Synthesis and Antiproliferative Activity of C3' and B-ring Modified Paclitaxel Analogs

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Abstract

The natural product, paclitaxel, has made tremendous contributions in supplying the arsenal of anticancer therapeutics, and was FDA approved for clinical use in 1992. In order to design simplified analogs, the conformation that paclitaxel adopts when binding to tubulin has been the subject of ongoing studies. Much evidence has led to a T-taxol proposal and a C3' constrained analog has been designed and synthesized as a test of this conformation. In the search for more active analogs, a number of modifications have been made to paclitaxel by other researchers. However, the nature of the alterations, and combinations thereof, have not been exhausted. To this end, synthesis of northern hemisphere B-ring analogs is underway.

To Ester, Britannia, and Joy

Acknowledgments

Proverbs three verses five and six say, trust in the Lord with all your heart, lean not on your own understanding, in all your ways acknowledge Him, and He will direct your path. I acknowledge, with thanks, Jesus Christ, the Creator of all things seen and unseen, reacted and unreacted, for still working on me. I acknowledge, with thanks, Prof. D. G. I. Kingston, my advisor, for having me in his group, for inviting me to Blacksburg Christian Fellowship, and for his prayers. I continue to be overwhelmed by the amount of time that he affords me, knowing that it must be difficult, considering his commitments. Also amazing, though expected considering his level of knowledge and experience, is the information, strategies, and tips that he readily makes available to me. He has helped me a lot, is very patient, and cares.

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I acknowledge, with thanks, my parents for their prayers. I acknowledge, with thanks, Kingston group members, Virginia Tech Analytical Services, and the National Institute of Health for funding. I acknowledge, with thanks, all who are assisting in ways that I will more fully understand some day.

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List of Abbreviations

AcOH…….. ……..Acetic Acid

CaH_2……...Calcium Hydride

CAN……..Ceric Ammonium Nitrate

$CDCl_3$……..... Deuterated Chloroform

CD_3OD…… Deuterated Methanol

CH_3CN……. ……..Acetonitrile

CH_2Cl_2…….. ……Dichloromethane

10-DAB……...10-Deacetyl Baccatin

DMAP……..Dimethylaminopyridine

DMF……. Dimethylformamide

Et_3N……Triethylamine

EtOAc……..Ethyl Acetate

EtOH……..… Ethanol

FCC…….Flash Column Chromatography

HCl…….. Hydrogen chloride

H_2O……...Water

HF•py……...……....Pyridinium Hydrofluoride

HRFABMS……..High Resolution Fast Atom Bombardment Mass Spectra

K_2CO_3……...Potassium Carbonate

KI……..……. Potassium Iodide

KOH…….…….. Potassium Hydroxide

$MgSO_4$…….. Magnesium Sulfate

N_2…….Nitrogen

Na…….Sodium

$NaHCO_3$……Sodium Bicarbonate

NAMFIS……. NMR Analysis of Molecular Flexibility In Solution

Na_2SO_4……..Sodium Sulfate

$Na_2S_2O_5$……...Sodium Metabisulfite

NH_4Cl…….....Ammonium Chloride

$N_2H_4 \bullet H_2O$.....Hydrazine Monohydrate

NMR……...Nuclear Magnetic Resonance

NOC…… *N*-nitroso Compound

Pd/C…….....Palladium on Activated Carbon

PMA…….Phosphomolybdic Acid

ppm…….Parts Per Million

PTLC……...Preparative TLC

REDOR…….Rotational Echo Double Resonance

ROS……...Reactive Oxygen Species

RTI……..Research Triangle Institute

SARs……...Structure Activity Relationships

SmI_2…….....Samarium (II) Iodide

$SOCl_2$…….....Thionyl Chloride

TBSCl…….*t*-Butyldimethylsilyl Chloride

TESCl…….……....Chlorotriethylsilane

THF…….....Tetrahydrofuran

TIPSCl.....Triisopropylchlorosilane

TLC……..Thin Layer Chromatography

TMS……..Tetramethylsilane

UV……Ultraviolet

1. Introduction

1.1 Cancer

By definition, cancer is a disease caused by an uncontrolled division of abnormal cells in a part of the body, or a malignant growth or tumor resulting from such a division of cells.[1] The cancerous cell has survival advantages over neighboring cells, as the latter rigidly adhere to the cycle of life and death, while the cancer cell proliferates in a disorderly fashion.[2] Tumor cells invasively infiltrate surrounding tissue, or spread to other organs of the body through a process known as metastasis. In cancer cells, mitosis occurs more often, and the material making up the chromosomes, chromatin, is in more abundance. These qualities enable the rapidly proliferating tumor cells to overpower normally functioning cells in the vicinity. Abnormal division of any of the various cell types in the body can result in cancer. Therefore, more than a hundred different kinds of the disease exist, varying in their behavior and in their response to treatment. Cancers of the lung, colon/rectum, breast, and prostate account for more than half of all cancer cases.[3]

A number of environmental, behavioral, and genetic factors promote carcinogenesis. The World Health Organization reports that the single largest preventable cause of cancer in the world today is tobacco use. It causes about 30% of all cancer deaths in developing countries, which include deaths from cancer of the oral cavity, larynx, oesophagus and stomach, and 80-90% of all lung cancer deaths.[4] Many agents, such as sources of radiation, chemicals, and microbes, result in cancer, though it is naive to pinpoint a single cause. Solar ultraviolet radiation is a major carcinogen that can result in skin cancer. Agents in tobacco smoke, and aflatoxin, a compound produced

by a mold of poorly stored peanuts and other grains, are known chemicals that lead to carcinogenesis. Stomach cancer caused by *Helicobacter pylori*, and cancer of the cervix, major causes of which are human papillomaviruses, are some microbial carcinogens.[5]

Like tobacco smoking, about 30% of all cancers are associated with different dietary factors. The link between carcinogenesis and food intake is complex, however, since many foods possess compounds that exhibit both harmful and beneficial properties. Examples are caffeine, soy sauce, and red wine, all of which were shown to have negative effects on, or interactions with DNA, but also have compounds that inhibit, mask, reduce, or in some way counteract the harmful effects.[6] Notwithstanding the obvious advantages of a plant-based diet, vegetables are a major source of nitrate, an *N*-nitroso compound (NOC) precursor. NOCs are powerful chemical carcinogens, but vegetables are also a source of vitamin C, an inhibitor of *N*-nitrosation.[7] Another unexpected study result involves the consumption of a known anti-oxidant, beta-carotene, which leads to increased risk of lung cancer and mortality in heavy smokers and asbestos workers when taken alone or in combination with vitamins A and E.[8] Despite these unusual results, anti-oxidants are known scavengers of reactive oxygen species (ROS). ROS result from inflammation and cellular stress produced by normal cellular respiration. However, as a consequence of environmental toxic agent exposure, excessive ROS production, in combination with an inadequate defense mechanism, may lead to oxidative stress that can damage DNA and increase cancer risk.[9] Further complexities arise from the hypothesis that many foods undergo chemical conversions by liver cells and bacteria in the colon, resulting in cancer causing species, though carcinogens are not present in the natural state.[10] Introduced chemical species may become concentrated in certain cells, or

be quickly metabolized and excreted. Indeed, a diet rich in fruits, vegetables, and whole grains, yet low in fatty meat, is expected to suspend or prevent carcinogenesis.[11]

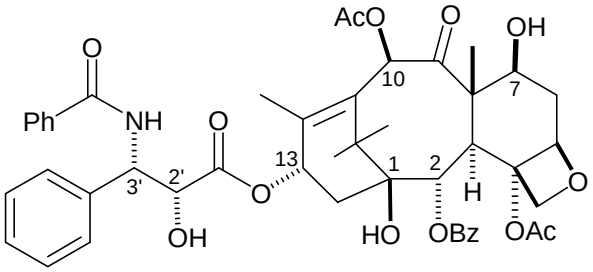
In addition to dietary habits, physical activity also plays a key role in cancer development. Studies observe an inverse association between physical activity and cancer incidence and mortality.[12,13,14,15] With abundant data on the causes and preventability of cancer, cases continue to rise year after year. In the United States, it is estimated that more than 1.4 million new cancer cases will be diagnosed in 2007,[4] and thus there continues to be an urgent need to explore new treatment options. Among the strategies employed in tackling the problem of cancer are chemotherapeutic agents. A successful anti-tumor drug that has been in clinical use for the past fifteen years and is the focus of this work is paclitaxel.

1.2 Paclitaxel

1.2.1 Historical Introduction

Taxol, a diterpenoid (**1.1**), first isolated in 1967 by Drs. Wall and Wani at the Research Triangle Institute (RTI), is an anticancer drug of paramount significance. In 1971, the RTI researchers reported the structure elucidation of taxol.[16] The compound was obtained from stem and bark collections by botanist Dr. Arthur Barclay, then working with the U.S. Department of Agriculture and the National Cancer Institute.[17] These collections were made in 1962 from *Taxus brevifolia* in Washington State, though taxol has been acquired from at least ten other species as well.[18] After extensive preclinical and clinical development, taxol entered clinical use for the treatment of ovarian cancer in 1992 and for treatment of breast cancer in 1994. It was introduced into clinical use by Bristol-Myers Squibb, who registered the trade name Taxol® and assigned

it the generic name of paclitaxel. Taxol® exceeded annual sales of $1.6 billion in 2000. The drug was initially produced by large-scale isolation from *T. brevifolia*, but it is now produced for Bristol-Myers Squibb by large-scale proprietary plant cell fermentation technology by Phyton Biotech, Inc. with factories in Germany.



1.1

1.2.2 Mechanism of Action

During cell division, genetic material-bearing chromosomes are transported to opposite sides of the cell via microtubules. In order for partitioning to be complete, the cell's microtubules are required to disassemble, allowing the membrane of the two daughter cells to form. An equilibrium between assembled and disassembled, or polymerized and depolymerized microtubules is observed in normally functioning cells. In 1979 Dr. Susan Horwitz at the Albert Einstein College of Medicine in the Bronx, discovered that paclitaxel binds to a microtubule protein, β–tubulin, and promotes polymerization of α– and β–tubulin, inhibiting disassembly.[19]

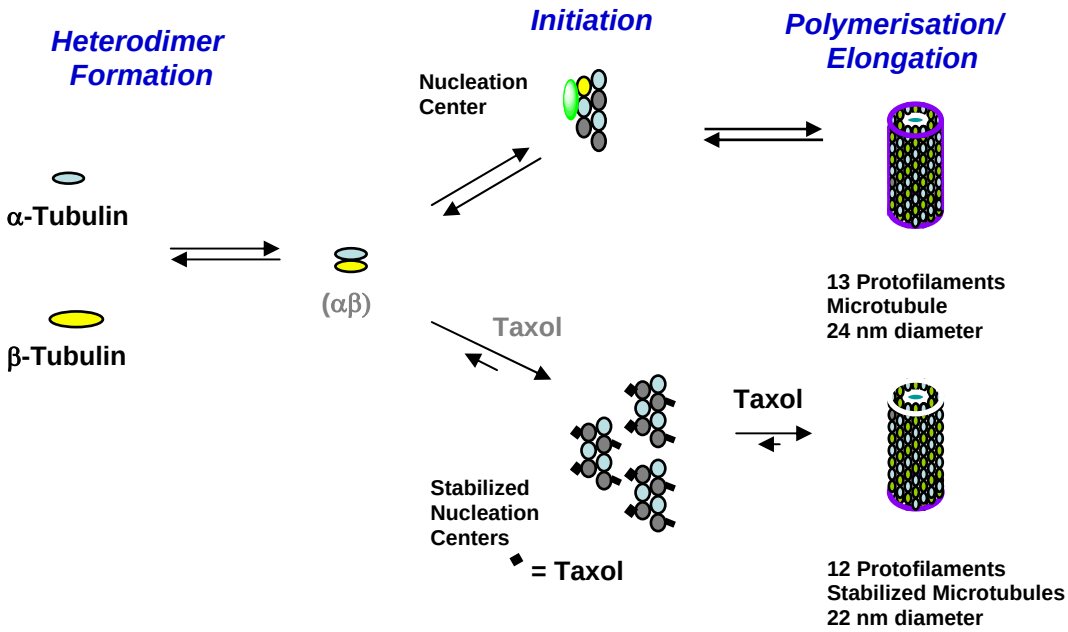
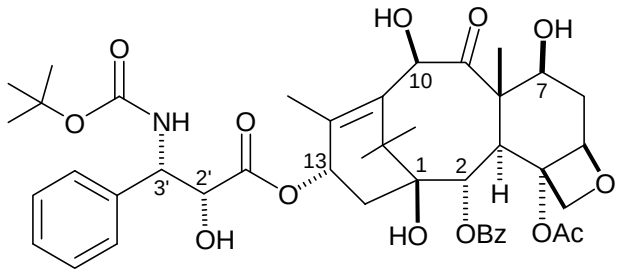


Figure 1.1 Taxol® mechanism of action – promotion of tubulin polymerization.[20]

This interruption of microscopic protocol results in the cell's death, and since tumor cells are dividing more rapidly than healthy cells, taxol is moderately selectively active against tumor cells. Paclitaxel is now used for the treatment of various cancer types, most notably ovarian, breast, and small cell lung cancers, and for AIDS-related Kaposi's sarcoma.

The importance of paclitaxel as an anticancer drug has led to extensive studies on its structure-activity relationships and on structural modifications to the molecule.[21] Many regions of the core ring structure and side-chain have been modified.[22,23,24] Such work has brought about the development of several analogs that are in clinical trial as second-generation taxanes. An example of this is the semisynthetic analog docetaxel (Taxotere®) (**1.2**) which is now in clinical use.



1.2

Along with the benefits that paclitaxel has brought to the treatment of cancer, there are challenges as well. A major hurdle to overcome is enabling selective targeting of tumor cells. The issue of severe side-effects results from poor selectivity, where healthy cells are also targeted by the drug. New strategies that address this drawback include delivery in a non-cytotoxic form, a prodrug, that will undergo a specific type of activation in the tumor cell.[25] Other challenges involve the limited solubility of paclitaxel, as it is intravenously administered. Solubilizing agents that aid in administration pose side-effect concerns, in addition to those of the drug itself.

Structure-activity relationship studies have revealed that altering the diterpene or side-chain of paclitaxel in some positions brings about improved activity. The C3′ phenyl or a close analog thereof, and the N-acyl groups are required for Taxol® to exhibit activity as a tubulin depolymerization inhibitor (Figure 1.2).

In summary, researchers have pointed out the major identifiable causes of cancer, and though many of these factors are preventable, cancer continues to adversely affect survival and quality of life. The drug Taxol has been successfully in clinical use for some time now, but has been the focus of continued studies. These have included conformational studies directed toward revealing a better understanding of how the

compound binds to tubulin. This could lead to improvements in drug design and clarifications of binding site interactions of other compounds that are structurally dissimilar to paclitaxel.

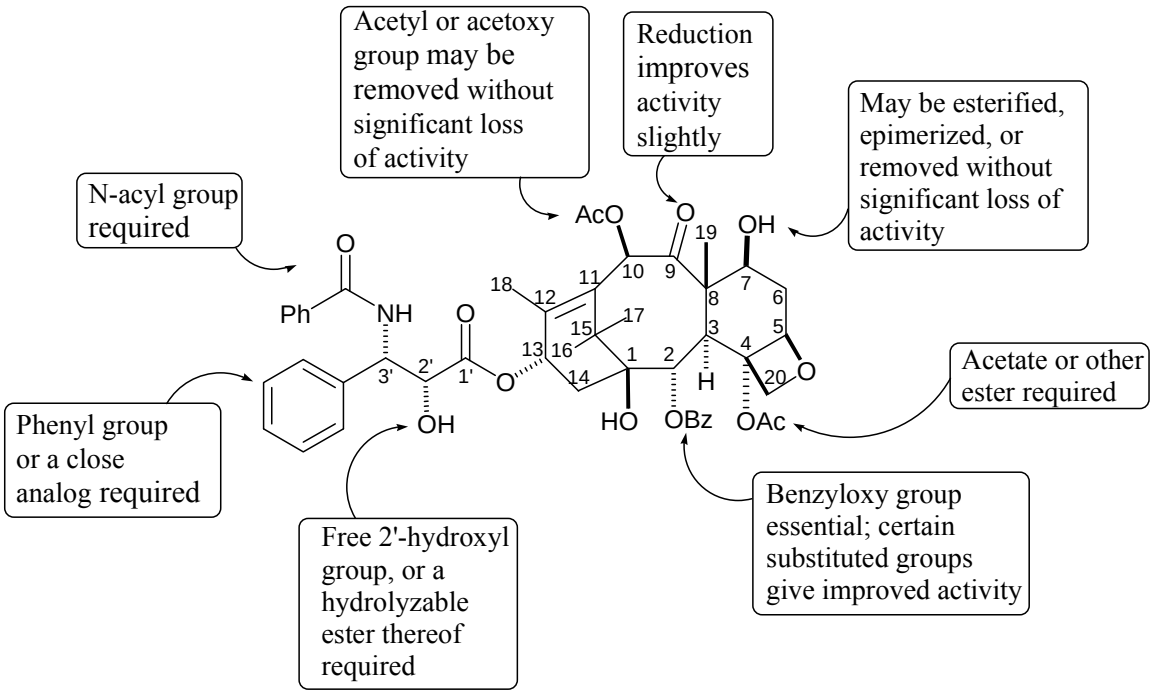


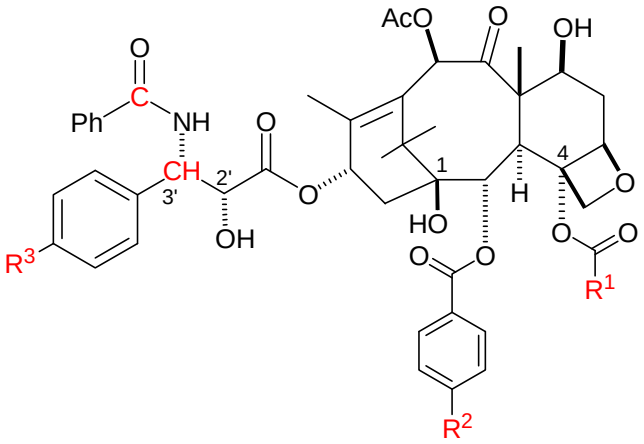
Figure 1.2 The Structure-Activity Relationships of paclitaxel.[26]

2. Synthesis and Antiproliferative Activity of a C3'- constrained Paclitaxel Analog

2.1 Introduction

The conformation that taxol adopts when binding to tubulin is significant, because it could help explain why structurally diverse natural products, such as epothilone and discodermolide, have a similar mechanism of action and compete for the same binding site. Additionally, the binding conformation could aid in the design of simplified and/or more active taxol analogs. ^{1}H-NMR spectrometry has been carried out to define two major conformations, the polar[27,28,29] and the non-polar[30,31] conformation. More recent work (Figure 2.1) by Dr. J. Snyder using NMR Analysis of Molecular Flexibility In Solution (NAMFIS) NMR methodology discovered the T-taxol conformation.[32] A combination of Rotational Echo Double Resonance (REDOR) NMR studies of labeled taxol bound to microtubules (Table 2.1) and the synthesis of constrained analogs with activities equal to or greater than taxol has provided positive support for the T-taxol conformation.[33,34,35]

Table 2.1. Interatomic distances for paclitaxel conformations as compared to REDOR-determined separations for paclitaxel on tubulin.[35]

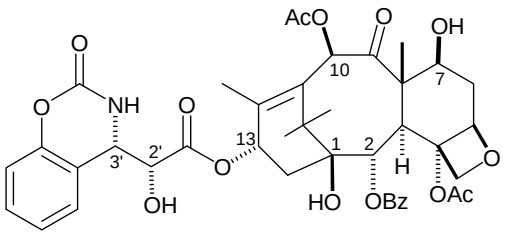


	Distances, Å			
Separation	Polar model[36]	Nonpolar model[37]	T-Taxol model	REDOR distance
R^1-R^2	7.4	8.0	7.9	7.8
R^1-R^3	5.5	7.2	6.6	6.3
R^2-R^3	4.5	12.5	12.2	>8
R^2-CH	9.6	8.5	9.9	10.3
R^2-C	10.4	6.2	9.1	9.8

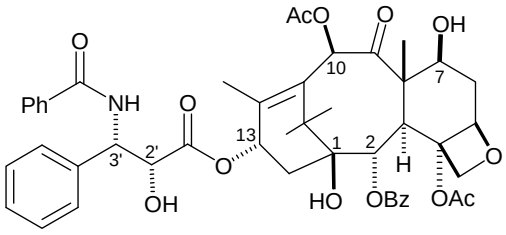
Despite the strong support for the T-taxol conformation derived from the work described above, it is possible to provide additional support by the synthesis of an analog that is constrained *not* to adopt the T-taxol conformation. If the T-taxol comformation is indeed the only important tubulin-binding conformation, then such a constrained analog should be inactive. In the design of such a constrained analog, it is important to maintain all the functionality of taxol known to be necessary for activity, so that the activity (or lack of activity) of the constrained analog could be attributed solely to the deviation of its conformation from that of T-taxol.

The key elements on the side chain of taxol that are needed for activity include the free 2'-OH group, or a hydrolyzable ester thereof. Also necessary for activity is the

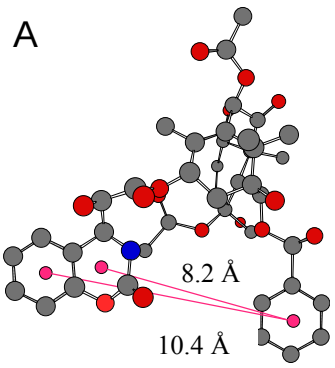
3'-N-acyl or N-COO group and a C3' phenyl or alkyl substituent. An example of a taxol derivative that maintains activity is docetaxel (Taxotere®) [38] (**1.2**). Based on these considerations, the C3' constrained analog (**2.1**) was designed, maintaining all the elements necessary for activity. That is, this analog possesses a free 2'-OH group, a 3'-N-COO group and a C3' phenyl group. Absent any conformational liabilities, it would thus be expected to be equipotent with docetaxel.



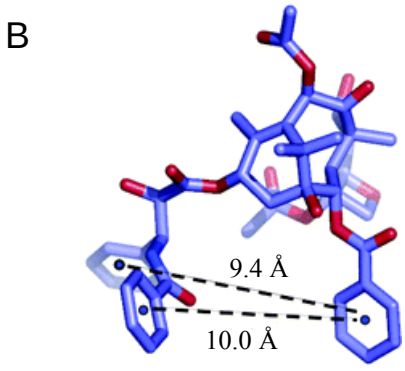
2.1



Taxol



C3' Constrained Analog



T-Taxol

Figure 2.1 Conformational comparison of, A: C3' constrained analog; B: the T-Taxol model, reprinted with permission from Snyder *et al.*[39] Copyright 2006 American Chemical Society.

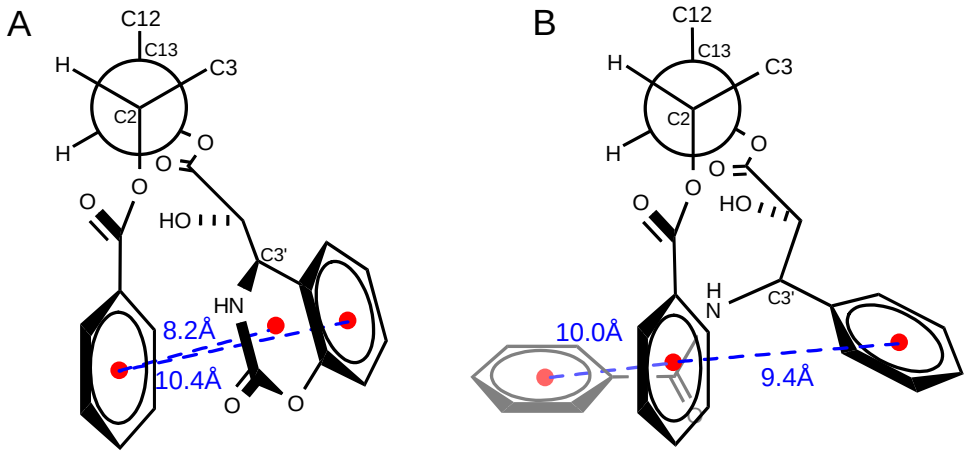


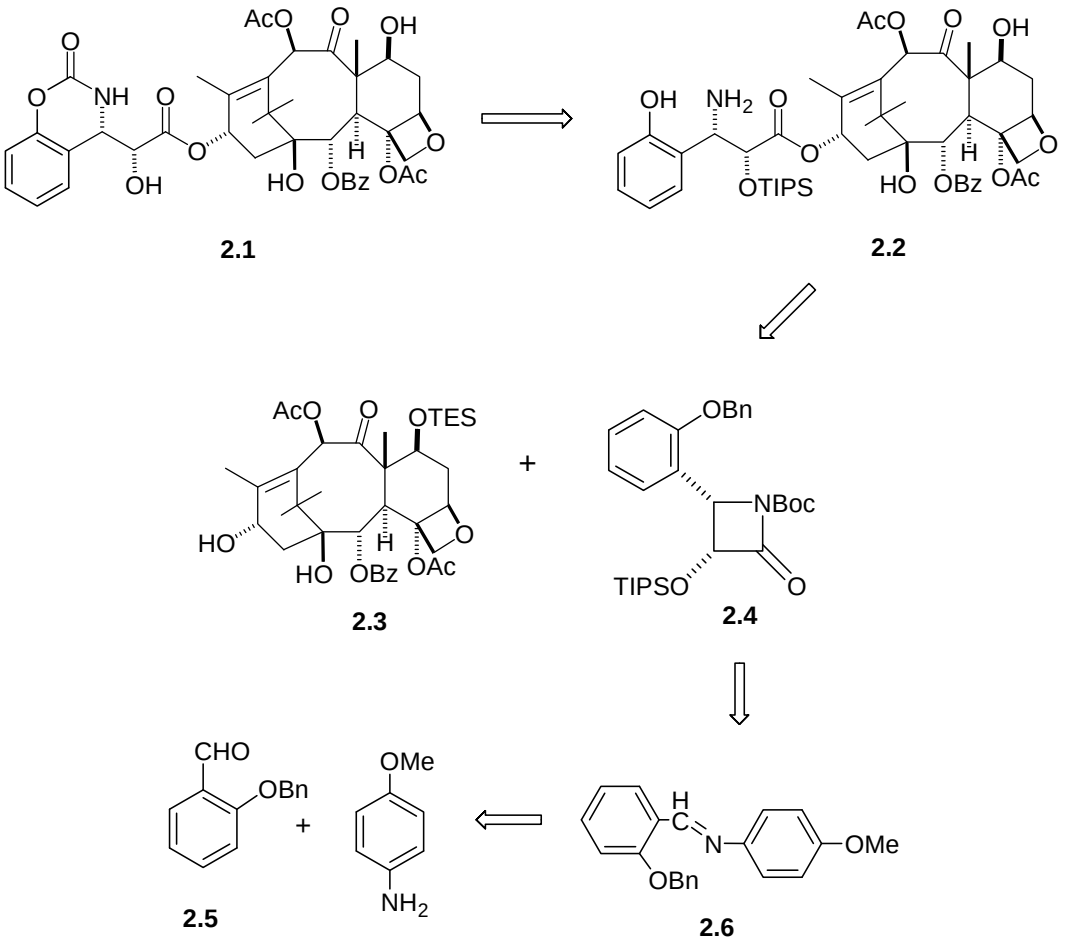
Figure 2.2 Newman projections showing a conformational comparison of, A: the C3' constrained analog; B: the T-Taxol model with measurements from Snyder *et al.*[32] Note that C2 is superimposed on C13; C1 and C14 lie between C2 and C13 and are not depicted in this drawing.

Similarities between the C3' constrained analog and T-taxol are shown in Figure 2.1, where distances in Angstroms from the 2-benzoyl group to the 3'-phenyl rings are pointed out. Figure 2.2, however, shows more clearly the effects of the 3'-phenyl and 3'-N-acyl linkage. With C2 superimposed on C13, taxol adopts a T-shape with the 3'-N-acyl and phenyl groups to the left and right respectively, and the 2-benzoyl group in the middle. C1 and C14 lie between C2 and C13 and are not depicted in Figure 2.2. The C3' constrained analog is forced not to adopt this configuration, however, as both C3' rings are confined to the right of the 2-benzoyl group. Based on this analysis, the C3' constrained analog would be expected *not* to be as active as taxol.

