# Total Synthesis of Bioactive Natural Products

BY

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A Thesis Presented to the

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DEANSHIP OF GRADUATE STUDIES

This thesis, written by **Shamsuddeen Abdullahi Haladu** under the direction of his thesis advisor and approved by his thesis committee, has been presented to and accepted by the Dean of Graduate Studies, in partial fulfillment of the requirements for the degree of **MASTER OF SCIENCE IN CHEMISTRY**.

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# DEDICATION

*Dedicated to my parents, brothers*

*and sisters.*

# ACKNOWLEDGMENTS

All praise is to Allah for giving me the opportunity to accomplish this research. I have neither power nor ability except with Allah. His peace and blessings be upon his messenger Muhammad, his family members, his companions and those who will follow him in righteousness to the Day of Judgment.

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**عنوان الرسالة** : التصنيع التكاملي للمنتجات الطبيعية ذات التأثير الحيوي.

**التخصـــــــص** : الكيـــميـــاء

**تاريخ التخرج :** يونيو 2010

وفي الدراسة الحالية تم إنجاز تركيب مجموع spermatinamine المنتجات الطبيعية البحرية ، وmethyltransferase isoprenylcysteine الكربوكسيل (Icmt) المانع ، وAspergillusol ألف ، مثبط α-glucosidase باستخدام chapprao متقاربة. وإلى جانب هذه ، كان ما مجموعه التوليفي الأول 2' - 3' ميثوكسي - prenyl -licodione ، مثبط Icmt ، حاول أيضا. عرض جميع المنتجات الطبيعية الثلاث الأنشطة البيولوجية قوية. مثبطات Icmt هي الأهداف المحتملة المضادة للسرطان المخدرات ، في حين lAspergilluso ألف ، كما يحمل وعدا المخدرات المضادة لمرض السكر. وقد تحقق ذلك خطوة رئيسية من amidation في التوليف spermatinamine عن طريق تحويل حمض hydroxamic لحمض كلور تليها تكثيفه مع أمين الاقتضاء ، مع العائد الإجمالي من 52 ٪. تم تصنيعه من قبل وionAspergillusol estrificat من سيطة ، ومناسبة erythritol حامض hydroxamic ، في حضور دي سي سي مع العائد المرتفع عموما (60 ٪). وعبرت الميزة الرئيسية لتجميع 2' - 3' ميثوكسي - licodione -prenyl -claisen التكثيف من وسيطة الرئيسيان مع العمالة من مختلف الفئات واقية والقواعد. واقترح اتباع نهج أفضل الاصطناعية التي تنطوي على التكثيف من مشتقات الكومارين وشريك جرينارد.

**ما جســـــتير فـــي العلـــوم الكيميائيـــــة**

**جامعة الملك فهد للبـــــترول و المعادن**

**الظهران – الســـــعودية**

**يونيـــو 2010**

# THESIS ABSTRACT

**Name:** **Shamsuddeen Abdullahi Haladu**

**Title:** **Total Synthesis of Bioactive Natural Products**

**Major:** **Chemistry**

**Date:** **June 2010**

In the current study the total synthesis of the marine natural products spermatinamine, an isoprenylcysteine carboxyl methyltransferase (Icmt) inhibitor, and Aspergillusol A, an α-glucosidase inhibitor were accomplished by using a convergent appraoch. Besides these, the first total synthesis of 2'-methoxy-3'-prenyl-licodione, an Icmt inhibitor, was also attempted. All the three natural products exhibited potent biological activities. The Icmt inhibitors are potential anticancer drug targets, while Aspergillusol A, holds promise as antidiabetic drug. The key step of amidation in spermatinamine synthesis was achieved by transforming the hydroxamic acid to acid chloride followed by condensing it with the appropriate amine, with an overall yield of 52%. Aspergillusol A was synthesized by estrification of intermediates, erythritol and appropriate hydroxamic acid, in the presence of DCC with a high overall yield (60%). Key feature of synthesis of 2'-methoxy-3'-prenyl-licodione is crossed-claisen condensation of the two key intermediates with employment of various protective groups and bases. A better synthetic approach involving condensation of coumarin derivative and Grignard partner was proposed.

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**Dhahran, Saudi Arabia**
**June 2010**

# CHAPTER 1

## 1.0 INTRODUCTION AND LITERATURE REVIEW

### 1.1 Introduction to the natural product syntheses

Natural product synthesis is the art and science of constructing the molecules of nature in the laboratory and has been a very attractive area for organic researchers across the globe today. The enthusiasm to mimic nature and to discover its secrets, by exploring efficient ways to synthesize novel and important bioactive natural products, pushes the scientists to develop new synthetic methodologies and to explore new chemical reactivity.[1] A flagship of organic synthesis,[1] natural product synthesis is an efficient tool to evaluate the power of existing synthetic methods.

The infinite chemical diversity of the natural products provides an enormous challenge for synthetic chemists to establish cost-effective means for the construction of these unique structures in larger amounts in order to carry out further biological investigations and pharmacological studies.[2]

Since nature remains the main source of bioactive constituents or leading compounds, natural product synthesis will continue to be the leading science with vast opportunities for new developments and discoveries.[3] The advances in drug design and structure-activity relationship studies have paved a way towards modification of the structure of

natural products in order to elevate their potency and augment their selectivity for the betterment of their pharmacological properties.[3]

## 1.2 Marine Natural Products

The Oceans, inhabiting various living organisms have become a great source of multitude of active metabolites which can be an ideal resource for the discovery of new drugs.

Vast and unique organic chemical structures have been observed in the extracts of marine organisms. Many of them have been shown to be promising candidates as anticancer agent as well as antibiotics.[4] TZT-1027 is used in cancer chemotherapy, for the treatment of leukemia, breast and lung carcinoma and it was developed from marine origin natural product[7] (Dolastatin 10) (Figure 1).

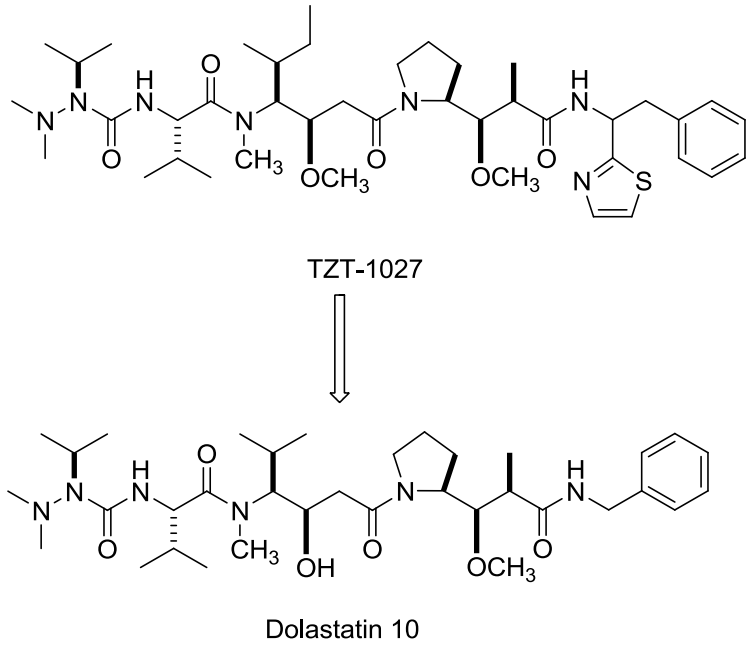



**Figure 1: Marine based anti-cancer drugs**

Sponges have proved to be the richest source of marine natural products with interesting biomedical potentials. Organic compounds synthesized by both sponges and microorganisms therein were found to possess potent anticancer, antibiotic, antifungal, antiviral, antiparasitic, and antifouling activities.[6] During the search for novel and new anti-cancer drugs, enormous work has been carried out in order to screen the crude extracts of marine organisms for biological activity. That research has led to many promising findings such as antitumor and/or cytotoxic activities. Further efforts have to be focused on translating these bioactivities into useful drugs by using effective pre-fractionation strategies, advanced identification techniques, and novel synthetic methods.[7]

### 1.3 Introduction to Icmt Inhibitors

The protein prenylation, a process initiated by covalent attachment of 15-carbon farnesyl or a 20-carbon geranylgeranyl isoprenoids to a conserved cysteine residue, modifies many key regulatory proteins in eukaryotic cells at their C-terminus.[8] This processing which is critical for the correct localization and function of these proteins has only been studied since 1980s.[9] However, because of the importance of the biological functions of many prenylated proteins, the ensuing 20 years has attracted a lot of interest to study this protein modification pathway.[8,10] For instance, due to critical involvement in many types of cancers, members of the Ras GTPase family are extensively studied.[11] The majority of prenylated proteins contain a C-terminal CaaX (C = cysteine residue that is modified, a's = aliphatic residues, and X can be any of a number of amino acids such as cysteine,

serine, methionine, alanine) motif.[8] The nature of the X residue dictates whether the protein is farnesylated or geranylgeranylated on the cysteine residue of the CaaX sequence.[12] When X is serine, cysteine, alanine or glutamine, the 15-carbon farnesyl group is added to the cysteine residue by protein farnesyltransferase (FTase), whereas if the X is leucine, then the 20-carbon geranylgeranyl group is added by protein geranylgeranyltransferase type I (GGTase-I), followed by proteolytic removal of the aaX residues by the endoprotease Rcel.[13,14] The resultant exposed carboxyl group on prenylated cysteine is then methylated by isoprenylcysteine carboxylmethyltransferase (Icmt).[15,16]

The three-step modification of CaaX proteins is generally important for membrane association and protein localization in the cell as well as in protein-protein interactions,[17,18] which are indispensable for many specific functions of these proteins. Recent studies have shown that even though methylation as the third step is less important for hydrophobicity of the CaaX proteins, especially those that are modified by the 20-carbon geranylgeranyl isoprenoid,[18,19] the modification is nevertheless important to the function of these proteins.[21,23]

Prenylation of the CaaX proteins has attracted considerable interest, in large part because of the key role of the activated form of Ras in the pathogenesis in the human cancers [11] and that the growth of Ras dependent tumors in mice can be inhibited by pharmacological blockade of FTase by FTIs (farnesyltransferase inhibitors).[24-26] In addition, Ras GTPases and other CaaX proteins are involved in an array of signaling pathways that are important in other pathologies dependent on aberrant proliferation,

such as inflammation[11,27]. However, FTIs have not performed up to expectation in solid tumors and failed to respond in many types of cancer, even those with activated RAS oncogenes[28-31]. The multifactorial nature of human cancer and "alternative prenylation", a process whereby CaaX proteins including some Ras isoforms can be modified by GGTase-I when FTase is inhibited, cause this variability[32-33]. The disclosure of alternative prenylation sparked interest in finding inhibitors of GGTase-I and activated forms of both farnesylated and geranylgeranylated CaaX proteins by inhibition of the distal processing steps in the pathway, *i.e.*, Rce1 or Icmt, since there is a single enzyme for both of these steps that processes both farnesylated and geranylgeranylated proteins.[34-35] Thus, the blockade of one of these steps would be expected to impact all Ras isoforms. Indeed, recent studies have shown that genetic disruption of Icmt in cells dramatically attenuates their ability to be transformed by oncogenic K-Ras[23] and treatment of a human colon cancer cell line with a specific Icmt inhibitor blocks anchorage-independent growth of the cancer cells [22].

Considering the fact that Icmt-catalyzed CaaX protein methylation plays a crucial role in oncogenesis, the quest for specific inhibitors of this process has increased in recent years. One of the approaches adopted in the pursuit of anti-cancer drugs is the development of Icmt inhibitors[36] and there are ongoing efforts to assess the potential of targeting Icmt in anticancer drug discovery. The discovery of new Icmt inhibitors concluded bioassay-directed purification of extracts of *Hovea parvicalyx I.* Thomps (*Fabaceae*) affording two new prenylated β-hydroxychalcone derivatives (**1**) and (**2**)[37], which showed inhibition of Icmt with an $IC_{50}$ of 30 and 17 $\mu$M, respectively (assay

performed in duplicate on two independent days). In addition, the Australian marine sponge, *Pseudoceratina sp*., yielded spermatinamine (**3**)[38], a novel alkaloid with a bromotyrosyl-spermine-bromotyrosyl sequence, showing inhibition of Icmt at an $IC_{50}$ of 1.9 $\mu$M (assay performed in duplicate on five independent days). Spermatinamine (**3**) is the first natural product inhibitor of Icmt. Compounds (**1-3**) (Figure 2) are considered a new addition to the small list of inhibitors of Icmt.[37,38]

### 1.4 Literature Review of Icmt Inhibitors

Interest in targeting Icmt in cancer therapy goes back to as early as 1991 when farnesylcysteine analogue N-acetyl-S-farnesyl-L-cysteine (AFC; **5**, Fig. 2) was studied as an inhibitor of carboxyl methylation of CaaX proteins[40]. In this study, although AFC was reported to inhibit methylation of Ras in transformed fibroblast cells but it had little effect on the rates of proliferation of these cells. Another prenylcysteine analogue farnesylthiosalisylic acid (FTS; **6**, Figure. 2) was found to inhibit the methylation of GTP-binding proteins such as Ras[41] in a cell-free system and FTS treatment interferes with the growth of human H-Ras-transformed Rat1 cells, but has only minimal cytotoxicity in a variety of other transformed cell lines.[42] These studies have disclosed that all prenylated proteins are not equally affected by the treatment of cells with the inhibitor especially Ras proteins, which were seen to be more affected by FTS treatment than some other CaaX proteins. This finding revealed that the cellular activity of FTS was more likely due to its ability to dislodge Ras from membranes rather than its ability to inhibit CaaX protein methylation.[42,43] A number of studies show doubt on whether the observed biological effects of treating cells with prenylcysteine analogues were actually

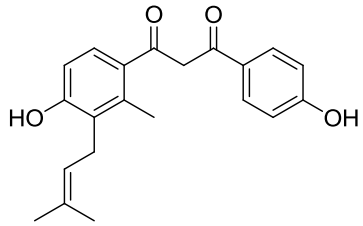
due to Icmt inhibition. For instance, inhibition of macrophage chemotaxis by AFC was later linked to the direct blockade of the interaction between receptor and G-proteins (the latter of which, of course, contain a CaaX protein subunit) rather than inhibition of carboxyl methylation.[44] Additional studies have concluded that compounds such as AFC have significant effects on cells via an impact on processes that do not involve inhibition of Icmt.[45,46]

Mechanistically distinct approaches, to bring about increased levels of AdoHcy(S-adenosylhomocysteine(AdoHcy)) in cells, to target Icmt have been employed. Using a variety of methods, the inhibition of Icmt was demonstrated to be resulted from proliferation in a number of cell types,[47] and an increase in apoptosis in endothelial cells in particular.[48,49] The classic anticancer therapeutic methotrexate was also employed to elevate AdoHcy in cancer cells, which profoundly inhibited Ras methylation coupled with mislocalization and a significant decrease in Ras signaling[50]. Although AdoHcy is not a selective inhibitor of Icmt, but rather a general inhibitor of cellular methyltransferases.[51] These studies nonetheless supported the hypothesis that targeting Icmt might inhibit the proliferation of cancer cells and enhance their apoptotic death.

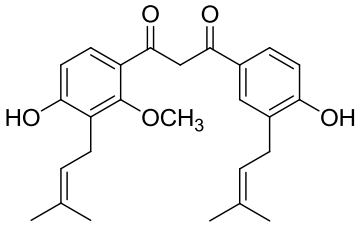
In an attempt to move beyond substrate- and product-based inhibitors of Icmt and discover a pharmacological agent with higher potency and selectivity, the screening of a diverse chemical library has led to the identification of a selective small-molecule inhibitor of Icmt, cysmethynil (**7**, Figure. 2).[22] Treatment of human colon cancer cells with cysmethynil generated many of the same cellular characteristics noted above with the Icmt knockout models, including Ras mislocalization, impaired Ras signaling and

inhibition of oncogenesis as assessed by tumor cell growth in soft agar. Moreover, these effects were reversible upon overexpression of Icmt, indicating mechanism based activity of the compound. Also, cysmethynil treatment did not impair the proper localization of membrane protein modified by myristol/palmitoyl, demonstrating that the compound does not cause a global disruption of protein trafficking to the cell membrane. The identification of cysmethynil as an Icmt inhibitor has provided a selective pharmacological tool to probe the potential functional consequences of CaaX protein methylation in cellular systems and also the involvement of Icmt in both normal and pathological cellular processes.

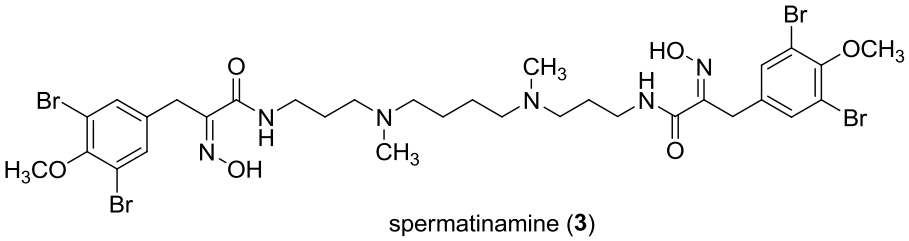
The search for new Icmt inhibitor was extended to natural sources and purification of extracts of *Hovea parvicalyx* I. Thomps (Fabaceae) afforded two new prenylated *β*-hydroxychalcone derivatives (**1**) and (**2**)[37], whereas Buchanan *et al*., has reported the isolation of spermatinamine (**3**) (see Figure 2) from the Australian marine sponge *Pseudoceratina* sp, the first natural product inhibitor of Icmt.[38] The same research group has reported the isolation of aplysamine 6 (**4**)[36], an inhibitor of Icmt with an $IC_{50}$ of 14 $\mu$M.



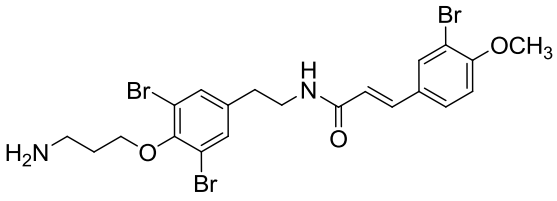
2'-methoxy-3'-prenyl-licodione (**1**)



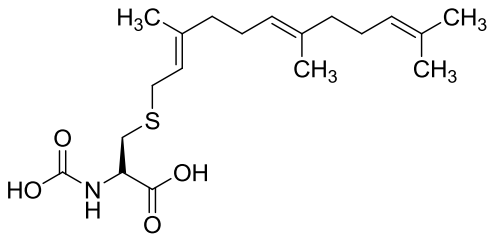
2'-methoxy-3',3''-diprenyl-licodione (**2**)



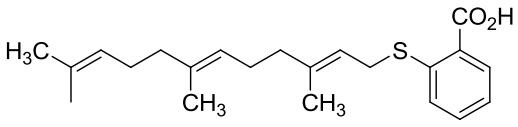
spermatinamine (**3**)



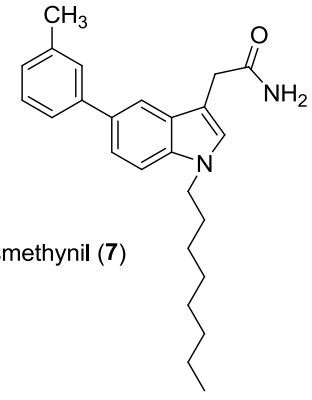
aplysamine 6 (**4**)



N-acetyl-S-farnesyl-L-cysteine (**5**)



farnesylthiosalisylic acid (**6**)



cysmethynil (**7**)

**Figure 2: Examples of Icmt Inhibitors**

## 1.5 Introduction and Literature Review of α-Glucosidase Inhibitors

### 1.5.1 α- Glucosidase

α–Glucosidase and α–Amylase are enzymes that catalyze the metabolism of carbohydrates. Glycoside trimming enzymes are important in a broad range of metabolic pathways, for processing of glycoproteins and glycolipids, and for the digestion of carbohydrates in the gut. α-amylases present in the saliva and pancreas are responsible for the breakdown of complex polysaccharides into oligo- and disaccharides, and preparing them for absorption. α -Glucosidase is a collective name for the enzymes maltase, sucrase, isomaltase and glucoamylase, and is a membrane bound enzyme present in the brush border of the small intestine. It is present in relatively high concentrations in the proximal part of the jejunum and gradually decreases in the distal region, with practically zero levels at the ileum. This enzyme catalyzes the final step in the digestive process of carbohydrates, which is the conversion of the disaccharides sucrose and maltose into glucose.

### 1.5.2 α-Glucosidase Inhibitors

α-Glucosidase inhibitors (acarbose **8**, miglitol **10**, voglibose **9**) (Figure 3) are drugs that delay the breakdown of carbohydrates in the gut, and consequently slow down the absorption of sugars into the blood stream. Such processes control postprandial glucose levels and suppress postprandial hyperglycemia. These inhibitors are grouped as antihyperglycemic drugs and patients with type 2 diabetes may use them therapeutically.[53]

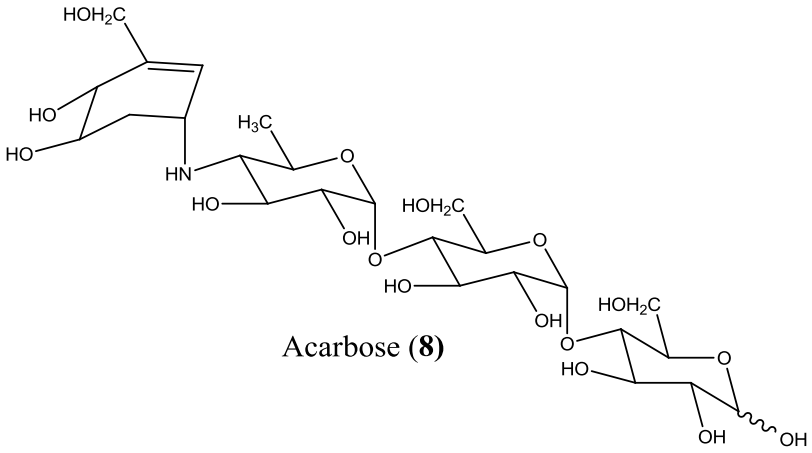
In was discovered in the 1970s that inhibition of all or some of the intestinal disaccharidases and pancreatic α-amylase by inhibitors could regulate the absorption of carbohydrate and these inhibitors could be used therapeutically in the oral treatment of the non-insulin-dependent diabetes mellitus (type II diabetes).[54] Valiolamine **(12**, Figure 3), produced by *Streptomyces hygroscopicus var. limoneus* was found to inhibit pig intestinal maltase and sucrase with $IC_{50}$ values of 2.2 and 0.049 mM, respectively.[54] Several *N*-substituted valiolamine derivatives were synthesized to enhance its α-glucosidase inhibitory activity in vitro and one simple derivative Voglibose (**9**, Figure 3), which was obtained by reductive amination of valiolamine with dihydroxyacetone, was selected as the potential oral antidiabetic agent and has been commercially available for the treatment of diabetes in Japan since 1994. Nojirimycin (**15**, Figure 3), a potent inhibitor of α- and β-glucosidases, isolated from *Bacillus* species was discovered as the first glucose analog with the nitrogen atom in place of the ring oxygen. Another potent α-glucosidase inhibitor Genistein **16** a soy isoflavone isolated from the fermentation broths of *Streptomyces* species has been demonstrated to be a reversible, non-competitive enzyme inhibitor.[55]

The presence of polyhydroxy groups on Nojirimycin and Genistein is critical for α-glucosidase inhibition activity, since most mimic the natural substrates maltose and sucrose. However, because this Nojirimycin (iminosugar) with the hydroxyl group at C-1 is fairly unstable, it is usually stored as bisulfite adducts or it may be reduced by catalytic hydrogenation with a platinum catalyst or by $NaBH_4$ to 1-deoxynojirimycin (DNJ) (**11**, Figure 3). DNJ was later isolated from the roots of mulberry trees and called molanoline. Similarly, Salacinol (**13**, Figure 3) and kotalanol (**14**, Figure 3) have been identified as α-

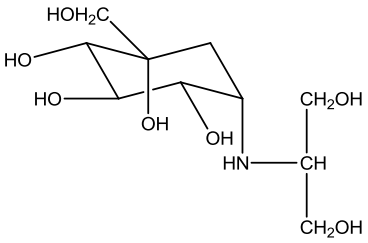
glucosidase-inhibiting components from the water-soluble fraction of the roots and stems of *S. reticulate*.[53]

Among the carboxylic acid derivatives, of particular interest are two bioactive compounds isolated from the rhizomes of *Kaempferia galanga*, 4-methyl-transcinnamic acid (**17**, Figure 3), which is a non competitive inhibitor of the enzyme, and its corresponding ethyl ester **18**, which competitively inhibits maltase. The methoxy derivative of cinnamic acid showed improved enzyme inhibitory activity, but replacing the electron rich hydroxy groups on the molecule, or introduction of an electron withdrawing nitro group renders the compound inactive. [56]

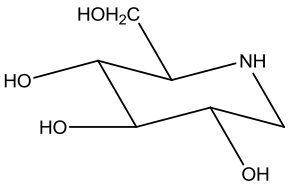
Recently, in outgoing efforts to discover new bioactive chemical entities from marine sources, chemical exploration of the fungus *Aspergillus aculeatus* has led to the isolation and structure elucidation of aspergillusol A **19**, a tyrosine-derived metabolite featuring hydroxyphenylpyruvic acid oxime moieties linked to erythritol through ester linkage.[58] The aspergillusol A **19** selectively inhibited α-glucosidase from the yeast *Saccharomyces cerevisiae* with the $IC_{50}$ value of 456 ± 2 ($\mu$M).



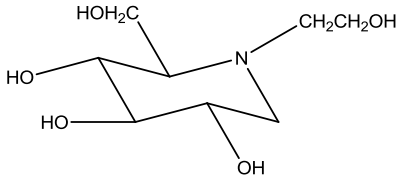

Acarbose (**8**)



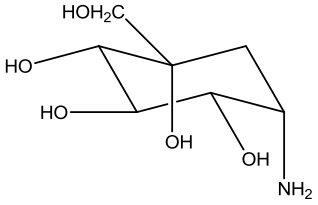

Voglibose (**9**)



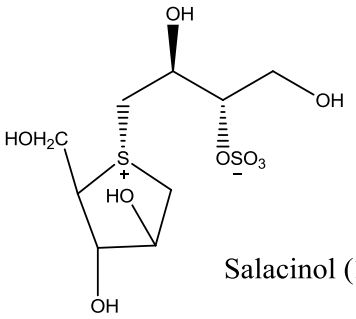

Deoxynogirimycin **(11)**



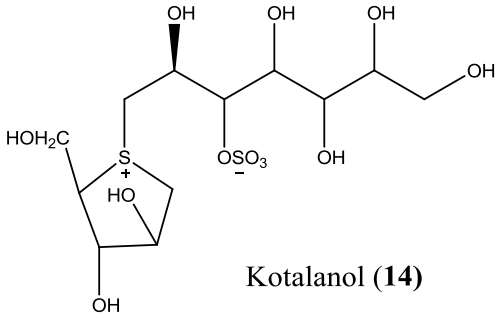

Miglitol (**10)**



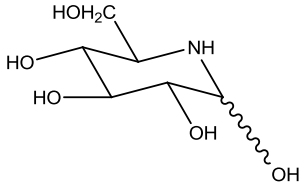

Valiolamine (**12)**



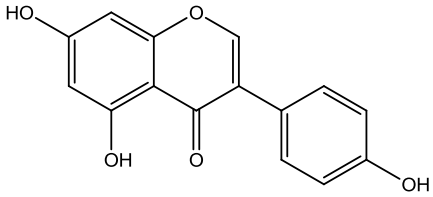
Salacinol (**13**)



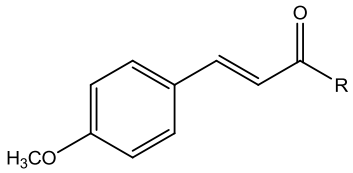
Kotalanol (**14**)



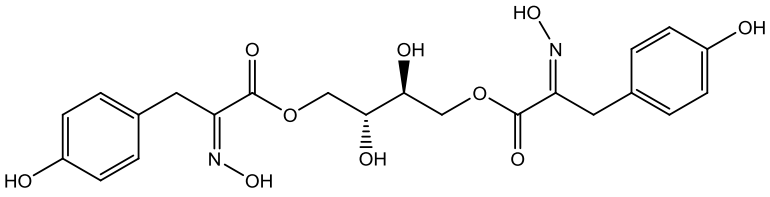
Nogirimycin (**15**)



Genistein (**16**)



R= -H: 4-methoxytranscinnamic acid( **17**)
R= -$C_2H_5$: Ethyl ester (**18**)



Aspergillusol A (**19**)

**Figure 3: α-Glucosidase Inhibitors**

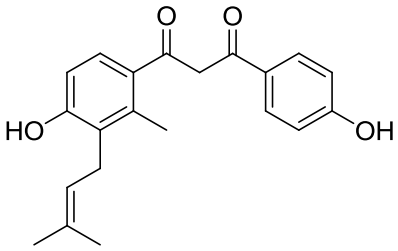
# CHAPTER 2

## 2.0 OBJECTIVES AND WORK PLAN

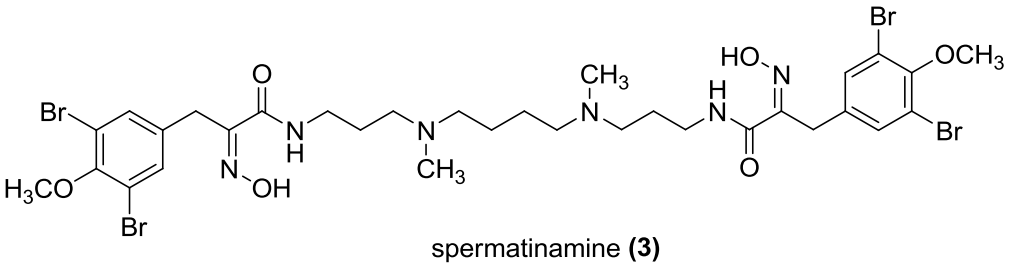
The following are the objectives of this research studies

1) To achieve the total synthesis of four different natural products, sprermatinamine **3** and a prenylated *β*-hydroxychalocone derivative **1**. These compounds are potential anticancer agents, while Aspergillusol A **19**, isolated from the fungus *Aspergillus aculeatus*, exhibits anti-diabetic activity.

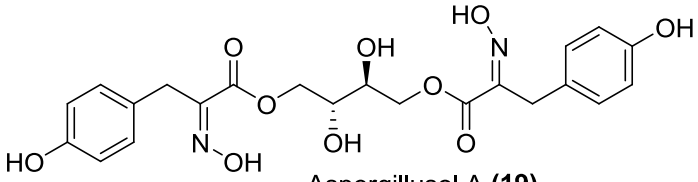
2) Objective 1 would help to establish a facile and cost-effective synthetic methods to access these compounds in large quantities. This in turn would serve to carry out further screening and pharmacological studies and help in discovering more potent anti-cancer and anti-diabetic drugs.




2'-methoxy-3'-prenyl-licodione (**1**)




spermatinamine **(3)**




Aspergillusol A **(19)**

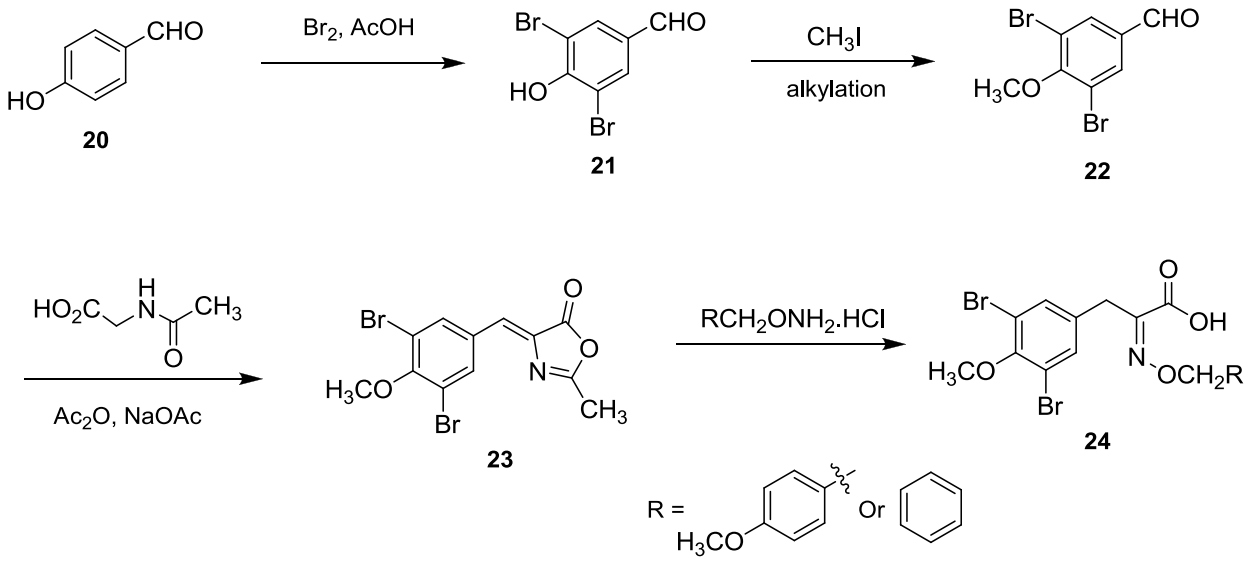
**Figure 4: Target Molecules**

## 2.1 Methodology and the Work Plan

### 2.1.1 Synthesis of Spermatinamine

In order to accomplish the synthesis of target molecule **3**, intermediate **24** would be required, which would be synthesized as outlined in Scheme 1. Bromination of the aldehyde **20**[38,40] followed by methylation would generate aldehyde **22**. Exposure of the latter to acetylglycine and acetic anhydride at higher temperature would furnish

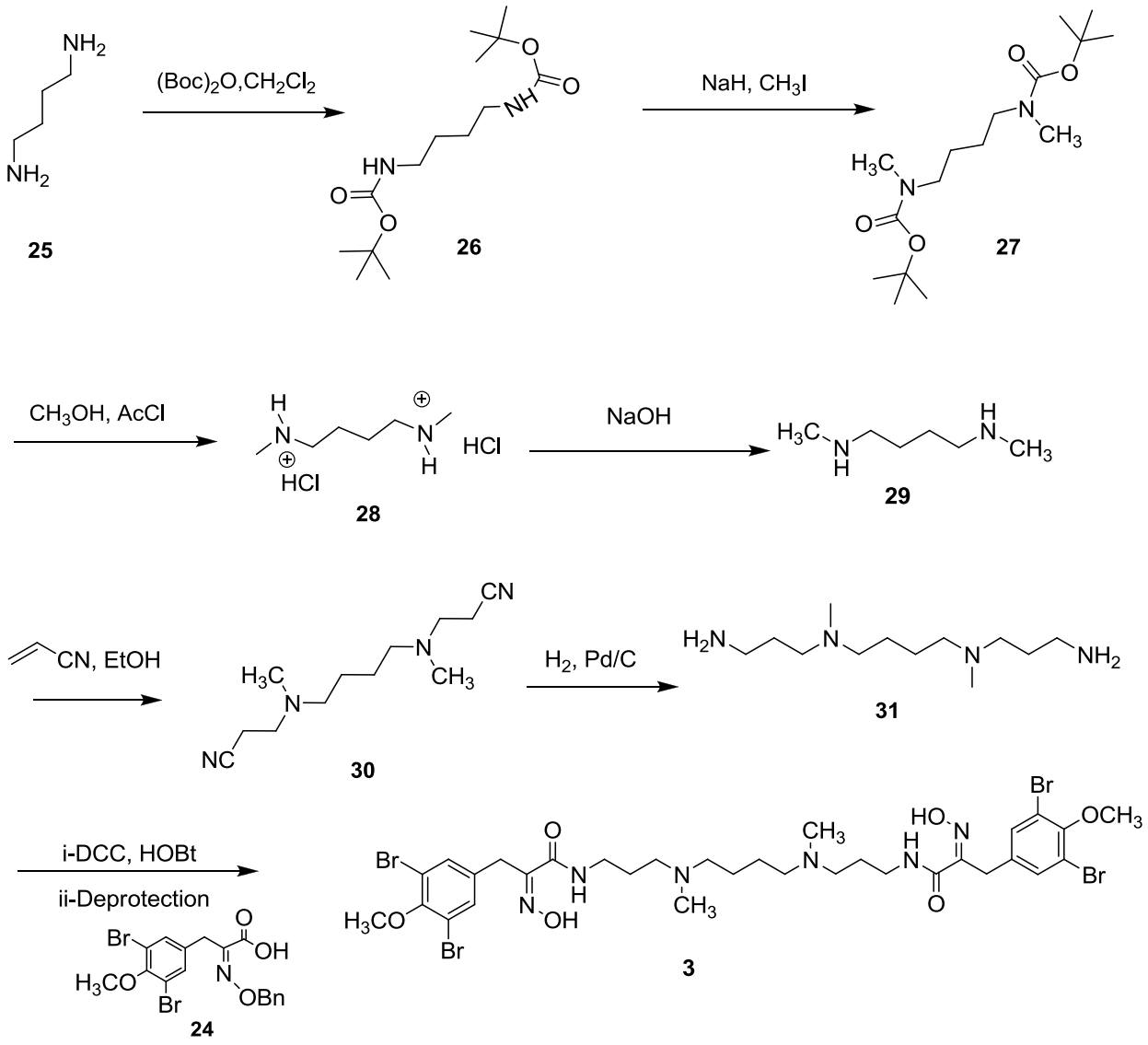
intermediate **23**, which would be then treated with 4-methoxybenzyloxylamine hydrochloride[59] or benzyloxylamine hydrochloride to produce the target intermediate **24** (Scheme 1).




