Synthesis of Paclitaxel Analogs

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ABSTRACT

Paclitaxel is one of the most successful anti-cancer drugs, particularly in the treatment of breast cancer and ovarian cancer. For the investigation of the interaction between paclitaxel and MD-2 protein, and development of new antagonists for lipopolysaccharide, several C10 A-*nor*-paclitaxel analogs have been synthesized and their biological activities have been evaluated. In order to reduce the myelosuppression effect of the paclitaxel, several C3′ and C4 paclitaxel analogs have been synthesized and their biological evaluation have been studied

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1.1 Introduction to microtubules

In eukaryotic cells, microtubules not only perform as a basic part of the cellular components helping maintain cell shape and polarity, but they also play an essential role in the transport of vesicles, mitochondria, and in cell signaling and in cell division and mitosis.[1] Each microtubule is a long hollow cylinder with a diameter of 24 nanometers. It is composed of 13 protofilaments made up of tubulin protein dimers.[2] Each tubulin dimer is composed of α-tubulin and β-tubulin subunits with a molecular mass of 100 kD. α-Tubulin and β-tubulin monomers are two closely-related proteins with about 450 amino acids each and are 50% identical at the amino acid level.[3,4] Tubulin dimers will assemble into long protofilaments, and the interactions between the tubulin dimers give the microtubule a tubular shape.

Besides their definite shape, microtubules also have a specific polarity due to the head-to-tail assembly of α- and β-tubulin dimers, and this polarity is very important for the segregation of chromosomes. The faster growing end is termed the “plus” end, which grows 2-3 times faster than the slow growing end which is termed the “minus” end.[5] The plus end is composed of β-tubulin subunits while the minus end is composed of α-tubulin subunits.[6]

It is believed that the polymerization of microtubules has two steps: nucleation and elongation. At first, about 6-12 tubulin dimers are formed in the nucleation step. Next, GTP bound tubulin dimers are added to the nucleus and then form protofilaments. At the same time, perpendicular assembly occurs, and the edges of protofilaments meet together to form a microtubule. The assembly of microtubules is a competition between addition and dissociation of tubulin dimers. After rapid elongation, the addition and dissociation of dimers becomes balanced to form a steady state. The polymerization and dissociation of microtubules is controlled by the hydrolysis of GTP bound to tubulin.[7] Both tubulins will bind to GTP, but the GTP bound to α-tubulin cannot be hydrolyzed while GTP bound to β-tubulin can be hydrolyzed.[8,9] Tubulin-bound GTP is hydrolyzed to GDP-phosphate (Pi) once β-tubulin adds to the plus end of microtubule. Microtubules are stable when the plus end is GTP or GDP-Pi, but once the Pi leaves GDP, the microtubules are dissociated rapidly.

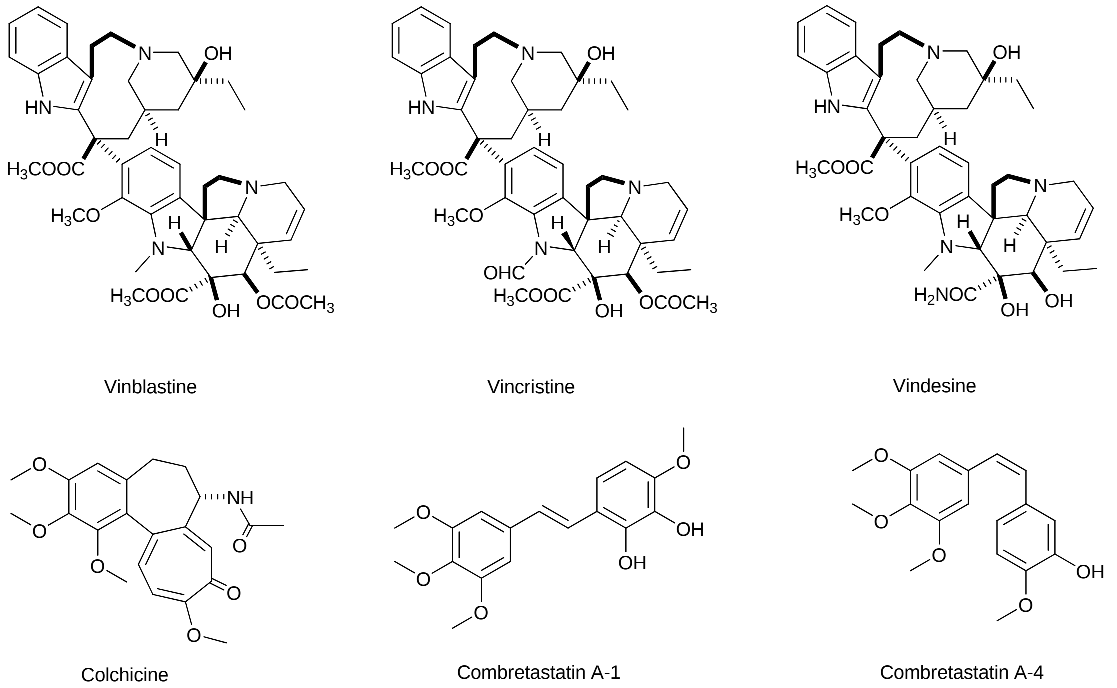
There are two different kinds of polymerization dynamics which affect the biological function of microtubules. The first one is called dynamic instability.[10] In this process, the two ends of the microtubule switch between growth and shortening. The other one is called as treadmilling.[11,12] In this process, the plus end undergoes net growth and the minus end undergoes net shortening.[13]

These kinds of microtubule dynamics have an important role in helping cells undergo mitosis. The mitotic phase of the cell cycle can be divided into several subphases, including prophase, metaphase, anaphase, and telophase. This event requires microtubules to have the ability to undergo rapid growth and shortening. In prometaphase, the spindle microtubules need to grow and shorten rapidly to search for the chromosomes and to move all the chromosomes to the metaphase plate in metaphase. Later in anaphase, the microtubules shorten very rapidly to segregate the chromosomes and move them to two opposite sides of the cell and then disappear in telophase, forming two new cells.[14,15]

Because of the importance of microtubules in mitosis, they are potential targets for drugs for different diseases, such as cancer, parasitic diseases and neuronal diseases. Two different kinds of tubulin-interactive agents are known: microtubule depolymerizing agents and tubulin polymerizing agents.

1.1.1 Microtubule depolymerizing agents:

Microtubule depolymerizing agents inhibit the assembly of tubulin into microtubules and depolymerize microtubules, preventing the cell from undergoing mitosis. So far, several of these agents have been found, including the Vinca alkaloids, colchicine, and the combretastatins (Figure 1.1). Most of them either bind to the so-called vinblastine site or the colchicine site on tubulin.[16,1]


Vinblastine

Vincristine

Vindesine

Colchicine

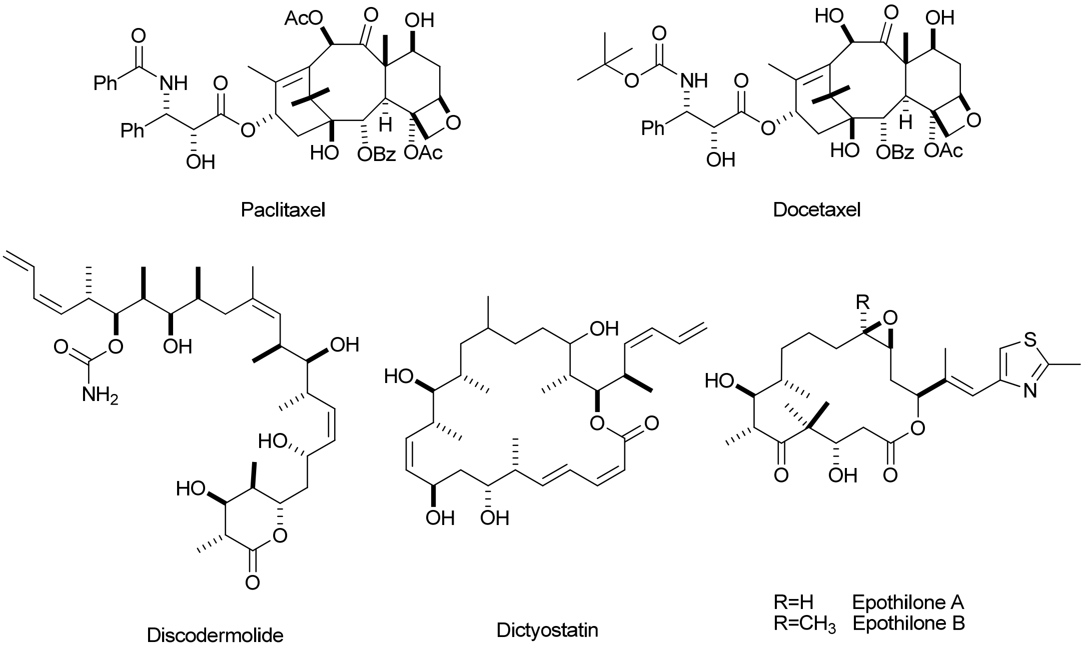
Combretastatin A-1

Combretastatin A-4

Figure 1.1 Structures of Vinca alkaloids, colchicine, and the combretastatins

1.1.2 Tubulin polymerizing agents

Tubulin polymerizing agents stimulate the polymerization of microtubules. These agents include paclitaxel, docetaxel, discodermolide, dictyostatin, and the epothilones (Figure 1.2).[13,1]



Paclitaxel

Docetaxel

Discodermolide

Dictyostatin

R=H Epothilone A
R=CH_3 Epothilone B

Figure 1.2 Structure of polymerizating agents

1.2 Introduction to paclitaxel

Paclitaxel, a well-known anti-cancer drug, belongs to the group of tubulin-polymerizing agents. It was isolated from the bark of the *Pacific Yew* tree by Monroe E. Wall and Mansukh C. Wani in 1967.[17] However, the structure of paclitaxel was not determined until 1971, when it was named taxol. Although taxol showed great cytotoxic activity to KB cells,[18] its development was quite slow due to the low isolated yield (0.02% w/w) and poor water solubility. Development became a priority after the discovery in 1976 that taxol showed excellent activity against solid tumors. The mechanism of taxol in killing cancer cells was discovered in 1979,[19] when it was found that taxol worked as a cell division blocker by binding to β-tubulin and stabilizing microtubules.[20] In 1992, the Food and Drug Administration (FDA) approved taxol for treatment of ovarian cancer, and in 1994, for breast cancer. It was renamed paclitaxel in 1992 after Bristol-Myers squibb trademarked the name Taxol for its formulation of drug.

1.2.1 Mechanism of action of paclitaxel

The cell cycle can be separated into four distinct phases: the G_1 phase, the S phase, the G_2 phase, and the M (Mitosis) phase. During mitosis, microtubules perform the essential role described earlier. In 1979, Dr. Horwitz and her coworkers discovered the mechanism of action of paclitaxel.[19] In this paper and subsequent ones,[21-24] she showed that paclitaxel has a high affinity for β-tubulin and when it binds it stabilizes the microtubules, breaking the dynamic balance between polymerization and depolymerization. It thus blocks cell division and causes cell death by apoptosis. The shapes of microtubules bound to paclitaxel are quite different from those of normal ones. The average diameter changed from 24 nm in normal microtubules to 22 nm. The number of protofilaments also changed from 12 to 13. Besides stabilization of microtubules, paclitaxel also lowers the critical concentration of tubulin for polymerization, which increases the rate of polymerization.

Recently, increasing evidence supports the hypothesis that paclitaxel may also induce apoptosis through the TLR4 immune pathway. This aspect of its action will be discussed later.[25,26]

1.2.2 Side effects of paclitaxel

Although paclitaxel can induce cancer cell death by apoptosis, normal healthy cells cannot avoid damage, which leads to some side effects of the drug. The common side effects include hair loss, mouth sores, low blood cell count, nausea and vomiting, bone marrow suppression and numbness and pain in the hands.[27]

1.2.3 Structure-activity relationships (SAR)

Since the discovery of paclitaxel, many chemists and biologists have studied its structure and bioactivity. So far, thousands of paclitaxel derivates have been synthesized and most of the positions of paclitaxel have been modified. Based on those studies, a structure-activity relationships diagram can be constructed (Figure 1.3).[28]

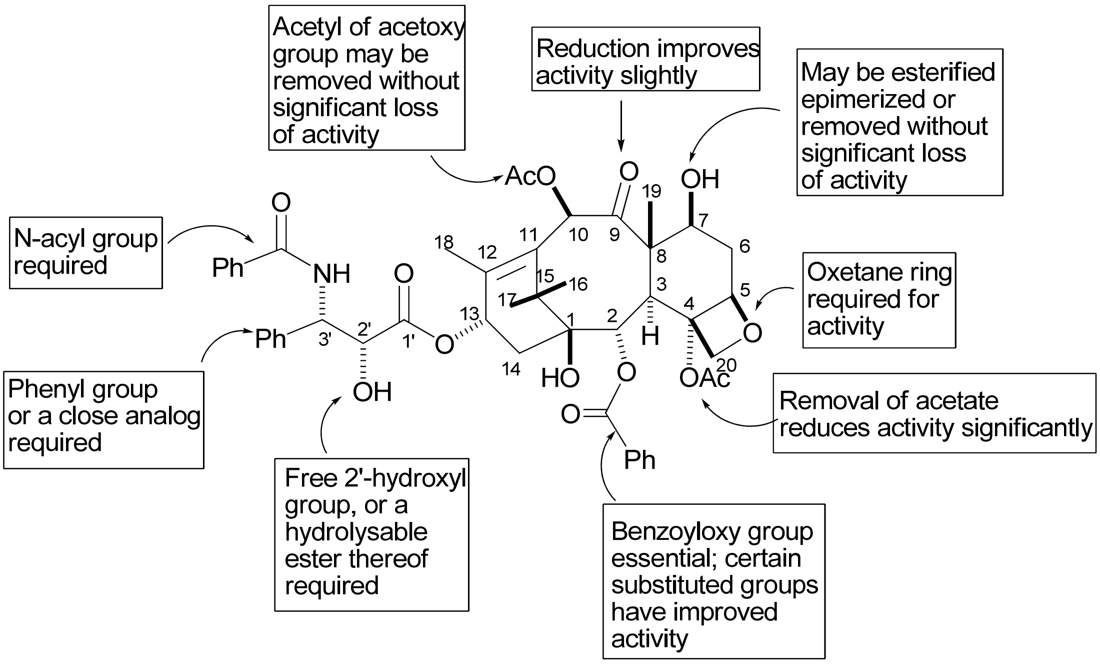


Figure 1.3 SAR of Paclitaxel

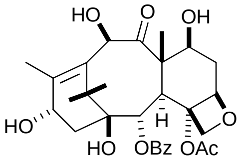
Although the structure of paclitaxel is very complicated, it can be separated into two major parts: the side chain and the tetracyclic ring. The side chain can be removed selectively using various methods, but without the side chain paclitaxel loses almost all of its bioactivity. It has been shown that the 2′R, 3′S stereochemistry is necessary for maximum activity. An N-acyl group at C3′ is required for bioactivity, and a change of acyl group on this position slightly reduces activity except for the N-Boc group. The paclitaxel analog docetaxel differs from taxol by having an N-Boc group as well as a 10-deacetyl group, and it is a drug with less myelotoxicity in the treatment of breast cancer.

The tetracyclic ring system can be separated into two hemispheres: the northern one and the southern one. The substituents on the southern hemisphere are essential for the bioactivity of paclitaxel. Opening of the oxetane ring and removal of the C2 benzoyloxy group reduce activity significantly. However, using other acyl groups to replace the acetyl group at C4 only changes the activity slightly. Compared to the southern hemisphere, substituents on the northern hemisphere can be modified without significant changes in activity.

Although a lot of work has been done on the structure and activity of paclitaxel, it still needs further investigation in modifying its structure to find more active compounds and to lower its side effects.

1.2.4 Semisynthesis of paclitaxel

Paclitaxel has proved to be one of the best drugs in the treatment of cancer. The initial supply of paclitaxel from *Taxus brevifolia* could not satisfy the market requirement and became an urgent problem. It was solved by a semisynthetic method developed in 1988 using 10-deacetylbaccatin III (10-DAB, Figure 1.4) as the precursor.[29] The yield of 10-deacetylbaccatin III isolated from the leaves of the European yew, *Taxus baccata*, is approximately 0.1% w/w, which is much higher than the yield of paclitaxel isolated from the bark of *Taxus brevifolia* (approximately 0.01%). In addition, harvesting the leaves does not kill the plant, and the European yew is easily grown. These factors make 10-DAB much cheaper than paclitaxel, and it is thus a perfect precursor for the synthesis of paclitaxel.



10-deacetylbaccatin III

Figure 1.4 Structure of 10-DAB

Using 10-DAB as the precursor, several semisynthetic methods have been published since 1988. For example, Greene and Potier first used the protected stereochemically correct side chain acid to couple with 7-TES-baccatin III in 80% yield;[30] Kingston and Gennari both used an oxazoline as a protected side chain to do the coupling,[31] and Holton and Swindell both used an oxazinone as the protected side chain.[32] Among all the semisynthetic methods developed, Holton's method (Figure 1.5) using a β-lactam as a protected side chain proved to be the most efficient, with yields over 90%.[35] In the initial version of this method, the coupling was accomplished using DMAP in pyridine. Later, Ojima changed the base to NaH or NaHMDS instead of DMAP in pyridine, which reduced the time from 12h to 3h and used a smaller amount of β-lactam (1.5 eq). Later, Bristol-Myers Squibb licensed the patent from Holton to use in their production of paclitaxel.

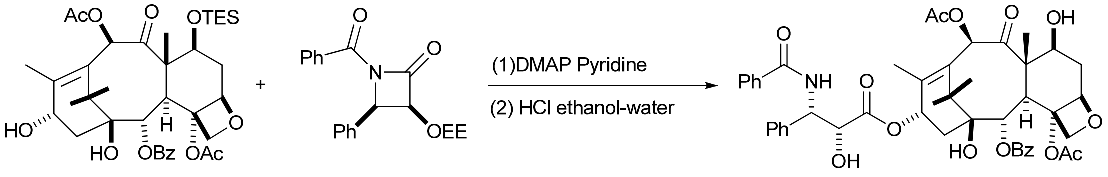


Figure 1.5 Holton semisynthesis for paclitaxel

The challenging project of the total synthesis of paclitaxel was finished separately by Dr. Holton,[33,34] Dr. Nicolaou,[35] Dr. Danishefsky and others using different synthetic routes.[36]

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Chapter 2: The design and synthesis of new antagonists for pro-inflammatory lipopolysaccharide ligands: C10-acyl-A-nor-paclitaxel derivatives

2.1 Introduction to inflammation

Inflammation is the response of living tissue when it suffers from infection or injury caused by bacteria, chemicals, trauma, heat and other physical reasons.[1] It is characterized by increased blood flow, increased temperature, redness, swelling and pain.[2] Based on its mechanism and its duration, it is categorized into two different kinds of inflammation: acute inflammation and chronic inflammation. The causes and mechanism for acute inflammation are much clearer than for chronic inflammation. In general, the acute inflammatory response is triggered by tissue injury or infection leading to the secretion of a variety of cytokines, bioactive amines, chemokines and lipid mediators by the resident tissue cells such as dendritic cells, mast cells and macrophages.[3] The major function of these inflammatory mediators is increasing vascular permeability and accumulating leukocytes (mainly neutrophils) to the site of injury. Once the neutrophils reach the injured tissue and become activated, they will try to kill the invading substance and eliminate the infectious agents. Later, the repair process is executed mainly by recruited macrophages and tissue-resident cells. The transition from inflammation to resolution is very important, and is controlled by mediators.

However, it is possible that the acute inflammatory reaction cannot eliminate the pathogen successfully. In this case, macrophages and T cells will take the place of neutrophils to eliminate the pathogen. If these cells still cannot solve the problem, a chronic inflammatory state occurs. So far, a clear mechanism of chronic inflammatory has not been discovered. The characteristics of chronic inflammation are various, based on the different effector class of T cells present in the injured tissue. Chronic inflammation is associated with several chronic diseases such as Alzheimer's disease, heart disease, diabetes, arthritis, irritable bowel syndrome, Parkinson's disease and so on. In addition, a lot of research has shown that chronic infection or injured tissue is associated with carcinogenesis.[4]

Although inflammation is a salutary response to the injured tissue, the inappropriate control of pro-inflammatory and anti-inflammatory cytokines can result in serious diseases.

2.1.1 The inflammatory pathway

The inflammatory response is a very complicated process associated with many different cells (leukocytes, macrophages, T cells, and dendritic cells) and a large number of cytokines, leading to a large and complicated network. It can be dissected into four parts: inducers, sensors, mediators and effectors.[1b]

2.1.1.1 Inducers

Inducers are the substances that can initiate the inflammatory response. They can be classified into two groups: exogenous and endogenous. Exogenous inducers can be either microbial or non-microbial. There are two classes of microbial inducers: pathogen-associated molecular patterns (PAMPs) and virulence factors. PAMPs, specific surface molecules of the bacteria, are related to a corresponding set of receptors such as toll-like receptors (TLRs). Virulence factors are restricted to pathogens which can be detected by specialized sensors. Endogenous inducers can be defined as substances which are produced by damaged or stressed tissues. For example, the necrotic cell, when the cellular membrane is disrupted, will release a variety of cellular components which can be endogenous inducers to trigger inflammation.

2.1.1.2 Sensors

Once the inducers invade our immune system, they will be detected by the sensors on the cells and then activate the production of specific sets of mediators. Different inducers may have different sensors. For example, lipopolysacchride (LPS) will be detected by TLR4; pore-forming exotoxins are detected by NALP3, and TLR2 is an important sensor for the inducers from Gram-positive bacteria.

2.1.1.3 Mediators

Mediators are the substances that come from plasma proteins or are secreted by cells activated by exogenous or endogenous inducers. The major function of mediators is the recruitment of leukocytes and activating these recruited cells to produce their own mediators and modulating the inflammatory response. There are many types of mediators such as cytokines, chemokines, lipid mediators, vasoactive amines, proteolytic enzymes, and vasoactive peptides.

Cytokines are comprised of a number of small proteins secreted by specific immune cells, most importantly by mast cells and macrophages.[5] They can be classified into two different groups: pro-inflammatory cytokines and anti-inflammatory cytokines. The role of proinflammatory cytokines is to increase the inflammatory response, and include tumor necrosis factor α (TNF-α), interleukin (IL)-1β, IL-6, IL-12, IL-18, and interferon γ. In contrast, anti-inflammatory cytokines are used to suppress inflammatory reaction, and include IL-4, IL-10, IL-13, and transforming growth factor β (TGF-β).[6]

Tumor necrosis factor α (TNF-α) is a major mediator of inflammation which can stimulate the acute phase reaction.[7] Besides the function of inducing inflammation, it also can induce apoptosis and inhibit tumorigenesis by activating the nuclear factor kappa beta (NF-κB) pathway. It exists in all cells involved in inflammation and can activate cells to synthesize more on their own. This kind of positive feedback can amplify the inflammatory response quickly. The level of TNF-α is an important marker of inflammation.

Lipid mediators derived from phospholipids are one large type of inducers. For example, phosphatidycholine can be converted to arachidonic acid and lysophosphatidic acid by cytosolic phospholipase A_2. Later, arachidonic acid can be metabolized to generate prostaglandins PGE2 and PGI2, which can cause vasodilation and fever by pathways involving cyclooxygenases (COX1 and COX2). Inhibition of COX has been one major method to reduce inflammation.

Nitric oxide and histamine are another two important mediators in inflammation.[8] The effect of nitric oxide is to prevent aggregation of platelets and promote vasodilation. Histamine is a well-known chemical mediator in acute inflammation, which can also cause vasodilation and increased vascular permeability.

2.1.1.4 Effectors of inflammation

The effectors of inflammation are the tissues or cells affected by the specific mediators.

Examples of inflammatory pathways are listed out in Table 2.1.

Table 2.1 Examples of inflammatory pathways[9]

Inducers	Sensors	Mediators	Effectors
LPS	TLR4	TNF-α IL-6 PGE_2	Endothelial cells, leukocytes
Allergens	lgE	Vasoactive amines	Endothelial cells and smooth muscle cells
Collagen	Hageman factor	Bradykinin	Endothelial cells and smooth muscle cells

2.1.2 The function of NF-κB

Nuclear factor kappa beta (NF-κB) is the transcription factor activated by proinflammatory stimuli and stressed conditions. NF-κB exists in almost all animal cell types and performs essential roles in the immune system. It was first discovered by David Baltimore in B cells in 1986. Later, a lot of evidence showed that NF-κB is actually a family of proteins composed of five related transcription factors: NF-κB1 (p50/p105), NF-κB2 (p52/p100), p65 (RelA), RelB, and c-Rel.[10] The NF-κB family can combine with DNA and regulate the expression of inflammatory cytokines (such as TNF-α), growth factors, chemokines, inhibitors of apoptosis, cyclo-oxgenase 2 (COX-2), inducible nitric oxide synthase (Inos) and cytoprotective proteins. So the activation of NF-κB is very important to inflammation and apoptosis,[11] and the pathological dysregulation of NF-κB is linked to a number of inflammatory diseases and cancer.

2.2 Lipopolysaccharide and inflammation

Endotoxins exist in the outer membrane of Gram-negative bacteria cells and play an important role in the structural integrity of the bacteria.[12] Compared to endotoxins, lipopolysaccharide (LPS) is a single compound type with no or only trace amounts of proteins. LPS is composed of three parts: an acylated glycolipid (Lipid A), a surface carbohydrate polymer (O-specific chain) and a core oligosaccharide. By activating a cascade of host-mediated responses, LPS can stimulate immunological cells to express various pro-inflammatory factors, such as interleukin-1(IL-1), IL-6, nitric oxide, vasoactive amines, and tumor necrosis factor-α (TNF-α). The result of these proinflammatory factors is to induce acute inflammation and sepsis. Much evidence indicates that lipid A is the major PAMP of LPS. The innate immune system is highly sensitive to Lipid A, even at low concentrations. The immune response for Lipid A, named endotoxic shock, is so robust and sensitive that it causes about 200,000 deaths each year in the United Stated, and it has become a major clinical problem. Considering the great damage caused by LPS, it is necessary to further explore its signaling pathway and discover novel compounds to counteract inflammation and other diseases caused by LPS.

2.2.1 The signaling pathways for LPS

It is believed that LPS produces its effect primarily through the TLR4 signaling pathways to activate NF-κB, enabling the expression of pro-inflammatory factors.[13,14,15] LPS does not bind TLR4 directly but interacts with several proteins, including LPS binding protein (LBP), CD14 and MD-2. At first, LPS binds with LBP, a soluble protein, which can convert LPS from oligomeric micelles to monomers and helps the delivery of LPS to CD14. Later, CD14 helps the transfer of LPS to the TLR4/MD-2 receptor. MD-2 is a soluble protein associated with TLR4 by non-covalent interaction. MD-2 is necessary for the activation of TLR4 by LPS. On the other hand, TLR4 can promote the interaction between LPS and MD-2.

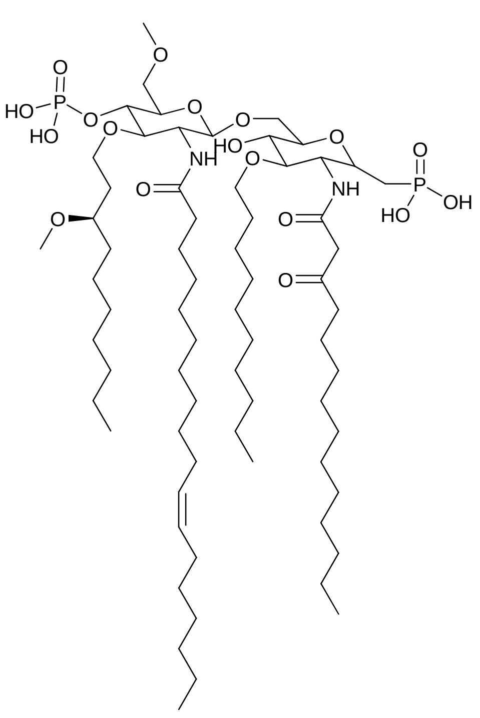
TLR4 belongs to the family of toll-like-receptors (TLRs),[16] which are expressed on the antigen present cells such as macrophage and dendritic cells.[17] The family of TLRs is one of the important pattern recognition receptors which can recognize different pathogen-associated molecular patterns (PAMPs). There are 11 human TLRs and 13 mouse TLRs. And each of them may respond to different PAMPs. Activated by LPS, TLR4 will undergo oligomerization and recruit adaptors including MyD88, TIRAP, TRIF, TRAM and SARM. The TLR4 signaling pathway can be classified into two pathways: MyD88 dependent, and MyD88 independent pathway.[18]

In the MyD88-dependent pathway, with LPS stimulation, MyD88 activates IL-1 receptor-associated kinase-4 (IRAK-4) which can activate and degrade IRAK-1. IRAK-1 contacts TRAF6 which will form a complex with UBC13 and UEV1A. This complex can activate transforming growth factor-β-activated kinase 1 (TAK1) and mitogen-activated protein kinase (MAPK) pathway. TAK1 then activates IKK which can degrade IκB, enabling the activation of NF-κB. The MAPK pathway leads to the production of another transcription factor AP-1. These two transcription factors can control the expression of proinflammatory cytokines and chemokines. The other

MyD88-independent pathway requires adaptors TRIF and TRAM. This pathway will activate interferon regulatory factor 3 (IRF3) which can translocate into the nucleus and express interferon α and β.

