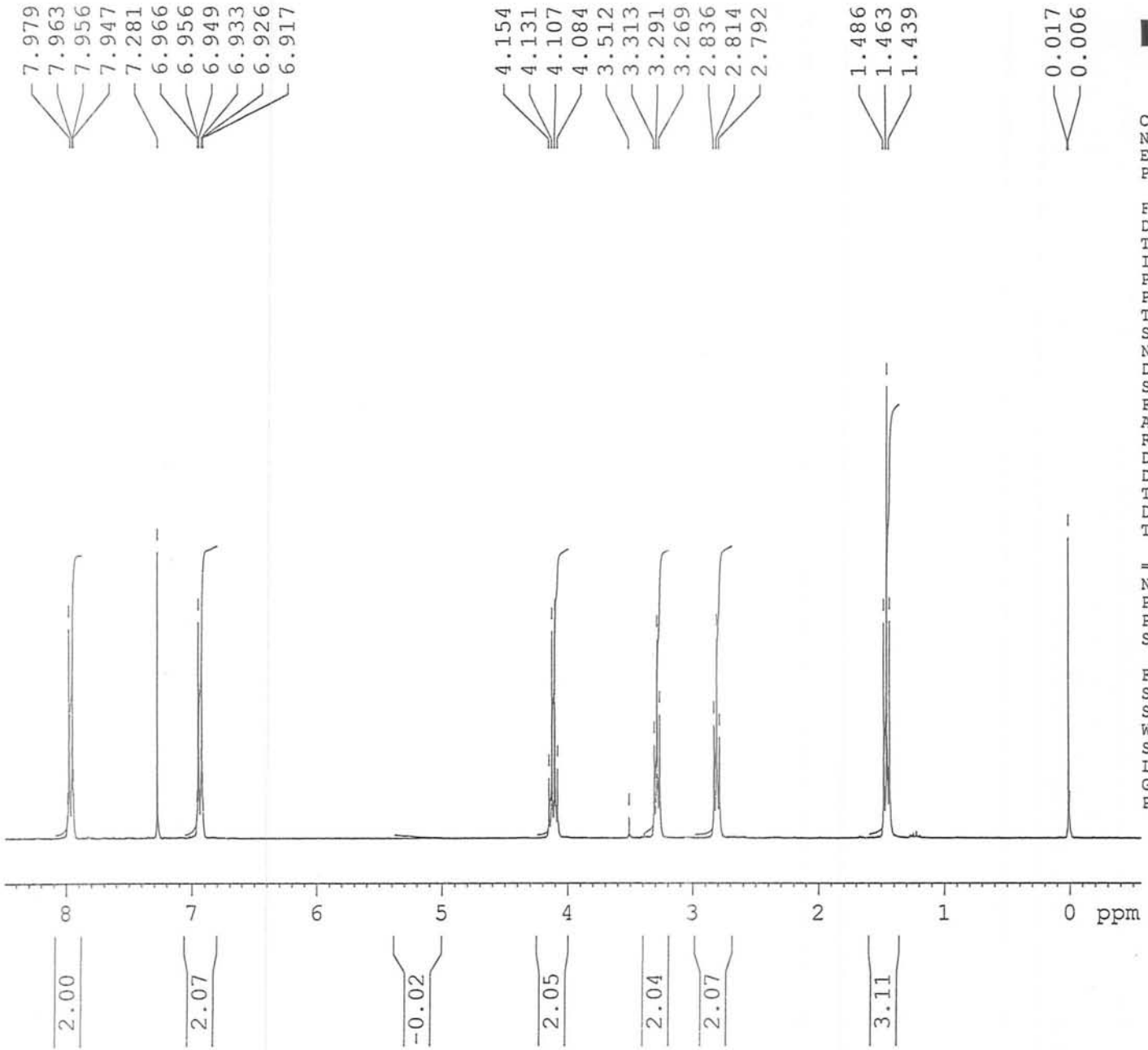


Name
Bpa(2) ——

Dr. AURANGZEB HASSAN/SAJID ALI/BPA_1HNMR_CDCL3



BRUKER

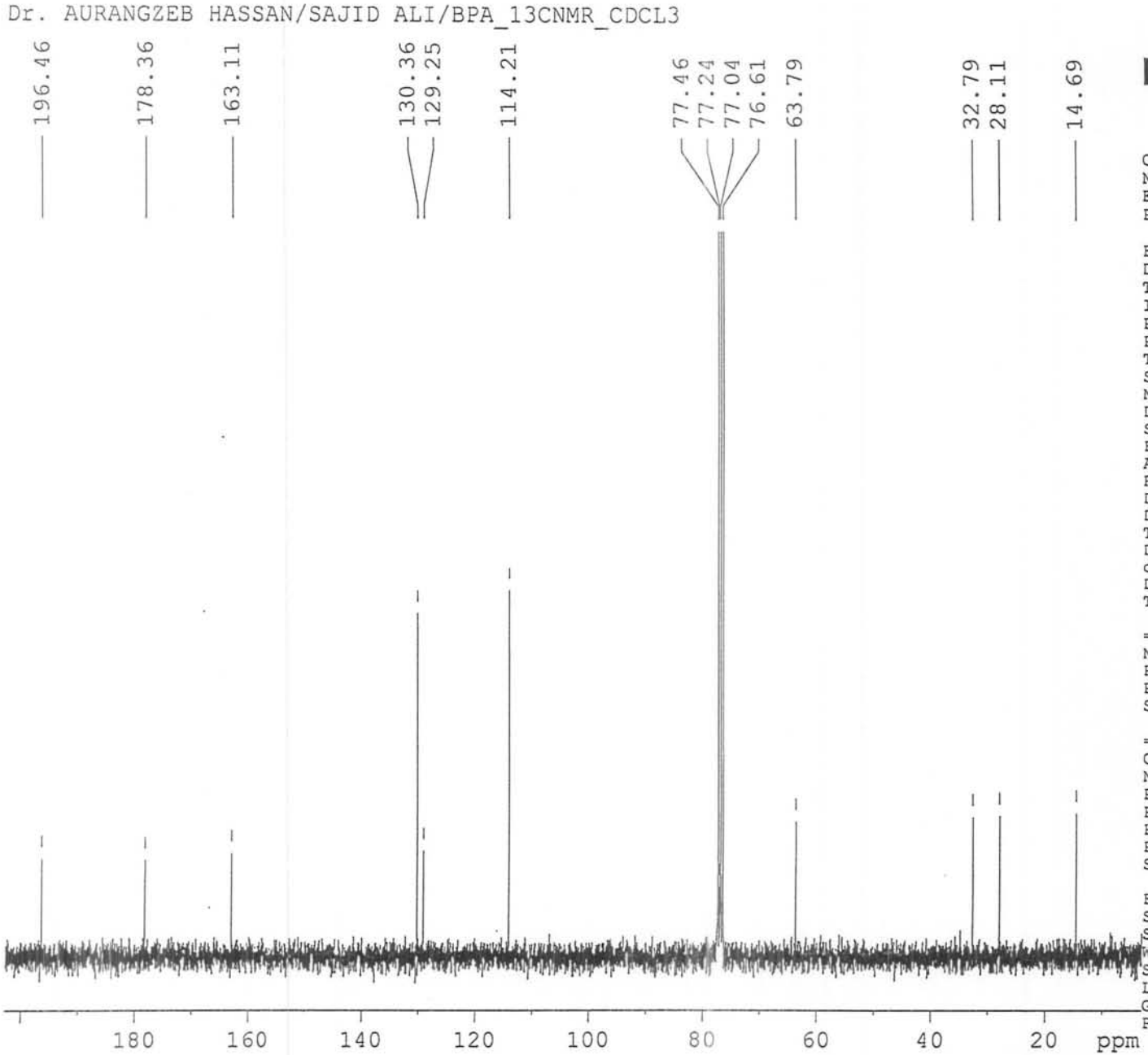
Current Data Parameters
NAME BPA_1HNMR_CDCL3
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20061206
Time 11.46
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 645.1
DW 81.000 usec
DE 6.00 usec
TE 291.5 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz

F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Dr. AURANGZEB HASSAN/SAJID ALI/BPA_13CNMR_CDCL3