2.2 Synthesis

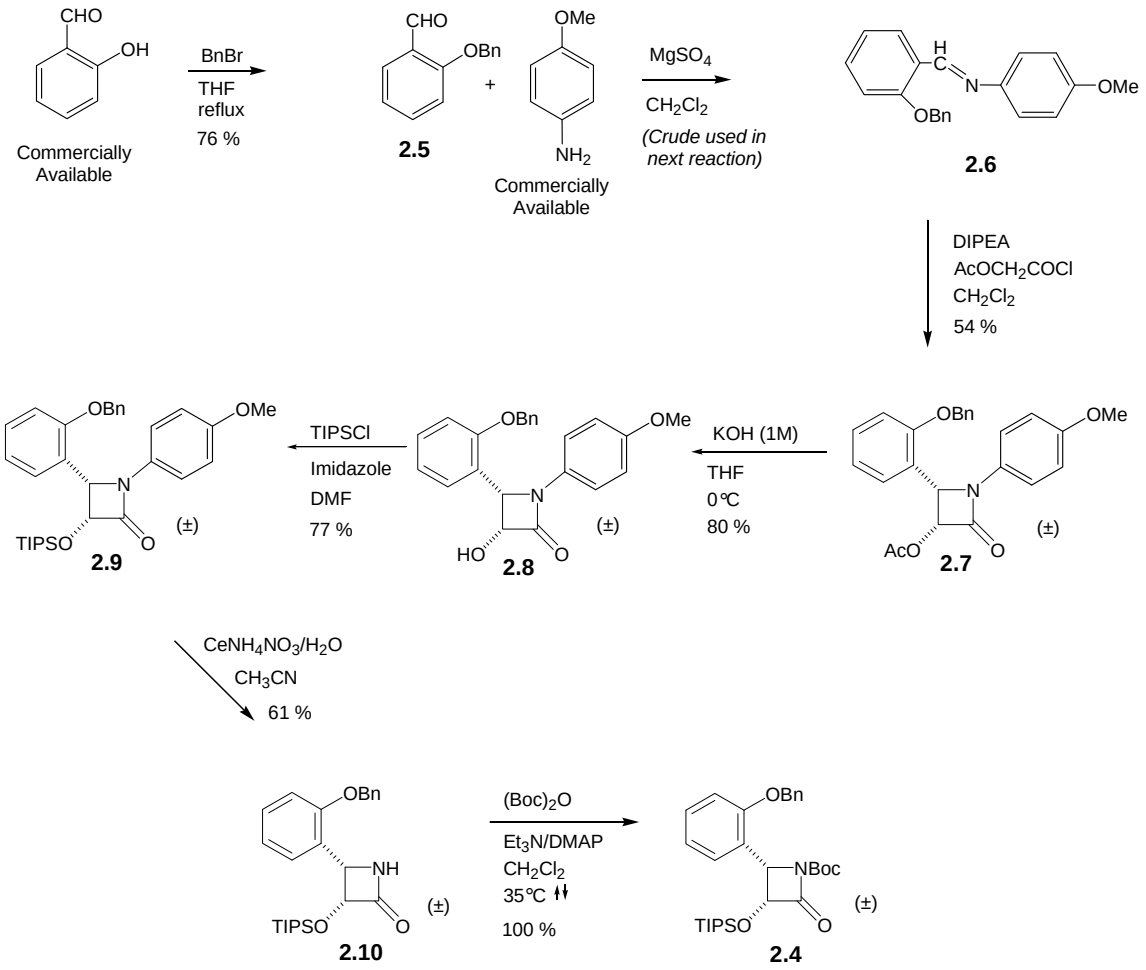
The compound that was synthesized resulted from the coupling of a baccatin III-derived taxoid to a side-chain produced from an anisidine-derived β-lactam (Scheme 2.1).

The baccatin III intermediate, 10-deacetylbaccatin (10-DAB) (Scheme 2.3), which is commercially available, was protected as its 7-triethylsilyl (TES) ether and then acetylated at the C10 position as previously discussed, using the Baloglu method.[40]



Scheme 2.1 Synthetic strategy of a C3′ constrained taxol analog.

Synthesis of β-lactam **2.4** began with commercially available salicylaldehyde, from which benzyl ether **2.5** was obtained in good yield (Scheme 2.2).[41] Reaction of **2.5** with *p*-anisidine in the presence of $MgSO_4$ yielded imine **2.6**.

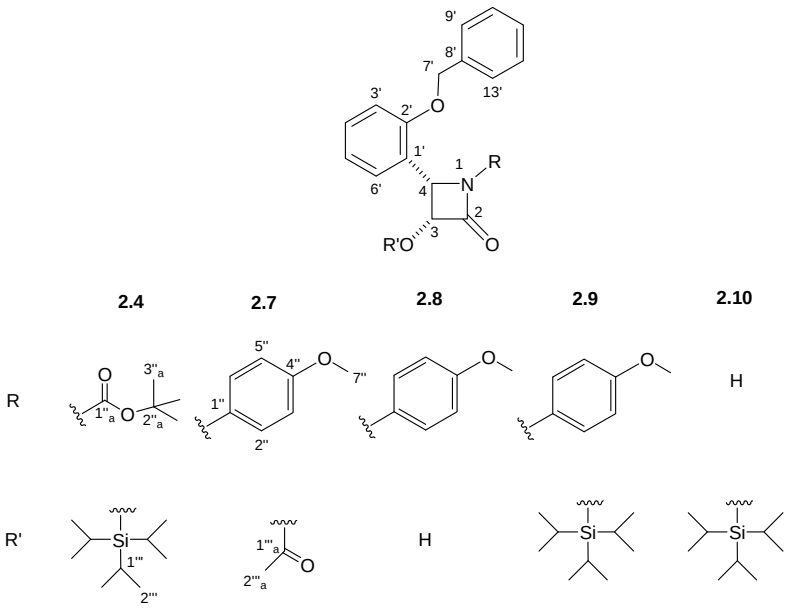


Scheme 2.2 Synthesis of the side chain component of the C3' constrained analog.

This was then used without purification to produce the racemic acetylated β-lactam **2.8** by condensation with acetoxyacetyl chloride in the presence of Hünig's base. This reaction was followed by attempted enzymatic kinetic resolution with lipase from *Pseudomonas cepacia*.[42] In an attempt to get complete conversion, the resolution was allowed to run for eight weeks, and the progress was monitored by TLC. Although this resolution method has worked well for simple β-lactams, in this case the reaction was very slow, presumably because of the steric hindrance due to the *ortho*-benzyl

substituent, and only a 15 % conversion was observed. The decision was thus made to complete the synthesis using the partially resolved racemic mixture, supported by a recent publication that confirms the rationale for proceeding with the majority racemate.[43] This publication reported high diastereoselectivities for the desired 2'*R*,3'*S* side chain when racemic β-lactams were coupled to the baccatin core through kinetic resolution. Acetate **2.8** was deacetylated with potassium hydroxide to give the alcohol **2.10**. Protection of the hydroxyl group of **2.10** as its triisopropylsilyl derivative yielded silyl ether **2.11**. This compound was subjected to treatment with aqueous ceric ammonium nitrate (CAN) to remove the *p*-methoxyphenyl protecting group and yield amide **2.12**. The desired β-lactam **2.4** was then obtained in quantitative yield by treatment with di-*tert*-butyldicarbonate in the presence of triethylamine and dimethylaminopyridine (DMAP).

Table 2.2. ^{1}H NMR Data for Compounds **2.4, 2.7, 2.8, 2.9, and 2.10** ($CDCl_3$)



No.	**2.4**	**2.7**	**2.8**	**2.9**	**2.10**
	δ_H[1]	δ_H[1]	δ_H[1]	δ_H[1]	δ_H[1]
2					
3	5.63, 1H, d (5.7)	5.82, 1H, d (5.0)	5.54, 1H, d (4.7)	5.72, 1H, d (4.9)	5.37, 1H, d (4.8)
4	5.15, 1H, d (5.9)	6.06, 1H, d (5.0)	5.14, 1H, m	5.24, 1H, d (5.5)	5.18, 1H, t (4.6)
3'	7.25-6.91	7.49-6.79	7.40-6.81	7.41-6.78	7.41-6.92
4'					
5'					
6'					
7'	5.05, 2H, d (6.8)	5.11, 2H, s	5.14, 2H, s	5.10, 2H, d (11.1)	5.03, 2H, s
9'	7.38-6.91	7.49-6.79	7.40-6.81	7.41-6.78	7.41-6.92
10'					
11'					
12'					
13'					
2", 6"		7.49-6.79	7.40-6.81	7.41-6.78	
3", 5"					
7"		3.75, 3H, s	3.75, 3H, s	3.75, 3H, s	
3"$_a$	1.44, 9H, s				
1'"	0.96, 3H, m			0.99, 3H, m	0.95, 3H, m
2'"	0.86, 18H, m			0.89, 18H, m	0.87, 18H, m
1'"$_a$					
2'"$_a$		1.73, 3H, s			

[1] intrgt, mult (*J*, Hz)

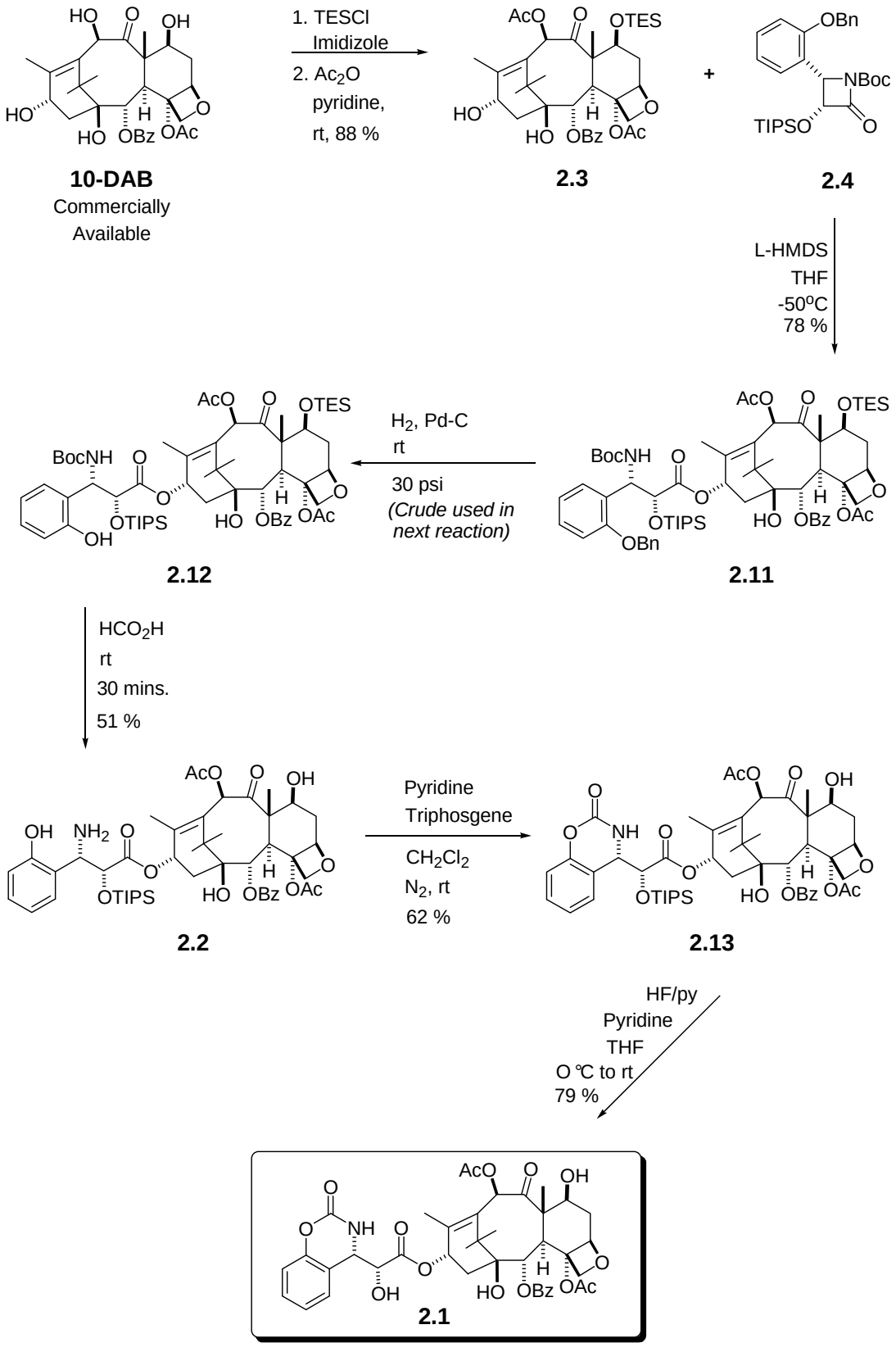
Table 2.3. ^{13}C NMR Data for Compounds **2.4, 2.7, 2.8, 2.9, and 2.10** ($CDCl_3$)

No.	**2.4**	**2.7**	**2.8**	**2.9**	**2.10**
	δ_C[1]	δ_C[1]	δ_C[1]	δ_C[1]	δ_C[1]
2	166.6 (C)	168.9 (C)	165.9 (C)	166.1 (C)	156.7 (C)
3	111.5 (CH)	112.1 (CH)	112.8 (CH)	111.4 (CH)	79.8 (CH)
4	77.7 (CH)	76.1 (CH)	77.6 (CH)	70.1 (CH)	70.0 (CH)
1', 2', 3', 4', 5', 6'	157.0-122.7	156.9 -114.5	156.9 -114.5	157.0 -114.4	137.1 -111.1
7'	83.3 (CH_2)	70.6 (CH_2)	70.7 (CH_2)	57.3 (CH_2)	53.8 (CH_2)
8', 9', 10', 11', 12', 13'	137.1-120.6	136.9-114.5	136.6-114.5	137.1-114.4	128.8-111.1
1"					
2", 6"		136.9-114.5	136.6-114.5	137.1-114.4	
3", 5"					
4"		156.6 (C)	156.4 (C)	156.2 (C)	
7"		55.5 (CH_3)	55.6 (CH_3)	55.7 (CH_3)	
1"$_a$	148.3 (C)				
2"$_a$	70.1 (C)				
3"$_a$	28.1 (CH_3)				
1'"	11.9 (CH)			12.1 (CH)	12.0 (CH)
2'"	17.5 (CH_3)			17.6 (CH_3)	17.6 (CH_3)
1'"$_a$		161.9 (C)			
2'"$_a$		20.1 (CH_3)			

[1](mult)

With the two necessary intermediates in hand, the side chain was attached to the baccatin by reaction of **2.3** with **2.4**, aided by lithium bis(trimethylsilyl)amide (Scheme 2.3). This step required fresh base and a concentrated reaction mixture; it failed when

either of these conditions was not met. The coupling was followed by subjecting the coupled product **2.13** to hydrogenation to cleave the C3' benzyl, yielding phenol **2.14**. The Boc protecting group and the C7 triethyl silyl groups were then removed by treatment with formic acid, yielding amine **2.2**. The key bridging carbamate linkage was introduced by reaction of **2.2** with triphosgene, resulting in bridge formation between the C3'N and the phenolic hydroxyl group to give the carbonate **2.15**. The final step used HF/pyridine to cleave the triisopropyl silyl protecting group at the C2′ position, leading to the desired C3′ constrained analog **2.1**. The 'H NMR spectrum of the final product shows that the coupling of **2.3** and **2.4** had indeed proceeded stereoselectively, since there was no observable doubling of signals due to the presence of two diastereomers. This result is consistent with previous observations on coupling of β-lactams with protected baccatin III derivatives.[43]



Scheme 2.3 Synthesis of C3′ constrained analog.

2.3 Results and Conclusion

Antiproliferative activity against the A2780 ovarian cancer cell line for the C3' constrained analog was measured at an IC_{50} value of 19 μg/mL. When compared to the 0.01 μg/mL IC_{50} value of taxol, this much reduced activity provides added evidence for the importance of the T-taxol conformation.

2.4 Experimental

2.4.1 General Methods

10-deacetylbaccatin was obtained from DABUR Chemicals in India. Sigma-Aldrich Co. and VWR were the sources of the remaining chemical reagents and materials, unless otherwise stated. Tetrahydrofuran (THF) was distilled from Na/benzophenone, and CH_2Cl_2 over CaH_2, both under N_2. Reactions and flash column chromatography (FCC) separations were monitored by analytical thin layer chromatography (TLC), using aluminum-backed (silica gel 60 F_{254} plates) from Merck KGaA. TLC plates were analyzed with 254 nm UV light and immersion in a phosphomolybdic acid/ethanol (PMA) stain. FCC was performed using Silia*Flash*® P60, 40-63 μm silica gel from SiliCycle® Inc. Analtech Inc. supplied preparative TLC (PTLC) glass-backed Silica Gel GF plates UNIPLATES™. ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ or CD_3OD on a Varian Inova 400, a Varian Unity 400, or a JEOL Eclipse 500 spectrometer. Chemical shifts were calibrated using the 0.0 ppm tetramethylsilane (TMS) peak or the solvent peaks as internal standards, and are reported in δ-values. Coupling constants (*J* values) are reported in Hertz. High Resolution Fast Atom Bombardment mass spectra (HRFABMS) were obtained on a JEOL 110HX high-resolution double-focusing mass spectrometer by Analytical Services.

2.4.2 β-Lactam Preparation Procedures

2-Benzyloxybenzaldehyde (2.5) To a solution of salicylaldehyde (2.0 mL, 18.8 mmol) in anhydrous THF (20 mL), was added benzyl bromide (2.9 mL, 24.4 mmol).[12] The resulting solution was stirred under reflux at 65 ºC for 5.5 h, at which time 5.0 g of K_2CO_3 and 5.0 g of KI were added to the reaction mixture, since TLC showed mainly starting material. TLC indicated the absence of starting material at 18.5 h, and the reaction mixture was diluted with THF (10 mL). The suspension was filtered through Celite® and the filtrate concentrated under reduced pressure. The residue was purified by FCC (10 % EtOAc/hexane to yield **2.5** as a solid (3.8 g, 95.5 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (1H, s), 7.86 (1H, d, *J* = 7.7), 7.54 (1H, t, *J* = 7.9), 7.46-7.34 (5H, m), 7.05 (2H, t, *J* = 8.2), 5.20 (2H, s); ^{13}C NMR δ 189.9, 161.2, 136.2, 136.1, 128.9, 128.6, 128.4, 127.4, 125.3, 121.2, 113.2.

(2-Benzyloxybenzylidene)-(4-methoxyphenyl)-imine (2.6) A solution of benzyl ether **2.5** (3.8 g, 17.9 mmol) in CH_2Cl_2 (45 mL) was treated with *p*-anisidine (2.7 g, 21.5 mmol) and $MgSO_4$ (25.0 g) at rt. Positive pressure was established and maintained within the reaction vessel by installing a N_2-filled balloon for moisture exclusion, and the reaction mixture was stirred for 53 h. The reaction mixture was then filtered through Celite® and concentrated under reduced pressure. The crude of imine **2.6** was used in the next reaction without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (1H, d, *J* = 4.2), 8.18 (1H, m), 7.44-7.31 (6H, m), 7.23-7.20 (2H, m), 7.04 (1H, t, *J* = 7.7), 6.99 (1H, d, *J* = 8.6), 6.91 (2H, m), 5.15 (2H, s), 3.81 (3H, s); ^{13}C NMR δ 158.7, 158.2, 154.6, 145.8, 136.8, 132.4, 128.8, 128.2, 127.7, 127.4, 125.6, 122.5, 121.4, 116.6, 115.0, 114.5, 112.8, 70.6, 55.6.

2-(2-Benzyloxyphenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl acetate (2.7) Imine **2.6** (24.7 g, 77.9 mmol) dissolved in CH_2Cl_2 (65.0 mL) under N_2 atmosphere was treated with Hünig's base (40.7 mL, 223.6 mmol) at rt. The mixture was cooled to –78 °C and acetoxyacetyl chloride (10.0 mL, 93.5 mmol) was added. The reaction mixture was allowed to warm to rt and stirred for 21.5 h, and was then concentrated under reduced pressure. The residue was purifed by FCC (20 % EtOAc/Hexane to yield **2.7** as a solid (17.5 g, 54.0 %). ^{1}H NMR (400 MHz, $CDCl_3$): 7.49 (2H, d, *J* = 7.1), 7.41 (2H, t, *J* = 7.1), 7.35 (1H, m), 7.27 (3H, d, *J* = 9.1), 7.21 (1H, dd, *J* = 7.5, 1.6), 6.99 (1H, d, *J* = 8.1), 6.91 (1H, t, *J* = 7.5), 6.79 (2H, d, *J* = 8.9), 6.06 (1H, d, *J* = 5.0), 5.82 (1H, d, *J* = 5.0), 5.11 (2H, s), 3.75 (3H, s), 1.73 (3H, s); ^{13}C NMR δ 168.9, 161.9, 156.9, 156.6, 136.8, 130.5, 129.8, 128.8, 128.5, 128.2, 127.7, 120.9, 120.7, 118.8, 114.4, 112.1, 76.1, 70.6, 55.5, 20.1.

Attempted preparation of (3*R*,4*S*)-acetic acid 2-(2-benzyloxyphenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl ester A solution of **2.7** (1.0 g, 2.4 mmol) in CH_3CN (20 mL) was treated with a pH 7.2 phosphate buffer (50 mL) and lipase (1.3 g) at rt and stirred for ~ 6.5 weeks. The organic phase was extracted with CH_2Cl_2 (3×50 mL), and washed with brine (40 mL). The crude product was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (30 % EtOAc/hexane) to yield a racemic mixture as a solid. NMR data same as **2.7**. HRFABMS *m/z* 418.1640 (–3.5 ppm/–1.4 mmu) [M + H$^+$] (calcd for $C_{25}H_{24}NO_5$, 418.1654).

4-(2-Benzyloxyphenyl)-3-hydroxy-1-(4-methoxyphenyl)-azetidin-2-one (2.8) A solution of KOH/H_2O (1M, 135 mL) was cooled to 0 °C and lactam **2.7** (2.1 g, 5.0 mmol), dissolved

in THF (110 mL), was added. The resulting suspension was stirred for 1 h at 0 °C. The organic phase was extracted with EtOAc, washed with saturated NH_4Cl solution, then deionized water, and finally brine. Drying with anhydrous Na_2SO_4 and concentration followed, and the residue was purified by FCC (30 % EtOAc/hexane to yield **2.8** as a solid (1.2 g, 80.4 %); mp 220–221 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (4H, m), 7.29 (5H, m), 7.16 (1H, d, *J* = 7.1), 7.03 (1H, d, *J* = 8.2), 6.95 (1H, t, *J* = 7.5), 6.81 (2H, d, *J* = 8.8), 5.54 (1H, d, *J* = 4.7), 5.14 (3H, s), 3.75 (3H, s); ^{13}C NMR: δ 165.9, 156.9, 156.4, 136.6, 131.0, 129.9, 128.9, 128.7, 128.4, 127.6, 122.2, 118.8, 114.5, 112.8, 77.6, 70.7, 55.6; HRFABMS *m/z* 376.1535 (–3.7 ppm/–1.4 mmu) [M + H^+] (calcd for $C_{23}H_{21}NO_4$, 376.1549).

4-(2-Benzyloxyphenyl)-1-(4-methoxyphenyl)-3-triisopropylsilanyloxyazetidin-2-one (2.9) To a solution of alcohol **2.8** (1.2 g, 3.2 mmol) in DMF (22 mL), was added imidazole (653.3 mg, 9.6 mmol), followed by TIPSCl (750 μL, 3.5 mmol). The mixture was stirred under N_2 atmosphere overnight. The organics were diluted with EtOAc, washed with deionized water and brine, then dried over anhydrous Na_2SO_4 and concentrated. The crude product was subjected to FCC on silica gel with 20 % EtOAc in hexane and yielded **2.9** (1.3 g, 2.4 mmol, 76.5 %) as a white solid; mp 124–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (4H, m), 7.26 (5H, m), 6.99 (1H, d, *J* = 8.2), 6.90 (1H, t, *J* = 7.4), 6.78 (1H, dd, *J* = 9.1, 2.2), 5.72 (1H, d, *J* = 4.9), 5.24 (1H, d, *J* = 5.5), 5.10 (2H, d, *J* = 11.1), 3.75 (3H, s), 0.99 (3H, m), 0.89 (18H, m); ^{13}C NMR: δ 166.1, 157.0, 156.2, 137.1, 131.2, 129.3, 129.2, 129.1, 128.8, 128.2, 127.6, 122.5, 120.8, 118.8, 114.4, 111.4, 70.1, 57.3, 55.7, 17.6, 12.1; HRFABMS *m/z* 532.2903 (+3.7 ppm/+2.0 mmu) [M + H^+] (calcd for $C_{32}H_{42}NO_4Si$, 532.2883).

4-(2-Benzyloxyphenyl)-3-triisopropylsilanyloxyazetidin-2-one (2.10) A solution of lactam **2.9** (335.8 mg, 0.6 mmol) in CH_3CN (14.5 mL) was cooled to 0 °C and a solution of ceric ammonium nitrate (CAN) (693.0 mg, 1.3 mmol) in water (5.8 mL) was added over 15 min. The reaction mixture was stirred for 67 min at 0 °C, diluted with EtOAc (20 mL), washed with water (50 mL), saturated $Na_2S_2O_5$ solution (30 mL), and saturated $NaHCO_3$ solution (30 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. FCC on silica gel with 20 % EtOAc in hexane yielded compound **2.10** (164.1 mg, 0.4 mmol, 61.1 %) as a white solid; mp 118.5–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (6H, m), 7.25 (1H, m), 7.00 (1H, t, *J* = 7.3), 6.92 (1H, d, *J* = 8.1), 5.97 (1H, bs), 5.37 (1H, d, *J* = 4.8), 5.18 (1H, dd, *J* = 4.6, 3.0), 5.03 (2H, s), 0.95 (3H, m), 0.87 (18H, m); ^{13}C NMR: δ 156.7, 137.1, 128.8, 128.7, 128.6, 128.0, 127.4, 125.2, 120.5, 111.1, 79.8, 70.0, 53.8, 53.7, 17.6, 12.0; HRFABMS *m/z* 426.2461 (–0.8 ppm/–0.4 mmu) [M + H$^+$] (calcd for $C_{25}H_{36}NO_3Si$, 426.2464).

2-(2-Benzyloxyphenyl)-4-oxo-3-triisopropylsilanyloxyazetidine-1-carboxylic acid *tert*-butyl ester (2.4) A solution of β-lactam **2.10** (135.3 mg, 0.3 mmol), DMAP (9.7 mg, 79.6 μmol), and di-*tert*-butyl dicarbonate (83.3 mg, 0.3 mmol) in CH_2Cl_2 (3.0 mL), at rt under N_2 atmosphere and equipped with a reflux condenser, was treated with Et_3N (133.1 μL, 1.0 mmol). The reaction mixture was warmed to 35 °C and refluxed for 17.5 h, followed by quenching with saturated NH_4Cl solution (5.0 mL), extraction with CH_2Cl_2 (3×6.0 mL), drying over anhydrous Na_2SO_4, and concentration under reduced pressure. FCC on silica gel with 30 % EtOAc in hexane yielded compound **2.4** (167.1 mg, 0.3 mmol, quantitative yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (5H, m), 7.25 (2H, m), 6.97 (1H, t, *J* =

7.5), 6.91 (1H, d, *J* = 8.2), 5.63 (1H, d, *J* = 5.7), 5.15 (1H, d, *J* = 5.9), 5.05 (2H, d, *J* = 6.8), 1.44 (9H, s), 0.96 (3H, m), 0.86 (18H, m); ^{13}C NMR: δ 166.6, 157.0, 148.3, 137.1, 129.1, 128.6, 128.2, 128.0, 127.5, 122.7, 120.6, 111.5, 83.3, 77.7, 70.1, 30.1, 28.1, 17.5, 11.9.

2.4.3 Baccatin Core Preparation Procedures

7-Triethylsilylbaccatin (2.3) To a solution of 10-DAB (306.8 mg, 0.6 mmol) in pyridine (2.0 mL) was added imidazole (276.8 mg, 4.1 mmol) and TESCl (243.7 μL, 1.5 mmol). A positive pressure was established and maintained within the reaction vessel by installing a N_2-filled balloon for moisture exclusion and the reaction mixture was stirred for 9 min. Acetic anhydride (1.4 mL, 14.5 mmol) was then added dropwise and stirring was continued for an additional 5.3 h. At this time, the reaction mixture was diluted with EtOAc (2 mL) and quenched with saturated $NaHCO_3$ solution (5.0 mL). The organic layer was then washed with deionized water (5.0 mL) and brine (5.0 mL). The crude product was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. FCC on silica gel with 70 % EtOAc in hexane yielded compound **2.3** (343.2 mg, 0.5 mmol, 84.4 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (2H, d, *J* = 7.1), 7.60 (1H, t, *J* = 7.3), 7.47 (2H, t, *J* = 7.7), 6.46 (1H, s), 5.63 (1H, d, *J* = 6.9), 4.96 (1H, d, *J* = 8.1), 4.83 (1H, dd, *J* = 12.3, 7.5), 4.48 (1H, dd, *J* = 10.5, 6.5), 4.29 (1H, d, *J* = 8.4), 4.13 (1H, d, *J* = 8.2), 3.88 (1H, d, *J* = 6.9), 2.53 (1H, m), 2.28 (3H, s), 2.26 (2H, m), 2.19 (3H, s), 2.18 (3H, s), 2.09 (1H, bs), 1.87 (1H, t, *J* = 14.3), 1.68 (3H, s), 1.63 (1H, s), 1.19 (3H, s), 1.04 (3H, s), 0.92 (9H, t, *J* = 7.9), 0.60 (6H, m); ^{13}C NMR: δ 170.9, 169.6, 167.3, 133.8, 130.3, 129.6, 128.8, 84.4, 81.0, 78.9, 76.7, 76.0, 74.9, 72.6, 68.1, 58.9, 47.5, 43.0, 38.5, 37.4, 27.0, 22.9, 21.2, 20.3, 15.2, 10.2, 7.0, 5.5.