2.3 Paclitaxel and A-*nor*-paclitaxel, potential antagonists to LPS

Recent research showed that paclitaxel can induce apoptosis of cancer cells through the TLR4 pathway by binding to MD-2.[19,20] Paclitaxel and LPS share the same signaling pathway (TLR4).[21,22] Paclitaxel can bind to MD-2, but showed different effects on the TNF-α level between murine and human systems. In murine macrophages, paclitaxel increases the TNF-α level in a dose-dependent manner, while human THP-1 monocytes gave a poor response, although human MD-2 and mouse MD-2 proteins share 56% identity at the amino acid level. The different effects may be in part due to the surface charge distribution, the binding pocket size, the binding point of MD-2, and different interactions between paclitaxel and MD-2. It is believed that the size of the binding pocket and the mode of interaction of paclitaxel are very important, but the specific mechanism is still not clear. The work showed that paclitaxel can bind to MD-2 and compete with LPS, reducing the expression of TNF-α. In addition, in human monocytes, it did not lead to the increase of TNF-α. This suggests that paclitaxel and its derivatives might serve as antagonists to LPS. Using antagonists to treat LPS-induced inflammation is not a new idea; some of these antagonists have been under clinical trial, such as Eritoran (Figure 2.1).[23]

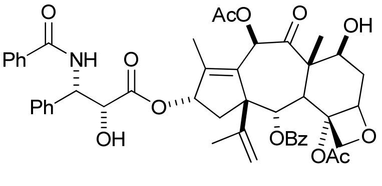


Eritoran

Figure 2.1 The structure of Eritoran

Eritoran (E5564) is a novel antagonist of endotoxin-directed sepsis, and is under Phase III clinical trial.[24] The structure of eritoran is similar to that of Lipid A, so eritoran can bind to TLR4 and block the binding of LPS.

Inspired by the activities of paclitaxel, we elected to design other paclitaxel derivatives that could potentially serve as antagonists of LPS. The lead compound for this work was A-*nor*-paclitaxel (Figure 2.2).



A-nor-paclitaxel

Figure 2.2 The structure of A-*nor*-paclitaxel

A-*nor*-paclitaxel was synthesized through ring contraction of a C2′ and C7 protected paclitaxel.[25,26] It is three times less active than paclitaxel in a tubulin depolymerization assay, but has much less antiproliferative activity than paclitaxel (Table 2.2).[25,26]

Table 2.2 Bioactivity of paclitaxel and A-*nor*-paclitaxel[26]

Compound	A2780 IC_{50} (μg/mL)	ID_{50} (μM) in tubulin depolymerization assay
Paclitaxel	0.014	0.3
A-*nor*-paclitaxel	3.1	0.9

Considering the reduced antiproliferative activity of A-*nor*-paclitaxel, it was submitted to our collaborators at Emory University for evaluation in an assay for inhibition of TNFα. The biological experiment was performed in a human acute monocytic leukemia cell line (THP-1 cells) by measuring the level of human TNFα (one important indicator in inflammation) after incubation with the test compound and NMB (meningococcal endotoxin). NMB is a potent activator for the TLR4 signaling pathway and promotes the production of proinflammatory factors such as TNFα. The results in Table 2.3 indicated that both paclitaxel and A-*nor*-paclitaxel decreased the level of human TNFα (hTNFα) compared to the control (NMB+DMSO), but that A-*nor*-paclitaxel did it more effectively. This result, coupled with the reduced antiproliferative activity, indicated that A-*nor*-paclitaxel might be a better antagonist than paclitaxel with less cytotoxity.

Table 2.3 h-TNFα level in THP-1 cell

Compound	h-TNFα (pg/mL)
Paclitaxel/NMB	2600±50
A-*nor*-paclitaxel/NMB	2050±50
DMSO/NMB	3250±50

*NMB (meningococcal endotoxin), a proinflammatory compound;
*The data were produced by Dr. Zimmer (Emory University).

This preliminary result then led to the proposal that A-*nor*-paclitaxel analogs might show even better activity than A-*nor*-paclitaxel itself. This part of the research thus focused on the design and synthesis of A-*nor*-paclitaxel analogs as potential inhibitors of TNFα formation in response to NMB.

2.4 Design and synthesis of C10 A-*nor*-paclitaxel analogs

2.4.1 Design of C10 A-*nor*-paclitaxel analogs

Since A-*nor*-paclitaxel showed better suppression of hTNFα than paclitaxel with less antiproliferative activity, we chose to design additional A-*nor*-paclitaxel analogs to test their ability to inhibit LPS. Considering the structure-activity relationships (SAR) of paclitaxel,[27] changes of substituents on the northern hemisphere do not affect the bioactivity as much as changes to the southern hemisphere. Compared to changes at the C7 position, modification at the C10 position was selected since this position could be modified on paclitaxel with improved activity in some cases. Replacing the acetyl group at C10 with other acyl groups may thus be helpful for finding some effective anti-inflammatory compounds. Based on this idea, we designed the synthesis of A-*nor*-paclitaxel analogs with changes at C10. These changes include the replacement of the acetyl group with other acyl groups including substituted benzoyl groups, saturated fatty acids, and polyethylene glycol groups which can increase the solubility of A-*nor*-paclitaxel.

2.4.2 Synthesis of C10-A-*nor*-paclitaxel analogs (2.10-2.13 and 2.27-2.30)

A series of C10-paclitaxel analogs has been prepared using different acyl groups, but A-*nor*-paclitaxels with modified C10 acyl groups have not previously been synthesized. We designed the known compound 2′-(tert-butyldimethylsilyl)-7-(triethylsilyl)-10-deacetylpaclitaxel (Figure 2.3) as the key intermediate.[28] This can then be acylated at C10 by coupling with different acids in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and 4-dimethylamino-pyridine (DMAP).[29]

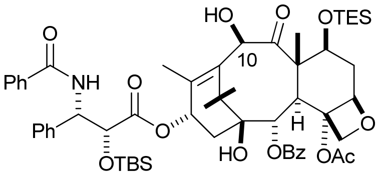


Figure 2.3 2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-deacetyl paclitaxel

Then, the modified and protected paclitaxel was caused to undergo ring contraction using thionyl chloride and pyridine at low temperature (-20 °C).[30] The proposed mechanism is shown in Figure 2.4.

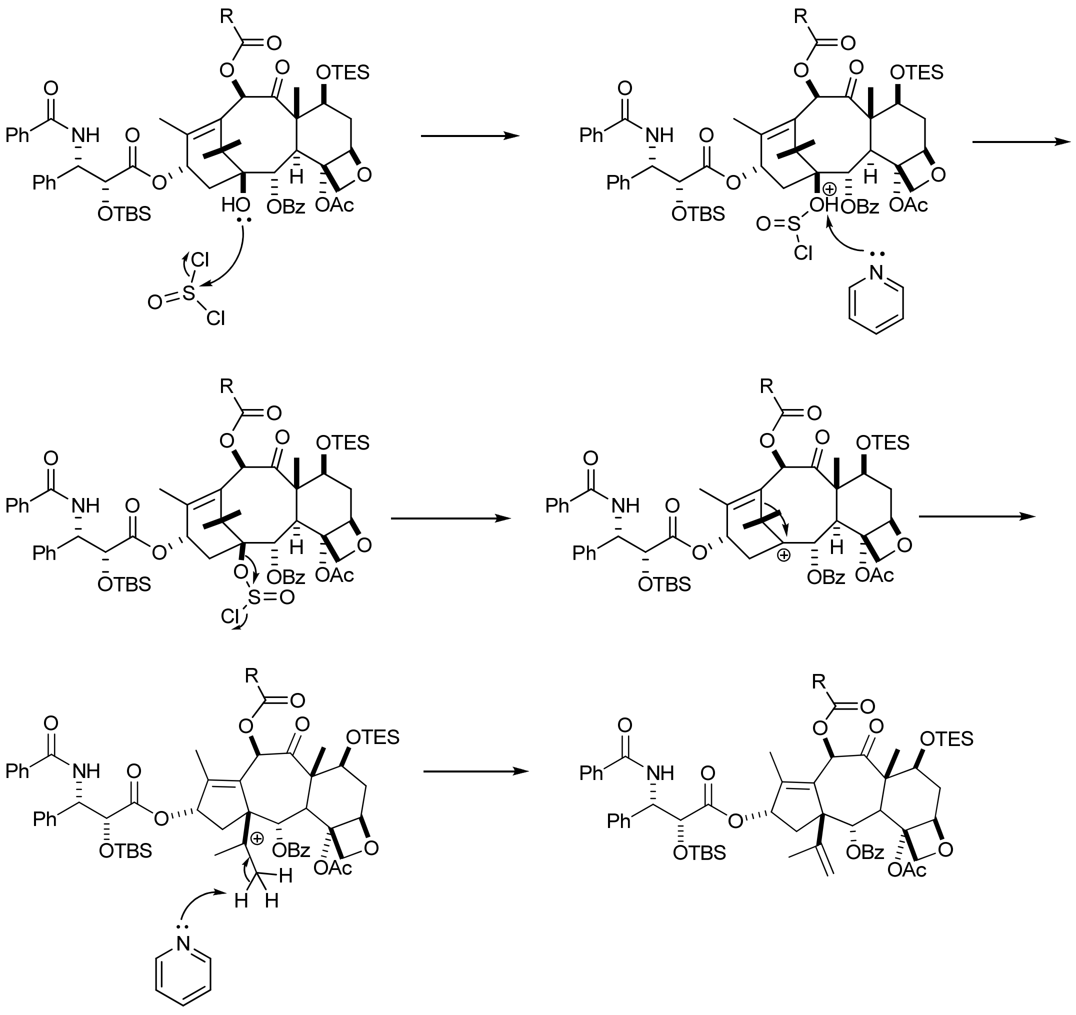
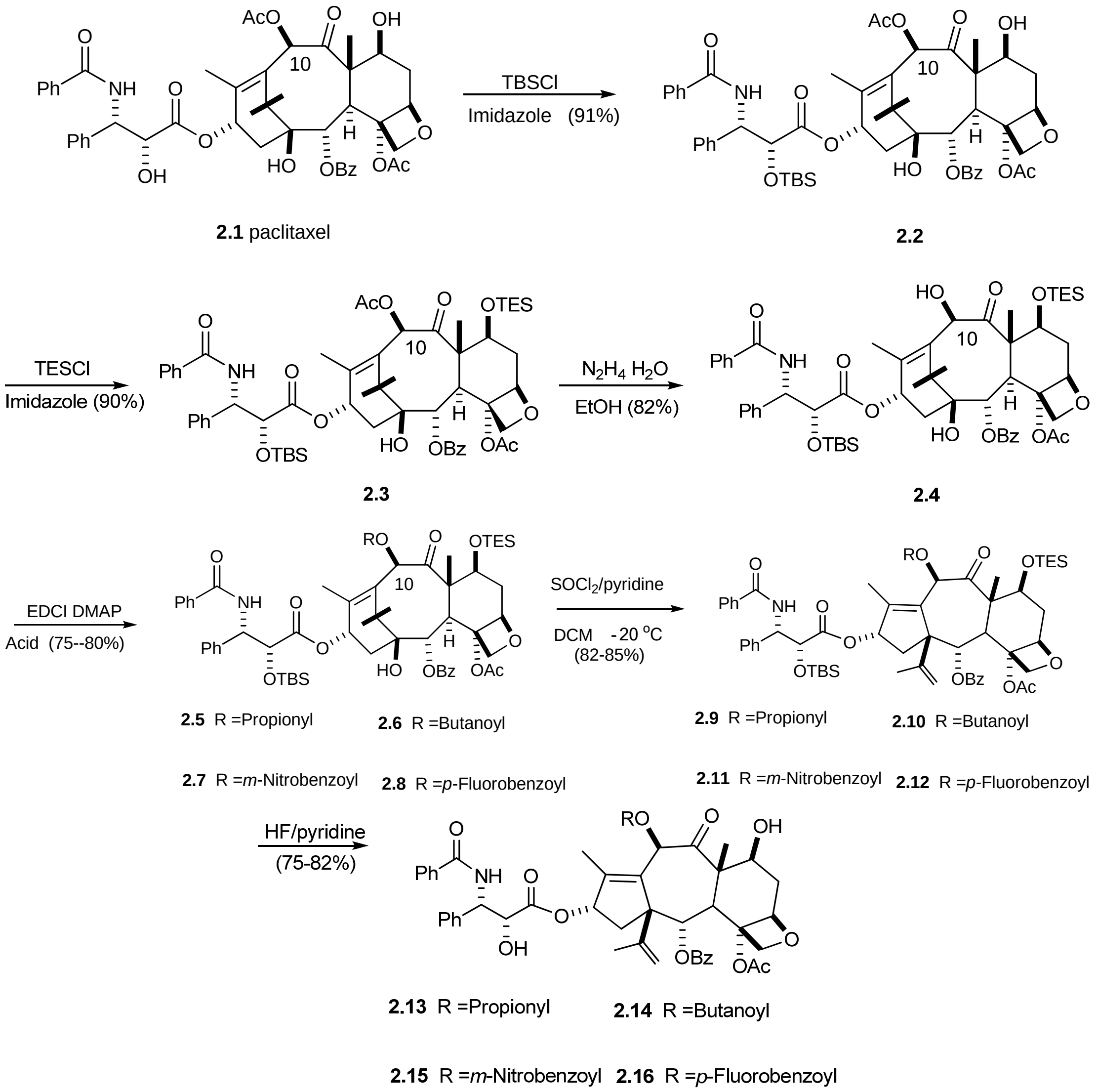


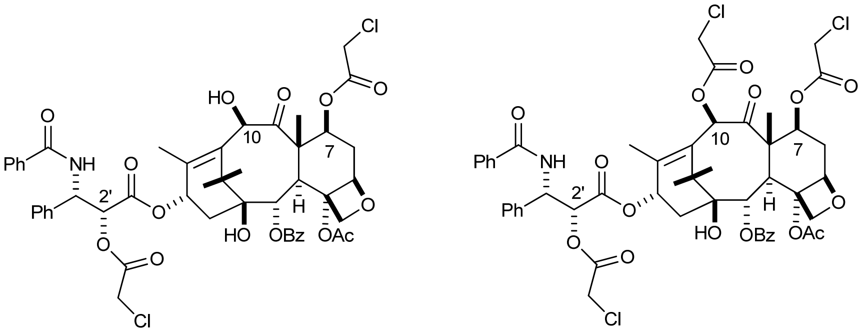
Figure 2.4 The mechanism for ring contraction

Deprotection of the silyl ether protecting groups was then effected by treatment with pyridine hydrofluoride (HF/pyridine) solution. The complete synthetic route is shown in Scheme 2.1.



Scheme 2.1 Synthesis of C-10-A-*nor*-paclitaxel analogs

Although the esterification reaction between the carboxylic acid and the C10 hydroxy group in Scheme 2.1 was clean with few byproducts, the time of the reaction was long (>24 h), the conversion rate was not higher than 80 percent, and isolation of the target compounds was difficult due to the small difference in structure and polarity between the products and starting material. In addition, several carboxylic acids could not be reacted with the C10 hydroxy group using 2′-(tert-butyldimethylsilyl) -7-(triethylsilyl)-10-deacetyl paclitaxel. It is believed that the triethylsilyl group at C7 may cause steric hindrance to acylation at the C10 hydroxy group.[31] It was reported that using a smaller protective group such as the chloroacetyl group at C7 could solve this problem. But this method still could not avoid the low yield problem, because attempted synthesis of the diacyl derivative yielded the triacyl protected derivative (Figure 2.5).[31,32]

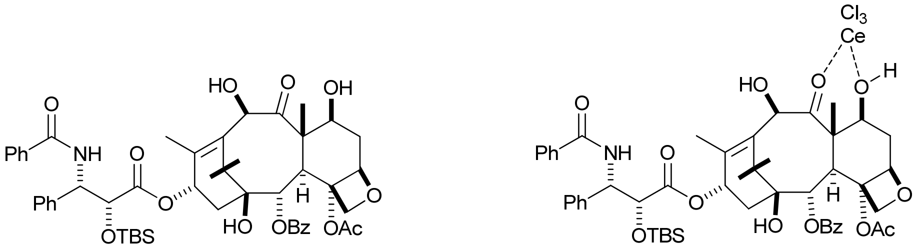


2',7-bis(chloroacetyl)-10-deacetylpaclitaxel

2',7,10-tri(chloroacetyl)-paclitaxel

Figure 2.5 Structures of 2',7-bis(chloroacetyl)-10-deacetylpaclitaxel and 2',7,10-tri(chloroacetyl)-paclitaxel

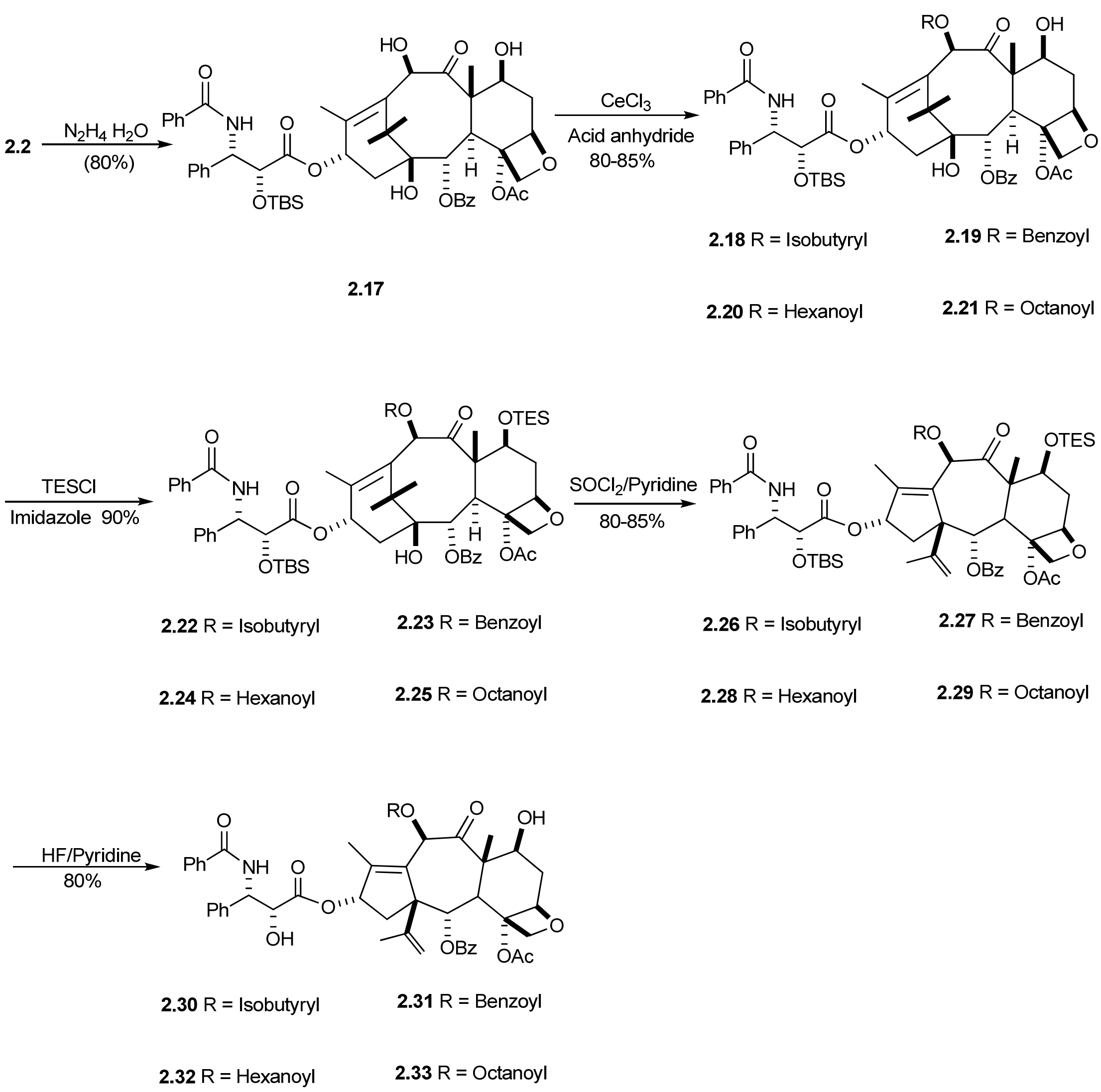
A better way to solve this problem was by using 2′-(tert-butyldimethylsilyl)-10-deacetylpaclitaxel (Figure 2.6) as the starting material and esterifying at C10 selectively in the presence of $CeCl_3$.[28, 33, 34] It was reported that 10-deacetyl paclitaxel and baccatin III could be selectively protected at C10 in the presence of Lewis acid such as $CeCl_3$ or CuCl. Under this method, the esterification reaction was much easier and faster (<3h). The mechanism may be due to the formation of a six membered ring complex with cerium (III) deactivating the C7 hydroxy group (Figure 2.6).



2.17 **2.17**

Figure 2.6 Structure of 2′-(*tert*-butyldimethylsilyl)-10-deacetylpaclitaxel and the mechanism of selective esterification using $CeCl_3$

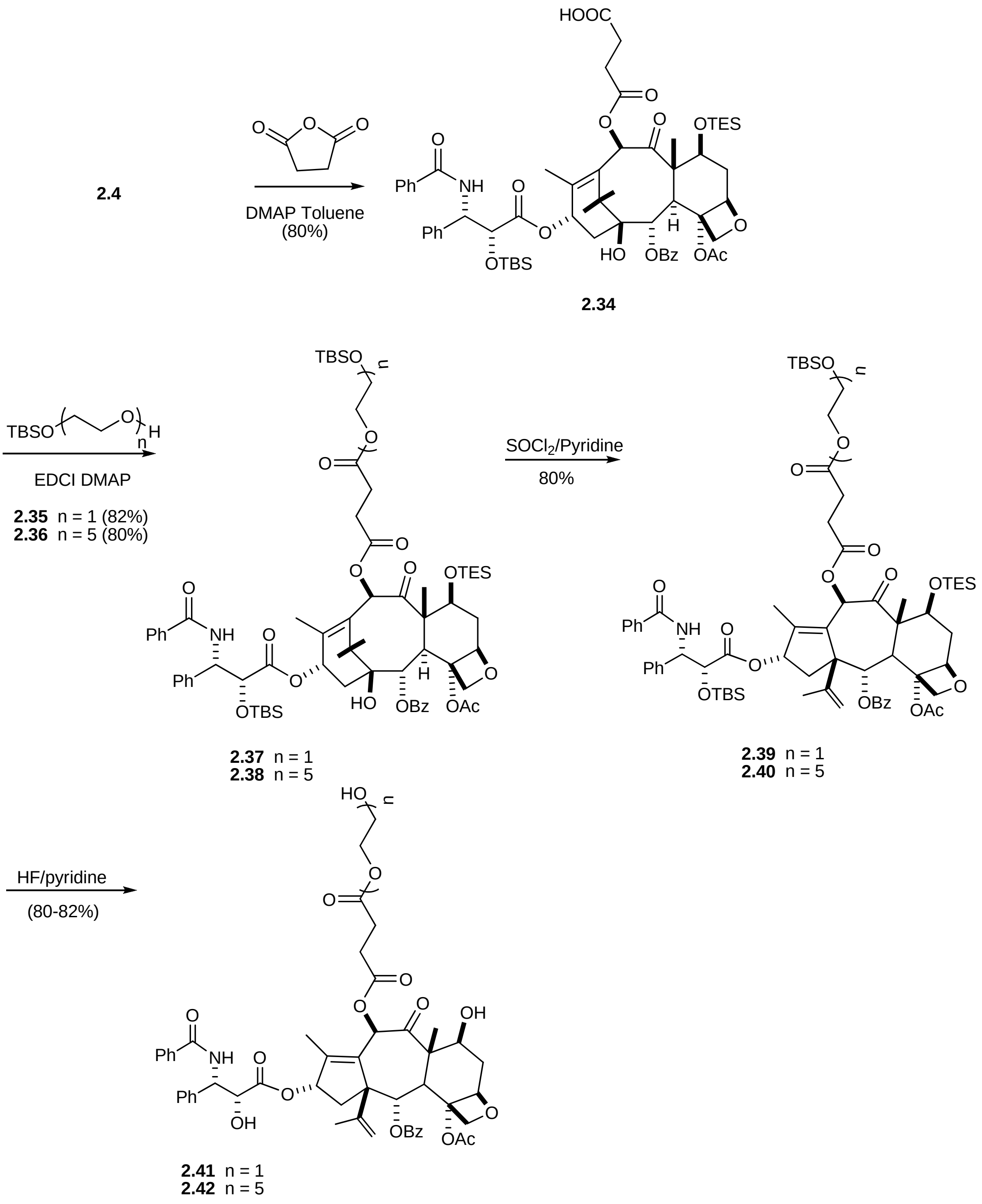
In order to avoid byproducts of the ring contraction, it was necessary to protect the C10 acyl derivatives at C7 with the triethylsilyl group. The protected compound then underwent ring contraction with thionyl chloride and deprotection using HF-pyridine to obtain the expected compounds. The complete synthetic route is shown below in Scheme 2.2.



Scheme 2.2 The synthesis of C10-acyl-A-*nor*-paclitaxel analogs

2.4.3 Synthesis of C10-PEG-A-*nor*-paclitaxel analogs (2.38-2.39)

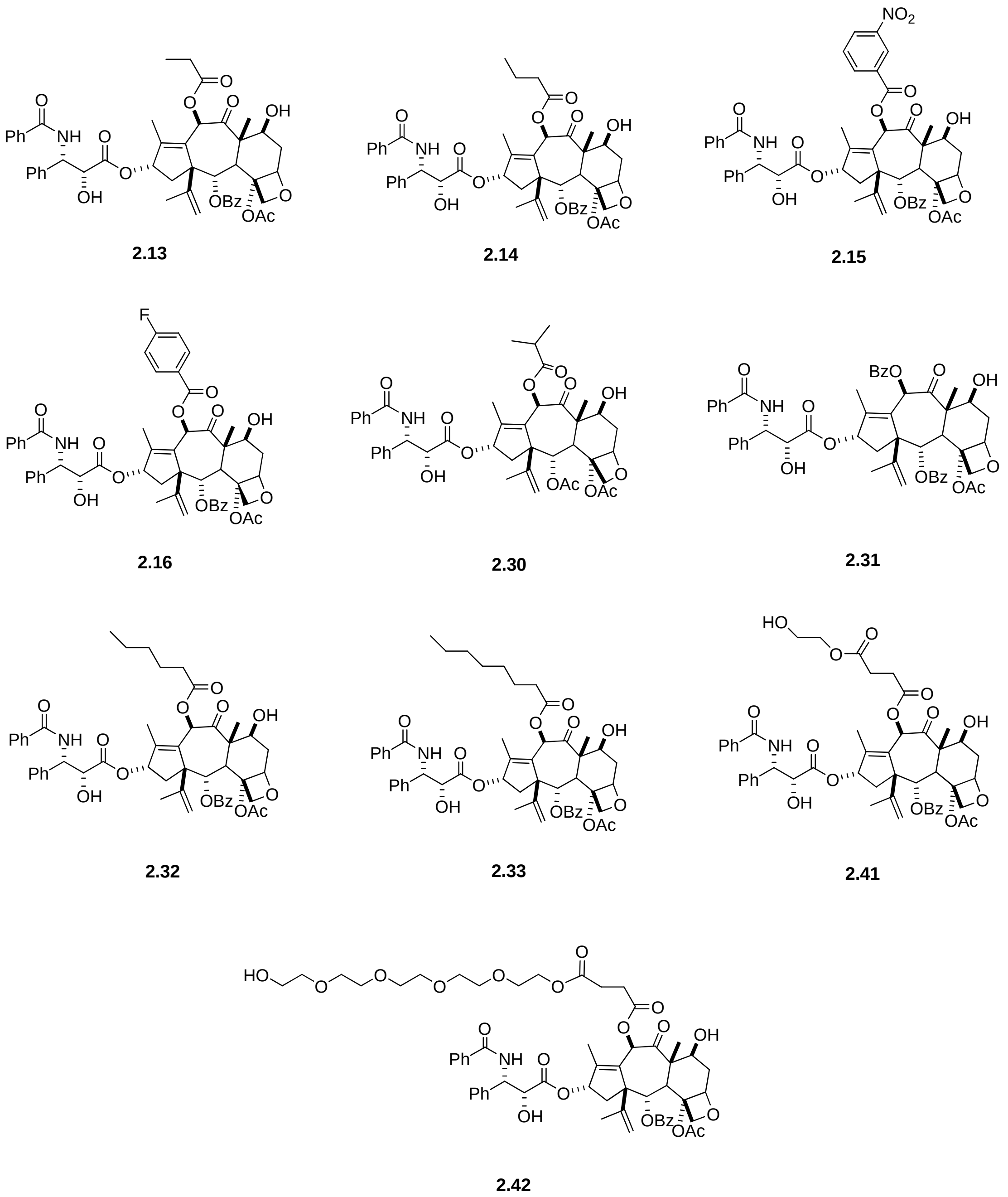
A big problem with paclitaxel and A-*nor*-paclitaxel is their low solubility in water.[35] In order to solve this problem and possibly obtain a more potent agent, we designed two analogs with polyethylene glycols (PEGs) linked to C10 on paclitaxel using succinic acid as the linking agent.[36,37] After the completion of coupling with PEG, the derivatives underwent ring contraction and deprotection as before. The synthetic route is shown below in Scheme 2.3.



