UNIVERSITY OF IOANNINA

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DEPARTMENT OF MATERIALS SCIENCE AND ENGINEERING

Synthetic Studies on Kinamycin Antibiotics: Stereoselective Synthesis of the Highly Oxygenated D-Ring and Construction of the ABD-Ring System of Kinamycins

Maria-Dimitra Ouzouni

B. Sc. in Chemisty

Ph. D. Thesis

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«Η έγκριση της διδακτορικής διατριβής από το Τμήμα Μηχανικών Επιστήμης Υλικών της Σχολής Θετικών Επιστημών του Πανεπιστημίου Ιωαννίνων δεν υποδηλώνει αποδοχή των γνωμών του συγγραφέα Ν. 5343/32, άρθρο 202, παράγραφος 2»

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Abstract

This thesis entails a strategy for the synthesis of the kinamycin family of antitumor antibiotics and its structural analogues, where a concise and stereoselective synthesis of the highly oxygenated D-ring as well as the construction of the ABD-ring system of kinamycins was achieved. Access to the highly oxygenated D-ring was provided from commercially available 3-methylcyclohexen-2-one, with key steps including a regioselective isomerization of a *cis*-epoxyalcohol, a regioselective reductive opening of a benzylidene ketal and a stereoselective *α*-hydroxy directed ketone reduction.

Model studies indicated that the assembly of the ABD-ring system of kinamycins was feasible via a metal-catalyzed Ullmann coupling reaction strategy. Indeed, coupling of a highly oxygenated cyclohexenone D-ring with a bromonaphthaldehyde AB-ring fragment, gave access to a highly functionalized kinamycin ABD-ring intermediate that may provide access to kinamycin F and its structural analogs.

Furthermore, the chemistry that was developed here may be amenable to asymmetric synthesis and provide access to optically active material.

Τίτλος Διδακτορικής Διατριβής

«Ανάπτυξη Μεθοδολογίας για την Σύνθεση των Αντικαρκινικών Αντιβιοτικών της Οικογένειας των Κιναμικινών»

Περίληψη

Στη παρούσα διδακτορική διατριβή περιγράφεται η ανάπτυξη μιας μεθοδολογίας για τη σύνθεση των αντικαρκινικών αντιβιοτικών της οικογένειας των κιναμικινών καθώς και των δομικών αναλόγων τους. Ειδικότερα, επιτεύχθηκε η στερεοεκλεκτική σύνθεση του D-δακτυλίου καθώς και του ABD-τρικυκλικού συστήματος δακτυλίων των κιναμικινών.

Πρόσβαση στον πολυοξυγονωμένο D-δακτύλιο επιτεύχθηκε σε δώδεκα βήματα από την εμπορικά διαθέσιμη 3-μεθυλο-2-κυκλοεξενόνη, με κομβικά σημεία της σύνθεσης την τοποεκλεκτική ισομερίωση μιας *cis*-εποξυαλκοόλης, την εκλεκτική αναγωγική διάνοιξη μιας ακετάλης και την στερεοεκλεκτική αναγωγή μιας *α*-υδροξυ κετόνης.

Δοκιμαστικές αντιδράσεις με απλούστερα υποστρώματα υπέδειξαν πως η σύνθεση του ενδιάμεσου ABD-συστήματος δακτυλίων των κιναμικινών θα ήταν κατορθωτή διαμέσου μιας αντίδρασης σύζευξης τύπου Ullmann. Επιβεβαίωση της υπόθεσης αυτής επαληθεύτηκε με την αντίδραση σύζευξης μιας ιωδοενόνης (οξειδωμένος D-δακτύλιος) και μιας βρωμοναφθαλδεΰδης (AB-δικυκλικό σύστημα), σχηματίζοντας επιτυχώς το ενδιάμεσο ABD-τρικυκλικό σύστημα των κιναμικινών. Το τελευταίο αποτελεί κατάλληλο υπόστρωμα για την ολοκλήρωση του ABCD-τετρακυκλικού συστήματος της κιναμικίνης F και των αναλόγων της.

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Finally, I would like to express my deepest and special thanks to my family for their great love and support, not only during the past five years, but ever since I was born. I want them to be aware that I wouldn't have made it this far without them.

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« ***This thesis is dedicated to my parents for their endless love, support and encouragement*** »

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Table of Contents

PART I

Synthetic Studies of Kinamycin Antibiotics

CHAPTER 1

Diazobenzo[*b*]fluorene Antitumor Antibiotics

1.1 Natural Products: a Constant Source of New Drugs

Nature has ever since been representing a great source of inspiration for chemists by feeding them with new ideas and materials. Natural products are a limitless category of that "gifts" from the natural world to organic synthetic chemistry. In this field, natural products are defined as chemical compounds or substances which are produced and can be obtained by living-organisms that found in nature like animals, terrestrial plants, marine organisms or microorganisms (e.g bacterium or fungus).

Research on natural products has been associated with the discovery, isolation and characterization of pure organic compounds which are known as metabolites. Metabolites, as intermediates or products of the metabolism, are typically small organic compounds either with simple as well as with more complex structure. Predominately, most organic molecules in the natural product category are secondary metabolites rather than primary. Primary metabolites, like naturally-occurring carbohydrates, amino acids, proteins and nucleic acids, are key intermediates and products of metabolism. They are directly involved in normal growth, development and reproduction of a living organism. On the other hand, secondary metabolites act mostly as toxins against various biological threats or as supporting agents to facilitate the process of reproduction. Even if their absence would not immediately cause death, it would obviously impair the organism. In this category are included alkaloids, terpenoids, steroids, carbohydrates, phenolics or polyketides.

Secondary metabolites tend to attract a very lively interest which depends on the fact that many of those compounds provide notable pharmacological and biological activities for use in pharmaceutical drug discovery and drug design. Those who succeed in inhibiting the growth of bacteria or other microorganisms, they are known as antibiotics or antibacterial agents. Antibiotics can show inhibitory activity *in vivo* (inside the living organism) or *in vitro* (in an artificial environment outside the living organism). When an antibiotic indicates strong inhibitory activity in comparison with limited toxicity *in vivo*, then it can be preferable for the cure of various bacterial infections. Valuable source of antibiotics can be various fungi, algae, sponges, soft corals or microorganisms including bacteria like *Actinomycetes*. However, plants usually do not attract the same interest.

The challenging structures of natural products coupled with their unique biological properties have been rendered them as an innovation engine in the area of chemistry and biology. Due to continuous research on natural products, the scientific community has witnessed advancements on new synthetic strategies and technologies as well as in the area of chemical biology.[1] Thousands of pure natural compounds, coming from a variety of microorganisms or other natural sources, have already been fully characterized. Some of them, including their semi-synthetic derivatives and/or analogues are used as effective drugs. For instance, taxol is one of the most intriguing natural product, which was isolated in 1962 from the Pacific yew tree and its structure was reported in 1971 (Figure 1).[2] It took more than 20 years for taxol to be approved by the Food and Drug Administration (FDA) in 1992 for the treatment of ovarian cancer. For more than two decades synthetic chemists were trying to construct taxol's complex molecular architecture via multiple strategies. Finally, in 1994, two essentially simultaneous reports described two distinctly different total syntheses of taxol. These first two syntheses, by Nicolaou[3, 4] and Holton,[5] were followed by those of Danishefsky,[6] Wender,[7] Mukaiyama[8] and Kuwajima.[9] All these syntheses, which are characterized by novel strategies and risky tactics, contributed to the advancement of total synthesis and enabled investigations in biology and medicine.

Penicillins are a group of antibiotics derived from Penicillium fungi (Figure 1). They were originally isolated by Ernest Duchesne, a medical student, in the late 19th Century. Then they were re-discovered for their antibiotic properties by Alexander Fleming in the secretion of the mold Penicillium notatum in 1928.[10] Penicillin was found to show remarkable antibacterial properties according to Chain and Florey.[11] They are one of the first type of antibiotics that were effective against many, previously, serious diseases, such as syphilis, and infections caused by staphylococci and streptococci. Nowadays they are used in the treatment of bacterial infections caused by susceptible, more often Gram-positive, organisms. Its molecular structure, which contains a unique and strained β-lactam ring, was confirmed via X-ray crystallographic analysis. At the same time penicillin became an interesting synthetic target, and the first synthesis of penicillin V was achieved in 1957 by Sheehan at the Massachusetts Institute of Technology.[12]

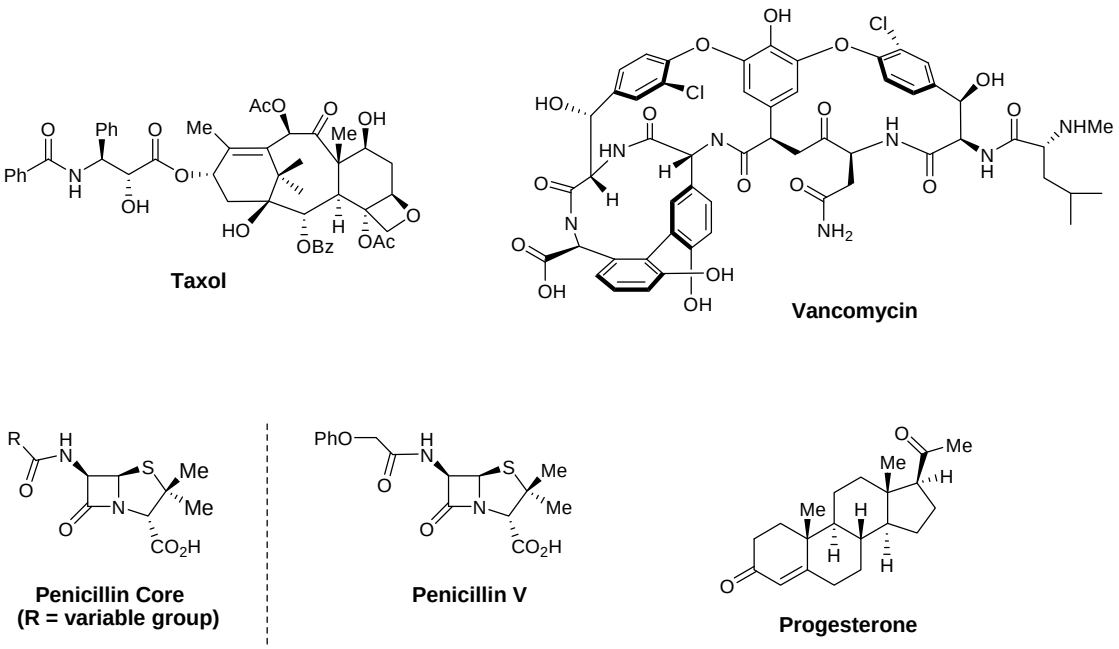


Figure 1. Structures of remarkable natural products

Also, vancomycin is a representative of the glycopeptide class of antibiotics (Figure 1). It was isolated from the actinomycete Amycolatopsis orientalis in the 1950s and used for over four decades as a weapon of last resort to combat bacterial diseases. The vancomycin was finally yielded to structural elucidation in 1982.[13] Within a few years, it became the subject of synthetic investigations, primarily as a consequence of its novel molecular architecture, important biological action, medical applications, and intriguing mechanism of action. As a synthetic target, vancomycin offered a unique opportunity to synthetic chemists to develop new synthetic technologies and strategies. Among the most intriguing structural features of the molecule were its two 16-membered bisaryl ether macrocycles and its 12-membered bisaryl ring system, each of which is associated with an atropisomerism problem. The attachment of the two carbohydrate moieties onto the heptapeptide aglycon system added to the challenge presented by this target molecule. In early 1999 the first total synthesis of vancomycin appeared in the literature by Nicolaou[14] followed by another report of the aglycon synthesis by the Boger group.[15]

Progesterone is a member of the steroid class of compounds that is found everywhere in nature (Figure 1). Willard Myron Allen co-discovered progesterone with his professor George Washington Corner at the University of Rochester Medical School in 1933.[16] Allen first determined its melting point, molecular weight, and partial molecular structure. He

also gave it the name Progesterone from **Proge**stational **Ster**oidal ket**one**. As a steroid hormone, progesterone is involved in the female menstrual cycle, pregnancy and embryogenesis of humans and other species. Its linearly fused polycyclic carbon framework is characteristic for numerous natural products of steroidal or triterpenoid structures. A number of semisyntheses of progesterone have been reported starting from a variety of steroids. A total synthesis of progesterone through a biomimetic strategy was reported by W. S. Johnson in 1971.[17]

1.2 The Kinamycin Family of Natural Products

In 1970, Omura and co-workers obtained a strain of *Streptomyces* from a soil sample collected in Murayama (Saitama-ken, Japan). Murayama is a small town situated in the north of Tokyo Metropolis' central area. Based on its origin, the bacteria strain was named as *Streptomyces murayamaensis* and it resembles *Nocardia* in several morphological properties such as the fragmentation of the mycelium. This microorganism was capable of producing some bright golden-yellow crystalline compounds which were later identified and named as kinamycin A, B, C and D.[18] Very soon after that, *Streptomyces murayamaensis* was patented and samples were deposited to the American Type Culture Collection by Kyowa Fermentation Industrial Co., Ltd. under the registration number of ATCC 21414, which was then made available to the scientific public.

The initially discovered *Streptomyces murayamaensis* is the most frequently used bacterium to produce the valuable natural kinamycins through fermentation.[19] The fermentation process of the *Streptomyces murayamaensis* is a complicated and a very sensitive biological process. It is important to note that small variations in experimental conditions (i.e. the conditions of cultivation or the components of the media) may significantly affect the fermentation result. These effects were examined in detail by Gould's group.[19] *Streptomyces* is the largest and most interesting genus of *Actinobacteria*. They are Gram-positive aerobic bacteria and sometimes they can cause human infections. It is known that, apart from kinamycins, *Streptomyces* produce also other useful and effective antibiotics like streptomycin or tetracycline. *Streptomyces* have the ability to produce kinamycins but they have not been genetically engineered and optimized for such

purpose. However, the genes in *Streptomyces murayamaensis* that are responsible for producing kinamycins were already identified, cloned and heterologously expressed by Gould in 1998.[20] Unfortunatelly, the gene(s) responsible for the formation of the kinamycin's diazo group were neither identified nor expressed.

Until 1989, *Streptomyces murayamaensis* was the only bacterium known to produce kinamycins. Later the same year, various kinamycins were discovered from *Streptomyces saccharothrix* (strain MI293-N4),[21] from an unidentified *Actinomycete* (strain A83016) in 1992,[22] and finally from *Streptomyces chattanoogensis subsp. taitungensis* (strain IY2-13/CCRC 15124) in 1994.[23] These findings have expanded the sources for the natural kinamycins which were known at that time. It is important to mention that even if each individual *Streptomyces* would produce unique natural kinamycins, there are some kinamycins which were isolated and identified from more than one Streptomyces source. For instance, kinamycin D was initially obtained from *Streptomyces murayamaensis*[18] and later was also isolated from *Streptomyces chattanoogensis subsp. Taitungensis*.[23]

Up until now, there have been about 20 compounds that constitute the family of kinamycin antibiotics produced and isolated by certain species of *Streptomyces* or *Actinomycetes* (Figure 2, Table 1). The kinamycins were found to be strongly active against Gram-positive bacteria but less effective against Gram-negative bacteria. Several kinamycins have also exhibited antitumor properties.

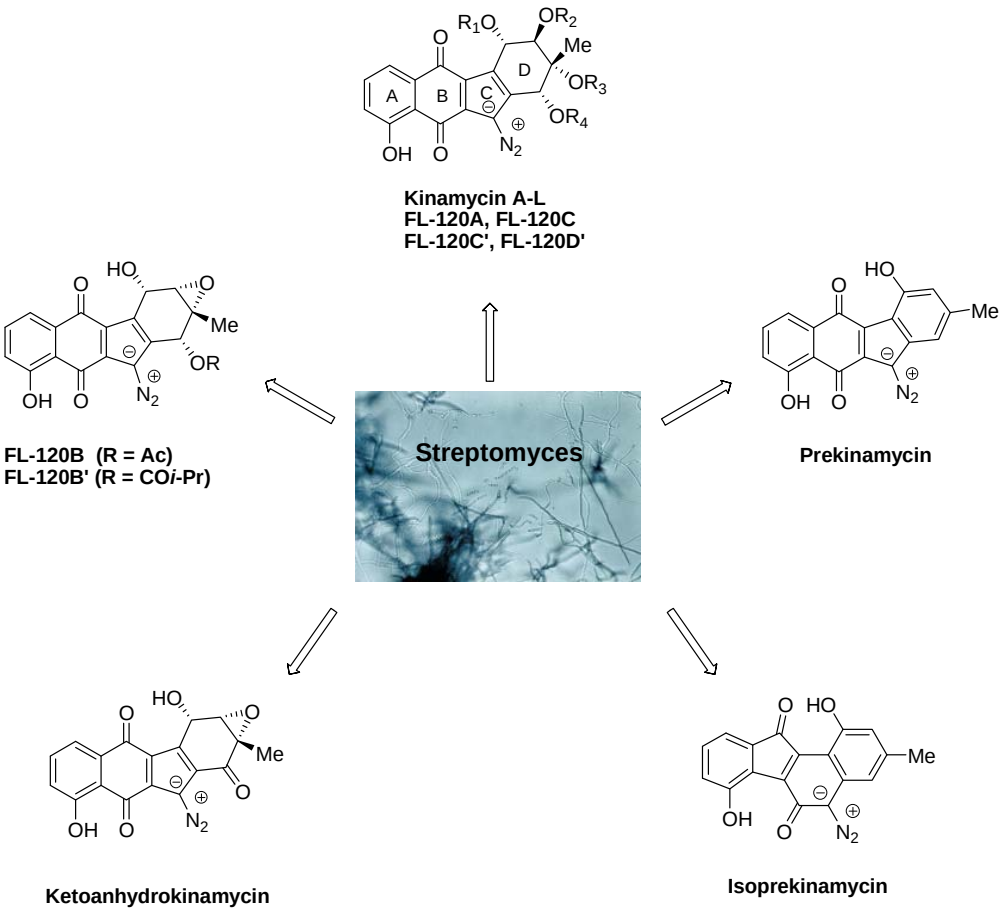


Figure 2. General structures of natural kinamycins isolated to date

Table 1. Substituent variations of all known kinamycins

Name	Isolation (year)	R_1	R_2	R_3	R_4
Kinamycin A	1970[18]	Ac	Ac	Ac	H
Kinamycin B	1970[18]	H	H	Ac	H
Kinamycin C	1970[18]	Ac	Ac	H	Ac
Kinamycin D	1970[18]	H	Ac	H	Ac
Kinamycin E	1989[19,24]	H	H	H	Ac
Kinamycin F	1989[19,24]	H	H	H	H
Kinamycin G	1989[21]	Ac	Ac	CO*i*-Pr	Ac
Kinamycin H	1989[21]	Ac	Ac	H	CO*i*-Pr
Kinamycin I	1992[22]	Ac	CO*i*-Pr	H	CO*i*-Pr
Kinamycin J	1973[25]	Ac	Ac	Ac	Ac (semi-synthetic)
Kinamycin K	1989[19,24]	H	Ac	H	H
Kinamycin L	1992[22]	Ac	Ac	CO*i*-Pr	CO*i*-Pr
FL-120A	1994[23,26]	H	Ac	CO*i*-Pr	Ac
FL-120C	1994[23,26]	H	Ac	H	CO*i*-Pr
FL-120C’	1994[23,26]	H	Ac	H	COEt
FL-120D’	1994[23,26]	H	H	H	CO*i*-Pr
FL-120B	1994[23,26]	Ac	-	-	-
FL-120B’	1994[23,26]	CO*i*-Pr	-	-	-
Ketoanhydromycin	1989[19,24]	-	-	-	-
Prekinamycin	1994[27,28]	-	-	-	-
Isoprekinamycin	1989[19,24,29]	-	-	-	-

One of their remarkable structural features is a very rare and unusually stable diazo moiety (-C=N^+=N^- ↔ -C^--N^+≡N) in the five membered C-ring. Kinamycins are known since 1970’s and their *C*-diazo group was incorrectly assigned in 1971 as an *N*-cyano (-N-C≡N) group based on limited spectroscopic data and wrong interpretation of chemical degradation studies (Figure 3).[30] This incorrect assignment of the structure of kinamycins lasted for 23 years until 1994 when Gould determined the correct structure from the

analysis of high quality X-ray data derived from the (+)-*α*-methylbutyrate of natural kinamycin D.[31] At the same time, Dmitrienko's group[32] confirmed the presence of the C-diazo moiety with subsequent synthetic and spectroscopic findings. A controversy regarding the structural assignment of the isomeric prekinamycin and isoprekinamycin also arose right after their isolation and characterization. These compounds differ in the arrangement of their carbocyclic skeleton but it could not be distinguished until another structural revision was established.[29]

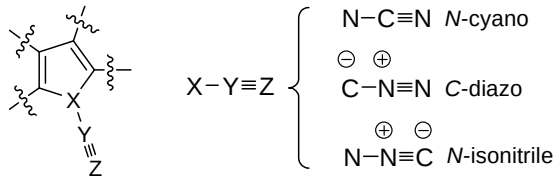
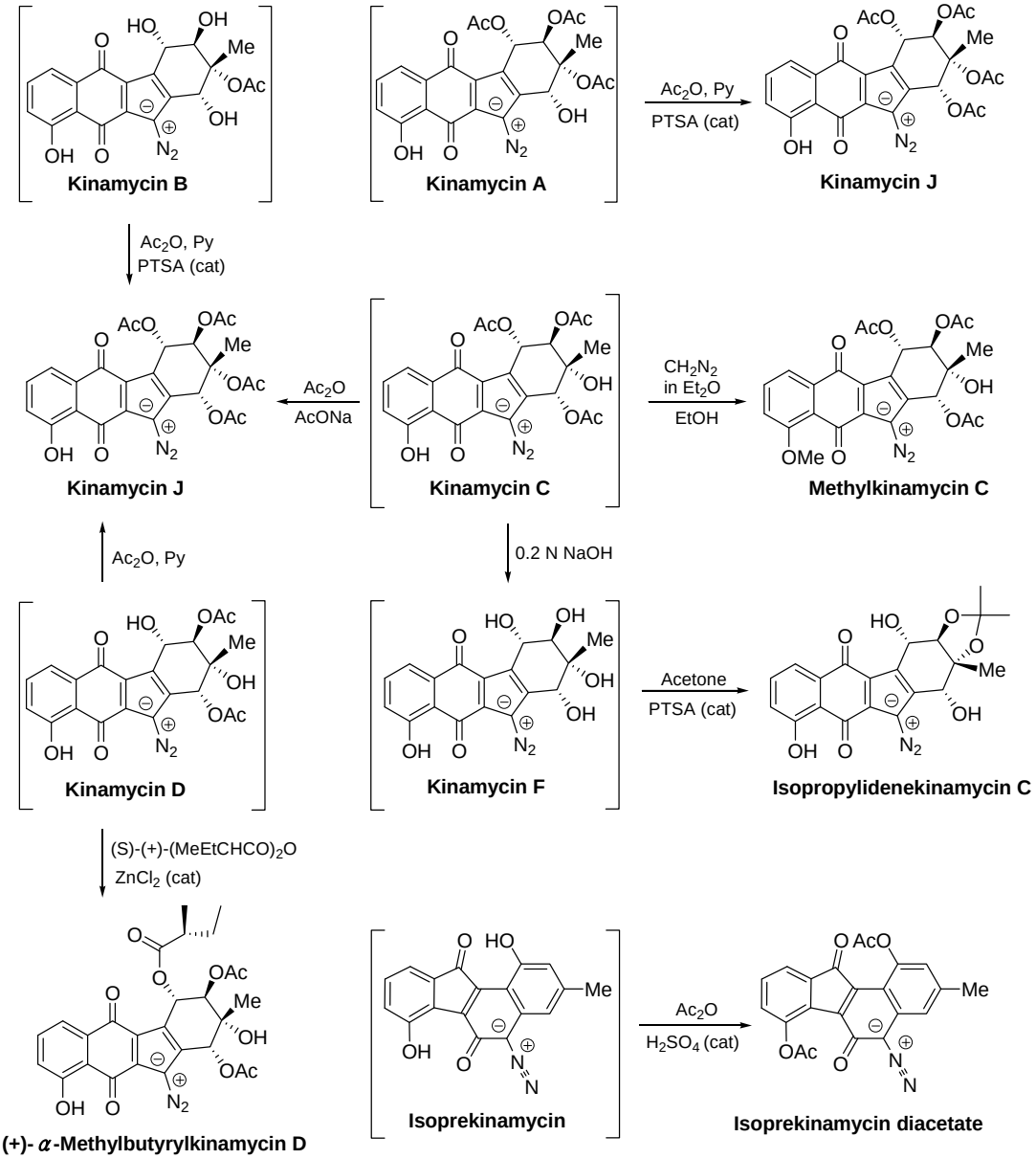


Figure 3. The 5-membered core of kinamycins

During the structural determination of the kinamycins,[24, 25, 31, 33] some simple semi-synthetic derivatives were synthesized which later on were found to be natural kinamycins (Scheme 1). For instance the product of deacetylation[25] of kinamycin C, upon basic hydrolysis, is the natural kinamycin F which was isolated as a bacterial metabolite in 1989.[24] The above experimental processes indicated that the diazo group is quite stable under the rather harsh hydrolysis conditions in contrast with most diazo compounds which are usually unstable under such reaction conditions.



Scheme 1. Some semi-synthetic kinamycin derivatives

The four rings of kinamycins are indicated as ring A, B, C and D respectively, with the A-ring bearing a single hydroxyl group in all natural kinamycins. The numbering system of kinamycins is denoted as suggested by Gould[31] and shown in Figure 4. The kinamycin skeleton can be defined as either a benzo[*a*]fluorene core or a benzo[*b*]fluorene core based on the relative orientation of the remaining 6-membered ring (Figure 4). Kinamycins containing the isomeric benzo[*c*]fluorene core have not been isolated yet.

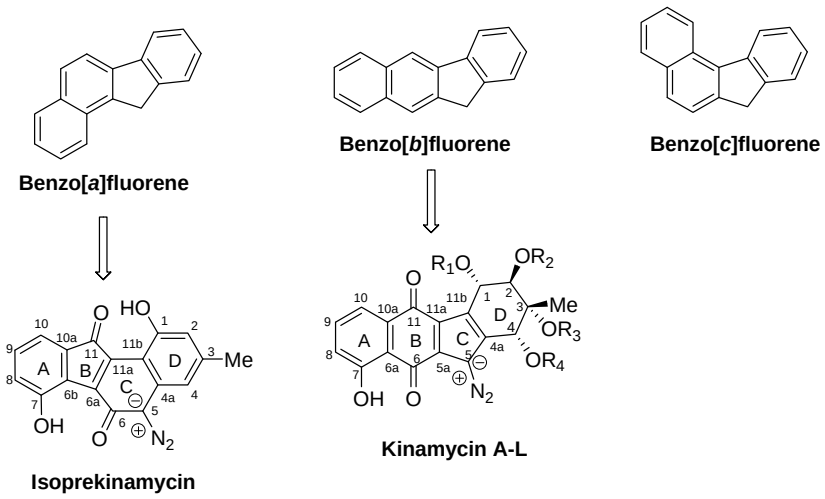
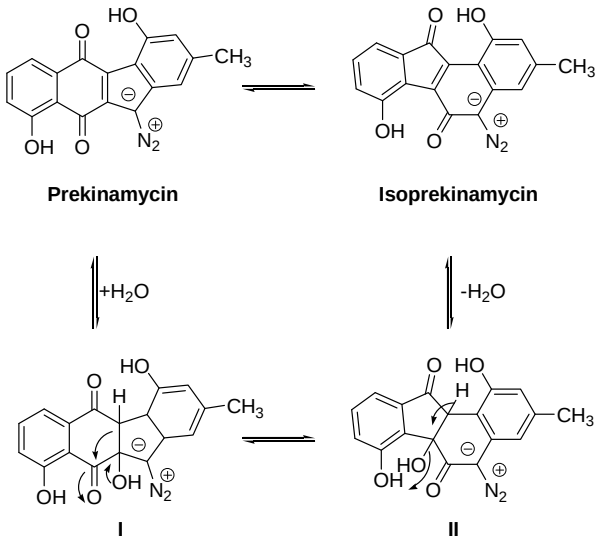


Figure 4. Orientation of the benzofluorene skeleton

The benzo[*b*]fluorene skeleton of all natural kinamycins (except isoprekinamycin) is common but with various substituents and different degrees of oxidation on their D-ring. The majority of kinamycins contain a highly oxygenated cyclohexene D-ring bearing acyloxy and/or hydroxy substituents. FL-120B, FL-120B' and ketoanhydromycin have an epoxide functional group within the saturated D-ring. Prekinamycin posses a fully aromatized D-ring and its structural isomer isoprekinamycin is the only member of the kinamycin family that indicates a benzo[*a*]fluorene skeleton (Figure 2). Production of benzo[*a*]fluorene and benzo[*b*]fluorene ring systems has shown that these two structures have almost the same stability. Based on this data, Dmitrienko and Proteau proposed a reversible interconversion between these two types of skeleton rings through a possible enzyme-catalyzed rearrangement (Scheme 2).[29]



Scheme 2. Possible interconversion between diazobenzo[*a*]fluorene and diazobenzo[*b*]fluorene structures

The existence of naturally-occuring diazo compounds is extremely rare, and except for kinamycins there is a small number of diazo-compounds that are reported in the literature (Figure 5).[34-44] These naturally-occuring diazo compounds were produced by certain strains of *Streptomyces* or *Actinomycetes*, except SQ30957 which was isolated from a fungus. In many cases, these diazo compounds were found to be active against various bacteria and tumor cells. Amongst them, Lomaiviticins A and B are of great importance. They were identified in an investigation that originally targeted the marine invertebrates as a possible source of enediyne-type anticancer agents. They were isolated by He and his collaborators from the fermentation broth of *Micromonospora lomaivitiensis* (Actinomycete strain LL-371366) in 2001.[44] The bacterium was hosted by Polysyncratan lithostrotum, a Fijian marine ascidian commonly known as a sea squirt.

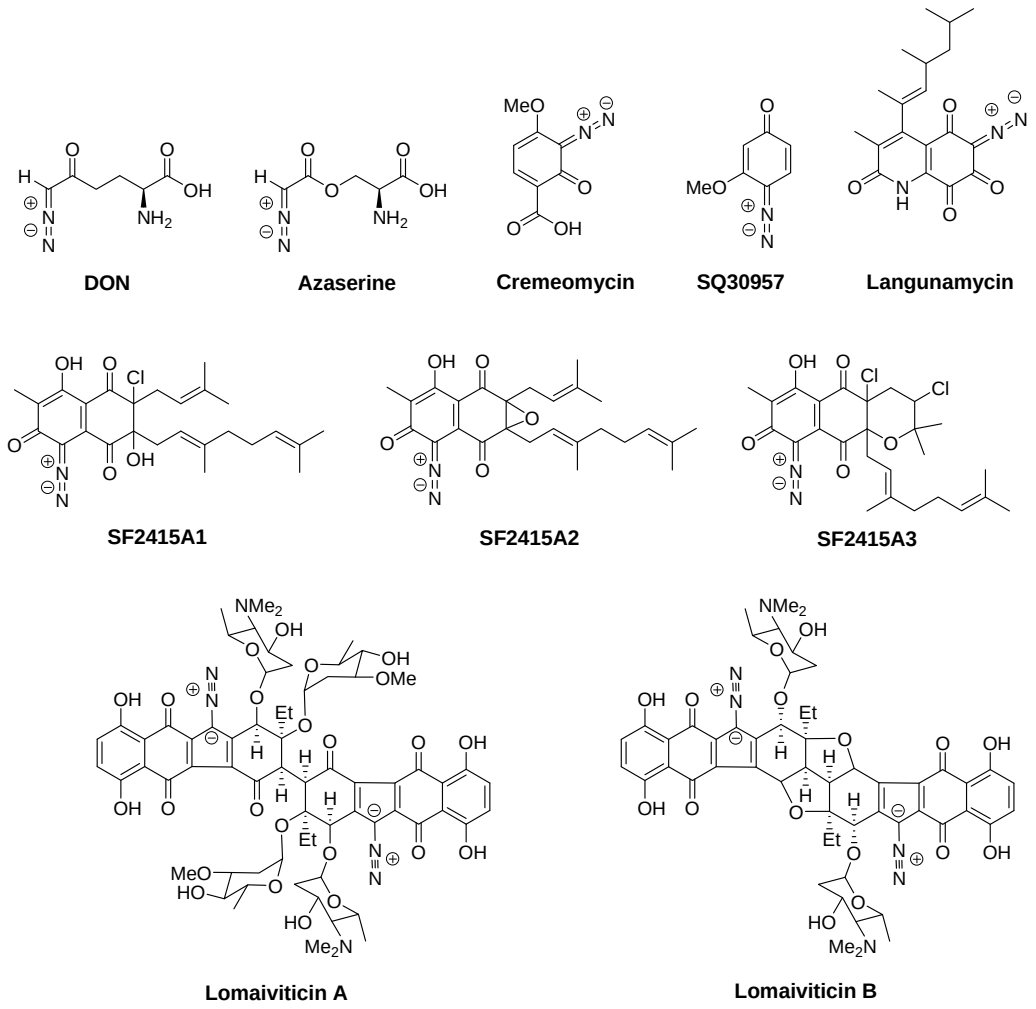


Figure 5. Some other naturally-occurring diazo compounds

Lomaiviticins are dimeric glycosides whose monomeric subunit resembles the structure of kinamycins. Lomaiviticin B is the bis-hemiketal derived from lomaiviticin A. Both lomaiviticins exhibited extremely potent DNA-damaging activities in a biochemical induction assay (BIA) with a minimum induction concentration ≤ 0.1 ng/spot. Especially, lomaiviticin A showed cytotoxicity with an ultra low level IC_{50} of about 0.01-98 ng/mL against a very broad range of cancer cells and bacteria.[44] Several synthetic efforts to lomaiviticins have been reported since their isolation,[45-48] and an elegant enantioselective synthesis of the (-)-lomaiviticin aglycon in 11 steps was completed in 2011 by Herzon.[49]

The presence of benzo[*b*]- and benzo[*a*]fluorene cores are very rare structures within the natural products (Figure 6) and a few of them have been isolated.[20, 50-58] These natural

products except for shikometaboline A and B, are produced exclusively by certain species of *Streptomyces*.

The unique biological profile of the diazobenzofluorene antibiotics coupled with their challenging structures, has made them the focus of multi-disciplinary research by many laboratories worldwide since their initial discovery in 1970. A great deal of efforts have been devoted to various aspects of kinamycins over the past few decades, from isolation, structure characterization, and mechanism of action studies to total synthesis.

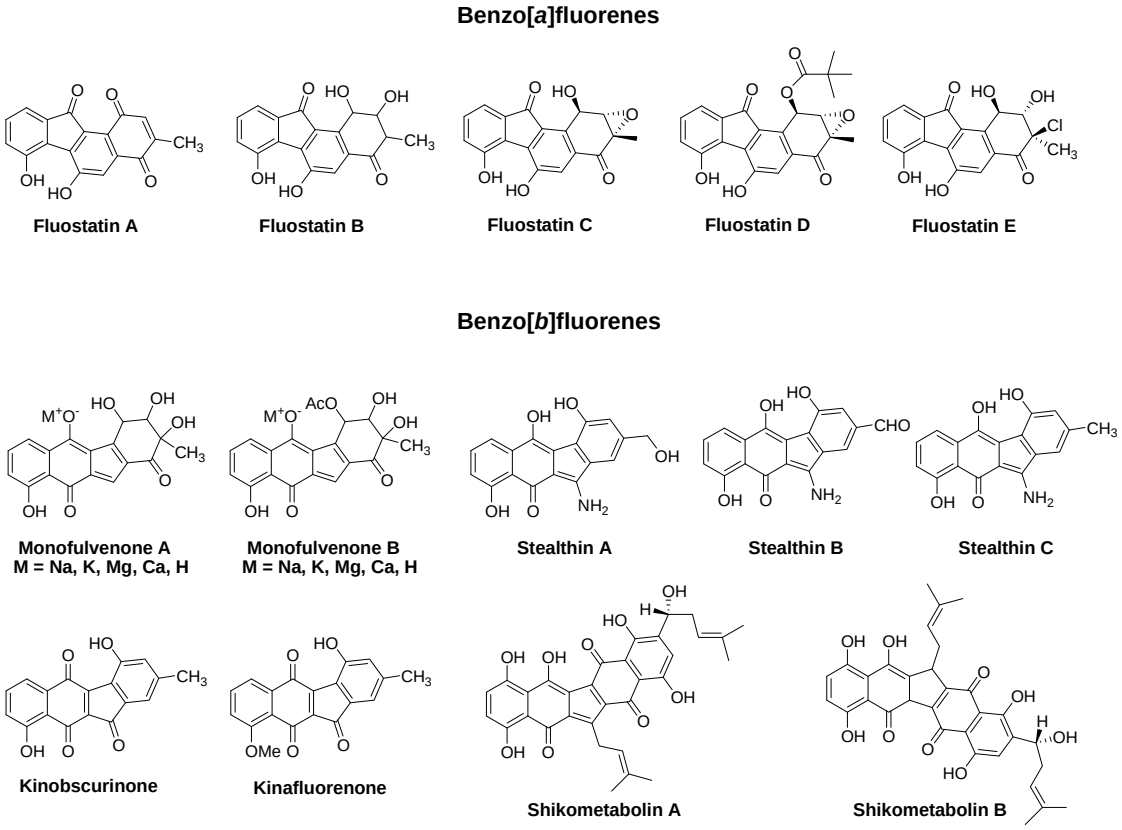


Figure 6. Some natural products containing benzo[*b*]- and benzo[*a*]fluorene cores

1.3 Structural Determination of Kinamycins: From *N*-cyanobenzocarbazoles to Diazobenzofluorenes

When Omura and his co-workers isolated kimamycins A, B, C and D, they went ahead with the characterization of these interesting natural compounds. They used techniques like ^{1}H-NMR, mass spectroscopy (MS), infrared (IR), UV-VIS spectrometry and chemical derivatization and degradation studies. These spectroscopic techniques in combination with the common spectroscopic rules managed to determine the bulk of the tetracyclic system of kinamycins as well as the majority of the substituents and functional groups.[25, 33] However, there was a controversial linear triatomic moiety containing two nitrogen and one carbon atoms with a strong IR absorption at 2155 cm^{-1}, which was common for kinamycins A-D. For this triatomic moiety, three possible structural sequences were assigned: a *C*-diazo (-C=N^{+}=N^{-} ↔ -C^{-}-N^{+}≡N), an *N*-cyano (-N-C≡N) or an *N*-isonitrile (-N-N^{+}≡C^{-}) (Figure 7).

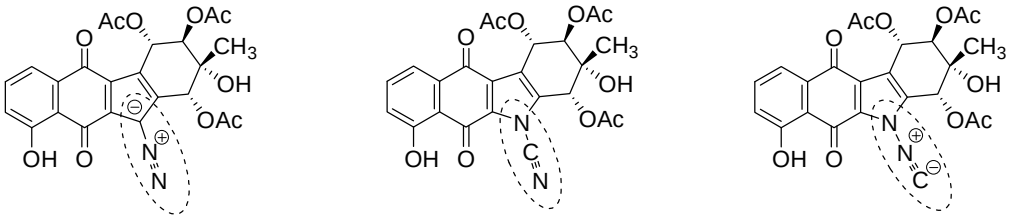


Figure 7. Possible structures for the triatomic moiety of kinamycins

Omura has never considered the possibility of the *C*-diazo group, mainly because this functionality was extremely unstable and there were very few natural products isolated containing this functionality at that time. For that reason, Omura decided to make a choice between the two remaining options. Due to the lack of further spectroscopic information, some qualitative chemical experiments were carried out in order to distinguish the *N*-cyano from the *N*-isonitrile group. For instance, hydrolysis of the kinamycin F in refluxing 30% aqueous KOH released ammonia but not formic acid.[33] Also the reaction of the kinamycin F under acidic conditions in refluxing 10% HCl in MeOH led to the detection of ammonia and not formic acid.[25] It is known that the cyano group would release ammonia but not formic acid under either acidic or basic hydrolysis. In contrast, the isonitrile group would

lead to formic acid but not ammonia under the same conditions. These results in conjunction with the lack of ^{13}C-NMR spectra of the isolated kinamycins as well as the absence of comparable spectroscopic data from related N-CN compounds, led to the conclusion that the triatomic functional group was the *N*-cyano and not the *N*-isonitrile one.

The proposed *N*-cyanobenzo[*b*]carbazole structure seemed to be in agreement with the evidence acquired at that time. Later on, when Gould started his biosynthetic studies he was able to observe and assign the ^{13}C spectrum for all carbons atoms except for the cyanamide carbon of kinamycin D.[59, 60] That carbon was expected to have a chemical shift of ca. 110-120 ppm. When Gould fed *Streptomyces* with ^{15}N-labeled ammonium sulfate as the sole nitrogen source, a doubly-labeled [$^{15}N_2$]kinamycin D was produced. This [$^{15}N_2$]kinamycin D enabled Gould to identify the "missing" NMR signal of the "cyanamide carbon" of kinamycins, which appeared as a doublet of doublets (dd, J = 21.2 Hz and 5.4 Hz) at a chemical shift of 78.5 ppm due to the coupling between ^{13}C and the two adjacent ^{15}N atoms.[61] The previously recorded ^{13}C spectrum of the non-labeled kinamycin D was examined carefully, showing a very weak singlet at 78.5 ppm that it was difficult to be observed earlier because of the solvent peak of $CDCl_3$ at 77 ppm which was considered as an impurity. The carbon signal at 78.5 ppm was attributed to the "*N*-cyano carbon" but there was a notable deviation from the normally expected value at 110-120 ppm. This chemical shift difference could not be ignored and it was attributed on different electronic environment on the skeleton.[61] However, according to the literature it is supported that ^{13}C atoms promptly connected to diazo groups in some diazo compounds have a range of chemical shifts from 60 to 80 ppm.[62] That surely was more compatible with the observed chemical shift for the supposed *N*-cyano moiety of kinamycin D (78.5 ppm) rather than the chemical shifts of the *N*-cyano compounds in general. This observation was the stimulus for reconsidering the possibility that the structure of the *N*-cyano group within the kinamycins was not the right one. A series of N-cyanoindolediones and N-cyanobenzocarbazoles, prepared during the early synthetic studies towards the construction of the incorrectly assigned N-cyanobenzocarbazole skeleton of kinamycins, also revealed a different ^{13}C chemical shift for the N-CN carbons (Figure 8).[63, 64]

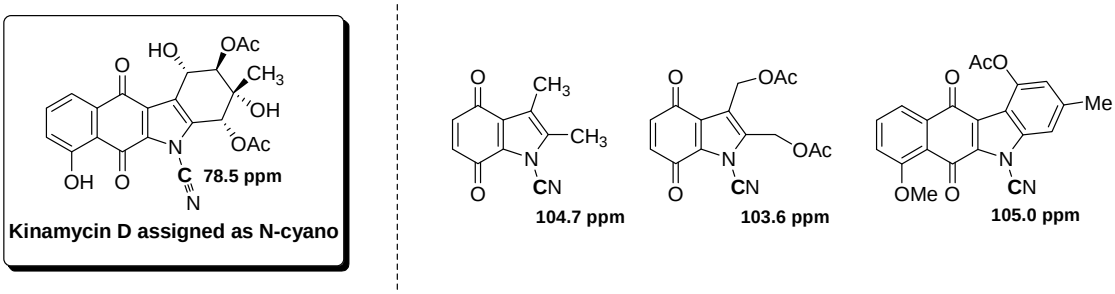


Figure 8. Comparison of ^{13}C NMR chemical shifts between the initially assigned structure of kinamycin D and model N-CN compounds

These *N*-cyano carbons in ^{13}C NMR spectroscopy had the expected chemical shifts of ca. 105-112 ppm, but they were poorly matched with the observed values for natural kinamycins (Figure 8). Additionally, these model *N*-cyano compounds have a specific IR band in the range from 2240 to 2250 cm^{-1} for the *N*-cyano group in contrast with the kinamycins which contained it at 2155 cm^{-1}. These findings enhanced the suspicion that the fundamendal skeleton core of kinamycins was a diazobenzo[*b*]fluorene rather than a cyanobenzo[*b*]carbazole.[32] At the same time with the spectroscopic discovery, Gould's group provided independently some results from a very careful and precise X-ray crystallographic study for the (+)-*α*-methylbutyrate of kinamycin D, which confirmed the presence of the diazo group.[31] The superior quality of Gould's X-ray data, when compared to Omura's X-ray results, made the corresponding conclusion more convincing and trustworthy.