2.4.4 Coupling of β-Lactam and Baccatin Core

2'-*O*-(Triisopropyl)-3'-*o*-benzyloxyphenyl-3'-(*N*-*tert*-butyloxycarbonyl)-7-*O*-triethylsilyl-paclitaxel (2.11) To a stirred solution of β-lactam **2.4** (97.3 mg, 185.2 μmol) in THF (1 mL), was added protected baccatin **2.3** (25.8 mg, 36.8 μmol) in solution in THF (1 mL) via cannula. The solution was cooled to –50 °C and treated with 1M lithium bis(trimethylsilyl) amide in THF (55.3 μL, 55.3 mmol) and stirred for 30 min. The reaction was quenched with saturated NH_4Cl solution (5 mL) and the organic layer extracted with EtOAc, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. FCC on silica gel with 20 % EtOAc in hexane yielded compound **2.11** (35.2 mg, 28.7 mol, 78.0 %) as a white solid. The reaction was run multiple times resulting in sufficient material for the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (2H, d, *J* = 7.7), 7.44 (10H, m), 6.95 (2H, d, *J* = 7.1), 6.44 (1H, s), 6.29 (1H, t, *J* = 8.9), 5.66 (1H, d, *J* = 7.1), 5.47 (1H, d, *J* = 10.1), 5.40 (1H, d, *J* = 9.9), 5.24 (1H, d, *J* = 11.9), 5.16 (2H, m), 4.92 (1H, d, *J* = 8.9), 4.49 (1H, t, *J* = 6.3), 4.28 (1H, d, *J* = 8.5), 4.13 (1H, d, *J* = 8.3), 3.81 (1H, d, *J* = 6.7), 2.55 (3H, s), 2.29 (1H, t, *J* = 12.5), 2.17 (3H, s), 1.99 (1H, d, *J* = 9.1), 1.85 (3H, s), 1.69 (3H, s), 1.56 (3H, s), 1.25 (15H, m), 0.96 (9H, t, *J* = 7.7), 0.84 (21H, m), 0.61 (6H, q, *J* = 7.7); ^{13}C NMR: δ 202.1, 169.5, 167.3, 155.1, 141.2, 136.4, 133.6, 130.5, 129.4, 129.2, 129.0, 128.7, 128.4, 128.0, 121.3, 111.8, 84.5, 80.7, 79.7, 79.4, 76.7, 75.2, 72.4, 70.6, 70.5, 58.4, 57.8, 46.7, 43.5, 37.4, 28.4, 26.8, 22.7, 21.1, 18.0, 17.8, 14.5, 12.5, 12.4, 10.3, 7.0, 5.9, 5.5, 5.3; HRFABMS *m/z* 1226.6276 (+0.6 ppm/+0.8 mmu) [M + H^+] (calcd for $C_{67}H_{96}NO_{16}Si_2$, 1226.6268).

2.4.5 Cyclization and Deprotection

2'-*O*-(Triisopropyl)-3'-(*o*-hydroxyphenyl)-3'-(*N*-*tert*-butyloxycarbonyl)-7-*O*-triethylsilyl-paclitaxel (2.12) A solution of silyl ether **2.11** (66.4 mg, 54.2 μmol) in EtOAc (2 mL) was treated with 10 % Pd/C (65.0 mg). The resulting mixture was subjected to hydrogenation at 30 psi at rt for 90 h. The reaction mixture was filtered through Celite® and the filtrate was concentrated under vacuum. The product **2.12** (40.9 mg) was used directly in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (2H, d, *J* = 7.3), 7.60 (1H, t, *J* = 7.5), 7.49 (2H, t, *J* = 7.6), 7.23 (1H, d, *J* = 7.3), 7.14 (1H, t, *J* = 7.5), 6.88 (1H, t, *J* = 7.3), 6.82 (1H, d, *J* = 7.9), 6.44 (1H, s), 6.20 (1H, t, *J* = 8.9), 5.67 (1H, d, *J* = 6.9), 5.53 (1H, s), 5.35 (1H, d, *J* = 6.9), 5.02 (1H, d, *J* = 3.8), 4.93 (1H, d, *J* = 8.1), 4.46 (1H, dd, *J* = 10.5, 6.5), 4.27 (1H, d, *J* = 8.5), 4.16 (1H, d, *J* = 8.7), 3.81 (1H, d, *J* = 7.1), 2.52 (1H, m), 2.43 (3H, s), 2.30 (1H, s), 2.17 (3H, s), 2.07 (1H, s), 1.91 (3H, s), 1.68 (3H, s), 1.63 (1H, s), 1.32 (9H, s), 1.20 (6H, d, *J* = 6.7), 1.02 (21H, d, *J* = 4.2), 0.92 (11H, m), 0.58 (6H, m).

2'-*O*-(Triisopropyl)-3'-*o*-hydroxyphenyl-3'-(*N*-debenzoyl)-7-*O*-triethylsilyl-paclitaxel (2.2) Formic acid (96 %, 1.0 mL) was added to **2.12** (41.5 mg, 36.58 μmol) and the resulting mixture was stirred at rt for 1 h. The acid was evaporated and the residue was neutralized by adding saturated $NaHCO_3$ solution. The crude product was extracted with CH_2Cl_2 (3×6.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. FCC on silica gel with 40 % EtOAc in hexane yielded compound **2.2** (17.3 mg, 18.8mol, 51.3%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (2H, d, *J* = 8.2), 7.71 (1H, t, *J* = 7.5), 7.60 (2H, t, *J* = 7.5), 6.86 (2H, t, *J* = 7.7), 6.80 (1H, t, *J* = 7.5), 6.67 (1H, t, *J* = 7.3), 6.21 (1H, s), 5.88 (1H, t, *J* = 8.6), 5.54 (1H, d, *J* = 6.8), 4.90 (1H, d, *J* = 9.5), 4.67 (1H, d, *J* = 9.2), 4.34 (1H,

dd, *J* = 10.4, 6.8), 4.27 (1H, d, *J* = 9.0), 4.22 (1H, d, *J* = 8.4), 4.18 (1H, d, *J* = 8.2), 3.59 (1H, d, *J* = 7.1), 2.51 (1H, m), 2.41 (1H, s), 2.22 (3H, s), 2.21 (3H, s), 1.82 (4H, s), 1.62 (3H, s), 1.51 (6H, m), 1.18 (24H, s), 1.07 (3H, s).

Compound 2.13 A solution of **2.2** (5.8 mg, 6.3 μmol) in CH_2Cl_2 (250 μL) under N_2 was treated with pyridine (12.6 μL, 155.9 μmol) followed by triphosgene (4.1 mg, 13.6 μmol) in CH_2Cl_2 (250 μL). The resulting mixture was stirred at rt for 3.75 h. The reaction mixture was quenched with deionized water (0.5 mL) and then washed with additional water (3×3.0 mL), extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. FCC of the crude product on silica gel with 50 % EtOAc in hexane yielded compound **2.13** as a white solid (3.7 mg, 3.9 μmol, 62.0 %). The reaction was run multiple times resulting in sufficient material for the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (2H, d, *J* = 7.3), 7.67 (1H, t, *J* = 7.5), 7.54 (2H, t, *J* = 8.2), 7.25 (1H, m), 7.10 (3H, m), 6.26 (2H, s), 5.89 (1H, d, *J* = 2.7), 5.62 (1H, d, *J* = 7.1), 4.91 (1H, d, *J* = 7.7), 4.64 (1H, q, *J* = 3.1), 4.49 (1H, d, *J* = 5.9), 4.37 (1H, m), 4.26 (1H, d, *J* = 8.4), 4.10 (1H, d, *J* = 8.4), 3.72 (1H, d, *J* = 7.0), 2.53 (1H, m), 2.43 (1H, d, *J* = 4.0), 2.24 (1H, s), 2.04 (2H, s), 1.90 (4H, m), 1.75 (1H, s), 1.64 (3H, s), 1.59 (5H, s), 1.27 (6H, m), 1.13 (3H, s), 1.08 (18H, s).

Compound 2.1 A solution of **2.13** (10.5 mg, 11.7 μmol) in THF (500 μL) was treated with pyridine (9.5 μL, 117.4 μmol) and the resulting solution was cooled to 0 °C. Pyridinium hydrofluoride (0.7 μL, 41.1 μmol) was added, and the reaction mixture was allowed to warm to rt and stirred for 22 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated $NaHCO_3$ solution. The organic layer was extracted with CH_2Cl_2 (3×6.0 mL),

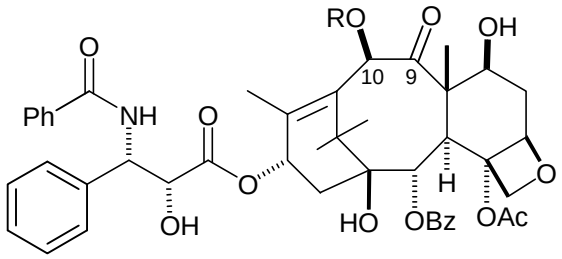
dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. FCC on silica gel with 80 % EtOAc in hexane yielded compound **2.1** (6.9 mg, 8.7 μmol, 79.1 %) as a white solid; mp 192–193 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 7.98 (2H, d, *J* = 7.6), 7.58 (1H, t, *J* = 7.6), 7.46 (2H, t, *J* = 7.8), 7.21 (2H, m), 6.84 (1H, t, *J* = 7.6), 6.79 (1H, t, *J* = 8.0), 6.39 (1H, s), 6.20 (1H, t, *J* = 8.7), 5.57 (1H, d, *J* = 7.3), 5.17 (1H, d, *J* = 5.7), 4.93 (1H, d, *J* = 5.7), 4.53 (2H, s), 4.23 (1H, dd, *J* = 11.0 and 6.6), 4.06 (2H, s), 3.75 (1H, d, *J* = 7.1), 2.35 (1H, m), 2.23 (3H, m), 2.09 (3H, s), 2.06 (3H, s), 1.91 (3H, s), 1.82 (3H, s), 1.69 (1H, m), 1.56 (3H, s), 1.19 (2H, m), 1.06 (3H, s); ^{13}C NMR: δ 205.3, 171.9, 171.3, 170.8, 167.7, 156.9, 141.9, 135.4, 134.7, 131.3 (×2), 129.9, 128.9, 126.1, 121.0, 116.8, 101.2, 86.1, 82.3, 80.8, 79.3, 77.5, 76.9 76.3, 73.3, 72.5, 59.4, 57.4, 48.2, 44.8, 37.7, 37.0, 30.9, 27.1, 22.3, 20.9, 14.9, 10.6; HRFAB MS *m/z* 792.2876 (+1.1 ppm/+0.9 mmu) [M + H^+] (calcd for $C_{41}H_{46}NO_{15}$, 792.2867).

3. Synthesis of Northern Hemisphere B-ring Modified Paclitaxel Analogs

3.1 Inroduction

The Structure Activity Relationships (SARs) of paclitaxel indicate that the C9 and C10 positions, the northern hemisphere of the B-ring, may undergo modification, and that activity can be enhanced, relative to the parent compound, by making suitable alterations.[44] Most C10 modified analogs with improved bioactivity have also had side chain modifications.[26] Further information on the influence of the C10 acetoxy on activity lie in the microtubule binding of analogs modified in that position.[45] In addition to the similar activity in the microtubule assay, C10 modified analogs also show comparative activity to taxol in the human colon carcinoma cell line (HCT116) (Table 3.1).[46,47,48,49,50,51] Microtubule assay and HCT116 activities are similar to that of taxol, with the exception of compound **3.6** in the colon cells and compound **3.8** in microtubules. Despite this finding, **3.6** in the microtubule assay, and **3.8** in the colon cells show activities equal to or very similar to taxol's.

Table 3.1. Structure and activity of C10 modified taxol analogs.[43]

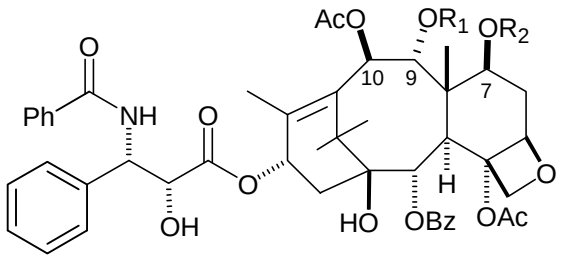


Compound	R	Tubulin activity ED_{50}/ $ED_{50\ (Taxol)}$	HCT 116[c] ED_{50}/ $ED_{50\ (Taxol)}$
Taxol	Ac		
3.1	OH	1.3[a]	
3.2	H	0.5[b]	1.75
3.3	OCOBu	1.5	1.7
3.4	OCOcyclopro	1.1	1.1
3.5	$OCON(Me)_2$	1.0	0.5
3.6	OMe	1.0	6
3.7	OCOOMe	1.1	1.5
3.8	COPh	19	1.1

[a] Microtubule disassembly assay.
[b] Microtubule assembly assay.
[c] Human colon carcinoma cell line.

Methylation of the C9 hydroxyl group of a 9(*R*)-dihydrotaxane analog to give **3.11** increased its potency (Table 3.2).[52] Increased microtubule activity was observed in compounds **3.9** to **3.11**, whereas substitution at C7 led to reduced tubulin activity and significant loss of cytotoxicity of compounds **3.13** to **3.16**.[53] Studies directed towards enhanced solubility and stability have been a major focus when modifying the C9 and C10 positions.[54,55,56]

Table 3.2. Structure and activity of C9 modified taxol analogs.[51,52]

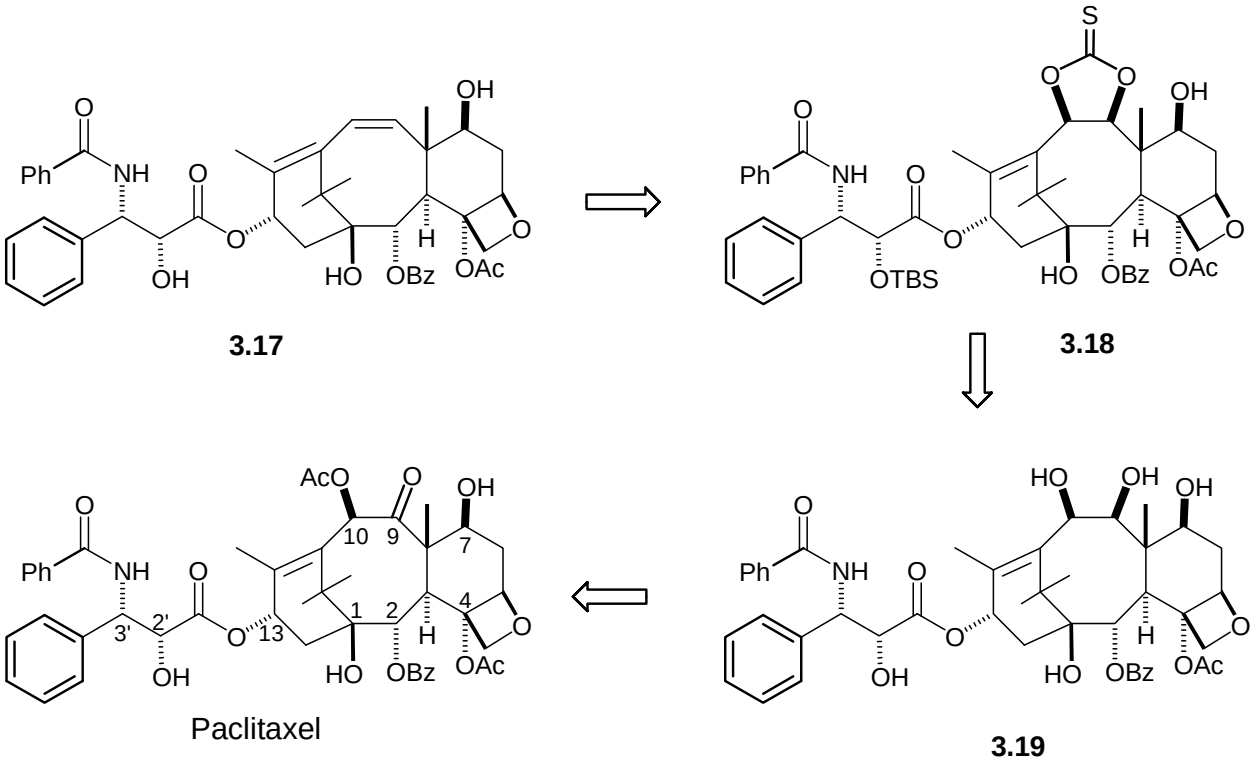


Compound	R_1	R_2	Tubulin activity ED_{50}/ $ED_{50\ (Taxol)}$	HT-29[a]
3.9	H	H	0.75	6.4
3.10	Ac	H	0.83	1.9
3.11	Me	H	0.35	0.15
3.12	H	CH_2CHCH_2	1.4	1.2
3.13	H	$(CH_2)_2OH$	1.77	10
3.14	H	$(CH_2)_2OAc$	2.47	31
3.15	H	$(CH_2)_2NEt_2$	2.61	108
3.16	H	$CH_2CH(OH)CH_2OH$	2.02	310

[a] Human colon adenocarcinoma cell line.

The aim of this synthesis was to synthesize previously inaccessible taxol analogs via a 1,2-diol (**3.19**), and a C9, C10 olefin (**3.17**), as key intermediates (Scheme 3.1). The olefin would allow a number of substituents to be added resulting in various analogs. The first two steps of the synthesis, a hydroxyl protection and a deacetylation, went well. Making the 1,2-diol, the first key intermediate, proved to be more challenging and time consuming than anticipated. Several attempts, changing the form of the metal reagent and altering the reaction time, finally led to the C9, C10 diol. The next step to the thiocarbonate **3.18**, which would be convertible to olefin **3.17**, also presented challenges. In this light, a cyclic sulfite

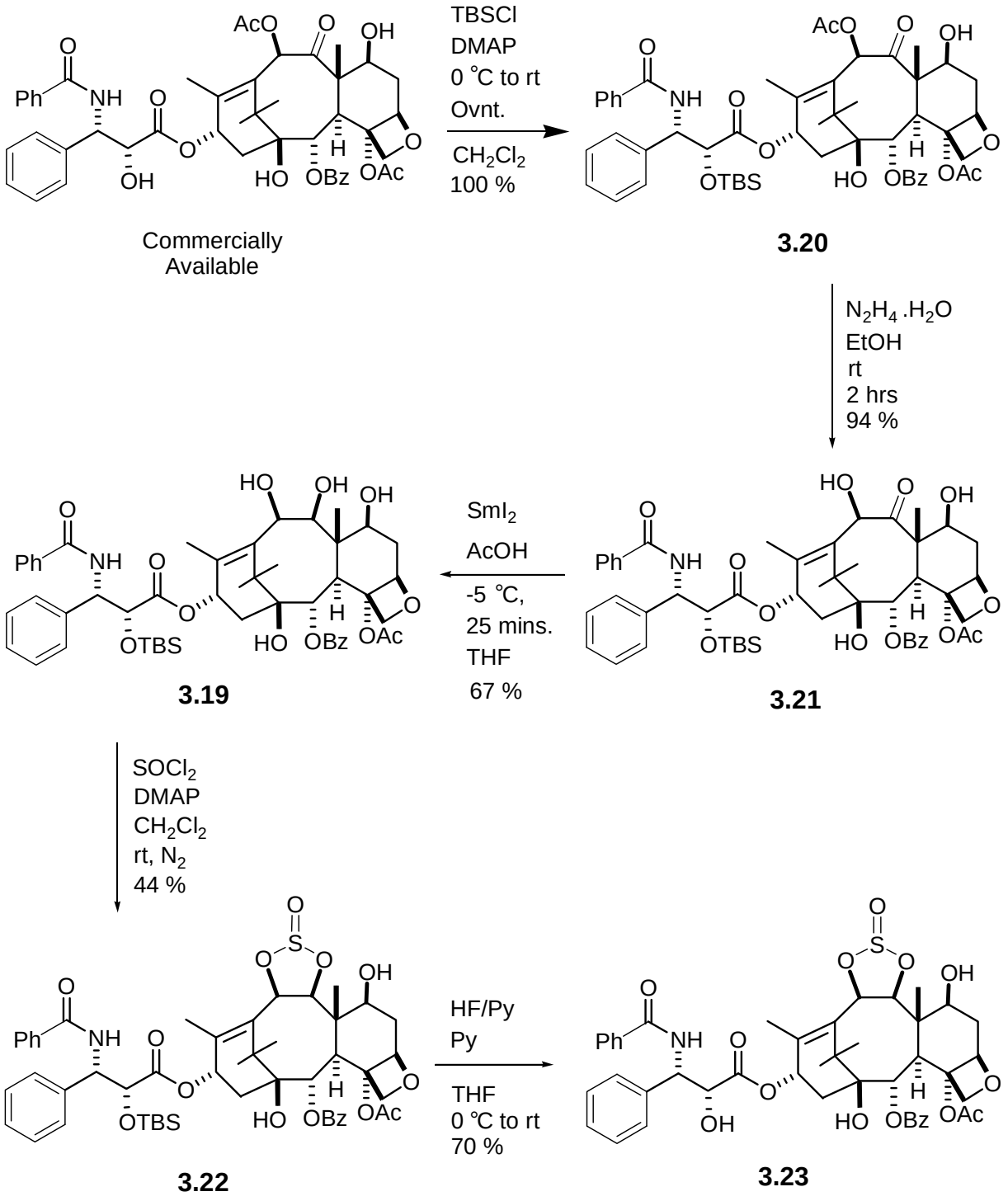
was made to test the ability of diol **3.19** to form cyclic esters at the C9 and C10 positions. This compound was successfully prepared and antiproliferative activity results are presented.



Scheme 3.1 Synthetic strategy of northern hemisphere B-ring modified paclitaxel analogs.

3.2 Synthesis

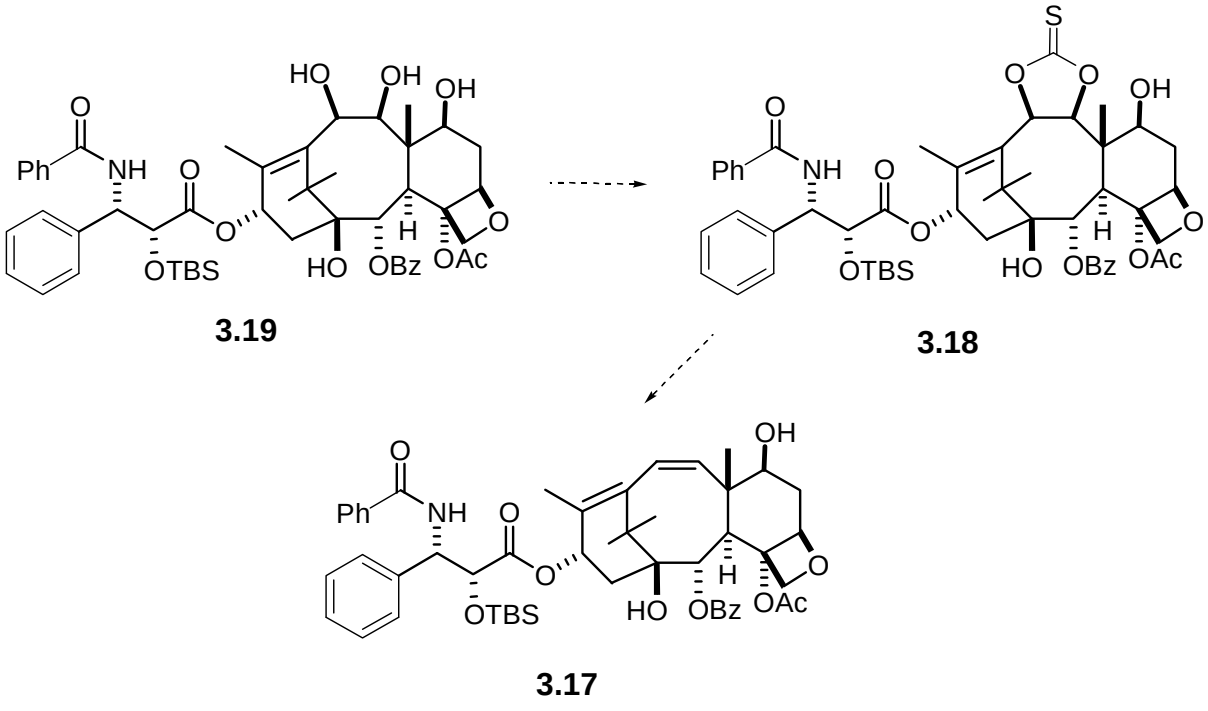
Synthesis of the northern hemisphere B-ring modified taxol analog began with commercially available paclitaxel, which was protected at the 2'-position as its TBS ether, giving a quantitative yield of **3.20** (Scheme 3.2).[57] Deacetylation at C10, with hydrazine monohydrate, followed and gave **3.21** in good yield.[58] Reduction of **3.21** with SmI_2 allowed



Scheme 3.2 Synthesis of northern hemisphere B-ring modified paclitaxel analogs I.

formation of the C9, C10 diol **3.19** with a fair yield.[59] The initial attempt using samarium chips and diiodoethane was unsuccessful. The same conditions were followed using powdered samarium, but no product was detected. The reported intense blue-green color of SmI_2[60] was not observed in the reaction mixture, which led to the use of SmI_2 powder. The expected blue-green color was observed immediately upon addition of solvent, and resulted in the desired product, but in low yield. This change in the form of the reducing agent also posed challenges, since the conditions that led to product formation were not reproducible. Several attempts to accumulate the 1,2-diol resulted in low yields or no product. Finally, SmI_2 in THF stabilized with Sm chips resulted in consistently better yields after the reaction time was adjusted.

Diol **3.19** was converted to its cyclic sulfite **3.22** in a yield of just over 40 % using $SOCl_2$ and DMAP as base.[61] Removal of the 2'-TBS group from **3.22** gave the free alcohol



Scheme 3.3 Synthesis of northern hemisphere B-ring modified paclitaxel analogs II.

3.23 in good yield.

The synthesis of cyclic sulfite **3.23** (Scheme 3.2) demonstrated that it is possible to prepare cyclic derivatives at the C9, C10 positions of paclitaxel. The next step was the preparation of the cyclic thiocarbonate **3.18**, which was expected to undergo a Barton-type deoxygenation[62] reaction to generate alkene **3.17**. Alkene **3.17** could then serve as a precursor to a variety of other paclitaxel analogs. Initial attempts at preparing **3.18** from **3.19** were unsuccessful. Diol **3.19** and dimethylamino-pyridine in CH_2Cl_2 under nitrogen atmosphere was cooled to O °C and treated with thiophosgene and stirred.[63] Since no product was detected, the reaction mixture was warmed at ten-degree intervals to rt, while monitoring progress by TLC. Other attempts were made with increased reaction time, however no product has been detected to date.

3.3 Result

Antiproliferative activity against the A2780 ovarian cancer cell line for cyclic sulfite **3.23** was measured at an IC_{50} value of 0.03 μg/mL, slightly less active than taxol at 0.01 μg/mL. This result confirms the previous observations that modifications at the C9, C10 positions do not make significant differences to the bioactivity of paclitaxel.

3.4 Experimental

3.4.1 General Methods

Chemical reagents and materials were supplied by Sigma-Aldrich Co. and VWR, unless otherwise stated. Tetrahydrofuran (THF) was distilled from Na/benzophenone, and dichloromethane (CH_2Cl_2) from CaH_2, both under N_2. Reactions and flash column

chromatography (FCC) were monitored with analytical thin layer chromatography (TLC) plates (silica gel 60 F_{254}, with aluminum support) from Merck KGaA. TLC plates were analyzed with 254 nm UV light and immersion in a phosphomolybdic acid/ethanol (PMA) stain. FCC was performed using Silia*Flash*® P60, 40-63 μm silica gel from SiliCycle® Incorporated. Analtech Incorporated supplied preparative TLC (PTLC) glass-backed UNIPLATES™ Silica Gel GF plates. ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ or CD_3OD on a Varian Inova 400, a Varian Unity 400, or a JEOL Eclipse 500 spectrometer. Chemical shifts were calibrated using the 0.0 ppm tetramethylsilane (TMS) peak or the solvent peaks as internal standards and are reported as δ-values relative to the standard. Coupling constants (*J* values) are reported in Hertz, and High Resolution Fast Atom Bombardment mass spectra (HRFABMS) were obtained from a high-resolution double-focusing mass spectrometer by Analytical Services.

3.4.2 Preparation Procedures

2'-O-(*tert*-Butyldimethylsilyl)-paclitaxel (3.20) A solution of paclitaxel (260.5 mg, 0.3 mmol) in CH_2Cl_2 (10 mL), cooled to 0 °C was treated with DMAP (1.5 g, 12.2 mmol) and TBSCl (1.8 g, 12.2 mmol) and allowed to warm to rt. The reaction mixture was stirred overnight. The reaction was quenched with brine, and the resulting mixture was washed with 10 % HCl and saturated $NaHCO_3$ solution. The CH_2Cl_2 layer was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. FCC of the crude product on silica gel with 50 % EtOAc in hexane yielded compound **3.20** (295.7 mg, 0.3 mmol, quantitative yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (2H, d, *J* = 8.2), 7.73 (2H, d, *J* = 8.2), 7.60 (1H, t, *J* = 7.5), 7.52 (3H, m), 7.40 (4H, m), 7.32 (3H, d, *J* = 7.3),

7.07 (1H, d, *J* = 8.8), 6.29 (2H, t, *J* = 9.3), 5.74 (1H, d, *J* = 8.8), 5.69 (1H, d, *J* = 7.1), 4.98 (1H, d, *J* = 8.8), 4.66 (1H, s), 4.44 (1H, m), 4.30 (1H, d, *J* = 8.4), 4.27 (1H, d, *J* = 8.3), 3.82 (1H, d, *J* = 7.1), 2.58 (4H, t, m), 2.48 (1H, s), 2.40 (1H, dd, *J* = 14.9, 9.3), 2.23 (3H, s), 2.13 (1H, dd, *J* = 14.8, 8.8), 1.90 (4H, m), 1.82 (1H, s), 1.69 (3H, s), 1.24 (3H, s), 1.13 (3H, s), 0.80 (9H, s), –0.04 (3H, s), –0.29 (3H, s); ^{13}C NMR: δ 203.9, 171.5 (×2), 170.3, 167.2, 142.6, 138.4, 134.2, 133.8, 133.1, 132.0, 130.4, 129.3, 129.0 (×2), 128.9 (×2), 128.9, 128.2, 127.2, 126.6, 84.6, 81.3, 79.3, 76.6, 75.7, 75.4, 75.3, 72.3, 71.6, 58.7, 55.8, 45.7, 43.4, 36.0, 35.7, 26.9, 25.7, 23.2, 22.5, 21.0, 18.3, 15.1, 9.8, 0.2, –5.1, –5.6.