Scheme 2.3 The synthesis of C10 PEG A-*nor*-paclitaxel analogs

2.5 Biological evaluations of all analogs and conclusion

In our research, we prepared ten different A-*nor*-paclitaxel analogs (Scheme 2.4) and tested their biological activities (Table 2.4).



Scheme 2.4 C10 PEG A-*nor*-paclitaxel analogs

Table 2.4 A-*nor*-paclitaxel derivatives bioassay results

Compound with NMB	Substituents at C10	IC_{50} against A2780 (μg/mL)	h-TNFα (pg/mL)
DMSO	/	/	3250±50
Paclitaxel	Acetyl	0.014	2600±50
A-*nor*-paclitaxel	Acetyl	3.10	2050±50
2.13	Propionyl	0.40	2400±50
2.14	Butanoyl	0.13	2300±50
2.15	*m*-Nitrobenzoyl	2.50	3000±50
2.16	*p*-Fluorobenzoyl	1.90	4600±50
2.30	2-Methylpropanoyl	0.40	2400±50
2.31	Benzoyl	1.40	3750±50
2.32	Hexanoyl	0.65	2200±50
2.33	Octanoyl	2.40	3000±50
2.41	MonoPEG succinate	0.20	2500±50
2.42	PentaPEG succinate	1.80	3550±50

*NMB (meningococcal endotoxin), a proinflammatory compound;

*The data were provided by Ms. Peggy Brodie (Virginia Tech) and Dr. Shanta Zimmer (Emory University).

We tested all the C10-acyl A-*nor*-paclitaxel analogs and found that all of them, as expected, had lower antiproliferative activities than paclitaxel (Table 2.4). Most of them also reduced the expression of TNF-α (Table 2.4). Compounds **2.13**, **2.14**, **2.30**, **2.32**, **2.41** showed better activities than paclitaxel in the suppression of TNF-α, while compounds **2.14** and **2.32** showed the best activity among these A-*nor*-paclitaxel analogs. However, compared to these analogs, A-*nor*-paclitaxel still showed the best activity in the suppression of TNF-α. In the case of analogs with aromatic substituents at C10, compounds **2.15**, **2.16**, and **2.31**, compound **2.16** (*p*-fluorobenzoyl-A-*nor* -paclitaxel) showed the lowest activity in reducing the expression of TNF-α, compound **2.31** (10-benzoyl-A-nor-paclitaxel) showed less activity than paclitaxel and compound **2.15** (*m*-nitrobenzoyl-A-*nor*-paclitaxel) showed only slightly reduced activity compared with paclitaxel. For the A-*nor*-paclitaxel analog modified with PEG, although compound **2.42** with a longer PEG chain would have improved water solubility, it showed less biological activity than the shorter one (compound **2.41**) in both of the bioassays. 10-Hexanoyl-A-nor-paclitxel (**2.32**) proved to be the best compound of those prepared, with better activity and less antiproliferative activity than paclitaxel.

In summary, most of the A-*nor*-paclitaxel derivatives showed activity in suppressing TNF-α with less antiproliferative activity than paclitaxel, and they thus have the potential to act as antiinflammatory agents. However, the activity of even the most active compound is less than ideal, and so more work will be needed to develop improved compounds of this structured class.

2.6 Experimental section:

General experimental methods

^{1}H and ^{13}C NMR spectra were obtained on a Varian Inova spectrometers at 400 MHz or a JEOL Eclipse spectrometer at 500 MHz. High-resolution mass spectra were obtained on an agilent 6220 accurate-mass TOF LC/MS instrument. Chromatography on a silica gel column was used to purify compounds using EtOAc/hexanes as solvents.

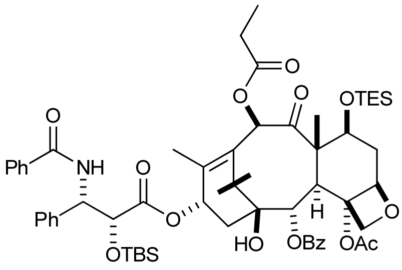
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-deacetyl paclitaxel (2.4)

This compound was synthesized from paclitaxel by the literature method.[28]

General method for the preparation of 2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl) -10-acyl paclitaxels (2.5-2.8)

A mixture of 1 equivalent of the carboxylic acid and 1 equivalent of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) in dichloromethane (DCM) (1.5 mL) was stirred at room temperature for 10 min. And catalytic amount of 4-(dimethylamino)pyridine (DMAP) was then added to the mixture, which was stirred for 5 min. To this solution, 0.1 equivalent of 2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)-10-deacetylpaclitaxel (**2.4**, 35 mg) was added and the mixture stirred for 24 h. The reaction was quenched with saturated $NaHCO_3$ solution (10 mL), extracted with ethyl acetate (3×10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography (40% ethyl acetate in hexanes) to obtain the desired product, in a yield of 75-80%.

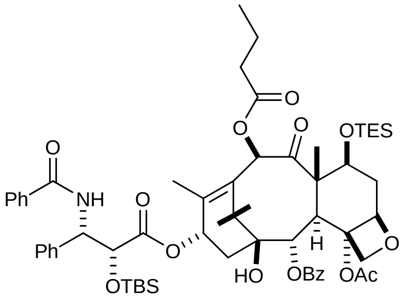
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-propionyl paclitaxel (2.5)



2.5

Compound **2.5** was a known compound and was obtained in a yield of 80% (29.5 mg). Its NMR spectra matched the literature data.[38] HRMS (FAB+) calcd for $C_{60}H_{81}NO_{14}Si_2Na$ $[M+Na]^+$ *m/z* 1118.5093, found 1118.5113.

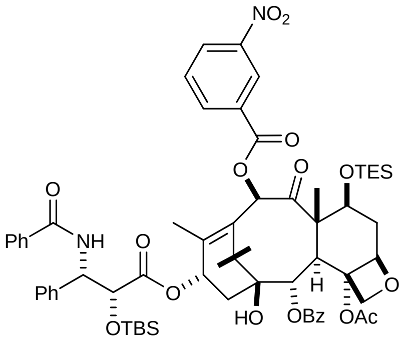
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-butanoyl paclitaxel (2.6)



2.6

The yield for compound **2.6** was 78% (29 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (2H, d, *J* = 8.0), 7.74 (2H, d, *J* = 8.0), 7.59 (1H, m), 7.49 (3H, m), 7.37 (4H, m), 7.31 (3H, m), 7.05 (1H, d, *J* = 8.9), 6.25 (1H, t, *J* = 8.7), 5.73 (2H, dd, *J* = 1.9, 8.8), 5.70 (1H, d, *J* = 7.1), 4.95 (1H, d, *J* = 9.6), 4.66 (1H, d, *J* = 2.2), 4.48 (1H, dd, *J* = 6.6, 10.5), 4.31 (1H, d, *J* = 8.4), 4.20 (1H, d, *J* = 8.4), 3.84 (1H, d, *J* = 7.1), 2.57 (3H, s), 2.52 (1H, m), 2.40 (3H, m), 2.10 (1H, m), 2.02 (3H, s), 1.92 (1H, m), 1.73 (2H, m), 1.69 (3H, s), 1.21 (3H, s), 1.16 (3H, s), 0.99 (3H, t, *J* = 7.4), 0.92 (9H, t, *J* = 7.9), 0.79 (9H, s), 0.57 (6H, m), -0.03 (3H, s), -0.30 (3H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.78, -5.09, 5.39, 6.86, 10.23, 13.78, 14.33, 18.19, 18.56, 21.60, 23.21, 25.60, 26.64, 35.68, 36.28, 37.34, 43.40, 46.77, 55.75, 58.52, 71.49, 72.30, 74.76, 75.04, 75.20, 76.67, 78.98, 81.31, 84.33, 126.53, 127.08, 128.01, 128.79, 128.80, 128.82, 129.32, 130.31, 131.85, 133.70, 133.91, 134.18, 138.41, 140.11, 166.93, 167.18, 170.23, 171.51, 171.94, 201.82. HRMS (FAB+) calcd for $C_{61}H_{83}NO_{14}Si_2Na$ $[M+Na]^+$ *m/z* 1132.5249, found 1132.5282.

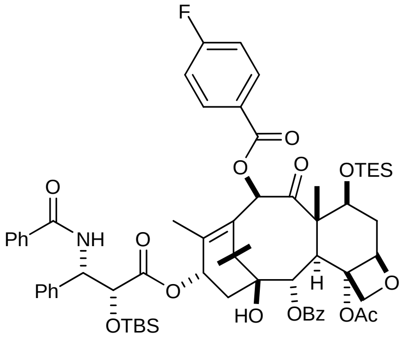
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-(*m*-nitrobenzoyl) paclitaxel (2.7)



2.7

Compound **2.7** was a known compound and was obtained in a yield of 76% (30 mg). Its NMR spectra matched the literature data.[29] HRMS (FAB+) calcd for $C_{64}H_{80}N_2O_{16}Si_2Na$ $[M+Na]^+$ *m/z* 1211.4944, found 1211.4954.

2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-(*p*-fluorobenzoyl) paclitaxel (2.8)



2.8

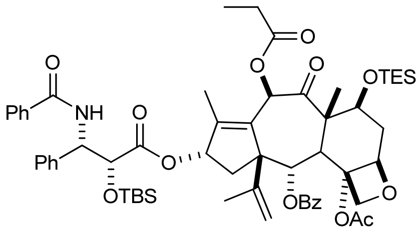
Compound **2.8** was obtained in a yield of 75% (29 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (4H, m), 7.72 (2H, m), 7.60 (1H, m), 7.50 (5H, m), 7.39 (4 H, m), 7.32

(3H, m), 7.14 (2H, t, *J* = 8.7), 7.07 (1H, d, *J* = 8.9), 6.65 (1H, s), 6.27 (1H, t, *J* = 9.2), 5.74 (2H, m), 4.98 (1H, d, *J* = 9.7), 4.68 (1H, d, *J* = 2.2), 4.55 (1H, dd, *J* = 6.6, 10.6), 4.34 (1H, d, *J* = 8.3), 4.23 (1H, d, *J* = 8.3), 3.90 (1H, d, *J* = 6.9), 2.60 (3H, s), 2.54 (1H, m), 2.43 (1H, m), 2.12 (1H, m), 2.11 (3H, s), 1.94 (1H, m), 1.73 (3H, s), 1.33 (3H, s), 1.18 (3H, s), 0.89 (9H, t, *J* = 7.9), 0.79 (9H, s), 0.57 (6H, m), -0.03 (3H, s), -0.29 (3H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.76, -5.10, 5.40, 6.82, 10.23, 14.45, 18.21, 22.01, 23.23, 25.60, 26.70, 35.67, 37.34, 43.50, 46.82, 55.72, 58.59, 71.52, 72.39, 75.04, 75.20, 75.65, 76.67, 78.94, 81.32, 84.37, 115.72, 115.90, 126.53, 127.08, 128.05, 128.81, 128.82, 128.85, 129.31, 130.33, 131.89, 132.42, 132.50, 133.64, 133.74, 134.15, 138.34, 140.78, 164.15, 167.10, 167.13, 170.30, 171.51, 201.77. HRMS (FAB+) calcd for $C_{64}H_{80}FNO_{14}Si_2Na$ $[M+Na]^+$ *m/z* 1184.4999, found 1184.5019.

General method for the preparation of 2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)-10-acyl A-*nor*-paclitaxels (2.9-2.12)

A mixture of 2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)-10-acyl paclitaxel (25 mg) and anhydrous pyridine (150 μL) in dichloromethane (5ml) was stirred at -20 °C for 10 min. To the mixture, 50 μL thionyl chloride was added. The reaction was warmed to room temperature and stirred for 10 min. Then it was quenched by saturated $NaHCO_3$ solution (10 mL), extracted with ethyl acetate (3×10 mL), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (25% ethyl acetate in hexanes) to obtain the desired product (yields 82-85%).

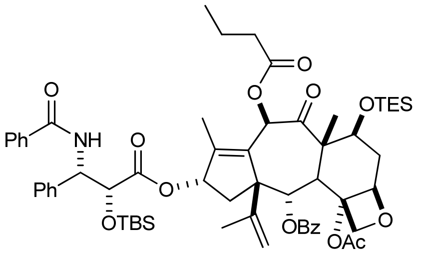
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-propionyl-A-*nor*-paclitaxel (2.9)



2.9

Compound **2.9** was obtained in a yield of 85% (21 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.05 (2H, d, *J* = 7.1), δ 7.72 (2H, d, *J* = 7.1), 7.53 (1H, t, *J* = 7.4), 7.45 (3H, m), 7.36 (4H, t, *J* = 7.0), 7.29 (3H, m), 7.07 (1H, d, *J* = 8.9), 6.44 (1H, s), 5.83 (1H, t, *J* = 6.9), 5.68 (1H, dd, *J* = 1.7, 8.9), 5.55 (1H, d, *J* = 7.7), 5.04 (1H, t, *J* = 8.4), 4.75 (1H, s), 4.67 (1H, s), 4.58 (1H, d, *J* = 2.0), 4.55 (1H, dd, *J* = 7.4, 9.4), 4.27 (1H, d, *J* = 8.1), 4.21 (1H, d, *J* = 8.1), 3.55 (1H, d, *J* = 7.7), 2.63 (1H, m), 2.50 (3H, s), 2.42 (3H, m), 1.93 (2H, m), 1.75 (3H, s), 1.66 (3H, s), 1.63 (3H, s), 1.17 (3H, t, *J* = 7.6), 0.94 (9H, t, *J* = 7.9), 0.77 (9H, s), 0.61 (6H, m), -0.12 (3H, s), -0.32 (3H, s). ^{13}C NMR (500 MHz, CDCl$_3$) δ -5.88, -5.43, 5.37, 6.97, 9.21, 9.29, 11.40, 14.33, 18.28, 20.81, 22.33, 25.56, 27.40, 38.43, 38.75, 44.06, 55.97, 56.85, 63.30, 70.49, 70.58, 72.69, 74.77, 75.59, 77.99, 79.12, 84.76, 113.13, 126.49, 127.05, 127.89, 128.70, 128.75, 128.83, 129.19, 130.04, 131.75, 133.52, 134.35, 137.12, 138.70, 144.22, 145.22, 165.41, 166.81, 170.56, 171.11, 172.32, 201.85. HRMS (FAB+) calcd for $C_{60}H_{79}NO_{13}Si_2Na$ [M+Na]$^+$ *m/z* 1100.4987, found 1100.4987.

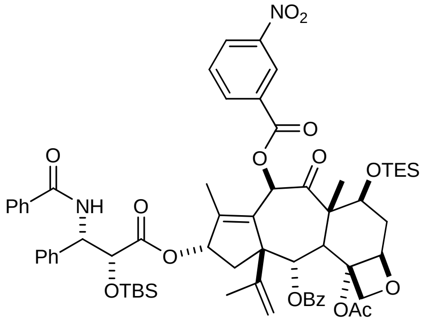
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-butyryl-A-*nor*-paclitaxel (2.10)



2.10

The yield for compound **2.10** was 84% (20.6 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.05 (2H, d, J = 7.1), 7.72 (2H, d, J = 7.1), 7.53 (1H, t, J = 7.4), 7.43 (3H, m), 7.35 (7H, m), 7.08 (1H, d, J = 8.9), 6.44 (1H, s), 5.82 (1H, t, J = 7.6), 5.68 (1H, dd, J = 1.7, 8.8), 5.55 (1H, d, J = 7.7), 4.75 (1H, s), 4.66 (1H, s), 4.58 (1H, d, J = 2.0), 4.55 (1H, dd, J = 7.4, 9.4), 4.27 (1H, d, J = 8.1), 4.21 (1H, d, J = 8.1), 3.55 (1H, d, J = 7.6), 2.61 (1H, m), 2.50 (3H, s), 2.37 (3H, m), 1.95 (2H, m), 1.75 (3H, s), 1.68 (2H, m), 1.66 (3H, s), 1.63 (3H, s), 0.98 (3H, t, J = 7.4), 0.94 (9H, t, J = 7.9), 0.77 (9H, s), 0.61 (6H, m), -0.12 (3H, s), -0.32 (3H, s). ^{13}C NMR (500 MHz, CDCl$_3$) δ -5.88, -5.42, 5.38, 6.98, 9.22, 11.41, 13.73, 18.28, 18.57, 20.81, 22.34, 25.57, 35.93, 38.44, 38.74, 44.07, 55.98, 56.87, 63.30, 70.41, 70.58, 72.70, 74.77, 75.59, 78.01, 79.13, 84.76, 113.14, 126.49, 127.06, 127.89, 128.71, 128.76, 128.84, 129.20, 130.05, 131.75, 133.52, 134.36, 137.18, 138.70, 144.22, 145.16, 165.41, 166.82, 170.56, 171.13, 171.49, 201.81. HRMS (FAB+) calcd for $C_{61}H_{81}NO_{13}Si_2Na$ $[M+Na]^+$ m/z 1114.5144, found 1114.5148.

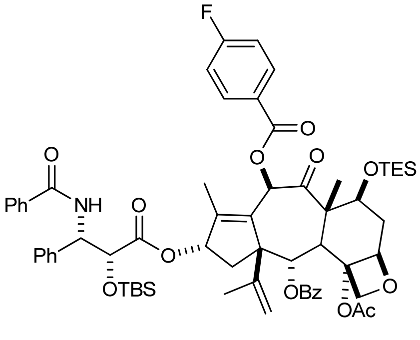
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-(*m*-nitrobenzoyl)-A-*nor*-paclitaxel (2.11)



2.11

The yield for compound **2.11** was 84% (20 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (1H, t, J = 2.0), 8.43 (1H, dd, J = 1.2, 8.2), 8.32 (1H, d, J = 7.8), 8.08 (2H, d, J = 7.2), 7.73 (2H, d, J = 7.2), 7.65 (1H, t, J = 8.0), 7.55 (1H, t, J = 7.4), 7.53 (3H, m), 7.35 (7H, m), 7.09 (1H, d, J = 9.0), 6.67 (1H, s), 5.90 (1H, t, J = 7.6), 5.70 (1H, dd, J = 1.4, 8.9), 5.65 (1H, d, J = 7.7), 5.06 (1H, d, J = 8.7), 4.91 (1H, s), 4.85 (1H, s), 4.63 (1H, dd, J = 7.5, 9.3), 4.59 (1H, d, J = 2.0), 4.30 (1H, d, J = 8.1), 4.23 (1H, d, J = 8.1), 3.65 (1H, d, J = 7.6), 2.66 (1H, m), 2.53 (3H, s), 2.45 (1H, m), 2.05 (1H, m), 1.95 (1H, m), 1.79 (3H, s), 1.74 (3H, s), 1.73 (3H, s), 0.96 (9H, t, J =7.9), 0.76 (9H, s), 0.67 (6H, m), -0.14 (3H, s), -0.32 (3H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.86, -5.45, 5.42, 7.02, 9.21, 11.53, 18.28, 20.90, 22.42, 25.56, 38.48, 38.70, 44.28, 55.93, 57.14, 63.45, 70.39, 72.24, 72.82, 74.71, 75.59, 78.01, 79.12, 84.78, 113.44, 124.98, 126.50, 127.07, 127.75, 127.94, 128.74, 128.79, 128.89, 129.13, 129.83, 130.08, 131.30, 131.82, 133.64, 134.30, 135.45, 136.30, 138.62, 144.19, 146.28, 148.41, 162.74, 165.43, 166.89, 170.66, 171.12, 201.26. HRMS (FAB+) calcd for $C_{64}H_{78}N_2O_{15}Si_2Na$ $[M+Na]^+$ m/z 1193.4838, found 1193.4850.

2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-(*p*-fluorobenzoyl)-A-*nor*-paclitaxel (2.12)



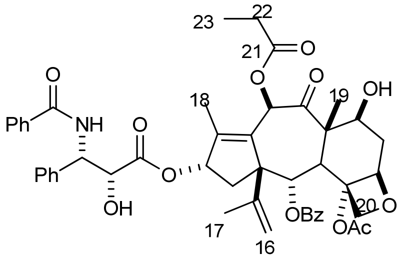
2.12

The yield for compound **2.12** was 82% (19.5 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.07 (2H, dd, J = 1.3, 8.4), 8.01 (2H, m), 7.72 (2H, dd, J = 1.3, 8.4), 7.54 (1H, t, J = 7.4), 7.44 (3H, m), 7.36 (4H, t, J =7.6), 7.31 (3H, m), 7.10 (3H, m), 6.67 (1H, d, J = 0.9), 5.86 (1H, m), 5.69 (1H, dd, J = 1.8, 8.9), 5.62 (1H, d, J = 7.7), 5.06 (1H, d, J = 8.1), 4.86 (1H, s), 4.77 (1H, s), 4.63 (1H, dd, J = 7.4, 9.4), 4.58 (1H, d, J = 2.0), 4.30 (1H, d, J = 8.1), 4.23 (1H, d, J = 8.1), 3.63 (1H, d, J = 7.7), 2.65 (1H, m), 2.52 (3H, s), 2.45 (1H, m), 2.00 (2H, m), 1.77 (3H, s), 1.72 (3H, s), 1.70 (3H, s), 0.95 (9H, t, J = 7.9), 0.76 (9H, s), 0.66 (6H, m), -0.14 (3H, s), -0.32 (3H, s). ^{13}C NMR (500 MHz, CDCl$_3$) δ -5.88, -5.46, 5.41, 7.00, 9.20, 11.50, 18.27, 20.94, 22.37, 25.56, 38.46, 38.79, 44.20, 55.96, 56.98, 63.41, 70.57, 71.35, 72.79, 74.76, 75.59, 77.99, 79.14, 84.80, 113.24, 115.80, 125.72, 126.50, 127.07, 127.92, 128.72, 128.77, 128.87, 129.17, 130.07, 131.79, 132.40, 132.47, 133.59, 134.33, 136.88, 138.66, 144.37, 145.85, 163.74, 165.45, 166.87, 170.64, 171.13, 201.63. HRMS (FAB+) calcd for $C_{64}H_{78}FNO_{13}Si_2Na$ [M+Na]$^+$ *m/z* 1166.4893, found 1166.4912.

General method for the preparation of 10-acyl-A-*nor*-paclitaxels:

To a solution of 10-acyl-A-*nor*-paclitaxel (16 mg) in dry THF (2 mL), HF-pyridine (70%, 200 μL) was added at 0 °C and stirred for 1 h. The reaction was warmed to room temperature and stirred for 9 h. The reaction was diluted with ethyl acetate, quenched with sodium bicarbonate, extracted with ethyl acetate (3×10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by TLC plate (silica gel, 1000 μ, 60% ethyl acetate in hexanes) to obtain desired products (yields 75-82%).

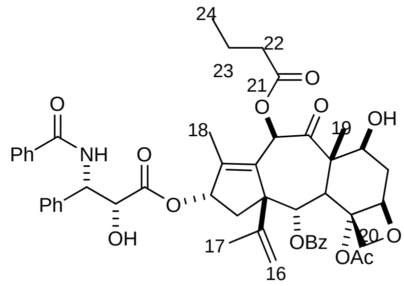
10-Propionyl-A-*nor*-paclitaxel (2.13)



2.13

The yield for compound **2.13** was 82% (10.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (2H, d, J = 6.7, ArH), 7.68 (2H, d, J = 6.7, ArH), 7.53 (1H, t, J = 7.4, ArH), 7.41 (7H, m, ArH), 7.33 (3H, m, ArH), 6.92 (1H, d, J = 9.2, CONH), 6.34 (1H, s, H10), 5.72 (2H, m, H7, H2′), 5.49 (1H, d, J = 8.2, H2), 5.05 (1H, d, J = 8.1, H5), 4.79 (1H, s, H16a), 4.71 (2H, s, H16b, H2′), 4.66 (1H, t, J = 8.6, H7), 4.32 (1H, d, J = 8.1, H20a), 4.19 (1H, d, J = 8.1, H20b), 3.51 (1H, d, J = 8.2, H3), 3.35 (1H, d, J = 3.7, 2′OH), 2.63 (1H, m, H6a), 2.46 (3H, m, H14a, 22CH_2), 2.37 (3H, s, 4OAc), 2.07 (1H, m, H14b), 1.93 (1H, m, H6b), 1.72 (3H, s, 18CH_3), 1.65 (3H, s, 17CH_3), 1.60 (3H, s, 19CH_3), 1.19 (3H, t, J =7.6, 23CH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.35, 9.07, 11.79, 20.74, 22.00, 27.41, 35.91, 39.27, 44.54, 54.85, 56.77, 63.95, 70.94, 71.59, 72.74, 73.41, 74.62, 79.08, 79.23, 85.02, 113.59, 126.92, 127.09, 128.27, 128.71, 128.85, 129.05, 129.22, 130.14, 131.93, 133.66, 133.97, 135.71, 138.37, 144.97, 145.16, 165.38, 166.84, 170.58, 172.71, 174.79, 203.42. HRMS (FAB+) calcd for $C_{48}H_{51}NO_{13}Na$ [M+Na]$^+$ *m/z* 872.3258, found 872.3270.

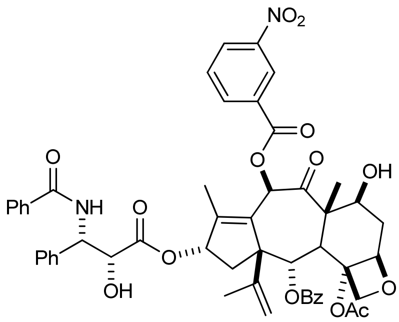
10-Butanoyl-A-*nor*-paclitaxel (2.14)



2.14

The yield for compound **2.14** was 80% (10.1 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (2H, d, J = 7.3, ArH), 7.68 (2H, d, J = 7.3, ArH), 7.53 (1H, t, J = 7.4, ArH), 7.42 (7H, m, ArH), 7.33 (3H, m, ArH), 6.91 (1H, d, J = 9.2, CONH), 6.34 (1H, s, H10), 5.72 (2H, m, H7, H2′), 5.49 (1H, d, J = 8.2, H2), 5.05 (1H, d, J = 8.5, H5), 4.79 (1H, s, H16a), 4.71 (2H, m, H16b, H2′),4.66 (1H, t, J = 8.9, H7), 4.32 (1H, d, J = 8.1, H20a), 4.19 (1H, d, J = 8.1, H20b), 3.50 (1H, d, J = 8.2, H3), 3.33 (1H, d, J = 4.3, 2′OH), 2.61 (1H, m, H6a), 2.43 (3H, m, H6b, 22CH_2), 2.37 (3H, s, 4OAc), 2.05 (1H, m, H14b), 1.92 (1H, m, H6b), 1.72 (3H, s, 18CH_3), 1.69 (2H, m, 23CH_2), 1.65 (3H, s, 17CH_3), 1.60 (3H, s, 19CH_3), 0.99 (3H, t, J =7.4, 24CH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.34, 11.80, 13.70, 18.47, 20.74, 22.00, 35.91, 39.27, 44.56, 54.84, 56.78, 63.96, 70.95, 71.52, 72.75, 73.40, 74.62, 79.08, 79.24, 85.03, 113.60, 126.91, 127.09, 128.28, 128.71, 128.86, 129.06, 129.23, 130.14, 131.93, 133.65, 133.97, 135.73, 138.37, 144.97, 145.10, 165.37, 166.83, 170.57, 172.72, 174.05, 203.38. HRMS (FAB+) calcd for $C_{49}H_{53}NO_{13}Na$ [M+Na]$^+$ *m/z* 886.3414, found 886.3427.