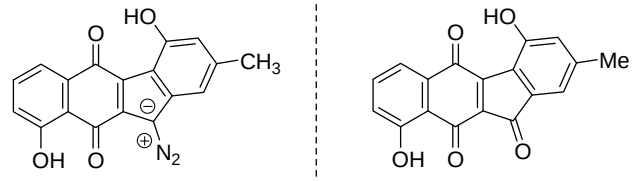
The revised structure of kinamycins in 1994, from *N*-cyanobenzo[*b*]carbazoles to diazobenzo[*b*]fluorenes, generated a major change in the chemistry and biochemistry of kinamycins. All synthetic strategies were reorganized according to the new structure and all initial knowledge towards the biosynthetic studies was reconsidered.

1.4 Biological Activity of Kinamycins and their Mechanism of Action as Antitumor Agents

All reports for the antimicrobial activities of natural and semi-synthetic kinamycins indicated that they are strongly active against Gram-positive bacteria but less effective

towards Gram-negative bacteria.[18, 19, 21, 22, 25, 26, 33] The intravenous acute toxicity (LD_{50}) of natural kinamycins, as antibiotics, in mice was found to be moderate. LD_{50} is about 30-40 mg/kg for each kinamycin A–D,[18] 35.36 mg/kg for FL-120A, > 50 mg/kg for FL-120B and 6.97 mg/kg for FL-120C'.[23] For kinamycin H it was reported that the lethal dose in mice was 0.5 mg per mouse but a reduction of the dose by half showed no toxicity.[21] Comparing with some common antibiotics such as streptomycin, mitomycin C and vancomycin, kinamycin D exhibits a moderate antimycoplasmal activity but with unknown mode-of-action.[65] In addition, kinamycin D possessed moderate antifungal activities at a concentration of 10–100 μg/mL against certain plant-pathogenic and agriculture-related fungi, comparable to other quinone-type antibiotics such as antimycin, nanaomycin A, oligomycin and ikutamycin.[66] This particular kinamycin also demonstrated significant herbicidal activity (30–80% inhibition of plant growth) against radish. Such antifungal and herbicidal activity of kinamycin D was considered to be effective through possible inhibition of the biosynthesis of cellulose.[66] An additional important biological activity of kinamycins, is their antitumor activity. Early antitumor tests of kinamycin C and D towards EHRLICH ascites carcinoma and sarcoma-180 indicated that, kinamycin C showed some survival effect by intraperitoneal injection at 0.1 and 1 mg/kg, yet kinamycin D was found to have no tumor inhibition effect.[30] Kinamycins G and H were found in a clonogenic assay to possess cytotoxicity against L1210 leukemia: IC_{50}: 0.72 μg/mL (kinamycin G), 0.38 μg/mL (kinamycin H) and IMC carcinoma cells:IC_{50}: 0.88 μg/mL (kinamycin G), 0.72 μg/mL (kinamycin H) in suspension culture. They also exhibited cytotoxicity against LX-1 human lung carcinoma: IC_{50}: 0.542 μg/mL (kinamycin G), 0.790 μg/mL (kinamycin H) and SC-6 human stomach carcinoma: IC_{50}: 2.50 μg/mL (kinamycin G), 0.760 μg/mL (kinamycin H).[21] More recent studies from Dmitrienko indicate that isoprekinamycin significantly inhibits the growth of Chinese hamster ovary (CHO) cells (IC_{50} = 5.8 μM) and K562 human leukemia cells (IC_{50} = 6.4 μM), comparable to the clinically useful anticancer agent etoposide (CHO: IC_{50} = 1.4 μM; K562: IC_{50} = 3.4 μM).[67] Also, in a recent physical organic chemistry study with prekinamycin and simpler analogues, a series of such compounds demonstrated significant growth inhibitory activity (GI_{50}) against pancreas, breast, lung, colon and prostrate tumor cells at a concentration of ca. 0.41–7.3 μg/mL when they were screened against a 60-cell human cancer panel.[68]

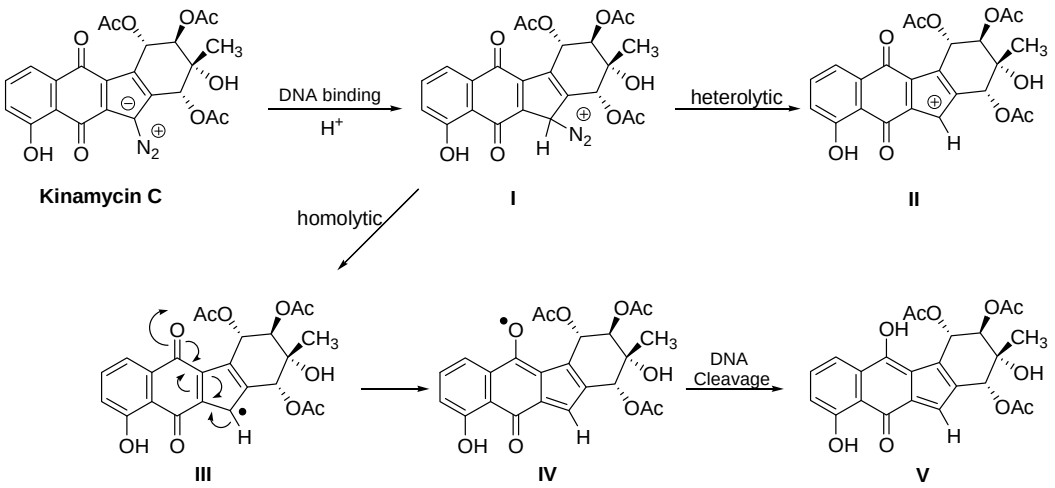
The presence of the 5-diazo fluorene group in the kinamycin family of antitumor antibiotics would lead one to think of an active role for the diazo group. The hypothesis may be substantiated by the fact that kinafluorenone,[24] one of the precursors in kinamycin biosynthesis which lacks the diazo moiety, shows no antibiotic activity against *B.subtillis* ATCC 6633, known to be very sensitive to kinamycins. However, prekinamycin,[54] which is similar to kinafluorenone but retains the diazo group, shows activity towards Gram-positive bacteria (Figure 9).



Prekinamycin (active) | **Kinafluorenone (inactive)**

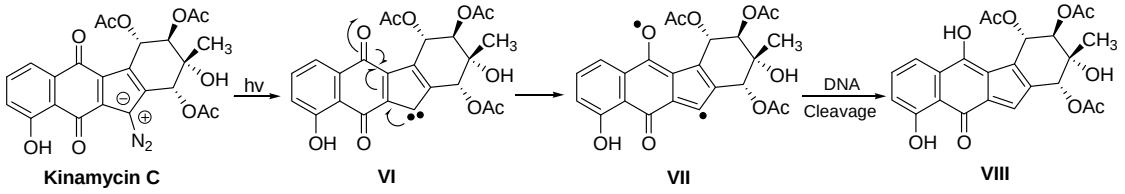
Figure 9. The diazo group determines the activity of benzo[*b*]fluorene structures

Kinamycins are highly active DNA cleaving agents and their unique cytotoxicity profile, compared to other known DNA-damaging anticancer drugs such as adriamycin and mitomycin C, may suggest a different mechanism of interaction with DNA. Although their mechanism of action has not yet been determined, studies with model diazobenzo[*b*]fluorene compounds have indicated that the diazo group plays a key role in the biological activity of these compounds. Additionally, the presence of a redox-active quinone in close proximity to the diazo functionality suggests that the natural product may use the quinone-diazo combination as an intramolecular redox switch to promote nitrogen release and activate the drug for DNA cleavage. The protonation of kinamycins, perhaps under physiologically relevant pHs after DNA binding, may generate unstable diazonium ions[69] or diazonium-like species such as **I**.[70] These intermediates could undergo a heterolytic cleavage with a spontaneous loss of nitrogen (N_2) to generate carbocation **II**, which is capable of cleaving DNA via alkylation. Alternatively, they could be reductively activated via a homolytic cleavage to yield radical species **III**, which is capable of inflicting DNA damage via the vinyloxy radical species **IV** (Scheme 3).



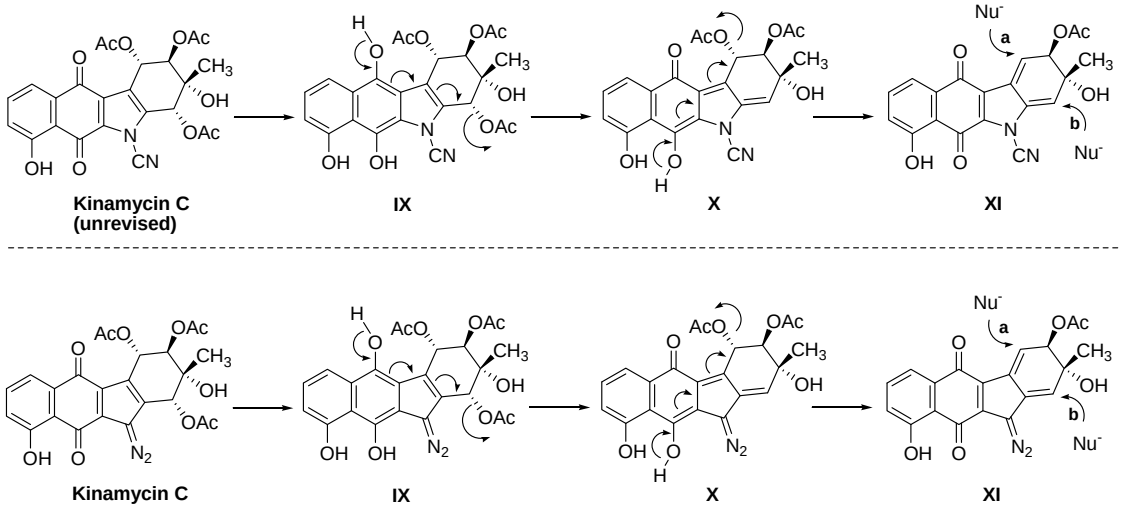
Scheme 3. Proposed mechanism of DNA cleavage triggered by protonation

The intermediacy of a kinamycin carbene species such as **VI** that could account for DNA cleavage was also reported.[71] Photolytic decomposition of kinamycin C leads to carbene **VI**, which itself may induce DNA cleavage or rearrange to the more reactive diradical species **VII** (Scheme 4). The rearrangement to **VII** leads to a vinylic carbon centered radical similar to that present in neocarzinostatin.



Scheme 4. Proposed photochemical DNA cleavage with kinamycin C

The bioreductive alkylation mechanism of interaction of kinamycins with DNA, which was proposed as early as in 1977 when they were still perceived as N-cyanocarbazoles, should still hold and is worth mentioning.[72] Moore suggested that these indole quinones with potential leaving groups as acetates could interact with nucleophilic sites in DNA (Scheme 5). Their function as a bioreductive alkylating agent is outlined in Scheme 5 with kinamycin C (shown as carbazoloquinone cyanamides) as the model drug.



Scheme 5. Bioreductive alkylation mechanism of the interaction of kinamycin C with DNA

The mechanism involves the bioreduction of quinone moiety to hydroquinone intermediate **IX**, which can rearrange to semiquinone **X** via the loss of an acetate in ring D.[72] A similar reversion to the quinone can lead to the proposed active form **XI** of kinamycin C, which may act as a trap for the nucleophilic sites of DNA. Nucleophilic attack of DNA can occur on intermediate **XI** through pathways *a* or *b* and it will most likely be dependent on the mode of binding of kinamycins to DNA. This mechanism of activation and reaction with DNA should not be affected by the reassigned structures of these drugs as diazo-containing natural products.

Given the rich biological profile of kinamycins, more efforts are needed in order to further elucidate the mechanism of action of these antibiotics. Nevertheless, functional groups, such as diazo and diazonium capable of inducing cleavage in DNA, hold promise in the development of DNA damaging drugs. This data, coupled with the fact that diazobenzo[*b*]fluorene groups are stable entities in the kinamycin antibiotics, promises an exciting new arena for the development of DNA targeted agents.[69a, c]

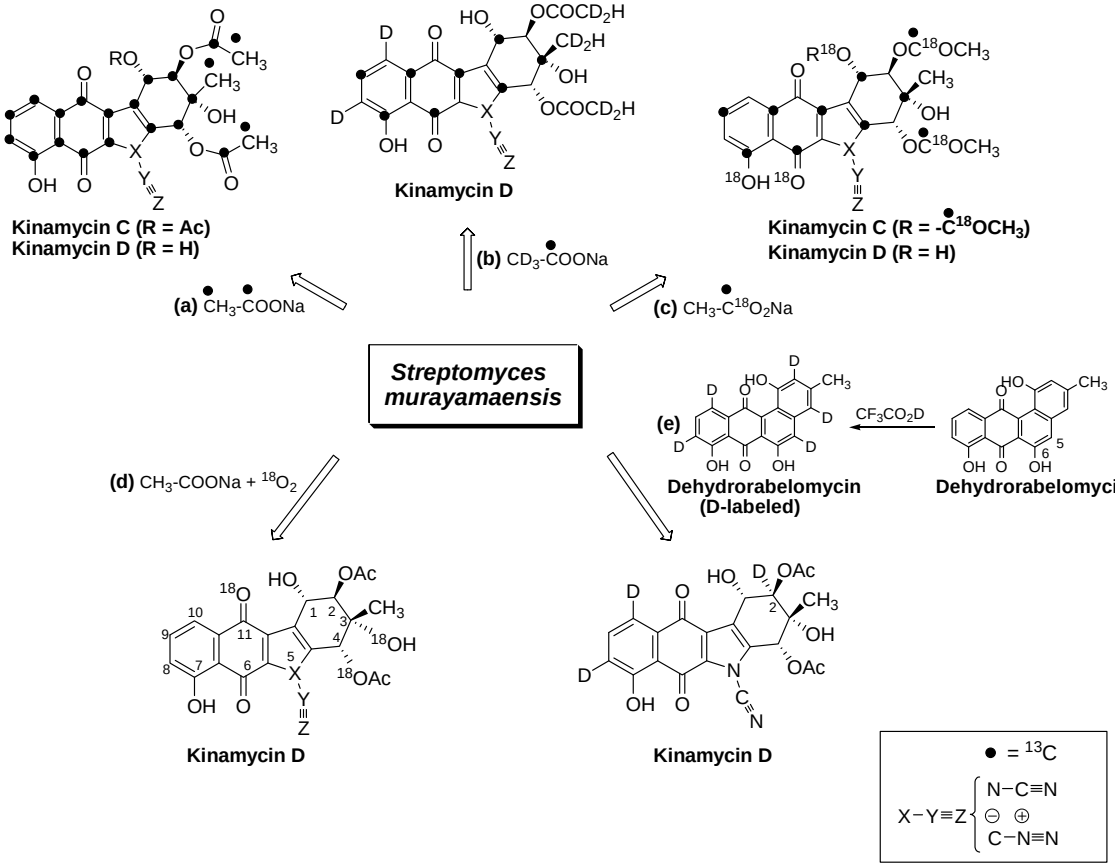
1.5 Biosynthesis of Kinamycins

1.5.1 Origins of C, H, and O Atoms in the Kinamycin Skeleton

During the period from 1970 until 1990, several efforts were carried out to address the biosynthetic pathway of kinamycins. Initially, Omura tried to study the origin of the "cyanamide carbon" of kinamycins by using IR spectroscopy. Gould worked on the isotope labeling of kinamycin precursors and NMR analysis in order to enlighten the biosynthesis of kinamycin antibiotics. The majority of studies concerning the biosynthesis of kinamycins was completed before the structural revision in 1994. Based on the new structural assignment, it was necessary to reexamine the already known biosynthetic mechanisms as well as the intermediate metabolites that were involved. Fortunately, all new biosynthetic studies, using the revised structure, were in agreement with the already known results using the incorrect structure. The extensive analysis of the results were reviewed in detail by Gould.[73, 20]

Gould fed *Streptomyces murayamaensis* with a variety of isotope-labeled sodium acetate and metabolite intermediates (Scheme 6). The derived amounts of isotope-labeled kinamycin C and kinamycin D were examined with NMR analysis to determine the distribution of isotopic atoms.[24, 60, 61, 74, 75] The observed concentration of ^{13}C revealed that the entire skeleton of kinamycin was of polyketide origin and all carbons, except the "cyanamide" one, were derived from acetate [Scheme 6 (a-c)]. Also, it was found that oxygen at C-1, C-6 and C-7 was derived from acetate, the oxygen at C-2 from water and finally the oxygen at C-3, C-4, C-11 came from air (O_2) [Scheme 6 (c), (d)]. Dehydrorabelomycin, a product during the fermentation of *Streptomyces murayamaensis*, was determined to be the key biosynthetic intermediate for kinamycins [Scheme 6 (e)]. The origin of the "cyanamide carbon" which was later became the diazo carbon, remained a mystery until the work by Omura in 1976. In this work, *Streptomyces murayamaensis* were fed with $CH_3{}^{13}COONa$ and $^{13}CH_3COONa$ and the resulting kinamycin D was characterized with IR spectroscopy.[76] Only in the case of $CH_3{}^{13}COONa$ it was observed a shift from 2155 to 2139 cm^{-1}, perceived as the stretching frequency of the isotope ^{13}C-N triple bond within the *N*-cyano group, which is assigned today to the diazo stretching. This observation indicated that the previously assigned "cyanamide carbon" (today the diazo

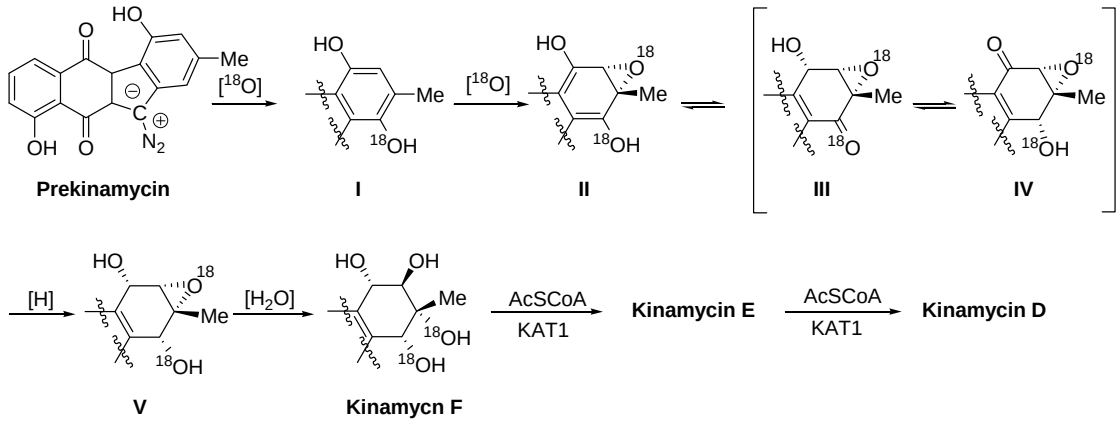
carbon) was derived from the carbonyl carbon of the acetate. Gould reexamined Omura's observation by feeding bacteria with either $CH_3{}^{13}COONa$ or $^{13}CH_3COONa$ and he was led to the same results.[61] However, the results of the more credible NMR spectroscopy also provided an alternative option where the "cyanamide carbon" (today assigned as the diazo carbon) could be derived from the methyl carbon of the acetate on the grounds that ^{13}C enrichment of the "cyanamide carbon" was only observed in kinamycin D derived from $^{13}CH_3COONa$.[61] Given that the observed level of the isotope enrichment for the "cyanamide carbon" was similar to other carbons of the kinamycin skeleton, it was further proposed that the "cyanamide carbon" was derived from C-5 of dehydrorabelomycin [Scheme 6 (e)].



Scheme 6. Biosynthetic origins of carbon, oxygen and hydrogen atoms of kinamycins

1.5.2 Oxidative Elaboration of the D-Ring of Kinamycins

Results from the previous labeling studies incorporating $CH_3{}^{13}C^{18}O_2Na$ (Scheme 6 (c) shed some light regarding the oxidative elaboration of the D-ring of kinamycins (Scheme 7).[75] Given that kinamycin D [Scheme 6 (b)] does not incorporate any deuterium labeling at C-4, it may indicate that an oxidation of the aromatic D-ring of prekinamycin can occur leading to hydroquinone **I** which could be further oxidized to epoxide **II**. Then tautomerization of epoxide **II** can lead to epoxyquinol **III** and/or **IV** which can undergo astereoselective reduction to generate epoxy diol **V**. Then, epoxide opening with water at the less hindered C-2 position would establish the highly oxygenated D-ring providing entry to kinamycin F.



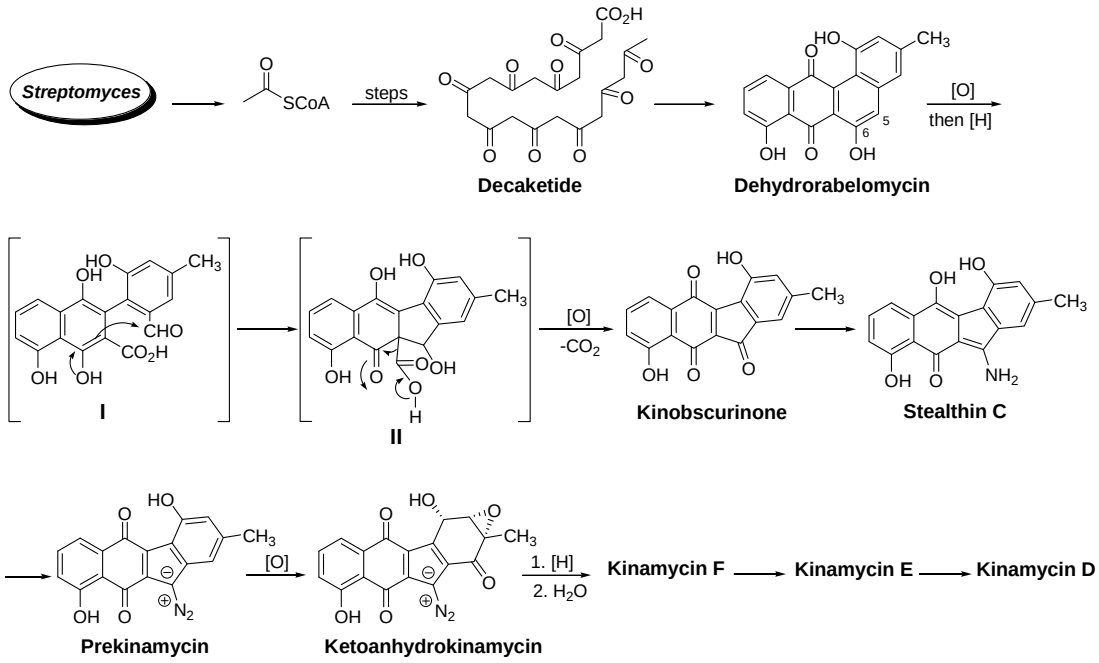
Scheme 7. Oxidative elaboration of the D-ring of kinamycins

That study also proved the correct stereochemistry of the D-ring indicating that each atom was derived from the correct source as found by the labeling studies (Scheme 6). The proposed mechanism for the D-ring construction was also enhanced by the isolation of minor metabolites like ketoanhydrokinamycin, prekinamycin, kinamycin F and kinamycin E from *Streptomyces murayamaensis* and its mutants. In 1996 Gould isolated a relatively large enzyme from *Streptomyces murayamaensis*, known as kinamycin acetytransferase I (KAT 1),[77] which was responsible for two subsequent acetylations of kinamycin F (Scheme 7). Firstly, acylation at the C-4 position generates kinamycin E followed by acylation at C-2 resulting in kinamycin D. There are two more kinamycin acetytransferases

which are required to account for the remaining three other acetylation patterns on the kinamycin D-ring.[73]

1.5.3 The Biosynthetic Pathway of Kinamycins

The understanding of kinamycin biosynthesis on the level of molecular biology was greatly promoted after successfully cloning the genomic DNA (genes) of *Streptomyces murayamaensis* and heterologously expressing the genes when the DNA was transferred into *Streptomyces lividinas* ZX7.[20] The genetic studies identified two clusters of polyketide synthase (PKS) genes, among which only one was responsible for producing the kinamycins through a decaketide intermediate (Scheme 8). The other gene was likely responsible for producing murayaquinone, a metabolite previously isolated from *Streptomyces murayamaensis*, through a different (but unknown) decaketide pathway. The expression of a particular kinamycin gene cluster in *Streptomyces lividinas* ZX7 was not complete, but it led only to the production and isolation of several already known intermediate metabolites observed in the biosynthetic pathway of kinamycins. Among them are dehydrorabelomycin, kinobsuricone and stealthin C. Assembly of evidence from all these biosynthetic studies led to a hypothetical biosynthetic mechanism for kinamycins involving a polyketide precursor. The mechanism involves the condensation of a decaketide followed by aromatization and decarboxylation to yield dehydrorabelomycin, the key intermediate in the whole biosynthetic sequence (Scheme 8).

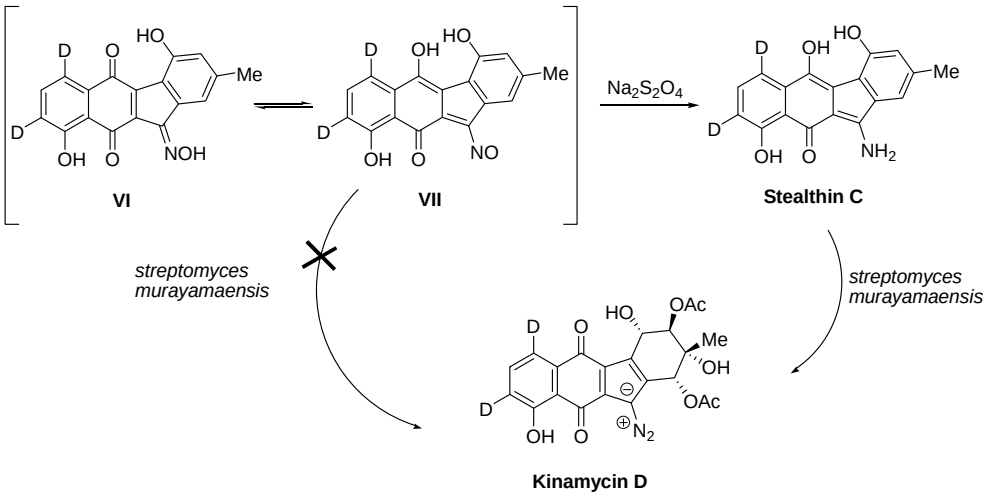


Scheme 8. Proposed biosynthetic pathway of benzo[*b*]fluorene-type kinamycins

Dehydrorabelomycin can undergo an oxidative ring opening at C-5 and C-6 followed by reduction of the quinone to afford **I**. Then **II** would result via an electrophilic cyclization of **I** providing entry to the benzo[*b*]fluorene moiety for first time. The resulting dihydroquinone would be oxidized to produce kinobscurinone which could afford stealthin C via an amination process. Stealthin C, which possesses an essential amino functionality at C-5, could undergo an oxidative incorporation of the second nitrogen atom to yield prekinamycin. Oxidation of prekinamycin to ketoanhydrokinamycin followed by ketone reduction and epoxide opening, generates kinamycin F. Then, further D-ring acetylations can lead to kinamycins E and D.

The intermediacy of sealthin C, a metabolite isolated from a mutant MC2 *Streptomyces murayamaensis*,[27] in the kinamycin biosynthetic pathway was nicely demonstrated by Gould. When *Streptomyces murayamaensis* was fed with deuterium-labeled stealthin, the production of deuterium-labeled kinamycin D was observed. On the contrary, there was no production of labeled kinamycin D when *Streptomyces murayamaensis* was fed with a similar synthetic compound such as **VII**, thus confirming the presence of stealthin C as a critical intermediate in the kinamycin biosynthetic pathway (Scheme 9). However, the

genes and the products related with the last steps for the formation of the diazo group have not been identified yet.



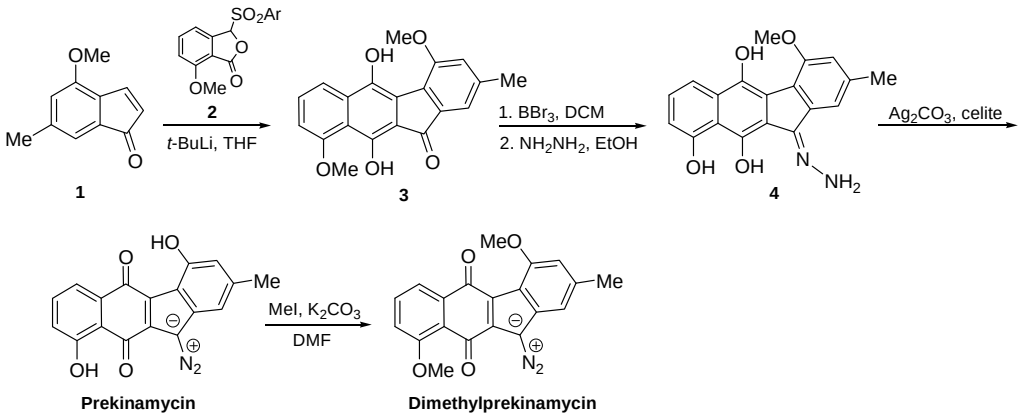
Scheme 9. Stealthin C as a critical intermediate in the biosynthesis of kinamycins

1.6 Previous Synthetic Work

1.6.1 Total Synthesis of Prekinamycin

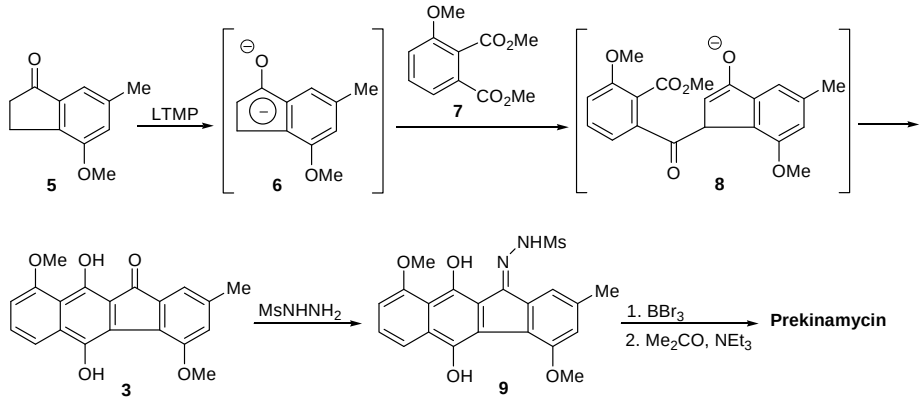
The name and structure of prekinamycin was assigned to an isolated purple metabolite from *Streptomyces* in 1989.[19, 24] However, in 2000 it was found that this compound was in fact isoprekinamycin.[29] The real prekinamycin was isolated in 1994[27] but it was correctly characterized in 1996.[28] Synthetic studies towards prekinamycin facilitated the correct structure assignment.[32]

The first total synthesis of prekinamycin was achieved by Hauser in 1996 and it was based on a phthalide annelation methodology.[78] As shown in Scheme 10, regioselective condensation of indenone **1** with phthalide sulfone **2** yielded the benzo[*b*]fluorine ketone **3**. Demethylation of **3** with BBr_3 followed by reaction with hydrazine and a Ag_2CO_3 mediated oxidation of the intermediate hydrazone, gave prekinamycin. Further elaboration of prekinamycin with MeI and K_2CO_3 in DMF produced the dimethyl derivative of prekinamycin (**4**).



Scheme 10. Hauser's total synthesis of prekinamycin

Another remarkable total synthesis of prekinamycin was reported by Birman in 2007.[79] This work confirmed its primary goal to demonstrate a general procedure for the construction of a functionalized benzo[*b*]fluorenone core via a base-induced double anionic condensation. (Scheme 11)

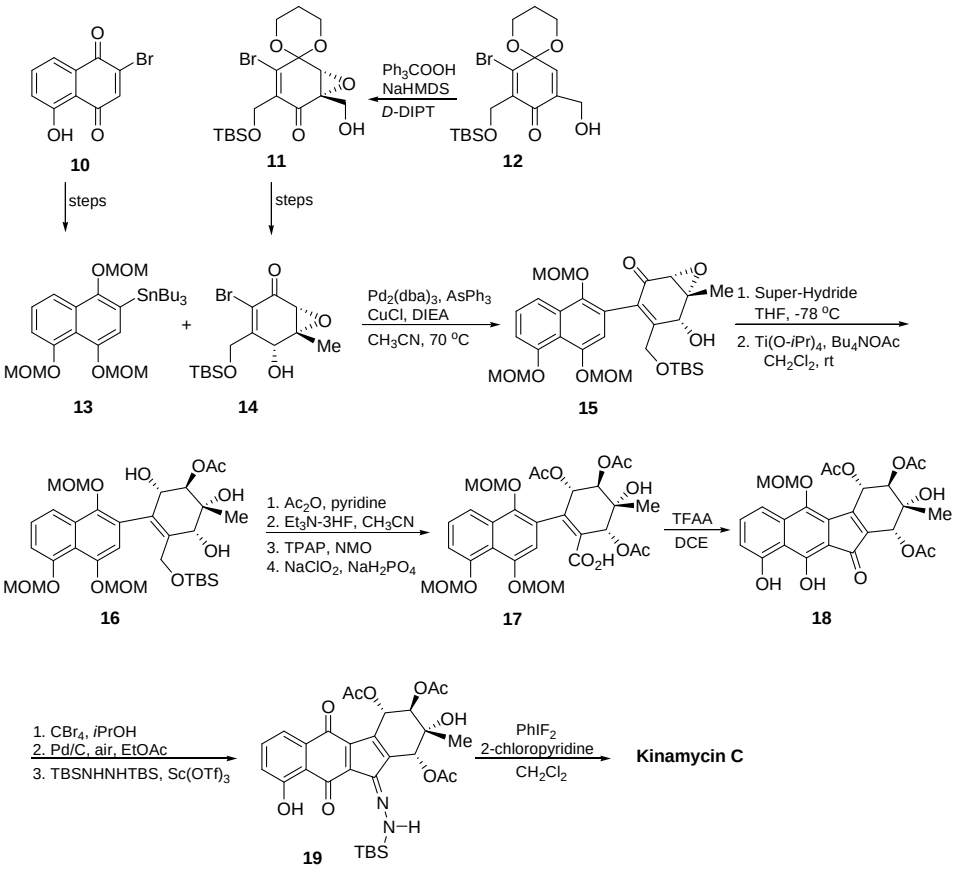


Scheme 11. Birman's total synthesis of prekinamycin

The total synthesis of prekinamycin was achieved in a straightforward manner starting from indanone **5** and its dianion **6**. Bis-acylation of dianion **6** with the unsymmetrical phthalate diester **7** produced directly the desired tetracycle **3** which was subsequently converted to mesylhydrazone **9**. Total demethylation with BBr_3 followed by treatment with triethylamine under an air atmosphere gave prekinamycin.

1.6.2 The First Enantioselective Total Synthesis of Kinamycin C by Porco

The first enantioselective total synthesis of kinamycin C was reported by Porco in 2006 (Scheme 12).[80] The strategy involved the preparation of the two key fragments **13** and **14**. The MOM-protected arylstannane **13** was readily available from 1,5-naphthalenediol **10**. Bromoenone **14** was derived from epoxy alcohol **11** after a sequence of steps including a hydroxyl-directed reduction, selective mesylation of the primary hydroxyl and reductive demesylation. Chiral epoxy alcohol **11** was the product of an asymmetric allylic epoxidation of the achiral bromoquinone monoketal **12**.



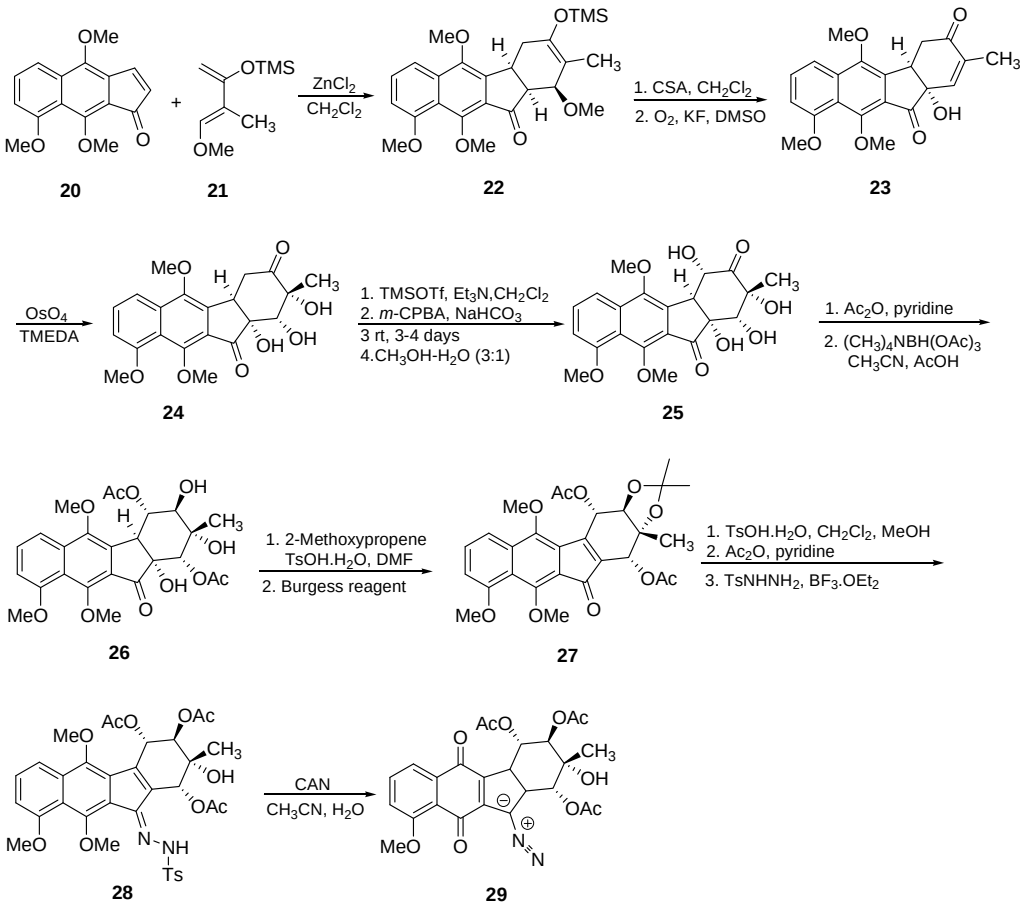
Scheme 12. The first enantioselective synthesis of kinamycin C by Porco

A Stille coupling reaction between compounds **13** and **14** afforded the coupling product **15**, thus establishing the crucial connection between the AB-ring and D-ring components. Stereoselective reduction of enone **15** with Super-Hydride followed by a regioselective epoxide ring opening with Bu_4NOAc afforded triol **16**, setting the stereochemistry of the

D-ring of kinamycins. Acylation of **16** followed by silyl ether deprotection and sequential oxidations with TPAP and $NaClO_2$ yielded carboxylic acid **17**. An efficient intramolecular Friedel-Crafts acylation of **17** with TFAA, with concomitant MOM deprotection of the two phenolic hydroxyls at the south side of the molecule, effected C-ring closure and formationof the desired enone **18**. MOM deprotection of **18**, followed by hydroquinone oxidation and condensation with 1,2-bis(*tert*-butyldimethylsilyl)-hydrazine gave hydrazone **19**. Finally, oxidation of **19** installed the diazo functionality and gave access to kinamycin C.

1.6.3 Total Synthesis of (±)-*O*-Methylkinamycin C by Kumamoto

In 2007 Kumamoto accomplished the total synthesis of racemic (±)-*O*-methylkinamycin C (Scheme 13).[81] This strategy is based on the Diels-Alder reaction between benzo[*f*]indenone **20** and Danishefsky-type diene **21** in order to construct the highly functionalized ABCD-ring system of kinamycins.[82, 83] Indenone **20** underwent a Lewis acid catalyzed cycloaddition with diene **21** to generate tetracycle **22**. Then, hydrolysis of the enol ether in **22** followed by ketone hydroxylation gave enone **23**, which underwent a diastereoselective hydroxyl-directed dihydroxylation to generate *cis*-triol **24**. Conversion of **24** to the silyl enol ether followed by an oxidation with *m*-CPBA, isomerization of the C-1 hydroxyl and TMS deprotection, resulted in tetrol **25**. Selective acetylation of the less hindered secondary hydroxyl groups followed by a diastereoselective hydroxyl-directed ketone reduction with $(CH_3)_4NBH(OAc)_3$, provided tetracycle **26** with the desired D-ring stereochemistry. Protection of the *trans*-diol moiety in **26** as the acetonide and subsequent dehydration of the tertiary alcohol with Burgess reagent gave benzofluorenone **27**. Acetonide cleavage, acetylation of the resulting secondary alcohol and then ketone condensation with tosylhydrazine produced hydrazone **28**. Finally, CAN-mediated oxidation of hydrazone **28** gave (±)-*O*-methylkinamycin C (**29**).