2'-O-(*tert*-Butylmethylsilyl)-10-deacetyl-paclitaxel (3.21) To a solution of **3.20** (271.2 mg, 0.3 mmol) in EtOH (20 mL) was added N_2H_4•H_2O (2.9 mL) at rt and the resulting mixture was stirred for 30 min. The solution was diluted with EtOAc and quenched with saturated NH_4Cl solution. The organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. FCC of the crude product on silica gel with 50 % EtOAc in hexane yielded compound **3.21** (244.7 mg, 0.3 mmol, 94.4 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (2H, d, *J* = 7.1), 7.74 (2H, d, *J* = 7.0), 7.60 (1H, t, *J* = 7.3), 7.52 (3H, m), 7.40 (4H, dd, *J* = 14.7, 7.3), 7.32 (3H, d, *J* = 7.3), 7.09 (1H, d, *J* = 8.8), 6.30 (1H, t, *J* = 8.6), 5.70 (2H, m), 5.19 (1H, s), 4.96 (1H, d, *J* = 7.5), 4.65 (1H, d, *J* = 2.0), 4.32 (1H, d, *J* = 8.6), 4.26 (1H, d, *J* = 8.4), 4.24 (1H, m), 4.19 (1H, s), 3.94 (1H, d, *J* = 7.1), 2.57 (4H, m), 2.37 (1H, dd, *J* = 14.7, 9.5), 2.09 (1H, dd, *J* = 15.0, 8.6), 1.92 (3H, s), 1.86 (1H, m), 1.75 (3H, s), 1.68 (2H, m), 1.21 (3H, s), 1.10 (3H, s), 0.80 (9H, s), –0.03 (3H, s), –0.29 (3H, s); ^{13}C NMR: δ 211.6, 171.4, 170.4, 167.3, 167.1, 138.8, 138.5, 135.9, 134.2, 133.8, 132.0, 130.4, 129.4, 129.0, 128.9 (×2), 128.1, 127.2, 126.6, 84.4, 81.3, 79.0, 77.5,

76.8, 75.3, 75.1, 74.6, 72.1, 71.6, 57.7, 55.8, 46.5, 43.3, 37.1, 36.2, 26.5, 25.7, 23.2, 21.3, 18.3, 14.5, 10.1, 0.2, –5.1, –5.7 (×2); HRFABMS *m/z* 926.4154 (+3.0 ppm/+2.8 mmu) [M + H^+] (calcd for $C_{51}H_{64}NO_{13}Si$, 926.4147).

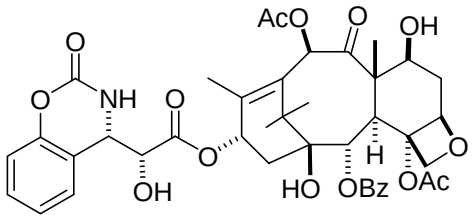
2'-O-(*tert*-Butyldimethylsilyl)-9-dihydro-10-deacetyl-paclitaxel (**3.19**) Compound **3.21** (23.6 mg) in THF (250 μL) was treated with AcOH (84.8 μL) at rt, cooled to –7 °C, and then stirred for 10 min. SmI_2 solution in THF (0.1M, 2.0 mL, 0.2 mmol) was added over a 5 min period and the mixture was stirred for 10 min. The reaction was then quenched using 5 mL of sat. $NaHCO_3$ solution. Extraction with CH_2Cl_2 (3×5.0 mL) was followed by drying over anhydrous Na_2SO_4, and concentration under reduced pressure. Preparative TLC of the crude product on silica gel (50 % EtOAc in hexane) yielded compound **3.19** (15.7 mg, 16.9 μmol, 66.4 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (2H, d, *J* = 7.3), 7.78 (2H, d, *J* = 7.0), 7.59 (1H, t, *J* = 7.3), 7.48 (5H, m), 7.39 (4H, d, *J* = 3.5), 7.31 (1H, m), 7.13 (1H, d, *J* = 8.8), 6.25 (1H, t, *J* = 9.2), 6.15 (1H, d, *J* = 5.1), 5.74 (1H, d, *J* = 9.0), 5.25 (1H, s), 5.07 (1H, d, *J* = 3.7), 4.68 (1H, d, *J* = 1.8), 4.35 (1H, d, *J* = 8.1), 4.31 (1H, d, *J* = 8.0), 4.04 (1H, s), 3.34 (1H, s), 2.98 (1H, d, *J* = 4.9), 2.65, 2.54 (3H, s), 2.35 (2H, m), 2.15 (1H, dd, *J* = 15.4, 9.7), 2.04 (1H, m), 1.96 (1H, s), 1.75 (3H, s), 1.72 (3H, s), 1.65 (6H, m), 1.30 (3H, s), 0.80 (9H, s), –0.04 (3H, s), –0.34 (3H, s); ^{13}C NMR: δ 172.1, 170.3, 167.4, 167.0, 138.6, 138.1, 134.9, 134.4, 133.7, 132.0, 130.4, 129.6, 128.9, 128.0, 127.2, 126.6, 86.6, 82.6, 78.9, 75.3, 74.4, 72.8, 72.2, 71.7, 55.8, 53.6, 48.6, 44.5, 44.0, 35.7, 33.6, 29.9, 29.0, 25.7, 24.4, 23.7, 18.3, 14.9, 14.6, –5.0, –5.7; HRFABMS *m/z* 928.4394 (+4.9 ppm/+4.5 mmu) [M + H^+] (calcd for $C_{51}H_{66}NO_{13}Si$, 928.4303).

Protected Cyclic Sulfite (3.22) Diol **3.19** (13.6 mg, 14.6 μmol) and DMAP (7.2 mg, 58.6 μmol) in CH_2Cl_2 (1.0 mL) at rt were treated with $SOCl_2$ (3.2 μL, 43.9 μmol) and stirred for 24 min. The reaction mixture was quenched with brine (2.0 mL), extracted with CH_2Cl_2 (3×2.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. PTLC of the crude product on silica gel with 30 % EtOAc in hexane yielded compound **3.22** (6.2 mg, 6.4 μmol, 43.7 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (2H, d, *J* = 7.3), 7.78 (2H, d, *J* = 7.3), 7.57 to 7.29 (11H, m), 7.10 (1H, d, *J* = 9.0), 6.38 (1H, d, *J* = 7.7), 5.94 (1H, t, *J* = 8.1), 5.69 (1H, d, *J* = 9.3), 5.64 (1H, d, *J* = 5.3), 5.60 (1H, d, *J* = 5.1), 4.97 (1H, d, *J* = 8.1), 4.94 (1H, s), 4.74 (1H, s), 4.60 (1H, d, *J* = 2.6), 4.34 (2H, dd, *J* = 13.3, 7.7), 3.88 (1H, m), 2.99 (1H, d, *J* = 7.3), 2.75 (1H, m), 2.45 (3H, s), 2.23 (1H, dd, *J* = 13.6, 7.0), 2.00 (1H, dd, *J* = 8.6, 3.7), 1.90 (1H, m), 1.87 (3H, s), 1.85 (3H, s), 1.56 (6H, s), 0.79 (9H, s), –0.07 (3H, s), –0.32 (3H, s); ^{13}C NMR: δ 194.7, 191.0, 180.0, 176.8, 171.3, 170.5, 168.4, 165.9, 146.8, 143.4, 134.5, 133.7, 130.2, 128.9, (×2), 128.0, 127.2, 126.6, 113.4, 84.6, 81.2, 79.9, 75.9, 75.6, 62.8, 60.6, 55.9, 53.6, 45.0, 43.1, 25.7, 22.7, 21.2, 20.9, 18.4, 14.4, 12.0, 11.5, –5.2, –5.8.

Cyclic Sulfite 3.23 To protected cyclic sulfite **3.22** (11.5 mg, 11.8 μmol) in anhydrous THF (0.5 mL) was added pyridine (9.6 μL, 0.1 μmol), cooled to –5 °C, treated with HF•py (0.7 μL, 41.4 μmol), and allowed to warm to rt. The resulting mixture was stirred for 45 h. The reaction mixture was diluted with CH_2Cl_2 (1.0 mL) and quenched with sat. $NaHCO_3$ solution (1.0 mL). The organic materials were extracted with CH_2Cl_2 (3×2.0 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. PTLC of the crude product on silica gel (50 % EtOAc in hexane) yielded compound **3.23** (7.1 mg, 8.3 μmol, 70.0 %) as a

white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (2H, d, *J* = 7.1), 7.80 (2H, d, *J* = 8.4), 7.59 (1H, t, *J* = 7.5), 7.54 to 7.32 (11H, m), 7.13 (1H, d, *J* = 9.5), 6.45 (1H, d, *J* = 7.7), 5.88 (1H, t, *J* = 7.7), 5.78 (1H, d, *J* = 9.2), 5.60 (1H, d, *J* = 5.5), 5.56 (1H, d, *J* = 5.5), 4.96 (1H, s), 4.92 (1H, d, *J* = 8.4), 4.77 (1H, s), 4.74 (1H, m), 4.49 (1H, d, *J* = 8.4), 4.15 (1H, d, *J* = 8.1), 3.81 (1H, q, *J* = 8.8), 2.96 (1H, d,), 2.70 (1H, m), 2.36 (1H, m), 2.29 (3H, s), 2.00 (1H, dd, 14.1, 8.1), 1.87 (3H, s), 1.85 (1H, m), 1.64 (3H, s), 1.60 (3H, s), 1.56 (3H, s); ^{13}C NMR: δ 172.3, 170.9, 166.9, 165.9, 146.0, 143.4, 138.3, 135.1, 134.0, 133.7, 132.1, 130.0, 129.8, 129.1, 128.9, 128.4, 127.2, 127.1, 113.1, 84.6, 81.4, 80.9, 80.3, 75.5, 74.9, 73.9, 72.1, 69.0, 63.2, 55.1, 44.8, 43.4, 39.0, 38.4, 22.4, 20.9, 12.1, 11.4; HRFABMS *m/z* 842.2869 (+2.7ppm/+2.3 mmu) [M – OH] (calcd for $C_{45}H_{48}NO_{13}S$, 842.2846).

4. Appendix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OBz
OAc

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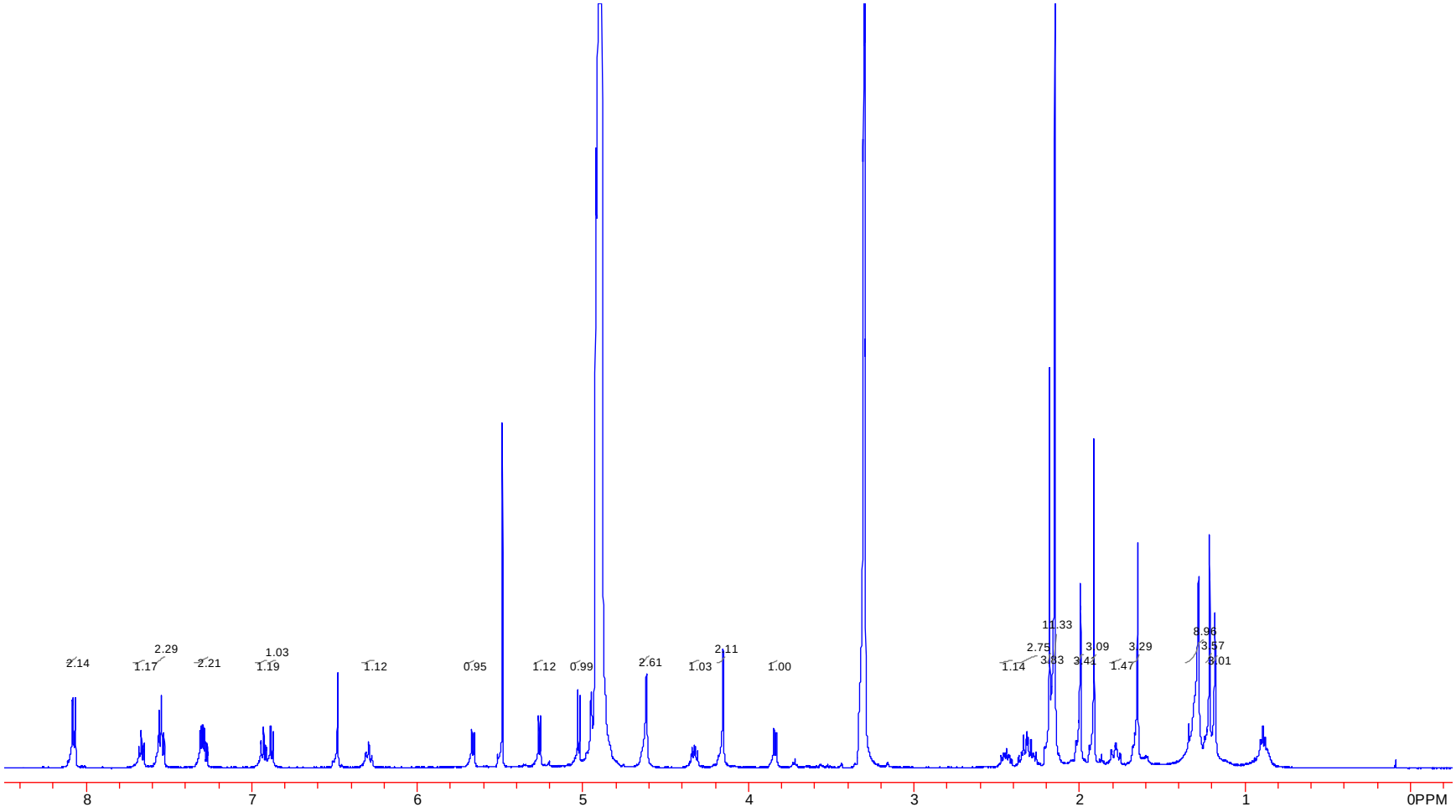
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3.41
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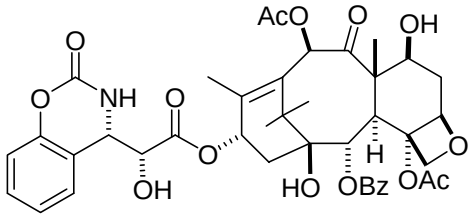
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O
HO
OBz
OAc
OH

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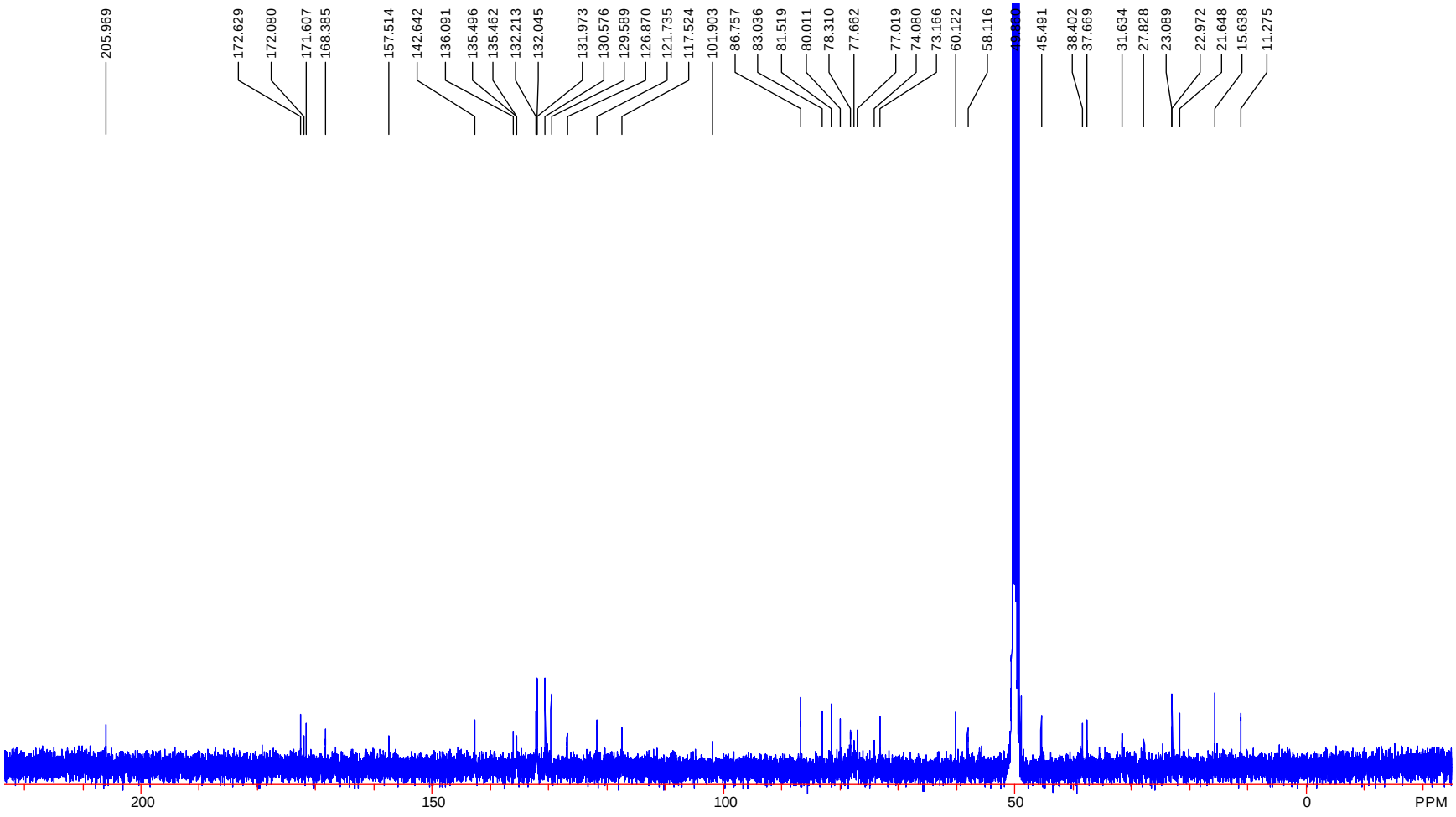
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101.903
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83.036
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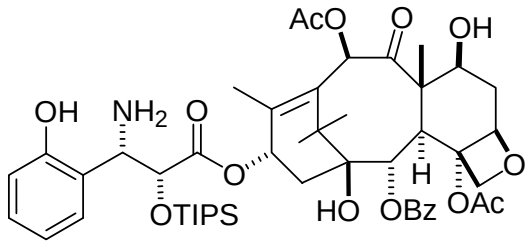
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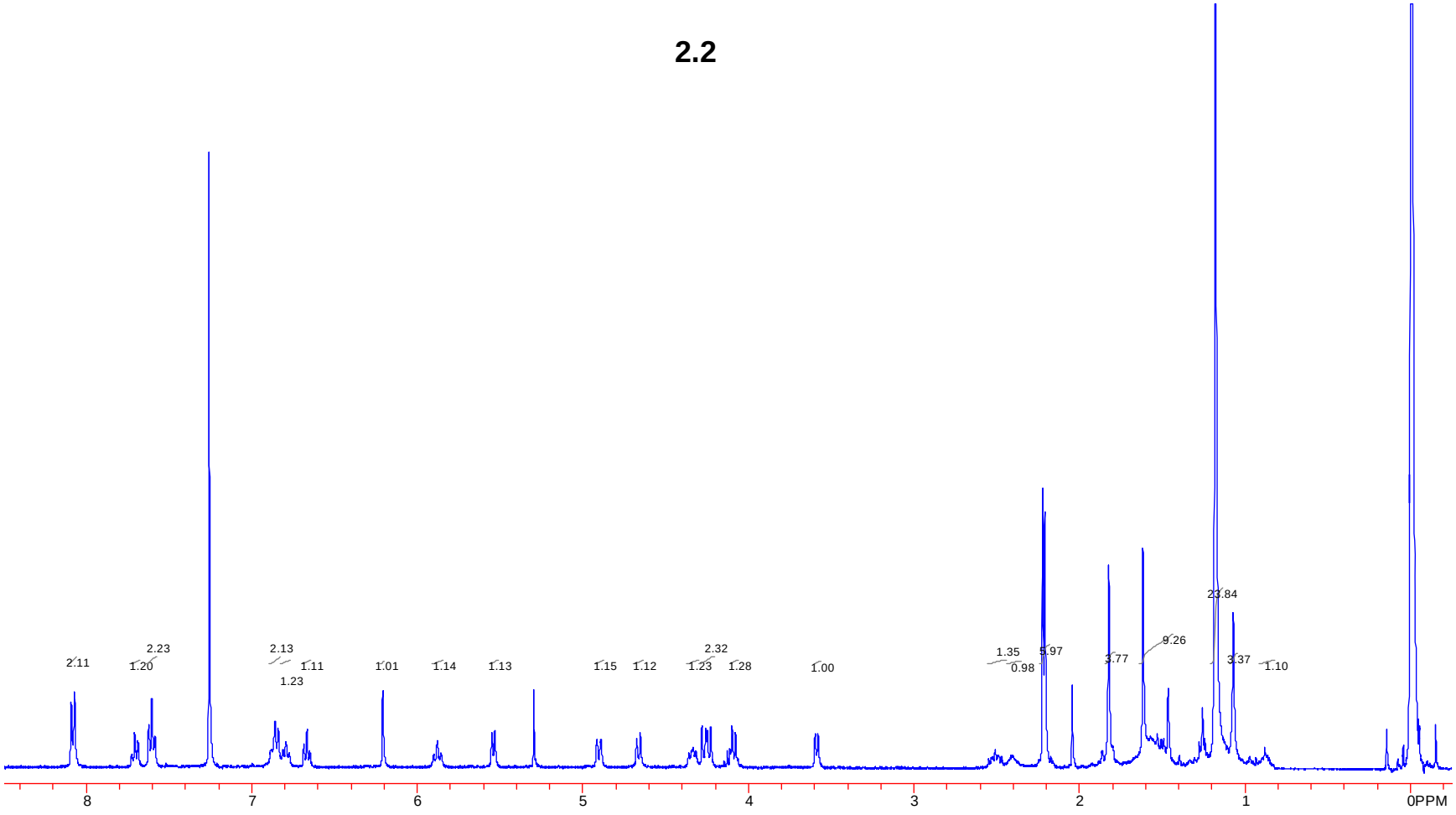
2.2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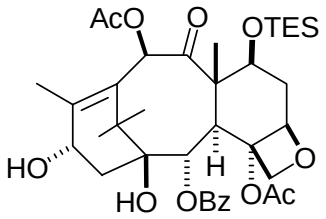
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HO
OBz
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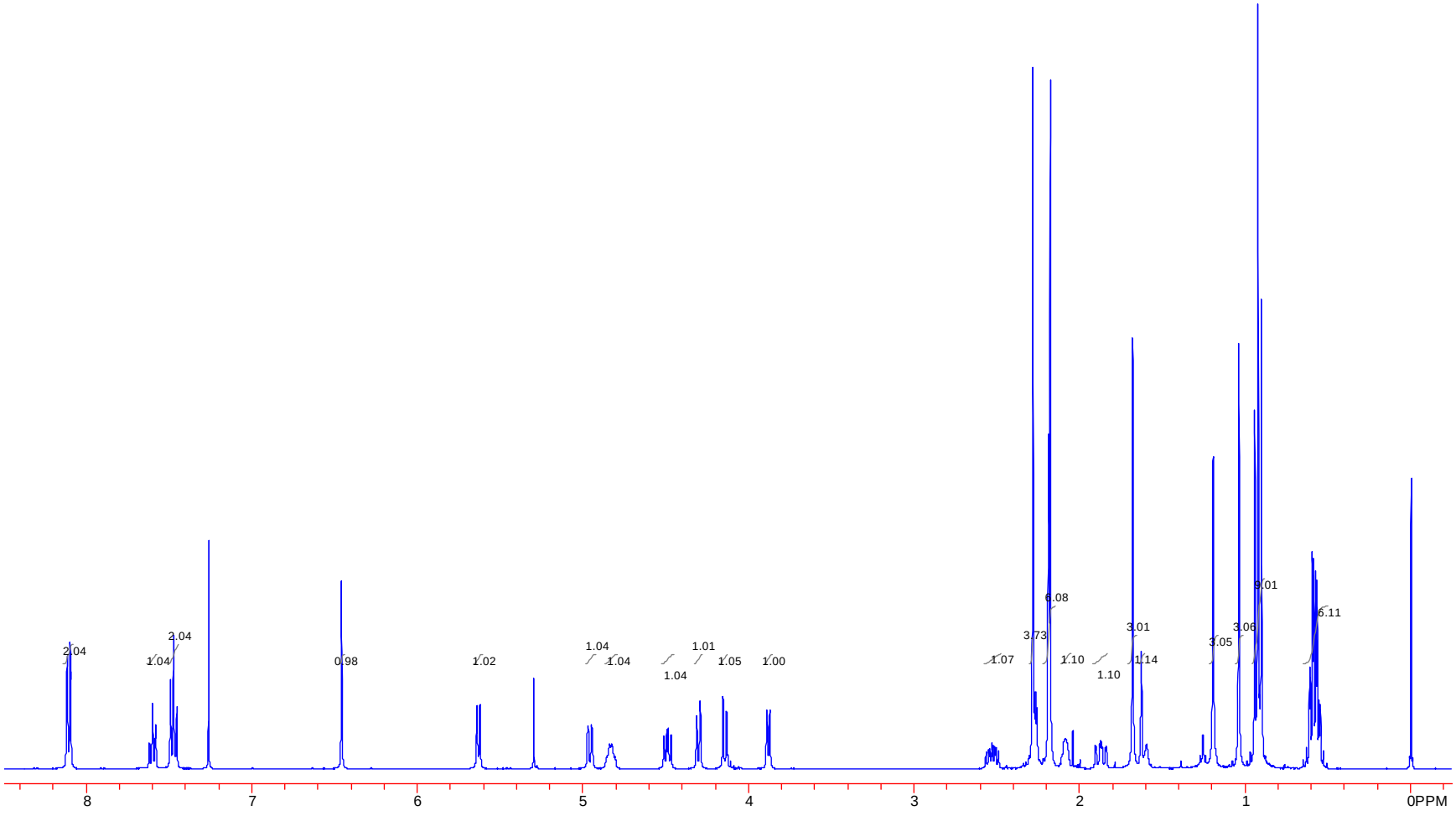
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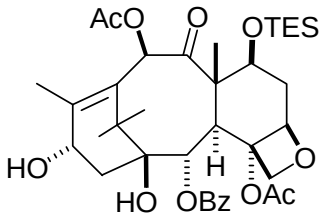
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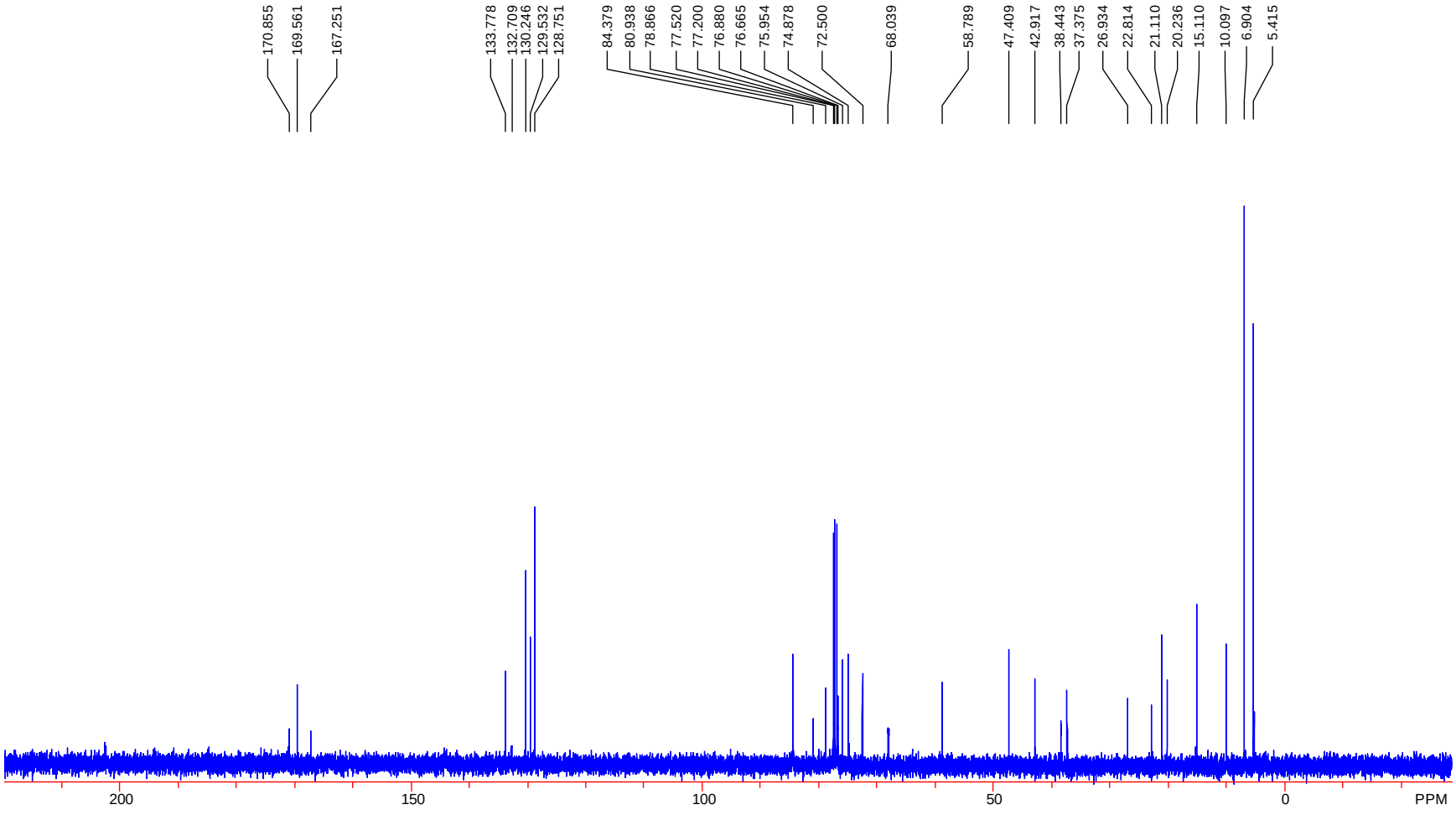
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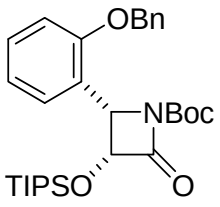
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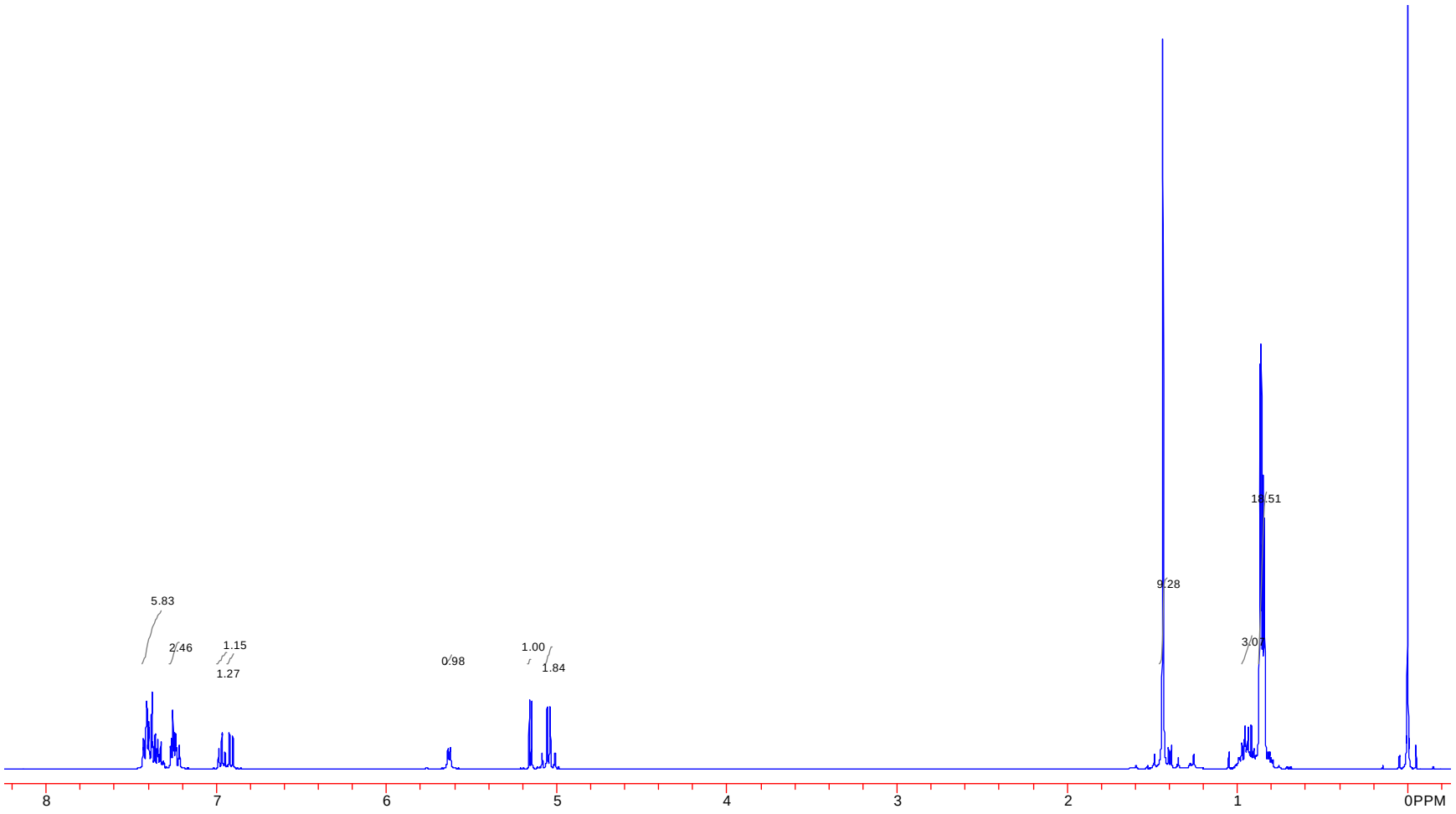
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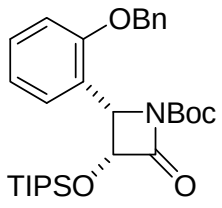
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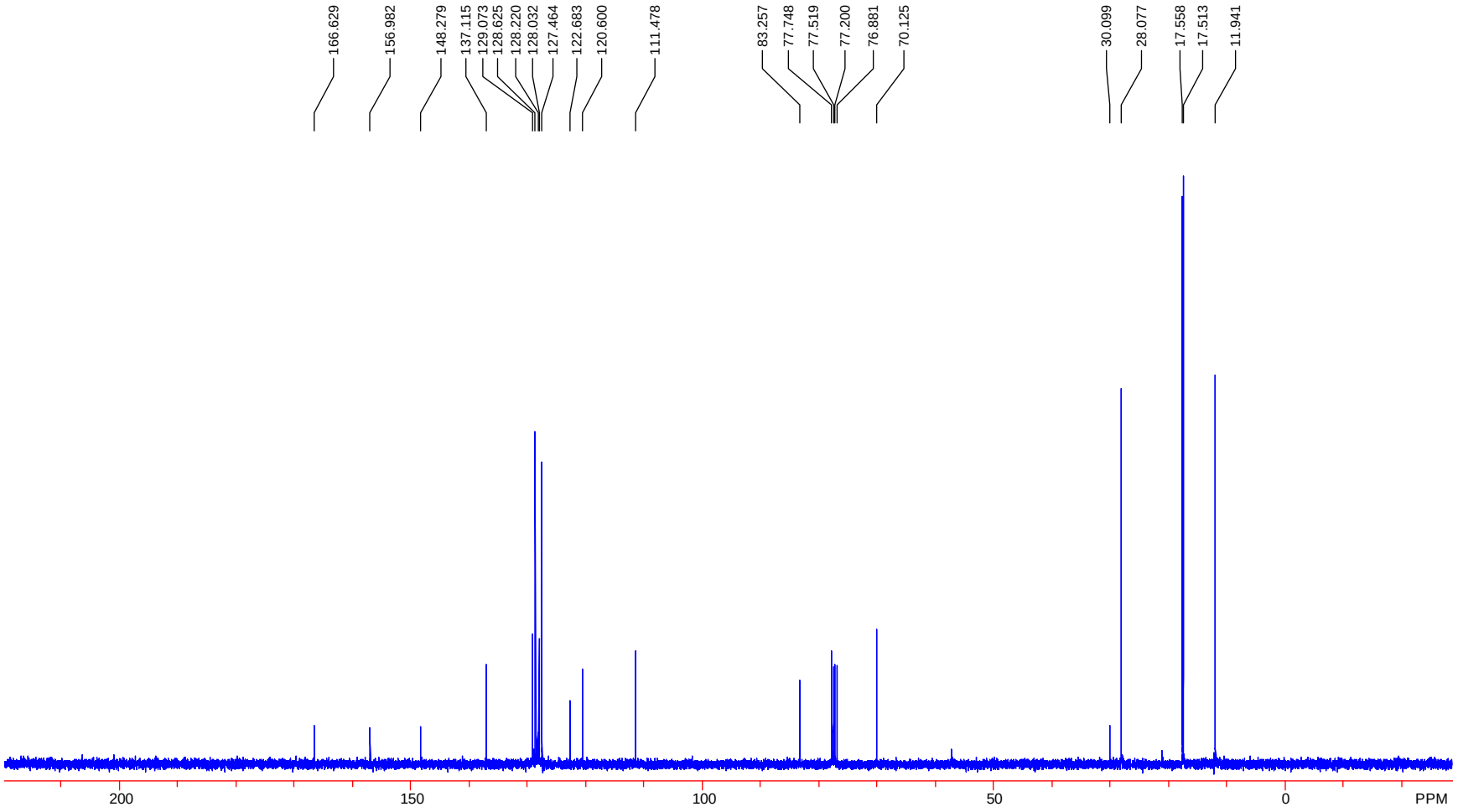
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77.519
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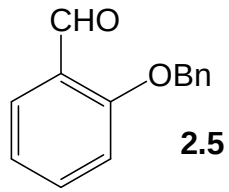

