ABSTRACT

Synthesis and Biological Evaluation of Potential Vascular Disrupting and Antimitotic Agents Utilizing Benzosuberene, Benzocyclooctene, and Indene Molecular Frameworks

Christine A. Herdman, Ph.D.

Mentor: Kevin G. Pinney, Ph.D.

An investigational approach to cancer treatment involves the use of therapeutic agents that selectively target tumor-associated vasculature. A subset of these compounds is referred to as vascular disrupting agents (VDAs). The majority of clinically-relevant VDAs function biologically as inhibitors of tubulin polymerization, thus interfering with the dynamic instability inherent to the tubulin-microtubule protein system. As a key component of the cytoskeleton associated with eukaryotic cells, this protein system provides shape and structural stability to the endothelial cells that line the vasculature. Tumor associated vasculature provides a promising target for cancer therapeutics due to its primitive nature and abhorrent structure. Microtubule depolymerization leads to endothelial cell morphology changes (flat to round), which results in vasculature collapse and shut down of blood flow, ultimately leading to tumor necrosis. Tumors larger than 2-3 mm^3 require their own vasculature for the transportation of oxygen and nutrients, as well as the disposal of waste. Selective targeting of tumor-associated vasculature results

from the structural differences inherent to these vessels versus those feeding healthy tissue.

The natural products combretastatin A-1 (CA1), combretastatin A-4 (CA4), and colchicine are potent inhibitors of tubulin polymerization. While toxicity associated with colchicine treatment limited its use as an anticancer therapeutic, CA1 and CA4, as their corresponding water-soluble prodrug salts CA1P and CA4P respectively, have shown promising results in clinical trials. Drawing on structural similarities inherent to these three natural products, the Pinney Research Group at Baylor University has developed a variety of potent inhibitors of tubulin polymerization that function as VDAs. A benzosuberene-based compound (referred to as KGP18) has emerged as a highly promising agent for further investigation. Using KGP18 as a model, several new analogues have been synthesized and evaluated biologically to expand the structure activity relationship (SAR) profile of the benzosuberene class of compounds and to investigate the efficacy associated with benzocyclooctene and indene ring systems bearing similar functional group motifs. The synthesized target molecules have been evaluated for their ability to inhibit tubulin polymerization (assembly) as well as their cytotoxicity against three human cancer cell lines (NCI-H460, SK-OV-3, and DU-145) in collaborative studies.

In a related study, multi-walled carbon nanotubes (MWCNTs) have been evaluated for their ability to selectively deliver VDAs to tumors and/or tumor-associated vasculature. Initial studies have included dispersion assays of MWCNTs in a variety of organic solvents, as well as adsorption studies utilizing two water-soluble phosphate prodrug salts (CA4P and KGP265).

Synthesis and Biological Evaluation of Potential Vascular Disrupting and Antimitotic Agents Utilizing Benzosuberene, Benzocyclooctene, and Indene Molecular Frameworks

by

Christine A. Herdman, B.S.

A Dissertation

Approved by the Department of Chemistry and Biochemistry

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Patrick J. Farmer, Ph.D., Chairperson

Submitted to the Graduate Faculty of
Baylor University in Partial Fulfillment of the
Requirements for the Degree
of

Doctor of Philosophy

Approved by the Dissertation Committee

_____

Kevin G. Pinney, Ph.D., Chairperson

_____

Charles M. Garner, Ph.D.

_____

Robert R. Kane, Ph.D.

_____

Mary L. Trawick, Ph.D.

_____

Christopher M. Rios, Ph.D.

Accepted by the Graduate School

August 2016

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J. Larry Lyon, Ph.D., Dean

Page bearing signatures is kept on file in the Graduate School.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

ACKNOWLEDGMENTS

First and foremost, I cannot express enough gratitude to my mentor, Dr. Kevin G. Pinney. Without his superior expertise and unending support, I would never have been able to complete such an accomplishment. I will forever be indebted to his kindness and leadership.

I would also like to thank my committee members, Dr. Garner, Dr. Kane, Dr. Trawick and Dr. Rios, as well as the entire department of chemistry and biochemistry. Everyone's continued efforts to help me with my projects, as well as maintaining the flow of the department has made my career exceptionally enjoyable.

Next, I would like to thank the Pinney group as well as the other graduate students and friends, especially Lindsay Jones, Sara Schlesinger, and Dana Horgen, for their help with all my endeavors, but also for being an outlet and shoulder to lean on when chemistry or graduate school seemed like it was too much to handle. Without them, I for sure would've been miserable.

Lastly, I would like to thank my loving parents and amazing sister. Without their love and support, nothing would be possible. Thank you for encouraging me to always follow my dreams and helping me make them possible.

I'm sure there are plenty of people I have forgotten, but please know if you are a part of my life, you too have helped me along this journey, and for that I am forever grateful.

DEDICATION

Dedicated to
Mary Jane, David, and Jen Herdman

As well as
Sally Van Dyke

In Memory of
Ethel and Robert Herdman and Karen Van Dyke

CHAPTER ONE

Introduction

Cancer continues to be one of the most devastating diseases across the globe. In 2014, there were an estimated 1.7 million new cases of cancer and almost 600,000 deaths resulting from cancer.[1] The highest incidence of cancer for males occurs in the prostate, while for females it occurs in the breast tissue. However, the largest number of deaths for both men and women attributed to cancer occurs in the lung and bronchi.[2]

Tumors are classified as either benign or malignant. Benign tumors do not spread and do not invade other tissues, and are not considered a threat to life. Malignant tumors, however, invade neighboring organs, can spread throughout the host, and are life threating. Cancer by definition is malignant, and usually forms a solid mass.[3]

The primary problem with treating cancer is that no two cancers are exactly alike. The disease differs from person to person and within each location in the body, thus making treatment quite difficult.[4] Because the disease is unique to each individual, combination therapies are often used to most effectively destroy the cancer.[5] One developing type of treatment is the use of targeted therapies. These therapies target specific cites of cancer cells that ultimately makes them different from normal, healthy cells.[6–9]

Vascular Targeting Therapies

In 1971, Judah Folkman noted that tumors between 2 and 3 mm^3 stopped growing if they were unable to produce their own vasculature.[10,11] Folkman determined that by limiting the development of the vasculature and thus inhibiting the flow of nutrients and

oxygen, it could be possible to target tumor vasculature as a form of cancer treatment.[12] Folkman is credited with coining the term "anti-angiogenesis" which refers to treatments, methods, or processes that prevent the formation and development of new vasculature.[10]

Following Folkman's discovery in 1971, Juliana Denekamp observed that the obstruction of the blood vessels of solid tumors led to tumor regression.[13–16] This blockade of blood flow, which was related to morphology changes of vascular endothelial cells, resulted in tumor cell death due to a lack of necessary oxygen and nutrients, ultimately leading to widespread necrosis.[14] Denekamp also reported that tumor cells farther from blood vessels are radioresistant due to lack of oxygen and chemoresistant due to nutritional deprivation, thus other methods rather than chemotherapy and radiotherapy of tumor therapy were necessary for treatment.[15]

Since Folkman's and Denekamp's discoveries, targeting tumor vasculature has grown into a substantial research area for cancer therapeutics, and the information surrounding tumor vasculature has become more complex. Over 90% of cancers present as solid tumors, relying on its own vasculature for the supply of oxygen and nutrients (Figure 1.1).[17] The neovasculature found in expanding tumors is vastly different from that found in healthy tissue. The density of the vasculature varies throughout the tumor, with greater densities seen in areas of active growth and less vasculature in regions of necrosis.[18] Tumor vasculature tends to be chaotic due to the rapid proliferation of the tumor.[11,12,14,15,19] Throughout the vasculature, excessive branching, misshapen vessels, leakiness between the lining endothelial cells, areas of hypoxia, and blind ends are all observed.[3,11,20] The vessels also lack the organization of arterioles, capillaries, and venules.[18] These structural failures causes nutritional and oxygen deprivation to the

tumor, as well as increased interstitial fluid pressure.[3,11] Because of the necessity for solid tumors to supply nutrients and oxygen and dispel waste throughout, as well as the immaturity and chaotic nature of the vasculature, the blood vessels provide an optimal target for potential cancer therapies.[11]

Vascular targeting therapies are divided into two main areas: angiogenesis inhibiting agents (AIAs) and vascular disrupting agents (VDAs). These two approaches vary in their physiological target, the type of disease that is likely to be susceptible to such therapies, and the treatment scheduling.[13] Angiogenesis inhibitors block the formation of new vasculature, are beneficial to early stage metastatic disease, and require chronic administration.[13,21] VDAs, on the other hand, target established vasculature, are given acutely, and would be more beneficial in use against advanced diseases.[13,22]

Angiogenesis Inhibiting Agents

Angiogenesis is the process of new blood vessel formation from preexisting vasculature.[23] Under normal physiological conditions, angiogenesis is only promoted during pregnancy, wound healing, and the menstrual cycle.[24] This process is usually extremely controlled and self-limited, but is aberrant in tumor vasculature and necessary for tumor perseverance and metastases.[25] Due to the rapid growth of many tumors, cancerous cells up-regulate proangiongenic factors such as vascular endothelial growth factor (VEGF) and platelet-derived endothelial growth factor, which stimulate the formation of new vessels.[18,26] These factors, in turn, bind to their respective receptors on endothelial cells and activate otherwise dormant cells, which begin to infiltrate the tumor. Of all the angiogenic factors, VEGF is considered the most potent and specific, due to its

necessity for endothelial cell proliferation and blood vessel formation. It is also key in endothelial cell survival signaling in newly formed vessels.[22]

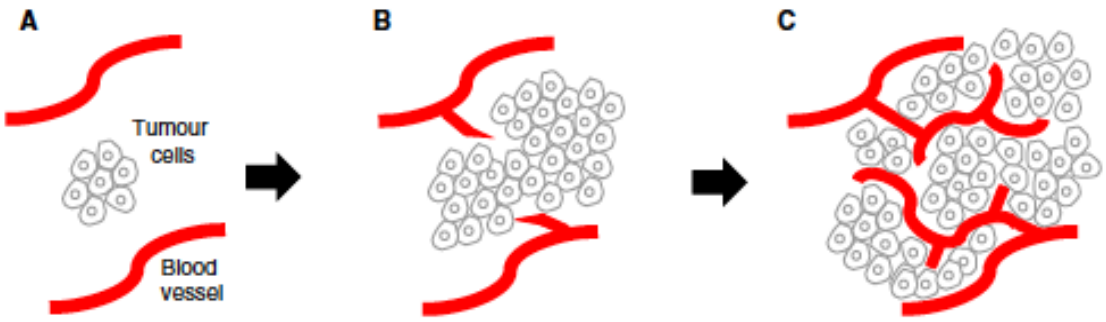


Figure 1.1 Progression of tumor vasculature. In A, small tumors can survive by leaching oxygen and nutrients from surrounding blood vessels. However, as the tumor grows (B), pro-angiogenic factors are released from the tumor to promote vessel growth from existing vasculature to the tumor. Large tumors (C) require their own vasculature to provide nutrients and to rid itself of waste (directly reproduced (with permission) from reference [26]).

Angiogenesis inhibitors block the growth of new vessels, however, they do not necessarily affect the established vasculature. These agents interact with a number of endothelial targets, which results in an antiangiogenic process. These processes can include the inhibition of endothelial cell migration or proliferation, the induction of apoptosis in endothelial cells, the inhibition of pericyte adherence to endothelial cells, as well as other processes.[20] Many angiogenic inhibitors have been developed, and several have gained FDA approval for therapeutic uses in various cancers, the most famous of these being bevacizumab (Avastin®).[25,27]

Bevacizumab is a monoclonal antibody that inhibits the VEGF signaling pathway.[27] It has demonstrated promising results in both preclinical and clinical trials, however only against certain cancer cell lines.[28] The activity of bevacizumab is significantly increased when combined with chemotherapy.[26,27] Because the vasculature

of tumors is known to be leaky with increased interstitial fluid pressure, it is believed that by suppressing VEGF signaling, the vessels go through what is known as vascular normalization, which increases the delivery of chemotherapy.[26,29,30] The presence of VEGF allows for the survival and proliferation of endothelial cells, while the overexpression of VEGF, like that observed in tumors, leads to abnormal vasculature. By down-regulating the signaling of VEGF, the vasculature actively repairs itself to resemble normal vasculature.[30] The normalized vessels are less tortuous and allow for increased tumor oxygenation and penetration of drugs, improving the effectiveness of chemotherapy.[30]

While many antiangiogenic therapies have improved the treatment outcome for different types of cancers, the overall benefit of antiangiogenic therapies is lacking. Many patients benefit from prolonged progression free survival when given antiangiogenic therapies, however the cancer tends to progress in those with heavy disease burden.[31]

Vascular Disrupting Agents

The second type of vascular targeting therapy involves the use of vascular disrupting agents (VDAs). Unlike anti-angiogenic agents, VDAs target already established tumor vasculature, shutting down the tumor blood vessels, ultimately leading to cell death.[12] VDAs can be further divided into biological agents and small molecules, however both types of therapy produce the same tumor necrosis. This necrosis is observed within 95% of the tumor, however a rim of viable cells tend to survive, due to their ability to acquire nutrients from blood vessels affiliated with normal tissue.[12,14]

The majority of small-molecule VDAs interact with tubulin as their mechanism of action, and these agents are continuing to grow as an area of research in VTA therapy.[32]

Tubulin is comprised of two tubulin monomers, the α and β subunit.[33] The heterodimers polymerize in order to form microtubules which are approximately 20-24 nm in diameter.[33]

The vast majority of tubulin destabilizing agents bind to the colchicine-binding site on β-tubulin,[32] causing microtubule depolymerization, cytoskeletal rearrangements, and activation of actin stress fibers in endothelial cells.[21] The endothelial cells lose their shape, round up, and detach, which causes resistance to blood flow (Figure 1.2).[12,34]

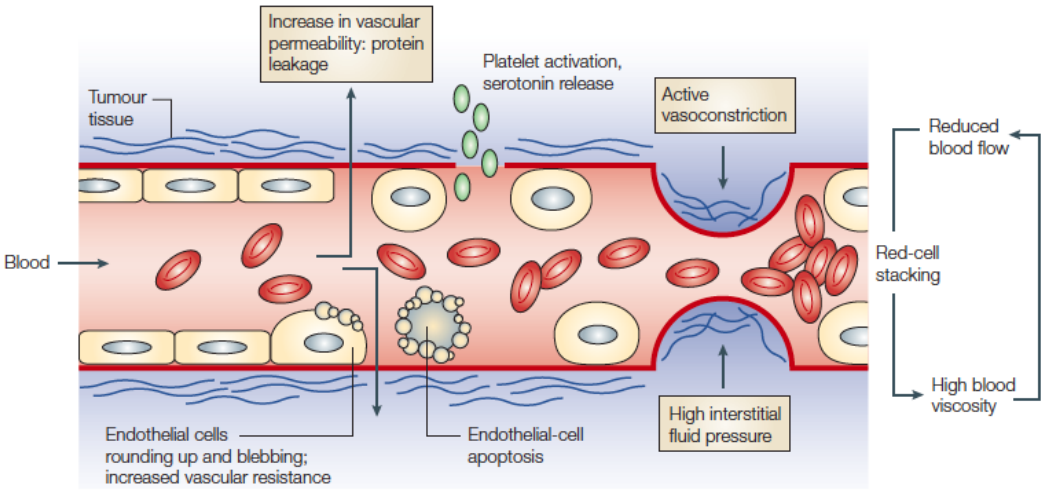


Figure 1.2. Mechanism of vascular shutdown by a tubulin disrupting agent (directly reproduced (with permission) from reference [34]).

As blood flow through the tumor is diminished, cells begin to die, ultimately leading to extensive tumor necrosis.[12,34] After administration of a VDA, blood flow stops almost entirely after about one hour, remains quite low for 24 hours, and then blood flow gradually reestablishes itself (due to the viable rim).[35] Tumors can become necrotic within 24 hours of a VDA dose,[36] and in tumors where the vasculature is vigorous and persistent, the necrosis can effect more than 90% of the tumor.[35,37]

In the 1940s, colchicine was first shown to have antitumor effects (Figure 1.3).[17,38] Colchicine is a known tubulin-binding natural product from the autumn crocus *Colchicum autumnale*[39] and has demonstrated tumor regression and tumor necrosis, which is attributed to vascular shutdown. However, colchicine is extremely toxic, and thus use of colchicine as a cancer therapeutic could not be continued.[12,39]

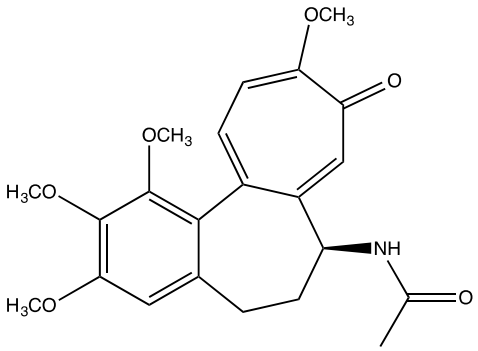


Figure 1.3. The structure of colchicine.

Combretastatin A-4 (CA4) and combretastatin A-1 (CA1) (figure 1.4) are also well known tubulin-binding agents, originally isolated by George Pettit from the African bushwillow tree *Combretum caffrum.*[40] Both CA4 and CA1 are structurally similar to colchicine and also bind to the colchicine binding site on tubulin. The phosphate prodrug combretastatin A-4P (CA4P) and combretastatin A-1P (CA1P) (Figure 1.4) were synthesized to improve the solubility of CA4 and CA1 in aqueous solutions.[41,42]

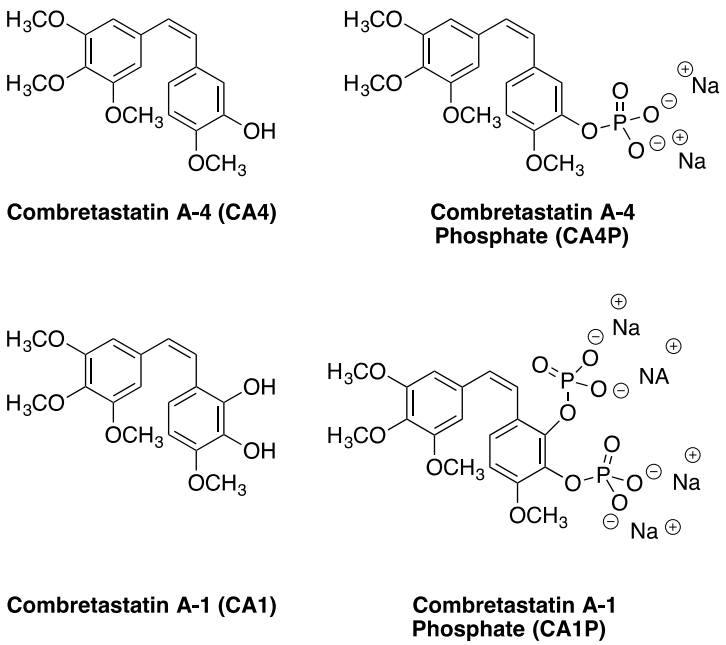


Figure 1.4: The structures of combretastatin A-4, combretastatin A-1, and their phosphate prodrugs, CA4P and CA1P.

The phosphates CA1P and CA4P are cleaved by naturally occurring phosphatase enzymes after administration, thus revealing the parent compounds CA4 and CA1 which are then able to interact with the with tubulin-microtubule protein system.[34] Unlike colchicine, CA4P shows antivascular effects well below the maximum tolerated dose, thus allowing for a wide therapeutic window.[34] Moderate doses of CA4P in animal models showed a significant decrease in blood flow to P22 rat carcinomas after 5 minutes and almost complete vascular shutdown after 20 minutes.[34,37]

Through 2014, three phase I clinical trials have been completed with CA4P as a single agent for treatment of anaplastic thyroid cancer. In all three studies, blood flow to the tumor was significantly reduced in the majority of patients.[43–45] Four phase I clinical trials as CA4P in combination with another anti-cancer agent were also studied. In these studies, CA4P was administered with carboplatin or paclitaxel, radiotherapy, with

radioimmunotherapy alone or in combination with an anti-carcinoembryonic antigen antibody, or with the known antiangiogenic agent bevacizumab.[44,46–49] In all four studies, it was reported that the combination of CA4P with another anti-cancer agent showed promising tumor responses.[44,46–49]

In addition to the phase I clinical trials, several phase II studies by the National Cancer Institute and many phase II/III trials by OXiGENE, Inc. (now Mateon Therapeutics) have been completed. The first study evaluated the efficiency of CA4P to treat anaplastic thyroid cancer as a single agent, and the second study examined CA4P in combination with doxorubicin, cisplatin, and radiation therapy.[44,50] In both studies, no significant tumor response was observed, however in the first study the disease was stabilized in roughly 25% of the patients.[44,50] In the first phase II/III study, CA4P with carboplatin and paclitaxel was compared to carboplatin and paclitaxel alone, and it was determined that CA4P increased the overall survival of the patients.[44,51] OXiGENE, Inc. has also completed a phase II study of CA4P in combination with bevacizumab against recurrent ovarian cancer as well as a phase II study (safety and efficacy) of the combination of carboplatin, paclitaxel, bevacizumab, and CA4P to treat non-small cell lung cancer, both with promising results.[52,53] They are currently in the process of studying CA4P in combination with pazopanib against advanced recurrent ovarian cancer.[53]

Efforts by the Pinney Research Group (Baylor University) focus on synthesizing potential vascular disrupting agents, using scaffolds similar to those incorporated in both colchicine and the combretastatins, which feature a trimethoxy aryl ring moiety. These scaffolds include, for example, benzo[*b*]thiophenes,[54] CA4 and CA1 analogues,[55–60]

indenes,[61] dihydronaphthalenes,[62] benzosuberenes,[62–64] indoles,[65,66] and benzocyclooctenes. Some of the most potent analogues to emerge from these investigations included OXi8006,[65,66] OXi8007,[65,66] OXi6196,[61,67] OXi6197,[67] KGP18[61,62,64,68] and its corresponding phosphate salt KGP265,[61,64] and KGP156[61,63,64,69] (figure 1.5).

All of the described compounds demonstrate inhibition of tubulin polymerization either comparable to or better than CA4, and KGP18 has also exhibited cytotoxicity to several cancer cell lines. Continued efforts in the Pinney Research Group have focused on synthesizing new analogues that could function as anticancer and vascular disrupting agents. This research will be discussed throughout chapters two and three.

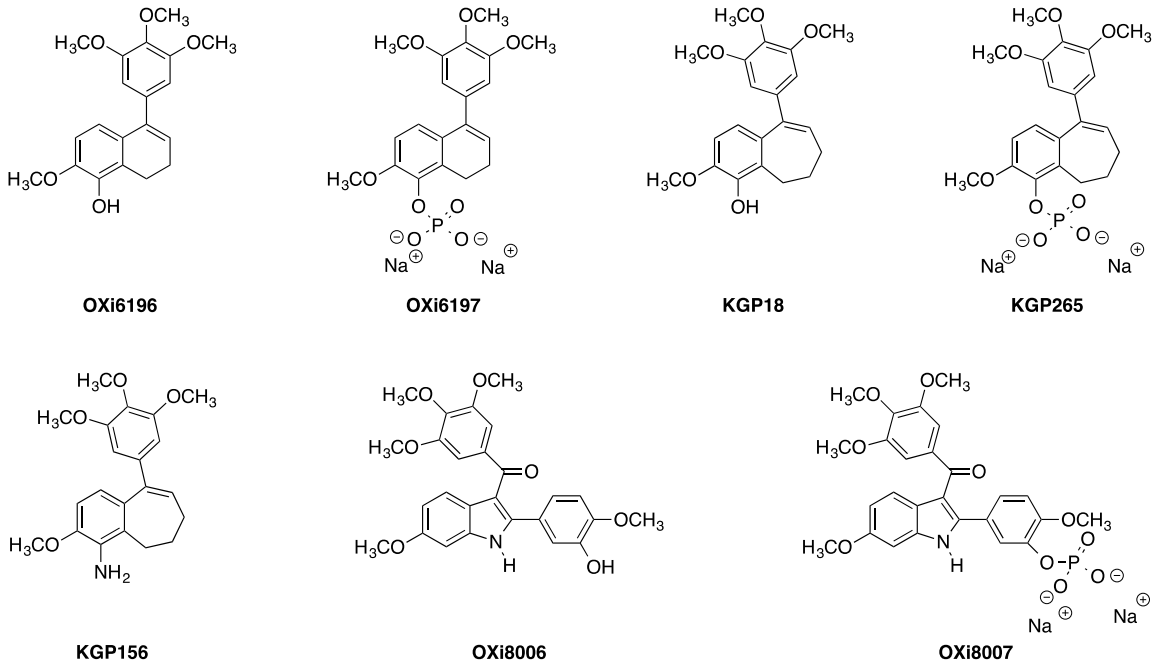


Figure 1.5. Lead compounds to emerge from the Pinney Research Group: OXi6196,[61,67] OXi6197,[67] KGP18,[61,62,64,68] KGP265,[61,64] KGP165,[61,63,64,69] OXi8006,[65,66] and OXi8007.[65,66]

Chapter two of this dissertation is a previously published manuscript. Christine A. Herdman (one of several co-authors) contributed to this manuscript through the synthesis of twelve of the twenty-two final compounds including full characterization, which included proton and carbon NMRs, HPLC, and HRMS. In addition, Christine A. Herdman contributed a significant amount to the writing and editing of the manuscript, as well as the preparation of the supporting data. Dr. Laxman Devkota, Dr. Chen-Ming Lin, and Haichan Niu synthesized the other ten compounds as well as characterized them by NMR, HPLC, and HRMS. They helped write, edit, and prepare the supporting data. Dr. Tracy Strecker from the Trawick Research Group at Baylor University performed the cytotoxicity studies. Dr. Clinton George and Dr. Rajendra Tanpure originally synthesized some of the analogues, however, they were resynthesized by Christine A. Herdman, Dr. Laxman Devkota, or Dr. Chen-Ming Lin. Dr. Ernest Hamel at the National Cancer Institute performed the inhibition of tubulin polymerization studies. Ramona Lopez and Dr. Li Liu of Dr. Ralph Mason's Research Group at the University of Texas Southwestern Medical Center (UTSW) in Dallas, Texas performed the BLI imaging studies.

Chapter three of this dissertation is a manuscript that is in the very final stages of editing prior to being submitted for publication consideration. Christine A. Herdman (one of several co-authors) contributed to this manuscript through the synthesis of all of the final compounds including full characterization, which included proton and carbon NMRs, HPLC, and HRMS. In addition, Christine A. Herdman contributed a significant amount to the writing and editing of the manuscript, as well as the preparation of the supporting data. Dr. Tracy Strecker from the Trawick Research Group at Baylor

University performed the cytotoxicity studies. Dr. Ernest Hamel at the National Cancer Institute performed the inhibition of tubulin polymerization studies. Ramona Lopez and Dr. Li Liu of Dr. Ralph Mason's Group at UT Southwestern performed the BLI imaging studies.

Carbon Nanotubes as a Drug Delivery System

Within the past twenty years,[70] carbon nanotubes (CNTs) have become an exploding field of research for their broad range of potential applications from energy storage devices to drug delivery systems.[71] CNTs can be divided into two major types: single walled nanotubes (SWCNT) and multi walled nanotubes (MWCNT) (figure 1.6). SWCNTs have an approximate diameter of 1 nm, while MWCNTs have diameters ranging from 2-50 microns.[71] In both SWCNTs and MWNCTs, the tubes are rolled up graphene sheets forming cylinders that can be grown to up to potentially 20 cm in length.[72]

Because of their strong van der Waals forces, CNTs tend to clump into bundles rather exist as individual tubes. This clumping causes the tubes to be insoluble in media and limits the tubes applications.[71] In order to overcome the strong van der Waals forces, functionalization of the CNTs such as chopping and oxidation have improved the both the biocompatibility and the solubility of the CNTs.[71,74]

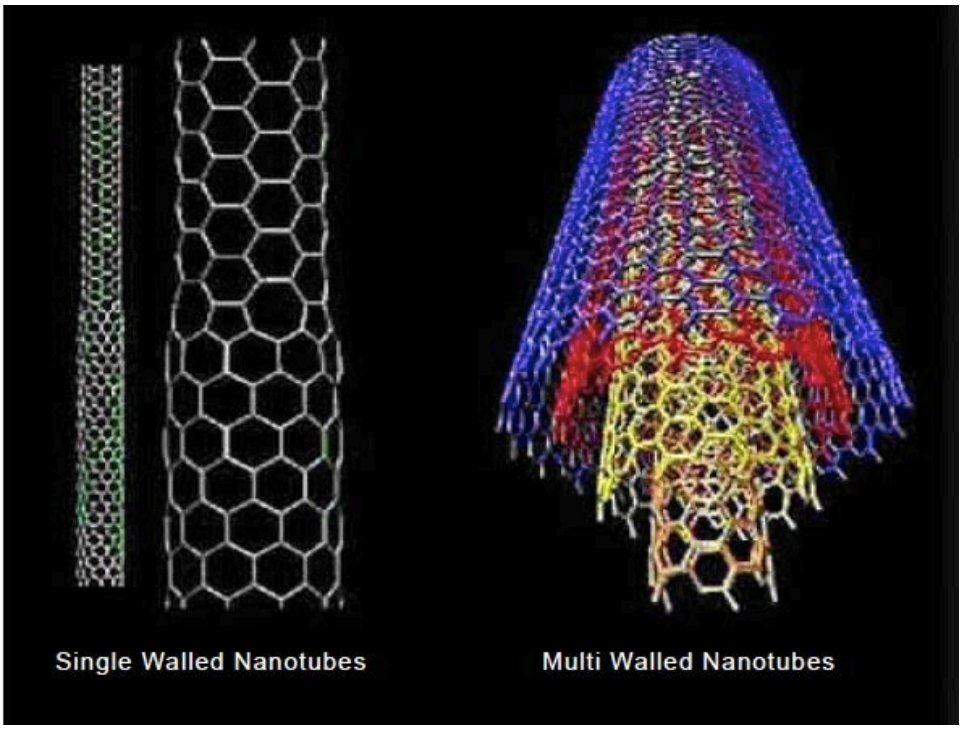


Figure 1.6. SWCNT vs. MWCNT (directly reproduced (with permission) from ref [73]).

Functionalization of the CNTs can include non-covalent functionalization at both the tips and the sidewalls, covalent functionalization, and encapsulation of bioactive molecules. The most common of the non-covalent methods is to adsorb functional moieties to the external walls through pi interactions.[74] CNTs can also be chemically modified to introduce carboxylic groups, which through subsequent amidations, esterifications, or formation of salts, various amide and ester links can be synthesized to covalently bond molecules to CNTs.[71,74–76]

More recently, CNTs have been examined as a drug delivery system. MWCNTs have become especially promising due to their complete internalization by cells as well as their almost complete loss in toxicity (especially observed in the oxidized MWCNT),[77,78] however SWCNT have also been used as promising drug delivery systems. In one study, doxorubicin, a DNA intercalating agent for the treatment of a

variety of cancers, was combined with oxidized SWCNT as well as monoclonal antibody and fluorescein.[74,79] Normally, doxorubicin (DOX) has low selectivity, inefficient distribution, and is unable to cross cellular barriers. However while complexed with the SWCNTs, the antibody recognized the tumor while the SWCNT delivered doxorubicin into the cancer cells where it was then released.[74,79] In another DOX study, DOX loaded onto pegylated SWCNT by pi-pi stacking was studied *in vivo* for its biodistribution and therapeutic efficacy. It was found that DOX-CNT had prolonged blood circulation compared to the free DOX and had a higher tumor specific uptake (figure 1.7).[74,80] Countless studies have been done utilizing similar drug delivery systems, all improving results from administration of just the parent compound, whether through improving targeting, selectivity, cytotoxicity, or prolonged drug release.[79–95]

Paclitaxel is universal frontline cancer therapy and a well-known robust antimitotic agent. However, like DOX, has poor solubility, low distribution, and lacks selectivity.[96,97] In a similar drug delivery system, MWCNTs were complexed to paclitaxel with folic acid and quantum dots to improve the delivery of paclitaxel and improve antitumor activity. Folic acid was used as the targeting ligand, which can bind to receptors on the cancer cells, delivering the paclitaxel to the tumor. The quantum dots were used as fluorescence labeling probes to track the intracellular transport. In this study, paclitaxel bound to MWCNTs improved the delivery of the anticancer drug.[96]

The biggest concern with the use of CNTs is the potential cytotoxic effects of the tubes themselves. The reported toxic side effects vary greatly depending on the study, mostly due to the size of the CNTs, metal impurities, length of the tubes, surface areas,

dispersion and aggregation, functionalization, administration, cell types, and the types of studies, making it hard to compare CNTs across the board.[98,99]

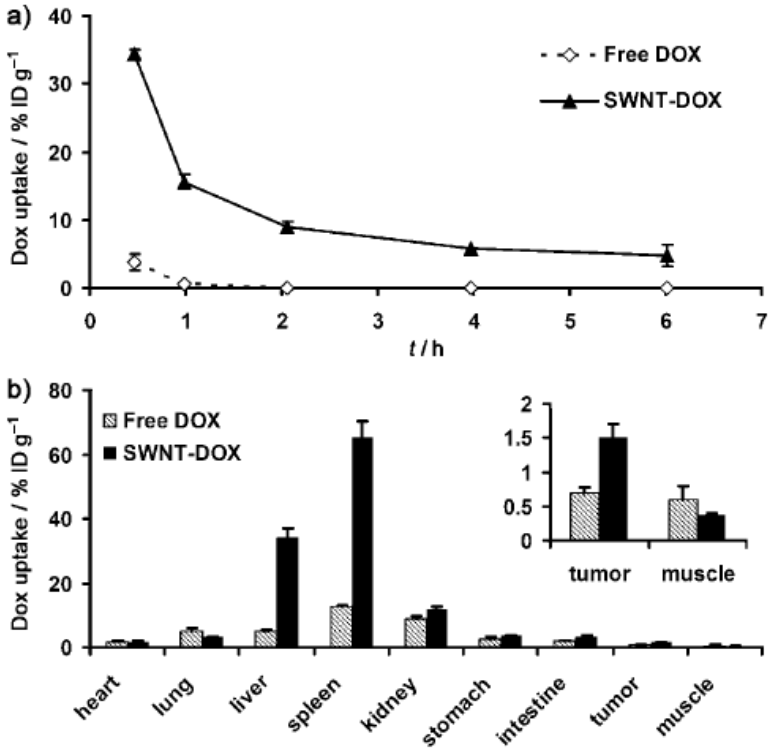


Figure 1.7. a) Concentration of free DOX vs. SWCNT-DOX at different time points after injection. b) SWNT–DOX had higher tumor-specific uptake free DOX. Biodistribution in major organs measured 6 h after injection (directly reproduced (with permission) from ref. [80]).

There are several general tendencies seen through most of these studies, however. Highly purified CNTs that carry no metal impurities from development exhibit little to no toxic behavior in human cells. Longer CNTs with larger diameters tend to have a greater toxicity, as they are not as easily cleared from cell systems.[99] By functionalizing CNTs, toxicity can all be but diminished, as functionalization has shown to improve the dispersibility and biocompability.[99–101]

Toxicity also fluctuate depending on the method of administration of the CNTs. Very few studies have looked at oral and IV administration, which would be more relevant to drug delivery, but in the few studies completed, the results found that CNTs only caused mild inflammation.[99,102] While some studies found that inhalation resulted in severe inflammation, others resulted in no tissue damage or toxicity.[99,103–105]

In a continued effort to try to selectively deliver active compounds to tumors, the Pinney Research Group has begun research into utilizing carbon nanotubes as a way to transport synthesized molecules to tumors. Preliminary work with carbon nanotubes with compounds synthesized within the Pinney Research Group will be reviewed in Chapter Four. Medical Grade Molecular Rebar (MGMR™) CNTs were used in these experiments. MGMR carbon nanotubes differ from traditional commercialized carbon nanotubes. Through their proprietary process, they are able to deliver unbundled, discrete tubes that are 99.9% pure and open on both ends.[106,107] The tubes are 800-1000 nm in length, have an outer diameter of 12-15 nm, and an inner diameter of 4-5 nm.[106,107] They can be customized to length and functionalization, depending on the application, making them optimal for synthesis and drug delivery.[108]

CHAPTER TWO

Structural Interrogation of Benzosuberene-Based Inhibitors of Tubulin Polymerization

This chapter published as: Herdman, C. A.; Devkota, L.; Lin, C. M.; Niu, H.; Strecker, T. E.; Lopez, R.; Liu, L.; George, C. S.; Tanpure, R. P.; Hamel, E.; Chaplin, D. J.; Mason, R. P.; Trawick, M. L.; Pinney, K. G. Structural Interrogation of Benzosuberene-Based Inhibitors of Tubulin Polymerization. *Bioorganic and Medicinal Chemistry* **2015**, *23*, 7497-7520.

The author Christine A. Herdman contributed to this manuscript through the synthesis of twelve of the twenty-two final compounds including full characterization, which included proton and carbon NMRs, HPLC, and HRMS. In addition, Christine A. Herdman contributed a significant amount to the writing and editing of the manuscript, as well as the preparation of the supporting data.

Abstract

The discovery of 3-methoxy-9-(3′,4′,5′-trimethoxyphenyl)-6,7-dihydro-5*H*-benzo[7]annulen-4-ol (a benzosuberene-based analogue referred to as KGP18) was originally inspired by the natural products colchicine and combretastatin A-4 (CA4). The relative structural simplicity and ease of synthesis of KGP18, coupled with its potent biological activity as an inhibitor of tubulin polymerization and its cytotoxicity (*in vitro*) against human cancer cell lines, has resulted in studies focused on new analogue design and synthesis. Our goal was to probe the relationship of structure to function in this class of anticancer agents. A series of twenty-two new benzosuberene-based analogues of KGP18 was designed and synthesized. These compounds vary in their methoxylation pattern and separately incorporate trifluoromethyl groups around the pendant aryl ring for

the evaluation of the effect of functional group modifications on the fused six-membered aromatic ring. In addition, the 8,9-saturated congener of KGP18 has been synthesized to assess the necessity of unsaturation at the carbon atom bearing the pendant aryl ring. Six of the molecules from this benzosuberene-series of compounds were active (IC_{50} <5 μM) as inhibitors of tubulin polymerization while four analogues were comparable (IC_{50} approximately 1 μM) in their tubulin inhibitory activity to CA4 and KGP18. The potency of a bis-trifluoromethyl analogue 74 and the unsaturated KGP18 derivative 73 as inhibitors of tubulin assembly along with their moderate cytotoxicity suggested the potential utility of these compounds as vascular disrupting agents (VDAs) to selectively target microvessels feeding tumors. Accordingly, water-soluble and DMSO-soluble phosphate prodrug salts of each were synthesized for preliminary *in vivo* studies to assess their potential efficacy as VDAs.

Introduction

As solid tumors grow beyond approximately 1 mm^3 in size, they require an ever larger vascular network to supply oxygen and nutrients to the cells and remove cellular waste products.[11] Since the vasculature feeding tumors tends to grow rapidly to keep up with tumor expansion, it has a tendency to vary in diameter and incorporate bulges and blind ends, rendering it somewhat fragile and chaotic in character.[21,34,109] The primitive nature of the vascular network in tumors makes it a promising target for cancer therapy.

There are two types of antivascular therapies: angiogenesis inhibiting agents (AIAs) and vascular disrupting agents (VDAs).[17,22,32] AIAs inhibit the formation of new vasculature in developing tumors, while VDAs damage the already existing tumor vasculature.[17,110,111] VDAs are further subdivided into biologics and small-molecule

anticancer agents. Inhibitors of tubulin polymerization represent one class of small-molecule VDAs. These compounds disrupt the tubulin-microtubule protein system and cause structural changes to the endothelial cells lining the vasculature, in response to cell signaling events. These morphological changes eventually lead to irreversible damage to the tumor vasculature, thus starving the tumor of nutrients and oxygen, ultimately leading to tumor necrosis.[42,112–119]

One class of VDAs interact with the colchicine site on β-tubulin near the α,β-tubulin heterodimer interface. Two of the most potent colchicine site binding VDAs are the natural products combretastatin A-4 (CA4)[40] and combretastatin A-1 (CA1)[120] originally isolated from *Combretum caffrum*, the South African bushwillow tree (Fig. 2.1). The corresponding phosphate prodrug salts combretastatin A-4P (CA4P)[36,41] and combretastatin A-1P (CA1P)[42] have improved water solubility and have been extensively evaluated in both pre-clinical experiments and clinical studies in humans.[44,121–125]

Significant structural similarities exist among the natural products colchicine, CA4, and CA1 (Fig. 2.1), including a trimethoxy phenyl ring, a separate *p*-methoxy phenyl moiety, and bridging functionality connecting the two rings at a comparable centroid to centroid distance. The relative structural simplicity of CA4 has inspired the synthesis of a vast array of synthetic analogues and derivatives in which both aryl rings and the ethylene bridge have been structurally modified.

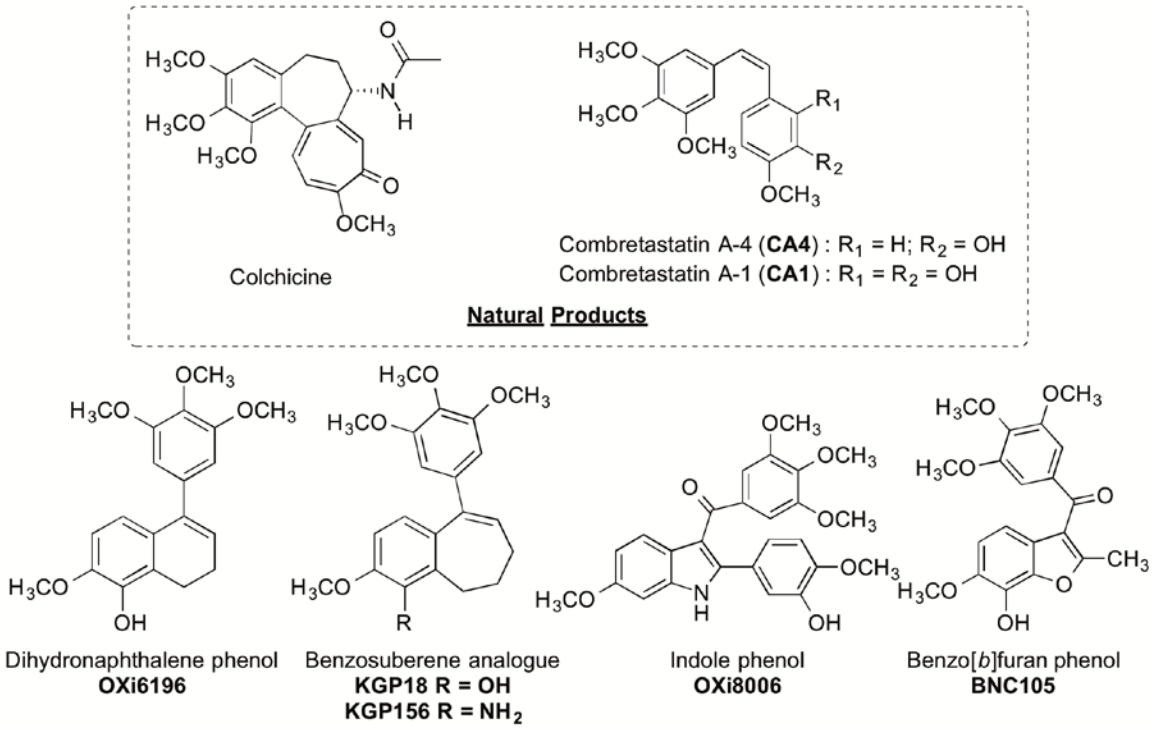


Figure 2.1. Representative small-molecule inhibitors of tubulin polymerization: colchicine, combretastatins (CA4, CA1),[40,120] dihydronaphthalene analogue (OXi6196),[61,62,67] benzosuberene analogues (KGP18 and KGP156),[62–64] indole analogue (OXi8006)[66] and benzo[*b*]furan analogue (BNC105).[126]

An early initial molecular design paradigm led us to utilize clinically relevant non-steroidal, selective estrogen receptor modulators (SERMs) and related compounds as molecular templates modified to mimic colchicine and CA4.[33,58,127] This led us to the discovery and establishment of benzo[*b*]thiophene,[54,128,129] benzofuran,[129,130] dihydronaphthalene, [61,62,67] benzosuberene,[61–64,67] and indole-based[66] analogues as potent inhibitors of tubulin polymerization (Fig. 2.1). Two benzosuberene analogues (referred to as KGP18[62,64] and its amino congener KGP156[61,63]) are especially promising anticancer agents based, in part, on their pronounced cytotoxicity against human cancer cell lines and their efficacy as inhibitors of tubulin polymerization. Our previous studies in this area[62–64] resulted in two separate synthetic strategies towards the pendant 9-aryl, fused

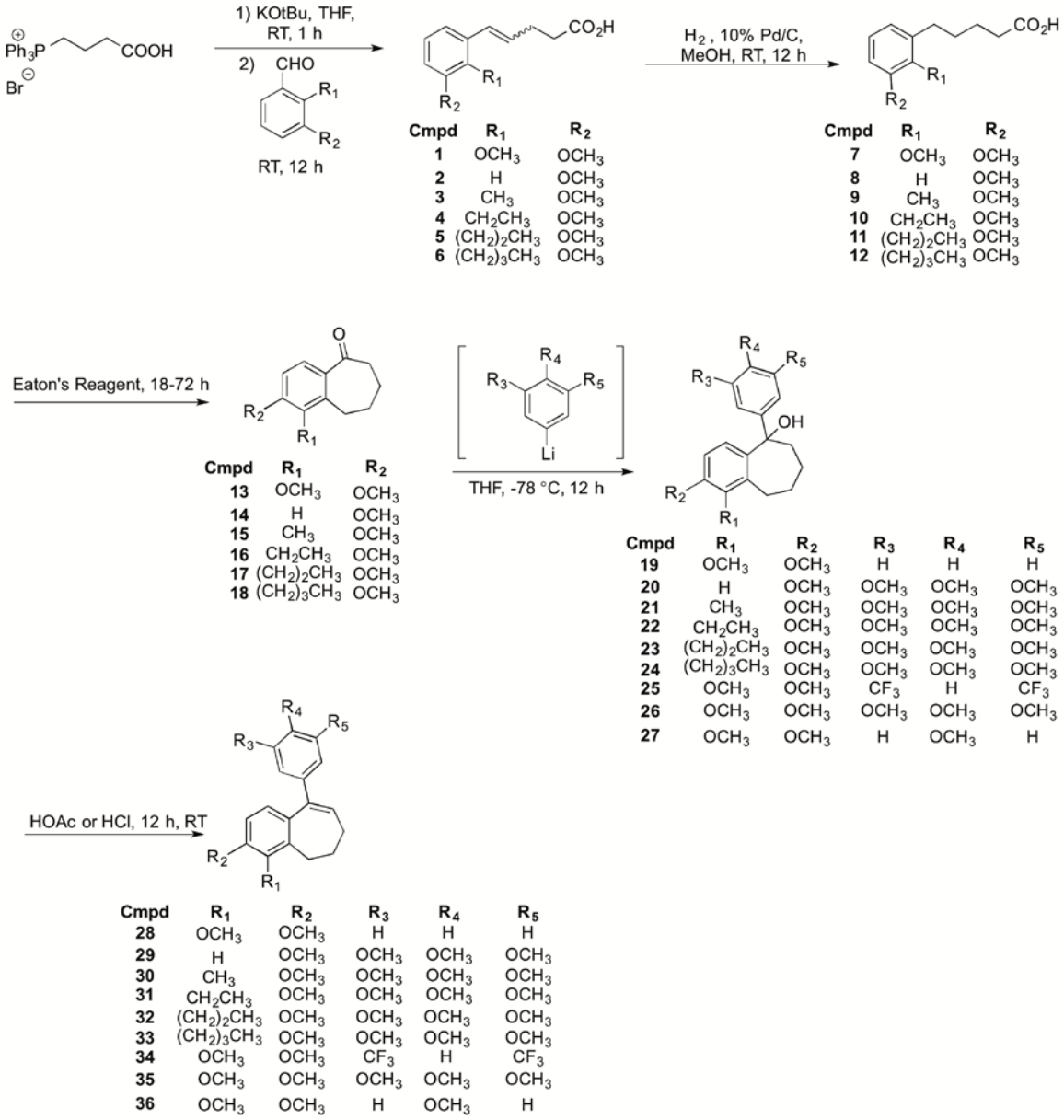
six-seven ring system present in the benzosuberene analogues KGP18 and KGP156. These studies included a variety of functional group modifications designed to probe structural diversity as it relates to biological function. Inspired by our original work with these and related benzosuberene analogues, Maderna and co-workers at Pfizer developed a separate synthetic approach utilizing a ring-closing metathesis (RCM) reaction to form the benzosuberene molecular core and a Suzuki coupling to install the pendant aryl ring.[131] They prepared and evaluated a series of structurally diverse benzosuberene analogues.[132] Using KGP18 and KGP156 as models, we developed a series of analogues to analyze further functional group modifications for their effects on cytotoxicity and inhibition of tubulin polymerization.

Results and Discussion

Synthesis

Twenty-two benzosuberene analogues (Fig. 2.2) were synthesized and evaluated for both their ability to inhibit tubulin polymerization and for their *in vitro* cytotoxicity against selected human cancer cell lines. Structural modifications to the R_1 and R_2 positions of the fused aryl ring as well as the pendant aryl ring were explored in order to evaluate their impact on tubulin dynamics and cytotoxicity. The synthesis of each benzosuberene analogue involved a Wittig olefination reaction followed by hydrogenation to afford carboxylic acid derivatives 7-12. An intramolecular Friedel-Crafts annulation facilitated by Eaton's reagent (7.7 weight percent P_2O_5 in CH_3SO_3H)[133,134] yielded benzosuberone analogues 13-18, which were subsequently

treated with requisite aryl-lithium reagents to generate tertiary alcohols 19-27, which upon dehydration afforded the final benzosuberene analogues 28-36 (Scheme 2.1).



Cmpd	R_1	R_2
1	OCH_3	OCH_3
2	H	OCH_3
3	CH_3	OCH_3
4	CH_2CH_3	OCH_3
5	$(CH_2)_2CH_3$	OCH_3
6	$(CH_2)_3CH_3$	OCH_3

Cmpd	R_1	R_2
7	OCH_3	OCH_3
8	H	OCH_3
9	CH_3	OCH_3
10	CH_2CH_3	OCH_3
11	$(CH_2)_2CH_3$	OCH_3
12	$(CH_2)_3CH_3$	OCH_3

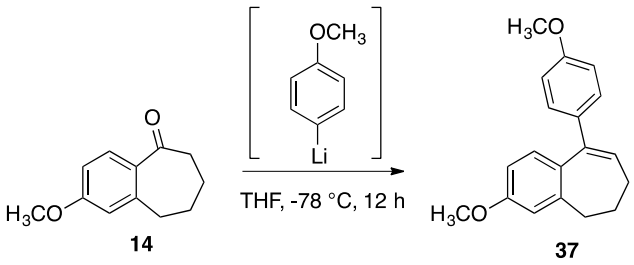
Cmpd	R_1	R_2
13	OCH_3	OCH_3
14	H	OCH_3
15	CH_3	OCH_3
16	CH_2CH_3	OCH_3
17	$(CH_2)_2CH_3$	OCH_3
18	$(CH_2)_3CH_3$	OCH_3

Cmpd	R_1	R_2	R_3	R_4	R_5
19	OCH_3	OCH_3	H	H	H
20	H	OCH_3	OCH_3	OCH_3	OCH_3
21	CH_3	OCH_3	OCH_3	OCH_3	OCH_3
22	CH_2CH_3	OCH_3	OCH_3	OCH_3	OCH_3
23	$(CH_2)_2CH_3$	OCH_3	OCH_3	OCH_3	OCH_3
24	$(CH_2)_3CH_3$	OCH_3	OCH_3	OCH_3	OCH_3
25	OCH_3	OCH_3	CF_3	H	CF_3
26	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
27	OCH_3	OCH_3	H	OCH_3	H

Cmpd	R_1	R_2	R_3	R_4	R_5
28	OCH_3	OCH_3	H	H	H
29	H	OCH_3	OCH_3	OCH_3	OCH_3
30	CH_3	OCH_3	OCH_3	OCH_3	OCH_3
31	CH_2CH_3	OCH_3	OCH_3	OCH_3	OCH_3
32	$(CH_2)_2CH_3$	OCH_3	OCH_3	OCH_3	OCH_3
33	$(CH_2)_3CH_3$	OCH_3	OCH_3	OCH_3	OCH_3
34	OCH_3	OCH_3	CF_3	H	CF_3
35	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
36	OCH_3	OCH_3	H	OCH_3	H

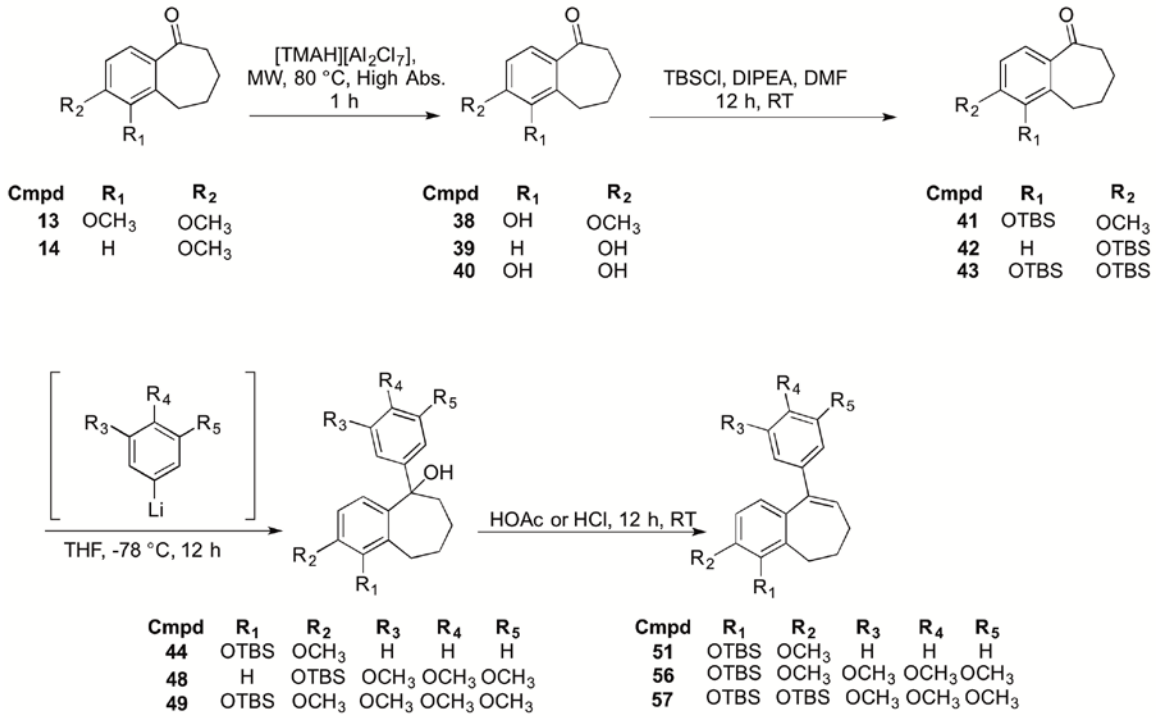
Scheme 2.1. Synthesis of benzosuberene analogues 28-36.

Concomitant elimination accompanied the addition of 4-methoxyphenyl lithium, which resulted in benzosuberene analogue 37 (Scheme 2.2).



Scheme 2.2 Synthesis of benzosuberene analogue 37.

Benzosuberone analogues 13 and 14 were also subjected to a demethylation reaction using the ionic liquid $[TMAH][Al_2Cl_7]$[135] to afford phenolic derivatives 38-40. We previously demonstrated the regioselective demethylation of compound 13.[64,135] Protection of the phenolic moieties as their corresponding *tert*-butyldimethylsilyl (TBS) ethers followed by nucleophilic addition with an appropriately substituted lithiated aryl ring produced tertiary alcohols 44-50, which were subsequently dehydrated to yield TBS protected benzosuberene analogues 51-57 (Scheme 2.3). Removal of the TBS protecting groups upon treatment with TBAF resulted in benzosuberene analogues 64-70 (Scheme 2.4). In our hands, desired benzosuberene analogues 61, 62, and 71 were not accessible by the methodology involving aryl lithium addition, instead yielding recovered starting material. It is possible that competing enolate formation was faster than 1,2-carbonyl addition in these cases. Alternatively, the synthesis of analogues 61, 62, and 71 was accomplished using a Suzuki coupling to attach the pendant aryl ring, similar to the methodology of Maderna and co-workers.[131] Vinyl triflates 58, 59, and 60 were reacted with the corresponding boronic acids to generate target benzosuberene analogues 61 and 62 and TBS protected compound 63, which, after deprotection with TBAF, afforded benzosuberene analogue 71 (Scheme 2.4).

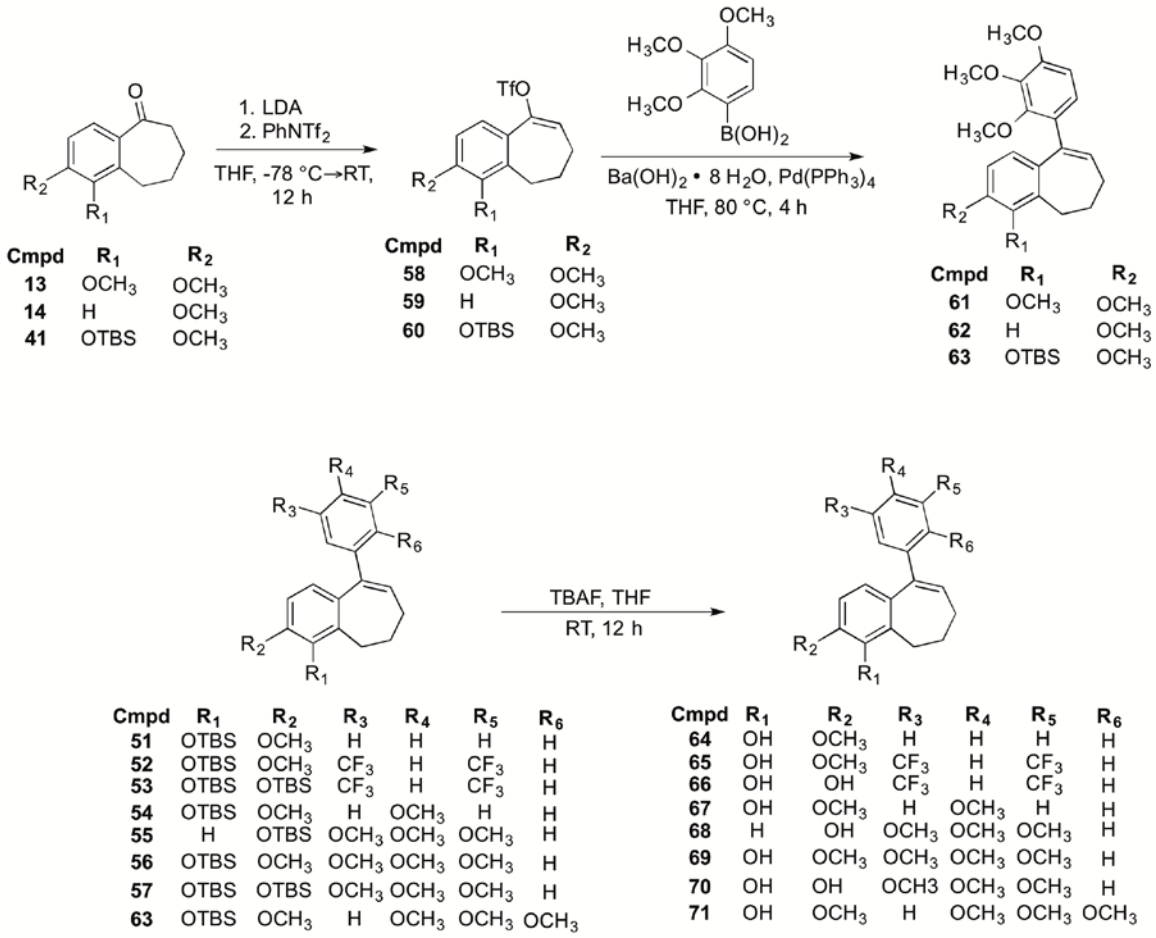


Scheme 2.3. Synthesis of TBS protected analogues 51-57.

The double bond of benzosuberene 69 (KGP18) was reduced to afford benzosuberane analogue 72, which was subsequently converted to its corresponding phosphate salt 73. Benzosuberene analogue 65 was also converted to its phosphate prodrug salt 74 under analogous reaction conditions (Scheme 2.5).

Biological Evaluation

Each of the twenty-two analogues was evaluated biologically for its ability to inhibit tubulin polymerization (cell free assay), as well as its cytotoxicity against human cancer cell lines [SK-OV-3 (ovarian), NCI-H460 (lung), and DU-145 (prostate)]. It is important to note that these two assays, while providing complementary structure activity relationship (SAR) information, represent very different approaches to analyzing the biological activity of the target benzosuberene analogues. It is common for biologically



Cmpd	R_1	R_2
13	OCH_3	OCH_3
14	H	OCH_3
41	OTBS	OCH_3

Cmpd	R_1	R_2
58	OCH_3	OCH_3
59	H	OCH_3
60	OTBS	OCH_3

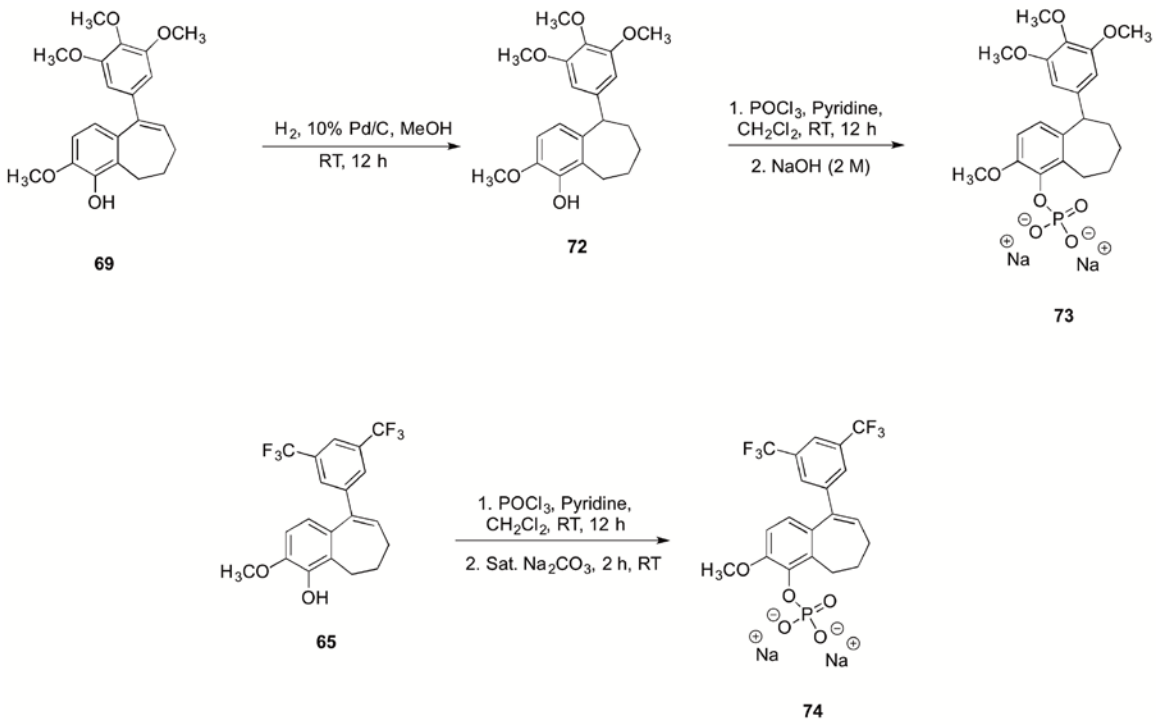
Cmpd	R_1	R_2
61	OCH_3	OCH_3
62	H	OCH_3
63	OTBS	OCH_3

Cmpd	R_1	R_2	R_3	R_4	R_5	R_6
51	OTBS	OCH_3	H	H	H	H
52	OTBS	OCH_3	CF_3	H	CF_3	H
53	OTBS	OTBS	CF_3	H	CF_3	H
54	OTBS	OCH_3	H	OCH_3	H	H
55	H	OTBS	OCH_3	OCH_3	OCH_3	H
56	OTBS	OCH_3	OCH_3	OCH_3	OCH_3	H
57	OTBS	OTBS	OCH_3	OCH_3	OCH_3	H
63	OTBS	OCH_3	H	OCH_3	OCH_3	OCH_3

Cmpd	R_1	R_2	R_3	R_4	R_5	R_6
64	OH	OCH_3	H	H	H	H
65	OH	OCH_3	CF_3	H	CF_3	H
66	OH	OH	CF_3	H	CF_3	H
67	OH	OCH_3	H	OCH_3	H	H
68	H	OH	OCH_3	OCH_3	OCH_3	H
69	OH	OCH_3	OCH_3	OCH_3	OCH_3	H
70	OH	OH	OCH3	OCH_3	OCH_3	H
71	OH	OCH_3	H	OCH_3	OCH_3	OCH_3

Scheme 2.4. Synthesis of benzosuberene analogues 61, 62, and 64-71.

active, small-molecule inhibitors of tubulin polymerization to demonstrate IC_{50} values in the low micromolar range (in this type of cell free assay) while demonstrating sub-micromolar to nanomolar GI_{50} values in terms of cytotoxicity against human cancer cell lines. This activity differential may be due, in part, to requisite stoichiometry differences in regard to the number of molecules of inhibitor bound to tubulin in a cell-based assay versus a pure protein assay, as well as practical assay limits (in the low micromolar range) in the pure protein assay (no cells and no additional microtubule-associated proteins).



Scheme 2.5. Synthesis of reduced benzosuberane analogue 72 and phosphate salts 73 and 74.

Inhibitor generated interference within the dynamic that is inherent to the tubulin-microtubule protein system in cells may influence signal transduction leading to an amplification of activity in cell-based assays.[66,136] An initial structure-activity analysis for the 22 compounds for which we obtained biological data (Table 2.1), is perhaps best accomplished by focusing on the studies on the presumptive intracellular target, tubulin. The most extensive data were obtained for effects on tubulin assembly, in part because we have rarely observed substantial inhibition of colchicine binding (> 50%, with 5 μM inhibitor) if the assembly IC_{50} is > 3 μM.

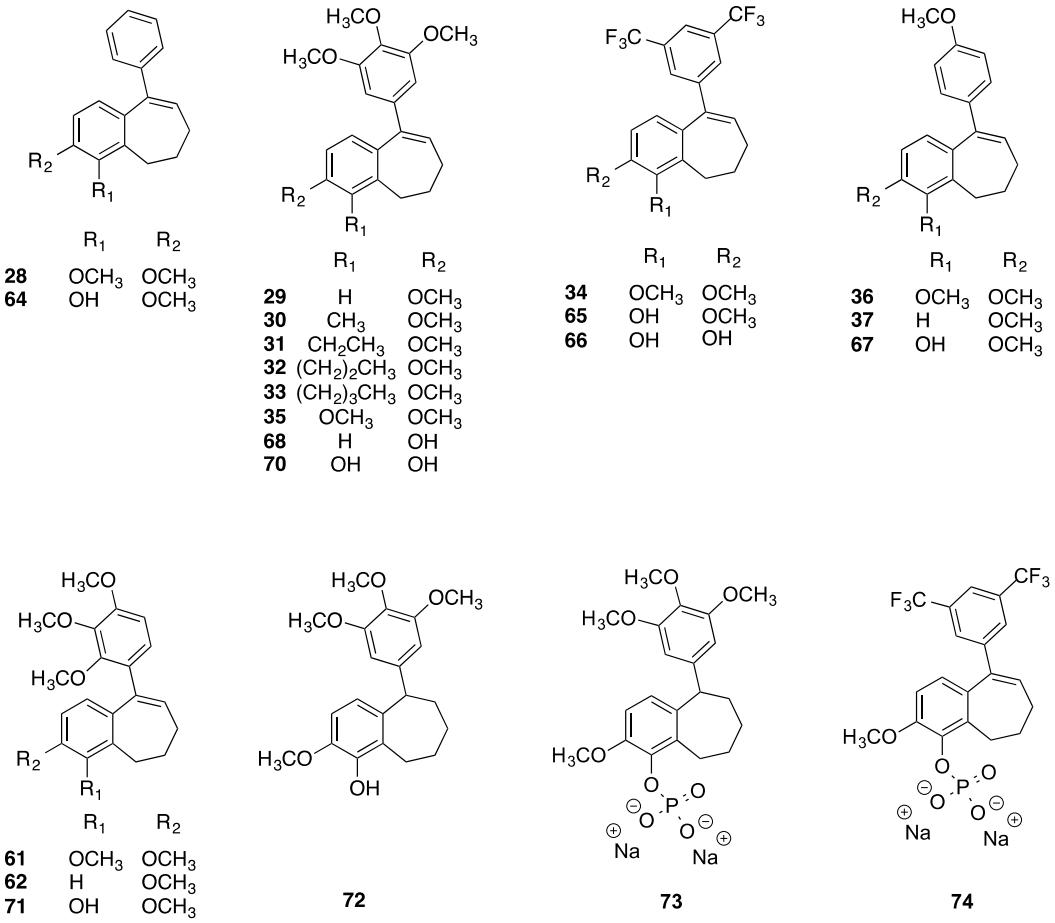


Figure 2.2. Compilation of synthesized benzosuberene analogues.

Table 2.1. Inhibition of tubulin polymerization, percent inhibition of colchicine binding, and cytotoxicity of the target benzosuberene analogues

Compound	Inhibition of tubulin polymerization IC_{50} (μM) ± SD	% Inhibition of colchicine binding ± SD	GI_{50} (μM) SRB assay[a]		
			SK-OV-3	NCI-H460	DU-145
CA4	1.0[b]	84 ± 3 (1 μM), 98 ± 0.007 (5 μM)	0.00455	0.00223[c]	0.00327[c]
CA4P	>40[b]	nr	0.00119	0.00194[c]	0.00323[c]
KGP18	1.4[d]	nr	0.0000543[e]	0.0000418[e]	0.0000249[e]
28	>20	nr	32.7	37.5	89.3

29	1.0 ± 0.02	37 ± 5 (1 μM), 72 ± 0.8 (5 μM)	0.0516	0.0527	0.0619
30	1.6 ± 0.2	65 ± 0.6 (5 μM)	0.330	0.422	0.644
31	>20	nr	0.568	0.763	1.51
32	>20	nr	2.96	3.32	6.03
33	>20	nr	11.5	16.1	12.2
34	>20	nr	31.1	25.5	52.1
35	3.1 ± 0.03	30 ± 4 (5 μM), 56 ± 4 (50 μM)	0.277	0.593	0.708
36	>20	nr	20.5	33.4	48.3
37	>20	nr	40.7	57.7	68.7
61	>20	nr	6.96	10.5	26.2
62	1.2 ± 0.007	36 ± 5 (1 μM), 69 ± 3 (5 μM)	0.0432	0.120	0.0562
64	>20	nr	0.557	0.652	4.40
65	3.8 ± 0.3	8.5 ± 4 (5 μM), 37 ± 5 (50 μM)	4.81	4.39	4.92
66	>20	nr	16.8	25.0	21.8
67	7.4 ± 0.06	nr	18.4	10.6	8.59
68	2.7 ± 0.1	27 ± 5 (5 μM)	0.527	0.647	1.02
70	7.7 ± 0.2	nr	0.346	0.691	1.53
71	11 ± 0.4	nr	3.53	4.24	7.54
72	0.70 ± 0.1	21 ± 0.9 (1 μM), 67 ± 0.6 (5 μM)	0.408	0.141	0.570
73	>20	nr	0.357	0.145	0.753
74	>20	nr	17.2	16.3	17.5

[a] Average of n ≥ 3 independent determinations
[b] Data from ref. [137]
[c] For additional data, see ref. [137]
[d] Data from ref. [64]
[e] For additional data, see ref. [62]
nr = not reported

Ten of the evaluated compounds were active inhibitors of tubulin polymerization (IC_{50} values < 20 μM). Structural variability was tolerated (in terms of retained tubulin inhibitory activity) by the incorporation of several groups (H, OCH_3, CH_3) at R_1 while the pendant 3,4,5-trimethoxyaryl motif reminiscent of CA4 and colchicine was maintained. This mirrored our previous observations with other functional groups [OH (parent KGP18), NH_2 (parent KGP156), Br, Cl] situated at R_1 in this same molecular template. Replacement of the R_2 methoxy group with a hydroxyl group, while either maintaining R_1 = OH or modifying R_1 to be a hydrogen atom, led to analogues (70 and 68, respectively) that were also active inhibitors of tubulin polymerization. Variation of the methoxylation pattern (2,3,4-trimethoxy) within the pendant aryl ring also led to active inhibitors of tubulin polymerization when R_1 was H or OH (62 and 71, respectively). Replacement of the trimethoxyaryl ring with either a 3,5-bis-trifluoromethyl aryl ring or a 4-methoxyaryl ring with maintenance of R_1 = OH (compounds 65 and 67, respectively) resulted in benzosuberene analogues that were still inhibitory against tubulin polymerization. Intriguingly, the double-bond reduced analogue 72 was the most active inhibitor of tubulin assembly within the entire series of benzosuberene analogues analyzed. Loss of inhibition of tubulin polymerization was observed when the trimethoxy aryl substituent was replaced with an unsubstituted phenyl ring (28 and 64). While the R_1 methyl analogue 30 functioned as an inhibitor of tubulin polymerization, extension of the alkyl chain to ethyl, propyl, and butyl resulted in the loss of inhibitory activity (as observed with compounds 31, 32, and 33). While ten of the analogues inhibited tubulin assembly, only 29, 30, 62, and 72 demonstrated inhibition values (1.0 μM, 1.6 μM, 1.2

μM, and 0.70 μM, respectively) comparable to those observed with lead compounds KGP18 and CA4.

Molecular docking studies were carried out on several analogues that were active inhibitors of tubulin polymerization (compounds 29, 62 and 72), and compared to compound **33** with an IC_{50} > 20 μM (inactive) in this assay. Docking placed the trimethoxyphenyl ring of all three active analogues in a similar position to that of the trimethoxyphenyl moiety of *N*-deacetyl-*N*-(2-mercaptoacetyl)-colchicine in the structure co-crystallized with tubulin. In contrast, modeling placed multiple top conformations of compound 33 with its trimethoxyphenyl ring outside of this pocket (see Supplementary Data).

Among the twenty-two benzosuberene analogues investigated in this study, the most cytotoxic agents were compounds 29 and 62 (for example, GI_{50} = 0.0516 μM and 0.0432 μM, respectively, against the SK-OV-3 cell line). Both of these compounds bear trimethoxy aryl groups, but, unlike KGP18, they each contain a hydrogen atom at the R_1 position, rather than a hydroxyl group. The cytotoxicity, inhibition of colchicine binding, and the inhibition of tubulin polymerization correlate well for these compounds. Compounds 31 and 64 were not inhibitors of tubulin polymerization (IC_{50} > 20 μM), but they were found to be cytotoxic (GI_{50} < 1 μM) against two of the three cell lines utilized in this study. Although these compounds are structurally similar to others in this library, they may have an alternate mechanism of inhibiting cell growth. We note the strong antitubulin activity of compound 72, in which the double bond in the seven-membered fused ring was reduced, although this modification appears to be associated with reduced cytotoxicity. This reduction in cytotoxicity (for compound 72) correlates with a decrease

in the percent inhibition of colchicine binding (at 1 μM) relative to compounds 29 and 62, although all three compounds (29, 62, and 72) are comparable in the colchicine binding assay at 5 μM.

Two compounds, 65 and the strong tubulin inhibitor 72, were selected for conversion to prodrugs (74 and 73, respectively) by phosphorylation, in order to improve water-solubility and potentially bioavailability. As with CA4 (phosphorylated to CA4P), this synthetic transformation eliminated ($IC_{50} > 20$ μM) the ability to inhibit tubulin polymerization (cell-free assay), while the cytotoxicity was maintained presumably due to phosphatase activity present in the cell-based assay.

We previously demonstrated that dynamic bioluminescence imaging (BLI) provides a facile indication of vascular disruption in luciferase transfected tumors.[32,138,139] Analysis is noninvasive, and each tumor acts as its own control. Specifically, the substrate luciferin normally diffuses into the blood stream following subcutaneous injection, and, when it reaches a tumor, light emission occurs. Vascular disruption impairs delivery, and reduced light emission is observed. Analogue 73 showed no obvious acute toxicity over 24 h to breast tumor bearing SCID mice following IP administration of saline solutions delivering doses up to 40 mg/kg. Doses of 20 or 30 mg/kg showed a similar modest reduction of BLI signal 4 h after administration. At 40 mg/kg there was approximately a 50% reduction of the emitted signal. In each case, the signal generally returned to its original level within 24 h. By comparison, saline controls showed a highly reproducible signal, and CA4P (a well-established VDA in clinical development) showed greater than 90% reduction at 4 h, which remained depressed (>75%, after 24 h). These data are presented in Figures 3 and 4. Patterns of light emission

are presented in Figure 5. The signal intensity for saline emphasizes reproducibility of signal (hence assessment of vasculature) for repeat measurements. As reported previously, CA4P[32,138,139] caused significant vascular impairment at 4 h. Compound 73 had little effect at 20 or 30 mg/kg, but caused about 50% reduction in light emission at 40 mg/kg. While these initial, preliminary studies at 20, 30, and 40 mg/kg suggested a potential VDA mechanism for analogue 73, future dose escalation studies will be necessary to establish a maximum tolerated dose (MTD) in this mouse model and to confirm the extent to which analogue 73 is capable of disrupting tumor-associated vasculature.

Conclusion

In summary, the results of these experiments have expanded our SAR knowledge regarding effects that modifications of the benzosuberene skeleton play in relationship to cytotoxicity and antitubulin activity. The most promising analogues evaluated in this study demonstrated inhibition of tubulin assembly comparable to CA4 and KGP18, but these compounds had reduced inhibitory effects on colchicine binding and on cell growth. Preliminary *in vivo* BLI evaluation of the VDA capability of benzosuberene analogue **73** against an MDA-MB-231-luc xenograft (in a SCID mouse model) showed efficacy, but, at the doses examined, the effect of 73 was less pronounced than that obtained with an established VDA (in this case, CA4P) currently in clinical development. Future studies with compound 73 and related benzosuberene analogues involving dose escalation and other tumor models to assess vascular damage appear warranted.

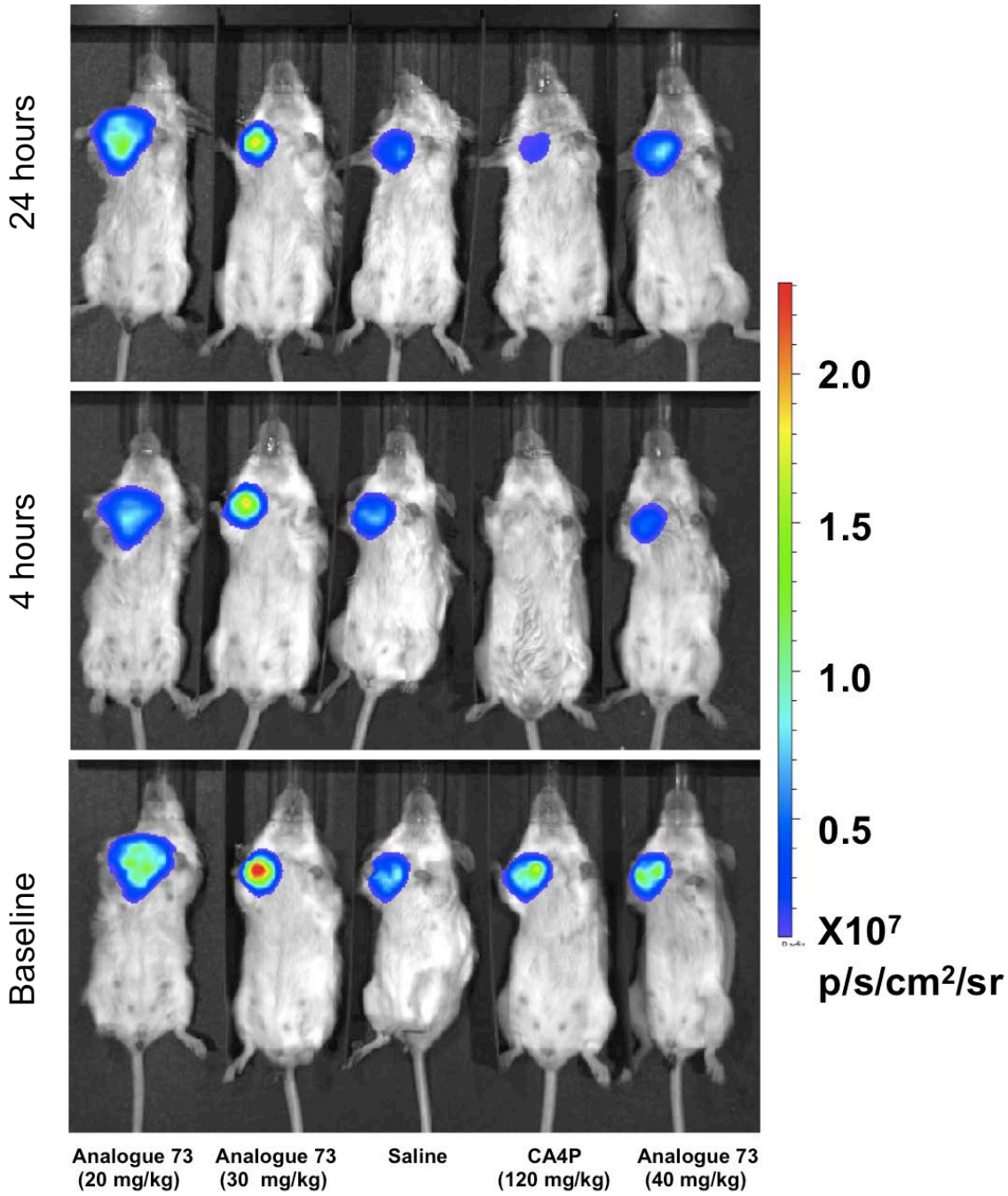


Figure 2.3. BLI assessment of vascular disruption caused in MDA-MB-231-luc orthotopic human tumor xenografts by analogue 73. Dynamic BLI was performed at baseline (bottom row), 4 h after VDA administration (middle), and after 24 h (top), and images are shown for representative mice 17 min after administering fresh luciferin substrate on each occasion to each animal. Images show bioluminescent signal intensity overlaid on photographs of the mice. Analogue 73 was administered at 20, 30 or 40 mg/kg IP in saline, and additional mice received saline control or CA4P (120 mg/kg) for comparison. Analogue 73 caused a reduced signal at all doses at 4 h with substantial recovery by 24 h.

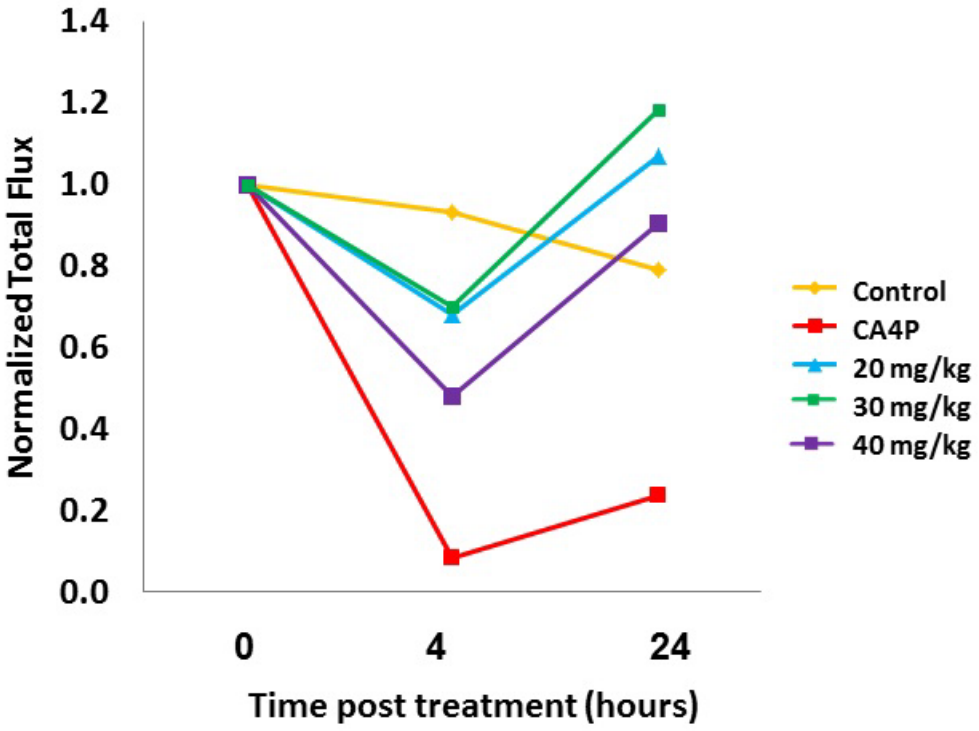


Figure 2.4. Vascular disruption caused by analogue 73. Relative signal intensity is plotted for the mice shown in Fig. 2.3.

Experimental Section

Chemistry

General Materials and Methods. Tetrahydrofuran (THF), dichloromethane, ethanol, methanol, dimethylformamide (DMF), and acetonitrile were used in their anhydrous forms. Reactions were performed under nitrogen gas, unless otherwise specified. Thin-layer chromatography (TLC) plates (precoated glass plates with silica gel 60 F254, 0.25 mm thickness) were used to monitor reactions. Purification of intermediates and products was carried out with a Biotage Isolera or Teledyne Combiflash flash purification system using silica gel (200−400 mesh, 60 Å) or RP-18

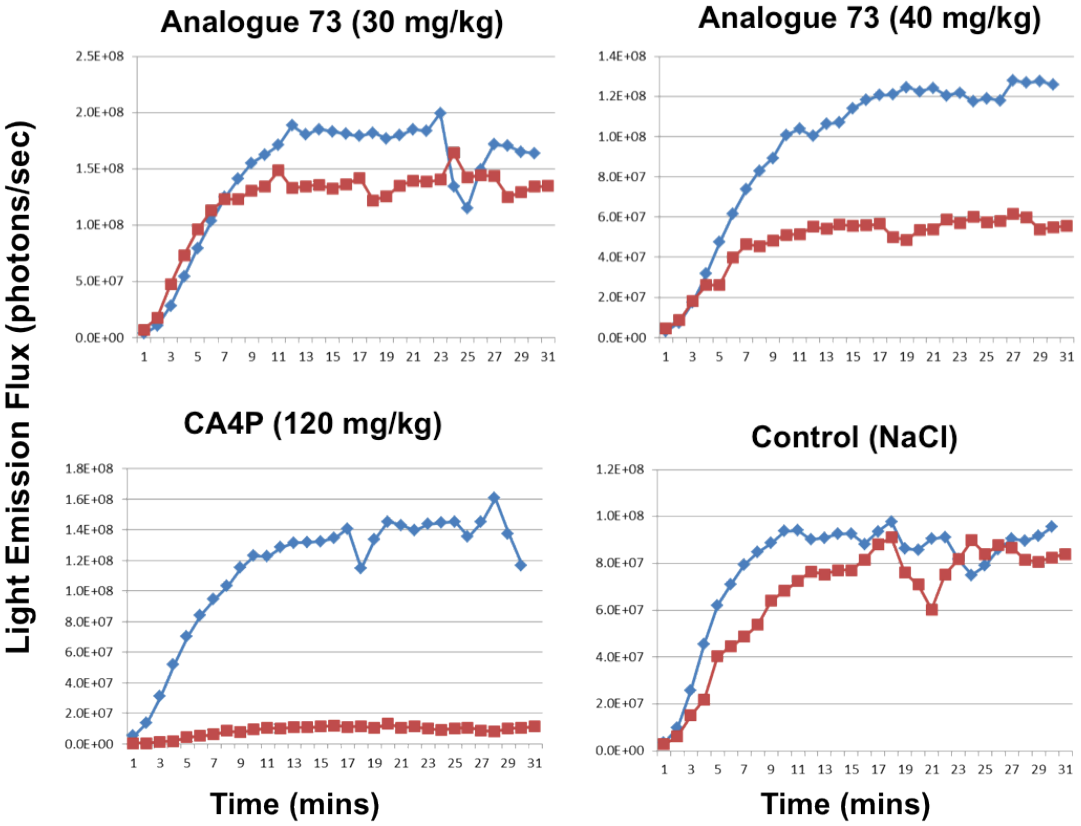


Figure 2.5 Dynamic bioluminescence with respect to vascular disruption. Graphs show evolution of light emission from individual MDA-MB-231-*luc* tumors following administration of luciferin substrate subcutaneously in the fore back region of each mouse at baseline (blue) and 4 h after administration of agent (red). Analogue 73 had a modest effect at 30 mg/kg and a greater effect at 40 mg/kg. By comparison control saline showed a high degree of reproducibility and CA4P showed >90% reduction in light emission.

pre-packed columns or manually in glass columns. Intermediates and products synthesized were characterized on the basis of their ^{1}H NMR (500 or 300 MHz), ^{13}C NMR (125 or 75 MHz), ^{19}F (470 MHz) and ^{31}P NMR (200 or 120 MHz) spectroscopic data using a Varian VNMRS 500 MHz or a Bruker DPX 300 MHz instrument. Spectra were recorded in $CDCl_3$, D_2O, $(CD_3)_2CO$, or CD_3OD. All chemical shifts are expressed in ppm (δ), and peak patterns are reported as broad (br), singlet (s), doublet (d), triplet (t),

quartet (q), pentet (p), sextet (sext), septet (sept), double doublet (dd), double double doublet (ddd), and multiplet (m).

Purity of the final compounds was further analyzed at 25 °C using an Agilent 1200 HPLC system with a diode-array detector (λ = 190−400 nm), a Zorbax XDB-C18 HPLC column (4.6 mm Å~ 150 mm, 5 μm), and a Zorbax reliance cartridge guard-column; Method A: solvent A, acetonitrile, solvent B, 0.1% TFA in H_2O; or Method B: solvent A, acetonitrile, solvent B, H_2O; gradient, 10% A/90% B to 100% A/0% B over 0 to 40 min; post-time 10 min; flow rate 1.0 mL/min; injection volume 20 μL; monitored at wavelengths of 210, 230, 254, 280, and 320 nm. Mass spectrometry was carried out under positive or negative ESI (electrospray ionization) using a Thermo Scientific LTQ OrbitrapDiscovery instrument.

5-(2´,3´-Dimethoxyphenyl)pent-4-enoic acid (1).[61,64] To dissolved 3-(carboxypropyl)triphenyl phosphonium bromide (13.04 g, 30.39 mmol) in THF (500 mL) was added potassium *tert*-butoxide (7.43 g, 66.2 mmol), and the reaction mixture was stirred at room temperature for 1 h. 2,3-Dimethoxybenzaldehyde (5.02 g, 30.1 mmol) dissolved in THF (100 mL) was added, and the mixture was stirred at room temperature for 12 h. The THF was removed under reduced pressure, and the resulting material was quenched with 2 M HCl (75 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were evaporated under reduced pressure, and the crude reaction product was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280

nm] to afford compound 1 (5.39 g, 21.5 mmol, 72%) as a yellow oil. NMR characterization was conducted after the next step.

5-(2´,3´-Dimethoxyphenyl)pentanoic acid (7).[61,64,140] To dissolved carboxylic acid **1** (5.39 g, 21.5 mmol) in methanol (100 mL) was added 10% palladium on carbon (0.43 g) and hydrogen gas. The reaction mixture was stirred at room temperature for 12 h and filtered through Celite®, and the Celite® was washed with EtOAc (3 x 50 mL). The combined organic phase (MeOH and EtOAc) was evaporated under reduced pressure. The resulting organic material was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford carboxylic acid 7 (4.45 g, 18.7 mmol, 82%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.67 (1H, s), 6.99 (1H, t, *J* = 8 Hz), 6.78 (2H, m), 3.86 (3H, s), 3.84 (3H, s), 2.68 (2H, t, *J* = 8 Hz), 2.41 (2H, t, *J* = 7.5 Hz), 1.70 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 152.7, 147.1, 135.8, 123.8, 121.9, 110.2, 60.6, 55.6, 34.0, 30.8, 29.4, 24.5.

1,2-Dimethoxy-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-one (13).*[61,64,141] To carboxylic acid **7** (3.55 g, 14.9 mmol) was added Eaton's reagent (29 mL, 3 g per mmol of compound **7**), and the reaction mixture was stirred at room temperature for 12 h. It was then poured over ice and neutralized with sodium bicarbonate. The reaction mixture was extracted with EtOAc (3 x 50 mL), and the combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The reaction product was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc;

solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford benzosuberone 13 (2.43 g, 11.0 mmol, 74%) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (1H, d, *J* = 8.5 Hz), 6.67 (1H, d, *J* = 9 Hz), 3.72 (3H, s), 3.62 (3H, s), 2.83 (2H, t, *J* = 6 Hz), 2.50 (2H, t, *J* = 6 Hz), 1.66 (2H, p, *J* = 6.5 Hz), 1.59 (2H, p, *J* = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 155.9, 145.8, 135.5, 132.6, 125.2, 109.6, 60.8, 55.6, 40.4, 24.7, 23.0, 20.7.

[TMAH][Al_2Cl_7].[135] To dry dichloromethane (150 mL) was added $AlCl_3$ (19.84 g, 149.1 mmol), and the mixture was stirred and cooled to 0 °C. Trimethylamine hydrochloride (7.11 g, 74.5 mmol) was added, and the reaction mixture was allowed to stir for 2 h at room temperature. The resulting liquid was stored at room temperature under nitrogen.

*1-Hydroxy-2-dimethoxy-6,7,8,9-tetrahydro-*5H*-benzo[7]annulen-5-one (38).*[61,64,142] To benzosuberone 13 (1.01 g, 4.54 mmol) in a 20 mL microwave vial was added [TMAH][Al_2Cl_7] (18.3 mL, 9.08 mmol), and the mixture was subjected to microwave irradiation for 1 h at 80 °C on high absorbance. The solution was then poured into water (50 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford benzosuberone 38 (0.61 g, 3.0 mmol, 65%) as a yellow oil. ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.24 (1H, d, *J* = 8.5 Hz), 6.67 (1H, d, *J* = 9 Hz), 6.26 (1H, s), 3.78 (3H, s), 2.93 (2H, t, *J* = 5.5 Hz), 2.61 (2H, t, *J* = 6.5 Hz), 1.71 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0, 149.5, 142.5, 133.0, 127.8, 120.7, 107.9, 55.9, 40.6, 24.4, 23.0, 21.2.

*1-((*tert-*Butyldimethylsilyl)oxy)-2-dimethoxy-6,7,8,9-tetrahydro*-5H-*benzo[7]annulen-5-one (41).*[61,64] Benzosuberone 38 (2.16 g, 10.5 mmol) was dissolved in dimethylformamide (50 mL). TBSCl (3.16 g, 21.0 mmol) and DIPEA (5.50 mL, 31.6 mmol) were added, and the solution was stirred for 12 h at room temperature. The reaction mixture was washed with water and extracted with EtOAc (5 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford TBS protected analogue 41 (2.37 g, 7.38 mmol, 71%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, d, *J* = 8.5 Hz), 6.62 (1H, d, *J* = 9 Hz), 3.67 (3H, s), 2.88 (2H, t, *J* = 5.5 Hz), 2.53 (2H, t, *J* = 5.5 Hz), 1.64 (4H, m), 0.89 (9H, s), 0.06 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 152.9, 141.6, 132.9, 132.7, 122.2, 108.6, 54.6, 40.5, 26.0, 24.6, 23.8, 21.1, 18.8, -4.0.

*4-((*tert-*Butyldimethylsilyl)oxy)-3-methoxy-6,7-dihydro*-5H-*benzo[7]annulen-9-yl trifluoromethanesulfonate (60).* To an oven-dried flask, diisopropylamine (0.18 mL, 1.3 mmol) dissolved in THF (50 mL) was added and cooled to -78 °C, and *n*-BuLi (0.51 mL, 1.3 mmol) was added. The reaction mixture was stirred for 15 min. TBS protected 41

(0.37 g, 1.2 mmol) dissolved in THF (10 mL) was added dropwise, and the reaction mixture was stirred for 2 h at -78 °C. *N*-Phenyl-bis(trifluoromethanesulfonimide) (0.45 g, 1.3 mmol) dissolved in THF (10 mL) was then added dropwise, and the reaction mixture was stirred for 12 h while warming from -78 °C to room temperature. After 12 h, the THF was evaporated under reduced pressure, and the resulting solid was washed with water (50 mL) and extracted with EtOAc (3 x 50 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford triflate 60 (0.17 g, 0.38 mmol, 33%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (1H, d, *J* = 8.5 Hz), 6.79 (1H, d, *J* = 8.5 Hz), 6.09 (1H, t, *J* = 6.5 Hz), 3.82 (3H, s), 2.88 (2H, t, *J* = 6 Hz), 2.15 (2H, q, *J* = 6.5 Hz), 2.03 (2H, p, *J* = 6.5 Hz), 1.03 (9H, s), 0.20 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 146.5, 132.9, 130.9, 129.9, 126.0, 120.9, 119.7, 108.8, 54.7. 30.5, 26.0, 25.0, 24.5, 18.9, 4.0.

tert-*Butyl((3-methoxy-9-(2´,3´,4´-trimethoxyphenyl)-6,7-dihydro*-5H-*benzo[7]annulen-4-yl)oxy)dimethylsilane (63).* Triflate 60 (0.17 g, 0.38 mmol) was dissolved in THF (25 mL) and 2,3,4-trimethoxyphenyl boronic acid (0.09 g, 0.41 mmol), barium hydroxide octahydrate (0.18 g, 0.57 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.013 g, 0.011 mmol) were added to the solution and refluxed at 80 °C for 2 h. The solution was then filtered through Celite®, and the Celite® was washed with dichloromethane. The organic solution (dichloromethane and THF) was evaporated under reduced pressure. The crude reaction

product was purified using flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 63 (0.07 g, 0.15 mmol, 41%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (1H, d, *J* = 8.5 Hz), 6.64 (1H, d, *J* = 8.5 Hz), 6.60 (1H, d, *J* = 8 Hz), 6.44 (1H, d, *J* = 8 Hz), 6.10 (1H, t, *J* = 7 Hz), 3.87 (3H, s), 3.83 (3H, s), 3.76 (3H, s), 3.38 (3H, s), 2.89 (2H, t, *J* = 6.5 Hz), 2.12 (2H, p, *J* = 7 Hz), 1.95 (2H, q, *J* = 7 Hz), 1.05 (9H, s), 0.22 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 151.7, 148.5, 142.4, 140.3, 135.8, 132.5, 131.1, 128.2, 124.9, 120.7, 108.0, 106.6, 105.2, 60.6, 60.4, 55.9, 54.6, 33.8, 26.2, 25.5, 24.2, 19.0, -3.9.

3-Methoxy-9-(2´,3,´4´-trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulen-4-ol (71).* TBS-protected benzosuberene 63 (0.068 g, 0.146 mmol) was dissolved in THF (5 mL), and tetrabutylammonium fluoride (0.18 mL, 0.18 mmol) was added. The reaction was stirred at room temperature for 12 h, washed with water, extracted with EtOAc (3 x 25 mL), dried over sodium sulfate, and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] to afford benzosuberene analogue 71 (0.053 g, 0.15 mmol, 96%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (1H, d, *J* = 8.5 Hz), 6.63 (1H, d, *J* = 8.5 Hz), 6.61 (1H, d, *J* = 8.5 Hz), 6.37 (1H, d, *J* = 8.5 Hz), 6.10 (1H, t, *J* = 7 Hz), 5.71 (1H, s), 3.87 (3H, s), 3.85 (3H, s), 3.82 (3H, s), 3.42 (3H, s), 2.87 (2H, t, *J* = 7 Hz), 2.15 (2H, p, *J* = 7 Hz), 1.96 (2H, q, *J* = 7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0,

151.8, 144.7, 142.39, 142.36, 140.0, 136.2, 131.0, 128.6, 126.8, 125.0, 119.0, 107.3, 106.6, 60.7, 60.5, 55.94, 55.90, 33.6, 25.6, 23.4. HRMS: Obsvd 379.1516 [M + Na^+], Calcd for $C_{21}H_{24}O_5Na$: 379.1516. HPLC (Method B): 16.18 min.

3,4-Dimethoxy-6,7-dihydro-5H-*benzo[7]annulen-9-yl trifluoromethanesulfonate (58).* Diisopropylamine (0.84 mL, 6.0 mmol) was dissolved in THF (20 mL) and cooled to -78 °C. *n*-BuLi (2.4 mL, 6.0 mmol) was added dropwise, and the solution was stirred for 15 min. Benzosuberone 13 (1.2 g, 5.4 mmol) dissolved in THF (10 mL) was added dropwise, and the reaction was stirred for 2 h at -78 °C. *N*-Phenyl-bis(trifluoromethanesulfonimide) (2.14 g, 5.99 mmol) dissolved in THF (10 mL) was then added dropwise, and the reaction mixture was stirred for 12 h while warming from -78 °C to room temperature. After 12 h, the THF was evaporated under reduced pressure, and the resulting solid was washed with water (50 mL) and extracted with EtOAc (3 x 50 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford triflate 58 (1.01 g, 2.87 mmol, 50%) as a yellow oil. NMR characterization was performed after the next step.

3,4-Dimethoxy-9-(2´,3´,4´-trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulene (61).* Triflate 58 (0.46 g, 1.3 mmol) was dissolved in THF (25 mL) and 2,3,4-trimethoxyphenyl boronic acid (0.31 g, 1.4 mmol), barium hydroxide octahydrate (0.62 g, 2.0 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.05 g, 0.04 mmol) were added

to the solution, which was refluxed at 80 °C for 2 h. The solution was then filtered through Celite®, and the Celite® was washed with dichloromethane. The organic solution (dichloromethane and THF) was evaporated under reduced pressure. The crude reaction product was purified using flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 45%A / 55%B (10 CV), 45%A / 55%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 61 (0.07 g, 0.19 mmol, 15%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (1H, d, *J* = 8.5 Hz), 6.64 (2H, overlapping d, *J* = 8.5 Hz), 6.58 (1H, d, *J* = 8.5 Hz), 6.11 (1H, t, *J* = 7 Hz), 3.86 (3H, s), 3.84 (3H, s), 3.82 (3H, s), 3.81 (3H, s), 3.38 (3H, s), 2.86 (2H, t, *J* = 7 Hz), 2.15 (2H, p, *J* = 6 Hz), 1.95 (2H, q, *J* = 7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 151.7, 151.0, 146.2, 142.4, 140.1, 135.9, 134.9, 130.8, 128.4, 124.9, 123.5, 108.9, 106.7, 61.2, 60.6, 60.3, 55.9, 55.6, 34.4, 25.4, 23.9. HRMS: Obsvd 393.1740 [M + Na^+], Calcd for $C_{22}H_{26}O_5Na$: 393.1672. HPLC (Method B): 18.25 min.

*1-((*tert-*Butyldimethylsilyl)oxy)-2-methoxy-5-phenyl-6,7,8,9-tetrahydro*-5H-*benzo[7]annulen-5-ol (44).* To an oven dried flask, THF (50 mL) and phenyl bromide (0.69 mL, 6.5 mmol) were added, and the solution was cooled to -78 °C. *n*-BuLi (2.74 mL, 6.86 mmol) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h. TBS-protected 41 (1.55 g, 4.83 mmol) in THF (25 mL) was then added dropwise to the flask, and the reaction mixture was stirred while warming from -78 °C to room temperature over 12 h. The reaction mixture was washed with water and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash

chromatography using a pre-packed 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford tertiary alcohol 44 (0.80 g, 2.01 mmol, 42%) as a clear oil. NMR characterization was performed after the next step.

tert-*Butyl((3-methoxy-9-phenyl-6,7-dihydro*-5H-*benzo[7]annulen-4-yl)oxy)dimethylsilane (51).* Acetic acid (10 mL) was added to alcohol 44 (0.80 g, 2.0 mmol), and the reaction mixture was stirred for 12 h at room temperature. The mixture was washed with water and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate. The organic phase was evaporated under reduced pressure, and the crude reaction product was purified by flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] to afford benzosuberene **51** (0.38 g, 1.0 mmol, 49%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (5H, m), 6.70 (1H, d, *J* = 8 Hz), 6.60 (1H, d, *J* = 8.5 Hz), 6.37 (1H, t, *J* = 7.5 Hz), 3.81 (3H, s), 2.79 (2H, t, *J* = 7 Hz), 2.13 (2H, p, *J* = 7 Hz), 1.98 (2H, q, *J* = 7.5 Hz), 1.07 (9H, s), 0.26 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 143.0, 142.8, 141.6, 134.1, 133.3, 128.0, 127.3, 126.8, 122.1, 108.8, 108.4, 54.7, 33.8, 26.2, 25.6, 24.2, 19.0, -3.80.

3-Methoxy-9-phenyl-6,7-dihydro-5H-*benzo[7]annulen-4-ol (64).* TBS-protected benzosuberene 51 (0.38 g, 1.0 mmol) was dissolved in THF (25 mL), TBAF (1.20 mL, 1.20 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h.

The solution was washed with water and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 3%A / 97%B (1 CV), 3%A / 97%B → 30%A / 70%B (10 CV), 30%A / 70%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] to afford benzosuberene analogue 64 (0.12 g, 0.45 mmol, 44%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (5H, m), 6.71 (1H, d, *J* = 8.5 Hz), 6.54 (1H, d, *J* = 8.5 Hz), 6.38 (1H, t, *J* = 7.5 Hz), 5.77 (1H, s), 3.91 (3H, s), 2.79 (2H, t, *J* = 7 Hz), 2.16 (2H, p, *J* = 7 Hz), 1.99 (2H, q, *J* = 7Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 142.8, 142.7, 142.4, 134.6, 128.02, 128.00, 127.8, 127.6, 126.9, 120.6, 107.7, 55.9, 33.5, 25.7, 23.5. HRMS: Obsvd 267.1385 [M + H^+], Calcd for $C_{18}H_{19}O_2$: 267.1380. HPLC (Method B): 17.89 min.

((5-(3´, 5´-Bis(trifluoromethyl)phenyl)-2-methoxy-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-1-yl)oxy)(tert-butyl)dimethylsilane (45).* 1-Bromo-3,5-bis(trifluoromethyl)benzene (0.36 g, 1.2 mmol) was dissolved in THF (13 mL), and the reaction flask was cooled to −78 °C. *n*-BuLi (0.55 mL, 2.5 M) was added to the reaction mixture, which was stirred for 1 h. Ketone 41 (0.29 g, 0.91 mmol) was dissolved in THF (5 mL) and slowly added to the reaction mixture over a period of 15 min. The reaction mixture was stirred for 20 h while warming from −78 °C to room temperature. The reaction mixture was diluted with H_2O (25 mL) and extracted with EtOAc (2 × 25 mL), and the organic extract was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B →

60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford alcohol 45 (0.40 g, 0.75 mmol, 82%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (1H, s), 7.74 (2H, s), 6.95 (1H, d, *J* = 8.7 Hz), 6.70 (1H, d, *J* = 8.7 Hz), 3.80 (3H, s), 3.32 (1H, ddd, *J* = 14.8, 7.6, 2.0 Hz), 2.57 (1H, ddd, *J* = 14.2, 7.6, 3.0 Hz), 2.41 (1H, s), 2.34 – 2.21 (1H, m), 2.16 (1H, ddd, *J* = 13.8, 10.3, 3.1 Hz), 1.97 – 1.90 (1H, m), 1.75 – 1.68 (1H, m), 1.67 – 1.57 (1H, m), 1.56 – 1.48 (1H, m), 0.99 (9H, s), 0.18 (3H, s), 0.17 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.9, 149.7, 142.5, 137.1, 132.7, 131.6 (q, *J* = 33.2 Hz), 127.3 (q, *J* = 3 Hz), 123.5 (q, *J* = 272.8 Hz), 121.2 (hept, *J* = 3.8 Hz), 120.3, 108.6, 79.8, 54.8, 41.6, 26.7, 26.2, 25.3, 25.3, 19.1, -3.94, -3.95.

((9-(3´,5´-Bis(trifluoromethyl)phenyl)-3-methoxy-6,7-dihydro-5H-*benzo[7]annulen-4-yl)oxy)(*tert-*butyl)dimethylsilane (52).* 2 M HCl (8 mL, 16 mmol) was added to a well-stirred solution of alcohol 45 (0.68 g, 1.3 mmol) in EtOH (5 mL), and the reaction mixture was stirred for 12 h at ambient temperature. The reaction mixture was then extracted with EtOAc (4 × 15 mL), and the organic extract was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 15%A / 85%B (10 CV), 15%A / 85%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 52 (0.43 g, 0.84 mmol, 66%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (1H, s), 7.74 (2H, s), 6.73 (1H, d, *J* = 8.5 Hz), 6.50 (1H, t, *J* = 7.1 Hz), 6.49 (1H, d, *J* = 8.5 Hz), 3.84 (3H, s), 2.80 (2H, t, *J* = 6.9 Hz), 2.16 (2H, p, *J* = 7.0 Hz), 2.04 (2H, q, *J* = 7.1 Hz), 1.07 (9H, s), 0.27 (6H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.3, 145.0, 142.1, 141.1, 133.5, 132.5,

131.5 (q, *J* = 33.3 Hz), 130.8, 128.0 (q, *J* = 3.4 Hz), 123.7 (q, *J* = 272.7 Hz), 121.9, 120.6 (hept, *J* = 3.7 Hz), 109.0, 54.8, 33.8, 26.3, 26.0, 24.4, 19.2, -3.6.

9-(3´,5´-Bis(trifluoromethyl)phenyl)-3-methoxy-6,7-dihydro-5H-*benzo[7]annulen-4-ol (65).* To a solution of TBS-protected analogue 52 (0.43 g, 0.84 mmol) in THF (5 mL) was added TBAF (1.0 mL, 1 M in THF), and the reaction mixture was stirred for 18 h at ambient temperature and then concentrated under reduced pressure. The reaction mixture was washed with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organic extract was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 6%A / 94%B (1 CV), 6%A / 94%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] to afford phenolic benzosuberene analogue 65 (0.26 g, 0.66 mmol, 78%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (1H, s), 7.74 (2H, s), 6.74 (1H, d, *J* = 8.3 Hz), 6.51 (1H, t, *J* = 7.3 Hz), 6.45 (1H, d, *J* = 8.4 Hz), 5.83 (1H, s), 3.93 (3H, s), 2.79 (2H, t, *J* = 6.9 Hz), 2.19 (2H, p, *J* = 7.1 Hz), 2.05 (2H, q, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.8, 144.9, 142.9, 140.8, 133.0, 131.5 (q, *J* = 33.4 Hz), 131.2, 128.03, 127.99, 123.6 (q, *J* = 272.8 Hz), 120.6 (hept, *J* = 3.9 Hz), 120.4, 108.2, 56.1, 33.4, 26.1, 23.7. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -62.80. HRMS: Obsvd 401.0963 $[M - H]^-$, Calcd for $C_{20}H_{15}F_6O_2$: 401.0976. HPLC (Method B): 20.39 min.

9-(3´,5´-Bis(trifluoromethyl)phenyl)-3-methoxy-6,7-dihydro-5H-*benzo[7]annulen-4-yl disodium phosphate (74).* To a well-stirred solution of phenol 65 (0.10 g, 0.25 mmol) in CH_2Cl_2 (10 mL), $POCl_3$ (153.3 mg, 1.00 mmol) and pyridine (70.8 mg, 0.9 mmol)

were added to the reaction flask. After the reaction mixture was stirred for 15 h at ambient temperature, the solvent was evaporated under reduced pressure. Saturated aqueous Na_2CO_3 (20 mL) was added to the flask, and the reaction mixture was stirred for another 2 h. The reaction mixture was concentrated to dryness with a stream of N_2 gas and purified by flash chromatography using a prepacked C-18 30 g reversed phase column [solvent A: acetonitrile; solvent B: water; gradient: 30%A / 70%B (1 CV), 30%A / 70%B → 100%A / 0%B (10 CV), 100%A / 0%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford phosphate salt 74 (0.043 g, 0.082 mmol, 33 %) as a white solid. ^{1}H NMR (D_2O, 500 MHz) δ 7.96 (1H, s), 7.87 (2H, s), 6.91 (1H, d, *J* = 8.6 Hz), 6.72 (1H, d, *J* = 8.4 Hz), 6.62 (1H, t, *J* = 7.4 Hz), 3.84 (3H, s), 2.76 (2H, t, *J* = 7.0 Hz), 2.17 (2H, p, *J* = 7.1 Hz), 1.97 (2H, q, *J* = 7.2 Hz). ^{13}C NMR (CD_3OD, 125 MHz) δ 153.1, 146.6, 142.0, 141.9, 137.2, 133.3, 132.6 (q, *J* = 33.0 Hz), 132.4, 129.0 (q, *J* = 2.5 Hz), 124.9 (q, *J* = 271.3 Hz), 125.2 (hept, *J* = 3.8 Hz), 121.2, 111.1, 56.4, 34.6, 26.9, 25.9. ^{19}F NMR (D_2O, 470 MHz) δ -62.8. ^{31}P NMR (D_2O, 200 MHz) δ -3.5. HRMS: Obsvd 527.0429 $[M + H]^+$, Calcd for $C_{19}H_{16}F_6O_2Na_2O_5P$: 527.0429. HPLC (Method A): 13.79 min.

*1-((*tert-*Butyldimethylsilyl)oxy)-5-(4-hydroxyphenyl)-2-methoxy-6,7,8,9-tetrahydro*-5H-*benzo[7]annulen-5-ol (47).* To a solution of 4-methoxyphenyl bromide (0.52 g, 2.8 mmol) in THF (40 mL) at -78 ºC was added *n*-BuLi (0.34 mL, 2.5 M in hexanes), and the reaction mixture was stirred for 30 min. Benzosuberone 41 (0.61 g, 1.9 mmol) in THF (20 mL) was added dropwise over a period of 15 min. The reaction mixture was allowed to reach room temperature over 12 h. Upon completion, water was added, and the mixture was extracted with EtOAc (3 x 20 mL). The organic extract was

washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 50 g silica column [solvent A: EtOAc, solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford alcohol 47 (0.32 g, 0.75 mmol, 39%) as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (1H, d, *J* = 8.6 Hz), 7.15 (2H, d, *J* = 8.8 Hz), 6.81 (2H, d, *J* = 8.8 Hz), 6.73 (1H, d, *J* = 8.7 Hz), 3.81 (3H, s), 3.79 (3H, s), 3.30 (1H, dd, *J* = 14.6, 7.5 Hz), 2.67 – 2.59 (1H, m), 2.14 – 2.04 (2H, m), 1.77 – 1.65 (2H, m), 1.35 – 1.25 (2H, m), 0.99 (9H, s), 0.20 (3H, s), 0.14 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.7, 149.2, 141.8, 139.0, 137.6, 132.7, 128.3, 119.1, 113.6, 107.8, 79.4, 55.2, 54.6, 41.2, 27.1, 26.7, 26.1, 25.5, -3.86, -4.22.

tert-*Butyl((3-methoxy-9-(4´-methoxyphenyl)-6,7-dihydro*-5H-*benzo[7]annulen-4-yl)oxy)dimethylsilane (54).* Tertiary alcohol 47 (0.53 g, 1.2 mmol) was dissolved in acetic acid (5 mL) and refluxed for 5 h. No apparent change in TLC was observed, so water (15 mL) was added to the reaction mixture, which was refluxed for 2 h. The solvents were evaporated, and the resulting product was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, evaporated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc, solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford a clear oil that solidified as a colorless solid of TBS-protected benzosuberene analogue 54 (0.43 g, 1.1 mmol, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20 (2H, d, *J* = 8.7 Hz), 6.83 (2H, d, *J* = 8.8 Hz), 6.68 (1H, d,

J = 8.4 Hz), 6.58 (1H, d, *J* = 8.4 Hz), 6.26 (1H, t, *J* = 7.3 Hz), 3.81 (3H, s), 3.79 (3H, s), 2.75 (2H, t, *J* = 6.9 Hz), 2.09 (2H, p, *J* = 7.1 Hz), 1.93 (2H, q, *J* = 7.2 Hz), 1.04 (9H, s), 0.23 (6H, s). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.7, 148.5, 142.4, 141.5, 135.5, 134.3, 133.3, 129.0, 125.7, 122.0, 113.4, 108.3, 55.3, 54.7, 33.94, 26.2, 25.5, 24.2, 19.0, -3.9.

3-Methoxy-9-(4´-methoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulen-4-ol (67).* The TBS-protected analogue 54 (0.33 g, 0.8 mmol) was dissolved in THF (5 mL). To the solution, TBAF-3 H_2O (0.96 mmol) was added, and the mixture was stirred for 3 h at room temperature. The reaction was quenched with water (15 mL), followed by the evaporation of organic solvent under reduced pressure. The resultant aqueous phase was then extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine solution, dried over Na_2SO_4, filtered, evaporated under reduced pressure, and purified by flash chromatography using a pre-packed 40 g silica column [solvent A, EtOAc, solvent B, hexanes; gradient 0%A/ 100%B →100%A/ 0%B over 9.0 min; flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford the benzosuberene analogue 67 (0.21 g, 0.71 mmol, 89%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21 (2H, d, *J* = 8.7 Hz), 6.83 (2H, d, *J* = 8.7 Hz), 6.70 (1H, d, *J* = 8.4 Hz), 6.54 (1H, d, *J* = 8.4 Hz), 6.28 (1H, t, *J* = 7.4 Hz), 5.72 (1H, s), 3.90 (3H, s), 3.81 (3H, s), 2.75 (2H, t, *J* = 7.0 Hz), 2.13 (2H, p, *J* = 7.0 Hz), 1.95 (2H, q, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.8, 144.9, 142.4, 142.2, 135.3, 134.8, 129.0, 127.8, 126.1, 120.6, 113.4, 107.6, 55.9, 55.3, 33.7, 25.6, 23.5. HRMS: Obsvd 297.1492 [M + H^+], Calcd for $C_{19}H_{21}O_3$: 297.1485. HPLC (Method B): 17.42 min.

*1-((*tert-*Butyldimethylsilyl)oxy)-2-methoxy-5-(3´,4´,5´-trimethoxyphenyl)-6,7,8,9-tetrahydro*-5H-*benzo[7]annulen-5-ol (49).*[61,64] To an oven dried flask, THF (50 mL) and 3,4,5-trimethoxyphenyl bromide (2.46 g, 9.97 mmol) were added, and the solution was cooled to -78 °C. *n*-BuLi (4.2 mL, 10 mmol) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h. Benzosuberone 41 (2.37 g, 7.38 mmol) was then added dropwise to the flask, and the reaction mixture was stirred while warming from -78° C to room temperature over 12 h. The reaction mixture was washed with water and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 80%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford compound 49 (1.80 g, 3.70 mmol, 50%) as a clear oil. NMR characterization was performed after the next step.

tert-*Butyl((3-methoxy-9-(3´,4´,5´-trimethoxyphenyl)-6,7-dihydro*-5H-*benzo[7]annulen-4-yl)oxy)dimethylsilane (56).* Acetic acid (20 mL) was added to tertiary alcohol 49 (1.80 g, 3.70 mmol), and the reaction mixture was stirred for 12 h at room temperature. The mixture was washed with water and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford TBS-protected benzosuberene

56 (1.43 g, 8.38 mmol, 83%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (1H, d, *J* = 8.5 Hz), 6.61 (1H, d, *J* = 8.5 Hz), 6.50 (2H, s), 6.32 (1H, t, *J* = 7.5 Hz), 3.85 (3H, s), 3.78 (3H, s), 3.77 (6H, s), 2.78 (2H, t, *J* = 7 Hz), 2.11 (2H, p, *J* = 7 Hz), 1.95 (2H, q, *J* = 7.5 Hz), 1.06 (9H s), 0.25 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 148.6, 143.1, 141.5, 138.6, 137.3, 133.8, 133.2, 126.7, 122.4, 108.4, 105.3, 60.7, 56.0, 54.5, 34.0, 26.2, 25.6, 24.2, 19.0, -3.8.

3-Methoxy-9-(3´,4´,5´-trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulen-4-ol (69).*[61,62,64,67,131] Benzosuberene 56 (1.43 g, 3.04 mmol) was dissolved in THF (10 mL), TBAF (3.65 mL, 3.6 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. The solution was washed with water and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure affording benzosuberene 69 (0.66 g, 1.9 mmol, 61%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (1H, d, *J* = 8.5 Hz), 6.58 (1H, d, *J* = 8 Hz), 6.51 (2H, s), 6.35 (1H, t, *J* = 7 Hz), 5.74 (1H, s), 3.93 (3H, s), 3.87 (3H, s), 3.81 (6H, s), 2.77 (2H, t, *J* = 7 Hz), 2.15 (2H, p, *J* = 7 Hz), 1.97 (2H, q, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 145.0, 142.8, 142.3, 138.5, 137.3, 134.2, 127.7, 127.2, 120.8, 107.6, 105.3, 60.9, 56.1, 55.9, 33.6, 25.7, 23.5.

2-Methoxy-5-(3´,4´,5´-trimethoxyphenyl)-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-1-ol (72).* To benzosuberene 69 (0.66 g, 1.9 mmol) was added methanol (50 mL) and 10% Pd/C (0.42 g). Hydrogen gas was added, and the reaction mixture was stirrred at room temperature for 12 h. The reaction mixture was filtered through Celite®, and the Celite® was washed with EtOAc (3 x 30 mL). The organic phase (MeOH and

EtOAc) was evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] to afford benzosuberane analogue 72 (0.16 g, 0.45 mmol, 24%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (1H, d, *J* = 8.5 Hz), 6.47 (2H, s), 6.17 (1H, d, *J* = 8 Hz), 5.84 (1H, s), 4.17 (1H, d, *J* = 9.5 Hz), 3.89 (3H, s), 3.84 (9H, s), 3.28 (1H, q, *J* = 7.5 Hz), 2.73 (1H, t, *J* = 12 Hz), 2.17(1H, m), 2.02 (2H, m), 1.86 (2H, m), 1.46 (1H, q, *J* = 12 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 144.7, 142.6, 141.2, 139.6, 136.2, 128.4, 118.6, 108.1, 105.7, 60.9, 56.1, 55.9, 49.5, 34.7, 30.6, 27.2, 25.4. HRMS: Obsvd 381.1764 [M + Na^+], Calcd for $C_{21}H_{26}O_5Na^+$: 381.1672. HPLC (Method B): 15.30 min.

2-Methoxy-5-(3´,4´,5´-trimethoxyphenyl)-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-1-yl disodium phosphate (73).* To benzosuberene analogue 72 dissolved in CH_2Cl_2 (25 mL) was added $POCl_3$ (0.11 mL, 1.1 mmol) and pyridine (0.1 mL, 1 mmol), and the reaction mixture was stirred at room temperature for 12 h. 2 M NaOH (1.69 mL, 3.38 mmol) was added, and the reaction was stirred for 5 min and extracted with CH_2Cl_2, and the organic layer was evaporated under reduced pressure. NaOH (2 mL, 2 M) was added to the resulting oil, and the solution was refluxed at 60 °C for 15 min. Water was removed under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 12 g C-18 column [solvent A: water; solvent B: acetonitrile; gradient: 0%A / 100%B (1 CV), 0%A / 100%B → 100%A / 0%B (10 CV), 0%A / 100%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] to afford the benzosuberane phosphate salt 73 (0.024 g, 0.050 mmol, 17%) as a white solid. ^{1}H NMR

(500 MHz, D_2O) δ 6.43 (2H, s), 6.36 (1H, d, *J* = 8.5 Hz), 6.07 (1H, d, *J* = 8.5 Hz), 4.04 (1H, d, *J* = 9.5 Hz), 3.61 (6H, s) 3.60 (3H, s), 3.56 (3H, s), 3.26 (1H, m), 2.55 (1H, t, *J* = 12 Hz), 1.90 (1H, m), 1.65 (4H, m), 1.16 (1H, q, *J* = 10.5 Hz). ^{13}C NMR (125 MHz, D_2O) δ 152.2, 150.3, 142.8, 140.5, 140.4, 139.0, 137.3, 134.6, 121.8, 108.6, 105.9, 60.8, 55.4, 48.6, 33.7, 30.0, 33.7, 29.7, 26.6. ^{31}P NMR (200 MHz, D_2O, 85% phosphoric acid reference) δ 0.97. HRMS: Obsvd 483.1190 [M + H^+], Calcd for $C_{21}H_{26}O_5Na_2P^+$: 483.1155. HPLC (Method A): 14.23 min.

1,2-Dimethoxy-5-(4´-methoxyphenyl)-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-ol (27).* To a solution of 4-methoxyphenyl bromide (0.719 g, 3.84 mmol) in THF (50 mL) at -78 ºC was added *n*-BuLi (2.6 mL, 2.5 M in hexanes), and the reaction mixture was stirred for 30 min. Benzosuberone 13 (0.58 g, 2.6 mmol) in THF (15 mL) was added dropwise over 15 min. The reaction mixture was warmed to room temperature over 12 h. Upon completion, water was added, and the mixture was extracted with EtOAc (3 x 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 80 g silica column [solvent A, EtOAc, solvent B, hexanes; gradient 0%A/ 100%B →100%A/ 0%B over 20.3 min; flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford alcohol 27 (0.45 g, 1.4 mmol, 54%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (1H, d, *J* = 8.7 Hz), 7.15 (2H, d, *J* = 8.8 Hz), 6.83 (2H, d, *J* = 8.8 Hz), 6.79 (1H, d, *J* = 8.7 Hz), 3.89 (3H, s), 3.79 (3H, s), 3.75 (3H, s), 3.25 – 3.18 (1H, m), 2.67 – 2.59 (1H, m), 2.15 – 2.08 (2H, m), 1.93 – 1.86 (1H, m), 1.80 – 1.69 (2H, m), 1.43 – 1.35 (1H, m). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.8, 151.7, 146.3, 139.1, 137.5, 135.4, 128.2, 122.31, 113.7, 108.8, 79.4, 61.0, 55.6, 55.2, 41.2, 27.3, 26.6, 25.2.

3,4-Dimethoxy-9-(4´-methoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulene (36).* Tertiary alcohol analogue 27 (0.401 g, 1.22 mmol) was dissolved in acetic acid (10 mL), and the mixture was stirred for 12 h at ambient temperature. Water (30 mL) was added, and the reaction mixture was stirred for 2 h. The reaction mixture was extracted with EtOAc (3 x 20 mL). The organic solvent was evaporated under reduced pressure and the residue extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc, solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford benzosuberene analogue 36 (0.31 g, 1.0 mmol, 82%) as a clear oil. ^{1}H NMR (CD_3OD, 500 MHz) δ 7.17 (2H, d, *J* = 8.8 Hz), 6.87 (1H, d, *J* = 8.5 Hz), 6.86 (2H, d, *J* = 8.8 Hz), 6.71 (1H, d, *J* = 8.5 Hz), 6.30 (1H, t, *J* = 7.4 Hz), 3.89 (3H, s), 3.85 (3H, s), 3.81 (3H, s), 2.74 (2H, t, *J* = 7.0 Hz), 2.15 (2H, p, *J* = 7.1 Hz), 1.94 (2H, q, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.8, 151.3, 146.1, 142.2, 135.9, 135.2, 134.3, 129.0, 125.9, 125.0, 113.5, 109.2, 61.2, 55.6, 55.3, 34.6, 25.5, 24.0. HRMS: Obsvd 281.1597 [M + H^+], Calcd for $C_{19}H_{23}O_2$: 281.1536. HPLC (Method B): 19.08 min.

1,2-Dimethoxy-5-phenyl-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-ol (19).* To an oven dried flask, THF (50 mL) and phenylbromide (0.25 mL, 2.4 mmol) were added, and the solution was cooled to -78 °C. *n*-BuLi (1.0 mL, 2.5 mmol) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h. Benzosuberone 13 (0.39 g, 1.8 mmol) was then added dropwise to the flask, and the reaction mixture was stirred while

warming from -78 °C to room temperature over 12 h. The reaction mixture was washed with water and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford tertiary alcohol 19 (0.29 g, 0.97 mmol, 55%) as a pale yellow oil. NMR characterization was performed after the next step.

3,4-Dimethoxy-9-phenyl-6,7-dihydro-5H-*benzo[7]annulene (28).* Acetic acid (15 mL) was added to tertiary alcohol 19 (0.29 g, 0.97 mmol), and the reaction mixture was stirred for 12 h at room temperature. The mixture was washed with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 50%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] to afford benzosuberene analogue 28 (0.10 g, 0.36 mmol, 37%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (5H, m), 6.78 (2H, s), 6.40 (1H, t, *J* = 7.5 Hz), 3.91 (3H, s), 3.90 (3H, s), 2.81 (2H, t, *J* = 7 Hz), 2.19 (2H, p, *J* = 7Hz), 2.01 (2H, q, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 146.1, 142.9, 142.6, 135.9, 134.2, 128.1, 128.0, 127.5, 127.0, 125.1, 109.4, 61.2, 55.6, 34.5, 25.6, 24.1.HRMS: Obsvd 303.1363 [M + Na^+], Calcd for $C_{19}H_{20}O_2Na$: 303.1356. HPLC (Method B): 19.93 min.

1,2-Dimethoxy-5-(3´,4´,5´-trimethoxyphenyl)-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-ol (26).*[61] To a solution of 3,4,5-trimethoxyphenyl bromide (0.67 g, 2.7 mmol) in THF (100 mL) at -78 °C was added *n*-BuLi (1.1 mL, 2.5 M in hexanes), and the reaction mixture was stirred for 30 min. Benzosuberone 13 (0.60 g, 2.7 mmol) in THF (15 mL) was added dropwise over 15 min. The reaction mixture was warmed to room temperature over 12 h. Water was added, and the mixture was extracted with EtOAc (100 mL). The organic extract was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc, solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 56%A / 44%B (9.2 CV), 56%A / 44%B (1 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford alcohol 26 (0.39 g, 0.99 mmol, 34%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (1H, d, *J* = 8.7 Hz), 6.75 (1H, d, *J* = 8.8 Hz), 6.49 (2H, s), 3.87 (3H, s), 3.83 (3H, s), 3.74 (3H, s), 3.73 (6H, s), 3.26 – 3.20 (1H, m), 2.56 (1H, ddd, *J* = 14.1, 6.9, 3.0 Hz), 2.38 – 2.30 (1H, m), 2.21 – 2.21 (1H, m), 2.11 (1H, ddd, *J* = 14.0, 10.7, 3.1 Hz), 1.93 (1H, ddd, *J* = 15.3, 7.4, 3.8 Hz), 1.81-1.71 (2H, m), 1.50-1.42 (1H, m). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 153.0, 151.8, 146.2, 141.6, 138.6, 137.2, 135.5, 123.0, 108.8, 104.2, 79.9, 61.0, 60.8, 56.1, 55.5, 41.3, 27.1, 26.3, 25.1.

3,4-Dimethoxy-9-(3´,4´,5´-trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulene (35).*[61] Tertiary alcohol analogue 26 (0.5 g, 1 mmol) was dissolved in acetic acid (10 mL) and refluxed for 2 h. Water (30 mL) was added, and the reaction was refluxed for 2 h. The white precipitate thus obtained was filtered and washed with hexanes. On drying, it afforded benzosuberene analogue 35 (0.444 g, 1.2 mmol, 93%) as a colorless solid, which

was not further purified. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.79 (1H, d, *J* = 8.5 Hz), 6.77 (1H, d, *J* = 8.5 Hz), 6.51 (2H, s), 6.35 (1H, t, *J* = 7.3 Hz), 3.90 (3H, s), 3.89 (3H, s), 3.88 (3H, s), 3.82 (6H, s), 2.77 (2H, t, *J* = 7.0 Hz), 2.17 (2H, p, *J* = 7.1 Hz), 1.98 (2H, q, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 152.9, 151.5, 146.1, 142.9, 138.4, 137.4 135.9, 133.8, 127.1, 125.3, 109.3, 105.3, 61.3, 60.9, 56.17, 55.6, 34.6, 25.6, 24.2. HRMS: Obsvd 393.1682 [M + Na^+], Calcd for $C_{22}H_{26}O_5Na$: 393.1672. HPLC (Method B): 17.52 min.

5-(3´,5´-Bis(trifluoromethyl)phenyl)-1,2-dimethoxy-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-ol (25).* To a solution of 1-bromo-3,5-bis(trifluoromethyl)benzene (0.36 g, 1.2 mmol) in THF (13 mL) at −78 °C was added *n*-BuLi (0.55 mL, 2.5 M), and the reaction mixture was stirred for 1 h. Benzosuberone 13 (0.20 g, 0.91 mmol) in THF (5 mL) was added dropwise over 15 min. The reaction mixture was stirred for 20 h and was warmed to room temperature. The reaction mixture was diluted with H_2O (25 mL) and extracted with EtOAc (2 × 25 mL). The organic extract was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (15 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford alcohol 25 (0.45 g, 1.0 mmol, 84%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (1H, s), 7.67 (2H, s), 6.92 (1H, d, *J* = 8.7 Hz), 6.63 (1H, d, *J* = 8.8 Hz), 3.76 (3H, s), 3.67 (3H, s), 3.16 (1H, ddd, *J* = 14.6, 7.8, 1.9 Hz), 2.50 (1H, s), 2.46 (1H, ddd, *J* = 14.3, 8.2, 2.8 Hz), 2.37 – 2.24 (1H, m), 2.06 (1H, ddd, *J* = 14.2, 9.6, 3.0 Hz), 1.91 – 1.85 (1H, m), 1.73 – 1.61 (1H, m), 1.59 – 1.50 (2H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.4, 149.8, 146.6, 137.2, 135.6,

131.6 (q, *J* = 33.1 Hz), 127.1 (q, *J* = 3.8 Hz), 123.5 (q, *J* = 272.7 Hz), 123.7, 121.3 (hept, *J* = 4.0 Hz), 109.5, 79.8, 61.1, 55.7, 41.6, 27.0, 25.2, 24.8.

9-(3´,5´-Bis(trifluoromethyl)phenyl)-3,4-dimethoxy-6,7-dihydro-5H-*benzo[7]annulene (34).* To a solution of tertiary alcohol 25 (0.45 g, 1.0 mmol) in EtOH (10 mL) was added 2 M HCl (10 mL, 20 mmol), and the reaction mixture was stirred overnight. The reaction mixture was then extracted using EtOAc (4 × 15 mL). The organic extract was dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 34 (0.22 g, 0.54 mmol, 54%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (1H, s), 7.71 (2H, s), 6.77 (1H, d, *J* = 8.5 Hz), 6.63 (1H, d, *J* = 8.5 Hz), 6.49 (1H, t, *J* = 7.3 Hz), 3.90 (3H, s), 3.88 (3H, s), 2.76 (2H, t, *J* = 6.9 Hz), 2.18 (2H, p, *J* = 7.1 Hz), 2.03 (2H, q, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.2, 146.6, 144.7, 140.8, 136.1, 132.4, 131.6 (q, *J* = 33 Hz), 131.1, 128.0 (q, *J* = 3.8 Hz), 124.8, 123.6 (q, *J* = 272.7 Hz), 120.7 (hept, *J* = 4.0 Hz), 109.9, 61.4, 55.8, 34.3, 26.0, 24.3. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -62.81. HRMS: Obsvd 401.0965 $[M - CH_3]^-$, Calcd for $C_{20}H_{15}F_6O_2$: 401.0976. HPLC (Method B): 21.57 min.

1,2-Dihydroxy-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-one (40).*[61,143] Ketone 13 (0.88 g, 4.0 mmol) was added to the ionic liquid [TMAH][Al_2Cl_7](20.0 mL, 0.497 M). The reaction mixture was subjected to microwave irradiation at 80 °C and 1 atm for 1 h. H_2O (20 mL) was added to the mixture, and the resulting brown liquid was extracted with

dichloromethane (3 x 20 mL). The organic extracts were dried over Na_2SO_4, filtered, evaporated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 60%A / 40%B (13 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford benzosuberone 40 (0.50 g, 2.6 mmol, 65%) as a brown solid. ^{1}H NMR ($(CD_3)_2CO$, 500 MHz) δ 7.14 (1H, d, *J* = 8.3 Hz), 6.78 (1H, d, *J* = 8.8 Hz), 3.07 – 2.99 (2H, m), 2.67 – 2.59 (2H, m), 1.84 – 1.77 (2H, m), 1.77 – 1.71 (2H, m). ^{13}C NMR ($(CD_3)_2CO$, 126 MHz) δ 205.4, 148.1, 142.0, 132.3, 128.9, 120.6, 112.3, 40.3, 24.4, 22.8, 21.0.

*1,2-Bis((*tert*-butyldimethylsilyl)oxy)-6,7,8,9-tetrahydro*-5H-*benzo[7]annulen-5-one (43).*[61] To a solution of catechol 40 (0.68 g, 3.5 mmol) and DIPEA (2.7 mL, 16 mmol) in DMF (5 mL) at 0 °C was added TBSCl (1.60 g, 10.6 mmol) in portions. The reaction mixture was stirred for 18 h, diluted with H_2O (5 mL), and extracted with Et_2O (2 × 20 mL). The organic extract was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 0%A / 100%B (1 CV), 0%A / 100%B → 30%A / 70%B (10 CV), 30%A / 70%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford ketone 43 (1.51 g, 3.59 mmol, 99%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (1H, d, *J* = 8.5 Hz), 6.75 (1H, d, *J* = 8.5 Hz), 2.97 – 2.94 (2H, m), 2.70 (2H, t, *J* = 6.2 Hz), 1.89 – 1.70 (4H, m), 1.02 (9H, s), 0.96 (9H, s), 0.24 (6H, s), 0.15 (6H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.3, 151.2, 143.9, 135.5, 134.0, 122.6, 118.6, 41.0, 26.5, 26.5, 25.3, 25.1, 21.9, 19.2, 18.9, -3.15, -3.19.

*1,2-Bis((*tert*-butyldimethylsilyl)oxy)-5-(3´,4´,5´-trimethoxyphenyl)-6,7,8,9-tetrahydro*-5H-*benzo[7]annulen-5-ol (50).*[61] To a solution of 3,4,5-trimethoxyphenyl bromide (0.458 g, 1.85 mmol) in THF (20 mL) at -78 °C was added *n*-BuLi (0.96 mL, 2.5 M in hexanes), and the reaction mixture was stirred for 1 h. Benzosuberone 43 (0.639 g, 1.51 mmol) in THF (20 mL) was added dropwise over 15 min. The reaction mixture was stirred while warming to room temperature over 12 h. Water was added, and the mixture was extracted with EtOAc (4 x 20 mL). The organic extract was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc, solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 42%A / 58%B (6 CV), 42%A / 58%B→70%A / 30%B (1 CV), 70%A / 30%B → 100%A/0%B, 100%A/0% B (1.1 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford alcohol 50 (0.480 g, 0.81 mmol, 54%) as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10 (1H, d, *J* = 8.7 Hz), 6.72 (1H, d, *J* = 8.6 Hz), 6.46 (2H, s), 3.83 (3H, s), 3.74 (6H, s), 3.23 – 3.15 (1H, m), 2.57 (1H, ddd, *J* = 14.0, 6.2, 3.0 Hz), 2.23 – 2.07 (3H, m), 1.94 – 1.84 (1H, m), 1.81 – 1.66 (2H, m), 1.46 – 1.33 (1H, m), 1.00 (9H, s), 0.95 (9H, s), 0.24 (3H, s), 0.23 (3H, s), 0.15 (3H, s), 0.10 (3H, s). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 152.9, 146.4, 143.7, 141.8, 139.1, 137.1, 133.9, 120.0, 117.5, 104.1, 80.0, 60.8, 56.0, 40.9, 26.8, 26.3, 26.2, 26.1, 25.9, 18.9, 18.6, -3.4, -3.6.

((9-(3´,4´,5´-Trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulene-3,4-diyl)bis(oxy))bis(tert-butyldimethylsilane) (57).*[61] Tertiary alcohol 50 (0.44 g, 0.75 mmol) was dissolved in acetic acid (5 mL) and stirred for 12 h at room temperature. The reaction was quenched with water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined

organic extract was washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford the clear oil of TBS-protected benzosuberene analogue 57 (0.38 g, 0.66 mmol, 89%), which was used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.69 (1H, d, *J* = 8.4 Hz), 6.52 (1H, d, *J* = 8.4 Hz), 6.45 (2H, s), 6.33 (1H, t, *J* = 7.3 Hz), 3.85 (3H, s), 3.78 (6H, s), 2.70 (2H, t, *J* = 6.9 Hz), 2.10 (2H, q, *J* = 7.0 Hz), 1.95 (2H, q, *J* = 7.0 Hz), 1.04 (9H, s), 0.95 (9H, s), 0.24 (6H, s), 0.20 (6H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.7, 145.9, 143.4, 143.0, 138.6, 137.1, 134.4, 134.2, 126.8, 122.7, 117.9, 105.0, 60.9, 56.0, 33.9, 26.27, 26.25, 25.7, 24.5, 18.9, 18.7, -3.3, -3.4.

9-(3´,4´,5´-Trimethoxyphenyl)-6,7-dihydro-5H-benzo[7]annulene-3,4-diol (70). The di-TBS-protected analogue 57 (0.32 g, 0.56 mmol) was dissolved in THF (5 mL). To the solution, TBAF-3 H_2O (1.4 mmol) was added and stirred for 3 h at room temperature. The reaction was quenched with water (15 mL), and the organic solvent was evaporated under reduced pressure. The resulting aqueous phase was then extracted with EtOAc (3 x 20 mL). The combined organic extract was washed with brine, dried over Na_2SO_4, filtered, evaporated under reduced pressure and purified by flash chromatography using a pre-packed 25 g silica gel column [solvent A, EtOAc, solvent B, hexanes; gradient 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (5.2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford catechol analogue 70 (0.17 g, 0.49 mmol, 88%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.68 (1H, d, *J* = 8.2 Hz), 6.52 (1H, d, *J* = 8.2 Hz), 6.49 (2H, s), 6.33 (1H, t, *J* =7.4 Hz), 5.29 (1H, s), 5.28 (1H, s), 3.86 (3H, s), 3.79 (6H, s), 2.71 (2H, t, *J* = 7.0 Hz), 2.15 (2H, p, *J* = 7.1 Hz), 1.96 (2H, q, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 152.8, 142.9, 141.8, 140.8, 138.3, 137.3, 134.1,

128.5, 127.0, 121.7, 112.3, 105.3, 60.9, 56.1, 33.8, 25.6, 23.8. HRMS: Obsvd 365.1444 [M + H^+], Calcd for $C_{12}H_{23}O_5$: 365.1359. HPLC (Method B): 16.18 min.

*5-(3´,5´-Bis(trifluoromethyl)phenyl)-1,2-bis((*tert-*butyldimethylsilyl)oxy)-6,7,8,9-tetrahydro*-5H-*benzo[7]annulen-5-ol (46).* 1-Bromo-3,5-bis(trifluoromethyl)benzene (0.36 g, 1.2 mmol) was dissolved in THF (13 mL) at −78 °C and *n*-BuLi (0.55 mL, 2.5 M) was then added. The reaction mixture was stirred for 1 h, and then ketone 43 (0.38 g, 0.91 mmol) in THF (5 mL) was added dropwise over 15 min. The reaction mixture was stirred for 20 h, warming from −78 °C to room temperature, and then diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The organic extract was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 100%A / 0%B (10 CV), 100%A / 0%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford alcohol 46 (0.43 g, 0.68 mmol, 74%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (1H, s), 7.72 (2H, s), 6.92 (1H, d, *J* = 8.6 Hz), 6.73 (1H, d, *J* = 8.7 Hz), 3.25 (1H, ddd, *J* = 14.7, 7.6, 1.9 Hz), 2.57 (1H, ddd, *J* = 14.2, 7.3, 3.1 Hz), 2.31 (1H, s), 2.22 – 2.14 (2H, m), 1.96 – 190 (1H, m), 1.74 – 170 (1H, m), 1.64 – 1.58 (1H, m), 1.54 – 148 (1H, m), 1.01 (9H, s), 0.97 (9H, s), 0.26 (3H, s), 0.23 (3H, s), 0.19 (3H, s), 0.09 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.7 , 147.2 , 144.3 , 137.6 , 134.0, 131.6 (q, *J* = 33.1 Hz), 127.2 (q, *J* = 3.2 Hz), 123.5 (q, *J* = 273.0 Hz), 121.3 (hept, *J* = 4.0 Hz), 120.6 , 118.3 , 79.8 , 41.2 , 26.8 , 26.39 , 26.35 , 25.9 , 25.2 , 19.0 , 18.7 , -3.1 , -3.2 , -3.5 , -3.9.

*((9-(3´,5´-Bis(trifluoromethyl)phenyl)-6,7-dihydro-*5H*-benzo[7]annulene-3,4-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (53).* Tertiary alcohol 46 (0.43 g, 0.67 mmol) was dissolved in EtOH (5 mL) and 2 M HCl (10 mL, 20 mmol) was then added. The reaction mixture was stirred overnight and then extracted using EtOAc (4 × 15 mL). The organic extract was dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 15%A / 85%B (10 CV), 15%A / 85%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 53 (0.22 g, 0.35 mmol, 53%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (1H, s), 7.69 (2H, s), 6.72 (1H, d, *J* = 8.4 Hz), 6.49 (1H, t, *J* = 7.2 Hz), 6.40 (1H, d, *J* = 8.4 Hz), 2.73 (2H, t, *J* = 6.9 Hz), 2.15 (2H, p, *J* = 7.0 Hz), 2.03 (2H, q, *J* = 7.1 Hz), 1.07 (9H, s), 0.98 (9H, s), 0.26 (6H, s), 0.23 (6H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.8, 145.0, 144.0, 141.1, 134.7, 133.0, 131.5 (q, *J* = 33.0 Hz), 130.8 , 127.9 (q, *J* = 3.1 Hz), 123.6 (q, *J* = 272.7 Hz), 122.3, 120.6 (hept, *J* = 3.9 Hz), 118.5, 33.8, 26.43 , 26.39, 26.1, 24.8, 19.1, 18.9, -3.1, -3.2.

*9-(3´,5´-Bis(trifluoromethyl)phenyl)-6,7-dihydro-*5H*-benzo[7]annulene-3,4-diol (66).* TBS-protected analogue 53 (0.43 g, 0.84 mmol) was dissolved in THF (5 mL), and TBAF (1.00 mL, 1 M in THF) was added to the reaction flask. The reaction mixture was stirred for 18 h at ambient temperature, concentrated under reduced pressure, and H_2O (5 mL) was then added. The reaction mixture was extracted with EtOAc (3 x 10 mL). The organic extract was dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A /

40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford catechol 66 (0.077 g, 0.20 mmol, 57 %) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (1H, s), 7.71 (2H, s), 6.71 (1H, d, *J* = 8.2 Hz), 6.50 (1H, t, *J* = 7.3 Hz), 6.38 (1H, d, *J* = 8.2 Hz), 5.36 (1H, s), 5.25 (1H, s), 2.73 (2H, t, *J* = 6.9 Hz), 2.19 (2H, p, *J* = 7.0 Hz), 2.04 (2H, q, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.7, 142.4, 141.43 , 140.9, 132.9, 131.6 (q, *J* = 32.9 Hz), 131.1 , 128.8, 128.0 (q, *J* = 2.9 Hz), 123.6 (q, *J* = 272.7 Hz), 121.2, 120.7 (hept, *J* = 3.9 Hz), 112.9, 33.7, 26.0, 23.9. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -62.83. HRMS: Obsvd 387.0805 $[M - H]^-$, Calcd for $C_{19}H_{13}F_6O_2$: 387.0820. HPLC (Method B): 18.11 min.

5-(3´-Methoxyphenyl)pent-4-enoic acid (2).[61,64] To dissolved 3-(carboxypropyl)triphenyl phosphonium bromide (15.92 g, 37.09 mmol) in THF (500 mL) was added potassium *tert*-butoxide (8.20 g, 73.4 mmol), and the reaction mixture was stirred at room temperature for 1 h. 3-Methoxybenzaldehyde (4.5 mL, 37 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. The THF was evaporated, and the resulting material was quenched with 2 M HCl (75 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate, filtered, and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 12%A / 88%B (1 CV), 12%A / 88%B → 70%A / 30%B (10 CV), 70%A / 30%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford carboxylic acid 2 (5.63 g, 27.3 mmol, 74%) as a yellow solid. NMR characterization was performed after the next step.

5-(3´-Methoxyphenyl)pentanoic acid (8).[61,64,140] To dissolved carboxylic acid 2 (5.63 g, 27.3 mmol) in MeOH (100 mL) was added 10% palladium on carbon (0.44 g) and hydrogen gas. The reaction was stirred at room temperature for 12 h. The reaction mixture was then filtered through Celite®, and the Celite® was washed with EtOAc (3 x 50 mL). The organic phase (MeOH and EtOAc) was evaporated under reduced pressure to afford carboxylic acid 8 (4.27 g, 20.5 mmol, 75%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.2 (1H, s), 7.03 (1H, d, *J* = 8 Hz), 6.62 (2H, d, *J* = 5 Hz), 6.59 (1H, d, *J* = 8.5 Hz), 3.59 (3H, s), 2.44 (2H, t, *J* = 7.5 Hz), 2.21 (2H, d, *J* = 7.5 Hz), 1.52 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 159.7, 143.7, 129.4, 120.9, 114.3, 111.1, 55.0, 35.6, 34.1, 30.7, 24.5.

2-Methoxy-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-one (14).* To carboxylic acid 8 (4.43 g, 21.3 mmol) was added Eaton's reagent (43 mL, 3 g per mmol of compound 8), and the mixture was stirred at room temperature for 12 h. The mixture was then poured over ice and neutralized with sodium bicarbonate. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate, evaporated under reduced pressure, and purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 30%A / 70%B (10 CV), 30%A / 70%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford benzosuberone 14 (2.80 g, 14.7 mmol, 70%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (1H, d, *J* = 8.5 Hz), 6.61 (1H, dd, *J* = 8.5, 2.5 Hz), 6.51 (1H, d, *J* = 2.5 Hz), 3.63 (3H, s), 2.70 (2H, t, *J* = 6 Hz), 2.51 (2H, t, *J* = 6 Hz), 1.67 (2H, p, *J* = 7.5 Hz), 1.59 (2H, p, *J* = 5.5 Hz). ^{13}C NMR

(125 MHz, $CDCl_3$) δ 203.5, 162.5, 144.1, 131.3, 131.0, 114.7, 111.6, 55.1, 40.5, 32.6, 24.9, 20.5.

2-Hydroxy-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-one (39).*[61,142] To benzosuberone 14 (0.89 g, 4.7 mmol) in a 20 mL microwave vial was added [TMAH][Al_2Cl_7] (22 mL, 0.53 M), and the reaction mixture was subjected to microwave irradiation for 1 h at 80 °C. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7% / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford alcohol 39 (0.66 g, 3.8 mmol, 80%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (1H, d, *J* = 8.5 Hz), 6.75 (1H, dd, *J* = 8.5, 2.5 Hz), 6.67 (1H, d, *J* = 2 Hz), 3.84 (1H, s), 2.87 (2H, t, *J* = 6 Hz), 2.71 (2H, t, *J* = 6 Hz), 1.82 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 159.9, 144.8, 131.6, 131.3, 116.3, 113.7, 40.7, 32.7, 25.0, 20.7.

*2-((*tert-*Butyldimethylsilyl)oxy)-6,7,8,9-tetrahydro*-5H-*benzo[7]annulen-5-one (42).*[61] Phenol 39 (0.42 g, 2.4 mmol) was dissolved in dimethylformamide (50 mL). TBSCl (0.72 g, 4.8 mmol) and DIPEA (1.24 mL, 7.14 mmol) were added, and the solution was stirred for 12 h at room temperature. The reaction mixture was washed with water (50 mL) and extracted with EtOAc (5 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 50 g silica column

[solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford TBS-protected 42 (0.53 g, 1.82 mmol, 77%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (1H, d, *J* = 8.5 Hz), 6.64 (1H, dd, *J* = 8.5, 2 Hz), 6.56 (1H, d, *J* = 2 Hz), 2.77 (2H, t, *J* = 6 Hz), 2.59 (2H, t, *J* = 6 Hz), 1.75 (2H, p, *J* = 6.5 Hz), 1.68 (2H, p, *J* = 6 Hz), 0.90 (9H, s), 0.14 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 159.0, 143.9, 132.0, 130.9, 120.8, 117.8, 40.5, 32.5, 25.5, 25.0, 20.6, 18.0, -4.5.

*2-((*tert-*Butyldimethylsilyl)oxy)-5-(3´,4´,5´-trimethoxyphenyl)-6,7,8,9-tetrahydro-*5H-*benzo[7]annulen-5-ol (48).*[61] To an oven dried flask, THF (50 mL) and 3,4,5-trimethoxyphenyl bromide (1.01 g, 4.04 mmol) were added, and the solution was cooled to -78 °C. *n*-BuLi (1.71 mL, 4.27 mmol) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h. Benzosuberone 42 (0.53 g, 3.0 mmol) in THF (25 mL) was then added dropwise to the flask, and the reaction mixture was stirred while warming from -78 °C to room temperature over 12 h. The reaction mixture was washed with water and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford tertiary alcohol 48 (0.470 g, 1.02 mmol, 34%) as a clear oil. NMR characterization was performed after the next step.

tert-*Butyldimethyl((9-(3´,4´,5´-trimethoxyphenyl)-6,7-dihydro*-5H-*benzo[7]annulen-3-yl)oxy)silane (55).*[61] Acetic acid (10 mL) was added to tertiary alcohol 48 (0.47 g, 1.0 mmol), and the reaction mixture was stirred for 12 h at room temperature. The mixture was washed with water and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure to afford protected benzosuberene 55 (0.39 g, 0.89 mmol, 87%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (1H, d, *J* = 8 Hz), 6.77 (1H, d, *J* = 2.5 Hz), 6.67 (1H, dd, *J* = 8.5, 2.5 Hz), 6.49 (2H, s), 6.34 (1H, t, *J* = 7 Hz), 3.86 (3H, s), 3.79 (6H, s), 2.60 (2H, t, *J* = 7 Hz), 2.15 (2H, p, *J* = 7.5Hz), 1.96 (2H, q, *J* = 7 Hz), 1.00 (9H, s), 0.23 (6H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 152.8, 143.7, 142.8, 138.4, 137.3, 133.0, 130.5, 127.0, 120.0, 117.3, 105.2, 60.9, 56.1, 35.0, 32.6, 25.7, 25.5, 18.2, -4.3.

9-(3´,4´,5´-Trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulen-3-ol (68).*[61] TBS-protected 55 (0.39 g, 0.89 mmol) was dissolved in THF (25 mL), TBAF (1.06 mL, 1.06 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. The solution was washed with water and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 68 (0.13 g, 0.40 mmol, 45%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (1H, d, *J* = 8 Hz), 6.78 (1H, d, *J* = 3 Hz), 6.67 (1H, dd, *J* = 8.5 Hz, 2.5 Hz), 6.50 (2H, s), 6.33 (1H, t, *J* = 7.5 Hz), 6.21 (1H,

s), 3.88 (3H, s), 3.79 (6H, s), 2.59 (2H, t, *J* = 7 Hz), 2.14 (2H, p, *J* = 7 Hz), 1.95 (2H, q, *J* = 7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 152.8, 144.0, 142.7, 138.7, 137.0, 132.1, 130.7, 127.1, 115.4, 112.9, 105.3, 61.0, 56.1, 35.0, 32.6, 25.5. HRMS: Obsvd 349.1417 [M + Na^+], Calcd for $C_{20}H_{22}O_4Na$: 349.1410. HPLC (Method B): 14.30 min.

2-Methoxy-5-(3´,4´,5´-trimethoxyphenyl)-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-ol (20).*[61,62,67] To an oven dried flask, THF (50 mL) and 3,4,5-trimethoxyphenyl bromide (2.82 g, 11.4 mmol) were added, and the solution was cooled to -78 °C. *n*-BuLi (4.9 mL,12 mmol) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h. Benzosuberone 14 (1.60 g, 8.41 mmol) was then added dropwise to the flask, and the reaction mixture was stirred while warming from -78° C to room temperature over 12 h. The reaction mixture was washed with water and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford tertiary alcohol 20 (2.29 g, 6.48 mmol, 76%) as a light yellow oil. NMR characterization was performed after the next step.

3-Methoxy-9-(3´,4´,5´-trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulene (29).*[61,62,67] Acetic acid (15 mL) was added to tertiary alcohol 20 (2.29 g, 6.38 mmol), and the reaction mixture was stirred for 12 h at room temperature. The mixture was washed with water and extracted with EtOAc (3 x 30 mL). The combined organic phase was

dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 29 (0.362 g, 1.06 mmol, 17%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (1H, d, *J* = 8.5 Hz), 6.84 (1H, d, *J* = 2.5 Hz), 6.74 (1H, dd, *J* = 8.5, 2.5 Hz), 6.53 (2H, s), 6.37 (1H, t, *J* = 7.5 Hz), 3.78 (3H, s), 3.81 (3H, s), 3.79 (6H, s) 2.65 (2H, t, *J* = 7 Hz), 2.18 (2H, p, *J* = 7 Hz), 1.98 (2H, q, *J* = 7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 152.8, 143.7, 142.7, 138.5, 137.3, 132.3, 130.5, 126.8, 113.8, 111.1, 105.1, 60.7, 55.9, 54.9, 35.0, 32.7, 25.4. HRMS: Obsvd 363.1574 [M + Na^+], Calcd for $C_{21}H_{24}O_4Na$: 363.1567. HPLC (Method B): 18.33 min.

3-Methoxy-6,7-dihydro-5H-*benzo[7]annulen-9-yl trifluoromethanesulfonate (59).* To an oven dried flask, diisopropylamine (1.74 mL, 12.4 mmol) dissolved in THF (50 mL) was added and cooled to -78 °C. Then *n*-BuLi (5.0 mL, 12 mmol) was added, and the reaction was stirred for 15 min. Benzosuberone 14 (2.14 g, 11.3 mmol) dissolved in THF was added dropwise and stirred for 2 h at -78 °C. *N*-Phenyl-bis(trifluoromethanesulfonimide) (4.42 g, 12.4 mmol) dissolved in THF was then added dropwise, and the reaction mixture was stirred for 12 h while warming from -78 °C to room temperature. After 12 h, the THF was evaporated under reduced pressure, and the resulting solid was washed with water and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B

(1 CV), 2%A / 98%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford triflate 59 (2.28 g, 7.07 mmol, 68%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) 7.51(1H, d, *J* = 8.5 Hz), 6.86 (1H, dd, *J* = 8.5, 2.5 Hz), 6.81 (1H, d, *J* = 3 Hz), 6.15 (1H, t, *J* = 6 Hz), 3.79 (3H, s), 2.77 (2H, t, *J* = 6.5 Hz), 2.20 (2H, q, *J* = 7 Hz), 2.04 (2H, q, *J* = 7 Hz).

3-Methoxy-9-(2´,3´,4´-trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulene (62).* Triflate 59 (2.28 g, 7.07 mmol) was dissolved in THF, and 2,3,4-trimethoxyphenyl boronic acid (1.65 g, 7.78 mmol), barium hydroxide octahydrate (3.35 g, 10.6 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.24 g, 0.21 mmol) were added to the solution and refluxed at 80 °C for 2 h. The solution was then filtered through Celite®, and the Celite® was washed with dichloromethane (3 x 30 mL). The combined organic solution (THF and dichloromethane) was evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography using a pre-packed 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 45%A / 55%B (10 CV), 45%A / 55%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 62 (1.05 g, 3.08 mmol, 44%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (1H, d, *J* = 8.5 Hz), 6.88 (1H, d, *J* = 2.5 Hz), 6.77 (1H, dd, *J* = 8.5, 2.5 Hz), 6.58 (2H, s), 6.41 (1H, t, *J* = 7.5 Hz), 3.91 (3H, s), 3.83 (3H s), 3.82 (6H, s), 2.69 (2H, t, *J* = 7 Hz), 2.21 (2H, p, *J* = 7 Hz), 2.00 (2H, q, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 153.4, 152.8, 143.6, 142.7, 138.3, 137.4, 132.3, 130.4, 126.7, 123.5, 113.8, 111.1, 105.2, 60.6, 60.1, 55.8, 54.8, 35.0, 32.7, 25.4. HRMS: Obsvd 363.1573 [M + Na^+], Calcd for $C_{21}H_{24}O_4Na$: 363.1567. HPLC (Method B): 18.23 min.

3-Methoxy-9-(4´-methoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulene (37).* To a solution of 4-methoxyphenyl bromide (0.886 g, 4.73 mmol) in THF (50 mL) at -78 ºC was added *n*-BuLi (3.4 mL, 2.5 M in hexanes), and the reaction mixture was stirred for 30 min. Benzosuberone 14 (0.601 g, 3.15 mmol) in THF (25 mL) was added dropwise over a period of 15 min. The reaction mixture was stirred while warming to room temperature over 12 h. Water was added, and the mixture was extracted with EtOAc (100 mL). The organic extract was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and subjected to flash chromatography using a pre-packed 40 g silica column [solvent A, EtOAc, solvent B, hexanes; gradient 0%A/100%B →100%A/0%B over 22.9 min; flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford benzosuberene analogue 37 (0.32 g, 1.1 mmol, 36%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.20 (2H, d, *J* = 8.7 Hz), 6.94 (1H, d, *J* = 8.4 Hz), 6.83 (2H, d, *J* = 8.5 Hz), 6.82 (1H, d, *J* = 2.5 Hz), 6.73 (1H, dd, *J* = 8.5, 2.7 Hz), 6.29 (1H, t, *J* = 7.5 Hz) 3.83 (3H, s), 3.81 (3H, s), 2.63 (2H, t, *J* = 7.0 Hz), 2.16 (2H, p, *J* = 7.1 Hz), 1.96 (2H, q, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.8, 158.3, 143.8, 142.1, 135.3, 133.0, 130.4, 125.9, 113.9, 113.5, 113.5, 111.1, 55.3, 55.2, 35.2, 32.8, 25.4. HRMS: Obsvd 311.1713 [M + H^+], Calcd for $C_{20}H_{21}O_3$: 311.1642. HPLC (Method B): 17.65 min.

3-Methoxy-2-methylbenzaldehyde.[144] *N´,N´,N´*-trimethylethylene diamine (1.84 mL, 14.3 mmol) was dissolved in benzene (25 mL) and cooled to 0° C. *n*-BuLi (5.5 mL, 13 mmol) was added dropwise, and the reaction mixture was stirred for 10 min at room temperature. The reaction mixture was again cooled to 0° C, and *m*-anisaldehyde (1.54 mL, 13.3 mmol) was added. The reaction mixture was stirred for 15 min at room temperature and then cooled to 0° C. Phenyllithium (22.0 mL, 40.0 mmol) was added

dropwise. The reaction mixture was stirred for 12 h at room temperature. THF (20 mL) was then added, and the reaction mixture was cooled to -78 °C. Methyl iodide (5.0 mL, 80 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was poured into cold 10% HCl (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified using a pre-packed 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford 3-methoxy-2-methylbenzaldehyde (2.01 g, 14.3 mmol, 98%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (1H, s), 7.10 (1H, d, *J* = 8 Hz), 6.98 (1H, t, *J* = 8 Hz), 6.74 (1H, d, *J* = 8 Hz), 3.54 (3H, s), 2.23 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 157.8, 134.9, 128.9, 126.3, 122.7, 114.8, 55.3, 10.0.

5-(3´-Methoxy-2´-methylphenyl)pent-4-enoic acid (3). To dissolved 3-(carboxypropyl)triphenyl phosphonium bromide (6.55 g, 15.3 mmol) in THF was added potassium *tert*-butoxide (3.30 g, 29.0 mmol), and the reaction mixture was stirred at room temperature for 1 h. 3-Methoxy-2-methylbenzaldehyde (2.01 g, 13.4 mmol) dissolved in THF was added to the original reaction mixture, and the reaction mixture was stirred at room temperature for 12 h. The THF was evaporated, and the resulting material was quenched with 2 M HCl (75 mL) and extracted with EtOAc (3 x 100 mL). The combined organic phase was evaporated under reduced pressure and purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 12%A / 88%B (1 CV), 12%A / 88%B → 75%A / 25%B (10 CV),

75%A / 25%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford carboxylic acid 3 (2.12 g, 9.62 mmol, 69%) as a yellow oil. NMR characterization was performed after the next step.

5-(3´-Methoxy-2´-methylphenyl)pentanoic acid (9). To dissolved carboxylic acid 3 (2.12 g, 9.62 mmol) in MeOH (100 mL) was added 10% palladium on carbon (0.44 g) and hydrogen gas. The reaction mixture was stirred at room temperature for 12 h. The mixture was then filtered through Celite®, and the Celite® was washed with EtOAc (3 x 50 mL). The combined organic phase (MeOH and EtOAc) was evaporated under reduced pressure. The residue was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford carboxylic acid 9 (1.20 g, 5.40 mmol, 59%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.94 (1H, s), 7.23 (1H, t, *J* = 8 Hz), 6.91 (1H, d, *J* = 7.5 Hz), 6.84 (1H, d, *J* = 8.5 Hz), 3.93 (3H, s), 2.77 (2H, t, *J* = 8 Hz), 2.51 (2H, t, *J* = 7 Hz), 2.34 (3H, s), 1.86 (2H, p, *J* = 7.5 Hz), 1.75 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 157.9, 141.6, 126.1, 124.5, 121.6, 108.0, 55.5, 34.1, 33.4, 30.0, 24.7, 11.3.

2-Methoxy-1-methyl-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-one (15).* To carboxylic acid 9 (1.20 g, 5.40 mmol) was added Eaton's reagent (10.8 mL, 3 g per mmol of compound 9), and the mixture was stirred at room temperature for 12 h. It was then poured over ice and neutralized with sodium bicarbonate. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium

sulfate, evaporated under reduced pressure, and purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford benzosuberone **15** (2.43 g, 11.0 mmol, 74%) as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (1H, d, *J* = 8.5 Hz), 6.64 (1H, d, *J* = 8.5 Hz), 3.72 (3H, s), 2.76 (2H, t, *J* = 6 Hz), 2.53 (2H, t, *J* = 6 Hz), 2.09 (3H, s), 1.69 (2H, p, *J* = 7.5 Hz), 1.61 (2H, p, *J* = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9, 160.4, 140.4, 132.6, 127.4, 123.7, 107.6, 55.4, 40.4, 27.0, 24.1, 20.6, 11.0.

2-Methoxy-1-methyl-5-(3,´4´,5-trimethoxyphenyl)-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-ol (21).* To an oven dried flask, THF (50 mL) and 3,4,5-trimethoxyphenyl bromide (0.85 g, 3.4 mmol) were added, and the solution was cooled to -78 °C. *n*-Buli (1.5 mL, 3.6 mmol) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h. Benzosuberone 15 (0.52 g, 2.6 mmol) was then added dropwise to the flask, and the reaction mixture was stirred while warming from -78 °C to room temperature over 12 h. The reaction mixture was washed with water and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 60%A / 50%B (10 CV), 60%A / 50%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford tertiary alcohol 21 (2.29 g, 6.39 mmol, 76%) as a light yellow oil. NMR characterization was performed after the next step.

3-Methoxy-4-methyl-9-(3´,4´,5´-trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulene (30).* Acetic acid (15 mL) was added to tertiary alcohol 21 (0.48 g, 1.3 mmol), and the reaction mixture was stirred for 12 h at room temperature. The mixture was washed with water and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 30 (0.16. g, 0.45 mmol, 36%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (1H, d, *J* = 8.5 Hz), 6.69 (1H, d, *J* = 8.5 Hz), 6.53 (2H, s), 6.33 (1H, t, *J* = 7 Hz), 3.87 (3H, s), 3.82 (3H s,) 3.80 (6H, s), 2.69 (2H, t, *J* = 6.5 Hz), 2.29 (3H, s), 2.12 (2H, p, *J* = 7 Hz), 1.91 (2H, q, *J* = 7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 152.8, 143.5, 141.6, 138.5, 137.3, 132.9, 127.4, 126.4, 123.1, 107.4, 105.3, 60.8, 56.1, 55.4, 34.0, 27.7, 25.5, 11.8. HRMS: Obsvd 377.1731 [M + Na^+], Calcd for $C_{22}H_{26}O_5Na$: 377.1723. HPLC (Method B): 19.56 min.

2-Ethyl-3-methoxybenzaldehyde.[145] *N',N'N'*-trimethylethlene diamine (1.36 mL, 10.5 mmol) was dissolved in benzene (25 mL) and cooled to 0° C. *n*-BuLi (4.05 mL, 10.1 mmol) was added dropwise, and the reaction mixture was stirred for 10 min at room temperature. The reaction mixture was again cooled to 0 °C, *m*-anisaldehyde (1.34 mL, 9.84 mmol) was added, and the reaction mixture was stirred for 15 min at room temperature. The reaction mixture was then cooled to 0 °C, and phenyllithium (16.4 mL, 29.5 mmol) was added dropwise. The reaction mixture was stirred overnight at room

temperature. THF (20 mL) was then added, and the reaction mixture was cooled to -78 °C. Ethyl iodide (3.7 mL, 59 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was poured into cold 10% HCl (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford 2-ethyl-3-methoxybenzaldehyde (0.91 g, 5.6 mmol, 57%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (1H, s), 7.37 (1H, dd, *J* = 7.5, 1 Hz), 7.23 (1H, t, *J* = 8 Hz), 7.01 (1H, dd, *J* = 8.5, 1 Hz), 3.79 (3H, s), 3.01 (2H, q, *J* = 7.5 Hz), 1.14 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 157.6, 135.9, 134.4., 126.7, 122.6, 115.5, 55.7, 17.5, 15.3.

5-(2´-Ethyl-3´-methoxyphenyl)pent-4-enoic acid (4). To dissolved 3-(carboxypropyl)triphenyl phosphonium bromide (3.56 g, 8.30 mmol) in THF (500 mL) was added potassium *tert*-butoxide (2.03 g, 18.1 mmol), and the reaction mixture was stirred at room temperature for 1 h. 2-Ethyl-3-methoxybenzaldehyde (1.35 g, 8.22 mmol) dissolved in THF (100 mL) was added to the original reaction mixture and stirred at room temperature for 12 h. The THF was evaporated, and the resulting material was quenched with 2 M HCl (75 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was evaporated under reduced pressure and purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow

rate: 50 mL/min; monitored at 254 and 280 nm] to afford carboxylic acid 4 (1.78 g, 7.60 mmol, 92%) as an orange-yellow oil. NMR characterization was performed after the next step.

5-(2´-Ethyl-3´-methoxyphenyl)pentanoic acid (10). To dissolved carboxylic acid 4 (1.78 g, 7.60 mmol) in MeOH (50 mL) was added 10% palladium on carbon (0.58 g) and hydrogen gas. The reaction was stirred at room temperature for 12 h. The reaction mixture was then filtered through Celite®, and the Celite® was washed with EtOAc (3 x 50 mL). The combined organic phase (MeOH and EtOAc) was evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford carboxylic acid 10 (0.79 g, 3.3 mmol, 44%) as a clear oil. It is likely in this case that the carboxylic acid became methylated. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (1H, t, J = 8 Hz), 6.82 (1H, d, J = 7.5 Hz), 6.75 (1H, d, J = 8.5 Hz), 3.83 (3H, s), 3.70 (3H, s), 2.76 (2H, q, J = 7.5 Hz), 2.70 (2H, t, J = 8 Hz), 2.39 (2H, J = 7.5 Hz), 1.79 (2H, p, J = 7 Hz), 1.68 (2H, p, J = 8 Hz), 1.22, (3H, t, J = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 157.6, 140.9, 130.6, 126.2, 121.7, 108.1, 55.2, 21.2, 33.9, 32.6, 21.1, 25.1, 19.2, 14.5.

*1-Ethyl-2-methoxy-6,7,8,9-tetrahydro-*5H*-benzo[7]annulen-5-one (16).* To carboxylic acid 10 (0.79 g, 3.3 mmol) was added Eaton's reagent (6.7 mL, 3 g per mmol of compound 10), and the reaction mixture was stirred at room temperature for 12 h. The mixture was then poured over ice and neutralized with sodium bicarbonate. The aqueous

layer was extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate, evaporated under reduced pressure, and purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford benzosuberone **16** (0.32 g, 1.6 mmol, 52%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (1H, d, *J* = 8.5 Hz), 6.70 (1H, d, *J* = 8.5 Hz), 3.77 (3H, s), 2.82 (2H, t, *J* = 6 Hz), 2.65 (2H, q, *J* = 7.5 Hz), 2.57 (2H, t, *J* = 6 Hz), 1.75 (2H, p, *J* = 7 Hz), 1.66 (2H, p, *J* = 6.5 Hz), 1.03 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.3, 160.3, 139.5, 132.9, 130.0, 127.7, 108.0, 55.4, 40.4, 25.3, 24.9, 20.4, 18.9, 14.5.

1-Ethyl-2-methoxy-5-(3´,4´,5´-trimethoxyphenyl)-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-ol (22).* To an oven dried flask, THF (50 mL) and 3,4,5-trimethoxyphenyl bromide (0.52 g, 2.1 mmol) were added, and the solution was cooled to -78 °C. *n*-BuLi (0.88 mL, 2.2 mmol) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h. Benzosuberone 16 (0.32 g, 1.54 mmol) was then added dropwise to the flask, and the reaction mixture was stirred while warming from -78° C to room temperature over 12 h. The reaction mixture was washed with water and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford tertiary

alcohol 22 (0.20 g, 0.52 mmol, 33%) as a light yellow oil. NMR characterization was performed after the next step.

4-Ethyl-3-methoxy-9-(3´,4´,5´-trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulene (31).* Acetic acid (15 mL) was added to tertiary alcohol 22 (0.20 g, 0.52 mmol), and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was washed with water and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 50%B (10 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 31 (0.085 g, 0.32 mmol, 45%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (1H, d, *J* = 8.5 Hz), 6.69 (1H, d, *J* = 8.5 Hz), 6.52 (2H, s), 6.32 (1H, t, *J* = 7.5 Hz), 3.86 (3H, s), 3.83 (3H, s), 3.81 (6H, s), 2.78 (2H, q, *J* = 7.5 Hz), 2.69 (2H, t, *J* = 6.5 Hz), 2.14 (2H, p, *J* = 7 Hz), 1.92 (2H, q, *J* = 7 Hz), 1.18 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 153.1, 143.8, 141.3, 139.0, 137.6, 133.4, 129.9, 127.9, 126.7, 107.8, 105.6, 61.2, 56.4, 55.7, 35.2, 27.5, 25.7, 20.0, 15.2. HRMS: Obsvd 391.1891 [M + Na^+], Calcd for $C_{23}H_{28}O_4Na$: 391.1880. HPLC (Method B): 20.66 min.

3-Methoxy-2-propylbenzaldehyde.[146] *N´,N´,N´*-trimethylethlene diamine (1.55 mL, 12.0 mmol) was dissolved in benzene (25 mL) and cooled to 0° C. *n*-BuLi (4.6 mL, 11 mmol) was added dropwise, and the reaction mixture was stirred for 10 min at room temperature. The reaction mixture was again cooled to 0 °C, and *m*-anisaldehyde (1.30

mL, 11.2 mmol) was added. The reaction mixture was stirred for 15 min at room temperature and cooled to 0° C. Phenyllithium (18.7 mL, 33.7 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. THF (20 mL) was then added, and the reaction mixture was cooled to -78° C. Propyl iodide (6.7 mL, 67.32 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was poured into cold 10% HCl (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford 3-methoxy-2-propylbenzaldehyde (1.82 g, 10.2 mmol, 91%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.19 (1H, s), 7.32 (1H, d, *J* = 8 Hz), 7.16 (1H, t, *J* = 7.5 Hz), 6.95 (1H, d, *J* = 8 Hz), 3.71 (3H, s), 2.94 (2H, t, *J* = 7 Hz), 1.48 (2H, sext, *J* = 7.5 Hz), 0.88 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 157.8, 134.8, 134.3, 126.7, 122.3, 115.3, 55.5, 25.8, 24.2, 14.0.

5-(3´-Methoxy-2´-propylphenyl)pent-4-enoic acid (5). To dissolved 3-(carboxypropyl)triphenyl phosphonium bromide (4.43 g, 10.3 mmol) in THF (500 mL) was added potassium *tert*-butoxide (2.52 g, 22.5 mmol), and the reaction mixture was stirred at room temperature for 1 h. 3-Methoxy-2-propylbenzaldehyde (1.82 g, 10.2 mmol) dissolved in THF (100 mL) was added to the original reaction mixture and stirred at room temperature for 12 h. The THF was evaporated, and the residue was quenched with 2 M HCl (75 mL) and extracted with EtOAc (3 x 100 mL). The combined organic

phase was evaporated under reduced pressure and purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford compound 5 (2.25 g, 9.06 mmol, 89%) as a yellow oil. NMR characterization was performed after the next step.