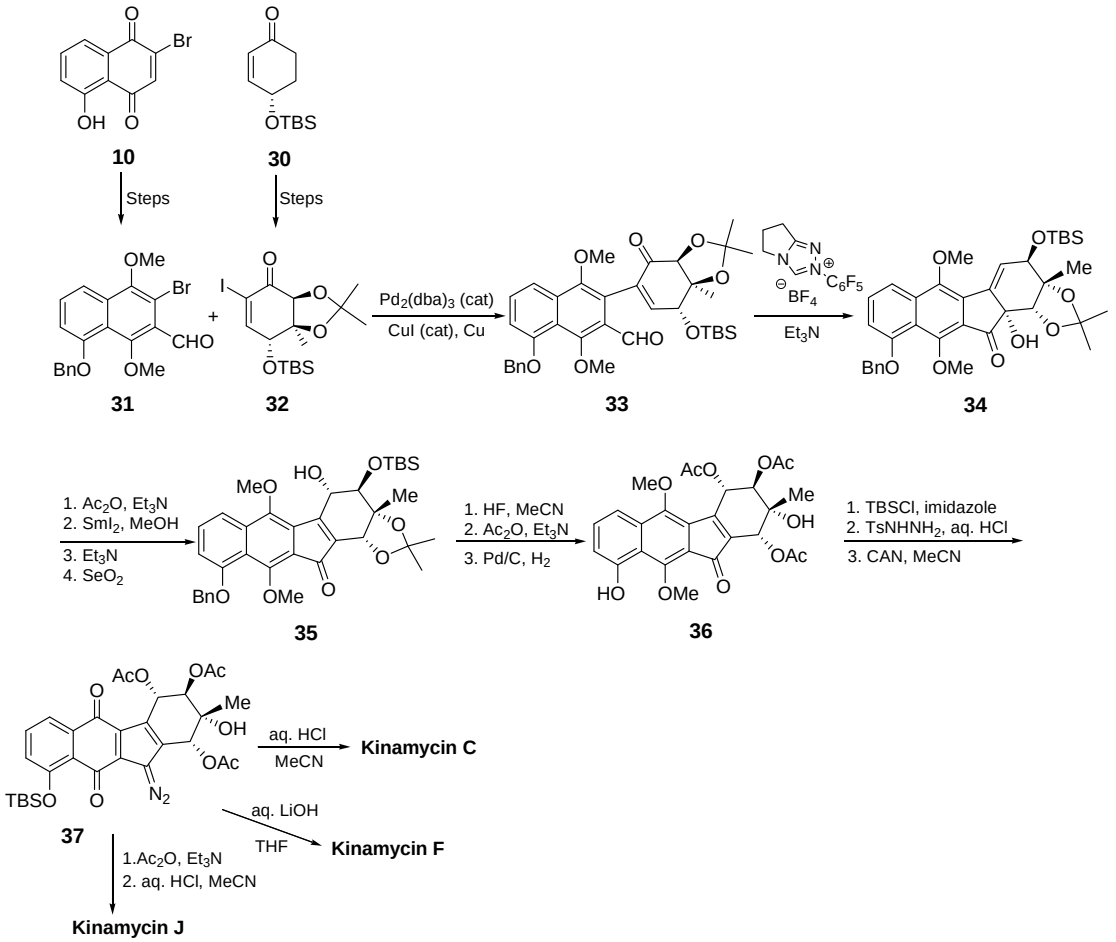


Scheme 13. Total synthesis of (±)-*O*-methylkinamycin C by Kumamoto

1.6.4 Enantioselective Total Synthesis of Kinamycins C, F, J by Nicolaou

The same year Nicolaou published the enantioselective total synthesis of kinamycins C, F and J (Scheme 14).[84] The strategy involved the Ullmann coupling reaction between the AB-ring fragment bromonaphthaldehyde **31** and chiral D-ring fragment iodoenone **32** towards the construction of ABD-ring system enone **33**. Treatment of **33** with Rovis catalyst led to an intramolecular benzoin-like condensation affording hydroxyketone **34** and assembling the kinamycin tetracyclic ring system. Substrate **34** was subjected to an allylic transposition in order to establish the D-ring stereochemistry and generate the desired benzofluorenone **35**. This transposition was achieved succefully via a series of transformations. First, acylation of alcohol **34** followed by reductive cleavage of the resulting tertiary acetate with SmI_2, double bond migration and a SeO_2 mediated stereoselective allylic oxidation, provided compound **35**. Removal of the TBS and

acetonide groups followed by acetylation and debenzylation, afforded benzofluorenone **36**. Temporary protection of the phenolic hydroxyl group of **36** as the TBS ether followed by hydrazone formation with $TsNHNH_2$ and a CAN-mediated oxidation step, gave the TBS-protected kinamycin **37**. Disilylation of **37** under mild acidic conditions afforded kinamycin C. Acetylation of **37** and subsequent cleavage of the TBS group gave kinamycin J. Finally, removal of the acetate and TBS groups of **37** under basic hydrolysis with LiOH produced kinamycin F.

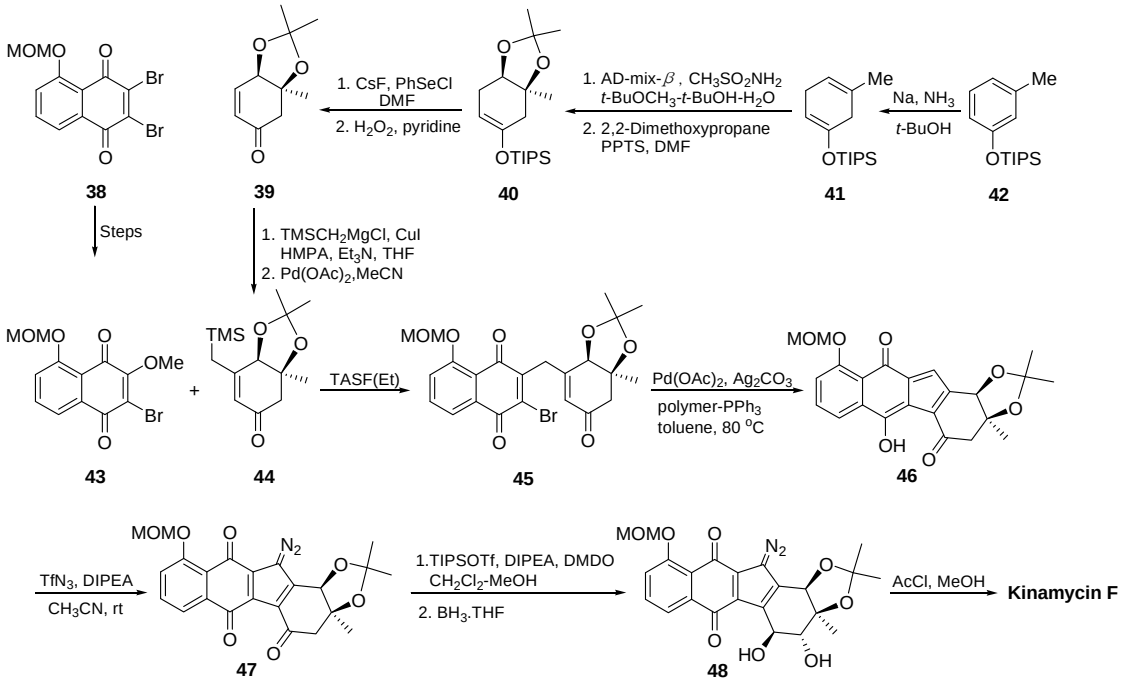


Scheme 14. Total synthesis of kinamycins C, F, J by Nicolaou

1.6.5 Enantioselective Total Synthesis of Kinamycin F by Herzon

An elegant enantioselective total synthesis of kinamycin F, as a convergent entry to the diazofluorene antitumor antibiotics, was reported by Herzon in 2010 (Scheme 15).[85] The synthesis involved the intermediacy of two key fragments, such as the D-ring enone

44 and AB-ring naphthoquinone **43**. The synthesis of enone **44** commenced with the Birch reduction of protected phenol **42** to cyclohexadiene derivative **41**. Sharpless asymmetric dihydroxylation of **41** followed by protection of the resulting chiral vicinal diol, gave the silyl enol ether **40** which was converted to enone **39**. Then, a copper-mediated 1,4-addition of $TMSCH_2MgCl$ to enone **39** followed by a palladium-mediated oxidation of the resulting enol ether, formed the desired compound **44**. Bromojuglone **43**, a versatile AB-ring component of kinamycins, was formed from dibromojuglone **38** via a three step sequence. Enone **44** underwent a TASF(Et) mediated γ-alkylation with compound **43** to form the ABD-ring adduct **45**, which underwent an intramolecular Pd-mediated cyclization to give compound **46** and provide acces to the kinamycin tetracyclic ring system. Compound **46** was a prime candidate to undergo a diazo transfer reaction with TfN_3 to generate diazofluorene **47**. Stereoselective C-2 hydroxylation of ketone **47** followed by a α-hydroxy directed ketone reduction gave the MOM-protected kinamycin **48** which was deprotected to yield kinamycin F.



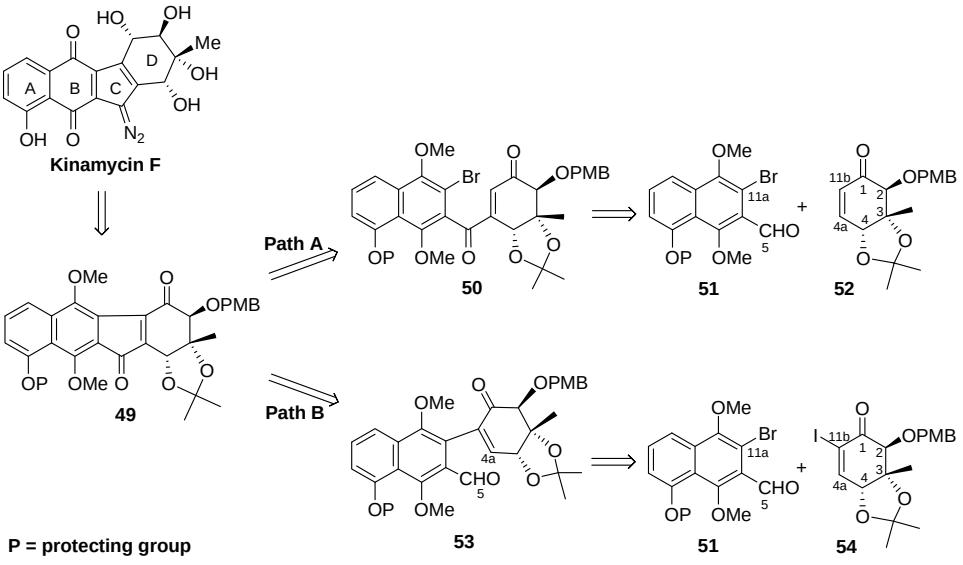
Scheme 15. Enantioselective total synthesis of kinamycin F by Herzon

CHAPTER 2

Stereoselective Synthesis of the Highly Oxygenated D-Ring and Construction of the ABD-Ring System of Kinamycins

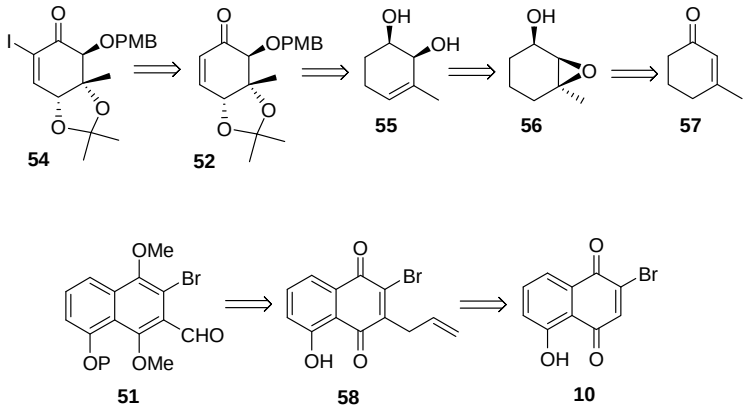
2.1 Proposed Strategy for the Synthesis of Kinamycin F and its Structural Analogues

We envisioned that access to kinamycin F and its structural analogues could be achieved from benzofluorenone **49**, a highly functionalized tetracyclic intermediate which may become accessible by two different synthetic pathways as shown in Scheme 16. According to path A, entry to the key intermediate **49** was envisioned as the outcome of an intramolecular Heck reaction of *β*-acyl enone **50**, which could in turn be derived from the *β*-functionalization of enone **52** with bromonaphthaldehyde **51** via a phosphoniosilylation strategy. Alternatively, access to benzofluorenone **49** could be gained from the intramolecular cyclization (i.e. phosphoniosilylation) of *α*-naphthylcyclohexenone **53**, envisioned as the product of a metal-catalyzed Ullmann type coupling of aldehyde **51** with *α*-iodocyclohexenone **54**.



Scheme 16. Retrosynthetic analysis for the synthesis of kinamycins

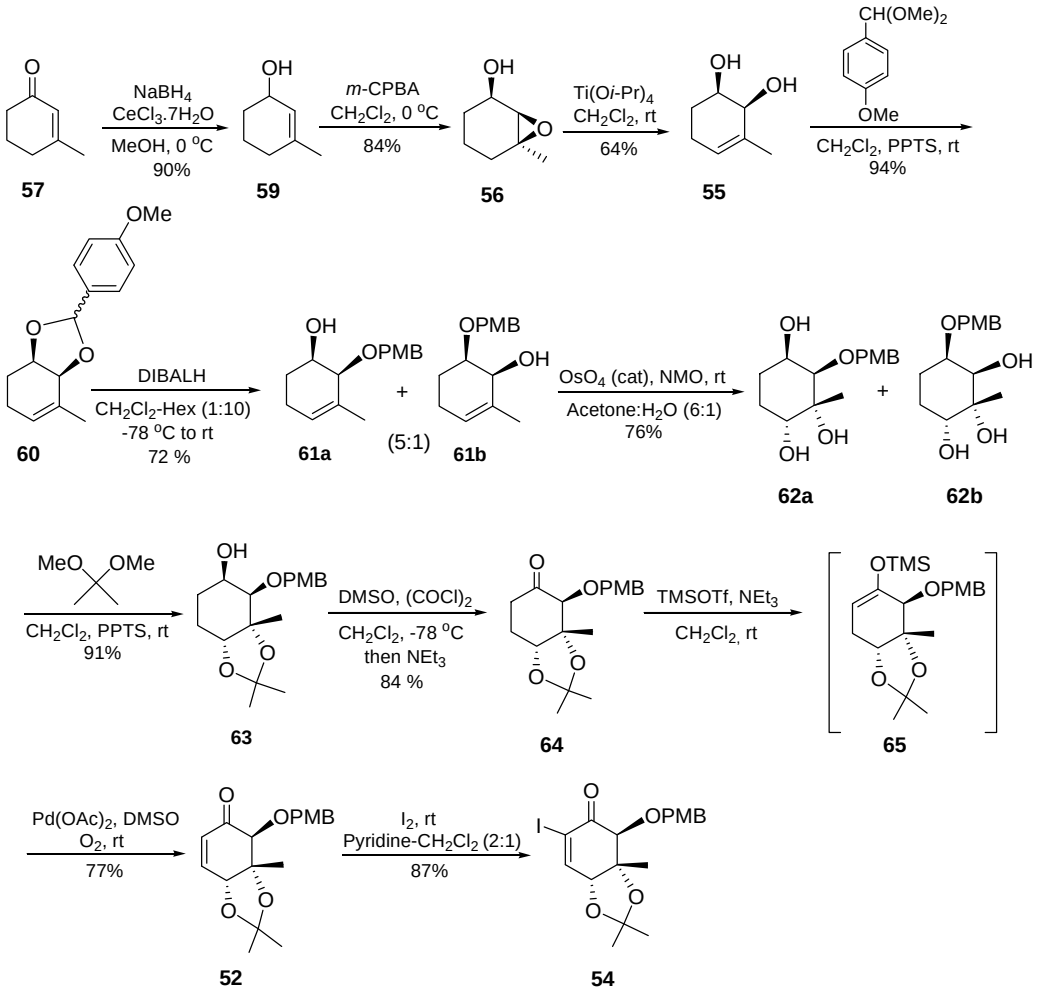
Iodoenone **54**, a highly oxygenated D-ring precursor which contains in place the latent C-2, C-3 and C-4 kinamycin chiral centers, could be readily available by the iodination of **52**. Cyclohexenone **52** could result from cyclohexenediol **55**, the product of a regioselective isomerization of epoxyalcohol **56**. Entry to **56** could in turn be achieved from commercially available 3-methyl-2-cylohexenone **57**. AB-ring fragment **51** could be prepared from naphthoquinone **58**, which is the product of an allylation reaction of bromojuglone **10** (Scheme 17).



Scheme 17. Retrosynthetic analysis of the two key kinamycin fragments

2.2 Entry to a Highly Oxygenated Cyclohexenone D-Ring Fragment

The synthesis of the D-ring fragment commenced with the Luche reduction of cyclohexenone **57** to cyclohexenol **59**[86] which was directly epoxidized with *meta*-chloroperoxybenzoic acid (*m*-CPBA) to generate epoxy alcohol **56**[87] (Scheme 18). Compound **56** underwent a Ti(O*i*Pr)$_4$ mediated regioselective isomerization to produce *cis*-diol **55** in 64% yield.[88] The protection of diol **55** with *p*-methoxybenzaldehyde dimethyl acetal afforded benzylidene ketal **60** in 94% yield as a mixture of diastereomers.



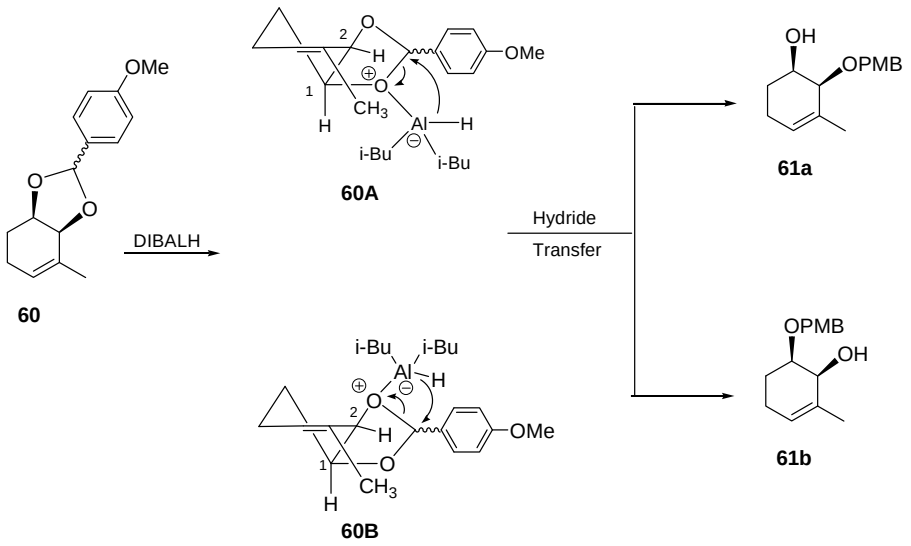
Scheme 18. A regio- and stereoselctive synthesis of D-ring components **52** and **54**

After a great deal of experimentation, the regioselective reductive opening of ketal **60** to alcohol **61a** was achieved (Table 2). The reductive ring opening of ketal **60** with diisobutylaluminum hydride (DIBALH)[89] in a mixture of CH_2Cl_2/hexane (1:10) at –78 °C proceeded from the less-hindered site and gave an inseparable mixture of alcohols **61a** and **61b** in 72% yield, in which the desired regioisomer **61a** (PMB = *p*-methoxybenzyl) was the major product (**61a**/**61b** = 5:1). However, alcohols **61a** and **61b** were obtained as a 1:1 mixture when CH_2Cl_2 was utilized as the sole reaction solvent. The observed regiochemical outcome was determined by ^{1}H NMR analysis of the mixture of the corresponding acetates of **61a** and **61b**.

Table 2. Reaction conditions for the reductive opening of ketal **60**

Reagent	Equivalents	Solvent	Temperature	Ratio 61a/61b
$LAH/AlCl_3$	4.6/4	THF	rt	(1:1)
$LAH/AlCl_3$	4.6/4	THF	-40 ^oC to rt	SM
DIBALH	2	CH_2Cl_2	0 ^oC to rt	(1:1)
DIBALH	4	THF	-78 ^oC to rt	SM
DIBALH	6	CH_2Cl_2	-78 ^oC to rt	(1:1)
DIBALH	6	CH_2Cl_2:Hexane (1:1)	-78 ^oC to rt	(3:1)
DIBALH	6	CH_2Cl_2:Hexane (1:9)	-78^oC to rt	(3:1)
DIBALH	6	Hexane	-78 ^oC to rt	(4:1)
DIBALH	6	CH_2Cl_2:Hexane (1:10)	-78 ^oC to rt	(5:1)

The regioselective reductive ring opening of ketal **60** to give **61a** in CH_2Cl_2/hexane (1:10) may presumably involve the association of DIBALH at the less sterically hindered site of the ketal, that is, the O-1 atom could form aluminum complex **60A**, which could then undergo a hydride transfer through a four-centered transition state or an oxocarbenium ion (Scheme 19).[90] Apart from steric factors that may favor the kinetic and thermodynamic formation of complex **60A** over **60B**, in which aluminum complexation occurs at the more sterically hindered ketal O-2 atom, electronic factors should be considered as well. For example, the presence of nonpolar hexane in the solvent system may increase the Lewis acid character of the aluminum and, thus, enhance its complexation with the more nucleophilic ketal O-1 atom and lead to the predominant formation of complex **60A**. On the contrary, the use of the more polar CH_2Cl_2 as the sole reaction solvent most likely enables the equal coordination of DIBALH at both ketal oxygens to give aluminum complexes **60A** and **60B** and result in a 1:1 mixture of **61a** and **61b**, respectively (Scheme 19).



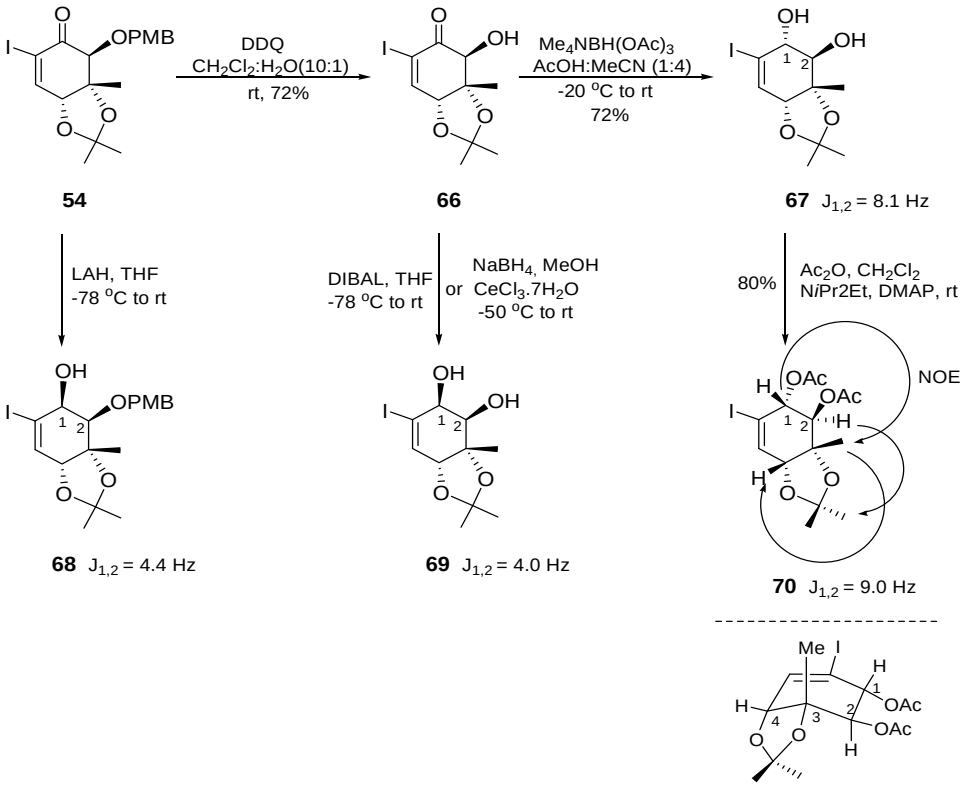
Scheme 19. Likely mechanism for the observed regioselectivity in the reductive opening of ketal **60**

Hydroxylation of the mixture of cyclohexenols **61a** and **61b** with catalytic OsO_4 occurred from the opposite face of the allylic oxygen[91] to produce triols **62a** and **62b**, which established the stereochemistry at the C-2, C-3, and C-4 chiral centers. The separation of the resulting mixture by flash chromatography enabled the isolation of the desired triol **62a** in 76% yield. Protection of the *cis*-diol moiety in **62a** as an acetonide gave alcohol **63** in 91% yield, which underwent a Swern[92] oxidation to generate ketone **64** in 84% yield. Treatment of **64** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and NEt_3 resulted in the intermediate trimethylsilyl enol ether, which underwent a Saegusa–Ito[93] oxidation of afford enone **52** in 77% yield. The clean formation of the desired trimethlsilyl enol ether of ketone **64** was also observed upon treatment of the ketone with lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran (THF) followed by the addition of TMSCl. Finally, iodination[94] of **52** by treatment with iodine and pyridine under Baylis–Hillman conditions,[95] produced the desired α-iodocyclohexenone **54** in 87% yield (Scheme 18).

2.3 Stereoselective Synthesis of the Highly Oxygenated D-Ring of Kinamycins

Enone **52** and iodoenone **54** are versatile synthons of the D-ring of kinamycins, which possess the desired stereochemistry at the latent C-2, C-3 and C-4 kinamycin chiral centers but not at C-1. Furthermore, their stereoselective reduction to the corresponding

cyclohexenol with the desired *trans*-stereochemistry between the C-1 and C-2 chiral centers would establish the D-ring of kinamycins. Attempts to stereoselectively reduce iodoenone **54** with lithium aluminum hydride (LAH) to the corresponding D-ring cyclohexenol were not fruitful and *cis*-alcohol **68** ($J_{1,2}$ = 4.4 Hz in $CDCl_3$) was formed as the sole product (Scheme 20). In the hope to achieve the desired stereochemistry via an *α*-hydroxy directed ketone reduction, enone **54** was converted into hydroxyketone **66** upon treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 20).



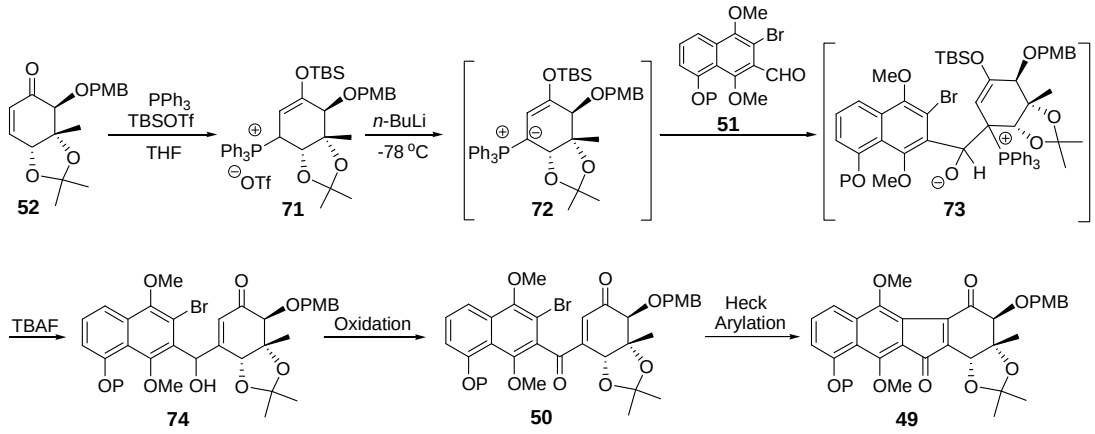
Scheme 20. Entry to the D-ring of kinamycins via an *α*-hydroxy directed ketone reduction.

However, reduction of **66** with a series of reducing agents such as $NaBH_4/CeCl_3.7H_2O$ or DIBALH resulted in *cis*-diol **69** ($J_{1,2}$ = 4.0 Hz in $CDCl_3$). On the contrary, compound **66** underwent a facile *α*-hydroxy directed ketone reduction with $Me_4NBH(OAc)_3$[96] to yield *trans*-diol **67** ($J_{1,2}$ = 8.1 Hz in $CDCl_3$). The conversion of **67** to diacetate **70** clerly confirmed the desired *trans*-stereochemistry ($J_{1,2}$ = 9.0 Hz in $CDCl_3$). The observed coupling constants are consistent with the half-chair being the predominant conformation in which the C-1 and C-2 hydroxy or acetoxy groups are in pseudoequatorial orientations and are comparable to $J_{1,2}$ values reported for kinamycins A, C, D, E and J.[97] Nuclear

Overhauser effect spectroscopy (^{1}H-^{1}H NOESY) on diacetate **70** revealed contacts between H-1 and the C-3 methyl, H-4 and the C-3 methyl, and between H-2 and the α-methyl of the acetonide, which confirmed the assigned structure of D-ring cyclohexene **70**.

2.4 Model Studies for the Assembly of the ABD-Ring System via a Phosphoniosilylation Strategy

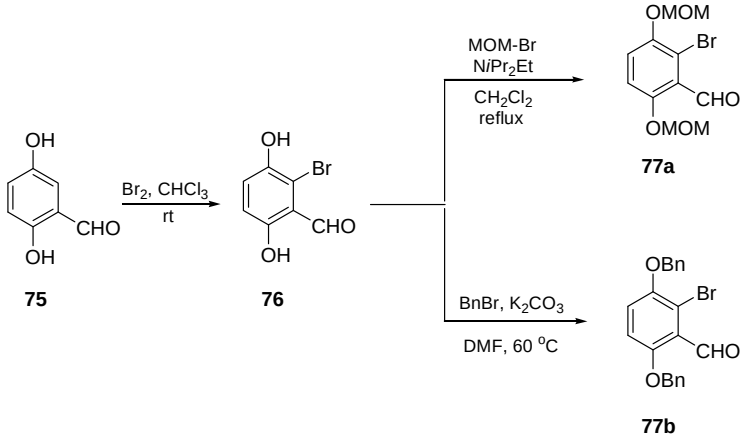
A phosphoniosilylation process[98] seemed a viable strategy for the preparation of the functionalized enone **50**, a versatile intermediate that could undergo an intramolecular arylation to benzofluorenone **49** (Scheme 16, Path A). According to this strategy, treatment of enone **52** with PPh_3 and TBSOTf would give phosphonium salt **71**, which could be deprotonated to ylide **72** upon treatment with a strong base such a *n*-BuLi. Although ylide **72** may suffer a competitive β-alkoxy elimination and decompose, we surmised that ylide addition to bromonaphthaldehyde **51** may proceed faster than its decomposition and afford adduct **73**. Then fluoride treatment of adduct **73** will restore the enone functionality and result in the secondary alcohol **74** which could subsequently be oxidized to the desired β-acylenone **50** (Scheme 21).



Scheme 21. Proposed strategy for the construction of the kinamycin ABD-ring system via a phosphoniosilylation chemistry

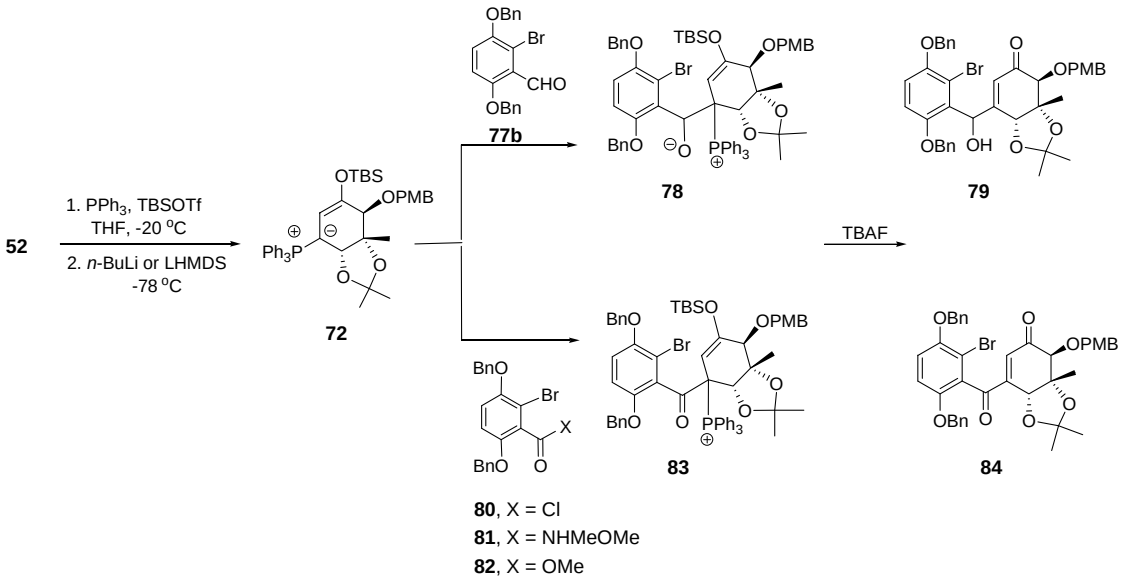
In order to assess the feasibility of the functionalization of enone **52** via this strategy, we opted to employ simpler benzaldehyde substrates before we embarked on the synthesis

of naphthaldehyde **51**. Therefore, two model aldehydes **77a** and **77b** were selected for these coupling experiments (Scheme 22). They were prepared by the alkylation of bromobenzaldehyde **76**, derived by the bromination of 2,5-dihydroxybenzaldehyde **75**. Protection of the two hydroxyl groups with MOM-Br (methoxymethyl bromide) and N*i*Pr$_2$Et (Hunig's base) in CH_2Cl_2 yielded aldehyde **77a**. Also, alkylation of **76** with BnBr and K_2CO_3 in DMF afforded the dibenzyl protected substrate **77b**.



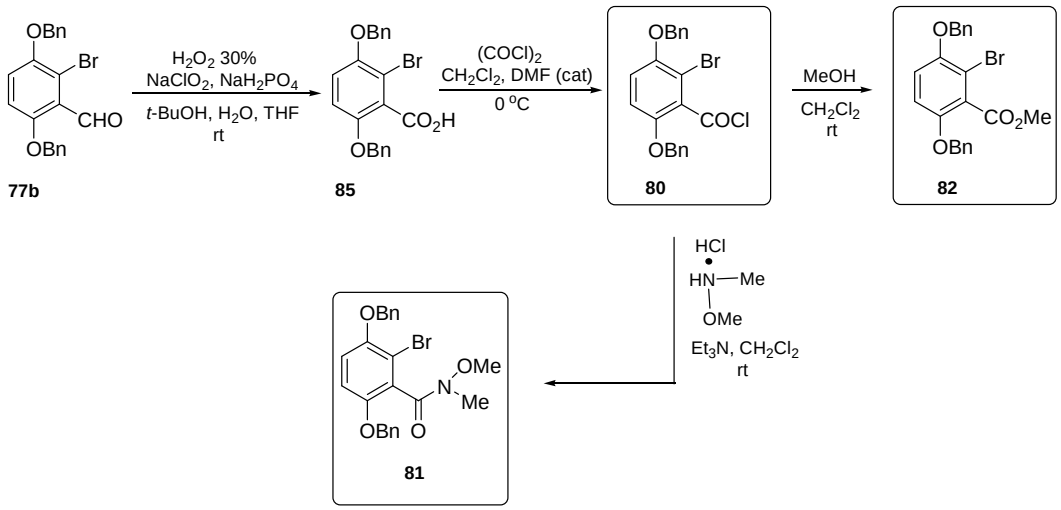
Scheme 22. Synthesis of model benzaldehydes for the phosphoniosilylationchemistry

When cyclohexenone **52** was treated with PPh_3 and TBSOTf in THF at -20 ^oC, TLC indicated the consumption of starting material and the formation of a new baseline spot, which was perceived as the phosphonium salt **71**. In the hope to generate ylide **72**, the reaction mixture was cooled at -78 ^oC and then treated with *n*-BuLi. Then, aldehyde **77b** was added to ylide **72** followed by quenching of the reaction mixture with TBAF (Scheme 23). Although TLC indicated the presence of a new spot along with starting materials **52** and **77b**, ^1H NMR spectrum of the crude reaction mixture did not contain any signals corresponding to the desired product **79**. Attempts to identify the new product were not fruitful at that time. Same results were obtained when LHMDS was employed as a base for the deprotonation of compound **71**.



Scheme 23. Model studies for the *β*-functionalization of D-ring cyclohexenone **52**

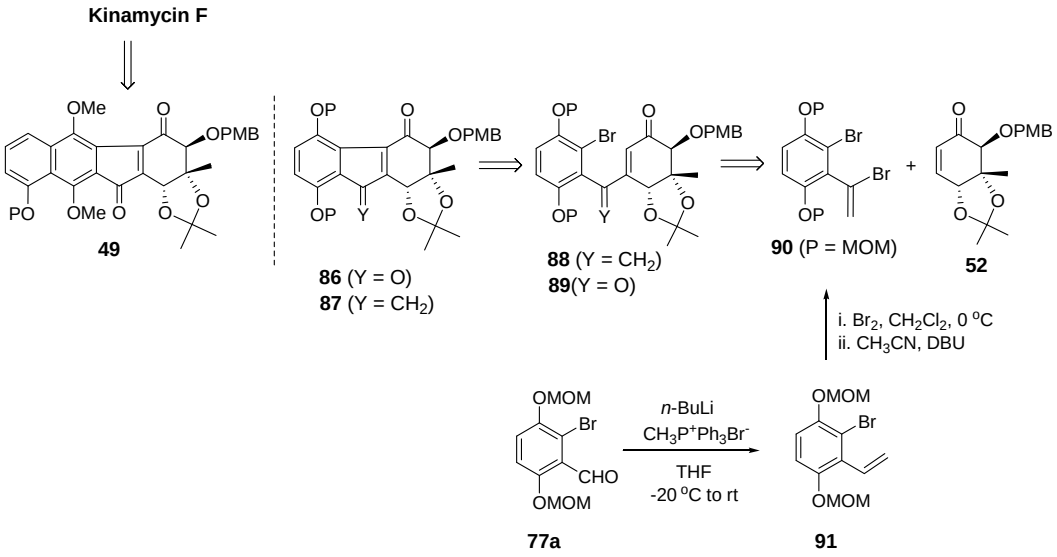
Given that the *β*-acylation of cyclic enones with chloroformates and acyl chlorides was reported,[99] the functionalization of enone **52** with substrates such as acid chloride **80**, Weinreb amide **81** and ester **82** towards enone **84** seemed a viable alternative (Scheme 23). Access to these substrates was provided by the oxidation of benzaldehyde **77b** with $NaClO_2$ to benzoic acid **85** which was smoothly converted to acid chloride **80**. Subsequent treatment with methanol gave methyl ester **82** (Scheme 24). Attempts to prepare Weinreb amide **81** from acid **85** and *N*, *O*-dimethylhydroxylamine via an HBTU mediated coupling, were not fruitful and starting material acid was recovered in most cases (Scheme 24). However, the desired amide **81** was prepared from chloride **80** upon treatment with Et_3N and *N*, *O*-dimethylhydroxylamine in CH_2Cl_2. After a great deal of experimentation, we realized that access to the desired *β*-acyl cyclohexenone **84** from substrates **80**, **81**, and **82** via an intermolecular phosphoniosilylation chemistry was not feasible. Starting material cyclohexenone **52** along with some unidentified byproducts were observed in most cases. Based on this data, we opted to abandon the phosphoniosilylation strategy and explore other approaches.



Scheme 24. Synthesis of various model carbonyl substrates for the *β*-functionalization of cyclohexenone **52**

2.5 Model Studies for the Assembly of the ABCD-Ring System via a Heck Reaction Strategy

We surmised that access to a *β*-functionalized cyclohexenone **89** and subsequently to diketone **86** (Y = O), which is reminiscent of our key kinamycin intermediate benzofluorenone **49**, could be achieved via the intermolecular Heck reaction of vinyl bromide **90** with cyclohexenone **52**. The intermolecular Heck reaction of aryl bromides with cyclic enones has been recently reported[100] despite its limitations. We hoped that bromide **90** would undergo a selective palladium catalyzed Heck reaction with enone **52** to give compound **88** (Y = CH_2). Then, oxidation of the styrene double bond would give *β*-acyl enone **89**. Should compound **88** undergo a tandem Heck reaction, tricyclic ketone **87** would result in one step which could be oxidized as well to model diketone **86** (Scheme 25). Alternatively, access to **86** could be gained from the intramolecular Heck arylation of *β*-acyl cyclohexenone **89**.



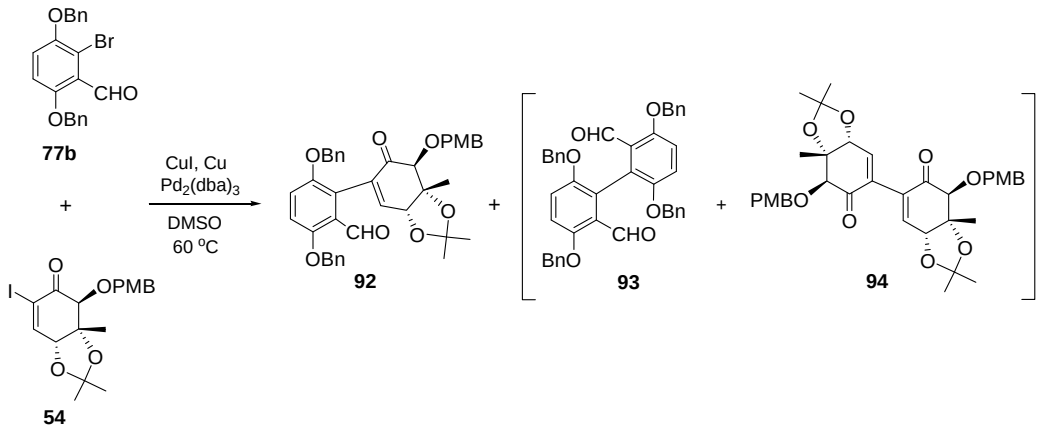
Scheme 25. Proposed strategy for the construction of the ABCD-ring system via a Heck reaction

In order to test this rather ambitious approach, the synthesis of vinyl bromide **90** was required. Freshly prepared MOM-protected benzaldehyde **77a** was subjected to a Wittig olefination reaction with methyltriphenylphosphinium bromide to give styrene **91**. Bromination of **91** with Br_2 in CH_2Cl_2 followed by treatment of the resulting dibromide with DBU in CH_3CN, produced the desired bromide analogue **90**. When a mixture of bromide **90** and cyclohexenone **52** with catalytic $Pd(OAc)_2$ and Cs_2CO_3 or NEt_3 was heated in DMF, starting material **52** was mainly observed along with a early eluting byproduct in TLC. This byproduct may presumably result from the dimerization of bromide **90**. Same results were observed when toluene was utilized as the reaction solvent. Also, addition of PPh_3 in the reaction mixture did not lead to the formation of Heck products **88** or **87**, given that the metal catalyzed dimerization of bromide **90** was found to proceed faster than the addition to the double bond of cyclohexenone **52**.

2.6 Model Studies for the Construction of the ABD-Ring System via an Ullmann Coupling

We realized that D-ring iodocyclohexenes **67** and **70** (Scheme 20) are ideal candidates to participate in a Suzuki or Stille reaction with an appropriate AB-ring fragment to

assemble the ABD-ring system of kinamycins. However, their precursor α-iodocyclohexene **54** appeared to be an attractive candidate for an Ullmann[101] type reaction with bromonaphthaldehyde **51** (Scheme 16). This direct coupling would obviate the preparation of the boronated and stanylated AB-ring fragments. In order to test the feasibility of this chemistry, model studies were carried out with bromobenzaldehyde **77b**. We found that when a mixture of **54** and **77b** was treated with CuI (0.4 eq), Cu (10 eq) and $Pd_2(dba)_3$ (0.1 eq) in DMSO and then heated at 60-70 ^oC, compound **92** was formed indeed in 60% (Scheme 26). The efficient formation of the latent C-11a-C-11b kinamycin bond, led us to consider the application of this chemistry in the real system with bromonaphthaldehyde **51**. Formation of a small amount of the dimerization byproducts **93** and **94** were also observed under these reaction conditions.

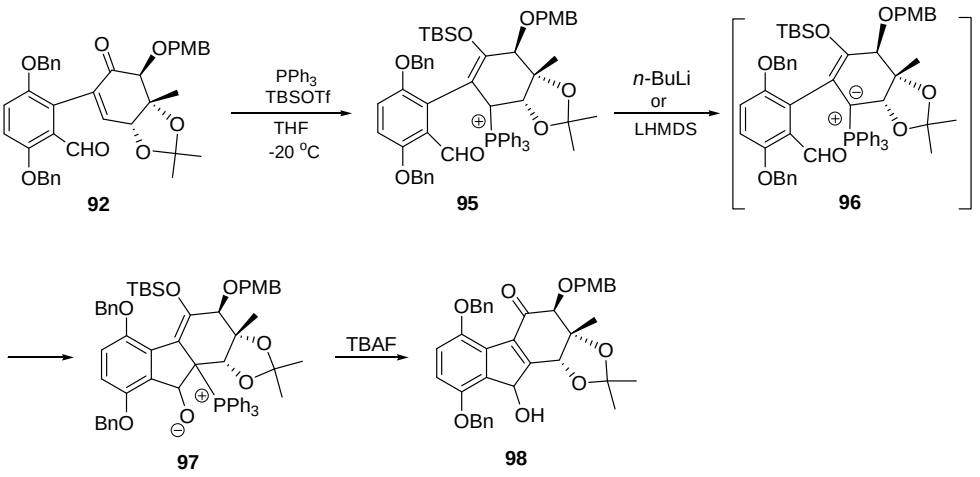


Scheme 26. Formation of the latent C-11a-C11b kinamycin bond on a model system via an Ullmann coupling reaction

2.7 Revisiting the Intramolecular Phosphoniosilylation Strategy on the Model Ullmann Coupling Adduct

Although the intermolecular phosphoniosilylation chemistry has failed to achieve the desired β-functionalization of cyclohexenone **52**, the idea of exploring the intramolecular version of this strategy on the model Ullmann adduct **92** was quite tempting. We surmised that deprotonation of phosphonium salt **95** to ylide **96** followed by ylide addition to the neighboring carbonyl, would afford adduct **97** which could then collapse to the tricyclic

compound **98** (Scheme 27). However, after several attempts compound **98** remained elusive. A small amount of starting material **92** along with unidentified decomposition byproducts were observed.