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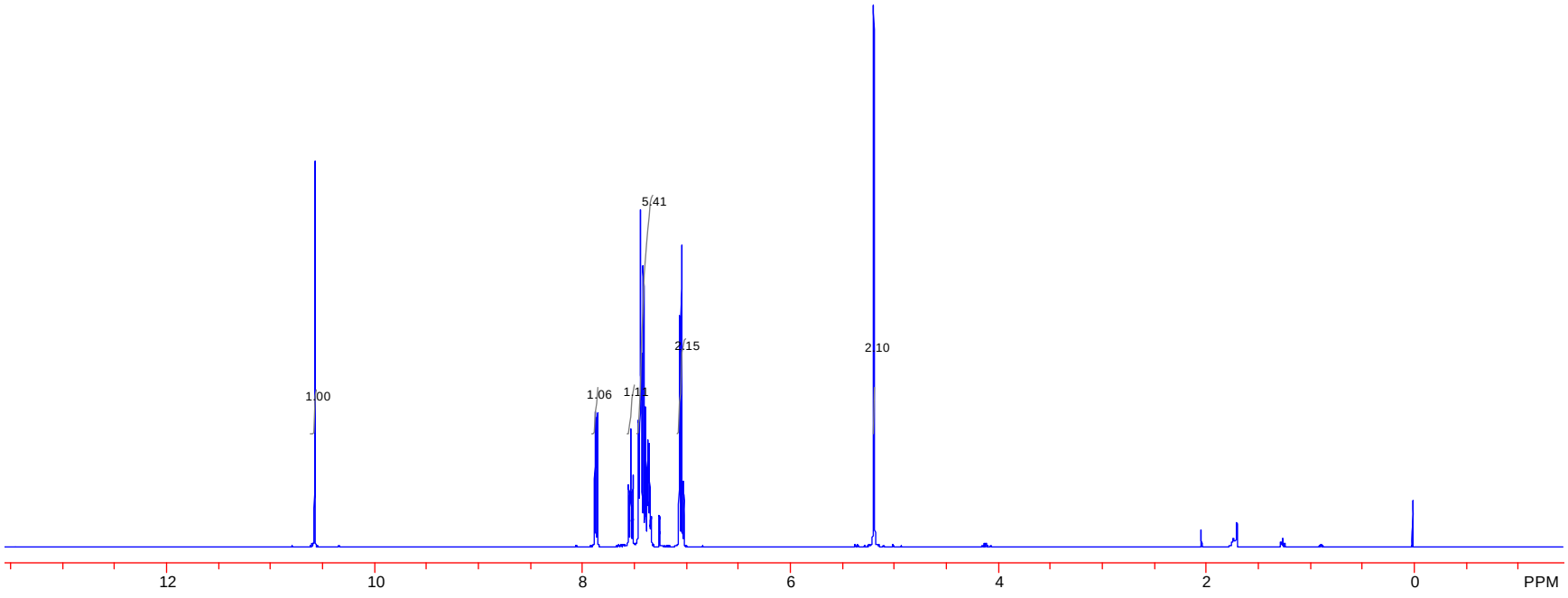

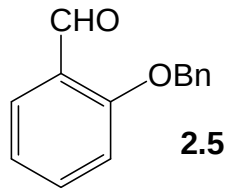
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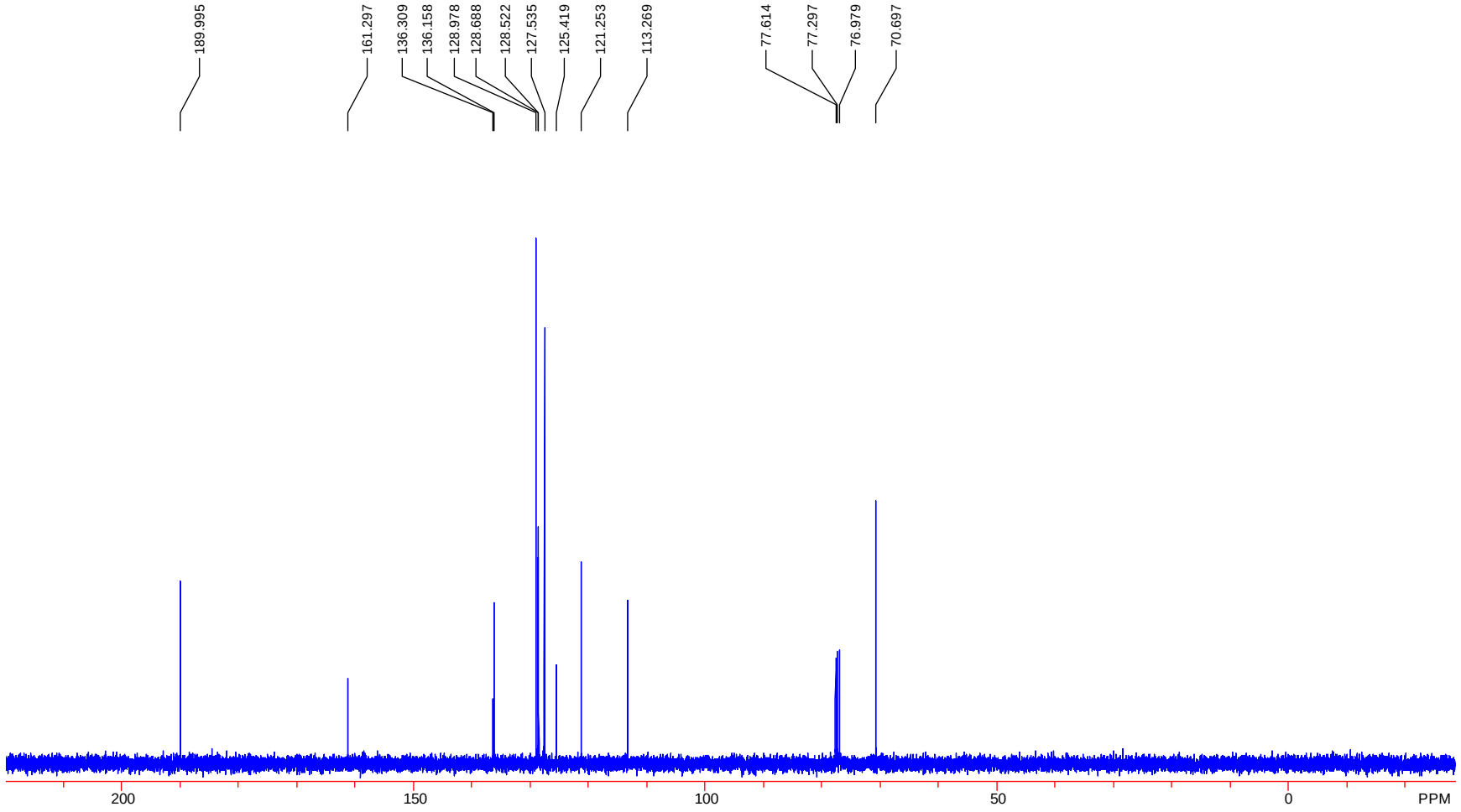
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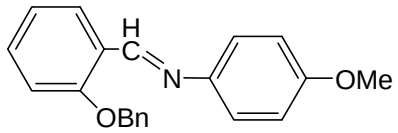

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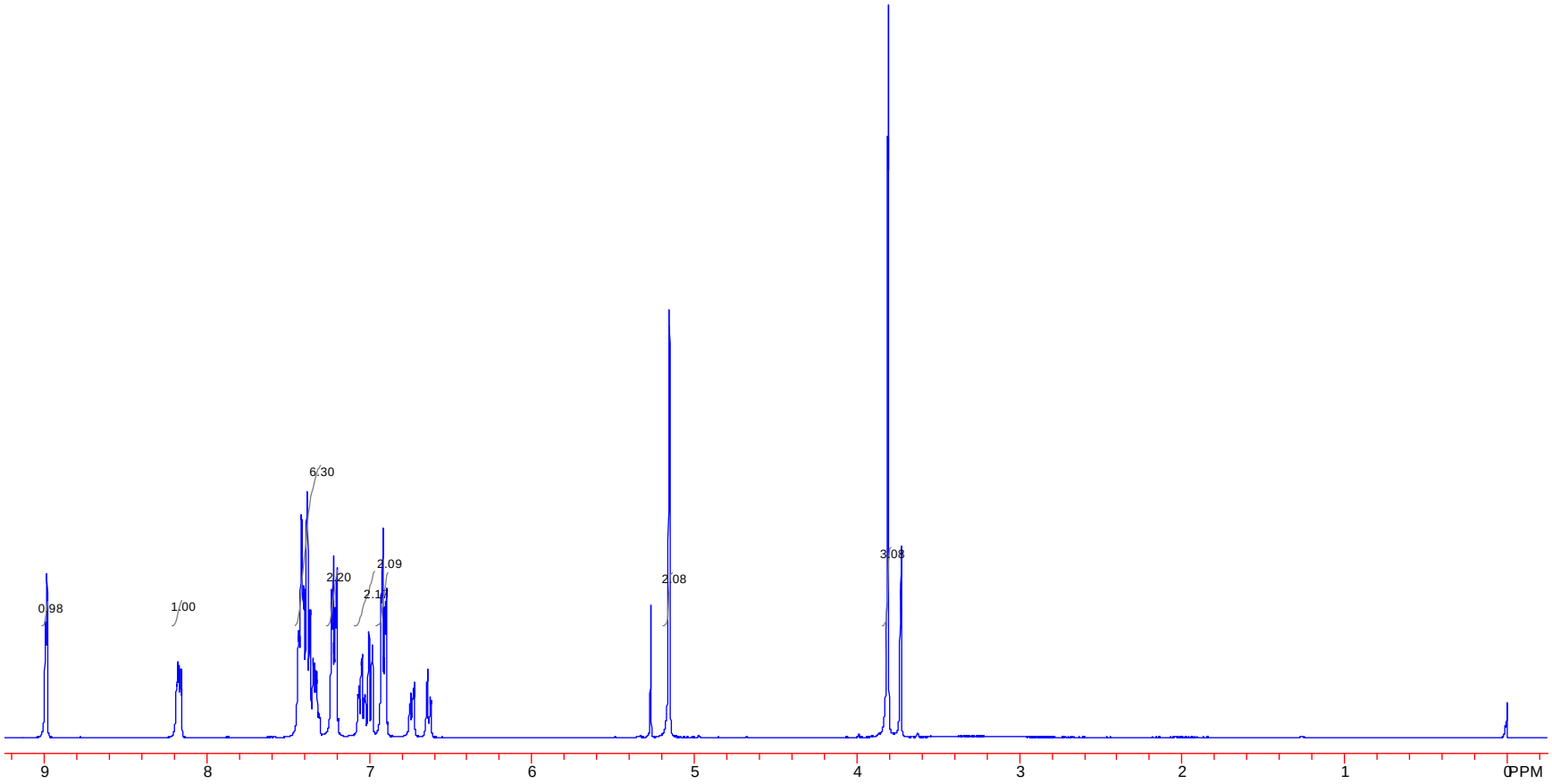

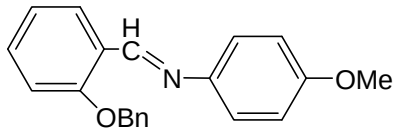
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OBn

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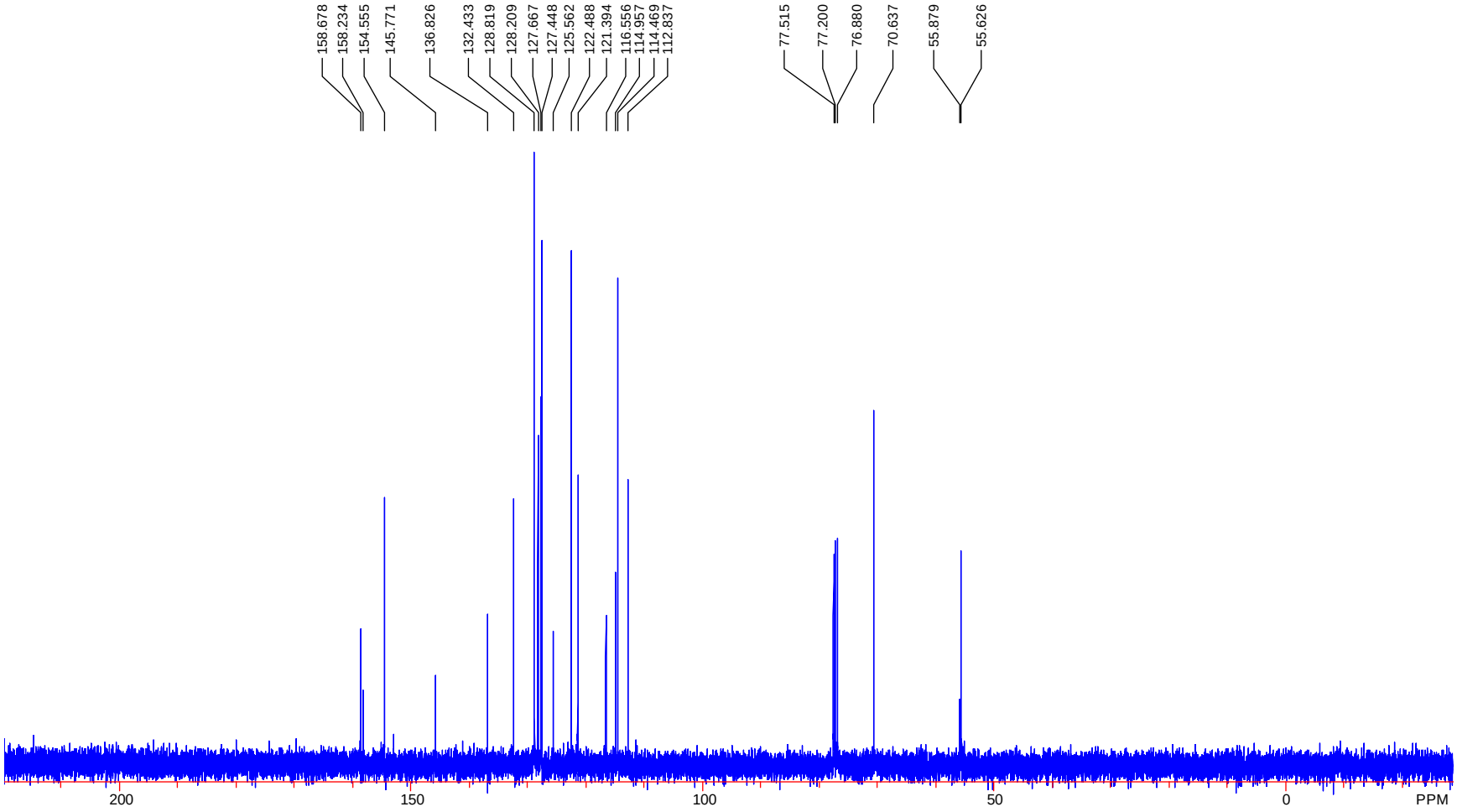
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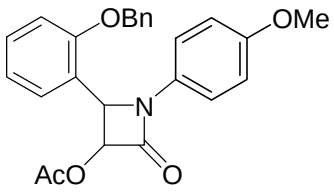
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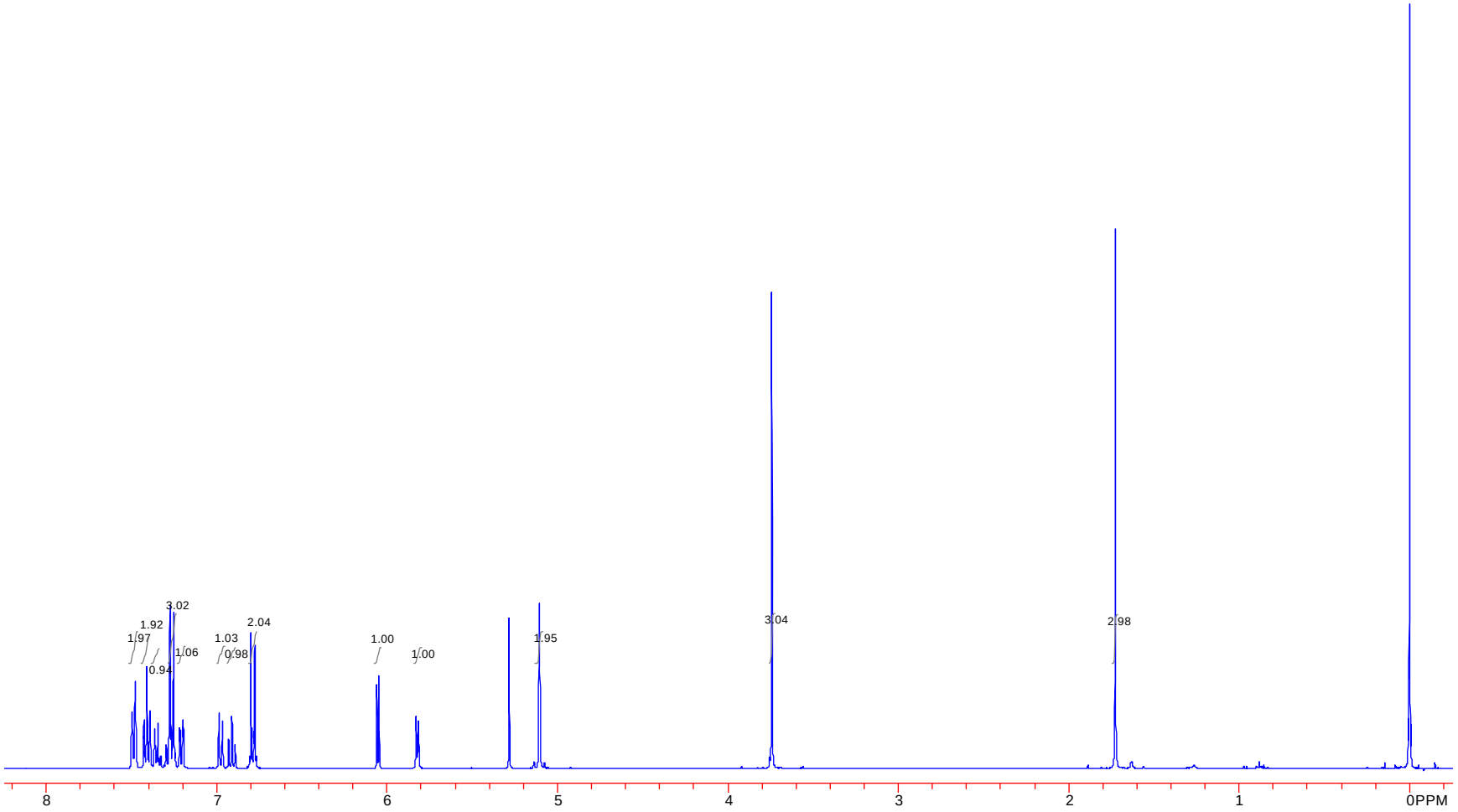
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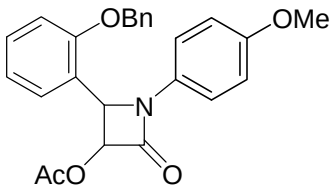
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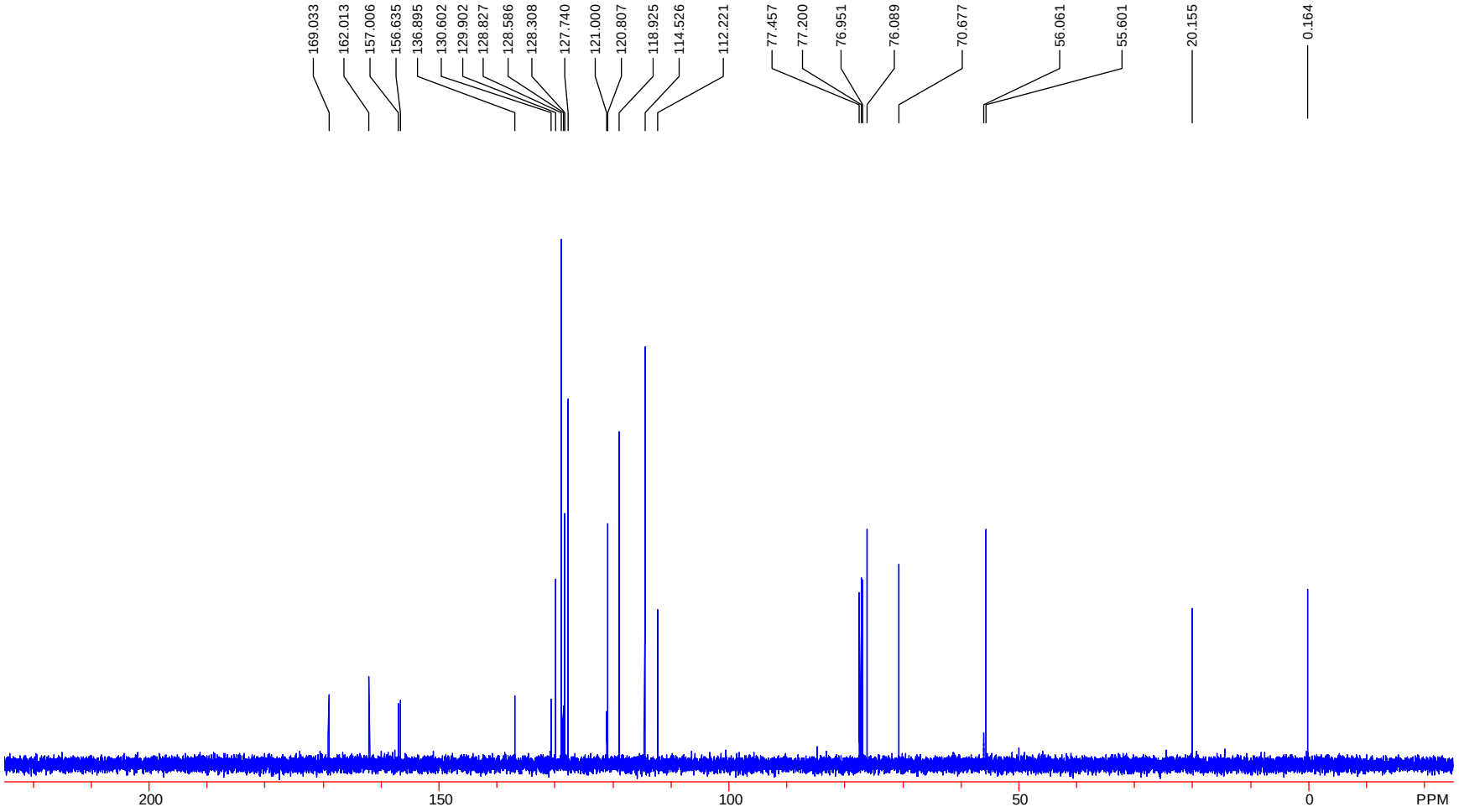
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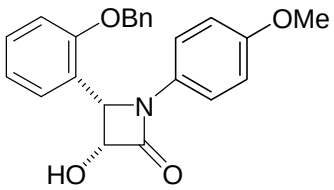