5-(3´-Methoxy-2´-propylphenyl)pentanoic acid (11). To dissolved compound 5 (2.25 g, 9.06 mmol) in MeOH (50 mL) was added 10% palladium on carbon (0.47 g) and hydrogen gas. The reaction mixture was stirred at room temperature for 12 h. The mixture was then filtered through Celite®, and the Celite® was washed with EtOAc (3 x 50 mL). The combined organic phase (MeOH and EtOAc) was evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford compound 11 (0.87 g, 3.5 mmol, 38%) as a clear oil. It is likely that the carboxylic acid was methylated during this reaction. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (1H, t, *J* = 8 Hz), 6.83 (1H, d, *J* = 7.5 Hz), 6.75 (1H, d, *J* = 8 Hz), 3.82 (3H, s), 3.71 (3H, s), 2.71 (4H, m), 2.40 (2H, t, *J* = 7.5 Hz), 1.79 (2H, p, *J* = 7.5 Hz), 1.66 (4H, m), 1.09 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 157.5, 140.9, 128.8, 125.9, 121.2, 107.6, 54.8, 50.9, 33.5, 32.3, 30.7, 27.8, 24.7, 23.1, 14.2.

2-Methoxy-1-propyl-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-one (17).* To carboxylic acid 11 (0.87 g, 3.5 mmol) was added Eaton's reagent (7.0 mL, 3 g per mmol

of compound 11), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then poured over ice and neutralized with sodium bicarbonate. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford benzosuberone **17** (0.56 g, 2.41 mmol, 69%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (1H, d, *J* = 8.5 Hz), 6.68 (1H, d, *J* = 8.5 Hz), 3.75 (3H, s), 2.81 (2H, t, *J* = 6.5 Hz), 2.59 (4H, m), 1.74 (2H, p, *J* = 7 Hz), 1.65 (2H, p, *J* = 6 Hz), 1.42 (2H, sext, *J* = 7.5 Hz), 0.91 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.2, 160.4, 139.7, 132.9, 128.5, 127.6, 107.8, 55.2, 40.3, 27.6, 25.3, 24.8, 23.2, 20.3, 14.2.

2-Methoxy-1-propyl-5-(3´,4´,5´-trimethoxyphenyl)-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-ol (23).* To an oven dried flask, THF (50 mL) and 3,4,5-trimethoxyphenyl bromide (0.80 g, 3.3 mmol) were added, and the solution was cooled to -78 °C. *n*-BuLi (1.4 mL, 3.4 mmol) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h. Benzosuberone 17 (0.56 g, 2.4 mmol) was then added dropwise to the flask, and the reaction mixture was stirred while warming from -78° C to room temperature over 12 h. The reaction mixture was washed with water and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction product was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B:

hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford tertiary alcohol **23** (0.53g, 1.3 mmol, 52%) as a colorless oil. NMR characterization was performed after the next step.

3-Methoxy-4-propyl-9-(3´,4´,5´-trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulene (32).* Acetic acid (10 mL) was added to tertiary alcohol 23 (0.53 g, 1.3 mmol), and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was washed with water and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 32 (0.13 g, 0.34 mmol, 25%) as a cream-colored solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (1H, d, *J* = 8.5 Hz), 6.70 (1H, d, *J* = 8.5 Hz), 6.53 (2H, s), 6.33 (1H, t, *J* = 7.5 Hz), 3.88 (3H, s), 3.84 (3H, s), 3.82 (6H, s), 2.72 (4H, m), 2.15 (2H, p, *J* = 7 Hz), 1.93 (2H, q, *J* = 7 Hz), 1.59 (2H, sext, *J* = 7 Hz), 1.04 (3H, t, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 152.8, 143.5, 141.3, 138.7, 137.3, 133.1, 128.3, 127.6, 126.4, 107.5, 105.3, 60.9, 56.2, 55.4, 35.0, 28.6, 27.3, 25.5, 23.8, 14.5. HRMS: Obsvd 405.2043 [M + Na^+], Calcd for $C_{24}H_{30}O_4Na^+$: 405.2036. HPLC (Method B): 21.53 min.

*2-(2´,3´-Dimethoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole***.**[147,148] A mixture of 2,3-dimethoxybenzoic acid (5.00 g, 27.5 mmol) in $SOCl_2$ (10 mL) was stirred at room

temperature for 24 h. The excess of $SOCl_2$ was evaporated under reduced pressure, and the residue was diluted with CH_2Cl_2. (80 mL). This solution was added dropwise to a solution of 2-amino-2-methylpropan-1-ol (4.89 g, 55 mmol) in CH_2Cl_2 (150 mL) at -10 °C and stirred for 20 h while warming to room temperature. The resulting suspension was filtered, and the filtrate was evaporated to give the crystalline amide. The latter was treated dropwise with $SOCl_2$ (10 mL) and stirred at room temperature for another 7 h. The mixture was then poured into diethyl ether (400 mL) to form a suspension, which was then cooled to 0° C, and aqueous NaOH solution (20%, 100 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A/ 93%B (3 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/ 40%B (1 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford 2-(2,3-dimethoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (5.22 g, 22.2 mmol, 81%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31-7.00 (3H, m), 4.11 (2H, s), 3.86 (6H, m), 1.39 (6H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.3, 153.3, 148.7, 123.8, 123.4, 122.6, 115.0, 79.2, 67.3, 61.4, 56.1, 28.3.

2-(2´-Butyl-3´-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole.[149] A solution of 2-(2,3-dimethoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (5.02 g, 21.4 mmol) in THF (80 mL) was stirred and cooled to -40 °C in a cyclohexanone/dry ice bath. *n*-BuLi (13 mL, 2.5 M) was added dropwise to the reaction flask. The reaction mixture was stirred for 5 h while warming to 0° C. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether (3 x 30 mL). The combined organic phase was dried with

Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A/ 93%B (3 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/40%B (1 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford 2-(2-butyl-3-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole as yellow liquid (4.99 g, 19.1 mmol, 89%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.23 (1H, dd, *J* = 7.5 Hz, 1.2 Hz), 7.15 (1H, t, *J* = 8.0 Hz), 6.91 (1H, dd, *J* = 8.1, 1.1 Hz), 4.07 (2H, s), 3.82 (3H, s), 1.53-1.47 (2H, m), 1.38 (6H, s), 1.41-1.33 (4H, m), 0.93 (3H, t, *J* = 7.4Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.0, 157.7, 132.0, 129.2, 126.1, 121.9, 112.3, 78.8, 67.7, 55.7, 32.4, 28.4, 26.5, 23.1, 14.0.

*2-Butyl-3-methoxybenzoic acid***.**[149,150] A solution of 2-(2-butyl-3-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (4.69 g, 17.95 mmol) in 4.5 M HCl (100 mL) was refluxed for 21 h. After cooling to room temperature, the reaction mixture was extracted with diethyl ether (3 x 30 mL), and the combined organic phase was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A/ 93%B (3 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/40%B (1 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford 2-butyl-3-methoxybenzoic acid as a colorless liquid (2.45 g, 11.8 mmol, 65%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (1H, dd, *J* = 7.9 Hz, 1.1 Hz), 7.24 (1H, t, *J* = 8.0 Hz), 7.05 (1H, dd, *J* = 8.3 Hz, 0.9 Hz), 3.87 (3H, s), 3.01 (2H, m), 1.54 (2H, m), 1.43 (2H, m), 0.95 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1, 158.0, 134.5, 129.9, 126.2, 122.9, 114.4, 55.8, 32.4, 26.3, 23.1, 13.9.

(2-Butyl-3-methoxyphenyl)methanol. 2-butyl-3-methoxybenzoic acid (2.45 g, 11.8 mmol) was dissolved in THF (40 mL) and stirred for 10 min. $LiAlH_4$ (7.6 mL, 2.0 M) was then added dropwise, and the reaction mixture was stirred for 10 h while warming to room temperature. The reaction was carefully quenched with a H_2O/THF (1:4) solution, followed by aqueous NaOH (15%, 20 mL), and a precipitate formed. The unwanted precipitate was was removed by filtration through Celite®. The Celite® and unwanted precipitate were washed with CH_2Cl_2. The H_2O/THF/CH_2Cl_2 filtrate was extracted with EtOAc (3 x 30 mL), and the organic layer was rinsed with brine and dried with Na_2SO_4. The crude reaction product was purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A/ 93%B (3 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/ 40%B (1 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford (2-butyl-3-methoxyphenyl)methanol as a colorless liquid (1.94 g, 9.97 mmol, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.19 (1H, t, *J* = 8.5 Hz), 7.01 (1H, d, *J* = 7.6 Hz), 6.83 (1H, d, *J* = 8.3 Hz), 4.72 (2H, d, *J* = 5.3 Hz), 3.83 (3H, s), 2.69 (2H, t, *J* = 7.4 Hz), 1.49 (4H, m), 0.95 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.7,139.6, 129.8, 126.6, 120.4, 110.0, 63.2, 55.5, 32.4, 25.5, 23.1, 14.0.

*2-Butyl-3-methoxybenzaldehyde***.** To a well stirred solution of pyridinium chlorochromate (2.586 g, 12 mmol) in CH_2Cl_2 (20 mL) at room temperature, (2-butyl-3-methoxyphenyl)methanol (1.936 g, 9.97 mmol) dissolved in CH_2Cl_2 (15 mL) was slowly added via syringe. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through Celite®, and the Celite® was washed thoroughly with CH_2Cl_2. The filtrate was concentrated under reduced pressure and further purified

by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A/ 93%B (3 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/ 40%B (1 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford 2-butyl-3-methoxybenzaldehyde as a dark yellow liquid (1.91 g, 9.93 mmol, 99%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.34 (1H, s), 7.46 (1H, dd, *J* = 7.8 Hz, 1.1 Hz), 7.30 (1H, t, *J* = 8.0 Hz), 7.09 (1H, dd, *J* = 8.1 Hz, 0.75 Hz), 3.87 (3H, s), 3.06 (2H, m), 1.53 (2H, m), 1.42 (2H, m), 0.95 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.3, 157.8, 135.0, 134.7, 126.7, 122.1, 115.5, 55.8, 33.5, 23.8, 22.8, 13.9.

5-(2´-Butyl-3´-methoxyphenyl)pent-4-enoic acid (6). A mixture of 3-(carboxypropyl) triphenylphosphonium bromide (4.52 g, 10.6 mmol) and potassium *tert*-butoxide (2.62 g, 23.2 mmol) in THF (100 mL) was stirred for 1 h at room temperature. 2-Butyl-3-methoxybenzaldehyde (2.03 g, 10.6 mmol) in THF (20 mL) was added dropwise to the reaction mixture and stirred for 12 h at room temperature. The reaction was quenched with 2 M HCl (15 mL), then extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A/ 93%B (3 CV), 7%A/ 3%B → 60%A/40% B (10 CV), 60%A/ 40%B (1 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford carboxylic acid 6 (2.38 g, 9.07 mmol, 86%). NMR characterization was performed after the next step.

5-(2´-Butyl-3´-methoxyphenyl)pentanoic acid (12). Carboxylic acid 6 (2.38 g, 9.07 mmol) was mixed with 10% Pd/C (0.15 g). Methanol (25 mL) was slowly added, and the reaction mixture was stirred for 12 h at room temperature under a H_2 atmosphere. The suspension was filtered through Celite®, and the Celite® was rinsed with EtOAc. The filtrate (MeOH and EtOAc) was concentrated under reduced pressure, and the crude reaction product was purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 20%A/ 80%B (3 CV), 20%A/ 80%B → 100%A/ 0%B (10 CV), 100%A/ 0%B (1 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford carboxylic acid 12 (1.48 g, 56.0 mmol, 61%) as a yellow-brown liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.09 (1H, t, *J* = 7.9 Hz), 6.77 (1H, d, *J* = 7.6 Hz), 6.72 (1H, d, *J* = 8.1 Hz), 3.81 (3H, s), 2.63 (4H, m), 2.40 (2H, t, *J* = 7.3 Hz), 1.75 (2H, m), 1.64 (2H, m), 1.44 (4H, m), 0.96 (3H, t, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.4, 157.7, 141.1, 129.5, 126.1, 121.5, 108.1, 55.4, 34.0, 32.5, 32.3, 30.8, 25.7, 24.8, 23.2, 14.0.

1-Butyl-2-methoxy-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-one (18).* Eaton's reagent (28 mL) was added to carboxylic acid 12 (1.48 g, 5.6 mmol) and sonicated until the 12 dissolved. The reaction mixture was then stirred at room temperature for 12 h. Ice was poured into the reaction flask, and then the reaction mixture was neutralized with a sat. $NaHCO_3$ solution and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A/ 93%B (3 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/ 40%B (1 CV); flow rate: 40 mL/min;

monitored at 254 and 280 nm] to afford ketone 18 (1.13 g, 4.59 mmol, 82%) as a yellow liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (1H, d, *J* = 8.6 Hz), 6.77 (1H, d, *J* = 8.6 Hz), 3.86 (3H, s), 2.89 (2H, m), 2.67 (4H, m), 1.83 (2H, p, *J* = 6.5 Hz), 1.75 (2H, m), 1.42 (4H, m), 0.96 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.8, 160.6, 139.8, 133.0, 128.9, 127.7, 108.0, 55.5, 40.5, 32.5, 26.5, 25.5, 25.5, 23.0, 20.0, 20.5, 14.0.

1-Butyl-2-methoxy-5-(3´,4´,5´-trimethoxyphenyl)-6,7,8,9-tetrahydro-5H-*benzo[7]annulen-5-ol (24).* 5-Bromo-1,2,3-trimethoxybenzene (1.70 g, 6.9 mmol) was dissolved in THF (20 mL) and cooled to -78 °C. *n*-BuLi (4.06 mL, 2.5 M) was added dropwise, and the reaction mixture was stirred at -78° C. After 1 h, ketone 18 (1.13 g, 4.6 mmol) in THF (15 mL) was added dropwise to the reaction flask. The reaction mixture was stirred for 12 h while warming to room temperature. The reaction was quenched with water (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A/ 93%B (3 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/ 40%B (1 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford tertiary alcohol 24 (0.76 g, 1.8 mmol, 40%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (1H, d, *J* = 8.7 Hz), 6.72 (1H, d, *J* = 8.8 Hz), 6.51 (2H, s), 3.84 (3H, s), 3.82 (3H, s), 3.74 (6H, s), 2.96 (2H, m), 2.67 (4H, m), 1.82 (4H, m), 1.39 (4H, m), 0.92 (3H, t, *J* = 6.9 Hz).

4-Butyl-3-methoxy-9-(3´,4´,5´-trimethoxyphenyl)-6,7-dihydro-5H-*benzo[7]annulene (33).* The tertiary alcohol 24 (0.76 g, 1.8 mmol) was dissolved in acetic acid (10 mL), and the reaction mixture was stirred for 6 h. The reaction was

quenched with water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A/93%B (3 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/ 40%B (1 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford benzosuberene 33 (0.76 g, 1.8 mmol, quantitative) as a yellowish oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.84 (1H, d, *J* = 8.5 Hz), 6.69 (1H, d, *J* = 8.5 Hz), 6.51 (2H, s), 6.32 (1H, t, *J* = 7.4 Hz), 3.86 (3H, s), 3.83 (3H, s), 3.81 (6H, s), 2.74 (2H, m), 2.68 (2H, t, *J* = 6.9 Hz), 2.13 (2H, p, *J* = 7.0 Hz), 1.91 (2H, q, *J* = 7.3 Hz), 1.53 (2H, m), 1.46 (2H, m), 0.98 (3H, t, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.4, 152.8, 143.5, 141.2, 138.7, 137.3, 133.1, 128.5, 127.5, 126.4, 107.5, 105.3, 60.9, 56.2, 55.4, 34.9, 32.9, 27.3, 26.3, 25.5, 23.2, 14.1. HRMS: Obsvd 397.2374 $[M+H]^+$, calcd for $C_{25}H_{33}O_4$: 397.2373. HPLC (Method B): 22.30 min.

Biological Evaluations

SRB Assay.[151,152] Inhibition of human cancer cell growth was assessed using the sulforhodamine B assay, as previously described.[151] Cancer cell lines were plated at 9000 cells/well into 96-well plates using DMEM supplemented with 5% fetal bovine serum/ 1% gentamicin sulfate and incubated for 24 h. Serial dilutions of the compounds were then added. After 48 h, the cells were fixed with trichloroacetic acid, washed, dried, stained with sulforhodamine B dye (Acid red 52), solubilized, and read at 540 nm and normalized to 630 nm with an automated Biotek plate reader. A growth inhibition of 50% (GI_{50} or the drug concentration causing 50% reduction in the net protein increase) was calculated from the absorbance data.

Colchicine Binding Assay. Inhibition of [^{3}H]colchicine binding to tubulin was determined using 0.1 mL reaction mixtures. Each reaction mixture contained 1.0 μM tubulin, 5.0 μM [^{3}H]colchicine (from Perkin-Elmer), 5% (v/v) dimethyl sulfoxide, potential inhibitors at 1.0, 5.0 or 50 μM and components that were previously demonstrated to stabilize the colchicine binding activity of tubulin[153] (1.0 M monosodium glutamate [adjusted to pH 6.6 with HCl in a 2.0 M stock solution], 0.5 mg/mL bovine serum albumin, 0.1 M glucose-1-phosphate, 1.0 mM $MgCl_2$, and 1.0 mM GTP). Incubation was for 10 min at 37 °C, a time point at which the binding reaction in the control is 40-60% complete. Reactions were stopped by adding 2.0 mL of ice-cold water and placing the samples on ice. Each sample was poured onto a stack of two DEAE-cellulose filters, followed immediately by 6 mL of ice-cold water, and the water was aspirated under reduced vacuum. The filters were washed with 2 mL water x 3 and, following removal of excess water under a strong vacuum, placed into vials containing 5 mL of Biosafe II scintillation cocktail. Samples were counted the next day in a Beckman scintillation counter. Samples with potential inhibitors were compared to controls with no inhibitor to determine percent inhibition. All samples were corrected for the amount of colchicine that bound to the filters in the absence of tubulin.

Inhibition of Tubulin Polymerization. Tubulin assembly experiments were performed using 0.25 mL reaction mixtures (final volume).[154] The mixtures contained 1 mg/mL (10 μM) purified bovine brain tubulin, 0.8 M monosodium glutamate (pH 6.6, as above), 4% (v/v) dimethyl sulfoxide, 0.4 mM GTP, and varying compound concentrations. Initially, all components except GTP were preincubated for 15 min at 30

°C in 0.24 mL. After chilling the mixtures on ice, 10 μL of 10 mM GTP was added. The reaction mixtures were then transferred to cuvettes held at 0 °C in Beckman DU-7400 and DU-7500 spectrophotometers equipped with electronic temperature controllers. The temperature was jumped to 30 °C over about 30 s, and polymerization was followed turbidimetrically at 350 nm for 20 min. Each reaction set included a reaction mixture without compound, and the IC_{50} was defined as compound concentration that inhibited extent of assembly by 50% after 20 min at 30 °C.

In Vivo Tumor Model. Human breast cancer cells, MDA-MB-231(ATCC), were transfected with a lentivirus containing a firefly luciferase reporter. Highly expressing stable clones were isolated to create the cell line, MDA-MB-231-luc, which was kindly provided by Dr. Edward Graves, Stanford University.[138] Induction of tumors was carried out by injecting 10^6 cells mixed with 30% Matrigel™ (BD Biosciences, San Jose, CA) into the mammary fat pads of female SCID mice (UTSW breeding colony). Tumors were allowed to grow to a size of approximately 5 mm in diameter, determined by calipers, before selection for BLI or histological analysis. All animal procedures were approved by the University of Texas Southwestern Medical Center Institutional Animal Care and Use Committee.

In Vivo Bioluminescence Imaging (BLI). Bioluminescence imaging was carried out as described previously.[155] Briefly, anesthetized, tumor bearing mice (O_2, 2% isoflurane, Henry Schein Inc., Melville, NY) were injected subcutaneously in the fore-back neck region with 80 μL of a solution of luciferase substrate, *D*-luciferin (sodium salt, 120 mg/kg, in saline, Gold Biotechnology, St. Louis, MO). Mice were maintained

under anesthesia (2% isoflurane in oxygen, 1 dm^3/min), while baseline bioluminescence imaging was performed using a Xenogen IVIS® Spectrum (Perkin-Elmer, Alameda, CA). A series of BLI images was collected over 35 min using the following settings: auto exposure time, f-stop = 2, Field of view = D, binning = 4 (medium). Light intensity-time curves obtained from these images were analyzed using Living Image® software. Mice were injected intraperitoneally with either 120 μL of saline (vehicle), CA4P (provided by OXiGENE 120 mg/kg in saline as used previously[32] or analogue 73 (20, 30 or 40 mg/kg) in saline immediately after baseline BLI. Bioluminescence imaging was repeated, with new luciferin injections 4 and 24 h later. Dosing with 20 and 30 mg/kg was repeated in a separate cohort of mice.

Acknowledgements

The authors are grateful to the National Cancer Institute of the National Institutes of Health (Grant No. 5R01CA140674 to K.G.P, M.L.T, and R.P.M), the Cancer Prevention and Research Institute of Texas (CPRIT, Grant No. RP140399 to K.G.P., M.L.T., and R.P.M.), and OXiGENE, Inc. (grant to K.G.P. and M.L.T.) for their financial support of this project, and to the NSF for funding the Varian 500 MHz NMR spectrometer (Grant no. CHE-0420802). The content is solely the responsibility of the authors and does not necessarily reflect the official views of the National Institutes of Health. The authors would also thank Dr. James Karban and Dr. Michelle Nemec (Director) for the use of the shared Molecular Biosciences Center at Baylor University, Dr. Alejandro Ramirez (Mass Spectrometry Core Facility, Baylor University) and Dr. Kevin Klausmeyer and Marissa Penney (X-ray analysis). The authors are grateful to Mr. Tyler Goddard (Baylor University) for his contributions to the synthesis of certain

analogues, and to Jeni Gerberich (UTSW) and Dr. Li Li (UTSW) for valuable technical assistance. Imaging was facilitated with the assistance of Resources of the Harold C. Simmons Cancer Center supported through an National Institutes of Health National Cancer Institute Cancer Center Support Grant [Grant 1P30 CA142543], specifically, the Southwestern Small Animal Imaging Resource, and Live Cell Imaging Resource. The IVIS Spectrum was purchased with support of 1S10RR024757.

Supplementary Data

Supplementary data including ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, ^{31}P NMR, HPLC, HRMS for final target compounds and intermediates (^{1}H NMR, ^{13}C NMR, ^{19}F NMR only), X-ray crystallography for compound 72, an alternative synthetic procedure for compound 30, and molecular docking for compounds 29, 62, and 72 associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.bmc.2015.10.012.

CHAPTER THREE

Synthesis and Biological Evaluation of Benzocyclooctene-based and Indene-based Anticancer Agents that Function as Inhibitors of Tubulin Polymerization

This paper will be published as: Herdman, C.A., Strecker, T.E., Tanpure, R.P. Chen, Z., Winters, A., Gerberich, J., Liu, L., Hamel, E., Mason, R.P., Chaplin, D.J., Trawick, M.L., Pinney, K.G. Synthesis and Biological Evaluation of Benzocyclooctene-based and Indene-based Anticancer Agents that Function as Inhibitors of Tubulin Polymerization.

The author Christine A. Herdman contributed to this manuscript through the synthesis of all eight final compounds including full characterization, which included proton and carbon NMRs, HPLC, and HRMS. In addition, Christine A. Herdman contributed a significant amount to the writing and editing of the manuscript, as well as the preparation of the supporting data.

Abstract

The natural products colchicine and combretastatin A-4 (CA4) have been inspirational for the design and synthesis of structurally related analogues and spin-off compounds as inhibitors of tubulin polymerization. The discovery that a water-soluble phosphate prodrug salt of CA4 (referred to as CA4P) is capable of imparting profound and selective damage to tumor-associated blood vessels paved the way for the development of a new therapeutic approach for cancer treatment utilizing small-molecule inhibitors of tubulin polymerization that also act as vascular disrupting agents (VDAs). Combination of salient structural features associated with colchicine and **CA4** led to the design and synthesis of a variety of fused aryl-cycloalkyl and aryl-heterocyclic compounds that function as inhibitors of tubulin polymerization. Prominent among these

compounds is a benzosuberene analogue (referred to as KPG18), which demonstrates sub-nM cytotoxicity against human cancer cell lines and functions (when administed as a water-soluble prodrug salt) as a VDA in mouse models. Structure activity relationship considerations led to the evaluation of benzocyclooctyl [6,8 fused] and indene [6,5 fused] ring systems. Four benzocyclooctene and four indene analogues were prepared and evaluated biologically. Three of the benzocyclooctene analogues were active as inhibitors of tubulin polymerization (IC_{50} < 5 μM), and benzocyclooctene phenol 23 was comparable to KGP18 in terms of potency. The analogous indene-based compound 31 also functioned as an inhibitor of tubulin polymerization (IC_{50} = 11 μM) with reduced potency. The most potent inhibitor of tubulin polymerization from this group was benzocyclooctene analogue 23, and it was converted to its water-soluble prodrug salt 24 to assess its potential as a VDA. Preliminary *in vivo* studies, which utilized the MCF7-luc-GFP-mCherry breast tumor in a SCID mouse model, demonstrated that treatment with 24 (120 mg/kg) resulted in significant vascular shutdown, as evidenced by bioluminescence imaging at 4 h post administration, and that the effect continued at both 24 and 48 h. Contemporaneous studies with CA4P, a clinically relevant VDA, were carried out as a positive control

Introduction

The colchicine site located on the β-subunit of the α,β-tubulin heterodimer continues to serve as a rich and productive target for a wide-range of structurally diverse small-molecule anticancer agents. Through a direct binding interaction at the colchicine site, these compounds inhibit the polymerization of the tubulin heterodimer into microtubules. Disruption of the inherent dynamic relationship between microtubules and tubulin

heterodimers leads to two mechanistically distinct, yet complementary, cancer treatment strategies. One approach centers on the well known cytotoxic effect that results when disruption of the tubulin-microtubule system, caused by treatment with small-molecule inhibitors of tubulin polymerization or depolymerization, impacts the ability of cancer cells to divide. A wide-range of small-molecule therapeutic agents has been discovered and developed that function as antiproliferative agents through this mechanism (Fig. 3.1).

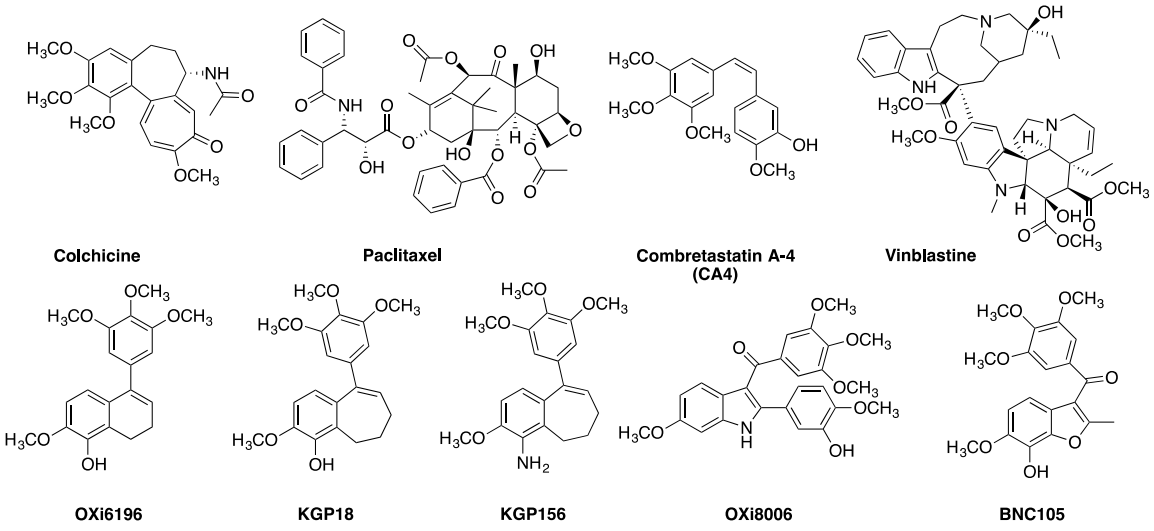


Figure 3.1. Representative small-molecule anti-proliferative agents including colchicine,[39] paclitaxel,[156,157] CA4,[40] vinblastine,[158,159] OXi6196,[61,67] KGP18,[62,64,68] KGP156,[63,64,69] OXi8006,[66] and BNC105.[126,160]

This approach, while productive as an anticancer strategy, has limitations and challenges since both neoplastic and healthy cells are impacted. Targeting strategies such as the use of antibody-drug conjugates (ADCs) bearing active payloads have been successful with two FDA approved ADCs currently available.[161–163] In another example, the targeting of tumor hypoxia with bioreductively activatable prodrug conjugates (BAPCs) has been

explored[164,165] with recent clinical trials involving PR-104[166,167] and TH-302[168–170] serving as representative examples (Fig. 3.2).

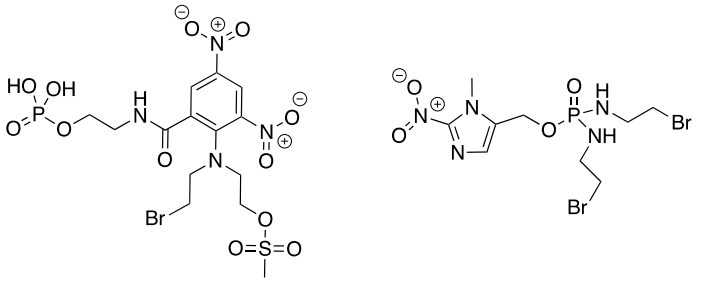


Figure 3.2. Structures of PR-104 and TH-302.

PR-104 is hydrolyzed to its alcohol parent compound by available phosphatases and, under hypoxic conditions, is activated by NADPH-cytochrome P450 reductases to the reactive nitrogen mustards that crosslink to DNA and ultimately cause tumor cytotoxicity.[166] TH-302 utilizes a similar hypoxia reduction strategy in order to release its 2-nitroimidazole trigger leaving the bromo-isophosphoramide mustard to cross link with DNA.[170] The targeting of tumor hypoxia has also been examined with BAPCs that incorporate the tubulin-active natural product combretastatin A-4 (CA4).[171] These strategies, along with others, continue to represent areas of ongoing research effort.

A second mechanistic approach to cancer therapy involving inhibition of the tubulin-microtubule protein system centers on selective disruption of existing vasculature feeding tumors, leading to limitation of oxygen and nutrient delivery to the cells and impedance of the ability of these cells to clear cellular waste products. This ultimately leads to tumor

necrosis. This approach to targeting existing tumor-feeding vasculature utilizes anticancer agents referred to as vascular disrupting agents (VDAs) and is unique and mechanistically distinct from the fairly well-established and more commonly described therapeutic approach employing angiogenesis inhibiting agents (AIAs) that impede the formation of new vessels.[14,17,22] Rapid neovascularization occurs when tumors grow larger than about 1 mm^3, as they can no longer acquire sufficient nutrients from the surrounding vasculature.[19] Such tumors require their own vascular network to supply oxygen and nutrients and remove waste products.[11,17,22] Because of their rapid growth and development, these vessels feature irregular branching and diameter, poor wall structure, abnormal bulges, and blind ends.[3,15,19,21,34] This immature vasculature provides an attractive target for cancer therapy. Therapeutic agents that target tumor vasculature are referred to as vascular targeting agents, which can be divided into the AIAs and VDAs.[3,14,17] AIAs inhibit the growth of new vasculature to the tumor, while VDAs damage already sprouted vessels.[12,21,26,29,34,172] VDAs are sub-divided into biological agents and small-molecule therapeutics (Fig. 3.3),[12] and treatment with either of these entities leads to tumor necrosis.

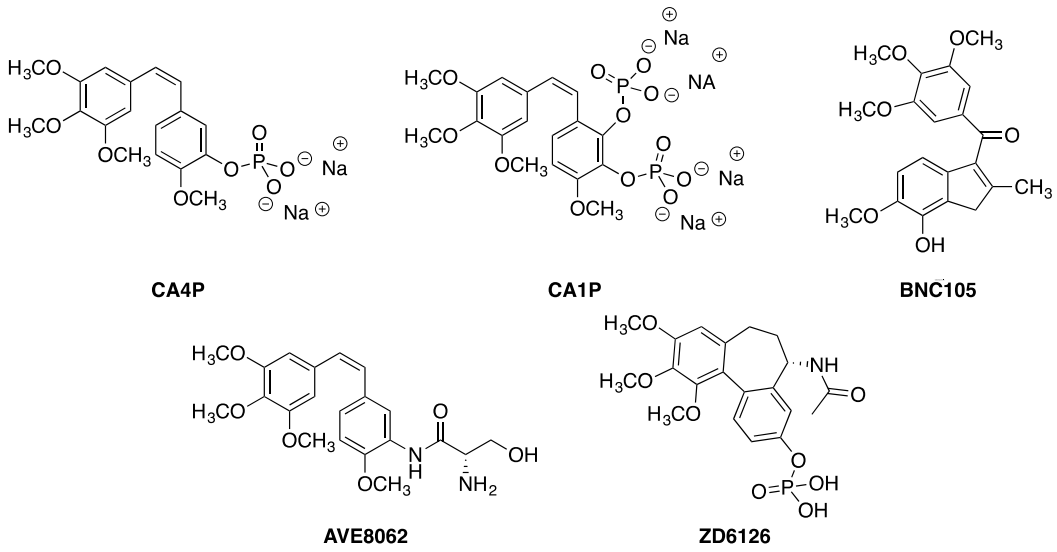


Figure 3.3. Several clinically relevant VDAs including CA4P,[41,44,49,123,173] CA1P,[42,173] BNC105,[123,126,160,173,174] AVE8062,[173,175–177] and ZD6126.[44,173,178]

Colchicine, a natural product originally isolated from the autumn crocus, *Colchicum autumnale*, and the namesake for the colchicine site on tubulin,[39,179] is a potent inhibitor of tubulin polymerization, but colchicine has a narrow therapeutic window limiting its development as an anticancer agent.[32,34,36] Another natural product binding to the colchicine site on tubulin is CA4 (Fig. 3.1).[40] Originally isolated from the African bushwillow tree, *Combretum caffrum*, and synthesized by Pettit and co-workers, CA4 binds tightly to the colchicine site on tubulin and functions as a VDA.[36,122,180,181] Combretastatin A-4P [(CA4P**),** Fig. 3.3] was synthesized as a water-soluble prodrug salt for therapeutic use,[36,41,122,181] and both CA4 and CA4P are now being evaluated in clinical trials.[43–45,49,121,123]

Drawing upon the key structural motifs of colchicine and CA4, the Pinney Research Group (Baylor University) has a long-standing interest in the discovery and development of new small-molecule anticancer agents that function as highly cytotoxic agents and/or

as potent VDAs. Representative examples within this library include combretastatin,[55,56,58,60] benzo[*b*]thiophene,[54] dihydronaphthalene,[62] benzosuberene,[62–64,68] and indole-based analogues.[65,66] The Pinney Research Group had previously shown that expansion of the fused alkyl ring of the dihydronaphthalene anticancer agent known as OXi6196 (Fig. 3.1) by one carbon to the fused seven-membered ring benzosuberene anticancer agent known as KGP18 (Fig. 3.1) was an effective design paradigm, since KGP18 was highly cytotoxic against human cancer cell lines and strongly inhibits tubulin polymerization.

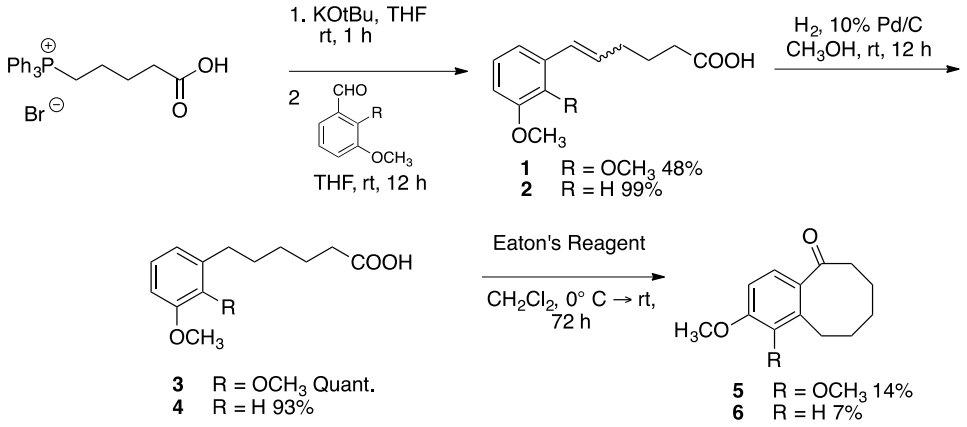
To further elucidate the structure activity relationship (SAR) considerations associated with functionalized fused aryl-carbocyclic ring systems that mimic colchicine and CA4 and their interaction with the tubulin-microtubule system, benzocyclooctene (fused 6,8 ring system) analogues and corresponding indene (fused 6,5 ring system) analogues were prepared by chemical synthesis and subjected to preliminary biological evaluation.

Results and Discussion

Synthesis

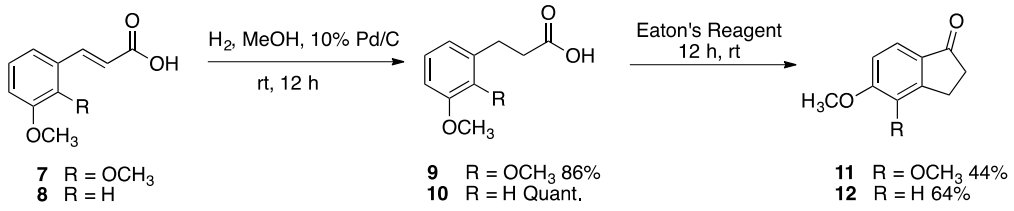
Four benzocyclooctene analogues and four indene analogues were synthesized to further investigate SAR considerations associated with fused aliphatic ring structures and corresponding cytotoxicity and inhibition of tubulin polymerization. These analogues were prepared utilizing a synthetic strategy reminiscent of that employed for a variety of benzosuberene analogues developed in the Pinney Research Group.[64,68] The synthesis of each benzocyclooctene analogue was initiated with a Wittig olefination followed by catalytic hydrogenation to afford carboxylic acids 3 and 4 (Scheme 3.1). A Friedel-Crafts intramolecular annulation was accomplished using Eaton's reagent (7.7 weight

percent P_2O_5 in CH_3SO_3H),[133] and the reaction was diluted and cooled in order to facilitate the construction of benzocyclooctanones 5 and 6 (Scheme 3.1). Without dilution and cooling, the desired product was not formed and only starting material remained.



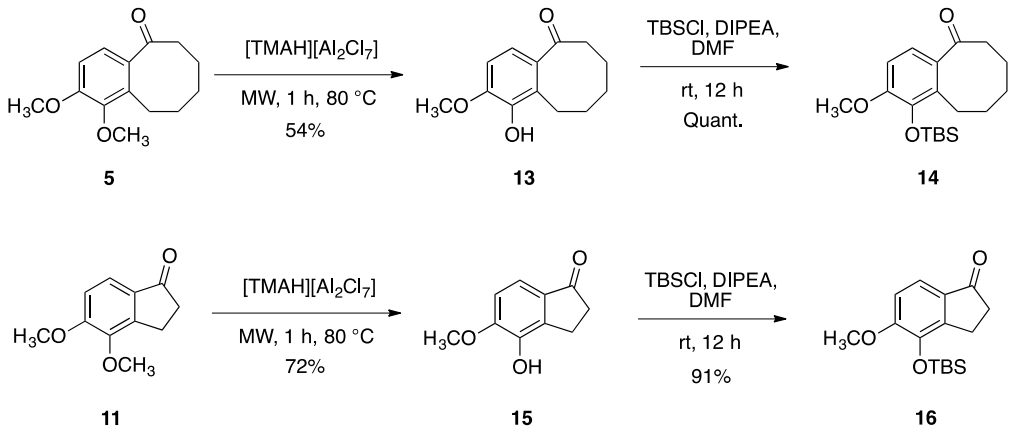
Scheme 3.1. Synthesis of benzocyclooctanone analogues 5 and 6.

A similar catalytic reduction was utilized with starting material *trans*-2,3-dimethoxycinnamic acid to afford carboxylic acids 9 and 10, which were cyclized with Eaton's reagent to their corresponding indanone analogues 11 and 12 (Scheme 3.2).



Scheme 3.2. Synthesis of indanone analogues 11 and 12.

Benzocyclooctanone 5 and indanone 11 bearing the *ortho* dimethoxy motif were each subjected to a selective demethylation[64,68,135] to afford phenolic analogues 13 and 15, which were subsequently protected with TBS to yield 14 and 16 (Scheme 3.3).

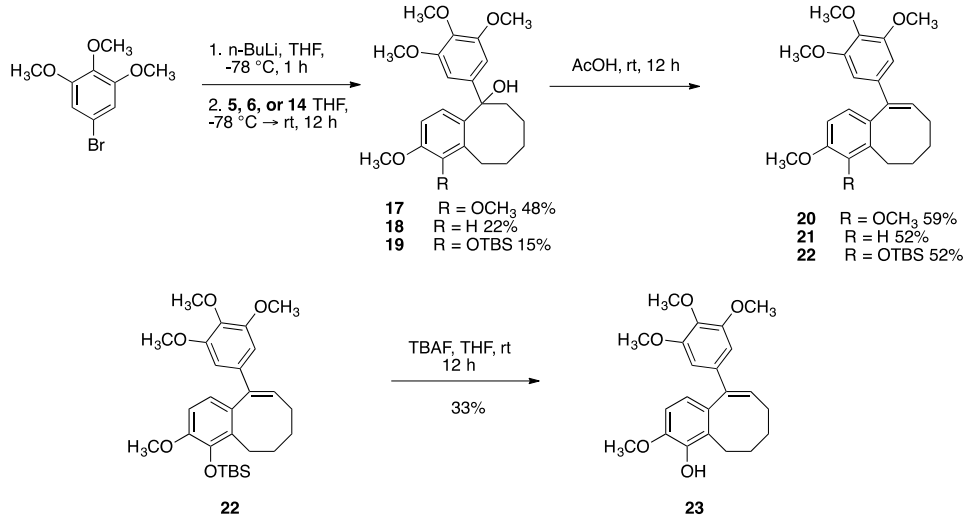


5 **13** **14**

11 **15** **16**

Scheme 3.3. Synthesis of TBS-protected benzocyclooctanone 14 and indanone 16.

Trimethoxyphenyllithium (prepared from the corresponding aryl bromide) underwent a 1,2-addition reaction to benzocyclooctanone analogues 5, 6 and 14 to afford the corresponding tertiary alcohols 17, 18, and 19. Subsequent dehydration afforded benzocyclooctene analogues 20 and 21 and TBS-protected analogue 22, which underwent deprotection to afford phenolic benzocyclooctene 23 (Scheme 3.4).



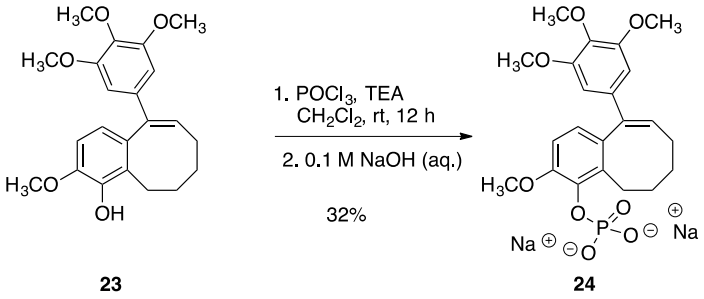
17 R = OCH_3 48%
18 R = H 22%
19 R = OTBS 15%

20 R = OCH_3 59%
21 R = H 52%
22 R = OTBS 52%

22 **23**

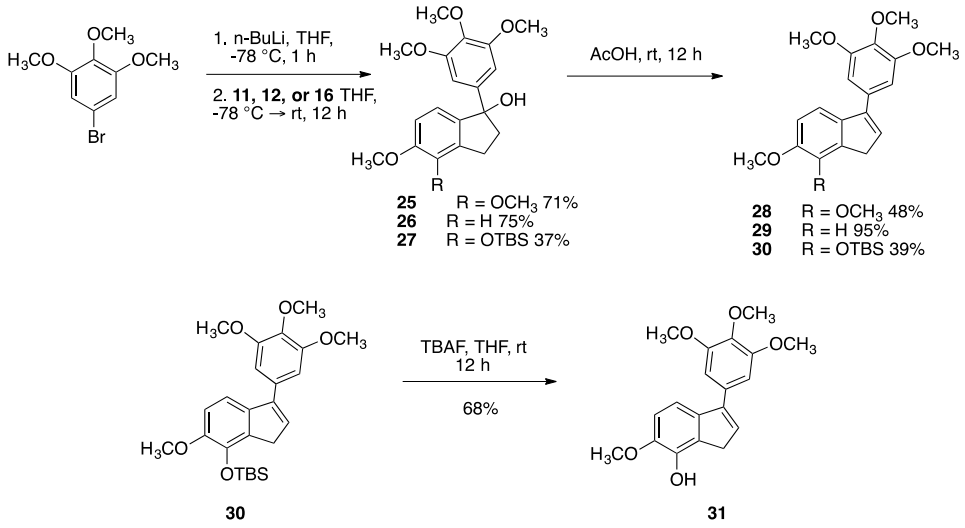
Scheme 3.4. Synthesis of target benzocyclooctene analogues 20, 21, and 23.

Phenolic analogue 23 was converted to its corresponding phosphate prodrug salt 24, in order to increase water solubility for *in vivo* studies (Scheme 3.5).



Scheme 3.5. Conversion of analogue 23 to its corresponding phosphate prodrug salt 24**.**

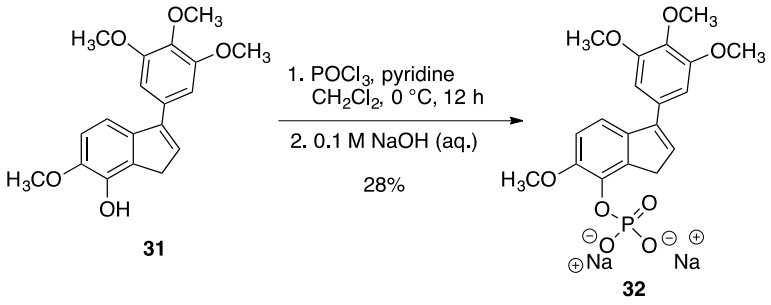
Analogous aryl addition reactions were carried out on indanone intermediates 11, 12, and 16 to generate the corresponding tertiary alcohols 25, 26, and 27 (Scheme 3.6). Subsequent dehydration afforded indene analogues 28 29, and 30. Removal of the TBS group afforded phenolic indene 31.



Scheme 3.6. Synthesis of target indene compounds 28, 29, and 31.

The indene phenol **31** was also converted to its corresponding phosphate salt 32 (Scheme 3.7). While TEA proved to be an acceptable base (due to ease of removal) for use in the

synthesis of the eight membered ring phosphate salt 24, in the synthesis of the indene phosphate salt 32 TEA proved to be hard to remove during purification. Altering the base to pyridine solved this problem and allowed the water-soluble phosphate salt 32 to be synthesized in high purity.



Scheme 3.7. Synthesis of target indene water-soluble analogue 32**.**

Due to their increased size, eight membered rings are the first in the homologous series (3, 4, 5, 6, 7 – membered rings) that can accommodate both *Z* and *E* double bond configurations.[182,183] However, in our hands only the Z configurations were synthesized. X-ray crystal structures were obtained for benzocyclooctene analogues 20 and 23 to confirm their Z double bond configuration (see Supplementary Data).

Biological Evaluation

The four target benzocyclooctene and four indene analogues were evaluated for their cytotoxicity against human cancer cell lines and for their abilities to inhibit tubulin polymerization and colchicine binding to tubulin (Table 3.1).

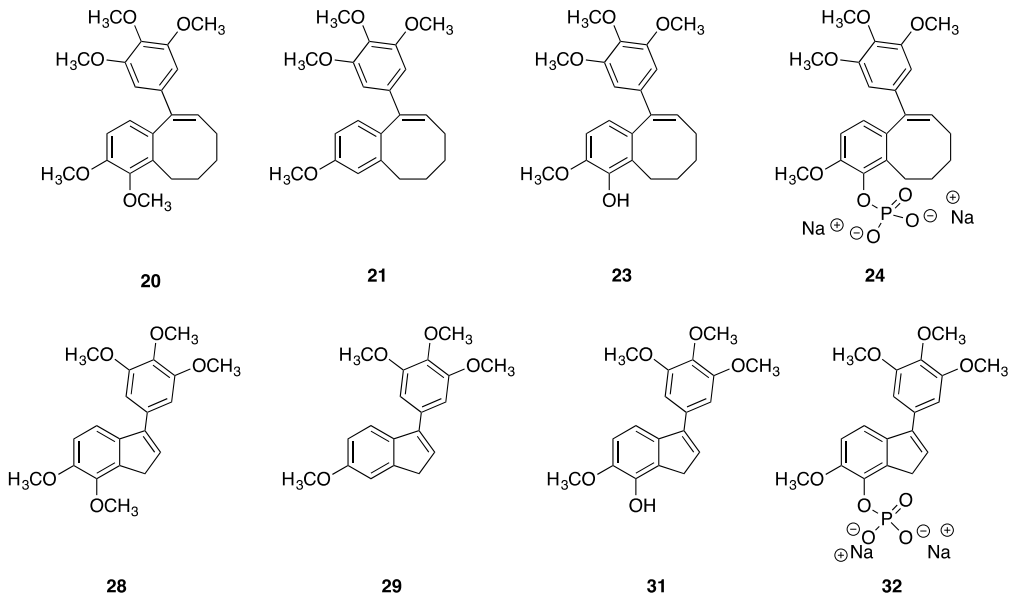


Figure 3.4. Compilation of synthesized benzocyclooctene analogues **20**, **21**, **23**, and **24** and indene analogues 28, 29, 31, and 32.

Among the seven compounds synthesized for this study and analyzed biologically, only the target benzocyclooctene analogues (20, 21, and 23) had activities as inhibitors of tubulin polymerization similar to those of CA4 and KGP18. Benzocyclooctene phenol 23 demonstrated the lowest IC_{50} value (1.2 μM) among the compounds evaluated in this study. A binding study utilizing radiolabeled colchicine demonstrated that at a concentration of 5 μM, phenol 23 inhibited colchicine binding by 78%, 20% less than the activity obtained with 5 μM CA4 (used as a positive control)**.** Considering the three indene analogues, only phenolic indene 31 demonstrated modest inhibition of tubulin polymerization, with an IC_{50} value of 11 μM.

Table 3.1. Inhibition of tubulin polymerization [(expressed as half maximal inhibitory concentration (IC_{50})] and cytotoxicity [expressed as growth inhibition of 50% (GI_{50})] of the eight target analogues synthesized.

Compound	Inhibition of tubulin polymerization IC_{50} (μM) ± SD	% Inhibition of colchicine binding ± SD	GI_{50} (μM) SRB assay[a]		
			NCI-H460	DU-145	SK-OV-3
CA4	1.0[b]	98 ± 0.007	0.00500[c,d]	0.00602[c,d]	0.00506[d]
CA4P	>20[b]	nr[e]	0.00282[c]	0.00336[c]	0.00190
KGP18	1.4[f]	nr[e]	0.0000418[g]	0.0000249[g]	0.0000543[g]
20	4.5 ± 0.5	31 ± 0.6	0.395	0.448	0.512
21	3.0 ± 0.1	29 ± 5	0.431	0.570	0.400
23	1.2 ± 0.1	78 ± 4	0.107	0.105	0.0811
24	>20	nd[h]	0.0260	0.0410	0.0366
28	>20	nd[h]	42.2	34.6	9.46
29	>20	nd[h]	4.02	4.66	6.15
31	11 ± 2	17 ± 5	0.388	0.362	0.704
32	>20	nd[h]	1.50	3.34	0.334

[a] Average of n ≥ 3 independent determinations

[b] Data from ref. [137]

[c] For additional data, see ref. [137]

[d] Data from ref. [69]

[e] nr = not reported

[f] For additional data, see ref. [63]

[g] For additional data, see ref. [62]

[h] nd = not determined

Benzocyclooctene phenol 23 and its corresponding phosphate prodrug salt 24 were the most cytotoxic analogues in these series against the three human cancer cell lines examined (for example, GI_{50} = 0.105 and 0.0410 μM against DU-145 (prostate) for analogues 23 and 24, respectively). While structurally similar to KGP18, differing by the addition of one carbon to the aliphatic ring, the phenolic benzocyclooctene analogue is dramatically less cytotoxic than its benzosuberene counterpart. Compounds 23 and 24 had GI_{50} values in the submicromolar range, while the values obtained with KGP18 were all subnanomolar.

Dynamic bioluminescence imaging

Bioluminescence imaging (BLI) is a highly valuable modality with diverse applications in a wide range of biological models and systems.[138,184,185] BLI is a particularly useful tool for assessing and quantifying *in vivo* blood flow reduction following treatment with a VDA.[32,138,139,155,186] In the current study MCF7 human breast cancer cells, which had been previously transfected stably to express the enzyme

luciferase, as well as two fluorescent proteins, as designated by MCF7-luc-GFP-mCherry, were implanted in in SCID mice, as described previously.[155] Since the luciferase substrate luciferin can be delivered to the tumor via the blood stream, damage to the vessels by a VDA can be quantified by measurement of reduced bioluminescence upon injection of luciferin.[32] In the study shown in Fig. 3.5, three mice bearing the MCF7-luc-GFP-mCherry breast tumor were injected ip with analogue 24 (120 mg/kg), and BLI assessment was performed at baseline (0 h, pre-administration) and at 4, 24, and 48 h after administration of 24. In a contemporaneous study, one mouse was treated with CA4P (120 mg/kg) as a positive control, and an additional mouse was treated with saline alone (Fig. 3.5). A limited dose escalation study with analogue 24 in non-tumor bearing SCID mice (60-150 mg/kg, unpublished data) suggested that a dose of 120 mg/kg was tolerated and likely below the maximum tolerated dose (MTD), which has not yet been determined. The optimal CA4P dose in SCID mice for evaluation of VDA efficacy has been previously established at 120 mg/kg.[138] Single dose treatment with both analogue 24 and CA4P resulted in a significant reduction in bioluminescence (approximately 80% decrease as compared to baseline or saline control; $p<0.05$) at 4 h after compound injection. While bioluminescence intensity in the mouse treated with compound 24 recovered somewhat at 24 and 48 h, it remained significantly below baseline values ($p<0.005$). In this study, the BLI data for both analogue 24 and CA4P at 4 h were statistically different from the saline control, but not from each other or from the data obtained at other time points (Fig 3.5). Following the 48 h time point BLI mice were sacrificed and tumors excised and prepared for histology. Routine staining using H&E indicated much more extensive necrosis throughout the tumors following administration

of 24 or CA4P each at 120 mg/kg, as compared with saline control (Fig. 3.6). Thus, analogue 24 is a good candidate for further assessment and may be a therapeutically useful VDA.

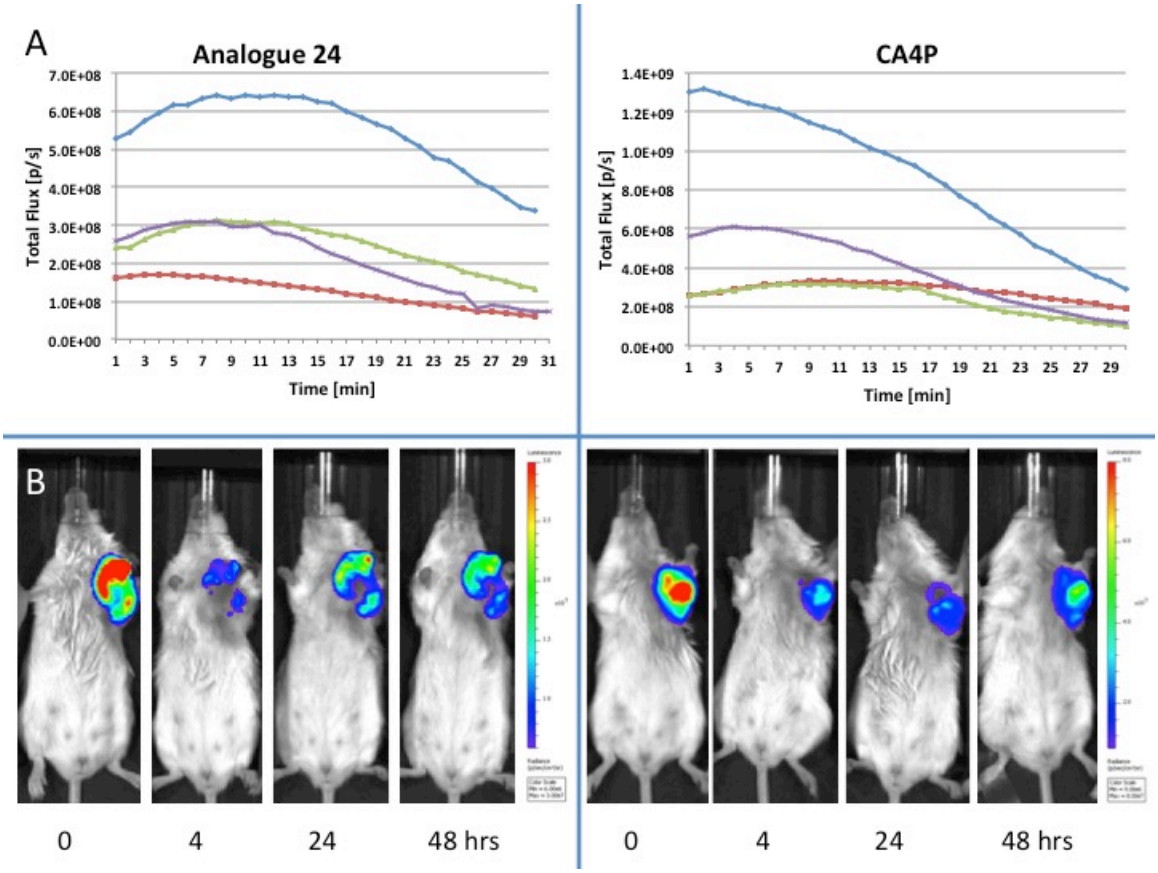


Figure 3.5. Dynamic bioluminescence with respect to vascular disruption. A) Graphs show evolution of light emission from individual MCF7-luc-GFP-mCherry breast tumors following administration of luciferin substrate subcutaneously in the fore-back region of each mouse at time 0. Respective curves are baseline (blue), 4 h (red), 24 h (green) and 48 h (purple) post administration of VDA. Left hand panel shows representative mouse with 120 mg/kg analogue 24 and right hand panel shows CA4P (120 mg/kg). B) Photographs show selected images at the 10 min. time point. Left hand group for analogue **24** and right hand group for CA4P for the same mice used to generate the curves for part A. Respective images are each scaled to same values.

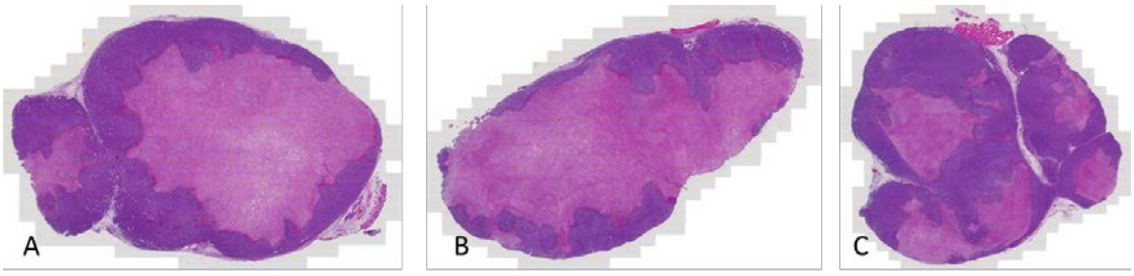


Figure 3.6. Histological assessment of tumor necrosis. H&E stained tumor cross sections showing necrotic (pink) and viable (purple) regions at 48 h post treatment for A: Analogue 24 (120 mg/kg) B: CA4P (120 mg/kg) C: Saline.

Conclusions

These studies, which focused on indene and benzocyclooctene ring systems, expanded the known SAR associated with the effect that fused aliphatic ring size plays in regard to cytotoxicity and inhibition of tubulin polymerization. From the group of eight analogues prepared by chemical synthesis with seven compounds evaluated biologically, three benzocyclooctene analogues were strong inhibitors of tubulin polymerization and one indene analogue was a modest inhibitor. The most promising compound (benzocyclooctene analogue 23) was prepared and evaluated as its corresponding water-soluble phosphate salt 24. It demonstrated significant *in vivo* reduction of blood flow (as evidenced by BLI) in an MCF7-luc-GFP-mCherry tumor model in SCID mice, and the results indicated that 24 should undergo further evaluation as a VDA for potential cancer treatment.

Experimental Section

General Materials and Methods

Tetrahydrofuran (THF), CH_2Cl_2, ethanol, methanol, dimethylformamide (DMF), and acetonitrile were used in their anhydrous forms. Reactions were performed under nitrogen gas. Thin-layer chromatography (TLC) plates (precoated glass plates with silica gel 60 F254, 0.25 mm thickness) were used to monitor reactions. Purification of intermediates and products was carried out with a Biotage Isolera flash purification system using silica gel (200−400 mesh, 60 Å). Intermediates and products synthesized were characterized on the basis of their ^{1}H NMR (500 or 600 MHz) and ^{13}C NMR (125 or 150 MHz) spectroscopic data using a Varian VNMRS 500 MHz or a Bruker Ascend 600 MHz instrument. Spectra were recorded in $CDCl_3$ and D_2O. All chemical shifts are expressed in ppm (δ), coupling constants (J) are presented in Hz, and peak patterns are reported as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), septet (sept), and multiplet (m).

Purity of the target compounds was further analyzed at 25 °C using an Agilent 1200 HPLC system with a diode-array detector (λ = 190−400 nm), a Zorbax XDB-C18 HPLC column (4.6 mm Å~ 150 mm, 5 μm), and a Zorbax reliance cartridge guard-column; method A: solvent A, acetonitrile, solvent B, H_2O; gradient, 10% A/90% B to 100% A/0% B or method B: solvent A, acetonitrile, solvent B, 0.1% TFA in H_2O over 0 to 40 min; post-time 10 min; flow rate 1.0 mL/min; injection volume 20 μL; monitored at wavelengths of 210, 254, 230, 280, and 360 nm. Mass spectrometry was carried out under positive ESI (electrospray ionization) using a Thermo Scientific LTQ Orbitrap Discovery instrument.

6-(2´,3´-Dimethoxyphenyl)hex-5-enoic acid (1).[61] To a well-stirred solution of 4-(carboxybutyl)triphenyl phosphonium bromide (13.47 g, 30.39 mmol) dissolved in THF (500 mL) at rt was added potassium *tert*-butoxide (7.43 g, 66.2 mmol). After 1 h, 2,3-dimethoxybenzaldehyde (5.02 g, 30.1 mmol) dissolved in THF (100 mL) was added to the original reaction mixture, and stirring at room temperature was continued. After 12 h, the THF was evaporated under reduced pressure, and the resulting material was quenched with 2 M HCl (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were evaporated under reduced pressure. Purification by flash column chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 50%A / 50%B (10 CV), 50%A / 50%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] afforded compound 1 (3.61 g, 14.4 mmol, 48%) as a yellow oil. NMR characterization was determined after the next step.

6-(2´,3´-Dimethoxyphenyl)hexanoic acid (3). [61] To a well-stirred solution of carboxylic acid 1 (3.61 g, 14.4 mmol) dissolved in MeOH (150 mL) was added 10% Pd on carbon (0.74 g) and H_2 gas (balloon), and the reaction was stirred at room temperature for 12 h. The reaction mixture was then filtered through Celite®, the Celite® was washed with EtOAc (3 x 50 mL), and the filtrate (MeOH and EtOAc) was evaporated under reduced pressure. The organic material was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford carboxylic acid 3 (3.63 g, 14.4 mmol, quantitative) as a colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 11.83 (1H, s), 7.01

(1H, t, *J* = 9.5 Hz), 6.80 (2H, *J* = 10 Hz), 3.88 (3H, s), 3.86 (3H, s), 2.68 (2H, t, *J* = 9 Hz), 2.39 (2H, t, *J* = 16 Hz), 1.70 (4H, m), 1.46 (2H, p, *J* = 9.5 Hz). ^{13}C NMR ($CDCl_3$, 150 Hz) δ 180.1, 152.7, 147.1, 136.2, 123.8, 121.9, 110.2, 60.5, 55.5, 34.0, 30.4, 29.6, 28.9, 24.5.

1,2-Dimethoxy-benzocylcooct-5-one (5). [61] To carboxylic acid 3 (4.40 g, 17.4 mmol) was added Eaton's reagent (35 mL, 3 g per mmol of compound **3**), and the mixture was stirred at room temperature for 12 h, at which time it was poured over ice, which was allowed to melt, and the solution was neutralized with sodium bicarbonate. The organic layer was extracted with EtOAc (3 x 50 mL), dried over sodium sulfate, evaporated under reduced pressure, and purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford ketone 5 (0.58 g, 2.5 mmol, 14 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.35 (1H, d, *J* = 8.4 Hz), 6.65 (1H, d, *J* = 9 Hz), 3.69 (3H, s), 3.59 (3H, s), 2.94 (2H, t, *J* = 6.6 Hz), 2.73 (2H, t, *J* = 6.6 Hz), 1.59 (4H, m), 1.27 (2H, p, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 150 Hz) δ 204.9, 155.5, 146.2, 134.7, 133.5, 124.8, 109.6, 60.7, 55.6, 43.9, 27.0, 25.4, 24.7, 24.1.

[TMAH][Al_2Cl_7]. [135] To dry CH_2Cl_2 (150 mL) was added $AlCl_3$ (19.84 g, 149.08 mmol), which was stirred and cooled to 0 °C. Trimethylamine hydrochloride (7.11 g, 74.54 mmol) was added, and the mixture was stirred for 2 h at room temperature. The resulting liquid was stored at room temperature under nitrogen.

1-Hydroxy-2-methoxy-benzocyclooct-5-one (13). To ketone 5 (0.57 g, 2.3 mmol) in a 20 mL microwave vial was added [TMAH][Al_2Cl_7] (7.54 mL, 4.69 mmol), and the mixture was reacted in a microwave for 1 h at 80 °C. The solution was poured into water (50 mL), extracted with EtOAc (3 x 25 mL), dried over sodium sulfate, and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography using a pre-packed 50 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] affording phenol 13 (0.28 g, 1.3 mmol, 54%) as a clear oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.23 (1H, d, *J* = 8.4 Hz), 6.73 (1H, d, *J* = 8.4 Hz), 6.11 (1H, s) 3.85 (3H, s), 3.06 (2H, t, *J* = 6.6 Hz), 2.88 (2H, t, *J* = 6.6 Hz), 1.75 (4H, m), 1.49 (2H, p, *J* = 6 Hz). ^{13}C NMR ($CDCl_3$, 150 Hz) δ 206.4, 148.7, 142.9, 133.7, 126.7, 120.1, 107.9, 56.0, 44.4, 25.9, 25.7, 25.3, 23.9.

*1-((*tert-*Butyldimethylsilyl)oxy)-2-methoxy-benzocyclooct-5-one (14).* Phenol 13 (0.22 g, 1.0 mmol) was dissolved in DMF (50 mL). TBSCl (0.30 g, 2.0 mmol) and DIPEA (0.52 mL, 3.0 mmol) were added, and the reaction was stirred for 12 h at room temperature. The reaction mixture was washed with water (50 mL), extracted with EtOAc (5 x 30 mL), dried over sodium sulfate, and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] affording TBS-protected ketone 14 (0.31 g, 0.93 mmol, quantitative) as a white solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.04 (1H, d, *J* =8.4 Hz), 6.56 (1H, d, *J* = 9 Hz), 3.62 (3H, s), 2.87 (2H, t, *J* = 6 Hz), 2.69 (2H, t, *J* = 7.2 Hz), 1.58

(4H, m), 1.33 (2H, p, *J* = 3 Hz), 0.81 (9H, s), 0.00 (6H, s). ^{13}C NMR ($CDCl_3$, 150 Hz) δ 207.1, 151.9, 141.9, 133.7, 131.5, 120.9, 108.5, 54.5, 44.5, 26.2, 26.0, 25.8, 25.5, 23.7, 18.8, -3.9.

*1-((*tert-*Butyldimethylsilyl)oxy)-2-methoxy-5-(3´,4´,5´- trimethoxyphenyl)-benzocyclooctan-5-ol (19).* To an oven dried flask containing THF (50 mL) was added 3,4,5-trimethoxyphenyl bromide (0.20 g, 0.81 mmol), and the solution was cooled to -78 °C. *n*-BuLi (1.3 mL, 0.85 mmol) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h. TBS-protected 14 (0.20 g, 0.60 mmol) was added dropwise to the flask, and the reaction mixture was stirred while warming from -78 °C to room temperature over 12 h, at which time the reaction mixture was washed with water, extracted with EtOAc (3 x 50 mL), dried over sodium sulfate, and evaporated under reduced pressure. The organic material was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] affording tertiary alcohol 19 (0.044 g, 0.088 mmol, 15%) as a yellow oil. NMR characterization was performed after the next step.

*1-((*tert-*Butyldimethylsilyl)oxy)-2-methoxy-5-(3´,4´,5´-trimethoxyphenyl)benzocyclooct-5-ene (22).* Acetic acid (10 mL) was added to tertiary alcohol 19 (0.044 g, 0.088 mmol), and the reaction mixture was stirred for 12 h at room temperature, at which time the mixture was washed with water (50 mL), extracted with EtOAc (3 x 30 mL), and dried over sodium sulfate. The organic phase was evaporated

under reduced pressure, and the crude reaction mixture was purified by flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 2%A / 98%B (1 CV), 2%A / 98%B → 20%A / 80%B (10 CV), 20%A / 80%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] affording TBS-protected 22 (0.022 g, 0.045 mmol, 52%) as a clear oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.68 (1H, d, *J* = 8.4 Hz), 6.56 (1H, d, *J* = 8.4 Hz), 6.42 (2H, s), 6.19 (1H, t, *J* = 7.8 Hz), 3.84, (3H, s), 3.80 (3H, s), 3.78 (6H, s), 3.27 (1H, overlapping doublets, *J* = 12.6 Hz), 2.23 (1H, m), 1.96 (1H, m), 1.75 (1H, m), 1.66 (1H, q, *J* = 22 Hz), 1.37 (2H, m), 1.02 (9H, s), 0.27 (3H, s), 0.24 (3H, s).

1-Hydroxy-2-methoxy-5-(3´,4´,5´- trimethoxyphenyl)-benzocyclooct-5-ene (23).[61] TBS-protected benzocyclooctene 22 (0.022 g, 0.045 mmol) was dissolved in THF (10 mL), TBAF (0.031 g, 0.099 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. The solution was washed with water (50 mL), extracted with EtOAc (3 x 30 mL), dried over sodium sulfate, and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 3%A / 97%B (1 CV), 3%A / 97%B → 30%A / 70%B (10 CV), 30%A / 70%B (2 CV); flow rate: 36 mL/min; monitored at 254 and 280 nm] affording benzocyclooctene 23 (0.0053 g, 0.014 mmol, 33%) as a white solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.70 (1H, d, *J* = 8.4 Hz), 6.53 (1H, d, *J* = 8.4 Hz), 6.43 (2H, s), 6.21 (1H, t, *J* = 8.4 Hz), 5.76 (1H, s), 3.92 (3H, s), 3.84 (3H, s), 3.78 (6H, s), 3.25 (1H, dd, *J* = 12.6, 7.8 Hz), 2.30 (2H, m), 2.03 (1H, m), 1.79 (1H, m), 1.68 (1H, dt, *J* = 22.2, 11.4 Hz), 1.45 (1H, qd, *J* = 13.2, 4.8 Hz), 1.34 (1H, qd, *J* = 13.2, 4.8 Hz) ^{13}C NMR ($CDCl_3$, 150 MHz) δ 152.8, 145.3, 142.7, 139.7, 139.1, 137.1,

132.3, 129.8, 129.7, 120.3, 107.8, 104.6, 60.9, 56.1, 56.0, 28.3, 26.5, 25.8, 24.7. HRMS: Obsvd 393.1693 [M + Na^+], Calcd for $C_{22}H_{26}O_5Na$: 393.1672. HPLC: 16.61 min.

Sodium 2-methoxy-5-(3´,4´,5´- trimethoxyphenyl)-benzocyclooct-5-en-1-yl phosphate (24). Phosphorus oxychloride (0.18 mL, 1.9 mmol) was cooled to 0 °C in CH_2Cl_2 (10 mL) and triethylamine (0.68 mL, 4.9 mmol) was added, and the reaction mixture was stirred for 5 min. Benzocyclooctene 23 (0.14 g, 0.38 mmol) in CH_2Cl_2 (5 mL) was added to the reaction dropwise, and the reaction mixture was stirred at 0 °C for 1 h and then warmed to room temperature over 12 h. The mixture was then evaporated under reduced pressure. CH_2Cl_2 (10 mL) was added to the resulting residue, and the resulting solution was again evaporated under reduced pressure. This was repeated two more times. The resulting solid was dissolved in a mixture of THF and water (2:1, 6 mL total) and stirred for 1 h. The solution was then cooled to 0 °C, and 0.1 M NaOH was added until a pH of 10 was achieved. The solution was then evaporated under reduced pressure, and the crude product was purified by a C18 30 g reversed phase column [solvent A: acetonitrile; solvent B: water; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 100%A / 0%B (10 CV), 100%A / 0%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford phosphate salt 24 (0.06 g, 0.12 mmol, 32%) as a brown solid. ^{1}H NMR (D_2O, 600 MHz) δ 6.69 (1H, d, *J* = 8.4 Hz), 6.52 (2H, s), 6.47 (1H, d, *J* = 8.4 Hz), 6.20 (1H, t, *J* = 7.4 Hz), 3.72 (3H, s), 3.67 (6H, s), 3.63 (3H, s), 3.45 (1H, dd, *J* = 13.2, 8.4 Hz), 2.14 (1H, dt, *J* = 13.8, 8.4), 2.05 (1H, t, *J* = 12 Hz), 1.91 (1H, m), 1.63 (1H, m), 1.43 (1H, dt, *J* = 22.2, 12 Hz), 1.30 (1H, qd, *J* = 13.2, 4.8 Hz), 1.16 (1H, qd, *J* = 13.2, 4.8 Hz). ^{13}C NMR (D_2O, 150 MHz) δ 152.2, 151.4 (d, *J* = 2.25 Hz), 141.1 (d, *J* = 6.75 Hz), 140.0, 138.8, 138.0 (d, *J* = 3.38 Hz), 135.8, 131.5, 131.2, 123.8, 109.5, 104.9, 60.9,

56.0, 55.6, 28.1, 26.6, 26.3, 23.8. ^{31}P NMR (D_2O, 242 MHz) δ -0.25. HRMS: Obsvd 495.1249 [M + H], Calcd for $C_{22}H_{26}O_8Na_2P^+$: 495.1155 HPLC: 5.46 min.

1,2-Dimethoxy-5-(3´,4´,5´- trimethoxyphenyl)-benzocyclooctan-5-ol (17). To an oven dried flask, THF (50 mL) and 3,4,5-trimethoxyphenyl bromide (0.26 g, 1.0 mmol), were added, and the solution was cooled to -78 °C. *n*-BuLi (0.44 mL, 1.1 mmol) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h. Benzocyclooctone 5 (0.18 g, 0.77 mmol) was added dropwise to the flask, and the reaction was stirred while warming from -78 °C to room temperature over 12 h, at which time the reaction mixture was washed with water (50 mL), extracted with EtOAc (3 x 50 mL), dried over sodium sulfate, and evaporated under reduced pressure. The crude product was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] affording tertiary alcohol 17 (0.15 g, 0.37 mmol, 48%) as a clear oil. NMR characterization was performed after the next step.

1,2-Dimethoxy-5-(3´,4´,5´- trimethoxyphenyl)-benzocyclooct-5-ene (20). Acetic acid (20 mL) was added to tertiary alcohol 17 (0.15 g, 0.37 mmol), and the reaction mixture was stirred for 12 h at room temperature, at which time the mixture was washed with water (50 mL), extracted with EtOAc (3 x 30 mL), and dried over sodium sulfate. The organic phase was evaporated under reduced pressure, and the crude organic product was purified by flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A /

40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] affording benzocyclooctene 20 (0.082 g, 0.213 mmol, 59%) as a white solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.74 (1H, d, *J* = 8.5 Hz), 6.72 (1H, d, *J* = 8 Hz), 6.41 (2H, s), 6.21 (1H, dd, *J* = 10.8, 9 Hz), 3.93 (3H, s), 3.88 (3H, s), 3.84 (3H, s), 3.78 (6H, s), 3.24 (1H, dd, *J* = 15, 9.6 Hz), 2.27 (2H, m), 2.06 (1H, m), 1.77 (1H, m), 1.65 (1H, dt, *J* = 25.2, 12.6 Hz), 1.37 (2H, m). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 152.8, 151.8, 146.3, 139.7, 139.0, 137.5, 137.2, 131.9, 129.7, 124.8, 109.5, 104.7, 60.9, 60.7, 56.1, 55.6, 28.3, 27.8, 26.0, 24.6. HRMS: Obsvd 407.1859 [M + Na^+], Calcd for $C_{19}H_{28}O_2Na$: 407.1829. HPLC: 18.53 min.

6-(3´-Methoxyphenyl)hex-5-enoic acid (2). [187] To a well-stirred solution of 4-(carboxybutyl)triphenyl phosphonium bromide (16.29 g, 36.75 mmol) dissolved in THF (500 mL) at rt was added potassium *tert*-butoxide (9.09 g, 81.0 mmol). After 1 h, 2,3-dimethoxybenzaldehyde (4.47 mL, 36.8 mmol) dissolved in THF (100 mL) was added to the original reaction mixture, and the resulting reaction mixture was stirred at room temperature for 12 h. The THF was evaporated under reduced pressure, and the resulting material was quenched with 2 M HCl (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was evaporated under reduced pressure and purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 80%A / 20%B (10 CV), 80%A / 20%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] affording carboxylic acid 2 (8.01 g, 36.7 mmol, 99%) as a yellow oil. NMR characterization was performed after the next step.

6-(3´-Methoxyphenyl)hexanoic acid (4). [188,189] To dissolved carboxylic acid 2 (8.01 g, 36.7 mmol) in MeOH (150 mL) was added 10% Pd on carbon (0.46 g) and H_2 gas (balloon). The reaction mixture was stirred at room temperature for 12 h. The mixture was then filtered through Celite®, the Celite® was washed with EtOAc (3 x 50 mL), and the filtrate (MeOH and EtOAc) was evaporated under reduced pressure. The combined organic material was purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford carboxylic acid 4 (7.53 g, 33.9 mmol, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.21 (1H, t, *J* = 10.2 Hz), 6.78 (1H, d, *J* = 9.6 Hz), 6.76 (2H, m), 3.81 (3H), 2.62 (2H, t, *J* = 9 Hz), 2.38 (2H, t, *J* = 9 Hz), 1.67 (4H, overlapping pentets, *J* = 9 Hz), 1.41 (2H, p, *J* = 9.6 Hz).

2-Methoxy-benzocyclooct-5-ene (6). [133,189–191] Carboxylic acid 4 (7.53 g, 33.9 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Eaton's reagent (68 mL, 3 g per mmol of compound 4) was added, and the mixture was stirred while warming to room temperature over 12 h, at which time it was poured over ice, which was allowed to melt, and the solution was neutralized with $NaHCO_3$. The organic layer was extracted with EtOAc (3 x 50 mL), dried over sodium sulfate, evaporated under reduced pressure, and purified by flash chromatography using a pre-packed 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 40 mL/min; monitored at 254 and 280 nm] to afford ketone 6 (0.45 g, 2.2 mmol, 7 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.81 (1H, d, *J* = 9 Hz), 6.63 (1H, dd, *J* = 9, 2.4 Hz), 6.51 (1H, d, *J* = 3 Hz), 3.65

(3H, s), 2.94 (2H, t, *J* = 6.6 Hz), 2.81 (2H, t, *J* = 7.2 Hz), 1.67 (2H, p, *J* = 7.2 Hz), 1.61 (2H, p, *J* = 6.6 Hz), 1.26 (2H, p, *J* = 6 Hz). ^{13}C NMR ($CDCl_3$, 150 Hz) δ 202.4, 162.8, 143.1, 132.2, 131.4, 116.5, 111.5, 55.1, 42.6, 35.3, 27.6, 24.5, 23.0.

2-Methoxy-5-(3´,4´,5´-trimethoxyphenyl)-benzocyclooctan-5-ol (18). To an oven dried flask containing THF (50 mL) was added 3,4,5-trimethoxyphenyl bromide (0.73 g, 3.0 mmol), and the solution was cooled to -78 °C. *n*-BuLi (4.9 mL, 3.1 mmol) was slowly added to the reaction mixture, which was then stirred at -78 °C for 1 h. Ketone 6 (0.45 g, 2.2 mmol) was then added dropwise to the flask, and the reaction mixture was stirred while warming from -78 °C to room temperature over 12 h, at which time the reaction mixture was washed with water, extracted with EtOAc (3 x 50 mL), dried over sodium sulfate, and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography using a pre-packed 25 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7%A / 93%B (1 CV), 7%A / 93%B → 60%A / 40%B (10 CV), 60%A / 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 and 280 nm] to afford tertiary alcohol 18 (0.18 g, 0.48 mmol, 22%) as a yellow oil. NMR characterization was performed after the next step.

2-Methoxy-5-(3´,4´,5´-trimethoxyphenyl)-benzocyclooct-5-ene (21). Acetic acid (10 mL) was added to tertiary alcohol 18 (0.18 g, 0.48 mmol), and the reaction mixture was stirred for 12 h at rt, at which time the mixture was washed with water (50 mL), extracted with EtOAc (3 x 30 mL), and dried over sodium sulfate. The organic phase was evaporated under reduced pressure, and the crude reaction mixture was purified by flash chromatography using a pre-packed 10 g silica column [solvent A: EtOAc; solvent B:

hexanes; gradient: 5%A / 95%B (1 CV), 5%A / 95%B → 40%A / 60%B (10 CV), 40%A / 60%B (2 CV); flow rate: 12 mL/min; monitored at 254 and 280 nm] to afford benzocyclooctene 21 (0.089 g, 0.25 mmol, 52%) as a white solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.95 (1H, d, *J* = 8.4 Hz), 6.85 (1H, d, *J* = 2.4 Hz), 6.73 (1H, dd, *J* = 6.4, 2.4 Hz), 6.44 (2H, s), 6.24 (1H, dd, *J* = 9, 7.8 Hz), 3.863 (3H, s), 3.857 (3H, s), 3.80 (6H, s), 2.83 (1H, dd, *J* = 13.2, 7.8 Hz), 2.56 (1H, t, *J* = 12.6 Hz), 2.29 (1H, dt, *J* = 13.8, 7.8 Hz), 2.07 (1H, m), 1.80 (1H, m) 1.64 (1H, dt, *J* = 21, 10.8 Hz), 1.41 (1H, qd, *J* = 12.6, 4.8 Hz), 1.34 (1H, qd, *J* = 13.2, 5.4 Hz). ^{13}C NMR ($CDCl_3$, 150 Hz) δ 159.0, 152.8, 144.6, 139.7, 139.0, 137.1, 130.7, 129.3, 114.0, 111.4, 104.6, 60.9, 56.1, 55.2, 33.5, 28.8, 28.3, 24.9. HRMS: Obsvd 377.1724 [M + Na^+], Calcd for $C_{22}H_{26}O_4Na$: 377.1723. HPLC: 19.29 min.

3-(2´,3´-Dimethoxyphenyl)propanoic acid (9) [192,193] *Trans*-2,3-dimethoxycinnamic acid (7) (5.00 g, 24.0 mmol) was dissolved in MeOH (100 mL), 10% Pd on carbon (0.82 g) was added, and the mixture was stirred for 12 h under H_2 (balloon). The mixture was then filtered through Celite®, the Celite® was washed with EtOAc (2 x 50 mL). The organic layer (EtOAc and MeOH) was dried over sodium sulfate, concentrated and purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 7%A/ 93%B (1 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/40%B (2 CV); flow rate: 40 mL/min; monitored at 254 nm and 280 nm] to afford carboxylic acid 9 (4.34 g, 20.6 mmol, 86%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.91 (1H, s), 6.97 (1H, t, *J* = 8 Hz), 6.78 (2H, d, *J* = 8 Hz), 3.85 (3H, s), 3.80 (3H, s), 2.98 (2H, t, *J* = 7.5 Hz), 2.67 (2H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 179.4, 152.7, 147.1, 133.9, 124.0, 121.7, 111.0, 60.4, 55.5, 34.7, 25.3.

*4,5-Dimethoxy-2,3-dihydro-1*H-*inden-1-one (11)* [192,194] Carboxylic acid 9 (4.99 g, 23.7 mmol) was mixed with Eaton's reagent (47.5 mL, 3 g per mmol of carboxylic acid 9) and stirred for 72 h at room temperature. The mixture was then poured over ice, neutralized, and extracted with EtOAc (3 x 75 mL). The organic layer was dried over sodium sulfate, concentrated and purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 7%A/93%B (1 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/ 40%B (2 CV); flow rate: 40 mL/min; monitored at 254 nm and 280 nm] to afford ketone 11 (2.01 g, 10.5 mmol, 44%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.06 (1H, d, *J* = 8.4 Hz), 6.62 (1H, d, *J* = 8.4 Hz), 3.61 (3H, s), 3.57 (3H, s), 2.70 (2H, t, *J* = 5.4 Hz), 2.25 (2H, t, *J* = 5.4 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 204.6, 157.1, 147.4, 145.0, 130.7, 119.4, 112.0, 59.8, 55.8, 36.0, 22.1.

*4-Hydroxy-5-methoxy-2,3-dihydro-1*H-*inden-1-one (15)*[135,195,196] Ketone 11 (0.70 g, 3.2 mmol) was added to a 20 mL microwave vial with [TMAH][Al_2Cl_7] (10.0 mL, 7.26 mmol) and microwaved for 1 h at 80 °C. The mixture was poured into water, extracted with CH_2Cl_2 (3 x 30 mL), dried over sodium sulfate and purified by flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 12%A/ 88%B (1 CV), 12%A/ 88%B → 100%A/ 0%B (10 CV), 100%A/ 0%B (2 CV); flow rate: 50 mL/min; monitored at 254 nm and 280 nm] to afford phenol 15 (0.42 g, 2.36 mmol, 72%) as a brown solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.35 (1H, d, *J* = 10.2 Hz), 6.92 (1H, d, *J* = 10.2 Hz), 5.81 (1H, s), 3.97 (3H, s), 3.07 (2H, t, *J* = 6.6 Hz), 2.69 (2H, t, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 206.0, 150.9, 142.1, 140.5, 131.4, 116.1, 110.4, 56.4, 36.5, 21.9.

*4-((*tert-*Butyldimethylsilyl)oxy)-5-methoxy-2,3-dihydro-1*H-*inden-1-one (16)*

Phenol 15 (0.90 g, 5.1 mmol) was dissolved in DMF (25 mL), and TBSCl (0.71 g, 4.7 mmol) was added, followed by the addition of DIPEA (1.24 mL, 7.08 mmol). The mixture was stirred for 12 h at room temperature, washed with water, and extracted with EtOAc (5 x 50 mL). The organic layer was dried over sodium sulfate, concentrated and purified by flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 7%A/ 93%B (1 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/ 40%B (2 CV); flow rate: 50 mL/min; monitored at 254 nm and 280 nm] to afford TBS-protected 16 (0.63 g, 2.2 mmol, 91%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (1H, d, *J* = 8.5 Hz), 6.83 (1H, d, *J* = 8.5 Hz), 3.81 (3H, s), 2.94 (2H, t, *J* = 6 Hz), 2.56 (2H, t, *J* = 6 Hz), 0.95 (9H, s), 0.12 (6H s). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 205.8, 155.0, 146.3, 141.4, 131.1, 117.4, 111.5, 55.4, 36.4, 25.9, 22.9, 18.6, -4.1.

*4-((*tert-*Butyldimethylsilyl)oxy)-5-methoxy-1-(3´,4´,5´-trimethoxyphenyl)-2,3-dihydro-1*H-*inden-1-ol (27).* 5-Bromo-1,2,3-trimethoxybenzene (0.51 g, 2.1 mmol) was dissolved in THF (25 mL) and cooled to -78 °C. *n*-BuLi (1.22 mL, 3.05 mmol) was added dropwise, and the reaction mixture was stirred for 1 h. TBS-protected 16 (0.43 g, 1.53 mmol) was dissolved in THF (10 mL) and added dropwise to the reaction flask, and the mixture was stirred for 12 h while warming to room temperature, at which time it was washed with water, extracted with EtOAc (3 x 30 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 7%A/ 93%B (2 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/40%B (2 CV); flow rate: 50 mL/min; monitored at 254

nm and 280 nm] to afford tertiary alcohol 27 (0.37 g, 0.80 mmol, 37%) as a yellow oil. NMR characterization was performed after the next step.

tert-*Butyl((6-methoxy-3-(3´,4´,5´-trimethoxyphenyl)-1*H-*inden-7-yl)oxy)dimethylsilane (30).* Acetic acid (15 mL) was added to tertiary alcohol 27 (0.37 g, 0.80 mmol), and the reaction mixture was stirred at room temperature for 12 h, at which time it was washed with water and extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over sodium sulfate, concentrated, and purified by flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 7%A/ 93%B (1 CV), 7%A/ 93%B → 60%A/40%B (10 CV), 60%A/40%B (2 CV); flow rate: 25 mL/min; monitored at 254 nm and 280 nm] to afford TBS-protected 30 (0.14 g, 0.32 mmol, 39%) as a clear oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.92 (1H, d, *J* = 6.5 Hz), 6.64 (1H, d, *J* = 7 Hz), 6.59 (2H, s), 6.19 (1H, t, *J* = 2 Hz), 3.69 (9H, s), 3.62 (3H, s), 3.23 (2H, d, *J* = 2 Hz), 0.84 (9H, s), 0.00 (6H, s). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 153.3, 148.8, 144.9, 141.2, 138.2, 137.5, 135.7, 132.1, 128.8, 113.2, 110.3, 104.7, 61.0, 56.2, 55.6, 35.9, 26.1, 18.7, -4.1.

*6-Methoxy-3-(3´,4´,5´-trimethoxyphenyl)-1*H-*inden-7-ol (31)*[61] TBS-protected 30 (0.46 g, 1.0 mmol) was dissolved in THF (5 mL), TBAF (5.2 mL, 5.2 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h, at which time the mixture was washed with water, extracted with EtOAc (3 x 40 mL), dried with sodium sulfate, evaporated under reduced pressure, and purified by flash chromatography using a prepacked 25 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 12%A/ 88%B (1 CV), 12%A/ 88%B → 100%A/ 0%B (10 CV), 100%A/ 0%B (2 CV); flow rate:

25 mL/min; monitored at 254 nm and 280 nm] to afford indene 31 (0.23 g, 0.70 mmol, 68%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.08 (1H, d, *J* = 7.8 Hz), 6.87 (1H, d, *J* = 7.8 Hz), 6.80 (2H, s), 6.46 (1H, t, *J* = 2.4 Hz), 5.78 (1H, s), 3.94 (3H, s), 3.91 (9H, s), 3.48 (2H, d, *J* = 2.4 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 153.3, 144.9, 144.8, 141.8, 139.7, 138.7, 137.6, 131.9, 129.37, 139.35, 111.7, 109.2, 104.8, 61.0, 56.5, 56.2, 34.8. HRMS: Obsvd 351.1203 $[M+Na]^+$, calcd for $C_{19}H_{20}O_5Na$: 351.1208. HPLC: 12.84 min.

*Sodium 6-methoxy-3-(3´,4´,5´-trimethoxyphenyl)-1*H*-inden-7-yl phosphate (32).* $POCl_3$ (0.26 mL, 2.8 mmol) was cooled to 0 °C in CH_2Cl_2 (10 mL). Indene 31 (0.23 g, 0.70 mmol) and pyridine (0.20 mL, 2.5 mmol) in CH_2Cl_2 (5 mL) was added to the reaction mixture dropwise, and the reaction mixture was stirred at 0 °C for 1 h. The mixture was then warmed to room temperature over 12 h. The mixture was then evaporated under reduced pressure. CH_2Cl_2 (10 mL) was added to the resulting residue, and the mixture was again evaporated under reduced pressure. This was repeated two more times. The resulting solid was dissolved in a mixture of THF and water (2:1, 6 mL total) and stirred for 1 h. The solution was then cooled to 0 °C, and 0.1 M NaOH was added until a pH of 10 was achieved. The solution was then evaporated under reduced pressure, and the crude product was purified by a C18 30 g reversed phase column [solvent A: acetonitrile; solvent B: water; gradient: 10%A / 90%B (1 CV), 10%A / 90%B → 100%A / 0%B (10 CV), 100%A / 0%B (2 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] to afford phosphate salt 32 (0.09 g, 0.20 mmol, 28%) as a light brown solid. ^{1}H NMR (600 MHz, D_2O) δ 6.98 (1H, d, *J* = 8.4 Hz), 6.81 (1H, d, *J* = 7.8 Hz), 6.67 (2H, s), 6.39 (1H, t, *J* = 1.8 Hz), 3.79 (3H, s), 3.68 (6H, s), 3.65 (3H, s), 3.58 (2H, s). ^{13}C NMR (150 MHz, D_2O) δ 152.4, 150.0 (d, *J* = 3 Hz), 142.8, 139.5 (d, *J* = 6.4 Hz), 138.2

(d, *J* = 2.5 Hz), 137.4, 136.0, 132.4, 130.8, 115.0, 111.1, 104.8, 60.9, 56.3, 55.9, 36.3. ^{31}P NMR (242 MHz, D_2O) δ 0.60. HRMS: Obsvd 453.0687 [M + H], Calcd for $C_{19}H_{20}O_8Na_2P^+$: 453.0686 HPLC: 4.04 min.

*4,5-Dimethoxy-1-(3´,4´,5´-trimethoxyphenyl)-2,3-dihydro-1*H-*inden-1-ol (25).* 5-Bromo-1,2,3-trimethoxybenzene (1.60 g, 6.47 mmol) was dissolved in THF (50 mL) and cooled to -78 °C. *n*-BuLi (2.7 mL, 6.8 mmol) was added dropwise, and the reaction mixture was stirred for 1 h. Ketone 11 (0.92 g, 4.79 mmol) was dissolved in THF (10 mL) and added dropwise to the reaction flask, and the mixture was stirred for 12 h while warming to room temperature, at which time it was washed with water, extracted with EtOAc (3 x 30 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 10%A/ 90%B (1 CV), 10%A/ 90%B → 80%A/ 20%B (10 CV), 80%A/ 20%B (1 CV); flow rate: 50 mL/min; monitored at 254 nm and 280 nm] to afford tertiary alcohol 25 (1.221 g, 3.39 mmol, 71%) as an orange oil. NMR data was collected after the subsequent step.

*6,7-Dimethoxy-3-(3´,4´,5´-trimethoxyphenyl)-1*H-*indene (28).* Acetic acid (25 mL) was added to tertiary alcohol 25 (1.22 g 3.39 mmol), and the mixture was stirred at room temperature for 12 h. The mixture was washed with water, extracted with EtOAc (3 x 30 mL), dried over sodium sulfate, concentrated under reduced pressure, and purified by flash chromatography using a prepacked 50 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 7%A/ 93%B (1 CV), 7%A/ 93%B → 60%A/ 40%B (10 CV), 60%A/ 40%B (2 CV); flow rate: 40 mL/min; monitored at 254 nm and 280 nm] to afford

indene 28 (0.56 g, 1.64 mmol, 48%) as a brown solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.28 (1H, d, *J* = 8 Hz), 6.93 (1H, d, *J* = 8.5 Hz), 6.83 (2H, s), 6.44 (1H, s), 3.99 (3H, s), 3.93 (3H, s), 3.91 (9H, s), 3.53 (2H, s). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 153.1, 150.2, 145.2, 144.5, 138.2, 137.4, 136.4, 131.6, 128.6, 115.2, 110.9, 104.5, 60.6, 59.8, 56.0, 55.8, 35.2. HRMS: Obsvd 365.1385 $[M+Na]^+$, calcd for $C_{20}H_{22}O_5Na$: 365.1359. HPLC: 14.96 min.

3-(3´-Methoxyphenyl)propanoic acid (10)[197] 3-methoxycinnamic acid (8) (3.56 g, 19.98 mmol) was dissolved in MeOH (100 mL), and 10% Pd on carbon (0.44 g) was added. The mixture was stirred for 12 h at room temperature under H_2 (balloon). The reaction mixture was then filtered through Celite®, and the Celite® was washed with EtOAc (3 x 30 mL). The filtrate (EtOAc and MeOH) was evaporated under reduced pressure resulting in carboxylic acid 10 (3.59 g, 19.7 mmol, quantitative). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 11.93 (1H, s), 7.27 (1H, t, *J* = 7.5 Hz), 6.88 (2H, m), 6.83 (1H, d, *J* = 8 Hz), 3.79 (3H, s), 2.99 (2H, t, *J* = 7 Hz), 2.73 (2H, t, *J* = 7 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 179.2, 159.9, 142.0, 129.6, 120.7, 114.2, 111.6, 54.9, 35.5, 30.6.

*5-Methoxy-2,3-dihydro-1*H*-inden-1-one* (12)[67,198] Eaton's reagent (43 mL, 3 g/mmol of carboxylic acid 10) was added to carboxylic acid **10** (3.95 g, 21.9 mmol), and the reaction mixture was stirred at room temperature for 72 h. It was then poured over ice, neutralized, and extracted with EtOAc (3 x 50 mL). The organic layer was dried over sodium sulfate, concentrated, and purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 12%A/ 88%B (1 CV), 12%A/ 88%B → 100%A/ 0%B (10 CV), 100%A/ 0%B (10 CV); flow rate: 50 mL/min; monitored at 254 nm and 280 nm] to afford ketone 12 (2.26 g, 13.9 mmol, 64%)

as a green solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.49 (1H, d, *J* = 7.5 Hz), 6.72 (2H, m), 3.72 (3H, s), 2.91 (2H, t, *J* = 6 Hz), 2.48 (2H, t, *J* = 5.5 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 205.0, 165.1, 158.1, 130.2, 125.0, 115.2, 109.6, 55.5, 36.3, 25.7.

*5-Methoxy-1-(3´,4´,5´-trimethoxyphenyl)-2,3-dihydro-1*H-*inden-1-ol (26)* [67]

5-Bromo-1,2,3-trimethoxybenzene (1.95 g, 7.91 mmol) was dissolved in THF (50 mL), and the mixture was cooled to -78 °C. *n*-BuLi (3.3 mL, 8.3 mmol) was added dropwise, and the reaction mixture was stirred for 1 h. Ketone 12 (0.95 g, 5.86 mmol) was dissolved in THF (10 mL) and added dropwise to the reaction flask, and the mixture was stirred for 12 h warming to room temperature, at which time it was washed with water, extracted with EtOAc (3 x 30 mL), dried over sodium sulfate, concentrated under reduced pressure, and purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 10%A/ 90%B (1 CV), 10%A/ 90%B → 80%A/ 20%B (10 CV), 80%A/ 20%B (2 CV); flow rate: 50 mL/min; monitored at 254 nm and 280 nm] to afford tertiary alcohol 26 (1.45 g, 4.39 mmol, 75%) as a yellow oil. NMR data was collected after the subsequent step.

*6-Methoxy-3-(3´,4´,5´-trimethoxyphenyl)-1*H-*indene (29)*[67] Acetic acid (25 mL) was added to tertiary alcohol 26 (1.45 g 4.39 mmol) and stirred at room temperature for 12 h. The mixture was washed with water, extracted with EtOAc (3 x 30 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexane; gradient: 7%A/ 93%B (1 CV), 7%A/93%B → 60%A/ 40%B (10 CV), 60%A/ 40%B (1 CV); flow rate: 50 mL/min; monitored at 254 nm and 280 nm] to afford indene 29 (1.30 g, 4.16 mmol, 95%) as a red-

yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.47 (1H, d, *J* = 8.5 Hz), 7.08 (1H, d, *J* = 2 Hz), 6.86 (1H, dd, *J* = 10.5, 2 Hz), 6.81 (2H, s), 6.38 (1H, t, *J* = 2 Hz), 3.90 (3H, s), 3.87 (6H, s), 3.79 (3H, s), 3.40 (2H, d, *J* = 1 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 150.1, 153.3, 146.7, 144.6, 137.6, 136.8, 132.0, 128.4, 120.5, 111.8, 110.6, 104.7, 60.8, 56.1, 55.4, 38.0. HRMS: Obsvd 335.1281 $[M+Na]^+$, calcd for $C_{19}H_{20}O_4Na$: 335.1254. HPLC: 15.95 min.

Biological Evaluations

SRB Assay [151,152]. Inhibition of growth of human cancer cells was assessed using the sulforhodamine B assay (SRB), as previously described.[151] Cancer cell lines (DU-145, SK-OV-3, and NCI-H460) were plated at 7500-8000 cells/well into 96-well plates using DMEM supplemented with 5% fetal bovine serum/ 1% gentamicin sulfate and incubated for 24 h at 37°C in a humidified incubator. Compound serial dilutions were then added. After 48 h treatment, the cells were fixed with trichloroacetic acid (10% final concentration), washed, dried, stained with sulforhodamine B dye (Acid red 52), washed to remove excess dye, and dried. SRB dye was solubilized, and absorbances were measured at wavelength 540 nm and normalized to values at wavelength 630 nm using an automated Biotek plate reader. A growth inhibition of 50% (GI_{50} or the drug concentration causing 50% reduction in the net protein increase) was calculated from the absorbance data.

Colchicine Binding Assay. Inhibition of [^{3}H]colchicine binding to tubulin was measured using reaction mixtures (100 μL each) containing 1.0 μM tubulin, 5.0 μM

[^{3}H]colchicine (from Perkin-Elmer), 5% (v/v) dimethyl sulfoxide, potential inhibitors at 5.0 μM, and components that stabilize the colchicine binding activity of tubulin [153] (1.0 M monosodium glutamate [adjusted to pH 6.6 with HCl in a 2.0 M stock solution], 0.5 mg/mL bovine serum albumin, 0.1 M glucose-1-phosphate, 1.0 mM $MgCl_2$, and 1.0 mM GTP). Incubation was for 10 min at 37 °C, a time point selected because the binding reaction in control reaction mixtures is 40-60% complete. Reactions were stopped with 2.0 mL of ice-cold water, and the reaction mixtures were placed on ice. Each sample was poured onto a stack of two DEAE-cellulose filters (from Whatman), followed by 6 mL of ice-cold water. The samples were aspirated under reduced vacuum. The filters were washed three times with 2 mL water and placed into vials containing 5 mL of Biosafe II scintillation cocktail. Samples were counted 18 h later in a Beckman scintillation counter. Samples with inhibitors were compared to samples with no inhibitor, and percent inhibition was determined. All samples were corrected for the amount of radiolabel bound to the filters in the absence of tubulin.

Inhibition of Tubulin Polymerization. Tubulin polymerization experiments were performed in 0.25 mL reaction mixtures (final volume).[154] The mixtures contained 1 mg/mL (10 μM) purified bovine brain tubulin, 0.8 M monosodium glutamate (pH 6.6), 4% (v/v) dimethyl sulfoxide, 0.4 mM GTP, and different compound concentrations. All reaction components except GTP were preincubated for 15 min at 30 °C in 0.24 mL. The mixtures were cooled to 0 °C, and 10 μL of 10 mM GTP were added. Reaction mixtures were transferred to cuvettes held at 0 °C in Beckman DU-7400 and DU-7500 spectrophotometers equipped with electronic temperature controllers. The temperature was jumped to 30 °C, taking about 30 s, and polymerization was followed at 350 nm for

20 min. The IC_{50} was defined as the compound concentration that inhibited extent of polymerization by 50% after 20 min.

In Vivo *Tumor Model.* Human breast cancer cells, MCF7-luc-GFP-mCherry (ATCC), were transfected sequentially with a lentivirus containing firefly luciferase reporter, GFP and mCherry reporter genes, as described previously.[155] Highly expressing stable clones were isolated. Induction of tumors was carried out by injecting 10^6 cells mixed with 50% Matrigel™ (BD Biosciences, San Jose, CA) into the right upper ventral mammary fat pads of female SCID-NOD mice (UTSW breeding colony). Tumors were allowed to grow to a size of 10-12 mm in diameter, determined by calipers, before selection for BLI. All animal procedures were approved by the University of Texas Southwestern Medical Center Institutional Animal Care and Use Committee.

BLI. BLI was carried out as described previously.[155] Briefly, anesthetized, tumor bearing mice (O_2, 2% isoflurane, Henry Schein Inc., Melville, NY) were injected subcutaneously in the fore-back neck region with 80 μL of a solution of luciferase substrate, *D*-luciferin (sodium salt, 120 mg/kg, in saline, Gold Biotechnology, St. Louis, MO). Mice were maintained under anesthesia (2% isoflurane in oxygen, 1 dm^3/min) while baseline BLI was performed using a Caliper Xenogen IVIS® Spectrum (Perkin-Elmer, Alameda, CA). A series of BLI images was collected over 35 min using the following settings: auto exposure time, f-stop = 2, Field of view = D, binning = 4 (medium). Light intensity-time curves obtained from these images were analyzed using Living Image® software and light emission compared based on area under the light emission curve. Mice were injected intraperitoneally with either 120 μL of saline

(vehicle), CA4P (provided by Mateon Therapeutics, Inc.; 120 mg/kg in saline as used previously[32] or analogue 24 (120 mg/kg) in saline immediately after baseline BLI. BLI was repeated, with new luciferin injections, 4, 24, and 48 h later.

*Histology***.** Following the 48 h BLI data acquisition, the tumors were excised, bisected and fixed in 4% paraformaldehyde solution. Tumor tissue was processed for paraffin embedding, sectioned and stained by routine methods. H&E staining was performed on one cross section from each tumor. Whole mount high resolution microscopy was obtained using a Zeiss Axioscan Z1 digital slide scanner.

Acknowledgements

The authors are grateful to the National Cancer Institute of the National Institutes of Health (Grant No. 5R01CA140674 to K.G.P, M.L.T, and R.P.M), the Cancer Prevention and Research Institute of Texas (CPRIT, Grant No. RP140399 to K.G.P., M.L.T., and R.P.M.), and Mateon Therapuetics, Inc. (grant to K.G.P. and M.L.T.) for their financial support of this project. The content is solely the responsibility of the authors and does not necessarily reflect the official views of the National Institutes of Health. The authors would also thank Dr. Craig Moehnke and Dr. Michelle Nemec (Director) for the use of the shared Molecular Biosciences Center at Baylor University, Dr. Alejandro Ramirez (Mass Spectrometry Core Facility, Baylor University) and Dr. Kevin Klausmeyer and Marissa Penney (X-ray analysis). The authors are grateful to Mr. Jack Littlejohn and Mr. Jake Lofman (Baylor University) for their contributions to the synthesis of certain analogues. John Shelton (JAR Molecular Pathology core, UTSW) prepared the H&E stained sections. Imaging was facilitated with the assistance of

resources of the Harold C. Simmons Cancer Center supported through a National Institutes of Health National Cancer Institute Cancer Center Support Grant [Grant 1P30 CA142543], specifically, the Southwestern Small Animal Imaging Resource, and Live Cell Imaging Resource. The IVIS Spectrum was purchased with support of 1S10RR024757.

Supplementary Data

Supplementary data including 1H NMR, 13C NMR, 31P NMR, HPLC, HRMS for target compounds and intermediates (1H NMR, 13C NMR, only) and X-ray crystallography for compound 20 and 23 associated with this article can be found in the online Supplementary data file.

CHAPTER FOUR

Carbon Nanotubes as a Drug Delivery System – Preliminary Studies

In order to better understand how carbon nanotubes would interact with compounds synthesized in the Pinney Research Group, preliminary studies were carried out in order to evaluate several optimal synthetic conditions. In collaboration with Molecular Rebar Design (MRD, Austin, TX) and BioPact Ventures, LLC (Austin, TX), initial studies focused on determining how well multi-walled carbon nanotubes (MWCNTs) dispersed in different organic solvents that could be used for either adsorption of compounds synthesized in the Pinney Research Group or to synthetically alter the MWCNTs to facilitate adherence of the compounds to the surface. The MWCNTs from Molecular Rebar Design and BioPact Ventures, LLC are unique MWCNTs that are discrete, multi-walled, CNTs referred to as Medical Grade Molecular Rebar (MGMR™). As a reminder, introductory material on CNTs can be found in Chapter 1.

Dispersion Experiments

In the first dispersion experiment, 1 mg/mL of MWCNTs were sonicated in either deionized (DI)H_2O or DMSO for 10 minute increments. These solvents were chosen as they could easily be used in both synthesis and cytotoxicity cell line testing. After the first ten minutes, the MWCNTs in H_2O appeared to be evenly dispersed (dispersion in this case is considered even distribution of MWCNTs on the filter paper when the solution is applied by the end of pipette tip) (Figure 4.1). However, over the course of an hour, the MWCNTs were never dispersed evenly throughout DMSO (Figure 4.2).

In the second dispersion experiment, MWCNTs dispersed in water were compared to MWCNTs dispersed in dichloromethane. MWCNTs were also dispersed in a 1:10 mixture of the MWCNTS/water solution and 10% fetal bovine serum (FBS) with media (which would be used in cytotoxicity cell line studies). Again, 1 mg/mL solutions of MWCNTs in either water or dichloromethane were sonicated, this time for 30 minutes, and then were tested for dispersion using the quick touch pipette method. Both appeared to be evenly dispersed in solution after 30 minutes (Figure 4.3).

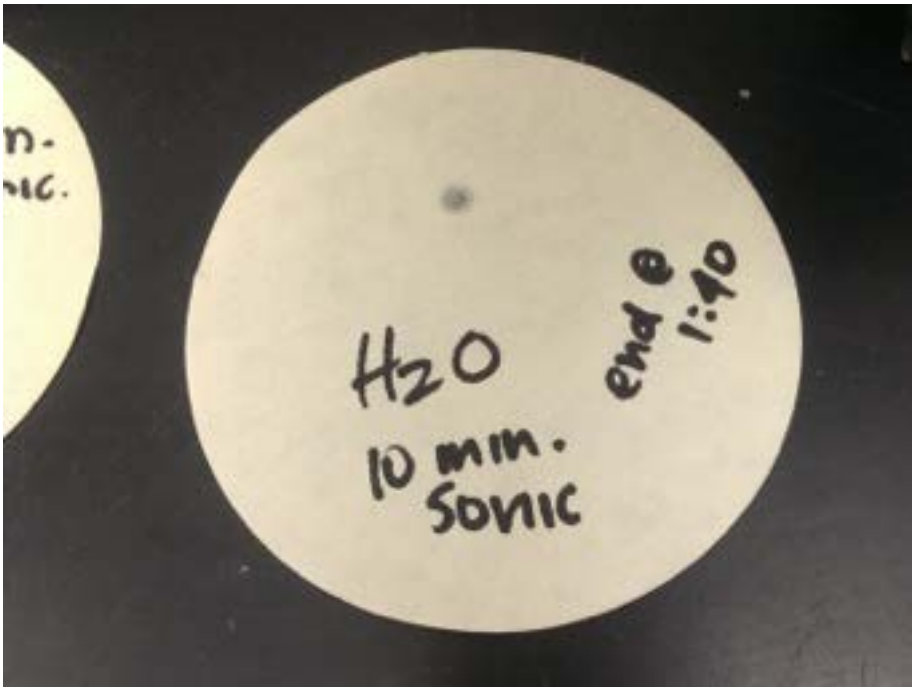


Figure 4.1. 1 mg/mL of MWCNTs in H_2O sonicated for ten minutes.

100 μl of the MWCNTs in water was added to 900 μl 10% FBS with media and sonicated for 30 minutes. The MWCNTs appear to be dispersed in this solution as well.

Uptake Experiments

The next preliminary experiments were done in collaboration with Molecular Rebar in Austin, Texas. There, the drug uptake by the MWCNTs was determined for both CA4P and KGP265 (Figure 4.5).

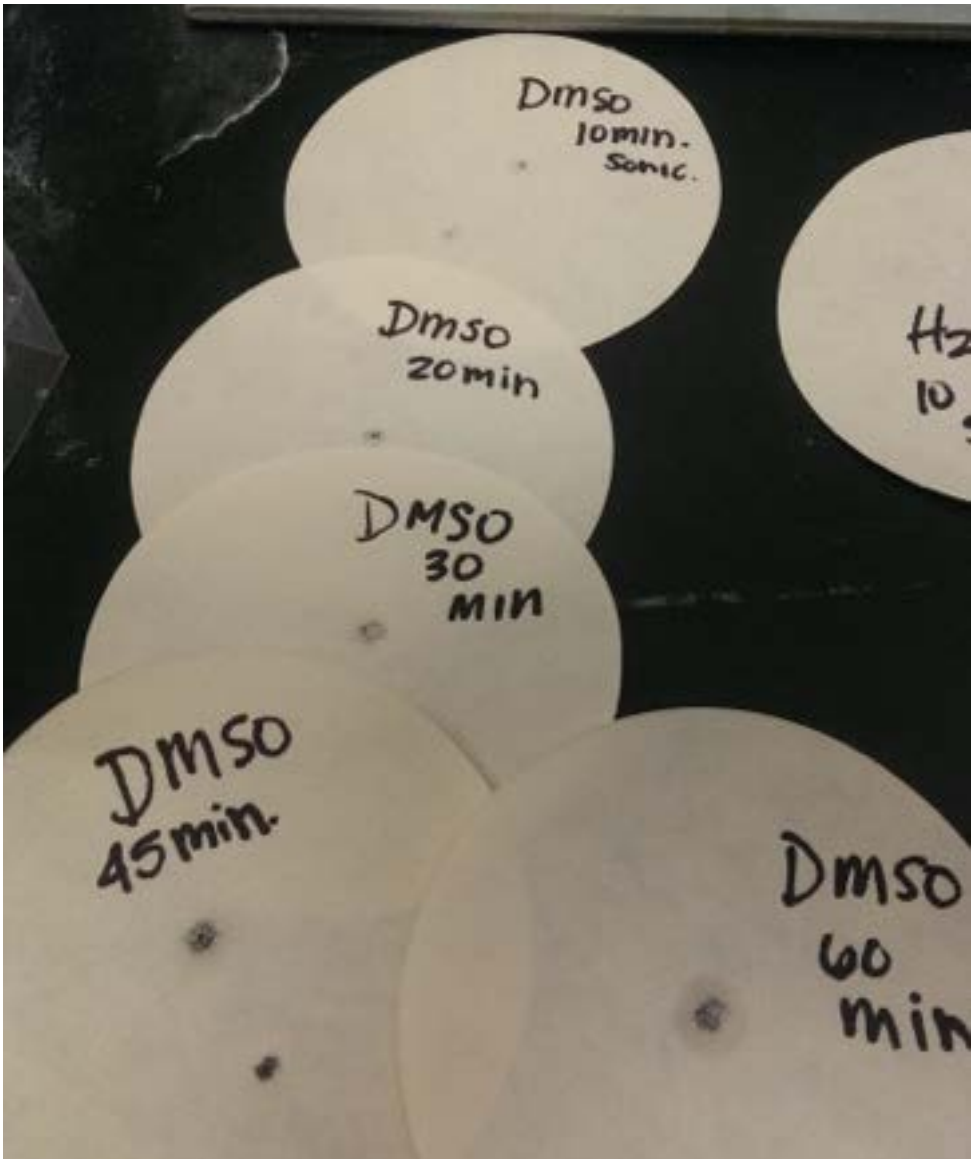


Figure 4.2. 1 mg/ mL of MWCNTs in DMSO sonicated for 10 minute intervals over an hour. Even dispersion is not seen for the DMSO samples (evident with the clumping seen on the filter papers).

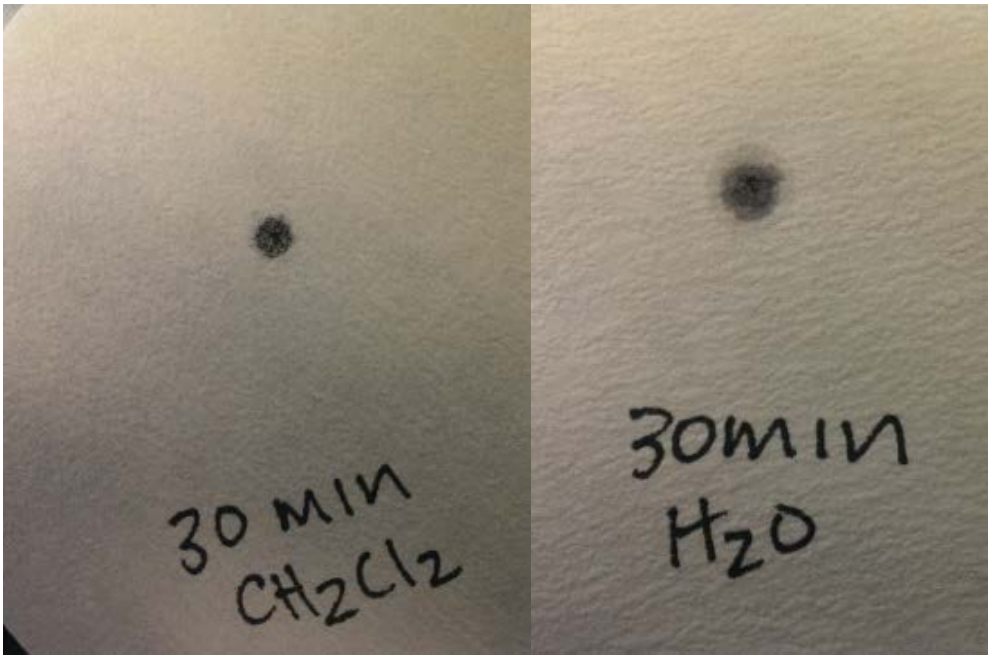


Figure 4.3. 1 mg/mL of MWCNTs in dichloromethane or water after 30 minutes of sonication. Both appear to be dispersed in their given solutions.

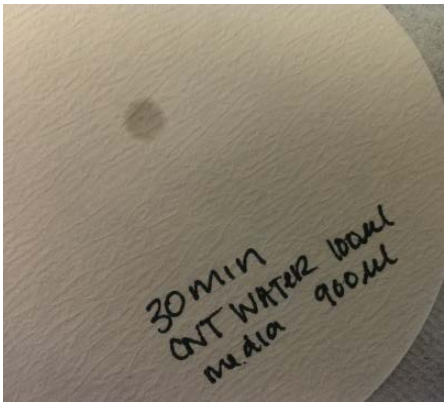


Figure 4.4**.** 100 µl of the MWCNTs/water solution added to 900 µl 10% FBS with media after 30 minutes of sonication. The nanotubes appear to be dispersed.

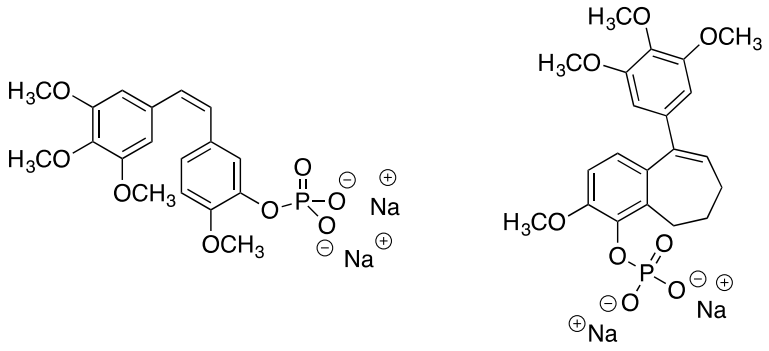


Figure 4.5. Structures of CA4P and KGP265.

CA4P Uptake Experiment

A stock solution of 0.045 g/L (0.114 mM) CA4P in water was used to create four different concentrations. These solutions were analyzed by UV-Vis in order to determine a calibration curve. The data were analyzed graphically (Figure 4.6) using the concentrations of 0.015 g/L, 0.03 g/L, 0.045 g/L, and 0.06 g/L CA4P in water ultimately leading to an extinction coefficient of 10338 M^{-1} cm^{-1}

Using the stock solution of CA4P in water (0.045 g/L) and a stock solution of MWCNTs also in water (11.1 mg into 100 mL; 0.111 g/L), varying weight to weight ratios (1:1, 3:1, 6:1, 9:1; CA4P:MWCNTs) were evaluated for uptake of CA4P by MWCNTs. For each ratio, 5 mL of the CA4P stock solution was used with varying amounts of the MWCNTs stock solution. The combined CA4P-MWCNT solution was sonicated in ice water for ten minutes, and the solutions were then filtered through 0.5 μm PVDF filters, leaving any unbound CA4P in water. The filtrate was then analyzed by UV-Vis to determine the concentration of free CA4P, which could be correlated to the uptake of CA4P by the MWCNTs. In this first uptake experiment, the only uptake of

CA4P by the MWCNTs was seen in the 1:1 weight to weight ratio (and this was seen at a 0.10 grams of CA4P per gram of MWCNTs).

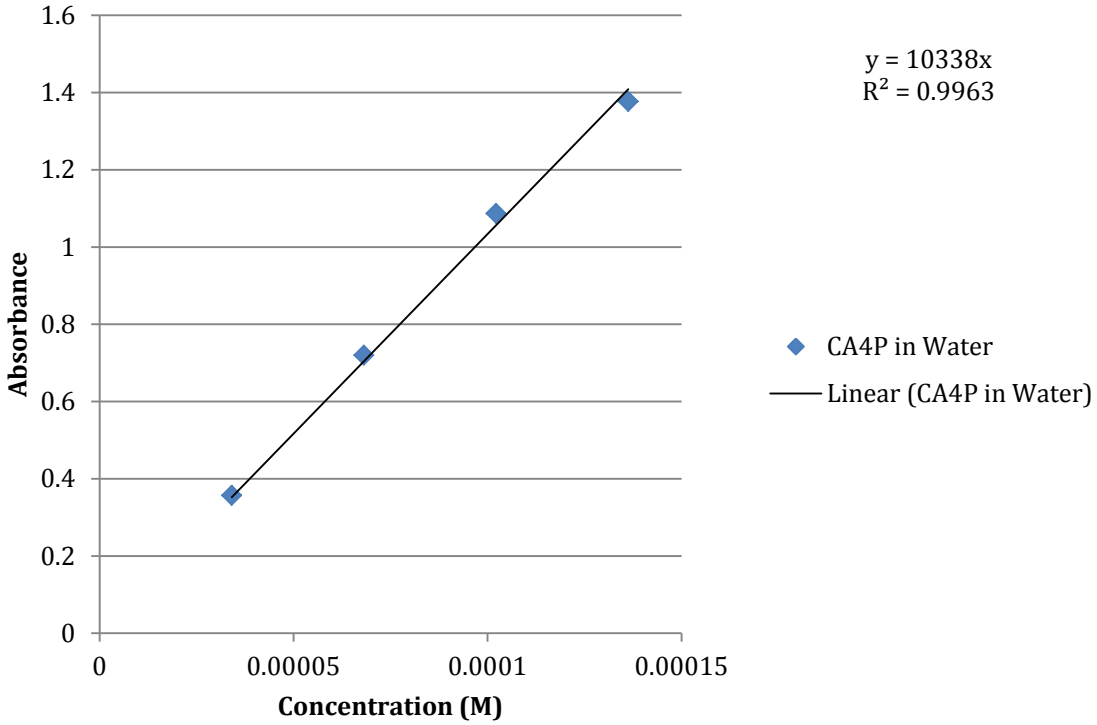


Figure 4.6. Calibration curve for CA4P in water.

Because only minimal amounts of CA4P were shown to interact with the MWCNTs, a second uptake experiment was performed using more concentrated stock solutions of both the MWCNTs (55.5 mg into 50 mL of water; 1.11 g/L) and CA4P (0.5 g/L). Weight to weight ratios of 5:1 and 9:1 CA4P to MWCNTs were examined using the same parameters as outlined previously. It was found that in the 5:1 CA4P:MWCNT weight to weight ratio there was a ratio of 0.59 grams of CA4P per gram of MWCNTs, however, for 9:1, the ratio was only 0.017 grams of CA4P per gram of MWCNTs.

One more uptake experiment was explored using CA4P that examined using CA4P in the presence of an excess of MWCNTs. Stock solutions of 1.11 g/L MWCNTs and 0.5 g/L CA4P were used, and a weight to weight ratio of 1:5 CA4P:MWCNTs was mixed. It was expected that there would be a high uptake of CA4P due to the excess of CNTs, however, the gram to gram ratio (CA4P:MWCNT) for the experiment was only 0.039.

KGP265 Uptake Experiment

Following a similar strategy to the CA4P uptake experiment, a stock solution of 0.0665 g/L (0.138 mM) KGP265 in water was used to create four different concentrations. These solutions were analyzed by UV-Vis in order to determine a calibration curve. The data were analyzed graphically (Figure 4.7) using the concentrations of 0.015 g/L, 0.025 g/L, 0.031 g/L, and 0.049 g/L KGP265 in water ultimately leading to an extinction coefficient of 13294 M^{-1} cm^{-1}.

Using the stock solution of KGP265 in water (0.00665 g/L) and a stock solution of MWCNTs also in water (10.0 mg into 100 mL; 0.10 g/L), varying weight to weight ratios (1:1, 3:1, 6:1, 9:1; KGP265:MWCNTs) were evaluated for uptake of KGP265 by MWCNTs. For each ratio, 5 mL of the KGP265 stock solution was used with varying amounts of the MWCNTs stock solution.

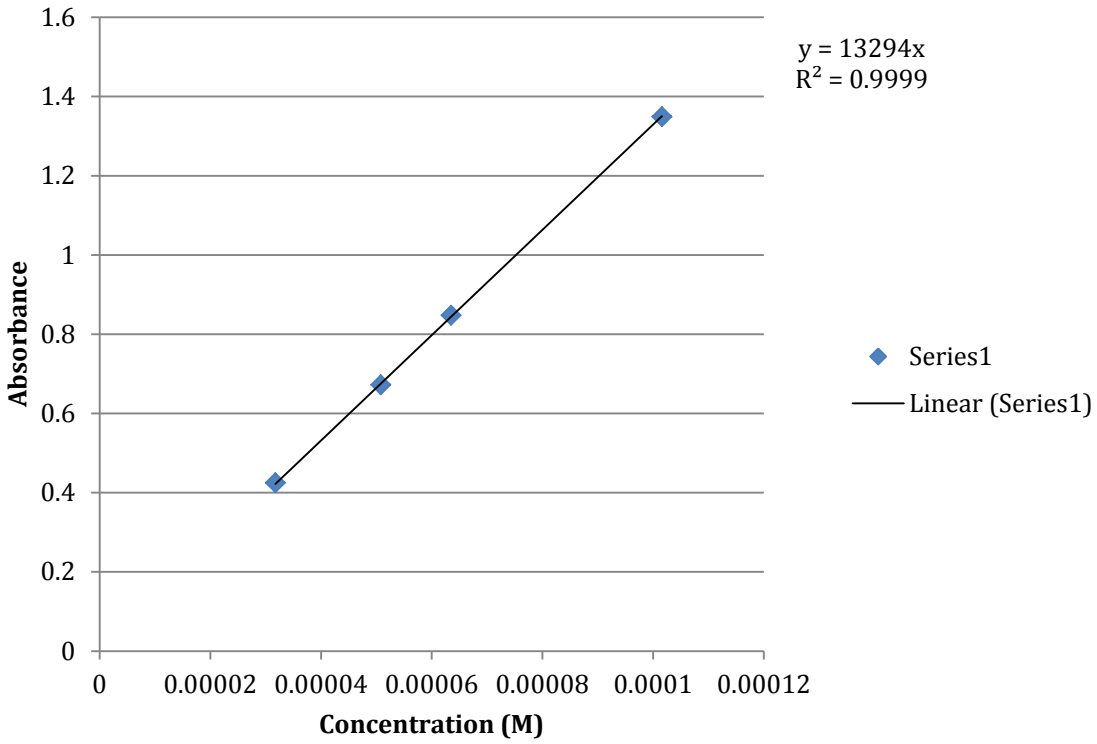


Figure 4.7. Calibration curve for KGP265 in water.

The combined KGP265-MWCNT solution was sonicated in ice water for ten minutes, and the solutions were then filtered through 0.5 μm PVDF filters, leaving any unbound KGP265 in water. The filtrate was then analyzed by UV-Vis to determine the concentration of free KGP265, which could be correlated to the uptake of KGP265 by the MWCNTs. Uptake of KGP265 by the MWCNTs was seen in each of the ratio experiments, with the most uptake seen in the 6:1 and 9:1 ratios (a 3.1 gram to gram ratio was seen in both the 6:1 and 9:1 experiments).

Because KGP265 had such a high uptake onto the MWCNTs, it shows promise as a candidate for potential use with MWCNTs as a drug delivery system. It was surprising that CA4P, while water soluble, did not interact as favorably with the MWCNTs in these preliminary experiments. At best, CA4P was only 50% adsorbed by the MWCNTs, but

this was only observed under very specific ratio conditions. It is interesting to note that CA4P in water acts as a good surfactant for the MWCNTs, dispersing the tubes evenly throughout the solution, however the interaction between the tubes and CA4P may be very weak, and as the poorly bound CA4P-MWCNTs is pressurized through the microfilter, the compound could be removed from the tubes.

Future work is still needed to further develop MWCNTs as a drug delivery system, specifically with the Pinney Research Group compounds in mind. First, many of the phosphate salts synthesized in the Pinney Research Group that also have cytotoxic and tubulin polymerization inhibitory effects should be studied for their uptake with MWCNTs to see if they also are as promising as KGP265 in this regard. Second, for non-water soluble compounds, functionalization of the MWCNTs could allow for the covalent bonding of compounds to the MWCNTs, which would permit their use as a drug delivery system. Developing this functionalization technique and studying its mechanism of action will be key for future MWCNT work.

CHAPTER FIVE

Conclusions

A focused small library of compounds has been synthesized that utilized either the benzosuberene, benzocyclooctene, or indene molecular frame-work and mimicked structural features reminiscent of the natural products combretastatin A-4 and colchicine. These analogues helped further the understanding in which functional modifications to the aryl rings of the benzosuberene and the ring size of the alkyl ring affected biological activity. Two manuscripts were prepared that describe these research developments, a benzosuberene analogue paper, in which the author synthesized twelve of the twenty-two final compounds, and a benzocyclooctene and indene paper, in which the author synthesized all eight of the final target compounds.

The most promising new target molecule to emerge from these studies was a benzocyclooctene analogue (referred to as KGP481), which is the water-soluble phosphate prodrug of the eight membered phenolic compound KGP433. While less cytotoxic in comparision to the benzosuberene phenolic moiety KGP18, KGP481 demonstrated promising results both as an inhibitor of tubulin polymerization and as a vascular disrupting agent, as evidenced by bioluminescence imaging studies. Further biological evaluation of this benzocyclooctene analogue and additional structure activity relationship studies should be carried out to further explore the full biological potential of KGP481 and structurally similar molecules.

The preliminary work with the MWCNTs showed initial promise as a method to adsorb VDAs and utilize the MWCNTs for drug delivery to tumors. While CA4P had

minimal adsorption to the MWCNTs used in this study, KGP265 was readily adsorbed. Future studies should include the adsorption of other water-soluble phosphate salts by MWCNTs, as well as cytotoxicity studies of KGP265 adsorbed onto MWCNTs.

APPENDICES

APPENDIX A

Supporting Information: Structural Interrogation of Benzosuberene-Based Inhibitors of Tubulin Polymerization

This appendix published as supporting information: Herdman, C. A.; Devkota, L.; Lin, C. M.; Niu, H.; Strecker, T. E.; George, C. S.; Tanpure, R. P.; Hamel, E.; Chaplin, D. J.; Mason, R. P.; Trawick, M. L.; Pinney, K. G. Structural Interrogation of Benzosuberene-Based Inhibitors of Tubulin Polymerization. *Bioorganic and Medicinal Chemistry* **2015**, *23*, 7497-7520.

Structural Interrogation of Benzosuberene-Based Inhibitors of Tubulin Polymerization

Christine A. Herdman[a], Laxman Devkota[a], Chen-Ming Lin[a], Haichan Niu[a], Tracy E. Strecker[a], Ramona Lopez[b], Li Liu[b], Clinton S. George[a], Rajendra P. Tanpure[a], Ernest Hamel[c], David J. Chaplin[a,d], Ralph P. Mason[b], Mary Lynn Trawick[a], and Kevin G. Pinney[a]*

[a] Department of Chemistry and Biochemistry, Baylor University, One Bear Place #97348, Waco, Texas 76798-7348, United States

[b] Department of Radiology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9058, United States

[c] Screening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Frederick National Laboratory for Cancer Research, National Institutes of Health, Frederick, MD 21702, United States

[d] OXiGENE Inc., 701 Gateway Boulevard, Suite 210, South San Francisco, California 94080, United States

*Corresponding author. Tel.: +1 254 710 4117; fax: +1 254 710 4272.

E-mail address: Kevin_Pinney@baylor.edu (K.G. Pinney).

Appendix A Table of Contents

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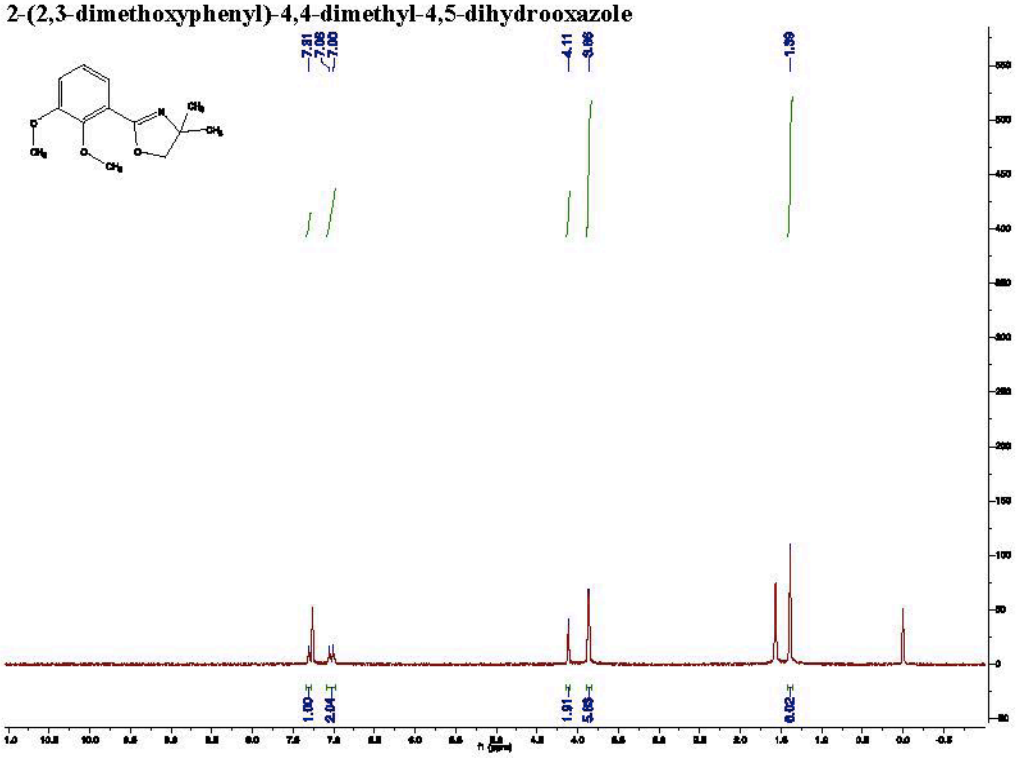

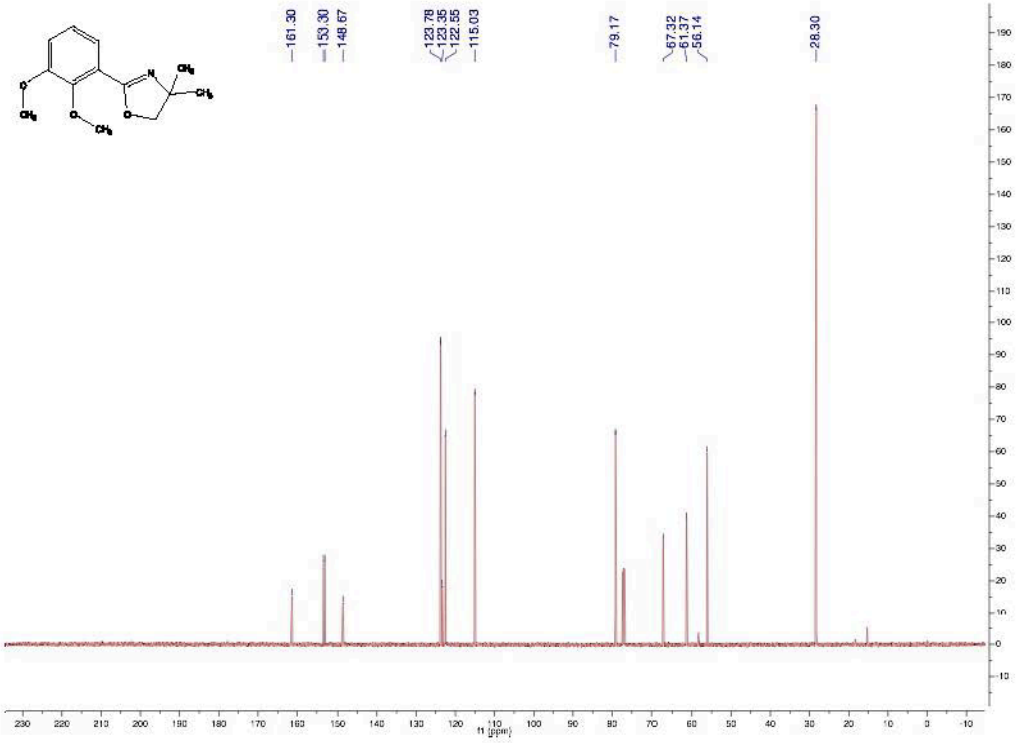

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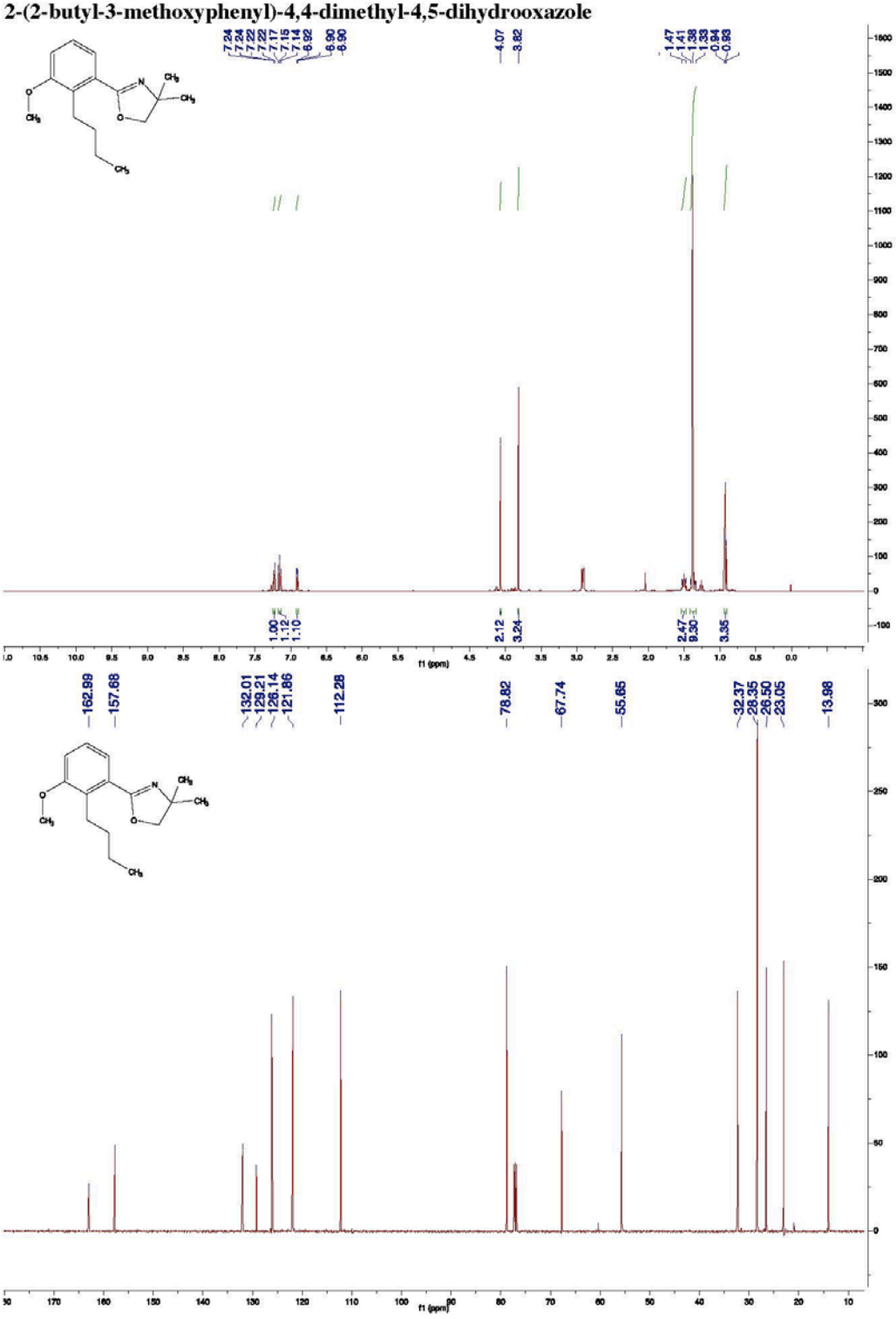

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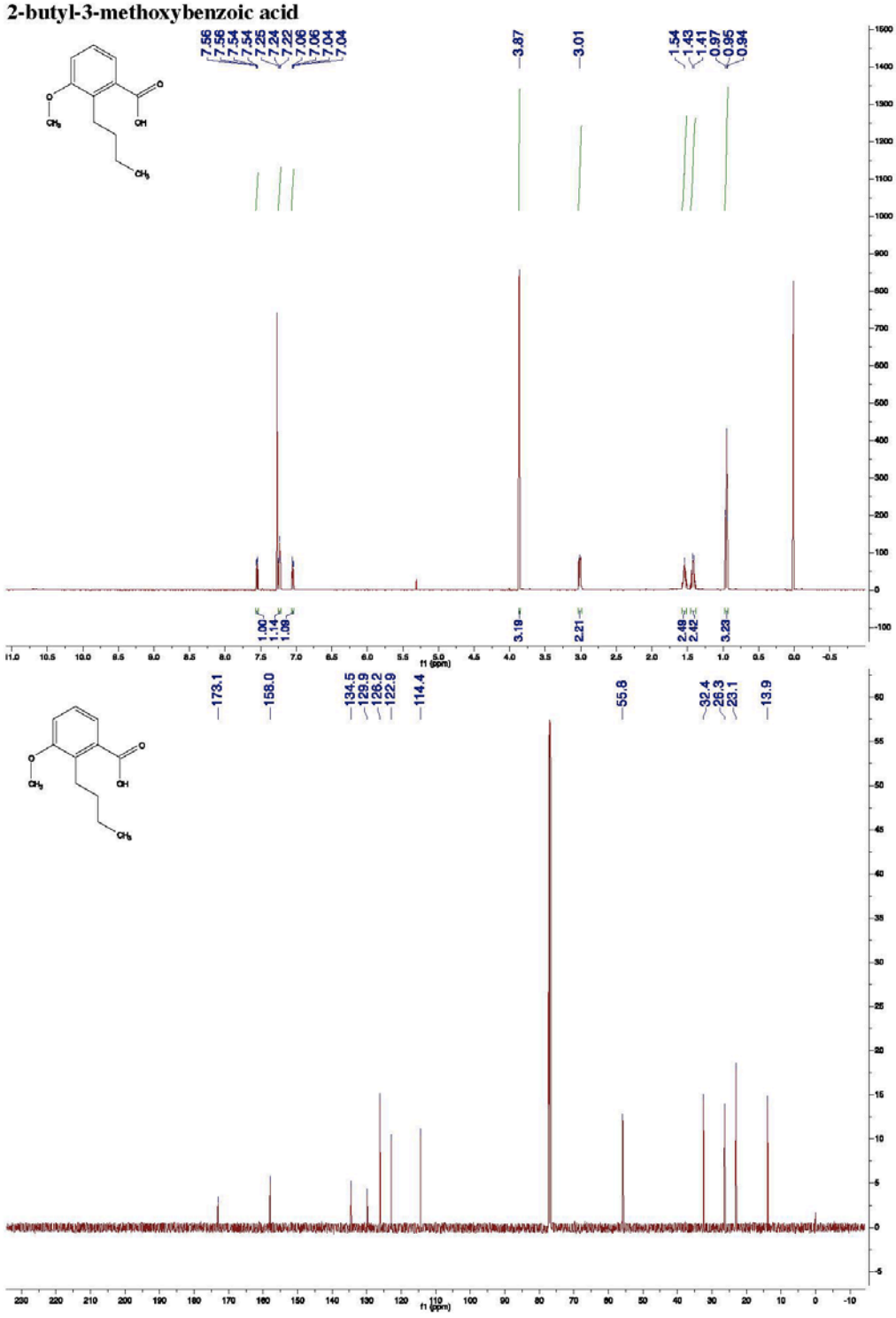

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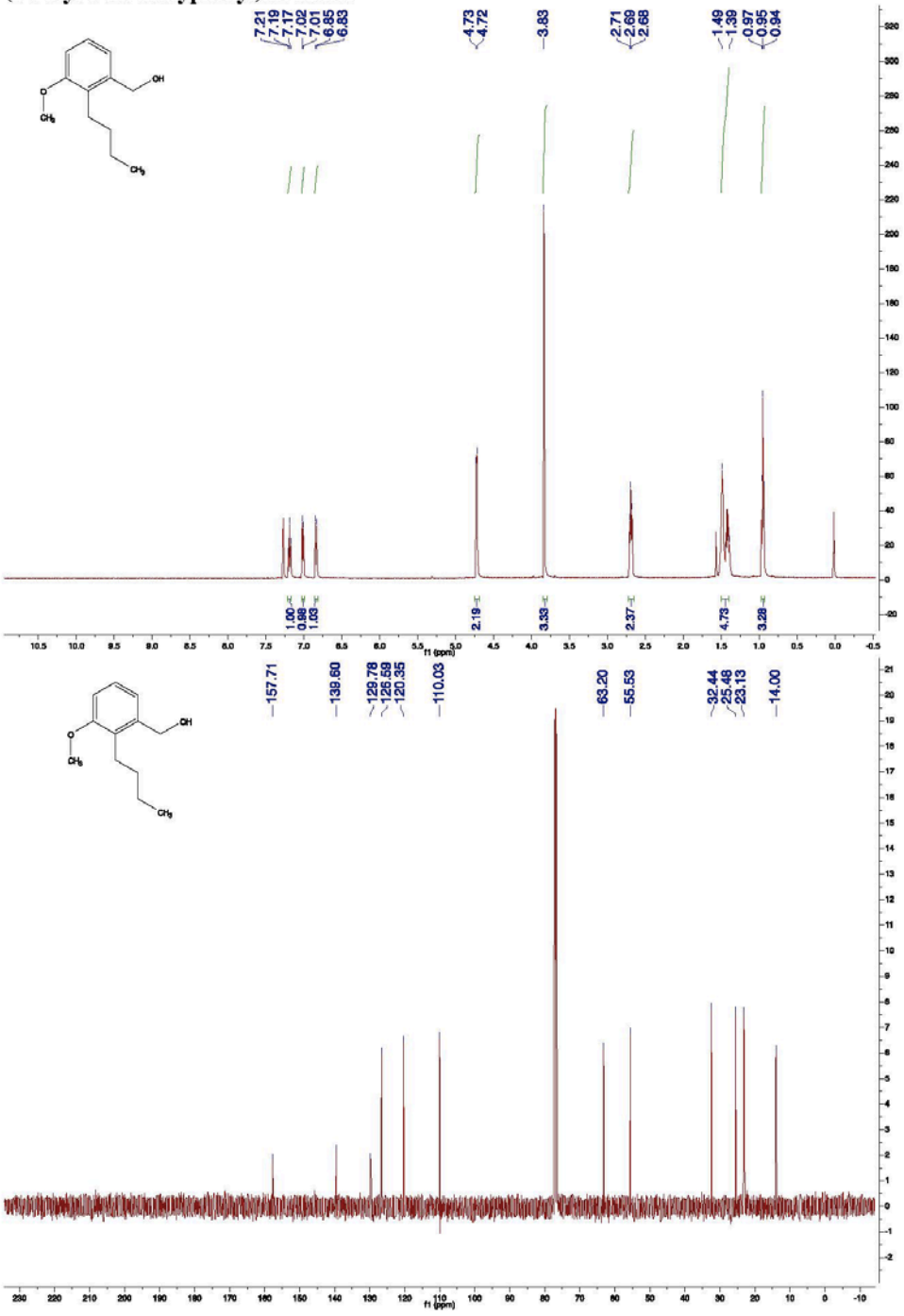

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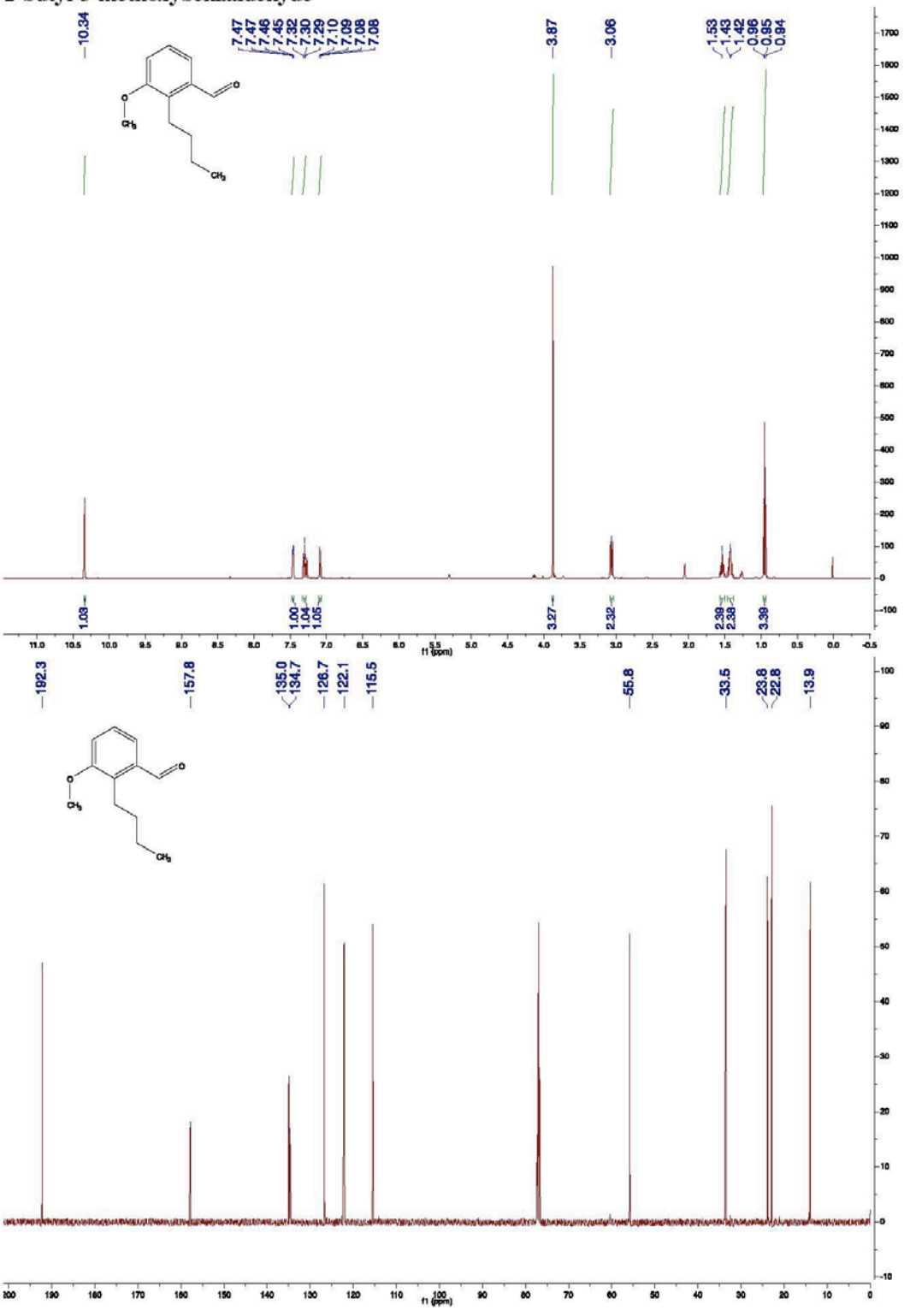

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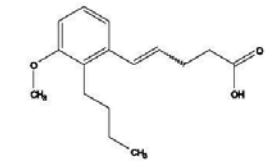

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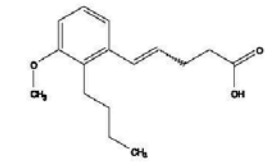