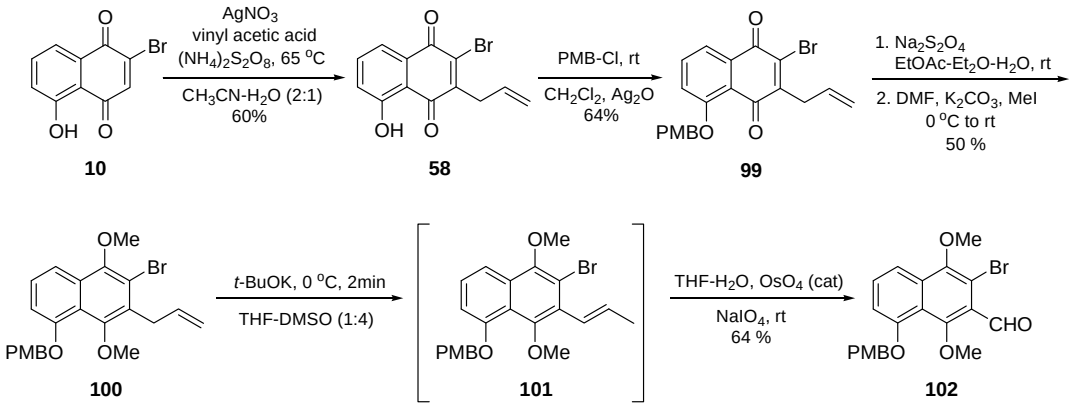


Scheme 27. Application of the phosphoniosilylation chemistry on Ullmann adduct **22**

2.8 Application into the Real System: Construction of the AB-Ring Fragment of Kinamycins

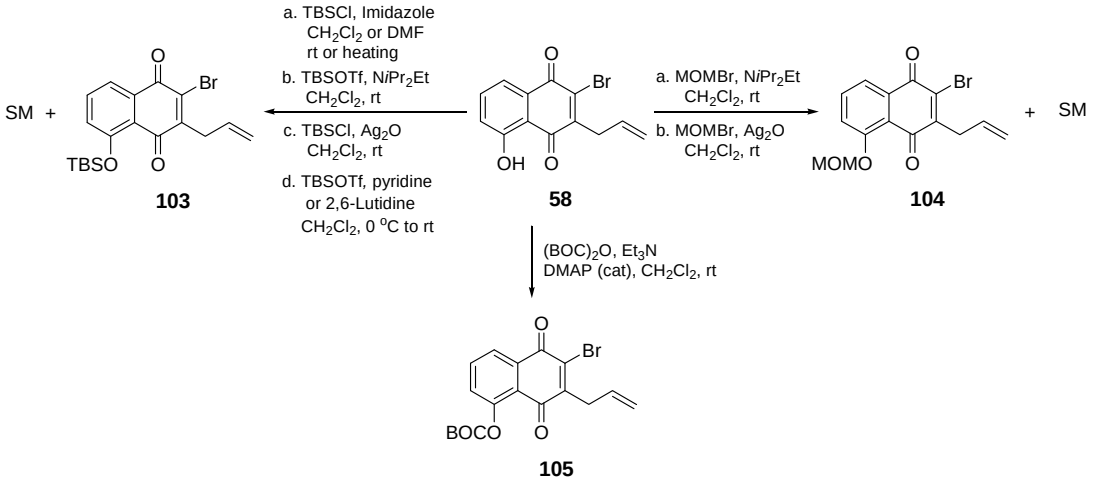
The synthesis of the AB-ring fragment bromonaphthaldehyde **102** was achieved in a straight forward manner starting from the readily available bromojuglone **10**[102] by employing a modified version of the protocol that was used by Nicolaou[84] to prepare a similar substrate (Scheme 28). The allylation of **10** with vinyl acetic acid in the presence of silver nitrate and ammonium persulfate[103] afforded naphthalenedione **58**,[84] which was converted into substrate **99** upon treatment with PMB-Cl and freshly prepared Ag_2O. The reduction of quinone **99** with $Na_2S_2O_4$ gave the intermediate hydroquinone, which was successfully methylated with MeI and K_2CO_3 to provide bromonaphthalene derivative **100**. The isomerization of the allyl group in **100** with *t*-BuOK was proved quite tricky. Attempts to isomerize the allyl group in **100** by treatment with *t*-BuOK (use as solid or solution) in THF as the reaction solvent, employing existing literature protocols, described for the syntheses of similar systems,[84, 103b, c] were not fruitful, and starting material was recovered. The use of solid *t*-BuOK in DMF or DMSO was found to be disastrous leading to the decomposition of starting material. Also, starting material was recovered when

NaOEt in THF or KOH in EtOH-THF was utilized. However, dropwise addition of a solution of **100** in DMSO to a solution of *t*-BuOK in THF effected the successful isomerization of **100** to provide internal olefin **101**, which underwent a Lemieux–Johnson oxidation to afford aldehyde **102** (Scheme 28).



Scheme 28. Synthesis of the AB-ring fragment bromonaphthaldehyde **102**

The protection of the hydroxyl group of naphthalenedione **58** was not as straightfoward as it was initially thought, and thus a variety of protecting groups were tested under a wide range of reaction conditions. The idea of having a MOM group in naphthoquinone **104** captured our attention, given the stability of the protecting group in similar naphthoquinone systems coupled with its facile removal under mild acidic conditions. However, attempts to protect the phenolic hydroxyl group in **58** as the MOM ether, using MOM-Br and Hunig's base or Ag_2O in CH_2Cl_2, were not fruitful. The desired product **104** was formed in low yields and found to gradually decompose back to starting naphthalenedione **58**. The use of an excess of reagents or heating the reaction mixture did not improve the yield of MOM ether **104**. Protection of naphthalenedione **58** as the TBS ether **103** with TBSCl or TBSOTf, gave mainly starting material and a small amount of the desired product accompanied with byproducts arising from the migration of the double bond of the allyl group. Also, protection of **103** as the BOC carbonate **105** with $(BOC)_2O$ was not successful and starting material was recovered (Scheme 29). Finally, protection of **58** was achieved upon treatment with PMB-Cl and freshly prepared Ag_2O to afford PMB ether **99** in 64% yield.



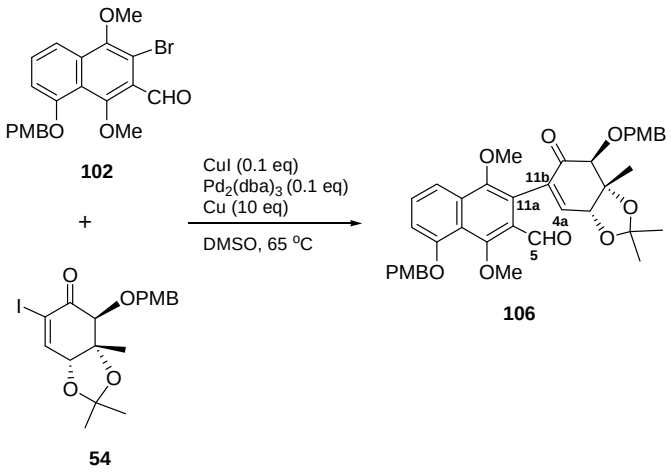
Scheme 29. Various reaction conditions for the protection of naphthalenedione **58**

2.9 Assembly of the Kinamycin ABD-Ring System via an Ullmann Coupling

After having established access to bromonaphthaldehyde **102**, we turned our attention to the assembly of the kinamycin ABD-ring system via an Ullmann coupling. We found that formation of adduct **106** was not very efficient when we applied the conditions utilized in our model Ullmann coupling studies. This protocol, which involved the addition of the metal catalysts to a solution iodoenone **54** and bromonaphthaldehyde **102** in DMSO followed by heating at 65 °C, afforded low yields (ca. 20-30%) of the desired compound **106** as well as other dimerization byproducts. The byproduct resulting from the dimerization of **102** was separated by flash column chromatograpy, but separation of the byproduct from the dimerization of iodoenone **54** proved difficult. Thus, the isolated adduct **106** ended up containing a small amount of dimer **94** as a coeluting impurity.

However, after careful experimentation, iodoenone **54** and bromonaphthaldehyde **102** underwent a facile Ullmann coupling reaction to form the latent C-11a-C-11b kinamycin bond and generate *α*-naphthylcyclohexenone **106** in 62% yield. Indeed, the dropwise addition of a solution of **102** in DMSO to a mixture of iodoenone **54**, $Pd_2(dba)_3$, copper, and CuI in DMSO followed by heating the reaction mixture at 65 °C for 2 h, was required to minimize the dimerization of bromonaphthaldehyde **102** and iodoenone **54** and ensure the formation of the product (Scheme 30). Compound **106** incorporates the ABD-ring

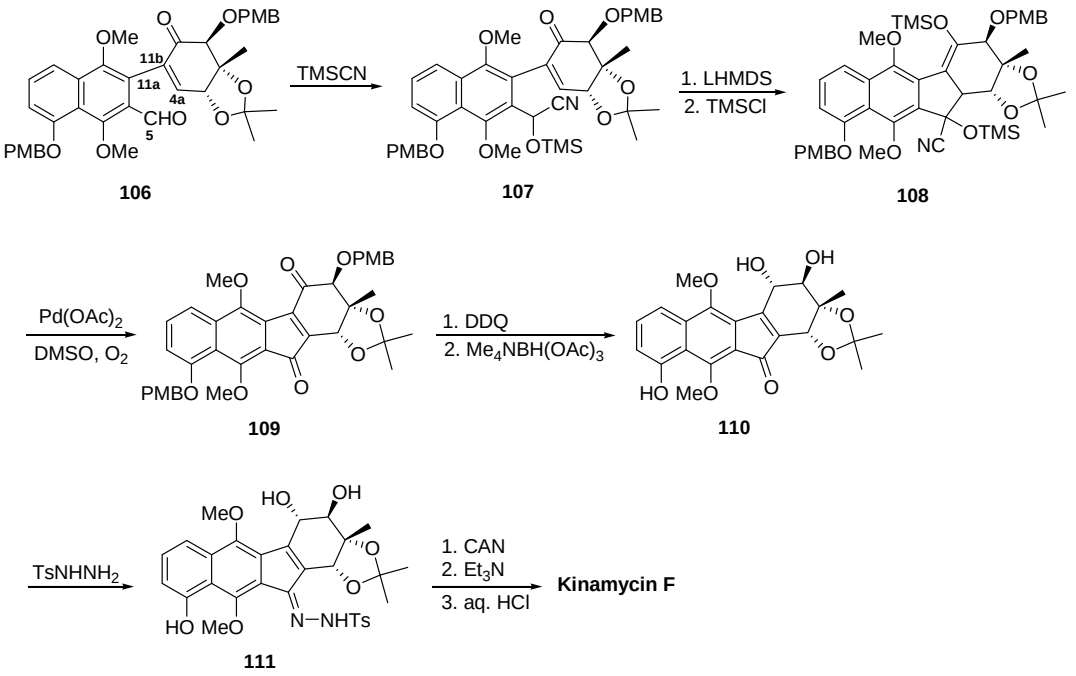
system of kinamycins and contains the appropriate functionality to enable the C-ring closure by a C-4a-C-5 bond connection.



Scheme 30. Construction of the kinamycin ABD-ring system via an Ullamnn coupling reaction

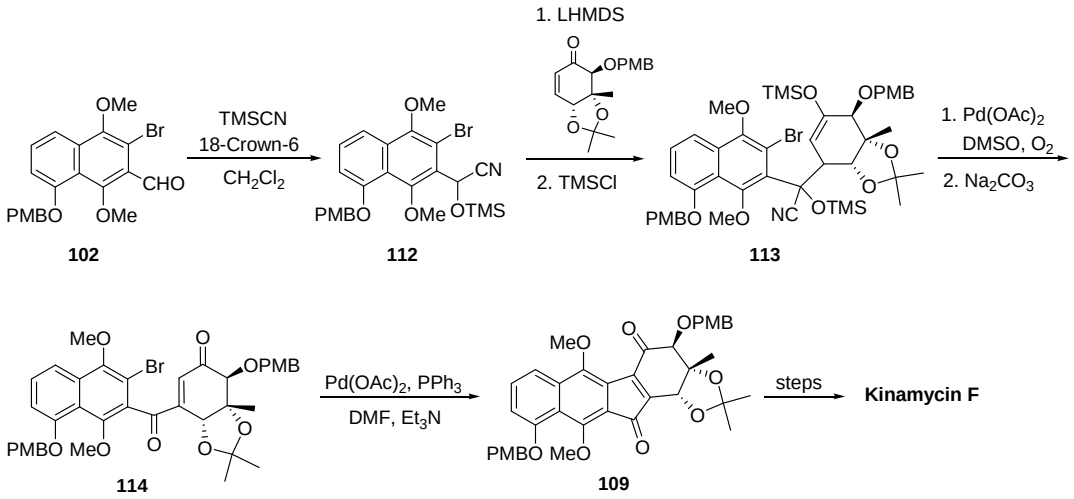
2.10 Future Plans

The readily available α-naphthylcyclohexenone **106** is a highly functionalized intermediate which can provide access to the target kinamycins. For example, cyanation of the aldehyde group in **106** should render the corresponding cyanohydrin silyl ether **107** an appropriate substrate for an intramolecular cyanohydrin anion alkylation[104] towards **108**. Then a Saegusa-Ito oxidation of the intermediate enol silyl ether **108** would give benzofluorenone **109**. Oxidative removal of both PMB groups with DDQ followed by a stereoselective α-hydroxy-directed ketone reduction would give *trans*-diol **110**. Then treatment of **110** with $TsNHNH_2$ or $MsNHNH_2$ would give hydrazone **111** which could be converted to kinamycin F after a CAN-mediated oxidation and cleavage of the acetonide group under mild acidic conditions (Scheme 31).



Scheme 31. Proposed strategy for the conversion of addut **106** to kinamycin F

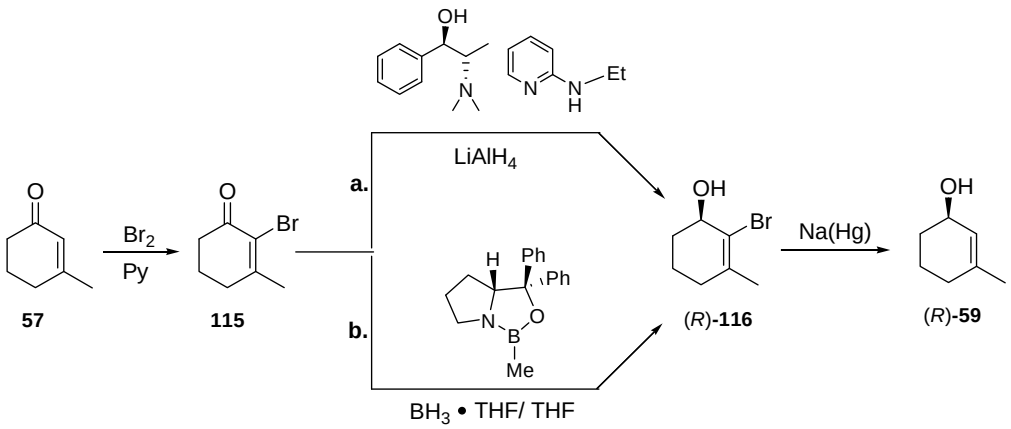
A reverse strategy that could also provide access to our key benzofluorenone **109** will be explored. For example treatment of aldehyde **102** with TMSCN and 18-crown-6[105] will afford cyanohydrin silyl ether **112** which could undergo an intermolecular cyanohydrin anion alkylation with **52** to give the Michael adduct **113**.[104] Palladium-mediated oxidation of the enol silyl ether in **113** followed by basic work up would give the β-acyl cyclohexeneone **114** which could undergo a Heck arylation reaction to provide benzofluorenone **109** (Scheme 32).



Scheme 32. The cyanohydrin anion alkylation/Heck arylation route to benzofluorenone **109**

Furthermore, the chemistry developed here may be amenable to asymmetric synthesis given that access to optically active material can be achieved by either the enzymatic resolution[106] of racemic allylic alcohol **59** or the chiral reduction[107] of cyclohexenone **57** (Scheme 33).

Access to chiral allylic alcohol (*R*)-**59** can be achieved by the asymmetric reduction of bromoenone **115**, derived by the bromination of **57**, as described in the literature. Reduction of **115** with $LiAlH_4$ in the presence of (1 *R*, 2 *S*)-(-)-N-methylephedrin and 2-(Ethyl-1-amino)pyridine[107a] or borane in the presence of a chiral oxazoborolidine[107b] will result in the allylic alcohol (*R*)-**116** in high enantiomeric exceess. Then debromination upon treatment with Na(Hg)[108] in MeOH will give the optically active alcohol (*R*)-**59** (Scheme 33).



Scheme 33. Access to chiral **(*R*)-59** by the asymmetric reduction of bromoenone **115**

2.11 Conclusions

In summary, in this thesis it was established a concise and efficient method for the regio- and stereoselective synthesis of the highly oxygenated D-ring of the kinamycin family of antitumor antibiotics. Access to the highly oxygenated D-ring cyclohexenone **54** and cyclohexene **67** was gained from the commercially available 3-methyl-2-cyclohexenone in 10 and 12 steps, respectively. Key steps include the regioselective isomerization of *cis*-epoxyalcohol **56**, regioselective reductive opening of benzylidene ketal **60** and the stereoselective α-hydroxy directed reduction of ketone **66**. Nuclear Overhauser effect spectroscopy (^{1}H-^{1}H NOESY) on diacetate **70** confirmed the assigned structure of the D-ring cyclohexene **70**.

The described work was completed utilizing readily available as well as user-friendly reagents. In addition, the stereo- and regioselective nature of the developed chemistry obviated the need of tedious chromatographic separation of undesired isomeric products, rendering this chemistry amenable to large scale synthesis.

This study also achieved the construction of the ABD-ring system of kinamycins α-naphthylcyclohexenone **106** via the Ullmann coupling of AB-ring fragment bromonaphthaldehyde **102** and the D-ring fragment α-iodocyclohexenone **54**. Compound **106** is a highly functionalized intermediate which could provide access to the tetracyclic ring system of kinamycins and their structural analogues. Furthermore, the chemistry that

was developed here may be amenable to asymmetric synthesis and provide facile access to optically active material.

CHAPTER 3

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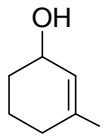
CHAPTER 4

Experimental

General Experimental Methods: All commercially available chemicals were used without further purification. All reactions were performed under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), acetonitrile (CH_3CN), dimethylformamide (DMF), and dimethylsulfoxide (DMSO) were purchased in anhydrous form and used without further purification. Air- and moisture-sensitive liquids were transferred via syringe. Organic solutions were concentrated by rotary evaporation at 40 ^oC. Flash-column chromatography was performed with silica gel 60 (230-400 mesh) as described by Still *et al*.[109] Thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 plates and the eluent used is reported in parenthesis. TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous potassium permanganate solution ($KMnO_4/H_2SO_4$) followed by heating. Infrared spectra were recorded on a Shimadzu 8400S FT-IR spectrometer. The ^1H NMR spectroscopic data were recorded on a 250 MHz or 400 MHz Bruker Avance FT-NMR spectrometer. The ^{13}C NMR spectroscopic data were recorded at 62.9 MHz. Distortionless enhancement by polarization transfer spectra [DEPT (135)] were recorded at 62.9 MHz. ^{13}C NMR and [DEPT (135)] data are combined and represented as follows: chemical shift, carbon type obtained from [DEPT (135)] experiments. The ^1H-^1H NOESY spectroscopic data were recorded with a 500 MHz Bruker Avance FT-NMR spectrometer. Chemical shifts are reported in ppm relative to the solvent signal. Multiplicity is indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. (broad), dd (doublet of doublets), and ddd (doublet of doublets of doublets). ESI (electrospray ionization) mass spectra were recorded with an Agilent 1100 Series LC/MSD instrument. High resolution mass spectra were obtained under electrospray ionization conditions with a Thermo Scientific LC–MS/linear trap quadrupole (LTQ)-Orbitrap mass spectrometer.

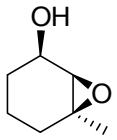
Cyclohexenol 59



Reference: Magnusson, G.; Thorén, S. *J. Org. Chem.* **1973**, *38*, 1380-1384.

It was isolated in 92% yield and used directly in the next step without any further purification. Spectroscopic data were identical to those reported in literature. For experimental details and analytical data, see: Umland, K.-D.; Palisse, A.; Haug, T. T.; Kirsch, S. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 9965-9968.

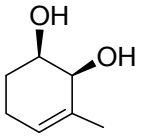
Epoxyalcohol 56



Reference: Magnusson, G.; Thorén, S. *J. Org. Chem.,* **1973**, *38*, 1380-1384.

It was isolated in 84% yield and used directly in the next step without any further purification. Spectroscopic data were identical to those reported in literature. For experimental details and analytical data, see: Umland, K.-D.; Palisse, A.; Haug, T. T.; Kirsch, S. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 9965-9968.

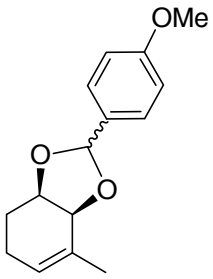
Diol 55



A solution of epoxyalcohol **56** (5.4 g, 42.0 mmol) in CH_2Cl_2 (90 mL) was treated with Ti(O*i*-Pr)$_4$ (22.5 mL, 75.6 mmol) and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the resulting residue was dissolved in Et_2O (80 mL) followed by addition of water (50 mL). A white precipitate was formed which was treated dropwise in an ice with concentrated HCl until it was gradually dissolved, leaving two clear phases. The ether phase was separated and the

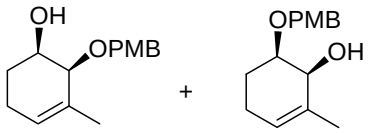
remaining aqueous phase was extracted with EtOAc (3 × 60 mL). The combined organic phase was washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:4 to 1:2) afforded diol **55** (3.44 g, 64%) as a pale yellow oil. R_f = 0.28 ($KMnO_4$, Hex:EtOAc/1:1). 250 MHz ^{1}H NMR ($CDCl_3$) δ 5.56 (m, 1 H), 3.93 (d, 1 H, J = 3.6 Hz,), 3.76 (m, 1 H), 2.20-1.95 (br s, 4 H), 1.81 (d, 3 H, J = 1.7 Hz), 1.70 (m, 2 H). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 133.7 (C), 125.7 (CH), 70.3 (CH), 69.8 (CH), 25.6 (CH_2), 24.0 (CH_2), 20.9 (CH_3). IR (film) νmax 3369, 3032, 2937, 2914, 1647 cm^{-1}. HRMS (ESI-LTQ) for $C_7H_{12}O_2Na$ [M+Na$^+$]: calcd, 151.0730; found, 151.0721.

Ketal 60



To a solution of diol **55** (467 mg, 3.64 mmol) in CH_2Cl_2 (15 mL), 4-methoxybenzaldehyde dimethyl acetal (1.2 mL, 7.2 mmol) and pyridinium *p*-toluenesulfonate (92 mg, 0.37 mmol) were added. The reaction mixture was stirred at room temperature for 1 h, diluted with water (10 mL) and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:4) afforded ketal **60** as a colorless oil (833 mg, 94%). R_f = 0.58 (UV/$KMnO_4$, Hex:EtOAc/4:1). 250 MHz ^{1}H NMR (CD_3OD, as a mixture of diastereomers) δ 7.39 (d, 2 H, J = 8.7 Hz), 6.93 (d, 2 H, J = 8.8 Hz), 5.82 (s, 0.3 H), 5.79 (s, 0.7 H), 4.59-4.31 (m, 2 H), 3.81 (s, 3 H), 2.31-1.85 (m, 4 H), 1.80 (s, 3 H). 62.9 MHz ^{13}C NMR (CD_3OD, as a mixture of diastereomers) δ 162.0 (C), 161.9 (C), 133.1 (C), 132.3 (C), 132.0 (C), 131.5 (C), 129.6 (CH), 129.1 (CH), 128.4 (CH), 126.7 (CH), 114.6 (CH), 104.8 (CH), 104.7 (CH), 103.4 (CH), 77.3 (CH), 77.0 (CH), 76.0 (CH), 75.5 (CH), 55.7 (CH_3), 53.1 (CH_3), 26.9 (CH_2), 26.4 (CH_2), 22.0 (CH_2), 21.4 (CH_2), 20.7 (CH_3), 20.3 (CH_3). IR (film) νmax 3005, 2934, 2918, 2839, 1643, 1614, 1516 cm^{-1}. HRMS (ESI-LTQ) for $C_{15}H_{18}O_3Na$ [M+Na$^+$]: calcd, 269.1148; found, 269.1148.

Cyclohexenols 61a and 61b

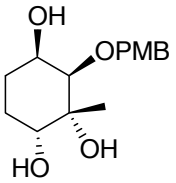


61a **61b**

(61a/61b=5)

A solution of ketal **60** (3.22 g, 13.0 mmol) in 90 mL of CH_2Cl_2-Hex (1:10) at -78 ^oC was treated dropwise with a solution (1 M in Hexanes) of diisobutylaluminium hydride (78 mL, 78.0 mmol). The reaction mixture was gradually warmed up to 0 ^oC over a period of 2 h and then carefully quenched with acetone (10 mL) and methanol (10 mL). The resulting mixture was stirred vigorously at room temperature and then filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the resulting oil was dissolved in EtOAc (80 mL) and then washed with water (70 mL). The aqueous phase was extracted with EtOAc (4 × 60 mL) and the combined organic layer was washed with brine (70 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:6) afforded an inseparable mixture of regioisomeric alcohols **61a** and **61b** (6a:6b = 5:1) as a colorless oil (2.32 g, 72%). R_f = 0.38 (UV/$KMnO_4$, Hex:EtOAc/4:1). For alcohol **61a**: 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 2 H, J = 8.5 Hz), 6.89 (d, 2 H, J = 8.6 Hz), 5.55 (s, 1 H), 4.65 (ABq, 2 H, J = 11.2 Hz), 3.93 (br s, 1 H), 3.81 (s, 4 H), 2.34 (br s, 1 H), 2.16 (br s, 1 H), 2.04-1.83 (m, 1 H), 1.73 (s, 3 H), 1.68-1.59 (m, 2 H). IR (film) νmax 3421, 3036, 2999, 2934, 2914, 2876, 2842, 1639, 1612, 1585, 1514 cm^{-1}. HRMS (ESI-LTQ) for $C_{15}H_{20}O_3Na$ [M+Na^+]: calcd, 271.1305; found, 271.1303.

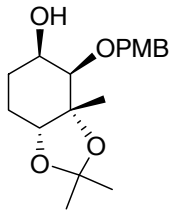
Triol 62a



To a solution of alcohols **61a** and **61b** (1.31 g, 5.3 mmol) in 40 mL of Acetone-H_2O (6:1), *N,N*-methylmorpholine oxide (931 mg, 7.94 mmol) and 4% aqueous OsO_4 (1.65 mL, 0.2 mmol) were added. The reaction mixture was stirred at room temperature for 18 h,

concentrated to a reduced volume (10 mL), diluted with water (15 mL) and then extracted with EtOAc (4 × 40 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (3:1) afforded the desired triol **62a** (1.14 g, 76%) as a white solid. R_f = 0.23 (UV/$KMnO_4$, Hex:EtOAc/1:3). 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.28 (d, 2 H, J = 8.9 Hz), 6.90 (d, 2 H, J = 8.6 Hz), 4.62 (ABq, 2 H, J = 11.3 Hz), 4.12 (m, 1 H), 3.81 (s, 3 H), 3.72 (m, 1 H), 3.58 (d, 1 H, J = 3.3 Hz), 2.13-1.99 (br s, 3 H), 1.87-1.76 (m, 2 H), 1.74-1.58 (m, 2 H), 1.36 (s, 3 H). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 159.5 (C), 130.5 (C), 129.4 (CH), 114.1 (CH), 82.7 (CH), 74.8 (C), 73.5 (CH), 73.4 (CH_2), 67.6 (CH), 55.4 (CH_3), 25.4 (CH_2), 25.1 (CH_2), 23.1 (CH_3). IR (film) νmax 3412, 2932, 2870, 1643, 1614, 1514 cm^{-1}. HRMS (ESI-LTQ) for $C_{15}H_{22}O_5Na$ [M+Na$^+$]: calcd, 305.1359; found, 305.1359.

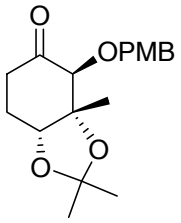
Alcohol 63



A solution of triol **62a** (847 mg, 3.0 mmol) in CH_2Cl_2 (35 mL) was treated with 2,2-dimethoxypropane (737 μL, 6.0 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate (37 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for 7 h, quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:6) afforded alcohol **63** (880 mg, 91%) as a pale yellow oil. R_f = 0.28 (UV/$KMnO_4$, Hex:EtOAc/4:1). 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 2 H, J = 8.6 Hz), 6.88 (d, 2 H, J = 8.6 Hz), 4.78 (d, 1 H, J = 11.6 Hz), 4.58 (d, 1 H, J = 11.6 Hz), 4.04 (q, 1 H, J = 3.0 Hz), 3.99 (t, 1 H, J = 2.8 Hz), 3.81 (s, 3 H), 3.52 (d, 1 H, J = 3.1 Hz), 2.15-1.95 (m, 2 H), 1.90-1.80 (m, 1 H), 1.79-1.70 (m, 2 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.38 (s, 3 H). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 159.4 (C), 130.8 (C), 129.5 (CH), 113.9 (CH), 107.5 (C), 82.8 (C), 81.7 (CH), 80.5 (CH), 72.2 (CH_2), 68.5 (CH), 55.4 (CH_3), 28.4 (CH_3), 27.4 (CH_3), 24.5 (CH_2), 20.5 (CH_3), 20.0 (CH_2). IR (film) νmax

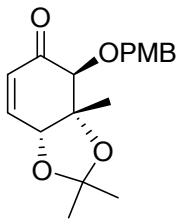
3418, 2935, 1639 cm^{-1}. HRMS (ESI-LTQ) for $C_{18}H_{26}O_5Na$ [M+Na^+]: calcd, 345.1672; found, 345.1665.

Ketone 64



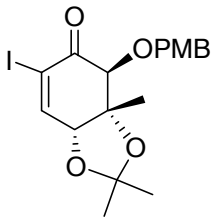
A solution of oxalyl chloride (1.1 mL, 9.9 mmol) in CH_2Cl_2 (20 mL) at -78 ^oC under an argon atmosphere, was treated dropwise with DMSO (1.4 mL, 19.8 mmol) and then with alcohol **63** (800 mg, 2.48 mmol) as a solution (15 mL) in CH_2Cl_2-DMSO (3:1). After stirring at -78 ^oC for 15 min, the reaction mixture was treated with Et_3N (6.2 mL, 44.6 mmol) and gradually warmed up to 0 ^oC over a period of 2 h. It was then quenched with water (20 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:8) afforded ketone **64** (670 mg, 84%) as a colorless oil. R_f = 0.33 (UV/$KMnO_4$, Hex:EtOAc/4:1). 250 MHz ^1H NMR ($CDCl_3$) δ 7.26 (d, 2 H, J = 8.6 Hz), 6.86 (d, 2 H, J = 8.6 Hz), 4.62 (d, 1 H, J = 11.8 Hz), 4.42 (d, 1 H, J = 11.8 Hz), 4.09 (t, 1 H, J = 3.0 Hz), 3.80 (s, 3 H), 3.76 (s, 1 H), 2.63-2.47 (m, 1 H), 2.36-2.16 (m, 3 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 1.30 (s, 3 H). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 208.8 (C), 159.6 (C), 129.8 (CH), 129.5 (C), 113.9 (CH), 108.7 (C), 85.6 (C), 84.5 (CH), 79.0 (CH), 72.3 (CH_2), 55.4 (CH_3), 33.1 (CH_2), 27.5 (CH_3), 26.6 (CH_3), 23.3 (CH_2), 20.8 (CH_3). IR (film) νmax 2984, 2934, 2837, 1724, 1637, 1612, 1585, 1514 cm^{-1}. HRMS (ESI-LTQ) for $C_{18}H_{24}O_5Na$ [M+Na^+]: calcd, 343.1516; found, 343.1516.

Cyclohexenone 52



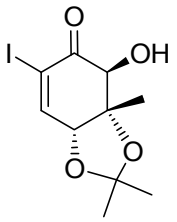
A solution of ketone **64** (200 mg, 0.62 mmol) in CH_2Cl_2 (15 mL) was treated with Et_3N (522 μL, 3.7 mmol) and TMSOTf (340 μL, 1.9 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with water (10 mL) and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude trimethylsilyl enol ether. The resulting enol ether was dissolved in DMSO (2 mL) and treated with $Pd(OAc)_2$ (14 mg, 0.06 mmol). The reaction mixture was degassed under vacuum and stirred at room temperature for 48 h under an oxygen atmosphere (ballon). It was then quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:6) afforded cyclohexenone **52** (147 mg, 77%) as a colorless oil. R_f = 0.23 (UV/$KMnO_4$, Hex:EtOAc/4:1). 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.31 (d, 2 H, J = 8.6 Hz), 6.86 (d, 2 H, J = 8.6 Hz), 6.76 (dd, 1 H, J = 10.2, 4.4 Hz), 6.12 (d, 1 H, J = 10.2 Hz), 4.83 (d, 1 H, J = 11.9 Hz), 4.63 (d, 1 H, J = 11.9 Hz), 4.45 (d, 1 H, J = 4.5 Hz), 4.16 (s, 1 H), 3.79 (s, 3 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 1.29 (s, 3 H). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 197.4 (C), 159.6 (C), 140.1 (CH), 130.7 (CH), 130.1 (CH), 129.6 (C), 113.9 (CH), 110.8 (C), 83.7 (C), 82.2 (CH), 78.0 (CH), 73.0 (CH_2), 55.4 (CH_3), 28.0 (CH_3), 27.6 (CH_3), 19.6 (CH_3). IR (film) νmax 3047, 2986, 2935, 2868, 2837, 1703, 1637, 1612, 1514 cm^{-1}. HRMS (ESI-LTQ) for $C_{18}H_{22}O_5Na$ [M+Na$^+$]: calcd, 341.1359; found, 341.1361.

Iodocyclohexenone 54



A solution of cyclohexenone **52** (140 mg, 0.44 mmol) in CH_2Cl_2 (2 mL) and pyridine (4 mL) was treated with I_2 (335 mg, 1.32 mmol). After stirring at room temperature for 18 h, the reaction mixture was quenched with water (4 mL) and aqueous $Na_2S_2O_3$ (3 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (7 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:6) afforded iodocyclohexenone **54** (170 mg, 87%) as a colorless oil. R_f = 0.40 (UV/$KMnO_4$, Hex:EtOAc/4:1). 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.46 (d, 1 H, J = 4.6 Hz), 7.28 (d, 2 H, J = 8.6 Hz), 6.87 (d, 2 H, J = 8.7 Hz), 4.75 (d, 1 H, J = 11.7 Hz), 4.51 (d, 1 H, J = 11.7 Hz) 4.37 (d, 1 H, J = 4.6 Hz), 4.17 (s, 1 H), 3.79 (s, 3 H), 1.42 (s, 3 H), 1.37 (s, 3 H), 1.26 (s, 3 H). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 191.4 (C), 159.7 (C), 149.5 (CH), 130.2 (CH), 129.0 (C), 114.0 (CH), 111.4 (C), 105.0 (C), 83.5 (C), 81.0 (CH), 79.6 (CH), 73.0 (CH_2), 55.4 (CH_3), 28.0 (CH_3), 27.9 (CH_3), 20.2 (CH_3). IR (film) 3038, 2986, 2934, 2868, 2835, 1711, 1612, 1514 νmax cm^{-1}. HRMS (ESI-LTQ) for $C_{18}H_{20}IO_5$ [M-H$^+$]: calcd, 443.0361; found, 443.0364.

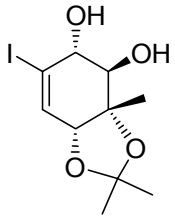
Hydroxyketone 66



A biphasic solution of iodocyclohexenone **54** (25 mg, 0.056 mmol) in 3 mL of CH_2Cl_2-H_2O (10:1) was treated with DDQ (19 mg, 0.08 mmol). The reaction mixture was stirred at room temperature for 18 h, diluted with water (10 mL) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to

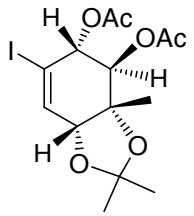
give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:8) afforded hydroxyketone **66** (13 mg, 72%) as a pale yellow oil. R_f = 0.20 (UV/$KMnO_4$, Hex:EtOAc/4:1). 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1 H, J = 5.2 Hz), 4.66 (s, 1 H), 4.41 (d, 1 H, J = 5.2 Hz), 3.26 (br s, 1 H), 1.58 (s, 3 H), 1.45 (s, 3 H), 1.26 (s, 3 H). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 193.6 (C), 148.8 (CH), 111.8 (C), 103.1 (C), 83.8 (C), 79.8 (CH), 77.4 (CH), 28.2 (CH_3), 27.3 (CH_3), 18.0 (CH_3). IR (film) νmax 3582, 2409, 2305, 1703, 1601, 1551 cm^{-1}. HRMS (ESI-LTQ) for $C_{10}H_{13}IO_4Na$ [M+Na$^+$]: calcd, 346.9751; found, 346.9746.

Cyclohexene *trans*-diol 67



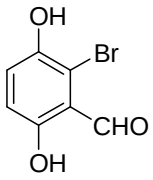
A solution of hydroxyketone **66** (18 mg, 0.055 mmol) and $Me_4NBH(OAc)_3$ (71 mg, 0.27 mmol) in CH_3CN (2 mL) at -20 ^{o}C, was treated with acetic acid (500 μL). The reaction mixture was gradually warmed up and stirred at room temperature overnight. It was then quenched with aqueous $NaHCO_3$ (5 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:3) afforded diol **67** (13 mg, 72%) as a colorless oil. R_f = 0.18 (UV/$KMnO_4$, Hex-EtOAc/2:1). 250 MHz ^{1}H NMR ($CDCl_3$) δ 6.56 (dd, 1 H, J = 4.7, 1.2 Hz), 4.14 (d, 1 H, J = 4.6 Hz), 3.93 (d, 1 H, J = 8.2 Hz), 3.87 (d, 1 H, J = 8.1 Hz), 2.71 (br s, 2 H), 1.49 (s, 3 H), 1.41 (s, 3 H), 1.32 (s, 3 H). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 133.9 (CH), 110.8 (C), 109.2 (C), 81.4 (C), 80.0 (CH), 75.7 (CH), 74.7 (CH), 28.7 (CH_3), 27.3 (CH_3), 18.0 (CH_3). IR (film) νmax 3418, 1643, 1637, 1439, 1379 cm^{-1}. HRMS (ESI-LTQ) for $C_{10}H_{15}IO_4Na$ [M+Na$^+$]: calcd, 348.9907; found, 348.9903.

Diacetate 70



A solution of diol **67** (8 mg, 0.025 mmol), $NiPr_2Et$ (9 μL, 0.05 mmol), acetic anhydride (12 μL, 0.125 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (1 mL) was stirred at room temperature overnight. The reaction mixture was diluted with water (3 mL) and a few drops of 1 N HCl and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:6) afforded diacetate **70** (8.2 mg, 80%) as a colorless oil. R_f = 0.33 (UV/$KMnO_4$, Hex:EtOAc/4:1). 250 MHz ^{1}H NMR (CD_3OD) δ 6.73 (dd, 1 H, J = 5.1, 1.9 Hz), 5.48 (ddd, 1 H, J = 9.0 Hz, 1.8, 0.8 Hz), 5.35 (d, 1 H, J = 9.0 Hz), 4.26 (d, 1 H, J = 5.0 Hz), 2.11 (s, 3 H), 2.07 (s, 3 H), 1.46 (s, 3 H), 1.38 (s, 3 H), 1.37 (s, 3 H). 250 MHz 1H NMR ($CDCl_3$) δ 6.67 (dd, 1 H, J = 5.3, 1.8 Hz), 5.48 (ddd, 1 H, J = 9.0 Hz, 1.8, 0.8 Hz), 5.42 (d, 1 H, J = 9.0 Hz), 4.12 (d, 1 H, J = 5.3, 0.8 Hz), 2.13 (s, 3 H), 2.08 (s, 3 H), 1.51 (s, 3 H), 1.38 (s, 6 H). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 169.9 (C), 169.8 (C), 135.4 (CH), 111.2 (C), 103.2 (C), 80.1 (CH), 79.9 (C), 73.5 (CH), 73.2 (CH), 28.0 (CH3), 27.2 (CH3), 21.1 (CH3), 21.0 (CH3), 18.1 (CH3). IR (film) νmax 2982, 2935, 2866, 1755, 1634, 1377, 1232, 1215 cm-1. HRMS (ESI-LTQ) for $C_{14}H_{19}IO_6Na$ [M+Na+]: calcd, 433.0119; found, 433.0123.

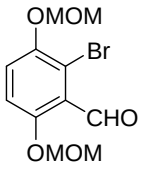
Bromobenzaldehyde 76



To a solution of 2,5-dihydroxybenzaldehyde **75** (1 g, 7.2 mmol) in $CHCl_3$ (35 mL), Br_2 (386 μL, 7.5 mmol) in $CHCl_3$ (25 mL) was added dropwise. The reaction mixture was stirred at room temperature for 4 h, diluted with aqueous $Na_2S_2O_3$ (25 mL) and then

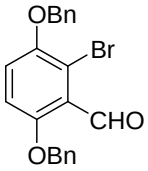
extracted with $CHCl_3$ (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give bromobenzaldehyde **76** as a yellow solid (1.52 g, 97 %). 250 MHz ^{1}H NMR ($CDCl_3$) δ 11.64 (s, 1 H), 10.27 (s, 1 H), 7.24 (d, 2 H), 6.92 (d, 1 H, J = 9.1 Hz), 5.35 (s, 1 H).

Protected benzaldehyde 77a



To a solution of bromobenzaldehyde **76** (320 mg, 1.5 mmol) in CH_2Cl_2 (12 mL), Hunig's base (770 μL, 4.4 mmol) and MOMBr (361 μL, 1.5 mmol) were added. The reaction mixture was refluxed for 6 h, diluted with H_2O (10 mL) and then extracted with CH_2Cl_2 (3 × 12 mL). The combined organic layer was washed with aqueous NaOH 1 N (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:6) afforded protected benzaldehyde **77a** (300 mg, 66%) as a pale yellow oil. 250 MHz ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1 H), 7.27 (d, 1 H, J = 9.2 Hz), 7.13 (d, 1 H, J = 9.2 Hz), 5.19 (s, 4 H), 3.51 (s, 3 H), 3.48 (s, 3 H).

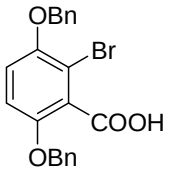
Protected benzaldehyde 77b



To a solution of bromobenzaldehyde **76** (300 mg, 1.4 mmol) in DMF (5 mL), K_2CO_3 (573 mg, 4.1 mmol) and benzyl bromide (329 μL, 2.8 mmol) were added. The reaction mixture was stirred at room temperature overnight, diluted with H_2O (15 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with H_2O (3 × 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:8) afforded protected benzaldehyde **77b** (200 mg, 36%) as a pale yellow oil. 250 MHz ^{1}H

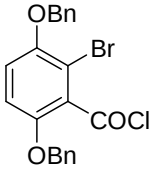
NMR ($CDCl_3$) δ 10.46 (s, 1 H), 7.48-7.32 (m, 10 H), 7.05 (d, 1 H, J = 9.1 Hz), 6.92 (d, 1 H, J = 9.1 Hz), 5.12 (s, 4 H).

