Synthesis and Biological Evaluation of Paclitaxel Analogs

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ABSTRACT

The complex natural product paclitaxel (Taxol®), first isolated from *Taxus brevifolia*, is a member of a large family of taxane diterpenoids. Paclitaxel is extensively used for the treatment of solid tumors, particularly those of the breasts and ovaries. In order to obtain additional information about the mechanism of action of paclitaxel and the environment of the paclitaxel-binding site, several fluorescent analogs of paclitaxel were synthesized, and their biological activities have been evaluated. For the investigation of possible synergistic effects, concurrent modifications on selected positions have been performed and their biological evaluation were studied.

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To people and their families who live with cancer

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1. INTRODUCTION

1.1 Cancer: An Overview

Cancer is a group of diseases characterized by either uncontrolled cell proliferation or the failure of cells to die normally. Cancer can start in any organ of the body and may affect one of every two American men and one of every three American women at some point in their lives. This makes it the second leading cause of death after heart disease in the United States, with 560,000 mortalities every year.[1] Cancer occurs when cells act abnormally and keep dividing and forming new cells without any control or order. All organs of the body are made up of cells, which divide to form new ones when the body needs them. If cells divide when new ones are not needed, they form a mass of excess tissue, called a tumor. Tumors can be benign, not life-threatening; or malignant, cancerous. The cells in malignant tumors can damage and invade nearby tissues and organs, resulting in destruction. If malignancy was all that cancer was about, then it would be possible to cure it by surgery and radiation therapy. Unfortunately, cancer cells often break away from the malignant tumor and travel through the bloodstream to form new tumors in other parts of the body. This spreading of cancer, which is responsible for most of the mortality, is called metastasis.

There are more than 100 different varieties of cancer, which can be divided into six major categories. Carcinomas, the most common type of cancer, originate in tissues that cover a surface or line a cavity of the body. Sarcomas begin in tissue that connects, supports or surrounds other tissues and organs. Lymphomas are cancers of the lymph system, the circulatory system that bathes and cleanses the body's cells. Leukemias

[1] a) Ruddon, R. W. *Cancer Biology 3rd Edition*, Oxford University Press: New York, **1995** b) http://www.dfri.harvard.edu

involve blood-forming tissues and blood cells. As their name indicates, brain tumors are cancers that begin in the brain, and skin cancers, including dangerous melanomas, originate in the skin.*

The generation of cancer, carcinogenesis, is correlated with mutagenesis, a change in the sequence of DNA (deoxyribonucleic acid).[2] Cancer originates as a result of cancer causing agents, carcinogens, that damage DNA, the molecule that stores the genetic information in cells. Although some genetic mutations are harmless to cells, others kill them. When carcinogens cause mutations in genes that control cell growth, they may initiate cancer. Mutated genes leading to cancer are called oncogenes. Tumor suppressor genes, another class of genes, suppress cell growth and division unless mutations weaken or destroy their function. When carcinogens cause mutations, activating one or more oncogenes and deactivating one or more tumor suppressor genes, cancer starts. The speed of invasion of the body by cancer as a result of this depends on the potency of the carcinogen, the length of exposure to it, and the ability of the individual's body to repair the damaged DNA.[3]

Even though in the beginning of a new millenium accomplishments in science bring hope to our lives, the causes of cancer are still not clear. Generally cancer cannot be blamed on a single cause. It is well known that smoking tobacco products is a major factor. Diet, genetic mutation, exposure to ultraviolet (UV) light and carcinogenic chemicals may also cause cancer. Carcinogens may be chemical, physical or viral, and each works differently. Chemical carcinogenesis occurs when DNA is damaged following exposure to a chemical carcinogen. Some occupations like dye, chemical, leather and petroleum products manufacturing are at high risk of exposure to cancer-

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* Descriptions obtained from reference 1b

[2] Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K.; Watson, J. D. *Molecular Biology of The Cell 3rd Edition*, Garland Publishing: New York, **1994**

[3] Ward, D. E. *The Cancer Handbook: A Guide for the Nonspecialist,* Cushing-Malloy: Michigan, **1994**

causing chemicals. Dusts of substances like asbestos, zeolite, nickel and hardwood may also causecancer when inhaled for a certain amount of time. Tobacco is responsible for a significant portion of all cancers. Lung, mouth, throat, esophagus, pancreas, bladder and kidney cancers are all associated with tobacco usage. Alcohol users have an increased risk of getting mouth, pharynx, larynx, esophagus, and liver cancers. Chemical additives in food cause another high risk. Aromatic amines and polycyclic hydrocarbons formed by overcooking and charcoal grilling; aflatoxin B_1, a naturally occurring chemical found in some molds that grow on foods and peanuts; chemical species known as free radicals; and high-fat / low-fiber diets are all associated with damaging cells in ways leading to cancer. Atmospheric and water pollutants like aromatic hydrocarbons and chlorinated compounds are all linked to cancer. Physical carcinogenesis occurs when DNA is damaged by physical carcinogens. The most famous physical carcinogens are radiation and UV light. Long exposure to sunlight; x-rays; gamma rays; electron, proton, neutron beams and contact with radioactive materials are known to cause cancer. Radiation has both a direct and indirect damaging effect on DNA. Direct damage is when radiation breaks chemical bonds in DNA, causing a mutation; whereas indirect damage is when radiation breaks down other molecules in the cell, causing formation of free radicals, that can damage DNA.

Although they are implicated as a possible cause, viruses usually do not induce cancer by themselves. They are thought to contribute to the process at an early stage leading to cancer, which develops only after exposure to one or more cofactors. An example would be, the hepatitis B virus, which causes liver cancer along with aflatoxin and alcohol as cofactors. Viral carcinogenesis occurs when an oncogene of a virus is introduced into the DNA of the cell, or by insertion of its own genes into the host cell in a way disrupting the regulation of cell growth and division. Epstein-Barr virus (EBV), Hepatitis B virus (HBV), Human Immune Deficiency virus (HIV), Human Papillomaviruses (HPV), Human T-cell lymphotropic virus Type 1 (HTLV-1), Human T-cell lymphotropic virus Type 2 (HTLV-2), and Kaposi's-Sarcoma-Associated Herpesvirus (KSHP) are examples of viruses that may cause cancer.

Because most cancers develop late in life, it is considered a disease of aging. Increased life expectancy due to advancements in medicine makes it possible for people to "survive" until they get cancer. Industrialization and its effects on nature may be the cause of a serious number of cancer cases in the near future. With new technology, it is possible for high profit-seeking farmers to grow genetically engineered fruits, vegetables and grains. Although this type of food when consumed may not seem to be harmful on mankind today, no one can comment on how carcinogenic it will be on long exposure. Combining all these factors, along with new ones to come, makes cancer one of the deadliest diseases. Nearly 1.4 million new cases of cancer are diagnosed in the United States each year, a figure that does not include the 900,000 cases of skin cancer diagnosed annually.*

The best way to reduce mortality rates from cancer is to prevent it. Smokers can quit smoking; meat lovers can change their diet to diets low in fat, high in natural fiber and rich in fruits and vegetables; sunlight fans can reduce the time that they are exposed to UV light. Chemoprevention, on the other hand, is simply prevention with drugs. The number of potentially chemopreventive agents such as dietary supplements, hormones, vitamins, aspirin and other synthetic agents is increasing.[4] There is no guarantee, however, that preventive measures will eliminate the chance of getting cancer. Anybody, at any age, can be diagnosed with cancer. Following the diagnosis of cancer, the patient has to be treated in order to cure the disease or relieve its symptoms.

The oldest and the most common treatment of cancer is surgery. Reconstructive surgery is when a part of the body is replaced with another one. Hormone therapy, which is often used as a follow-up to surgery, is to prevent the supply of hormones needed for growth to cancer cells. Radiation therapy, which utilizes photon and particle beams to

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* Statistical information obtained from reference 1b

[4] Kelloff, G. J.; Charles, W. B.; Winfred, F. M.; Steele, V. E. in *Cancer Chemoprevention*, Wattenberg, L.; Lipkin, M.; Boone, C. W.; Kelloff, G. J.; Ed.; CRC Press: Florida, **1992**, 41-56

deliver ionizing radiation, is used in the treatment of more than half of the cancer cases. High energy x-rays are used to damage cancer cells and to stop them from growing and spreading. Radiation therapy can be used to shrink a tumor before surgery or it can be used after surgery. Like surgery, it is a local treatment, affecting only the cells in the treated area.[5]

The use of drugs to kill cancer cells is called chemotherapy. Unlike surgery and radiation therapy it is systemic, and works throughout the body. A single drug or a combination of drugs may be used. Chemotherapy is often used following surgery to kill any hidden cancer cells that remain in the body. Although synthetic and semisynthetic ones are known, a large portion of the chemotherapeutic agents on the market today have been isolated from nature.

[5]Breast Cancer Treatments, *St. Luke's Episcopal Hospital Homepage*, www.sleh.com/fact-c01-options.html

1.2 Natural Products in Cancer Chemotherapy

Chemotherapy is one of the most effective weapons in the fight against cancer. Most chemotherapeutic drugs are cytotoxic; they work by killing cells. The ideal drug of our dreams would be one that would selectively destroy the cancer cells, while not hurting or damaging the normal ones. So, *how does the drug differentiate between a cancer cell and a normal cell?* Reality is far from dreams. It is important to note that chemotherapeutic agents damage both normal cells and cancer cells, since cancer cells are only slightly different from normal cells at one point: they do not have any control on their growth and reproduction. Other than that, their biological behavior and chemical processes are almost the same. The whole idea of chemotherapy relies on a very narrow criterion. The drug has to be administered over a period of time, giving normal cells a chance to recover, while leaving the cancer cells dead. Ironically, cancer cells are not invaders from outer space, they are directly descended from one of the cells in the body. However, somewhere along the line, a normal cell turned into a killer. Cancer cells are found to be abnormally mutable, which also helps them to develop resistance to anticancer drugs. At the same time, defects of DNA metabolism with such mutability may cause cancer cells to be vulnerable to certain types of therapeutic attack. This may explain the observation that many tumor cells are destroyed more easily than normal ones.

Although chemotherapy is a powerful weapon against cancer, cytotoxic drugs also kill normal cells in the intestines, in hair follicles, and among blood cells in the bone marrow, causing side effects like nausea, vomiting, hair loss, diarrhea, and a drop in the number of white blood cells.

When designing a potential anticancer drug, it is important to understand the life of a cell, by studying the pathway it undergoes during its lifetime, the cell cycle (Figure 1).

Following cell division, a cell enters an inactive stage. During this passive period, it is not chemically getting ready for division.

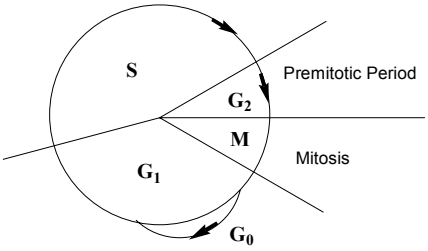

Figure 1 Life cycle of a cell.[6]

This phase is known as G_1, with subphase G_0, being total inactivity. DNA is synthesized in the next phase, known as S. Following the S phase, RNA (ribonucleic acid) and proteins of the cell are synthesized in the G_2 phase (synthesis of RNA also accomplished in G_1). The cell divides in the last phase, M, the mitotic phase, forming the daughter cells. The daughter cells then continue the cycle, by entering phases G_1-G_0.

Studying the cell cycle can provide information about the proportion of cells in each of these phases. For different types of cancers, approximations can be made, and drugs can be designed in a way to target the cells in each of these phases.

Most chemotherapeutic drugs fall into six classes based on their mechanism of action:

1. Alkylating Agents: They block DNA replication and cell division by preventing DNA from uncoiling, leading to cell death. Nitrogen mustards, aziridines, and esters of methanesulfonic acid are some examples.

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[6] Figure reproduced from Gringauz, A. *Introduction to Medicinal Chemistry: How Drugs Act and Why*, Wiley-VCH. Inc., New York, **1997**, p.103

2. Antimetabolites: They disrupt nucleic acid synthesis either by substituting for biosynthetic precursors of DNA/RNA or by inhibition of normal precursor biosynthesis. Some prevent DNA from replicating properly, thereby leading to cell death. These include folic acid antagonists, purine antagonists and pyrimidine antagonists.

3. Carcinolytic Antibiotics: They inhibit DNA and/or RNA synthesis by binding to DNA. Actinomycin (Cosmogen®) is useful for the treatment of Wilm's tumor in childrens' kidneys and for Ewing's and Kaposi's sarcoma. Mithramycin (Mithracin®) and Bleomycin (Blenoxane®) are other examples.

4. Hormonal Agents: Tumors of the ovary, breast and prostate are dependent on estrogen and/or androgenic hormones associated with them to a certain degree, due to the hormonal requirements of the tissues that they are made of.[6] The cancerous condition may be treated if the source of these hormones are minimized. Estrogenic and androgenic compounds, and recently antiestrogens are used for hormonal therapy. It is advantageous that toxicities and mortalities witnessed with the alkylating agents, antimetabolites and cytotoxic antibiotics are not seen with this type of drugs, since their mechanism is hormonal.

5. Mitotic Inhibitors: They inhibit cell division by preventing formation of the microtubules critical to mitosis. Examples include plant alkaloids such as vincristine (Oncovin®) isolated from periwinkle (*Catharanthus roseus*). This is an antimitotic agent and is used in combination with other agents for the treatment of a wide variety of cancers, including leukemia, bladder cancer, testicular cancer,[7] and lymphomas such as Hodgkin's disease.[8] Teniposide (Vumon®), a chemical analog of the natural product

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[7] Neuss, N.; Neuss, M. N. Therapeutic Use of Bisindole Alkaloids from Ctaharanthus' in *The Alkaloids*, Volume 37, Brossi, A.; Suffness, M.; Ed.; Academic Press: New York, **1990**, 229-239

[8] Eric, J. L.; Wen, Y. L. *Structure Activity Relationship Analysis of Anticancer Chinese Drugs and Related Plants*; Oriental Healing Arts Institute: California, **1985**

podophyllotoxin, shows activity against Hodgkin's disease and other malignant lymphomas, pediatric refractory neuroblastoma, and brain tumors in adults.[9] Camptothecin, isolated from the tree *Camptotheca acuminata*,[10] has good activity against various cancers in the laboratory,[11] but it has a too low a solubility to be useful for clinical applications. Various water-soluble analogs of camptothecin (e.g., topotecan) have found significant clinical use (Figure 2).

6. Miscellaneous chemotherapeutic agents that do not belong to any of these five classes above. Procarbazine (Matulane®) and L-Asparaginase are examples for this class.

The discovery of new chemotherapeutic agents is a challenging task. In the course of searching for new anticancer drugs, natural products are a plentiful source of lead compounds. Drugs discovered from nature have played a dominant role in pharmaceutical care for the treatment of various diseases, especially cancer.[12]

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[9] Kingston, D. G. I. In *Cancer Growth and Progression*; *Cancer Growth in Man*, Wooley, P.V.; Ed.; Kluwer Academic Publishers: **1989**, 152-158

[10] Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. Plant Antitumor Agents: I. The Isolation and Structure of Camptothecin, A Novel Alkaloidal Leukemia and Tumor Inhibitor from *Camptotheca acuminata*, *J. Am. Chem. Soc.,* **1966**, *88*, 3888-3890

[11] Suffness, M.; Cordell, G. A. Antitumor Alkaloids in *The Alkaloids*, Volume 25, Brossi, A.; Ed.; Academic Press: New York, **1985**, 1-369

[12] Pezzuto, J. M. *Biochemical Phramacology*, **1997**, *53*, 121-133

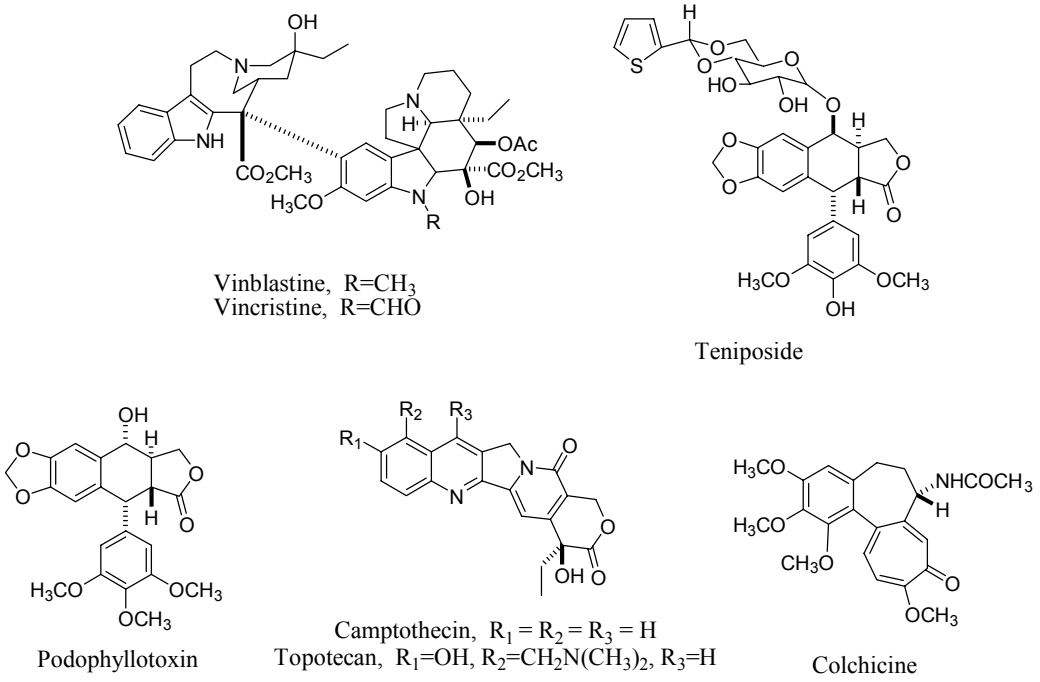

Figure 2 Selected anticancer agents from natural products

The most important member of the clinically useful anticancer agents isolated from natural products is paclitaxel (Taxol®), which was found in the bark of the western yew (*Taxus brevifolia*) (Figure 3).[13]

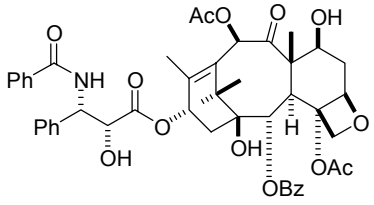

Figure 3 Paclitaxel (Taxol®)

Taxol falls under the category of mitotic inhibitors and has an unusual mechanism of action, differing from that of antimicrotubule agents such as colchicine and

[13] The name Taxol, originally assigned by Dr. Monroe Wall in 1971, has been trademarked by Bristol-Myers Squibb, which offers the generic name paclitaxel instead. In this thesis the name Taxol will be capitalized in recognition of Bristol-Myers Squibb's trademark.

the vinca alkaloids; this will be discussed later in detail. The structure of Taxol is very unusual, consisting of a bridged tetracyclic skeleton with a β-phenylisoserine side chain. The 3-dimensional structure of Taxol has a so called "inverted cup" shape (Figure 4). Chemically, Taxol belongs to a large family of complex natural products, the taxane diterpenoids.[14]

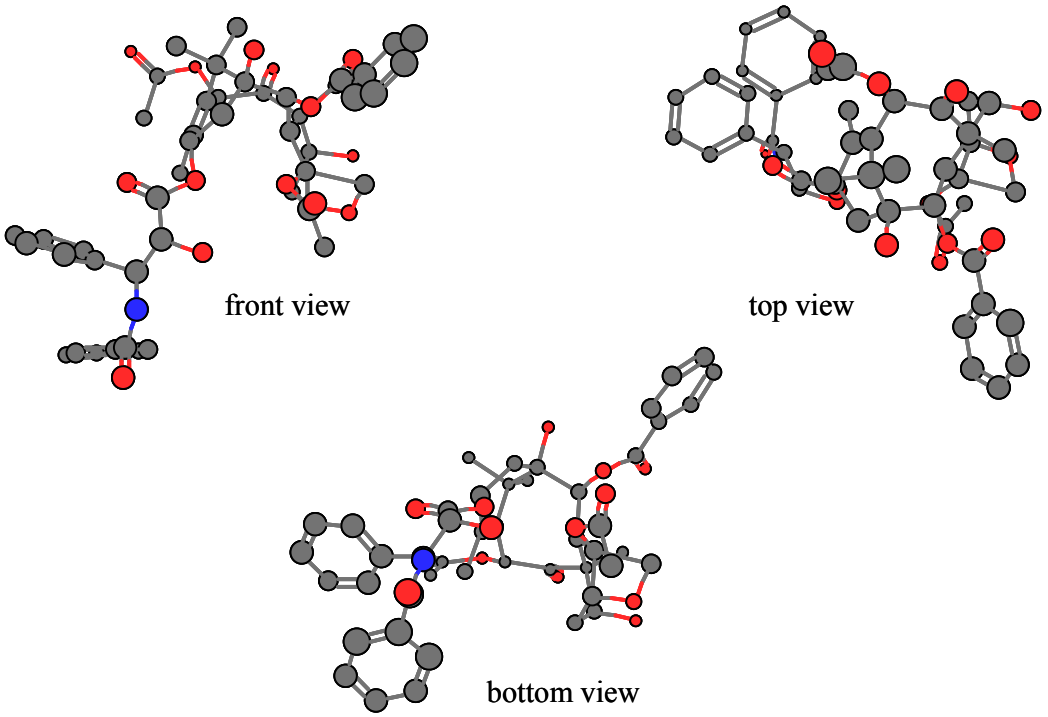

Figure 4 3-Dimensional structures of paclitaxel[15]

[14] Baloglu, E.; Kingston, D. G. I. The Taxane Diterpenoids, *J. Nat. Prod.*, **1999**, *62*, 1448-1472
[15] Structures obtained from template structure of Taxol from Chem-3D Pro Version 4.0

1.3 The Taxane Diterpenoids

The first taxane diterpenoid, taxine, was introduced to the world of chemistry almost one and a half centuries ago by Lucas.[16] Graf, however, reported that taxine is actually a mixture of at least eleven compounds,[17] and three of the pure components, named as taxines A, B and C, are members of the class of 2(3→20)-*abeo*-taxanes (Figure 5).[18]

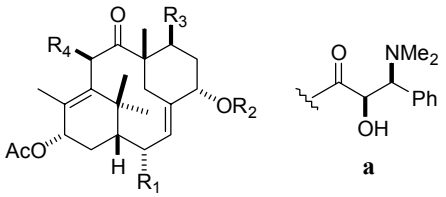

Figure 5 Structures of taxines

Table 1 Taxines

Name	R_1	R_2	R_3	R_4
Taxine A	OAc	a	OH	OH
Taxine B	OAc	H	OAc	OAc
Taxine C (2-Deacetyltaxine A)	OH	a	OH	OH

[16] Lucas, H. *Arch. Pharm. (Weinheim, Ger.)*, **1856**, *85*, 145-149
[17] Graf, E. *Angew. Chem.*, **1956**, *68*, 249
[18] a) Graf, E.; Berthold, H. *Pharmazeut. Zent.*, **1957**, *96*, 385-395 b) Graf, E.; Kirfel, A.; Wolff, G. J.; Breitmeier, E. *Leibigs. Ann. Chem.*, **1982**, 376-381 b) Yue, Q.; Fang, Q-C.; Liang, X-T.; He, C-H.; Jing, X-L. *Planta Med.*, **1995**, *61*, 371-377 c) Barboni, L.; Gariboldi, P.; Appendino, G.; Enriu, R.; Gabetta, B.; Iwasaki, S.; Naito, M.; Tsuruo, T. *Tetrahedron*, **1994**, *50*, 7401-7416 d) Poupat, C.; Ahond, A.; Potier, P. *J. Nat. Prod.*, **1994**, *57*, 1468-1469 e) For detailed information about this class of taxanes, please see ref. 14

Most taxane diterpenoids, or taxoids, consist of a basic pentamethyl [9.3.1.0] tricyclopentadecane skeleton, known as the normal taxane skeleton, and they have a unique numbering system (Figure 6).

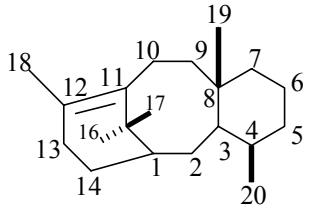

Figure 6 Taxane skeleton numbering system

The second largest class of this family is that of taxoids that have an 11(15→1)-*abeo*-taxane skeleton. Taxoids of this class were first isolated in the early 1990s (Figure 7).

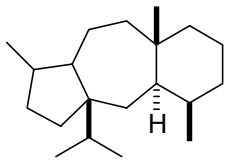

Figure 7 11(15→1)-*abeo*-taxane skeleton

In addition to these major classes, several other classes of taxoids have been reported. Bicyclic taxoids, 2(3→20)-*abeo*-taxoids, and miscellaneous taxoids are some of the smaller classes of taxoids that have been isolated to date.[14]

Taxol is the most renowned and the most studied member of the large family of taxane diterpenoids. There are over 350 cousins of Taxol in this family, classified according to their structural differences. Taxol belongs to a subclass of the taxoids with a normal taxane skeleton, known as "taxoids with an oxetane ring and a phenylisoserine side chain". The fame of Taxol is due to its unusual mechanism of action and concomitantly, its effective anticancer activity.

1.4 Four Decades With Taxol

In 1962, as part of a screening program for potential anticancer agents, a large number of plant samples were collected by the U.S. Department of Agriculture (USDA), and extracts of these samples were submitted to the U.S. National Cancer Institute (NCI) in order to be tested for anticancer activity. Along with many other plant samples collected in the state of Washington, some yew samples found their way to the NCI.

Taxus brevifolia, commonly known as the Pacific Yew (or Western Yew), which grows in the Pacific Northwest of Northern America, was one of the species subject to screening. It was 1964 when the first samples of *T. brevifolia*, including bark, twigs, leaves and fruits collected in 1962, arrived at the laboratories of Dr. Monroe Wall at Research Triangle Institute (RTI). The cytotoxicity of bark extracts to KB cells, derived from a nasopharyngeal tumor, was confirmed in the same year. The isolation of Taxol was finally completed by 1967. Approximately 0.5 g of pure compound was isolated from 12 kg of air dried stem and bark of *T. brevifolia*, corresponding to a yield of 0.004%.[19] After vigorous studies towards determination of the structure of the pure compound by a combination of spectroscopic techniques and chemical degradation, the physical and the chemical properties of the compound were reported. The molecular formula of $C_{47}H_{51}NO_{14}$, corresponding to a molecular weight of 853, suggested that the compound probably contained the taxane skeleton.[20] Named Taxol by its discoverers since it contained some hydroxyl groups and had a taxane skeleton, this novel compound was first reported in 1971.[21]

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[19] Wall, M. E.; Wani, M. C. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; American Chemical Society: Washington, DC, **1995**; Vol. ACS Symposium Series 583, p 18-30

[20] Please see ref. 19 for detailed physical and chemical properties of Taxol.

[21] Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325-2327

Despite its promising activity and novel structure, initial interest in Taxol was not high due to its scarcity, poor aqueous solubility (less than 0.01 mg/mL),[22] and the lack of information about its mechanism of action. This unfortunate delay came to an end in 1974, however, when it was found at NCI that Taxol has good activity in a B16 mouse melanoma model. By 1977, based on its activity against B16, Taxol was finally selected as a development candidate. In 1979 Horwitz and her colleagues disclosed the unique mechanism of action of Taxol.[23] By binding to microtubules and stabilizing them, Taxol promoted the polymerization of tubulin molecules to microtubules, leading to cell death and apoptosis. All other antimitotic agents bound to tubulin and inhibited its polymerization to microtubules, thereby leading to cell death.[24]

This discovery increased interest in the development of Taxol as a drug. In order to overcome the solubility problem, Cremophor formulation was selected at NCI in 1980 and toxicology studies were initiated.

In 1982, toxicology studies were completed and Taxol was approved by NCI for Investigational New Drug Application (INDA) filing. The INDA was approved by the U.S. Food and Drug Administration (FDA) in 1984 and Phase I clinical trials were initiated. One year later, in 1985 NCI approved Taxol for Phase II clinical trials. Scarcity, however, was still a problem, although the isolation of 10-deacetylbaccatin III (structure shown in Figure 8) from the renewable leaves of *Taxus baccata*, which was a readily accessible starting material for the semisynthesis of Taxol, pointed the way to a solution of this problem.[25]

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[22] Adams, J. D.; Flora, K. F.; Goldspiel, B. R.; Wilson, J. W.; Arbuck, S. G.; Finley, R. *Monogr. of Natl. Cancer Inst.* **1993**, *15*, 141
[23] Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665-667
[24] Horwitz, S. B.; Davidson, M. W.; Holton, R. A. *Trends Pharmacol. Sci.* **1992**, *13*, 134-136
[25] Denis, J.-N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917-5919

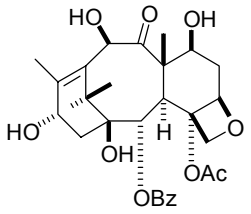

Figure 8 10-Deacetylbaccatin III

Striking clinical results with advanced ovarian cancer were reported in 1989.[26] Also in 1989 Bristol-Myers Squibb Co. was selected to commercialize Taxol. Taxol was approved by the FDA for the treatment of ovarian cancer in December 1992 and for the treatment of breast cancer in April 1994. Taxol was first marketed by Bristol-Myers Squibb Co. in 1993 and by 1998 annual worldwide sales surpassed 1 billion U.S. dollars, making it eligible to receive the title of "blockbuster drug". In 1997 Taxol was approved for the treatment of AIDS-related Kaposi's sarcoma.

With global sales over 1.5 billion U.S. dollars in 2000, Taxol proved that it *is* the most lucrative anticancer drug in history.

[26] McGuire, W. P.; Rowinsky, E. K.; Rosenshein, N. B.; Grumbine, F. C.; Ettinger, D. S.; Armstrong, D. K.; Donehower, R. C. *Ann. Intern. Med.* **1989**, *111*, 273-279

1.5 Mechanism of Action of Taxol

All eucaryotic cells have an internal skeleton, the cytoskeleton, that gives the cell its shape, its capacity to move and its ability to arrange the movement of its organelles. Unlike a skeleton made of bone, the cytoskeleton is a highly dynamic structure, composed of a network of protein filaments; the actin filaments, the intermediate filaments and microtubules.

Microtubules are long, hollow cylinders, formed from molecules of tubulin (Figure 9). With an outer diameter of 25 nm, and an inner diameter of about 15 nm, they are much more rigid than actin filaments.

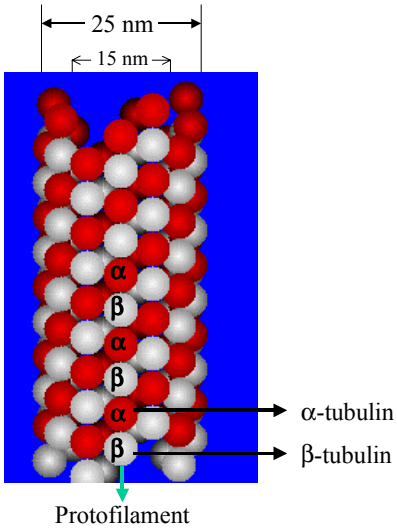

Figure 9 Microtubules

(Reproduced by permission from http://nessie.bch.ed.ac.uk/PAUL/TEACHING/IF/mt.htm)

The wall of the microtubule consists of protofilaments which are linear polymers of tubulin molecules. Tubulin, in turn, is a heterodimeric protein, consisting of two similar but distinct polypeptide subunits, α- and β-tubulin, that are tightly linked to each

other. Each of these polypeptides has a diameter of about 4-5 nm and a molecular weight of about 50,000.

Microtubules form by the reversible polymerization of tubulin dimers. The α and β subunits are synthesized as separate polypeptides, which then form the dimeric tubulin molecules. As the dimers polymerize, they form rings, then uncoil into protofilaments, which associate side-by-side into sheets.

As the sheet grows, it begins to roll up, eventually closing to form a microtubule when the number of laterally aligned protofilaments reaches 13. After this process, the microtubule elongates by addition of dimers to the ends of the protofilaments.

Microtubules are highly labile structures that are sensitive to specific antimitotic drugs.[27] The target of a variety of specific antimitotic drugs that act by interfering with the exchange of tubulin subunits between the microtubules and the free tubulin is the mitotic spindle. One of these drugs is colchicine (structure shown in Figure 2), an alkaloid isolated from the meadow saffron. Colchicine binds to tubulin, and prevents its polymerization to microtubules, causing the rapid disappearance of the mitotic spindle. Due to this temporary disruption of the spindle, many abnormally dividing cells die. Antimitotic drugs like colcemid, a drug closely related to colchicine, and vinblastine and vincristine, whose effects are similar to those of colchicine, are thus cytotoxic agents.

In contrast, Horwitz and collaborators discovered that Taxol has the opposite effect.[23] Taxol preferentially binds to microtubules, rather than to tubulin dimers, at sites

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[27] a) DeBrabander, M. Microtubule dynamics during the cell cycle: the effects of Taxol and nocodazole on the microtubule system of Pt K2 cells at different stages of the mitotic cycle. *Int. Rev. Cytol.* **1986**, *101*, 215-274 b) Inouse, S. Cell division and the mitotic spindle. *J. Cell. Biol.* **1981**, *91*, 131-147 c) Salmon, E. D.; McKeel, M.; Hays, T. Rapid rate of tubulin dissociation from microtubules in the mitotic spindle *in vivo* measured by blocking polymerization with colchicine. *J. Cell. Biol.* **1984**, *99*, 1066-1075

different than vinblastine, colchicine and podophyllotoxin.[28]

It has been shown that in the presence of Taxol, the microtubule cytoskeleton is reorganized, and stable bundles of microtubules are formed.[29] Taxol blocks cells in the G_2/M phase of the cell cycle, thus making it impossible for the cells to form a normal mitotic apparatus. Replication is inhibited or proceeds very slowly. Taxol is of great interest because of this property, which until recently was unique to Taxol and related analogs.

Taxol also eliminates the need for organizing centers by lowering the critical concentration of tubulin necessary for polymerization, resulting in polymerization of tubulin at many sites in addition to the organizing centers.[30] Tubulin as a pure polymer appears to be the target for Taxol, since Taxol's biochemical effects on microtubules formed from microtubule protein (including the so-called microtubule-associated proteins) are also observed with polymer formed from pure tubulin, and Taxol can eliminate the requirement for microtubule-associated proteins in microtubule formation.[31,32] The binding of Taxol to assembled microtubules is also non-covalent and reversible.[33]

Many therapeutic agents eliminate tumor cells by inducing apoptotic cell death.[34] Apoptosis is an evolutionarily conserved physiological process that ensures the

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[28] Sackett, D.; Fojo, T. Taxanes. *Cancer Chemother. Biol. Response Modifiers* **1997**, *17*, 59-79
[29] Horwitz, S. B. Taxol (paclitaxel): Mechanism of action. *Annals of Oncology*, **1994**, *5(6)*, 3-6
[30] De Brabander, M.; Geuens, G.; Nuydens, R.; Willerbords, R.; De Mey, J. Taxol Induces the Assembly of Free Microtubules in Living Cells and Blocks the Organizing Capacity of the Centrosomes and Kinetochores, *Proc. Natl. Acad. Sci. USA,* **1981**, *78*, 5608
[31] Hamel, E.; Del Campo, A. A.; Lowe, M. C.; Lin, C. M. Interactions of Taxol, Microtubule-Associated Proteins and Guanine Nucleotides in Tubulin Polymerization, *J. Biol. Chem*, **1981**, *256*, 11887
[32] Schiff, P. B.; Horwitz, S. B. Taxol Assembles Tubulin in the Absence of Exogeneous Guanosine-5'-Triposphate or Microtubule-Associated Proteins, *Biochemistry,* **1981**, *20*, 3247
[33] Parness, J.; Horwitz, S. B. Taxol Binds of Polymerized Tubulin *in vitro*, *J. Cell. Biol.*, **1981**, *91*, 479
[34] Thompson, C. B. *Science*, **1995**, *267*, 1456-1462

elimination of unwanted or damaged cells from multicellular organisms.[35] It is therefore important to understand the mechanism of apoptosis in order to solve the puzzle for the prevention and treatment of many diseases. Taxol has been shown to induce apoptosis, but studies towards discovery of the details of this process are still in progress.[36]

As noted earlier, this unusual mechanism of action is no longer unique to Taxol. Other novel natural products such as the epothilones (from a soil bacterium),[37] discodermolide (from a Caribbean sponge),[38] eleutherobin (from an octocoral),[39] and laulimalide (from a Pacific sponge)[40] have also been reported to share Taxol's mechanism of action in promoting microtubule assembly and have shown potential anticancer activity (Figure 10).

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[35] Wyllie, A. H. *Br. J. Cancer*, **1993**, *67*, 205-208

[36] a) Srivastava, R. K.; Mi, Q-S.; Hardwick, J. M.; Longo, D. L. Deletion of the loop region of Bcl-2 completely blocks paclitaxel-induced apoptosis. *Proc. Natl. Acad. Sci. USA.*, **1999**, *96*, 3775-3780 b) Haldar, S.; Basu, A.; Croce, C. M. *Cancer Res.*, **1997**, *57*, 229-233 c) Ham, J.; Babij, C.; Whitfield, J.; Pfarr, C. M.; Lailemand, D.; Yaniv, M.; Rubin, I. *Neuron*, **1995**, *14*, 927-939 d) Srivastava, R. K.; Srivastava, A. R.; Korsmeyer, S. J.; Nesterova, M.; Cho-Chung, X.; Longo, D. L. *Mol. Cell. Biol.*, **1998**, *18*, 3509-3517 e) Haldar, S.; Basu, A.; Croce, C. M. *Cancer Res.*, **1998**, *58*, 1609-1615

[37] a) Wessjohann, L., Epothilones: Promising Natural Products With Taxol-like Activity, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, *No:7*, 715-718 b) Hofle, G.; Bedorf, N.; Reichenbach, H. *Angew. Chem. Intl. Ed. Engl.*, **1996**, *35*, 2801

[38] Day, B. W.; Rosenkranz, H. S.; Gunasekera, S. P.; Longley, R. E.; Lin, M. C.; Hamel, E.; Kowalski, R. J.; Haar, E. Discodermolide, A Cytotoxic Marine Agent That Stabilizes Microtubules More Potently Than Taxol, *Biochemistry*, **1996**, *35*, 243-250

[39] Long, B. H.; Carboni, J. M.; Wasserman, A. J.; Cornell, L. A.; Cassaza, A. M.; Jensen, P. R.; Lindel, T.; Fenical, W.; Fairchild, C. R. *Cancer Res.*, **1998**, *58*, 1111-1115

[40] a) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J. *J. Org. Chem.*, **1988**, *53*, 3644-3646 b) Quinoa, E.; Kakou, Y.; Crews, P. J. *J. Org. Chem.*, **1988**, *53*, 3642-3644 c) Tanaka, J. I.; Higa, T.; Bernardinelli, G.; Jefford, C. W. *Chemistry Lett.*, **1996**, 255

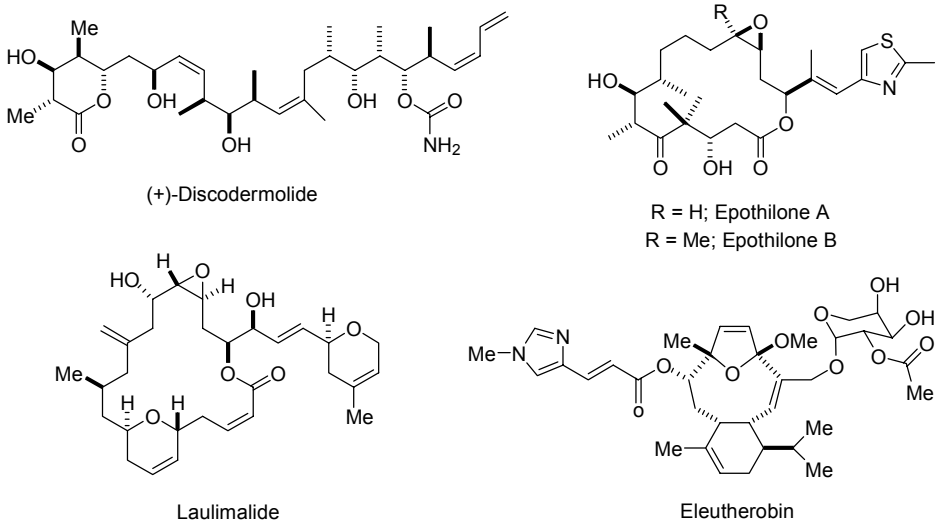

Figure 10 Natural products that show Taxol-like activity

1.6 Structure-Activity Relationships of Taxol

Studies on structure-activity relationships (SAR) of lead compounds can provide useful information about the mode of action of the molecule, the role of certain functional groups and conformations in the action, and the essential structural requirements for improvement of the biological activity. Synthesizing analogs of a natural product with potential activity will not only help in identifying functional groups or structural features that are responsible for specific interactions of the molecule in the body, but may also yield information about the binding environment of the molecule by making use of appropriate techniques like fluorescent and photoaffinity labeling.*

The SAR of Taxol have been investigated for more than twenty years and are summarized in Figure 11.[41] General trends about the biological data of numerous derivatives of Taxol modified at each functional group and the taxane core will be provided here, since detailed information can be found in a number of comprehensive reviews.[42] A knowledge of SAR of Taxol will help in the design and synthesis of new analogs, with improved physical, chemical and biological properties.

It is already well known that the C-13 side chain with a free hydroxyl group at the

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* Discussed in detail in Section 1.7

[41] This figure is reproduced from a review by Kingston, D. G. I. *Trends Biotechnol.* **1994**, *12*, 222-227

[42] a) Kingston, D. G. I. *Trends Biotechnol.* **1994**, *12*, 222-227 b) Kingston, D. G. I. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; American Chemical Society: Washington, DC, 1995; Vol. ACS Symposium Series 583, 203-216 c) Georg, G. I.; Harriman, G. C. B.; Vander Velde, D. G.; Boge, T. C.; Cheruvallath, Z. S.; Datta, A.; Hepperle, M.; Park, H.; Himes, R. H.; Jayasinghe, L. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; American Chemical Society: Washington, DC, 1995; Vol. ACS Symposium Series 583, 217-232 d) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Clowers, J. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press, Inc.: Boca Raton, FL, 1995, 317-375 e) Kingston, D. G. I. *Pure & Appl. Chem.* **1998**, *70*, 331-334 f) Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 726-734 g) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15-44 h) Nicolaou, K. C.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2079-2090

C-2' position, the ester groups at C-2 and C-4, the oxetane ring, and the rigid taxane structure are all crucial for activity. Modifications in the northern hemisphere of the molecule, which consists of C-6 to C-12, do not result in drastic changes in activity.

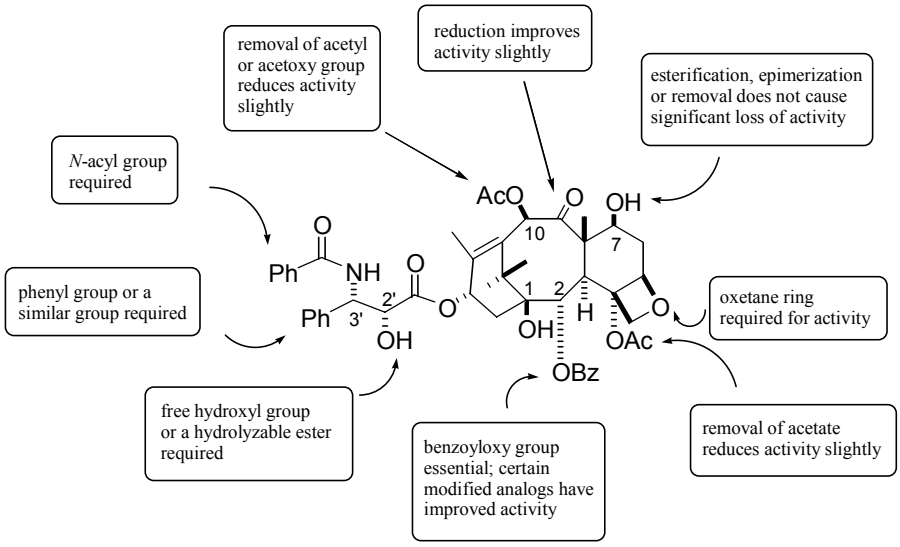

Figure 11 Structure-activity relationships of Taxol

Modifications in the southern hemisphere, which consists of carbons 14 and 1-5, including the oxetane ring, on the other hand, have dramatic effects on the strong anticancer activity of Taxol. The oxetane ring, for example, is one of four structural features regarded to be essential for biological activity, and has been of great interest to many researchers.[43]

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[43] a) Wang, M.; Cornett, B.; Nettles, J.; Liotta, D. C.; Snyder, J. P. *J. Org. Chem.* **2000**, *65*, 1059-1068 b) Fenoglio, I.; Nano, G. M.; Vander Velde, D. G.; Appendino, G. *Tetrahedron Lett.* **1996**, *37*, 3203-3206 c) Marder-Karsenti, R.; Dubois, J.; Bricard, L.; Guenard, D.; Gueritte-Voegelein, F. *J. Org. Chem.* **1997**, *62*, 6631-6637 d) Gunatilaka, A. A. L.; Ramdayal, F. D.; Sarragiotto, M. H.; Kingston, D. G. I.; Sackett, D. L.; Hamel, E. *J. Org. Chem.* **1999**, *64*, 2694-2703 e) Kingston, D. G. I.; Magri, N. F.; Jitrangsri, C. *Studies in Org. Chem.* **1986**, *26*, 219-235 f) Samaranayake, G.; Magri, N. F.; Jitrangsri, C.; Kingston, D. G. I. *J. Org. Chem.* **1991**, *56*, 5114-5119 g) Wahl, A.; Gueritte-Voegelein, F.; Guenard, D.; Le Goff, M.; Potier, P. *Tetrahedron* **1992**, *48*, 6965-6974 h) Chen, S.; Huang, S.; Wei, J.; Farina, V. *Tetrahedron* **1993**, *49*, 2805-2828 i) Gueritte-Voegelein, F.; Guenard, D.; Potier, P. *J. Nat. Prod.* **1987**, *50*, 9-18 j) Appendino, G.; Danieli, B.; Jakupovic, J.; Belloro, E.; Scambia, G.; Bombardelli, E. *Tetrahedron Lett.* **1997**, *38*, 4273-4276 k) Nicolaou, K. C.; Claiborne, C. F.; Nantermet, P. G.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1994**, *116*, 1591-1592 l) Shintani, Y.; Tanaka, T.; Nozaki, Y. *Cancer Chemother. Pharmacol.* **1997**, *40*, 513-520 m) Klar, U.; Graf, H.; Schenk, O.; Rohr, B.; Schulz, H. *Bioorg. & Med. Chem. Lett.* **1998**, *8*, 1397-1402

1.7 Analysis of the Binding of Taxol to Microtubules

As noted previously, the microtubule stabilizing agents Taxol and its semi-synthetic cousin docetaxel (Taxotere®) (Figure 12), are effective in the treatment of solid tumors. Since the antitumor activity of Taxol is related to its tubulin-polymerization activity, an understanding of the binding of Taxol to tubulin is a key first step to an understanding of its anticancer activity.

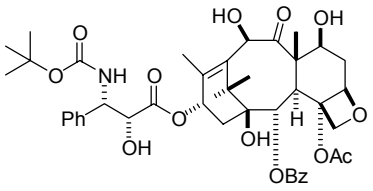

Figure 12 Docetaxel (Taxotere®)

Taxol binds stoichiometrically to β-tubulin on the assembled tubulin heterodimers in microtubules, causing conformational perturbations that alter the structure of the microtubule and lead to microtubule stabilization, and, in cells, bundling of the microtubules.[44] This alteration of the normal microtubule dynamics in cells leads to communicational problems between the nucleus and the membrane, causing inability to complete mitosis and, eventually, cell death.

Although a great deal is known about the paclitaxel-tubulin interaction from the recent accomplishments of several laboratories investigating tubulin pharmacology, there is still a lot to learn. Several techniques have been employed to investigate this interaction.

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[44] Day, B. W. *TiPS* **2000**, *21*, 321-323

1.7.1 Photoaffinity Labeling

Photoaffinity labeling methods can be used to discover the nature of binding of Taxol to tubulin on the molecular level. These methods can help to define the molecular contacts between Taxol and its cellular target, the microtubule, specifically β-tubulin. To this end, radioactivity labeled photoaffinity analogs of Taxol have been prepared by several groups.[45]

Photoreactive analogs [^{3}H]3'-(*p*-azidobenzamido)paclitaxel (Figure 13) and [^{3}H]2-(*m*-azidobenzoyl)paclitaxel (Figure 14) have identified the N-terminal[46] 31 amino acids and a peptide consisting of amino acid residues 217-231 of β-tubulin, respectively, as two domains of the binding site.[47]

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[45] a) Rao, S.; Horwitz, S. B.; Ringel, I. *J. Natl. Cancer Inst.* **1992**, *84*, 785-788 b) Georg, G. I.; Harriman, G. C. B. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 735-738 c) Carboni, J. M.; Farina, V.; Rao, S.; Hauck, S. I.; Horwitz, S. B.; Ringel, I. *J. Med. Chem.* **1993**, *36*, 513-515 d) Rimoldi, J. M.; Kingston, D. G. I.; Chaudhary, A. G.; Samaranayake, G.; Grover, S.; Hamel, E. *J. Nat. Prod.* **1993**, *56*, 1313-1330 e) Combeau, C.; Commercon, A.; Mioskowski, C.; Rousseau, B.; Aubert, F.; Goeldner, M. *Biochemistry* **1994**, *33*, 6676-6683 f) Georg, G. I.; Harriman, G. C. B.; Park, H.; Himes, R. H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 487-490 g) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 335-338 h) Rao, S.; Krauss, N. E.; Heerding, J. M.; Swindell, C. S.; Ringel, I.; Orr, G. A.; Horwitz, S. B. *J. Biol. Chem.* **1994**, *269*, 3132-3134 i) Swindell, C. S.; Heerding, J. M.; Krauss, N. E.; Horwitz, S. B.; Rao, S.; Ringel, I. *J. Med. Chem.* **1994**, *37*, 1446-1449 j) Dasgupta, D.; Park, H.; Harriman, G. C. B.; Georg, G. I.; Himes, R. H. *J. Med. Chem.* **1994**, *37*, 2976-2980 k) Georg, G. I.; Boge, T. C.; Park, H.; Himes, R. H. *Bioorg. & Med. Chem. Lett.* **1995**, *5*, 615-620 l) Rao, S.; Orr, G. A.; Chaudhary, A. G.; Kingston, D. G. I.; Horwitz, S. B. *Journal of Biological Chemistry* **1995**, *270*, 20235-20238 m) Georg, G. I.; Liu, Y.; Boge, T. C.; Himes, R. H. *Bioorg. & Med. Chem. Lett.* **1997**, *7*, 1829-1832

[46] N-terminal (amino terminus): The end of a polypeptide chain that carries a free α-amino group. (This information has been obtained from Reference 2)

[47] Please see references 52 h and 52 l

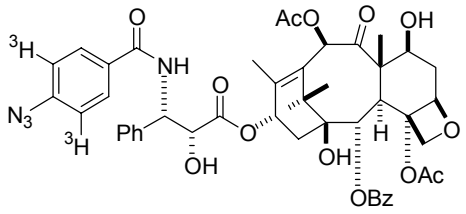

Figure 13 [^{3}H]3'-(*p*-azidobenzamido)paclitaxel

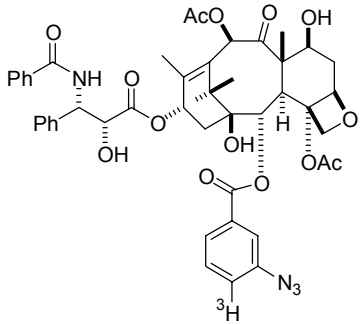

Figure 14 [^{3}H]2-(*m*-azidobenzoyl)paclitaxel

A recent report by Horwitz and collaborators determined the site of photoincorporation of a third photoaffinity analog of Taxol, [^{3}H]7-(benzoyldi hydrocinnamoyl)paclitaxel (Figure 15), prepared by the Ojima group.[48]

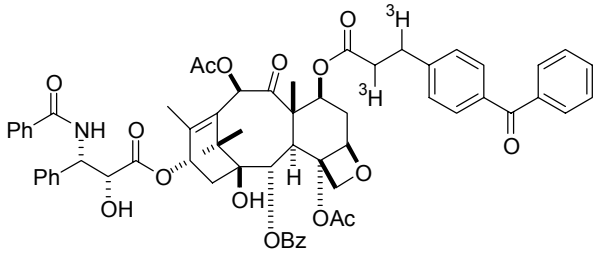

Figure 15 [^{3}H]7-benzoyldihydrocinnamoyl)paclitaxel

It is noted that this analog stabilizes microtubules polymerized in the presence of GTP,[49] but unlike Taxol, does not promote tubulin polymerization. By the help of electron crystallography, this photoaffinity labeled analog of Taxol identified ^{282}Arg in β-tubulin as the site of photoincorporation. In conjunction with the data available from the first two photoaffinity labeled analogs (shown in figures 13 and 14), this result has

[48] Rao, S.; He, L. F.; Chakravarty, S.; Ojima, I.; Orr, G. A.; Horwitz, S. B. *Journal of Biological Chemistry* **1999**, *274*, 37990-37994

[49] GTP (guanosine 5'-triphosphate): Major nucleoside triphosphate used in the synthesis of RNA and in some energy-transfer reactions. Has a special role in microtubule assembly, protein synthesis and cell signaling. (This information has been obtained from Reference 2)

allowed visualization of the contact regions between the Taxol analogs and β-tubulin by molecular modeling. These studies are in agreement with the investigations reported by Nogales and co-workers, where a qualitative model of the α,β-tubulin dimer fitted to a 3.7 Å density map was obtained by electron crystallography of zinc-induced tubulin sheets.[50]

Photoaffinity labeling techniques are currently being used by several research groups. Two new photoreactive Taxol derivatives developed by the Ojima group showed excellent preliminary results on the photoaffinity labeling of tubulin and P-glycoprotein,[51] and comprehensive results of these studies will be reported in near future.

1.7.2 Fluorescent Labeling

Fluorescent analogs of a drug can provide information about the environment of the bound form of the drug and the interaction of the drug with its cellular binding site. They may also be used for the direct visualization and *in situ* localization of these binding structures. The synthesis and biological evaluation of several fluorescent analogs of Taxol have been reported to date as tools to carry out investigations of Taxol-microtubule

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[50] a) Nogales, E.; Wolf, S. G.; Downing, K. H. *Nature* **1998**, *391*, 199-203 b) Nogales, E.; Whittaker, M.; Milligan, R. A.; Downing, K. H. *Cell* **1999**, *96*, 79-88

[51] Ojima, I.; Bounaud, P. Y.; Ahern, D. G. *Bioorganic & Medicinal Chemistry Letters* **1999**, *9*, 1189-1194

interactions.[52] The fluorophores used in these studies vary from (dimethylamino)benzoyl, (dimethylamino)phenyl, and *m*-aminobenzoyl to the complex structures of lissamine rhodamine B, fluorescein and difluorofluorescein. Examples of the fluorophores used in some of these studies are shown in Figure 16.

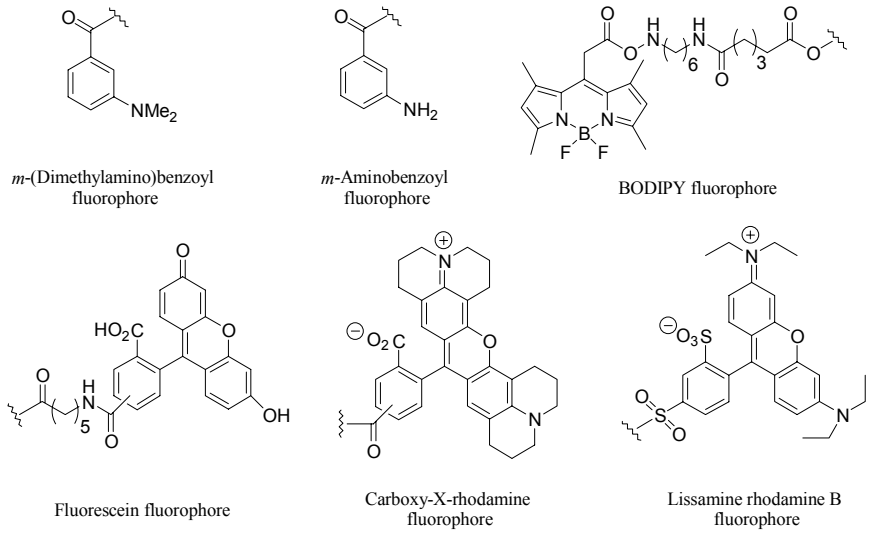

Figure 16 Examples of fluorophores

[52] a) Sengupta, S.; Boge, T. C.; Georg, G. I.; Himes, R. *Biochemistry* **1995**, *34*, 11889-11894 b) Souto, A. A., Acuna, A. U.; Amat-Guerri, F.; Abal, M.; Barasoain, I.; Andreu, J. M. In *Cytoskeleton and Cancer* Les Embiez (Var), France, Sept. 17-20, 1995, p 29 c) Souto, A. A.; Acuna, A. U.; Andreu, J. M.; Barasoain, I.; Abal, M.; Amat-Guerri, F. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2710-2712 d) Dubois, J.; LeGoff, M.-T.; Gueritte-Voegelein, F.; Guenard, D.; Tollon, Y.; Wright, M. *Bioorg. Med. Chem.* **1995**, *3*, 1357-1368 e) Guy, R. K.; Scott, Z. A.; Sloboda, R. D.; Nicolaou, K. C. *Chem. & Biol.* **1996**, *3*, 1021-1031 f) Han, Y.; Ghaudhary, A. G.; Chordia, M. D.; Sackett, D. L.; Perez-Ramirez, B.; Kingston, D. G. I.; Bane, S. *Biochemistry* **1996**, *35*, 14173-14183 g) Sengupta, S.; Boge, T. C.; Liu, Y.; Hepperle, M.; Georg, G. I.; Himes, R. H. *Biochemistry* **1997**, *36*, 5179-5184 h) Georg, G. I.; Liu, Y.; Boge, T. C.; Himes, R. H. *Bioorg. & Med. Chem. Lett.* **1997**, *7*, 1829-1832 i) Krishna, A. G.; Kumar, D. V.; Khan, B. M.; Rawal, S. K.; Ganesh, K. N. *Biochimica et Biophysica Acta* **1998**, *1381*, 104-112 j) Han, Y.; Malak, H.; Chaudhary, A. G.; Chordia, M. D.; Kingston, D. G. I.; Bane, S. *Biochemistry* **1998**, *37*, 6636-6644 k) Bicamumpaka, C.; Page, M. *International Journal of Molecular Medicine* **1998**, *2*, 161-165 l) Li, Y.; Edsall, R.; Jagtap, P. G.; Kingston, D. G. I.; Bane, S. *Biochemistry* **2000**, *39*, 616-623 m) Li, Y.; Poliks, B.; Cegelski, L.; Poliks, M.; Gryczynski, Z.; Piszczek, G.; Jagtap, P. G.; Studelska, D. R.; Kingston, D. G. I.; Schaefer, J.; Bane, S. *Biochemistry* **2000**, *39*, 281-291 n) Diaz, J. F.; Strobe, R.; Engelborghs, Y.; Souto, A. A.; Andreu, J. M. *Journal of Biological Chemistry* **2000**, *275*, 26265-26276

These probes have been attached to different positions on Taxol, with the positions of attachment guided by the results of the SAR studies, since the biological activity of these fluorescent analogs should at least be comparable to that of Taxol.

It was found that, in addition to binding to microtubules, Taxol could bind to tubulin heterodimers.[54a] Similar results were obtained by the Page group,[54k] however, a competition between Taxol and its fluorescent analogs was not detected. It was proposed by Sengupta et al.[54a] that this lack of competition was due to the low binding affinity and to the difficulty of saturating the binding sites under the experimental conditions used. However, the Page group did not exclude a non-specific interaction as well as an interaction with another protein in the solution.

The Page group was able to observe the labeling of spindle shaped cytoplasmic filaments extending from the center to the periphery of the cell, by making use of fluorescent microscopy. It was also observed that the nucleolar labeling was constant and intense. The same results were observed by the Nicolaou group,[54e] but these investigations proposed the presence of intranuclear tubulin or a previously detected receptor of paclitaxel in the nucleolus, rather than the proposal of Sengupta et al. However, it was noted by the Page group that intranuclear tubulin has already been reported without any mention of a nucleolar preferential localization, and intranuclear tubulin is accepted by the Page group as a solid hypothesis and as worth further investigation.

Fluorescent labeling studies are currently employed by several research groups. Fluorescent analogs of Taxol represent an interesting alternative to photoaffinity labeling studies. It is hoped that these analogs will prove useful for the study of the binding environment of Taxol.

1.8 Combinatorial Chemistry

Finding lifesaving drugs is not an easy task. Millions of dollars are spent on the discovery of a promising new drug, and tens of millions of dollars are required for preclinical and clinical studies. For every 10,000 compounds screened only one or two will be approved by the FDA and find their way into pharmacies. The need to develop faster, more economical methods for the discovery of new drugs will speed the development of new techniques. The development of high-yielding synthetic reactions and combinatorial tools will help the generation of more efficient libraries. Especially, the development of automated methods to prepare, analyze, and purify new compounds will allow combinatorial chemistry to become a more effective technique in the hands of the researcher.

Combinatorial chemistry is a popular method in the field of synthetic organic chemistry. It was developed by researchers in order to produce new drug candidates rapidly, efficiently and cost effectively. It is used by scientists to create large number of molecules, called libraries, that can be screened efficiently. By producing larger, more diverse compound libraries, it is possible to find novel compounds of significant therapeutic and commercial value or to optimize the activity and properties of a known lead compound. Nowadays, combinatorial chemistry is accepted as a subfield of chemistry that aims to simultaneously produce large number of fully characterized compounds by using small numbers of reagents in all combinations. Unlike conventional organic synthesis, the goal is not to produce a single product, but to synthesize many compounds, all at once. In this part, a general overview of combinatorial chemistry is provided.

Detailed information can be found in several comprehensive reviews.[53]

Combinatorial chemistry was first reported by Furka et al. at international meetings in Prague and Budapest in 1988.[54] It was 1991 when the first publications by three different groups appeared.[55, 56, 57]

Combinatorial chemistry can be performed both in solution and on a solid phase. Many combinatorial libraries are currently produced using solid phase synthesis techniques. Solid phase synthesis is a rapidly growing area of synthetic organic chemistry that enables full automation, and thus offers many advantages.[58] The most important advantage of solid phase synthesis is that it allows the use of excess reagents to drive reactions to completion. These excess reagents can then be removed easily by simple washing during filtration, without the need for any work-up. One other advantage of solid phase synthesis when compared to solution phase methods is the ease of automation and the pseudo-dilution effect, which is useful for cyclisation reactions.[59] The extra labor required in developing a solid phase route, the limitations of the current range of commercially available supports and linkers, and difficulties in monitoring reactions are the main disadvantages of solid phase synthesis.

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[53] a) Lowe, G. *Chem. Soc. Rev.* **1995**, *24*, 309-317 b) Czarnik, A. W.; DeWitt, S. H. Ed.: *A Practical Guide To Combinatorial Chemistry*, American Chemical Society, **1997** c) Bunin, B. A. *The Combinatorial Index*; Academic Press: San Diego, **1998** d) Terret, N. K. *Combinatorial Chemistry*; Oxford University Press: New York, **1998** e) Wilson, S. R.; Czarnik, A. W. Eds.: *Combinatorial Chemistry Synthesis and Application*; John Wiley & Sons, Inc.: New York, **1997** f) Gordon, E. M.; Kerwin Jr., J. F. Eds.: *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Wiley-Liss Inc.: New York, **1998** g) Balkenhohl, F.; Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem.-Int. Ed. En.* **1996**, *35*, 2288-2337

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[55] Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *Int. J. Pept. Protein Res.*, **1991**, *37*, 487

[56] Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature (London)*, **1991**, *354*, 84

[57] Lam, K.; Salmon, S.; Hersh, E.; Hruby, V.; Kazmierski, W.; Knapp, R. *Nature (London)*, **1991**, *354*, 82

[58] a) Brown, A. R.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Synlett* **1998**, 817-27 b) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091-2157

[59] Jayalekshmy, P.; Mazur, S. *J. Am. Chem Soc.*, **1976**, *98*, 6710

Solid phase synthesis techniques can be applied to natural products. Depending on the complexity of the molecule, the researcher should consider various aspects when working on the synthesis plan. Every reaction step has to be examined individually. The availability of the individual building blocks from which the products are formed to reach the desired library size must be known. The position of the attachment of the molecule to the solid support must be identified. The products formed must be as diverse as possible. The reaction conditions should be suitable for automation. Knowing the pluses and minuses of each step makes the choice of building blocks easier and enables a successful synthesis.

A multistep solid phase synthesis of a complex natural product epothilone A that has Taxol-like activity was reported by Nicolaou and co-workers in 1997 (Scheme 1).[60] Starting with Merrifield resin, the requisite fragments were coupled together sequentially through an aldol reaction, an esterification reaction, and an olefin metathesis reaction. The synthesis of epothilone A was then completed by desilylation followed by epoxidation.

This study not only represents a new concept for the total synthesis of complex natural products, but also opens a way for the construction of large combinatorial libraries of epothilones.

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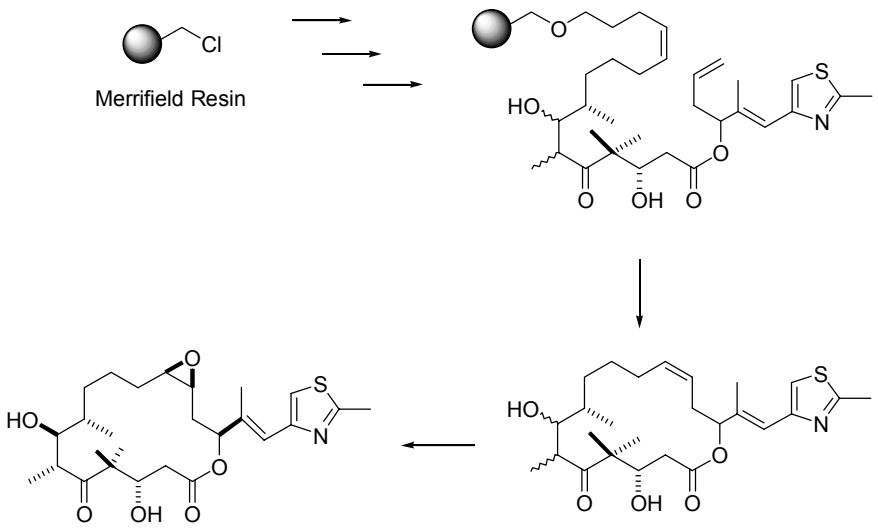
[60] Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature*, **1997**, *387*, 268-272



Scheme 1 Solid-phase synthesis of epothilone

Xiao et al. reported that radiofrequency encoded combinatorial (REC) libraries of complex natural products like Taxol can also be constructed.[61] Employing the noninvasive REC strategy and novel solid phase synthesis techniques, Xiao et al. demonstrated the construction of the first 400-membered taxoid library (Figure 17).

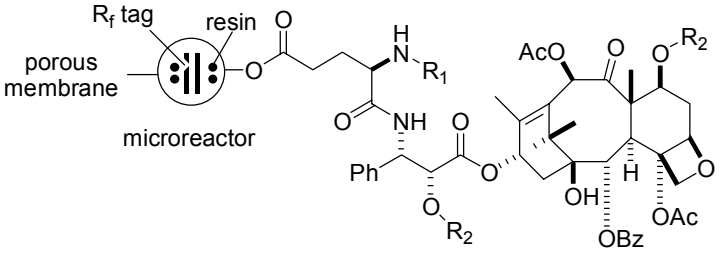


Figure 17 Taxoid library

The encouraging results of the study of Xiao et al. show that complex, delicate molecular structures like Taxol can be manipulated on solid supports, and thus combinatorial libraries of such molecules can be constructed.

[61] Xiao, X.-Y.; Parandoosh, Z.; Nova, M. P. *J. Org. Chem.* **1997**, *62*, 6029-6033

The need to produce larger numbers of compounds rapidly will always keep solid phase synthesis a popular method. It will not replace, however, complement conventional synthesis methods, since not all structures are suitable for combinatorial chemistry.

2. SYNTHESIS AND MICROTUBULE BINDING OF FLUORESCENT LABELED TAXOIDS

2.1 Introduction

Fluorescence spectroscopy is a powerful tool for the study of biological systems, especially for the investigation of ligand-receptor interactions. Fluorescence spectroscopy has also been extensively applied to the study of Taxol-microtubule interactions. The fluorophores used for these studies are most commonly attached to Taxol through the C-7 position, since this position the most synthetically accessible site on the northern hemisphere of Taxol. In addition, modifications in this portion of the molecule appear to be better tolerated with respect to antimicrotubule activity than modifications in the southern hemisphere. In order to obtain additional information about the mechanism of action of Taxol, and the environment of the Taxol-binding site, several fluorescent analogs of Taxol have been synthesized.

2.2 Synthesis of Fluorescent Analogs Modified at the C-10 Position

Because fluorescent analogs of Taxol with modification at the C-10 position have been sparsely studied, this position was chosen to initiate the investigations into the northern hemisphere of Taxol. The first label chosen was 7-(diethylamino)coumarin-3-carboxylic acid. This fluorophore had not previously been used as a probe for the Taxol-tubulin interaction. Other coumarin derivatives have been used to label Taxol, but the resulting probes had absorption maxima at high energy (~370 nm).[62] The electron withdrawing group at the C-3 position of 7-(diethylamino)coumarin yields a probe that is excited by visible light (410-430 nm) and is also environmentally sensitive.[63] The second

[62] Evangelio, J. A.; Abal, M.; Barasoain, I.; Souto, A. A.; Lillo, M. P.; Acuna, A. U.; Amat-Guerri, F.; Andreu, J. M. *Cell Motility and the Cytoskeleton* **1998**, *39*, 73-90
[63] Bangar Raju, B.; Varadarajan, T. S. *J. Phys. Chem. A* **1994**, *98*, 8903-8905

analog selected was the 10-deacetyl-10-(*m*-aminobenzoyl) derivative. Reported herein are the synthesis of these two C-10 modified fluorescent Taxol analogs, a fluorescent baccatin derivative, and their *in vitro* tubulin binding properties.

The sequence leading to the required fluorescent Taxol analogs is shown in Scheme 2. The known paclitaxel derivative (**1**)[64] was esterified at the C-10 position with 3-nitrobenzoic acid, employing the carbodiimide-based coupling protocol to yield the paclitaxel analog **2**. Removal of both silyl protecting groups followed by hydrogenation gave the desired amine (**4**, BTax)* in good yield. Starting from the common intermediate **1**, CTax was prepared by acylation at C-10 in the same fashion, utilizing 7-(diethylamino)coumarin-3-carboxylic acid, followed by simultaneous removal of the protecting groups to give **3**. When the same conditions for the preparation of **2** were applied for the synthesis of **3**, the reaction yield for the acylation of the C-10 OH was observed to be a low 10%. In order to overcome the problem, which was presumed to be due to low solubility of 7-(diethylamino)coumarin-3-carboxylic acid in toluene, the reaction conditions for the preparation of **3** were slightly modified. The solvent system was changed to CH_2Cl_2/DMF, and a water soluble derivative of the carbodiimide-based esterification agent, which facilitated the purification process, was used; as a result of these modifications the yield was improved to 95%.

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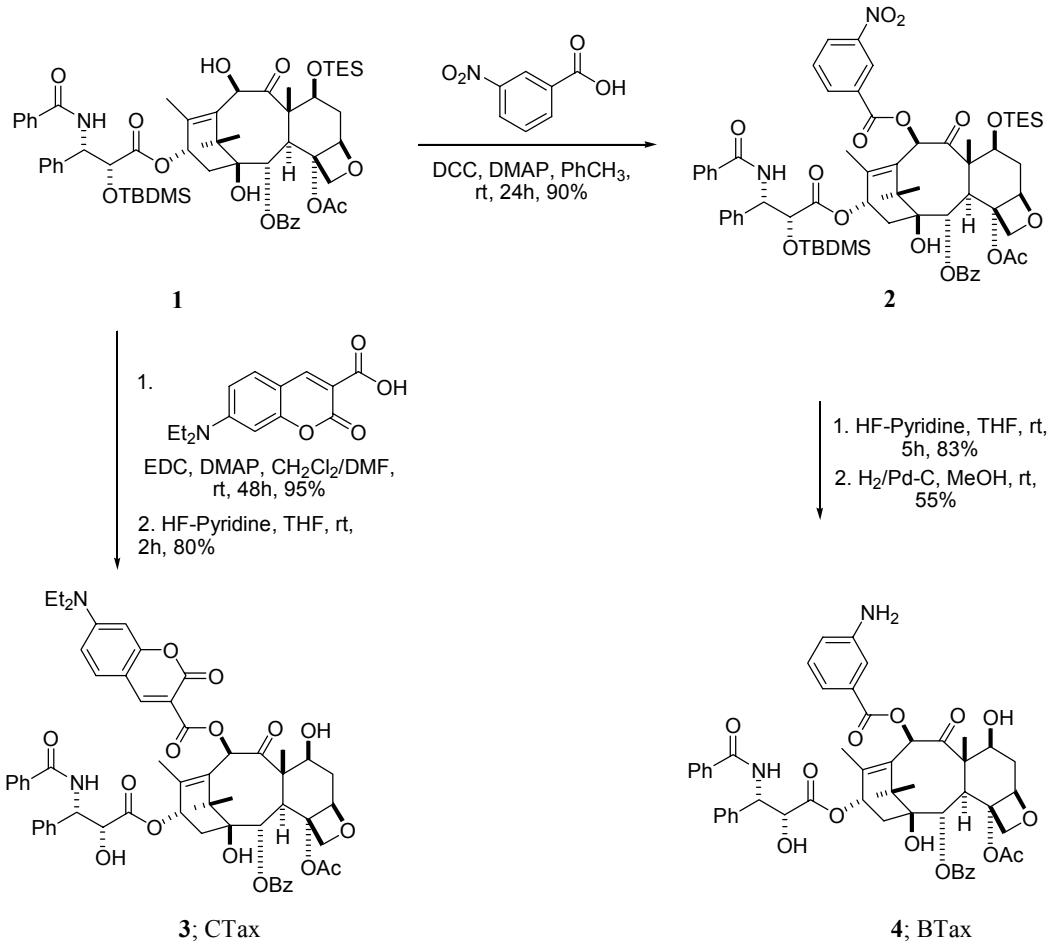
[64] Paclitaxel derivative **1** was prepared by protecting the known 10-deacetyl-2'-(*tert*-butyldimethylsilyl) paclitaxel as its triethylsilyl ether at C-7 position. Datta, A.; Hepperle, M.; I., G. G. *J. Org. Chem.* **1995**, *60*, 761-763

* Throughout this dissertation 10-deacetyl-10-(*m*-aminobenzoyl)paclitaxel (**4)** will be referred as BTax and 10-deacetyl-10-[7-(diethylamino) coumarin-3-carboxy]paclitaxel (**3**) will be referred as CTax for convenience.

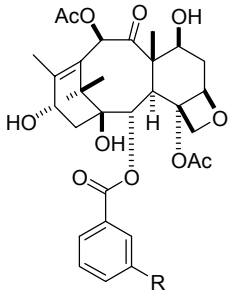


Scheme 2 Synthesis of fluorescent labeled Taxol analogs modified at the C-10 position.

A baccatin derivative was selected as another taxoid that would also facilitate the use of fluorescence spectroscopic techniques. A fluorescent baccatin derivative has not previously been reported, and it was hoped that such a derivative would provide useful information for understanding the effects of Taxol upon binding to microtubules. Although baccatin III itself does not bind strongly to microtubules, it was recently shown by Horwitz and Kingston that 2-debenzoyl-2-(*m*-azidobenzoyl)baccatin III has a much enhanced activity (Figure 18).[65] It was thus of interest to investigate the binding of fluorescent (*m*-azidobenzoyl)baccatin III derivatives to tubulin. However, attempts to

[65] He, L.; Jagtap, P. G.; Kingston, D. G. I.; Shen, H.-J.; Orr, G. A.; Horwitz, S. B. *Biochemistry* **2000**, *39*, 3972-3978

prepare such derivatives were unsuccessful, and the synthesis of the related compound 2-debenzoyl-2-(*m*-methoxybenzoyl)baccatin III was thus undertaken. 2-Debenzoyl-2-(*m*-methoxybenzoyl)paclitaxel has comparable activity to 2-debenzoyl-2-(*m*-azidobenzoyl) paclitaxel,[66] and thus the substitution of the azido group by the methoxy group was expected to lead to active baccatin III derivatives.



R = H; Baccatin III
R = N_3; 2-Debenzoyl-2-(*m*-azidobenzoyl)baccatin III
R = OMe; 2-Debenzoyl-2-(*m*-methoxybenzoyl)baccatin III

Figure 18 Baccatin III derivatives

The precursor 7,13-di(triethylsilyl)baccatin III (**5**) was converted to 2-debenzoyl-7,13-di(triethylsilyl)baccatin III (**6**) by reduction with Red-Al, a known procedure.[67] Reesterification with 3-anisic acid employing the carbodiimide-based coupling protocol provided 2-debenzoyl-2-*m*-methoxybenzoyl-7,13-di(triethylsilyl)baccatin III (**7**). Selective removal of the C-10 acetyl group yielded 2-debenzoyl-2-*m*-methoxybenzoyl-10-deacetyl-7,13-di(triethylsilyl)baccatin III (**8**). Acylation of **8** with 3-nitrobenzoic acid in the presence of EDC* gave 2-debenzoyl-2-*m*-methoxybenzoyl-10-deacetyl-10-*m*-nitrobenzoyl-7,13-di(triethylsilyl) baccatin III (**9**). Simultaneous removal of both silyl protecting groups followed by hydrogenation furnished the proposed amine **10** in good yield (Scheme 3).

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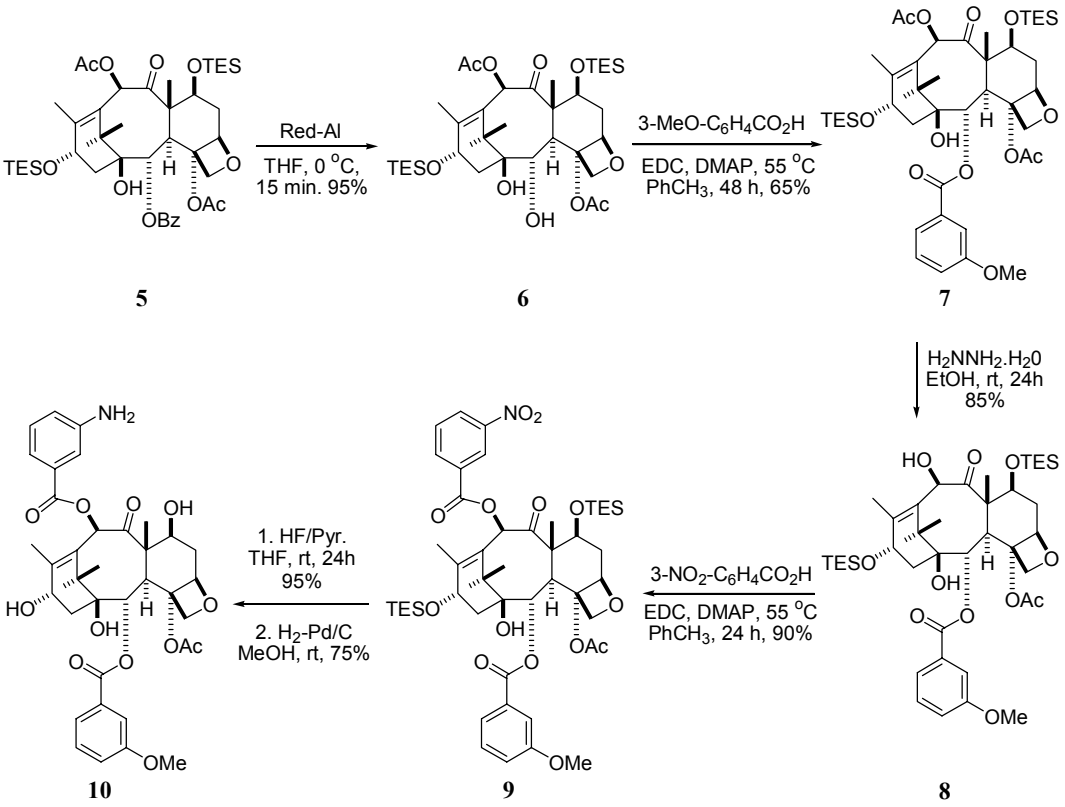
[66] a) Chaudhary, A. G.; Gharpure, M. M.; Rimoldi, J. M.; Chordia, M. D.; Gunatilaka, A. A. L.; Kingston, D. G. I.; Grover, S.; Lin, C. M.; Hamel, E. *J. Am. Chem. Soc.* **1994**, *116*, 4097-4098 b) Kingston, D. G. I.; Chaudhary, A. G.; Chordia, M. D.; Gharpure, M.; Gunatilaka, A. A. L.; Higgs, P. I.; Rimoldi, J. M.; Samala, L.; Jagtap, P. G.; Giannakakou, P.; Jiang, Y. Q.; Lin, C. M.; Hamel, E.; Long, B. H.; Fairchild, C. R.; Johnston, K. A. *J. Med. Chem.* **1998**, *41*, 3715-3726

[67] Chen, S.; Farina, V.; Wei, J.; Long, B.; Fairchild, C.; Mamber, S. W.; Kadow, J. F.; Vyas, D.; Doyle, T. W. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 479-482

* EDC = (1-[3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride)



Scheme 3 Synthesis of the fluorescent labeled baccatin analog.

2.3 Microtubule Activity of the Fluorescent Analogs Modified at the C-10 Position*

The activities of the fluorophores were assessed by their abilities to induce purified tubulin to assemble *in vitro*. Both BTax and CTax were nearly equipotent to Taxol in promoting tubulin assembly. BTax is slightly more potent than Taxol (Figure 19), while CTax is slightly less potent than Taxol (Figure 20).

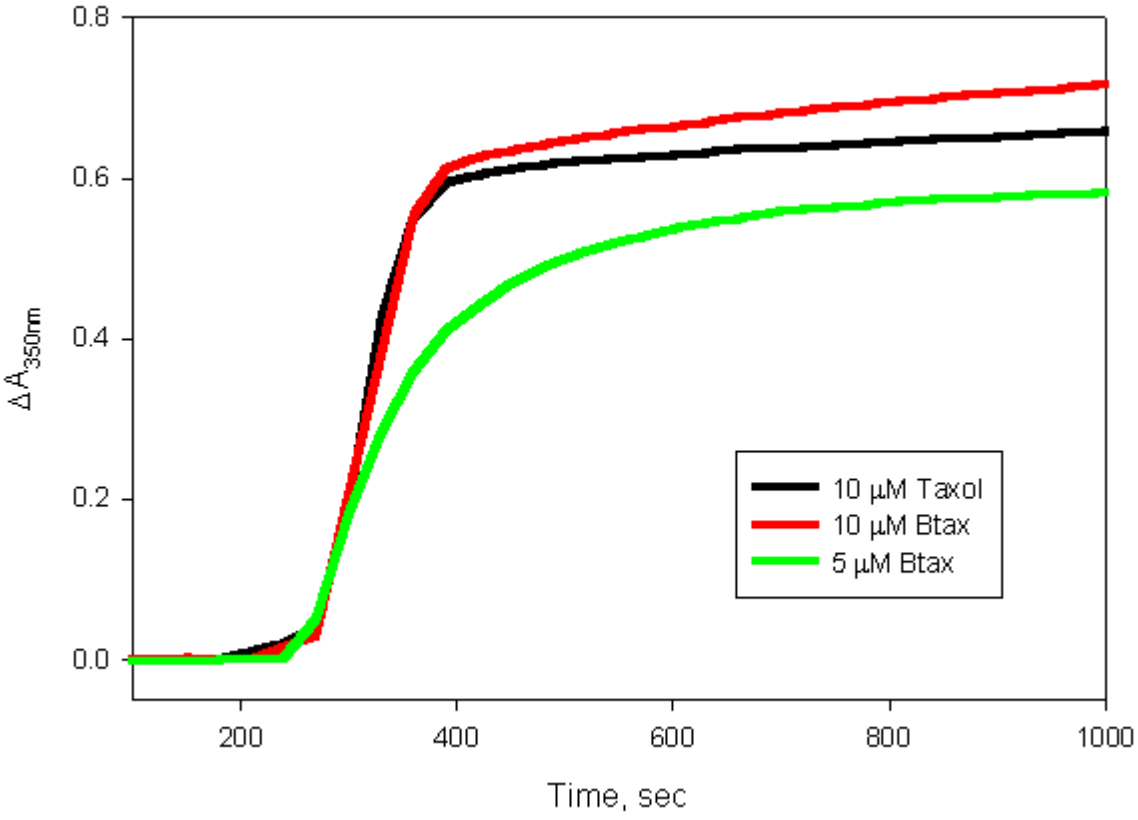


Figure 19 Promotion of tubulin assembly by paclitaxel and BTax.

Tubulin in PMEG buffer (0.1 M Pipes, 1 mM $MgSO_4$, 2 mM EGTA and 0.1 mM GTP, pH 6.9) was equilibrated to 37 °C prior to addition of the ligand. Assembly was monitored by apparent light scattering (absorption at 350 nm).

* Microtubule binding studies were conducted at Dr. Susan Bane's laboratories in the Department of Chemistry at State University of New York at Binghamton. The results shown herein were obtained from Dr. Susan Bane.

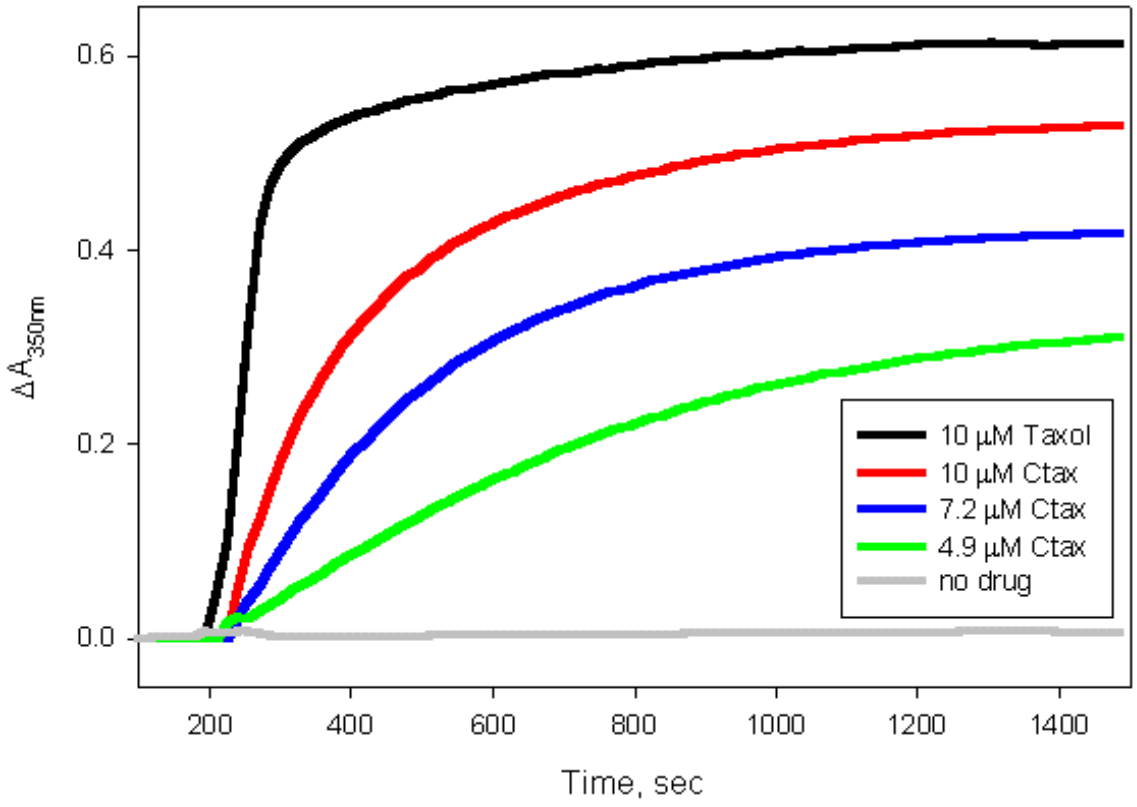


Figure 20 Promotion of tubulin assembly by paclitaxel and CTax.

Tubulin in PMEG buffer (0.1 M Pipes, 1 mM $MgSO_4$, 2 mM EGTA and 0.1 mM GTP, pH 6.9) was equilibrated to 37 °C prior to addition of the ligand. Assembly was monitored by apparent light scattering (absorption at 350 nm).

The absorption, excitation and emission spectra of the two fluorescent ligands were obtained in a variety of solvents and bound to microtubules. The effect of microtubule binding on the emission spectra of the drugs is illustrated in Figures 21a and 21b. The emission intensity of BTax increased and underwent a small blue shift upon microtubule binding (Figure 21a).

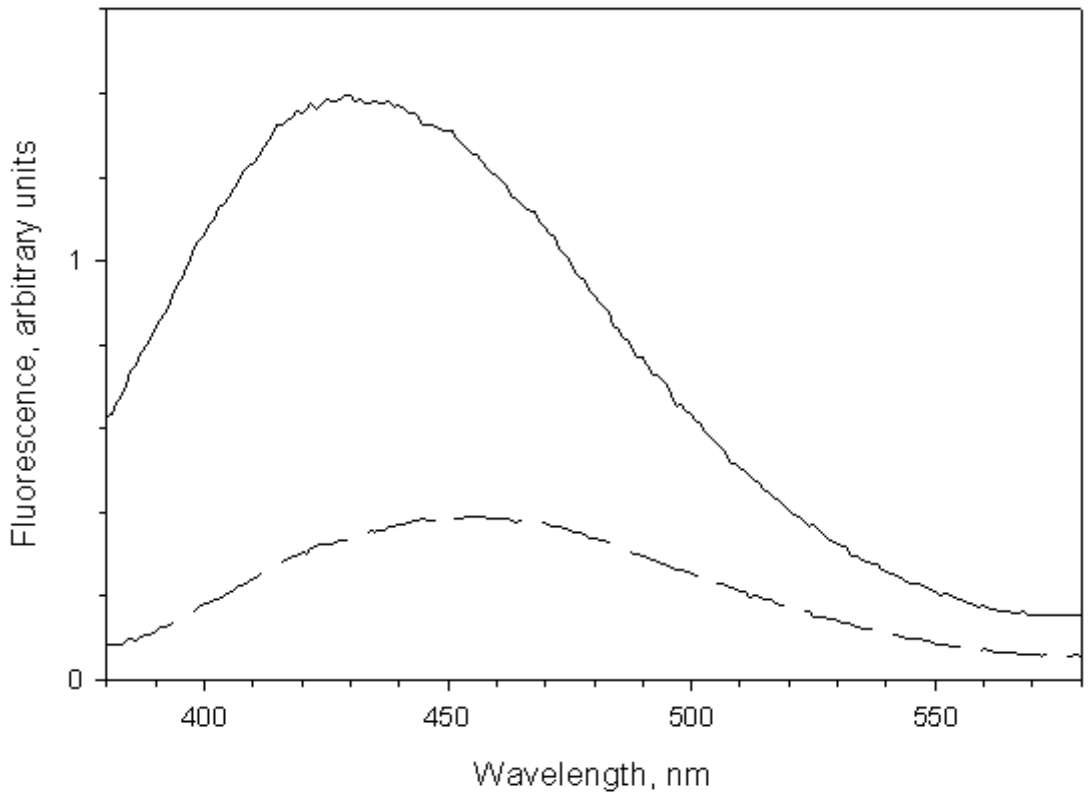


Figure 21a Emission spectra of BTax in the presence and absence of tubulin.

Solid curve: BTax (10 μM) in PMEG buffer was incubated with 10 μM tubulin at 37 °C prior to collection of the emission spectrum. Dashed curve: Emission spectrum of 10 μM BTax in PMEG buffer. The excitation wavelength was 320 nm.

Microtubule binding by CTax is accompanied by a significant increase in emission intensity (Figure 21b).

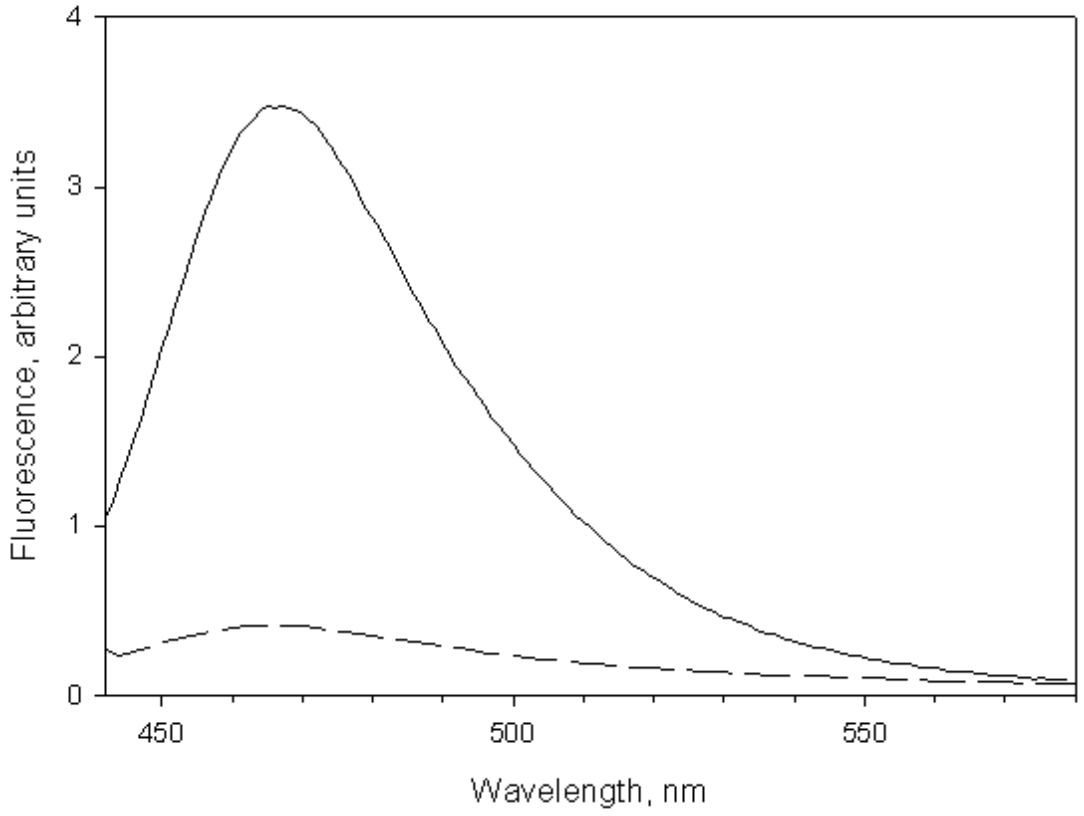


Figure 21b Emission spectra of CTax in the presence and absence of tubulin.

Solid curve: CTax (10 μM) in PMEG buffer was incubated with 10 μM tubulin at 37 °C prior to collection of the emission spectrum. Dashed curve: Emission spectrum of 10 μM CTax in PMEG buffer. The excitation wavelength was 420 nm.

Since the absorption maximum of the BTax ligand in buffer is near 320 nm, ultraviolet radiation is required for excitation of this fluorophore. CTax possesses photochemical properties that make it more useful than BTax as a fluorescent probe, since both absorption and emission maxima are in the visible region of the electromagnetic spectrum. It was observed that the emission intensity is strongly affected by environmental polarity (Table 2).

Table 2 Absorption and emission maxima and relative emission intensity of Ctax in solvent and bound to microtubules

Solvent	Absorption Maximum, nm	Emission Maximum, nm	Relative Fluorescence Intensity[a]
Dioxane	413	447	42
Ethyl Acetate	415	452	40
Dimethylsulfoxide	427	469	18
Acetonitrile	422	464	1.0
Ethanol	423	461	0.11
Methanol	424	462	0.27
2%DMSO/Water	428[b]	462[b]	0.06
Microtubules	430[c]	468	4.8[d]

[a]For solvents: Intensity at emission maximum, normalized to acetonitrile value. The absorptivity of the solvent samples at the excitation wavelength (420 nm) was equal. For microtubules: Intensity of bound drug relative to free drug. [b]Without DMSO co-solvent and at higher concentrations the ligand undergoes self-association. The absorption maximum of aggregated samples is 434 nm and the emission maximum is 530 nm. [c]Approximate value due to turbidity of microtubule-containing solution. [d]Concentration of free drug at 0.4 μM, concentration of bound drug at 0.4 μM in presence of 5 μM tubulin.

Figure 22 illustrates the possible binding site interactions between C-10 labeled Taxol and tubulin. The conformation and orientation of CTax is based on the Bane-Kingston-Schaefer model of the Taxol-tubulin interaction.[52m] The C-10 substituent lies in a crevasse in the surface of the binding site and is exposed to solvent. The small change in emission energy observed when BTax and CTax bind to microtubules indicates that the substituent is solvent accessible. This model is also consistent with the structure-activity data for C-10 analogs of Taxol.[68] The C-10 fluorophore in this model is in close proximity to an arginine residue.

[68] Kant, J.; O'Keeffe, W. S.; Chen, S.-H.; Farina, V.; Fairchild, C.; Johnston, K.; Kadow, J. F.; Long, B. H.; Vyas, D. *Tetrahedron Lett.* **1994**, *35*, 5543-5546

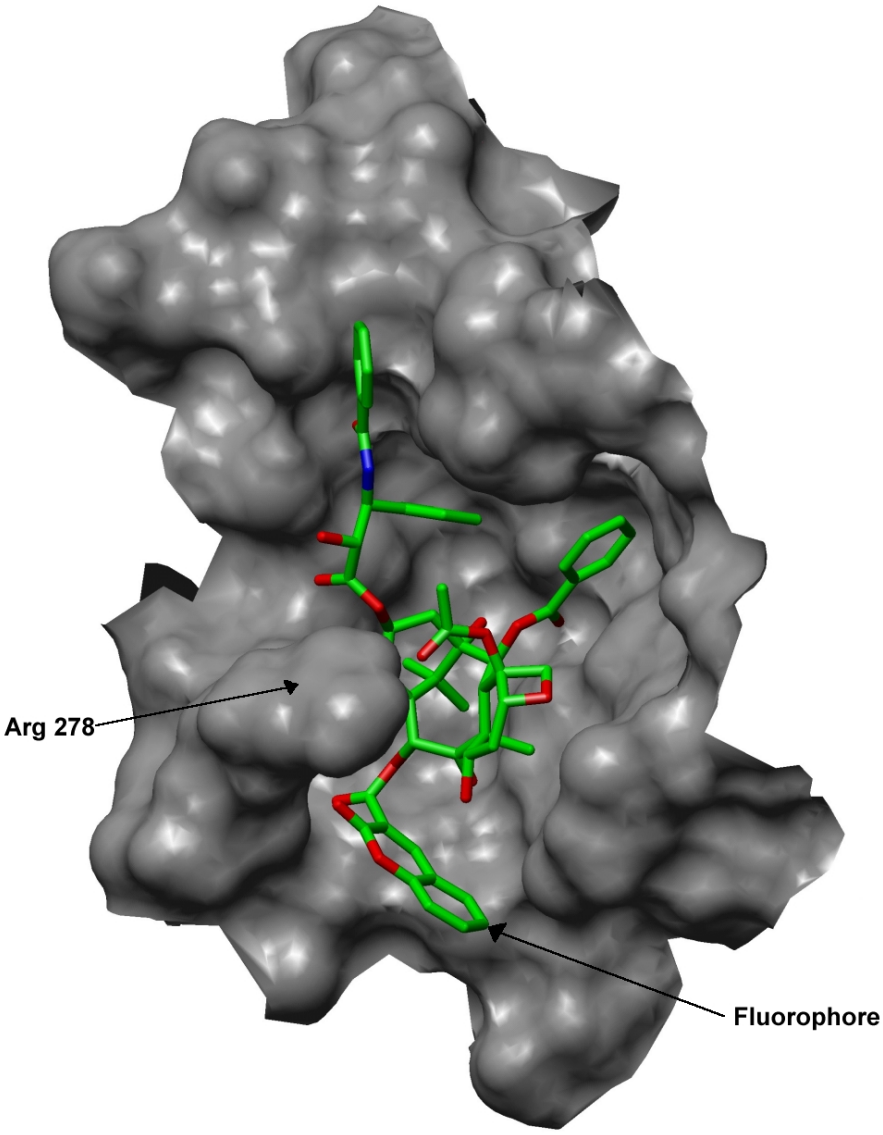


Figure 22 Model of CTax bound to microtubules.

CTax was docked into the paclitaxel binding site as described in Li et al.[54m] and the resulting complex was minimized in vacuum. Amino acid residues within 6 Å of the ligand are shown.

2.4 Discussion

Two new fluorescent labeled analogs of Taxol and the first example of a fluorescent baccatin derivative in which the fluorophore is attached to these taxoids at the C-10 position have been prepared. The studies have defined that the C-10 position can be used for preparation of fluorescent derivatives of Taxol since these analogs retain good *in vitro* assembly-promoting activity. According to these studies, the small change in emission intensity when BTax binds to microtubules limits its utility as a probe, however, it might be more useful than the coumarin fluorophore for probing the local environment. The increase in intensity of BTax is likely to be due to a polarity change in the environment. The 7-(diethylamino)coumarin-3-carbonyl fluorophore, which has not been previously used to fluorescently label Taxol, however, produces a probe with many possible utilities. The coumarin fluorophore is more useful for visualizing Taxol bound to tubulin using fluorescence microscopy. It is useful for the investigation of biological systems. Since the probe can be excited with visible light, the fluorescent Taxol-microtubule association can be readily observed in standard plate readers and possibly in live cells. Unlike the rhodamine and fluorescein Taxol derivatives, the emission intensity of the diethylaminocoumarin fluorophore in CTax undergoes a large change in emission intensity upon microtubule binding. Thus, background fluorescence due to unbound ligand will be low when CTax is used as a probe.

3. SYNTHESIS AND BIOLOGICAL EVALUATION OF TAXOL ANALOGS MODIFIED AT MORE THAN ONE SITE

3.1 Introduction

Many derivatives of Taxol have been reported to date, some of which have been found to be more, and some less potent than Taxol. The SAR of Taxol have been extensively studied and as discussed earlier, it is well known that certain modifications at certain positions may result in critical differences in its activity. Most of the SAR studies reported to date have focused primarily on modifications at only one position and their effects on the activity, but a few have involved in manipulations at more than one site.[69] *How would the activity be affected if Taxol was synchronously modified at more than one site? Would it be possible to observe a synergistic effect if the groups that are already known to increase the activity at certain positions were introduced at the same time?* In order to answer these questions, concurrent modifications on selected positions were performed and their biological evaluations were studied. The biological activity of these analogs were evaluated in two different assay systems. One of them was for their ability to assemble microtubular protein,* the other one was for their cytotoxicity against human ovarian cancer (A2780) cells. These data are summarized in tabular form, together with the data for Taxol itself for comparison.

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[69] a) Yuan, H.; Fairchild, C. R.; Liang, X.; Kingston, D. G. I. *Tetrahedron* **2000**, *56*, 6407-6414 b) Chordia, M. D.; Yuan, H. Q.; Jagtap, P. G.; Kadow, J. F.; Long, B. H.; Fairchild, C. R.; Johnston, K. A.; Kingston, D. G. I. *Bioorg. Med. Chem.* **2001**, *9*, 171-178

* Microtubule binding studies were conducted at Dr. Susan Bane's laboratories in the Department of Chemistry at State University of New York at Binghamton. The results shown herein are obtained from Dr. Susan Bane.

3.2 C-3'N and C-10 Mono-Modified Taxol Analogs

Prior to the synthesis of Taxol analogs modified at more than one site, the methods that would be used for the syntheses should be extended to the preparation of Taxol analogs with variable substituents modified at only one site. By preparing analogs modified at only one site, with the same substituents used for the synthesis of Taxol analogs modified at more than one site, it should be possible to find out which group is actually responsible for the activity. In addition, studying the activities of the mono-modified analogs would enable a determination as to whether a synergistic effect was observed or not. The C-3'N and C-10 mono-modified Taxol analogs (Figure 23) were thus prepared according to the procedures described in the literature.[70]

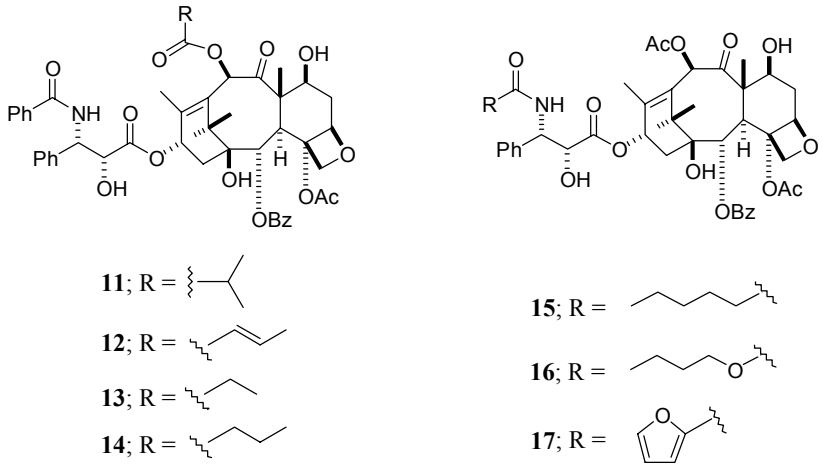


Figure 23 C-3'N and C-10 mono-modified Taxol analogs

[70] For the synthesis of these analogs please see: a) *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M., Eds.; American Chemical Society: Washington, DC, 1995; Vol. 583 and the references cited therein.

3.2.1 Synthesis of C-10 Modified Taxol Analogs

Starting with the known precursor **1**, the C-10 hydroxyl group was acylated with the desired carboxylic acids via the carbodiimide-based coupling protocol, followed by removal of the silyl protecting groups in the presence of HF-pyridine to give the C-10 modified Taxol analogs **11-14** (Figure 24).