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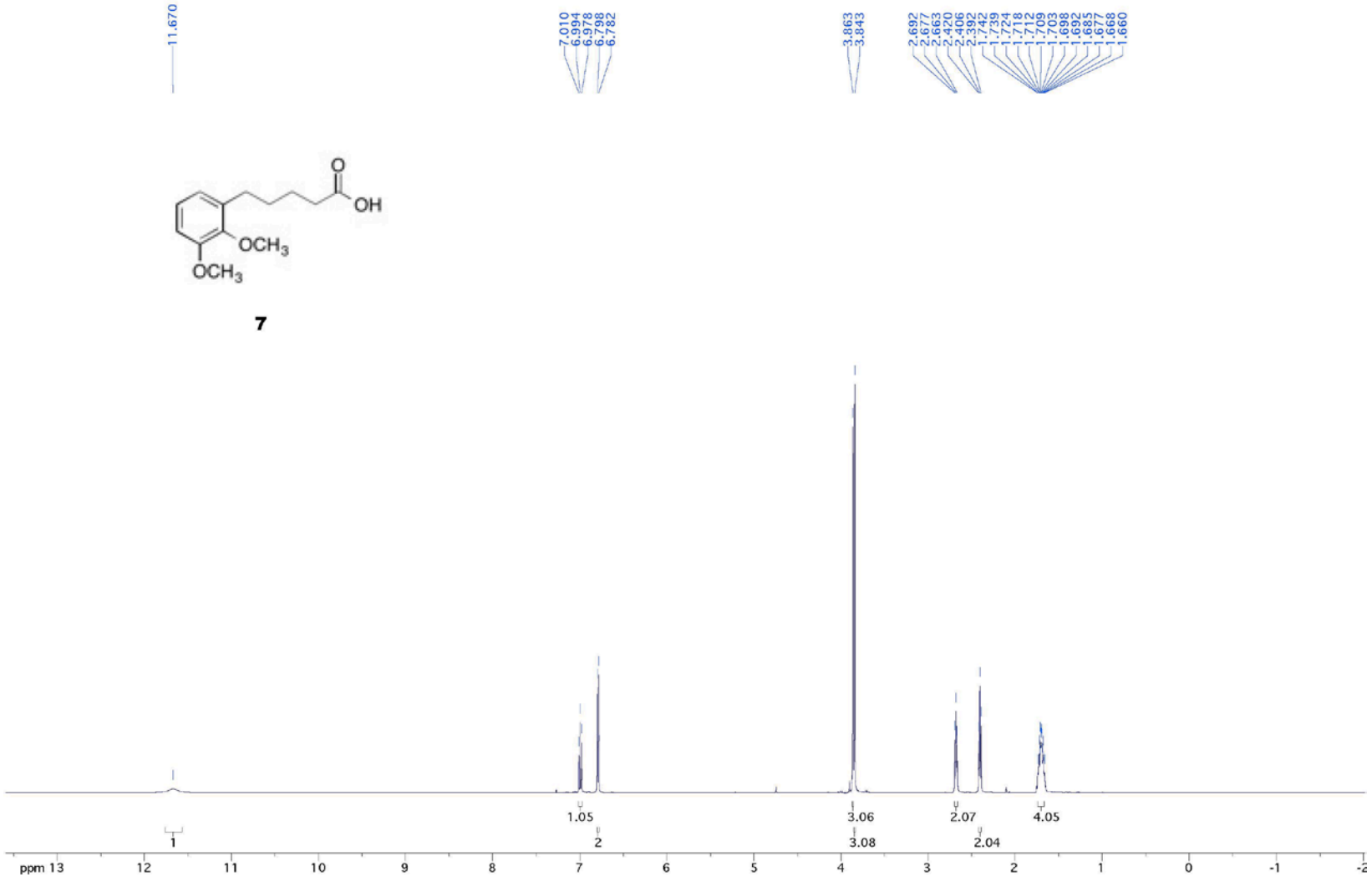
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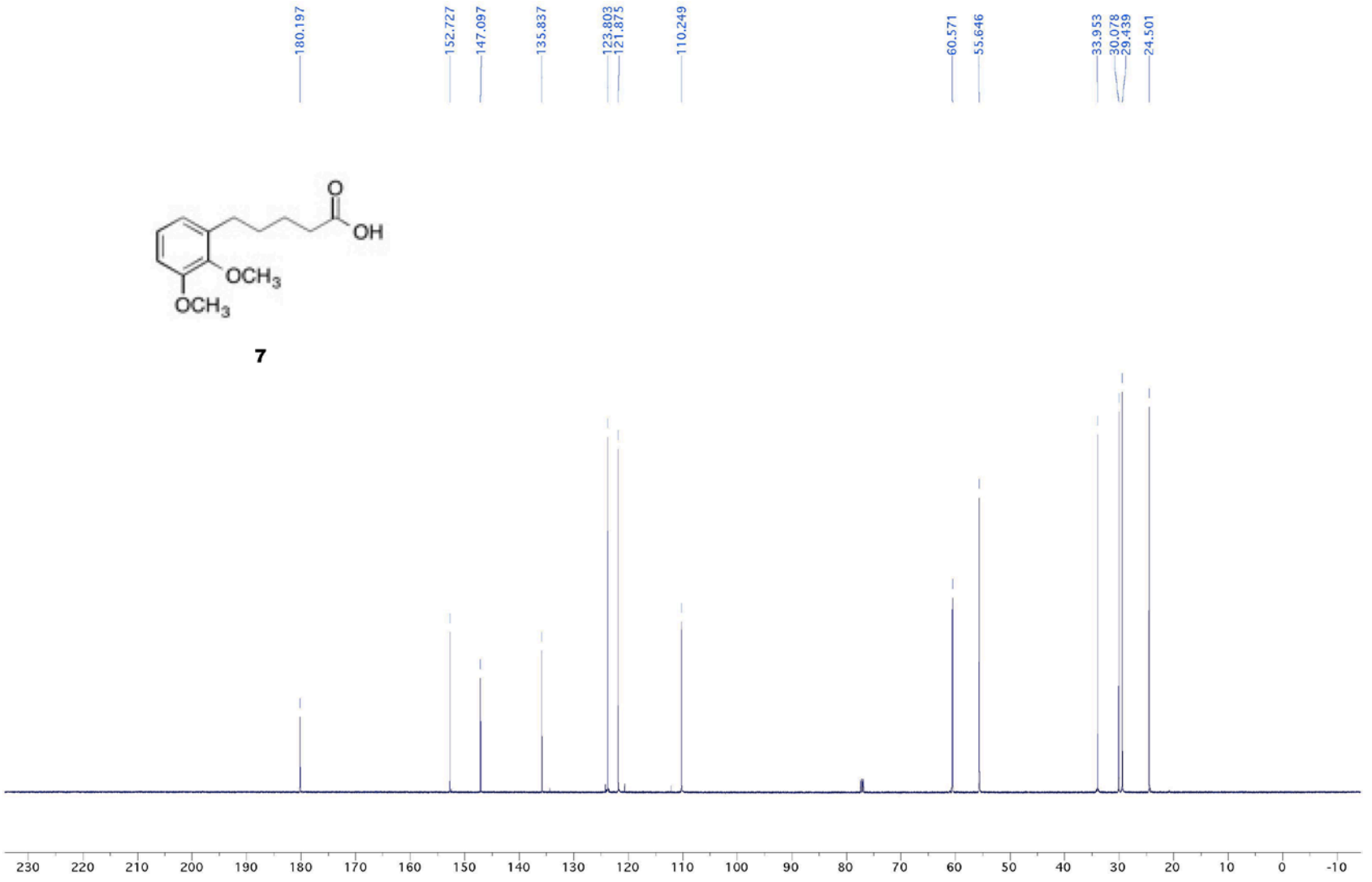
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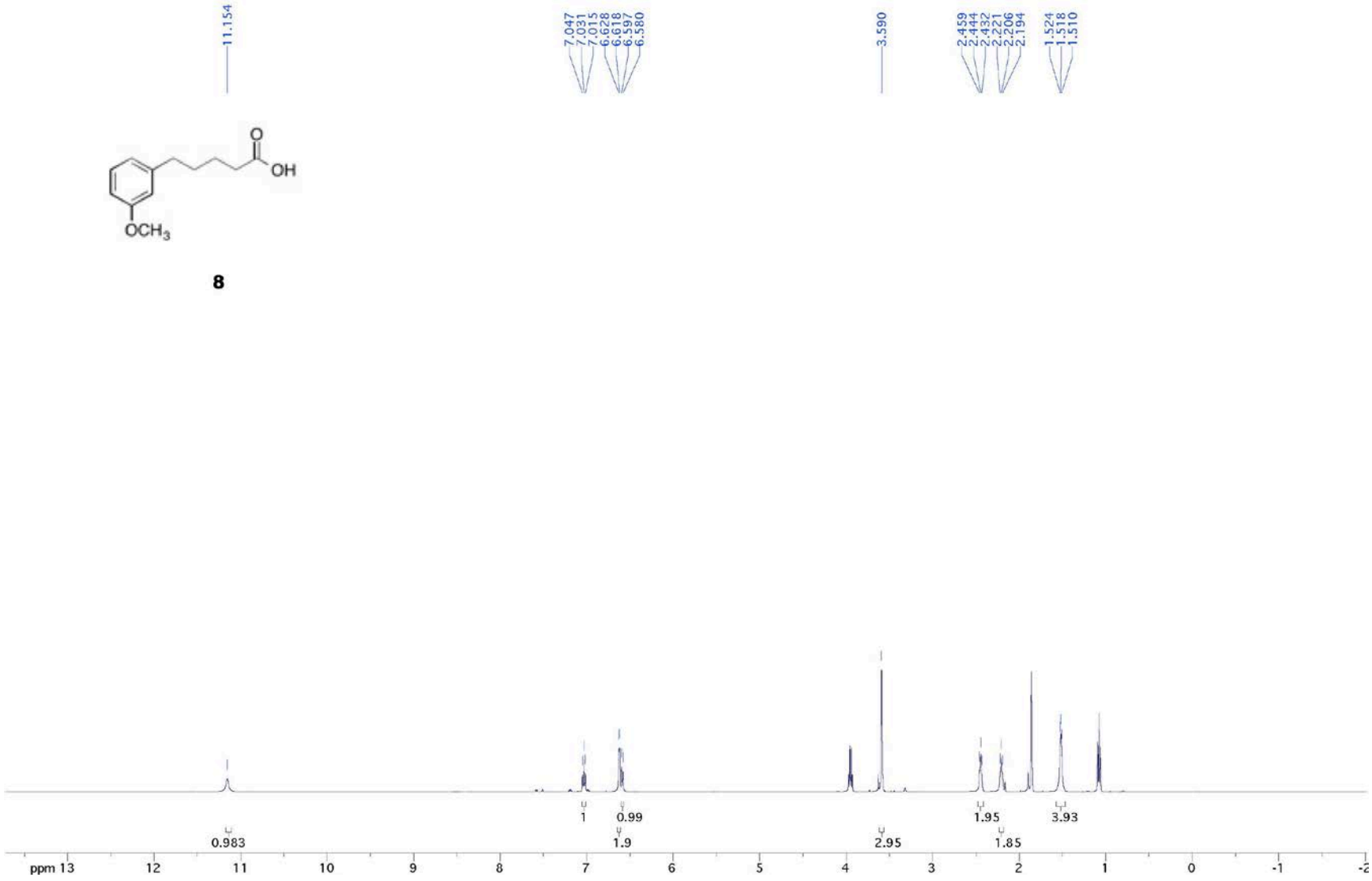
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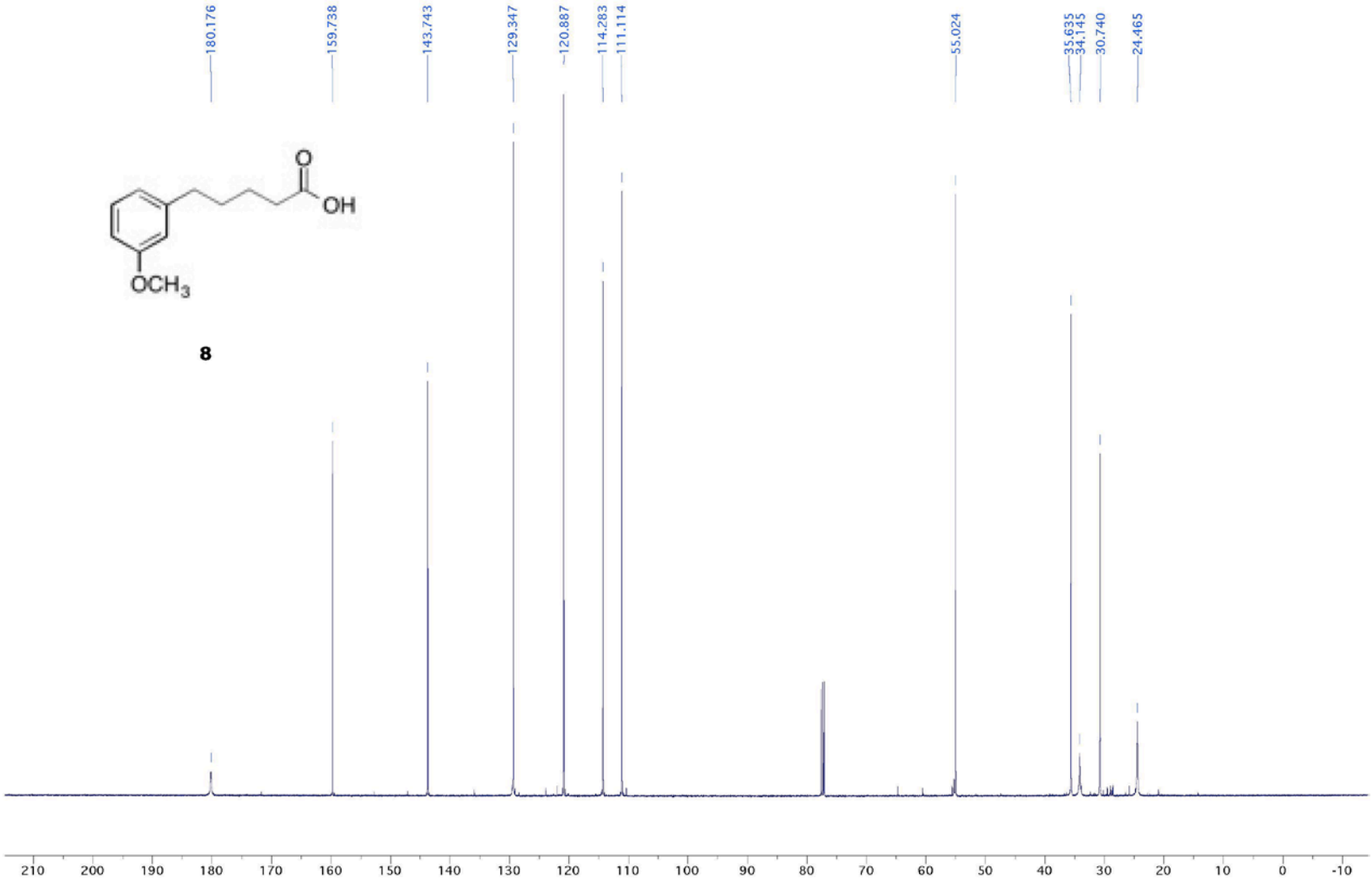
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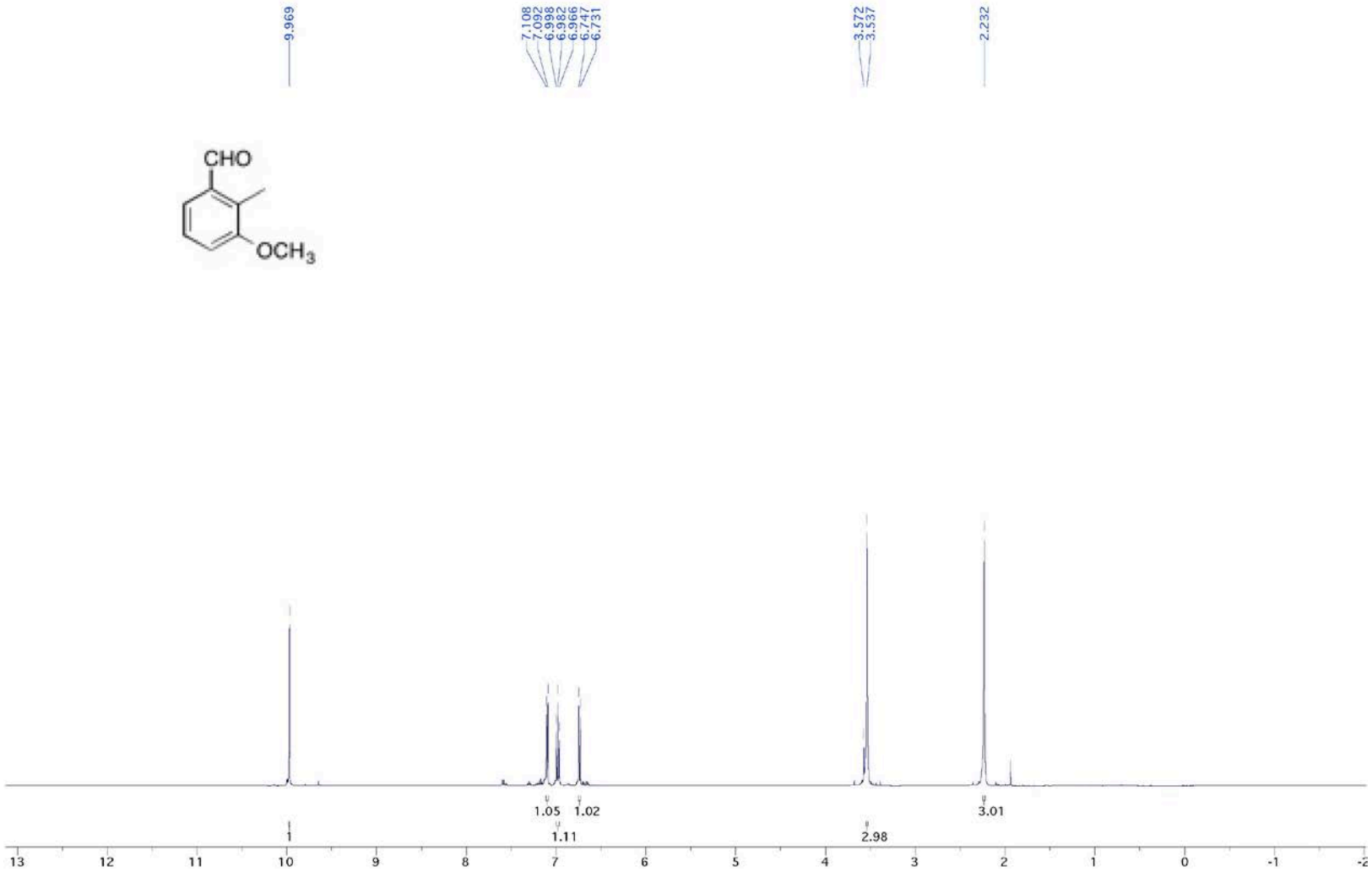
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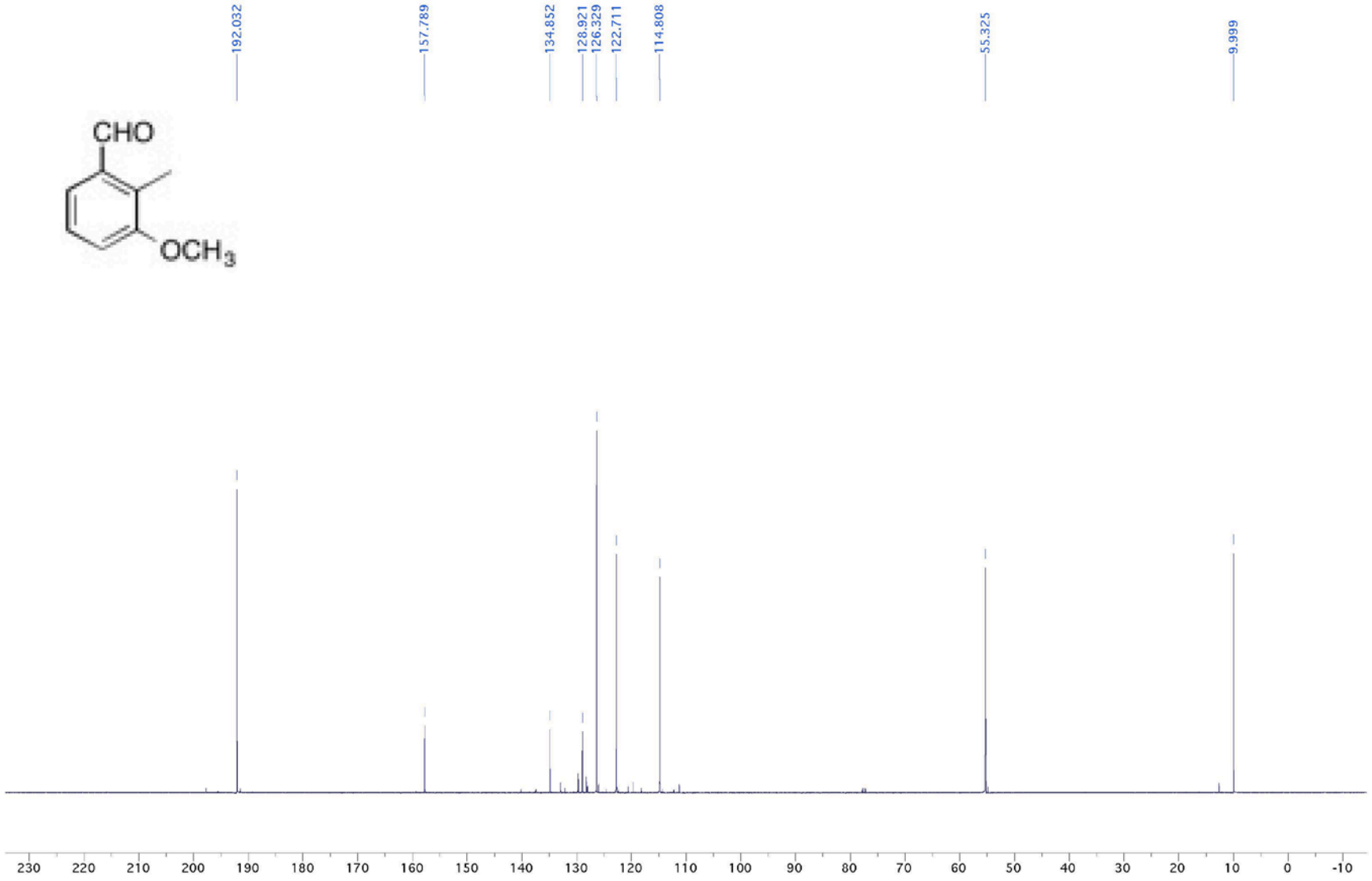
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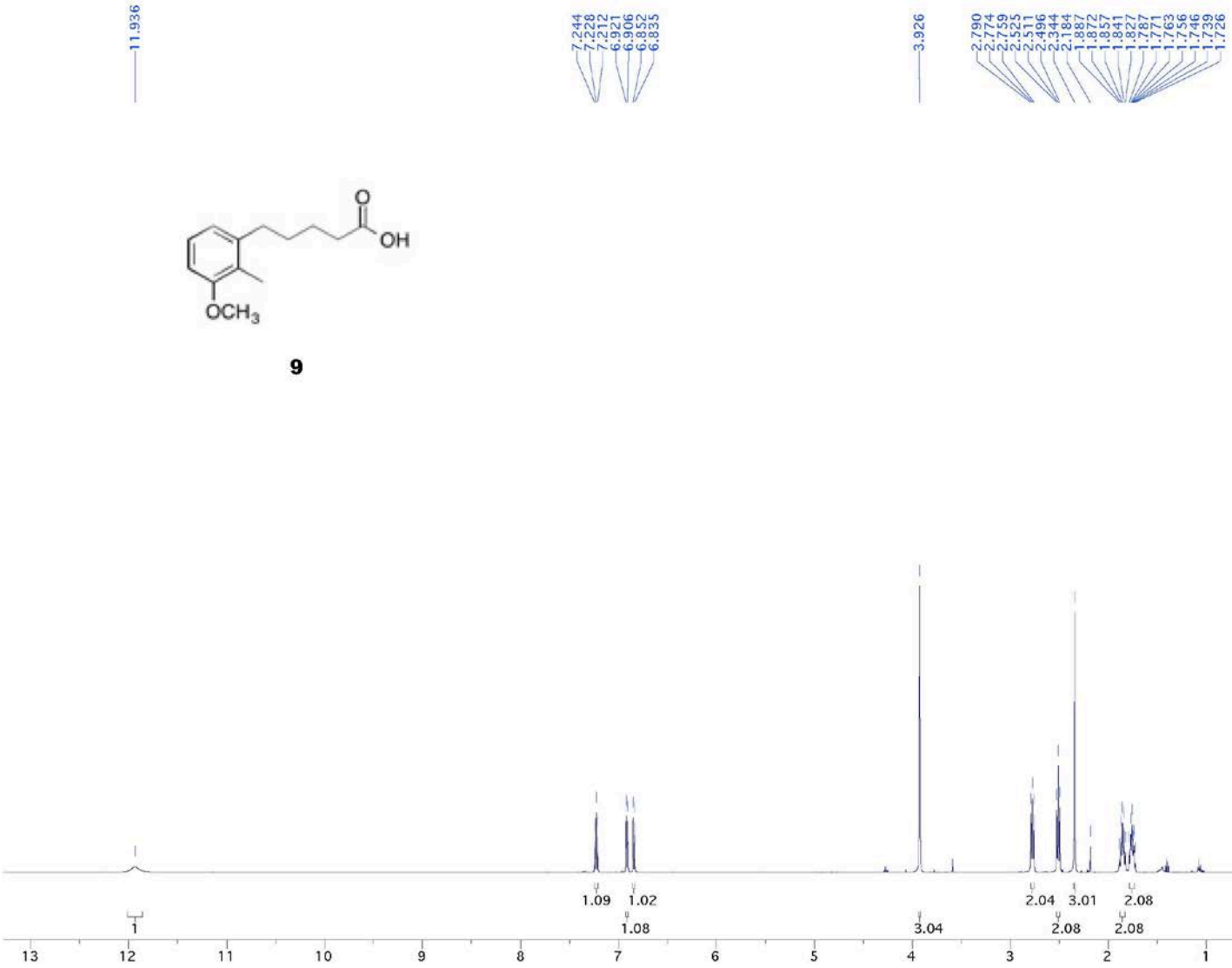
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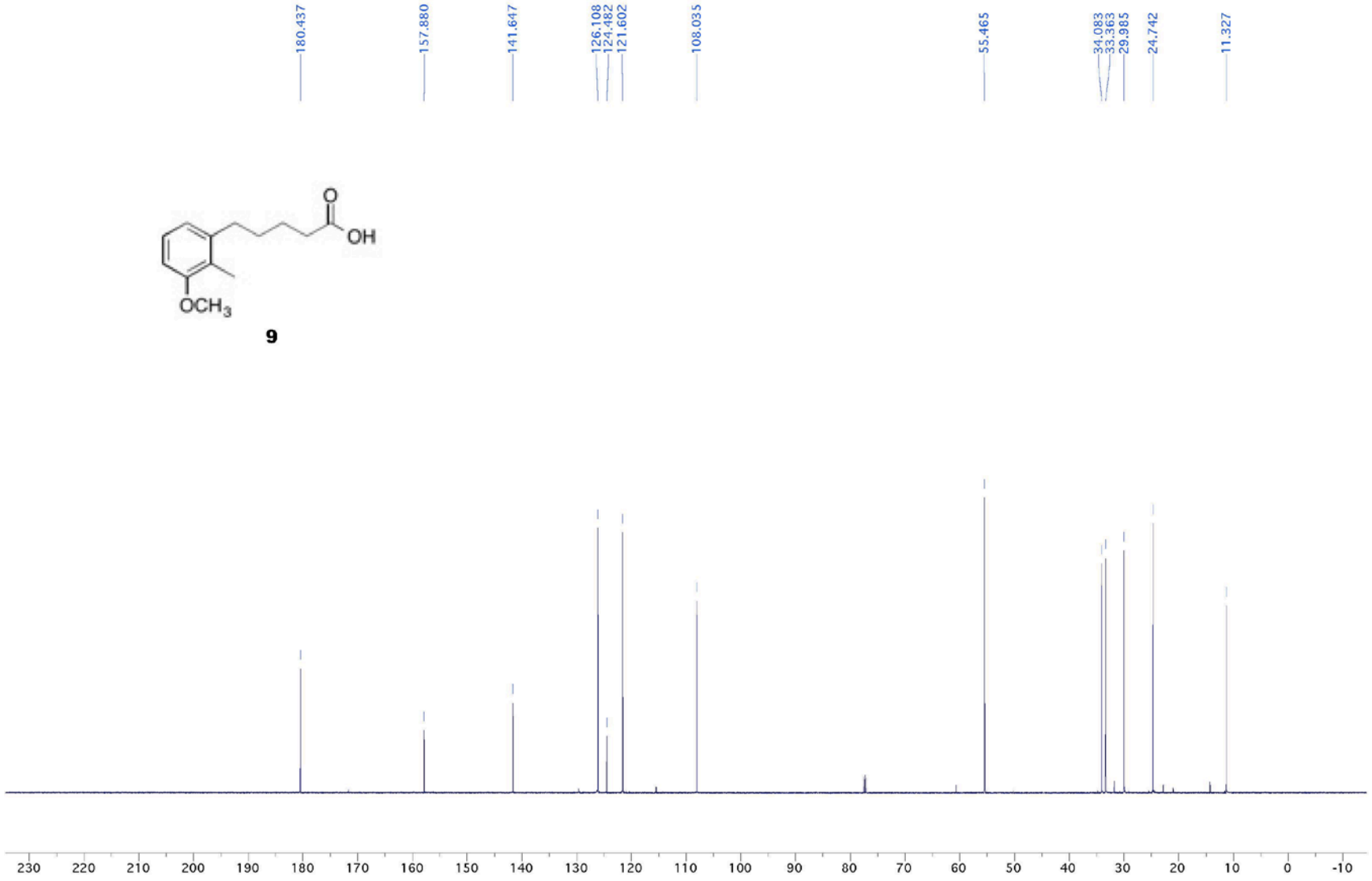
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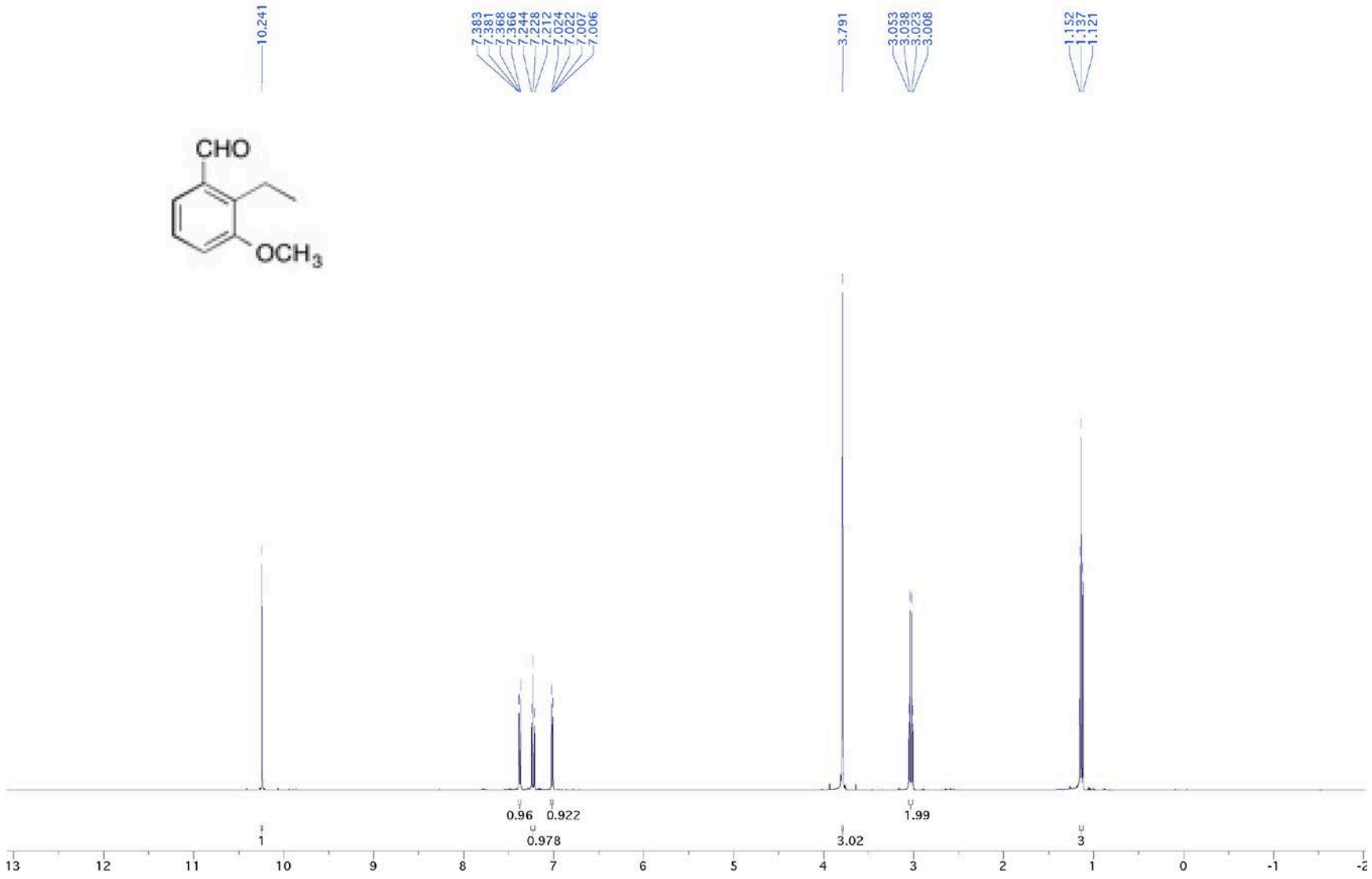
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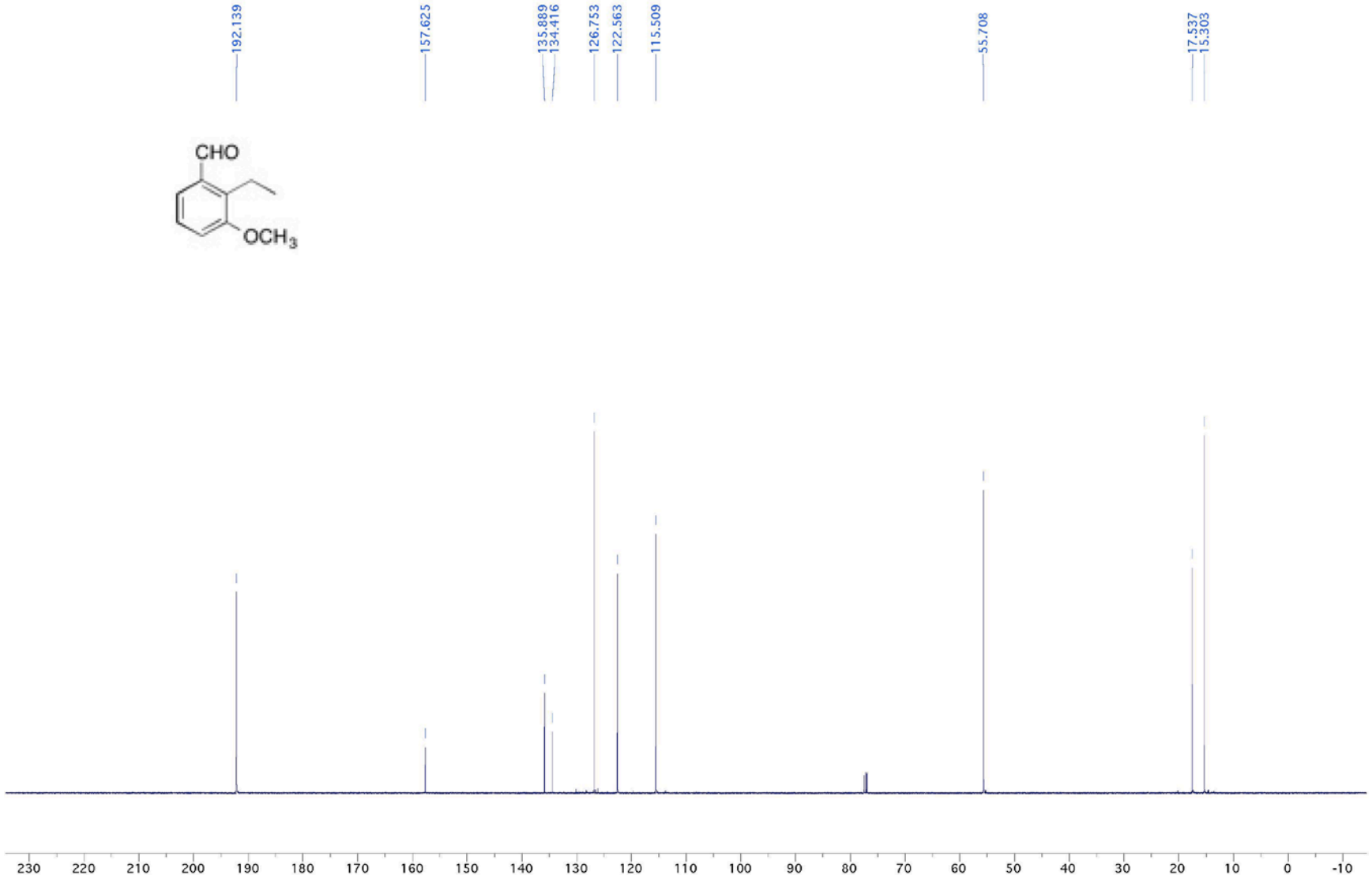
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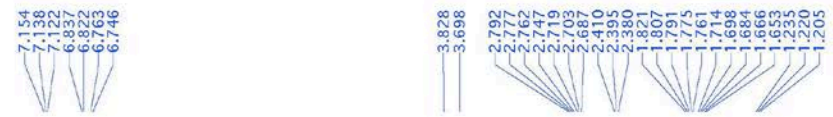
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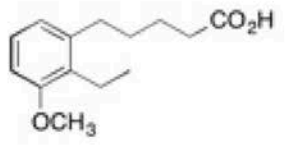
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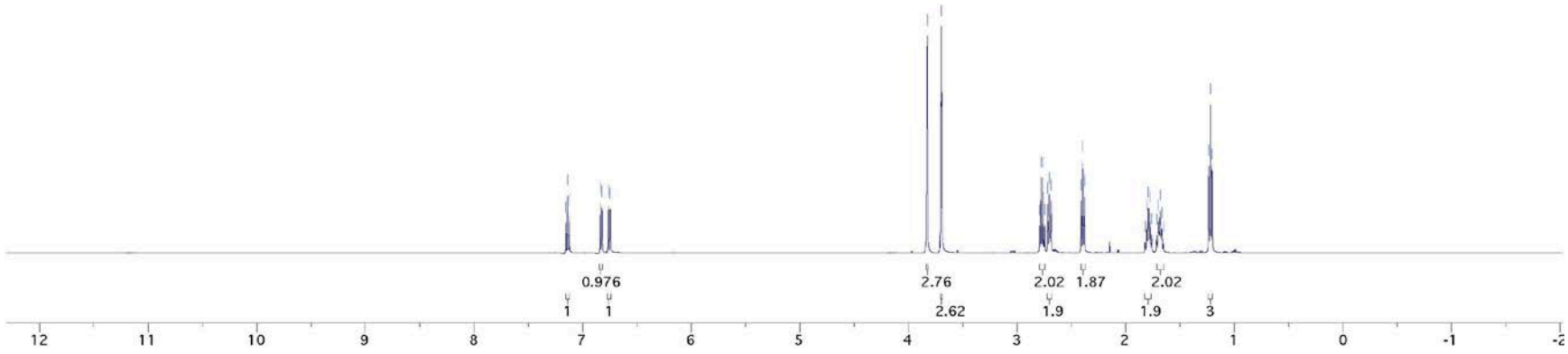
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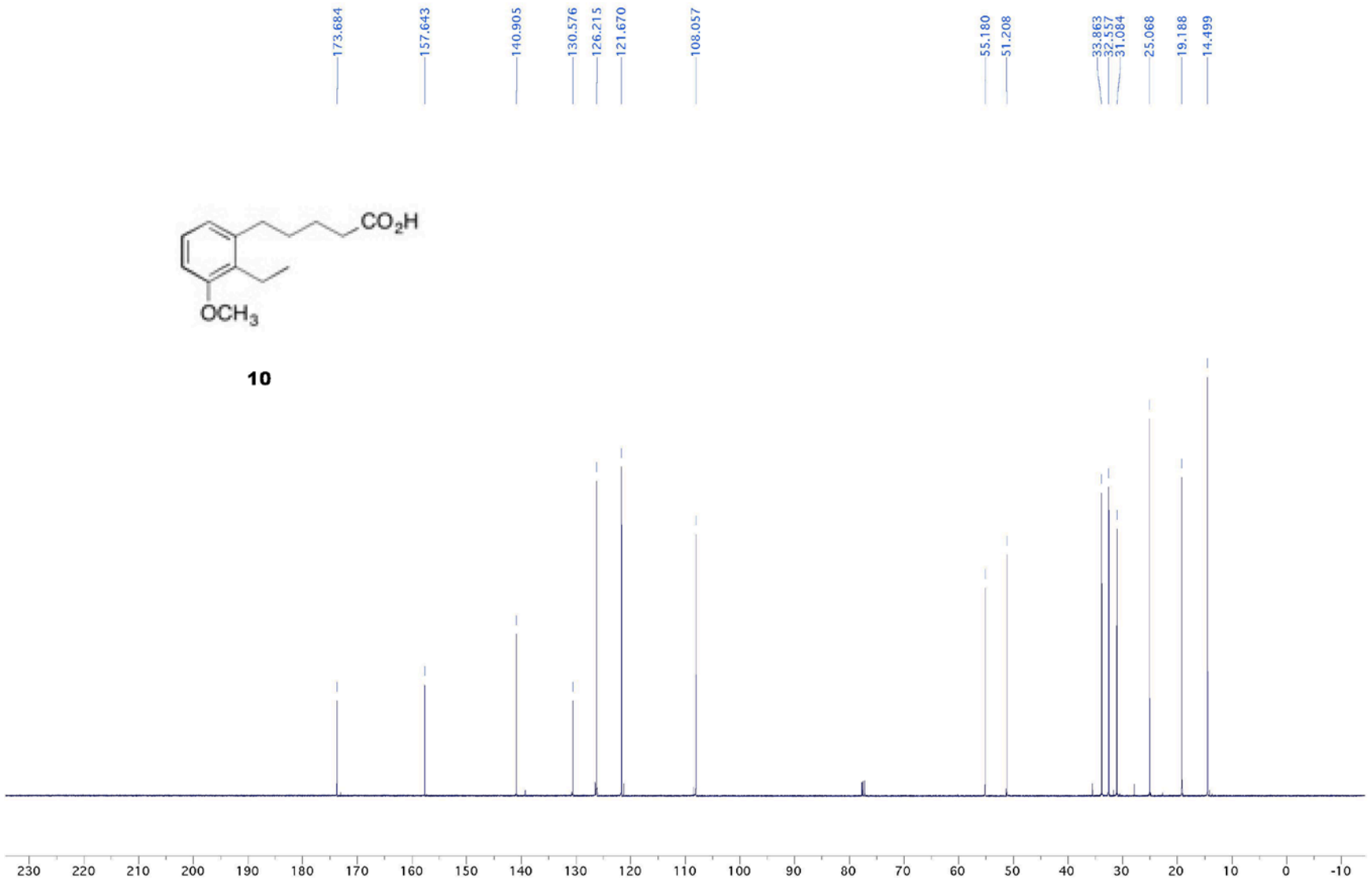
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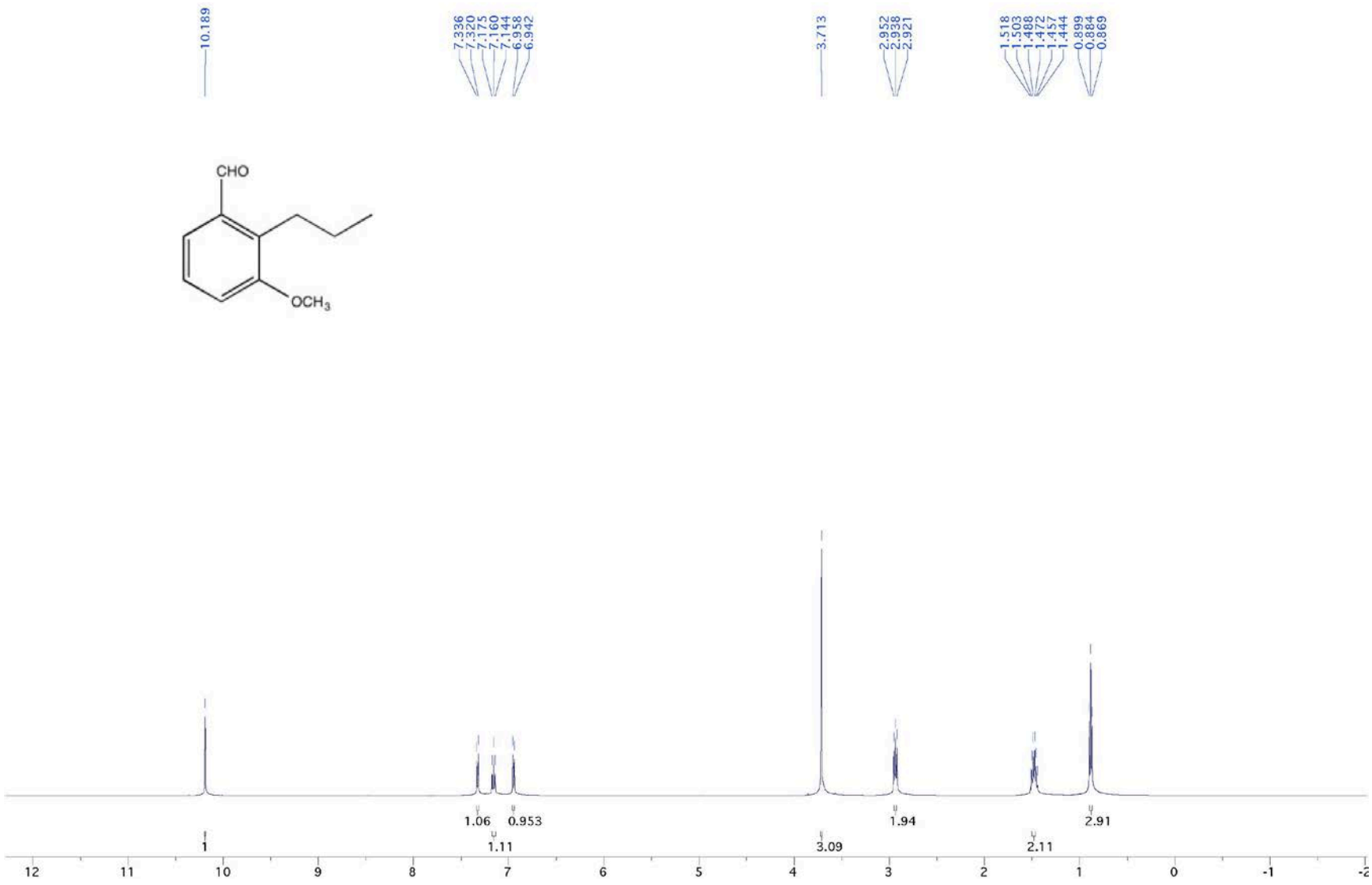
130.576
126.215
121.670
108.057
55.180
51.208
33.863
32.557
31.084
25.068
19.188
14.499
CO2H
OCH3
10
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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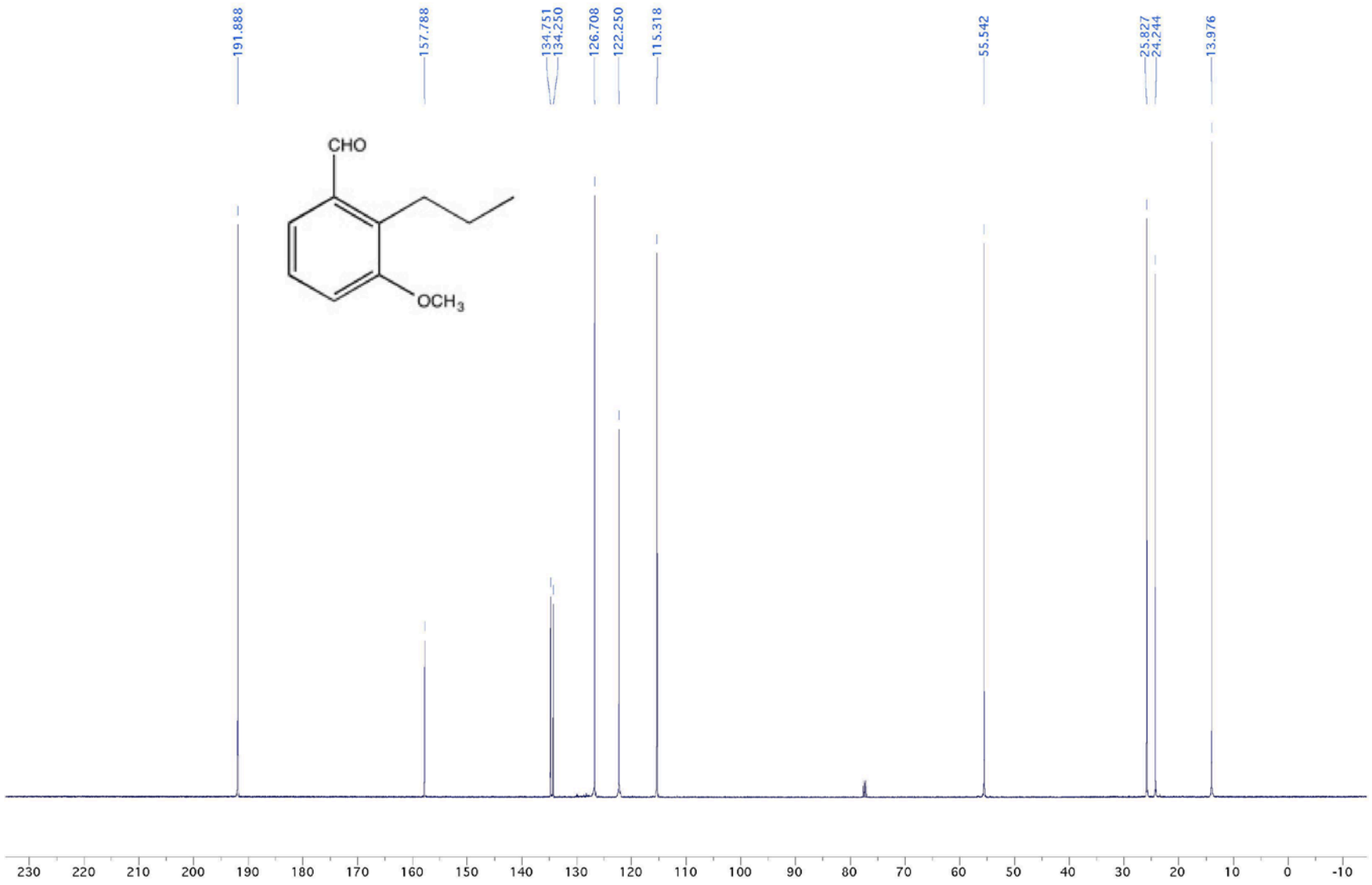
7.320
7.175
7.160
7.144
6.958
6.942
3.713
2.952
2.938
2.921
1.518
1.503
1.488
1.472
1.457
1.444
0.899
0.884
0.869
CHO
OCH3
1.06
0.953
1.94
2.91
1
1.11
3.09
2.11
12
11
10
9
8
7
6
5
4
3
2
1
0
-1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134.751
134.250
126.708
122.250
115.318
55.542
25.827
24.244
13.976
CHO
OCH3
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
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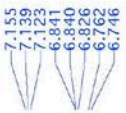
60
50
40
30
20
10
0
-10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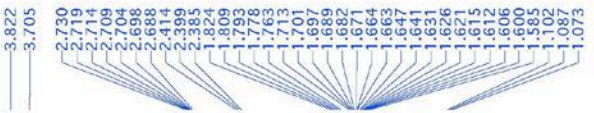
7.139
7.123
6.841
6.840
6.826
6.762
6.746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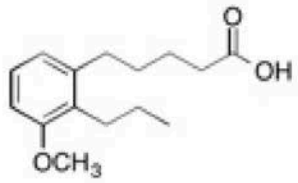
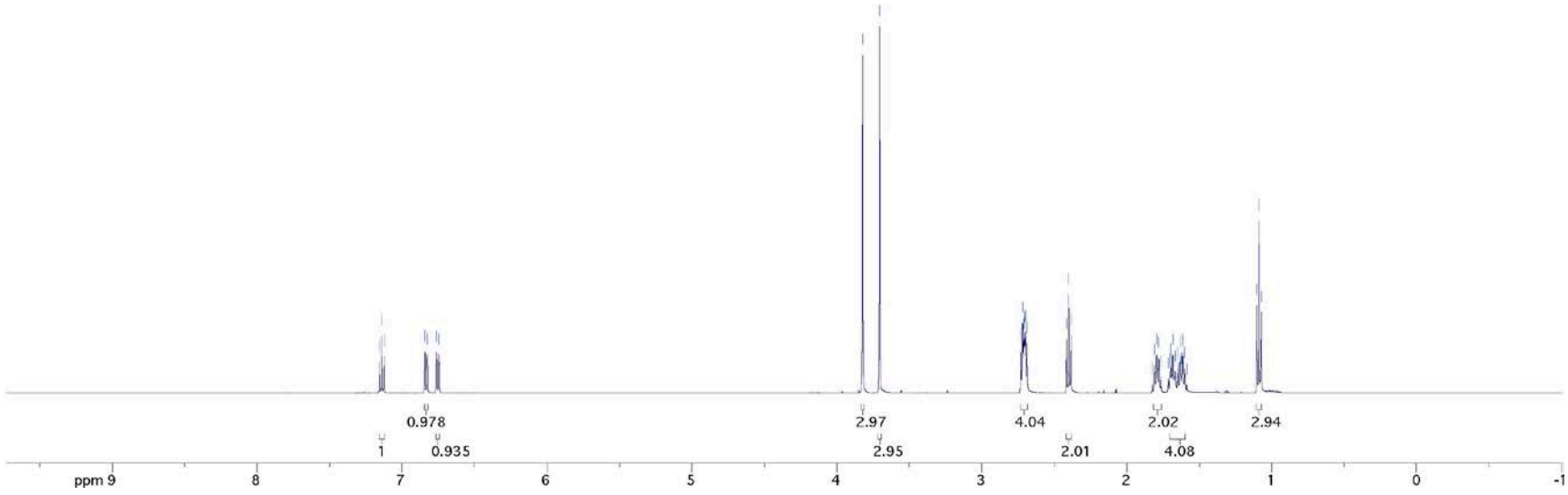
3.705
2.730
2.719
2.714
2.709
2.704
2.698
2.688
2.414
2.399
2.385
1.824
1.809
1.793
1.778
1.763
1.713
1.701
1.697
1.689
1.682
1.671
1.664
1.663
1.647
1.641
1.631
1.626
1.621
1.615
1.612
1.606
1.600
1.585
1.102
1.087
1.073


O
OH
OCH3

11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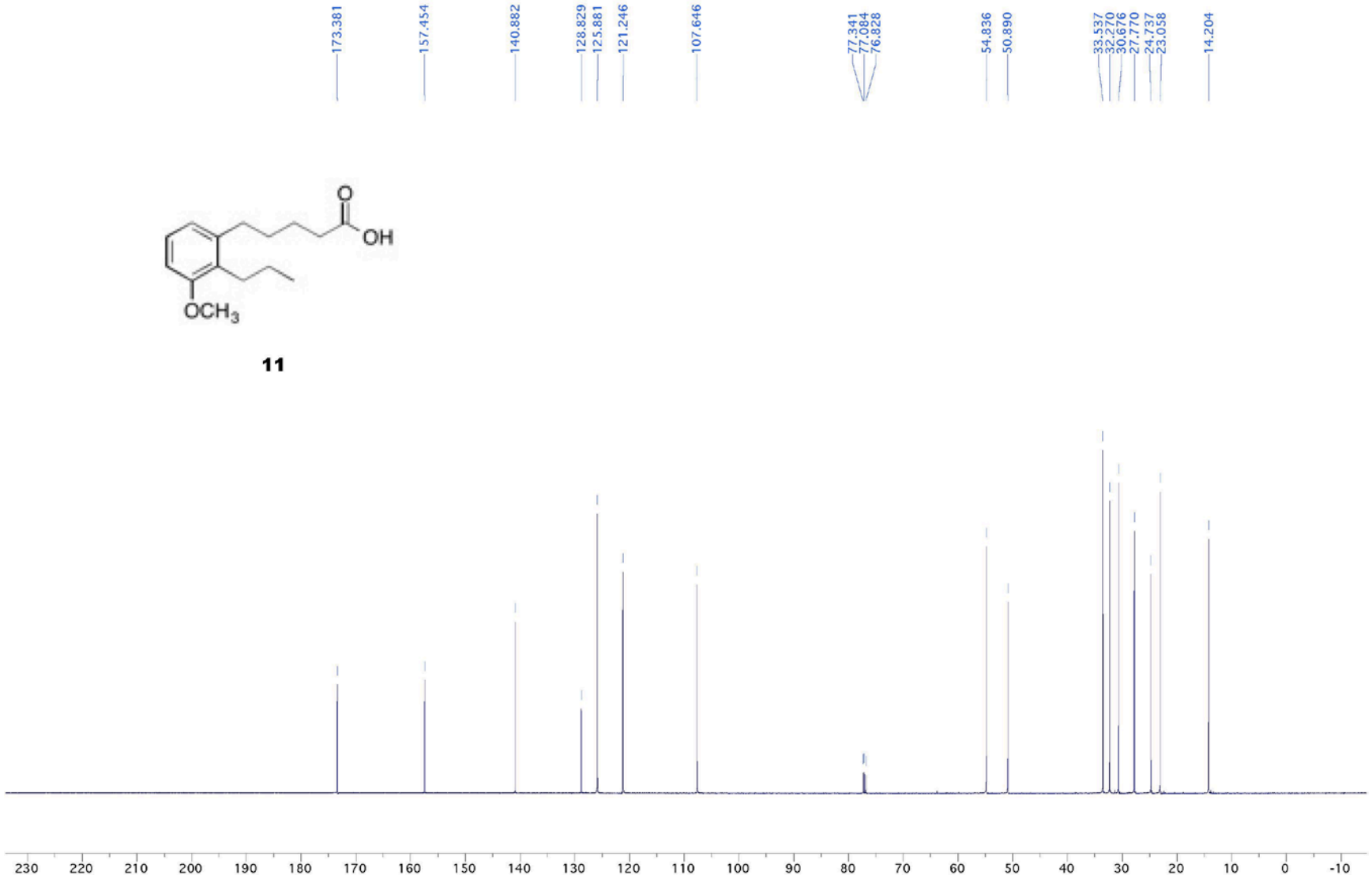
2.97
4.04
2.02
2.94
1
0.935
2.95
2.01
4.08
ppm 9
8
7
6
5
4
3
2
1
0
-1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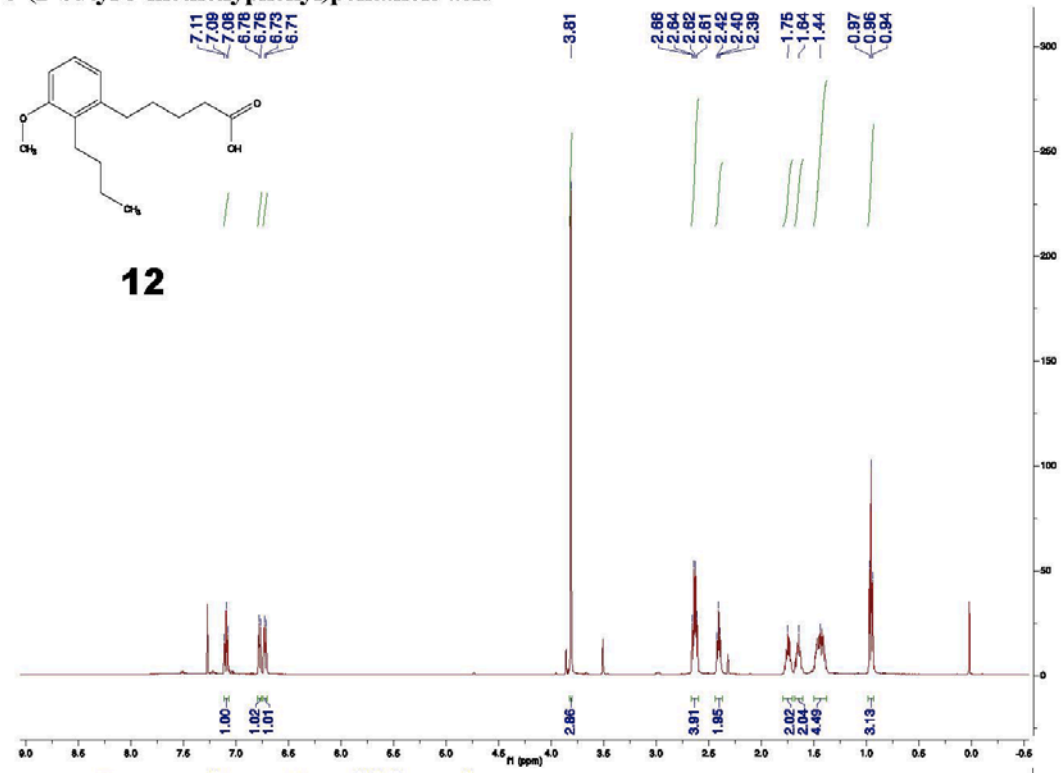
140.882
128.829
125.881
121.246
107.646
77.341
77.084
76.828
54.836
50.890
33.537
32.270
30.676
27.770
24.737
23.058
14.204
O
OH
OCH3
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

11

5-(2-butyl-3-methoxyphenyl)pentanoic acid



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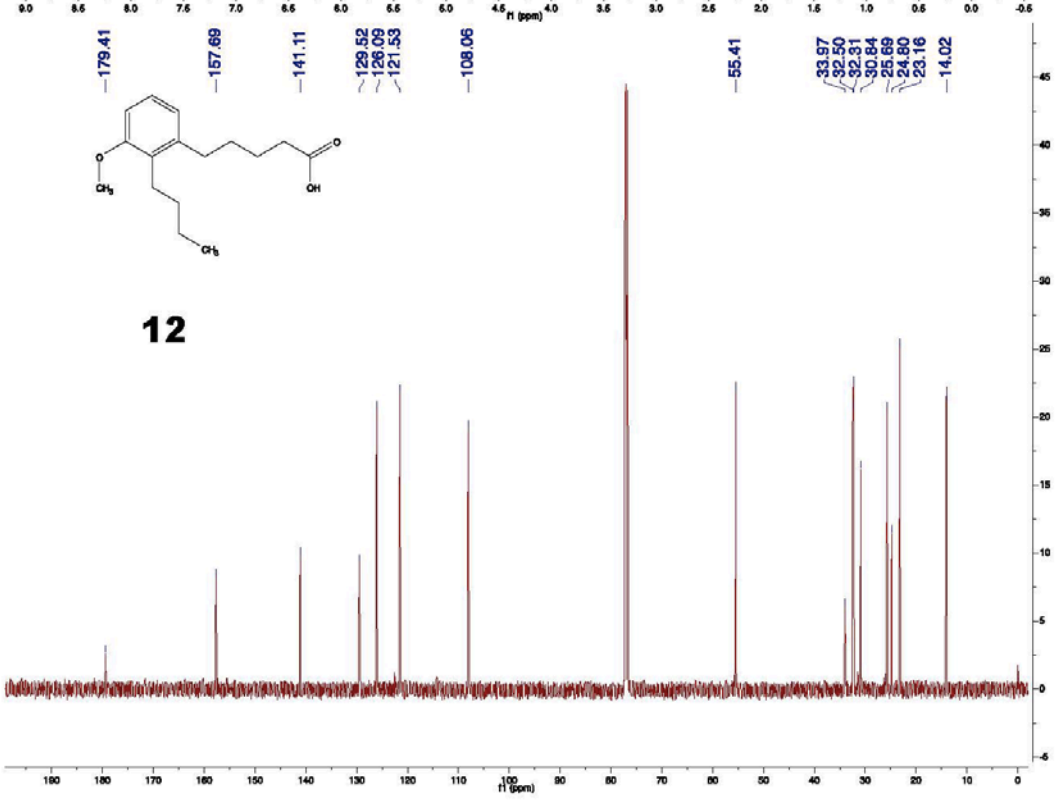
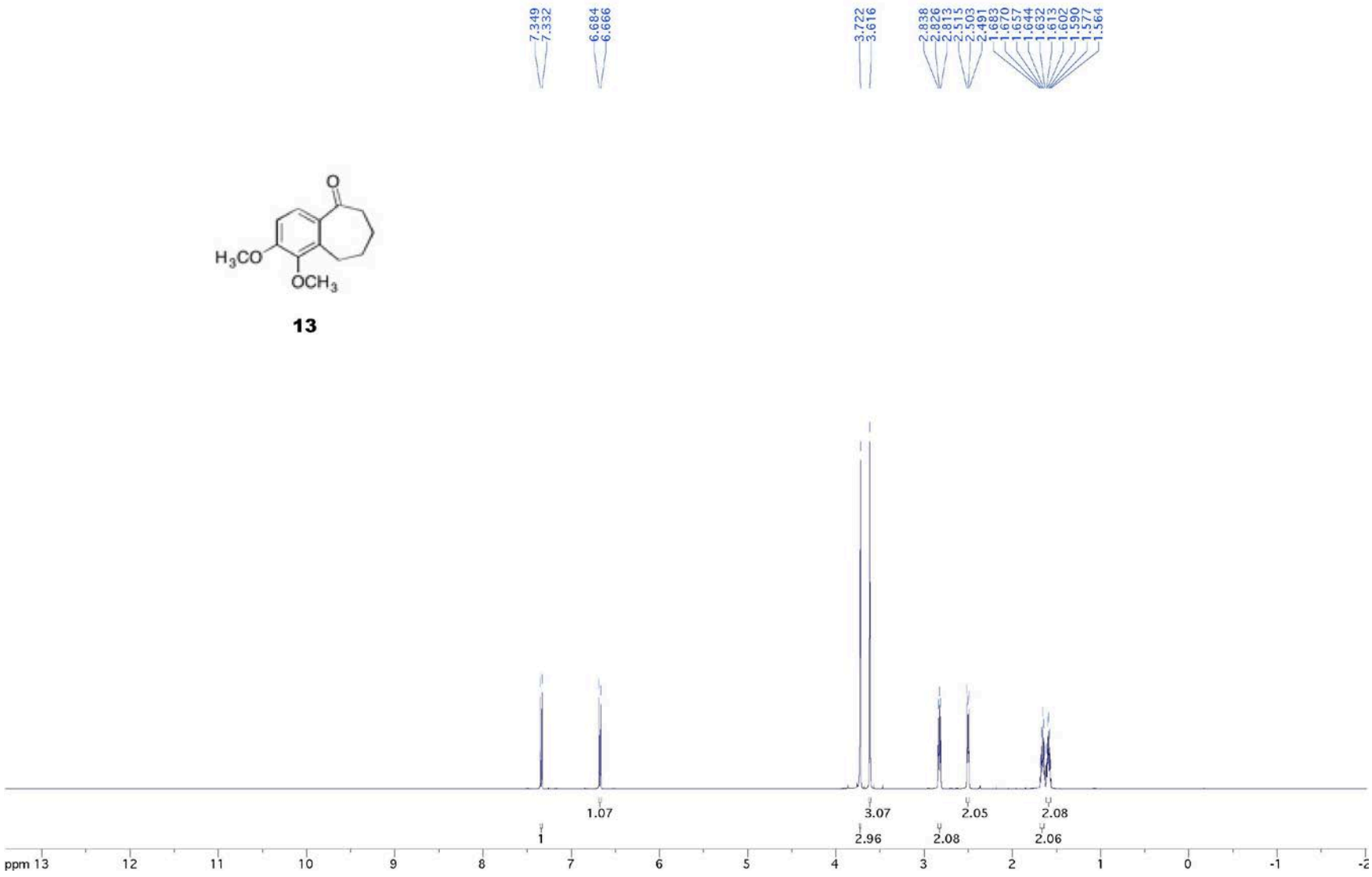


12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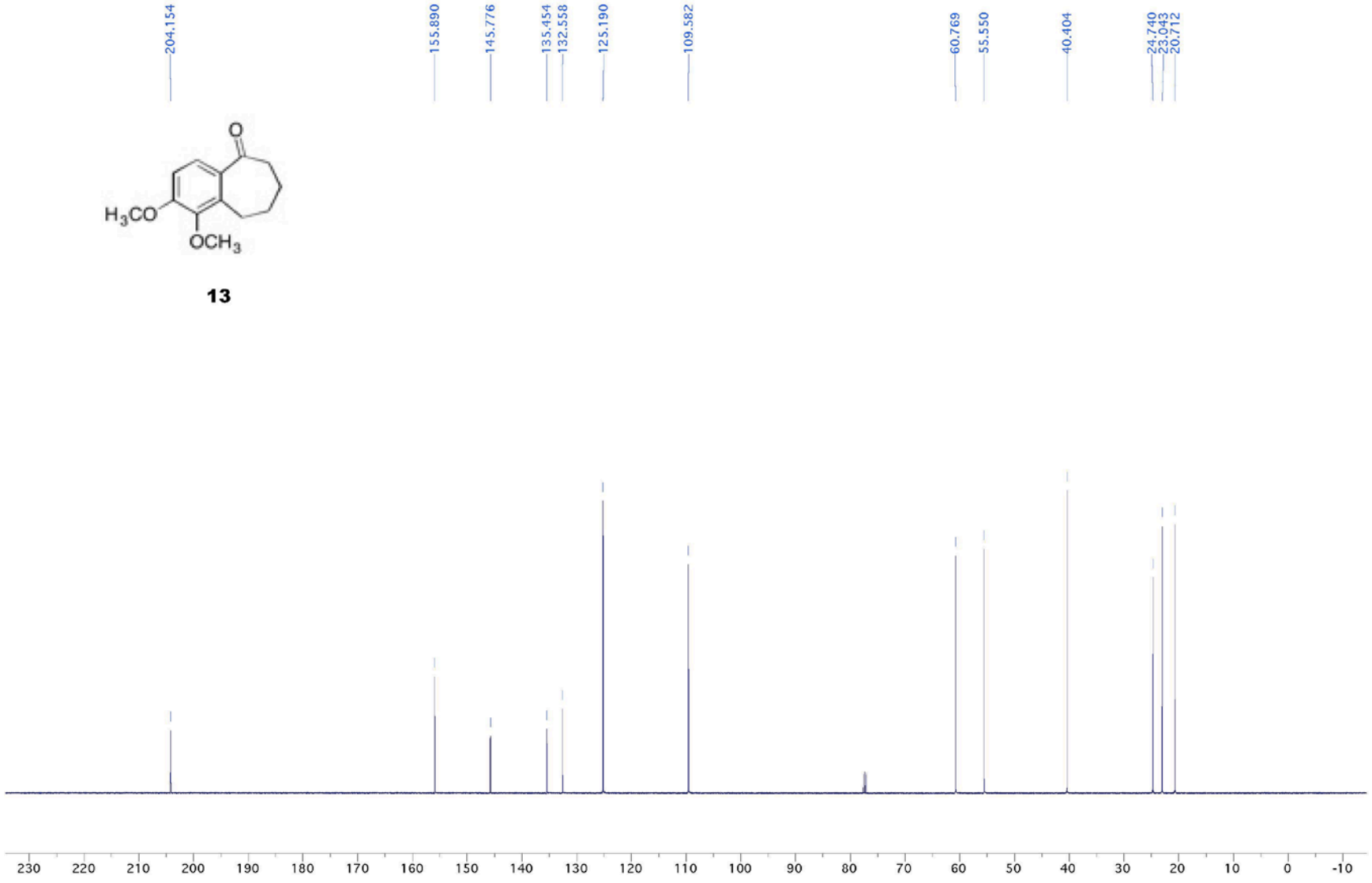
6.666
3.722
3.616
2.838
2.826
2.813
2.515
2.503
2.491
1.683
1.670
1.657
1.644
1.632
1.613
1.602
1.590
1.577
1.564
O
H3CO
OCH3
13
1.07
3.07
2.05
2.08
1
2.96
2.08
2.06
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1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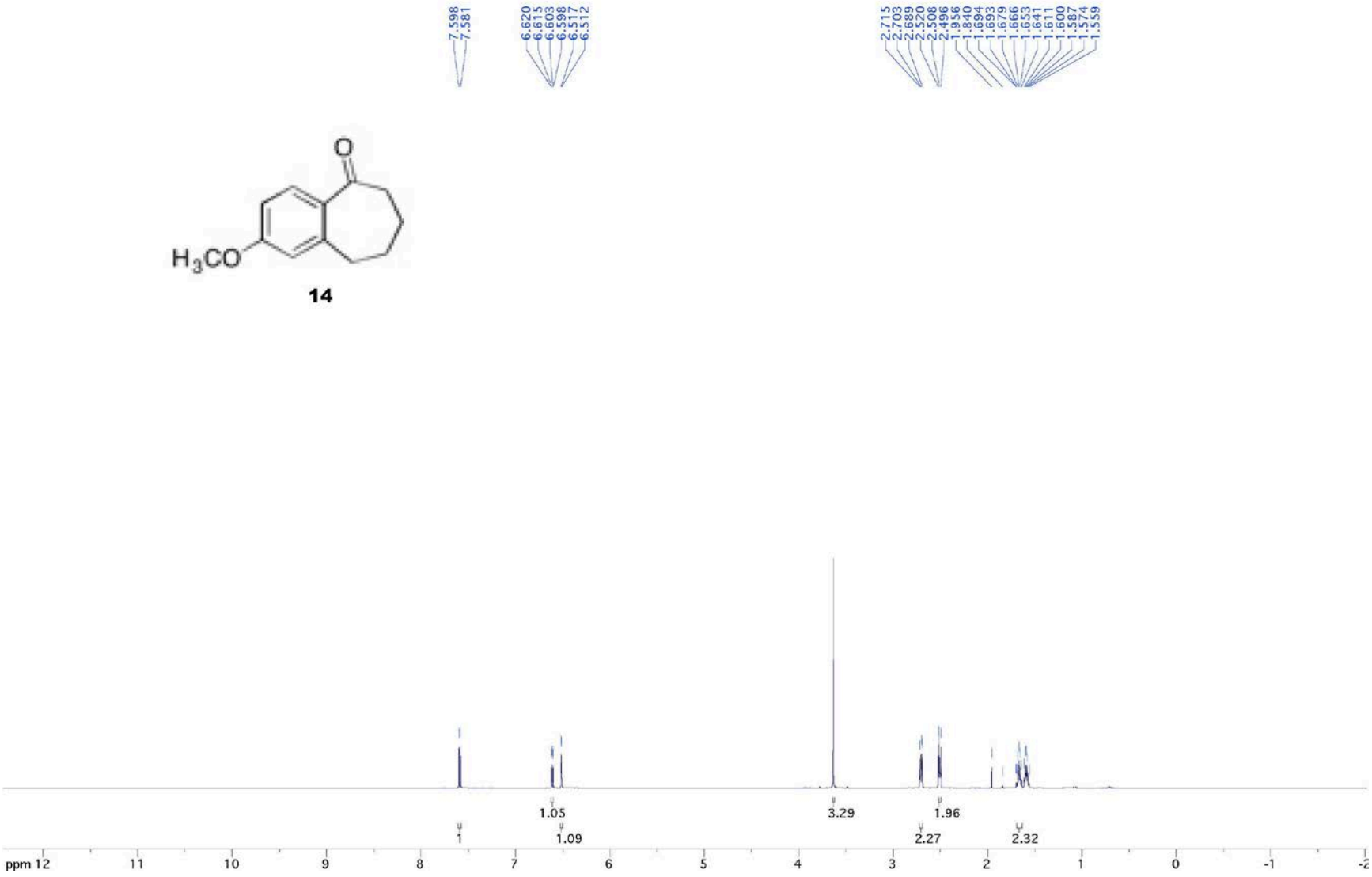
155.890
145.776
135.454
132.558
125.190
109.582
60.769
55.550
40.404
24.740
23.043
20.712
O
H3CO
OCH3
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

13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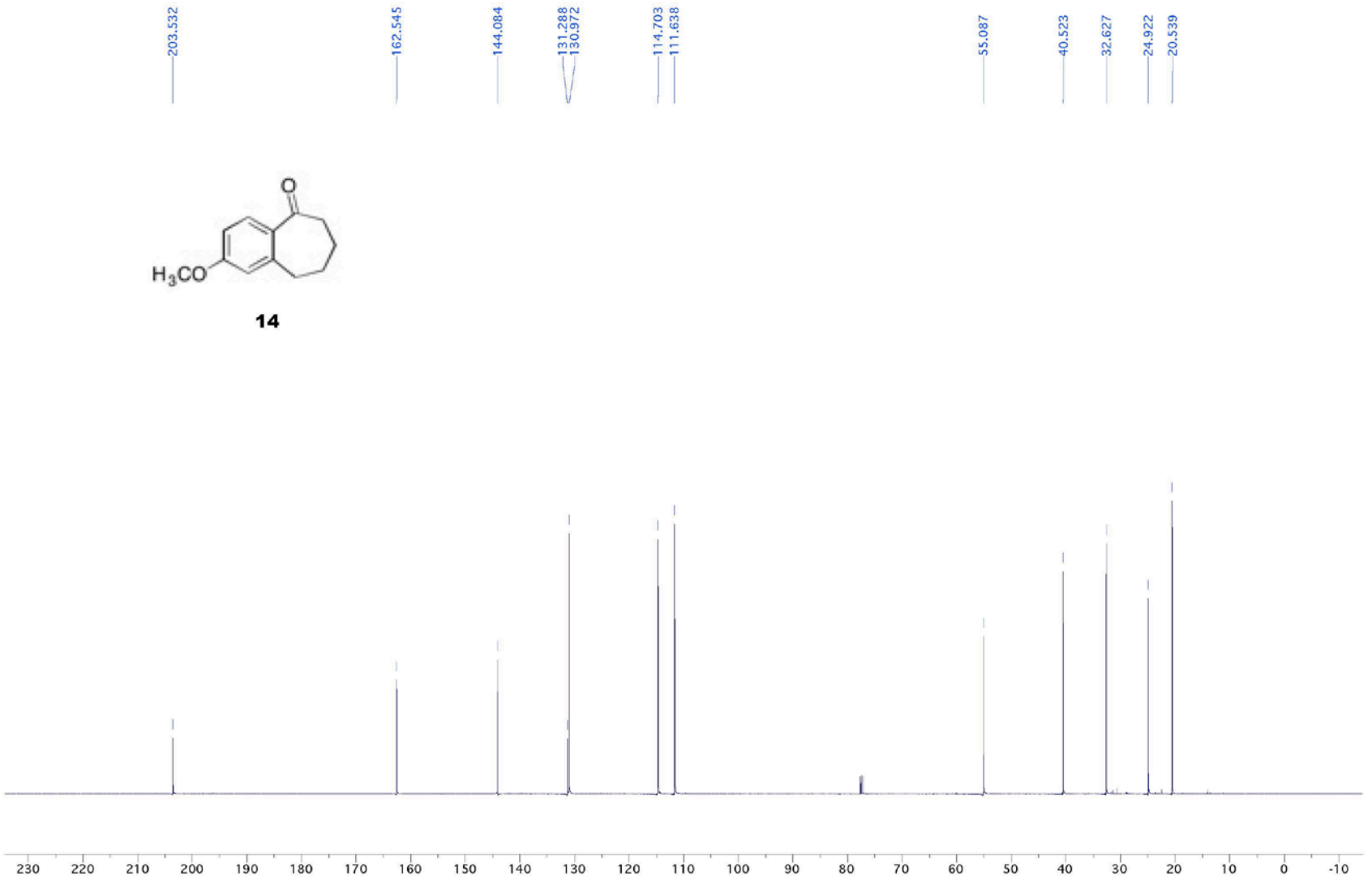
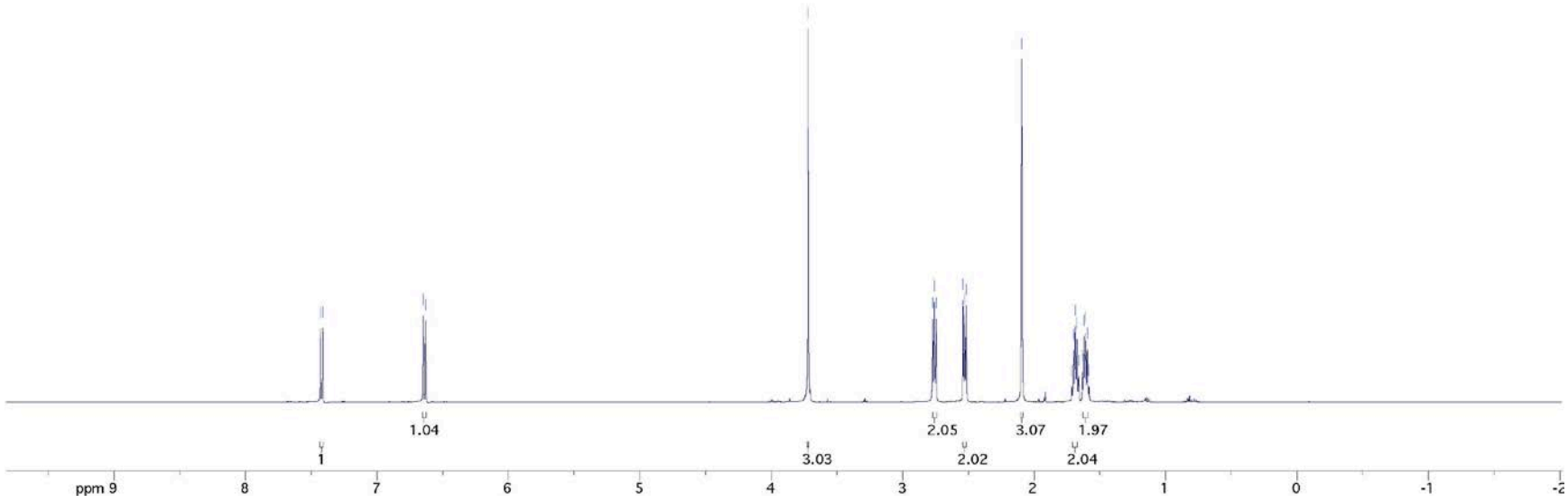
7.581
6.620
6.615
6.603
6.598
6.517
6.512
2.715
2.703
2.689
2.520
2.508
2.496
1.956
1.840
1.694
1.693
1.679
1.666
1.653
1.641
1.611
1.600
1.587
1.574
1.559
O
H3CO
14
1.05
3.29
1.96
1
1.09
2.27
2.32
ppm 12
11
10
9
8
7
6
5
4
3
2
1
0
-1


203.532
162.545
144.084
131.288
130.972
114.703
111.638
55.087
40.523
32.627
24.922
20.539
O
H3CO
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

14


7.430
7.413
6.648
6.631
3.719
2.771
2.759
2.745
2.541
2.529
2.517
2.094
1.714
1.699
1.686
1.673
1.661
1.632
1.620
1.609
1.596
1.583
O
H3CO

15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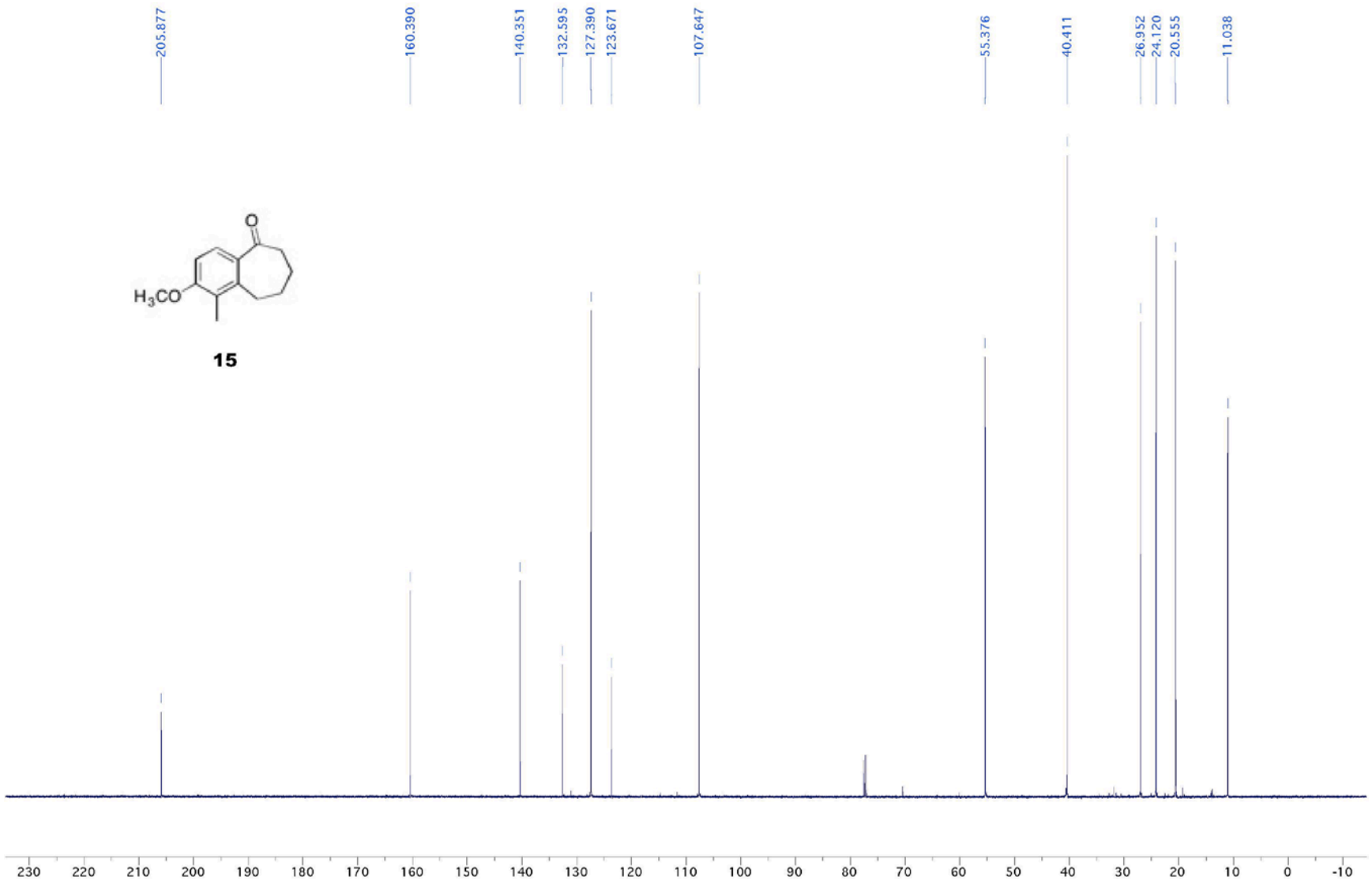
3.03
2.05
2.02
3.07
1.97
2.04
1
ppm 9
8
7
6
5
4
3
2
1
0
-1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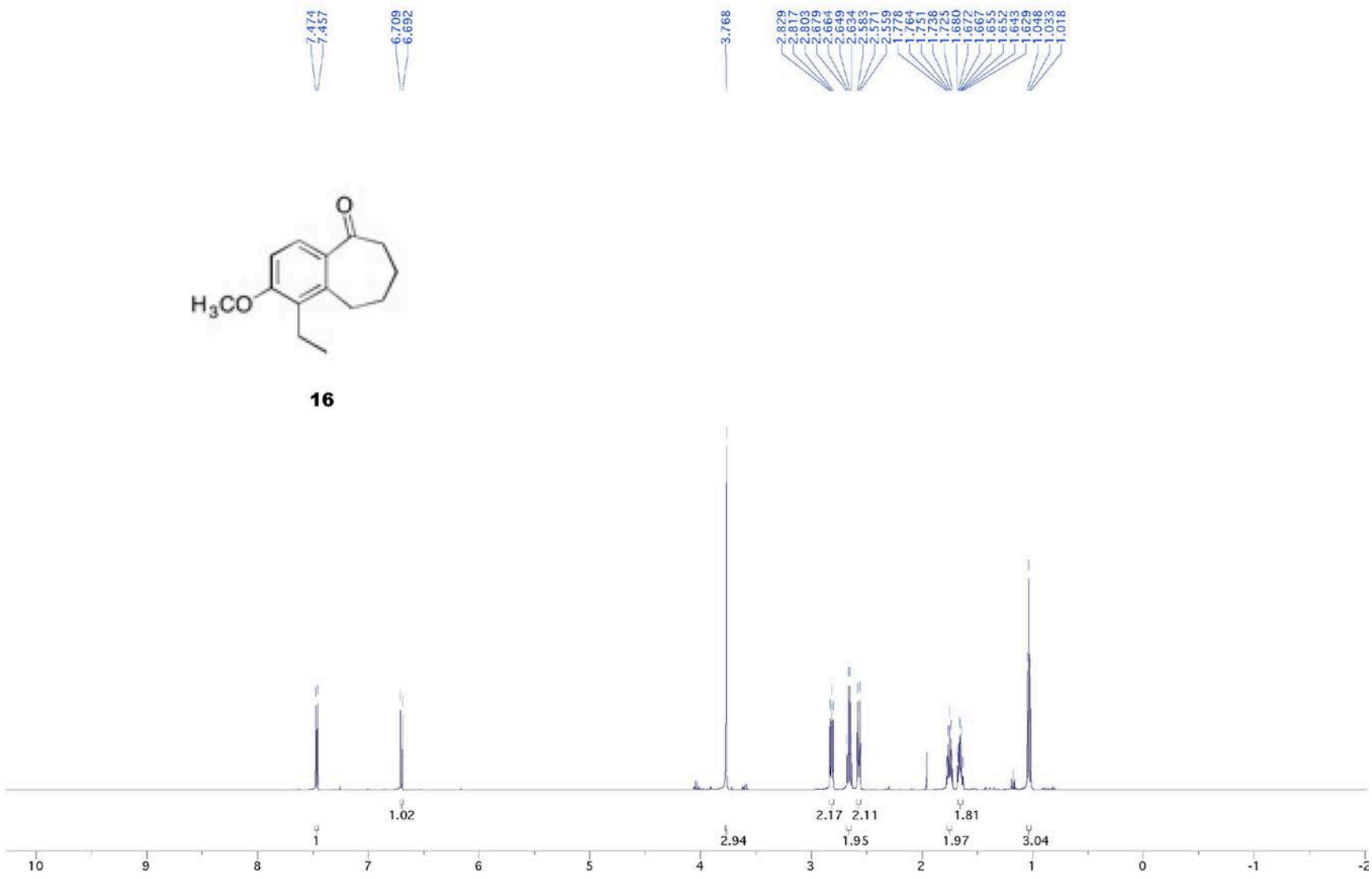
132.595
127.390
123.671
107.647
55.376
40.411
26.952
24.120
20.555
11.038
O
H3CO
15
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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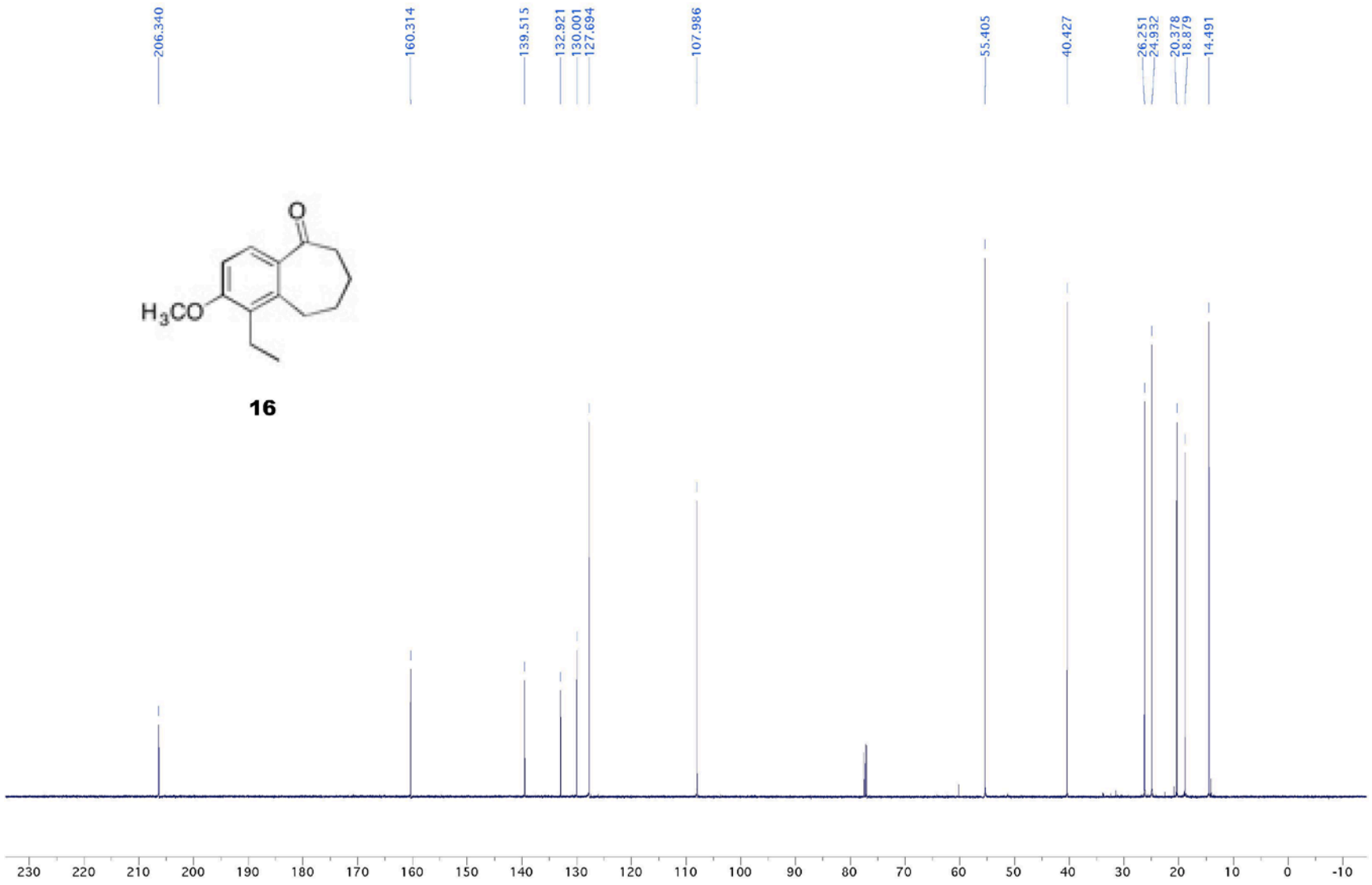
7.457
6.709
6.692
3.768
2.829
2.817
2.803
2.679
2.664
2.649
2.634
2.583
2.571
2.559
1.778
1.764
1.751
1.738
1.725
1.680
1.672
1.667
1.655
1.652
1.643
1.629
1.048
1.033
1.018
O
H3CO
16
1.02
2.17
2.11
1.81
1
2.94
1.95
1.97
3.04
10
9
8
7
6
5
4
3
2
1
0
-1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132.921
130.001
127.694
107.986
55.405
40.427
26.251
24.932
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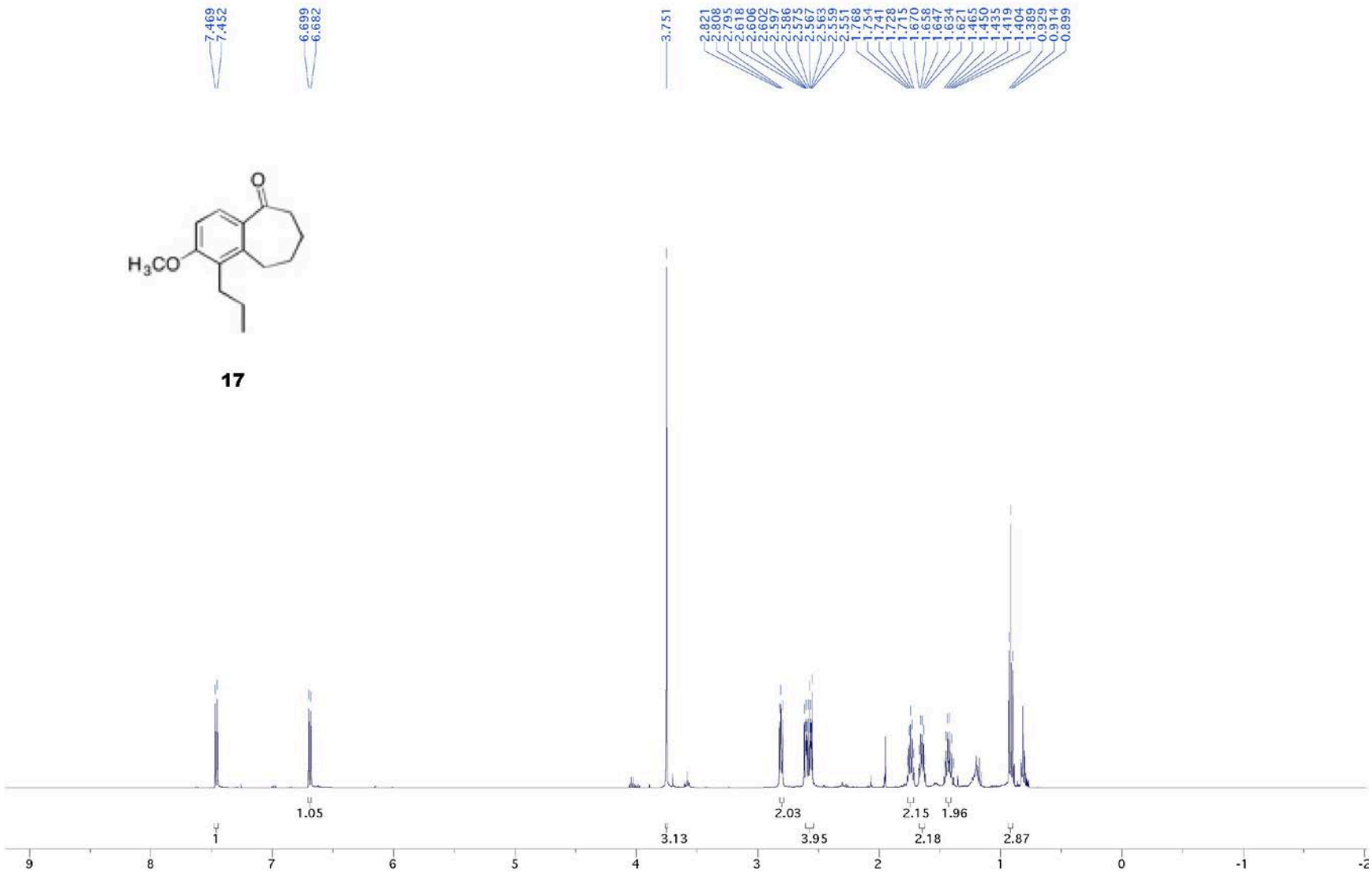
18.879
14.491
O
H3CO
16
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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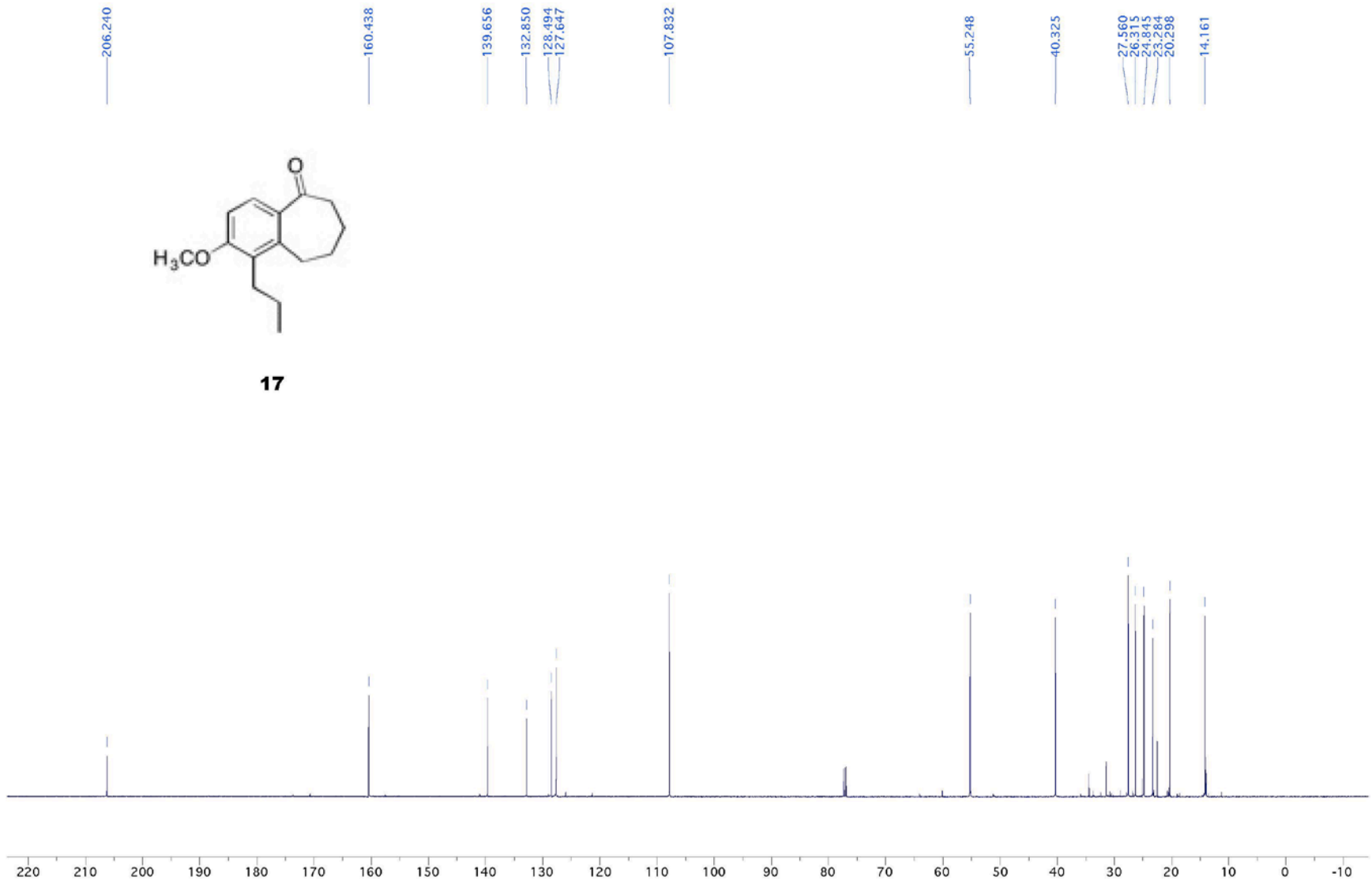
2.808
2.795
2.618
2.606
2.602
2.597
2.586
2.575
2.567
2.563
2.559
2.551
1.768
1.754
1.741
1.728
1.715
1.670
1.658
1.647
1.634
1.621
1.465
1.450
1.435
1.419
1.404
1.389
0.929
0.914
0.899
O
H3CO
17
1.05
2.03
2.15
1.96
1
3.13
3.95
2.18
2.87
9
8
7
6
5
4
3
2
1
0
-1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127.647
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55.248
40.325
27.560
26.315
24.845
23.284
20.298
14.161
O
H3CO
220
210
200
190
180
170
160
150
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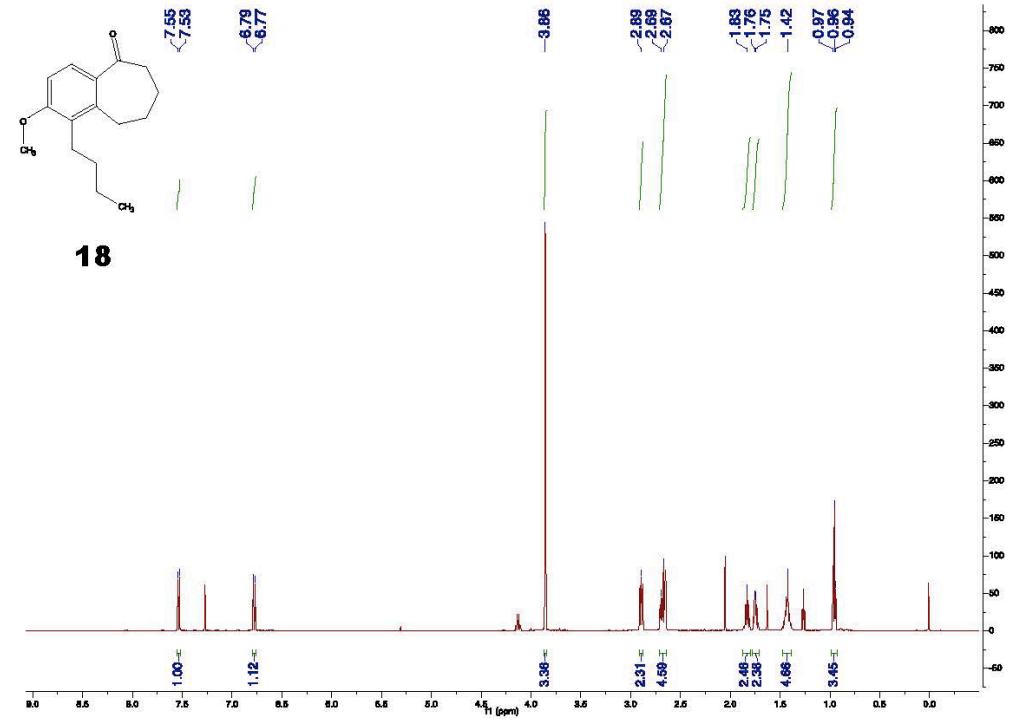
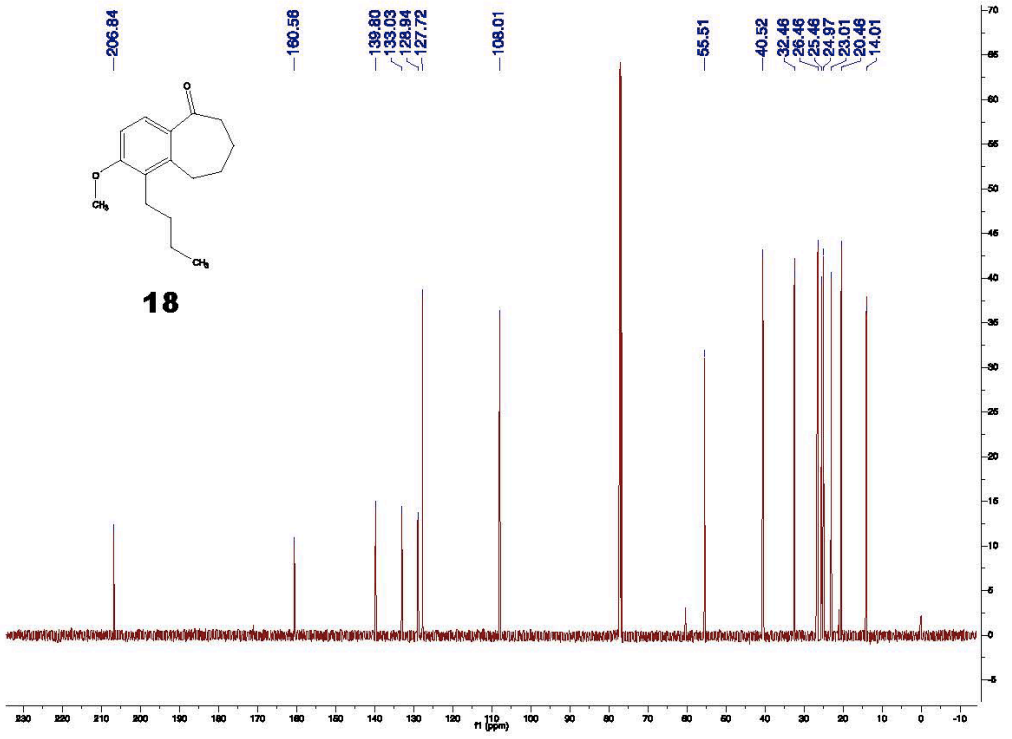
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

17


7.55
7.53
6.79
6.77
3.86
2.89
2.69
2.67
1.83
1.76
1.75
1.42
0.97
0.96
0.94
18
1.00
1.12
3.38
2.31
4.59
2.46
2.38
4.66
3.45
f1 (ppm)


206.84
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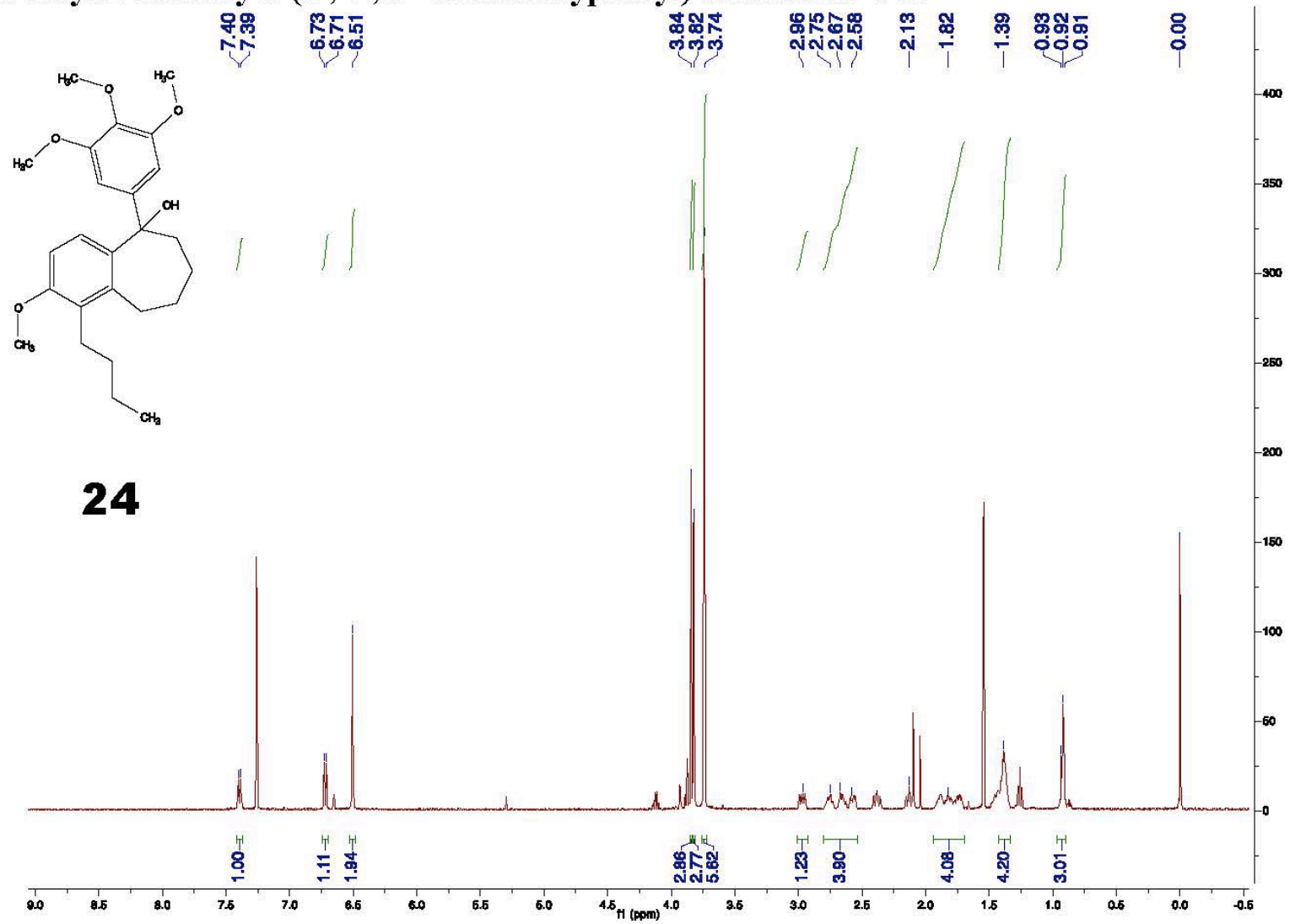
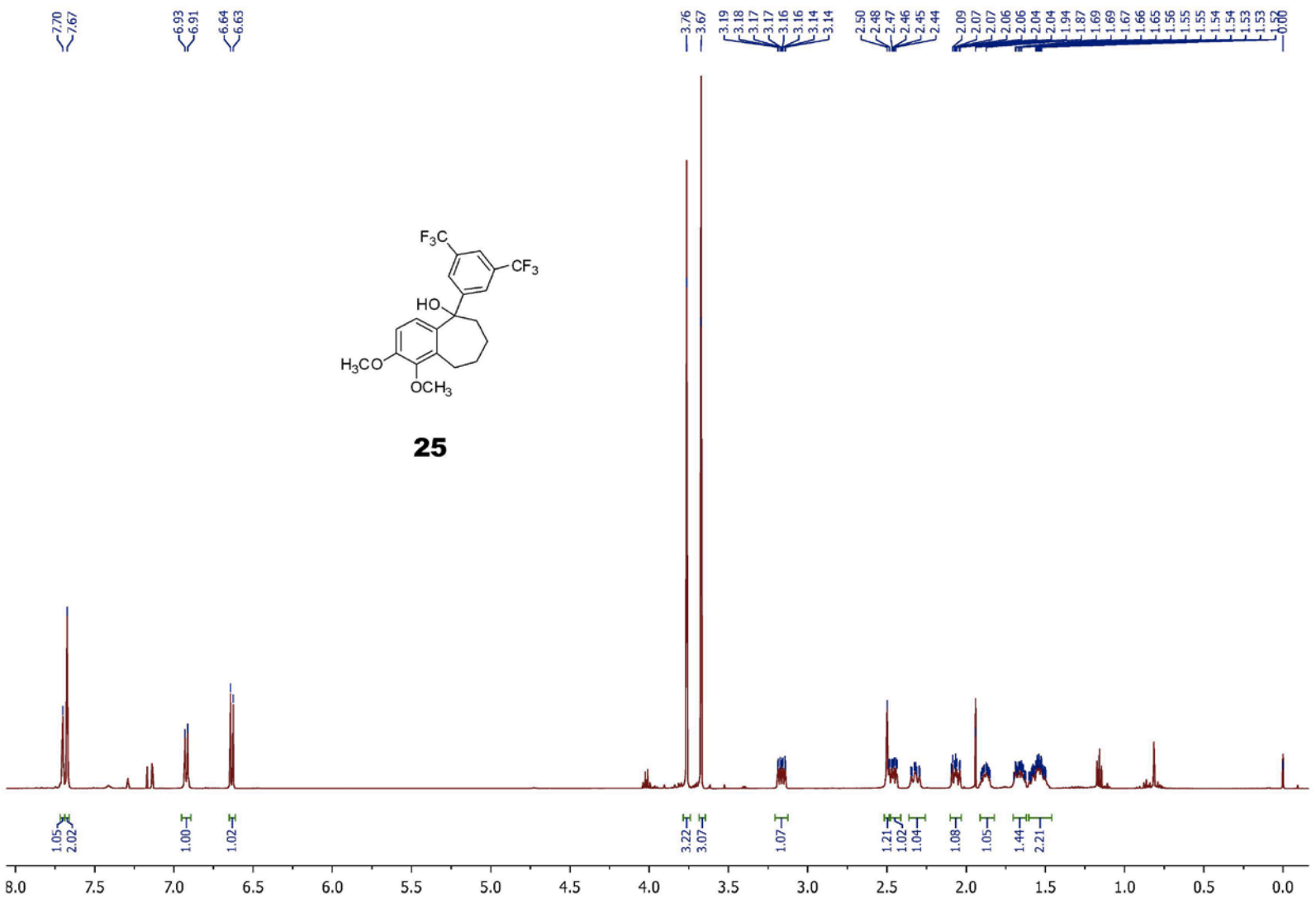
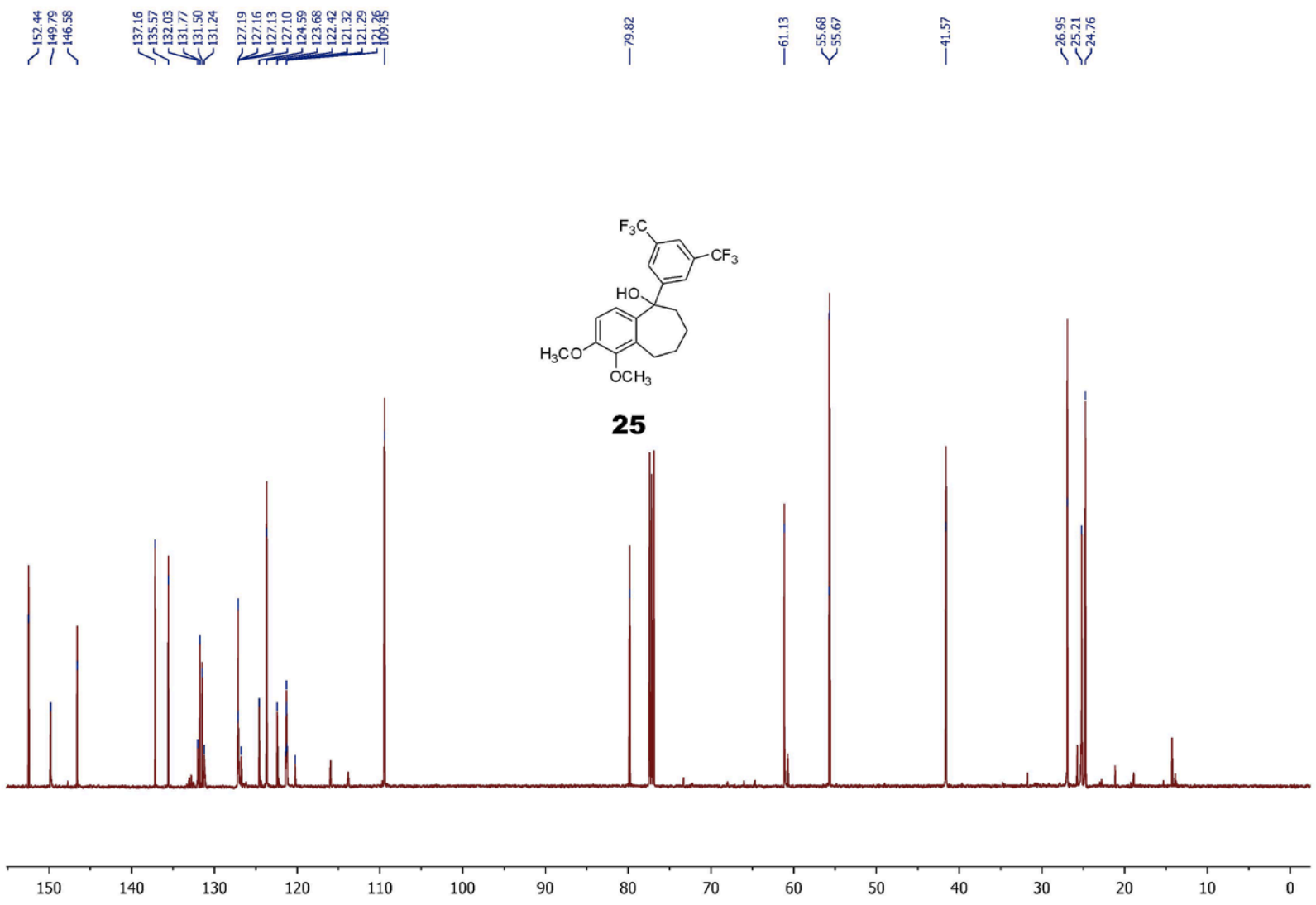
133.03
128.94
127.72
108.01
55.51
40.52
32.46
26.46
25.46
24.97
23.01
20.46
14.01
18
f1 (ppm)

1-butyl-2-methoxy-5-(3', 4', 5'- trimethoxyphenyl)-benzosuber-5-ol




F3C
CF3
HO
H3CO
OCH3
25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149.79
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137.16
135.57
132.03
131.77
131.50
131.24
127.19
127.16
127.13
127.10
124.59
123.68
122.42
121.32
121.29
79.82
61.13
55.68
55.67
41.57
26.95
25.21
24.76
F3C
CF3
HO
H3CO
OCH3
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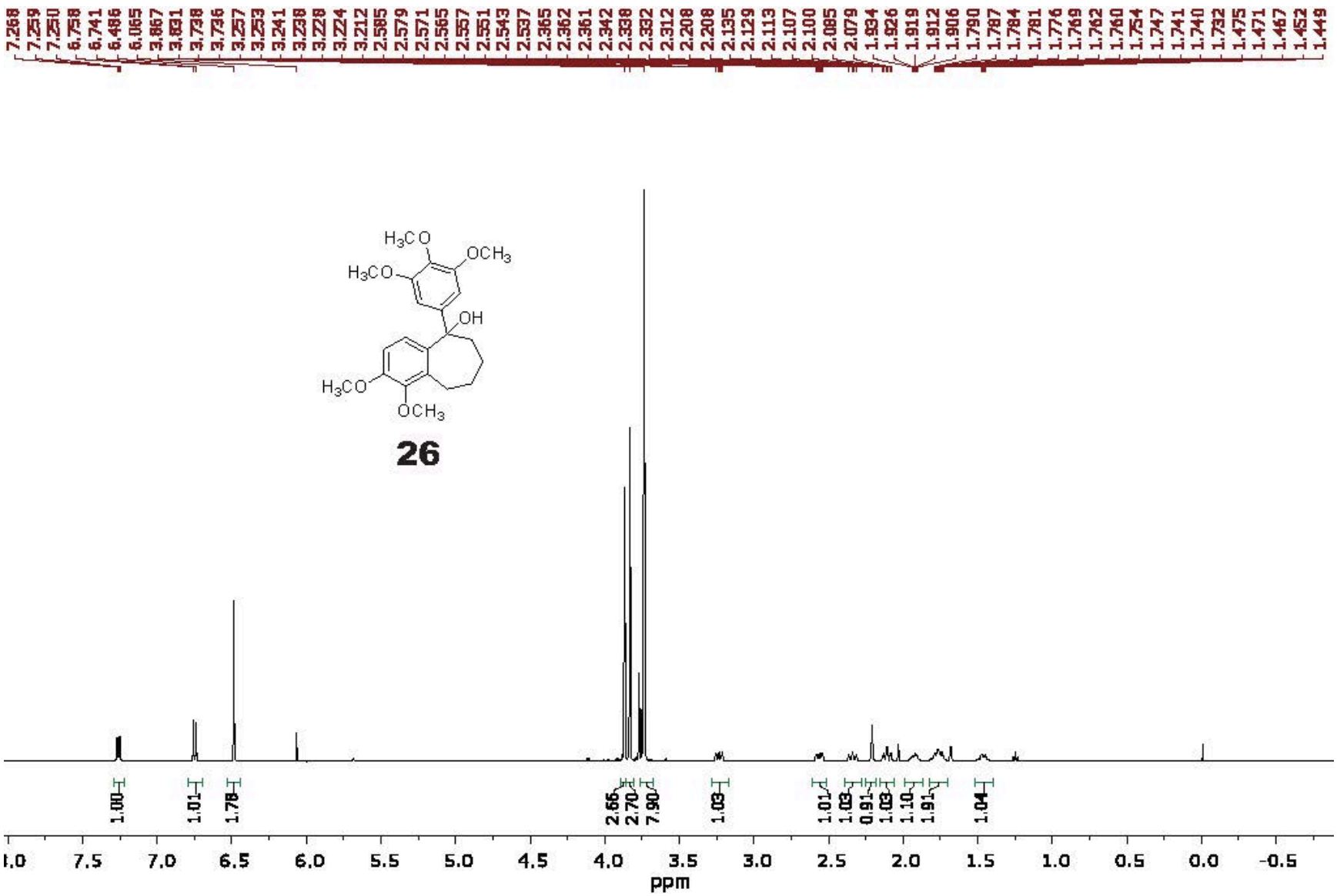
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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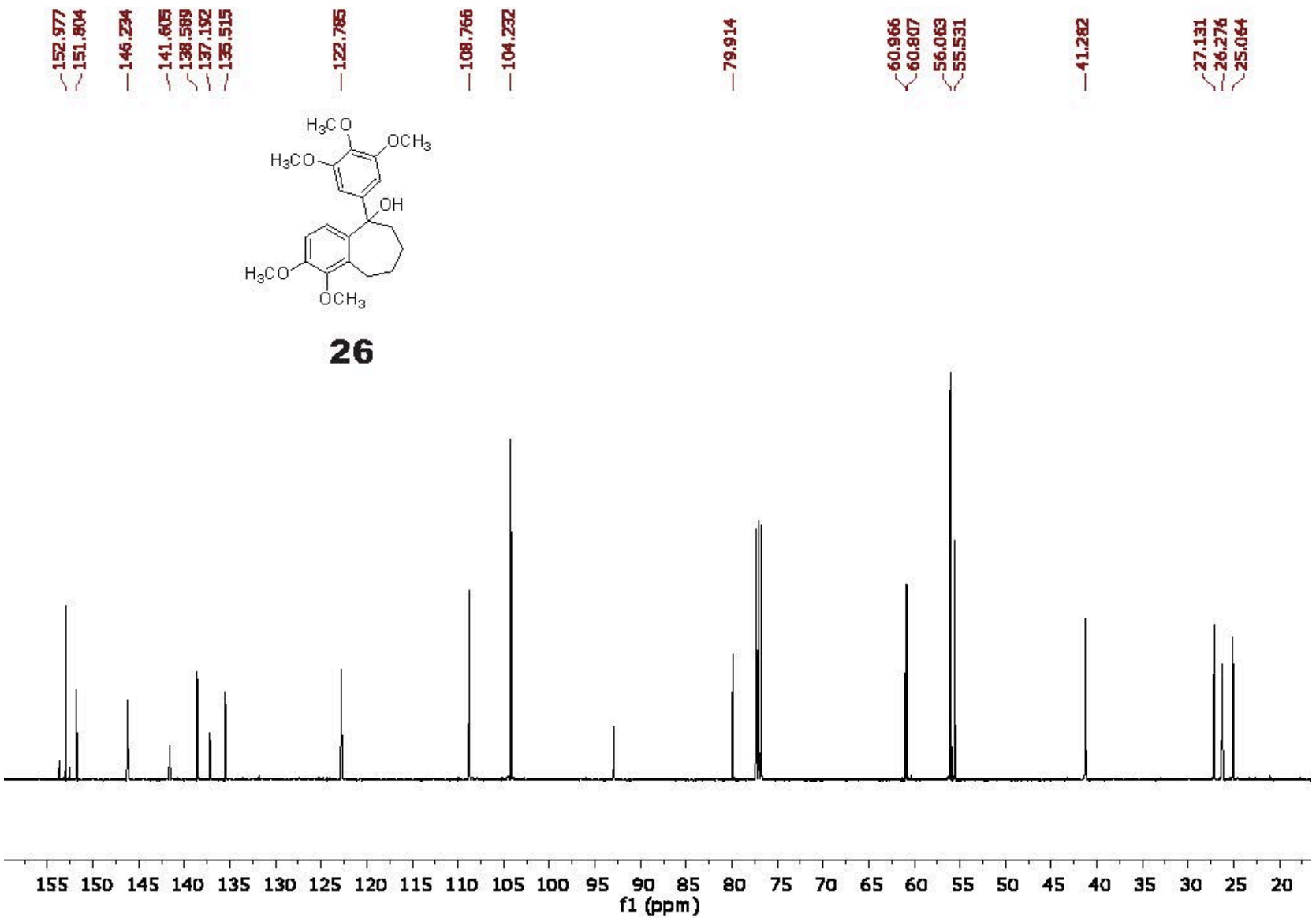
6.486
6.065
3.867
3.831
3.738
3.736
3.257
3.253
3.241
3.238
3.228
3.224
3.212
2.585
2.579
2.571
2.565
2.557
2.551
2.543
2.537
2.365
2.362
2.361
2.342
2.338
2.332
2.312
2.208
2.208
2.135
2.129
2.113
2.107
2.100
2.085
2.079
1.934
1.926
1.919
1.912
1.906
1.790
1.787
1.784
1.781
1.776
1.769
1.762
1.760
1.754
1.747
1.741
1.740
1.732
1.475
1.471
1.467
1.452
1.449
H3CO
OCH3
H3CO
OH
H3CO
OCH3
26
1.00
1.01
1.78
2.66
2.70
7.90
1.03
1.01
1.03
0.91
1.03
1.10
1.91
1.04
ppm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141.605
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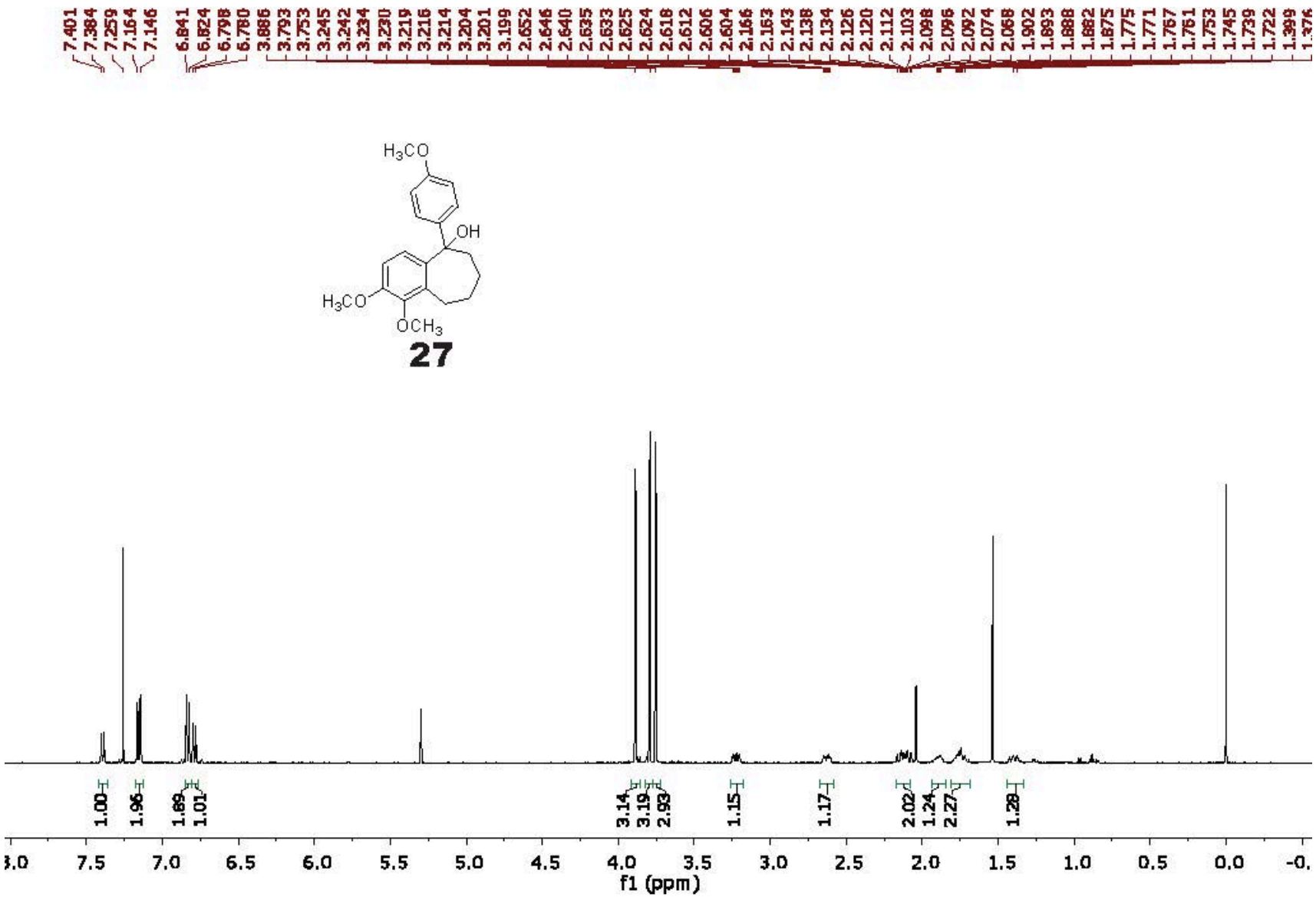
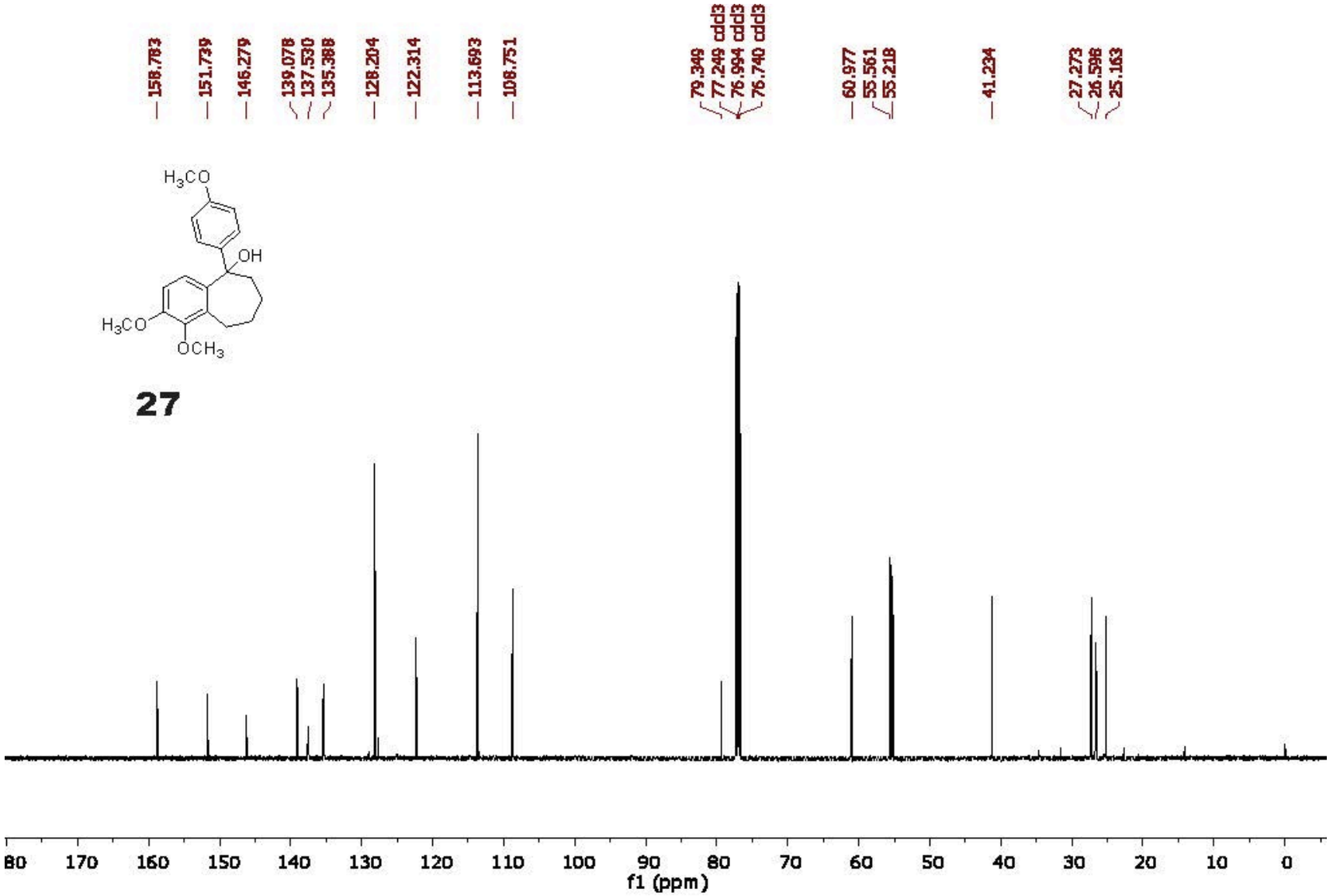
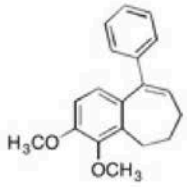
137.192
135.515
122.785
108.766
104.232
79.914
60.966
60.807
56.063
55.531
41.282
27.131
26.276
25.064
H3CO
OCH3
H3CO
OH
H3CO
OCH3
26
155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

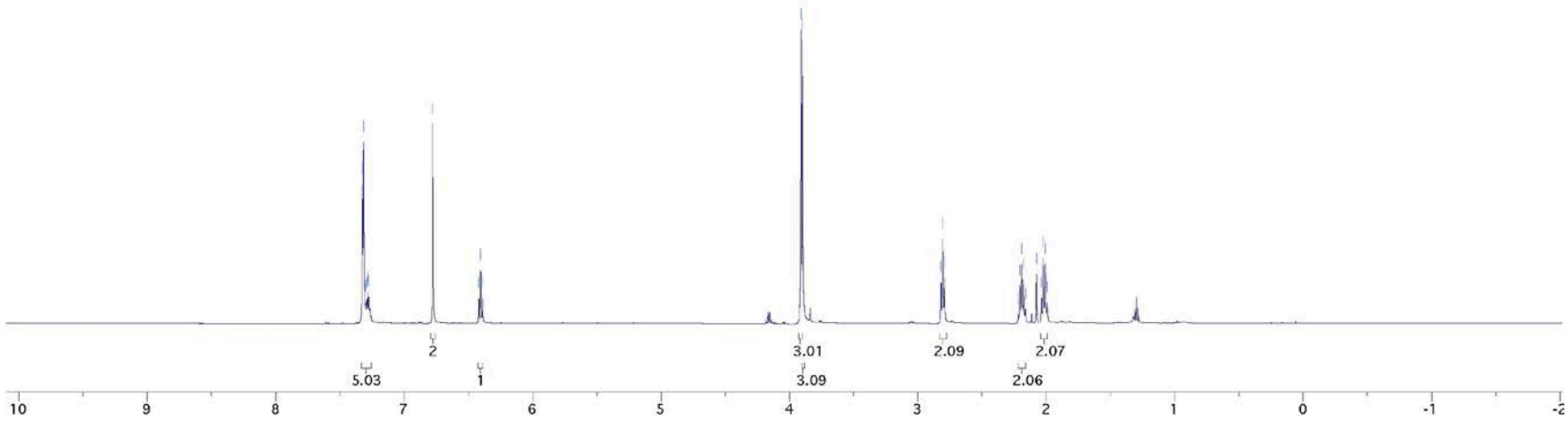

7.401
7.384
7.259
7.164
7.146
6.841
6.824
6.798
6.780
3.886
3.793
3.753
3.245
3.242
3.234
3.230
3.219
3.216
3.214
3.204
3.201
3.199
2.652
2.646
2.640
2.635
2.633
2.625
2.624
2.618
2.612
2.606
2.604
2.166
2.163
2.143
2.138
2.134
2.126
2.120
2.112
2.103
2.098
2.096
2.092
2.074
2.068
1.902
1.893
1.888
1.882
1.875
1.775
1.771
1.767
1.761
1.753
1.745
1.739
1.722
1.399
H3CO
OH
H3CO
OCH3
27
1.00
1.96
1.89
1.01
3.14
3.19
2.93
1.15
1.17
2.02
1.24
2.27
1.28
f1 (ppm)

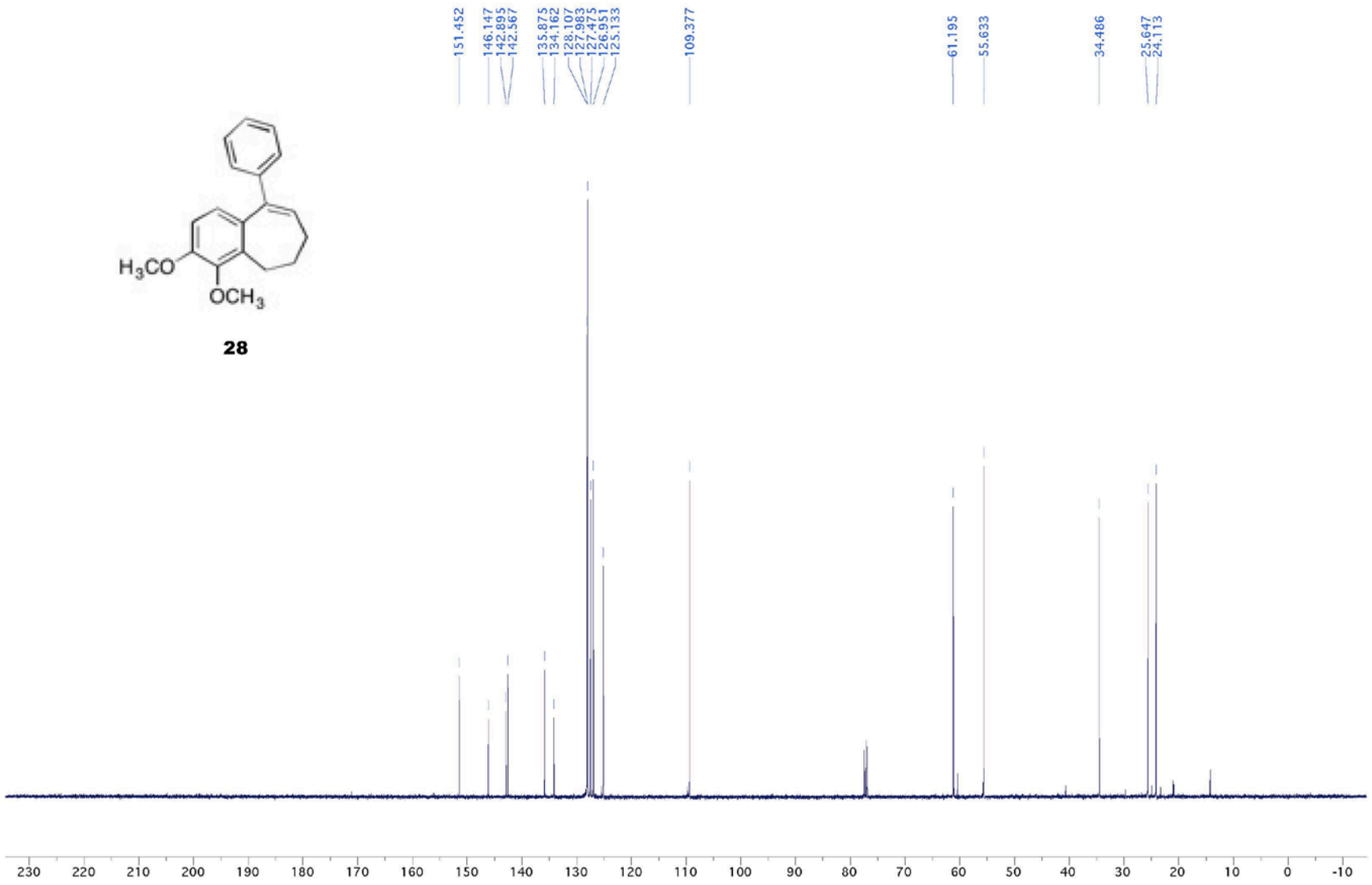

158.783
151.739
146.279
139.078
137.530
135.388
128.204
122.314
113.693
108.751
79.349
77.249 cdcl3
76.994 cdcl3
76.740 cdcl3
60.977
55.561
55.218
41.234
27.273
26.598
25.163
H3CO
OH
H3CO
OCH3
27
f1 (ppm)


7.326
7.317
7.301
7.293
7.286
7.277
6.778
6.419
6.404
6.389
3.910
3.898
2.820
2.806
2.792
2.219
2.205
2.191
2.177
2.163
2.076
2.036
2.022
2.008
1.993


H3CO
OCH3

28


2
3.01
2.09
2.07
5.03
1
3.09
2.06
10
9
8
7
6
5
4
3
2
1
0
-1


151.452
146.147
142.895
142.567
135.875
134.162
128.107
127.983
127.475
126.951
125.133
109.377
61.195
55.633
34.486
25.647
24.113
H3CO
OCH3
28
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_3_134000010.D
Sample Name: CAH_3_134

HPLC for Compound 28

```
==================================================================
Acq. Operator   : Christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 1/9/2014 3:11:56 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 1/9/2014 3:02:55 PM by Christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\CAH_3_134000010.D\DA.M (MASTERMETHOD.M)
Last changed    : 2/25/2014 11:06:43 AM by Christine
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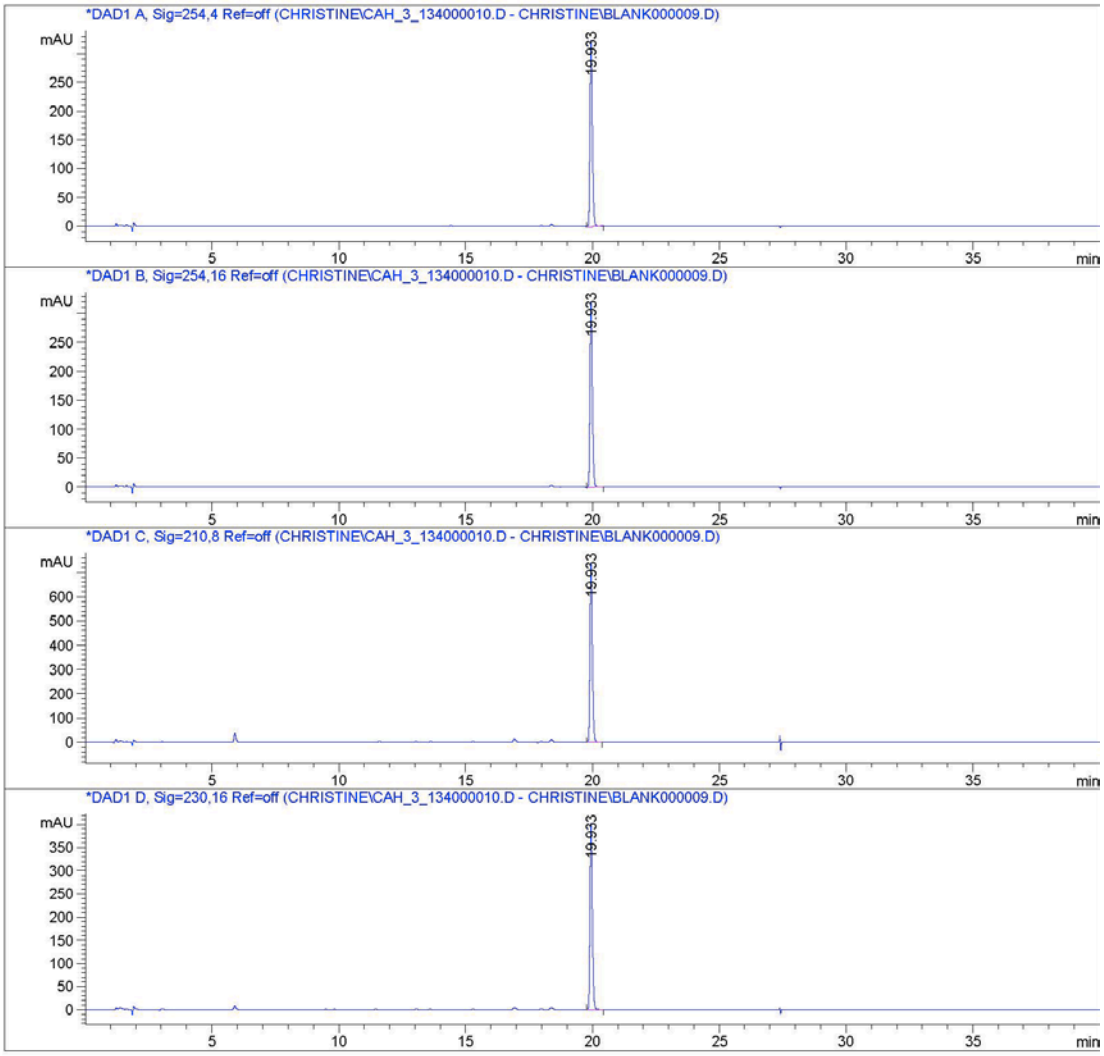
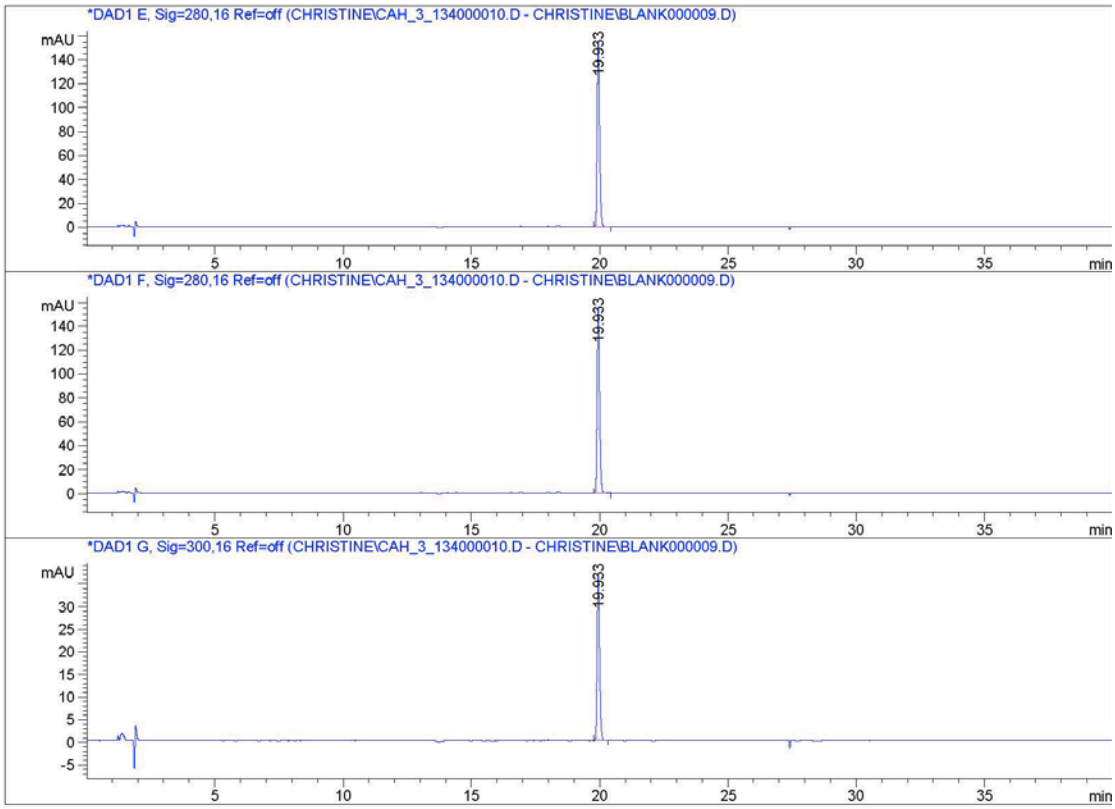


Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_3_134000010.D
Sample Name: CAH_3_134




```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=off
 Signal has been modified after loading from rawdata file!

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.933 BB    0.1000 2109.92017  323.73047 100.0000

Totals :                  2109.92017  323.73047
```

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_3_134000010.D
Sample Name: CAH_3_134

Signal 2: DAD1 B, Sig=254,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.933	BB	0.1000	2092.94263	321.40930	100.0000
Totals :				2092.94263	321.40930	

Signal 3: DAD1 C, Sig=210,8 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.933	BB	0.0995	4793.37109	740.26355	100.0000
Totals :				4793.37109	740.26355	

Signal 4: DAD1 D, Sig=230,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.933	BB	0.0994	2596.50854	401.65051	100.0000
Totals :				2596.50854	401.65051	

Signal 5: DAD1 E, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.933	BB	0.0995	1007.30444	155.69983	100.0000
Totals :				1007.30444	155.69983	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_3_134000010.D
Sample Name: CAH_3_134

Signal 6: DAD1 F, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

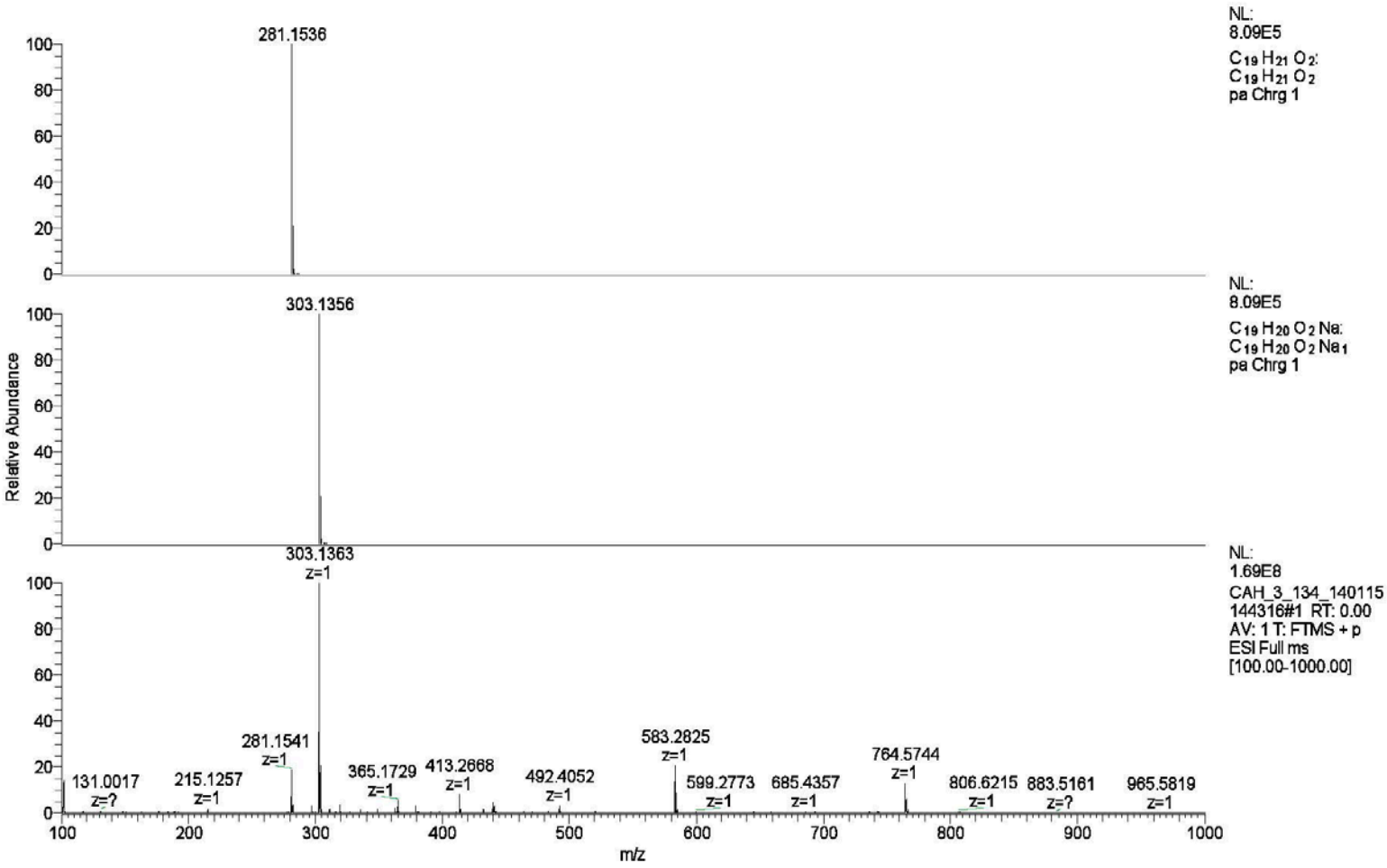
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.933	BB	0.0995	1007.30444	155.69983	100.0000
Totals :				1007.30444	155.69983	

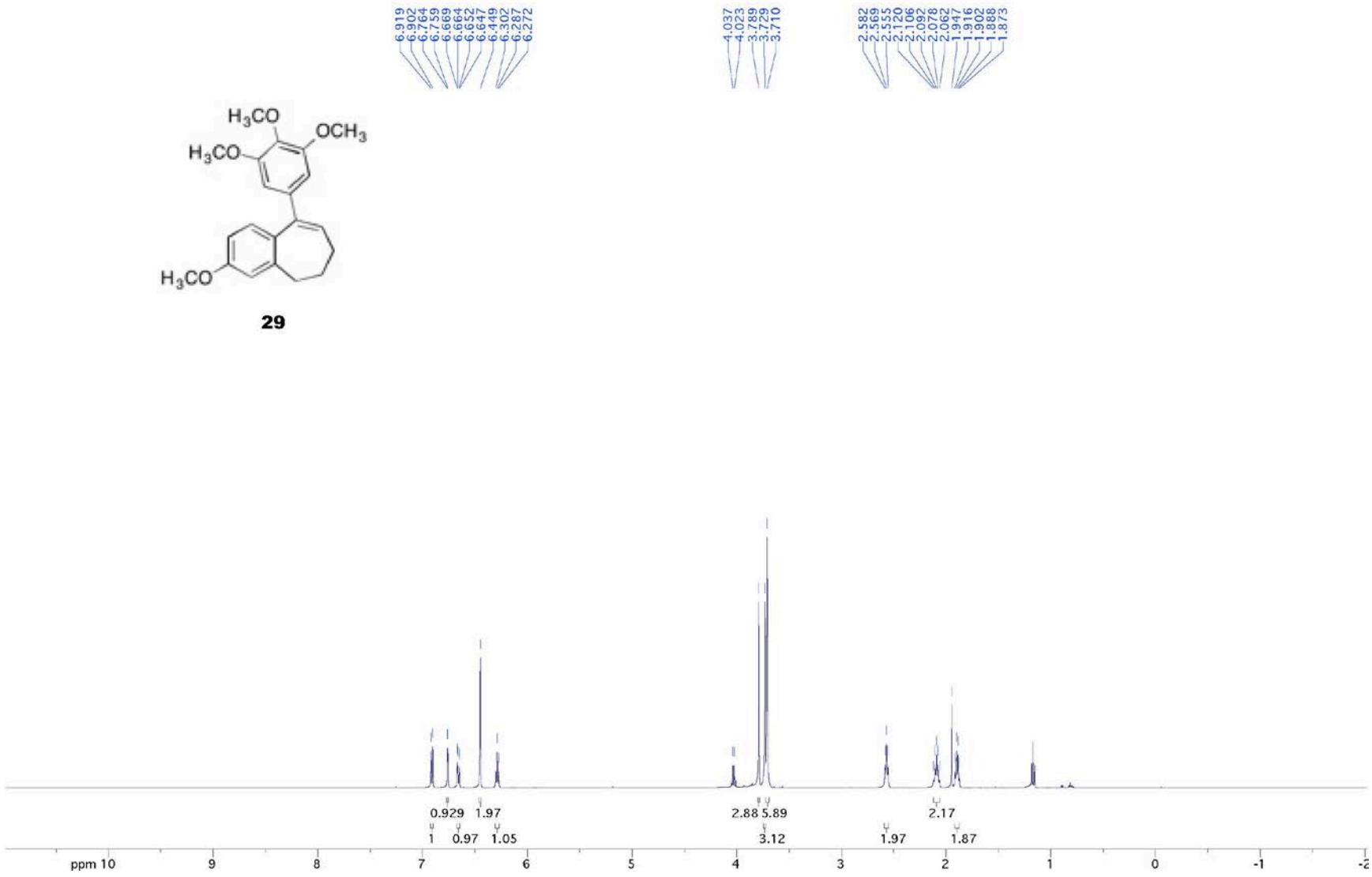
Signal 7: DAD1 G, Sig=300,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.933	BB	0.1001	240.84787	36.89976	100.0000
Totals :				240.84787	36.89976	

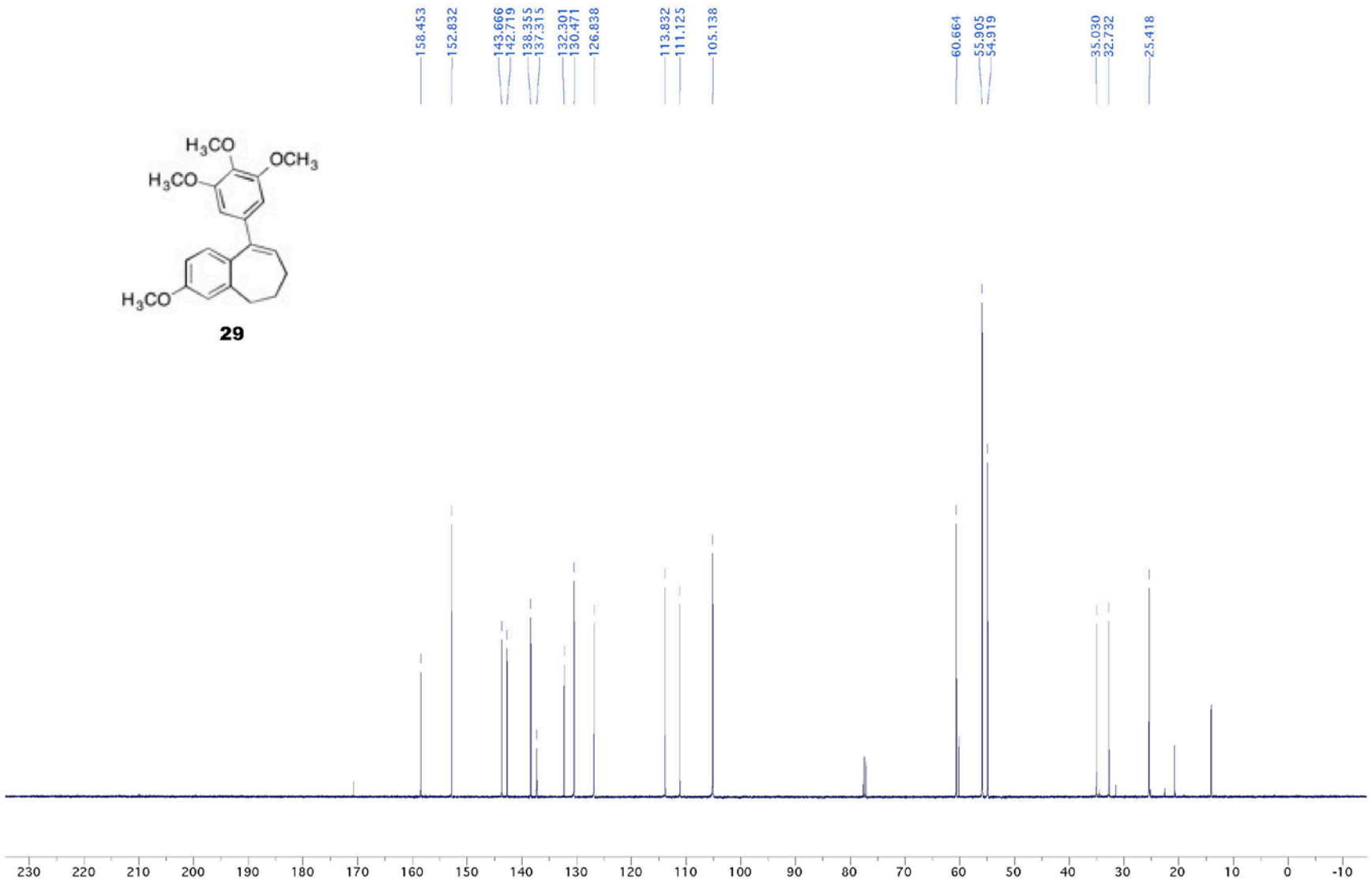
*** End of Report ***

HRMS for Compound 28




6.919
6.902
6.764
6.759
6.669
6.664
6.652
6.647
6.449
6.302
6.287
6.272
4.037
4.023
3.789
3.729
3.710
2.582
2.569
2.555
2.120
2.106
2.092
2.078
2.062
1.947
1.916
1.902
1.888
1.873
H3CO
OCH3
H3CO
H3CO
0.929
1.97
2.88
5.89
2.17
1
0.97
1.05
3.12
1.97
1.87
ppm 10
9
8
7
6
5
4
3
2
1
0
-1

29


158.453
152.832
143.666
142.719
138.355
137.315
132.301
130.471
126.838
113.832
111.125
105.138
60.664
55.905
54.919
35.030
32.732
25.418
H3CO
OCH3
H3CO
H3CO
29
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_3_123000004.D
Sample Name: CAH_3_123

HPLC for compound 29

```
==========================================================================
Acq. Operator   : Christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 10/9/2013 11:38:16 AM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 10/9/2013 11:36:20 AM by Christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\CAH_3_123000004.D\DA.M (MASTERMETHOD.M)
Last changed    : 10/9/2013 3:39:32 PM by Christine
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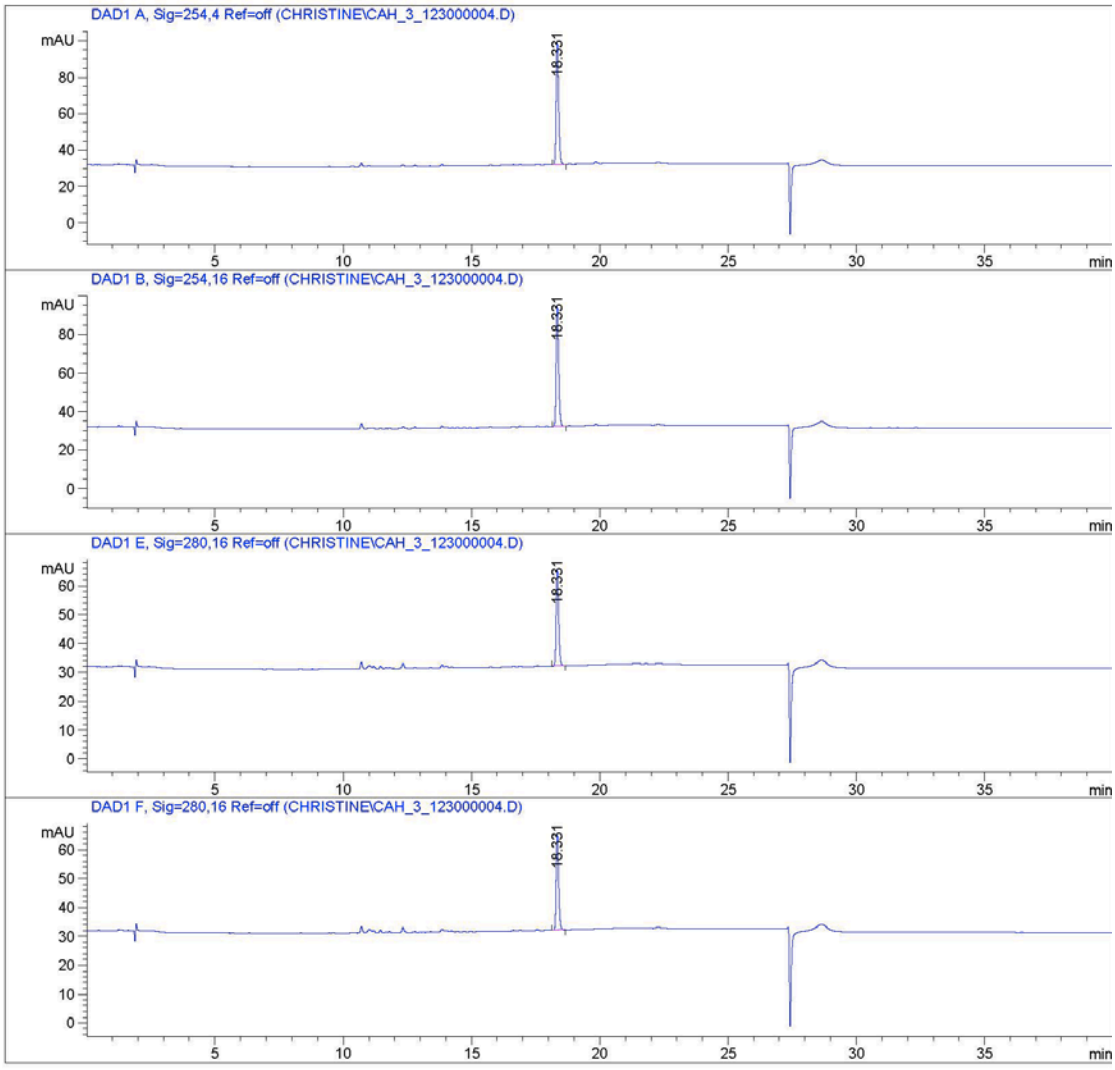


Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_3_123000004.D
Sample Name: CAH_3_123

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.331	BB	0.1006	444.65436	67.72849	100.0000
Totals :				444.65436	67.72849	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.331	BB	0.1008	414.83444	63.04776	100.0000
Totals :				414.83444	63.04776	

Signal 3: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.331	BB	0.1004	220.03041	33.57787	100.0000
Totals :				220.03041	33.57787	

Signal 4: DAD1 F, Sig=280,16 Ref=off

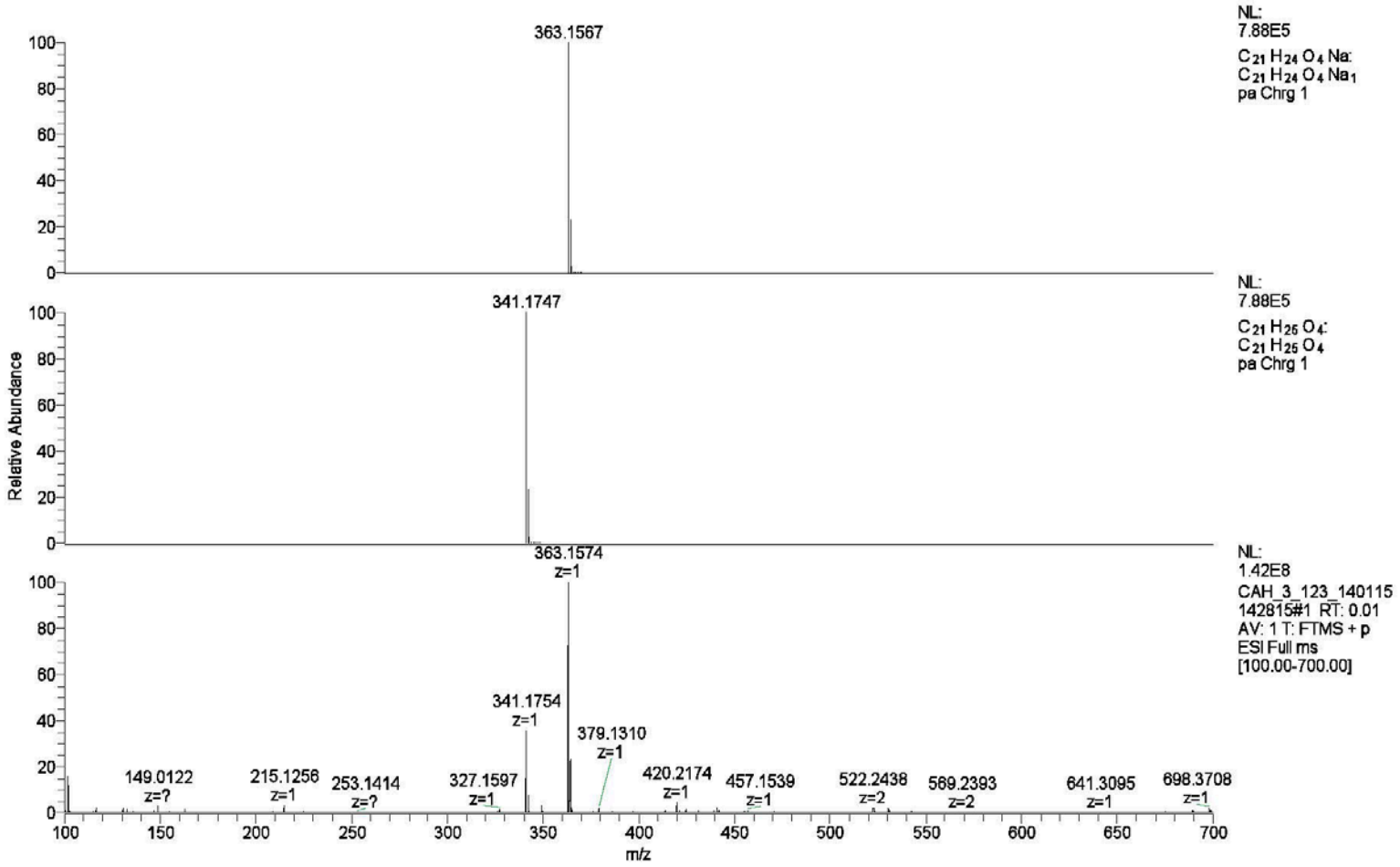
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.331	BB	0.1004	220.03041	33.57787	100.0000
Totals :				220.03041	33.57787	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_3_123000004.D
Sample Name: CAH_3_123

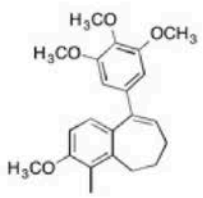
==========

*** End of Report ***

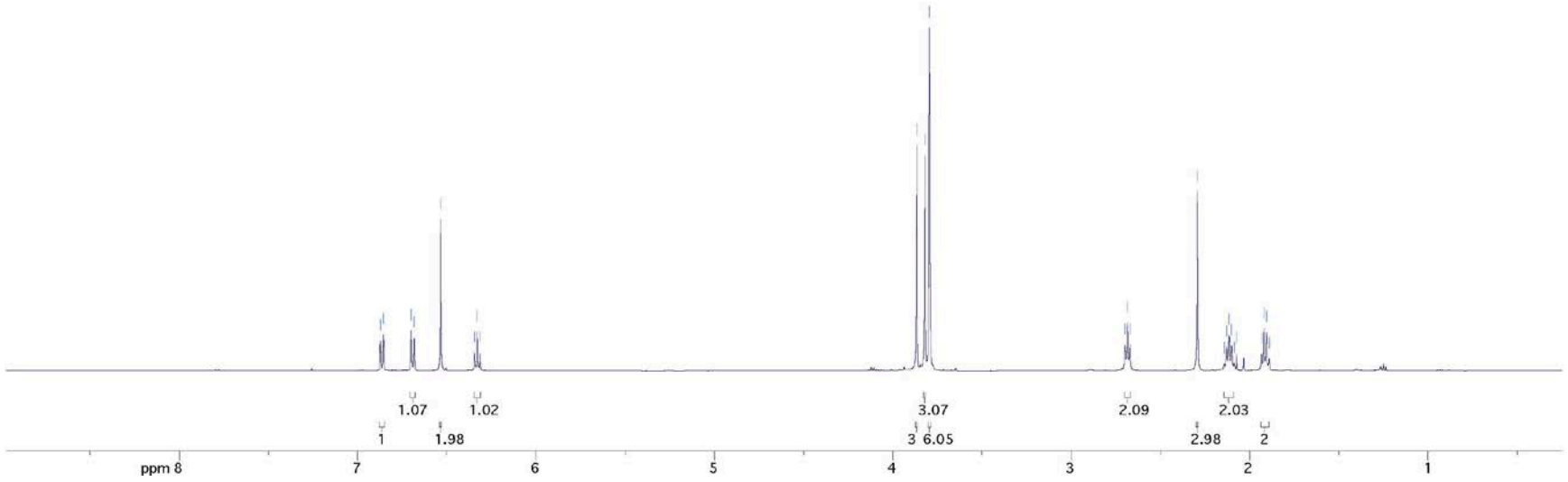
HRMS for compound 29

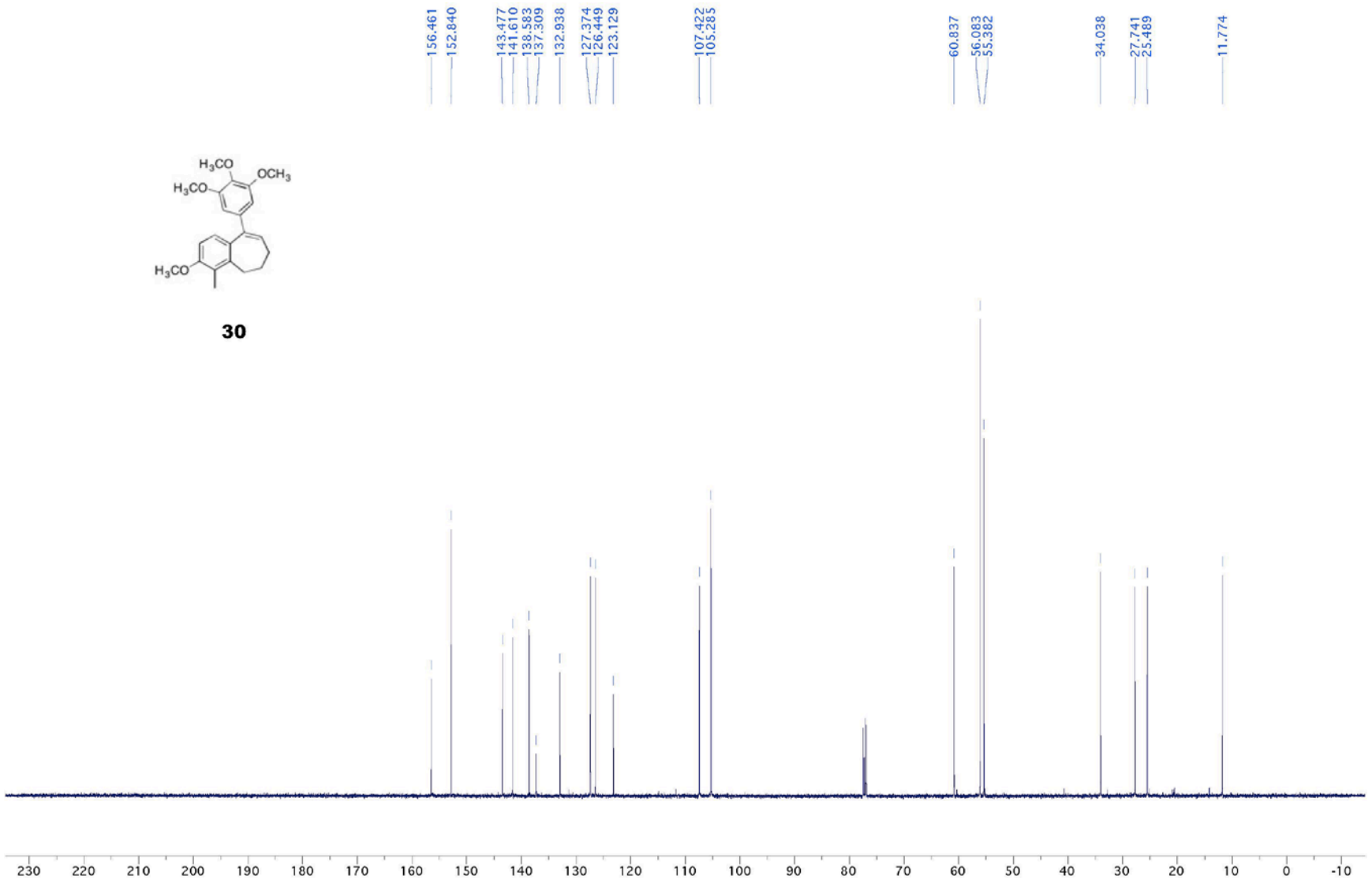



6.872
6.855
6.700
6.683
6.534
6.343
6.329
6.314
3.866
3.820
3.795
2.698
2.685
2.671
2.293
2.143
2.129
2.115
2.101
2.087
2.073
1.934
1.920
1.905
1.891


H3CO
OCH3
H3CO
H3CO

30


1.07
1.02
3.07
2.09
2.03
1
1.98
3
6.05
2.98
2
ppm 8
7
6
5
4
3
2
1

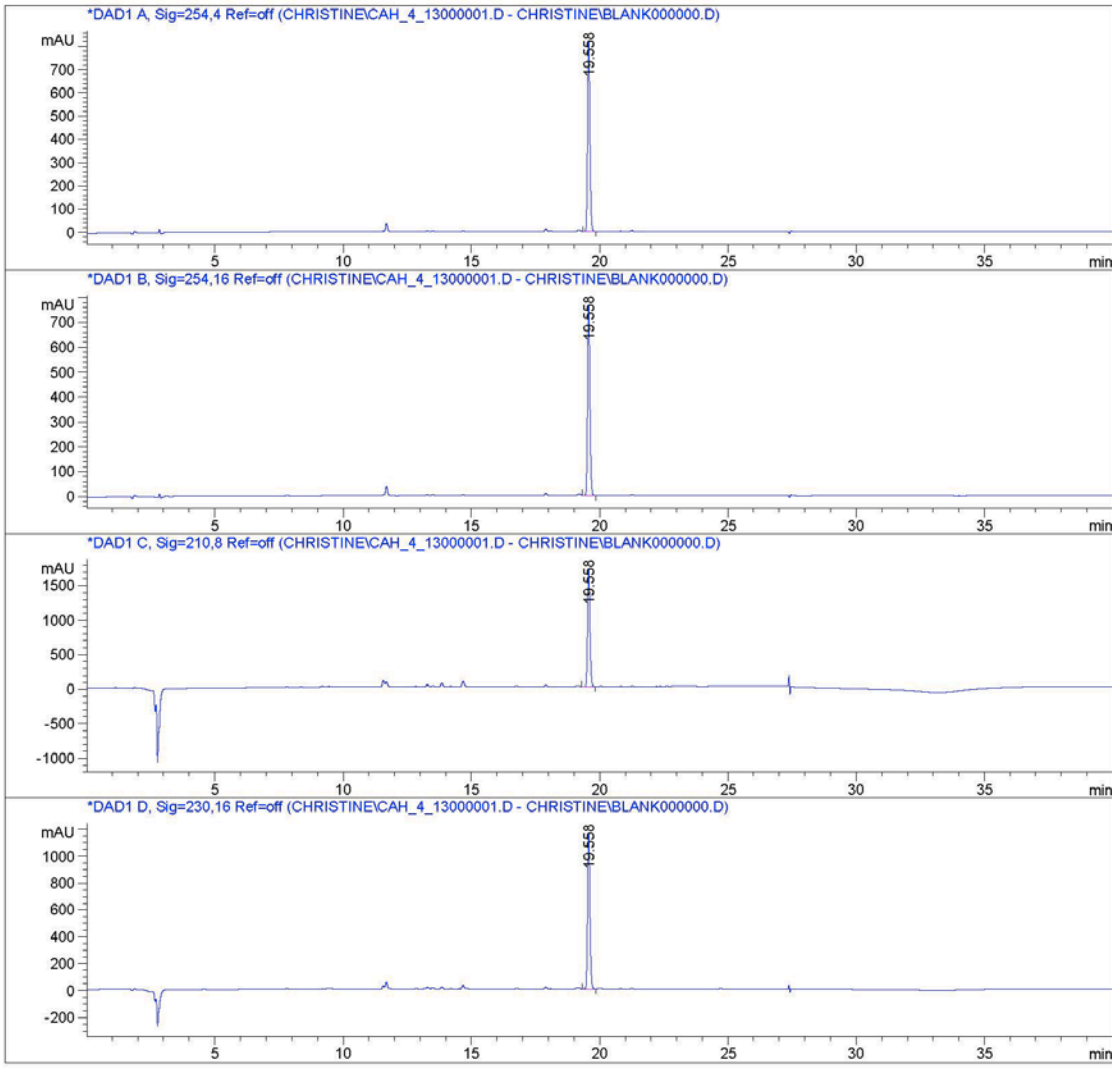

156.461
152.840
143.477
141.610
138.583
137.309
132.938
127.374
126.449
123.129
107.422
105.285
60.837
56.083
55.382
34.038
27.741
25.489
11.774
H3CO
OCH3
H3CO
H3CO
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

30

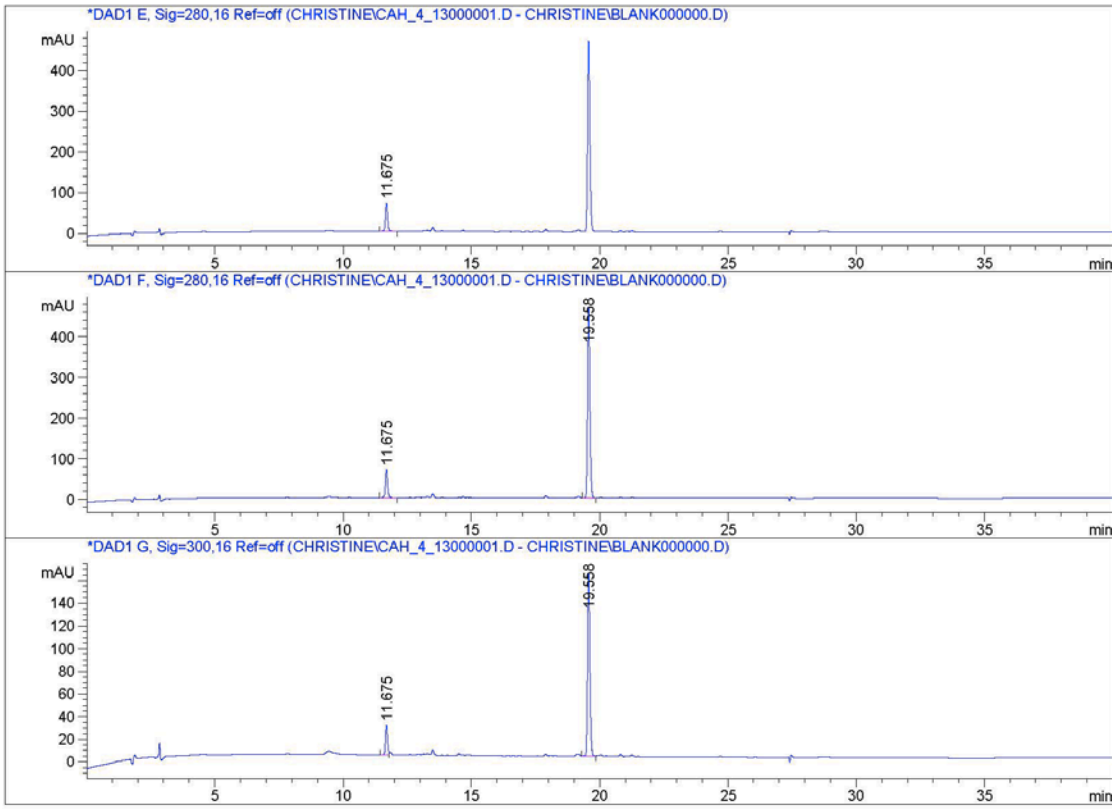
Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_13000001.D
Sample Name: CAH_4_13

HPLC for compound 30

```
==========================================================================
Acq. Operator   : Christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 2/25/2014 9:28:56 AM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 8/6/2013 10:18:10 PM by Blake
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\CAH_4_13000001.D\DA.M (MASTERMETHOD.M)
Last changed    : 2/25/2014 10:59:23 AM by Christine
```



Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_13000001.D
Sample Name: CAH_4_13



==========

Area Percent Report

==========

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.558	VV	0.0950	5127.37158	819.62360	100.0000
Totals :				5127.37158	819.62360	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_13000001.D
Sample Name: CAH_4_13

Signal 2: DAD1 B, Sig=254,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.558	VV	0.0950	4792.61084	765.89771	100.0000
Totals :				4792.61084	765.89771	

Signal 3: DAD1 C, Sig=210,8 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.558	VV	0.0978	1.07562e4	1701.31848	100.0000
Totals :				1.07562e4	1701.31848	

Signal 4: DAD1 D, Sig=230,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.558	VV	0.0952	7260.10791	1157.33716	100.0000
Totals :				7260.10791	1157.33716	

Signal 5: DAD1 E, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.675	BB	0.0895	420.21866	70.51888	100.0000
Totals :				420.21866	70.51888	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_13000001.D
Sample Name: CAH_4_13

Signal 6: DAD1 F, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

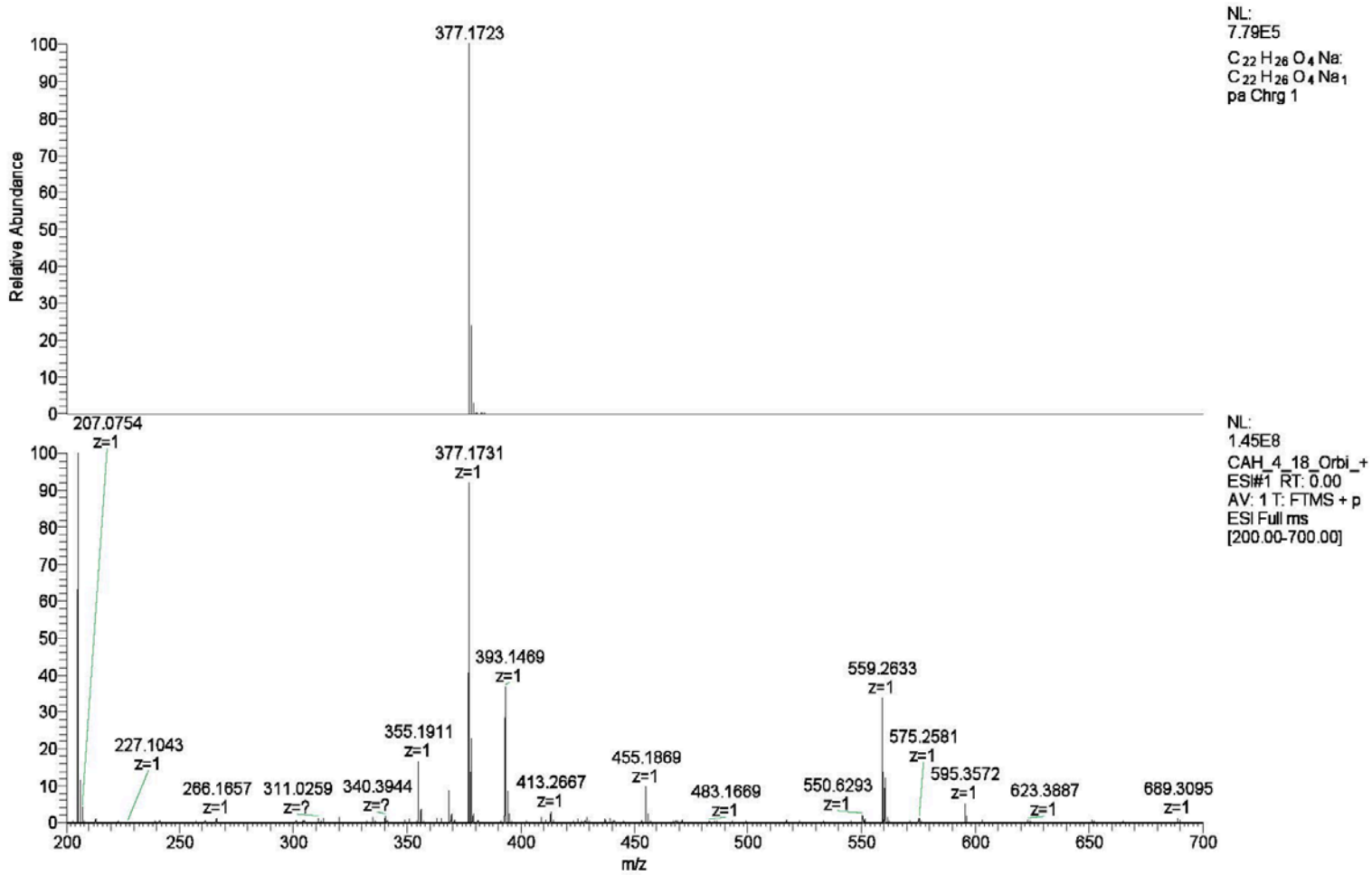
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.675	BB	0.0895	420.21866	70.51888	12.5043
2	19.558	VV	0.0950	2940.38770	469.76230	87.4957
Totals :				3360.60635	540.28118	

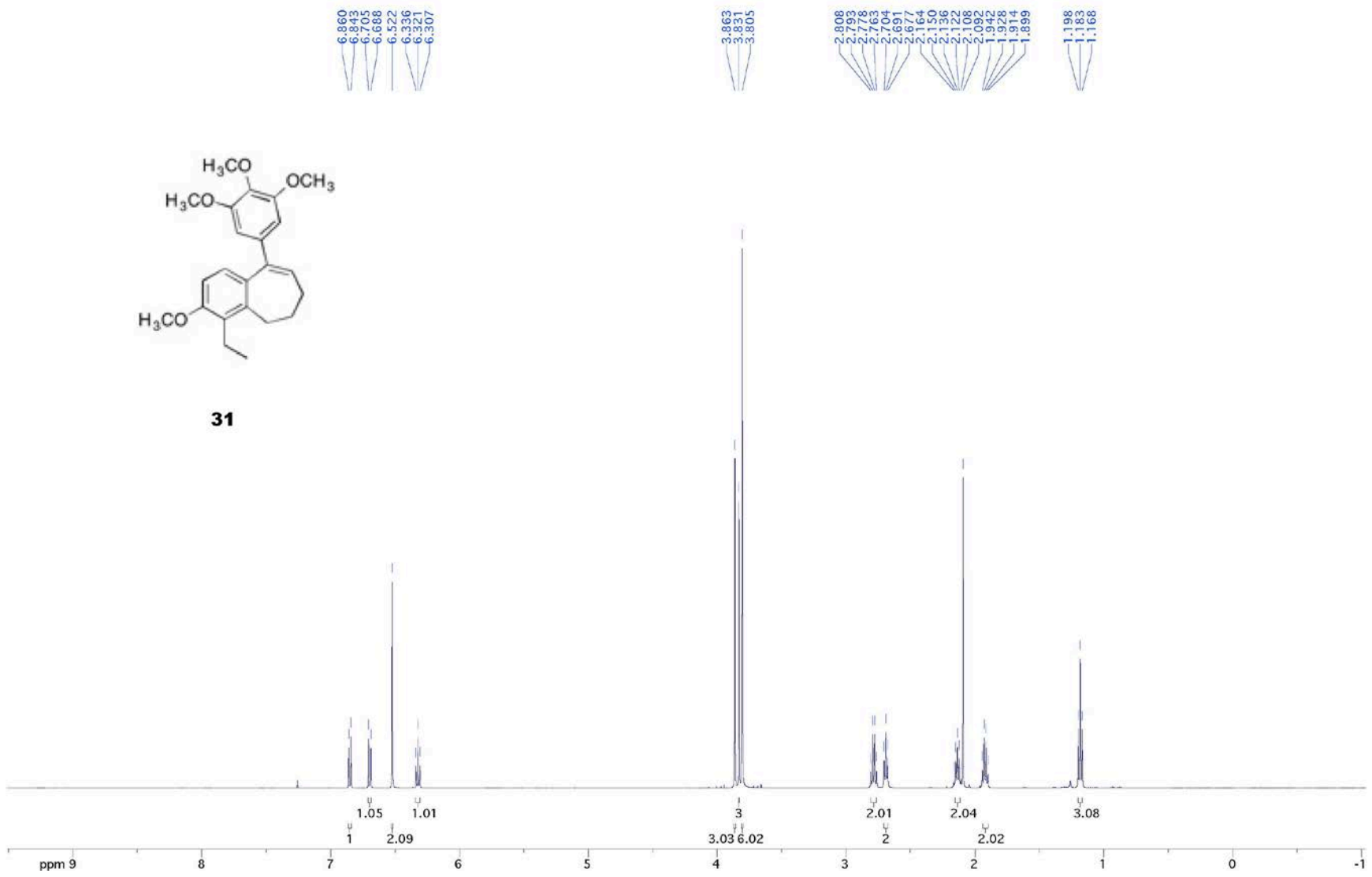
Signal 7: DAD1 G, Sig=300,16 Ref=off
Signal has been modified after loading from rawdata file!