BRUKER

Current Data Parameters
NAME BPA_13CNMR_CDCL3
EXPNO 1
PROCNO 1

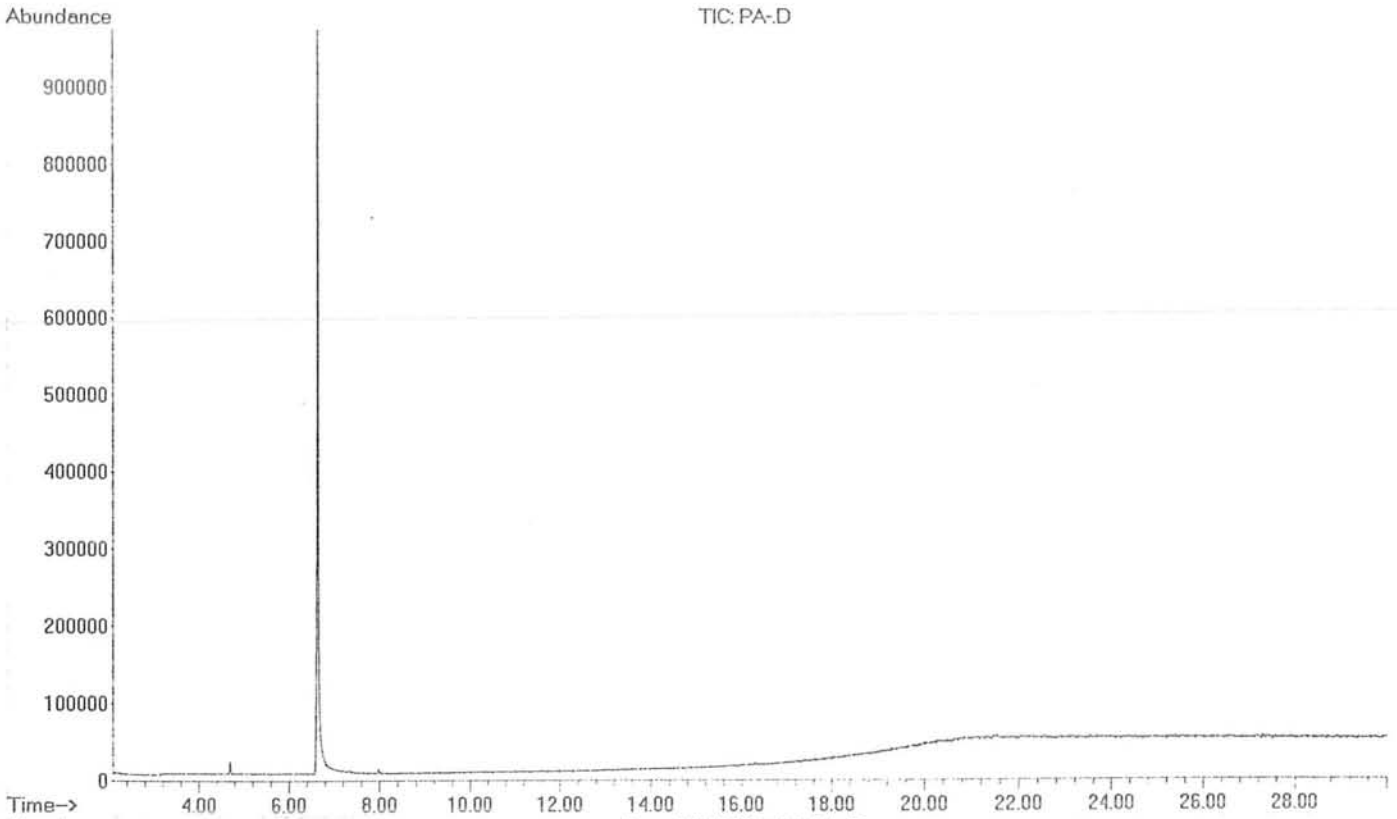
F2 - Acquisition Parameters
Date_ 20061206
Time 11.42
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 1290.2
DW 27.800 usec
DE 6.00 usec
TE 292.1 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

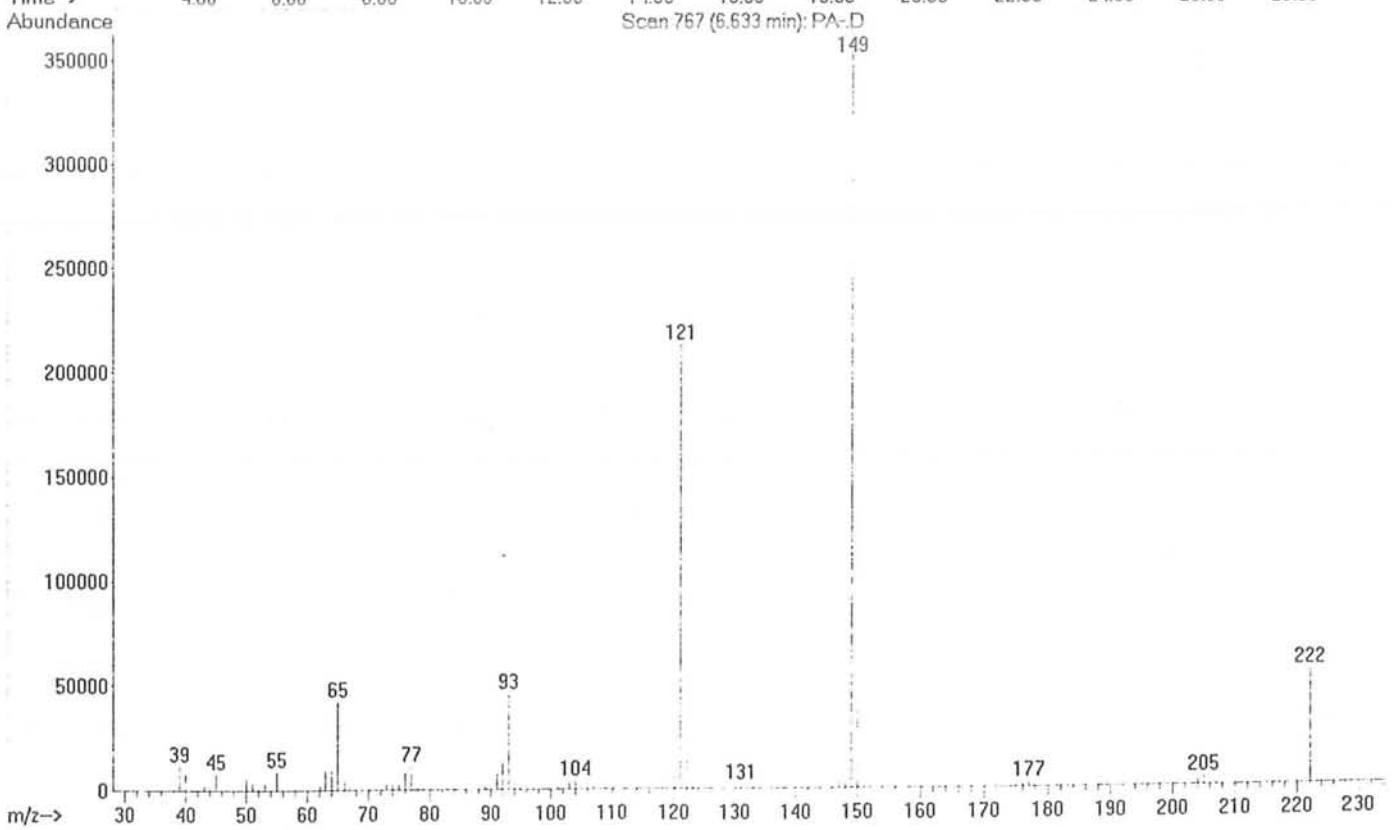
======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz

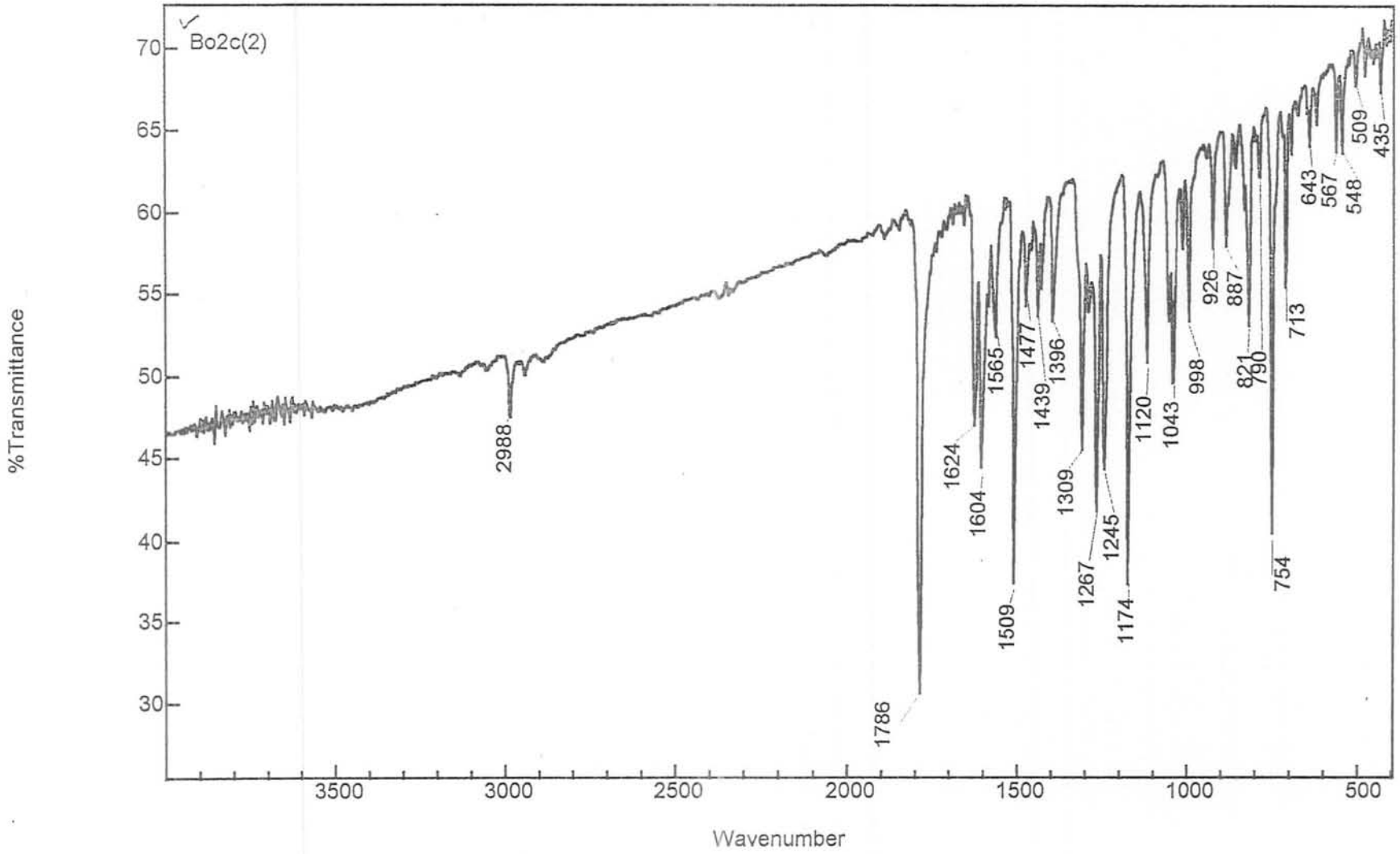
F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

File :D:\MSDChem\1\DATA\Prof.Dr.Aurangzeb\Sajid Ali\PA-.D
Operator : FARHAN
Acquired : 14 Nov 2006 13:00 using AcqMethod LIQUID.M
Instrument : Agilent GCMS
Sample Name: SAJID ALI/CHEMISTRY QAU
Misc Info : 200-300'C 5'C/MIN
Vial Number: 1



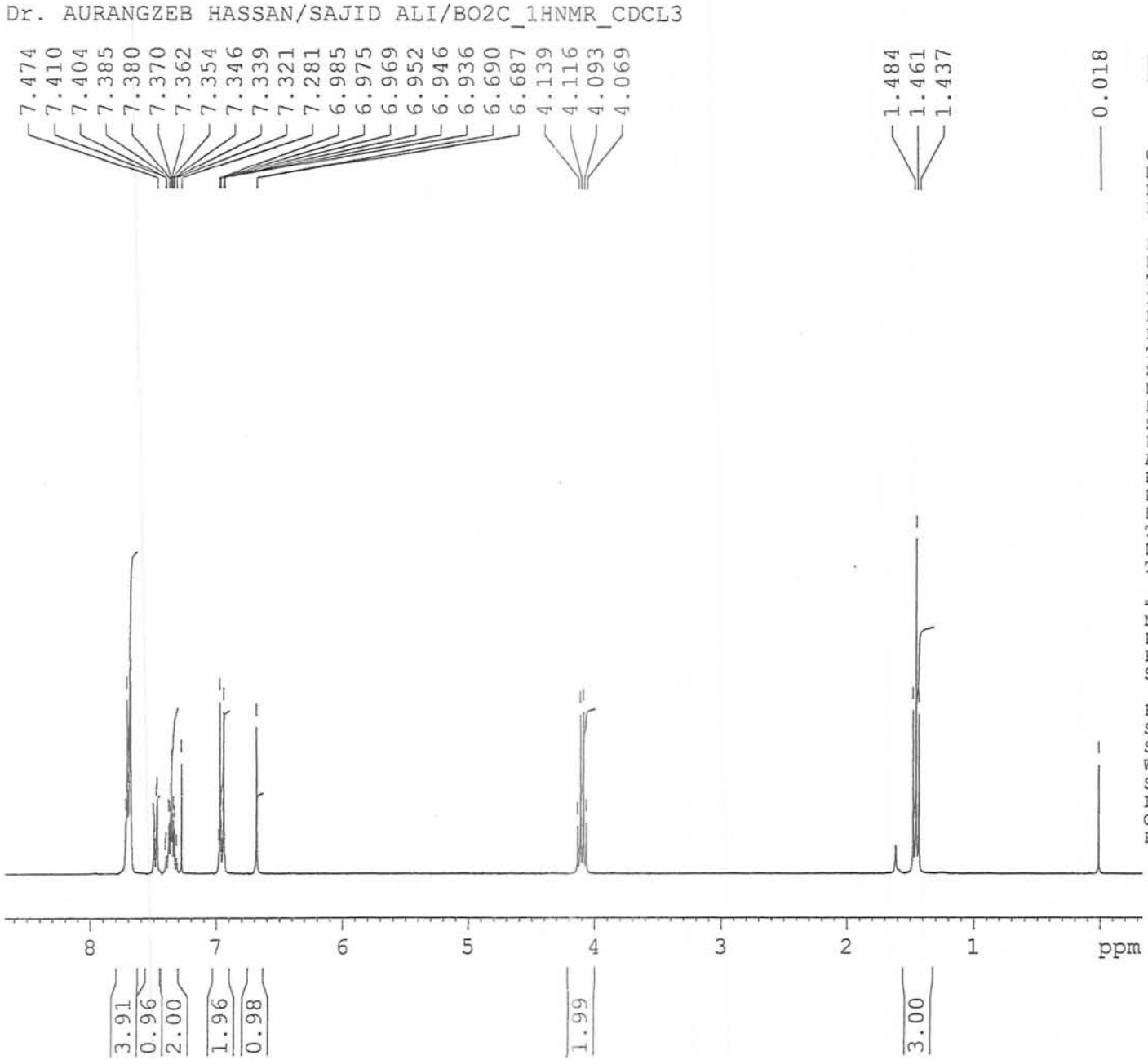


Bio-Rad Merlin



Name
Bo2c(2) ——

Dr. AURANGZEB HASSAN/SAJID ALI/BO2C_1HNMR_CDCL3



BRUKER

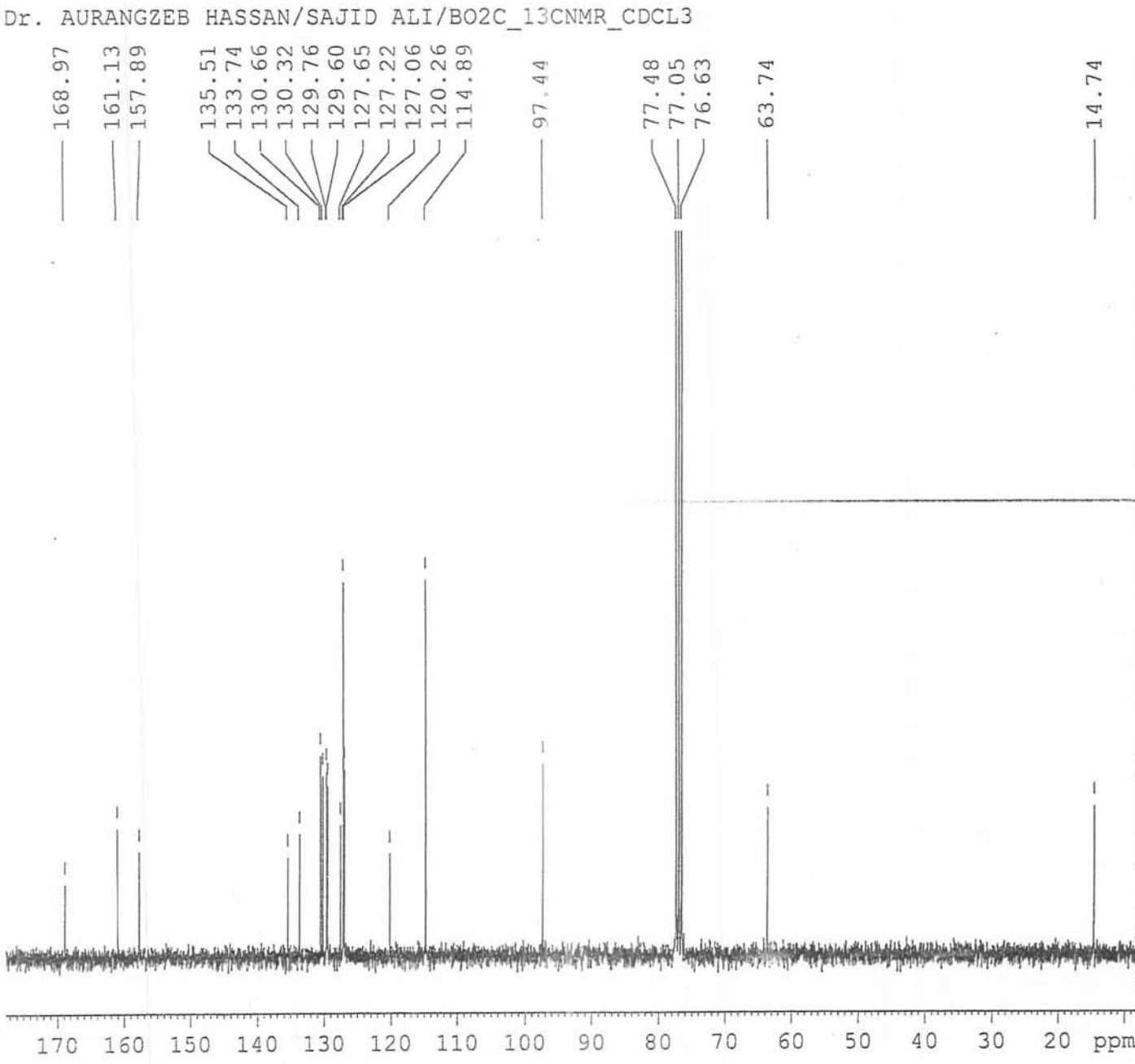
Current Data Parameters
NAME BO2C_1HNMR_CDCL3
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20061130
Time 14.17
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 4
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 322.5
DW 81.000 usec
DE 6.00 usec
TE 290.9 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz