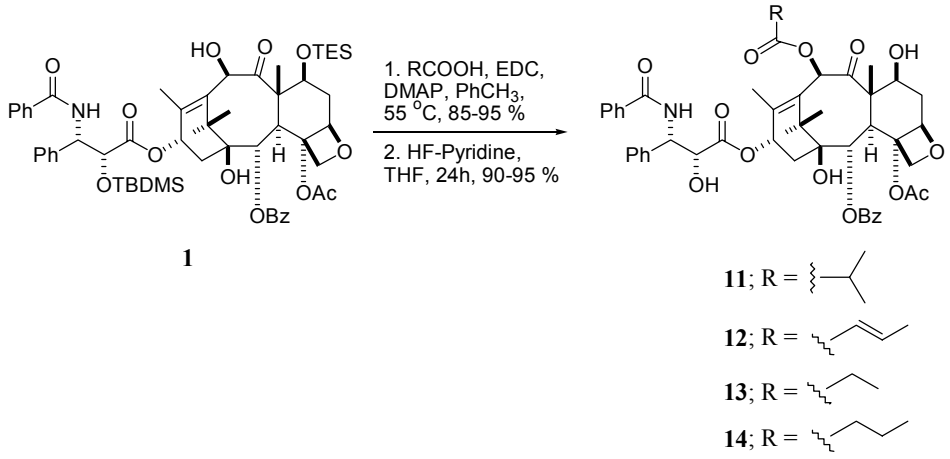
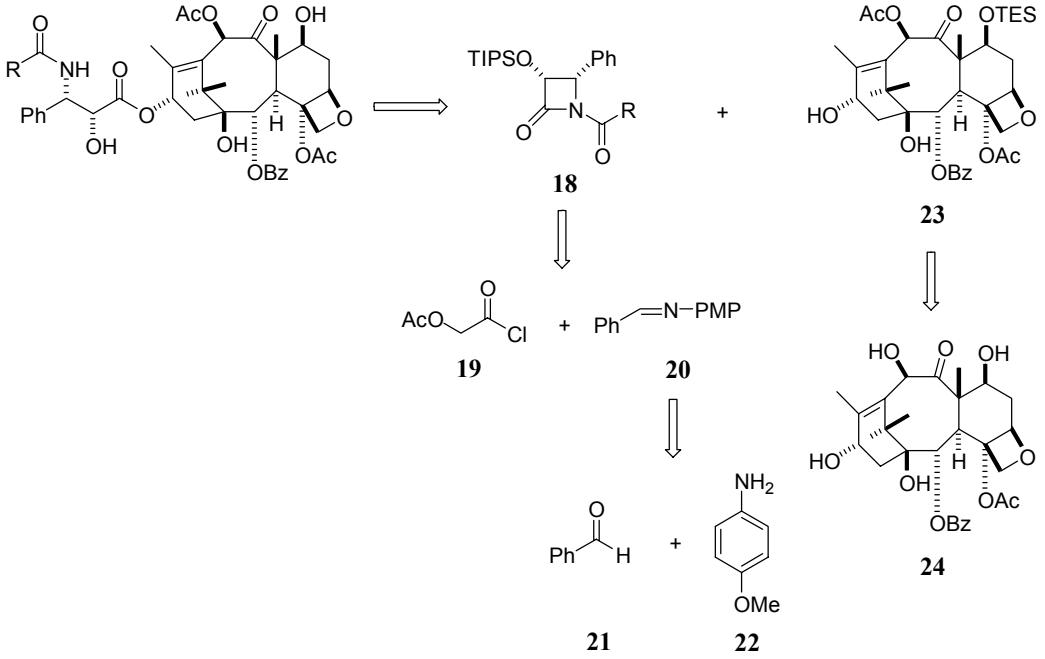


Figure 24 Synthesis of C-10 modified Taxol analogs

3.2.2 Retrosynthetic Analysis of C-3'N Modified Taxol Analogs

The synthesis involved two major fragments, the β-lactam (**18**) and the basic ring skeleton of the target molecule, 7-(triethylsilyl)baccatin III (**23**). The union of acetoxyacetyl chloride (**19**) and *N*-(4-methoxyphenyl)benzaldimine (**20**), which could be

prepared from commercially available starting materials, benzaldehyde (**21**) and *p*-anisidine (**22**) would furnish the β-lactam by the highly convergent method.[71,72] The commercially available 10-deacetylbaccatin III (10-DAB, **24**) could be used for the construction of 7-(triethylsilyl)baccatin III (Scheme 4).



Scheme 4 Retrosynthetic analysis of C-3'N modified Taxol analogs

3.2.3 Synthesis of C-3'N Modified Taxol Analogs

The sequence leading to the required β-lactams is shown in Figure 25. The known β-lactam derivative **25**[72] was initially converted to amide **26** (CAN, H_2O,

[71] Brieva, R.; Crich, J. Z.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 1068-1075
[72] Palomo, C.; Arrieta, A.; Cossio, F.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 6429-6432

CH_3CN),[72] which was then acylated with the desired acyl chloride to give the β-lactams **27**-**29**.

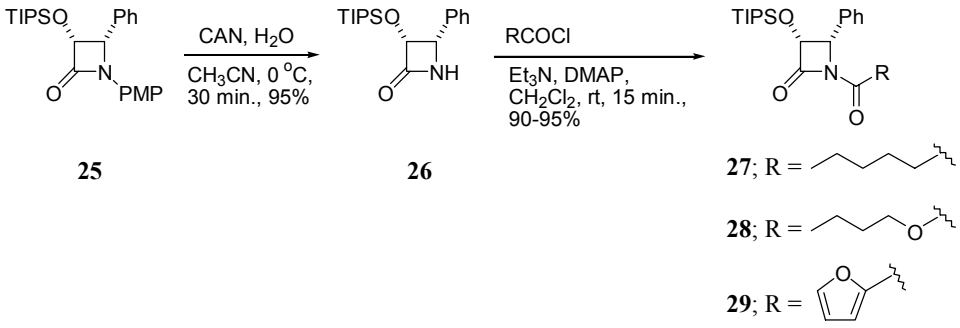


Figure 25 Synthesis of β-lactams **27**-**29**

Selective acylation of the C-10 hydroxyl group by acetic anhydride following Holton's protocol followed by protection of the C-7 OH group as its triethylsilyl ether yielded 7-(triethylsilyl)baccatin III (Figure 26).[73]

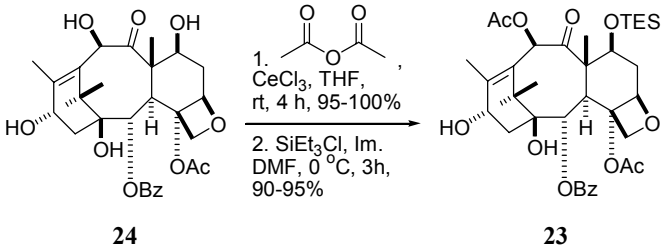
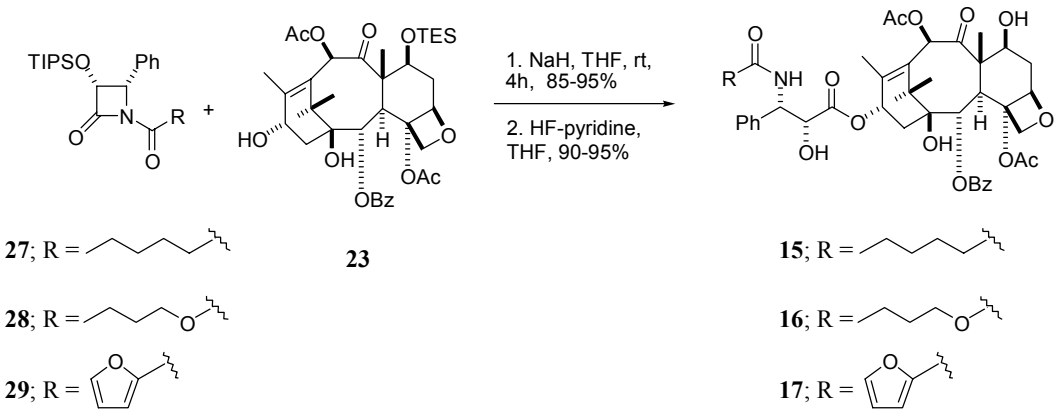


Figure 26 Synthesis of 7-(triethylsilyl)baccatin III

The β-lactams **27**-**29** were coupled with 7-(triethylsilyl)baccatin III (**23**) in the presence of NaH, followed by removal of the protecting groups gave the desired C-3'N modified Taxol analogs **15**-**17** in good yield (Figure 27).

[73] Holton, R. A.; Zhang, Z.; Clarke, P. A.; H., N.; Procter, D. J. *Tetrahedron Lett.* **1998**, *39*, 2883-2886



27; R = **23** **15**; R =

28; R = **16**; R =

29; R = **17**; R =

Figure 27 Synthesis of C-3'N modified Taxol analogs

3.3 Biological Evaluation of C-3'N and C-10 Mono-Modified Taxol Analogs

In the cytotoxicity test using the A2780 human ovarian cancer cell line the compounds **11-14** showed significantly increased cytotoxicity as compared with Taxol, with IC_{50} values less than 0.00122 μg/mL. Compounds **15** and **16** showed slightly better cytotoxic activity than Taxol, and compound **17** showed a diminished average cytotoxic activity with an IC_{50} value of 14.5 μg/mL. None of these analogs showed comparable activity to Taxol in the microtubule assembly assay (Table 3).

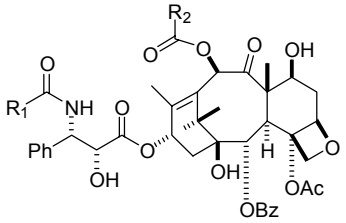


Table 3 Biological evaluation of the mono-modified Taxol analogs

Structure	R_1	R_2	Cytotoxic Activity (IC_{50}) (μg/mL) (A2780)	I_{50} (μM) Microtubule Assembly Assay
11	Ph	*i*Pr	<0.00122	2.55 ± 0.65
12	Ph	-CH=CH-Me	<0.00122, <0.00122	N/A
13	Ph	Et	<0.00122, <0.00122	N/A
14	Ph	Pr	<0.00122, <0.00122	5.70 ± 1.07
15	Pentyl	Me	0.07, 0.13	2.50 ± 0.57
16	BuO	Me	0.05, 0.04	3.78 ± 1.55
17	2-Furyl	Me	14.1, 14.9	2.10 ± 0.29
Taxol	Ph	Me	0.136 ± 0.08 (7)	0.55 ± 0.1

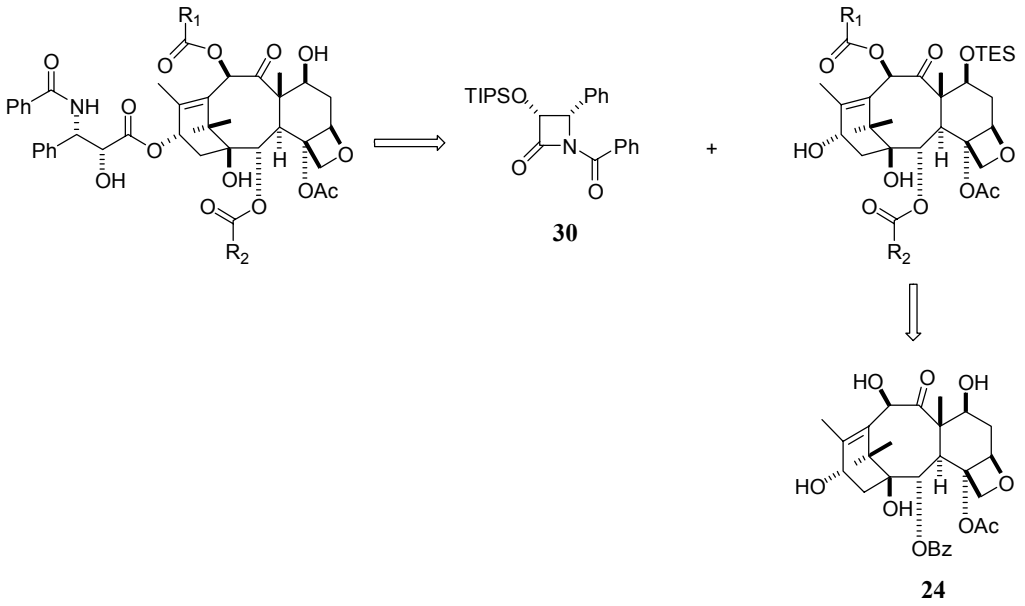
3.4 Synthesis of C-2 - C-10 Modified Taxol Analogs

The design of the targeted analogs and choice of the groups to be introduced to these compounds followed a careful study of the reported SAR information of Taxol. The SAR of Taxol as described in section 1.6 and its known patterns of reactivity were considered. To maximize the probability of synthesizing a more potent analog, *m*-azido and *m*-chloro benzoyl groups were selected to replace the benzoyl group at the C-2 position.[74] At the same time, 4 different groups with different sizes were explored for the C-10 position.

3.4.1 Retrosynthetic Analysis for the Synthesis of C-2 - C-10 Modified Taxol Analogs

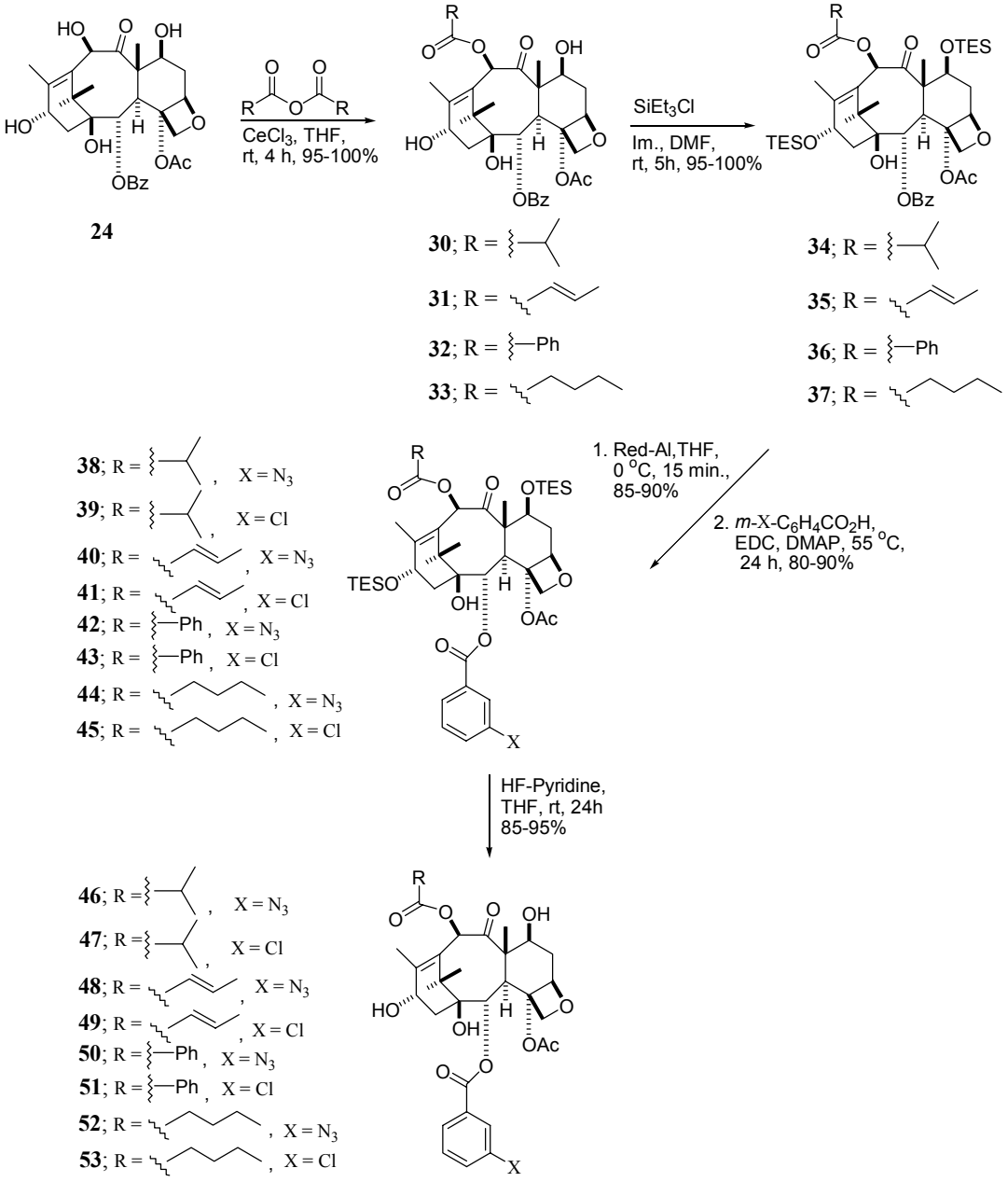
The planned synthesis involved two major fragments, the β-lactam (**30**) and the basic ring skeleton of the target molecule, the suitably decorated baccatin moiety. As previously discussed, the β-lactam could be prepared by the literature methods. The commercially available 10-deacetylbaccatin III (10-DAB, **24**) could be used for the construction of the desired baccatin derivative (Scheme 5).

[74] These groups are known to increase activity when replaced the C-2 benzoyl group. For detailed information please see Kingston, D. G. I.; Chaudhary, A. G.; Chordia, M. D.; Gharpure, M.; Gunatilaka, A. A. L.; Higgs, P. I.; Rimoldi, J. M.; Samala, L.; Jagtap, P. G.; Giannakakou, P.; Jiang, Y. Q.; Lin, C. M.; Hamel, E.; Long, B. H.; Fairchild, C. R.; Johnston, K. A. *J. Med. Chem.* **1998**, *41*, 3715-3726



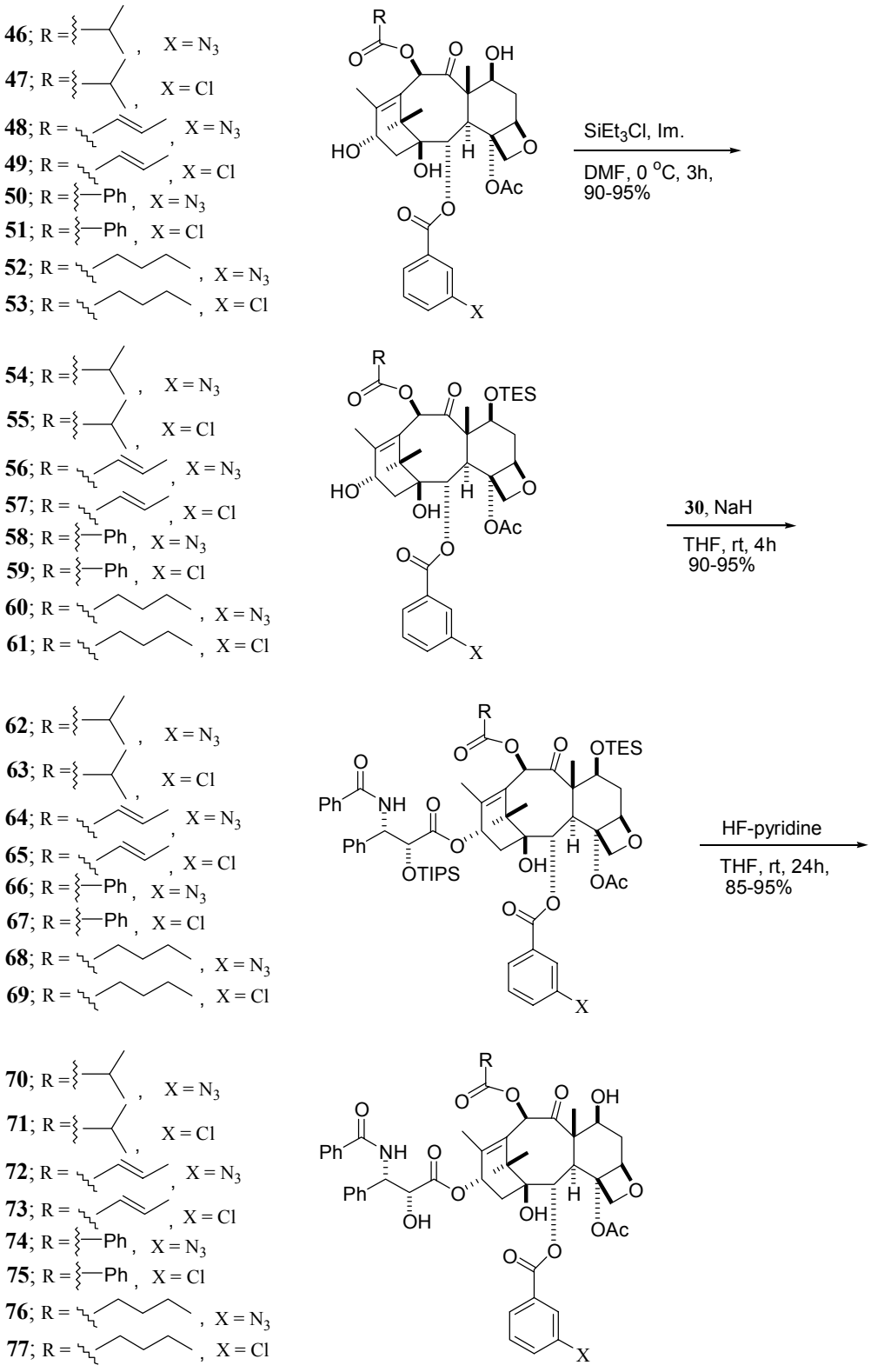
Scheme 5 Retrosynthetic analysis of C-2 - C-10 modified Taxol analogs

The synthesis started from the easily accessible natural product 10-DAB (**24**). Selective acylation of the C-10 hydroxyl group following Holton's protocol yielded the four baccatins **30-33** esterified at the C-10 position. Exhaustive protection of the remaining secondary hydroxyl groups as their triethylsilyl ethers provided the baccatin derivatives **34-37**. Selective removal of the C-2 benzoyl group with Red-Al, followed by carbodiimide-based reesterification with either *m*-azido or *m*-methoxybenzoic acid in the presence of EDC afforded the baccatins **38-45**. The silyl protecting groups were then unveiled to give the baccatin analogs **46-53** (Scheme 6).



Scheme 6 Synthesis of C-2 - C-10 Modified Baccatin Analogs

In order to convert these new baccatin analogs to Taxol derivatives, the silyl protecting groups for the C-7 hydroxyls were reconstituted to give analogs **54-61**, which were coupled with the β-lactam derivative (**30**) to give the protected Taxol derivatives **62-69**. Simultaneous removal of the silyl protecting groups with HF/Pyridine furnished the new Taxol analogs (**70-77**) modified at the C-2 and C-10 positions (Scheme 7).



Scheme 7 Synthesis of C-2 - C-10 modified Taxol analogs

3.5 Biological Evaluation of C-2 - C-10 Modified Taxol Analogs

In the cytotoxicity test using the A2780 human ovarian cancer cell line the compounds **70** and **71** showed significantly increased activity and compounds **74-77** showed comparable activity to Taxol. However, compounds **70** and **74** were the only compounds that showed increased activity when compared to Taxol in the microtubule assembly assay (Table 4).

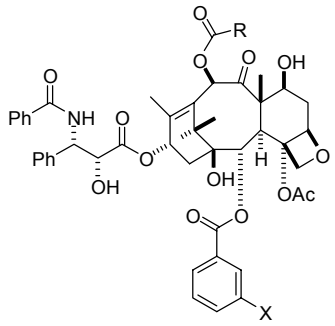


Table 4 Biological evaluation of C-2 - C-10 modified Taxol analogs

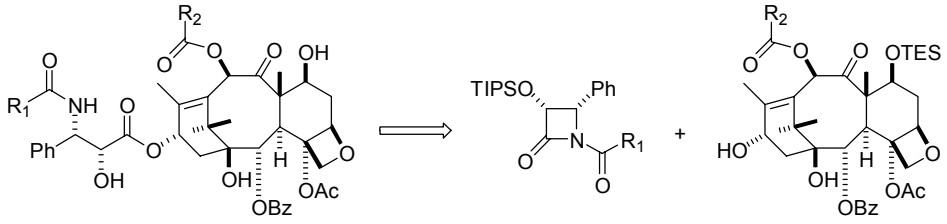
Structure	R	X	Average Activity (IC_{50}) (μg/mL) (A2780)	I_{50} (μM) Microtubule Assembly Assay
70	*i*Pr	N_3	0.014, <0.00122	0.32 ± 0.15
71	*i*Pr	Cl	0.007, 0.08	1.50 ± 0.45
72	-CH=CH-Me	N_3	2.2	2.47 ± 1.02
73	-CH=CH-Me	Cl	0.24, 0.22	1.09 ± 0.33
74	Ph	N_3	0.17, 0.15	0.29 ± 0.002
75	Ph	Cl	0.17, 0.2	1.08 ± 0.34
76	Bu	N_3	0.07, 0.14	3.90 ± 0.49
77	Bu	Cl	0.19, 0.17	0.776 ± 0.17
Taxol	Me	H	0.136 ± 0.08 (7)	0.55 ± 0.1

3.6 Synthesis of C-3'N - C-10 Modified Taxol Analogs

The SAR studies on the effects of modifications at the C-3' nitrogen showed that analogs without a 3'-amino group or a 3'-*N*-acyl group are significantly less active than Taxol.[75] It is also known that aliphatic and heteroaromatic *N*-acyl analogs are slightly more active than Taxol.[76] Therefore, an aliphatic, a heteroaromatic and a heteroaliphatic group were selected to be substituted for the phenyl ring of the benzoyl group at the C-3'N position.

3.6.1 Retrosynthetic Analysis for the Synthesis of C-3'N - C-10 Modified Taxol Analogs

Inspection of the target Taxol analog suggested that the β-lactam synthon method could also be applied for the modifications of the selected positions. Thus, the desired enantiomerically pure β-lactams would be prepared in the same fashion and the required baccatin derivatives could be achieved through the same procedure shown earlier (Scheme 8).



Scheme 8 Retrosynthetic analysis of C-3'N - C-10 modified Taxol analogs

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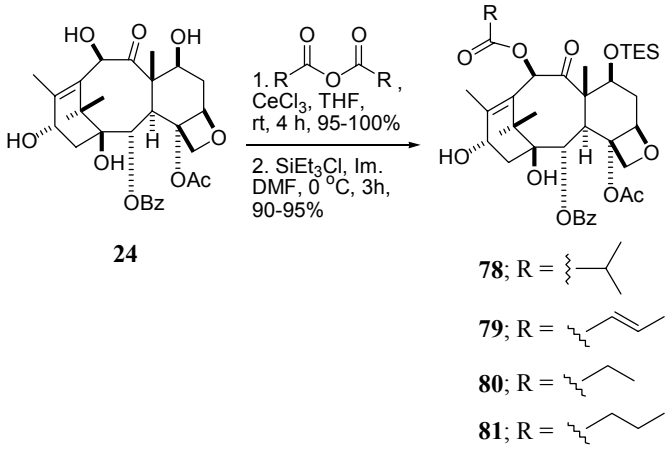
[75] Gueritte-Voegelein, F.; Guenard, D.; Lavelle, F.; Le Goff, M.-T.; Mangatal, L.; Potier, P. *J. Med. Chem.* **1991**, *34*, 992-998

[76] a) Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Clowers, J. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press, Inc.: Boca Raton, FL, **1995**, p 317-375 b) Georg, G. I.; Harriman, G. C. B.; Vander Velde, D. G.; Boge, T. C.; Cheruvallath, Z. S.; Datta, A.; Hepperle, M.; Park, H.; Himes, R. H.; Jayasinghe, L. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; American Chemical Society: Washington, DC, **1995**; Vol. ACS Symposium Series 583, p 217-232

The synthesis of the baccatin core, requiring proper acylations at the C-10 position and conversion of the C-7 hydroxyl to the triethylsilyl ether, was carried out in the same fashion described earlier to provide baccatin derivatives **78-81** (Scheme 9).



24

78; R =

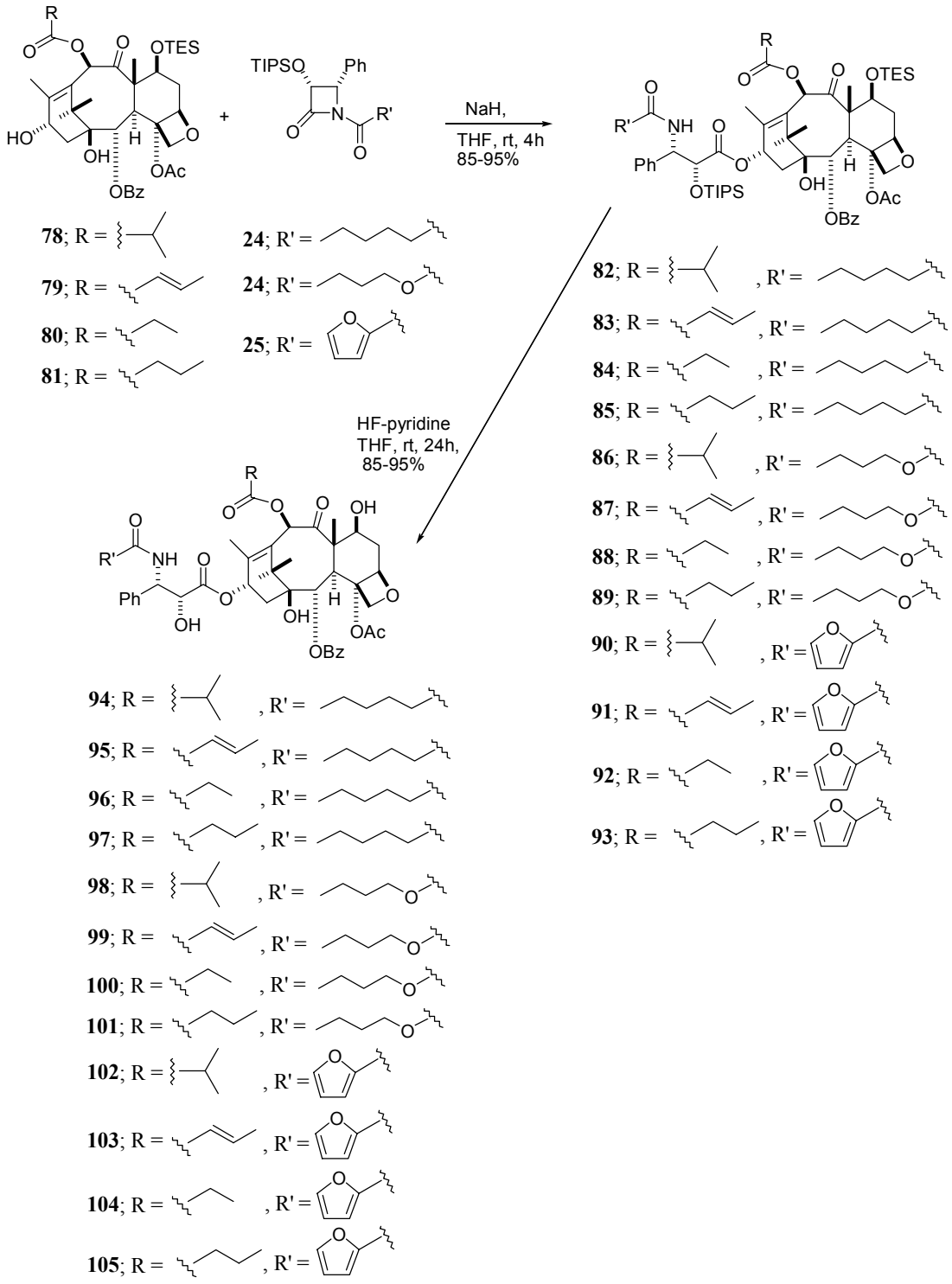
79; R =

80; R =

81; R =

Scheme 9 Synthesis of baccatin derivatives **78-81**

The completion of the synthesis of the targeted Taxol analogs is presented in Scheme 10. The coupling of the baccatin derivatives **78-81** with the β-lactams **27-29** in the presence of NaH yielded the protected Taxol derivatives **82-93**. Unmasking of the silyl protecting groups gave the desired C-3'N - C-10 modified Taxol analogs **94-105** in good yield (Scheme 10).



Scheme 10 Synthesis of C-3'N - C-10 modified Taxol analogs

3.7 Biological Evaluation of C-3'N - C-10 Modified Taxol Analogs

In the cytotoxicity test using the A2780 human ovarian cancer cell line all the compounds in this series showed significantly increased activity as compared with Taxol. However, compounds **104** and **105** were the only compounds that showed only increased activity when compared to Taxol in the microtubule assembly assay (Table 5).

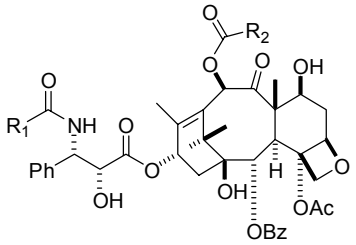
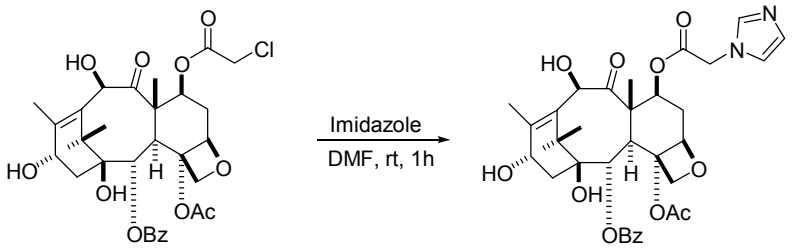


Table 5 Biological evaluation of C-3'N - C-10 Modified Taxol Analogs

Structure	R_1	R_2	Average Activity (IC_{50}) (μg/mL) (A2780)	I_{50} (μM) Microtubule Assembly Assay
94	Pentyl	*i*Pr	<0.00122 (5)	1.20 ± 0.31
95	Pentyl	-CH=CH-Me	0.01, <0.00122	3.58 ± 0.64
96	Pentyl	Pr	<0.00122 (2)	1.62 ± 0.57
97	Pentyl	Et	0.04, 0.02	3.90 ± 1.08
98	Butoxy	*i*Pr	0.007 ± 0.005 (3)	2.03 ± 0.17
99	Butoxy	-CH=CH-Me	0.022, 0.03	4.85 ± 2.44
100	Butoxy	Pr	0.06, 0.02	4.99 ± 2.32
101	Butoxy	Et	<0.00122 (2)	2.88 ± 1.26
102	2-Furyl	*i*Pr	0.001 ± 0.001 (5)	1.00 ± 0.17
103	2-Furyl	-CH=CH-Me	0.02 ± 0.01 (3)	1.10 ± 0.52
104	2-Furyl	Pr	0.002 ± 0.001 (4)	0.36 ± 0.13
105	2-Furyl	Et	0.004 (2)	0.49 ± 0.08
Taxol	Ph	Me	0.136 ± 0.08 (7)	0.55 ± 0.1

3.8 C-10-Deacetyl - C-7 Modified Taxol Analogs

During studies of synchronous multiple modifications it was observed that the chlorine of the chloroacetyl group can be substituted in an S_N2 fashion with imidazole at room temperature (Scheme 11).



106 **107**

Scheme 11 Substitution of chlorine with imidazole on baccatin

Although substitution reactions of chlorine α to carbonyl groups with nucleophilic amines are common in the literature, they have not yet been observed on taxoids. These substitutions were thus selected for further exploration, not only because they might lead to more active Taxol analogs, but also because some of these analogs might have improved water-solubility as compared to Taxol.

The synthesis started from Taxol, and 2'-(*tert*-butyldimethylsilyl)-10-deacetylpaclitaxel (**108**) was prepared according to the known procedure.[66] Acylation of the C-7 position with chloroacetyl chloride provided 2'-(*tert*-butyldimethylsilyl)-10-deacetyl-7-chloroacetylpaclitaxel (**109**). The *tert*-butyldimethylsilyl group was removed to give **110**, and the stage was set for the substitution reactions with selected nucleophilic amines (Figure 28).

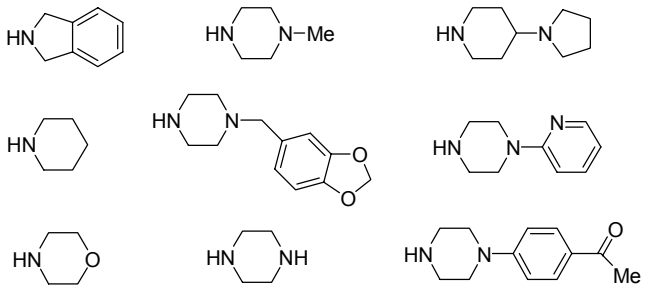
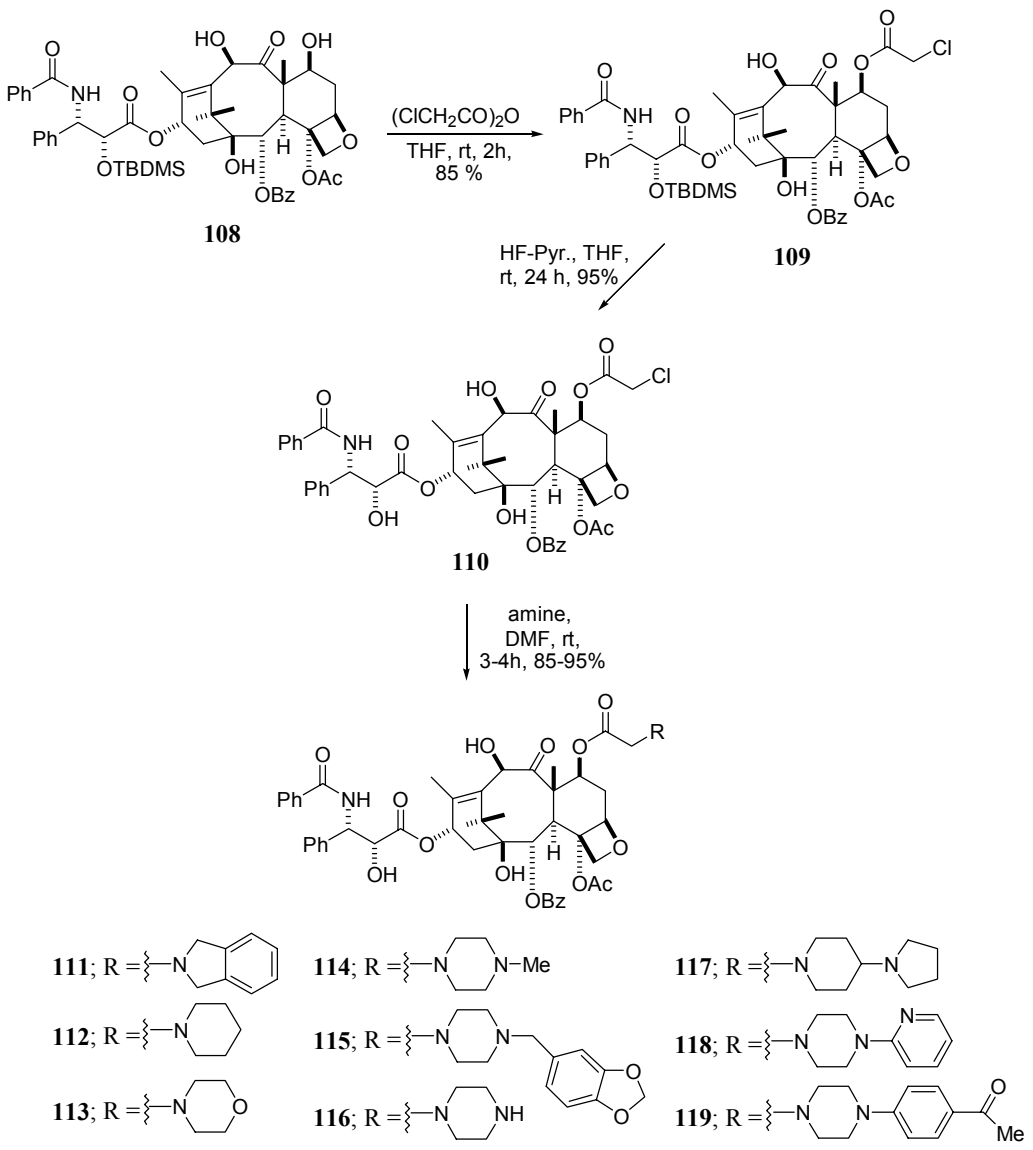


Figure 28 Nucleophilic amines selected for substitution

The substitution reactions afforded the new Taxol derivatives **111-119** in good yields (Scheme 12).



Scheme 12 Synthesis of C-10-Deacetyl - C-7 Modified Taxol Analogs

3.9 Biological Evaluation of C-10-Deacetyl - C-7 Modified Taxol Analogs

In the cytotoxicity test using the A2780 human ovarian cancer cell line all the compounds in this series showed comparable activity to Taxol. Compounds **114** and **117** showed promising activity in both assays. Compound **118** showed almost twice as much cytotoxic activity as Taxol, although it was not as active as Taxol in the microtubule binding assay (Table 6).

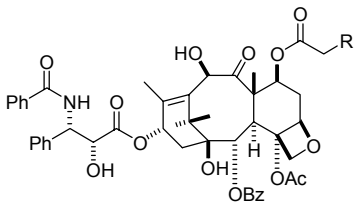
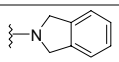
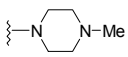
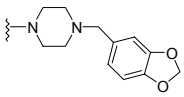
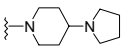
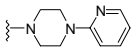
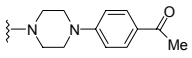


Table 6 Biological evaluation of C-10-deacetyl - C-7 modified Taxol analogs

Structure	R	Average Activity (IC_{50}) (μg/mL) (A2780)	I_{50} (μM) Microtubule Assembly Assay
111		0.25 ± 0.07 (5)	2.04 ± 0.94
112		0.18, 0.25	1.02 ± 0.15
113		0.25, 0.2	1.30 ± 0.32
114		0.67 ± 0.35 (3)	0.59 ± 0.22
115		0.03, 0.02	7.80 ± 2.33
116		0.86 ± 0.1 (3)	N/A
117		0.96	0.85 ± 0.37
118		0.014, 0.11	1.65 ± 0.75
119		0.9 ± 0.04 (3)	4.34 ± 0.62
Taxol	H ; (C-10 = OAc)	0.136 ± 0.08 (7)	0.55 ± 0.1

*3.9.1 Water Solubility Evaluation of **118***

Due to its promising cytotoxic activity, a comparison of the water solubility of analog **118** (as its hydrochloride salt) and Taxol was made. Taxol and **118** were partitioned between 1-octanol and 0.1N aqueous HCl solution and were shaken vigorously for 1 hour. After the layers were separated the UV absorbance of solutions of Taxol and **118** at 229 nm in 1-octanol and 0.1N aqueous HCl were determined (Table 7). The results indicated that the hydrochloride salt of **118** is approximately 9 times more soluble in 0.1N aqueous HCl than Taxol. Its improved cytotoxicity and solubility make **118** an attractive candidate for further development as a drug candidate.

Table 7 Evaluation of the water-solubility of the hydrochloride salt of **118**

Compound	1-Octanol (X)	0.1N aq. HCl soln. (Y)	Ratio (Y/X)
Taxol	0.876 A	0.015 A	0.017
118	0.832 A	0.129 A	0.155

3.10 Synthesis of C-3'N - C-3' Modified Taxol Analogs

The importance of the side chain for the biological activity of Taxol has been discussed earlier. Substitution of the C-3' phenyl group of the side chain with other groups or substituted phenyl moieties was found to give compounds with similar but slightly less activity than Taxol in the microtubule assembly assay, and also to have lower cytotoxicity against B16 melanoma cells compared to that of Taxol.[77] Removal of the phenyl group, however, caused a very significant drop in both the microtubule assembly activity and cytotoxicity.[78]

The Taxol analogs **120** and **121** have been reported by the Ojima group,[79] and indicate that the C-3' phenyl group is not absolutely essential for the biological activity of Taxol, since these analogs were more active than Taxol. It was thus decided to include these analogs, together with the new analog **122**, in the group of derivatives of Taxol to be studied (Figure 29).

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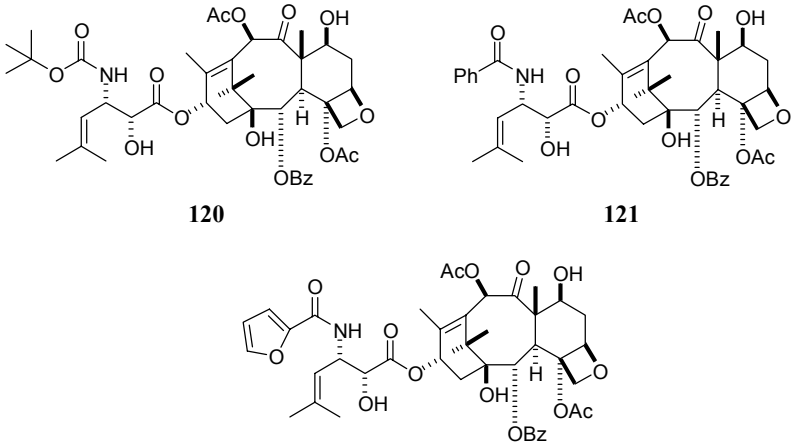
[77] Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Clowers, J. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC Press, Inc.: Boca Raton, FL, 1995, p 317-375

[78] Swindell, C. S.; Krauss, N. E.; Horwitz, S. B.; Ringel, I. *J. Med. Chem.* **1991**, *34*, 1176-1184

[79] Ojima, I.; Park, Y. H.; Fenoglio, I.; Duclos, O.; Sun, C.-M.; Kuduk, S. D.; Zucco, M.; Appendino, G.; Pera, P.; Veith, J. M.; Bernacki, R. J.; Bissery, M.-C.; Combeau, C.; Vrignaud, P.; Riou, J. G.; Lavelle, F. In *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; American Chemical Society: Washington, DC, 1995; Vol. ACS Symposium Series 583, p 262-275



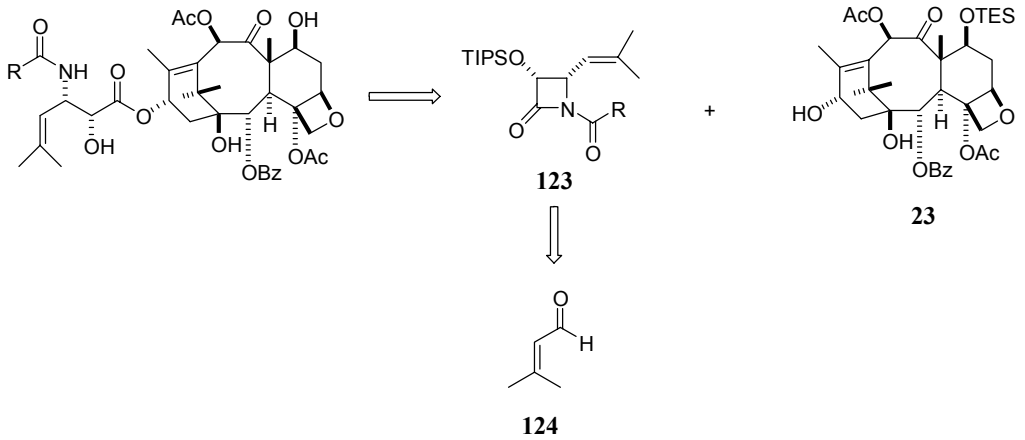
120 **121**

122

Figure 29 Taxol analogs modified at the C-3'N and C-3'

3.10.1 Retrosynthetic Analysis for the Synthesis of C-3'N - C-3' Modified Taxol Analogs

The required β-lactam derivative (**123**) could be prepared in the same fashion discussed earlier, except in this case the precursor should be 3-methyl-2-butenal (**124**) instead of benzaldehyde. Similarly, the baccatin core in this case should be 7-(triethylsilyl)baccatin III (**23**), and it could also be prepared by the known methods shown earlier (Scheme 13).

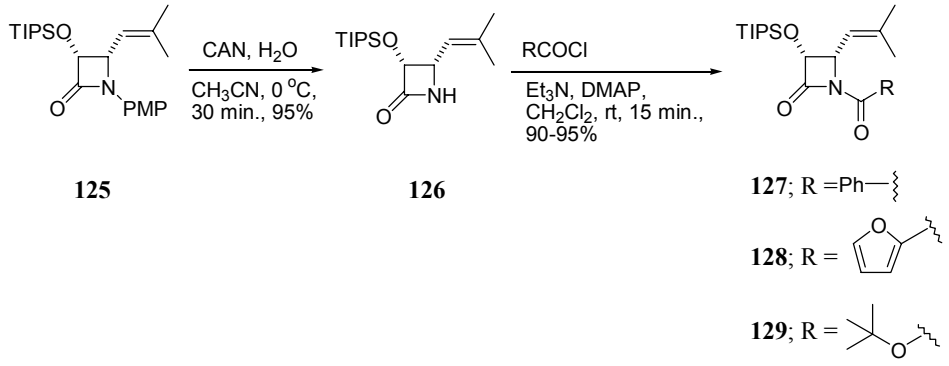


123 **23**

124

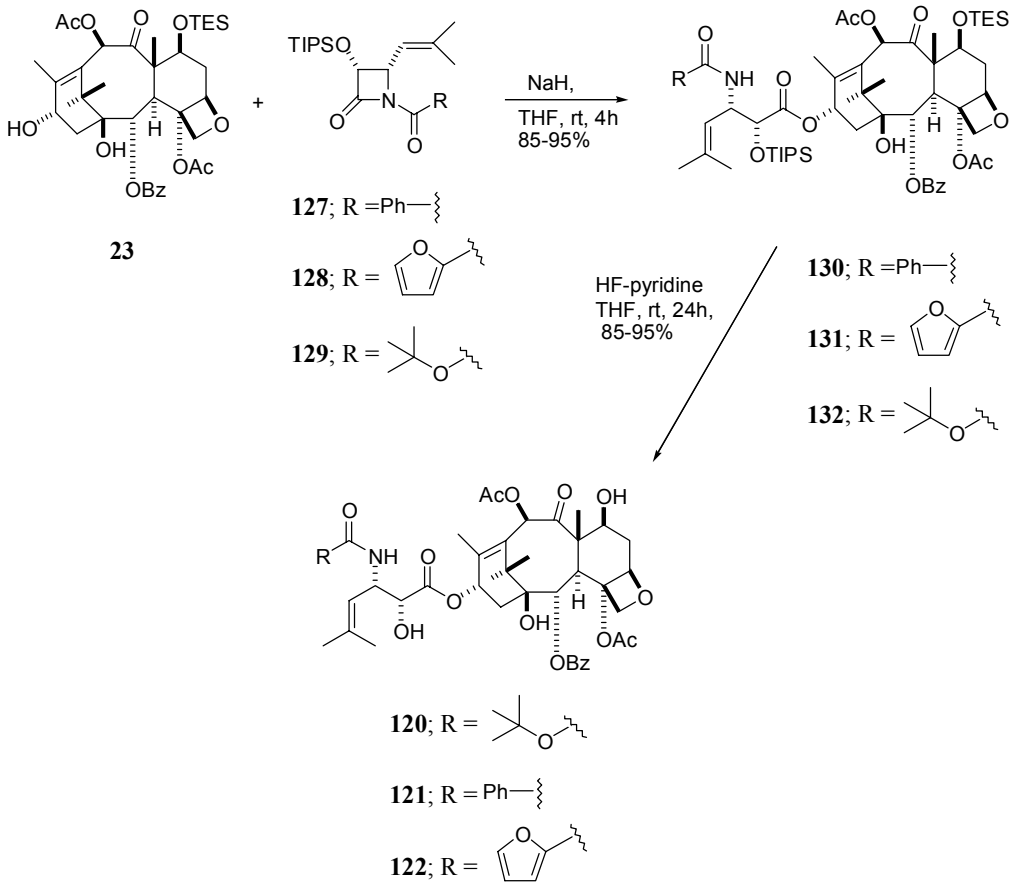
Scheme 13 Retrosynthetic analysis of C-3'N - C-3' modified Taxol analogs

The required β-lactams (**127-129**) was prepared starting from 3-methyl-2-butenal. The desired acylations were performed as shown earlier (Scheme 14).



Scheme 14 Synthesis of β-lactams **127-129**

The synthesis of the targeted Taxol analogs were completed as shown in Scheme 15. The coupling of the β-lactam derivatives **127-129** with 7-(triethylsilyl)baccatin III (**23**) in the presence of NaH gave the protected Taxol derivatives **130-132**. The silyl protecting groups were then unmasked to yield C-3'N - C-3' modified Taxol analogs (**120-122**) in good yield.



Scheme 15 Synthesis of C-3'N - C-3' modified Taxol analogs

3.11 Biological Evaluation of C-3'N - C-3' Modified Taxol Analogs

Although compounds **120** and **121** showed better cytotoxic activity than Taxol against human ovarian cancer cells (A2780), the new analog **122** did not show an improved cytotoxic activity, but it rather showed the reverse. The microtubule binding assay results of the new analog also showed weaker activity than Taxol (Table 8).

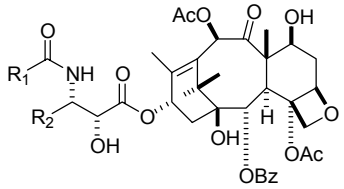


Table 8 Biological evaluation of C-3'N - C-3' modified Taxol analogs

Structure	R_1	R_2	Activity (IC_{50}) (μg/mL) (A2780)	I_{50} (μM) Microtubule Assembly Assay
120	*t*BuO	$(CH_3)_2CH=CH$	0.007, 0.008	7.27 ± 3.39
121	Ph	$(CH_3)_2CH=CH$	0.06, 0.00122	N/A
122	2-Furyl	$(CH_3)_2CH=CH$	4.6, 4.1	1.25 ± 0.35
Taxol	Ph	Ph	0.136 ± 0.08	0.55 ± 0.1

3.12 Discussion

Mitotic inhibitors fall into two classes. Members of one class inhibit tubulin self-assembly and depolymerize microtubules. Members of the other class stabilize microtubules and promote polymerization of tubulin to microtubules. Taxol, along with other compounds that share the same type of activity (shown in Figure 11) belongs to the second class. Because this second class is a small one, and because Taxol is an important pharmaceutical, the discovery of analogs with improved bioactivity is likely to lead to improved anticancer drugs.

Many studies have been reported in recent years that concentrate both on finding more effective derivatives, and determining the binding environment and binding site of Taxol. With the hope of providing answers to some of the remaining questions, several analogs of Taxol modified at more than one site were synthesized. The bioactivities of these new analogs were evaluated in two different assay systems, and the results of this work are briefly analyzed and discussed in this section.

The C-2 - C-10 modified Taxol analogs **70** and **71** showed significantly improved cytotoxic activity compared with Taxol, and compounds **74**-**77** showed comparable cytotoxic activity to that of Taxol. Compounds **70** and **74** were the only two out of eight compounds that also showed increased activity when compared to Taxol in the microtubule assembly assay. Although compounds **70** and **71** showed improved activity relative to Taxol, this improvement is not significantly greater than would have been expected from the C-2 substituent alone. Thus Kingston and collaborators have shown that 2-(*m*-azidobenzoyl)taxol and 2-(*m*-chlorobenzoyl)taxol have increased cytotoxicity in the A2780 cell line compared with Taxol by factors of 5.6 and 20 respectively.[74] These compounds also had improved tubulin assembly activities by factors of 2.7 and 1.1 respectively.[74] The improvements in activity of compounds **70** and **71** are of comparable

magnitudes to these values, suggesting that the effect of the C-10 substituent is not significant, while the activities of compounds **72-77** indicates that the C-10 substituent has *reduced* their activity as compared with the corresponding C-10 acetyl analogs.

All of the C-3'N - C-10 modified analogs showed significant increases in cytotoxicity against A2780 human ovarian cancer cells when compared to Taxol, but only compounds **104** and **105** showed increased activity when compared to Taxol in the microtubule assembly assay. This disconnect between improved cytotoxicity and tubulin assembly activity is not unprecedented, but it is nevertheless unusual; in the case of the 2-acyl analogs of Taxol, for example, a reasonably good correlation between cytotoxicity and tubulin assembly activity was observed.[74]

Although all the C-10-deacetyl - C-7 modified analogs showed comparable activity to Taxol in the cytotoxicity test using the A2780 human ovarian cancer cell line, compounds **114** and **117** were the only compounds that showed comparable activity in the microtubule assembly assay. Compound **118** showed about twice as much cytotoxic activity as Taxol, although it was not as active as Taxol in the microtubule binding assay. Because of this improved cytotoxicity and the improved solubility of its hydrochloride salt, **118** is an attractive candidate for further development as a drug candidate.

While the known C-3' - C-3'N modified Taxol derivatives (**120** and **121**) gave results consistent with the reported data,[79] the new analog of the C-3' - C-3'N modified Taxol derivatives (**122**) showed a significant decrease in the cytotoxicity. The 3'-N-(2-furoyl) group can thus either increase activity (as for example with compounds **104** and **105**) or decrease activity, as with compounds **122** and **17**.

Given the available data, it was of interest to attempt to evaluate whether any synergistic effects were observed. A comparison of selected data for the C-3'-N - C-10 analogs is shown in Table 9. These data indicate that replacement of the C-10 acetyl

group with C-10 propanoyl or butanoyl groups (compounds **13** and **14**) results in a significant increase in cytotoxicity to the A2780 cell line, while replacement of the C-3'-N benzoyl group with a 2-furoyl group gave a product (**17**) with significantly *decreased* cytotoxicity and microtubule assembly activity. Interestingly, replacement of *both* C-3'-N benzoyl with a 2-furoyl group and C-10 acetate with a butanoyl group (compound **104**) gave a product with improved cytotoxicity and *also improved microtubule assembly activity*. This improvement in the microtubule assembly activity would not have been predicted, and indicates a probable positive synergistic effect.

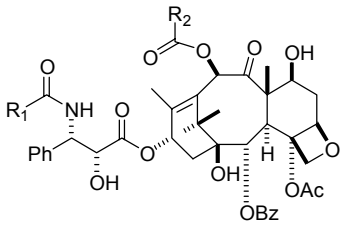


Table 9 Evidence for positive synergistic effect

Structure	R_1	R_2	Cytotoxic Activity (IC_{50}) (μg/mL) (A2780)	I_{50} (μM) Microtubule Assembly Assay
13	Ph	Et	<0.00122, <0.00122	N/A
14	Ph	Pr	<0.00122, <0.00122	5.70 ± 1.07
17	2-Furyl	Me	14.1, 14.9	2.10 ± 0.29
104	2-Furyl	Pr	0.002 ± 0.001 (4)	0.36 ± 0.13
105	2-Furyl	Et	0.004 (2)	0.49 ± 0.08
Taxol	Ph	Me	0.136 ± 0.08 (7)	0.55 ± 0.1

In most cases, however, synergism was either absent or was exerted in a negative way. Although the C-10 modified analogs **104** and **105** bearing a 2-furoyl group at the C-3'N position, and the C-3'N modified analog **120** and compound **121** bearing an isobutenyl group at the C-3' position, showed enhanced cytotoxic activity in the A2780

human ovarian cancer cell line as compared with Taxol, the C-3'N – C-3' modified analog **122** bearing both of these substituents (2-furoyl and isobutenyl), surprisingly showed diminished activity (Table 10). It is concluded that this type of effect is an evidence of a negative synergism. The activities of C-3'N-(2-furoyl) substituted Taxol analogs is thus surprisingly sensitive to the nature of the other substituents on the molecule.

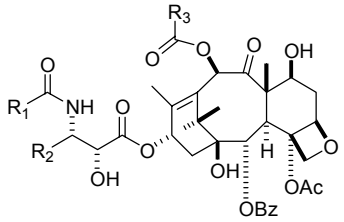


Table 10 Evidence for negative synergistic effect

Structure	R_1	R_2	R_3	Cytotoxic Activity (IC_{50}) (μg/mL) (A2780)	I_{50} (μM) Microtubule Assembly Assay
120	tBuO	$(CH_3)_2CH=CH$	Me	0.007, 0.008	7.27 ± 3.39
121	Ph	$(CH_3)_2CH=CH$	Me	0.06, 0.00122	N/A
122	2-Furyl	$(CH_3)_2CH=CH$	Me	4.6, 4.1	1.25 ± 0.35
17	2-Furyl	Ph	Me	14.1, 14.9	2.10 ± 0.29
104	2-Furyl	Ph	Pr	0.002 ± 0.001 (4)	0.36 ± 0.13
105	2-Furyl	Ph	Et	0.004 (2)	0.49 ± 0.08
Taxol	Ph	Ph	Me	0.136 ± 0.08	0.55 ± 0.1

In conclusion, it appears that simultaneously modifying two or more substituents on the Taxol system produces effects on the bioactivity of Taxol which are not simply the sum of the effects of the individual modifications. The reasons for this complex situation arenot currently understood, and additional studies in this area are needed.

4. COMBINATORIAL APPROACHES TO TAXOL ANALOGS

4.1 Introduction

Modifications of natural products in order to study their SAR is a traditional and useful strategy toward the discovery of lead compounds. Production of analogs of a compound that is already known to show a particular biological activity may result in an increase in this activity. Sometimes, this modification may be trivial, easy and inexpensive to bring about, and sometimes it may be hard and costly. But, the strategy is to synthesize as many compounds as possible, and fast.

The revolutionary techniques developed with the advent of combinatorial chemistry have introduced a new dimension to the identification and optimization of lead compounds. Improved technology has made it possible to generate many new derivatives of a molecule, known as libraries, in shorter periods of time compared to conventional methods. The production of larger and more diverse libraries may result in finding novel lead compounds of enhanced value.

Despite extensive studies of the SAR of Taxol, the application of combinatorial chemistry techniques to the Taxol template has the potential of unveiling new analogs of Taxol with improved biological properties. In search of such molecules, several analogs of Taxol modified at more than one site have been prepared employing conventional methods.[80] *Is it possible to prepare large numbers of these analogs by combinatorial chemistry techniques? Is it possible to apply combinatorial chemistry techniques to a complex, delicate natural product like Taxol?*

[80] Please see Section 2.

4.1.1 The site of immobilization

Studies to find answers to these questions requires a comprehensive study of the SAR of Taxol. Since the solid phase synthesis method was chosen to be tackled for the application of combinatorial chemistry techniques, the most suitable site for immobilization on resin should primarily be identified. It is concluded that this site should:

- be easily accessible. Ideally, Taxol should be able to be immobilized on the resin through this site with high yield.

- not be one of the sites to be modified. Since this site would be blocked by the resin and unmasked after performing modifications on the targeted sites, overall this site would be untouched. SAR information suggests that modifications on certain positions of Taxol decrease the biological activity. The site chosen to be linked to the resin could thus be one that is crucial for the activity, since it would be blocked throughout the modification process and then revealed unmodified.

4.1.2 The resin

The choice of a suitable resin with appropriate linker is the core of solid phase synthesis. The resin should:

- allow immobilization of Taxol through the selected site with high yield.

- be stable to the proposed modification conditions at the certain positions.

- be easily removed in high yield, after the completion of the proposed modifications.

4.1.3 The selection

In light of the reported SAR studies and the statements above, the C-2' OH was

selected to be the site for the immobilization on resin, since it:

- is crucial for biological activity, and thus should not be modified
- is the most reactive hydroxyl group on Taxol, which makes it the easiest to be accessed.

After many trials on several resins with different linkers, the polystyrene-diethylsilane (PS-DES) linker was chosen to be applied for the combinatorial synthesis of Taxol analogs (Figure 30).[81]

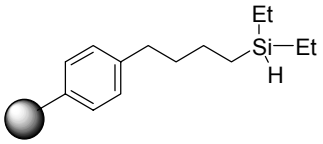


Figure 30 PS-DES Resin

Silyl derivatives are extensively used in synthetic organic chemistry for the protection of various functional groups such as alcohols, phenols, etc.[82] Silyl derivatives are propitious by virtue of their inert character to numerous synthetic transformations, and they can be easily removed under selective conditions that are applicable to the delicate nature of Taxol.

At first glance, one might have immediate questions about the reactivity of this resin, since it is well known that silyl derivatives are typically furnished by the reaction of silyl chlorides, not silanes, and the alcohols, phenols, etc. as the counter functionalities. Although a silyl chloride functionality is not present in the PS-DES resin, the resin offers the advantage of stability toward moisture. It therefore has a long shelf life and it can

[81] Kingston, D. G. I.; Jagtap, P. G. Unpublished results, Department of Chemistry, Virginia Tech.
[82] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd ed.; John Wiley & Sons, Inc.: New York, 1999.

readily be transformed into a reactive silyl chloride derivative.[83] Moreover, the PS-DES resin may also be reacted with alcohols (alcoholysis) and carbonyl compounds (hydrosilylation) in 1-methyl-2-pyrrolidinone (NMP) using Wilkinson's catalyst ($RhCl(PPh_3)_3$) to give the corresponding resin-bound silyl ethers.[84]

Argonaut Technologies' first silicon linker, PS-DES, is a 1% crosslinked, gel-type polystyrene which has been functionalized with a butyl diethyl silane moiety.[85] PS-DES is similar to a triethylsilyl (TES) group in terms of chemical stability, which makes it suitable and useful for solid phase synthesis of Taxol analogs.

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[83] Hu, Y. H.; Porco, J. A.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518-4521

[84] Hu, Y. H.; Porco, J. A. *Tetrahedron Lett.* **1998**, *39*, 2711-2714.

[85] This information has been obtained from http://www.argotech.com. For more detailed information regarding PS-DES resin, including the physical properties and additional references, please visit the internet address provided.

4.2 Strategies Toward Modifications at C-10 and C-3'N Positions

4.2.1 The Plan

In order to employ solid phase synthesis techniques for the preparation of new analogs of Taxol, an appropriate Taxol analog should be designed. The appropriate analog should bear protecting groups at the C-10 and the C-3'N positions that could be removed selectively in the presence of one another and the resin, in order to allow the desired modifications when on the resin (Figure 31).

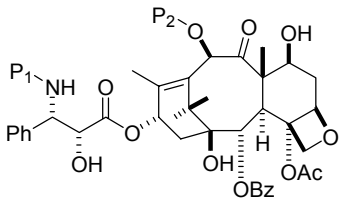


Figure 31 Target Taxol analog

With the desired protecting groups in place, the target Taxol analog could be immobilized on the resin through the C-2' OH. According to the plan, once immobilization was completed, the C-3'N protecting group (P_1) would be removed, and C-3' NH_2 would immediately be rederivatized by the desired group (R_1). This process would be followed by removal of the C-10 protecting group (P_2) and rederivatization of the C-10 OH with another group (R_2). Once the modifications were completed, the new Taxol analog would be liberated from the resin to give the desired Taxol analog (Figure 32).

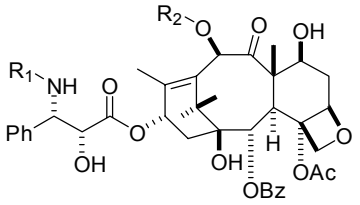


Figure 32 Desired Taxol analog modified at the C-3'N and C-10 positions

4.2.2 The Synthesis

The target Taxol analog (Figure 31), with the required protecting groups could be synthesized as discussed in the retrosynthetic pathway shown in Scheme 8. At this time, the key point would be the selection of the protecting groups, P_1 and P_2. The most important prerequisite for the selection would be the removal conditions of these protecting groups. The removal conditions of these protecting groups should not be:

- in acidic media, since the resin is labile to acidic conditions.
- in basic media, since the Taxol skeleton is not stable to basic conditions.

It was concluded that the acetate ester would be suitable for the protection of the C-10 OH, since it could be removed by hydrazine monohydrate, in the presence of the resin. Although not listed above as one of the undesired removal conditions, protecting groups that can be removed by hydrogenation were omitted as well. Even after many trials under various conditions attempts towards the removal of the benzyloxycarbonyl (CBz) group was not successful by hydrogenolysis.[81] The chloroacetate group was thus selected for the investigation for the protection of the C-3' NH_2 group, since chloroacetyl esters can be cleaved in the presence of other esters such as acetates and benzoates because of the large difference in the hydrolysis rates for esters bearing electron-withdrawing groups (Figure 33).[81] It was hoped that this relative ease of hydrolysis would also apply to chloroacetamides.

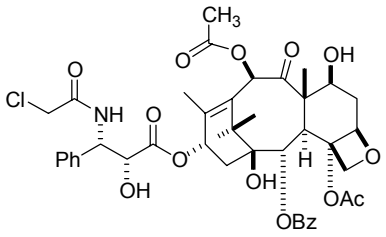
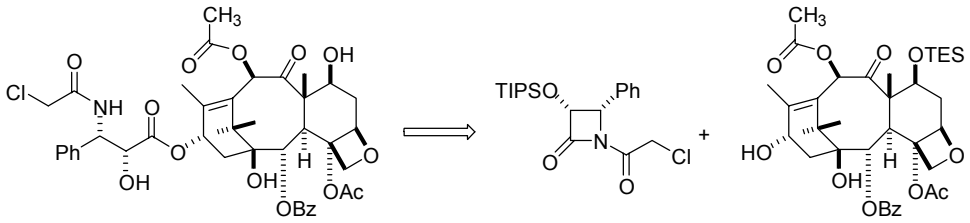


Figure 33 Target Taxol analog prior to immobilization on resin

4.2.3 Synthesis of the target Taxol analog

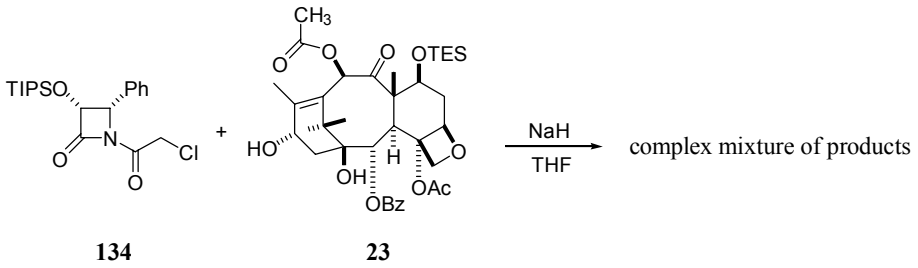
Coupling of the β-lactam derivative **134** and the 7-(triethylsilyl)baccatin III (**23**), in the presence of NaH, followed by the cleavage of the silyl protecting groups should yield the target Taxol analog **133** as shown in the retrosynthetic analysis (Scheme 16).



133 **134** **23**

Scheme 16 Retrosynthetic analysis of the target Taxol analog

The syntheses of the β-lactam **134** and 7-(triethylsilyl)baccatin III (**23**), were performed as reported earlier. The coupling of the β-lactam and the baccatin core, however, unexpectedly gave a complex mixture of products (Scheme 17), presumably due to nucleophilic attack on the chloroacetyl group as well as or instead of on the β-lactam carbonyl group. Since the purpose of this study was to develop available synthetic routes rather than carry out a mechanistic study, these reaction products were not characterized further.



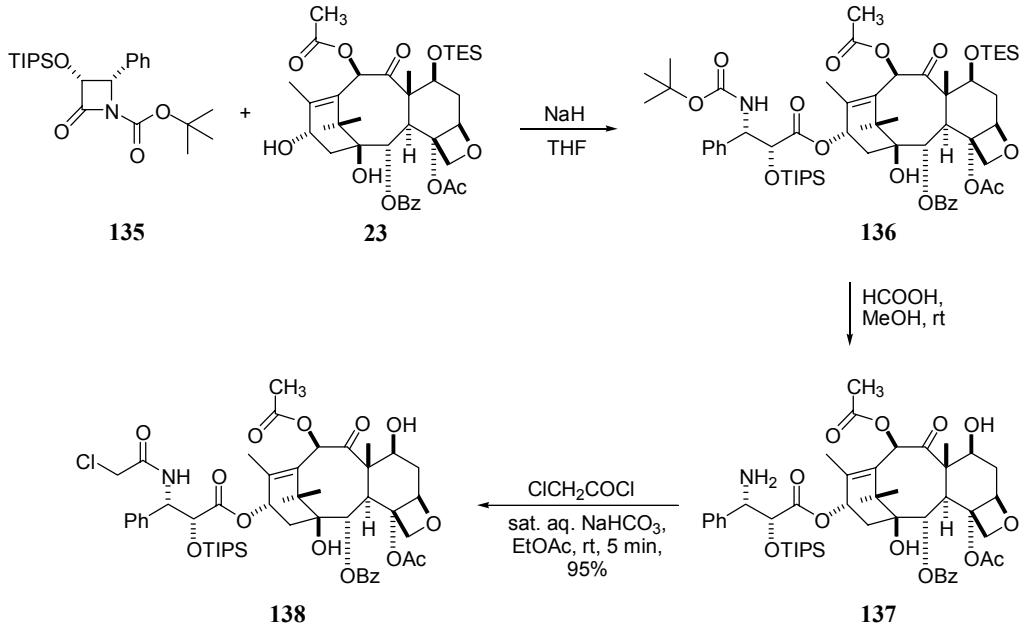
134 **23**

Scheme 17 Failure of the coupling process

4.2.3.1 New Approach

Since the chloroacetyl approach failed, another protecting group was thus considered in place of the chloroacetyl group, that would allow undergoing the coupling process. This new protecting group should be able to be replaced after the coupling process with the required chloroacetyl group. Therefore, the *t*-butyl carbamate (BOC) group was chosen, and the desired β-lactam (**135**) was prepared accordingly. The β-lactam **135** was then coupled with the baccatin core to give the coupled product (**136**). During the removal of the BOC protecting group with formic acid, the triethylsilyl (TES) group at the C-7 position was also cleaved to give **137**. At this point the BOC group was also considered to be employed as the protecting group for the C-3' NH_2, however, this idea was not pursued due to two major reasons. First of all, any reaction to be performed on resin should be a clean and high yielding one. Formic acid removes the BOC group but not in good yield (~50% yield). Moreover, as noted earlier, the resin is similar to a TES group in terms of chemical reactivity, and a TES group was removed during this reaction, so it was presumed that should formic acid was used to remove the BOC group while Taxol was anchored on the resin, the resin would be cleaved as well. Therefore it

was decided to continue trials using the chloroacetyl group as the protecting group for the C-3' NH_2. Selective acylation of the free amine at the C-3' position was performed efficiently with chloroacetyl chloride under Schotten-Baumann conditions to give the desired Taxol template (**138**) (Scheme 18).[86]



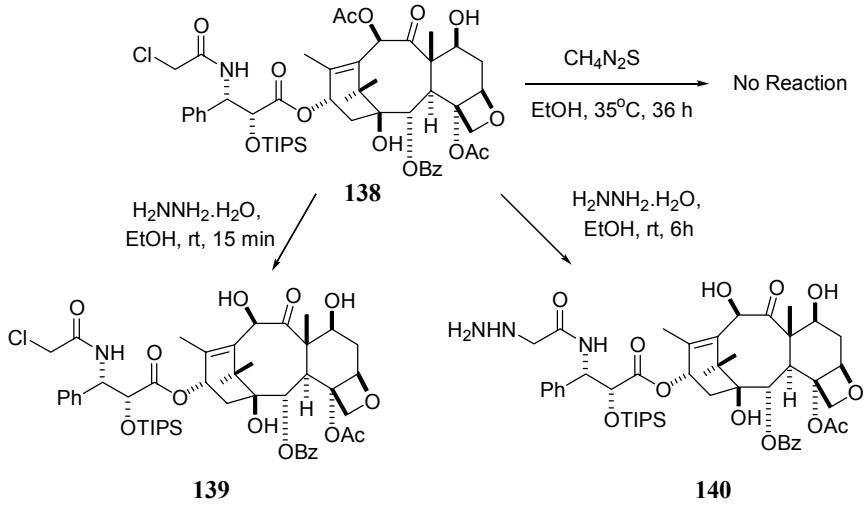
135 **23** **136** **138** **137**

Scheme 18 Synthesis of the desired template

This template (**138**) should easily adapt to the conditions that would be used for the projected modifications while on resin, since it bears the required groups to be replaced at the desired positions, and a silyl protecting group at the C-2' OH position, which resembles the linker on the resin. Presumably, if the desired modifications would take place smoothly on the template, then it would be possible to assume that the proposed modifications would also take place easily while the template was anchored on

[86] Georg, G. I.; Boge, T. C.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 335-338

resin. Thus, it would be wise to experiment with the removal conditions for the chloroacetyl group prior to removing the triisopropylsilyl (TIPS) group and immobilizing the template on the resin. In order to remove the chloroacetyl group selectively, several conditions were tested. The results of these studies are shown in Scheme 19.



Scheme 19 Studies toward the removal of the chloroacetyl group on the template

The first condition employed to remove the chloroacetyl group selectively involved thiourea, which is known to cleave chloroacetyl esters.[87] However even prolonged reaction periods and higher temperatures did not yield the desired product.

Hydrazine monohydrate was then investigated as the cleavage reagent. Almost immediately after addition of hydrazine monohydrate to the template in ethanol, a product with a lower R_f value was observed on thin layer chromatography (TLC) plate. It was found that the product (**139**) was the C-10 deacetylated analog, and the chloroacetyl group was still intact at the C-3' N position.

[87] Naruto, M.; Ohno, K.; Naruse, N.; Takeuchi, H. *Tetrahedron Lett.* **1979**, 251

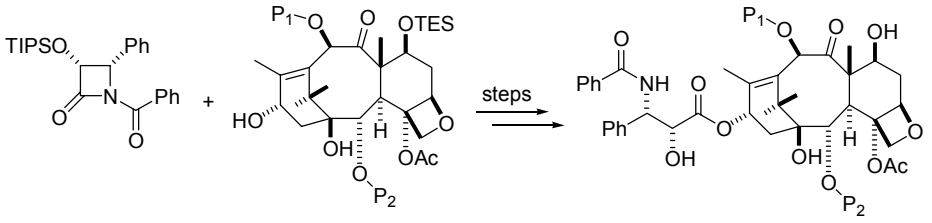
On further reaction of **138** with hydrazine monohydrate, another product started to form, which had an even lower R_f value. Although this product was not fully characterized, its ^1H NMR spectrum suggested that the product was consistent with the structure shown as **140**; again it was not the desired product.

The limitations of the reagents that could be employed for the selective removal of the chloroacetyl group at the C-3' N position, combined with the unexpected results of the trials of the suitable ones, led to the abandonment of this approach.

4.3 Strategies Toward Modifications at the C-2 and C-10 Positions

4.3.1 The Plan

The strategy for the applications of the solid phase synthesis techniques for the preparation of C-2 and C-10 modified Taxol analogs was based on the retrosynthetic analysis indicated in Scheme 20, and required the synthesis of the target Taxol analog (**144**) prior to immobilization on resin.



30 **141** **142**

Scheme 20 Retrosynthetic analysis for the solid phase synthesis of C-2 and C-10 modified Taxol analogs

Thus, it was anticipated that the coupling of an appropriately decorated baccatin core bearing the protecting groups P_1 and P_2 (**141**) with the known β-lactam derivative (**30**) would yield the target Taxol derivative **142**. The silyl groups could then be removed and the resulting Taxol analog could be immobilized on resin. Following immobilization, the protecting groups would be substituted with the required groups to give the desired Taxol analog after being liberated from the solid support (Figure 34).

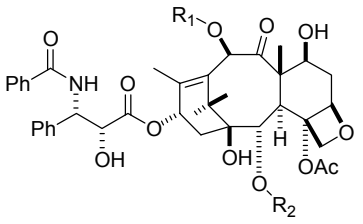


Figure 34 Desired Taxol analog modified at the C-2 and C-10 positions

After careful studies the protecting groups, P_1 and P_2, were elected to be the acetate ester for the C-10 position and the chloroacetate ester for the C-2 position, respectively, based on the reasons stated earlier. Thus, the library of taxol analogs modified at the C-2 and C-10 positions was planned to be generated from the target Taxol analog shown in Figure 35.

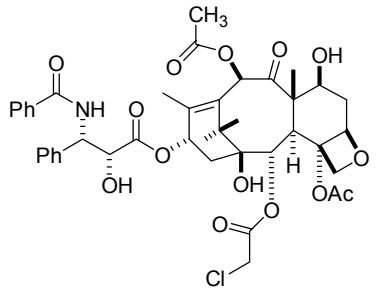
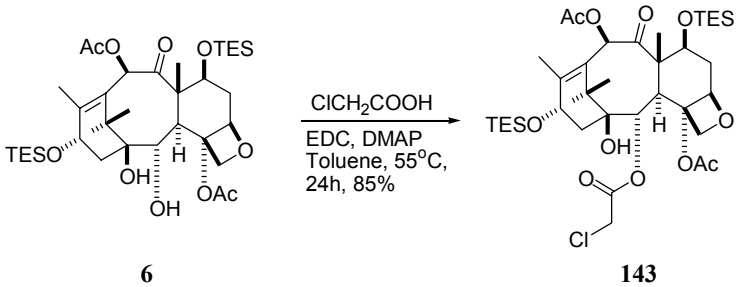


Figure 35 Target Taxol analog prior to immobilization on resin

4.3.2 The synthesis

The sequence leading to the required baccatin core is shown in Scheme 21. The known baccatin derivative **6** was simply esterified in the same fashion shown earlier at the C-2 position with chloroacetic acid in the presence of EDC to give the required baccatin core **143**.

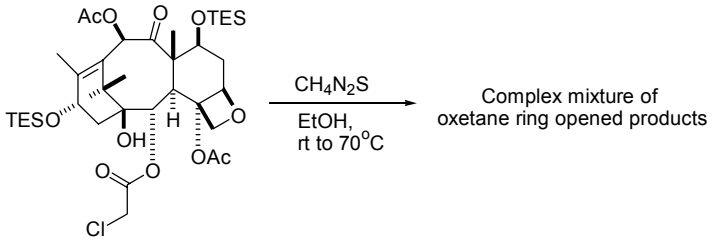


6 **143**

Scheme 21 Synthesis of the required baccatin core

According to the synthesis plan, the next step would be the concomitant removal of the two silyl protecting groups at positions C-7 and C-13, followed by reprotection of the C-7 OH group with TES group for the coupling with the β-lactam derivative to give the target Taxol analog. However, before continuing the synthesis any further, in order to study the applicability of these protecting groups for the desired modifications, the removal conditions for the elected protecting groups were tested.

The studies toward cleaving the chloroacetyl group gave discouraging results. Several attempts at different temperatures for the selective hydrolysis of the chloroacetate ester gave only oxetane ring opened products (Scheme 22). This approach was thus discontinued.



Scheme 22 Studies toward selective hydrolysis of the C-2 chloroacetate ester

4.4 Discussion

The possibility of preparing large, searchable libraries of lead compounds has captured the imagination of the drug discovery community in the last decade. The conventional pattern of the lead development has dramatically accelerated by the introduction of the combinatorial chemistry techniques to the world of drug discovery.

In this study it was proposed to synthesize and test the bioactivity of a wide range of Taxol analogs by employing combinatorial chemistry techniques, since these techniques are known to be the most efficient way of preparing analogs of lead compounds. But the question was, whether a complex natural product like Taxol was really suitable for these methods or not. After detailed studies towards the immobilization site and the choice of resin, it was found that Taxol could be immobilized through the C-2' OH group on a resin which has similar reactivity to a triethylsilyl group.[81] With this information in hand, numerous trials were conducted in order to be able to apply combinatorial chemistry techniques on certain sites of Taxol.

The positions chosen to perform concurrent modifications employing combinatorial chemistry techniques were the C-3' N - C-10 and the C-2 - C-10. In order to start synthesis, suitable protecting groups should be selected, however, the chances were limited due to the complex and labile nature of Taxol, as the removal conditions of many common protecting groups were not suitable either for the resin or for Taxol itself. The chloroacetyl group was investigated as a protecting group for both the C-3' N and the C-2 positions, but in both cases it could not be removed under any selected conditions tested.

After several attempts, trials on application of combinatorial chemistry techniques for the simultaneous modifications at the selected positions were discontinued. It is concluded that new protecting groups are required if the C-3' N and C-2 positions on Taxol are to be modified by combinatorial chemistry techniques.

5. SUMMARY

Two new fluorescent labeled analogs of Taxol and the first example of a fluorescent baccatin derivative in which the fluorophore is attached to these taxoids at the C-10 position have been prepared. One of the fluorescent labels chosen was 7-(diethylamino)coumarin-3-carboxylic acid, which had not previously been used as a probe for the Taxol-tubulin interaction. The second one was *m*-aminobenzoic acid. Although this probe was used on Taxol previously, it was not attached to the C-10 position. It is found that the C-10 position can be used for preparation of fluorescent derivatives of taxoids since these analogs retain good *in vitro* assembly-promoting activity. The potential utility of the two probes employed was evaluated. The *m*-aminobenzoyl group was found to be useful for probing the local environment and the coumarin probe proved to be a promising one towards visualizing Taxol bound to tubulin using fluorescence microscopy.

A number of Taxol analogs were synthesized by classical techniques, with various substituents at the C-2, C-3', C-3'-N, C-7 and C-10 positions. The cytotoxicities of these analogs against the A2780 human ovarian cancer cell line and microtubule assembly activities of most of them were determined. Several analogs had improved cytotoxicity as compared with Taxol, and a few had improved tubulin assembly activity, but only three compounds had improved cytotoxicity *and* improved tubulin assembly activity. Some compounds were anticipated to have improved water-solubility as compared with Taxol, and one of these (**118**) is a candidate for future development based on its improved cytotoxicity. A preliminary evaluation of possible synergistic effects on the activity of the analogs was made, and it was concluded that there was probably a positive synergistic effect in one case (Table 9). Effects of a negative synergism were summarized in Table 10 and these were discussed.

Attempts were made to develop novel solid phase synthesis of Taxol analogs, but these were unsuccessful, and it is concluded that improved protecting groups are required before this will be a feasible approach.

6. EXPERIMENTAL SECTION

6.1 General Methods

Chemicals were obtained from Aldrich Chemical Co. and were used without further purification, unless otherwise noted. 7-(diethylamino)coumarin-3-carboxylic acid was obtained from Molecular Probes Inc. All anhydrous reactions were performed in oven-dried glassware under argon. Tetrahydrofuran (THF) was distilled over sodium/benzophenone, dichloromethane was distilled over calcium hydride, and toluene was distilled over sodium prior to use. All reactions were monitored by E. Merck analytical thin layer chromatography (TLC) plates (silica gel 60 GF, aluminum back) and analyzed with 254 nm UV light and/or vanillin/sulfuric acid spray and/or phosphomolybdic acid/ethanol spray. Silica gel for column chromatography was purchased from E. Merck (230-400 mesh). Preparative thin layer chromatography (PTLC) plates (silica gel 60 GF) were purchased from Analtech. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ or CD_3OD on Varian Unity 400 spectrometer (operating at 399.951 MHz for ^{1}H and 100.578 MHz for ^{13}C) and were assigned by comparison of chemical shifts and coupling constants with those of related compounds. Chemical shifts were reported as δ-values relative to tetramethylsilane (TMS) as internal reference, and coupling constants were reported in Hertz. Mass spectra (HRFABMS and LRFABMS) were obtained at Nebraska Center for Mass Spectrometry, University of Nebraska and at Analytical Services in the Department of Chemistry at Virginia Tech. The phrase "worked-up in the usual way" refers to diluting the reaction mixture with an excess amount of organic solvent, washing with water and brine, drying over anhydrous sodium sulfate and evaporating the solvent in *vacuo* unless otherwise noted. The known intermediates were prepared following the procedures that are reported in the literature, and NMR data of these compounds were identical to those in literature.

2'-*O*-(*tert*-Butyldimethylsilyl)-7-*O*-triethylsilyl-10-deacetyl-10-*m*-nitrobenzoylpaclitaxel (2).

To a stirred suspension of 3-nitrobenzoic acid (0.095 g, 0.56 mmol) in toluene (dry, 1 mL) under argon was added 1,3-dicyclohexylcarbodiimide (0.115 g, 0.56 mmol) and the reaction mixture was stirred for 15 min. 4-(dimethylamino)pyridine (cat. 0.002 g) was then added and the reaction mixture was stirred for additional 5 min. 2'-*O*-(*tert*-butyldimethylsilyl)-7-*O*-triethylsilyl-10-deacetylpaclitaxel (**1**) (0.058 g, 0.056 mmol) was then introduced and the reaction mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC (40% EtOAc/Hexane) and by the completion of the reaction, the reaction mixture was diluted with EtOAc, washed with water, sat. aq. $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (40% EtOAc/Hexane), and the desired product was isolated in 90% yield. ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.91 (t, 1H), 8.45 (d, 2H), 8.14 (d, 2H), 7.74-7.25 (m, 14H), 7.06 (d, J=9.2, 1H, NH), 6.71 (s, 1H), 6.28 (t, 1H), 5.77 (s, 1H), 5.75 (s, 1H), 4.98 (d, J=8, 1H), 4.69 (d, J=4, 1H), 4.56 (m, 1H), 4.34 (d, J=8.4, 1H), 4.23 (d, J=8.4, 1H), 3.89 (d, J=6.8, 1H), 2.60 (s, 3H), 2.56 (m, 1H), 2.46 (m, 1H), 2.14 (m, 1H), 2.11 (s, 3H), 1.94 (m, 1H), 1.85 (s, 1H), 1.74 (s, 3H), 1.68 (s, 1H), 1.35 (s, 3H), 1.21 (s, 3H), 0.90 (t, 9H), 0.79 (s, 9H), 0.58 (m, 6H), -0.02 (s, 3H), -0.28 (s, 3H). HRFABMS *m/z* calculated for $C_{64}H_{80}N_2O_{16}Si_2$ $(M+Na)^+$ 1211.4943, found 1211.4950, Δ -0.5 ppm.

10-Deacetyl-10-*m*-nitrobenzoylpaclitaxel.

To a stirred solution of 2'-*O*-(*tert*-butyldimethylsilyl)-7-*O*-triethylsilyl-10-deacetyl-10-*m*-nitrobenzoylpaclitaxel (**2**) (0.05 g, 0.042 mmol) in THF (dry, 3 mL) was added 0.8 mL of pyridine at 0 ^{o}C, stirred for 5 min. where 0.8 mL of HF-pyridine was introduced. The reaction mixture was allowed to come to room temperature and further stirred overnight

for 24 h. The reaction mixture was then diluted with EtOAc, washed with sat. aq. $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (40% EtOAc/Hexane) and the desired product was isolated in 83% yield. ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.87 (t, 1H), 8.45 (d, 1H), 8.39 (d, 1H), 8.12 (d, 2H), 7.73-7.25 (m, 14H), 7.04 (d, J=9.2, 1H, NH), 6.58 (s, 1H), 6.25 (t, 1H), 5.79 (d, J=8, 1H), 5.72 (d, J=6.8, 1H), 4.96 (d, J=7.6, 1H), 4.8 (s, 1H), 4.46 (m, 1H), 4.31 (d, J=8.4, 1H), 4.20 (d, J=8.4, 1H), 3.85 (d, J=6.8, 1H), 2.57 (m, 1H), 2.46 (d, 1H), 2.39 (s, 3H), 2.36 (m, 2H), 2.04 (s, 1H), 2.03 (s, 3H), 1.86 (s, 3H), 1.70 (s, 3H), 1.32 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.01, 172.71, 170.41, 167.17, 166.89, 164.2, 148.27, 142.73, 137.8, 135.47, 133.73, 132.6, 131.95, 130.2, 130.17, 129.85, 128.99, 128.71, 128.65, 128.33, 127.98, 124.89, 84.3, 81.07, 78.86, 76.49, 74.83, 73.13, 72.25, 60.38, 58.63, 55.09, 45.8, 43.21, 35.87, 35.71, 26.99, 22.6, 22.12, 14.91, 14.15, 9.61 HRFABMS *m/z* calculated for $C_{52}H_{52}N_2O_{16}$ $(M+Na)^+$ 983.3214, found 983.3210, Δ 0.4 ppm.

10-Deacetyl-10-*m*-aminobenzoylpaclitaxel (4).

To a stirred solution of 10-deacetyl-10-*m*-nitrobenzoylpaclitaxel (0.025 g, 0.026 mmol) in MeOH (0.01 L) was added palladium, 5 wt. % on activated carbon (0.1 mg) and H_2 gas was bubbled through a balloon at room temperature for 5 min. The reaction mixture was filtered through Celite® and applied on a PTLC plate (EtOAc/Hexanes:10 %) to give the desired product with 55% yield. ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.12 (d, 2H), 7.73 (d, 2H), 7.60 (t, 1H), 7.53-7.34 (m, 14H), 7.24 (d, 1H), 7.04 (d, J=8.8 1H, NH), 6.90 (d, J=7.6, 1H), 6.49 (s, 1H), 6.24 (t, 1H), 5.80 (d, J=8.8, 1H), 5.72 (d, J=7.2, 1H), 4.96 (d, J=7.6, 1H), 4.8 (s, 1H), 4.47 (m, 1H), 4.32 (d, J=8, 1H), 4.20 (d, J=8, 1H), 3.85 (d, J=6.8, 1H), 3.82 (bs, 2H), 3.62 (bs, 1H), 2.67 (d, 1H), 2,55 (m, 1H), 2,39 (s, 3H), 2.34 (m, 3H), 1.89 (m, 2H), 1.81 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.3 (s, 3H), 1.24 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.45, 172.66, 170.38, 167.05, 166.97, 166.57, 146.56, 142.07, 137.89, 133.72, 133.59, 133.24, 131.96, 130.19, 129.97, 129.41, 129.13, 129.01, 128.72, 128.69, 128.37, 127.02, 120.17, 120.08, 115.59, 84.44, 81.18, 79.04,

76.49, 75.85, 74.95, 73.17, 72.38, 72.25, 58.66, 55.03, 45.72, 43.22, 35.72, 29.68, 27.04, 22.63, 22.07, 14.88, 9.57 HRFABMS *m/z* calculated for $C_{52}H_{54}N_2O_{14}$ $(M+Na)^+$ 953.3472, found 953.3438, Δ -1.1 ppm.

2'-*O*-(*tert*-Butyldimethylsilyl)-7-*O*-triethylsilyl-10-deacetyl-10-[7-(diethylamino)coumarin-3-carboxy]paclitaxel.

To a stirred suspension of 7-(diethylamino)coumarin-3-carboxylic acid (0.1 g, 0.38 mmol) in CH_2Cl_2:DMF (3 mL : 0.1 mL) was added 1-[3-(dimethylamino)propyl-3-ethylcarbodi- imide hydrochloride (0.074 g, 0.38 mmol) at room temperature and the reaction mixture was stirred for 15 min. 4-(dimethylamino)pyridine (cat. 0.002 g) was then added and the reaction mixture was stirred for another 5 min. 2'-*O*-(*tert*-butyldimethylsilyl)-7-*O*-triethylsilyl-10-deacetylpaclitaxel (0.025 g, 0.024 mmol) was then introduced at room temperature and the reaction mixture was further stirred for 24 h. The reaction mixture was diluted with EtOAc, washed with water, sat. aq. $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (40% EtOAc/Hexane) and the desired product was isolated in 95% yield. ^1H NMR ($CDCl_3$, 399.951 MHz) δ 8.63 (s, 1H), 8.14 (d, 2H), 7.75 (d, 2H), 7.6 (t, 2H), 7.54-7.3 (m, 12H), 7.09 (d, J=8.4, 1H, NH), 6.65 (d, J=8.8, 1H), 6.6 (s, 1H), 6.46 (s, 1H), 6.31 (t, 1H), 5.74 (t, 2H), 4.98 (d, J=8.4, 1H), 4.68 (d, J=2.4, 1H), 4.54 (m, 1H), 4.35 (d, J=8.8, 1H), 4.23 (d, J=8.8, 1H), 3.91 (d, J=7.2, 1H), 3.46 (m, 4H), 2.60 (s, 3H), 2.57 (m, 1H), 2.41 (m, 1H), 2.16 (s, 3H), 2.11 (m, 1H), 1.93 (t, 1H), 1.75 (s, 3H), 1.67 (s, 1H), 1.33 (s, 3H), 1.21 (m, 12H), 0.90 (t, 9H), 0.79 (s, 9H), 0.58 (m, 6H), -0.00 (s, 3H), -0.28 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.36, 171.13, 170.16, 167.07, 166.84, 161.80, 158.47, 158.17, 152.96, 149.28, 140.89, 138.32, 134.04, 133.59, 133.3, 131.71, 131.42, 130.21, 129.12, 128.73, 128.68, 128.65, 127.86, 126.98, 126.41, 109.61, 108.12, 107.74, 105.33, 96.78, 84.28, 81.12, 79.47, 78.98, 75.17, 75.04, 74.94, 72.22, 71.16, 58.44, 55.6, 46.79, 45.15, 43.36, 37.22, 35.62, 26.34, 23.13, 21.7, 18.09, 14.47, 12.38, 10.17, 6.75, 5.26, -5.16, -5.88. LRFABMS *m/z* found for $C_{71}H_{90}N_2O_{16}Si_2$ $(M+H)^+$ 1283.5.

10-deacetyl-10-[7-(diethylamino)coumarin-3-carboxy]paclitaxel (3).

To a stirred solution of 2'-*O*-(*tert*-butyldimethylsilyl)-7-*O*-triethylsilyl-10-deacetyl-10-[7-(diethylamino)coumarin-3-carboxy]paclitaxel (0.025 g, 0.02 mmol) in THF (1.2 mL) was added 0.4 mL of pyridine at 0 ^{o}C, stirred for 5 min. where 0.4 mL of HF-pyridine was introduced. The reaction mixture was allowed to come to room temperature and further stirred overnight for 24 h. The reaction mixture was then diluted with EtOAc, washed with sat. aq. $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (40% EtOAc/Hexane) and the desired product was isolated in 80% yield. ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.48 (s, 1H), 8.14 (d, 2H), 7.76 (d, 2H), 7.6 (t, 1H), 7.52-7.33 (m, 12H), 7.09 (d, J=8.8, 1H, NH), 6.61 (dd, J=8.8,2.0 1H), 6.52 (s, 1H), 6.45 (s, 1H), 6.25 (t, 1H), 5.8 (dd, J=8.8,2.4, 1H), 5.71 (d, J=6.8, 1H), 4.96 (d, J=9.6, 1H), 4.8 (s, 1H), 4.45 (m, 1H), 4.31 (d, J=8, 1H), 4.20 (d, J=8, 1H), 3.87 (d, J=7.2, 1H), 3.59 (bs, 1H), 3.47 (m, 3H), 2.58 (m, 1H), 2.39 (s, 3H), 2.33 (m, 2H), 1.89 (m, 1H), 1.82 (s, 2H), 1.76 (d, 1H), 1.70 (s, 3H), 1.32 (s, 3H), 1.24 (m, 9H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.65, 172.56, 170.40, 166.98, 164.32, 158.80, 153.23, 150.22, 141.79, 137.89, 133.68, 133.63, 133.18, 131.92, 131.47, 130.19, 129.16, 128.99, 128.68, 128.34, 127.04, 109.73, 107.84, 107.37, 96.77, 84.44, 81.18, 79.04, 75.73, 74.96, 73.23, 72.38, 72.19, 58.69, 55.01, 45.79, 45.19, 43.27, 35.74, 35.66, 26.57, 22.63, 21.66, 14.92, 12.43, 9.58. LRFABMS *m/z* found for $C_{59}H_{63}N_2O_{16}$ 1055.6 $(M+H)^+$. HPLC retention time 17.5 min. at λ_{max} 227 nm.

2-Debenzoyl-2-*m*-methoxybenzoyl-7,13-di(triethylsilyl)baccatin III (7).

To a stirred suspension of 3-anisic acid (0.214 g, 1.41 mmol) in toluene (2 mL) was added 1-[3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (0.270 g, 1.41 mmol) at room temperature and the reaction mixture was stirred for 15 min. 4-(dimethylamino)pyridine (cat. 0.002 g) was then added and the reaction mixture was stirred for another 5 min. 2-Debenzoyl-7,13-di(triethylsilyl)baccatin III (**6**; 0.05 g, 0.07

mmol) was then introduced at room temperature and the reaction mixture was warmed up to 55 ^{o}C and further stirred for 48 h. The reaction mixture was cooled down to room temperature, diluted with EtOAc, washed with water, sat. aq. $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (40% EtOAc/Hexane) and the desired product was isolated in 65% yield. ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.69 (d, 1H), 7.61 (s, 1H), 7.36 (t, 1H), 7.12 (d, 1H), 6.46 (s, 1H), 5.63 (d, J=7.2, 1H), 4.94 (d, J=10 1H), 4.92 (t, 1H), 4.47 (m, 1H), 4.33 (d, J=8.4, 1H), 4.14 (d, J=8.4, 1H), 3.85 (s, 3H), 3.82 (d, J=7.2, 1H), 2.50 (m, 1H), 2.26 (s, 3H), 2.22 (m, 1H), 2.17 (s, 3H), 2.15 (d, 1H), 2.10 (s, 3H), 1.86 (m, 1H), 1.66 (s, 3H), 1.60 (s, 1H), 1.18 (s, 3H), 1.10 (s, 3H), 1.00 (t, 9H), 0.91 (t, 9H), 0.67 (m, 6H), 0.56 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.33, 169.86, 169.24, 167.01, 159.64, 145.47, 131.55, 130.66, 129.58, 122.5, 120.2, 114.35, 84.16, 80.77, 79.42, 76.46, 75.68, 75.3, 72.12, 68.43, 58.26, 55.31, 46.87, 42.99, 39.87, 37.16, 26.45, 22.35, 21.17, 20.95, 14.82, 10.07, 6.93, 6.74, 5.23, 4.81.

2-Debenzoyl-2-*m*-methoxybenzoyl-10-deacetyl-7,13-di(triethylsilyl)baccatin III (8).

To a stirred solution of 2-debenzoyl-2-*m*-methoxybenzoyl-7,13-di(triethylsilyl)baccatin III (**7**; 0.02 g, 0.023 mmol) in EtOH (2 mL) at room temperature was added 0.4 ml of hydrazinemonohydrate. The reaction mixture was stirred for 24 h. The progress of the reaction was monitored by TLC (10% EtOAc/Hexane) and formation of a product less polar compared to the starting material was observed. The reaction mixture was diluted with EtOAc, washed with sat. aq. $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (10% EtOAc/Hexane) and the desired product was isolated in 85% yield. ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.69 (d, 1H), 7.61 (s, 1H), 7.36 (t, 1H), 7.13 (dd, J=8,2.4 1H), 5.6 (d, J=7.2, 1H), 5.14 (s, 1H), 4.95 (t, 1H), 4.93 (d, 1H), 4.39 (m, 1H), 4.34 (d, J=8, 1H), 4.26 (s, 1H), 4.16 (d, J=8, 1H), 3.88 (d, J=7.2, 1H), 3.85 (s, 3H), 2.45 (m, 1H), 2.27 (s, 3H), 2.22 (m, 1H), 2.02 (s, 3H), 1.89 (m, 1H), 1.71 (s, 3H), 1.56 (s, 1H), 1.15 (s, 3H), 1.07 (s, 3H), 1.00 (t, 9H),

0.93 (t, 9H), 0.67 (m, 6H), 0.56 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 210.46, 169.96, 166.96, 159.64, 143.5, 138.19, 133.93, 130.69, 129.58, 128.01, 122.48, 120.22, 114.33, 84.2, 80.68, 79.51, 76.50, 75.37, 74.56, 72.76, 68.45, 57.63, 55.31, 46.66, 42.93, 40.20, 37.18, 26.57, 22.31, 20.68, 14.96, 10.06, 6.93, 6.73, 5.11, 4.82.

2-Debenzoyl-2-*m*-methoxybenzoyl-10-deacetyl-10-*m*-nitrobenzoyl-7,13-di(triethylsilyl)baccatin III (9).

To a stirred suspension of 3-nitrobenzoic acid (0.031 g, 0.18 mmol) in toluene (2 mL) was added 1-[3-(dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (0.036 g, 0.18 mmol) at room temperature and the reaction mixture was stirred for 15 min. 4-(dimethylamino)pyridine (cat. 0.002 g) was then added and the reaction mixture was stirred for another 5 min. 2-Debenzoyl-2-*m*-methoxybenzoyl-10-deacetyl-7,13-di(triethylsilyl)baccatin III (**8**; 0.01 g, 0.012 mmol) was then introduced at room temperature and the reaction mixture was warmed up to 55 ^{o}C and further stirred for 24 h. The reaction mixture was cooled down to room temperature, diluted with EtOAc, washed with water, sat. aq. $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (10% EtOAc/Hexane) and the desired product was isolated in 90% yield.

2-Debenzoyl-2-*m*-methoxybenzoyl-10-deacetyl-10-*m*-nitrobenzoylbaccatin III.

To a stirred solution of 2-debenzoyl-2-*m*-methoxybenzoyl-10-deacetyl-10-*m*-nitrobenzoyl-7,13-di(triethylsilyl)baccatin III (**9**; 0.014 g, 0.014 mmol) in THF (0.75 mL) was added 0.2 ml of pyridine at 0 ^{o}C, stirred for 5 min. where 0.2 ml of HF-pyridine was introduced. The reaction mixture was allowed to come to room temperature and further stirred overnight for 24 h. The reaction mixture was then diluted with EtOAc, washed with sat. aq. $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product

was applied on a PTLC plate (40% EtOAc/Hexane) and the desired product was isolated in 95% yield. ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.89 (t, 1H), 8.48 (d, 1H), 8.42 (d, 1H), 7.70 (m, 2H), 7.64 (m, 1H), 7.39 (t, 1H), 7.14 (dd, J=8.4,2.8 1H), 6.62 (s, 1H), 5.67 (d, J=6.8, 1H), 5.01 (d, J=7.6, 1H), 4.93 (t, 1H), 4.54 (m, 1H), 4.37 (d, J=8.4, 1H), 4.17 (d, J=8.4, 1H), 3.94 (d, J=6.8, 1H), 3.87 (s, 3H), 2.61 (m, 1H), 2.34 (d, 2H), 2.28 (s, 3H), 2.12 (s, 3H), 1.9 (m, 1H), 1.69 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.53, 170.65, 166.91, 164.34, 159.66, 148.3, 147.21, 135.54, 131.38, 131.1, 130.46, 129.84, 129.67, 127.95, 124.87, 127.47, 120.03, 114.75, 84.35, 80.77, 78.98, 76.4, 74.86, 72.28, 67.95, 58.76, 55.4, 46.21, 42.74, 38.58, 35.68, 34.11, 28.26, 27.17, 23.11, 22.61, 21.68, 21.32, 21.16, 19.25, 19.17, 18.99, 18.93, 17.81, 15.66, 9.42.

2-Debenzoyl-2-*m*-methoxybenzoyl-10-deacetyl-10-*m*-aminobenzoylbaccatin III (10).

To a stirred solution of 2-debenzoyl-2-*m*-methoxybenzoyl-10-deacetyl-10-*m*-nitrobenzoylbaccatin III (0.01 g, 0.013 mmol) in MeOH (0.01 L) was added palladium, 5 wt. % on activated carbon (0.1 mg). H_2 gas was bubbled through a balloon at room temperature for 30 min. The reaction mixture was filtered through Celite® and applied on a PTLC plate (EtOAc/Hexanes: 70 %) to give the desired product with 75% yield. ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.72 (d, 1H), 7.65 (s, 1H), 7.50 (d, 1H), 7.39 (t, 2H), 7.31-7.21 (m, 2H), 7.16 (dd, J=8.4,2 1H), 6.93 (bs, 1H), 6.55 (s, 1H), 5.66 (d, J=6.8, 1H), 5.02 (d, J=8.8, 1H), 4.92 (t, 1H), 4.55 (m, 1H), 4.35 (d, J=8, 1H), 4.18 (d, J=8, 1H), 3.95 (d, J=6.8, 1H), 3.87 (s, 3H), 2.6 (m, 2H), 2.32 (d, 2H), 2.28 (s, 3H), 2.09 (s, 3H), 1.89 (m, 1H), 1.69 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.99, 170.63, 166.93, 159.65, 146.45, 131.91, 130.54, 130.18, 129.65, 129.41, 122.48, 120.16, 120.02, 114.7, 84.48, 80.86, 79.5, 79.09, 76.43, 74.99, 72.38, 69.82, 68.01, 58.76, 55.4, 46.21, 42.74, 38.58, 35.68, 34.11, 28.26, 27.17, 23.11, 22.61, 21.68, 21.32, 21.16, 19.25, 19.17, 18.99, 18.93, 17.81, 15.66, 9.42. HRFABMS *m/z* calculated for $C_{37}H_{44}NO_{12}$ $(M+H)^+$ 694.2864, found 694.2837, Δ 3.7ppm.

General procedure for the esterification of C-2 hydroxyl of 7,13-di(triethylsilyl)baccatin III derivatives. Synthesis of the baccatin derivatives 38-45.