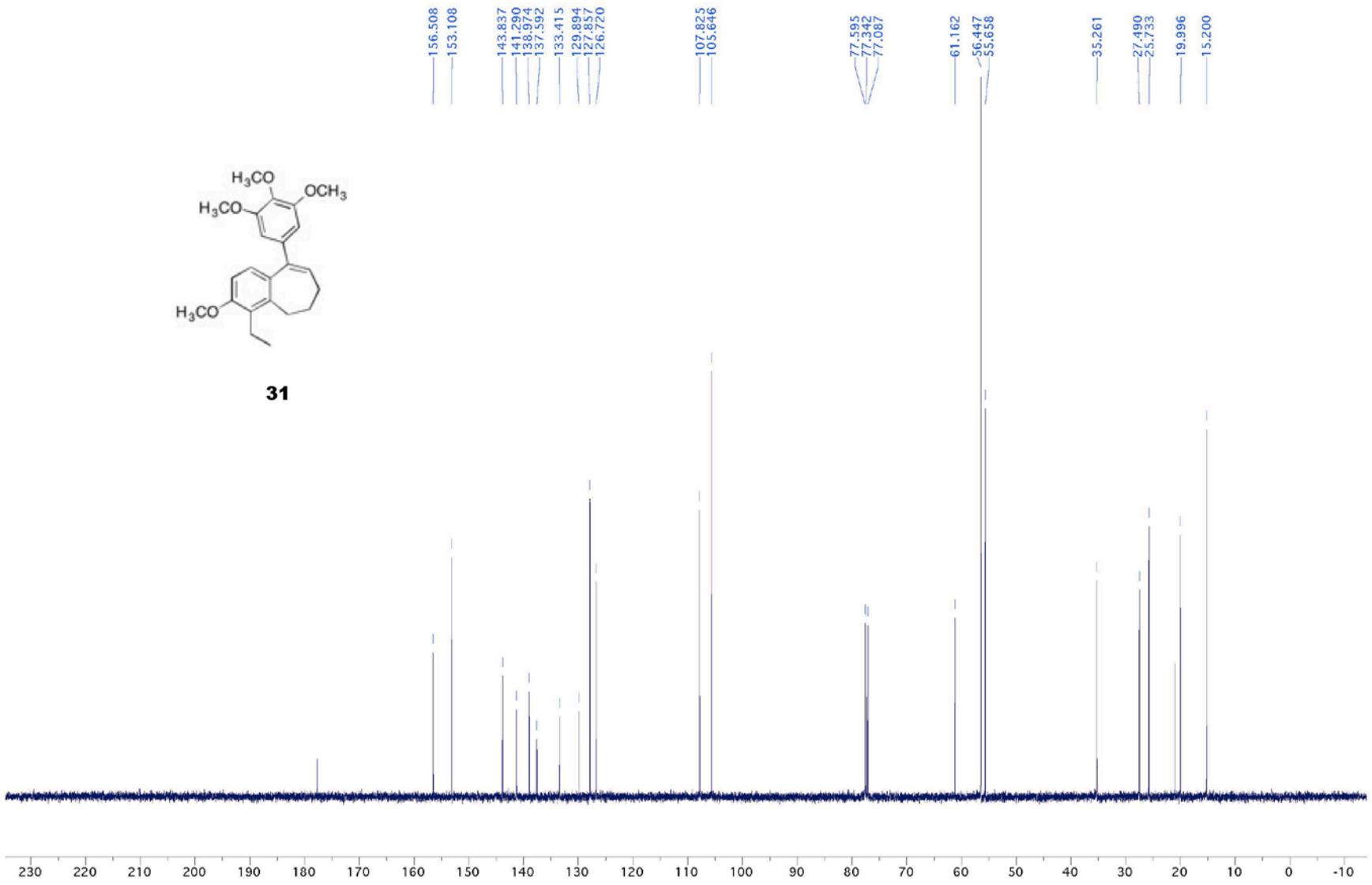
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.675	BV	0.0861	149.43964	26.37713	12.7927
2	19.558	VV	0.0955	1018.72174	161.60686	87.2073
Totals :				1168.16138	187.98399	

*** End of Report ***

HRMS for compound 30




6.860
6.843
6.705
6.688
6.522
6.336
6.321
6.307
3.863
3.831
3.805
2.808
2.793
2.778
2.763
2.704
2.691
2.677
2.164
2.150
2.136
2.122
2.108
2.092
1.942
1.928
1.914
1.899
1.198
1.183
1.168
H3CO
OCH3
H3CO
H3CO
31
1.05
1.01
3
2.01
2.04
3.08
1
2.09
3.03
6.02
2
2.02
ppm 9
8
7
6
5
4
3
2
1
0
-1

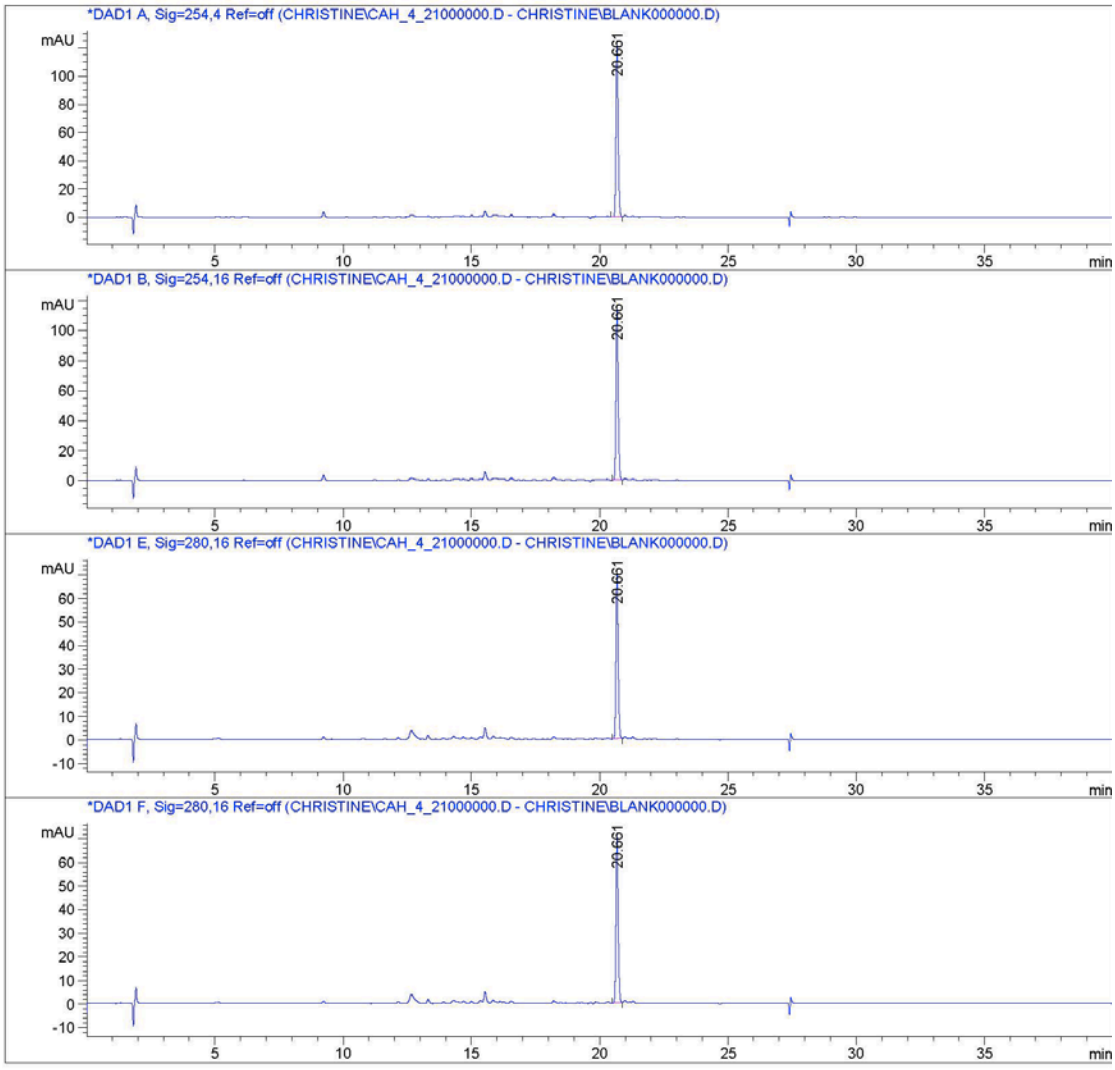

156.508
153.108
143.837
141.290
138.974
137.592
133.415
129.894
127.857
126.720
107.825
105.646
77.595
77.342
77.087
61.162
56.447
55.658
35.261
27.490
25.733
19.996
15.200
H3CO
OCH3
H3CO
H3CO
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

31

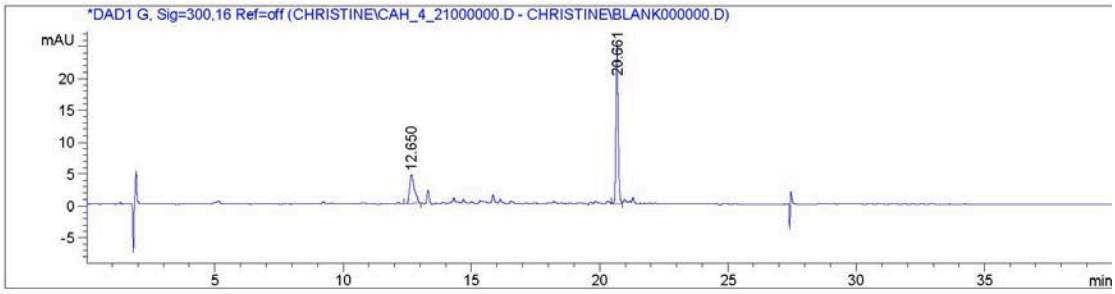
Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_21000000.D
Sample Name: CAH_4_21

HPLC for compound 31

Acq. Operator : Christine
Acq. Instrument : Instrument 1 Location : -
Injection Date : 2/25/2014 1:47:25 PM
Acq. Method : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed : 2/25/2014 1:25:25 PM by Christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\CAH_4_21000000.D\DA.M (MASTERMETHOD.M)
Last changed : 2/25/2014 2:37:40 PM by Christine



Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_21000000.D
Sample Name: CAH_4_21



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Area Percent Report

==========

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.661	BV	0.0908	733.27759	124.40224	100.0000
Totals :				733.27759	124.40224	

Signal 2: DAD1 B, Sig=254,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.661	BV	0.0906	685.97784	116.60737	100.0000
Totals :				685.97784	116.60737	

Signal 3: DAD1 E, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_21000000.D
Sample Name: CAH_4_21

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.661	BV	0.0908	424.10693	71.94486	100.0000
Totals :				424.10693	71.94486	

Signal 4: DAD1 F, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

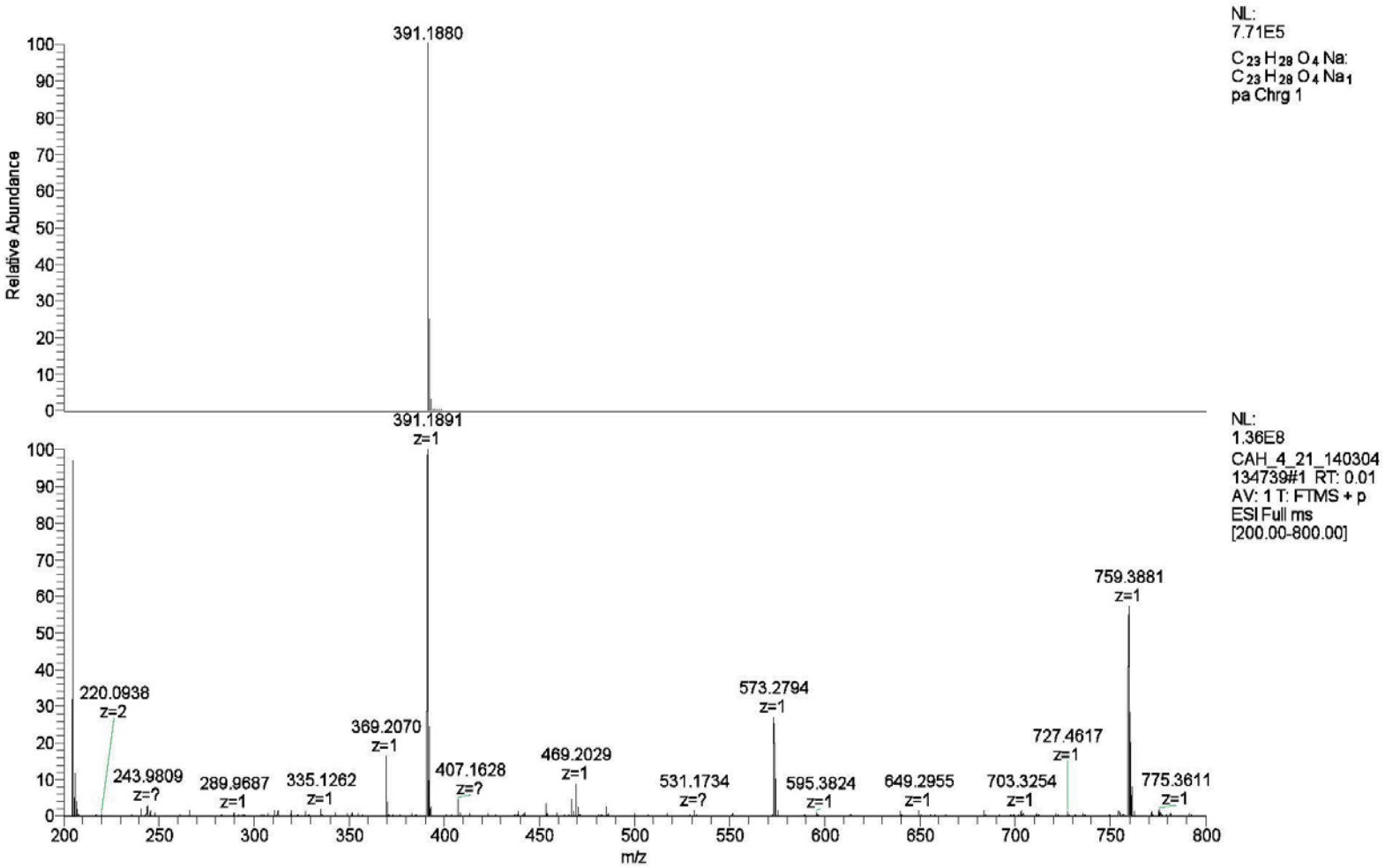
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.661	BV	0.0908	424.10693	71.94486	100.0000
Totals :				424.10693	71.94486	

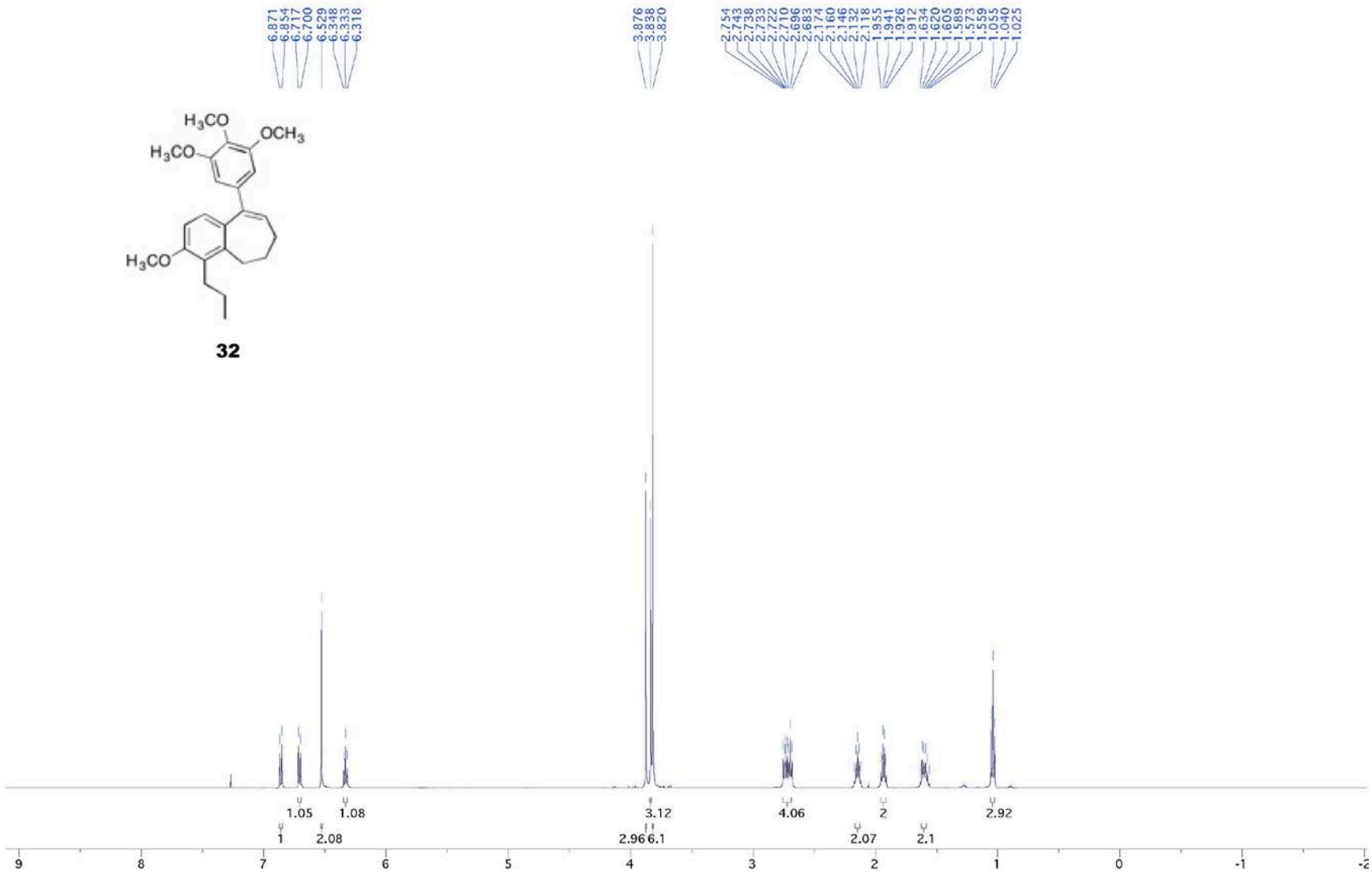
Signal 5: DAD1 G, Sig=300,16 Ref=off
Signal has been modified after loading from rawdata file!

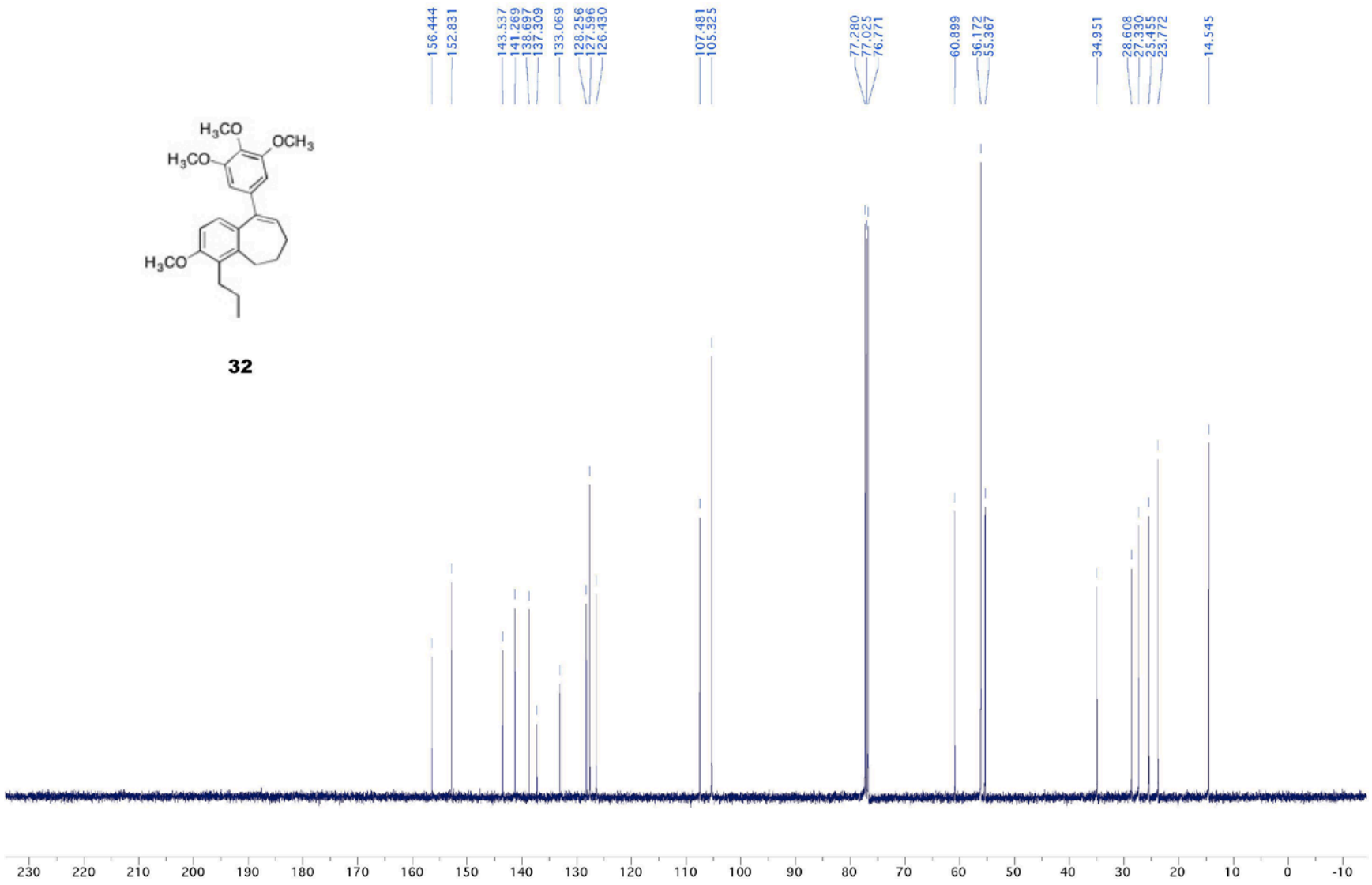
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.650	BB	0.1914	58.18542	4.48376	27.7229
2	20.661	BV	0.0916	151.69656	25.41301	72.2771
Totals :				209.88199	29.89677	

*** End of Report ***

HRMS for compound 31




6.871
6.854
6.717
6.700
6.529
6.348
6.333
6.318
3.876
3.838
3.820
2.754
2.743
2.738
2.733
2.722
2.710
2.696
2.683
2.174
2.160
2.146
2.132
2.118
1.955
1.941
1.926
1.912
1.634
1.620
1.605
1.589
1.573
1.559
1.055
1.040
1.025
H3CO
OCH3
H3CO
H3CO
32
1.05
1.08
3.12
4.06
2
2.92
1
2.08
2.96
6.1
2.07
2.1
9
8
7
6
5
4
3
2
1
0
-1


156.444
152.831
143.537
141.269
138.697
137.309
133.069
128.256
127.596
126.430
107.481
105.325
77.280
77.025
76.771
60.899
56.172
55.367
34.951
28.608
27.330
25.455
23.772
14.545
H3CO
OCH3
H3CO
H3CO
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

32

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_29000003.D
Sample Name: CAH_4_29

HPLC for compound 32

```
==========================================================================
Acq. Operator   : Christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 5/19/2014 3:07:57 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 5/19/2014 3:05:49 PM by Christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\CAH_4_29000003.D\DA.M (MASTERMETHOD.M)
Last changed    : 5/19/2014 4:47:24 PM by Christine
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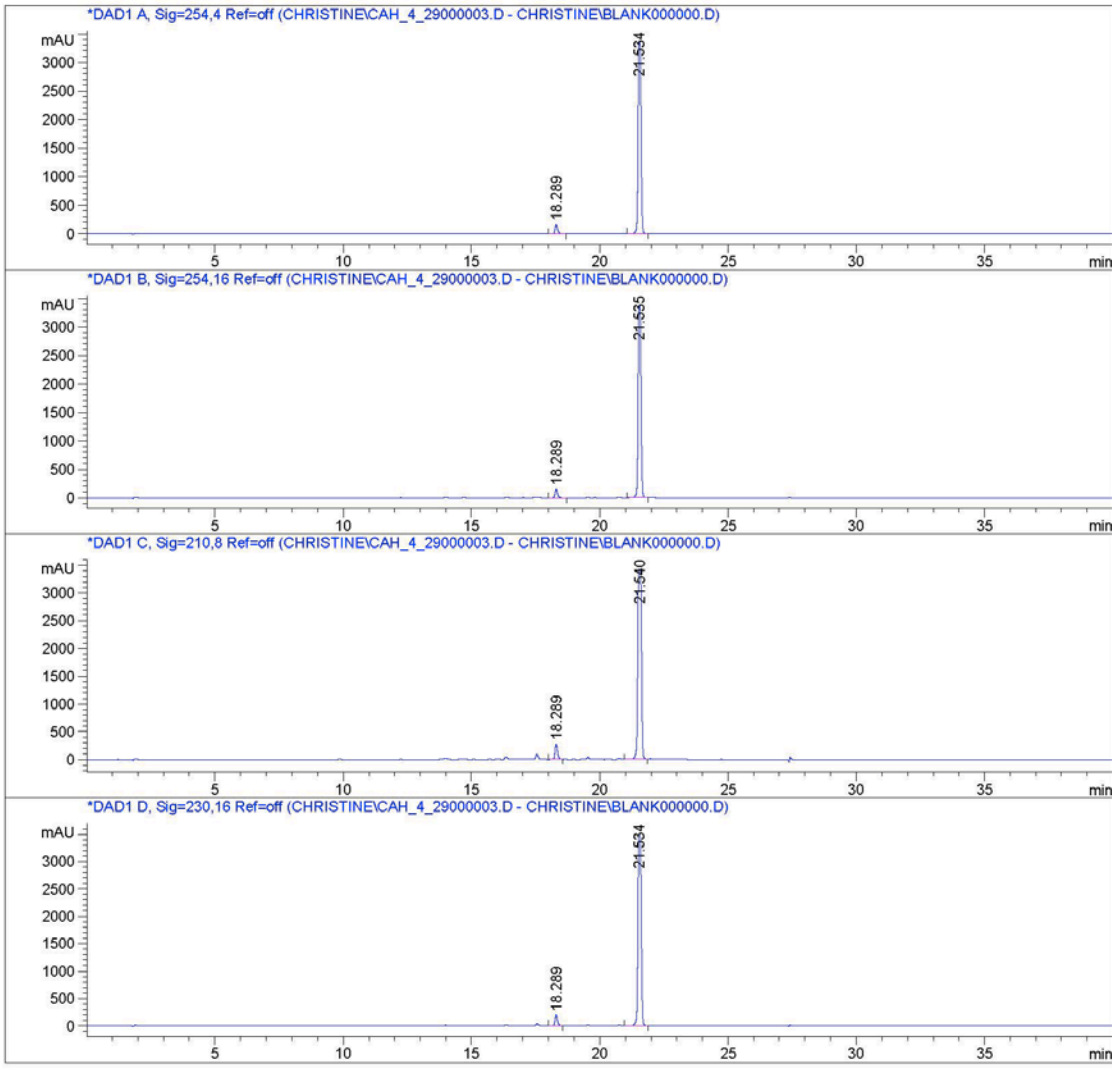
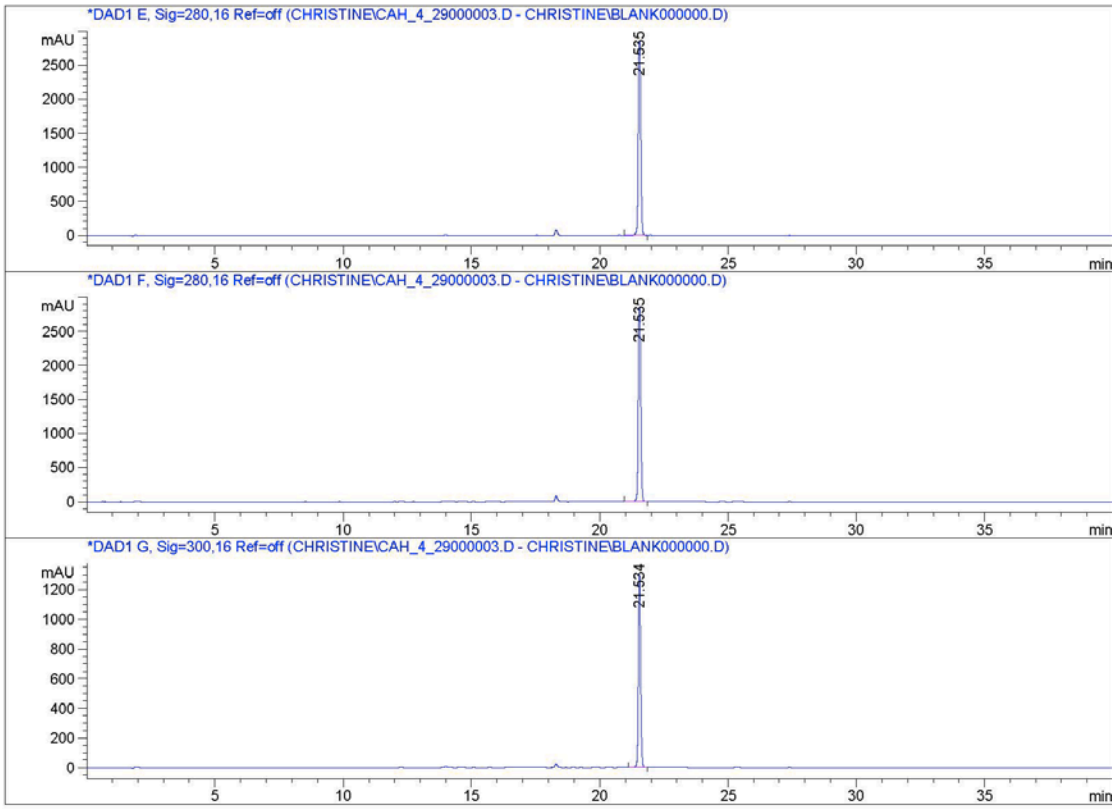


Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_29000003.D
Sample Name: CAH_4_29




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=off
 Signal has been modified after loading from rawdata file!

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  18.289 BB    0.0993 1064.28625  160.63548   3.8307
   2  21.534 BB    0.1285 2.67186e4  3368.47388  96.1693

Totals :                  2.77828e4  3529.10936
```

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_29000003.D
Sample Name: CAH_4_29

Signal 2: DAD1 B, Sig=254,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.289	BB	0.1013	982.76642	148.33012	3.6253
2	21.535	BB	0.1243	2.61255e4	3375.99023	96.3747
Totals :				2.71083e4	3524.32036	

Signal 3: DAD1 C, Sig=210,8 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.289	BV	0.1015	1865.43298	280.66962	5.1837
2	21.540	BV	0.1622	3.41209e4	3424.46191	94.8163
Totals :				3.59864e4	3705.13153	

Signal 4: DAD1 D, Sig=230,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.289	BV	0.1014	1306.26282	196.81532	4.0403
2	21.534	BV	0.1430	3.10247e4	3515.33618	95.9597
Totals :				3.23309e4	3712.15150	

Signal 5: DAD1 E, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.535	BV	0.1074	1.94384e4	2855.78076	100.0000
Totals :				1.94384e4	2855.78076	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_29000003.D
Sample Name: CAH_4_29

Signal 6: DAD1 F, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

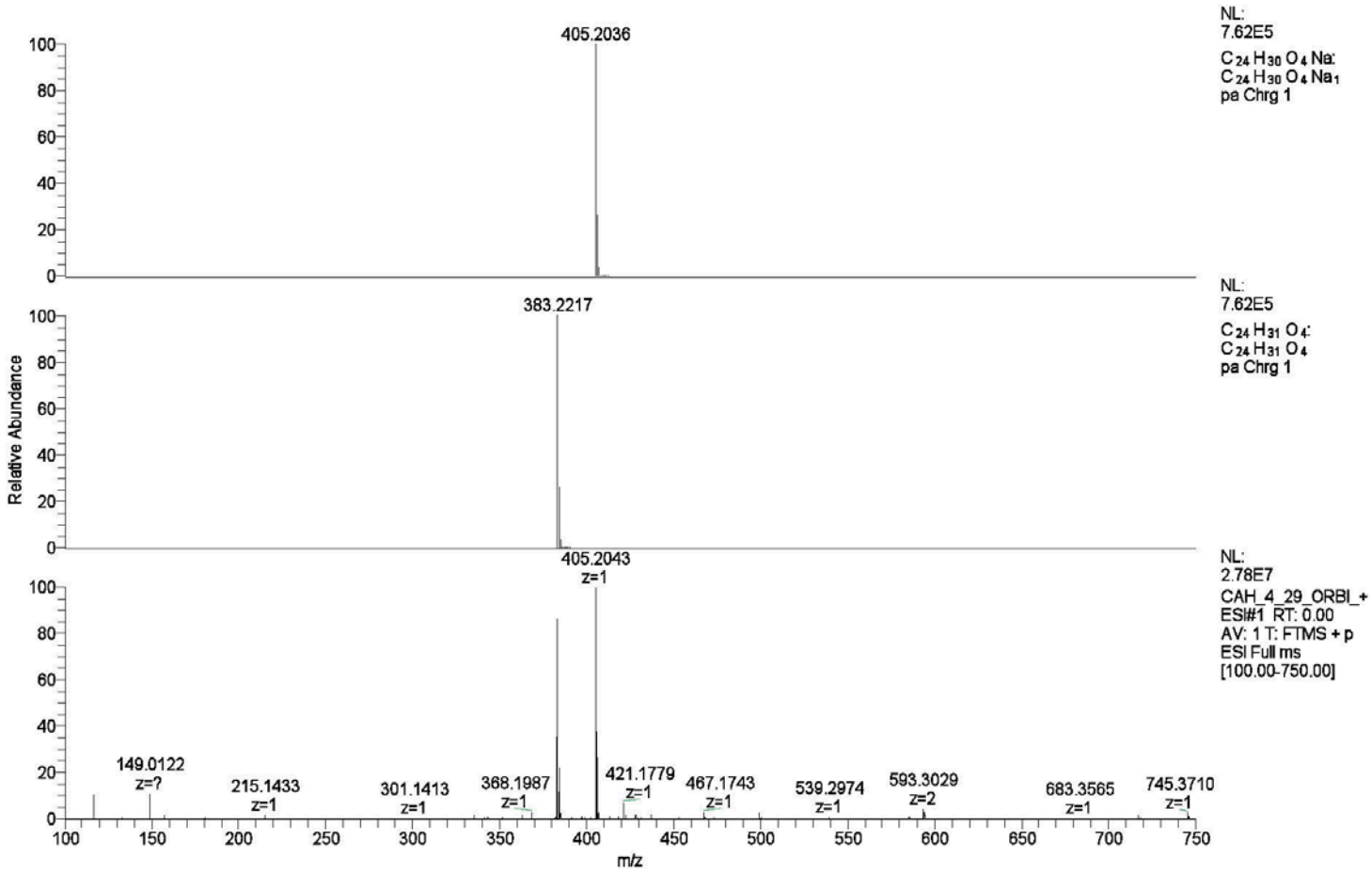
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.535	BV	0.1074	1.94384e4	2855.78076	100.0000
Totals :				1.94384e4	2855.78076	

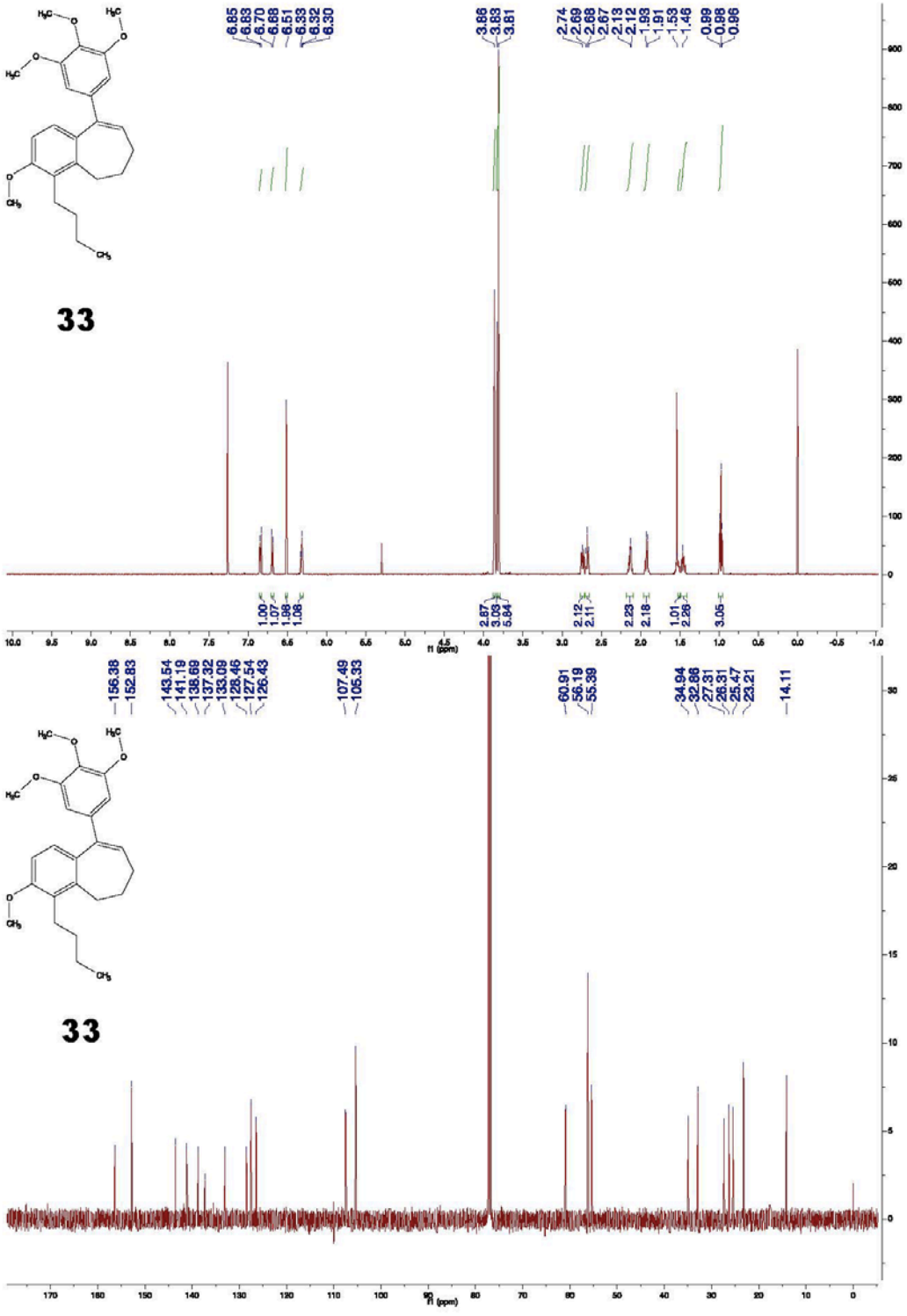
Signal 7: DAD1 G, Sig=300,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.534	BV	0.0938	7832.92432	1309.62927	100.0000
Totals :				7832.92432	1309.62927	

*** End of Report ***

HRMS for compound 32

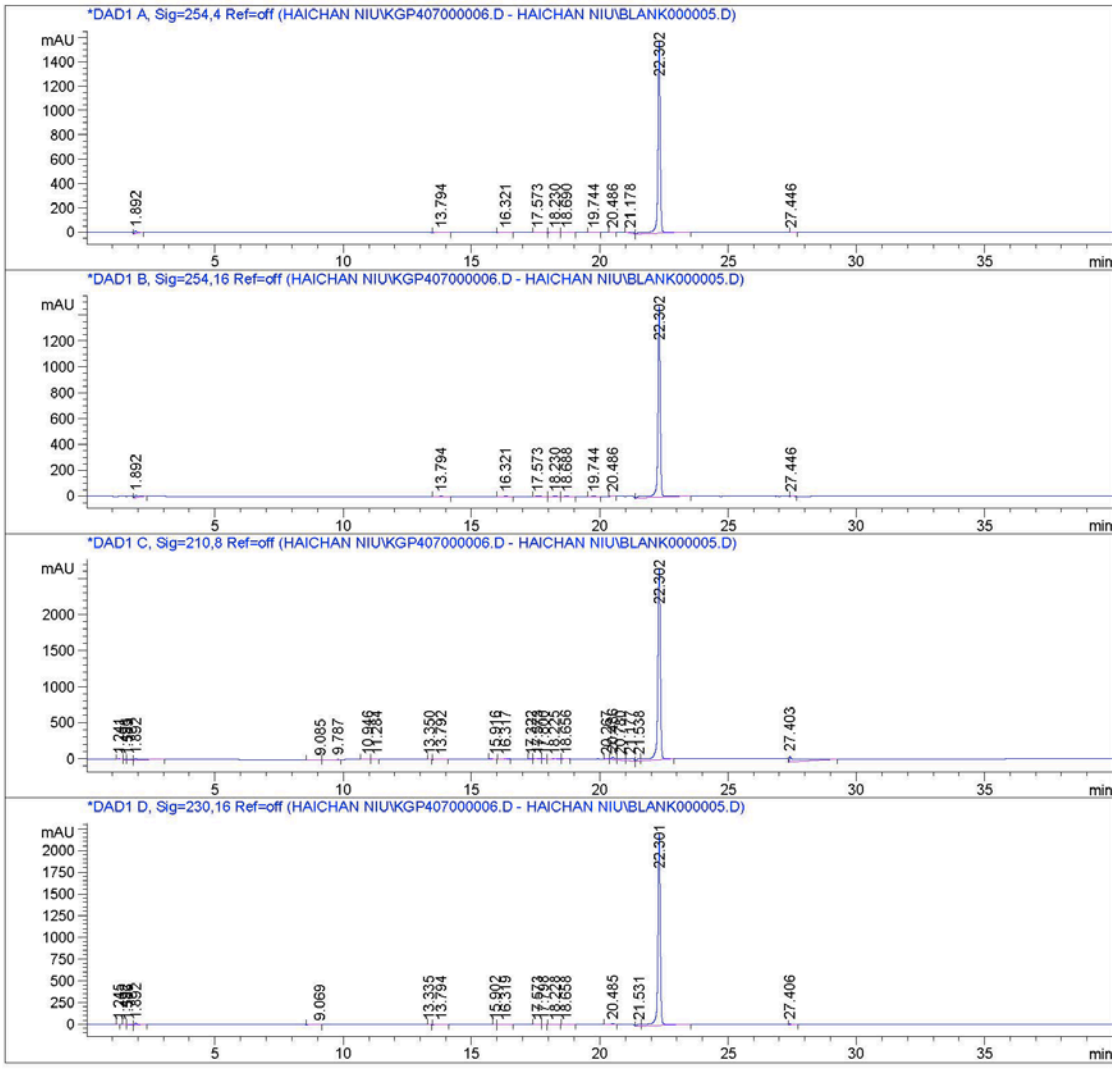



33
6.85
6.83
6.70
6.68
6.51
6.33
6.32
6.30
3.86
3.83
3.81
2.74
2.69
2.68
2.67
2.13
2.12
1.93
1.91
1.53
1.48
0.89
0.88
0.86
1.00
1.07
1.98
1.06
2.87
3.09
5.84
2.12
2.11
2.23
2.18
1.01
2.28
3.05
f1 (ppm)
33
156.38
152.83
143.54
141.19
138.69
137.32
133.09
128.46
127.54
126.43
107.49
105.33
60.91
56.19
55.39
34.94
32.86
27.31
26.31
25.47
23.21
14.11
f1 (ppm)

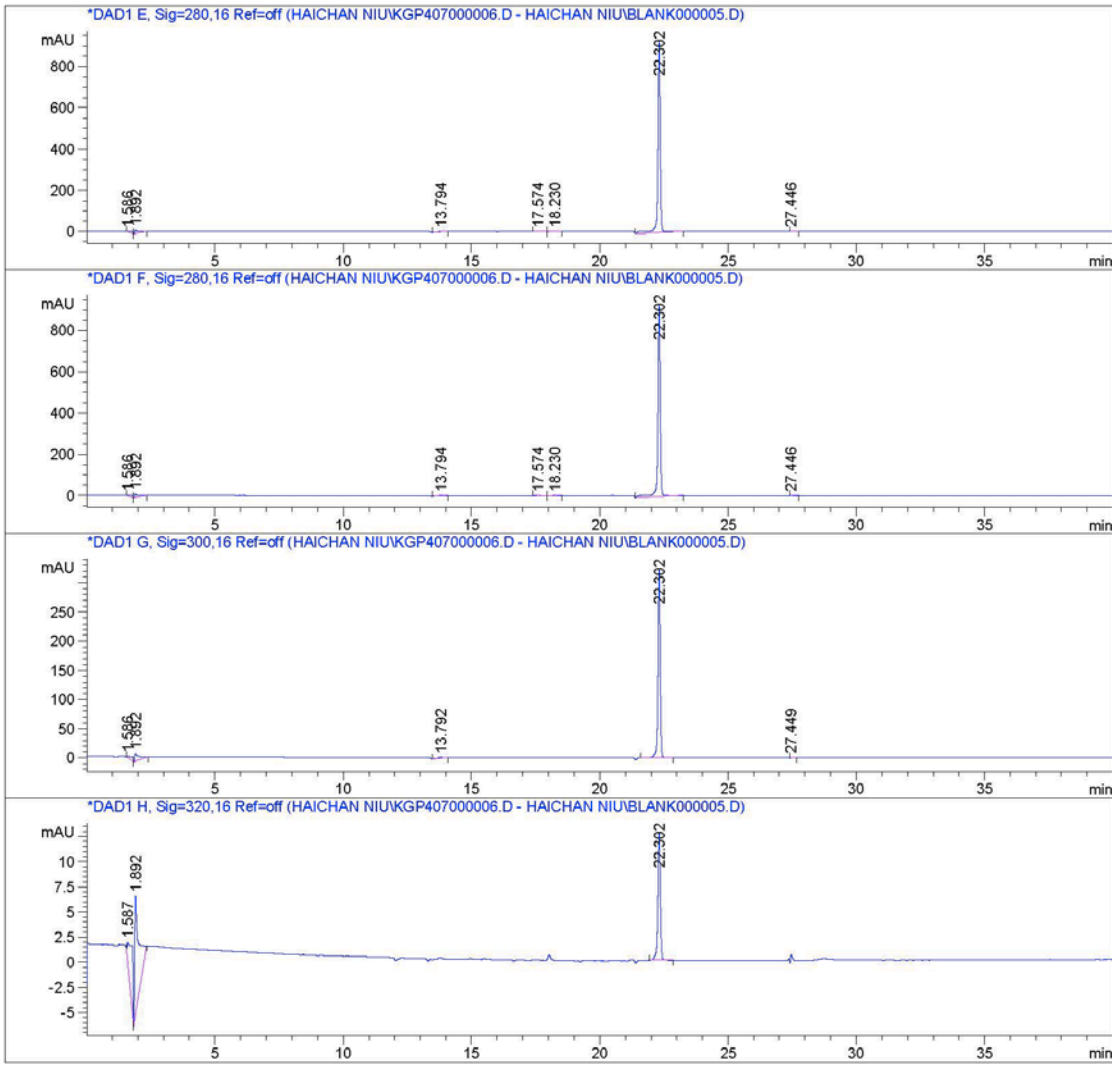
Data File C:\CHEM32\1\DATA\HAICHAN NIU\KGP407000006.D
Sample Name: KGP407

HPLC for compound 33

Acq. Operator : HAICHAN NIU
Acq. Instrument : Instrument 1 Location : -
Injection Date : 5/22/2014 5:52:09 PM
Acq. Method : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed : 5/22/2014 5:43:44 PM by HAICHAN NIU
Analysis Method : C:\CHEM32\1\DATA\HAICHAN NIU\KGP407000006.D\DA.M (MASTERMETHOD.M)
Last changed : 5/22/2014 7:08:38 PM by HAICHAN NIU



Data File C:\CHEM32\1\DATA\HAICHAN NIU\KGP407000006.D
Sample Name: KGP407



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Data File C:\CHEM32\1\DATA\HAICHAN NIU\KGP407000006.D
Sample Name: KGP407

Signal 1: DAD1 A, Sig=254,4 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.892	BB	0.1220	205.61472	23.05705	1.8377
2	13.794	BB	0.2701	37.55608	1.82508	0.3357
3	16.321	BB	0.2518	29.26817	1.48607	0.2616
4	17.573	BB	0.2588	59.74598	2.94312	0.5340
5	18.230	BV	0.2229	63.97398	3.75268	0.5718
6	18.690	VB	0.2388	31.14396	1.72357	0.2784
7	19.744	BB	0.1574	17.63064	1.54186	0.1576
8	20.486	BB	0.0941	8.51472	1.41805	0.0761
9	21.178	BB	0.2529	172.74390	8.96248	1.5439
10	22.302	BB	0.0998	1.05476e4	1581.28418	94.2714
11	27.446	BB	0.0992	14.75580	2.12002	0.1319
Totals :				1.11886e4	1630.11415	

Signal 2: DAD1 B, Sig=254,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.892	BB	0.1472	257.07364	23.21323	2.4674
2	13.794	BB	0.2658	42.60092	2.10777	0.4089
3	16.321	BB	0.2519	29.39858	1.49186	0.2822
4	17.573	BB	0.2544	55.46112	2.78468	0.5323
5	18.230	BV	0.2228	58.92264	3.45830	0.5655
6	18.688	VB	0.2361	29.00475	1.62596	0.2784
7	19.744	BB	0.1552	15.84321	1.40894	0.1521
8	20.486	BB	0.0947	10.03956	1.65767	0.0964
9	22.302	BB	0.0997	9906.66016	1486.84314	95.0838
10	27.446	BB	0.0952	13.86449	2.04266	0.1331
Totals :				1.04189e4	1526.63420	

Signal 3: DAD1 C, Sig=210,8 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.241	BV	0.1166	112.43739	12.53983	0.4377
2	1.498	VV	0.0978	86.76828	12.38144	0.3378
3	1.583	VB	0.2030	212.25829	12.96423	0.8263

Data File C:\CHEM32\1\DATA\HAICHAN NIU\KGP407000006.D
Sample Name: KGP407

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
4	1.892	BB	0.2722	610.39325	28.00976	2.3763
5	9.085	BB	0.3602	37.33203	1.28795	0.1453
6	9.787	BB	0.2183	29.35772	1.72761	0.1143
7	10.946	BB	0.2118	16.74347	1.06277	0.0652
8	11.284	BB	0.0998	9.72657	1.45764	0.0379
9	13.350	BB	0.0951	9.75790	1.69781	0.0380
10	13.792	BB	0.2570	68.78865	3.59853	0.2678
11	15.916	BB	0.1142	30.48277	3.85870	0.1187
12	16.317	BB	0.1950	49.96380	3.36880	0.1945
13	17.322	BV	0.1185	11.81782	1.52267	0.0460
14	17.573	VV	0.1797	82.90123	6.05778	0.3227
15	17.800	VB	0.1581	45.04564	4.68686	0.1754
16	18.225	BV	0.2371	97.94218	5.36237	0.3813
17	18.656	VB	0.1299	51.54269	5.90078	0.2007
18	20.267	BV	0.1402	54.50468	5.57007	0.2122
19	20.486	VV	0.1512	369.62842	33.90767	1.4390
20	20.780	VV	0.2662	439.56110	21.00230	1.7112
21	21.177	VB	0.2569	660.56427	32.80515	2.5716
22	21.538	BV	0.1592	361.84375	36.00524	1.4087
23	22.302	VB	0.1133	1.93617e4	2647.61377	75.3753
24	27.403	BB	0.3710	2875.97852	92.43199	11.1962
Totals :				2.56870e4	2976.82171	

Signal 4: DAD1 D, Sig=230,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.245	BB	0.0525	6.08144	1.75071	0.0372
2	1.492	BV	0.0864	23.75330	3.93887	0.1453
3	1.586	VB	0.2551	169.37418	8.12729	1.0359
4	1.892	BB	0.1505	300.81332	26.48990	1.8398
5	9.069	BB	0.3211	40.21803	1.57932	0.2460
6	13.335	BB	0.1097	11.15828	1.59429	0.0682
7	13.794	BB	0.2532	86.28983	4.55197	0.5277
8	15.902	BB	0.0896	8.10509	1.39794	0.0496
9	16.319	BB	0.2450	47.99840	2.51118	0.2936
10	17.573	BV	0.1604	43.86290	3.69786	0.2683
11	17.798	VB	0.1637	28.22668	2.79859	0.1726
12	18.228	BB	0.2038	54.62132	3.54339	0.3341
13	18.658	BB	0.1438	20.38937	2.05419	0.1247
14	20.485	BB	0.1017	46.16708	6.93190	0.2824
15	21.531	BV	0.1647	265.59775	25.25007	1.6244
16	22.301	VB	0.1035	1.50731e4	2211.43604	92.1866
17	27.406	BB	0.0975	124.87911	16.64479	0.7638

Data File C:\CHEM32\1\DATA\HAICHAN NIU\KGP407000006.D
Sample Name: KGP407

Totals :	1.63506e4	2324.29829	

Signal 5: DAD1 E, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.586	BB	0.3822	88.06649	2.77503	1.3521
2	1.892	BB	0.1496	198.73843	17.89013	3.0512
3	13.794	BB	0.2504	67.00623	3.57945	1.0287
4	17.574	BB	0.2352	23.93932	1.31028	0.3675
5	18.230	BB	0.2013	23.77900	1.54734	0.3651
6	22.302	BB	0.0984	6101.15137	931.20624	93.6697
7	27.446	BB	0.1011	10.79483	1.48062	0.1657
Totals :				6513.47568	959.78909	

Signal 6: DAD1 F, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.586	BB	0.3822	88.06649	2.77503	1.3521
2	1.892	BB	0.1496	198.73843	17.89013	3.0512
3	13.794	BB	0.2504	67.00623	3.57945	1.0287
4	17.574	BB	0.2352	23.93932	1.31028	0.3675
5	18.230	BB	0.2013	23.77900	1.54734	0.3651
6	22.302	BB	0.0984	6101.15137	931.20624	93.6697
7	27.446	BB	0.1011	10.79483	1.48062	0.1657
Totals :				6513.47568	959.78909	

Signal 7: DAD1 G, Sig=300,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.586	BB	0.3828	66.66472	2.09758	2.9911
2	1.892	BB	0.1638	167.54794	13.59008	7.5176
3	13.792	BB	0.2464	39.83583	2.16750	1.7874
4	22.302	BB	0.0922	1948.63611	324.06201	87.4318
5	27.449	BB	0.0828	6.06465	1.02903	0.2721
Totals :				2228.74926	342.94620	

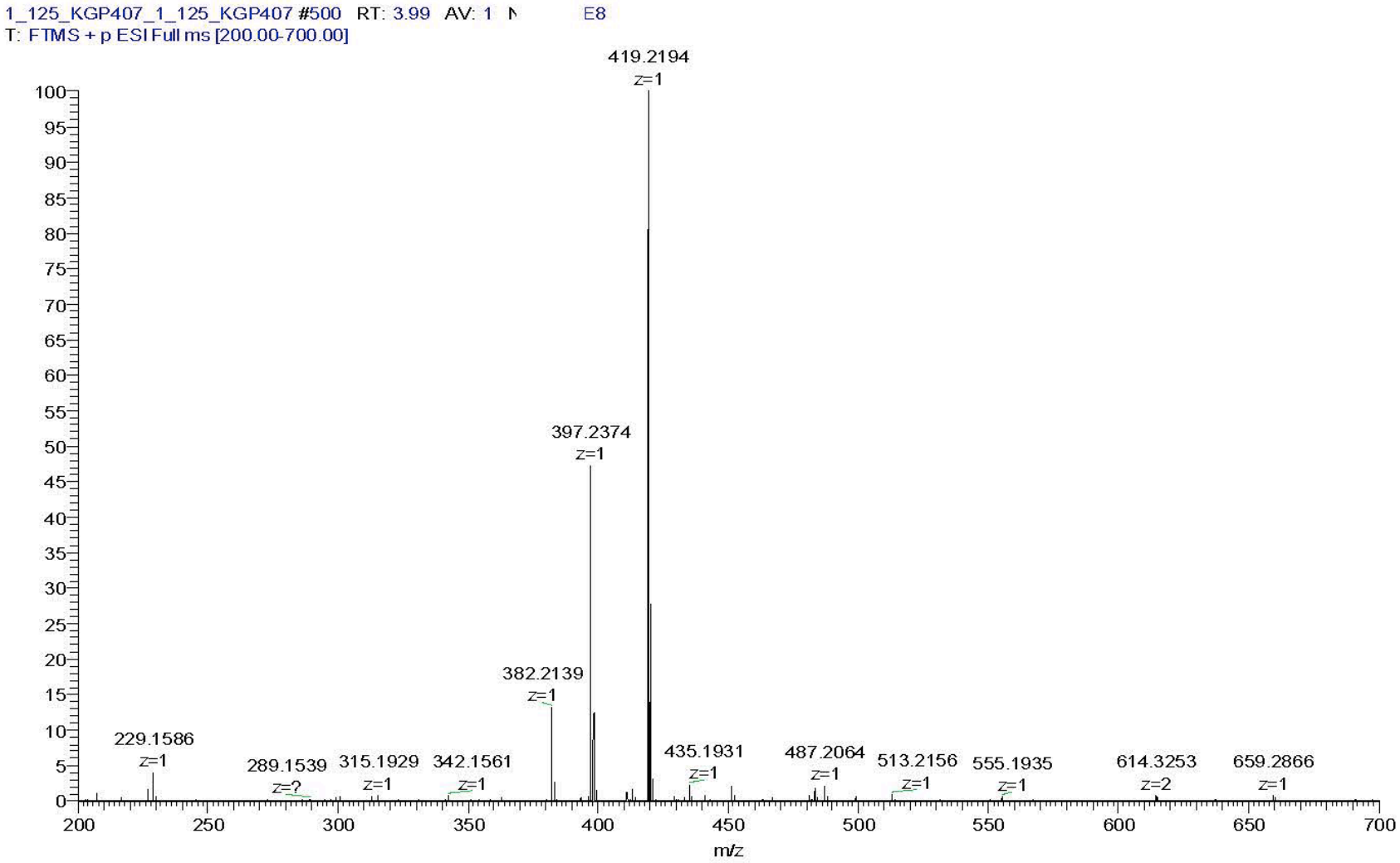
Data File C:\CHEM32\1\DATA\HAICHAN NIU\KGP407000006.D
Sample Name: KGP407

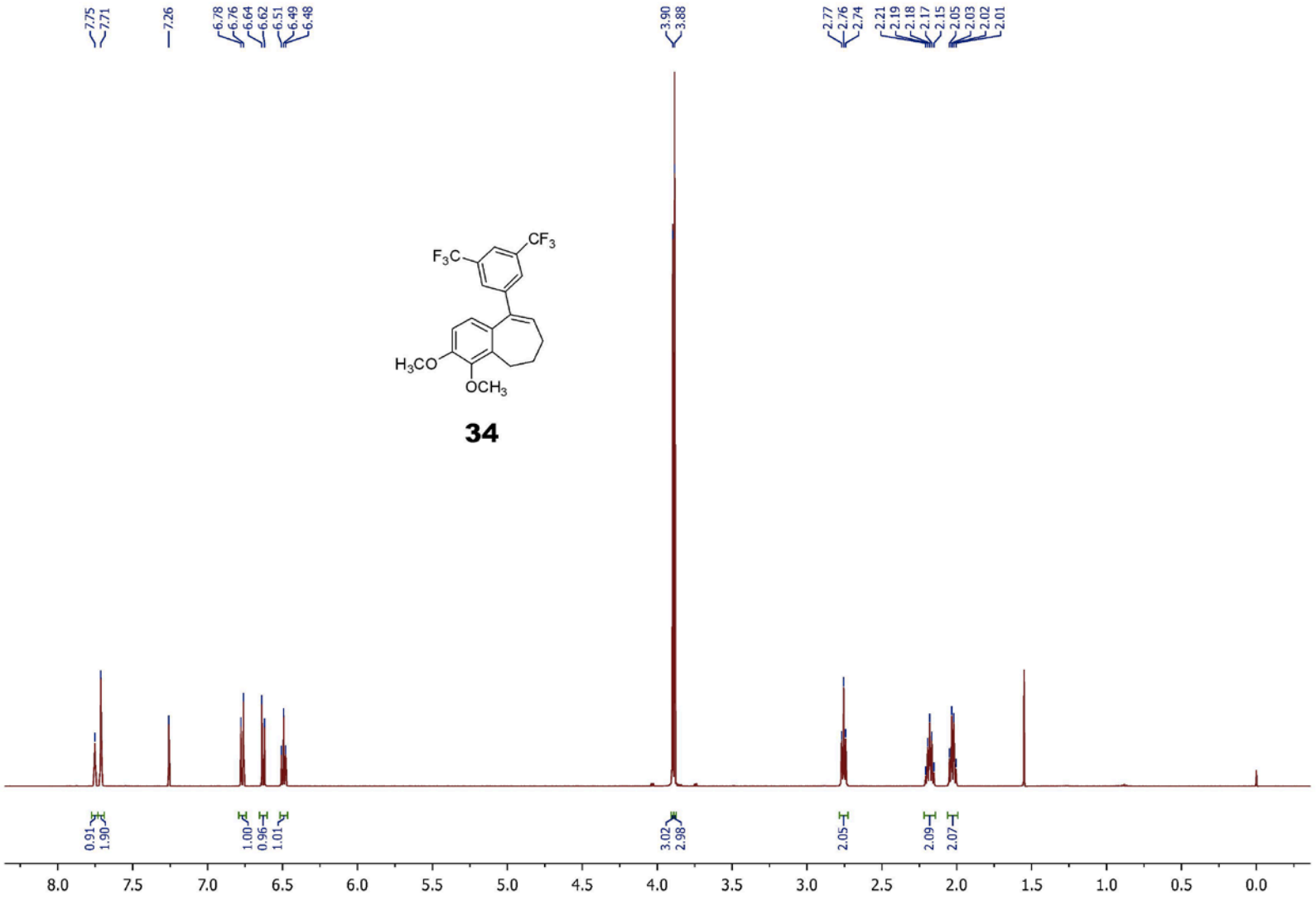
Signal 8: DAD1 H, Sig=320,16 Ref=off
Signal has been modified after loading from rawdata file!

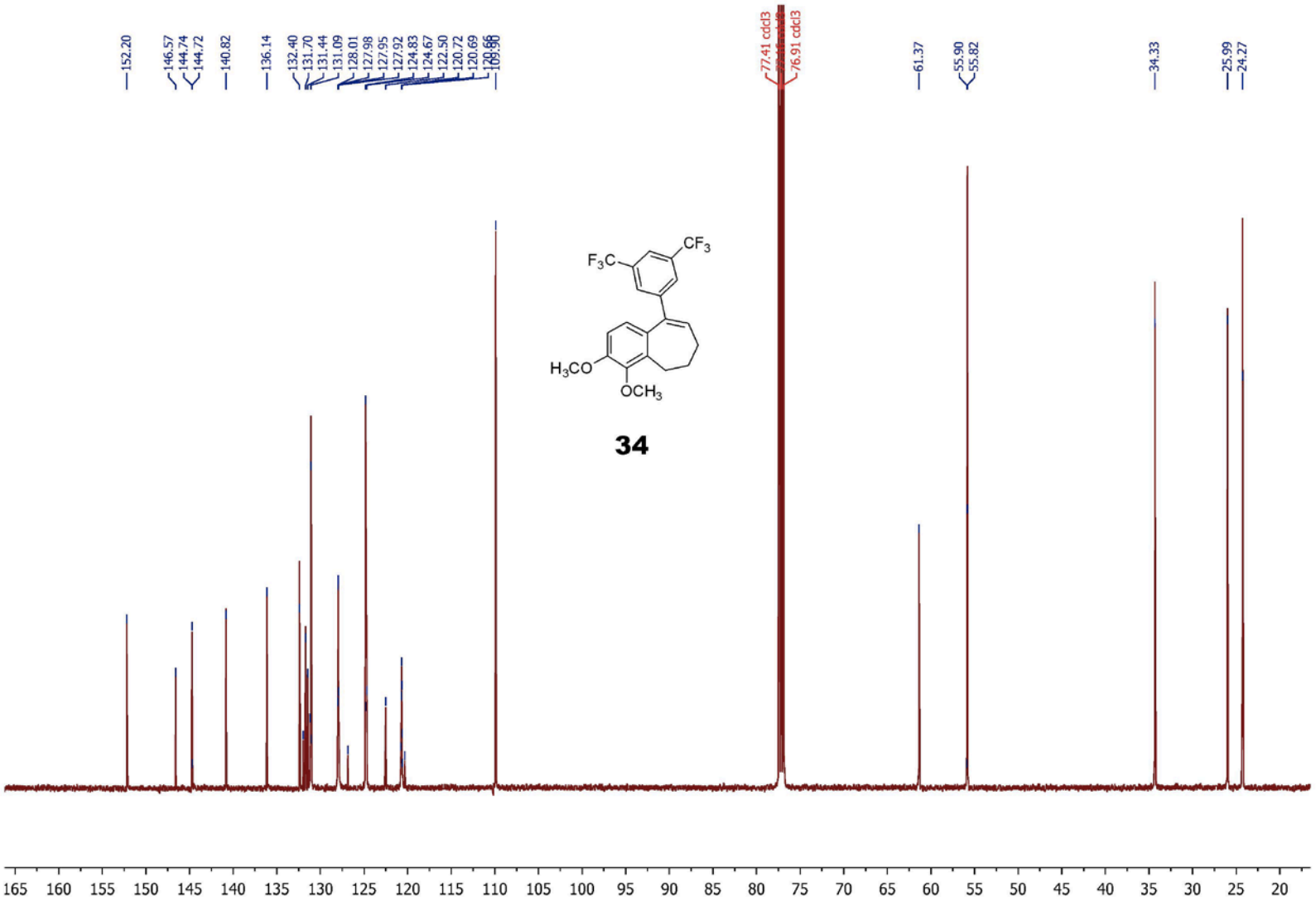
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.587	BB	0.3806	59.15536	1.87249	21.4918
2	1.892	BB	0.1479	130.22919	11.87656	47.3137
3	22.302	BB	0.1031	85.86178	12.66659	31.1945
Totals :				275.24632	26.41563	

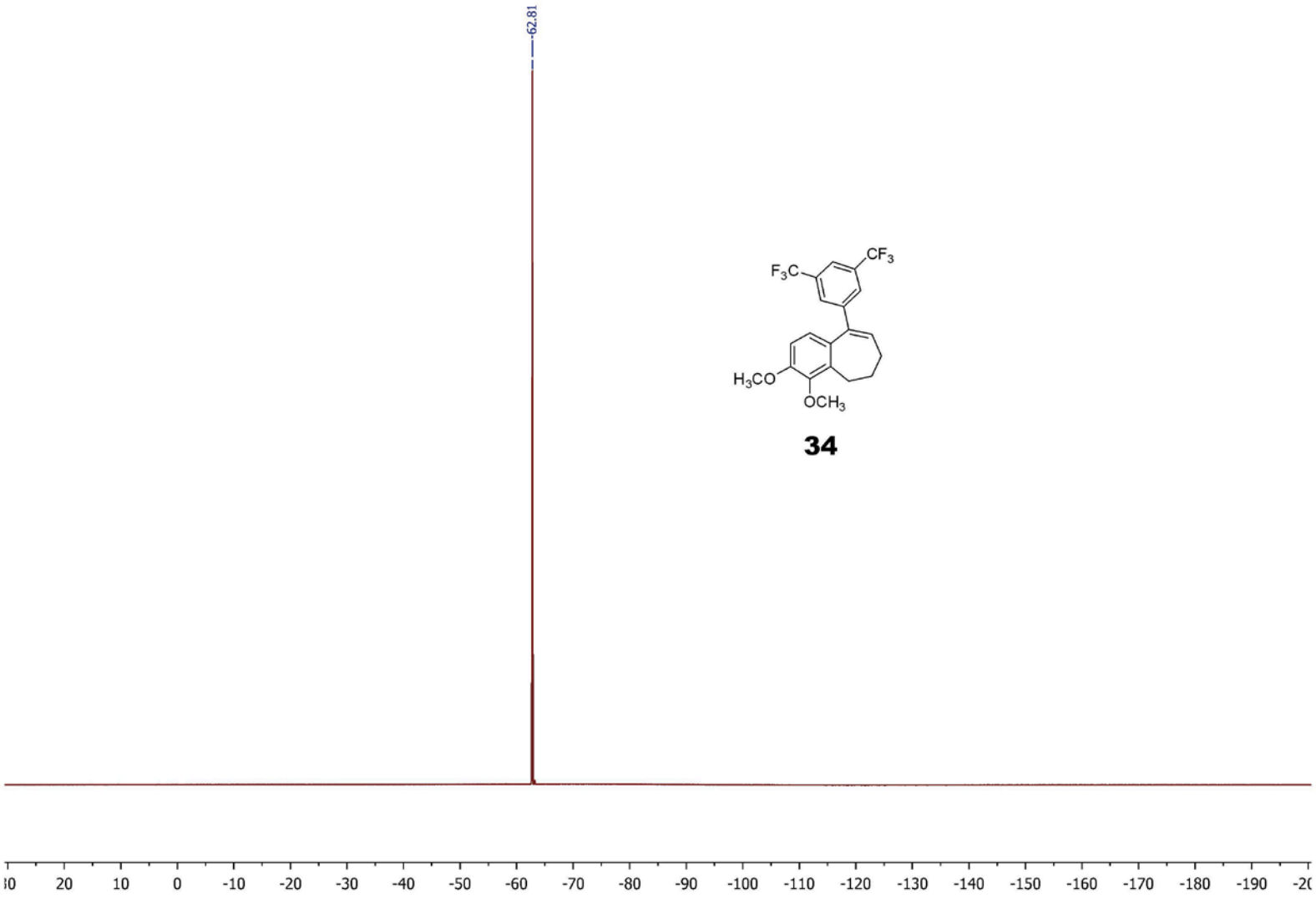
*** End of Report ***

HRMS for compound 33




7.75
7.71
7.26
6.78
6.76
6.64
6.62
6.51
6.49
6.48
3.90
3.88
2.77
2.76
2.74
2.21
2.19
2.18
2.17
2.15
2.05
2.03
2.02
2.01
F3C
CF3
H3CO
OCH3
34
0.91
1.90
1.00
0.96
1.01
3.02
2.98
2.05
2.09
2.07
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
0.0


152.20
146.57
144.74
144.72
140.82
136.14
132.40
131.70
131.44
131.09
128.01
127.98
127.95
127.92
124.83
124.67
122.50
120.72
120.69
77.41 cdcl3
76.91 cdcl3
61.37
55.90
55.82
34.33
25.99
24.27
F3C
CF3
H3CO
OCH3
34
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20


-62.81
F3C
CF3
H3CO
OCH3
34
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

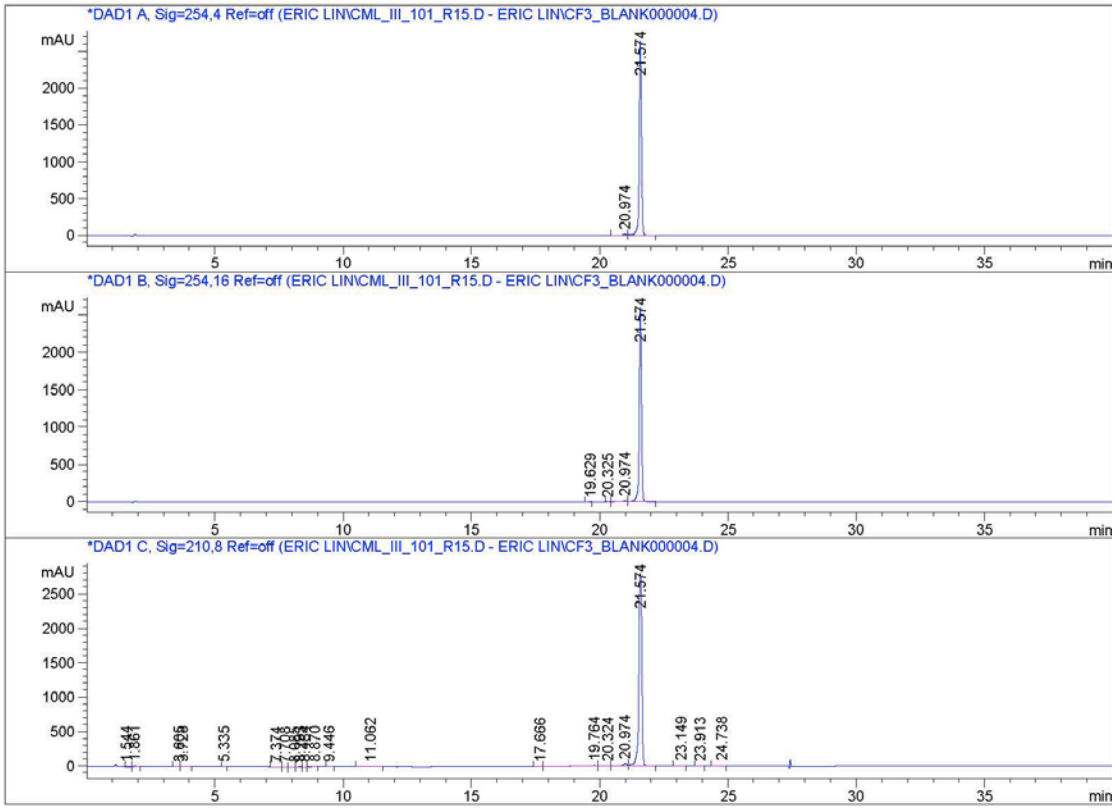
Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_101_R15.D
Sample Name: CML_III_101_r1

HPLC for compound 34

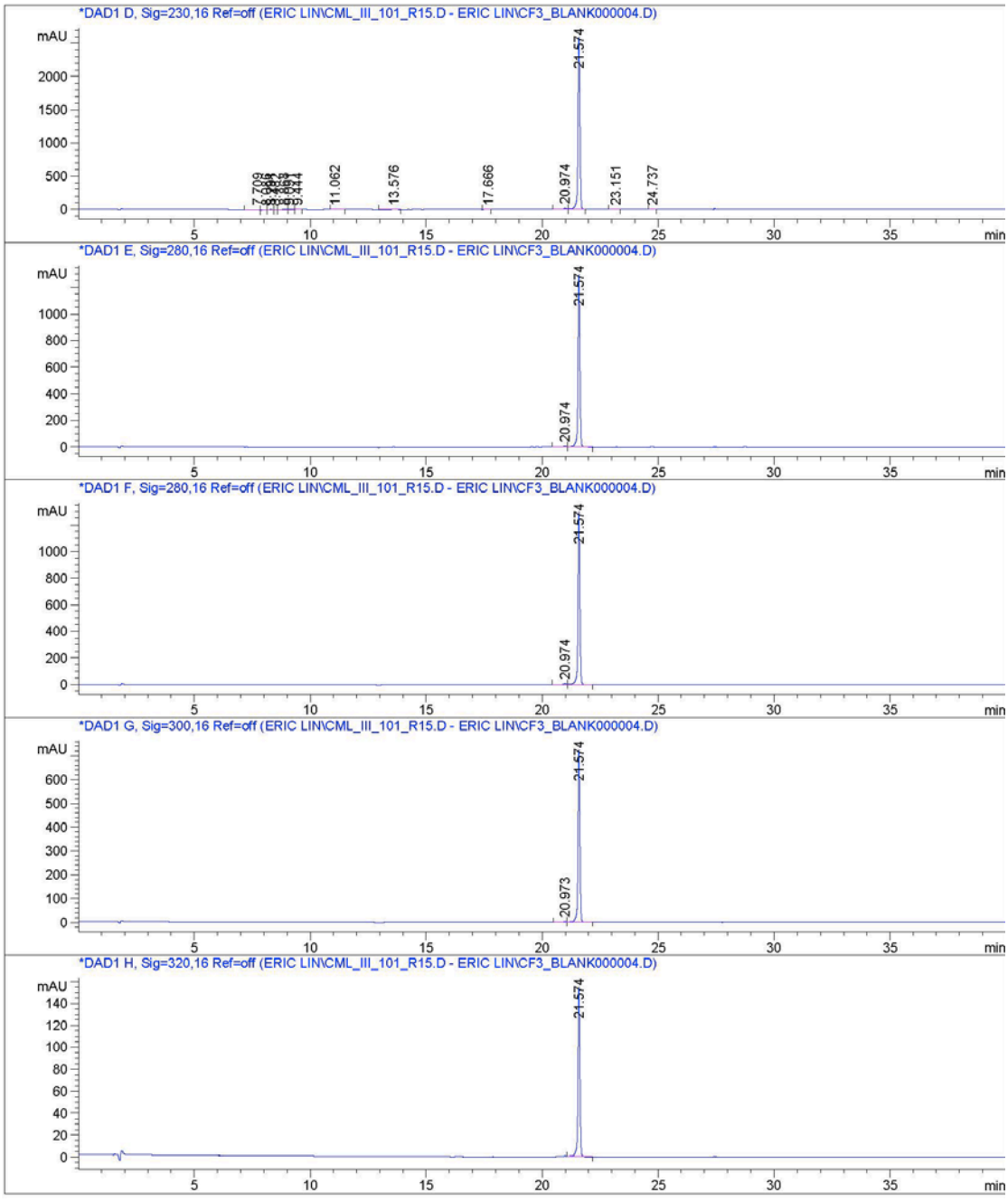
```
==========================================================================
Acq. Operator   : Eric Lin
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 3/11/2014 1:58:36 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 3/11/2014 1:55:06 PM by Eric Lin
Analysis Method : C:\CHEM32\1\DATA\ERIC LIN\CML_III_101_R15.D\DA.M (MASTERMETHOD.M)
Last changed    : 3/11/2014 2:57:57 PM by Eric Lin
Sample Info     : wash

                  Method:

                  0-25 min. (50:50 to 100:0) ACN:Water
                  25-30 min. (100:0) ACN:Water
                  30-35 min. (100:0 to 50:50) ACN:Water
                  35-40 min. (50:50) ACN:Water
```



Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_101_R15.D
Sample Name: CML_III_101_r1



Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_101_R15.D
Sample Name: CML_III_101_r1

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.974	BV	0.1266	162.18532	17.74556	0.9957
2	21.574	VB	0.0950	1.61269e4	2649.16064	99.0043
Totals :				1.62891e4	2666.90621	

Signal 2: DAD1 B, Sig=254,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.629	BV	0.1434	15.67968	1.50705	0.0984
2	20.325	BB	0.0837	7.84197	1.48258	0.0492
3	20.974	BV	0.1269	156.03926	17.03149	0.9797
4	21.574	VB	0.0944	1.57484e4	2610.57349	98.8727
Totals :				1.59279e4	2630.59461	

Signal 3: DAD1 C, Sig=210,8 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.544	VB	0.1616	91.00436	7.09602	0.3682
2	1.861	BB	0.1195	129.13742	16.46471	0.5225
3	3.605	BV	0.1238	19.76291	2.22098	0.0800
4	3.728	VB	0.1876	36.14043	2.74495	0.1462
5	5.335	BV	0.0699	7.31299	1.58168	0.0296
6	7.374	BV	0.3155	131.54974	5.77983	0.5323
7	7.708	VB	0.1477	82.41358	8.61145	0.3335
8	8.085	BV	0.1492	48.02391	5.04047	0.1943
9	8.293	VV	0.1788	82.41489	6.46100	0.3335

Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_101_R15.D
Sample Name: CML_III_101_r1

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
10	8.484	VB	0.1196	28.29939	3.60454	0.1145
11	8.870	BB	0.1467	40.12056	4.08138	0.1623
12	9.446	BB	0.1206	8.52363	1.05068	0.0345
13	11.062	BB	0.1804	111.10935	8.28815	0.4496
14	17.666	BV	0.1830	76.52775	5.76194	0.3097
15	19.764	VB	0.3768	263.92871	8.67955	1.0680
16	20.324	BV	0.1196	57.96089	6.93019	0.2345
17	20.974	VV	0.1513	427.89676	38.00670	1.7314
18	21.574	VB	0.1296	2.29555e4	2800.36768	92.8875
19	23.149	BB	0.0962	46.80672	7.35477	0.1894
20	23.913	BB	0.1068	15.62614	2.20080	0.0632
21	24.738	BB	0.1166	53.17654	7.00522	0.2152
Totals :				2.47132e4	2949.33269	

Signal 4: DAD1 D, Sig=230,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.709	BB	0.3239	249.13312	10.09571	1.5249
2	8.086	BV	0.1551	57.38152	5.81611	0.3512
3	8.291	VV	0.1863	98.30637	7.43379	0.6017
4	8.482	VB	0.1140	29.62998	4.01957	0.1814
5	8.868	BV	0.1762	75.49585	6.10649	0.4621
6	9.091	VV	0.1764	31.43843	2.34578	0.1924
7	9.444	VB	0.1488	19.71043	1.84204	0.1206
8	11.062	BB	0.1049	24.78027	3.57223	0.1517
9	13.576	BB	0.5029	106.49190	2.63814	0.6518
10	17.666	BB	0.1714	20.12987	1.66064	0.1232
11	20.974	BV	0.1380	173.49957	17.14832	1.0620
12	21.574	VB	0.0909	1.54119e4	2608.66772	94.3329
13	23.151	BB	0.1007	10.27145	1.52356	0.0629
14	24.737	BB	0.1105	29.60491	4.18738	0.1812
Totals :				1.63378e4	2677.05750	

Signal 5: DAD1 E, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.974	BV	0.1231	72.74569	8.22962	0.9803
2	21.574	VB	0.0858	7347.78955	1302.42627	99.0197

Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_101_R15.D
Sample Name: CML_III_101_r1

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
Totals :				7420.53524	1310.65589	

Signal 6: DAD1 F, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.974	BV	0.1231	72.74569	8.22962	0.9803
2	21.574	VB	0.0858	7347.78955	1302.42627	99.0197
Totals :				7420.53524	1310.65589	

Signal 7: DAD1 G, Sig=300,16 Ref=off
Signal has been modified after loading from rawdata file!

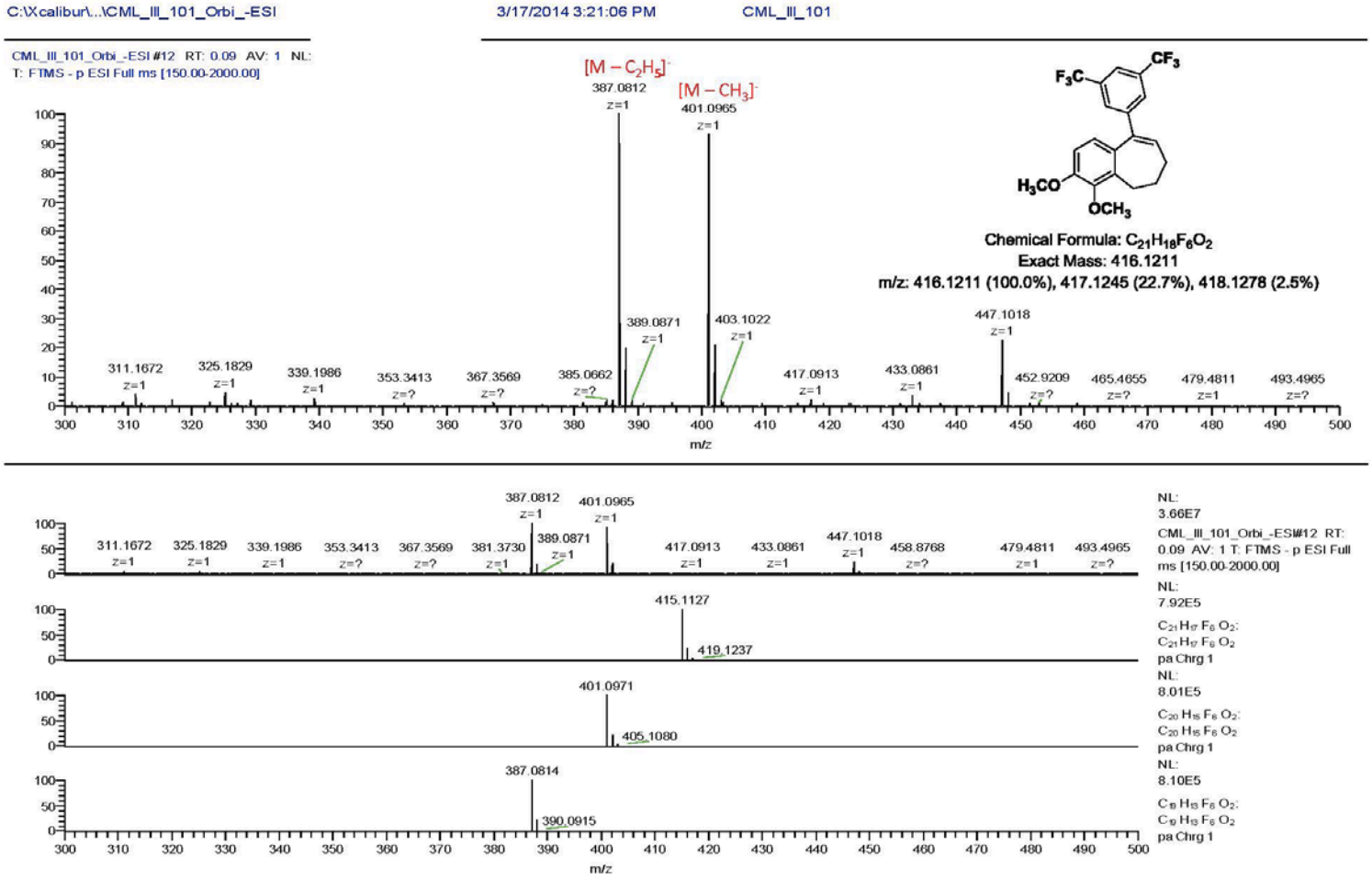
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.973	BV	0.1175	35.49311	4.24565	0.8536
2	21.574	VB	0.0860	4122.53955	729.12970	99.1464
Totals :				4158.03266	733.37535	

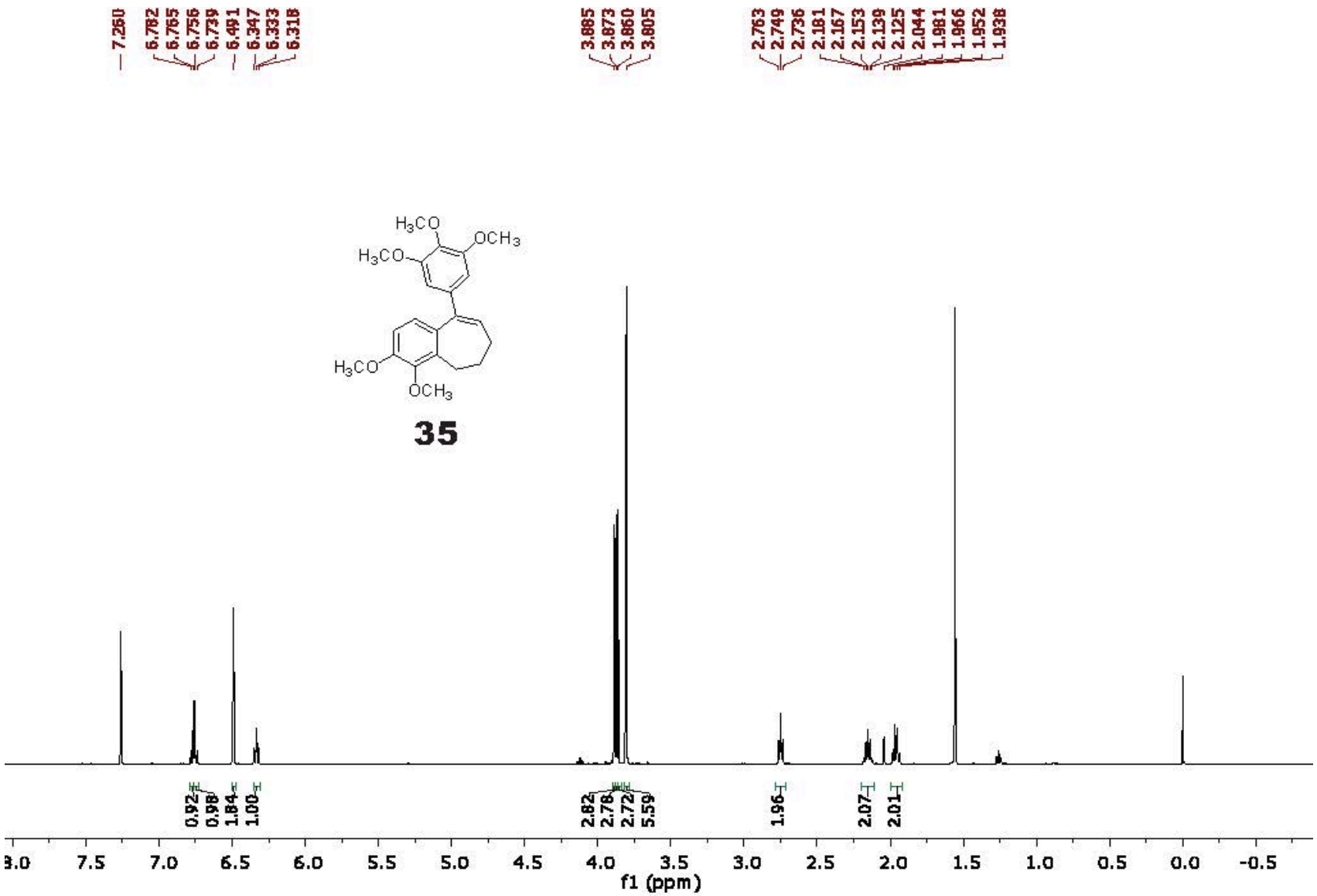
Signal 8: DAD1 H, Sig=320,16 Ref=off
Signal has been modified after loading from rawdata file!

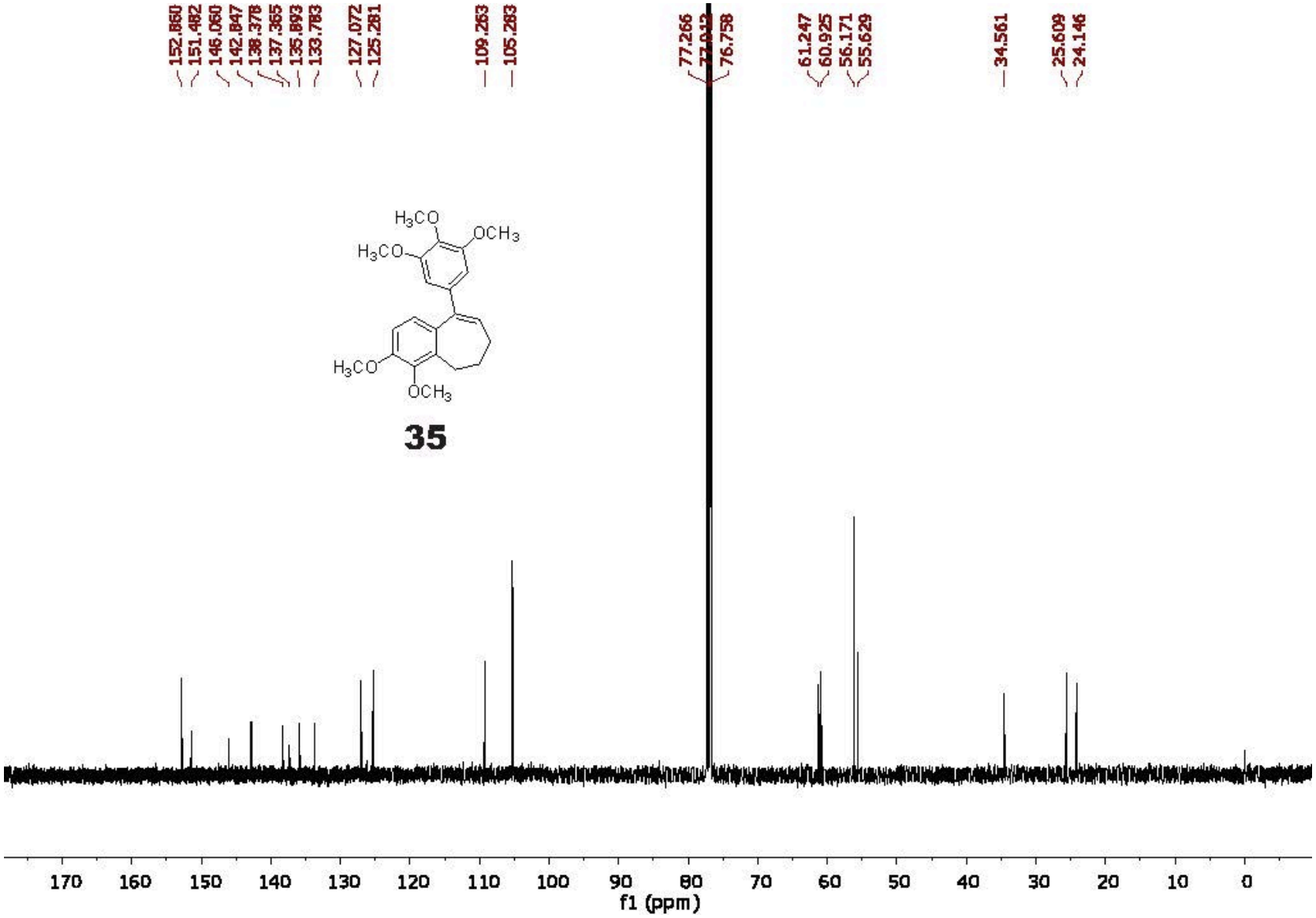
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.574	BB	0.0878	901.81482	155.12813	100.0000
Totals :				901.81482	155.12813	

*** End of Report ***

HRMS for compound 34



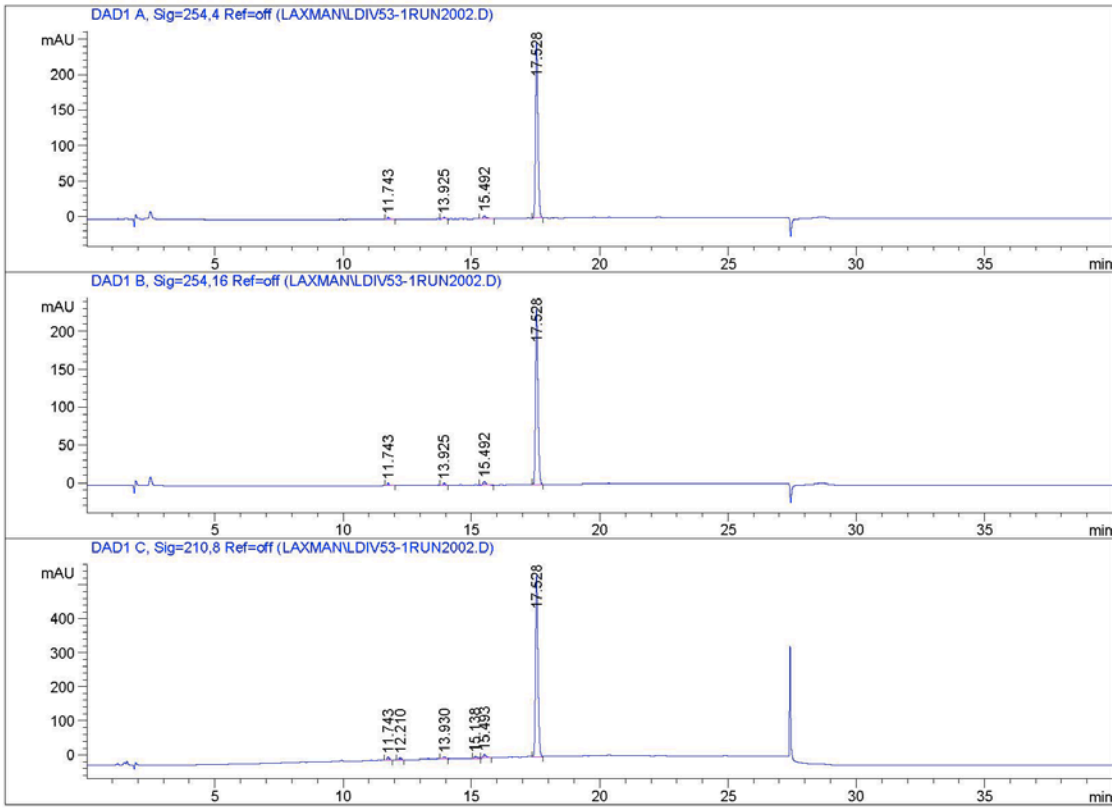

7.260
6.782
6.765
6.756
6.739
6.491
6.347
6.333
6.318
3.885
3.873
3.860
3.805
2.763
2.749
2.736
2.181
2.167
2.153
2.139
2.125
2.044
1.981
1.966
1.952
1.938
H3CO
OCH3
H3CO
H3CO
OCH3
35
0.92
0.98
1.84
1.00
2.82
2.78
2.72
5.59
1.96
2.07
2.01
f1 (ppm)


152.860
151.482
146.060
142.847
138.378
137.365
135.893
133.783
127.072
125.281
109.263
105.283
77.266
76.758
61.247
60.925
56.171
55.629
34.561
25.609
24.146
H3CO
OCH3
H3CO
H3CO
OCH3
35
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

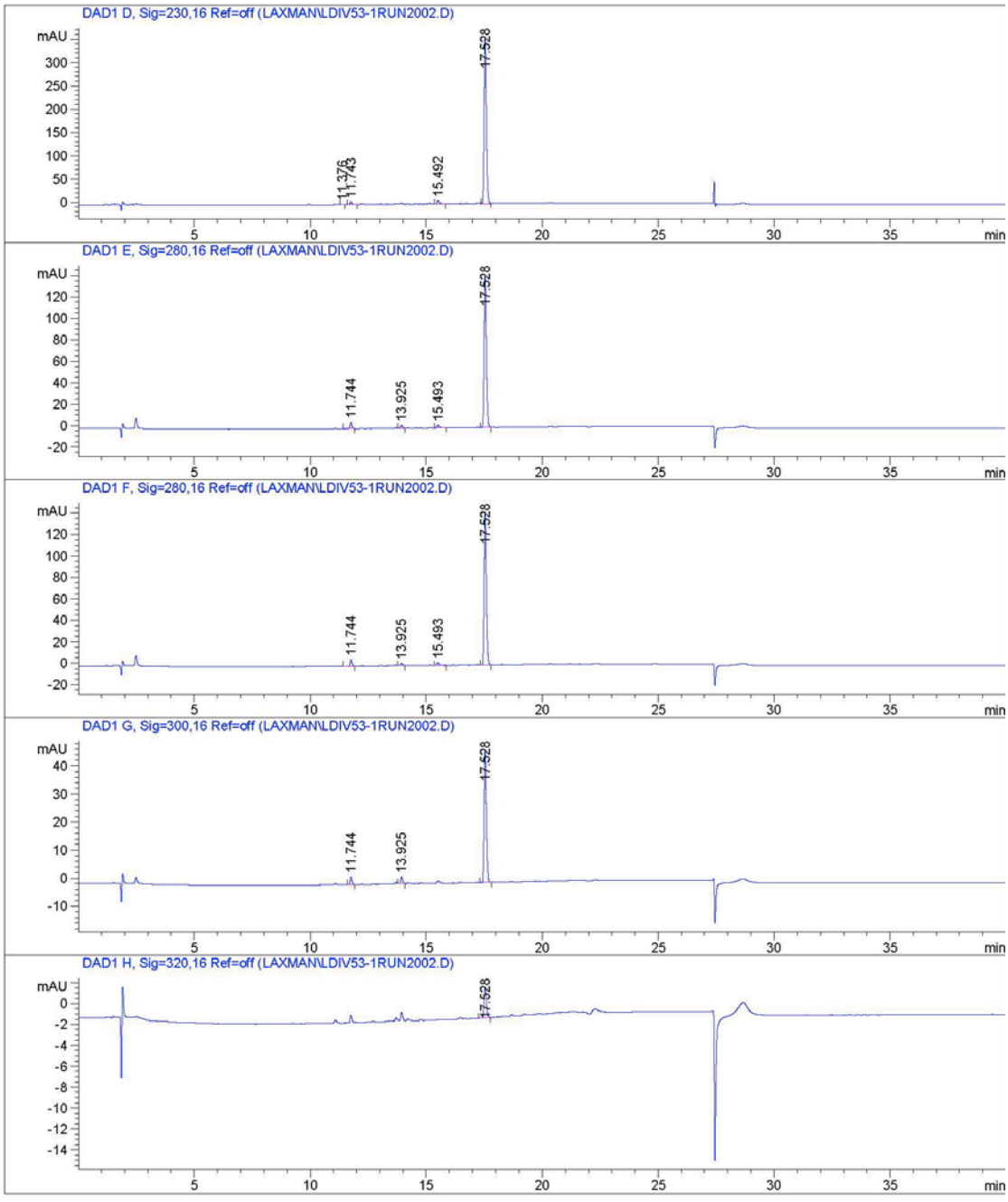
Data File C:\CHEM32\1\DATA\LAXMAN\LDIV53-1RUN2002.D
Sample Name: LD-IV-53-1A-run2

HPLC for compound 35

```
==========================================================================
Acq. Operator   : Laxman
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 1/28/2014 4:36:52 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 1/28/2014 4:31:37 PM by Laxman
Analysis Method : C:\CHEM32\1\DATA\LAXMAN\LDIV53-1RUN2002.D\DA.M (MASTERMETHOD.M)
Last changed    : 1/28/2014 5:32:55 PM by Laxman
Sample Info     : run2
```



Data File C:\CHEM32\1\DATA\LAXMAN\LDIV53-1RUN2002.D
Sample Name: LD-IV-53-1A-run2



Data File C:\CHEM32\1\DATA\LAXMAN\LDIV53-1RUN2002.D
Sample Name: LD-IV-53-1A-run2

==========

Area Percent Report

==========

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.743	BB	0.0826	14.26201	2.65778	0.8361
2	13.925	BB	0.0929	13.40179	2.14591	0.7857
3	15.492	BB	0.1162	36.18954	4.57916	2.1215
4	17.528	BB	0.1009	1641.95728	249.16393	96.2567
Totals :				1705.81062	258.54678	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.743	BB	0.0825	15.31448	2.85651	0.9551
2	13.925	BB	0.0930	13.93967	2.22854	0.8693
3	15.492	BB	0.1162	34.20804	4.32975	2.1333
4	17.528	BB	0.1009	1540.03906	233.65747	96.0423
Totals :				1603.50126	243.07228	

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.743	VB	0.0846	46.10949	8.32722	1.2122
2	12.210	BB	0.0942	31.44279	5.22819	0.8266
3	13.930	VB	0.1058	44.68492	6.07767	1.1747
4	15.138	BB	0.1074	40.66746	5.55600	1.0691
5	15.493	BB	0.1166	84.69407	10.67318	2.2265
6	17.528	VV	0.1012	3556.32837	537.31000	93.4910
Totals :				3803.92710	573.17226	

Data File C:\CHEM32\1\DATA\LAXMAN\LDIV53-1RUN2002.D
Sample Name: LD-IV-53-1A-run2

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.376	BB	0.0778	5.07398	1.02429	0.2062
2	11.743	BB	0.0837	34.19037	6.25711	1.3895
3	15.492	VB	0.1148	57.49661	7.38936	2.3366
4	17.528	VV	0.1010	2363.93970	358.03088	96.0677
Totals :				2460.70065	372.70165	

Signal 5: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.744	BB	0.0836	33.69853	6.18095	3.3237
2	13.925	BB	0.0929	16.22744	2.59767	1.6005
3	15.493	BB	0.1161	21.33865	2.70186	2.1046
4	17.528	BB	0.1010	942.63556	142.84668	92.9712
Totals :				1013.90018	154.32717	

Signal 6: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.744	BB	0.0836	33.69853	6.18095	3.3237
2	13.925	BB	0.0929	16.22744	2.59767	1.6005
3	15.493	BB	0.1161	21.33865	2.70186	2.1046
4	17.528	BB	0.1010	942.63556	142.84668	92.9712
Totals :				1013.90018	154.32717	

Signal 7: DAD1 G, Sig=300,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.744	BB	0.0831	15.00270	2.77378	4.3629
2	13.925	BB	0.0900	14.52386	2.41986	4.2237
3	17.528	BB	0.1013	314.33951	47.44872	91.4134
Totals :				343.86607	52.64236	

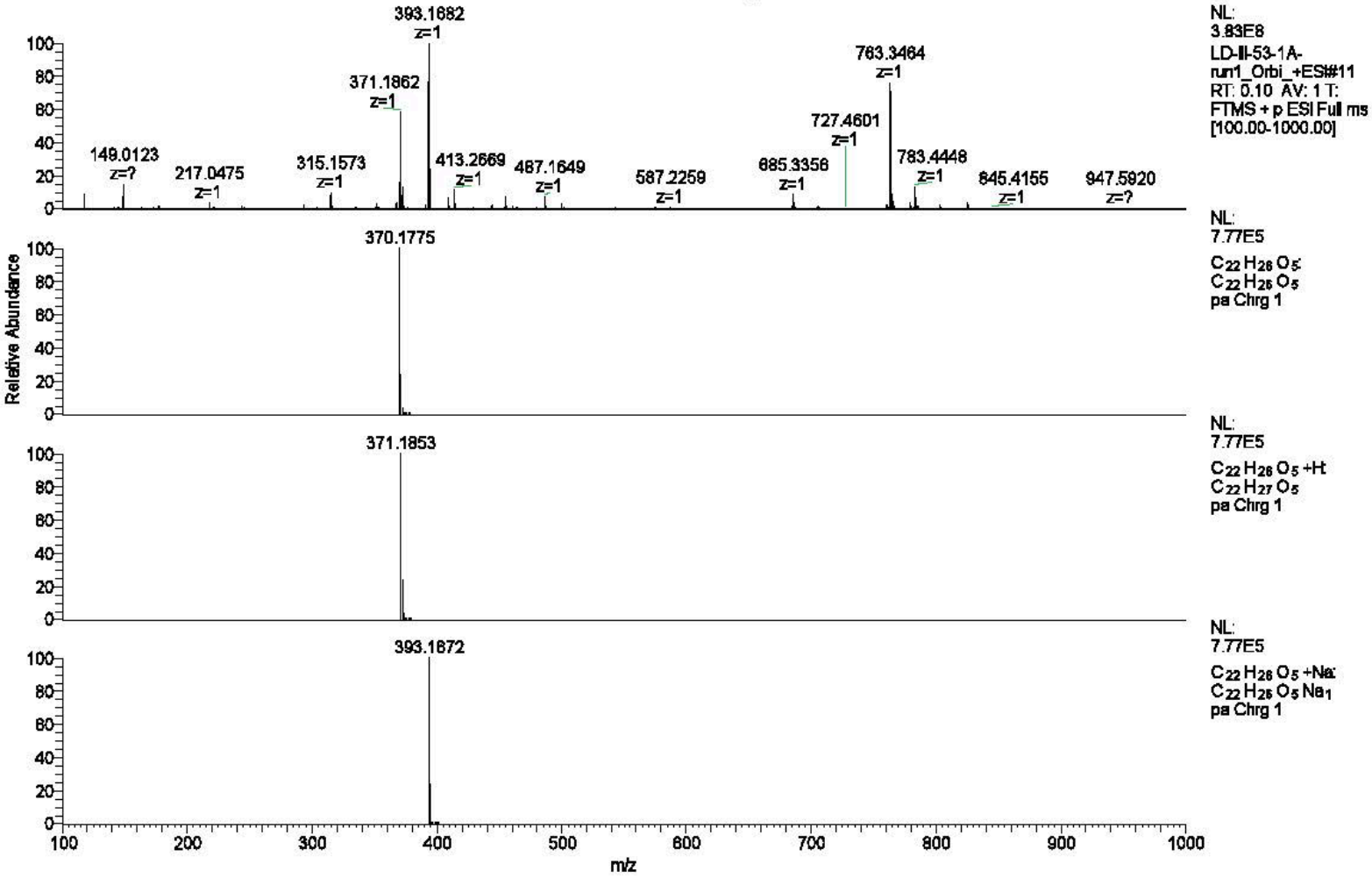
Data File C:\CHEM32\1\DATA\LAXMAN\LDIV53-1RUN2002.D
Sample Name: LD-IV-53-1A-run2

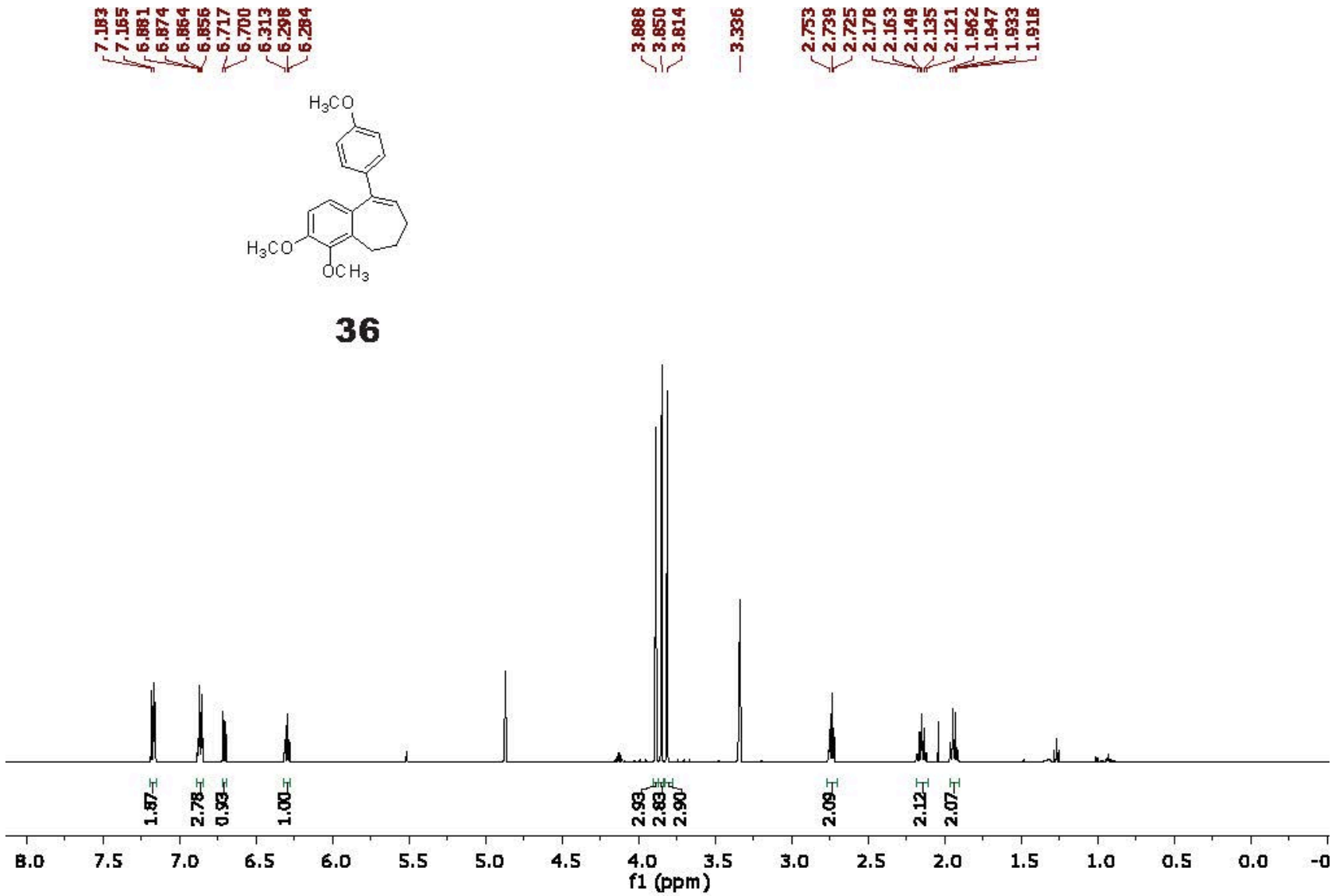
Signal 8: DAD1 H, Sig=320,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.528	BB	0.1072	20.50176	2.94557	100.0000
Totals :				20.50176	2.94557	

*** End of Report ***

HRMS for compound 35

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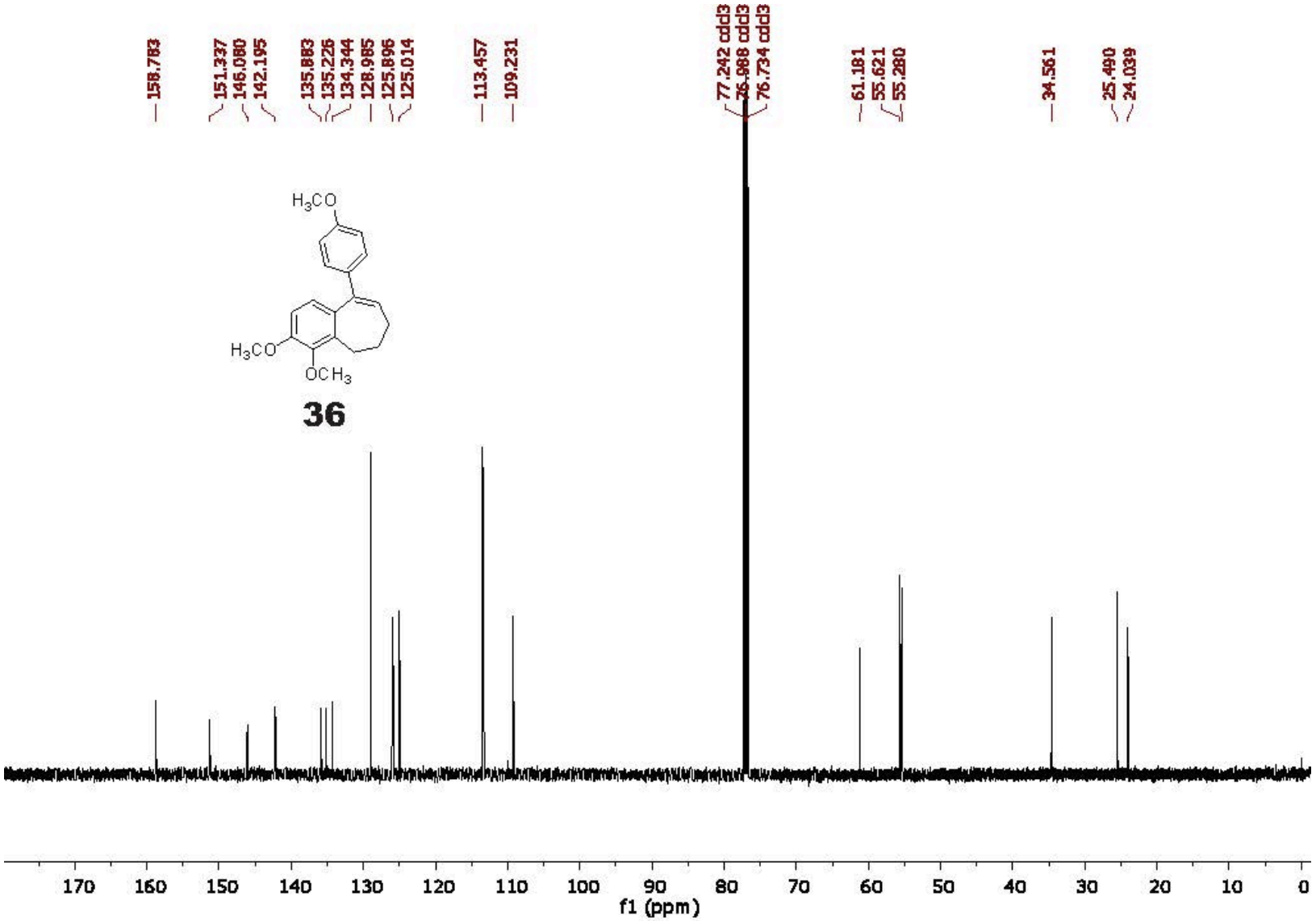
7.165
6.881
6.874
6.864
6.856
6.717
6.700
6.313
6.298
6.284
3.888
3.850
3.814
3.336
2.753
2.739
2.725
2.178
2.163
2.149
2.135
2.121
1.962
1.947
1.933
1.918
H3CO
H3CO
OCH3
36
1.87
2.78
0.93
1.00
2.93
2.83
2.90
2.09
2.12
2.07
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


158.783
151.337
146.080
142.195
135.883
135.226
134.344
128.985
125.896
125.014
113.457
109.231
77.242 cdcl3
76.988 cdcl3
76.734 cdcl3
61.181
55.621
55.280
34.561
25.490
24.039
H3CO
H3CO
OCH3
36
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Data File C:\CHEM32\1\DATA\LAXMAN\LDIV139-1ARUN01.D
Sample Name: LD-IV-139-1A-1

HPLC for compound 36

```
==========================================================================
Acq. Operator   : Laxman
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 1/30/2014 10:16:04 AM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 1/30/2014 9:43:27 AM by Laxman
Analysis Method : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 1/30/2014 11:06:05 AM by Laxman
Sample Info     : Run1
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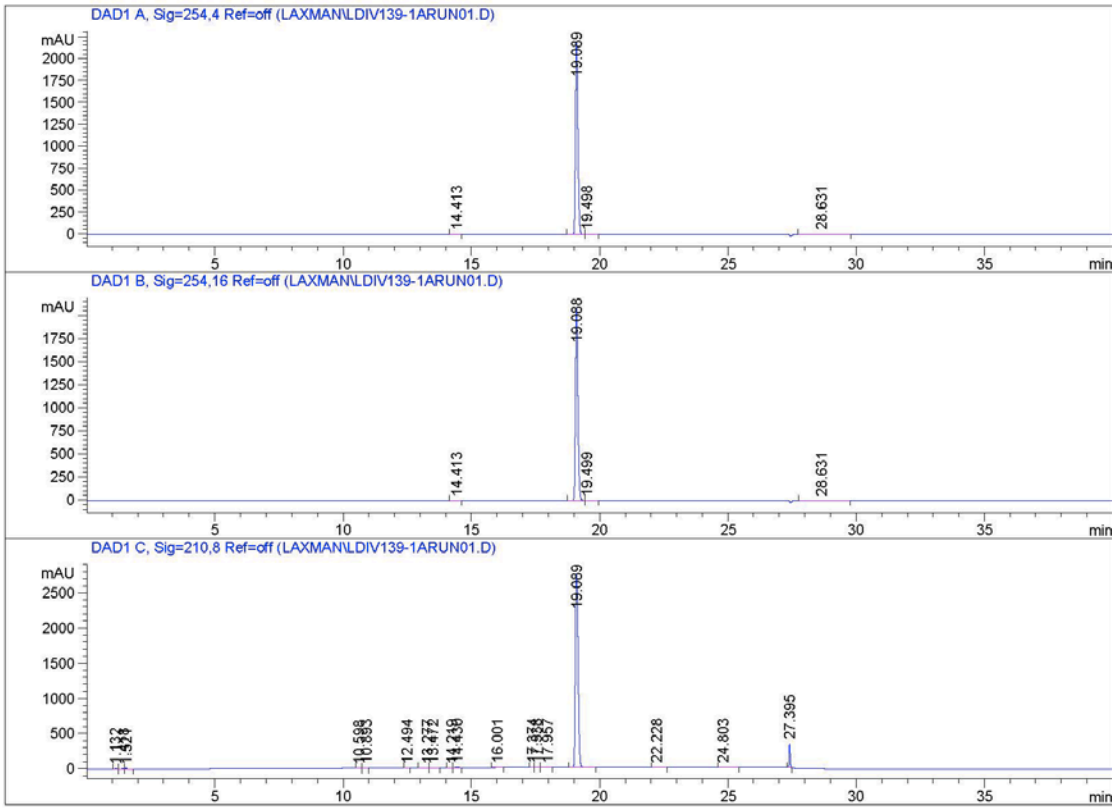
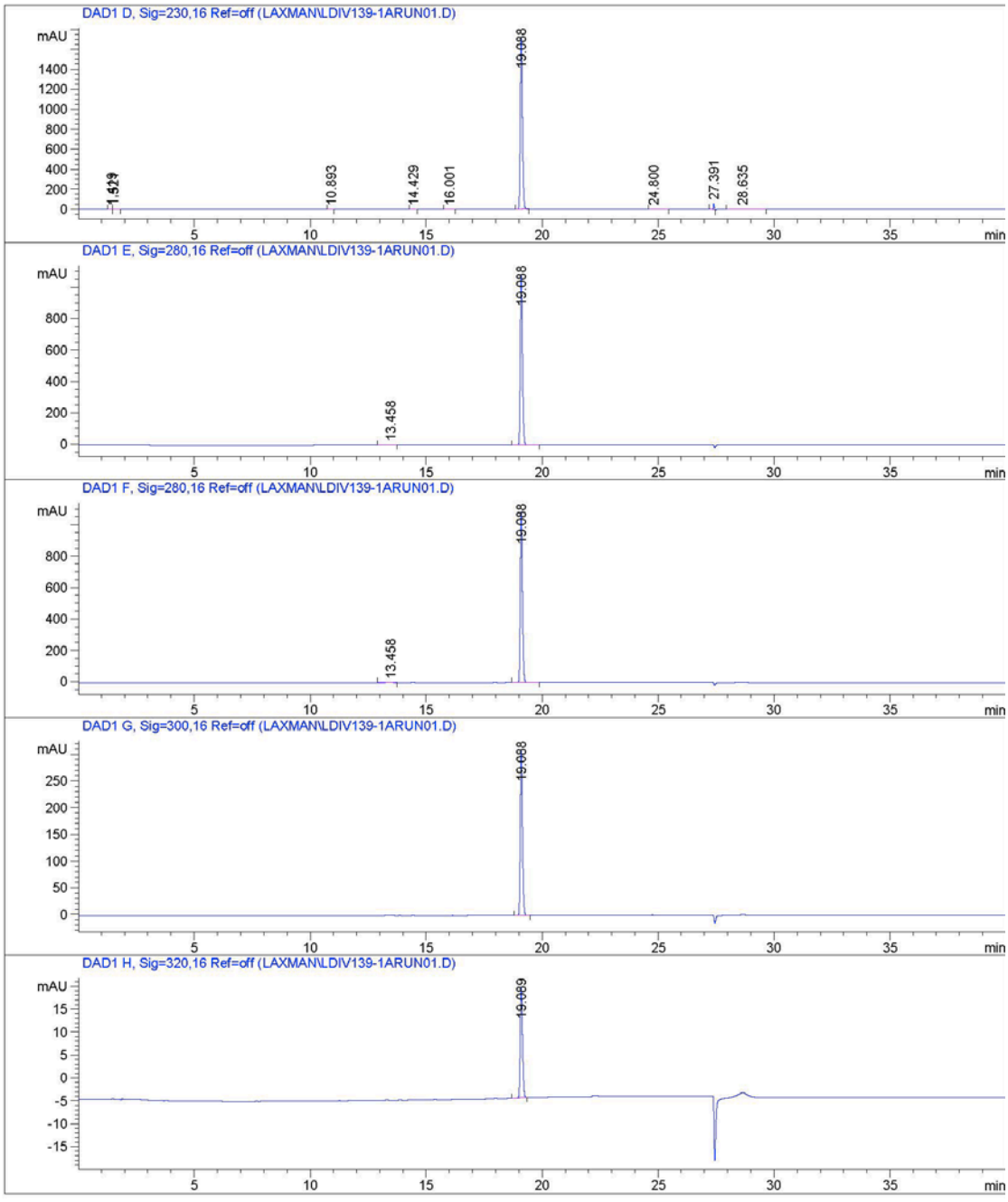


Data File C:\CHEM32\1\DATA\LAXMAN\LDIV139-1ARUN01.D
Sample Name: LD-IV-139-1A-1



Data File C:\CHEM32\1\DATA\LAXMAN\LDIV139-1ARUN01.D
Sample Name: LD-IV-139-1A-1

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.413	BB	0.1604	21.42000	2.07520	0.1499
2	19.089	BV	0.0989	1.41765e4	2207.01196	99.1916
3	19.498	VB	0.1340	18.92470	1.93655	0.1324
4	28.631	BB	0.4860	75.18730	2.19272	0.5261
Totals :				1.42921e4	2213.21642	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.413	BB	0.1601	19.95540	1.93899	0.1477
2	19.088	BV	0.0986	1.34034e4	2097.21265	99.1985
3	19.499	VB	0.1348	17.67035	1.79536	0.1308
4	28.631	BB	0.4580	70.67089	2.11384	0.5230
Totals :				1.35117e4	2103.06084	

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.132	BB	0.0614	14.57730	3.58883	0.0679
2	1.418	BV	0.0759	48.01664	10.02032	0.2238
3	1.521	VB	0.0610	54.63629	13.01121	0.2547
4	10.598	BB	0.0938	8.46140	1.41429	0.0394
5	10.893	BB	0.0874	14.87960	2.57484	0.0694
6	12.494	BB	0.1000	8.76446	1.38110	0.0409
7	13.277	BV	0.1336	24.42828	2.55433	0.1139
8	13.472	VV	0.2102	32.02443	2.02785	0.1493
9	14.219	BV	0.0878	7.31985	1.29744	0.0341
10	14.430	VB	0.1658	35.88203	3.38270	0.1673

Data File C:\CHEM32\1\DATA\LAXMAN\LDIV139-1ARUN01.D
Sample Name: LD-IV-139-1A-1

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
11	16.001	BB	0.1367	17.37272	1.73647	0.0810
12	17.374	BV	0.0930	7.81489	1.32111	0.0364
13	17.538	VB	0.0939	12.18892	1.97756	0.0568
14	17.957	BB	0.1325	13.73361	1.53351	0.0640
15	19.089	BB	0.1154	2.01518e4	2751.83130	93.9339
16	22.228	BB	0.1848	28.84549	2.29175	0.1345
17	24.803	BB	0.1325	21.64288	2.41514	0.1009
18	27.395	BB	0.0445	950.77936	341.76141	4.4319
Totals :				2.14531e4	3146.12117	

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.419	BV	0.0785	8.55047	1.64809	0.0759
2	1.521	VB	0.0891	11.86712	1.79461	0.1053
3	10.893	BB	0.0867	7.44412	1.30266	0.0661
4	14.429	VB	0.1630	15.97235	1.53950	0.1418
5	16.001	BB	0.1503	12.82694	1.16594	0.1138
6	19.088	BB	0.0976	1.09185e4	1729.82043	96.9030
7	24.800	BB	0.1450	15.16185	1.53794	0.1346
8	27.391	BB	0.0488	207.03316	65.66882	1.8374
9	28.635	BB	0.4285	70.09544	2.34659	0.6221
Totals :				1.12674e4	1806.82458	

Signal 5: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.458	BB	0.2502	33.25743	1.77782	0.4806
2	19.088	BB	0.0978	6887.35742	1088.69373	99.5194
Totals :				6920.61486	1090.47154	

Signal 6: DAD1 F, Sig=280,16 Ref=off

Data File C:\CHEM32\1\DATA\LAXMAN\LDIV139-1ARUN01.D
Sample Name: LD-IV-139-1A-1

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.458	BB	0.2502	33.25743	1.77782	0.4806
2	19.088	BB	0.0978	6887.35742	1088.69373	99.5194
Totals :				6920.61486	1090.47154	

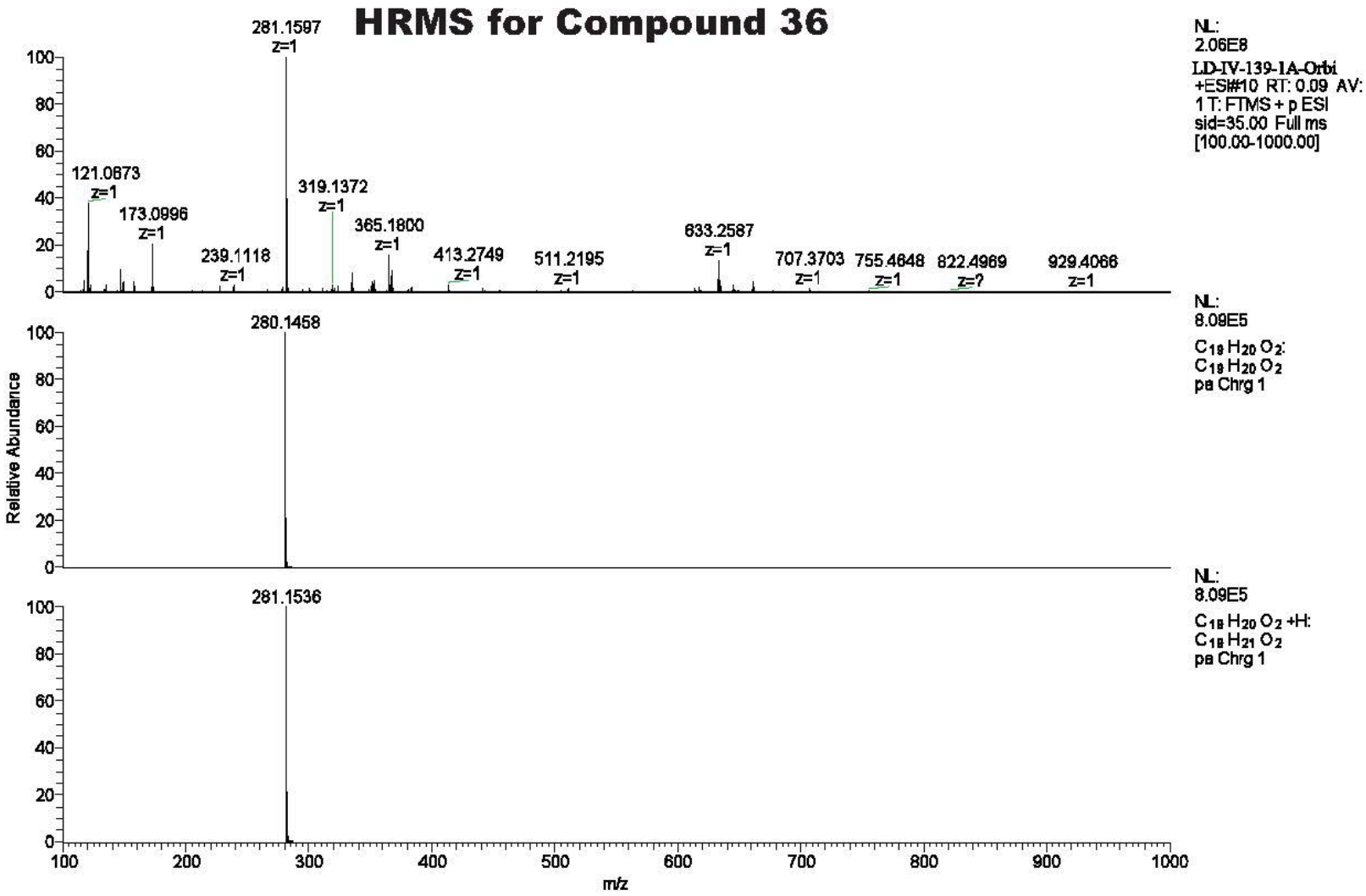
Signal 7: DAD1 G, Sig=300,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.088	BB	0.0978	1975.91748	312.50003	100.0000
Totals :				1975.91748	312.50003	

Signal 8: DAD1 H, Sig=320,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.089	BB	0.1021	162.21338	24.24150	100.0000
Totals :				162.21338	24.24150	

*** End of Report ***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z=1
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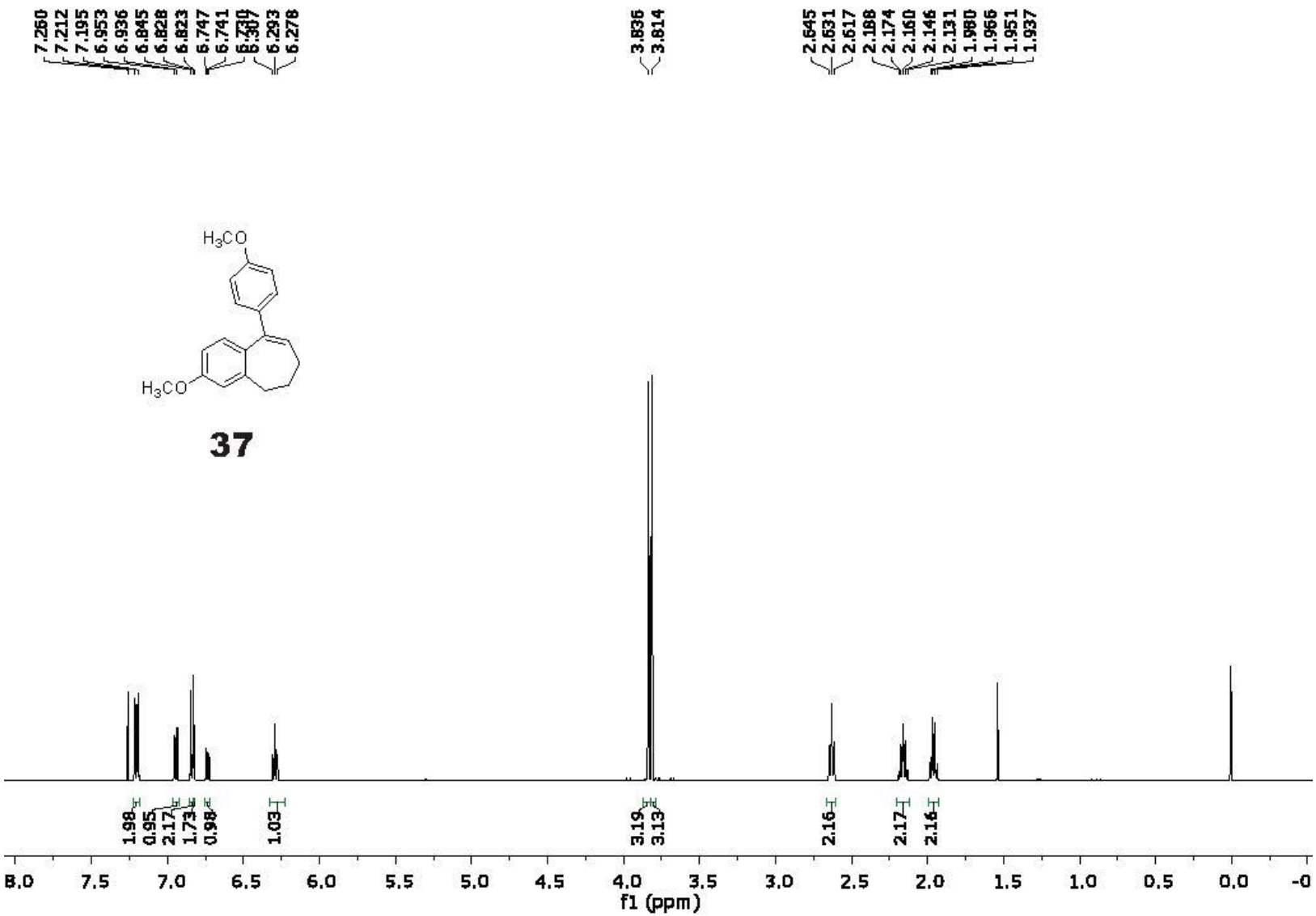
z=1
239.1118
z=1
319.1372
z=1
365.1800
z=1
413.2749
z=1
511.2195
z=1
633.2587
z=1
707.3703
z=1
755.4648
z=1
822.4969
z=?
929.4066
z=1
NL:
2.06E8
LD-IV-139-1A-Orbi
+ESI#10 RT: 0.09 AV:
1 T: FTMS + p ESI
sid=35.00 Full ms
[100.00-1000.00]
280.1458
NL:
8.09E5
C18 H20 O2:
C18 H20 O2
pa Chrg 1
281.1536
NL:
8.09E5
C18 H20 O2 +H:
C18 H21 O2
pa Chrg 1
Relative Abundance
m/z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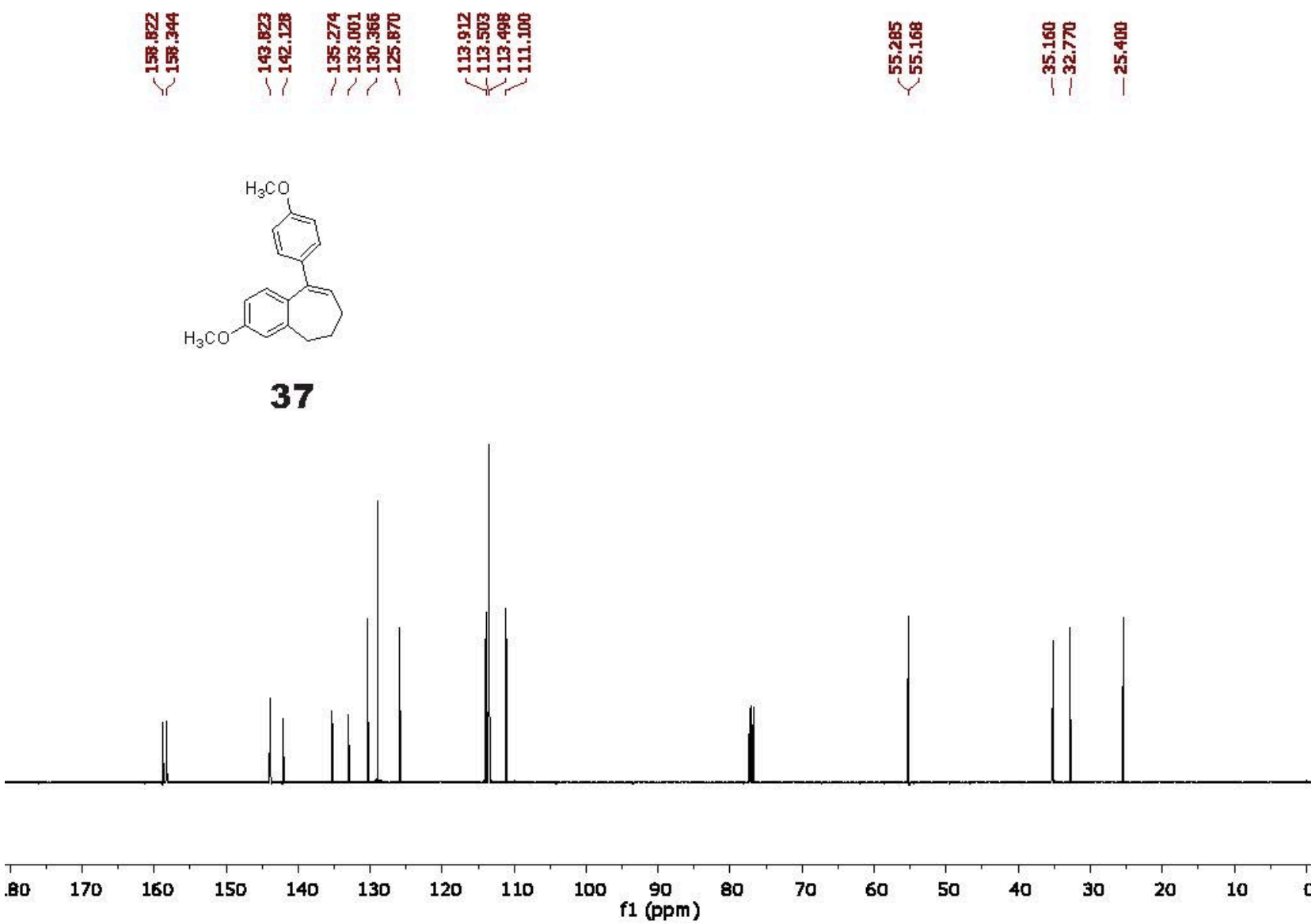
7.195
6.953
6.936
6.845
6.828
6.823
6.747
6.741
6.293
6.278
3.836
3.814
2.645
2.631
2.617
2.188
2.174
2.160
2.146
2.131
1.980
1.966
1.951
1.937
H3CO
H3CO
37
1.98
0.95
2.17
1.73
0.98
1.03
3.19
3.13
2.16
2.17
2.16
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)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125.870
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113.503
113.498
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55.285
55.168
35.160
32.770
25.400
H3CO
H3CO
37
f1 (ppm)

Data File C:\CHEM32\1\DATA\LAXMAN\LDIV137-1A-RUN1.D
Sample Name: LD-IV-137-1A-Run1

HPLC for compound 37

```
==========================================================================
Acq. Operator   : Laxman
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 1/24/2014 4:55:16 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 1/24/2014 4:30:40 PM by Laxman
Analysis Method : C:\CHEM32\1\DATA\LAXMAN\LDIV137-1A-RUN1.D\DA.M (MASTERMETHOD.M)
Last changed    : 1/24/2014 6:21:25 PM by Laxman
Sample Info     : Run1-Mastermethod
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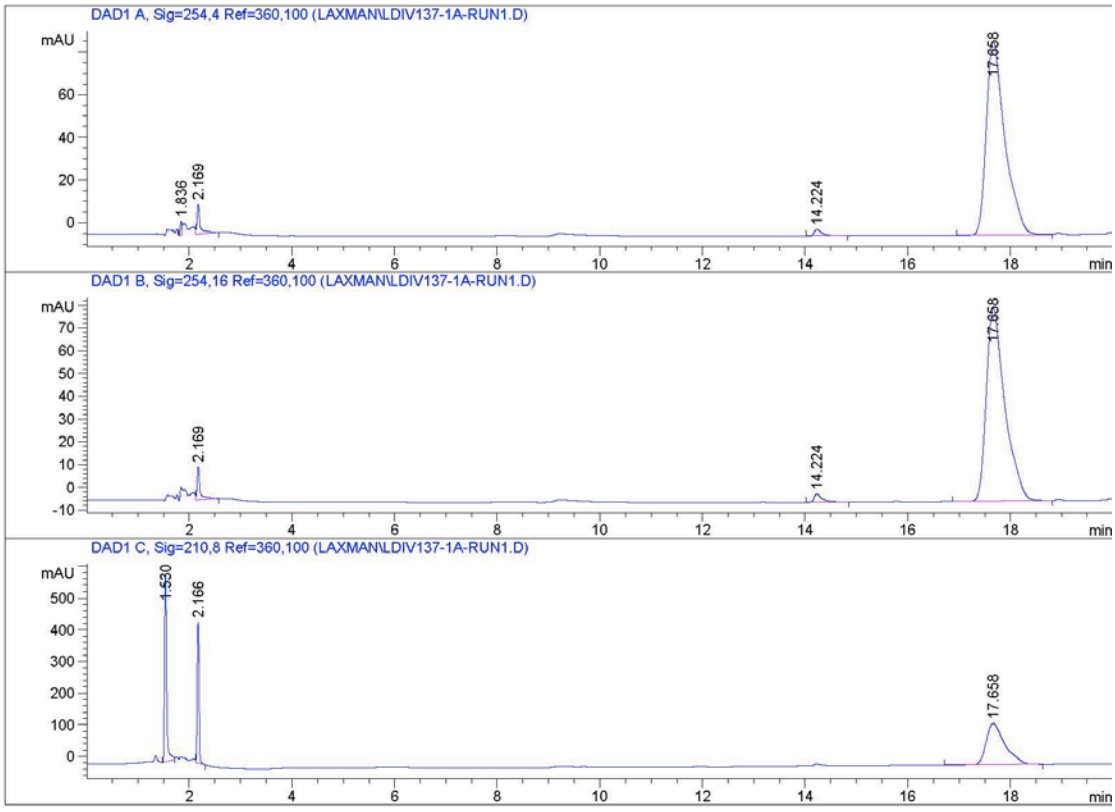
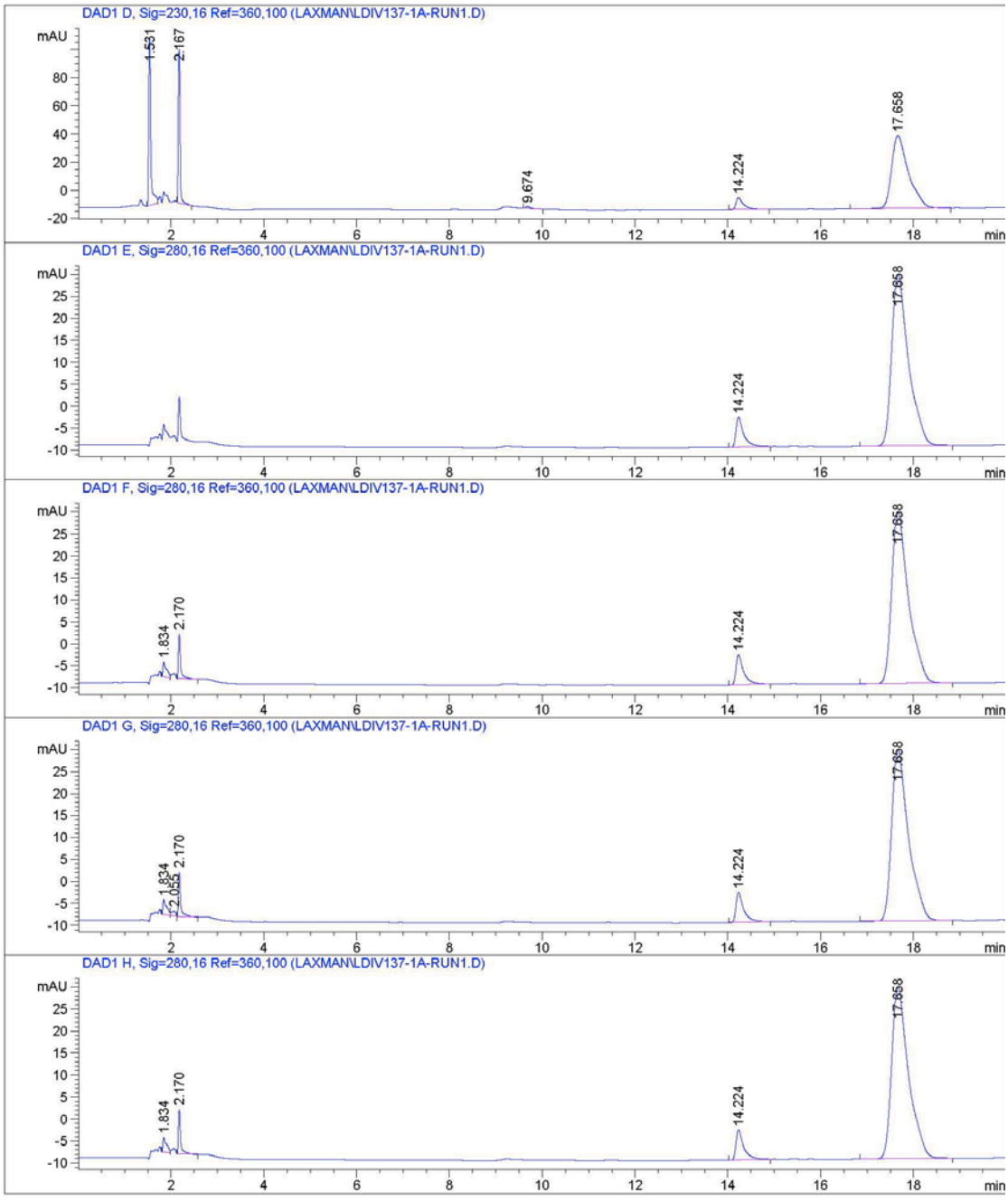


Data File C:\CHEM32\1\DATA\LAXMAN\LDIV137-1A-RUN1.D
Sample Name: LD-IV-137-1A-Run1



Data File C:\CHEM32\1\DATA\LAXMAN\LDIV137-1A-RUN1.D
Sample Name: LD-IV-137-1A-Run1

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.836	BV	0.0409	18.19539	6.45327	0.7590
2	2.169	VB	0.0613	58.36508	13.82253	2.4345
3	14.224	BB	0.1651	36.58915	3.20765	1.5262
4	17.658	BV	0.3693	2284.27368	90.85317	95.2804
Totals :				2397.42330	114.33662	

Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.169	VB	0.0590	58.52003	14.53531	2.6126
2	14.224	BB	0.1630	43.06221	3.77694	1.9225
3	17.658	BV	0.3693	2138.35132	85.04366	95.4649
Totals :				2239.93356	103.35591	

Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.530	BV	0.0460	1748.86523	600.82697	28.3435
2	2.166	VB	0.0416	1125.40662	444.25931	18.2392
3	17.658	BB	0.3717	3295.98486	130.90834	53.4173
Totals :				6170.25671	1175.99461	

Data File C:\CHEM32\1\DATA\LAXMAN\LDIV137-1A-RUN1.D
Sample Name: LD-IV-137-1A-Run1

Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.531	BV	0.0484	378.01849	121.24623	18.1187
2	2.167	VB	0.0430	291.49344	109.53181	13.9715
3	9.674	BB	0.1070	11.05938	1.48353	0.5301
4	14.224	BB	0.1651	97.43915	8.54247	4.6703
5	17.658	BB	0.3736	1308.33740	51.63680	62.7095
Totals :				2086.34786	292.44084	

Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.224	BB	0.1659	78.54280	6.84231	7.4125
2	17.658	BB	0.3691	981.05591	39.04969	92.5875
Totals :				1059.59871	45.89200	

Signal 6: DAD1 F, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.834	BV	0.0789	19.77675	3.44678	1.7756
2	2.170	BB	0.0512	34.41515	10.23419	3.0899
3	14.224	BB	0.1659	78.54280	6.84231	7.0518
4	17.658	BB	0.3691	981.05591	39.04969	88.0826
Totals :				1113.79061	59.57297	

Signal 7: DAD1 G, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.834	BV	0.0789	19.77675	3.44678	1.7652
2	2.055	VB	0.0840	6.56384	1.16043	0.5859
3	2.170	BB	0.0512	34.41515	10.23419	3.0718
4	14.224	BB	0.1659	78.54280	6.84231	7.0105
5	17.658	BB	0.3691	981.05591	39.04969	87.5666

Data File C:\CHEM32\1\DATA\LAXMAN\LDIV137-1A-RUN1.D
Sample Name: LD-IV-137-1A-Run1

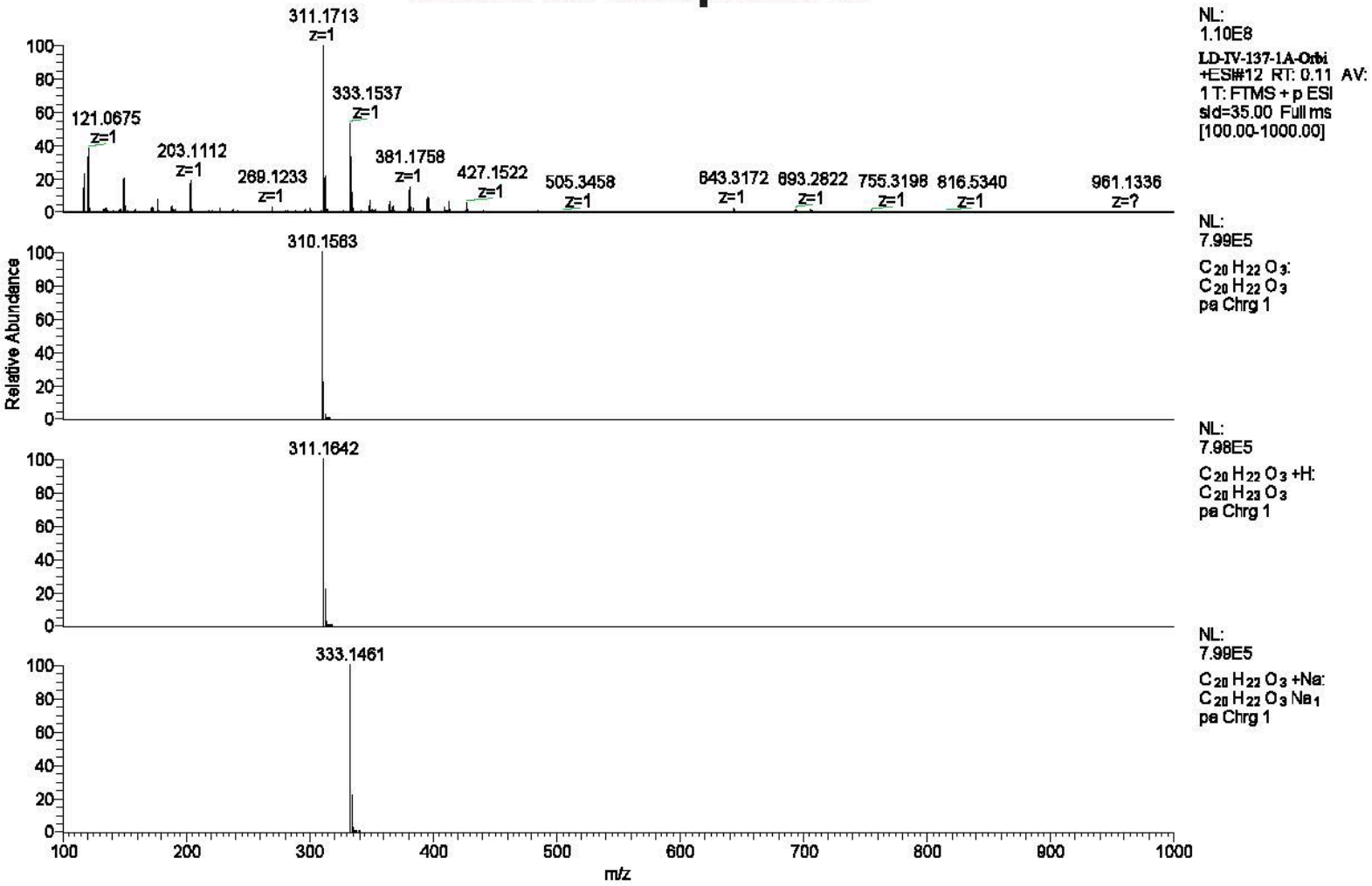
Totals :	1120.35444	60.73339

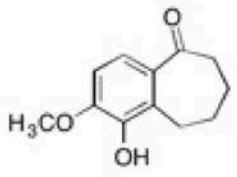
Signal 8: DAD1 H, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.834	BV	0.0789	19.77675	3.44678	1.7756
2	2.170	BB	0.0512	34.41515	10.23419	3.0899
3	14.224	BB	0.1659	78.54280	6.84231	7.0518
4	17.658	BB	0.3691	981.05591	39.04969	88.0826
Totals :				1113.79061	59.57297	

*** End of Report ***

HRMS for compound 37

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H3CO
OH

38


7.250
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2.925
2.911
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1.710
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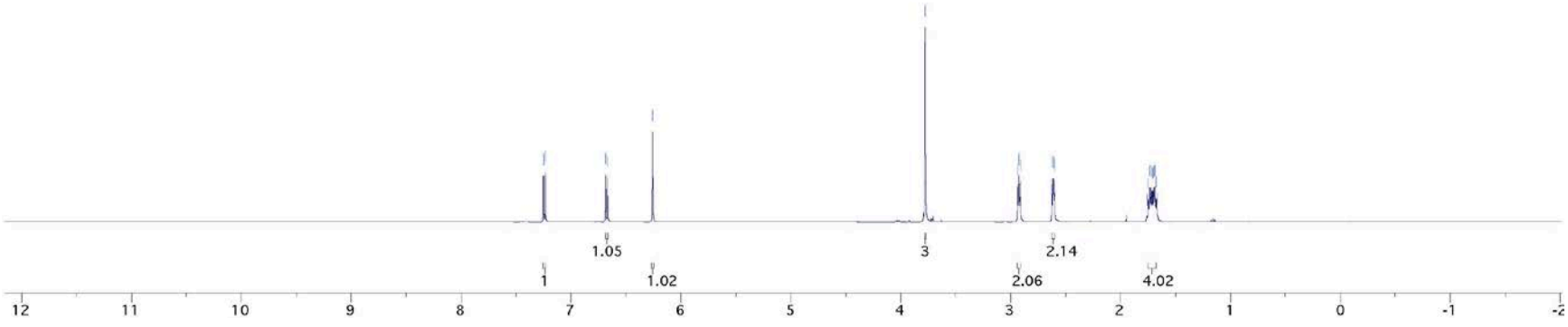
1.663


1.05
3
2.14
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4.02
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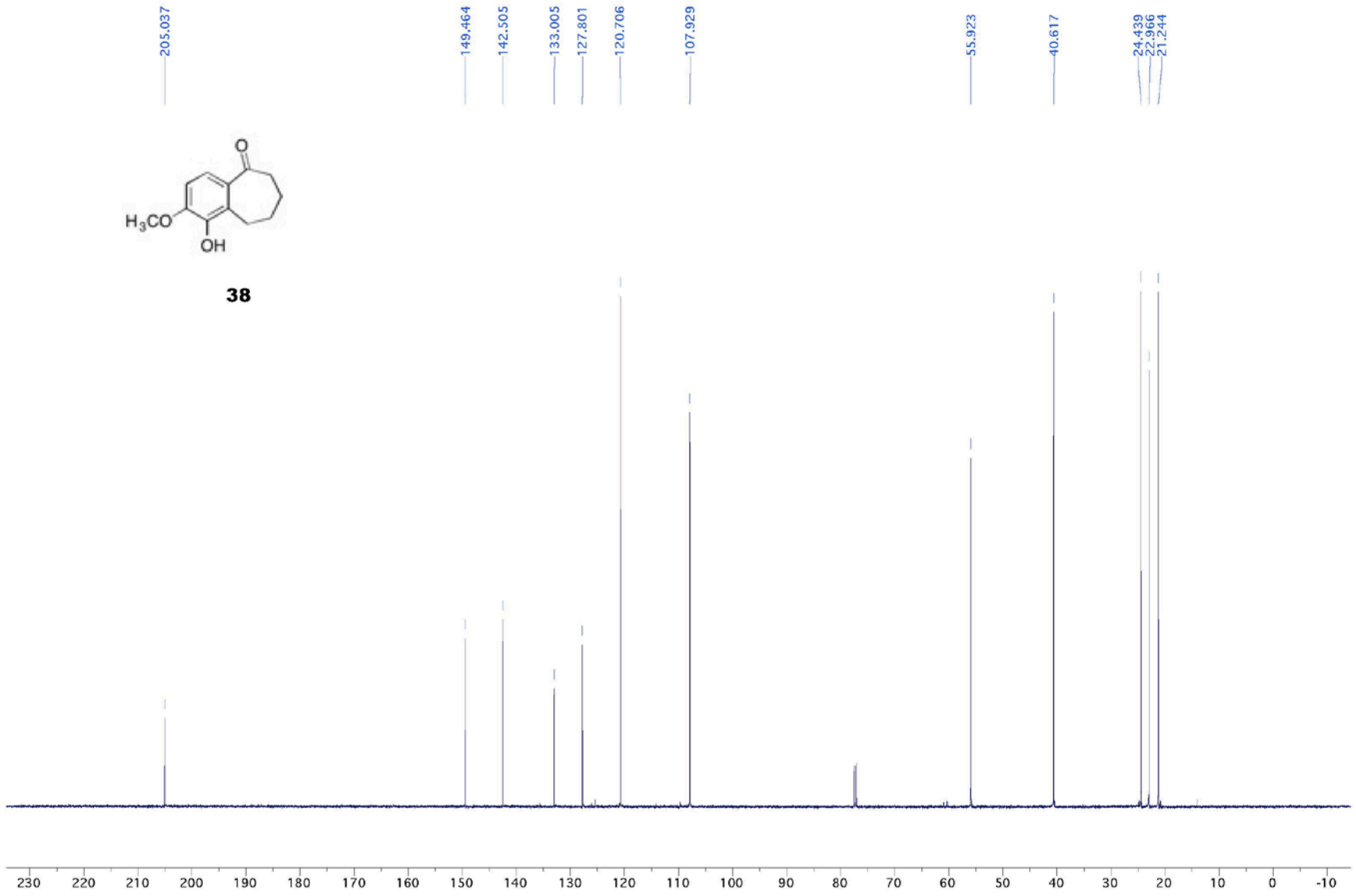
11
10
9
8
7
6
5
4
3
2
1
0
-1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127.801
120.706
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55.923
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24.439
22.966
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O
H3CO
OH
38
230
220
210
200
190
180
170
160
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120
110
100
90
80
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60
50
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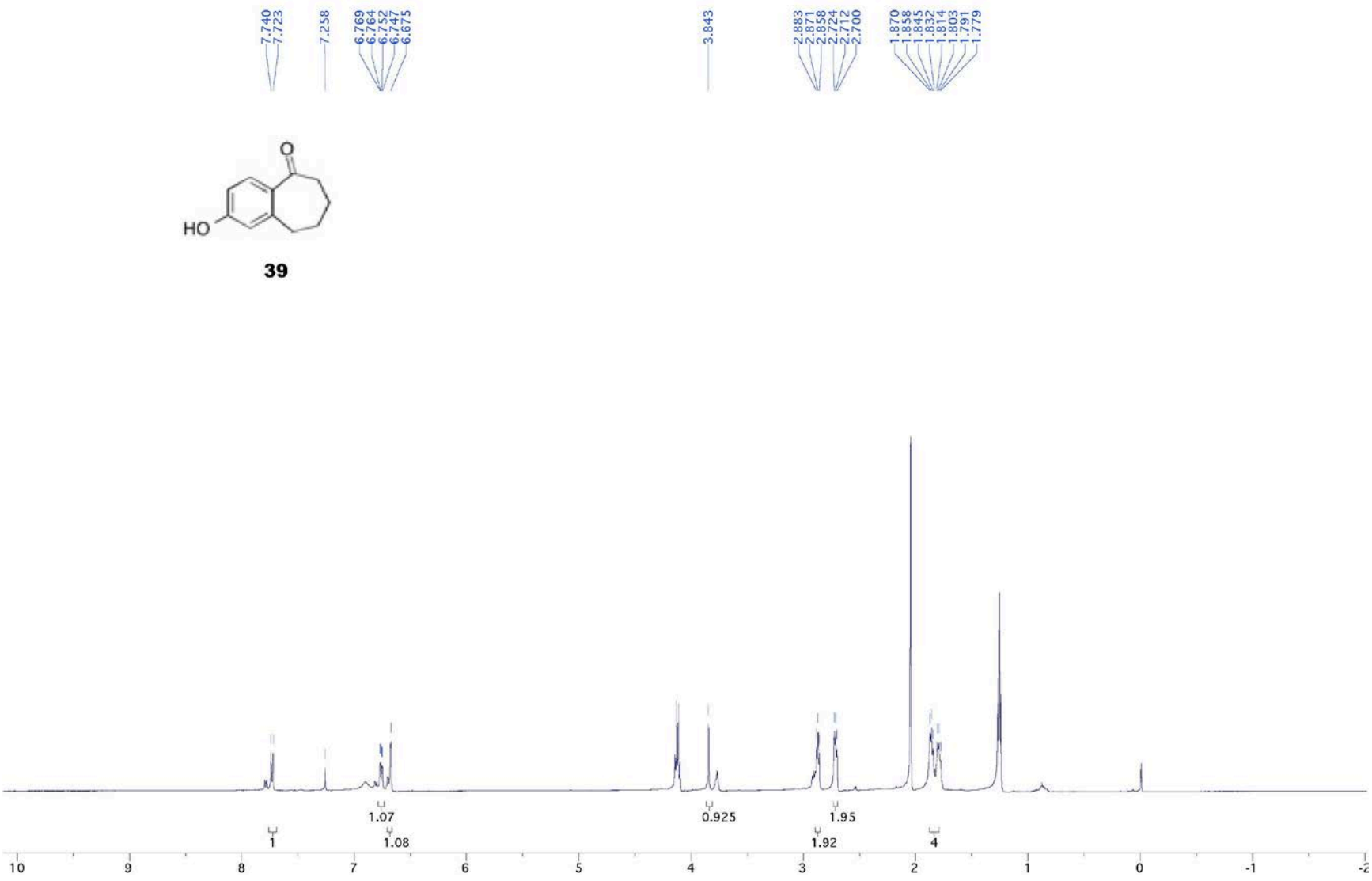
30
20
10
0
-10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6.769
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2.883
2.871
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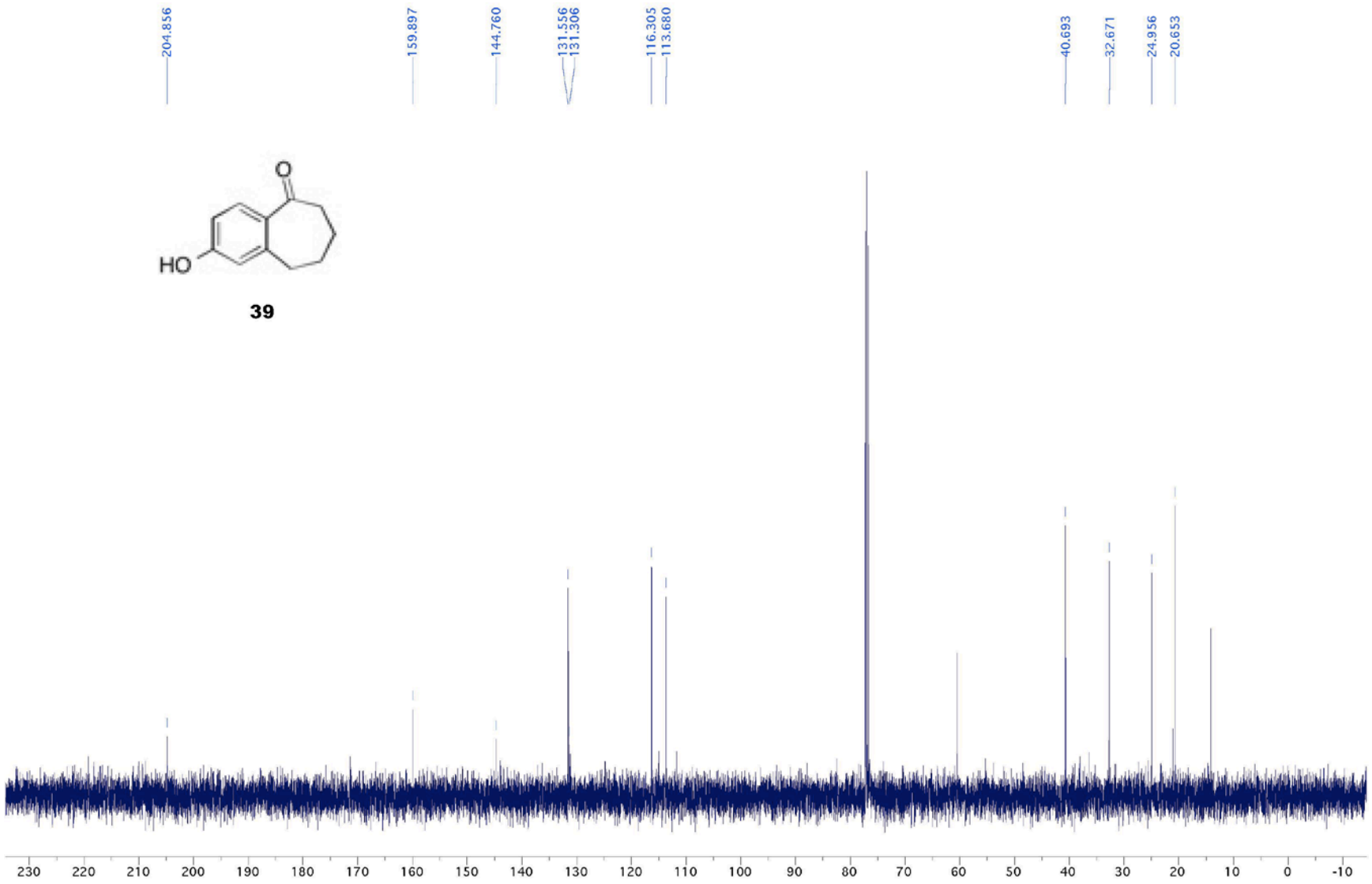
2.712
2.700
1.870
1.858
1.845
1.832
1.814
1.803
1.791
1.779
O
HO
1.07
0.925
1.95
1
1.08
1.92
4
10
9
8
7
6
5
4
3
2
1
0
-1