F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Dr. AURANGZEB HASSAN/SAJID ALI/BO2C_13CNMR_CDCL3



BRUKER

Current Data Parameters
NAME BO2C_13CNMR_CDCL3
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20061130
Time 14.11
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 1149.4
DW 27.800 usec
DE 6.00 usec
TE 291.4 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

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perator    : FARHAN AHMED
cquired    : 19 Dec 2006  14:01     using AcqMethod LIQUID.M
nstrument :    Agilent GCMS
ample Name: SAJID ALI / CHEMISTRY QAU
isc Info   : 150-250'C   10'C/MIN
ial Number: 1
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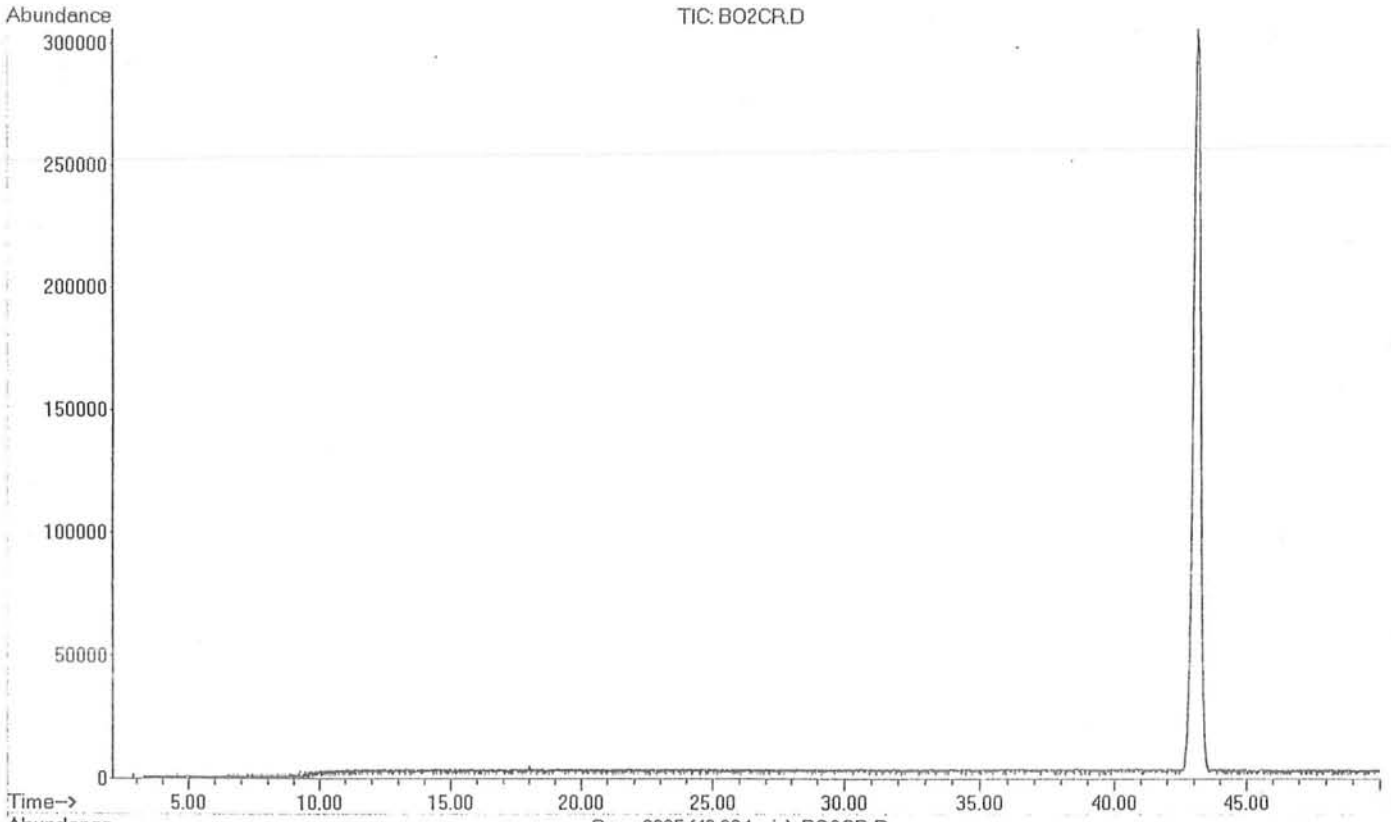
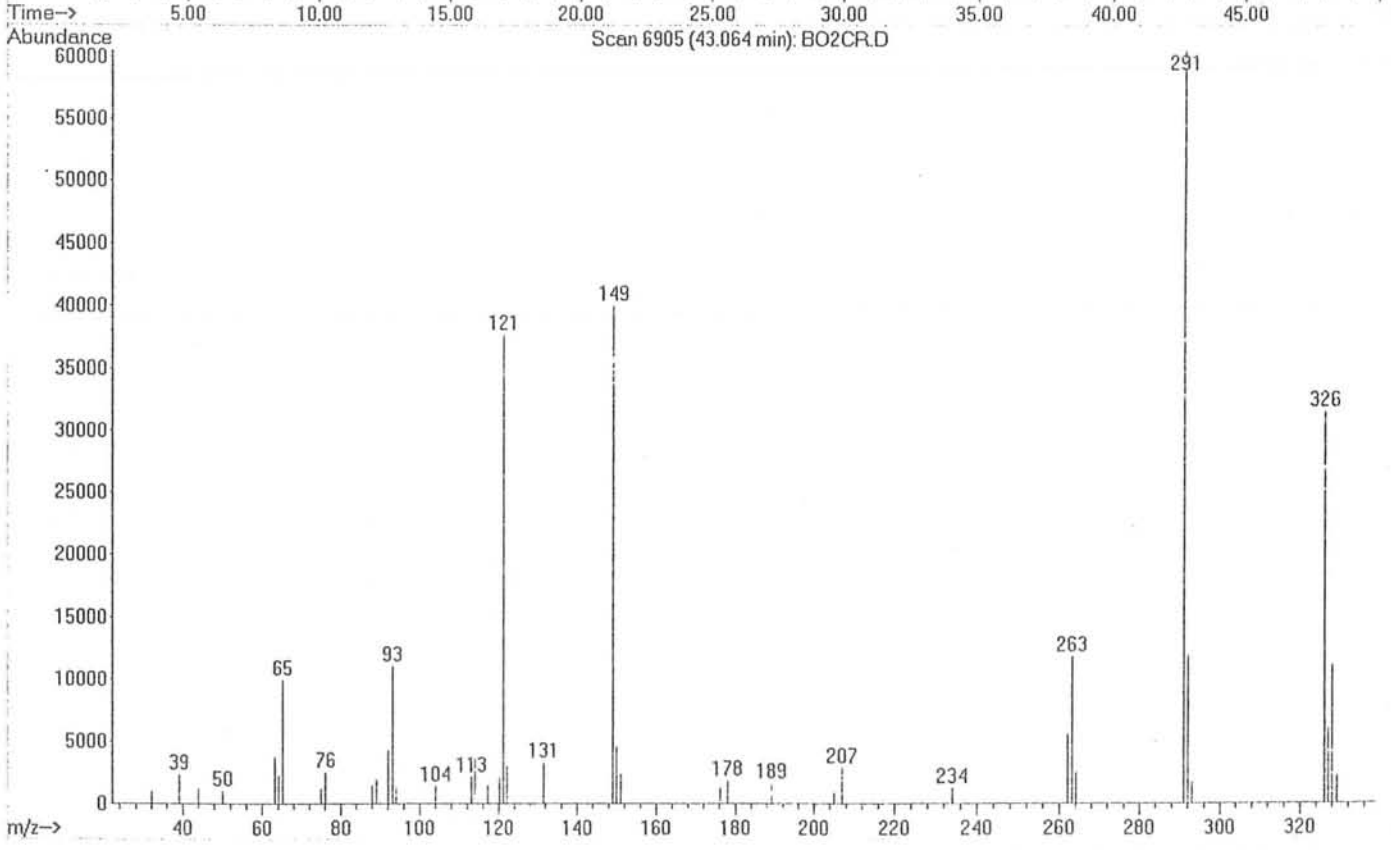
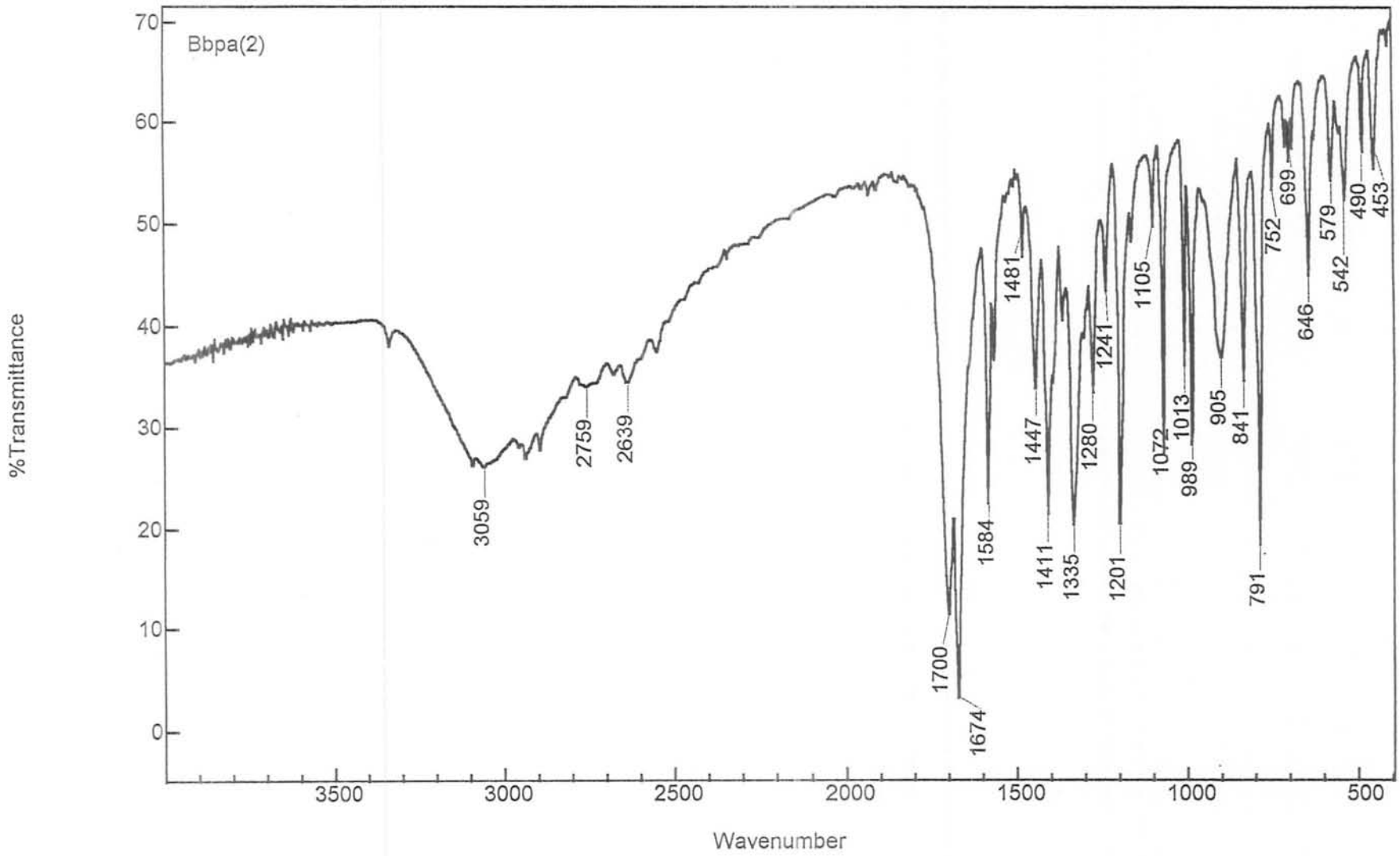