**Scheme 1: Work plan of the synthesis of Intermediate 24**

The other intermediate **31** needed to execute the synthesis of the target molecule **3** will be synthesized as follows. Protection of butane-1,4-diamine **25** with $(Boc)_2O$ followed by alkylation of the resulting dicarbamate **26** with methyliodide in presence of sodium hydride as a base will furnish compound **27**. Deprotection of **27** in a mixture of methanol and acetyl chloride will yield *N,N'*-dimethylbutane-1,4-diamine hydrochloride **28** which will be treated with aqueous NaOH to librate the free amine **29**. Compound **29** will be subjected to Michael addition with acrylonitrile to yield the intermediate **30**, which will be subjected to hydrogenation using palladium on activated charcoal to produce

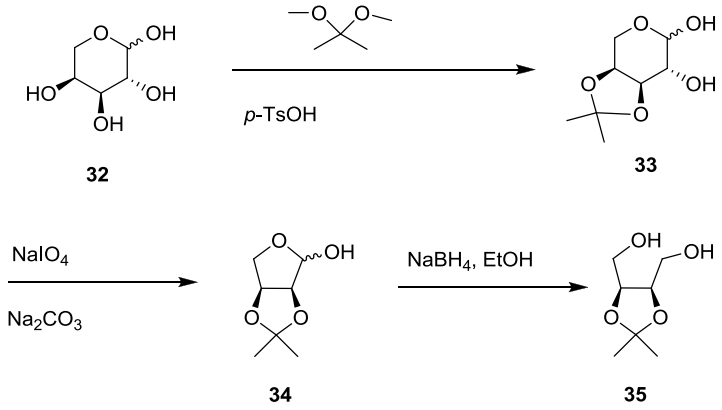
tetraamine **31**. Amidation of the latter amine **31** with **24,** followed by the deprotection of the resulting oxime would produce spermatinamine **3** (Scheme 2).




**Scheme 2: Work plan of the synthesis of spermatinamine**

## 2.2 Synthesis of Aspergillusol A (19)

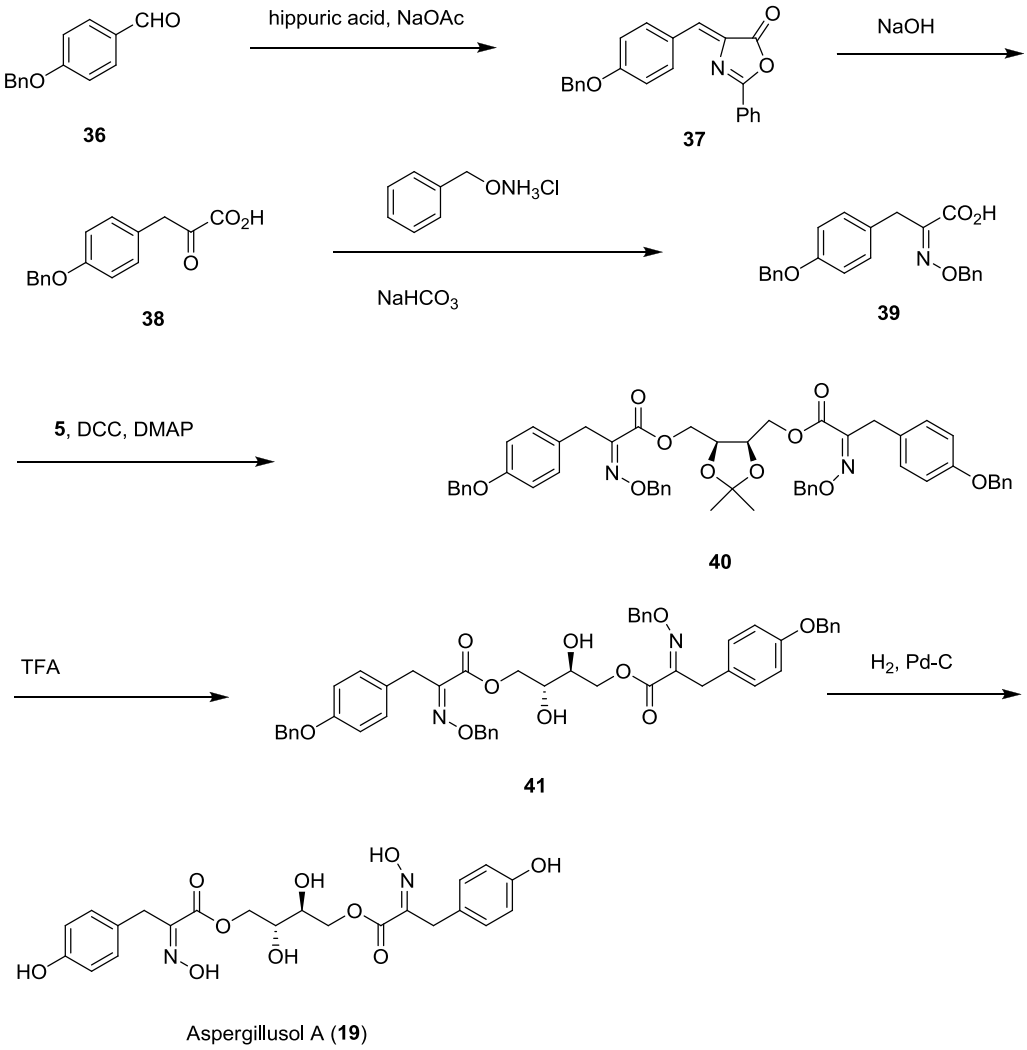
To achive the synthesis of Aspergillusol A **19**, the key intermediate erythritol **35** according to[67] would be synthesized as follows: Selective protection of *L*-arabinose to form the acetonide **33**, followed by oxidative cleavage with sodium periodate to produce the intermediate **34**. Reduction of the latter with sodiumborohydride will furnish **35** (Scheme 3).




**Scheme 3: Work plan of the synthesis of erythritol derivative**

The synthesis of pyruvic acid oxime **39**, required to furnish the synthesis of aspergillusol **19** will start from the reaction of aldehyde **36** with hippuric acid and sodium acetate at higher temperature to get intermediate **37**, which will be subjected to basic hydrolysis to produce pyruvic acid **38**. Condensation of the latter acid **38** with benzyloxylamine hydrochloride would then produce **39**.

Condensation of the pyruvic acid oxime **39** with erythritol **35** in presence of DCC and DMAP will produce Aspergillusol A **19** (Scheme 4).

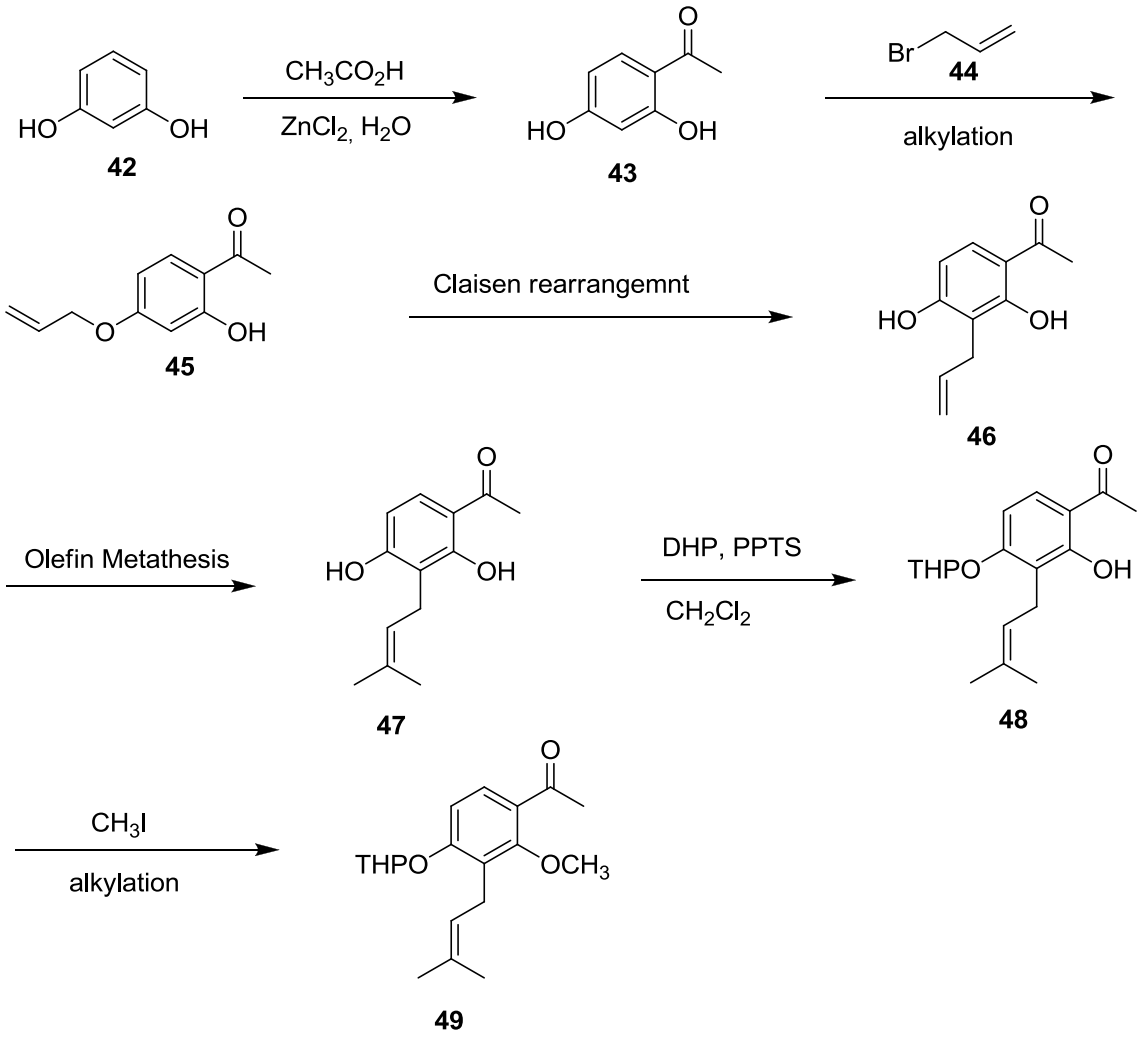



**Scheme 4: Work plan of the syntthesis of Aspergillusol A**

## 2.3 Synthesis of *β*-Hydroxychalcone Derivative

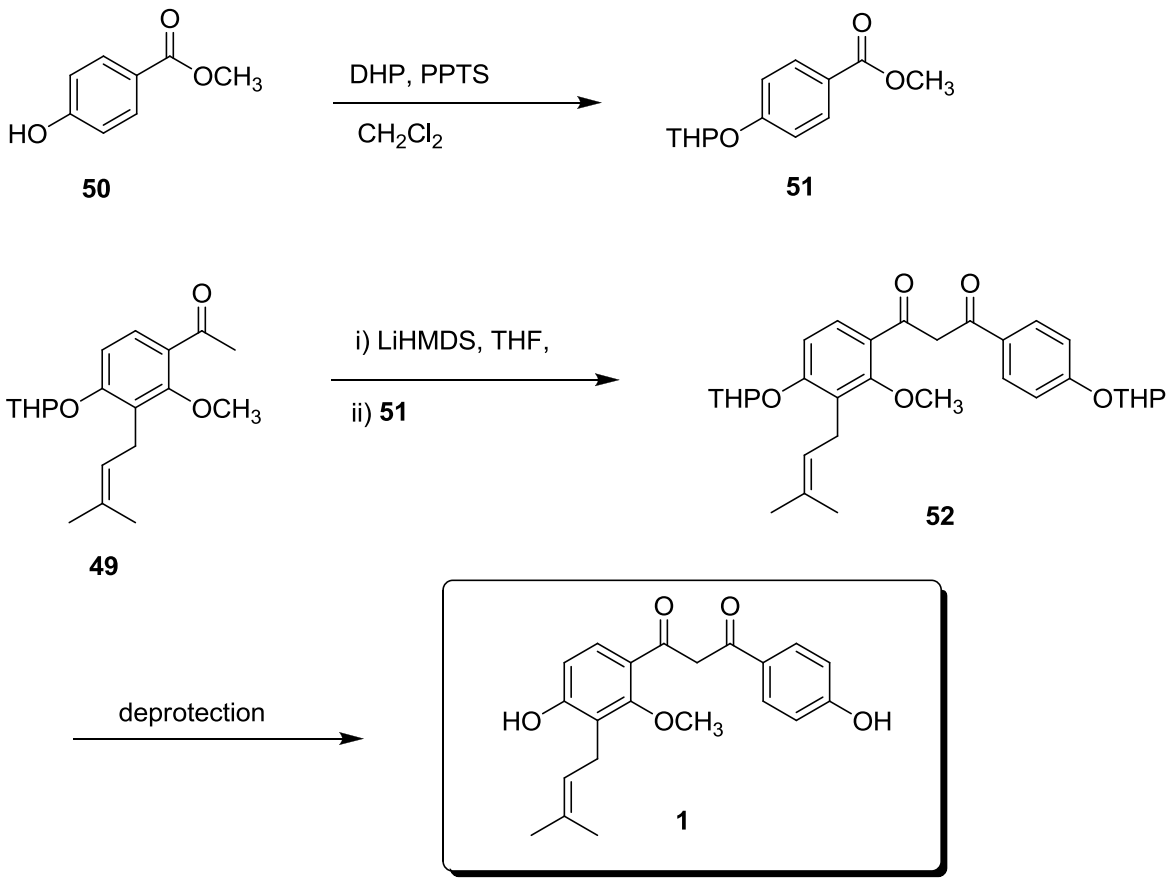
In the course of synthesis of target molecules **1**, we would need a key intermediate **49**, which in turn would be synthesized as outlined in Scheme 5. Acetylation of 1,3-dihydroxybenzene **42** in acetic acid would furnish **43**,[52] which would be subjected to alkylation with allyl bromide **44** to obtain compound **45**. The claisen rearrangement of

the latter would generate intermediate **46**, which would be subjected to olefin metathesis using second generation-Grubbs catalyst would render compound **47**. The regioselective protection of **47** with DHP would generate phenol **48**, which would be alkylated with methyl iodide to give the desired intermediate **49**.




**Scheme 5: Work plan of the synthesis of 49**

Synthesis of the target molecule **1** would be accomplished as outlined in Scheme 6. Protection of **50** would yield intermediate **51**. Condensation of **49** and **51**, using a suitable base at low temperature will construct 1,3-dione **52**,[60] which will be finally deprotected to produce the desired target compound **1**.



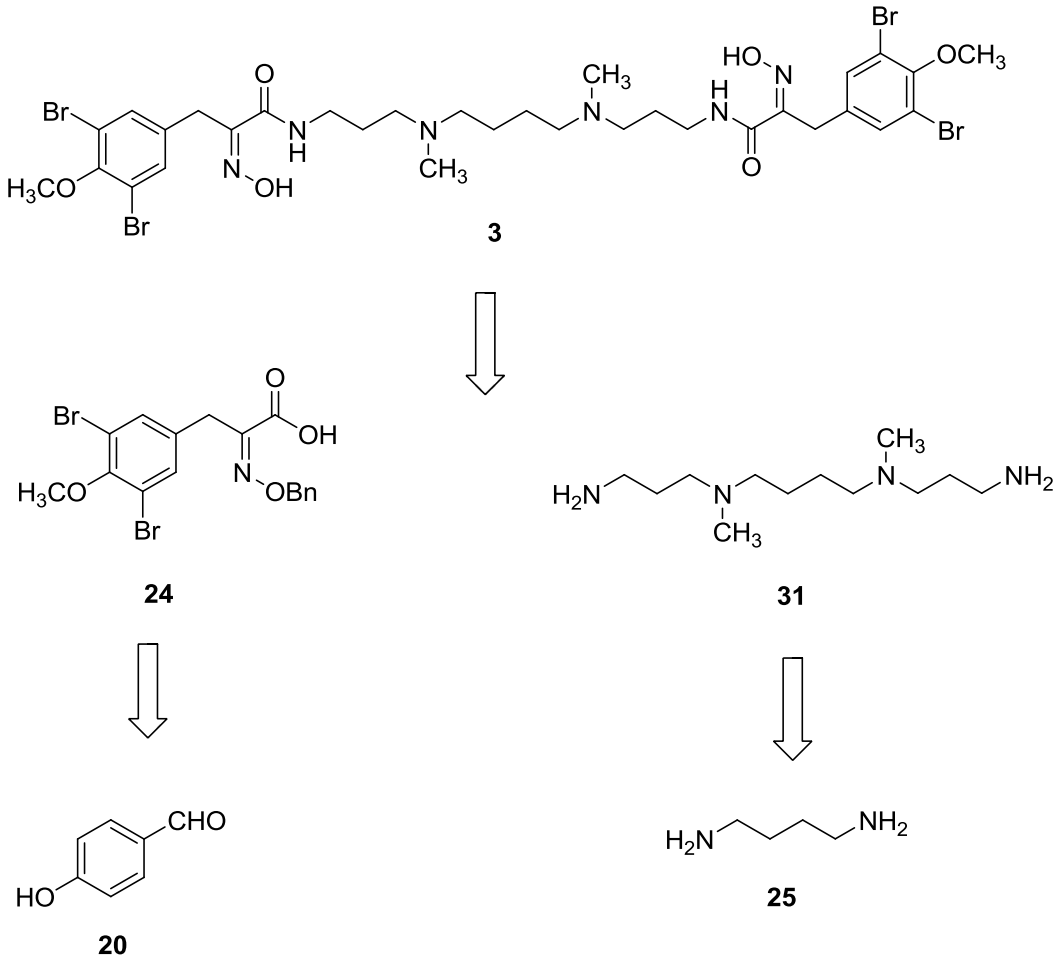

**Scheme 6: Work Plan of the synthesis of 1**

# CHAPTER 3

# 3.0 RESULTS AND DISCUSSIONS

## 3.1 Synthesis of Spermatinamine (3)

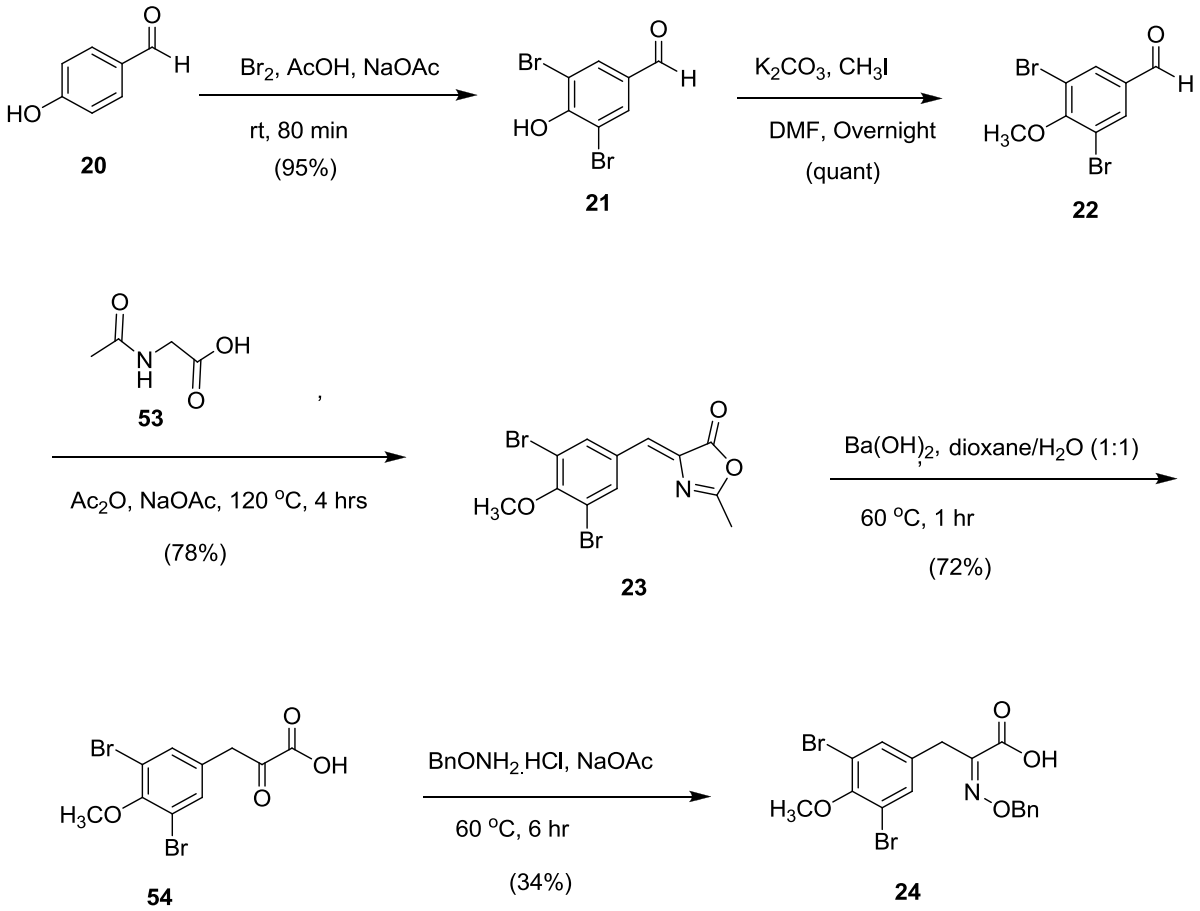
Retrosynthetically, the synthesis of spermatinamine **3** was envisioned from two key intermediates namely: the dibromotyrosine derivative **24** and spermine derivative **31**, which in turn could be realized from aldehyde **20** and the diamine **25**, respectively (Scheme 7).




**Scheme 7: Retrosynthesis of Spermatinamine**

The synthesis of intermediate **24** was commenced from the bromination of aldehyde **20** to get the dibromoaldehyde **21** in 95% yield, which was subjected to alkylation with iodomethane in DMF, using $K_2CO_3$ as a base to obtain methyl ether **22** in quantitative yield (Scheme 8). Aldehyde **22** was condensed with *N*-acetyl glycine **53** in acetic anhydride to yield the intermediate **23** in 78% yield. The hydrolysis of compound **23** in

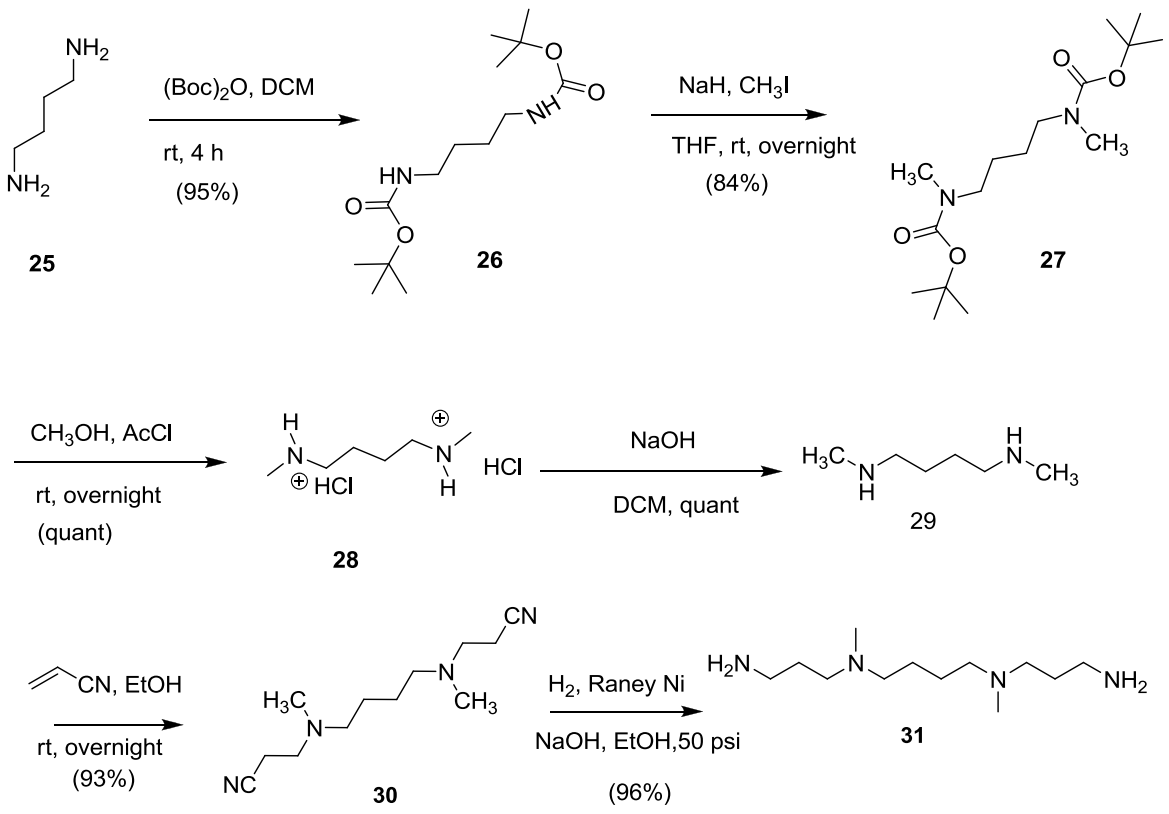
basic condition yielded the *α*-ketoacid **54**, which was condensed *in situ* with benzyloxylamine to obtain the desired dibromotyrosine derivative **24** (34% for two steps)




**Scheme 8: Synthesis of intermediate 24**

The synthesis of the intermediate **31** was started from *N*-protection of butane-1,4-diamine (**25**) with $(Boc)_2O$ in dichloromethane at room temperature to get compound **26**, which was subjected to alkylation with iodomethane in THF to furnish the intermediate

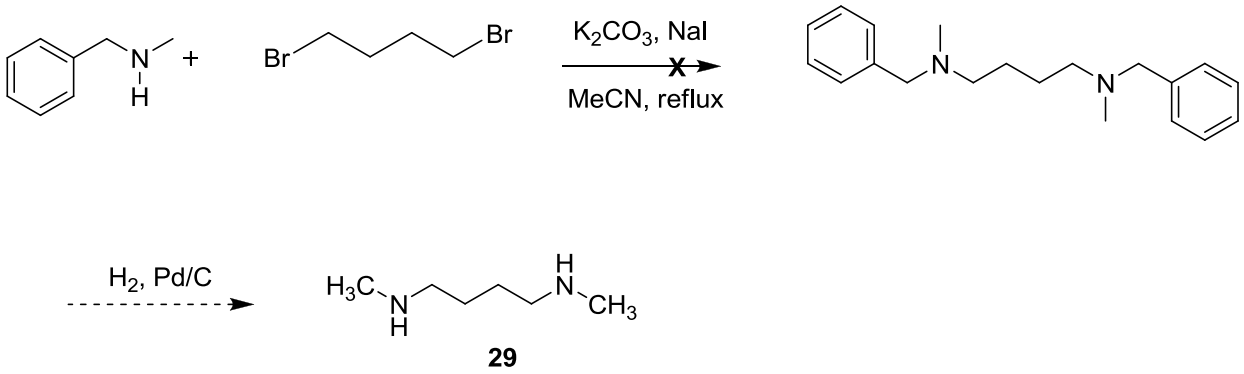
**27** in high yield (80% for two steps) (Scheme 9). The deprotection of compound **27** was carried out in methanol at $0^{o}$C, followed by the dropwise addition of acetyl chloride, stirring the reaction mixture overnight at room temperature to obtain the desired *N,N'*-dimethylbutane-1,4-diamine hydrochloride **28** in quantitative yield. Compound **28** was transformed to its free amine form **29** by treating it with aqueous NaOH, followed by extraction with dichloromethane. Michael addition of compound **29** with acrylonitrile in ethanol, stirring the overnight at room temperature to get the intermediate **30** in 93% yield. The desired spermine derivative **31** was finally obtained from compound **30** by subjecting it to hydrogenation in a pressure vessel in parr apparatus in a mixture of ethanol and aqueous sodium hydroxide at 50 psi for 6 h, using Ra-Ni as the catalyst. Initial attempt to hydrogenate **30** using Palladium on activated charcoal gave a complex mixture of products, difficult to identify by NMR.




**Scheme 9: Synthesis of Dimethylspermine**

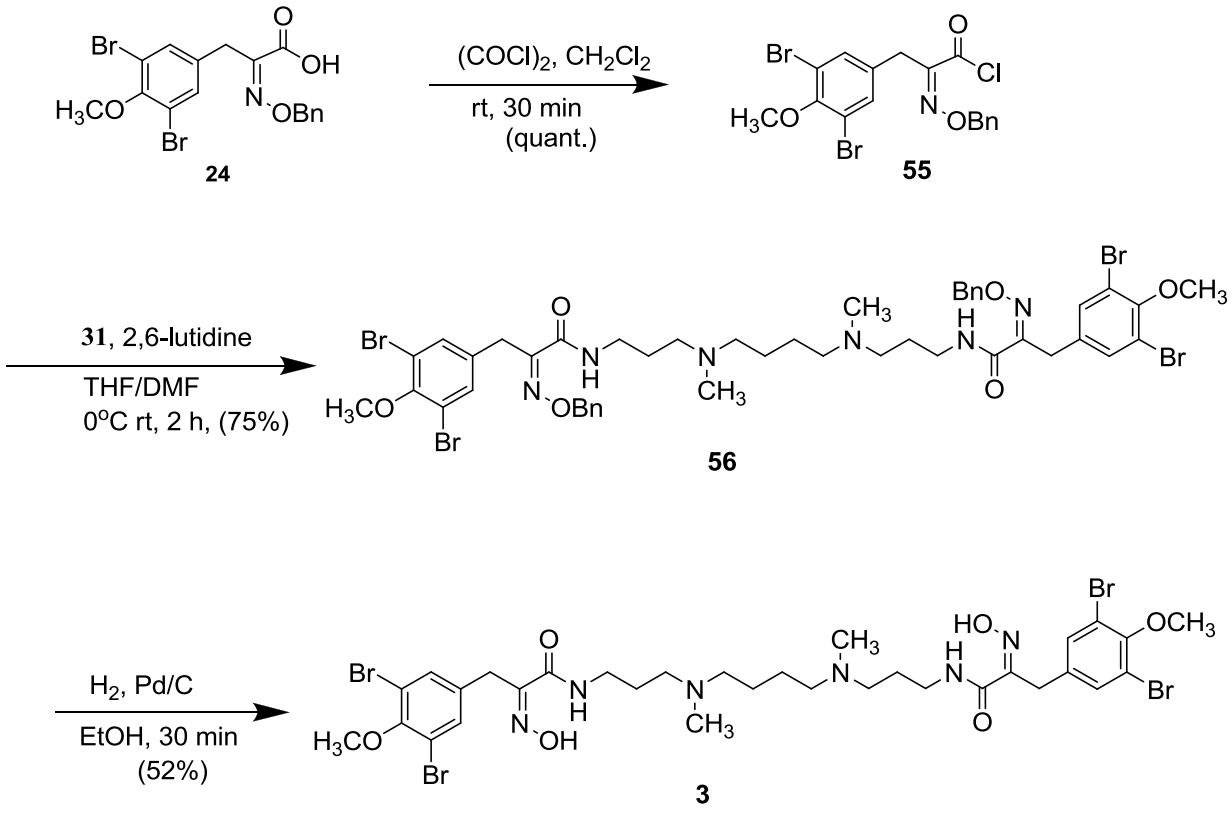
An attempt to access intermediate **29** through reaction of methylamine hydrochloride and 1,4-dibromobutane was not successful, ending up with mixture of products.

In another attempt to access **29**, 1,4-dibromobutane was reacted with *N*-methylbenzylamine in the presence of potassium carbonate and catalytic amount of sodium iodide in acetonitrile[69] but the reaction did not yield the desired product (Scheme 10)**.**




**Scheme 10: Synthesis of intermediate 29**

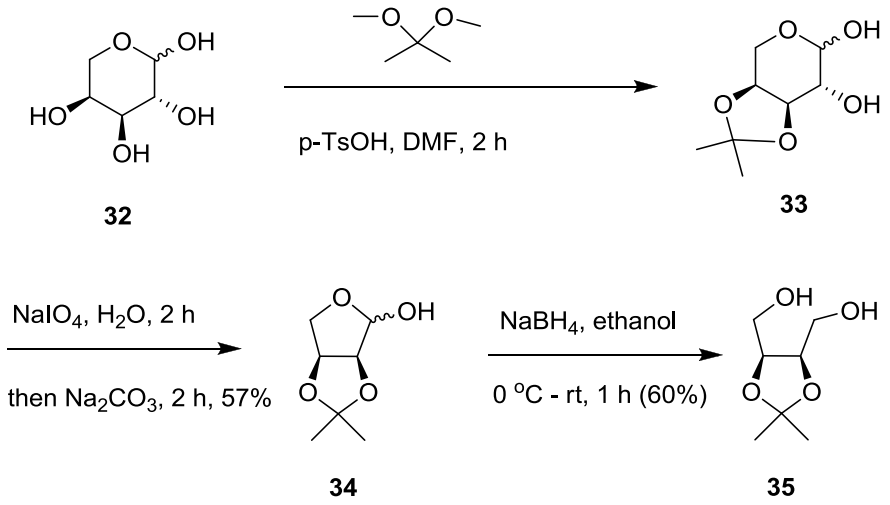
To prepare the advanced intermediate **56**, coupling of the two key intermediates, the protected oxime acid **24** and the dimethyl spermine **31** was achieved through the activation of **24** to the corresponding acid chloride **55**, followed by adding it at 0 $^{o}$C to a solution of **31** in a mixture of THF and DMF, using 2,6- lutidine as a base and stirring the reaction mixture at room temperature for 2 h (Scheme 11). Hydrogenation of **56** in parr vessel at 30 psi, using palladium on activated charcoal afforded the target spermatinamine **3** in 52% yield. Initial use of coupling agents (DDC, HOBt and 2,6 lutidine) to generate **56** proved unsuccessful.




**Scheme 11: Final steps of the synthesis of spermatinamine**

## 3.2 Synthesis of Aspergillusol A (19)

The synthesis was started with the preparation of protected erythritol derivative **35**, as outlined in Scheme 12. Based on wang's procedures,[66] *L*-arabinose was selectively protected as its acetonide **33** by reacting it with 2,2-dimethoxypropane in DMF which was reacted, without purification, with sodium periodate to afford 2,3-*O*-isopropylidene-*L*-erythrose **34**.

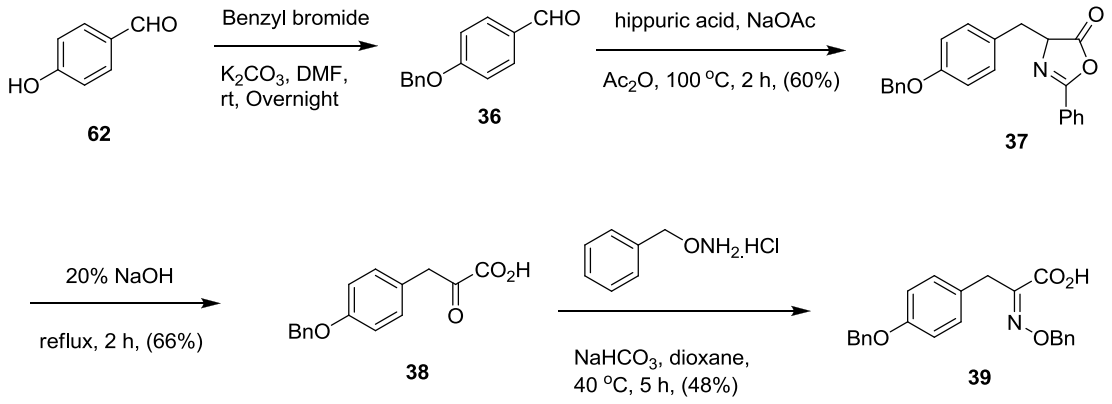



**Scheme 12: Synthesis of erythritol derivative**

The subsequent reduction of **34** with sodium borohydride in methanol to erythritol derivative **35**[65] was not satisfactory in our hands, yielding only 10% of the desired **35**. However, the yield of compound **35** was improved to 60% by optimizing the reaction conditions by carrying it out in ethanol and neutralizing it with acetic acid after reaction completion (Scheme 12).