39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24.956
20.653
O
HO
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230
220
210
200
190
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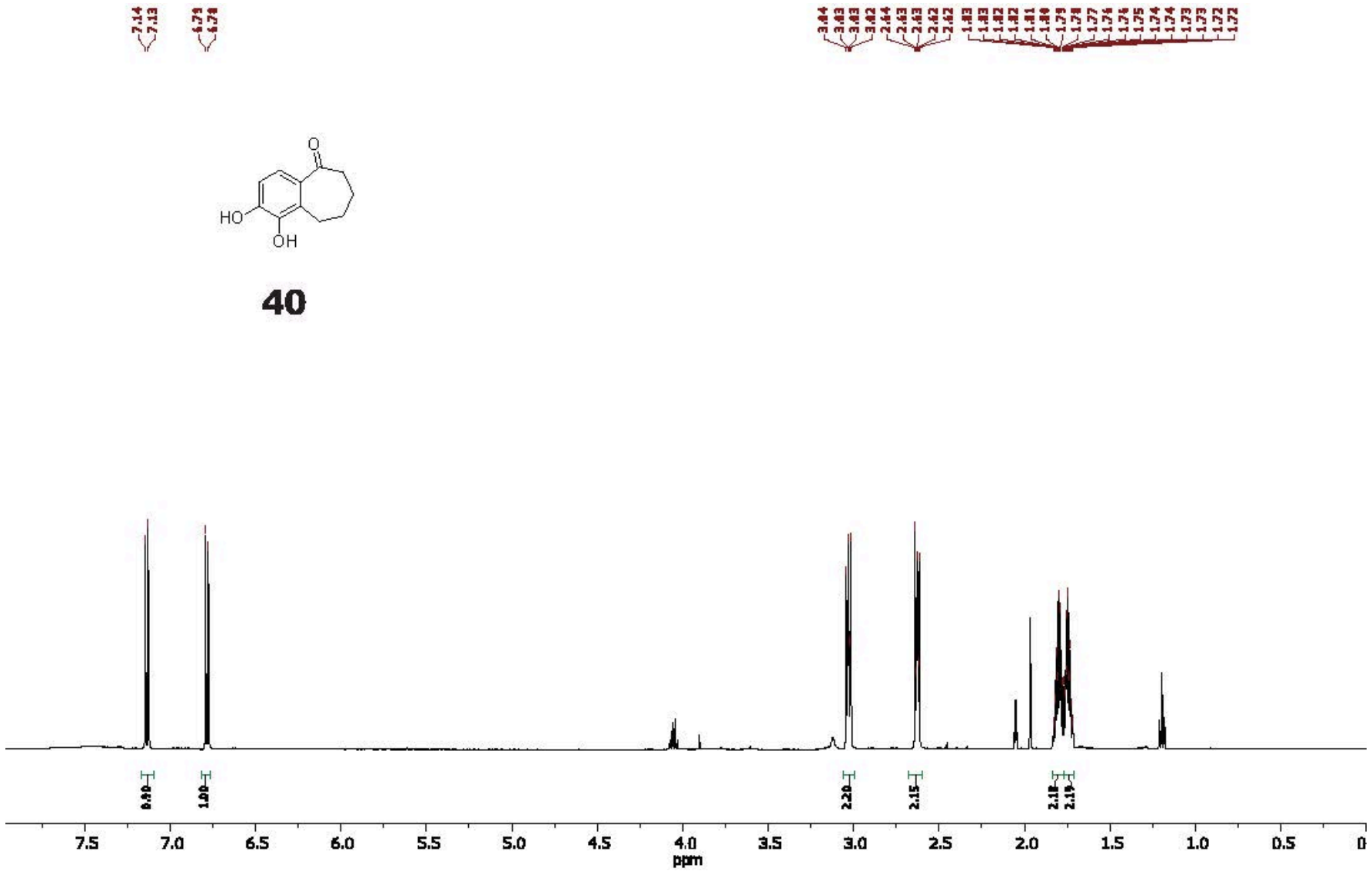
0
-10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1.77
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1.74
1.75
1.74
1.74
1.73
1.73
1.72
1.72
O
HO
OH
40
0.99
1.00
2.20
2.15
2.18
2.19
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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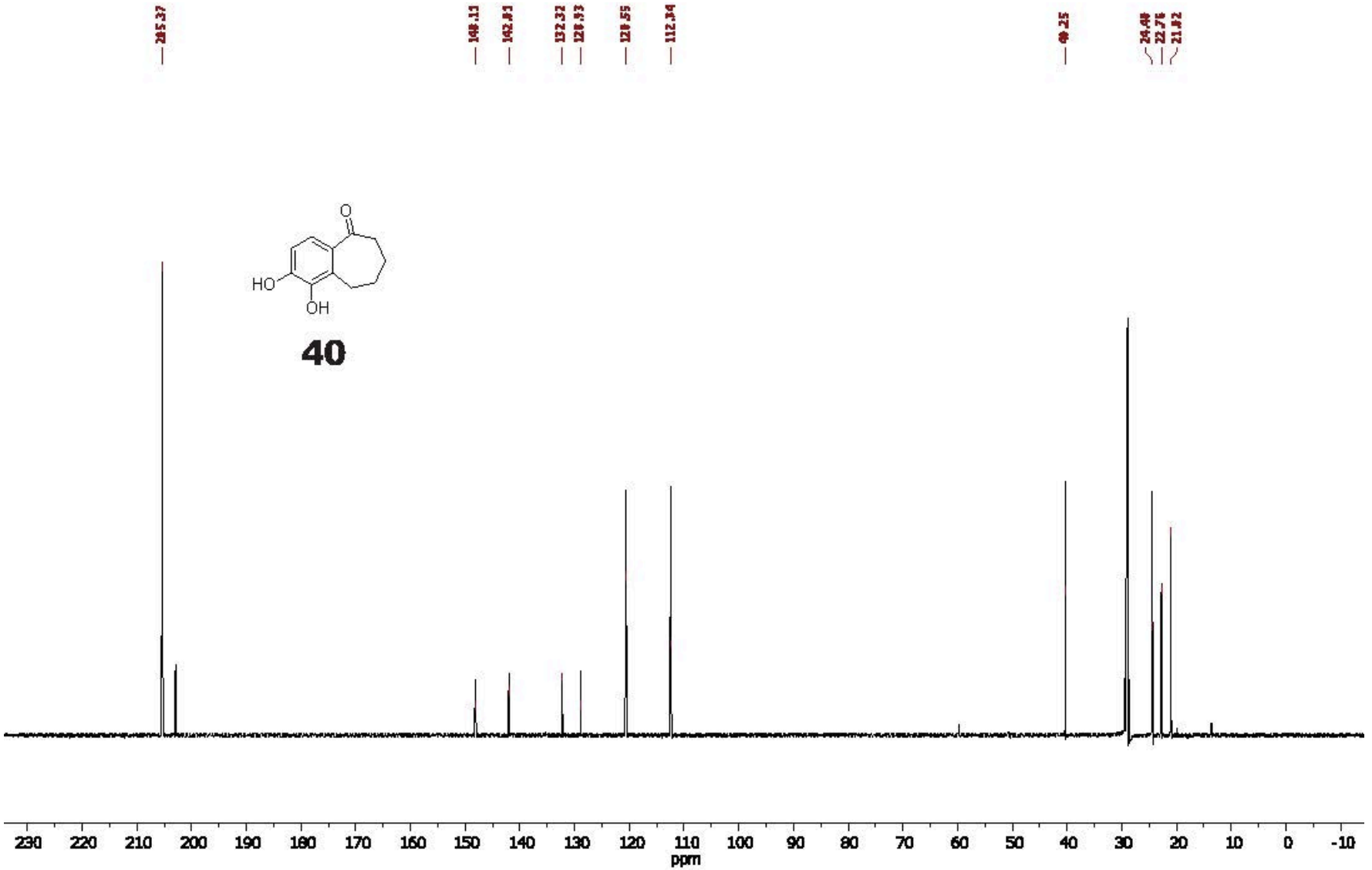
0
ppm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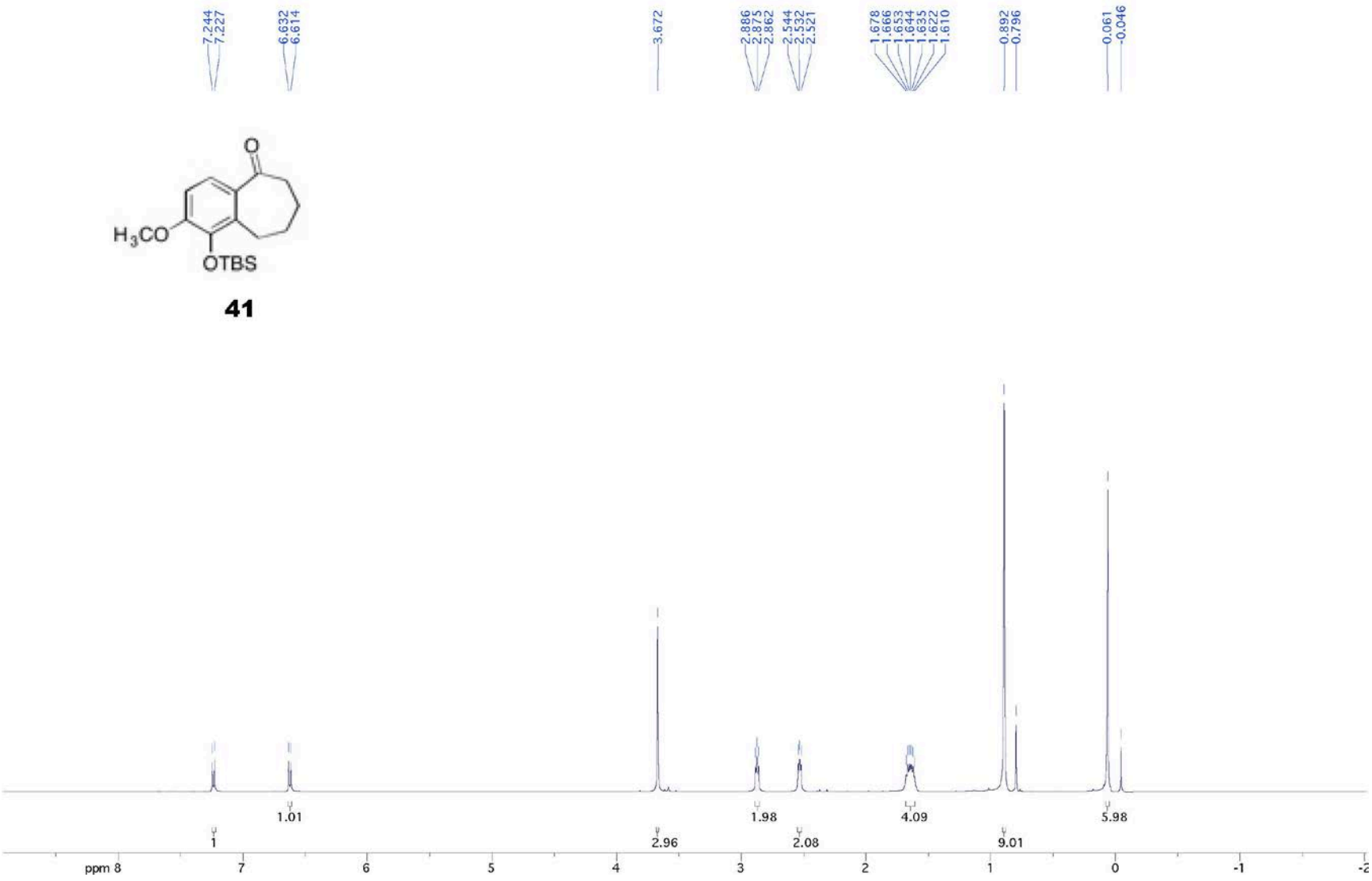
148.11
142.83
132.32
128.53
120.55
112.54
49.25
24.48
22.76
21.82
HO
OH
O
40
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm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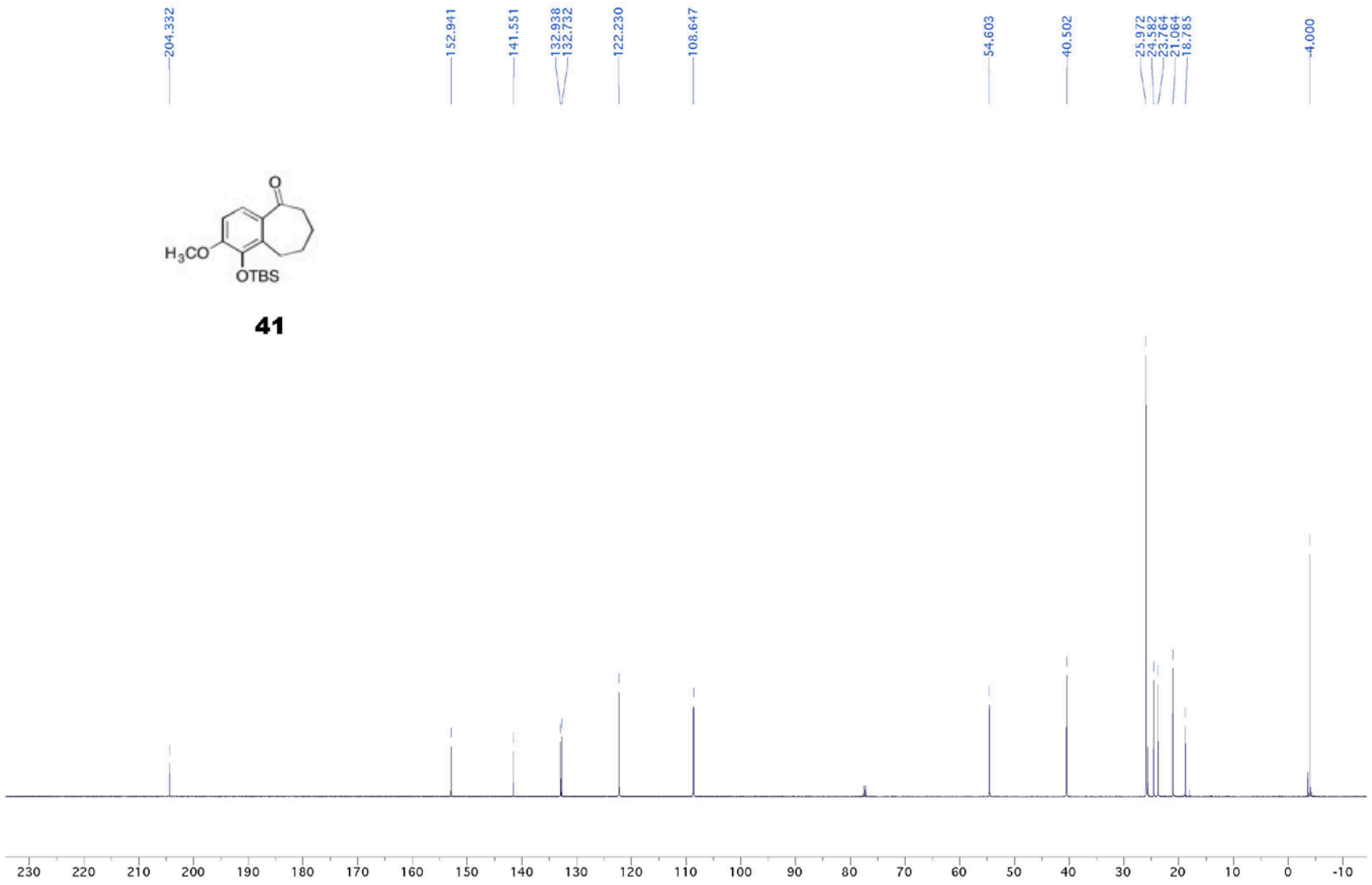
7.227
6.632
6.614
3.672
2.886
2.875
2.862
2.544
2.532
2.521
1.678
1.666
1.653
1.644
1.635
1.622
1.610
0.892
0.796
0.061
-0.046
O
H3CO
OTBS
41
1.01
1.98
4.09
5.98
1
2.96
2.08
9.01
ppm 8
7
6
5
4
3
2
1
0
-1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152.941
141.551
132.938
132.732
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108.647
54.603
40.502
25.972
24.582
23.764
21.064
18.785
4.000
O
H3CO
OTBS
41
230
220
210
200
190
180
170
160
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140
130
120
110
100
90
80
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60
50
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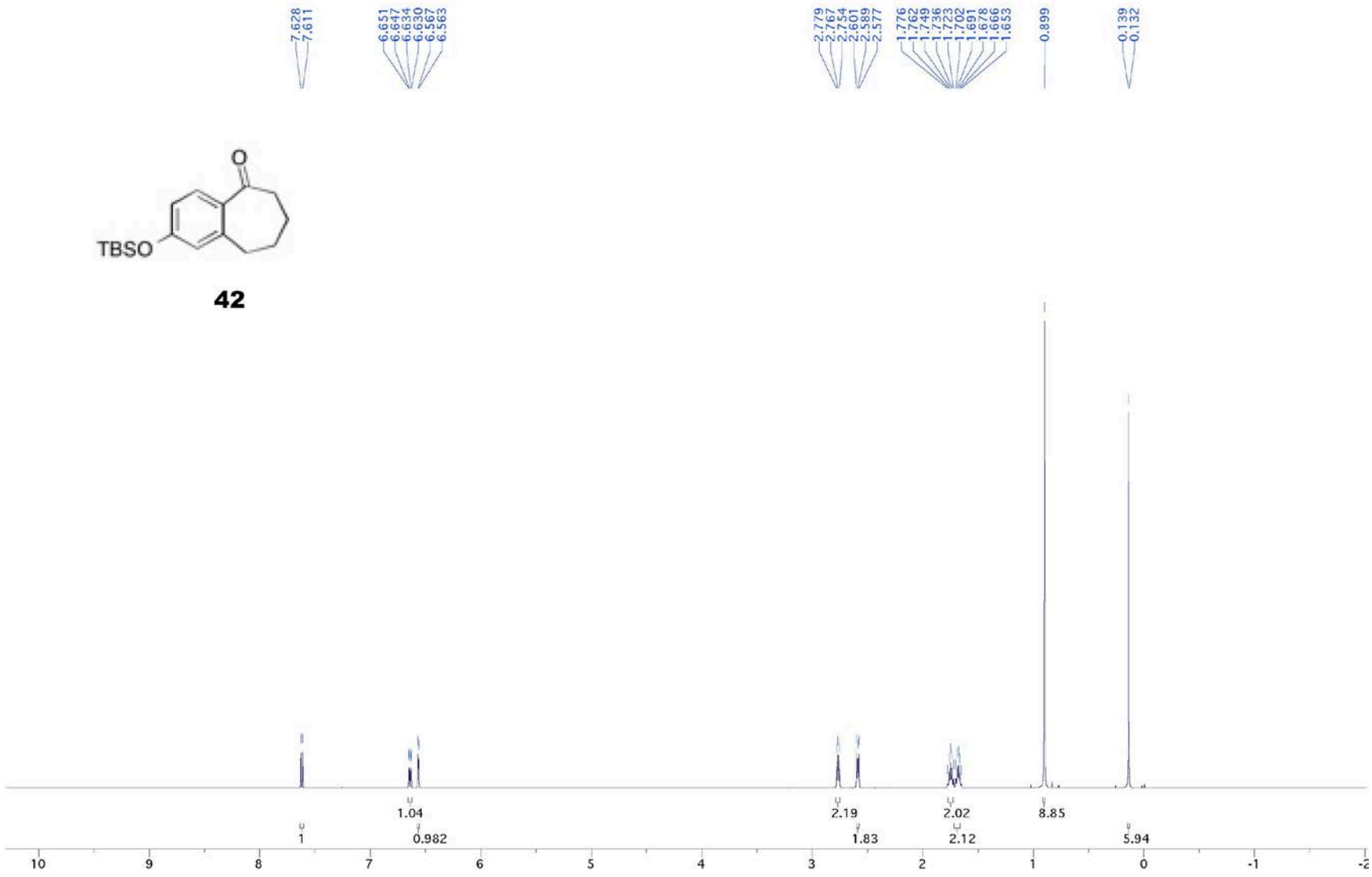
10
0
-10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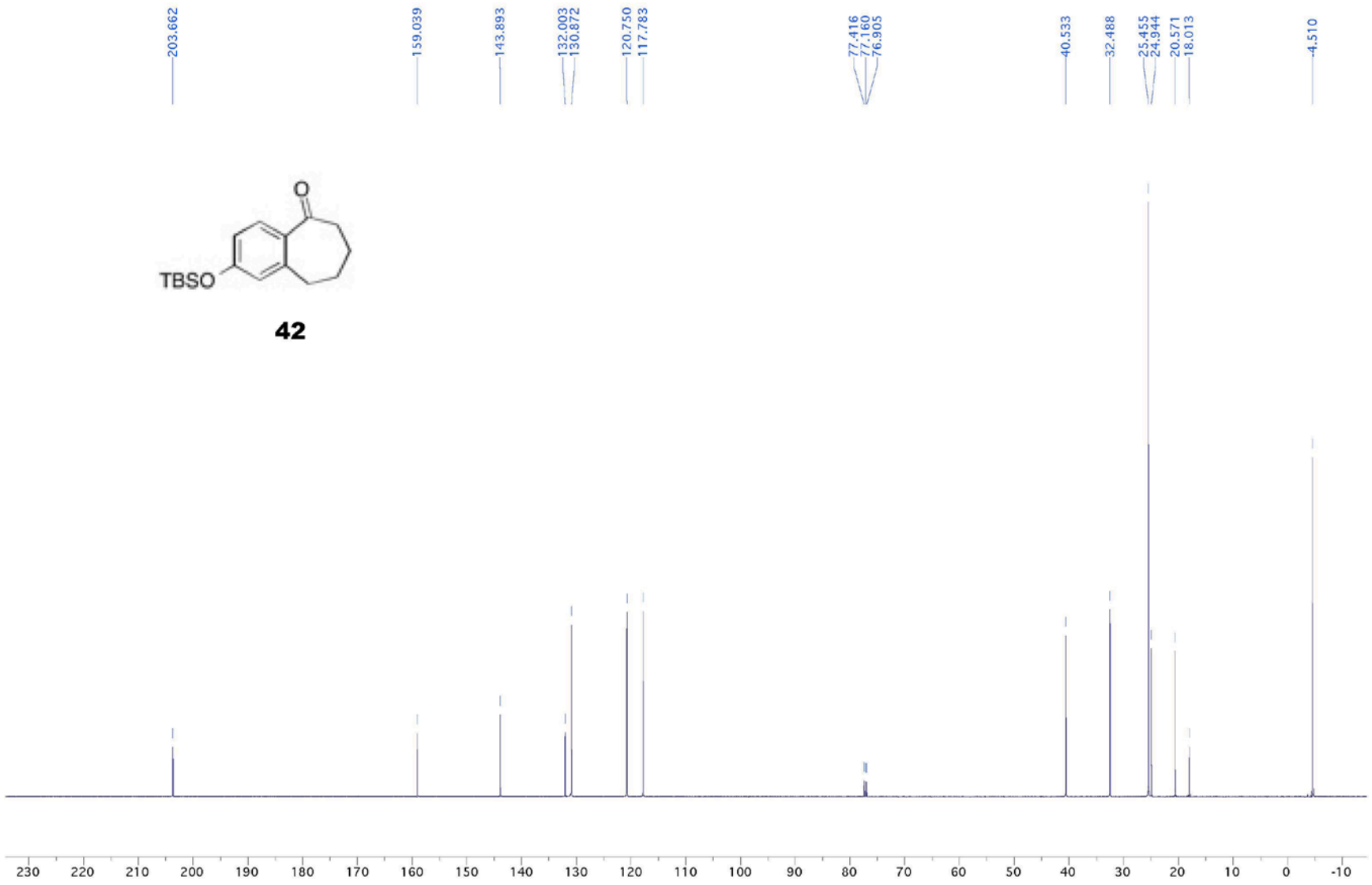
7.611
6.651
6.647
6.634
6.630
6.567
6.563
2.779
2.767
2.754
2.601
2.589
2.577
1.776
1.762
1.749
1.736
1.723
1.702
1.691
1.678
1.666
1.653
0.899
0.139
0.132
O
TBSO
42
1.04
0.982
2.19
1.83
2.02
2.12
8.85
5.94
10
9
8
7
6
5
4
3
2
1
0
-1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143.893
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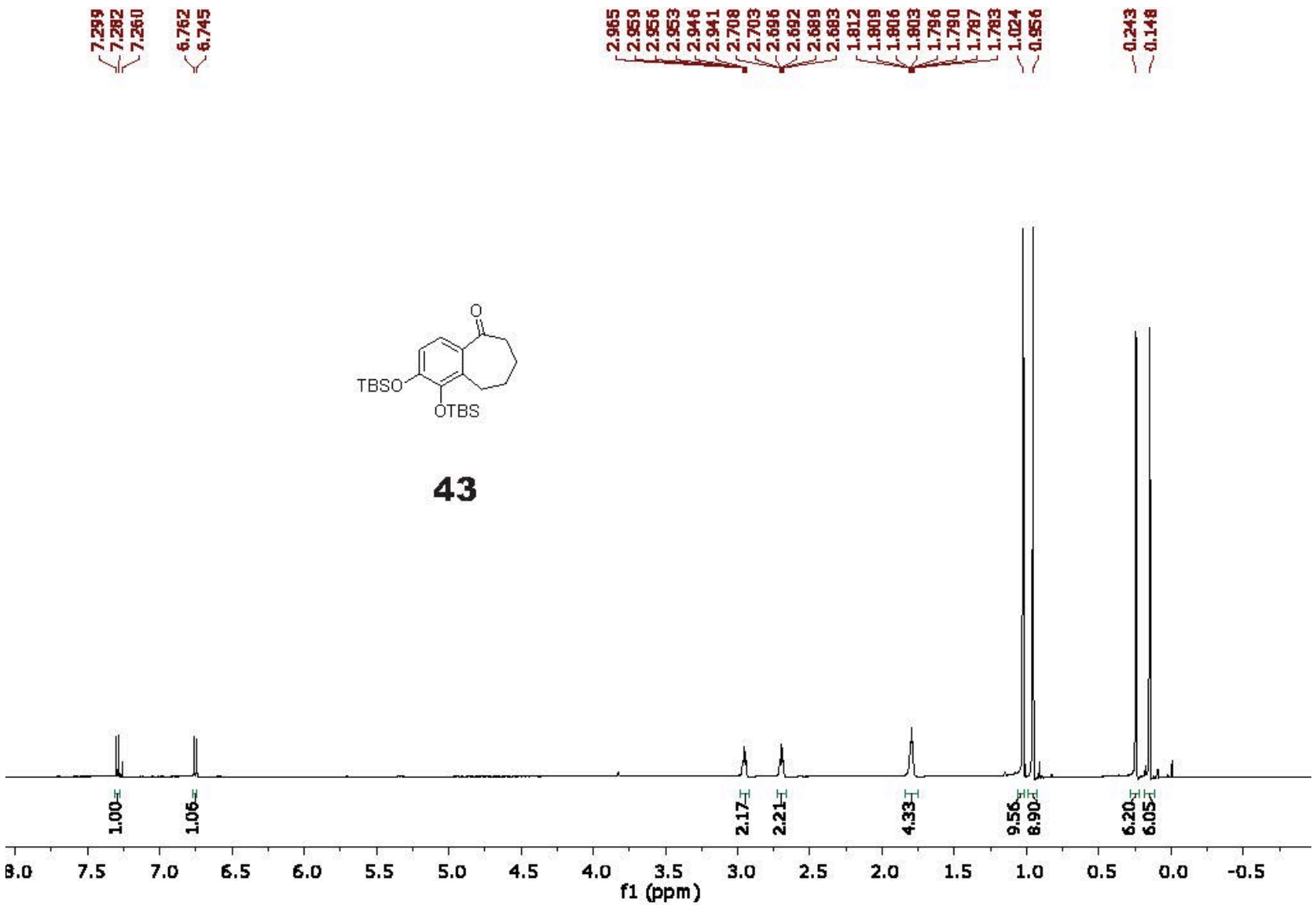
130.872
120.750
117.783
77.416
77.160
76.905
40.533
32.488
25.455
24.944
20.571
18.013
-4.510
O
TBSO
42
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10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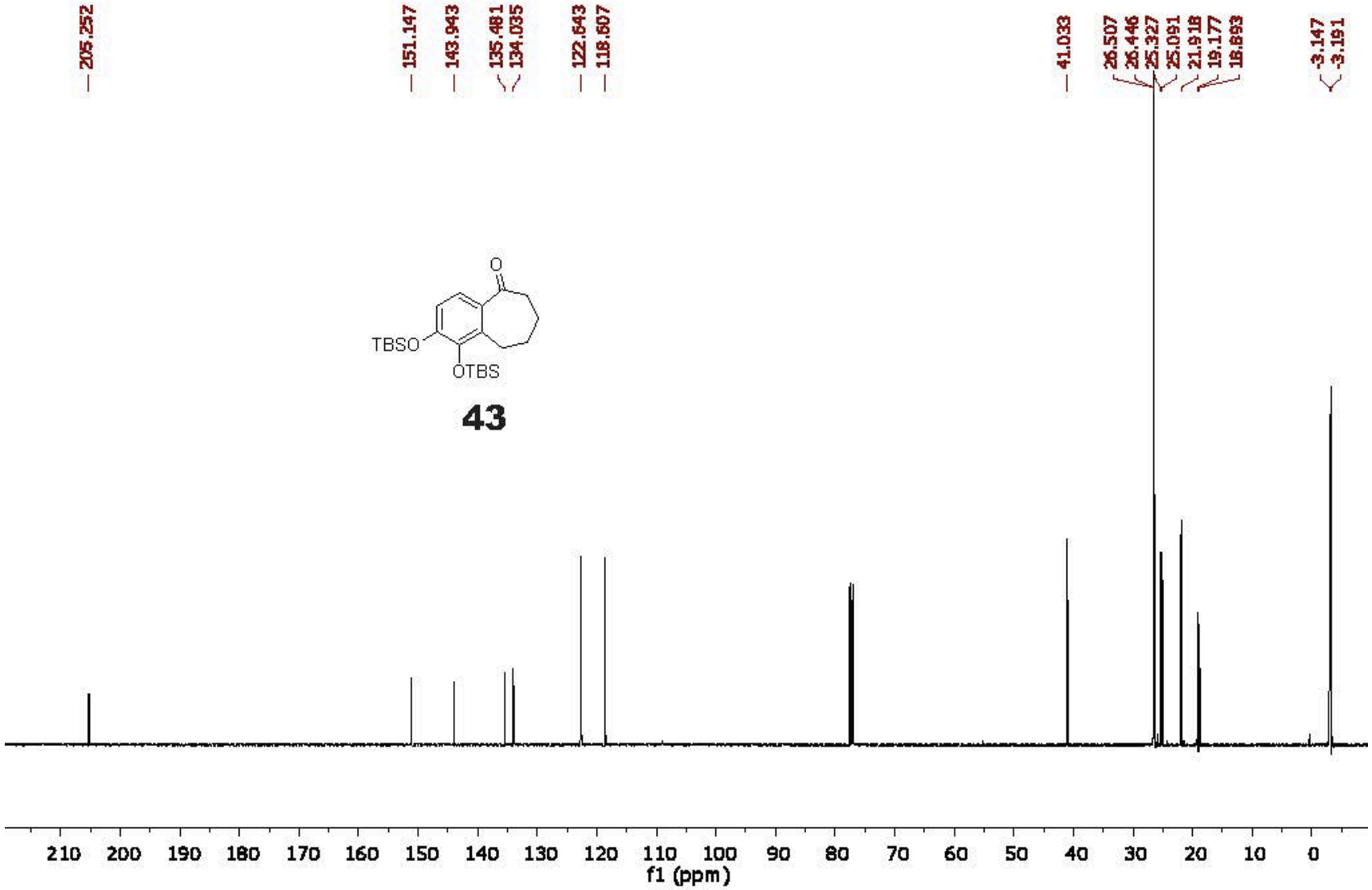
7.282
7.260
6.762
6.745
2.965
2.959
2.956
2.953
2.946
2.941
2.708
2.703
2.696
2.692
2.689
2.683
1.812
1.809
1.806
1.803
1.796
1.790
1.787
1.783
1.024
0.956
0.243
0.148
O
TBSO
OTBS
43
1.00
1.06
2.17
2.21
4.33
9.56
8.90
6.20
6.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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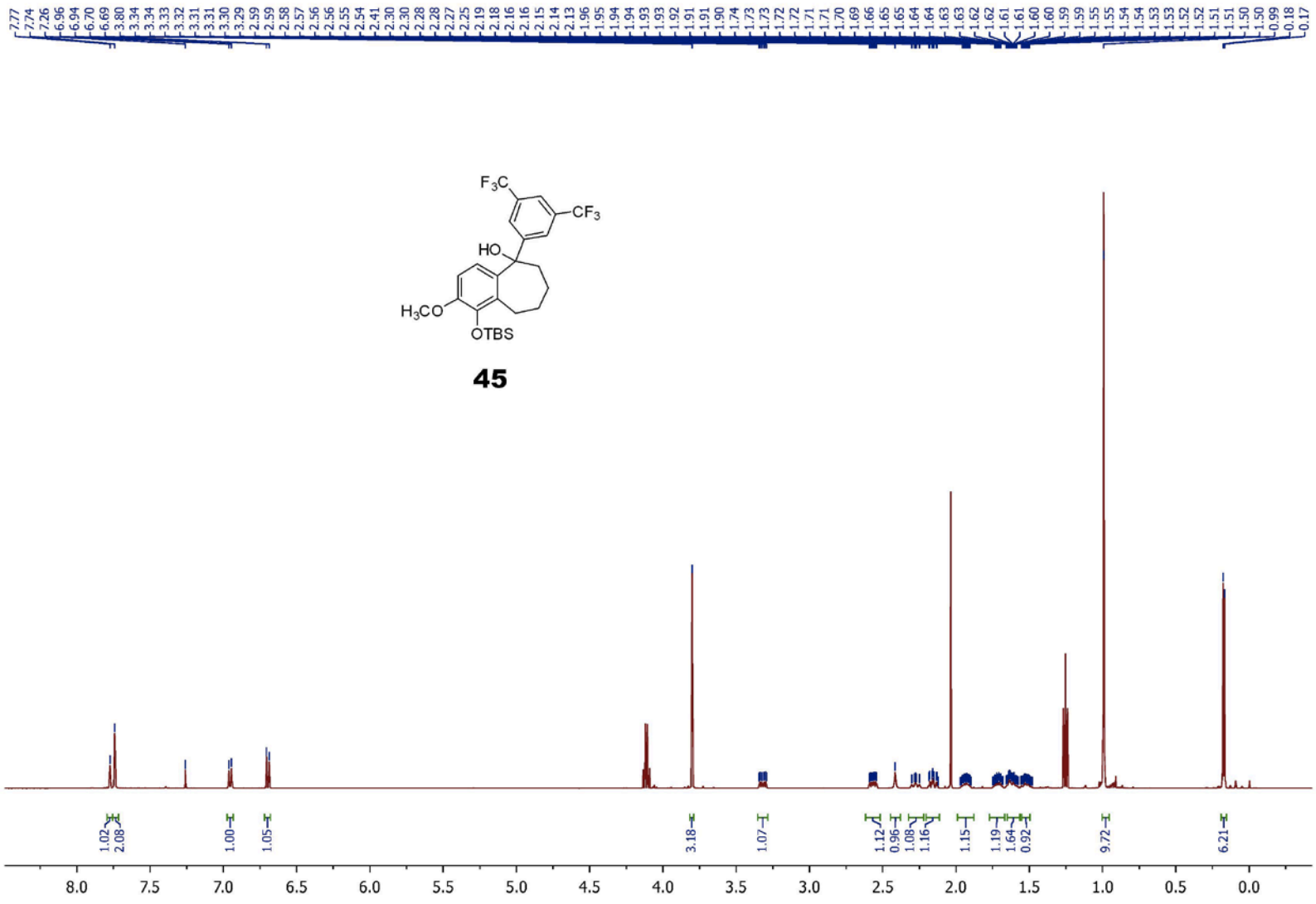
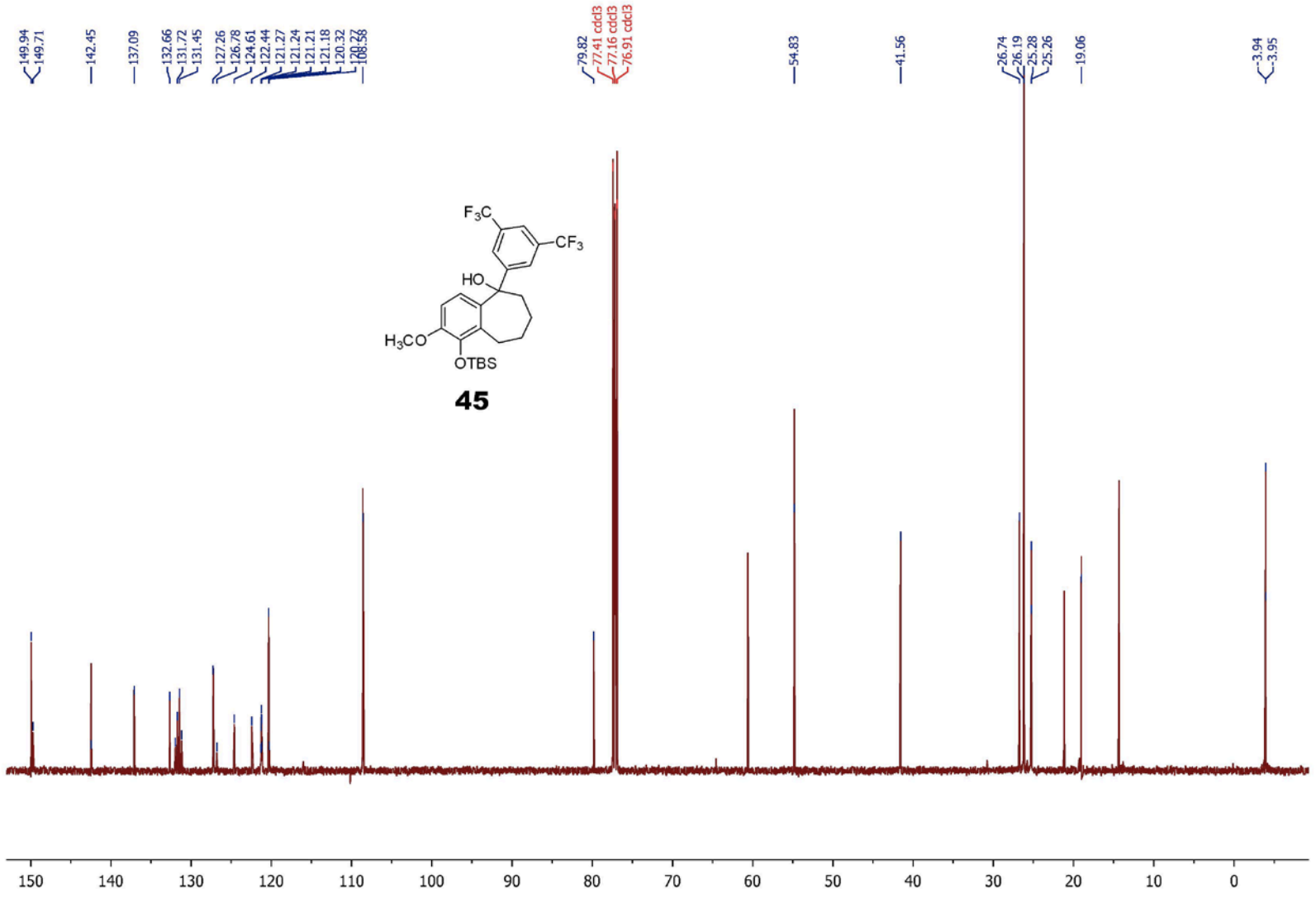
151.147
143.943
135.481
134.035
122.643
118.607
41.033
26.507
26.446
25.327
25.091
21.918
19.177
18.893
-3.147
-3.191
O
TBSO
OTBS
43
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.77 7.74 7.26 6.96 6.94 6.70 6.69 3.80 3.34 3.34 3.33 3.32 3.31 3.31 3.30 3.29 2.59 2.59 2.58 2.57 2.56 2.56 2.55 2.54 2.41 2.30 2.30 2.28 2.28 2.27 2.25 2.19 2.18 2.16 2.16 2.15 2.14 2.13 1.96 1.95 1.94 1.94 1.93 1.93 1.92 1.91 1.91 1.90 1.74 1.73 1.73 1.72 1.72 1.71 1.71 1.70 1.69 1.66 1.65 1.65 1.64 1.64 1.63 1.63 1.62 1.62 1.61 1.61 1.60 1.60 1.59 1.59 1.55 1.55 1.54 1.54 1.53 1.53 1.52 1.52 1.51 1.51 1.50 1.50 0.99 0.18 0.17
F3C
CF3
HO
H3CO
OTBS
45
1.02
2.08
1.00
1.05
3.18
1.07
1.12
0.96
1.08
1.16
1.15
1.19
1.64
0.92
9.72
6.21
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 0.0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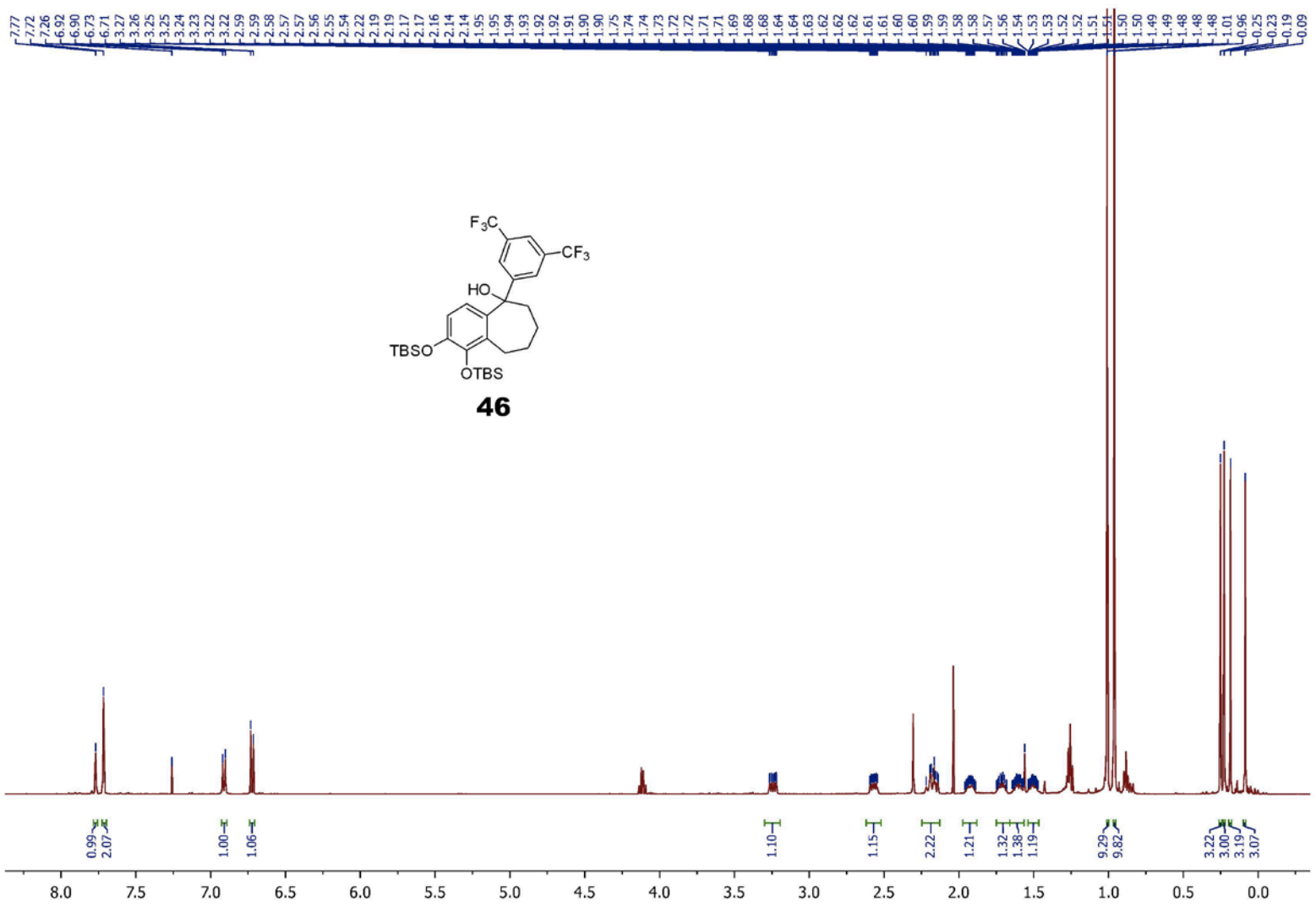
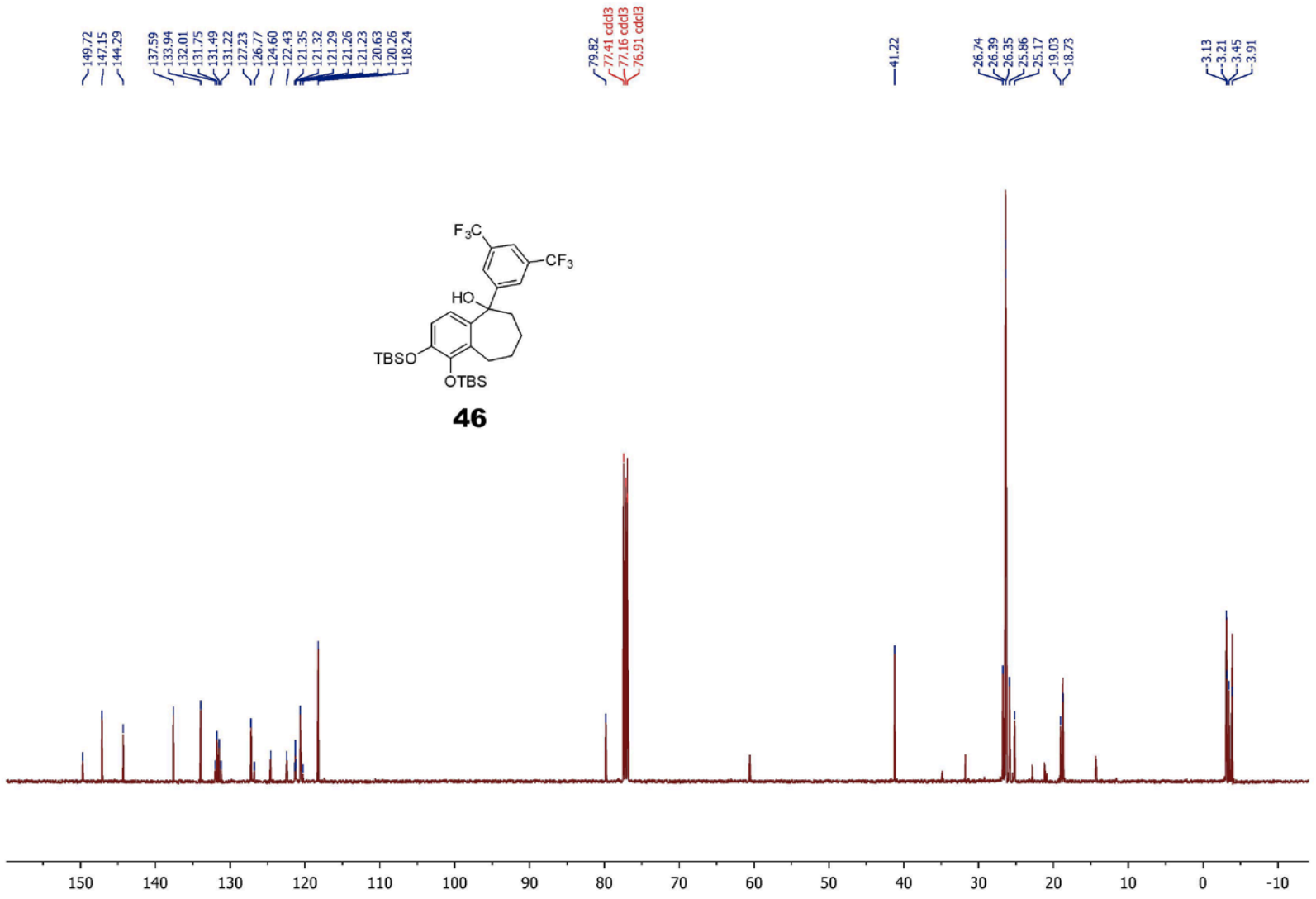
149.71
142.45
137.09
132.66
131.72
131.45
127.26
126.78
124.61
122.44
121.27
121.24
121.21
121.18
120.32
79.82
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
54.83
41.56
26.74
26.19
25.28
25.26
19.06
-3.94
-3.95
F3C
CF3
HO
H3CO
OTBS
45
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


F3C
CF3
HO
TBSO
OTBS
46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144.29
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132.01
131.75
131.49
131.22
127.23
126.77
124.60
122.43
121.35
121.32
121.29
121.26
121.23
120.63
120.26
118.24
79.82
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
41.22
26.74
26.39
26.35
25.86
25.17
19.03
18.73
-3.13
-3.21
-3.45
-3.91
F3C
CF3
HO
TBSO
OTBS
46
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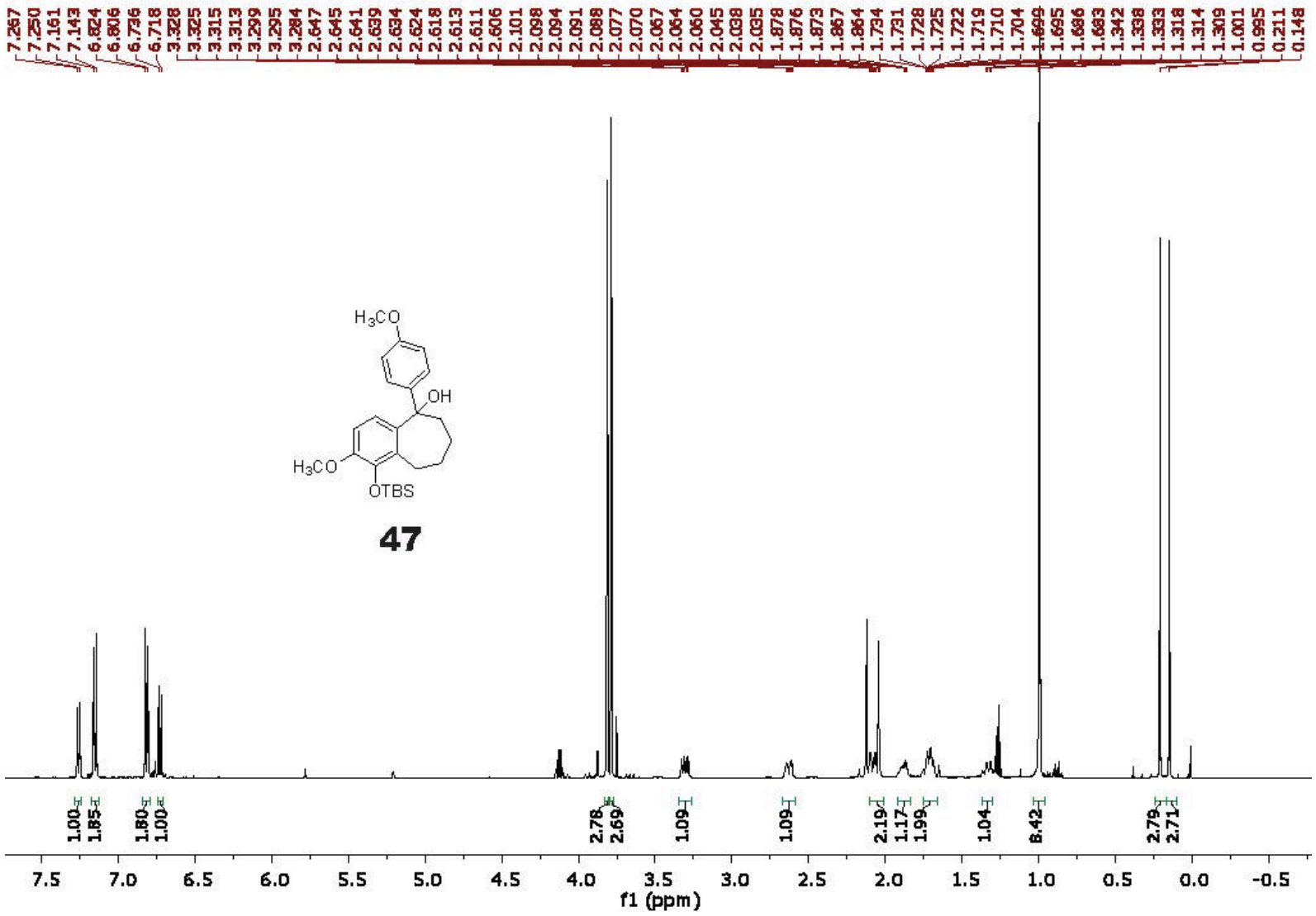
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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6.806
6.736
6.718
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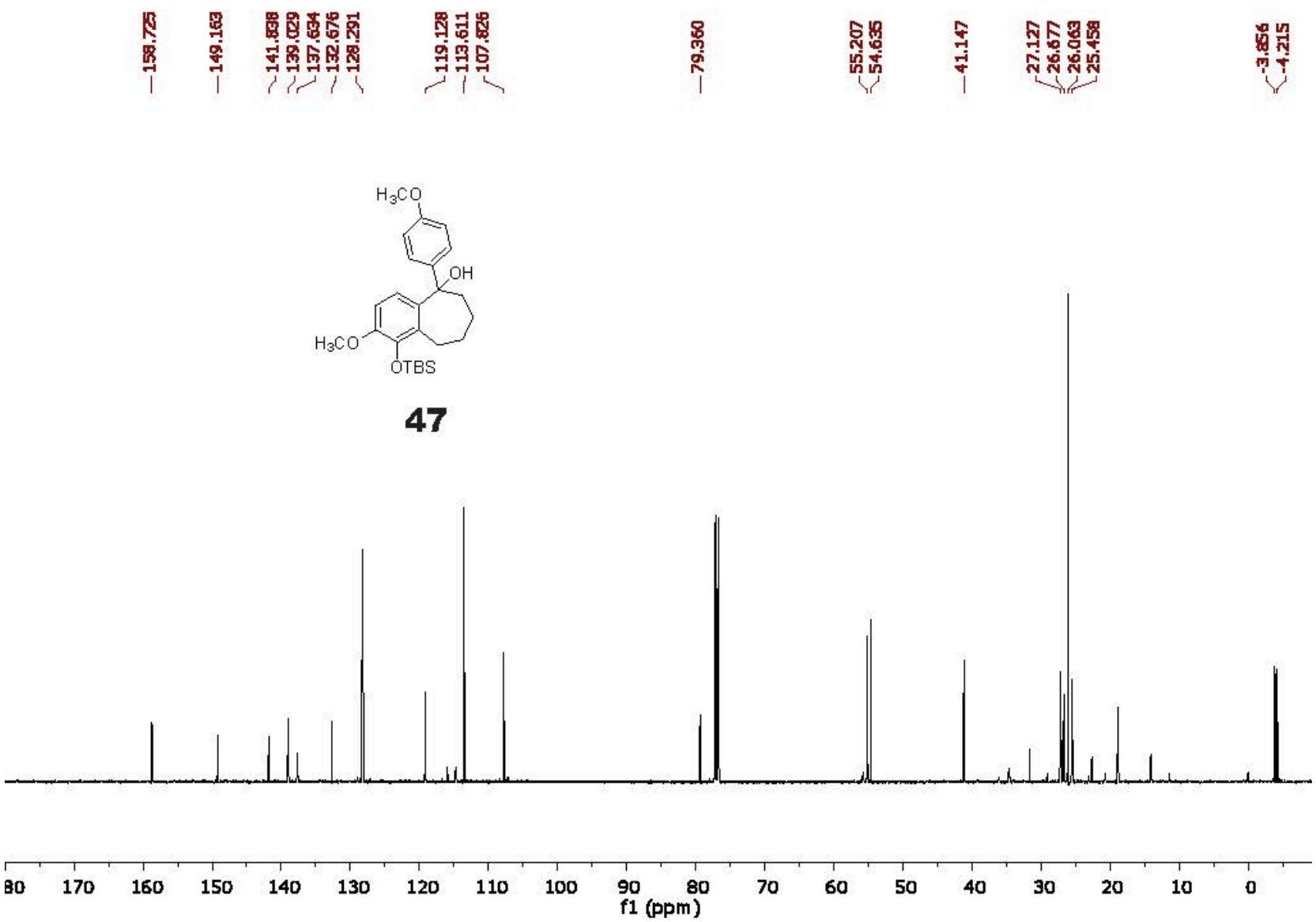
3.325
3.315
3.313
3.299
3.295
3.284
2.647
2.645
2.641
2.639
2.634
2.624
2.618
2.613
2.611
2.606
2.101
2.098
2.094
2.091
2.088
2.077
2.070
2.067
2.064
2.060
2.045
2.038
2.035
1.878
1.876
1.873
1.867
1.864
1.734
1.731
1.728
1.725
1.722
1.719
1.710
1.704
1.699
1.695
1.686
1.683
1.342
1.338
1.333
1.318
1.314
1.309
1.001
0.995
0.211
0.148
H3CO
OH
H3CO
OTBS
47
1.00
1.85
1.80
1.00
2.78
2.69
1.09
1.09
2.19
1.17
1.99
1.04
8.42
2.79
2.71
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
0.0
-0.5
f1 (ppm)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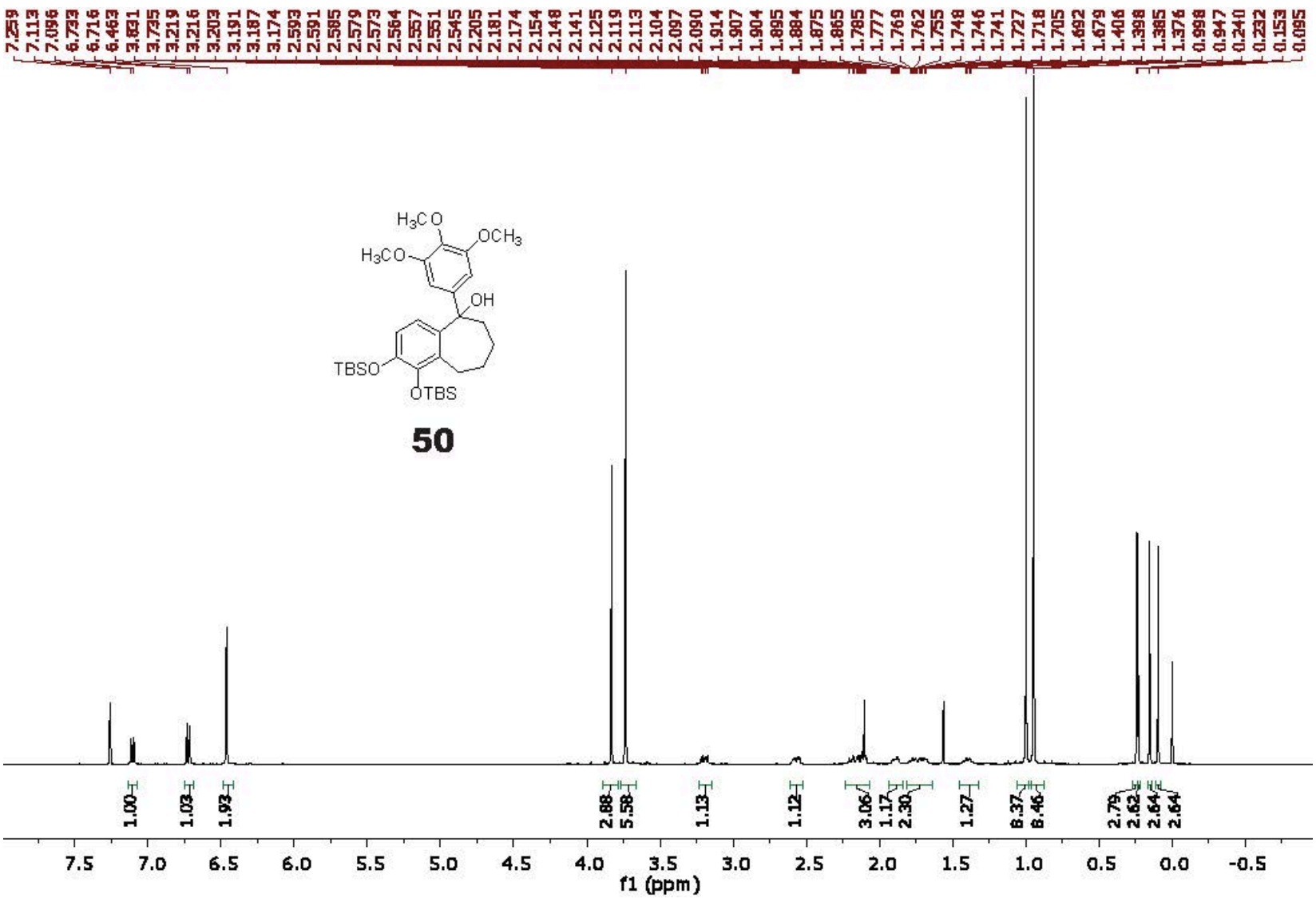
119.128
113.611
107.826
79.360
55.207
54.635
41.147
27.127
26.677
26.063
25.458
-3.856
-4.215
H3CO
OH
H3CO
OTBS
47
f1 (ppm)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3.216
3.203
3.191
3.187
3.174
2.593
2.591
2.585
2.579
2.573
2.564
2.557
2.551
2.545
2.205
2.181
2.174
2.154
2.148
2.141
2.125
2.119
2.113
2.104
2.097
2.090
1.914
1.907
1.904
1.895
1.884
1.875
1.865
1.785
1.777
1.769
1.762
1.755
1.748
1.746
1.741
1.727
1.718
1.705
1.692
1.679
1.406
1.398
1.385
1.376
0.998
0.947
0.240
0.232
0.153
0.095
H3CO
OCH3
H3CO
OH
TBSO
OTBS
50
1.00
1.03
1.93
2.88
5.58
1.13
1.12
3.06
1.17
2.30
1.27
8.37
8.46
2.79
2.62
2.64
2.64
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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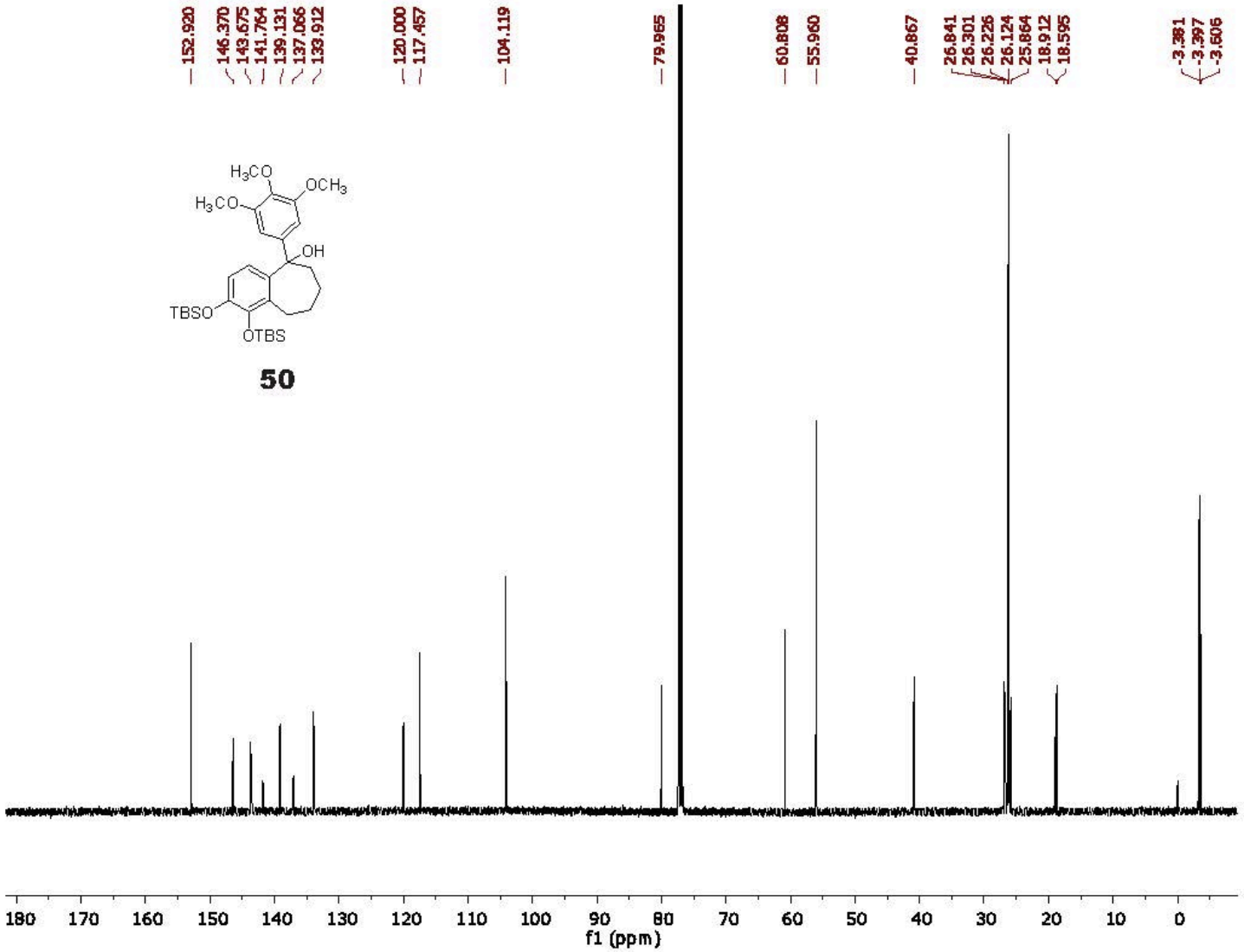
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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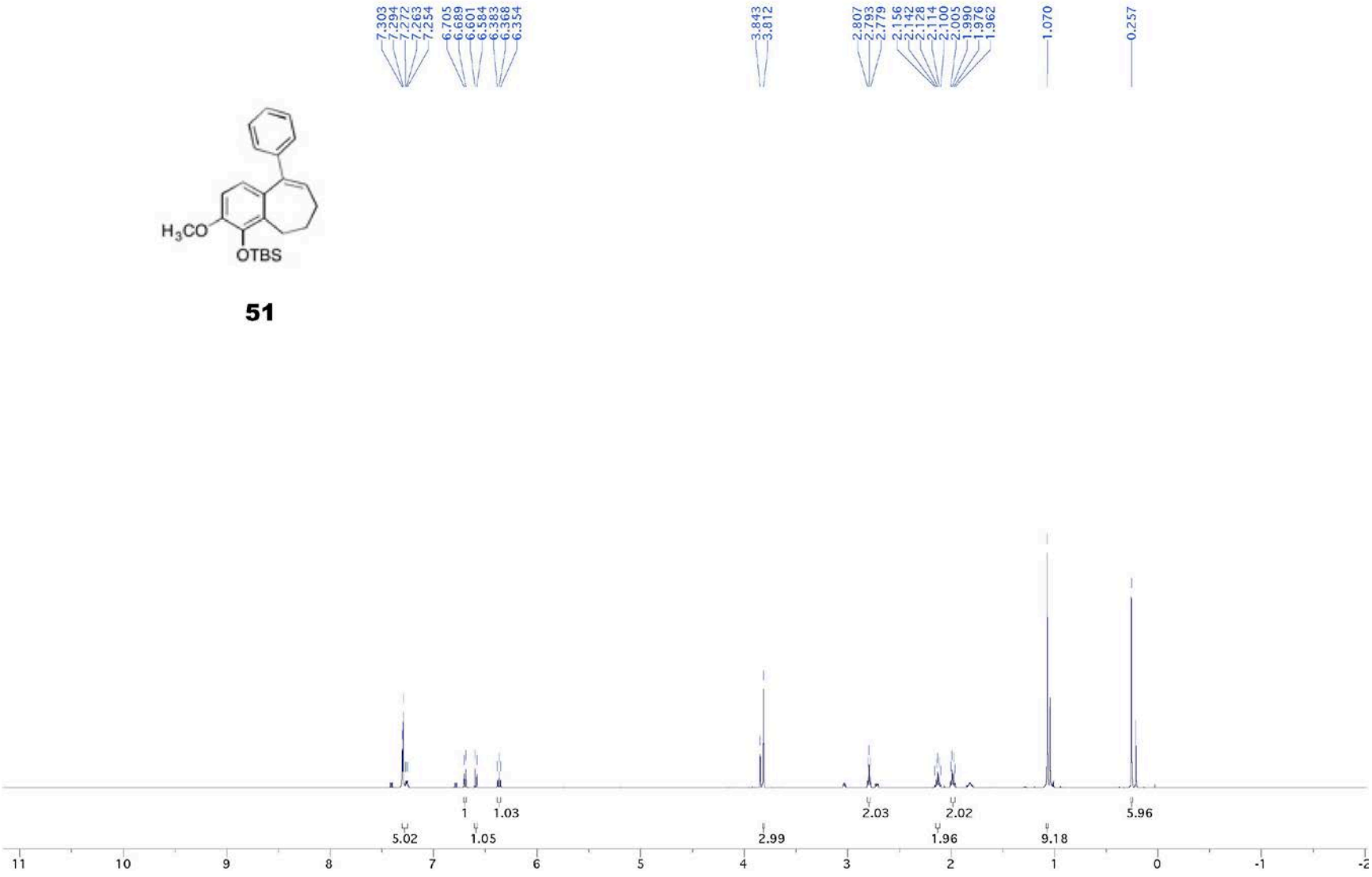
120.000
117.457
104.119
79.965
60.808
55.960
40.867
26.841
26.301
26.226
26.124
25.864
18.912
18.595
-3.381
-3.397
-3.606
H3CO
OCH3
H3CO
OH
TBSO
OTBS
50
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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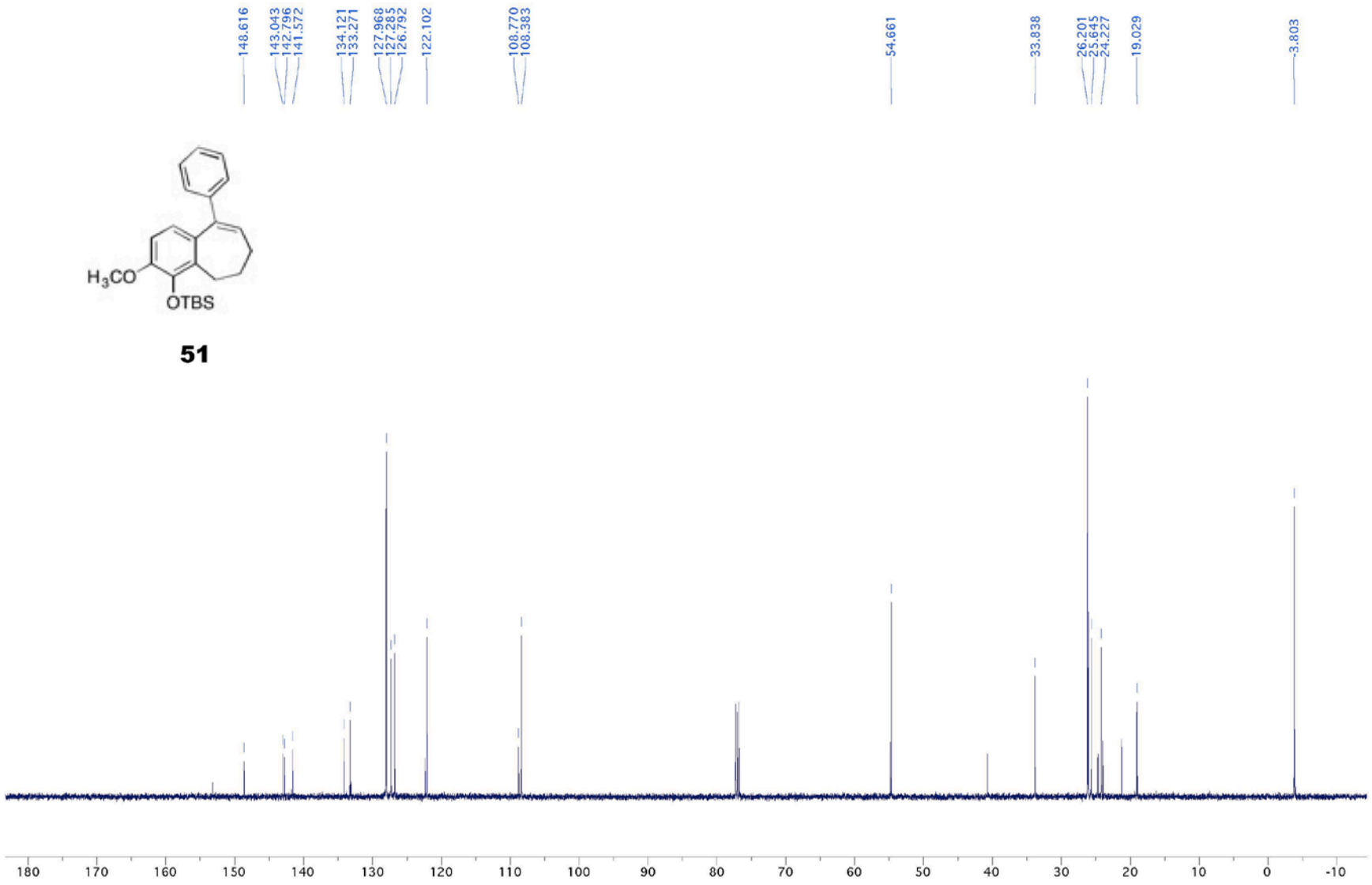
6.354
3.843
3.812
2.807
2.793
2.779
2.156
2.142
2.128
2.114
2.100
2.005
1.990
1.976
1.962
1.070
0.257
H3CO
OTBS
51
1
1.03
2.03
2.02
5.96
5.02
1.05
2.99
1.96
9.18
11
10
9
8
7
6
5
4
3
2
1
0
-1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127.285
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108.770
108.383
54.661
33.838
26.201
25.645
24.227
19.029
-3.803
H3CO
OTBS
51
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130
120
110
100
90
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50
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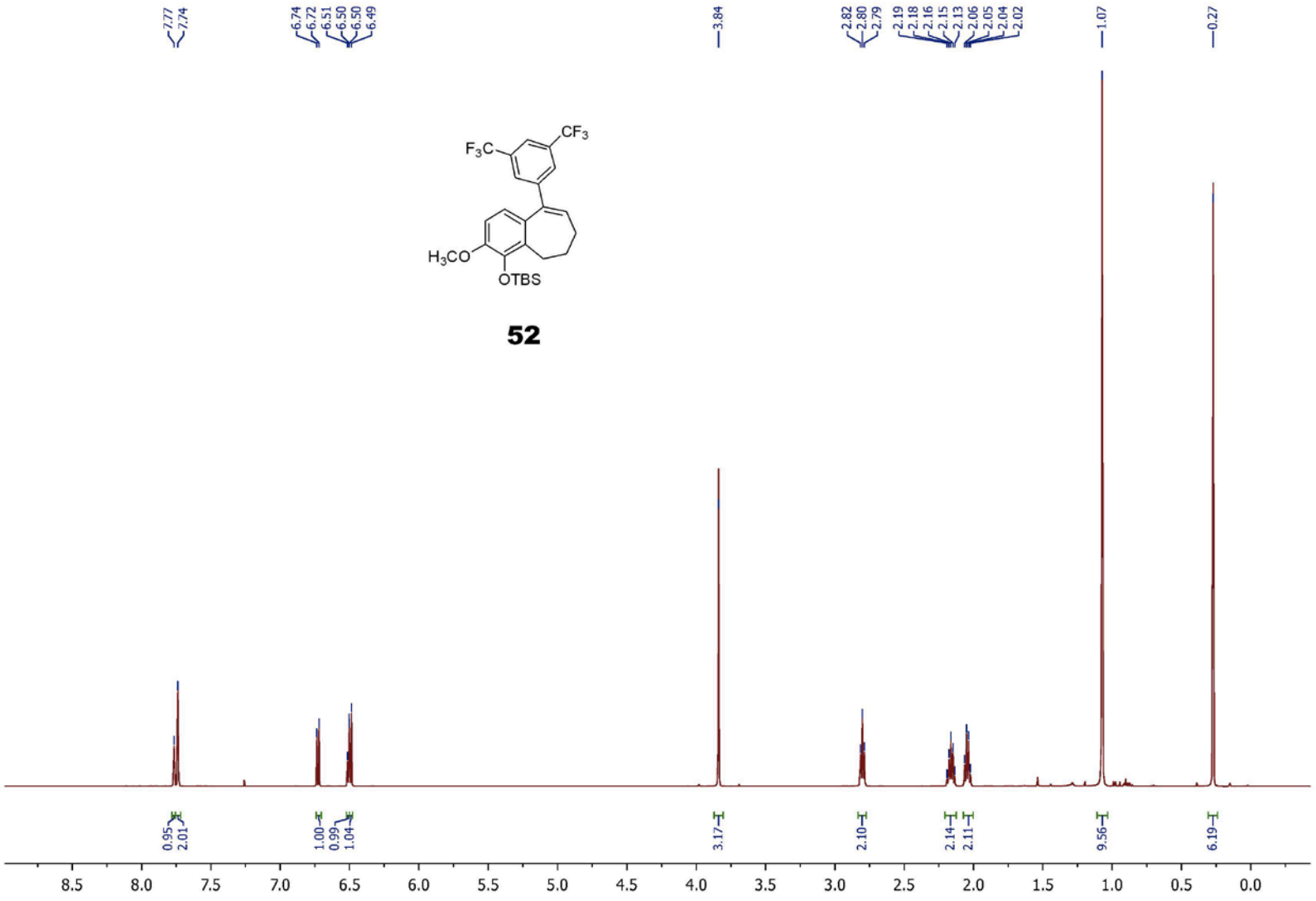
30
20
10
0
-10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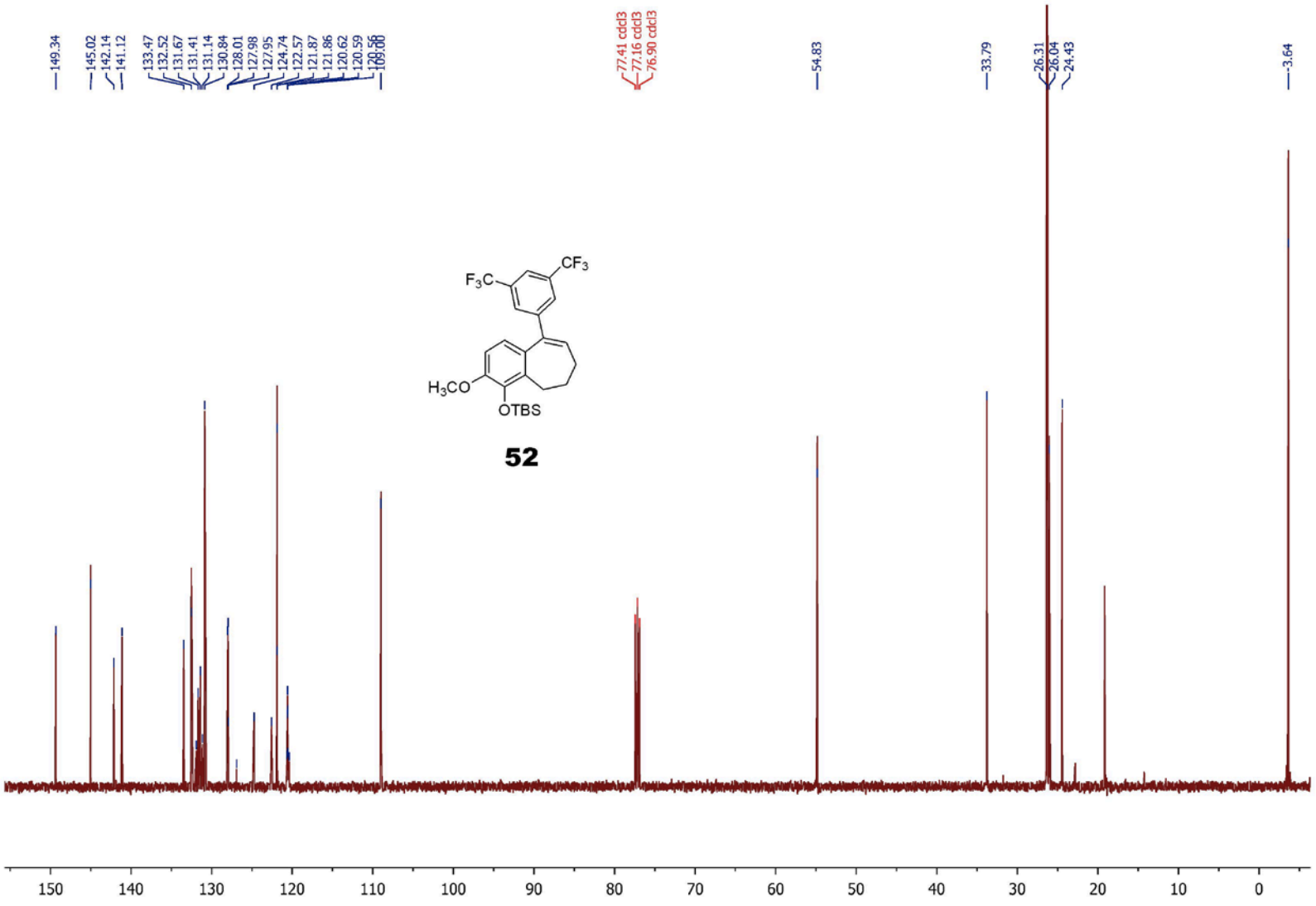
6.50
6.50
6.49
3.84
2.82
2.80
2.79
2.19
2.18
2.16
2.15
2.13
2.06
2.05
2.04
2.02
1.07
0.27
F3C
CF3
H3CO
OTBS
52
0.95
2.01
1.00
0.99
1.04
3.17
2.10
2.14
2.11
9.56
6.19
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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132.52
131.67
131.41
131.14
130.84
128.01
127.98
127.95
124.74
122.57
121.87
121.86
120.62
120.59
77.41 cdcl3
77.16 cdcl3
76.90 cdcl3
54.83
33.79
26.31
26.04
24.43
-3.64
F3C
CF3
H3CO
OTBS
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150
140
130
120
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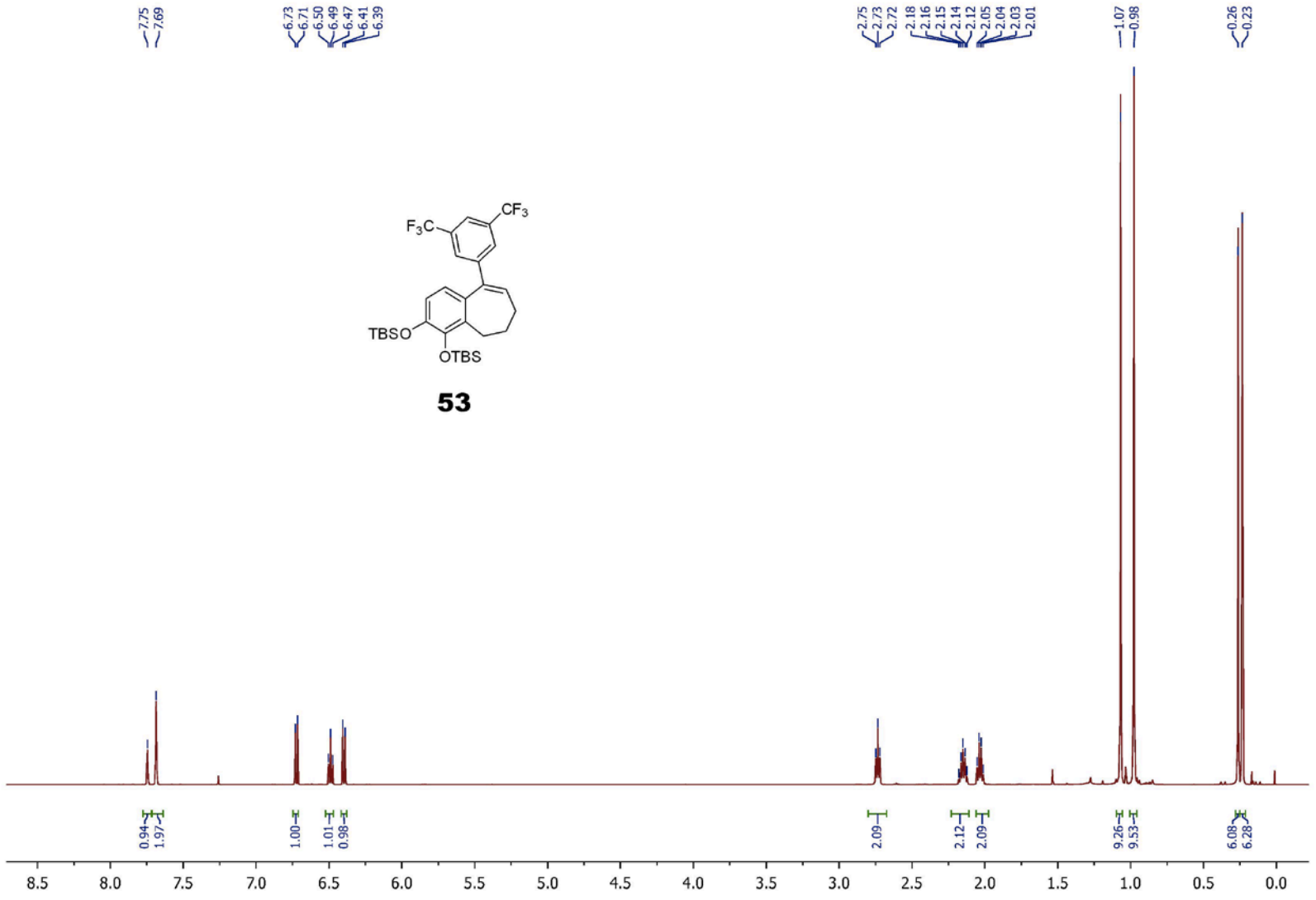
20
10
0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6.41
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2.75
2.73
2.72
2.18
2.16
2.15
2.14
2.12
2.05
2.04
2.03
2.01
1.07
0.98
0.26
0.23
F3C
CF3
TBSO
OTBS
53
0.94
1.97
1.00
1.01
0.98
2.09
2.12
2.09
9.26
9.53
6.08
6.28
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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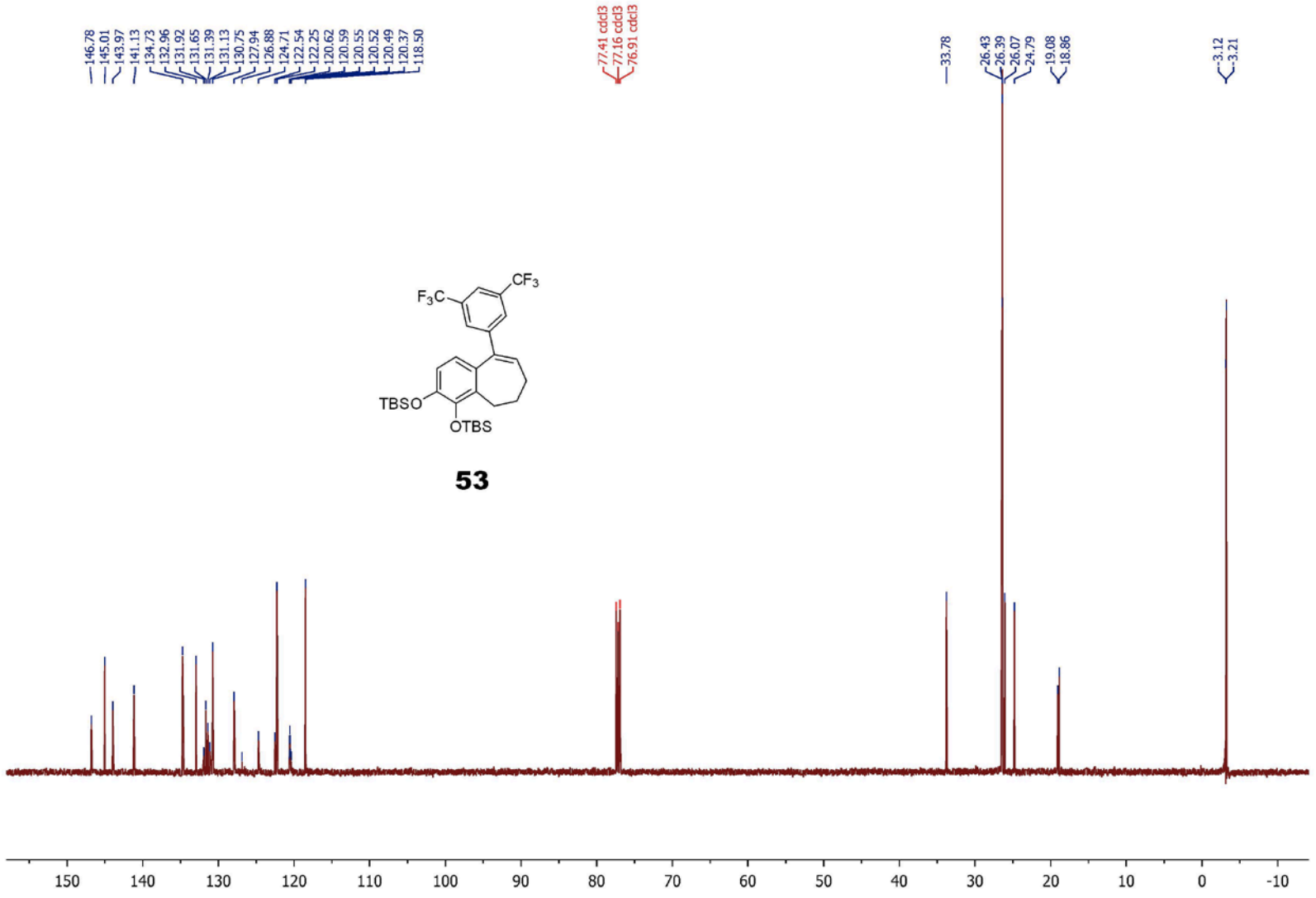
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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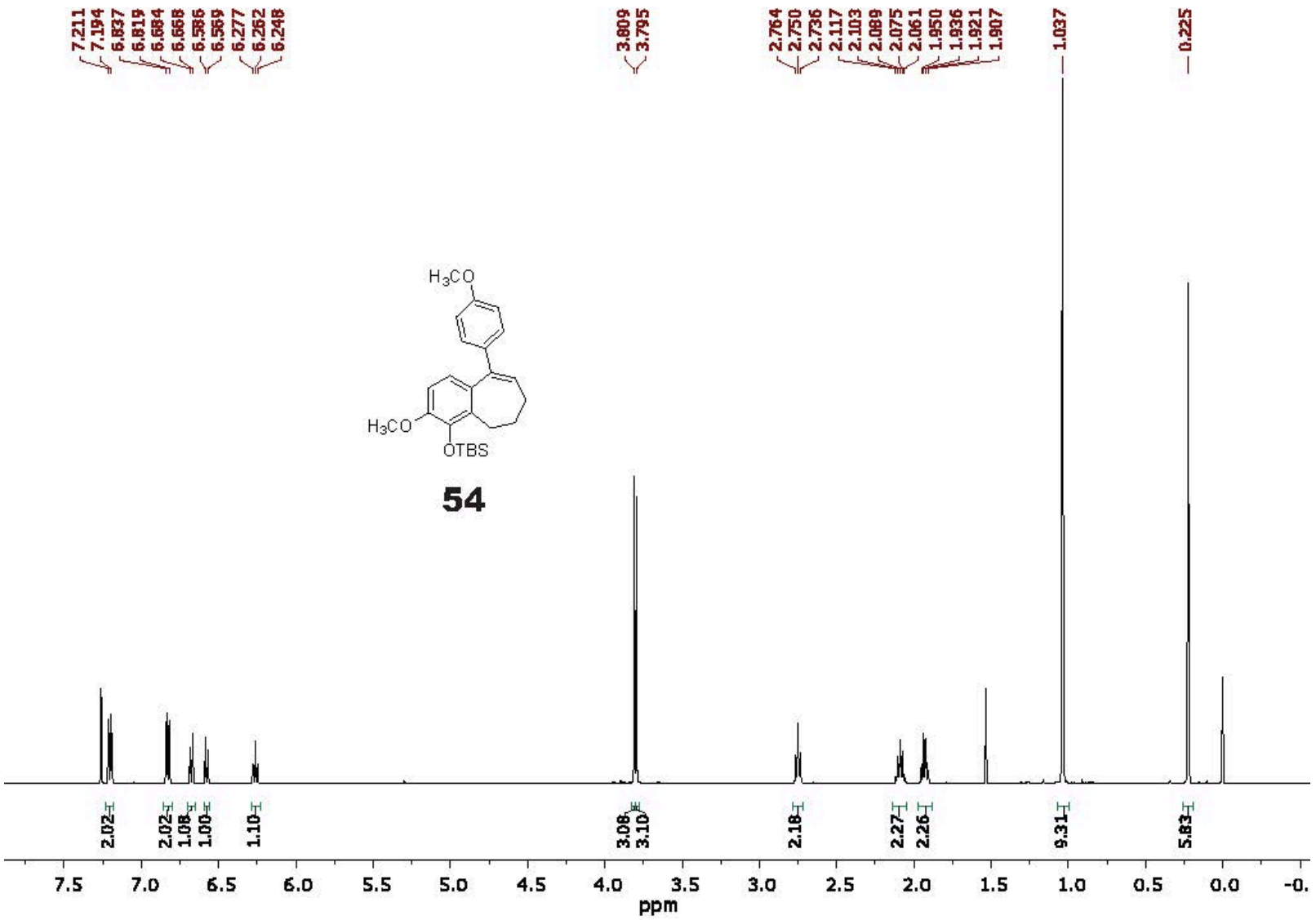
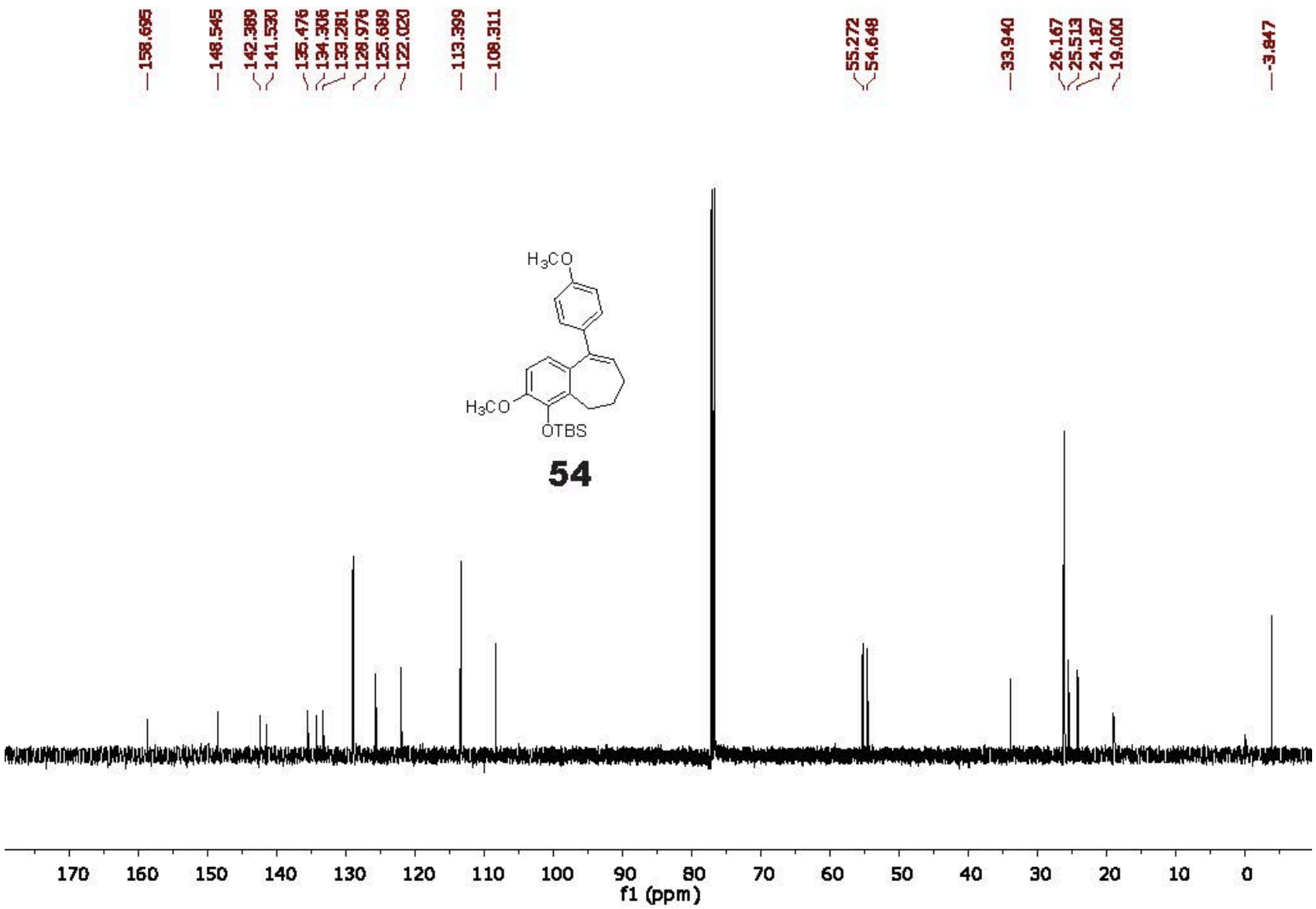
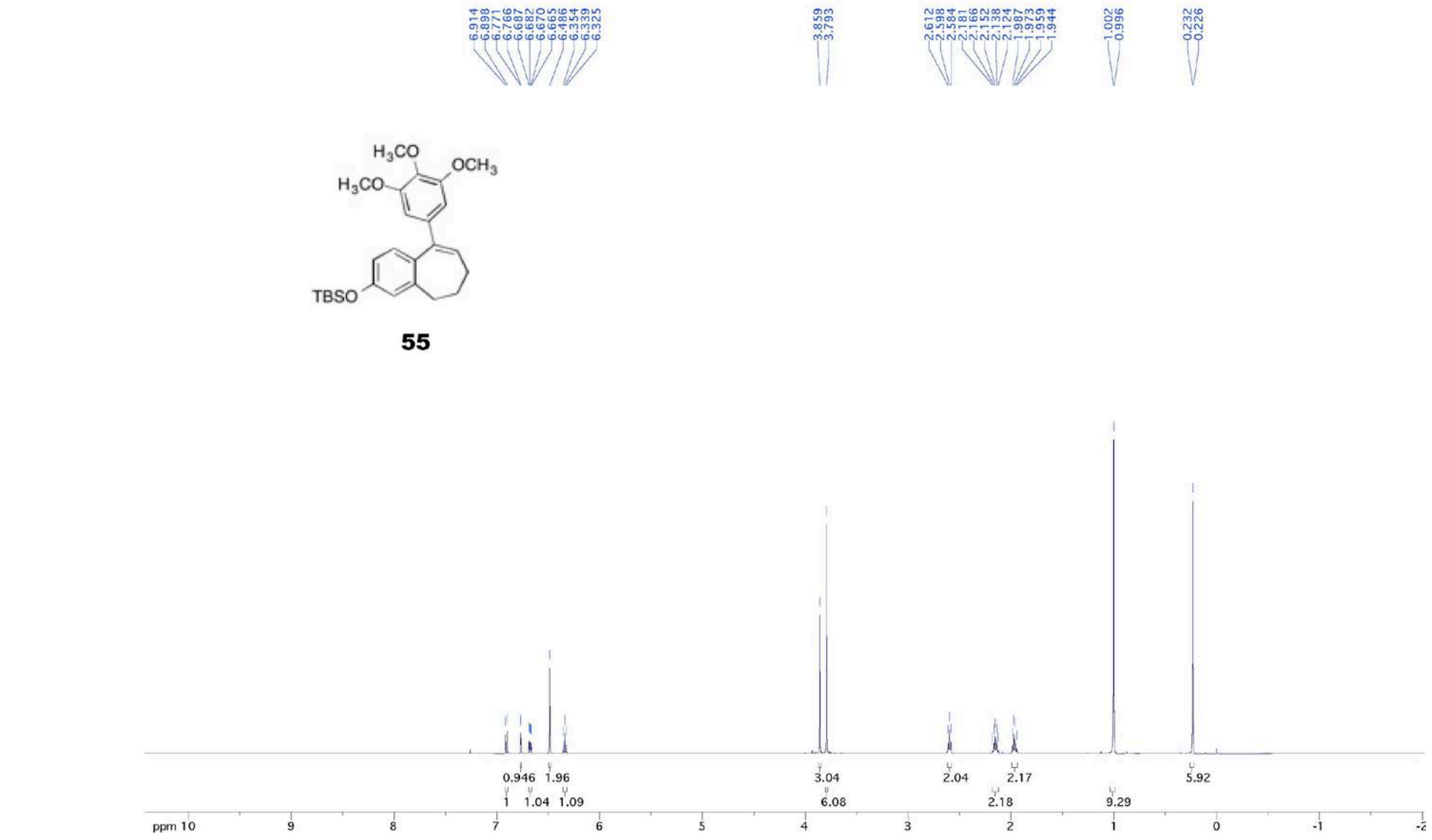
127.94
126.88
124.71
122.54
122.25
120.62
120.59
120.55
120.52
120.49
120.37
118.50
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
33.78
26.43
26.39
26.07
24.79
19.08
18.86
-3.12
-3.21
F3C
CF3
TBSO
OTBS
53
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


7.211
7.194
6.837
6.819
6.684
6.668
6.586
6.569
6.277
6.262
6.248
3.809
3.795
2.764
2.750
2.736
2.117
2.103
2.089
2.075
2.061
1.950
1.936
1.921
1.907
1.037
0.225
H3CO
H3CO
OTBS
54
2.02
2.02
1.08
1.00
1.10
3.08
3.10
2.18
2.27
2.26
9.31
5.83
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
0.0
-0.
ppm


158.695
148.545
142.389
141.530
135.476
134.306
133.281
128.976
125.689
122.020
113.399
108.311
55.272
54.648
33.940
26.167
25.513
24.187
19.000
-3.847
H3CO
H3CO
OTBS
54
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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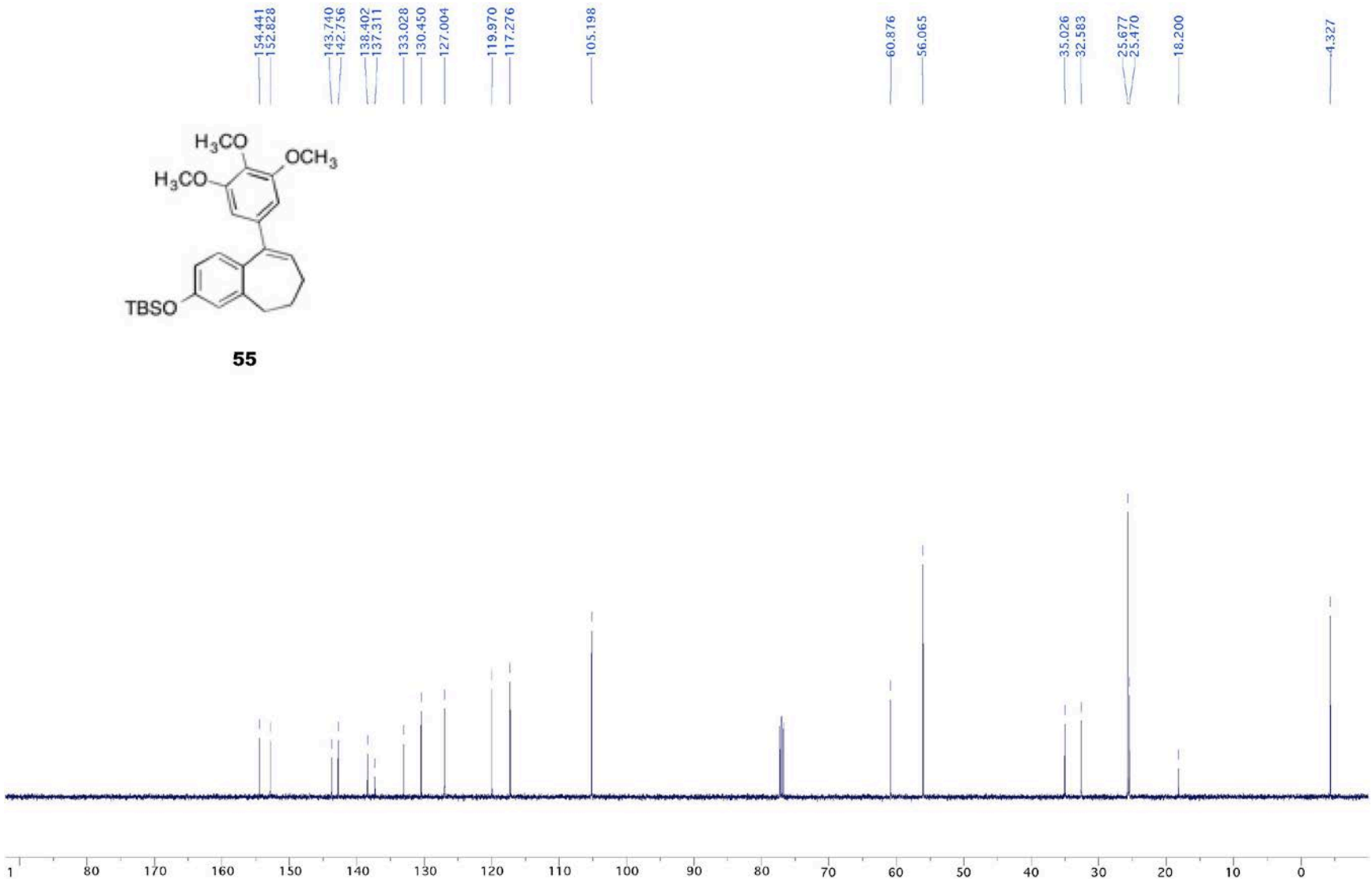
6.898
6.771
6.766
6.687
6.682
6.670
6.665
6.486
6.354
6.339
6.325
3.859
3.793
2.612
2.598
2.584
2.181
2.166
2.152
2.138
2.124
1.987
1.973
1.959
1.944
1.002
0.996
0.232
0.226
H3CO
OCH3
H3CO
TBSO
55
0.946
1.96
3.04
2.04
2.17
5.92
1
1.04
1.09
6.08
2.18
9.29
ppm 10
9
8
7
6
5
4
3
2
1
0
-1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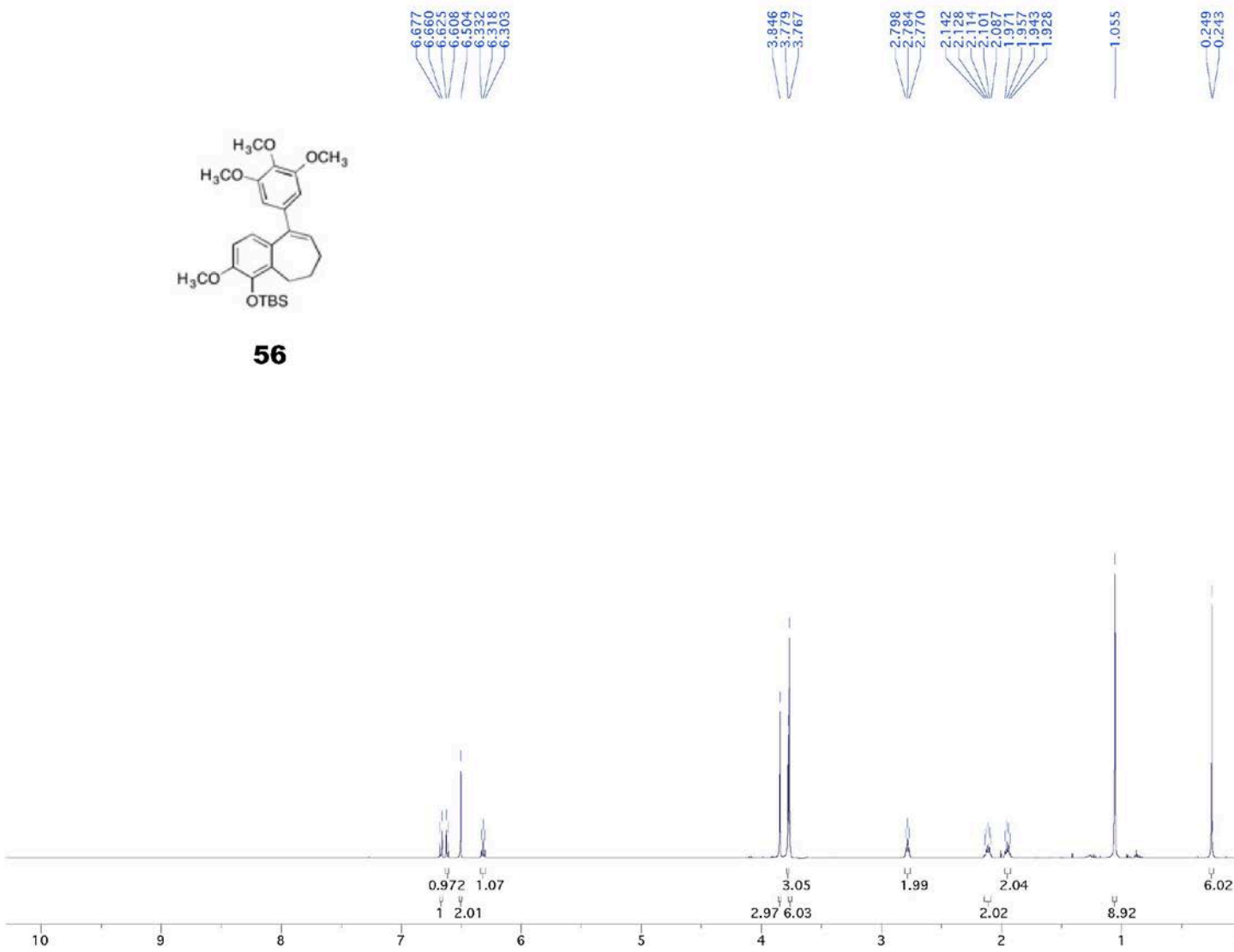
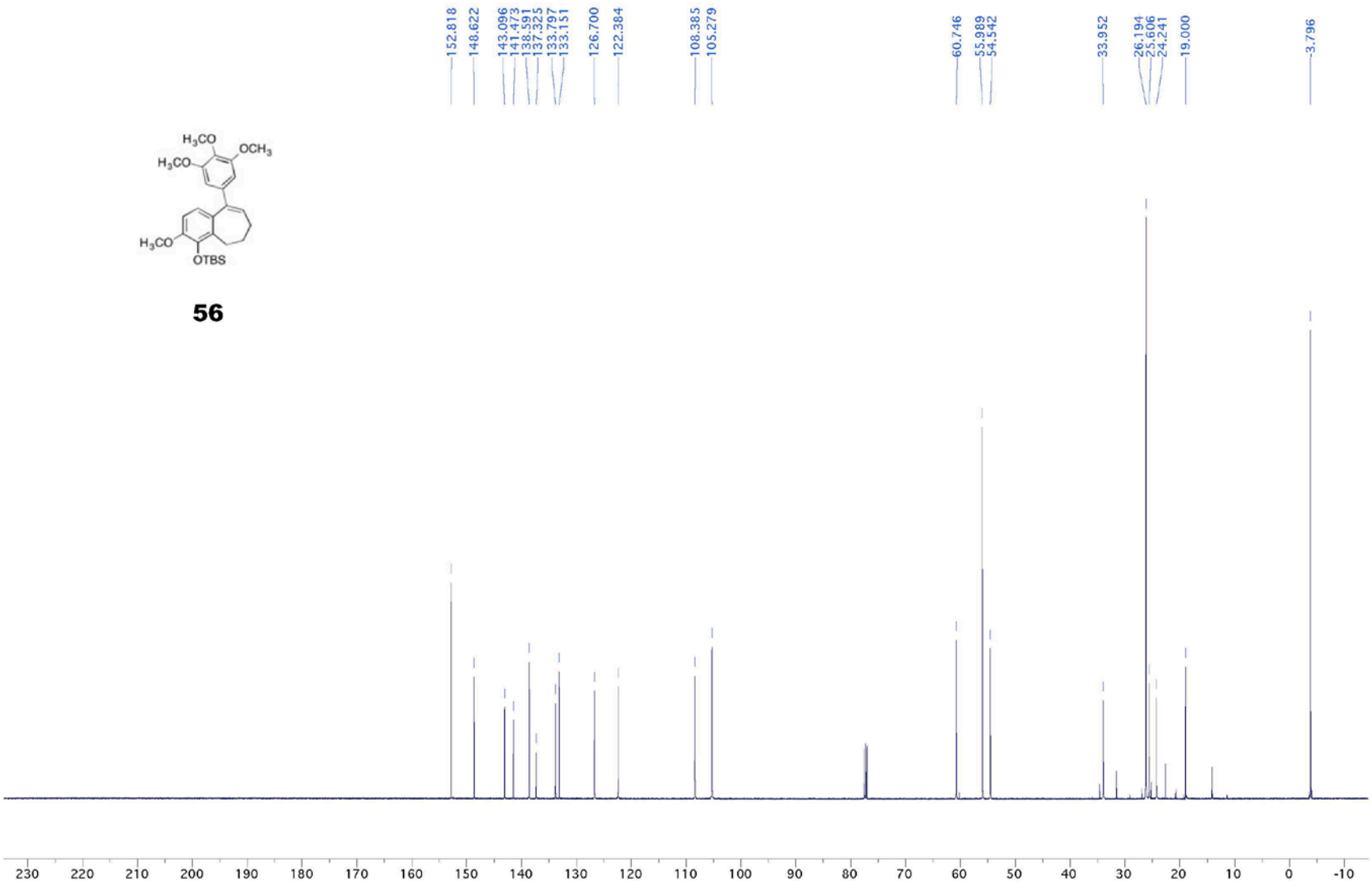
152.828
143.740
142.756
138.402
137.311
133.028
130.450
127.004
119.970
117.276
105.198
60.876
56.065
35.026
32.583
25.677
25.470
18.200
4.327
H3CO
OCH3
H3CO
TBSO
55
1
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


6.677
6.660
6.625
6.608
6.504
6.332
6.318
6.303
3.846
3.779
3.767
2.798
2.784
2.770
2.142
2.128
2.114
2.101
2.087
1.971
1.957
1.943
1.928
1.055
0.249
0.243
H3CO
OCH3
H3CO
H3CO
OTBS
0.972
1.07
3.05
1.99
2.04
6.02
1
2.01
2.97
6.03
2.02
8.92
10
9
8
7
6
5
4
3
2
1
0
-1

56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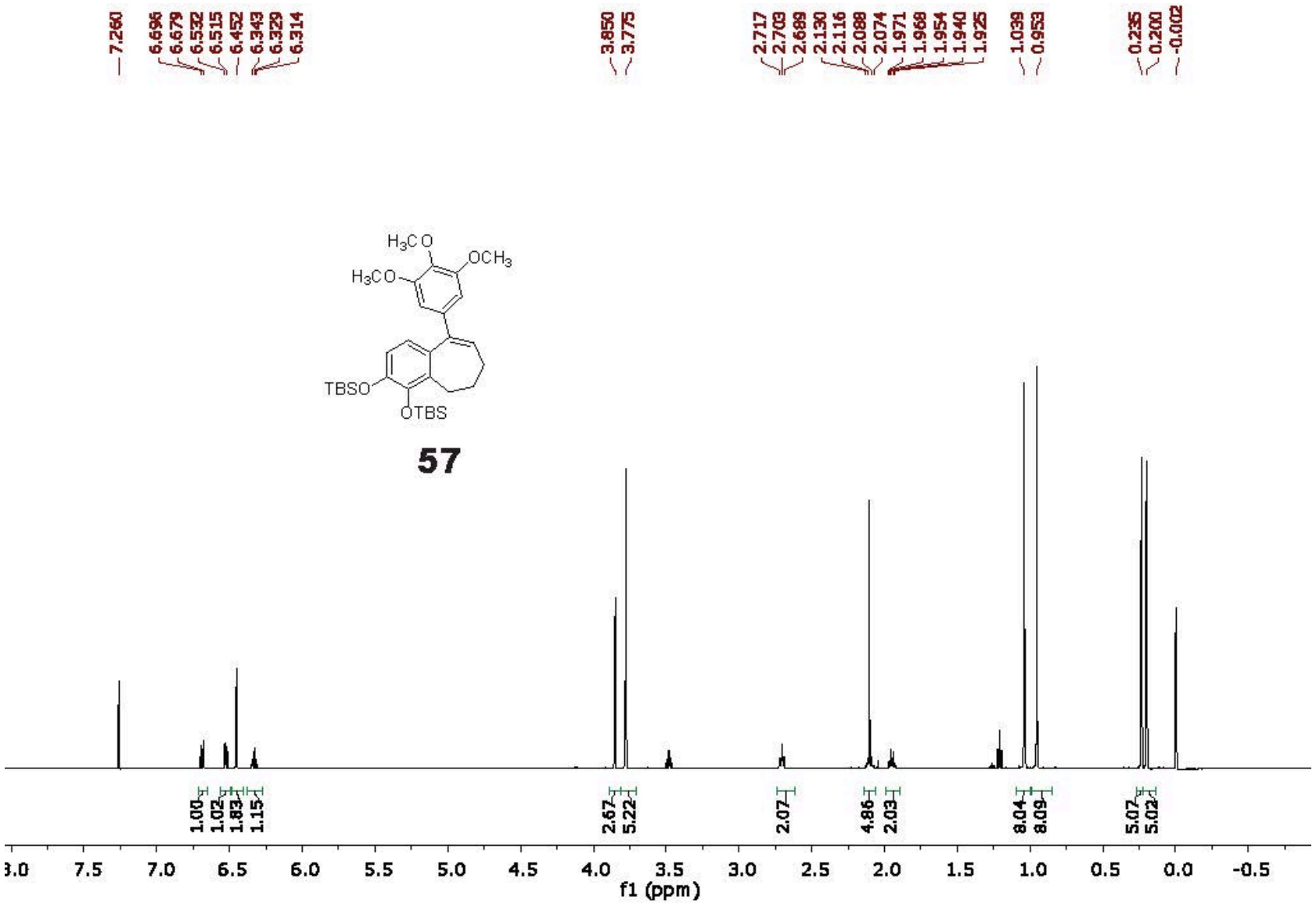
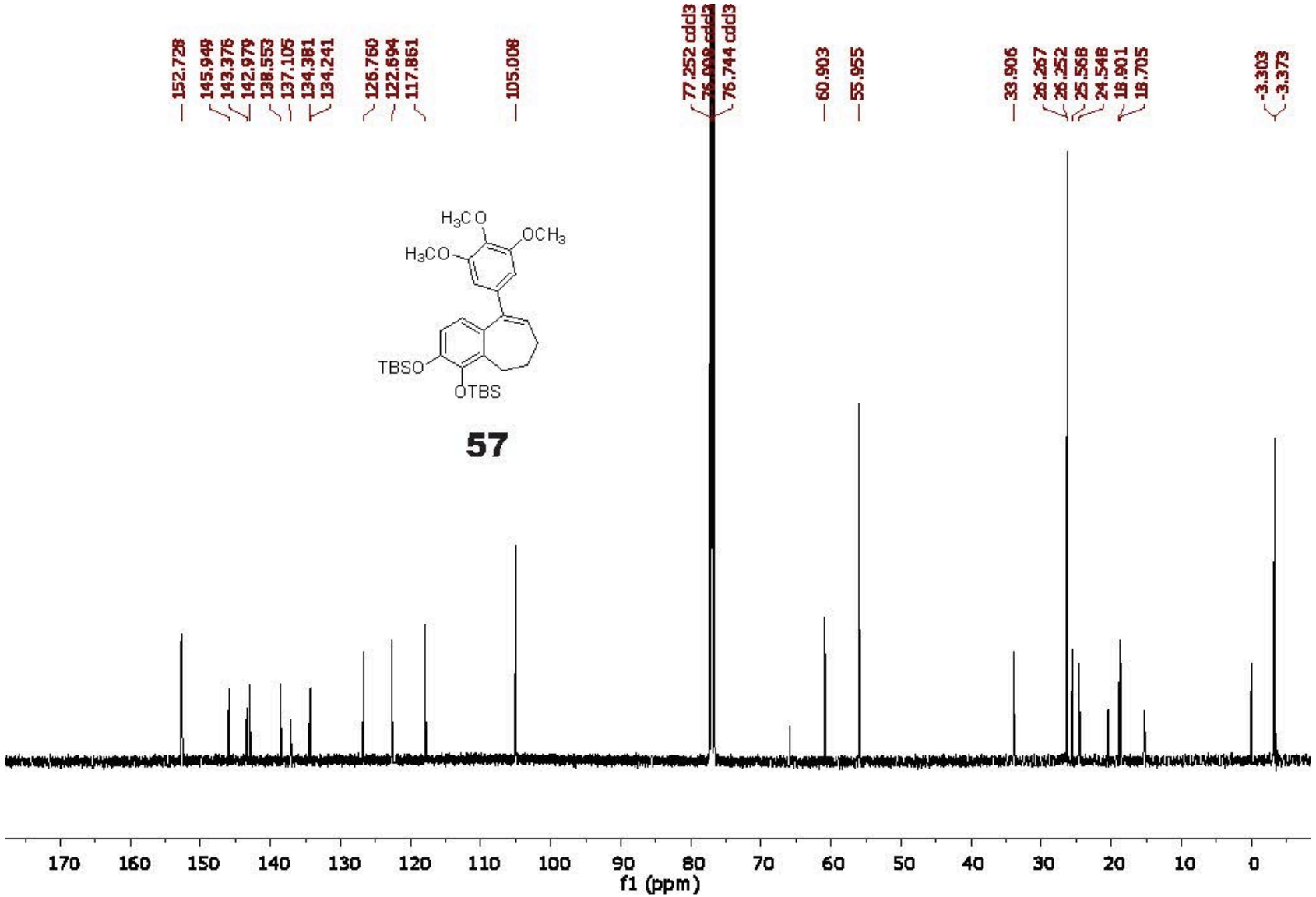
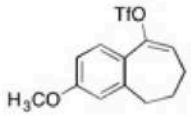
148.622
143.096
141.473
138.591
137.325
133.797
133.151
126.700
122.384
108.385
105.279
60.746
55.989
54.542
33.952
26.194
25.606
24.241
19.000
-3.796
H3CO
OCH3
H3CO
H3CO
OTBS
56
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

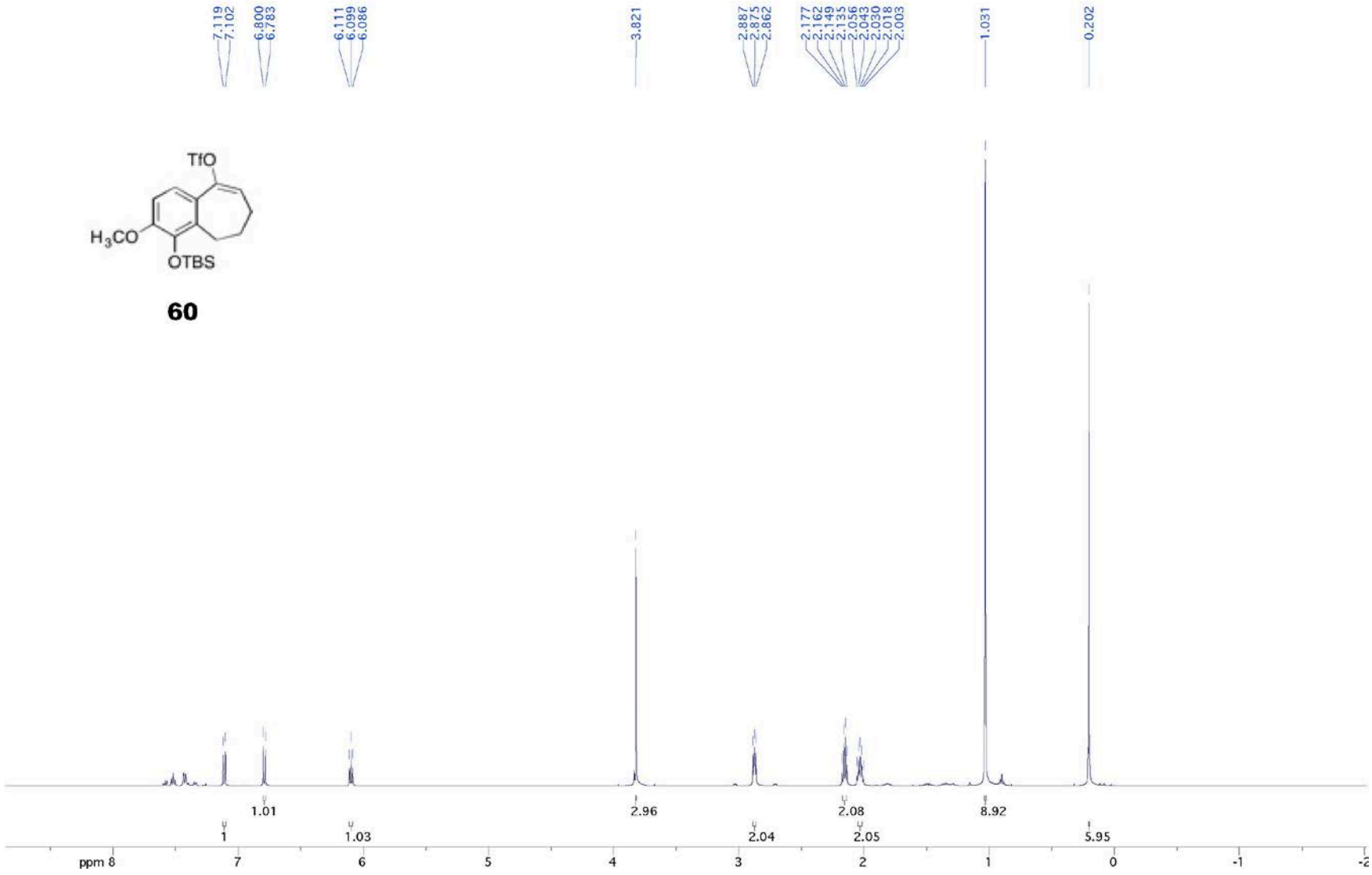

7.260
6.696
6.679
6.532
6.515
6.452
6.343
6.329
6.314
3.850
3.775
2.717
2.709
2.689
2.130
2.116
2.088
2.074
1.971
1.968
1.954
1.940
1.925
1.039
0.953
0.235
0.200
-0.002
H3CO
OCH3
H3CO
TBSO
OTBS
57
1.00
1.02
1.83
1.15
2.67
5.22
2.07
4.86
2.03
8.04
8.09
5.07
5.02
f1 (ppm)

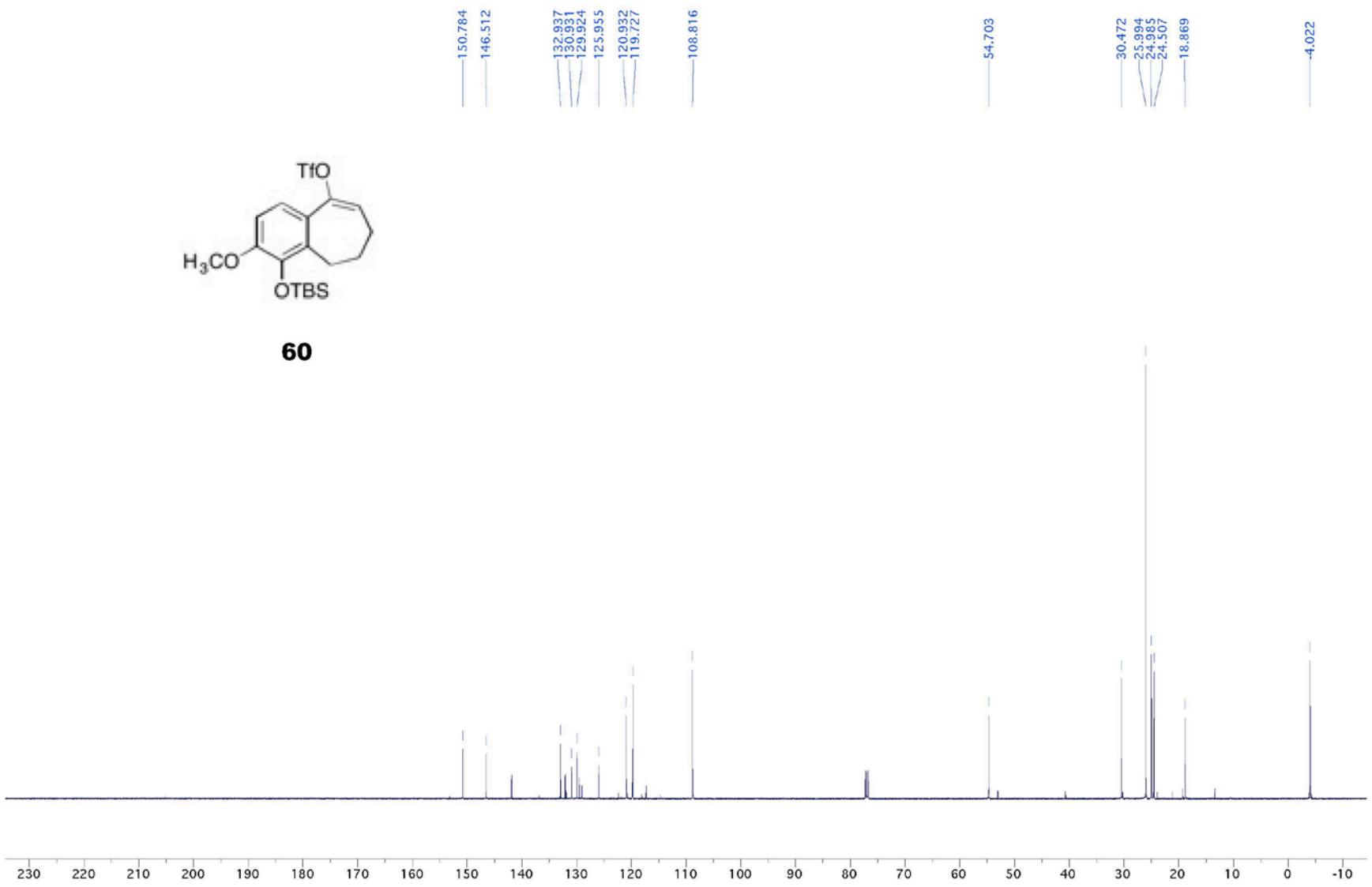

152.728
145.949
143.376
142.979
138.553
137.105
134.381
134.241
126.760
122.694
117.861
105.008
77.252 cdcl3
76.744 cdcl3
60.903
55.955
33.906
26.267
26.252
25.568
24.548
18.901
18.705
-3.303
-3.373
H3CO
OCH3
H3CO
TBSO
OTBS
57
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

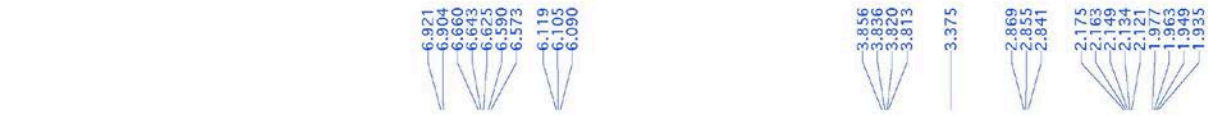

TfO
H3CO

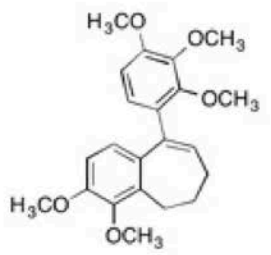
59

7.527
7.509
6.874
6.869
6.857
6.852
6.819
6.813
6.159
6.147
6.135
3.792
2.785
2.772
2.760
2.224
2.210
2.197
2.184
2.064
2.050
2.038
2.025
2.011
0.972
1
0.943
0.949
3.02
1.93
2.03
2.07

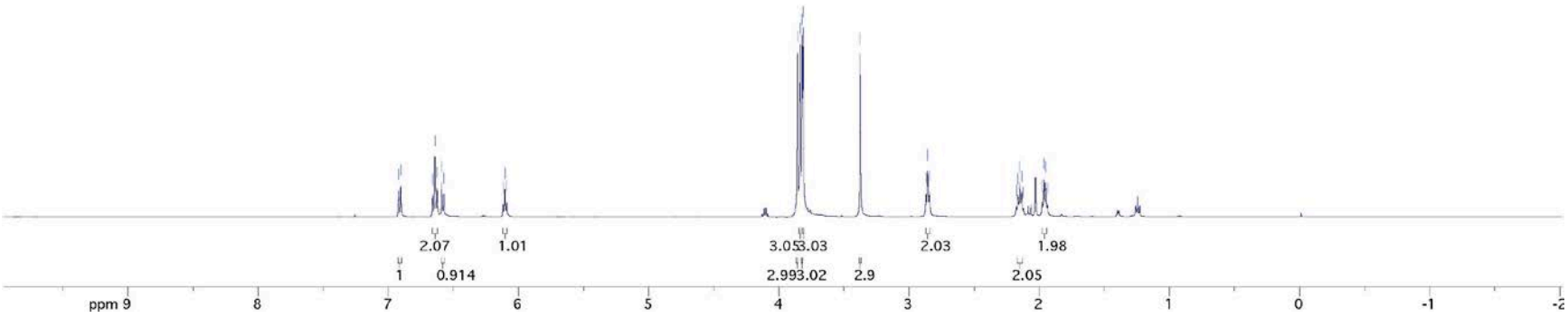

7.119
7.102
6.800
6.783
6.111
6.099
6.086
3.821
2.887
2.875
2.862
2.177
2.162
2.149
2.135
2.056
2.043
2.030
2.018
2.003
1.031
0.202
TfO
H3CO
OTBS
60
1.01
2.96
2.08
8.92
1
1.03
2.04
2.05
5.95
ppm 8
7
6
5
4
3
2
1
0
-1

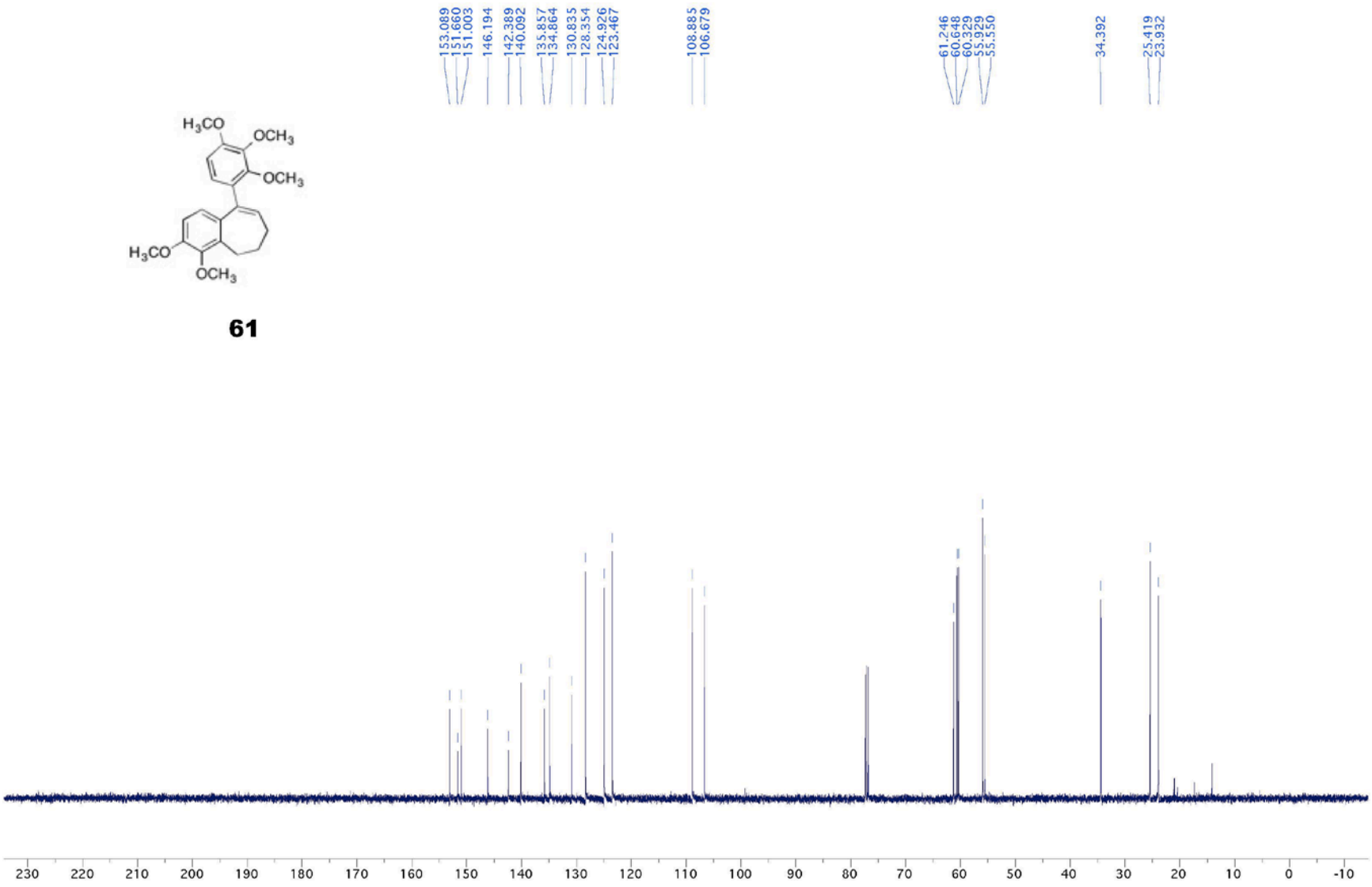

150.784
146.512
132.937
130.931
129.924
125.955
120.932
119.727
108.816
54.703
30.472
25.994
24.985
24.507
18.869
4.022
TfO
H3CO
OTBS
60
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


6.921
6.904
6.660
6.643
6.625
6.590
6.573
6.119
6.105
6.090
3.856
3.836
3.820
3.813
3.375
2.869
2.855
2.841
2.175
2.163
2.149
2.134
2.121
1.977
1.963
1.949
1.935


H3CO
OCH3
OCH3
H3CO
OCH3

61


2.07
1.01
3.05
3.03
2.03
1.98
1
0.914
2.99
3.02
2.9
2.05
ppm 9
8
7
6
5
4
3
2
1
0
-1


153.089
151.660
151.003
146.194
142.389
140.092
135.857
134.864
130.835
128.354
124.926
123.467
108.885
106.679
61.246
60.648
60.329
55.929
55.550
34.392
25.419
23.932
H3CO
OCH3
OCH3
H3CO
OCH3
61
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_3_51_CLEAN2.D
Sample Name: CAH_3_51_Clean

HPLC for compound 61

```
==========================================================================
Acq. Operator   : Christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 7/18/2013 10:11:00 AM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 7/18/2013 10:07:07 AM by Christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\CAH_3_51_CLEAN2.D\DA.M (MASTERMETHOD.M)
Last changed    : 7/18/2013 11:01:15 AM by Christine
Sample Info     :
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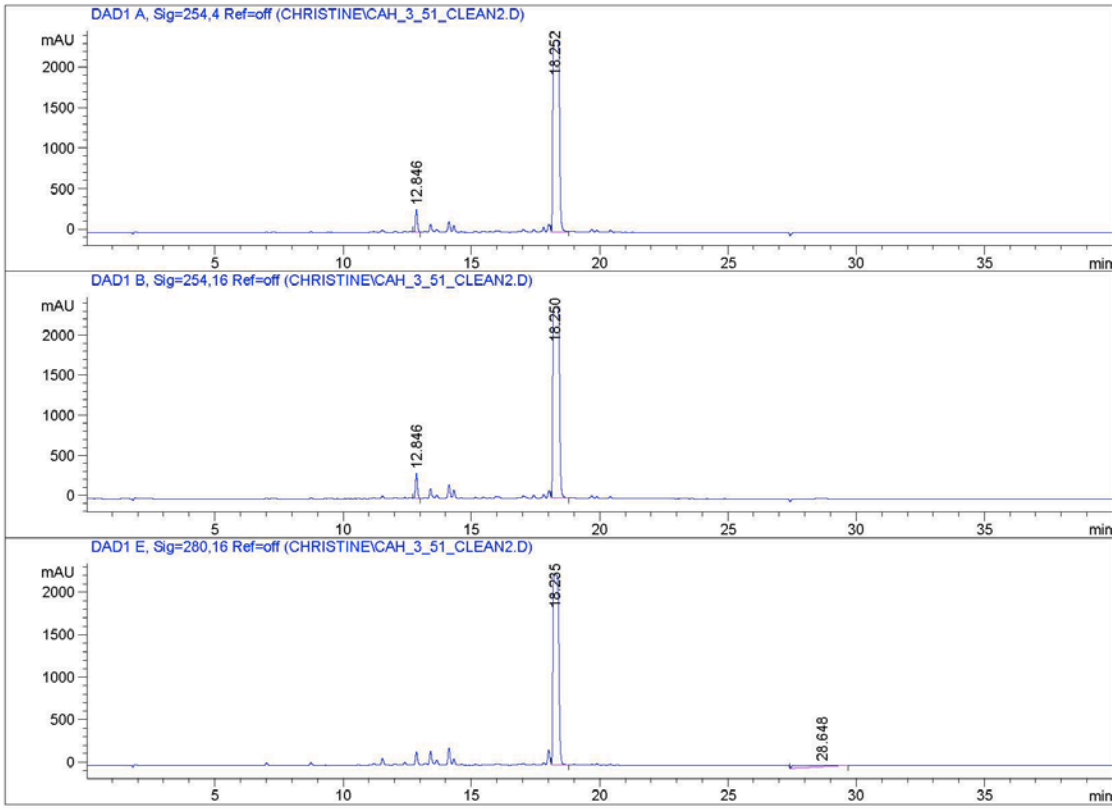
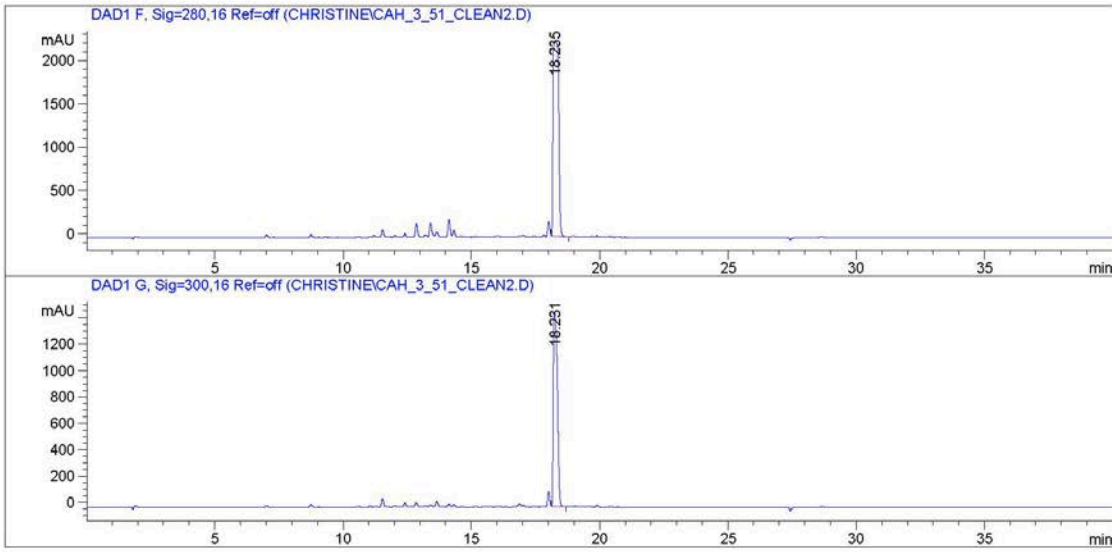


Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_3_51_CLEAN2.D
Sample Name: CAH_3_51_Clean



==========

Area Percent Report

==========

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.846	VB	0.0826	1498.54224	279.23978	3.5576
2	18.252	VV	0.2144	4.06234e4	2365.51514	96.4424
Totals :				4.21219e4	2644.75491	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.846	VB	0.0826	1700.93689	317.25293	3.9841
2	18.250	VV	0.2824	4.09918e4	2386.45435	96.0159

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_3_51_CLEAN2.D
Sample Name: CAH_3_51_Clean

Totals : 4.26927e4 2703.70728

Signal 3: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.235	VB	0.2472	3.38849e4	2256.16064	93.6335
2	28.648	BB	1.5395	2303.96753	18.24143	6.3665

Totals : 3.61888e4 2274.40207

Signal 4: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.235	VB	0.2472	3.38849e4	2256.16064	100.0000

Totals : 3.38849e4 2256.16064

Signal 5: DAD1 G, Sig=300,16 Ref=off

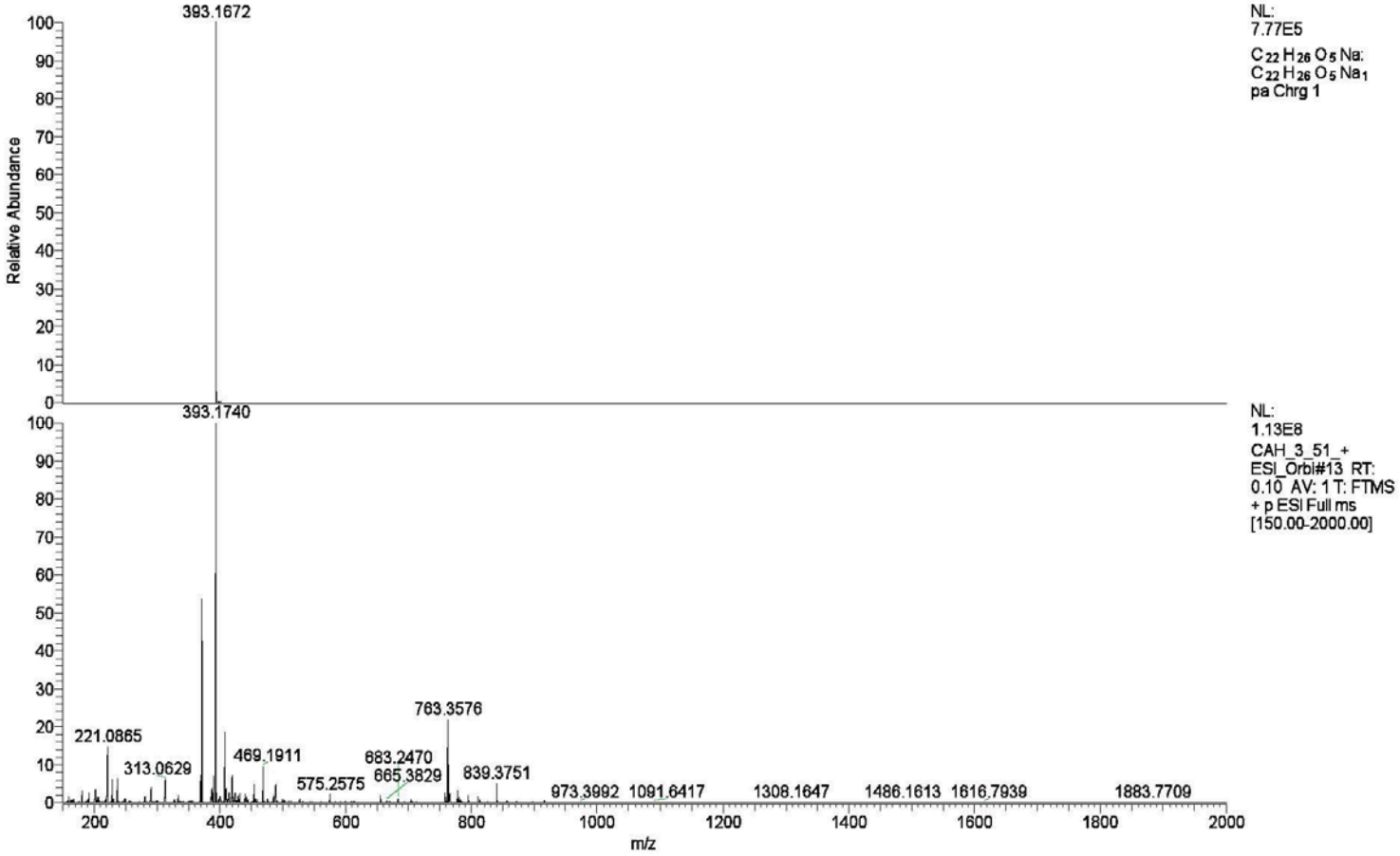
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.231	VB	0.1840	1.62398e4	1479.67639	100.0000

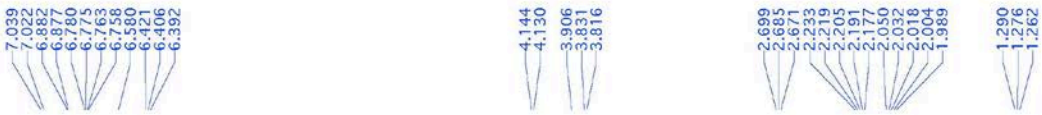
Totals : 1.62398e4 1479.67639

==========

*** End of Report ***

HRMS for compound 61

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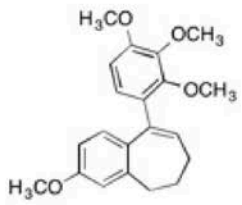
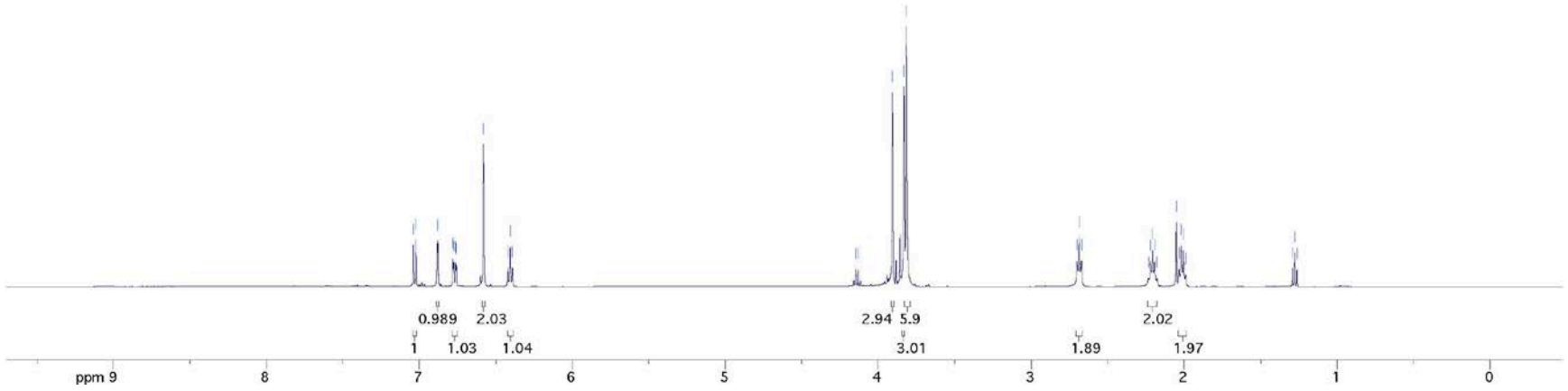
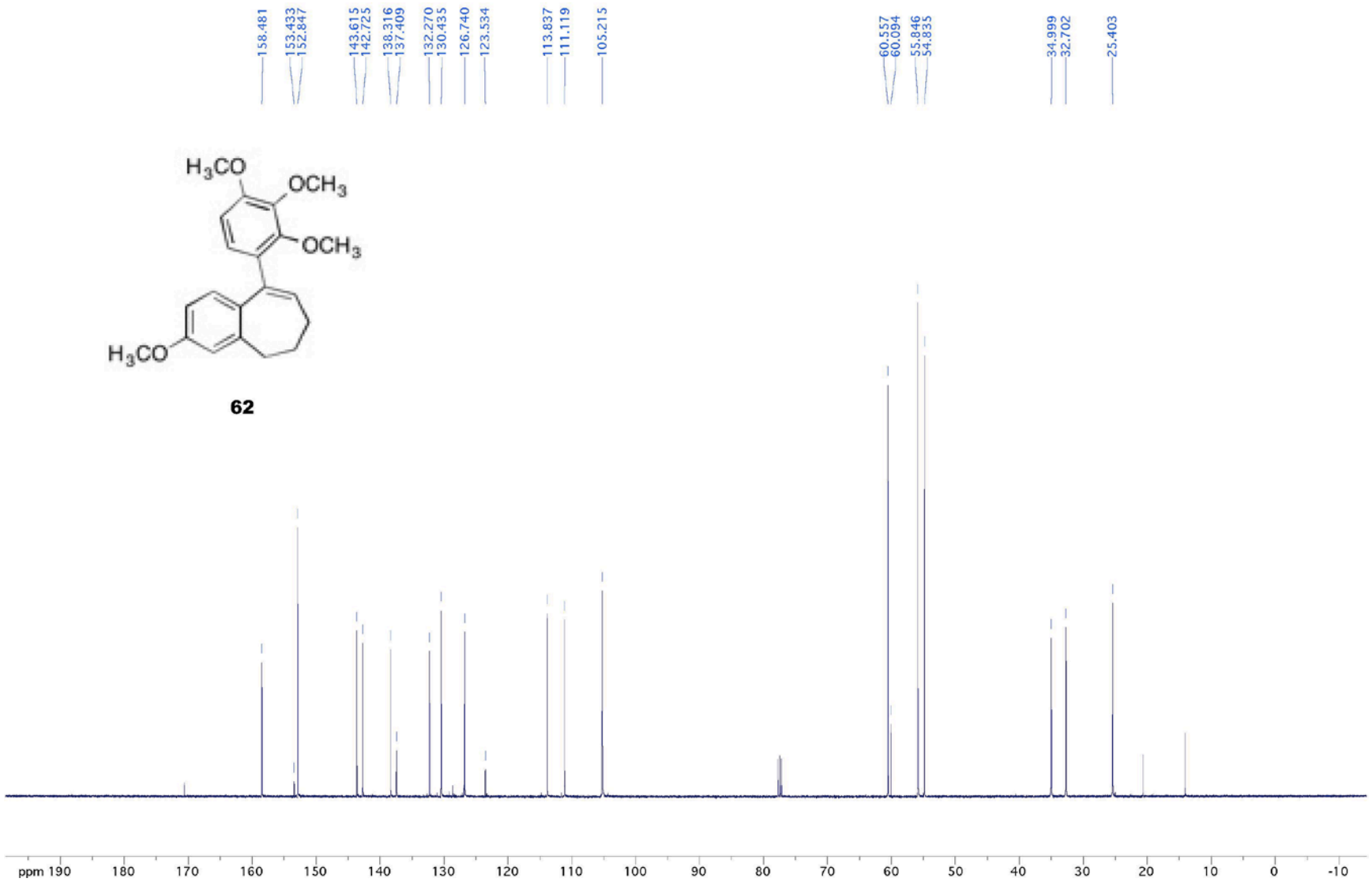
7.022
6.882
6.877
6.780
6.775
6.763
6.758
6.580
6.421
6.406
6.392
4.144
4.130
3.906
3.831
3.816
2.699
2.685
2.671
2.233
2.219
2.205
2.191
2.177
2.050
2.032
2.018
2.004
1.989
1.290
1.276
1.262


H3CO
OCH3
OCH3
H3CO

62


0.989
2.03
1
1.03
1.04
2.94
5.9
3.01
1.89
2.02
1.97
ppm 9
8
7
6
5
4
3
2
1
0


158.481
153.433
152.847
143.615
142.725
138.316
137.409
132.270
130.435
126.740
123.534
113.837
111.119
105.215
60.557
60.094
55.846
54.835
34.999
32.702
25.403
H3CO
OCH3
OCH3
H3CO
62
ppm 190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_18000001.D
Sample Name: CAH_4_18

HPLC for compound 62

```
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Acq. Operator   : Christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 5/19/2014 1:03:12 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 5/19/2014 1:01:32 PM by Christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\CAH_4_18000001.D\DA.M (MASTERMETHOD.M)
Last changed    : 5/19/2014 2:14:01 PM by Christine
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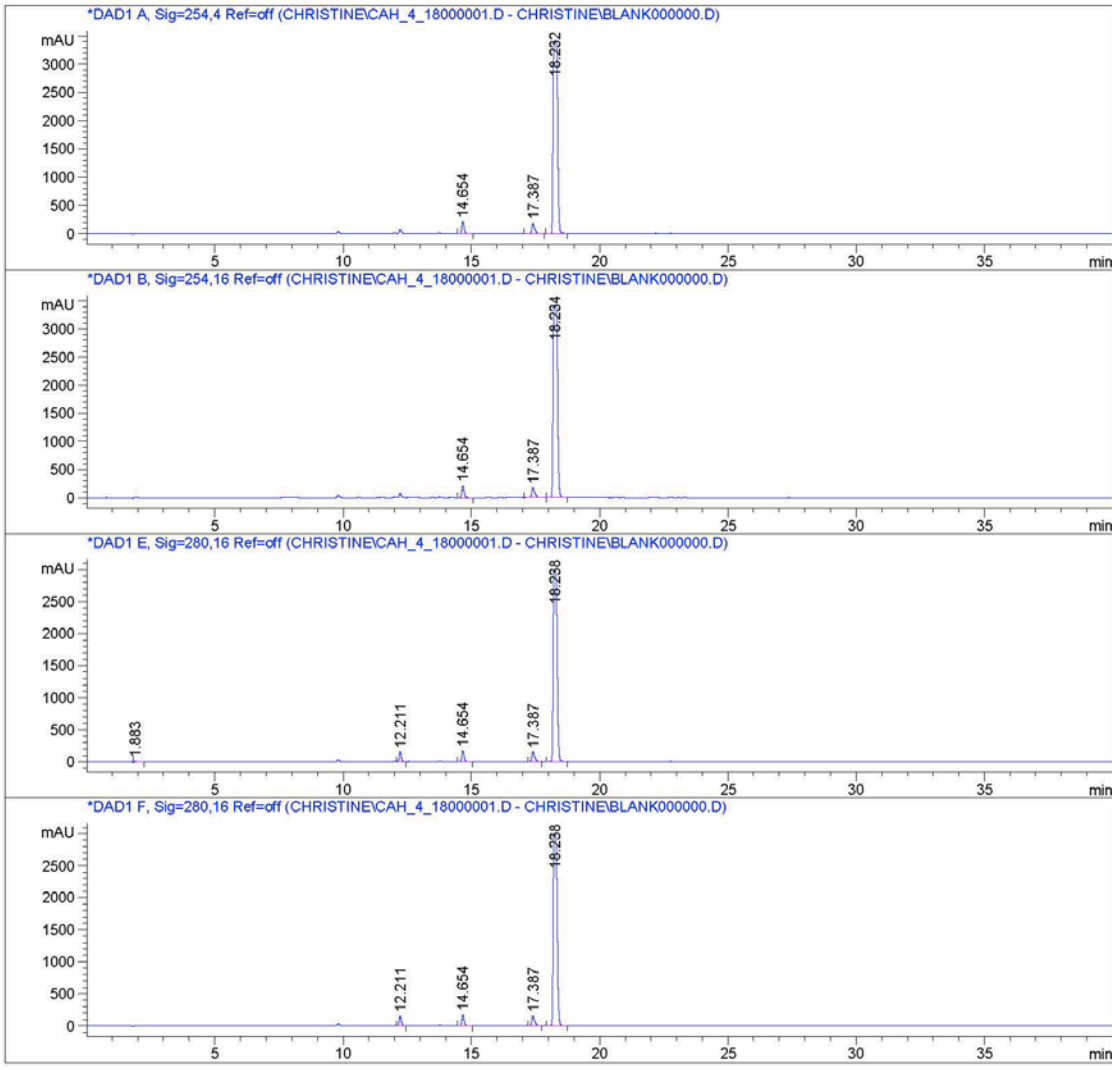
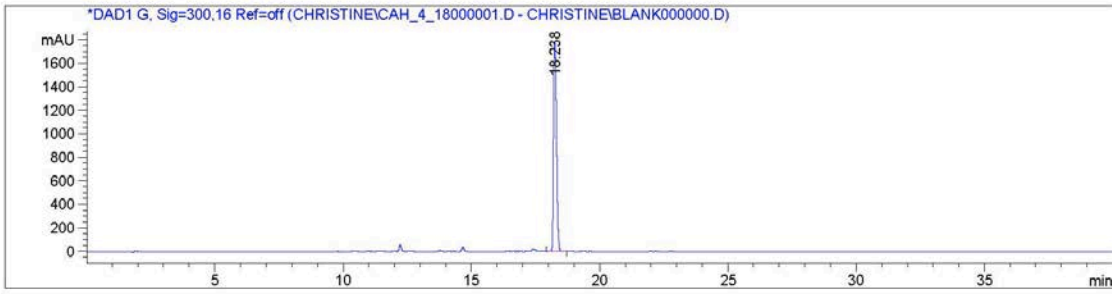


Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_18000001.D
Sample Name: CAH_4_18



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.654	BB	0.0924	1296.31226	214.94673	2.9570
2	17.387	BB	0.1137	1383.36279	176.06273	3.1556
3	18.232	BV	0.1989	4.11593e4	3408.02661	93.8875
Totals :				4.38390e4	3799.03607	

Signal 2: DAD1 B, Sig=254,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.654	BB	0.0924	1277.60864	211.86137	2.9561
2	17.387	BB	0.1133	1417.87061	181.21844	3.2806
3	18.234	BV	0.1921	4.05239e4	3422.38574	93.7633
Totals :				4.32194e4	3815.46556	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_18000001.D
Sample Name: CAH_4_18

Signal 3: DAD1 E, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.883	BB	0.1486	147.29576	14.24430	0.4289
2	12.211	VB	0.0867	883.39655	154.41168	2.5722
3	14.654	BB	0.0921	1038.45081	172.92358	3.0237
4	17.387	VV	0.1117	1195.93066	155.58759	3.4822
5	18.238	BV	0.1687	3.10785e4	3004.24097	90.4929
Totals :				3.43436e4	3501.40812	

Signal 4: DAD1 F, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

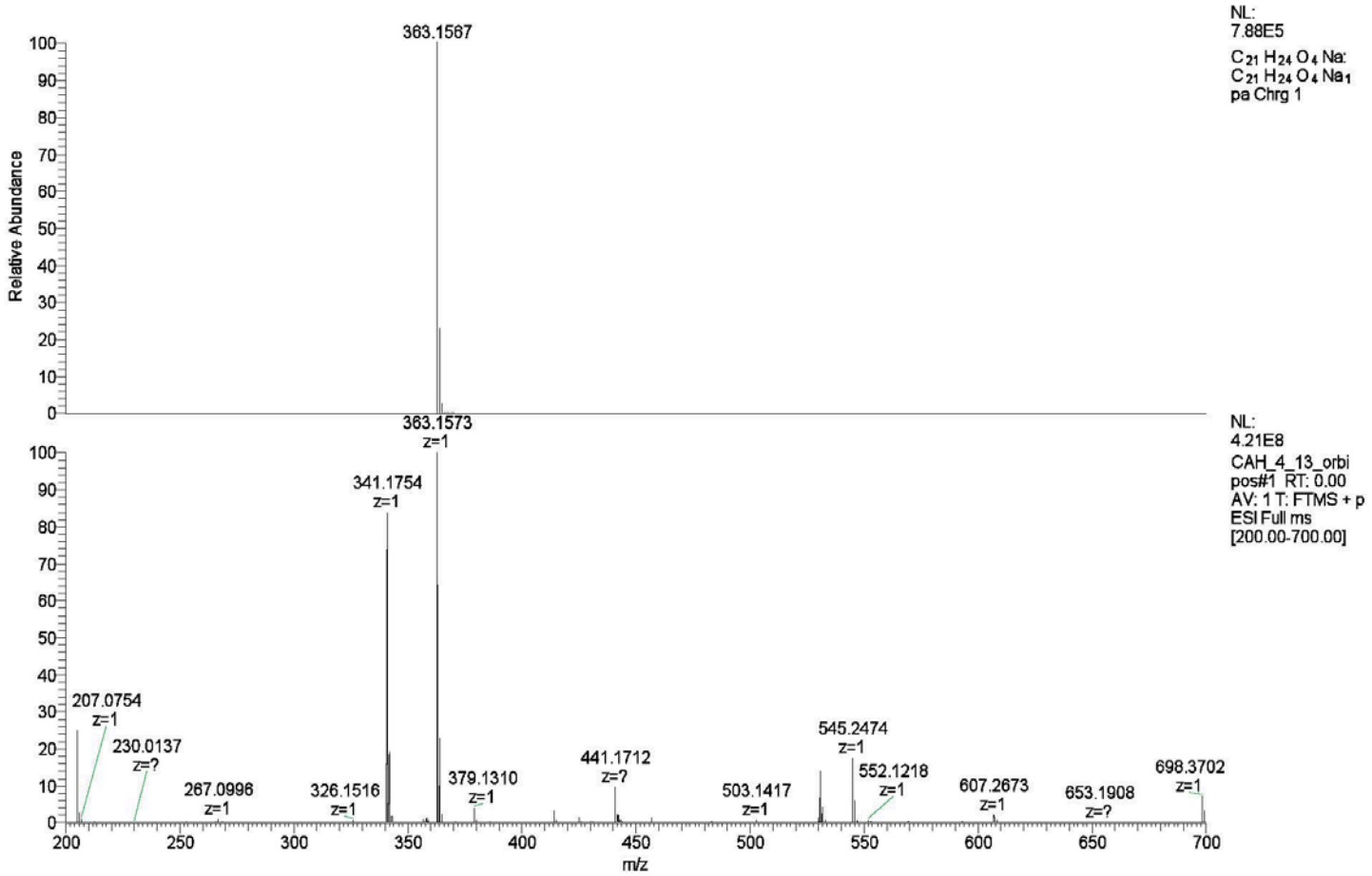
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.211	VB	0.0867	883.39655	154.41168	2.5833
2	14.654	BB	0.0921	1038.45081	172.92358	3.0367
3	17.387	VV	0.1117	1195.93066	155.58759	3.4972
4	18.238	BV	0.1687	3.10785e4	3004.24097	90.8827
Totals :				3.41963e4	3487.16382	

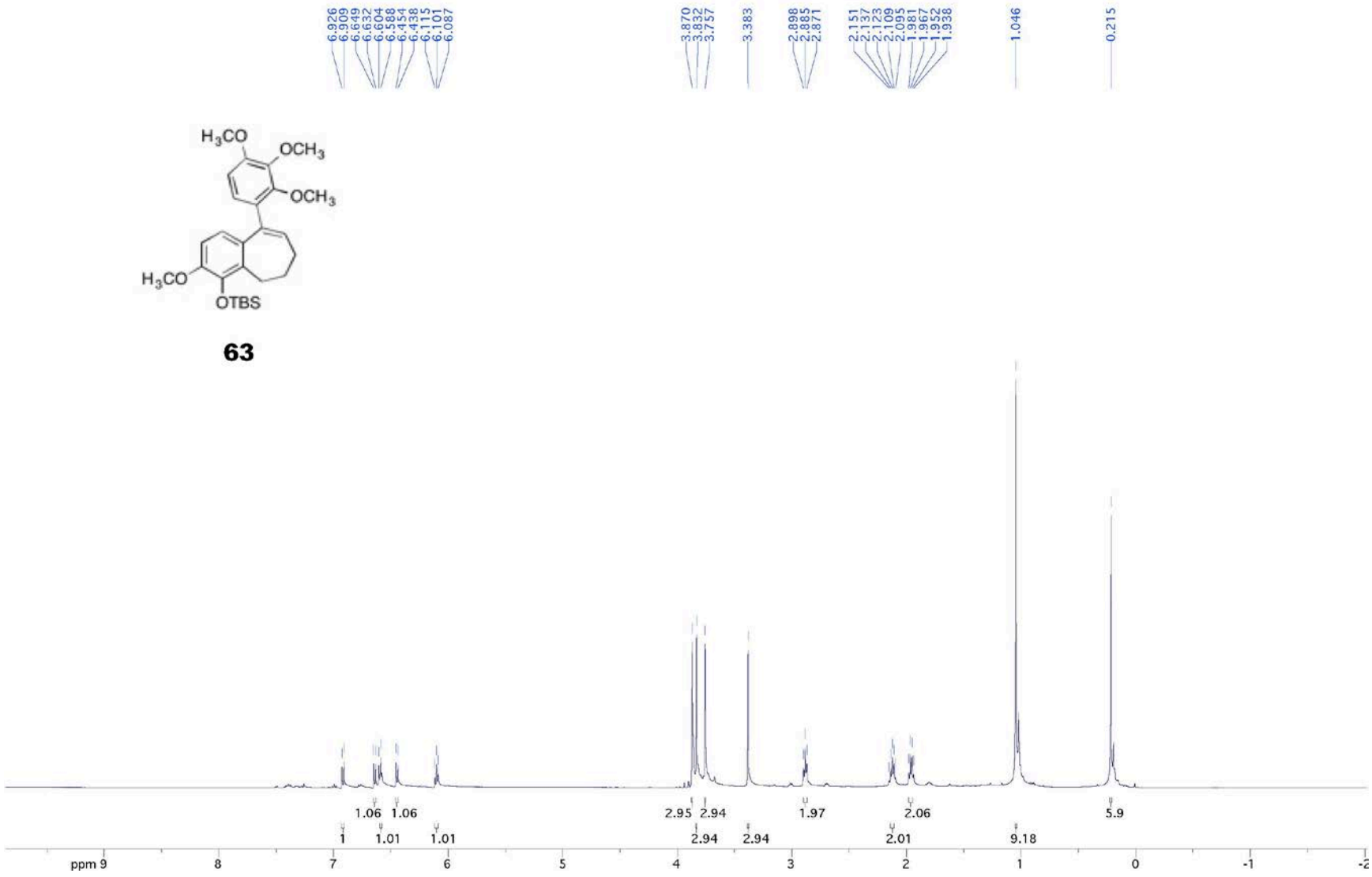
Signal 5: DAD1 G, Sig=300,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.238	BV	0.1329	1.45295e4	1785.51025	100.0000
Totals :				1.45295e4	1785.51025	

*** End of Report ***

HRMS for compound 62

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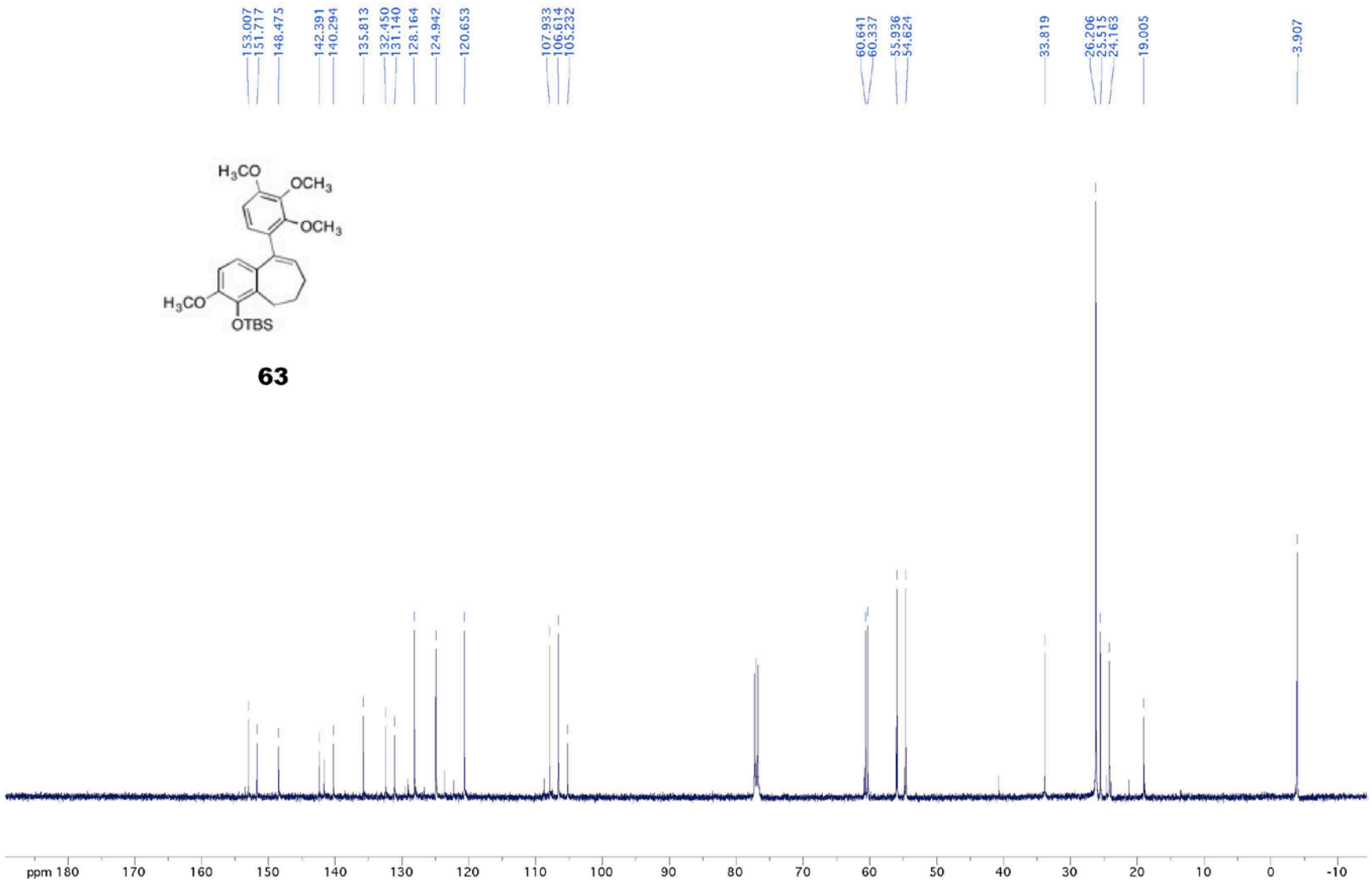
6.909
6.649
6.632
6.604
6.588
6.454
6.438
6.115
6.101
6.087
3.870
3.832
3.757
3.383
2.898
2.885
2.871
2.151
2.137
2.123
2.109
2.095
1.981
1.967
1.952
1.938
1.046
0.215
H3CO
OCH3
OCH3
H3CO
OTBS
63
1.06
1.06
1
1.01
1.01
2.95
2.94
2.94
2.94
1.97
2.01
2.06
9.18
5.9
ppm 9
8
7
6
5
4
3
2
1
0
-1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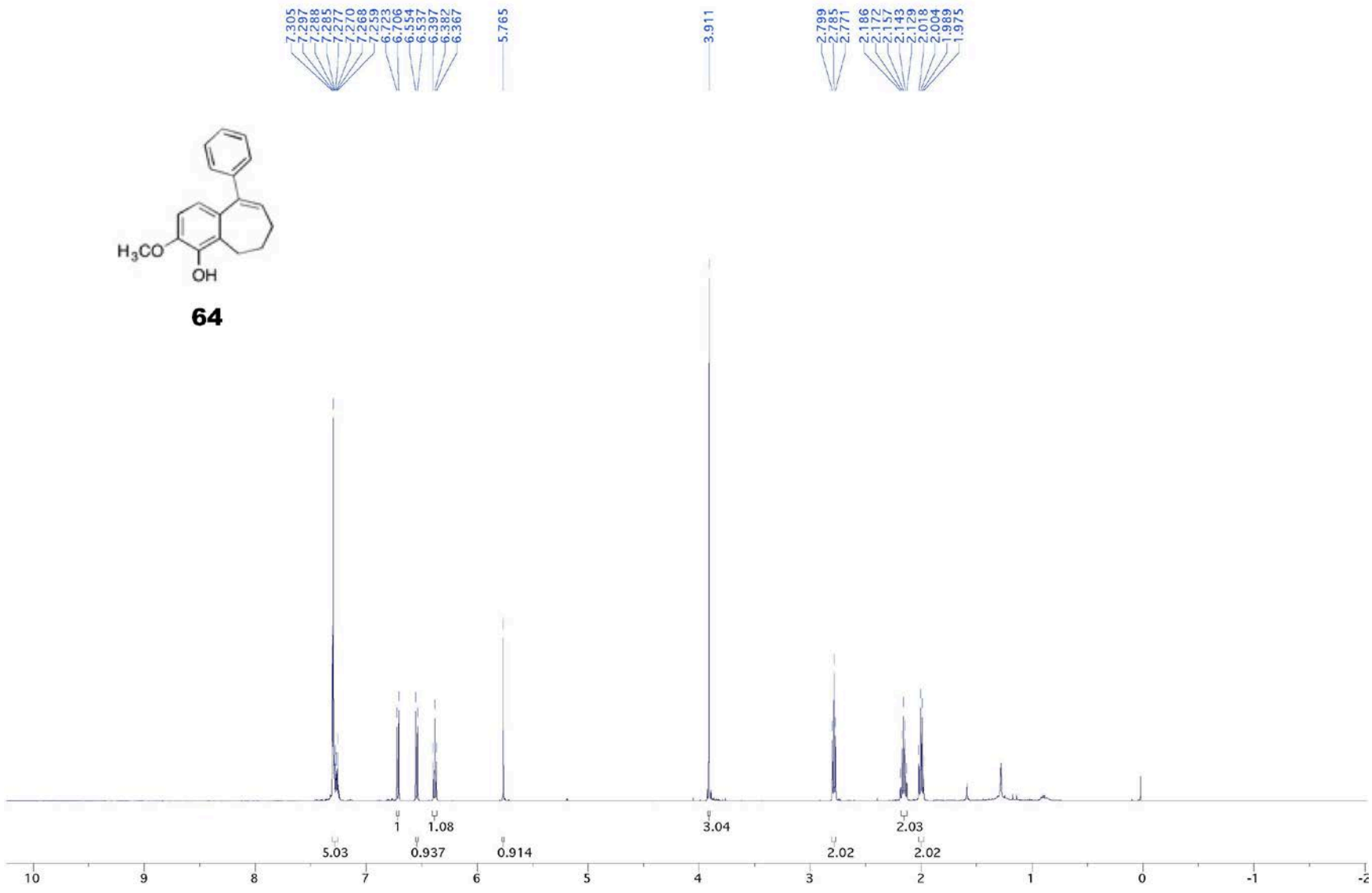
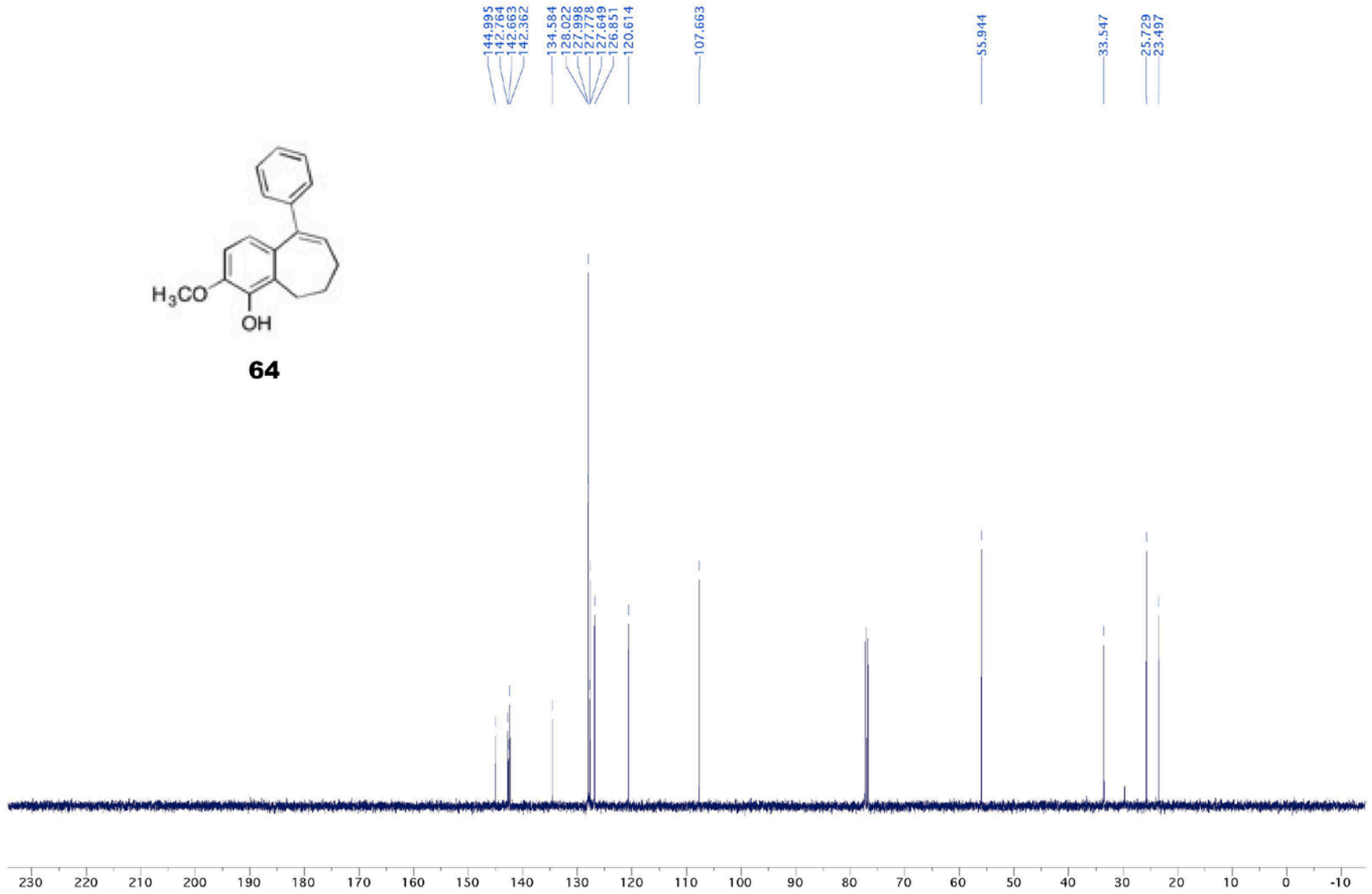
151.717
148.475
142.391
140.294
135.813
132.450
131.140
128.164
124.942
120.653
107.933
106.614
105.232
60.641
60.337
55.936
54.624
33.819
26.206
25.515
24.163
19.005
-3.907
H3CO
OCH3
OCH3
H3CO
OTBS
63
ppm 180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


7.305
7.297
7.288
7.285
7.277
7.270
7.268
7.259
6.723
6.706
6.554
6.537
6.397
6.382
6.367
5.765
3.911
2.799
2.785
2.771
2.186
2.172
2.157
2.143
2.129
2.018
2.004
1.989
1.975
H3CO
OH
64
1
1.08
3.04
2.03
5.03
0.937
0.914
2.02
2.02
10
9
8
7
6
5
4
3
2
1
0
-1


144.995
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142.663
142.362
134.584
128.022
127.998
127.778
127.649
126.851
120.614
107.663
55.944
33.547
25.729
23.497
H3CO
OH
64
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Data File C:\CHEM32\1\DATA\CHRISTINE\TG_1_77000003.D
Sample Name: TG-1-77