All reactions were performed as described for the synthesis of **9**, and the desired products were isolated in 80-90% yield.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-isopropanoyl-7,13-di(triethylsilyl) baccatin III (38).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.86 (d, 1H), 7.77 (s, 1H), 7.44 (t, 1H), 7.22 (d, 1H), 6.45 (s, 1H), 5.62 (d, J=7.2, 1H), 4.95 (d, J=8.8, 1H), 4.9 (t, 1H), 4.48 (m, 1H), 4.27 (d, J=8.4, 1H), 4.11 (d, J=8.4, 1H), 3.82 (d, J=7.2, 1H), 2.68 (m, 1H), 2.5 (m, 1H), 2.28 (s, 3H), 2.22 (m, 1H), 2.11 (s, 3H), 1.85 (m, 1H), 1.65 (s, 3H), 1.58 (s, 1H), 1.25 (d, 3H), 1.23 (d, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 1.00 (t, 9H), 0.91 (t, 9H), 0.67 (m, 6H), 0.57 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.4, 175.04, 170.00, 166.15, 145.45, 140.73, 131.54, 131.19, 130.07, 126.66, 124.25, 119.91, 84.23, 80.68, 79.48, 76.37, 75.68, 75.22, 72.06, 68.38, 58.23, 46.87, 42.95, 39.84, 37.13, 34.15, 26.42, 22.39, 21.2, 19.04, 18.9, 14.78, 10.07, 6.94, 6.78, 5.23, 4.81. LRFABMS *m/z* calculated for $C_{45}H_{70}N_3O_{11}Si_2$ $(M+H)^+$ 884.4549, found 884.5.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-isopropanoyl-7,13-di(triethylsilyl) baccatin III (39).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.09 (s, 1H), 7.94 (d, 1H), 7.56 (d, 1H), 7.4 (t, 1H), 6.44 (s, 1H), 5.56 (d, J=7.2, 1H), 4.95 (d, J=8, 1H), 4.88 (t, 1H), 4.46 (m, 1H), 4.25 (d, J=8.4, 1H), 4.11 (d, J=8.4, 1H), 3.82 (d, J=7.2, 1H), 2.67 (m, 1H), 2.5 (m, 1H), 2.28 (s, 3H), 2.22 (m, 1H), 2.11 (s, 3H), 1.85 (m, 1H), 1.65 (s, 3H), 1.58 (s, 1H), 1.25 (d, 3H), 1.23 (d, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 1.00 (t, 9H), 0.91 (t, 9H), 0.67 (m, 6H), 0.57 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.31, 175.03, 169.83, 165.65, 145.40, 134.68,

133.45, 131.48, 131.28, 130.19, 129.9, 128.17, 84.15, 80.64, 79.67, 76.27, 75.74, 75.18, 72.09, 68.35, 58.14, 46.91, 42.87, 39.89, 37.09, 34.13, 26.35, 22.23, 21.22, 19.03, 18.9, 14.75, 10.07, 6.91, 6.77, 5.23, 4.79.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-(2-butene)oyl-7,13-di(triethylsilyl) baccatin III (40).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.86 (d, 1H), 7.78 (s, 1H), 7.45 (t, 1H), 7.22 (d, 1H), 7.05 (m, 1H), 6.50 (s, 1H), 5.96 (d, J=15.6, 1H), 5.63 (d, J=6.8, 1H), 4.95 (d, J=8, 1H), 4.9 (t, 1H), 4.48 (m, 1H), 4.26 (d, J=8, 1H), 4.12 (d, J=8, 1H), 3.84 (d, J=7.2, 1H), 2.5 (m, 1H), 2.28 (s, 3H), 2.21 (m, 1H), 2.13 (s, 3H), 1.91 (d, J=6.8 3H), 1.84 (m, 1H), 1.66 (s, 3H), 1.57 (s, 1H), 1.21 (s, 3H), 1.09 (s, 3H), 1.00 (t, 9H), 0.91 (t, 9H), 0.67 (m, 6H), 0.57 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.4, 170.00, 166.16, 164.57, 145.56, 145.42, 140.73, 131.52, 131.21, 130.07, 126.67, 124.25, 122.42, 119.92, 84.25, 80.69, 79.48, 76.37, 75.7, 75.39, 72.1, 68.4, 58.26, 46.9, 42.98, 39.83, 37.15, 26.42, 22.39, 21.26, 18.10, 14.8, 10.04, 6.95, 6.74, 5.23, 4.81. LRFABMS *m/z* calculated for $C_{45}H_{68}ClO_{11}Si_2$ $(M+H)^+$ 875.3989 found 875.5.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-(2-butene)oyl-7,13-di(triethylsilyl) baccatin III (41).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.10 (s, 1H), 7.95 (d, 1H), 7.56 (d, 1H), 7.41 (t, 1H), 7.05 (m, 1H), 6.51 (s, 1H), 5.96 (d, J=15.6, 1H), 5.57 (d, J=6.8, 1H), 4.96 (d, J=9.2, 1H), 4.89 (t, 1H), 4.48 (m, 1H), 4.26 (d, J=8, 1H), 4.12 (d, J=8, 1H), 3.84 (d, J=7.2, 1H), 2.5 (m, 1H), 2.28 (s, 3H), 2.21 (m, 1H), 2.13 (s, 3H), 1.90 (d, J=6.8 3H), 1.84 (m, 1H), 1.66 (s, 3H), 1.55 (s, 1H), 1.19 (s, 3H), 1.08 (s, 3H), 1.00 (t, 9H), 0.91 (t, 9H), 0.67 (m, 6H), 0.57 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.38, 169.83, 16.69, 164.57, 145.54, 145.43, 134.7, 133.47, 131.45, 131.29, 130.2, 129.91, 128.18, 122.41, 84.18, 80.66,

79.69, 76.29, 75.77, 75.36, 72.14, 68.37, 58.18, 46.95, 42.91, 39.88, 37.12, 26.35, 22.24, 21.29, 18.10, 14.79, 10.05, 6.92, 6.74, 5.23, 4.80. LRFABMS *m/z* calculated for $C_{45}H_{68}N_3O_{11}Si_2$ $(M+H)^+$ 882.4392 found 882.5.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-benzoyl-7,13-di(triethylsilyl)baccatin III (42).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.14 (s, 1H), 8.12 (s, 1H), 7.86 (dt, 1H), 7.79 (t, 1H), 7.58 (tt, 1H), 7.46 (m, 3H), 7.22 (d, 1H), 6.71 (s, 1H), 5.68 (d, J=6.8, 1H), 4.98 (d, J=7.6, 1H), 4.93 (t, 1H), 4.55 (m, 1H), 4.3 (d, J=8.4, 1H), 4.14 (d, J=8.4, 1H), 3.9 (d, J=7.2, 1H), 2.5 (m, 1H), 2.3 (s, 3H), 2.24 (m, 1H), 2.2 (s, 3H), 1.88 (m, 1H), 1.68 (s, 3H), 1.6 (s, 1H), 1.32 (s, 3H), 1.18 (m, 1H), 1.12 (s, 3H), 1.00 (t, 9H), 0.91 (t, 9H), 0.67 (m, 6H), 0.58 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.25, 170.05, 166.18, 164.88, 145.97, 140.76, 133.05, 131.44, 131.20, 130.09, 130.05, 129.81, 128.43, 126.69, 124.28, 119.94, 84.27, 80.72, 79.54, 76.38, 76.09, 75.72, 72.17, 68.43, 58.32, 46.94, 43.05, 39.9, 37.17, 26.51, 22.41, 21.53, 14.91, 10.07, 6.95, 6.74, 5.26, 4.82. LRFABMS *m/z* calculated for $C_{48}H_{68}N_3O_{11}Si_2$ $(M+H)^+$ 918.4392 found 918.5.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-benzoyl-7,13-di(triethylsilyl)baccatin III (43).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.14 (s, 1H), 8.11 (s, 2H), 7.97 (d, 1H), 7.56 (d, 2H), 7.44 (m, 3H), 6.71 (s, 1H), 5.62 (d, J=7.2, 1H), 4.98 (d, J=8.8, 1H), 4.91 (t, 1H), 4.55 (m, 1H), 4.28 (d, J=8.4, 1H), 4.14 (d, J=8.4, 1H), 3.89 (d, J=7.6, 1H), 2.54 (m, 1H), 2.31 (s, 3H), 2.26 (m, 1H), 2.2 (s, 3H), 2.16 (m, 1H), 1.88 (m, 1H), 1.69 (s, 3H), 1.63 (s, 1H), 1.31 (s, 3H), 1.17 (m, 1H), 1.11 (s, 3H), 1.01 (t, 9H), 0.89 (t, 9H), 0.67 (m, 6H), 0.57 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.16, 169.87, 165.59, 164.86, 145.93, 134.71, 133.49, 133.04, 131.39, 131.28, 130.21, 130.03, 129.93, 129.81, 128.43, 128.19, 84.2,

80.68, 79.73, 76.05, 75.78, 72.2, 68.39, 58.23, 46.99, 42.98, 39.95, 37.13, 26.44, 22.55, 21.56, 14.88, 10.07, 6.92, 6.73, 5.26, 4.80. LRFABMS *m/z* calculated for $C_{48}H_{68}ClO_{11}Si_2$ $(M+H)^+$ 911.3989 found 911.5.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-pentanoyl-7,13-di(triethylsilyl)baccatin III (44).

^1H NMR ($CDCl_3$, 399.951 MHz) δ 7.85 (d, 1H), 7.77 (s, 1H), 7.44 (t, 1H), 7.21 (m, 1H), 6.47 (s, 1H), 5.61 (d, J=7.2, 1H), 4.95 (d, J=7.6, 1H), 4.9 (t, 1H), 4.8 (m, 1H), 4.27 (d, J=8, 1H), 4.11 (d, J=8, 1H), 3.82 (d, J=7.2, 1H), 2.43(m, 1H), 2.41 (m, 2H), 2.28 (s, 3H), 2.2 (m, 1H), 2.1 (s, 3H), 1.85 (m, 1H), 1.68 (m, 2H), 1.65 (s, 3H), 1.57 (s, 1H), 1.4 (m, 2H), 1.18 (s, 3H), 1.09 (s, 3H), 1.00 (t, 9H), 0.93 (s, 3H), 0.92 (t, 9H), 0.67 (m, 6H), 0.57 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.36, 171.93, 170.01, 166.16, 145.43, 140.73, 131.59, 131.19, 130.07, 126.67, 124.26, 119.91, 84.22, 80.68, 79.46, 76.37, 75.68, 75.35, 72.09, 68.38, 58.24, 46.85, 42.95, 39.81, 37.14, 34.06, 27.07, 26.43, 22.39, 22.20, 21.18, 14.79, 13.7, 10.06, 6.94, 6.77, 5.24, 4.80. LRFABMS *m/z* calculated for $C_{46}H_{72}N_3O_{11}Si_2$ $(M+H)^+$ 898.4705 found 898.5.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-pentanoyl-7,13-di(triethylsilyl)baccatin III (45).

^1H NMR ($CDCl_3$, 399.951 MHz) δ 8.09 (s, 1H), 7.94 (d, 1H), 7.54 (d, 1H), 7.4 (t, 1H), 6.47 (s, 1H), 5.56 (d, J=7.2, 1H), 4.95 (d, J=9.2, 1H), 4.88 (t, 1H), 4.46 (m, 1H), 4.25 (d, J=7.6, 1H), 4.11 (d, J=7.6, 1H), 3.81 (d, J=7.2, 1H), 2.49(m, 1H), 2.42 (m, 2H), 2.28 (s, 3H), 2.22 (m, 1H), 2.1 (s, 3H), 1.85 (m, 1H), 1.68 (m, 2H), 1.65 (s, 3H), 1.57 (s, 1H), 1.4 (m, 2H), 1.17 (s, 3H), 1.2 (s, 3H), 1.00 (t, 9H), 0.92 (s, 3H), 0.92 (t, 9H), 0.67 (m, 6H), 0.57 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.27, 171.92, 169.83, 165.67, 145.40, 134.69, 133.46, 131.52, 131.26, 130.19, 129.91, 128.17, 84.13, 80.64, 79.66,

76.27, 75.74, 75.31, 72.11, 68.34, 58.15, 46.89, 42.87, 39.86, 37.10, 34.05, 27.05, 26.36, 22.23, 22.19, 21.21, 14.76, 13.69, 10.06, 6.91, 6.76, 5.23, 4.79. LRFABMS *m/z* calculated for $C_{46}H_{72}ClO_{11}Si_2$ $(M+H)^+$ 891.4302 found 891.5.

General procedure for the removal of the triethylsilyl groups. Synthesis of the baccatin derivatives 46-53.

All reactions were performed as described for the synthesis of 2-debenzoyl-2-*m*-methoxybenzoyl-10-deacetyl-10-*m*-nitrobenzoylbaccatin III. For every 10 mg of the starting material 0.5 mL THF, 0.15 mL of pyridine and 0.15 mL of HF-pyridine was used and the desired products were isolated in 85-95% yield.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-isopropanoylbaccatin III (46).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.87 (d, 1H), 7.78 (s, 1H), 7.46 (t, 1H), 7.24 (dd, 1H), 6.30 (s, 1H), 5.6 (d, J=6.8, 1H), 4.99 (d, J=7.6, 1H), 4.88 (t, 1H), 4.46 (m, 1H), 4.3 (d, J=8.4, 1H), 4.12 (d, J=8.4, 1H), 3.89 (d, J=7.2, 1H), 2.73 (m, 1H), 2.56 (m, 1H), 2.29 (d, 2H), 2.27 (s, 3H), 2.04 (s, 3H), 1.86 (m, 1H), 1.65 (s, 3H), 1.61 (bs, 1H), 1.32 (d, 3H), 1.25 (d, 3H), 1.10 (s, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 204.09, 177.21, 170.67, 166.06, 146.27, 140.76, 131.82, 131.05, 130.11, 126.62, 124.24, 120.05, 84.49, 80.71, 79.07, 75.79, 75.3, 72.3, 67.85, 58.66, 46.1, 42.64, 38.55, 35.52, 34.03, 26.95, 22.58, 20.86, 19.16, 18.62, 15.71, 9.37. HRFABMS *m/z* calculated for $C_{33}H_{42}N_3O_{11}$ $(M+H)^+$ 656.2819, found 656.2843, Δ 3.6 ppm LRFABMS *m/z* found 656.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-isopropanoylbaccatin III (47).

^{1}H NMR (CD_3OD, 399.951 MHz) δ 8.13 (s, 1H), 8.03 (d, 1H), 7.65 (d, 1H), 7.52 (t, 1H), 6.49 (s, 1H), 5.6 (d, J=8, 1H), 5.03 (d, J=10, 1H), 4.85 (t, 1H), 4.38 (m, 1H), 4.17 (q, 2H), 3.93 (d, J=7.2, 1H), 2.71 (m, 1H), 2.48 (m, 1H), 2.38 (d, 1H), 2.34 (d, 1H), 2.28 (s,

3H), 2.07 (s, 3H), 1.79 (m, 1H), 1.64 (s, 3H), 1.27 (d, J=6.8, 3H), 1.24 (d, J=6.8, 3H), 1.13 (s, 3H), 1.07 (s, 3H) ^{13}C NMR (CD_3OD, 100.578 MHz) δ 205.54, 177.19, 171.88, 166.20, 147.5, 135.64, 134.33, 133.53, 132.8, 131.36, 130.98, 129.37, 85.85, 81.97, 79.33, 77.32, 76.79, 72.48, 68.07, 59.27, 43.97, 40.49, 37.52, 35.29, 27.17, 22.66, 21.59, 19.42, 19.36, 15.49, 10.30. HRFABMS *m/z* calculated for $C_{33}H_{42}ClO_{11}$ $(M+H)^+$ 649.2416, found 649.2390, Δ 4.0 ppm. LRFABMS *m/z* found 649.2.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-(2-butene)oylbaccatin III (49).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (t, 1H), 7.98 (d, 1H), 7.58 (d, 1H), 7.42 (t, 1H), 7.1 (m, 1H), 6.38 (s, 1H), 6.00 (d, J=15.6, 1H), 5.85 (d, J=6.8, 1H), 5.00 (d, J=7.6, 1H), 4.88 (t, 1H), 4.48 (m, 1H), 4.28 (d, J=8.4, 1H), 4.12 (d, J=8.4, 1H), 3.89 (d, J=6.8, 1H), 2.57 (m, 1H), 2.28 (s, 3H), 2.26 (m, 2H), 2.05 (s, 3H), 1.93 (d, J=6.8 3H), 1.86 (m, 1H), 1.66 (s, 3H), 1.19 (s, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 204.12, 170.55, 166.29, 165.63, 147.07, 146.49, 134.71, 133.60, 131.75, 131.11, 130.15, 129.97, 128.23, 121.68, 84.45, 80.71, 79.2, 76.25, 75.87, 75.35, 72.4, 67.87, 58.61, 46.10, 42.61, 38.52, 35.51, 26.99, 22.46, 20.98, 18.21, 15.59, 9.33. HRFABMS *m/z* calculated for $C_{33}H_{40}ClO_{11}$ $(M+H)^+$ 647.2259, found 647.2233, Δ 4.1 ppm. LRFABMS *m/z* found 647.2.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-(2-butene)oylbaccatin III (48).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.88 (dt, 1H), 7.78 (t, 1H), 7.47 (t, 1H), 7.23 (d, 1H), 7.15 (m, 1H), 6.38 (s, 1H), 6.00 (d, J=15.6, 1H), 5.61 (d, J=7.2, 1H), 5.00 (d, J=7.6, 1H), 4.89 (t, 1H), 4.48 (m, 1H), 4.30 (d, J=8, 1H), 4.13 (d, J=8, 1H), 3.9 (d, J=7.6, 1H), 2.68 (bs, 1H), 2.57 (m, 1H), 2.29 (d, 2H), 2.28 (s, 3H), 2.18 (bs, 1H), 2.05 (s, 3H), 1.94 (d, J=6.8 3H), 1.86 (m, 1H), 1.66 (s, 3H), 1.18 (s, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 204.17, 170.68, 166.3, 166.08, 147.06, 146.5, 140.78, 131.82, 131.07, 130.12, 126.64, 124.24, 121.7, 120.06, 84.51, 80.74, 79.10, 75.89, 75.35, 72.36, 67.9, 58.7, 46.07, 42.65,

38.53, 35.53, 29.68, 27.02, 22.59, 20.95, 18.21, 15.60, 9.35. HRFABMS *m/z* calculated for $C_{33}H_{40}N_3O_{11}$ $(M+H)^+$ 654.2663, found 654.2666, Δ 0.3 ppm. LRFABMS *m/z* found 654.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-benzoylbaccatin III (51).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.12 (d, 1H), 8.08 (s, 2H), 7.98 (d, 1H), 7.62 (m, 2H), 7.48 (m, 3H), 6.58 (s, 1H), 5.61 (d, J=7.2, 1H), 5.03 (d, J=8.8, 1H), 4.91 (t, 1H), 4.55 (m, 1H), 4.30 (d, J=8.4, 1H), 4.14 (d, J=8.4, 1H), 3.95 (d, J=7.2, 1H), 2.6 (m, 1H), 2.32 (d, 2H), 2.30 (s, 3H), 2.10 (s, 3H), 1.88 (m, 1H), 1.68 (s, 3H), 1.11 (s, 3H), 1.18 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.88, 170.57, 166.43, 165.63, 146.73, 134.72, 133.61, 131.63, 131.11, 130.16, 129.99, 129.93, 129.17, 128.5, 128.24, 84.44, 80.72, 79.2, 76.53, 76.26, 75.36, 72.38, 67.85, 58.65, 46.24, 42.68, 38.58, 35.65, 27.12, 22.46, 21.16, 15.65, 14.16, 9.39. HRFABMS *m/z* calculated for $C_{36}H_{40}ClO_{11}$ $(M+H)^+$ 683.2259, found 683.2267, Δ 1.1 ppm. LRFABMS *m/z* found 683.2.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-benzoylbaccatin III (50).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.10 (s, 1H), 8.08 (d, 1H), 7.88 (dt, 1H), 7.79 (t, 1H), 7.61 (tt, 1H), 7.47 (m, 3H), 7.23 (dd, 1H), 6.58 (s, 1H), 5.65 (d, J=6.8, 1H), 5.02 (d, J=7.6, 1H), 4.92 (t, 1H), 4.55 (m, 1H), 4.32 (d, J=8, 1H), 4.15 (d, J=8, 1H), 3.95 (d, J=6.8, 1H), 2.61 (m, 2H), 2.33 (d, 2H), 2.29 (s, 3H), 2.1 (s, 3H), 1.89 (m, 1H), 1.68 (s, 3H), 1.21 (s, 3H), 1.18 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.93, 170.71, 166.43, 166.08, 146.72, 140.78, 133.61, 131.70, 131.05, 130.12, 129.94, 129.18, 128.50, 126.64, 124.26, 120.07, 84.5, 80.72, 79.10, 76.55, 76.33, 75.34, 72.34, 67.88, 58.73, 46.19, 42.71, 38.58, 35.63, 27.14, 22.59, 21.12, 15.66, 9.39. HRFABMS *m/z* calculated for $C_{36}H_{40}N_3O_{11}$ $(M+H)^+$ 690.2663, found 690.2669, Δ 0.6 ppm. LRFABMS *m/z* found 690.2.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-pentanoylbaccatin III (52).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.86 (d, 1H), 7.77 (s, 1H), 7.45 (t, 1H), 7.24 (dd, 1H), 6.31 (s, 1H), 5.59 (d, J=6.8, 1H), 4.99 (d, J=7.6, 1H), 4.87 (t, 1H), 4.46 (m, 1H), 4.29 (d, J=8, 1H), 4.12 (d, J=8, 1H), 3.87 (d, J=7.2, 1H), 2.53(m, 1H), 2.28 (m, 2H), 2.28 (d, 2H), 2.27 (s, 3H), 2.03 (s, 3H), 1.85 (m, 1H), 1.68 (m, 2H), 1.65 (s, 3H), 1.36 (m, 2H), 1.18 (s, 3H), 1.09 (s, 3H), 0.93 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 204.11, 174.06, 170.64, 166.03, 146.43, 140.75, 131.74, 131.05, 130.09, 126.6, 124.22, 120.04, 84.48, 80.67, 79.03, 76.31, 75.9, 75.33, 72.28, 67.79, 58.62, 46.06, 42.61, 38.58, 35.49, 33.9, 26.92, 26.86, 22.55, 22.17, 20.87, 15.55, 13.69, 9.36. HRFABMS *m/z* calculated for $C_{34}H_{44}N_3O_{11}$ $(M+H)^+$ 670.2976, found 670.2994, Δ 2.6 ppm. LRFABMS *m/z* found 670.3.

2-Debenzoyl-2-*m*-cholorobenzoyl-10-deacetyl-10-pentanoylbaccatin III (53).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.09 (s, 1H), 7.96 (d, 1H), 7.56 (dd, 1H), 7.4 (t, 1H), 6.30 (s, 1H), 5.55 (d, J=6.8, 1H), 4.98 (d, J=8, 1H), 4.86 (t, 1H), 4.45 (m, 1H), 4.27 (d, J=8.4, 1H), 4.11 (d, J=8.4, 1H), 3.86 (d, J=6.8, 1H), 2.53 (m, 2H), 2.48 (m, 2H), 2.27 (d, 2H), 2.26 (s, 3H), 2.03 (s, 3H), 1.85 (m, 1H), 1.68 (m, 2H), 1.65 (s, 3H), 1.42 (m, 2H), 1.18 (s, 3H), 1.09 (s, 3H), 0.93 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 204.33, 174.33, 170.77, 165.84, 146.72, 134.96, 133.83, 131.92, 131.38, 130.39, 130.22, 128.46, 84.68, 80.90, 79.39, 76.5, 76.16, 75.62, 72.59, 68.01, 58.8, 46.36, 42.84, 38.87, 35.76, 34.16, 27.17, 27.12, 22.68, 22.43, 21.17, 15.81, 13.96, 9.62. HRFABMS *m/z* calculated for $C_{34}H_{44}ClO_{11}$ $(M+H)^+$ 663.2572, found 663.2541, Δ 4.6 ppm. LRFABMS *m/z* found 663.2.

General procedure for the selective triethylsilylation of the C-7 hydroxyl of the baccatin III derivatives 46-53. Synthesis of the baccatin derivatives 54-61.

To a stirred solution of the baccatin derivative (**46-53**) (0.02 mmol) in DMF (0.5 mL) was added imidazole (0.06 mmol) and the reaction mixture was cooled down to 0 ^{o}C. 0.022 mmol of chlorotriethylsilane was then introduced and the reaction mixture was stirred at this temperature for 3-4 h. The reaction mixture was allowed to come to room temperature, diluted with 5% $NaHCO_3$ in MeOH, stirred for 15 min. where further diluted with EtOAc, washed with sat. aq. $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (30% EtOAc/Hexane) and the desired product was isolated in 90-95% yield.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-isopropanoyl-7-triethylsilylbaccatin III (54).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.87 (d, 1H), 7.79 (s, 1H), 7.46 (t, 1H), 7.26 (dd, 1H), 6.45 (s, 1H), 5.61 (d, J=6.8, 1H), 4.97 (d, J=8, 1H), 4.83 (t, 1H), 4.49 (m, 1H), 4.30 (d, J=8.4, 1H), 4.12 (d, J=8.4, 1H), 3.9 (d, J=6.8, 1H), 2.71 (m, 1H), 2.55 (m, 1H), 2.28 (s, 3H), 2.26 (d, 2H), 2.21 (s, 3H), 1.87 (m, 1H), 1.67 (s, 3H), 1.25 (d, 3H), 1.23 (d, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 0.92 (t, 9H), 0.58 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.19, 175.28, 170.79, 166.15, 143.92, 140.74, 132.69, 131.13, 130.09, 126.66, 124.21, 120.07, 84.26, 80.81, 78.77, 76.43, 75.35, 75.13, 72.28, 67.9, 58.61, 47.23, 42.72, 38.17, 37.19, 34.13, 26.78, 22.70, 20.06, 19.06, 18.89, 14.96, 9.91, 6.77, 5.25. LRFABMS *m/z* calculated for $(M+H)^+$ $C_{39}H_{56}N_3O_{11}Si$ 770.3684, found 770.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-isopropanoyl-7-triethylsilylbaccatin III (55).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (s, 1H), 7.97 (d, 1H), 7.57 (d, 1H), 7.41 (t, 1H),

6.44 (s, 1H), 5.58 (d, J=7.2, 1H), 4.97 (d, J=8.8, 1H), 4.81 (t, 1H), 4.47 (m, 1H), 4.27 (d, J=8, 1H), 4.11 (d, J=8, 1H), 3.88 (d, J=6.8, 1H), 2.69 (m, 1H), 2.52 (m, 1H), 2.28 (s, 3H), 2.25 (d, 2H), 2.20 (s, 3H), 1.87 (m, 1H), 1.66 (s, 3H), 1.25 (d, 3H), 1.23 (d, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 0.91 (t, 9H), 0.57 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.17, 175.28, 170.63, 165.67, 143.95, 134.68, 133.54, 132.58, 131.17, 130.16, 129.93, 128.23, 84.18, 80.76, 78.87, 76.34, 75.33, 75.13, 72.31, 67.84, 58.53, 47.26, 42.66, 38.17, 37.16, 34.12, 26.73, 22.52, 20.08, 19.05, 18.87, 14.94, 9.89, 6.76, 5.23. LRFABMS *m/z* calculated for $(M+H)^+$ $C_{39}H_{56}ClO_{11}Si$ 763.3280, found 763.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-(2-butene)oyl-7-triethylsilylbaccatin III (57).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.12 (s, 1H), 7.97 (d, 1H), 7.57 (d, 1H), 7.42 (t, 1H), 7.07 (m, 1H), 6.50 (s, 1H), 5.98 (d, J=15.6, 1H), 5.57 (d, J=6.8, 1H), 4.98 (d, J=7.6, 1H), 4.82 (t, 1H), 4.49 (m, 1H), 4.28 (d, J=8, 1H), 4.12 (d, J=8, 1H), 3.90 (d, J=7.2, 1H), 2.5 (m, 1H), 2.28 (s, 3H), 2.21 (m, 1H), 2.22 (s, 3H), 1.90 (d, J=7.2 3H), 1.84 (m, 1H), 1.68 (s, 3H), 1.21 (s, 3H), 1.02 (s, 3H), 0.92 (t, 9H), 0.57 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.17, 170.67, 165.69, 164.7, 145.73, 143.94, 134.69, 133.55, 132.63, 131.19, 130.19, 129.93, 128.25, 122.27, 84.21, 80.80, 78.88, 76.36, 75.48, 75.14, 72.36, 67.9, 58.58, 47.29, 42.7, 38.16, 37.2, 26.74, 22.56, 20.13, 18.14, 14.94, 9.89, 6.74, 5.24. LRFABMS *m/z* calculated for $(M+H)^+$ $C_{39}H_{54}ClO_{11}Si$ 761.3124, found 761.3.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-(2-butene)oyl-7-triethylsilylbaccatin III (56).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.88 (d, 1H), 7.80 (s, 1H), 7.46 (t, 1H), 7.22 (d, 1H), 7.08 (m, 1H), 6.50 (s, 1H), 5.98 (d, J=15.6, 1H), 5.63 (d, J=6.8, 1H), 4.97 (d, J=8, 1H), 4.83 (t, 1H), 4.5 (m, 1H), 4.3 (d, J=8.4, 1H), 4.13 (d, J=8.4, 1H), 3.9 (d, J=7.2, 1H), 2.5 (m, 1H), 2.28 (s, 3H), 2.22 (m, 1H), 2.13 (s, 3H), 1.90 (d, J=6.8 3H), 1.87 (m, 1H), 1.64

(s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 0.91 (t, 9H), 0.57 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.21, 170.81, 166.16, 164.71, 145.73, 143.95, 140.75, 132.7, 131.14, 130.09, 126.67, 124.21, 122.29, 120.09, 84.28, 80.31, 78.77, 76.44, 75.5, 75.15, 72.32, 67.93, 58.65, 47.26, 42.75, 38.18, 37.22, 26.76, 22.71, 20.11, 18.15, 14.96, 9.9, 6.74, 5.25. LRFABMS *m/z* calculated for $(M+H)^+$ $C_{39}H_{54}N_3O_{11}Si$ 768.3528, found 768.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-benzoyl-7-triethylsilylbaccatin III (59).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.15 (s, 1H), 8.13 (d, 2H), 7.97 (d, 1H), 7.56 (d, 2H), 7.44 (m, 3H), 6.69 (s, 1H), 5.64 (d, J=6.8, 1H), 5.0 (d, J=7.6, 1H), 4.84 (t, 1H), 4.56 (m, 1H), 4.30 (d, J=8.4, 1H), 4.14 (d, J=8.4, 1H), 3.95 (d, J=7.6, 1H), 2.55 (m, 1H), 2.31 (s, 3H), 2.26 (m, 1H), 2.25 (s, 3H), 2.04 (s, 1H), 1.87 (m, 1H), 1.71 (s, 3H), 1.31 (s, 3H), 1.11 (s, 3H), 1.01 (t, 9H), 0.58 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.05, 170.69, 165.71, 165.35, 144.37, 134.71, 133.57, 133.17, 132.53, 131.19, 130.19, 129.96, 129.87, 129.81, 128.49, 128.26, 84.23, 80.81, 78.92, 76.17, 75.17, 72.42, 67.91, 58.64, 47.34, 42.76, 38.24, 27.20, 26.82, 22.56, 20.38, 15.06, 9.92, 6.72, 5.27. LRFABMS *m/z* calculated for $(M+H)^+$ $C_{42}H_{54}ClO_{11}Si$ 797.3124, found 797.3.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-benzoyl-7-triethylsilylbaccatin III (58).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.15 (s, 1H), 8.13 (d, 1H), 7.89 (dt, 1H), 7.79 (t, 1H), 7.59 (tt, 1H), 7.46 (m, 3H), 7.22 (d, 1H), 6.69 (s, 1H), 5.68 (d, J=7.2, 1H), 4.99 (d, J=8, 1H), 4.85 (t, 1H), 4.57 (m, 1H), 4.32 (d, J=8, 1H), 4.15 (d, J=8, 1H), 3.96 (d, J=7.2, 1H), 2.5 (m, 1H), 2.3 (s, 3H), 2.28 (m, 1H), 2.27 (s, 3H), 1.89 (m, 1H), 1.71 (s, 3H), 1.32 (s, 3H), 1.18 (m, 1H), 1.04 (s, 3H), 0.89 (t, 9H), 0.58 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.08, 170.82, 166.15, 165.02, 144.39, 140.75, 133.16, 132.58, 131.13, 130.09,

129.88, 129.81, 128.49, 126.66, 124.22, 122.09, 84.29, 80.83, 78.80, 76.43, 76.19, 75.17, 72.38, 67.93, 58.70, 47.29, 42.8, 38.25, 37.22, 26.83, 22.71, 20.35, 15.07, 9.92, 6.72, 5.27. LRFABMS *m/z* calculated for $(M+H)^+$ $C_{42}H_{54}N_3O_{11}Si$ 804.3528, found 804.4.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-pentanoyl-7-triethylsilylbaccatin III (60).

^1H NMR ($CDCl_3$, 399.951 MHz) δ 7.87 (d, 1H), 7.78 (s, 1H), 7.45 (t, 1H), 7.23 (m, 1H), 6.47 (s, 1H), 5.61 (d, J=6.8, 1H), 4.96 (d, J=8, 1H), 4.82 (t, 1H), 4.48 (m, 1H), 4.29 (d, J=8, 1H), 4.11 (d, J=8, 1H), 3.88 (d, J=6.8, 1H), 2.51 (m, 1H), 2.43 (m, 2H), 2.27 (s, 3H), 2.26 (d, 2H), 2.24 (s, 3H), 2.19 (s, 3H), 1.86 (m, 1H), 1.66 (s, 3H), 1.63 (m, 2H), 1.4 (m, 2H), 1.18 (s, 3H), 1.09 (s, 3H), 0.93 (s, 3H), 0.92 (t, 9H), 0.58 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.19, 172.09, 170.76, 166.12, 143.94, 140.72, 132.67, 131.13, 130.06, 126.64, 124.18, 120.06, 84.24, 80.78, 78.72, 76.42, 75.45, 75.14, 72.28, 67.85, 58.61, 47.19, 42.7, 38.21, 37.18, 34.02, 27.04, 26.75, 22.67, 22.17, 20.04, 14.94, 13.69, 9.89, 6.74, 5.24. LRFABMS *m/z* calculated for $(M+H)^+$ $C_{40}H_{58}N_3O_{11}Si$ 784.3841, found 784.4.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-pentanoyl-7-triethylsilylbaccatin III (61).

^1H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (s, 1H), 7.97 (d, 1H), 7.56 (d, 1H), 7.41 (t, 1H), 6.47 (s, 1H), 5.57 (d, J=7.2, 1H), 4.96 (d, J=7.6, 1H), 4.81 (t, 1H), 4.48 (m, 1H), 4.27 (d, J=7.6, 1H), 4.11 (d, J=7.6, 1H), 3.87 (d, J=6.8, 1H), 2.50 (m, 1H), 2.43 (m, 2H), 2.28 (s, 3H), 2.22 (m, 2H), 2.18 (s, 3H), 1.85 (m, 1H), 1.68 (m, 2H), 1.65 (s, 3H), 1.4 (m, 2H), 1.18 (s, 3H), 1.2 (s, 3H), 0.93 (s, 3H), 0.92 (t, 9H), 0.57 (m, 6H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 202.16, 172.08, 170.61, 165.64, 143.93, 134.67, 133.52, 132.6, 131.17, 130.15, 129.92, 128.21, 84.16, 80.74, 78.82, 76.34, 75.43, 75.14, 72.32, 67.81, 58.53, 47.23, 42.64, 38.19, 37.15, 34.01, 27.03, 26.72, 22.51, 22.16, 20.06, 14.91, 13.68, 9.88, 6.74, 5.23. LRFABMS *m/z* calculated for $(M+H)^+$ $C_{40}H_{58}ClO_{11}Si$ 777.3437, found 777.4.

General procedure for the coupling of the baccatin III derivatives (54-61) with the β-lactam (30). Synthesis of the paclitaxel derivatives 62-69.

To a stirred solution of the baccatin derivative (**54-61**) (0.04 mmol) in THF (2 mL) at 0 ^{o}C was added NaH (2 mmol). The mixture was stirred for 15 min., and then β-lactam (**30**; 0.08 mmol) was introduced. The reaction mixture was allowed to come to room temperature and further stirred for 4 h. The reaction mixture was cooled down to 0 ^{o}C, quenched with acetic acid, and diluted with EtOAc, washed with dil. NaOH solution (0.1 N) and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (30% EtOAc/Hexane) and the desired product was isolated in 90-95% yield.

2'-*O*-(Triisopropylsilyl)-2-debenzoyl-2-*m*-azidobenzoyl-7-*O*-triethylsilyl-10-deacetyl-10-isopropanoylpaclitaxel (62).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.92 (d, 1H), 7.83 (s, 1H), 7.73 (d, 2H), 7.5 (m, 2H), 7.42-7.21 (m, 8H), 7.12 (d, J=8.8, 1H, NH), 6.45 (s, 1H), 6.14 (t, 1H), 5.69 (m, 2H), 4.96 (d, J=9.2, 1H), 4.9 (s, 1H), 4.49 (m, 1H), 4.34 (d, J=8.4, 1H), 4.19 (d, J=8.4, 1H), 3.86 (d, J=6.8, 1H), 2.68 (m, 1H), 2.56 (m, 1H), 2.53 (s, 3H), 2.4 (m, 1H), 2.11 (m, 1H), 2.05 (s, 3H), 1.9 (m, 1H), 1.69 (s, 3H), 1.24 (d, 3H), 1.22 (d, 3H), 1.15 (s, 3H), 0.98-0.90 (m, 30H), 0.96 (s, 3H), 0.57 (m, 6H). LRFABMS *m/z* calculated for $(M+H)^+$ $C_{64}H_{88}N_4O_{14}Si_2$ 1192.5836, found 1192.5.

2'-*O*-(Triisopropylsilyl)-2-debenzoyl-2-*m*-chlorobenzoyl-7-*O*-triethylsilyl-10-deacetyl-10-isopropanoylpaclitaxel (63).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.13 (t, 1H), 8.03 (dt, 1H), 7.74 (d, 2H), 7.58-7.30 (m, 10H), 7.11 (d, J=8.8, 1H, NH), 6.45 (s, 1H), 6.15 (t, 1H), 5.70 (d, 1H), 5.66 (d, 1H), 4.96 (d, J=7.6, 1H), 4.91 (s, 1H), 4.47 (m, 1H), 4.31 (d, J=8, 1H), 4.18 (d, J=8, 1H), 3.85 (d, J=7.2, 1H), 2.68 (m, 1H), 2.56 (m, 1H), 2.53 (s, 3H), 2.39 (m, 1H), 2.18 (m, 1H),

2.05 (s, 3H), 1.9 (m, 1H), 1.69 (s, 3H), 1.24 (d, 3H), 1.22 (d, 3H), 1.15 (s, 3H), 0.98-0.90 (m, 30H), 0.96 (s, 3H), 0.57 (m, 6H). LRFABMS *m/z* calculated for $(M+H)^+$ $C_{64}H_{89}N_4O_{14}Si_2$ 1193.5914, found 1193.5.

2'-*O*-(Triisopropylsilyl)-2-debenzoyl-2-*m*-chlorobenzoyl-7-*O*-triethylsilyl-10-deacetyl-10-(2-butene)oylpaclitaxel (65).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.13 (t, 1H), 8.04 (dt, 1H), 7.73 (d, 2H), 7.58-7.30 (m, 10H), 7.11 (d, J=8.8, 1H, NH), 7.06 (m, 1H), 6.50 (s, 1H), 6.16 (t, 1H), 5.95 (d, J=15.6, 1H), 5.68 (m, 2H), 4.96 (d, J=8, 1H), 4.90 (s, 1H), 4.49 (m, 1H), 4.31 (d, J=8, 1H), 4.18 (d, J=8, 1H), 3.86 (d, J=6, 1H), 2.56 (m, 1H), 2.53 (s, 3H), 2.37 (m, 1H), 2.16 (m, 1H), 2.07 (s, 3H), 1.91 (d, 3H), 1.70 (s, 3H), 1.22 (s, 3H), 1.15 (s, 3H), 0.98-0.88 (m, 30H), 0.57 (m, 6H). LRFABMS *m/z* calculated for $(M+H)^+$ $C_{64}H_{89}ClNO_{14}Si_2$ 1186.5510, found 1186.6.

2'-*O*-(Triisopropylsilyl)-2-debenzoyl-2-*m*-azidobenzoyl-7-*O*-triethylsilyl-10-deacetyl-10-(2-butene)oylpaclitaxel (64).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.94 (d, 1H), 7.83 (t, 1H), 7.72 (d, 2H), 7.52-7.23 (m, 10H), 7.11 (d, J=8.8, 1H, NH), 7.06 (m, 1H), 6.50 (s, 1H), 6.16 (t, 1H), 5.95 (d, J=15.6, 1H), 5.68 (m, 2H), 4.96 (d, J=8.4, 1H), 4.90 (s, 1H), 4.49 (m, 1H), 4.31 (d, J=8.4, 1H), 4.18 (d, J=8.4, 1H), 3.86 (d, J=6, 1H), 2.58 (m, 1H), 2.53 (s, 3H), 2.4 (m, 1H), 2.16 (m, 1H), 2.07 (s, 3H), 1.92 (d, 3H), 1.70 (s, 3H), 1.24 (s, 3H), 1.15 (s, 3H), 0.98-0.88 (m, 30H), 0.57 (m, 6H) LRFABMS *m/z* calculated for $(M+H)^+$ $C_{64}H_{87}N_4O_{14}Si_2$ 1191.5757, found 1191.5.

2'-*O*-(Triisopropylsilyl)-2-debenzoyl-2-*m*-chlorobenzoyl-7-*O*-triethylsilyl-10-deacetyl-10-benzoylpaclitaxel (67).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.15 (t, 1H), 8.12 (d, 2H), 8.06 (d, 1H), 7.72 (d, 2H), 7.58-7.3 (m, 13H), 7.11 (d, J=8.8, 1H, NH), 6.69 (s, 1H), 6.19 (t, 1H), 5.71 (d, J=6.8, 1H), 5.68 (d, J=6.8, 1H), 4.98 (d, J=8, 1H), 4.92 (s, 1H), 4.55 (m, 1H), 4.31 (d, J=8.4, 1H), 4.21 (d, J=8.4, 1H), 3.92 (d, J=7.2, 1H), 2.57 (m, 1H), 2.53 (s, 3H), 2.39 (m, 1H), 2.21 (m, 1H), 2.14 (s, 3H), 1.93 (m, 1H), 1.73 (s, 3H), 1.34 (s, 3H), 1.18 (s, 3H), 0.98-0.88 (m, 30H), 0.59 (m, 6H). LRFABMS *m/z* calculated for $(M+H)^+$ $C_{67}H_{87}ClNO_{14}Si_2$ 1220.5354, found 1220.6.

2'-*O*-(Triisopropylsilyl)-2-debenzoyl-2-*m*-azidobenzoyl-7-*O*-triethylsilyl-10-deacetyl-10-benzoylpaclitaxel (66).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.1 (d, 2H), 7.93 (d, 1H), 7.85 (t, 1H), 7.72 (d, 2H), 7.58-7.23 (m, 13H), 7.11 (d, J=8.8, 1H, NH), 6.69 (s, 1H), 6.18 (t, 1H), 5.77 (d, J=7.2, 1H), 5.68 (d, J=9.6, 1H), 4.98 (d, J=8, 1H), 4.91 (s, 1H), 4.56 (m, 1H), 4.36 (d, J=8.4, 1H), 4.22 (d, J=8.4, 1H), 3.93 (d, J=6.8, 1H), 2.58 (m, 1H), 2.55 (s, 3H), 2.41 (m, 1H), 2.2 (m, 1H), 2.14 (s, 3H), 1.93 (m, 1H), 1.73 (s, 3H), 1.35 (s, 3H), 1.17 (s, 3H), 0.98-0.88 (m, 30H), 0.59 (m, 6H). LRFABMS *m/z* calculated for $(M+H)^+$ $C_{67}H_{87}N_4O_{14}Si_2$ 1227.5757, found 1227.5.

2'-*O*-(Triisopropylsilyl)-2-debenzoyl-2-*m*-azidobenzoyl-7-*O*-triethylsilyl-10-deacetyl-10-pentanoylpaclitaxel (68).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.92 (d, 1H), 7.83 (t, 1H), 7.73 (d, 2H), 7.52-7.23 (m, 10H), 7.12 (d, J=9.2, 1H, NH), 6.47 (s, 1H), 6.15 (t, 1H), 5.69 (m, 2H), 4.96 (d, J=8, 1H), 4.90 (s, 1H), 4.49 (m, 1H), 4.34 (d, J=8.4, 1H), 4.19 (d, J=8.4, 1H), 3.86 (d, J=7.2, 1H), 2.53 (s, 3H), 2.51 (m, 1H), 2.44 (m, 2H), 2.41 (m, 1H), 2.2 (m, 1H), 2.04 (s, 3H),

1.90 (m, 1H), 1.69 (s, 3H), 1.64 (m, 2H), 1.41 (m, 2H), 1.2 (s, 3H), 1.15 (s, 3H), 0.98-0.88 (m, 30H), 0.94 (t, 3H), 0.59 (m, 6H). LRFABMS *m/z* calculated for $(M+H)^+$ $C_{65}H_{91}N_4O_{14}Si_2$ 1207.6070, found 1207.5.

2'-*O*-(Triisopropylsilyl)-2-debenzoyl-2-*m*-chlorobenzoyl-7-*O*-triethylsilyl-10-deacetyl-10-pentanoylpaclitaxel (69).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.13 (s, 1H), 8.29 (dt, 1H), 7.73 (d, 2H), 7.56-7.23 (m, 10H), 7.11 (d, J=8.8, 1H, NH), 6.47 (s, 1H), 6.16 (t, 1H), 5.66 (m, 2H), 4.96 (d, J=7.6, 1H), 4.90 (s, 1H), 4.74 (m, 1H), 4.30 (d, J=8.4, 1H), 4.19 (d, J=8.4, 1H), 3.84 (d, J=7.2, 1H), 2.53 (s, 3H), 2.51 (m, 1H), 2.44 (m, 2H), 2.41 (m, 1H), 2.18 (m, 1H), 2.04 (s, 3H), 1.90 (m, 1H), 1.69 (s, 3H), 1.64 (m, 2H), 1.41 (m, 2H), 1.2 (s, 3H), 1.15 (s, 3H), 0.98-0.88 (m, 30H), 0.94 (t, 3H), 0.59 (m, 6H).

General procedure for the removal of the silyl protecting groups. Synthesis of the paclitaxel derivatives 70-77.

All reactions were performed as described for the synthesis of 2-debenzoyl-2-*m*-methoxybenzoyl-10-deacetyl-10-*m*-nitrobenzoylbaccatin III. For every 10 mg of the starting material 0.5 mL THF, 0.15 mL of pyridine and 0.15 mL of HF-pyridine was used and the desired products were isolated in 85-95% yield.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-isopropanoylpaclitaxel (70).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.91 (d, 1H), 7.82 (s, 1H), 7.71 (d, 2H), 7.51-7.23 (m, 10H), 6.90 (d, J=8.8, 1H, NH), 6.25 (s, 1H), 6.20 (t, 1H), 5.76 (d, J=8.8, 1H), 5.66 (d, J=7.2, 1H), 4.95 (d, J=8.8, 1H), 4.76 (m, 1H), 4.41 (m, 1H), 4.31 (d, J=8.4, 1H), 4.17 (d, J=8.4, 1H), 3.82 (d, J=6.8, 1H), 3.51 (d, J=5.2, 1H), 2.72 (m, 1H), 2.56 (m, 1H), 2.51 (d, 1H), 2.36 (s, 3H), 2.34 (m, 2H), 1.9 (m, 1H), 1.8 (s, 3H), 1.68 (s, 1H), 1.67 (s, 3H), 1.32

(d, 3H), 1.24 (s, 3H), 1.22 (d, 3H), 1.14 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.59, 177.19, 172.84, 170.34, 167.01, 166.03, 141.91, 140.78, 137.98, 133.63, 133.19, 131.95, 130.85, 130.24, 129.04, 128.68, 128.40, 127.11, 127.01, 126.82, 124.40, 120.13, 84.47, 81.13, 79.09, 76.40, 75.35, 75.17, 73.03, 72.47, 72.20, 58.59, 55.07, 45.59, 43.14, 35.65, 35.53, 34.03, 26.85, 22.68, 21.82, 19.19, 18.61, 14.84, 9.52. HRFABMS *m/z* calculated for $C_{49}H_{55}N_4O_{14}$ $(M+H)^+$ 923.3715, found 923.3752, Δ 4 ppm. LRFABMS *m/z* found 923.4.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-isopropanoylpaclitaxel (71).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (s, 1H), 8.01 (d, 1H), 7.72 (d, 2H), 7.58 (d, 1H), 7.53-7.32 (m, 9H), 6.97 (d, J=8.8, 1H, NH), 6.24 (s, 1H), 6.19 (t, 1H), 5.75 (dd, 1H), 5.61 (d, J=6.8, 1H), 4.95 (d, J=8, 1H), 4.76 (t, 1H), 4.38 (m, 1H), 4.27 (d, J=8.4, 1H), 4.15 (d, J=8.4, 1H), 3.80 (d, J=7.6, 1H), 3.64 (d, J=5.2, 1H), 2.72 (m, 1H), 2.55 (m, 1H), 2.52 (m, 1H), 2.35 (s, 3H), 2.30 (d, 2H), 1.86 (m, 1H), 1.78 (s, 3H), 1.74 (s, 1H), 1.66 (s, 3H), 1.31 (d, 3H), 1.24 (s, 3H), 1.22 (d, 3H), 1.13 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.49, 177.16, 172.70, 170.25, 167.09, 165.55, 141.85, 137.7, 134.72, 133.67, 133.61, 133.12, 131.95, 130.95, 130.22, 130.12, 129.03, 128.66, 128.39, 127.10, 127.01, 84.39, 81.11, 79.1, 76.33, 75.32, 75.14, 73.18, 72.29, 72.22, 58.51, 55.18, 45.66, 43.08, 35.61, 35.54, 34.01, 26.79, 22.48, 21.76, 19.16, 18.59, 14.82, 9.4. HRFABMS *m/z* calculated for $C_{49}H_{55}ClNO_{14}$ $(M+H)^+$ 916.3311, found 916.3315, Δ 0.4 ppm. LRFABMS *m/z* found 916.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-(2-butene)oylpaclitaxel (73).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.12 (s, 1H), 8.02 (d, 1H), 7.72 (d, 2H), 7.59 (dt, 1H), 7.50-7.23 (m, 9H), 7.10 (m, 1H), 6.95 (d, J=8.8, 1H, NH), 6.32 (s, 1H), 6.2 (t, 1H), 5.98 (d, J=15.6, 1H), 5.75 (dd, 1H), 5.62 (d, J=7.2, 1H), 4.96 (d, J=8, 1H), 4.76 (m, 1H), 4.42 (m, 1H), 4.38 (d, J=8.4, 1H), 4.16 (d, J=8.4, 1H), 3.81 (d, J=6.8, 1H), 3.55 (d, J=5.2,

1H), 2.63 (d, 1H), 2.56 (m, 1H), 2.36 (s, 3H), 2.31 (d, 2H), 1.95 (d, 3H), 1.87 (m, 1H), 1.78 (s, 3H), 1.69 (s, 1H), 1.67 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.59, 172.65, 170.26, 167.00, 166.21, 165.61, 147.34, 142.13, 137.93, 134.74, 133.69, 133.60, 133.11, 131.95, 130.94, 130.22, 130.12, 129.05, 128.68, 128.42, 127.10, 127.01, 121.54, 84.42, 81.13, 79.18, 76.35, 75.34, 75.24, 73.19, 72.31, 58.57, 55.18, 45.62, 43.08, 35.61, 35.53, 36.89, 22.49, 21.83, 18.24, 14.88, 9.47. HRFABMS *m/z* calculated for $C_{49}H_{53}ClNO_{14}$ $(M+H)^+$ 914.3155, found 914.3143, Δ 1.2 ppm. LRFABMS *m/z* found 914.3.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-(2-butene)oylpaclitaxel (72).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.91 (d, 1H), 7.82 (t, 1H), 7.71 (d, 2H), 7.52-7.23 (m, 10H), 7.10 (m, 1H), 6.91 (d, J=8.8, 1H, NH), 6.33 (s, 1H), 6.20 (t, 1H), 6.00 (d, J=14.8, 1H), 5.75 (d, J=8.8, 1H), 5.67 (d, J=8.8, 1H), 4.96 (d, J=9.2, 1H), 4.77 (m, 1H), 4.38 (m, 1H), 4.32 (d, J=8, 1H), 4.18 (d, J=8, 1H), 3.82 (d, J=6.8, 1H), 3.48 (d, J=5.6, 1H), 2.61 (d, 1H), 2.56 (m, 1H), 2.37 (s, 3H), 2.33 (d, 1H), 1.93 (d, 3H), 1.86 (m, 1H), 1.79 (s, 3H), 1.67 (s, 3H), 1.56 (s, 3H), 1.24 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.68, 195.74, 190.8, 186.66, 175.14, 172.79, 170.35, 168.67, 166.05, 147.34, 143.56, 142.16, 138.58, 137.95, 134.62, 133.62, 131.95, 130.24, 129.04, 128.41, 127.11, 126.82, 124.4, 121.55, 120.37, 84.48, 81.15, 79.14, 76.41, 75.25, 73.03, 72.25, 69.82, 58.61, 55.08, 45.55, 43.14, 35.64, 26.92, 22.67, 21.88, 18.93, 14.88, 9.49. HRFABMS *m/z* calculated for $C_{49}H_{52}N_4O_{14}Na$ $(M+Na)^+$ 943.3378, found 943.3370, Δ 0.8 ppm. LRFABMS *m/z* found 943.3.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-benzoylpaclitaxel (75).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.13 (s, 1H), 8.07 (d, 2H), 8.02 (d, 1H), 7.72 (d, 2H), 7.61-7.58 (m, 2H), 7.50-7.23 (m, 11H), 6.97 (d, J=8.8, 1H, NH), 6.52 (s, 1H), 6.22 (t, 1H), 5.78 (d, J=7.6, 1H), 5.66 (d, J=6.8, 1H), 4.97 (d, J=9.2, 1H), 4.77 (m, 1H), 4.48 (m,

1H), 4.30 (d, J=8.4, 1H), 4.17 (d, J=8.4, 1H), 3.87 (d, J=7.2, 1H), 3.59 (d, J=5.6, 1H), 2.63 (d, 1H), 2.59 (m, 1H), 2.37 (s, 3H), 2.34 (d, 2H), 1.90 (m, 1H), 1.82 (s, 3H), 1.76 (s, 1H), 1.69 (s, 3H), 1.65 (s, 1H), 1.32 (s, 3H), 1.25 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.34, 172.65, 170.3, 167.05, 166.37, 165.61, 142.31, 137.92, 134.75, 133.72, 133.6, 133.02, 131.95, 130.93, 130.24, 130.14, 129.97, 129.05, 129.06, 128.68, 128.55, 128.43, 128.39, 127.1, 84.41, 81.13, 79.18, 76.35, 75.89, 75.33, 73.19, 72.3, 58.61, 55.21, 45.75, 43.16, 35.66, 26.99, 22.49, 21.99, 14.93, 9.51. HRFABMS *m/z* calculated for $C_{52}H_{52}ClNO_{14}Na$ $(M+Na)^+$ 972.2975, found 972.2994, Δ 1.1 ppm. LRFABMS *m/z* found 972.3.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-benzoylpaclitaxel (74).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.08 (d, 2H), 7.93 (d, 1H), 7.83 (t, 1H), 7.71 (d, 2H), 7.62 (t, 1H), 7.52-7.23 (m, 12H), 6.92 (d, J=8.8, 1H, NH), 6.53 (s, 1H), 6.24 (t, 1H), 5.76 (d, J=7.2, 1H), 5.72 (d, J=7.2, 1H), 4.96 (d, J=9.6, 1H), 4.77 (m, 1H), 4.50 (m, 1H), 4.33 (d, J=8.4, 1H), 4.10 (d, J=8.4, 1H), 3.89 (d, J=7.2, 1H), 3.5 (d, J=5.2, 1H), 2.6 (d, 1H), 2.57 (m, 1H), 2.38 (s, 3H), 2.37 (d, 2H), 1.91 (m, 1H), 1.84 (s, 3H), 1.72 (s, 1H), 1.70 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.42, 172.79, 170.39, 167.00, 166.38, 166.05, 142.35, 140.78, 137.93, 133.71, 133.08, 131.95, 130.84, 130.25, 129.97, 128.68, 128.55, 128.42, 127.11, 126.82, 124.41, 120.14, 84.47, 81.14, 79.12, 76.41, 75.9, 75.36, 73.02, 72.24, 58.66, 55.1, 45.67. 43.21, 35.69, 27.27, 22.68, 22.03, 14.92, 9.53. HRFABMS *m/z* calculated for $C_{52}H_{53}N_4O_{14}$ $(M+H)^+$ 957.3558, found 957.3562, Δ 0.4 ppm. LRFABMS *m/z* found 957.3.

2-Debenzoyl-2-*m*-azidobenzoyl-10-deacetyl-10-pentanoylpaclitaxel (76).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 7.92 (d, 1H), 7.81 (t, 1H), 7.71 (d, 2H), 7.51-7.23 (m, 10H), 6.92 (d, J=8.8, 1H, NH), 6.27 (s, 1H), 6.21 (t, 1H), 5.76 (d, J=9.2, 1H), 5.67 (d, J=6.8, 1H), 4.95 (d, J=7.6, 1H), 4.76 (m, 1H), 4.41 (m, 1H), 4.31 (d, J=8, 1H), 4.18 (d,

J=8, 1H), 3.81 (d, J=6.8, 1H), 3.54 (d, J=5.6, 1H), 2.51 (m, 2H), 2.42 (m, 2H), 2.37 (s, 3H), 2.33 (d, 2H), 1.86 (m, 1H), 1.79 (s, 3H), 1.73 (s, 1H), 1.7 (m, 2H), 1.67 (s, 3H), 1.66 (s, 1H), 1.43 (m, 2H), 1.24 (s, 3H), 1.14 (s, 3H), 0.94 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.60, 174.02, 172.82, 170.35, 167.03, 166.02, 141.99, 140.77, 137.98, 133.62, 133.17, 131.95, 130.87, 130.24, 129.03, 128.68, 128.39, 127.11, 127.01, 126.82, 124.39, 120.13, 84.46, 81.12, 79.07, 76.40, 75.36, 73.03, 72.44, 72.19, 58.58, 55.09, 45.55, 43.13, 35.64, 35.51, 33.8, 26.87, 22.66, 21.81, 14.84, 13.71, 9.52. HRFABMS *m/z* calculated for $C_{50}H_{57}N_4O_{14}$ $(M+H)^+$ 937.3871, found 937.3843, Δ 3 ppm. LRFABMS *m/z* found 937.4.

2-Debenzoyl-2-*m*-chlorobenzoyl-10-deacetyl-10-pentanoylpaclitaxel (77).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (s, 1H), 8.01 (d, 1H), 7.71 (d, 2H), 7.57 (d, 1H), 7.53-7.25 (m, 9H), 6.98 (d, J=8.8, 1H, NH), 6.26 (s, 1H), 6.19 (t, 1H), 5.74 (d, J=9.6, 1H), 5.61 (d, J=7.2, 1H), 4.96 (d, J=8.4, 1H), 4.76 (m, 1H), 4.38 (m, 1H), 4.27 (d, J=8, 1H), 4.15 (d, J=8, 1H), 3.79 (d, J=7.2, 1H), 3.66 (d, J=5.2, 1H), 2.55 (m, 2H), 2.47 (m, 2H), 2.35 (s, 3H), 2.30 (d, 2H), 1.86 (m, 1H), 1.79 (s, 1H), 1.77 (s, 3H), 1.71 (m, 2H), 1.66 (s, 3H), 1.4 (m, 2H), 1.22 (s, 3H), 1.12 (s, 3H), 0.94 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.51, 173.99, 172.68, 170.25, 167.09, 165.55, 141.94, 137.96, 134.72, 133.67, 133.11, 131.94, 130.95, 130.11, 129.02, 128.65, 128.39, 127.01, 84.38, 81.1, 79.1, 76.34, 75.33, 75.25, 73.19, 72.27, 72.22, 58.11, 55.21, 45.62, 43.07, 35.61, 26.8, 22.47, 21.76, 14.83, 13.7, 9.49. HRFABMS *m/z* calculated for $C_{50}H_{57}ClNO_{14}$ $(M+H)^+$ 930.3468, found 930.3452, Δ 1.6 ppm. LRFABMS *m/z* found 930.3.

General procedure for the coupling of the baccatin III derivatives (78-81) with the β-lactams (27-29). Synthesis of the paclitaxel derivatives 82-93.

All reactions were performed as described for the synthesis of paclitaxel derivatives **62-69**, and the desired products were isolated in 85-95 % yield.

2'-*O*-(Triisopropylsilyl)-3'-*N*-debenzoyl-3'-*N*-hexanoyl-7-*O*-triethylsilyl-10-deacetyl-10-butanoylpaclitaxel (85).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.6-7.23 (m, 8H), 6.48 (s, 1H), 6.33 (d, J= 9.6, 1H, NH), 6.19 (t, 1H), 5.71 (d, J=7.2, 1H), 5.56 (d, J=9.2, 1H), 4.93 (d, J=8, 1H), 4.82 (s, 1H), 4.74 (m, 1H), 4.30 (d, J=8.4, 1H), 4.20 (d, J=8.4, 1H), 3.83 (d, J=7.2, 1H), 2.49 (s, 3H), 2.43 (m, 2H), 2.39 (m, 2H), 2.17 (t, 3H), 2.03 (s, 3H), 1.76 (m, 2H), 1.71 (m, 2H), 1.69 (s, 3H), 1.56 (m, 2H), 1.25 (m, 2H), 1.24 (m, 2H), 1.23 (s, 3H), 1.21 (t, 3H), 1.19 (s, 3H), 0.97 (m, 2H), 0.96-0.90 (m, 30H), 0.81 (t, 3H), 0.57 (m, 6H).

2'-*O*-(Triisopropylsilyl)-3'-*N*-debenzoyl-3'-*N*-hexanoyl-7-*O*-triethylsilyl-10-deacetyl-10-(2-butene)oylpaclitaxel (83).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.6-7.23 (m, 8H), 7.08 (m, 1H), 6.48 (s, 1H), 6.33 (d, J= 9.6, 1H, NH), 6.19 (t, 1H), 5.97 (d, J=15.6, 1H), 5.71 (d, J=7.2, 1H), 5.56 (d, J=9.2, 1H), 4.93 (d, J=8, 1H), 4.82 (s, 1H), 4.74 (m, 1H), 4.30 (d, J=8.4, 1H), 4.20 (d, J=8.4, 1H), 3.83 (d, J=7.2, 1H), 2.49 (s, 3H), 2.39 (m, 2H), 2.24 (t, 3H), 2.1 (s, 3H), 1.94 (d, 3H), 1.68 (s, 3H), 1.61 (m, 2H), 1.38 (m, 2H), 1.37 (m, 2H), 1.29 (s, 3H), 1.17 (s, 3H), 1.1-0.90 (m, 30H), 0.81 (t, 3H), 0.57 (m, 6H).

2'-*O*-(Triisopropylsilyl)-3'-*N*-debenzoyl-3'-*N*-hexanoyl-7-*O*-triethylsilyl-10-deacetyl-10-propanoylpaclitaxel (84).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.6-7.23 (m, 8H), 6.48 (s, 1H), 6.33 (d, J= 9.6, 1H, NH), 6.19 (t, 1H), 5.71 (d, J=7.2, 1H), 5.56 (d, J=9.2, 1H), 4.93 (d, J=8, 1H), 4.82 (s, 1H), 4.74 (m, 1H), 4.30 (d, J=8.4, 1H), 4.20 (d, J=8.4, 1H), 3.83 (d, J=7.2, 1H), 2.49 (s, 3H), 2.43 (m, 2H), 2.17 (t, 3H), 2.03 (s, 3H), 1.76 (m, 2H), 1.71 (m, 2H), 1.69 (s, 3H), 1.56 (m, 2H), 1.25 (m, 2H), 1.24 (m, 2H), 1.23 (s, 3H), 1.21 (t, 3H), 1.19 (s, 3H), 0.97 (m, 2H), 0.96-0.90 (m, 30H), 0.81 (t, 3H), 0.57 (m, 6H).

2'-*O*-(Triisopropylsilyl)-3'-*N*-debenzoyl-3'-*N*-hexanoyl-7-*O*-triethylsilyl-10-deacetyl-10-isopropanoylpaclitaxel (82).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.6-7.23 (m, 8H), 6.48 (s, 1H), 6.33 (d, J= 9.6, 1H, NH), 6.19 (t, 1H), 5.71 (d, J=7.2, 1H), 5.56 (d, J=9.2, 1H), 4.93 (d, J=8, 1H), 4.82 (s, 1H), 4.74 (m, 1H), 4.30 (d, J=8.4, 1H), 4.20 (d, J=8.4, 1H), 3.83 (d, J=7.2, 1H), 2.69 (m, 1H), 2.49 (s, 3H), 2.36 (m, 1H), 2.21 (m, 2H), 2.04 (s, 3H), 1.86 (m, 2H), 1.69 (s, 3H), 1.27-1.23 (m, 6H), 1.21 (d, 6H), 1.03 (s, 6H), 0.93-0.89 (m, 30H), 0.81 (t, 3H), 0.57 (m, 6H).

2'-*O*-(Triisopropylsilyl)-3'-*N*-debenzoyl-3'-*N*-furoyl-7-*O*-triethylsilyl-10-deacetyl-10-butanoylpaclitaxel (93).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.14 (d, 2H), 7.6 (tt, 1H), 7.52 (tt, 2H), 7.46 (m, 1H), 7.37-7.26 (m, 6H), 6.9 (d, J=3.6, 1H), 6.44 (s, 1H), 6.42 (m, 1H), 6.21 (t, 1H), 5.70 (d, 2H), 4.94 (m, 2H), 4.48 (m, 1H), 4.30 (d, J=8.4, 1H), 4.20 (d, J=8.4, 1H), 3.82 (d, J=6.8, 1H), 2.57 (s, 3H), 2.5 (m, 2H), 2.49 (m, 1H), 2.13 (m, 1H), 2.01 (s, 3H), 1.9 (m, 1H), 1.75 (s, 1H), 1.74 (m, 2H), 1.69 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 0.99 (t, 3H), 0.98-0.9 (m, 30H), 0.58 (m, 6H).

2'-*O*-(Triisopropylsilyl)-3'-*N*-debenzoyl-3'-*N*-furoyl-7-*O*-triethylsilyl-10-deacetyl-10-(2-butene)oylpaclitaxel (91).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.14 (d, 2H), 7.6 (tt, 1H), 7.52 (tt, 2H), 7.46 (m, 1H), 7.37-7.26 (m, 6H), 7.07 (m, 1H), 6.93 (d, J=3.2, 1H), 6.49 (s, 1H), 6.42 (m, 1H), 6.21 (t, 1H), 5.95 (d, J=15.6, 1H), 5.70 (m, 2H), 4.94 (m, 2H), 4.48 (m, 1H), 4.30 (d, J=8.4, 1H), 4.20 (d, J=8.4, 1H), 3.82 (d, J=6.8, 1H), 2.52 (s, 3H), 2.35 (m, 1H), 2.14 (m, 1H), 2.04 (s, 3H), 1.92 (d, 3H), 1.79 (s, 1H), 1.7 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H), 0.98-0.92 (m, 30H), 0.58 (m, 6H).

2'-*O*-(Triisopropylsilyl)-3'-*N*-debenzoyl-3'-*N*-furoyl-7-*O*-triethylsilyl-10-deacetyl-10-propanoylpaclitaxel (92).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.14 (d, 2H), 7.6 (tt, 1H), 7.52 (tt, 2H), 7.46 (m, 1H), 7.37-7.26 (m, 6H), 6.9 (d, J=3.6, 1H), 6.44 (s, 1H), 6.42 (m, 1H), 6.21 (t, 1H), 5.70 (d, 2H), 4.94 (m, 2H), 4.48 (m, 1H), 4.30 (d, J=8.4, 1H), 4.20 (d, J=8.4, 1H), 3.82 (d, J=6.8, 1H), 2.57 (s, 3H), 2.5 (m, 2H), 2.49 (m, 1H), 2.13 (m, 1H), 2.01 (s, 3H), 1.9 (m, 1H), 1.75 (s, 1H), 1.69 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 0.99 (t, 3H), 0.98-0.9 (m, 30H), 0.58 (m, 6H).

2'-*O*-(Triisopropylsilyl)-3'-*N*-debenzoyl-3'-*N*-furoyl-7-*O*-triethylsilyl-10-deacetyl-10-isopropanoylpaclitaxel (90).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.14 (d, 2H), 7.6 (tt, 1H), 7.52 (tt, 2H), 7.46 (m, 1H), 7.37-7.26 (m, 6H), 6.9 (d, J=3.6, 1H), 6.44 (s, 1H), 6.42 (m, 1H), 6.21 (t, 1H), 5.70 (d, 2H), 4.94 (m, 2H), 4.48 (m, 1H), 4.30 (d, J=8.4, 1H), 4.20 (d, J=8.4, 1H), 3.82 (d, J=6.8, 1H), 2.68 (m, 1H), 2.52 (s, 3H), 2.49 (m, 1H), 2.13 (m, 1H), 2.01 (s, 3H), 1.9 (m, 1H), 1.75 (s, 1H), 1.69 (s, 3H), 1.25 (s, 3H), 1.23 (d, 6H), 1.17 (s, 3H) 0.98-0.89 (m, 30H), 0.58 (m, 6H).

General procedure for the removal of the silyl protecting groups. Synthesis of the paclitaxel derivatives 94-105.

All reactions were performed as described for the synthesis of paclitaxel derivatives **70-77**. For every 10 mg of the starting material 0.5 mL THF, 0.15 mL of pyridine and 0.15 mL of HF-pyridine was used and the desired products were isolated in 85-95% yield.

3'-*N*-Debenzoyl-3'-*N*-hexanoyl-10-deacetyl-10-isopropanoylpaclitaxel (94).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.52-7.33 (m, 7H), 6.26 (s, 1H), 6.19 (t, 1H), 6.16 (d, J=8.8, 1H), 5.67 (d, J=7.2, 1H), 5.56 (d, J=9.2, 1H), 4.93 (d, J=8, 1H), 4.67 (m, 1H), 4.40 (m, 1H), 4.29 (d, J=8.4, 1H), 4.18 (d, J=8.4, 1H), 3.80 (d, J=7.2, 1H), 3.44 (d, J=5.2, 1H), 2.73 (m, 1H), 2.54 (m, 1H), 2.51 (s, 1H), 2.34 (s, 3H), 2.29 (m, 1H), 2.21 (t, 2H), 1.82 (s, 3H), 1.76 (s, 1H), 1.67 (s, 3H), 1.58 (s, 6H), 1.31 (d, 3H), 1.26 (d, 3H), 1.24-1.15 (m, 6H), 0.84 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.68, 177.20, 172.84, 170.23, 167.00, 141.85, 138.06, 133.71, 133.27, 130.22, 129.09, 128.97, 128.27, 126.96, 84.42, 81.12, 79.04, 76.47, 75.19, 74.94, 73.13, 72.41, 72.22, 58.61, 54.51, 45.60, 43.20, 36.59, 35.55, 34.04, 31.30, 26.83, 25.36, 22.61, 19.19, 18.62, 14.81, 13.84, 9.54. HRFABMS *m/z* calculated for $C_{48}H_{62}NO_{14}$ $(M+H)^+$ 876.4170, found 876.4099, Δ 8.1 ppm. LRFABMS *m/z* found 876.5

3'-*N*-Debenzoyl-3'-*N*-hexanoyl-10-deacetyl-10-(2-butene)oylpaclitaxel (95).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40-7.30 (m, 5H), 7.10 (m, 1H), 6.34 (s, 1H), 6.23 (d, NH, 1H), 6.21 (t, 1H), 5.99 (d, J=15.6, 1H), 5.67 (d, J=7.2, 1H), 5.57 (dd, 1H), 4.93 (d, 1H), 4.67 (m, 1H), 4.42 (m, 1H), 4.28 (d, J=8.8, 1H), 4.18 (d, J=8.8, 1H), 3.80 (d, J=7.2, 1H), 3.51 (d, J=5.6, 1H), 2.64 (d, 1H), 2.53 (m, 1H), 2.34 (s, 3H), 2.30 (t, 2H), 2.18 (t, 2H), 1.94 (d, 3H), 1.91 (s, 1H), 1.85 (dt, 1H), 1.81 (s, 3H), 1.68 (s, 3H), 1.67 (s, 3H), 1.56 (m, 2H), 1.27 (s, 3H), 1.25-1.20 (m, 5H), 1.16 (s, 3H), 0.83 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.75, 173.00, 172.80, 170.23, 166.95, 166.23, 147.26, 142.06, 138.05, 133.68, 133.26, 130.20, 129.13, 128.95, 128.68, 128.26, 126.95, 121.59, 84.43, 81.13, 78.98, 76.48, 75.28, 74.98, 73.11, 72.41, 72.24, 58.59, 54.51, 45.58, 43.20, 36.58, 35.63, 35.55, 31.29, 26.87, 25.35, 22.59, 22.28, 21.99, 18.23, 14.81, 13.84, 9.52 HRFABMS *m/z* calculated for $C_{47}H_{60}NO_{14}$ $(M+H)^+$ 874.4017, found 874.4013, Δ 3.5 ppm. LRFABMS *m/z* found 874.2

3'-*N*-Debenzoyl-3'-*N*-hexanoyl-10-deacetyl-10-propanoylpaclitaxel (96).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40-7.30 (m, 5H), 6.29 (s, 1H), 6.23 (d, NH, 1H), 6.21 (t, 1H), 5.67 (d, J=7.2, 1H), 5.57 (dd, 1H), 4.93 (d, 1H), 4.67 (m, 1H), 4.40 (m, 1H), 4.28 (d, J=8.8, 1H), 4.18 (d, J=8.8, 1H), 3.78 (d, J=7.2, 1H), 3.52 (d, J=5.6, 1H), 2.61-2.44 (m, 4H), 2.33 (s, 3H), 2.30 (t, 2H), 2.18 (t, 2H), 1.93 (s, 1H), 1.88 (dt, 1H), 1.81 (s, 3H), 1.70 (s, 3H), 1.67 (s, 3H), 1.56 (m, 2H), 1.25-1.22 (m, 11H), 1.14 (s, 3H), 0.83 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.73, 174.62, 173.03, 172.84, 170.23, 166.93, 141.89, 138.05, 133.68, 133.22, 130.20, 129.12, 128.95, 128.68, 128.26, 126.94, 84.40, 81.11, 78.94, 76.47, 75.36, 74.95, 73.11, 72.40, 72.18, 58.57, 54.52, 45.58, 43.20, 36.58, 35.63, 31.28, 27.55, 26.79, 25.35, 22.59, 22.28, 21.90, 14.79, 13.84, 9.55, 9.00 HRFABMS *m/z* calculated for $C_{47}H_{60}NO_{14}$ $(M+H)^+$ 862.4014, found 862.4013, Δ 2.3 ppm. LRFABMS *m/z* found 862.2.

3'-*N*-Debenzoyl-3'-*N*-hexanoyl-10-deacetyl-10-butanoylpaclitaxel (97).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40-7.33 (m, 5H), 6.28 (s, 1H), 6.22 (d, NH, 1H), 6.21 (t, 1H), 5.67 (d, J=7.2, 1H), 5.57 (dd, 1H), 4.93 (d, 1H), 4.67 (m, 1H), 4.40 (m, 1H), 4.28 (d, J=8.8, 1H), 4.18 (d, J=8.8, 1H), 3.78 (d, J=7.2, 1H), 3.51 (d, J=5.2, 1H), 2.58-2.40 (m, 4H), 2.34 (s, 3H), 2.29 (t, 2H), 2.18 (t, 2H), 1.90 (s, 1H), 1.84 (dt, 1H), 1.81 (s, 3H), 1.73 (m, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.56 (m, 2H), 1.25 (s, 3H), 1.22 (m, 5H), 1.14 (s, 3H), 1.02 (t, 3H), 0.83 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.68, 173.85, 172.84, 170.23, 166.94, 141.90, 138.05, 133.68, 133.26, 130.20, 129.12, 128.96, 128.68, 128.26, 126.95, 84.41, 81.11, 78.96, 76.47, 75.30, 74.95, 73.11, 72.40, 72.19, 58.57, 54.51, 45.57, 43.19, 36.58, 36.07, 35.63, 35.54, 31.29, 26.81, 25.35, 22.59, 22.28, 21.93, 18.41, 14.79, 13.84, 13.65, 9.55 HRFABMS *m/z* calculated for $C_{48}H_{62}NO_{14}$ $(M+H)^+$ 876.4170, found 876.4170, Δ 0 ppm. LRFABMS *m/z* found 876.3.

3'-*N*-Debenzoyl-3'-*N*-butoxycarbonyl-10-deacetyl-10-isopropanoylpaclitaxel (98).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.60 (t, 1H), 7.51-7.32 (m, 7H), 6.26 (s, 1H), 6.25 (t, 1H), 5.66 (d, J=7.2, 1H), 5.52 (d, J=9.2, 1H), 5.30 (d, 1H), 4.94 (d, J=8, 1H), 4.64 (s, 1H), 4.41 (m, 1H), 4.28 (d, J=8.4, 1H), 4.13 (d, J=8.4, 1H), 3.80 (d, J=7.2, 1H), 2.73 (m, 1H), 2.54 (m, 2H), 2.36 (s, 3H), 2.23 (m, 1H), 1.87 (t, 2H), 1.83 (s, 3H), 1.72 (d, 1H), 1.67 (s, 3H), 1.63 (d, 2H), 1.48 (m, 2H), 1.32 (d, 3H), 1.26 (d, 3H), 1.25-1.15 (m, 6H), 0.84 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.63, 197.00, 193.84, 177.20, 170.31, 133.73, 130.20, 129.07, 128.90, 128.68, 128.21, 126.73, 84.42, 79.17, 76.47, 75.17, 72.22, 65.36, 58.59, 45.65, 43.17, 35.55, 34.04, 30.88, 26.86, 22.60, 19.19, 18.62, 14.85, 13.62, 9.56. HRFABMS *m/z* calculated for $C_{47}H_{60}NO_{15}$ $(M+H)^+$ 878.3963, found 878.3975, Δ 1.2 ppm. LRFABMS *m/z* found 878.4.

3'-*N*-Debenzoyl-3'-*N*-butoxycarbonyl-10-deacetyl-10-(2-butene)oylpaclitaxel (99).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40-7.30 (m, 5H), 7.10 (m, 1H), 6.34 (s, 1H), 6.26 (t, 1H), 5.99 (d, J=15.6, 1H), 5.66 (dd, 1H), 5.56 (d, 1H), 5.30 (d, 1H), 4.93 (d, 1H), 4.64 (bs, 1H), 4.43 (m, 1H), 4.28 (d, J=8.4, 1H), 4.18 (d, J=8.4, 1H), 3.94 (d, 1H), 3.93 (m, 1H), 3.80 (d, J=7.2, 1H), 3.40 (d, J=5.2, 1H), 2.66 (d, 1H), 2.54 (m, 1H), 2.36 (s, 3H), 2.24 (m, 1H), 1.95 (d, 3H), 1.88 (dt, 1H), 1.82 (s, 3H), 1.79 (s, 1H), 1.67 (s, 6H), 1.48 (m, 2H), 1.27 (s, 3H), 1.16 (s, 3H), 0.82 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.72, 173.00, 172.80, 170.32, 167.03, 166.23, 147.29, 133.71, 130.20, 129.07, 128.88, 128.66, 128.19, 126.73, 121.58, 84.44, 81.14, 79.17, 76.47, 75.26, 74.97, 72.23, 65.34, 58.59, 45.62, 43.16, 35.54, 30.87, 26.91, 22.57, 18.84, 18.22, 14.83, 13.60, 9.52 HRFABMS *m/z* calculated for $C_{47}H_{58}NO_{15}$ $(M+H)^+$ 876.3806, found 876.3806 LRFABMS *m/z* found 876.1.

3'-*N*-Debenzoyl-3'-*N*-butoxycarbonyl-10-deacetyl-10-propanoylpaclitaxel (100).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40-7.30 (m, 5H), 6.29 (s, 1H), 6.26 (t, 1H), 5.66 (d, 1H), 5.54 (d, 1H), 5.30 (d, 1H), 4.93 (d, 1H), 4.64 (bs, 1H), 4.41 (m, 1H), 4.28 (d, J=8.4, 1H), 4.17 (d, J=8.4, 1H), 3.95 (d, 1H), 3.94 (m, 1H), 3.80 (d, J=7.2, 1H), 3.37 (d, J=5.2, 1H), 2.60-2.44 (m, 4H), 2.36 (s, 3H), 2.24 (m, 2H), 1.88 (dt, 1H), 1.83 (s, 3H), 1.77 (s, 1H), 1.67 (s, 3H), 1.63 (s, 3H), 1.48 (m, 2H), 1.27 (s, 3H), 1.23 (t, 3H), 1.14 (s, 3H), 0.82 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.69, 174.61, 172.80, 170.31, 167.03, 166.23, 133.71, 130.16, 130.19, 129.08, 128.89, 128.66, 128.19, 126.73, 84.40, 79.14, 76.47, 75.34, 74.94, 72.19, 65.35, 58.57, 45.62, 43.16, 35.52, 30.87, 27.54, 26.83, 22.58, 18.85, 14.83, 13.61, 9.55, 9.00 HRFABMS *m/z* calculated for $C_{46}H_{58}NO_{15}$ $(M+H)^+$ 864.3806, found 864.3806 LRFABMS *m/z* found 864.1.

3'-*N*-Debenzoyl-3'-*N*-butoxycarbonyl-10-deacetyl-10-butanoylpaclitaxel (101).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.61 (t, 1H), 7.50 (t, 2H), 7.40-7.30 (m, 5H), 6.29 (s, 1H), 6.26 (t, 1H), 5.66 (d, 1H), 5.54 (d, 1H), 5.30 (d, 1H), 4.93 (d, 1H), 4.64 (bs, 1H), 4.41 (m, 1H), 4.28 (d, J=8.4, 1H), 4.17 (d, J=8.4, 1H), 3.95 (d, 1H), 3.94 (m, 1H), 3.80 (d, J=7.2, 1H), 3.37 (d, J=5.2, 1H), 2.55-2.40 (m, 5H), 2.36 (s, 3H), 2.24 (m, 2H), 1.88 (dt, 1H), 1.83 (s, 3H), 1.72 (m, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.48 (m, 2H), 1.27 (s, 3H), 1.14 (s, 3H), 1.02 (t, 3H), 0.82 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.63, 173.83, 172.80, 170.30, 167.03, 166.23, 133.70, 133.20, 130.19, 129.07, 128.87, 128.66, 128.19, 126.71, 84.40, 81.12, 79.14, 76.46, 75.27, 74.94, 73.59, 72.18, 65.35, 58.57, 45.61, 43.16, 36.04, 35.53, 30.87, 26.84, 22.58, 18.83, 18.39, 14.83, 13.64, 13.60, 9.55 HRFABMS *m/z* calculated for $C_{47}H_{60}NO_{15}$ $(M+H)^+$ 878.3963, found 878.3962 Δ 3.0 ppm LRFABMS *m/z* found 878.2.

3'-*N*-Debenzoyl-3'-*N*-furoyl-10-deacetyl-10-isopropanoylpaclitaxel (102).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.14 (d, 2H), 7.6 (tt, 1H), 7.53-7.33 (m, 8H), 7.16 (d, J=9.2, 1H, NH), 7.01 (d, J=3.2, 1H), 6.46 (m, 1H), 6.28 (s, 1H), 6.23 (t, 1H), 5.74 (d, J=9.2, 1H), 5.66 (d, J=7.2, 1H), 4.94 (d, J=7.6, 1H), 4.76 (s, 1H), 4.40 (m, 1H), 4.29 (d, J=8.4, 1H), 4.19 (d, J=8.4, 1H), 3.79 (d, J=7.2, 1H), 3.60 (bs, 1H), 2.54 (m, 2H), 2.52 (m, 2H), 2.37 (s, 3H), 1.85 (m, 1H), 1.83 (s, 1H), 1.80 (s, 3H), 1.67 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.94, 174.87, 172.67, 170.61, 167.2, 1650, 158.1, 147.36, 144.58, 142.09, 138.07, 133.98, 133.46, 130.46, 129.38, 129.23, 128.95, 127.26, 115.46, 111.58, 84.64, 81.39, 79.26, 75.59, 75.16, 73.57, 72.54, 72.44, 58.83, 54.55, 45.86, 43.38, 35.86, 27.78, 27.09, 22.84, 22.05, 15.06, 9.79, 9.23. HRFABMS *m/z* calculated for $C_{47}H_{54}NO_{15}$ $(M+H)^+$ 872.3493, found 872.3433, Δ 6 ppm. LRFABMS *m/z* found 872.3.

3'-*N*-debenzoyl-3'-*N*-furoyl-10-deacetyl-10-(2-butene)oylpaclitaxel (103).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.12 (d, 2H), 7.62 (tt, 1H), 7.53-7.32 (m, 8H), 7.16 (d, J=8.8, 1H, NH), 7.10 (m, 1H), 7.01 (d, J=3.2, 1H), 6.46 (m, 1H), 6.32 (s, 1H), 6.23 (t, 1H), 6.00 (d, J=15.6, 1H), 5.74 (d, J=9.6, 1H), 5.67 (d, J=7.2, 1H), 4.94 (d, J=7.6, 1H), 4.76 (s, 1H), 4.43 (m, 1H), 4.29 (d, J=8.4, 1H), 4.19 (d, J=8.4, 1H), 3.81 (d, J=7.2, 1H), 2.55 (m, 1H), 2.37 (s, 3H), 2.3 (m, 2H), 1.95 (d, 3H), 1.86 (m, 2H), 1.8 (s, 3H), 1.68 (s, 3H), 1.25 (s, 3H), 1.15 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.71, 172.37, 170.37, 167.01, 166.23, 157.81, 147.28, 144.31, 142.04, 137.83, 133.74, 133.26, 130.23, 129.13, 128.99, 128.71, 128.36, 127.03, 121.58, 115.18, 112.33, 84.44, 81.17, 79.11, 76.5, 75.27, 74.95, 73.37, 72.3, 58.64, 54.3, 45.61, 43.14, 35.63, 26.95, 22.61, 21.89, 18.23, 14.85, 9.51. HRFABMS *m/z* calculated for $C_{47}H_{51}NO_{15}Na$ $(M+Na)^+$ 892.3156, found 892.3153, Δ 0.3 ppm. LRFABMS *m/z* found $(M+Na)^+$ 892.

3'-*N*-Debenzoyl-3'-*N*-furoyl-10-deacetyl-10-propanoylpaclitaxel (104).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.18 (d, 2H), 7.62 (tt, 1H), 7.53-7.33 (m, 8H), 7.16 (d, J=9.2, 1H, NH), 7.01 (d, J=3.6, 1H), 6.46 (m, 1H), 6.27 (s, 1H), 6.23 (t, 1H), 5.72 (d, J=8.4, 1H), 5.66 (d, J=7.2, 1H), 4.93 (d, 1H), 4.76 (s, 1H), 4.4 (m, 1H), 4.29 (d, J=8.4, 1H), 4.19 (d, J=8.4, 1H), 3.79 (d, J=7.2, 1H), 2.53 (m, 1H), 2.47 (m, 2H), 2.36 (s, 3H), 2.28 (m, 2H), 1.87 (m, 2H), 1.79 (s, 3H), 1.67 (s, 3H), 1.23 (s, 3H), 1.13 (s, 3H), 1.01 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.94, 174.87, 172.67, 170.61, 167.2, 165.05, 158.1, 147.36, 144.58, 142.09, 138.07, 133.98, 130.46, 129.38, 128.95, 128.61, 127.26, 115.46, 112.58, 84.64, 81.39, 79.26, 75.59, 75.16, 73.57, 72.54, 58.83, 54.55, 45.86, 43.38, 35.86, 27.78, 27.09, 22.84, 22.05, 15.06, 9.79, 9.23. HRFABMS *m/z* calculated for $C_{46}H_{52}NO_{15}$ $(M+H)^+$ 858.3337, found 858.3380, Δ 5.1 ppm. LRFABMS *m/z* found 858.3.

3'-*N*-Debenzoyl-3'-*N*-furoyl-10-deacetyl-10-butanoylpaclitaxel (105).

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.18 (d, 2H), 7.62 (tt, 1H), 7.53-7.33 (m, 8H), 7.16 (d, J=9.2, 1H, NH), 7.01 (d, J=3.6, 1H), 6.46 (m, 1H), 6.27 (s, 1H), 6.23 (t, 1H), 5.72 (d, J=8.4, 1H), 5.66 (d, J=7.2, 1H), 4.93 (d, 1H), 4.76 (s, 1H), 4.4 (m, 1H), 4.29 (d, J=8.4, 1H), 4.19 (d, J=8.4, 1H), 3.79 (d, J=7.2, 1H), 2.53 (m, 1H), 2.47 (m, 2H), 2.36 (s, 3H), 2.28 (m, 2H), 1.87 (m, 2H), 1.79 (s, 3H), 1.73 (m, 2H), 1.67 (s, 3H), 1.23 (s, 3H), 1.13 (s, 3H), 1.01 (t, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 203.64, 201.42, 198.87, 181.29, 173.85, 172.43, 170.36, 166.94, 157.86, 151.81, 147.6, 147.1, 144.35, 141.98, 141.83, 138.67, 137.82, 133.73, 133.27, 130.22, 122.15, 128.99, 128.36, 127.02, 115.22, 112.34, 84.4, 81.15, 79.01, 75.3, 74.92, 73.32, 72.31, 58.58, 54.31, 45.6, 43.14, 36.06, 35.64, 33.48, 26.86, 22.6, 21.85, 20.41, 18.4, 14.81, 13.64, 9.55. HRFABMS *m/z* calculated for $C_{47}H_{54}NO_{15}$ $(M+H)^+$ 872.3493, found 872.3508, Δ 1.5 ppm. LRFABMS *m/z* found 872.3.

7-Chloroacetyl-10-deacetylpaclitaxel (109).

To a stirred solution of 2'-*O*-(*tert*-butyldimethylsilyl)-7-chloroacetyl-10-deacetylpaclitaxel (**109**; 0.204 g, 0.203 mmol) in THF (12 mL) was added 3.2 ml of pyridine at 0 ^{o}C, stirred for 5 min. where 3.2 ml of HF-pyridine was introduced. The reaction mixture was allowed to come to room temperature and further stirred overnight for 24h. The reaction mixture was then diluted with EtOAc, washed with sat. aq. $NaHCO_3$ solution and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (60% EtOAc/Hexane) and the desired product was isolated in 95% yield. ^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.1 (d, 2H), 7.30 (d, 2H), 7.61 (tt, 1H), 7.52-7.32 (m, 10H), 7.16 (d, J=8.8, 1H, NH), 6.17 (t, 1H), 5.76 (d, J=9.2, 1H), 5.67 (d, J=6.8, 1H), 5.49 (m, 1H), 5.26 (s, 1H), 4.92 (d, J=8.8, 1H), 4.77 (s, 1H), 4.32 (d, J=8.8, 1H), 4.22 (d, J=8.8, 1H), 3.97 (m, 4H), 2.56 (m, 1H), 2.39 (s, 3H), 2.29 (m, 2H), 1.96 (m, 1H), 1.92 (s, 1H), 1.85 (s, 3H), 1.8 (s, 3H), 1.17 (s, 3H), 1.06 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 210.62, 172.51, 170.46, 167.09, 166.81, 166.36, 138.61, 137.89, 135.64, 133.73, 133.61, 131.90, 130.13, 129.05, 128.93, 128.72, 128.64, 128.26, 127.01, 126.95, 83.4, 80.49, 78.62, 76.51, 74.54, 74.48, 73.66, 73.16, 72.21, 60.37, 56.35, 54.99, 45.9, 42.83, 40.47, 35.93, 33.13, 26.24, 22.41, 20.46, 14.13, 14.09, 10.87.

General procedure for the substitution of chlorine with nucleophilic amines. Synthesis of the paclitaxel derivatives 111-119.

To a stirred solution of 7-chloroacetyl-10-deacetylpaclitaxel (**110**; 0.033 mmol) in DMF (0.3 mL) at room temperature was added the amine (shown in figure 25) (0.099 mmol) and stirred for 3-4 h. The reaction mixture was then diluted with EtOAc and worked-up in the usual way. Finally the crude product was applied on a PTLC plate (60-70% EtOAc/Hexane) and the desired product was isolated in 85-95% yield.

Paclitaxel derivative 111

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.75 (d, 2H), 7.61 (tt, 1H), 7.52-7.33 (m, 10H), 7.20 (s, 4H), 7.13 (d, J=8.8, 1H, NH), 6.18 (t, 1H), 5.78 (d, J=8.8, 1H), 5.67 (d, J=6.8, 1H), 5.49 (m, 1H), 5.35 (s, 1H), 4.92 (d, J=8.8, 1H), 4.77 (s, 1H), 4.34 (d, J=8.8, 1H), 4.22 (d, J=8.8, 1H), 4.15 (s, 4H), 4.05 (s, 1H), 3.97 (d, J=6.8, 1H), 3.67 (bs, 1H), 3.59 (s, 2H), 2.54 (m, 1H), 2.39 (s, 3H), 2.29 (m, 2H), 1.95 (m, 1H), 1.83 (s, 3H), 1.81 (s, 3H), 1.69 (s, 1H), 1.2 (s, 3H), 1.07 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 211.16, 172.49, 170.44, 166.90, 138.59, 137.92, 15.74, 133.76, 133.64, 131.91, 130.18, 129.06, 128.30, 127.17, 127.05, 127.00, 122.37, 85.55, 80.62, 78.73, 74.55, 73.22, 72.28, 58.58, 56.54, 55.32, 54.96, 46.00, 42.86, 35.96, 33.41, 26.29, 22.48, 20.48, 14.21, 10.96. HRFABMS *m/z* calculated for $C_{55}H_{59}N_2O_{14}$ $(M+H)^+$ 971.3966, found 971.4000, Δ 3.4 ppm. LRFABMS *m/z* found 971.4.

Paclitaxel derivative 112

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.75 (d, 2H), 7.60 (tt, 1H), 7.52-7.33 (m, 10H), 7.07 (d, J=8.8, 1H, NH), 6.18 (t, 1H), 5.79 (d, J=8.8, 1H), 5.66 (d, J=6.8, 1H), 5.53 (m, 1H), 5.30 (s, 1H), 4.90 (d, J=8.8, 1H), 4.77 (s, 1H), 4.32 (d, J=8.4, 1H), 4.21 (d, J=8.4, 1H), 3.96 (d, J=6.8, 1H), 3.69 (bs, 1H), 3.1 (s, 2H), 2.52 (m, 2H), 2.45 (m, 2H), 2.39 (s, 3H), 2.29 (m, 2H), 1.94 (m, 2H), 1.84 (s, 3H), 1.80 (s, 3H), 1.62-1.54 (m, 8), 1.25 (s, 3H), 1.19 (s, 3H).

Paclitaxel derivative 113

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.75 (d, 2H), 7.60 (tt, 1H), 7.52-7.33 (m, 10H), 7.09 (d, J=9.2, 1H, NH), 6.18 (t, 1H), 5.79 (d, J=8.8, 1H), 5.66 (d, J=6.8, 1H), 5.53 (m, 1H), 5.30 (s, 1H), 4.90 (d, J=8.8, 1H), 4.77 (s, 1H), 4.32 (d, J=8.4, 1H), 4.21 (d, J=8.4, 1H), 3.98 (s, 1H), 3.96 (s, 1H), 3.73 (t, 4H), 3.58 (bs, 1H), 3.13 (s, 2H), 2.53 (m,

5H), 2.39 (s, 3H), 2.29 (m, 2H), 1.94 (m, 1H), 1.84 (s, 3H), 1.81 (s, 3H), 1.73 (s, 1H), 1.18 (s, 3H), 1.07 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 211.04, 172.50, 170.42, 169.02, 166.96, 166.89, 138.61, 137.89, 135.71, 133.77, 133.64, 131.94, 130.17, 129.06, 128.99, 128.34, 127.02, 83.57, 80.63, 78.68, 76.57, 74.58, 74.47, 73.17, 72.33, 72.00, 66.72, 59.17, 56.47, 54.94, 52.99, 46.03, 42.89, 35.94, 33.46, 26.32, 22.47, 20.41, 14.17, 10.92. HRFABMS *m/z* calculated for $C_{51}H_{59}N_2O_{15}$ $(M+H)^+$ 939.3915, found 939.3914, Δ 0.1 ppm. LRFABMS *m/z* found 939.4.

Paclitaxel derivative 114

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.12 (d, 2H), 7.77 (d, 2H), 7.61 (tt, 1H), 7.53-7.26 (m, 10H), 7.15 (bs, 1H), 6.18 (t, 1H), 5.79 (d, J=8.8, 1H), 5.66 (d, J=6.8, 1H), 5.53 (m, 1H), 5.30 (s, 1H), 4.90 (d, J=8.8, 1H), 4.77 (s, 1H), 4.32 (d, J=8.4, 1H), 4.21 (d, J=8.4, 1H), 3.96 (d, J=6.8, 1H), 3.69 (bs, 1H), 3.42 (d, 2H), 3.25 (bs, 1H), 3.00 (bs, 5H), 2.76 (s, 2H), 2.58 (m, 2H), 2.4 (s, 3H), 2.28 (m, 2H), 2.03 (m, 2H), 1.83 (s, 3H), 1.81 (s, 3H), 1.62 (s, 1H), 1.21 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 210.88, 172.55, 170.3, 169.1, 167.12, 166.77, 138.53, 138.01, 135.7, 133.66, 131.88, 130.13, 129.13, 128.9, 128.7, 128.64, 128.21, 127.03, 126.95, 83.56, 80.61, 78.54, 76.53, 74.62, 74.43, 73.10, 72.16, 72.03, 58.73, 56.38, 55.00, 54.53, 55.32, 45.96, 45.71, 42.89, 35.2, 33.39, 26.27, 22.45, 20.50, 14.1, 10.91. HRFABMS *m/z* calculated for $C_{52}H_{62}N_3O_{14}$ $(M+H)^+$ 952.4232, found 952.4241, Δ 0.9 ppm. LRFABMS *m/z* found 952.4.

Paclitaxel derivative 115

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.74 (d, 2H), 7.60 (tt, 1H), 7.52-7.34 (m, 12H), 7.08 (d, J=8.8, 1H, NH), 6.85 (s, 1H), 6.73 (s, 2H), 6.17 (t, 1H), 5.9 (s, 2H), 5.78 (d, J=6.8, 1H), 5.66 (s, 1H), 5.5 (m, 1H), 5.27 (s, 1H), 4.91 (d, J=8.4, 1H), 4.77 (s, 1H), 4.32 (d, J=8.8, 1H), 4.21 (d, J=8.8, 1H), 4.02 (s, 1H), 3.96 (d, J=7.2, 1H), 3.52 (d,

J=4.4, 1H), 3.41 (s, 2H), 3.13 (s, 2H), 2.61-2.49 (m, 11H), 2.39 (s, 3H), 2.29 (m, 2H), 1.94 (m, 1H), 1.84 (s, 3H), 1.79 (s, 3H), 1.66 (s, 3H), 1.18 (s, 3H), 1.07 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 210.87, 172.45, 170.4, 169.22, 166.9, 147.59, 146.56, 138.54, 137.88, 135.7, 133.70, 131.94, 130.17, 128.99, 128.75, 128.71, 128.35, 127.02, 122.23, 109.51, 107.81, 100.84, 83.62, 80.69, 79.50, 78.69, 74.56, 74.49, 73.19, 72.35, 72.06, 69.82, 62.63, 59.00, 56.44, 54.91, 52.69, 52.6, 46.12, 42.92, 38.47, 35.91, 34.41, 33.47, 26.35, 22.49, 21.68, 20.36, 19.25, 17.82, 14.2, 10.92. HRFABMS *m/z* calculated for $C_{59}H_{66}N_3O_{16}$ $(M+H)^+$ 1072.4443, found 1072.4497, Δ 5.4 ppm. LRFABMS *m/z* found 1072.4.

Paclitaxel derivative 116

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.75 (d, 2H), 7.60 (tt, 1H), 7.52-7.33 (m, 10H), 7.11 (d, J=8.8, 1H, NH), 6.18 (t, 1H), 5.79 (d, J=8.8, 1H), 5.66 (d, J=6.8, 1H), 5.53 (m, 1H), 5.30 (s, 1H), 4.90 (d, J=8.8, 1H), 4.77 (s, 1H), 4.32 (d, J=8.4, 1H), 4.21 (d, J=8.4, 1H), 3.96 (d, J=6.8, 1H), 3.1 (d, 2H), 2.6 (m, 5H), 2.4 (s, 3H), 2.29 (m, 2H), 1.93 (m, 1H), 1.84 (s, 3H), 1.82 (s, 3H), 1.67 (s, 1H), 1.2 (s, 3H), 1.07 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 205.86, 172.54, 170.38, 169.14, 167.15, 138.47, 135.74, 133.69, 131.92, 130.19, 128.98, 128.77, 128.7, 128.32, 127.01, 83.63, 80.71, 78.76, 74.64, 73.22, 72.33, 72.04, 58.89, 56.43, 54.91, 52.29, 46.09, 42.95, 33.45, 26.29, 22.49, 20.48, 14.19, 10.94.

Paclitaxel derivative 117

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.75 (d, 2H), 7.61 (tt, 1H), 7.52-7.34 (m, 10H), 7.08 (d, J=8.8, 1H, NH), 6.18 (t, 1H), 5.78 (d, J=6.8, 1H), 5.66 (s, 1H), 5.5 (m, 1H), 5.29 (s, 1H), 4.91 (d, J=8.4, 1H), 4.77 (s, 1H), 4.32 (d, J=8.8, 1H), 4.21 (d, J=8.8, 1H), 4.01 (bs, 1H), 3.96 (d, J=7.2, 1H), 3.15 (s, 2H), 2.84 (t, 2H), 2.55 (m, 5H), 2.39 (s,

3H), 2.31-2.19 (m, 5H), 1.96 (m, 2H), 1.84 (s, 3H), 1.81 (s, 3H), 1.77 (m, 5H), 1.19 (s, 3H), 1.08 (s, 3H). HRFABMS *m/z* calculated for $C_{56}H_{68}N_3O_{14}$ $(M+H)^+$ 1006.4701, found 1006.4735, Δ 3.4 ppm. LRFABMS *m/z* found 1006.4.

Paclitaxel derivative 118

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.18 (d, 1H), 8.11 (d, 2H), 7.74 (d, 2H), 7.61 (tt, 1H), 7.52-7.34 (m, 13H), 7.1 (d, J=8.8, 1H, NH), 6.6 (m, 2H), 6.18 (t, 1H), 5.78 (d, J=6.8, 1H), 5.66 (s, 1H), 5.5 (m, 1H), 5.29 (s, 1H), 4.91 (d, J=8.4, 1H), 4.77 (s, 1H), 4.32 (d, J=8.8, 1H), 4.21 (d, J=8.8, 1H), 3.99 (bs, 1H), 3.97 (bs, 1H), 3.59 (m, 5H), 3.19 (s, 2H), 2.64 (t, 5H), 2.53 (m, 1H), 2.39 (s, 3H), 2.32 (m, 2H), 1.94 (m, 1H), 1.84 (s, 3H), 1.81 (s, 3H), 1.69 (s, 2H), 1.19 (s, 3H), 1.07 (s, 3H)) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 210.97, 172.47, 170.41, 169.12, 166.89, 159.38, 147.93, 138.58, 137.89, 137.47, 135.7, 133.76, 131.93, 130.16, 129.05, 128.75, 127.01, 126.99, 113.37, 107.09, 83.57, 80.64, 78.69, 74.56, 74.48, 73.18, 72.31, 72.03, 58.99, 56.45, 54.93, 52.48, 46.06, 45.02, 42.89, 35.94, 33.47, 26.32, 22.47, 20.4, 14.19, 10.92. HRFABMS *m/z* calculated for $C_{56}H_{63}N_4O_{14}$ $(M+H)^+$ 1015.4341, found 1015.4310, Δ 3.1 ppm. LRFABMS *m/z* found 1015.4.