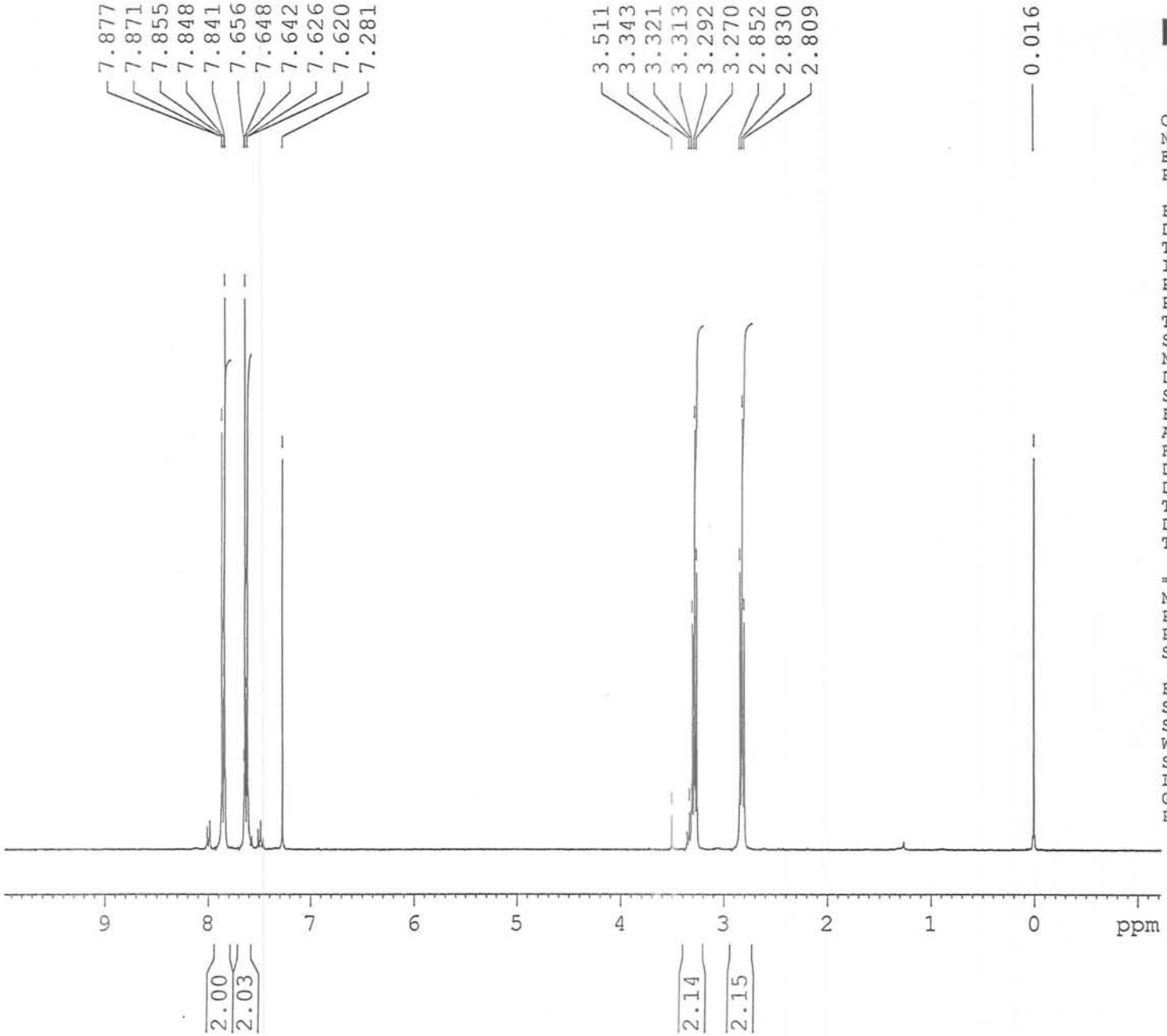


Bio-Rad Merlin



Name
Bbpa (2) ——

Dr. AURANGZEB HASSAN/SAJID ALI/BBPA_1HNMR_CDCL3



Current Data Parameters

NAME	BBPA_1HNMR_CDCL3
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20061226
Time	11.49
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	812.7
DW	81.000 usec
DE	6.00 usec
TE	292.7 K
D1	1.00000000 sec
TD0	1