HPLC for compound 64

```
==========================================================================
Acq. Operator   : Christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 12/30/2013 10:46:04 AM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 12/30/2013 10:42:27 AM by Christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\TG_1_77000003.D\DA.M (MASTERMETHOD.M)
Last changed    : 5/19/2014 12:27:06 PM by Christine
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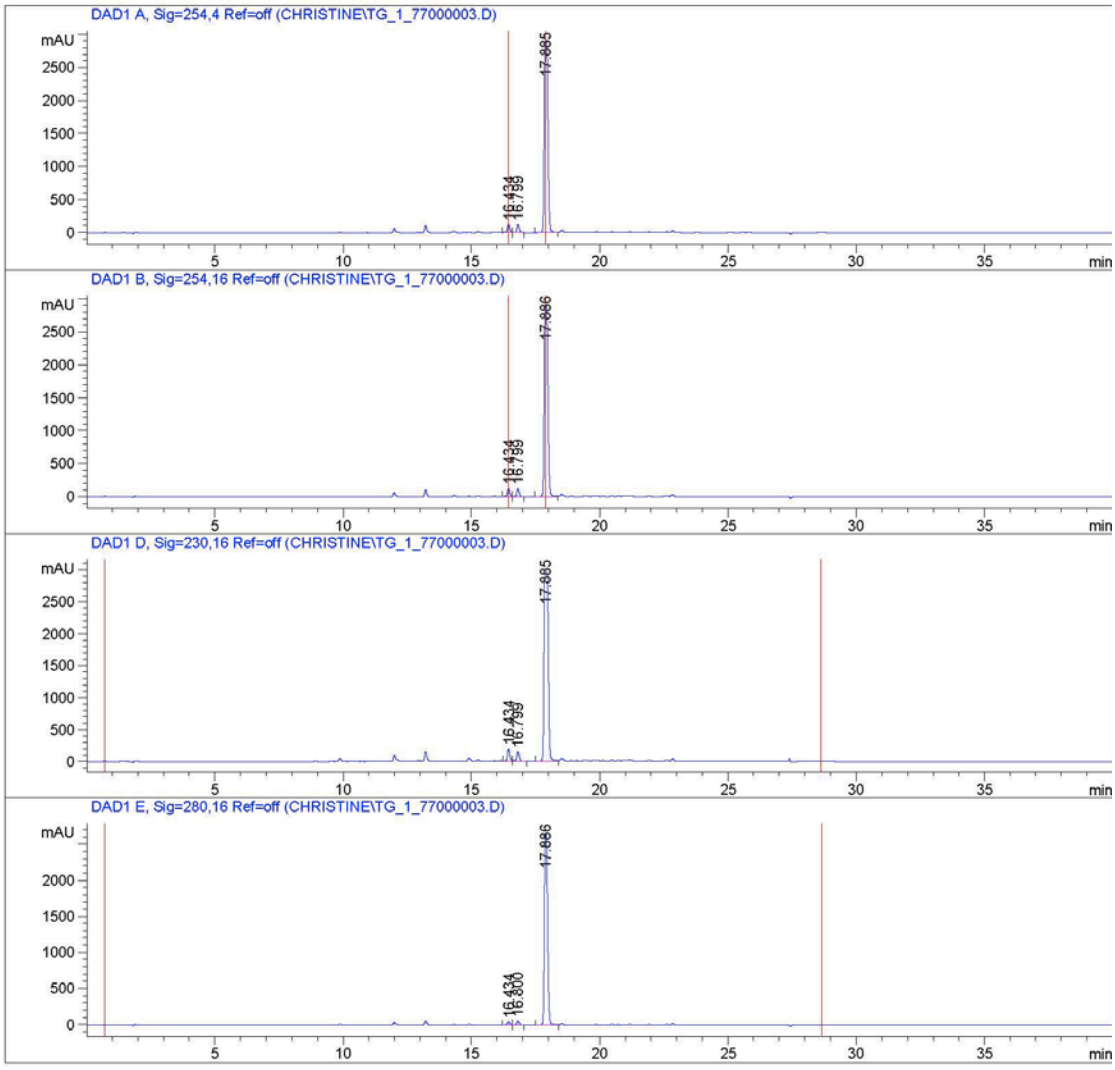
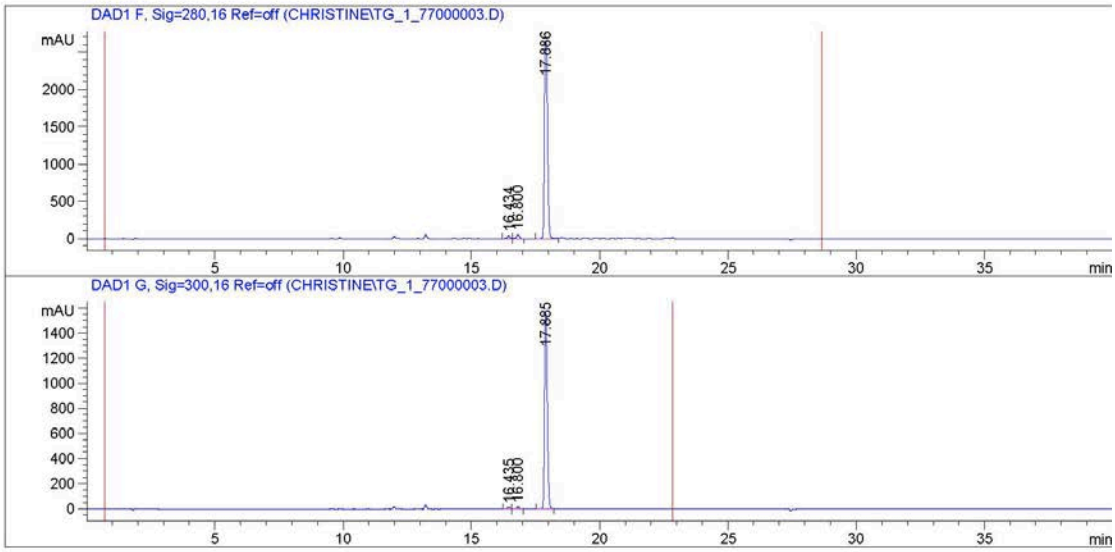


Data File C:\CHEM32\1\DATA\CHRISTINE\TG_1_77000003.D
Sample Name: TG-1-77



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.434	BV	0.1007	842.14648	124.77140	2.7087
2	16.799	VB	0.1029	830.52429	122.81729	2.6713
3	17.885	BV	0.1644	2.94180e4	2897.86890	94.6200
Totals :				3.10907e4	3145.45759	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.434	BV	0.1008	833.83966	123.42804	2.6899
2	16.799	VB	0.1030	826.67096	122.01691	2.6668

Data File C:\CHEM32\1\DATA\CHRISTINE\TG_1_77000003.D
Sample Name: TG-1-77

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
3	17.886	BV	0.1638	2.93381e4	2905.61011	94.6433
Totals :				3.09986e4	3151.05506	

Signal 3: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.434	BV	0.0987	1284.22107	195.25409	3.5227
2	16.799	VB	0.1065	1051.25366	148.74681	2.8837
3	17.885	BV	0.1846	3.41199e4	3002.46069	93.5936
Totals :				3.64554e4	3346.46159	

Signal 4: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.434	BV	0.1028	309.91739	44.74255	1.3397
2	16.800	VB	0.1064	410.00235	58.08295	1.7723
3	17.886	BV	0.1366	2.24138e4	2651.25903	96.8880
Totals :				2.31337e4	2754.08453	

Signal 5: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.434	BV	0.1028	309.91739	44.74255	1.3397
2	16.800	VB	0.1064	410.00235	58.08295	1.7723
3	17.886	BV	0.1366	2.24138e4	2651.25903	96.8880
Totals :				2.31337e4	2754.08453	

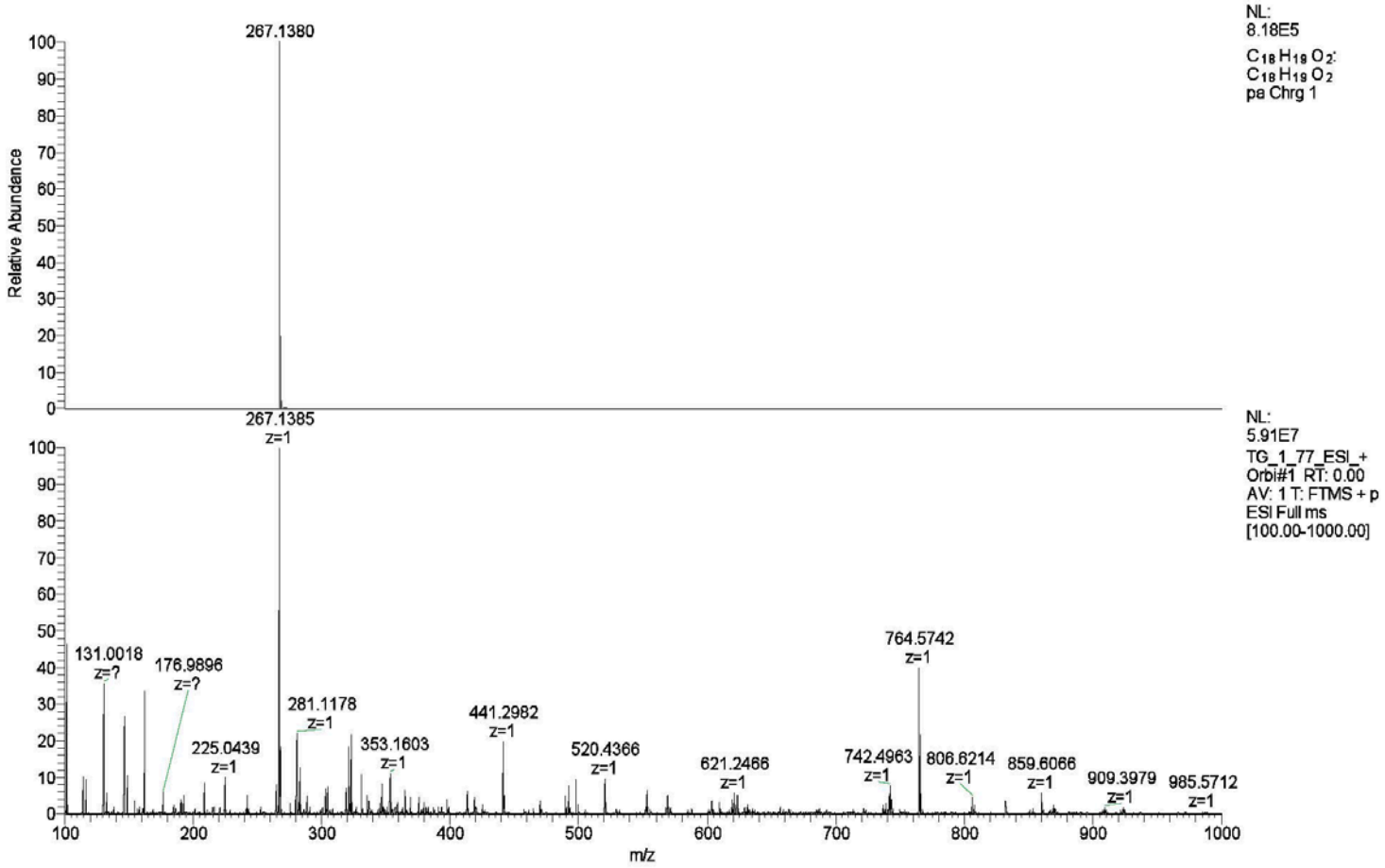
Data File C:\CHEM32\1\DATA\CHRISTINE\TG_1_77000003.D
Sample Name: TG-1-77

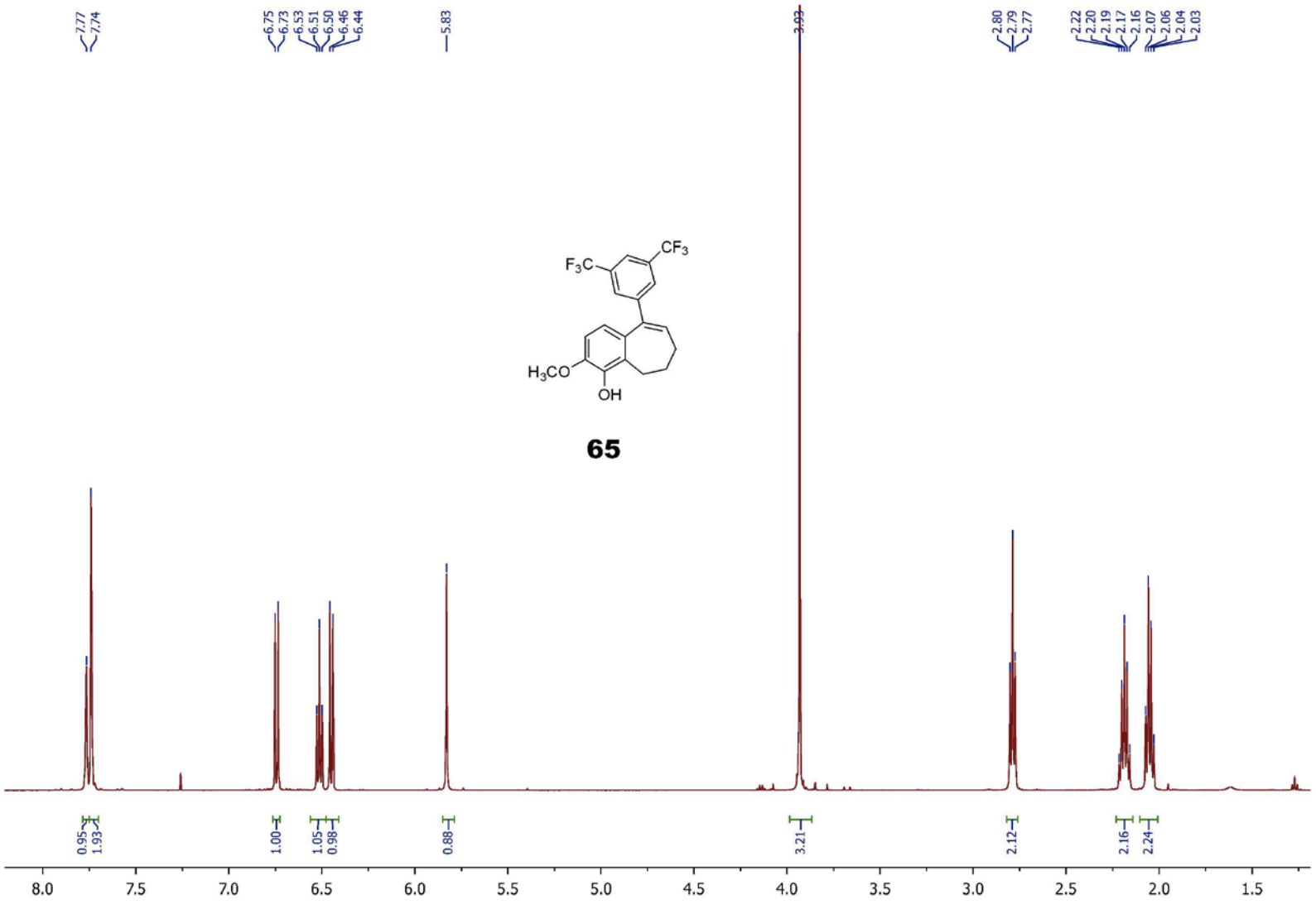
Signal 6: DAD1 G, Sig=300,16 Ref=off

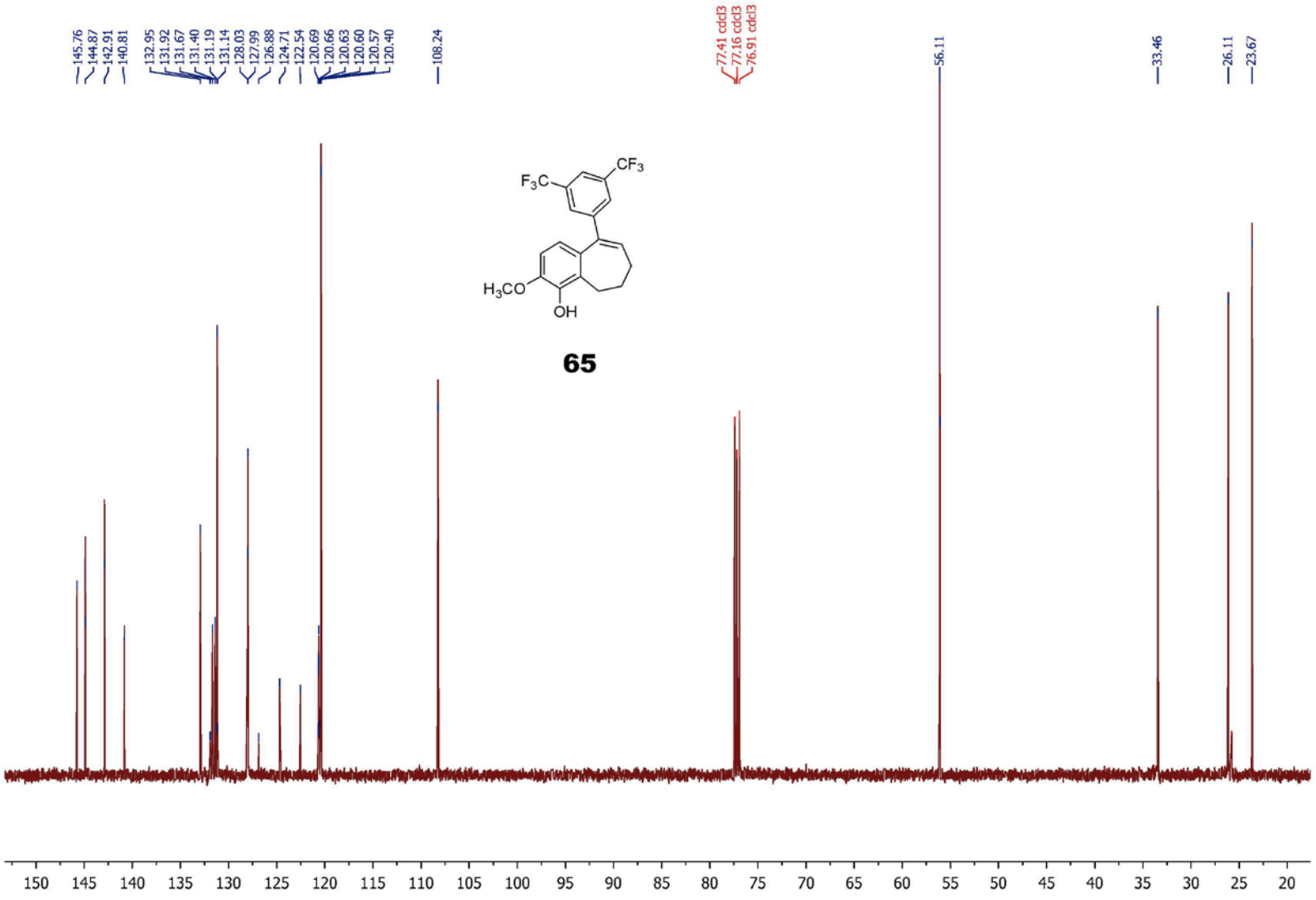
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.435	VV	0.1028	98.29136	14.19804	0.8305
2	16.800	VB	0.1115	128.30803	17.11167	1.0841
3	17.885	BV	0.1162	1.16091e4	1572.00085	98.0855
Totals :				1.18357e4	1603.31057	

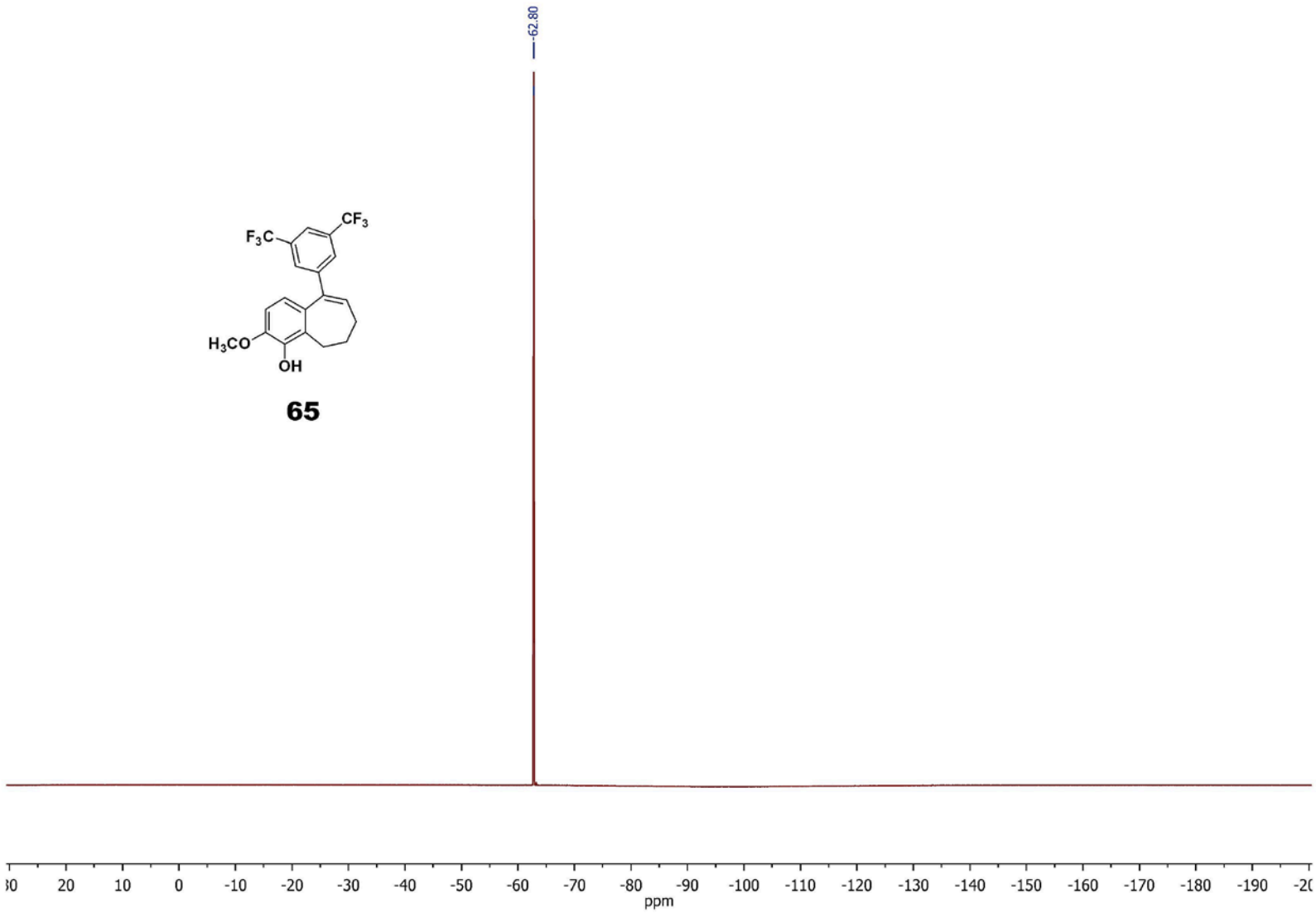
*** End of Report ***

HRMS for compound 64




7.77
7.74
6.75
6.73
6.53
6.51
6.50
6.46
6.44
5.83
3.93
2.80
2.79
2.77
2.22
2.20
2.19
2.17
2.16
2.07
2.06
2.04
2.03
F3C
CF3
H3CO
OH
65
0.95
1.93
1.00
1.05
0.98
0.88
3.21
2.12
2.16
2.24
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


145.76
144.87
142.91
140.81
132.95
131.92
131.67
131.40
131.19
131.14
128.03
127.99
126.88
124.71
122.54
120.69
120.66
120.63
120.60
120.57
120.40
108.24
77.41 cdcl3
77.16 cdcl3
76.91 cdcl3
56.11
33.46
26.11
23.67
F3C
CF3
H3CO
OH
65
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20


-62.80
F3C
CF3
H3CO
OH
65
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -20
ppm

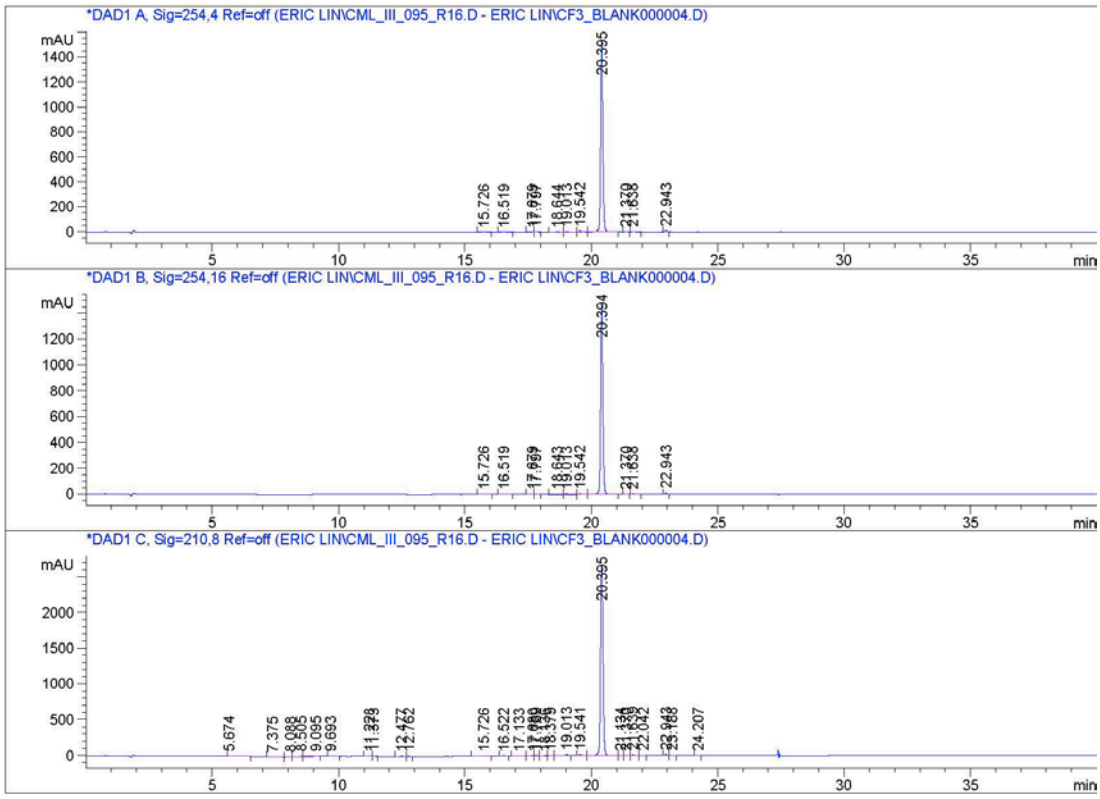
Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_095_R16.D
Sample Name: CML_III_095_r1

HPLC for compound 65

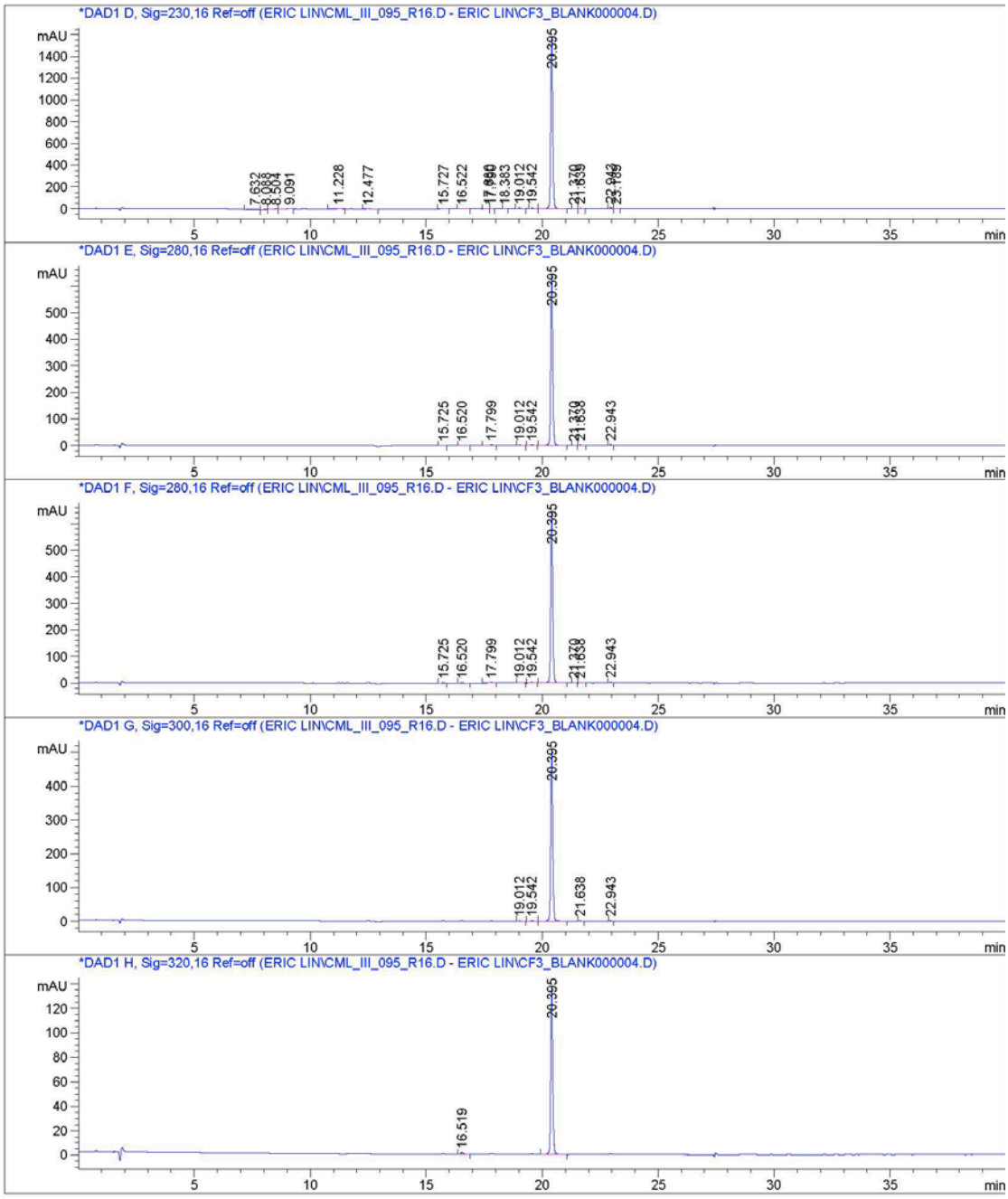
```
==================================================================
Acq. Operator   : Eric Lin
Acq. Instrument : Instrument 1                  Location :   -
Injection Date  : 3/11/2014 2:51:58 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 3/11/2014 2:48:52 PM by Eric Lin
Analysis Method : C:\CHEM32\1\DATA\ERIC LIN\CML_III_095_R16.D\DA.M (MASTERMETHOD.M)
Last changed    : 3/11/2014 3:54:40 PM by Eric Lin
Sample Info     : wash

                  Method:

                  0-25 min. (50:50 to 100:0) ACN:Water
                  25-30 min. (100:0) ACN:Water
                  30-35 min. (100:0 to 50:50) ACN:Water
                  35-40 min. (50:50) ACN:Water
```



Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_095_R16.D
Sample Name: CML_III_095_r1



Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_095_R16.D
Sample Name: CML_III_095_r1

==========

Area Percent Report

==========

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.726	BB	0.0982	20.13693	3.08261	0.2106
2	16.519	BB	0.1184	21.30018	2.68834	0.2227
3	17.679	BV	0.1106	17.70028	2.27860	0.1851
4	17.797	VB	0.1132	25.49945	3.33327	0.2667
5	18.644	BV	0.3221	61.30715	2.46542	0.6411
6	19.013	VB	0.1513	70.46623	6.35964	0.7369
7	19.542	BB	0.1120	57.89999	7.50579	0.6055
8	20.395	BB	0.0922	9198.03418	1528.99988	96.1876
9	21.370	BB	0.0791	13.52444	2.66984	0.1414
10	21.638	BB	0.0835	26.06196	4.78922	0.2725
11	22.943	VV	0.0783	50.66928	10.13774	0.5299
Totals :				9562.60008	1574.31034	

Signal 2: DAD1 B, Sig=254,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.726	BB	0.0983	19.38648	2.96598	0.2103
2	16.519	BB	0.1190	20.82996	2.61210	0.2260
3	17.679	BV	0.1112	17.47881	2.23609	0.1896
4	17.797	VB	0.1132	25.27899	3.30642	0.2742
5	18.643	BV	0.3208	56.03249	2.24808	0.6078
6	19.013	VB	0.1471	65.22282	6.08367	0.7075
7	19.542	BB	0.1113	54.82693	7.16507	0.5947
8	20.394	BB	0.0921	8872.07324	1475.70349	96.2390
9	21.370	BB	0.0791	12.99658	2.56620	0.1410
10	21.638	BB	0.0836	25.24567	4.63317	0.2739
11	22.943	VV	0.0783	49.41745	9.88459	0.5361
Totals :				9218.78941	1519.40486	

Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_095_R16.D
Sample Name: CML_III_095_r1

Signal 3: DAD1 C, Sig=210,8 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.674	VB	0.3926	44.06831	1.38739	0.2177
2	7.375	BB	0.4786	214.54793	5.86683	1.0599
3	8.088	BV	0.1815	70.84110	6.00896	0.3500
4	8.505	VV	0.2886	131.47398	5.84208	0.6495
5	9.095	VB	0.3278	81.57391	3.28358	0.4030
6	9.693	BB	0.2099	17.39349	1.11562	0.0859
7	11.228	BV	0.1006	57.96552	8.60018	0.2864
8	11.373	VB	0.0894	14.11614	2.37216	0.0697
9	12.477	BV	0.1629	46.31915	3.78189	0.2288
10	12.762	VB	0.1005	34.67432	5.15360	0.1713
11	15.726	BB	0.1044	51.22066	7.24781	0.2530
12	16.522	BB	0.1089	55.50475	7.80679	0.2742
13	17.133	BB	0.2957	60.25353	2.56871	0.2977
14	17.680	BV	0.1381	80.84849	7.85592	0.3994
15	17.789	VV	0.1288	75.16172	8.37082	0.3713
16	18.136	VB	0.2330	26.68663	1.61339	0.1318
17	18.379	BV	0.1083	47.17024	6.52840	0.2330
18	19.013	VB	0.1081	139.61841	18.91397	0.6897
19	19.541	VB	0.0978	95.36326	14.67350	0.4711
20	20.395	BV	0.1118	1.86236e4	2657.28906	92.0020
21	21.134	VV	0.1510	20.76570	2.03656	0.1026
22	21.370	VB	0.0898	37.02381	6.19101	0.1829
23	21.639	BB	0.0880	63.57571	10.91086	0.3141
24	22.042	BB	0.1008	7.01408	1.01333	0.0347
25	22.943	VV	0.0789	94.95434	18.80930	0.4691
26	23.188	VB	0.1056	43.21199	6.03252	0.2135
27	24.207	BB	0.1019	7.66240	1.17747	0.0379
Totals :				2.02426e4	2822.45171	

Signal 4: DAD1 D, Sig=230,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.632	BB	0.3457	244.82117	8.66334	2.3247
2	8.088	BV	0.1865	83.24166	6.91353	0.7904
3	8.504	VV	0.2903	155.94417	6.88412	1.4808
4	9.091	VB	0.3319	95.37034	3.78608	0.9056
5	11.228	BB	0.0986	26.37656	4.01844	0.2505
6	12.477	BB	0.3337	77.63901	2.88735	0.7372
7	15.727	BB	0.1022	20.69559	3.00905	0.1965
8	16.522	BB	0.1230	29.73312	3.57454	0.2823

Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_095_R16.D
Sample Name: CML_III_095_r1

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
9	17.680	BV	0.1323	34.43248	3.57857	0.3270
10	17.790	VB	0.1142	25.67534	3.39784	0.2438
11	18.383	BB	0.1008	12.53002	1.95390	0.1190
12	19.012	BB	0.0930	42.09318	6.91282	0.3997
13	19.542	VB	0.1016	41.41371	6.06741	0.3932
14	20.395	BB	0.0922	9513.58496	1581.17224	90.3374
15	21.370	BB	0.0906	17.37347	2.87103	0.1650
16	21.639	BB	0.1049	40.14706	5.51546	0.3812
17	22.943	VV	0.0787	58.11080	11.55836	0.5518
18	23.189	VB	0.1223	11.98790	1.39506	0.1138
Totals :				1.05312e4	1664.15915	

Signal 5: DAD1 E, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.725	BB	0.0922	7.46464	1.24071	0.1873
2	16.520	BB	0.1243	9.99923	1.18650	0.2509
3	17.799	BB	0.1403	28.14871	2.87234	0.7064
4	19.012	BB	0.1053	13.62076	1.90712	0.3418
5	19.542	BB	0.1191	24.31960	2.92321	0.6103
6	20.395	BB	0.0920	3864.91748	643.91962	96.9896
7	21.370	BB	0.0796	5.79338	1.13348	0.1454
8	21.638	BB	0.0838	11.43022	2.08863	0.2868
9	22.943	VB	0.0768	19.18251	3.93981	0.4814
Totals :				3984.87653	661.21142	

Signal 6: DAD1 F, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.725	BB	0.0922	7.46464	1.24071	0.1873
2	16.520	BB	0.1243	9.99923	1.18650	0.2509
3	17.799	BB	0.1403	28.14871	2.87234	0.7064
4	19.012	BB	0.1053	13.62076	1.90712	0.3418
5	19.542	BB	0.1191	24.31960	2.92321	0.6103
6	20.395	BB	0.0920	3864.91748	643.91962	96.9896
7	21.370	BB	0.0796	5.79338	1.13348	0.1454
8	21.638	BB	0.0838	11.43022	2.08863	0.2868
9	22.943	VB	0.0768	19.18251	3.93981	0.4814

Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_095_R16.D
Sample Name: CML_III_095_r1

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
Totals :				3984.87653	661.21142	

Signal 7: DAD1 G, Sig=300,16 Ref=off
Signal has been modified after loading from rawdata file!

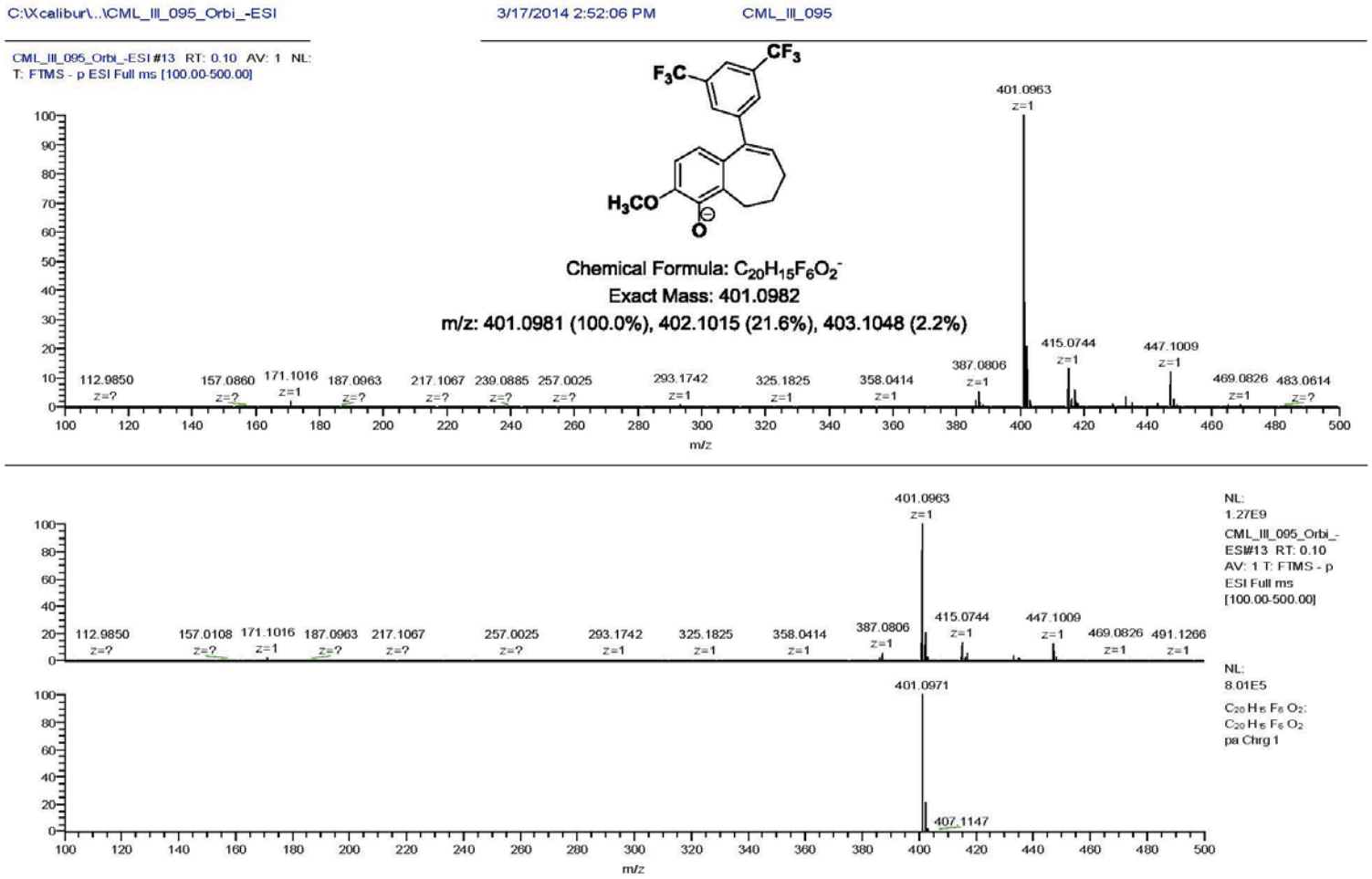
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.012	BB	0.1139	8.24947	1.04762	0.2664
2	19.542	BB	0.1270	16.53314	1.83632	0.5339
3	20.395	BB	0.0921	3057.46191	508.62131	98.7265
4	21.638	BB	0.0804	6.04191	1.16629	0.1951
5	22.943	BB	0.0767	8.61605	1.77379	0.2782
Totals :				3096.90248	514.44532	

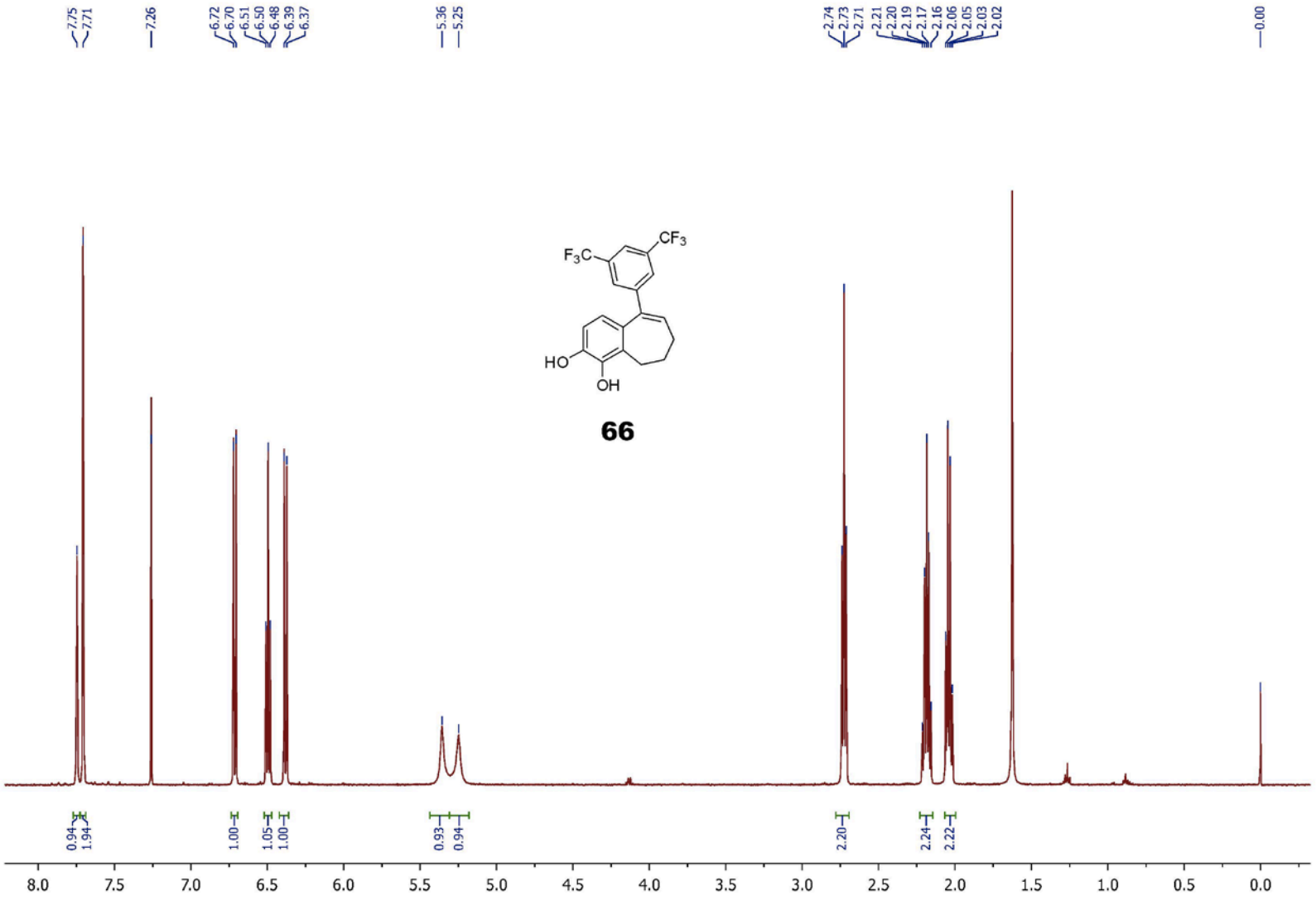
Signal 8: DAD1 H, Sig=320,16 Ref=off
Signal has been modified after loading from rawdata file!

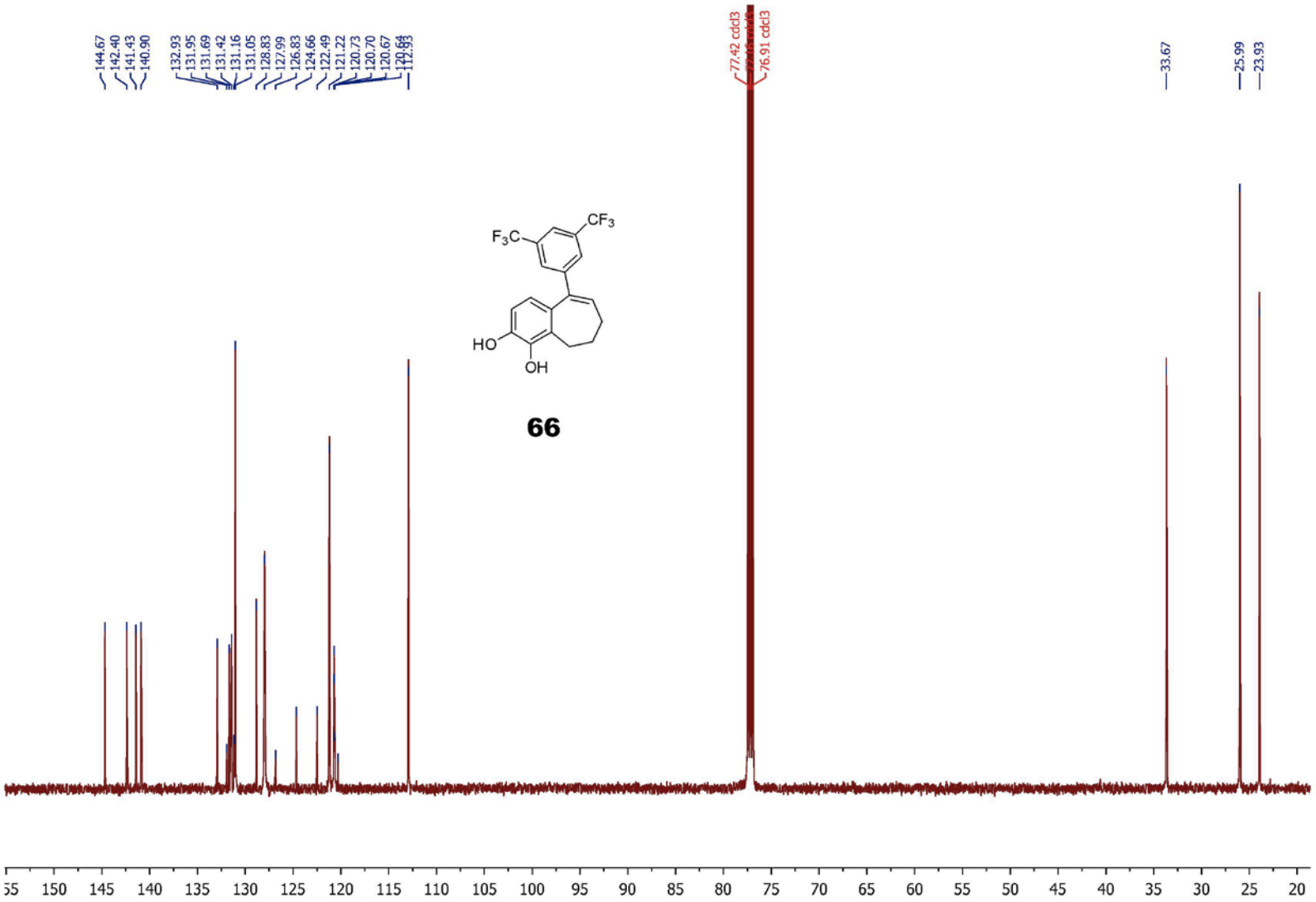
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.519	BB	0.1121	10.13603	1.37369	1.2035
2	20.395	BB	0.0928	832.06708	137.10928	98.7965
Totals :				842.20311	138.48297	

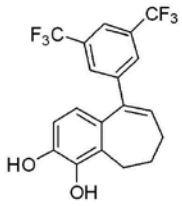
*** End of Report ***

HRMS for compound 65




7.75
7.71
7.26
6.72
6.70
6.51
6.50
6.48
6.39
6.37
5.36
5.25
2.74
2.73
2.71
2.21
2.20
2.19
2.17
2.16
2.06
2.05
2.03
2.02
0.00
F3C
CF3
HO
OH
66
0.94
1.94
1.00
1.05
1.00
0.93
0.94
2.20
2.24
2.22
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
0.0


144.67
142.40
141.43
140.90
132.93
131.95
131.69
131.42
131.16
131.05
128.83
127.99
126.83
124.66
122.49
121.22
120.73
120.70
120.67
77.42 cdcl3
76.91 cdcl3
33.67
25.99
23.93
F3C
CF3
HO
OH
66
55 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20


F3C
CF3
HO
OH

66

20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

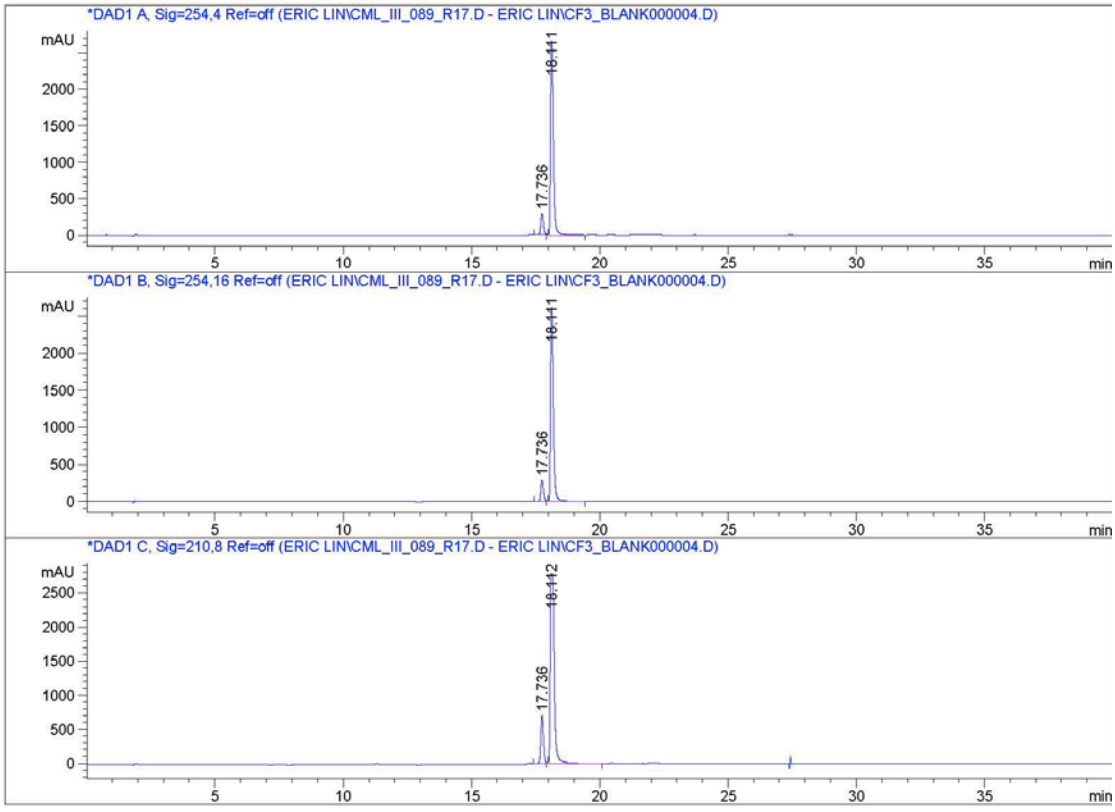
Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_089_R17.D
Sample Name: CML_III_089_r1

HPLC for compound 66

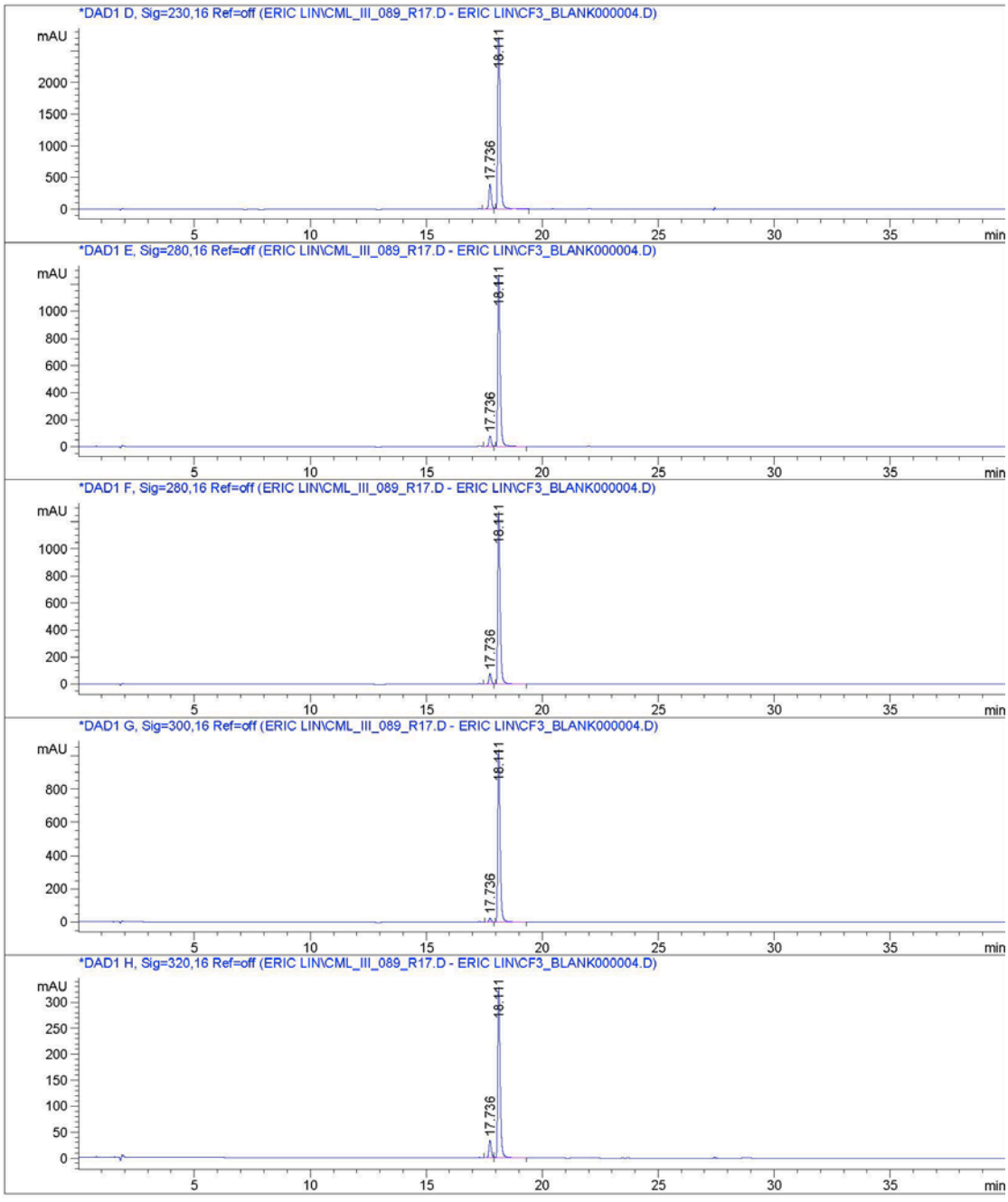
```
==========================================================================
Acq. Operator   : Eric Lin
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 3/11/2014 3:54:22 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 3/11/2014 3:42:14 PM by Eric Lin
Analysis Method : C:\CHEM32\1\DATA\ERIC LIN\CML_III_089_R17.D\DA.M (MASTERMETHOD.M)
Last changed    : 3/11/2014 4:44:37 PM by Eric Lin
Sample Info     : wash

                  Method:

                  0-25 min. (50:50 to 100:0) ACN:Water
                  25-30 min. (100:0) ACN:Water
                  30-35 min. (100:0 to 50:50) ACN:Water
                  35-40 min. (50:50) ACN:Water
```



Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_089_R17.D
Sample Name: CML_III_089_r1



Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_089_R17.D
Sample Name: CML_III_089_r1

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.736	BV	0.1074	2060.98120	295.51819	9.0361
2	18.111	VB	0.1228	2.07474e4	2666.64331	90.9639
Totals :				2.28084e4	2962.16150	

Signal 2: DAD1 B, Sig=254,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.736	BV	0.1074	2008.27014	287.96533	9.0541
2	18.111	VB	0.1198	2.01725e4	2620.97852	90.9459
Totals :				2.21808e4	2908.94385	

Signal 3: DAD1 C, Sig=210,8 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.736	BV	0.1083	4991.49316	707.71631	13.9556
2	18.112	VB	0.1746	3.07754e4	2790.98706	86.0444
Totals :				3.57669e4	3498.70337	

Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_089_R17.D
Sample Name: CML_III_089_r1

Signal 4: DAD1 D, Sig=230,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.736	BV	0.1078	2763.69995	394.30969	11.6487
2	18.111	VB	0.1197	2.09617e4	2726.13794	88.3513
Totals :				2.37254e4	3120.44763	

Signal 5: DAD1 E, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.736	BV	0.1070	546.02472	78.59853	5.7074
2	18.111	VB	0.1085	9020.88184	1274.97351	94.2926
Totals :				9566.90656	1353.57204	

Signal 6: DAD1 F, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.736	BV	0.1070	546.02472	78.59853	5.7074
2	18.111	VB	0.1085	9020.88184	1274.97351	94.2926
Totals :				9566.90656	1353.57204	

Signal 7: DAD1 G, Sig=300,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.736	BB	0.1042	170.52390	25.43328	2.2779
2	18.111	BB	0.1082	7315.54199	1038.30994	97.7221
Totals :				7486.06589	1063.74322	

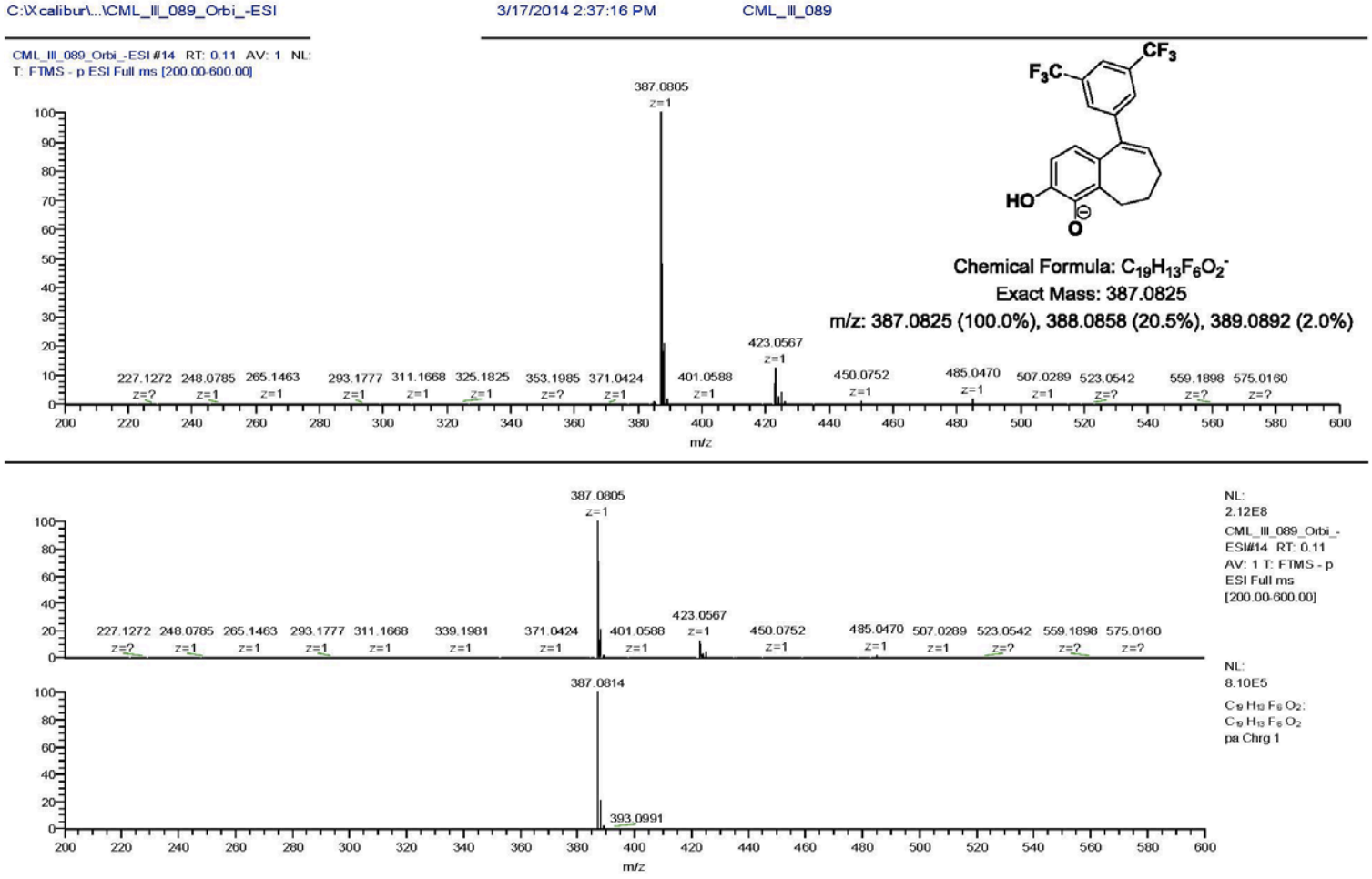
Data File C:\CHEM32\1\DATA\ERIC LIN\CML_III_089_R17.D
Sample Name: CML_III_089_r1

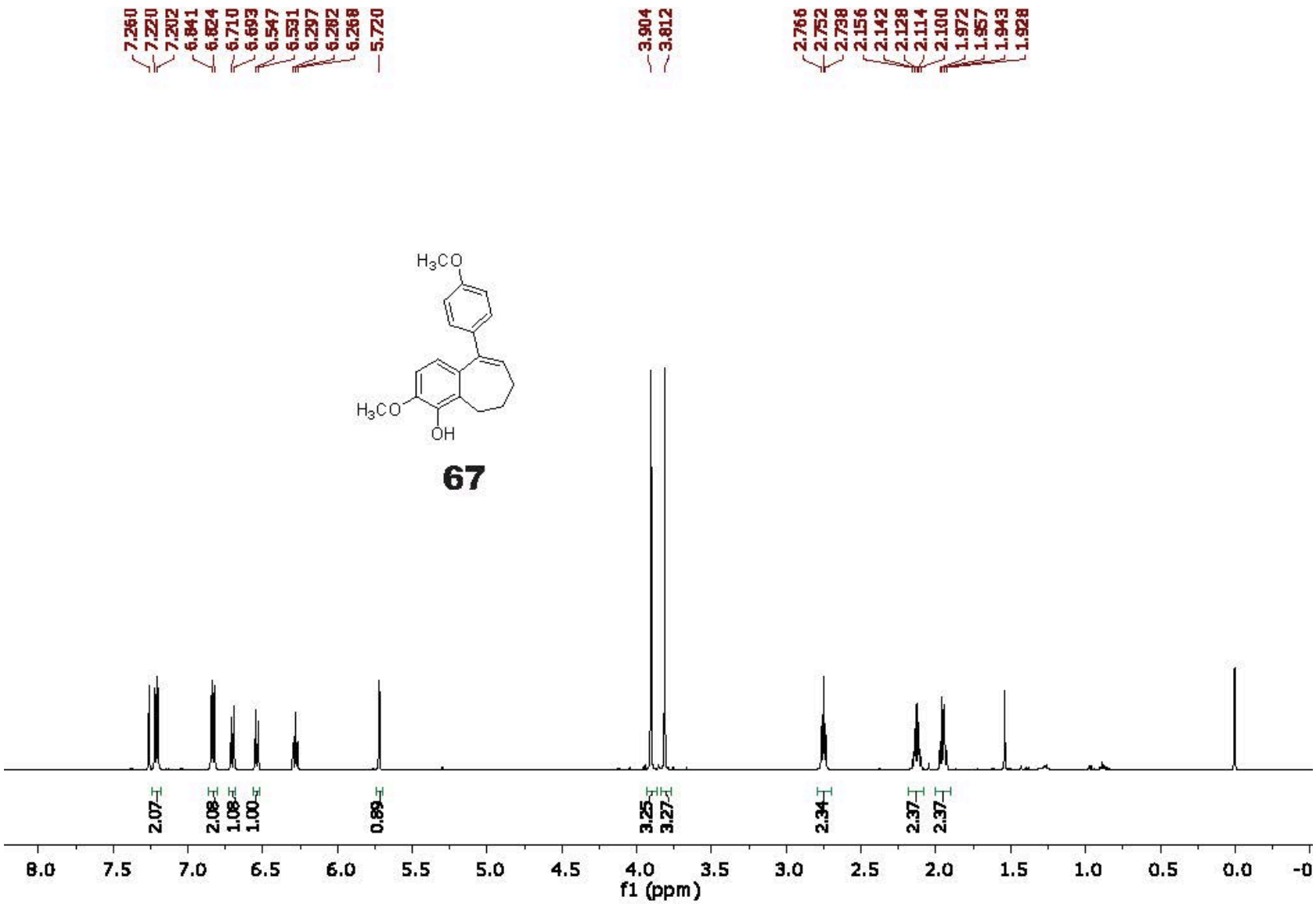
Signal 8: DAD1 H, Sig=320,16 Ref=off
Signal has been modified after loading from rawdata file!

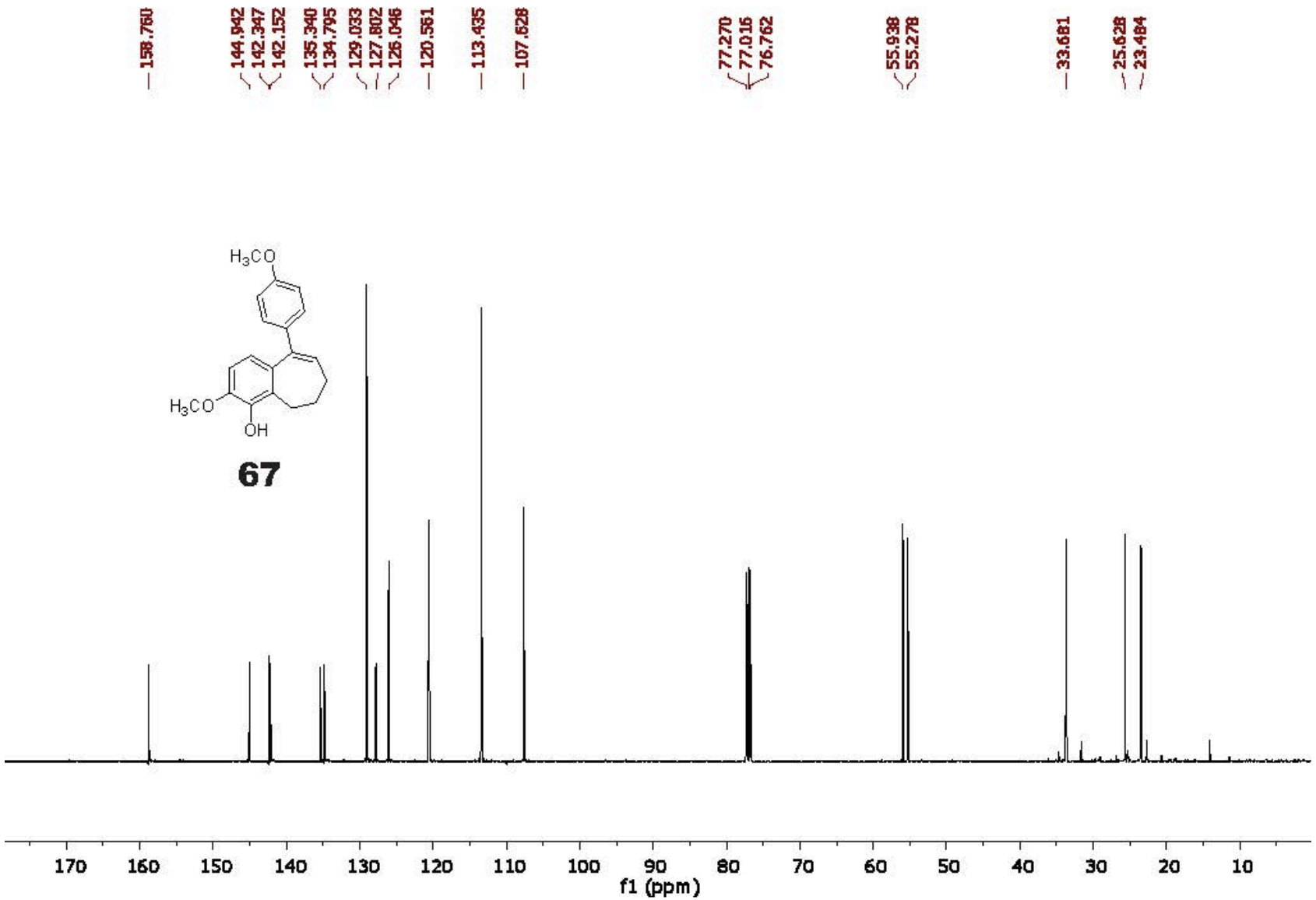
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.736	BV	0.1068	232.93462	33.65369	9.0931
2	18.111	VB	0.1086	2328.72632	328.78772	90.9069
Totals :				2561.66093	362.44141	

*** End of Report ***

HRMS for compound 66




7.260
7.220
7.202
6.841
6.824
6.710
6.693
6.547
6.531
6.297
6.282
6.268
5.720
3.904
3.812
2.766
2.752
2.738
2.156
2.142
2.128
2.114
2.100
1.972
1.957
1.943
1.928
H3CO
H3CO
OH
67
2.07
2.08
1.08
1.00
0.89
3.25
3.27
2.34
2.37
2.37
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
0.0
-0
f1 (ppm)


158.760
144.942
142.347
142.152
135.340
134.795
129.033
127.802
126.046
120.561
113.435
107.628
77.270
77.016
76.762
55.938
55.278
33.681
25.628
23.484
H3CO
H3CO
OH
67
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Data File C:\CHEM32\1\DATA\LAXMAN\LD-IV-131-1A\LDIV131-1ARUN02.D
Sample Name: LD-IV-131-1A-rerun-run1

HPLC for compound 67

```
==========================================================================
Acq. Operator   : Laxman
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 1/27/2014 5:37:35 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 1/27/2014 5:33:50 PM by Laxman
Analysis Method : C:\CHEM32\1\DATA\LAXMAN\LD-IV-131-1A\LDIV131-1ARUN02.D\DA.M (MASTERMETHOD.M)
Last changed    : 1/28/2014 10:47:18 AM by Laxman
                  (modified after loading)
Sample Info     : run1
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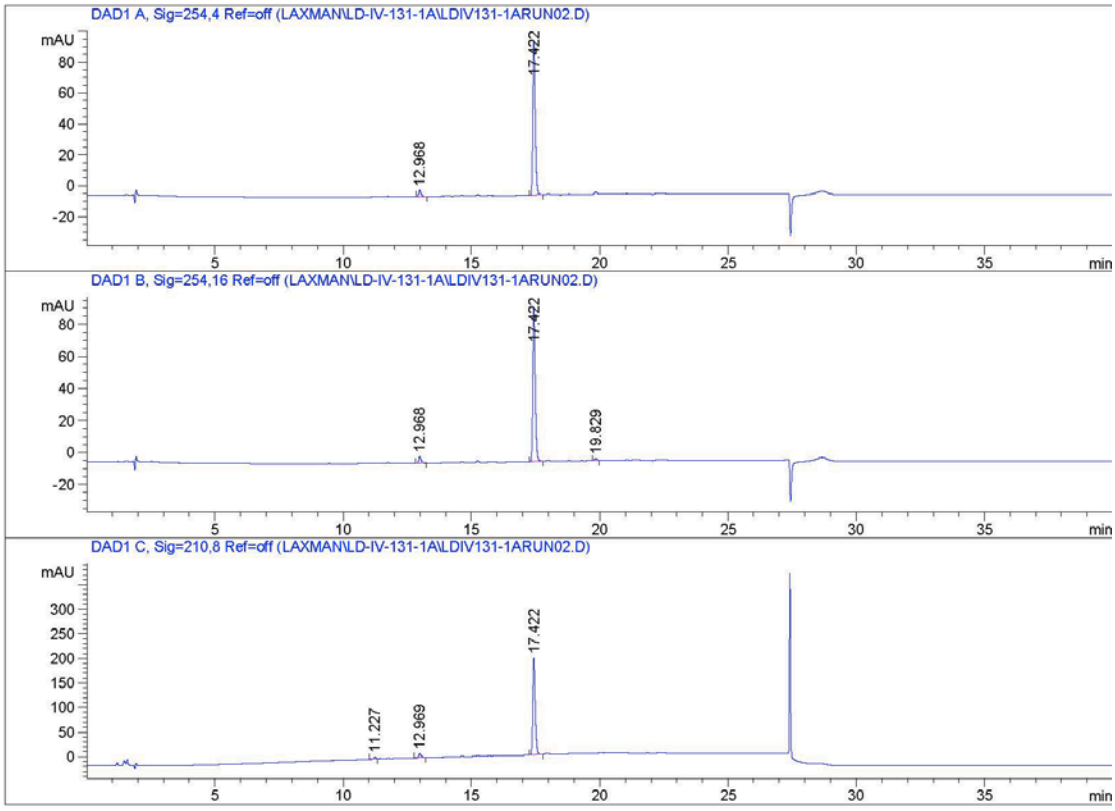
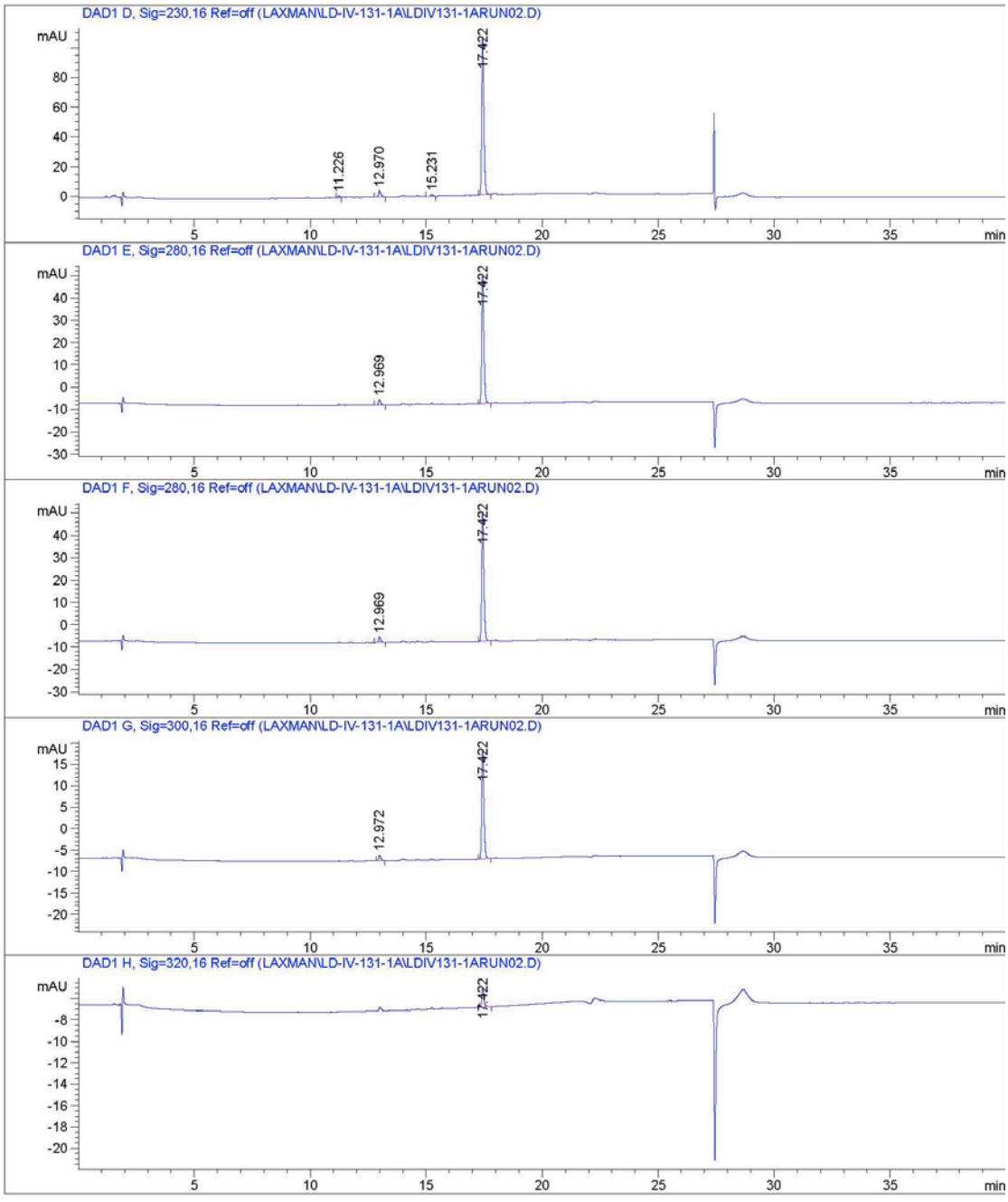


Data File C:\CHEM32\1\DATA\LAXMAN\LD-IV-131-1A\LDIV131-1ARUN02.D
Sample Name: LD-IV-131-1A-rerun-run1



Data File C:\CHEM32\1\DATA\LAXMAN\LD-IV-131-1A\LDIV131-1ARUN02.D
Sample Name: LD-IV-131-1A-rerun-run1

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.968	BB	0.0937	27.01311	4.27345	4.0000
2	17.422	BB	0.0976	648.31488	100.04857	96.0000
Totals :				675.32799	104.32202	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.968	BB	0.0938	26.28994	4.15377	3.9796
2	17.422	BB	0.0976	626.04687	96.60343	94.7661
3	19.829	BB	0.0944	8.28639	1.33497	1.2543
Totals :				660.62320	102.09217	

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.227	BV	0.0829	24.89905	4.61790	1.8119
2	12.969	BB	0.1030	61.09814	8.58504	4.4460
3	17.422	BV	0.1000	1288.22766	197.75839	93.7421
Totals :				1374.22486	210.96132	

Data File C:\CHEM32\1\DATA\LAXMAN\LD-IV-131-1A\LDIV131-1ARUN02.D
Sample Name: LD-IV-131-1A-rerun-run1

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.226	BB	0.0760	5.55864	1.15744	0.7525
2	12.970	BB	0.1029	31.45657	4.42585	4.2583
3	15.231	BB	0.1021	7.81155	1.13753	1.0575
4	17.422	BV	0.0980	693.87982	106.45760	93.9317
Totals :				738.70657	113.17843	

Signal 5: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.969	BB	0.0958	17.15126	2.64083	4.3596
2	17.422	BB	0.0977	376.26514	58.01117	95.6404
Totals :				393.41640	60.65200	

Signal 6: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.969	BB	0.0958	17.15126	2.64083	4.3596
2	17.422	BB	0.0977	376.26514	58.01117	95.6404
Totals :				393.41640	60.65200	

Signal 7: DAD1 G, Sig=300,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.972	BB	0.1010	9.45148	1.39534	5.3948
2	17.422	BB	0.0977	165.74431	25.52812	94.6052
Totals :				175.19579	26.92346	

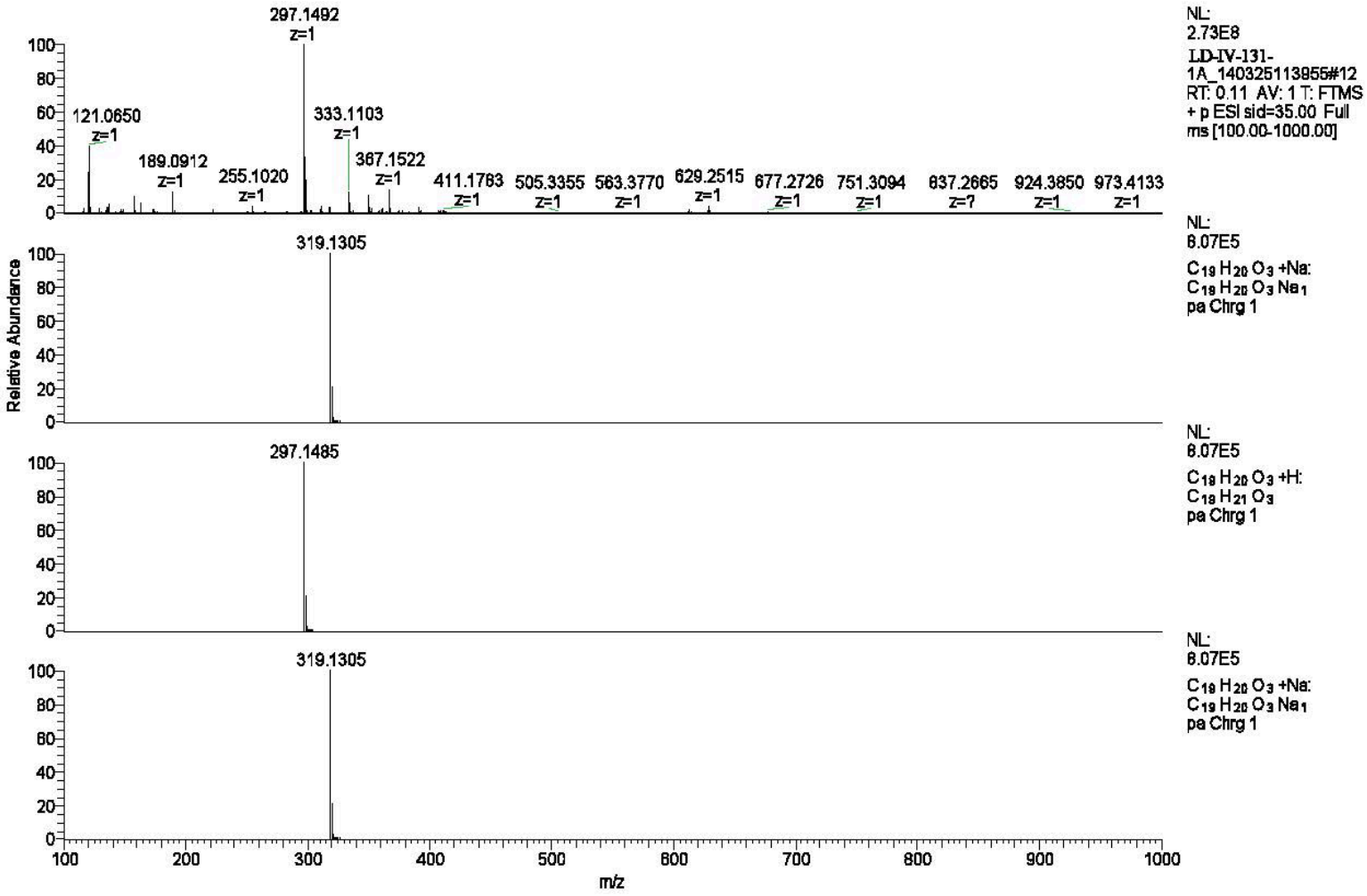
Data File C:\CHEM32\1\DATA\LAXMAN\LD-IV-131-1A\LDIV131-1ARUN02.D
Sample Name: LD-IV-131-1A-rerun-run1

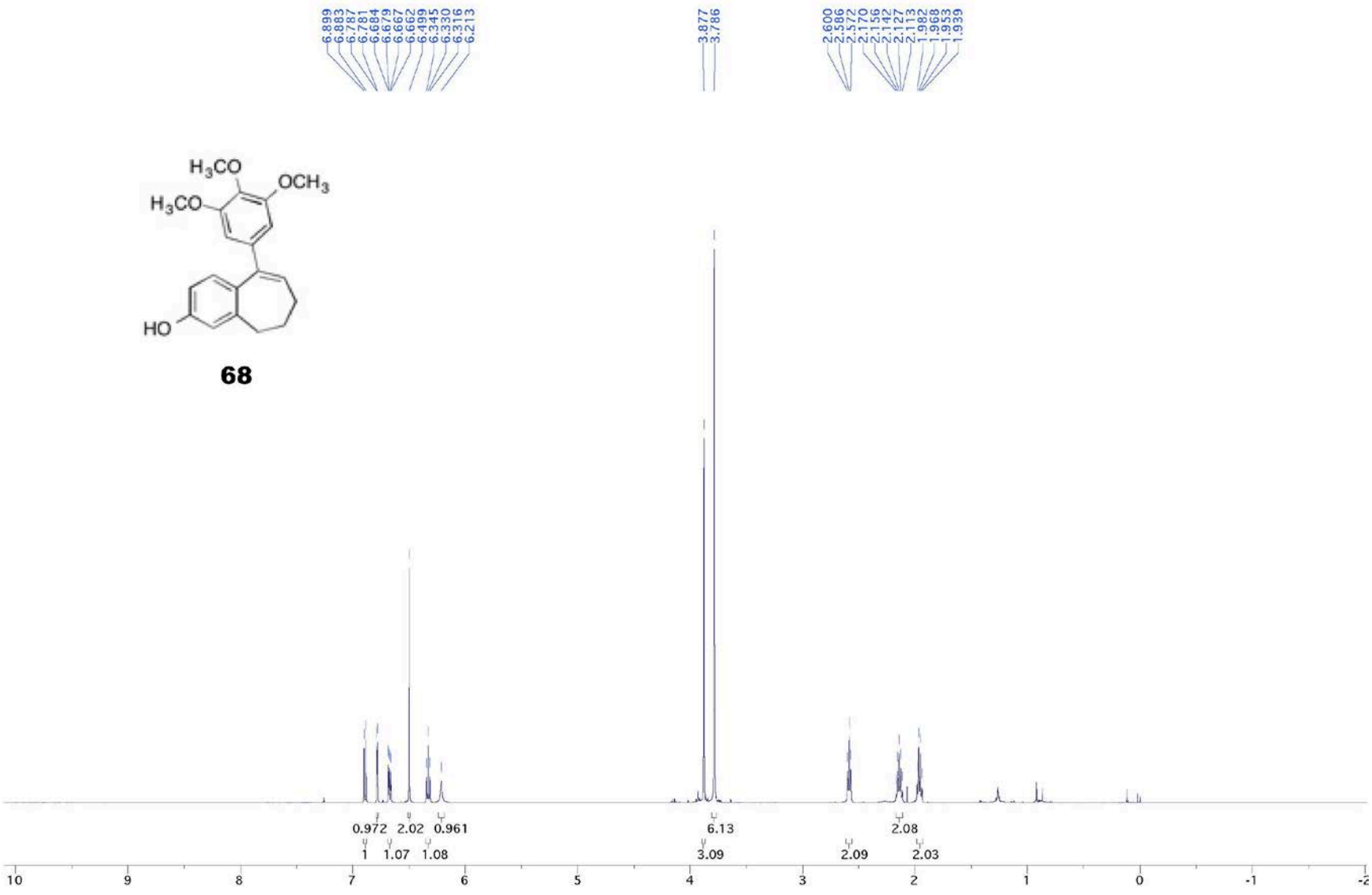
Signal 8: DAD1 H, Sig=320,16 Ref=off

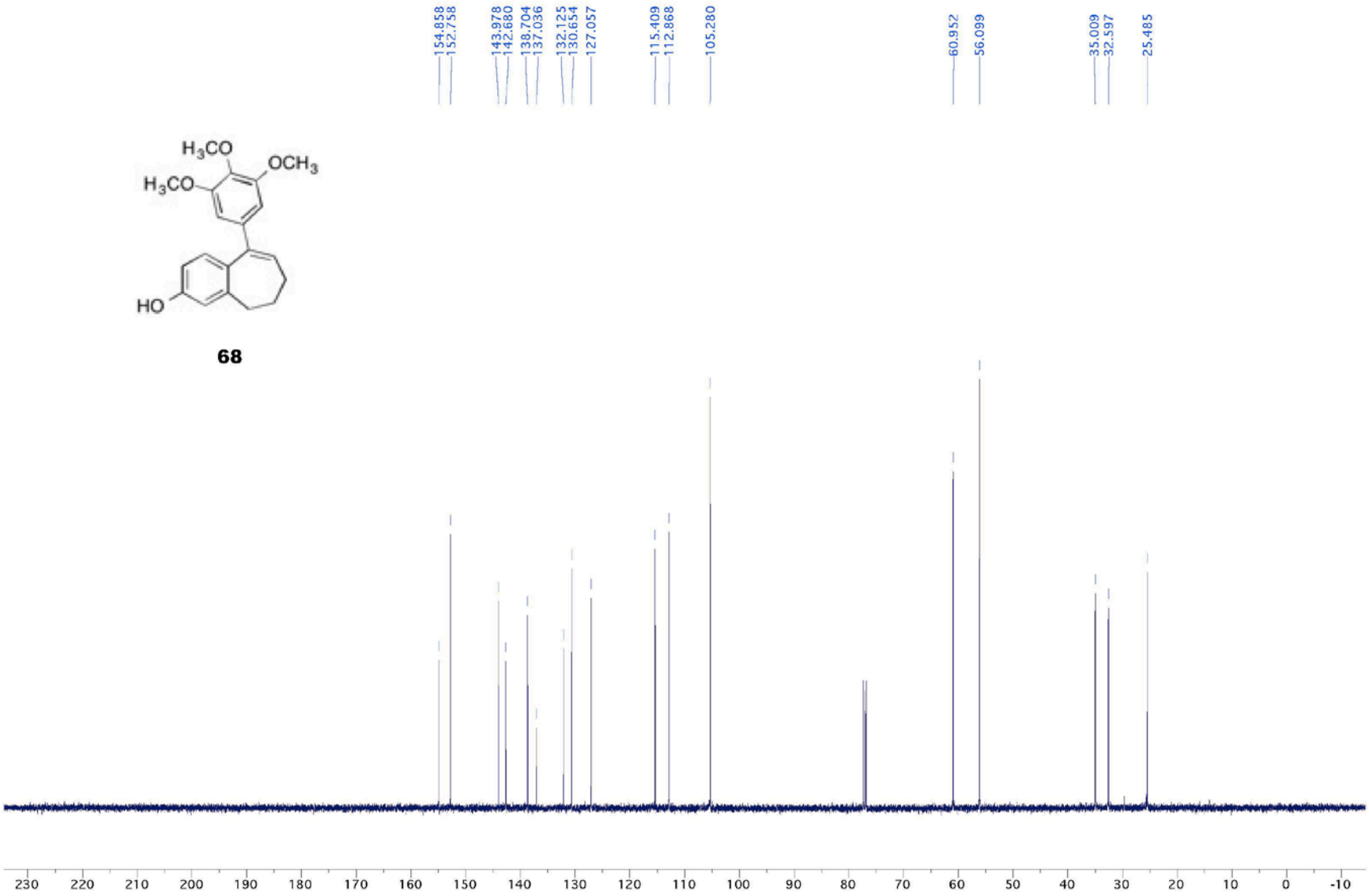
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.422	BB	0.1003	11.65500	1.73621	100.0000
Totals :				11.65500	1.73621	

*** End of Report ***

HRMS for compound 67




6.899
6.883
6.787
6.781
6.684
6.679
6.667
6.662
6.499
6.345
6.330
6.316
6.213
3.877
3.786
2.600
2.586
2.572
2.170
2.156
2.142
2.127
2.113
1.982
1.968
1.953
1.939
H3CO
OCH3
H3CO
HO
68
0.972
2.02
0.961
6.13
2.08
1
1.07
1.08
3.09
2.09
2.03
10
9
8
7
6
5
4
3
2
1
0
-1


154.858
152.758
143.978
142.680
138.704
137.036
132.125
130.654
127.057
115.409
112.868
105.280
60.952
56.099
35.009
32.597
25.485
H3CO
OCH3
H3CO
HO
68
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Data File C:\CHEM32\1\DATA\CHRISTINE\TG-1-78000007.D
Sample Name: TG-1-78

HPLC for compound 68

```
==========================================================================
Acq. Operator   : Christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 10/9/2013 1:55:20 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 10/9/2013 1:53:39 PM by Christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\TG-1-78000007.D\DA.M (MASTERMETHOD.M)
Last changed    : 10/9/2013 3:34:35 PM by Christine
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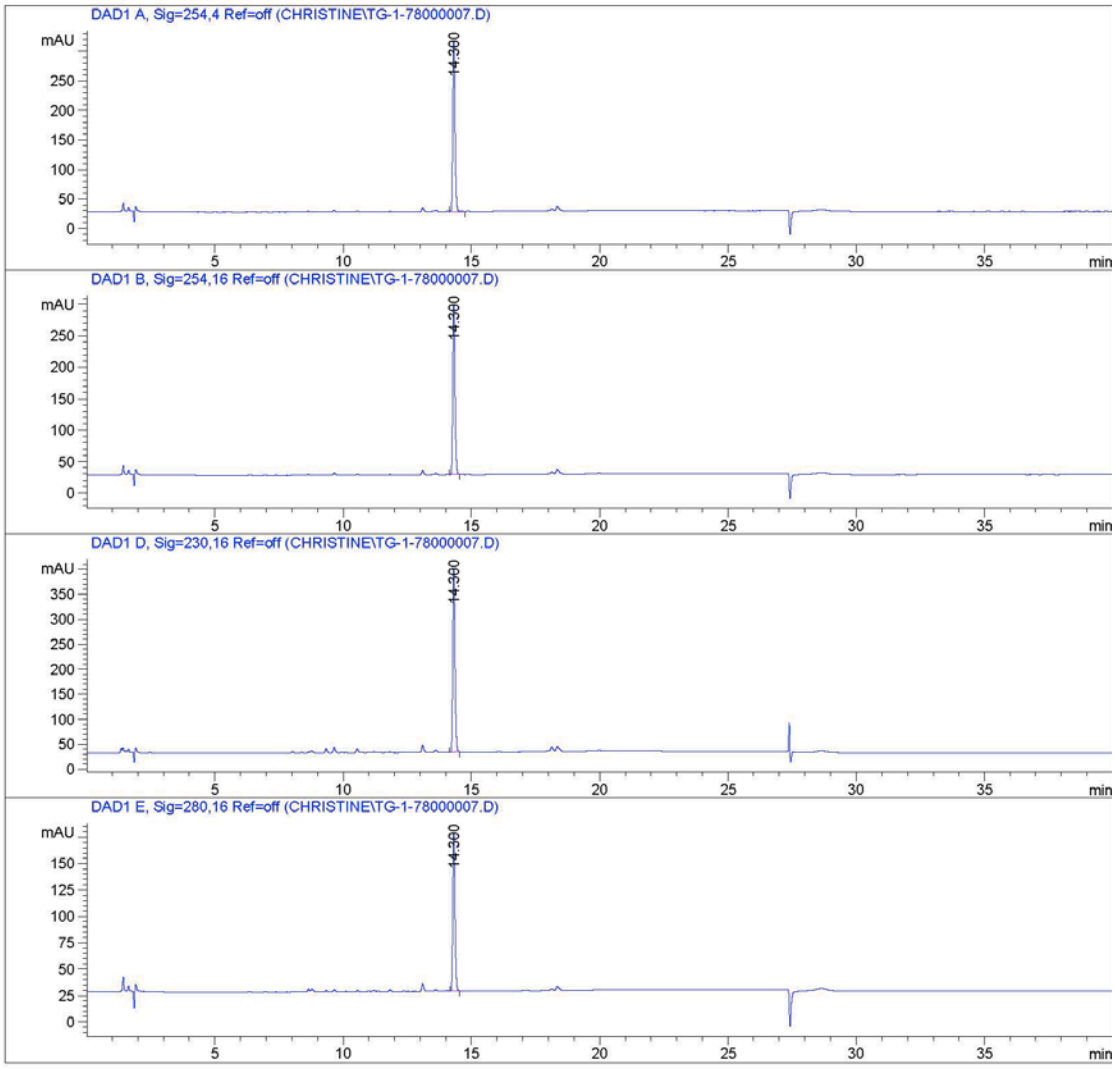
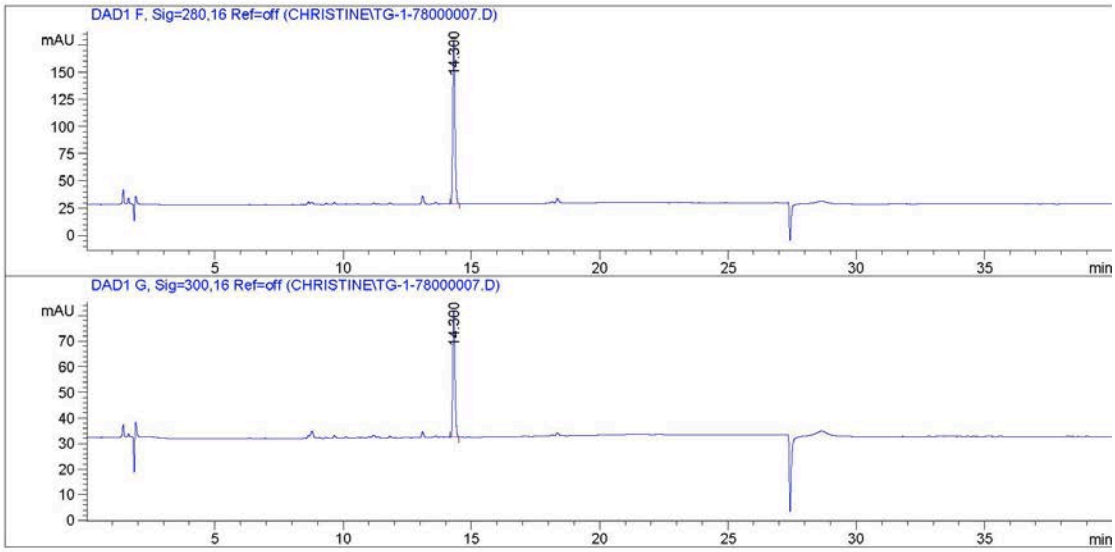


Data File C:\CHEM32\1\DATA\CHRISTINE\TG-1-78000007.D
Sample Name: TG-1-78



==========

Area Percent Report

==========

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.300	BB	0.0879	1684.01782	289.35425	100.0000
Totals :				1684.01782	289.35425	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.300	BB	0.0877	1571.10010	270.80679	100.0000
Totals :				1571.10010	270.80679	

Data File C:\CHEM32\1\DATA\CHRISTINE\TG-1-78000007.D
Sample Name: TG-1-78

Signal 3: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.300	BB	0.0878	2134.54639	367.43820	100.0000
Totals :				2134.54639	367.43820	

Signal 4: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.300	BB	0.0877	870.89191	150.12962	100.0000
Totals :				870.89191	150.12962	

Signal 5: DAD1 F, Sig=280,16 Ref=off

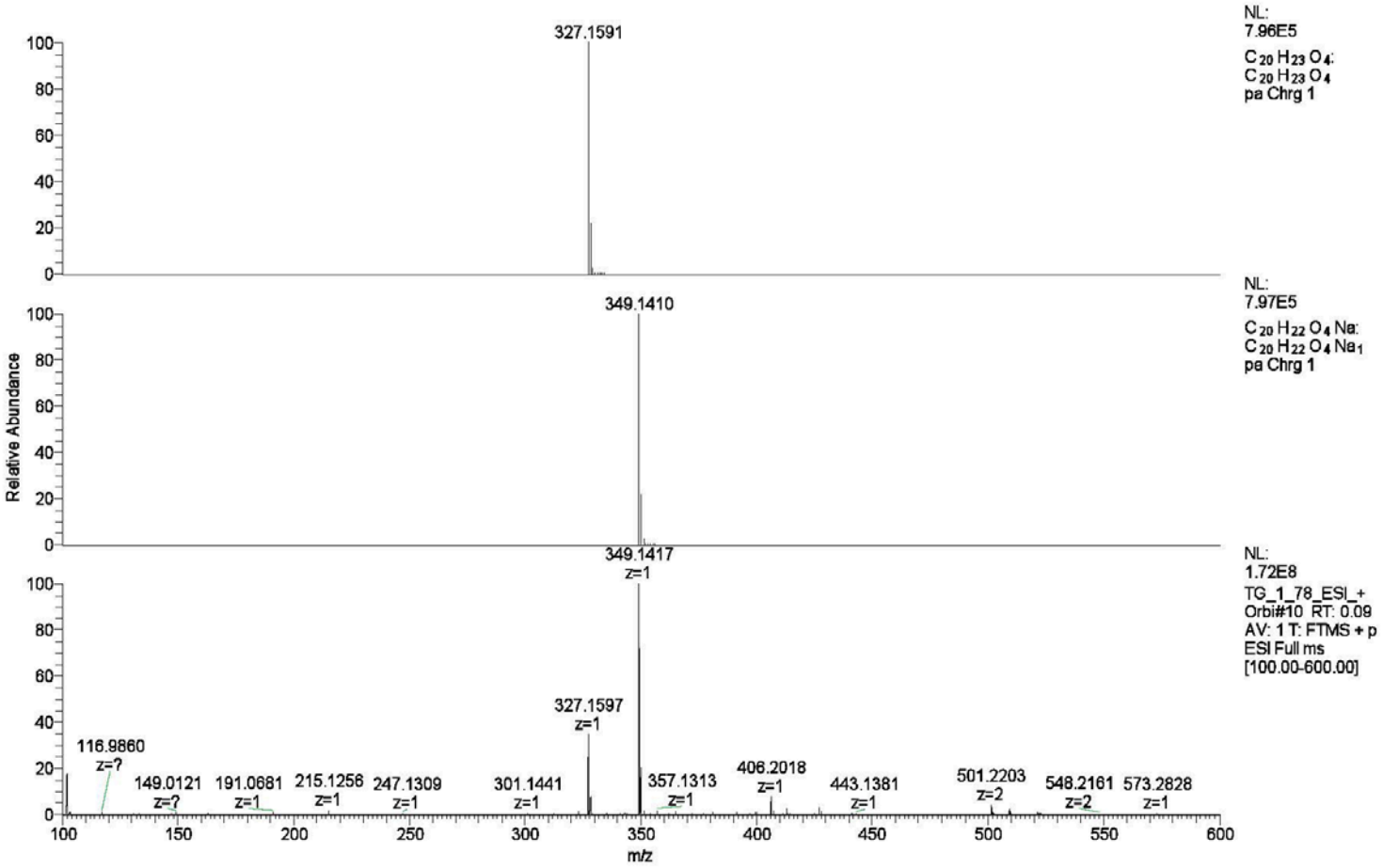
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.300	BB	0.0877	870.89191	150.12962	100.0000
Totals :				870.89191	150.12962	

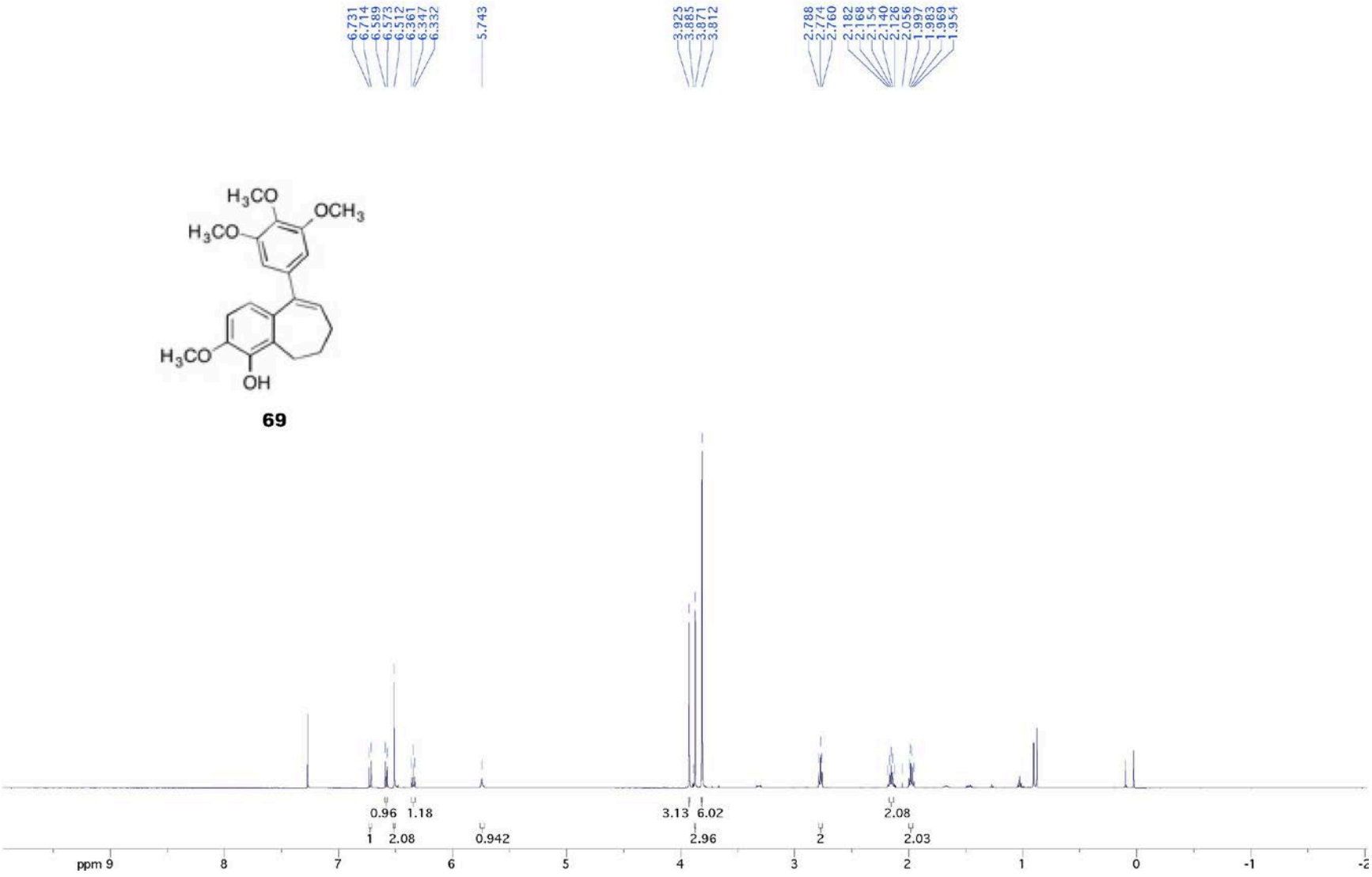
Signal 6: DAD1 G, Sig=300,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.300	BB	0.0877	285.43219	49.20289	100.0000
Totals :				285.43219	49.20289	

*** End of Report ***

HRMS for compound 68

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6.589
6.573
6.512
6.361
6.347
6.332
5.743
3.925
3.885
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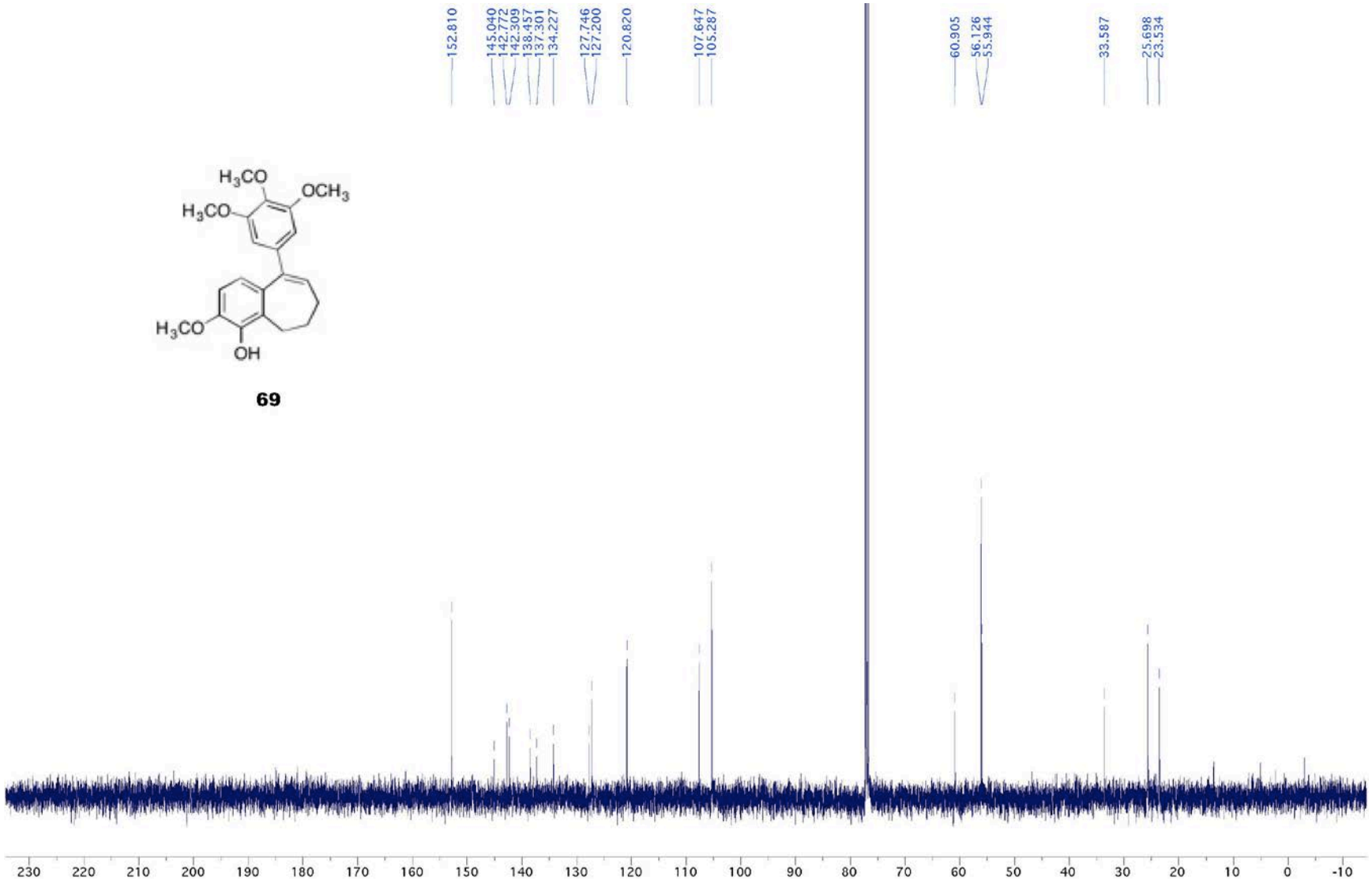
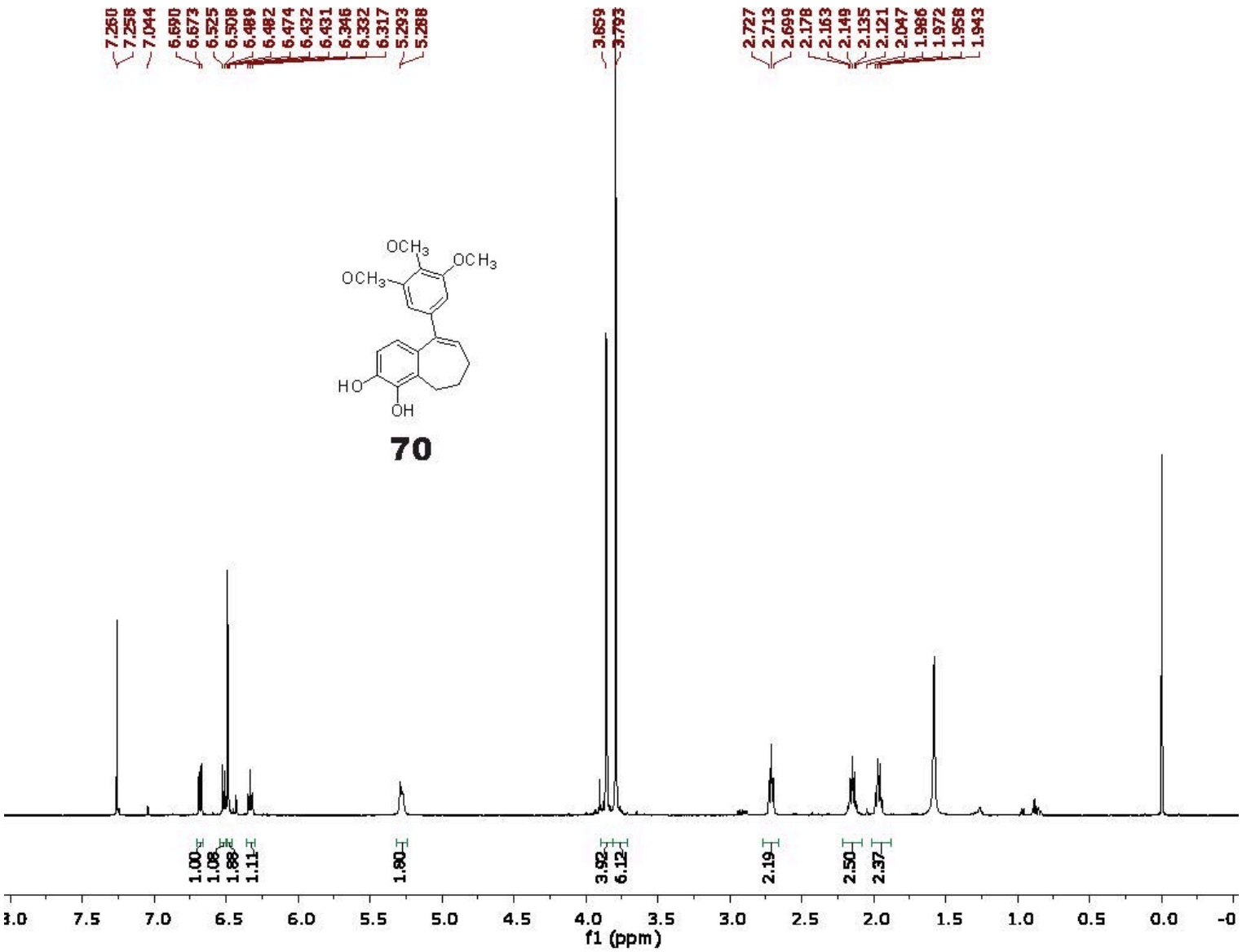
3.812
2.788
2.774
2.760
2.182
2.168
2.154
2.140
2.126
2.056
1.997
1.983
1.969
1.954
H3CO
OCH3
H3CO
H3CO
OH
69
0.96
1.18
3.13
6.02
2.08
1
2.08
0.942
2.96
2
2.03
ppm 9
8
7
6
5
4
3
2
1
0
-1


152.810
145.040
142.772
142.309
138.457
137.301
134.227
127.746
127.200
120.820
107.647
105.287
60.905
56.126
55.944
33.587
25.698
23.534
H3CO
OCH3
H3CO
H3CO
OH
69
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10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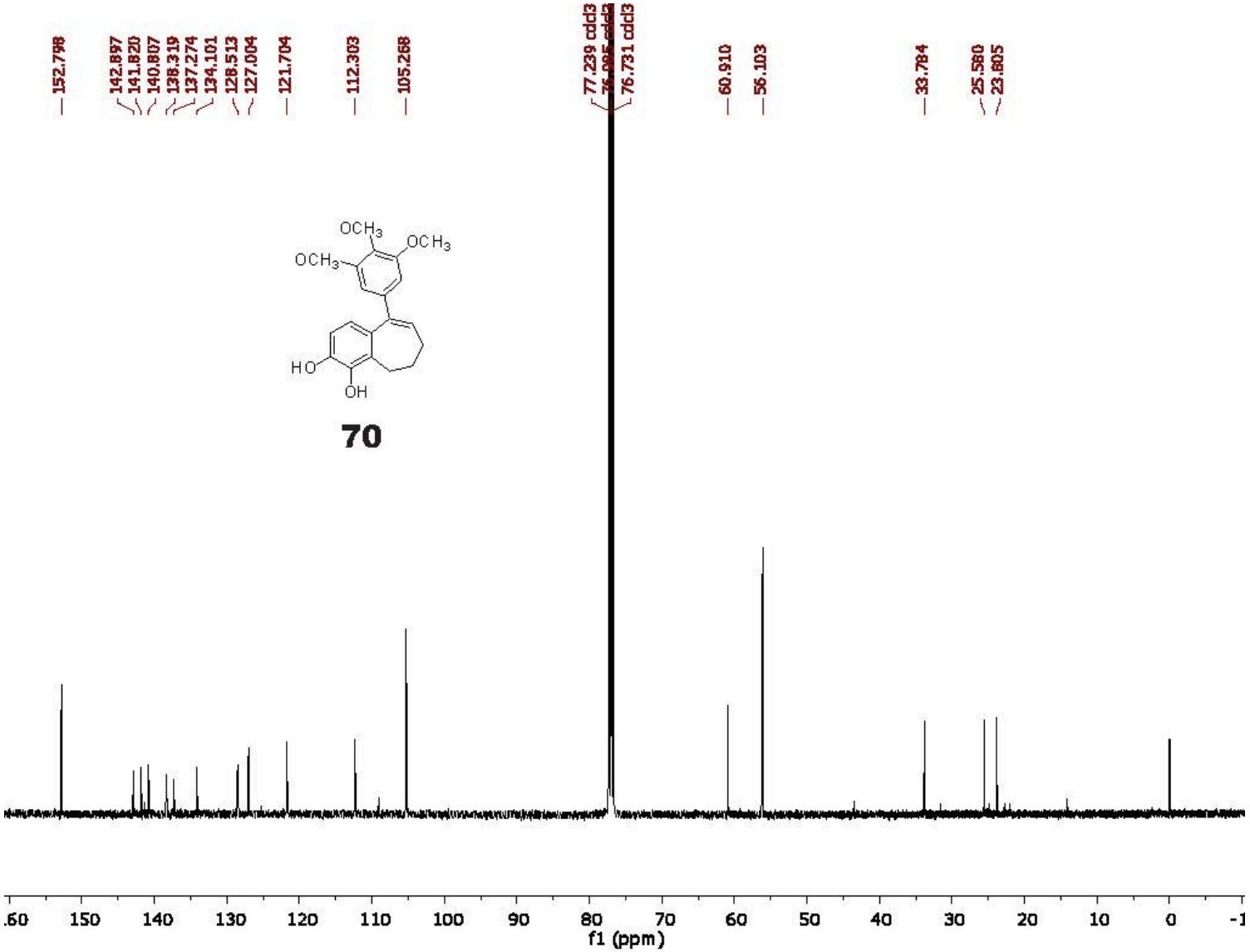
7.258
7.044
6.690
6.673
6.525
6.508
6.489
6.482
6.474
6.432
6.431
6.346
6.332
6.317
5.293
5.288
3.859
3.793
2.727
2.713
2.699
2.178
2.163
2.149
2.135
2.121
2.047
1.986
1.972
1.958
1.943
OCH3
OCH3
OCH3
HO
OH
70
1.00
1.08
1.88
1.11
1.80
3.92
6.12
2.19
2.50
2.37
f1 (ppm)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141.820
140.807
138.319
137.274
134.101
128.513
127.004
121.704
112.303
105.268
77.239 cdcl3
76.731 cdcl3
60.910
56.103
33.784
25.580
23.805
OCH3
OCH3
OCH3
HO
OH
70
f1 (ppm)

Data File C:\CHEM32\1\DATA\LAXMAN\LD-VI-73000001.D
Sample Name: LD-VI-73-1A-run1

HPLC for compound 70

```
==========================================================================
Acq. Operator   : Laxman
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 9/12/2014 2:43:59 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 9/12/2014 2:31:31 PM by Laxman
Analysis Method : C:\CHEM32\1\DATA\LAXMAN\LD-VI-73000001.D\DA.M (MASTERMETHOD.M)
Last changed    : 9/12/2014 5:02:51 PM by Eric Lin
Sample Info     : Method-Mastermethod
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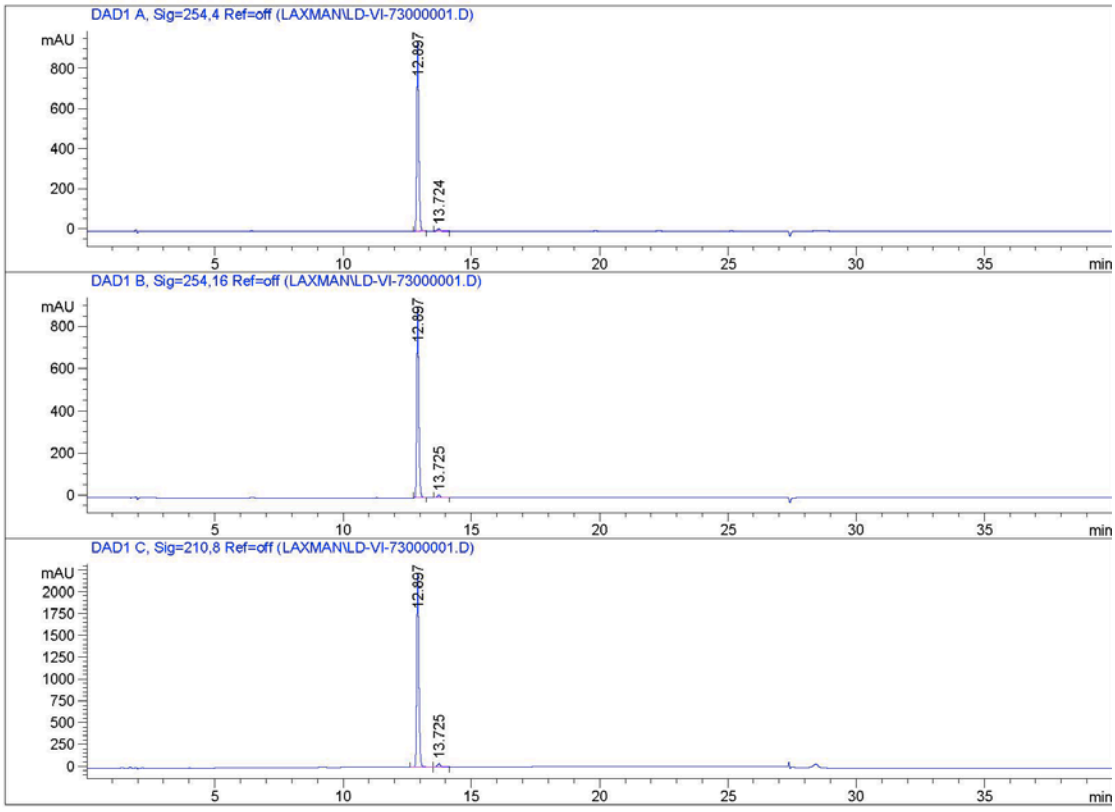
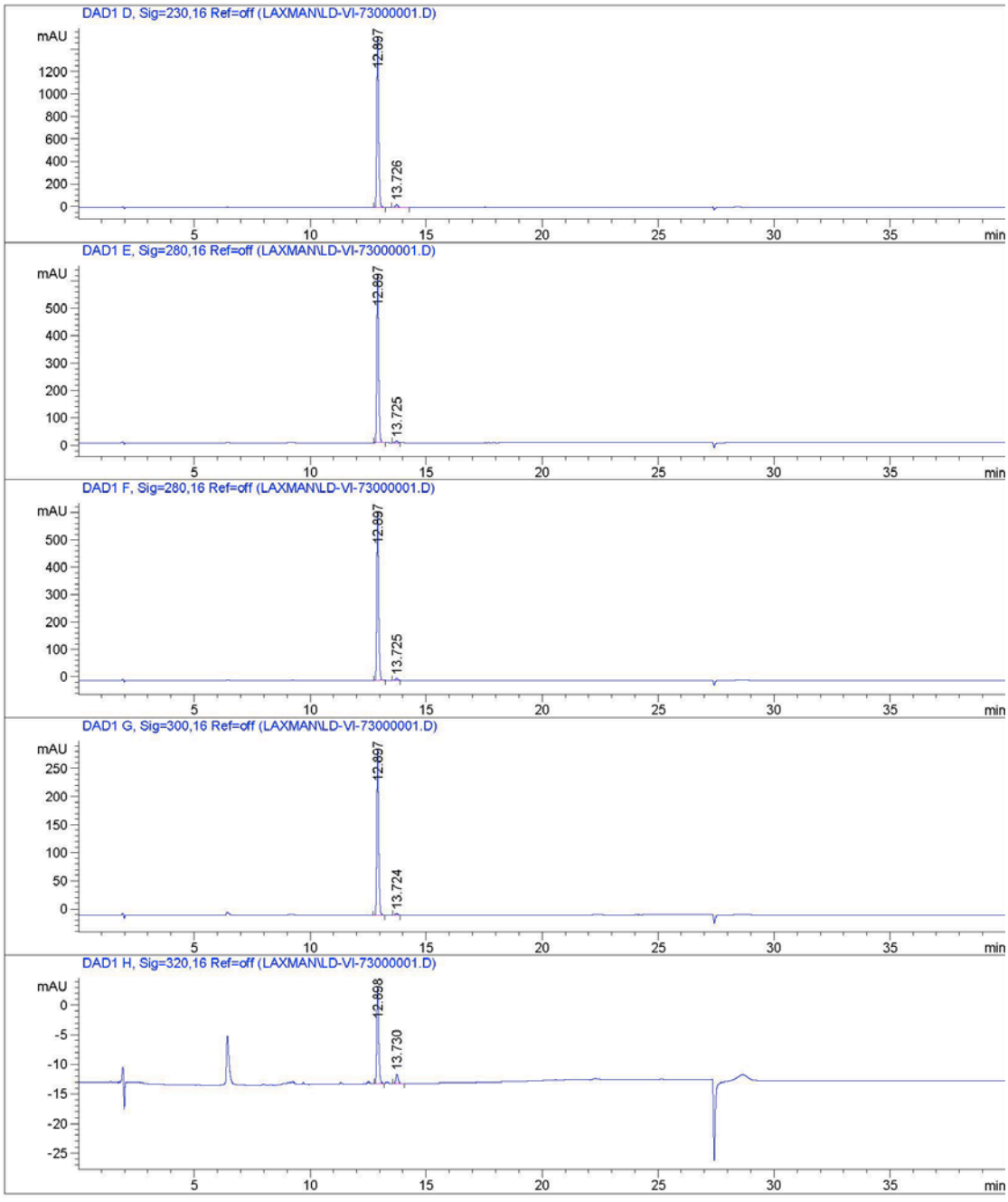


Data File C:\CHEM32\1\DATA\LAXMAN\LD-VI-73000001.D
Sample Name: LD-VI-73-1A-run1



Data File C:\CHEM32\1\DATA\LAXMAN\LD-VI-73000001.D
Sample Name: LD-VI-73-1A-run1

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.897	BB	0.0842	5219.16211	948.45355	98.1260
2	13.724	BB	0.1178	99.67384	11.89176	1.8740
Totals :				5318.83595	960.34531	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.897	BB	0.0842	4968.39111	902.85382	98.0270
2	13.725	BB	0.1175	100.00153	11.96880	1.9730
Totals :				5068.39264	914.82262	

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.897	BV	0.0898	1.29026e4	2218.69849	97.3838
2	13.725	VB	0.1184	346.62473	41.94163	2.6162
Totals :				1.32492e4	2260.64012	

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.897	BB	0.0850	8459.47461	1519.36890	97.5900
2	13.726	BB	0.1176	208.90370	25.50353	2.4100

Data File C:\CHEM32\1\DATA\LAXMAN\LD-VI-73000001.D
Sample Name: LD-VI-73-1A-run1

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
Totals :				8668.37831	1544.87242	

Signal 5: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.897	BB	0.0842	3387.88330	615.90149	98.2865
2	13.725	BV	0.1117	59.06462	7.51596	1.7135
Totals :				3446.94792	623.41745	

Signal 6: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.897	BB	0.0842	3387.88477	615.90149	98.2865
2	13.725	BV	0.1137	59.06182	7.51595	1.7135
Totals :				3446.94659	623.41744	

Signal 7: DAD1 G, Sig=300,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.897	BV	0.0844	1630.89148	295.33459	98.6910
2	13.724	BB	0.1092	21.63143	2.82855	1.3090
Totals :				1652.52291	298.16315	

Signal 8: DAD1 H, Sig=320,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.898	BB	0.0895	94.41895	16.31277	90.0631
2	13.730	BB	0.0986	10.41746	1.58729	9.9369
Totals :				104.83641	17.90006	

Data File C:\CHEM32\1\DATA\LAXMAN\LD-VI-73000001.D
Sample Name: LD-VI-73-1A-run1

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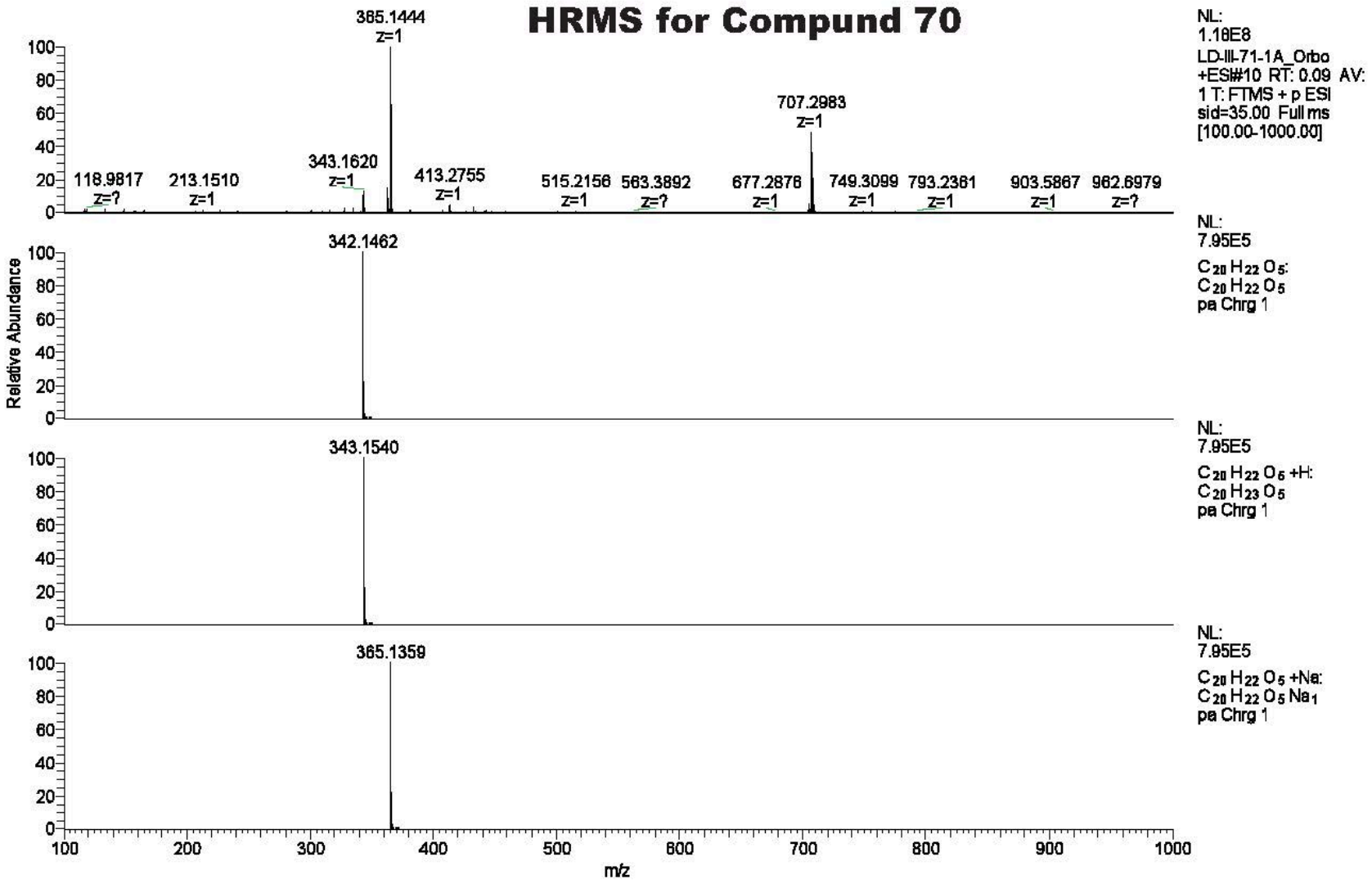
*** End of Report ***


HRMS for Compund 70
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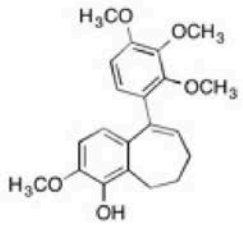
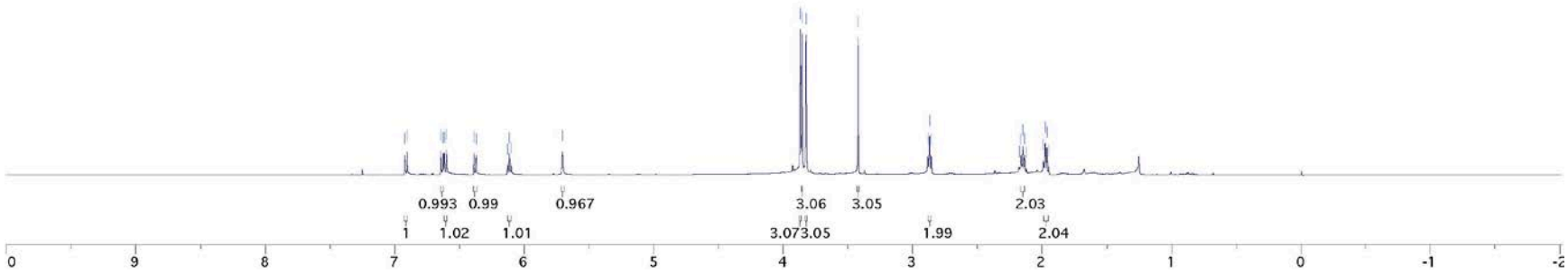
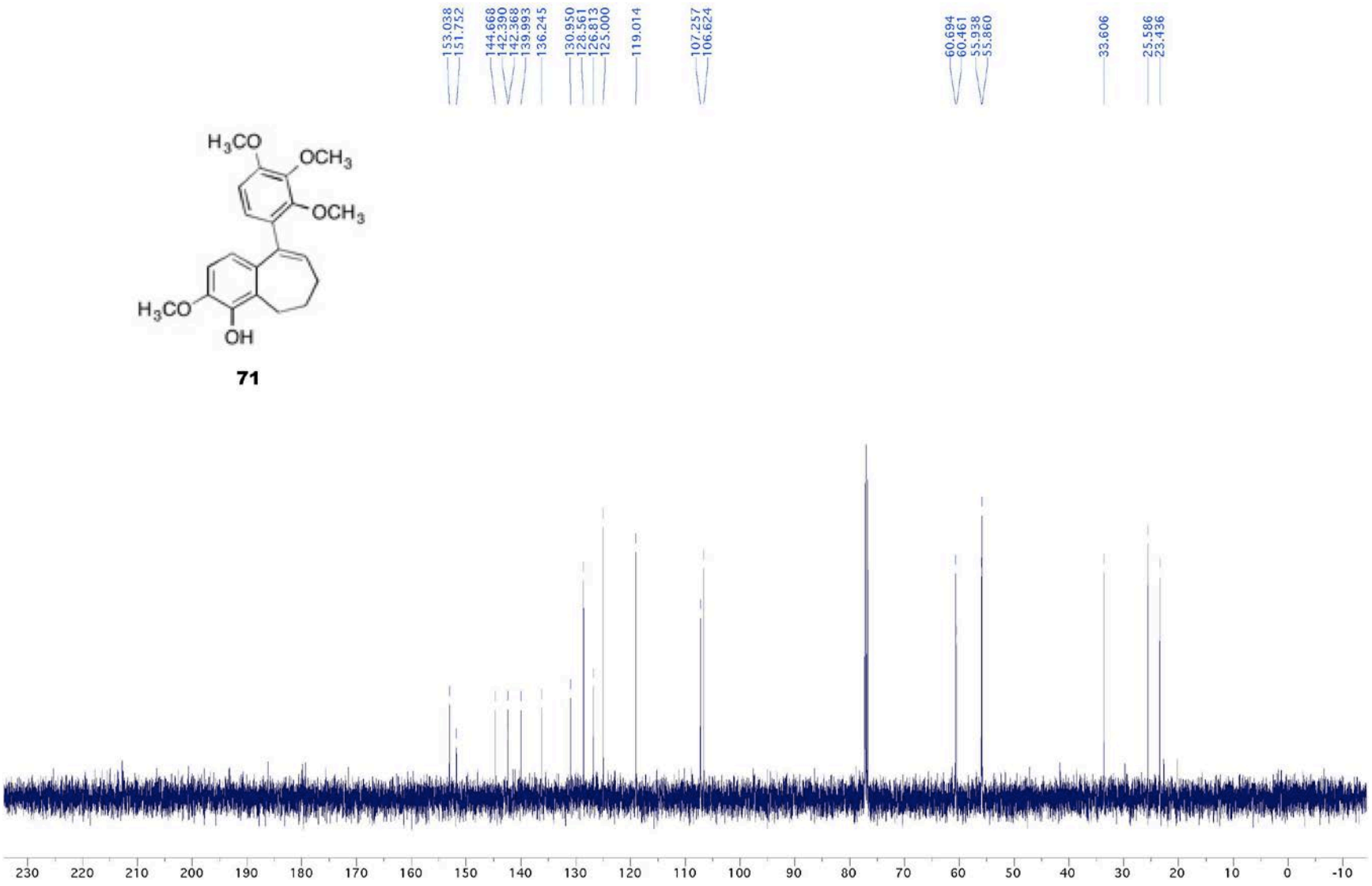
z=1
707.2983
z=1
343.1620
z=1
118.9817
z=?
213.1510
z=1
413.2755
z=1
515.2156
z=1
563.3892
z=?
677.2878
z=1
749.3099
z=1
793.2361
z=1
903.5867
z=1
962.6979
z=?
NL:
1.18E8
LD-III-71-1A_Orbo
+ESI#10 RT: 0.09 AV:
1 T: FTMS + p ESI
sid=35.00 Full ms
[100.00-1000.00]
342.1462
NL:
7.95E5
C20 H22 O5:
C20 H22 O5
pa Chrg 1
343.1540
NL:
7.95E5
C20 H22 O5 +H:
C20 H23 O5
pa Chrg 1
365.1359
NL:
7.95E5
C20 H22 O5 +Na:
C20 H22 O5 Na1
pa Chrg 1
Relative Abundance
m/z


6.923
6.906
6.645
6.628
6.617
6.600
6.389
6.372
6.130
6.116
6.101
5.705
3.866
3.853
3.823
3.421
2.883
2.869
2.855
2.177
2.163
2.149
2.135
2.121
1.991
1.977
1.963
1.948


H3CO
OCH3
OCH3
H3CO
OH

71

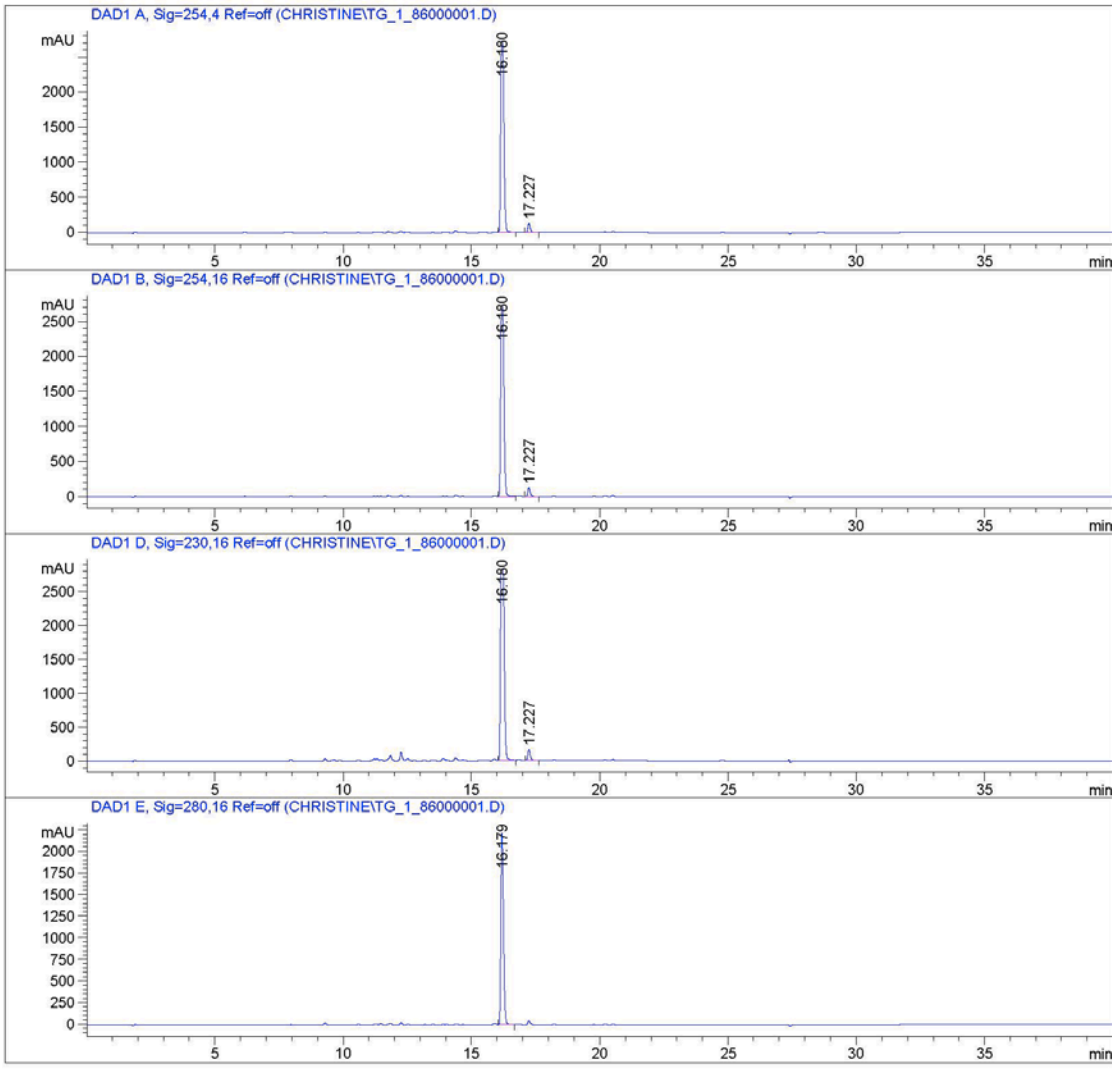

0.993
0.99
0.967
3.06
3.05
2.03
1
1.02
1.01
3.07
3.05
1.99
2.04
0
9
8
7
6
5
4
3
2
1
0
-1


153.038
151.752
144.668
142.390
142.368
139.993
136.245
130.950
128.561
126.813
125.000
119.014
107.257
106.624
60.694
60.461
55.938
55.860
33.606
25.586
23.436
H3CO
OCH3
OCH3
H3CO
OH
71
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

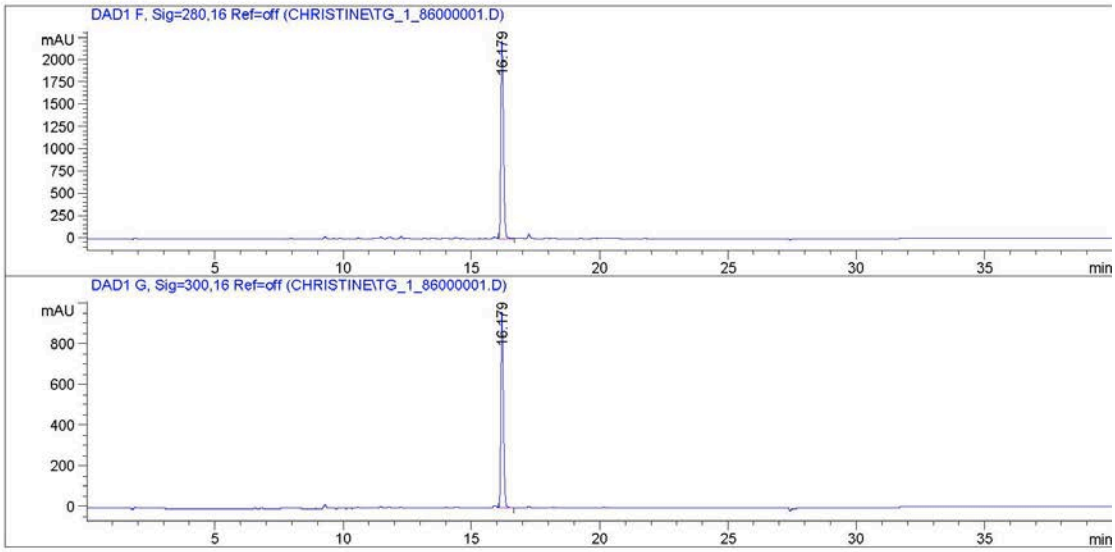
Data File C:\CHEM32\1\DATA\CHRISTINE\TG_1_86000001.D
Sample Name: TG_1_86

HPLC of compound 71

Acq. Operator : Christine
Acq. Instrument : Instrument 1 Location : -
Injection Date : 5/19/2014 11:07:23 AM
Acq. Method : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed : 5/19/2014 10:53:24 AM by Christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\TG_1_86000001.D\DA.M (MASTERMETHOD.M)
Last changed : 5/19/2014 12:11:57 PM by Christine



Data File C:\CHEM32\1\DATA\CHRISTINE\TG_1_86000001.D
Sample Name: TG_1_86



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.180	VV	0.1421	2.38945e4	2730.56470	96.5205
2	17.227	VB	0.1009	861.36761	130.67624	3.4795
Totals :				2.47558e4	2861.24094	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.180	VV	0.1423	2.39879e4	2735.90332	96.5594
2	17.227	VB	0.1008	854.72571	129.77695	3.4406

Data File C:\CHEM32\1\DATA\CHRISTINE\TG_1_86000001.D
Sample Name: TG_1_86

Totals :	2.48426e4	2865.68027	

Signal 3: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.180	BV	0.1687	2.92081e4	2822.58813	96.3796
2	17.227	BB	0.1002	1097.15686	168.01945	3.6204
Totals :				3.03053e4	2990.60759	

Signal 4: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.179	VV	0.1104	1.57028e4	2223.08569	100.0000
Totals :				1.57028e4	2223.08569	

Signal 5: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.179	VV	0.1104	1.57028e4	2223.08569	100.0000
Totals :				1.57028e4	2223.08569	

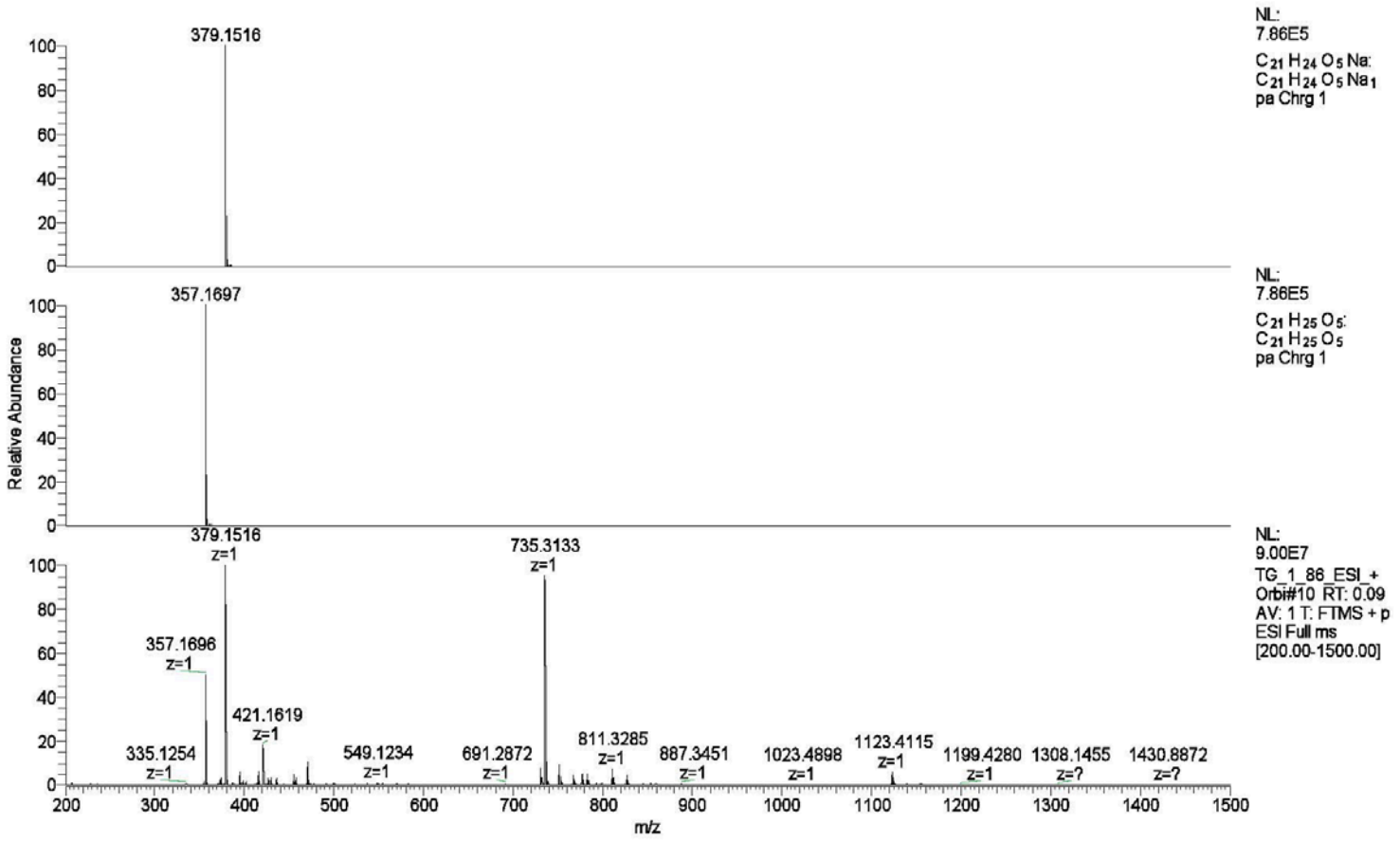
Signal 6: DAD1 G, Sig=300,16 Ref=off

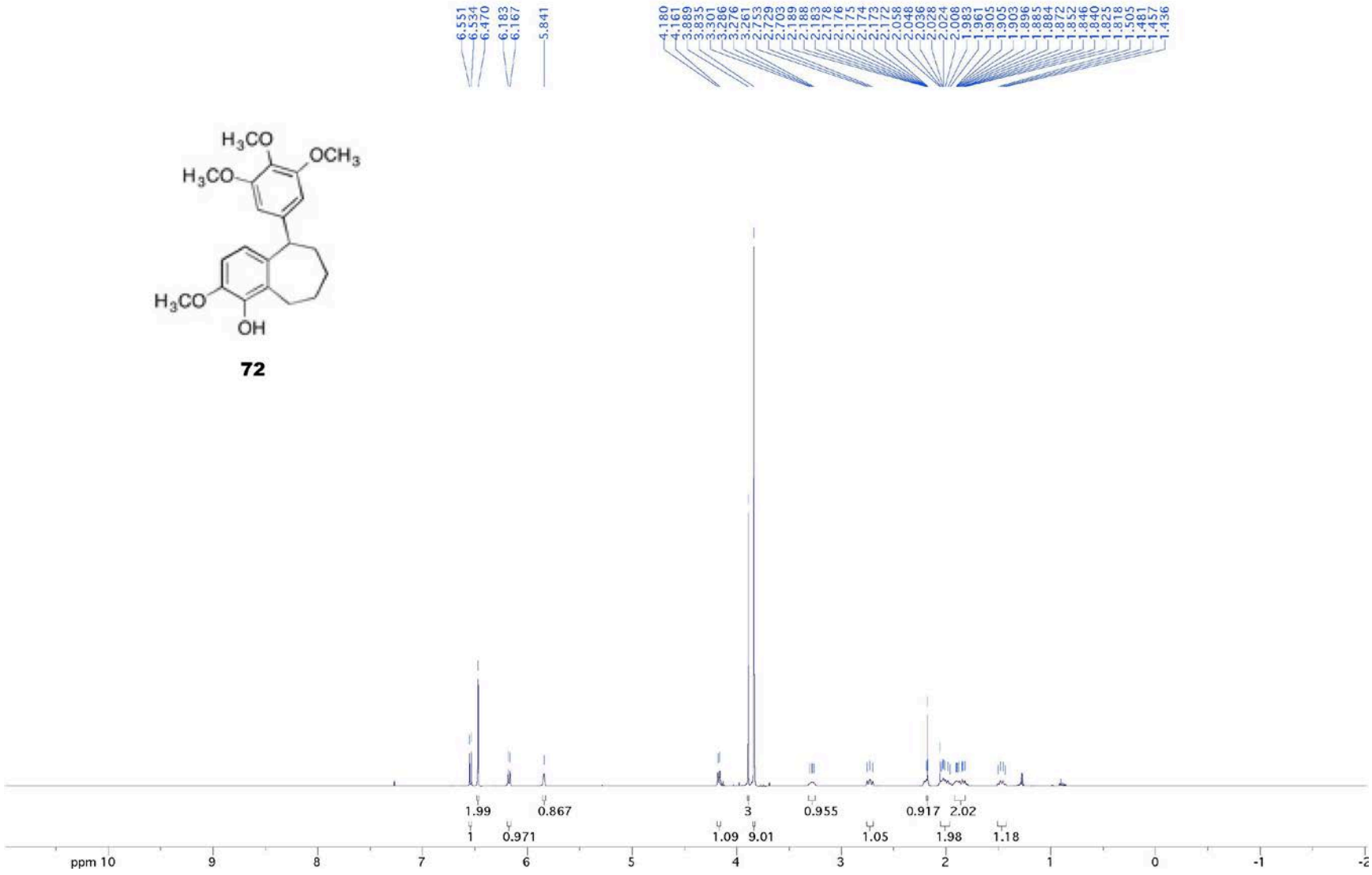
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.179	VV	0.1017	6443.40820	967.43469	100.0000
Totals :				6443.40820	967.43469	

*** End of Report ***

HRMS of compound 71

C:\Xcalibur\...\TG_1_86_ESI_+Orbi 1/13/2014 1:41:22 PM TG-1-86

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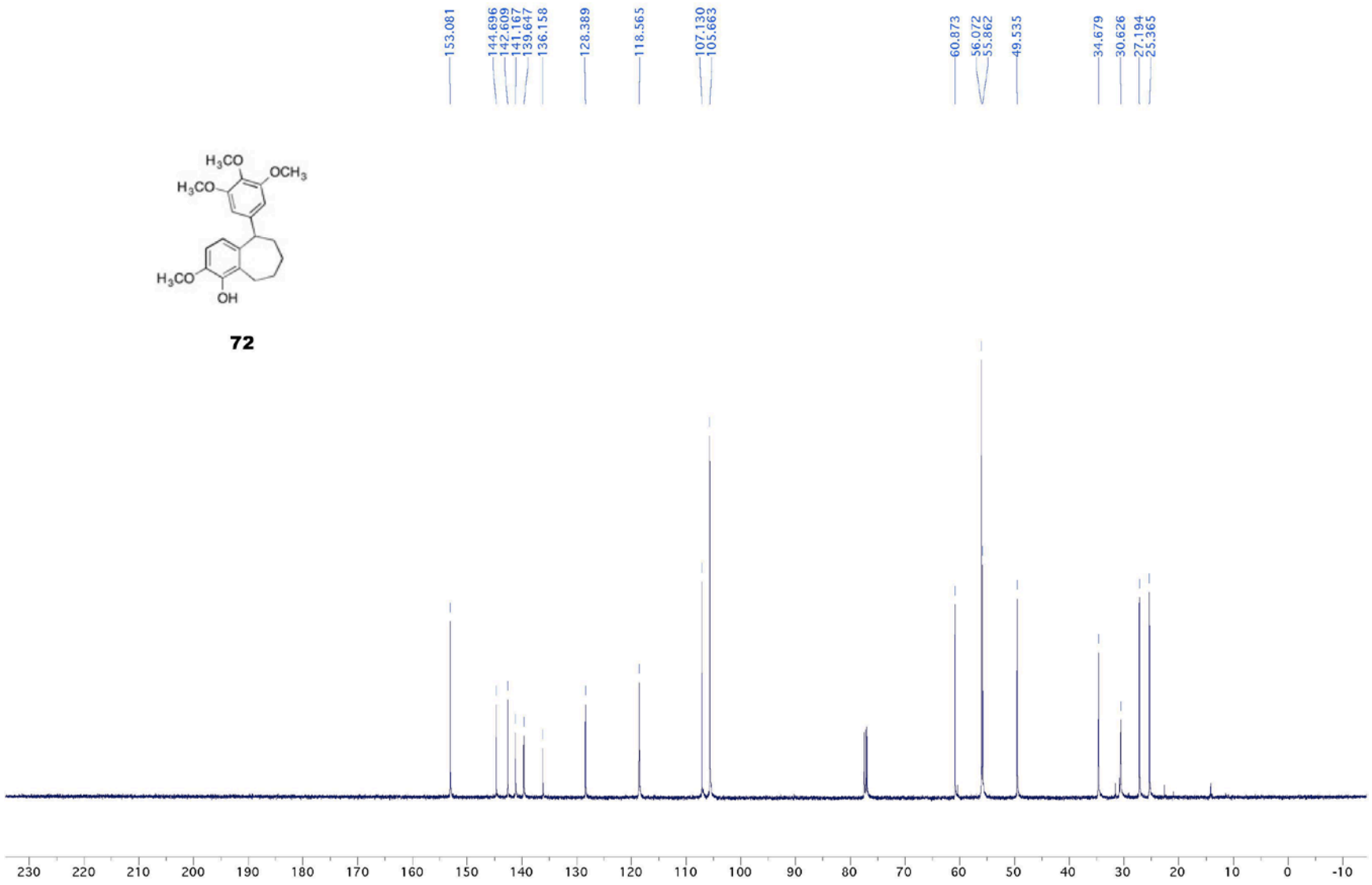
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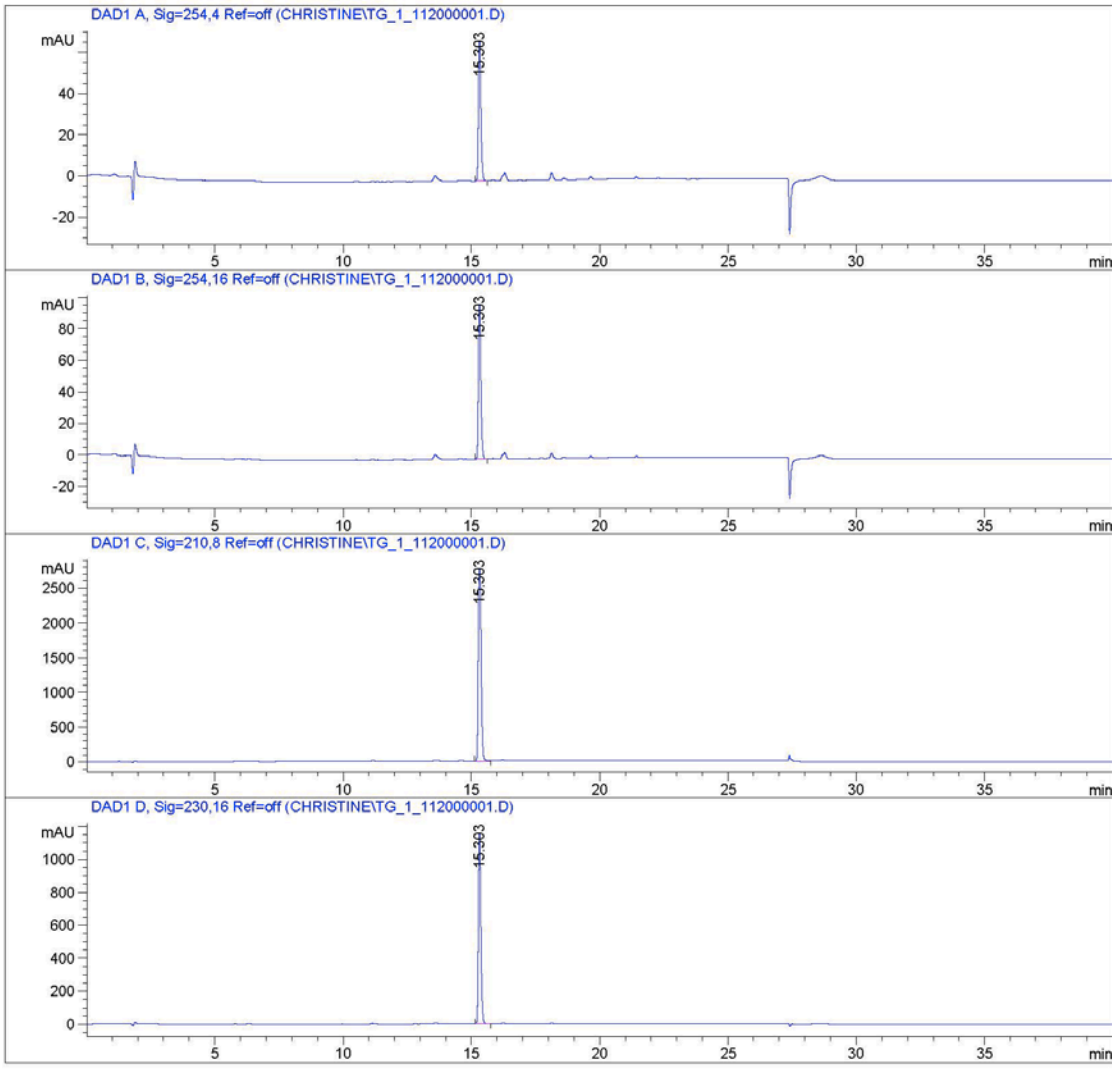

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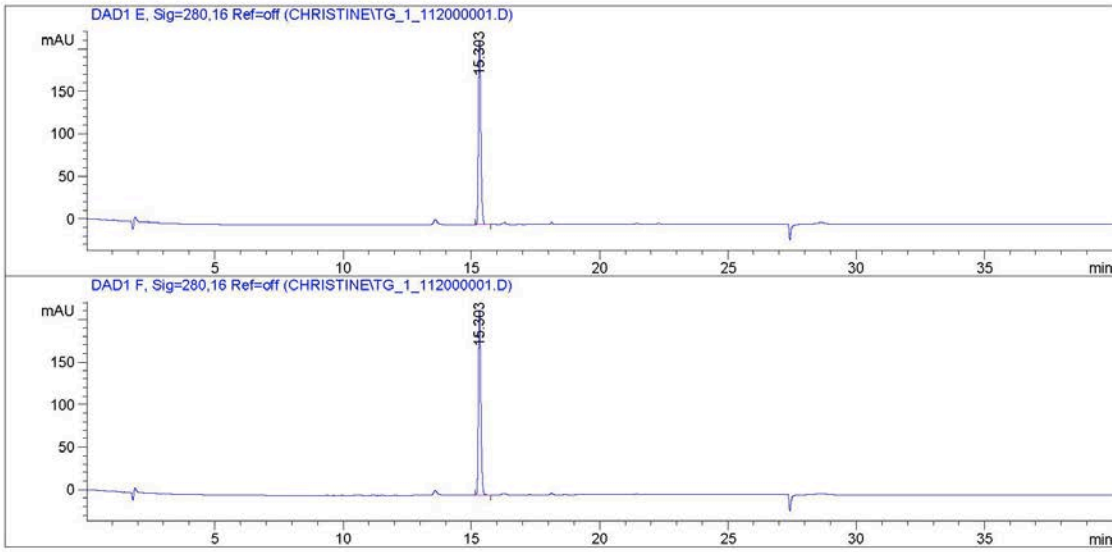

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Area Percent Report

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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.303	BB	0.1000	442.72894	67.97310	100.0000
Totals :				442.72894	67.97310	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.303	BB	0.0995	631.04565	97.49252	100.0000
Totals :				631.04565	97.49252	

Data File C:\CHEM32\1\DATA\CHRISTINE\TG_1_112000001.D
Sample Name: TG_1_112

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.303	BV	0.1224	2.13590e4	2755.23682	100.0000
Totals :				2.13590e4	2755.23682	

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.303	BB	0.0996	7499.44434	1157.97766	100.0000
Totals :				7499.44434	1157.97766	

Signal 5: DAD1 E, Sig=280,16 Ref=off

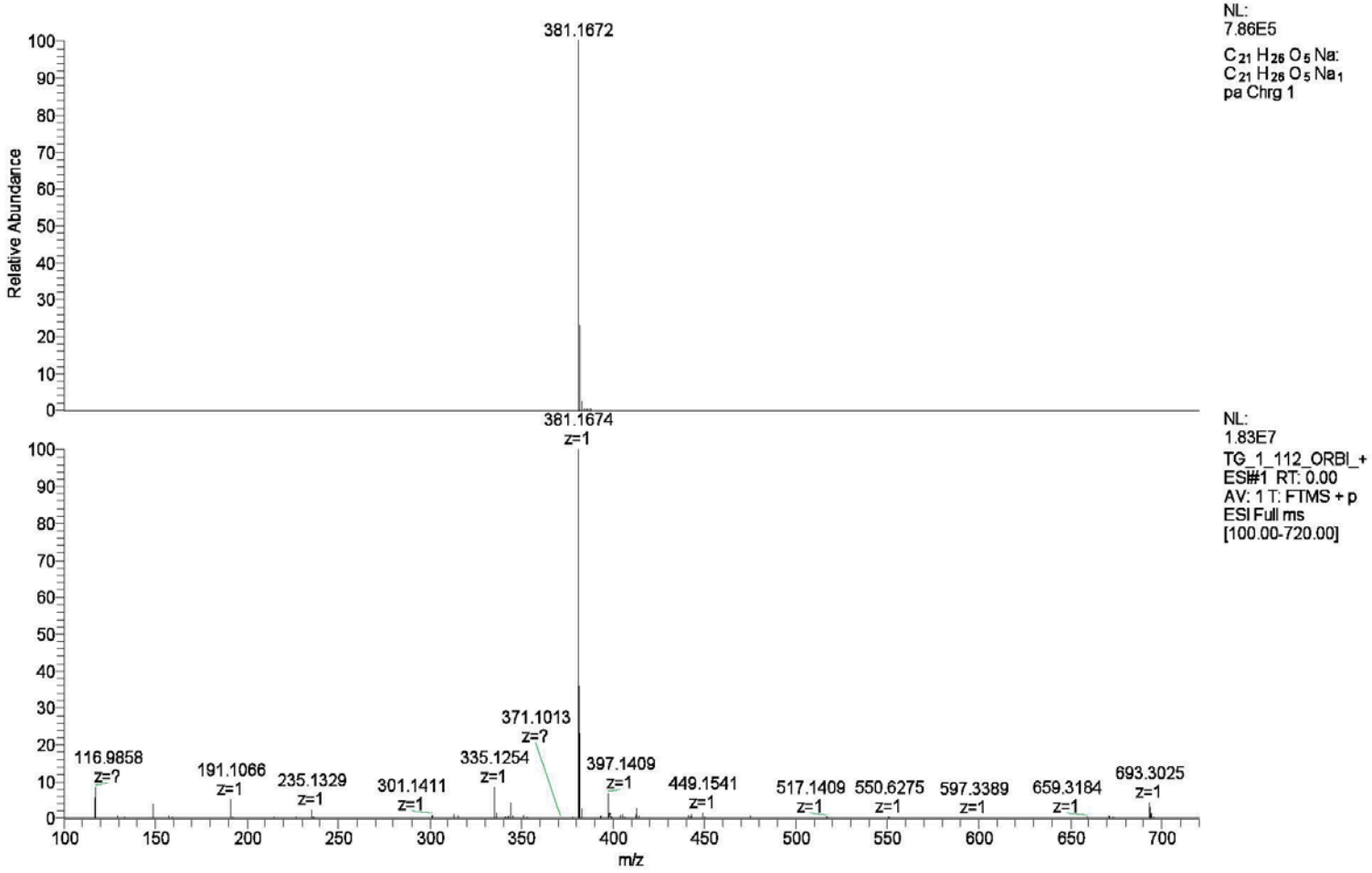
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.303	BB	0.0987	1380.06250	215.62195	100.0000
Totals :				1380.06250	215.62195	

Signal 6: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.303	BB	0.0987	1380.06250	215.62195	100.0000
Totals :				1380.06250	215.62195	

*** End of Report ***

HRMS of compound 72



X-ray Crystallographic Analysis:

X-ray crystallographic analysis of compound **72**.[S1] Crystallographic data were collected on a crystal of **72** with dimensions 0.30 x 0.17 x 0.14 mm^3. Data were collected at 150 K on a Bruker X8 Apex using Mo KR radiation (λ = 0.71073 Å). The structure was solved by direct methods after correction of the data using SADABS. Crystallographic data and definement details for the complex mentioned herein is found in the Supporting Information (Table S1-S5). The thermal ellipsoid plots at 50% probability for compound **73** is displayed in Figure S1. All data were processed using the Bruker AXS SHELXTL software, version 6.10.

Figure S1. X-ray crystallogaphy of compound **72**

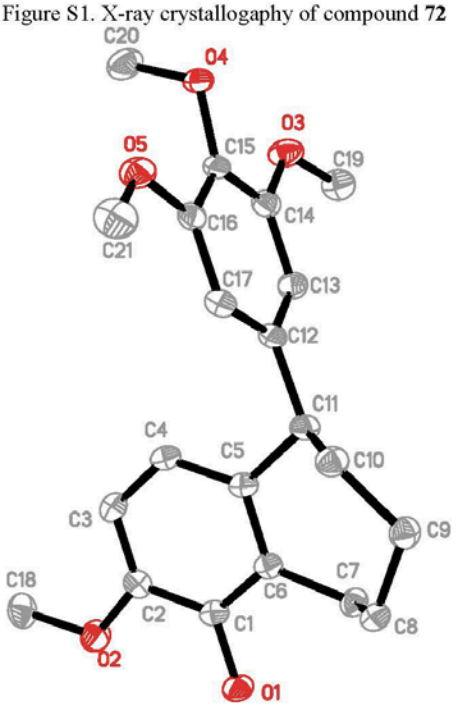


Table S1. Crystal data and structure refinement for Compound 72

Identification code	KP69	
Empirical formula	C21 H26 O5	
Formula weight	358.42	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P c a 21	
Unit cell dimensions	a = 16.5289(7) Å	α= 90°.
	b = 11.7370(4) Å	β= 90°.
	c = 9.4340(4) Å	γ = 90°.
Volume	1830.19(13) Å^3	
Z	4	
Density (calculated)	1.301 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	768	
Crystal size	0.303 x 0.165 x 0.144 mm^3	
Theta range for data collection	5.211 to 25.675°.	
Index ranges	-20<=h<=18, -14<=k<=12, -11<=l<=11	
Reflections collected	15353	
Independent reflections	3439 [R(int) = 0.0219]	
Completeness to theta = 25.242°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.987 and 0.981	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3439 / 1 / 238	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0270, wR2 = 0.0688	
R indices (all data)	R1 = 0.0283, wR2 = 0.0696	
Absolute structure parameter	0.27(19)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.164 and -0.148 e.Å^{-3}	

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Compound 72. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1246(1)	1871(1)	4248(2)	24(1)
O(2)	1430(1)	2238(1)	1512(2)	29(1)
O(3)	3644(1)	8680(1)	4127(2)	28(1)
O(4)	2556(1)	10180(1)	3151(2)	24(1)
O(5)	990(1)	9662(1)	2973(2)	26(1)
C(1)	1350(1)	2969(2)	3795(2)	20(1)
C(2)	1457(1)	3188(2)	2347(2)	20(1)
C(3)	1576(1)	4290(2)	1891(2)	22(1)
C(4)	1583(1)	5174(2)	2885(2)	21(1)
C(5)	1469(1)	4976(2)	4319(2)	19(1)
C(6)	1353(1)	3842(2)	4791(2)	18(1)
C(7)	1236(1)	3543(2)	6335(2)	21(1)
C(8)	465(1)	4047(2)	6998(2)	22(1)
C(9)	551(1)	5284(2)	7436(2)	23(1)
C(10)	674(1)	6106(2)	6204(2)	23(1)
C(11)	1482(1)	5954(2)	5399(2)	21(1)
C(12)	1759(1)	7070(2)	4737(2)	20(1)
C(13)	2579(1)	7317(2)	4714(2)	22(1)
C(14)	2852(1)	8337(2)	4136(2)	22(1)
C(15)	2300(1)	9113(2)	3569(2)	20(1)
C(16)	1482(1)	8849(2)	3561(2)	21(1)
C(17)	1208(1)	7832(2)	4148(2)	22(1)
C(18)	1560(1)	2377(2)	33(2)	30(1)
C(19)	4209(1)	7955(2)	4832(2)	29(1)
C(20)	2828(2)	10219(2)	1717(2)	33(1)
C(21)	138(1)	9516(2)	3108(3)	34(1)

Table S3. Bond lengths [Å] and angles [°] for Compound 72.