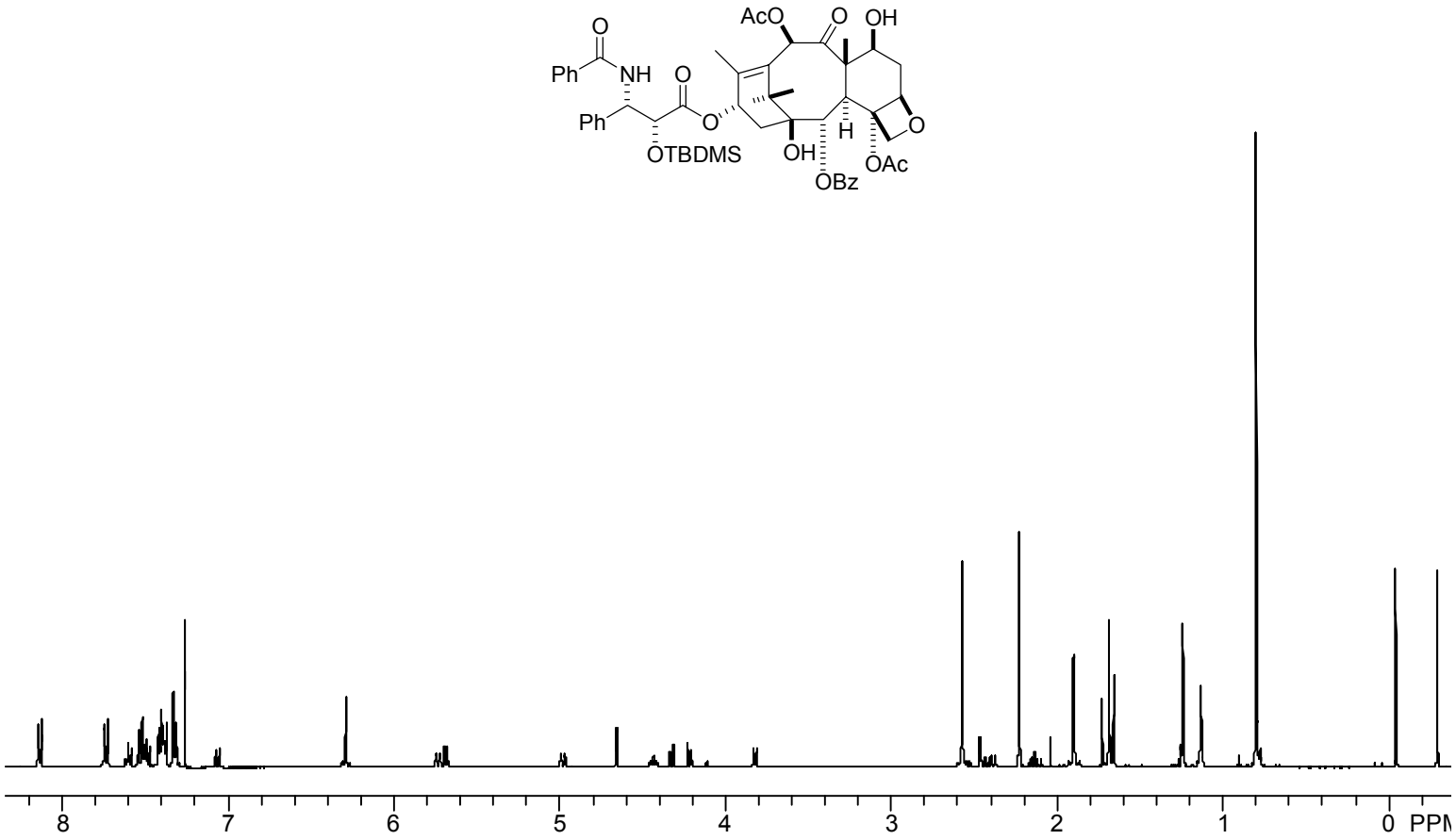
Paclitaxel derivative 119

^{1}H NMR ($CDCl_3$, 399.951 MHz) δ 8.11 (d, 2H), 7.85 (d, 2H), 7.74 (d, 2H), 7.62 (t, 1H), 7.53-7.34 (m, 12H), 7.05 (d, J=8.8, 1H, NH), 6.86 (d, J=8.8, 2H), 6.19 (t, 1H), 5.79 (d, J=8.8, 1H), 5.66 (d, J=6.8, 1H), 5.53 (m, 1H), 5.31 (s, 1H), 4.92 (d, J=8.8, 1H), 4.77 (s, 1H), 4.32 (d, J=8.4, 1H), 4.21 (d, J=8.4, 1H), 3.96 (d, 1H), 3.95 (s, 1H), 3.5 (d, 1H), 3.39 (t, 4H), 3.21 (s, 2H), 2.69 (t, 4H), 2.55 (m, 2H), 2.52 (s, 3H), 2.4 (s, 3H), 2.3 (s, 2H), 1.95 (m, 1H), 1.85 (s, 3H), 1.82 (s, 3H), 1.2 (s, 3H), 1.09 (s, 3H) ^{13}C NMR ($CDCl_3$, 100.578 MHz) δ 211.11, 195.75, 175.32, 172.52, 170.44, 166.91, 154.09, 138.67, 135.69, 133.8, 131.95, 130.39, 129.21, 128.77, 128.71, 127.02, 131.95, 130.37, 130.19,

129.2, 128.71, 127.02, 113.51, 83.57, 80.62, 78.71, 74.55, 73.17, 72.35, 72.1, 58.81, 56.5, 54.93, 52.25, 47.23, 42.93, 33.49, 26.34, 26.13, 22.49, 20.44, 14.21, 10.94. HRFABMS *m/z* calculated for $C_{59}H_{66}N_3O_{15}$ $(M+H)^+$ 1056.4494, found 1056.4519, Δ 2.5 ppm. LRFABMS *m/z* found 1056.5.