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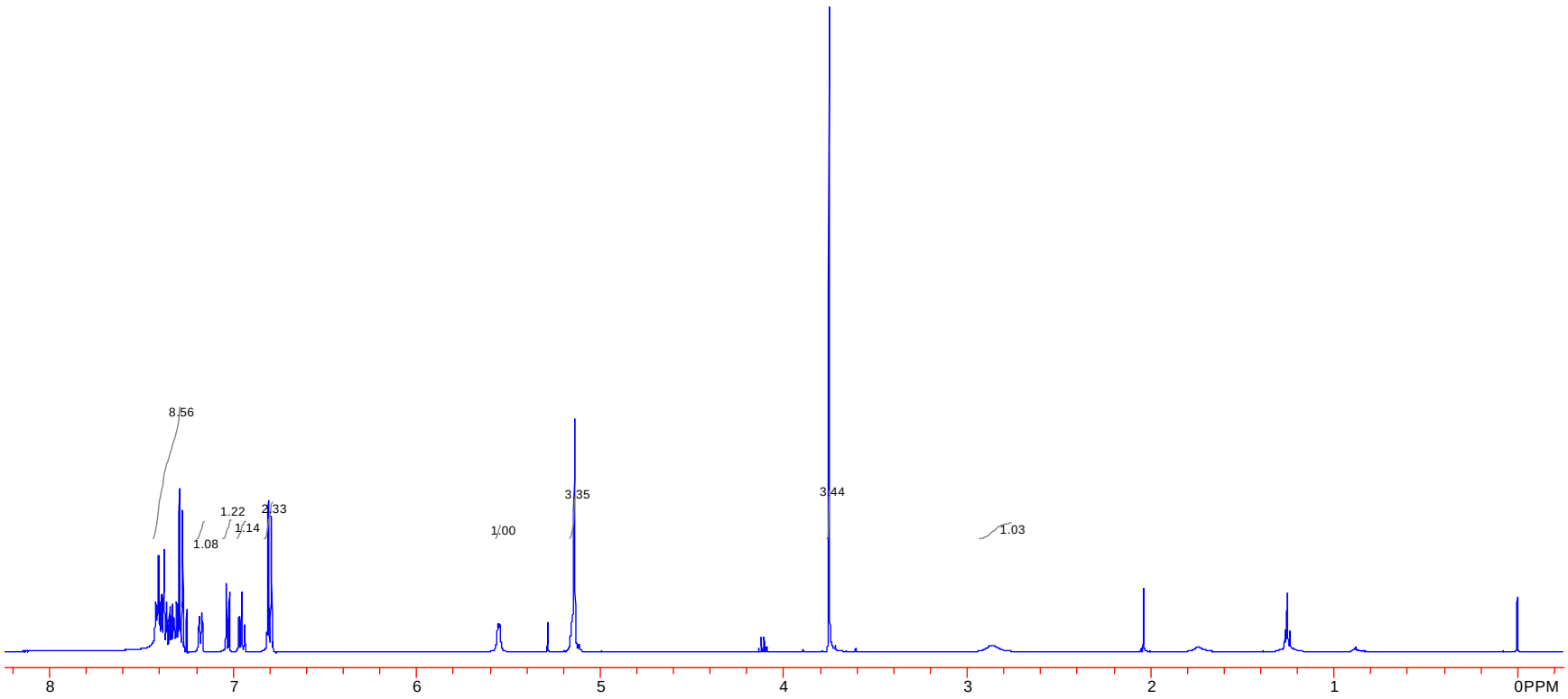

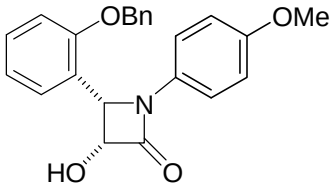
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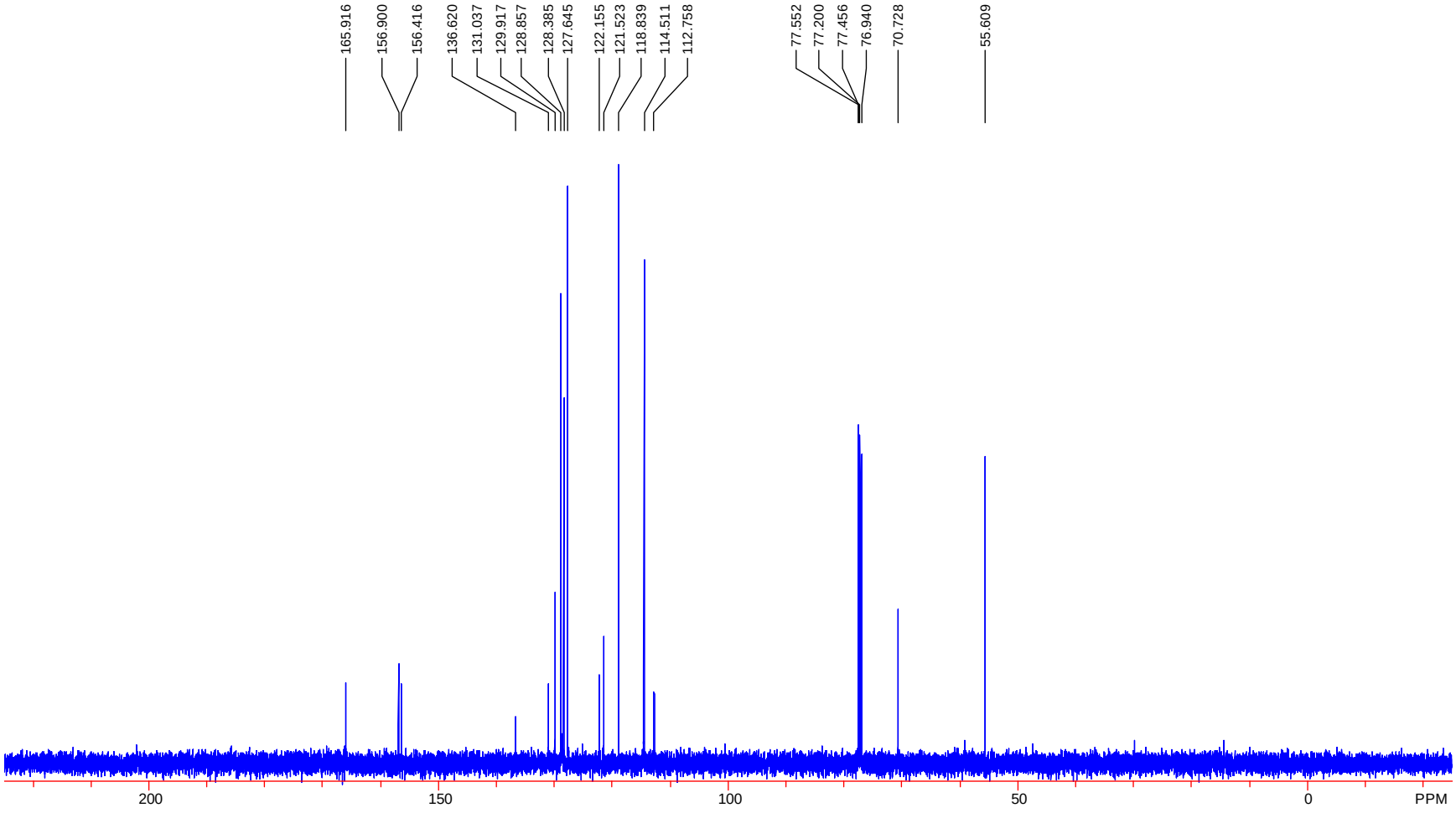
HO
O

2.8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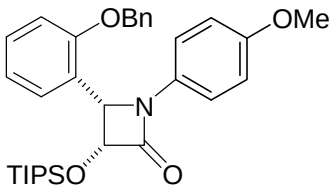
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O

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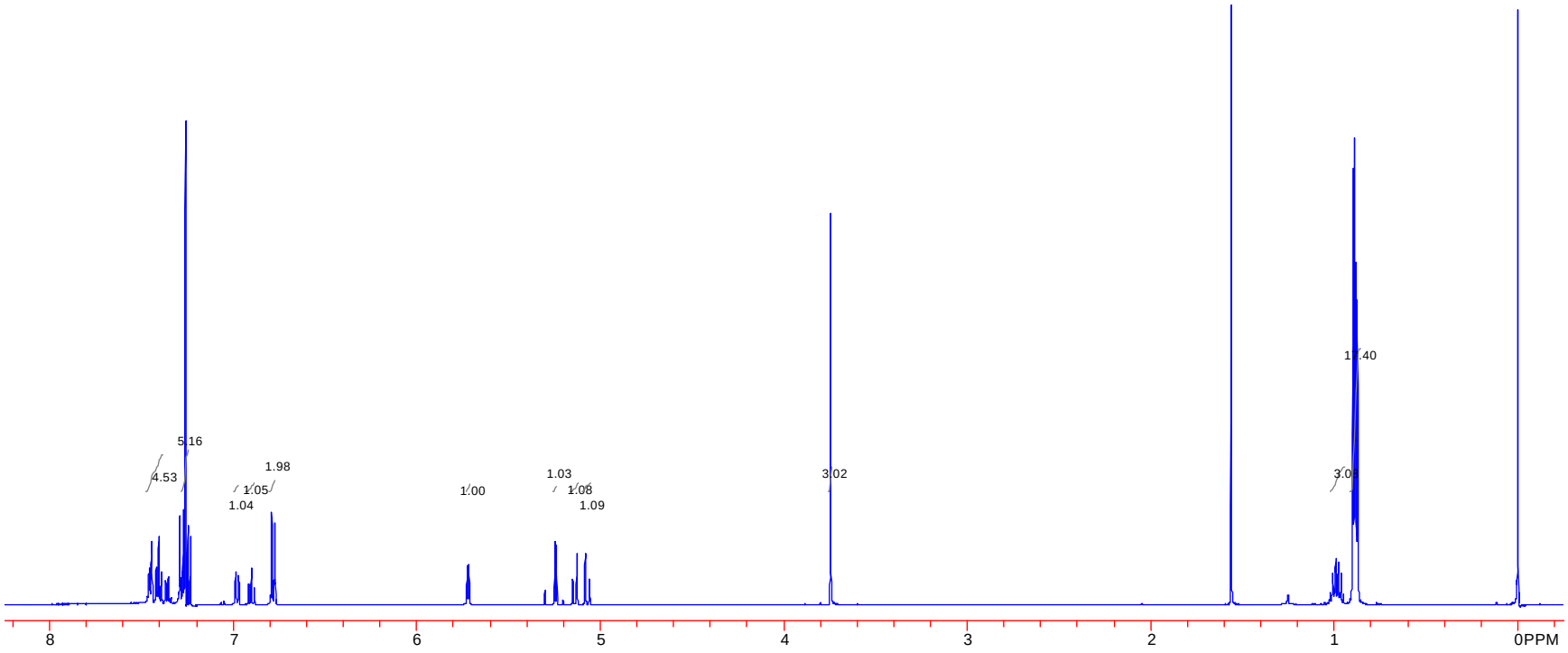
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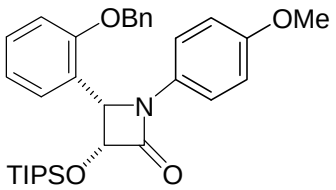
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TIPSO
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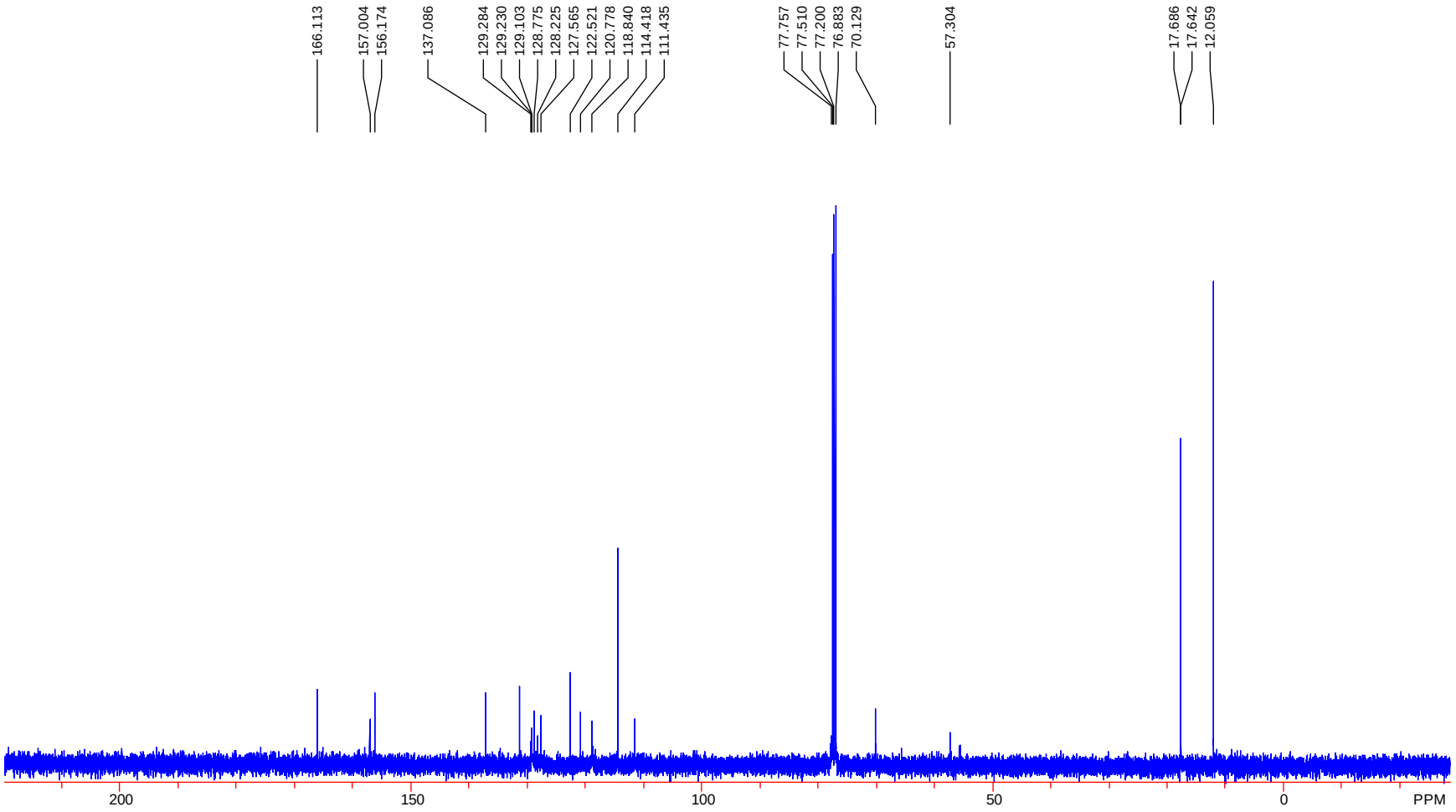
2.9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129.284
129.230
129.103
128.775
128.225
127.565
122.521
120.778
118.840
114.418
111.435
77.757
77.510
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76.883
70.129
57.304
17.686
17.642
12.059
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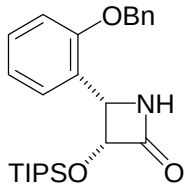
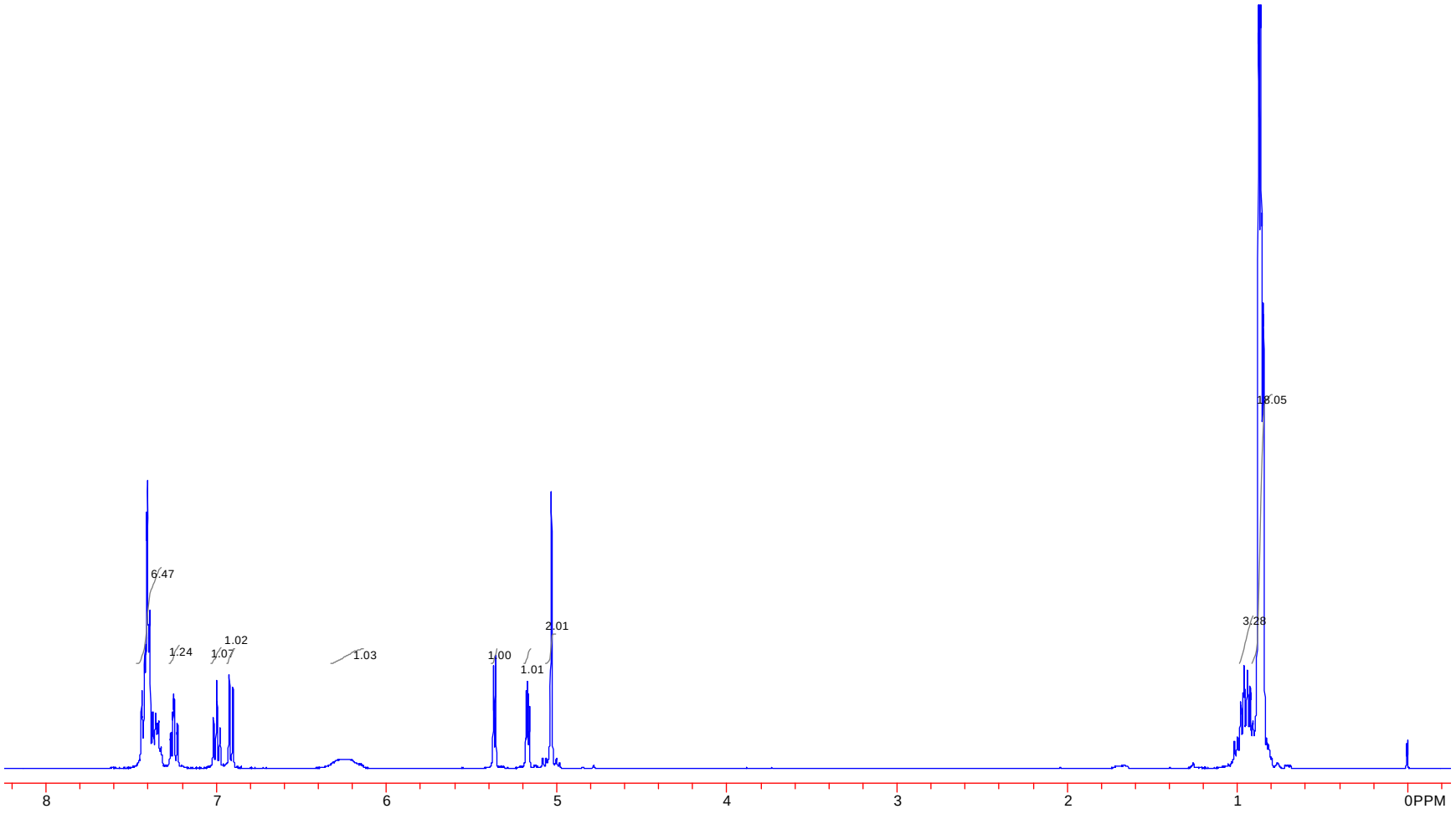
0
PPM


OBn
NH
TIPSO
O

2.10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1.07
1.02
1.03
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1.01
2.01
18.05
3.28
8
7
6
5
4
3
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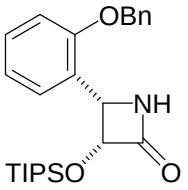
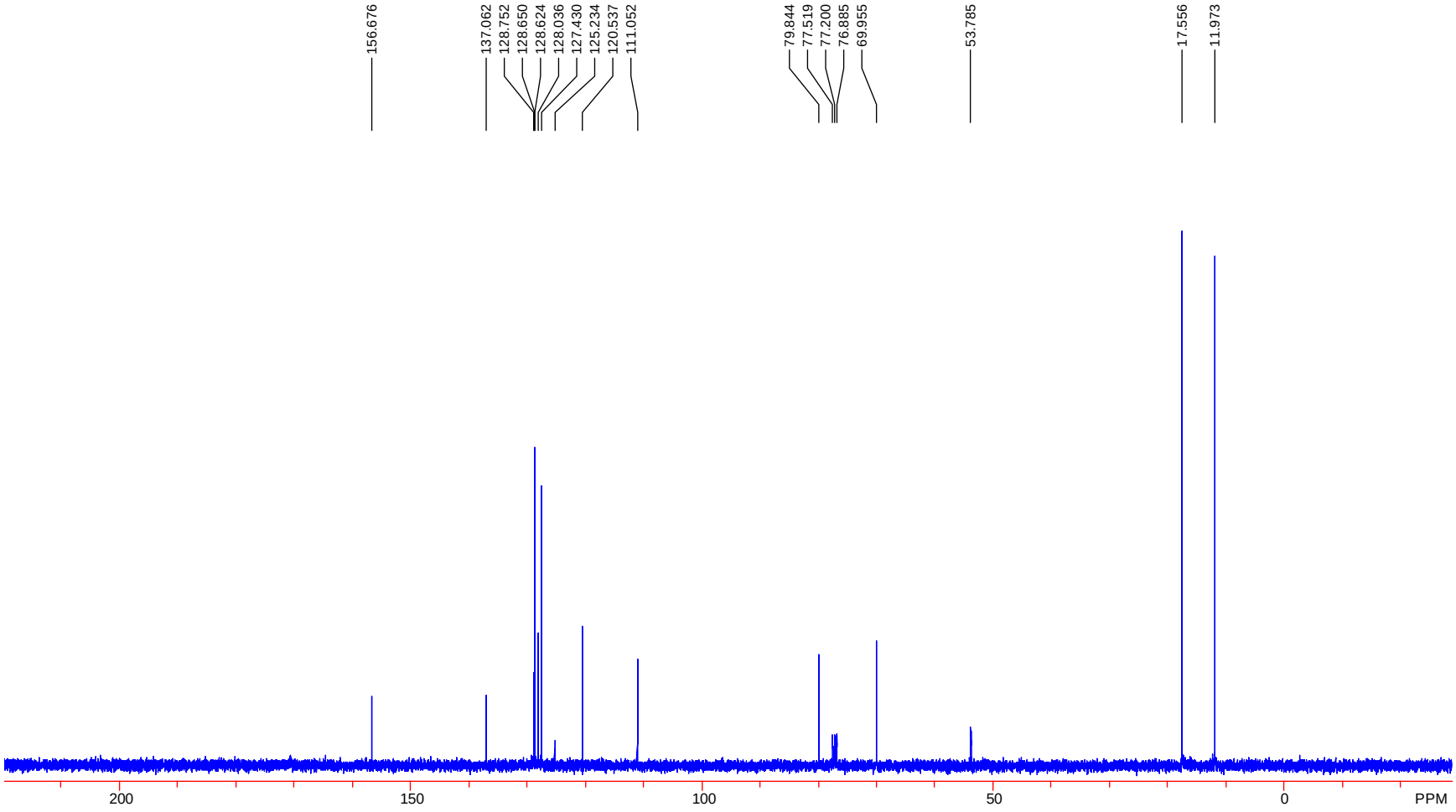
0PPM


OBn
NH
TIPSO
O

2.10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128.036
127.430
125.234
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111.052
79.844
77.519
77.200
76.885
69.955
53.785
17.556
11.973
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100
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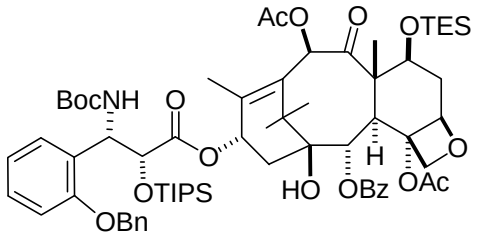
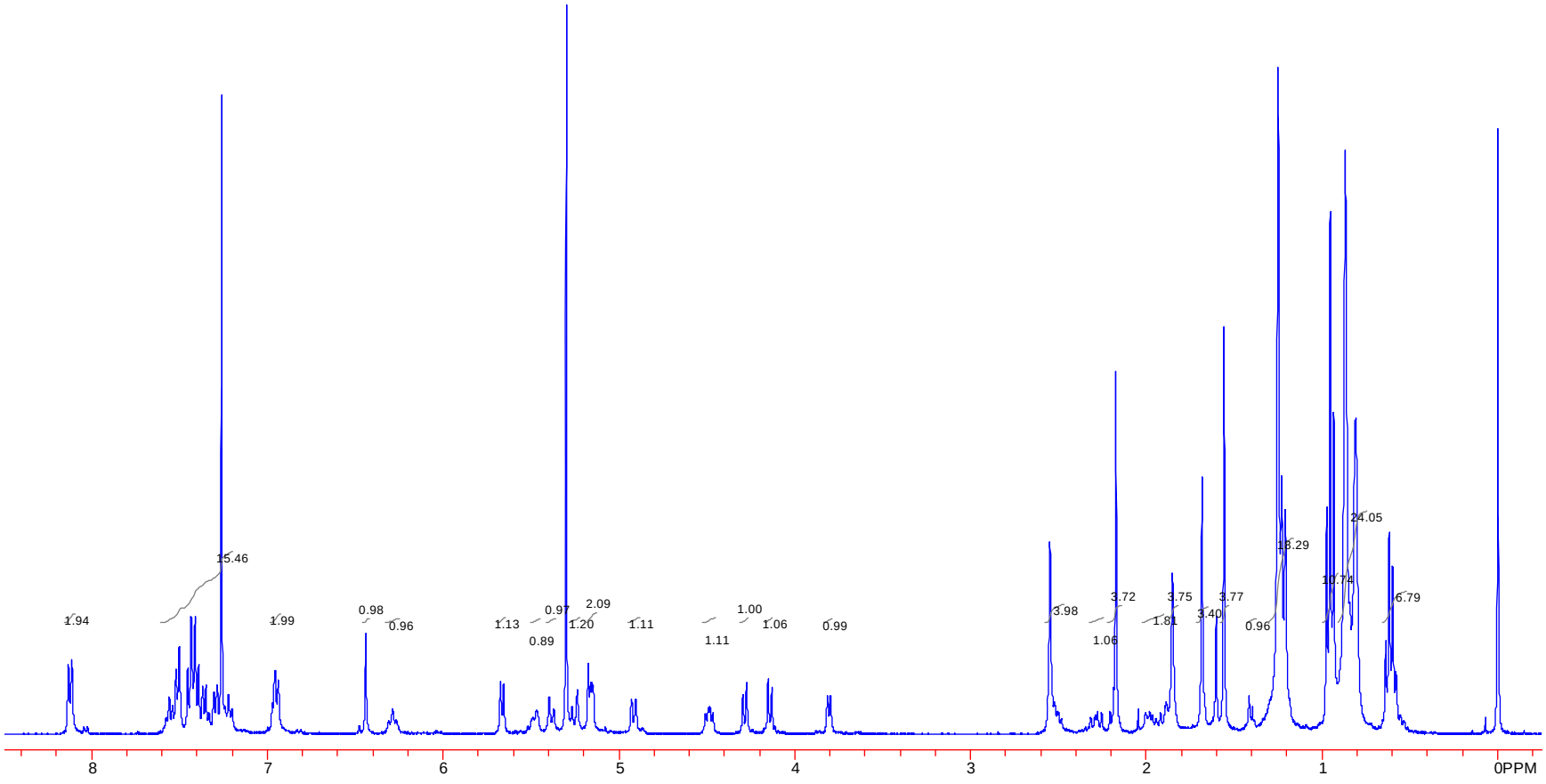
PPM