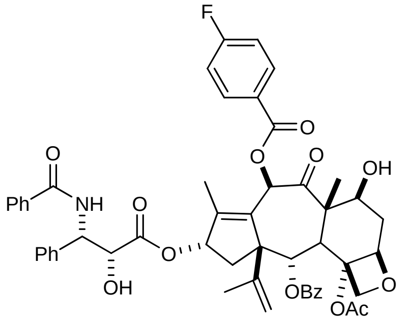
10-*m*-Nitrobenzoyl-A-*nor*-paclitaxel (2.15)



2.15

The yield for this compound was 81% (10.4 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.83 (1H, t, J = 2.0, ArH), 8.47 (1H, ddd, J = 1.1, 2.3, 8.2, ArH), 8.34 (1H, dt, J = 1.3, 7.8, ArH), 8.13 (2H, dd, J = 1.3, 8.4, ArH), 7.68 (3H, m, ArH), 7.55 (1H, t, J = 7.4, ArH), 7.43 (7H, m, ArH), 7.34 (3H, m, ArH), 6.91 (1H, d, J = 9.2, CONH), 6.63 (1H, s, H10), 5.82 (1H, m, H13), 5.74 (1H, dd, J = 2.3, 9.2, H3′), 5.58 (1H, d, J = 8.1, H2), 5.08 (1H, d, J = 8.0, H5), 4.92 (1H, s, H16a), 4.83 (1H, s, H16b), 4.72 (2H, m, H7, H2′), 4.34 (1H, d, J = 8.1, H20a), 4.22 (1H, d, J = 8.1, H20b), 3.60 (1H, d, J = 8.1, H3), 2.68 (1H, m, H6a), 2.51 (1H, m, H14a), 2.40 (3H, s, 10OAc), 2.13 (1H, m, H14b), 1.95 (1H, m, H6b), 1.76 (3H, s, 18CH$_3$), 1.71 (3H, s, 19CH$_3$), 1.70(3H, s, 17CH$_3$). ^{13}C NMR (500 MHz, CDCl$_3$) δ 8.48, 11.92, 20.83, 22.03, 36.22, 39.32, 44.56, 54.89, 56.92, 64.01, 70.84, 72.70, 73.04, 73.40, 74.60, 79.03, 79.18, 84.95, 113.62, 124.94, 126.93, 127.10, 128.30, 128.31, 128.73, 128.90, 129.07, 129.15, 130.06, 130.16, 130.55, 131.98, 133.74, 133.93, 135.25, 135.53, 138.30, 144.89, 146.32, 148.46, 164.60, 165.40, 166.89, 170.68, 172.71, 202.72. HRMS (FAB+) calcd for $C_{52}H_{50}N_2O_{15}Na$ $[M+Na]^+$ *m/z* 965.3108, found 965.3119.

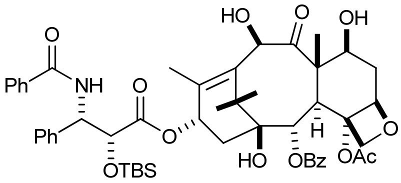
10-*p*-Fluorobenzoyl-A-*nor*-paclitaxel (2.16)



2.16

The yield for this compound was 78% (9.9 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (2H, d, *J* = 8.1, ArH), 8.04 (2H, m, ArH), 7.69 (2H, d, *J* = 8.1, ArH), 7.54 (1H, m, ArH), 7.42 (7H, m, ArH), 7.33 (3H, t, *J* = 7.4, ArH), 7.14 (2H, t, *J* = 7.8, ArH), 6.90 (1H, d, *J* = 9.5, CONH), 6.58 (1H, s, H10), 5.79 (1H, t, *J* = 6.9, H13), 5.75 (1H, d, *J* = 9.2, H3′), 5.55 (1H, dd, *J* = 1.3, 8.2, H2), 5.08 (1H, d, *J* = 9.0, H5), 4.90 (1H, s, H16a), 4.74 (3H, m, H16b, H7, H2′), 4.35 (1H, d, *J* = 8.1, H20a), 4.21 (1H, d, *J* = 8.1, H20b), 3.58 (1H, d, *J* = 8.1, H3), 3.33 (1H, d, *J* = 4.2, 2′OH), 2.67 (1H, m, H6a), 2.47 (1H, m, H14a), 2.39 (3H, s, 10OAc), 2.13 (1H, m, H14b), 1.96 (1H, m, H6b), 1.75 (3H, s, $18CH_3$), 1.69 (3H, s, $17CH_3$), 1.67(3H, s, $19CH_3$). ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.38, 11.87, 20.84, 22.02, 36.01, 39.43, 44.62, 54.84, 56.87, 64.02, 70.93, 72.27, 72.82, 73.39, 74.63, 79.09, 79.22, 85.03, 113.55, 115.91, 116.08, 124.94, 126.92, 127.09, 128.29, 128.72, 128.88, 129.06, 129.21, 130.16, 131.95, 132.59, 132.67, 133.69, 133.97, 135.69, 138.35, 145.12, 145.72, 165.40, 165.68, 166.84, 170.62, 172.75, 203.06. HRMS (FAB+) calcd for $C_{52}H_{50}FNO_{13}Na$ $[M+Na]^+$ *m/z* 938.3163, found 938.3172.

2′-(*tert*-Butyldimethylsilyl)-7,10-deacetylpaclitaxel (2.17)



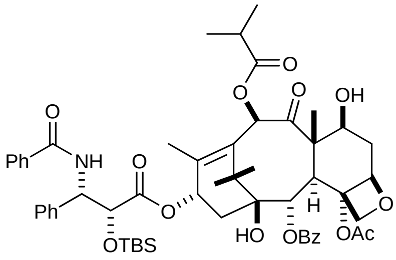
2.17

The preparation of compound **2.17** followed the literature method.[28]

2′-(*tert*-Butyldimethylsilyl)-10-acyl paclitaxels (2.18-2.21)

To a solution of 2′-(*tert*-butyldimethylsilyl)-10-deacetyl paclitaxel (**2.17**, 35 mg) in anhydrous THF (2 mL), catalytic amount of $CeCl_3$ was added and stirred for 15 min. Carboxylic acid anhydrate (10 eq) was added into the mixture solution and stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ solution (15 mL), extracted with ethyl acetate (3×10 mL), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (33% ethyl acetate in hexanes) to obtain the desired products.

2′-(*tert*-Butyldimethylsilyl)-10-isobutyryl paclitaxel (2.18)

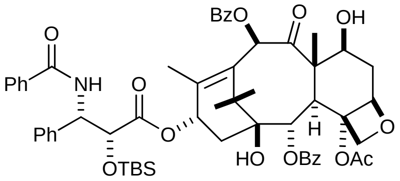


2.18

The yield for this compound was 86% (32.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (2H, d, J = 7.3), 7.73 (2H, d, J = 7.3), 7.59 (1H, m), 7.51 (3H, m), 7.39 (4H, m), 7.32 (2H, d, J = 7.3), 7.31 (1H, m), 7.07 (1H, d, J = 9.0), 6.27 (1H, s), 6.27 (1H, m), 5.74 (1H, dd, J = 1.6, 8.9), 5.68 (1H, d, J = 7.1), 4.97 (1H, dd, J = 1.7, 9.6), 4.66 (1H, d, J = 2.1), 4.43 (1H, m), 4.32 (1H, d, J = 8.5), 4.21 (1H, d, J = 8.5), 3.83 (1H, d, J =

7.1), 2.71 (1H, m), 2.56 (3H, s), 2.54 (1H, m), 2.39 (1H, m), 2.15 (1H, m), 1.89 (3H, s), 1.85 (1H, m), 1.68 (3H, s), 1.31 (3H, d, *J* = 7.0), 1.23 (3H, s), 1.23 (3H, d, *J* = 6.9), 1.13 (3H, s), 0.80 (9H, s), -0.04 (3H, s), -0.30 (3H, s). ^{13}C NMR (500 MHz, $CDCl_3$) *δ* -5.84, -5.28, 9.61, 14.84, 18.12, 18.63, 19.15, 22.32, 23.02, 25.49, 26.74, 34.03, 35.53, 35.82, 43.23, 45.53, 55.64, 58.51, 71.48, 72.14, 75.08, 75.15, 75.18, 76.46, 79.10, 81.16, 84.46, 126.41, 126.98, 127.99, 128.71, 128.74, 128.76, 129.14, 130.21, 131.79, 133.06, 133.64, 134.04, 138.22, 142.19, 166.95, 166.99, 170.10, 171.42, 177.19, 203.72. HRMS (FAB+) calcd for $C_{55}H_{69}NO_{14}SiNa$ $[M+Na]^+$ *m/z* 1018.4385, found 1018.4396.

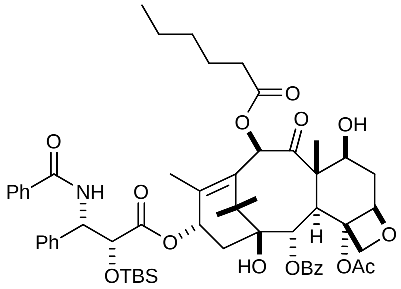
2′-(*tert*-Butyldimethylsilyl)-10-benzoyl paclitaxel (2.19)



2.19

The yield for this compound was 82% (32 mg). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.14 (2H, d, *J* = 7.2), 8.07 (2H, d, *J* = 7.2), 7.74 (2H, d, *J* = 7.2), 7.59 (2H, m), 7.48 (5H, m), 7.39 (4H, m), 7.33 (3H, m), 7.08 (1H, d, *J* = 8.9), 6.55 (1H, s), 6.33 (1H, t, *J* = 9.7), 5.74 (2H, m), 5.00 (1H, dd, *J* = 1.9, 9.5), 4.67 (1H, d, *J* = 2.2), 4.53 (1H,m), 4.33 (1H, d, *J* = 8.5), 4.23 (1H, d, *J* = 8.5), 3.90 (1H, d, *J* = 7.1), 2.62 (1H, m), 2.59 (3H, s), 2.45 (1H, m), 2.18 (1H, m), 2.03 (3H, s), 1.95 (3H, s), 1.90 (1H, m), 1.71 (3H, s), 1.32 (3H, s), 0.79 (9H, s), -0.05 (3H, s), -0.30 (3H, s). ^{13}C NMR (500 MHz, $CDCl_3$) *δ* -5.84, -5.28, 9.63, 14.97, 18.12, 22.57, 23.05, 25.48, 26.93, 35.65, 35.86, 43.31, 45.62, 55.64, 58.58, 71.41, 72.20, 75.12, 75.19, 75.91, 76.48, 79.18, 81.18, 84.48, 126.42, 126.99, 127.99, 128.51, 128.71, 128.74, 128.77, 129.09, 129.13, 129.95, 130.23, 131.79, 132.95, 133.64, 133.66, 134.04, 138.24, 142.69, 166.41, 166.94, 167.02, 170.16, 171.36, 203.57. HRMS (FAB+) calcd for $C_{58}H_{67}NO_{14}SiNa$ $[M+Na]^+$ *m/z* 1052.4228, found 1052.4250.

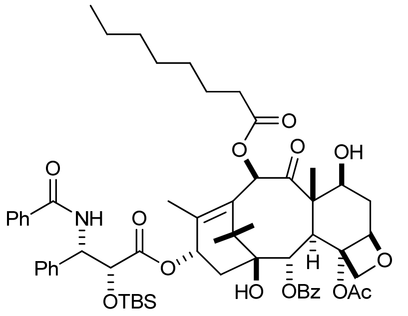
2′-(*tert*-Butyldimethylsilyl)-10-hexanoyl paclitaxel (2.20)



2.20

The yield for this compound was 85% (32.9 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (2H, d, *J* = 7.2), 7.73 (2H, d, *J* = 7.1), 7.59 (1H, t, *J* = 7.4), 7.50 (3H, m), 7.40 (4H, m), 7.31 (3H, m), 7.07 (1H, d, *J* = 8.9), 6.29 (1H, s), 6.29 (1H, m), 5.73 (1H, dd, *J* = 1.9, 8.9), 5.68 (1H, d, *J* = 7.1), 4.98 (1H, dd, *J* =1.9, 9.5), 4.66 (1H, d, *J* = 2.2), 4.44 (1H, m), 4.32 (1H, d, *J* = 8.4), 4.21 (1H, d, *J* = 8.4), 3.82 (1H, d, *J* = 7.1), 2.57 (3H, s), 2.44 (5H, m), 2.14 (1H, m), 1.90 (1H, m), 1.89 (3H, s), 1.72 (1H, m), 1.68 (3H, s), 1.35 (4H, m), 1.23 (3H, s), 1.12 (3H, s), 0.90 (3H, t, *J* = 7.1), 0.79 (9H, s), -0.05 (3H, s), -0.30(3H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.78, -5.10, 5.38, 6.87, 10.23, 13.96, 14.36, 18.20, 21.61, 22.39, 23.23, 24.73, 25.60, 26.65, 31.32, 34.30, 35.65, 37.33, 43.40, 46.76, 55.76, 58.50, 71.50, 72.30, 74.78, 75.03, 75.19, 76.67, 78.95, 81.30, 84.33, 126.52, 127.08, 128.03, 128.80, 128.82, 128.83, 129.30, 130.32, 131.87, 133.71, 133.89, 134.15, 138.38, 140.13, 166.98, 167.17, 170.24, 171.52, 172.18, 201.83. HRMS (FAB+) calcd for $C_{57}H_{73}NO_{14}SiNa$ $[M+Na]^+$ *m/z* 1046.4698, found 1046.4717.

2′-(*tert*-Butyldimethylsilyl)-10-octanoyl paclitaxel (2.21)



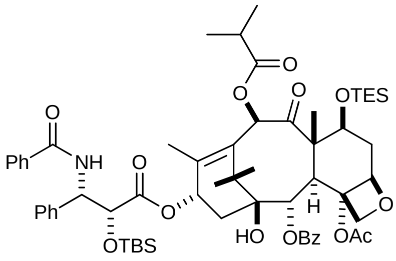
2.21

The yield for this compound was 80% (31.8 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.13 (2H, d, *J* = 7.2), 7.73 (2H, d, *J* = 7.2), 7.59 (1H, t, *J* = 7.4), 7.50 (3H, m), 7.39 (4H, m), 7.32 (3H, m), 7.06 (1H, d, *J* = 8.9), 6.28 (1H, s), 6.28 (1H, m), 5.73 (1H, dd, *J* = 2.0, 8.9), 5.68 (1H, d, *J* = 7.1), 4.98 (1H, dd, *J* =2.0, 9.6), 4.66 (1H, d, *J* = 2.2), 4.44 (1H, m), 4.32 (1H, d, *J* = 8.4), 4.21 (1H, d, *J* = 8.4), 3.82 (1H, d, *J* = 7.1), 2.57 (3H, s), 2.45 (4H, m), 2.12 (1H, m), 1.89 (3H, s), 1.70 (3H, m), 1.68 (3H, s), 1.31 (8H, m), 1.23 (3H, s), 1.12 (3H, s), 0.88 (3H, t, *J* = 6.9), 0.80 (9H, s), -0.05 (3H, s), -0.30 (3H, s). ^{13}C NMR (500 MHz, CDCl$_3$) δ -5.73, -5.18, 9.70, 14.15, 15.00, 18.23, 22.42, 22.67, 23.13, 24.91, 25.60, 26.87, 28.97, 29.12, 31.72, 34.25, 35.61, 35.91, 43.31, 45.59, 55.75, 58.61, 71.51, 72.27, 75.18, 75.29, 75.37, 76.57, 79.28, 81.25, 84.57, 126.51, 127.09, 128.09, 128.81, 128.84, 128.87, 129.21, 130.33, 131.89, 133.12, 133.76, 134.14, 138.35, 142.44, 166.97, 167.14, 170.22, 171.47, 174.17, 203.83. HRMS (FAB+) calcd for $C_{59}H_{77}NO_{14}SiNa$ $[M+Na]^+$ *m/z* 1074.5011, found 1074.5049.

2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-acyl paclitaxels (2.22-2.25)

To a solution of 2′-(*tert*-butyldimethylsilyl)-7-deacetyl-10-acyl paclitaxel (30 mg, 1 equivalent) in anhydrous dichloromethane (1 mL), 6 equivalent of imidazole was added, followed with 4 equivalent of chlorotriethylsilane and stirred overnight. It was quenched with saturated $NaHCO_3$ solution (15 mL), extracted with ethyl acetate (3×10 mL), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified with flash chromatography (30% ethyl acetate in hexanes) to obtain the desired products. The yield was around 90% in each case.

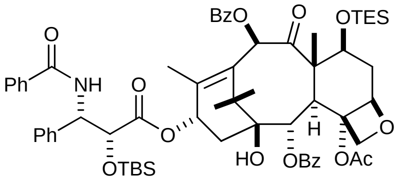
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-isobutyryl paclitaxel (2.22)



2.22

The yield for this compound was 91% (30.4 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (2H, d, J = 7.1), 7.74 (2H, d, J = 7.1), 7.59 (1H, m), 7.50 (3H, m), 7.38 (4H, m), 7.33 (3H, m), 7.07 (1H, d, J = 8.9), 6.44 (1H, s), 6.25 (1H, t, J = 9.7), 5.73 (1H, dd, J = 2.0, 8.9), 5.70 (1H, d, J = 7.1), 4.95 (1H, dd, J =1.8, 9.6), 4.32 (1H, d, J = 8.4), 4.21 (1H, d, J = 8.4), 3.84 (1H, d, J = 7.1), 2.67 (1H, m), 2.57 (3H, s), 2.41 (1H, m), 2.09 (1H, m), 2.03 (3H, s), 1.89 (1H, m), 1.70 (3H, s), 1.24 (3H, d, J = 7.0), 1.23 (3H, d, J = 7.0), 1.22 (3H, s), 0.91 (9H, t, J = 7.9), 0.79 (9H, s), 0.57 (6H, m), -0.02 (3H, s), -0.31 (3H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.88, -5.19, 5.28, 6.75, 10.12, 14.24, 18.09, 18.86, 19.03, 21.52, 23.12, 25.50, 26.53, 34.10, 35.57, 37.22, 43.30, 46.67, 55.66, 58.40, 71.46, 72.18, 74.56, 74.93, 75.08, 76.56, 78.85, 81.21, 84.24, 126.42, 126.97, 127.93, 128.69, 128.72, 128.73, 129.22, 130.22, 131.77, 133.61, 133.78, 134.07, 138.27, 140.05, 166.90, 167.06, 170.11, 171.46, 175.20, 201.78. HRMS (FAB+) calcd for $C_{61}H_{83}NO_{14}Si_2Na$ $[M+Na]^+$ *m/z* 1132.5249, found 1132.5279.

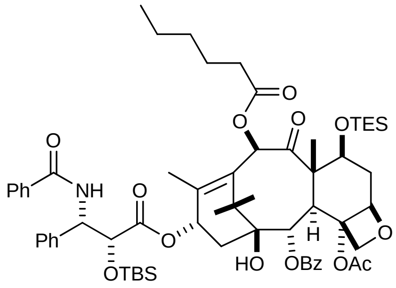
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-benzoyl paclitaxel (2.23)



2.23

The yield for this compound was 88% (29.3 mg). ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (2H, d, J = 7.1), 8.11 (2H, d, J = 7.1), 7.73 (2H, d, J = 7.1), 7.58 (2H, m), 7.52 (2H, t, J = 7.6), 7.47 (3H, m), 7.38 (4H, m), 7.32 (3H, m), 7.07 (1H, d, J = 8.9), 6.68 (1H, s), 6.28 (1H, t, J = 9.2), 5.75 (2H, m), 4.98 (1H, d, J = 9.6), 4.68 (1H, d, J = 2.2), 4.55 (1H, dd, J = 6.6, 10.6), 4.34 (1H, d, J = 8.4), 4.23 (1H, d, J = 8.4), 3.91 (1H, d, J = 7.0), 2.59 (3H, s), 2.55 (1H, m), 2.44 (1H, m), 2.13 (3H, s), 2.12 (1H, m), 1.93 (1H, m), 1.74 (3H, s), 1.35 (3H, s), 1.18 (3H, s), 0.89 (9H, t, J = 7.9), 0.79 (9H, s), 0.59 (6H, m), -0.03 (3H, s), -0.30 (3H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.86, -5.18, 5.30, 6.73, 10.15, 14.37, 18.11, 21.85, 23.15, 25.50, 26.58, 35.65, 37.26, 43.41, 46.74, 55.65, 58.49, 71.41, 72.28, 74.97, 75.10, 75.42, 76.58, 78.93, 81.23, 84.30, 126.44, 126.99, 127.93, 128.49, 128.70, 128.71, 128.75, 129.22, 129.80, 129.81, 130.24, 131.77, 133.19, 133.63, 133.65, 134.05, 138.29, 140.53, 165.01, 166.93, 167.08, 170.19, 171.38, 201.65. HRMS (FAB+) calcd for $C_{64}H_{81}NO_{14}Si_2Na$ $[M+Na]^+$ *m/z* 1166.5093, found 1166.5106.

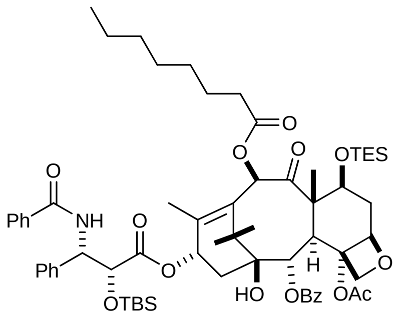
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-hexanoyl paclitaxel (2.24)



2.24

The yield for this compound was about 90% (30 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.13 (2H, d, *J* = 8.3), 7.73 (2H, d, *J* = 8.3), 7.59 (1H, t, *J* = 6.8), 7.49 (3H, m), 7.38 (4H, m), 7.31 (3H, m), 7.07 (1H, d, *J* = 8.8), 6.46 (1H, s), 6.25 (1H, t, *J* = 9.1), 5.73 (1H, d, *J* = 8.8), 5.70 (1H, d, *J* = 7.1), 4.95 (1H, d, *J* = 8.6), 4.66 (1H, d, *J* = 1.4), 4.47 (1H, dd, *J* = 6.6, 10.5), 4.31 (1H, d, *J* = 8.5), 4.20 (1H, d, *J* = 8.5), 3.84 (1H, d, *J* = 7.1), 2.58 (3H, s), 2.44 (4H, m), 2.10 (1H, m), 2.02 (3H, s), 1.90 (1H, m), 1.69 (3H, s), 1.68 (2H, m), 1.34 (4H, m), 1.21 (3H, s), 1.16 (3H, s), 0.92 (9H, t, *J* = 7.9), 0.90 (3H, m), 0.79 (9H, s), 0.58 (6H, m), -0.03 (3H, s), -0.31 (3H, s). ^{13}C NMR (500 MHz, CDCl$_3$) δ -5.78, -5.10, 5.38, 6.87, 10.23, 13.96, 14.35, 18.20, 21.61, 22.40, 23.23, 24.73, 25.61, 26.65, 31.32, 34.30, 35.65, 37.32, 43.39, 46.39, 55.76, 58.50, 71.50, 72.30, 74.78, 75.03, 75.19, 76.67, 78.95, 81.30, 84.34, 126.52, 127.08, 128.03, 128.79, 128.81, 128.84, 129.30, 130.31, 131.87, 133.72, 133.90, 134.16, 138.38, 140.13, 166.98, 167.17, 170.24, 171.52, 172.18, 201.83. HRMS (FAB+) calcd for $C_{63}H_{87}NO_{14}Si_2Na$ $[M+Na]^+$ *m/z* 1160.5562, found 1160.5597.

2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-octanoyl paclitaxel (2.25)



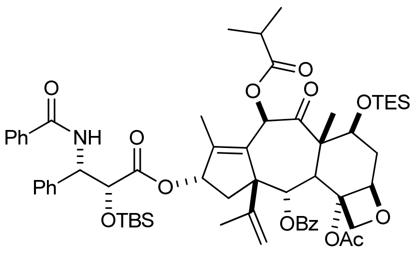
2.25

The yield for this compound was 89% (29.6 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.13 (2H, d, *J* = 7.2), 7.74 (2H, d, *J* = 7.2), 7.59 (1H, t, *J* = 7.4), 7.50 (3H, m), 7.38 (4H, m), 7.31 (3H, m), 7.06 (1H, d, *J* = 8.8), 6.47 (1H, s), 6.25 (1H, t, *J* = 9.2), 5.72 (1H, dd, *J* = 1.9, 8.9), 5.70 (1H, d, *J* = 7.1), 4.95 (1H, dd, *J* =1.7, 9.6), 4.66 (1H, d, *J* = 2.2), 4.47 (1H, dd, *J* = 6.6, 10.5), 4.32 (1H, d, *J* = 8.4), 4.20 (1H, d, *J* = 8.4), 3.84 (1H, d, *J* = 7.1), 2.58 (3H, s), 2.45 (4H, m), 2.09 (1H, m), 2.02 (3H, s), 1.89 (1H, m), 1.69 (3H, s), 1.66 (2H, m), 1.65 (3H, s), 1.29 (8H, m), 1.21 (3H, s), 1.16 (3H, s), 0.92 (9H, t, *J* = 7.9), 0.87 (3H, t, *J* = 7.0), 0.57 (6H, m), -0.03 (3H, s), -0.31 (3H, s). ^{13}C NMR (500 MHz, CDCl$_3$) δ -5.78, -5.10, 5.38, 6.87, 10.23, 14.15, 14.35, 18.20, 21.61, 22.70, 23.23, 25.06, 25.60, 26.65, 29.01, 29.16, 31.72, 34.35, 35.64, 37.32, 43.39, 46.76, 55.75, 58.50, 71.48, 72.30, 74.77, 75.03, 75.19, 76.67, 78.98, 81.30, 84.34, 126.52, 127.09, 128.03, 128.80, 128.82, 128.84, 129.29, 130.33, 131.87, 133.73, 133.89, 134.16, 138.40, 140.14, 166.94, 167.19, 170.24, 171.51, 172.18, 201.82. HRMS (FAB+) calcd for $C_{65}H_{91}NO_{14}Si_2Na$ $[M+Na]^+$ *m/z* 1188.5875, found 1188.5896.

General method for the 2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-acyl-A-*nor*-paclitaxels (2.26-2.29)

The general method for ring contraction was the same as before, using thionyl chloride and pyridine at low temperature to produce compounds **2.26-2.29**. The yields were about 80-85%.

2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-isobutyryl-A-*nor*-paclitaxel (2.26)

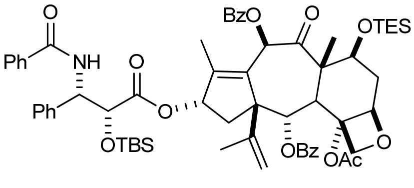


2.26

The yield for this compound was 84% (20 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.06 (2H, d, J = 7.1), 7.72 (2H, d, J = 7.1), 7.53 (1H, m), 7.43 (3H, m), 7.36 (4H, m), 7.31 (3H, m), 7.08 (1H, d, J = 8.9), 6.45 (1H, s), 5.83 (1H, t, J = 7.6), 5.69 (1H, dd, J = 1.8, 8.9), 5.55 (1H, d, J = 7.7), 5.04 (1H, d, J = 8.6), 4.77 (1H, s), 4.67 (1H, s), 4.58 (1H, d, J = 2.0), 4.55 (1H, dd, J = 7.4, 9.4), 4.27 (1H, d, J = 8.1), 4.21 (1H, d, J = 8.1), 3.55 (1H, d, J = 7.7), 2.64 (2H, m), 2.50 (3H, s), 2.41 (1H, m), 1.93 (2H, m), 1.75 (3H, s), 1.65 (3H, s), 1.63 (3H, s), 1.21 (3H, d, J = 7.0), 1.19 (3H, d, J = 7.0), 0.94 (9H, d, J = 7.9), 0.77 (9H, s), 0.63 (6H, m), -0.12 (3H, s), -0.32 (3H, s). ^{13}C NMR (500 MHz, CDCl$_3$) δ -5.98, -5.52, 5.28, 6.90, 9.12, 11.29, 18.18, 18.89, 19.01, 20.71, 22.24, 25.46, 34.03, 38.31, 38.66, 43.97, 55.89, 56.74, 63.21, 70.04, 70.50, 72.58, 74.68, 75.50, 77.90, 79.02, 84.67, 113.00, 126.39, 126.97, 127.81, 128.62, 128.67, 128.75, 129.09, 129.95, 131.68, 133.44, 134.24, 137.16, 138.59, 144.18, 145.06, 165.33, 166.74, 170.48, 171.06, 174.73, 201.80. HRMS (FAB+) calcd for

$C_{61}H_{81}NO_{13}Si_2Na$ $[M+Na]^+$ *m/z* 1114.5144, found 1114.5153.

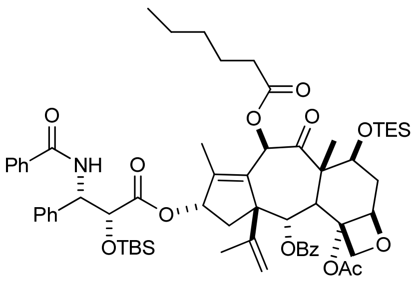
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-benzoyl-A-*nor*-paclitaxel (2.27)



2.27

The yield for this compound was 82% (21 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.08 (2H, d, J = 7.3), 8.00 (2H, d, J = 7.3), 7.73 (2H, d, J = 7.3), 7.55 (2H, m), 7.44 (5H, m), 7.34 (7H, m), 7.09 (1H, d, J = 8.9), 6.70 (1H, s), 5.86 (1H, t, J = 6.9), 5.69 (1H, d, J = 9.0), 5.62 (1H, d, J = 7.7), 5.07 (1H, d, J = 8.8), 4.88 (1H, s), 4.77 (1H, s), 4.30 (1H, d, J = 8.1), 4.23 (1H, d, J = 8.1), 3.64 (1H, d, J = 7.7), 2.66 (1H, m), 2.52 (3H, s), 2.45 (1H, m), 1.97 (2H, m), 1.77 (3H, s), 1.73 (3H, s), 1.70 (3H, s), 1.59 (1H, brs), 1.25 (1H, brs), 0.95 (9H, t, J = 7.9), 0.76 (9H, s), 0.65 (6H, m), -0.14 (3H, s), -0.32 (3H, s). ^{13}C NMR (500 MHz, CDCl$_3$) δ -5.98, -5.54, 5.38, 6.92, 9.11, 11.41, 18.18, 20.86, 22.28, 25.46, 38.38, 38.72, 44.11, 55.87, 56.86, 63.33, 70.53, 71.08, 72.69, 74.68, 75.48, 77.92, 79.07, 84.72, 113.13, 126.40, 126.98, 127.81, 128.42, 128.62, 128.67, 128.77, 129.11, 129.39, 129.79, 129.97, 131.68, 133.16, 133.47, 134.26, 136.95, 138.60, 144.29, 145.62, 164.57, 165.35, 166.76, 170.52, 171.01, 201.51. HRMS (FAB+) calcd for $C_{64}H_{79}NO_{13}Si_2Na$ $[M+Na]^+$ *m/z* 1148.4987, found 1148.4979.