7. APPENDIX

^{1}H and ^{13}C NMR spectra of the compounds synthesized are shown.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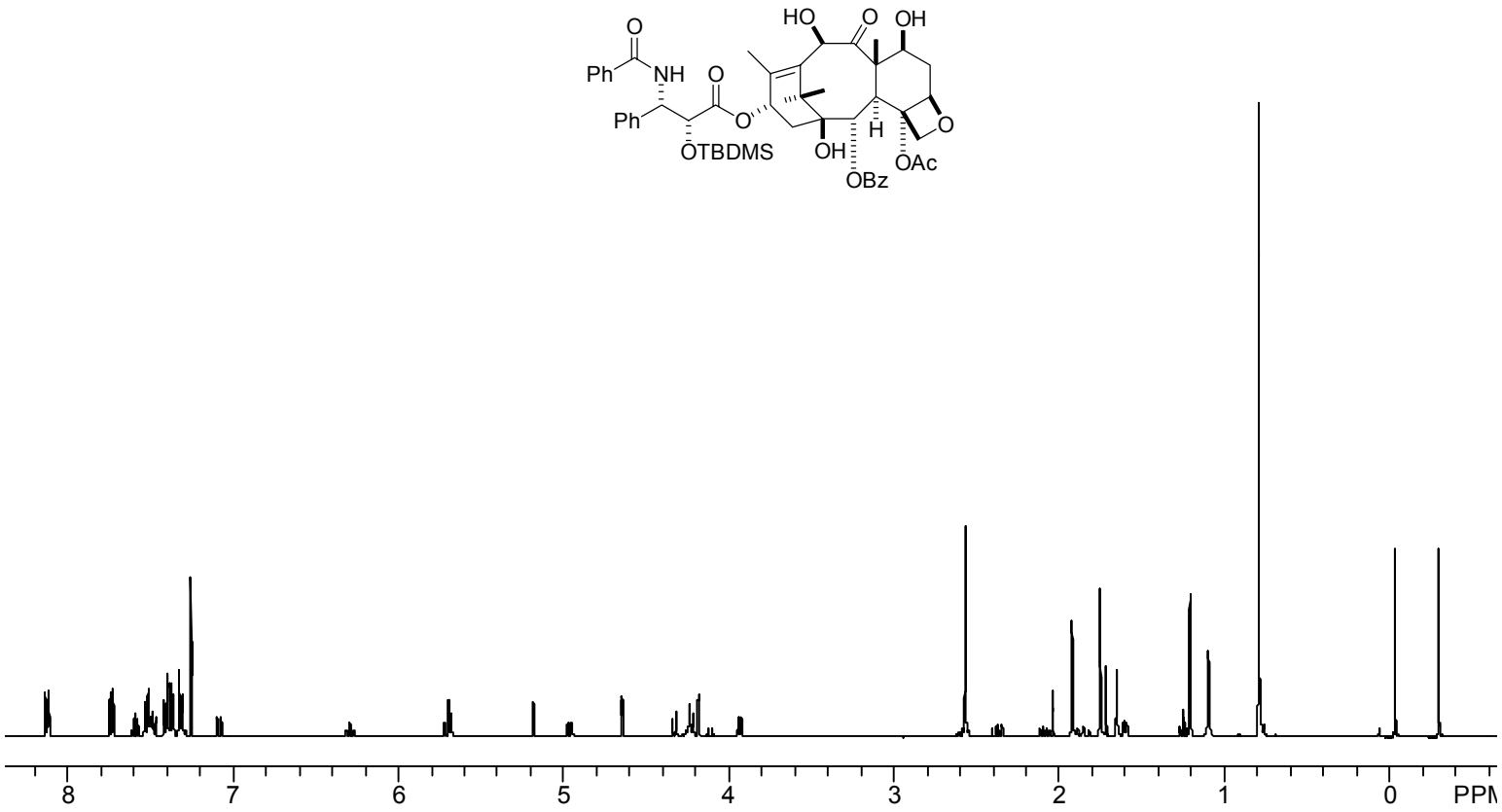
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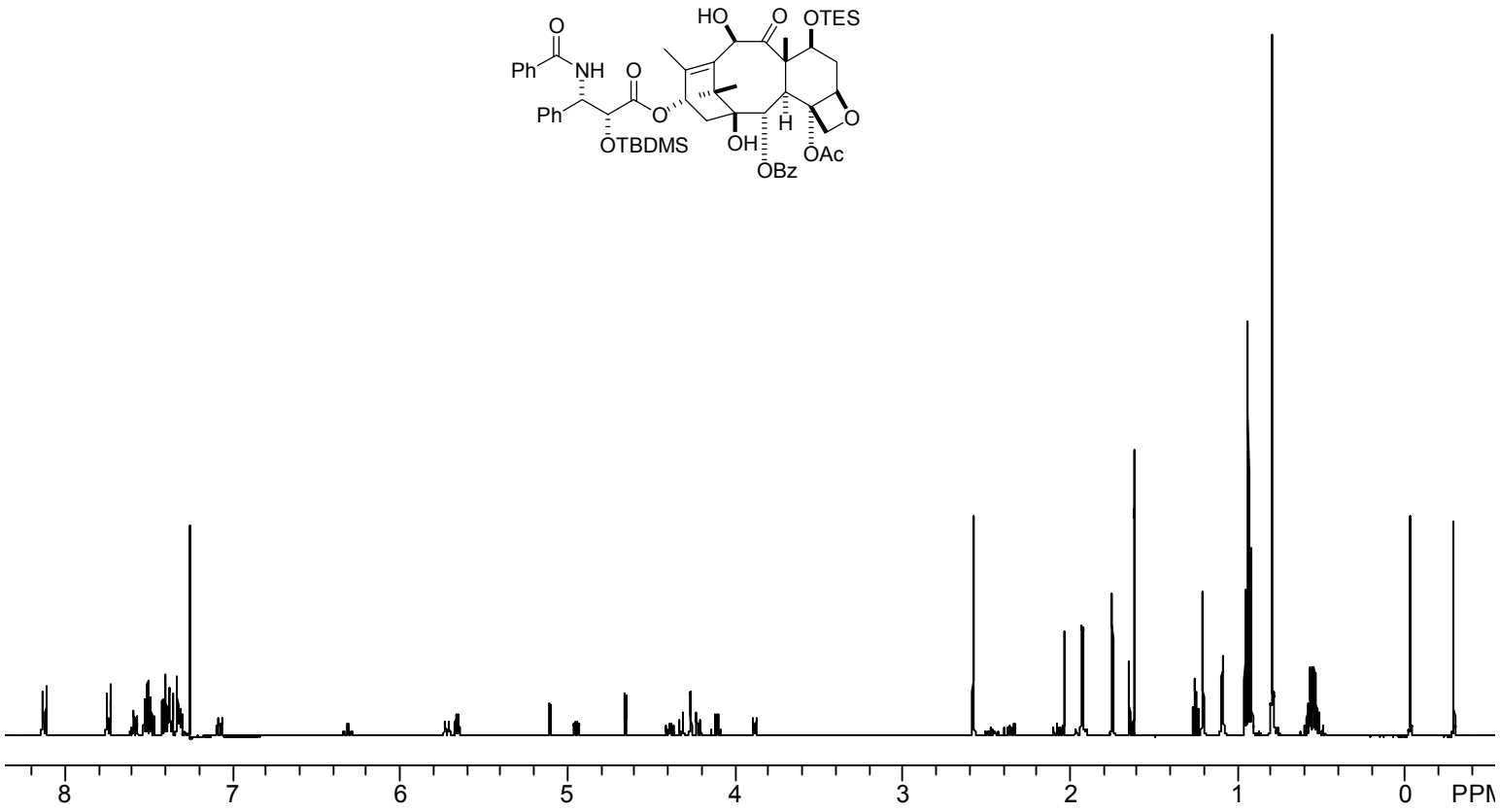
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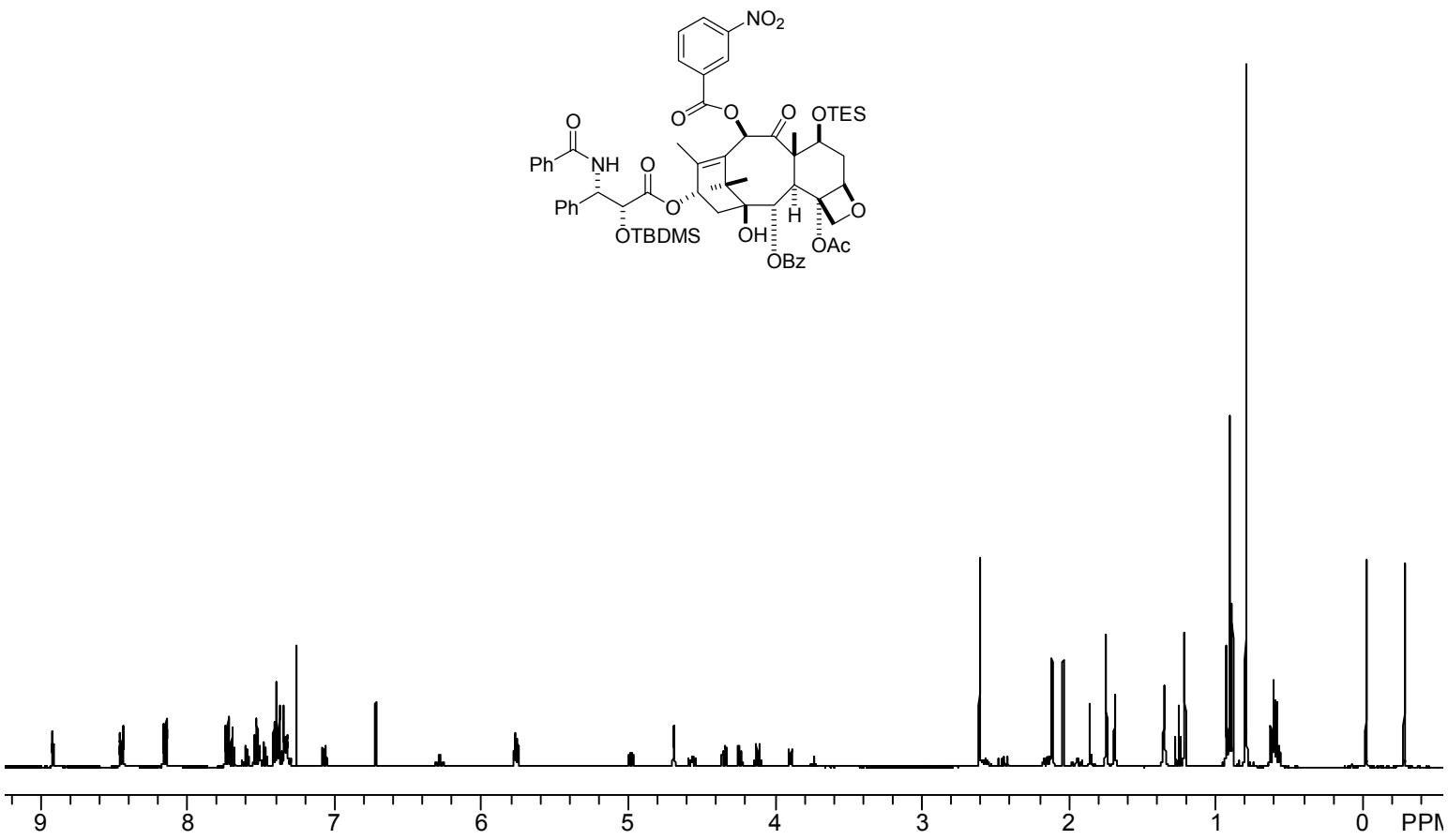
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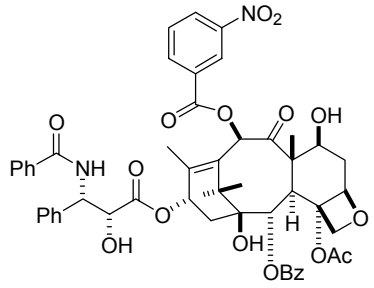
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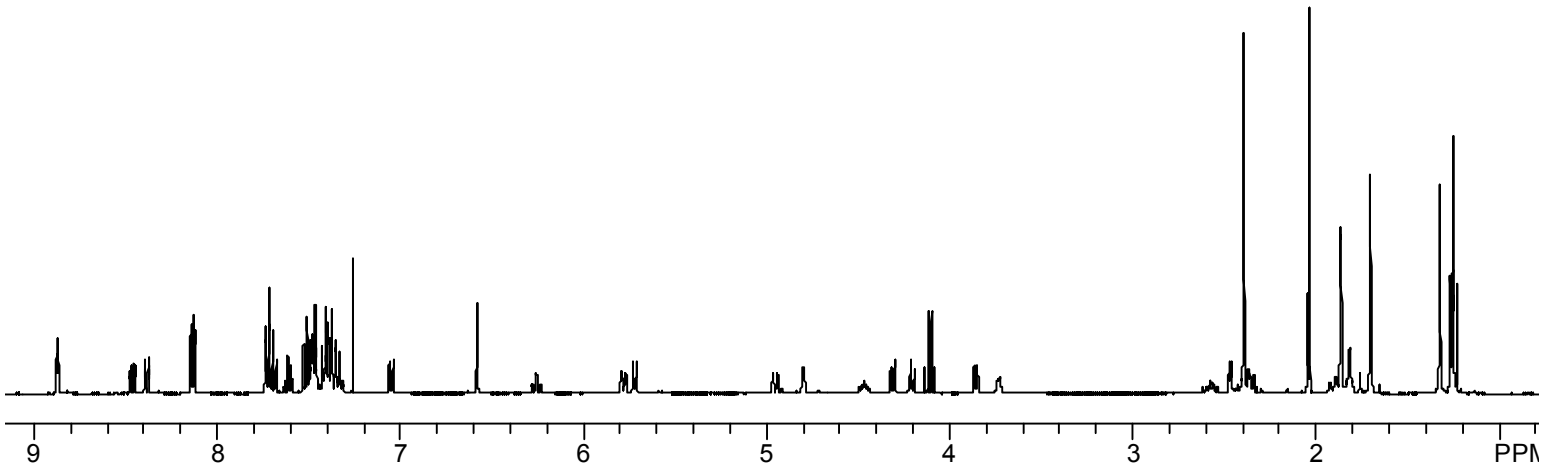
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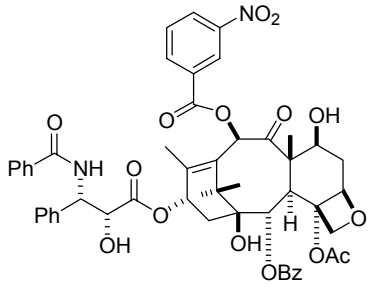
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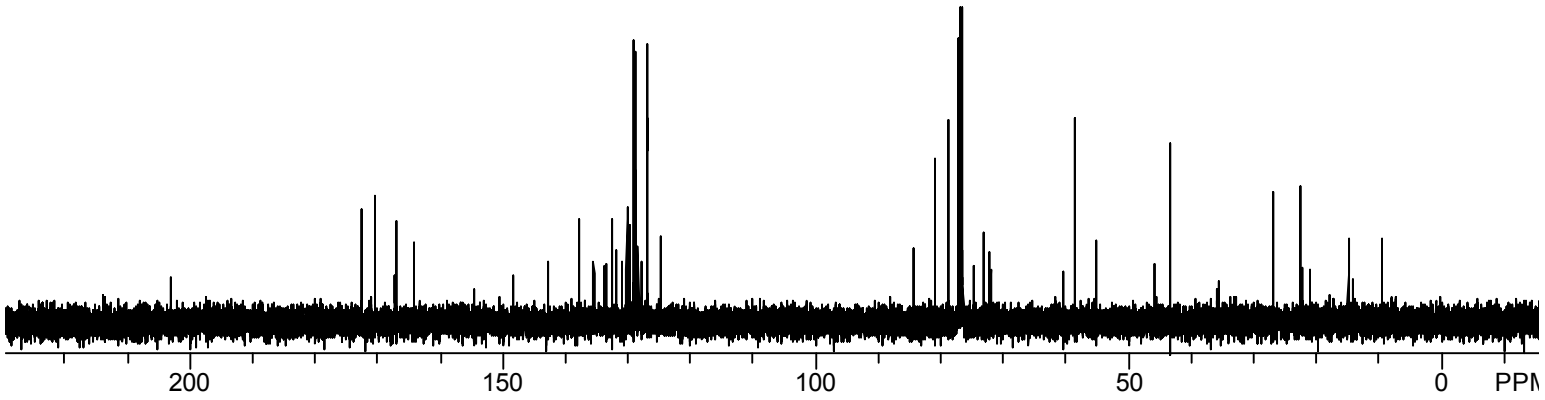
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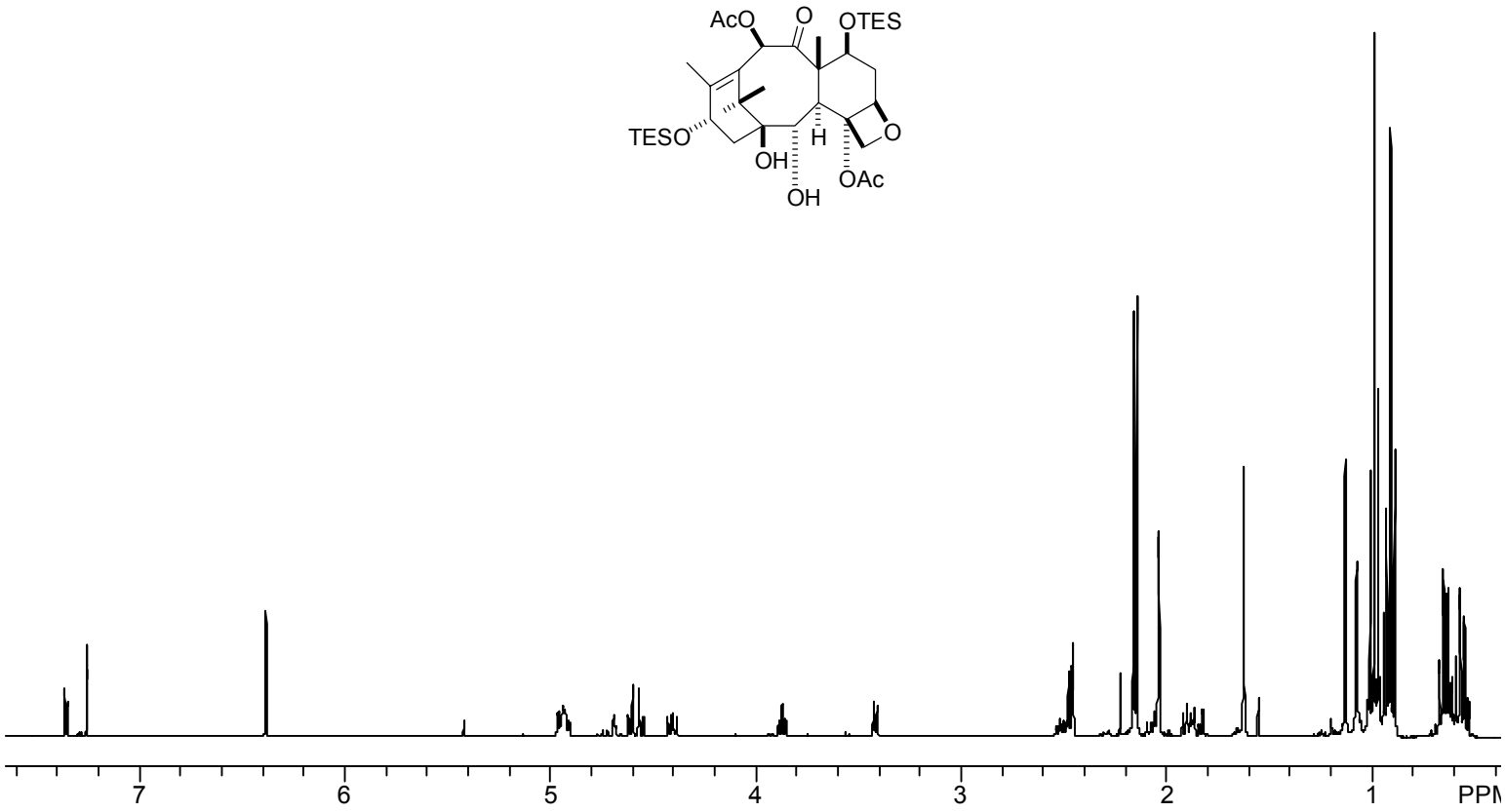
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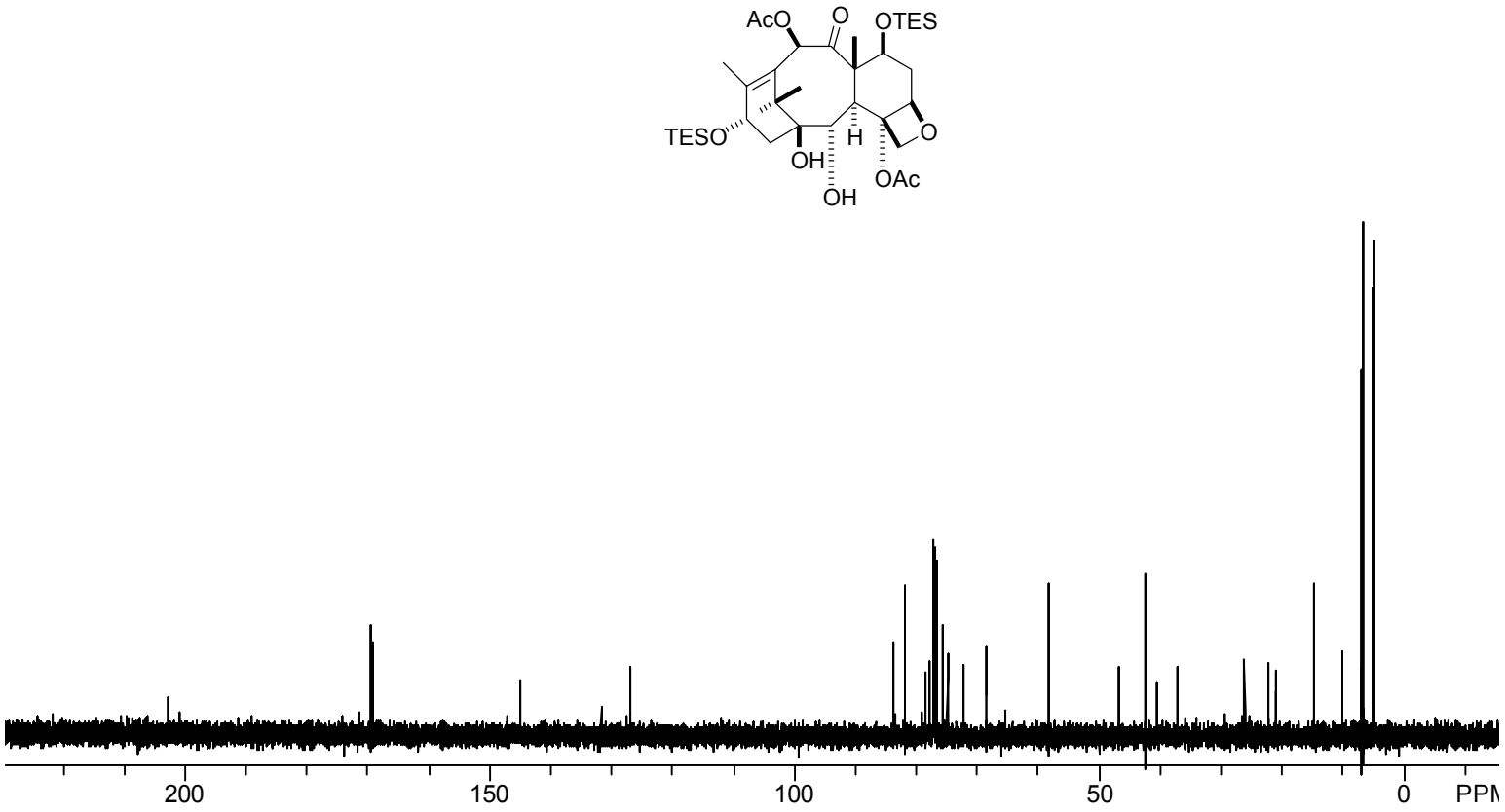
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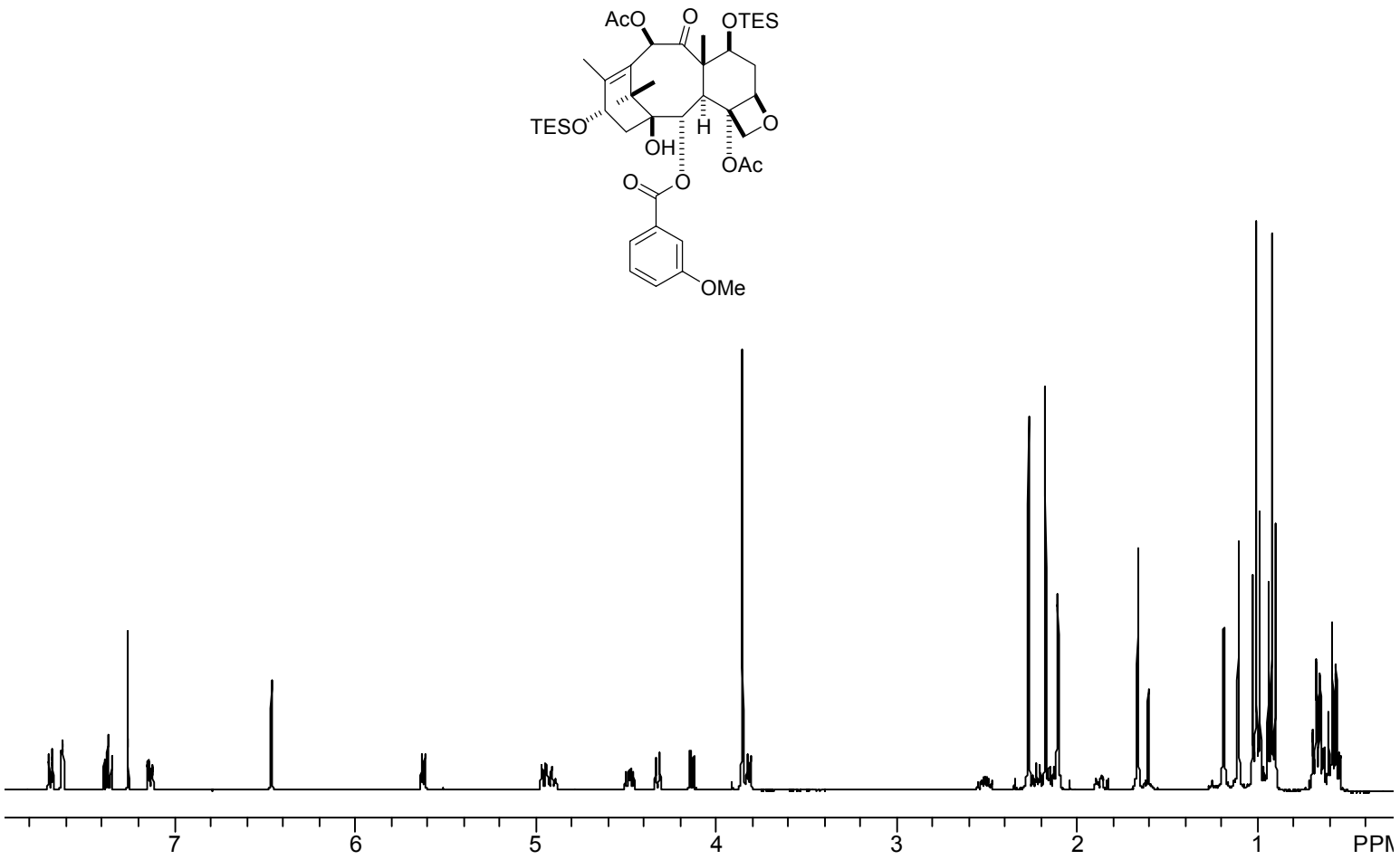
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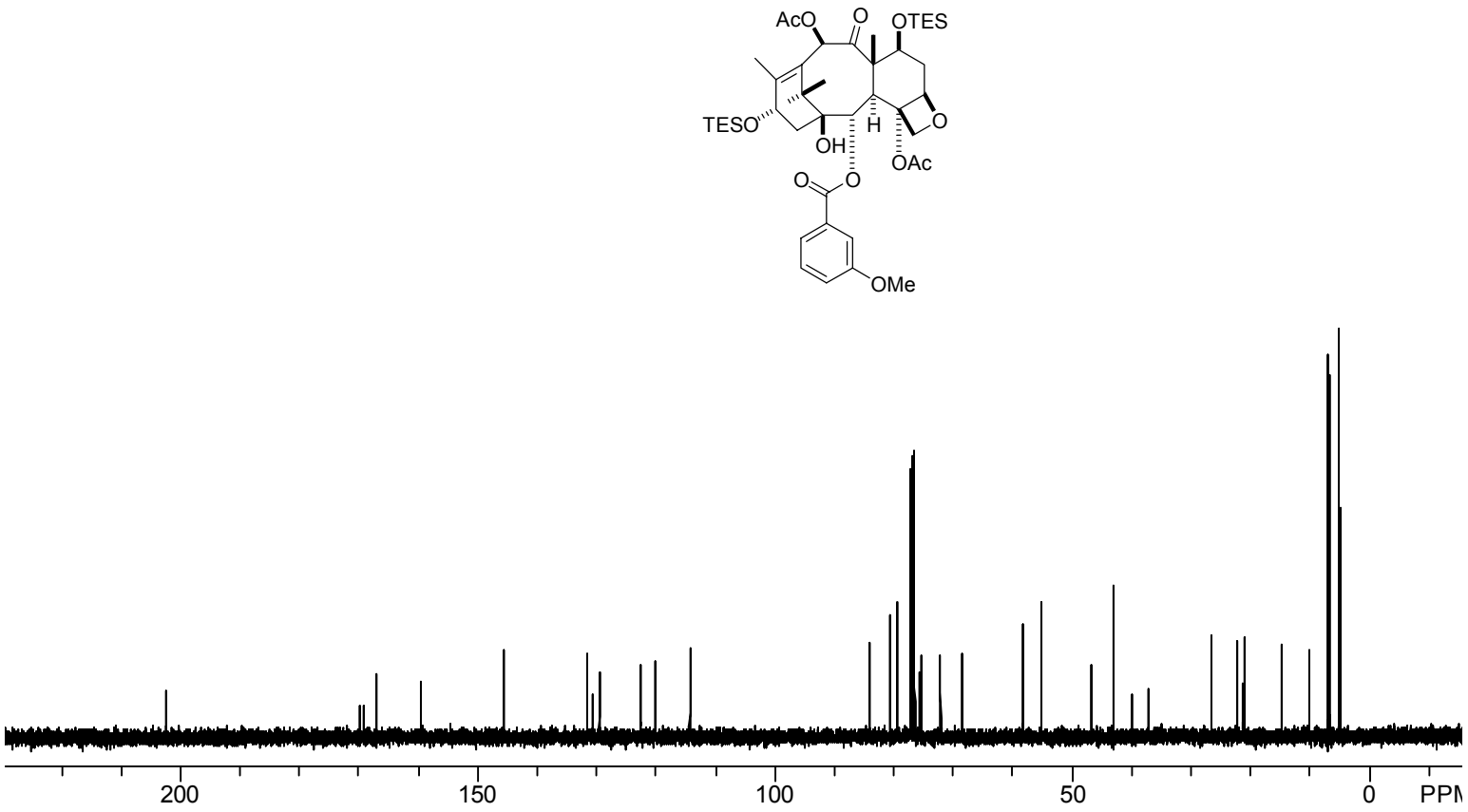
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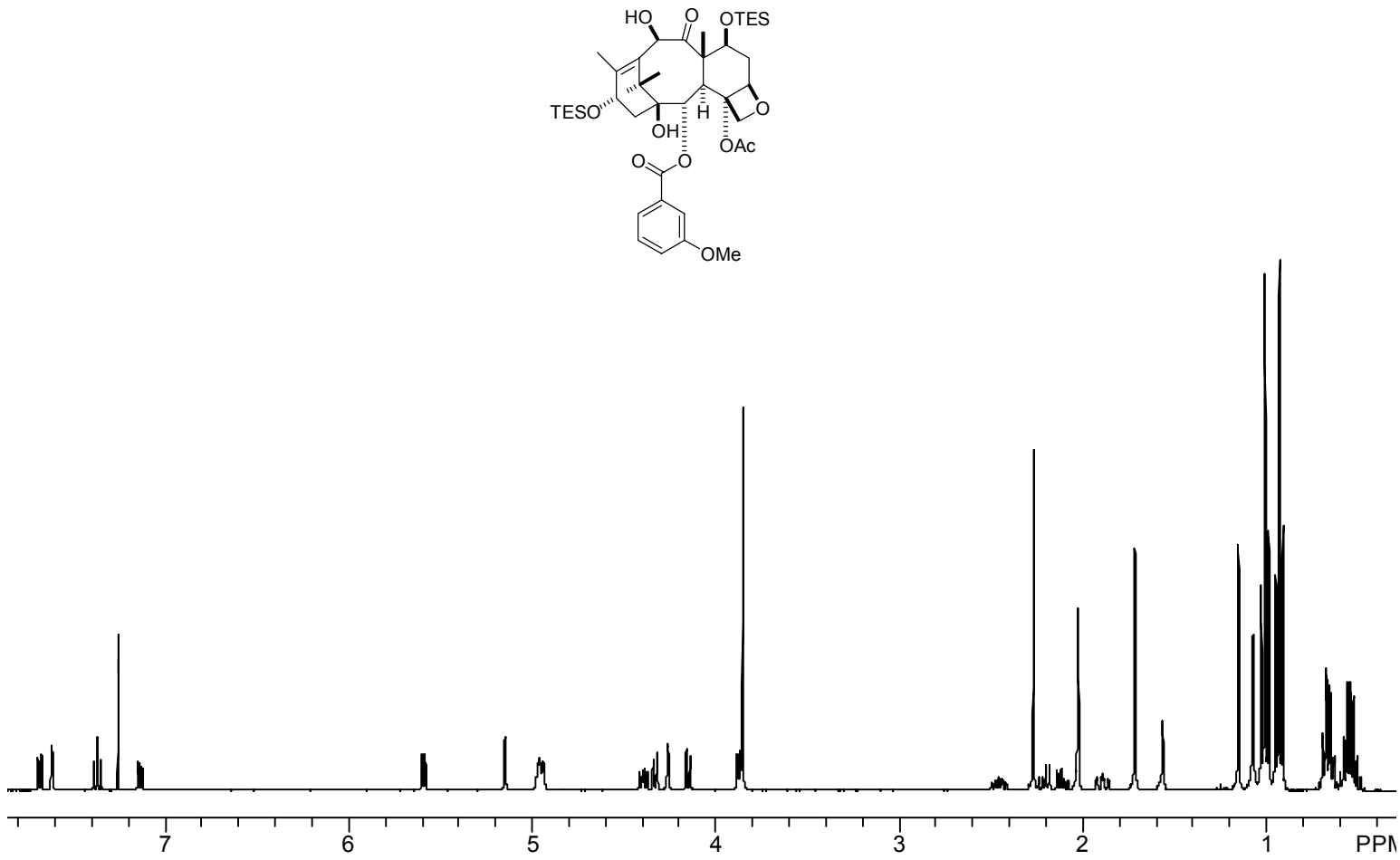
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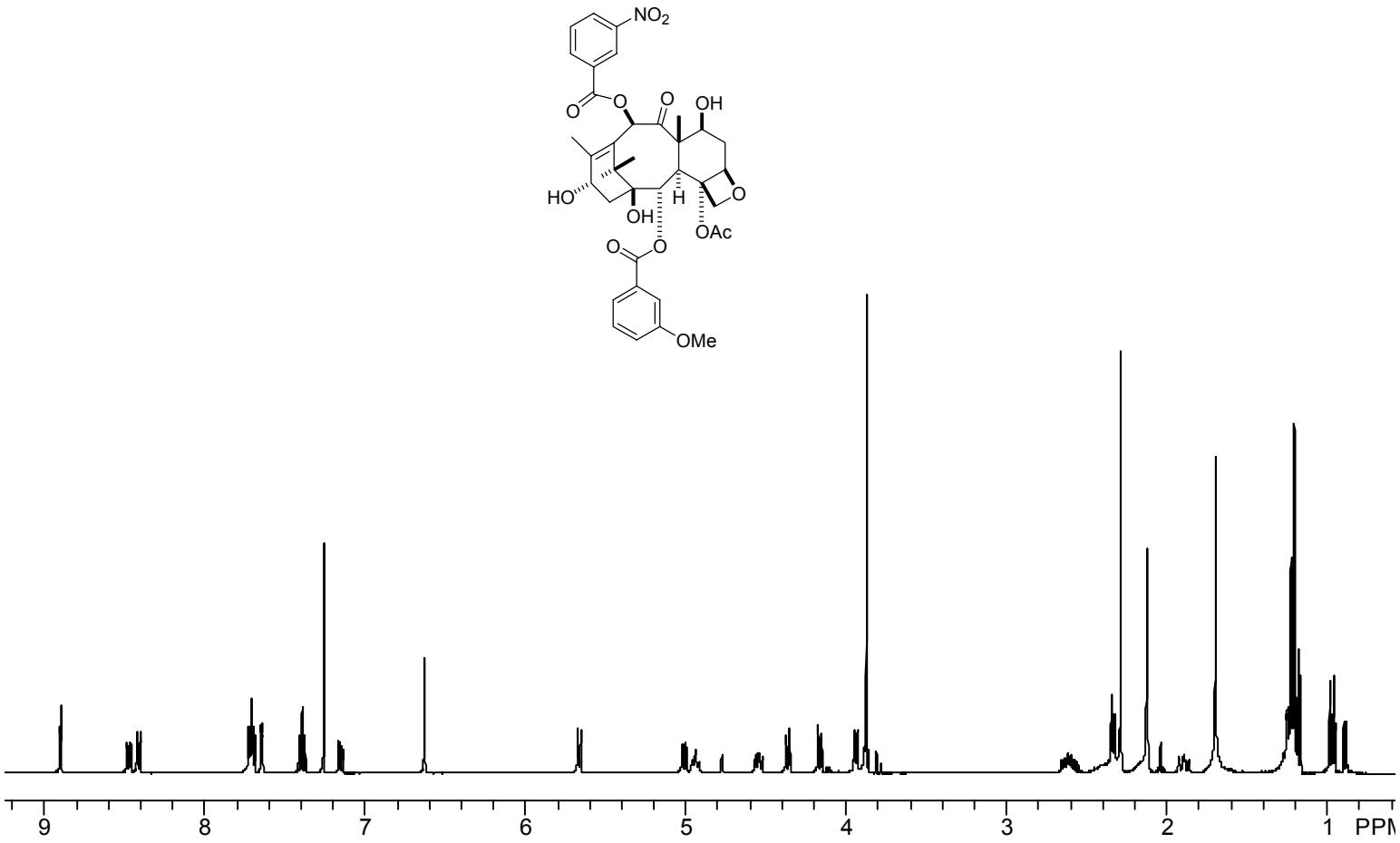
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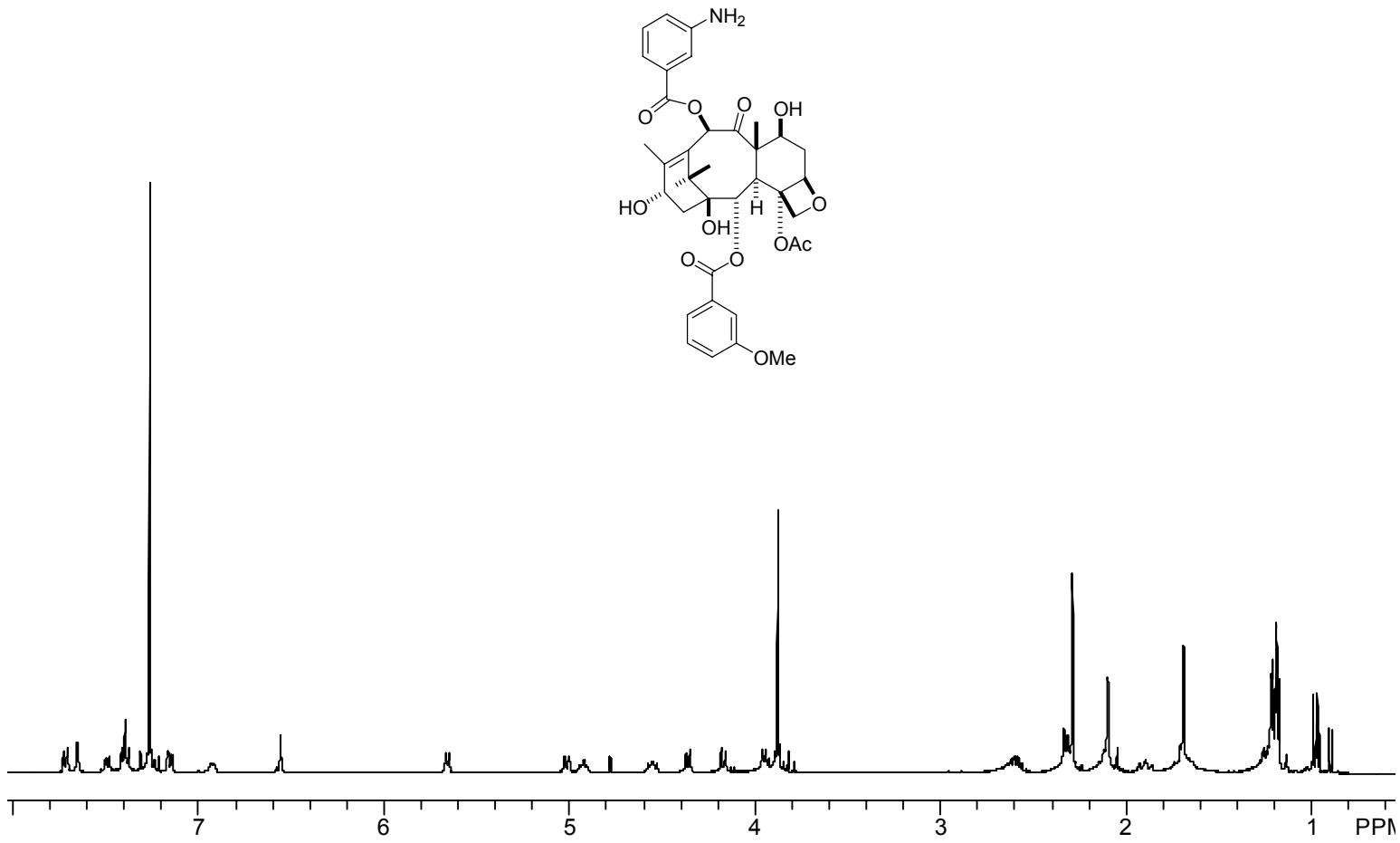
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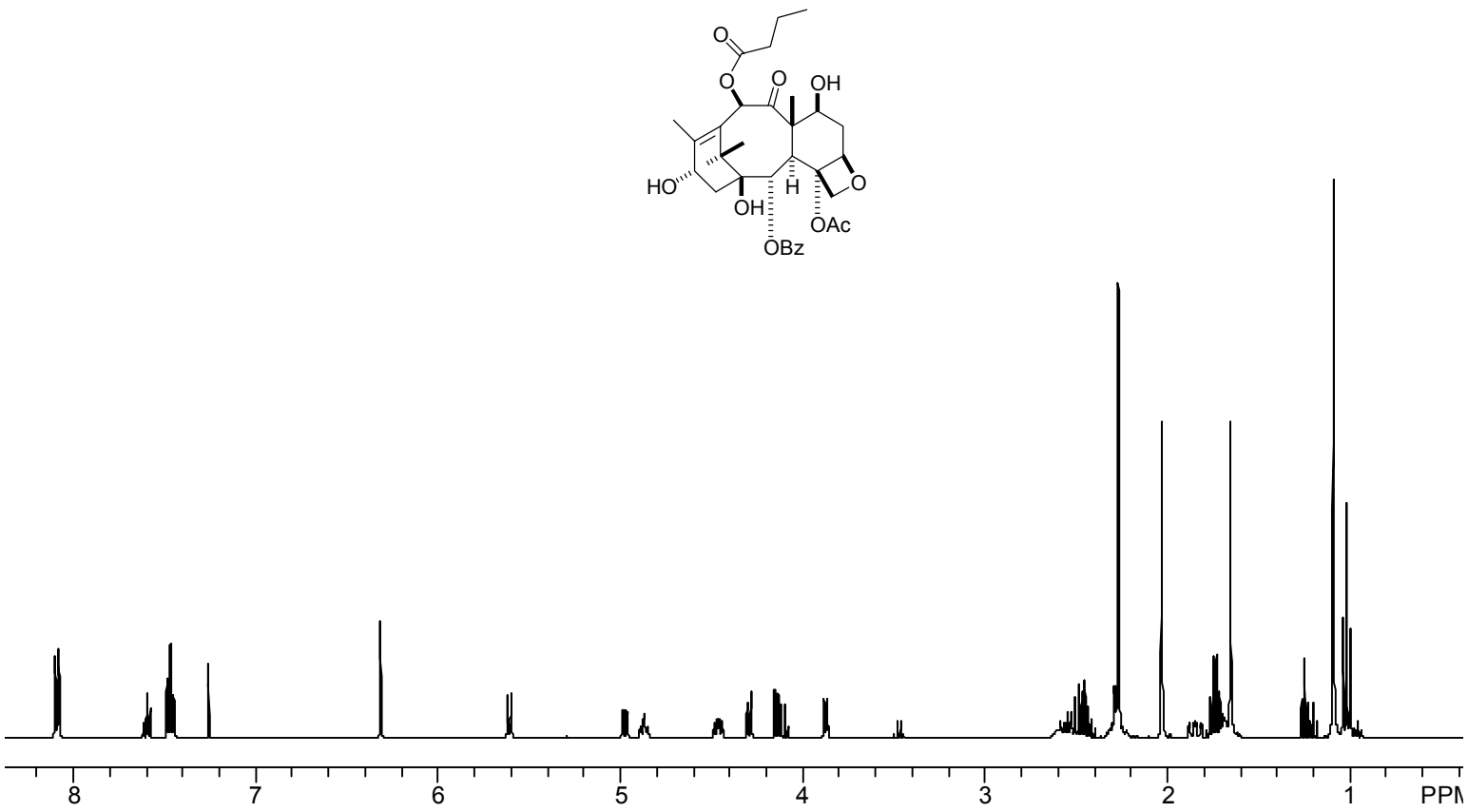
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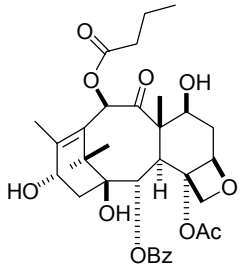
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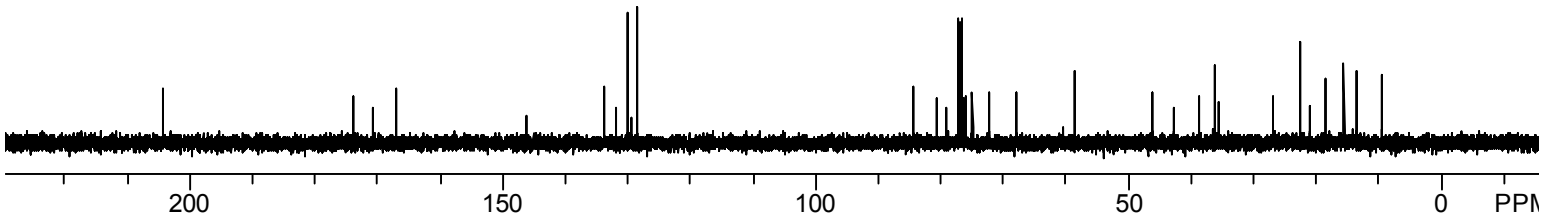
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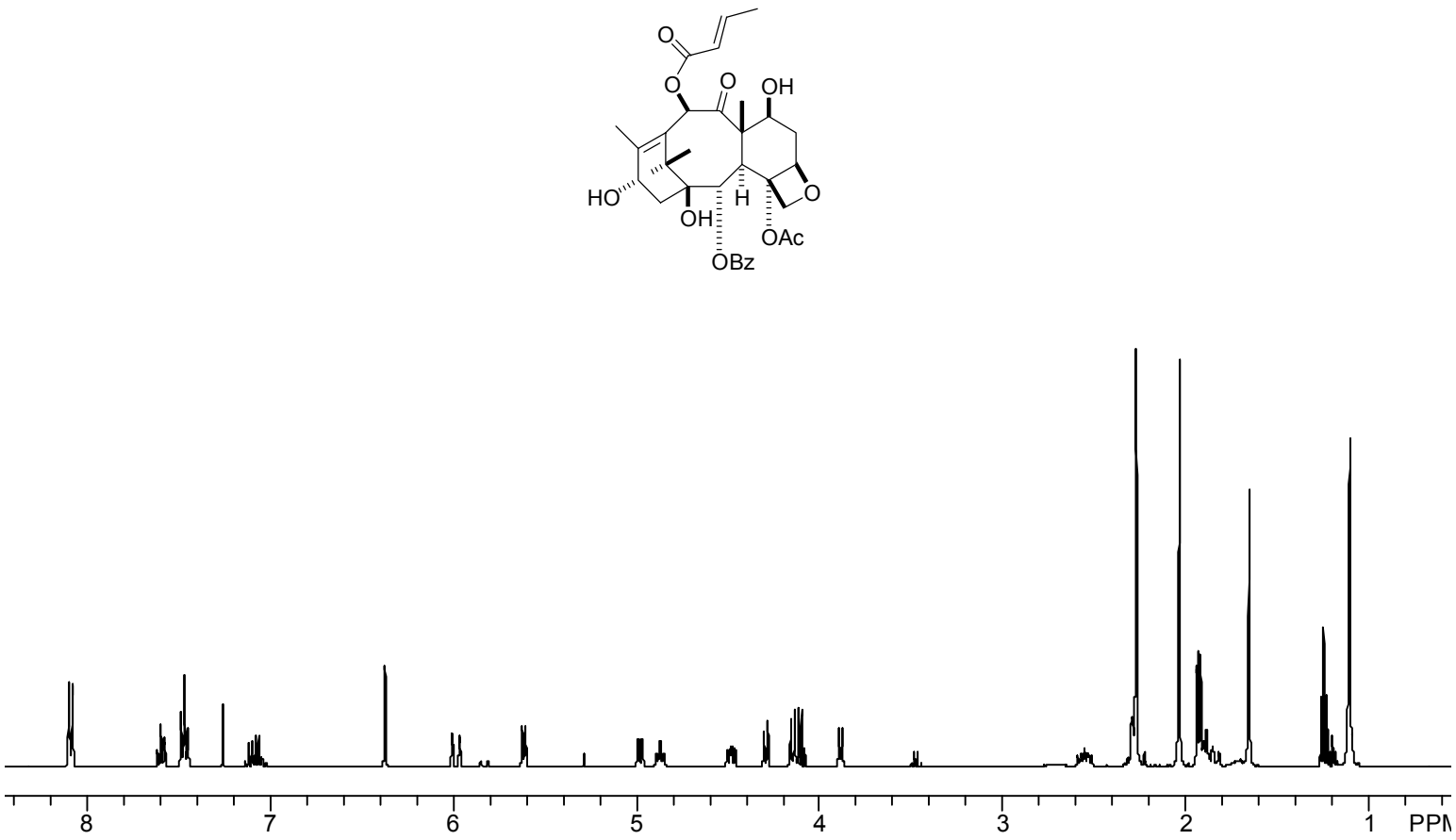
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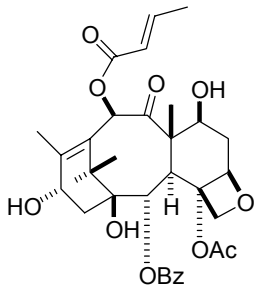
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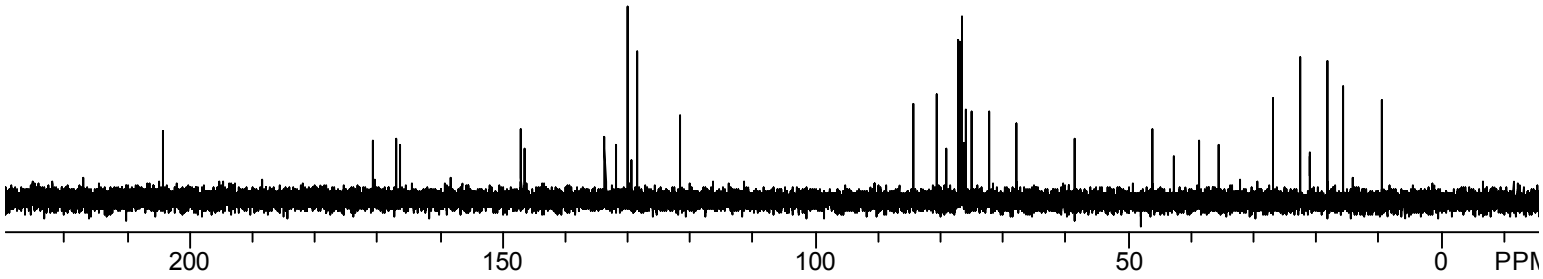
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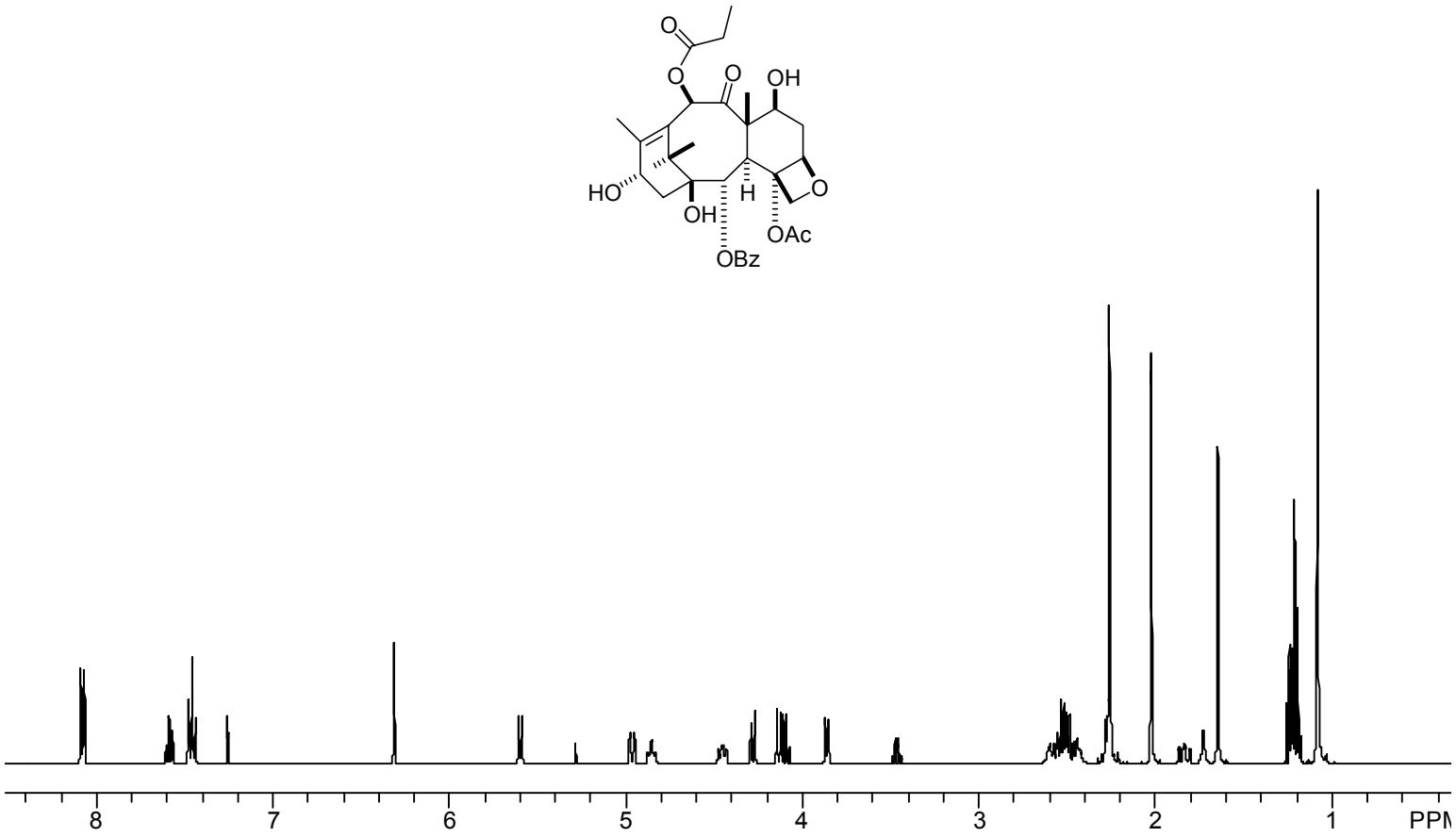
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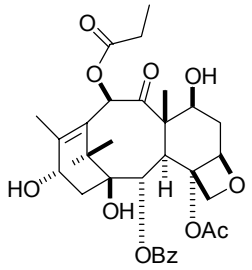
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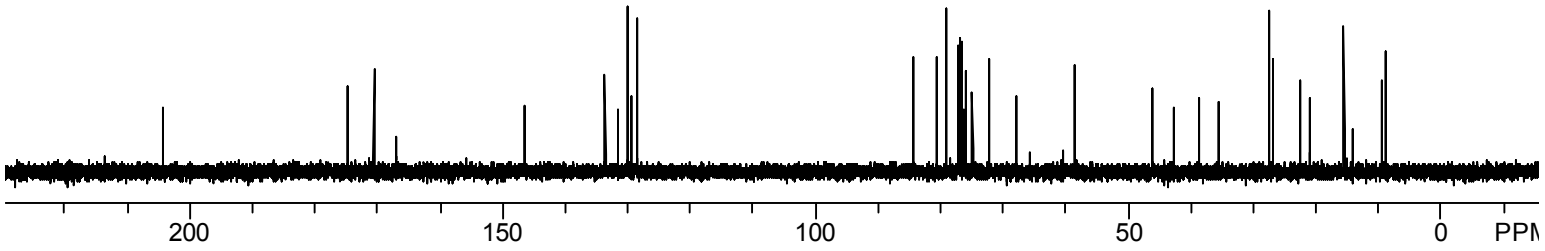
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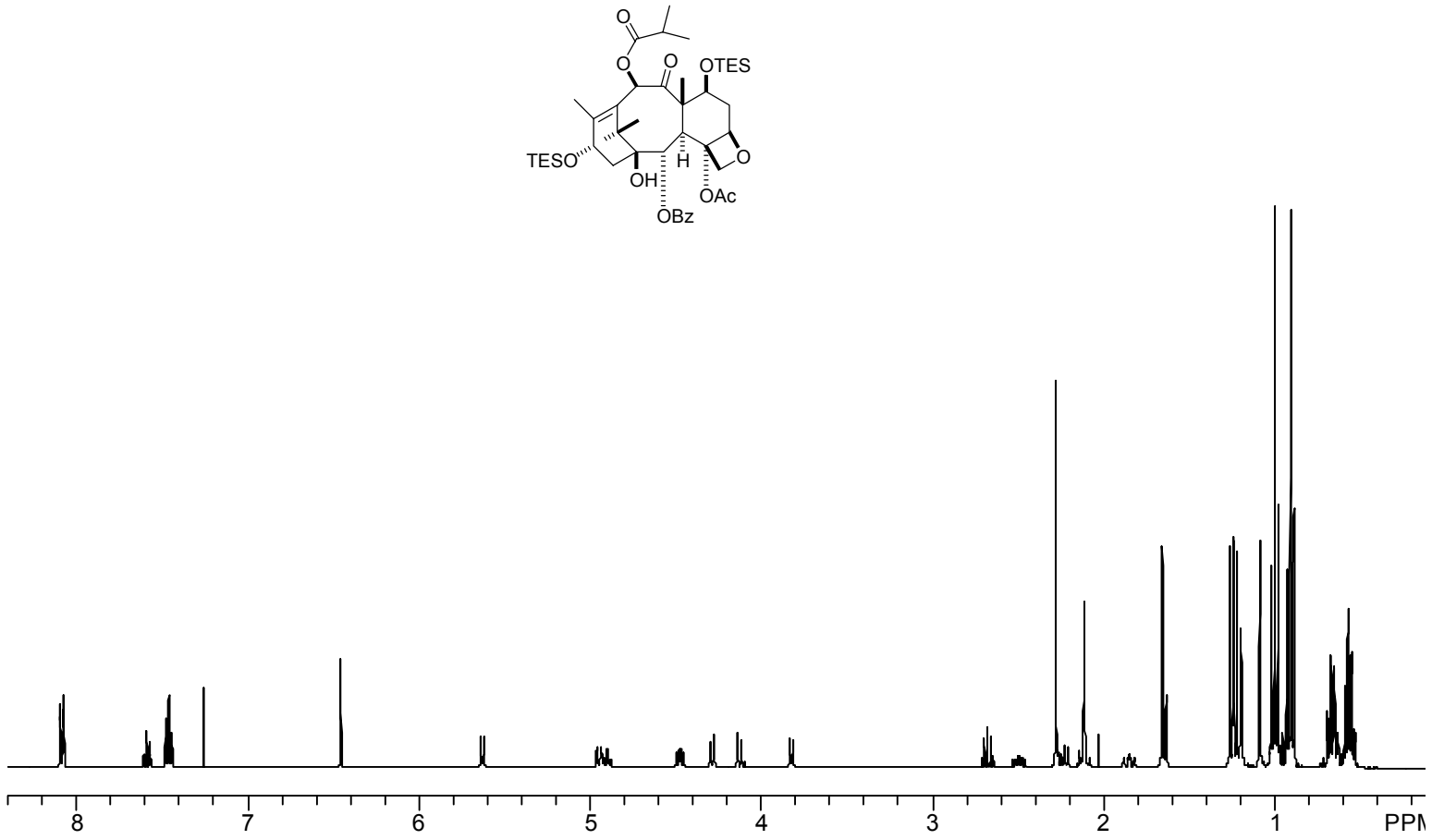
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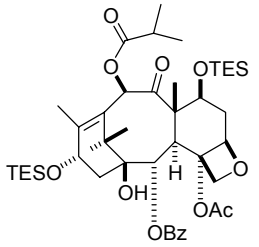
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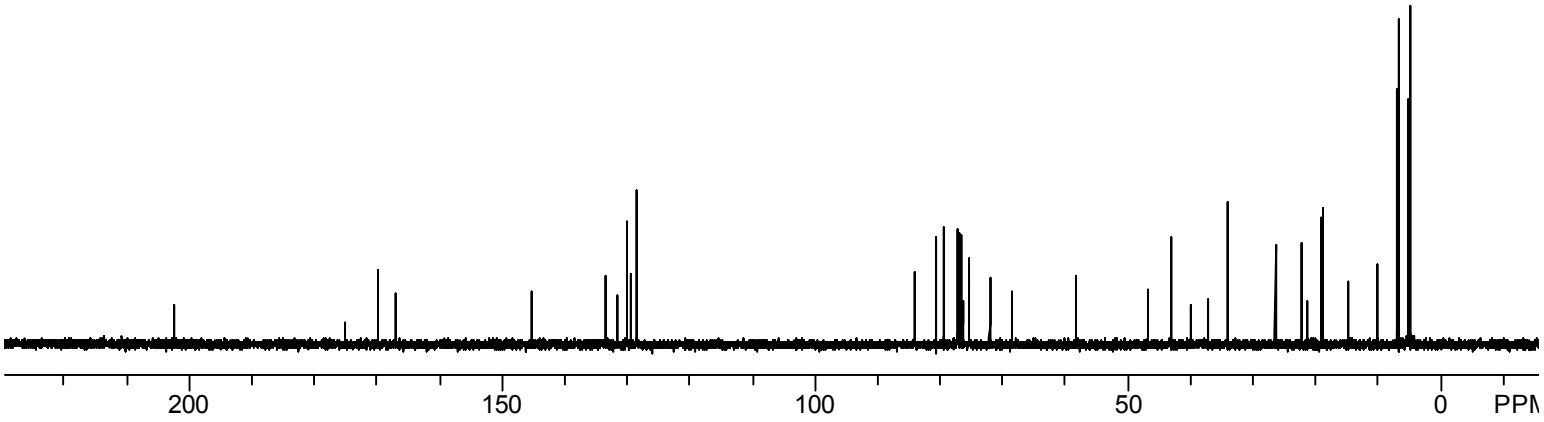
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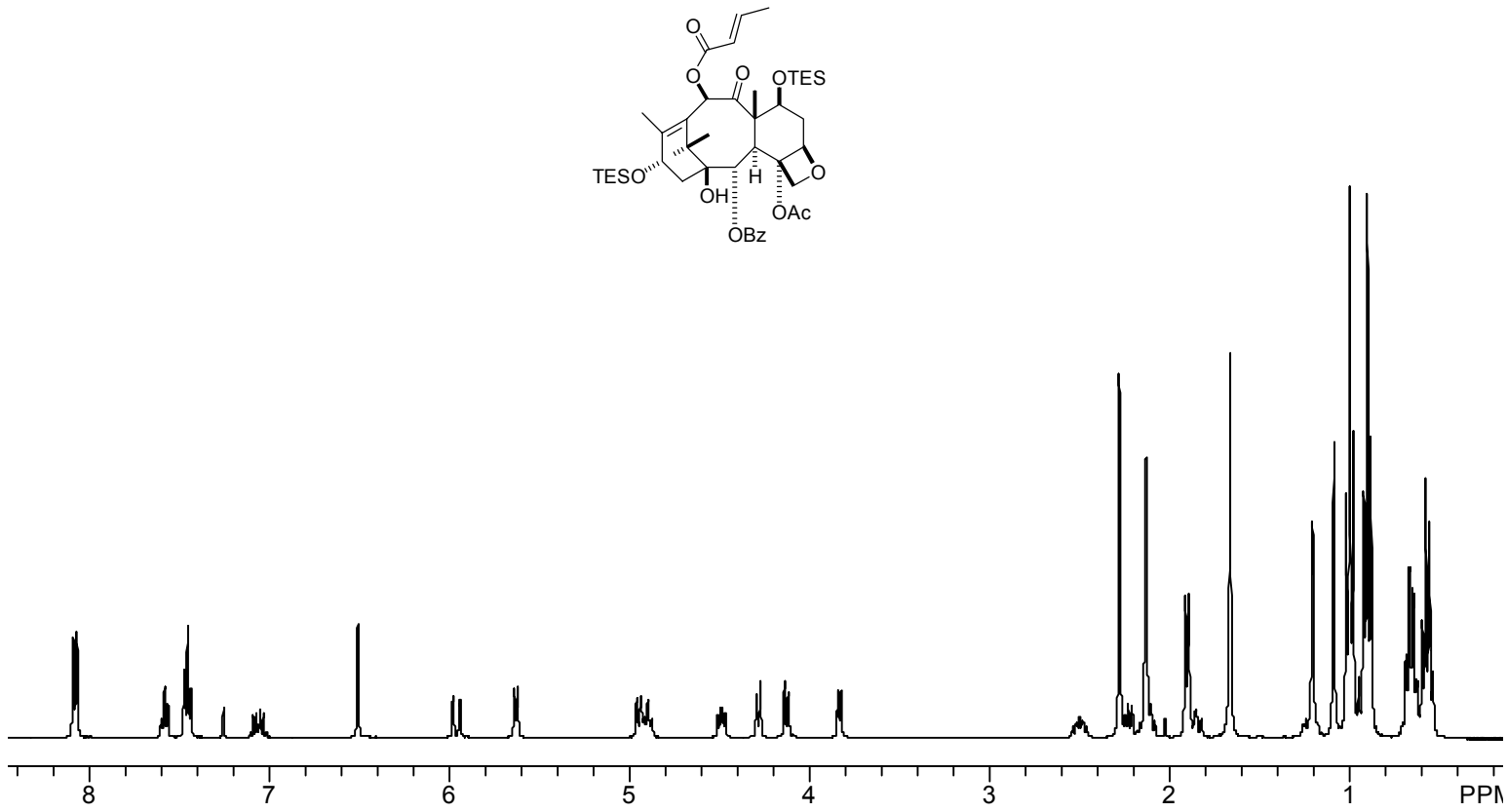
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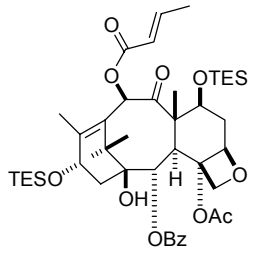
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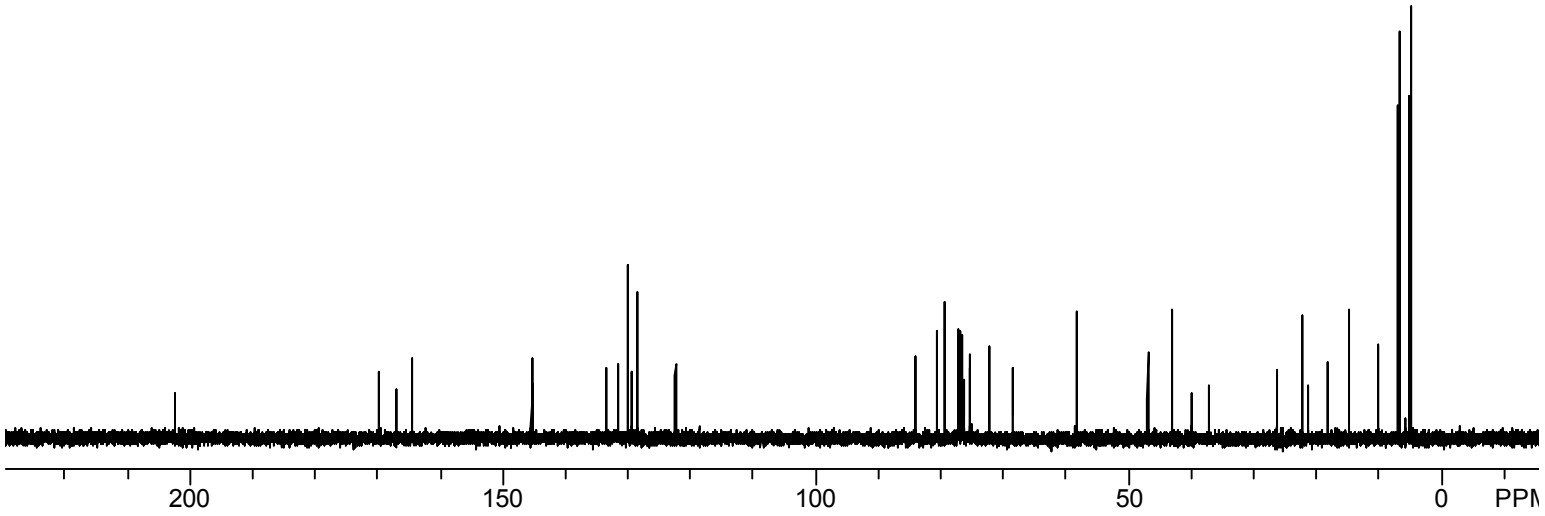
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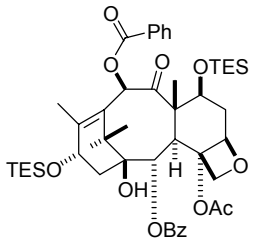
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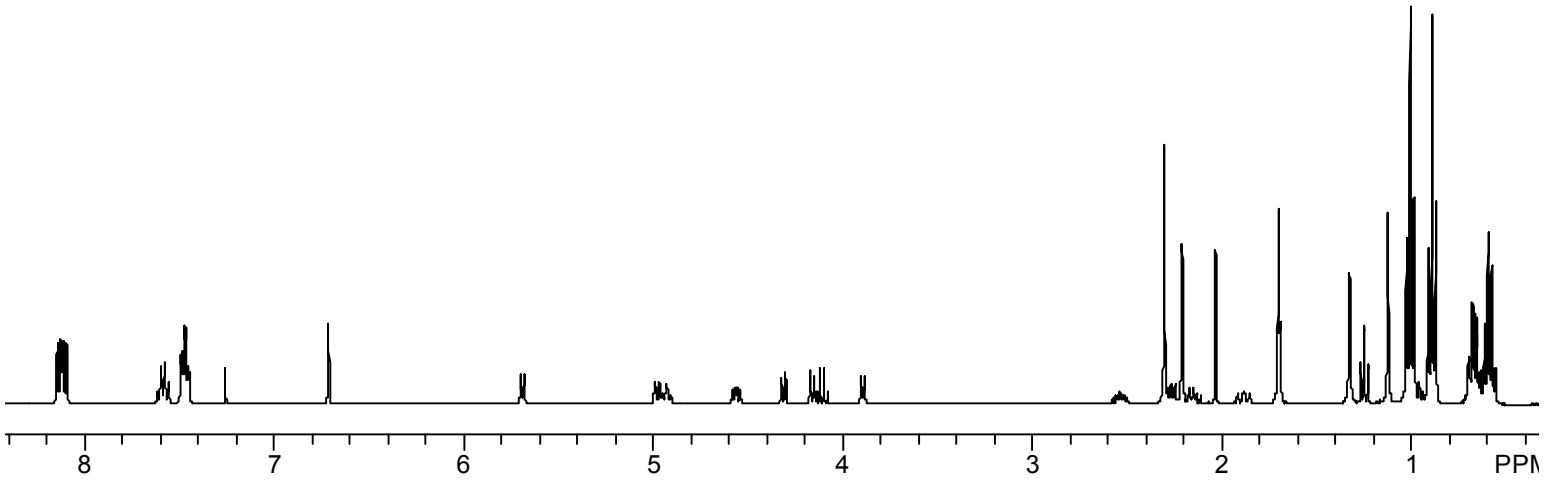
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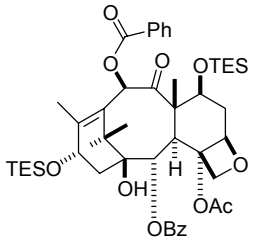
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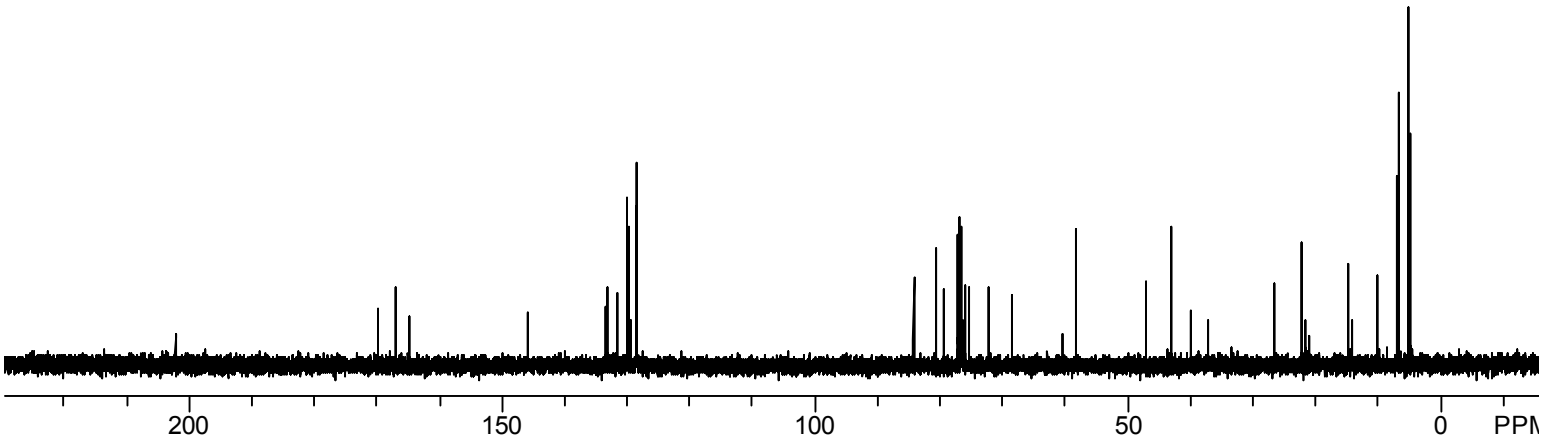
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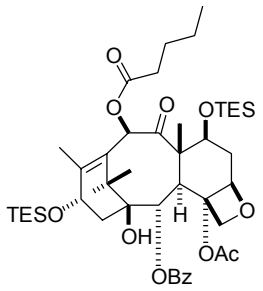
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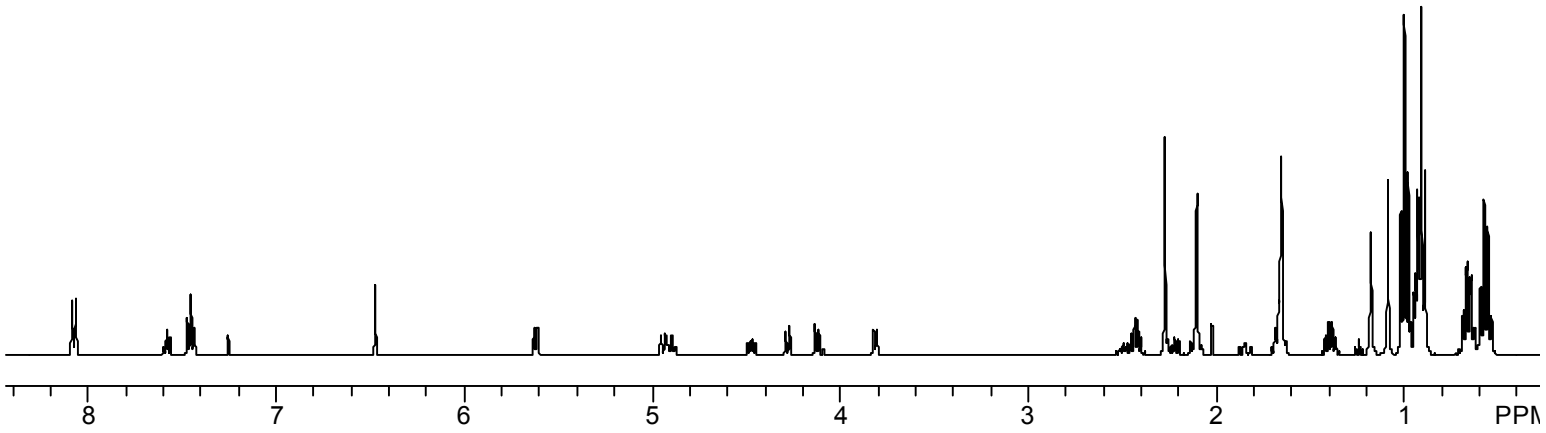
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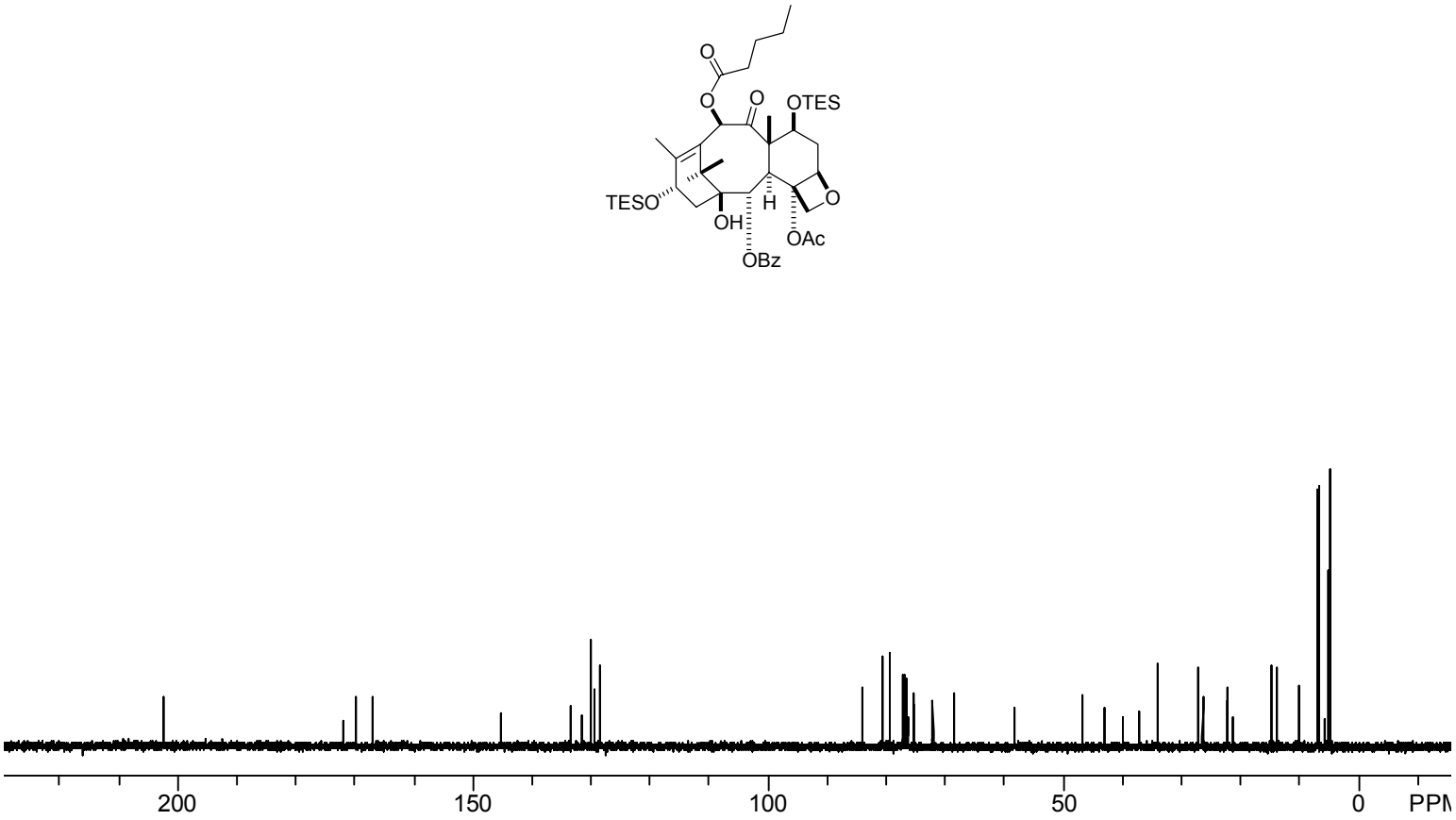
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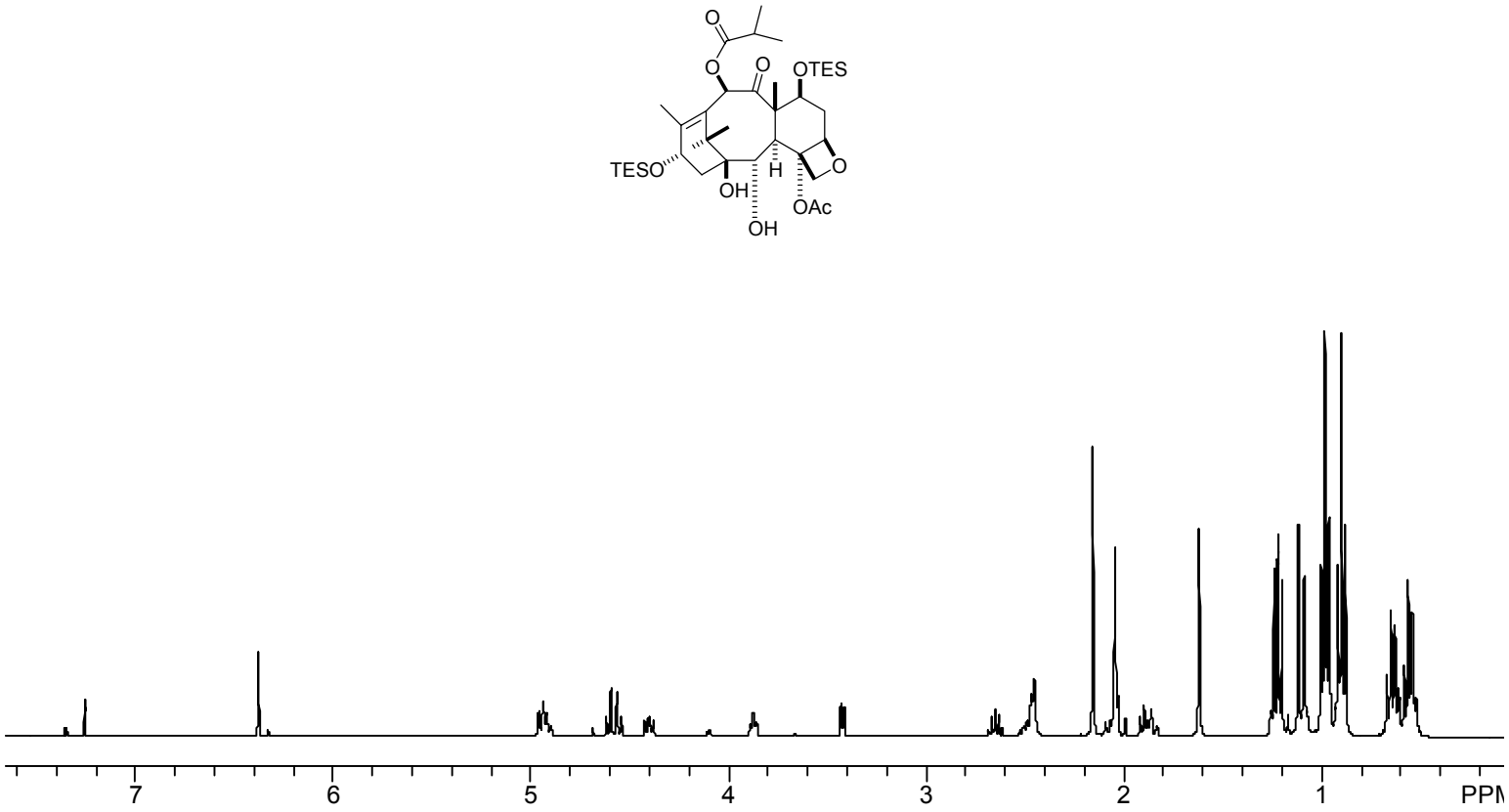
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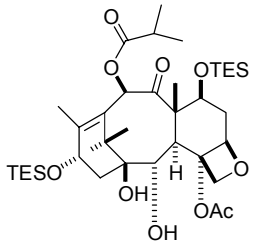
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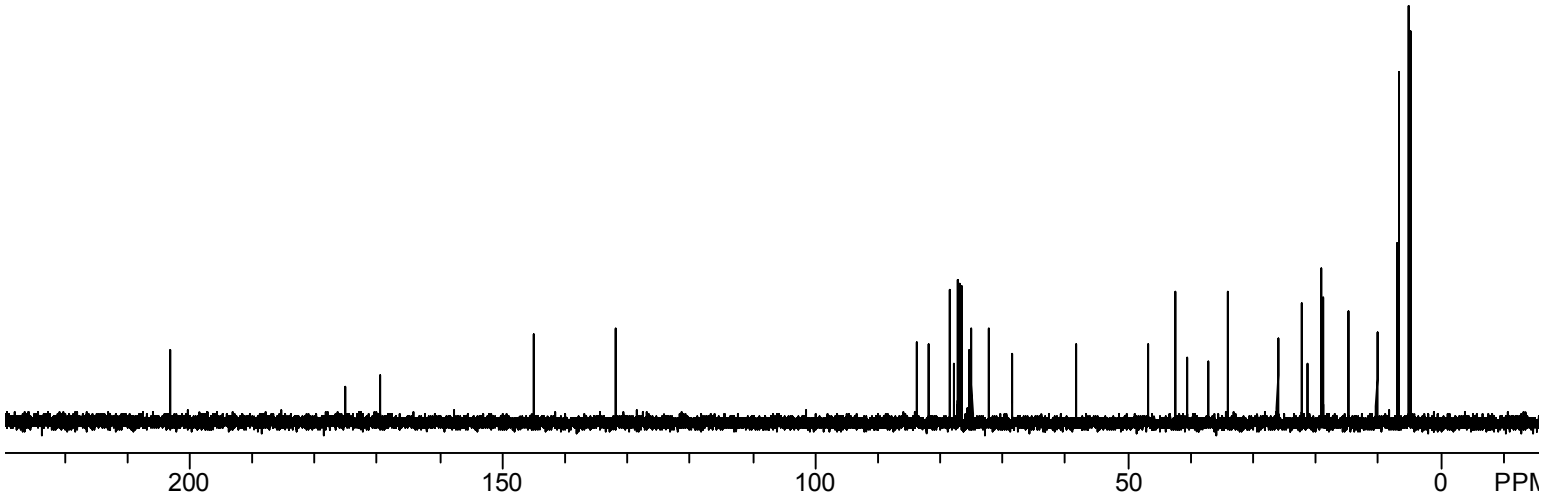
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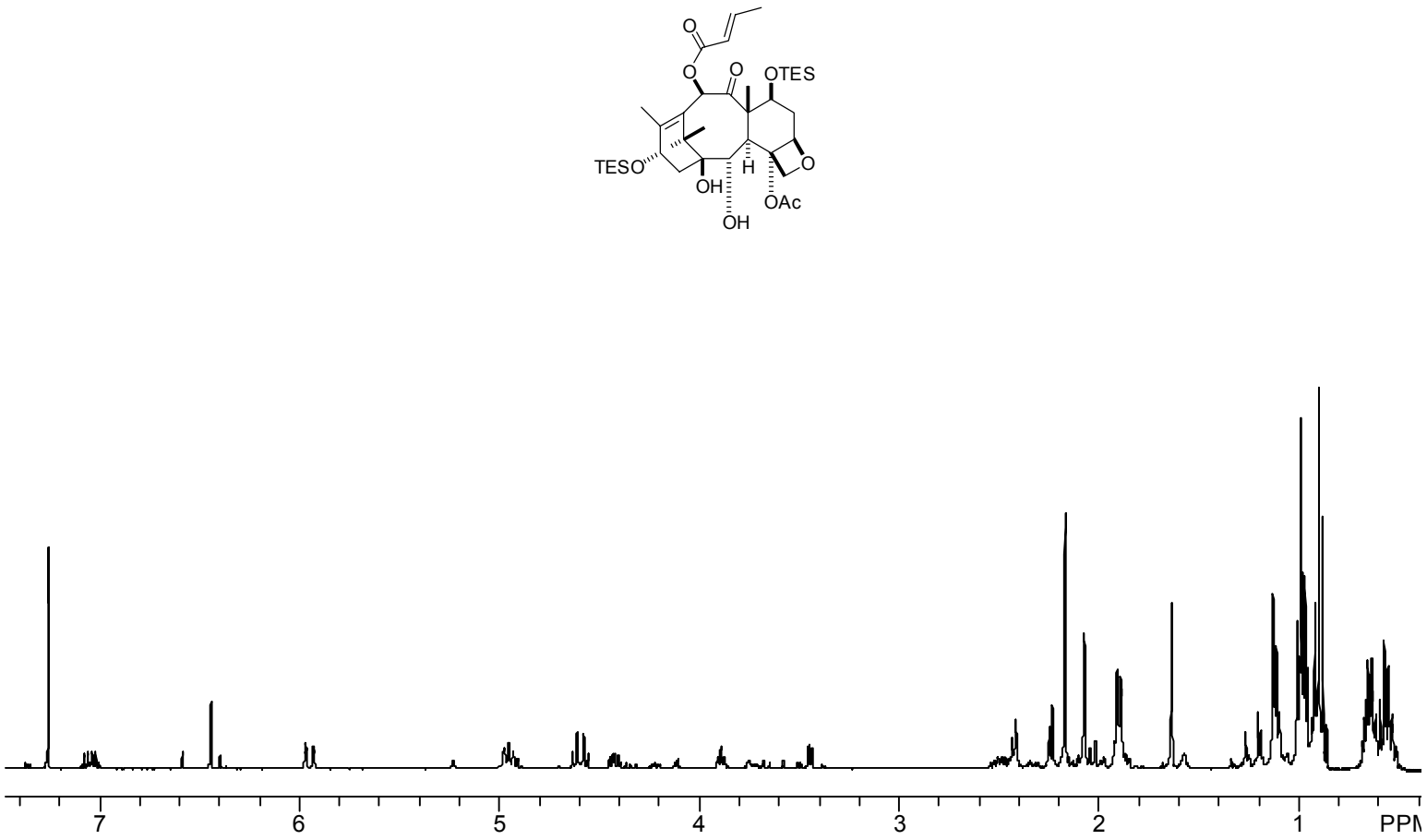
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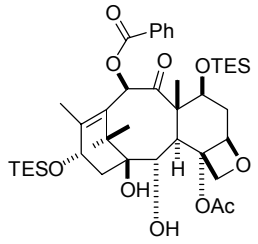
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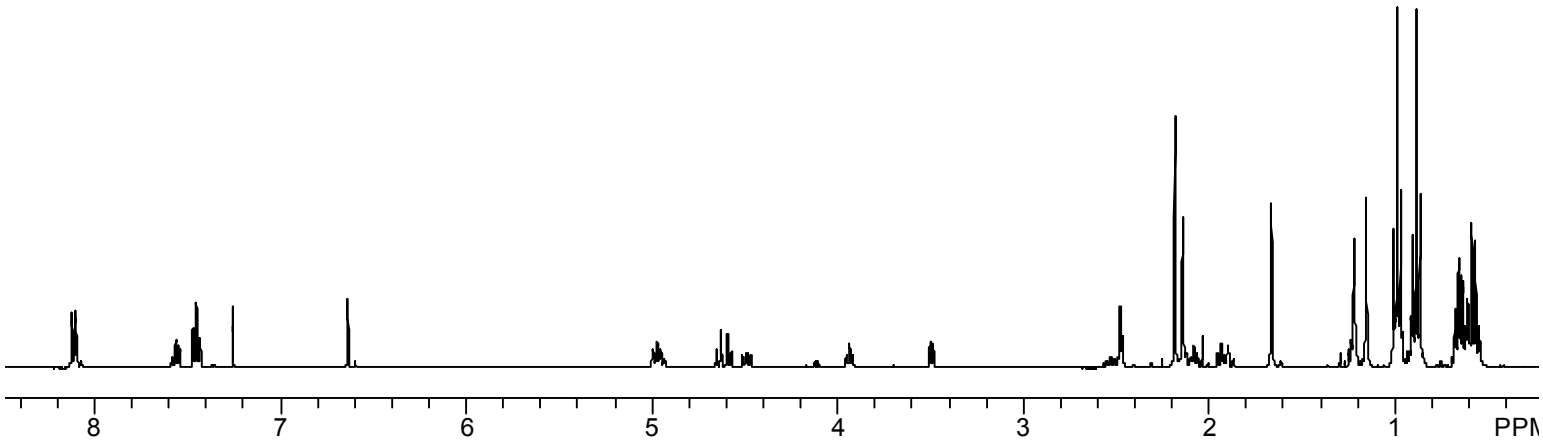
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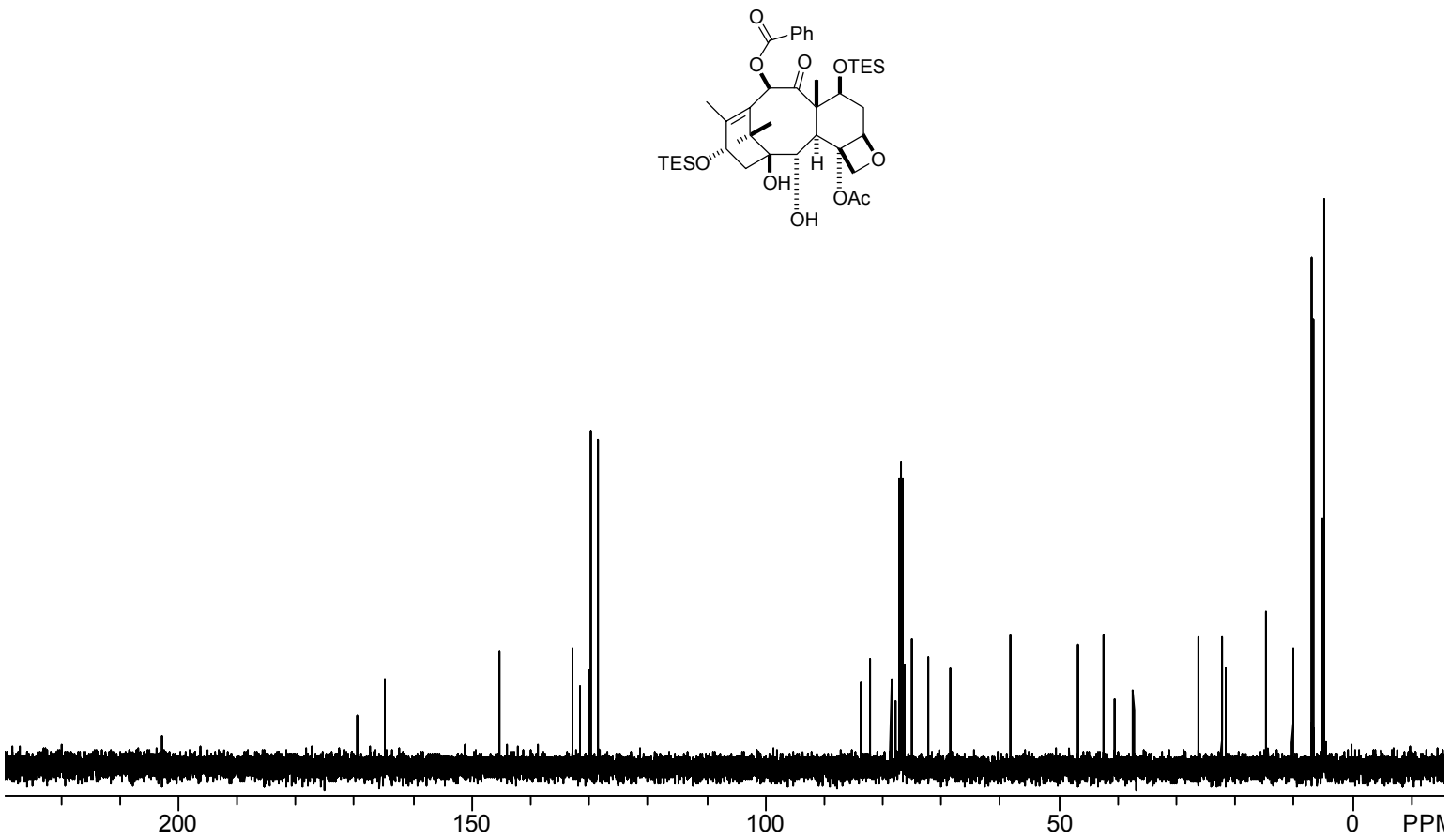
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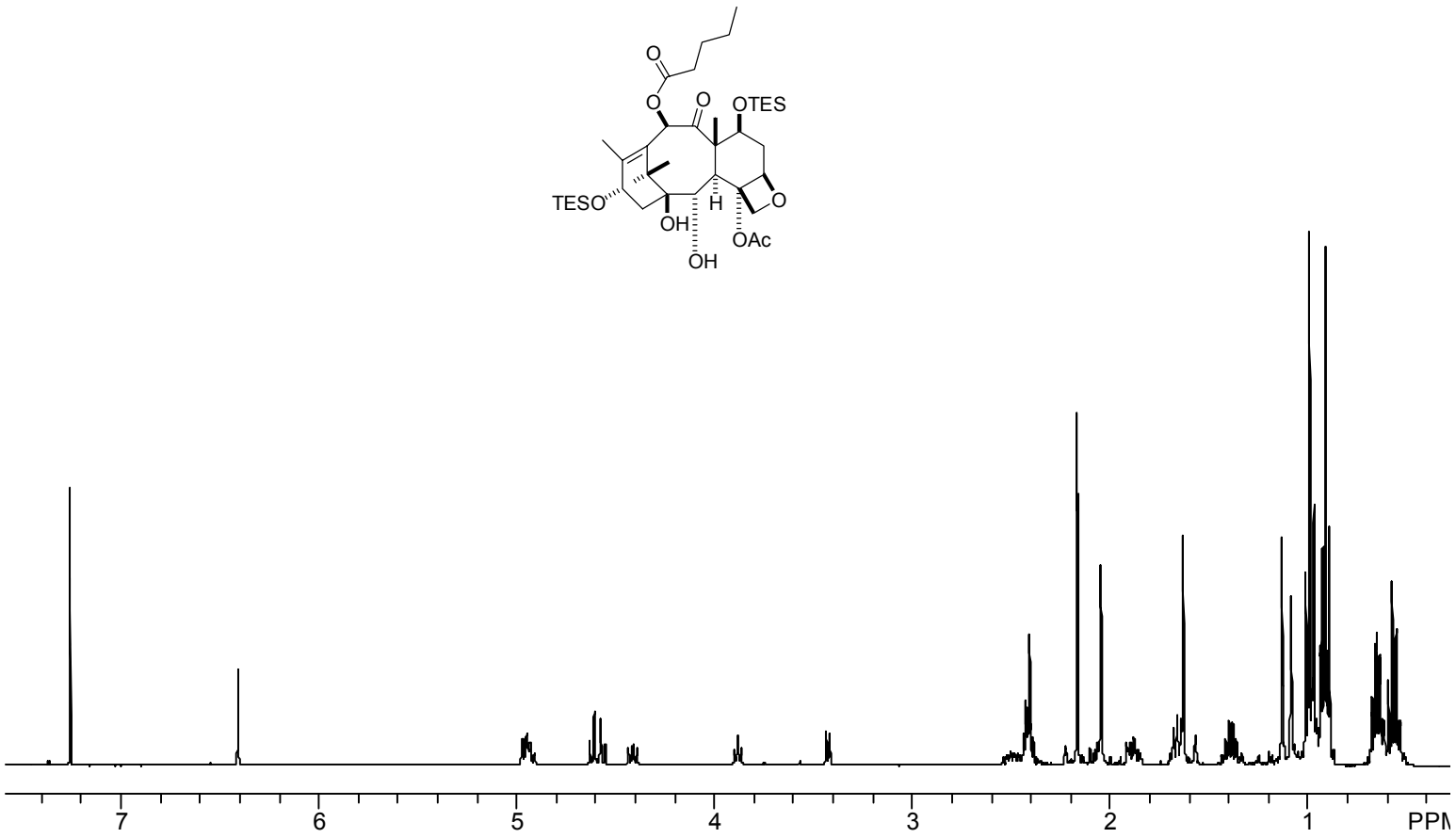
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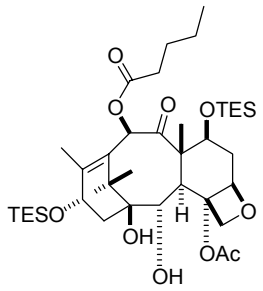
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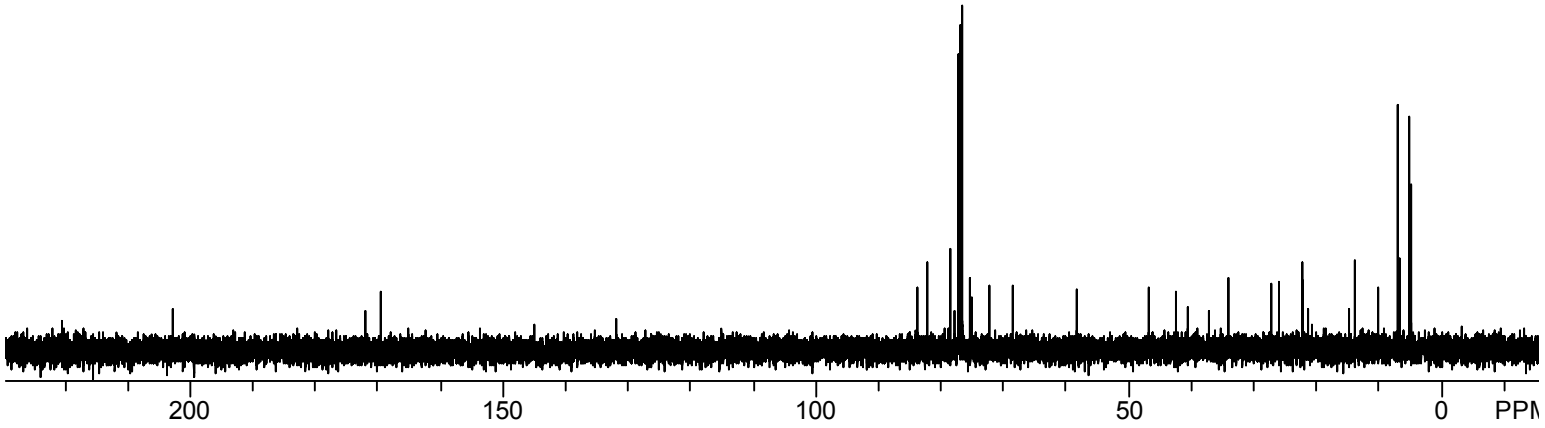
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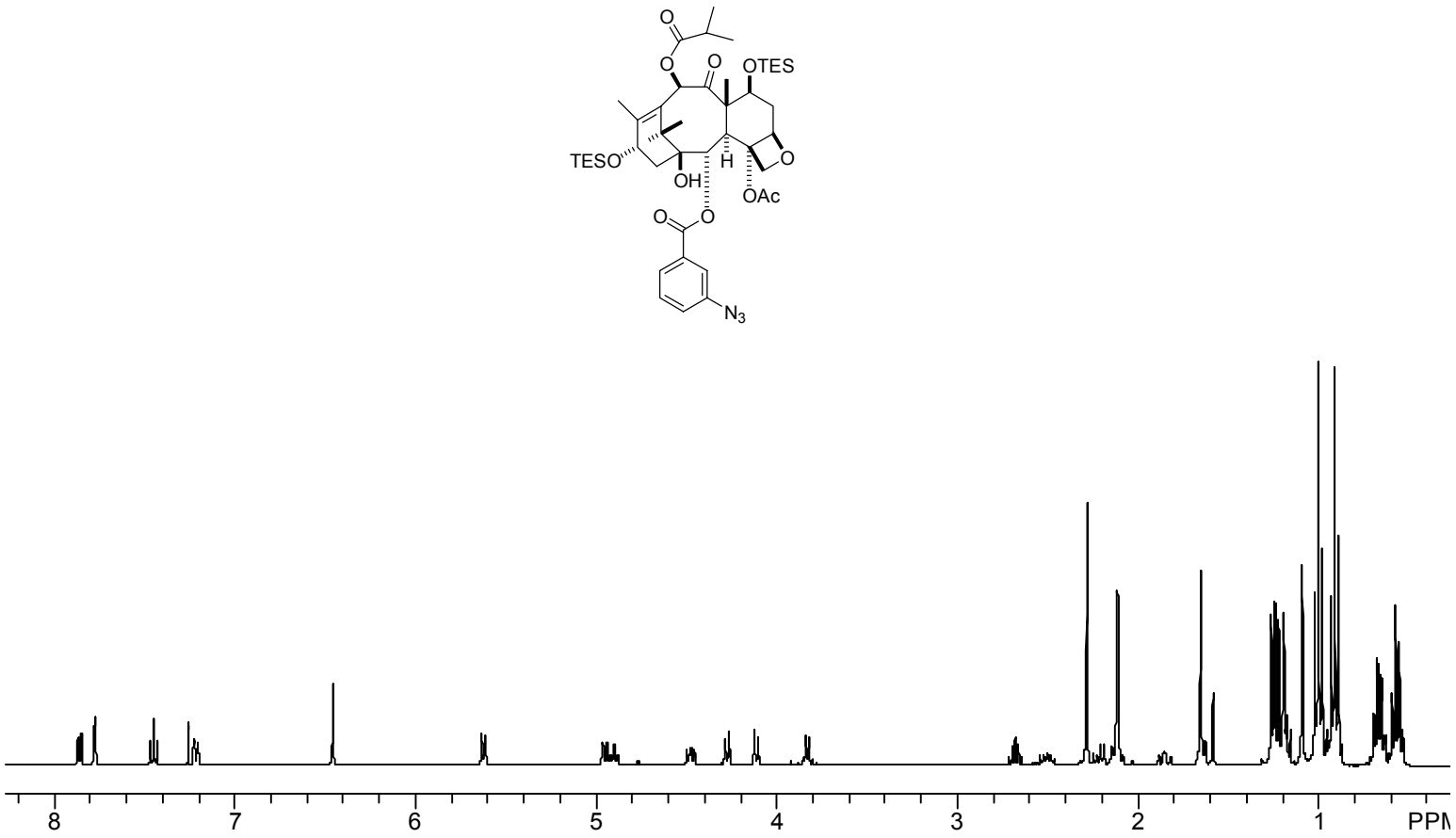
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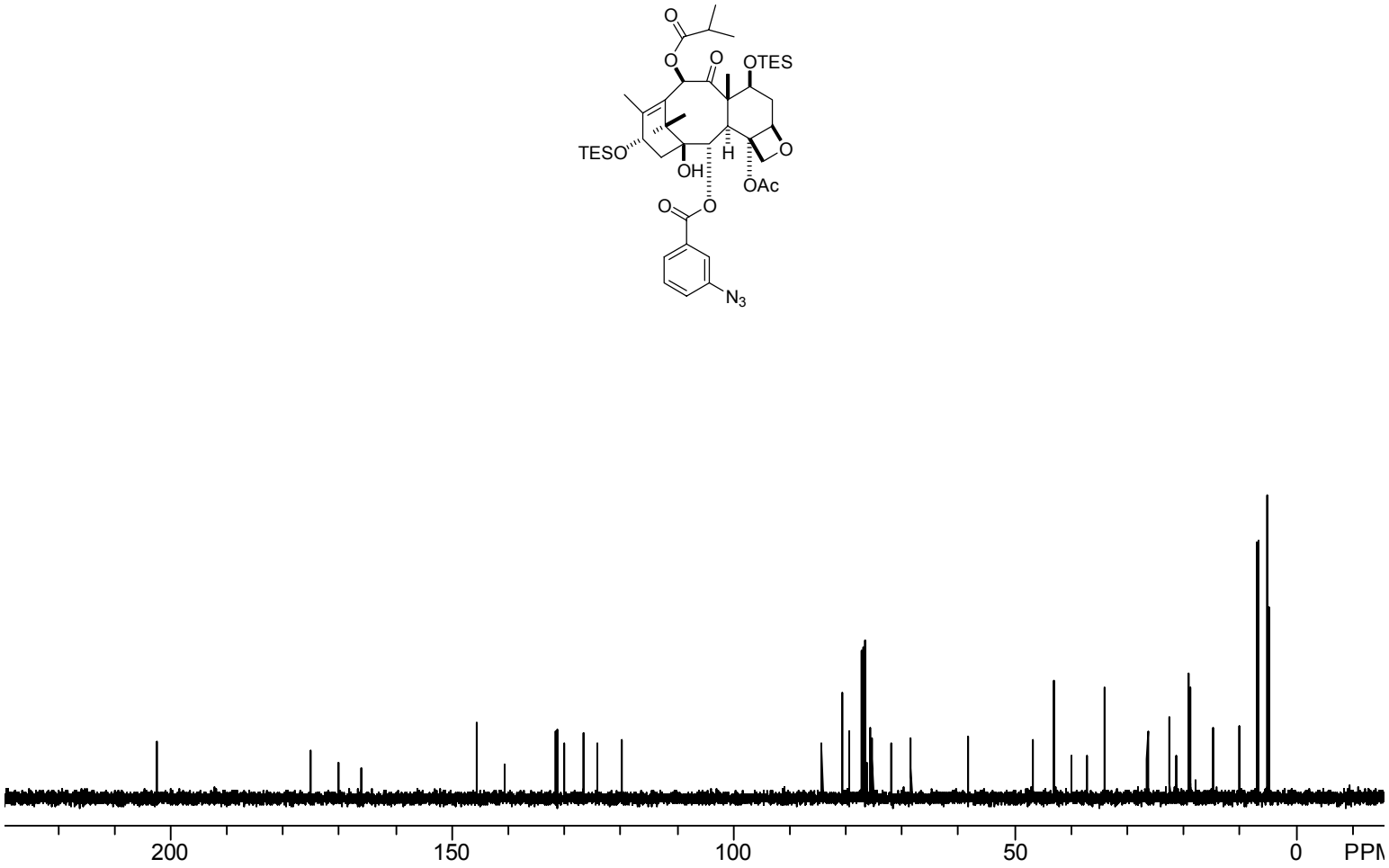
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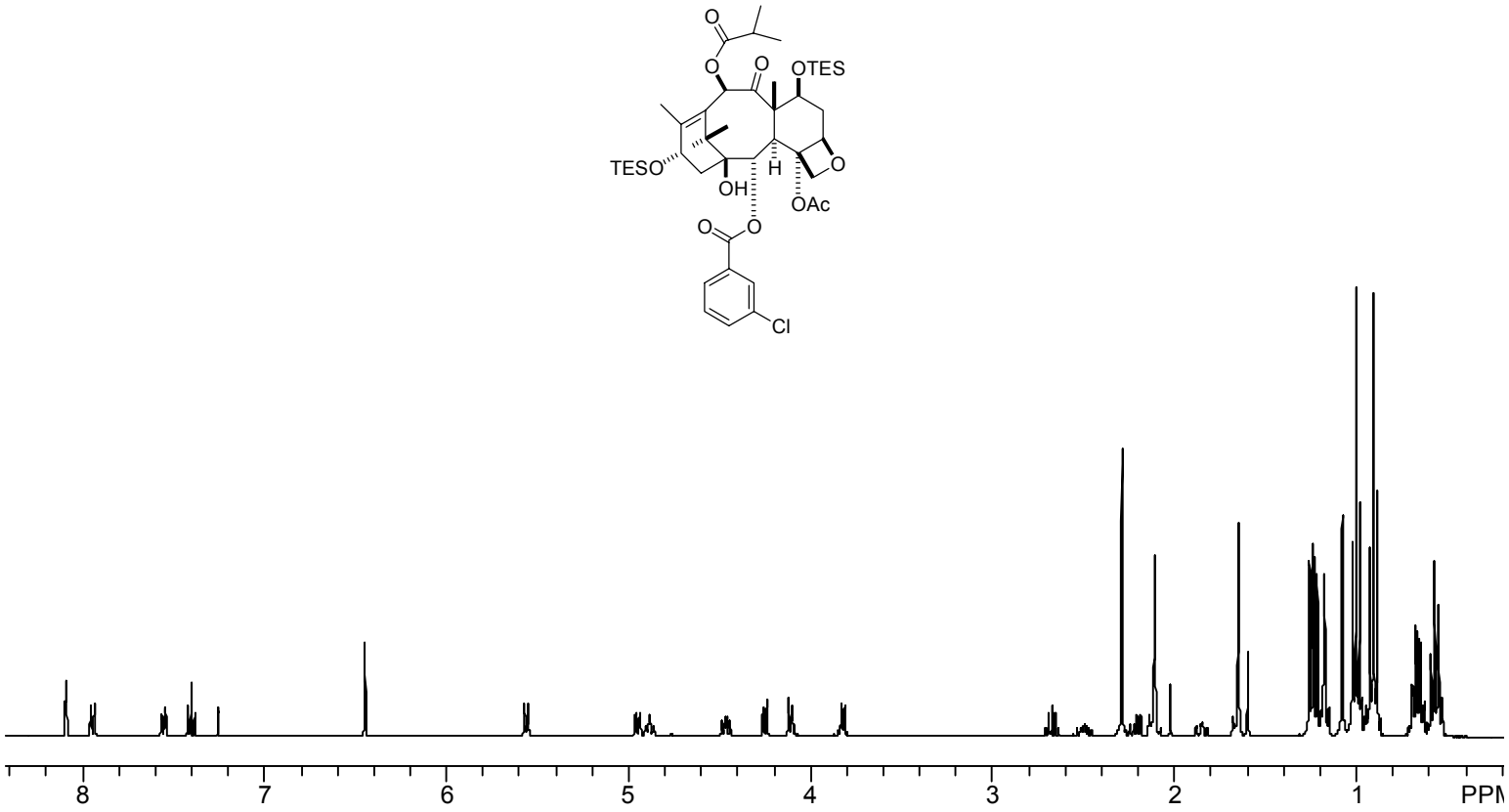
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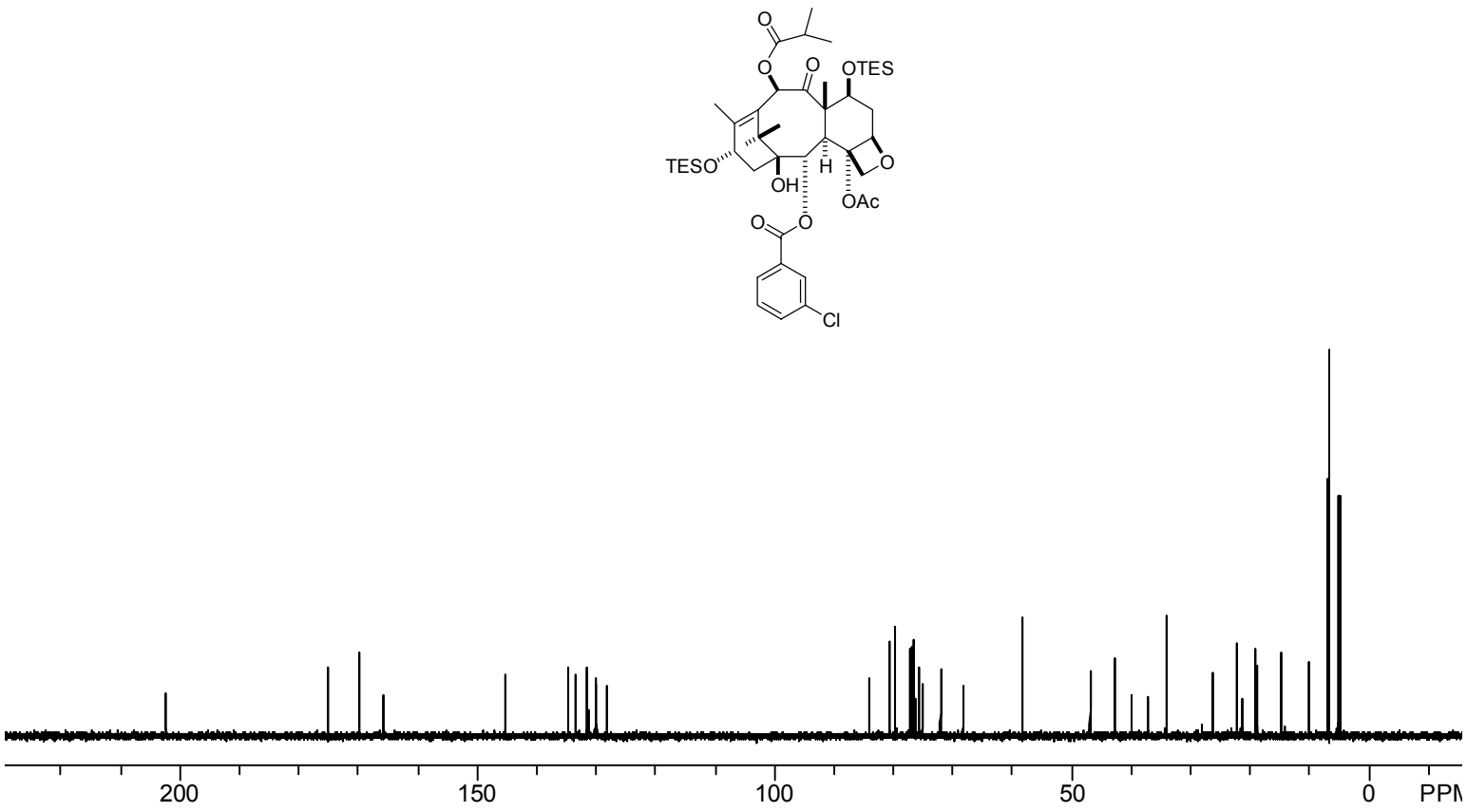
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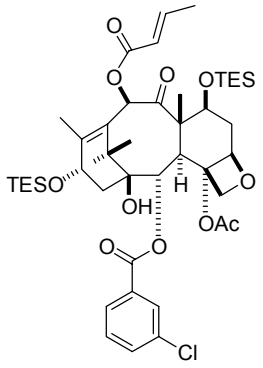
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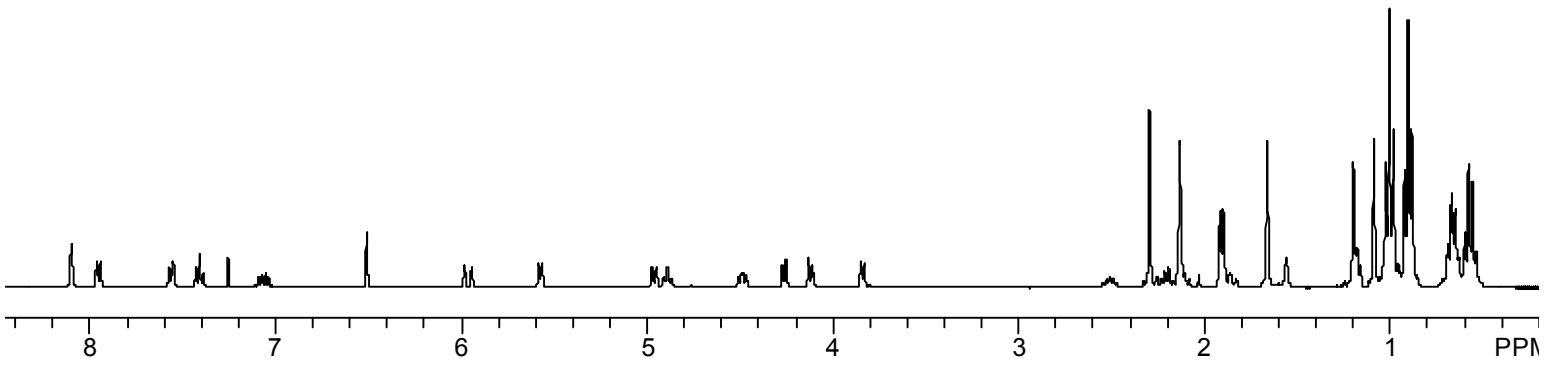
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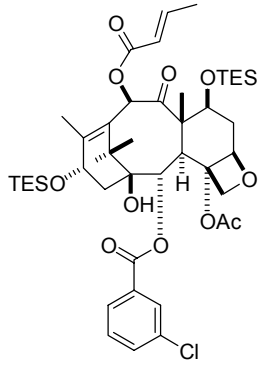
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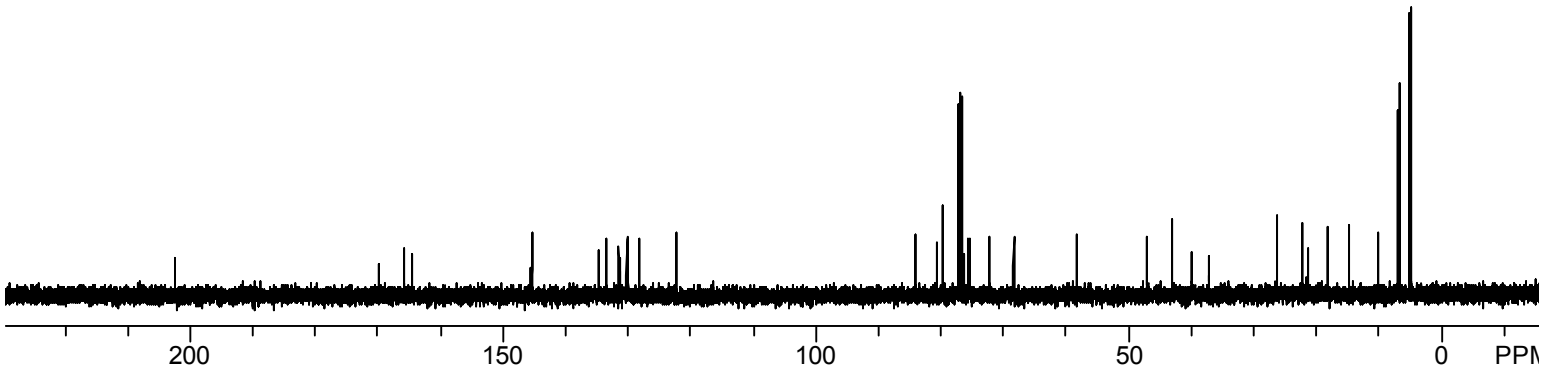
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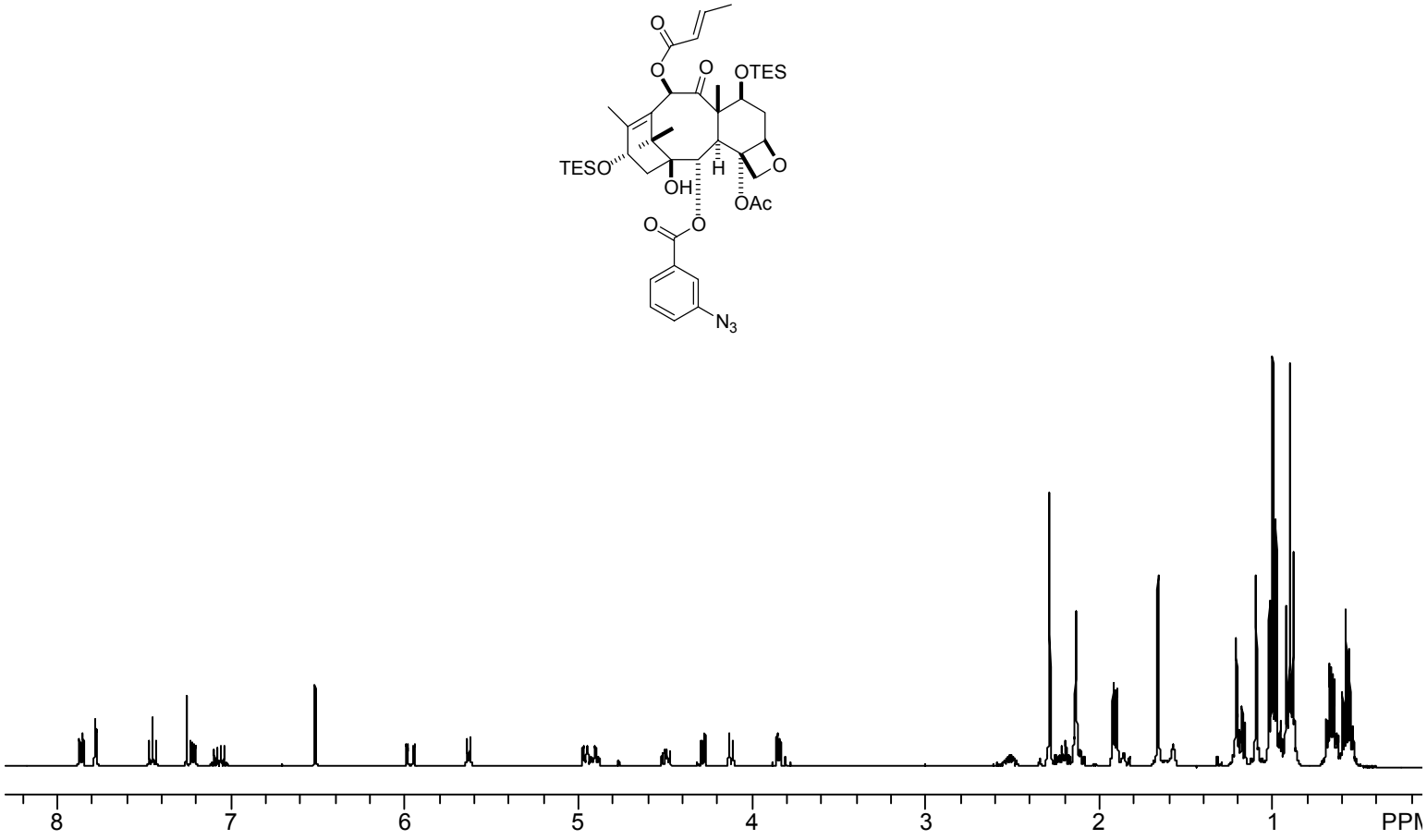
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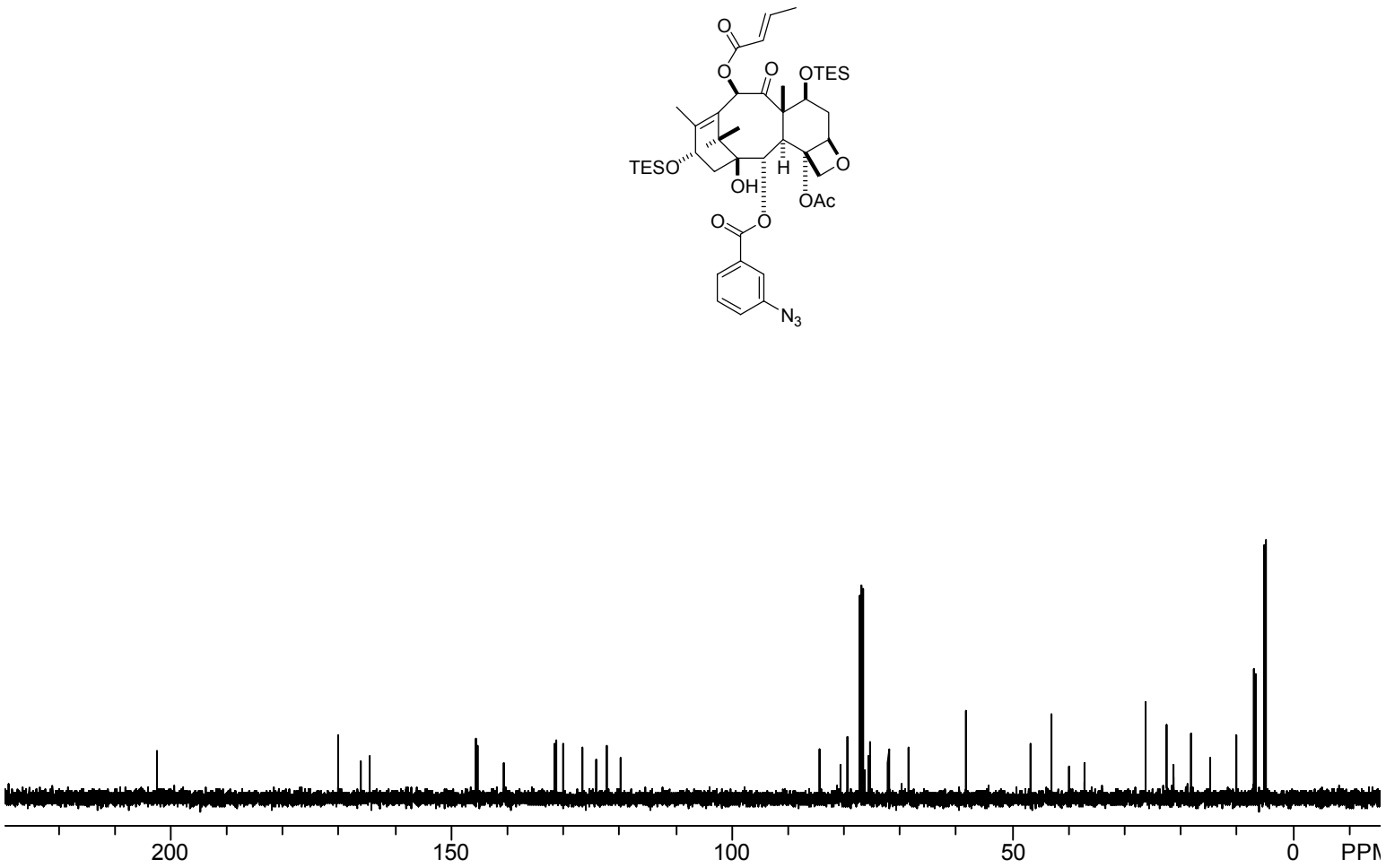
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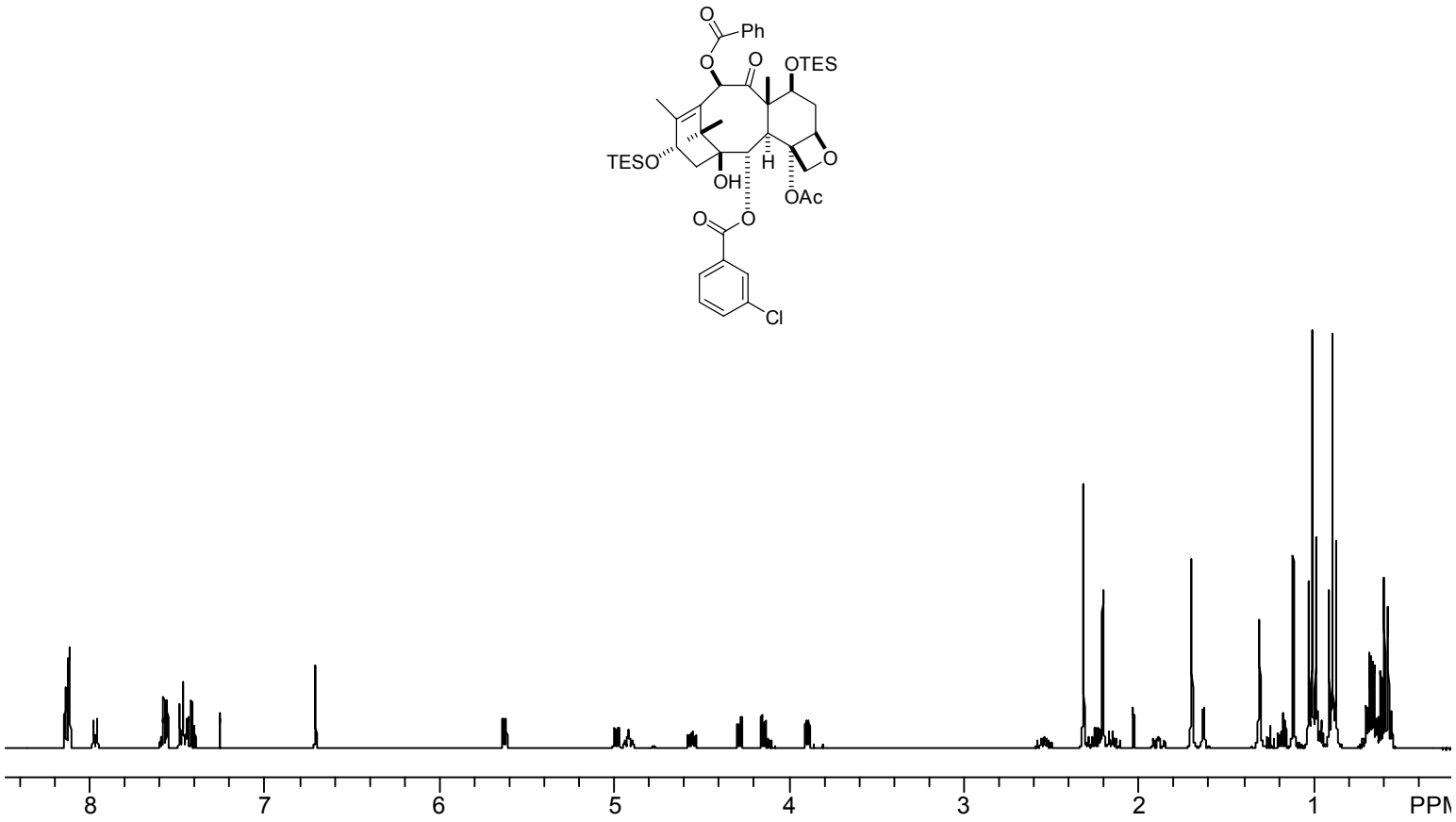
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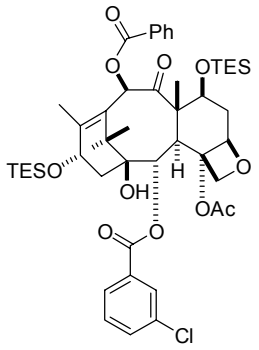