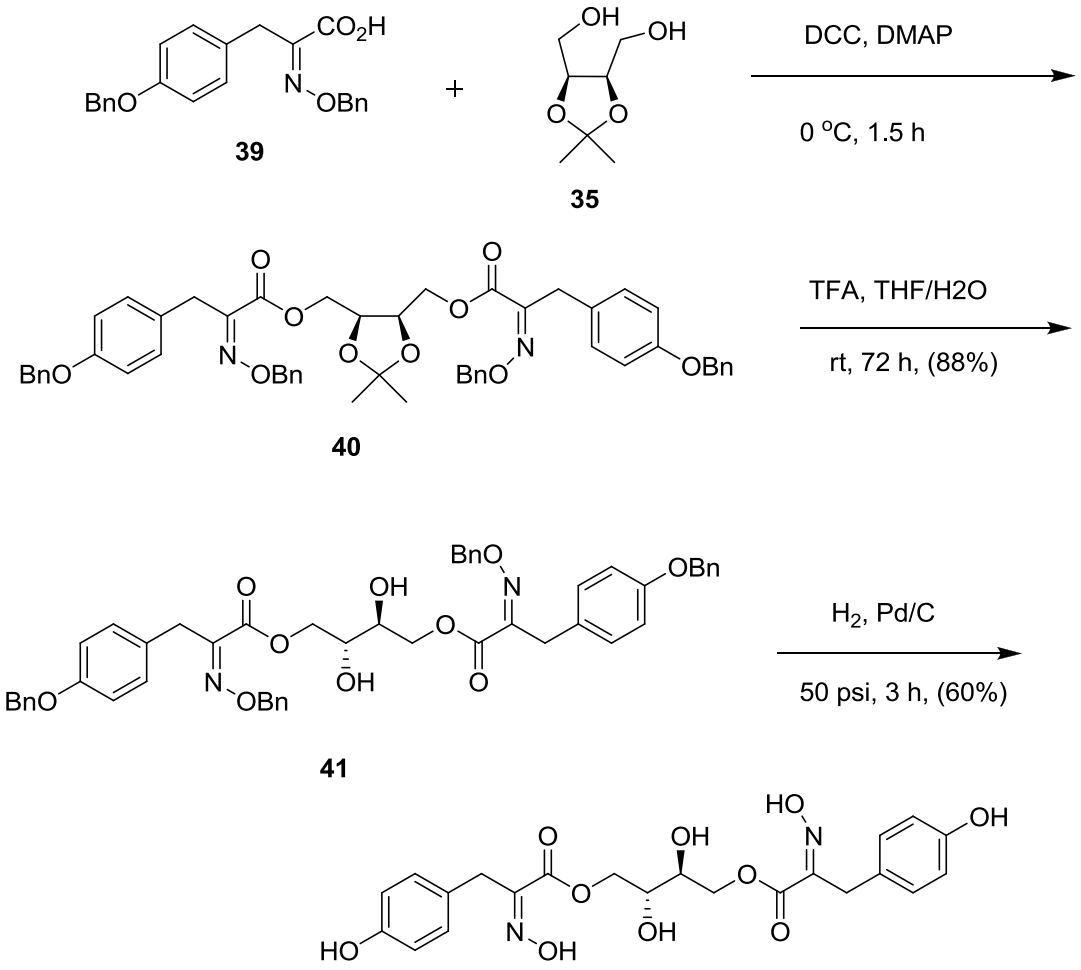
To acquire hydroxyphenylpyruvic acid oxime **39**, needed to be condensed with the erythritol derivative **35**, we were required to synthesize phenylpyruvic acid derivative **38**. The synthesis of **38** was achieved by reacting aldehyde **36** with hippuric acid to afford **37**, followed by the basic hydrolysis of **37**[69] to produce compound **38** (Scheme 13). The condensation of **38** with hydroxybenzylamine hydrochloride in dioxane at 40 $^{o}$C, using

sodiumbicarbonate as a base produced the desired phenylpyruvic acid oxime derivative **39** in 48% yield.




**Scheme 13: Synthesis of intermediate 39**

The estrification of oxime **39** with erythritol derivative **35** was attempted in $CH_2Cl_2$ by reacting it with DCC and a catalytic amount of 4-(dimethyamino)pyridine at 0 $^oC$ for 1.5 h to afford the desired ester **40** in 70% yield (Scheme 14). In an initial trial, the temperature of the reaction was raised to room temperature after the addition of DCC and 4-(dimethyamino) pyridine at 0 $^oC$ and the reaction was completed in 20 minutes but resulted with many side products and 25% yield of **40**.

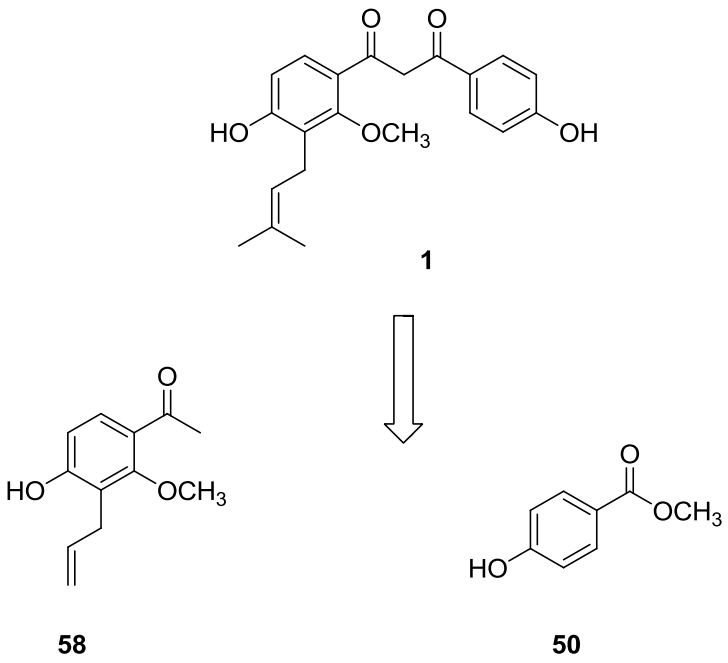



**Scheme 14: Final steps of the synthesis of Aspergillusol A**

The deprotection of the acetonide of **40** was first attempted with dilute HCl in THF at room temperature but the reaction gave 15% of the desired diol **41**. Thus the deprotection was carried out with TFA in a mixture of $H_2O$ and THF, and stirred for 72 h at room temperature to afford **41** in 88% yield. The deprotection of the benzyl groups were ensued by hydrogenation using a catalytic amount of Pd/C under the pressure of 50

psi in a mixture of THF and ethanol for 3 h to yield **19** in 58% yield (Scheme 14). The spectral data of **19** matched the reported values of the previously isolated material. [64]

### 3.3 Synthesis of 2'-methoxy-3'-prenyl-licodione (1)

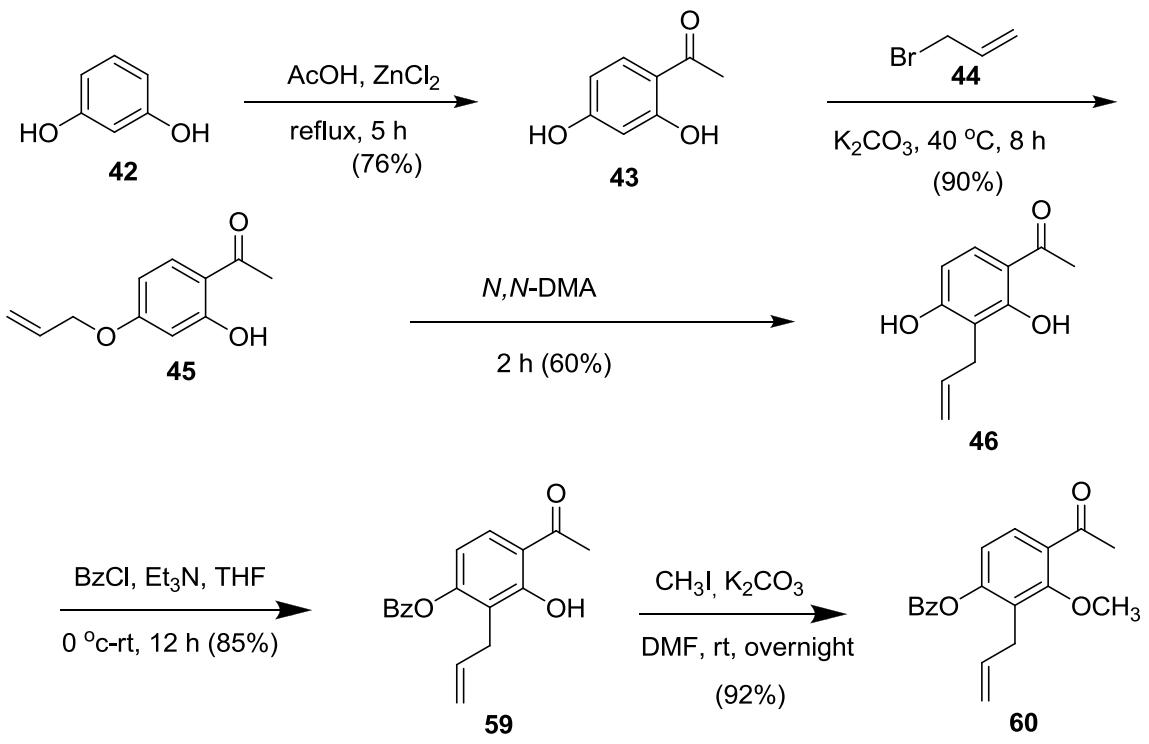



**Scheme 15: Retrosynthesis of 1**

From retrosynthesis standpoint the synthesis of **1** was envisioned from two key intermediates, the highly functionalized hydroxyketone **58** and the phenolic ester **50**, which were to be subjected to claisen condensation (Scheme 15).

### 3.3.1 Synthesis of the intermediate 58

The synthesis of **58** began from acetylation of resorcinol **42** refluxing with acetic acid in the presence of zinc chloride to yield the mono-acetylated resorcinol **43** in good yield (76%). The latter was subjected to alkylation with allylbromide in presence of potassium carbonate as a base to afford compound **45** in 90 % yield after separating the diallylated side-product by acid-base treatment (Scheme 16).

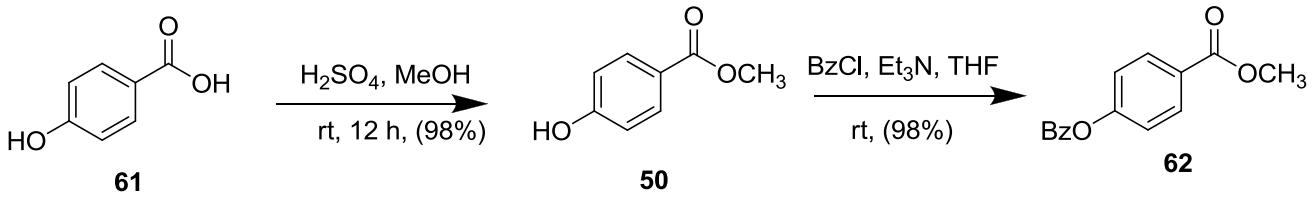



**Scheme 16: Synthesis of Intermediate 60**

Claisen rearrangement of intermediate **45** was executed in *N*,*N*-dimethylaniline at very high temperature to afford intermediate **46** in 60% yield. Regioselective protection with benzoyl chloride afforded **59**, which was subjected to methylation with iodomethane, using potassium carbonate as a base to produce **60**.

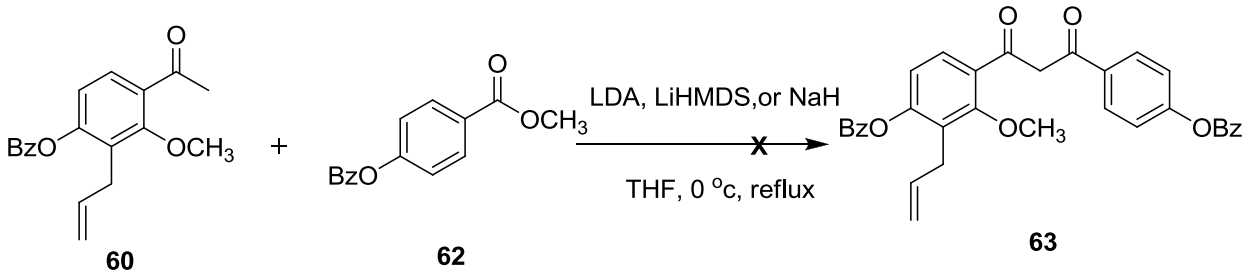
### 3.3.2 Synthesis of methyl 4-hydroxybenzoate (50)

Esterification of **61** in methanol and sulfuric acid afforded the intermediate **50** in 98% yield. The latter was treated with benzoyl chloride to generate intermediate **62**.



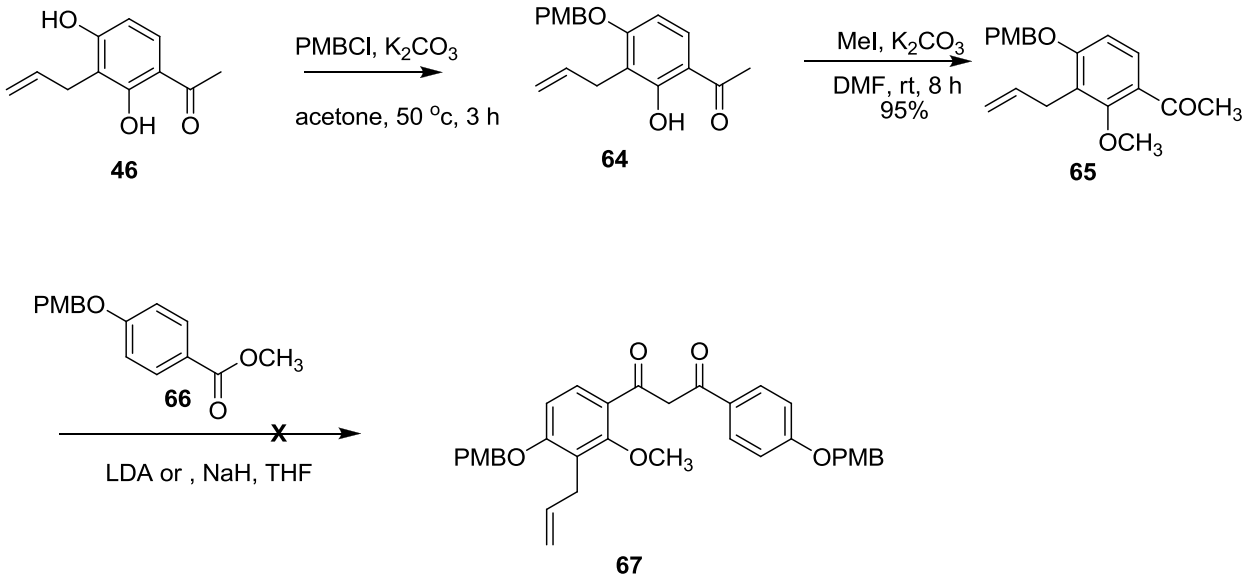

**Scheme 17: Synthesis of intermediate 62**

Having the desired intermediates (**60** and **62**) in hand, cross claisen condensation reaction of the two in presence of LDA as a base proved to be unsuccessful. Instead, benzoyl deprotection was only observed. We tried alternative basis such as LiHMDS and NaH, but no coupling product was observed in any case, the benzoyl group deprotection was witnessed instead (Scheme 18).



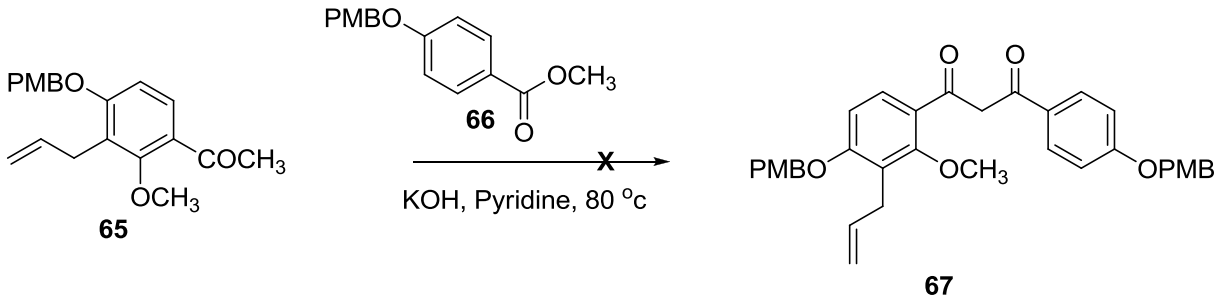

**Scheme 18: Synthesis of Intermediate 63**

With the aim to force the coupling conditions, the more robust *p*-methoxybenzyl (PMB) protection was chosen but yet the desired coupled product was not observed, and only the hydrolysis of the ester took place (Scheme 19).




**Scheme 19: Synthesis of Intermediate 67**

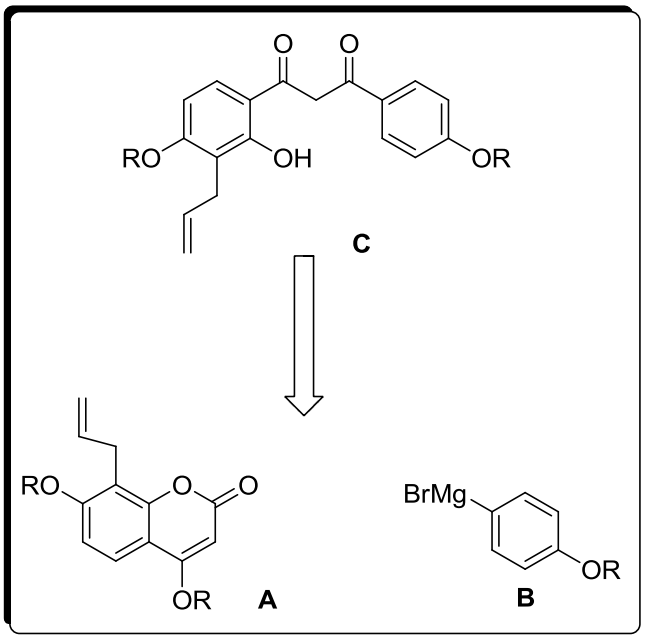
Cross – claisen reaction with potassium hydroxide in pyridine was also tried but it was not successful either.




**Scheme 20: KOH mediated Synthesis of Intermediate 67**

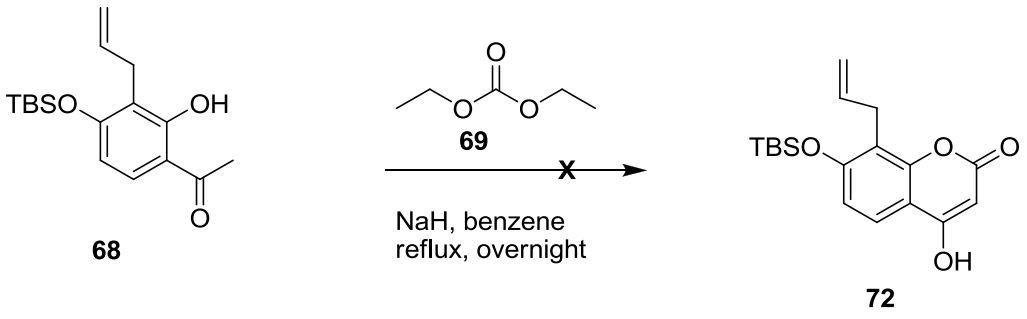
Owing to the failure in cross-claisen reaction, we opted another approach toward the synthesis of **1**.

The new approach involved the synthesis of the hydroxy-coumarin **A** derivative and grignard reagent **B** to access the coupled intermediate **C**, which will further undergo modifications to construct the final target **1**.



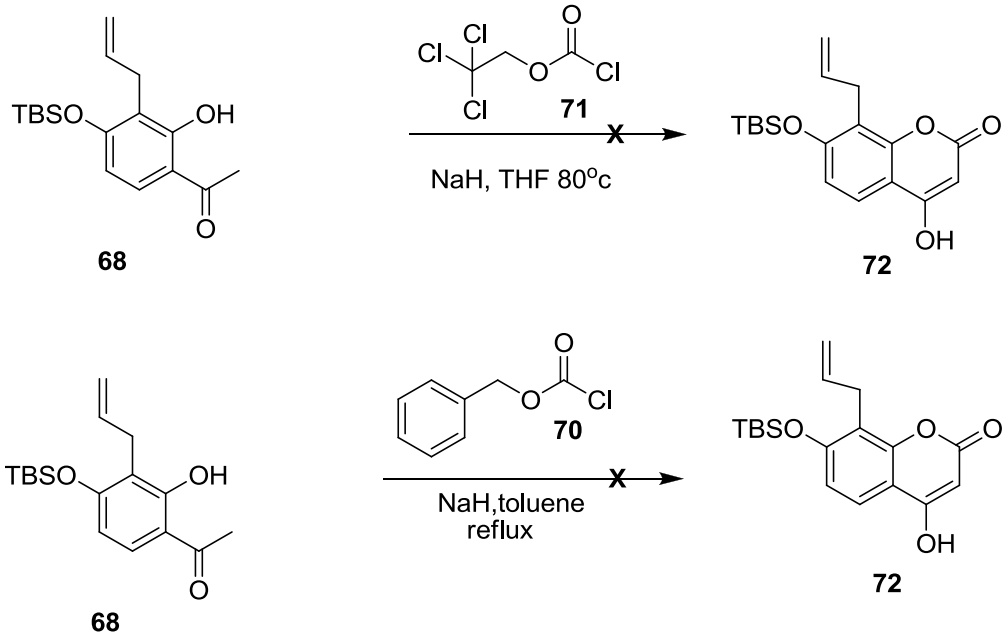

**Scheme 21: Alternate approach to synthesize 1**

To prepare the lactone **72** the hydroxyketone **68** was condensed with diethyl carbonate **69** using sodium hydride as a base under reflux[67] but no cyclization was observed. The starting compound **68** was recovered instead (Scheme 22).



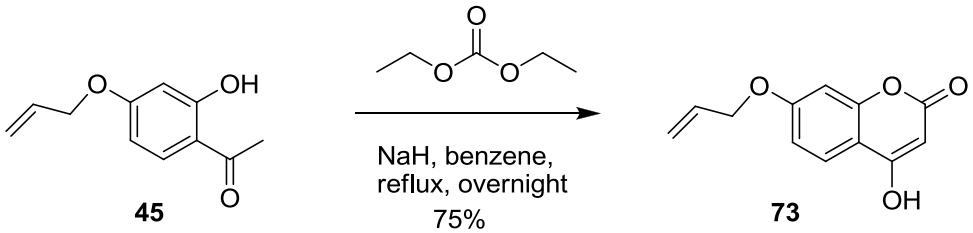

**Scheme 22: Synthesis of intermediate 72 with diethyl carbonate**

Cyclization with 2,2,2-trichloroethyl carbonochloridate **71** also met with failure. So was the case with benzylchloroformate (Scheme 23).



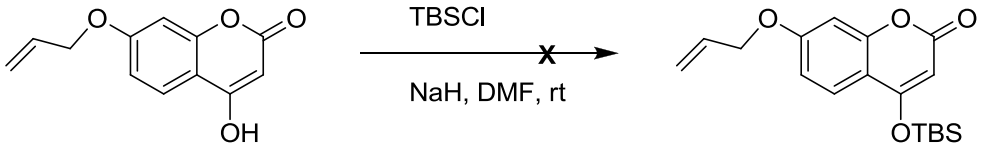

**Scheme 23: Synthesis of 72 with trichloroethyl carbonochloridate and benzochloroformate**

The cyclization of compound **45**, however, was successful by refluxing it with diethyl carbonate in dry benzene, using sodium hydride as a base (Scheme 24).



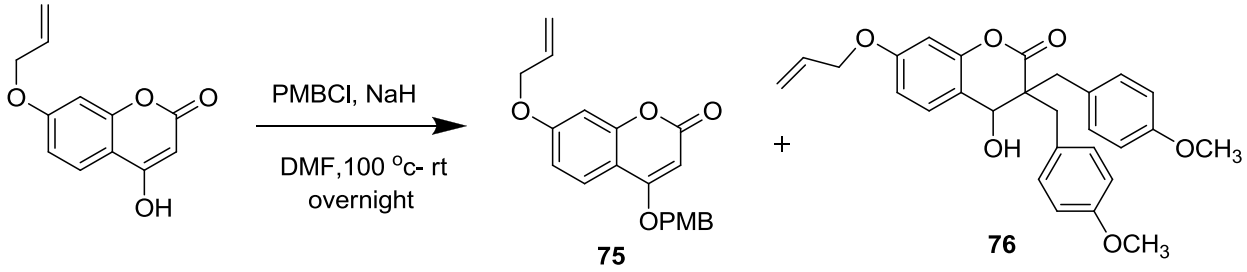

**Scheme 24: Synthesis of intermediate 73**

The next step was the protection of the hydroxyl group of coumarin derivative **73**, prior to claisen rearrangement. This was first attempted with TBSCl but the desired product was not obtained.




**Scheme 25: TBS protection of 73**

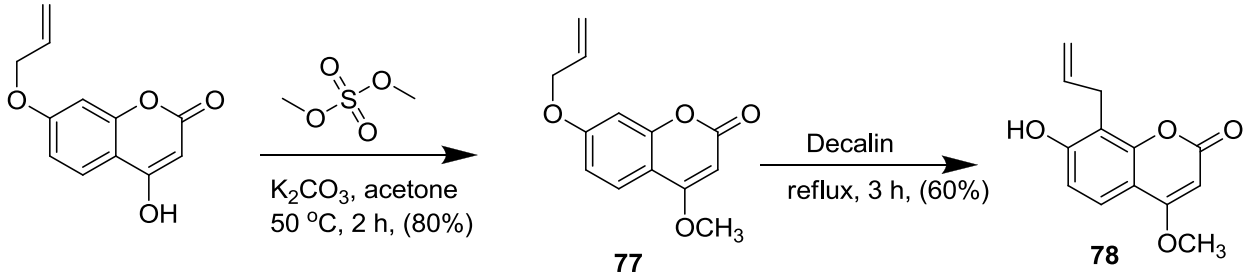
The protection was also tried using PMBCl in DMF heating the mixture at 100 $^{o}$C and then stirring at room temperature, using sodium hydride as a base,[68] which rendered a very low yield of the desired product **75** along with undesired C-dialkylated product **76** as the major product (Scheme 25).




75 76

**Scheme 26: PMB protection of 73**

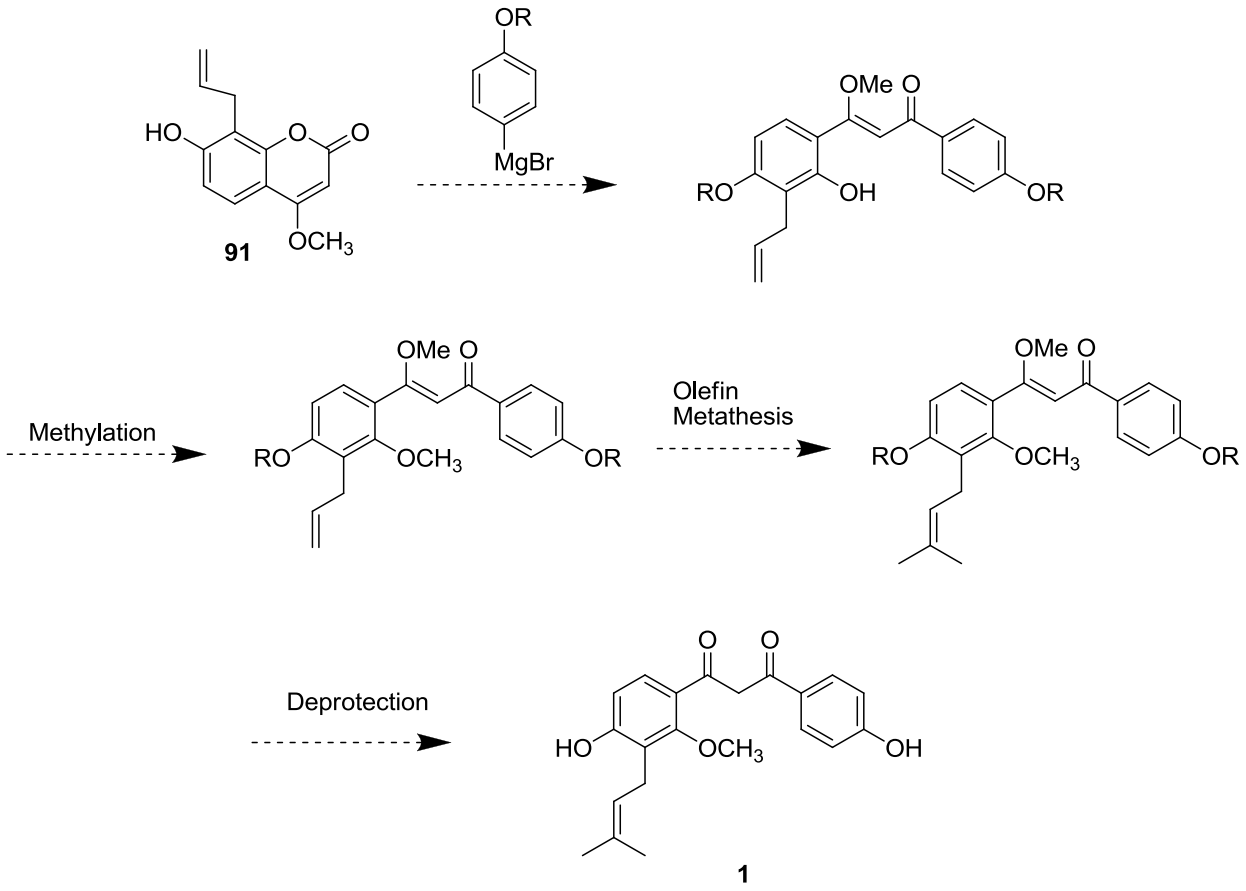
Protection with dimethyl sulfate and potassium carbonate in acetone was, however, successful rendering a high yield (80%) of the desired **77**. Claisen rearrangement of **77** was carried out in decalin[68] to yield **78** in 60% yield.




77 78

**Scheme 27: Synthesis of intermediate 78**

The next steps toward the total synthesis of our target molecule will require protection of the hydroxyl group using PMBCl or TBSCl followed by coupling of **78** with grignard reagent, methylation, olefin metathesis and finally deprotection to afford **1**.




**Scheme 28: Proposed route for the synthesis of 1**

# CHAPTER 4

# 4.0 EXPERIMENTAL WORK

## 4.1 Instrumentation and Chemicals

$^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on JEOL Lambda 500 and 400 MHz spectrometer. Chemical shifts were reported in ppm (δ) relative to tetramethyl silane (TMS) by using ($CDCl_3$), (DMSO) or methanol as deuterated solvents. Multiplicities were reported as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m), and coupling constants (J) were reported in hertz (Hz). IR Spectra were recorded on a NicoletTM 6700 FT-IR spectrometer from a thermo-electron by using a smart orbit for net samples, and they were reported in wave numbers ($cm^{-1}$) (Spectral resolution, 4 $cm^{-1}$; Number of scans, 4). Mass was determined by using Agilent 7000A Triple Quadrupole GC/MS.

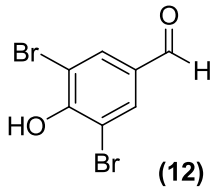
Elemental analysis was carried out on a EuroVector Elemental Analyzer Model EA3000. All mps are uncorrected. Thin layer chromatography (TLC) was frequently used to monitor reactions and to give qualitative determination of sample purity. TLC analyses were performed on silica gel Merck 60 F254 plates, and spots were visualized under a spectroline UV lamp operating at short and long wavelength ranges. Visualization was improved by dipping plates into a phosphomolybdic acid solution, and then by drying in a blast of hot air. Purification of the products was carried out either by recrystallization or by flash column chromatography. The column was packed with silica gel 100 from Fluka

Chemie AG (Buchs, Switzerland). Ethyl acetate, petroleum ether (boiling fraction 60-80) and hexane were used as eluting solvents, in volume-by-volume ratios as stated.

Chemicals were purchased from commercial sources, and they were used without any further purification unless otherwise specified. All solvents were of reagent grade, and dichloromethane was passed through alumina before use. Specially dried 53 (anhydrous) solvents were used where necessary. Glassware for moisture-sensitive reactions were oven dried at 120-140 °C for at least three hours and cooled in a desiccators prior to use. Some of the reactions were run in an inert atmosphere of nitrogen as stated.

## 4.2 Synthesis of Spermatinamine

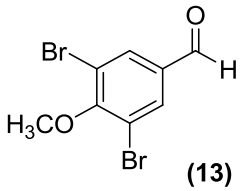
### 4.2.1 Synthesis of 3,5-Dibromo-4-hydroxybenzaldehyde (12)




**(12)**

Bromine (30.2 g, 190 mmol) in AcOH (50 mL) was added to a mixture of 4-hydroxybenzaldehyde (11 g, 90 mmol) and sodium acetate (22.9 g, 279 mmol) in AcOH (200 mL) at room temperature over 20 min. The reaction mixture was stirred for 1 h at room temperature. A solid precipitated after $H_2O$ (200 mL) was added. After filtration, the solid was washed with $H_2O$ and dried in a vacuum desiccators with $P_2O_5$ overnight to afford **12** as a pale-yellow solid (24.1 g, 96%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.43 (s, 1H), 8.00 (s, 2H), 9.80 (s, 1H); $^{13}$C NMR (75 MHz, acetone-$d_6$): $\delta$ 112.4, 132.7, 157.0, 135.0, 189.8.

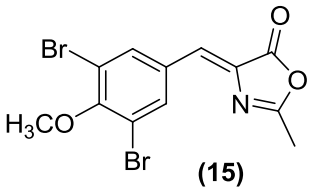
### 4.2.2 Synthesis of 3,5-dibromo-4-methoxybenzaldehyde (13)




**(13)**

To a mixture of aldehyde **12 (**3 g, 10.71 mmol) in DMF (30 mL) was added potassium carbonate (2.22 g, 16.1 mmol), followed by the addition of methyl iodide (1.98 g, 13.9 mmol) at room temperature and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (40 mL) and washed successively with water (20 mL), 2M HCl (20 mL x 2), brine (15 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to afford **13** as a yellow solid (3.05g, 97%). $^{1}$H NMR (500 MHz, $CDCl_3$): δ 3.97 (s, 3H), 8.03 (s, 2H), 9.86 (s, 1H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 119.31, 133.91, 134.20, 159.12, 188.43.

### 4.2.3 Synthesis of (Z)-4-(3,5-dibromo-4-methoxybenzylidene)-2-methyloxazol-5(4H)-one (15)

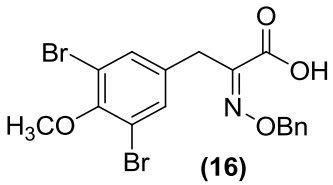



**(15)**

A mixture of aldehyde **13** (3.02 g, 8.05 mmol), sodium acetate (8.00 mg, 9.6 mmol), and *N*-acetylglycine (943 mg, 8.05 mmol) in $Ac_2O$ (12.5 mL) was stirred at 120 °C for 4 h. A yellow solid was crushed out upon cooling the reaction mixture to room temperature. After filtration, the solid was washed with cold 1:1 pentane/$Et_2O$ to yield **15**

as a yellow solid (2.92 g, 97%); mp: 154-155 $^{o}$C; IR (Neat) $\nu_{max}$ 3233, 2927, 1692, 1662, 1633, 1468, 1416, 1365, 1255, 1201, 981, 902, 721 cm$^{-1}$. $^{1}$H NMR (500 MHz, DMSO-$d_6$): δ 2.40 ( s, 3H), 3.83 (s, 3H), 7.16 (s, 1H), 8.47 (s, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): δ 15.52, 60.73, 117.89, 125.70, 132.28, 133.88, 135.65 , 154.94, 166.88, 168.04.

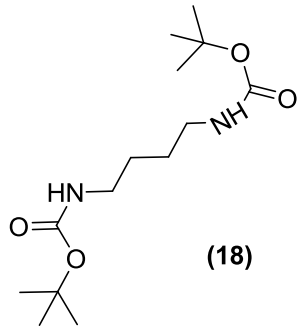
### 4.2.4 Synthesis of (Z)-2-(benzyloxyimino)-3-(3,5-dibromo-4-methoxyphenyl)propanoic acid (16)




**(16)**

A suspension of azlactone **15** (2.2 g, 4 mmol) and $Ba(OH)_2$ (4.8 g, 28 mmol) in a mixture of dioxane:$H_2O$ (1:1, 56 mL) was stirred at 60 °C for 1 h, followed by the addition of *O*-Benzylhydroxylamine hydrochloride (2.05 g, 12.8 mmol) and the mixture was stirred vigorously at the same temperature for 6 h. The reaction mixture was cooled to 0°C and acidified to pH 4 with 10% HCl and extracted with EtOAc (50 mL x 2). The combined organic extracts were washed with $H_2O$, dried over $MgSO_4$, and evaporated under reduced pressure. The yellow oily material was loaded on silica column eluting with EtOAc:MeOH (10:1) to afford **16** (1.37g, 75%) as a pale-yellow solid; mp: 115 $^{o}$C; IR (Neat) $\nu_{max}$ 3060, 2943, 1692, 1589, 1471, 1416, 1259, 1219, 991.1, 897, 738, 696 cm$^{-1}$. $^{1}$H NMR (500 MHz, $CDCl_3$): δ 3.80 (s, 2H), 3.83 (s, 3H), 5.30 (s, 2H), 7.40-7.26 (m, 7H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 29.13, 78.74, 117.99 (2C), 128.56 (2CH), 128.84 (3CH), 133.38 (2CH), 133.59, 135.36, 148.89, 153.03, 163.31.

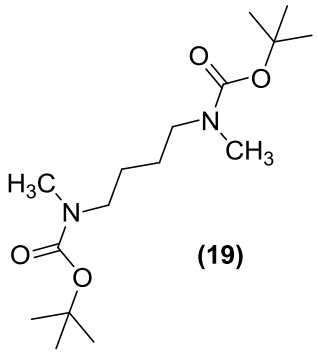
### 4.2.5 Synthesis of tert-butyl butane-1,4-diyldicarbamate (18)




**(18)**

To a solution of butane-1,4-diamine **17** (7 g, 79.4 mmol) in dichloromethane (100 mL) was added di-tert-butyl dicarbonate (38.1 g, 174.7 mmol) and the reaction mixture was stirred for 4 hours at room temperature. The solvent was evaporated under reduced pressure to yield white precipitates which were collected by filtration and washed with ether to yield **18** as a white solid (21.75 g, 95%). IR (Neat) $\nu_{max}$ 3335, 2975, 2936, 2868, 1686, 1528, 1315, 1362, 1276, 1167, 1014, 905, 661 $cm^{-1}$. $^{1}H$ NMR (500 MHz, $CDCl_3$) (data for monomer): δ 1.44 (s, 9H), 1.5 (s, 2H obscured by the preceding peak), 3.12 (s, 2H), 4.57 (br s, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$) (data for monomer): δ 27.39, 28.39 ($3CH_3$), 40.19, 79.13, 155.96.