Benzoic acid 85



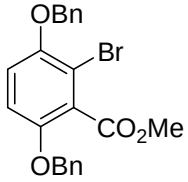
To a solution of bromobenzaldehyde **77b** (30 mg, 0.08 mmol) in *t*-BuOH (1.5 μL) and THF (0.5 mL), H_2O_2 30% (10 μL, 0.09 mmol) was added. Then, addition of a solution of $NaClO_2$ (8 mg, 0.09 mmol) and NaH_2PO_4 (12.5 mg, 0.09 mmol) in H_2O (1 mL) followed. The reaction mixture was stirred at room temperature for 6 h, diluted with H_2O (5 mL) and then extracted with EtOAc (3 × 5 mL). During the extraction, the pH of the aqueous phase was adjusted from 4 to 2 with the addition of a few drops of aqueous HCl 1 N. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. The crude product was used in the next step without any further purification. 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.48-7.27 (m, 10 H), 6.89 (d, 1 H, J = 9.1 Hz), 6.83 (d, 1 H, J = 9.1 Hz), 5.09 (s, 4 H).

Benzoyl chloride 80



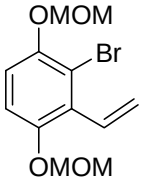
To a solution of bromobenzoic acid **85** (30 mg, 0.07 mmol) in CH_2Cl_2 (3 mL), oxalyl chroride (7.5 μL, 0.09 mmol) and a catalytic amount of DMF (1 drop) were added. The reaction mixture was stirred at 0 ^{o}C overnight and then concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:4) afforded protected bromobenzoyl chroride **80** (20 mg, 67%) as a pale yellow oil. 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.47-7.30 (m, 10 H), 6.92 (d, 1 H, J = 9.1 Hz), 6.85 (d, 1 H, J = 9.1 Hz), 5.11 (s, 2 H), 5.10 (s, 2 H).

Ester 82



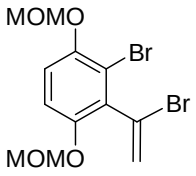
A solution of bromobenzoyl chloride **80** (20 mg, 0.05 mmol) with a catalytic amount of DMAP in MeOH (2 mL) was stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure to give the crude product which was diluted in EtOAc (5 mL) and H_2O (5 mL). It was then extracted with EtOAc (3 × 4 mL) and the combined organic layer was washed with aqueous HCl 1 N (4 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the ester **82** (20 mg, 95%) as a pale yellow oil. 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.45-7.27 (m, 10 H), 6.85 (d, 1 H, J = 9.1 Hz), 6.79 (d, 1 H, J = 9.1 Hz), 5.05 (s, 2 H), 5.03 (s, 2 H), 3.91 (s, 3 H).

Styrene 91



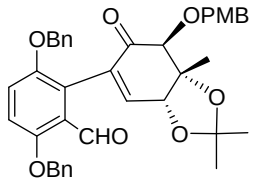
To a solution of methyltriphenylphosphonium bromide (94 mg, 0.3 mmol) in THF (3.5 mL), *n*-butyllithium (138 μL, 2 M, 0.3 mmol) was added at 0 ^{o}C and under argon atmosphere (balloon). Then a solution of aldehyde **77a** (40 mg, 0.1 mmol) in THF (1 mL) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with aqueous NH_4Cl (4 mL) and then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was washed with H_2O (2 × 4 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:8) afforded styrene **91** (24 mg, 62%) as a pale yellow oil. 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.05 (d, 1 H, J = 9.1 Hz), 6.99 (d, 1 H, J = 9.1 Hz), 6.80 (dd, 1 H, J = 11.8, 17.8 Hz), 5.88 (dd, 1 H, J = 2.0, 17.8 Hz), 5.60 (dd, 1 H, J = 2.0, 11.8 Hz), 5.18 (s, 2 H), 5.13 (s, 2 H), 3.52 (s, 3 H), 3.47 (s, 3 H).

Bromostyrene 90



To a solution of styrene **91** (15 mg, 0.05 mmol) in CH_2Cl_2 (2 mL), a solution of Br_2 in CH_2Cl_2 (196 μL, 0.5 M, 0.1 mmol) was added at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 10 min and then concentrated under reduced pressure to give the crude dibromide which was diluted in CH_3CN (2 mL) and treated with a portion of DBU (12 μL, 0.08 mmol). The reaction mixture was stirred at room temperature overnight and then quenched with aqueous HCl 1 N (2 drops) and H_2O (4 mL) followed by extraction with EtOAc (3 × 5 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:8) afforded bromostyrene **90** (15 mg, 75%) as a pale yellow oil. 250 MHz ^1H NMR ($CDCl_3$) δ 7.37 (d, 1 H, J = 13.9 Hz), 7.17 (d, 1 H, J = 13.9 Hz), 7.07 (d, 1 H, J = 9.3 Hz), 7.02 (d, 1 H, J = 9.2 Hz), 5.18 (s, 2 H), 5.16 (s, 2 H), 3.52 (s, 3 H), 3.47 (s, 3 H).

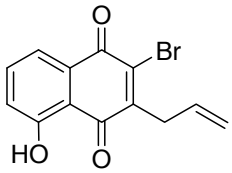
Phenylcyclohexenone 92



A solution of iodocyclohexenone **54** (78 mg, 0.05 mmol) and bromobenzaldehyde **77b** (105 mg, 0.07 mmol) in DMSO (400 μL) at room temperature was treated with CuI (14 mg, 0.07 mmol), $Pd_2(dba)_3$ (17 mg, 0.018 mmol) and Cu (112 mg, 1.76 mmol). The reaction mixture was heated at 65 ^oC for 2 h and then filtered through a Celite pad. The resulting filtrate was diluted with EtOAc (8 mL) and washed with water (7 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 8 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash

chromatography on silica gel with EtOAc-Hex (1:10 to 1:2) afforded phenylcyclohexenone **92** (67 mg, 60%) as a yellow oil. 250 MHz ^{1}H NMR ($CDCl_3$) δ 10.52 (s, 1 H), 7.50 (d, 2 H, J = 8.5 Hz), 7.44-7.39 (m, 5 H), 7.35-7.28 (m, 6 H), 7.19 (d, 1 H, J = 9.2 Hz), 7.02 (d, 1 H, J = 9.1 Hz), 6.88 (d, 2 H, J = 8.6 Hz), 6.45 (d, 1 H, J = 4.8 Hz), 4.95 (s, 1 H), 4.92 (s, 3H), 4.88 (s, 1 H), 4.58 (d, 1 H, J = 11.9 Hz), 4.44 (d, 1 H, J = 4.7 Hz), 3.79 (s, 3 H), 3.74 (s, 1 H), 1.57 (s, 3 H), 1.38 (s, 3 H), 1.28 (s, 3 H).

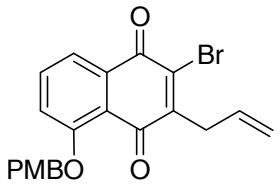
Hydroxynaphthoquinone 58



Reference: Nicolaou, K. C.; Li, H.; Nold, A. L.; Pappo, D.; Lenzen, A. *J. Am. Chem. Soc.* **2007**, *129*, 10356-10357.

It was isolated in 60% yield. Spectroscopic data were identical to those reported in literature.

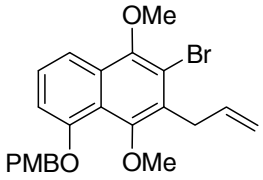
Benzyloxynaphthoquinone 99



To a solution of hydroxynaphthoquinone **58** (258 mg, 0.88 mmol) in CH_2Cl_2 (12 mL), *p*-methoxybenzyl chloride (239 μL, 1.76 mmol) and freshly prepared Ag_2O[110] (204 mg, 0.88 mmol) were added. After stirring at room temperature overnight, the reaction mixture was filtered through a Celite pad and the resulting filtrate was concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:5) afforded naphthoquinone **99** (233 mg, 64%) as a yellow oil. R_f = 0.35 (UV, Hex:EtOAc/4:1). 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.81 (d, 1 H, J = 7.5 Hz), 7.60 (t, 1 H, J = 8.3, 7.8 Hz), 7.46 (d, 2 H, J = 8.5 Hz), 7.33 (d, 1 H, J = 8.5 Hz), 6.94 (d, 2 H, J = 8.5 Hz), 5.87 (m, 1 H), 5.26 (dd, 1 H, J = 14.5, 1.5 Hz), 5.23 (s, 2 H), 5.13 (dd, 1 H, J =

10.0, 1.5 Hz), 3.82 (s, 3 H), 3.62 (d, 2 H, J = 6.5 Hz). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 180.1 (C), 178.3 (C), 159.6 (C), 159.2 (C), 150.8 (C), 136.8 (C), 134.8 (CH), 133.5 (C), 132.0 (CH), 130.2 (C), 128.6 (CH), 128.0 (C), 120.7 (CH), 120.3 (CH), 118.2 (CH_2), 114.3 (CH), 71.1 (CH_2), 55.4 (CH_3), 35.8 (CH_2). IR (film) νmax 1672, 1607, 1585, 1550, 1514 cm^{-1}. HRMS (ESI-LTQ) for $C_{21}H_{17}{}^{79/81}BrO_4Na$ [M+Na$^+$]: calcd, 435.0202/437.0182; found, 435.0207/437.0187.

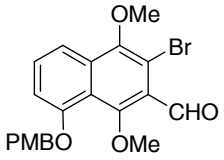
Bromonaphthalene 100



To a solution of naphthoquinone **99** (122 mg, 0.29 mmol) in EtOAc (3 mL) and Et_2O (8 mL), $Na_2S_2O_4$ (308 mg, 1.77 mmol) in water (10 mL) was added. After stirring at room temperature for 30 min, the biphasic reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude hydroquinone as yellow oil. A solution of the resulting hydroquinone in 4 mL of DMF was treated with K_2CO_3 (269 mg, 1.95 mmol) followed by the addition of MeI (110 μL, 1.77 mmol). The reaction mixture was stirred at room temperature overnight, diluted with water (10 mL) and then extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:20) afforded bromonaphthalene **100** (64 mg, 50 %) as a yellow oil. R_f = 0.60 (UV, Hex:EtOAc/4:1). 250 MHz ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 1 H, J = 8.3 Hz), 7.47 (d, 2 H, J = 8.5 Hz), 7.39 (t, 1 H, J = 8.1 Hz), 6.99 (d, 1 H, J = 7.8 Hz), 6.95 (d, 2 H, J = 8.5 Hz), 6.06 (m, 1 H), 5.13 (s, 2 H), 5.11 (dd, 1 H, J = 11.0, 1.0 Hz), 5.02 (dd, 1 H, J = 17.0, 1.3 Hz), 3.95 (s, 3 H). 3.84 (s, 3 H), 3.79 (d, 2 H, J = 5.7 Hz), 3.66 (s, 3 H). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 159.6 (C), 155.5 (C), 151.6 (C), 149.8 (C), 136.5 (CH), 130.7 (C), 129.9 (C), 129.6 (CH), 129.1 (C), 126.8 (CH), 120.7 (C), 117.7 (C), 115.8 (CH_2), 115.5 (CH), 114.1 (CH), 109.0 (CH), 71.6 (CH_2), 63.3 (CH_3), 61.3 (CH_3), 55.4 (CH_3), 34.5 (CH_2). IR (film)

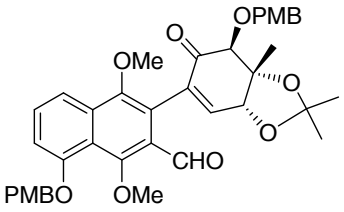
νmax 3011, 2961, 2930, 1637 cm^{-1}. HRMS (ESI-LTQ) for $C_{23}H_{24}{}^{79/81}BrO_4$ [M+H^+]: calcd, 443.0852/445.0832; found, 443.0863/445.0845.

Bromonaphthaldehyde 102



A solution of *t*-BuOK in THF (189 μL, 1 M, 0.19 mmol) in THF (250 μL) at 0 ^oC was treated dropwise with a solution (2 mL) of bromonaphthalene **100** (42 mg, 0.09 mmol) in THF-DMSO (1:8). After stirring for 2 min, the reaction mixture was diluted with water (4 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (6 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude vinyl bromonaphthalene **101**. A solution of the resulting vinyl bromonaphthalene **101** in 3 mL THF-H_2O (2:1) was treated with 4% aqueous OsO_4 (6 μL, 0.16 M, 0.01 mmol) and $NaIO_4$ (49 mg, 0.23 mmol). The reaction mixture was stirred at room temperature overnight, diluted with water (4 mL) and then extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:8) afforded bromonaphthaldehyde **102** (26 mg, 64 %) as a pale yellow oil. R_f = 0.33 (UV, Hex:EtOAc/4:1). 250 MHz ^1H NMR ($CDCl_3$) δ 10.5 (s, 1 H), 7.75 (d, 1 H, J = 8.4 Hz), 7.58 (t, 1 H, J = 8.1 Hz), 7.46 (d, 2 H, J = 8.6 Hz), 7.07 (d, 1 H, J = 7.8 Hz), 6.96 (d, 2 H, J = 8.6 Hz), 5.16 (s, 2 H), 3.96 (s, 3 H), 3.84 (s, 3 H), 3.28 (s, 3 H). 62.9 MHz ^{13}C NMR ($CDCl_3$) δ 190.9 (CH), 159.8 (C), 159.1 (C), 157.1 (C), 150.6 (C), 134.1 (C), 130.5 (CH), 129.6 (CH), 128.4 (C), 125.2 (C), 120.3 (C), 115.5 (CH), 114.2 (CH), 111.4 (C), 109.2 (CH), 71.5 (CH_2), 65.5 (CH_3), 61.4 (CH_3), 55.5 (CH_3). IR (film) νmax 3005, 2934, 2839, 1691, 1645, 1612, 1551, 1514, 1441, 1366 cm^{-1}. HRMS (ESI-LTQ) for $C_{21}H_{19}{}^{79/81}BrO_5Na$ [M+Na^+]: calcd, 453.0308/455.0288; found, 453.0302/455.0279.

Naphthylcyclohexenone 106



A solution of iodocyclohexenone **54** (14 mg, 0.03 mmol) in DMSO (500 μL) at room temperature was treated with CuI (2.3 mg, 0.012 mmol), $Pd_2(dba)_3$ (2.8 mg, 0.003 mmol) and Cu (20 mg, 0.31 mmol), followed by dropwise addition of a solution of bromonaphthaldehyde **102** (20 mg, 0.046 mmol) in DMSO (500 μL). The reaction mixture was heated at 65 ^oC for 2 h and then filtered through a Celite pad. The resulting filtrate was diluted with EtOAc (10 mL) and washed with water (10 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel with EtOAc-Hex (1:10 to 1:2) afforded naphthylcyclohexenone **106** (13 mg, 62 %) as a yellow oil. R_f = 0.28 (UV, Hex:EtOAc/2:1). 400 MHz ^1H NMR ($CDCl_3$) δ 10.47 (s, 1 H), 7.78 (d, 1 H, J = 8.2 Hz), 7.60 (t, 1 H, J = 8.1, 8.2 Hz), 7.53 (d, 2 H, J = 8.6 Hz), 7.48 (d, 2 H, J = 8.6 Hz), 7.09 (d, 1 H, J = 7.8 Hz), 6.97 (d, 2 H, J = 8.6 Hz), 6.89 (d, 2 H, J = 8.6 Hz), 6.56 (d, 1 H, J = 4.7 Hz), 5.19 (s, 2H), 5.05 (s, 1 H), 4.92 (d, 1 H, J = 11.8 Hz), 4.63 (d, 1 H, J = 4.9 Hz), 4.62 (d, 1 H, J = 11.8 Hz), 3.85 (s, 3 H), 3.80 (s, 6 H), 3.67 (s, 3 H), 1.44 (s, 3 H), 1.43 (s, 3 H), 1.26 (s, 3 H). 62.9 MHz ^{13}C NMR (CDCl3) δ 198.0 (C), 190.8 (CH), 161.5 (C), 159.8 (C), 159.4 (C), 156.9 (C), 151.7 (C), 138.9 (C), 135.0 (C), 133.4 (CH), 130.7(CH), 130.6 (CH), 130.5 (C), 129.6 (CH), 128.4 (C), 124.3 (C), 123.2 (C), 120.9 (C), 115.9 (CH), 114.2 (CH), 113.8 (CH), 110.5 (C), 109.6 (CH), 83.1 (CH), 78.8 (CH), 78.1 (C), 72.7 (CH2), 71.5 (CH2), 66.0 (CH3), 62.0 (CH3), 55.5 (2 × CH3), 27.7 (CH3), 27.1 (CH3), 19.1 (CH3). IR (film) νmax 2993, 2934, 2839, 1703, 1691, 1672, 1647, 1614 cm^{-1}. HRMS (ESI-LTQ) for $C_{39}H_{40}O_{10}Na$ [$M+Na^+$]; calcd, 691.2514; found, 691.2513.

PART II-Appendix

List of Abbreviations

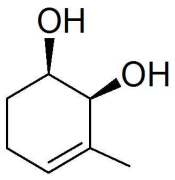
[H]	reducing agent
[O]	oxidizing agent
Ac	acetyl
aq.	aqueous
ATCC	American Type Culture Collection
Bn	benzyl
BOC	*tert*-butoxycarbonyl
br	broad
CAN	ceric ammonium nitrate
cat.	catalytic amount
CSA	camphorsulfonic acid
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine (Hünig's base)
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide

DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
Et	ethyl
eq.	equivalent
ESI	electronspray ionization
FT	Fourier transform
g	gram
h	hour
HBTU	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro- phosphate
HOBt	Hydroxybenzotriazole
Hz	Hertz
IC_{50}	half maximal (50%) inhibitory concentration
i-Pr	isopropyl
IR	infra-red
KAT 1	kinamycin acetyltransferase
L	liter
LAH	lithium aluminium hydride
LC	liquid chromatography
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet

Me	methyl
mg	milligram
min	minute
mL	milliliter
mmol	millimol
MOM	methoxymethyl
MS	mass spectrum
MW	molecular weight
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
OTf	triflate
Ph	phenyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium toluene-4-sulphonate
PTSA	*p*-toluenesulfonic acid
Py	pyridine
R*f*	retardation factor
RNA	ribonucleic acid
rt	room temperature
s	singlet

SM	starting material
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBS	*tert*-butyldimethylsilyl
TBSOTf	trifluoromethanesulfonic acid tert-butyldimethylsilyl ester
TBS	tert-butyldimethylsilyl
t	triplet
Tf	trifluoromethansulfonyl
t-Bu	*tert*-butyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilyl
Ts	*p*-toluenesulfonyl, tosyl
UV-VIS	ultraviolet-visible

^{1}H and ^{13}C NMR Spectra



55

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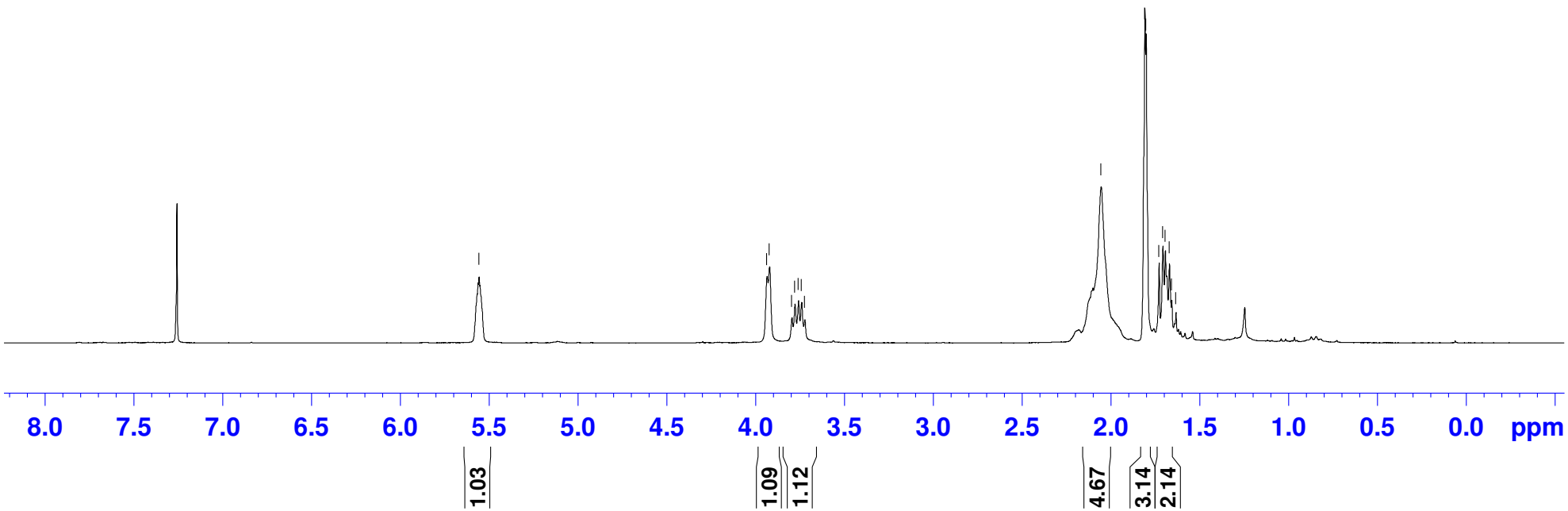

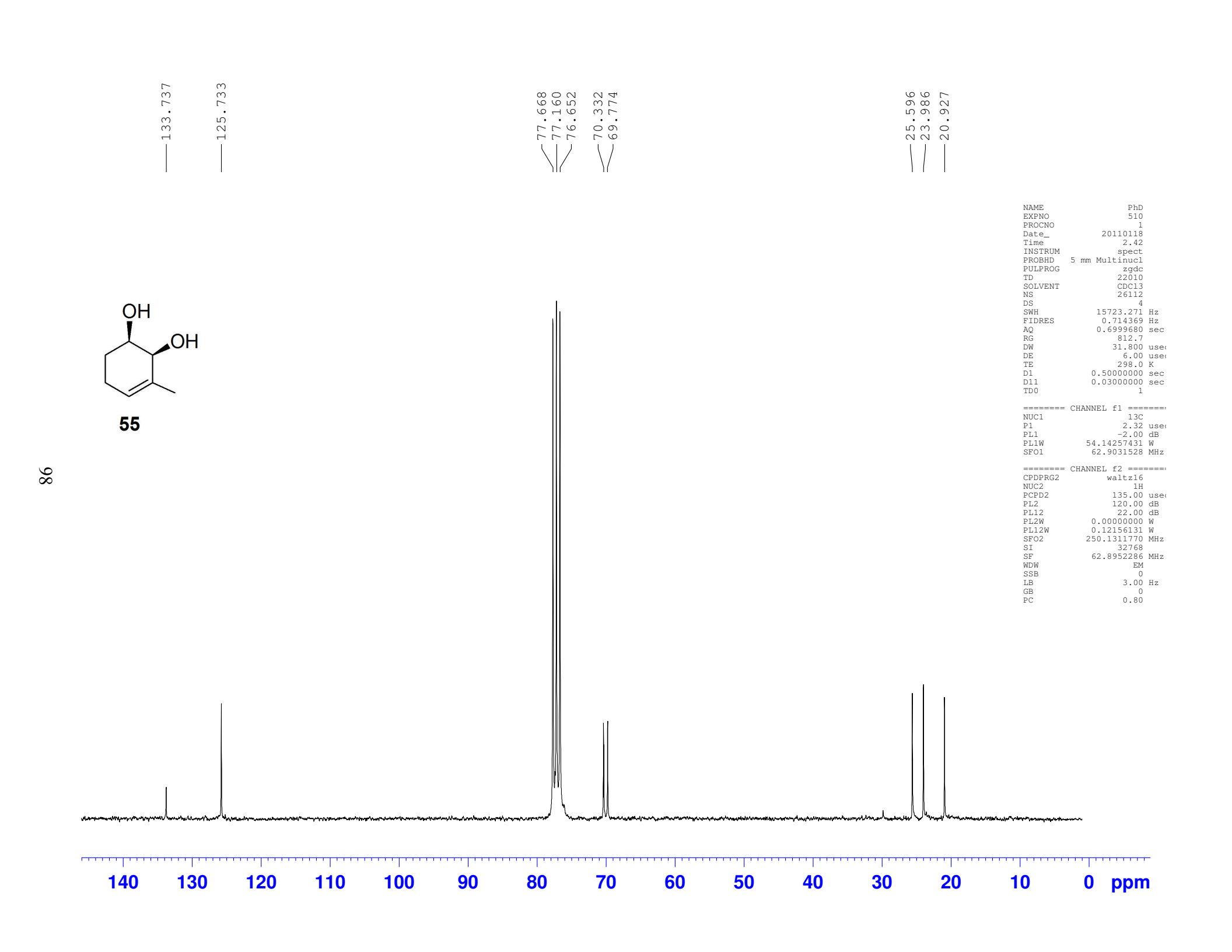
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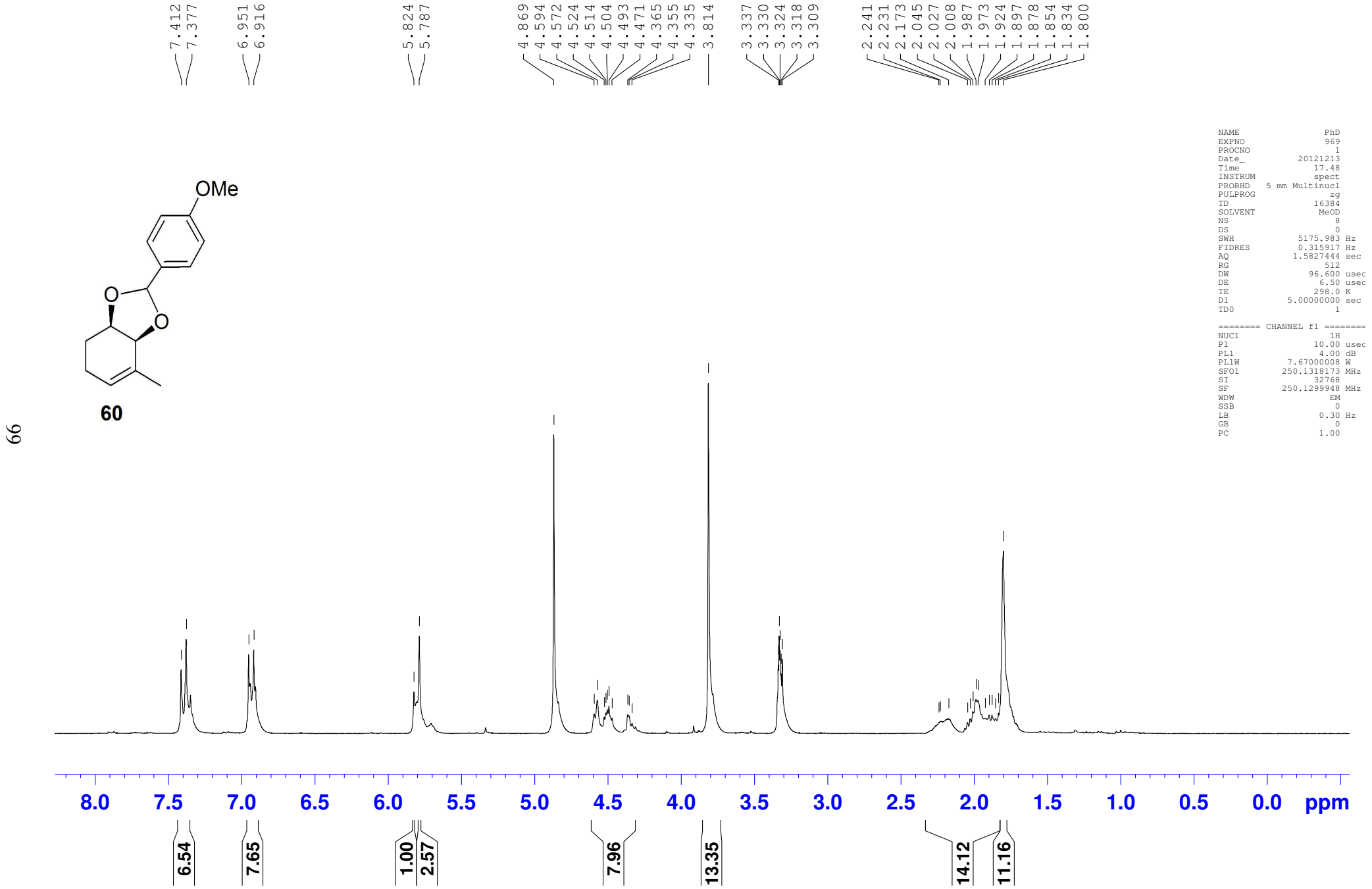
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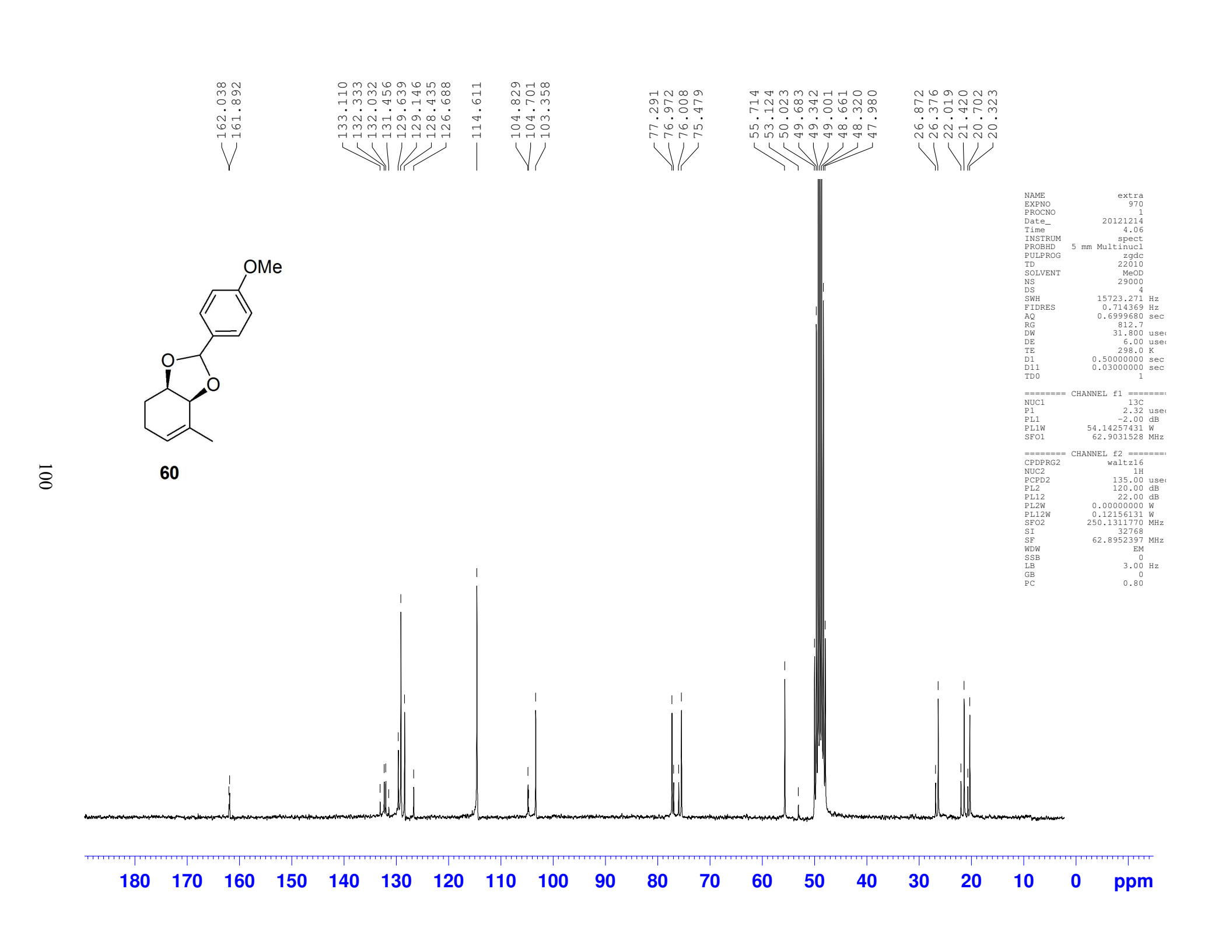
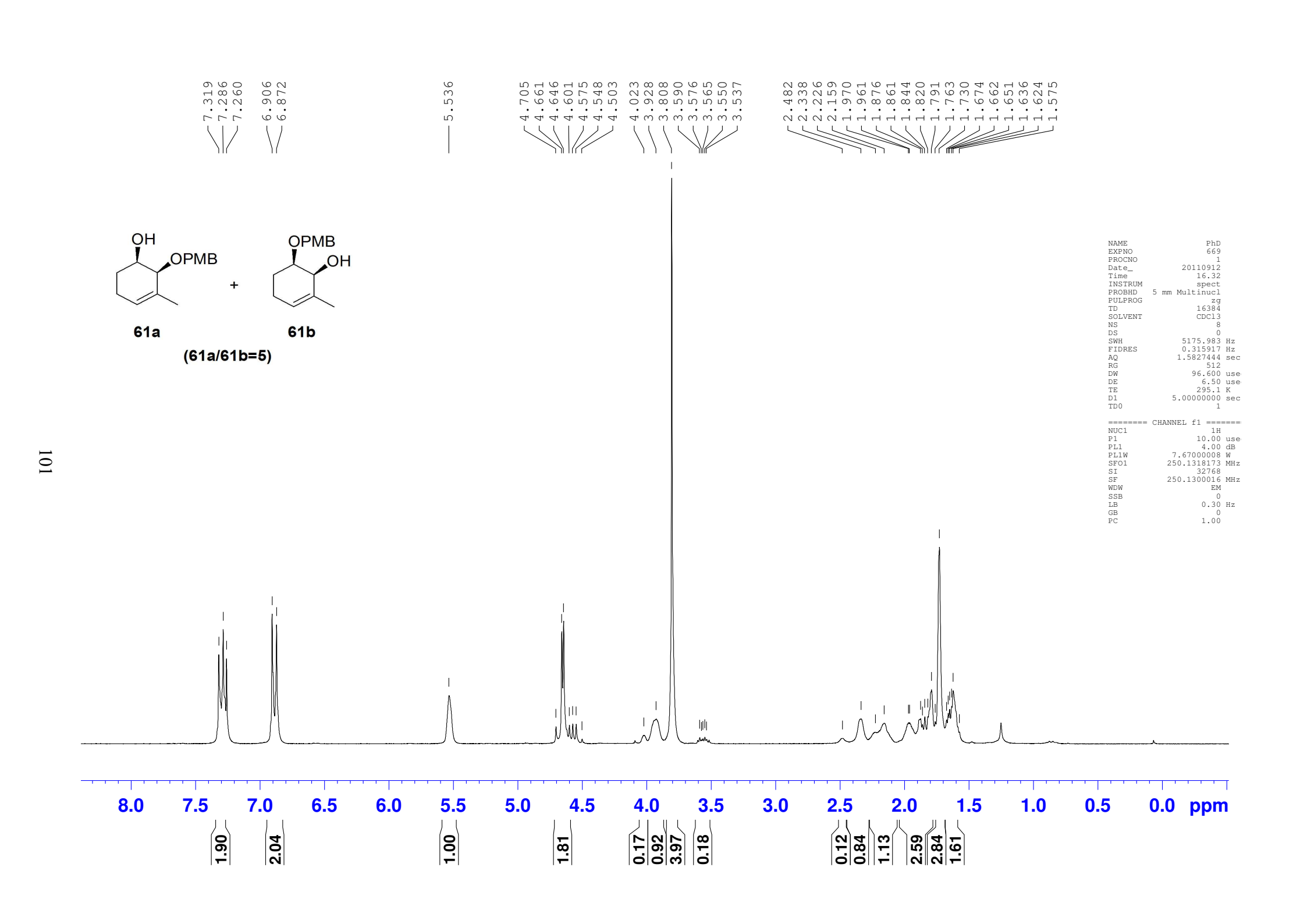
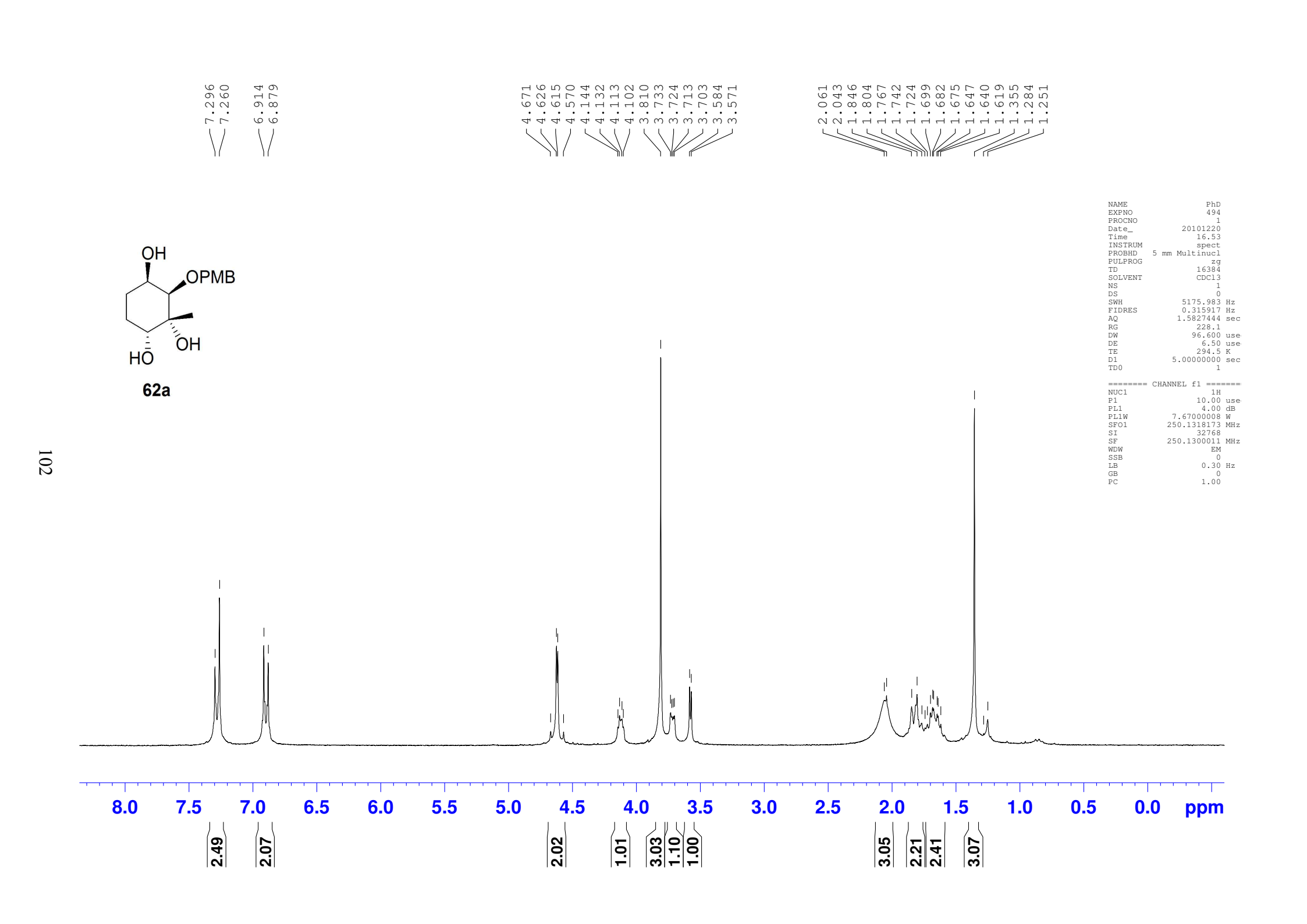
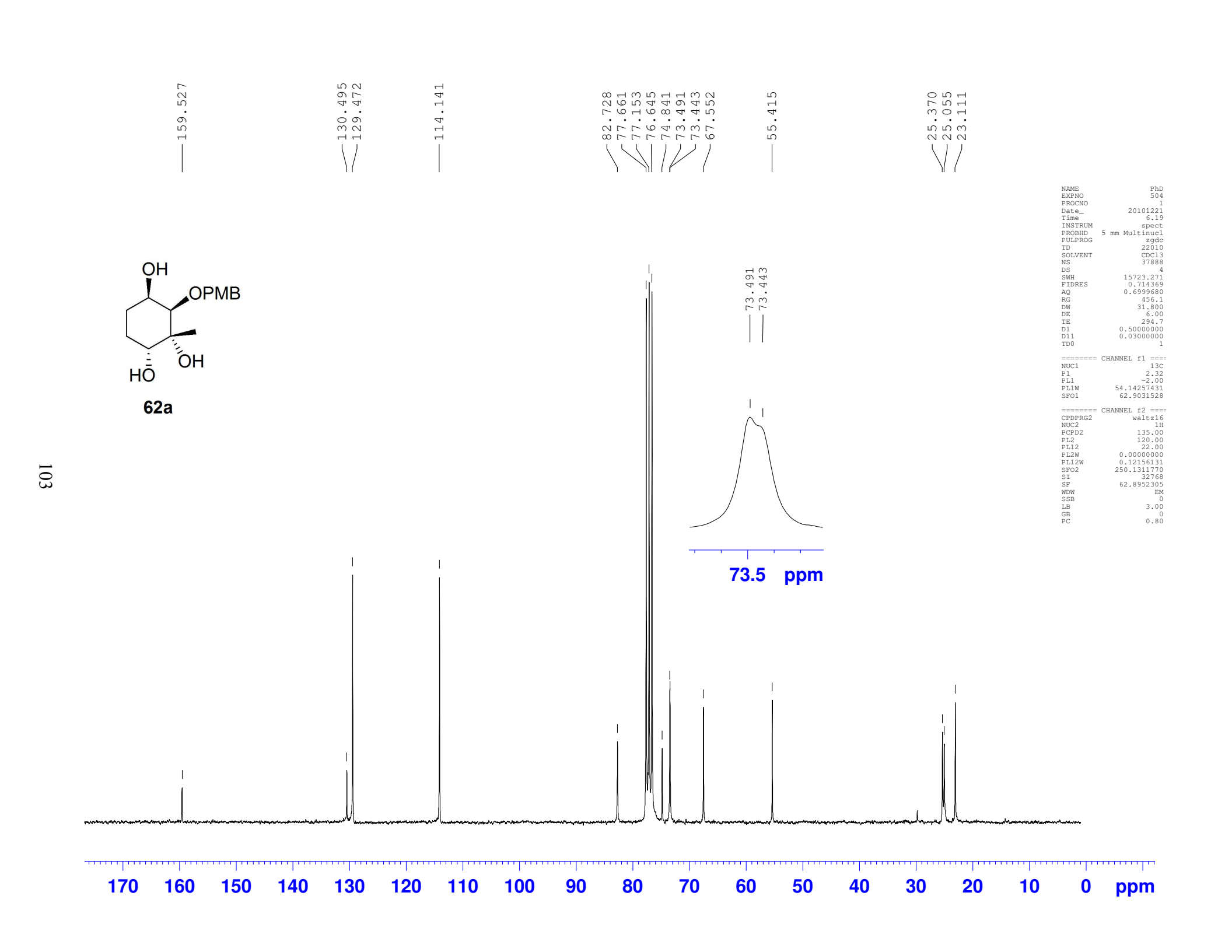
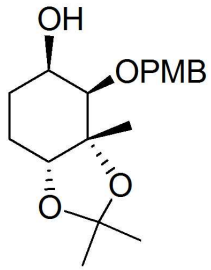
NUC1 1H
P1 10.00 usec
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1299948 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
6.54
7.65
1.00
2.57
7.96
13.35
14.12
11.16