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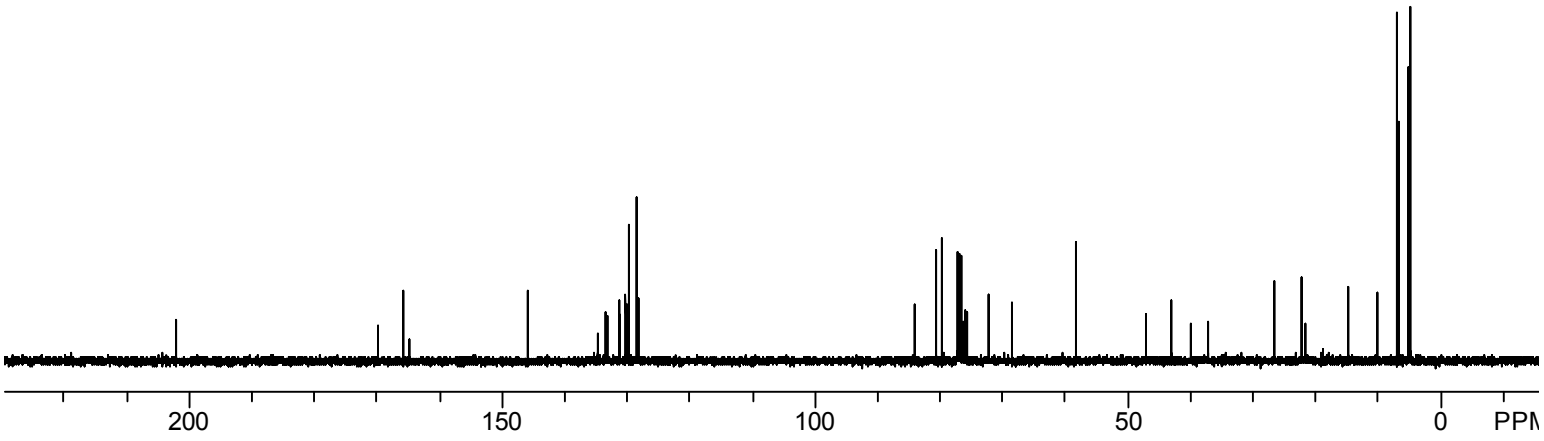
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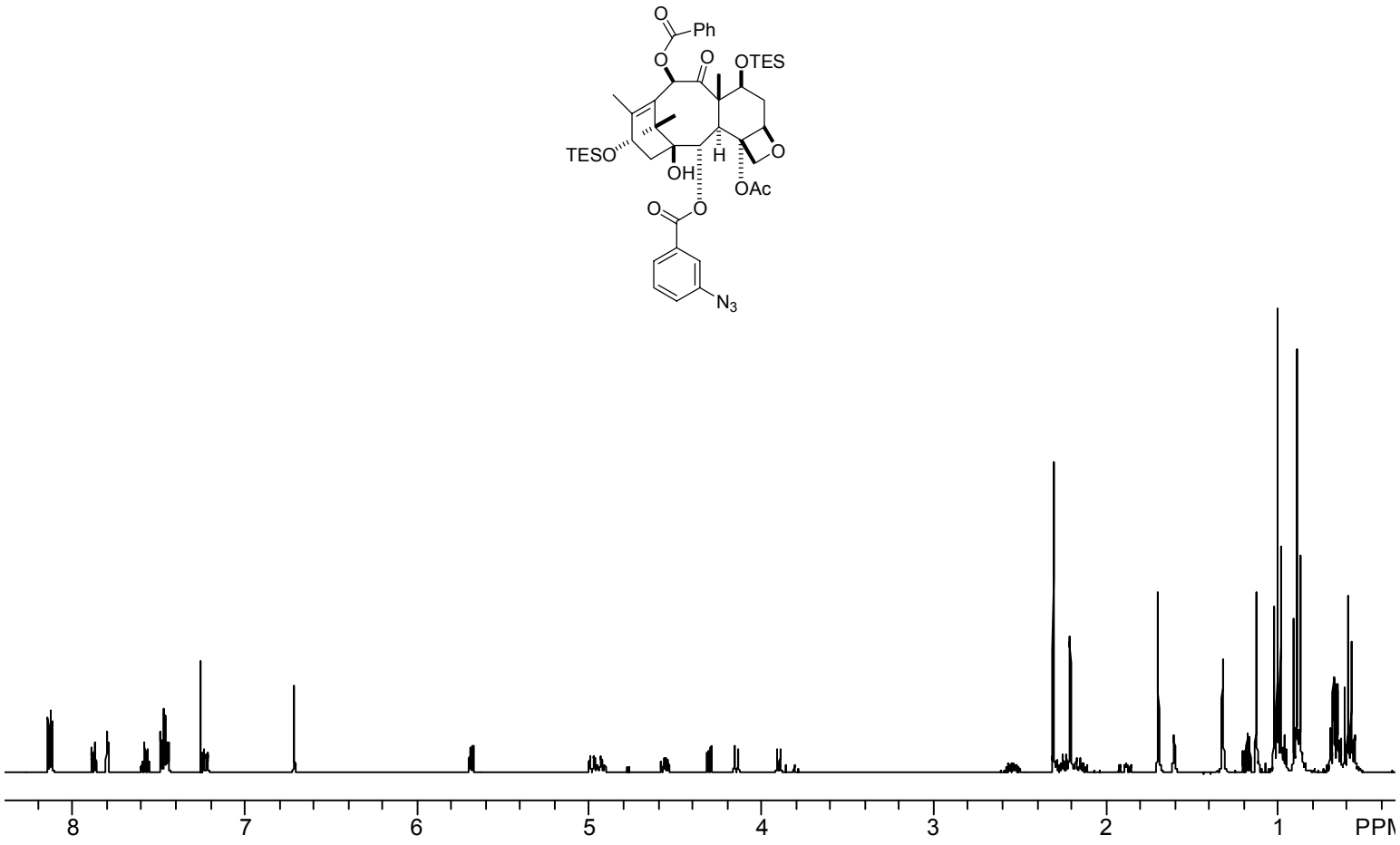
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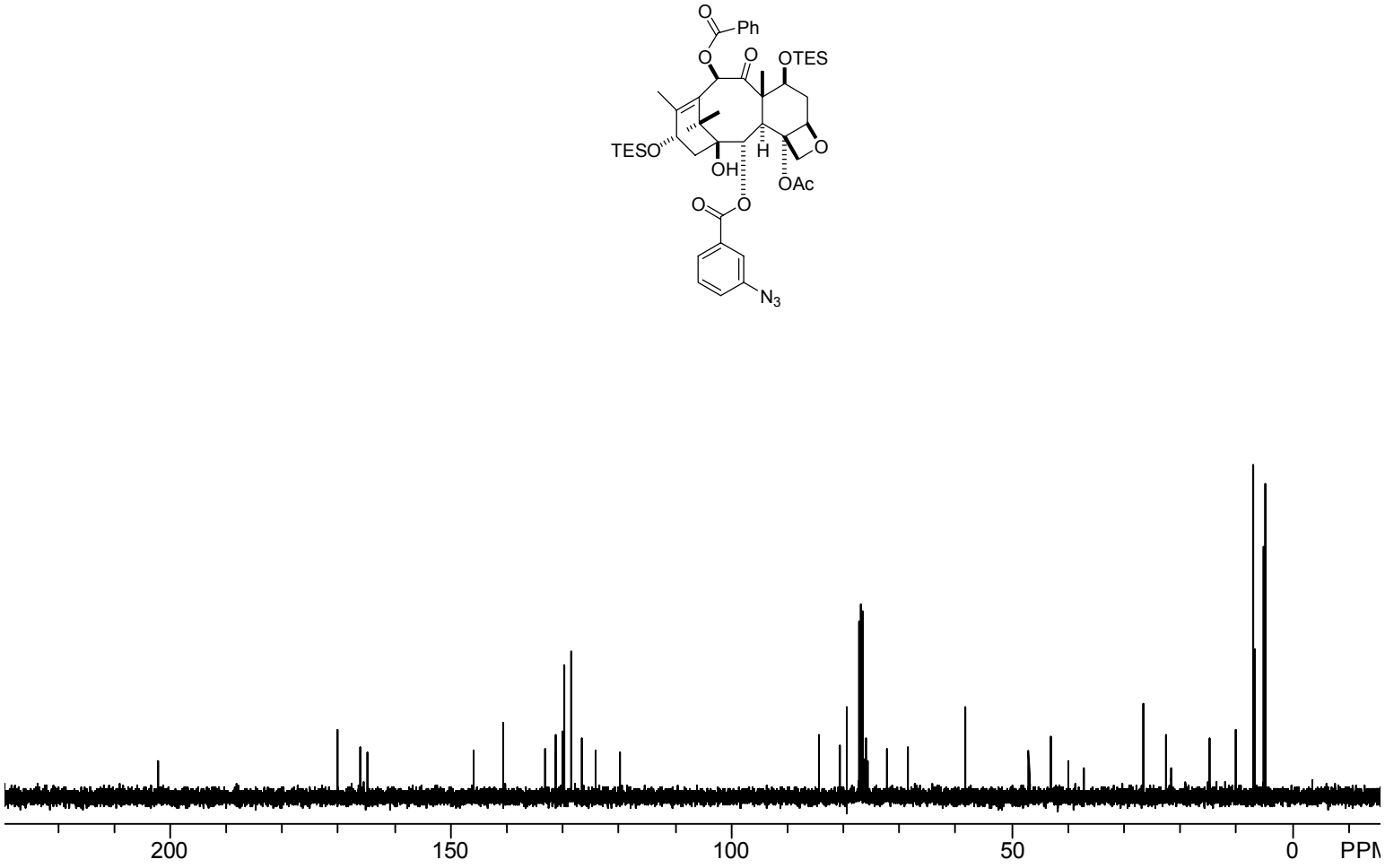
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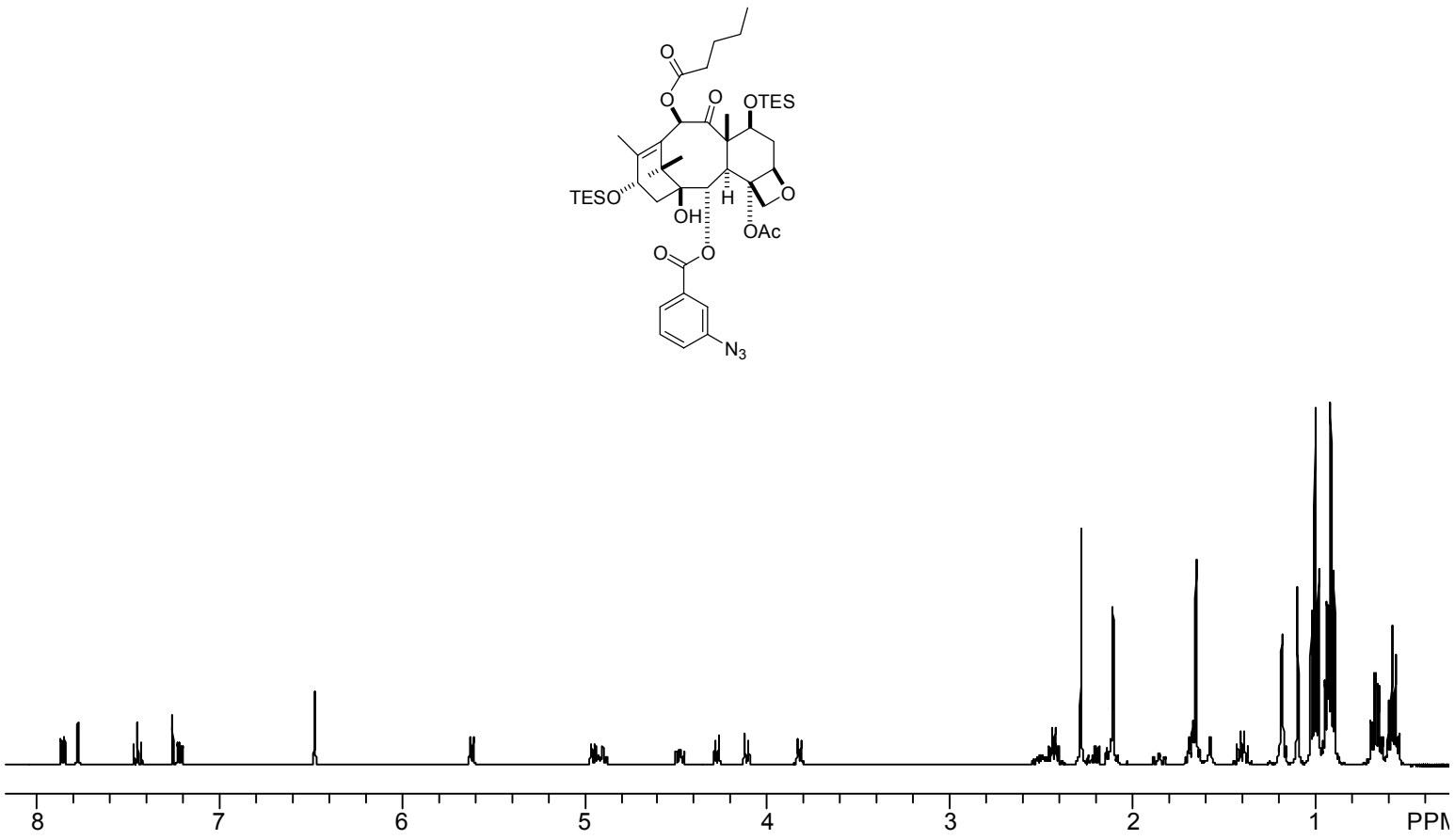
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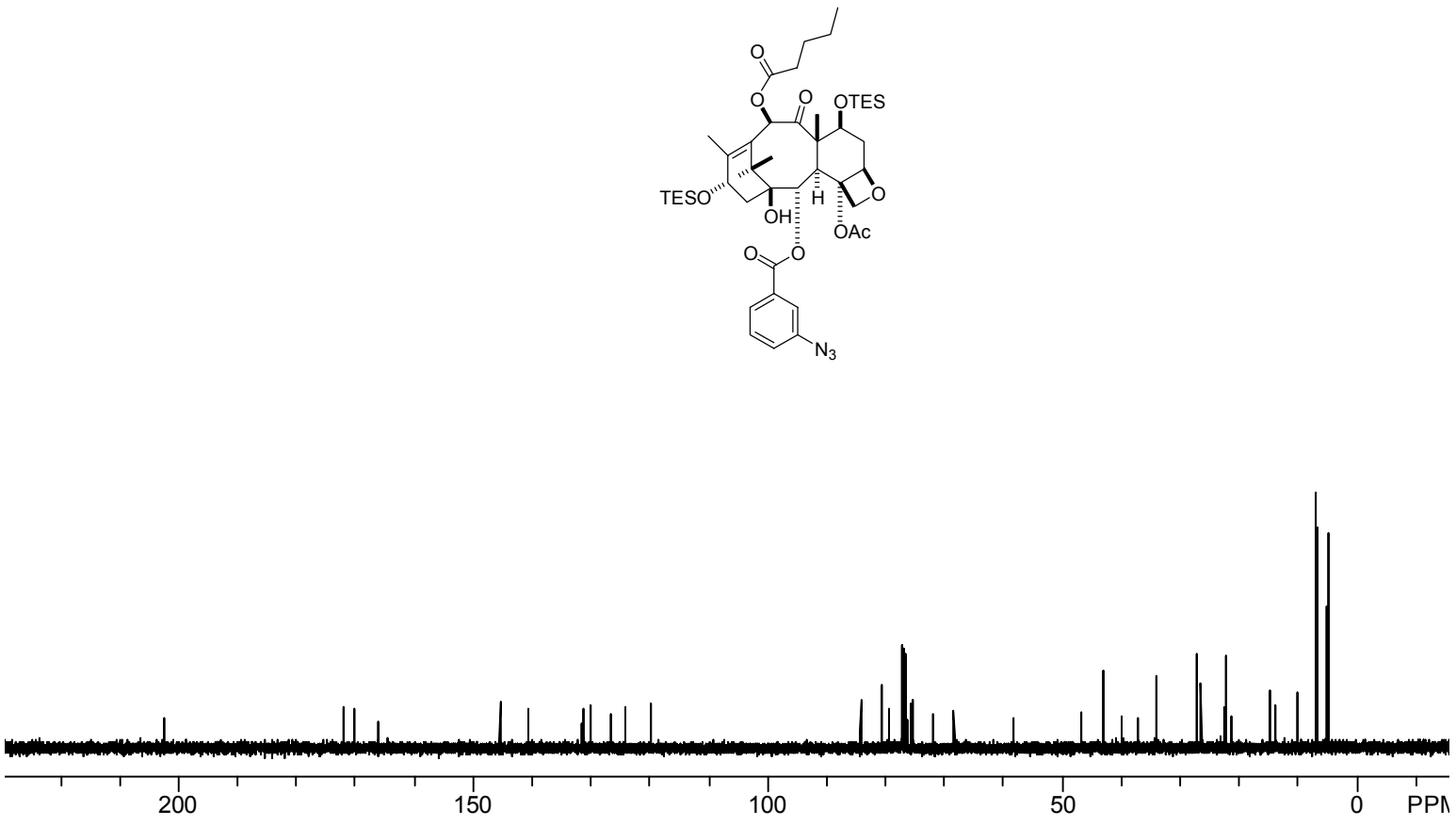
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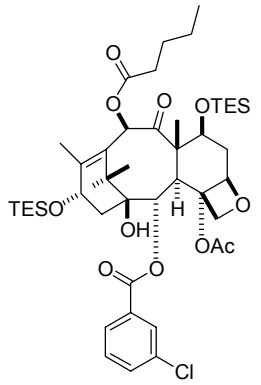
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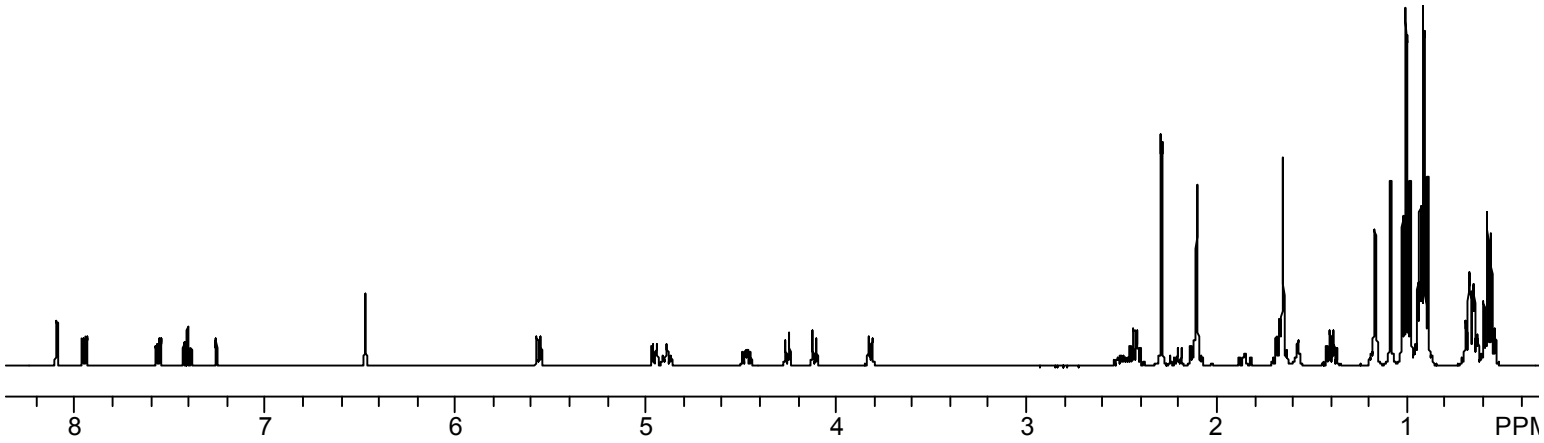
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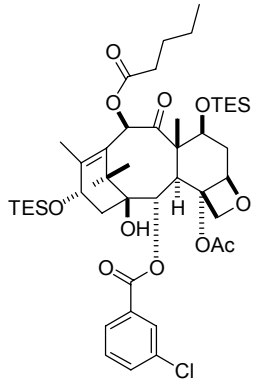
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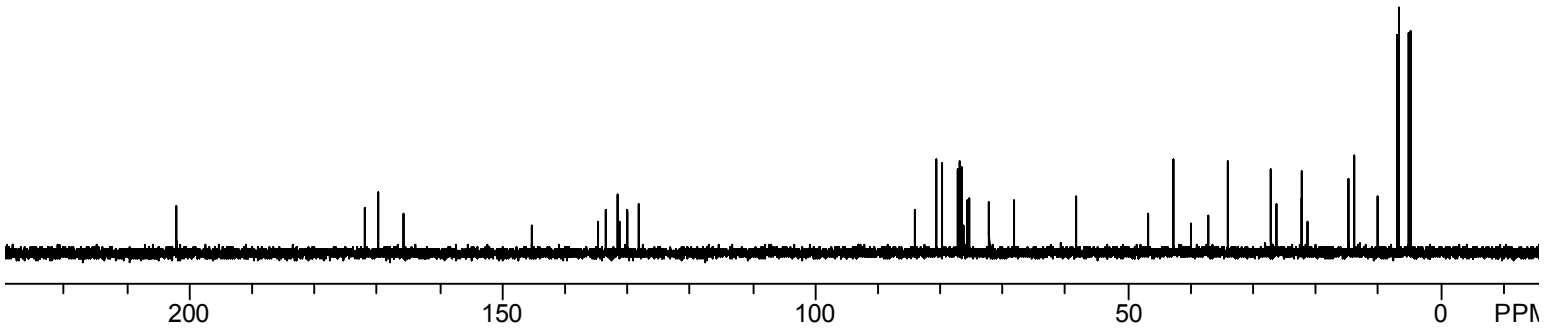
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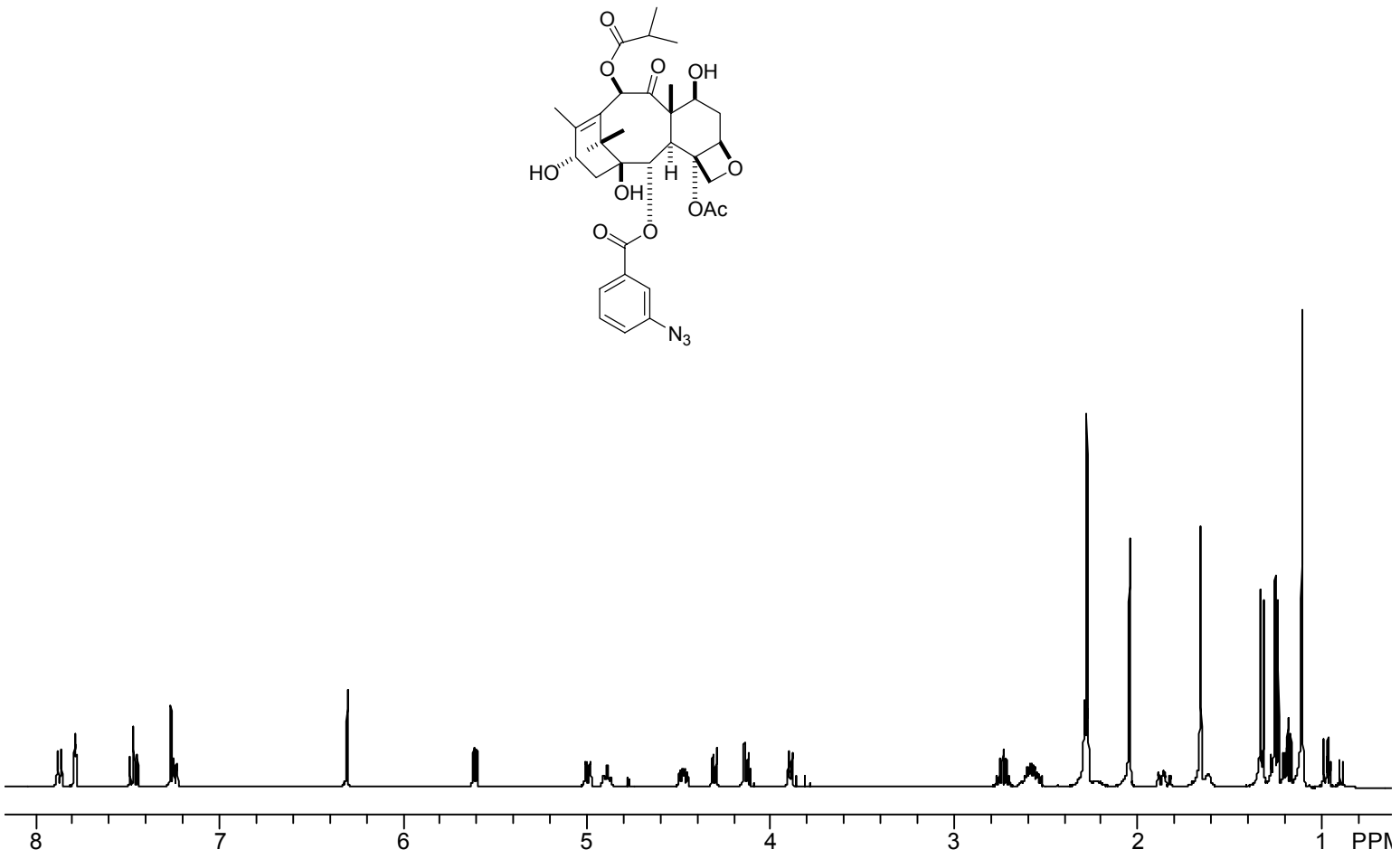
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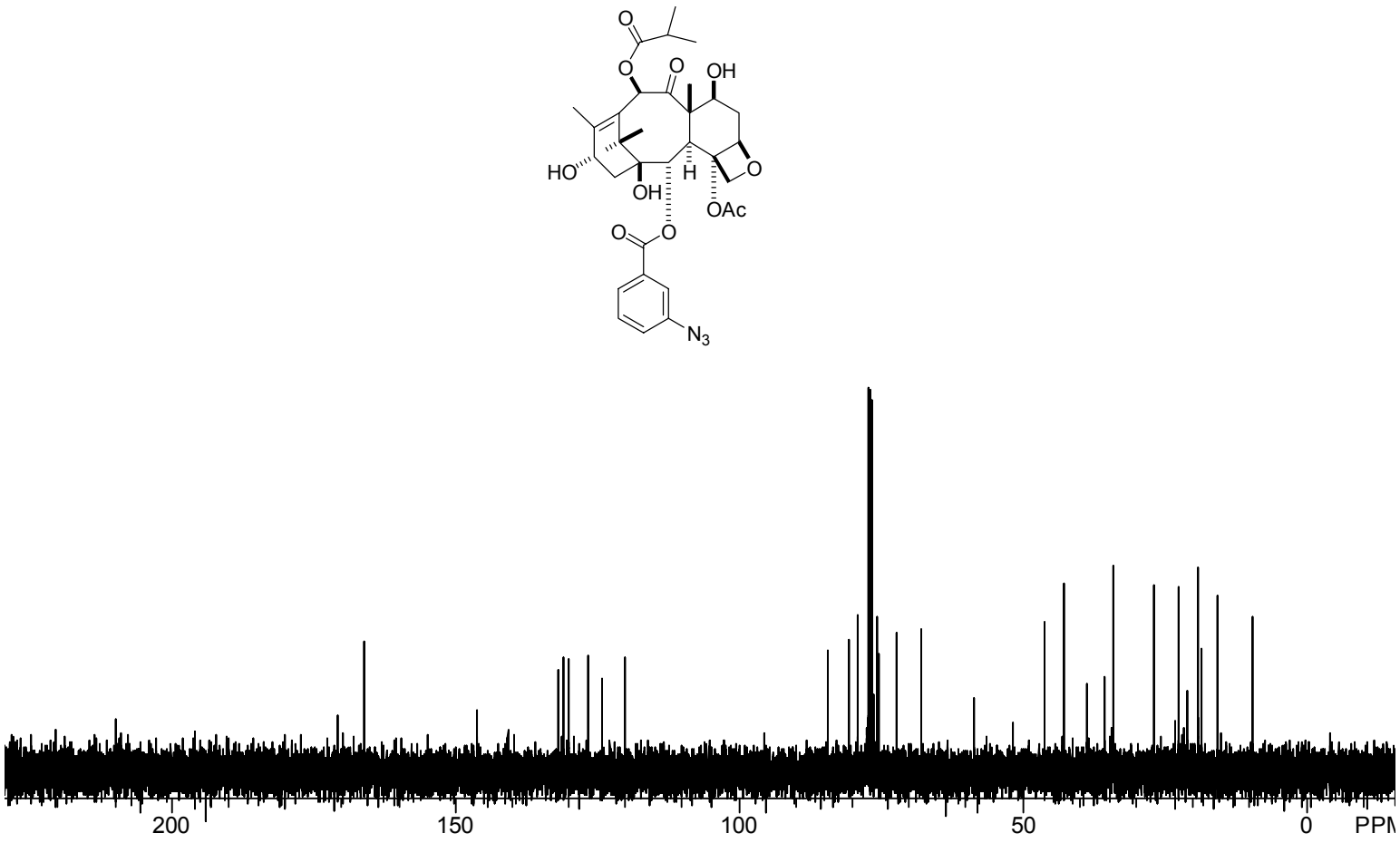
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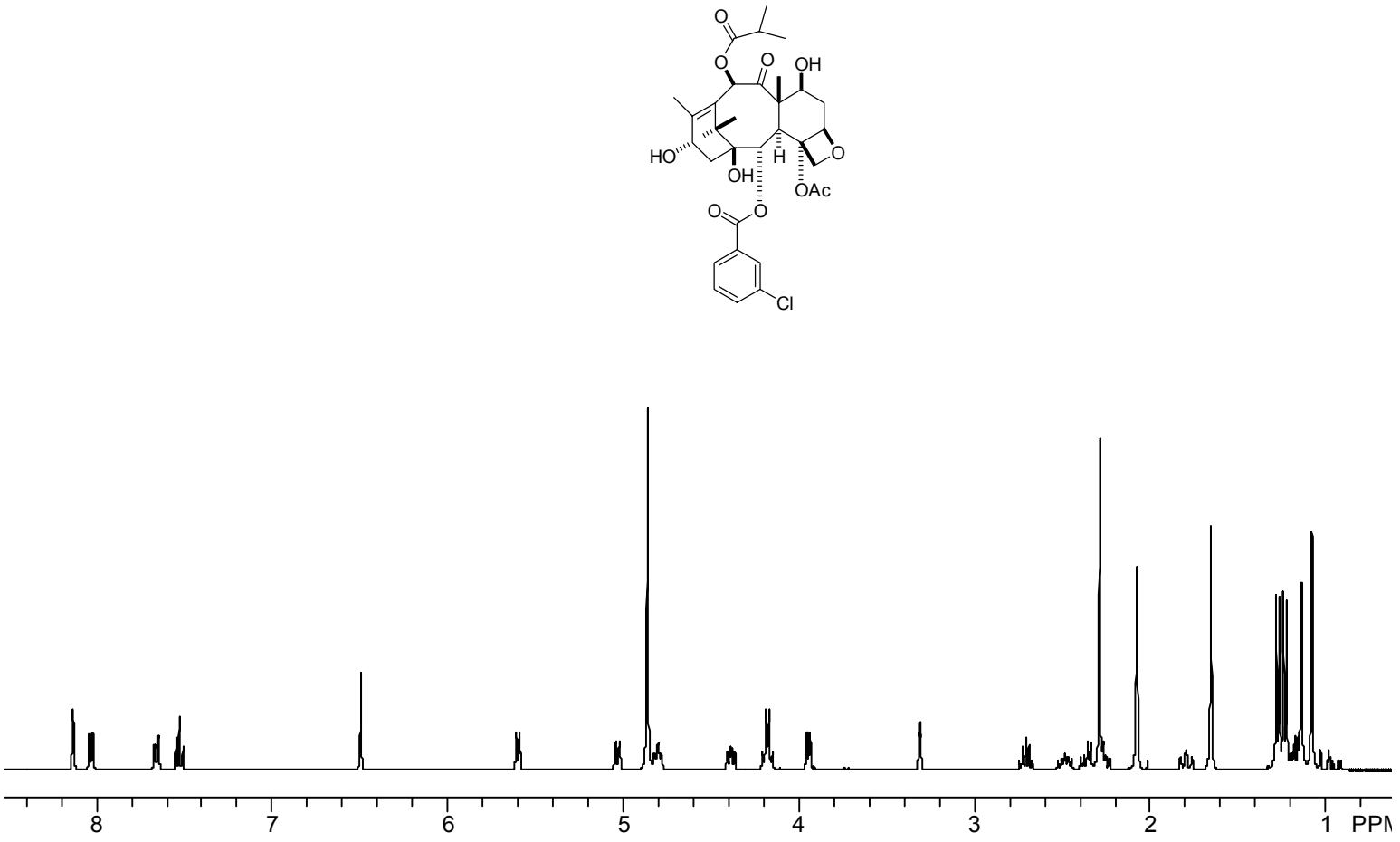
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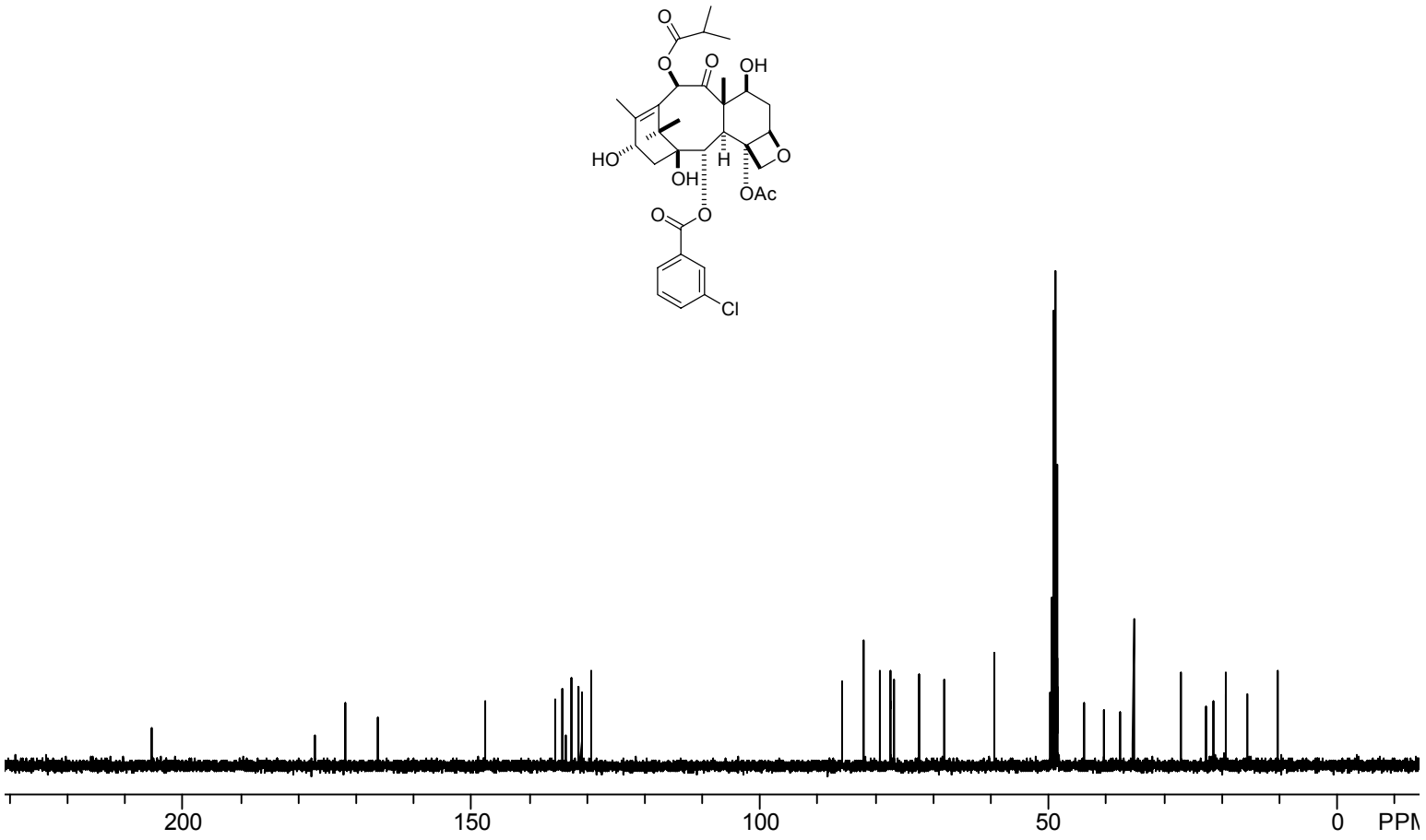
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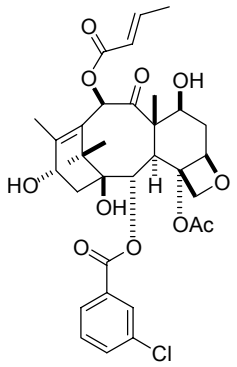
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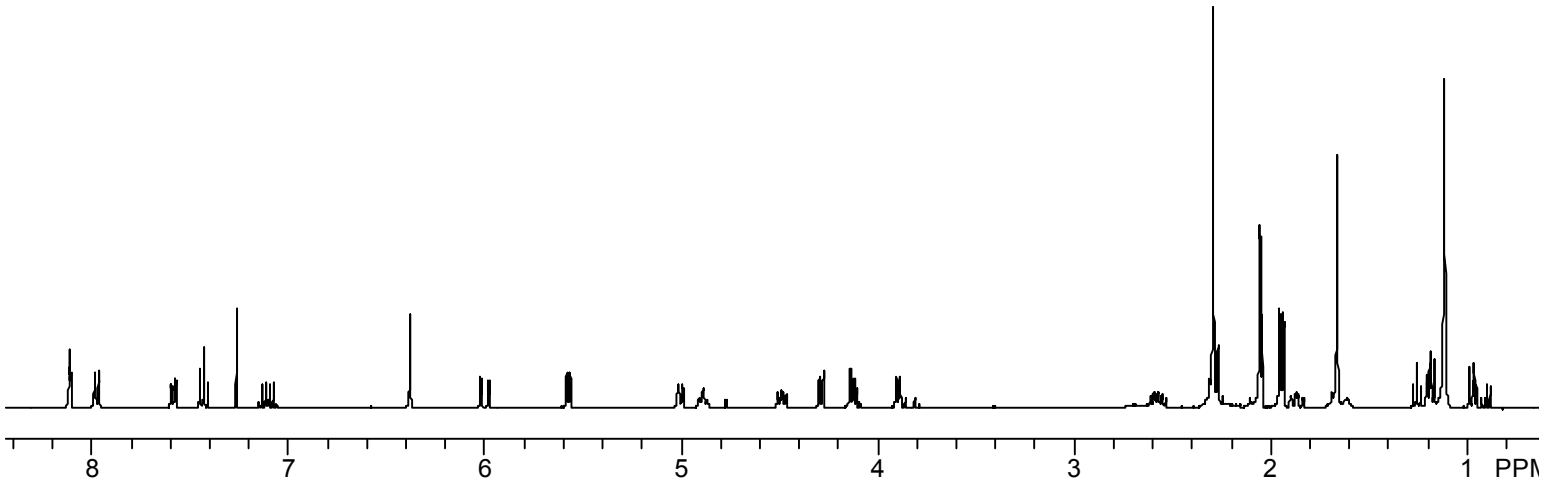
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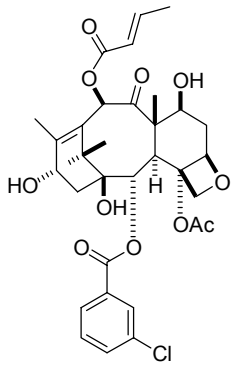
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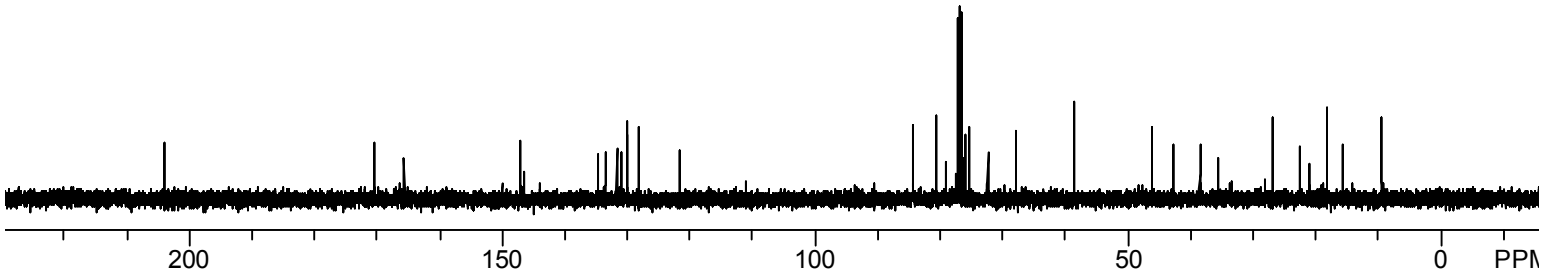
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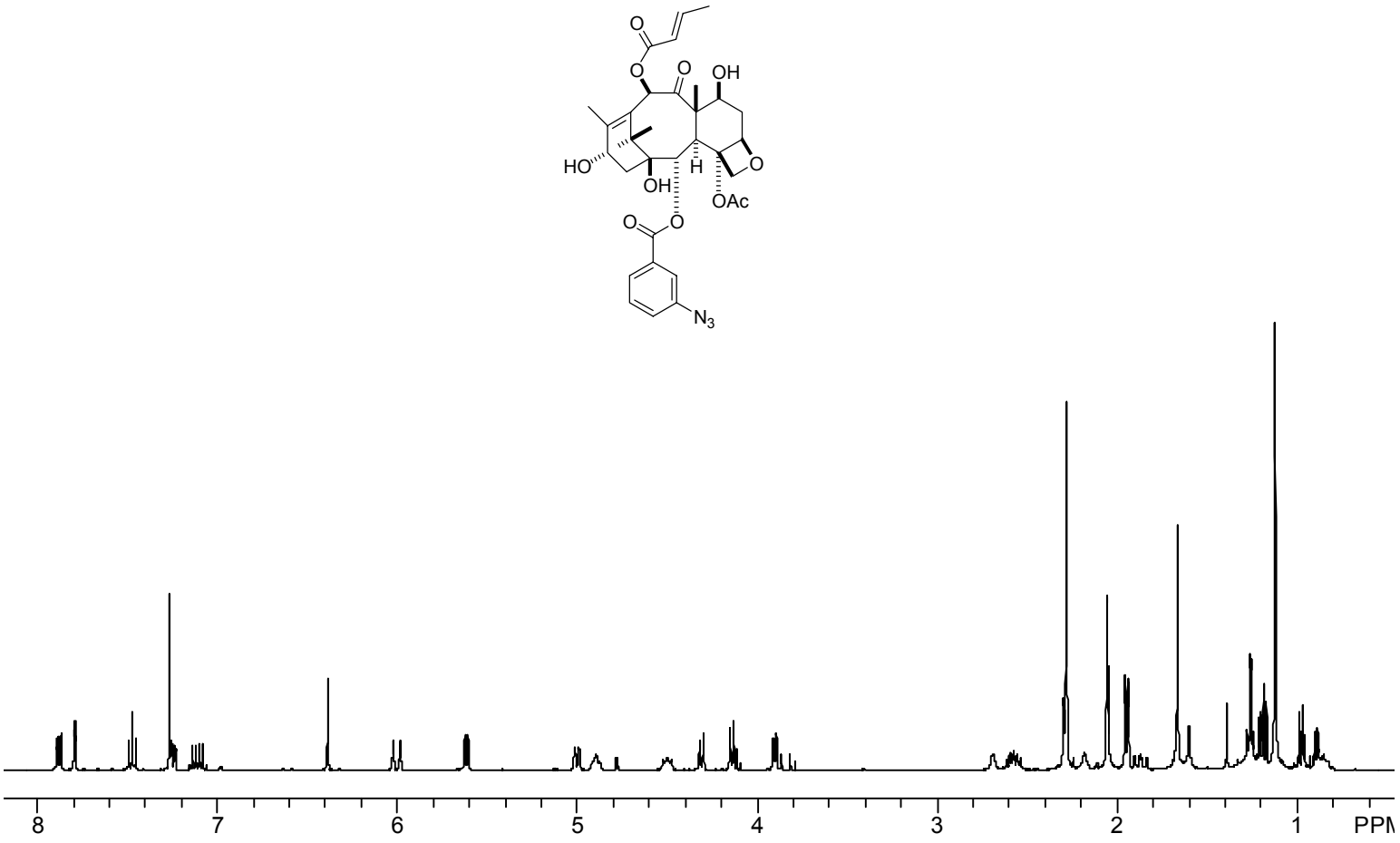
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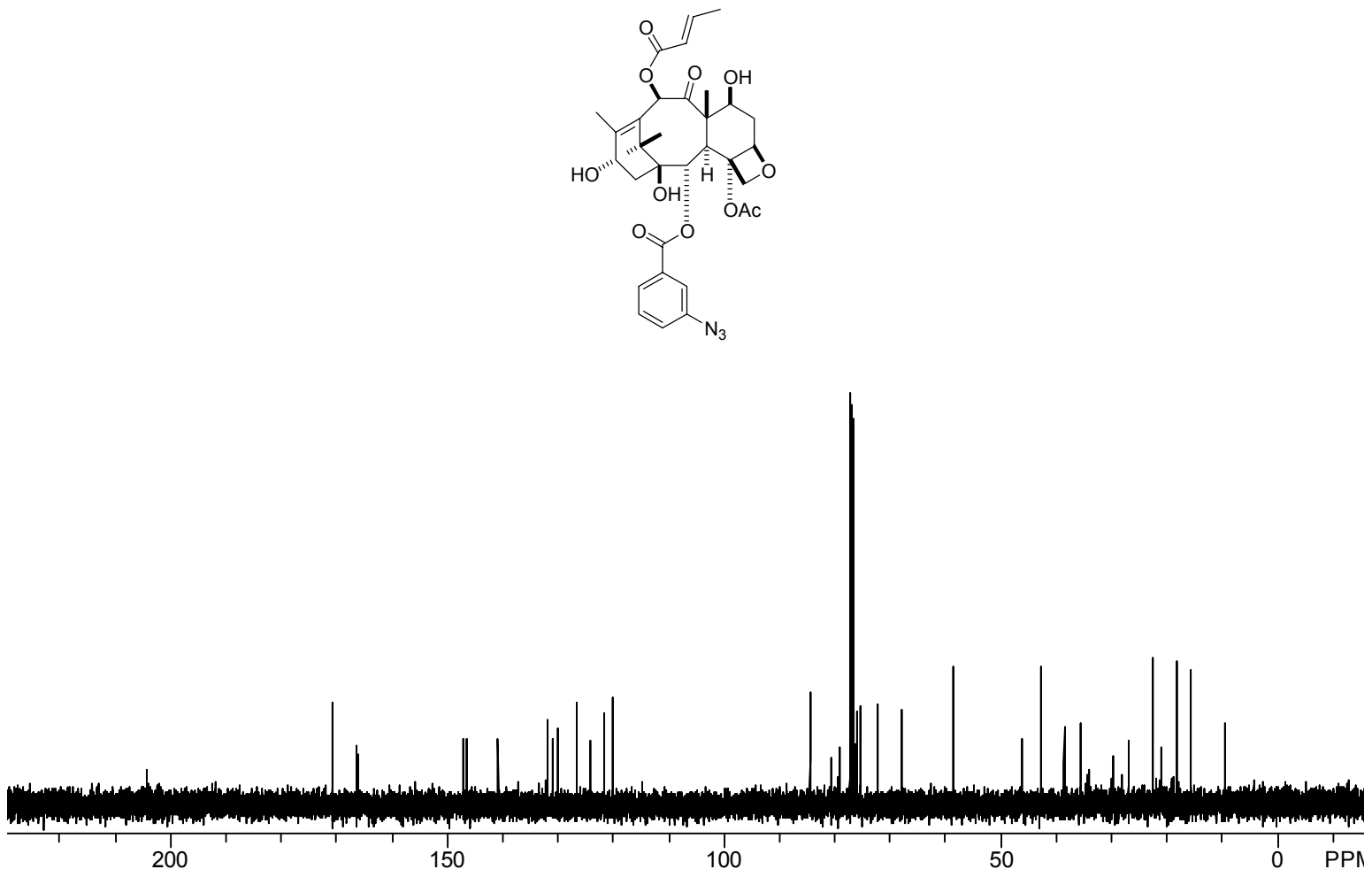
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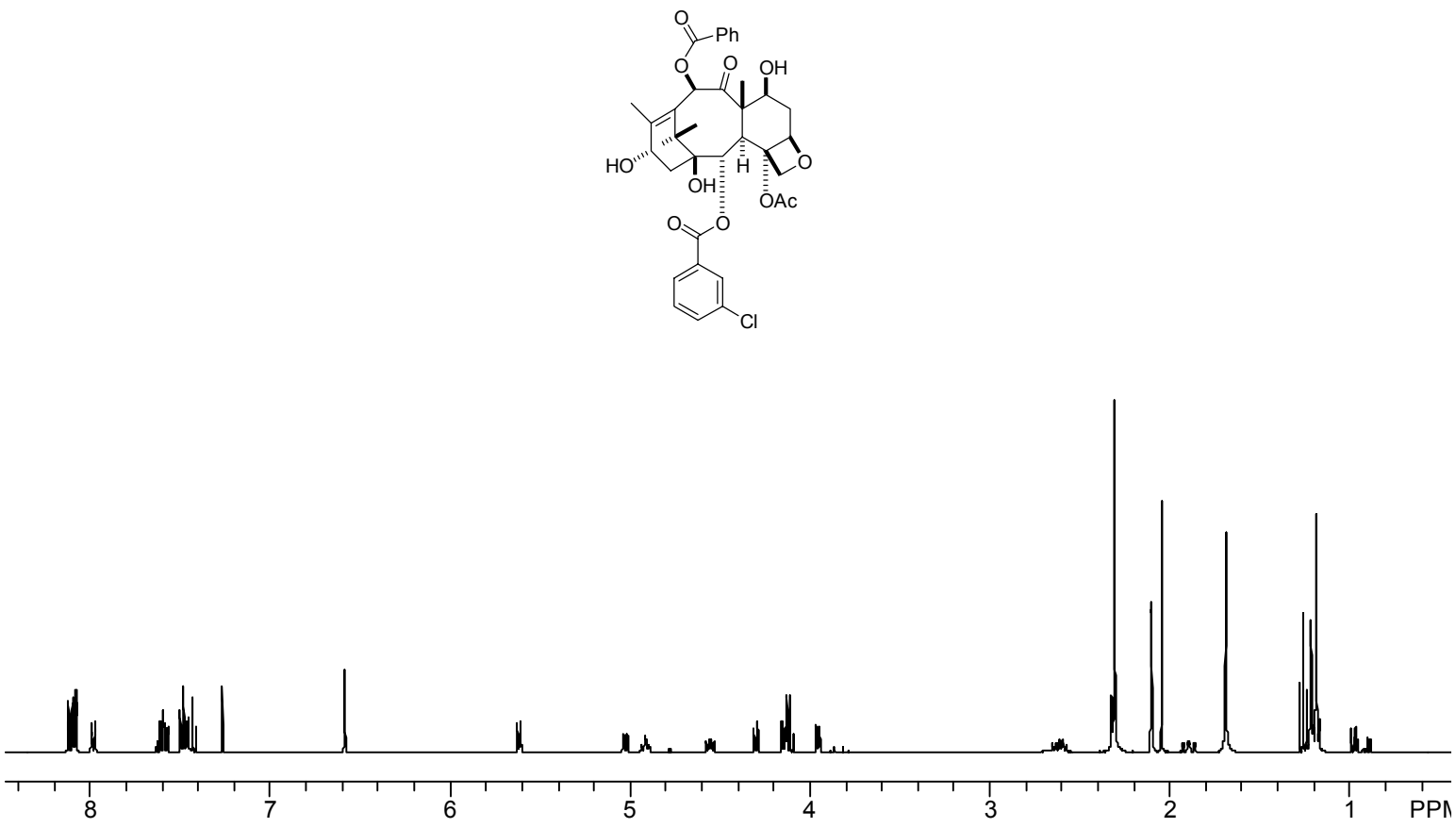
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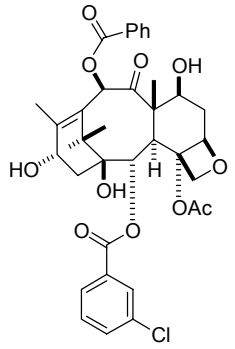
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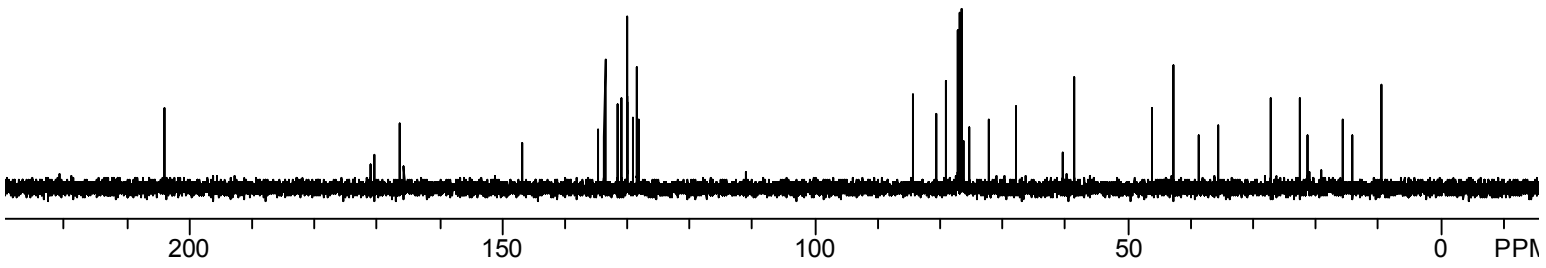
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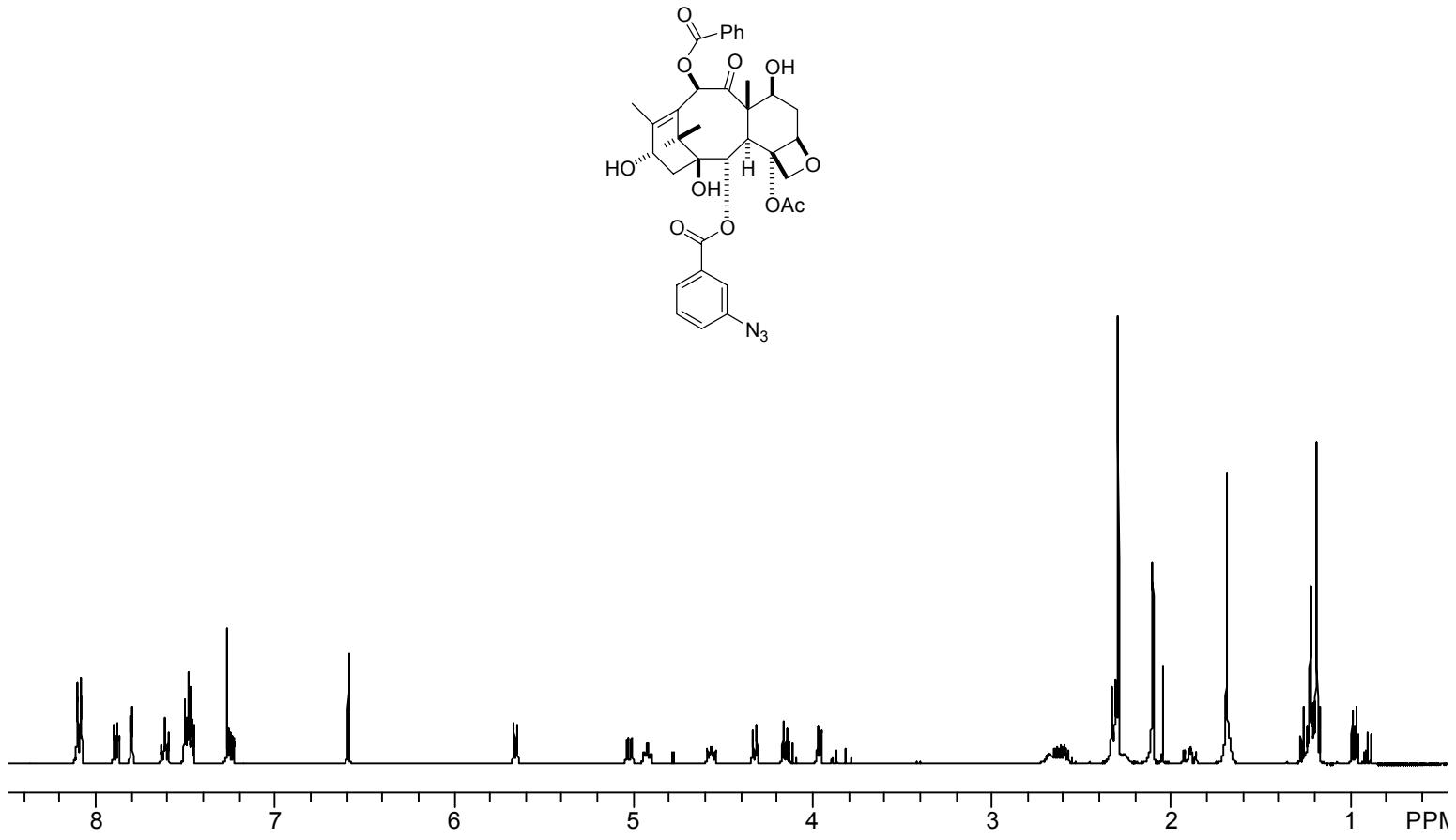
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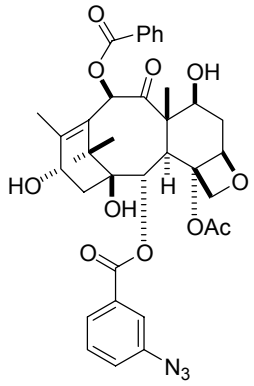
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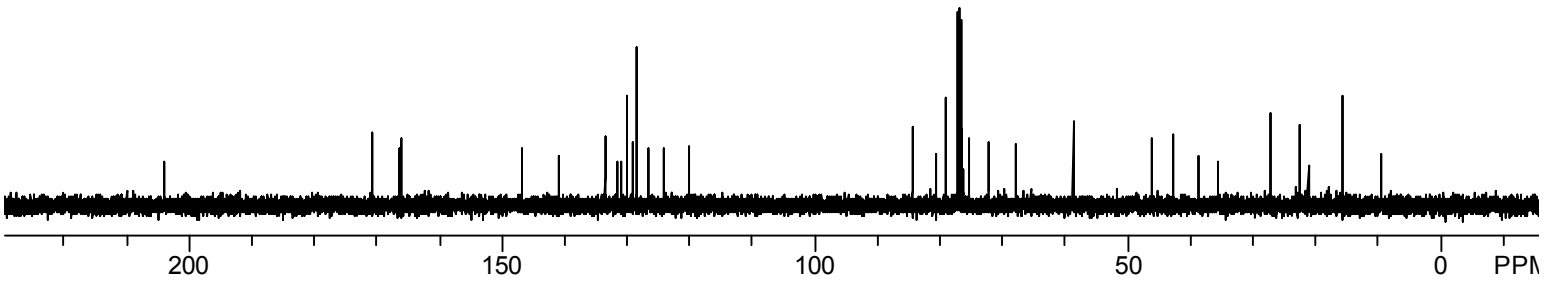
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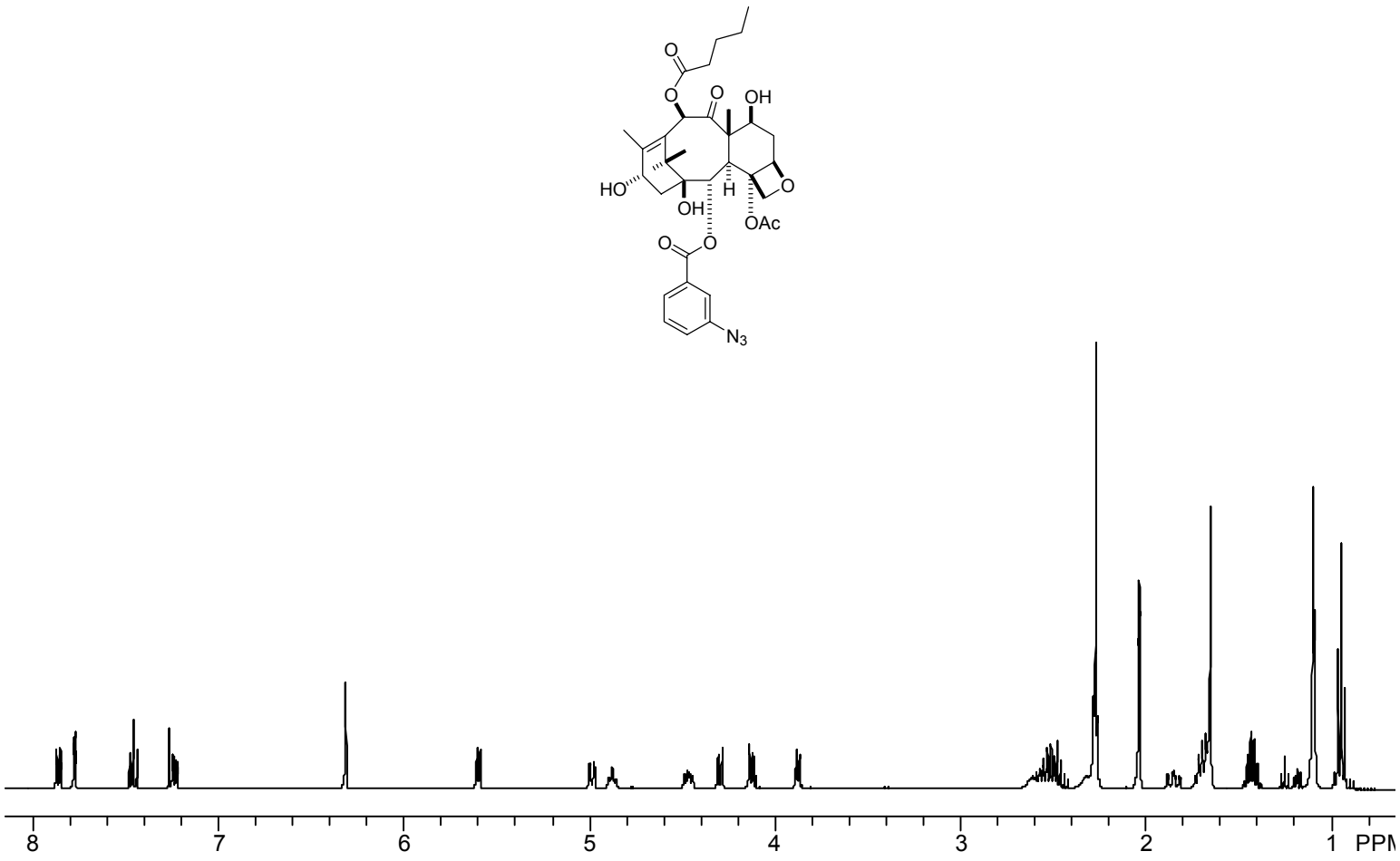
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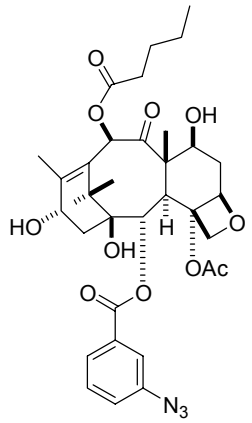
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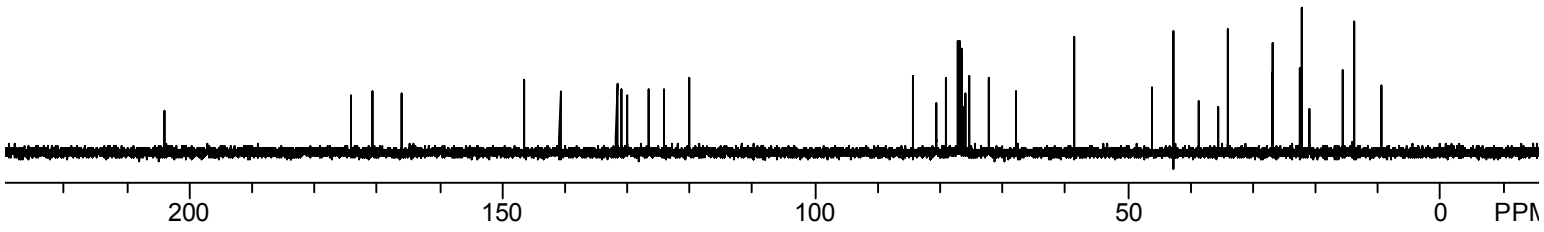
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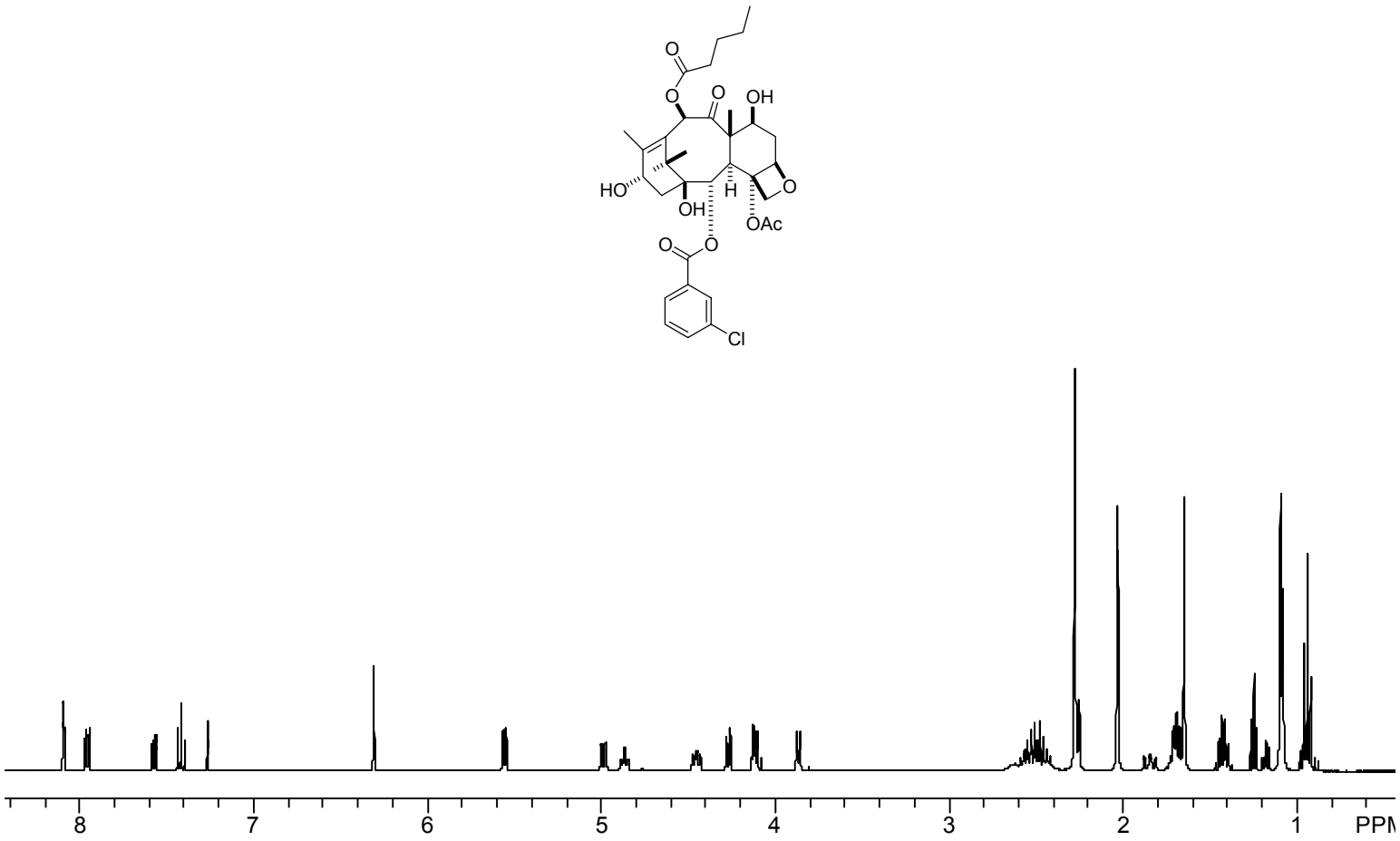
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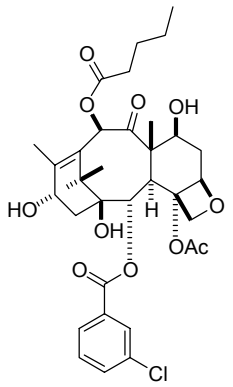
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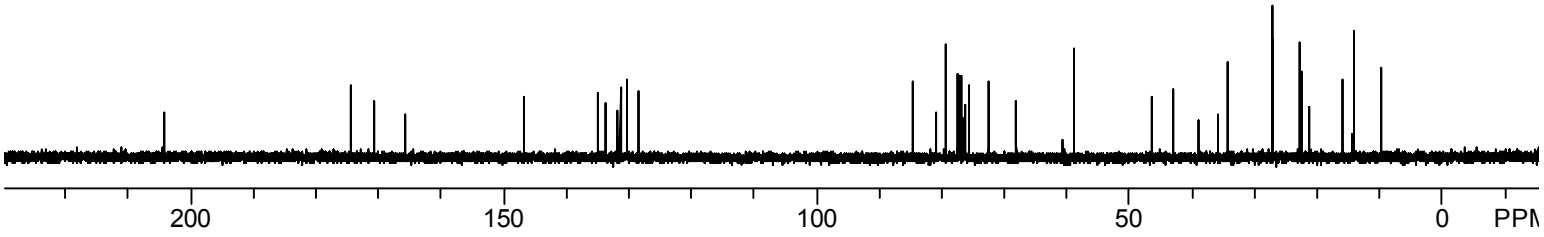
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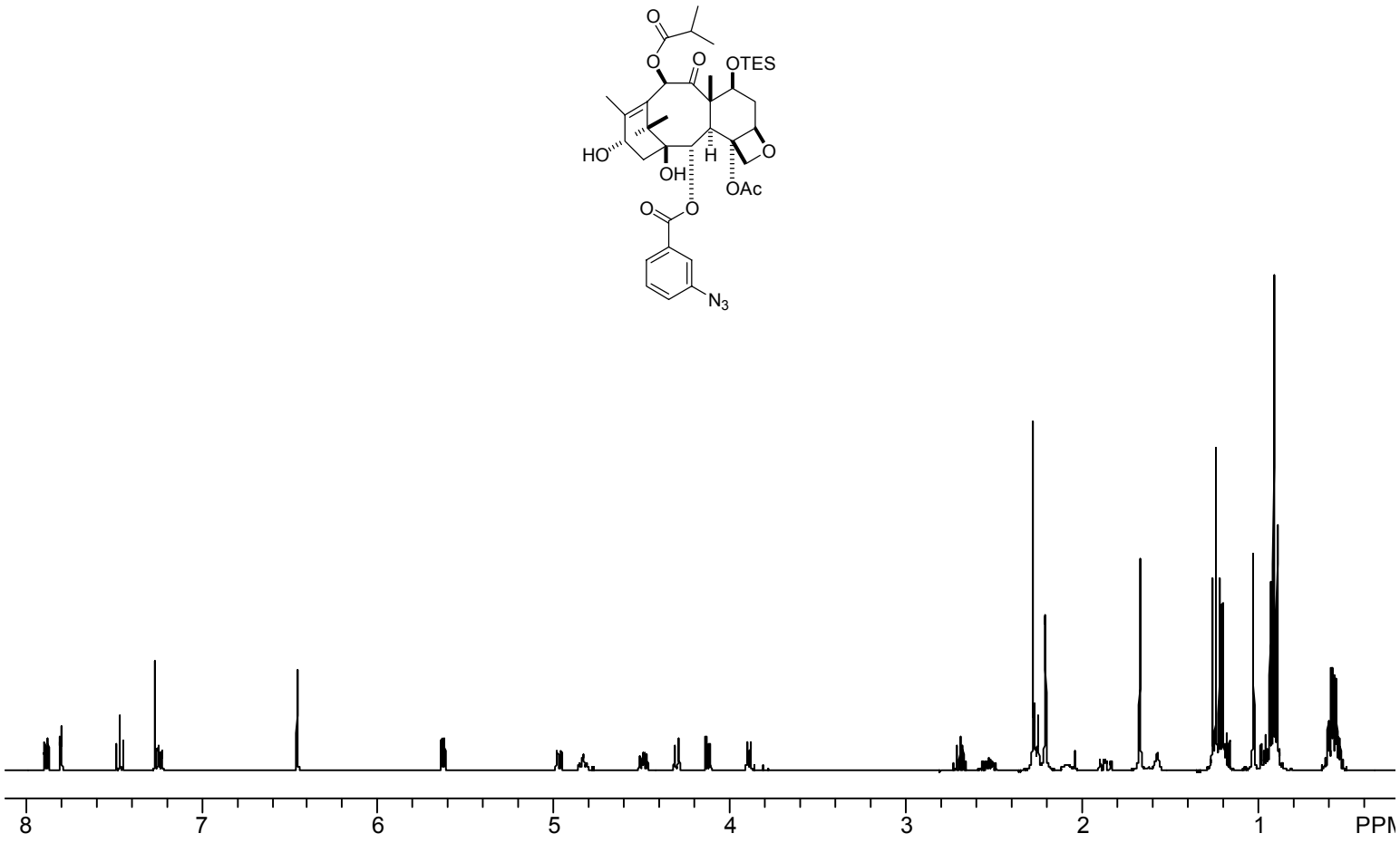
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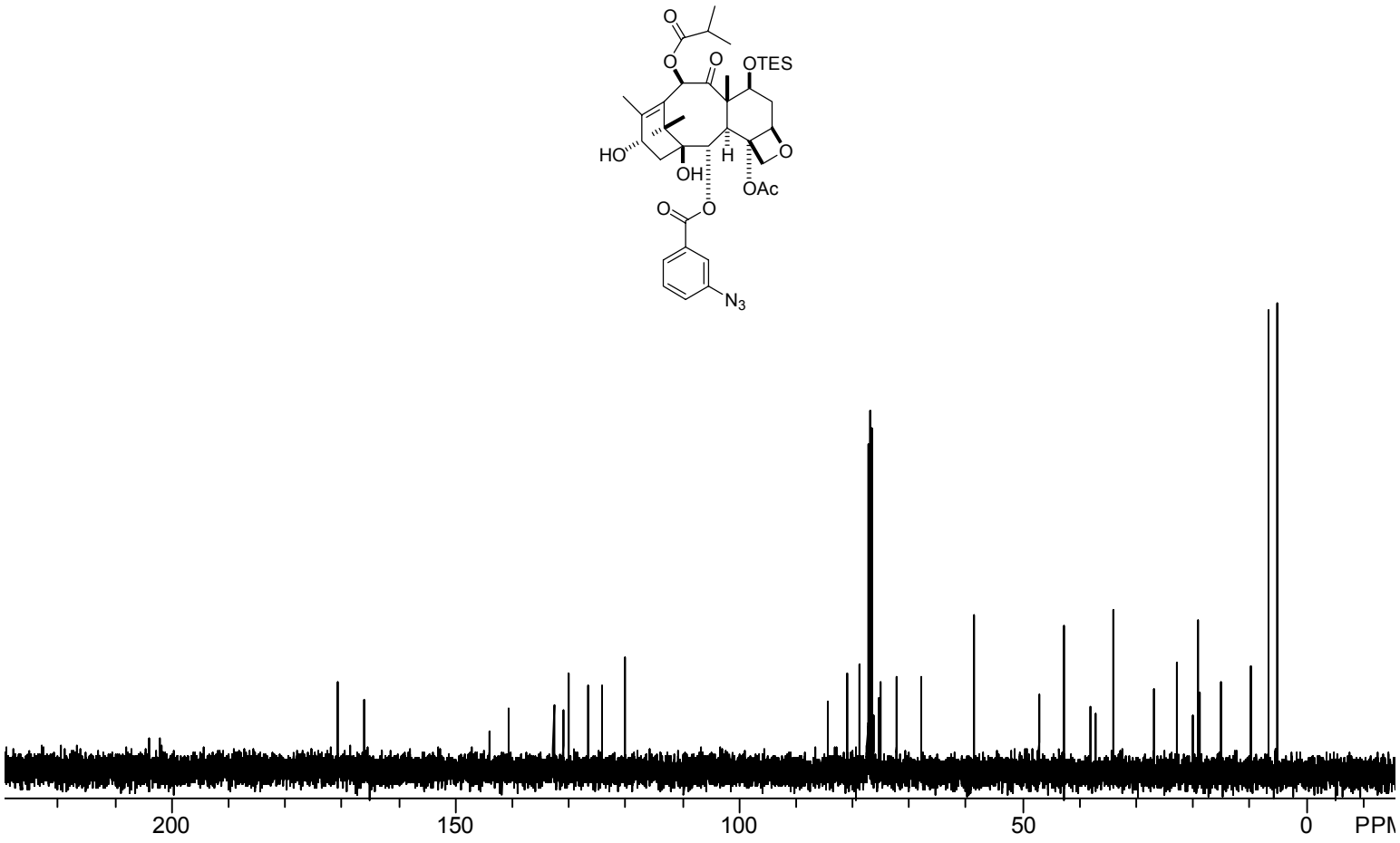
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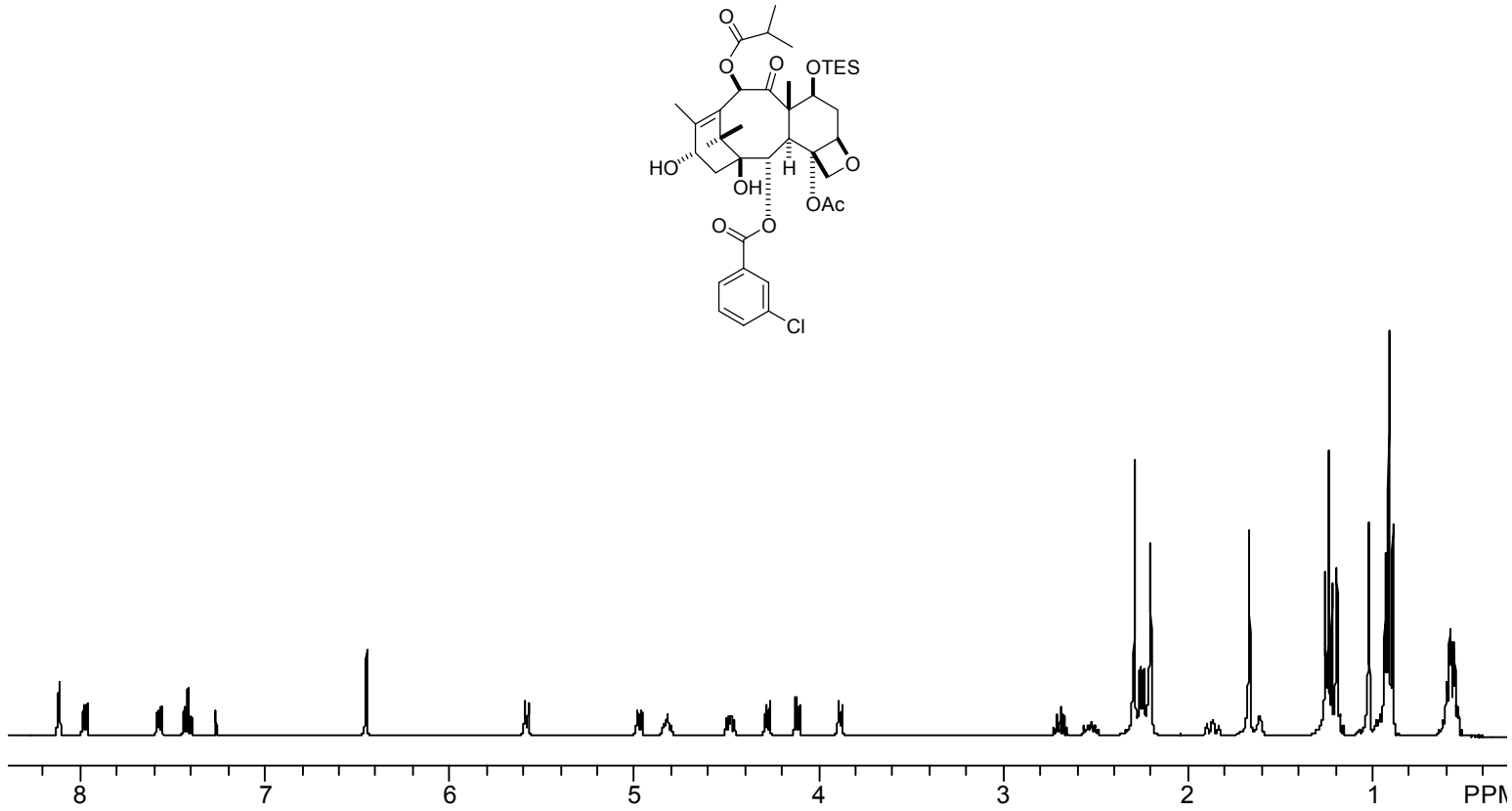
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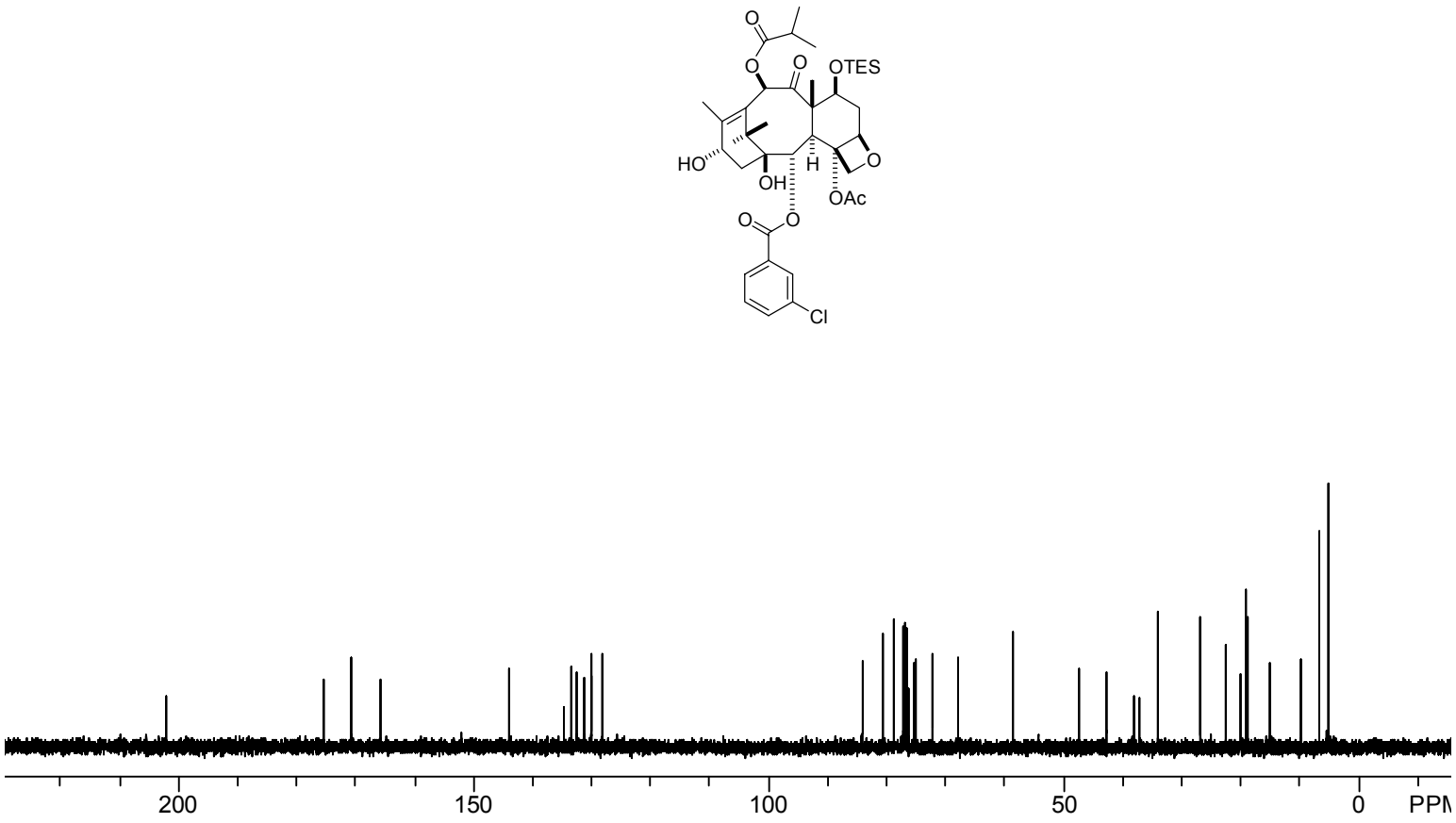
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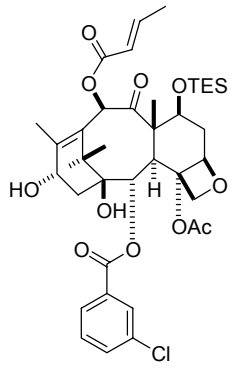
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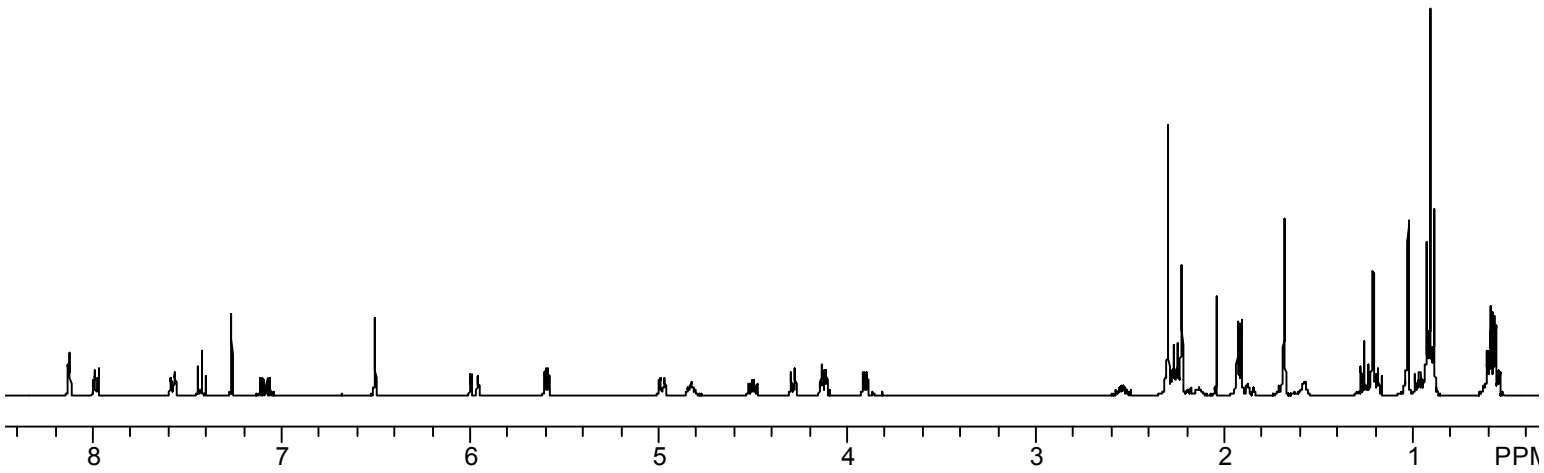
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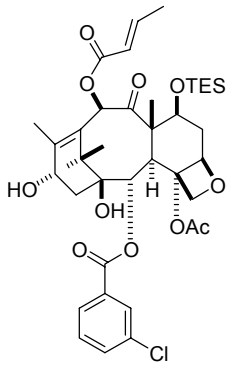
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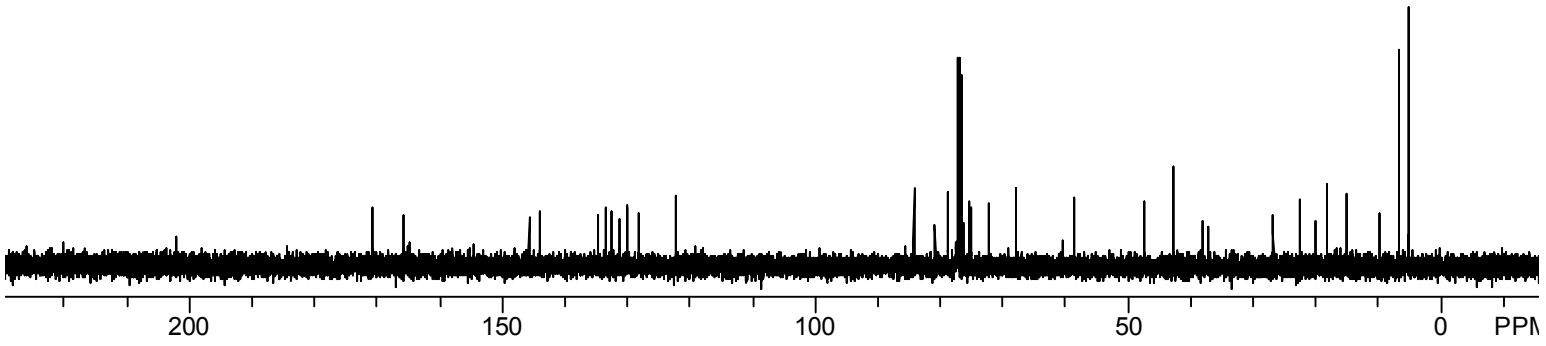
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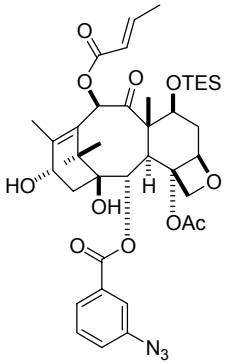
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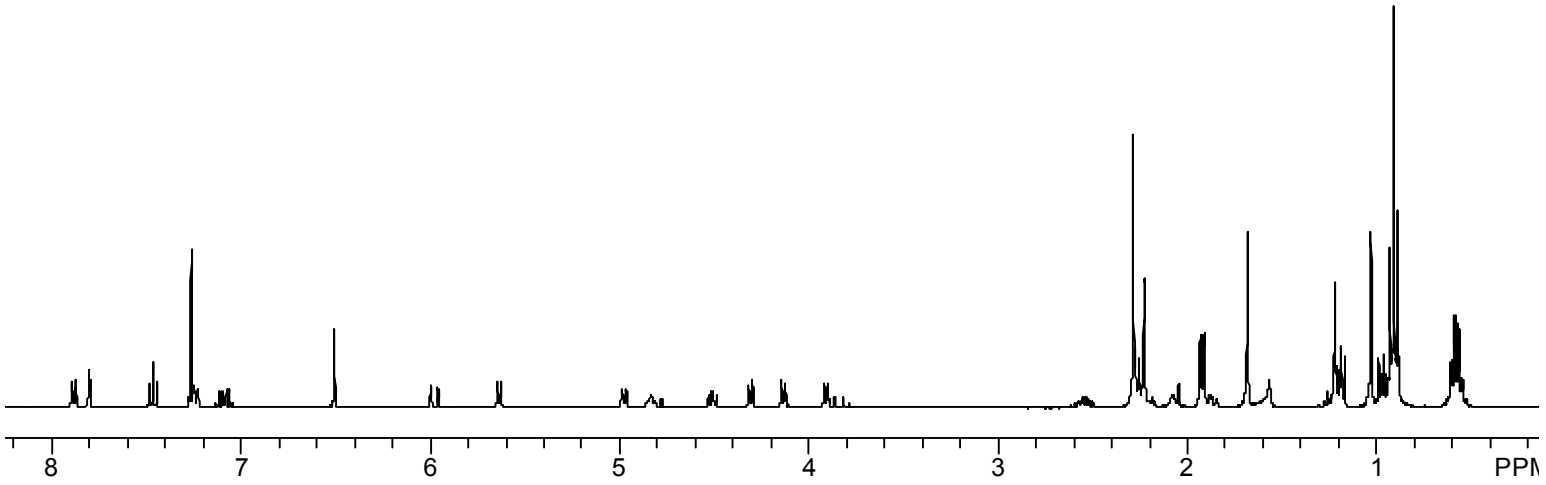
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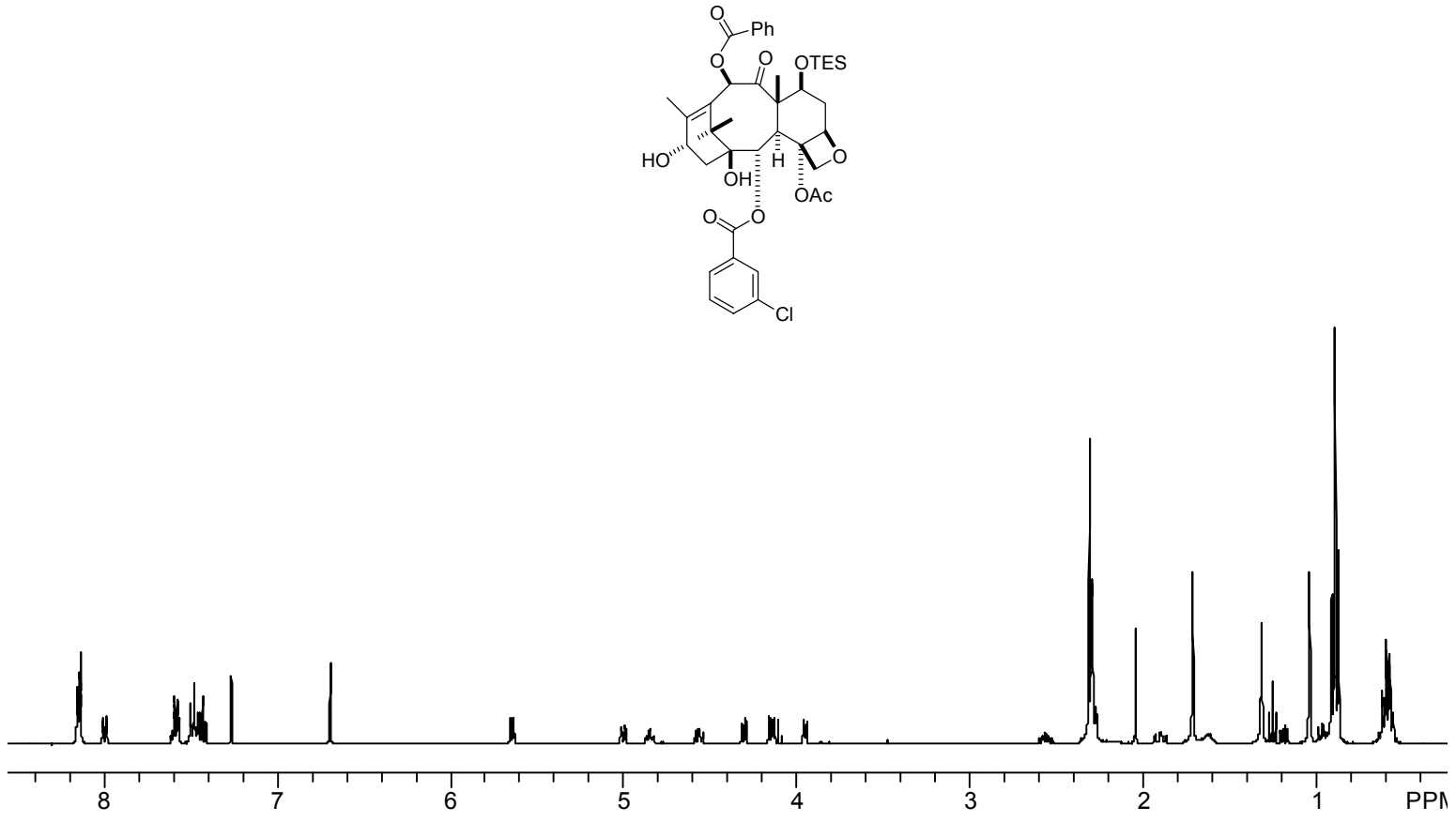
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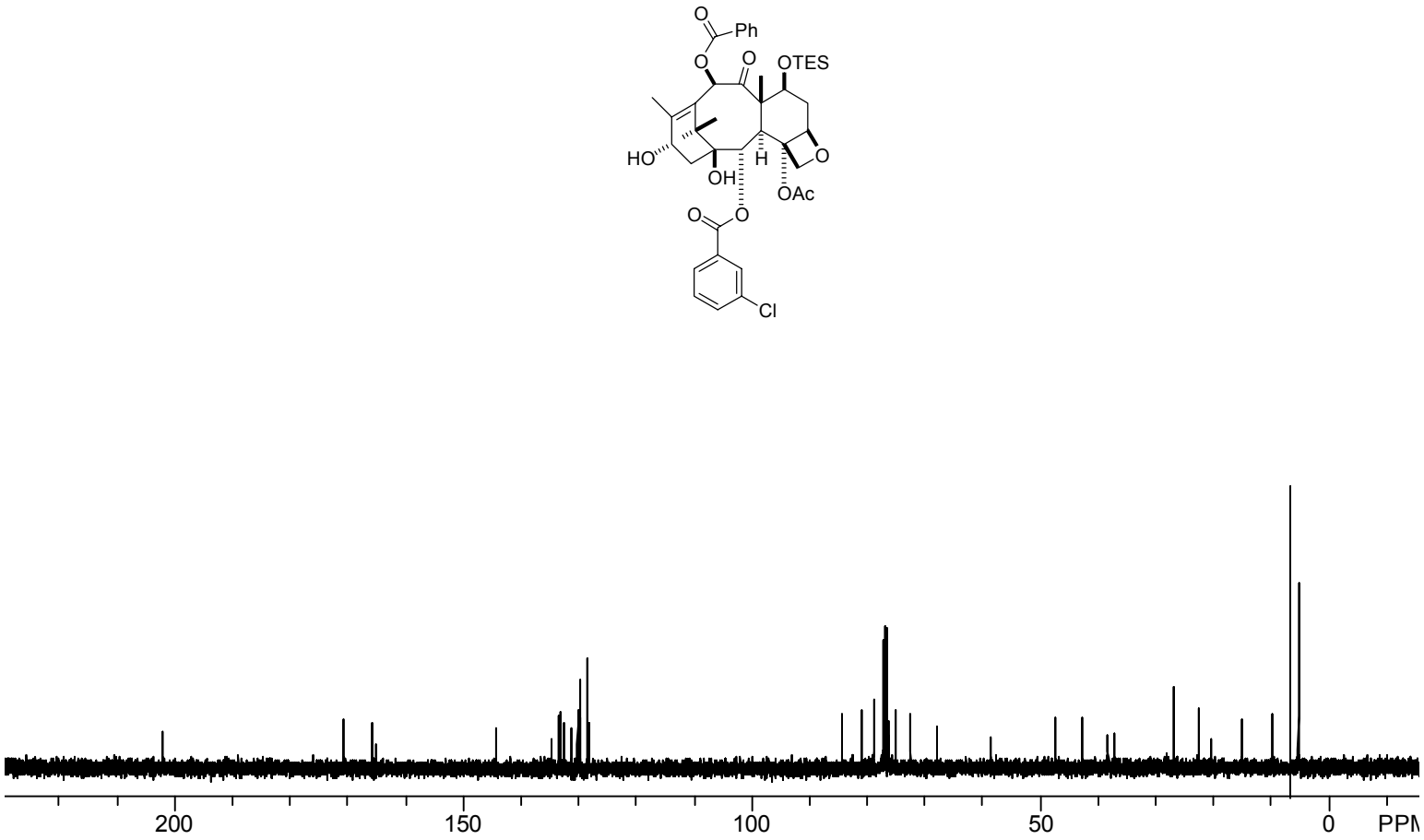
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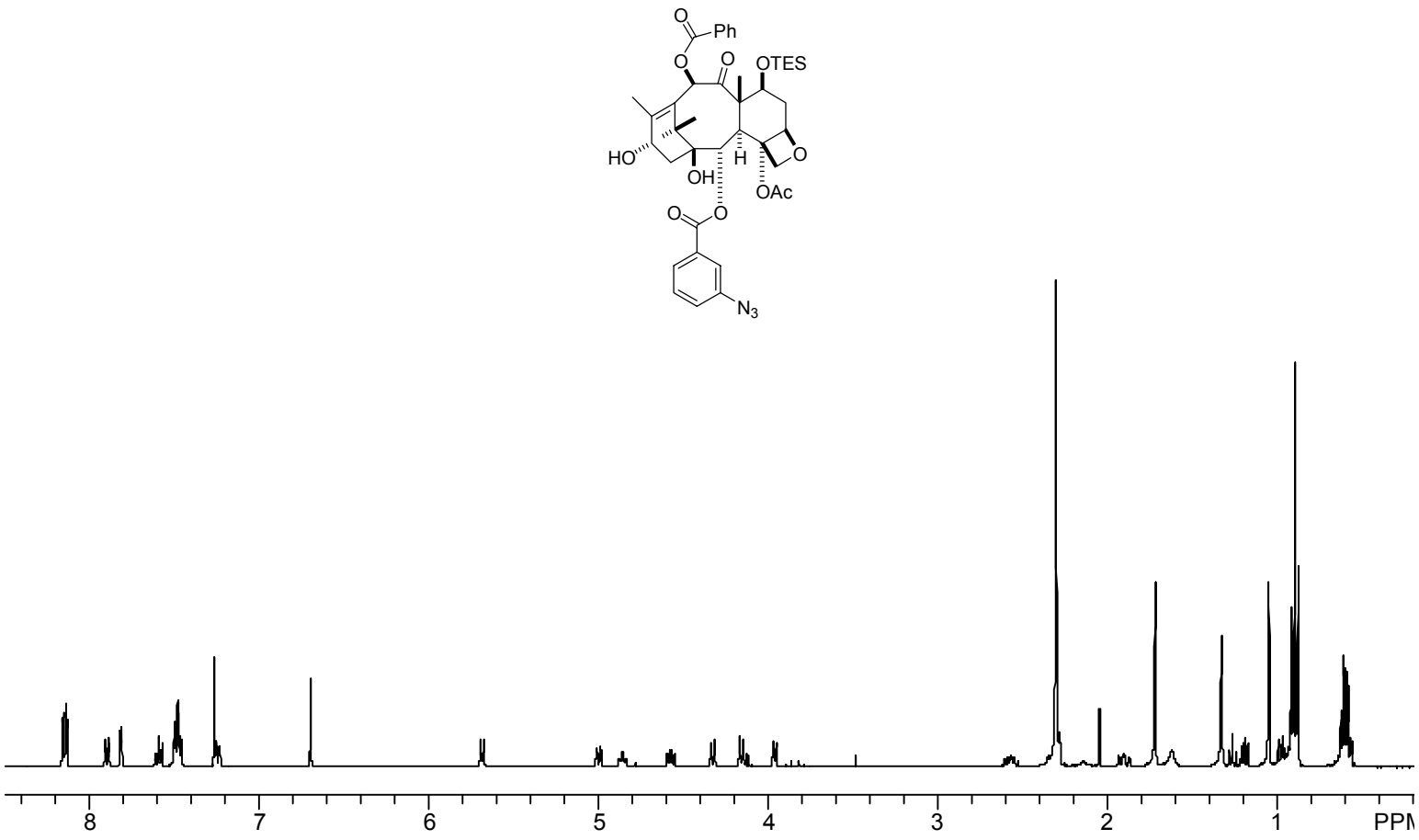
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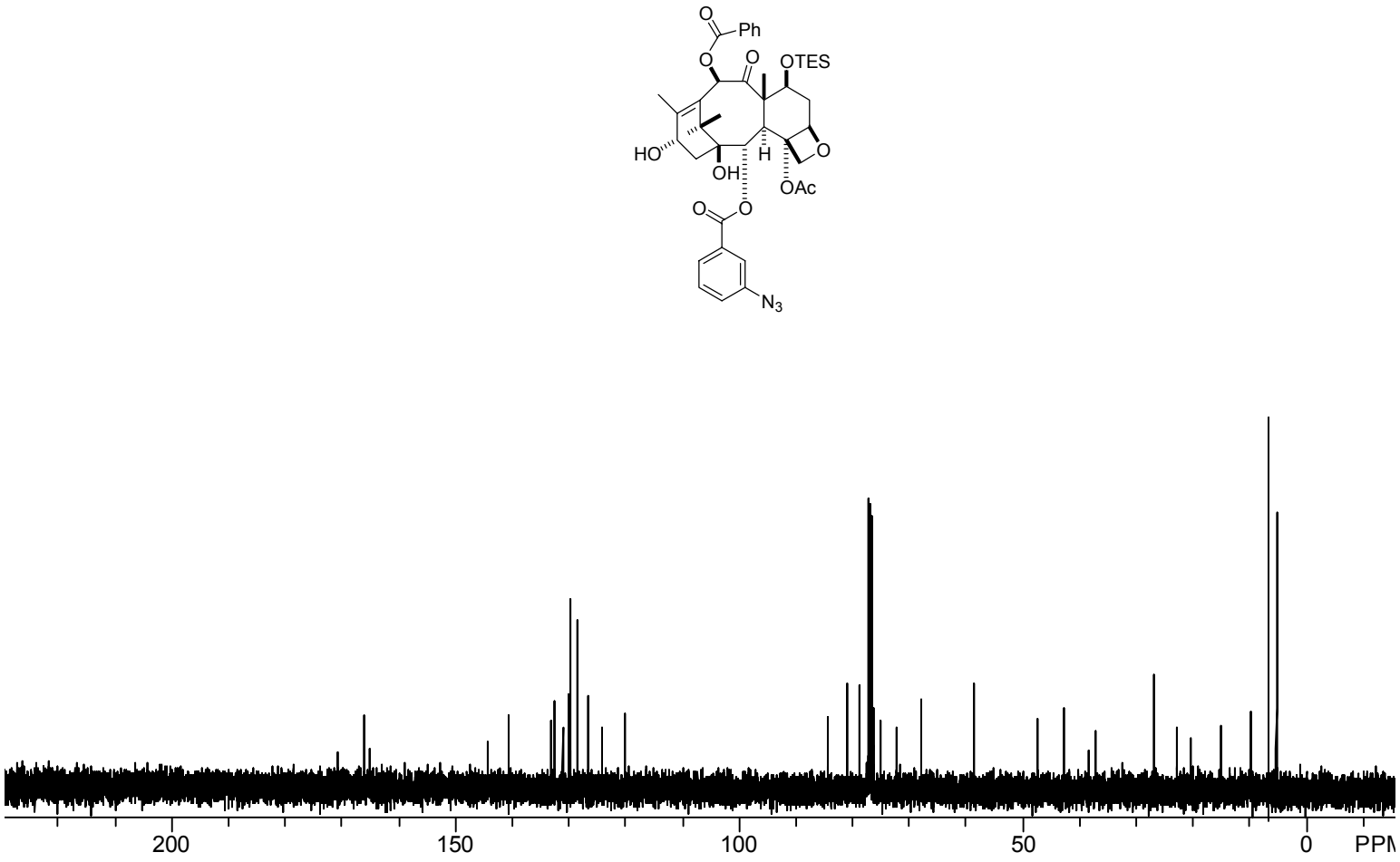
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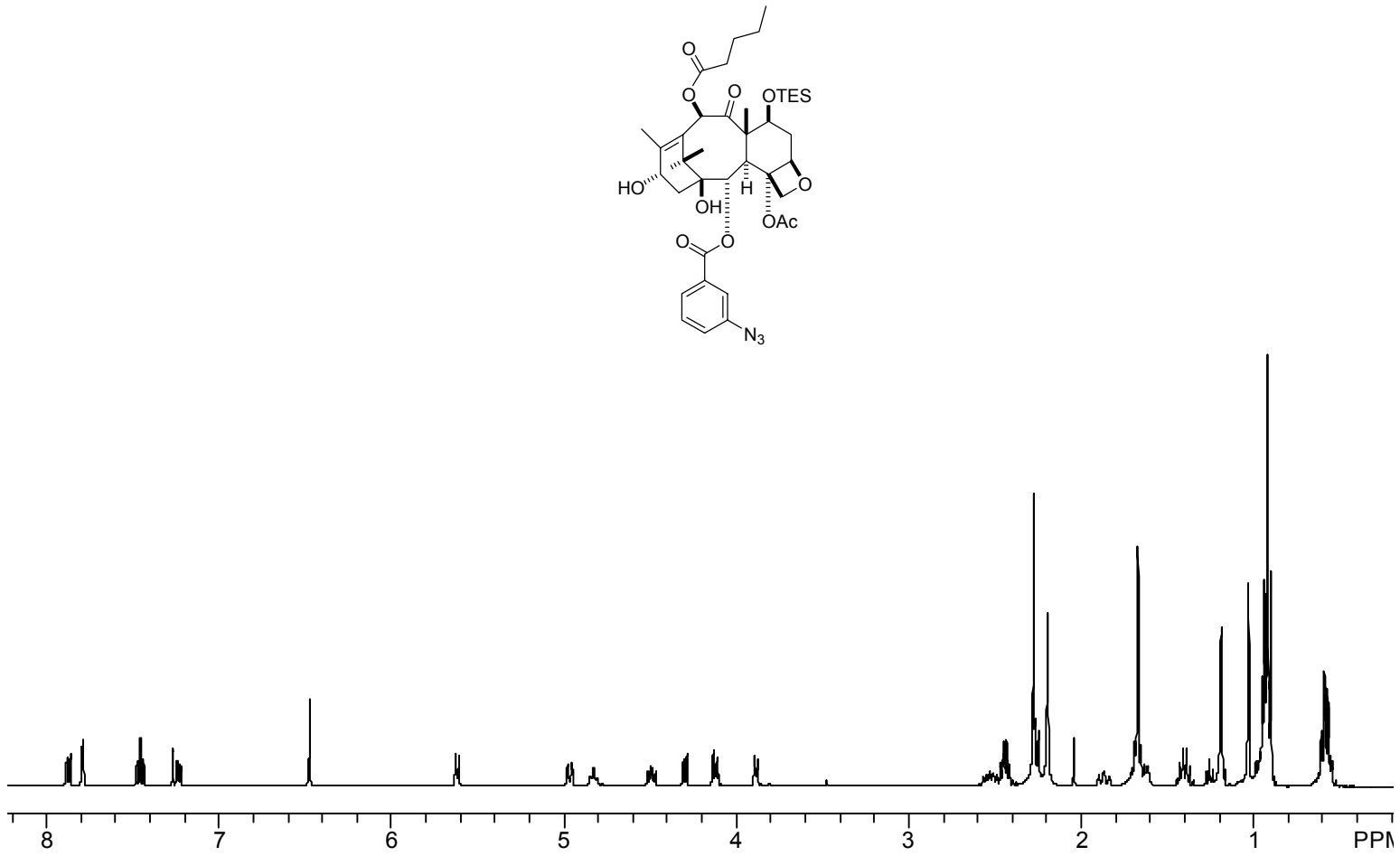
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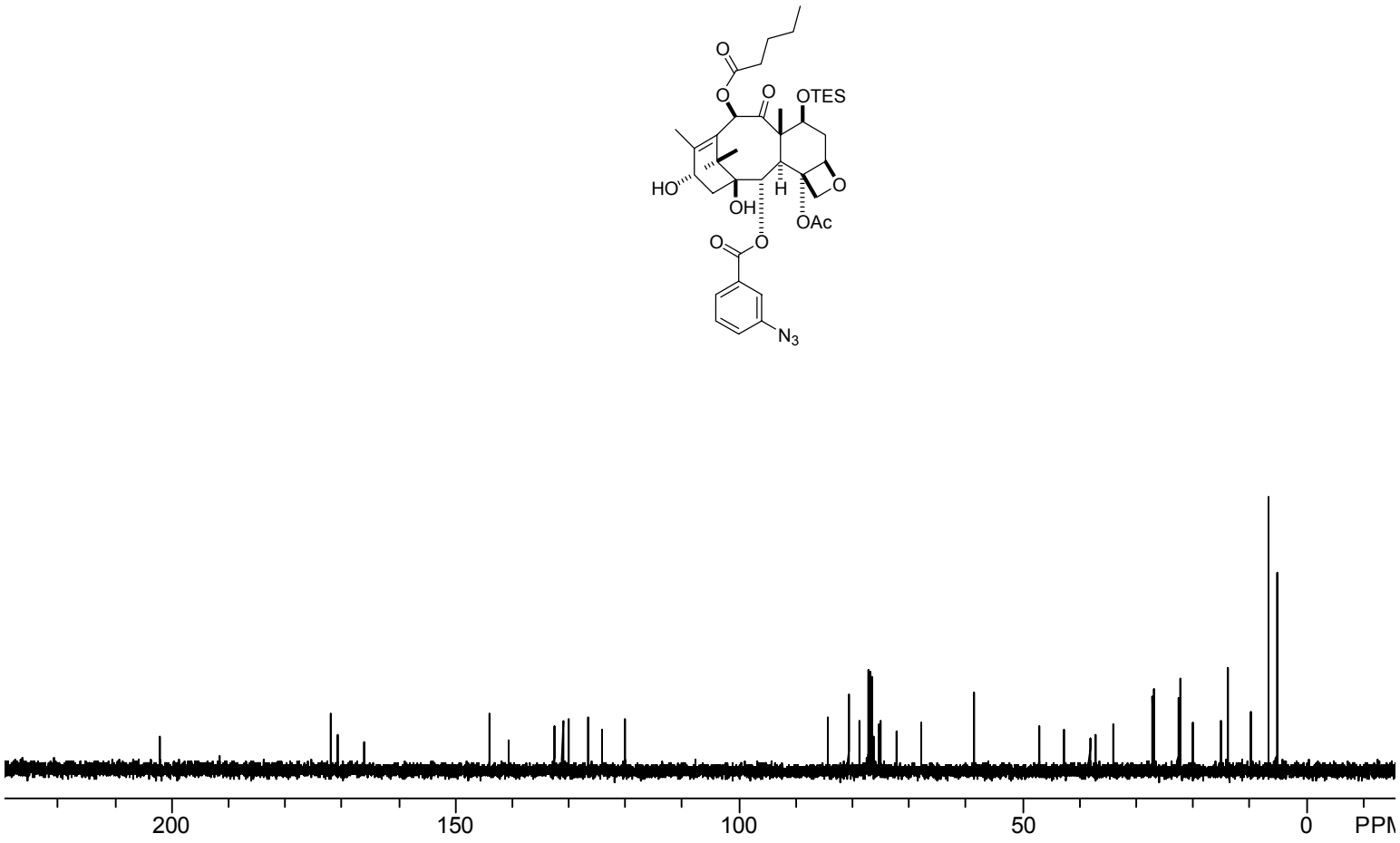
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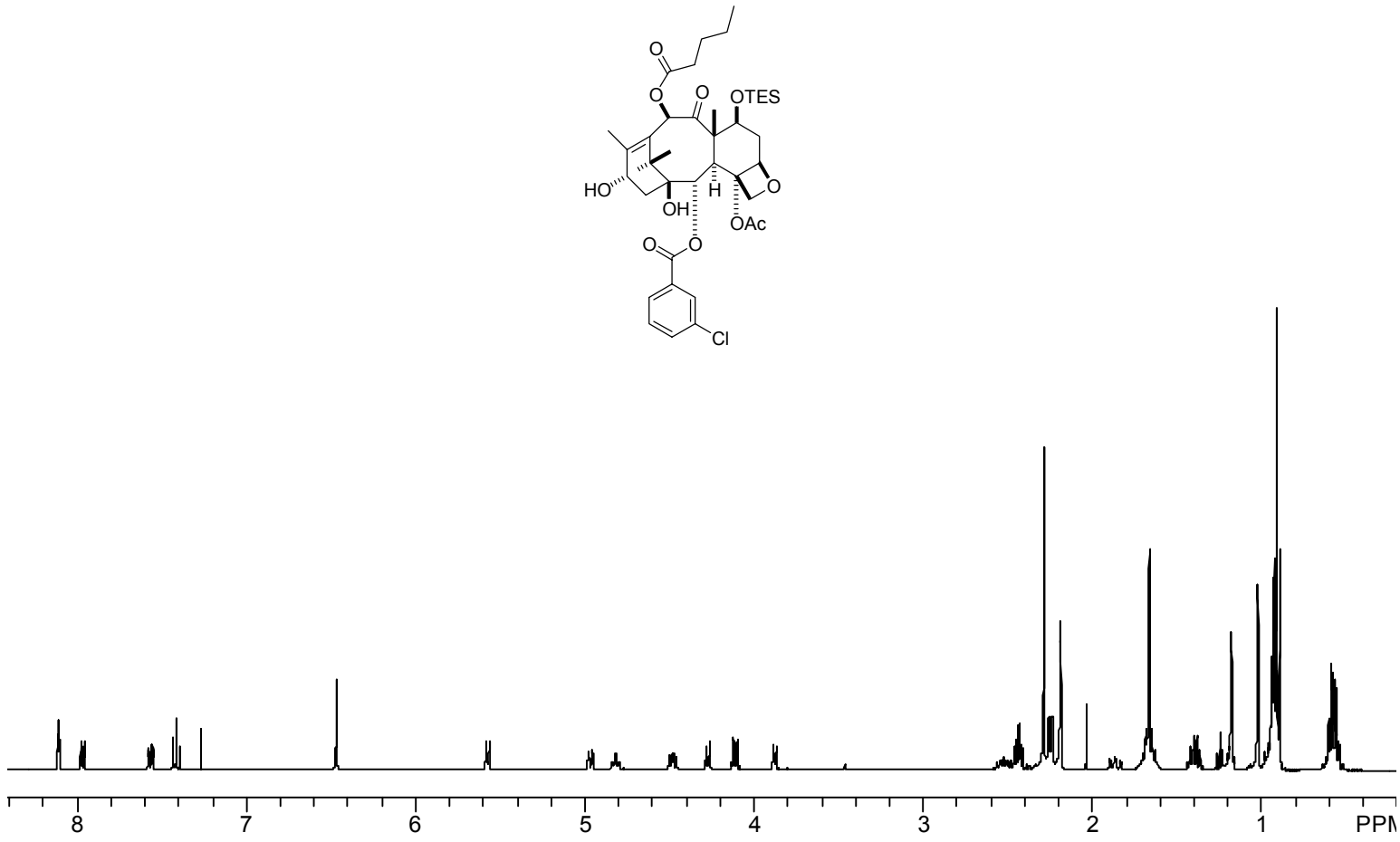
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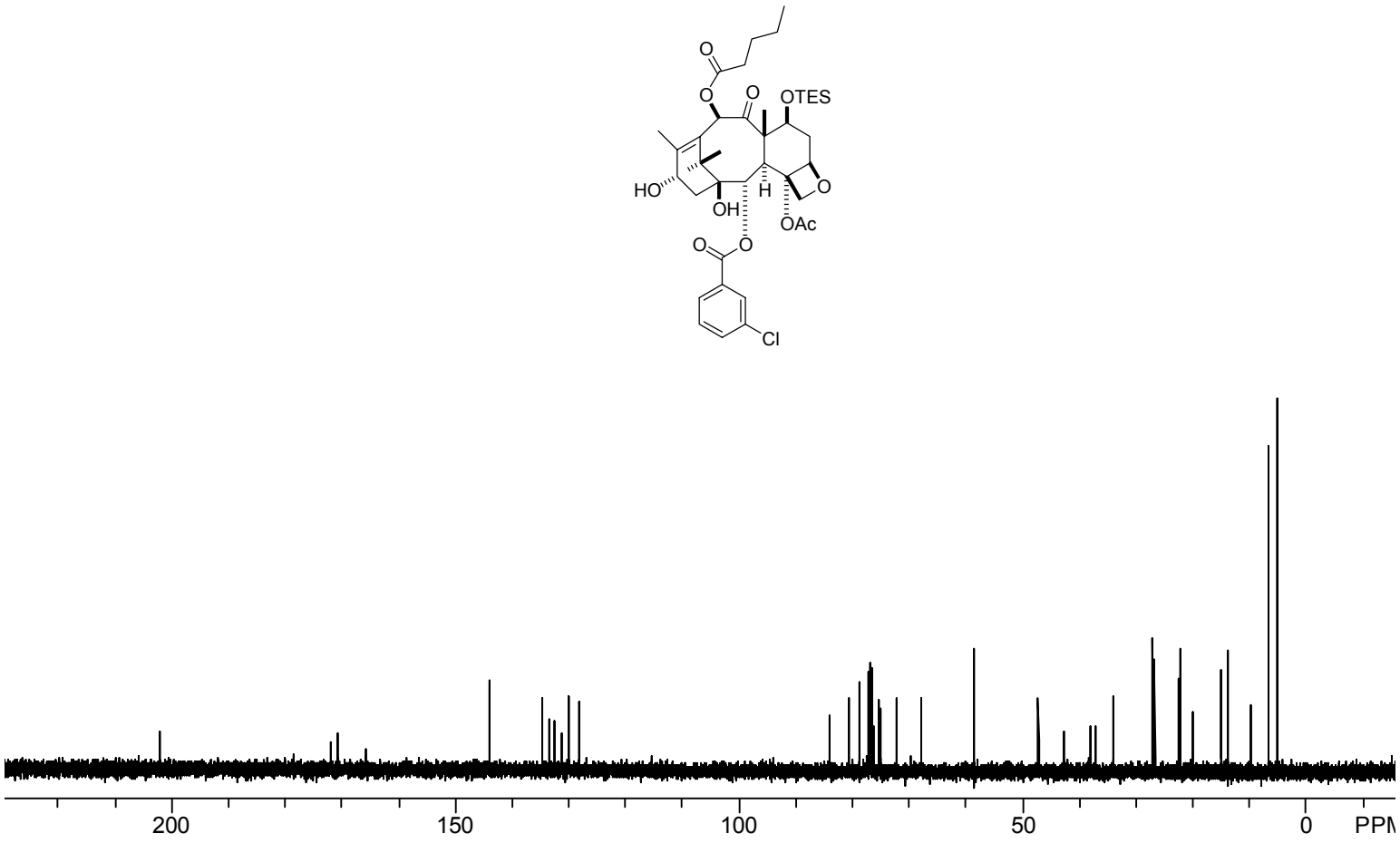
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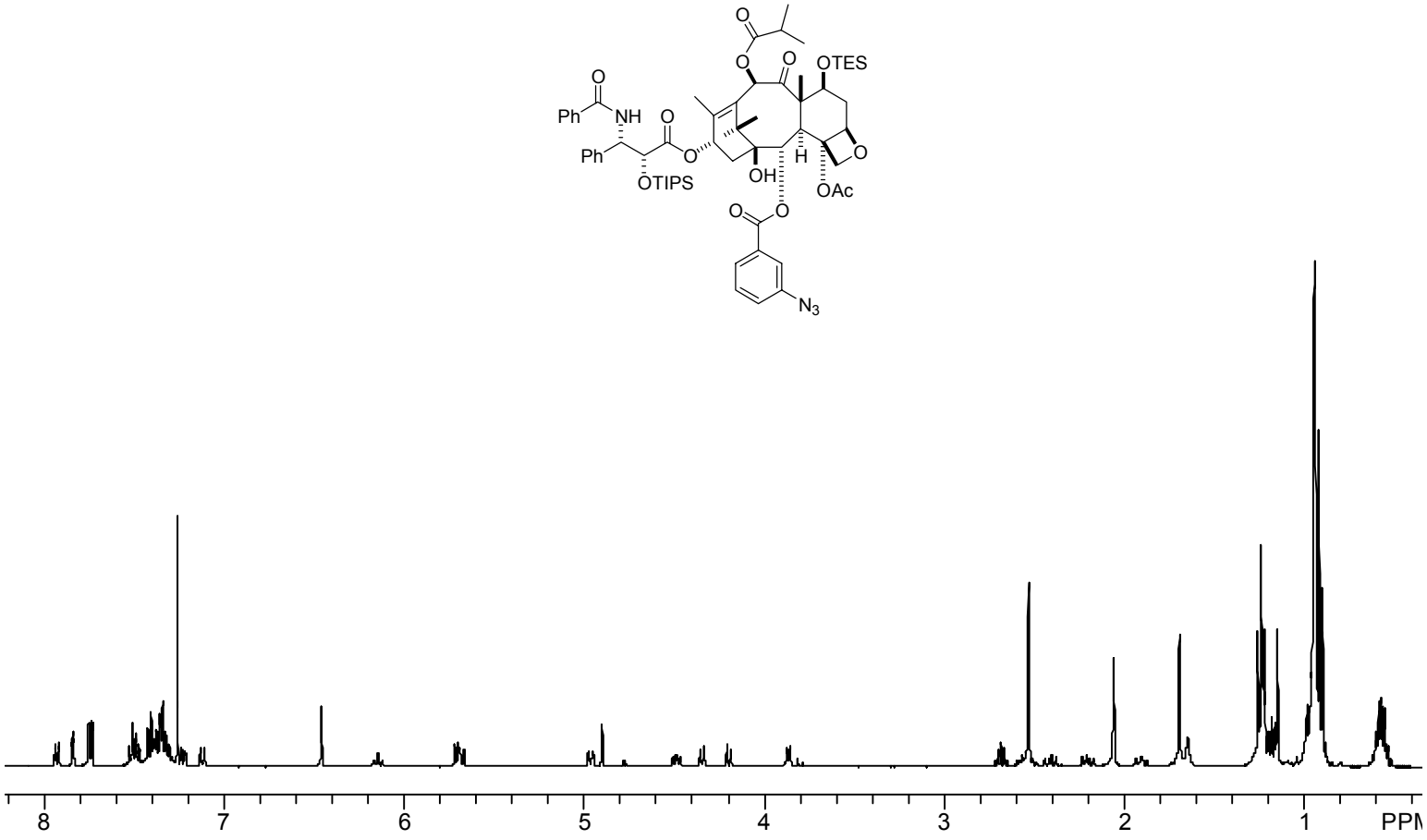
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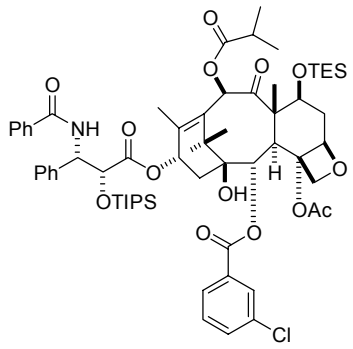
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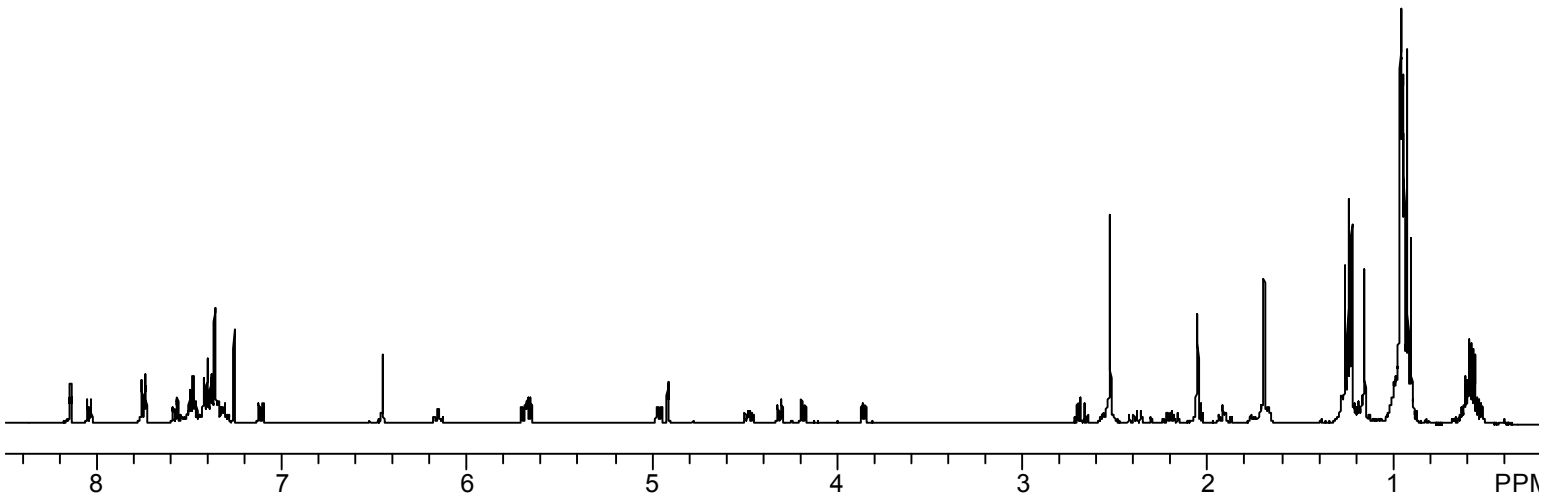
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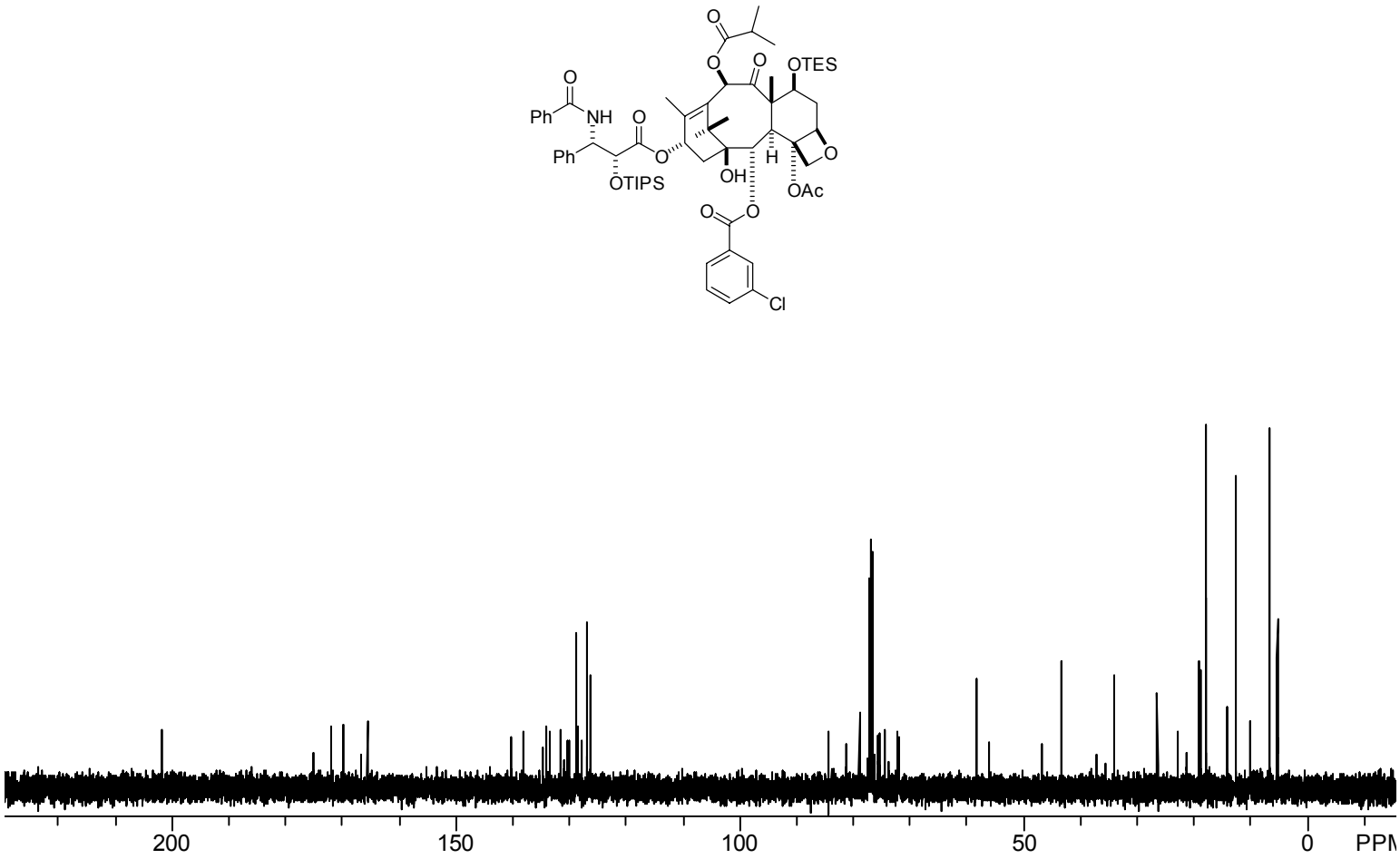
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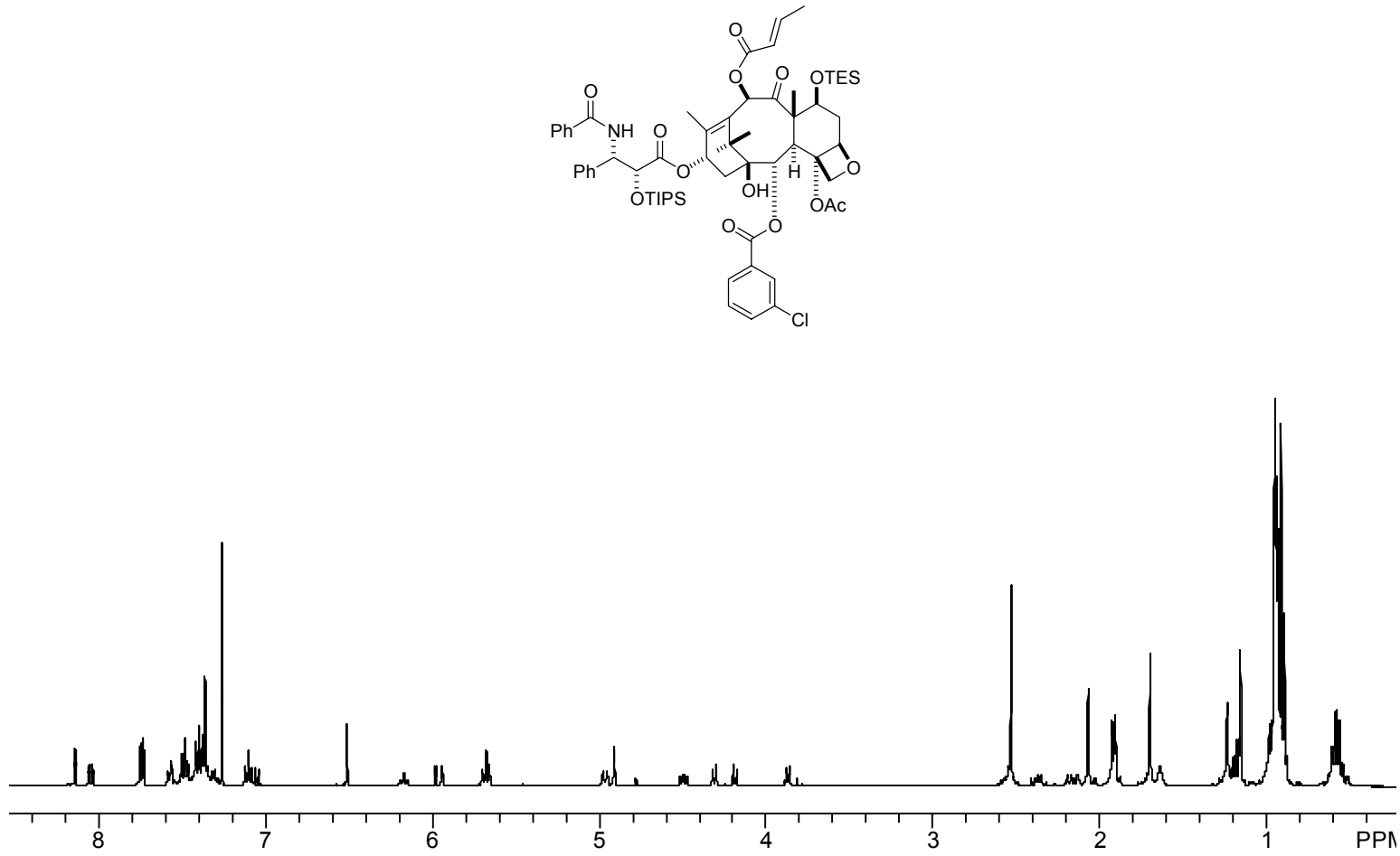
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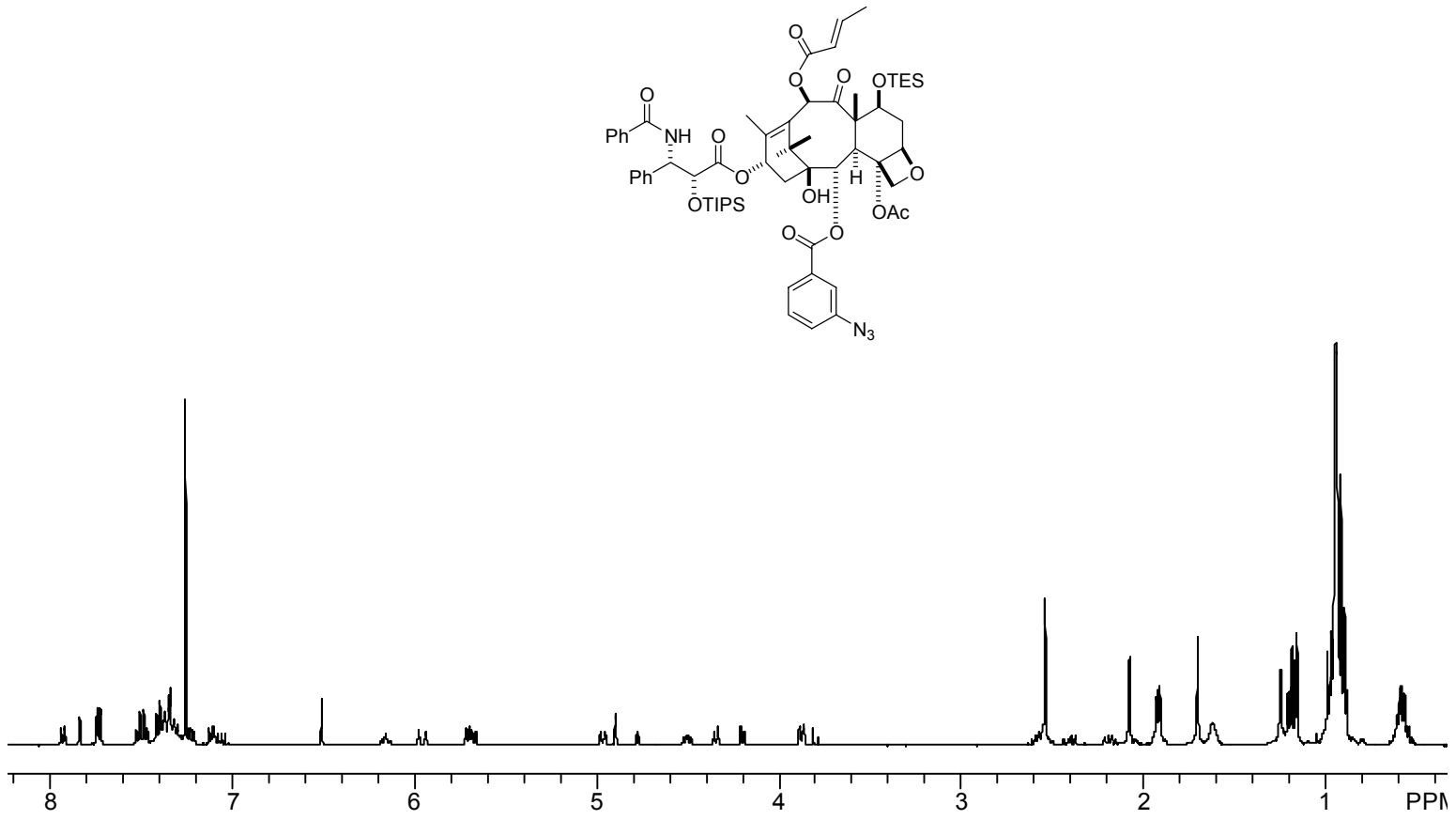
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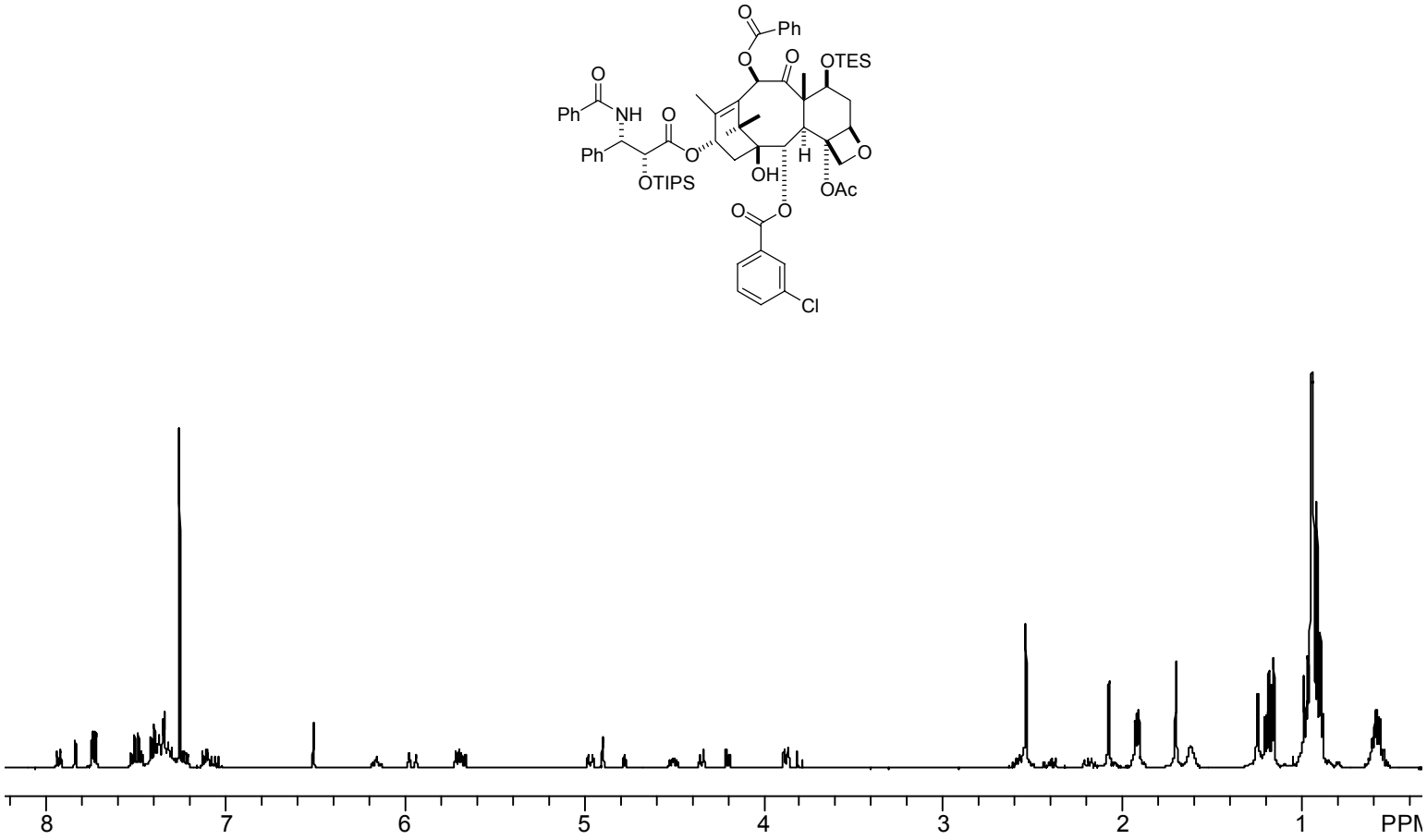
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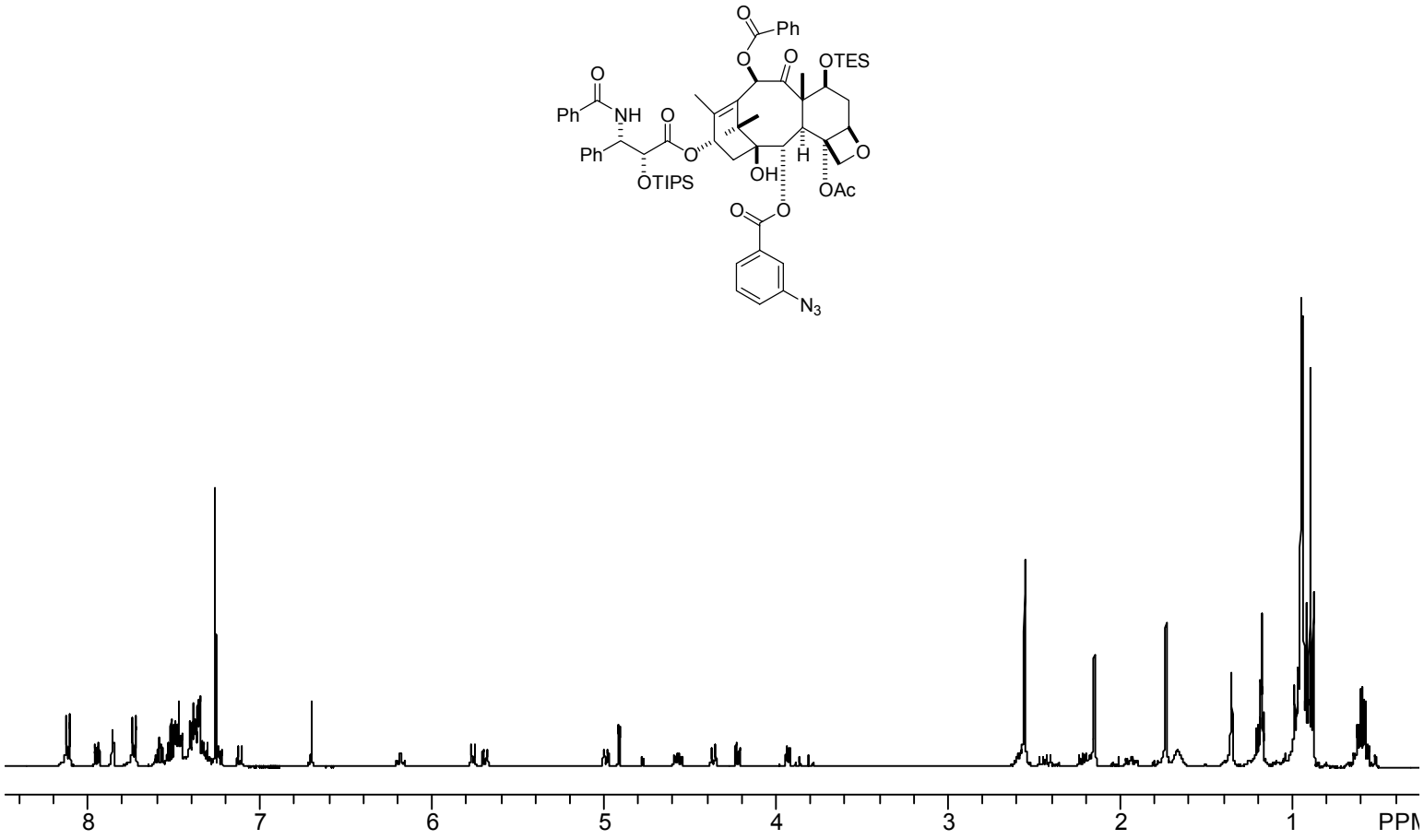
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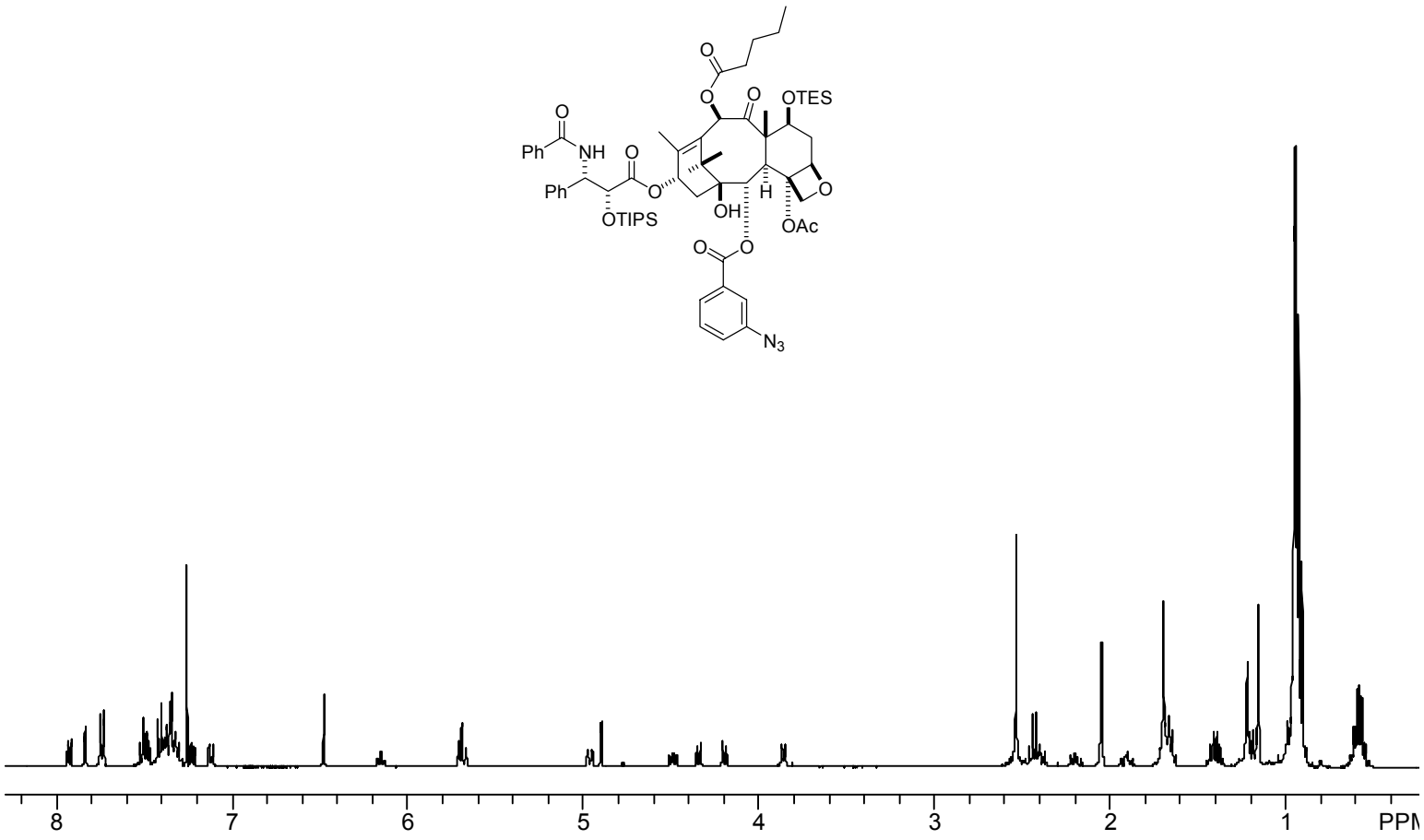