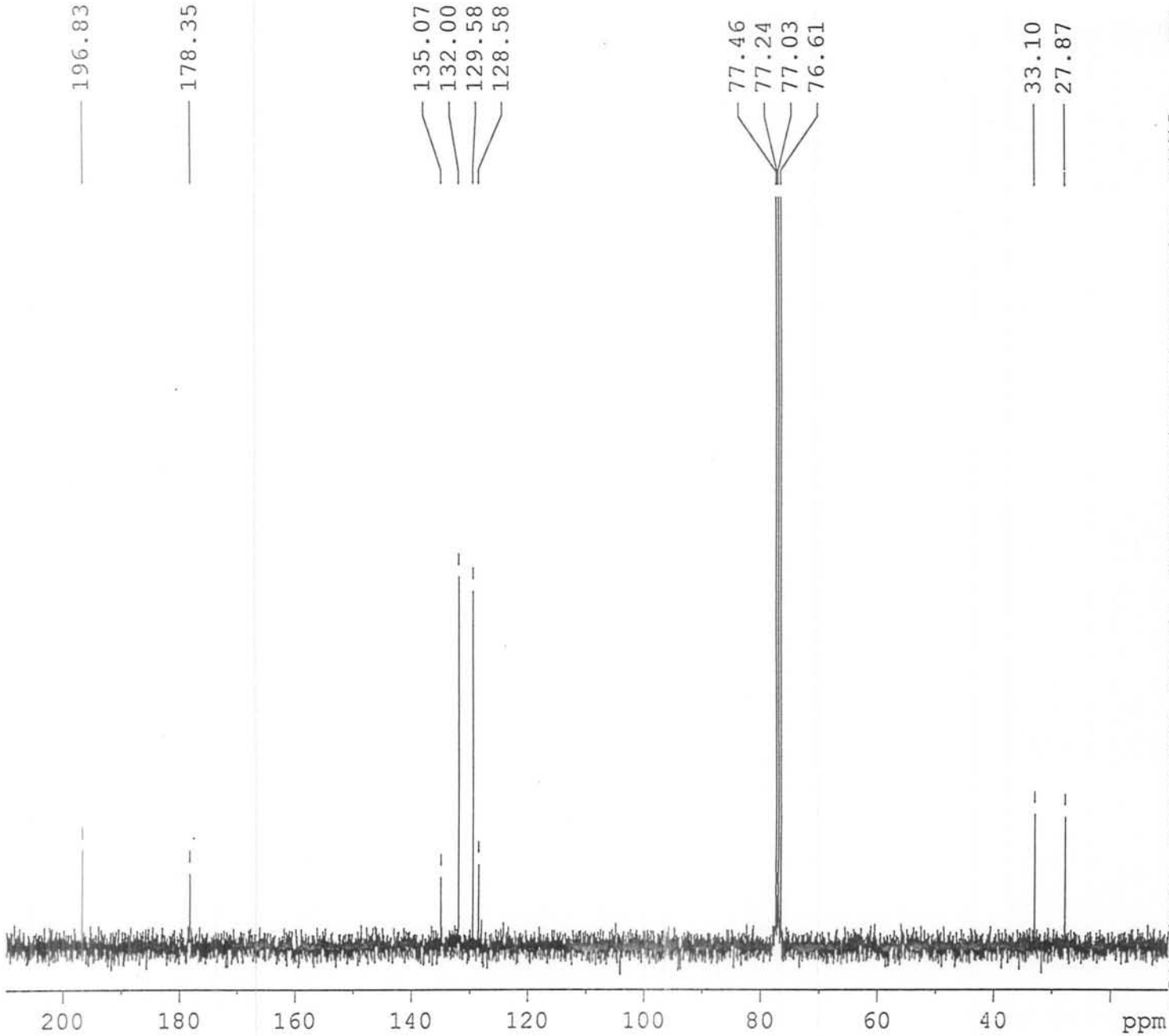
======== CHANNEL f1 ========

NUC1	1H
P1	9.00 usec
PL1	2.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

Dr. AURANGZEB HASSAN/SAJID ALI/BBPA_13CNMR_CDCL3



BRUKER

Current Data Parameters
NAME BBPA_13CNMR_CDCL3
EXPNO 1
PROCNO 1

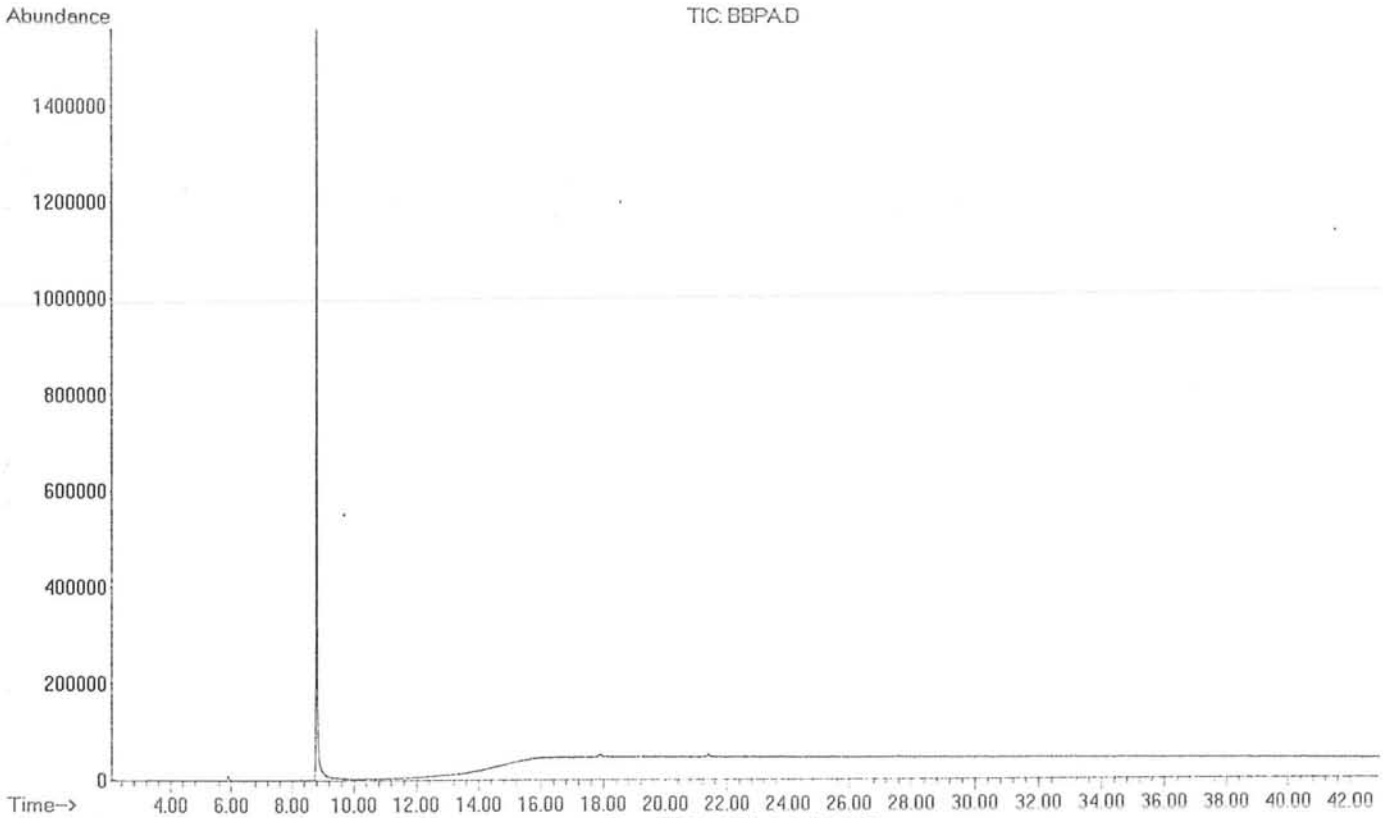
F2 - Acquisition Parameters
Date_ 20061226
Time 11.46
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 2
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 1448.2
DW 27.800 usec
DE 6.00 usec
TE 293.1 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