162.038
161.892
133.110
132.333
132.032
131.456
129.639
129.146
128.435
126.688
114.611
104.829
104.701
103.358
77.291
76.972
76.008
75.479
55.714
53.124
50.023
49.683
49.342
49.001
48.661
48.320
47.980
26.872
26.376
22.019
21.420
20.702
20.323
OMe
O
O
60
100
NAME extra
EXPNO 970
PROCNO 1
Date_ 20121214
Time 4.06
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT MeOD
NS 29000
DS 4
SWH 15723.271 Hz
FIDRES 0.714369 Hz
AQ 0.6999680 sec
RG 812.7
DW 31.800 use
DE 6.00 use
TE 298.0 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 2.32 use
PL1 -2.00 dB
PL1W 54.14257431 W
SFO1 62.9031528 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00 use
PL2 120.00 dB
PL12 22.00 dB
PL2W 0.00000000 W
PL12W 0.12156131 W
SFO2 250.1311770 MHz
SI 32768
SF 62.8952397 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 0.80
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.319
7.286
7.260
6.906
6.872
5.536
4.705
4.661
4.646
4.601
4.575
4.548
4.503
4.023
3.928
3.808
3.590
3.576
3.565
3.550
3.537
2.482
2.338
2.226
2.159
1.970
1.961
1.876
1.861
1.844
1.820
1.791
1.763
1.730
1.674
1.662
1.651
1.636
1.624
1.575
OH
OPMB
+
OPMB
OH
61a
61b
(61a/61b=5)
NAME PhD
EXPNO 669
PROCNO 1
Date_ 20110912
Time 16.32
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 512
DW 96.600 use
DE 6.50 use
TE 295.1 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 use
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300016 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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
1.90
2.04
1.00
1.81
0.17
0.92
3.97
0.18
0.12
0.84
1.13
2.59
2.84
1.61

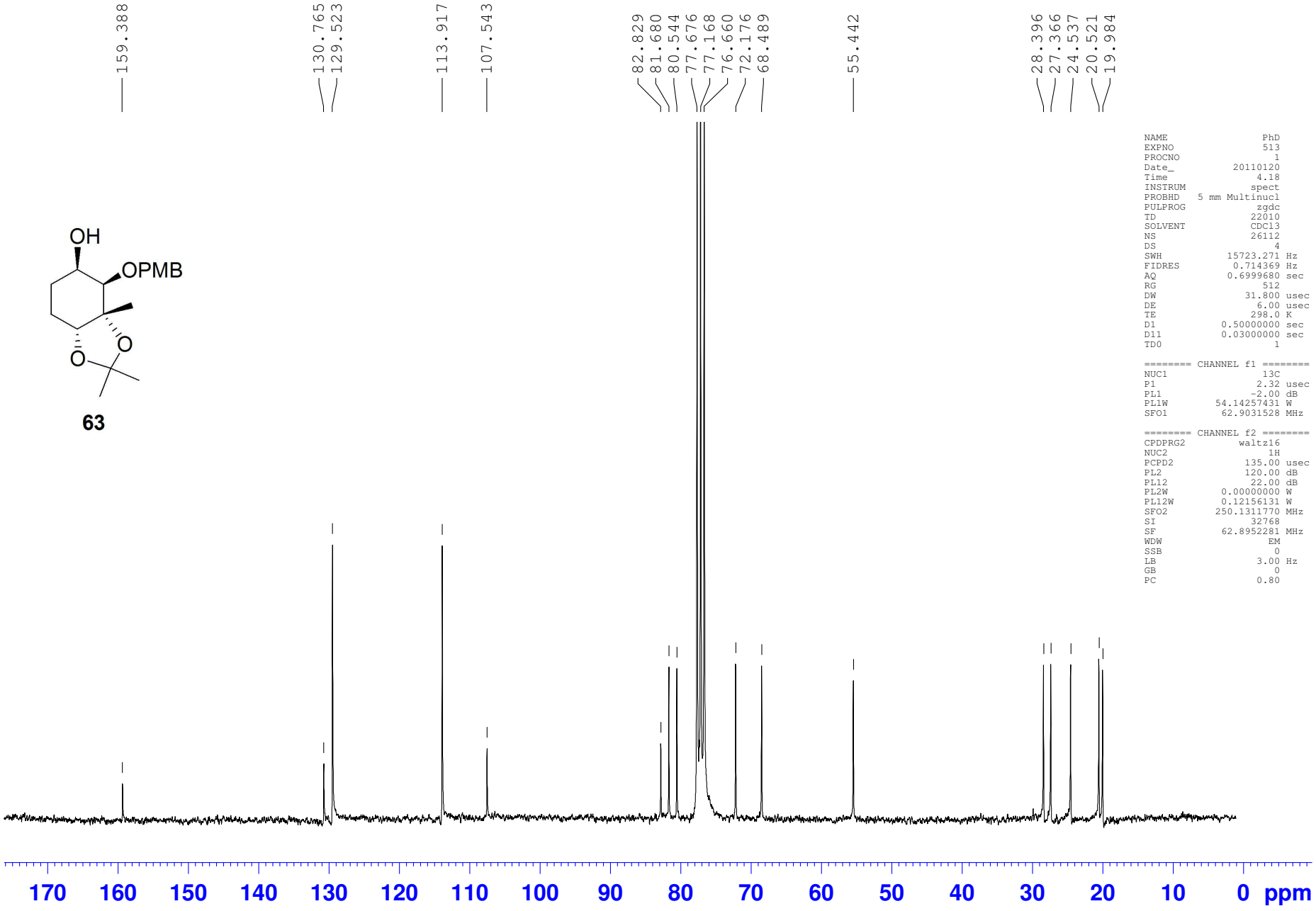

7.296
7.260
6.914
6.879
4.671
4.626
4.615
4.570
4.144
4.132
4.113
4.102
3.810
3.733
3.724
3.713
3.703
3.584
3.571
2.061
2.043
1.846
1.804
1.767
1.742
1.724
1.699
1.682
1.675
1.647
1.640
1.619
1.355
1.284
1.251
OH
OPMB
OH
HO
62a
NAME PhD
EXPNO 494
PROCNO 1
Date_ 20101220
Time 16.53
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 1
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 228.1
DW 96.600 use
DE 6.50 use
TE 294.5 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 use
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300011 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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
2.49
2.07
2.02
1.01
3.03
1.10
1.00
3.05
2.21
2.41
3.07

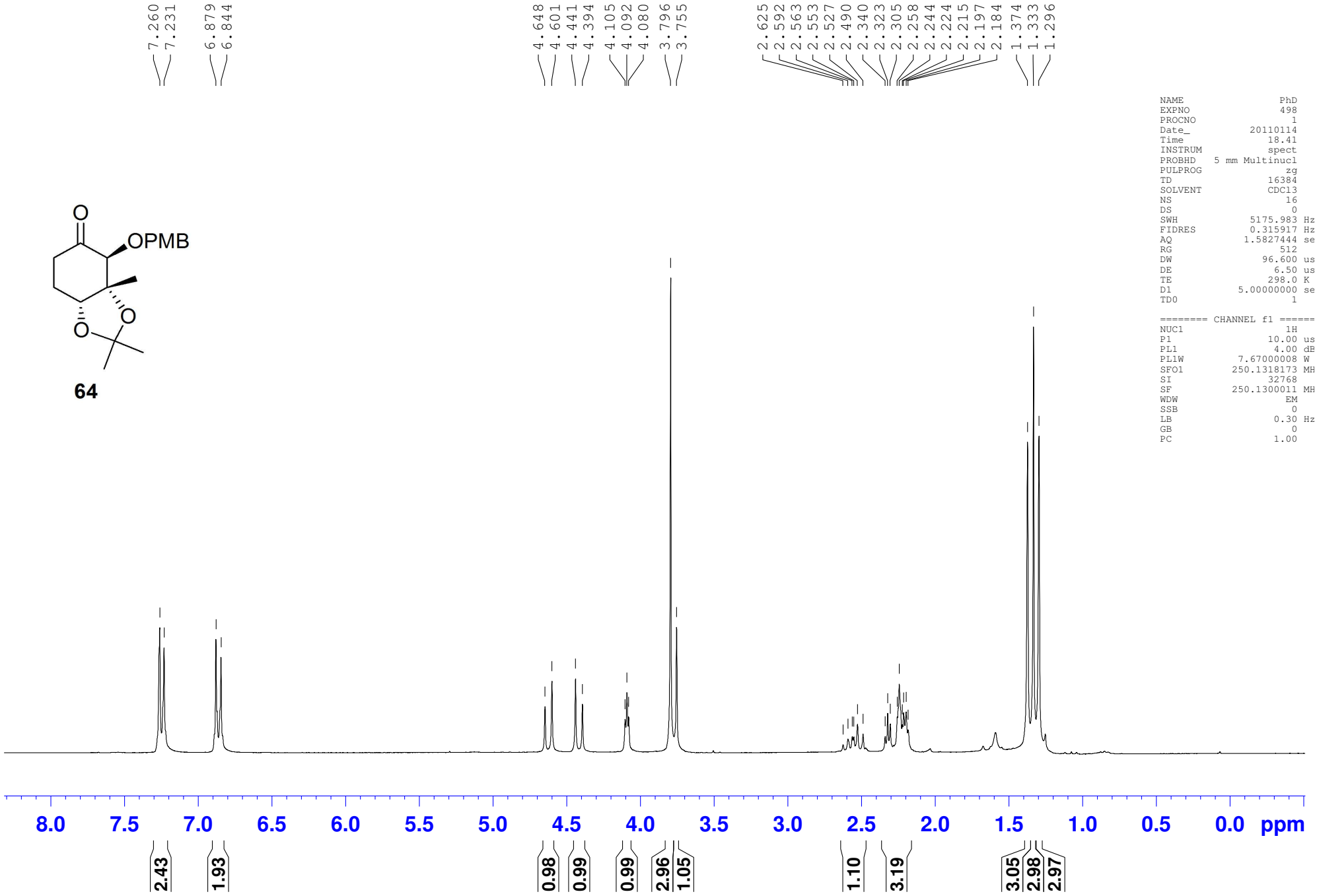

159.527
130.495
129.472
114.141
82.728
77.661
77.153
76.645
74.841
73.491
73.443
67.552
55.415
25.370
25.055
23.111
OH
OPMB
OH
HO
62a
73.491
73.443
73.5 ppm
NAME PhD
EXPNO 504
PROCNO 1
Date_ 20101221
Time 6.19
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT CDCl3
NS 37888
DS 4
SWH 15723.271
FIDRES 0.714369
AQ 0.6999680
RG 456.1
DW 31.800
DE 6.00
TE 294.7
D1 0.50000000
D11 0.03000000
TD0 1
======== CHANNEL f1 ====
NUC1 13C
P1 2.32
PL1 -2.00
PL1W 54.14257431
SFO1 62.9031528
======== CHANNEL f2 ====
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00
PL2 120.00
PL12 22.00
PL2W 0.00000000
PL12W 0.12156131
SFO2 250.1311770
SI 32768
SF 62.8952305
WDW EM
SSB 0
LB 3.00
GB 0
PC 0.80
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

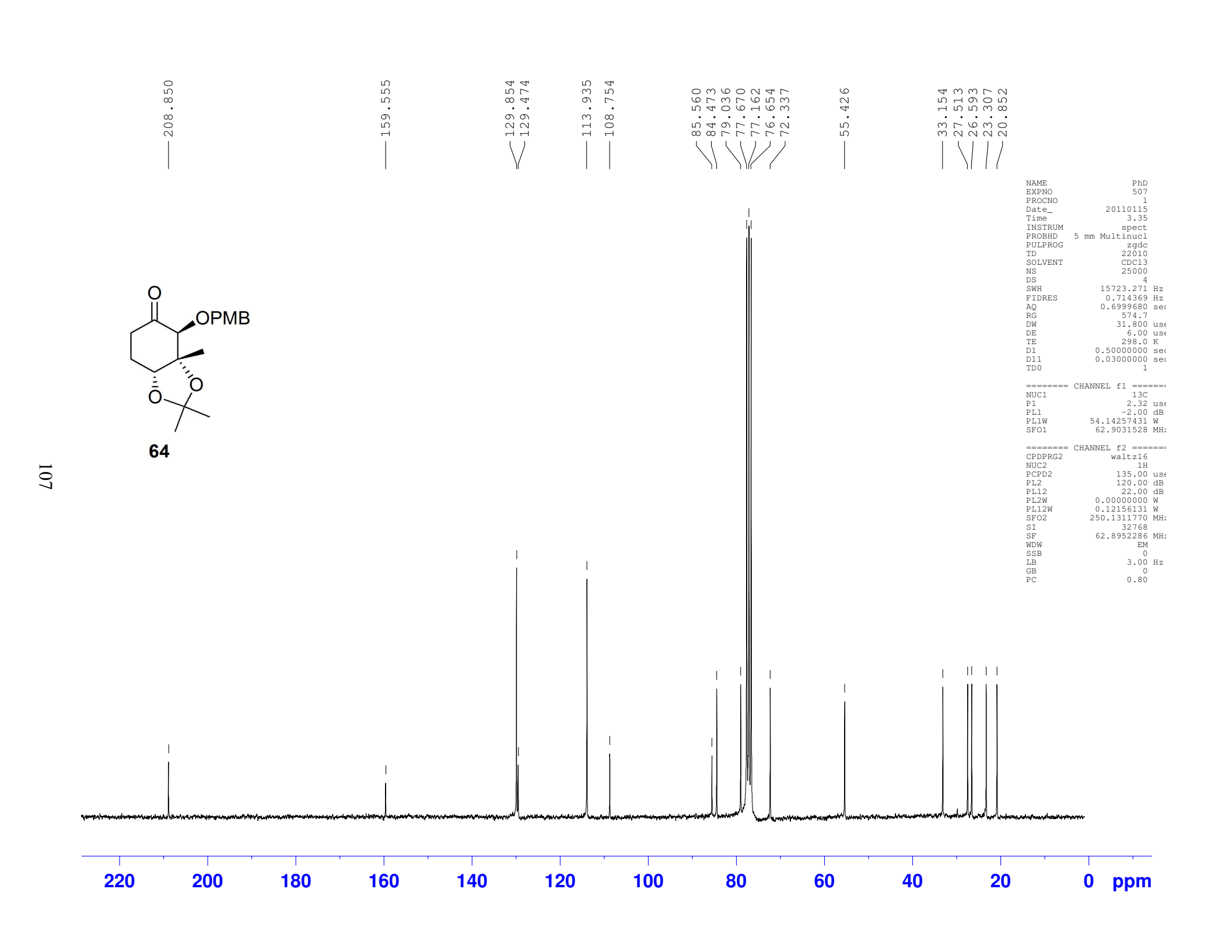

OH
OPMB
O
O

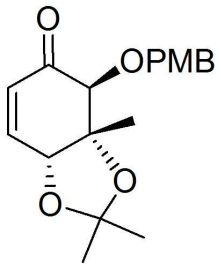
63

7.322
7.287
7.263
6.900
6.865
4.805
4.759
4.603
4.557
4.060
4.048
4.036
4.024
4.005
3.994
3.983
3.809
3.522
3.510
2.070
2.051
2.038
2.021
2.009
1.995
1.977
1.964
1.909
1.896
1.885
1.873
1.850
1.836
1.826
1.813
1.795
1.782
1.769
1.753
1.739
1.726
1.416
1.401
1.384
NAME PhD
EXPNO 502
PROCNO 1
Date_ 20110119
Time 19.01
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 512
DW 96.600 usec
DE 6.50 usec
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300006 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.16
2.12
1.08
1.09
1.04
1.08
3.24
1.04
1.97
1.40
2.05
3.14
3.03
3.84


159.388
130.765
129.523
113.917
107.543
82.829
81.680
80.544
77.676
77.168
76.660
72.176
68.489
55.442
28.396
27.366
24.537
20.521
19.984
OH
OPMB
O
O
63
NAME PhD
EXPNO 513
PROCNO 1
Date_ 20110120
Time 4.18
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT CDCl3
NS 26112
DS 4
SWH 15723.271 Hz
FIDRES 0.714369 Hz
AQ 0.6999680 sec
RG 512
DW 31.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 2.32 usec
PL1 -2.00 dB
PL1W 54.14257431 W
SFO1 62.9031528 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00 usec
PL2 120.00 dB
PL12 22.00 dB
PL2W 0.00000000 W
PL12W 0.12156131 W
SFO2 250.1311770 MHz
SI 32768
SF 62.8952281 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 0.80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


7.260
7.231
6.879
6.844
4.648
4.601
4.441
4.394
4.105
4.092
4.080
3.796
3.755
2.625
2.592
2.563
2.553
2.527
2.490
2.340
2.323
2.305
2.258
2.244
2.224
2.215
2.197
2.184
1.374
1.333
1.296
O
OPMB
O
O
64
NAME PhD
EXPNO 498
PROCNO 1
Date_ 20110114
Time 18.41
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 se
RG 512
DW 96.600 us
DE 6.50 us
TE 298.0 K
D1 5.00000000 se
TD0 1
======== CHANNEL f1 ======
NUC1 1H
P1 10.00 us
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MH
SI 32768
SF 250.1300011 MH
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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
2.43
1.93
0.98
0.99
0.99
2.96
1.05
1.10
3.19
3.05
2.98
2.97


208.850
159.555
129.854
129.474
113.935
108.754
85.560
84.473
79.036
77.670
77.162
76.654
72.337
55.426
33.154
27.513
26.593
23.307
20.852
NAME PhD
EXPNO 507
PROCNO 1
Date_ 20110115
Time 3.35
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT CDC13
NS 25000
DS 4
SWH 15723.271 Hz
FIDRES 0.714369 Hz
AQ 0.6999680 sec
RG 574.7
DW 31.800 use
DE 6.00 use
TE 298.0 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ======
NUC1 13C
P1 2.32 use
PL1 -2.00 dB
PL1W 54.14257431 W
SFO1 62.9031528 MH
======== CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00 use
PL2 120.00 dB
PL12 22.00 dB
PL2W 0.00000000 W
PL12W 0.12156131 W
SFO2 250.1311770 MH
SI 32768
SF 62.8952286 MH
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 0.80
OPMB
64
107
220
200
180
160
140
120
100
80
60
40
20
0
ppm



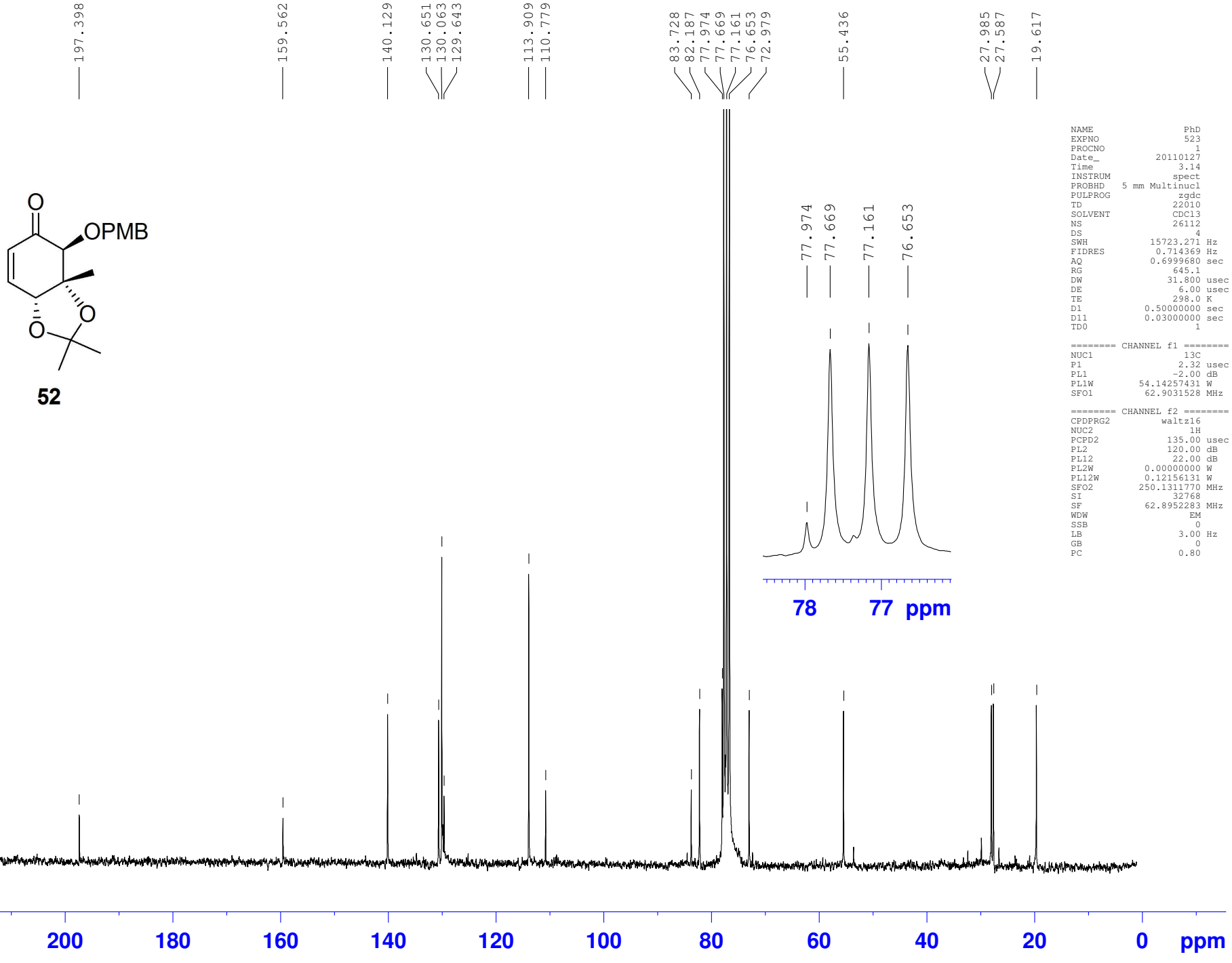
52

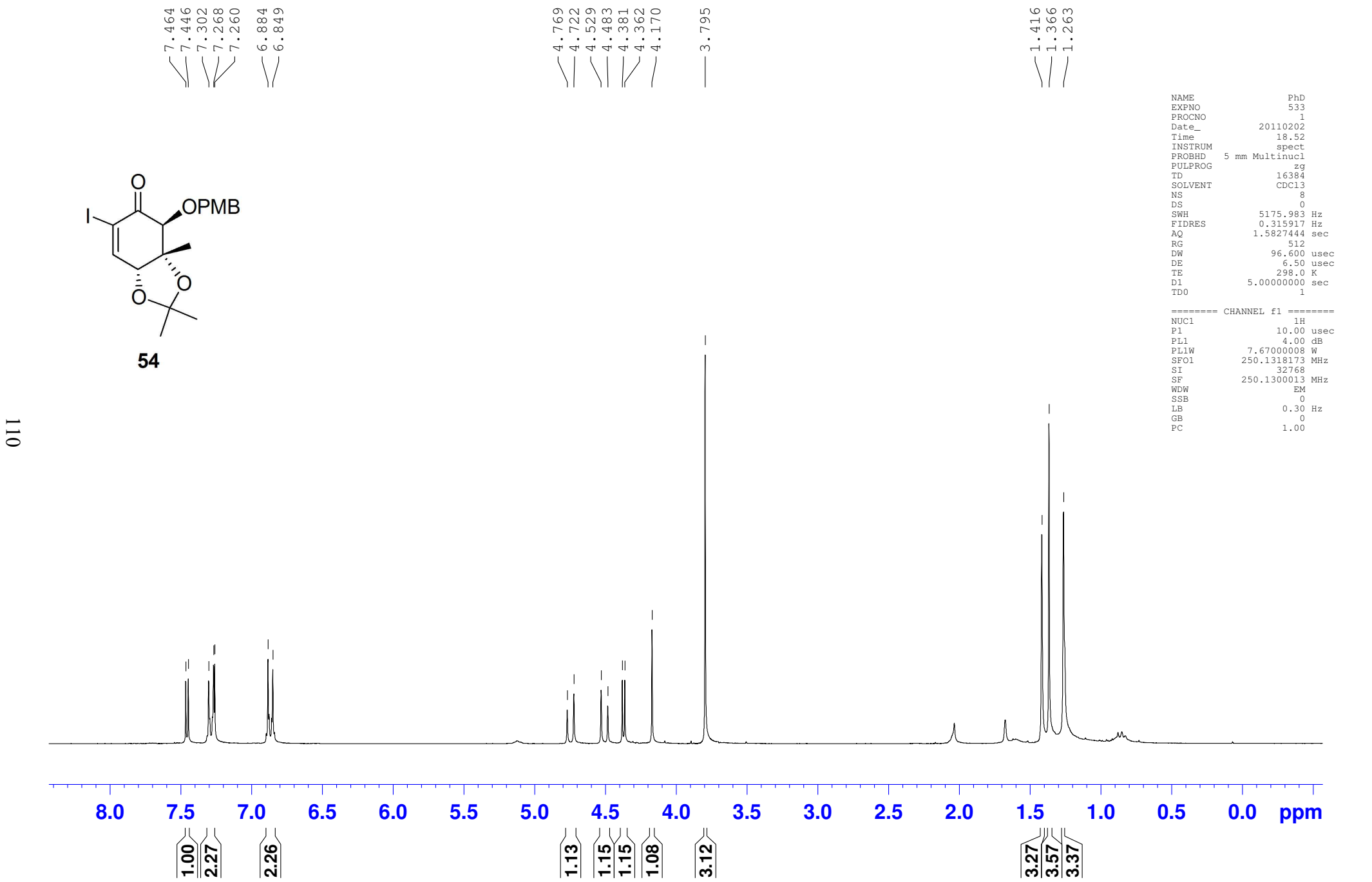
7.328 7.293 7.261 6.877 6.843 6.784 6.767 6.744 6.726 6.137 6.096 4.850 4.802 4.649 4.602 4.459 4.441 4.159 3.789 1.423 1.351 1.289

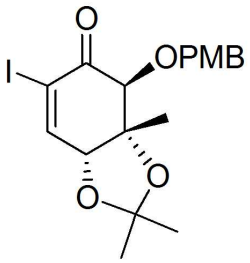
NAME	PhD
EXPNO	645
PROCNO	1
Date_	20110720
Time	13.51
INSTRUM	spect
PROBHD	5 mm Multinucl
PULPROG	zg
TD	16384
SOLVENT	CDCl3
NS	8
DS	0
SWH	5175.983 Hz
FIDRES	0.315917 Hz
AQ	1.5827444 sec
RG	256
DW	96.600 use
DE	6.50 use
TE	295.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 =======	
NUC1	1H
P1	10.00 use
PL1	4.00 dB
PL1W	7.67000008 W
SFO1	250.1318173 MHz
SI	32768
SF	250.1300011 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

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

2.20 2.35 1.11 1.00 1.14 1.24 1.03 0.97 3.73 3.18 3.28 3.54


197.398
159.562
140.129
130.651
130.063
129.643
113.909
110.779
83.728
82.187
77.974
77.669
77.161
76.653
72.979
55.436
27.985
27.587
19.617
OPMB
O
O
O
52
77.974
77.669
77.161
76.653
78
77 ppm
NAME PhD
EXPNO 523
PROCNO 1
Date_ 20110127
Time 3.14
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT CDCl3
NS 26112
DS 4
SWH 15723.271 Hz
FIDRES 0.714369 Hz
AQ 0.6999680 sec
RG 645.1
DW 31.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 2.32 usec
PL1 -2.00 dB
PL1W 54.14257431 W
SFO1 62.9031528 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00 usec
PL2 120.00 dB
PL12 22.00 dB
PL2W 0.00000000 W
PL12W 0.12156131 W
SFO2 250.1311770 MHz
SI 32768
SF 62.8952283 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 0.80
200
180
160
140
120
100
80
60
40
20
0
ppm


7.464
7.446
7.302
7.268
7.260
6.884
6.849
4.769
4.722
4.529
4.483
4.381
4.362
4.170
3.795
1.416
1.366
1.263
O
OPMB
I
O
O
54
NAME PhD
EXPNO 533
PROCNO 1
Date_ 20110202
Time 18.52
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 512
DW 96.600 usec
DE 6.50 usec
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300013 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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
1.00
2.27
2.26
1.13
1.15
1.15
1.08
3.12
3.27
3.57
3.37

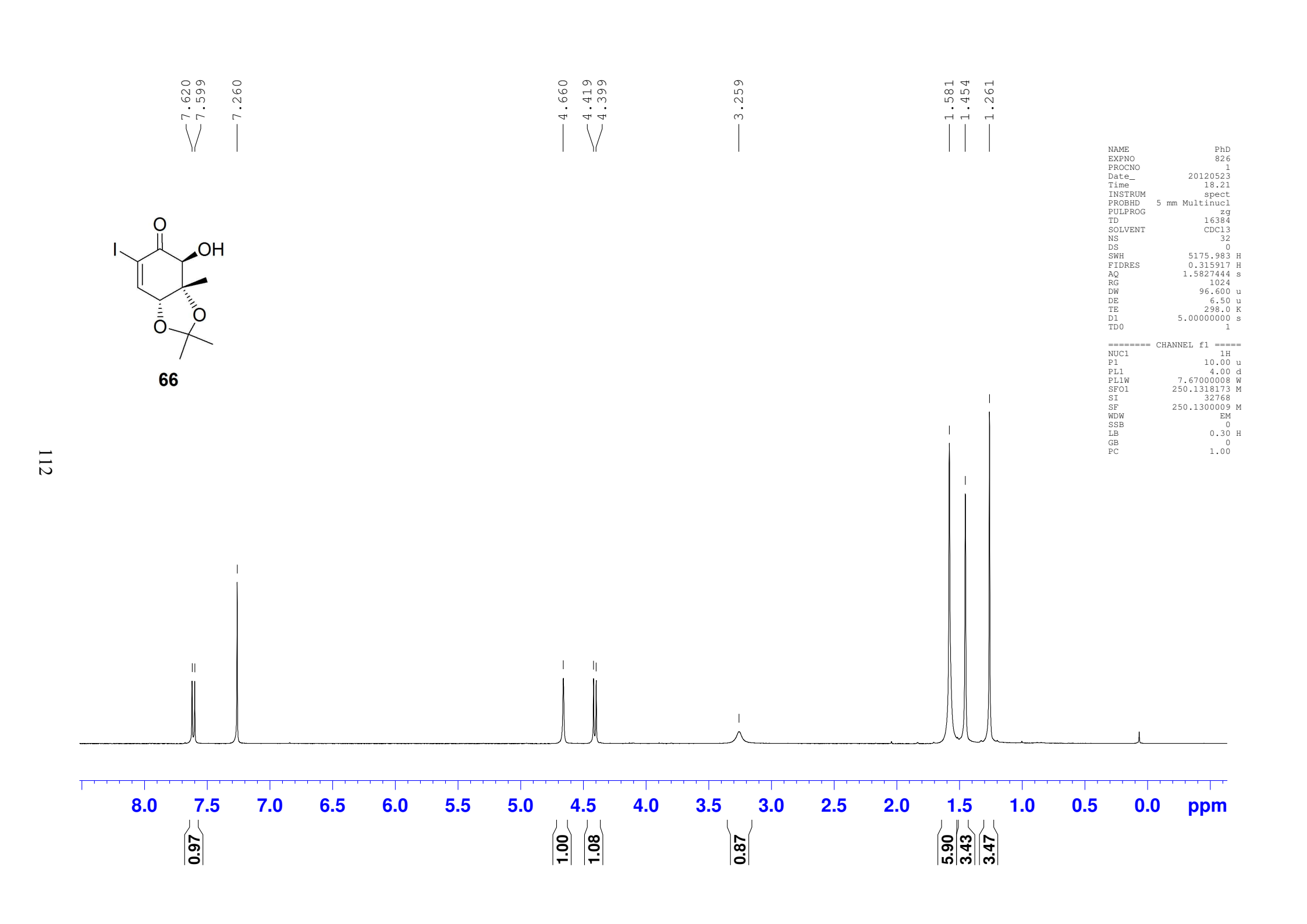


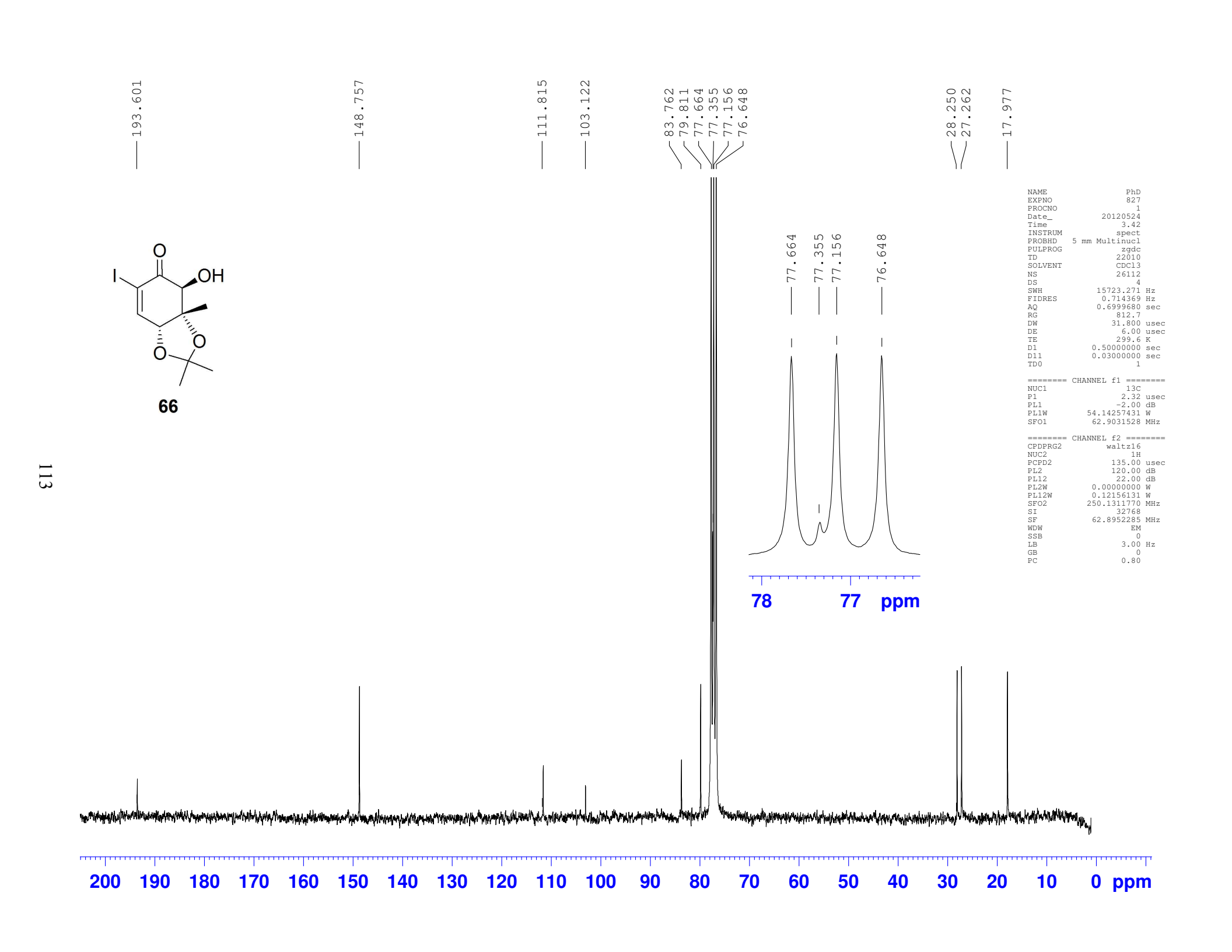
54

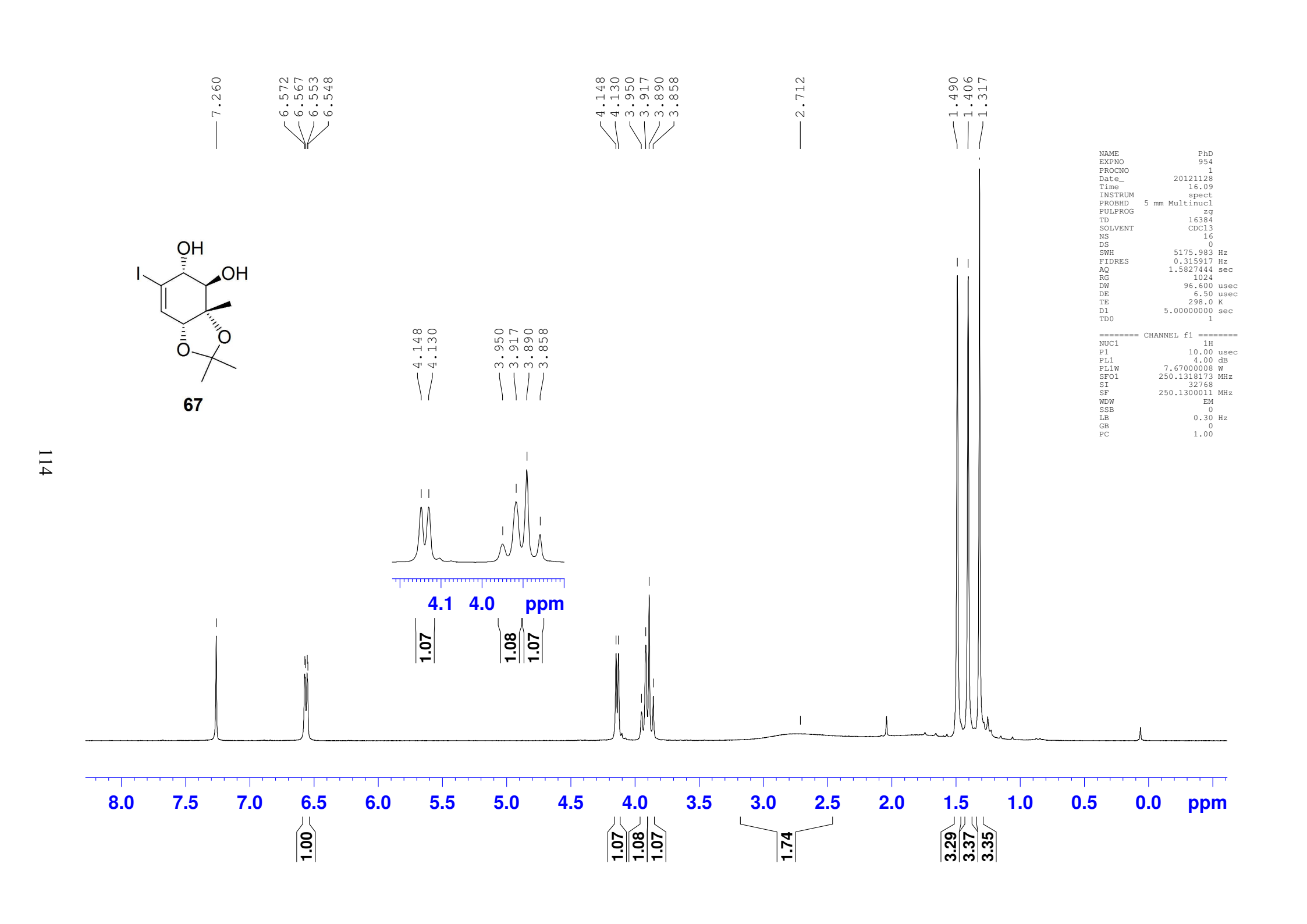
191.422
159.685
149.452
130.238
129.068
113.965
111.372
105.024
83.490
80.986
79.580
77.668
77.160
76.652
72.980
55.429
28.026
27.967
20.165

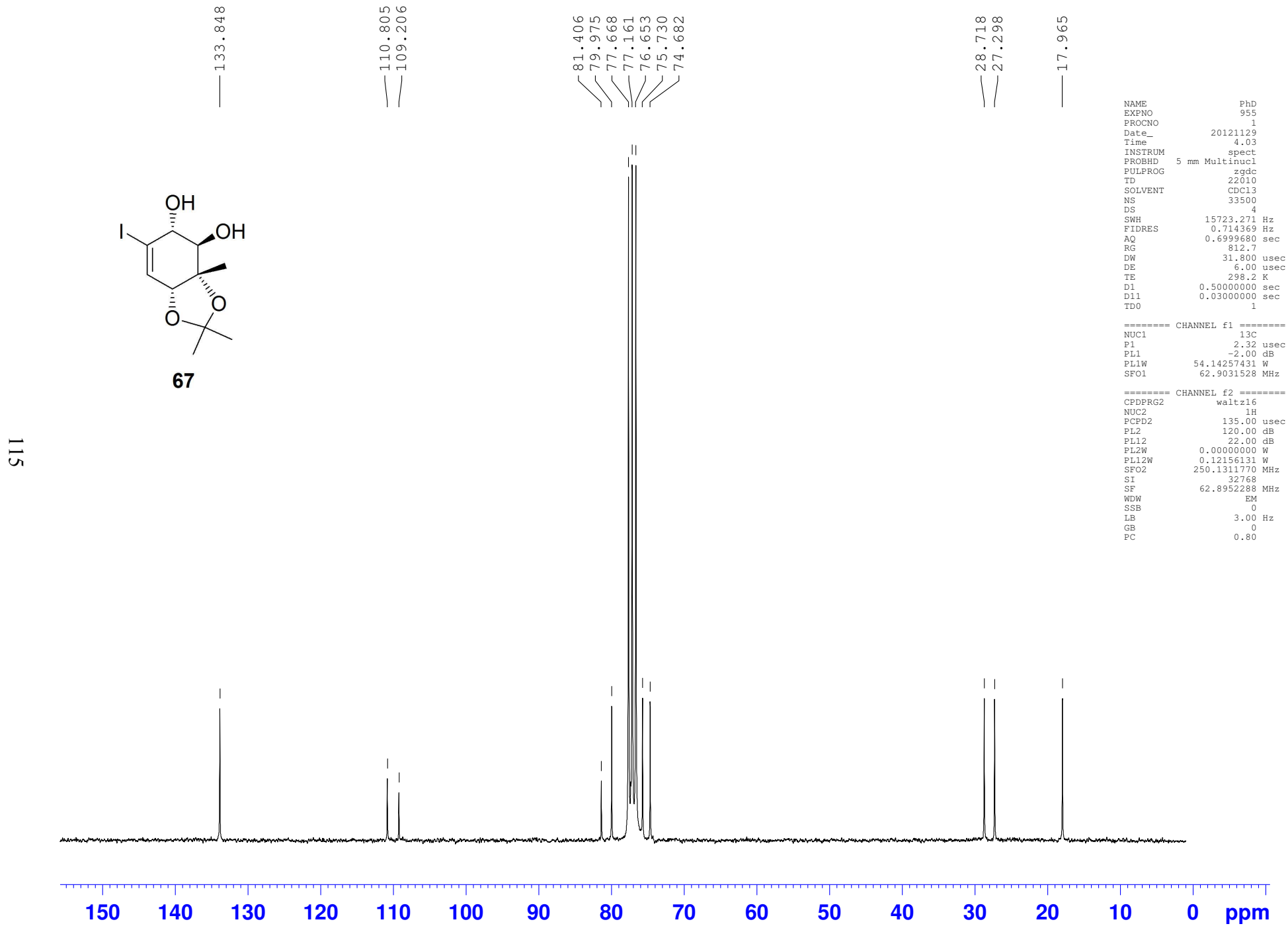
NAME	PhD
EXPNO	984
PROCNO	1
Date_	20130208
Time	5.10
INSTRUM	spect
PROBHD	5 mm Multinucl
PULPROG	zgdc
TD	22010
SOLVENT	CDCl3
NS	30000
DS	4
SWH	15723.271 Hz
FIDRES	0.714369 Hz
AQ	0.6999680 sec
RG	812.7
DW	31.800 usec
DE	6.00 usec
TE	298.0 K
D1	0.50000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	2.32 usec
PL1	-2.00 dB
PL1W	54.14257431 W
SFO1	62.9031528 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	135.00 usec
PL2	120.00 dB
PL12	22.00 dB
PL2W	0.00000000 W
PL12W	0.12156131 W
SFO2	250.1311770 MHz
SI	32768
SF	62.8952293 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	0.80