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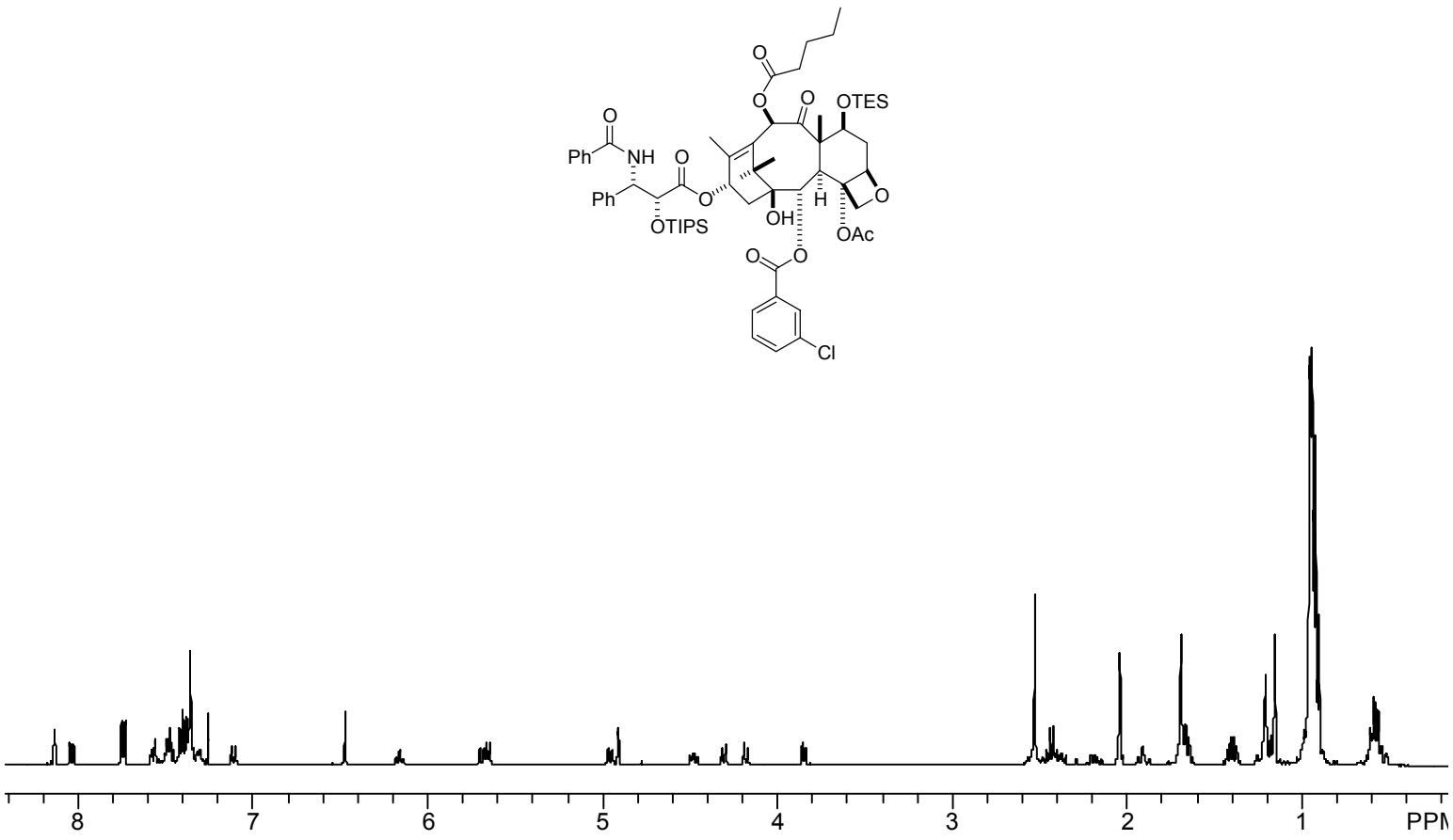
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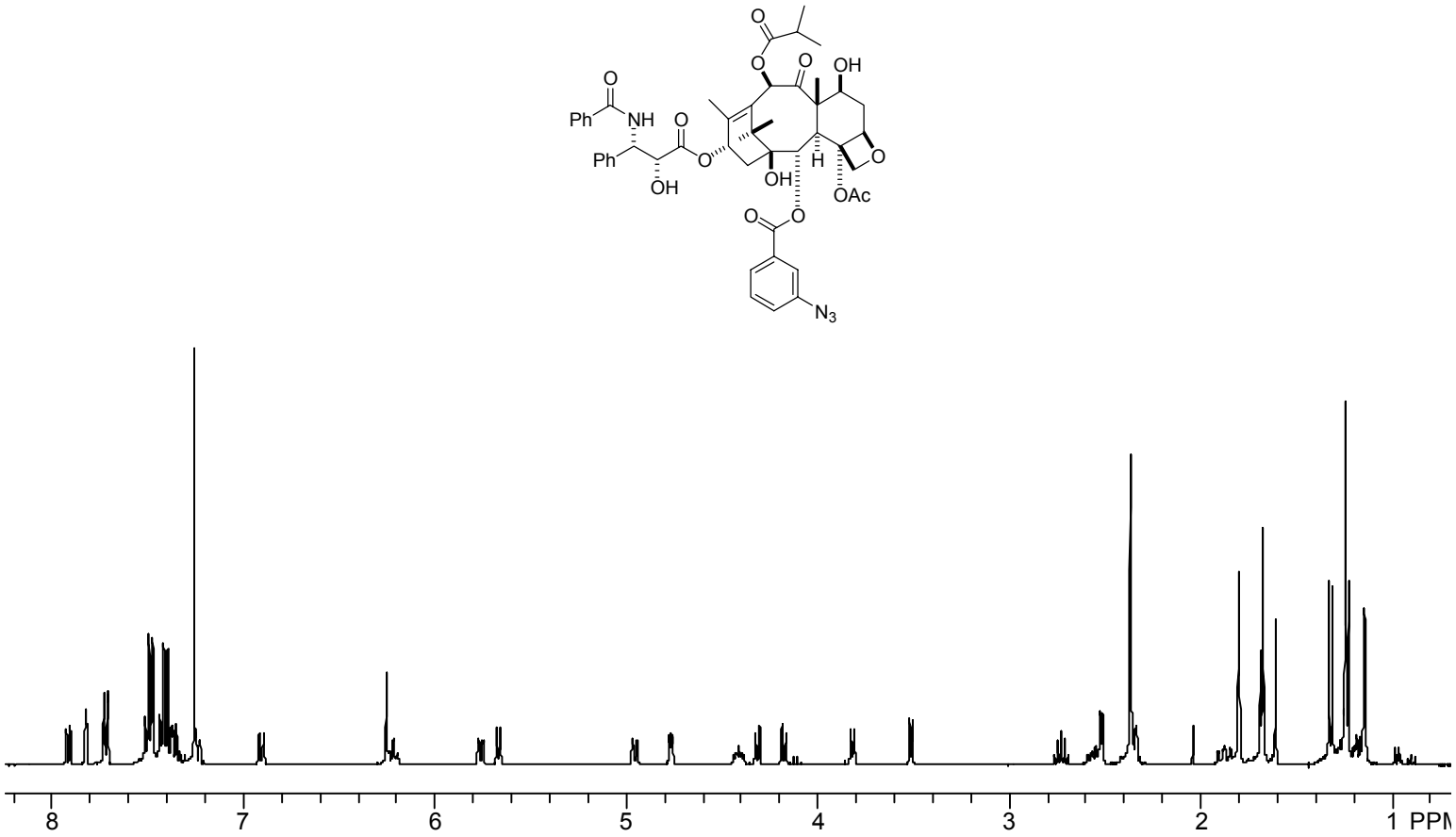
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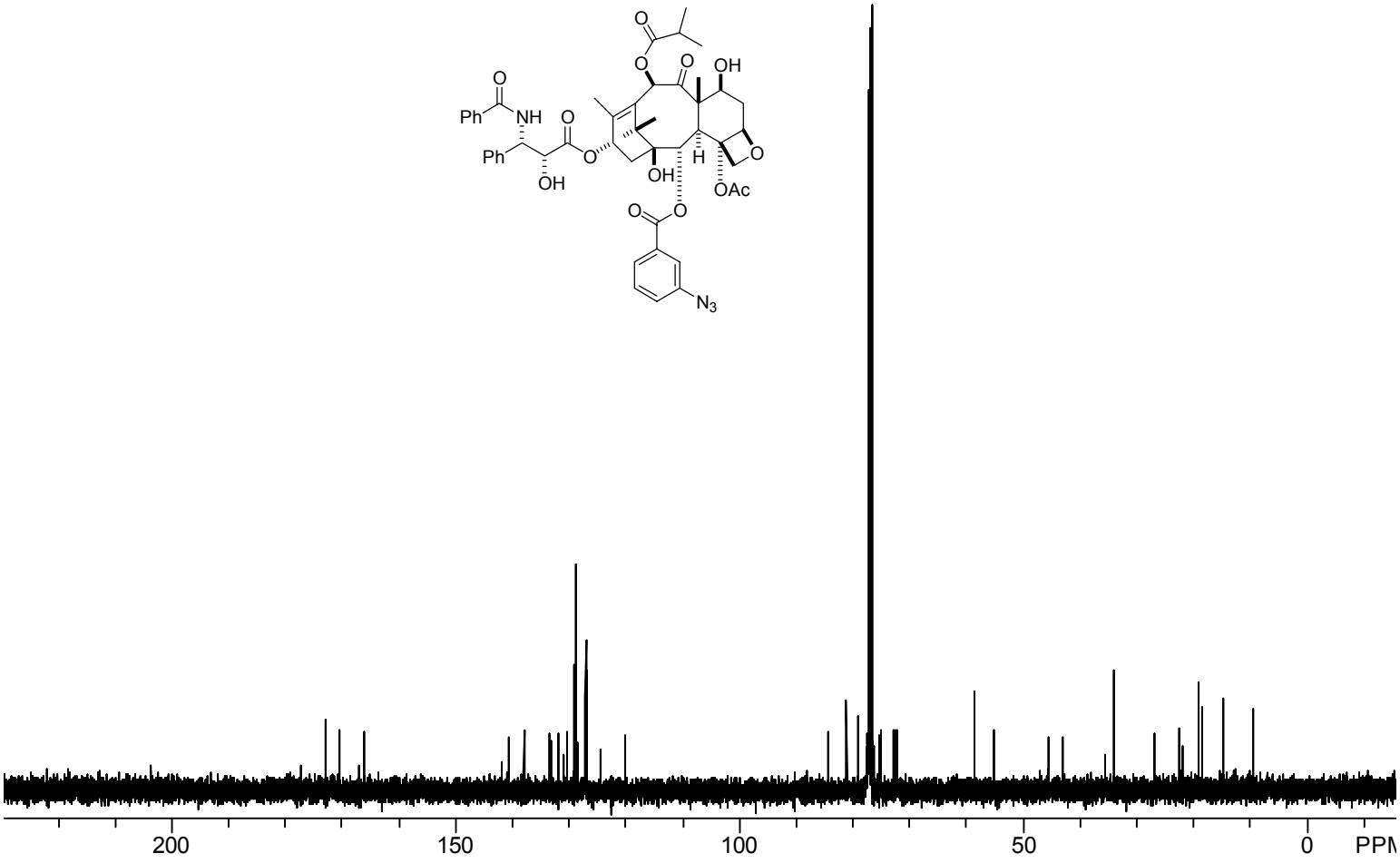
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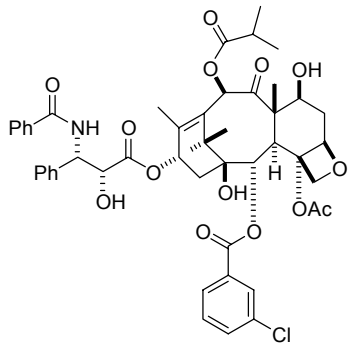
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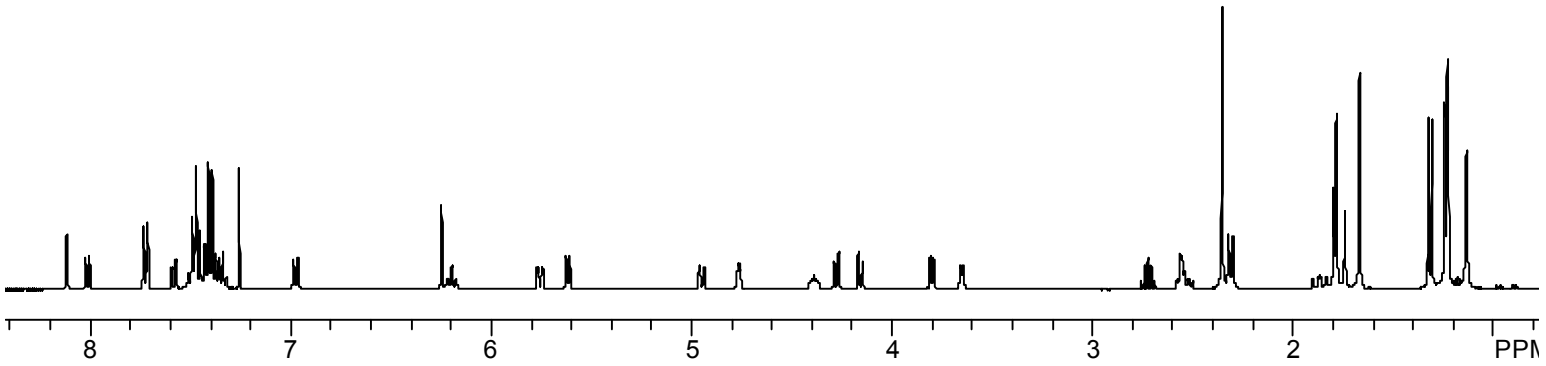
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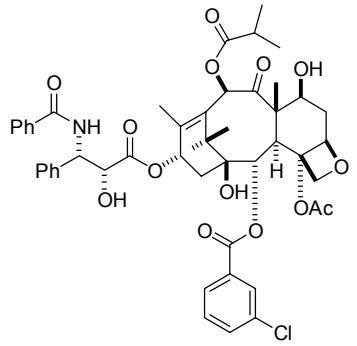
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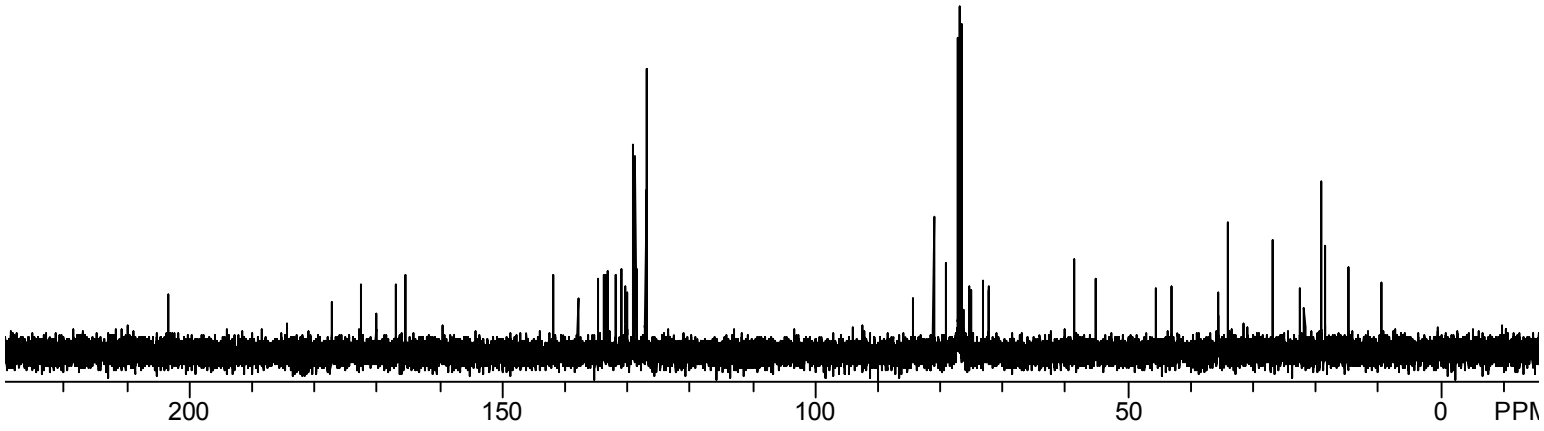
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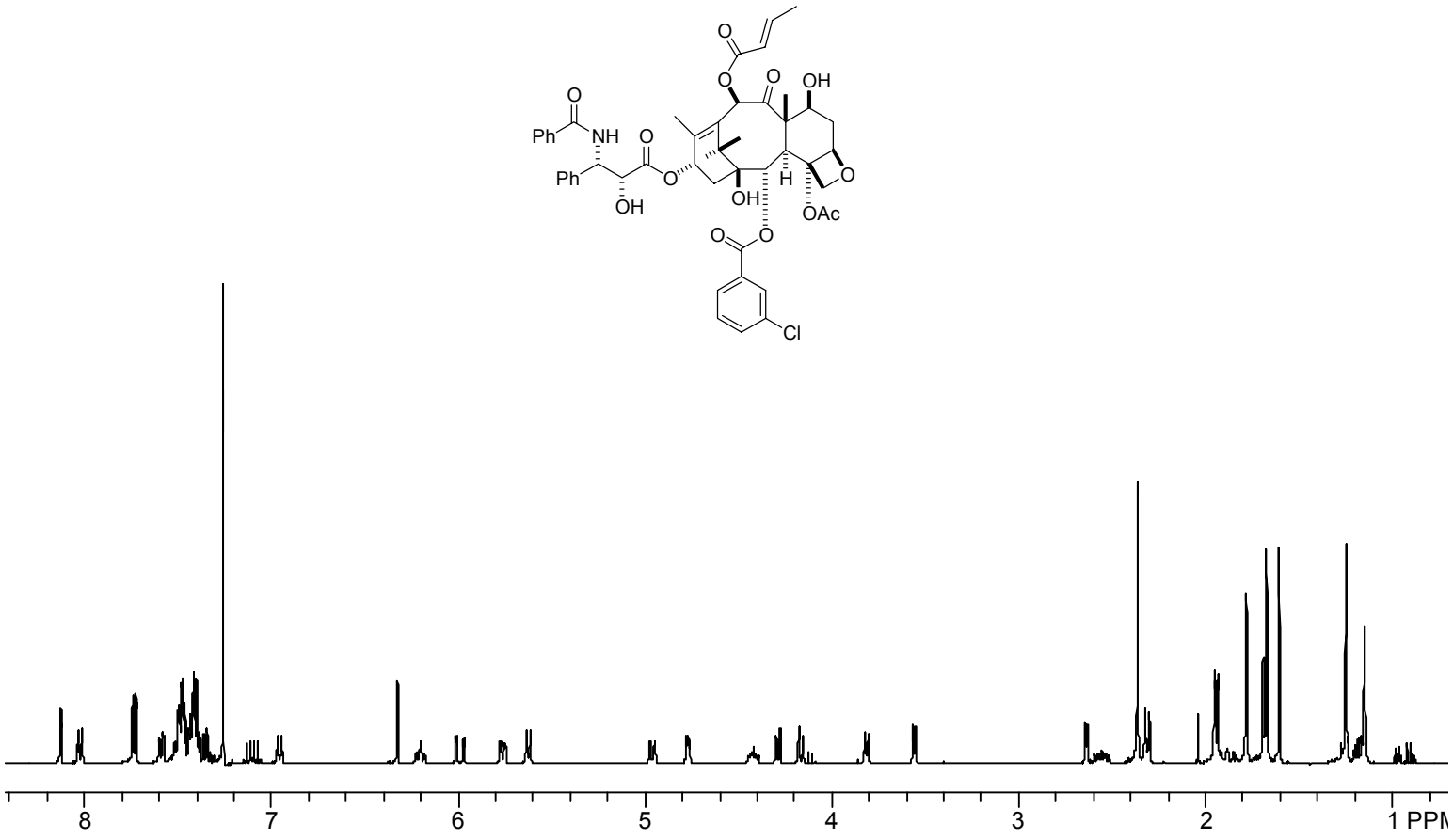
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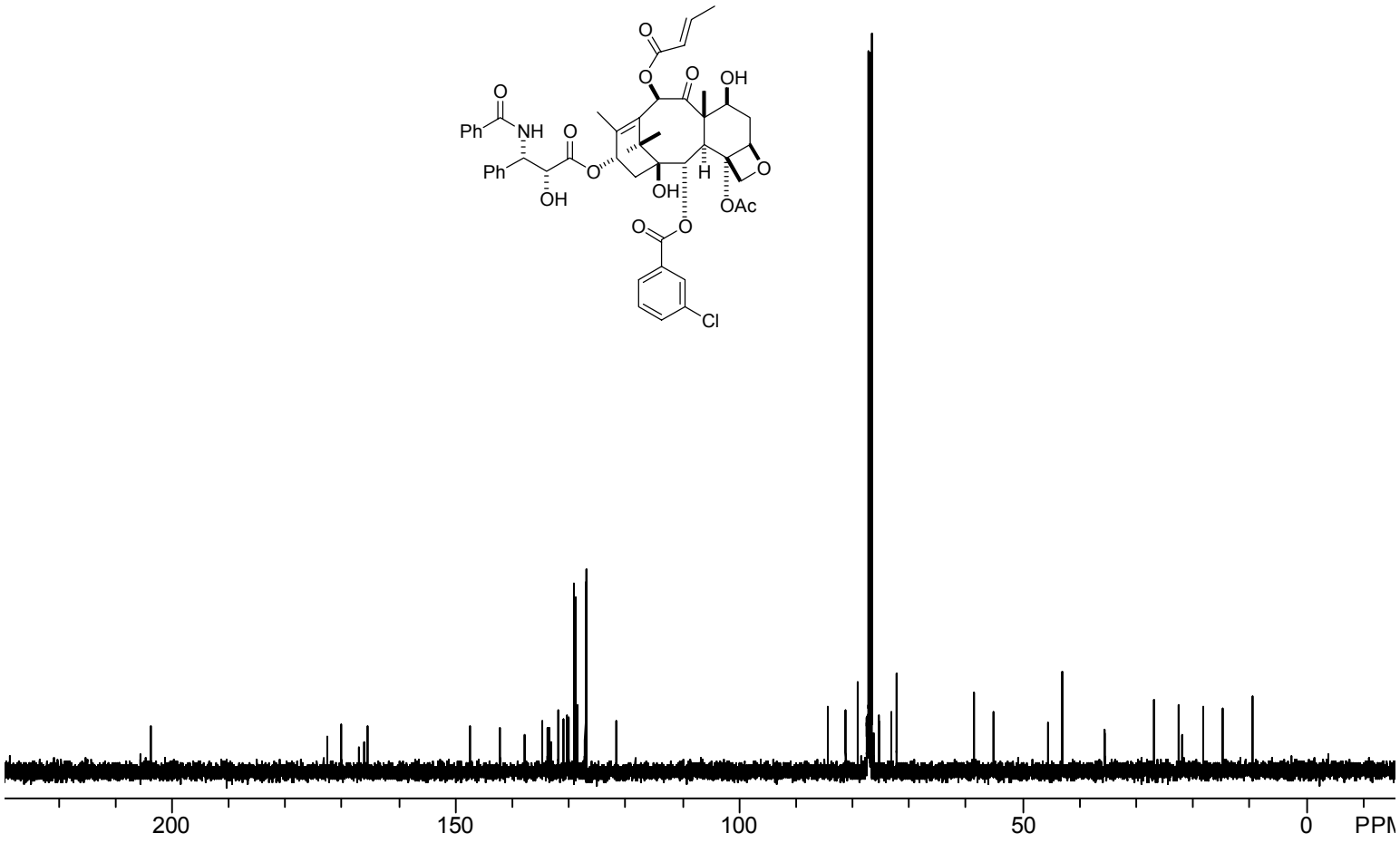
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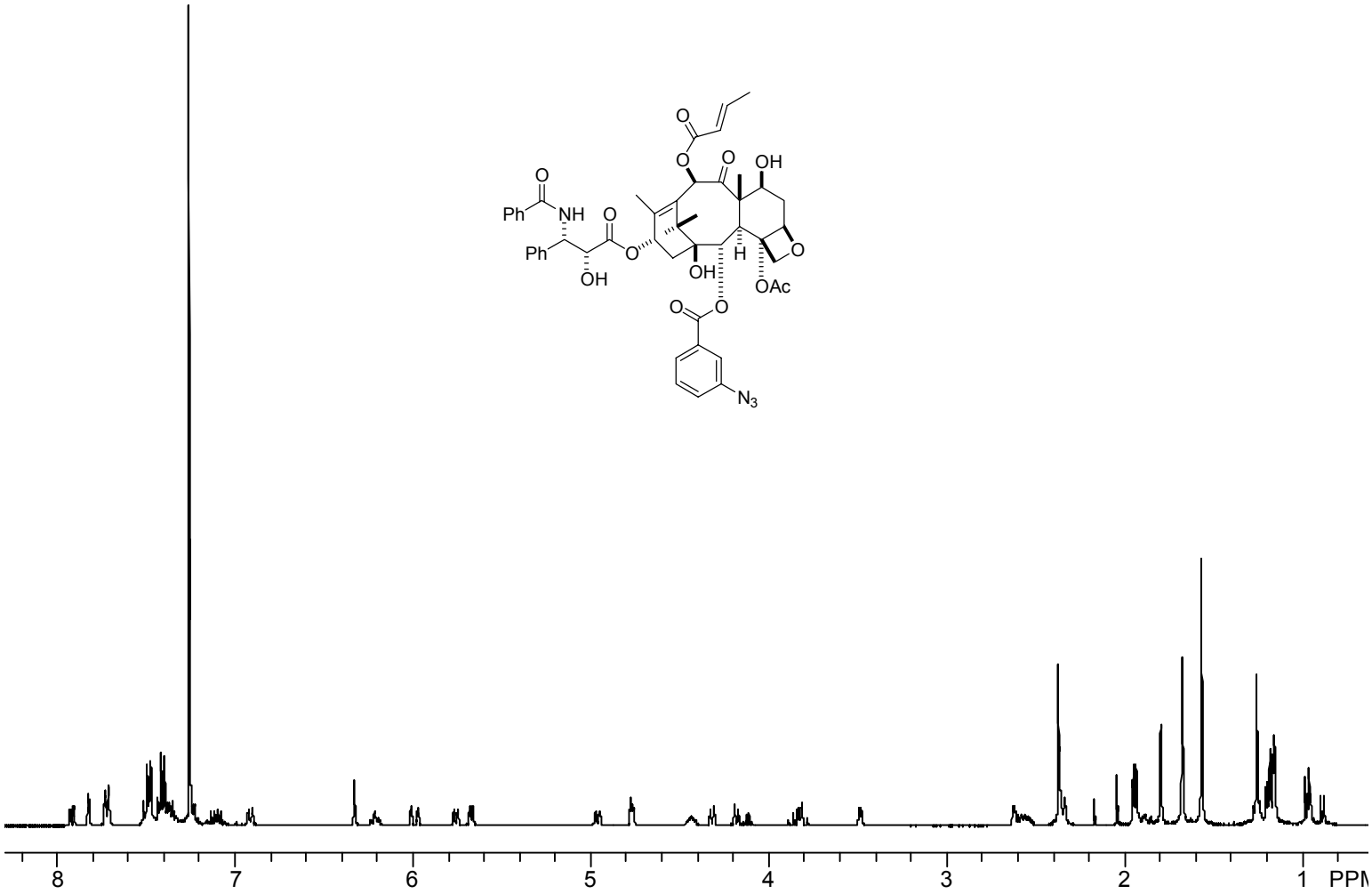
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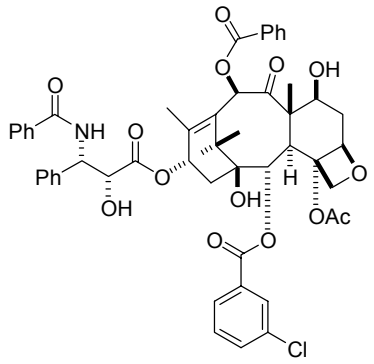
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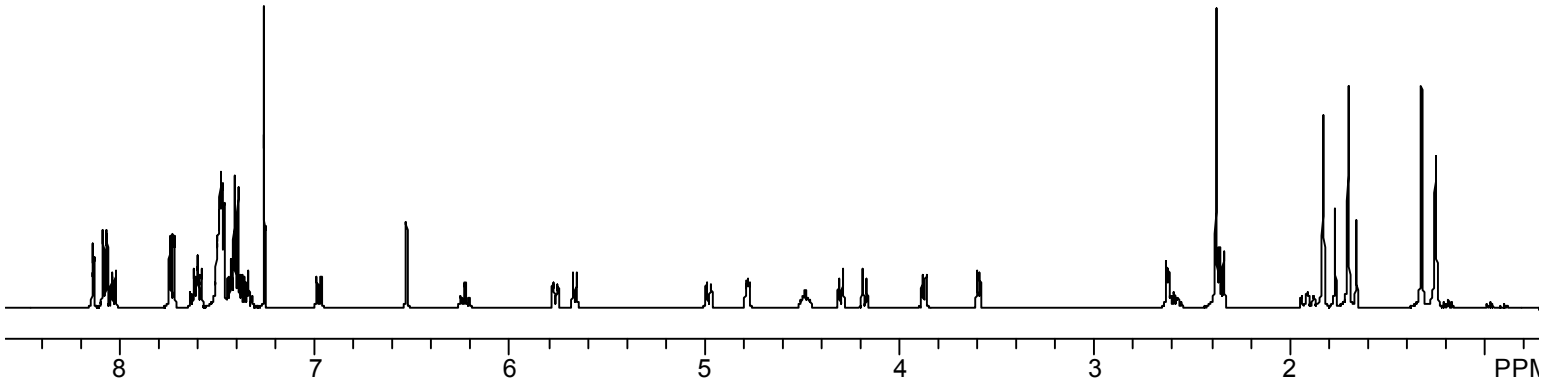
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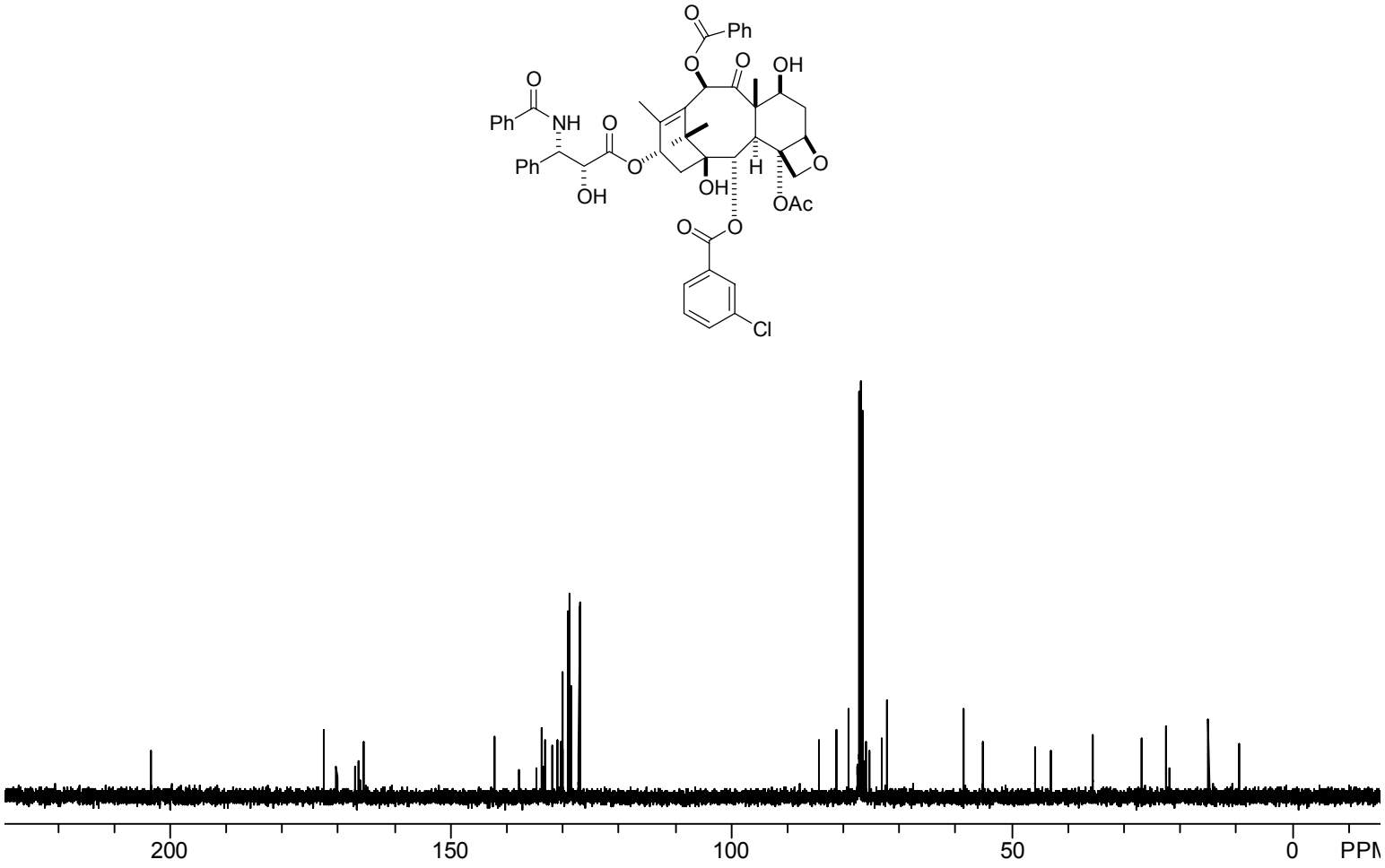
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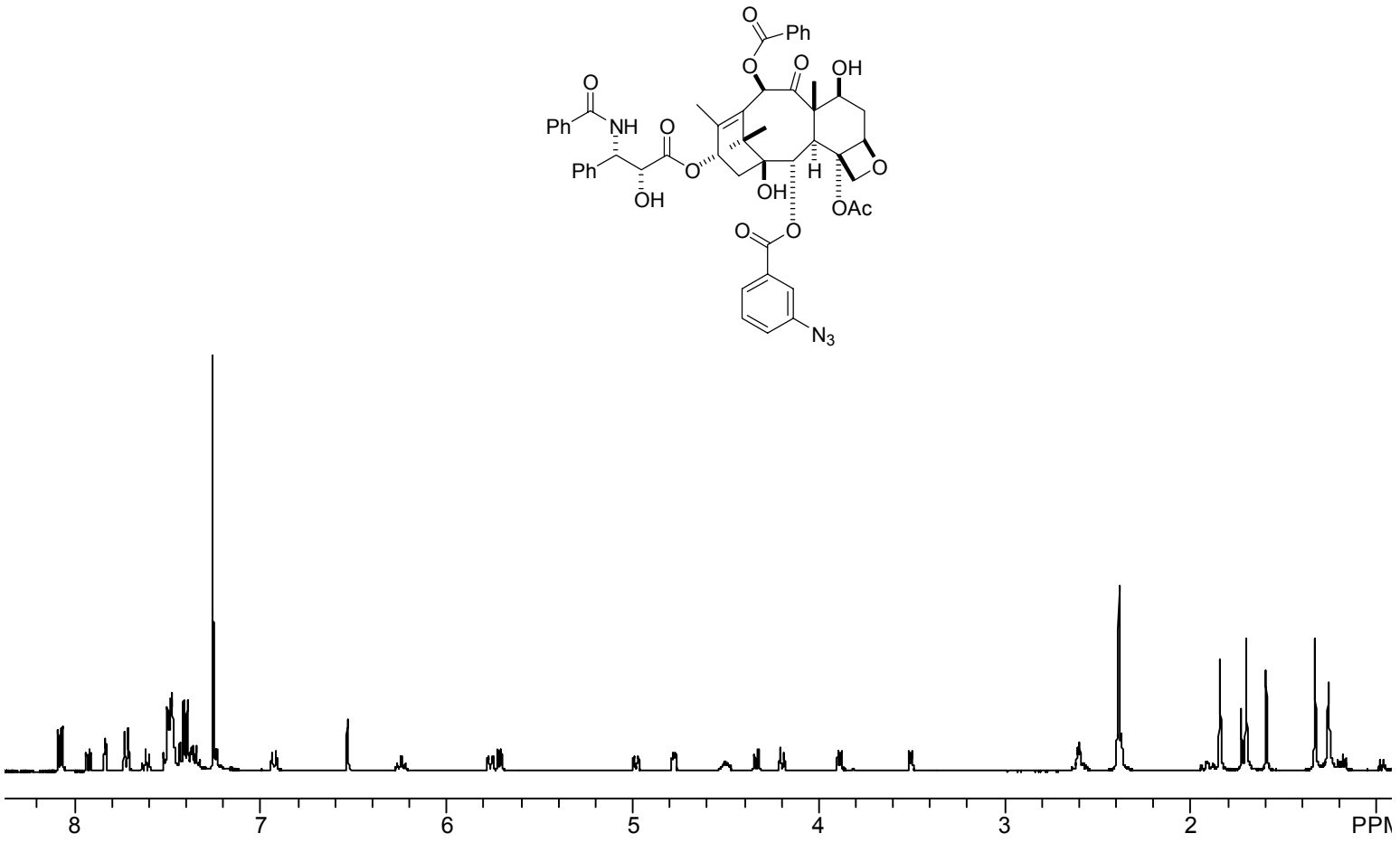
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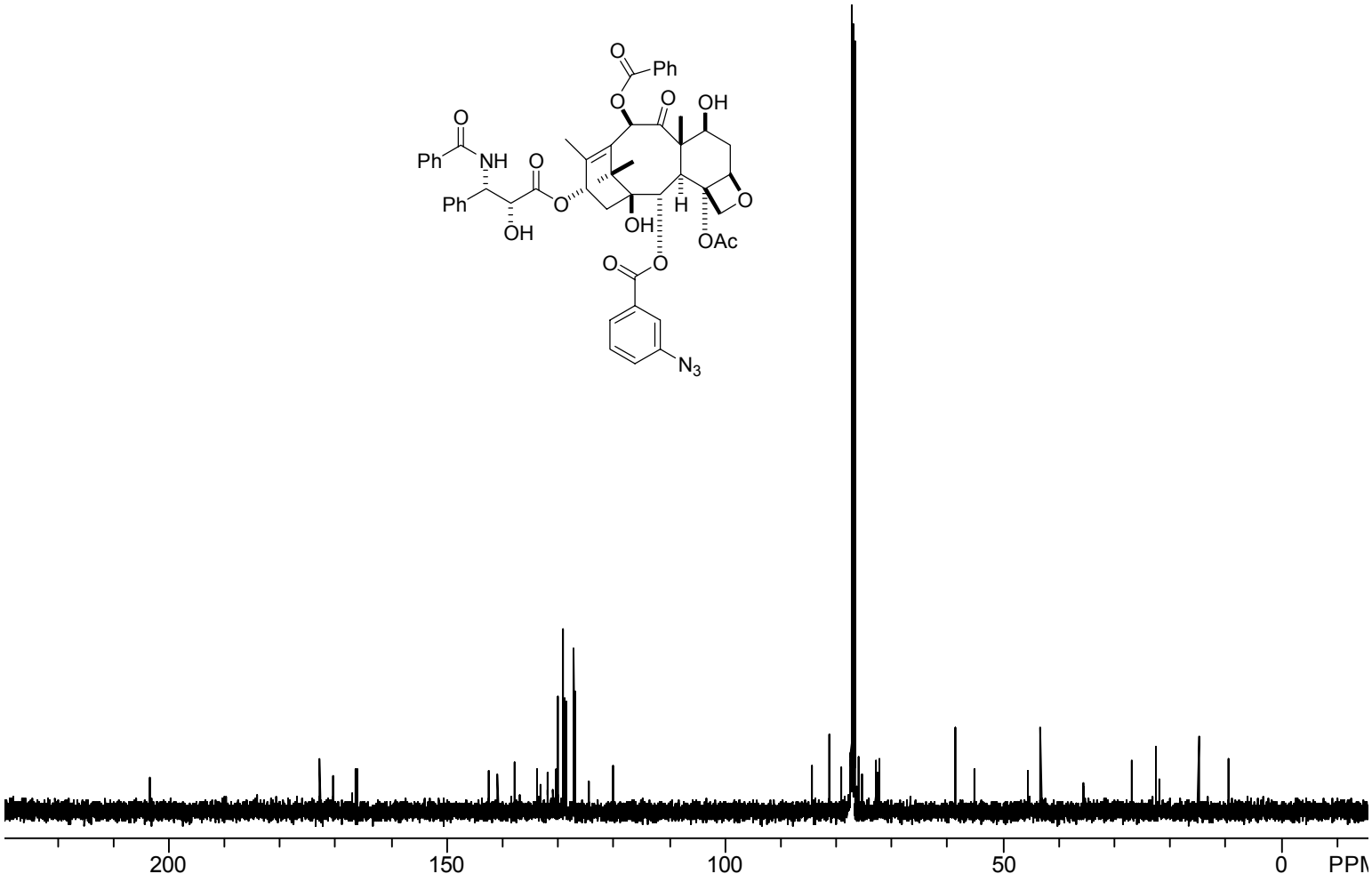
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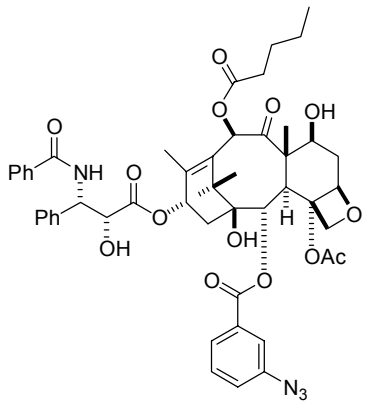
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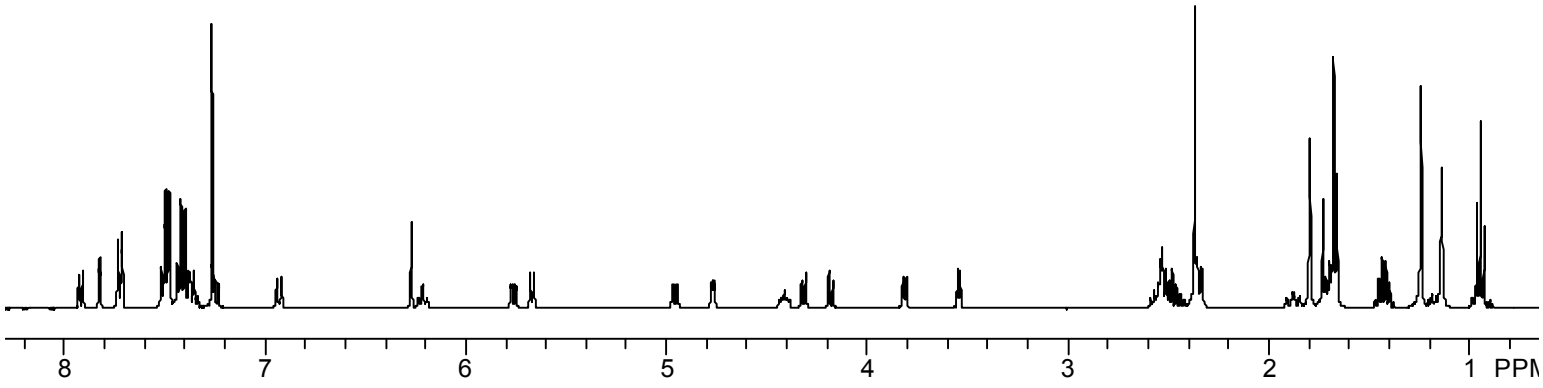
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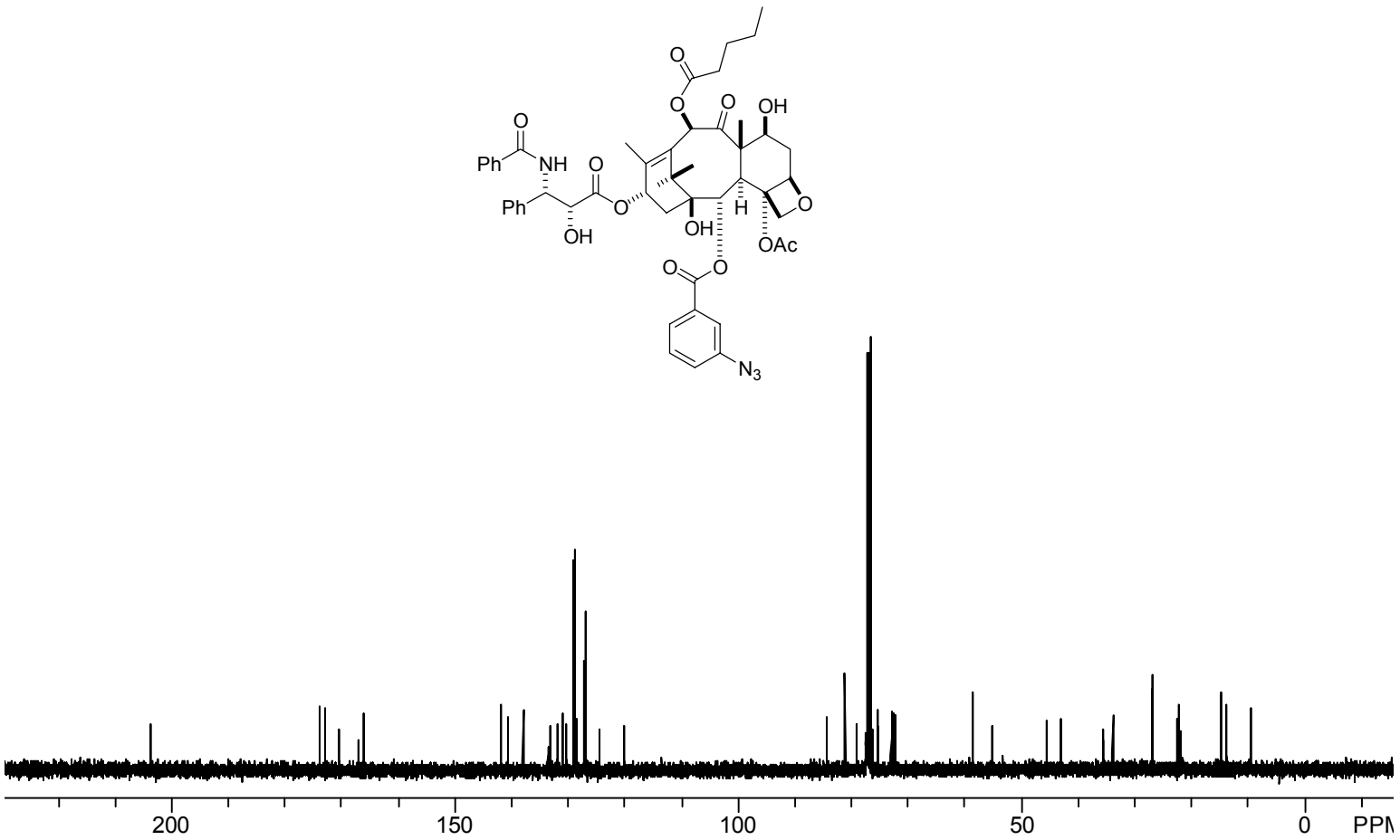
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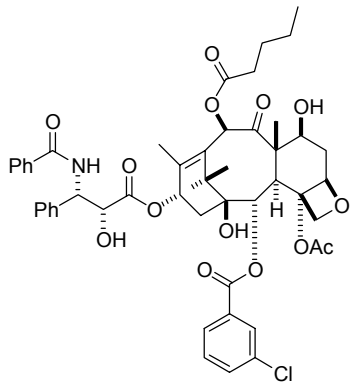
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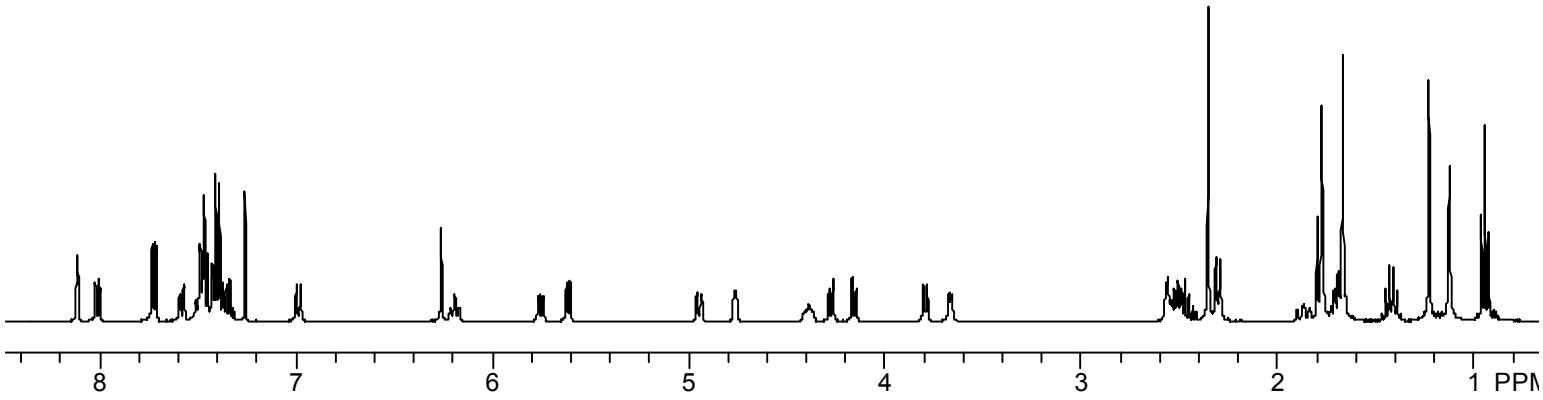
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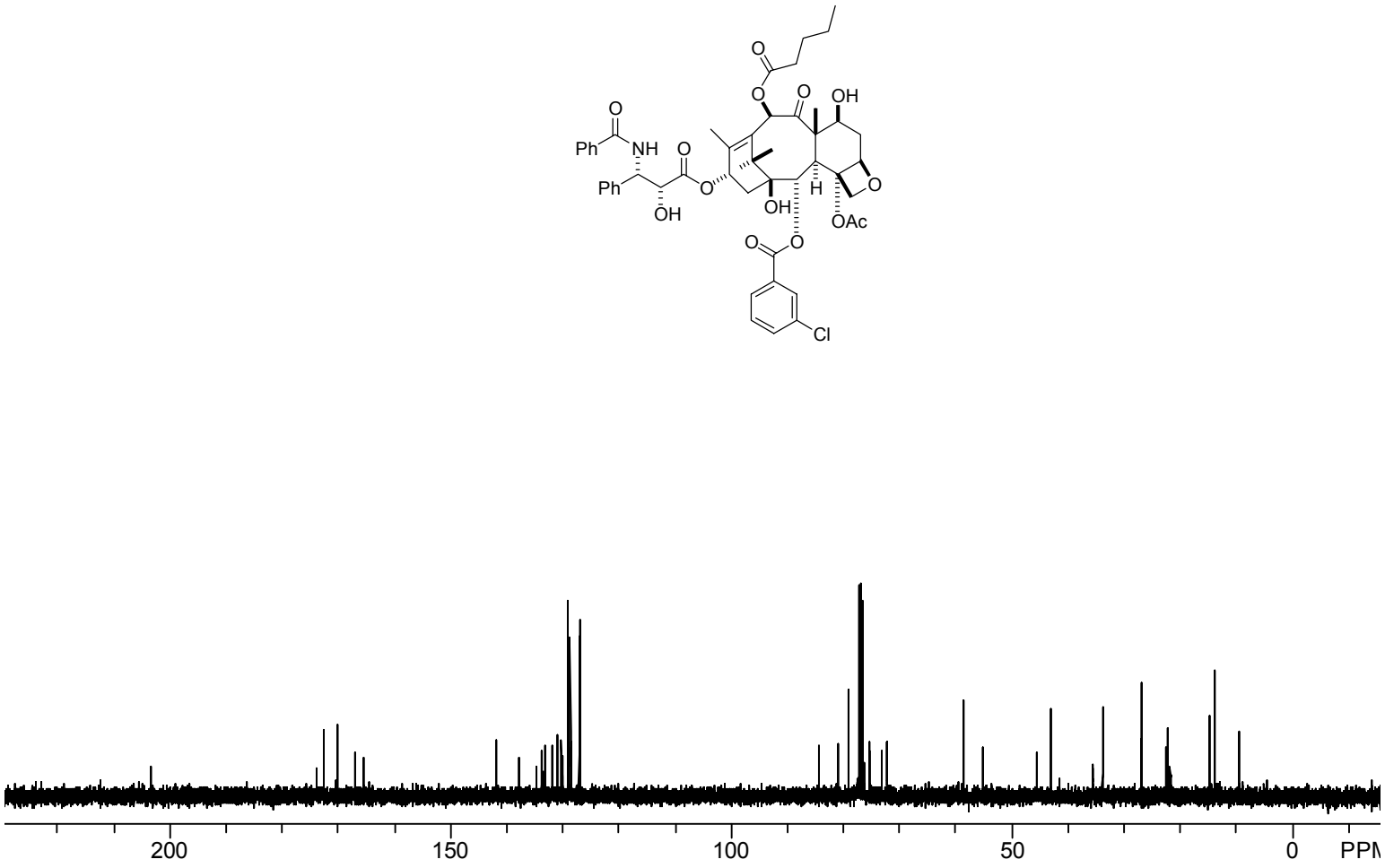
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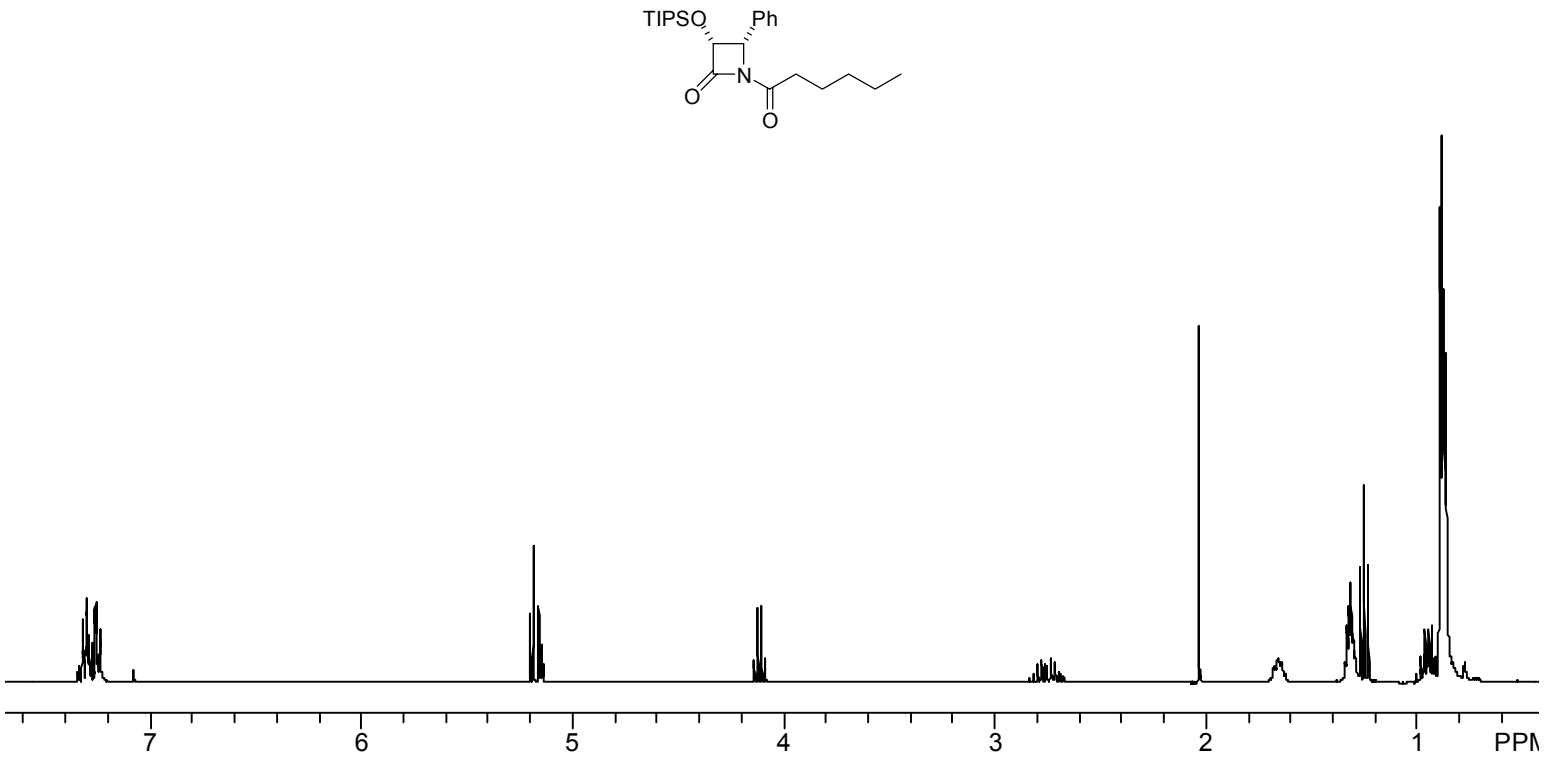
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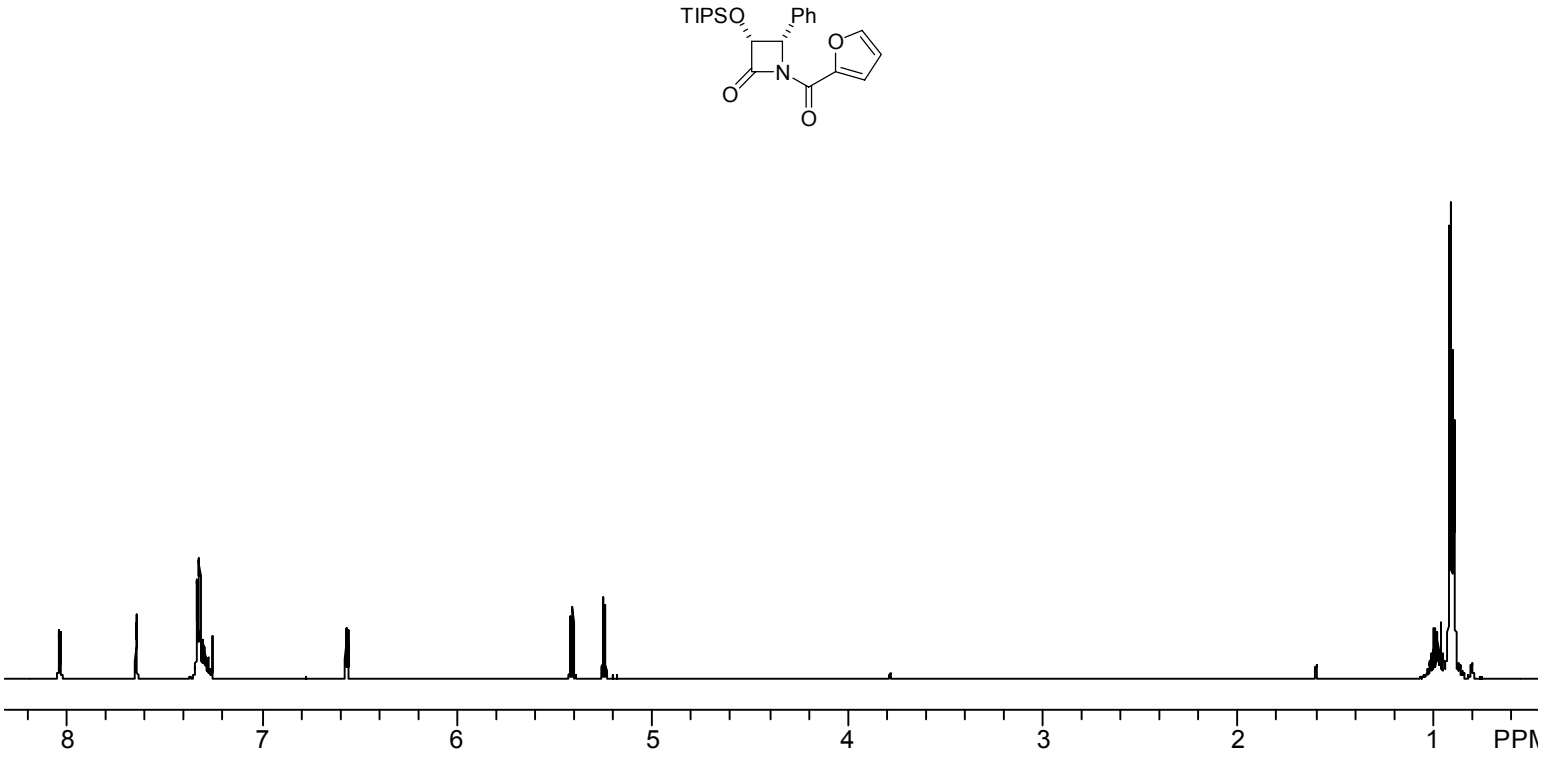
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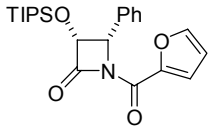
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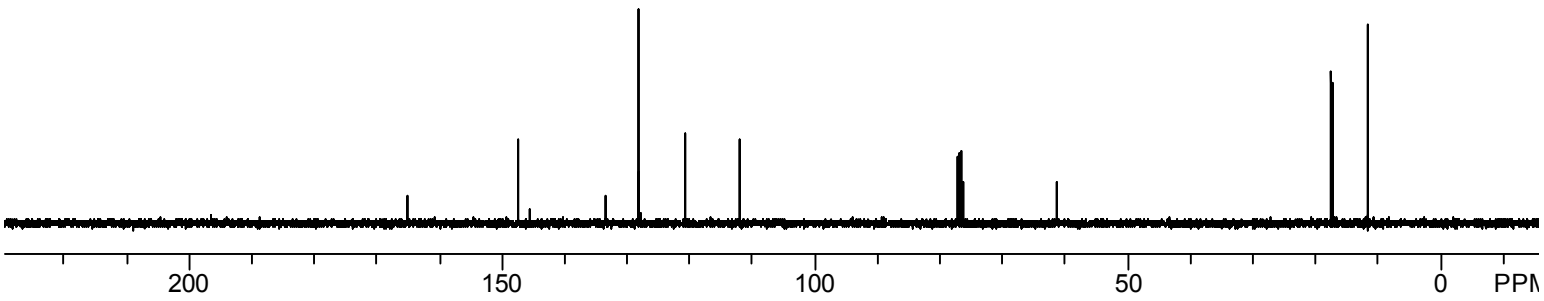
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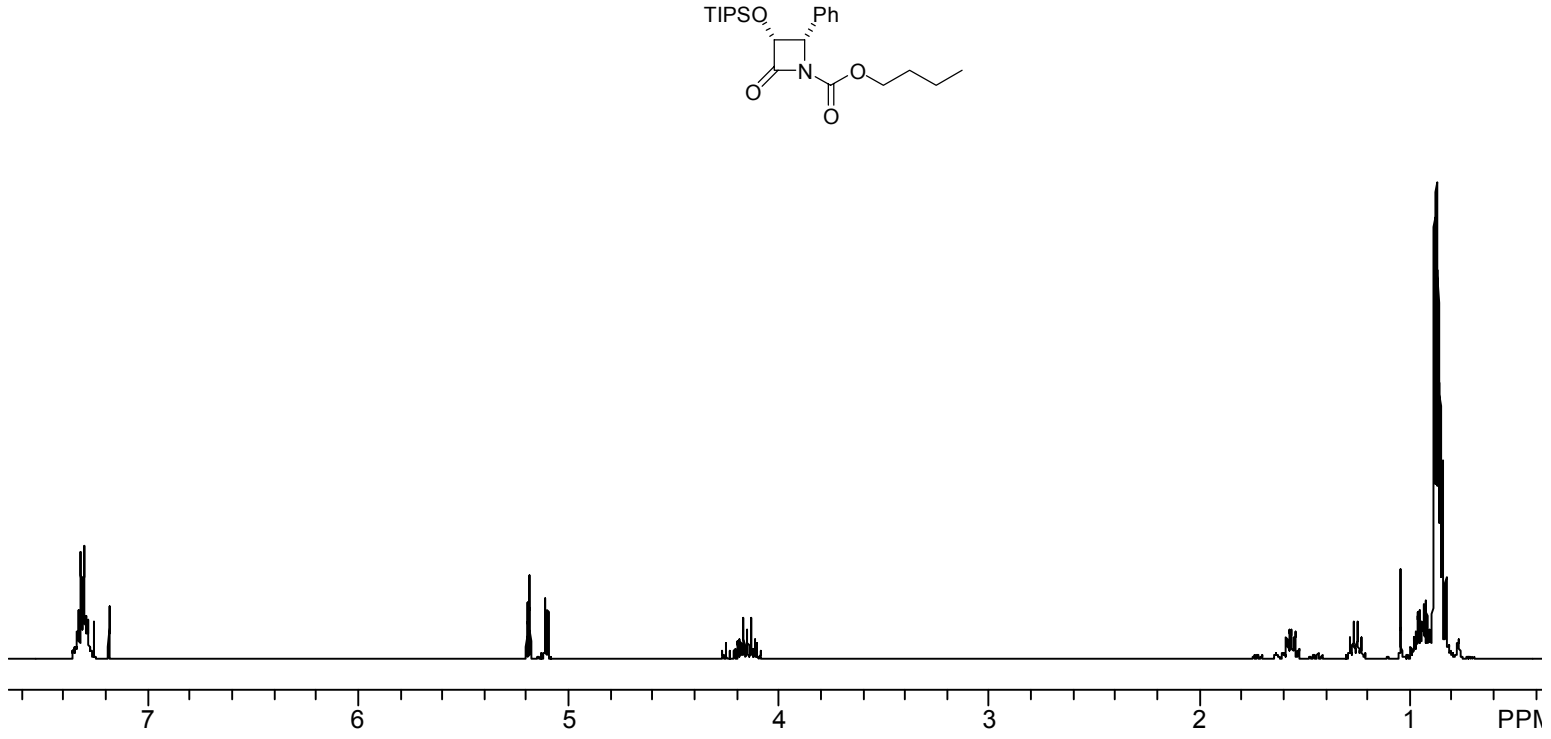
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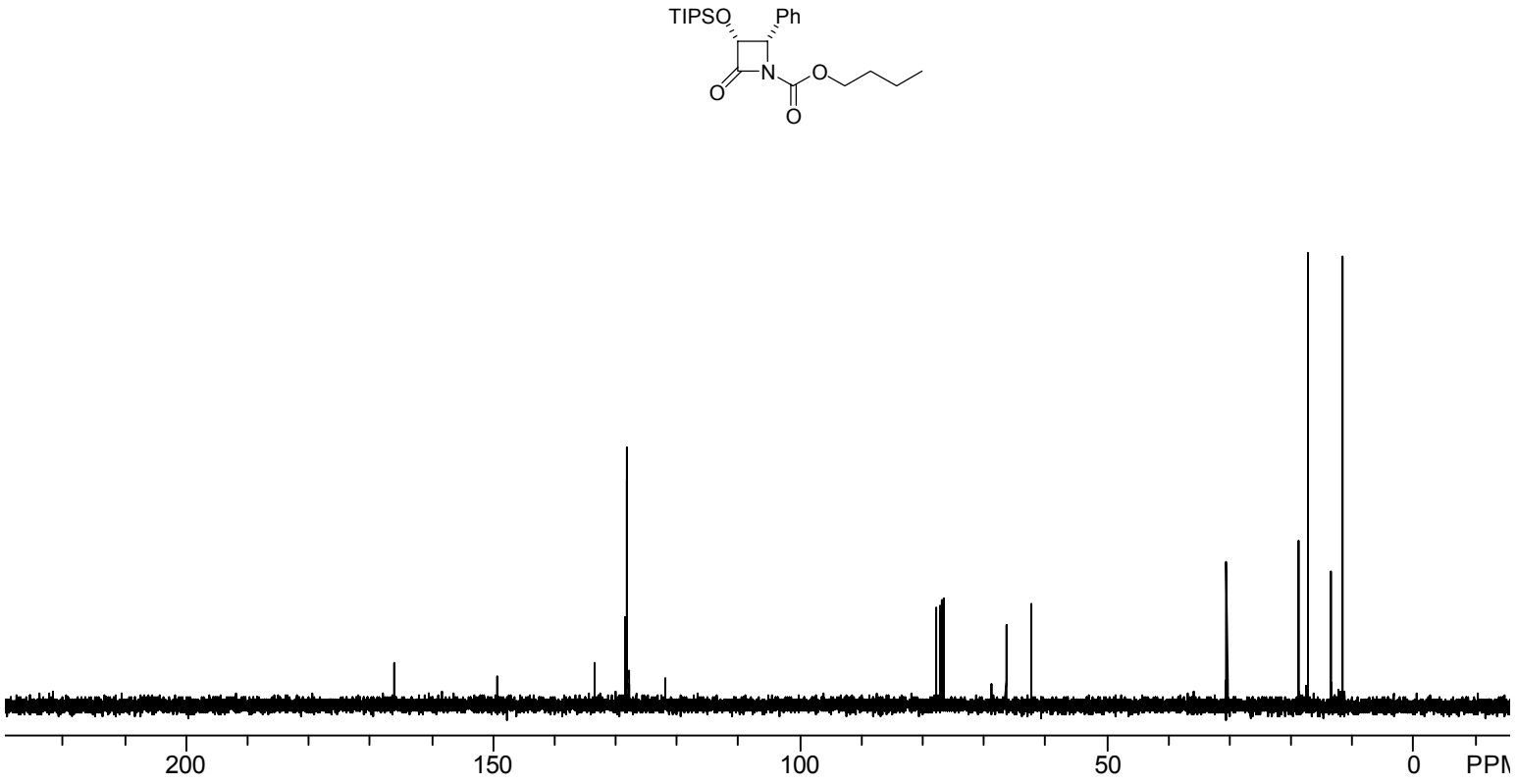
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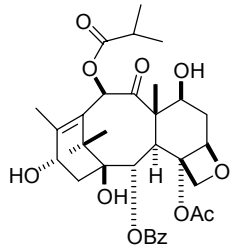
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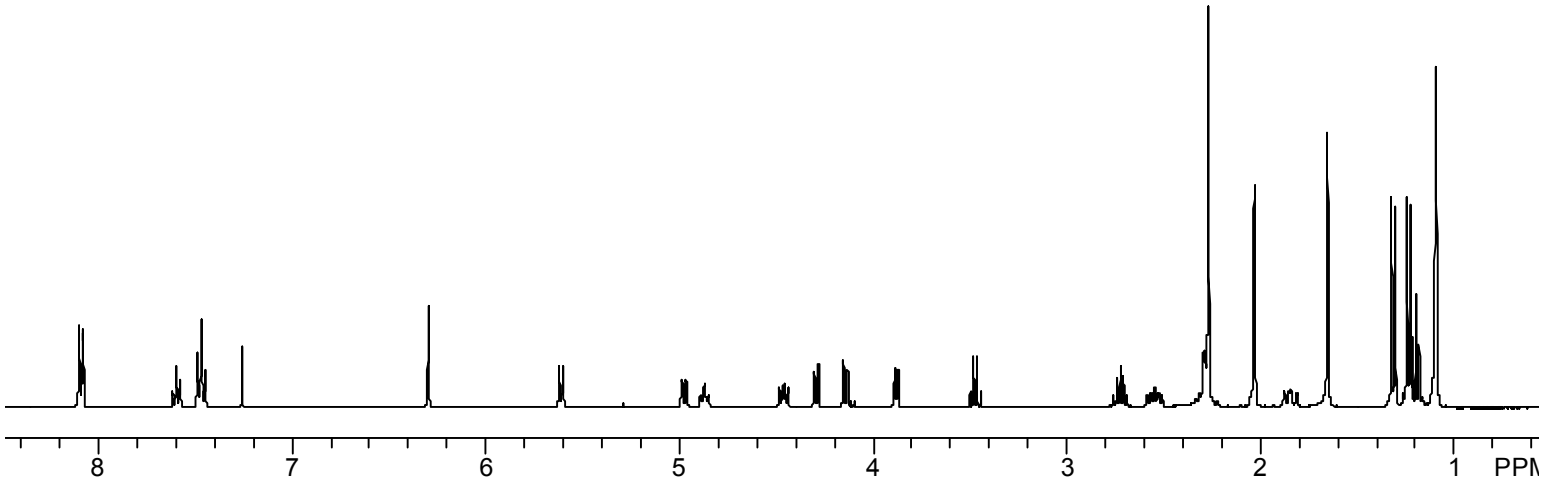
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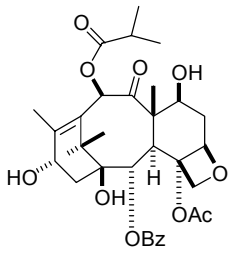
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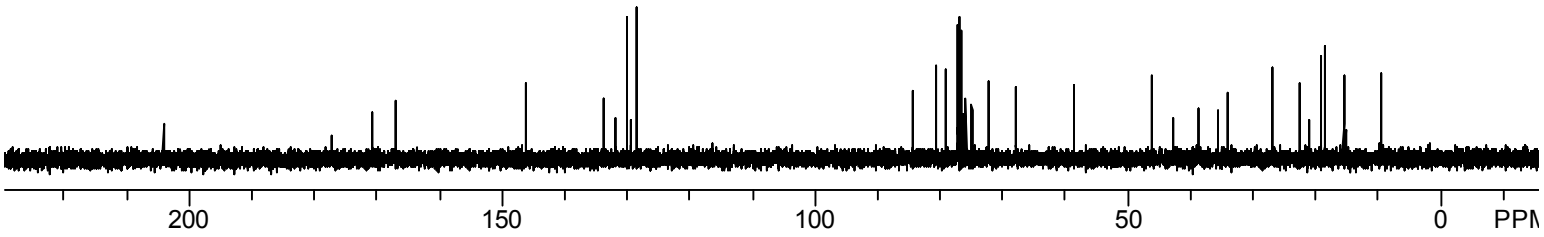
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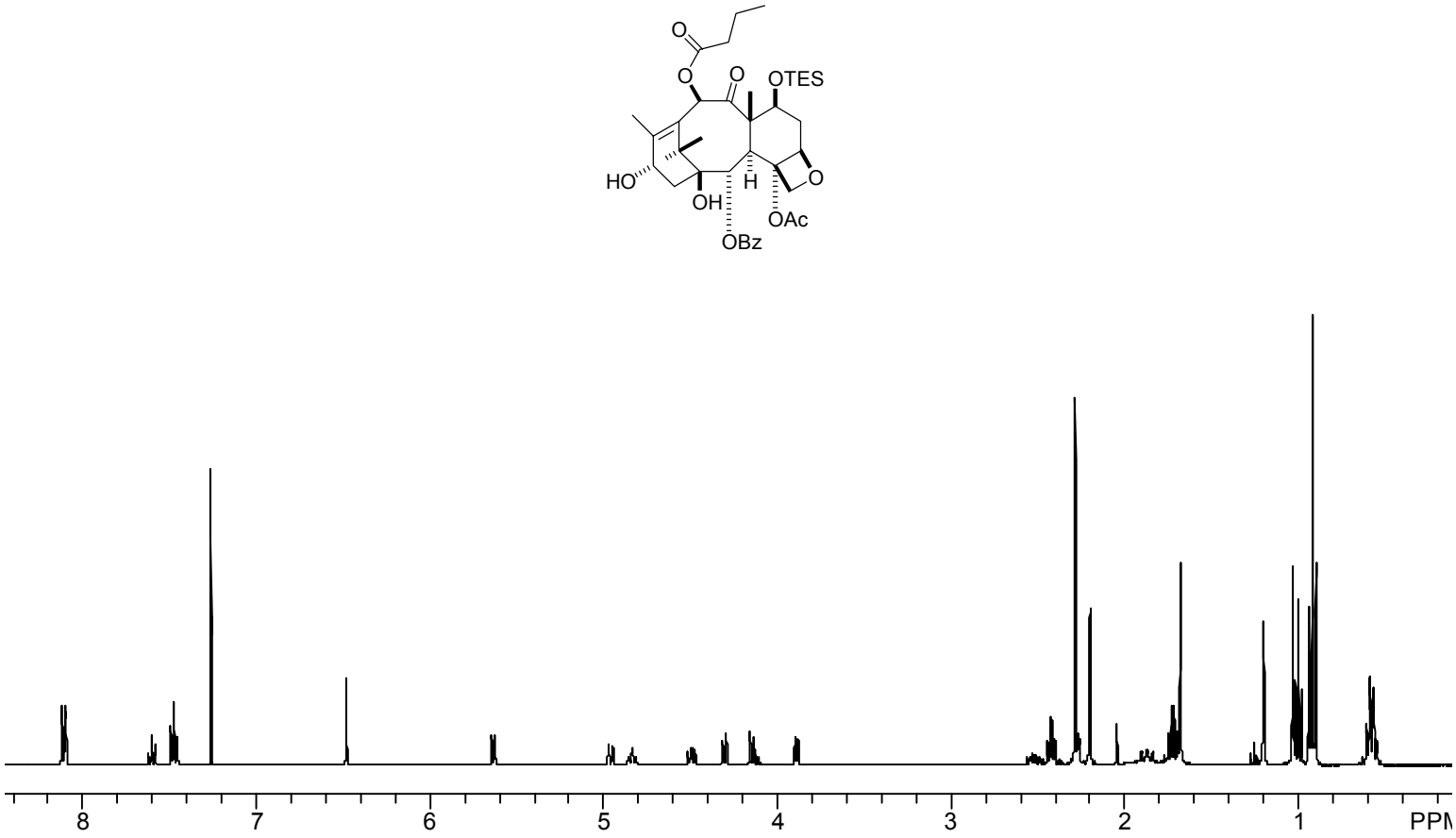
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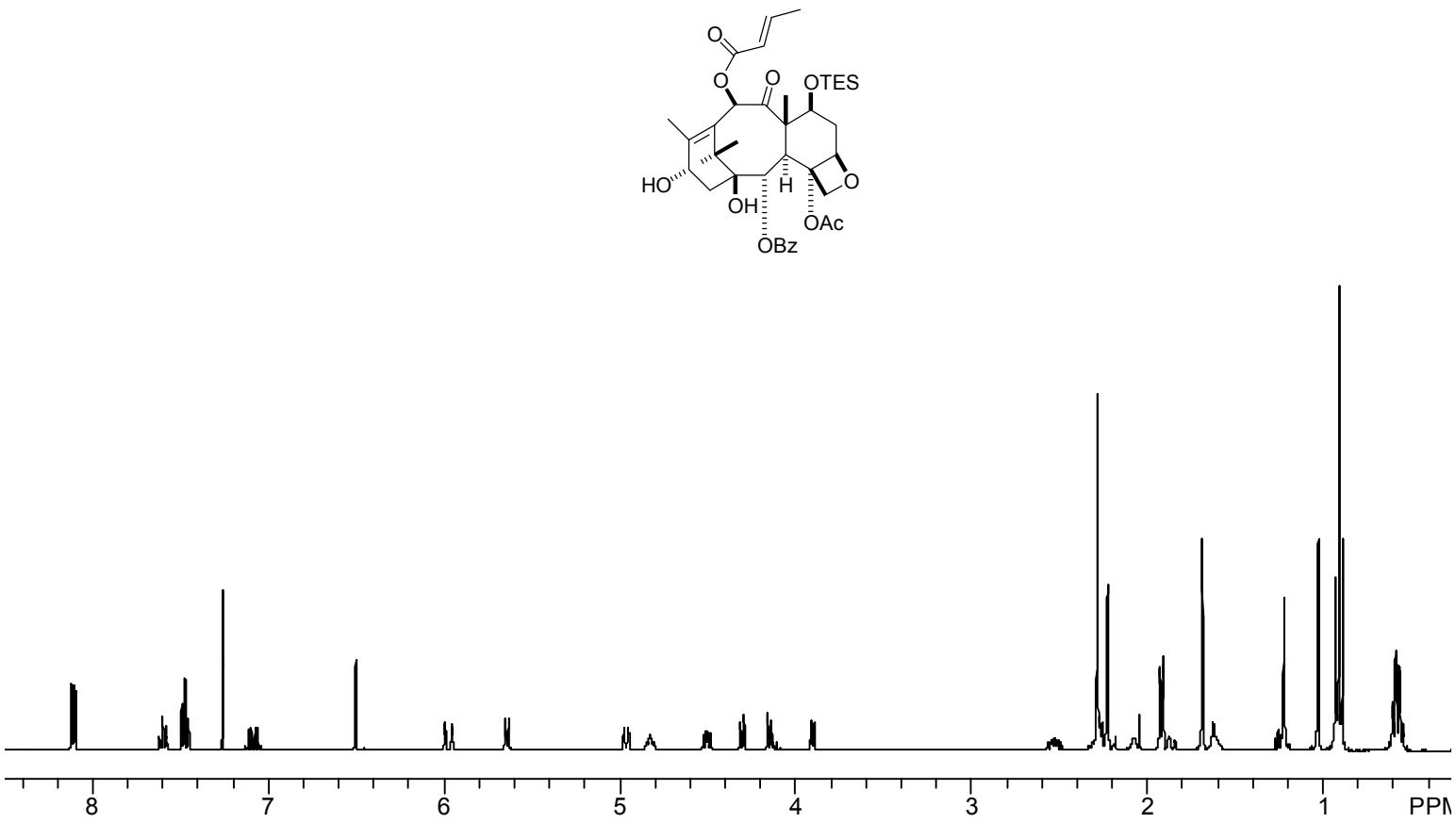
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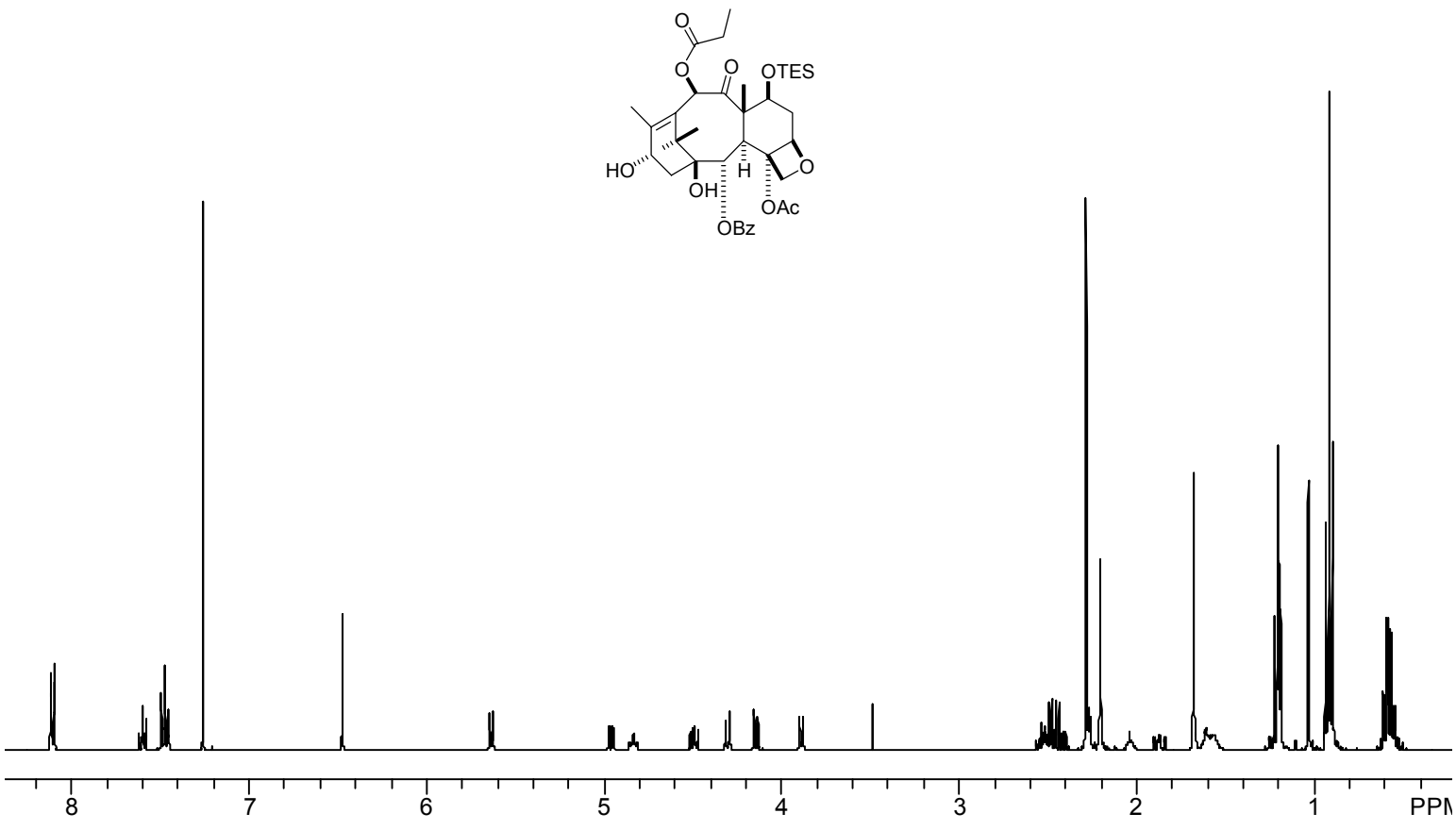
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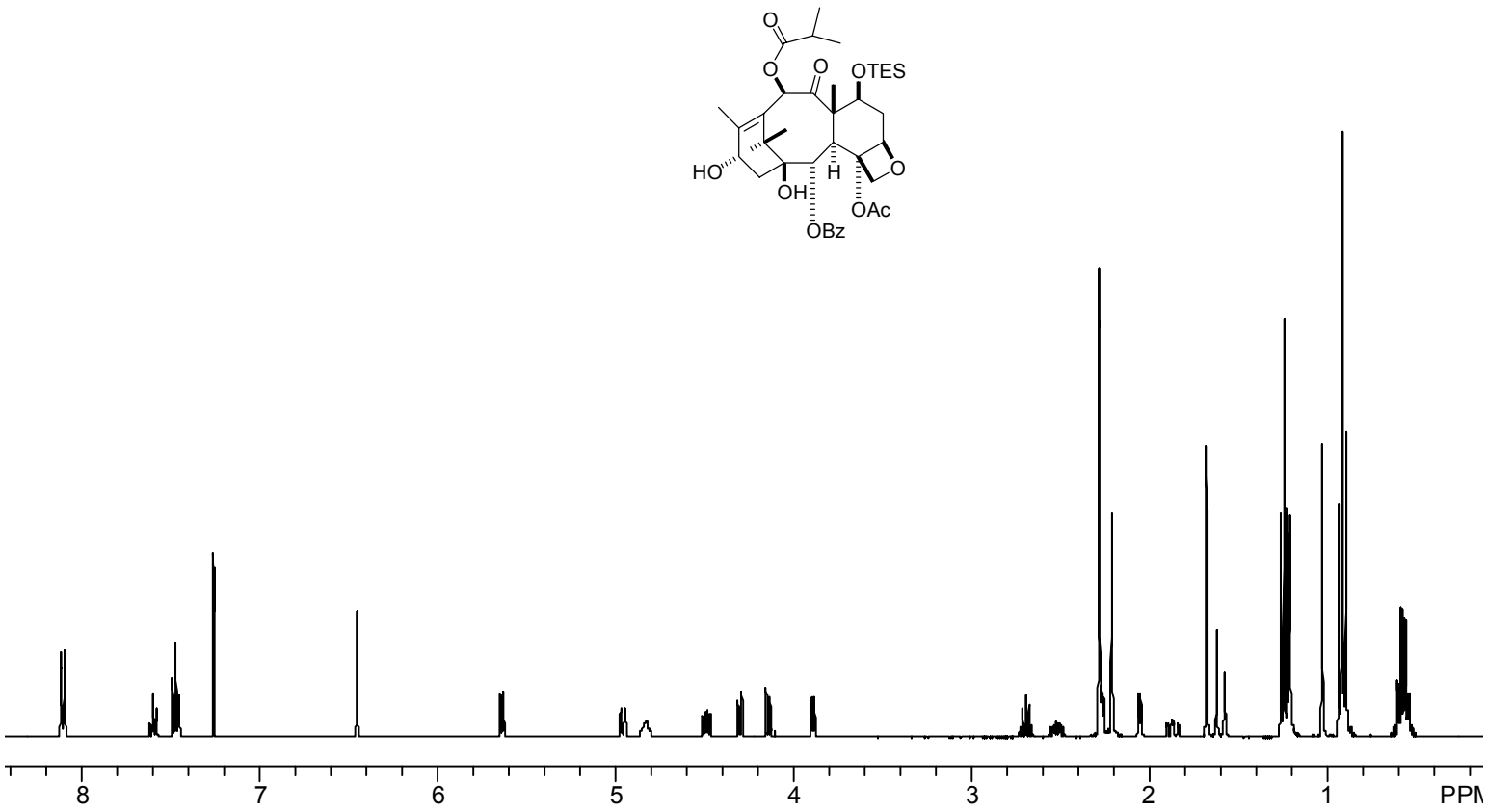
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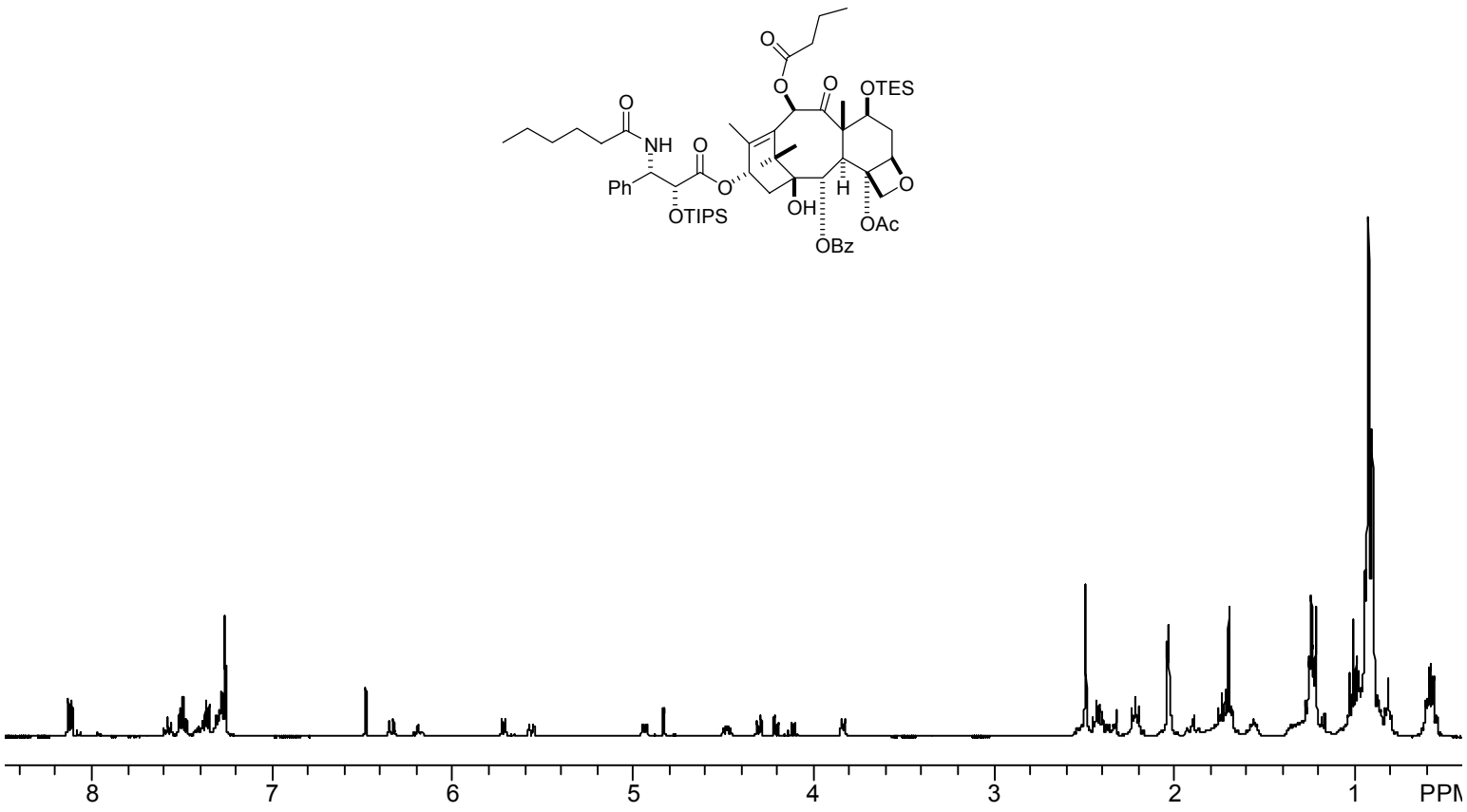
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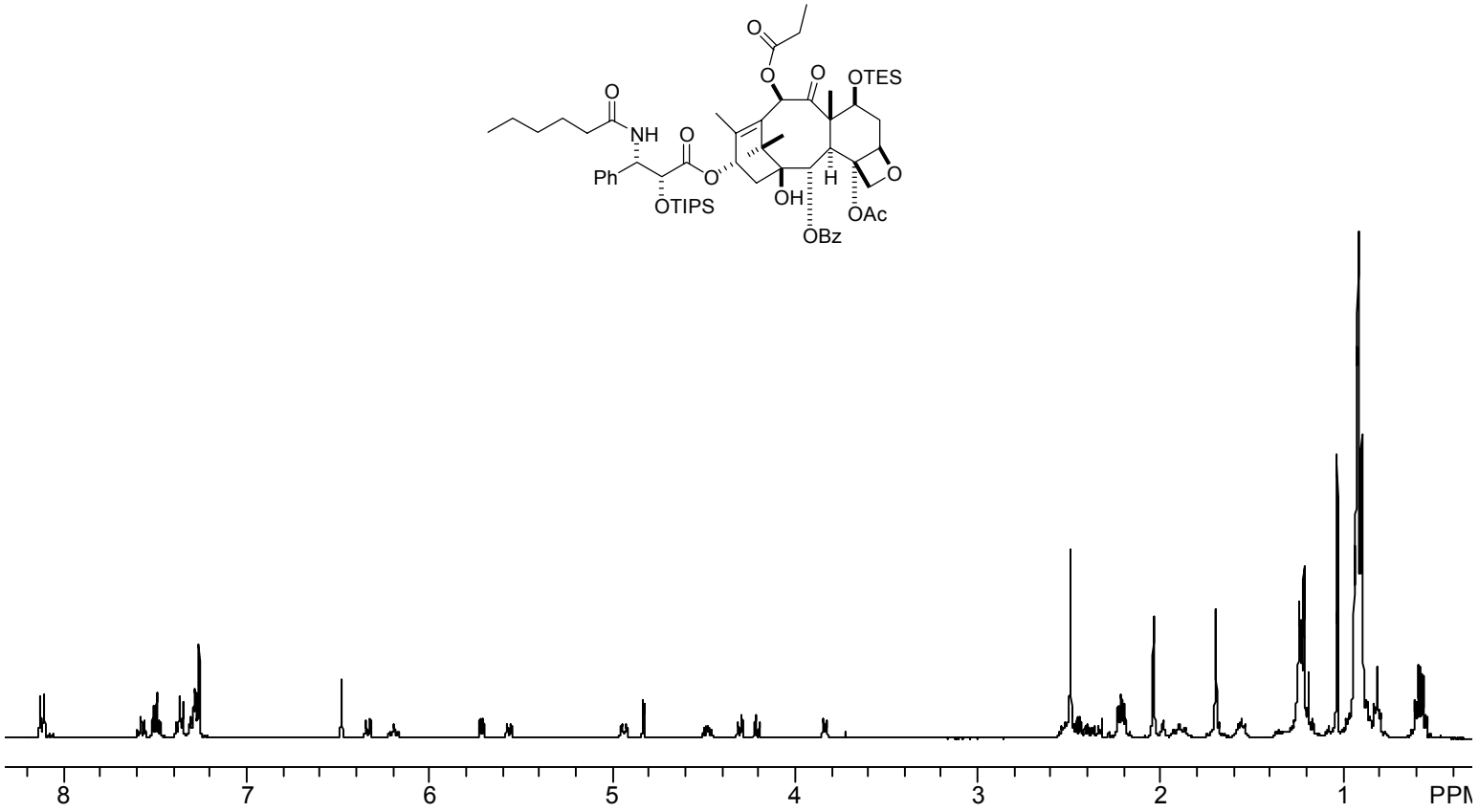
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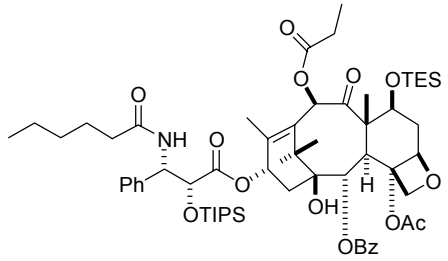
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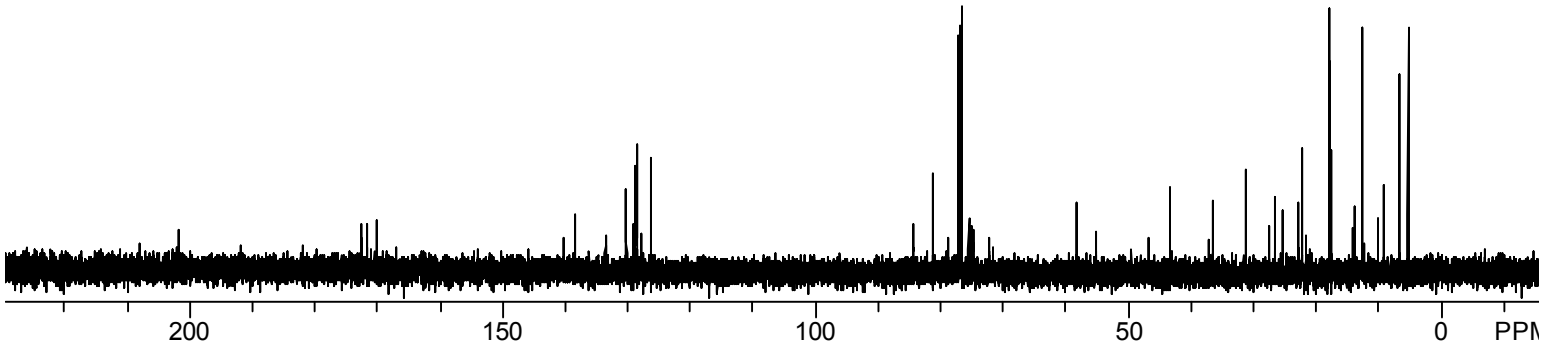
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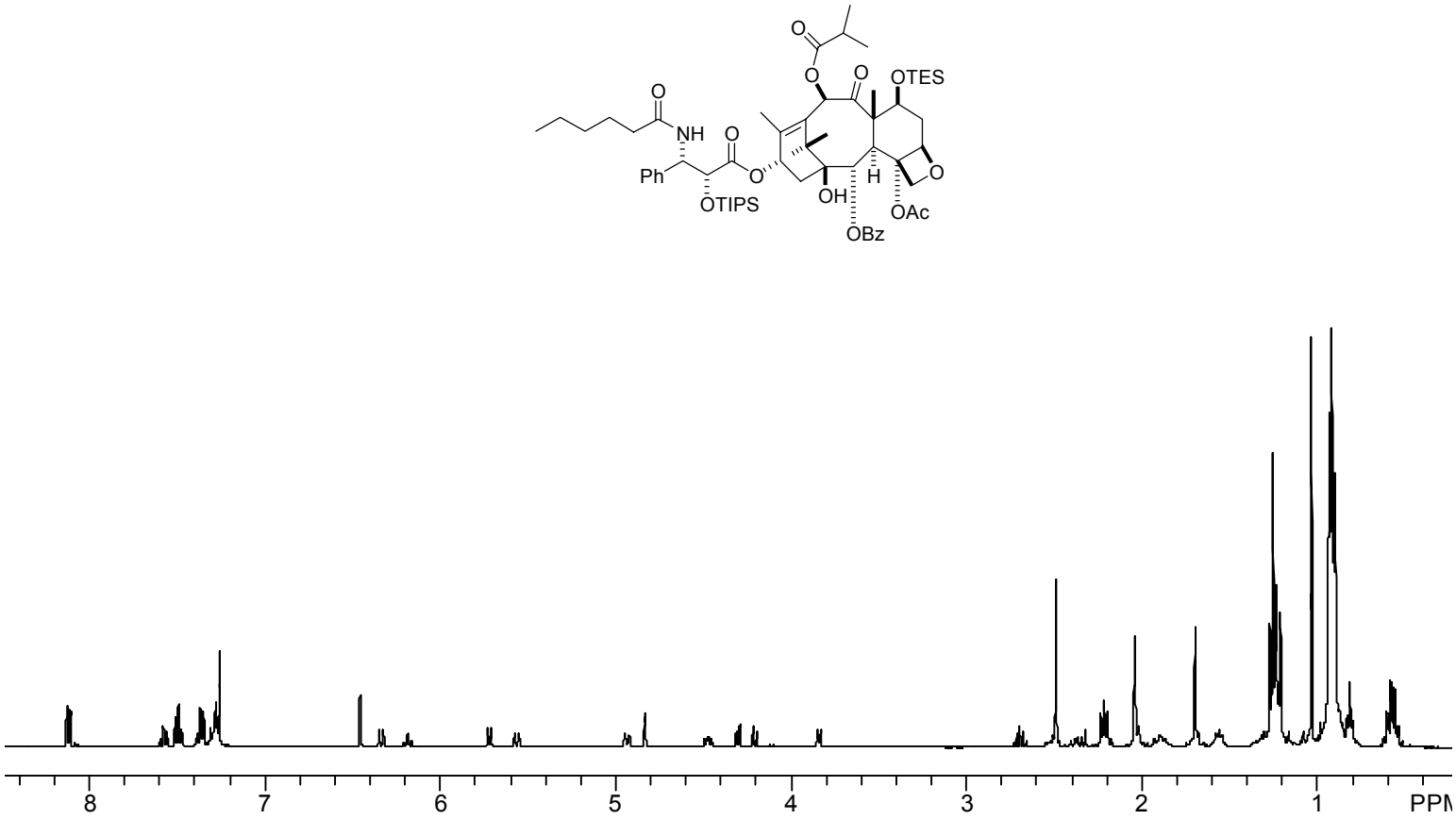
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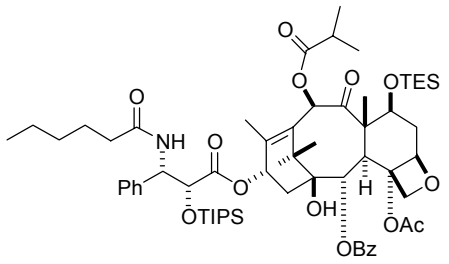
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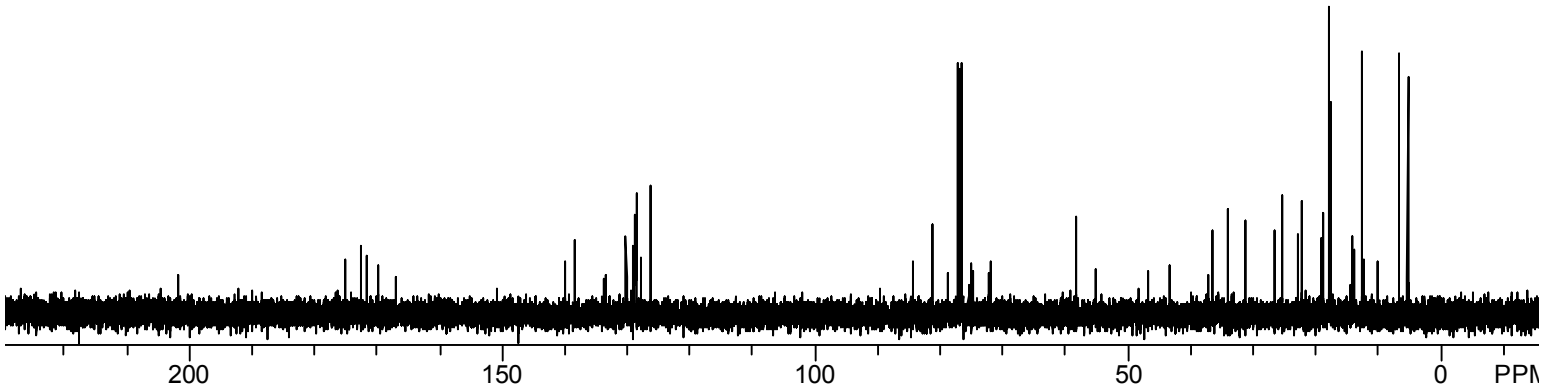
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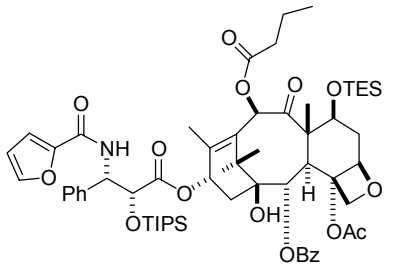
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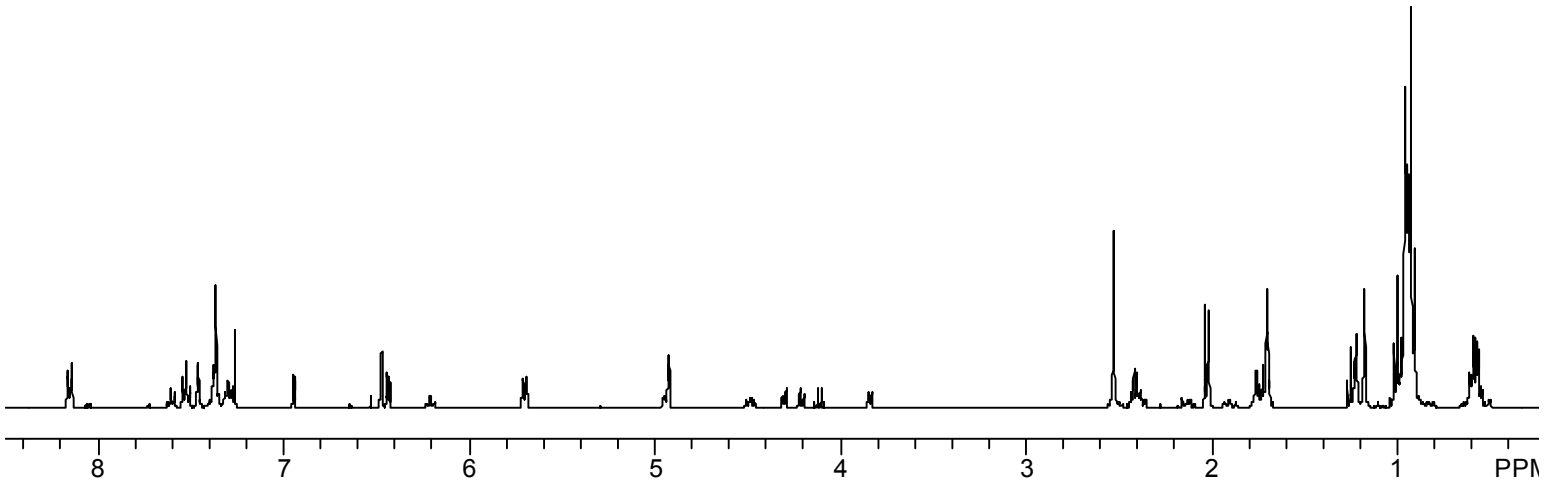
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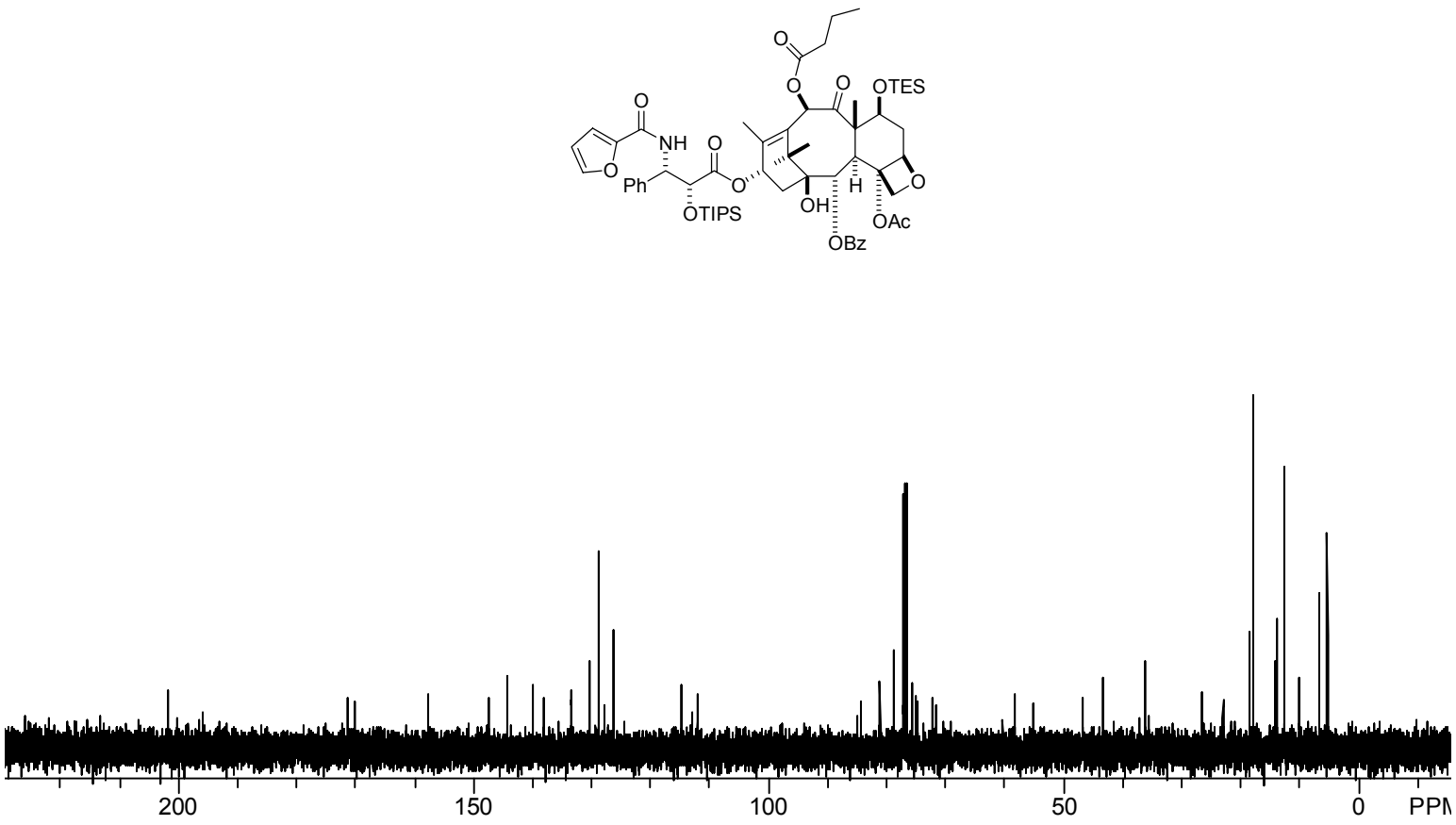
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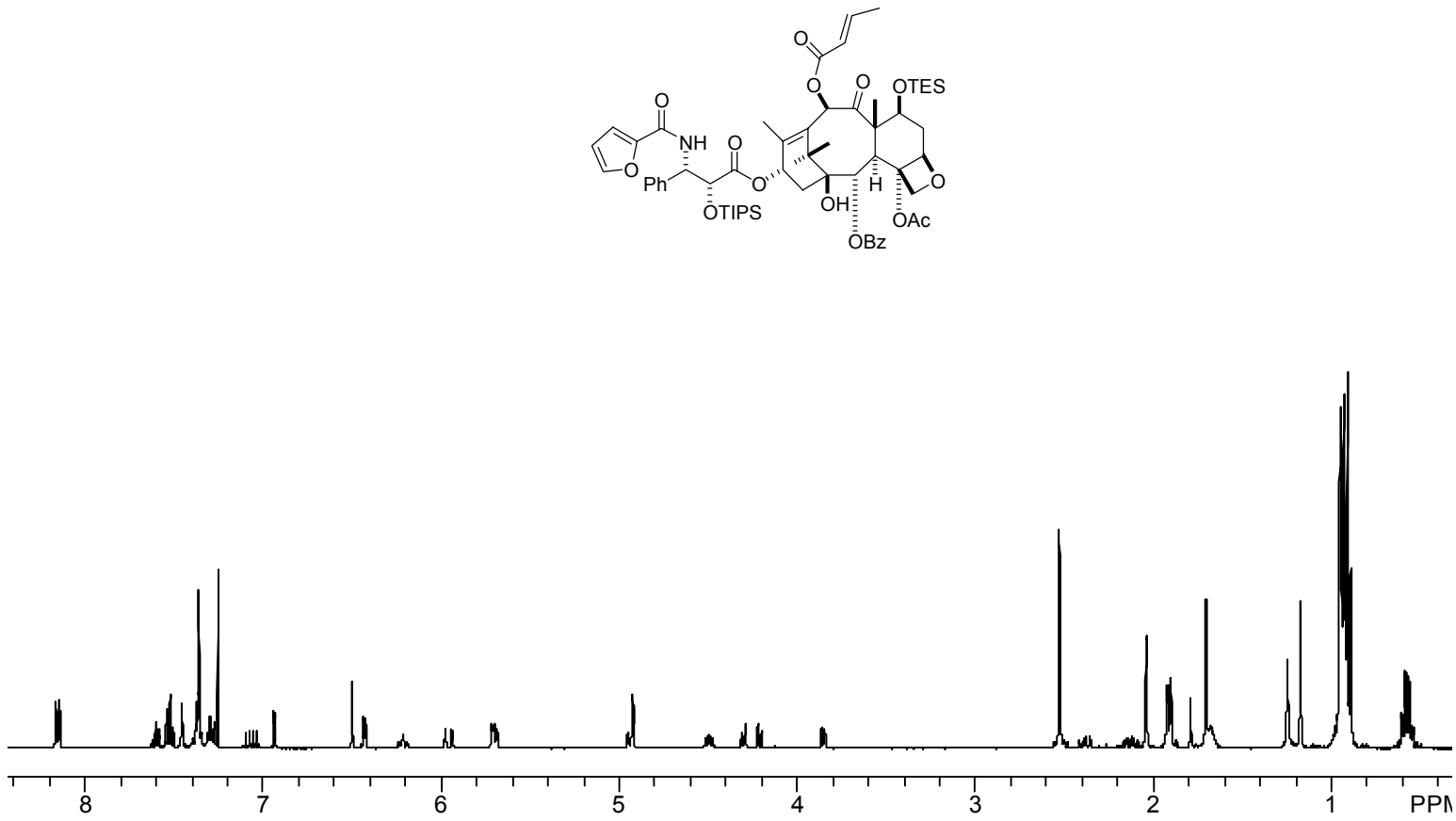
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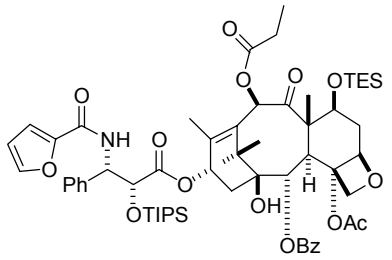
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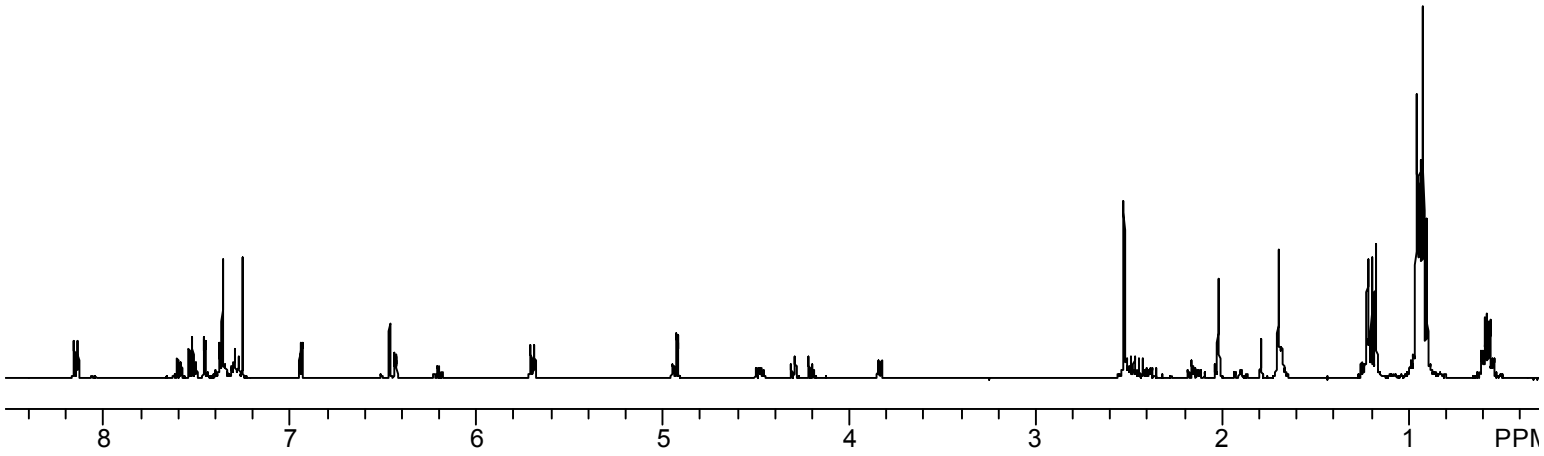
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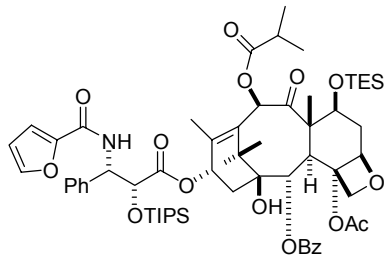
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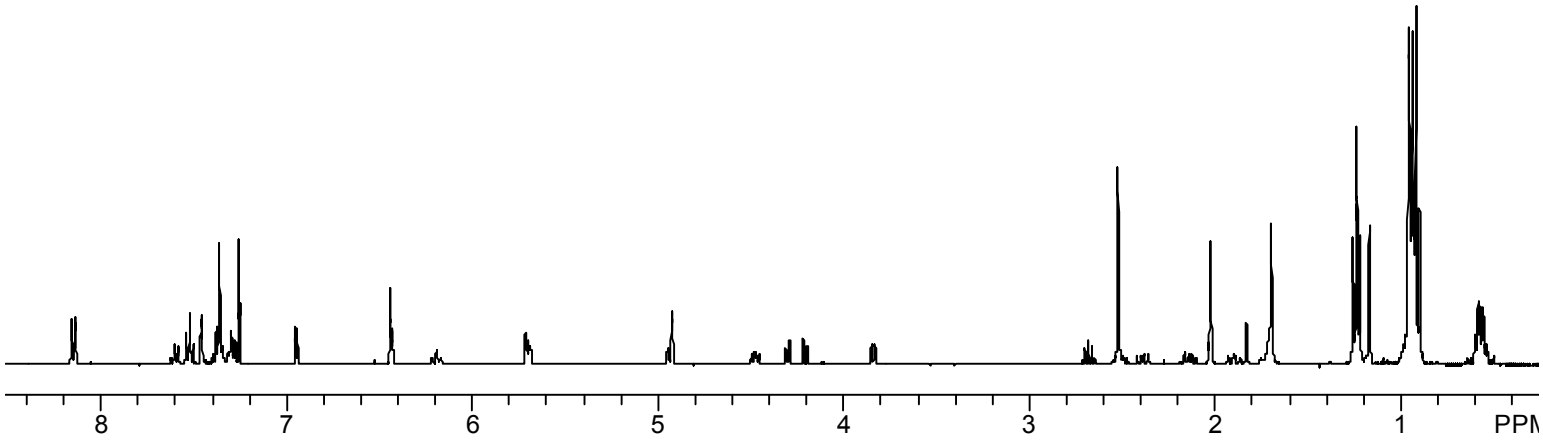
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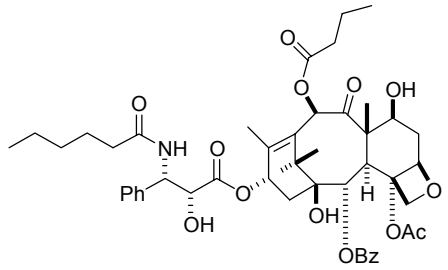
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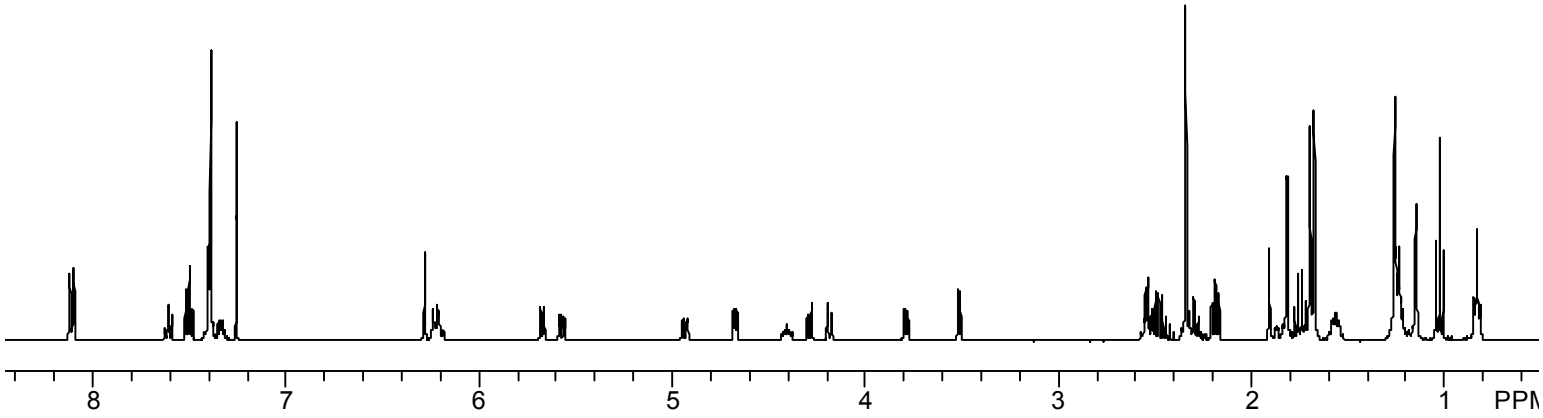
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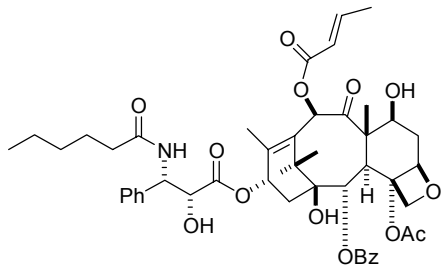
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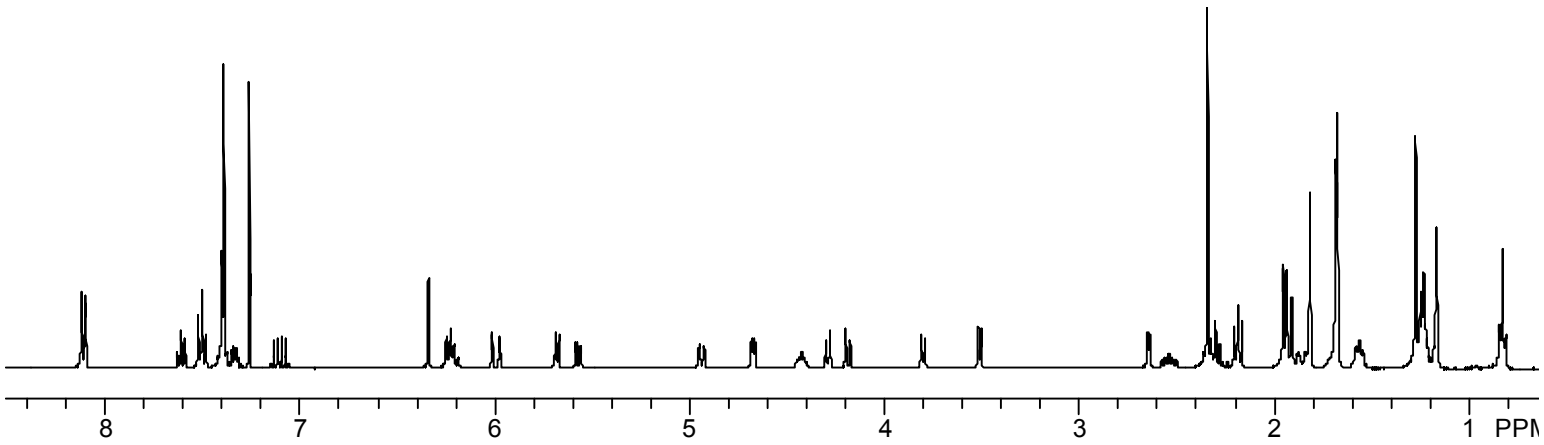
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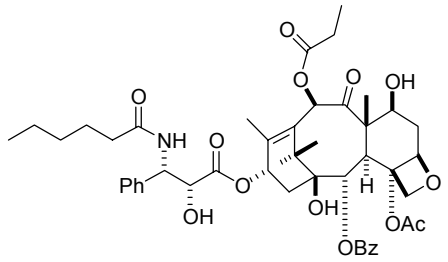
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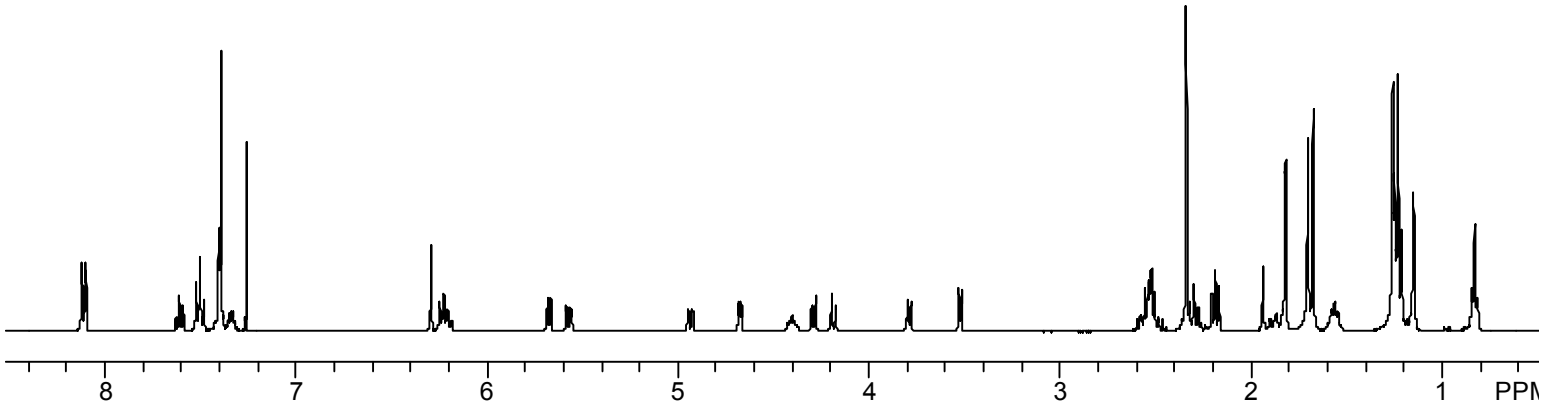
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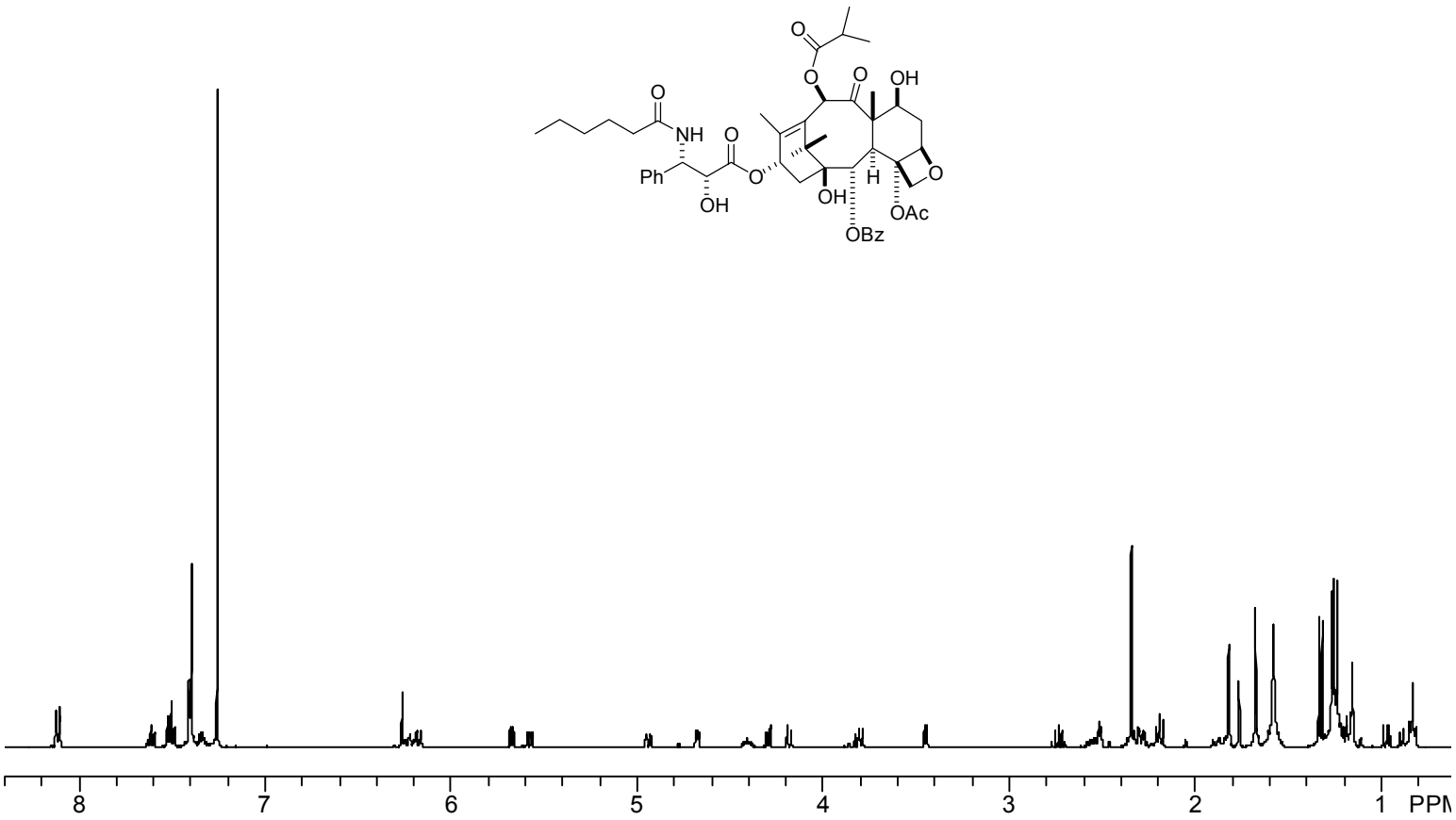
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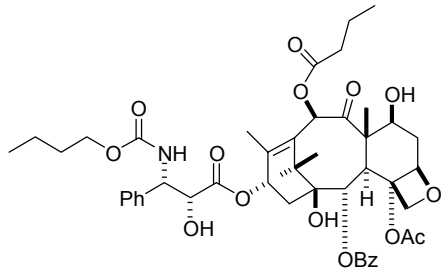