AcO
O
OTES
BocNH
O
O
H
O
OTIPS
HO
OBz
OAc
OBn

2.11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1.99
0.98
0.96
1.13
0.89
0.97
1.20
2.09
1.11
1.11
1.00
1.06
0.99
3.98
1.06
3.72
1.81
3.75
3.40
3.77
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13.29
10.74
24.05
6.79
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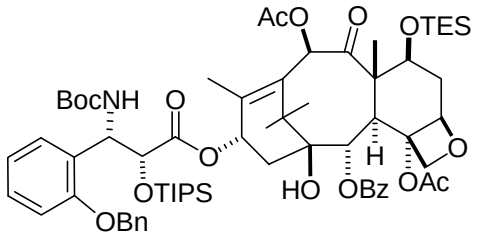
0PPM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OTES
BocNH
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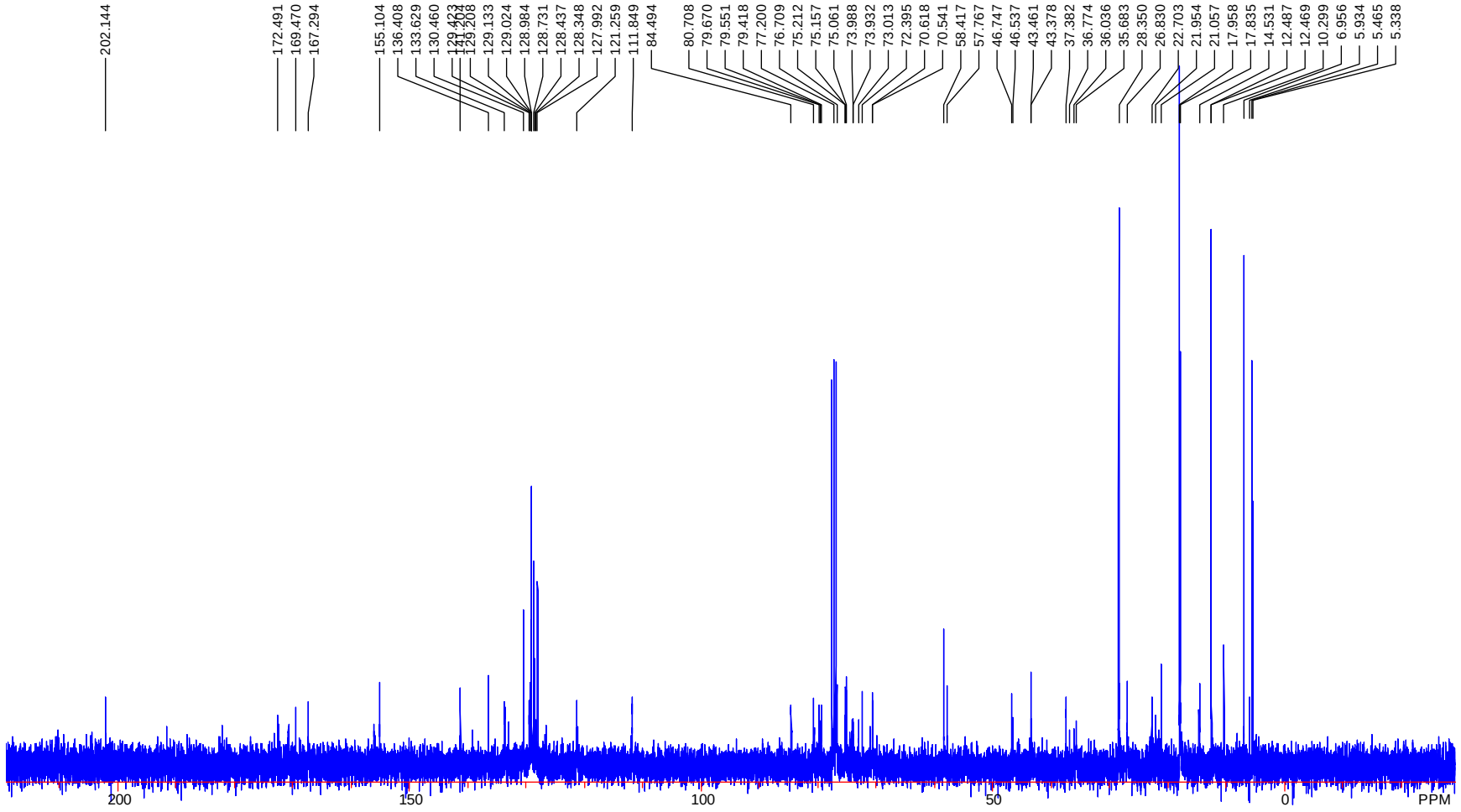
H
O
HO
OBz
OAc
OTIPS
OBn

2.11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129.133
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128.984
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128.437
128.348
127.992
121.259
111.849
84.494
80.708
79.670
79.551
79.418
77.200
76.709
75.212
75.157
75.061
73.988
73.932
73.013
72.395
70.618
70.541
58.417
57.767
46.747
46.537
43.461
43.378
37.382
36.774
36.036
35.683
28.350
26.830
22.703
21.954
21.057
17.958
17.835
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5.338
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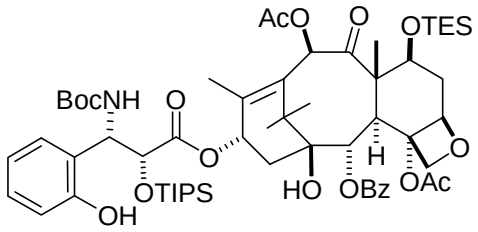
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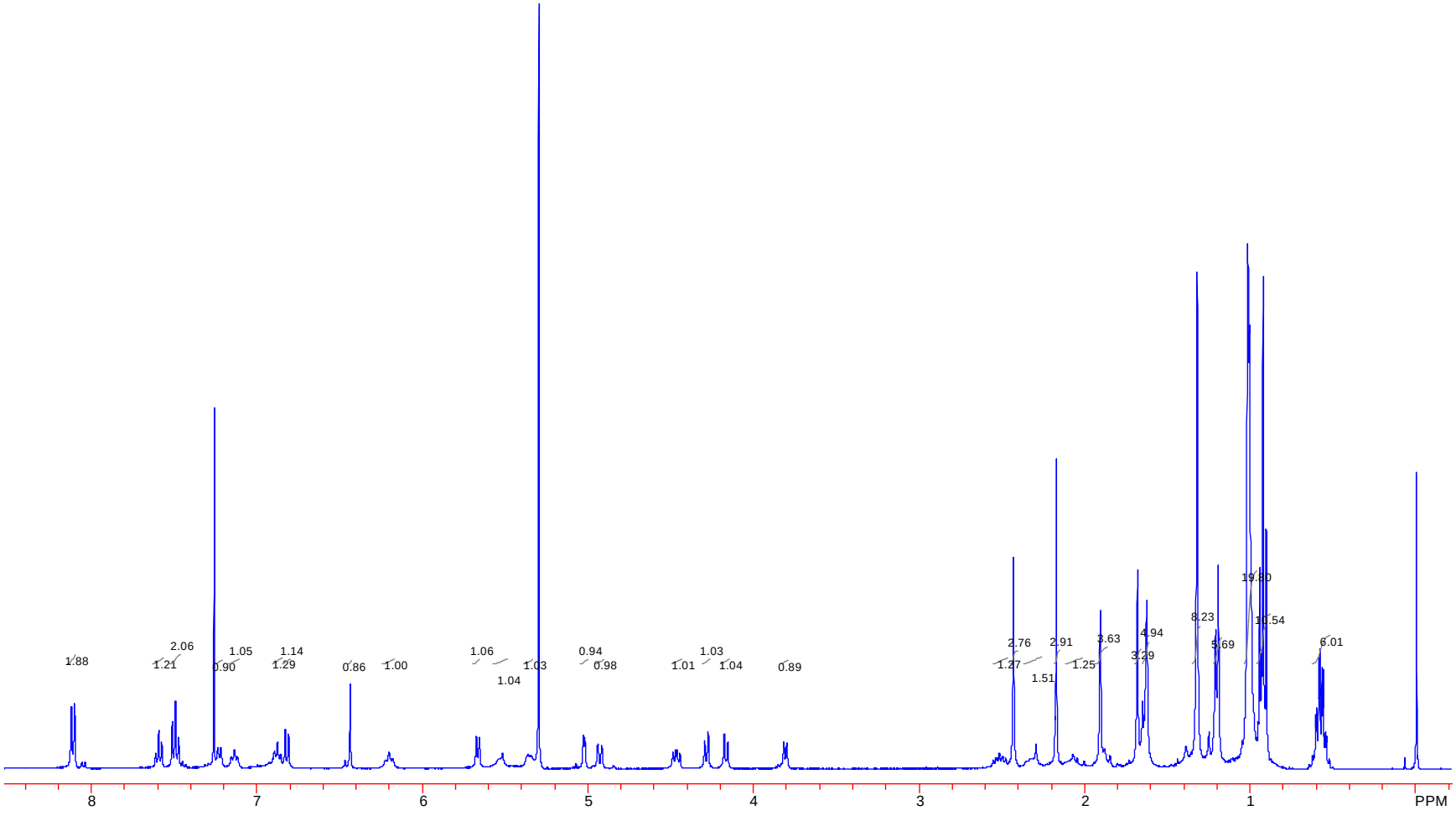
OTES
BocNH
O
O
H
O
OTIPS
HO
OBz
OAc
OH

2.12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1.21
1.05
0.90
1.14
1.29
0.86
1.00
1.06
1.04
1.03
0.94
0.98
1.01
1.03
1.04
0.89
2.76
1.27
2.91
1.51
2.63
1.25
4.94
3.29
8.23
5.69
19.80
10.54
6.01
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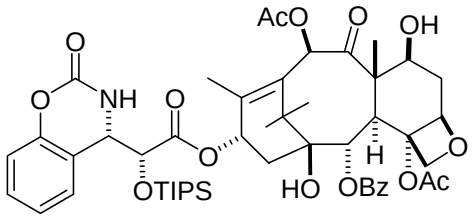
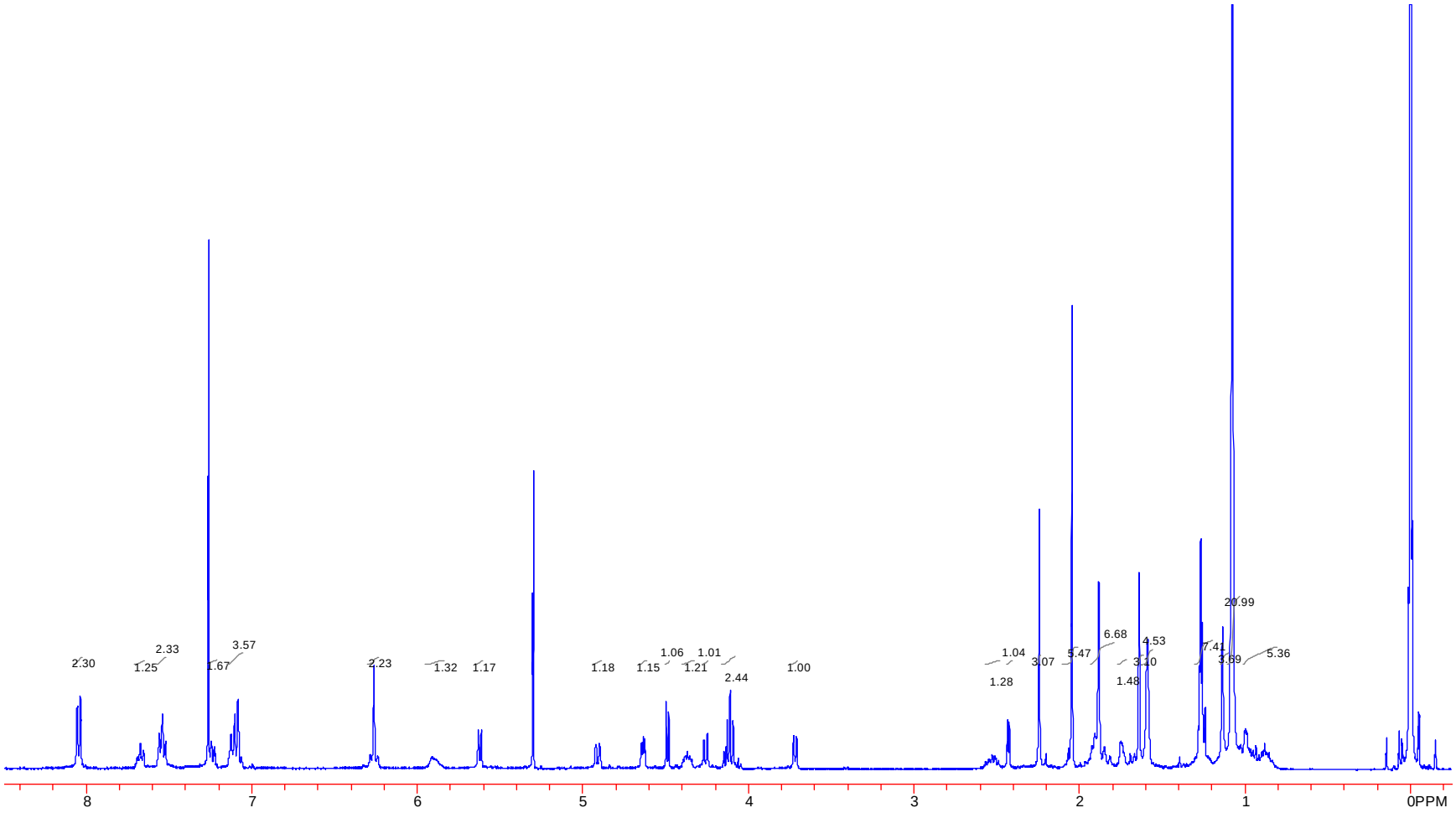
7
6
5
4
3
2
1
PPM


AcO
O
OH
O
NH
O
O
H
O
OTIPS
HO
OBz
OAc

2.13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3.57
2.23
1.32
1.17
1.18
1.15
1.06
1.01
1.21
2.44
1.00
1.28
1.04
3.07
5.47
6.68
1.48
4.53
3.10
7.41
3.89
20.99
5.36
8
7
6
5
4
3
2
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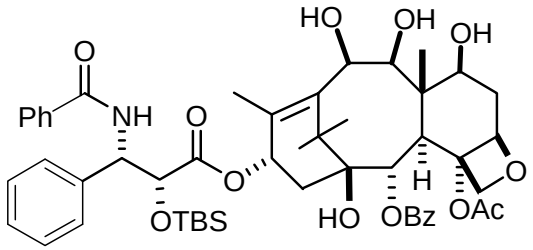
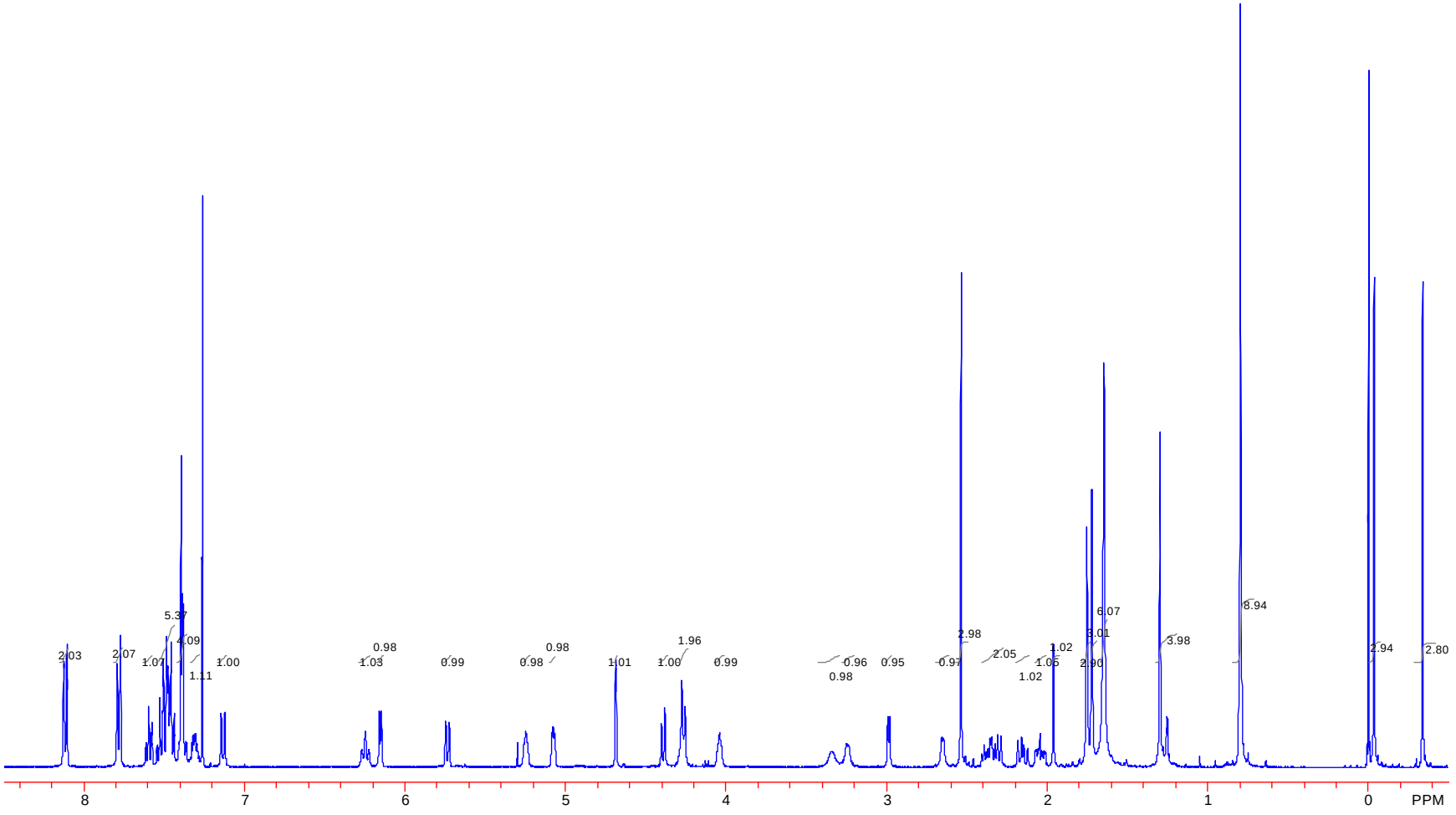
0PPM


HO
OH
OH
O
Ph
NH
O
O
O
H
OTBS
HO
OBz
OAc

3.19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2.07
1.07
5.37
1.09
1.11
1.00
0.98
1.03
0.99
0.98
0.98
1.01
1.96
1.00
0.99
0.96
0.98
0.95
0.97
2.98
2.05
1.02
1.05
1.02
6.07
3.01
2.90
3.98
6.94
2.94
2.80
8
7
6
5
4
3
2
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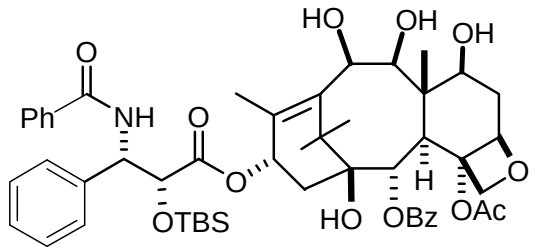
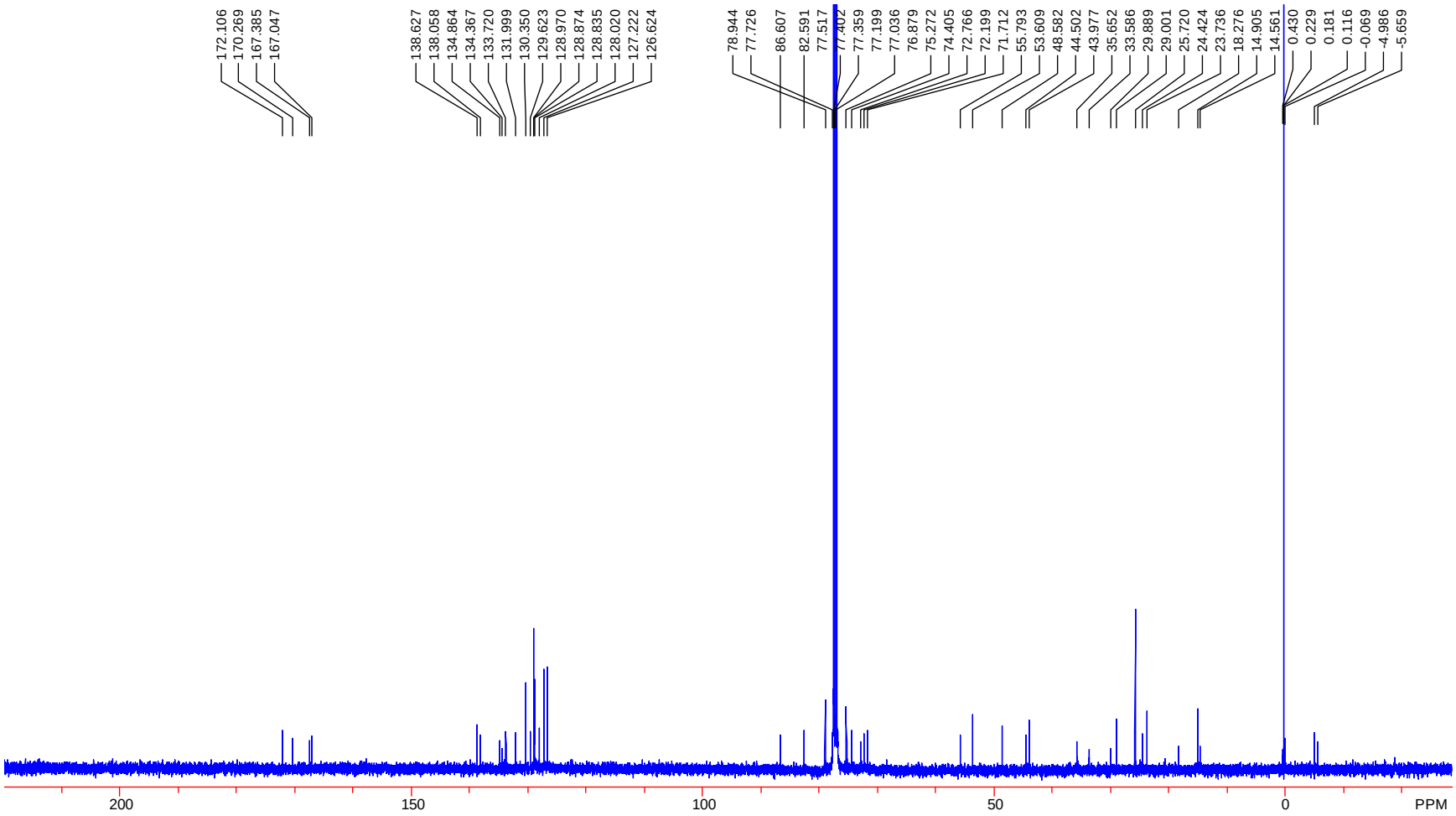
PPM


HO
OH
OH
O
Ph
NH
O
O
H
O
OTBS
HO
OBz
OAc

3.19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138.058
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134.367
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131.999
130.350
129.623
128.970
128.874
128.835
128.020
127.222
126.624
78.944
77.726
86.607
82.591
77.517
77.402
77.359
77.199
77.036
76.879
75.272
74.405
72.766
72.199
71.712
55.793
53.609
48.582
44.502
43.977
35.652
33.586
29.889
29.001
25.720
24.424
23.736
18.276
14.905
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0.181
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-5.659
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100
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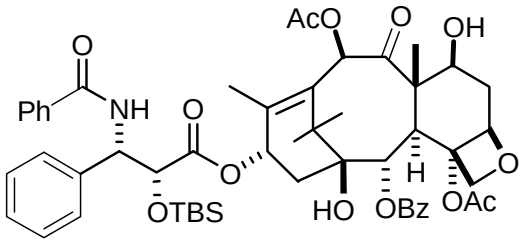
PPM


AcO
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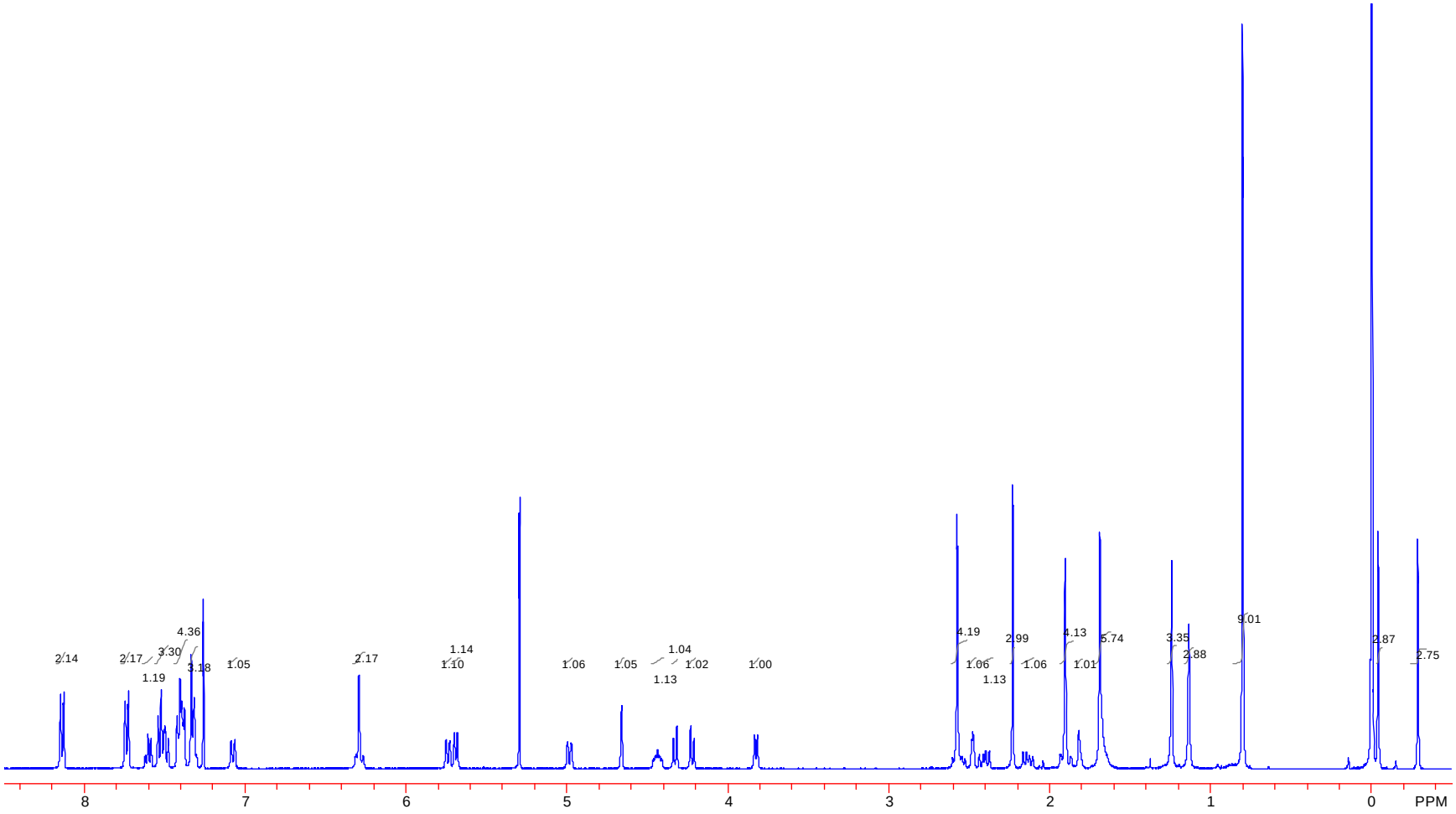
OH
O
Ph
NH
O
O
H
O
HO
OBz
OAc
OTBS

3.20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1.19
3.30
4.36
3.18
1.05
2.17
1.14
1.10
1.06
1.05
1.04
1.13
1.02
1.00
4.19
1.06
1.13
2.99
1.06
4.13
1.01
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9.01
2.87
2.75
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6
5
4
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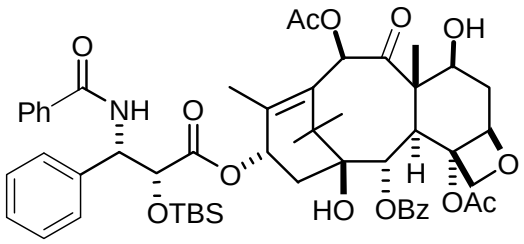
PPM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OH
O
Ph
NH
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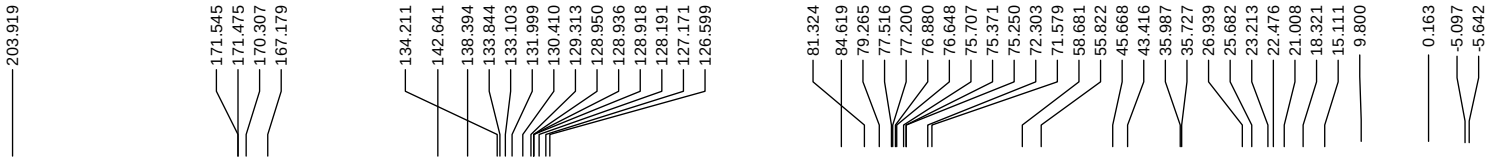
O
H
O
OTBS
HO
OBz
OAc