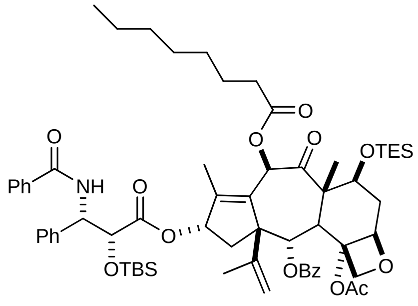
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-hexanoyl-A-*nor*-paclitaxel (2.28)



2.28

The yield for this compound was 83% (19 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.05 (2H, d, *J* = 6.9), 7.72 (2H, d, *J* = 6.9), 7.53 (1H, t, *J* = 7.4), 7.45 (3H, m), 7.36 (4H, t, *J* = 7.2), 7.31 (3H, m), 7.09 (1H, d, *J* = 8.9), 6.43 (1H, s), 5.83 (1H, t, *J* = 9.1), 5.68 (1H, dd, *J* = 1.7, 8.9), 5.55 (1H, d, *J* = 7.7), 5.04 (1H, d, *J* = 8.4), 4.76 (1H, s), 4.67 (1H, s), 4.58 (1H, d, *J* = 2.0), 4.55 (1H, dd, *J* = 7.4, 9.4), 4.27 (1H, d, *J* = 8.1), 4.21 (1H, d, *J* = 8.1), 3.55 (1H, d, *J* = 7.5), 2.63 (1H, m), 2.50 (3H, s), 2.37 (3H, m), 1.95 (2H, m), 1.75 (3H, s), 1.65 (3H, s), 1.63 (3H, s), 1.33 (4H, m), 0.94 (9H, t, *J* = 7.9), 0.89 (3H, t, *J* = 7.2), 0.77 (9H, s), 0.62 (6H, m), -0.12 (3H, s), -0.32 (3H, s). ^{13}C NMR (500 MHz, CDCl$_3$) δ -5.87, -5.43, 5.37, 7.00, 9.23, 11.43, 13.95, 18.28, 20.82, 22.35, 24.68, 25.56, 31.26, 33.94, 38.43, 38.72, 44.06, 55.99, 56.85, 63.29, 70.40, 70.57, 72.69, 74.77, 75.59, 77.99, 79.12, 84.76, 113.15, 126.49, 127.06, 127.91, 128.71, 128.76, 128.84, 129.18, 130.05, 131.77, 133.54, 134.33, 137.18, 138.69, 144.21, 145.17, 165.42, 166.84, 170.58, 171.14, 171.68, 201.80. HRMS (FAB+) calcd for $C_{63}H_{85}NO_{13}Si_2Na$ $[M+Na]^+$ *m/z* 1142.5457, found 1142.5478.

2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-octanoyl-A-*nor*-paclitaxel (2.29)



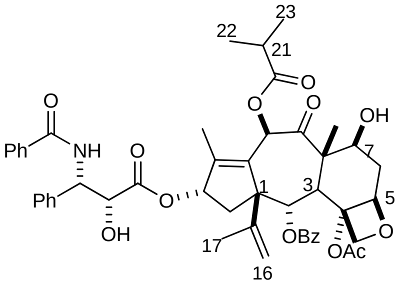
2.29

The yield for this compound was 80% (18 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.05 (2H, d, J = 7.3), 7.72 (2H, d, J = 7.3), 7.53 (1H, t, J = 7.4), 7.45 (3H, m), 7.36 (4H, m), 7.31 (3H, m), 7.08 (1H, d, J = 8.9), 6.43 (1H, s), 5.83 (1H, t, J = 7.5), 5.68 (1H, dd, J = 1.5, 8.8), 5.55 (1H, d, J = 7.7), 5.04 (1H, d, J = 8.6), 4.76 (1H, s), 4.67 (1H, s), 4.58 (1H, d, J = 1.9), 4.55 (1H, dd, J = 7.5, 9.4), 4.27 (1H, d, J = 8.1), 4.21 (1H, d, J = 8.1), 3.55 (1H, d, J = 7.7), 2.63 (1H, m), 2.50 (3H, s), 2.38 (3H, m), 1.93 (2H, m), 1.75 (3H, s), 1.65 (3H, s), 1.63 (3H, s), 1.62 (2H, m), 1.27 (8H, m), 0.94 (9H, t, J = 7.9), 0.87 (3H, t, J = 7.0), 0.77 (9H, s), 0.61 (6H, m), -0.12 (3H, s), -0.32 (3H, s). ^{13}C NMR (500 MHz, CDCl$_3$) δ -5.88, -5.44, 5.37, 7.01, 9.22, 11.44, 14.16, 18.29, 20.83, 22.35, 22.69, 25.03, 25.57, 28.99, 29.10, 31.73, 34.00, 38.43, 38.72, 44.06, 55.98, 56.85, 63.29, 70.39, 70.57, 72.69, 74.77, 75.59, 77.98, 79.12, 84.76, 113.15, 126.49, 127.06, 127.91, 128.71, 128.77, 128.84, 129.17, 130.05, 131.77, 133.54, 134.33, 137.18, 138.69, 144.20, 145.16, 165.42, 166.83, 170.58, 171.12, 171.68, 201.79. HRMS (FAB+) calcd for $C_{65}H_{89}NO_{13}Si_2Na$ $[M+Na]^+$ *m/z* 1170.5770, found 1170.5802.

General method for the preparation of 10-acyl-A-*nor*-paclitaxels (2.30-2.33)

The general method for the deprotection of silyl ether was under the treatment of pyridine hydrofluoride (HF/pyridine) solution as before. The yields were about 75-80%.

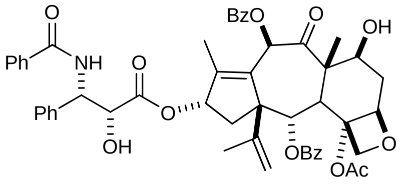
10-Isobutyryl A-*nor*-paclitaxel (2.30)



2.30

The yield for this compound was 80% (12 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.12 (2H, d, *J* = 7.1, ArH), 7.68 (2H, d, *J* = 7.1, ArH), 7.53 (1H, m, ArH), 7.42 (7H, m, ArH), 7.33 (3H, m, ArH), 6.91 (1H, d, *J* = 9.3, CONH), 6.32 (1H, s, H10), 5.73 (2H, m, H13, H3′), 5.48 (1H, d, *J* = 8.2, H2), 5.05 (1H, d, *J* = 8.1, H5), 4.70 (2H, m, H16a, H2′), 4.68 (1H, m, H7), 4.32 (1H, d, *J* = 8.1, H20a), 4.19 (1H, d, *J* = 8.1, H20b), 3.51 (1H, d, *J* = 8.1, H3), 3.35 (1H, d, *J* = 4.4, 2′OH), 2.65 (2H, m, H6, H21), 2.43 (1H, m, H14a), 2.38 (3H, s, 10OAc), 2.08 (1H, m, H14b), 1.92 (1H, m, H6), 1.72 (3H, s, 18CH$_3$), 1.66 (3H, s, 17CH$_3$), 1.60 (3H, s, 19CH$_3$), 1.24 (3H, d, *J* = 7.0, 21CH$_3$), 1.21 (3H, d, *J* = 7.0, 22CH$_3$). ^{13}C NMR (500 MHz, CDCl$_3$) δ 8.32, 11.79, 18.81, 18.99, 20.72, 22.00, 34.12, 35.90, 39.27, 44.58, 54.85, 56.78, 63.95, 70.96, 71.35, 72.77, 73.41, 74.61, 79.07, 79.20, 85.04, 113.54, 126.91, 127.11, 128.27, 128.70, 128.86, 129.05, 129.23, 130.14, 131.93, 133.66, 133.98, 135.83, 138.38, 145.04, 145.13, 165.38, 166.85, 170.57, 172.73, 177.31, 203.34. HRMS (FAB+) calcd for $C_{49}H_{53}NO_{13}Na$ [M+Na]$^+$ *m/z* 886.3414, found 886.3422.

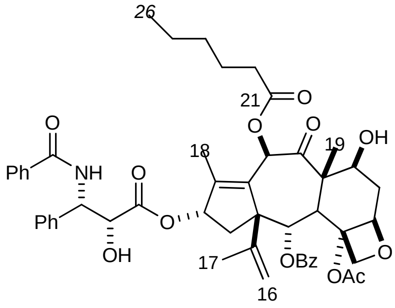
10-Benzoyl A-*nor*-paclitaxel (2.31)



2.31

The yield for this compound was 78% (10 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (2H, d, *J* = 7.0, ArH), 8.02 (2H, d, *J* = 7.0, ArH), 7.69 (2H, d, *J* = 7.0, ArH), 7.61 (1H, t, *J* = 7.5, ArH), 7.54 (1H, t, *J* = 7.5, ArH), 7.44 (9H, m, ArH), 7.33 (3H, m, ArH), 6.93 (1H, d, *J* = 9.2, CONH), 6.60 (1H, s, H10), 5.79 (1H, t, *J* = 7.2, H13), 5.75 (1H, dd, *J* = 2.2, 9.2, H3′), 5.55 (1H, d, *J* = 8.2, H2), 5.08 (1H, d, *J* = 8.2, H5), 4.92 (1H, s, H16a), 4.78 (1H, s, H16b), 4.76 (1H, m, H7), 4.71 (1H, dd, *J* =4.3, 2.3, H2′), 4.35 (1H, d, *J* = 8.3, H20a), 4.21 (1H, d, *J* = 8.3, H20b), 3.59 (1H, d, *J* = 8.2, H3), 3.37 (1H, d, *J* = 4.5, 2′OH), 2.80 (1H, d, *J* = 3.5, 7OH), 2.66 (1H, m, H6a), 2.49 (1H, m, H14a), 2.39 (3H, s, 4OAc), 2.13 (1H, m, H14b), 1.96 (1H, m, H6b), 1.75 (3H, s, $18CH_3$), 1.69 (3H, s, $17CH_3$), 1.67 (3H, s, $19CH_3$). ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.28, 11.76, 20.74, 21.92, 35.88, 39.28, 44.53, 54.76, 56.77, 63.93, 70.88, 72.04, 72.71, 73.31, 74.54, 79.01, 79.14, 84.96, 113.48, 126.82, 127.00, 128.17, 128.59, 128.61, 128.78, 128.95, 129.14, 129.89, 130.06, 131.84, 133.58, 133.85, 133.88, 135.69, 138.26, 145.02, 145.52, 165.30, 166.56, 166.75, 170.52, 172.62, 203.04. HRMS (FAB+) calcd for $C_{52}H_{51}NO_{13}Na$ $[M+Na]^+$ *m/z* 920.3258, found 920.3272.

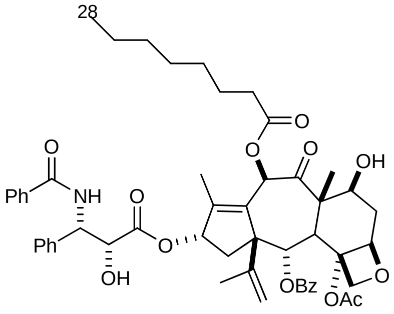
10-Hexanoyl A-*nor*-paclitaxel (2.32)



2.32

The yield for this compound was 80% (9.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (2H, d, *J* = 7.1, ArH), 7.68 (2H, d, *J* = 7.1, ArH), 7.53 (1H, t, *J* = 7.4, ArH), 7.45 (7H, m, ArH), 7.33 (3H, m, ArH), 6.90 (1H, d, *J* = 9.2, CONH), 6.33 (1H, s, H10), 5.72 (2H, m, H13, H3′), 5.49 (1H, d, *J* = 8.2, H2), 5.05 (1H, d, *J* = 8.6, H5), 4.78 (1H, s, H16a), 4.68 (3H, m, H16b, H2′, H7), 4.32 (1H, d, *J* = 8.2, H20a), 4.19 (1H, d, *J* = 8.2, H20b), 3.50 (1H, d, *J* = 8.2, H3), 3.31 (1H, d, *J* = 4.5, 2′OH), 2.62 (2H, m, H6a, CH_2), 2.43 (3H, m, H14a, CH_2), 2.38 (3H, s, 4OAc), 2.07 (1H, m, H14b), 1.95 (1H, m, H6b), 1.72 (3H, s, $18CH_3$), 1.66 (3H, s, $17CH_3$), 1.60 (3H, s, $19CH_3$), 1.33 (5H, m, CH_2), 0.89 (3H, t, *J* = 6.6, $26CH_3$). ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.33, 11.82, 13.88, 20.75, 21.98, 22.32, 24.54, 31.26, 33.90, 35.88, 39.27, 44.56, 54.78, 56.81, 63.97, 70.84, 71.52, 72.76, 73.39, 74.62, 79.02, 79.25, 85.03, 113.62, 126.90, 127.11, 128.29, 128.72, 128.85, 129.08, 129.22, 130.13, 131.93, 133.65, 133.93, 135.71, 138.36, 144.98, 145.08, 165.20, 166.77, 170.60, 172.69, 174.25, 203.31. HRMS (FAB+) calcd for $C_{51}H_{57}NO_{13}Na$ $[M+Na]^+$ *m/z* 914.3727, found 914.3743.

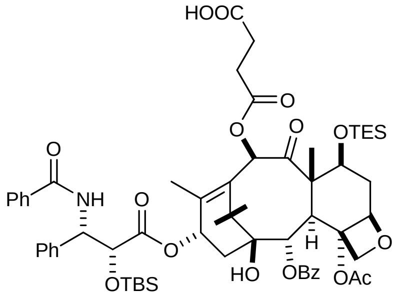
10-Octanoyl A-*nor*-paclitaxel (2.33)



2.33

The yield for this compound was 76% (9 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (2H, d, J = 8.4, ArH), 7.68 (2H, d, J = 8.4, ArH), 7.53 (1H, m, ArH), 7.42 (7H, m, ArH), 7.33 (3H, m, ArH), 6.91 (1H, d, J = 9.3, CONH), 6.33 (1H, s, H10), 5.72 (2H, m, H13, H3′), 5.49 (1H, d, J = 8.2, H2), 5.05 (1H, d, J = 8.9, H5), 4.78 (1H, s, H16a), 4.71 (3H, m, H16b, H2′, H7), 4.32 (1H, d, J = 8.1, H20a), 4.19 (1H, d, J = 8.1, H20b), 3.50 (1H, d, J = 8.2, H3), 3.33 (1H, d, J = 4.6, 2′OH), 2.63 (2H, m, H6a, CH_2), 2.44 (3H, m, H14a, CH_2), 2.38 (3H, s, 4OAc), 2.05 (1H, m, H14b), 1.92 (1H, m, H6b), 1.64 (1H, m, CH_2), 1.72 (3H, s, 18CH_3), 1.66 (3H, s, 17CH_3), 1.60 (3H, s, 19CH_3), 1.27 (8H, m, CH_2), 0.88 (3H, m, 28CH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.34, 11.82, 14.15, 20.76, 22.01, 22.68, 24.91, 28.96, 29.09, 31.70, 34.03, 35.87, 39.27, 44.56, 54.83, 56.77, 63.96, 70.94, 71.52, 72.76, 73.39, 74.62, 79.06, 79.23, 85.03, 113.61, 126.91, 127.10, 128.28, 128.71, 128.86, 129.06, 129.23, 130.15, 131.94, 133.66, 133.97, 135.73, 138.37, 144.98, 145.09, 165.38, 166.82, 170.56, 172.73, 174.24, 203.37. HRMS (FAB+) calcd for $C_{53}H_{61}NO_{13}Na$ $[M+Na]^+$ *m/z* 942.4040, found 941.9788.

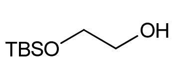
2′-(*tert*-Butyldimethylsilyl)-7-(triethylsilyl)-10-succinate paclitaxel (2.34)



2.34

This known compound was obtained by the literature method in a yield of 80%, and its NMR spectra matched the literature data.[39] HRMS (FAB+) calcd for $C_{61}H_{811}NO_{16}Si_2Na$ $[M+Na]^+$ *m/z* 1162.4991, found 1162.5010.

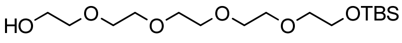
Synthesis of 2-(*tert*-butyldimethylsilyloxy) ethanol (2.35)



2.35

To a solution of ethylene glycol (0.5 mL) in dichloromethane (DCM), *tert*-butyldimethylsilyl chloride (1.4 g) and imidazole (2 g) were added. The mixture solution was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution (15 mL), extracted with ethyl acetate (3×10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography (30% ethyl acetate in hexanes) to get the desired product 773 mg (yield of 49%). ^1H NMR (500 MHz, $CDCl_3$) δ 3.70 (2H, m), 3.63 (2H, m), 0.90 (9H, s), 0.07 (6H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.25, 18.40, 25.95, 63.78, 64.16. HRMS (FAB+) calcd for $C_8H_{20}O_2SiNa$ $[M+Na]^+$ *m/z* 177.1310, found 177.1318.

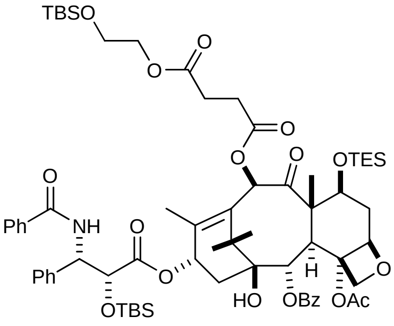
Synthesis of penta(ethylene glycol) TBS ether (2.36)



2.36

The synthesis of penta(ethylene glycol) TBS ether **2.36** followed the same method as used for compound **2.35** but using pentaethylene glycol as starting material. The yield was 35% (300 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (2H, t, J = 5.5), 3.70 (2H, m), 3.64 (12H, m), 3.59 (2H, m), 3.54 (2H, t, J = 5.5), 0.87 (9H, s), 0.04 (6H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.19, 18.44, 26.01, 61.82, 62.77, 70.41, 70.64, 70.66, 70.69, 70.70, 70.80, 72.63, 72.72. HRMS (FAB+) calcd for $C_{16}H_{36}O_6SiNa$ $[M+Na]^+$ *m/z* 375.2178, found 375.2168.

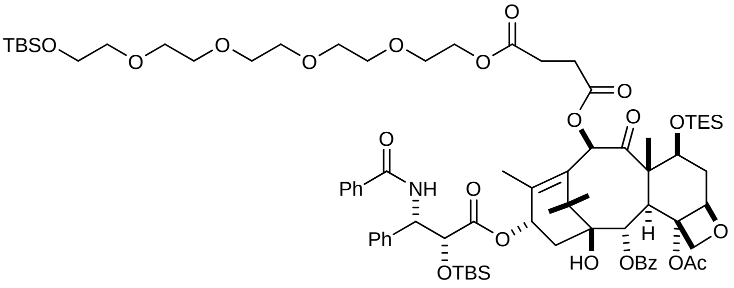
Synthesis of 2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)-10-[3-((2-*tert*-butyldimethylsilyloxy ethoxy)carbonyl)propanoyl] paclitaxel (2.37)



2.37

To the solution of compound **2.34** (37 mg) in dichloromethane (DCM) 2 mL, mono-ethylene glycol TBS ether **2.35** (17 mg), EDCI (18.7 mg), DMAP (12 mg) were added and the mixture solution was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution (15 mL), extracted with ethyl acetate (3×10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified with flash chromatography (30% ethyl acetate in hexanes) to obtain the desired product 35 mg (yield 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (2H, d, J = 7.1), 7.73 (2H, d, J = 7.1), 7.59 (1H, m), 7.50 (3H, m), 7.38 (4H, m), 7.31 (3H, m), 7.07 (1H, d, J = 8.9), 6.44 (1H, s), 6.25 (1H, t, J = 9.1), 5.72 (1H, dd, J = 1.9, 8.8), 5.69 (1H, d, J = 7.1), 4.94 (1H, dd, J = 1.8, 9.6), 4.66 (1H, d, J = 2.2), 4.46 (1H, dd, J =6.6, 10.6), 4.31 (1H, d, J = 8.4), 4.20 (1H, d, J = 8.4), 3.82 (3H, m), 2.76 (4H, m), 2.57 (3H, s), 2.52 (1H, m), 2.39 (1H, m), 2.08 (1H, m), 2.00 (3H, s), 1.90 (1H, m), 1.69 (3H, s), 1.19 (3H, s), 1.16 (3H, s), 0.91 (9H, t, J = 7.9), 0.88 (9H, s), 0.79 (9H, s), 0.57 (6H, m), 0.06 (6H, s), -0.03 (3H, s), -0.31 (3H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.77, -5.20, -5.09, 5.38, 6.87, 10.23, 14.39, 18.20, 18.41, 21.60, 23.23, 25.60, 25.93, 26.57, 29.22, 29.30, 35.66, 37.31, 43.36, 46.71, 55.74, 58.48, 61.27, 66.07, 71.45, 72.28, 74.99, 75.19, 75.21, 76.66, 78.94, 81.27, 84.31, 126.52, 127.09, 128.03, 128.79, 128.82, 128.84, 129.29, 130.32, 131.87, 133.59, 133.72, 134.15, 138.38, 140.40, 166.98, 167.15, 170.27, 170.48, 171.47, 172.03, 201.52. HRMS (FAB+) calcd for $C_{69}H_{99}NO_{17}Si_3Na$ $[M+Na]^+$ *m/z* 1320.6118, found 1320.6152.

Synthesis of 2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)-10-[3-((2-*tert*-butyl-Dimethylsilyloxy-pentaPEG)carbonyl)propanoyl]–paclitaxel (2.38)

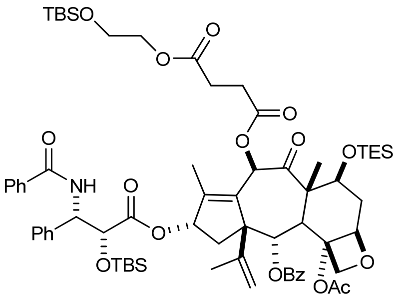


2.38

The synthesis of **2.38** followed the same procedure used for **2.37** but using penta-ethylene glycol TBS ether **2.36** as starting material. The yield was about 80%

(30 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (2H, d, J = 7.1), 7.73 (2H, d, J = 7.1), 7.59 (1H, t, J = 7.4), 7.50 (3H, m), 7.39 (4H, m), 7.31 (3H, m), 7.07 (1H, d, J = 8.9), 6.44 (1H, s), 6.25 (1H, t, J = 8.7), 5.72 (1H, dd, J = 1.9, 8.9), 5.68 (1H, d, J = 7.1), 4.93 (1H, dd, J =1.7, 9.7), 4.66 (1H, d, J = 2.2), 4.46 (1H, dd, J =6.7, 10.6), 4.31(1H, d, J = 8.4), 4.22 (2H, m), 4.20 (1H, d, J = 8.8), 3.82 (1H, d, J = 7.0), 3.82 (1H, t, J = 7.0), 3.75 (2H, t, J = 5.5), 3.69 (2H, m), 3.64 (14H, m), 3.54 (2H, t, J = 5.5), 2.78 (4H, m), 2.64 (1H, m), 2.57 (3H, s), 2.51 (1H, m), 2.39 (1H, m), 2.09 (1H, m), 1.99 (3H, s), 1.89 (1H, m), 1.68 (3H, s), 1.19 (3H, s), 1.16 (3H, s), 0.91 (9H, t, J =7.9), 0.88 (9H, s), 0.79 (9H, s), 0.57 (6H, m), 0.05 (6H, s), -0.03 (3H, s), -0.31(3H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.77, -5.18, -5.09, 5.38, 6.88, 10.23, 14.38, 18.21, 18.46, 19.13, 21.61, 23.22, 25.60, 26.01, 26.57, 29.18, 29.28, 35.69, 37.30, 43.37, 46.71, 55.73, 58.48, 62.79, 63.99, 69.15, 70.66, 70.67, 70.68, 70.72, 70.73, 70.80, 71.46, 72.28, 72.74, 74.99, 75.19, 75.22, 76.67, 78.92, 81.27, 84.31, 126.52, 127.08, 128.03, 128.79, 128.82, 128.83, 129.30, 130.32, 131.88, 133.60, 133.71, 134.14, 138.37, 140.38, 167.00, 167.13, 170.26, 170.45, 171.46, 172.05, 201.53. HRMS (FAB+) calcd for $C_{77}H_{115}NO_{21}Si_3Na$ $[M+Na]^+$ *m/z* 1496.7167, found 1496.7162.

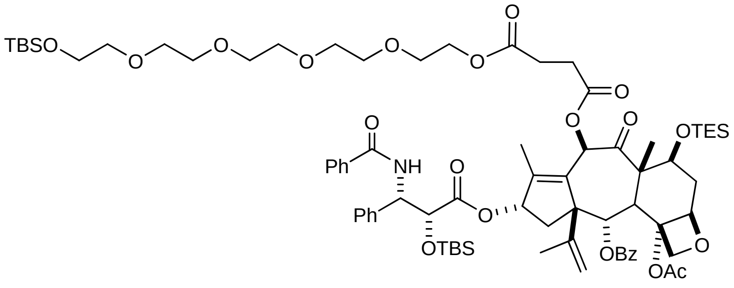
Synthesis of 2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)-10-[3-((2-*tert*-butyl-dimethylsilyloxy ethoxy)carbonyl)propanoyl]–A-*nor*-paclitaxel (2.39)



2.39

The method for ring contraction was the same as in the synthesis of **2.9** with thionyl chloride and pyridine at -20 °C, and the yield of compound **2.39** was 80% (20 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.05 (2H, d, J = 7.1), 7.72 (2H, d, J = 7.1), 7.53 (1H, m), 7.42 (3H, m), 7.34 (7H, m), 7.08 (1H, d, J = 8.9), 6.42 (1H, s), 5.82 (1H, t, J = 7.5), 5.67 (1H, d, J = 8.9), 5.54 (1H, d, J = 8.9), 5.03 (1H, d, J = 8.8), 4.74 (1H, s), 4.66 (1H, s), 4.58 (1H, d, J = 2.0), 4.54 (1H, m), 4.26 (1H, d, J = 8.1), 4.21 (1H, d, J = 8.1), 4.12 (2H, m), 3.80 (2H, m), 3.54 (1H, d, J = 7.7), 2.67 (5H, m), 2.50 (3H, s), 2.41 (1H, m), 1.93 (2H, m), 1.74 (3H, s), 1.67 (3H, s), 1.62 (3H, s), 0.93 (9H, t, J = 7.9), 0.88 (9H, s), 0.77 (9H, s), 0.60 (6H, m), 0.06 (6H, s), -0.12 (3H, s), -0.32 (3H, s). ^{13}C NMR (500 MHz, CDCl$_3$) δ -5.88, -5.40, -5.22, 5.36, 6.99, 9.20, 11.41, 18.28, 18.41, 20.83, 22.35, 25.57, 25.92, 28.83, 29.09, 38.41, 38.76, 44.06, 55.96, 56.84, 61.24, 63.28, 66.00, 70.50, 71.02, 72.71, 74.75, 75.56, 77.93, 79.07, 84.74, 113.18, 126.49, 127.06, 127.90, 128.71, 128.76, 128.85, 129.15, 130.05, 131.77, 133.55, 134.34, 136.64, 138.69, 144.16, 145.70, 165.42, 166.84, 170.17, 170.61, 171.05, 172.13, 201.63. HRMS (FAB+) calcd for $C_{69}H_{97}NO_{16}Si_3Na$ $[M+Na]^+$ *m/z* 1302.6012, found 1302.6041.