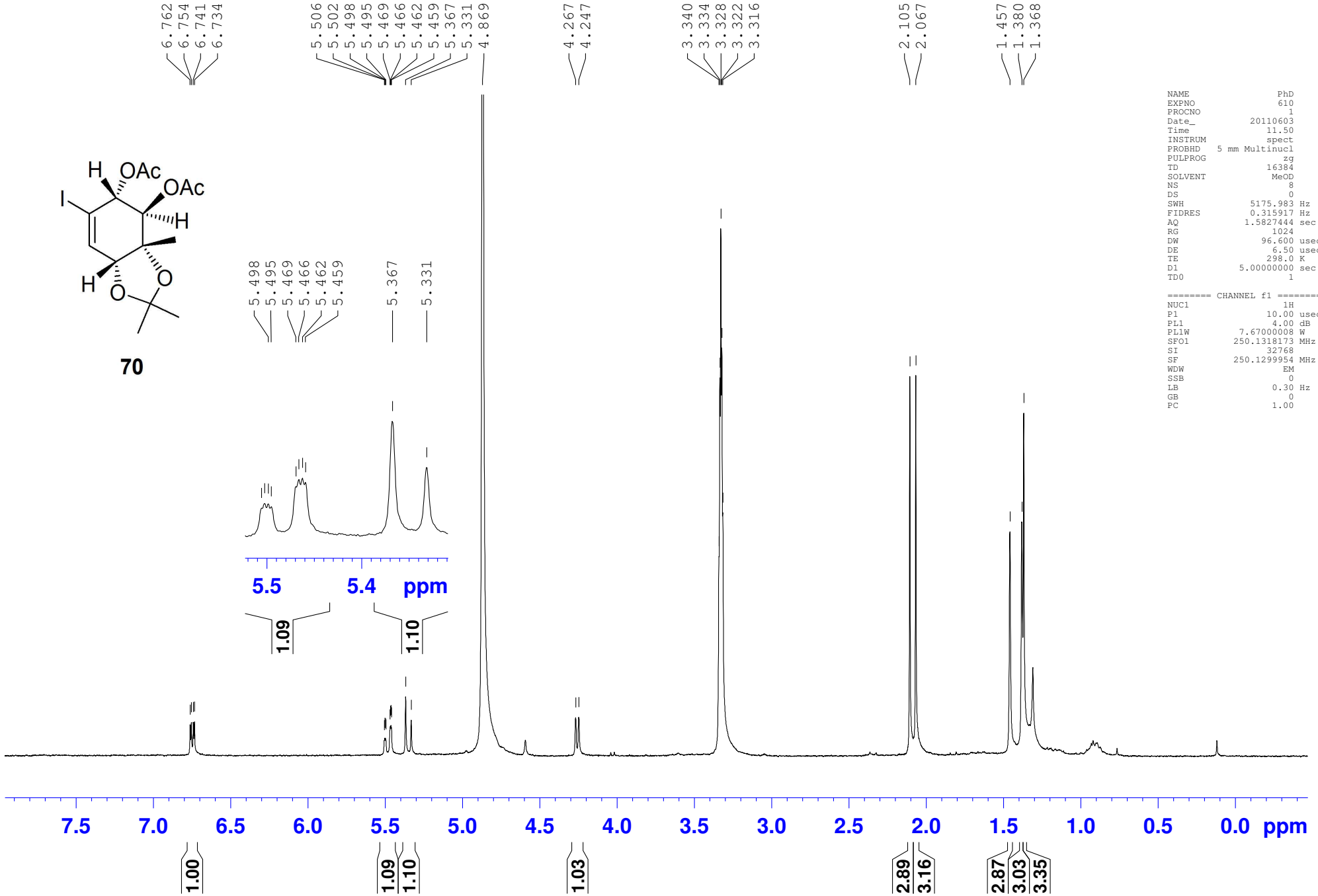
200 180 160 140 120 100 80 60 40 20 0 ppm

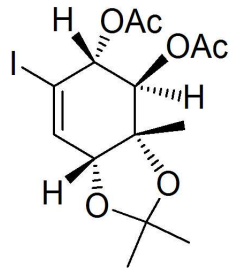

7.620
7.599
7.260
4.660
4.419
4.399
3.259
1.581
1.454
1.261
O
I
OH
O
O
66
NAME PhD
EXPNO 826
PROCNO 1
Date_ 20120523
Time 18.21
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 32
DS 0
SWH 5175.983 H
FIDRES 0.315917 H
AQ 1.5827444 s
RG 1024
DW 96.600 u
DE 6.50 u
TE 298.0 K
D1 5.00000000 s
TD0 1
======== CHANNEL f1 =====
NUC1 1H
P1 10.00 u
PL1 4.00 d
PL1W 7.67000008 W
SFO1 250.1318173 M
SI 32768
SF 250.1300009 M
WDW EM
SSB 0
LB 0.30 H
GB 0
PC 1.00
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
0.97
1.00
1.08
0.87
5.90
3.43
3.47


193.601
148.757
111.815
103.122
83.762
79.811
77.664
77.355
77.156
76.648
28.250
27.262
17.977
O
I
OH
O
O
66
77.664
77.355
77.156
76.648
78
77
ppm
NAME PhD
EXPNO 827
PROCNO 1
Date_ 20120524
Time 3.42
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT CDCl3
NS 26112
DS 4
SWH 15723.271 Hz
FIDRES 0.714369 Hz
AQ 0.6999680 sec
RG 812.7
DW 31.800 usec
DE 6.00 usec
TE 299.6 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 2.32 usec
PL1 -2.00 dB
PL1W 54.14257431 W
SFO1 62.9031528 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00 usec
PL2 120.00 dB
PL12 22.00 dB
PL2W 0.00000000 W
PL12W 0.12156131 W
SFO2 250.1311770 MHz
SI 32768
SF 62.8952285 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 0.80
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.260
6.572
6.567
6.553
6.548
4.148
4.130
3.950
3.917
3.890
3.858
2.712
1.490
1.406
1.317
OH
I
OH
O
O
67
NAME PhD
EXPNO 954
PROCNO 1
Date_ 20121128
Time 16.09
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 1024
DW 96.600 usec
DE 6.50 usec
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300011 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
4.1 4.0 ppm
1.07
1.08
1.07
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 ppm
1.00
1.07
1.08
1.07
1.74
3.29
3.37
3.35


133.848
110.805
109.206
81.406
79.975
77.668
77.161
76.653
75.730
74.682
28.718
27.298
17.965
OH
I
OH
O
O
67
NAME PhD
EXPNO 955
PROCNO 1
Date_ 20121129
Time 4.03
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT CDCl3
NS 33500
DS 4
SWH 15723.271 Hz
FIDRES 0.714369 Hz
AQ 0.6999680 sec
RG 812.7
DW 31.800 usec
DE 6.00 usec
TE 298.2 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 2.32 usec
PL1 -2.00 dB
PL1W 54.14257431 W
SFO1 62.9031528 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00 usec
PL2 120.00 dB
PL12 22.00 dB
PL2W 0.00000000 W
PL12W 0.12156131 W
SFO2 250.1311770 MHz
SI 32768
SF 62.8952288 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 0.80
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


6.762
6.754
6.741
6.734
5.506
5.502
5.498
5.495
5.469
5.466
5.462
5.459
5.367
5.331
4.869
4.267
4.247
3.340
3.334
3.328
3.322
3.316
2.105
2.067
1.457
1.380
1.368
H
OAc
OAc
I
H
H
O
O
70
5.5
5.4
ppm
1.09
1.10
NAME PhD
EXPNO 610
PROCNO 1
Date_ 20110603
Time 11.50
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT MeOD
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 1024
DW 96.600 usec
DE 6.50 usec
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1299954 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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
1.00
1.09
1.10
1.03
2.89
3.16
2.87
3.03
3.35



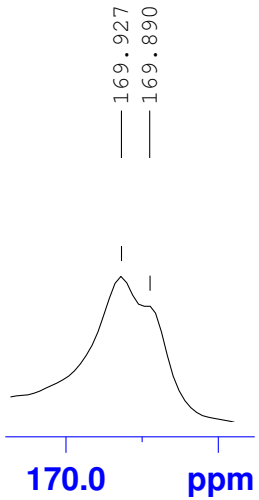
70

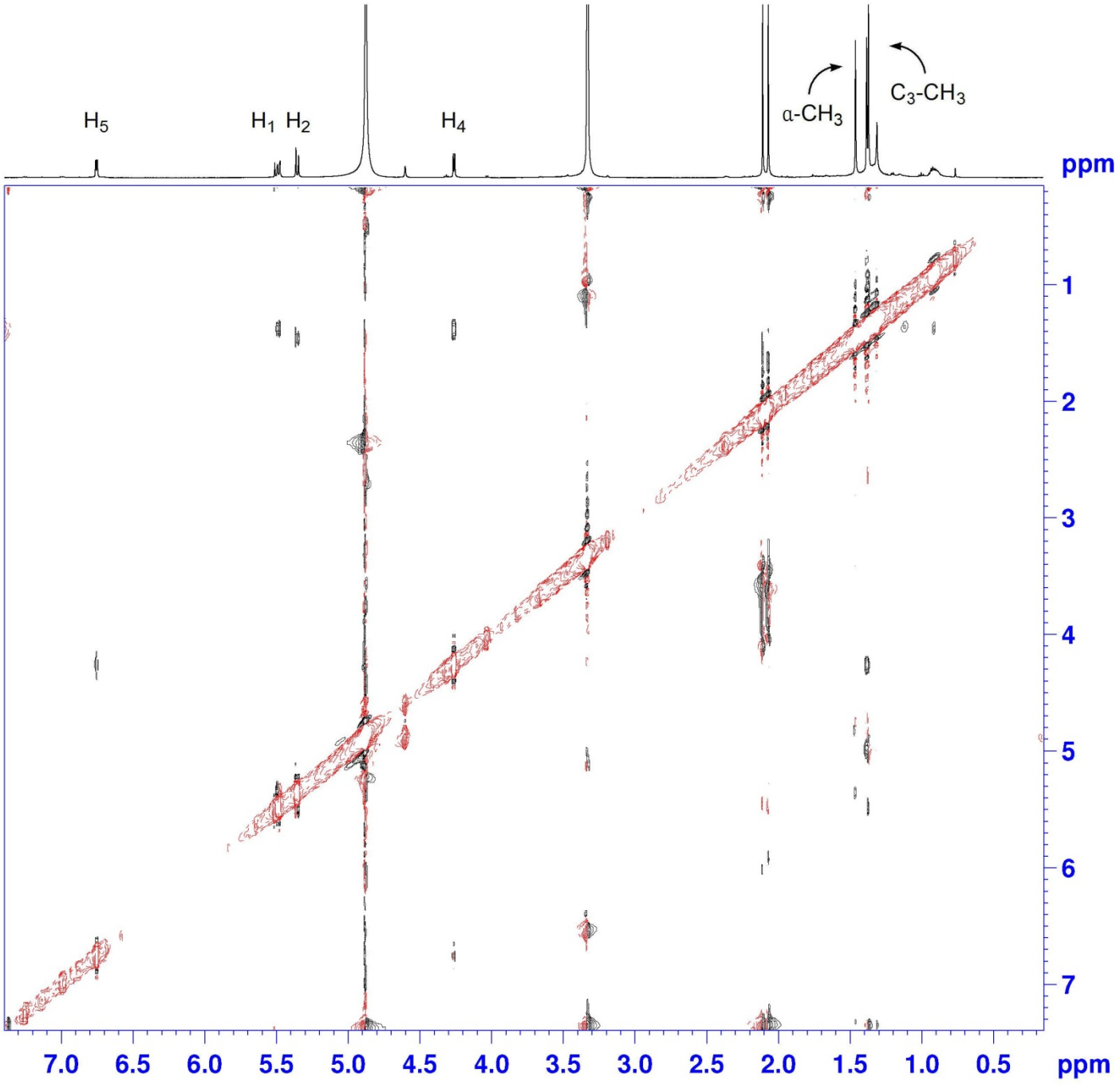
169.927
169.890
135.384
111.237
103.219
80.087
79.936
77.717
77.168
76.702
73.513
73.195
27.994
27.231
21.149
21.000
18.133

NAME PhD
EXPNO 965
PROCNO 1
Date_ 20121206
Time 4.32
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT CDCl3
NS 29000
DS 4
SWH 15723.271 Hz
FIDRES 0.714369 Hz
AQ 0.6999680 sec
RG 812.7
DW 31.800 usec
DE 6.00 usec
TE 295.8 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1

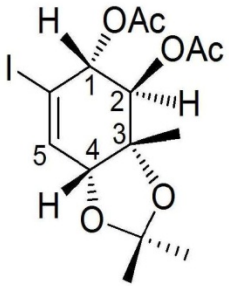
======== CHANNEL f1 ========
NUC1 13C
P1 2.32 usec
PL1 -2.00 dB
PL1W 54.14257431 W
SFO1 62.9031528 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00 usec
PL2 120.00 dB
PL12 22.00 dB
PL2W 0.00000000 W
PL12W 0.12156131 W
SFO2 250.1311770 MHz
SI 32768
SF 62.8952292 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 0.80

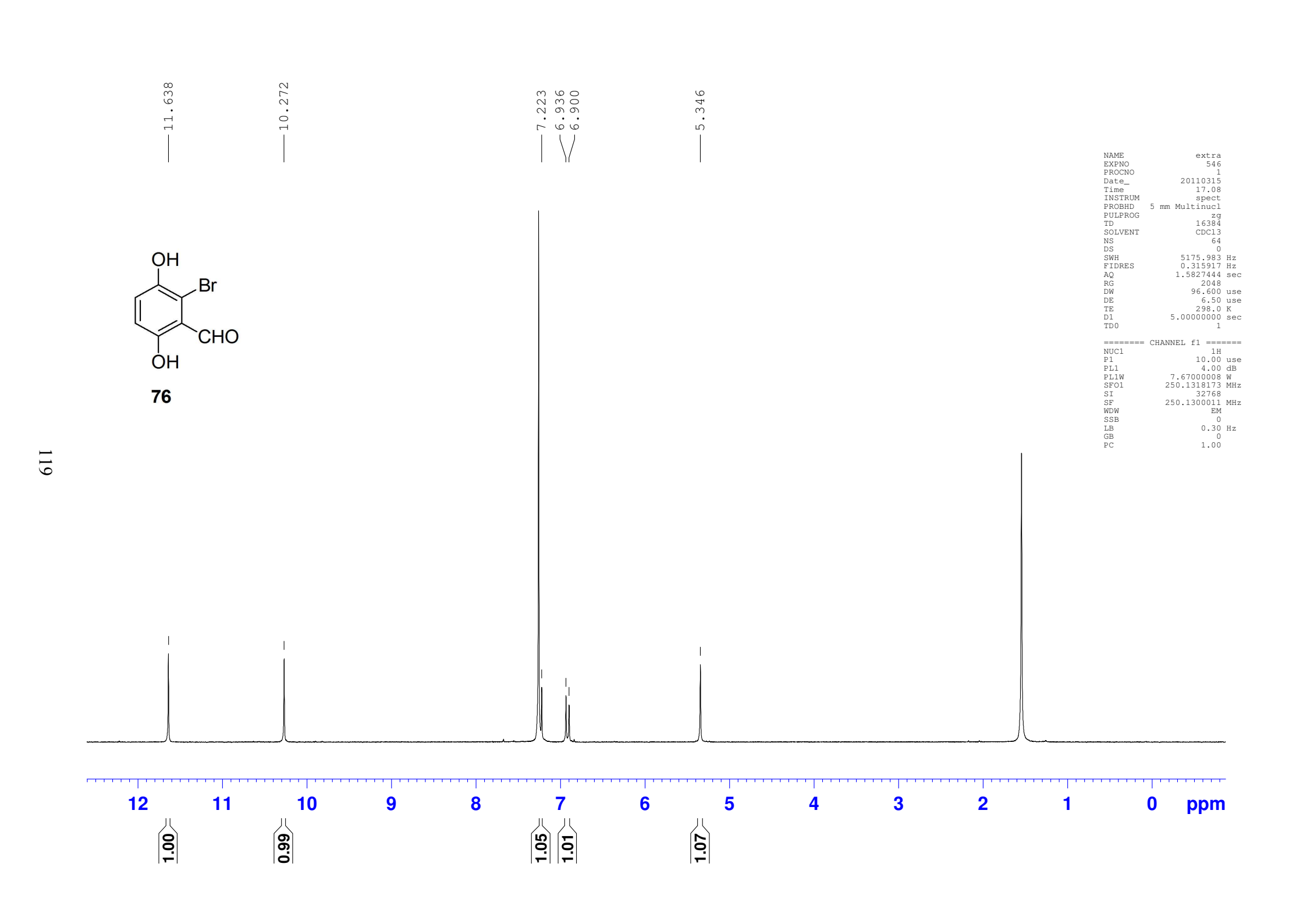


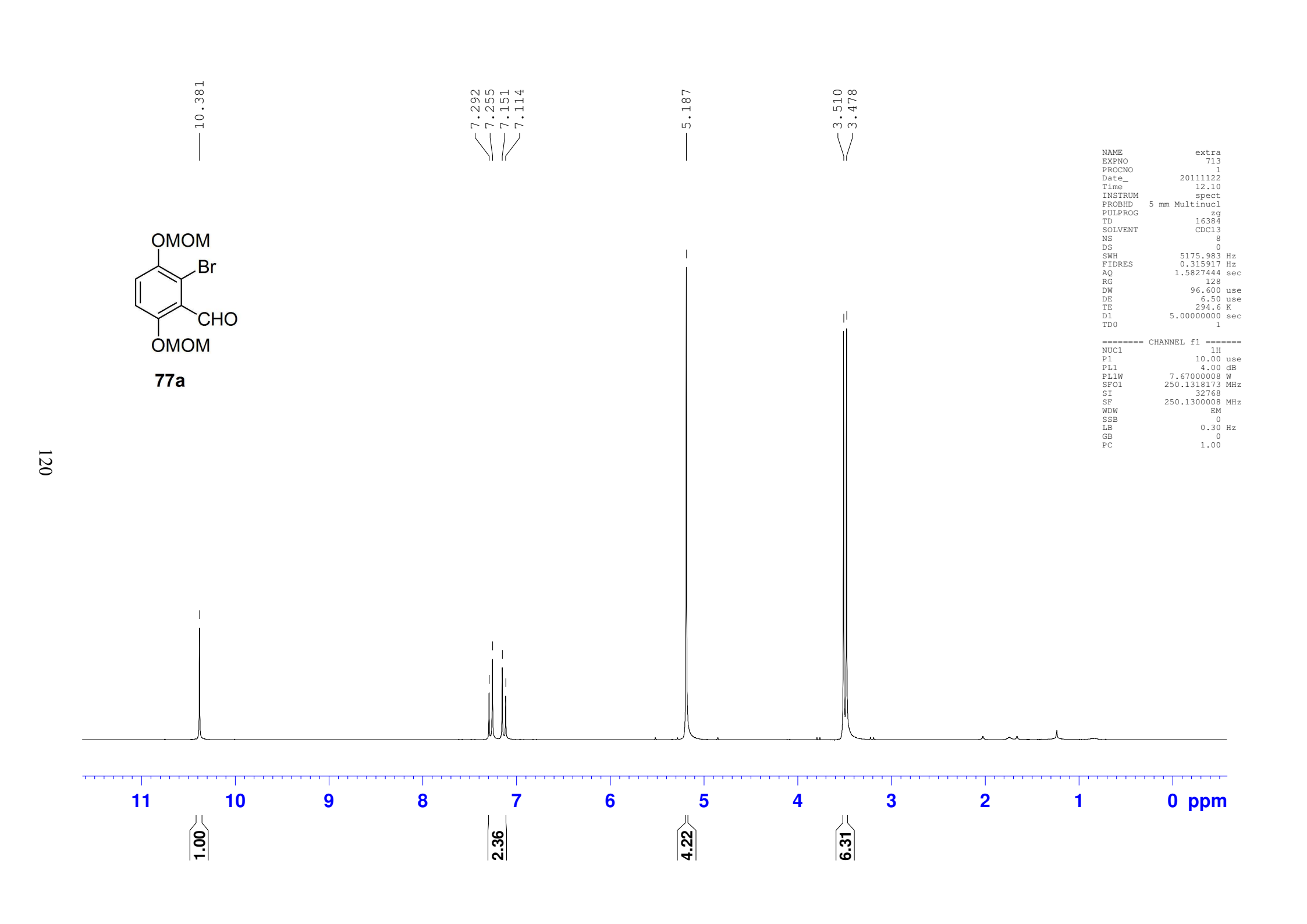


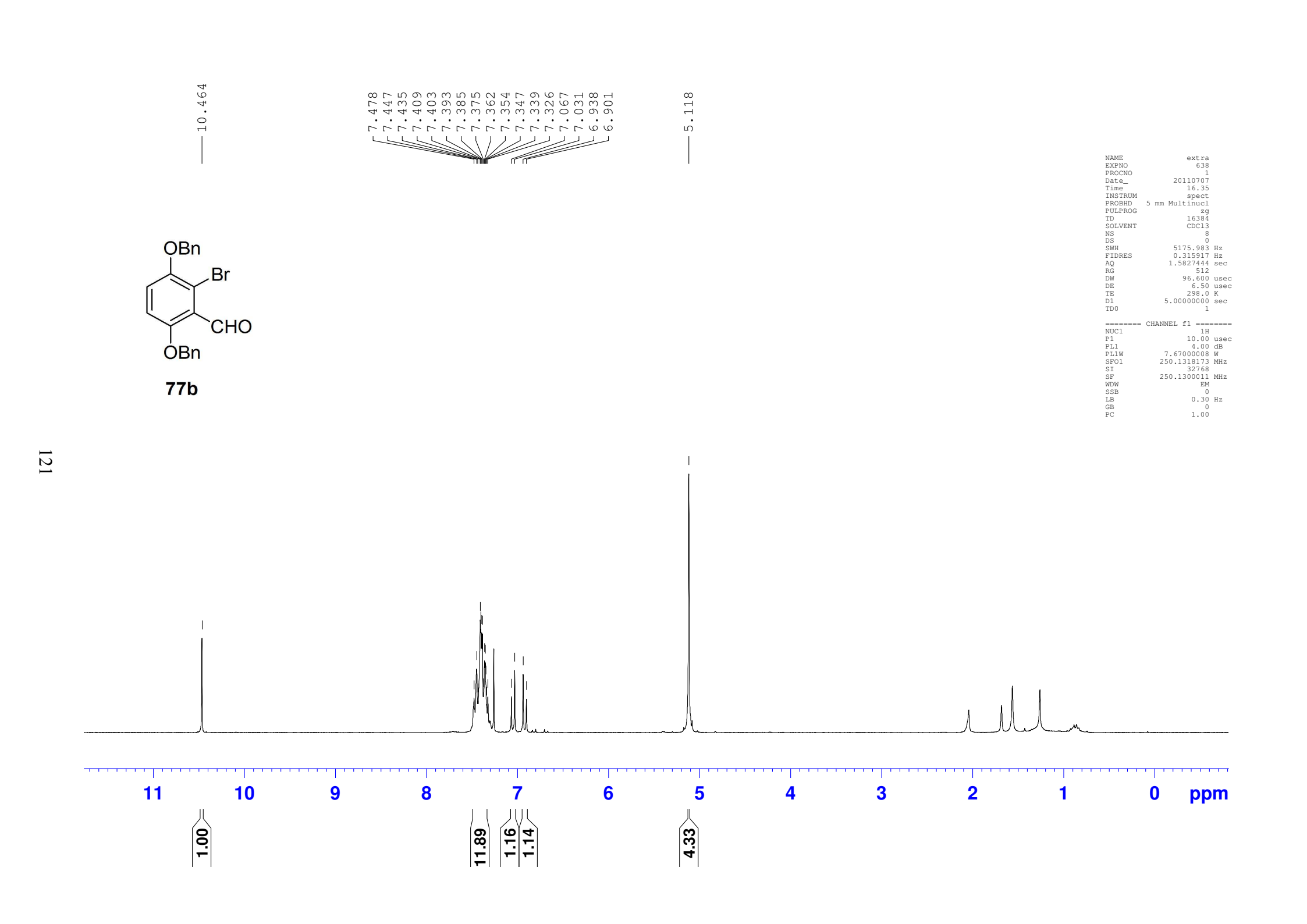

```
NAME                AV500
EXPNO                  34
PROCNO                  1
Date_            20110607
Time                 2.09
INSTRUM             spect
PROBHD   5 mm CPTCI 1H-
PULPROG          noesyph
TD                   2048
SOLVENT              MeOD
NS                      8
DS                      4
SWH            3623.188 Hz
FIDRES         1.769135 Hz
AQ             0.2826740 sec
RG                   20.2
DW             138.000 usec
DE               6.50 usec
TE                298.0 K
D0             0.00012801 sec
D1             1.91807997 sec
D8             0.30000001 sec
IN0            0.00027600 sec

======== CHANNEL f1 ========
NUC1                   1H
P1               7.85 usec
PL1                6.80 dB
PL1W        7.18986177 W
SFO1       500.1318872 MHz
NDO                     1
TD                    128
SFO1        500.1319 MHz
FIDRES       28.306160 Hz
SW            7.244 ppm
FnMODE     States-TPPI
SI                   1024
SF         500.1300000 MHz
WDW                QSINE
SSB                    2
LB              0.00 Hz
GB                     0
PC                  1.40
SI                   1024
MC2        States-TPPI
SF         500.1300000 MHz
WDW                QSINE
SSB                    2
LB              0.00 Hz
GB                     0
```

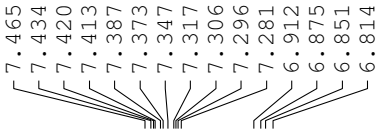


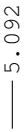
70

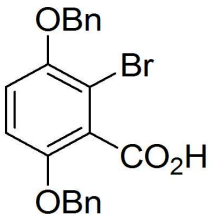

11.638
10.272
7.223
6.936
6.900
5.346
OH
Br
CHO
OH
76
NAME extra
EXPNO 546
PROCNO 1
Date_ 20110315
Time 17.08
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 64
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 2048
DW 96.600 use
DE 6.50 use
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 =======
NUC1 1H
P1 10.00 use
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300011 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.99
1.05
1.01
1.07


10.381
7.292
7.255
7.151
7.114
5.187
3.510
3.478
OMOM
Br
CHO
OMOM
77a
NAME extra
EXPNO 713
PROCNO 1
Date_ 20111122
Time 12.10
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 128
DW 96.600 use
DE 6.50 use
TE 294.6 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 =======
NUC1 1H
P1 10.00 use
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300008 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
11
10
9
8
7
6
5
4
3
2
1
0 ppm
1.00
2.36
4.22
6.31


10.464
7.478
7.447
7.435
7.409
7.403
7.393
7.385
7.375
7.362
7.354
7.347
7.339
7.326
7.067
7.031
6.938
6.901
5.118
OBn
Br
CHO
OBn
77b
NAME extra
EXPNO 638
PROCNO 1
Date_ 20110707
Time 16.35
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 512
DW 96.600 usec
DE 6.50 usec
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300011 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
11.89
1.16
1.14
4.33

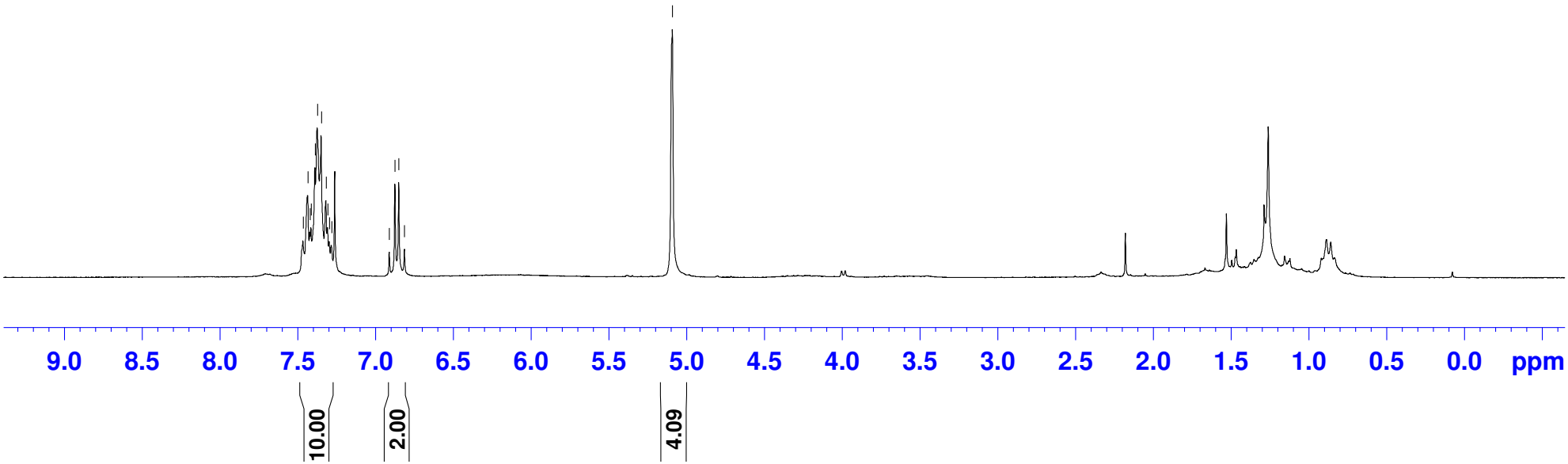


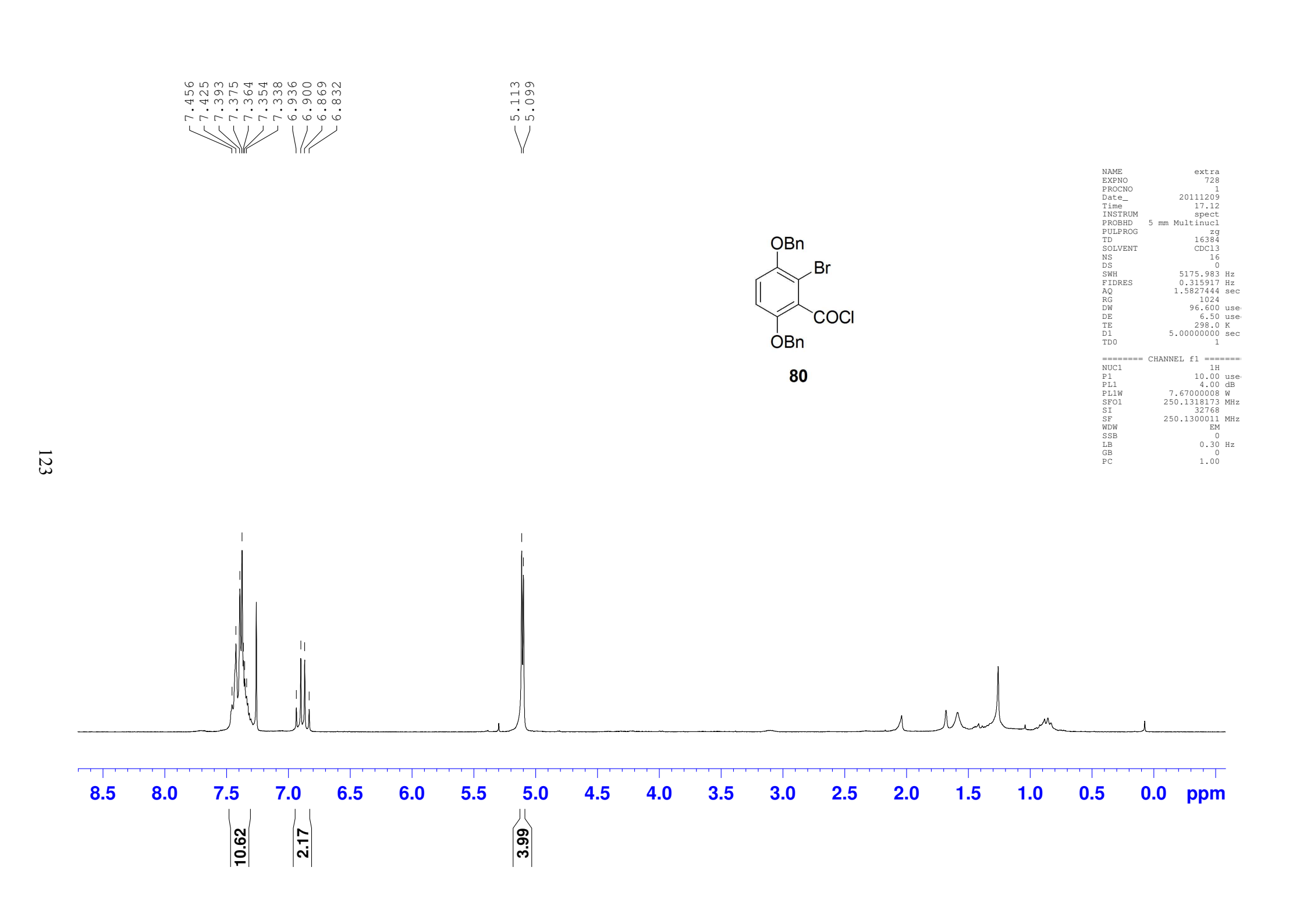


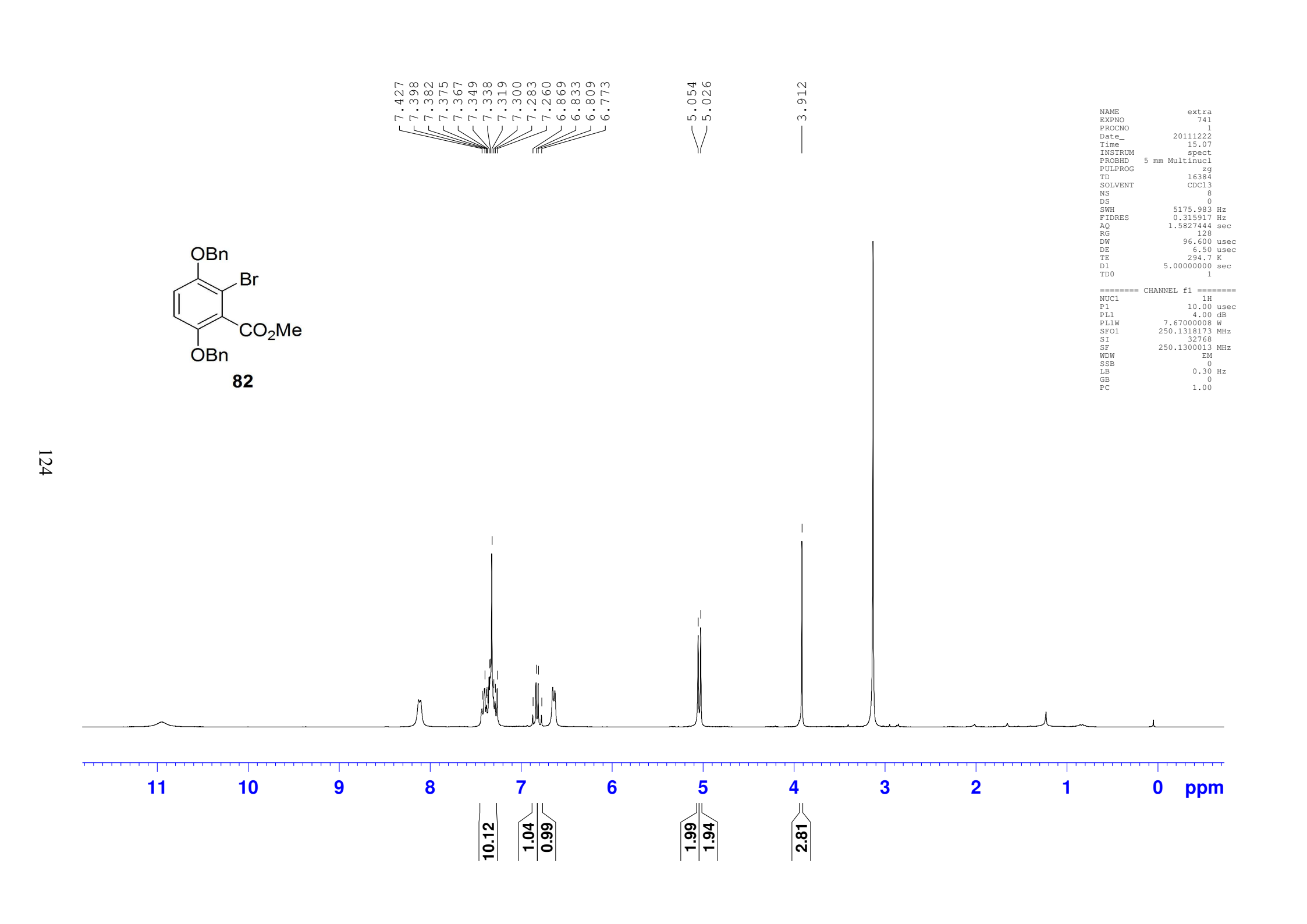


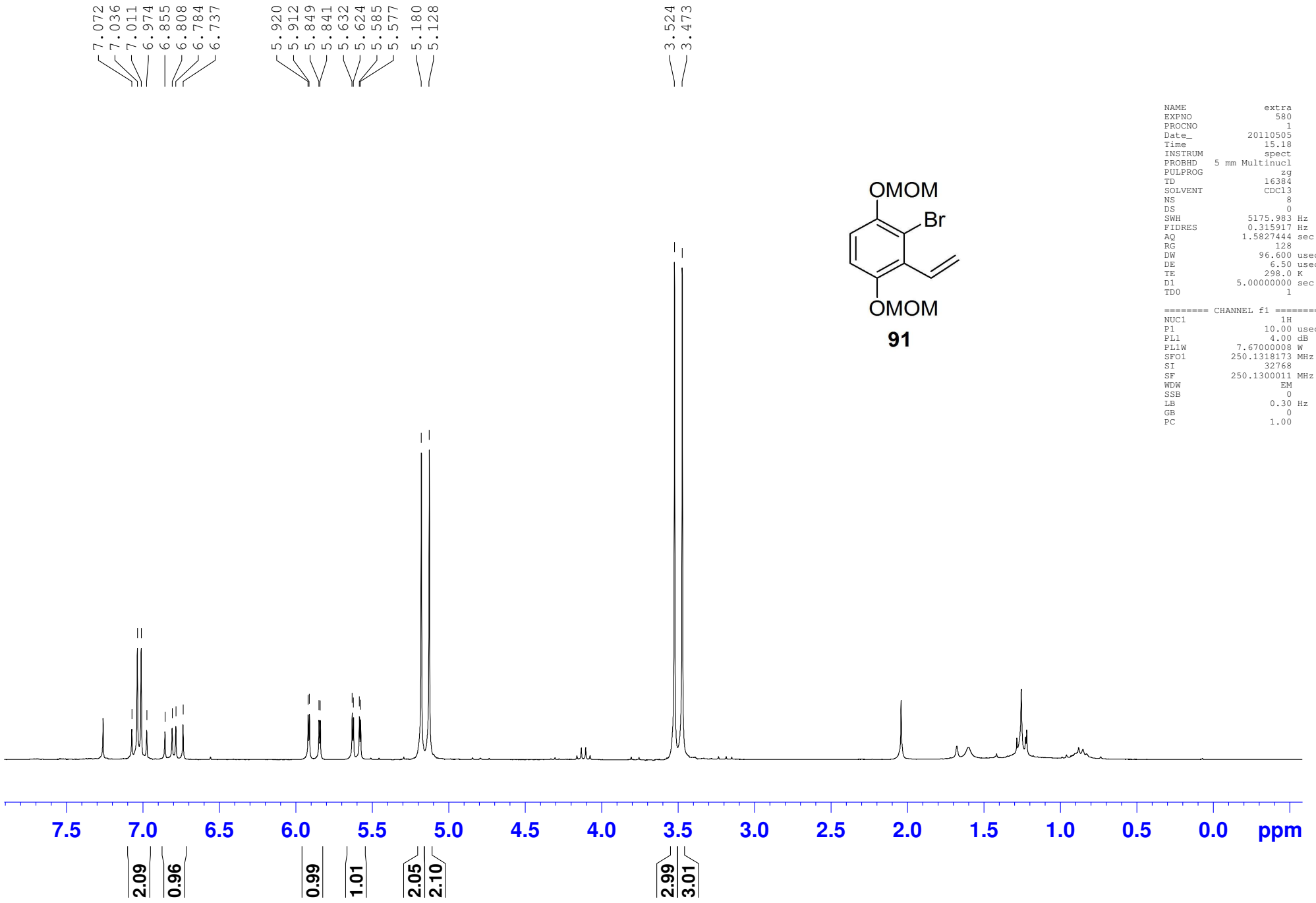
85

NAME	extra
EXPNO	724
PROCNO	1
Date_	20111206
Time	13.05
INSTRUM	spect
PROBHD	5 mm Multinucl
PULPROG	zg
TD	16384
SOLVENT	CDCl3
NS	8
DS	0
SWH	5175.983 Hz
FIDRES	0.315917 Hz
AQ	1.5827444 sec
RG	512
DW	96.600 usec
DE	6.50 usec
TE	298.0 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.00 usec
PL1	4.00 dB
PL1W	7.67000008 W
SFO1	250.1318173 MHz
SI	32768
SF	250.1300013 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00




7.456
7.425
7.393
7.375
7.364
7.354
7.338
6.936
6.900
6.869
6.832
5.113
5.099
OBn
Br
COCl
OBn
80
NAME extra
EXPNO 728
PROCNO 1
Date_ 20111209
Time 17.12
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 16
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 1024
DW 96.600 use
DE 6.50 use
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 use
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300011 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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
10.62
2.17
3.99