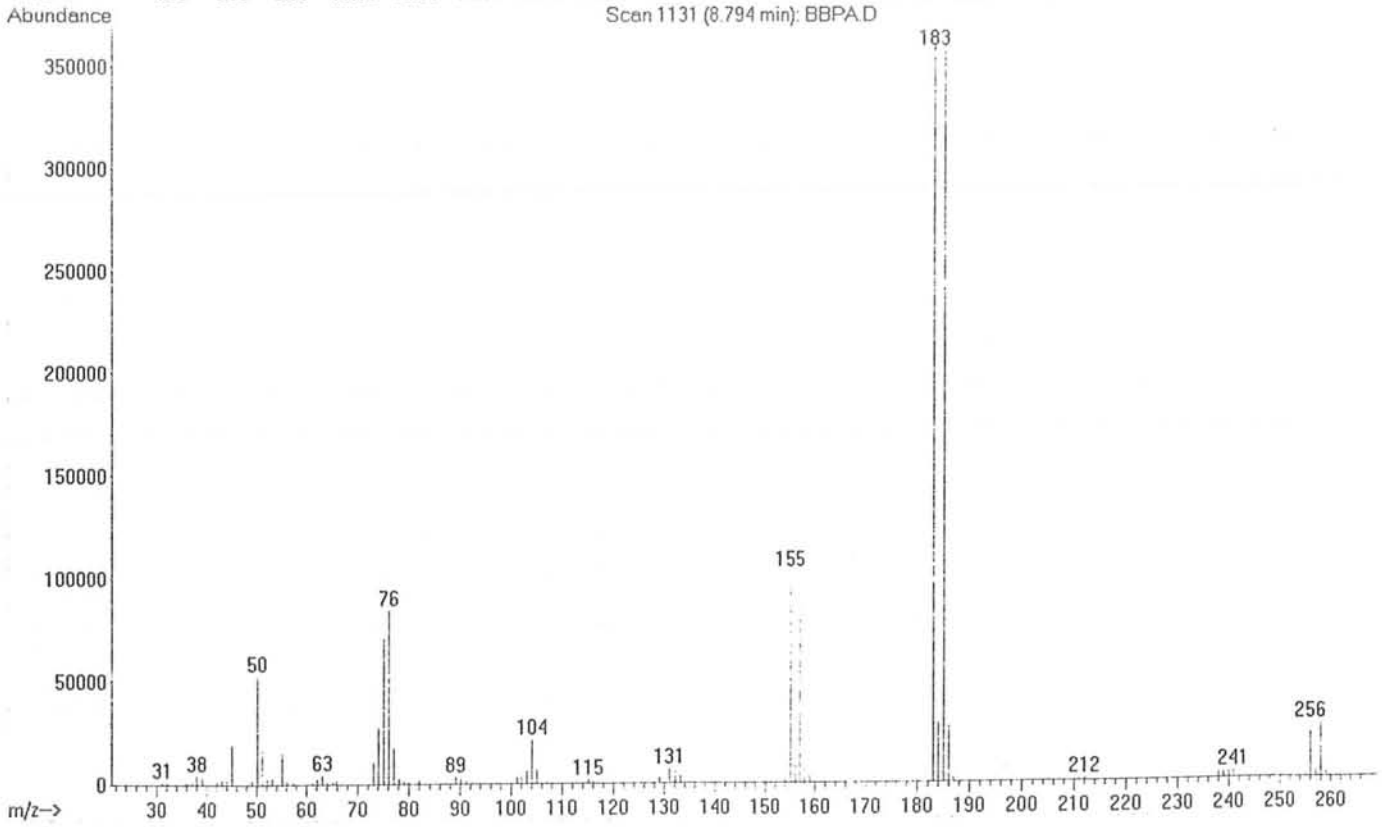
======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz

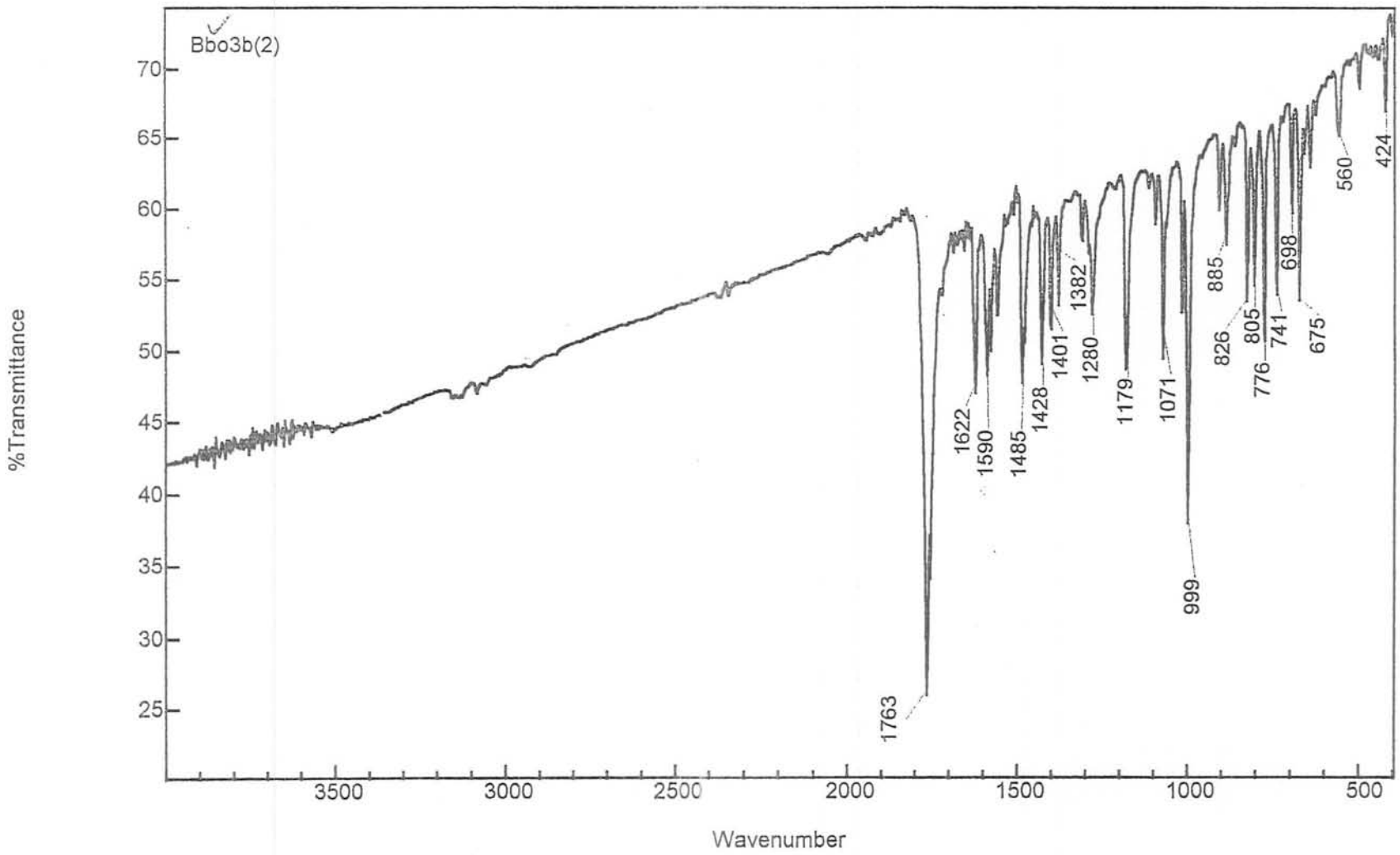
F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

File :D:\MSDChem\1\DATA\Prof.Dr.Aurangzeb\Sajid Ali\BBPA.D
Operator : FARHAN AHMED
Acquired : 19 Dec 2006 15:50 using AcqMethod LIQUID.M
Instrument : Agilent GCMS
Sample Name: SAJID ALI / CHEMISTRY QAU
Misc Info : 150-300'C 10'C/MIN
Vial Number: 1