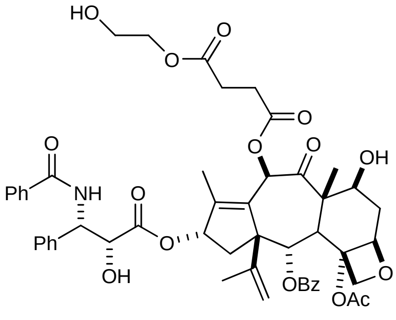
Synthesis of 2′-(*tert*-butyldimethylsilyl)-7-(triethylsilyl)-10-[3-((2-*tert*-butyldimethylsilyloxy-pentaPEG)carbonyl)propanoyl]–A-*nor*-paclitaxel (2.40)



2.40

The yield of this compound was 78% (18 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (2H, d, J = 7.1), 7.71 (2H, d, J = 7.1), 7.53 (1H, t, J = 7.4), 7.42 (3H, m), 7.36 (4H, m), 7.31 (3H, m), 7.09 (1H, d, J = 8.9), 6.41 (1H, s), 5.82 (1H, t, J = 7.6), 5.67 (1H, dd, J =1.6, 8.9), 5.54 (1H, d, J = 7.7), 5.03 (1H, d, J = 8.7), 4.74 (1H, s), 4.66 (1H, s), 4.57 (1H, d, J = 2.0), 4.54 (1H, dd, J =7.4, 9.4), 4.22 (4H, m), 3.75 (2H, t, J = 5.5), 3.69 (2H, m), 3.64 (14H, m), 3.54 (2H, t, J = 5.5), 3.53 (1H, m), 2.68 (5H, m), 2.50 (3H, s), 2.41 (1H, m), 1.93 (2H, m), 1.74 (3H, s), 1.67 (3H, s), 1.62 (3H, s), 0.93 (9H, t, J = 7.9), 0.87 (9H, s), 0.76 (9H, s), 0.61 (6H, m), 0.05 (6H, s), -0.12 (3H, s), -0.32(3H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ -5.88, -5.40, -5.18, 5.36, 7.00, 9.20, 11.42, 18.28, 20.84, 22.34, 25.57, 26.01, 28.81, 29.08, 38.41, 38.76, 44.06, 55.97, 56.84, 62.78, 63.27, 63.94, 69.14, 70.49, 70.67, 70.73, 70.81, 71.02, 72.74, 74.75, 75.56, 77.93, 79.07, 84.74, 113.19, 126.49, 127.06, 127.90, 128.71, 128.76, 128.85, 129.14, 130.05, 131.77, 133.55, 134.33, 136.64, 138.68, 144.15, 145.70, 165.42, 166.85, 170.16, 170.61, 171.06, 172.15, 201.63. HRMS (FAB+) calcd for $C_{77}H_{113}NO_{20}Si_3NH_4^+$ $[M+NH_4]^+$ *m/z* 1473.7507, found 1473.7449.

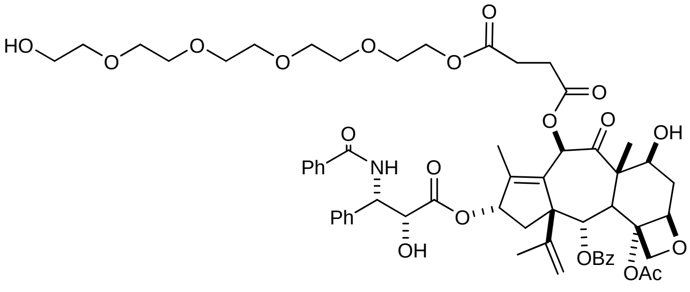
Synthesis of 10-[3-((2-*tert*-butyl-dimethylsilyloxy ethoxy)carbonyl)propanoyl]-A-*nor*-paclitaxel (2.41)



2.41

The yield for this compound was 82% (11 mg). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.11 (2H, d, *J* = 7.1, ArH), 7.68 (2H, d, *J* = 7.1, ArH), 7.53 (1H, m, ArH), 7.41 (7H, m, ArH), 7.33 (3H, m, ArH), 6.93 (1H, d, *J* = 9.2, CONH), 6.37 (1H, s, H10), 5.72 (1H, dd, *J* = 2.3, 9.2, H3′), 5.72 (1H, m, H13), 5.49 (1H, d, *J* = 8.2, H2), 5.04 (1H, d, *J* = 8.1, H5), 4.77 (1H, s, H16a), 4.70 (2H, m, H16b, H2′), 4.62 (1H, m, H7), 4.31 (1H, d, *J* = 8.2, H20a), 4.20 (3H, m, H20b, OCH$_2$), 3.81 (2H, d, *J* = 4.2, OCH$_2$), 3.50 (1H, d, *J* = 7.8, H3), 3.39 (1H, d, *J* = 4.6, 2′OH), 2.70 (5H, m, H6a, COCH$_2$), 2.43 (1H, m, H14a), 2.37 (3H, s, 4OAc), 2.10 (1H, m, H14b), 1.90 (1H, m, H6b), 1.71 (3H, s, 18CH$_3$), 1.67 (3H, s, 17CH$_3$), 1.60 (3H, s, 19CH$_3$). ^{13}C NMR (500 MHz, CDCl$_3$) δ 8.44, 11.80, 20.77, 21.99, 28.92, 29.06, 36.04, 39.24, 44.47, 54.87, 56.79, 61.07, 63.89, 66.60, 70.86, 72.10, 72.55, 73.39, 74.60, 78.98, 79.17, 84.97, 113.59, 126.91, 127.10, 128.27, 128.71, 128.87, 129.04, 129.17, 130.14, 131.94, 133.69, 133.96, 135.25, 138.36, 144.89, 145.75, 165.38, 166.87, 170.58, 172.10, 172.71, 172.81, 203.49. HRMS (FAB+) calcd for $C_{51}H_{55}NO_{16}Na$ $[M+Na]^+$ *m/z* 960.3418, found 960.3435.

Synthesis of 10-[3-((2-*tert*-butyl-Dimethylsilyloxy-pentaPEG)carbonyl)propanoyl]-A-*nor*-paclitaxel (2.42)



2.42

The yield for this compound was 80% (10 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (2H, d, J = 7.1, ArH), 7.69 (2H, d, J = 7.1, ArH), 7.53 (1H, t, J = 7.4, ArH), 7.41 (7H, m, ArH), 7.32 (3H, m, ArH), 7.01 (1H, d, J = 9.2, CONH), 6.36 (1H, s, H10), 5.71 (2H, m, H13, H3′), 5.48 (1H, d, J = 8.2, H2), 5.04 (1H, d, J = 8.4, H5), 4.76 (1H, s, H16a), 4.70 (2H, s, H16b, H2′), 4.63 (1H, t, J = 8.9, H7), 4.31 (1H, d, J = 8.1, H20a), 4.23 (2H, m, OCH_2), 4.19 (1H, d, J = 8.1, H20b), 3.69 (4H, m, OCH_2), 3.64 (12H, m, OCH_2), 3.58 (2H, m, OCH_2), 3.50 (1H, d, J = 8.0, H3), 2.75 (2H, m, $COCH_2$), 2.63 (3H, m, H6a, $COCH_2$), 2.42 (1H, m, H14a), 2.37 (3H, s, 4OAc), 2.07 (1H, m, H14b), 1.89 (1H, m, H6b), 1.71 (3H, s, $18CH_3$), 1.69 (3H, s, $17CH_3$), 1.59 (3H, s, $19CH_3$). ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.37, 11.80, 20.77, 21.99, 28.87, 28.89, 35.99, 39.25, 44.51, 54.87, 56.76, 61.78, 63.91, 64.04, 69.07, 70.34, 70.58, 70.59, 70.62, 70.63, 70.67, 70.89, 71.99, 72.59, 72.64, 73.40, 74.60, 79.00, 79.04, 85.00, 113.60, 126.92, 127.13, 128.21, 128.68, 128.87, 129.01, 129.20, 130.14, 131.88, 133.67, 134.02, 135.25, 138.46, 144.92, 145.77, 165.39, 166.86, 170.58, 172.05, 172.68, 172.70, 203.27. HRMS (FAB+) calcd for $C_{59}H_{71}NO_{20}Na$ $[M+Na]^+$ *m/z* 1136.4467, found 1136.4477.

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Chapter 3 Synthesis of C3′ and C4 modified paclitaxel analogs

3.1 Introduction to 2-methoxyestradiol (2ME2)

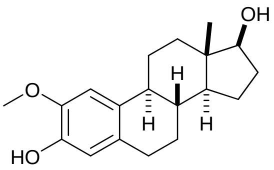


Figure 3.1 The structure of 2-methoxyestradiol (2ME2)

2-Methoxyestradiol (Figure 3.1) is an analog of the natural hormone estradiol with antitumor and antiangiogenic activity.[1,2] It is a microtubule-targeting drug (MTD), in the same class as the taxanes and the vinca alkaloids, and is currently in phase II oncology clinical trials. Its binding location on β-tubulin is the same as that of colchicine,[3] and it works as a microtubule depolymerizing agent, inducing mitotic arrest at the G_2-M transition.[4,5] Compared to other MTDs, 2ME2 is a promising drug with fewer side effects. It does not induce peripheral neuropathy and myelosuppression, which are the major limitations in the use of MTDs like paclitaxel. The reason for this is not quite clear, but recent research supports the idea that the insensitivity of β-tubulin isotype VI (Hβ1) to 2ME2 might contribute to that result.[6] The fact that cells expressing Hβ1 are insensitive to 2ME2 also supports this idea. So far, at least seven classes of human β-tubulin isotypes have been characterized, but the function of them is not very clear.[7,8] It is known that Hβ1 expression is confined to human hematopoietic tissues, especially those of peripheral blood and bone marrow.[9,10,11] This suggests that its lack of interaction with Hβ1 may be the reason that 2ME2 is not myelosuppressive.

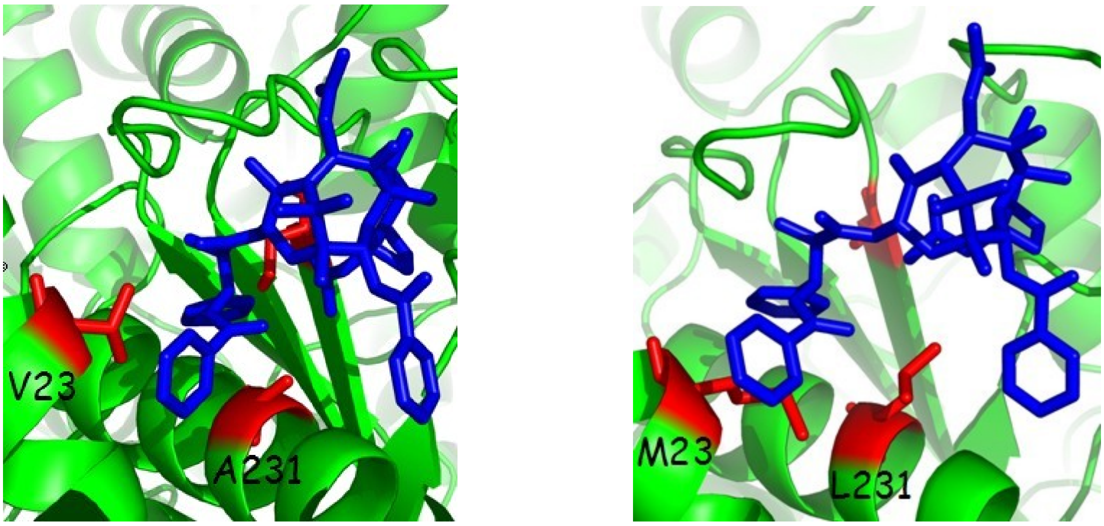
By comparing the difference between the structures of Hβ1 and those of other tubulin isotypes, it is believed that the change of amino acid 236 from Val to Ile is the key to its resistance to 2ME2. Val236 is a highly conserved residue for all tubulin isotypes except for class VI (Hβ1) tubulin, which instead has Ile236, and it resides in the 2ME2/colchicine binding site of tubulin. Besides Ile236, two other residues also have been changed in the 2ME2/colchicine binding site of Hβ1 tubulin, from Ile316 and Phe200 to Val316 and Tyr200. Our collaborator Dr. James Snyder has constructed a 3D model of the 2ME2/colchicine binding site, and this model shows that the substitution of these amino acids makes the 2ME2 binding pocket more sterically congested, reducing the binding ability of 2ME2 in Hβ1 tubulin.[6,12]

3.2 Design of new paclitaxel analogs to reduce paclitaxel's myelosuppression

The purpose of our research is aimed at discovering paclitaxel analogs which can discriminate between Hβ1 tubulin and other β tubulin isotypes, enabling them to act as anticancer agents with reduced myelosuppressive activity.

Although paclitaxel is one of the most effective antitumor drugs, and has been widely used in treating breast and ovarian carcinomas,[13,14] its use is limited by its adverse effects, including peripheral neuropathy and myelosuppression.[15]

Inspired by the example of 2ME2 explained above, we hypothesize that paclitaxel analogs may be designed which can discriminate between Hβ1 tubulin and other β tubulin isotypes, and thus do not induce myelosuppression. The paclitaxel binding pocket on β-tubulin has been modeled by Dr. Snyder, and it is known that Val23 and Ala231 in this pocket are replaced by Met23 and Leu231 in Hβ1 tubulin. In Dr. Snyder's optimized model, paclitaxel's benzamide phenyl ring fits snugly between Val23 and Ala231 in normal tubulin. But in Hβ1 tubulin, where these residues are replaced by the bulkier groups, Met23 and Leu231, there are additional steric constraints on the binding of paclitaxel (Figure 3.2). However, calculations provided by Dr. Snyder indicated that paclitaxel could still bind to Hβ1 tubulin because of the flexible nature of the binding site.[6]



Class I β-tubulin isotype

Class VI β-tubulin isotype (Hβ1)

Figure 3.2 3D model of the interaction between paclitaxel and β-tubulin binding pocket (Figure provided by Dr. J. P. Snyder)

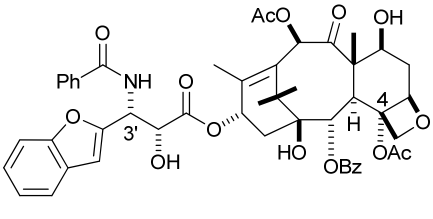
Although paclitaxel does not discriminate between the different β tubulin isotypes, it is hypothesized that paclitaxel analogs with increased steric bulk will not bind as well to Hβ1 tubulin as to other tubulin isotypes.

Based on the model developed by Dr. Snyder, paclitaxel analogs with increased bulk at C3′ may contribute to a decreased ability to bind to Hβ1 tubulin. According to the SAR of paclitaxel,[16] phenyl or a close analog is required at the C3′ position. However, Dr. Snyder's calculations indicate that a benzofuran group may be as effective as a phenyl group for normal tubulins, but will decrease binding to Hβ1 tubulin. In addition, modification at the C4 position with bulkier acyl groups may also contribute to a reduction of the binding to Hβ1 tubulin without changing the binding to other tubulins. Based on these analyses, we decided to modify C3′ with benzofuran-2-yl and benzofuran-3-yl groups, and to modify C4 with longer chain acyl groups, such as pentanoyl and octanoyl groups.

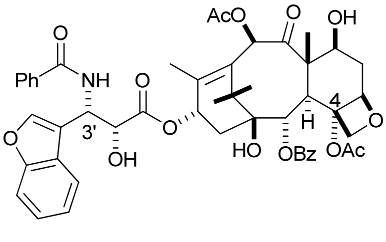
3.3 Synthesis and biological evaluation of C3′ and C4 modified paclitaxel analogs

3.3.1 Synthesis of C3′ modified paclitaxel analogs (3.1a and 3.1b)

The first two paclitaxel analogs prepared were the C3′ modified analogs **3.1a** and **3.1b** (Figure 3.3).



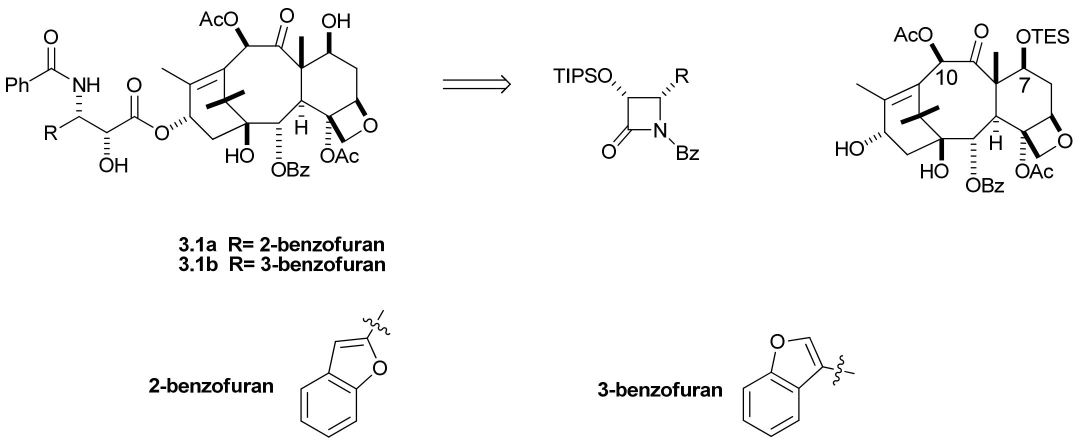
3.1a



3.1b

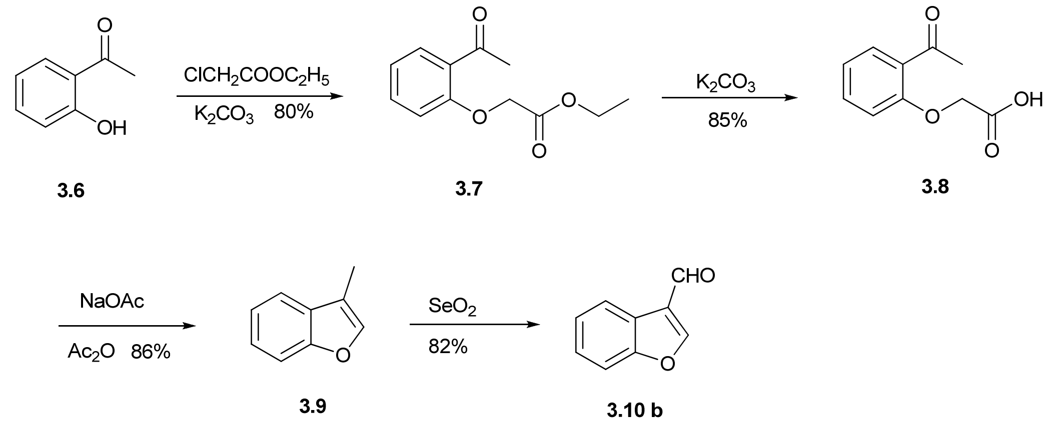
Figure 3.3 The structure of compounds **3.1a** and **3.1b**

The retrosynthesis of compounds **3.1a** and **3.1b** is shown in Scheme 3.1. This synthesis uses Holton's β-lactam method for attaching the side chain to the baccatin III core of paclitaxel, and it shows that two major fragments are necessary for the synthesis of **3.1a** and **3.1b**. One of them is the β-lactam part, and the other is the 7-triethylsilyl-10-acetyl-baccatin III.



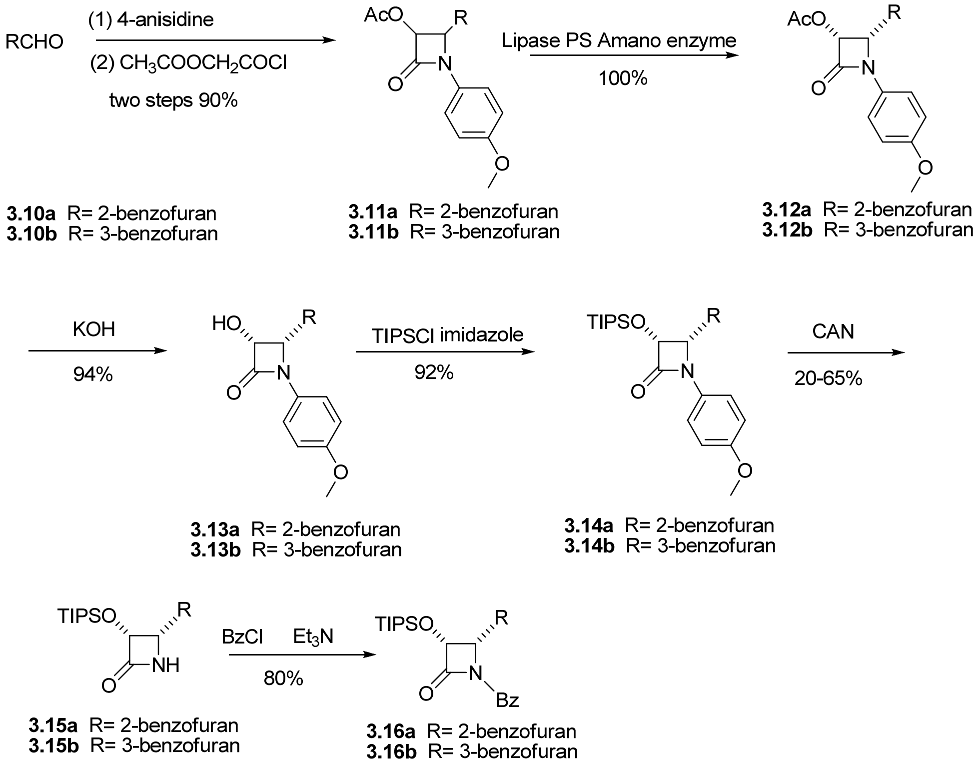
Scheme 3.1 The retrosynthesis of compounds **3.1a** and **3.1b**

The synthetic route for β-lactams are shown in Scheme 3.2 and 3.3. The synthesis of the β-lactams requires benzofuran-2-carbaldehyde or benzofuran-3-carbaldehyde as starting materials. Both benzofuran-2-carbaldehyde and benzofuran-3-carbaldehyde are commercially available, but the latter is expensive and not readily available. As a result, we elected to synthesize it from the commercially available compound 1-(2-hydroxyphenyl)ethanone by the literature method (Scheme 3.2).[17]



Scheme 3.2 Preparation of benzofuran-3-carbaldehyde

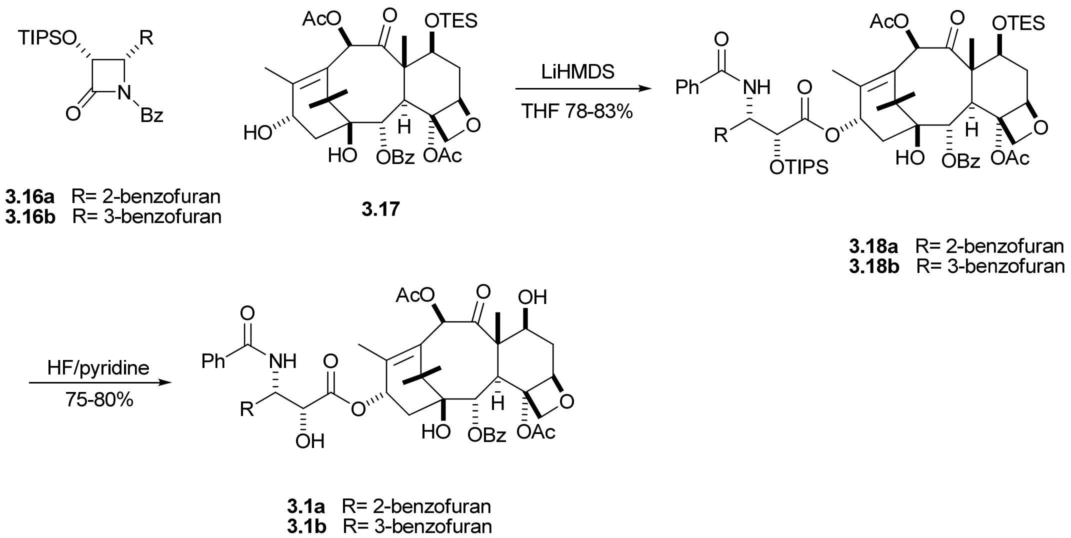
The β-lactams were then prepared by reaction of the aldehydes with *p*-anisidine to form imine intermediates, followed by reaction with acetoxyacetyl chloride to give the corresponding racemic β-lactams. These were resolved by treatment with PS-Amano lipase, which converts the racemic β-lactams to give the desired (+)-enantiomers (**3.12a and 3.12b**) and undesired (-)-alcohols. After separation of these products, the chiral β-lactams were hydrolyzed to secondary alcohols under basic conditions, followed by protection of the hydroxyl as its triisopropylsilyl ether. Cerium (IV) ammonium nitrate (CAN) was then used to deprotect the nitrogen, and finally the nitrogen was benzoylated to obtain the desired β-lactams **3.16a** and **3.16b** (Scheme 3.3).[18]



Scheme 3.3 Synthesis of β-lactams

The synthesis of the other fragment, 7-triethylsilyl-10-acetyl-baccatin III, a known compound, started from the commercially available compound, 10-deacetyl-baccatin III. In the presence of the Lewis acid $CeCl_3$, acetylation selectively occurred at the C10 position rather than the C7 position.[19,20] Finally, protection of the C7 hydroxyl group as its triethylsilyl ether yielded the final product **3.17**.

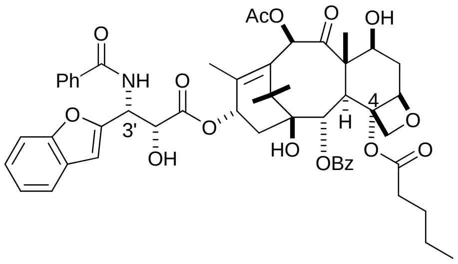
The coupling reactions between β-lactams (**3.16a** and **3.16b**) and 7-triethylsilyl-10-acetyl-baccatin III (**3.17**) were carried out in the presence of the strong base LiHMDS at -45 °C. Deprotection of the silyl group by HF/pyridine yielded the final desired compounds **3.1a** and **3.1b** (Scheme 3.4).



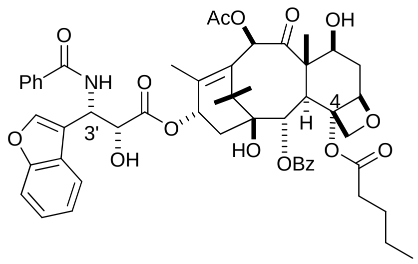
Scheme 3.4 The synthetic routes for the C3′ modified analogs **3.1a** and **3.1b**

3.3.2 Synthesis of the C3′ and C4 modified paclitaxel analogs 3.19a, 3.19b, 3.20a and 3.20b

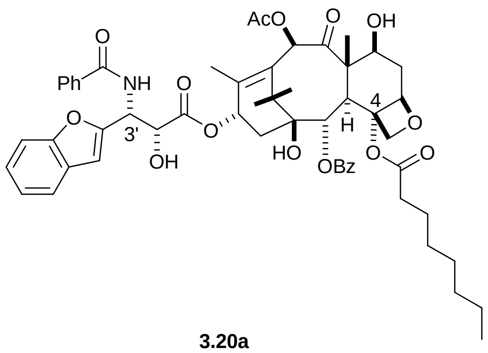
The second group of compounds prepared composed the analogs **3.19a**, **3.19b**, **3.20a** and **3.20b** with modified substituents at the C3′ and C4 positions (Figure 3.4).