O(1)-C(1)	1.369(2)
O(2)-C(2)	1.365(2)
O(2)-C(18)	1.421(2)
O(3)-C(14)	1.370(2)
O(3)-C(19)	1.428(3)
O(4)-C(15)	1.379(2)
O(4)-C(20)	1.427(3)
O(5)-C(16)	1.371(2)
O(5)-C(21)	1.425(3)
C(1)-C(6)	1.390(3)
C(1)-C(2)	1.401(3)
C(2)-C(3)	1.378(3)
C(3)-C(4)	1.398(3)
C(4)-C(5)	1.386(3)
C(5)-C(6)	1.416(2)
C(5)-C(11)	1.535(3)
C(6)-C(7)	1.511(3)
C(7)-C(8)	1.537(3)
C(8)-C(9)	1.516(3)
C(9)-C(10)	1.524(3)
C(10)-C(11)	1.547(3)
C(11)-C(12)	1.522(3)
C(12)-C(13)	1.386(3)
C(12)-C(17)	1.392(3)
C(13)-C(14)	1.391(3)
C(14)-C(15)	1.395(3)
C(15)-C(16)	1.387(3)
C(16)-C(17)	1.392(3)
C(2)-O(2)-C(18)	117.91(17)
C(14)-O(3)-C(19)	116.57(16)
C(15)-O(4)-C(20)	113.41(15)
C(16)-O(5)-C(21)	117.79(16)
O(1)-C(1)-C(6)	118.90(17)

O(1)-C(1)-C(2)	119.50(17)
C(6)-C(1)-C(2)	121.59(17)
O(2)-C(2)-C(3)	126.22(18)
O(2)-C(2)-C(1)	114.18(17)
C(3)-C(2)-C(1)	119.60(18)
C(2)-C(3)-C(4)	119.23(18)
C(5)-C(4)-C(3)	121.97(18)
C(4)-C(5)-C(6)	118.87(17)
C(4)-C(5)-C(11)	121.39(17)
C(6)-C(5)-C(11)	119.73(17)
C(1)-C(6)-C(5)	118.74(17)
C(1)-C(6)-C(7)	118.67(17)
C(5)-C(6)-C(7)	122.59(17)
C(6)-C(7)-C(8)	114.15(16)
C(9)-C(8)-C(7)	113.66(16)
C(8)-C(9)-C(10)	114.30(17)
C(9)-C(10)-C(11)	114.53(16)
C(12)-C(11)-C(5)	112.05(16)
C(12)-C(11)-C(10)	111.19(15)
C(5)-C(11)-C(10)	113.60(15)
C(13)-C(12)-C(17)	119.96(17)
C(13)-C(12)-C(11)	118.70(16)
C(17)-C(12)-C(11)	121.33(17)
C(12)-C(13)-C(14)	120.18(17)
O(3)-C(14)-C(13)	124.41(18)
O(3)-C(14)-C(15)	115.49(17)
C(13)-C(14)-C(15)	120.05(18)
O(4)-C(15)-C(16)	120.02(17)
O(4)-C(15)-C(14)	120.12(17)
C(16)-C(15)-C(14)	119.54(17)
O(5)-C(16)-C(15)	115.12(17)
O(5)-C(16)-C(17)	124.41(18)
C(15)-C(16)-C(17)	120.46(18)
C(16)-C(17)-C(12)	119.78(18)

Symmetry transformations used to generate equivalent atoms:

Table S4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Compound 72. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	36(1)	14(1)	24(1)	0(1)	3(1)	0(1)
O(2)	45(1)	21(1)	22(1)	-4(1)	2(1)	2(1)
O(3)	22(1)	26(1)	37(1)	6(1)	-1(1)	-5(1)
O(4)	38(1)	15(1)	21(1)	0(1)	3(1)	-5(1)
O(5)	28(1)	18(1)	34(1)	2(1)	-5(1)	4(1)
C(1)	17(1)	18(1)	25(1)	2(1)	1(1)	1(1)
C(2)	18(1)	21(1)	22(1)	-3(1)	1(1)	2(1)
C(3)	23(1)	24(1)	19(1)	3(1)	2(1)	2(1)
C(4)	21(1)	16(1)	24(1)	3(1)	2(1)	-1(1)
C(5)	16(1)	17(1)	23(1)	1(1)	1(1)	0(1)
C(6)	14(1)	19(1)	22(1)	2(1)	1(1)	1(1)
C(7)	25(1)	18(1)	19(1)	2(1)	1(1)	2(1)
C(8)	25(1)	22(1)	20(1)	2(1)	2(1)	-4(1)
C(9)	24(1)	24(1)	21(1)	-1(1)	4(1)	1(1)
C(10)	25(1)	18(1)	25(1)	0(1)	1(1)	1(1)
C(11)	23(1)	15(1)	23(1)	1(1)	-1(1)	-1(1)
C(12)	27(1)	15(1)	20(1)	-3(1)	0(1)	-3(1)
C(13)	26(1)	17(1)	24(1)	0(1)	-1(1)	2(1)
C(14)	24(1)	21(1)	21(1)	-2(1)	3(1)	-3(1)
C(15)	30(1)	14(1)	17(1)	-2(1)	2(1)	-5(1)
C(16)	28(1)	15(1)	19(1)	-3(1)	-2(1)	2(1)
C(17)	22(1)	18(1)	25(1)	-3(1)	-1(1)	-2(1)
C(18)	36(1)	32(1)	22(1)	-7(1)	1(1)	4(1)
C(19)	23(1)	30(1)	35(1)	2(1)	0(1)	0(1)
C(20)	47(1)	26(1)	26(1)	3(1)	10(1)	-3(1)
C(21)	29(1)	28(1)	46(1)	-2(1)	-4(1)	8(1)

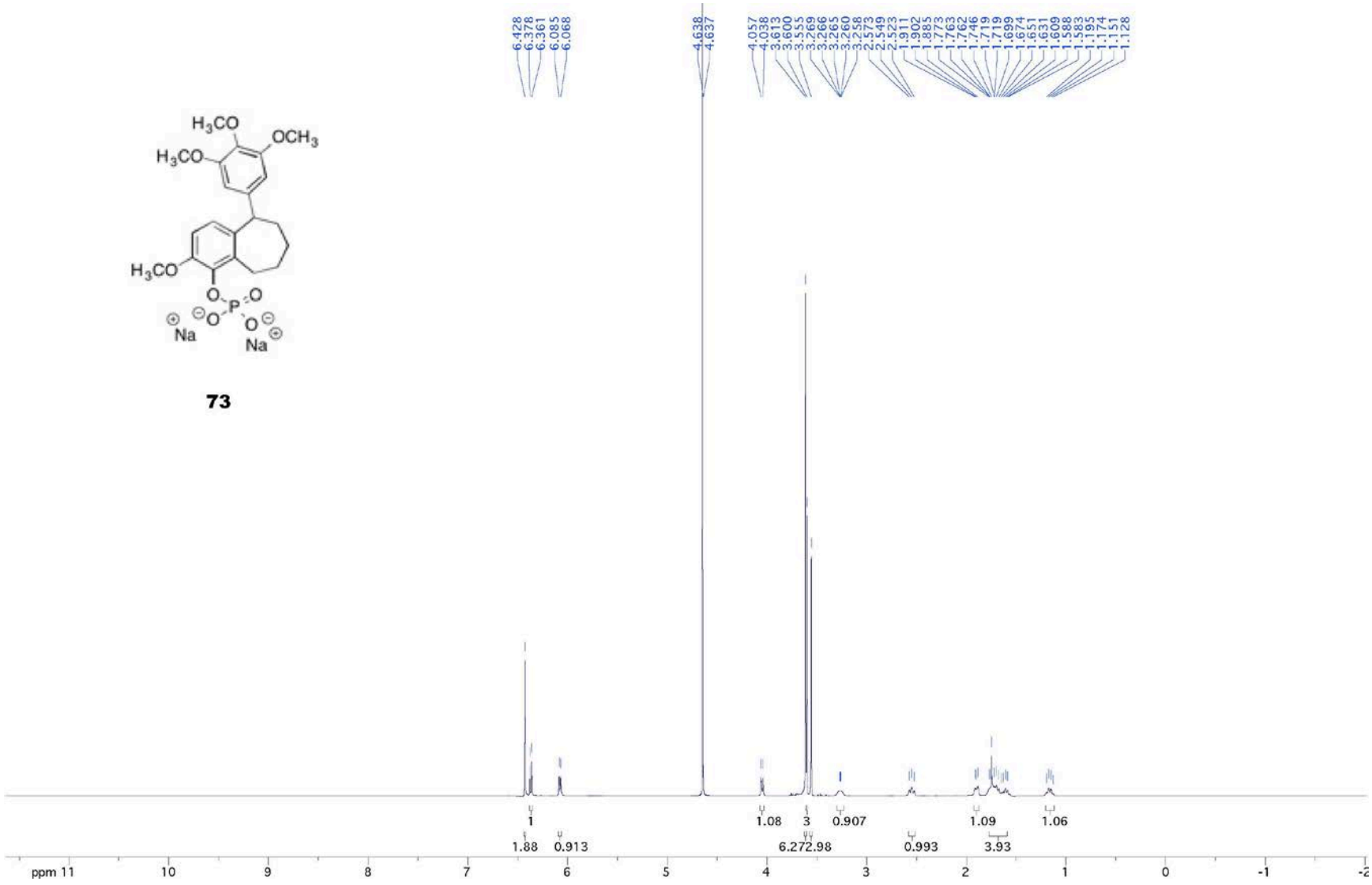
Table 5. Hydrogen bonds for 72 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(2)	0.85(3)	2.17(3)	2.635(2)	115(2)
O(1)-H(1)...O(4)#1	0.85(3)	2.47(3)	3.115(2)	133(2)
O(1)-H(1)...O(5)#1	0.85(3)	2.25(3)	2.8890(19)	133(2)

Symmetry transformations used to generate equivalent atoms:

#1 x,y-1,z

Crystallographic data for structure **72** (deposition number CCDC 1037721) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).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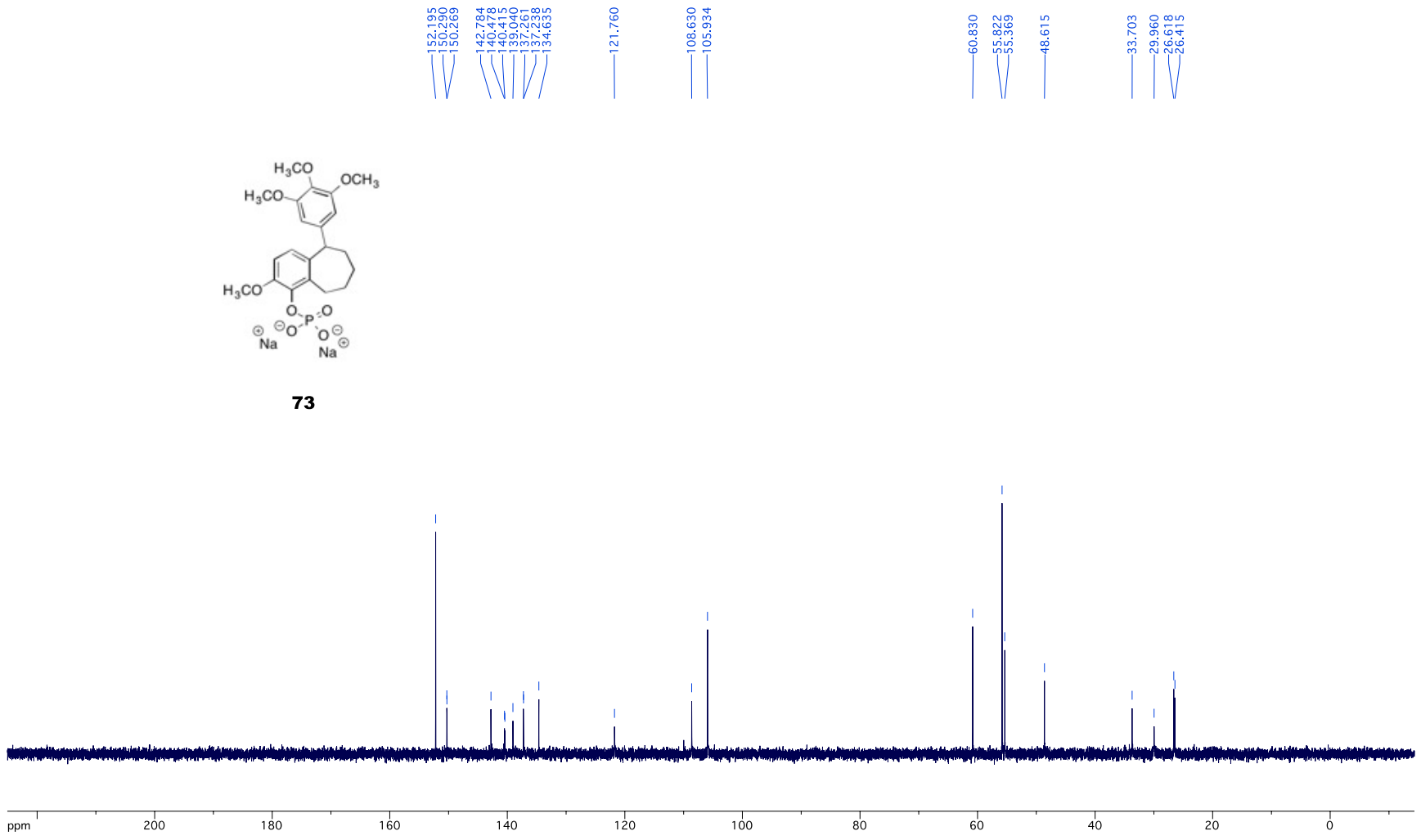
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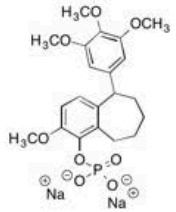
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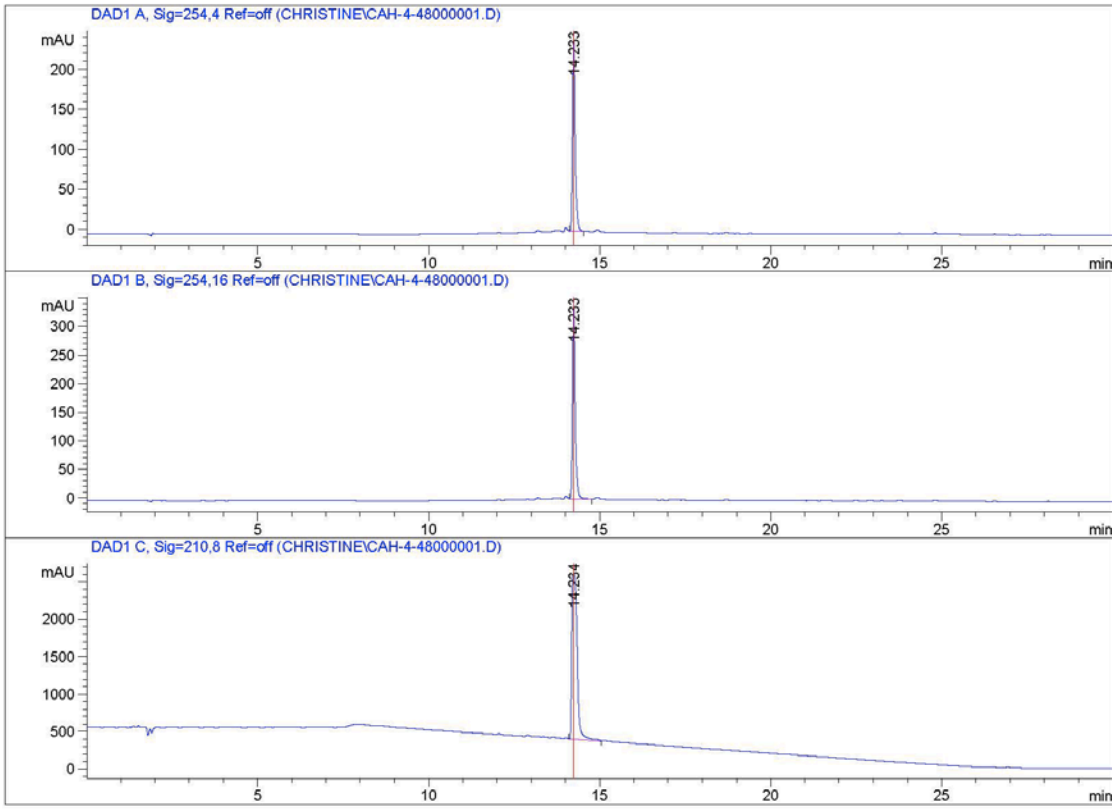

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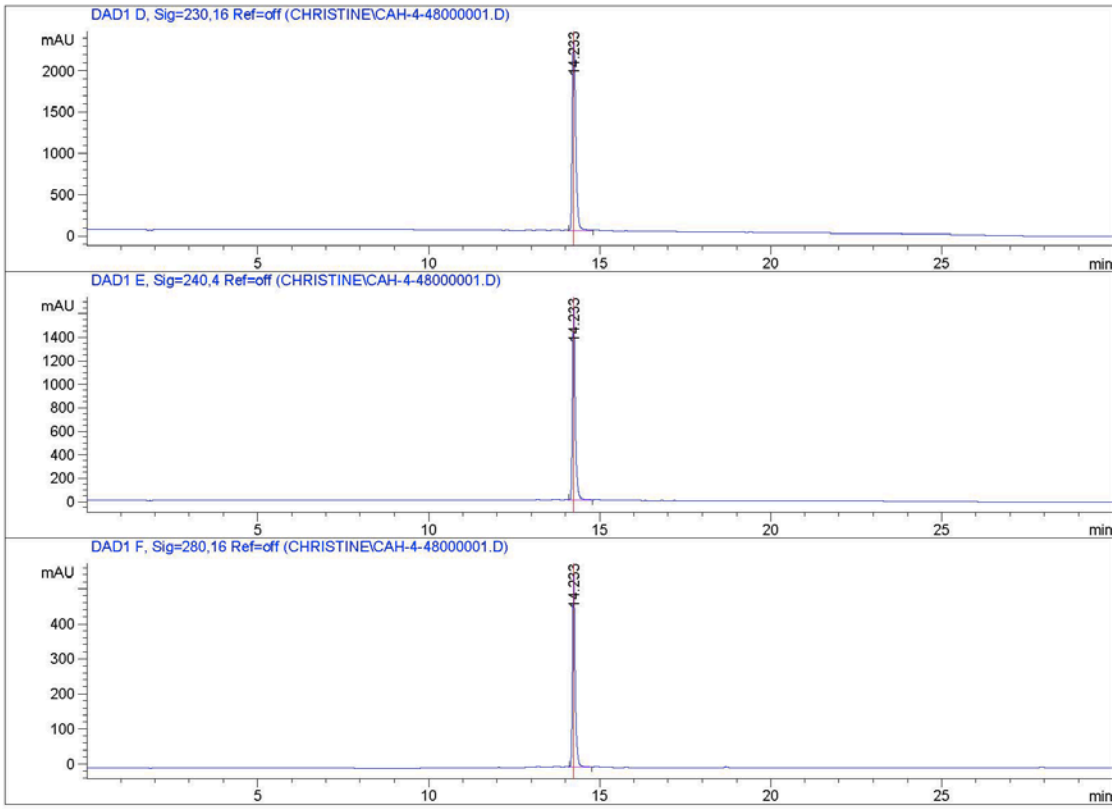
Sample Name: cah-4-48



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Area Percent Report

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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.233	VB	0.0823	1316.60486	238.95862	100.0000

Totals : 1316.60486 238.95862

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-4-48000001.D
Sample Name: cah-4-48

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.233	VV	0.0833	1889.52271	337.36499	100.0000
Totals :				1889.52271	337.36499	

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.234	VV	0.1789	2.45007e4	2218.16870	100.0000
Totals :				2.45007e4	2218.16870	

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.233	VV	0.1151	1.67958e4	2302.03564	100.0000
Totals :				1.67958e4	2302.03564	

Signal 5: DAD1 E, Sig=240,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.233	VV	0.0897	9544.16406	1644.86255	100.0000
Totals :				9544.16406	1644.86255	

Signal 6: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.233	VV	0.0826	3068.52466	554.10748	100.0000
Totals :				3068.52466	554.10748	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-4-48000001.D
Sample Name: cah-4-48

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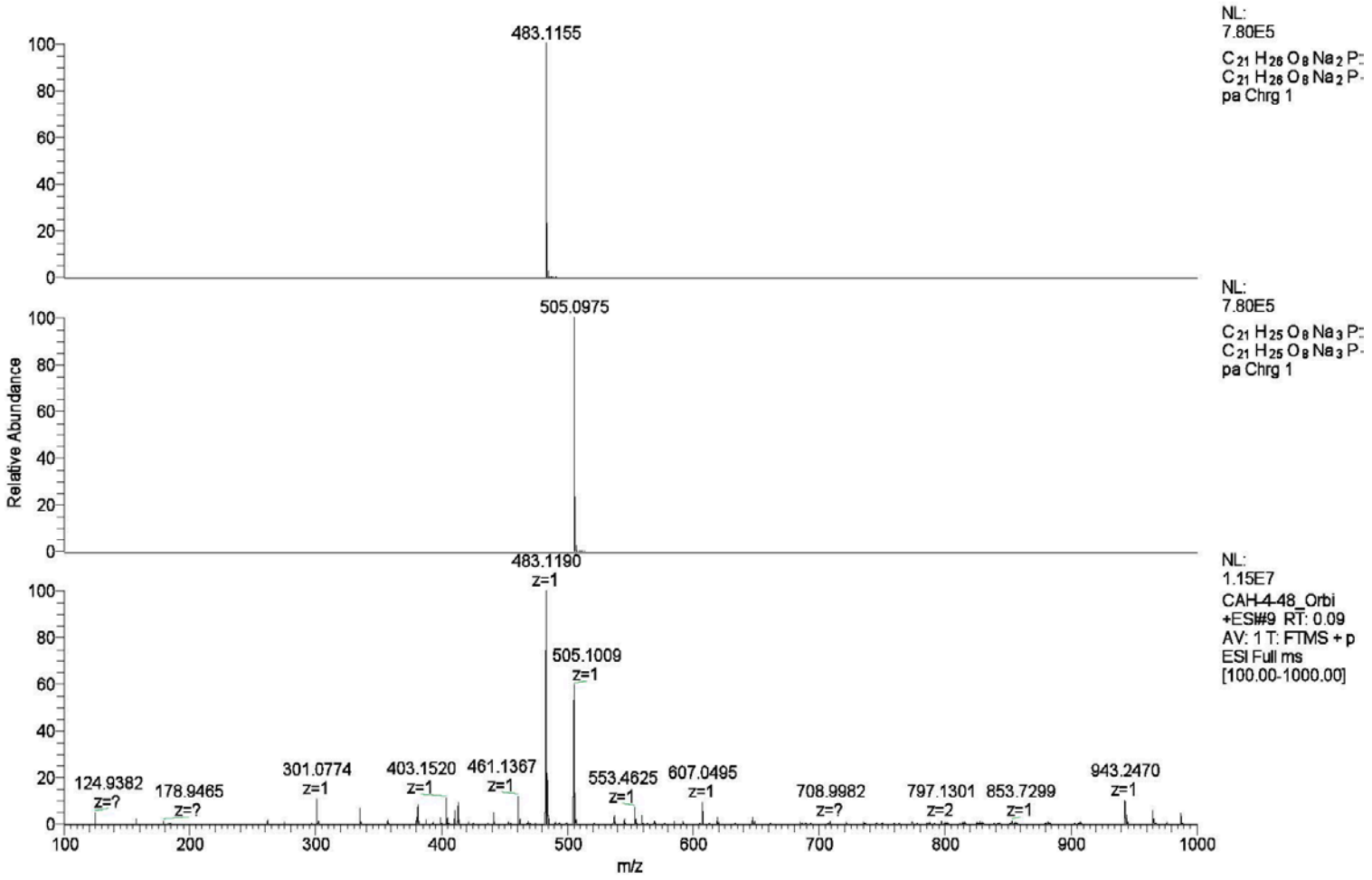
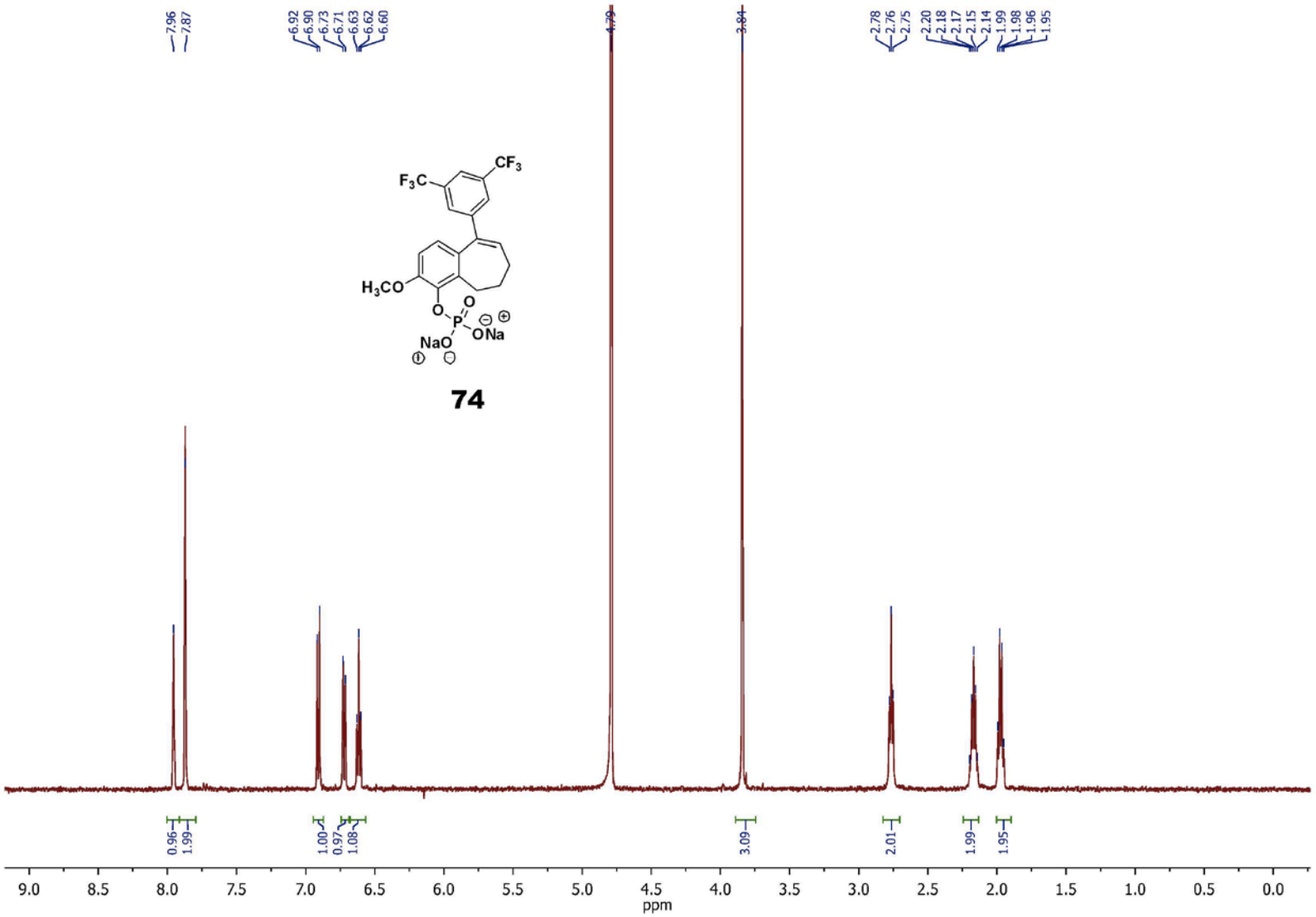
*** End of Report ***

HRMS of compound 73

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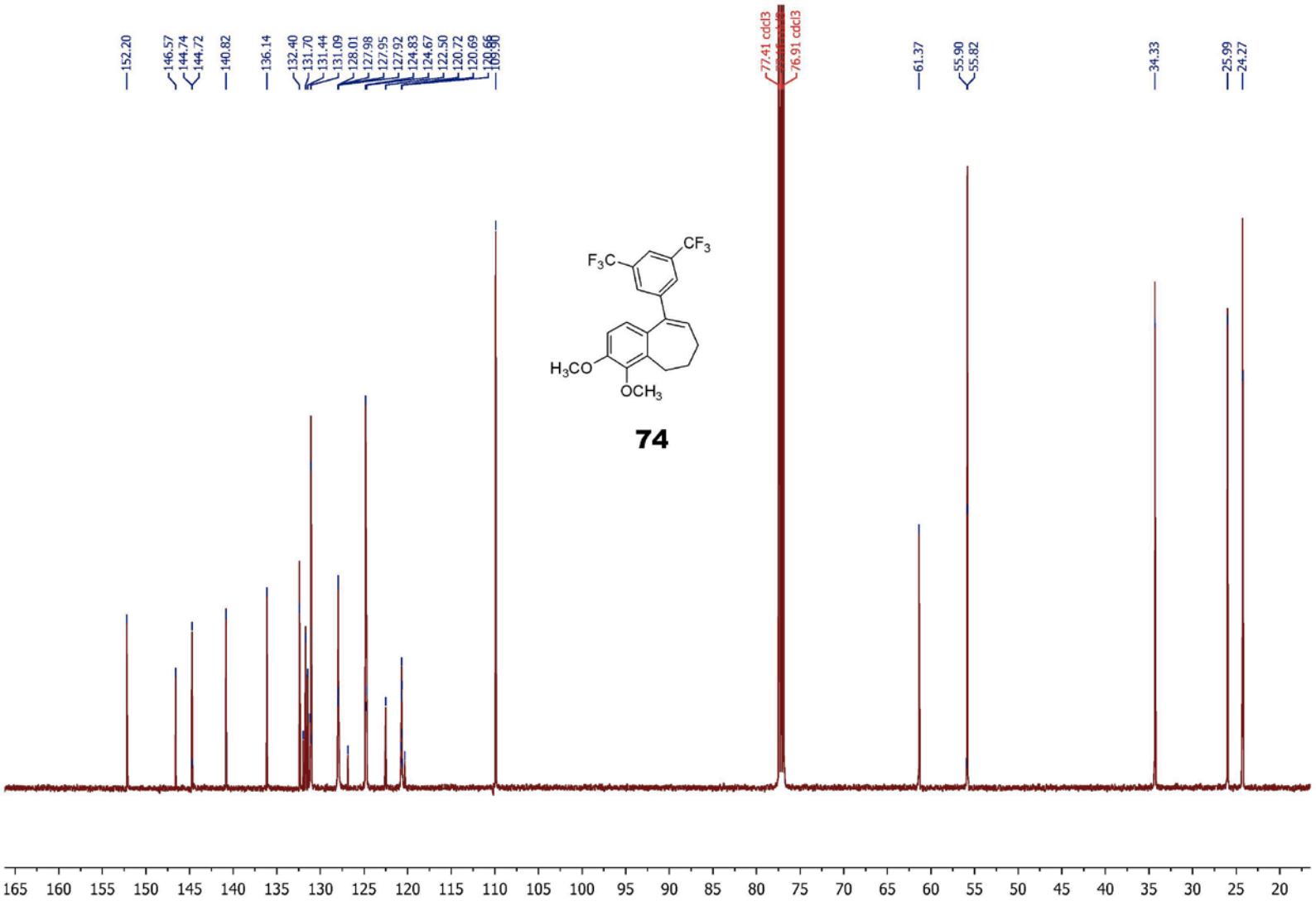
7.87
6.92
6.90
6.73
6.71
6.63
6.62
6.60
4.79
3.84
2.78
2.76
2.75
2.20
2.18
2.17
2.15
2.14
1.99
1.98
1.96
1.95
F3C
CF3
H3CO
O
P
O
ONa
NaO
74
0.96
1.99
1.00
0.97
1.08
3.09
2.01
1.99
1.95
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm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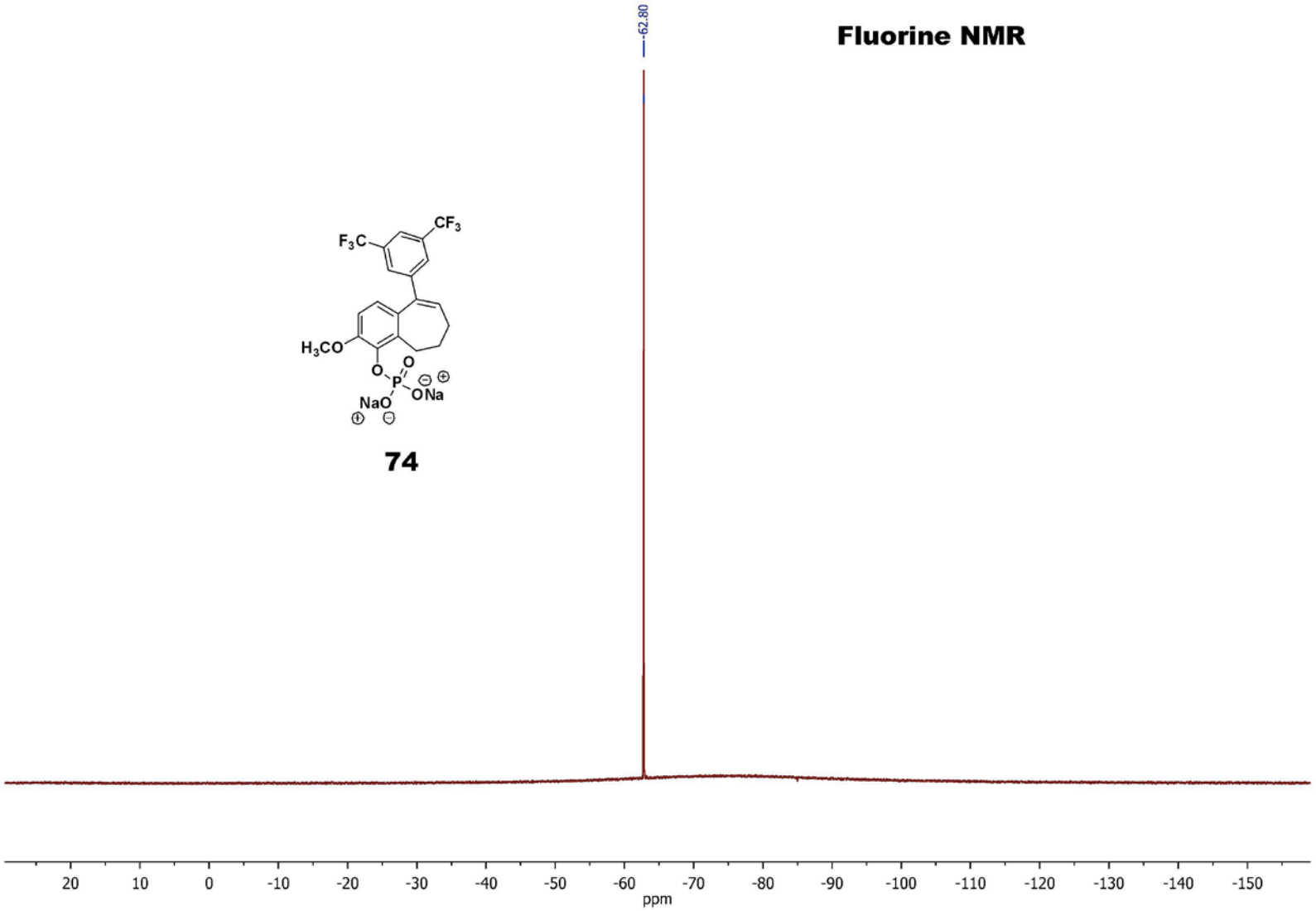
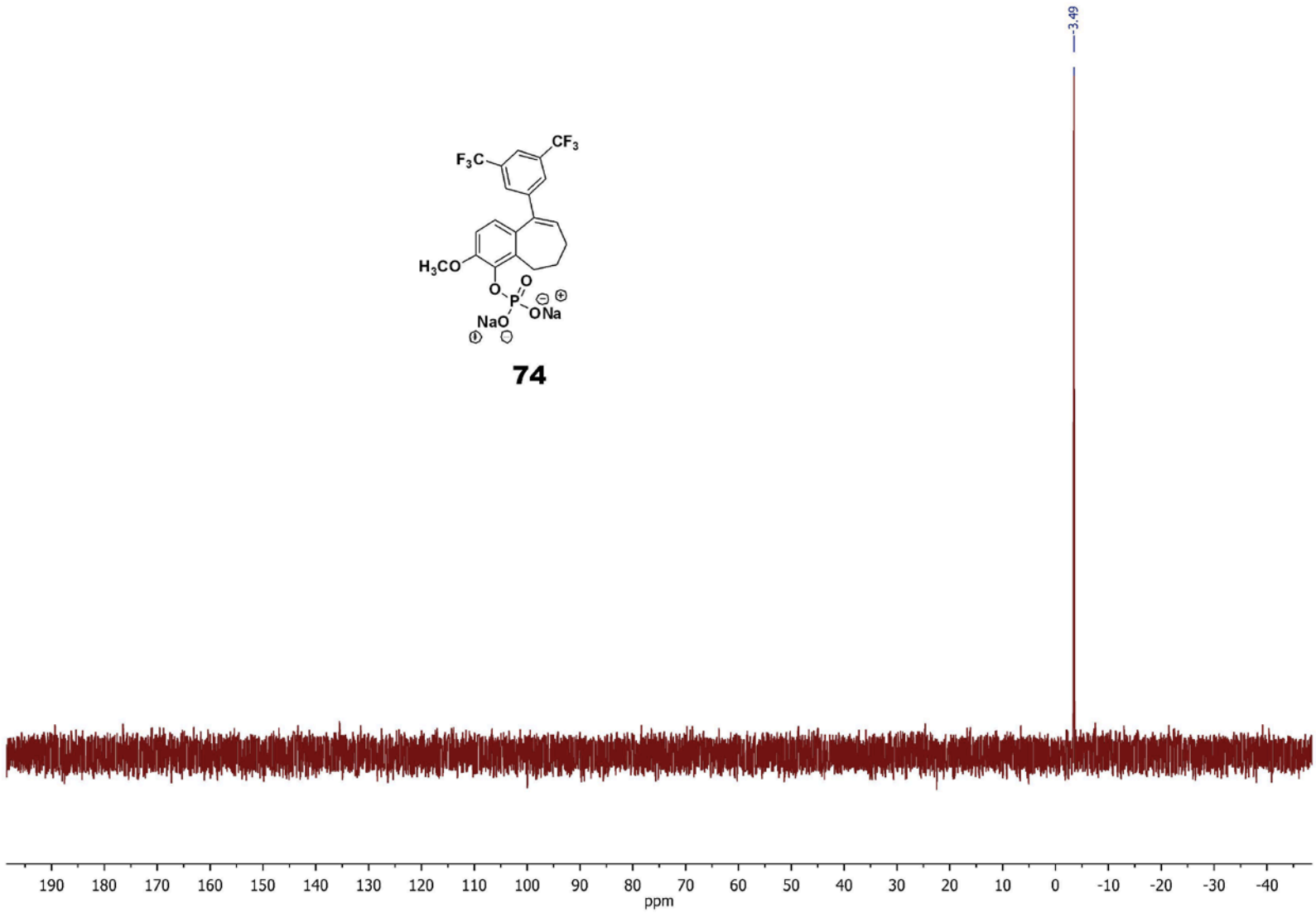
146.57
144.74
144.72
140.82
136.14
132.40
131.70
131.44
131.09
128.01
127.98
127.95
127.92
124.83
124.67
122.50
120.72
120.69
77.41 cdcl3
76.91 cdcl3
61.37
55.90
55.82
34.33
25.99
24.27
F3C
CF3
H3CO
OCH3
74
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20

Fluorine NMR



74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F3C
CF3
H3CO
O
P
NaO
ONa
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
ppm

74

Data File C:\CHEM32\1\DATA\ERIC LIN\CML-III-149-R26.D
Sample Name: CML-III-149-r2

HPLC of compound 74

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==========================================================================
Acq. Operator   : Eric Lin
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 8/4/2014 2:28:38 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 8/4/2014 1:46:20 PM by Eric Lin
Analysis Method : C:\CHEM32\1\DATA\ERIC LIN\CML-III-149-R26.D\DA.M (MASTERMETHOD.M)
Last changed    : 8/27/2014 12:20:33 PM by Christine
Sample Info     : mastermethod
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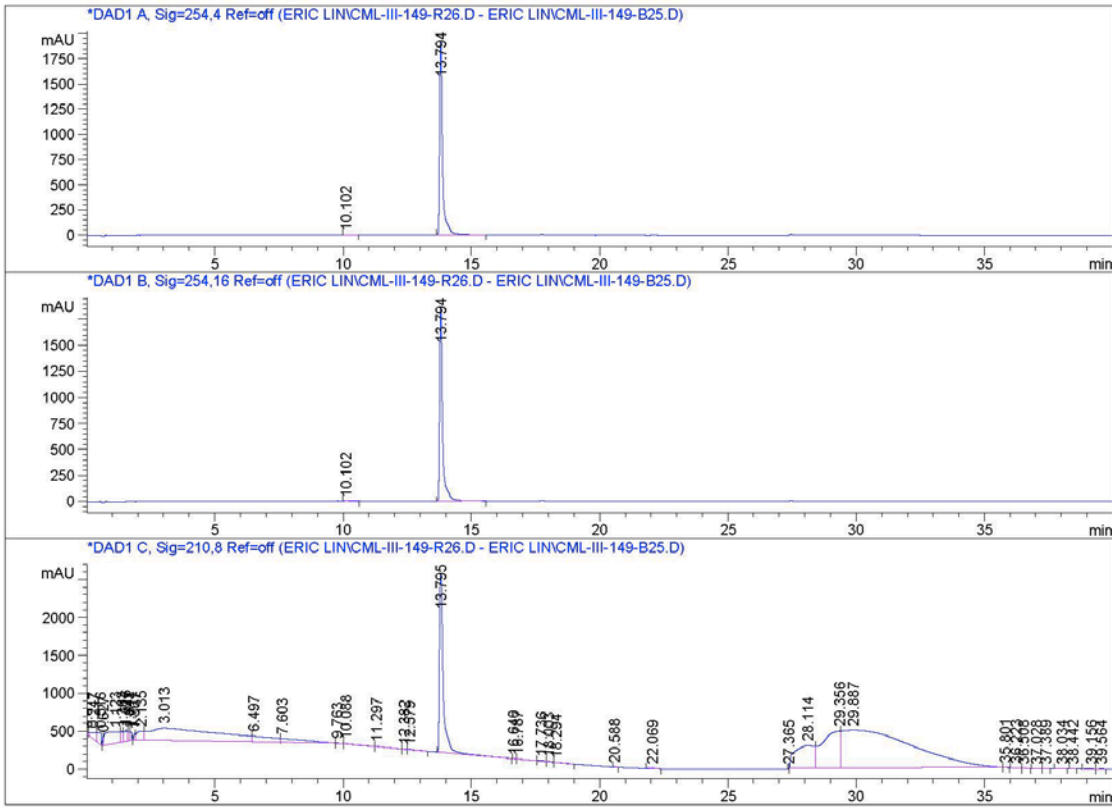
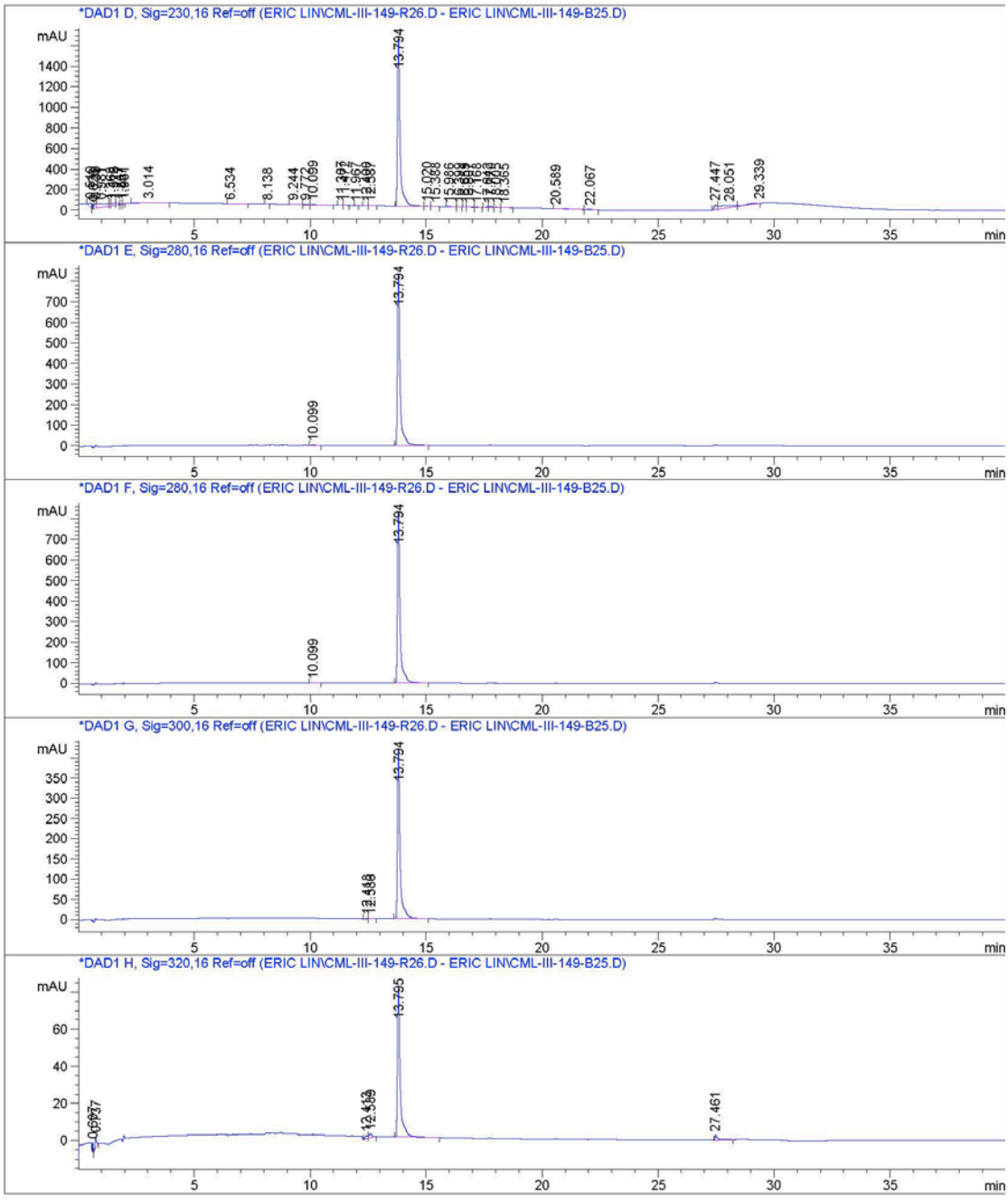


Data File C:\CHEM32\1\DATA\ERIC LIN\CML-III-149-R26.D
Sample Name: CML-III-149-r2



Data File C:\CHEM32\1\DATA\ERIC LIN\CML-III-149-R26.D
Sample Name: CML-III-149-r2

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.102	VB	0.1632	33.33345	2.91925	0.2180
2	13.794	VB	0.1164	1.52597e4	1926.53333	99.7820
Totals :				1.52930e4	1929.45257	

Signal 2: DAD1 B, Sig=254,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.102	VB	0.1638	32.29185	2.81660	0.2186
2	13.794	VB	0.1162	1.47398e4	1866.08594	99.7814
Totals :				1.47721e4	1868.90253	

Signal 3: DAD1 C, Sig=210,8 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.014	BV	0.1264	116.59129	15.36866	0.0538
2	0.247	VV	0.2472	1332.98865	78.86525	0.6147
3	0.516	VB	0.1533	1552.54041	154.45248	0.7159
4	0.627	BV	0.0341	268.13446	119.93959	0.1236
5	1.123	VV	0.5253	6208.21094	153.02040	2.8628
6	1.363	VV	0.0915	939.56226	141.51839	0.4333
7	1.516	VV	0.1314	1505.25952	149.60490	0.6941
8	1.647	VV	0.0561	475.18509	120.27156	0.2191
9	1.714	VB	0.0678	516.40662	116.22965	0.2381
10	1.861	BV	0.0728	400.88586	88.58305	0.1849
11	2.135	VV	0.3148	2428.47144	120.64979	1.1198

Data File C:\CHEM32\1\DATA\ERIC LIN\CML-III-149-R26.D
Sample Name: CML-III-149-r2

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
12	3.013	VV	2.2150	3.12489e4	168.24092	14.4098
13	6.497	VV	0.6875	4282.35107	75.98831	1.9747
14	7.603	VB	0.7892	3460.69922	52.62601	1.5958
15	9.763	BV	0.1387	32.96905	3.29470	0.0152
16	10.088	VV	0.3678	200.97350	6.81970	0.0927
17	11.297	VB	0.3651	246.68819	8.53868	0.1138
18	12.382	BV	0.1599	44.04943	4.35936	0.0203
19	12.579	VB	0.2161	158.32291	9.61325	0.0730
20	13.795	BB	0.1546	2.43593e4	2356.12231	11.2329
21	16.640	BV	0.0861	8.61282	1.51916	3.972e-3
22	16.787	VV	0.3534	50.88361	1.79118	0.0235
23	17.736	VV	0.1681	152.08693	13.23410	0.0701
24	18.003	VB	0.0973	85.28777	13.21263	0.0393
25	18.294	BB	0.1673	79.26408	6.19386	0.0366
26	20.588	BB	0.0775	27.55946	5.59449	0.0127
27	22.069	BB	0.2297	115.85145	7.27799	0.0534
28	27.365	BB	0.0195	6.61201	5.81724	3.049e-3
29	28.114	BV	0.7154	1.57789e4	300.12476	7.2761
30	29.356	VV	0.7563	2.42025e4	491.68054	11.1606
31	29.887	VB	2.3219	9.61836e4	501.41739	44.3533
32	35.801	BB	0.1517	22.13400	2.31238	0.0102
33	36.223	BV	0.2609	55.02095	3.04299	0.0254
34	36.508	VB	0.1819	36.04284	3.00632	0.0166
35	37.028	BV	0.1866	53.60883	4.38545	0.0247
36	37.389	VB	0.1591	49.88113	5.14453	0.0230
37	38.034	VB	0.1951	36.97443	2.81737	0.0171
38	38.442	BB	0.1327	14.78003	1.82136	6.816e-3
39	39.156	BB	0.2580	71.35019	3.96372	0.0329
40	39.564	BB	0.2068	48.35715	4.00710	0.0223
Totals :				2.16858e5	5322.47151	

Signal 4: DAD1 D, Sig=230,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.510	BB	0.1227	281.79205	33.32289	1.5359
2	0.626	BV	0.0323	62.86551	30.14817	0.3426
3	0.739	VV	0.1042	377.07275	48.78299	2.0552
4	0.981	VV	0.3857	1086.44214	37.98767	5.9214
5	1.368	VV	0.0797	151.39351	26.08789	0.8251
6	1.518	VV	0.1373	272.69882	25.79583	1.4863
7	1.717	VB	0.1341	182.61948	18.04617	0.9953
8	1.857	BB	0.0617	27.95403	7.81287	0.1524
9	1.961	BB	0.0545	20.80817	5.99101	0.1134
10	3.014	BB	0.6050	267.75238	5.56837	1.4593

Data File C:\CHEM32\1\DATA\ERIC LIN\CML-III-149-R26.D
Sample Name: CML-III-149-r2

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
11	6.534	BV	0.3767	57.15169	1.91202	0.3115
12	8.138	BB	0.0794	5.82987	1.14436	0.0318
13	9.244	BV	0.3169	31.18376	1.26792	0.1700
14	9.772	VV	0.1416	27.56984	2.68903	0.1503
15	10.099	VB	0.2091	71.74109	4.67413	0.3910
16	11.307	BV	0.1256	22.51918	2.69070	0.1227
17	11.472	VB	0.1012	16.75818	2.46791	0.0913
18	11.967	VB	0.0976	9.49871	1.50531	0.0518
19	12.400	BV	0.1513	21.66013	2.31095	0.1181
20	12.587	VB	0.1309	38.09042	4.15847	0.2076
21	13.794	VV	0.1147	1.28217e4	1649.89600	69.8822
22	15.020	VB	0.1292	30.51363	3.66408	0.1663
23	15.388	BB	0.1131	32.63912	4.37035	0.1779
24	15.986	BV	0.2081	21.80622	1.47846	0.1189
25	16.399	VB	0.1185	27.55081	3.40261	0.1502
26	16.659	BV	0.0876	26.69537	4.74829	0.1455
27	16.807	VB	0.1090	40.28115	5.52840	0.2195
28	17.168	BB	0.1287	25.67058	2.86103	0.1399
29	17.642	BV	0.1179	75.71060	9.61090	0.4126
30	17.770	VV	0.1174	90.70266	11.33053	0.4944
31	18.005	VB	0.1042	39.87554	5.66185	0.2173
32	18.365	BB	0.1760	27.57606	2.03578	0.1503
33	20.589	BB	0.1915	38.05714	2.58892	0.2074
34	22.067	BB	0.2146	74.61647	4.87451	0.4067
35	27.447	BV	0.1212	421.20547	46.70127	2.2957
36	28.051	VV	0.6665	1109.79724	22.15031	6.0487
37	29.339	VB	1.1831	409.78696	4.76587	2.2335
Totals :				1.83476e4	2050.03383	

Signal 5: DAD1 E, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.099	BB	0.1567	12.72469	1.13608	0.1970
2	13.794	BB	0.1140	6446.57959	835.78650	99.8030
Totals :				6459.30428	836.92258	

Data File C:\CHEM32\1\DATA\ERIC LIN\CML-III-149-R26.D
Sample Name: CML-III-149-r2

Signal 6: DAD1 F, Sig=280,16 Ref=off
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.099	BB	0.1567	12.72469	1.13608	0.1970
2	13.794	BB	0.1140	6446.57959	835.78650	99.8030
Totals :				6459.30428	836.92258	

Signal 7: DAD1 G, Sig=300,16 Ref=off
Signal has been modified after loading from rawdata file!

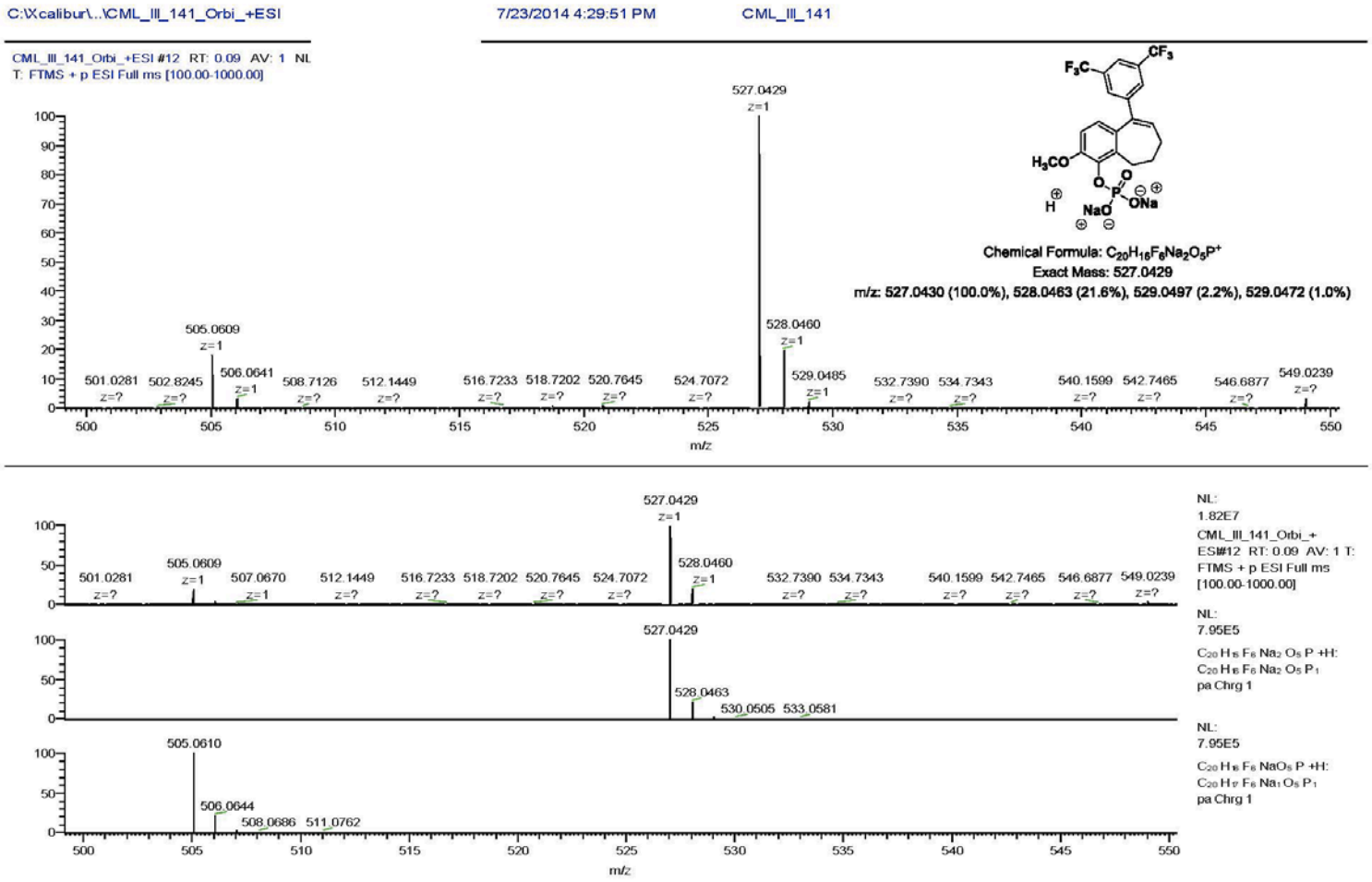
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.418	BV	0.1436	13.22460	1.48978	0.4033
2	12.586	VB	0.1478	14.48388	1.36451	0.4417
3	13.794	BB	0.1144	3251.21021	419.63831	99.1550
Totals :				3278.91869	422.49259	

Signal 8: DAD1 H, Sig=320,16 Ref=off
Signal has been modified after loading from rawdata file!

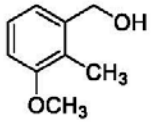
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.607	BB	0.0301	9.38681	4.94999	1.2174
2	0.737	BB	0.0659	29.25878	6.58113	3.7946
3	12.413	BV	0.1398	15.82891	1.84999	2.0529
4	12.589	VB	0.1340	22.26375	2.36228	2.8874
5	13.795	BB	0.1197	664.22479	80.99686	86.1439
6	27.461	BB	0.1347	30.10082	2.90944	3.9038
Totals :				771.06386	99.64970	

*** End of Report ***

HRMS of compound 74

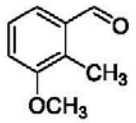


Alternative Synthesis for Compound **30**



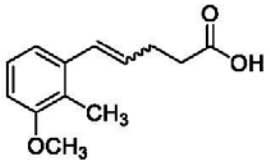
3-Methoxy-2-methylbenzoic acid

To a well-stirred and pre-cooled 0° C solution of 3-methoxy-2-methylbenzoic acid (500 mg, 3 mmol) in THF (150 mL), $LiAlH_4$ (1.13 mL, 2.0 M) was added, and the reaction was stirred warming from 0° C to room temperature over 12 h. The reaction mixture was quenched with 7 mL of 20% H_2O in THF added dropwise, and then 10 mL of 15-20% NaOH was added. After filtering through Celite®, the filtrate was extracted with EtOAc (3 x 50 mL). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7% A/ 93% B (3 CV), 7% A/ 93% B → 60% A/ 40% B (10 CV), 60% A/ 40% B (1 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording the alcohol (0.40 g, 2.67mmol, 89%) as a white powder. ^{1}H NMR (CDCl3, 500 MHz) δ 7.17 (1H, dd, J = 5.0 Hz, 10.0 Hz), 6.97 (1H, d, J = 5.0 Hz), 6.82 (1H, d, J = 10.0 Hz), 4.66 (2H, s), 3.83 (3H, s), 2.21 (3H, s). ^{13}C NMR (CDCl3, 125 MHz) δ 157.7, 139.9, 126.3, 124.7, 120.0, 109.8, 63.5, 55.6, 10.8.



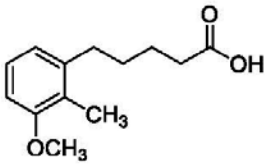
3-Methoxy-2-methylbenzaldehyde

To a well-stirred pyridinium chlorochromate (PCC) in CH_2Cl_2 (40 mL) solution, (3-methoxy-2-methylphenyl)methanol (3.22 g, 21.2 mmol) dissolved in CH_2Cl_2 (25 mL) was slowly added. The reaction mixture was stirred at room temperature for 12 h. The mixture was filtered through Celite®, and the Celite® was washed thoroughly with CH_2Cl_2 (2 x 30 mL). The filtrate was concentrated under reduced pressure and purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7% A/ 93% B (3 CV), 7% A/ 93% B → 60% A/ 40% B (10 CV), 60% A/ 40% B (1 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording the aldehyde (2.70 g, 18 mmol, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.31 (1H, s), 7.41 (1H, d, J = 10.0 Hz), 7.30 (1H, dd, J = 5.0 Hz, 10.0 Hz), 7.06 (1H, d, J = 10.0 Hz), 3.86 (3H, s), 2.53 (3H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.7, 158.1, 135.1, 129.6, 126.6, 123.0, 115.2, 55.9, 10.4.



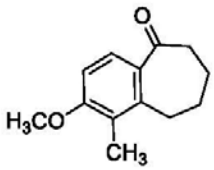
5-(3′-methoxy-2′-methylphenyl)pent-4-enoic acid

A mixture of 3-(carboxypropyl)triphenylphosphonium bromide (7.8 g, 18.2 mmol) and potassium *tert*-butoxide (4.5 g, 40.1 mmol) in THF (150 mL) was stirred for 1 h at room temperature. A 3-methoxy-2-methylbenzaldehyde (2.70 g, 18 mmol) solution in THF (20 mL) was added dropwise to the reaction mixture. The reaction was quenched with 2 M HCl (30mL), then extracted with EtOAc (3 x 50 mL). The organic extract was washed with brine, dried with Na_2SO_4, concentrated under reduced pressure, and then purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7% A/ 93% B (3 CV), 7% A/ 93% B → 60% A/ 40% B (10 CV), 60% A/ 40% B (1 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording 5-(3′-methoxy-2′-methylphenyl)pent-4-enoic acid (*E* & *Z*) (3.04 g, 13.8 mmol, 75%) as a pale yellow oil. NMR data was collected after the next step.



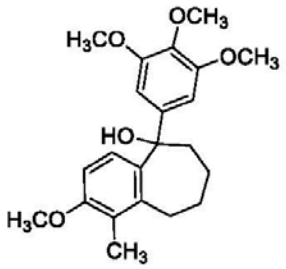
5-(3′-methoxy-2′-methylphenyl)pentanoic acid

5-(3′-Methoxy-2′-methylphenyl)pent-4-enoic acid (3.04 g, 13.8 mmol) was mixed with Pd/C powder quickly, and the reaction vessel was purged with nitrogen. Methanol (40 mL) was slowly added, and the reaction vessel was purged again with nitrogen. The reaction was stirred for 12 h at room temperature. The suspension was filtered through Celite®, and the Celite® was rinsed with EtOAc. The filtrate (combined MeOH and EtOAc) was concentrated under reduced pressure and purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7% A/ 93% B (3 CV), 7% A/ 93% B→60% A/ 40% B (10 CV), 60% A/ 40% B (1 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording 5-(3-methoxy-2-methylphenyl)pentanoic acid (2.1 g, 9.6 mmol 70%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42 (1H, dd, *J* =10.0 Hz, 5.0 Hz), 7.15 (1H, d, *J* = 5.0 Hz), 7.05 (1H, d, *J* =10.0 Hz), 4.15 (3H, s), 2.97 (2H, m), 2.73 (2H, t, *J* =5.0 Hz), 2.51 (3H, s), 2.06 (2H, m), 1.96 (2H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 180.1, 157.7, 141.6, 125.9, 124.6, 121.6, 107.9, 55.6, 34.0, 33.2, 29.9, 24.6, 11.2.



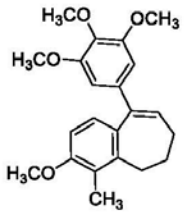
1,2-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one

Eaton's reagent (42 mL) was added to 5-(3′-methoxy-2′-methylphenyl)pentanoic acid (2.1 g, 9.6 mmol). The mixture was sonicated until dissolved and stirred at room temperature for 12 h. Ice was poured into the reaction flask, and the mixture was neutralized with sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was dried with Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7% A/ 93% B (3 CV), 7% A/ 93% B→60% A/ 40% B (10 CV), 60% A/ 40% B (1 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording the ketone product (1.87 g, 9.1 mmol, 94%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (1H, d, J = 10.0 Hz), 6.76 (1H, d, J = 10.0 Hz), 3.85 (3H, s), 2.88 (2H, m), 2.65 (2H, m), 2.21 (3H, s), 1.81 (2H, m), 1.73 (2H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.5, 160.5, 140.5, 132.7, 127.5, 123.9, 107.8, 55.6, 40.5, 27.1, 24.2, 20.6, 11.2.



2-Methoxy-1-methyl-5-(3′,4′,5′-trimethoxyphenyl)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ol

5-bromo-1,2,3-trimethoxybenzene (3.39 g, 13.7 mmol) was dissolved in THF (40 mL) and cooled to -78 °C. *n*-BuLi (5.49 mL, 2.5 M) was added dropwise, and the mixture was stirred at -78° C. After 1 h, the ketone (1.87 g, 9.1 mmol) in THF was added dropwise to the reaction flask. The reaction was allowed to stir for 12 h warming to room temperature. The reaction was quenched with water (100 mL) and extracted with EtOAc. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was further purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 10% A/ 93% B (3 CV), 10% A/ 93% B → 60% A/ 40% B (10 CV), 60% A/ 40% B (1 CV); flow rate: 25 mL/min; monitored at 254 and 280nm] affording the tertiary alcohol (2.38 g, 6.4 mmol, 70%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (1H, d, J = 10.0 Hz), 6.71 (1H, d, J = 10.0 Hz), 6.53 (2H, s), 3.84 (3H, s), 3.83 (3H, s), 3.75 (6H, s), 2.97 (2H, m), 2.55 (2H, m), 2.22 (3H, s), 1.84, (2H, m), 1.30, (2H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.7, 153.0, 142.4, 140.7, 137.6, 137.2, 125.3, 124.0, 107.2, 104.2, 80.0, 60.8, 56.1, 55.4, 41.4, 28.5, 26.1, 25.8, 11.9.



3-Methoxy-4-methyl-9-(3′,4′,5′-trimethoxyphenyl)-6,7-dihydro-5*H*-benzo[7]annulene
The tertiary alcohol (2.38 g, 6.4 mmol) was dissolved in acetic acid (15 mL) and stirred for 6 h. The reaction was quenched with water (100 mL) and then extracted with EtOAc. The organic phase was washed with brine, dried with Na_2SO_4, concentrated and purified by flash chromatography using a prepacked 100 g silica column [solvent A: EtOAc; solvent B: hexanes; gradient: 7% A/ 93% B (3 CV), 7% A/ 93% B → 60% A/ 40% B (10 CV), 60% A/ 40% B (1 CV); flow rate: 25 mL/min; monitored at 254 and 280 nm] affording **26** (1.78 g, 5.0 mmol, 78%) as a white powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.86 (1H, d, J = 10.0 Hz), 6.70 (1H, d, J =10.0 Hz), 6.52 (2H, s), 6.32 (1H, t, J = 7.5 Hz), 3.86 (3H, s), 3.84 (3H, s), 3.80 (6H, s), 2.68 (2H, t, J = 6.5 Hz), 2.29 (3H, s), 2.12 (2H, p, J = 7.0 Hz), 1.91 (2H, q, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.5, 152.8, 143.5, 141.7, 138.6, 137.3, 133.0, 127.4, 126.5, 123.2, 107.4, 105.3, 60.9, 56.1, 55.5, 34.0, 27.7, 25.5, 11.8. HRMS: Obsvd 355.1906 [M+H]+, calcd for $C_{22}H_{27}O_5$: 355.1904. HPLC (by method B): 19.87 min.

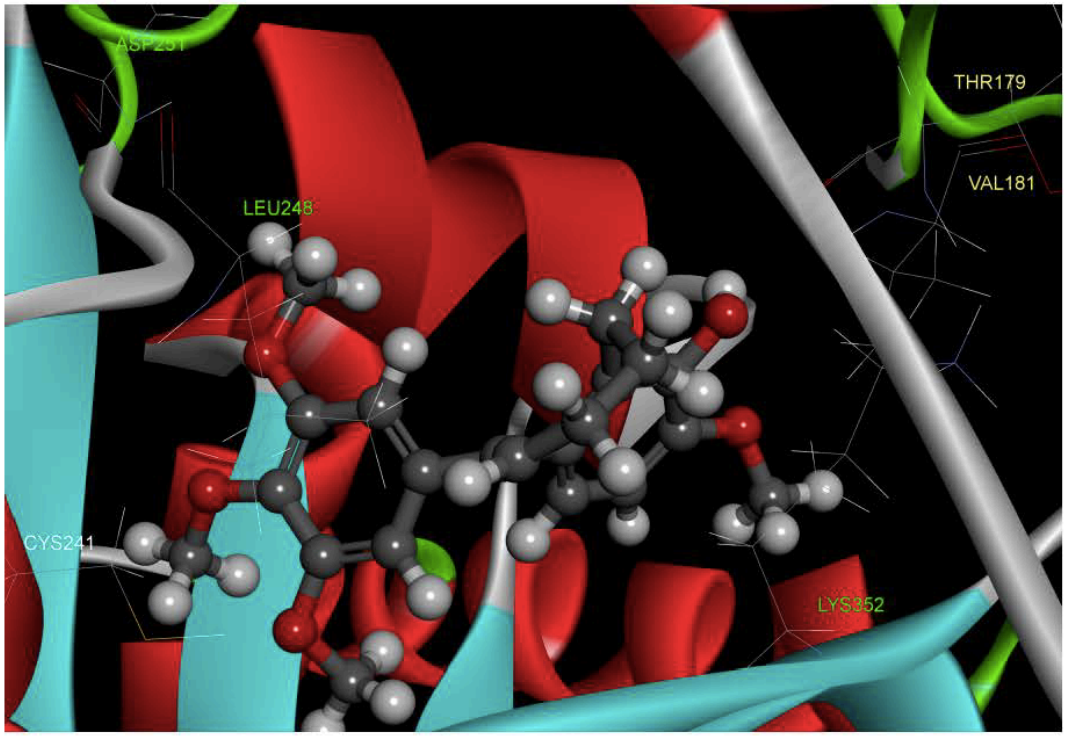
Compound	Inhibition of tubulin polymerization IC_{50} (μM) ± SD	% Inhibition of colchicine binding ± SD	GI_{50} (μM) SRB assay[a]		
			SK-OV-3	NCI-H460	DU-145
CA4	1.0[b]	84 ± 3 (1 μM), 98 ± 0.007 (5 μM)	0.00455 ± 0.00211	0.00223[c]	0.00327 ± 0.00215[c]
CA4P	>40[b]	nr	0.00119 ± 0.00124	0.00194[c]	0.00323 ± 0.00147[c]
KGP18	1.4[d]	nr	0.0000543[c]	0.0000418[c]	0.0000249[c]
28	>20	nr	32.7 ± 3.92	37.5 ± 4.21	89.3 ± 30.7
29	1.0 ± 0.02	37 ± 5 (1 μM), 72 ± 0.8 (5 μM)	0.0516 ± 0.0315	0.0527 ± 0.0184	0.0619 ± 0.00509
30	1.6 ± 0.2	65 ± 0.6 (5 μM)	0.330 ± 0.00624	0.422 ± 0.0104	0.644 ± 0.193
31	>20	nr	0.568 ± 0.0718	0.763 ± 0.130	1.51 ± 0.741
32	>20	nr	2.96 ± 0.804	3.32 ± 0.459	6.03 ± 0.0974
33	>20	nr	11.5 ± 5.87	16.1 ± 0.212	12.2 ± 7.59
34	>20	nr	31.1 ± 6.20	25.5 ± 4.01	52.1 ± 2.96
35	3.1 ± 0.03	30 ± 4 (5 μM), 56 ± 4 (50 μM)	0.277 ± 0.294	0.593 ± 0.109	0.708 ± 0.343
36	>20	nr	20.5 ± 13.6	33.4 ± 2.41	48.3 ± 38.3
37	>20	nr	40.7 ± 11.6	57.7 ± 19.1	68.7 ± 18.1
61	>20	nr	6.96 ± 0.503	10.5 ± 0.768	26.2 ± 7.83
62	1.2 ± 0.007	36 ± 5 (1 μM), 69 ± 3 (5 μM)	0.0432 ± 0.00826	0.120 ± 0.0179	0.0562 ±0.0269
64	>20	nr	0.557 ± 0.0358	0.652 ± 0.0543	4.40 ± 1.97
65	3.8 ± 0.3	8.5 ± 4 (5 μM), 37 ± 5 (50 μM)	4.81 ± 1.55	4.39 ± 1.36	4.92 ± 0.267
66	>20	nr	16.8 ± 9.60	25.0 ± 3.09	21.8 ± 0.607
67	7.4 ± 0.06	nr	18.4 ± 19.3	10.6 ± 5.26	8.59 ± 6.32
68	2.7 ± 0.1	27 ± 5 (5 μM)	0.527 ± 0.00634	0.647 ± 0.0160	1.02 ± 0.100
70	7.7 ± 0.2	nr	0.346 ± 0.127	0.691 ± 0.219	1.53 ± 1.02

71	11 ± 0.4	nr	3.53 ± 0.270	4.24 ± 0.208	7.54 ± 5.49
72	0.70 ± 0.1	21 ± 0.9 (1 μM), 67 ± 0.6 (5 μM)	0.408 ± 0.0883	0.141 ± 0.153	0.570 ± 0.147
73	>20	nr	0.357 ± 0.119	0.145 ± 0.161	0.753 ± 0.246
74	>20	nr	17.2 ± 4.94	16.3 ± 1.17	17.5 ± 1.55

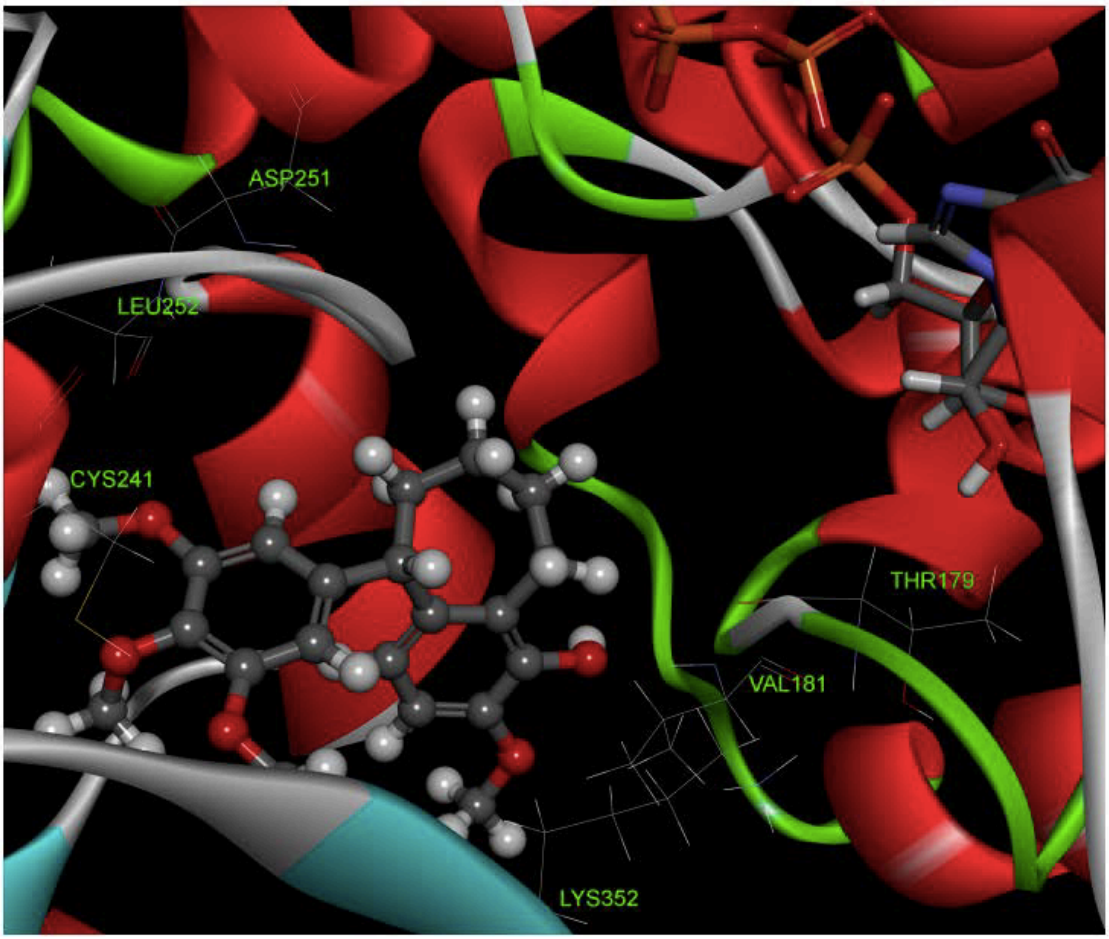
Molecular docking

Discovery Studio Client 4.5 (Accelrys) was used to carry out molecular docking studies on several analogues that were active inhibitors of tubulin polymerization (compounds **29**, **62** and **72**), the lead benzosuberene compound **KGP18**, colchicine, and compound **33** (IC_{50} > 20 μM in the tubulin polymerization assay). The X-ray structure of of *N*-deacetyl-*N*-(2-mercaptoacetyl)-colchicine (DAMA-colchicine) in the structure co-crystallized with tubulin (1SA0) was the starting structure for these studies. The protein was prepared and DAMA-colchicine was removed, and then docked (CDocker) to validate the docking procedure and parameters. There was excellent agreement between the docked and X-ray crystal structure of the ligand bound to tubulin.

The trimethoxyphenyl ring of colchicine, **KGP18** and all three active analogues was docked in a similar position to that of the trimethoxyphenyl moiety of *N*-deacetyl-*N*-(2-mercaptoacetyl)-colchicine in the structure co-crystallized with tubulin, and very close to the Cys241 residue of the beta subunit.

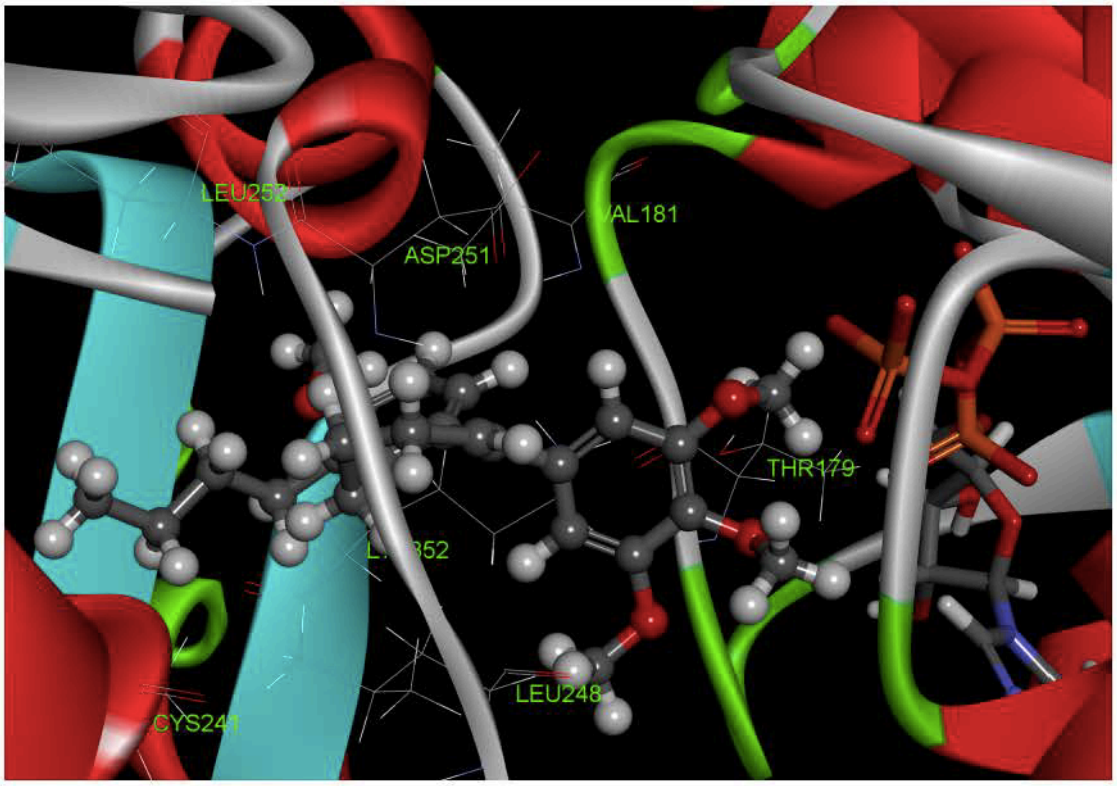


KGP18 (ball and stick) docked at the DAMA-colchicine binding site of tubulin (1SA0). THR179 and VAL181 (on the right side of the figure) are part of the alpha subunit. All other labeled residues are found in the tubulin beta subunit.



Compound **72** (ball and stick) docked at the DAMA-colchicine binding site of tubulin (1SA0). THR179 and VAL181 (on the right side of the figure) are part of the alpha subunit. All other labeled residues are found in the tubulin beta subunit.

In contrast, docking placed multiple top conformations of compound **33** (IC_{50} > 20 μM in the tubulin polymerization assay) with its trimethoxyphenyl ring outside of this pocket. In one top conformation shown below, the butyl chain is placed in the location of the trimethoxyphenyl ring of DAMA-colchicine, and the trimethoxyphenyl moiety of compound **33** is displaced toward the alpha subunit of tubulin.



Compound **33** (ball and stick) docked at the DAMA-colchicine binding site of tubulin (1SA0). THR179 and VAL181 (on the right side of the figure) are part of the alpha subunit. All other labeled residues are found in the tubulin beta subunit.

Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain.
Ravelli, R.B., Gigant, B., Curmi, P.A., Jourdain, I., Lachkar, S., Sobel, A., Knossow, M.
(2004) Nature **428:** 198-202
PubMed: 15014504
DOI: 10.1038/nature02393

APPENDIX B

Synthesis and Biological Evaluation of Benzocyclooctene-based and Indene-based Anticancer Agents that Function as Inhibitors of Tubulin Polymerization

Synthesis and Biological Evaluation of Benzocyclooctene-based and Indene-based Anticancer Agents that Function as Inhibitors of Tubulin Polymerization

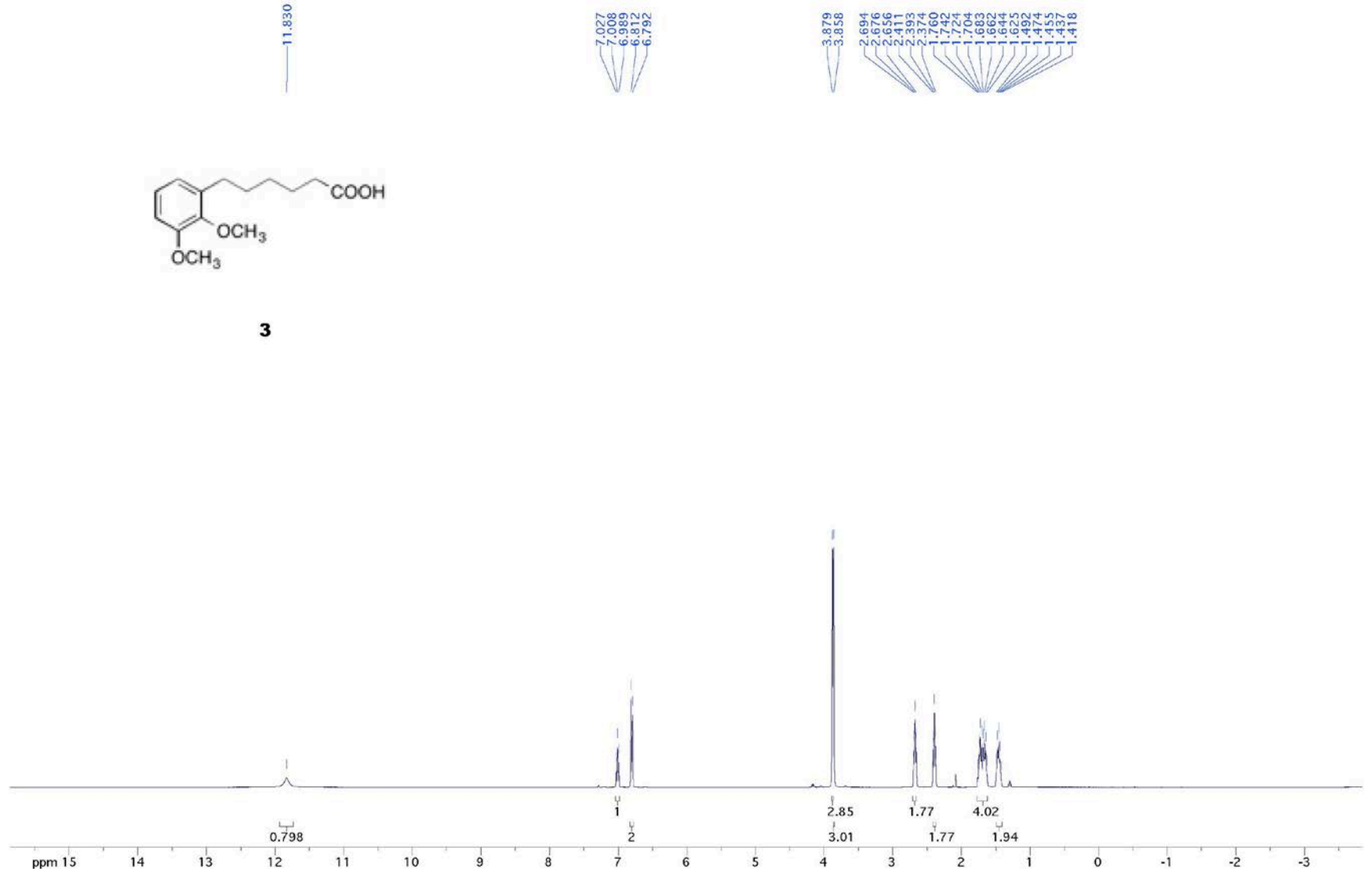
Christine A. Herdman[a], Tracy E. Strecker[a], Rajendra P. Tanpure[a], Zhi Chen[a], Alex Winters[b], Jeni Gerberich[b], Li Liu[b], Ernest Hamel[c], Ralph P. Mason[b], David J. Chaplin[a,d] Mary Lynn Trawick[a], and Kevin G. Pinney[a]*

[a]Department of Chemistry and Biochemistry, Baylor University, One Bear Place #97348, Waco, Texas 76798-7348, United States

[b]Screening Technologies Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Frederick National Laboratory for Cancer Research, National Institutes of Health, Frederick, MD 21702, United States

[c]Mateon Therapeutics, 701 Gateway Boulevard, Suite 210, South San Francisco, California 94080, United States

Appendix B Table of Contents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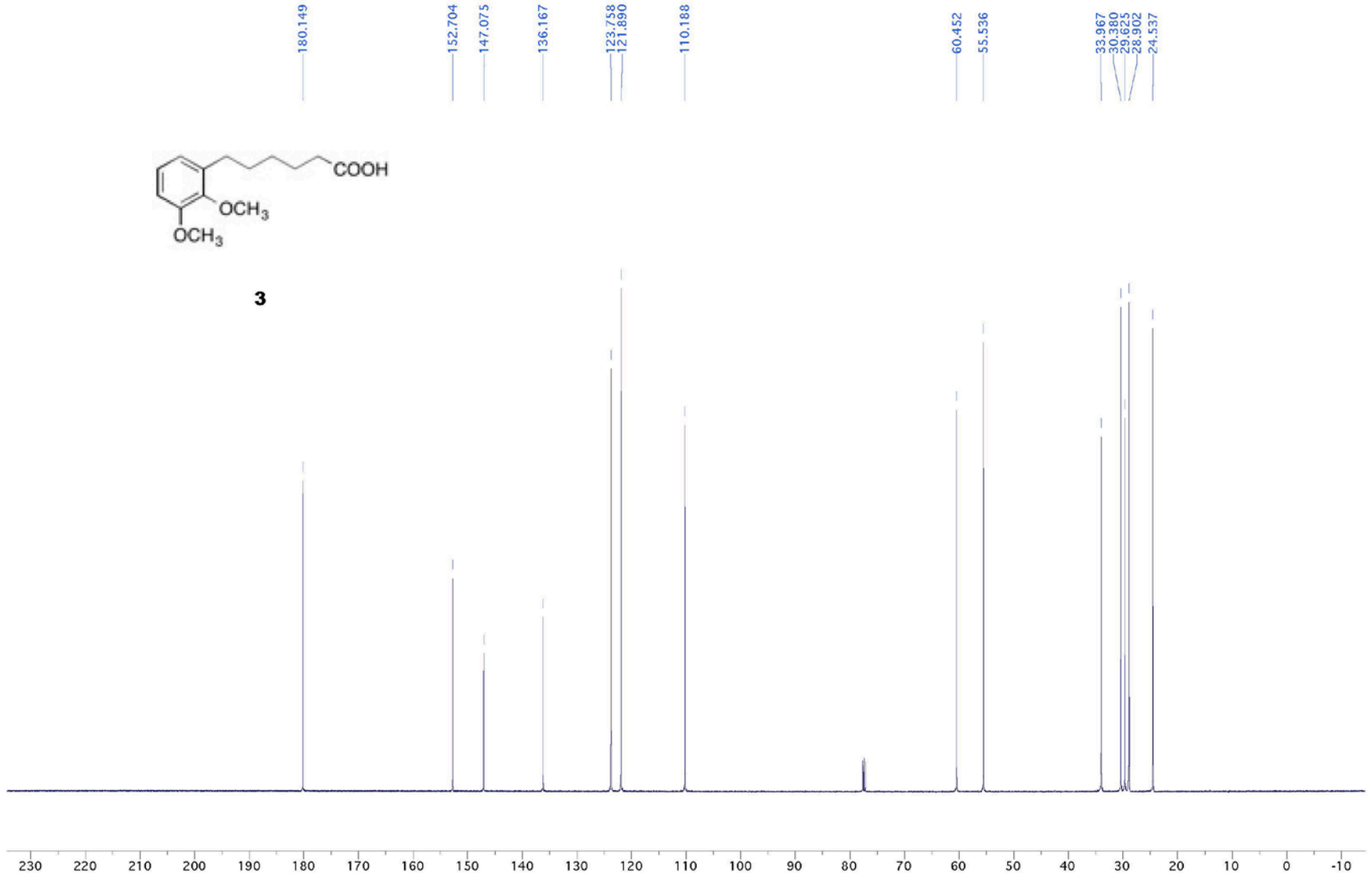
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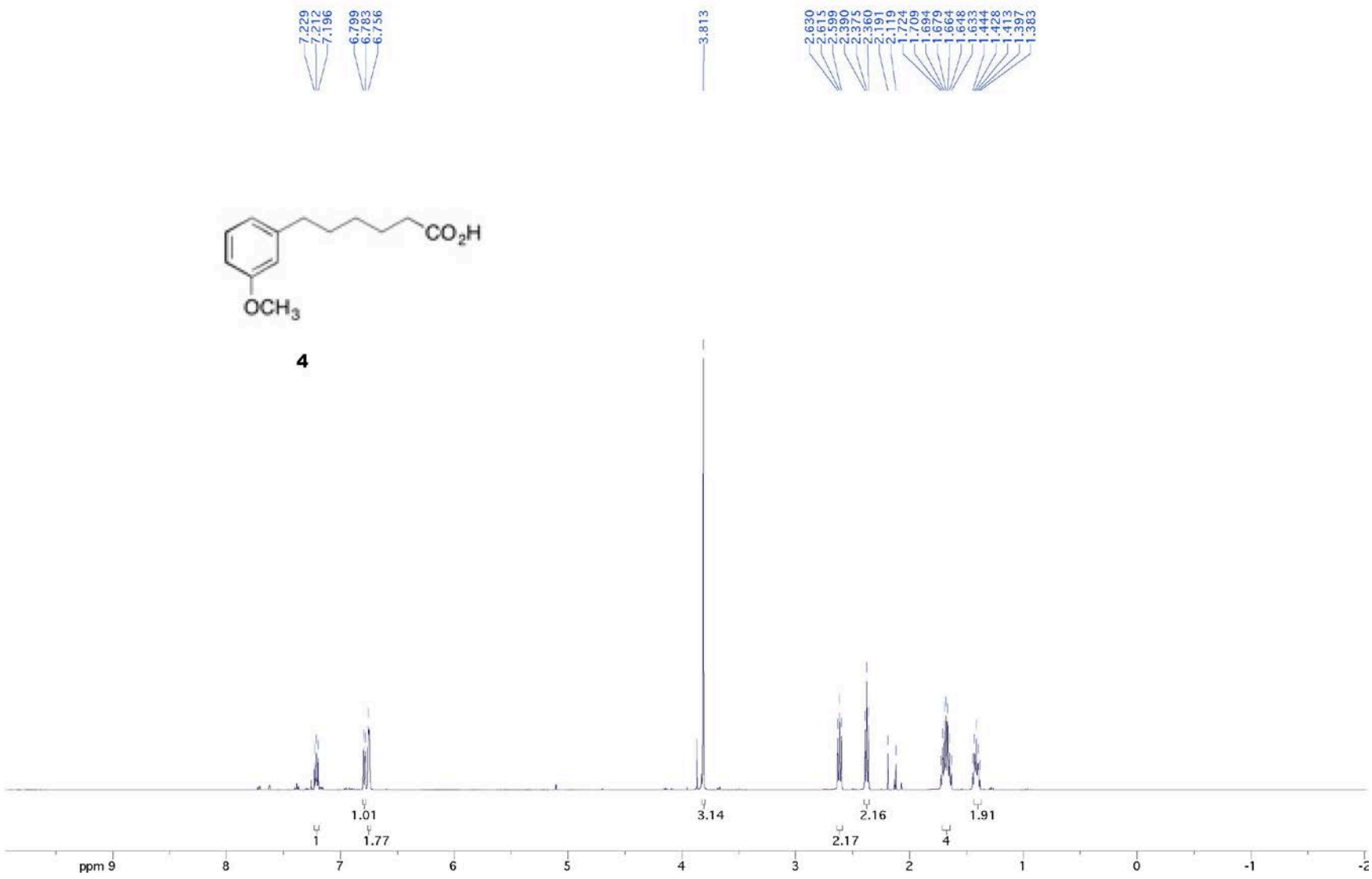
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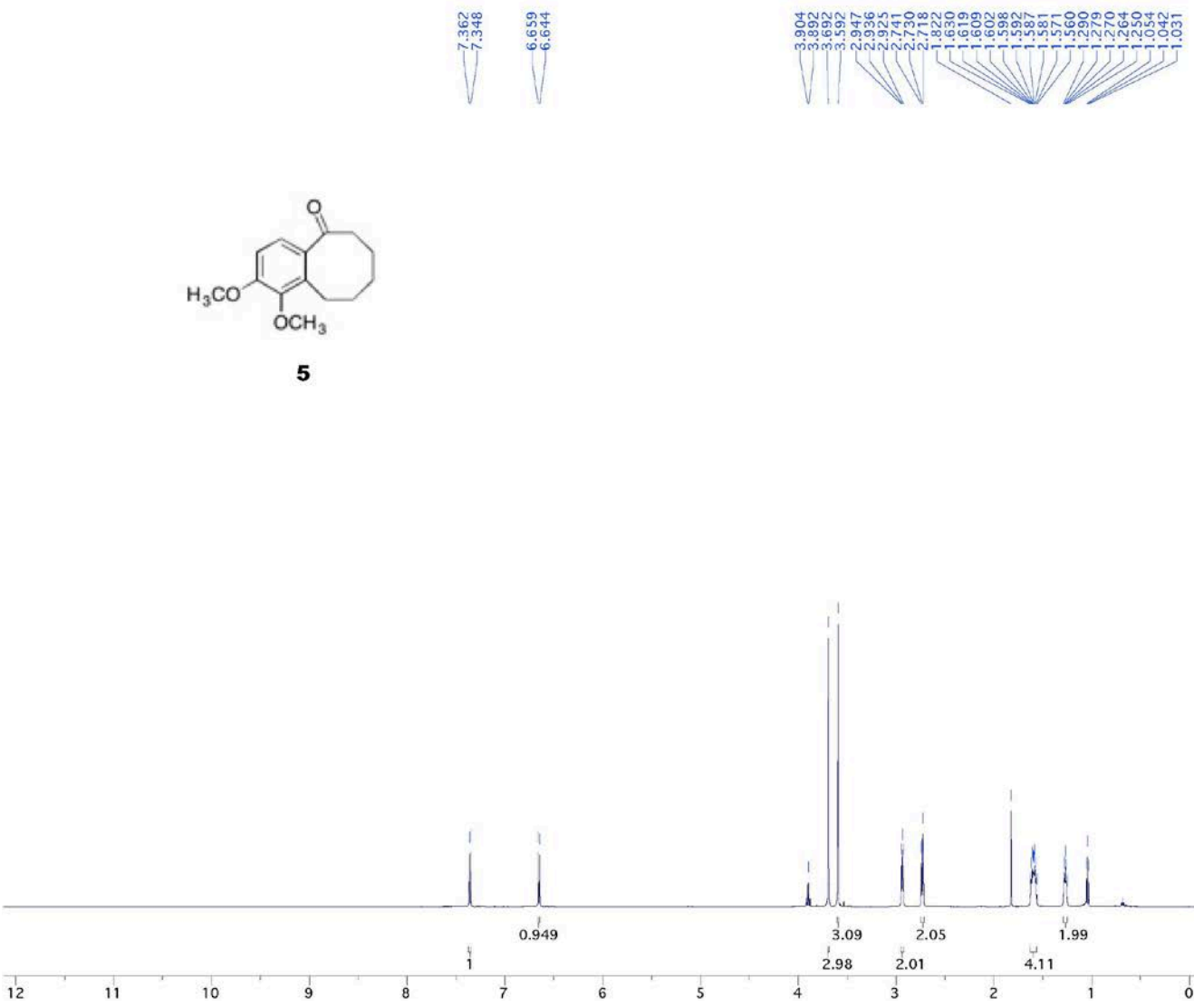
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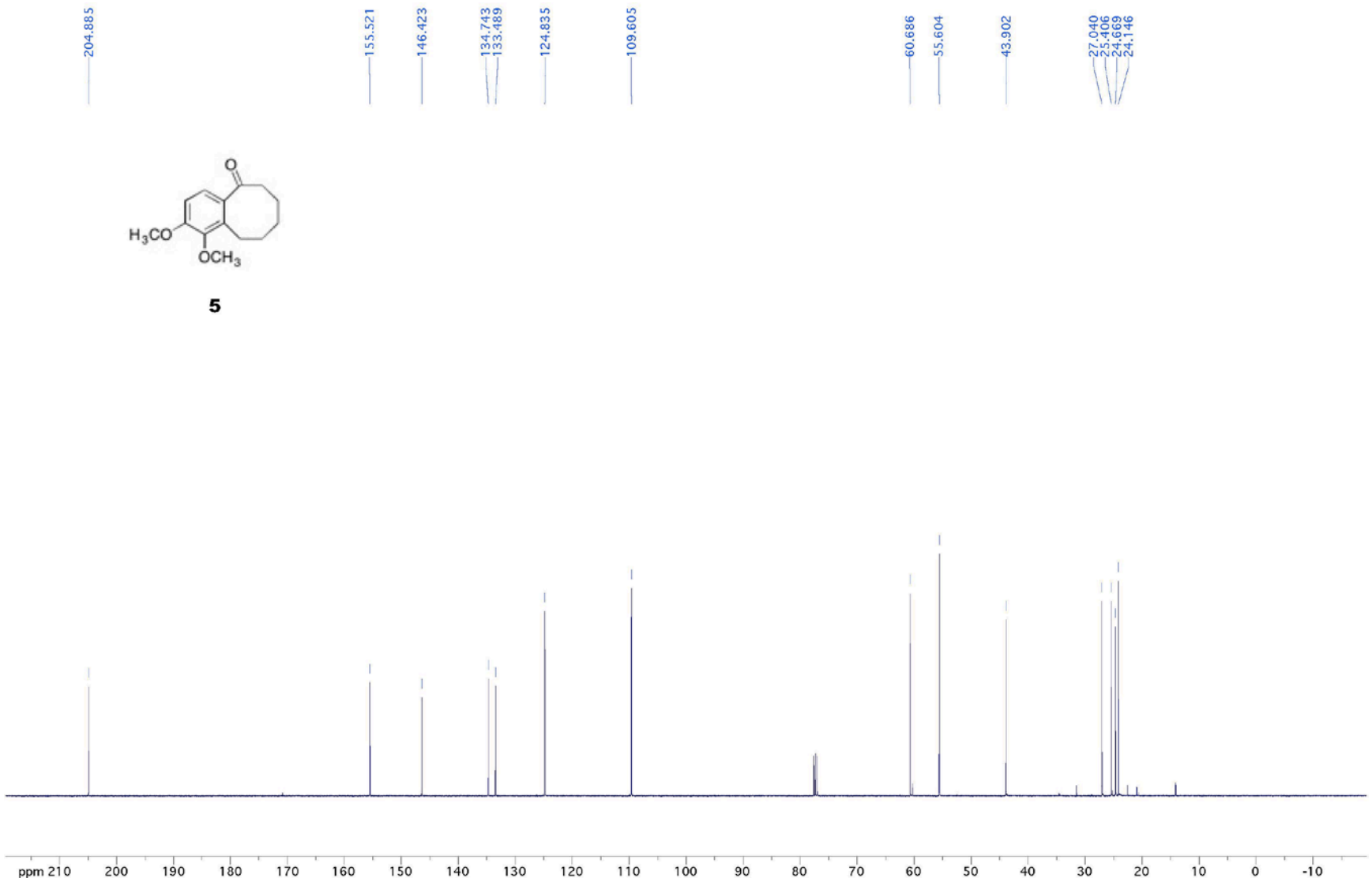
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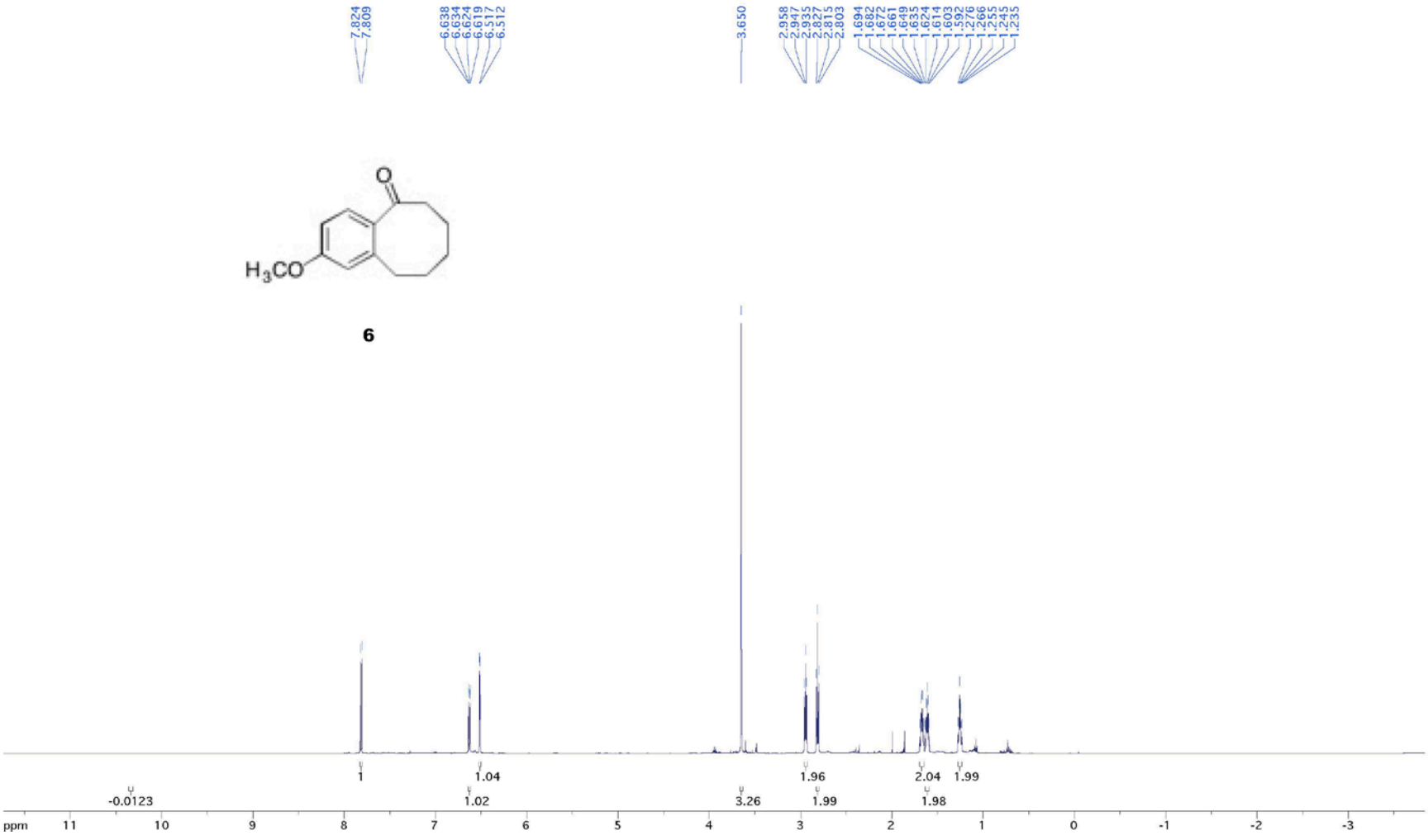
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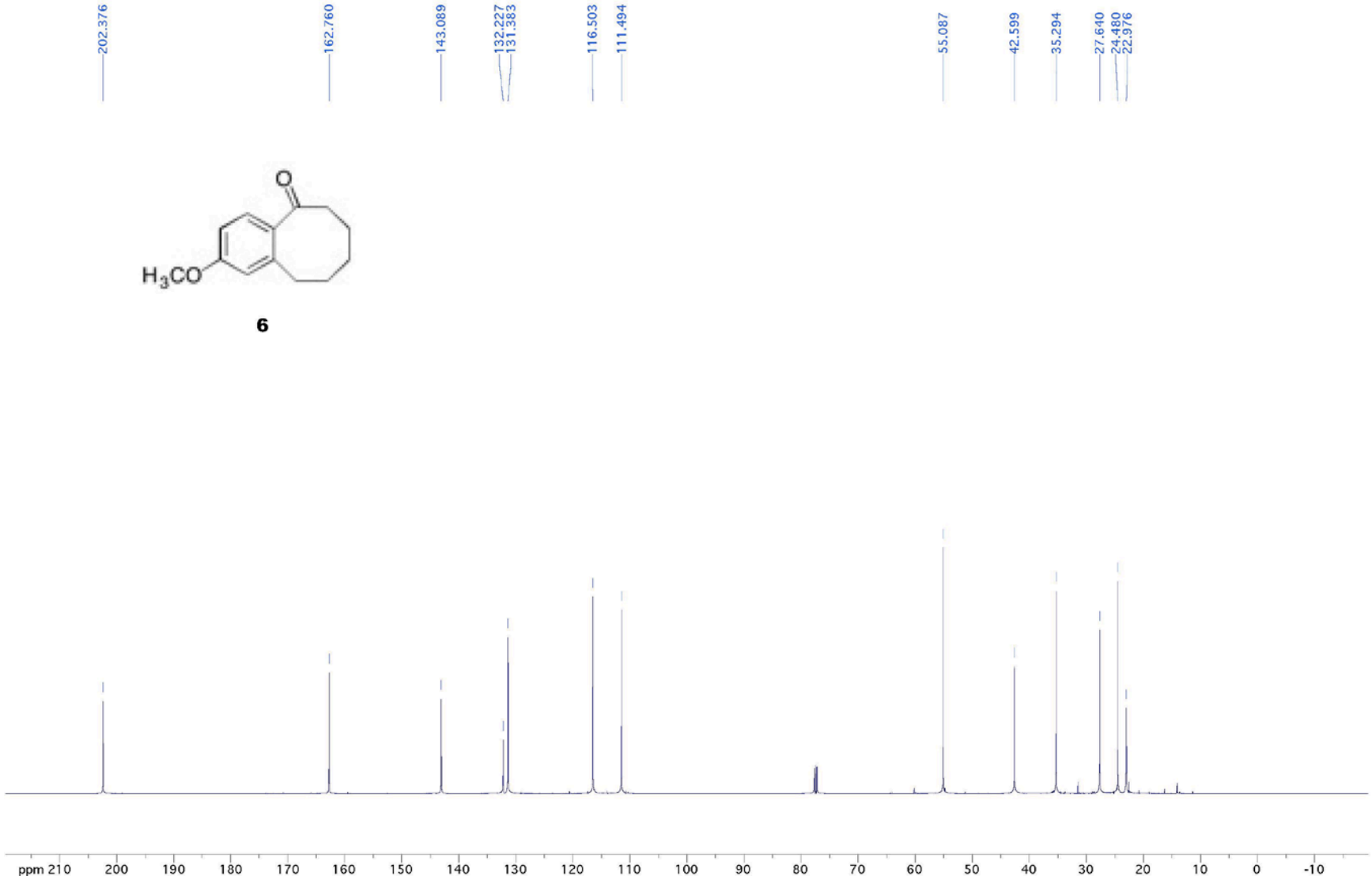
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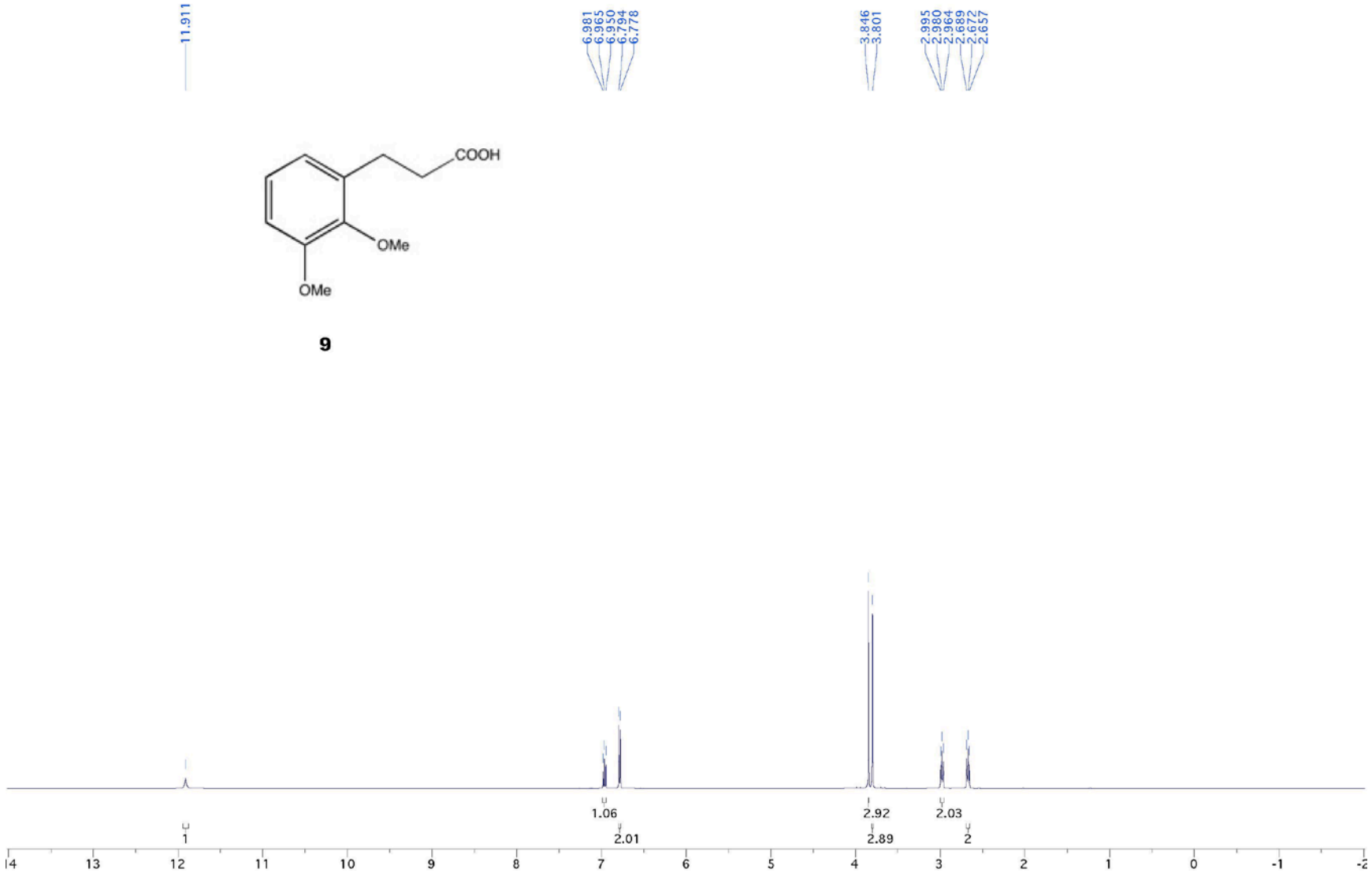
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3.846
3.801
2.995
2.980
2.964
2.689
2.672
2.657
COOH
OMe
OMe
1.06
2.92
2.03
1
2.01
2.89
2
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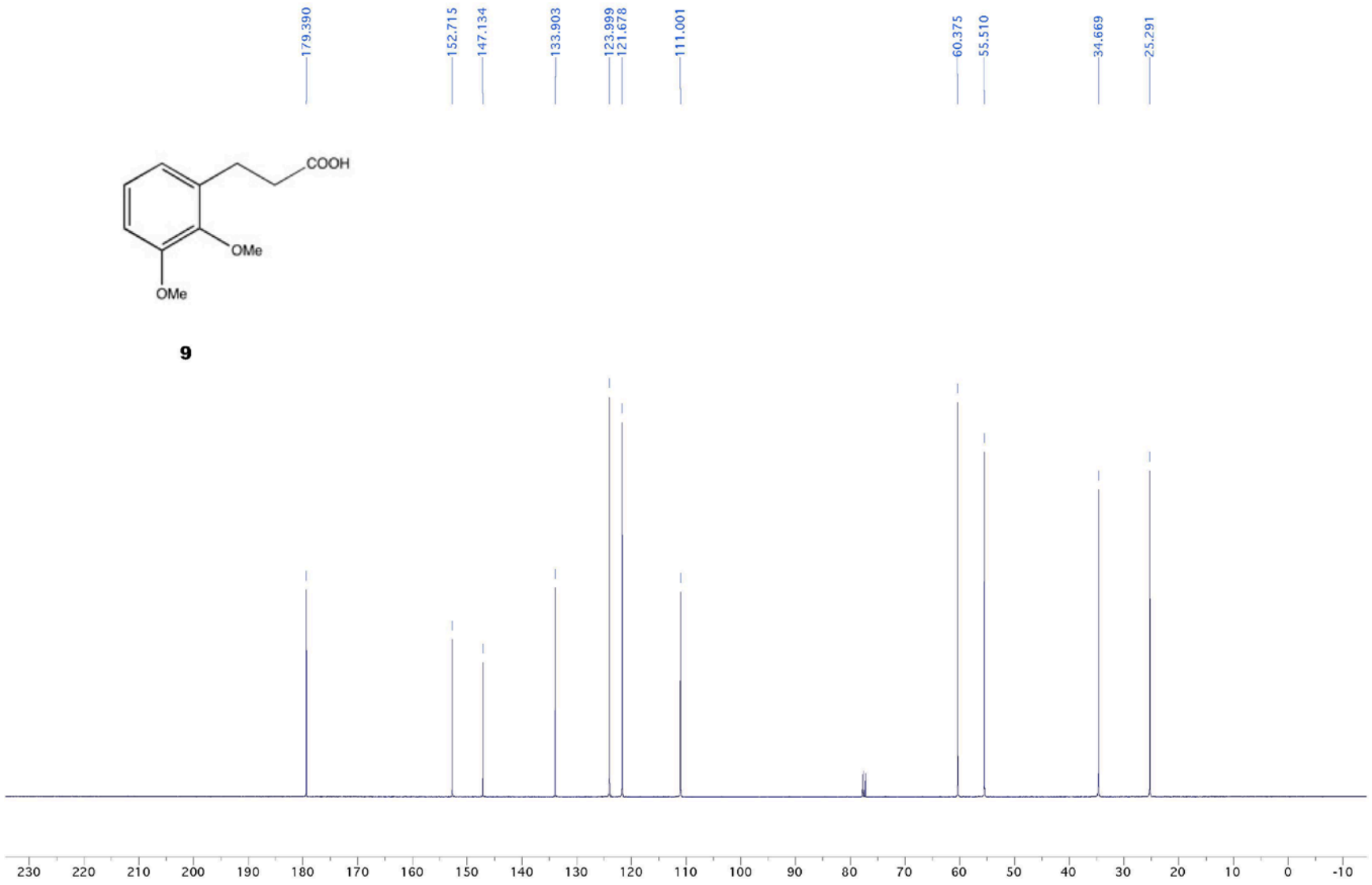
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1

9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COOH
OMe
OMe
9
230
220
210
200
190
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140
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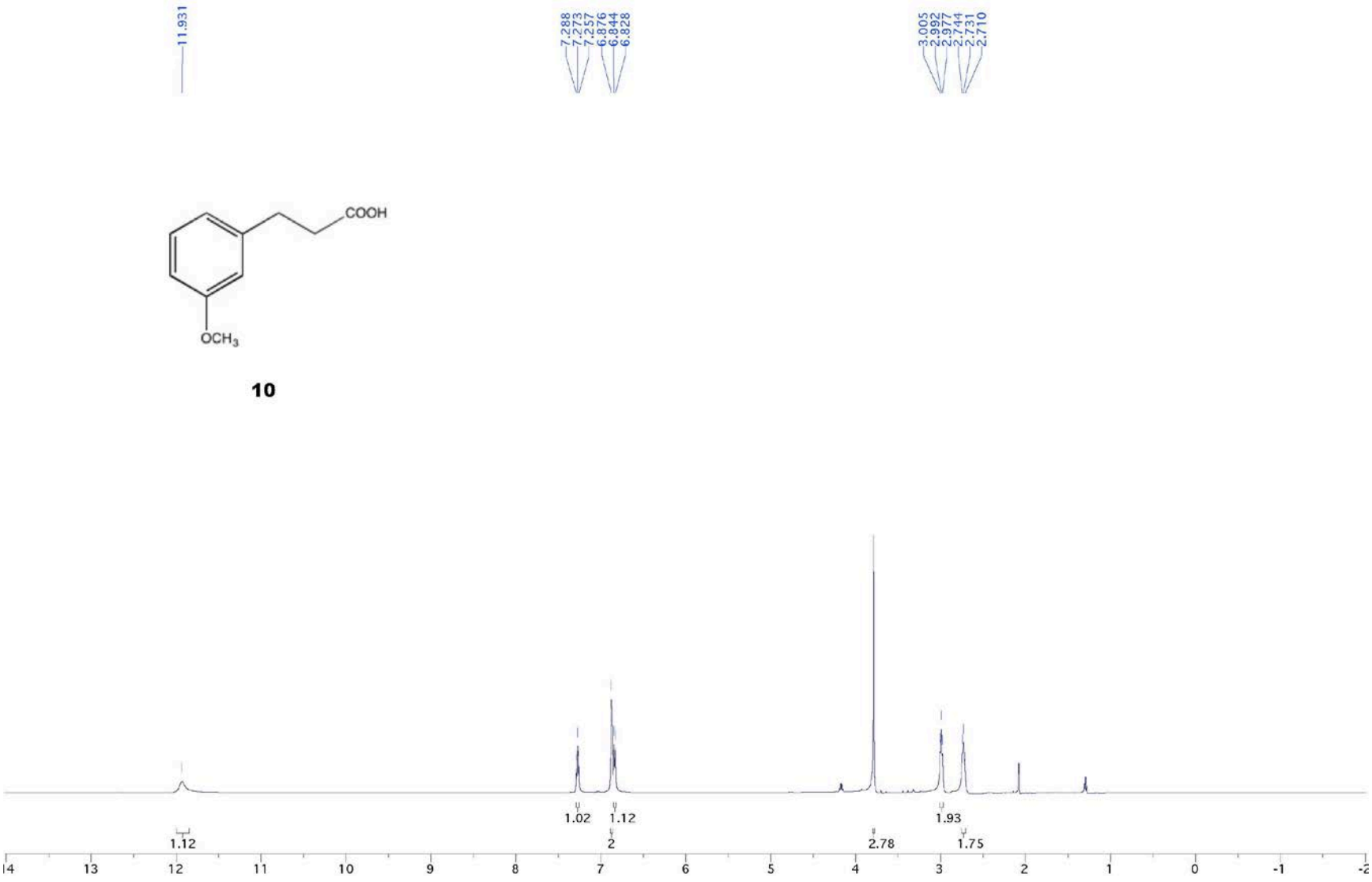
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2.744
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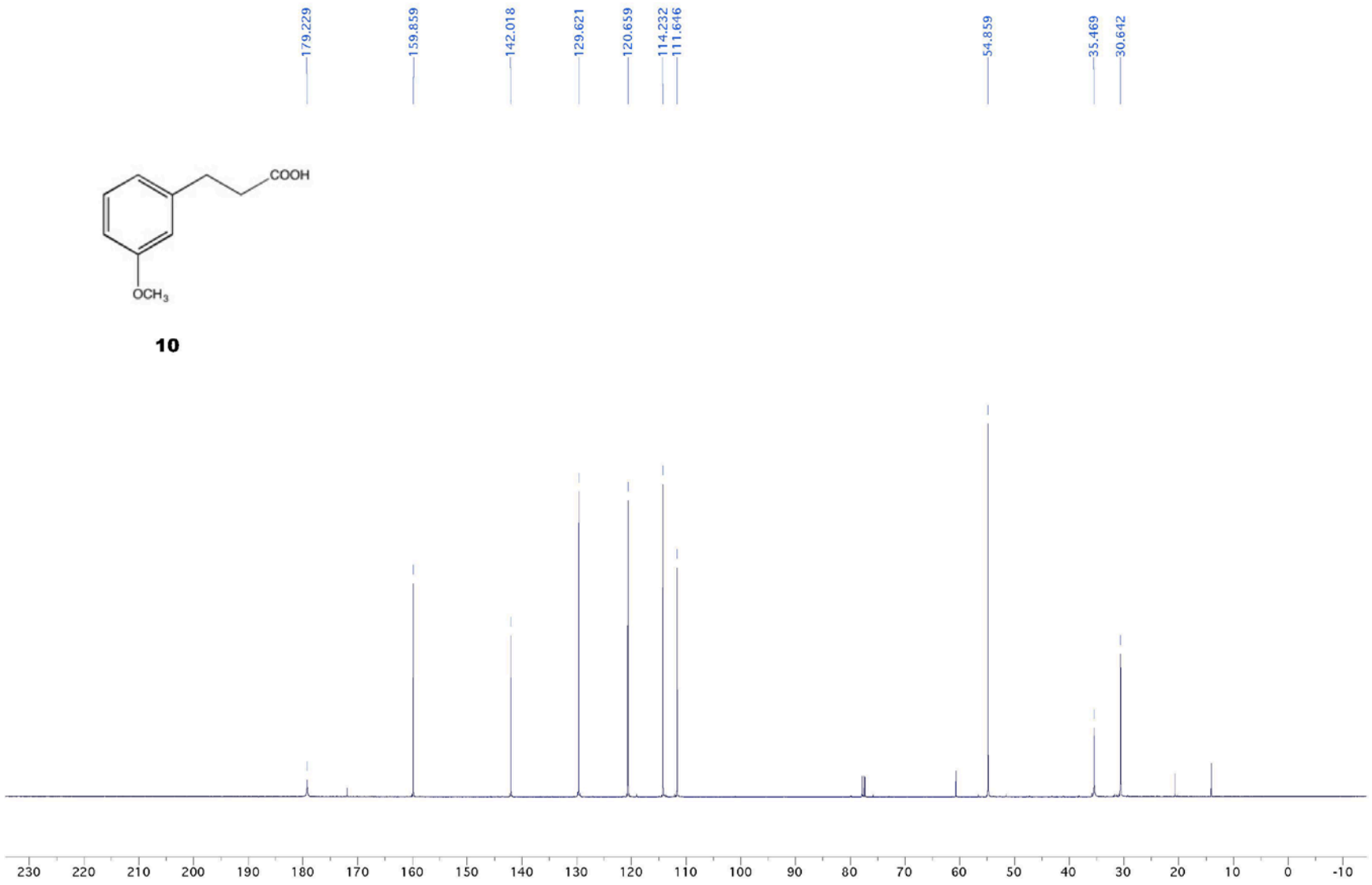
COOH
OCH3
1.12
1.02
1.12
1.93
1.12
2
2.78
1.75

10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114.232
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30.642
COOH
OCH3
230
220
210
200
190
180
170
160
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120
110
100
90
80
70
60
50
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10
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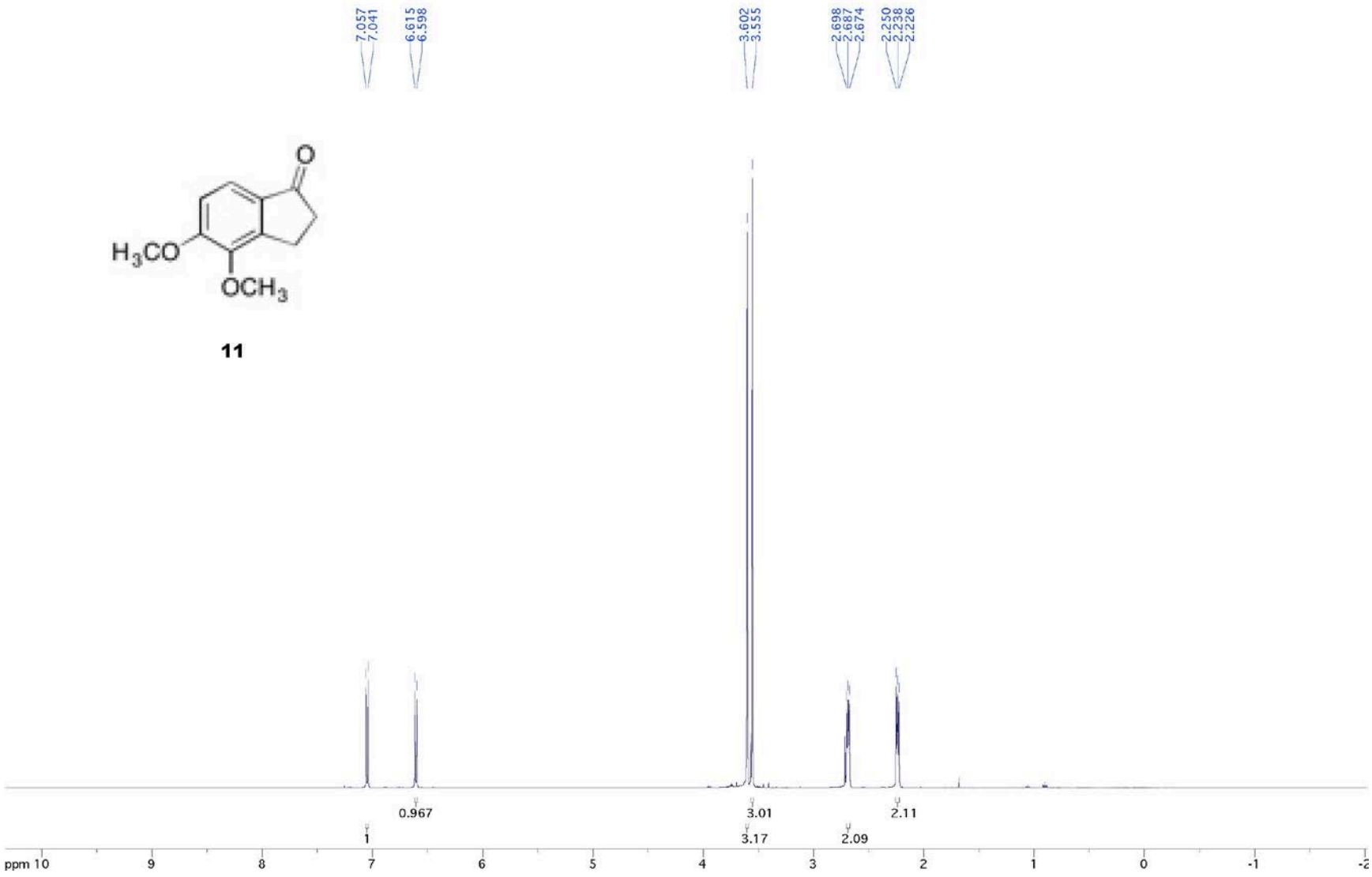
-10

10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3.602
3.555
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2.687
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2.250
2.238
2.226
O
H3CO
OCH3
11
0.967
3.01
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1
3.17
2.09
ppm 10
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8
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6
5
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0
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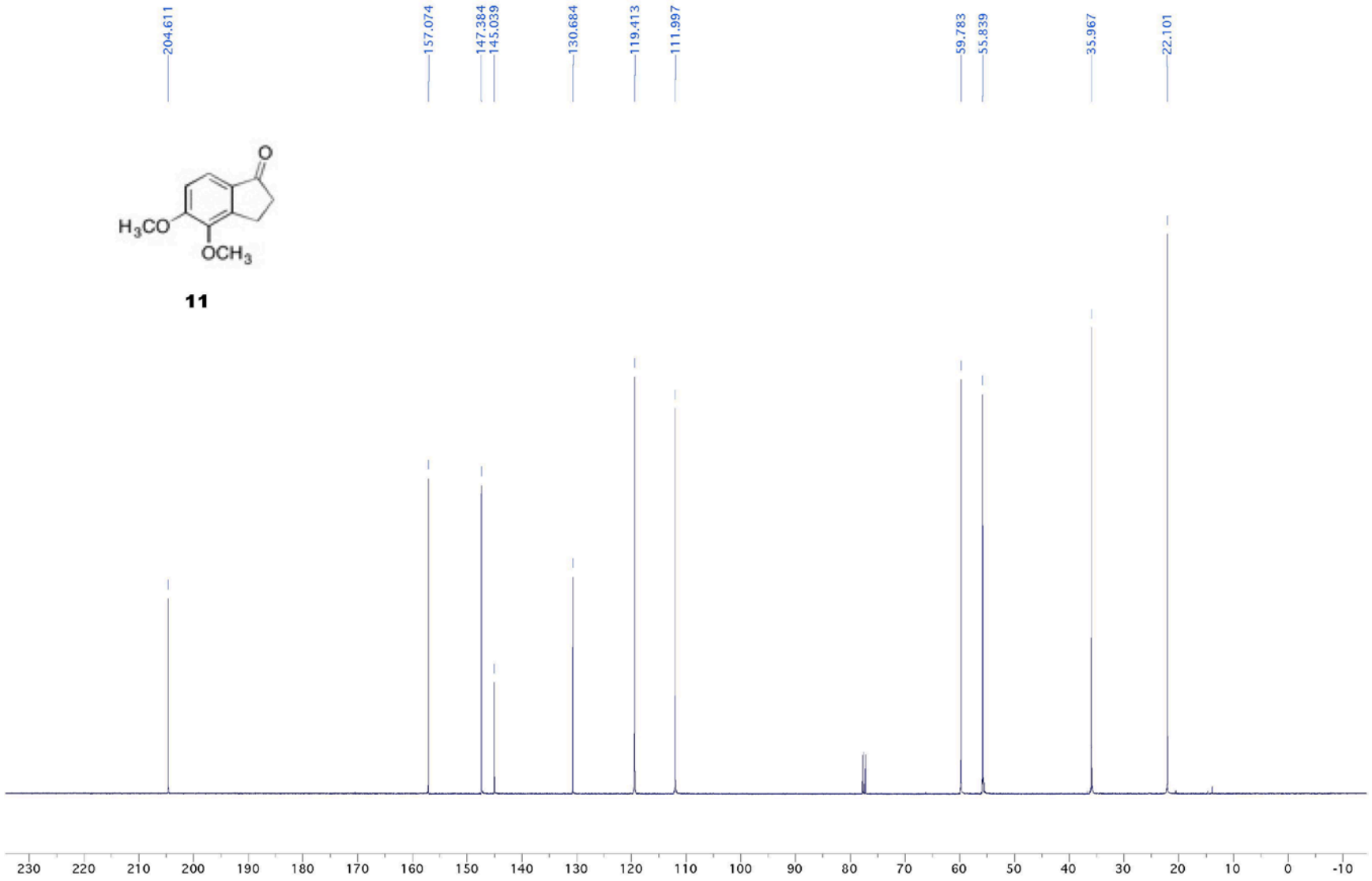
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O
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OCH3
11
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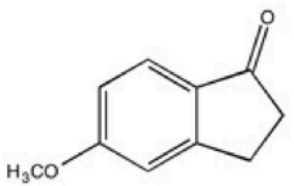
O
H3CO

12

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6.723
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2.918
2.906
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2.492
2.481
2.469
2.06
2.08
1
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2.07
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11
10
9
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6
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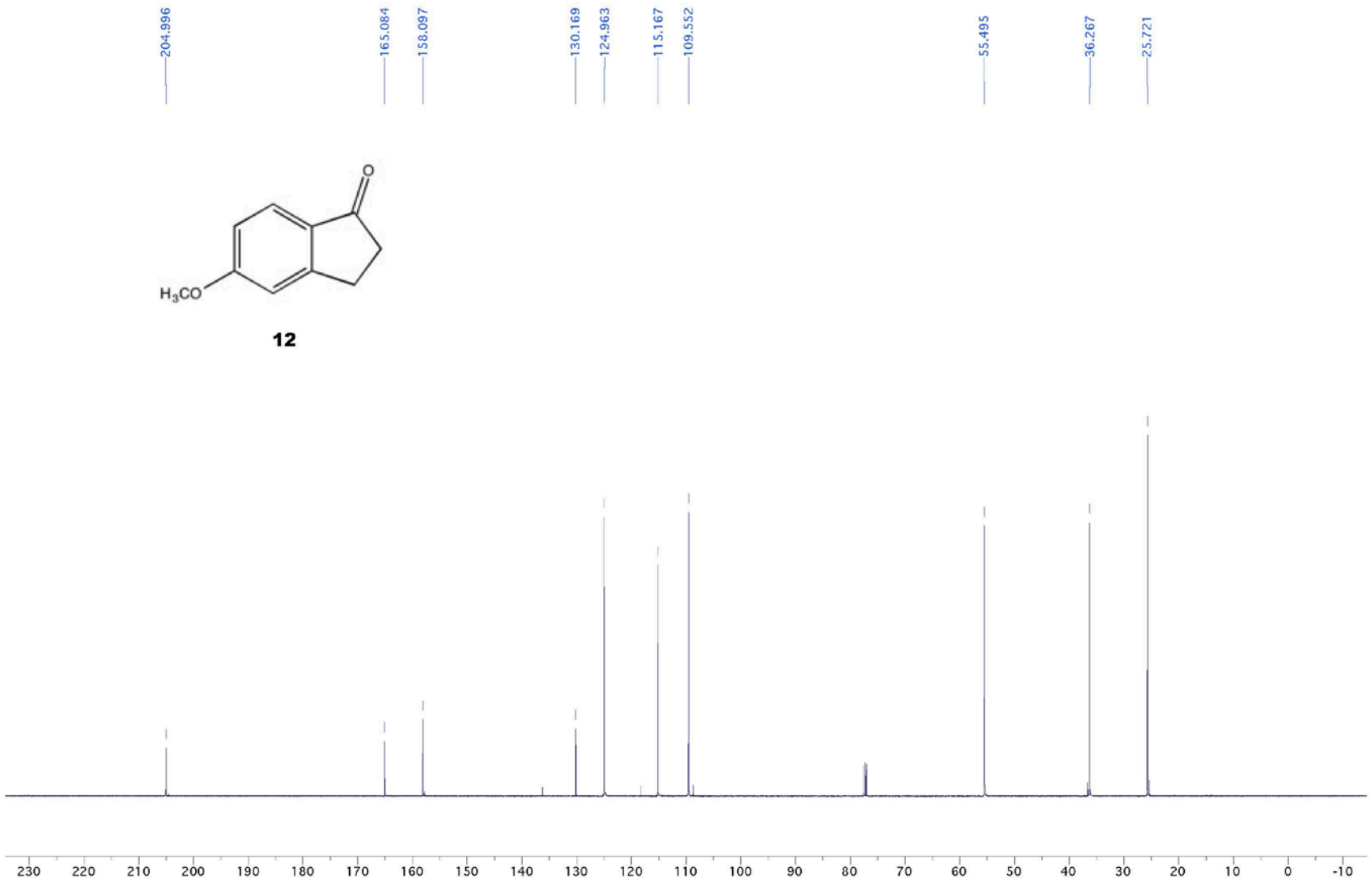
0
-1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200
190
180
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120
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80
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40
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10
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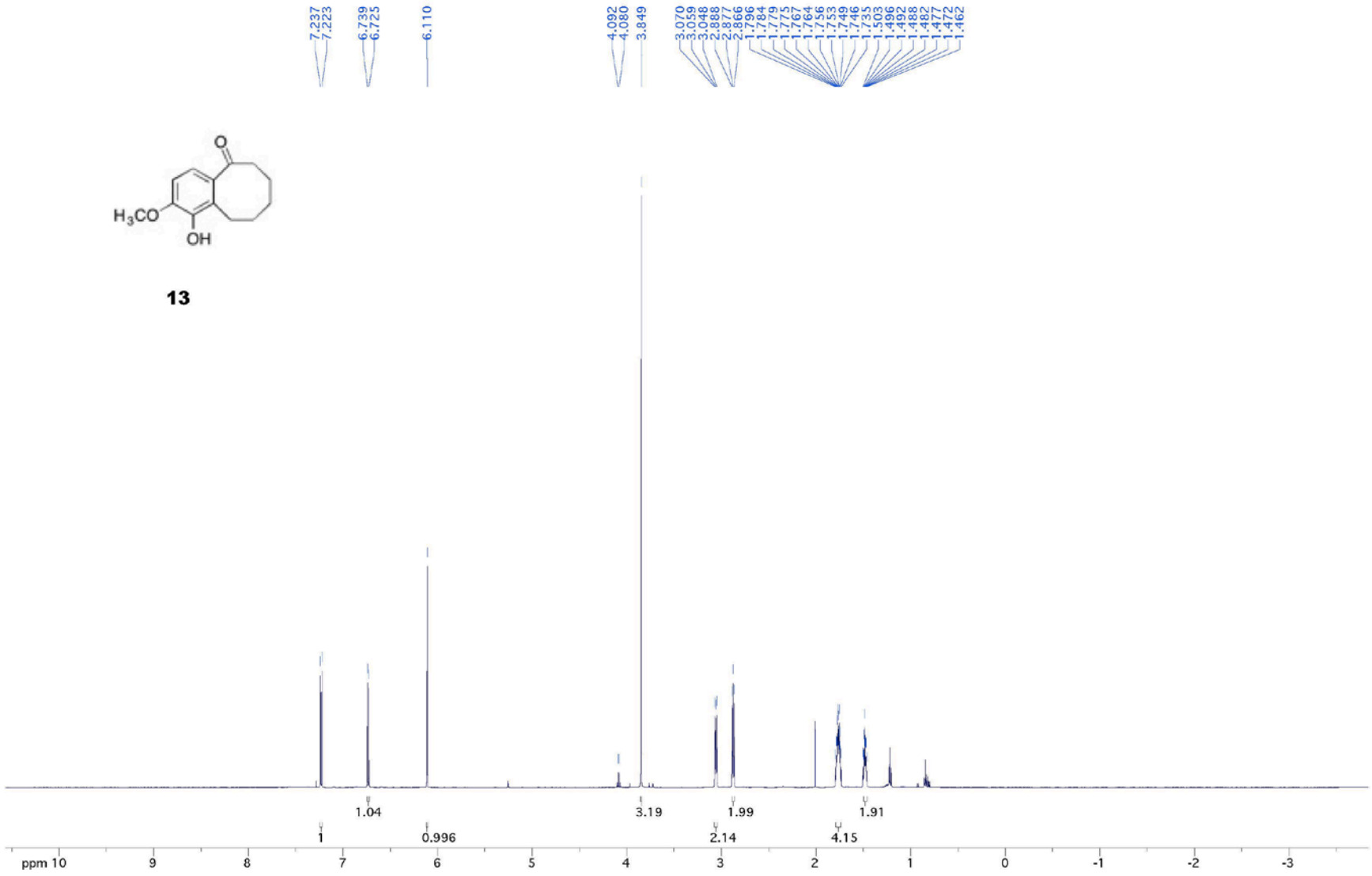
12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3.059
3.048
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2.877
2.866
1.796
1.784
1.779
1.775
1.767
1.764
1.756
1.753
1.749
1.746
1.735
1.503
1.496
1.492
1.488
1.482
1.477
1.472
1.462
O
H3CO
OH
13
1.04
0.996
3.19
1.99
2.14
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1
ppm 10
9
8
7
6
5
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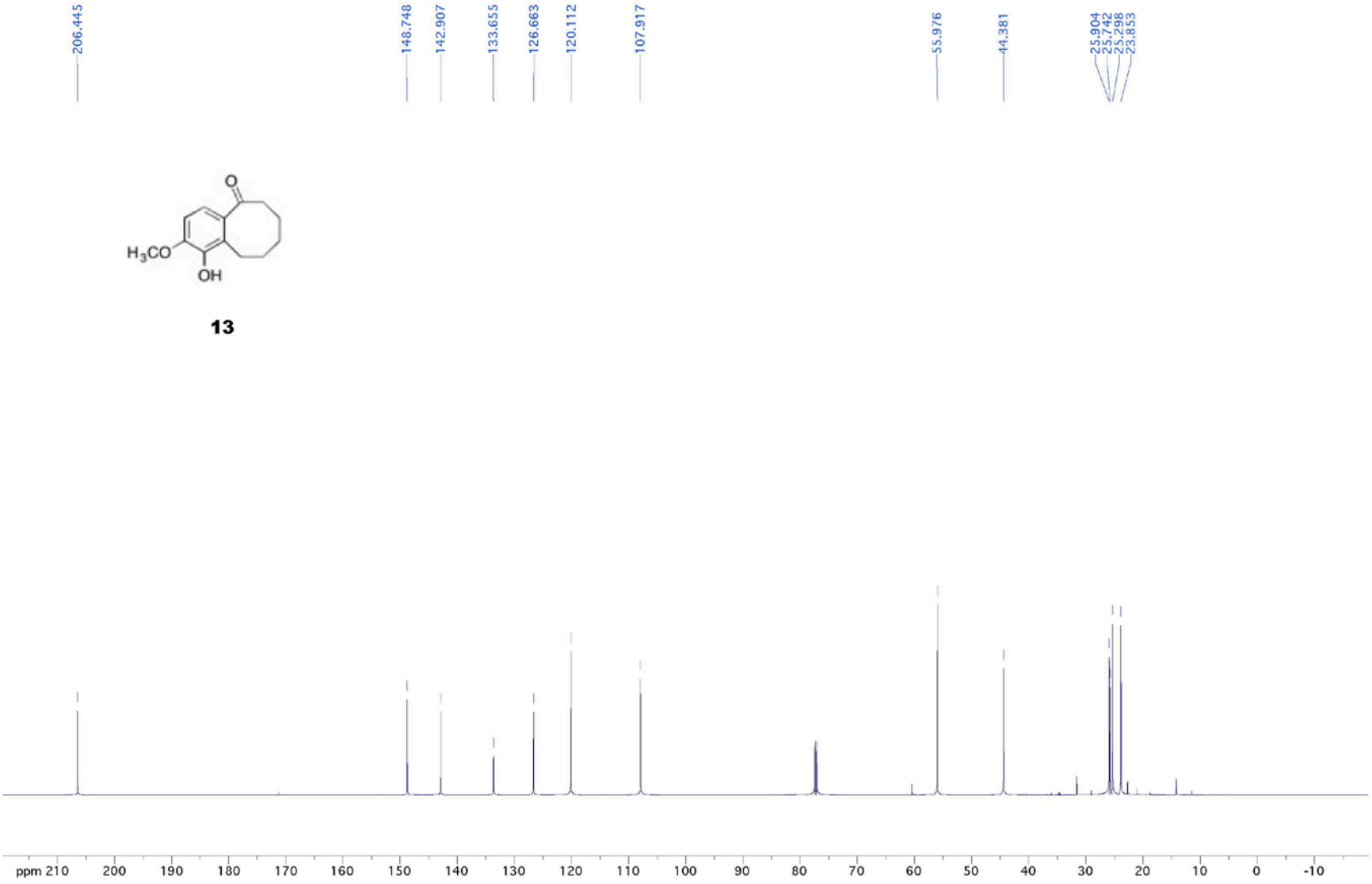
-1
-2
-3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133.655
126.663
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107.917
55.976
44.381
25.904
25.742
25.298
23.853
O
H3CO
OH
ppm 210
200
190
180
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160
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140
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120
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100
90
80
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50
40
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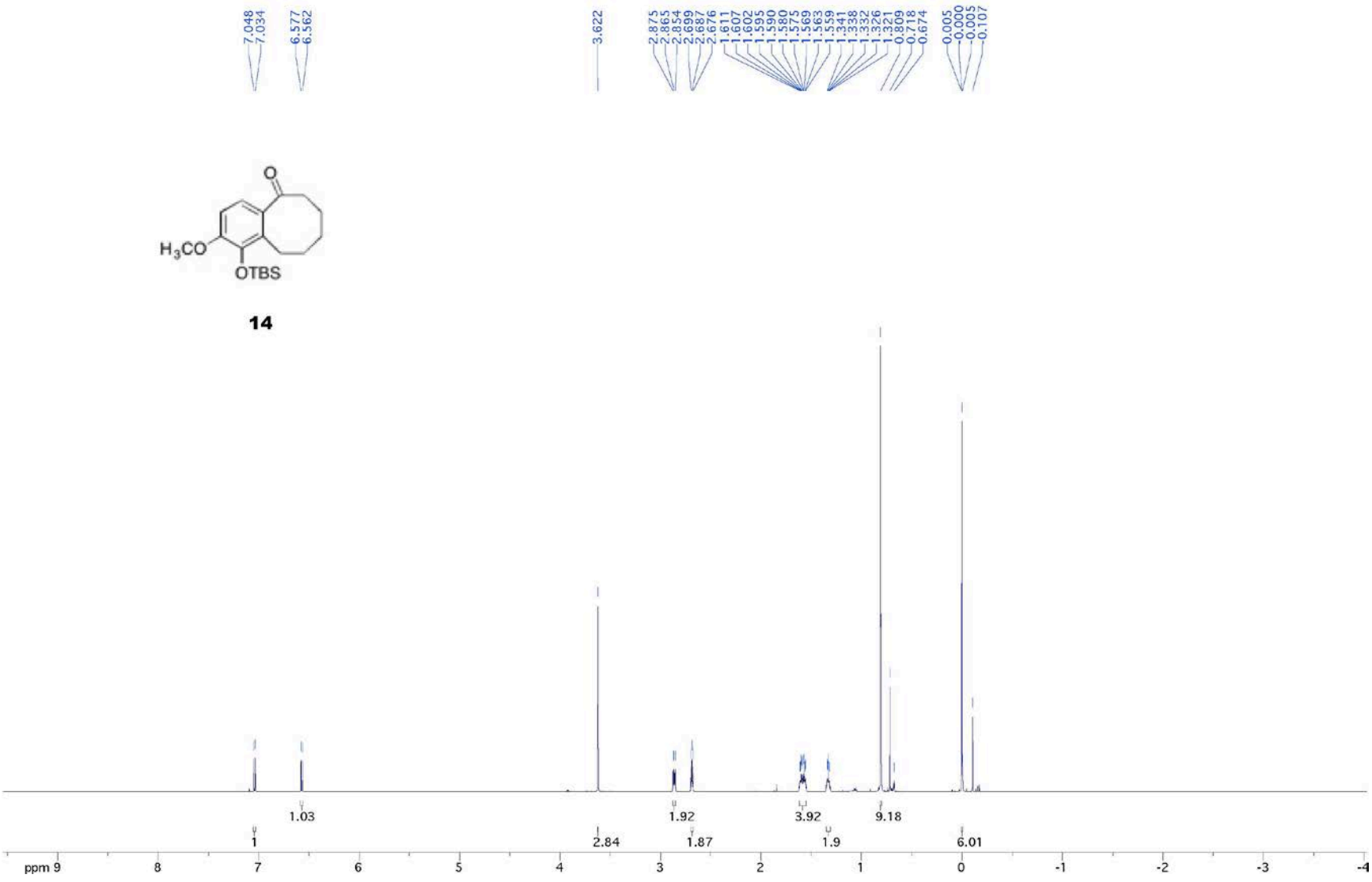
20
10
0
-10

13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2.854
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2.687
2.676
1.611
1.607
1.602
1.595
1.590
1.580
1.575
1.569
1.563
1.559
1.341
1.338
1.332
1.326
1.321
0.809
0.718
0.674
0.005
0.000
-0.005
-0.107
O
H3CO
OTBS
14
1.03
1.92
3.92
9.18
1
2.84
1.87
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6.01
ppm 9
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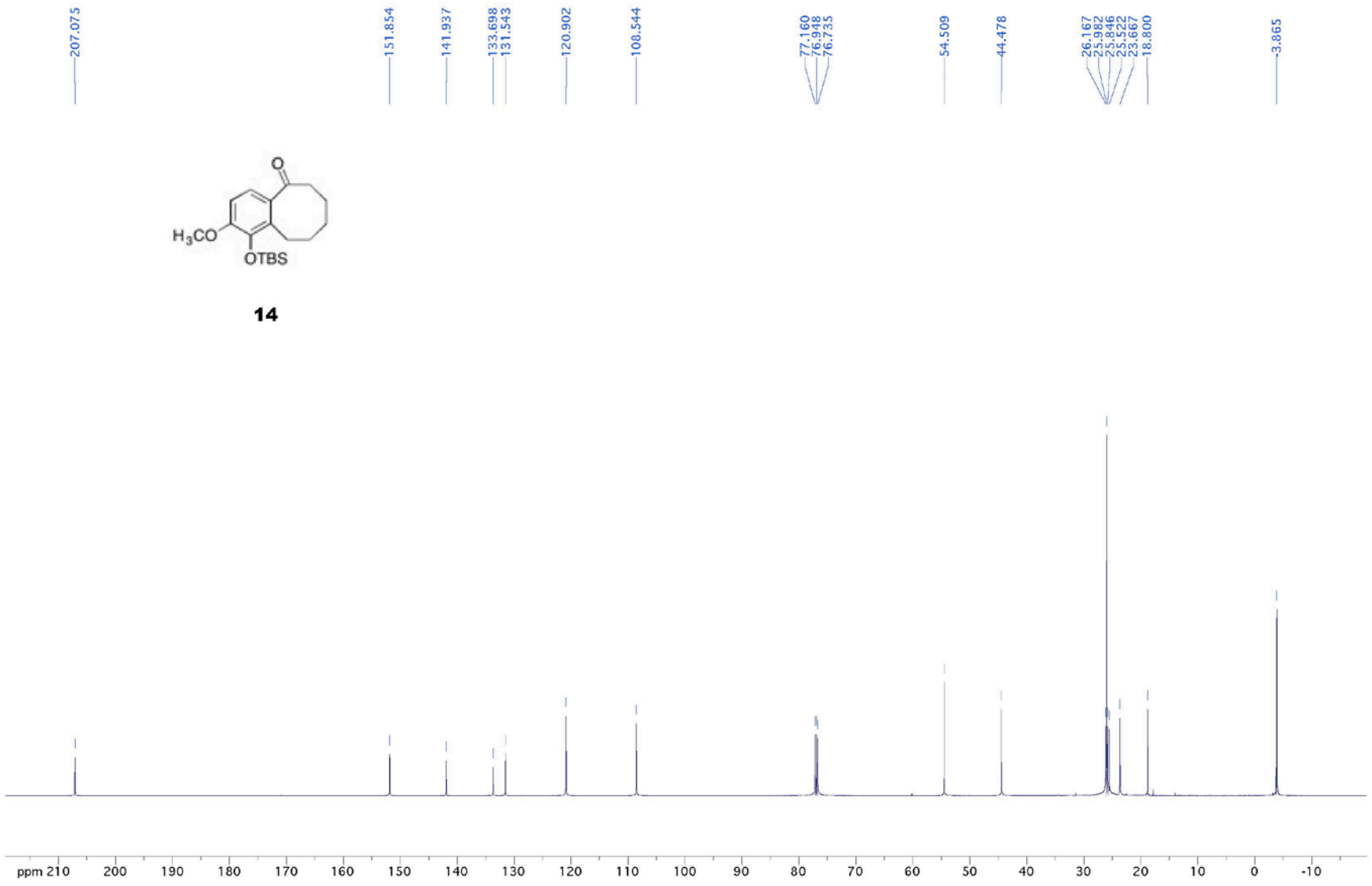
7
6
5
4
3
2
1
0
-1
-2
-3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120.902
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77.160
76.948
76.735
54.509
44.478
26.167
25.982
25.846
25.522
23.667
18.800
-3.865
O
H3CO
OTBS
ppm 210
200
190
180
170
160
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130
120
110
100
90
80
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50
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30
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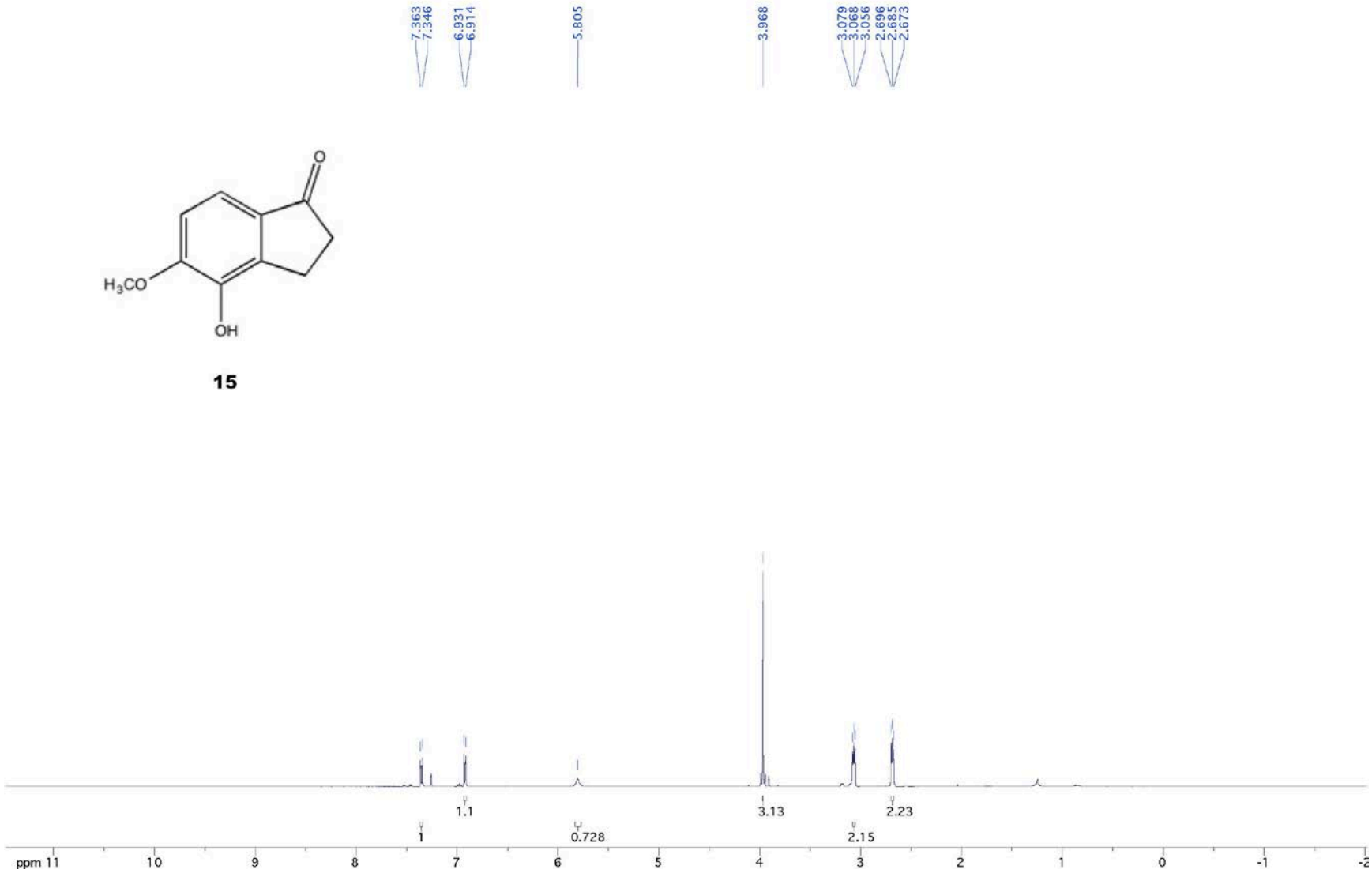
10
0
-10

14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5.805
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3.068
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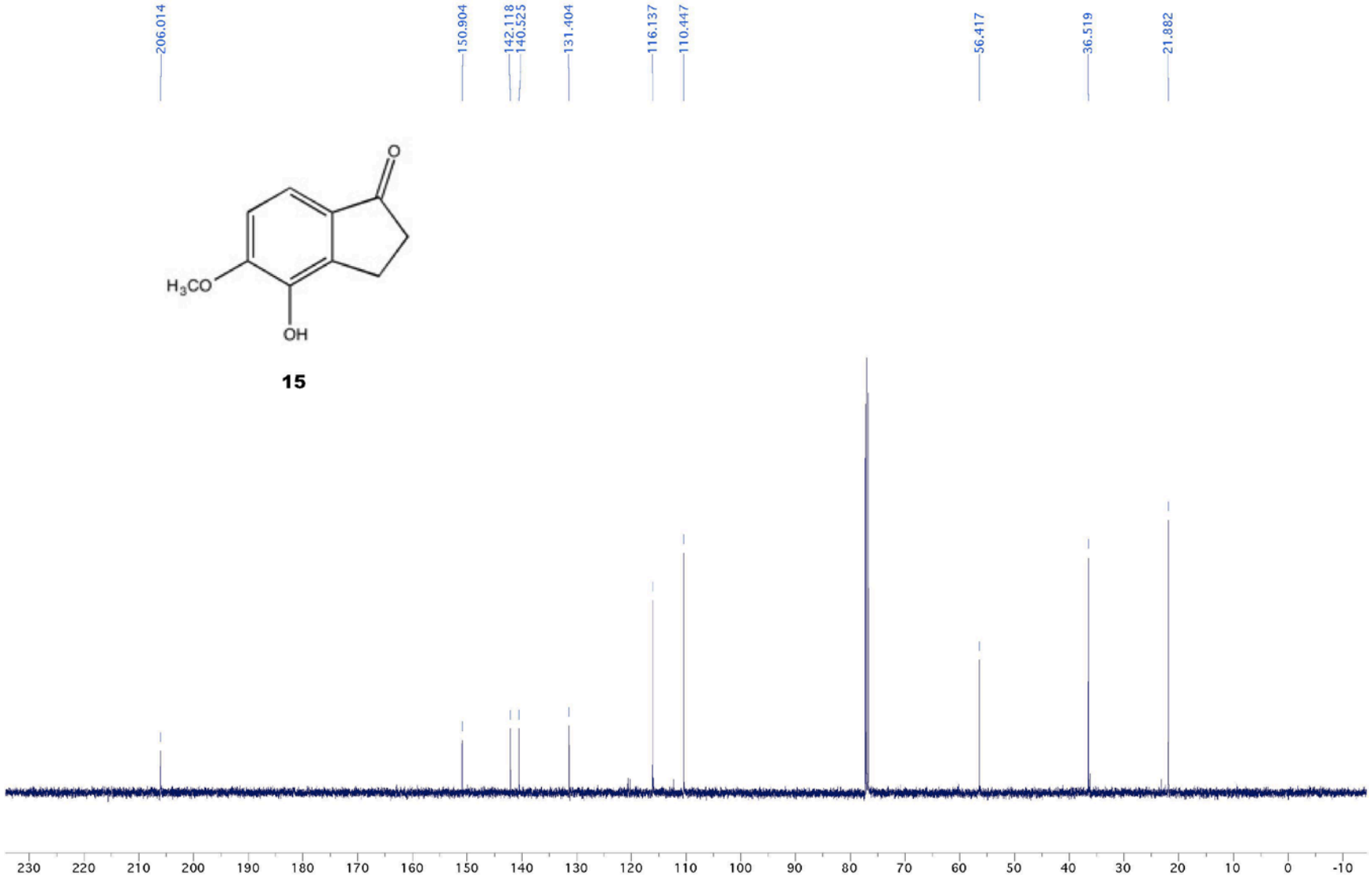
2.673
O
H3CO
OH
1.1
3.13
2.23
1
0.728
2.15
ppm 11
10
9
8
7
6
5
4
3
2
1
0
-1

15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140.525
131.404
116.137
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56.417
36.519
21.882
O
H3CO
OH
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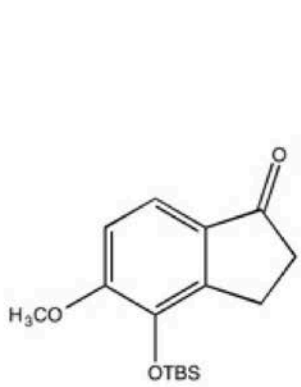
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


O
H3CO
OTBS

16

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2.944
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2.563
2.551
0.954
0.847
0.122
0.018
1.04
2.13
9.03
1
3.04
2.07
6.18
ppm 12
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10
9
8
7
6
5
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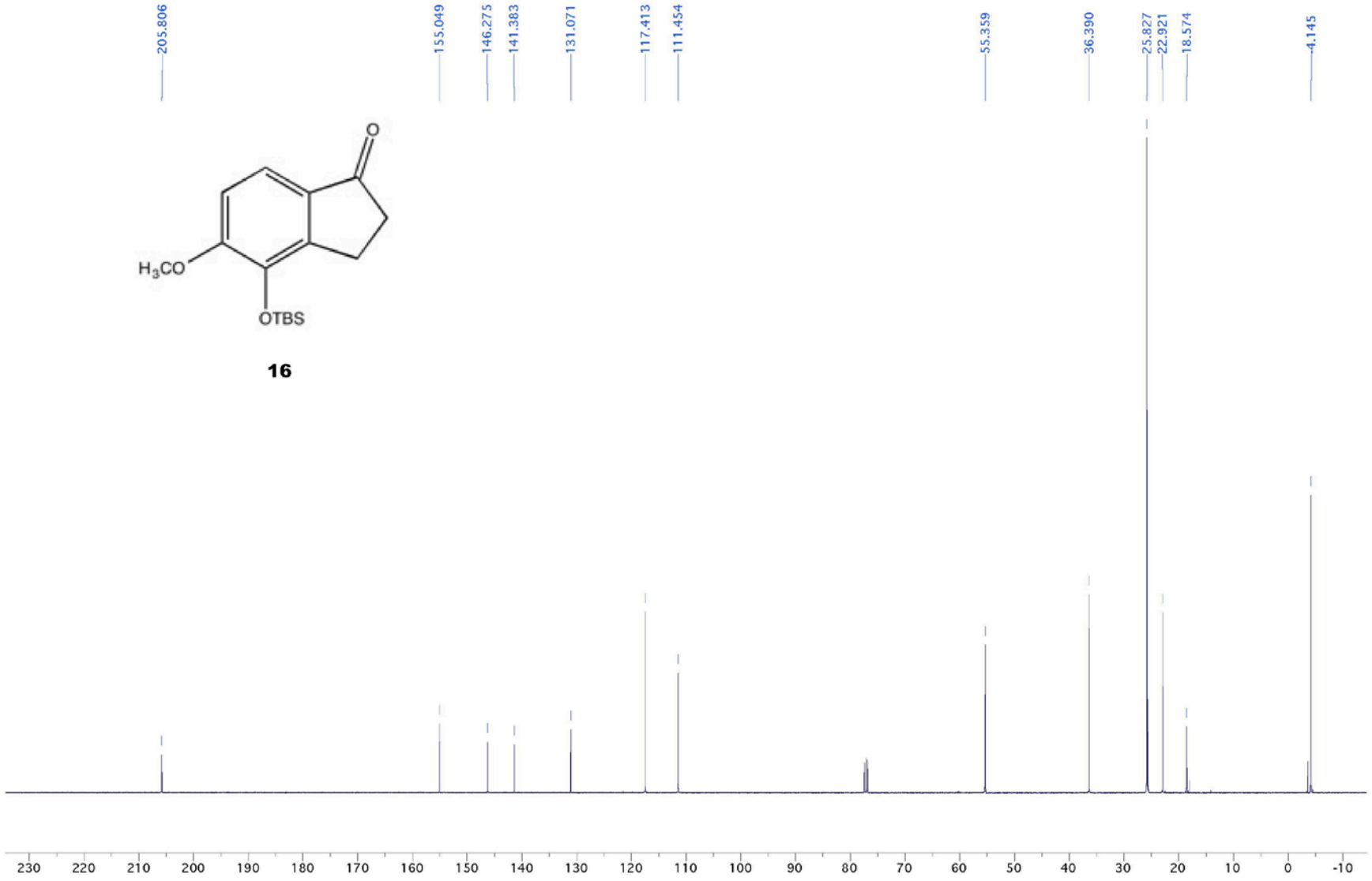
3
2
1
0
-1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111.454
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36.390
25.827
22.921
18.574
4.145
O
H3CO
OTBS
16
230
220
210
200
190
180
170
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150
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130
120
110
100
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80
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60
50
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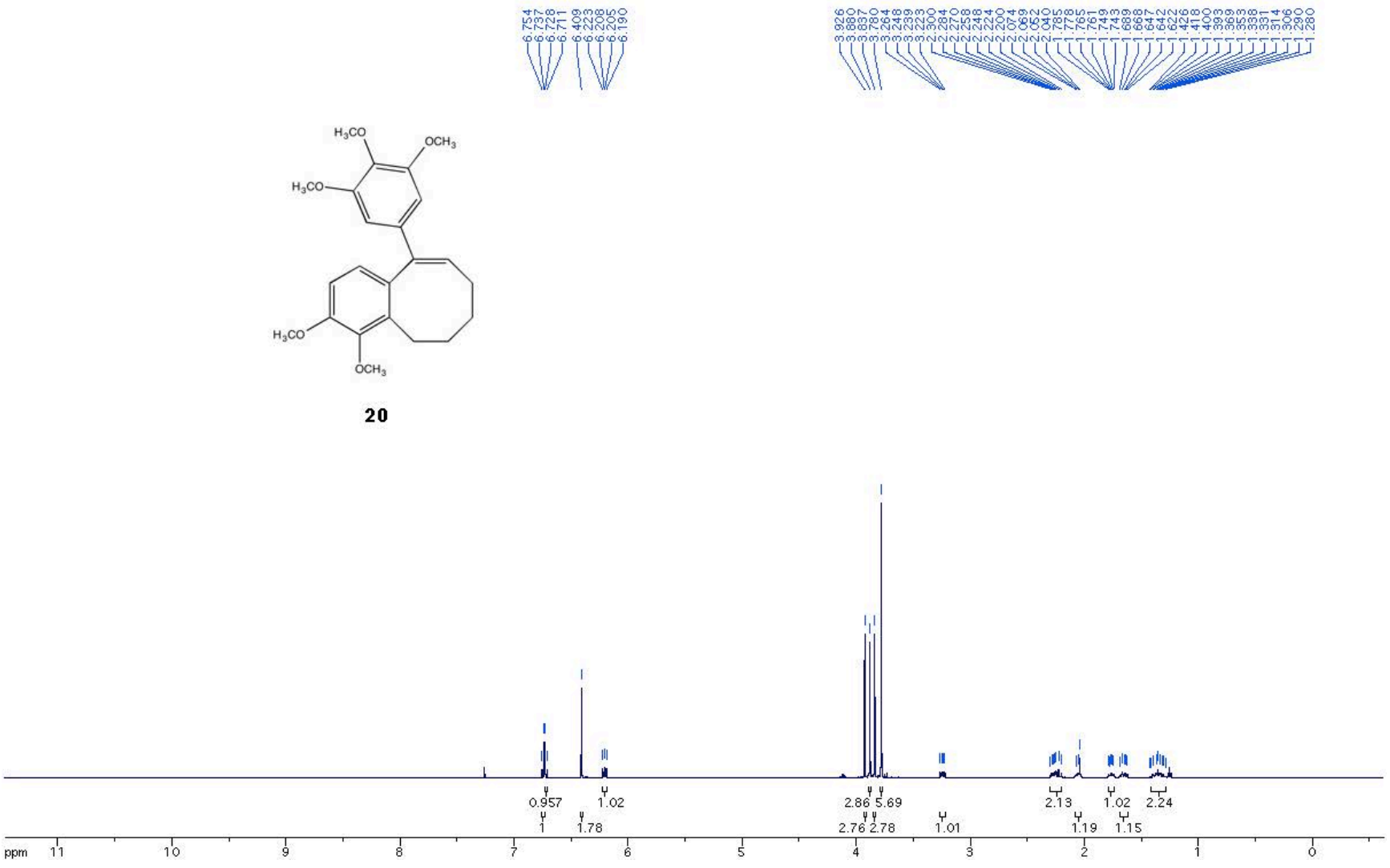
0
-10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3.239
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3.300
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2.258
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2.069
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1.778
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1.647
1.642
1.626
1.418
1.400
1.393
1.369
1.353
1.338
1.331
1.314
1.306
1.290
1.280
H3CO
OCH3
H3CO
H3CO
OCH3
0.957
1.02
2.86
5.69
2.13
1.02
2.24
1
1.78
2.76
2.78
1.01
1.19
1.15
ppm
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10
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8
7
6
5
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3
2
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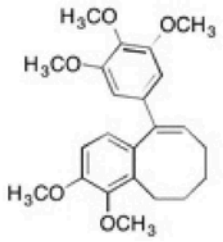
0

20


H3CO
OCH3
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H3CO
OCH3

20

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139.031
137.543
137.172
131.899
129.719
124.765
109.506
104.672
60.868
60.716
56.112
55.551
28.348
27.838
26.046
24.621
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_88000001.D
Sample Name: CAH_4_88

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Acq. Instrument : Instrument 1                    Location :   -
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Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 9/23/2014 8:17:01 AM by Christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\CAH_4_88000001.D\DA.M (MASTERMETHOD.M)
Last changed    : 9/23/2014 9:45:13 AM by Christine
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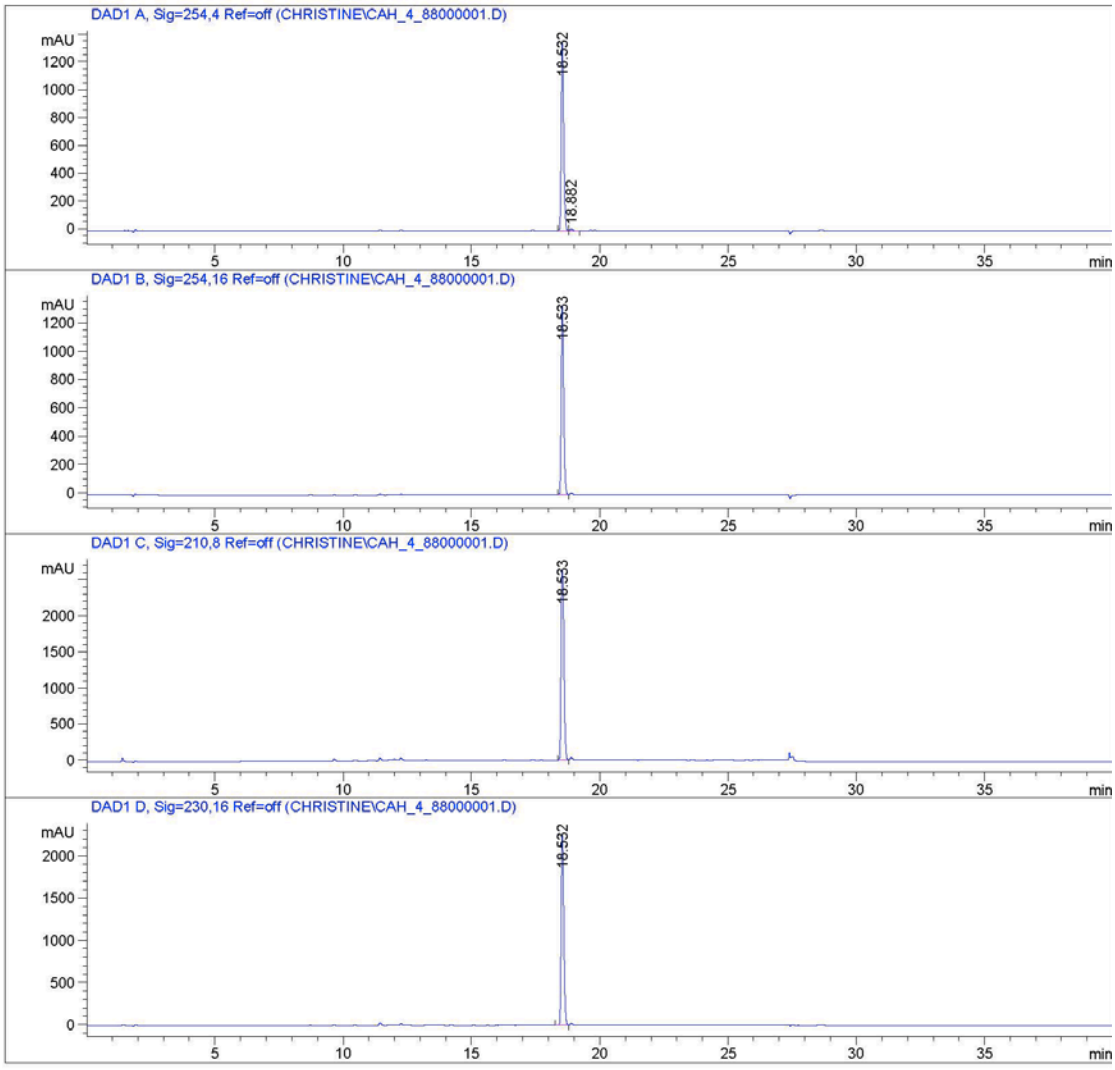

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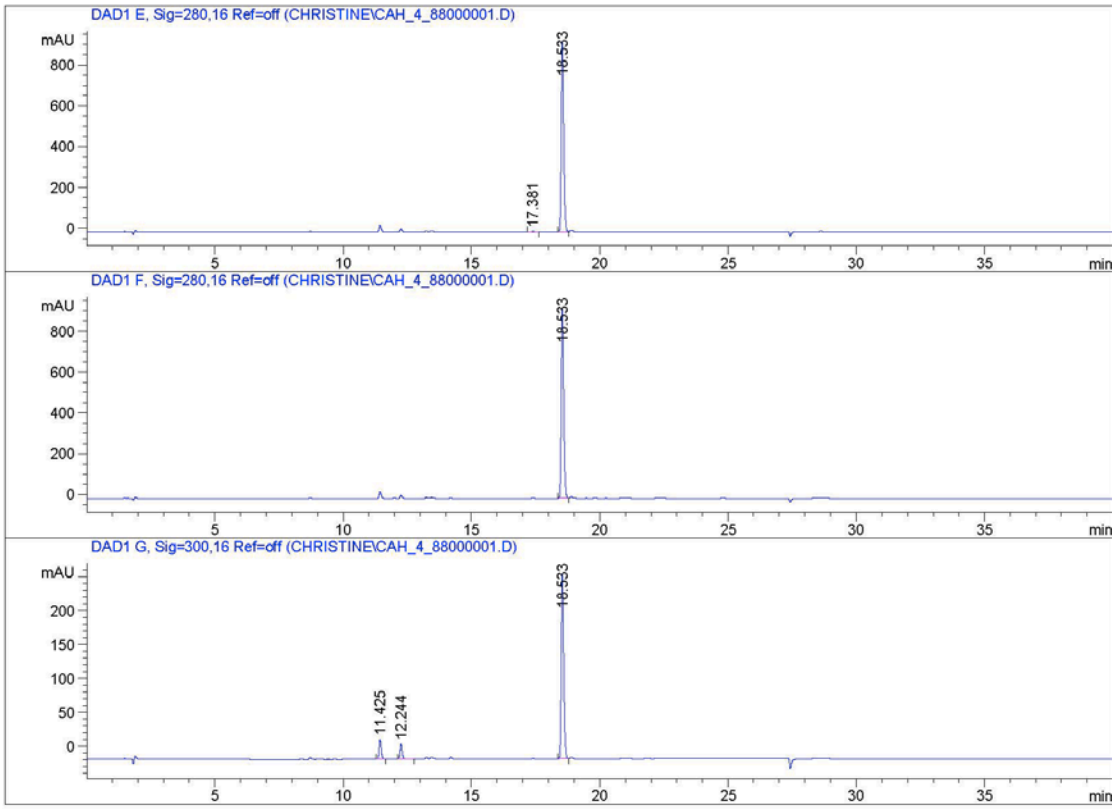
Sample Name: CAH_4_88



==========

Area Percent Report

==========

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.532	BV	0.0995	8838.96289	1365.10266	98.9235
2	18.882	VB	0.1004	96.18368	14.31833	1.0765

Totals : 8935.14657 1379.42099

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_88000001.D
Sample Name: CAH_4_88

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.533	BV	0.0995	8683.92773	1341.87500	100.0000
Totals :				8683.92773	1341.87500	

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.533	BV	0.1233	2.02628e4	2646.86206	100.0000
Totals :				2.02628e4	2646.86206	

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.532	BV	0.1082	1.56791e4	2280.01855	100.0000
Totals :				1.56791e4	2280.01855	

Signal 5: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.381	BB	0.1023	16.08844	2.39759	0.2640
2	18.533	BV	0.0995	6078.18750	939.42749	99.7360
Totals :				6094.27594	941.82508	

Signal 6: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.533	BV	0.0995	6078.18750	939.42749	100.0000

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_88000001.D
Sample Name: CAH_4_88

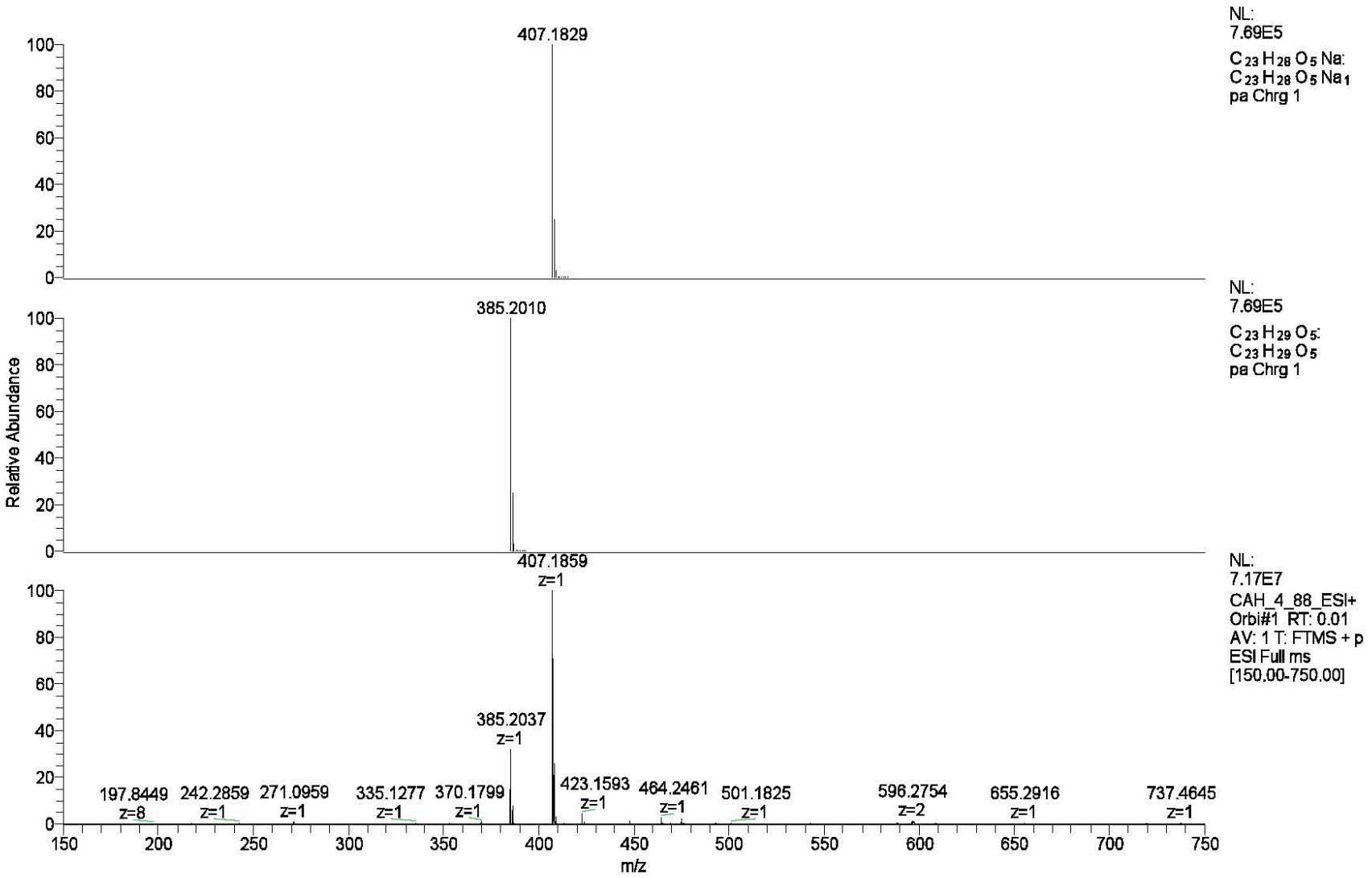
Totals : 6078.18750 939.42749

Signal 7: DAD1 G, Sig=300,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.425	BB	0.0866	167.73837	29.38750	8.0605
2	12.244	VB	0.0884	130.17458	22.87446	6.2554
3	18.533	BV	0.0998	1783.07324	274.61212	85.6840

Totals : 2080.98619 326.87408

*** End of Report ***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7.69E5
C23 H28 O5 Na:
C23 H28 O5 Na1
pa Chrg 1
385.2010
NL:
7.69E5
C23 H29 O5:
C23 H29 O5
pa Chrg 1
Relative Abundance
407.1859
z=1
NL:
7.17E7
CAH_4_88_ESI+
Orbi#1 RT: 0.01
AV: 1 T: FTMS + p
ESI Full ms
[150.00-750.00]
385.2037
z=1
197.8449
z=8
242.2859
z=1
271.0959
z=1
335.1277
z=1
370.1799
z=1
423.1593
z=1
464.2461
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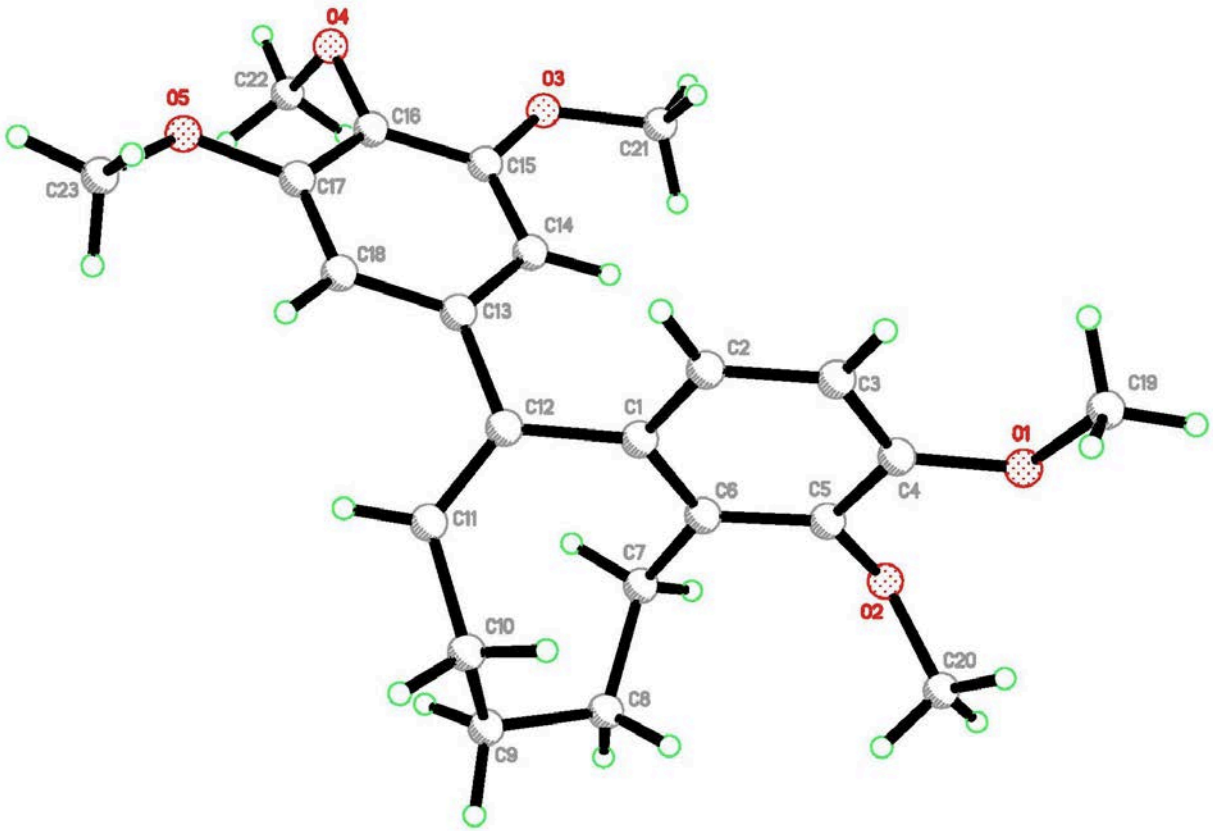
m/z


O4
C22
O5
C16
O3
C21
C23
C17
C15
C14
C18
C13
C2
C3
C19
C12
C1
O1
C6
C5
C4
C11
C7
O2
C10
C20
C8
C9

X-ray Crystallographic Analysis:

X-ray crystallographic analysis of compound **20**. Crystallographic data were collected on a crystal of **20** with dimensions 0.257 x 0.138 x 0.039 mm^3. Data were collected at 150 K on a Bruker X8 Apex using Mo KR radiation (λ = 0.71073 Å). The structure was solved by direct methods after correction of the data using SADABS. Crystallographic data and definement details for the complex mentioned herein is found in the Supporting Information (Table S1-S4). All data were processed using the Bruker AXS SHELXTL software, version 6.10.

Table 1. Crystal data and structure refinement for Compound 20.

Identification code	Compound 20	
Empirical formula	C23 H28 O5	
Formula weight	384.45	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 11.7350(5) Å	a= 90°.
	b = 9.4232(5) Å	b= 102.544(2)°.
	c = 18.5619(10) Å	g = 90°.
Volume	2003.60(17) $Å^3$	
Z	4	
Density (calculated)	1.275 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	824	
Crystal size	0.257 x 0.138 x 0.039 mm^3	
Theta range for data collection	2.436 to 29.679°.	
Index ranges	-16<=h<=12, -12<=k<=13, -25<=l<=23	
Reflections collected	13077	
Independent reflections	5627 [R(int) = 0.0336]	
Completeness to theta = 25.242°	99.3 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.902 and 0.885
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5627 / 0 / 253
Goodness-of-fit on F^2	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0541, wR2 = 0.1131
R indices (all data)	R1 = 0.0879, wR2 = 0.1267
Extinction coefficient	n/a
Largest diff. peak and hole	0.344 and -0.242 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Compound 20. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3173(1)	14383(1)	4025(1)	30(1)
O(2)	4861(1)	13357(1)	3412(1)	29(1)
O(3)	857(1)	9497(1)	770(1)	28(1)
O(4)	251(1)	6770(1)	589(1)	23(1)
O(5)	819(1)	4899(1)	1700(1)	27(1)
C(1)	3180(1)	10093(2)	3481(1)	20(1)
C(2)	2272(1)	10643(2)	3767(1)	23(1)
C(3)	2252(1)	12049(2)	3979(1)	24(1)
C(4)	3134(1)	12951(2)	3878(1)	22(1)
C(5)	4042(1)	12422(2)	3577(1)	21(1)
C(6)	4094(1)	10996(2)	3387(1)	19(1)
C(7)	5115(1)	10470(2)	3087(1)	24(1)
C(8)	6151(1)	9948(2)	3694(1)	30(1)
C(9)	6098(1)	8424(2)	3958(1)	32(1)
C(10)	4997(1)	8045(2)	4242(1)	28(1)
C(11)	3994(1)	7669(2)	3619(1)	24(1)
C(12)	3176(1)	8564(2)	3272(1)	21(1)
C(13)	2289(1)	8107(2)	2605(1)	21(1)
C(14)	1906(1)	9084(2)	2043(1)	21(1)
C(15)	1226(1)	8632(2)	1370(1)	21(1)
C(16)	907(1)	7212(2)	1263(1)	20(1)
C(17)	1222(1)	6255(2)	1844(1)	21(1)
C(18)	1921(1)	6696(2)	2514(1)	22(1)
C(19)	2327(2)	14928(2)	4397(1)	36(1)
C(20)	5700(1)	13882(2)	4028(1)	35(1)
C(21)	948(2)	10986(2)	893(1)	32(1)
C(22)	963(1)	6307(2)	95(1)	28(1)
C(23)	1023(2)	3932(2)	2307(1)	36(1)

Table 3. Bond lengths [Å] and angles [°] for Compound 20.