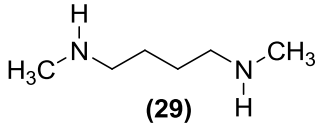
### 4.2.6 Synthesis of tert-butyl butane-1,4-diylbis(methylcarbamate) (19)




**(19)**

To a solution of **18** (20.28 g, 54.87 mmol) in THF (200 mL) at 0$^{o}$C was added sodium hydride (2.77 g, 115.2mmol), followed by dropwise addition of iodomethane (19.47 g, 137.2mmol). After being stirred overnight at room temperature, the reaction mixture was diluted with ethyl acetate (100 mL) and successively washed with water (30 mL), brine (30 mL), dried over sodium sulfate and concentrated under vacuum. The crude mixture was column chromatographed using ethyl acetate (100%) as an eluent to yield the title compound **19** as a yellow liquid (14.49 g, 85%). IR (Neat) $\nu_{max}$ 2972, 2928, 1687, 1455, 1393, 1364, 1311, 1217, 1153, 877, 732 cm$^{-1}$. $^{1}$H NMR (500 MHz, $CDCl_3$), (data for monomer): δ 1.45 (s, 9H), (s, 2H, obscured by the preceding peak), 2.82 (s, 3H), 3.21 (s, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$), (data for monomer): δ 24.93, 28.41 ($3CH_3$), 48.50, 155.75.

### 4.2.7 Synthesis of N,N'-dimethylbutane-1,4-diamine hydrochloride (29)

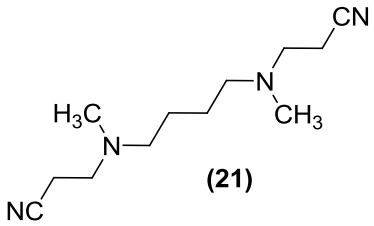



**(29)**

To a solution of compound **19** (14 g, 74 mmol) in methanol (100 mL) at 0 $^{o}$C was added acetyl chloride (6.3 mL, 89 mmol) dropwise and the reaction was stirred overnight at room temperature. The solvent was evaporated under vacuum to yield the corresponding ammonium salt (13.8 g, quantitative yield) as a white solid, which was converted to its free amine form by dissolving it in 10% aqueous NaOH and extracting it with dichloromethane (60 mL x 3). The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated *in vacuo* to yield compound **29** as a pale yellow oil. $^{1}$H NMR (500 MHz,

$CDCl_3$), (data for monomer): δ 1.52 (s, 2H), 1.65 (s, 2H), 2.42 (s, 3H), 2.58 (2H). $^{13}C$ NMR (125 MHz, $CDCl_3$), (data for monomer): δ 27.54, 36.34, 51.87.

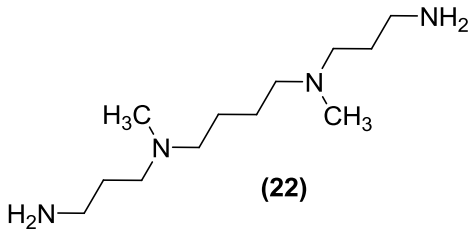
### 4.2.8 Synthesis of 3,3'-(butane-1,4-diylbis(methylazanediyl))dipropanenitrile (21)




**(21)**

To a solution of N,N'-dimethylbutane-1,4-diamine **29** (10 g, 86 mmol) in ethanol at $0^oC$ was added acrylonitrile (960 mg, 180.7 mmol) and the mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure to yield **21** as a yellow liquid (17.78 g, 93%). IR (Neat) $\nu_{max}$ 2940, 2851, 2798, 2246, 1728, 1460, 1368, 1255, 1136, 1048 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$), (data for monomer): δ 1.50 (m, 2H), 2.27 (s, 3H), 2.42 (s, 2H), 2.48 (t, 2H), 2.71 (m, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$), (data for monomer): δ 15.92, 24.66, 41.46, 52.51, 56.67, 118.86.

### 4.2.9 Synthesis of N-4,N-9-Dimethylspermine (22)

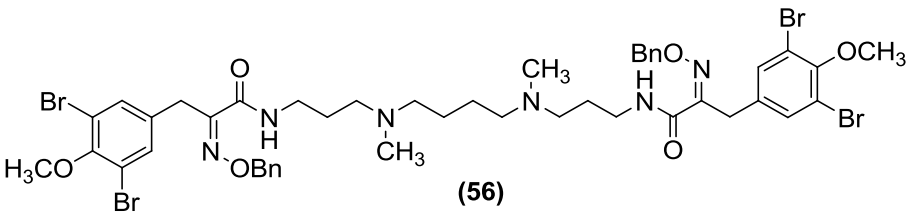



**(22)**

To a solution of **21** (3 g, 13.5 mmol) in ethanol (30 mL) was added Raney Nickel (approx. 10% w/w), followed by the addition of 50% aqueous sodium hydroxide (1.5 mL ). The mixture was hydrogenated overnight in a Paar shaker apparatus at a pressure of 50

psi at room temperature. The mixture was filtered through a pad of celite and concentrated *in vacuo* to get the title compound as pale yellow oil (2.99 g, 96%). IR (Neat) $\nu_{max}$ 3281, 2935, 2852, 2788, 1602, 1458, 1378, 1056 $cm^{-1}$.$^1$H NMR (500 MHz, $CDCl_3$), (data for monomer): δ 1.46 (m, 2H), 1.64-1.57 (m, 2H), 2.2 (s, 2H), 2.46-2.33 (m, 4H), 2.71 (t, 2H, *J* = 6.1), 3.42 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$), (data for monomer): δ 25.10, 30.73, 40.38, 42.10, 55.49, 57.74.

### 4.2.10 Synthesis of (2Z,2'Z)-N,N'-(3,3'-(butane-1,4-diylbis(methylazanediyl))bis(propane-3,1-diyl))bis(2-(benzyloxyimino)-3-(3,5-dibromo-4-methoxyphenyl)propanamide) (56)

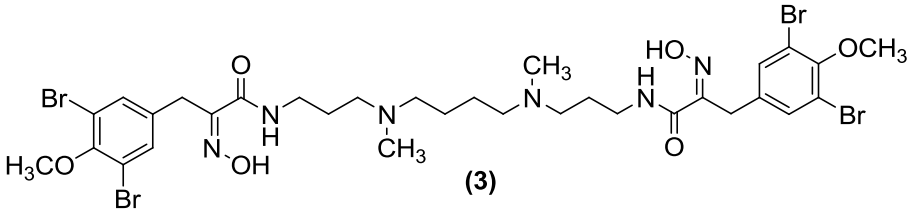



**(56)**

To a solution of **22** (1 g, 4.3 mmol) in a mixture of $CH_2Cl_2$ (15 mL) and DMF (3 mL) at 0$^o$C was added 2,6-lutidine (2 mL, 17.2 mmol) and after being stirred for 10 min, a solution of acid chloride **55** (6.2 g, 13 mmol) in $CH_2Cl_2$ (30 mL) was added dropwise. The reaction mixture was stirred for 6 h at room temperature, diluted with chloroform (50 mL) and the organic layer was washed with $H_2O$ (25 mL), dried over $Na_2SO_4$ and evaporated under vacuum. The light yellow oil was chromatographed on silica column eluting with EtOAc:MeOH: $NH_4OH$ (6:4:1) to yield **56** as a thick yellow liquid (3.56 g,

75%). IR (Neat) $\nu_{max}$ 2941, 2858, 2797, 1664, 1527, 1468, 1420, 1366, 1258, 1203, 996, 906,726 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$), (data for monomer): δ 1.43 (s, 2H, H-7), 1.66 (m, 2H, H-3), 2.15 (s, 3H, *N-CH₃*), 2.29 (br s, 2H, H-4), 2.40 (t, 2H, *J* = 4.88, H-6), 4.37 (q, 2H, H-2), 3.83 (s, 5H, 4'-O*Me*, *OCH₂*Ph), 5.20 (s, 2H, *OCH₂*Ph), 7.36-7.27 (m, 5H, *O*CH₂*Ph*), 7.44 (s, 2H, H-2', H-6'), 7.80 (br s, 1H, N-*H*). $^{13}C$ NMR (125.7 MHz, $CDCl_3$), (data for monomer): δ 24.96 (C-7), 26.00 (C-3), 28.72 (C-7'), 39.12 (C-2), 41.78 (4-N-*Me*), 56.25 (C-4), 57.82 (C-6), 60.45 (4'-O*Me*), 77.33 (*OCH₂*Ph), 117.62 (C-3', C-5'), 127.92 (*O*CH₂*Ph*), 128.24 (*O*CH₂*Ph*), 128.57 (*O*CH₂*Ph*), 133.43 (C-2', C-6'), 134.94 (C-1'), 136.39 (*O*CH₂*Ph*), 152.48 (C-8'), 151.52 (C-4'), 161.91 (C-9'').

### 4.2.11 Synthesis of Spermatinamine (3)

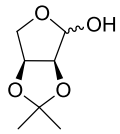



**(3)**

To a solution of **56** (0.2 g, 0.18 mmol ) in ethanol (10 mL) in a pressure vessel was added Pd-C (20 mg 10% wet basis) and the solution was subjected to hydrogenation in parr apparatus under the pressure of 40 psi for 0.5 h. The solution was filtered over a pad of celite, concentrated under vacuum and loaded over silica column eluting with MeOH:$NH_4OH$ (96:4) and then changing to (92:8) afforded the desired **3** as a white amorphous solid (0.087 g, 52%). mp: 170-172. IR (Neat) $\nu_{max}$ 3441, 3021, 2901, 2766, 1658, 1521, 1411, 1305, 1004, 730 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$), (data for monomer): δ 1.61 (s, 2H, H-7), 1.80 (m, 2H, H-3), 2.70 (s, 3H, *N-CH₃*), 3.02 (m, 2H, H-

4), 3.08 (t, 2H, *J* = 4.88, H-6), 3.20 (q, 2H, H-2), 3.72 (s, 3H, 4'-OMe,), 3.75 (s, 2H, H-7'), 7.45 (s, 2H, H-2', H-6'), 7.90 (br s, 1H, N-*H*). $^{13}$C NMR (125 MHz, DMSO-$d_6$), (data for monomer): δ 21.96 (C-7), 23.50 (C-3), 25.72 (C-7'), 36.62 (C-2), 38.78 (4-N-*Me*), 52.85 (C-4), 53.82 (C-6), 59.85 (4'-O*Me*), 117.52 (C-3', C-5'), 133.10 (C-2', C-6'), 134.98 (C-1'), 150.28 (C-8'), 151.49 (C-4'), 162.01 (C-9').

### 4.2.12 Synthesis of 2,3-O-Isopropylidene-L-erythrose (34)

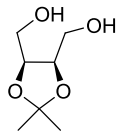



**(34)**

2,2-Dimethoxypropane (27 mL, 22.9 g, 0.220 mmol, 3.3 equiv) was added to a solution of *L*-arabinose **32** (10.0 g, 0.067 mol, 1.0 equiv) and p-toluenesulphonic acid monohydrate (150 mg, 0.8 mmol, 0.01 equiv) in dimethylformamide (130 mL). The resulting solution was stirred for 2 h, and then neutralized by solid sodium carbonate and concentrated under reduced pressure. The residue was partitioned between water (120 mL) and 40 ± 60$^{o}$C petroleum ether (60 mL). To the aqueous layer was then added sodium periodate (35.6 g, 0.166 mol, 2.5 equiv) portionwise, and the mixture was stirred for 2 h. Solid sodium carbonate was added and the slurry was stirred for 1 h. Water was then added (80 mL) and the aqueous layer was extracted with EtOAc (3 x 80 mL), and the combined organic extracts were concentrated under reduced pressure to yield a pale yellow oil. The crude product was purified by flash column chromatography on silica gel (EtOAc/hexane 7:13) to yield pure **34** (6.05 g, 57% from L-arabinose) as a mixture of

anomers (α:β 1:6): $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 1.36, 1.53 (2 s, 2 x 3H; $C(CH_3)2$), 2.09 (br s, 1H; OH), 3.53 (dd, $^{2}$J (H, H) = 11.1, $^{3}$J (H, H) = 3.7 Hz, 1H; CHH'), 3.96 (d, $^{2}$J (H, H) = 11.6 Hz, 1H; CHH'), 4.47 (dd, 3J (H, H) = 6.2, $^{3}$J (H, H) = 3.6 Hz, 1H; $CH_2CH$), 4.74 (dd, $^{3}$J (H, H) = 6.2, $^{3}$J (H, H) = 3.7 Hz, 1H; CHOHCH), 4.98 (s, 1H; CHOH); $^{13}$C NMR (100 MHz, $CDCl_3$ , DEPT): δ = 24.8, 25.9 (2 q, $C(CH_3)2$), 67.5 (t, $CH_2$), 78.2, 79.5 (2 d, 2 x CHO-), 97.4 (d, CHOH), 113.4 (s, $C(CH_3)_2$); β-anomer: $^{1}$H NMR (400 MHz, $CDCl_3$): δ = 1.30, 1.45 (2 s, 3H; $C(CH_3)_2$), 3.61 (br s, 1H; OH), 3.99 (d, $^{2}$J (H, H) = 10.4 Hz, 1H; CHH'), 4.05 (dd, $^{2}$J( H, H) = 10.4, $^{3}$J (H, H) = 3.5 Hz, 1H; CHH'), 4.55 (d, $^{3}$J (H, H)=5.9 Hz, 1H; CHOHCH), 4.82 (dd, $^{3}$J (H, H) = 5.9, $^{3}$J (H, H = 3.5 Hz, 1H; $CH_2CH$), 5.39 (s, 1H; CHOH); $^{13}$C NMR ($CDCl_3$ , 100 MHz): δ = 24.6, 26.1 (2 q, 2 x $C(CH_3)$), 71.8 (t, $CH_2$), 79.9 (d, $CH_2CH$), 85.1 (d, CHOHCH), 101.6 (d, CHOH), 112.2 (s, $C(CH_3)_2$); IR (film): v = 3426 $cm^{-1}$ (br, O-H stretch), 2987, 2943, 2882 (aliphatic C-H stretch), 1460; HRMS (CI): m/z: calcd for $C_7H_{16}NO_4$ : 178.1083; found: 178.1079 [$M^{+}$+$NH_4$].

### 4.2.13 2,3-O-Isopropylidene-erythritol (35)

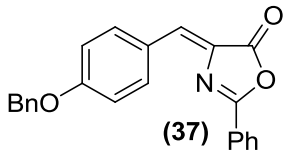



**(35)**

To a solution of **34** (0.48 g, 3 mmol) in ethanol (20 mL) at 0 $^{0}$C was added sodium borohydride (0.17, 4.5 mmol) and the reaction was stirred for 20 minutes at the same temperature, followed by stirring the solution for 1 hr at room temperature. The reaction mixture was neutralized with acetic acid and concentrated under reduced pressure, ethyl

acetate (35 mL) was added and washed with $H_2O$ (20 mL), brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated in a vacuum. The concentrate was purified by silica gel column chromatography using a mixture of hexane:ethyl acetate (6:4) and then changing to (1:1) afforded **35** as colorless thick oil (0.29 g, 60%).

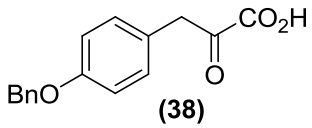
### 4.2.14 Synthesis of 4-(4-(benzyloxy)benzyl)-2-phenyloxazol-5(4H)-one (37)




**(37)**

A mixture of aldehyde **36** (3.00 g, 14 mmol), sodium acetate (1.4 g, 17.11 mmol), and hippuric acid (2.5 g, 14 mmol) in $Ac_2O$ (20 mL) was stirred at 120 °C for 3 h. A yellow solid was crushed out when the reaction mixture was cooled to room temperature. After filtration, the solid was washed with cold pentane:$Et_2O$ (8:2) to yield **37** as a yellow solid (3 g, 60%); mp: 143-145 $^{o}$C. IR (Neat) $\nu_{max}$ 3260, 2897, 1783, 1761, 1703, 1650, 1593, 1503, 1450, 1356, 1262, 1144, 980, 866, 808, 678 $cm^{-1}$. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 4.24 (s, 2H), 6.16 (d, 2H, *J* = 8.8), 6.30 (s, 1H), 6.54-6.41 (m, 5H), 6.62-6.58 (m,2H), 6.69-6.66 (m, 1H), 7.28-7.24 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 70.16, 115.40 (2CH), 125.86, 126.80 , 127.47 (2CH), 128.17 (2CH), 128.23, 128.70 (2CH), 128.88 (2CH), 131.25, 131.80, 132.99, 134.58 (2CH), 136.27, 161.36, 162.56, 167.95.

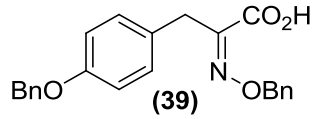
### 4.2.15 Synthesis of 3-(4-(benzyloxy)phenyl)-2-oxopropanoic acid (38)




**(38)**

A suspension of **37** (2 g, 5.6 mmol) in 20% NaOH (20 mL) was refluxed for 2 h. The mixture was cooled to room temperature and extracted with $Et_2O$ (50 mL). The aqueous layer was cooled on ice-bath and acidified to pH 4 with 2 M HCl and was extacted with EtOAc (50 mL x 2). The organic layer was washed with brine (20 mL), dried over $Na_2SO_4$ and evaporated under vacuum to give **38** as a pale yellow solid (1.0 g, 66%); mp: 173-175 $^oC$. IR (Neat) $\nu_{max}$ 3458, 3033, 2905, 2866, 1720, 1663, 1600, 1507, 1454, 1379, 1233, 1173, 1110, 1011, 863, 737 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO): δ 5.09 (s, 2H), 6.38 (s, 1H), 6.89 (d, 2H, *J* = 8.8), 7.44-7.31 (m,6H), 7.69 (d, 2H, *J* = 8.8). $^{13}C$ NMR (125 MHz, DMSO): δ 44.06, 69.22, 109.81, 114.75 (2CH), 127.85 (2CH), 128.48 (2CH), 130.84 (2CH), 131.03, 137.03, 140.21, 157.59, 166.59.

### 4.2.16 Synthesis of (Z)-3-(4-(benzyloxy)phenyl)-2-(benzyloxyimino)propanoic acid (39)

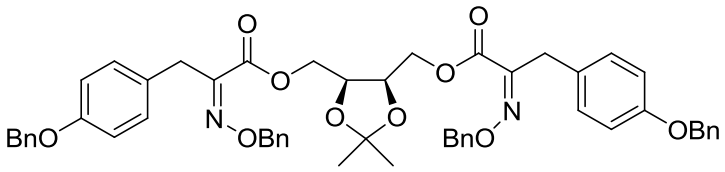



**(39)**

To a mixture of compound **38** (1 g, 3.7 mmol) and N-benzyloxylamine hydrochloride (0.65 g, 4.1 mmol) in dioxane (20 mL ) was added sodium hydrogen carbonate (1.1 g, 13 mmol) and the mixture was stirred at 40 $^oC$ for 5 h. The reaction was concentrated under reduced pressure, diluted with ethyl acetate (50 mL) and washed with $H_2O$ (20 mL), brine

(10 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated in a vacuum. The column chromatography purifications of the yellow oily material, eluting with ethyl acetate:hexanes (1:1) and then changing to (8:2) yielded the tile compound **38** as a light yellow solid (0.67 g, 48%). mp: 91-92 $^{o}$C. IR (neat) 3310, 3031, 1703, 1609, 1509, 1451, 1317, 1004, 984, 918, 757, 696 $cm^{-1}$. $^{1}$H NMR ($CDCl_3$, 500 MHz) δ: 3.86 (2H, s, H-1'), 5.02 (2H s, O*CH*$_2$Ph), 5.30 (2H, s, O*CH*$_2$Ph), 6.86 (2H, d, *J* = 8.5 Hz, H-2, H-6), 7.18 (2H, d, *J* = 8.5 Hz, H-3, H-5), 7.42-7.32 (10H, m, $OCH_2$*Ph*). $^{13}$C NMR (125.7 MHz, $CDCl_3$) δ: 29.5 (C-1'), 70.0 (O*CH*$_2$Ph), 78.3 (O*CH*$_2$Ph), 114.9 (C-2, C-6), 127.2(C-3, C-5), 127.4 ($OCH_2$*Ph*), 127.9 ($OCH_2$*Ph*), 128.3 ($OCH_2$*Ph*), 128.5 ($OCH_2$*Ph*), 128.6 ($OCH_2$*Ph*), 130.4 ($OCH_2$*Ph*), 135.8 ($OCH_2$*Ph*), 137.0 ($OCH_2$*Ph*), 150.3 (C-2'), 157.7 (C-1), 162.6 ($CO_2H$). Anal. Calcd for $C_{23}H_{21}NO_4$: C 73.58, H 5.64, N 3.73. Found C 73.54, H 5.70, N 3.70.

### 4.2.17 Synthesis of (2Z,2Z')-((4R,5S)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene) bis(3-(4-(benzyloxy)phenyl)-2-(benzyloxyimino) propanoate) (40)

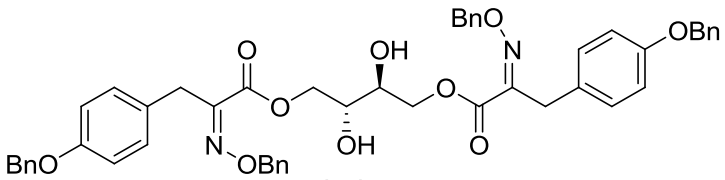



**(40)**

To a solution of mixture of oxime **39** (1.0 g, 2.66 mmol) and erythritol **35** (0.2 g, 1.21 mmol) in $CH_2Cl_2$ (20 mL) at 0 $^{o}$C was added dicyclohexylcarbodiimide (0.6 g, 2.91

mmol), followed by the addition of 4-(Dimethyamino)pyridine (0.032 g, 0.27 mmol) and the reaction mixture was aged for 1.5 h at the same temperature, cold water (20 mL) and $Et_2O$ (50 mL) were added and the organic layer was separated, cooled on ice bath and the solid was filtered. The organic layer was dried over anhydrous $Na_2SO_4$, filtered and evaporated under vacuum. Column chromatography over silica gel of the greenish oily material eluting with hexane:ethyl acetate (85:15) and then changing to (8:2) yielded the desired **40** (0.74 g, 70%) as a light green gum. IR (neat) 3031, 2930, 1723, 1609, 1509, 1453, 1372, 1241, 1195, 1123, 736, 697 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz) δ: 1.34 (3H, s, C($CH_3$)$_2$), 1.38 (3H, s, C($CH_3$)$_2$), 3.83 (4H, s, H-3', H-3''), 4.28 (2H, s, H-2, H-3), 4.37 (4H, m, H-1, H-4), 4.98 (4H, s, O$CH_2$Ph), 5.29 (4H, s, O$CH_2$Ph), 6.81 (4H, d, *J* = 8.5 Hz, H-6', H-8', H-6'', H-8''), 7.13 (4H, d, *J* = 8.5 Hz, H-5', H-9', H-5'', H-9''), 7.40-7.32 (20H, m, OCH$_2$*Ph*). $^{13}C$ NMR (125.7 MHz, $CDCl_3$) δ: 25.3 C($CH_3$)$_2$), 27.6 C($CH_3$)$_2$), 30.5 (C-3', C-3''), 69.4 (C-1, C-4), 69.9 (O$CH_2$Ph), 74.5 (C-2/C-3), 74.8 (C-2/C-3), 77.8 (O$CH_2$Ph), 109.5 (*C*(CH$_3$)$_2$), 114.7 (C-6', C-6'' C-8', C-8''), 127.4 (C-5', C-5'' C-9', C-9''), 128.0 (OCH$_2$*Ph*), 127.9 (OCH$_2$*Ph*), 128.2 (OCH$_2$*Ph*), 128.3 (OCH$_2$*Ph*), 128.4 (OCH$_2$*Ph*), 128.5 (OCH$_2$*Ph*), 130.2 (OCH$_2$*Ph*), 136.5 (OCH$_2$*Ph*), 137.0 (OCH$_2$*Ph*), 150.5 (C-2', C-2''), 157.5 (C-7', C-7''), 163.0 (C-1', C-1''). Anal. Calcd for $C_{53}H_{52}N_2O_{10}$: C 72.59, H 5.98, N 3.19. Found C 72.55, H 6.04, N 3.15. $^1H$

### 4.2.18 Synthesis of (2Z,2Z')-((2R,3S)-2,3-dihydroxy-butane-1,4-diyl) bis(3-(4-(benzyloxy)phenyl)-2-(benzyloxyimino)propanoate) (41)

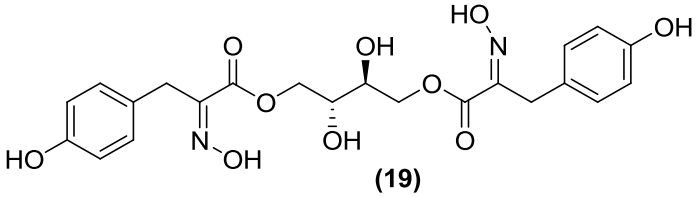



**(41)**

To a solution of compound **40** (0.3 g, 0.34 mmol) in a mixture of THF and $H_2O$ (2:1, 6 mL) at 0 $^oC$ was added trifluoroacetic acid (1.5 mL) and the reaction mixture was stirred at room temperature for 72 h, ethyl acetate (20 mL) was added and the organic layer was separated, washed with sat. $NaHCO_3$ (15 mL), brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered and evaporated. The colorless thick oil was resolved over silica column, eluting with hexane:ethyl acetate (6:4) and then changing to (1:1) produced the desired **41** as a white amorphous solid (0.25 g, 88%). MP: 101-102 $^oC$. IR (neat) 3370, 3040, 1720, 1610, 1502, 1460, 1375, 1230, 736, 690 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$) δ: 2.65 (br. s, 2H, OH), 3.78 (m, 2H, H-2, H-3), 3.86 (s, 4H, H-3', H-3''), 4.38-4.34 (m, 4H, H-1, H-4), 5.00 (s, 4H, O*CH*$_2$Ph), 5.29 (s, 4H, O*CH*$_2$Ph), 6.84 (d, 4H, *J* = 8.5 Hz, H-6', H-8', H-6'', H-8''), 7.13 (d, 4H, *J* = 8.5 Hz, H-5', H-9', H-5'', H-9''), 7.40-7.33 (m, 20H, OCH$_2$*Ph*). $^{13}C$ NMR (125.7 MHz, $CDCl_3$) δ: 30.5 (C-3', C-3''), 66.8 (C-1, C-4), 70.0 (C-2, C-3), 70.1 (O*CH*$_2$Ph), 77.9 (O*CH*$_2$Ph), 114.9 (C-6', C-6'' C-8', C-8''), 127.4 (C-5', C-5'' C-9', C-9''), 127.9 (OCH$_2$*Ph*), 128.3 (OCH$_2$*Ph*), 128.4 (OCH$_2$*Ph*), 128.5 (OCH$_2$*Ph*), 128.6 (OCH$_2$*Ph*), 130.1 (OCH$_2$*Ph*), 136.3 (OCH$_2$*Ph*), 137.0 (OCH$_2$*Ph*), 150.8 (C-2', C-

2''), 157.6 (C-7', C-7''), 163.5 (C-1', C-1''). Anal. Calcd for $C_{50}H_{48}N_2O_{10}$: C 71.76, H 5.78, N 3.35. Found C 71.70, H 5.82, N 3.30.

### 4.2.19 Synthesis of Aspergillusol A (19)

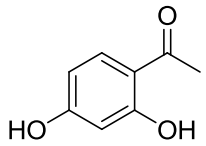



**(19)**

To a solution of **41** (0.15 g, 0.18 mmol) in a mixture of THF and ethanol (1:1, 10 mL) in a pressure vessel was added Pd-C (10% wet basis, 0.05 g) and the solution was subjected to hydrogenation in parr apparatus under the pressure of 50 psi for 3 h. The solution was filtered over a pad of celite, concentrated under vacuum and loaded over silica column eluting with $CH_2Cl_2$:MeOH (95:5) and then changing to (92:8) afforded the desired **19** as a light yellow amorphous solid (0.051 g, 60%). All the spectral data of **19** coincided with those of literature reported values.[65] NMR (500 MHz, DMSO-*d*6) δ: 3.65 ((m, 2H, H-2, H-3), 3.70 (s, 4H, H-3', H-3''), 4.10 (dd, 2H, *J* = 5.3, 11.1 Hz, H-1, H-4), 4.29 (br d, 2H, *J* = 10.8 Hz, H-1, H-4), 5.14 (br d, 2H, *J* = 5.2 Hz, 2-OH, 3-OH), 6.62 (4H, d, *J* = 8.5 Hz, H-6', H-8', H-6'', H-8''), 7.00 (4H, d, *J* = 8.5 Hz, H-5', H-9', H-5'', H-9''), 9.21 (s, 2H, Ar- OH), 12.38 (s, 2H, N-OH). $^{13}$C NMR (125.7 MHz, DMSO-*d*6) δ: 29.6 (C-3', C-3''), 67.1 (C-1, C-4), 69.4 (C-2/C-3), 115.5 (C-6', C-6'' C-8', C-8''), 126.8 (C-4′, C-4″), 130.1 (C-5', C-5'' C-9', C-9''), 150.5 (C-2′, C-2″), 156.1 (C-7′, C-7″), 164.2

(C-1′, C-1″). Anal. Calcd for $C_{22}H_{24}N_2O_{10}$: C 55.46, H 5.08, N 5.88. Found C 55.43, H 5.10, N 5.85.

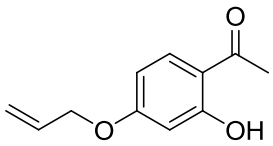
### 4.2.20 Synthesis of 1-(2,4-dihydroxyphenyl)ethanone (43)




**(43)**

A mixture of resorcinol **42** (17.6 g, 160 mmol) and $ZnCl_2$ (22.4 g, 164 mmol) in acetic acid (50 mL) was refluxed for 5 h. The reaction mixture was cooled to ~ 40$^{o}$C, poured on ice cold water (500 mL) and solid was filtered. Recrystallization from water gave **43** as reddish needles (16.5 g, 67%). $^{1}$H NMR (100 MHz, $CDCl_3$:$CD_3OD$): $\delta$ 2.51 (s, 3H), 3.10 (br s, 2H), 6.36 (s, 1H), 6.38 (d, 1H, $J$ = 8.8), 7.58 (d, 1H, $J$ = 8.8). $^{13}$C NMR (400 MHz, $CDCl_3$:$CD_3OD$): δ 26.00, 102.96, 108.29, 113.39, 132.98, 164.61(2C), 202.72.

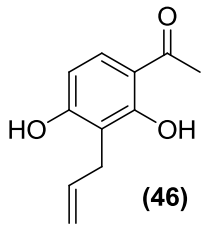
### 4.2.21 Synthesis of 1-(4-(allyloxy)-2-hydroxyphenyl)ethanone (45)




**(45)**

To a solution of **43** (10.6 g, 70 mmol) in acetone (100 mL) was added $K_2CO_3$ (20 g, 146 mmol) and the reaction was stirred for 10 min at room temperature, followed by the addition of allyl bromide (6.6 mL, 76.6 mmol) and the reaction mixture was stirred for 7 h at 40 $^oC$. The solvent was evaporated under vacuum, diluted with ether (150 mL) and washed with 2N NaOH (50 mL x 2). The white solid formed was collected through filtration and added to combined aqueous layers and acidified to pH ~ 4 with 20% HCl while cooling on ice-bath. The aqueous layer was then extracted with EtOAc (100 mL x 2) and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield **45** as a thick brown liquid (12.5 g, 93%). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 2.60 (s, 3H), 4.57 (d, 2H, $J$ = 4.9), 5.33 (d, 2H, $J$ = 8.55), 5.44 (d, 1H, $J$ = 17.1), 6.03 (m, 1H), 6.42 (s, 1H), 6.45 (m, 1H), 7.64 (d, 1H, $J$ = 5.3), 12.72 (s, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 26.17, 68.92, 101.63, 107.99, 113.96, 118.35, 132.14, 132.27, 165.11 (2CH), 202.55.

### 4.2.22 Synthesis of 1-(3-allyl-2,4-dihydroxyphenyl)ethanone (46)

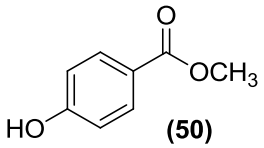



**(46)**

To a solution of **45** (5 g, 26 mmol) in *N,N'*dimethylaniline (7 mL) was bubbled $N_2$ for 5 min and the mixture was refluxed for 2 h. The reaction was cooled to room temperature, EtOAc (50 mL) was added and washed with 10% HCl (100 mL x 2). The

combined organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under vacuum to give a dark brown oily residue which was purified by silica gel column, eluting with EtOAc:hexane (1:9) to yield **46** as a pale yellow solid (2.7 g, 54%); mp: 110-115 $^{o}$C. IR (Neat) $\nu_{max}$ 3120, 2040, 1613, 1491, 1423, 1369, 1313, 1264, 1106, 1033, 914 cm$^{-1}$. $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.60 (s, 3H), 3.53 (d, 2H, $J$ = 6.1), 5.19 (t, 2H), 5.90 (s, 1H), 6.03 (m, 1H), 6.45 (d, 1H, $J$ = 8.85), 7.61 (d, 1H, $J$ = 8.5). $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 26.17, 26.64, 107.63, 112.57, 113.92, 116.06, 130.69, 135.48, 161.21, 162.75, 202.95.

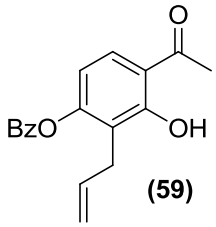
### 4.2.23 Synthesis of methyl 4-hydroxybenzoate (50)




**(50)**

To a solution of 4-hydroxy benzoic acid (2 g, 14.4 mmol) in $CH_3OH$ (50 mL) was added conc. $H_2SO_4$ (2 mL) and the reaction mixture was refluxed overnight. The excess methanol was evaporated off and the reaction mixture was poured onto ice cold water. Methyl-4-hydroxy benzoate was isolated as a white powder (1.1 g, 50%). IR (KBr) nmax: 3311, 1682, 1607, 1588, 1514, 1434, 1314, 1279, 1164, 849, 771 cm$^{-1}$. $^{1}$H NMR (500 MHz): $\delta$ 3.822 (s, 3H), 6.908-6.926 (d, 2H), 7.877-7.894 (d, 2H), $^{13}$C NMR (125.7 MHz, $CDCl_3$): $\delta$ 52.09, 115.34, 121.97, 131.94, 160.65, 167.57.

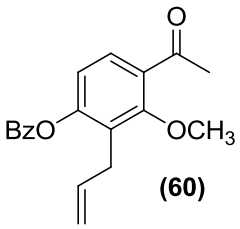
### 4.2.24 Synthesis of 4-acetyl-2-allyl-3-hydroxyphenyl benzoate (59)




**(59)**

To a solution of **46** (2 g, 10.40 mmol) in dichloromethane (30 mL) at 0 $^{o}$C was added $Et_3N$ (2.1 20.8 mmol), followed by the dropwise addition of benzoyl chloride (2.1 g, 13.52 mmol) and the stirring was continued at 0$^{o}$C for 30 minutes and then for 2 h at room temperature. Water (20 mL) was added and the organic layer was separated and washed with brine, dried over $Na_2SO_4$ and concentrated under vacuum to give **59** as an orange thick liquid (3.02 g, 98%). IR (Neat) $\nu_{max}$ 3075, 3005, 2922, 1725, 1615, 1500, 1411, 1365, 1230, 11180, 1069, 1020, 988, 912 cm$^{-1}$. $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.65 (s, 3H), 3.43 (d, 2H, *J* = 6.1), 4.98 (m, 2H), 5.90 (m, 1H), 6.80 (d, 1H, *J* = 8.55), 7.53 (t, 2H, *J* = 7.79), 7.67 (t, 1H, *J* = 7.60), 7.71 (d, 1H, *J* = 8.85), (d, 1H, *J* = 8.85), 8.20, (dd, 2H, *J* = 8.2, 1.2). $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 26.74, 27.72, 113.49, 115.51, 117.43, 121.45, 128.71 (2CH), 128.93, 129.38, 130.22 (2CH), 133.93, 134.73, 155.03, 162.25, 164.33, 203.90.

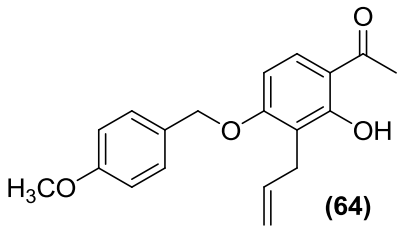
### 4.2.25 Synthesis of 4-acetyl-2-allyl-3-methoxyphenyl benzoate (60)




**(60)**

To a solution of **59** (3.0 g, 9.7 mmol) in DMF (30 mL) at 0 $^{o}$C was added $K_2CO_3$ (2.67 g, 19.3 mmol) and the mixture was stirred for 15 min at room temperature and then cooled to 0 $^{o}$C. Iodomethane (2.1 g, 14.55 mmol) was added drop wise to the mixture at 0 C and the reaction was stirred overnight at room temperature. The reaction was diluted with $H_2O$ (20 mL) and EtOAc (50 mL) and washed with 10% HCl (20 mL), brine (15 mL x 2), dried over anhydrous sodium sulfate and evaporated under vacuum to yield **60** as a yellow solid (2.89 g, 96%). mp 54-55 $^{o}$C. IR (Neat) $\nu_{max}$ 3740, 3073, 2938, 1736, 1679, 1445, 1404, 1360, 1236, 1167, 1067, 1026, 917 $cm^{-1}$. $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.65 (s, 3H), 3.46 (d, 2H, *J* = 7.00), 3.80 (s, 3H), 5.00 (m, 2H), 3.92 (m, 1H), 7.08 (d, 1H, *J* = 8.55), 7.53 (t, 2H), 7.62 (t, 1H), 7.66 (t, 1H), 8.18 (d, 2H, *J* = 8.55). $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 28.65, 30.18, 63.46, 114.79, 115.85, 118.74, 126.89, 128.57 (2CH), 128.68, 129.83 (2CH), 130.18, 131.17, 133.86, 135.38, 153.10, 158.93, 164.45.