3.20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138.394
133.844
133.103
131.999
130.410
129.313
128.950
128.936
128.918
128.191
127.171
126.599
81.324
84.619
79.265
77.516
77.200
76.880
76.648
75.707
75.371
75.250
72.303
71.579
58.681
55.822
45.668
43.416
35.987
35.727
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21.008
18.321
15.111
9.800
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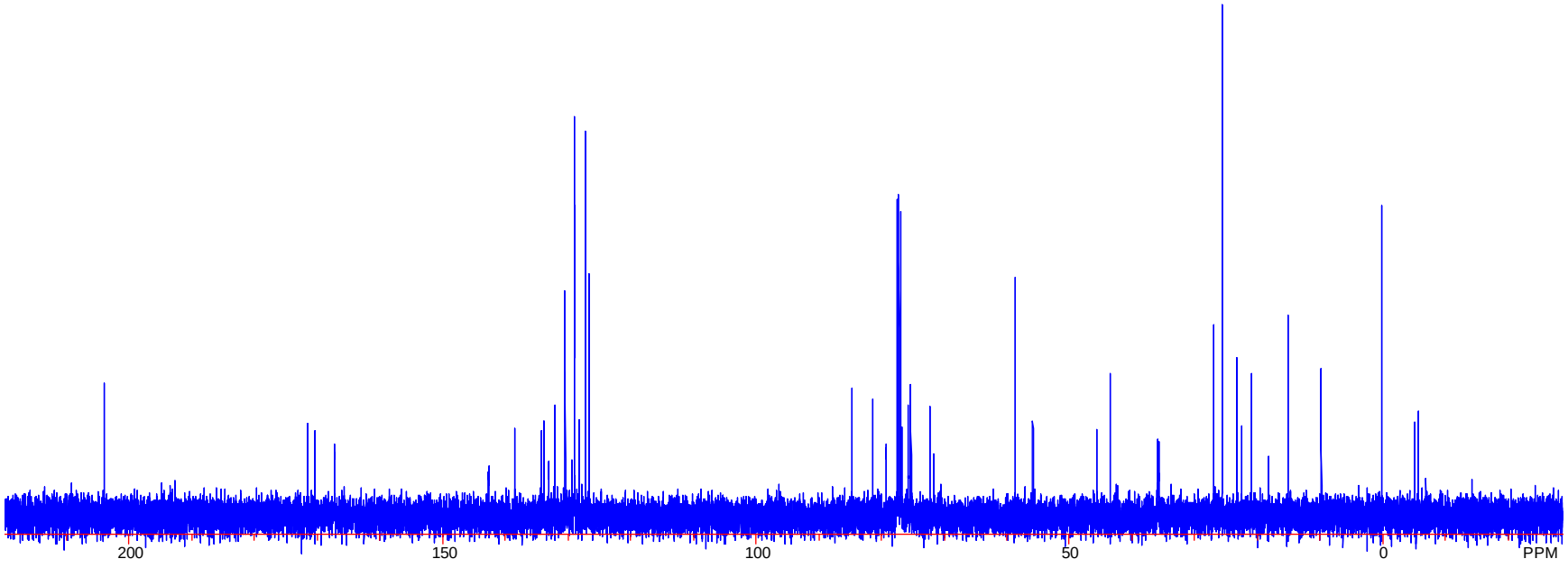
-5.097
-5.642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100
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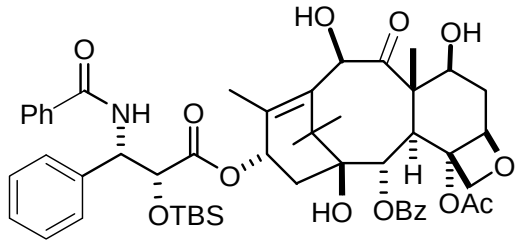
PPM


HO
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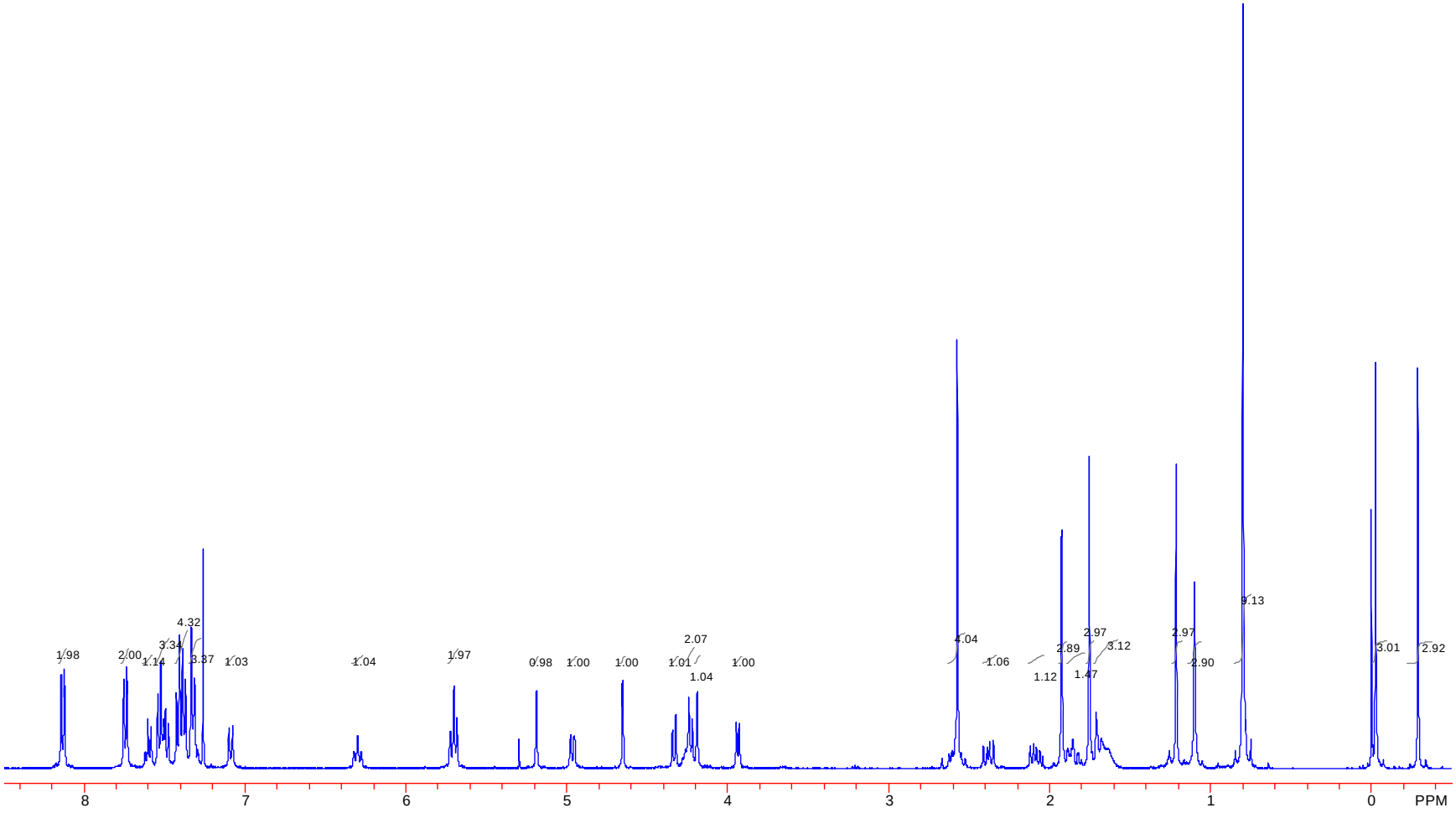
OH
O
Ph
NH
O
O
H
O
OTBS
HO
OBz
OAc

3.21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3.37
1.03
1.04
1.97
0.98
1.00
1.00
1.01
2.07
1.04
1.00
4.04
1.06
1.12
2.89
1.47
2.97
3.12
2.97
2.90
9.13
3.01
2.92
8
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6
5
4
3
2
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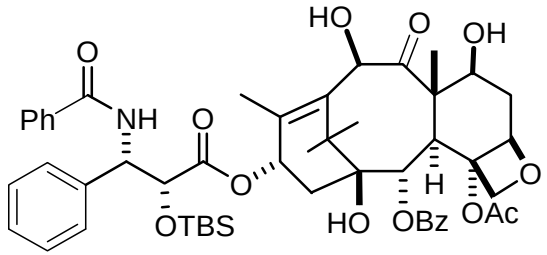
PPM


HO
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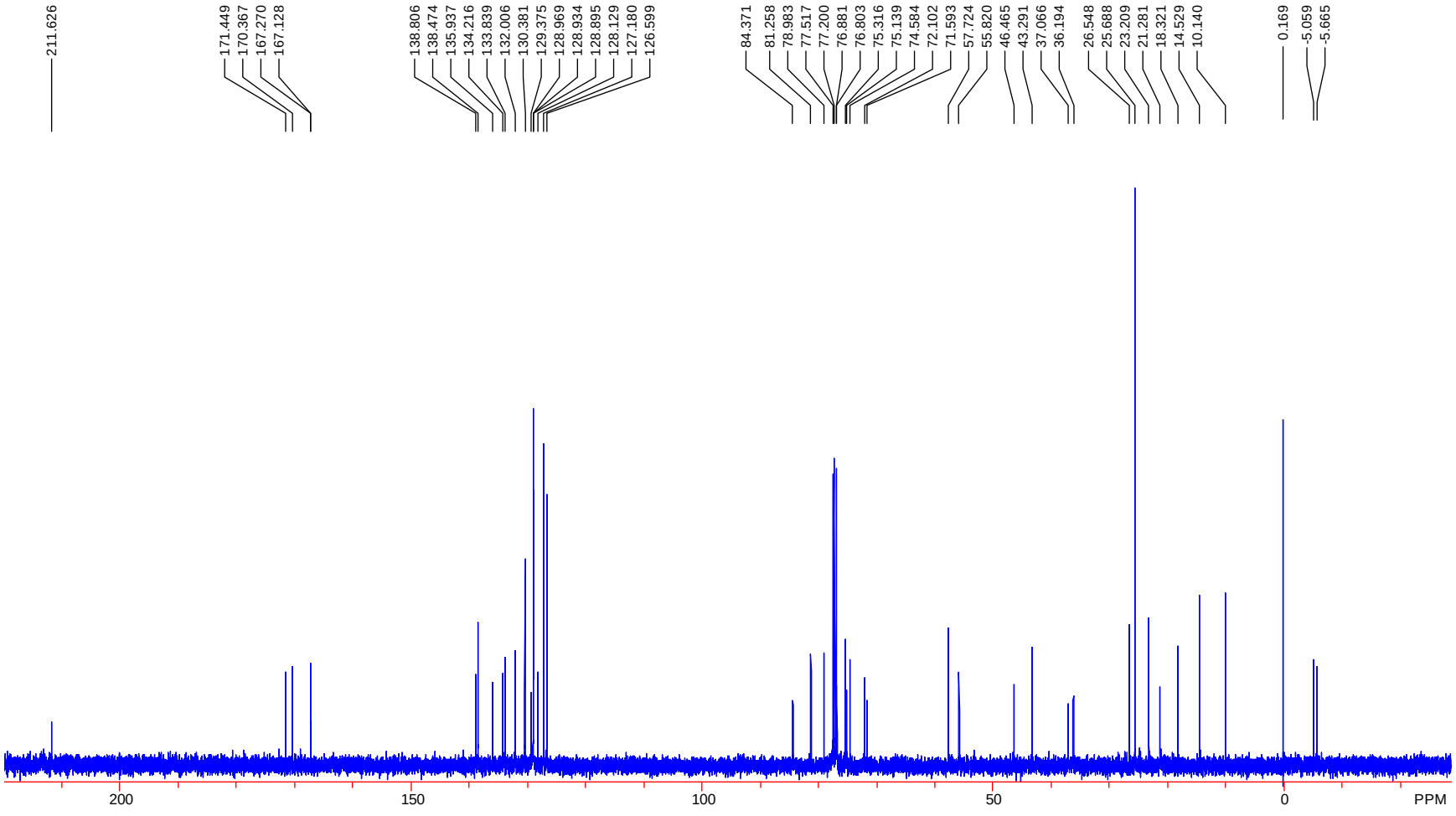
OH
O
Ph
NH
O
O
O
H
HO
OBz
OAc
OTBS

3.21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167.128
138.806
138.474
135.937
134.216
133.839
132.006
130.381
129.375
128.969
128.934
128.895
128.129
127.180
126.599
84.371
81.258
78.983
77.517
77.200
76.881
76.803
75.316
75.139
74.584
72.102
71.593
57.724
55.820
46.465
43.291
37.066
36.194
26.548
25.688
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21.281
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-5.059
-5.665
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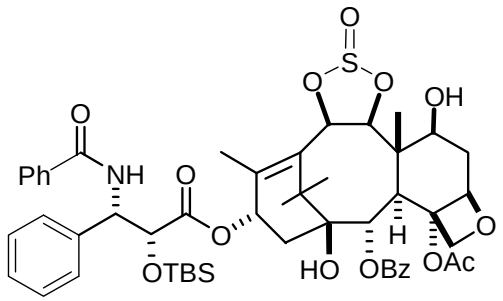
100
50
0
PPM


O
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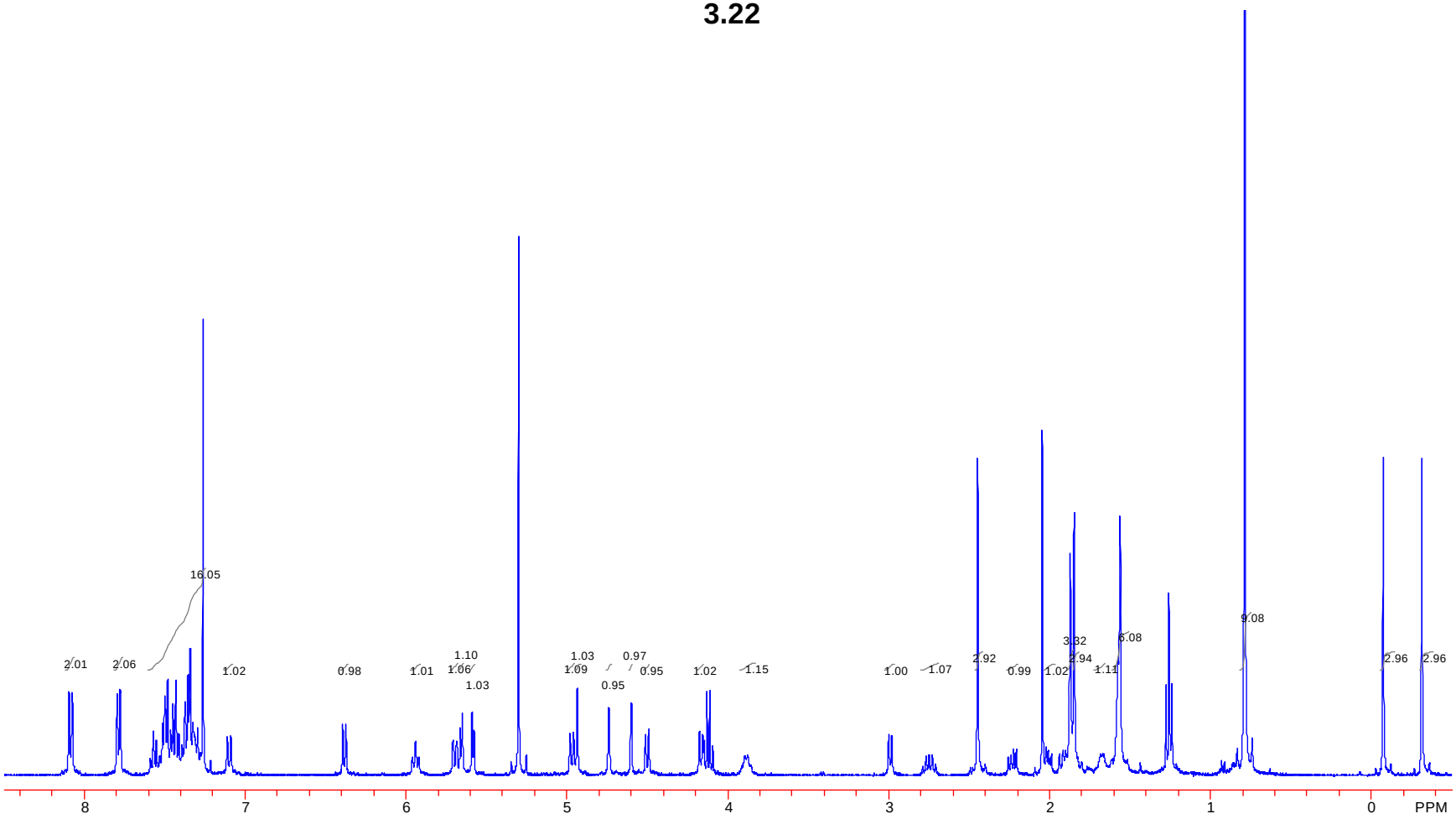
O
O
OH
O
Ph
NH
O
O
O
H
HO
OBz
OAc
OTBS

3.22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2.06
1.02
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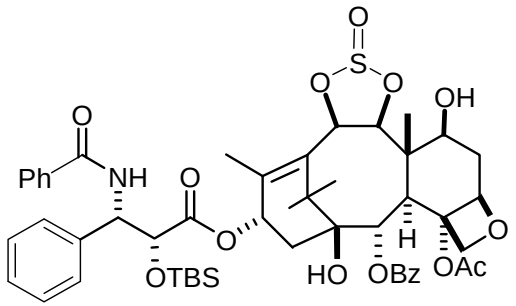
1.01
1.10
1.06
1.03
1.03
1.09
0.97
0.95
0.95
1.02
1.15
1.00
1.07
2.92
0.99
1.02
3.32
2.94
1.11
6.08
9.08
2.96
2.96
8
7
6
5
4
3
2
1
0
PPM


O
S
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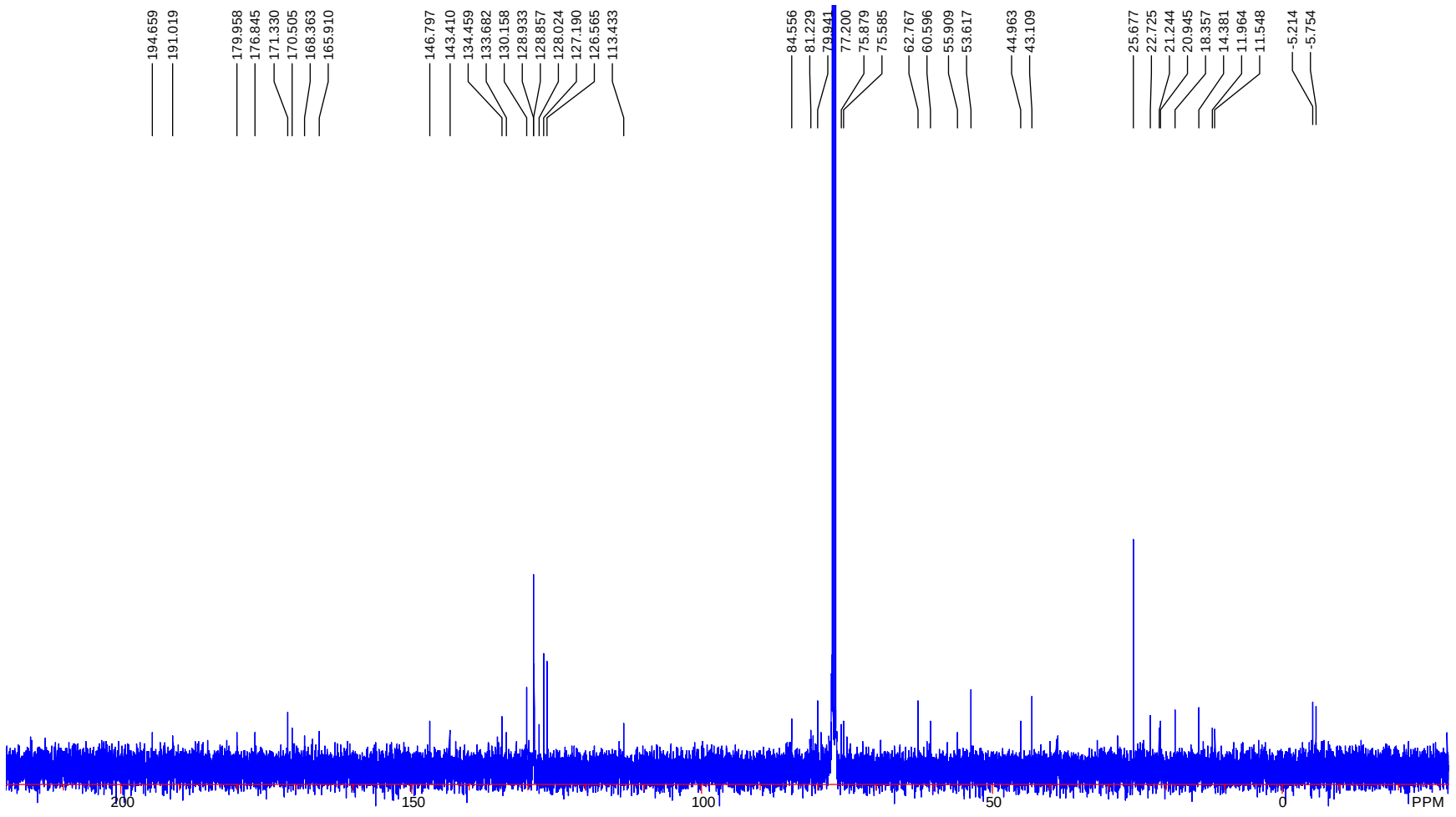
O
OH
O
Ph
NH
O
O
O
H
O
OTBS
HO
OBz
OAc

3.22


194.659
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179.958
176.845
171.330
170.505
168.363
165.910
146.797
143.410
134.459
133.682
130.158
128.933
128.857
128.024
127.190
126.565
113.433
84.556
81.229
79.941
77.200
75.879
75.585
62.767
60.596
55.909
53.617
44.963
43.109
25.677
22.725
21.244
20.945
18.357
14.381
11.964
11.548
-5.214
-5.754
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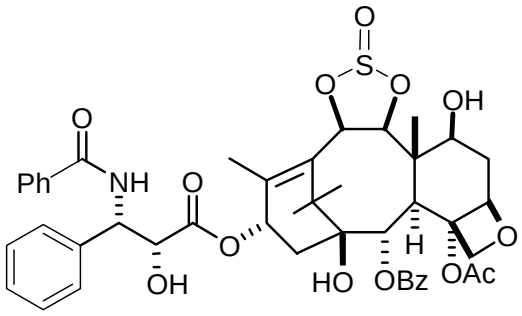
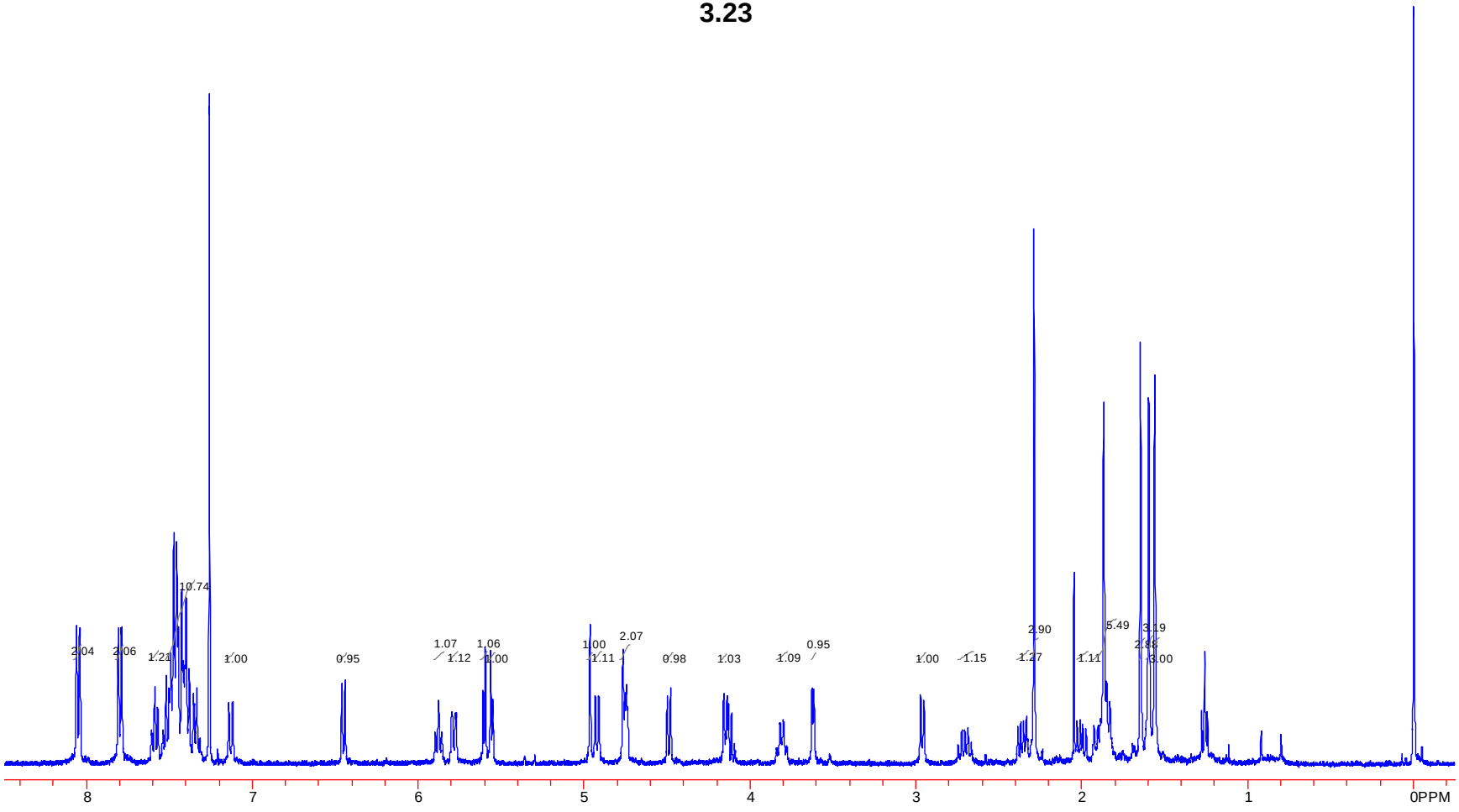
100
50
0
PPM


O
S
O
O
OH
O
Ph
NH
O
O
H
O
OH
HO
OBz
OAc

3.23


2.04
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0.95
1.07
1.12
1.06
1.00
1.00
1.11
2.07
0.98
1.03
1.09
0.95
1.00
1.15
1.27
2.90
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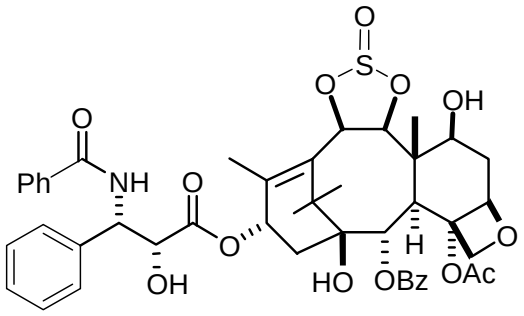
2.88
3.19
3.00
8
7
6
5
4
3
2
1
0PPM


O
S
O
O
OH
O
Ph
NH
O
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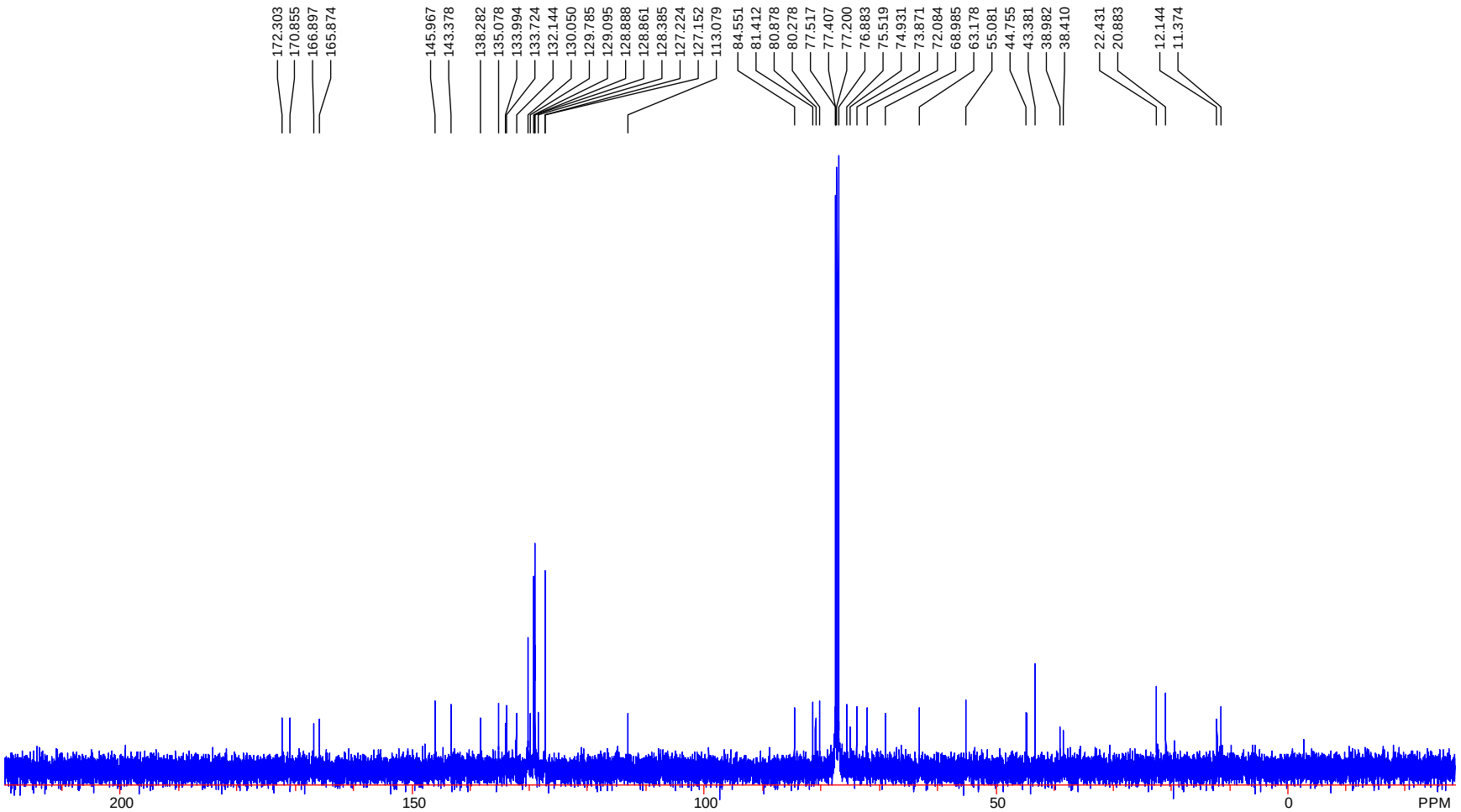
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… all you LORD Almighty …
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