O(1)-C(4)	1.3749(19)
O(1)-C(19)	1.4217(19)
O(2)-C(5)	1.3859(17)
O(2)-C(20)	1.426(2)
O(3)-C(15)	1.3706(18)
O(3)-C(21)	1.4221(19)
O(4)-C(16)	1.3838(16)
O(4)-C(22)	1.4353(17)
O(5)-C(17)	1.3686(18)
O(5)-C(23)	1.428(2)
C(1)-C(2)	1.390(2)
C(1)-C(6)	1.410(2)
C(1)-C(12)	1.492(2)
C(2)-C(3)	1.384(2)
C(3)-C(4)	1.384(2)
C(4)-C(5)	1.399(2)
C(5)-C(6)	1.394(2)
C(6)-C(7)	1.5094(19)
C(7)-C(8)	1.547(2)
C(8)-C(9)	1.523(2)
C(9)-C(10)	1.539(2)
C(10)-C(11)	1.5015(19)
C(11)-C(12)	1.334(2)
C(12)-C(13)	1.4964(19)
C(13)-C(14)	1.392(2)
C(13)-C(18)	1.397(2)
C(14)-C(15)	1.3947(19)
C(15)-C(16)	1.392(2)
C(16)-C(17)	1.393(2)
C(17)-C(18)	1.3957(19)
C(4)-O(1)-C(19)	117.05(13)
C(5)-O(2)-C(20)	115.76(12)
C(15)-O(3)-C(21)	117.25(12)

C(16)-O(4)-C(22)	112.51(10)
C(17)-O(5)-C(23)	116.68(12)
C(2)-C(1)-C(6)	119.28(14)
C(2)-C(1)-C(12)	120.02(13)
C(6)-C(1)-C(12)	120.69(12)
C(3)-C(2)-C(1)	121.86(13)
C(2)-C(3)-C(4)	119.33(13)
O(1)-C(4)-C(3)	124.69(13)
O(1)-C(4)-C(5)	115.74(13)
C(3)-C(4)-C(5)	119.51(14)
O(2)-C(5)-C(6)	119.14(12)
O(2)-C(5)-C(4)	119.07(14)
C(6)-C(5)-C(4)	121.62(13)
C(5)-C(6)-C(1)	118.33(12)
C(5)-C(6)-C(7)	119.47(13)
C(1)-C(6)-C(7)	122.20(14)
C(6)-C(7)-C(8)	113.40(12)
C(9)-C(8)-C(7)	116.92(13)
C(8)-C(9)-C(10)	115.17(13)
C(11)-C(10)-C(9)	111.52(13)
C(12)-C(11)-C(10)	125.74(15)
C(11)-C(12)-C(1)	121.55(13)
C(11)-C(12)-C(13)	121.10(14)
C(1)-C(12)-C(13)	117.06(12)
C(14)-C(13)-C(18)	119.84(13)
C(14)-C(13)-C(12)	118.93(13)
C(18)-C(13)-C(12)	121.00(13)
C(13)-C(14)-C(15)	119.92(14)
O(3)-C(15)-C(16)	115.38(12)
O(3)-C(15)-C(14)	124.30(14)
C(16)-C(15)-C(14)	120.30(14)
O(4)-C(16)-C(15)	119.85(13)
O(4)-C(16)-C(17)	120.45(13)
C(15)-C(16)-C(17)	119.67(12)
O(5)-C(17)-C(16)	115.50(12)
O(5)-C(17)-C(18)	124.35(13)

C(16)-C(17)-C(18)	120.14(14)
C(17)-C(18)-C(13)	119.88(14)

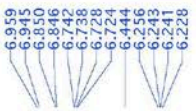
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Compound 20. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	34(1)	23(1)	36(1)	-4(1)	14(1)	1(1)
O(2)	33(1)	28(1)	29(1)	-2(1)	14(1)	-12(1)
O(3)	35(1)	24(1)	20(1)	0(1)	-4(1)	0(1)
O(4)	18(1)	30(1)	19(1)	-8(1)	-1(1)	0(1)
O(5)	29(1)	22(1)	26(1)	-4(1)	0(1)	-6(1)
C(1)	20(1)	24(1)	14(1)	1(1)	0(1)	-3(1)
C(2)	18(1)	30(1)	21(1)	0(1)	2(1)	-6(1)
C(3)	18(1)	30(1)	22(1)	-1(1)	4(1)	0(1)
C(4)	24(1)	22(1)	20(1)	-1(1)	3(1)	1(1)
C(5)	20(1)	24(1)	18(1)	2(1)	4(1)	-4(1)
C(6)	19(1)	24(1)	14(1)	0(1)	2(1)	-1(1)
C(7)	24(1)	26(1)	24(1)	-2(1)	9(1)	-2(1)
C(8)	19(1)	34(1)	37(1)	-3(1)	5(1)	-2(1)
C(9)	23(1)	35(1)	33(1)	-2(1)	-3(1)	3(1)
C(10)	28(1)	28(1)	23(1)	3(1)	-4(1)	-2(1)
C(11)	27(1)	23(1)	21(1)	-1(1)	0(1)	-5(1)
C(12)	21(1)	24(1)	17(1)	-1(1)	2(1)	-6(1)
C(13)	18(1)	25(1)	18(1)	-4(1)	2(1)	-2(1)
C(14)	21(1)	21(1)	20(1)	-3(1)	2(1)	-2(1)
C(15)	19(1)	25(1)	18(1)	-1(1)	2(1)	1(1)
C(16)	16(1)	25(1)	18(1)	-6(1)	1(1)	0(1)
C(17)	18(1)	20(1)	24(1)	-5(1)	4(1)	-2(1)
C(18)	22(1)	24(1)	20(1)	-1(1)	1(1)	-2(1)
C(19)	39(1)	33(1)	39(1)	-10(1)	14(1)	5(1)
C(20)	29(1)	34(1)	42(1)	-8(1)	10(1)	-12(1)
C(21)	40(1)	24(1)	27(1)	0(1)	-2(1)	0(1)

C(22)	27(1)	34(1)	23(1)	-8(1)	6(1)	-2(1)
C(23)	52(1)	24(1)	30(1)	0(1)	3(1)	-11(1)

Crystallographic data for structure **20** (deposition number CCDC 1046343) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).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6.241
6.228


3.863
3.857
3.798
2.849
2.836
2.827
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2.063
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1.786
1.670
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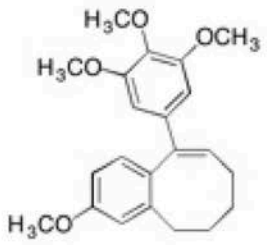
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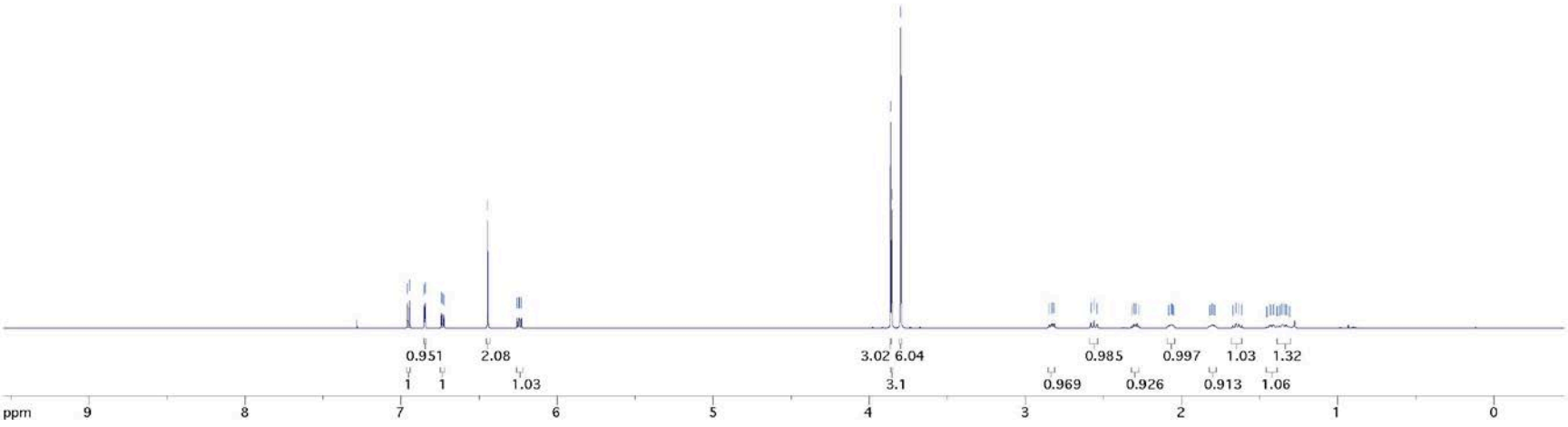
OCH3
H3CO
H3CO

21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7
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5
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3
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1
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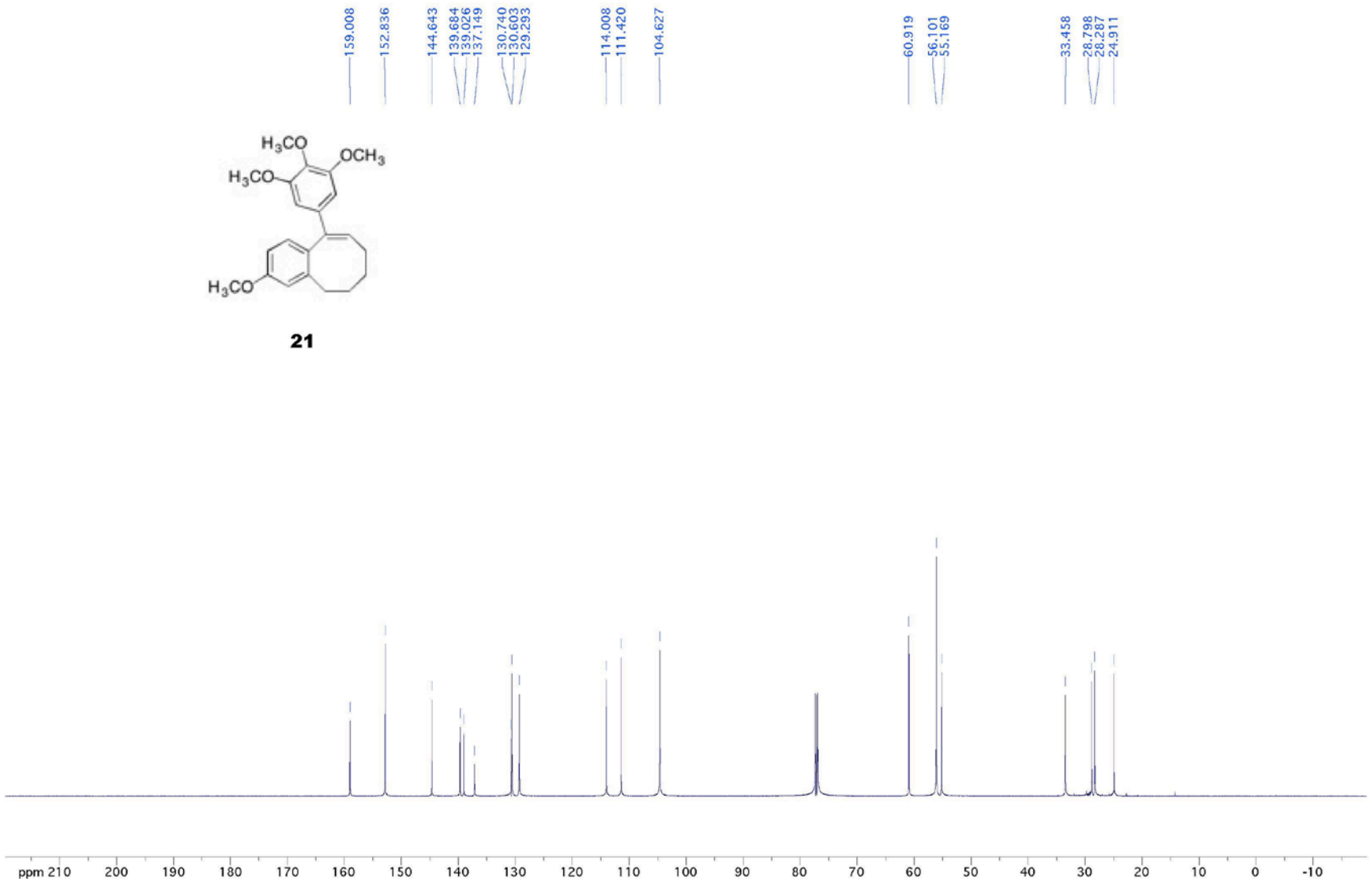
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56.101
55.169
33.458
28.798
28.287
24.911
H3CO
OCH3
H3CO
H3CO
ppm 210
200
190
180
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120
110
100
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80
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40
30
20
10
0
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21

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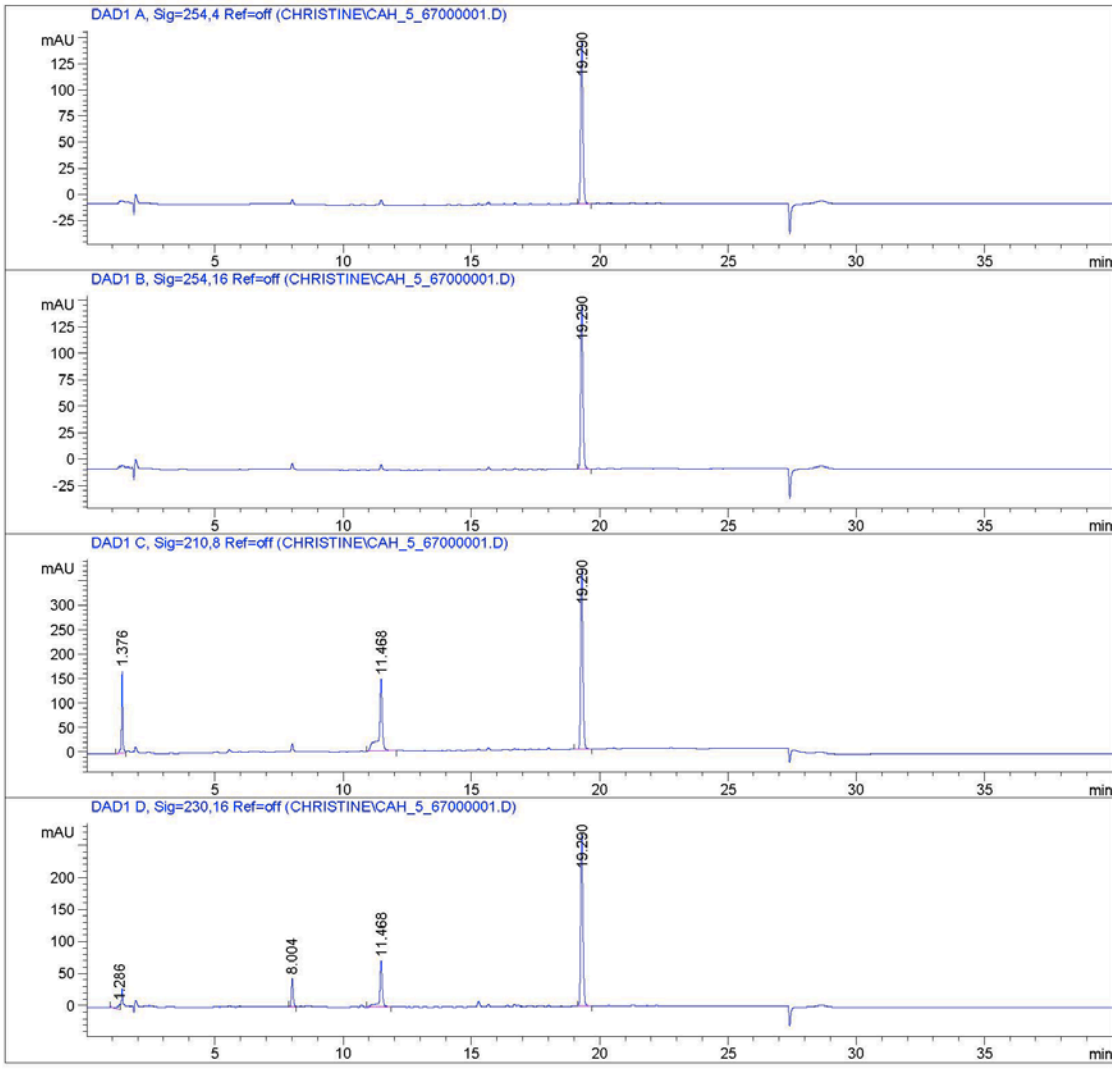

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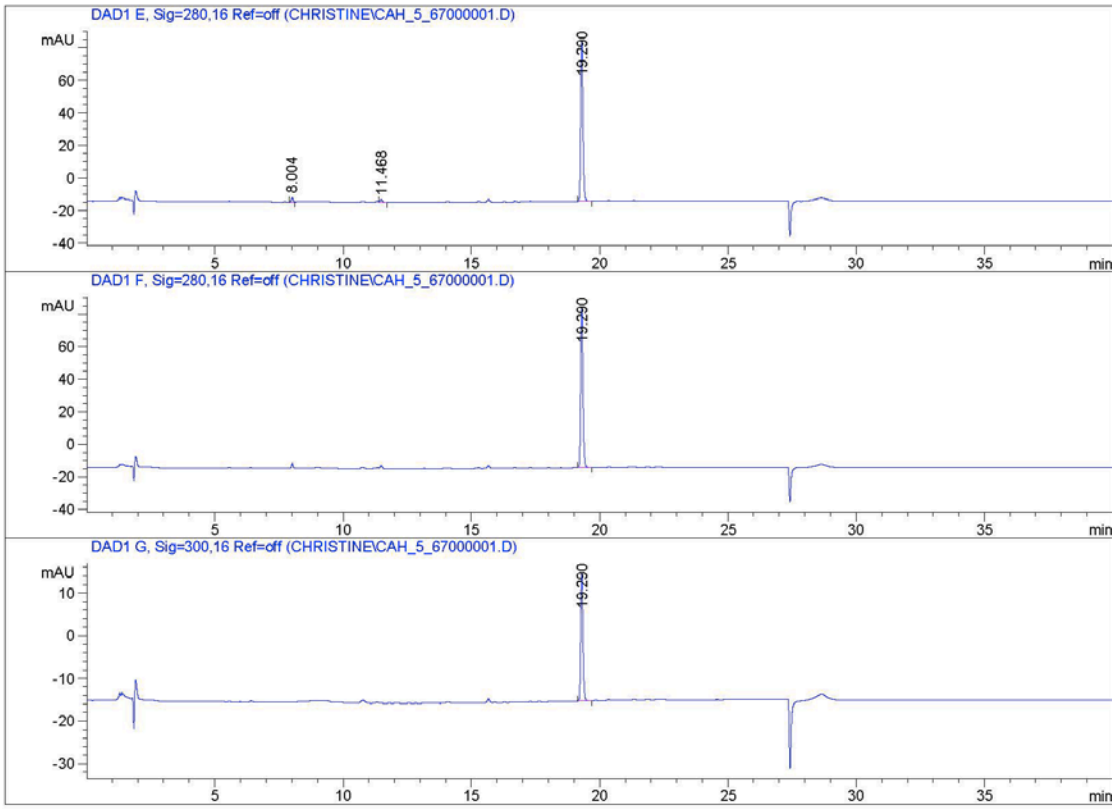

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Area Percent Report

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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.290	BB	0.0924	939.05951	155.64803	100.0000

Totals : 939.05951 155.64803

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_5_67000001.D
Sample Name: CAH_5_67

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.290	BB	0.0924	933.50537	154.77390	100.0000
Totals :				933.50537	154.77390	

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.376	BV	0.0514	566.59003	167.64386	13.7716
2	11.468	BB	0.1247	1325.44922	147.65602	32.2164
3	19.290	BB	0.0945	2222.16187	367.52441	54.0120
Totals :				4114.20111	682.82430	

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.286	BV	0.1040	63.83619	8.09134	2.6688
2	8.004	BB	0.0727	205.53131	43.84377	8.5927
3	11.468	BB	0.1019	497.50229	70.89946	20.7993
4	19.290	BB	0.0923	1625.05005	269.84534	67.9392
Totals :				2391.91984	392.67990	

Signal 5: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.004	BB	0.0713	12.97011	2.83754	2.0930
2	11.468	VB	0.0893	11.36858	1.91306	1.8346
3	19.290	BB	0.0924	595.34033	98.72345	96.0724
Totals :				619.67902	103.47405	

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Sample Name: CAH_5_67

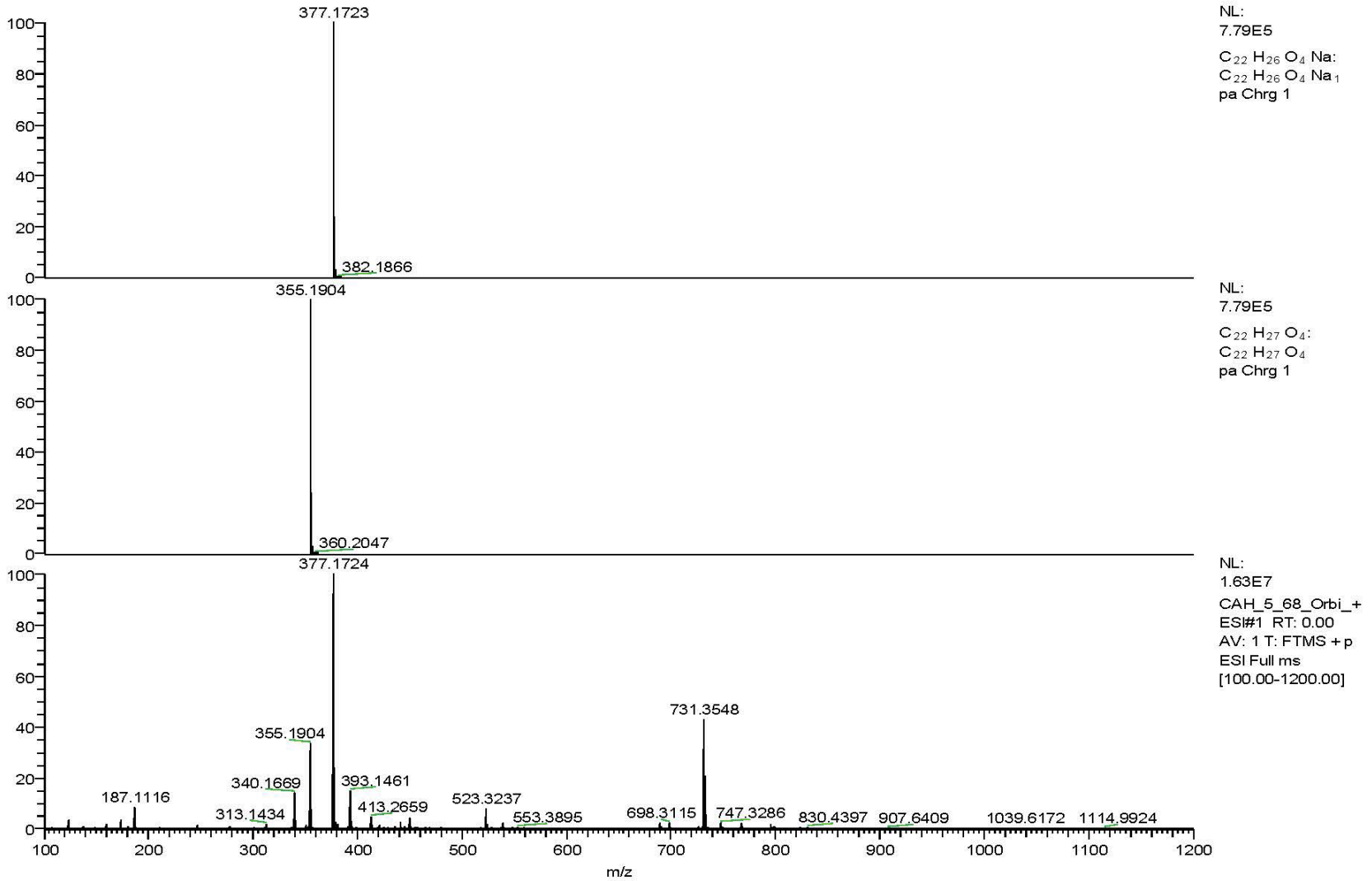
Signal 6: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.290	BB	0.0924	595.34247	98.72340	100.0000
Totals :				595.34247	98.72340	

Signal 7: DAD1 G, Sig=300,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.290	BB	0.0925	181.02713	29.95630	100.0000
Totals :				181.02713	29.95630	

*** End of Report ***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C22 H26 O4 Na:
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7.79E5
C22 H27 O4:
C22 H27 O4
pa Chrg 1
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393.1461
187.1116
313.1434
413.2659
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747.3286
830.4397
907.6409
1039.6172
1114.9924
NL:
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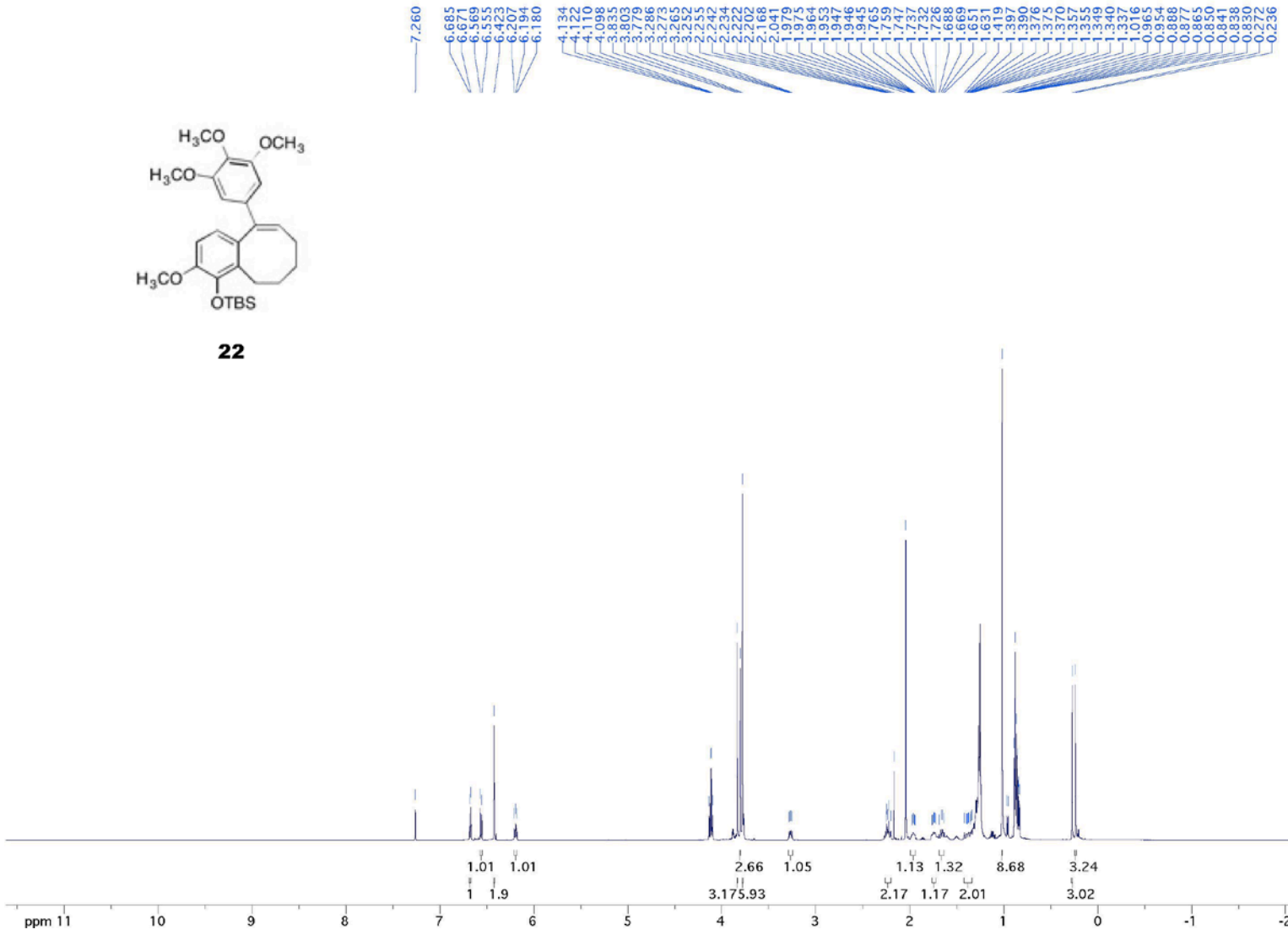
CAH_5_68_Orbi_+
ESI#1 RT: 0.00
AV: 1 T: FTMS + p
ESI Full ms
[100.00-1200.00]
m/z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3.835
3.803
3.779
3.286
3.273
3.265
3.252
2.255
2.242
2.234
2.222
2.202
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1.975
1.964
1.953
1.947
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1.340
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H3CO
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OTBS
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1
1.9
2.66
1.05
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3.24
2.17
1.17
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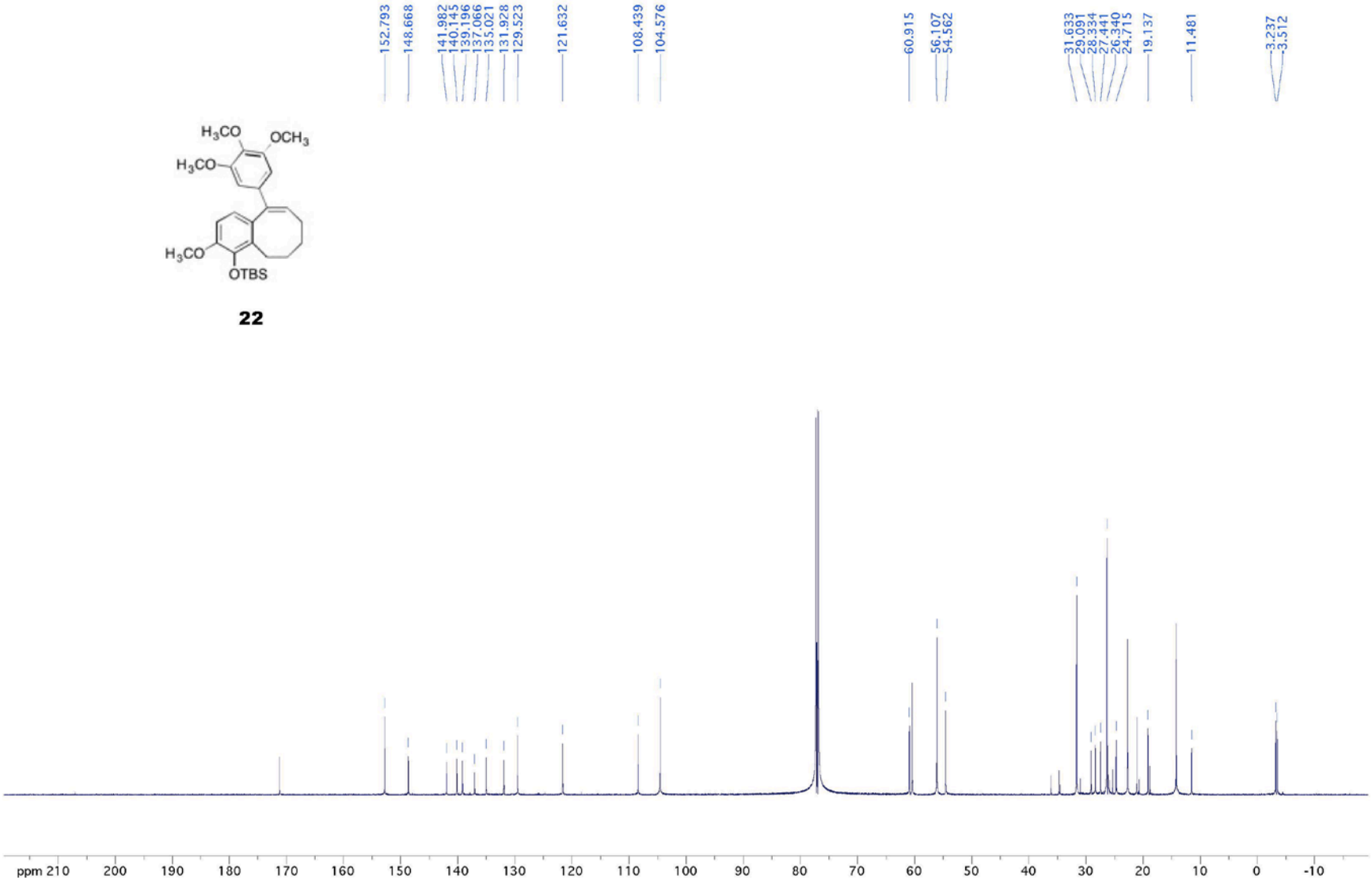
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56.107
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29.091
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27.441
26.340
24.715
19.137
11.481
3.237
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OCH3
H3CO
H3CO
OTBS
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10
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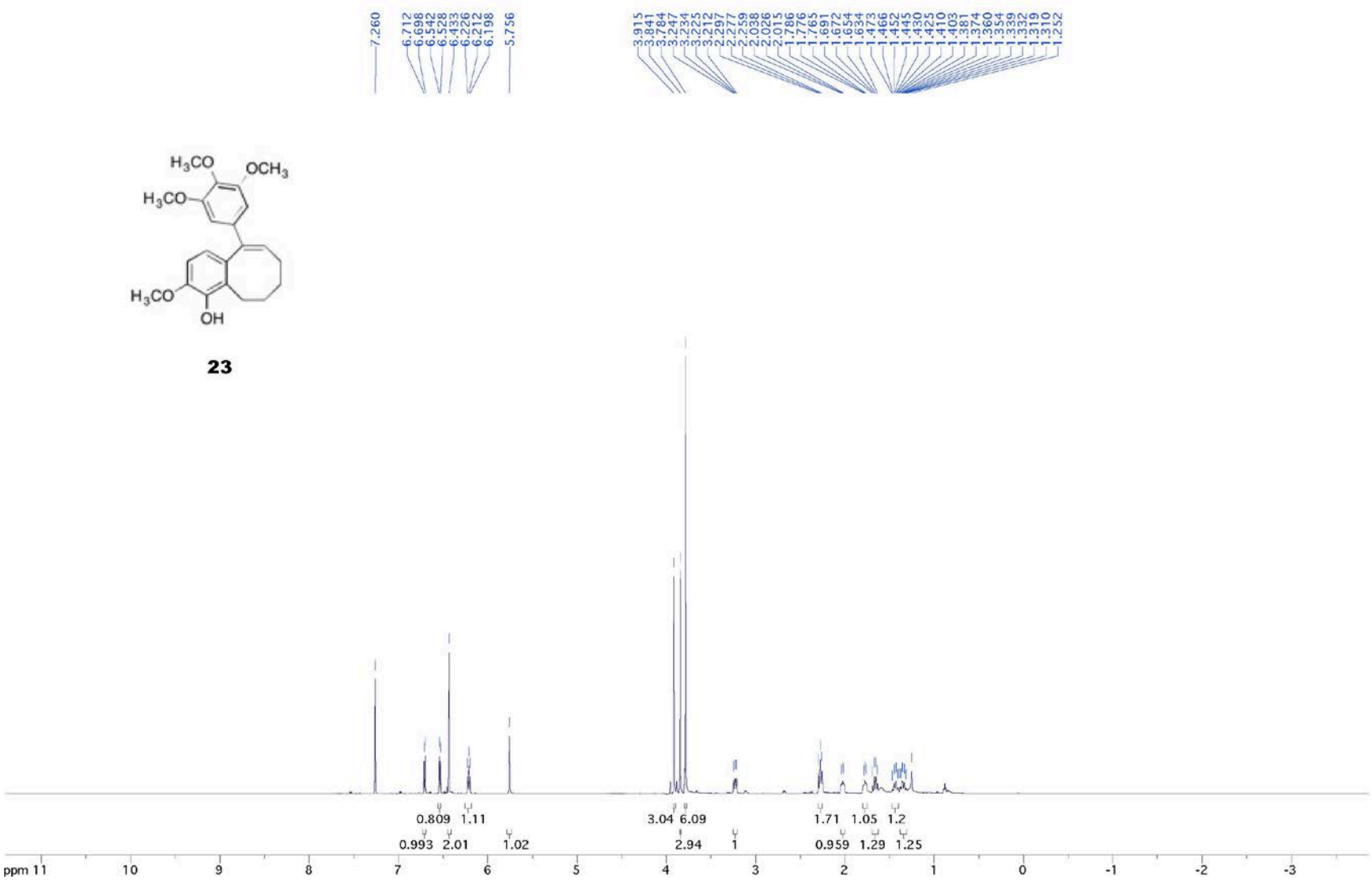
-10

22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H3CO
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H3CO
H3CO
OH
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3.04
6.09
1.71
1.05
1.2
0.993
2.01
1.02
2.94
1
0.959
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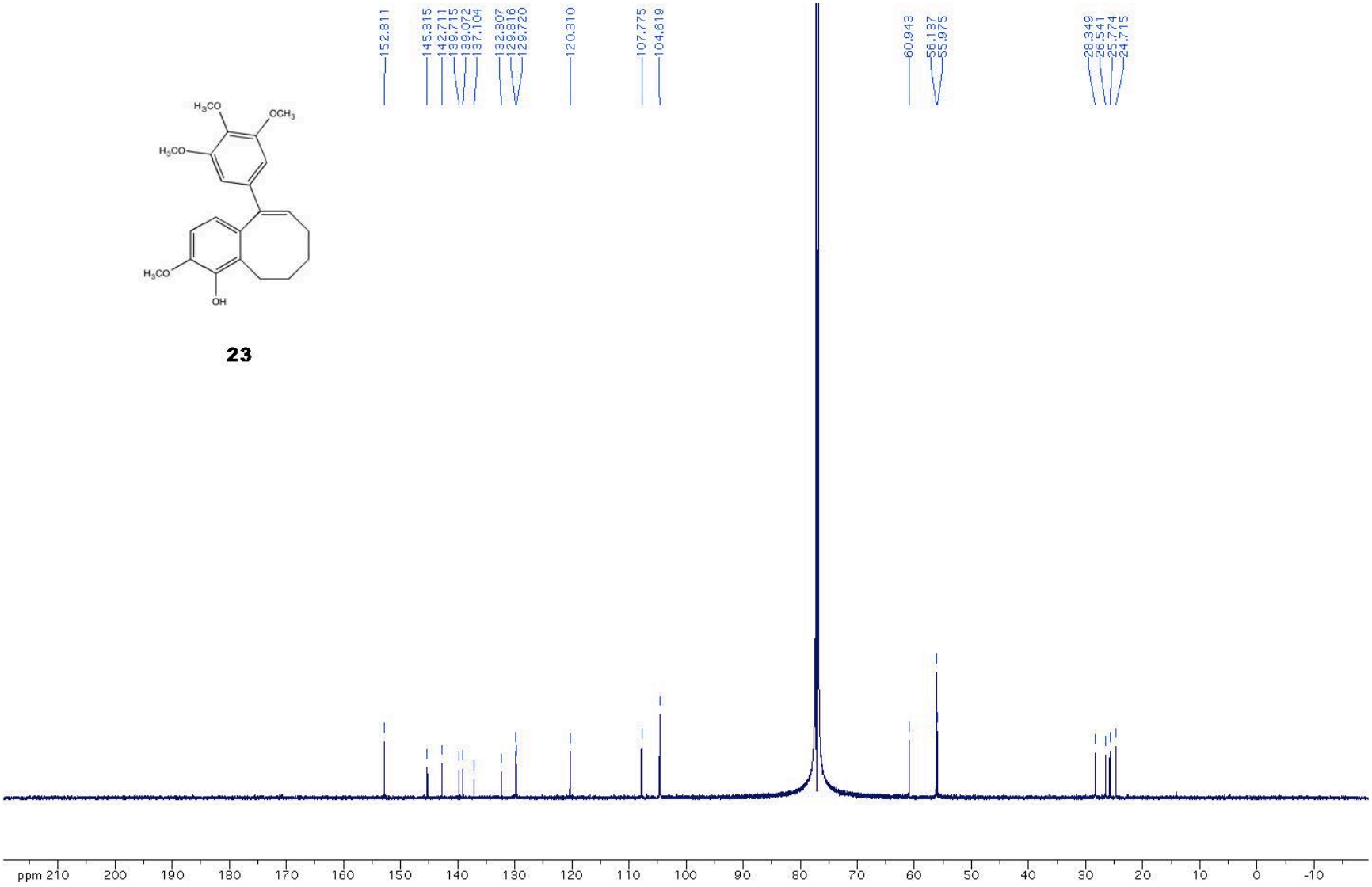
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28.349
26.541
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OH
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23

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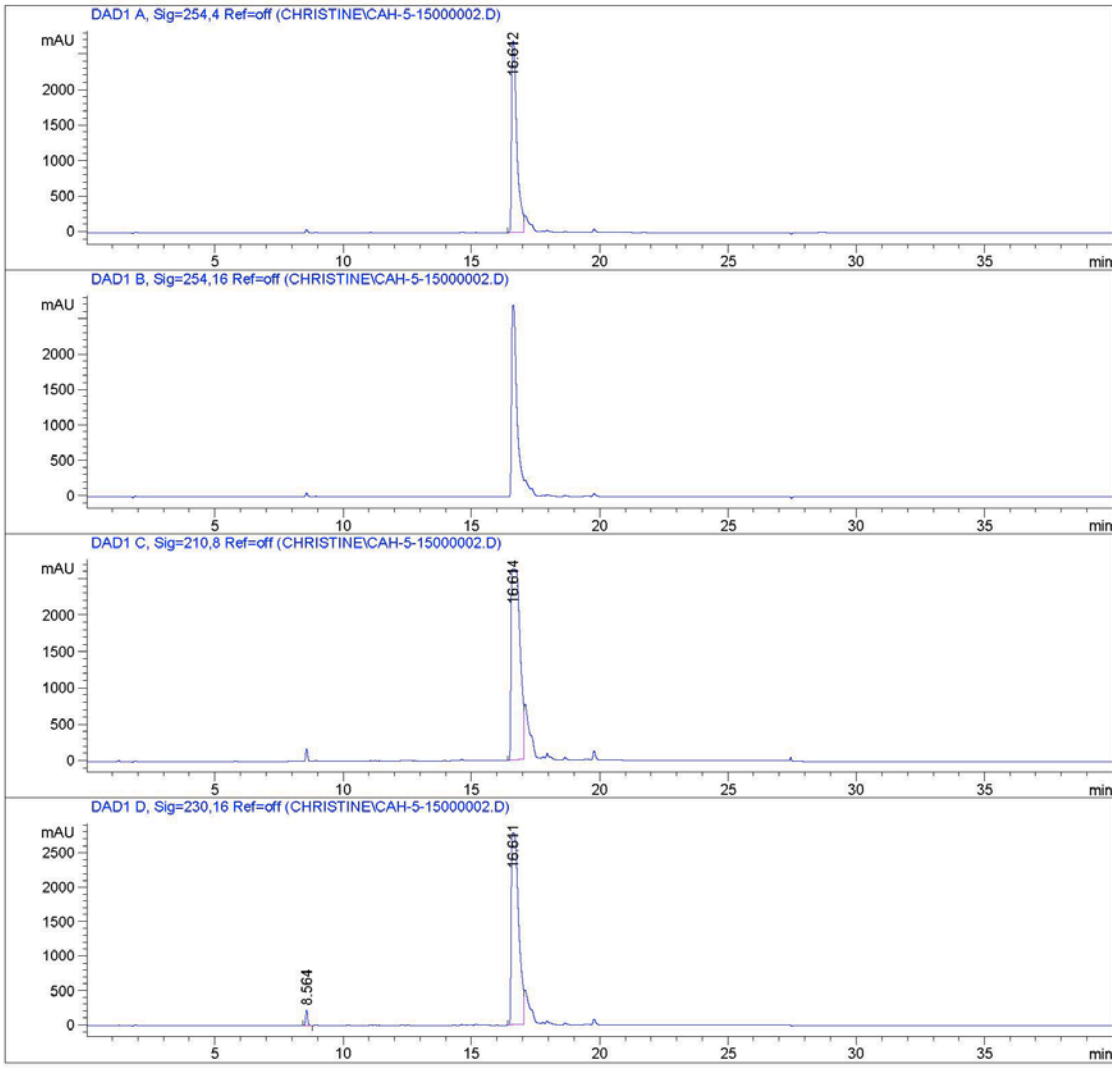

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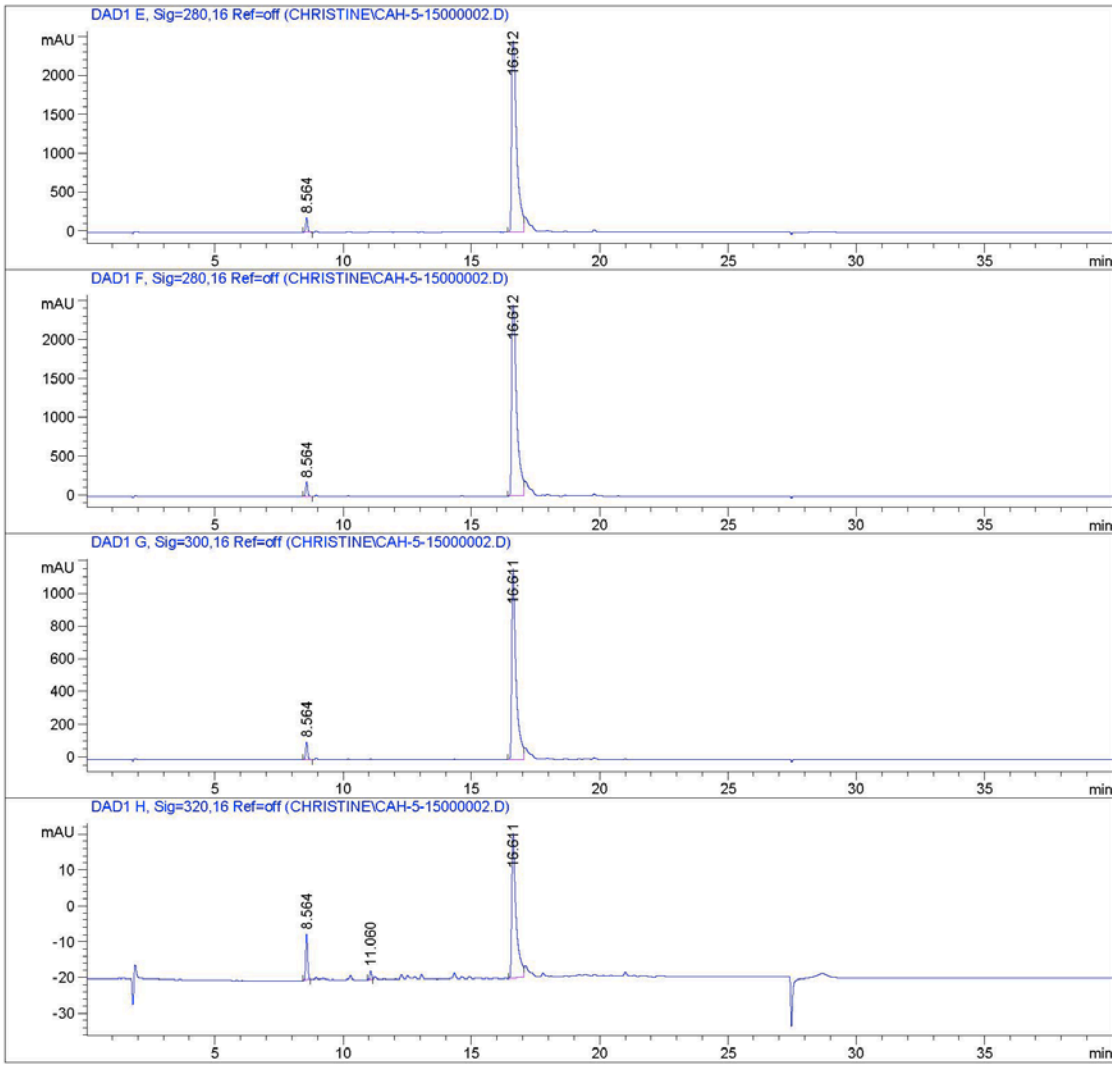

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Area Percent Report

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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-5-15000002.D
Sample Name: cah-5-15

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.612	BV	0.2164	3.88516e4	2691.22314	100.0000
Totals :				3.88516e4	2691.22314	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.614	BV	0.3761	6.34811e4	2625.34521	100.0000
Totals :				6.34811e4	2625.34521	

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.564	BB	0.0771	1163.02673	229.77750	2.0414
2	16.611	BV	0.3100	5.58100e4	2782.44800	97.9586
Totals :				5.69730e4	3012.22549	

Signal 5: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.564	BV	0.0773	953.32397	187.54671	2.7213
2	16.612	BV	0.2055	3.40785e4	2462.50952	97.2787
Totals :				3.50318e4	2650.05623	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-5-15000002.D
Sample Name: cah-5-15

Signal 6: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.564	BV	0.0773	953.32397	187.54671	2.7213
2	16.612	BV	0.2055	3.40785e4	2462.50952	97.2787
Totals :				3.50318e4	2650.05623	

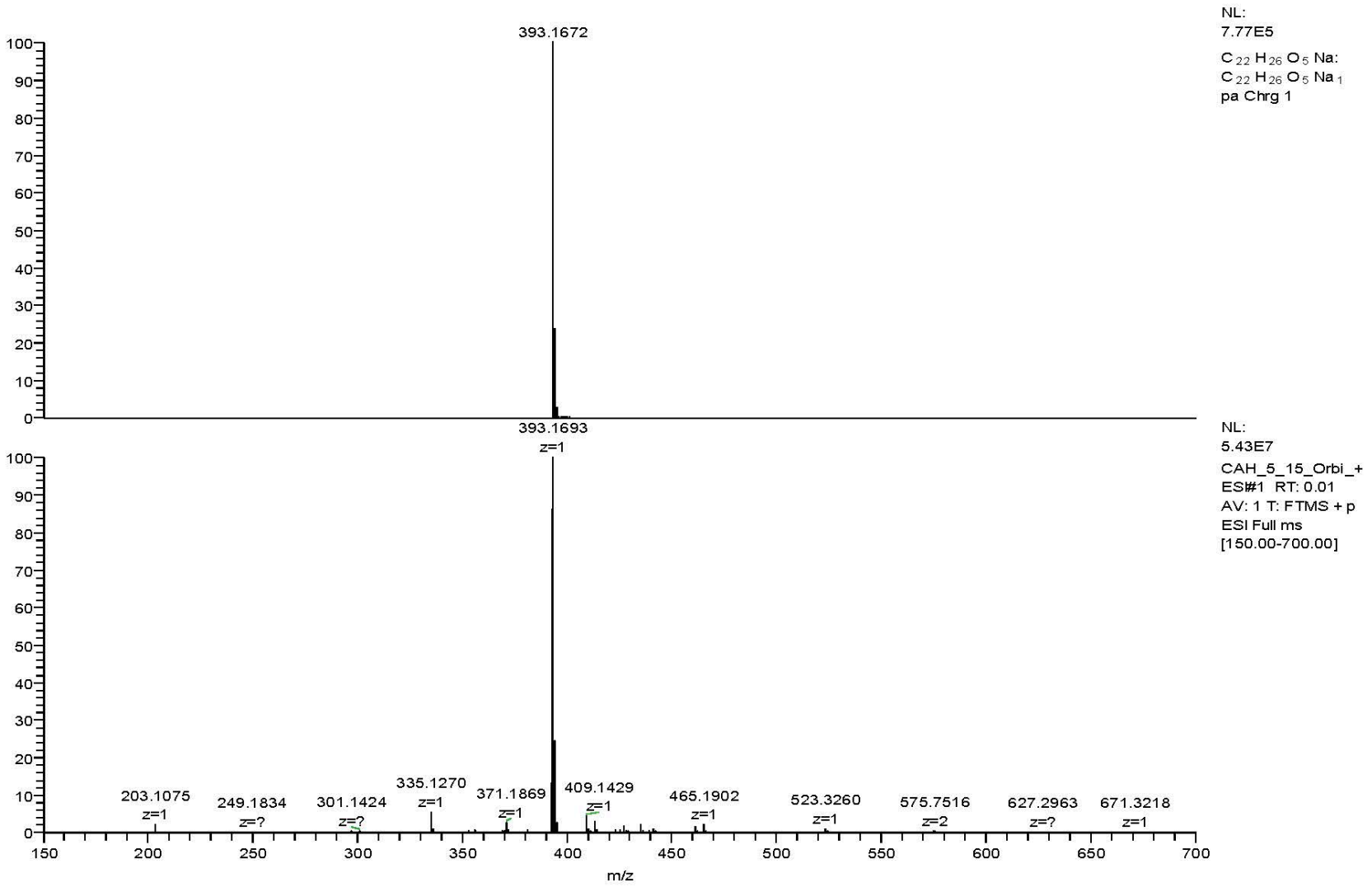
Signal 7: DAD1 G, Sig=300,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.564	BV	0.0773	555.76282	109.26016	3.9560
2	16.611	BV	0.1668	1.34929e4	1167.44519	96.0440
Totals :				1.40486e4	1276.70535	

Signal 8: DAD1 H, Sig=320,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.564	BB	0.0763	64.41962	12.88749	11.7453
2	11.060	BV	0.0800	13.31195	2.58971	2.4271
3	16.611	BV	0.1653	470.73935	40.60112	85.8276
Totals :				548.47093	56.07832	

*** End of Report ***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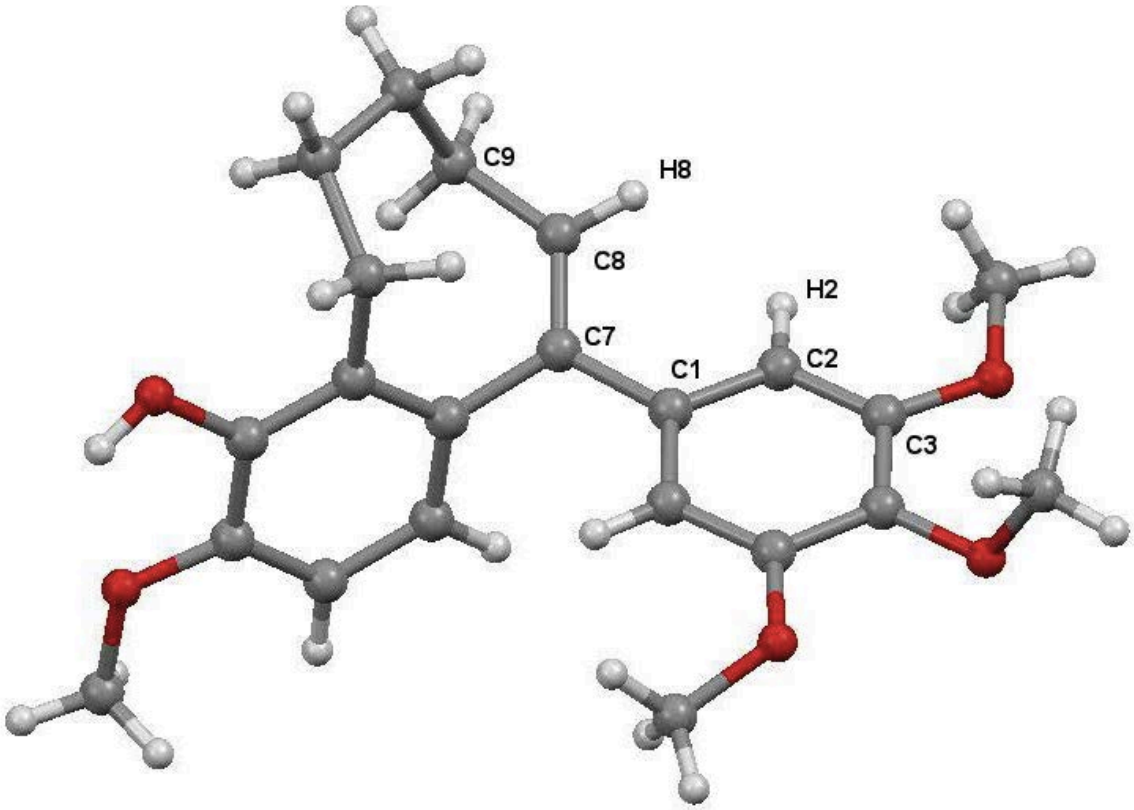
NL:
7.77E5
C 22 H 26 O 5 Na:
C 22 H 26 O 5 Na 1
pa Chrg 1
393.1693
z=1
NL:
5.43E7
CAH_5_15_Orbi_+
ESI#1 RT: 0.01
AV: 1 T: FTMS + p
ESI Full ms
[150.00-700.00]
203.1075 z=1
249.1834 z=?
301.1424 z=?
335.1270 z=1
371.1869 z=1
409.1429 z=1
465.1902 z=1
523.3260 z=1
575.7516 z=2
627.2963 z=?
671.3218 z=1
m/z


C9
H8
C8
H2
C7
C1
C2
C3

X-ray Crystallographic Analysis:

X-ray crystallographic analysis of compound **23**. Crystallographic data were collected on a crystal of **23** with dimensions 0.171 x 0.130 x 0.089 mm^3. Data were collected at 150 K on a Bruker X8 Apex using Mo KR radiation (λ = 0.71073 Å). The structure was solved by direct methods after correction of the data using SADABS. Crystallographic data and definement details for the complex mentioned herein is found in the Supporting Information (Table S5-S9). All data were processed using the Bruker AXS SHELXTL software, version 6.10.

Table 5. Crystal data and structure refinement for Compound 23.

Identification code	Compound 23	
Empirical formula	C22 H26 O5	
Formula weight	370.43	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 16.6410(12) Å	**a**= 90°.
	b = 11.1239(8) Å	**b**= 90°.
	c = 20.5570(13) Å	**g** = 90°.
Volume	3805.4(5) $Å^3$	
Z	8	
Density (calculated)	1.293 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	1584	
Crystal size	0.171 x 0.130 x 0.089 mm^3	
Theta range for data collection	2.963 to 26.370°.	
Index ranges	-20<=h<=20, -13<=k<=13, -25<=l<=24	
Reflections collected	80769	
Independent reflections	3865 [R(int) = 0.0567]	
Completeness to theta = 25.242°	99.7 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.966 and 0.959
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3865 / 0 / 252
Goodness-of-fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0365, wR2 = 0.0902
R indices (all data)	R1 = 0.0476, wR2 = 0.0964
Extinction coefficient	n/a
Largest diff. peak and hole	0.264 and -0.179 e.$Å^{-3}$

Table 6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Compound 23. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6253(1)	3752(1)	2758(1)	33(1)
O(2)	6709(1)	1740(1)	2161(1)	32(1)
O(3)	2132(1)	2432(1)	1252(1)	30(1)
O(4)	1339(1)	3655(1)	318(1)	32(1)
O(5)	2058(1)	5446(1)	-342(1)	33(1)
C(1)	5933(1)	3482(1)	2159(1)	25(1)
C(2)	6161(1)	2438(1)	1831(1)	25(1)
C(3)	5839(1)	2181(1)	1226(1)	28(1)
C(4)	5304(1)	2991(1)	949(1)	28(1)
C(5)	5079(1)	4044(1)	1265(1)	25(1)
C(6)	5379(1)	4281(1)	1893(1)	25(1)
C(7)	5110(1)	5342(1)	2301(1)	29(1)
C(8)	5675(1)	6433(1)	2275(1)	34(1)
C(9)	5567(1)	7256(1)	1691(1)	36(1)
C(10)	5583(1)	6606(1)	1029(1)	33(1)
C(11)	4779(1)	6077(1)	857(1)	29(1)
C(12)	4546(1)	4933(1)	936(1)	26(1)
C(13)	3728(1)	4541(1)	739(1)	26(1)
C(14)	3345(1)	3609(1)	1070(1)	26(1)
C(15)	2548(1)	3322(1)	933(1)	25(1)
C(16)	2122(1)	3961(1)	463(1)	26(1)
C(17)	2516(1)	4872(1)	119(1)	26(1)
C(18)	3313(1)	5152(1)	249(1)	27(1)
C(19)	6957(1)	652(1)	1853(1)	39(1)
C(20)	2608(1)	1511(1)	1544(1)	31(1)
C(21)	761(1)	4440(2)	613(1)	37(1)
C(22)	2446(1)	6392(1)	-692(1)	36(1)

Table 7. Bond lengths [Å] and angles [°] for Compound 23.

O(1)-C(1)	1.3737(16)
O(2)-C(2)	1.3762(16)
O(2)-C(19)	1.4259(17)
O(3)-C(15)	1.3756(16)
O(3)-C(20)	1.4281(16)
O(4)-C(16)	1.3796(16)
O(4)-C(21)	1.4350(18)
O(5)-C(17)	1.3722(16)
O(5)-C(22)	1.4294(17)
C(1)-C(6)	1.3917(19)
C(1)-C(2)	1.3966(19)
C(2)-C(3)	1.3834(19)
C(3)-C(4)	1.3894(19)
C(4)-C(5)	1.3902(19)
C(5)-C(6)	1.4090(18)
C(5)-C(12)	1.4902(19)
C(6)-C(7)	1.5153(18)
C(7)-C(8)	1.537(2)
C(8)-C(9)	1.521(2)
C(9)-C(10)	1.540(2)
C(10)-C(11)	1.505(2)
C(11)-C(12)	1.340(2)
C(12)-C(13)	1.4863(18)
C(13)-C(14)	1.3940(19)
C(13)-C(18)	1.3977(19)
C(14)-C(15)	1.3936(19)
C(15)-C(16)	1.3930(19)
C(16)-C(17)	1.3984(19)
C(17)-C(18)	1.3885(19)
C(2)-O(2)-C(19)	116.88(11)
C(15)-O(3)-C(20)	115.89(11)
C(16)-O(4)-C(21)	113.03(11)
C(17)-O(5)-C(22)	116.09(11)

O(1)-C(1)-C(6)	118.07(12)
O(1)-C(1)-C(2)	120.53(12)
C(6)-C(1)-C(2)	121.40(12)
O(2)-C(2)-C(3)	125.67(12)
O(2)-C(2)-C(1)	114.33(11)
C(3)-C(2)-C(1)	120.00(12)
C(2)-C(3)-C(4)	118.93(12)
C(3)-C(4)-C(5)	121.79(12)
C(4)-C(5)-C(6)	119.35(12)
C(4)-C(5)-C(12)	120.49(12)
C(6)-C(5)-C(12)	120.13(12)
C(1)-C(6)-C(5)	118.41(12)
C(1)-C(6)-C(7)	118.32(12)
C(5)-C(6)-C(7)	123.24(12)
C(6)-C(7)-C(8)	114.57(11)
C(9)-C(8)-C(7)	115.49(12)
C(8)-C(9)-C(10)	114.38(12)
C(11)-C(10)-C(9)	112.05(12)
C(12)-C(11)-C(10)	126.89(13)
C(11)-C(12)-C(13)	120.66(13)
C(11)-C(12)-C(5)	120.88(12)
C(13)-C(12)-C(5)	118.32(12)
C(14)-C(13)-C(18)	119.23(12)
C(14)-C(13)-C(12)	120.18(12)
C(18)-C(13)-C(12)	120.46(12)
C(15)-C(14)-C(13)	120.36(12)
O(3)-C(15)-C(16)	116.20(12)
O(3)-C(15)-C(14)	123.22(12)
C(16)-C(15)-C(14)	120.56(12)
O(4)-C(16)-C(15)	120.31(12)
O(4)-C(16)-C(17)	120.79(12)
C(15)-C(16)-C(17)	118.82(12)
O(5)-C(17)-C(18)	123.93(12)
O(5)-C(17)-C(16)	115.24(12)
C(18)-C(17)-C(16)	120.83(12)
C(17)-C(18)-C(13)	120.11(13)

Symmetry transformations used to generate equivalent atoms:

Table 8. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Compound 23. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	36(1)	37(1)	24(1)	-7(1)	-8(1)	10(1)
O(2)	32(1)	32(1)	31(1)	-6(1)	-4(1)	9(1)
O(3)	28(1)	27(1)	35(1)	3(1)	-3(1)	-2(1)
O(4)	26(1)	37(1)	34(1)	-2(1)	-8(1)	-4(1)
O(5)	31(1)	41(1)	26(1)	7(1)	-8(1)	-2(1)
C(1)	23(1)	32(1)	21(1)	-4(1)	1(1)	0(1)
C(2)	22(1)	28(1)	26(1)	-1(1)	2(1)	1(1)
C(3)	28(1)	29(1)	26(1)	-6(1)	3(1)	0(1)
C(4)	28(1)	33(1)	22(1)	-3(1)	-2(1)	-3(1)
C(5)	20(1)	31(1)	24(1)	-1(1)	2(1)	-2(1)
C(6)	20(1)	31(1)	24(1)	-4(1)	2(1)	0(1)
C(7)	27(1)	36(1)	24(1)	-4(1)	0(1)	7(1)
C(8)	29(1)	39(1)	35(1)	-14(1)	-4(1)	4(1)
C(9)	31(1)	34(1)	42(1)	-8(1)	2(1)	-5(1)
C(10)	30(1)	36(1)	34(1)	-1(1)	2(1)	-4(1)
C(11)	27(1)	34(1)	27(1)	0(1)	-1(1)	0(1)
C(12)	24(1)	33(1)	21(1)	-2(1)	0(1)	0(1)
C(13)	25(1)	29(1)	23(1)	-5(1)	0(1)	2(1)
C(14)	26(1)	27(1)	24(1)	-1(1)	-3(1)	4(1)
C(15)	27(1)	25(1)	23(1)	-3(1)	1(1)	0(1)
C(16)	24(1)	29(1)	24(1)	-7(1)	-4(1)	-1(1)
C(17)	29(1)	31(1)	19(1)	-3(1)	-4(1)	2(1)
C(18)	29(1)	30(1)	22(1)	-1(1)	0(1)	-2(1)
C(19)	39(1)	34(1)	43(1)	-10(1)	-4(1)	11(1)
C(20)	37(1)	27(1)	30(1)	1(1)	-2(1)	2(1)
C(21)	25(1)	48(1)	38(1)	7(1)	-4(1)	2(1)
C(22)	42(1)	33(1)	31(1)	5(1)	-11(1)	-3(1)

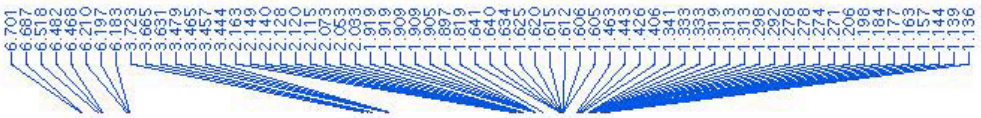
Table 9. Hydrogen bonds for Compound 23 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(2)	0.879(19)	2.202(18)	2.6623(14)	112.3(15)
O(1)-H(1)...O(3)#1	0.879(19)	2.152(19)	2.9046(14)	143.3(16)

Symmetry transformations used to generate equivalent atoms:

#1 x+1/2,y,-z+1/2

Crystallographic data for structure **23** (deposition number CCDC 1046344) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).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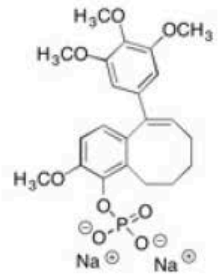
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O
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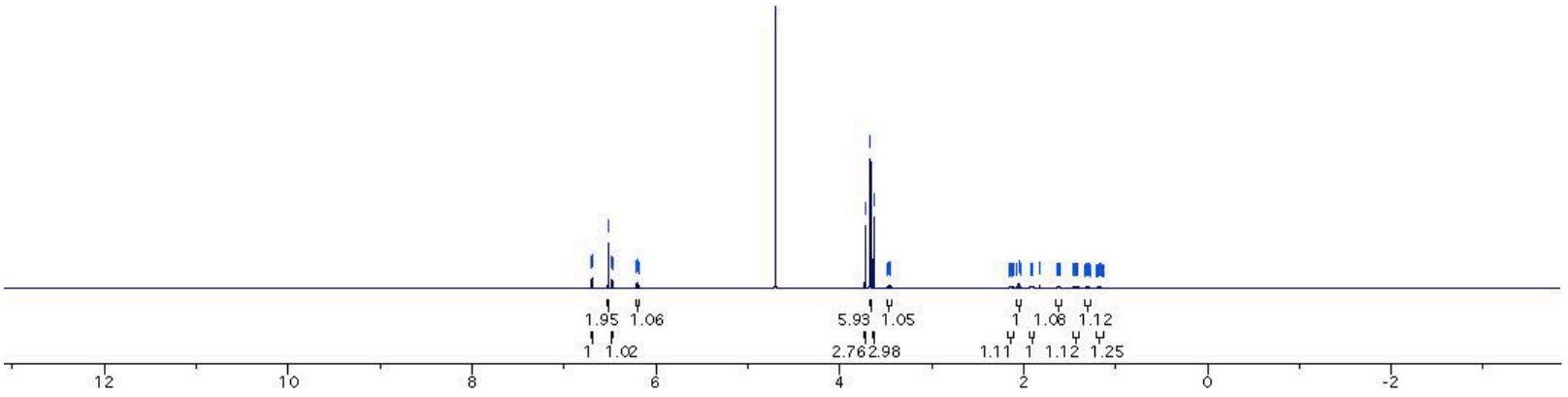
O
O
Na
Na

24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1
1.08
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1
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2.98
1.11
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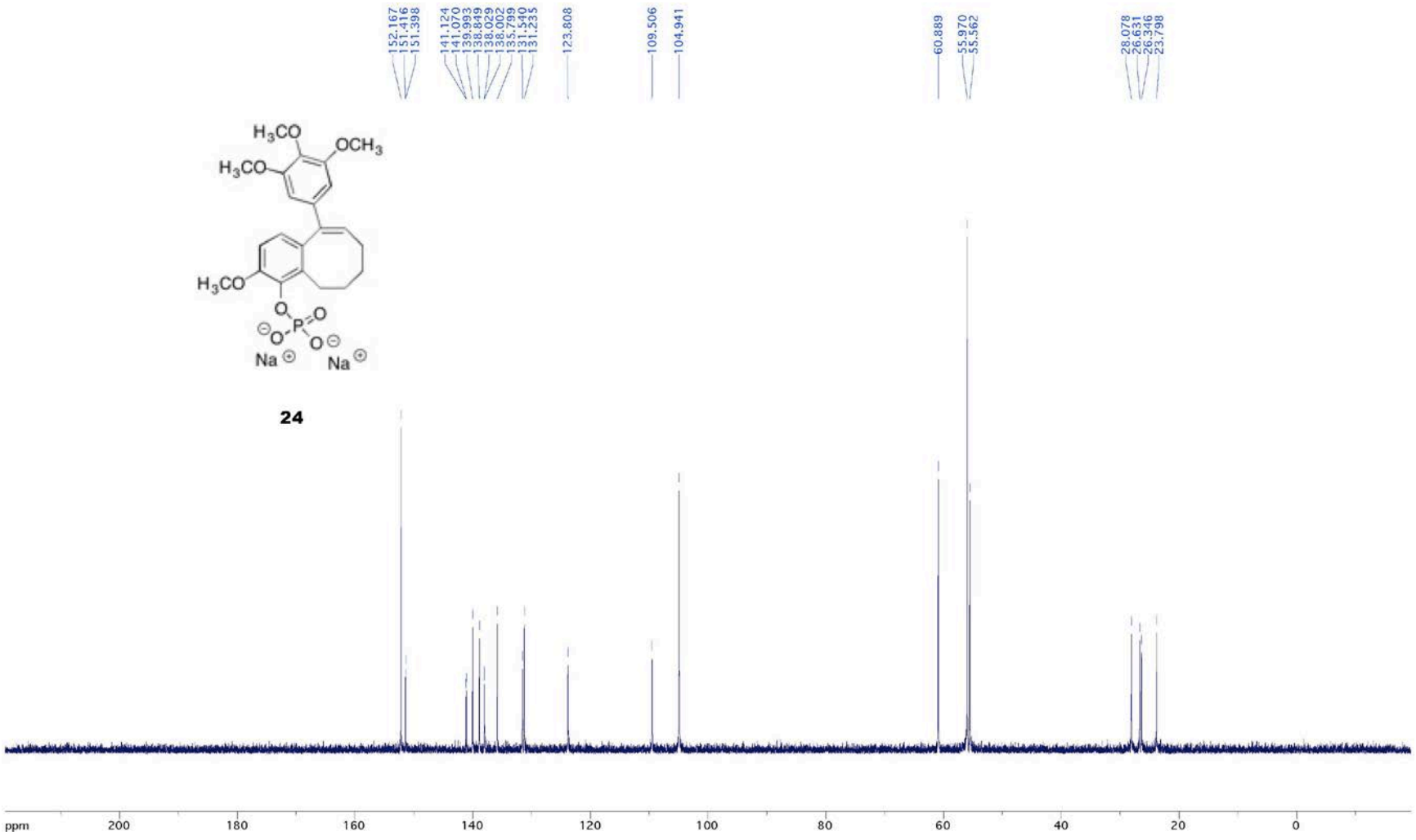
1.12
1.25
12
10
8
6
4
2
0
-2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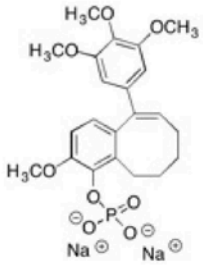
151.416
151.398
141.124
141.070
139.993
138.849
138.029
138.002
135.799
131.340
131.235
123.808
109.506
104.941
60.889
55.970
55.562
28.078
26.631
26.346
23.798
H3CO
OCH3
H3CO
H3CO
O
O
P
O
O
O
Na
Na
ppm
200
180
160
140
120
100
80
60
40
20
0

24



24

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_5_150000001.D
Sample Name: CAH_5_150

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Acq. Operator   : christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 1/19/2016 1:07:33 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 1/19/2016 1:04:30 PM by christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\CAH_5_150000001.D\DA.M (MASTERMETHOD.M)
Last changed    : 1/19/2016 1:58:42 PM by christine
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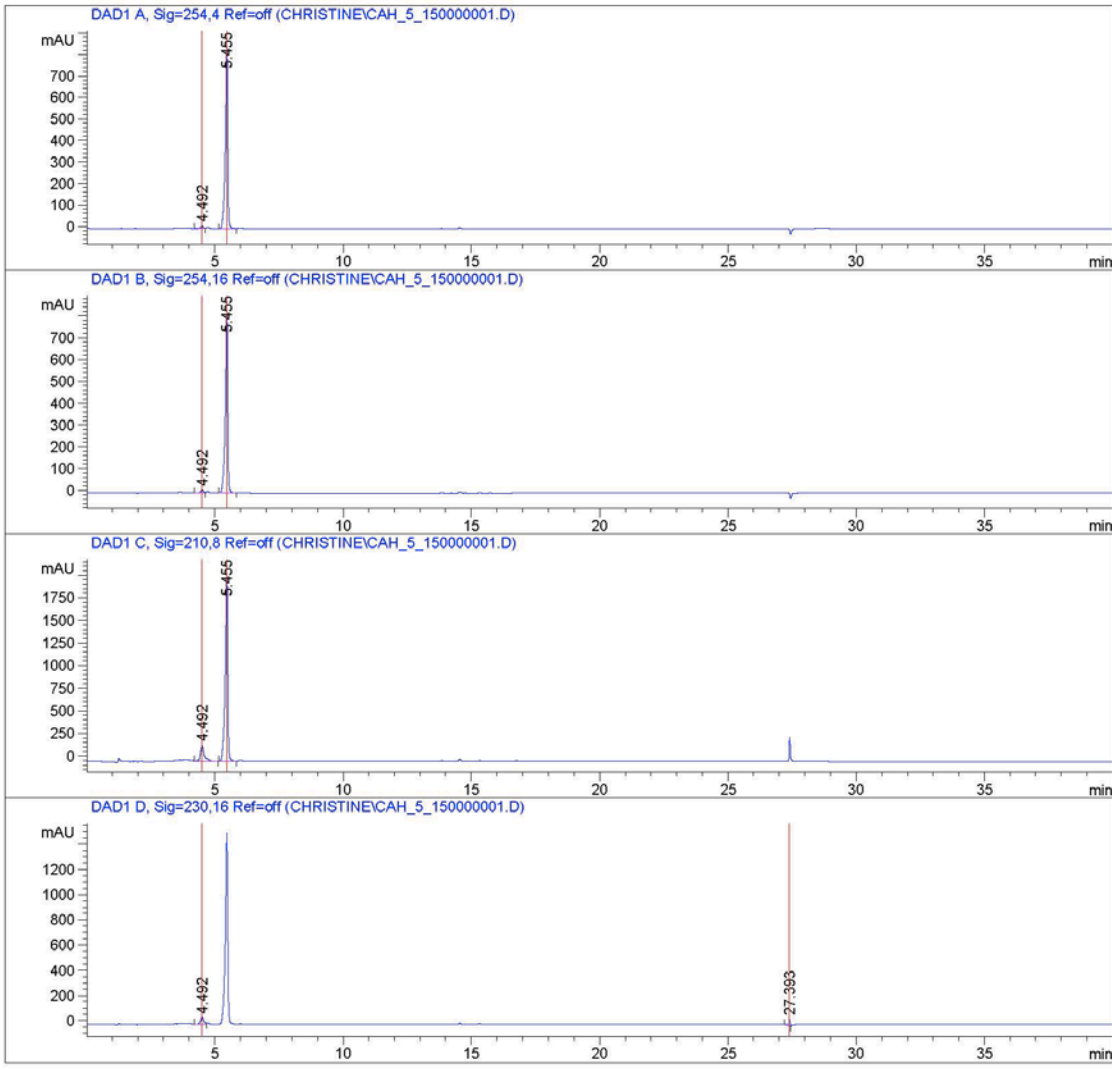
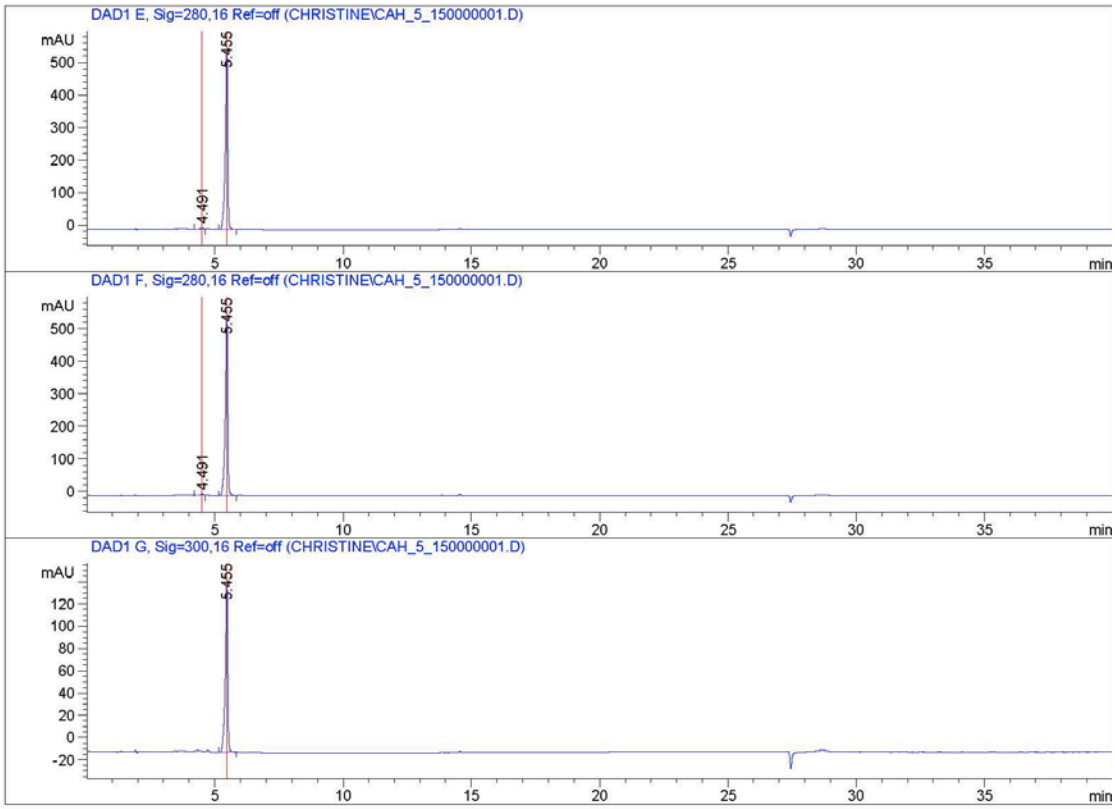


Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_5_150000001.D
Sample Name: CAH_5_150



==========

Area Percent Report

==========

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.492	BV	0.1295	91.48150	10.72987	1.5876
2	5.455	BV	0.0955	5670.79883	876.42407	98.4124

Totals : 5762.28033 887.15394

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_5_150000001.D
Sample Name: CAH_5_150

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.492	BV	0.1298	105.85542	12.38030	1.8594
2	5.455	BV	0.0955	5587.14062	863.45483	98.1406
Totals :				5692.99605	875.83513	

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.492	BB	0.1491	1733.28137	172.71095	10.5676
2	5.455	BV	0.1022	1.46685e4	2132.77539	89.4324
Totals :				1.64018e4	2305.48634	

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.492	BV	0.1383	472.28870	51.84144	70.2817
2	27.393	BB	0.0564	199.70493	52.48211	29.7183
Totals :				671.99362	104.32355	

Signal 5: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.491	BV	0.1358	47.16594	5.10381	1.2332
2	5.455	BV	0.0956	3777.51514	583.23889	98.7668
Totals :				3824.68107	588.34271	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_5_150000001.D
Sample Name: CAH_5_150

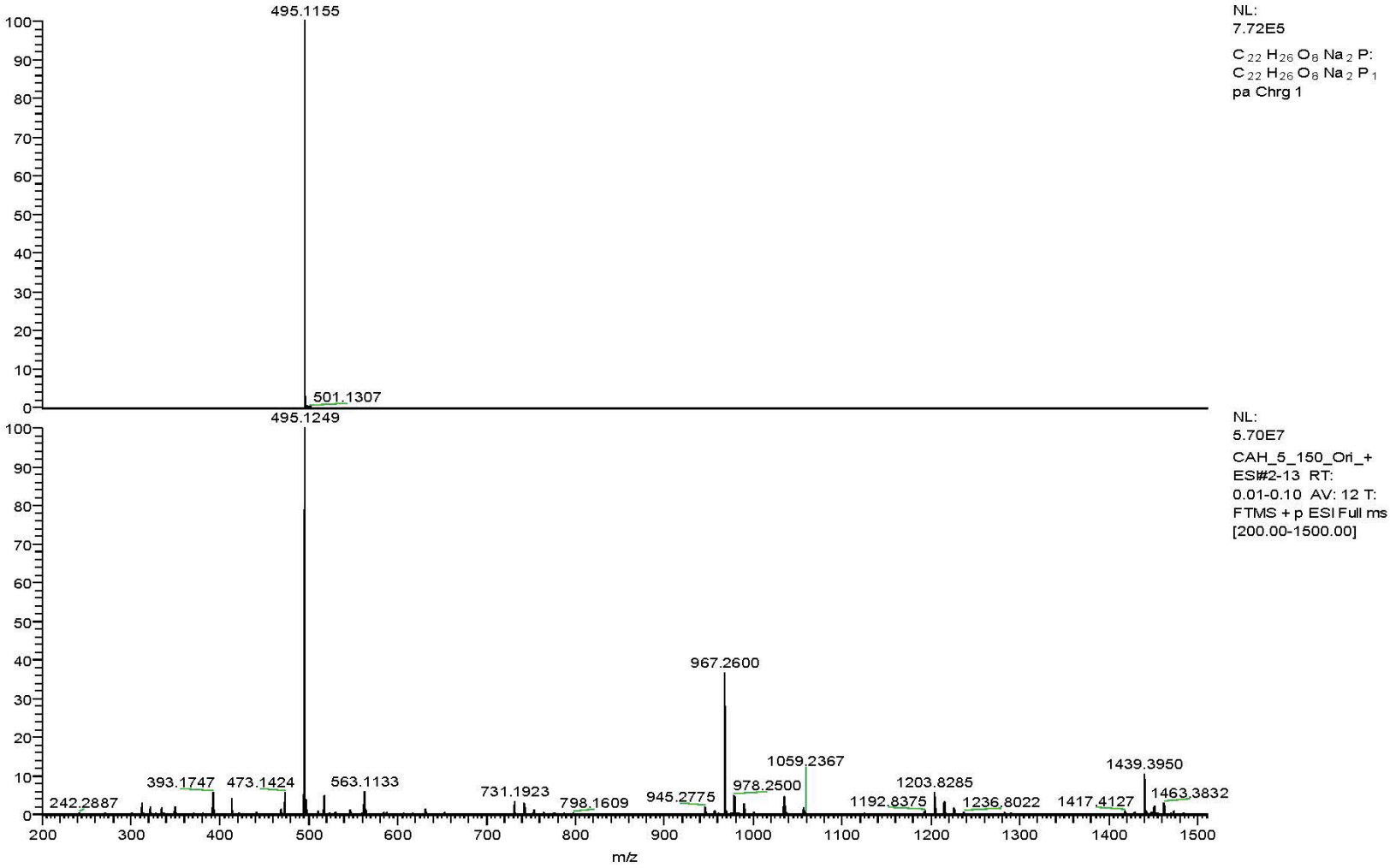
Signal 6: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.491	BV	0.1358	47.16594	5.10381	1.2332
2	5.455	BV	0.0956	3777.51514	583.23889	98.7668
Totals :				3824.68107	588.34271	

Signal 7: DAD1 G, Sig=300,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.455	BB	0.0960	1050.76099	161.39412	100.0000
Totals :				1050.76099	161.39412	

*** End of Report ***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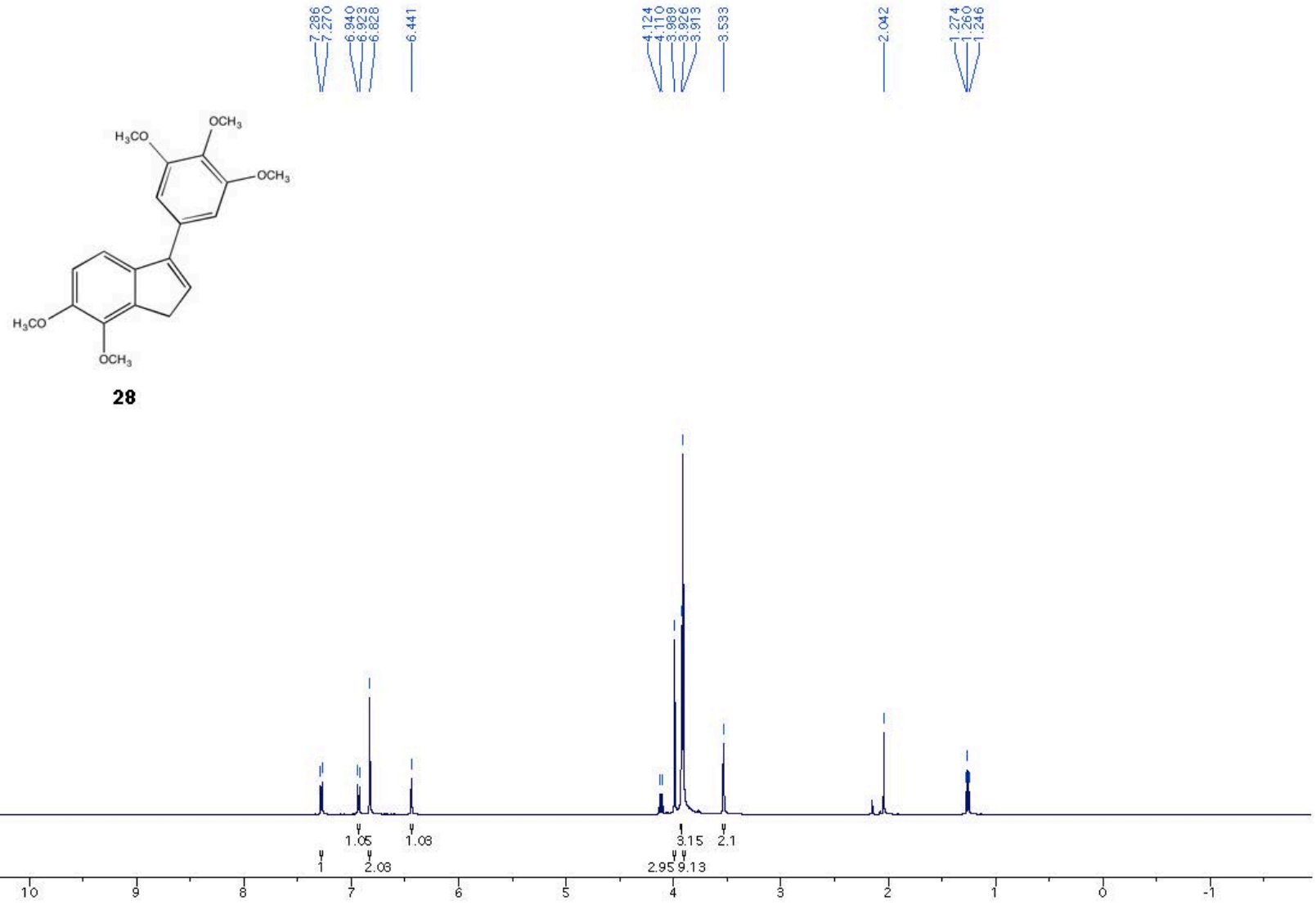
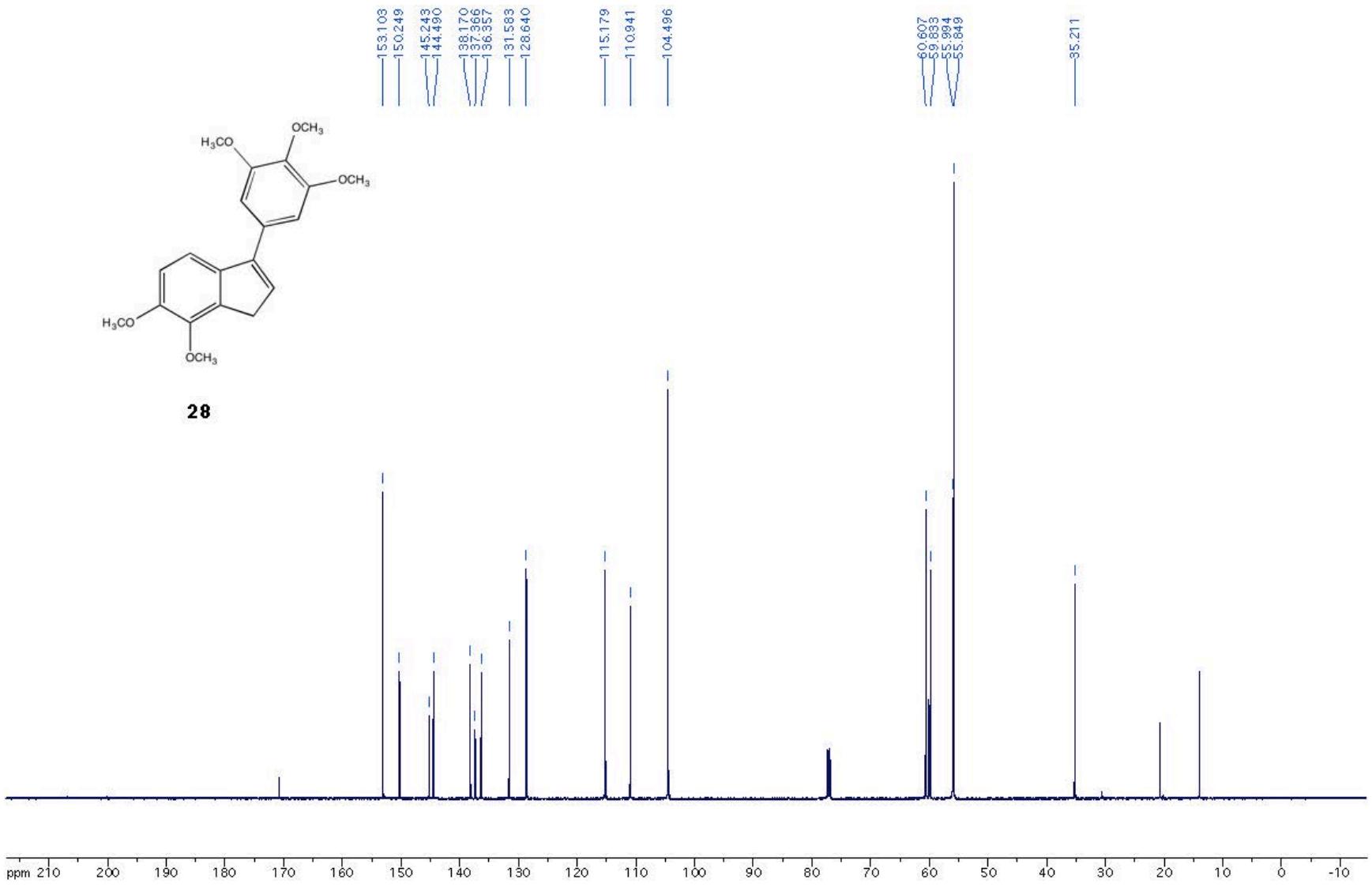
501.1307
NL:
7.72E5
C 22 H 26 O 8 Na 2 P:
C 22 H 26 O 8 Na 2 P 1
pa Chrg 1
495.1249
NL:
5.70E7
CAH_5_150_Ori_+
ESI#2-13 RT:
0.01-0.10 AV: 12 T:
FTMS + p ESI Full ms
[200.00-1500.00]
967.2600
1059.2367
1439.3950
393.1747
473.1424
563.1133
731.1923
978.2500
1203.8285
1463.3832
242.2887
798.1609
945.2775
1192.8375
1236.8022
1417.4127
m/z


7.286
7.270
6.940
6.923
6.828
6.441
4.124
4.110
3.989
3.926
3.913
3.533
2.042
1.274
1.260
1.246
H3CO
OCH3
OCH3
H3CO
OCH3
28
1
1.05
2.08
1.08
2.95
9.13
3.15
2.1
11
10
9
8
7
6
5
4
3
2
1
0
-1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144.490
138.170
137.366
136.357
131.583
128.640
115.179
110.941
104.496
60.607
59.833
55.994
55.849
35.211
H3CO
OCH3
OCH3
H3CO
OCH3
28
ppm 210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-4-54000002.D
Sample Name: CAH-4-54

```
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Acq. Operator   : christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 7/21/2014 2:36:52 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 7/21/2014 2:31:17 PM by christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\CAH-4-54000002.D\DA.M (MASTERMETHOD.M)
Last changed    : 7/21/2014 4:13:46 PM by christine
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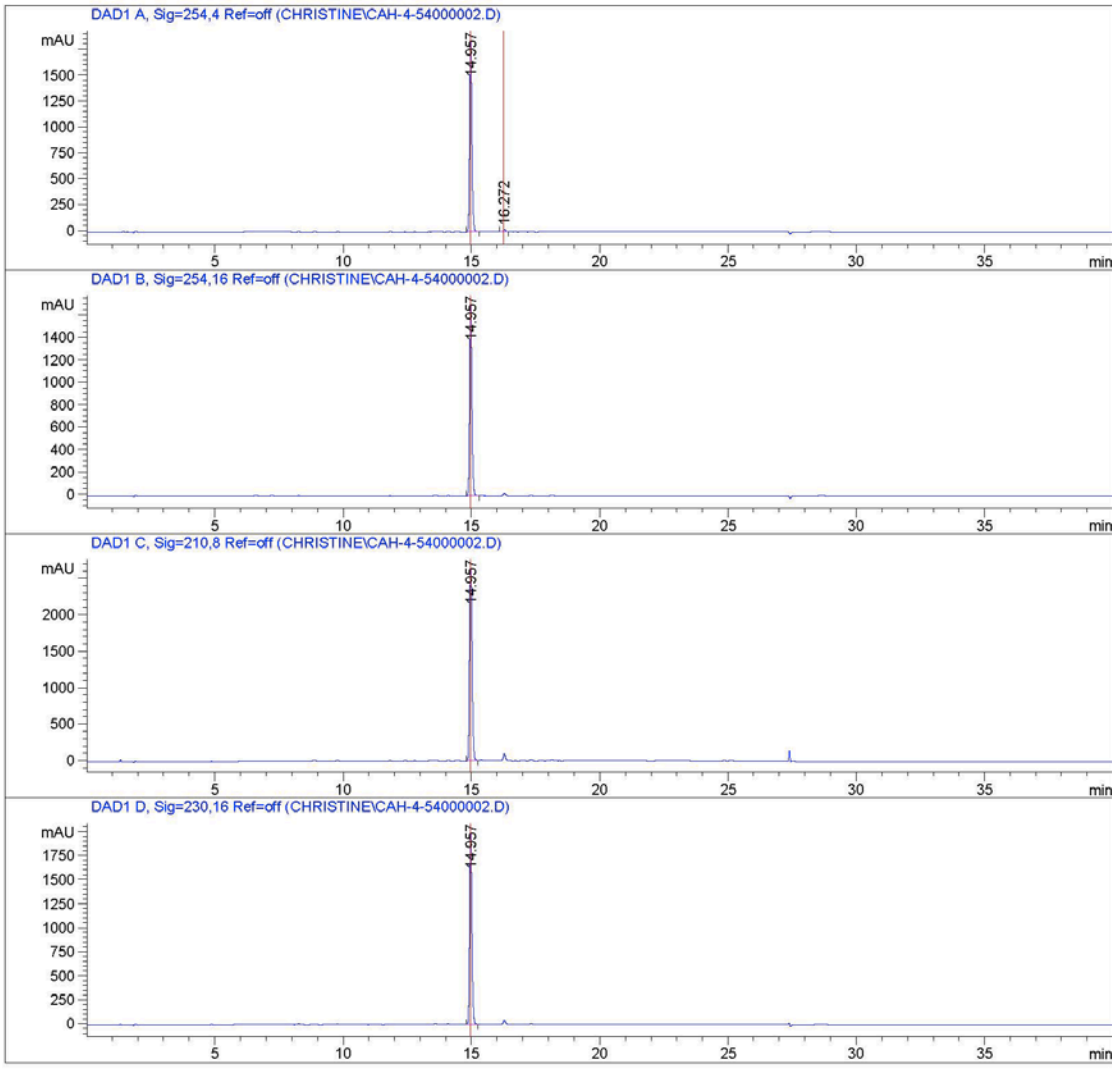
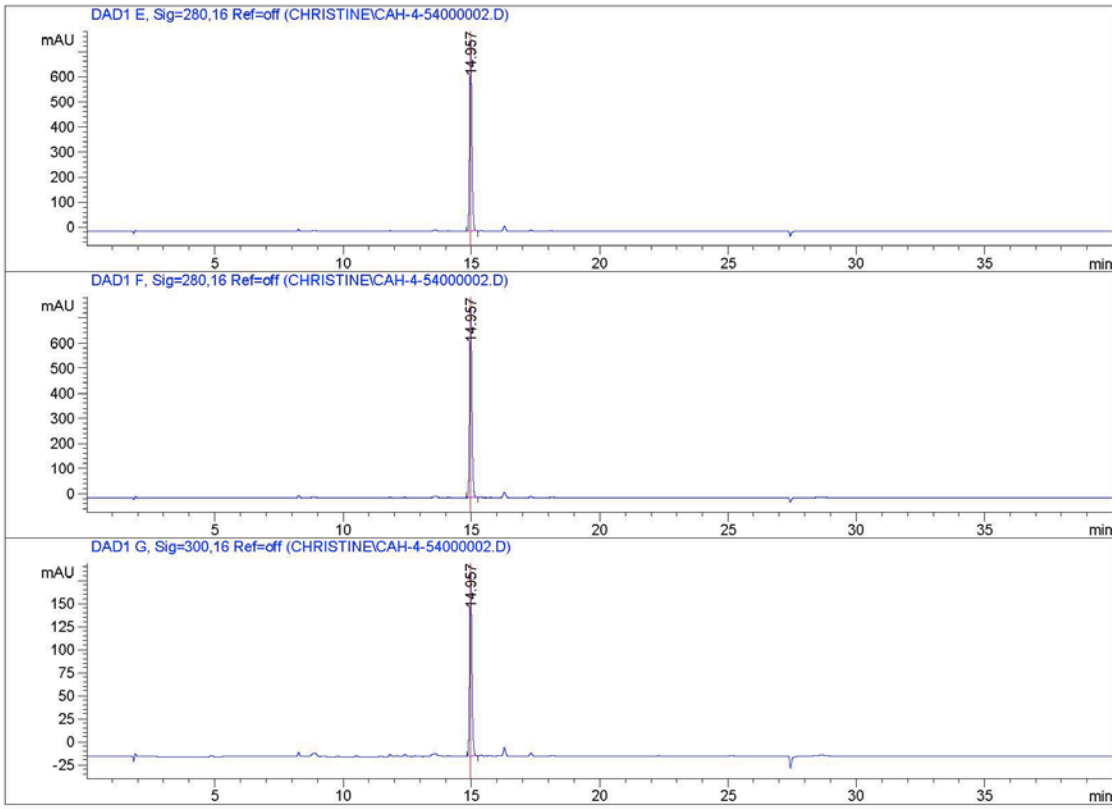


Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-4-54000002.D
Sample Name: CAH-4-54



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Area Percent Report

==========

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.957	BV	0.0962	1.14170e4	1843.72681	98.7691
2	16.272	BV	0.0979	142.28862	22.46073	1.2309

Totals : 1.15593e4 1866.18753

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-4-54000002.D
Sample Name: CAH-4-54

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.957	BV	0.0960	1.05029e4	1702.27014	100.0000
Totals :				1.05029e4	1702.27014	

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.957	BV	0.1179	1.93357e4	2627.26172	100.0000
Totals :				1.93357e4	2627.26172	

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.957	BV	0.0977	1.25838e4	1992.09021	100.0000
Totals :				1.25838e4	1992.09021	

Signal 5: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.957	BB	0.0951	4634.12646	760.19556	100.0000
Totals :				4634.12646	760.19556	

Signal 6: DAD1 F, Sig=280,16 Ref=off

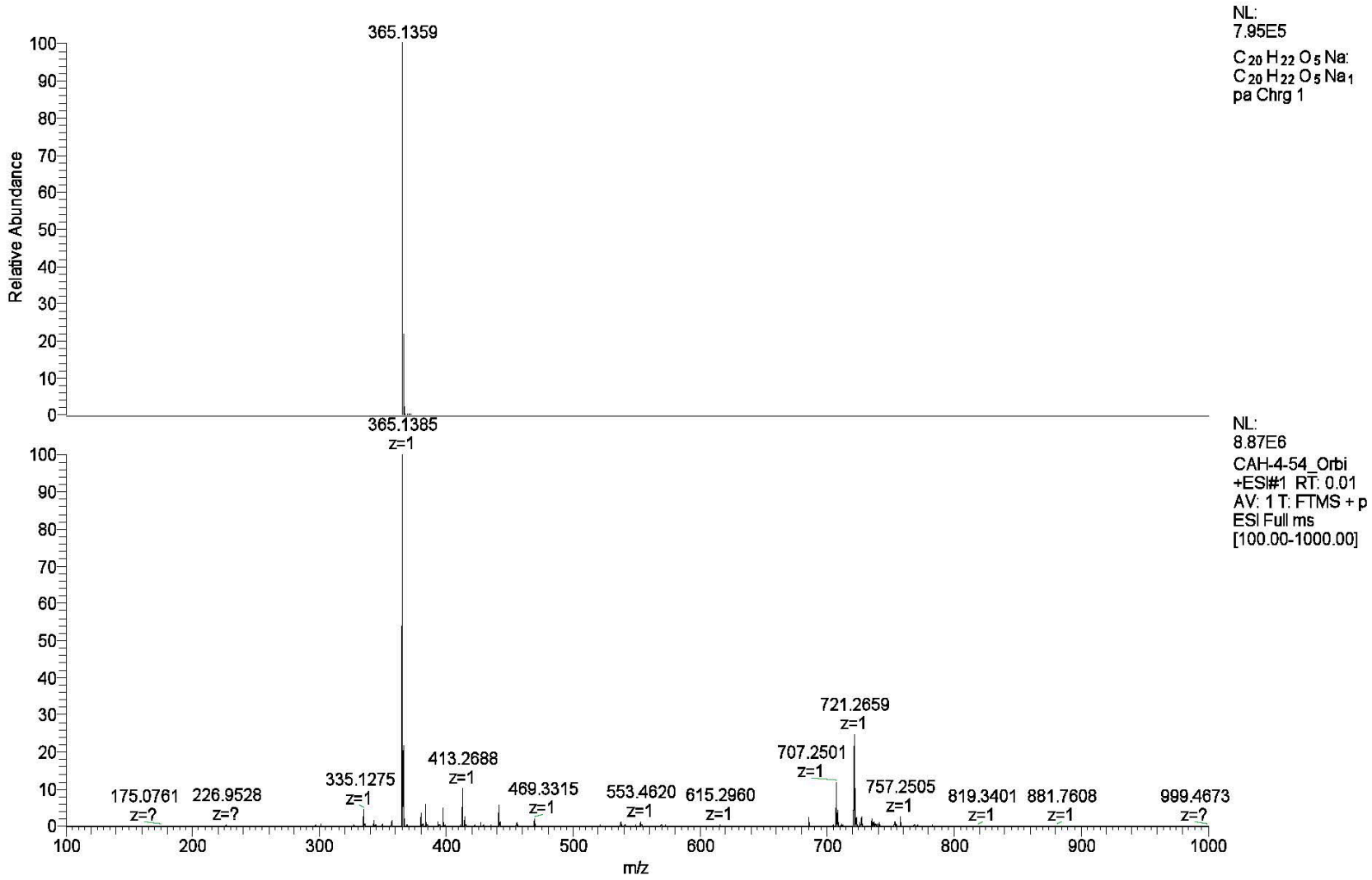
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.957	BB	0.0951	4634.12646	760.19556	100.0000
Totals :				4634.12646	760.19556	

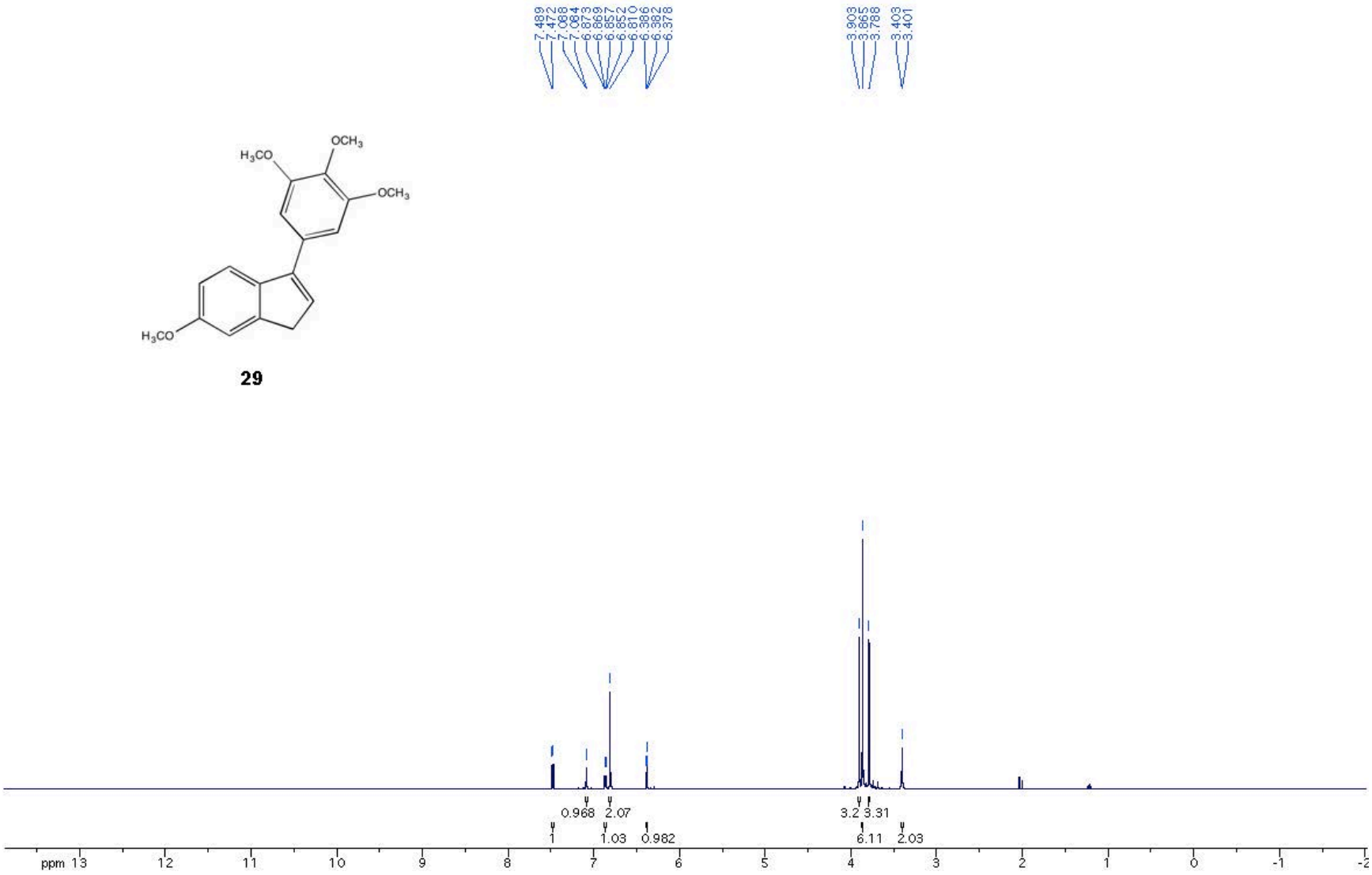
Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-4-54000002.D
Sample Name: CAH-4-54

Signal 7: DAD1 G, Sig=300,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.957	BB	0.0952	1213.09326	198.69473	100.0000
Totals :				1213.09326	198.69473	

*** End of Report ***


NL:
7.95E5
C20 H22 O5 Na:
C20 H22 O5 Na1
pa Chrg 1
365.1359
Relative Abundance
NL:
8.87E6
CAH-4-54_Orbi
+ESI#1 RT: 0.01
AV: 1 T: FTMS + p
ESI Full ms
[100.00-1000.00]
365.1385
z=1
175.0761
z=?
226.9528
z=?
335.1275
z=1
413.2688
z=1
469.3315
z=1
553.4620
z=1
615.2960
z=1
707.2501
z=1
721.2659
z=1
757.2505
z=1
819.3401
z=1
881.7608
z=1
999.4673
z=?
m/z


7.489
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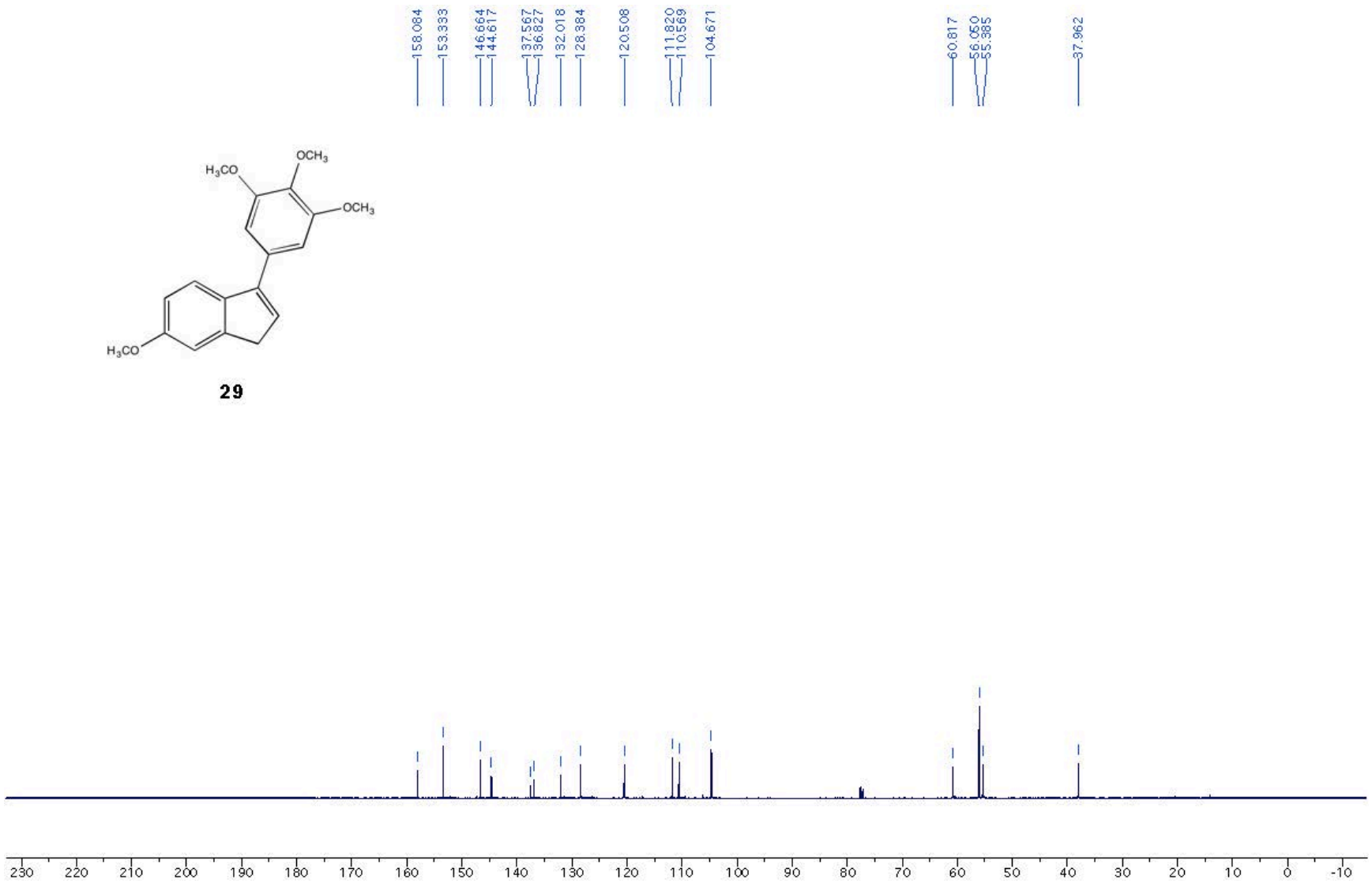
6.869
6.857
6.852
6.810
6.386
6.382
6.378
3.903
3.865
3.788
3.403
3.401
H3CO
OCH3
OCH3
H3CO
0.968
2.07
1.03
0.982
3.2
3.31
6.11
2.03
ppm 13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2

29


158.084
153.333
146.664
144.617
137.567
136.827
132.018
128.384
120.508
111.820
110.569
104.671
60.817
56.050
55.385
37.962
OCH3
H3CO
OCH3
H3CO
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

29

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_77000001.D
Sample Name: CAH_4_77

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Acq. Operator   : Christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 8/20/2014 12:17:48 PM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 8/20/2014 10:28:06 AM by Christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\CAH_4_77000001.D\DA.M (MASTERMETHOD.M)
Last changed    : 8/20/2014 1:08:14 PM by Christine
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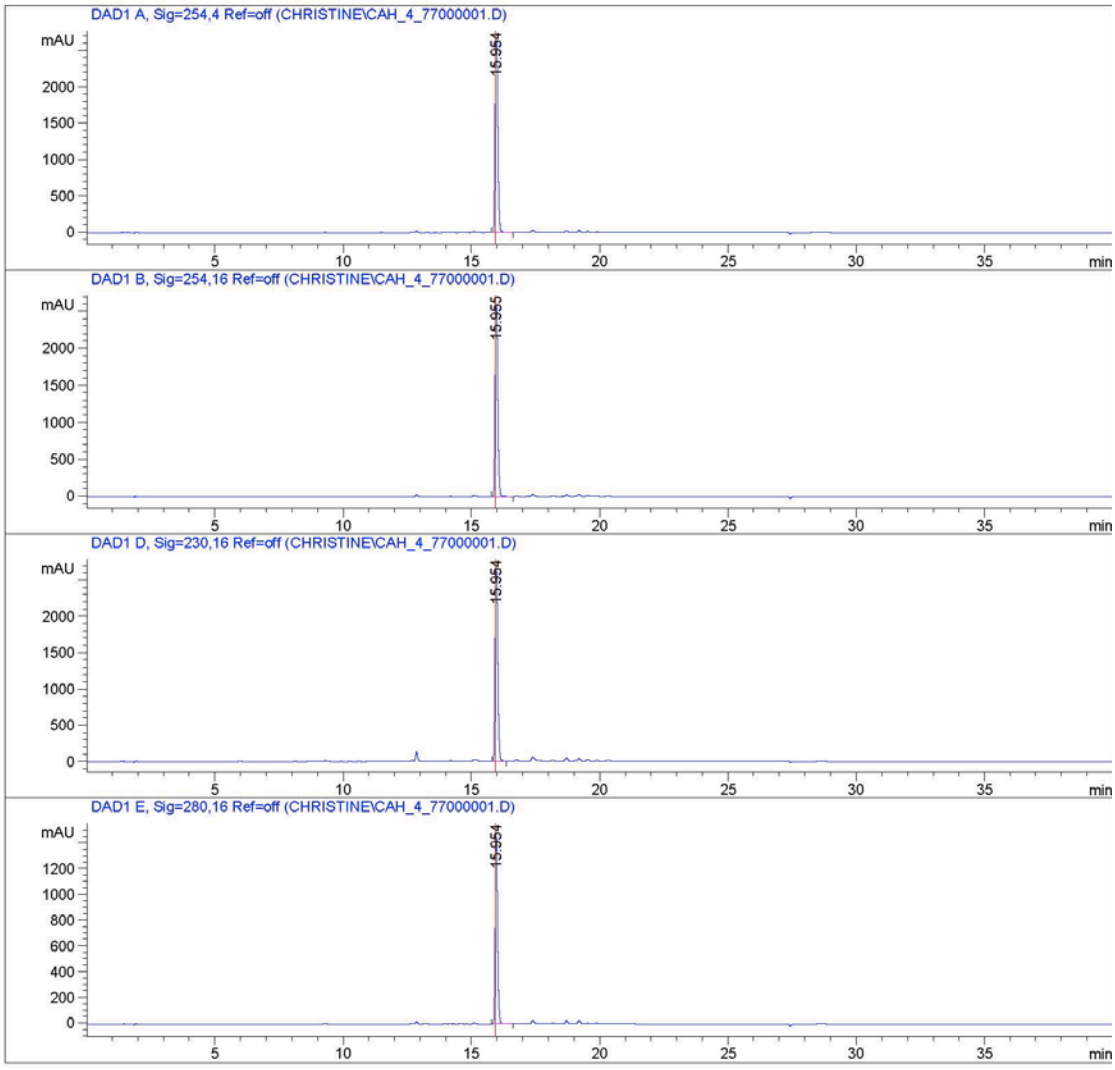
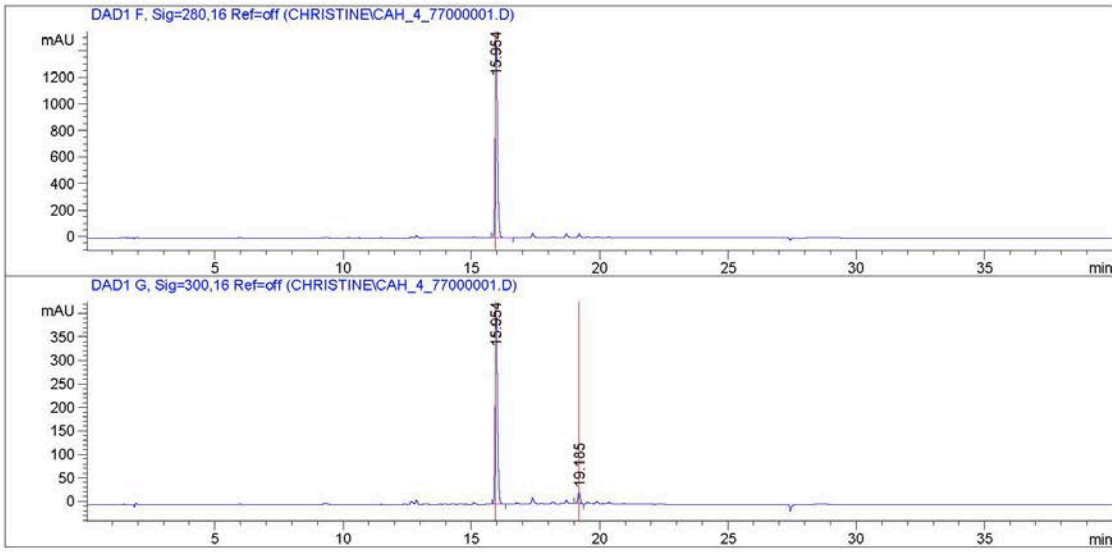


Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_77000001.D
Sample Name: CAH_4_77



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.954	BV	0.1202	1.98992e4	2632.82886	100.0000
Totals :				1.98992e4	2632.82886	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.955	BV	0.1145	1.87492e4	2588.72656	100.0000
Totals :				1.87492e4	2588.72656	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH_4_77000001.D
Sample Name: CAH_4_77

Signal 3: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.954	BV	0.1145	1.91852e4	2648.36694	100.0000
Totals :				1.91852e4	2648.36694	

Signal 4: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.954	BV	0.0965	9237.36035	1485.50195	100.0000
Totals :				9237.36035	1485.50195	

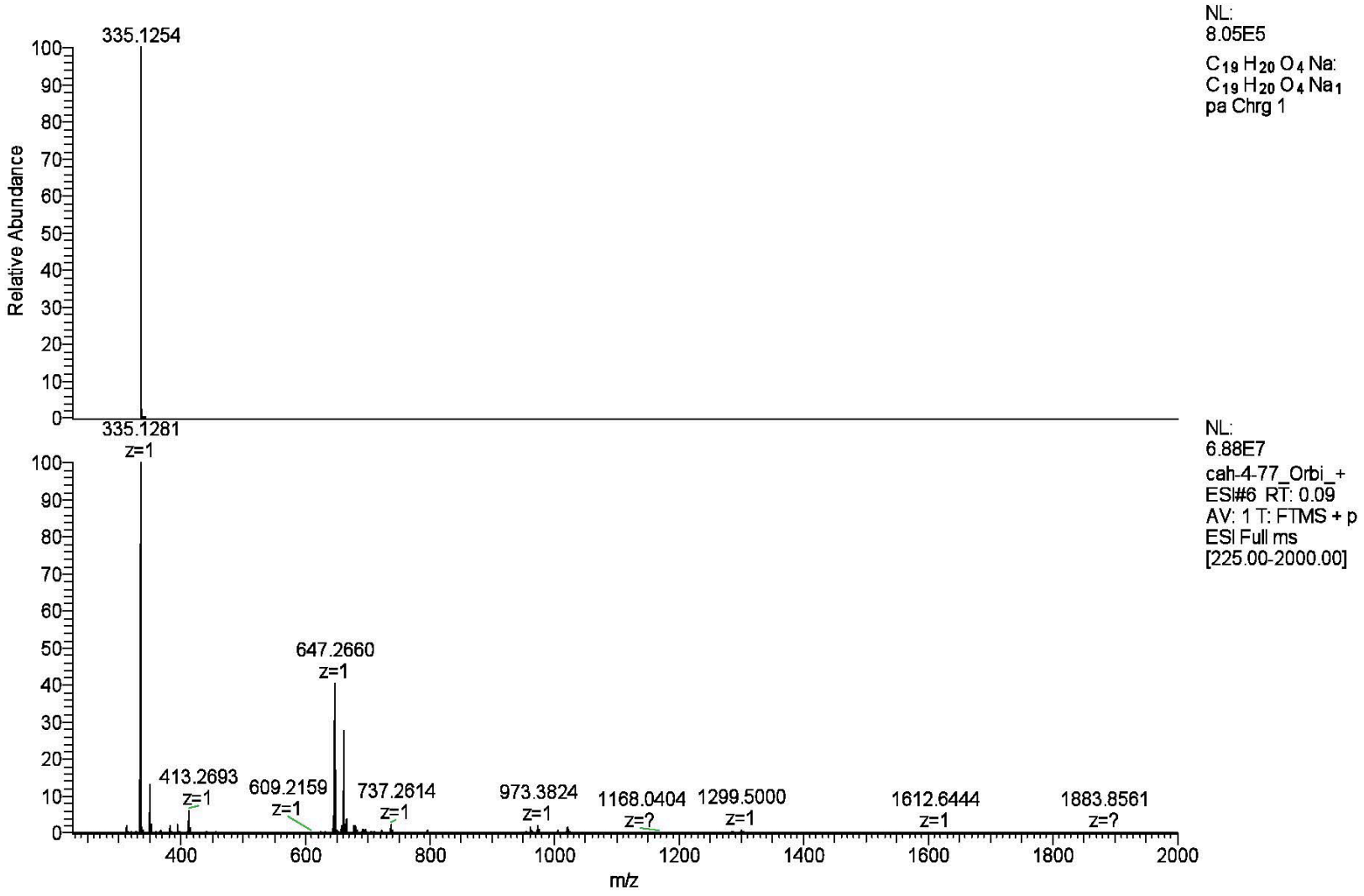
Signal 5: DAD1 F, Sig=280,16 Ref=off

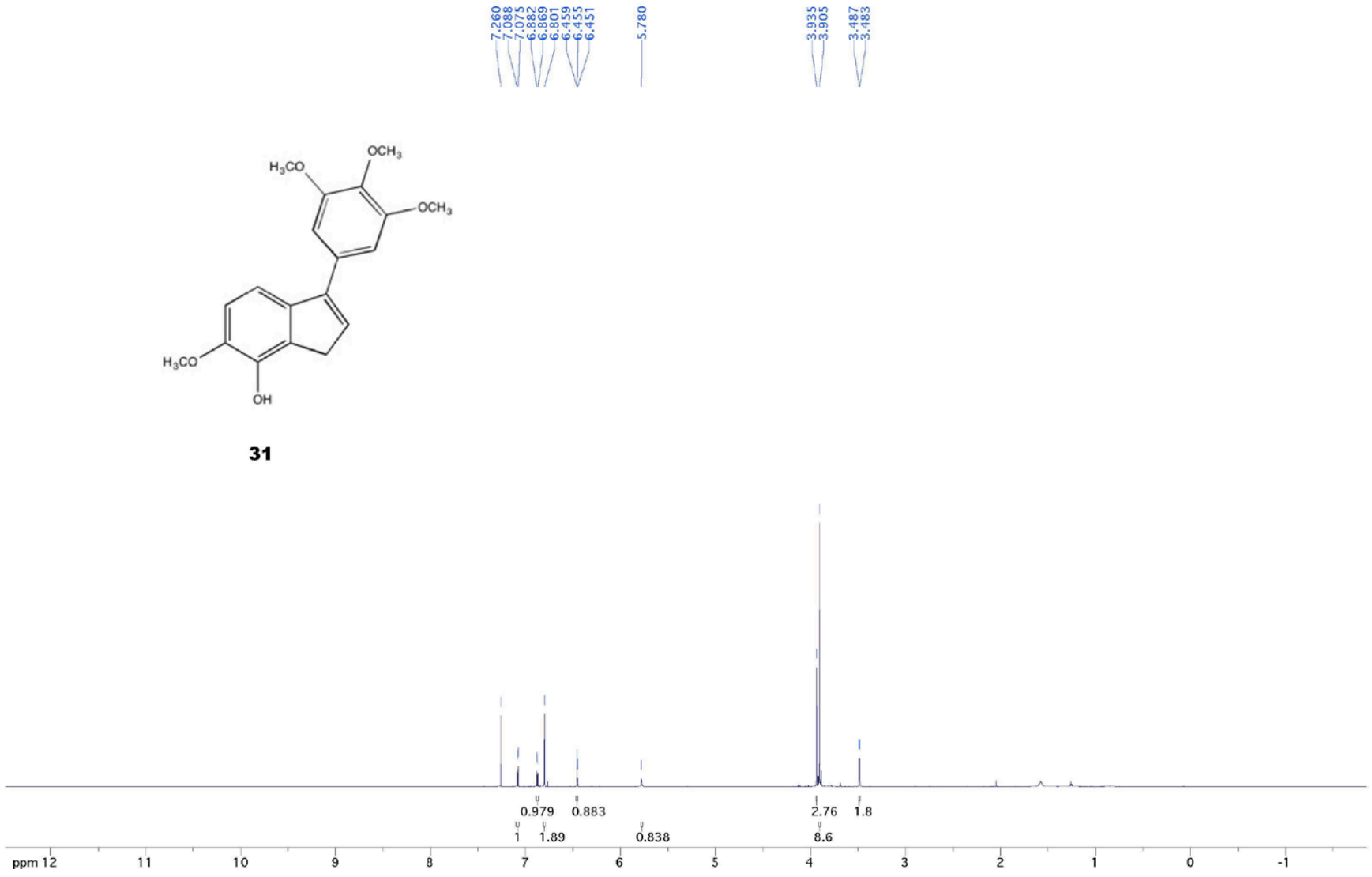
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.954	BV	0.0965	9237.36035	1485.50195	100.0000
Totals :				9237.36035	1485.50195	

Signal 6: DAD1 G, Sig=300,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.954	BB	0.0942	2545.80176	411.13858	94.1161
2	19.185	BB	0.0984	159.15662	24.96513	5.8839
Totals :				2704.95837	436.10371	

*** End of Report ***


NL:
8.05E5
C19 H20 O4 Na:
C19 H20 O4 Na1
pa Chrg 1
335.1254
Relative Abundance
NL:
6.88E7
cah-4-77_Orbi_+
ESI#6 RT: 0.09
AV: 1 T: FTMS + p
ESI Full ms
[225.00-2000.00]
335.1281
z=1
647.2660
z=1
413.2693
z=1
609.2159
z=1
737.2614
z=1
973.3824
z=1
1168.0404
z=?
1299.5000
z=1
1612.6444
z=1
1883.8561
z=?
m/z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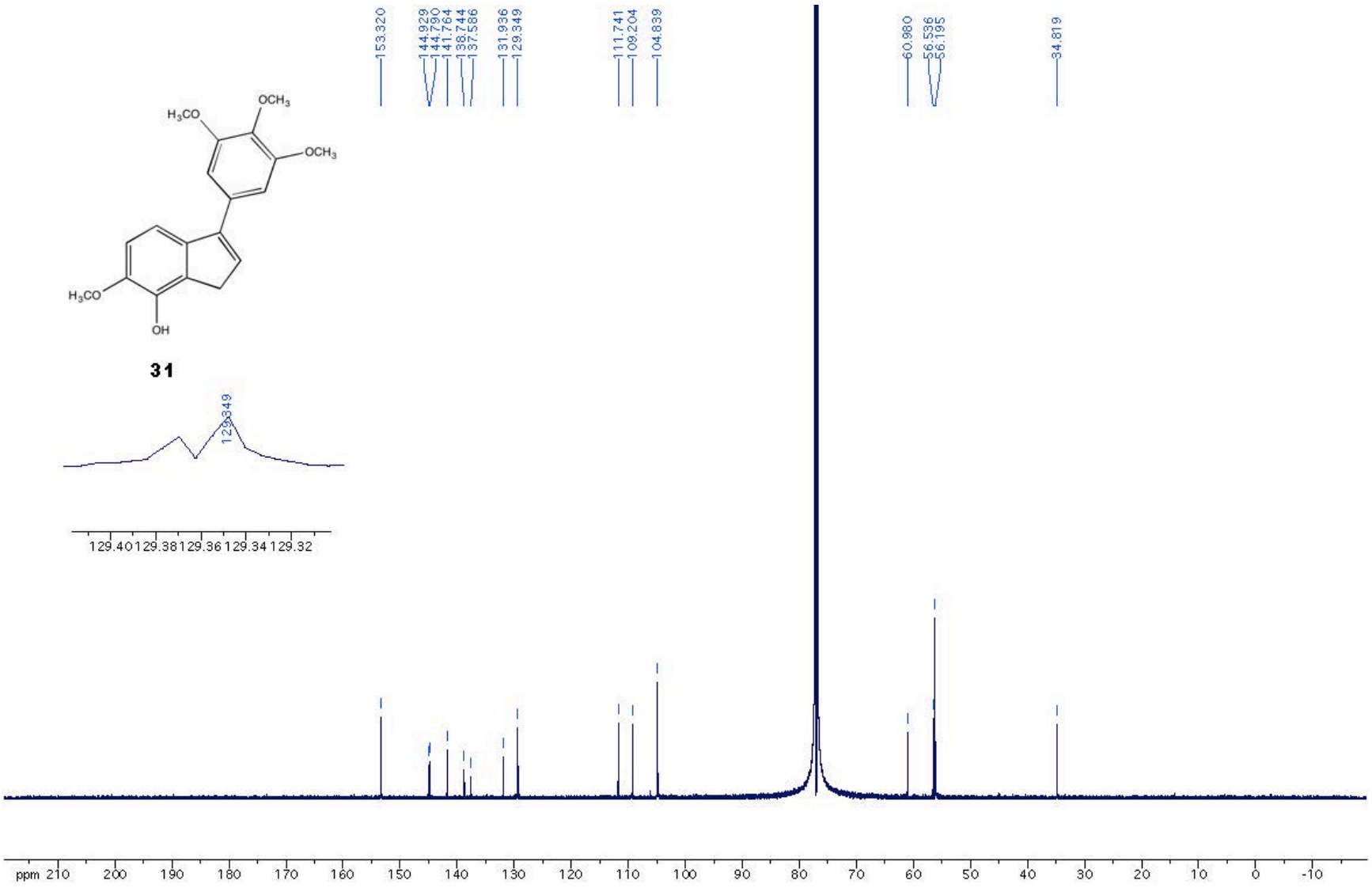
7.088
7.075
6.882
6.869
6.801
6.459
6.455
6.451
5.780
3.935
3.905
3.487
3.483
H3CO
OCH3
OCH3
H3CO
OH
0.979
0.883
2.76
1.8
1
1.89
0.838
8.6
ppm 12
11
10
9
8
7
6
5
4
3
2
1
0
-1

31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144.790
141.764
138.744
137.586
131.936
129.349
111.741
109.204
104.839
60.980
56.536
56.195
34.819
H3CO
OCH3
OCH3
H3CO
OH
31
129.349
129.40 129.38 129.36 129.34 129.32
ppm 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

Data File C:\CHEM32\1\DATA\CHRISTINE\JVL_1_103000001.D
Sample Name: JVL_1_103

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Acq. Operator   : christine
Acq. Instrument : Instrument 1                    Location :   -
Injection Date  : 9/2/2015 11:49:32 AM
Acq. Method     : C:\CHEM32\1\METHODS\MASTERMETHOD.M
Last changed    : 9/2/2015 11:46:00 AM by christine
Analysis Method : C:\CHEM32\1\DATA\CHRISTINE\JVL_1_103000001.D\DA.M (MASTERMETHOD.M)
Last changed    : 9/2/2015 1:22:35 PM by christine
Sample Info     :
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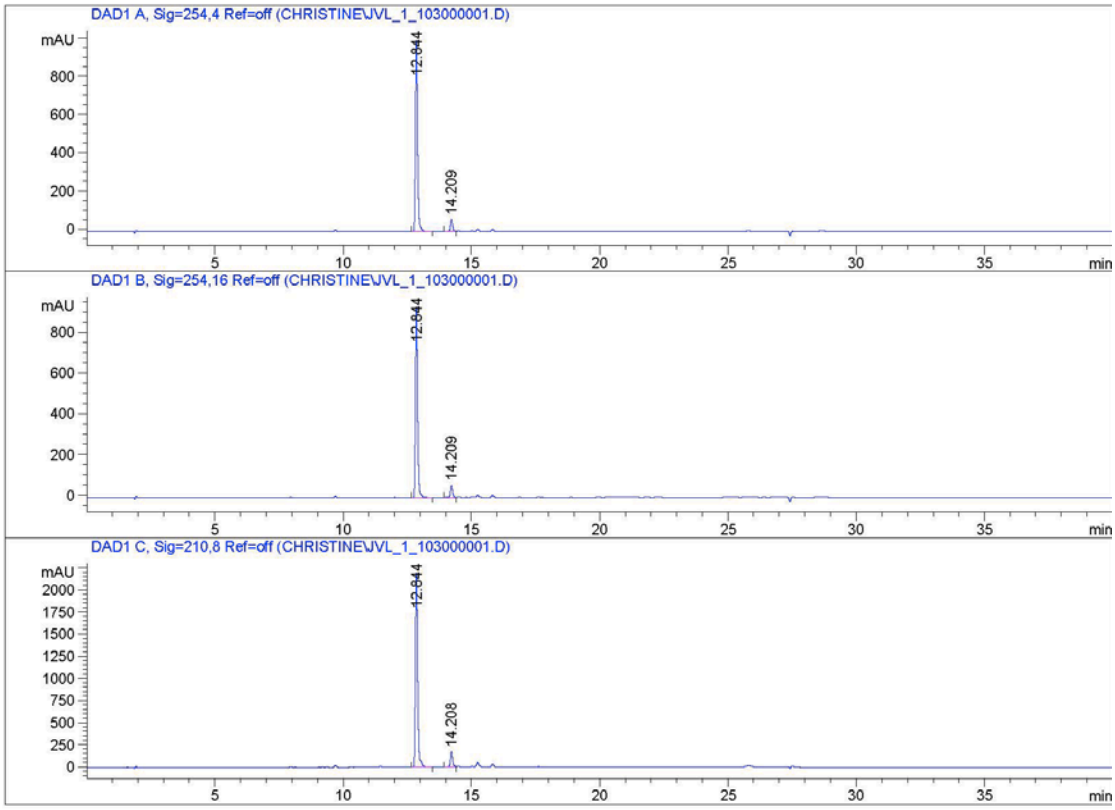

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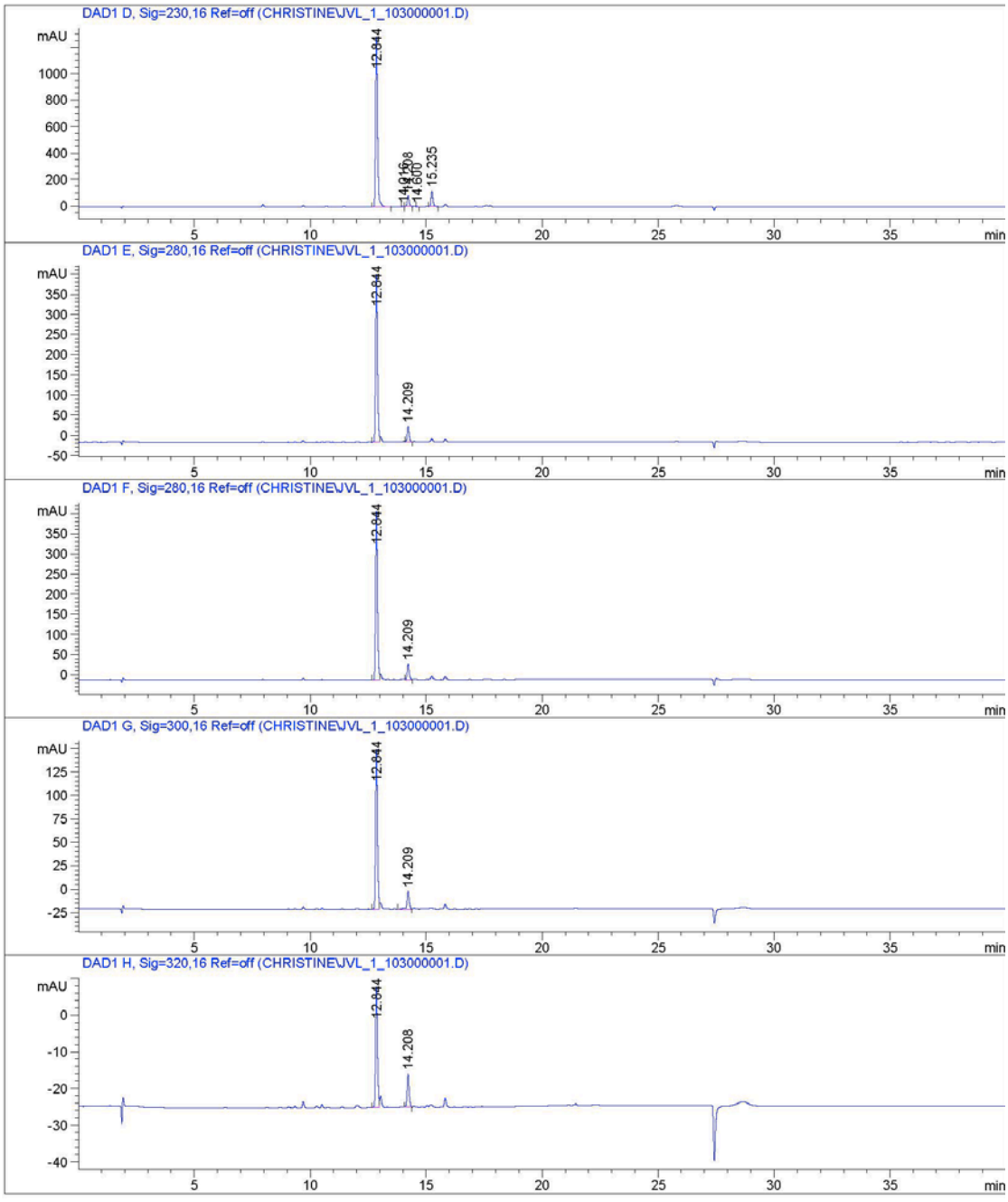
Sample Name: JVL_1_103



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Sample Name: JVL_1_103

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.844	VB	0.0879	5636.32080	997.72461	93.8211
2	14.209	VV	0.0889	371.19644	62.86393	6.1789
Totals :				6007.51724	1060.58854	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.844	VB	0.0880	5292.54199	935.98364	93.6462
2	14.209	VV	0.0893	359.09149	60.48515	6.3538
Totals :				5651.63348	996.46879	

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.844	VV	0.0925	1.32413e4	2191.42236	92.4869
2	14.208	VV	0.0904	1075.65198	178.37202	7.5131
Totals :				1.43170e4	2369.79439	

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.844	VV	0.0891	7398.26025	1285.71204	86.1586
2	14.016	VV	0.0917	9.59935	1.60752	0.1118

Data File C:\CHEM32\1\DATA\CHRISTINE\JVL_1_103000001.D
Sample Name: JVL_1_103

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
3	14.208	VB	0.0880	488.34366	83.83261	5.6871
4	14.600	VB	0.0731	5.42998	1.14918	0.0632
5	15.235	VB	0.0880	685.15985	117.48914	7.9792
Totals :				8586.79310	1489.79048	

Signal 5: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.844	BV	0.0868	2311.47363	416.20947	90.9454
2	14.209	VV	0.0889	230.13258	38.96600	9.0546
Totals :				2541.60622	455.17548	

Signal 6: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.844	BV	0.0868	2311.47461	416.20947	90.9454
2	14.209	VV	0.0889	230.13316	38.96600	9.0546
Totals :				2541.60777	455.17548	

Signal 7: DAD1 G, Sig=300,16 Ref=off

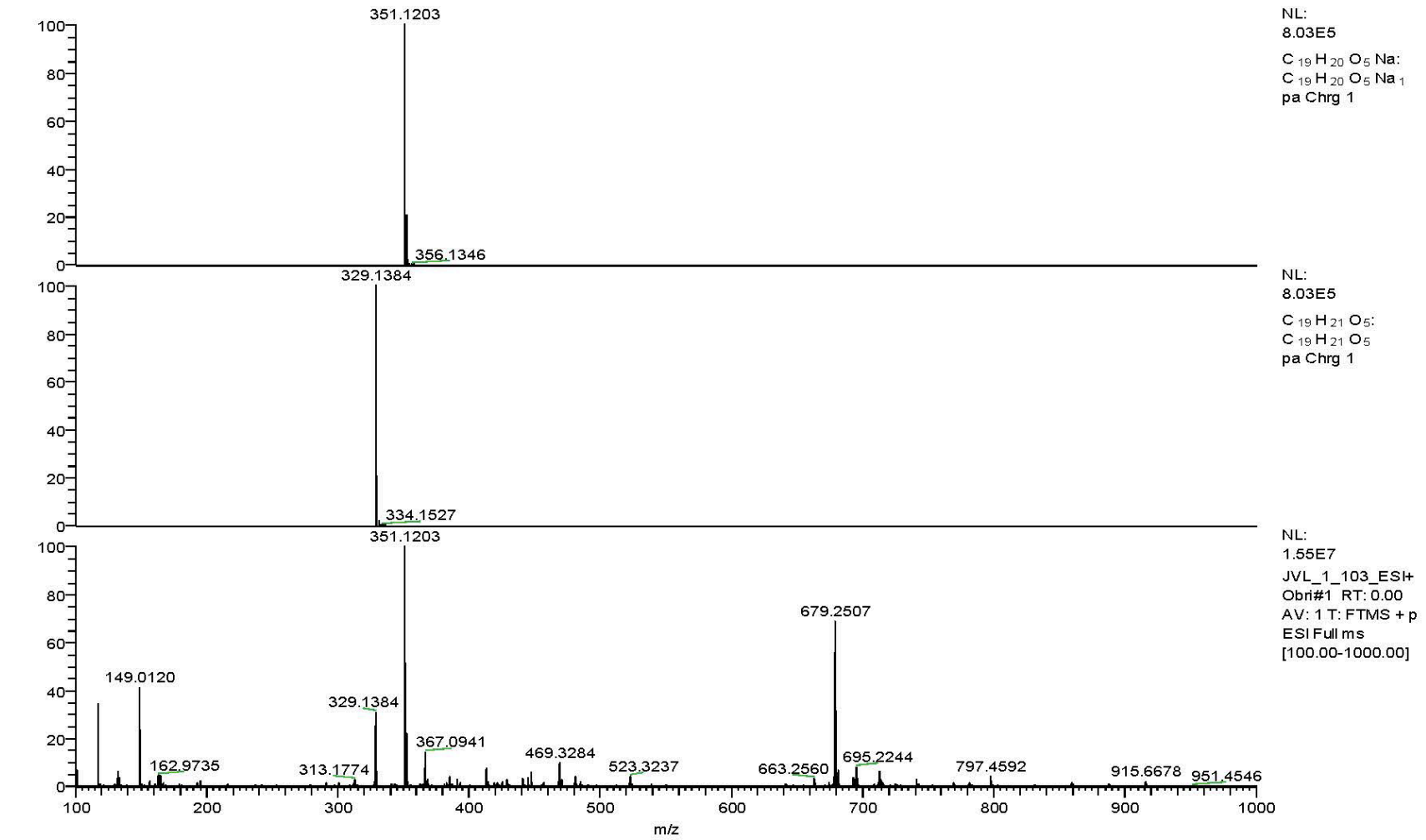
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.844	BV	0.0868	944.62726	170.05644	88.5016
2	14.209	BV	0.0946	122.72880	19.20041	11.4984
Totals :				1067.35606	189.25686	

Signal 8: DAD1 H, Sig=320,16 Ref=off

Data File C:\CHEM32\1\DATA\CHRISTINE\JVL_1_103000001.D
Sample Name: JVL_1_103

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.844	BV	0.0875	183.99568	32.77533	77.8242
2	14.208	BB	0.0874	52.42920	9.07247	22.1758
Totals :				236.42488	41.84780	

*** End of Report ***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C 19 H 20 O 5 Na:
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pa Chrg 1
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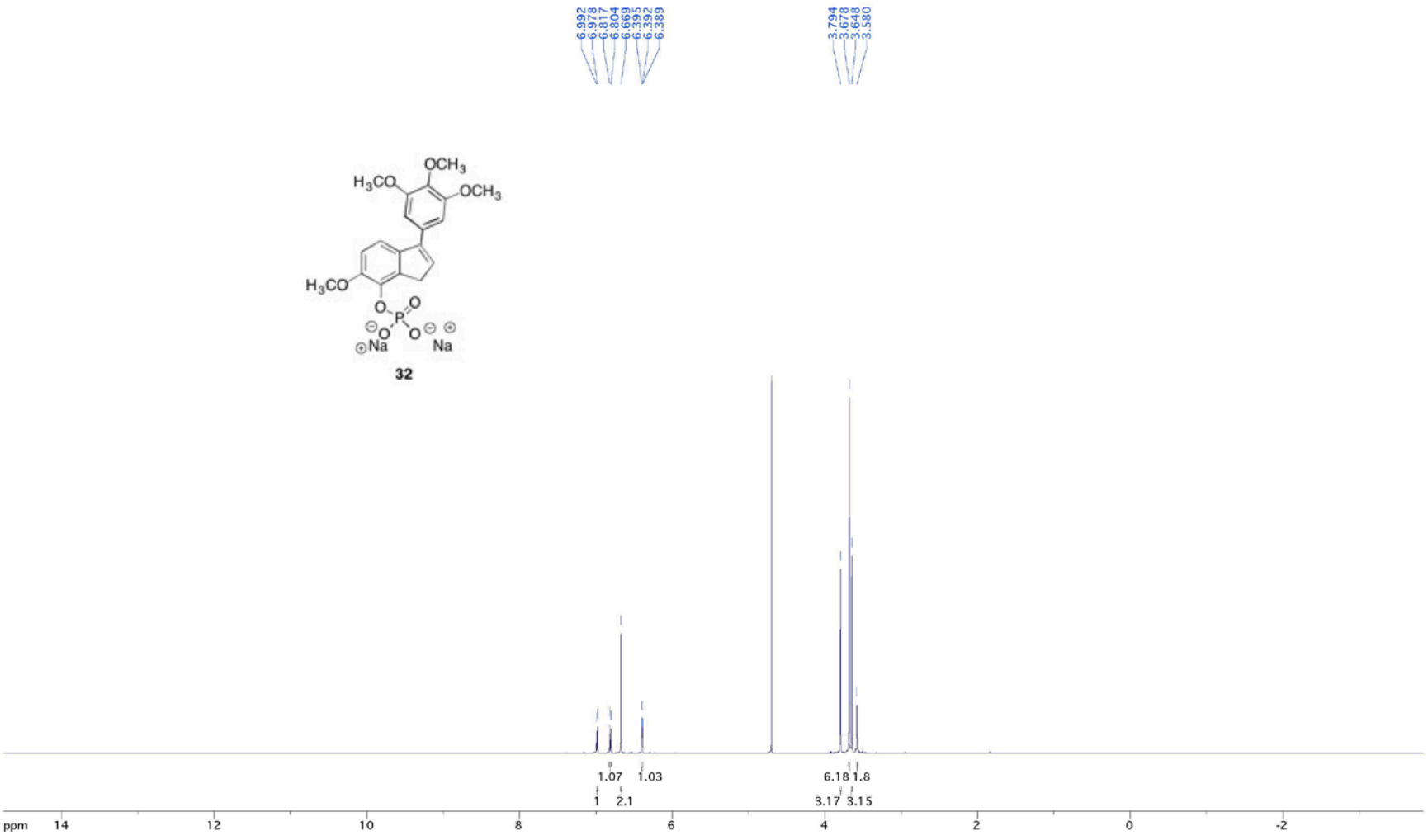
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1.03
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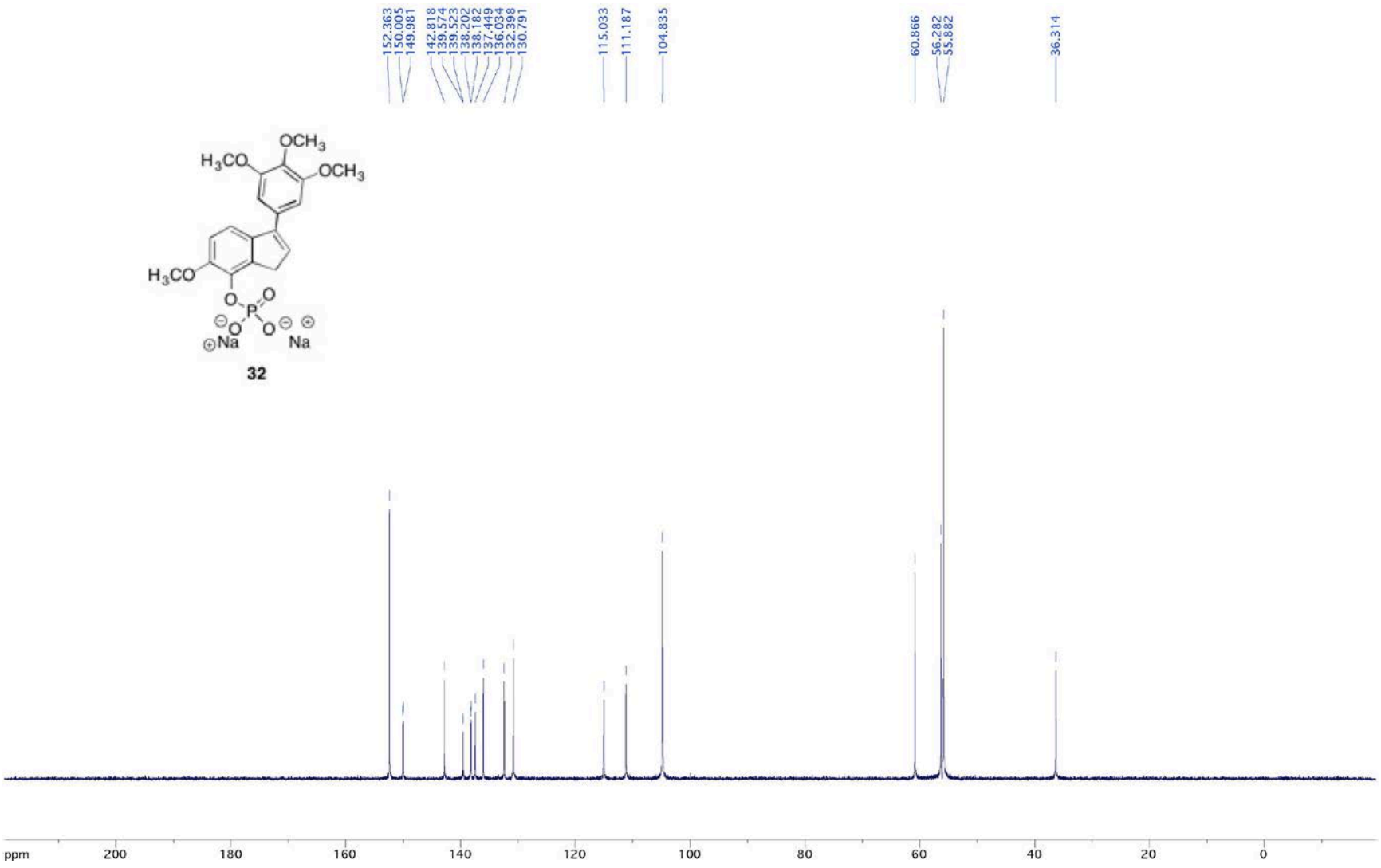
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H3CO
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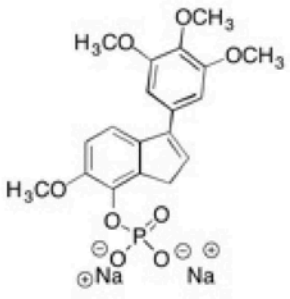

32

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-6-24000001.D
Sample Name: CAH-6-24

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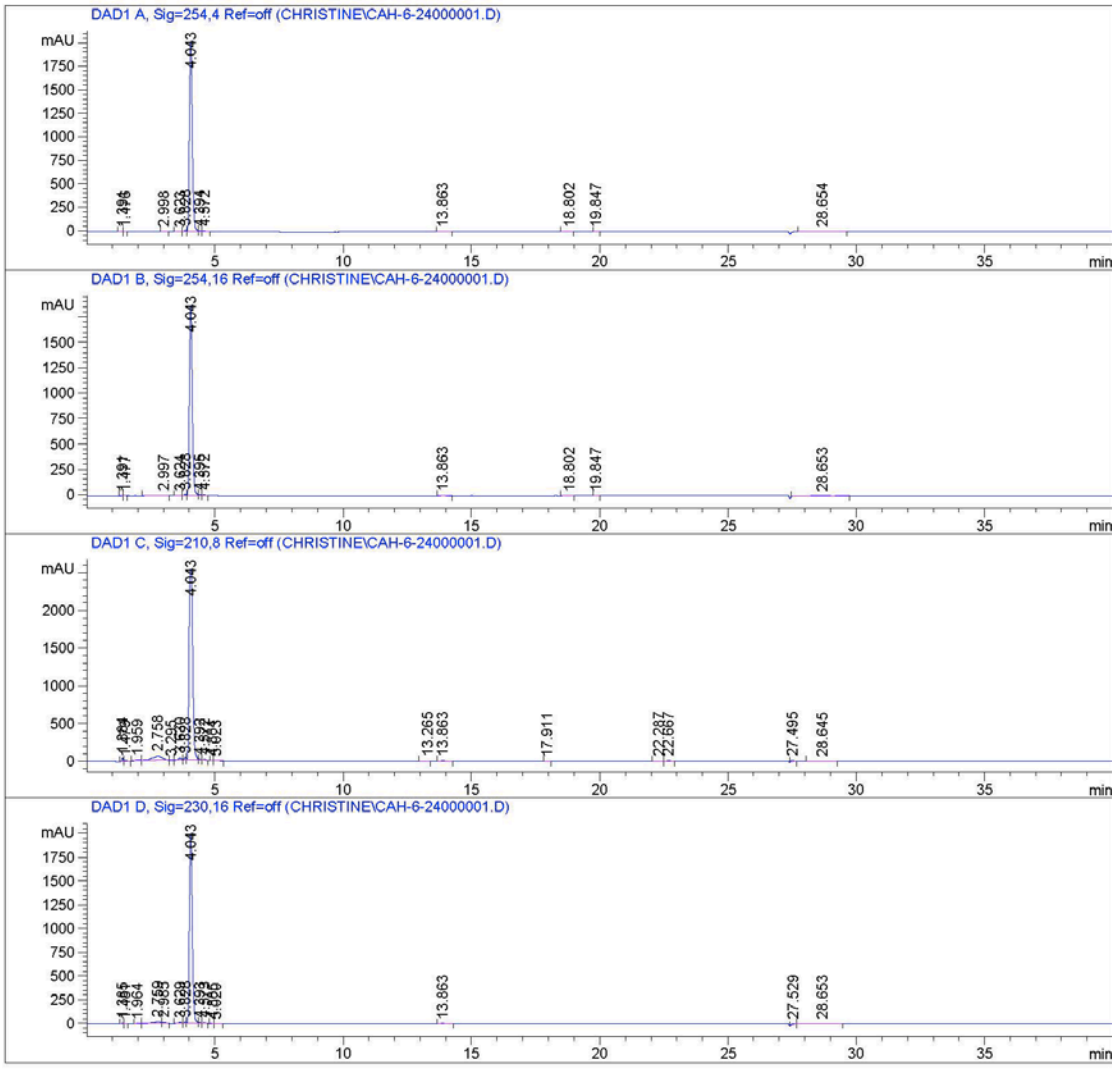

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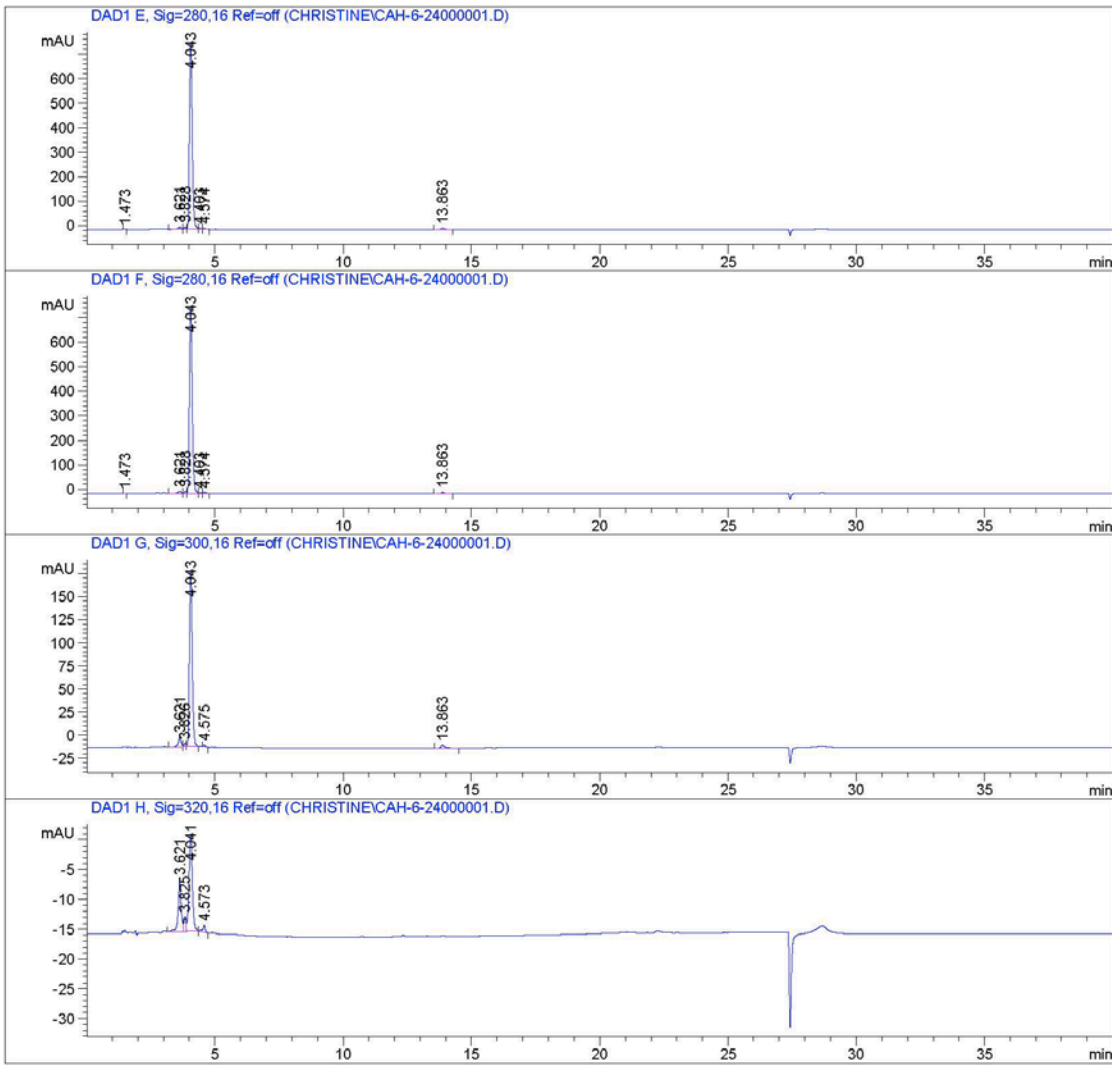
Sample Name: CAH-6-24



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Area Percent Report

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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-6-24000001.D
Sample Name: CAH-6-24

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.391	BV	0.0610	7.81049	1.85999	0.0488
2	1.476	VV	0.0836	10.12844	1.74734	0.0633
3	2.998	BB	0.1245	17.02232	1.97571	0.1064
4	3.623	BB	0.1181	25.76275	3.19316	0.1611
5	3.828	BV	0.0699	68.47198	14.82507	0.4281
6	4.043	VV	0.1199	1.56188e4	2025.83167	97.6627
7	4.394	VV	0.0885	55.33225	8.90629	0.3460
8	4.572	VB	0.1021	62.22238	8.63247	0.3891
9	13.863	BB	0.1367	25.87182	2.77756	0.1618
10	18.802	BB	0.1071	9.02090	1.29729	0.0564
11	19.847	BB	0.0948	8.76622	1.44499	0.0548
12	28.654	BB	0.4623	83.38203	2.58484	0.5214
Totals :				1.59925e4	2075.07638	

Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.391	BV	0.0591	7.21573	1.78816	0.0476
2	1.477	VV	0.0799	9.09765	1.66187	0.0601
3	2.997	BB	0.2996	70.14854	2.96901	0.4631
4	3.624	BB	0.1172	27.39253	3.42800	0.1808
5	3.828	BV	0.0679	59.99481	13.48118	0.3960
6	4.043	VV	0.1190	1.42912e4	1872.98071	94.3370
7	4.395	VB	0.0709	22.35714	4.74763	0.1476
8	4.572	BB	0.0769	27.41272	5.42608	0.1810
9	13.863	BB	0.1386	30.36974	3.26277	0.2005
10	18.802	BB	0.1084	8.06718	1.14245	0.0533
11	19.847	BB	0.0949	8.07938	1.32921	0.0533
12	28.653	BB	1.2066	587.76019	6.16329	3.8798
Totals :				1.51491e4	1918.38036	

Signal 3: DAD1 C, Sig=210,8 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.384	BV	0.0515	181.29756	53.53682	0.6562
2	1.479	VB	0.0908	101.26290	15.37472	0.3665
3	1.959	BV	0.1503	171.36317	16.61413	0.6203

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-6-24000001.D
Sample Name: CAH-6-24

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
4	2.758	VB	0.3937	1774.10779	62.39947	6.4215
5	3.295	BB	0.0764	12.51878	2.33929	0.0453
6	3.630	BB	0.1072	200.15843	28.07985	0.7245
7	3.828	BV	0.0671	138.52396	31.64297	0.5014
8	4.043	VV	0.1570	2.44912e4	2527.73950	88.6480
9	4.392	VB	0.0686	47.80655	10.59979	0.1730
10	4.572	BB	0.0760	63.74675	12.82641	0.2307
11	4.884	BV	0.0744	8.96094	1.85477	0.0324
12	5.023	VB	0.0880	45.50289	7.58052	0.1647
13	13.265	BB	0.1017	15.46335	2.20867	0.0560
14	13.863	BB	0.1410	53.45221	5.61953	0.1935
15	17.911	BB	0.0924	8.66976	1.47981	0.0314
16	22.287	BV	0.2091	18.72872	1.19320	0.0678
17	22.667	VV	0.1811	23.63048	1.95335	0.0855
18	27.495	BB	0.1340	202.18147	23.12298	0.7318
19	28.645	BB	0.4029	68.88494	2.55251	0.2493
Totals :				2.76275e4	2808.71828	

Signal 4: DAD1 D, Sig=230,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.385	BV	0.0537	35.52041	9.92666	0.2130
2	1.481	VB	0.0696	20.23402	4.24269	0.1213
3	1.964	BB	0.1094	26.49018	3.53564	0.1588
4	2.759	BV	0.3117	411.25793	18.47796	2.4656
5	2.985	VB	0.1213	112.17307	12.91943	0.6725
6	3.629	BB	0.1126	93.04063	12.53667	0.5578
7	3.828	BV	0.0669	73.80240	16.90789	0.4425
8	4.043	VV	0.1205	1.54928e4	1996.45898	92.8845
9	4.393	VB	0.0699	25.51955	5.52837	0.1530
10	4.573	BB	0.0735	34.24681	7.19496	0.2053
11	4.885	BV	0.0784	10.15930	2.02997	0.0609
12	5.020	VB	0.0851	14.67683	2.55004	0.0880
13	13.863	BB	0.1415	70.21961	7.34801	0.4210
14	27.529	BB	0.1549	158.54309	15.29897	0.9505
15	28.653	BB	0.4906	100.96045	2.97006	0.6053
Totals :				1.66797e4	2117.92632	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-6-24000001.D
Sample Name: CAH-6-24

Signal 5: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.473	VB	0.0704	5.48779	1.13574	0.0911
2	3.621	BV	0.1263	76.58023	8.56689	1.2716
3	3.828	VV	0.0811	48.96879	8.78171	0.8131
4	4.043	VV	0.1181	5779.64941	765.73773	95.9686
5	4.403	VV	0.1005	24.02273	3.48107	0.3989
6	4.574	VB	0.1010	32.78029	4.60598	0.5443
7	13.863	BB	0.1385	54.94780	5.91066	0.9124
Totals :				6022.43705	798.21977	

Signal 6: DAD1 F, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.473	VB	0.0704	5.48760	1.13574	0.0911
2	3.621	BV	0.1263	76.57832	8.56689	1.2716
3	3.828	VV	0.0811	48.96640	8.78171	0.8131
4	4.043	VV	0.1181	5779.65039	765.73773	95.9687
5	4.403	VV	0.1005	24.02216	3.48060	0.3989
6	4.574	VB	0.1010	32.77953	4.60598	0.5443
7	13.863	BB	0.1385	54.94532	5.91063	0.9123
Totals :				6022.42972	798.21928	

Signal 7: DAD1 G, Sig=300,16 Ref=off

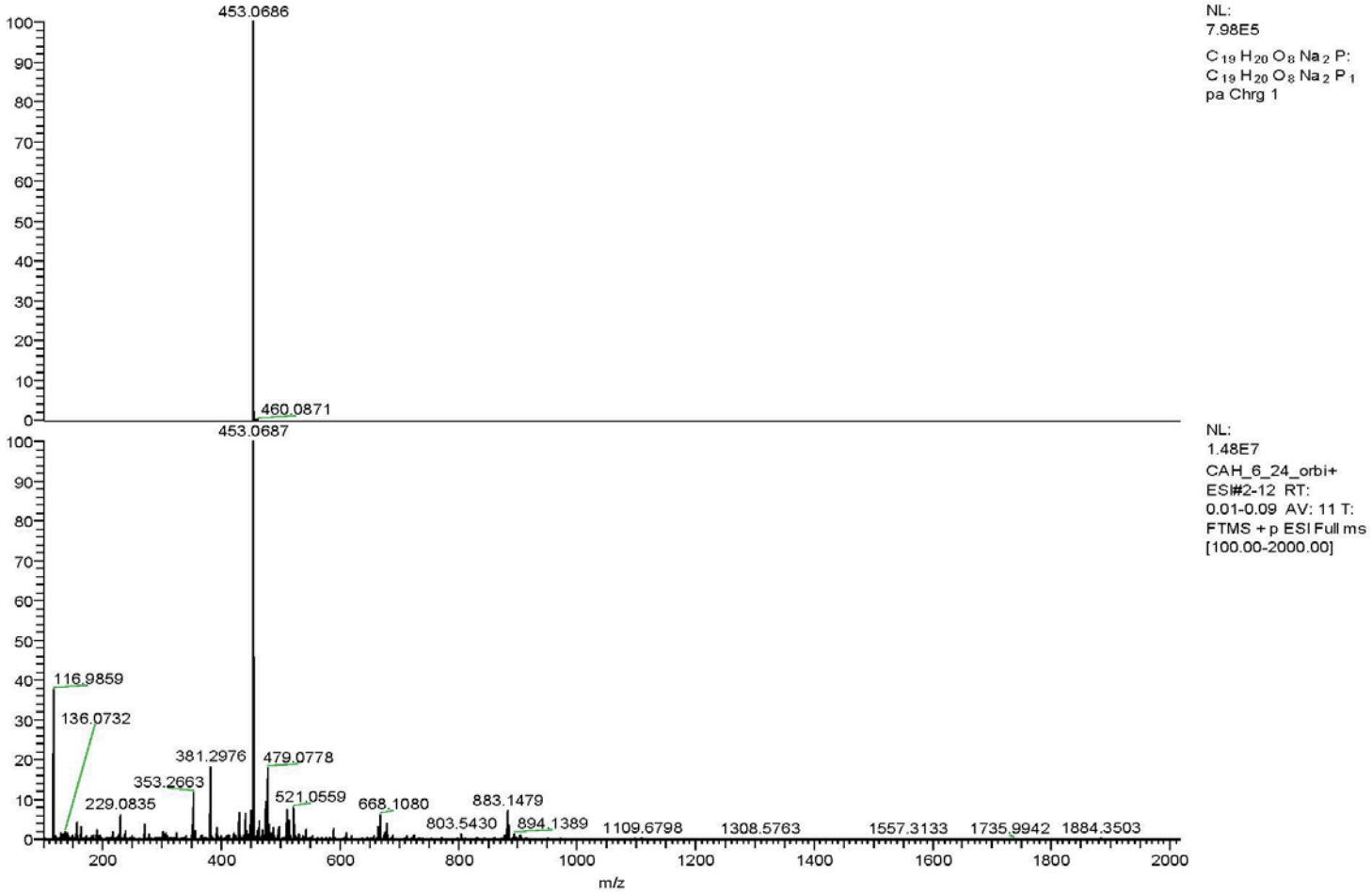
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.621	BV	0.1131	83.12932	10.64792	5.1879
2	3.826	VV	0.0800	20.97679	3.82476	1.3091
3	4.043	VB	0.1186	1452.70459	191.39255	90.6600
4	4.575	VB	0.0810	11.73287	2.17350	0.7322
5	13.863	BB	0.1406	33.82201	3.56693	2.1108
Totals :				1602.36558	211.60565	

Data File C:\CHEM32\1\DATA\CHRISTINE\CAH-6-24000001.D
Sample Name: CAH-6-24

Signal 8: DAD1 H, Sig=320,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.621	BV	0.1166	71.65930	8.83325	29.4579
2	3.825	VV	0.0844	14.51530	2.47418	5.9670
3	4.041	VB	0.1372	147.71956	16.38952	60.7250
4	4.573	BB	0.1057	9.36575	1.24525	3.8501
Totals :				243.25991	28.94220	

*** End of Report ***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m/z

APPENDIX C

Permissions

From: **Andy Reynolds** Andy.Reynolds@icr.ac.uk
Subject: RE: Permission to use Figure
Date: February 2, 2016 at 11:35 AM
To: Herdman, Christine A Christine_Herdman@baylor.edu

AR

Dear Christine

Yes, this is fine (and it is confirmed by the publisher's website - see attached). Please just cite the title, author, journal, publisher and date as seen in the attached.

May I ask, our of curiosity, how you will be using it?

Best, Andy

Andrew R. Reynolds PhD
Team Leader
Tumour Biology Team
Room 3C11.2 / 3N20
The Breakthrough Breast Cancer Research Centre
The Institute of Cancer Research
237 Fulham Road
London SW3 6JB
UK
Email: andrew.reynolds@icr.ac.uk
Tel: +44 (0)207 153 5235 (office)
Tel: +44 (0)207 153 5538 (lab)
FAX: +44 (0)207 153 5340
Web Page: http://www.icr.ac.uk/research/team_leaders/Reynolds_Andrew/
Google Scholar: http://scholar.google.co.uk/citations?hl=en&user=CUK2flsAAAAJ

From: Herdman, Christine A [Christine_Herdman@baylor.edu]
Sent: 02 February 2016 17:25
To: Andy Reynolds
Subject: Permission to use Figure

Hi Prof. Reynolds,

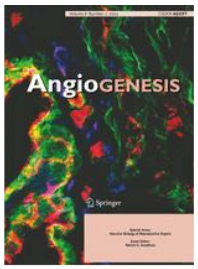
I realize that your article was published in an open access journal that says that you may freely use the content as long as you give credit, however, I just wanted to ask permission to use Fig. 1 from your paper

Anti-angiogenic therapy for cancer: current progress, unresolved questions and future directions of the of the angiogenesis in tumor growth and if there was any one else I would need to give credit to? Thank you for your consideration!

Christine

Christine Herdman
Pinney Research Group
Department of Chemistry and Biochemistry
Baylor University

"Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning. Curiosity has its own reason for existing." -Albert Einstein



Title: Anti-angiogenic therapy for cancer: current progress, unresolved questions and future directions

Author: Naveen S. Vasudev

Publication: Angiogenesis

Publisher: Springer

Date: Jan 1, 2014

Permissions Request

Title:	Disrupting tumour blood vessels
Author:	Gillian M. Tozer, Chryso Kanthou and Bruce C. Baguley
Publication:	Nature Reviews Cancer
Publisher:	Nature Publishing Group
Date:	Jun 1, 2005

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Licensed content date	Jun 1, 2005
Type of Use	reuse in a dissertation / thesis
Volume number	5
Issue number	6
Requestor type	academic/educational
Format	print and electronic
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	1
High-res required	no
Figures	figure 3
Author of this NPG article	no
Your reference number	None
Title of your thesis / dissertation	Synthesis and Biological Evaluation of Potential Vascular Disrupting Agents Utilizing Indene, Benzosuberene, and Benzocyclooctene Frameworks
Expected completion date	May 2016
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BHAWNA GAURI
School of Pharmacy
CHIRI Health Sciences
Curtin University, Perth (Western Australia)

+61-405688-481
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Review Article

Nanotherapeutics Magic Bullets- a Boon or Bane to Human Health

Bhawna Gauri*

Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala (Punjab), India

Corresponding Author : Bhawna Gauri
Division of Pharmaceutics
Department of Pharmaceutical Sciences and Drug Research
Punjabi University, Patiala (Punjab), India
Tel: +91-9541717458
E-mail: bhawna.gauri@gmail.com

Received April 23, 2012; **Accepted** June 04, 2012; **Published** June 10, 2012

Citation: Gauri B (2012) Nanotherapeutics Magic Bullets- a Boon or Bane to Human Health. J Nanomed Nanotechol 3:142. doi: 10.4172/2157-7439.1000142

Title: Supramolecular Stacking of Doxorubicin on Carbon Nanotubes for In Vivo Cancer Therapy

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