7.427
7.398
7.382
7.375
7.367
7.349
7.338
7.319
7.300
7.283
7.260
6.869
6.833
6.809
6.773
5.054
5.026
3.912
NAME extra
EXPNO 741
PROCNO 1
Date_ 20111222
Time 15.07
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 128
DW 96.600 usec
DE 6.50 usec
TE 294.7 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300013 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OBn
Br
CO2Me
OBn
82
11
10
9
8
7
6
5
4
3
2
1
0
ppm
10.12
1.04
0.99
1.99
1.94
2.81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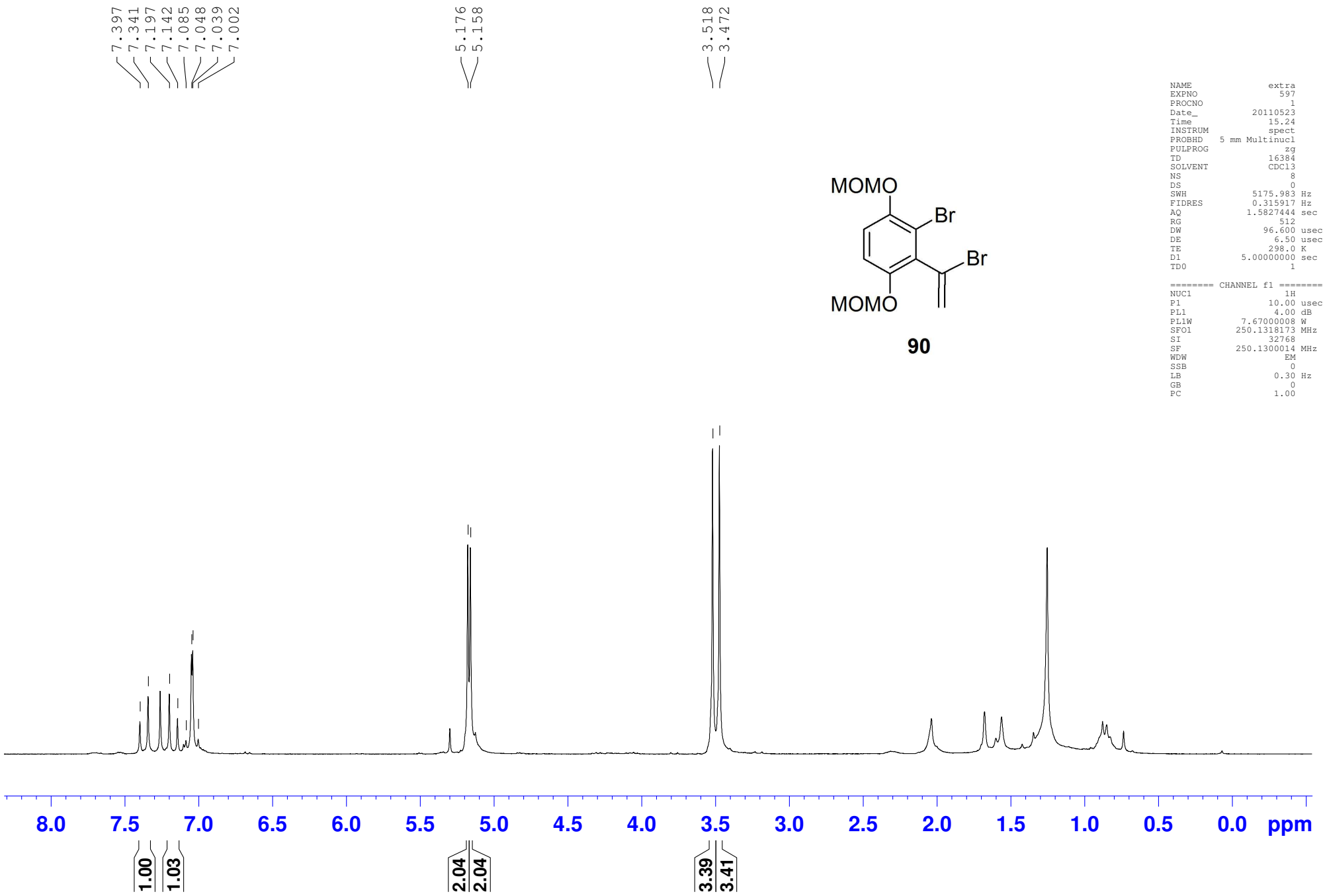
7.036
7.011
6.974
6.855
6.808
6.784
6.737
5.920
5.912
5.849
5.841
5.632
5.624
5.585
5.577
5.180
5.128
3.524
3.473
OMOM
Br
OMOM
91
NAME extra
EXPNO 580
PROCNO 1
Date_ 20110505
Time 15.18
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 128
DW 96.600 usec
DE 6.50 usec
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300011 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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
2.09
0.96
0.99
1.01
2.05
2.10
2.99
3.01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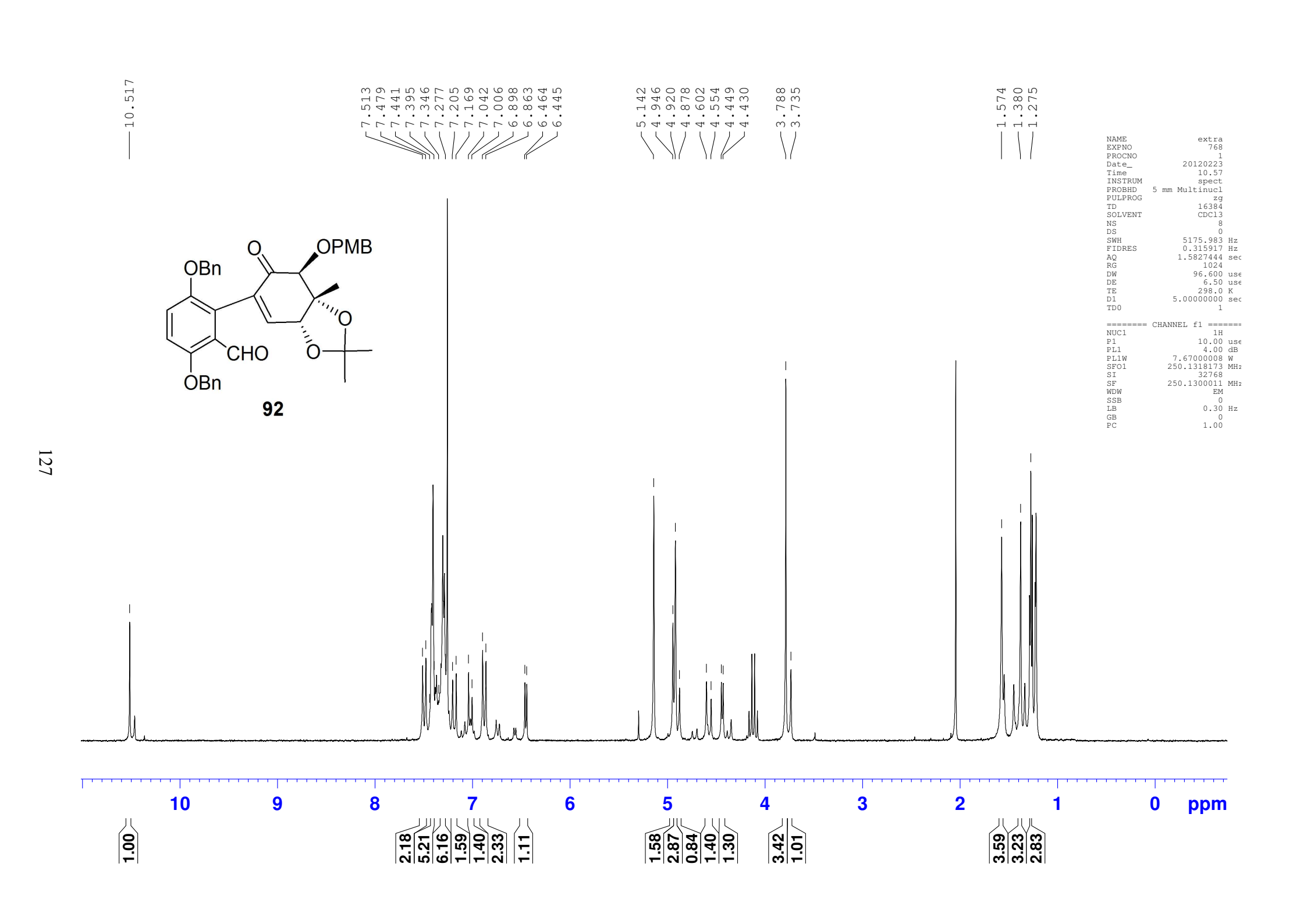
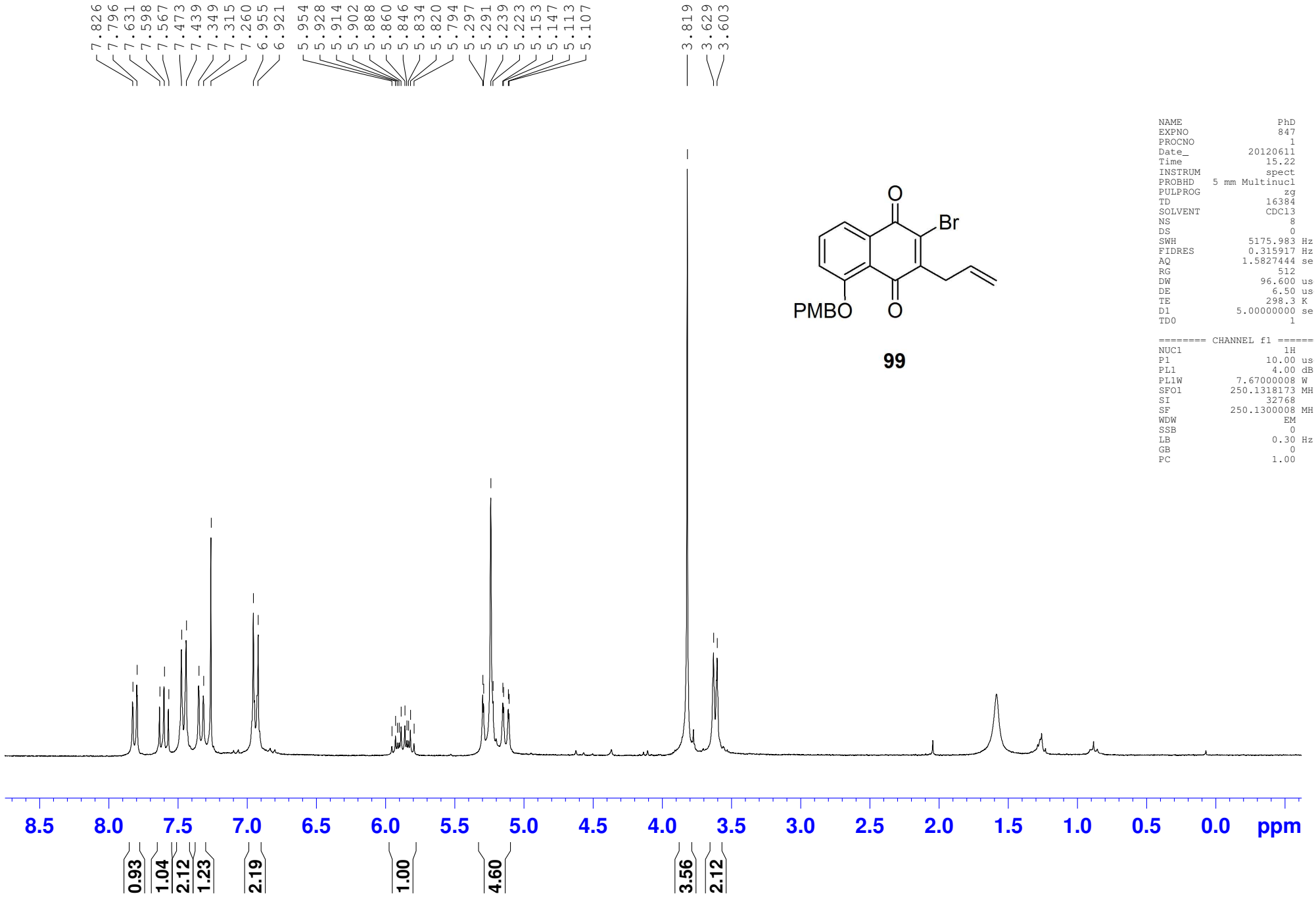
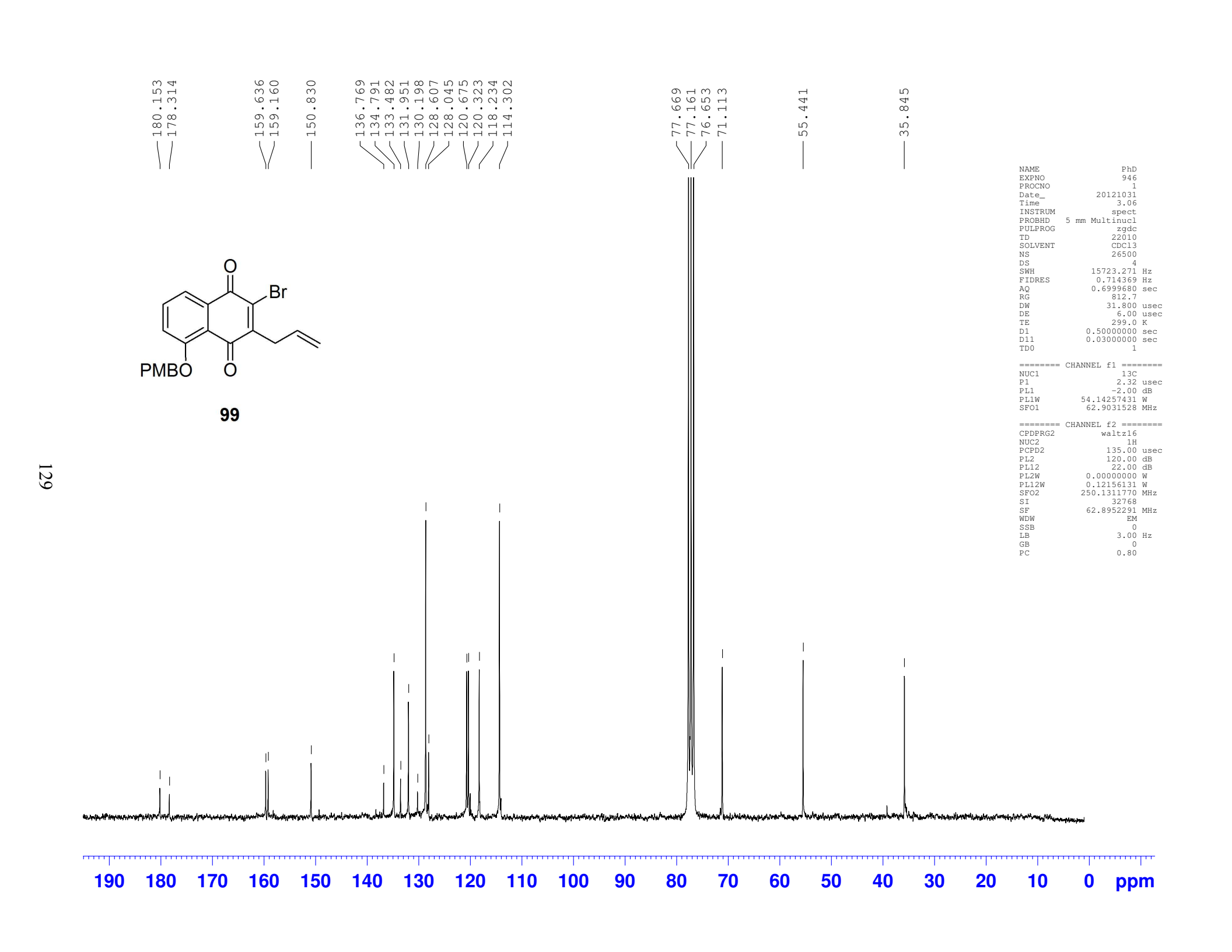
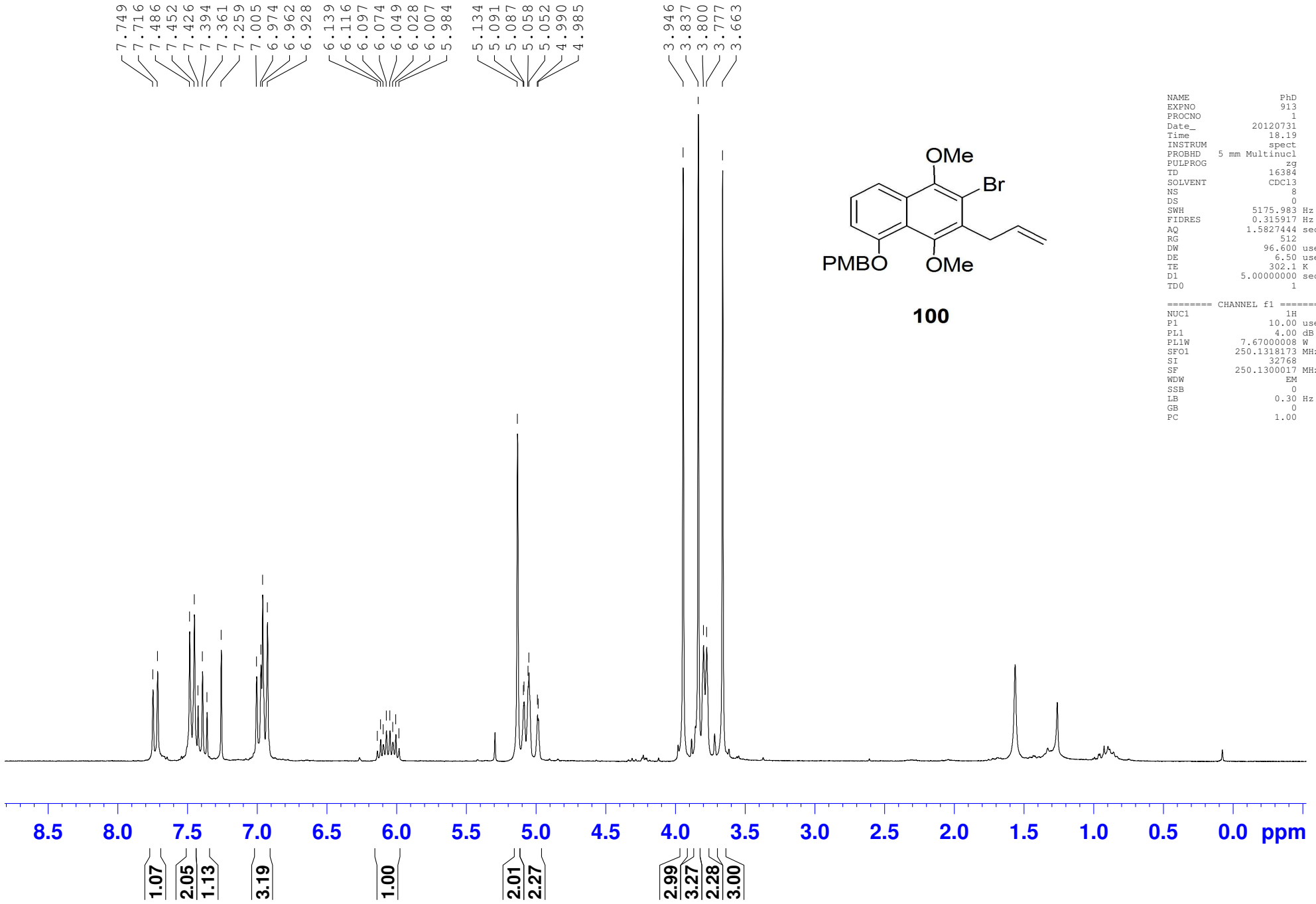
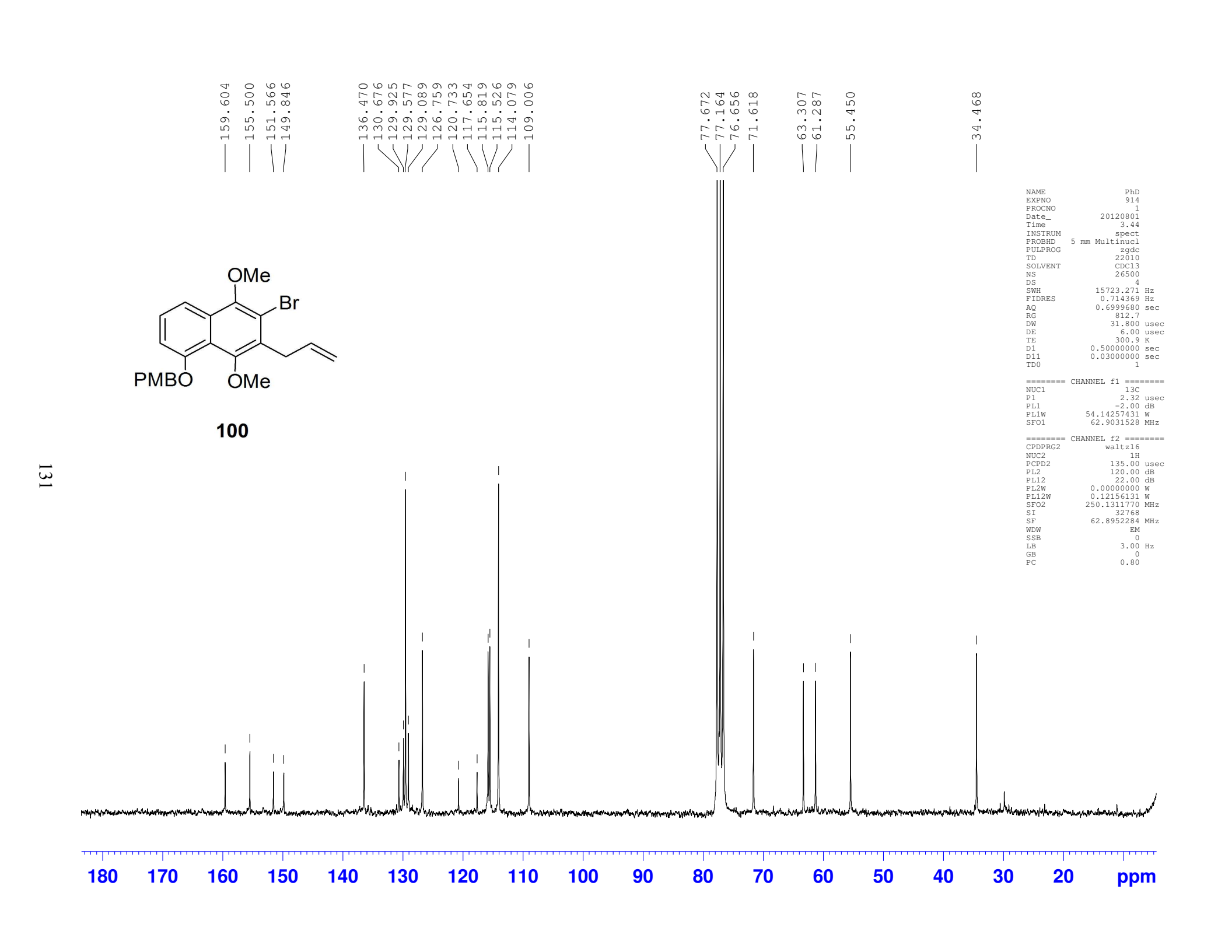
7.341
7.197
7.142
7.085
7.048
7.039
7.002
5.176
5.158
3.518
3.472
MOMO
Br
Br
MOMO
90
NAME extra
EXPNO 597
PROCNO 1
Date_ 20110523
Time 15.24
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 512
DW 96.600 usec
DE 6.50 usec
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300014 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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
1.00
1.03
2.04
2.04
3.39
3.41

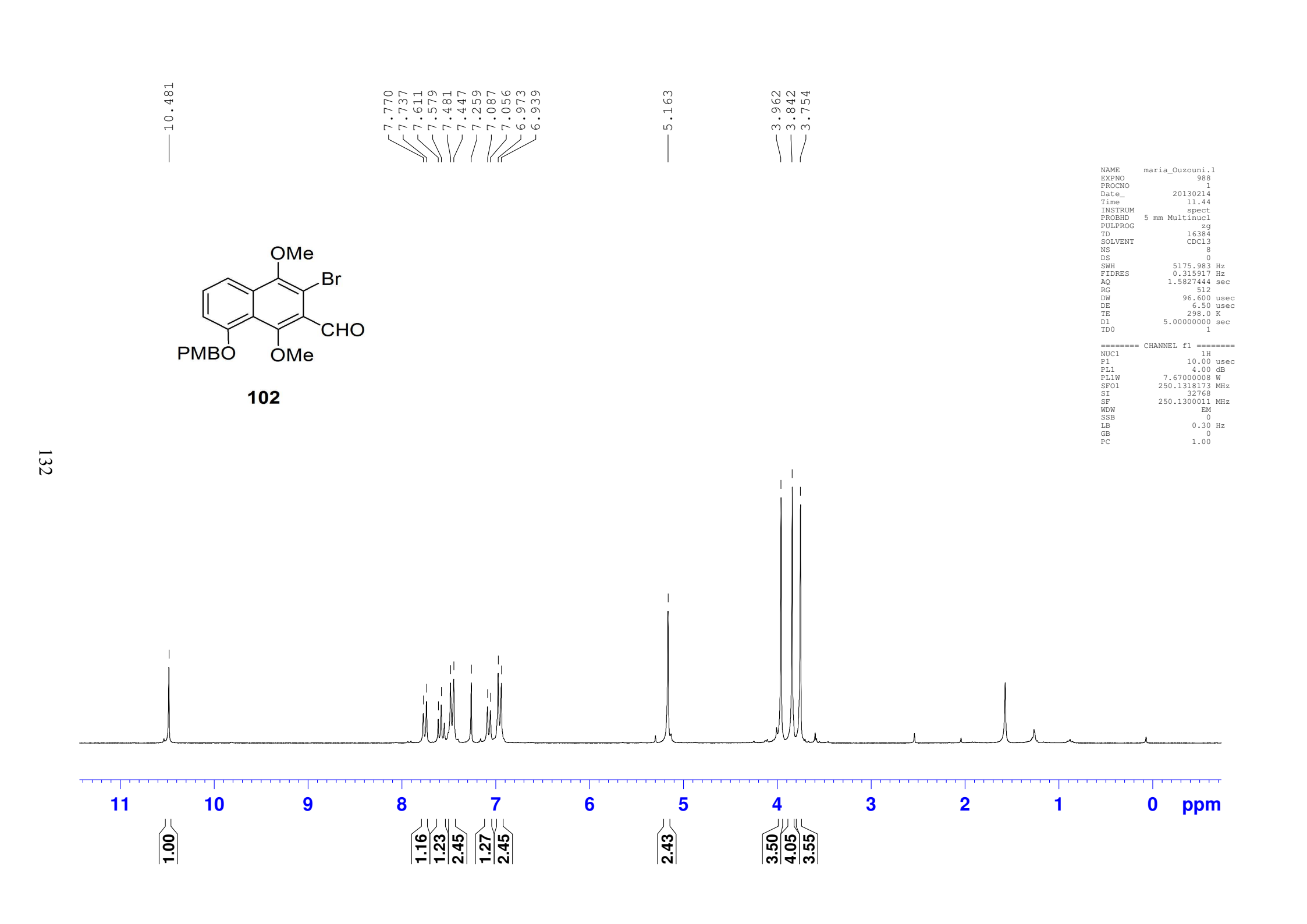

10.517
7.513
7.479
7.441
7.395
7.346
7.277
7.205
7.169
7.042
7.006
6.898
6.863
6.464
6.445
5.142
4.946
4.920
4.878
4.602
4.554
4.449
4.430
3.788
3.735
1.574
1.380
1.275
OBn
O
OPMB
CHO
O
O
OBn
92
NAME extra
EXPNO 768
PROCNO 1
Date_ 20120223
Time 10.57
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 1024
DW 96.600 use
DE 6.50 use
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 =======
NUC1 1H
P1 10.00 use
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300011 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.18
5.21
6.16
1.59
1.40
2.33
1.11
1.58
2.87
0.84
1.40
1.30
3.42
1.01
3.59
3.23
2.83

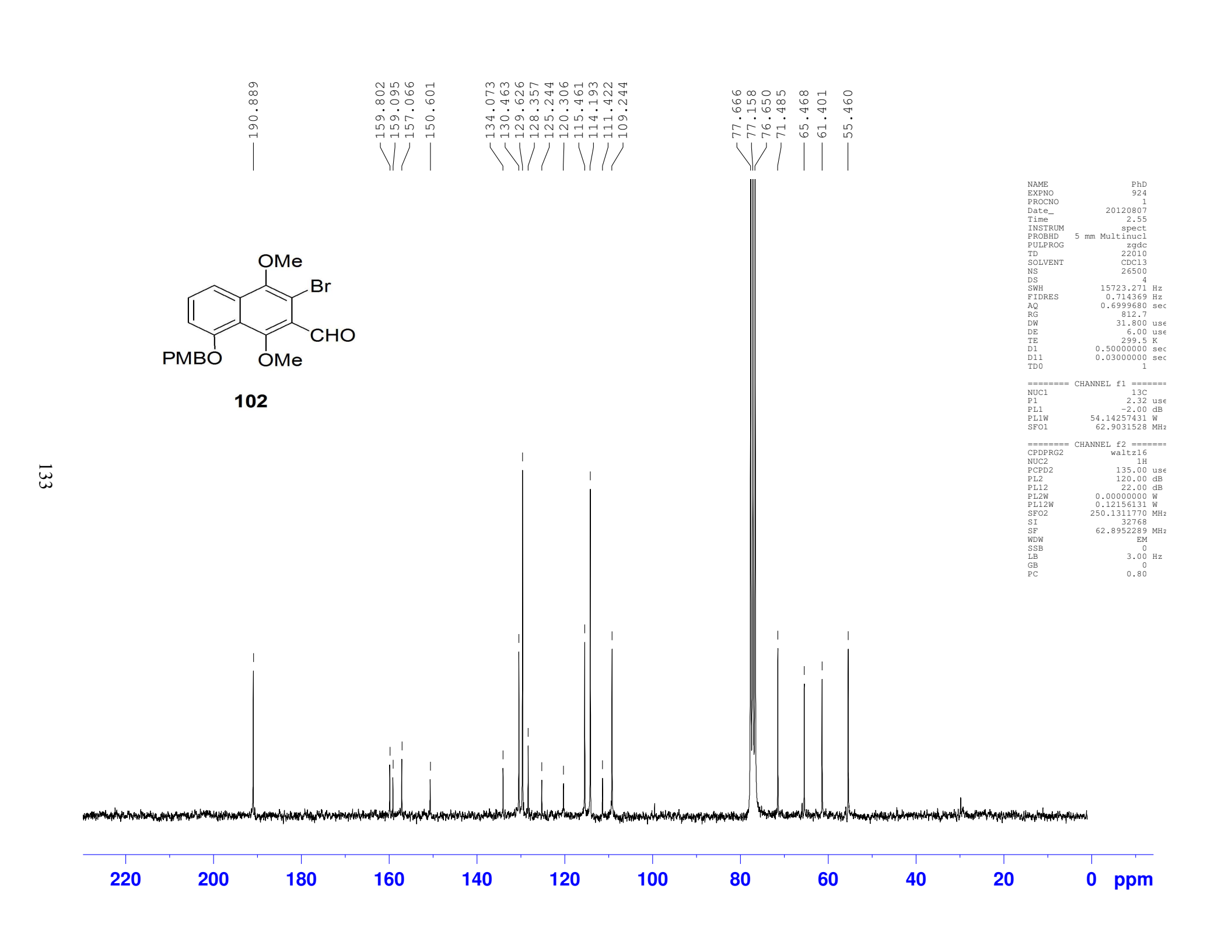

7.826
7.796
7.631
7.598
7.567
7.473
7.439
7.349
7.315
7.260
6.955
6.921
5.954
5.928
5.914
5.902
5.888
5.860
5.846
5.834
5.820
5.794
5.297
5.291
5.239
5.223
5.153
5.147
5.113
5.107
3.819
3.629
3.603
O
Br
PMBO
O
99
NAME PhD
EXPNO 847
PROCNO 1
Date_ 20120611
Time 15.22
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 se
RG 512
DW 96.600 us
DE 6.50 us
TE 298.3 K
D1 5.00000000 se
TD0 1
======== CHANNEL f1 ======
NUC1 1H
P1 10.00 us
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MH
SI 32768
SF 250.1300008 MH
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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
0.93
1.04
2.12
1.23
2.19
1.00
4.60
3.56
2.12

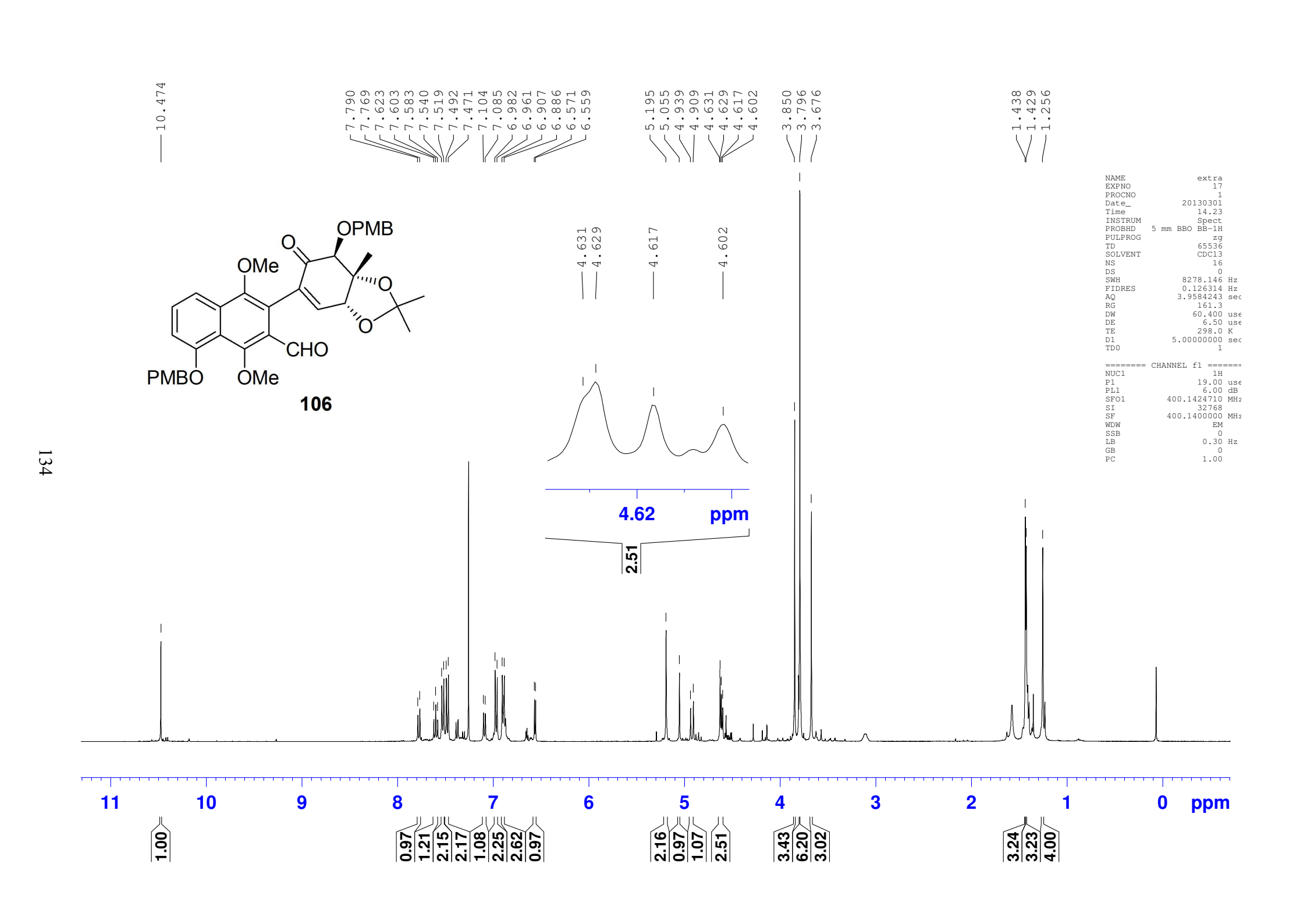

180.153
178.314
159.636
159.160
150.830
136.769
134.791
133.482
131.951
130.198
128.607
128.045
120.675
120.323
118.234
114.302
77.669
77.161
76.653
71.113
55.441
35.845
O
Br
PMBO
O
99
NAME PhD
EXPNO 946
PROCNO 1
Date_ 20121031
Time 3.06
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT CDC13
NS 26500
DS 4
SWH 15723.271 Hz
FIDRES 0.714369 Hz
AQ 0.6999680 sec
RG 812.7
DW 31.800 usec
DE 6.00 usec
TE 299.0 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 2.32 usec
PL1 -2.00 dB
PL1W 54.14257431 W
SFO1 62.9031528 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00 usec
PL2 120.00 dB
PL12 22.00 dB
PL2W 0.00000000 W
PL12W 0.12156131 W
SFO2 250.1311770 MHz
SI 32768
SF 62.8952291 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 0.80
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

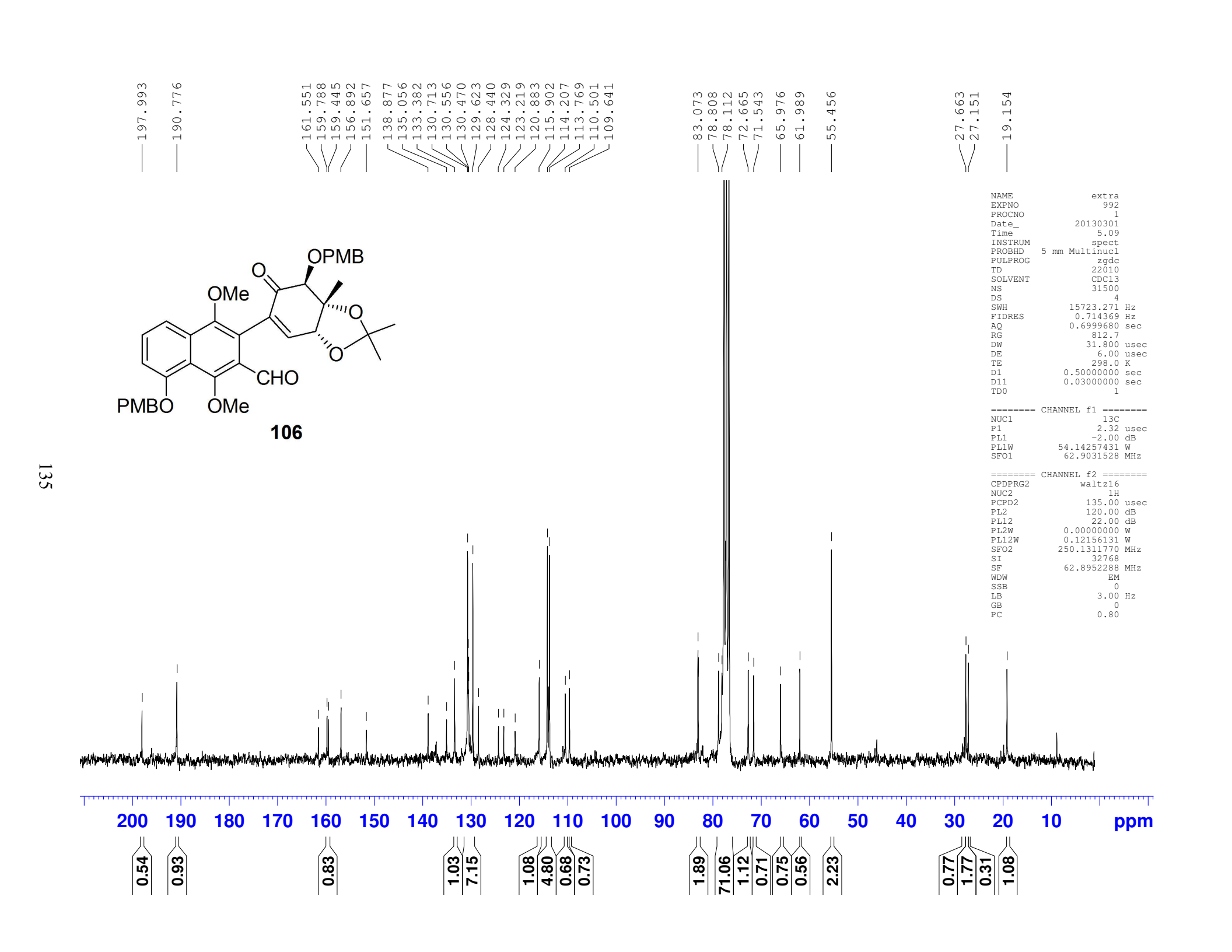

7.749
7.716
7.486
7.452
7.426
7.394
7.361
7.259
7.005
6.974
6.962
6.928
6.139
6.116
6.097
6.074
6.049
6.028
6.007
5.984
5.134
5.091
5.087
5.058
5.052
4.990
4.985
3.946
3.837
3.800
3.777
3.663
OMe
Br
PMBO
OMe
100
NAME PhD
EXPNO 913
PROCNO 1
Date_ 20120731
Time 18.19
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 512
DW 96.600 usec
DE 6.50 usec
TE 302.1 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300017 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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
1.07
2.05
1.13
3.19
1.00
2.01
2.27
2.99
3.27
2.28
3.00


159.604
155.500
151.566
149.846
136.470
130.676
129.925
129.577
129.089
126.759
120.733
117.654
115.819
115.526
114.079
109.006
77.672
77.164
76.656
71.618
63.307
61.287
55.450
34.468
OMe
Br
PMBO
OMe
100
NAME PhD
EXPNO 914
PROCNO 1
Date_ 20120801
Time 3.44
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT CDCl3
NS 26500
DS 4
SWH 15723.271 Hz
FIDRES 0.714369 Hz
AQ 0.6999680 sec
RG 812.7
DW 31.800 usec
DE 6.00 usec
TE 300.9 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 2.32 usec
PL1 -2.00 dB
PL1W 54.14257431 W
SFO1 62.9031528 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00 usec
PL2 120.00 dB
PL12 22.00 dB
PL2W 0.00000000 W
PL12W 0.12156131 W
SFO2 250.1311770 MHz
SI 32768
SF 62.8952284 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 0.80
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


10.481
7.770
7.737
7.611
7.579
7.481
7.447
7.259
7.087
7.056
6.973
6.939
5.163
3.962
3.842
3.754
OMe
Br
CHO
PMBO
OMe
102
NAME maria_Ouzouni.1
EXPNO 988
PROCNO 1
Date_ 20130214
Time 11.44
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg
TD 16384
SOLVENT CDCl3
NS 8
DS 0
SWH 5175.983 Hz
FIDRES 0.315917 Hz
AQ 1.5827444 sec
RG 512
DW 96.600 usec
DE 6.50 usec
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 4.00 dB
PL1W 7.67000008 W
SFO1 250.1318173 MHz
SI 32768
SF 250.1300011 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.16
1.23
2.45
1.27
2.45
2.43
3.50
4.05
3.55


190.889
159.802
159.095
157.066
150.601
134.073
130.463
129.626
128.357
125.244
120.306
115.461
114.193
111.422
109.244
77.666
77.158
76.650
71.485
65.468
61.401
55.460
OMe
Br
CHO
PMBO
OMe
102
NAME PhD
EXPNO 924
PROCNO 1
Date_ 20120807
Time 2.55
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT CDC13
NS 26500
DS 4
SWH 15723.271 Hz
FIDRES 0.714369 Hz
AQ 0.6999680 sec
RG 812.7
DW 31.800 use
DE 6.00 use
TE 299.5 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 =======
NUC1 13C
P1 2.32 use
PL1 -2.00 dB
PL1W 54.14257431 W
SFO1 62.9031528 MHz
======== CHANNEL f2 =======
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00 use
PL2 120.00 dB
PL12 22.00 dB
PL2W 0.00000000 W
PL12W 0.12156131 W
SFO2 250.1311770 MHz
SI 32768
SF 62.8952289 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 0.80
220
200
180
160
140
120
100
80
60
40
20
0
ppm


10.474
7.790
7.769
7.623
7.603
7.583
7.540
7.519
7.492
7.471
7.104
7.085
6.982
6.961
6.907
6.886
6.571
6.559
5.195
5.055
4.939
4.909
4.631
4.629
4.617
4.602
3.850
3.796
3.676
1.438
1.429
1.256
OPMB
O
OMe
O
O
CHO
PMBO
OMe
106
4.631
4.629
4.617
4.602
4.62
ppm
2.51
NAME extra
EXPNO 17
PROCNO 1
Date_ 20130301
Time 14.23
INSTRUM Spect
PROBHD 5 mm BBO BB-1H
PULPROG zg
TD 65536
SOLVENT CDC13
NS 16
DS 0
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 161.3
DW 60.400 use
DE 6.50 use
TE 298.0 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 =======
NUC1 1H
P1 19.00 use
PL1 6.00 dB
SFO1 400.1424710 MHz
SI 32768
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.97
1.21
2.15
2.17
1.08
2.25
2.62
0.97
2.16
0.97
1.07
2.51
3.43
6.20
3.02
3.24
3.23
4.00


197.993
190.776
161.551
159.788
159.445
156.892
151.657
138.877
135.056
133.382
130.713
130.556
130.470
129.623
128.440
124.329
123.219
120.883
115.902
114.207
113.769
110.501
109.641
83.073
78.808
78.112
72.665
71.543
65.976
61.989
55.456
27.663
27.151
19.154
OPMB
O
OMe
O
O
CHO
PMBO
OMe
106
NAME extra
EXPNO 992
PROCNO 1
Date_ 20130301
Time 5.09
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zgdc
TD 22010
SOLVENT CDCl3
NS 31500
DS 4
SWH 15723.271 Hz
FIDRES 0.714369 Hz
AQ 0.6999680 sec
RG 812.7
DW 31.800 usec
DE 6.00 usec
TE 298.0 K
D1 0.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 2.32 usec
PL1 -2.00 dB
PL1W 54.14257431 W
SFO1 62.9031528 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 135.00 usec
PL2 120.00 dB
PL12 22.00 dB
PL2W 0.00000000 W
PL12W 0.12156131 W
SFO2 250.1311770 MHz
SI 32768
SF 62.8952288 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 0.80
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
0.54 0.93 0.83 1.03 7.15 1.08 4.80 0.68 0.73 1.89 71.06 1.12 0.71 0.75 0.56 2.23 0.77 1.77 0.31 1.08