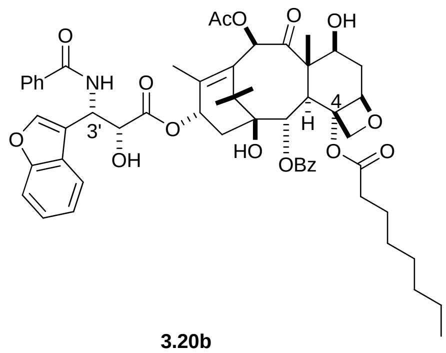
3.19a



3.19b



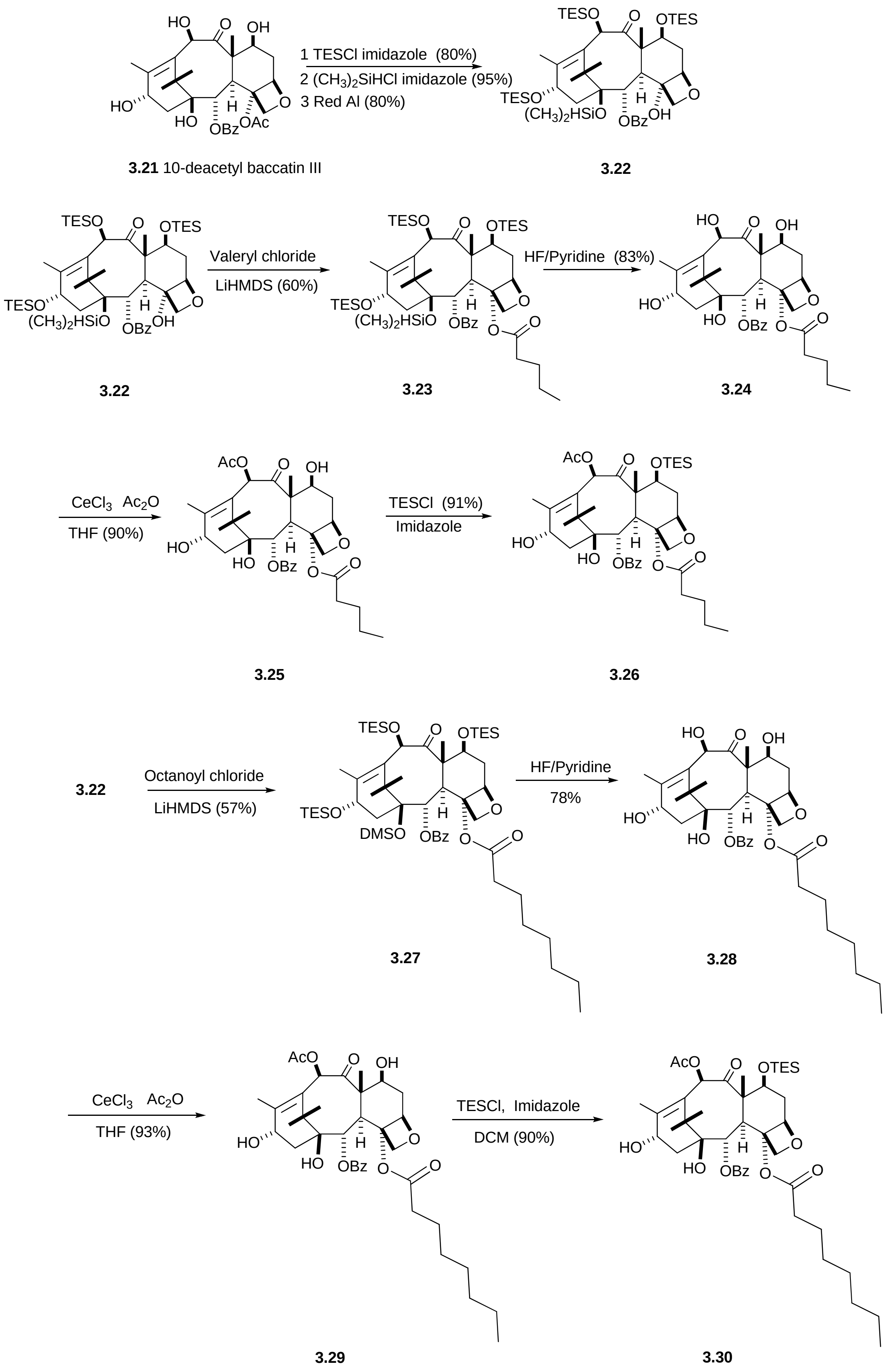
3.20a



3.20b

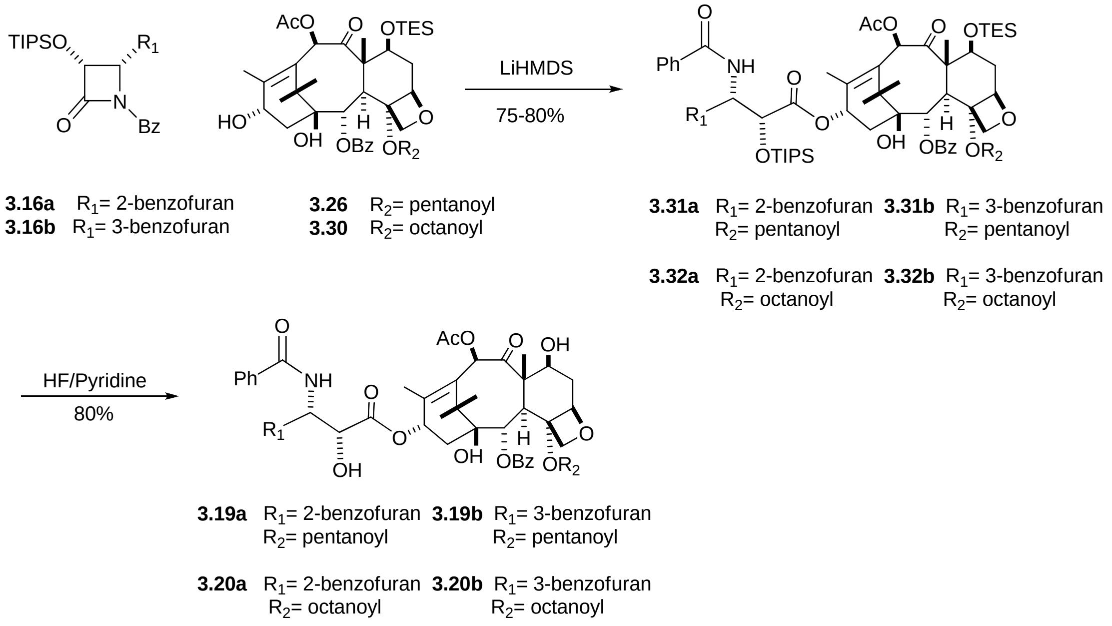
Figure 3.4 The structure of compounds **3.19a**, **3.19b**, **3.20a** and **3.20b**

The synthesis of these compounds can be accomplished by the coupling of the β-lactams (**3.16a** and **3.16b**) and suitable modified baccatin III derivatives. The synthetic routes are shown in Scheme 3.5.



Scheme 3.5 The synthetic routes for **3.26** and **3.30**

The only difference between **3.26** and **3.30** is the nature of the substituted group at C4. Compound **3.26** has a pentanoyl group, while compound **3.30** has an octanoyl substitution. They were thus made by similar synthetic routes. The synthesis of **3.26** and **3.30** started from 10-deacetylbaccatin III. This was protected by triethylsilyl groups at C7, C10 and C13, followed protection at C1 by a dimethylsilyl ether group, and selective hydrolysis at C4 position by treatment with Red Al to give the 4-deacetyl derivative **3.22**.[21] Compound **3.22** was reacylated at C4 using either pentanoyl chloride or octanoyl chloride to yield the corresponding esters **3.23** and **3.27**. Removal of the silyl groups occurred on the treatment with HF/pyridine. Selective acetylation at C10 as previously described and reprotection of the C7 hydroxyl group as its triethylsilyl ether gave the desired 4-acylbaccatin derivatives **3.26** and **3.30**. The coupling of β-lactams (**3.16a** and **3.16b**) and the baccatin cores (**3.26** and **3.30**) was accomplished by the treatment with LiHMDS. Deprotection with HF/pyridine then yielded the desired products **3.19a**, **3.19b**, **3.20a** and **3.20b** (scheme 3.6).



3.16a R_1= 2-benzofuran
3.16b R_1= 3-benzofuran

3.26 R_2= pentanoyl
3.30 R_2= octanoyl

3.31a R_1= 2-benzofuran R_2= pentanoyl **3.31b** R_1= 3-benzofuran R_2= pentanoyl

3.32a R_1= 2-benzofuran R_2= octanoyl **3.32b** R_1= 3-benzofuran R_2= octanoyl

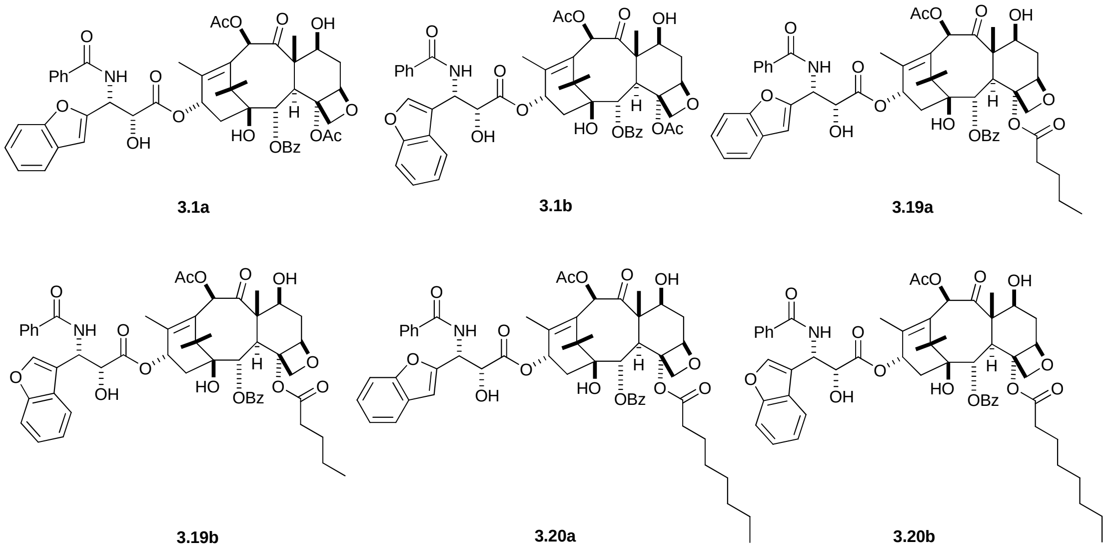
3.19a R_1= 2-benzofuran R_2= pentanoyl **3.19b** R_1= 3-benzofuran R_2= pentanoyl

3.20a R_1= 2-benzofuran R_2= octanoyl **3.20b** R_1= 3-benzofuran R_2= octanoyl

Scheme 3.6 The synthesis of **3.19a**, **3.19b**, **3.20a** and **3.20b**

3.4 Biological evaluation of C3′ and C4 modified paclitaxel analogs

We prepared six different C3′ and C4 modified paclitaxel analogs to study the interaction between paclitaxel analogs and Hβ1 tubulins (Figure 3.5).



3.1a **3.1b** **3.19a**

3.19b **3.20a** **3.20b**

Figure 3.5 The structures of paclitaxel analogs

The first evaluation was carried out at VPISU, and was a standard antiproliferative assay against the paclitaxel—sensitive ovarian cancer A2780 cell line (Table 3.1).

Table 3.1 A2780 Bioassay results

Compounds	IC_{50} against A2780 (µg/mL)
Paclitaxel	0.014
3.1a	0.030
3.1b	2.60
3.19a	0.005
3.19b	0.19
3.20a	3.30
3.20b	11.00

*The data were provided by Ms. Peggy Brodie (Virginia Tech)

The assay results against the A2780 cell line showed that only two of the analogs, compounds **3.1a** and **3.19a**, had antiproliferative activities comparable with that of paclitaxel. These analogs were thus selected more detailed evaluation by Dr. Evi Giannakakou in cells expressing the Hβ1 tubulin isotype and in cells lacking this isotype.

The bioassay experiments to determine the ability of the analogs to spare Hβ1 tubulin were carried out by Professor Evi Giannakakou at Weill Cornell Medical College of Cornell University School of Medicine in New York, and this section has been prepared with her assistance.

The conceptually simplest approach to obtaining these data is by direct observation of the ability of the analog to promote the polymerization of normal tubulin and Hβ1 tubulin, but this approach cannot be used because it has not yet proved possible to isolate homogeneous Hβ1 tubulin and test compounds against it directly. Therefore, Dr. Giannakakou had to exogenously introduce Hβ1 into two human epithelial cell lines that do not express endogenous Hβ1, namely the breast cancer MCF7 cell line and the human embryonic kidney cell line HEK293. To do so, she generated the above cell lines to stably express Hβ1 or an empty vector (EV) as a control. Following establishment of these stable cell populations she tested the activity of the analogs using two different assays. The first was inhibition of cell proliferation using the sulforhodamine B assay and the second was determination of the ability of each of the analogs to stabilize microtubules by using the cell-based tubulin polymerization assay used previously.[22,23,24] For the cytotoxicity assays she tested analog **3.1a** by incubating HEK293_wt Hβ1 pool or HEK293_EV. pool with increasing concentrations of the analog or paclitaxel as a control for 72 hr, and the IC_{50} of each compound was determined. This experiment was not carried out with compound **3.19a**. The results are shown in Table 3.2.

Table 3.2 Cytotoxicity of **3.1a** in normal and Hβ1-expressing HEK293 cells

Compound	IC_{50} to HEK293_EV pool cells	IC_{50} to HEK293_wt Hβ1 pool cells
Paclitaxel	14 nM	22 nM
3.1a	100 nM	83 nM

From this experiment it can be concluded that analog **3.1a** is less cytotoxic to HEK293 cells than is paclitaxel, consistent with its lesser antiproliferative activity against A2780 cells. In addition, and disappointingly, it was actually slightly more cytotoxic to Hβ1-expressing HEK293_wt Hβ1 pool cells than it was to HEK293_wt Hβ1 pool cells.

The second experiment was carried out on both analogs **3.1a** and **3.19a**, and the data are shown in Tables 3.3 and 3.4. In these experiments Hβ1 was exogenously expressed in normal breast cancer MCF7_EV cells by transfection with Hβ1-pIRESpuro2. This generated MCF7_wt Hβ1 pool cells, expressing Hβ1 tubulin. To investigate the effects of drug treatment on microtubule stabilization Dr. Giannakakou used a cell-based tubulin polymerization assay previously established in her laboratory.[23] This quantitative tubulin polymerization assay is based on the fact that drug-stabilized microtubule polymers are detergent insoluble when extracted in a hypotonic buffer and, therefore, remain in the pellet after centrifugation. Conversely, the pool of soluble tubulin dimers remains in the supernatant pool. The effects of the analogs on the microtubule polymer mass in normal cells and transfected cells were measured after a two hour incubation by extracting the cellular proteins and separating them by gel electrophoresis. The tubulins were visualized by treatment with antibodies; the antibody Rabbit anti-Hβ1 (Rb. Hβ1) recognizes only the human Hβ1 tubulin isotype,[6] while mouse β-Tub 2.1 (mTUBB2.1) recognizes all tubulin isotypes except Hβ1. These experiments thus allowed the tubulin-polymerizing abilities of the two analogs to be determined directly in cells.

Table 3.3 Tubulin polymerization activity of **3.1a** in wild type and Hβ1-expressing MCF7 cells

Compound	MCF7_EV visualized with mTUBB2.1				MCF7_wt Hβ1 pool visualized with Rb.Hβ1			
	Percent polymerized tubulin at the indicated concentrations				Percent polymerized tubulin at the indicated concentrations			
	Control	10 nM	100 nM	1000 nM	Control	10 nM	100 nM	1000 nM
paclitaxel	31	70	84	81	57	61	70	70
3.1a	19	50	53	51	33*	56	64	61

*underloaded

Table 3.4 Tubulin polymerization activity of **3.19a** in wild type and Hβ1-expressing MCF7 cells

Compound	MCF7_EV visualized with mTUBB2.1				MCF7_wt Hβ1 pool visualized with Rb.Hβ1			
	Percent polymerized tubulin at the indicated concentrations				Percent polymerized tubulin at the indicated concentrations			
	Control	10 nM	100 nM	1000 nM	Control	10 nM	100 nM	1000 nM
paclitaxel	32	66	73	78	12	25	20	25
3.19a	32	57	60	66	12	26	23	37

These experiments are difficult to interpret, because the ability of paclitaxel to polymerize Hβ1-tubulin differs significantly between the two experiments. In the experiment recorded in Table 3.3, paclitaxel was only slightly less effective at increasing tubulin polymer mass in MCF7_wt Hβ1 cells than in normal MCF7_EV cells. In the separate experiment recorded in Table 3.4, however, paclitaxel was markedly less effective at increasing tubulin polymer mass in MCF7_wt Hβ1 cells than in normal MCF7_EV cells. The reasons for this are not clear, and the work needs to be repeated.

What is clear, however, is that neither analog appears to reduce the percentage of microtubule polymer in Hβ1-expressing cells as compared with normal cells. Analog **3.1a** actually had a slightly higher activity against Hβ1-expressing cells than against normal cells (Table 3.3). Although analog **3.19a** was less active against the Hβ1-expressing cells, paclitaxel was also less active in this experiment, as noted above, and so no firm conclusion can be drawn at this point.

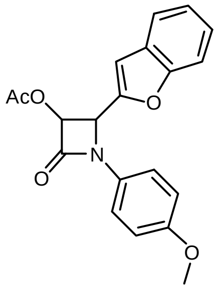
The biological data to date are thus disappointing, in that the two analogs tested are in favor of Hβ1 tubulin rather than against it. Additional experimental and computational work will be needed to develop an analog with the desired selectivity.

3.5 Experimental section

General experimental methods

^1H and ^{13}C NMR spectra were obtained on a Varian INOVA spectrometer at 400 MHz or a JEOL Eclipse spectrometer at 500 MHz. High-resolution mass spectra were obtained on an agilent 6220 accurate-mass TOF LC/MS instrument. Chromatography on a silica gel column was used to purify compounds using EtOAc/hexanes as solvents.

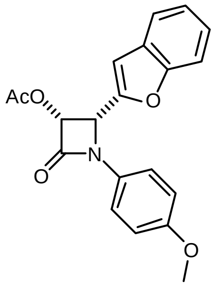
Synthesis of (3*R*,4*S* + 3*S*,4*R*)-1-(*p*-methoxyphenyl)-3-acetoxyl-4-(benzofuran-2-yl)-azetidin-2-one (3.11a).



3.11a

p-Anisidine (0.84 g, 6.8 mmol) was added to a solution of 1-benzofuran-2-carbaldehyde (1 g, 6.8 mmol) in dichloromethane (30 mL) at room temperature. A large excess of anhydrous $MgSO_4$ was then added and the slurry stirred at room temperature for 12 h. The brown solution was filtered and the residue was washed with dichloromethane. The filtrate containing crude imine was then concentrated and taken to the next step without purification. Anhydrous triethylamine (6 mL) was added to the crude imine in dichloromethane (30 mL) and the solution was cooled to -78 ^oC. To this solution, acetoxyacetyl chloride (2.8 g, 20.4 mmol) was added dropwise and the reaction mixture was allowed to warm up to room temperature slowly and stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution, and was then extracted with ethyl acetate (3 × 15 mL), dried over Na_2SO_4, and concentrated. The residue was then purified by flash chromatography (50% ethyl acetate in hexanes) to obtain β–lactam **3.11a** as a yellow solid (2.15 g, yield 90%). ^1H NMR (500 MHz, $CDCl_3$) δ 1.84 (3H, s), 3.75 (3H, s), 5.49 (1H, d, J = 4.8), 6.07 (1H, d, J = 4.8), 6.80 (1H, s), 6.82 (2H, d, J = 9.1), 7.24 (1H, m), 7.30 (1H, m), 7.34 (2H, d, J = 9.1), 7.48 (1H, d, J = 9.0), 7.54 (1H, d, J = 9.0). ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.28, 55.68, 55.90, 76.19, 107.85, 111.81, 114.81, 118.91, 121.58, 123.47, 125.16, 127.97, 130.43, 149.97, 155.55, 157.09, 161.21, 169.69. HRMS (FAB+) calcd for $C_{20}H_{17}NO_5Na$ $[M+Na]^+$ m/z 374.1004, found 374.1003.

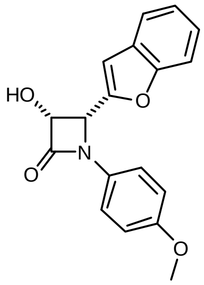
Synthesis of (3*R*,4*S*)-1-(*p*-methoxyphenyl)-3-acetoxyl-4-(benzofuran-2-yl)-azetidin-2-one (3.12a)



3.12a

A phosphate buffer (50 mL) at pH 7.2 was added to the racemic β–lactam **3.11a** (2 g) dissolved in CH_3CN (30 mL), and then immobilized Lipase PS Amano enzyme (2 g) was added to this solution. The mixture was stirred for 7 days, and the reaction was monitored by TLC and NMR. After completion of the reaction, water was added and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was then purified by flash chromatography (50% ethyl acetate in hexanes) to yield compound **3.12a** (1 g, yield 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84 (3H, s), 3.75 (3H, s), 5.49 (1H, d, J = 4.8), 6.07 (1H, d, J = 4.8), 6.80 (1H, s), 6.82 (2H, d, J = 9.1), 7.24 (1H, m), 7.30 (1H, m), 7.34 (2H, d, J = 9.1), 7.48 (1H, d, J = 9.0), 7.54 (1H, d, J = 9.0). ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.28, 55.68, 55.90, 76.19, 107.85, 111.81, 114.81, 118.91, 121.58, 123.47, 125.16, 127.97, 130.43, 149.97, 155.55, 157.09, 161.21, 169.69. HRMS (FAB+) calcd for $C_{20}H_{17}NO_5Na$ [M+Na]$^+$ *m/z* 374.1004, found 374.1003.

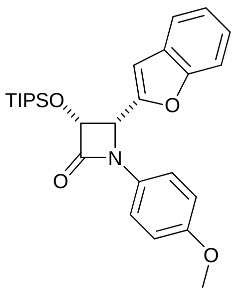
Synthesis of (3*R*,4*S*)-1-(*p*-methoxyphenyl)-3-hydroxy-4-(benzofuran-2-yl)-azetidin-2-one (3.13a)



3.13a

Compound **3.12a** (1 g, 2.67 mmol) dissolved in THF (20 mL) was slowly added to a 1M KOH solution (20mL) at 0 °C. The solution was stirred for 45 min at 0 °C and the mixture was then extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (70% ethyl acetate in hexanes) to give a white solid (776 mg, yield 94%). ^{1}H NMR (500 MHz, d_6-DMSO) δ 3.68 (3H, s), 5.28 (1H, dd, J = 2.5, 5.0), 5.53 (1H, d, *J* = 5.0), 6.47 (1H, d, *J* = 7.4), 6.90 (2H, d, *J* = 9.1), 6.92 (1H, s), 7.22 (1H, m), 7.27 (1H, m), 7.30 (2H, d, *J* = 9.1), 7.54 (1H, d, *J* = 8.0), 7.60 (1H, d, *J* = 8.0). ^{13}C NMR (500 MHz, d_6-DMSO) δ 55.79, 56.96, 77.88, 107.24, 111.73, 115.07, 118.58, 121.61, 123.46, 124.79, 128.48, 131.28, 152.93, 155.19, 156.33, 166.57. HRMS (FAB+) calcd for $C_{18}H_{15}NO_4Na$ $[M+Na]^+$ *m/z* 332.0898, found 332.0891.

Synthesis of (3*R*,4*S*)-1-(*p*-methoxyphenyl)-3-triisopropylsilyloxy-4-(benzofuran-2-yl)-azetidin-2-one (3.14a)

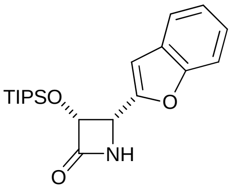


3.14a

Imidazole (616 mg, 9.06 mmol) was added at room temperature to a solution of (3*R*,4*S*)-1--1-(*p*-methoxyphenyl)-3-hydroxy-4-(benzofuran-2-yl)-azetidin-2-one (**3.13a** 700 mg, 2.27 mmol) in DMF (8 mL). Triisopropylsilyl (875 mg, 4.53 mmol) was then added slowly to that solution and the mixture stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (15% EtOAc in hexanes) to yield a white solid **3.14a** (935 mg, yield 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (9H, d, *J* = 2.0), 0.95 (9H, d, *J* = 2.0), 1.03 (3H, m), 3.73 (3H, s), 5.31 (1H, d, *J* = 4.9), 5.33 (1H, d, *J* = 4.9), 6.75 (1H, s), 6.80 (2H, d, *J* = 8.9), 7.20 (1H, m), 7.25 (1H, m), 7.36 (2H, d, *J* = 8.9), 7.44 (1H, d, *J* = 8.0), 7.50 (1H, d, *J* = 8.0).

^{13}C NMR (500 MHz, $CDCl_3$) δ 11.84, 17.51, 17.55, 55.52, 57.44, 78.41, 106.98, 111.26, 114.46, 118.60, 120.98, 122.86, 124.33, 128.18, 130.86, 151.35, 155.30, 155.46, 166.20. HRMS (FAB+) calcd for $C_{27}H_{35}NO_4SiNa$ $[M+Na]^+$ *m/z* 488.2233, found 488.2227.

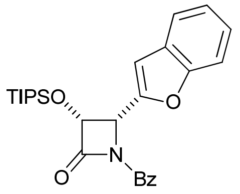
Synthesis of (3*R*,4*S*)-3-triisopropylsilyloxy-4-(benzofuran-2-yl)-azetidin-2-one (3.15a)



3.6

Compound **3.14a** (900 mg, 1.94 mmol) was dissolved in 8 mL CH_3CN and 8 mL THF and cooled to -5 °C. To this solution, a solution of CAN (6.38 g, 11.64 mmol) in water (8 mL) was added dropwise at the same temperature. The orange solution was stirred for 45 min and monitored by TLC. The mixture reaction was extracted with EtOAc and the organic phase was washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography (35% EtOAc in hexanes) to obtain a yellow liquid (415 mg, yield 65%). ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (9H, d, J = 1.5), 0.90 (9H, d, J = 1.5), 0.99 (3H, m), 4.93 (1H, d, J = 4.6), 5.25 (1H, dd, J = 1.7, 4.6), 6.75 (1H, s), 6.82 (1H, brs), 7.19 (1H, m), 7.23 (1H, m), 7.40 (1H, d, J = 8.0), 7.51 (1H, d, J = 8.0). ^{13}C NMR (500 MHz, $CDCl_3$) δ 11.79, 17.47, 17.52, 54.00, 80.56, 105.78, 111.11, 120.91, 122.78, 124.16, 128.20, 153.73, 155.31, 169.90. HRMS (FAB+) calcd for $C_{20}H_{29}NO_3SiNa$ $[M+Na]^+$ *m/z* 382.1814, found 382.1807.

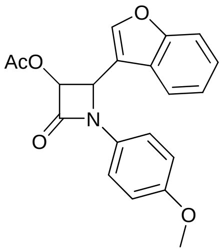
Synthesis of (3*R*,4*S*)-1-benzoyl-3-triisopropylsilyloxy-4-(benzofuran-2-yl)-azetidin-2-one (3.16a)



3.16a

Triethylamine (170 mg, 1.67 mmol), a trace amount of DMAP, and benzoyl chloride (120 mg, 0.84 mmol) were added to a solution of deprotected β-lactam **3.15a** (200 mg, 0.56 mmol) at 0 ^{o}C. The solution was allowed to warm up to room temperature and stirred overnight. Saturated $NaHCO_3$ solution was added to quench the reaction and the solution was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc in Hexanes) to obtain a yellow oily liquid (205 mg, yield 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (9H, s), 0.95 (9H, s), 1.03 (3H, m), 5.34 (1H, d, *J* = 6.0), 5.60 (1H, d, *J* = 6.0), 6.84 (1H, s), 7.20 (1H, m), 7.26 (1H, m), 7.50 (4H, m), 7.60 (1H, m), 8.07 (2H, d, *J* = 8.0). ^{13}C NMR (500 MHz, $CDCl_3$) δ 11.77, 17.43, 17.50, 55.55, 77.13, 106.75, 111.31, 121.01, 122.82, 124.39, 128.06, 128.30, 130.04, 131.89, 133.60, 150.73, 155.38, 164.80, 166.30.

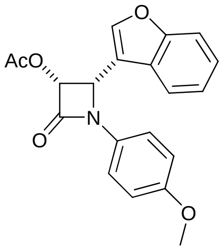
Synthesis of (3*R*,4*S* + 3*S*,4*R*)-1-(*p*-methoxyphenyl)-3-acetoxyl-4-(benzofuran-3-yl)-azetidin-2-one (3.11b).



3.11b

The synthetic method for **3.11b** was the same as described for compound **3.11a** except for the substitution of benzofuran-3-carbaldehyde for benzofuran-2-carbaldehyde. The yield was 1.91 g (85%) . ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (3H, s), 3.71 (3H, s), 5.55 (1H, d, J = 4.8), 6.09 (1H, d, J = 4.8), 6.77 (2H, d, J = 9.0), 7.21 (1H, m), 7.29 (1H, m), 7.34 (2H, d, J = 9.0), 7.46 (1H, d, J = 8.3), 7.58 (1H, d, J = 8.3), 7.65 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ 19.99, 54.48, 55.49, 76.46, 111.74, 113.85, 114.56, 118.71, 120.96, 123.35, 125.03, 125.81, 130.40, 144.90, 155.64, 156.84, 161.38, 169.46. HRMS (FAB+) calcd for $C_{20}H_{17}NO_5Na$ $[M+Na]^+$ *m/z* 374.1004, found 374.1003.

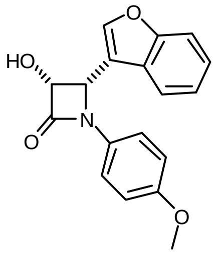
Synthesis of (3*R*,4*S*)-1-(*p*-methoxyphenyl)-3-acetoxyl-4-(benzofuran-3-yl)-azetidin-2-one (3.12b).



3.12b

The synthetic method for **3.12b** was the same as described for compound **3.12a**, except that the mixture had to be stirred for 20 days until it as complete as monitored by TLC. The yield was 950 mg (100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (3H, s), 3.71 (3H, s), 5.55 (1H, d, J = 4.8), 6.09 (1H, d, J = 4.8), 6.77 (2H, d, J = 9.0), 7.21 (1H, m), 7.29 (1H, m), 7.34 (2H, d, J = 9.0), 7.46 (1H, d, J = 8.3), 7.58 (1H, d, J = 8.3), 7.65 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ 19.99, 54.48, 55.49, 76.46, 111.74, 113.85, 114.56, 118.71, 120.96, 123.35, 125.03, 125.81, 130.40, 144.90, 155.64, 156.84, 161.38, 169.46. HRMS (FAB+) calcd for $C_{20}H_{17}NO_5Na$ $[M+Na]^+$ *m/z* 374.1004, found 374.1003.

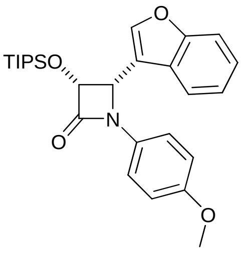
Synthesis of (3*R*,4*S*)-1-(*p*-methoxyphenyl)-3-hydroxy-4-(benzofuran-3-yl)-azetidin-2-one (3.13b)



3.13b

The synthetic method for **3.13b** was the same as described for compound **3.13a** with a yield of 90% (750 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (3H, s), 4.27 (1H, brs), 5.26 (1H, d, J = 5.0), 5.38 (1H, dd, J = 0.6, 5.0), 6.5 (2H, d, J = 9.0), 7.20 (1H, m), 7.28 (1H, m), 7.30 (2H, d, J = 9.0), 7.46 (1H, d, J = 8.3), 7.58 (1H, d, J = 8.3), 7.63 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ 55.45, 55.50, 77.17, 111.89, 114.45, 114.51, 118.81, 120.52, 123.34, 124.99, 126.56, 130.52, 144.56, 155.72, 156.65, 166.31. HRMS (FAB+) calcd for $C_{18}H_{15}NO_4Na$ $[M+Na]^+$ *m/z* 332.0898, found 332.0907.