### 4.2.26 Synthesis of 1-(3-allyl-2-hydroxy-4-(4-methoxybenzyloxy)phenyl)ethanone (64)

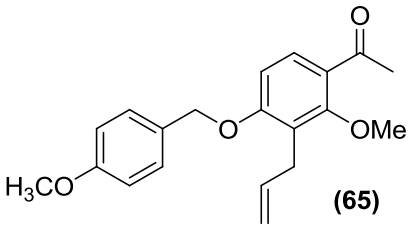



**(64)**

To a solution of **46** (2 g, 10.42 mmol) in acetone (20 mL) was added $K_2CO_3$ (2.87 g, 20.8 mmol) and after being stirred for 10 min at room temperature, 4-methoxybenzyl

chloride ( 1.74 g, 1.48 mL, 10.94 mmol) was added and the mixture was heated at 60$^{o}$C for 4 h. The solvent was evaporated under vacuum and the crude product was purified by silica column chromatography, eluting with EtOAc:hexane (1:20) and then changing to (2:10) yielded **64** as a white solid (3.1 g, 95%). IR (Neat) $\nu_{max}$ 2922, 2836, 1614, 1505, 1420, 1368, 1238, 1175, 1119, 1062, 908, 816, 726, 632 cm$^{-1}$. $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.53 (s, 3H), 3.55 (d, 2H, J = 6.1), 3.80 (s, 3H), 4.97 (m, 2H), 5.07 (s, 2H), 5.96 (m, 1H), 6.50 (d, 1H, *J* = 8.50), 6.90 (d, 2H, *J* = 8.55), 7.32 (d, 2H, *J* = 8.55), 7.58 (d, 1H, *J* = 9.75), 12.78 (s, 1H). $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 26.23, 26.80, 55.29, 70.03, 103.43, 114.04 (2CH), 114.41, 114.68, 115.93, 128.49, 128.76 (2CH). 130.12, 130.55, 135.89, 159.51, 161.99, 162.53.

### 4.2.27 1-(3-allyl-2-methoxy-4-(4-methoxybenzyloxy)phenyl)ethanone (65)

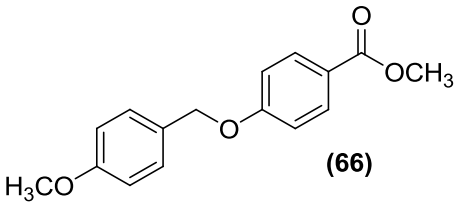



**(65)**

To a solution of **64** (1.3 g, 4.2 mmol) in DMF (15 mL) was added $K_2CO_3$ (1 g, 7.08 mmol) and the mixture was stirred for 15 min at room temperature and then cooled to 0 $^{o}$C. Iodomethane (8.4 mmol, 0.5 mL) was added dropwise to the reaction and the mixture was stirred overnight at room temperature. To the reaction was added $H_2O$ (20 mL), EtOAc (15 mL) and washed with 10% HCl, brine (10 mL x 2), dried over anhydrous

sodium sulfate and the solvent evaporated *in vacuo* to yield **65** as a yellow thick liquid (1.3 g, 95%). $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$ 2.27 (s, 3H), 3.48 (d, 2H, $J$ = 6.1), 3.76 (s, 3H), 3.82 (s, 3H), 5.00 (m, 4H), 5.97 (m, 1H), 6.76 (d, 1H, $J$ = 8.5), 6,91 (d, 2H, $J$ = 8.55), 7.33 (d, 2H, $J$ = 8.55), 7.60 (d, 1H, $J$ = 8.55). $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 28.07, 29.92, 55.21, 63.02, 70.03, 107.36, 113.91 (2CH), 114.92 (2CH), 122.56, 125.93, 128.45, 128.75 (2CH), 129.70, 136.44, 159.38, 160.96, 162.46, 199.00.

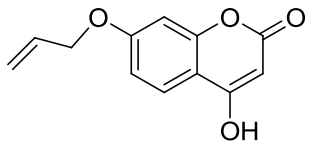
### 4.2.28 Synthesis of methyl 4-(4-methoxybenzyloxy)benzoate (66)




**(66)**

To a solution of **50** (2 g, 13.14 mmol) in DMF was added $K_2CO_3$ (3.63 g, 26.3 mmol) and after being stirred for 10 min at room temperature, 4-methoxybenzyl chloride (2.67 g, 17.1 mmol) was added and the stirring was continued at room temperature for 3 h. The reaction was diluted with EtOAc (30 mL) and washed with $H_2O$ (20 mL), 10% HCl (15 mL), brine (15 mL x 2), dried over anhydrous sodium sulfate and evaporated under vacuum to yield **66** as a white solid (3.50 g, 98%). $^{1}$H NMR (500 MHz, $CDCl_3$): $\delta$ 3.82 (s, 3H), 3.88 (s, 3H), 5.03 (s, 2H), 6.91 (m, 4H), 7.36 (d, 2H, $J$ = 8.55), 8.00 (d, 2H, $J$ = 9.75). $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 51.85, 55.31, 69.93, 114.11(2CH), 114.48 (2CH), 122.74, 128.28, 129.41(2CH), 131.59 (2CH), 159.65, 162.59, 166.86.

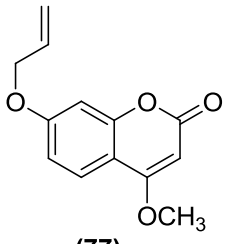
### 4.2.29 Synthesis of 7-(allyloxy)-4-hydroxy-2H-chromen-2-one (73)



**(73)**

A solution of **45** (35.8 g, 0.186 mol) in dry benzene (400 mL) was added with stirring to a suspension of NaH (10.4 g, 0.43 mol) in dry benzene (400 mL) over 30 min at reflux. After being stirred for 10 min, a solution of diethyl carbonate (46.4 g, 0.38 mmol) in dry PhH (400 mL) was added over 1 h, and the mixture was refluxed overnight. The reaction was cooled to room temperature and the mixture was poured onto ice-cold 2 N HCI (2 L), and the solid formed was filtered, and recrystallized from EtOH to give 30.5 g (75%) of **73**; mp: 235-236 $^{o}$C. $^{1}$H NMR (125.7 MHz, $CD_3OD$): $\delta$ 4.65 (d, 2H, $J$ = 4.8), 5.29 (d, 1H, $J$ = 10.4), 5.48 (t, 2H), 6.03 (m, 1H), 6.92 (s, 2H), 7.70 (d, 1H $J$ = 8). $^{13}$C NMR (400 MHz, $CD_3OD$): δ 69.13, 88.83, 101.60, 109.37, 112.73, 118.46, 124.75, 133.26, 155.62, 162.14, 162.82, 166.44.

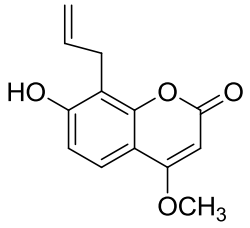
### 4.2.30 Synthesis of 7-(allyloxy)-4-methoxy-2H-chromen-2-one (77)



**(77)**

To a solution of **73** (5 g, 23 mmol) in acetone (50 mL) was added $K_2CO_3$ (3.8 g, 27.5 mmol) and the reaction was stirred at room temperature for 15 min. Dimethyl sulfate (3.5 g, 25.5 mmol) was added to the mixture and stirred at 50$^{o}$C for 2 h. The solid was filtered and the solvent was evaporated under vacuum to yield **77** as a white solid (4.25 g, 80%); mp: 70-73 $^{o}$C. IR (Neat) $\nu_{max}$ 3395, 3235, 3072, 2839, 2099, 1920, 1736, 1605, 1434, 1393, 1246, 1148, 1091, 1005, 968, 813, 572, 474 cm$^{-1}$. $^{1}$H NMR (400 MHz, $CD_3OD$): $\delta$ 3.92 (s, 3H), 4.55 (d, 2H, $J$ = 8.00), 5.30-5.27 (m, 1H), 5.41-5.36 (m, 1H), 5.51 (s, 1H), 6.02-5.96 (m, 1H), 6.81-6.75 (m, 2H), 7.65 (d, 1H, J= 8.8). $^{13}$C NMR (125.7 MHz, $CD_3OD$): δ 56.20, 69.21, 87.66, 101.35, 109.0, 112.68, 118.46, 124.04, 132.18, 155.02, 162.16, 163.37, 166.80.

### 4.2.31 Synthesis of 8-allyl-7-hydroxy-4-methoxy-2H-chromen-2-one (78)




**(78)**

A solution of **77** (3 g, 12.9 mmol) in decalin (5 mL) was refluxed under $N_2$ for 3 h, and the mixture was cooled to room temperature. The solid formed was filtered to get the title compound as a yellow solid (1.86 g, 62%); mp: 230-233 $^{o}$C. IR (Neat) $\nu_{max}$ 3086, 2193, 1686, 1603, 1570, 1508, 1437, 1385, 1311, 1231, 1108, 1050, 1011, 905, 803, 734 cm$^{-1}$.H NMR (400 MHz, $CDCl_3$:$CD_3OD$): $\delta$ 3.52 (d, 2H , $J$ = 7.6), 3.89 (s, 3H), 4.96 (m, 2H), 5.47 (s, 1H), 5.91 (m, 1H), 6.72 (d, 1H, $J$ = 8.8), 7.46 (d, 1H, $J$ = 8.8). $^{13}$C NMR

(125.7 MHz, $CDCl_3$:$CD_3OD$): δ 26.81, 56.08, 86.43, 108.01, 112.04, 113.65, 115.00, 121.46, 135.08, 152.66, 159.12, 164.68, 167.75.