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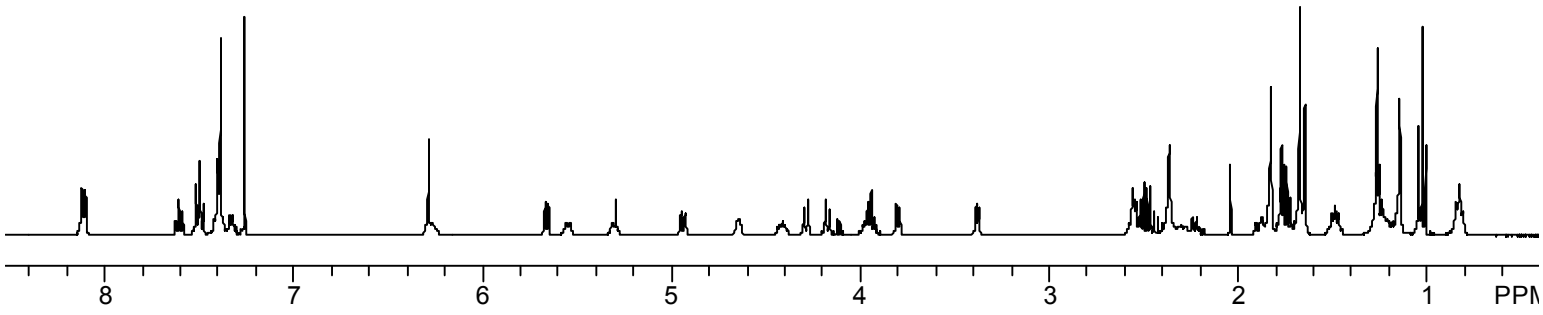
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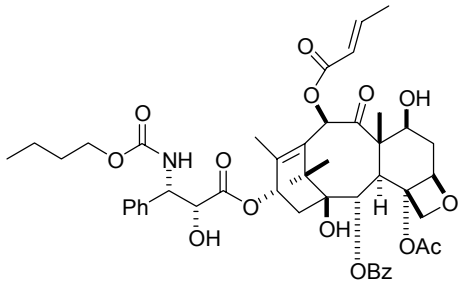
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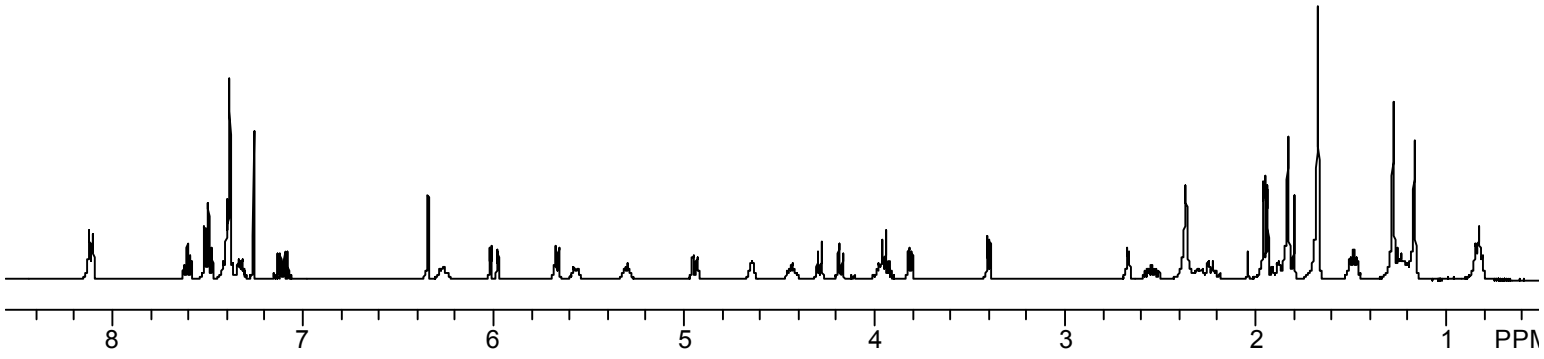
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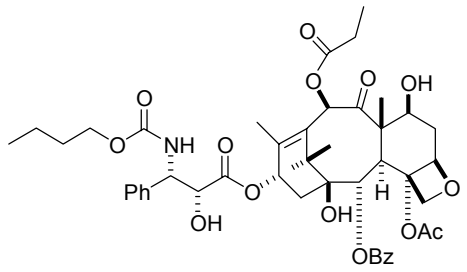
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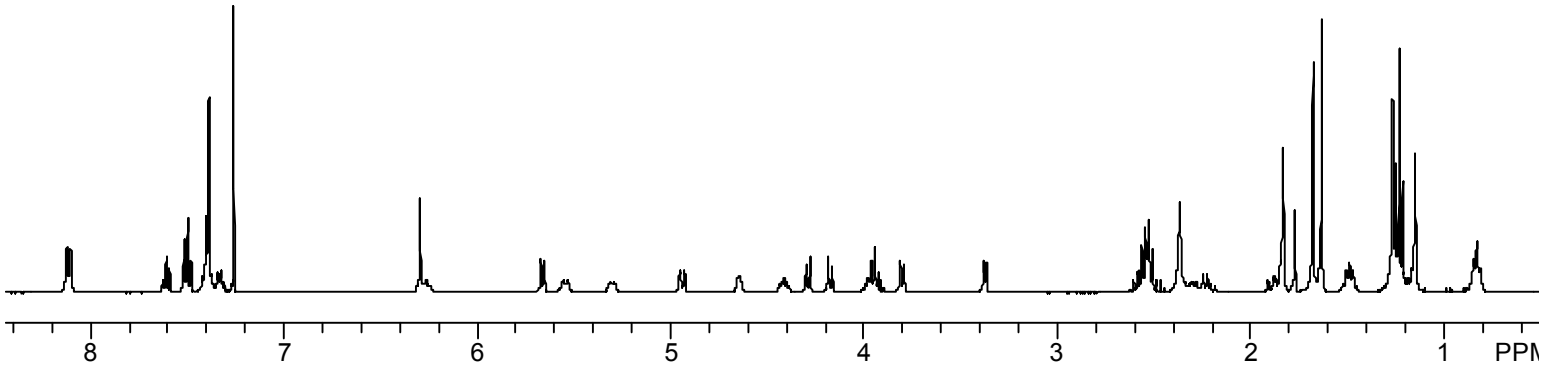
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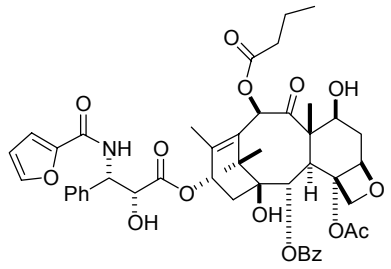
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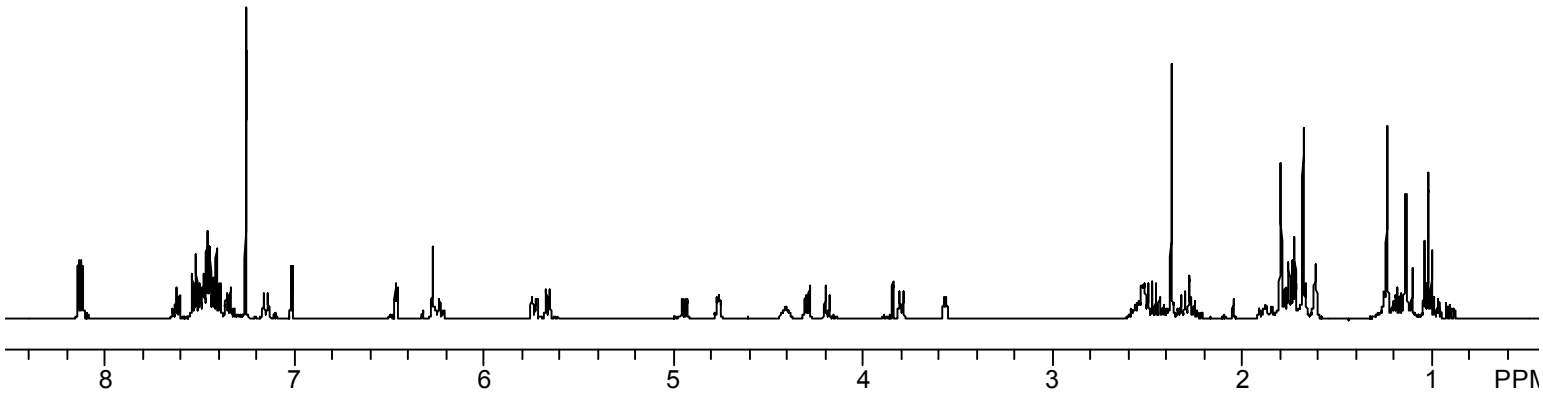
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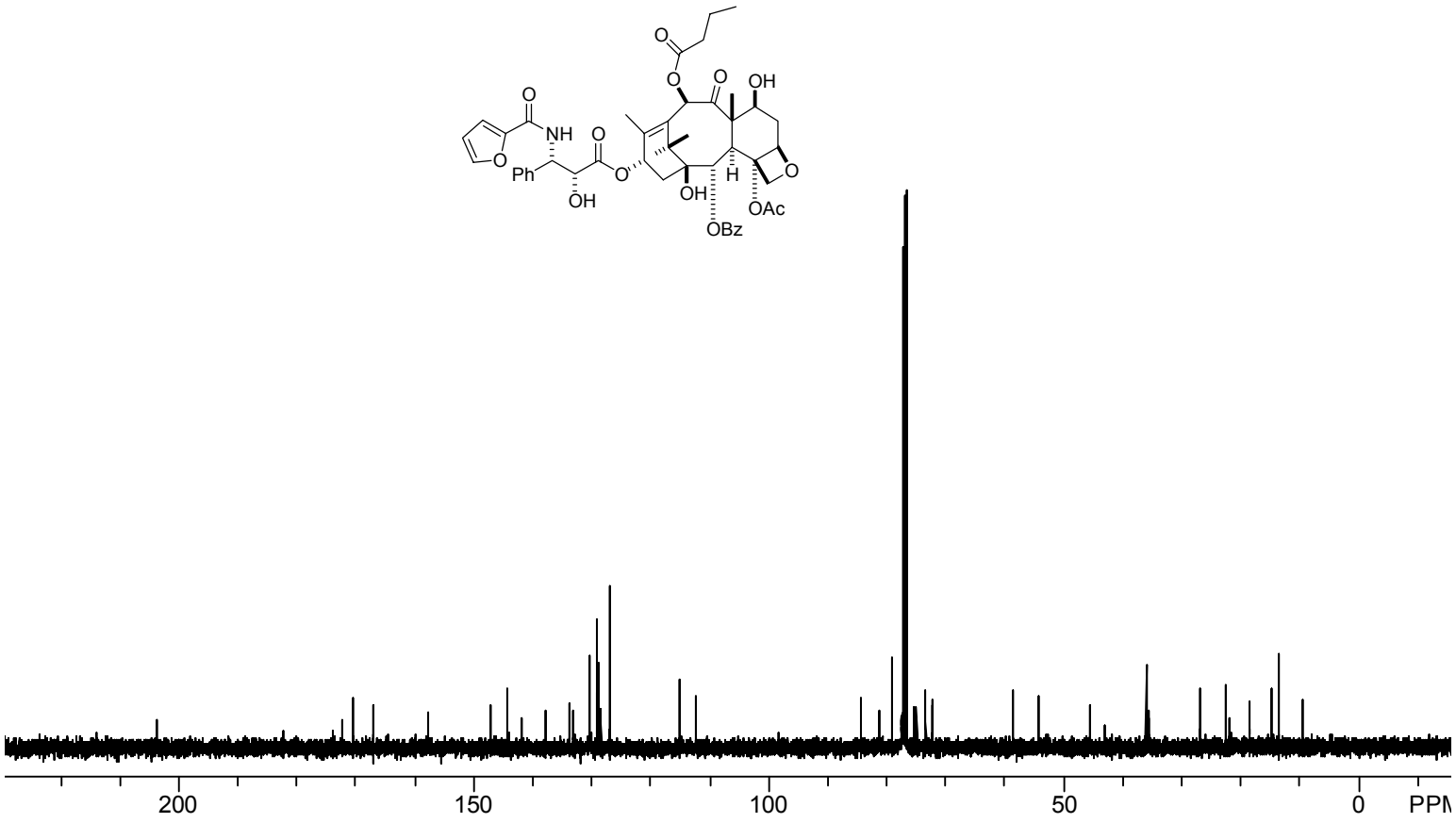
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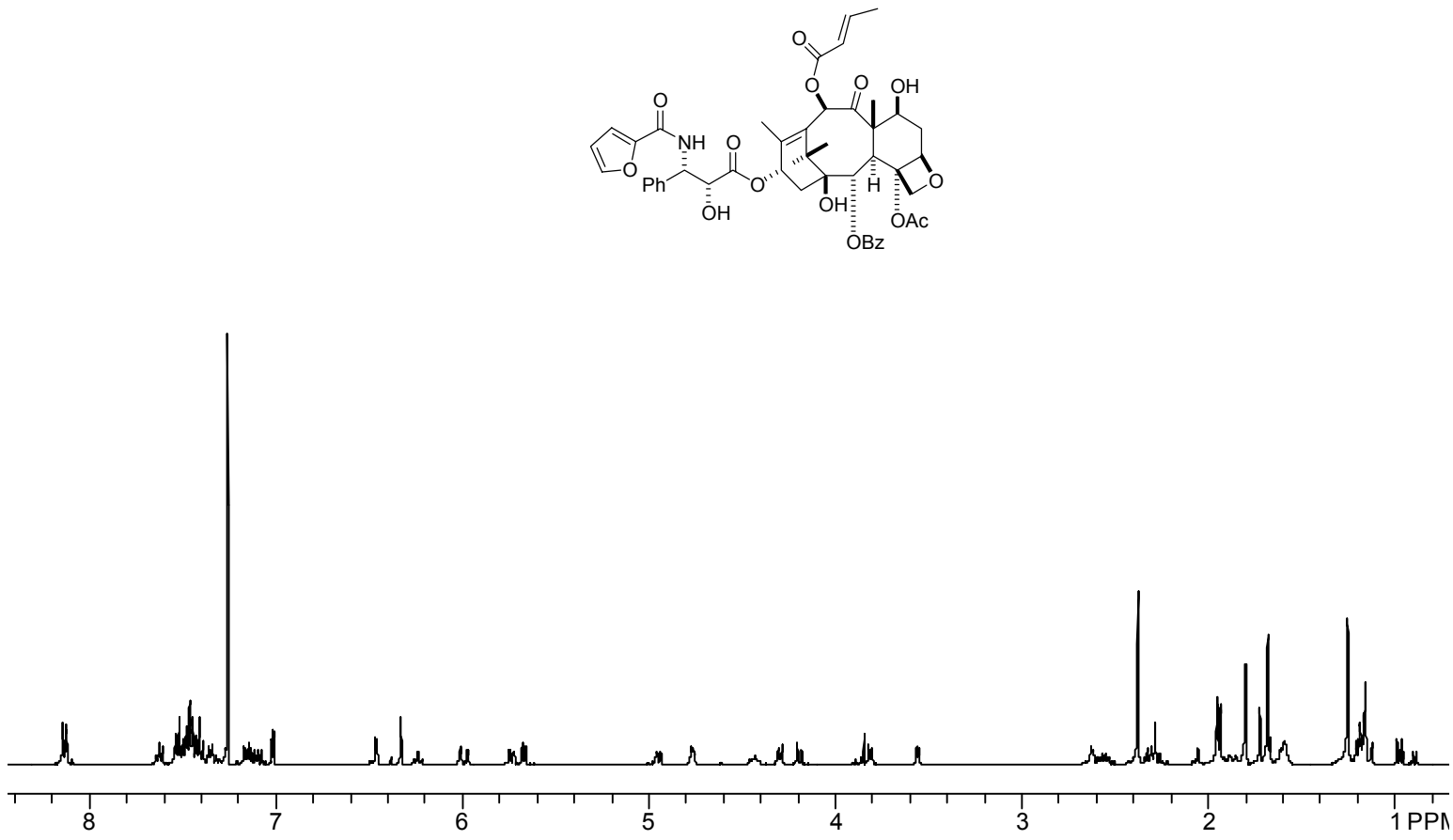
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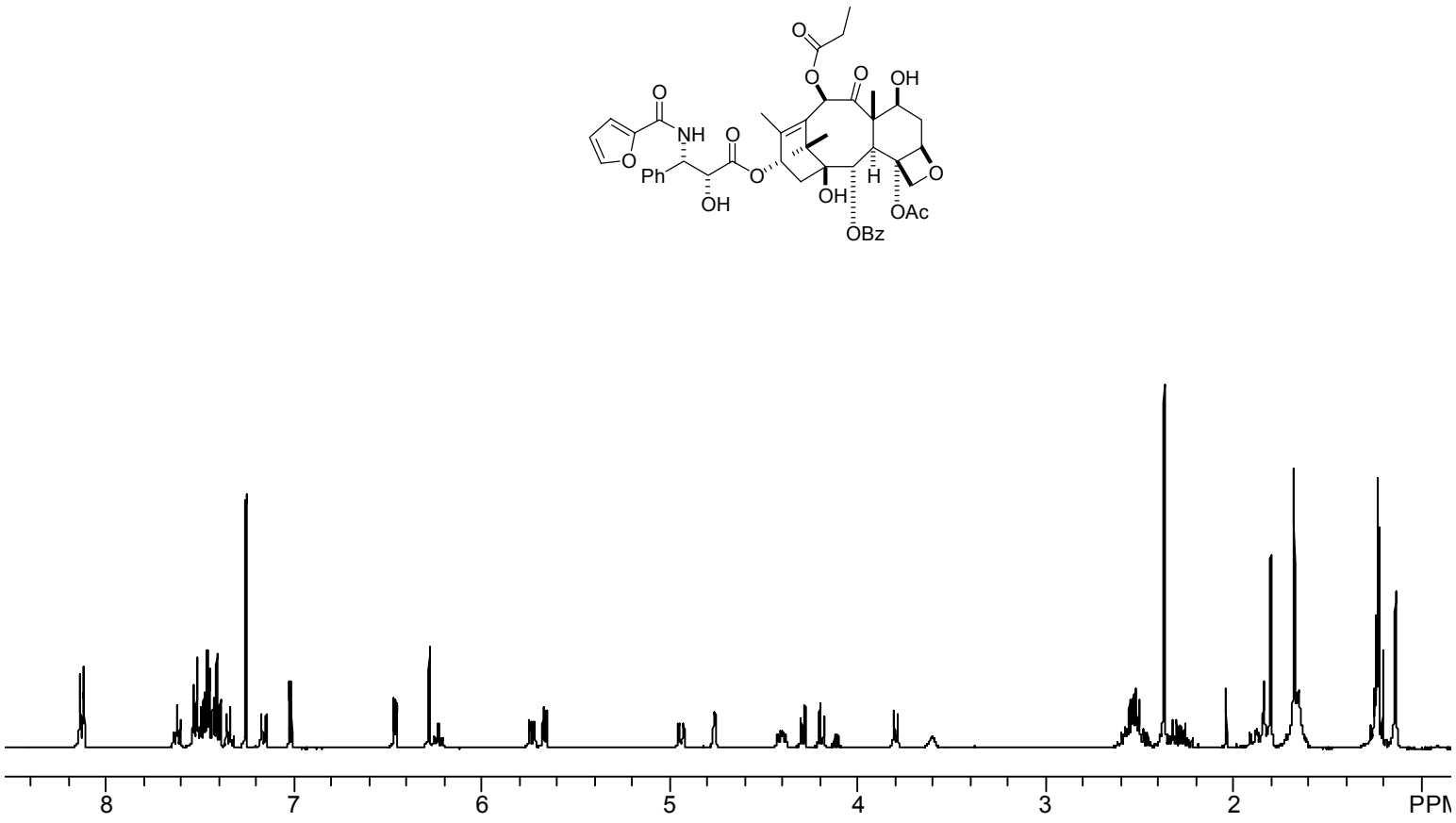
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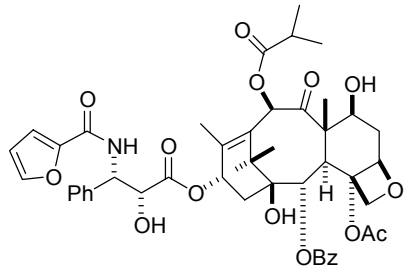
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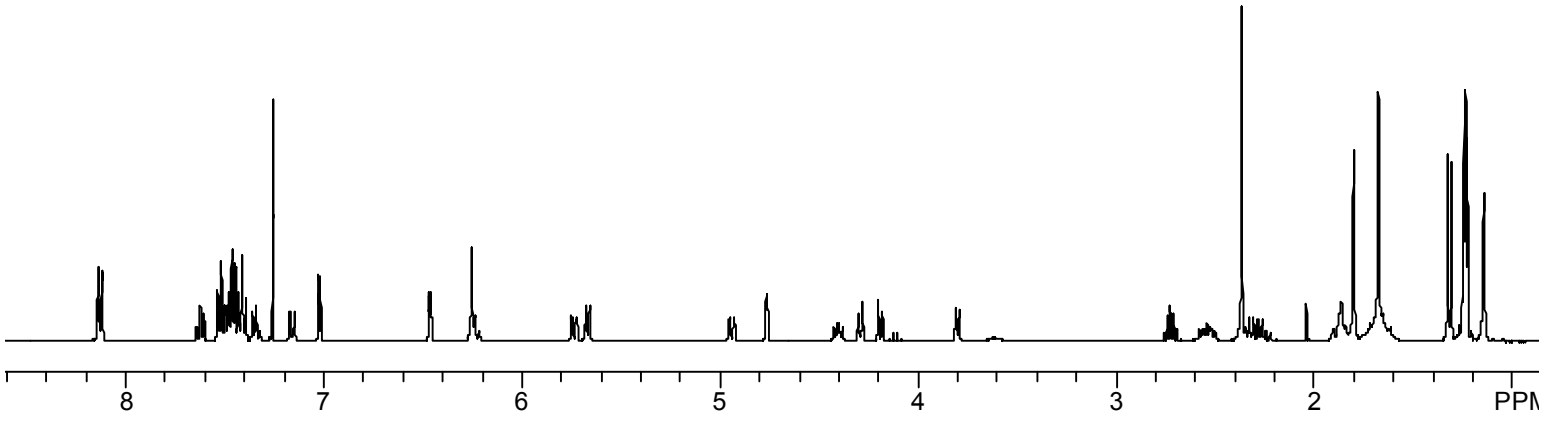
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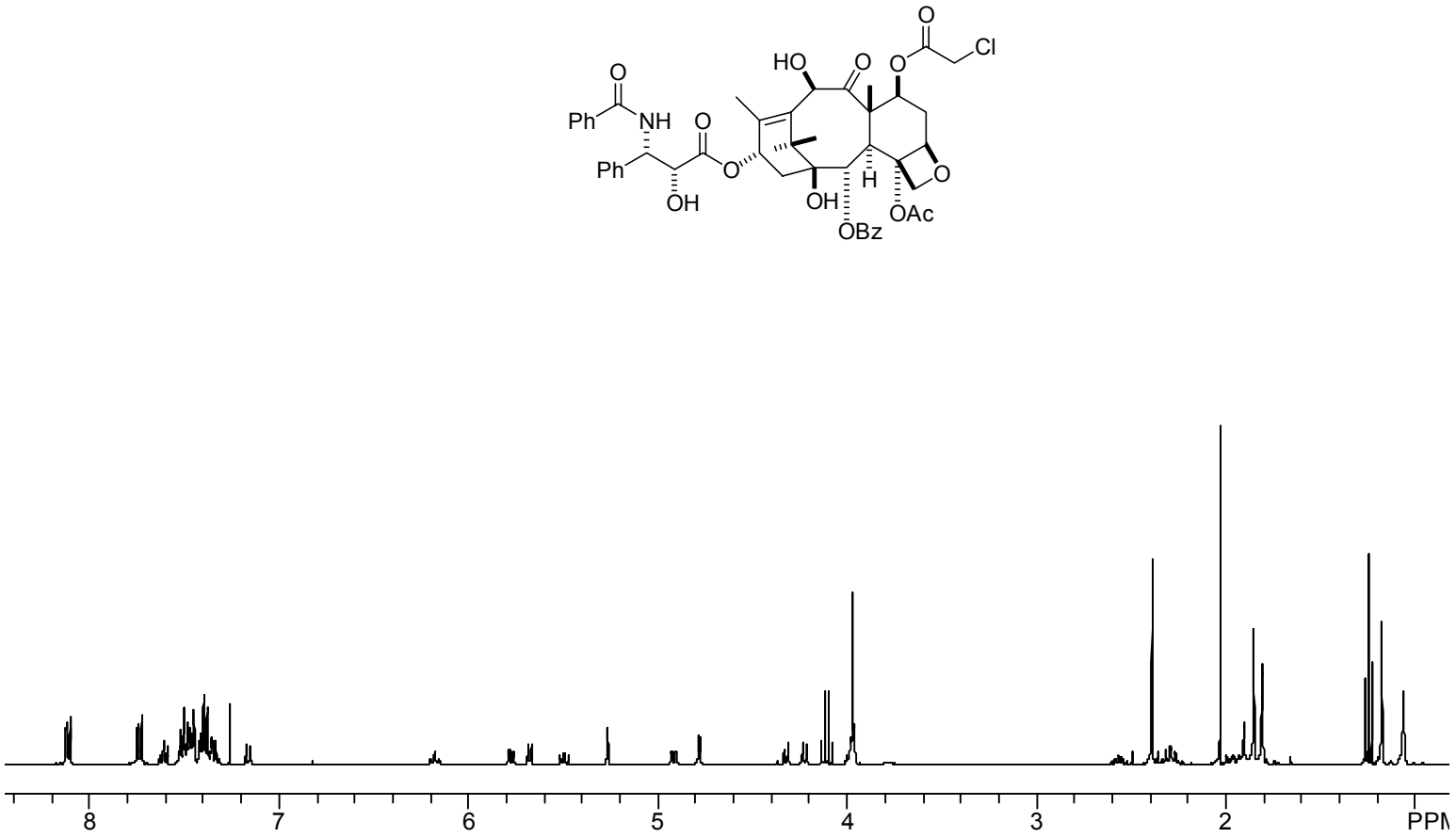
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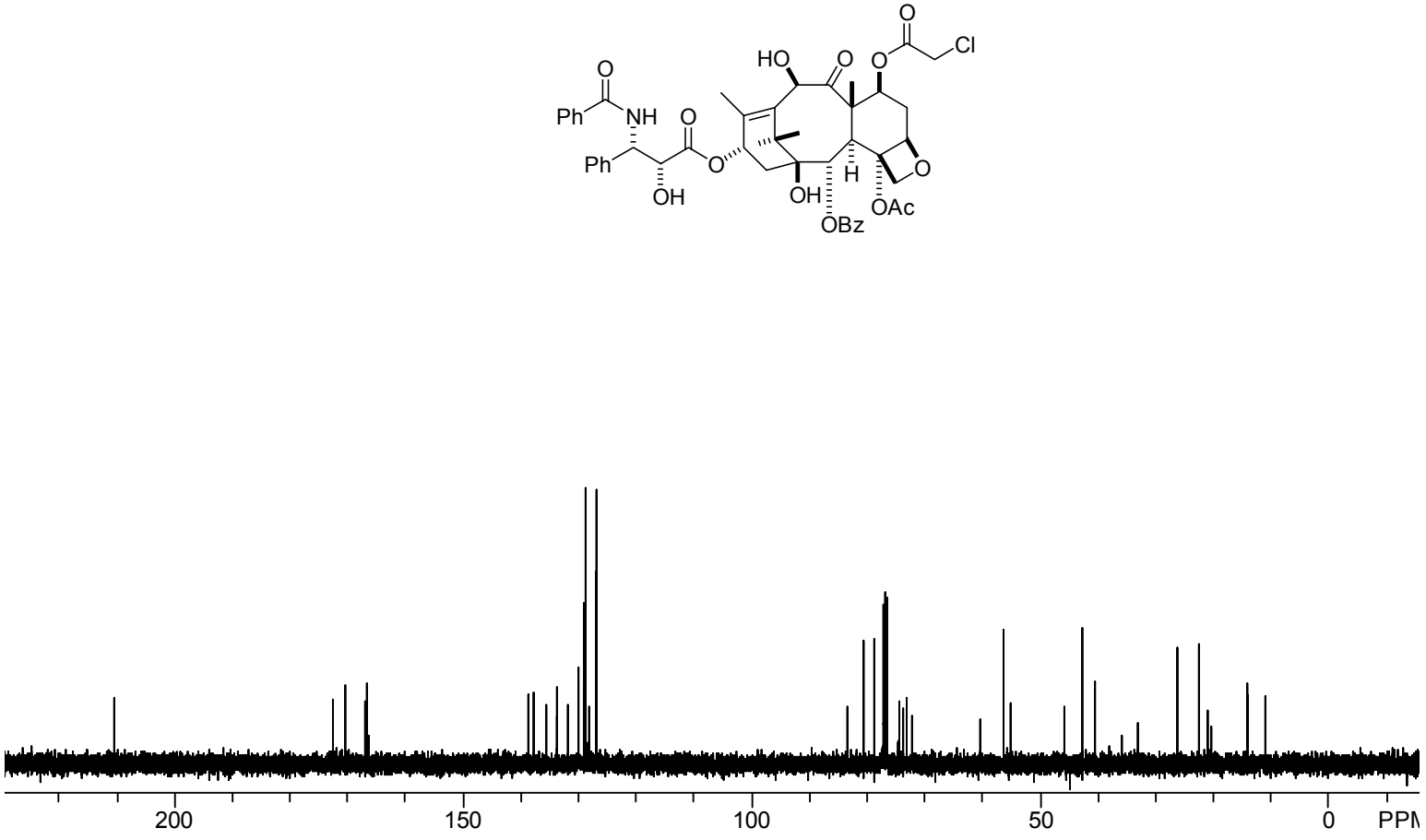
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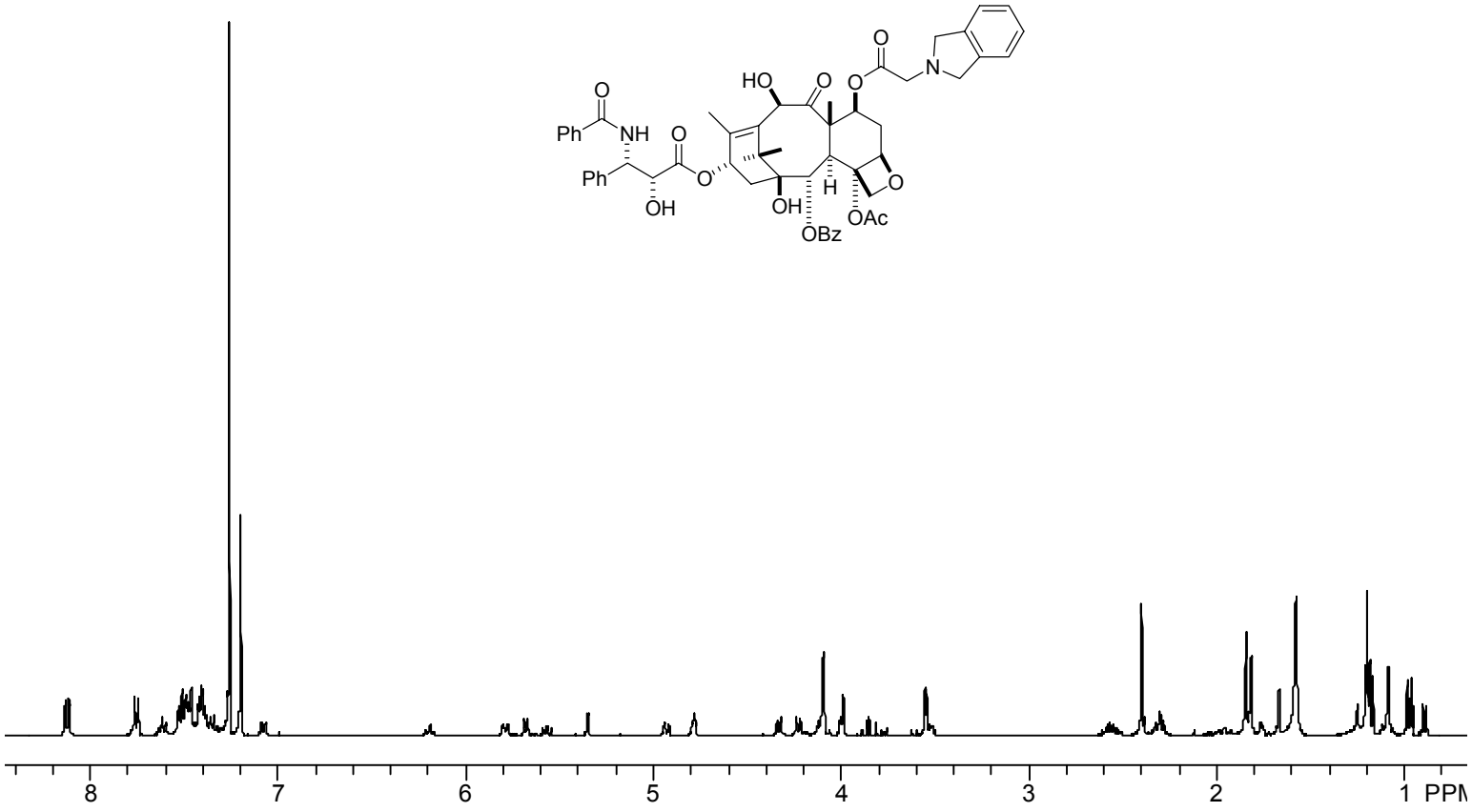
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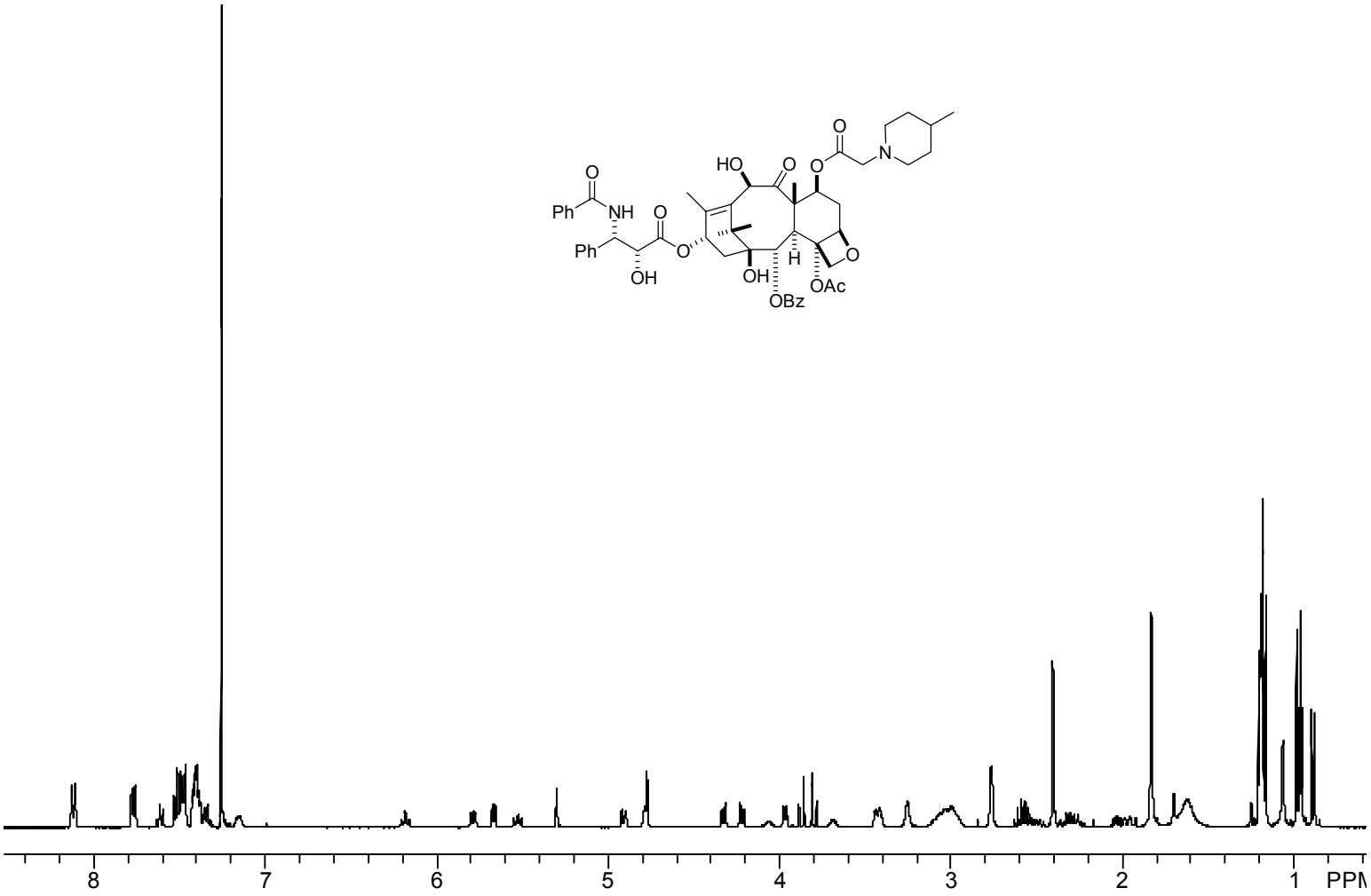
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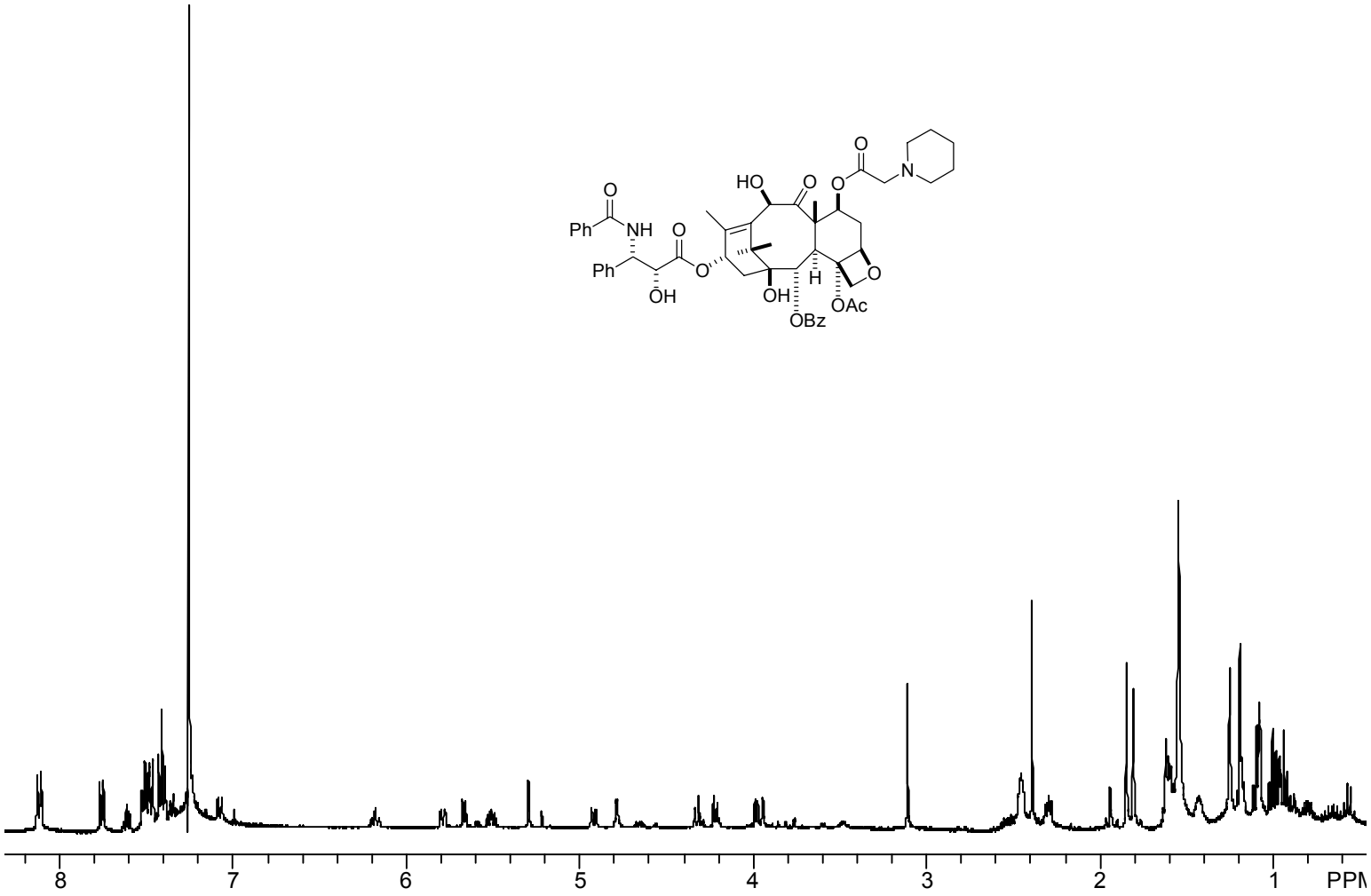
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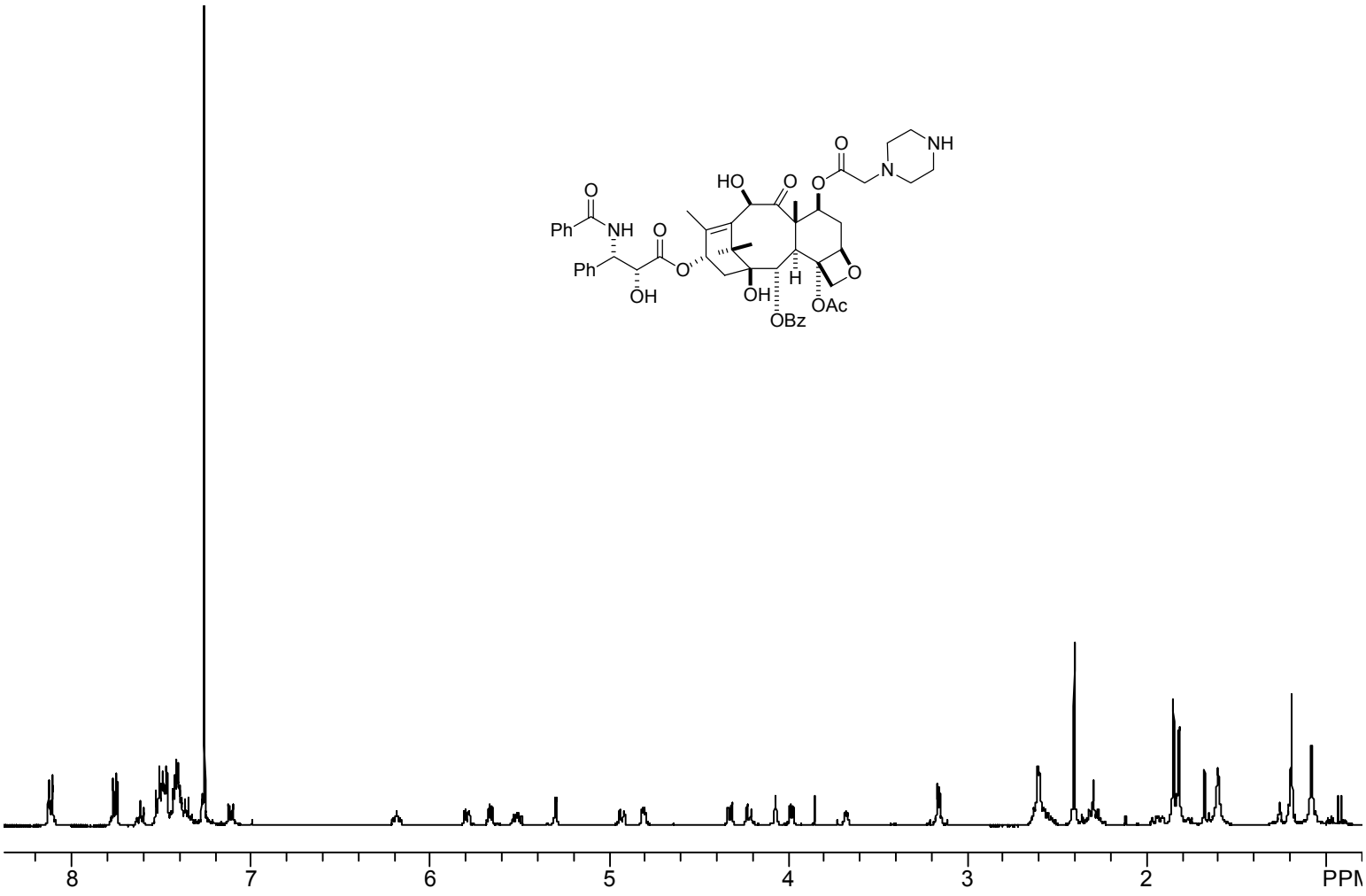
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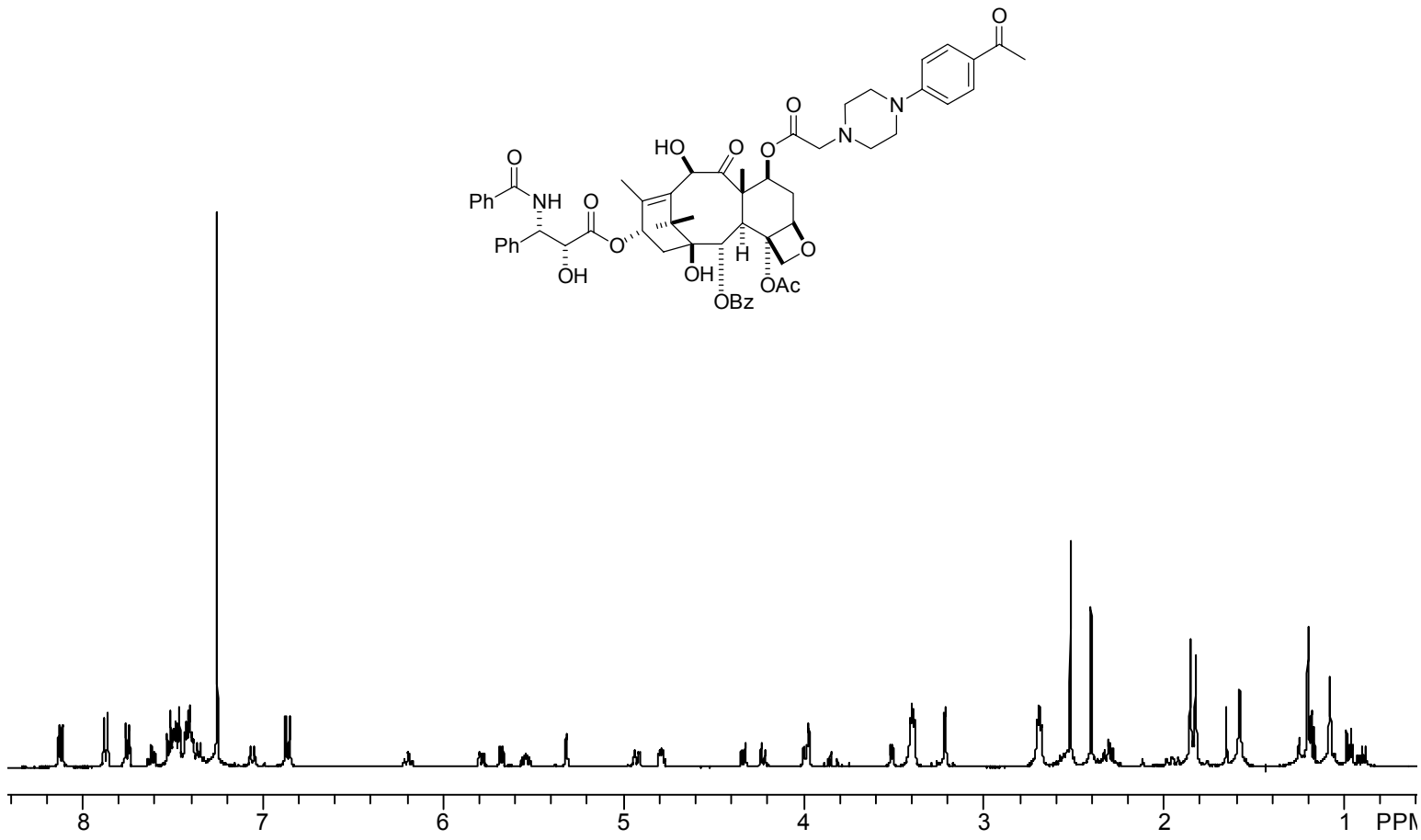
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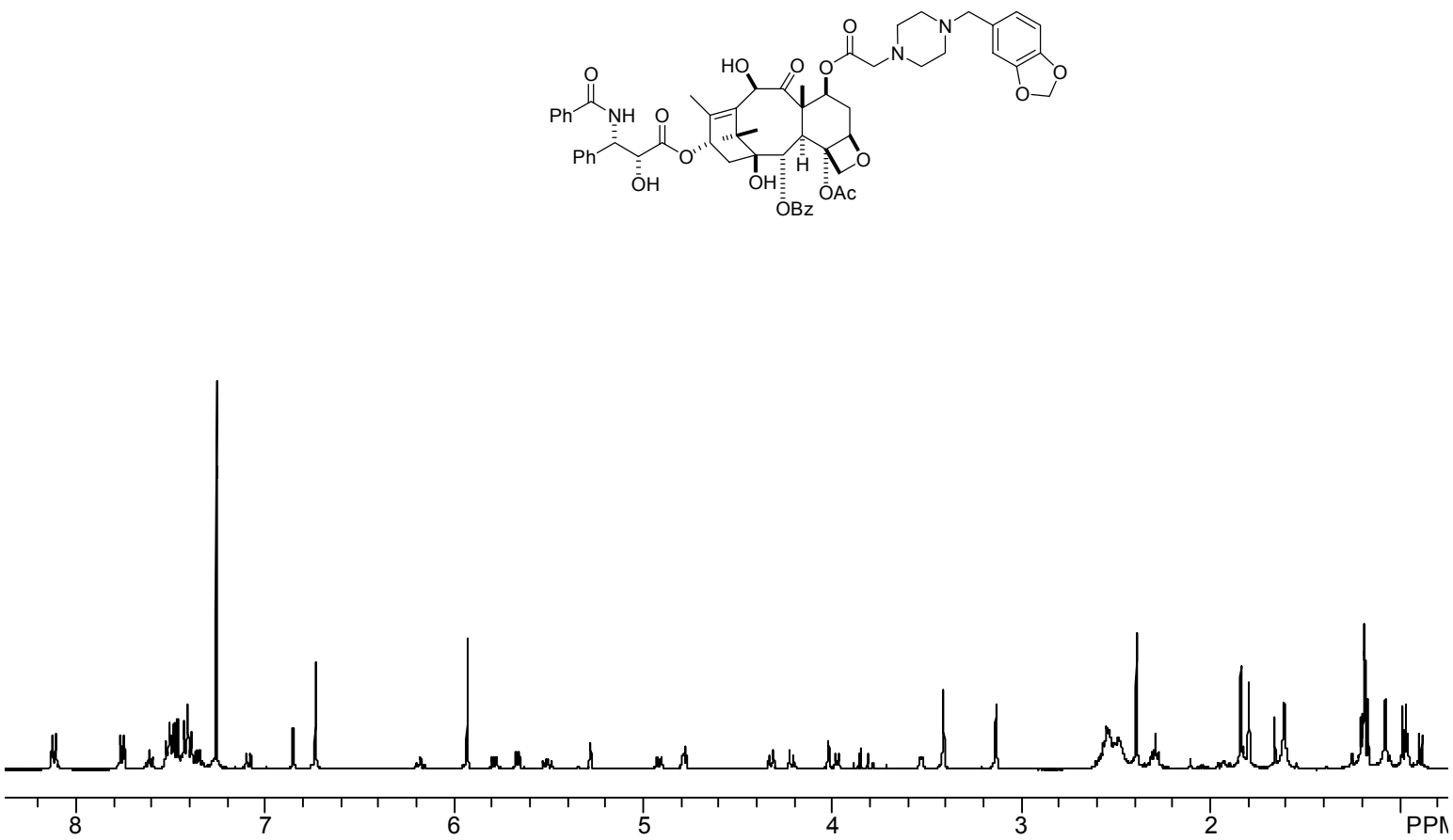
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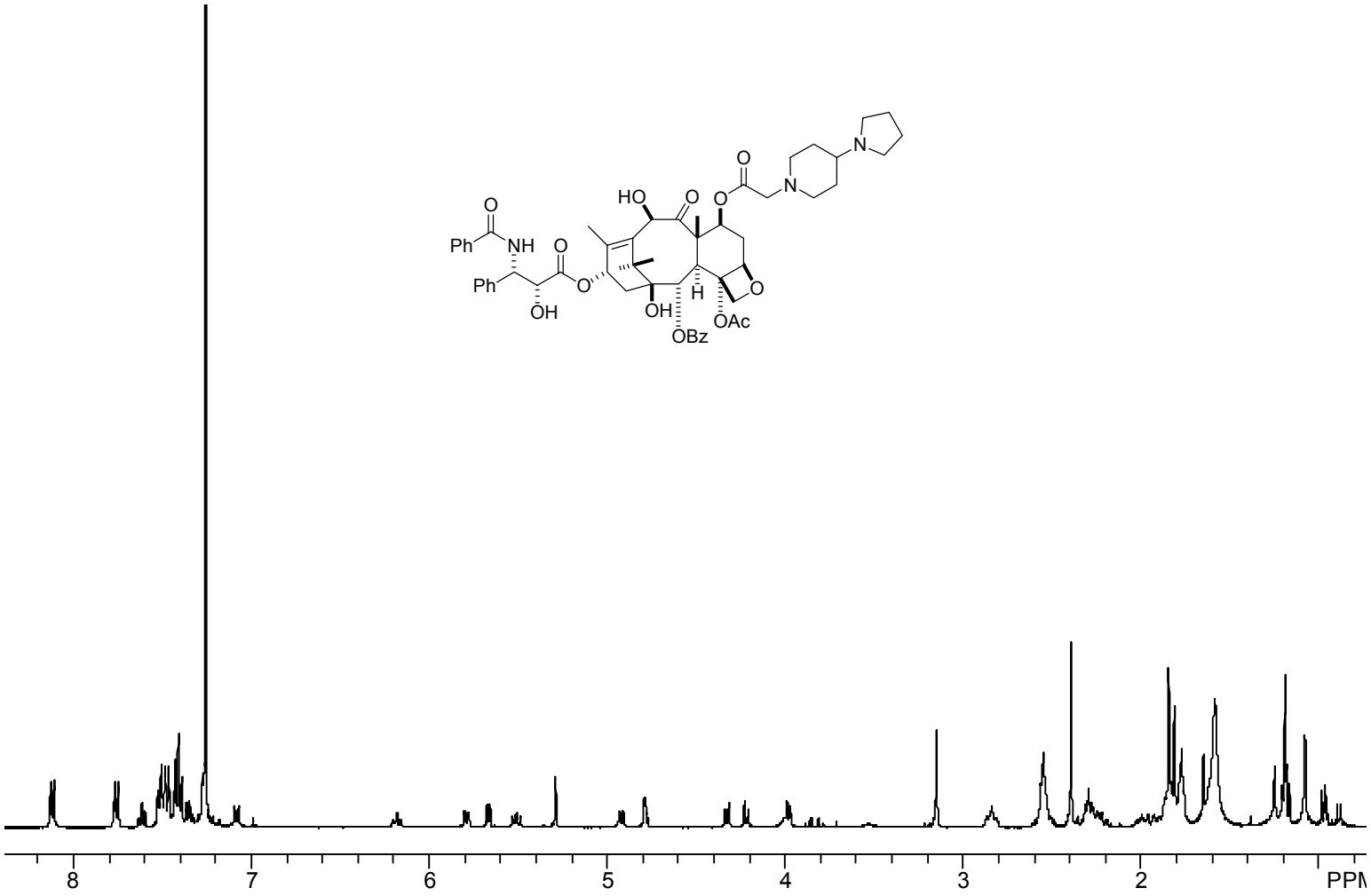
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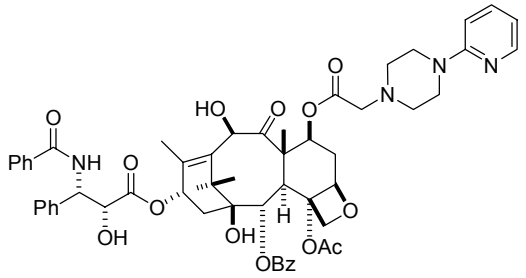
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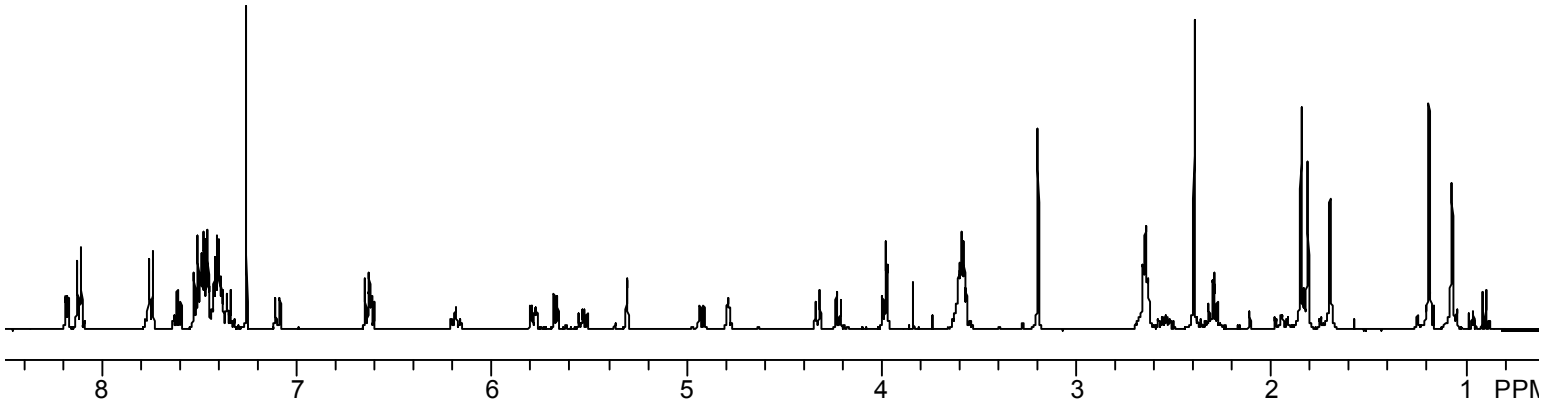
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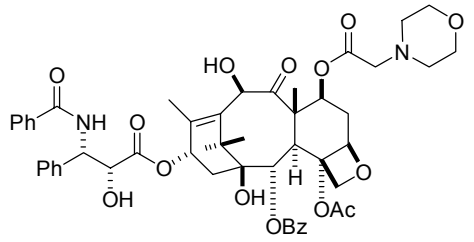
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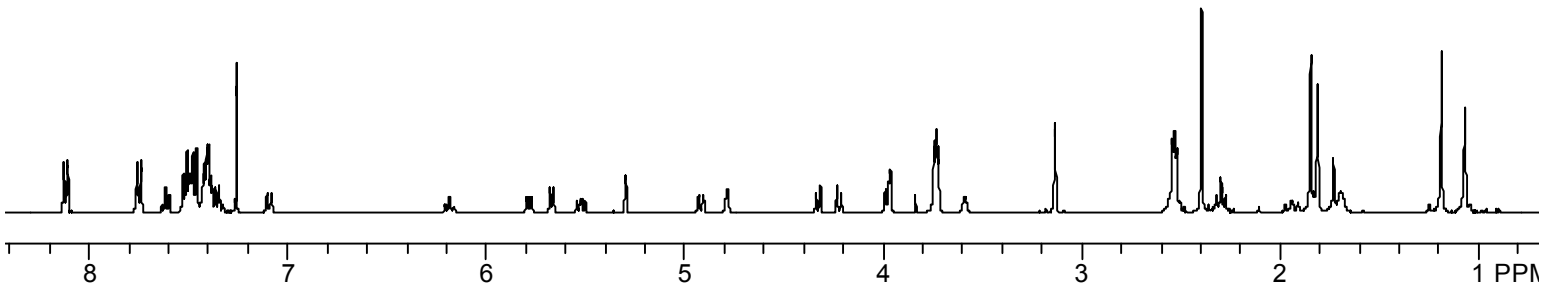
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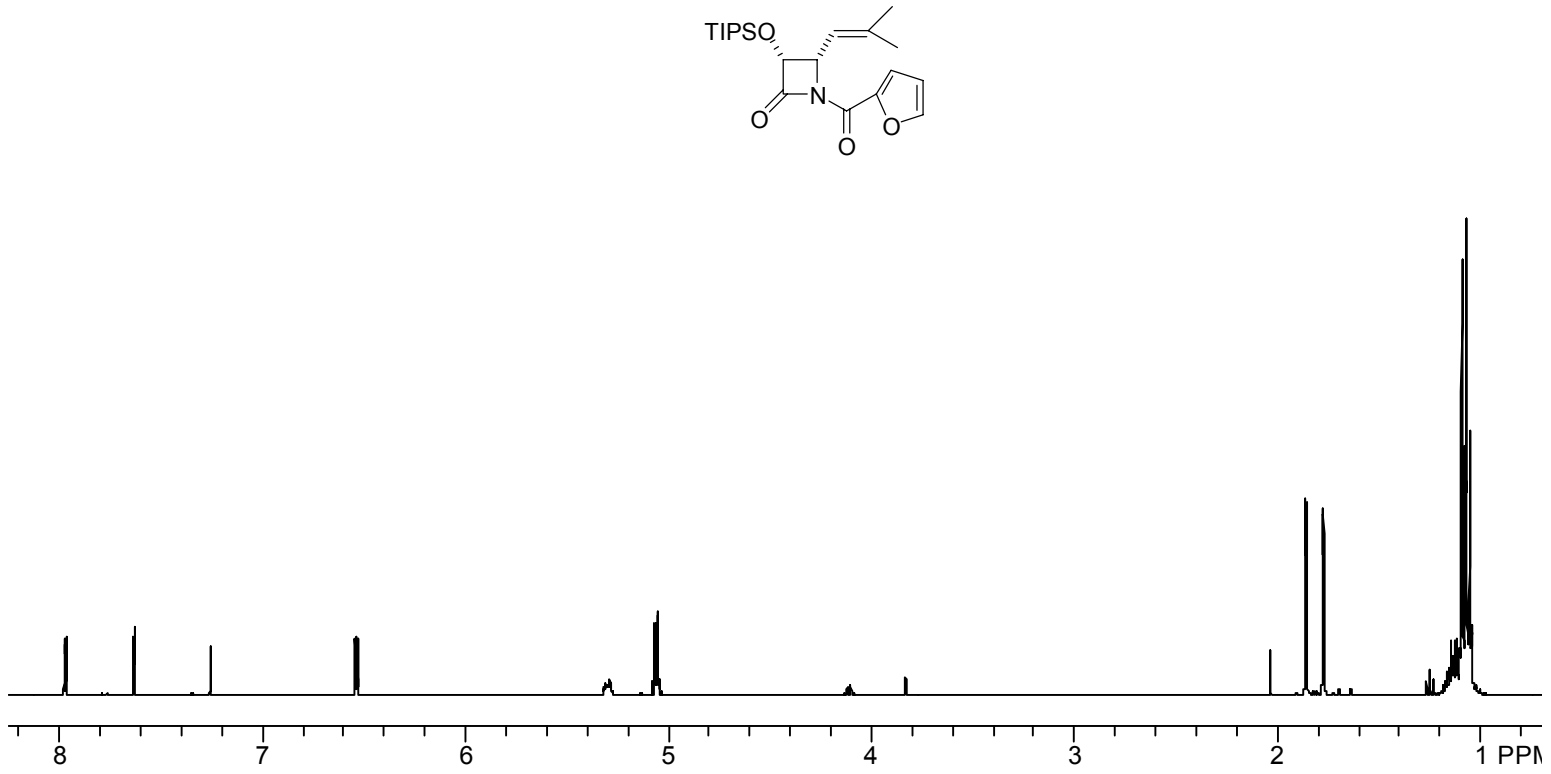
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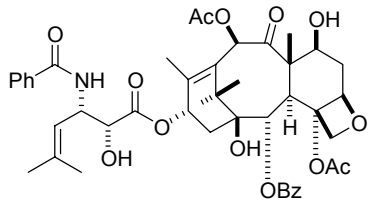
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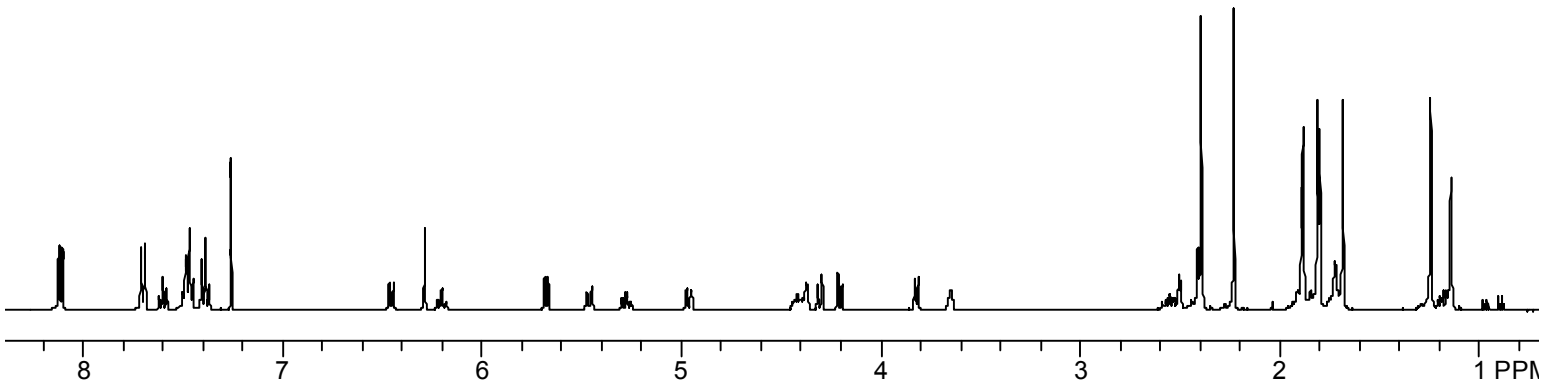
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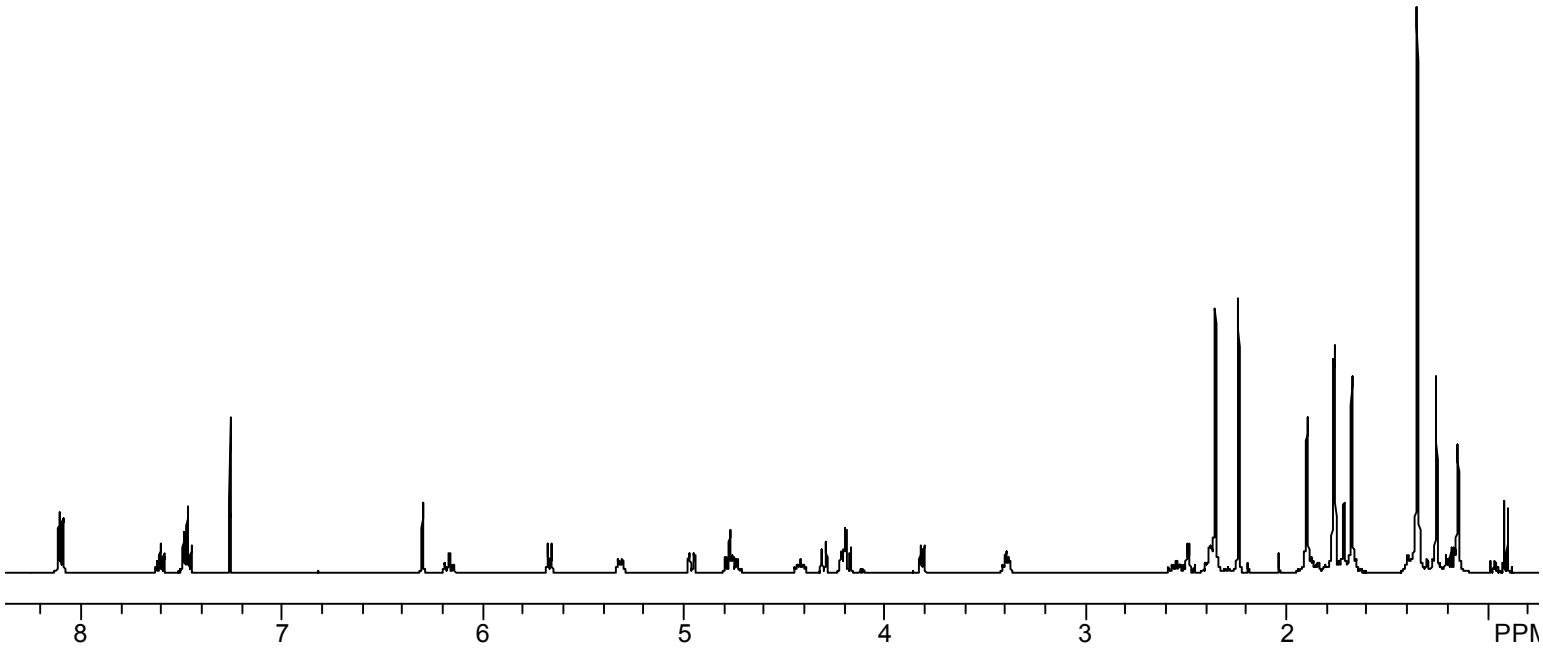
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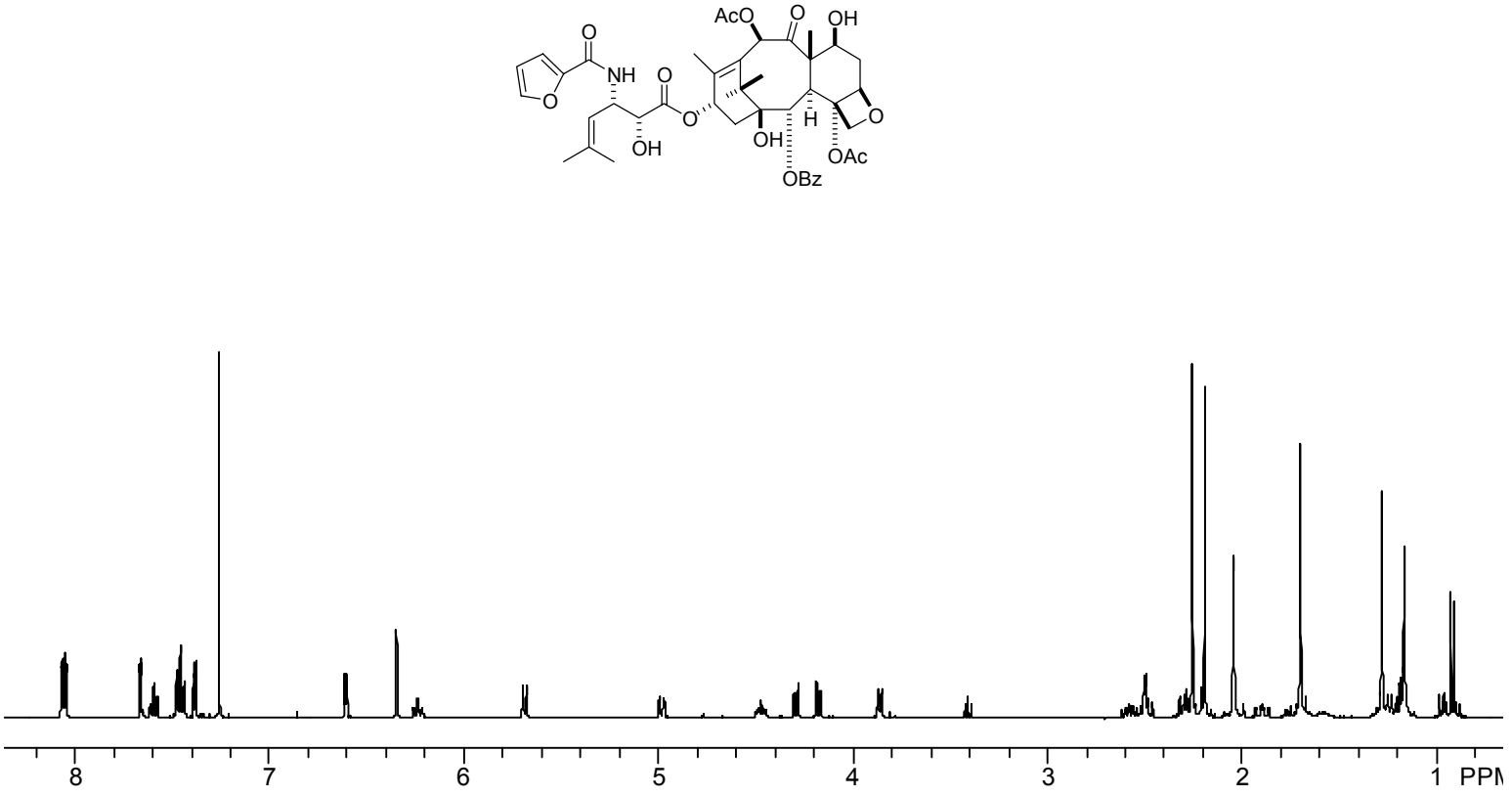
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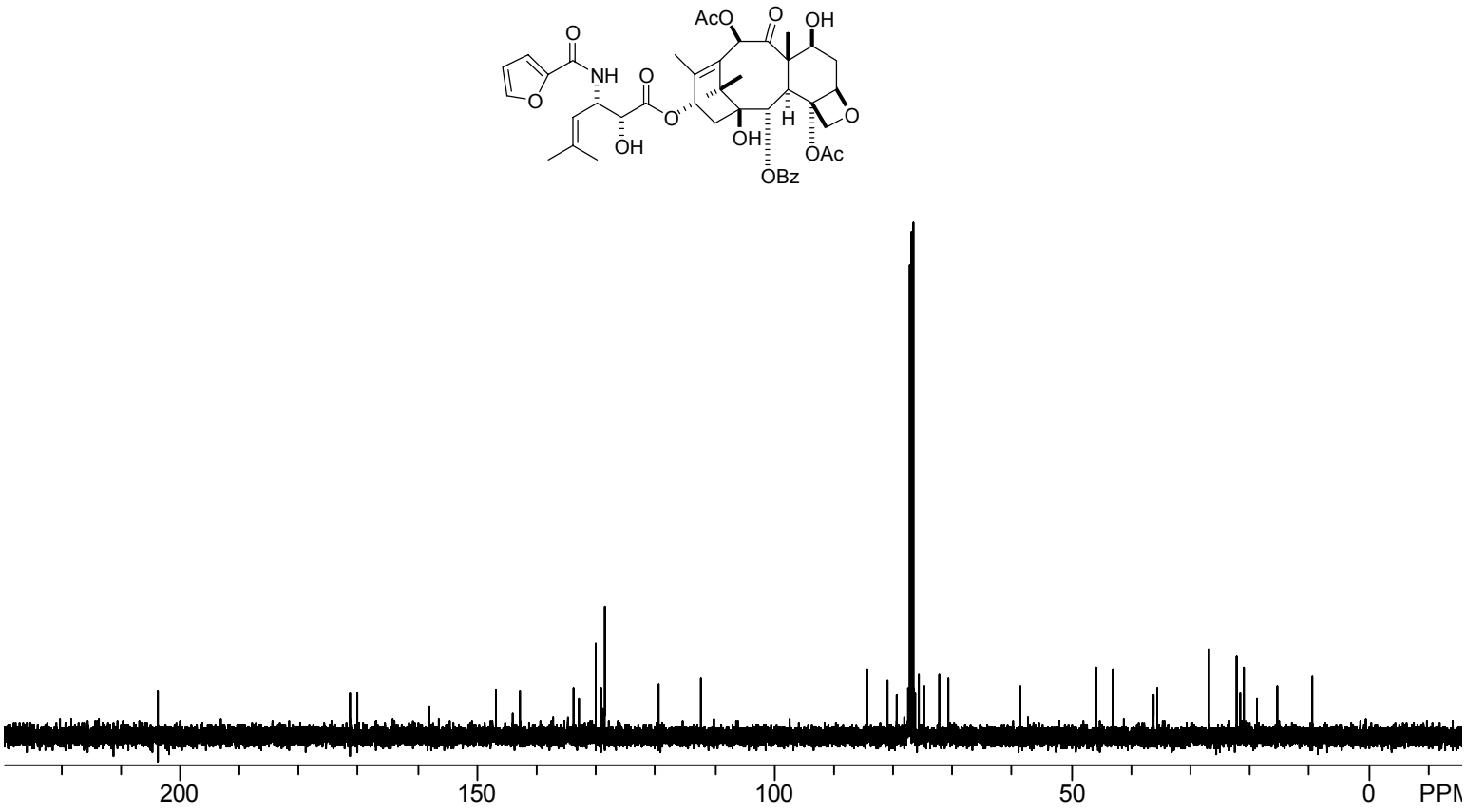
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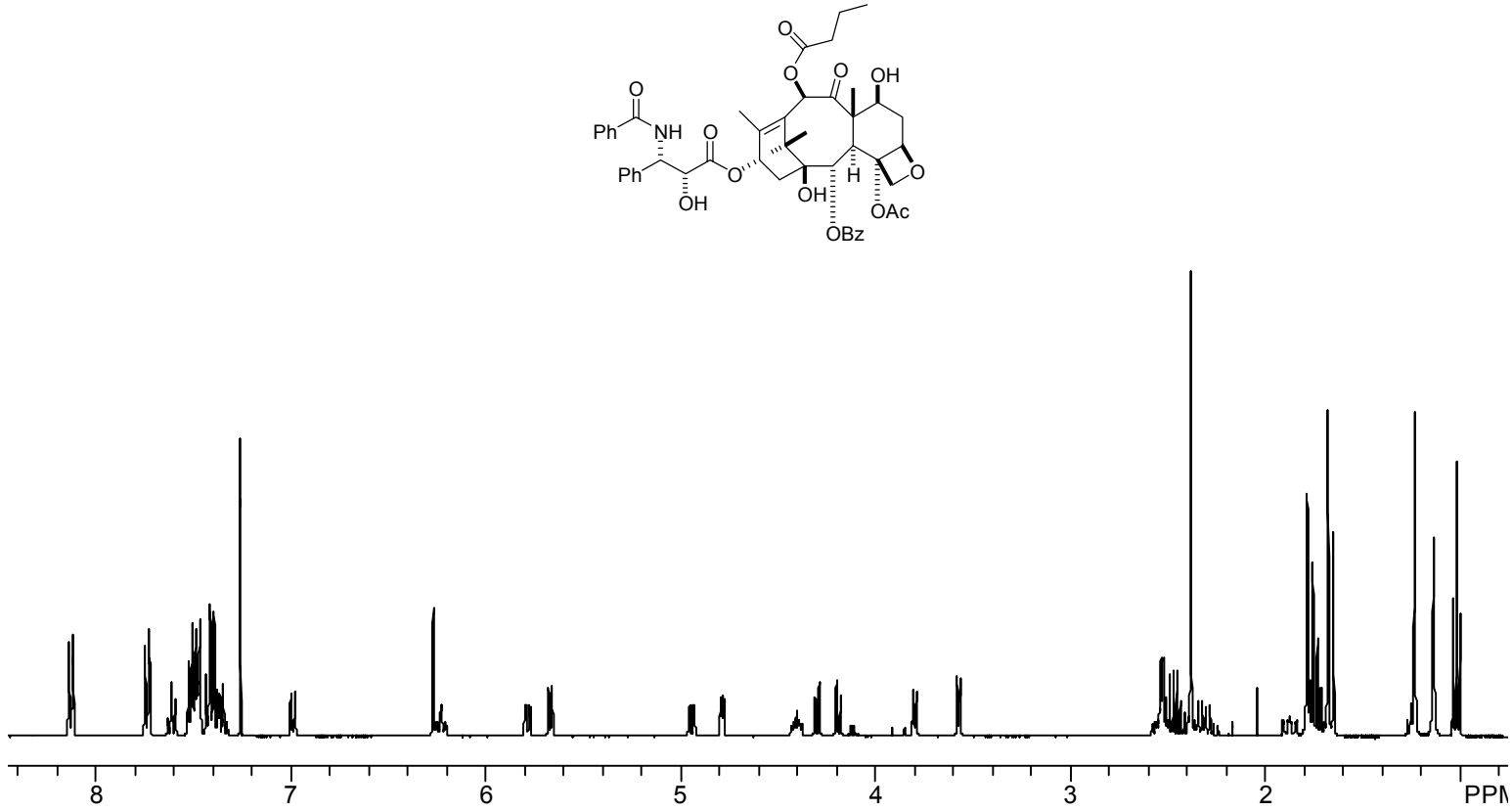
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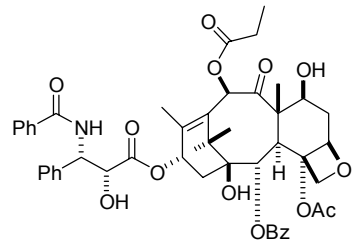
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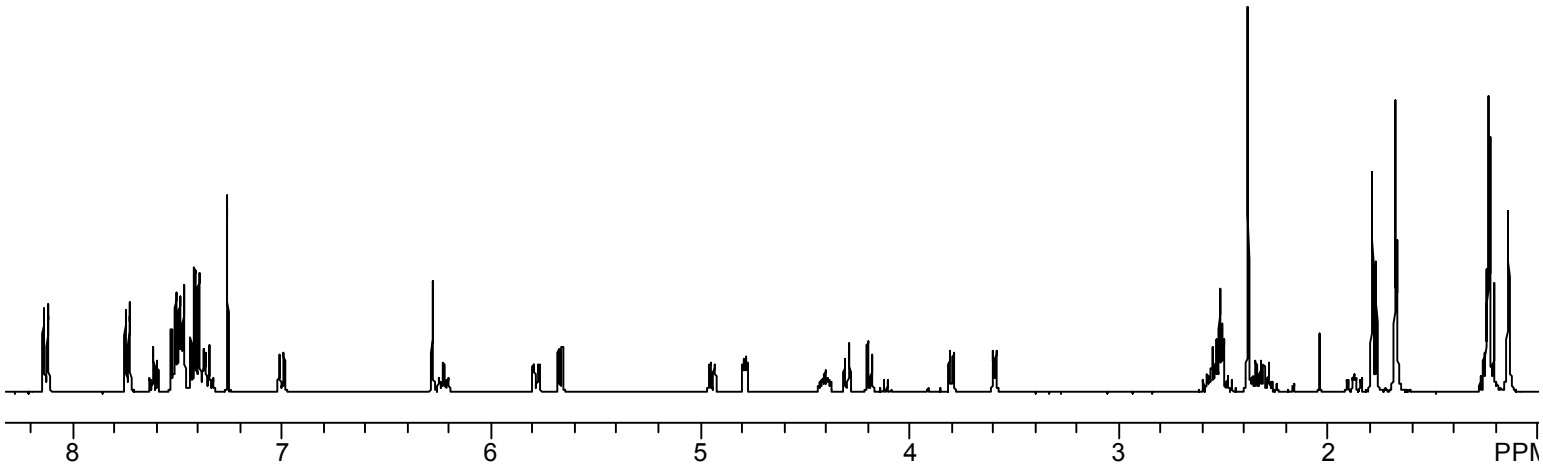
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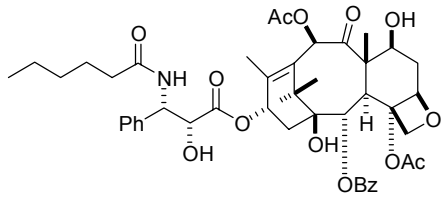
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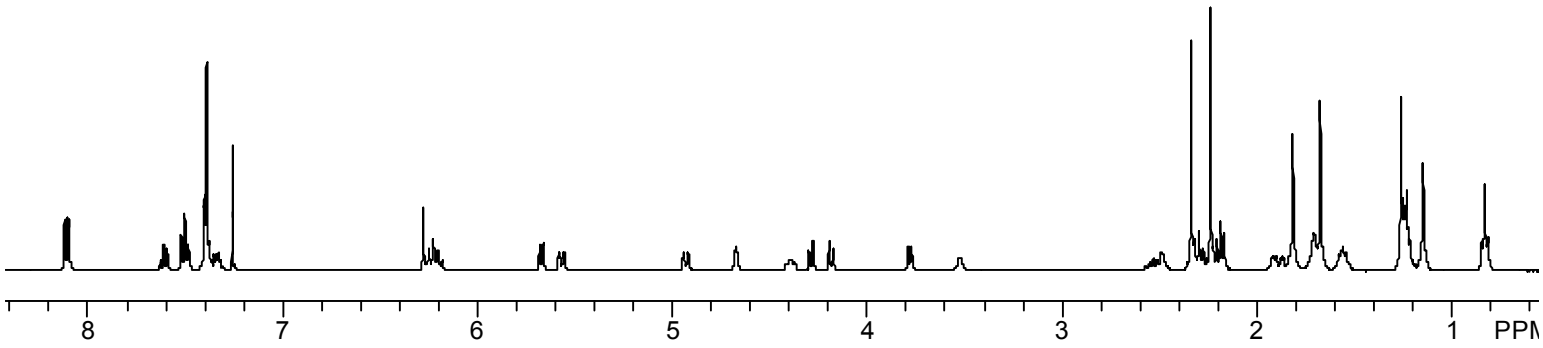
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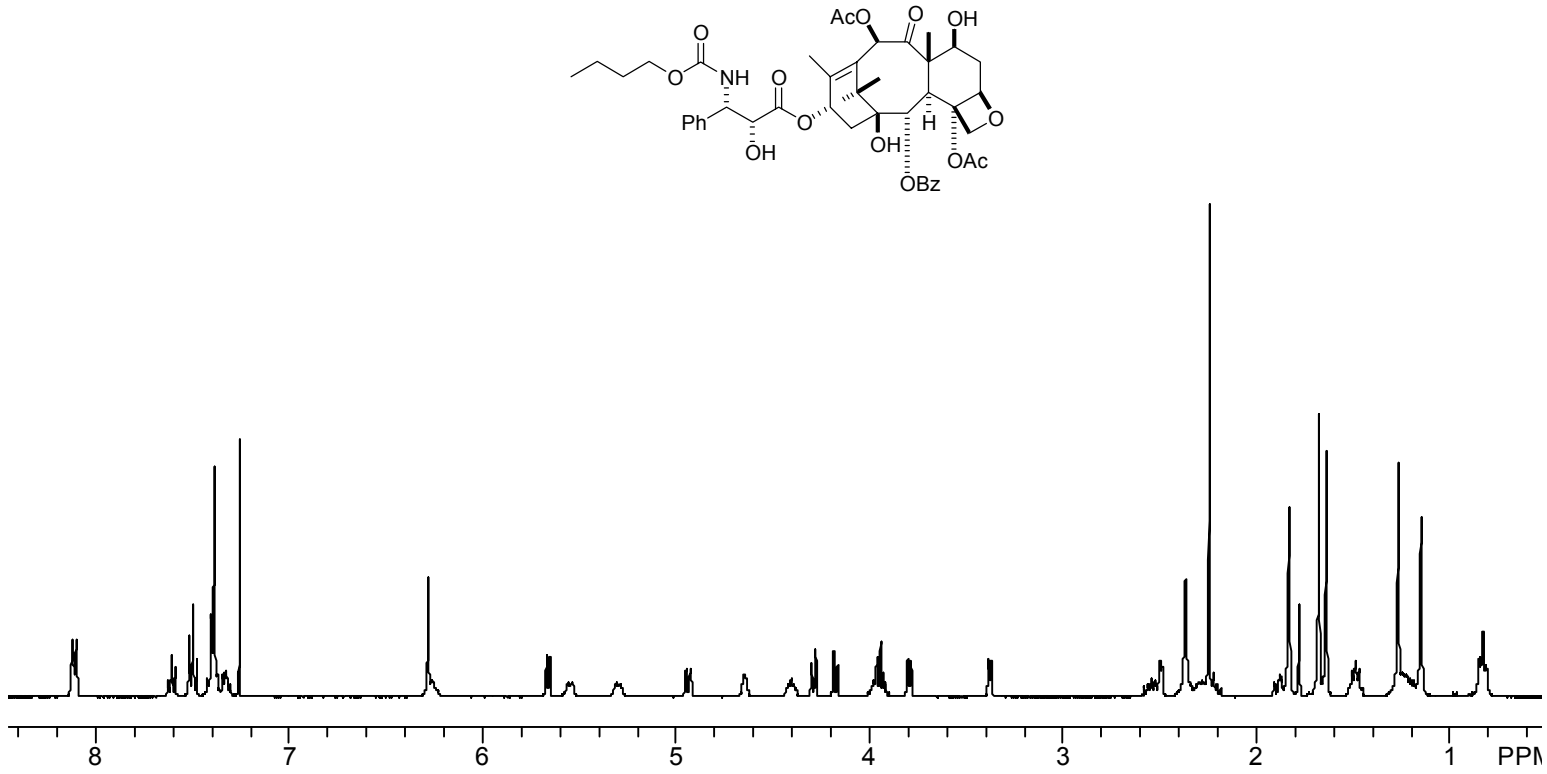
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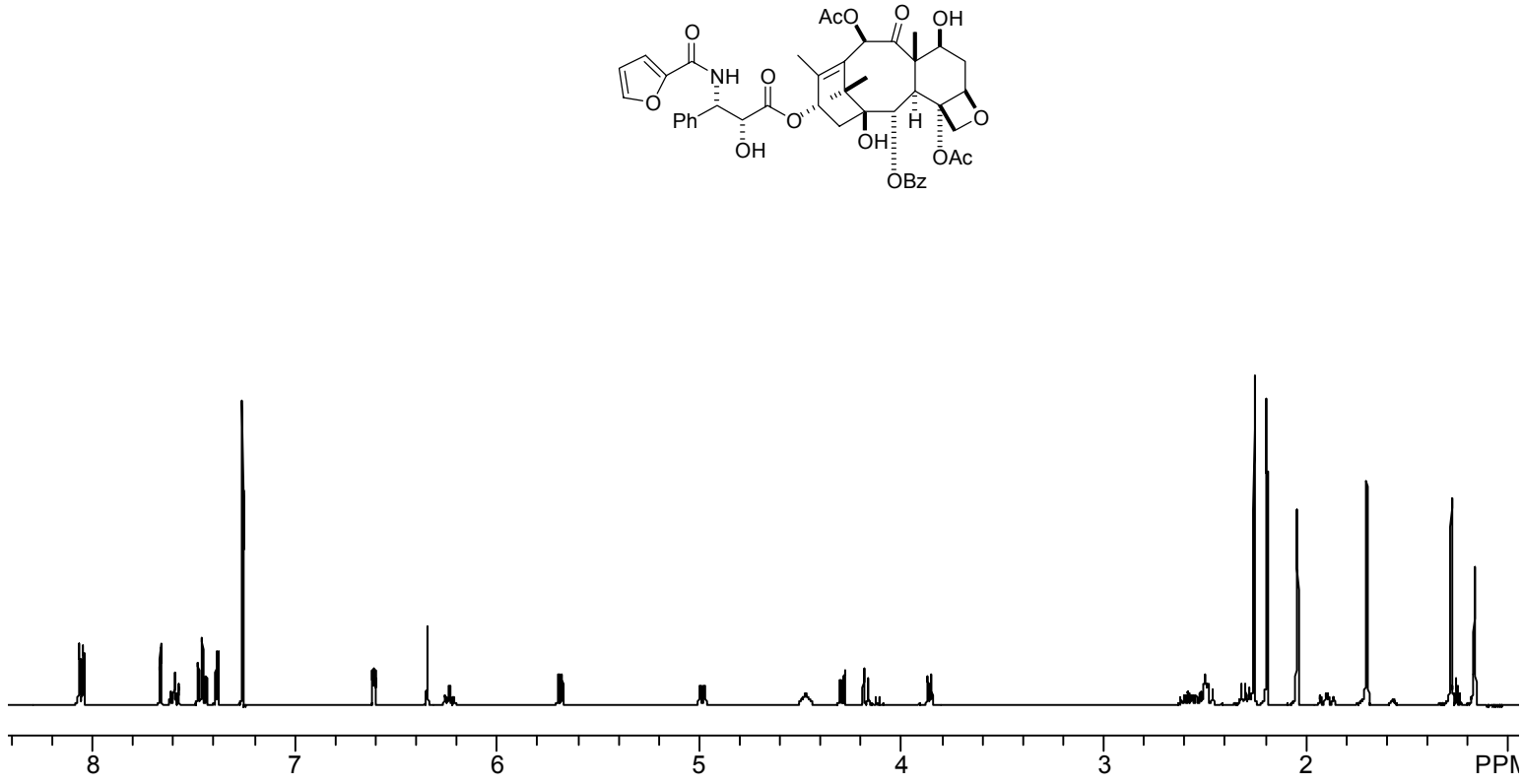
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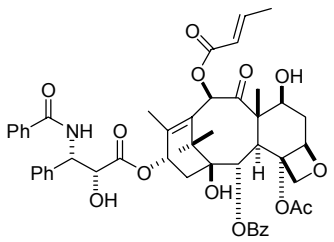
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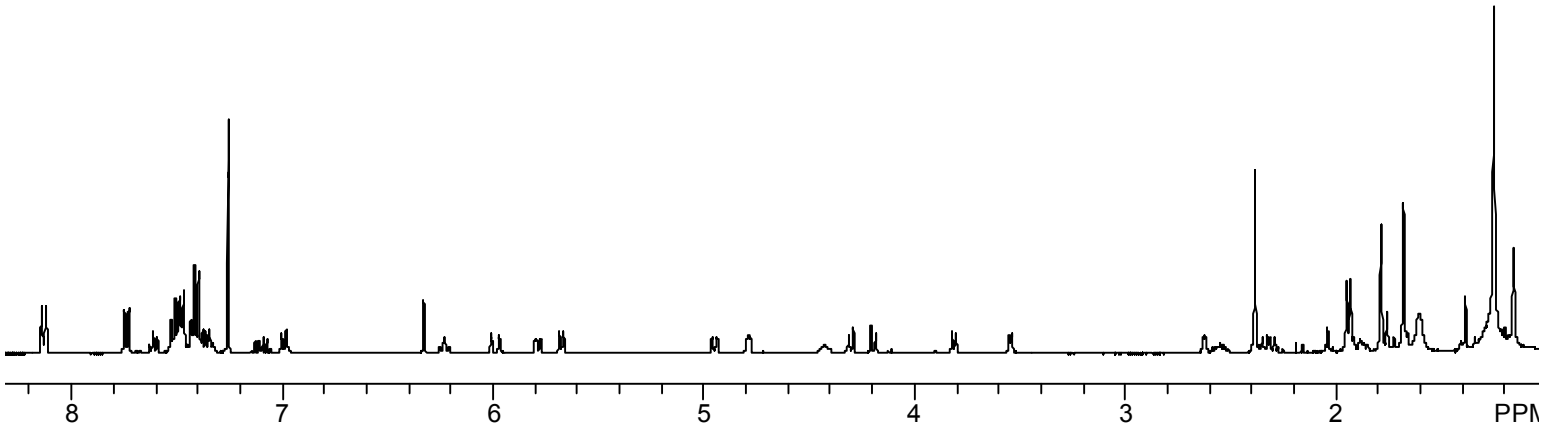
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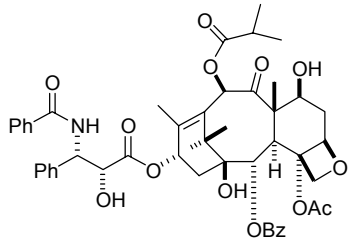
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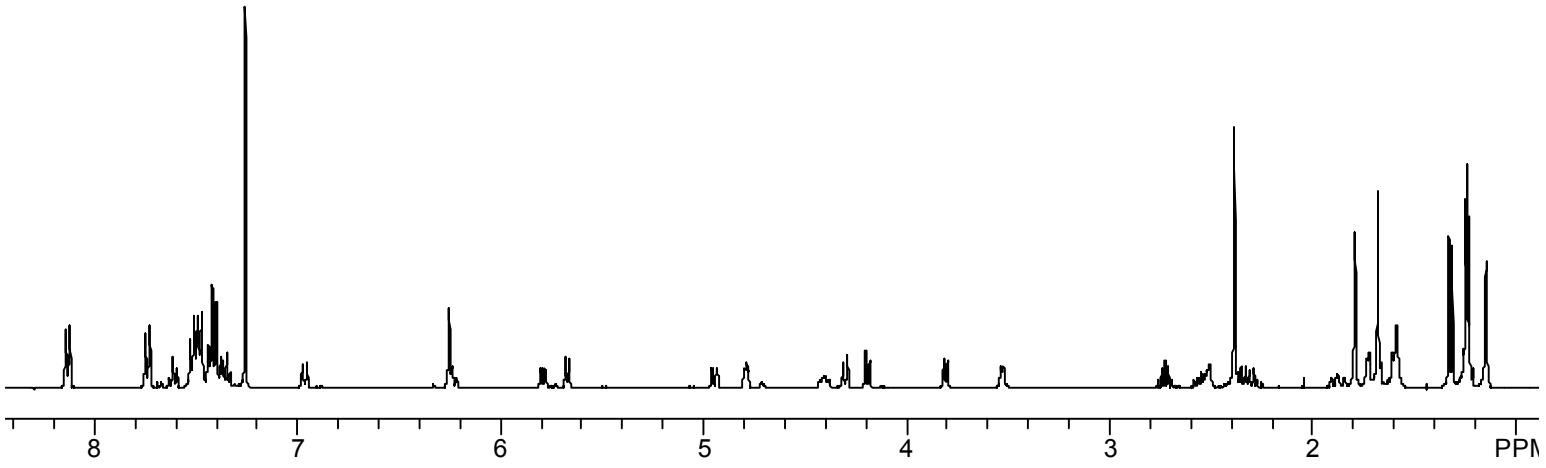
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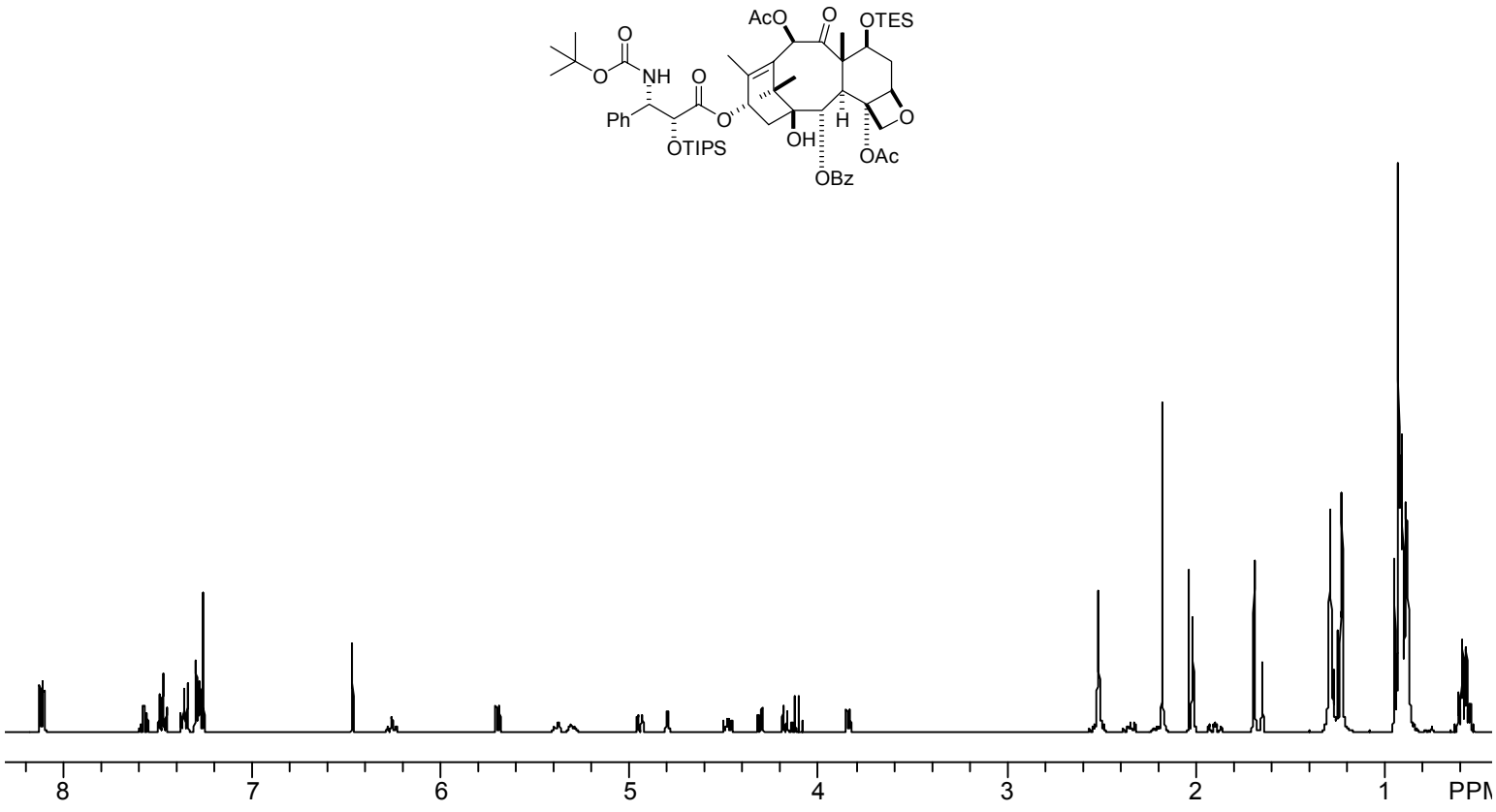
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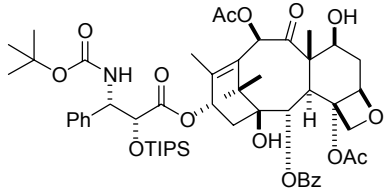
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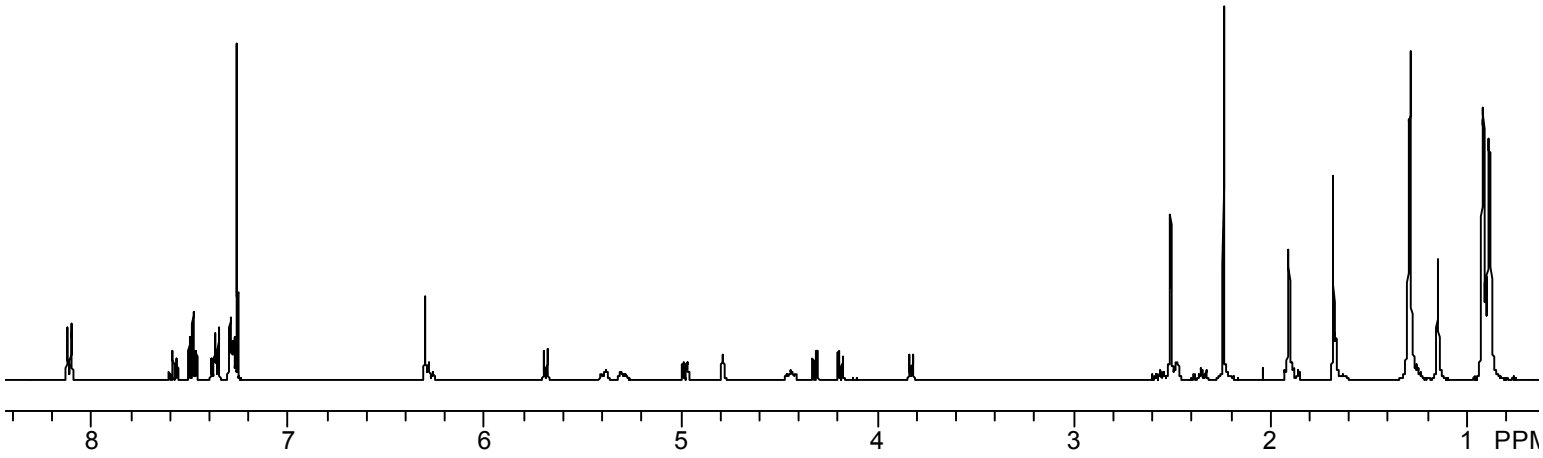
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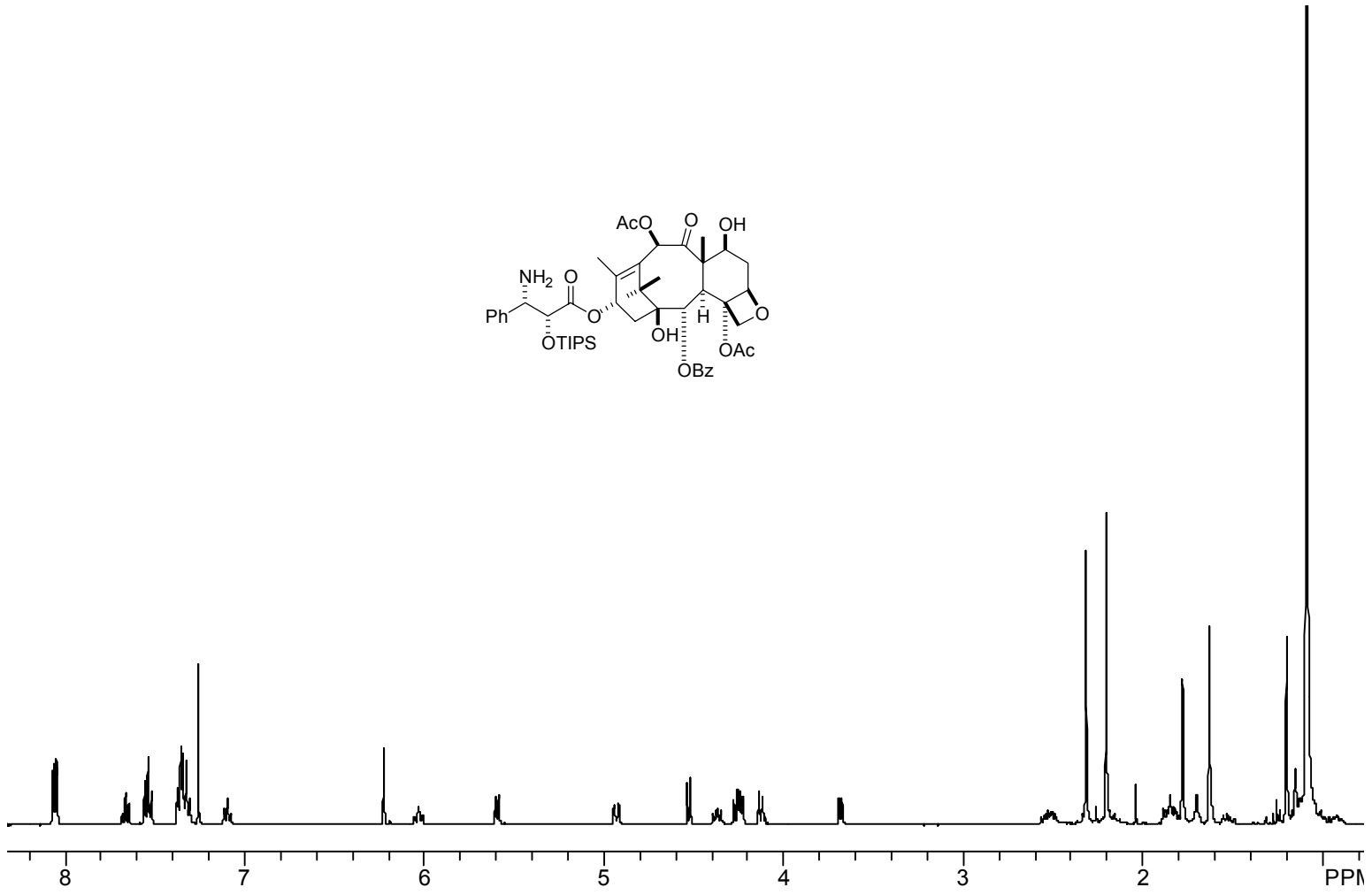
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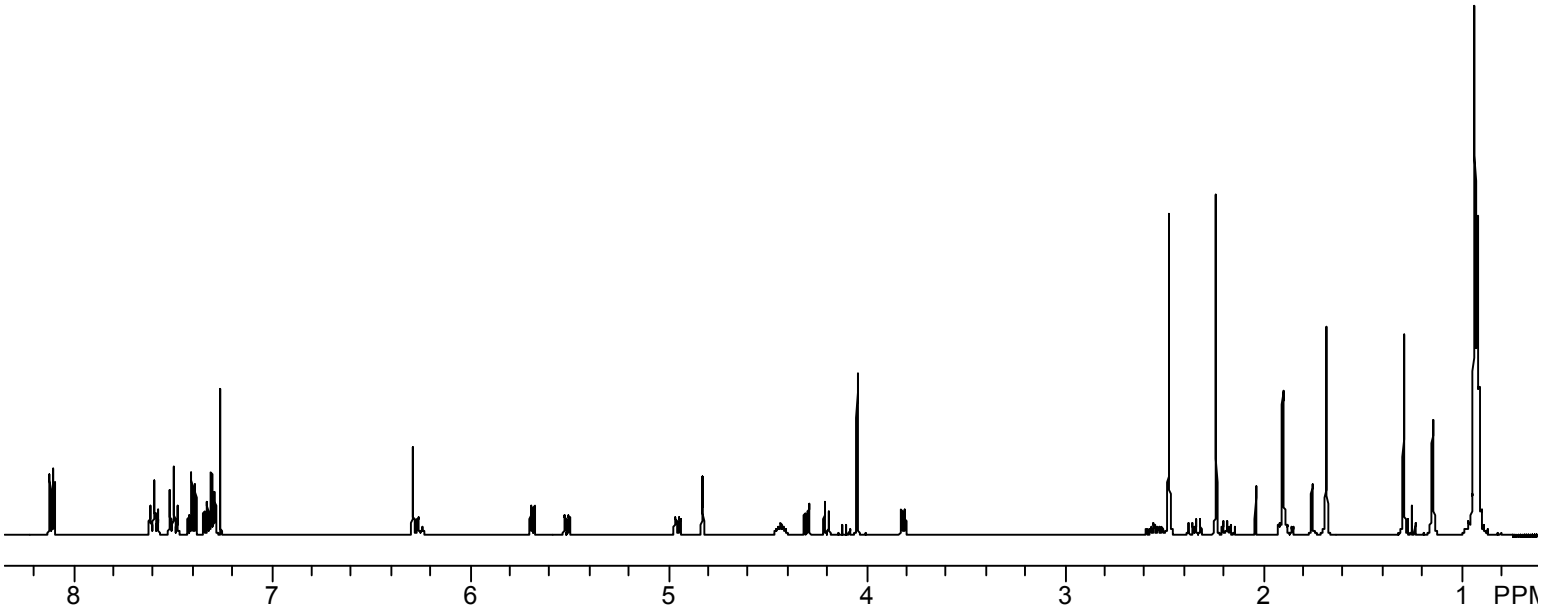
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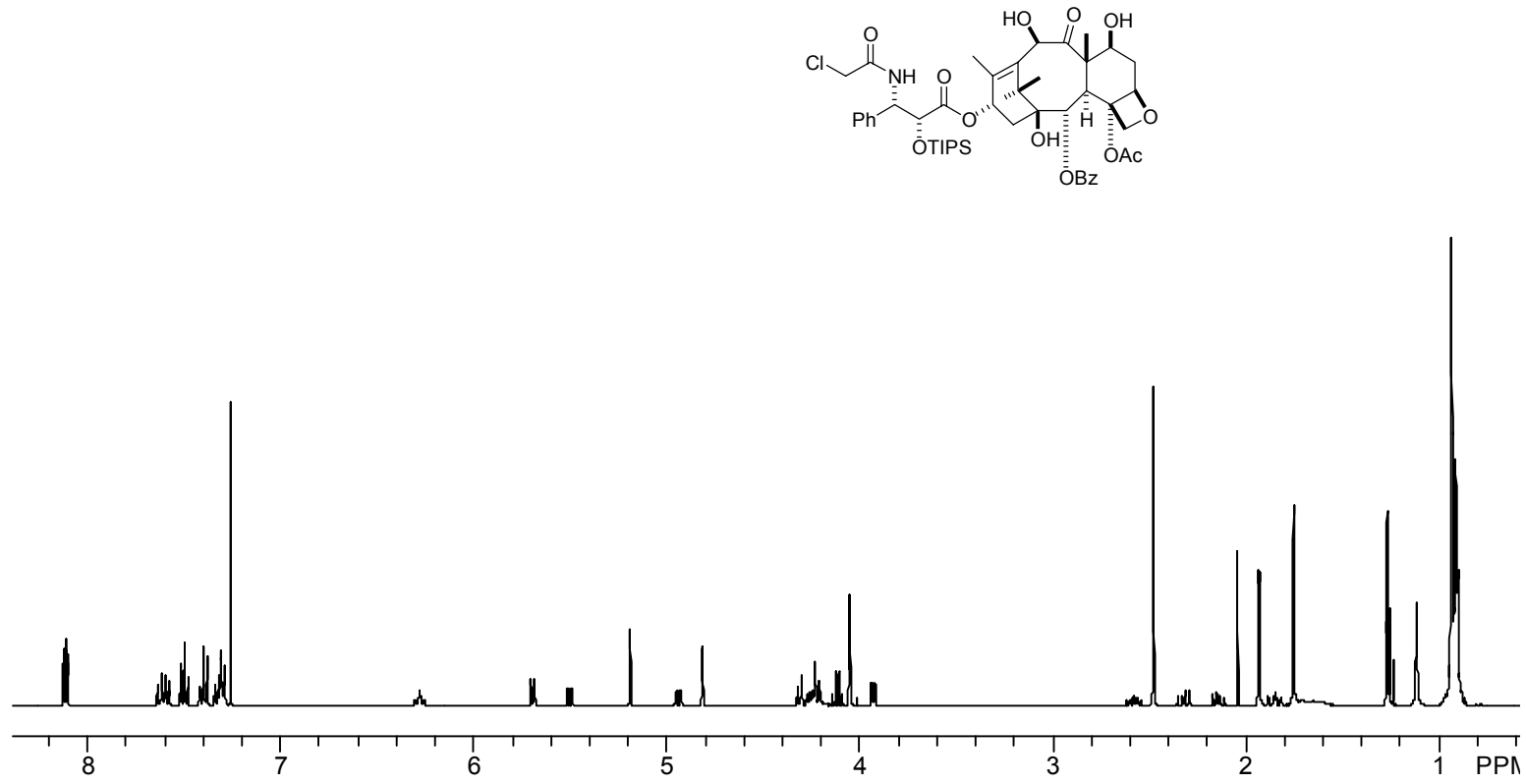
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Ph
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H
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OTIPS
OH
OAc
OBz
8
7
6
5
4
3
2
1
PPM

8. VITA

Erkan Baloglu

Erkan Baloglu was born on August 11, 1971 in Istanbul, Turkey. He started his education in chemistry in the Department of Chemistry at Istanbul Technical University, Istanbul, Turkey, where he graduated with a Bachelor of Science degree in Chemistry in February 1995.

He began his graduate studies in Chemistry in the Department of Chemistry at Virginia Polytechnic Institute and State University, Blacksburg, Virginia, where he received a Master of Science degree in August 1998. He continued his graduate studies towards a Doctor of Philosophy degree in Chemistry under the supervision of Dr. David G. I. Kingston in the Department of Chemistry at Virginia Tech. During his graduate studies, he held graduate teaching and research assistantships and served as head teaching assistant for two years.