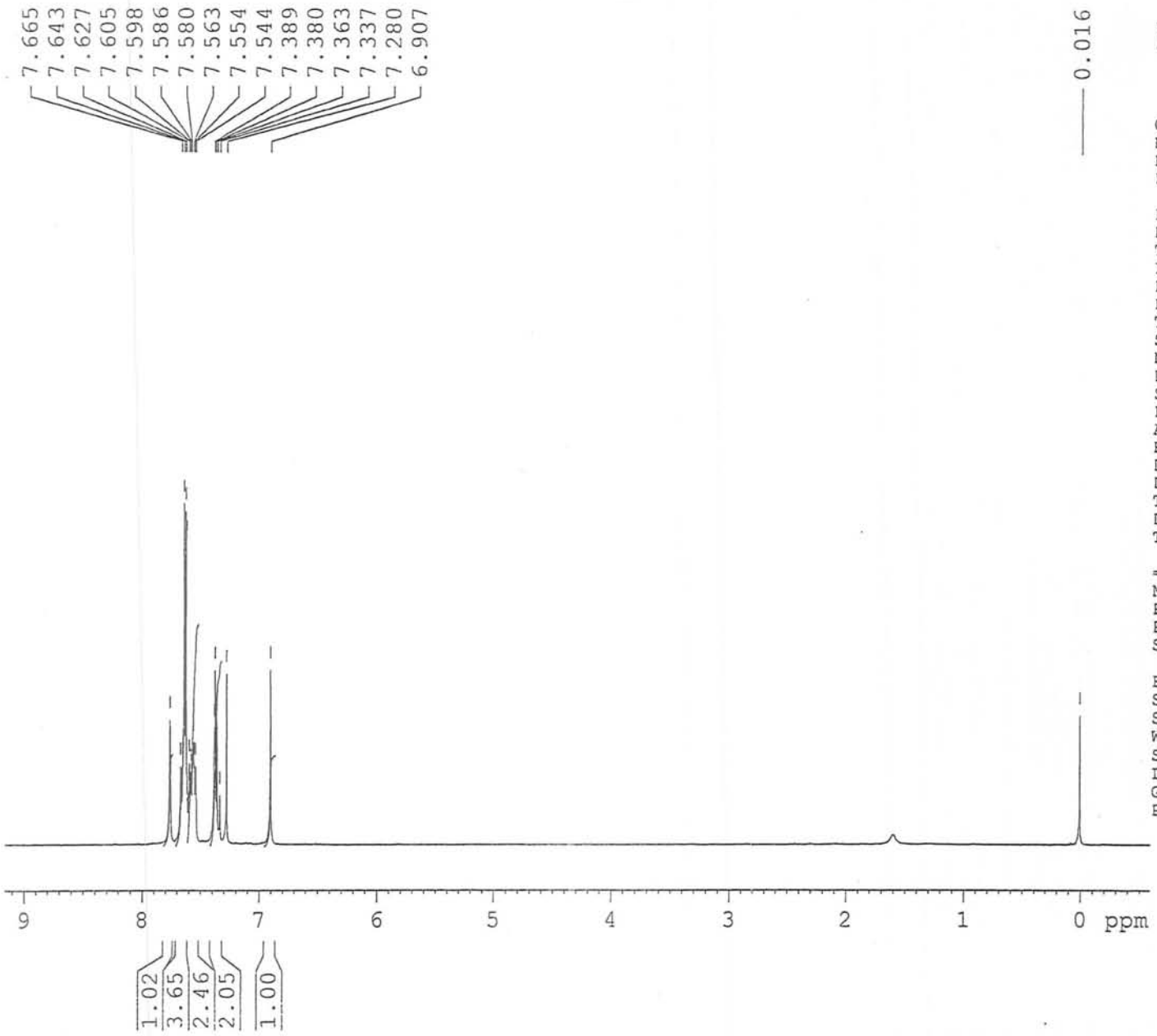


Bio-Rad Merlin



Name
Bbo3b(2)

Dr. AURANGZEB HASSAN/SAJID ALI/BBO3B_1HNMR_CDCL3



BRUKER

Current Data Parameters

NAME	BBO3B_1HNMR_CDCL3
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20070109
Time	12.28
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	724.1
DW	81.000 usec
DE	6.00 usec
TE	290.9 K
D1	1.00000000 sec
TD0	1

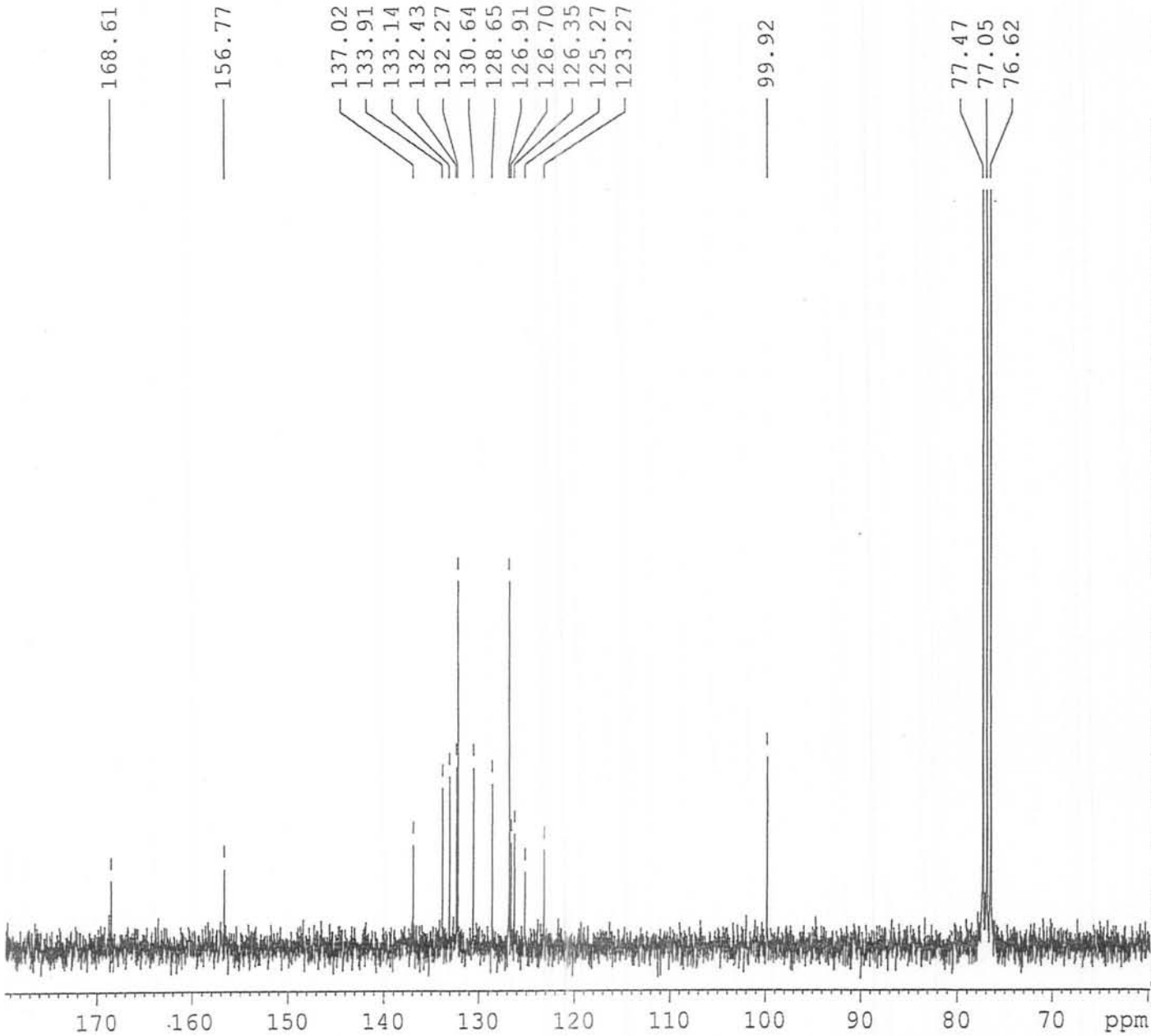
======== CHANNEL f1 ========

NUC1	1H
P1	9.00 usec
PL1	2.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

Dr. AURANGZEB HASSAN/SAJID ALI/BBO3B_13CNMR_CDCL3



BRUKER

Current Data Parameters
NAME BBO3B_13CNMR_CDCL3
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters

Date_	20070109	
Time	12.47	
INSTRUM	spect	
PROBHD	5 mm BBO BB-1H	
PULPROG	zgpg30	
TD	65536	
SOLVENT	CDCl3	
NS	256	
DS	2	
SWH	17985.611	Hz
FIDRES	0.274439	Hz
AQ	1.8219508	sec
RG	1290.2	
DW	27.800	usec
DE	6.00	usec
TE	291.6	K
D1	2.00000000	sec
d11	0.03000000	sec
DELTA	1.89999998	sec
TD0	1	

======== CHANNEL f1 ========

NUC1	13C	
P1	6.00	usec
PL1	-5.00	dB
SFO1	75.4752953	MHz

======== CHANNEL f2 ========

CPDPRG2	waltz16	
NUC2	1H	
PCPD2	80.00	usec
PL2	2.00	dB
PL12	20.98	dB
PL13	20.00	dB
SFO2	300.1312005	MHz

F2 - Processing parameters

SI	32768	
SF	75.4677490	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

File :D:\MSDCHEM\1\DATA\PROF.DR.AURANGZEB\SAJID ALI\Snapshot\BBO3B.D
Operator : FARHAN AHMED
Instrument : Agilent GCMS
Acquired : 10 Jan 2007 11:36 using AcqMethod LIQUID.M
Sample Name: SAJID ALI / CHEMISTRY QAU
Misc Info :