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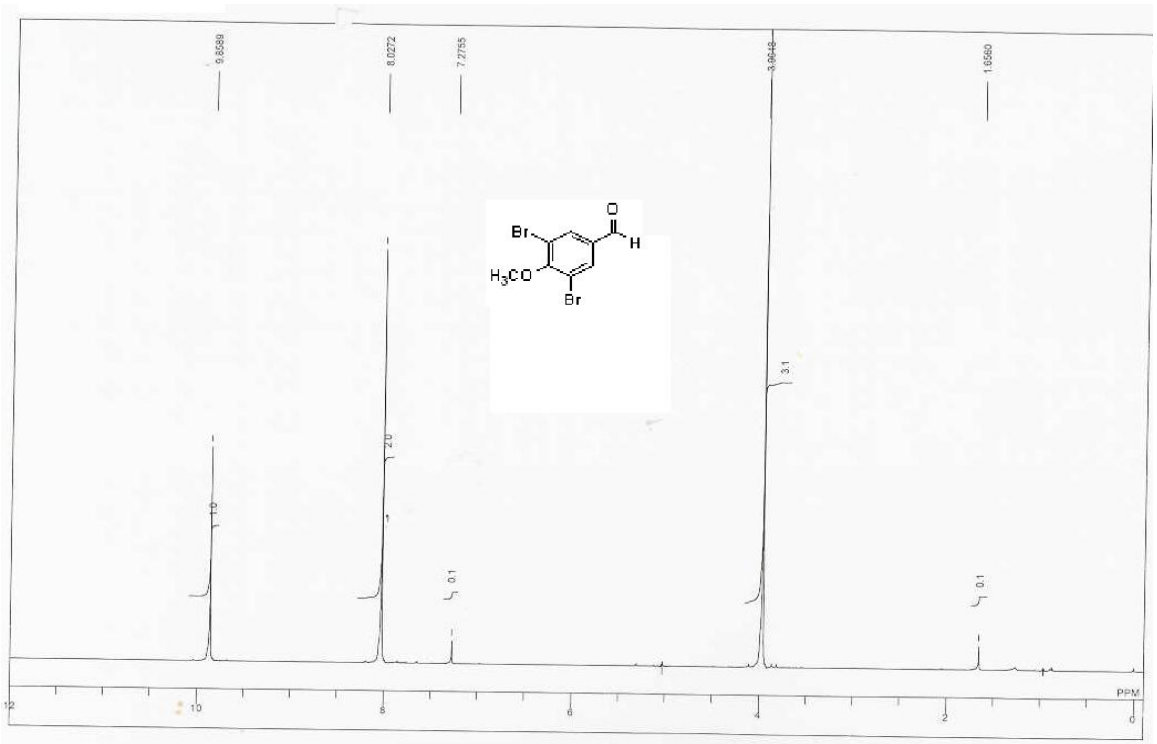
# APPENDIX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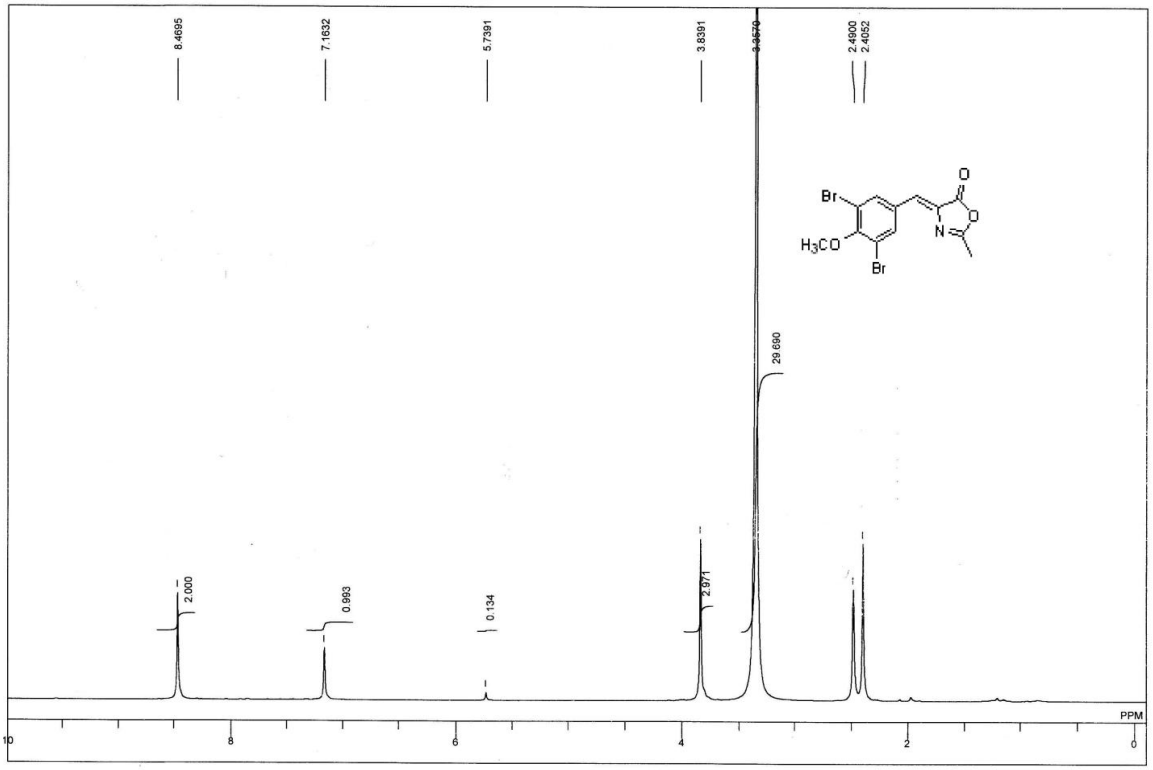
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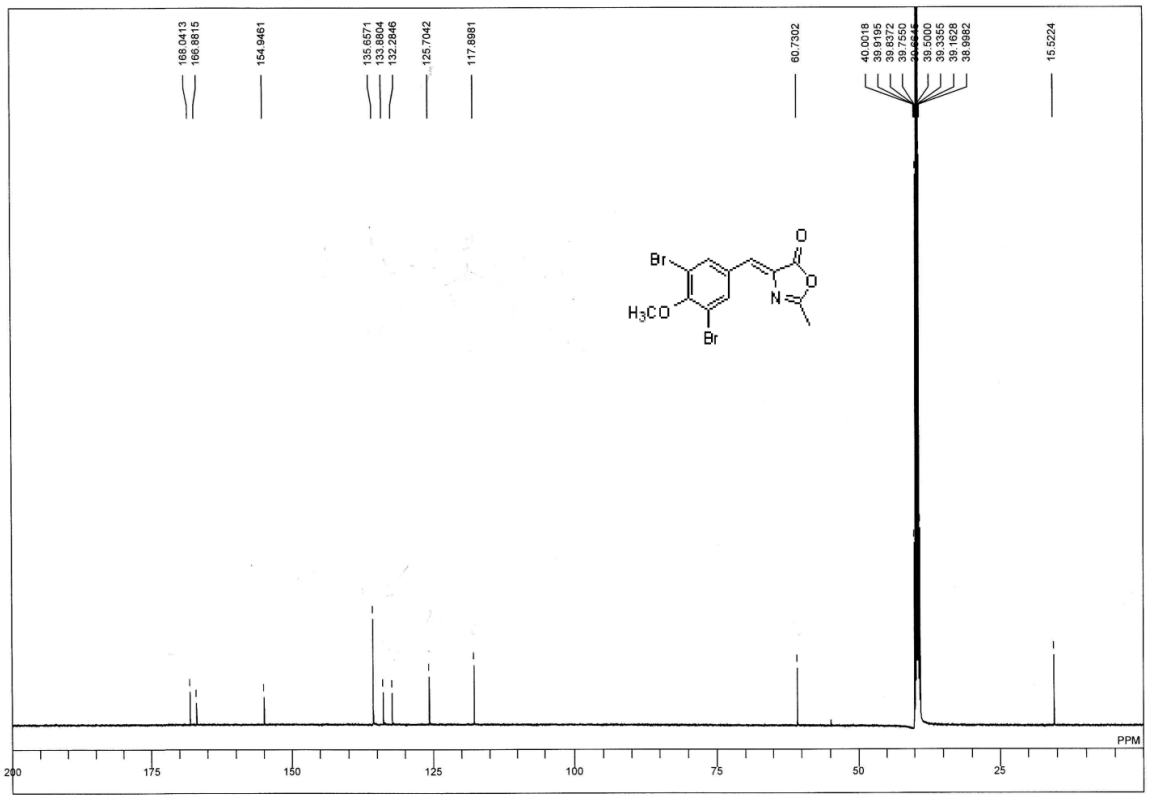
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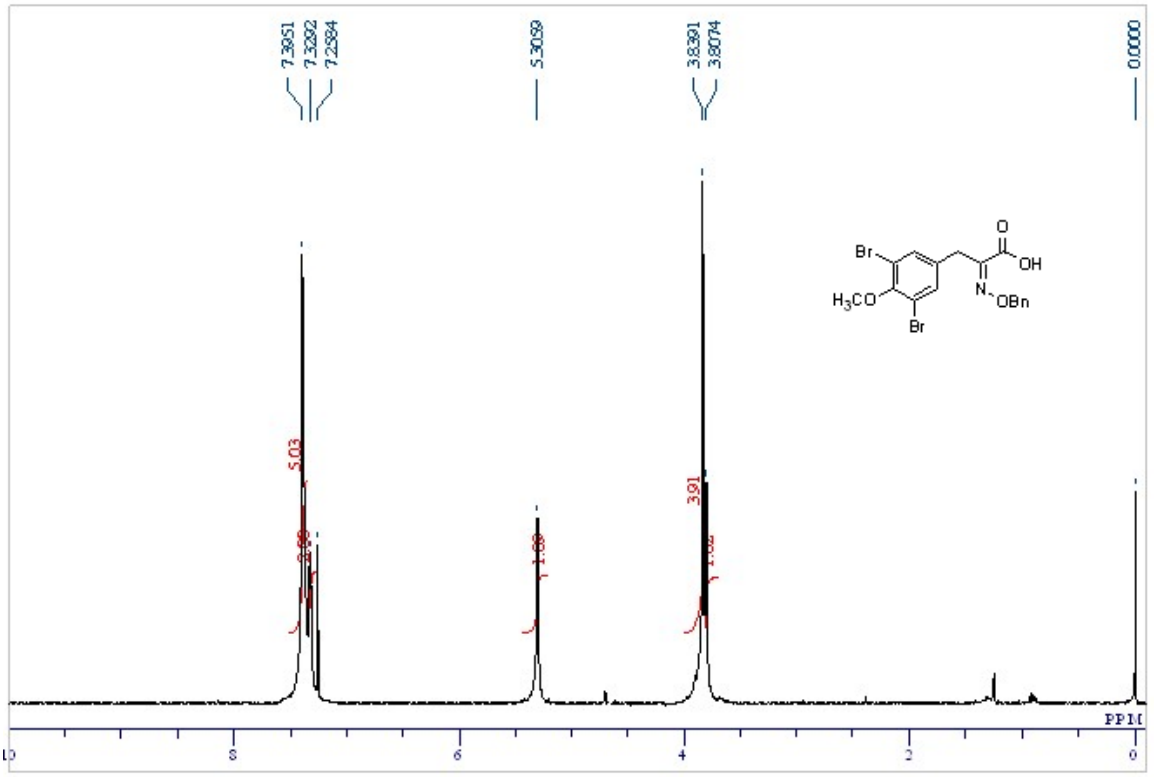
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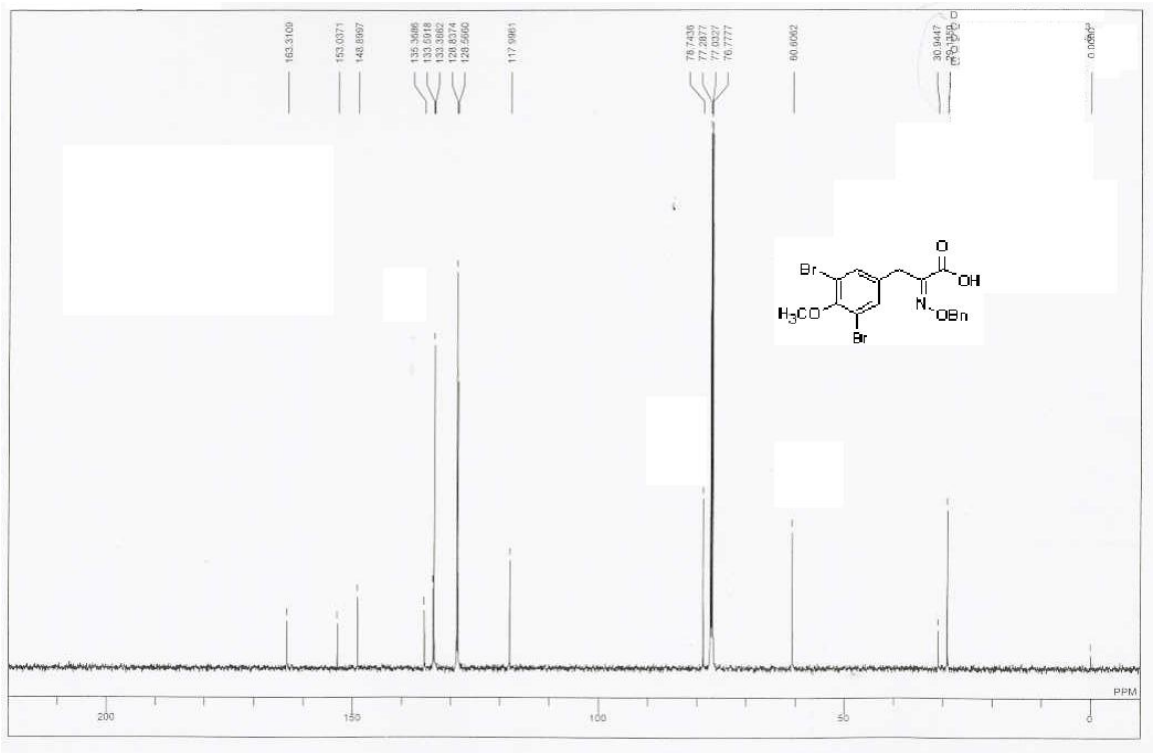
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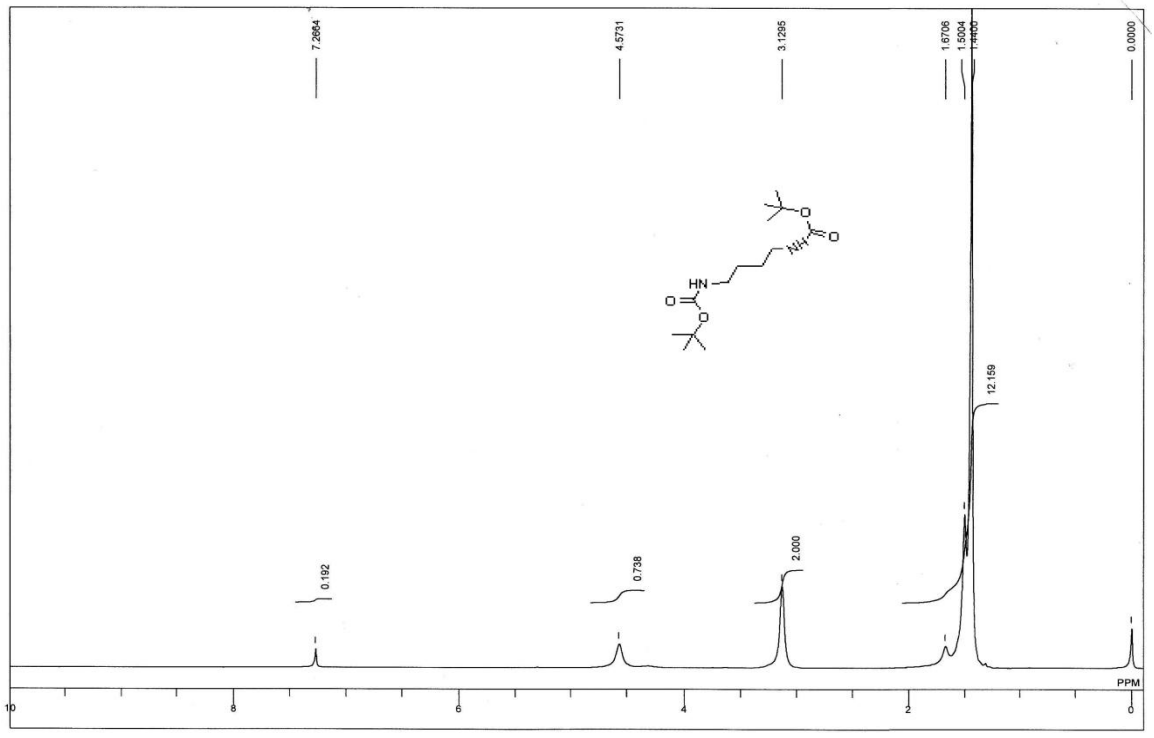
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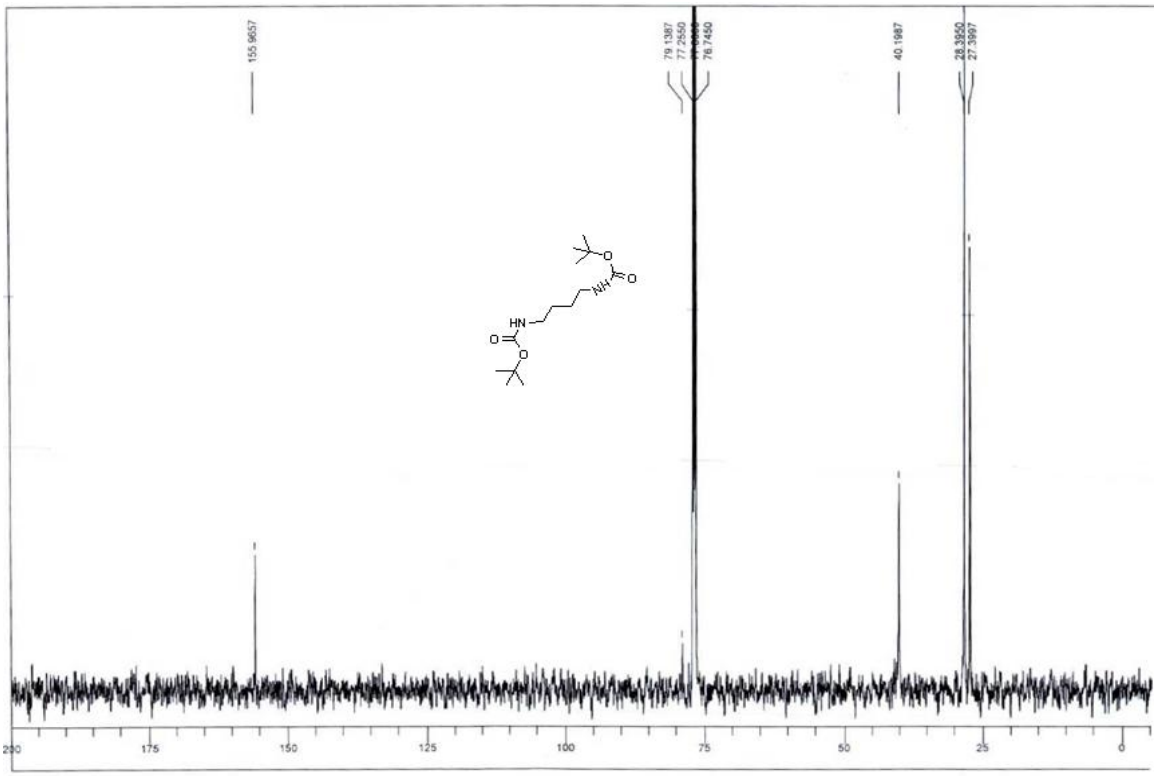
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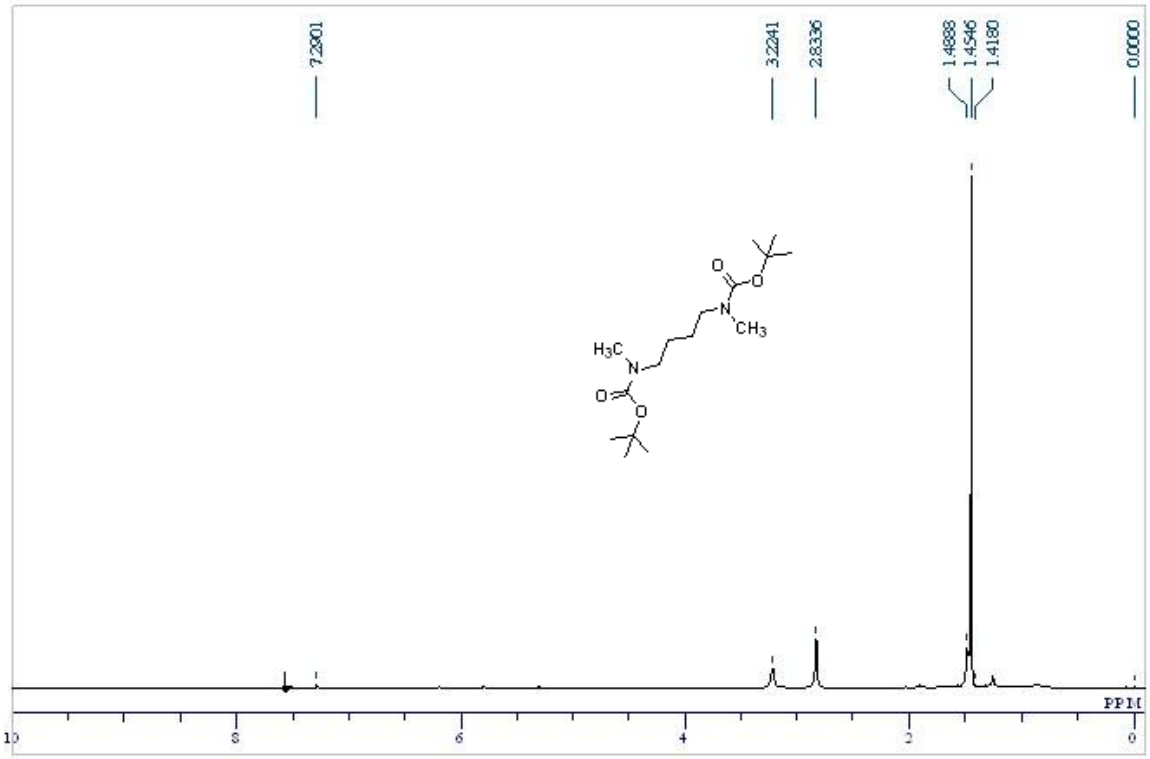
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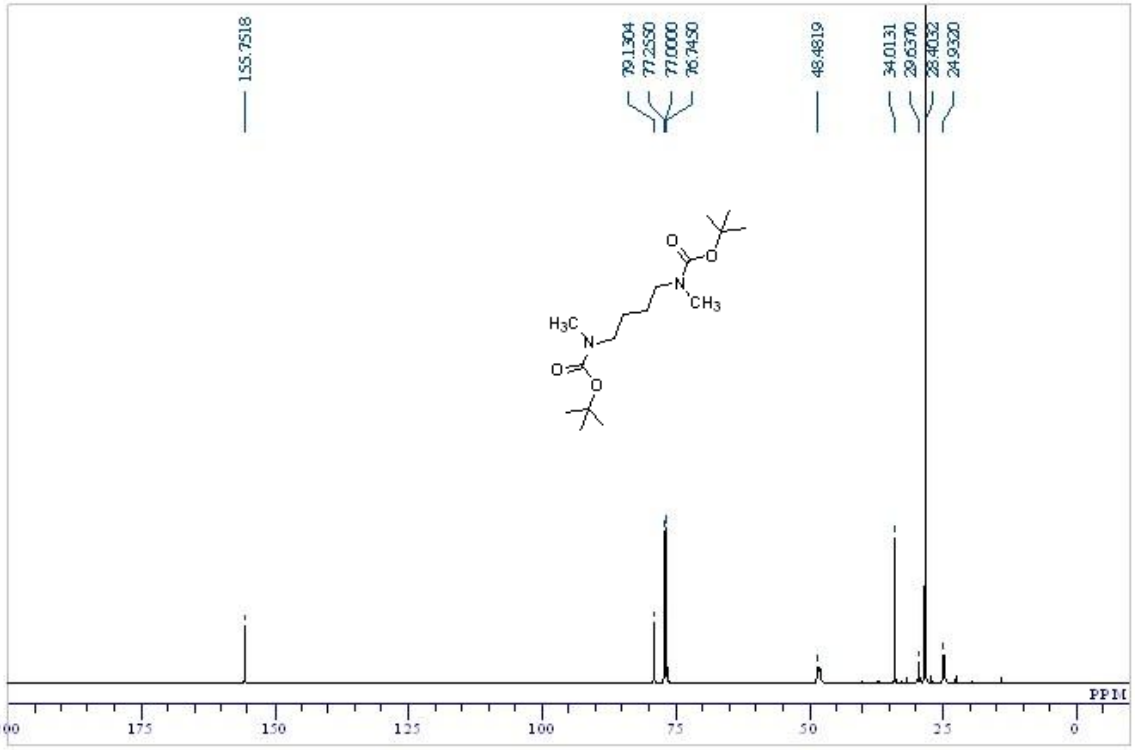
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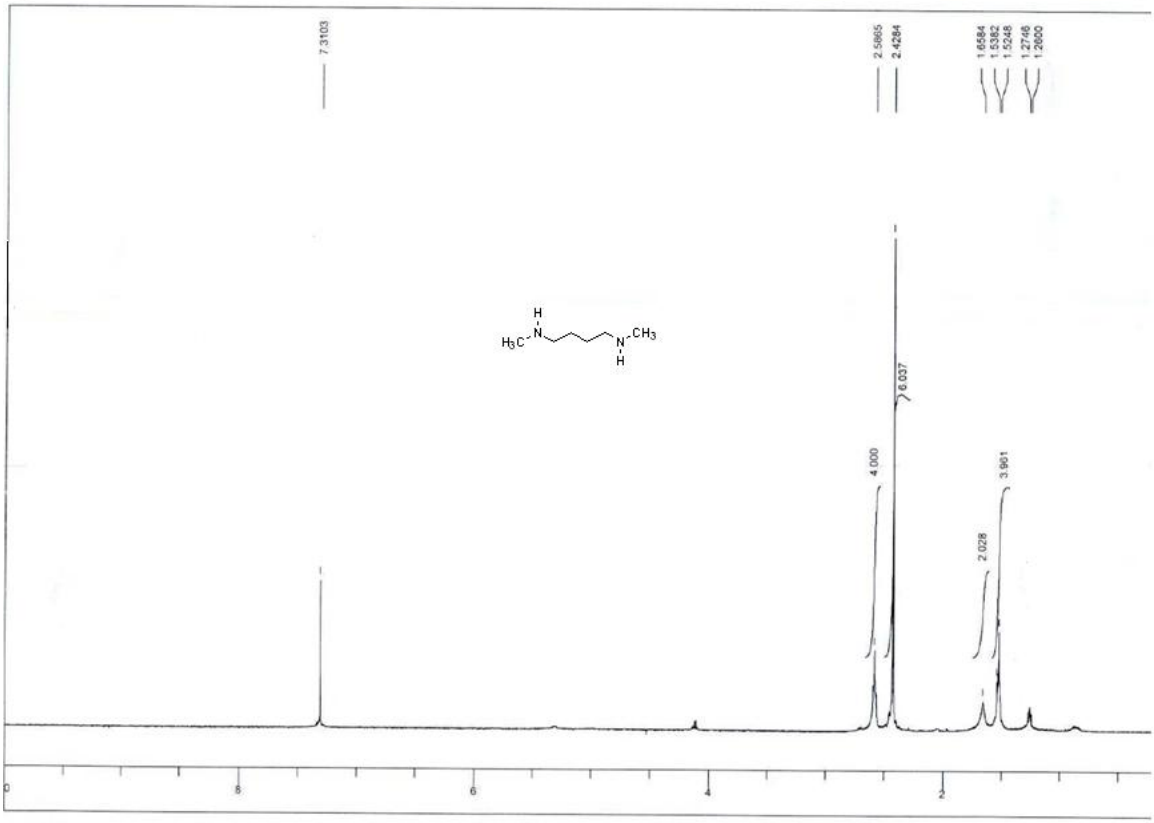
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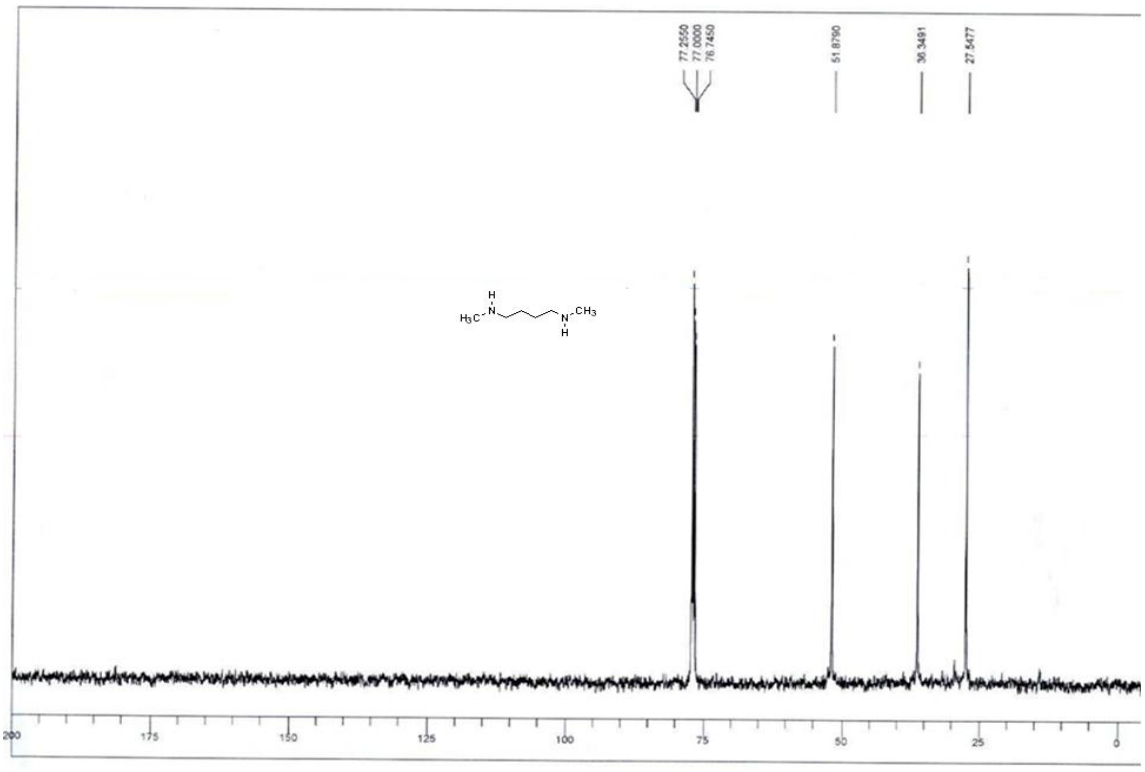
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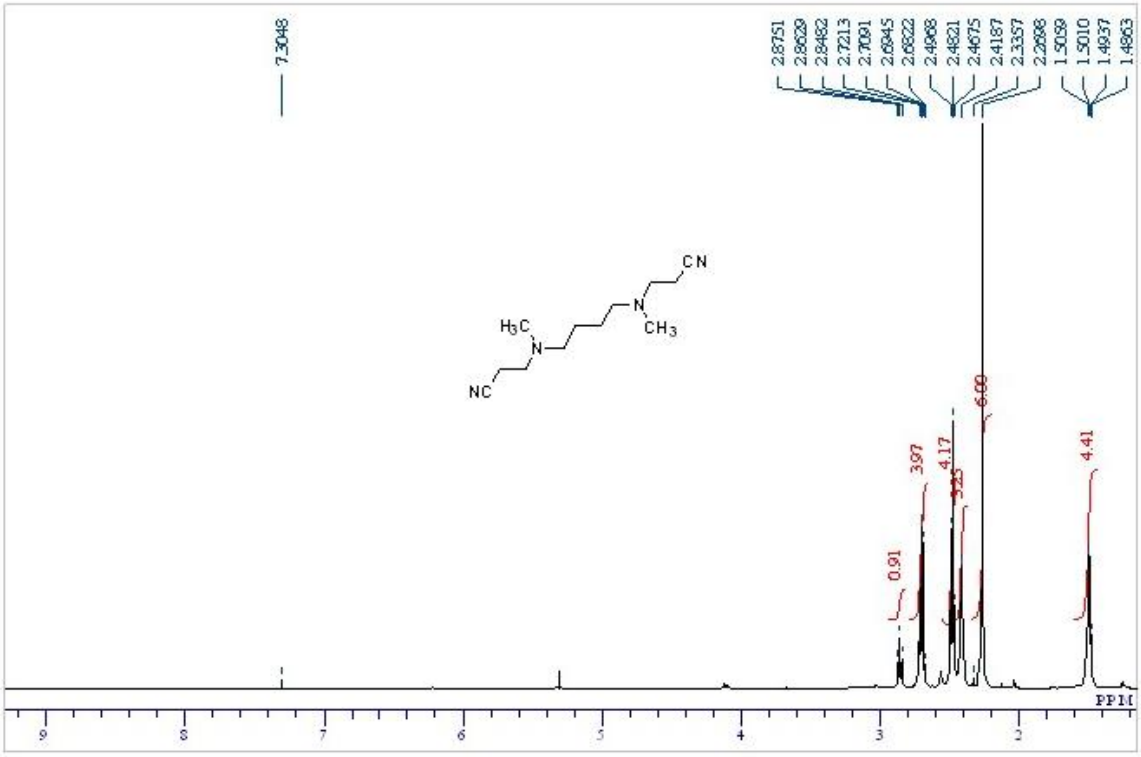
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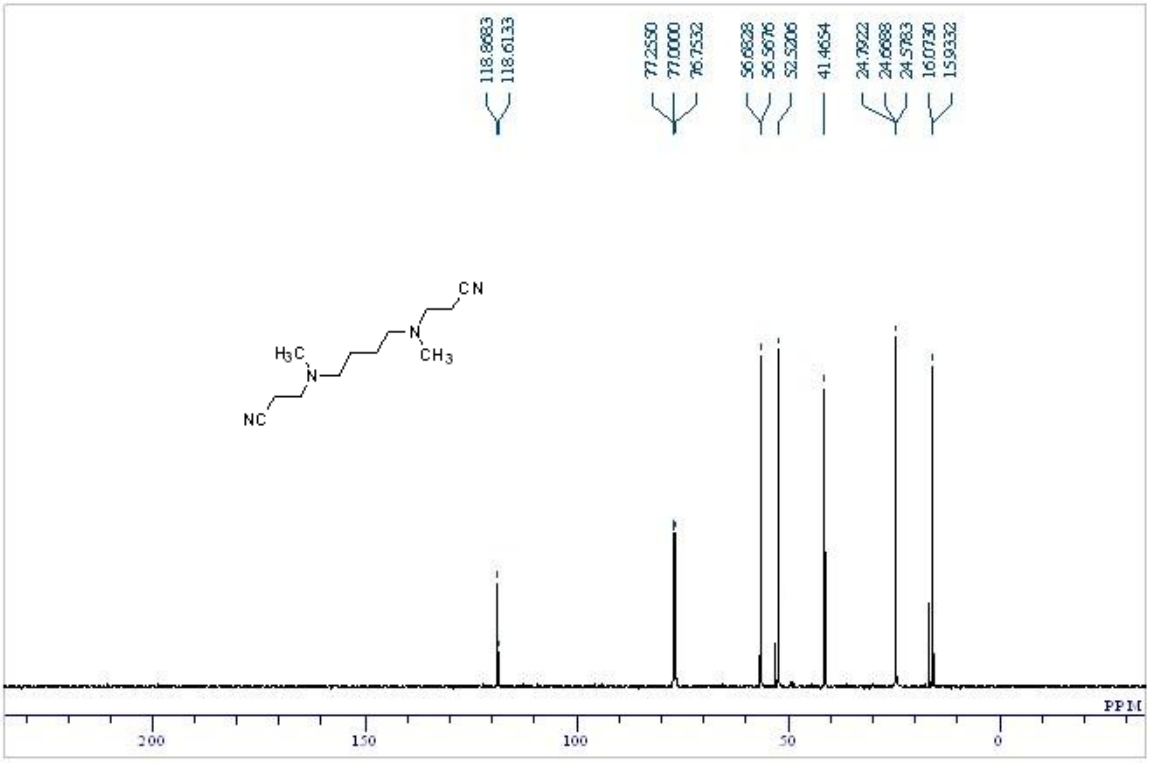
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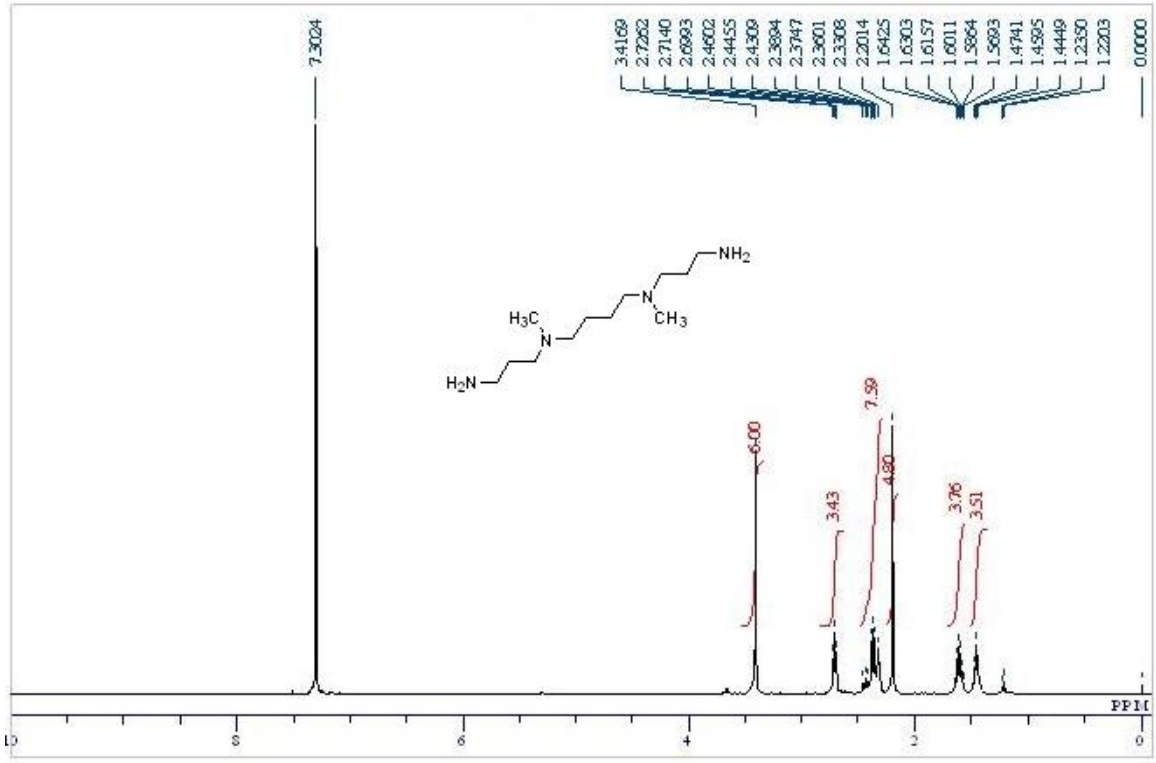
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N
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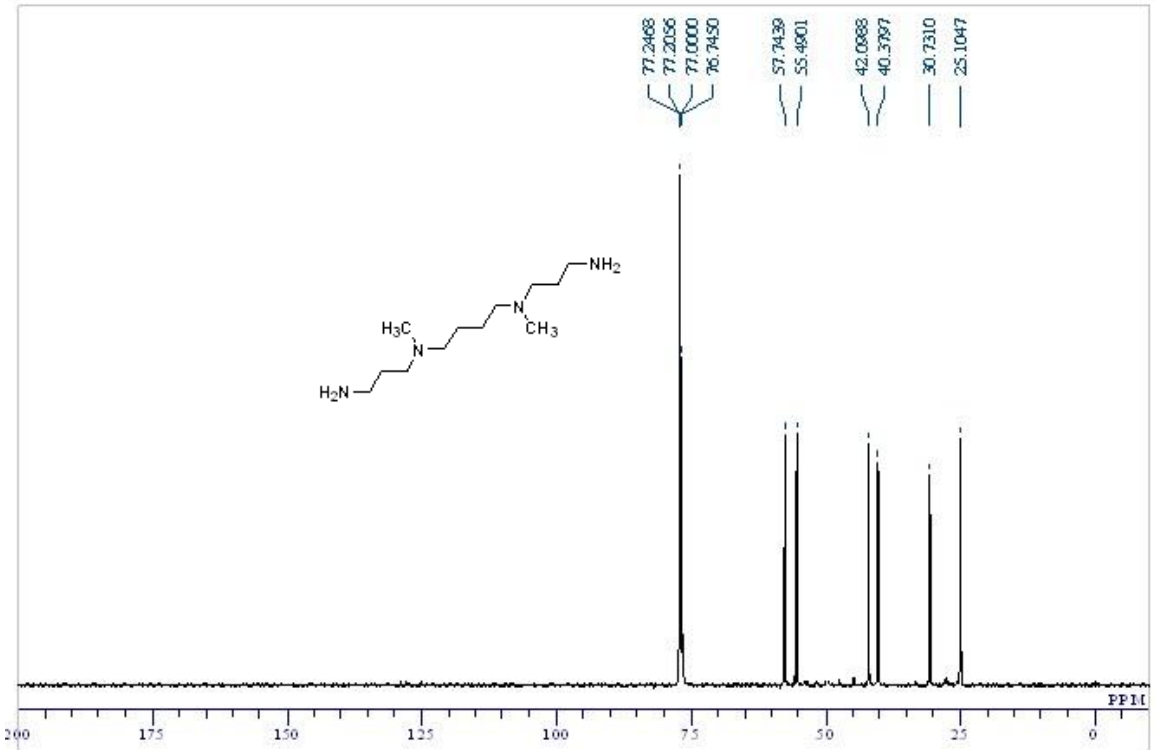
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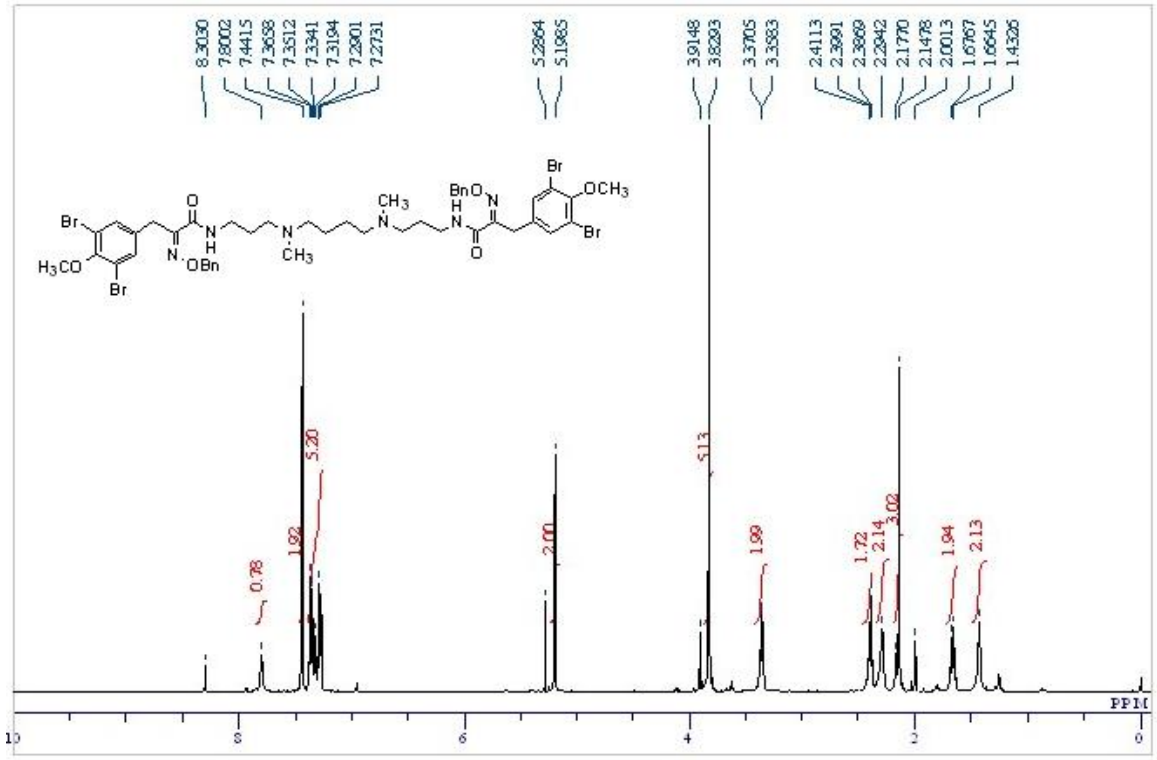
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2.1770
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1.6645
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0.78
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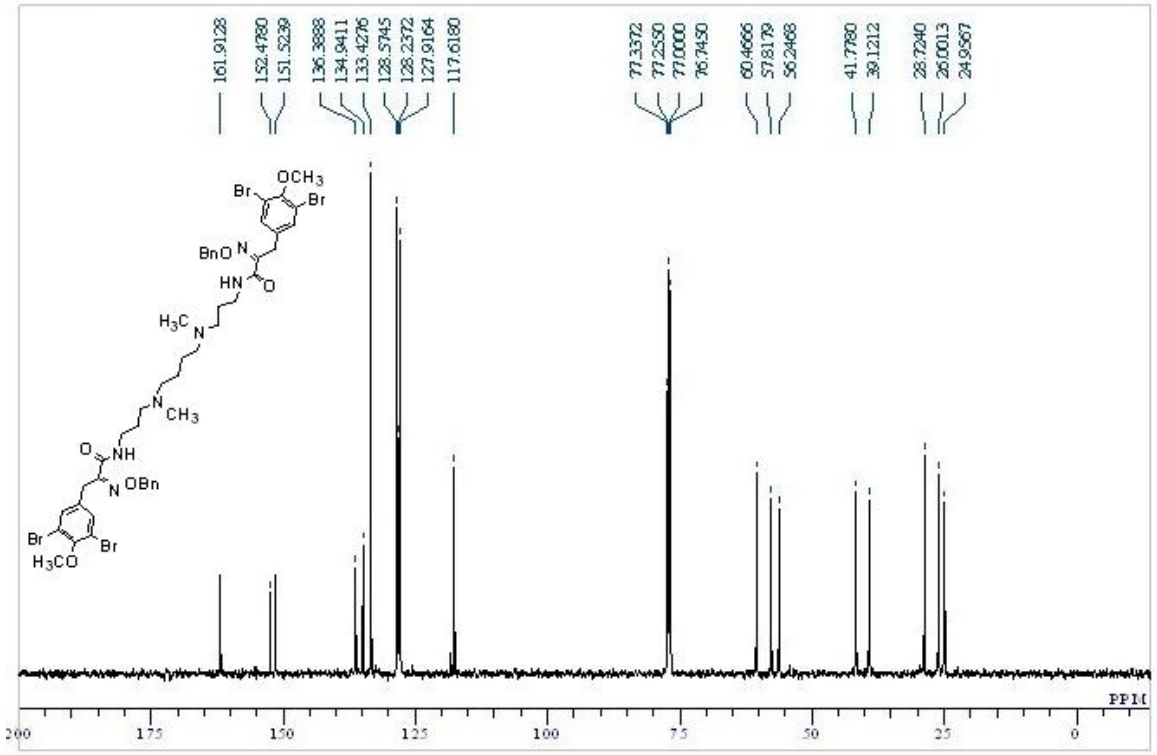
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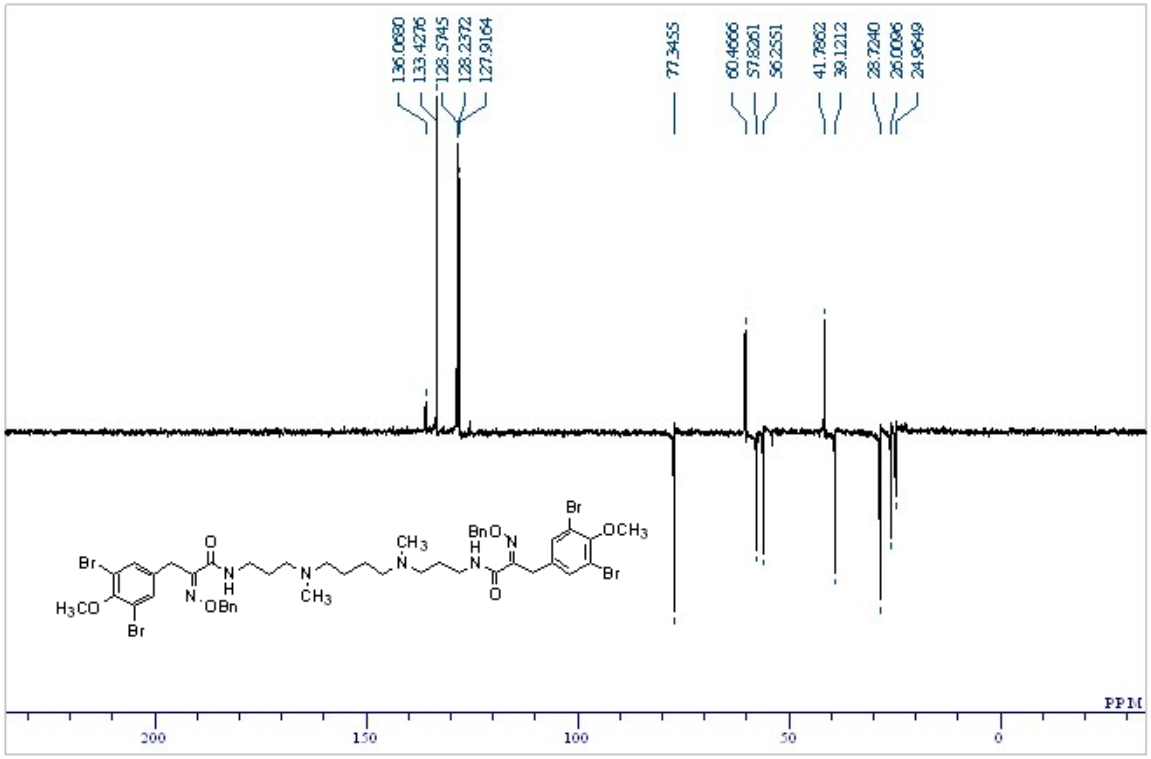
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BnO
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H
N
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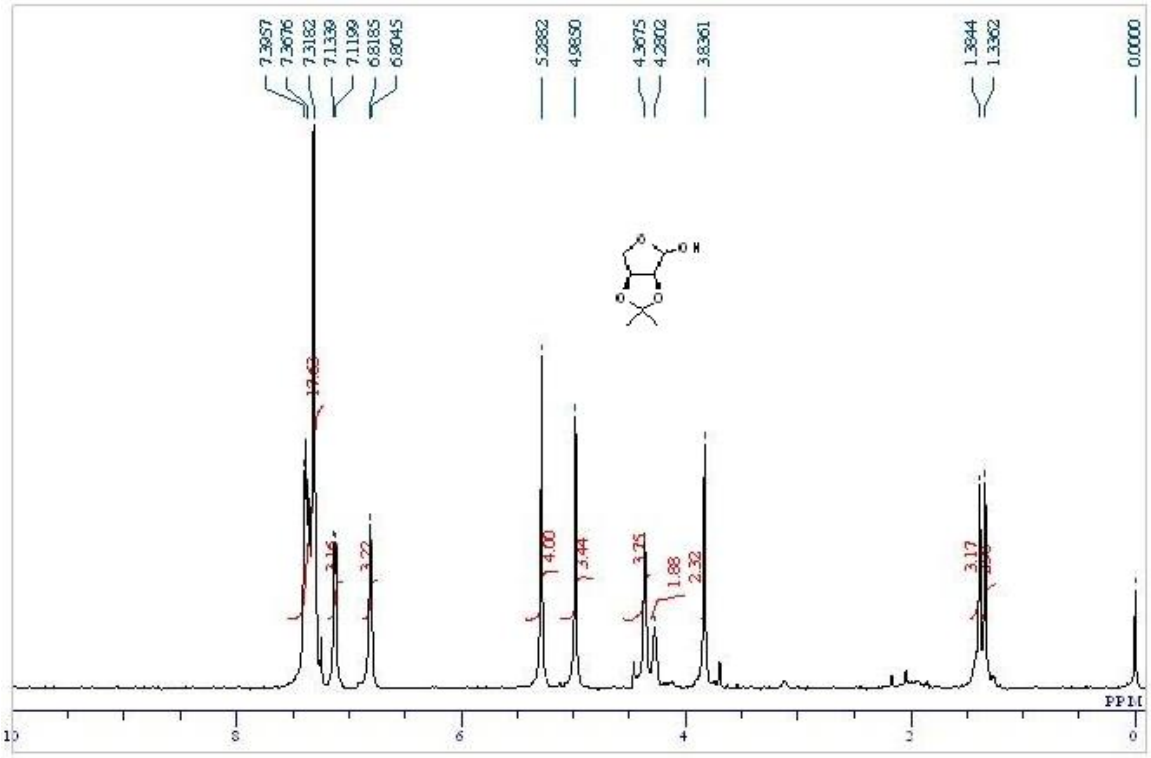
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4.00
3.44
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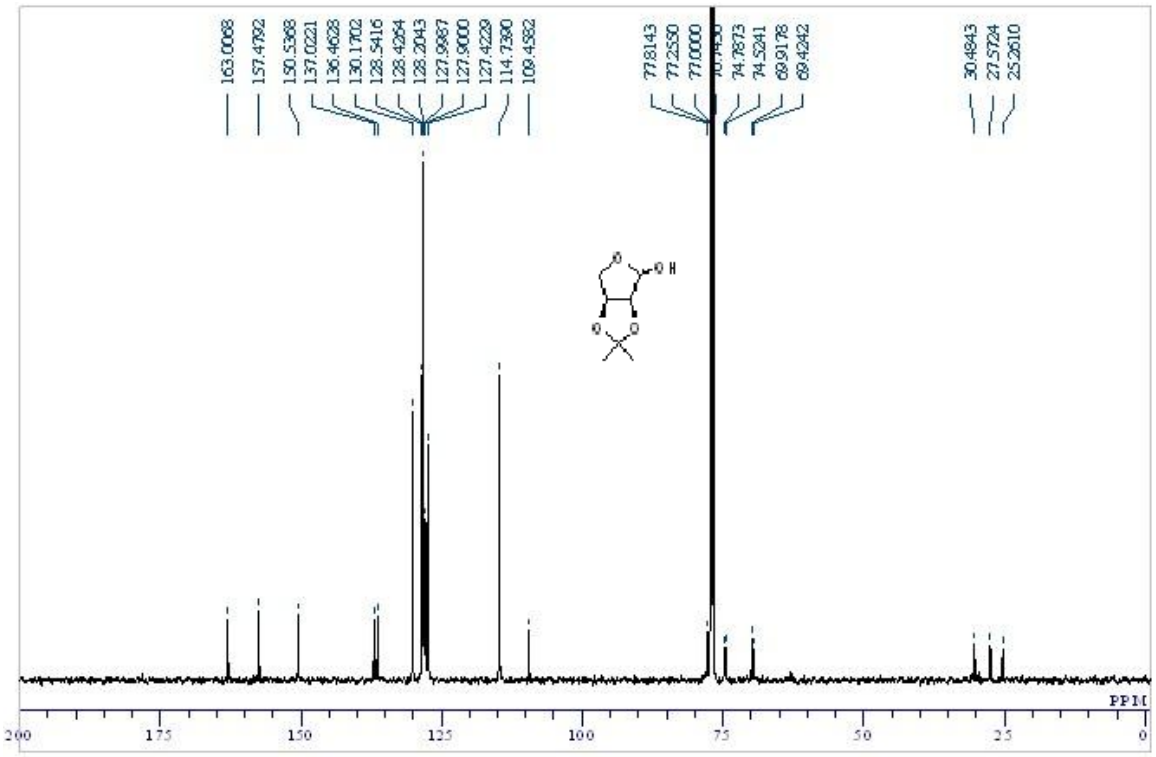
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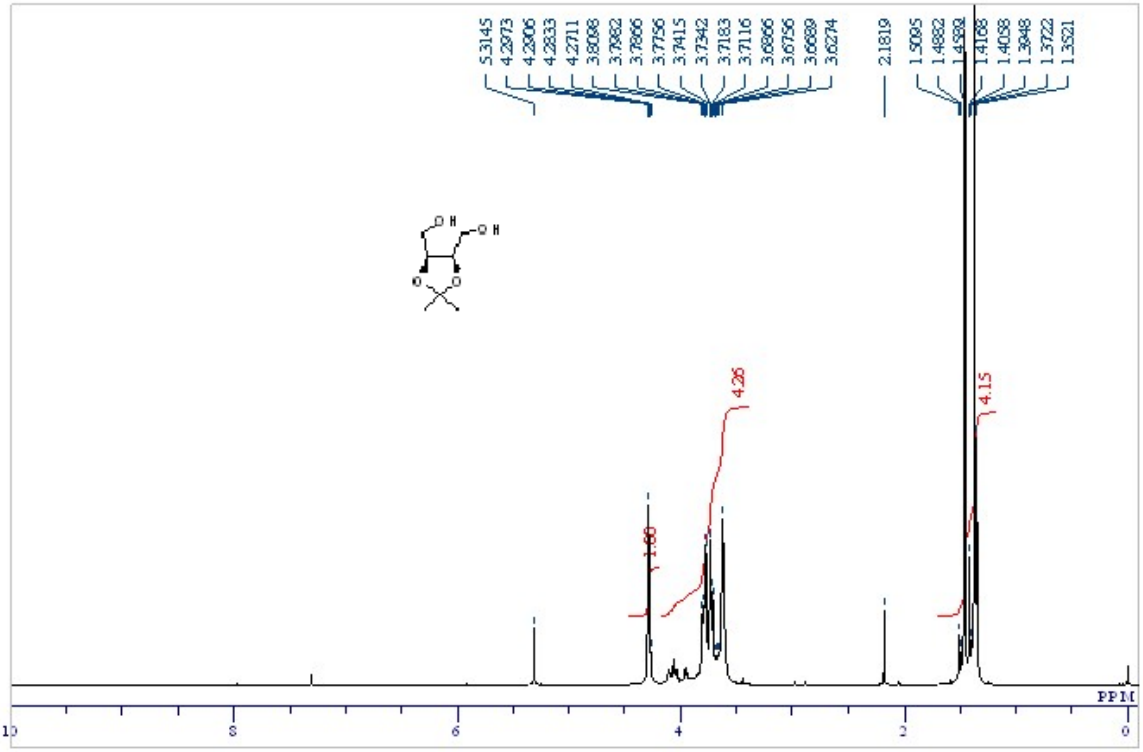
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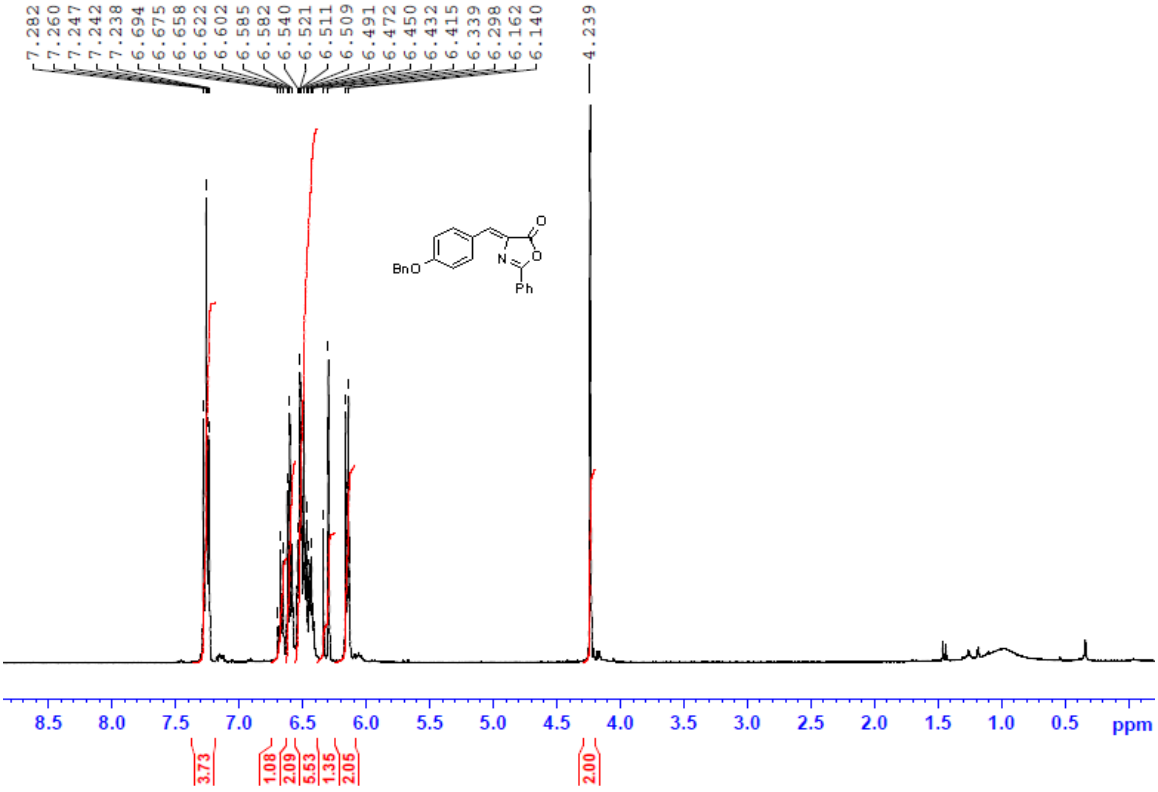
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6.540
6.521
6.511
6.509
6.491
6.472
6.450
6.432
6.415
6.339
6.298
6.162
6.140
4.239
BnO
O
N
O
Ph
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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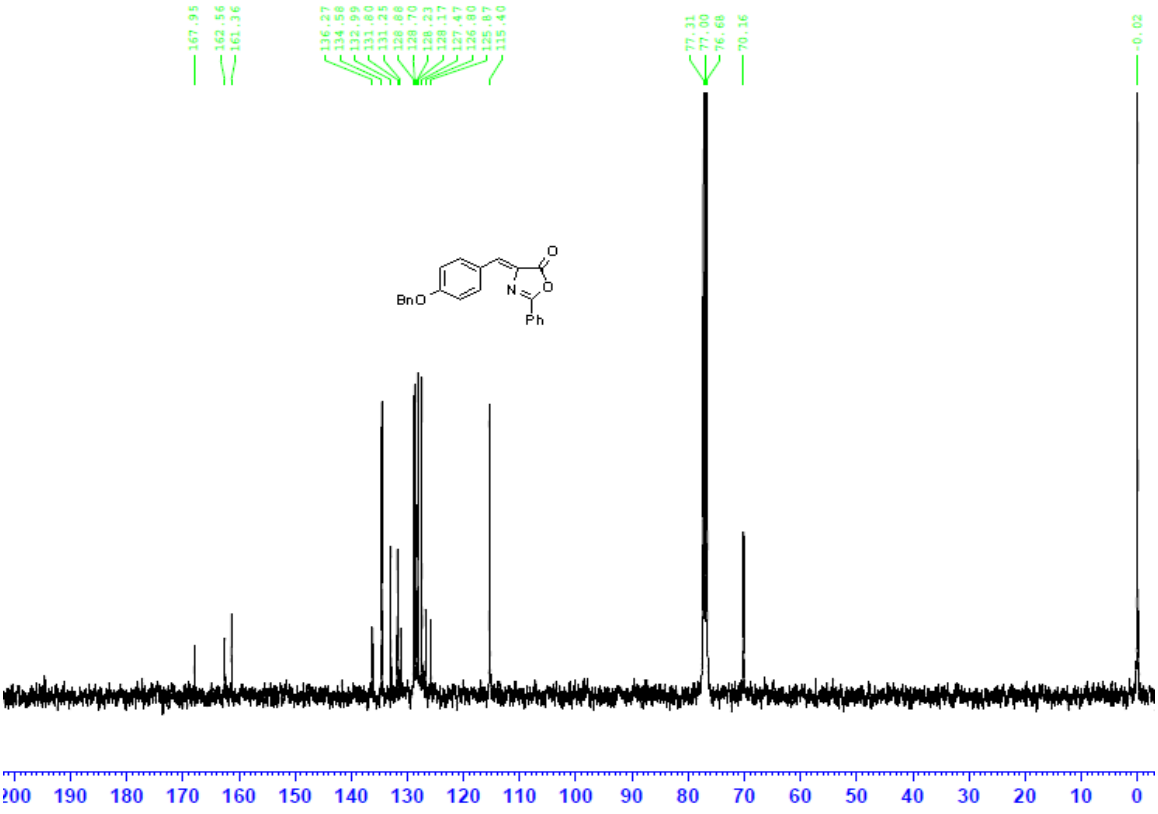
2.00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115.40
77.31
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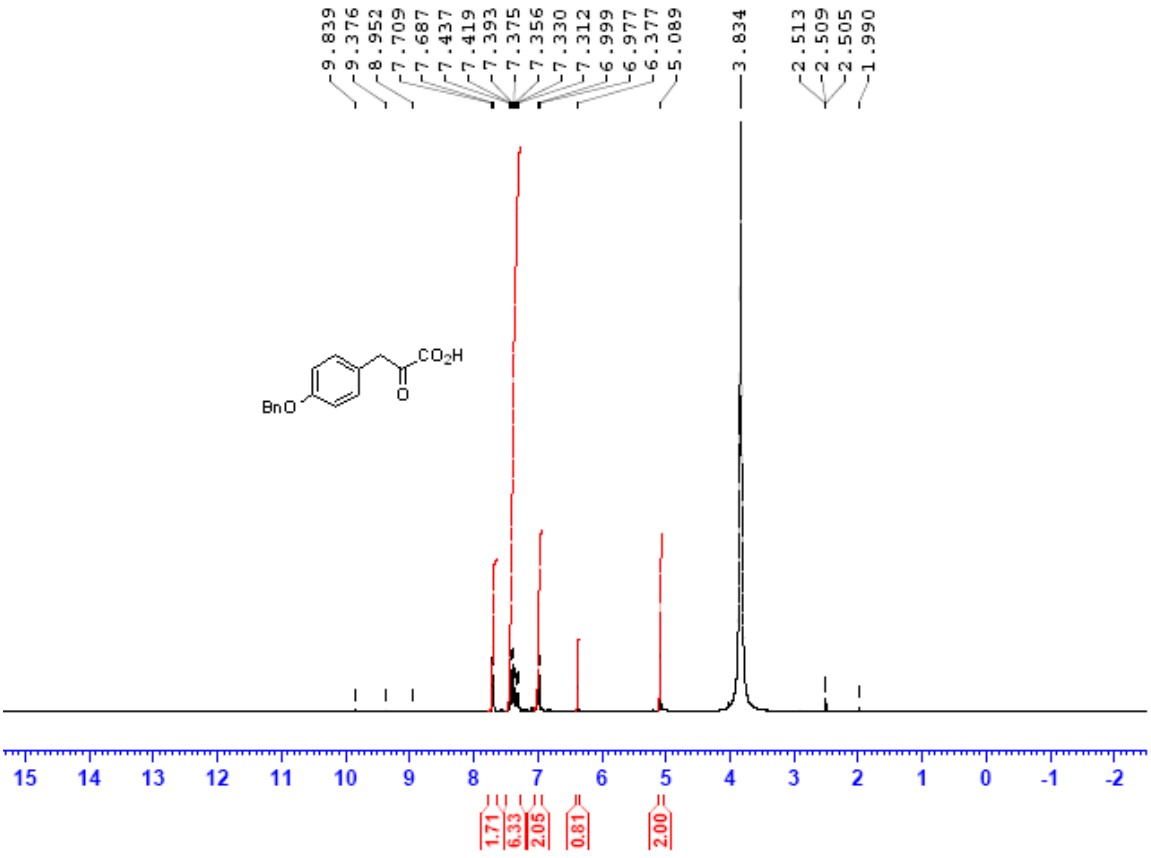
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5.089
3.834
2.513
2.509
2.505
1.990
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BnO
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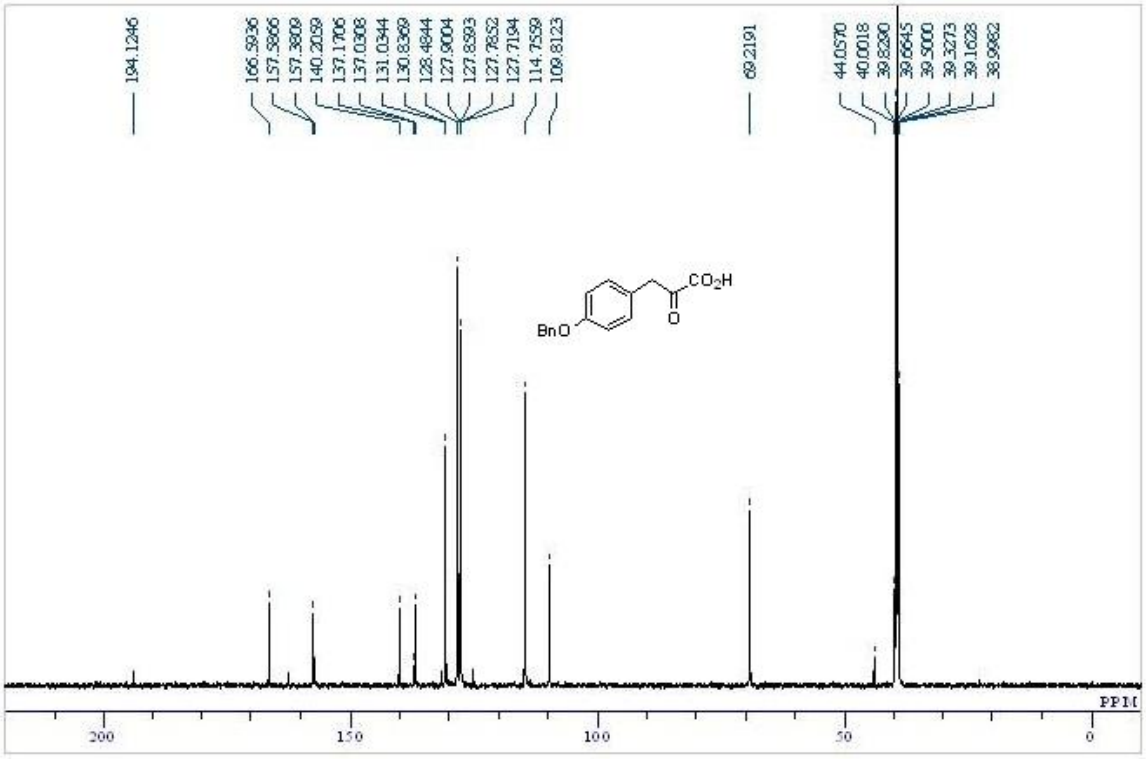
2.00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O
BnO
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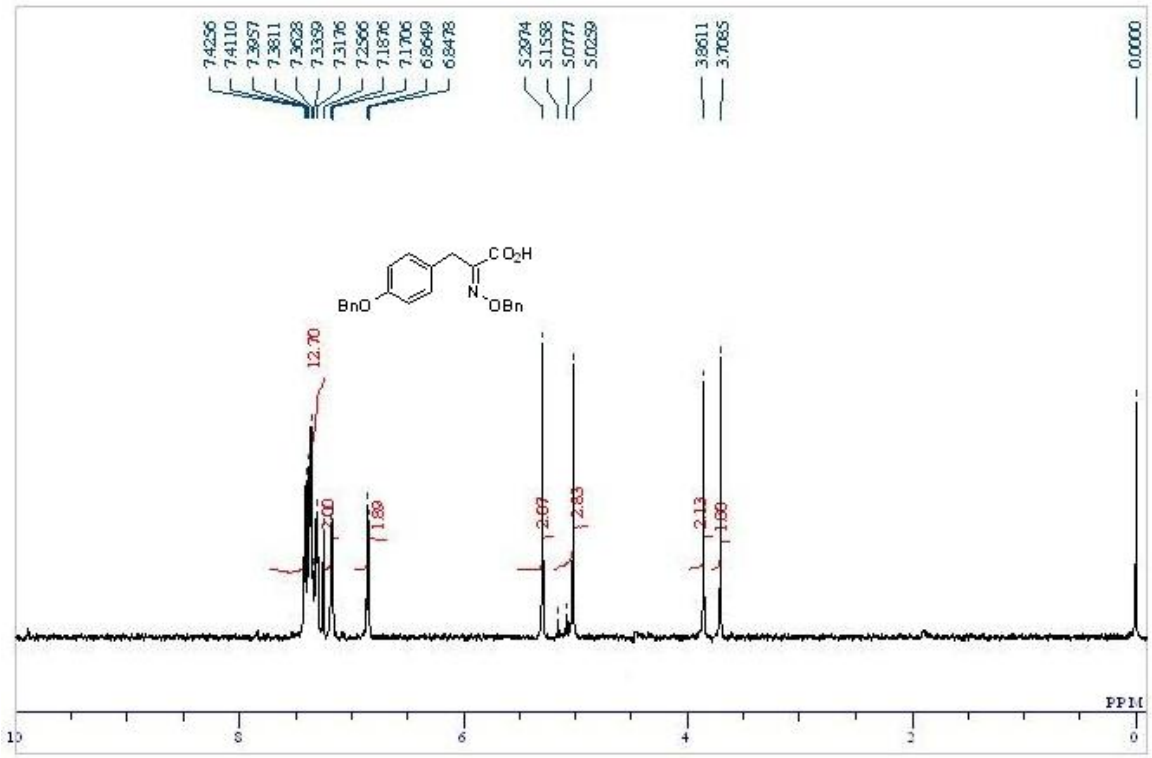
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OBn
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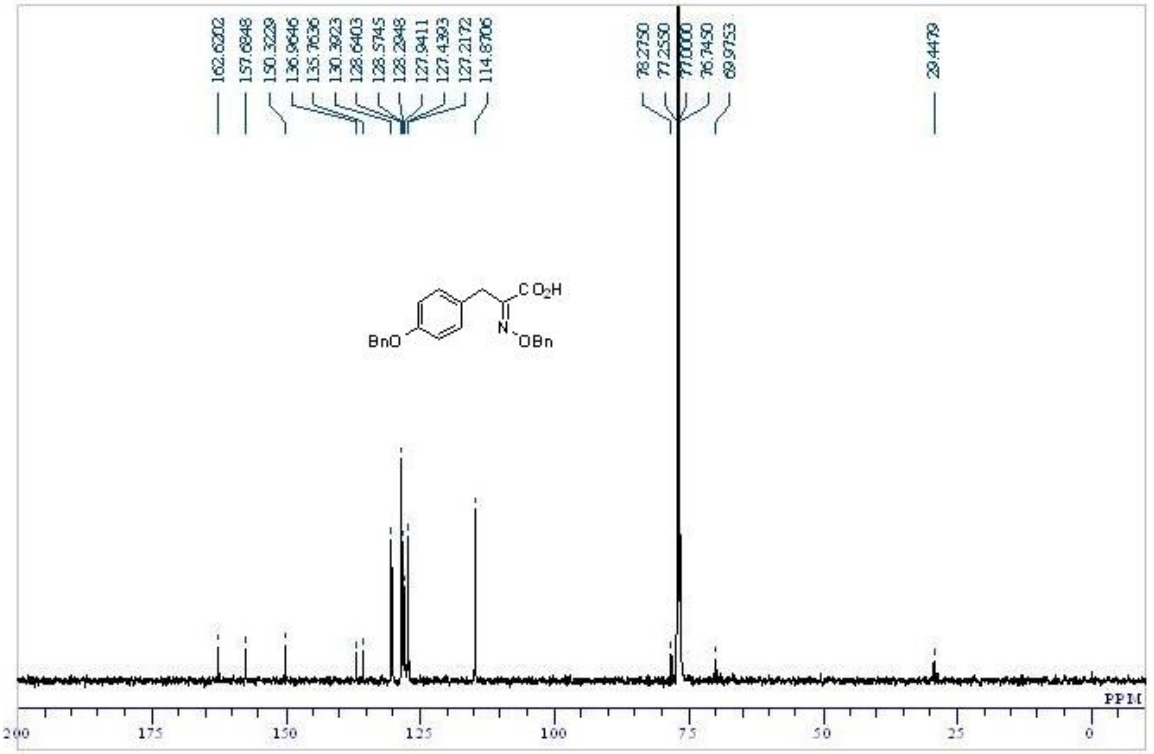
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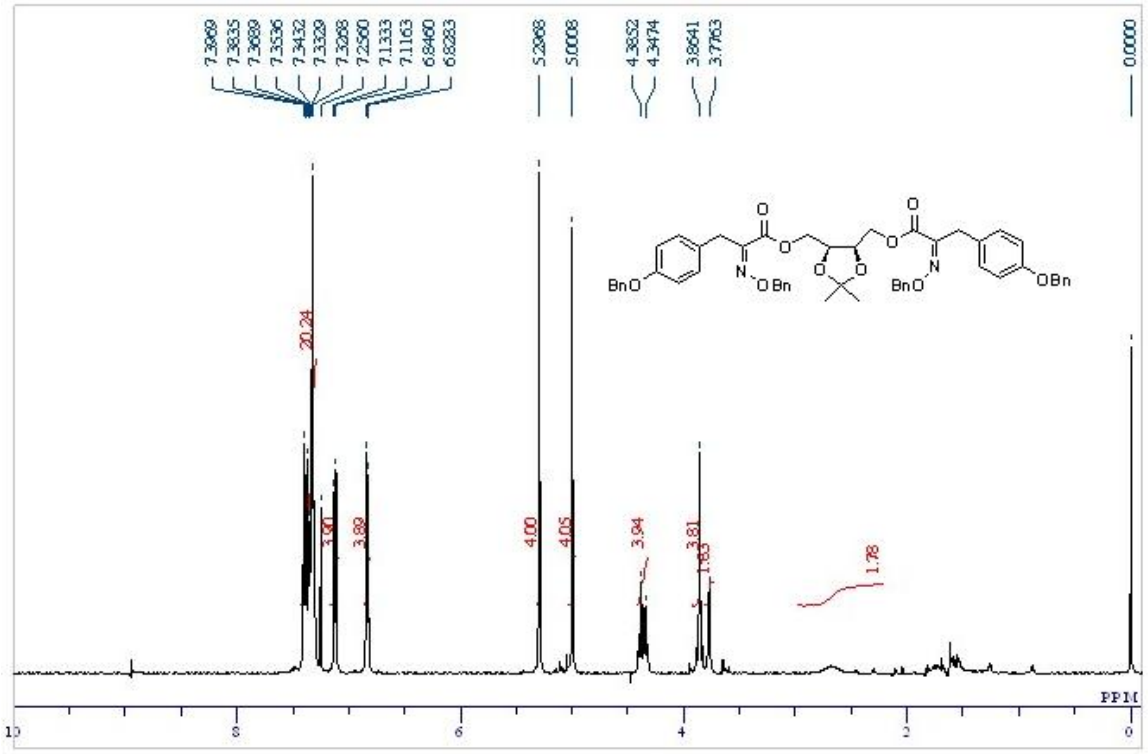
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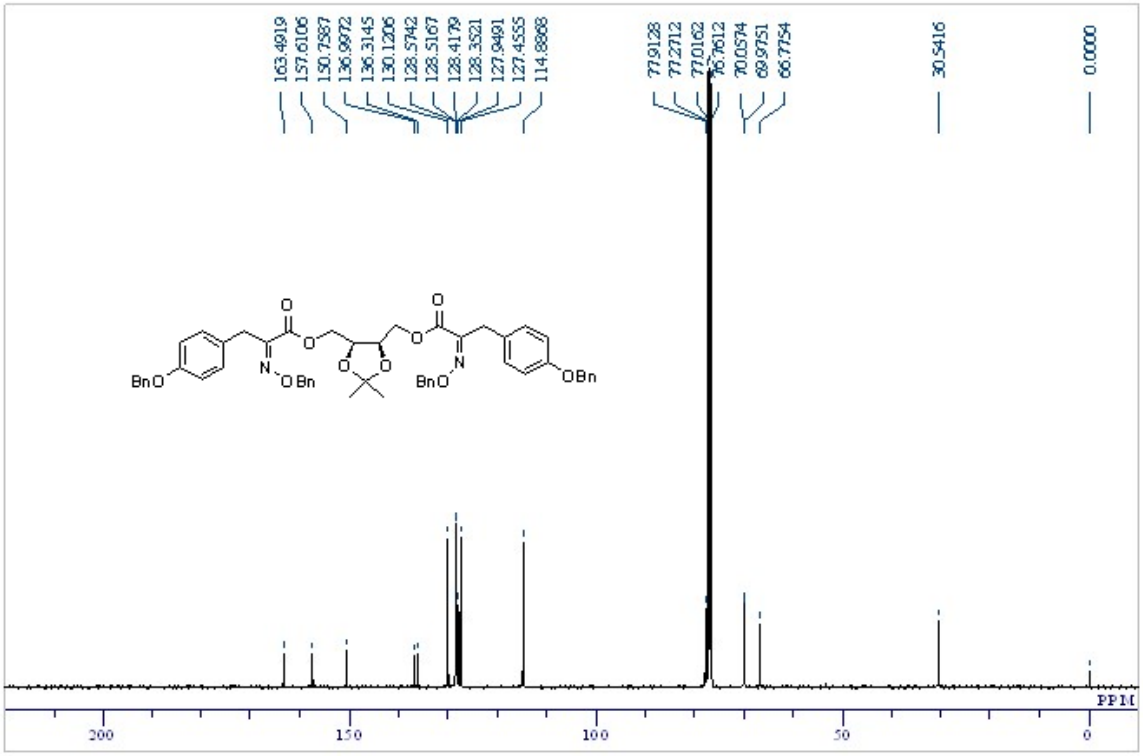
BnO
OBn
PPM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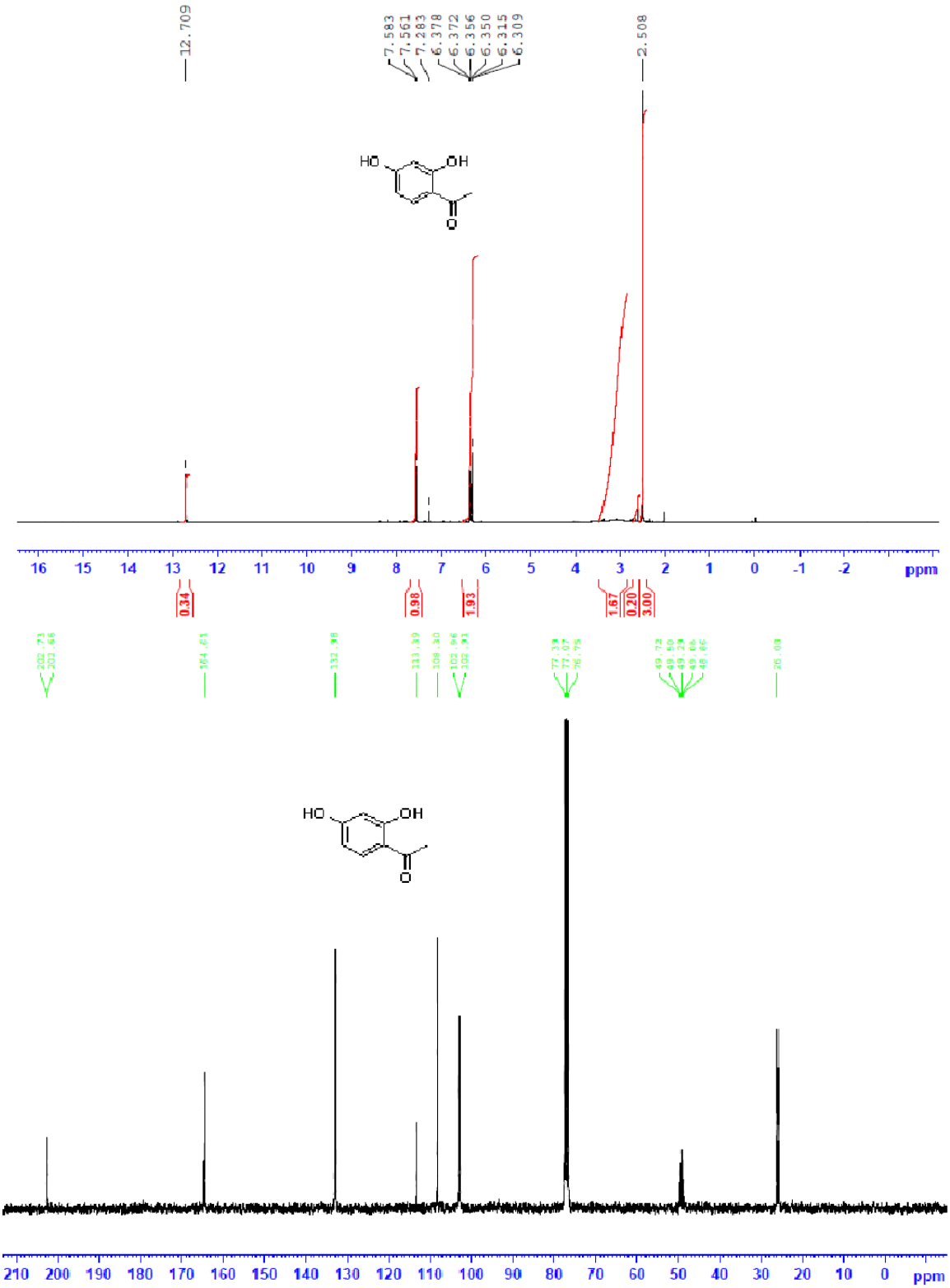
OBn
PPM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6.309
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OH
O
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
0.34
0.98
1.93
1.67
0.20
3.00
202.73
203.66
164.61
132.98
113.39
108.30
102.96
102.91
77.39
77.07
76.75
49.72
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OH
O
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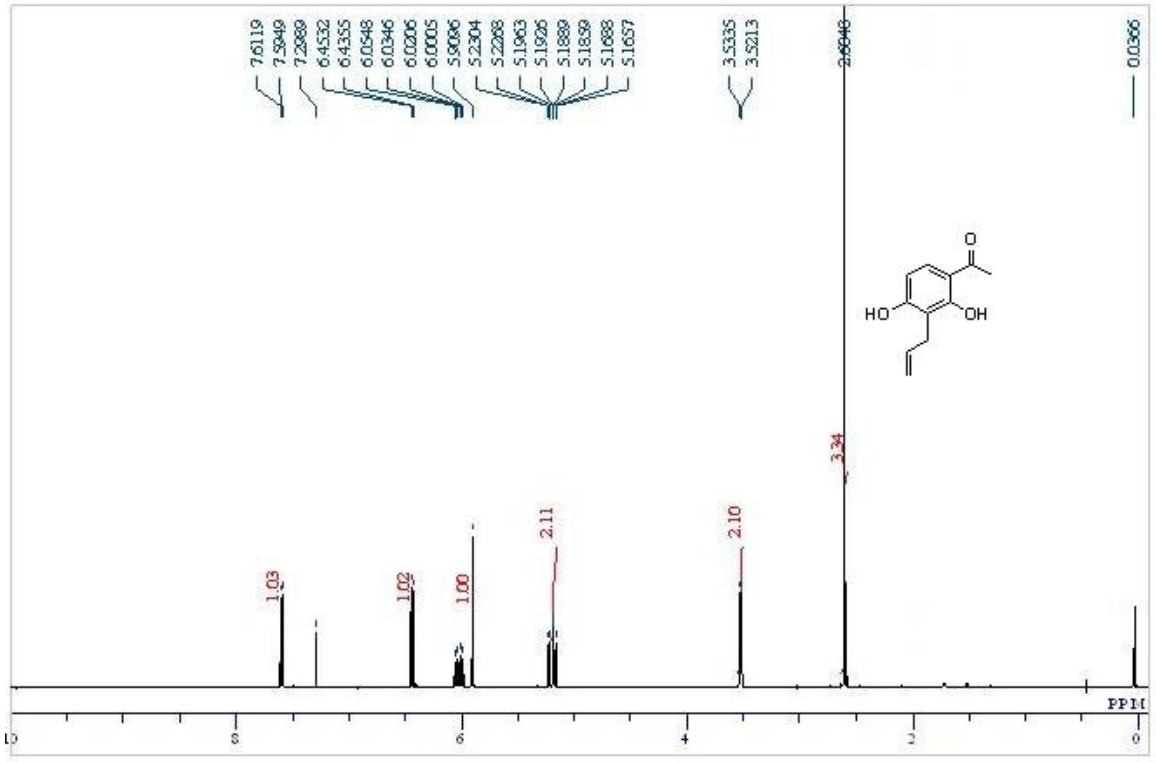
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5.1889
5.1839
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PPM
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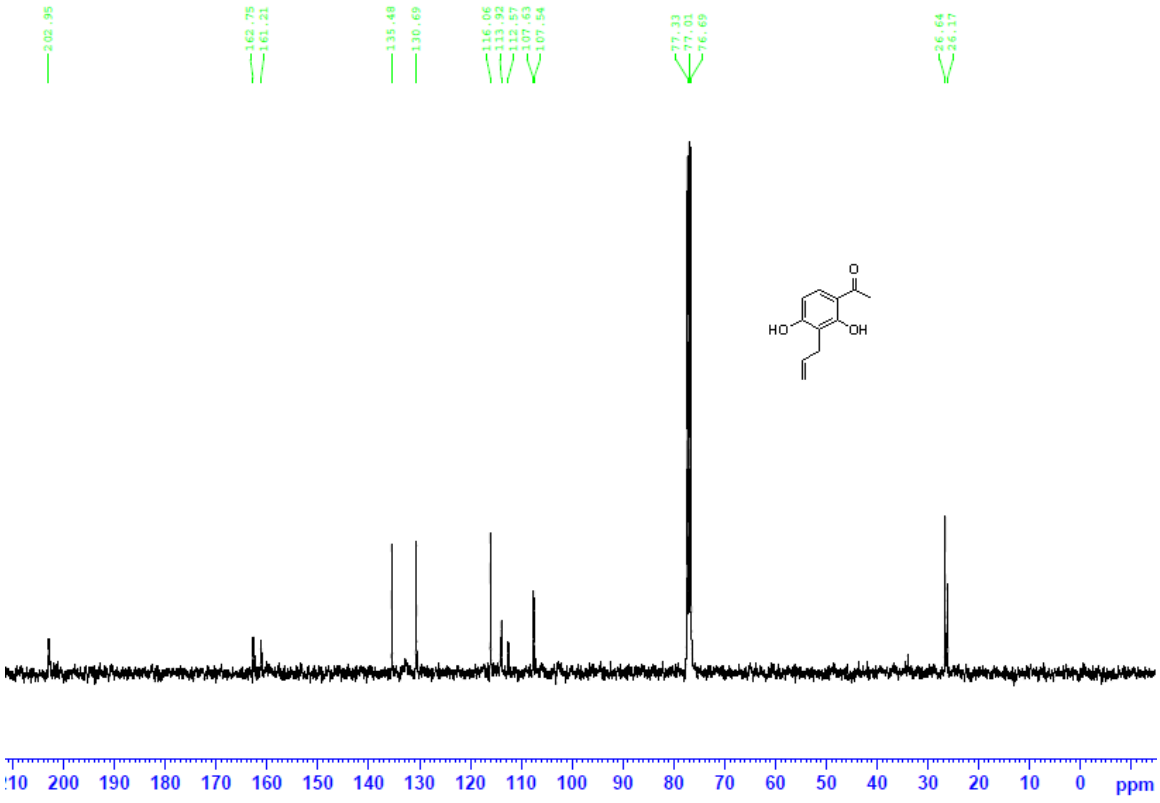
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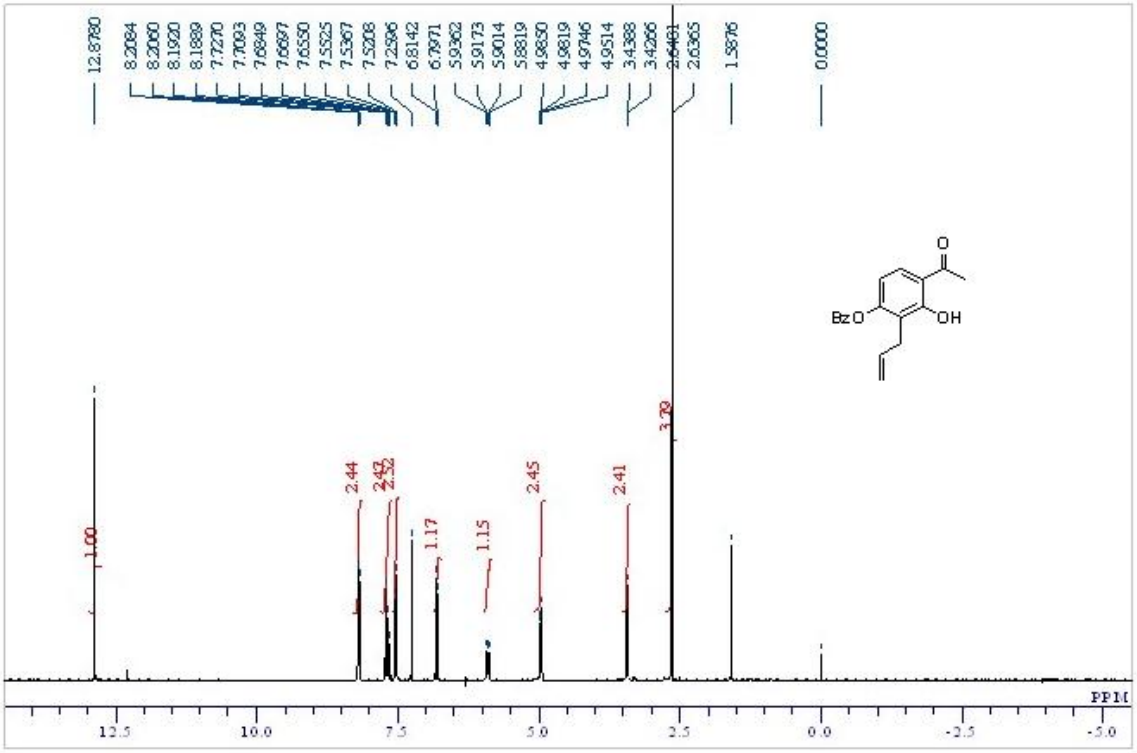
26.64
26.17
HO
OH
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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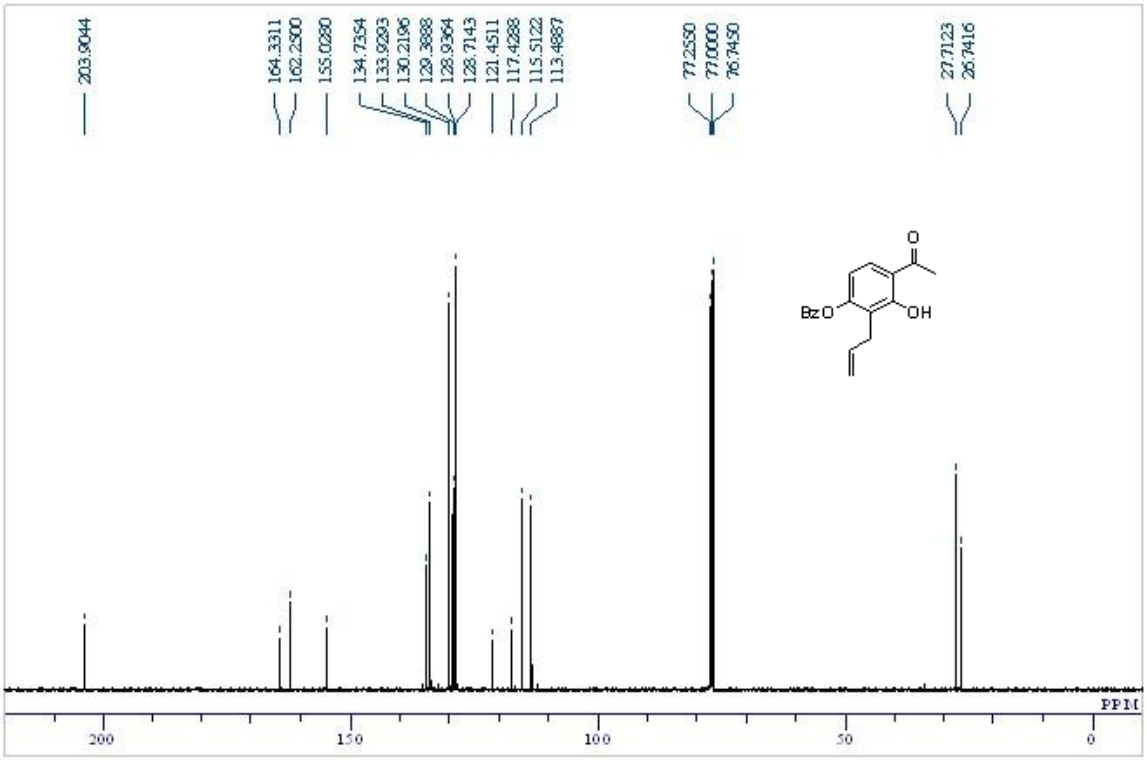
7.5525
7.5367
7.5208
7.2896
6.8142
6.7971
5.9362
5.9173
5.9014
5.8819
4.9850
4.9819
4.9746
4.9514
3.4388
3.4266
2.6461
2.6365
1.5876
0.0000
BzO
OH
1.00
2.44
2.43
2.42
1.17
1.15
2.45
2.41
3.79
PPM
12.5
10.0
7.5
5.0
2.5
0.0
-2.5
-5.0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162.2900
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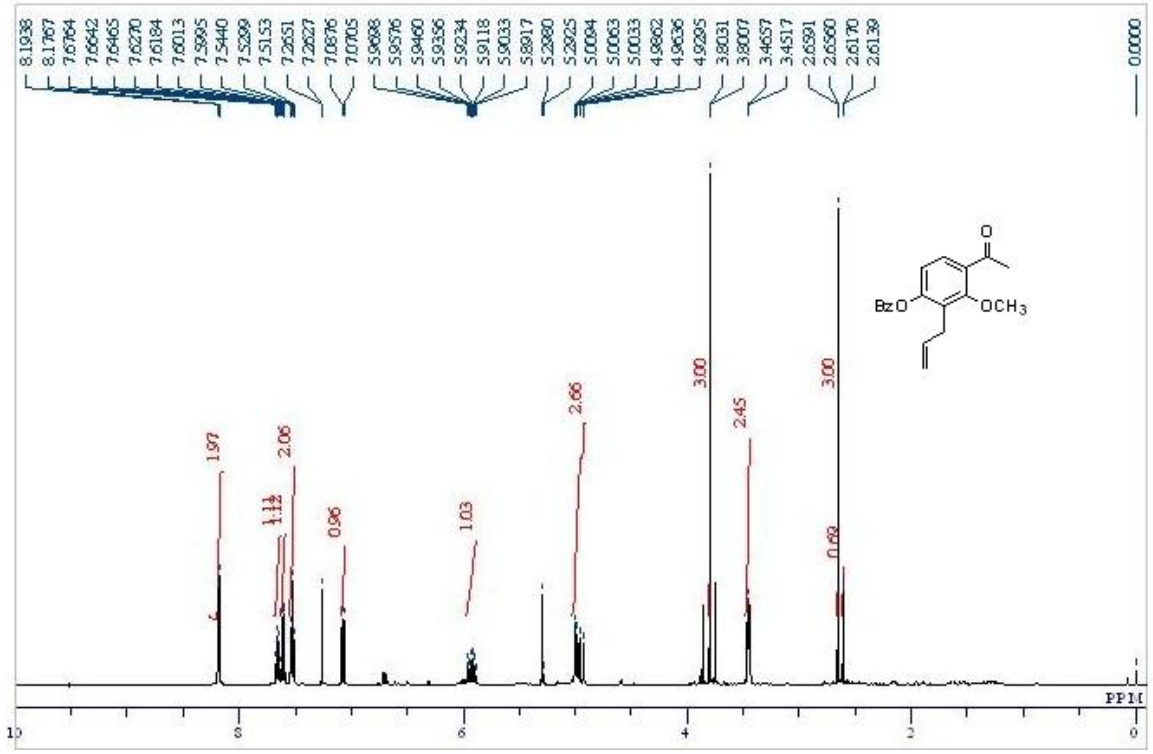
134.7354
133.9293
130.2196
129.3888
128.9364
128.7143
121.4511
117.4228
115.5122
113.4887
77.2550
77.0000
76.7450
27.7123
26.7416
BzO
OH
PPM
200
150
100
50
0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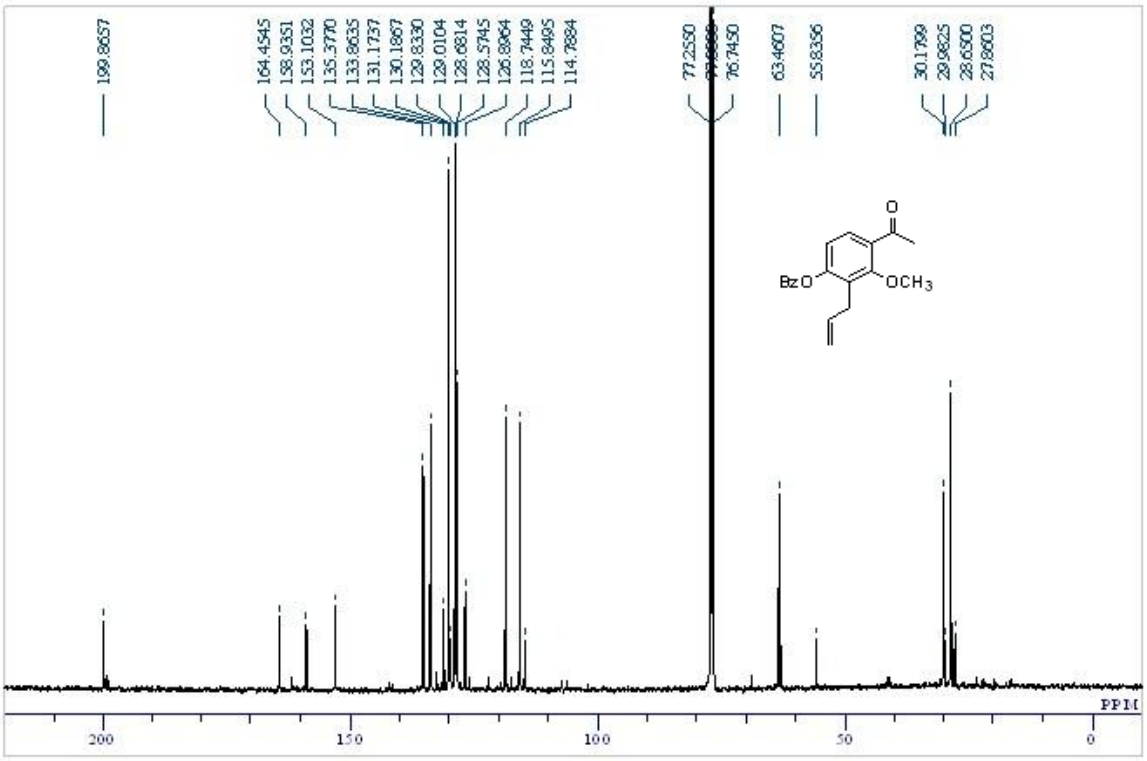
8.1767
7.6764
7.6642
7.6465
7.6270
7.6184
7.6013
7.5995
7.5440
7.5289
7.5153
7.2651
7.2627
7.0876
7.0705
5.9688
5.9576
5.9460
5.9356
5.9234
5.9118
5.9033
5.8917
5.2980
5.2925
5.0094
5.0063
5.0033
4.9862
4.9636
4.9295
3.8031
3.8007
3.4657
3.4517
2.6591
2.6560
2.6170
2.6139
0.0000
1.97
2.06
1.11
1.12
0.96
1.03
2.66
3.00
2.45
3.00
0.69
BzO
OCH3
O
PPM
10
8
6
4
2
0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164.4545
158.9351
153.1032
135.3770
133.8635
131.1737
130.1867
129.8330
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128.6814
128.5745
126.8864
118.7449
115.8495
114.7884
77.2550
76.7450
63.4607
55.8356
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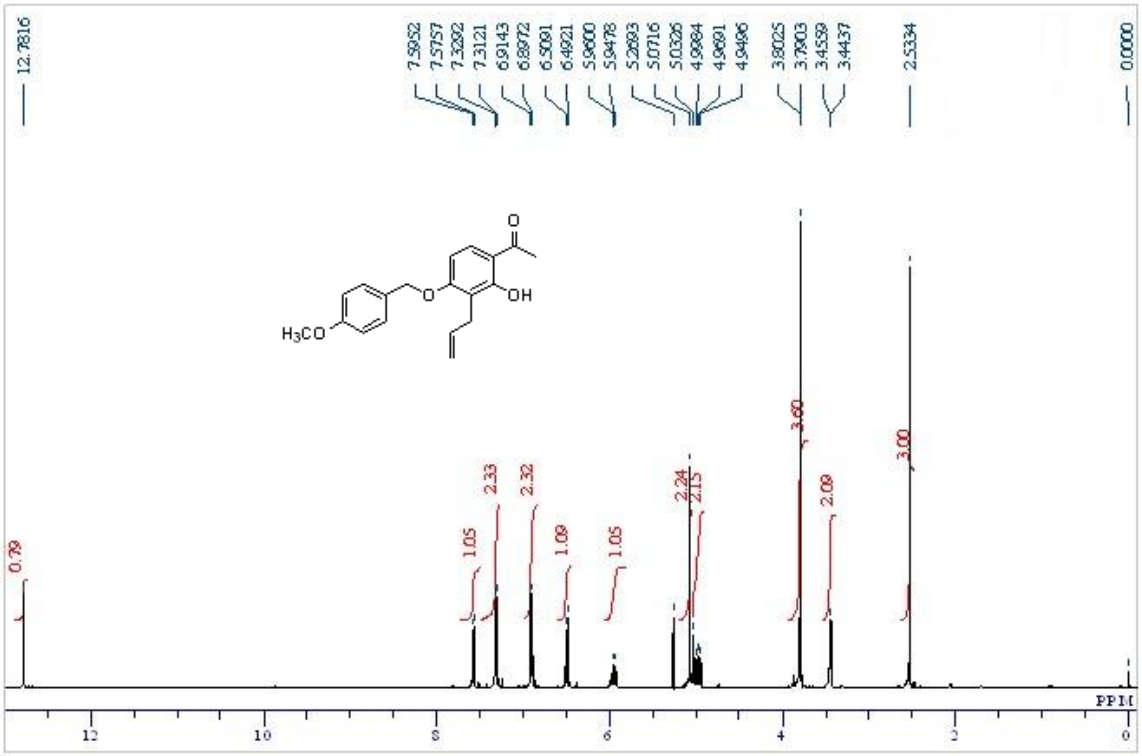
29.9825
28.6500
27.8603
BzO
OCH3
O
PPM
200
150
100
50
0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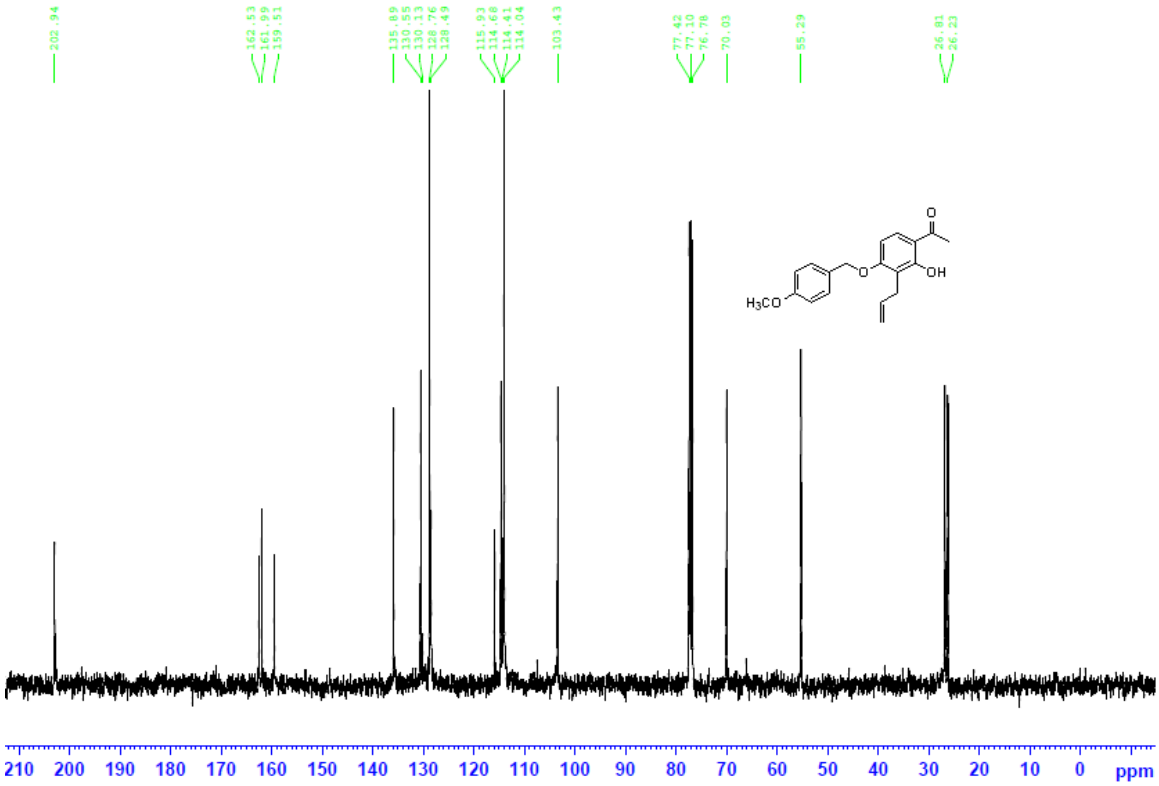
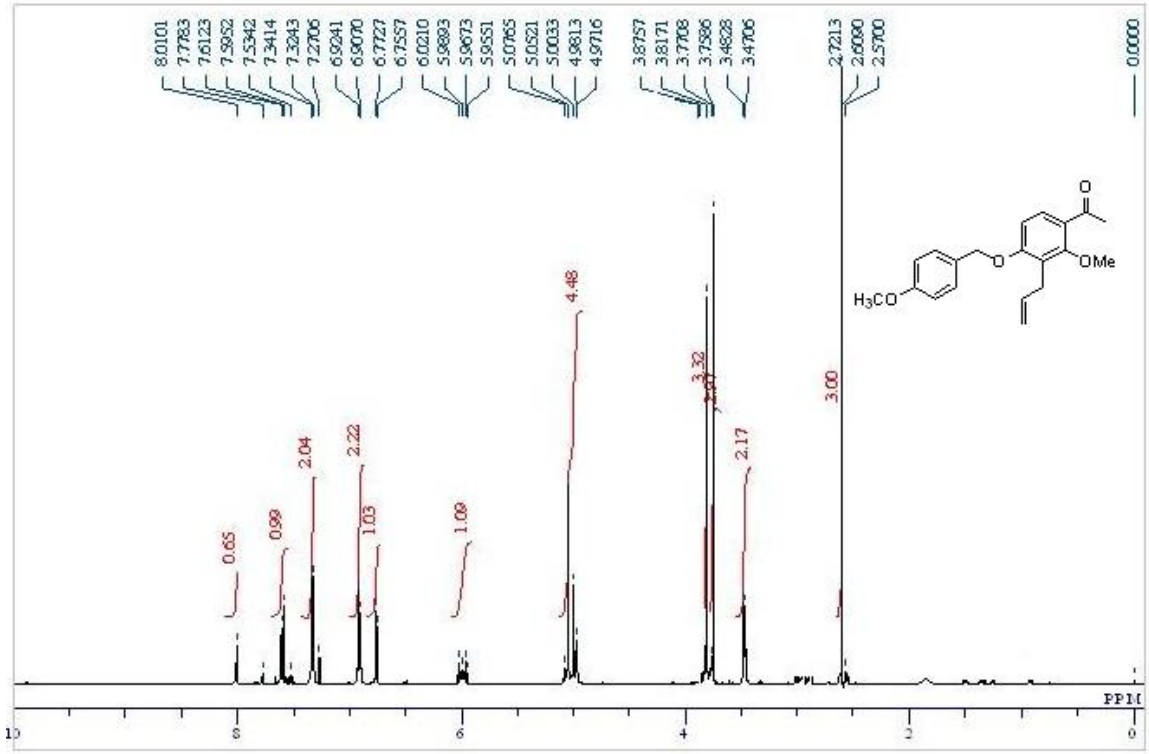
7.5952
7.5757
7.3282
7.3121
6.9143
6.8972
6.5091
6.4921
5.9600
5.3478
5.2693
5.0716
5.0326
4.9884
4.9691
4.9496
3.8025
3.7903
3.4539
3.4437
2.5334
0.0000
0.79
1.05
2.33
2.32
1.09
1.05
2.24
2.15
3.60
2.08
3.00
O
OH
H3CO
PPM
12
10
8
6
4
2
0


202.94
162.53
161.99
159.51
135.89
130.55
130.13
128.76
128.49
115.93
114.68
114.41
114.04
103.43
77.42
77.10
76.78
70.03
55.29
26.81
26.23
O
OH
H3CO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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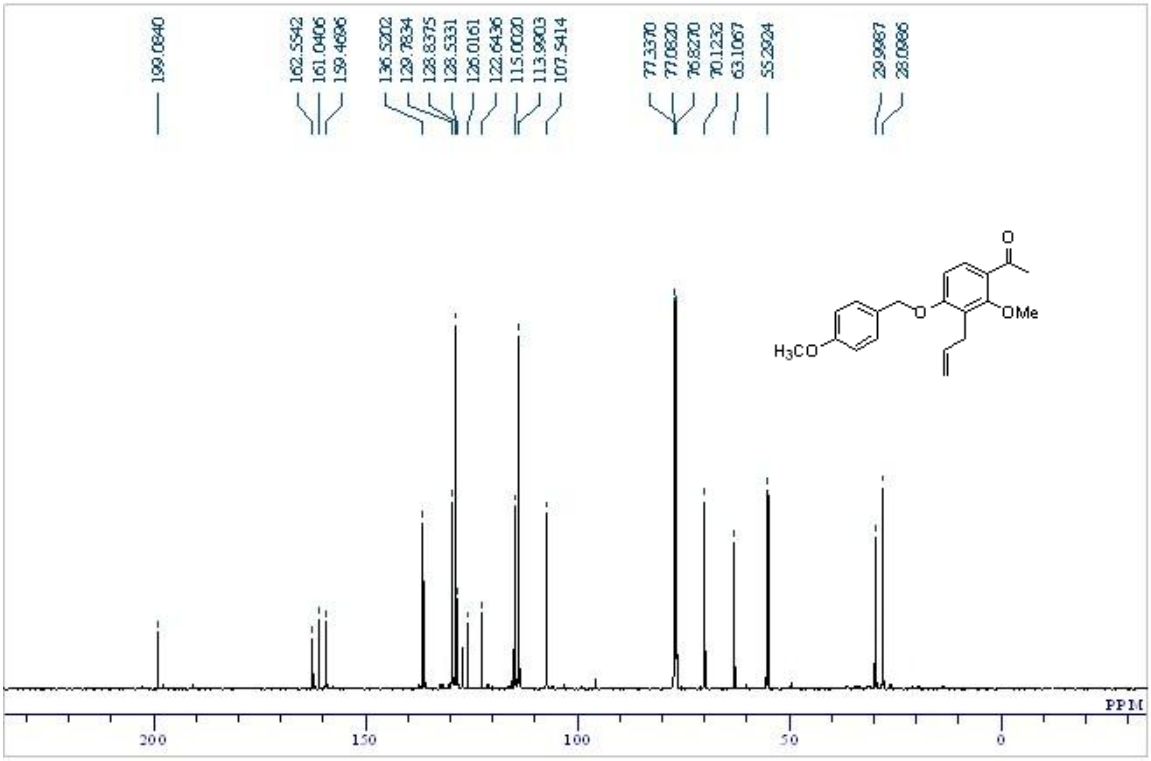
7.7783
7.6123
7.5952
7.5342
7.3414
7.3243
7.2706
6.9241
6.9070
6.7727
6.7557
6.0210
5.9883
5.9673
5.9551
5.0765
5.0521
5.0033
4.9813
4.9716
3.8757
3.8171
3.7708
3.7586
3.4828
3.4706
2.7213
2.6080
2.5700
0.0000
0.65
0.99
2.04
2.22
1.03
1.08
4.48
3.32
3.00
2.17
O
OMe
H3CO
PPM
10
8
6
4
2
0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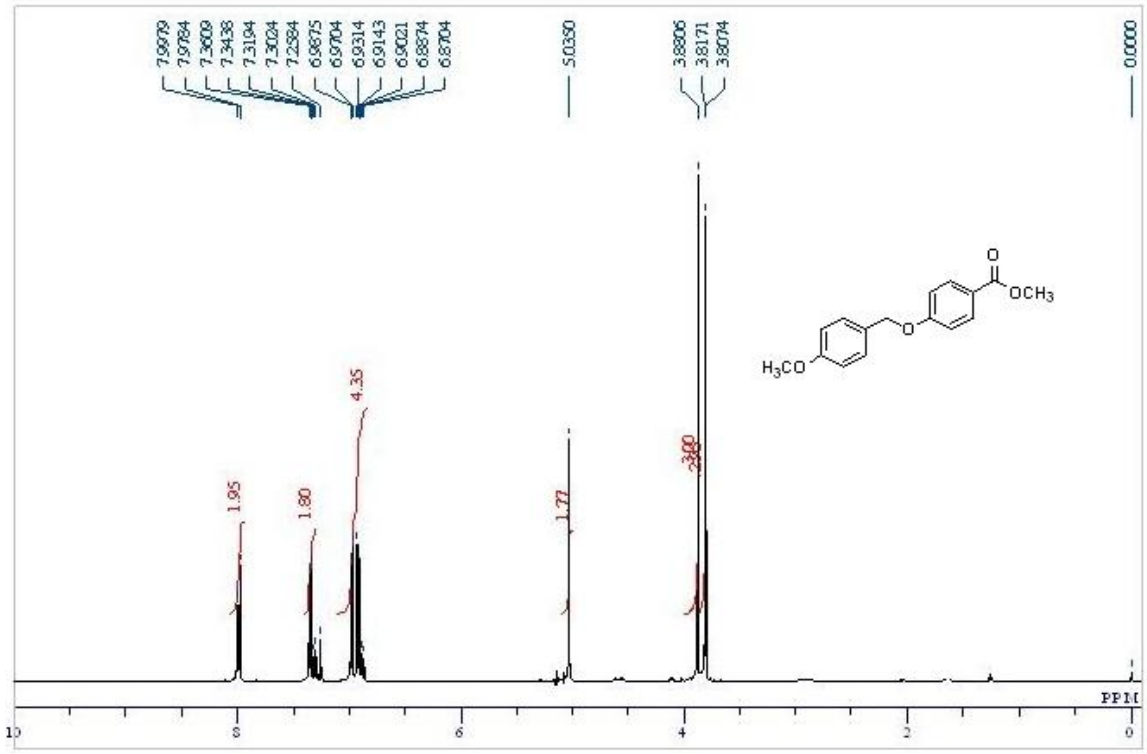
162.5542
161.0406
139.4696
136.5202
129.7834
128.8375
128.5331
126.0161
122.6436
115.0020
113.9803
107.5414
77.3370
77.0820
76.8270
70.1232
63.1067
55.2924
29.9987
28.0086
O
OMe
H3CO
PPM
200
150
100
50
0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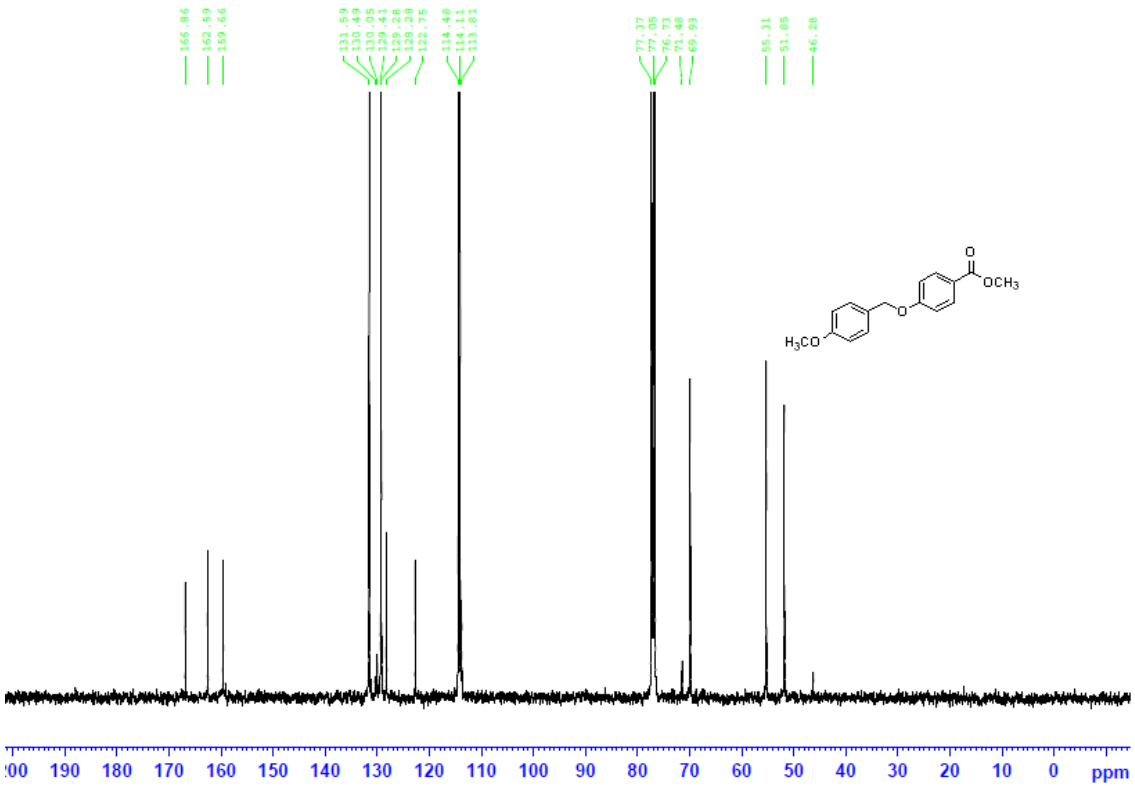
7.9784
7.3609
7.3438
7.3194
7.3024
7.2384
6.9875
6.9704
6.9314
6.9143
6.9021
6.8874
6.8704
5.0350
3.8806
3.8171
3.8074
0.0000
4.35
1.95
1.80
1.77
3.80
3.80
O
OCH3
H3CO
O
PPM
10
8
6
4
2
0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162.59
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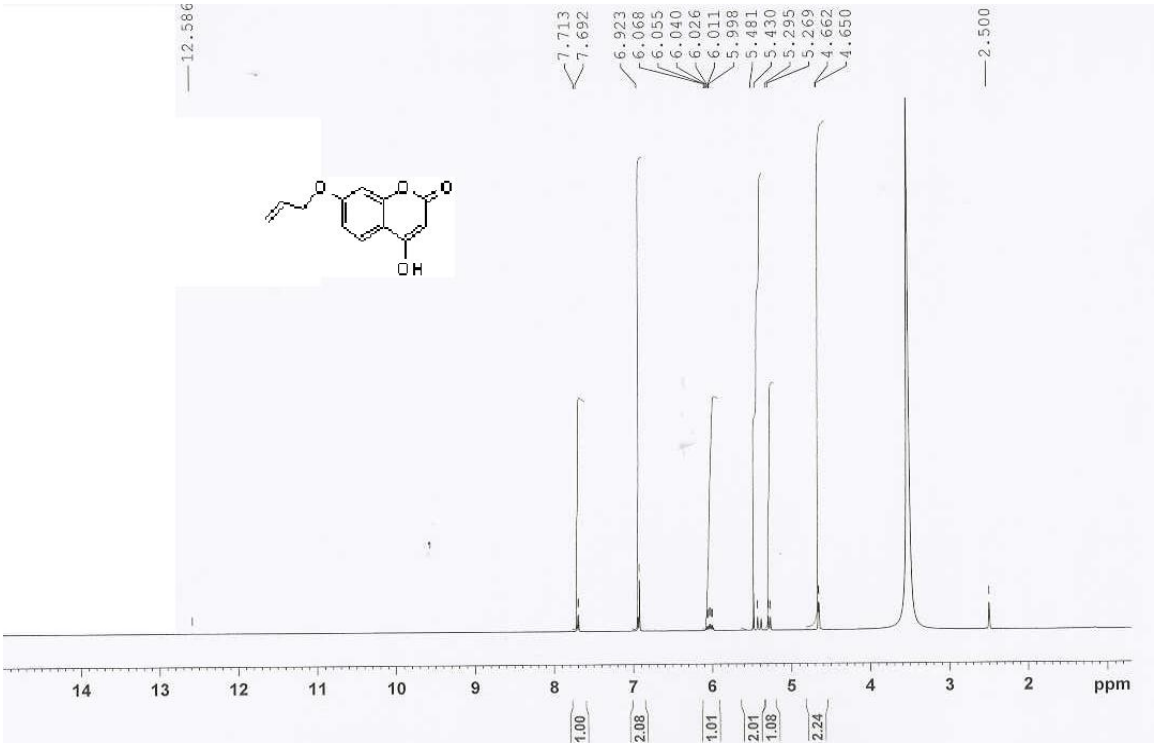
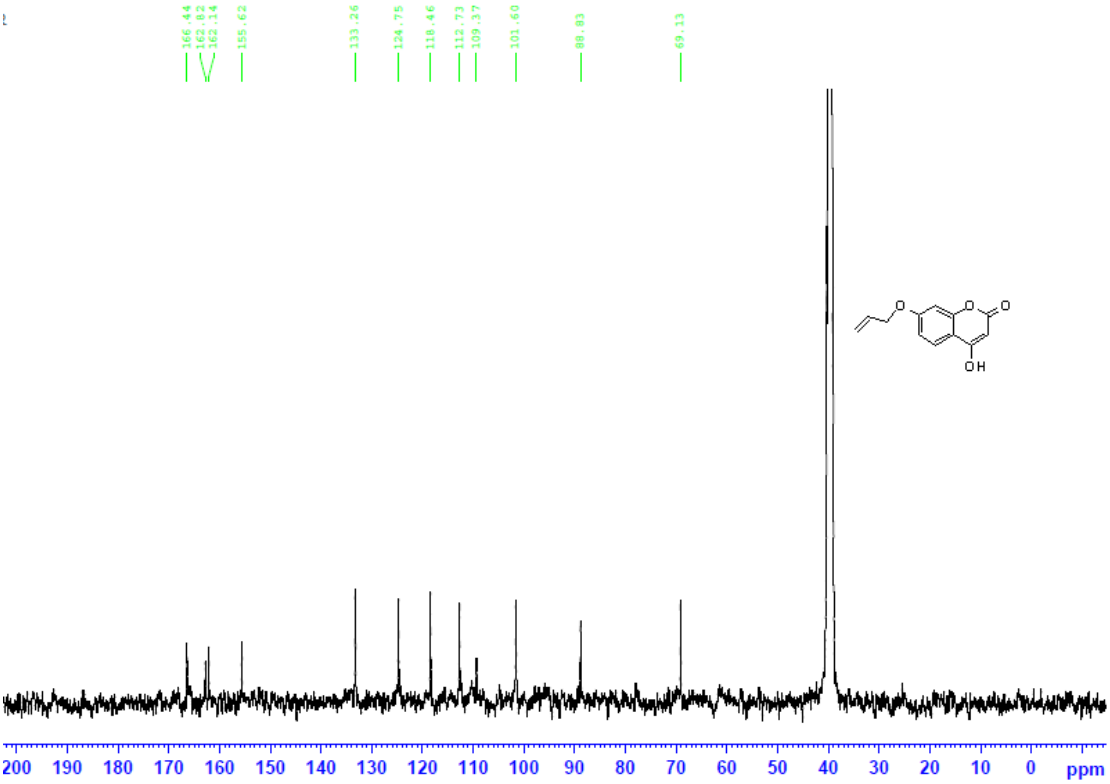
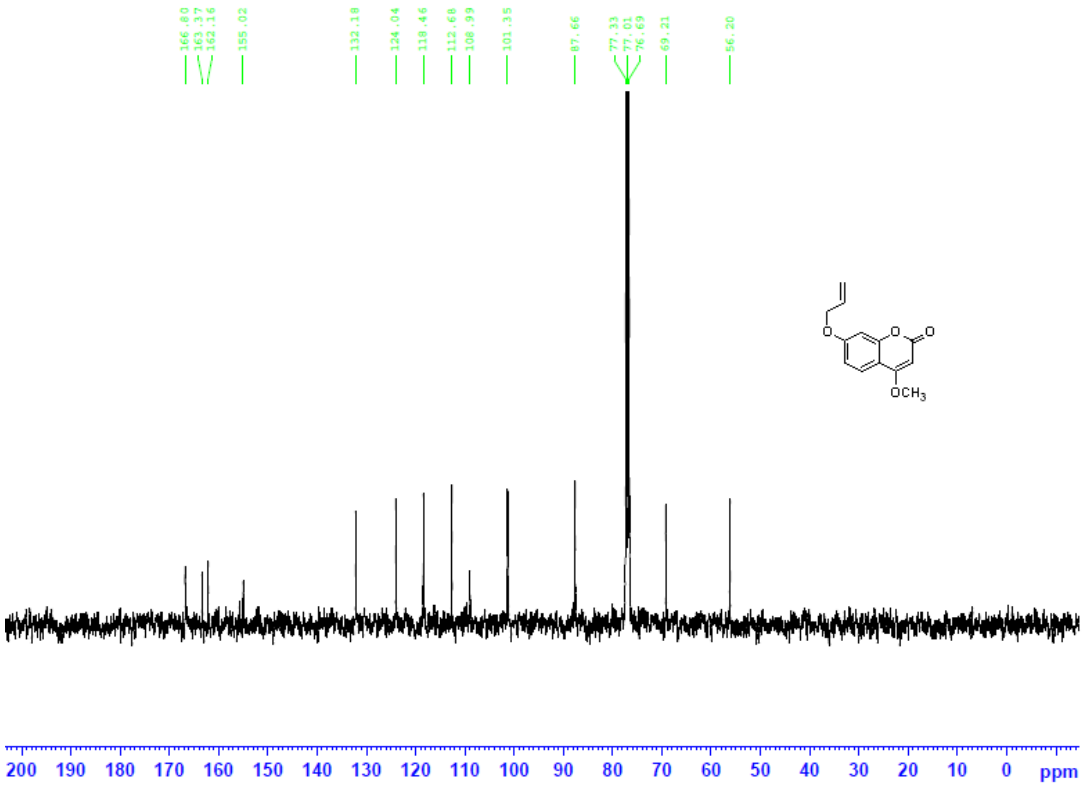
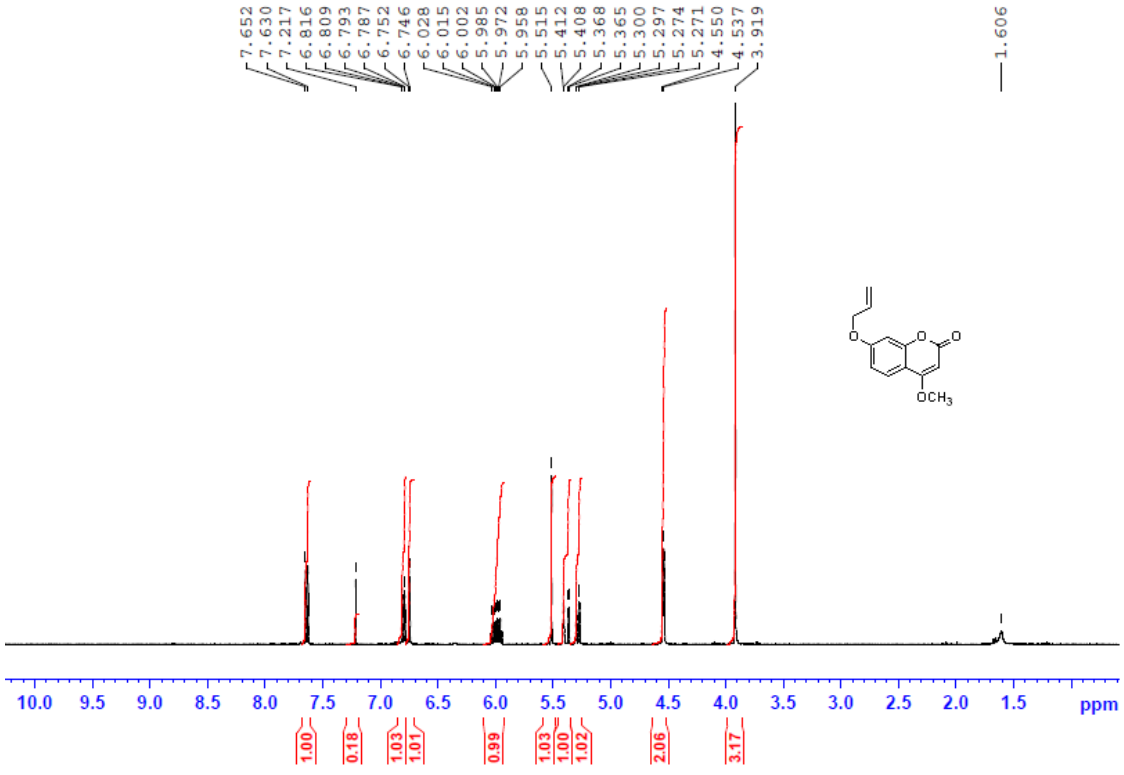
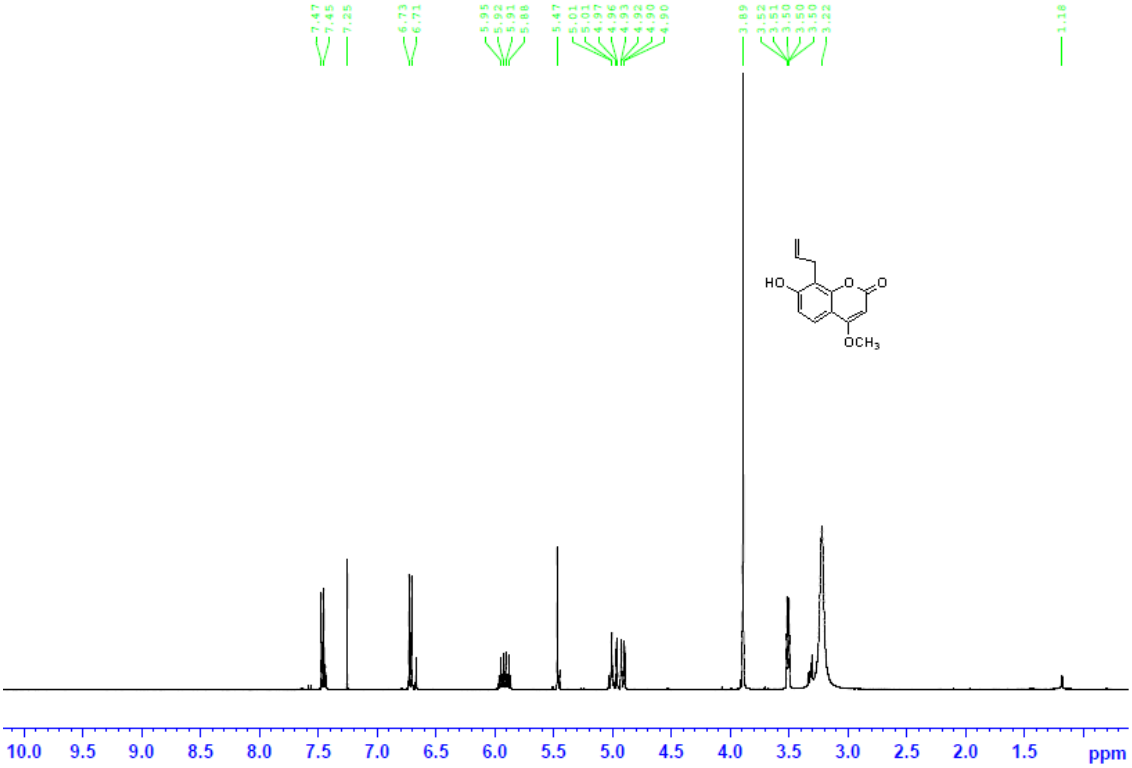
131.59
130.49
130.05
129.41
129.28
128.28
122.75
114.48
114.11
113.81
77.37
77.05
76.73
71.48
69.93
55.31
51.85
46.28
O
OCH3
H3CO
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

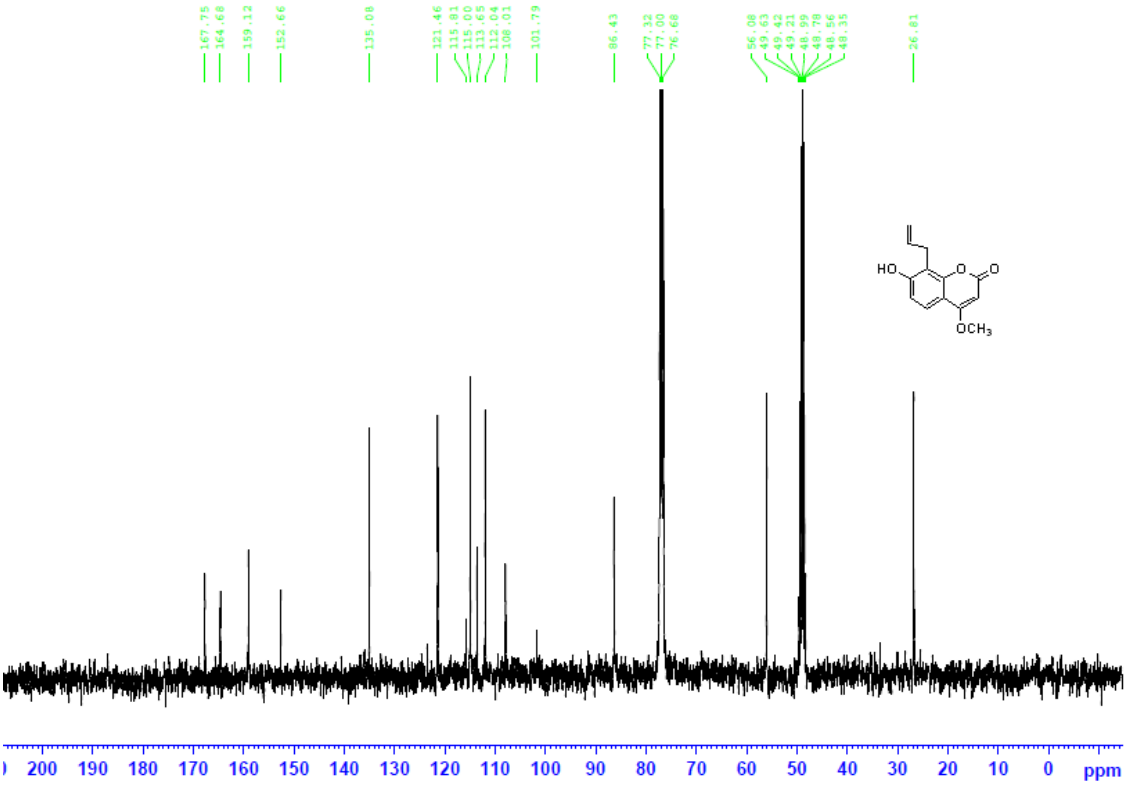

12.586
7.713
7.692
6.923
6.068
6.055
6.040
6.026
6.011
5.998
5.481
5.430
5.295
5.269
4.662
4.650
2.500
OH
14 13 12 11 10 9 8 7 6 5 4 3 2 ppm
1.00
2.08
1.01
2.01
1.08
2.24


166.44
162.82
162.14
155.62
133.26
124.75
118.46
112.73
109.37
101.60
88.83
69.13
OH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


166.80
163.37
162.16
155.02
132.18
124.04
118.46
112.68
108.99
101.35
87.66
77.33
77.01
76.69
69.21
56.20
OCH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.652
7.630
7.217
6.816
6.809
6.793
6.787
6.752
6.746
6.028
6.015
6.002
5.985
5.972
5.958
5.515
5.412
5.408
5.368
5.365
5.300
5.297
5.274
5.271
4.550
4.537
3.919
1.606
OCH3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
1.00
0.18
1.03
1.01
0.99
1.03
1.00
1.02
2.06
3.17


7.47
7.45
7.25
6.73
6.71
5.95
5.92
5.91
5.88
5.47
5.01
5.01
4.97
4.96
4.93
4.93
4.90
4.90
3.89
3.52
3.51
3.50
3.50
3.50
3.22
1.18
HO
O
O
OCH3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
ppm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164.68
159.12
152.66
135.08
121.46
115.81
115.00
113.65
112.04
108.01
101.79
86.43
77.32
77.00
76.68
56.08
49.63
49.42
49.21
48.99
48.78
48.56
48.35
26.81
HO
O
O
OCH3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

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