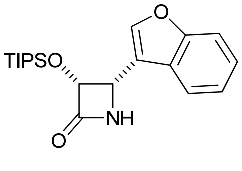
Synthesis of (3*R*, 4*S*)-1-(*p*-methoxyphenyl)-3-triisopropylsilyloxy-4-(benzofuran-3-yl)-azetidin-2-one (3.14b)



3.14b

The synthetic method for **3.14b** was the same as described for compound **3.14a**, with the yield of 91% (1010 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (9H, d, *J* = 6.0), 0.87 (9H, d, *J* = 6.0), 0.96 (3H, m), 3.67 (3H, s), 5.33 (1H, d, *J* = 4.9), 5.35 (1H, d, *J* = 4.9), 6.74 (2H, d, *J* = 9.2), 7.16 (1H, m), 7.24 (1H, m), 7.36 (2H, d, *J* = 9.2), 7.44 (1H, d, *J* = 7.8), 7.62 (1H, d, *J* = 7.8), 7.68 (1H, s). ^{13}C NMR (500 MHz, $CDCl_3$) δ 11.79, 17.45, 17.54, 55.42, 55.95, 78.15, 111.42, 114.43, 115.60, 118.51, 121.62, 122.94, 124.62, 127.02, 131.16, 144.32, 155.74, 156.37, 165.69. HRMS (FAB+) calcd for $C_{27}H_{35}NO_4SiNa$ $[M+Na]^+$ *m/z* 488.2233, found 488.2288.

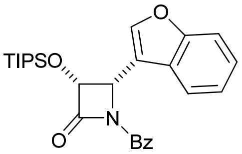
Synthesis of (3*R*,4*S*)-3-triisopropylsilyloxy-4-(benzofuran-3-yl)-azetidin-2-one (3.15b)



3.15b

Compound **3.15b** (200 mg, 0.43 mmol) was dissolved in CH_3CN (15 mL) and cooled to -5 °C. To this solution, a solution of cerium (IV) ammonium nitrate (CAN, 1.18 g, 2.15 mmol) in water (10 mL) was added dropwise at the same temperature. The orange solution was stirred for 20 min and monitored by TLC. The reaction mixture was then extracted with EtOAc, and the organic phase was washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography (35% EtOAc in hexanes) to obtain a yellow liquid (40 mg, yield 20%). HRMS (FAB+) calcd for $C_{20}H_{29}NO_3SiNa$ $[M+Na]^+$ *m/z* 382.1814, found 382.1841.

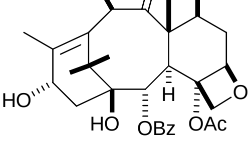
Synthesis of (3*R*,4*S*)-1-benzoyl-3-triisopropylsilyloxy-4-(benzofuran-3-yl)-azetidin-2-one (3.16b)



3.16b

The synthetic method for **3.16b** was the same as described for compound **3.16a** with the yield of 80% (41 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (9H, s), 0.89 (9H, s), 0.98 (3H, m), 5.38 (1H, d, J = 6.2), 5.67 (1H, d, J = 6.2), 7.26 (2H, m), 7.46 (1H, m), 7.47 (2H, d, J = 8.1), 7.57 (1H, m), 7.72 (1H, m), 7.80 (1H, s), 7.98 (2H, d, J = 8.1). ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.62, 17.29, 17.39, 54.04, 76.71, 111.49, 114.92, 121.42, 122.76, 124.44, 126.87, 128.13, 129.85, 131.92, 133.38, 144.61, 155.52, 165.39, 166.29.

Synthesis of 7-triethylsilyl-baccatin III (3.17)

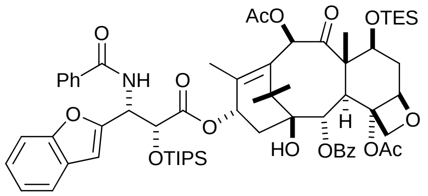


3.17

This compound was synthesized from commercially available

10-deacetylbaccatin III based on the literature method.[25]

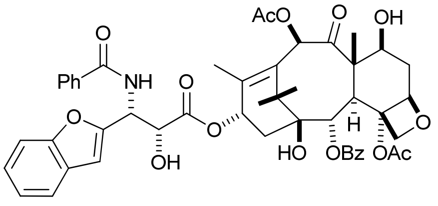
Synthesis of 2′-triisopropylsilyl-3′-(benzofuran-2-yl)-7-triethylsilylpaclitaxel (3.18a)



3.18a

To a solution of β–lactam **3.16a** (15 mg, 0.032 mmol) and baccatin **3.17** (15 mg, 0.021 mmol) in THF (2 mL), 1M LiHMDS (0.064 mmol) was added slowly at -45 °C, and the solution was stirred at -45 °C for 6 h with monitoring by TLC. The solution was quenched with saturated NH_4Cl and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to obtain compound **3.18a** (30 mg, yield 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (2H, d, J = 7.1), 7.77 (2H, d, J = 7.1), 7.53 (6H, m), 7.44 (3H, m), 7.31 (1H, td, J = 1.3, 8.3), 7.22 (1H, td, J = 1.0, 7.4), 7.06 (1H, d, J = 9.2), 6.66 (1H, s), 6.47 (1H, s), 6.21 (1H, t, J = 8.6), 5.92 (1H, d, J = 9.2), 5.71 (1H, d, J = 7.0), 5.30 (1H, s), 4.96 (1H, dd, J = 1.8, 9.6), 4.50 (1H, dd, J = 6.6, 10.5), 4.31 (1H, d, J = 8.4), 4.20 (1H, d, J = 8.4), 3.87 (1H, d, J = 7.0), 2.60 (3H, s), 2.54 (1H, m), 2.42 (1H, m), 2.20 (1H, m), 2.17 (3H, s), 2.08 (3H, s), 1.92 (1H, m), 1.70 (3H, s), 1.22 (3H, s), 1.16 (3H, s), 0.93 (30H, m), 0.58(6H, m). ^{13}C NMR (500 MHz, $CDCl_3$) δ 5.41, 6.84, 10.18, 12.45, 14.50, 17.77, 17.78, 20.96, 21.34, 23.17, 26.62, 35.67, 37.35, 43.40, 46.87, 52.21, 58.59, 71.62, 72.39, 72.65, 74.98, 75.19, 76.70, 78.70, 81.25, 84.39, 104.97, 110.85, 121.09, 123.25, 124.56, 127.14, 128.11, 128.82, 128.92, 129.33, 130.32, 132.15, 133.66, 133.74, 133.86, 140.20, 153.99, 155.03, 167.12, 167.24, 169.45, 170.49, 171.16, 201.87. HRMS (FAB+) calcd for $C_{64}H_{85}NO_{15}Si_2Na$ $[M+Na]^+$ *m/z* 1186.5355, found 1186.5292.

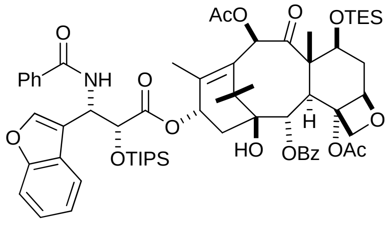
Synthesis of 3′-(benzofuran-2-yl) paclitaxel (3.1a)



3.1a

To a solution of **3.18a** (20 mg, 0.017 mmol) in THF (3 mL) at 0 °C, 70% hydrogen fluoride pyridine (0.24 mL) was added. The solution was stirred in a plastic vial overnight. Saturated $NaHCO_3$ was added to quench the reaction and the solution was extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography (50% EtOAc in hexanes) to obtain solid compound **3.1a** (12 mg, yield 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (2H, d, J = 7.3, ArH), 7.76 (2H, d, J = 7.3, ArH), 7.49 (7H, m, ArH), 7.41 (2H, t, J = 7.7, ArH), 7.25 (1H, m, ArH), 7.01 (1H, d, J = 9.3, CONH), 6.78 (1H, s, ArH), 6.29 (1H, s, H10), 6.25 (1H, t, J = 8.7, H13), 6.04 (1H, d, J = 9.3, H3′), 5.68 (1H, d, J = 7.0, H2), 5.00 (1H, s, H5), 4.95 (1H, dd, J = 1.6, 9.5, H2′), 4.42 (1H, m, H7), 4.30 (1H, d, J = 8.5, H20a), 4.19 (1H, d, J = 8.5, H20b), 3.82 (1H, d, J = 7.0, H3), 3.67 (1H, brs, 2′OH), 2.54 (1H, m, H6a), 2.48 (3H, s, 4OAc), 2.42 (1H, m, H14a), 2.32 (1H, m, H14b), 2.23 (3H, s, 10OAc), 1.87 (3H, s, $CH_3$18), 1.86 (1H, m, H6b), 1.68 (3H, s, $CH_3$19), 1.23 (3H, s, $CH_3$17), 1.14 (3H, s, $CH_3$16). ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.66, 14.98, 20.95, 21.92, 22.76, 26.91, 35.74, 43.30, 45.75, 50.64, 58.70, 71.51, 72.27, 72.68, 75.06, 75.67, 76.61, 79.04, 81.22, 84.53, 104.94, 111.27, 121.32, 123.39, 124.82, 127.26, 127.96, 128.85, 128.87, 129.23, 130.31, 132.33, 133.30, 133.40, 133.79, 141.95, 153.60, 155.07, 167.11, 167.25, 170.59, 171.36, 172.35, 203.75. HRMS (FAB+) calcd for $C_{49}H_{51}NO_{15}Na$ $[M+Na]^+$ *m/z* 916.315644, found 916.3150.

Synthesis of 2′-triisopropylsilyl-3′-(benzofuran-3-yl)-7-triethylsilylpaclitaxel (3.18b)

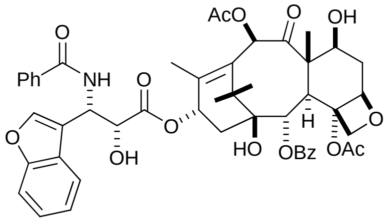


3.18b

To a solution of β–lactam **3.16b** (15 mg, 0.032 mmol) and baccatin **3.17** (15 mg, 0.021 mmol) in THF (2 mL), 1M LiHMDS (0.064 mmol) was added slowly at -45 °C, and the solution was stirred at -45 °C for 6 h with monitoring by TLC. The solution was then quenched with saturated NH_4Cl and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to obtain compound **3.18b** (29 mg, yield 78%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (2H, d, J = 8.2), 7.70 (4H, m), 7.60 (1H, m), 7.50 (4H, m), 7.34 (4H, m), 6.85 (1H, d, J = 9.2), 6.43 (1H, s), 6.22 (1H, t, J = 9.1), 6.04 (1H, d, J = 9.2), 5.68 (1H, d, J = 7.2), 5.14 (1H, d, J = 2.7), 4.90 (1H, d, J = 8.2), 4.47 (1H, dd, J = 6.6, 10.6), 4.27 (1H, d, J = 8.4), 4.20 (1H, d, J = 8.4), 3.83 (1H, d, J = 7.2), 2.50 (1H, m), 2.40 (3H, s), 2.38 (1H, m), 2.16 (3H, s), 2.14 (1H, m), 2.00 (3H, s), 1.89 (1H, m), 1.69 (3H, s), 1.21 (3H, s), 1.18 (3H, s), 1.02 (3H, m), 1.01

(9H, d, *J* = 6.0), 0.98 (9H, d, *J* = 6.5), 0.92 (9H, t, *J* = 7.9), 0.57 (6H, m). ^{13}C NMR (500 MHz, CDCl$_3$) δ 5.38, 6.88, 10.23, 12.84, 14.32, 18.00, 18.02, 20.97, 21.60, 22.90, 26.62, 35.87, 37.30, 43.38, 46.80, 49.26, 58.51, 71.78, 72.33, 74.03, 75.07, 76.69, 79.05, 81.14, 84.39, 112.06, 118.91, 119.66, 123.16, 125.15, 126.18, 127.01, 128.79, 128.81, 129.44, 130.38, 131.97, 133.60, 133.66, 133.82, 140.26, 142.69, 155.64, 166.94, 167.09, 169.42, 170.31, 171.50, 201.84. HRMS (FAB+) calcd for $C_{64}H_{86}NO_{15}Si_2$ $[M+H]^+$ *m/z* 1164.5536, found 1164.5565.

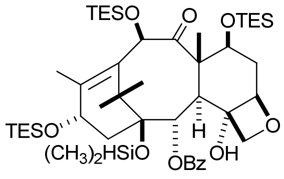
Synthesis of 3′-(benzofuran-3-yl) paclitaxel (3.1b)



3.1b

To a solution of **3.18b** (20 mg, 0.017 mmol) in THF (3 mL) at 0 °C, 70% hydrogen fluoride pyridine (0.24 mL) was added. The solution was stirred in a plastic vial overnight. Saturated NaHCO$_3$ was added to quench the reaction mixture, which was then extracted with EtOAc. The organic phase was washed with brine and dried over Na$_2$SO$_4$. After filtration and concentration, the residue was purified by flash chromatography (50% EtOAc in hexanes) to obtain a solid compound **3.1b** (11 mg, yield 75%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.18 (2H, d, *J* = 8.3, ArH), 7.91 (1H, s, ArH), 7.68 (3H, m, ArH), 7.63 (1H, t, *J* = 7.4, ArH), 7.52 (3H, m, ArH), 7.46 (1H, t, *J* = 7.4, ArH), 7.34 (3H,m, ArH), 7.29(1H, d, *J* = 7.6, ArH), 6.72 (1H, d, *J* = 9.2, CONH), 6.27 (1H, s, 10OAc), 6.25 (1H, m, 13H), 6.08 (1H, d, *J* = 9.4,), 5.68 (1H, d, *J* = 7.1, H3′), 4.88 (2H, m, H5, H2′), 4.39 (1H, m, H7), 4.28 (1H, d, *J* = 8.4, H20a), 4.20 (1H, d, *J* = 8.4, H20b), 3.80 (2H, m, H3, 2′OH), 2.49 (3H, m, H6a, $CH_2$14), 2.29 (3H, s, 4OAc), 2.23 (3H, s, 10OAc), 1.88 (1H, m, H6b), 1.86 (3H, s, $CH_3$18), 1.68 (3H, s, $CH_3$19), 1.24 (3H, s, $CH_3$17), 1.14 (3H, s, $CH_3$16). ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.67, 15.03, 20.95, 21.95, 22.62, 26.91, 35.67, 35.84, 43.26, 45.74, 47.41, 58.67, 72.26, 72.48, 72.80, 75.10, 75.67, 76.59, 79.15, 81.20, 84.49, 111.98, 118.55, 119.84, 123.30, 125.19, 126.35, 127.15, 128.77, 128.83, 129.33, 130.40, 132.13, 133.32, 133.44, 133.80, 142.03, 143.43, 155.37, 167.08, 167.14, 170.39, 171.38, 172.77, 203.76. HRMS (FAB+) calcd for $C_{49}H_{51}NO_{15}Na$ $[M+Na]^+$ *m/z* 894.3337, found 894.3351.

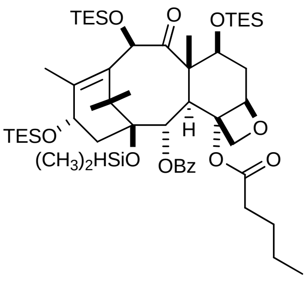
Synthesis of 1-dimethylsilyl-7,10,13-tris(triethylsilyl)-4-deacetyl baccatin III (3.22)



3.22

This compound was synthesized from commercially available 10-deacetylbaccatin III based on the literature method.[26] The overall yield from 1 g of 10-deacetyl baccatin III was 640 mg (yield 70%; literature 78%).

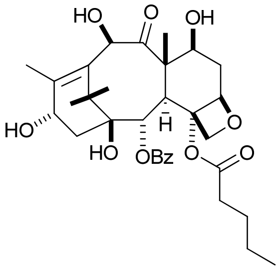
Synthesis of 1-dimethylsilyl-7,10,13-tris(triethylsilyl)-4-pentanoyl baccatin III (3.23)



3.23

To a solution of baccatin **3.22** (200 mg, 0.22 mmol) in 4 mL THF at 0 °C, 1M LiHMDS (0.33 mL) was added and the mixture was stirred for 10 min. Then valeryl chloride (40 mg, 0.33 mmol) was added and the solution was stirred for 5 h at 0 °C. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to obtain compound **3.23** (130 mg, yield 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (2H, d, J = 7.3), 7.56 (1H, t, J = 7.3), 7.44 (2H, t, J = 7.7), 5.70 (1H, d, J = 7.0), 5.14 (1H, s), 4.96 (1H, t, J = 8.4), 4.88 (1H, dd, J = 1.3, 9.4), 4.52 (1H, m), 4.37 (1H, m), 4.21 (2H, m), 3.81 (1H, d, J = 7.0), 2.60 (1H, m), 2.50 (2H, m), 2.27 (2H, m), 1.95 (3H, s), 1.87 (1H, m), 1.77 (2H, m), 1.64 (3H, s), 1.44 (2H, m), 1.17 (3H, s), 1.09 (3H, s), 0.98 (30H, m), 0.62 (18H, m), 0.04 (3H, d, J = 2.8), -0.31 (3H, d, J = 2.8). ^{13}C NMR (500 MHz, $CDCl_3$) δ 0.11, 0.44, 4.87, 5.33, 6.08, 6.96, 6.98, 7.08, 10.42, 14.07, 14.60, 21.61, 22.60, 27.41, 27.46, 35.55, 37.44, 39.37, 44.18, 46.73, 58.29, 68.41, 72.75, 75.74, 76.02, 81.00, 82.20, 84.36, 128.40, 130.23, 130.54, 133.26, 135.98, 138.58, 165.37, 172.46, 205.73. HRMS (FAB+) calcd for $C_{52}H_{90}O_{10}Si_4Na$ $[M+Na]^+$ *m/z* 1009.5508, found 1009.5521.

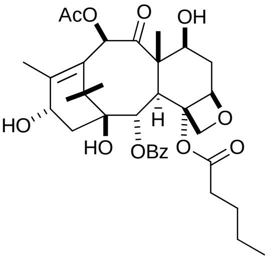
Synthesis of 4-pentanoyl-10-deacetyl baccatin III (3.24)



3.24

HF/pyridine (70% wt, 0.5 mL) was added dropwise to a solution of **3.23** (80 mg, 0.08 mmol) in THF (5 mL) at 0 °C. The solution was allowed to warm up to room temperature and stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (70% EtOAc in hexanes) to obtain compound **3.24** (40 mg, yield 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (2H, d, J = 7.1), 7.60 (1H, t, J = 7.4), 7.46 (2H, t, J = 7.8), 5.61 (1H, d, J = 7.0), 5.24 (1H, s), 4.91 (1H, dd, J = 1.9, 9.6), 4.83 (1H, t, J = 7.7), 4.30 (1H, d, J = 8.3), 4.22 (1H, d, J = 1.3), 4.16 (1H, dd, J = 0.7, J = 8.3), 3.98 (1H, d, J = 7.0), 2.57 (3H, m), 2.24 (2H, m), 2.04 (3H, s), 1.82 (1H, m), 1.72 (3H, s), 1.68 (2H, m), 1.42 (2H, m), 1.07 (6H, s), 0.98 (3H, t, J = 7.3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.86, 14.01, 15.14, 19.85, 22.42, 26.76, 26.78, 35.14, 37.08, 38.81, 42.70, 47.03, 57.77, 67.92, 72.14, 74.93, 75.08, 76.74, 78.92, 80.71, 84.45, 128.68, 129.45, 130.20, 133.77, 134.81, 142.51, 167.15, 173.57, 211.83. HRMS (FAB+) calcd for $C_{32}H_{42}O_{10}Na$ $[M+Na]^+$ m/z 609.2676, found 609.2689.

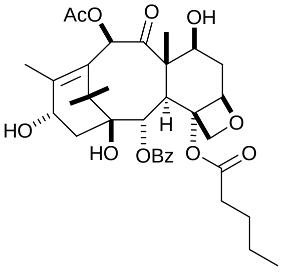
Synthesis of 4-pentanoyl baccatin III (3.25)



3.25

To a solution of 4-pentanoyl-10-deacetyl baccatin III **3.24** (35 mg, 0.06 mmol) in THF (2 mL), a catalytic amount of $CeCl_3$ was added at room temperature, followed by acetic anhydride (0.3 mmol). The solution was stirred for 3 h, quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to obtain compound **3.25** (34 mg, yield 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (2H, dd, J = 1.3, 8.5), 7.60 (1H, t, J = 7.4), 7.47 (2H, t, J = 7.8), 6.30 (1H, s), 5.60 (1H, d, J = 7.0), 4.93 (1H, dd, J = 1.8, 9.6), 4.86 (1H, m), 4.48 (1H, m), 4.29 (1H, d, J = 8.3), 4.14 (1H, d, J = 8.3), 3.87 (1H, d, J = 7.0), 2.56 (3H, m), 2.27 (2H, m), 2.23 (3H, s), 2.03 (3H, s), 1.84 (1H, m), 1.71 (2H, m), 1.66 (3H, s), 1.43 (2H, m), 1.09 (6H, s), 0.98 (3H, t, J = 7.3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.52, 14.01, 15.63, 20.99, 21.04, 22.42, 26.77, 27.03, 35.12, 35.66, 38.73, 42.79, 58.80, 46.20, 58.80, 68.02, 72.40, 75.03, 76.30, 76.57, 79.20, 80.76, 84.72, 128.67, 129.41, 130.21, 131.86, 133.77, 146.55, 167.15, 171.45, 173.45, 204.27. HRMS (FAB+) calcd for $C_{34}H_{44}O_{11}Na$ $[M+Na]^+$ m/z 651.2781, found 651.2788.

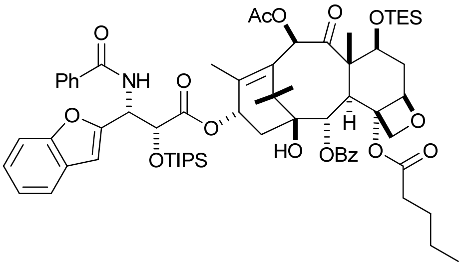
Synthesis of 4-pentanoyl-7-triethylsilyl baccatin III (3.26)



3.26

At room temperature, a solution of **3.25** (30 mg, 0.048 mmol) in DCM (2 mL) was treated with imidazole (16 mg, 0.24 mmol) and chlorotriethylsilane (11 mg, 0.072 mmol). The solution was stirred for 3 h, quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to obtain compound **3.26** (32 mg, yield 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (2H, d, *J* = 8.2), 7.59 (1H, t, *J* = 7.4), 7.46 (2H, t, *J* = 7.8), 6.45 (1H, s), 5.61 (1H, d, *J* = 7.0), 4.90 (1H, d, *J* = 7.9), 4.80 (1H, m), 4.48 (1H, dd, *J* = 6.8, *J* = 10.4), 4.29 (1H, d, *J* = 8.3), 4.13 (1H, d, *J* = 8.3), 3.86 (1H, d, *J* = 7.0), 2.56 (3H, m), 2.24 (2H, m), 2.16 (6H, s), 1.85 (1H, m), 1.72 (2H, m), 1.67 (3H, s), 1.43 (2H, m), 1.18 (3H, s), 1.02 (3H, s), 0.99 (3H, t, *J* = 7.4), 0.91 (9H, t, *J* = 7.9), 0.58 (6H, m). ^{13}C NMR (500 MHz, $CDCl_3$) δ 5.35, 6.83, 10.02, 14.01, 14.99, 20.17, 21.04, 22.48, 26.88, 26.94, 35.48, 37.36, 38.40, 42.88, 47.34, 58.79, 68.06, 72.42, 74.83, 75.88, 76.85, 78.81, 80.80, 84.48, 128.62, 129.48, 130.22, 132.73, 133.71, 144.06, 167.19, 169.47, 173.39, 202.31. HRMS (FAB+) calcd for $C_{40}H_{58}O_{11}SiNa$ $[M+Na]^+$ *m/z* 765.3646, found 765.3657.

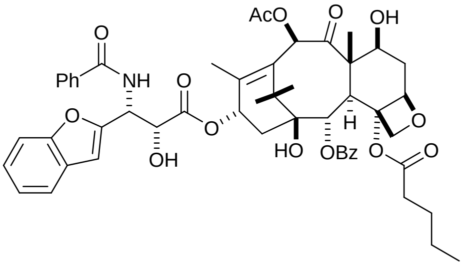
Synthesis of 2′-triisopropylsilyl-3′-(benzofuran-2-yl)-7-triethylsilyl-4-pentanoyl paclitaxel (3.31a)



3.31a

To a solution of β-lactam **3.16a** (15 mg, 0.032 mmol) and baccatin **3.26** (15 mg, 0.021 mmol) in THF, 1M LiHMDS (0.064 mmol) was added slowly at -45 °C, and the solution was stirred at -45 °C for 6 h with monitoring by TLC. The solution was quenched with saturated NH_4Cl and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to obtain compound **3.31a** (29 mg, yield 78%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.14 (2H, d, J = 7.2), 7.77 (2H, d, J = 7.2), 7.58 (1H, d, J = 7.4), 7.49 (4H, m), 7.43 (3H, m), 7.29 (1H, t, J = 6.9), 7.24 (1H, t, J = 7.5), 7.01 (1H, d, J = 9.2), 6.67 (1H, s), 6.47 (1H, s), 6.18 (1H, t, J = 9.1), 5.91 (1H, d, J = 9.2), 5.70 (1H, d, J = 7.1), 5.31 (1H, d, J = 1.5), 4.91 (1H, d, J = 8.1), 4.50 (1H, dd, J = 6.7, 10.5), 4.31 (1H, d, J = 8.4), 4.21 (1H, d, J = 8.4), 3.86 (1H, d, J = 7.1), 2.95 (1H, m), 2.74 (1H, m), 2.56 (1H, m), 2.42 (1H, m), 2.22 (1H, m), 2.17 (3H, s), 2.07 (3H, s), 1.86 (3H, m), 1.70 (3H, s), 1.42 (2H, m), 1.25 (3H, s), 1.16 (3H, s), 0.94 (33H, m), 0.59 (6H, m). ^{13}C NMR (500 MHz, $CDCl_3$) δ 5.40, 6.84, 10.16, 12.47, 13.94, 14.46, 17.78, 20.97, 21.42, 22.40, 26.61, 28.01, 29.79, 35.62, 36.15, 37.36, 43.40, 46.87, 52.28, 58.58, 71.86, 72.37, 72.60, 74.99, 75.17, 76.71, 78.81, 81.01, 84.56, 105.10, 110.78, 121.08, 123.22, 124.53, 127.13, 128.19, 128.77, 128.89, 129.34, 130.36, 132.10, 133.69, 133.76, 140.34, 154.07, 155.04, 167.11, 169.43, 171.36, 173.07, 201.93. HRMS (FAB+) calcd for $C_{67}H_{92}NO_{15}Si_2$ $[M+H]^+$ *m/z* 1206.6006, found 1206.6022.

Synthesis of 3′-(benzofuran-2-yl)-4-pentanoyl paclitaxel (3.19a)

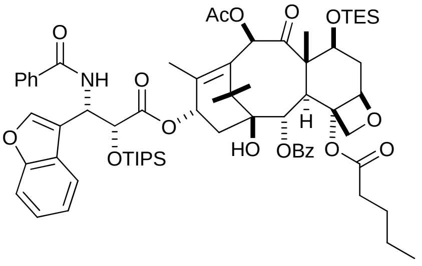


3.19a

To a solution of **3.31a** (20 mg, 0.017 mmol) in THF (3 mL) at 0 °C, hydrogen fluoride pyridine (70% wt, 0.24 mL) was added. The solution was stirred in a plastic vial overnight. Saturated $NaHCO_3$ was added to quench the reaction and EtOAc was used to do the extraction. The organic phase was washed with brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography (50% EtOAc in hexanes) to obtain solid compound **3.19a** (11.6 mg, yield 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (2H, d, *J* = 7.2, ArH), 7.75 (2H, d, *J* = 7.2, ArH), 7.60 (1H, d, *J* = 7.4, ArH), 7.55 (5H, m, ArH), 7.41 (2H, t, *J* = 7.9, ArH), 7.31 (1H, t, *J* = 6.9, ArH), 7.26 (1H, t, *J* = 7.6, ArH), 6.89 (1H, d, *J* = 9.4, CONH), 6.80 (1H, s, ArH), 6.29 (1H, s, 10OAc), 6.26 (1H, t, *J* = 8.9, H13), 6.03 (1H, d, *J* = 9.3, H3′), 5.68 (1H, d, *J* = 7.1, H2), 4.99 (1H, s, H5), 4.90 (1H, d, *J* = 7.8, H2′), 4.45 (1H, m, H7), 4.31 (1H, d, *J* = 8.5, H20a), 4.20 (1H, d, *J* = 8.5, H20b), 3.83 (1H, d, *J* = 7.1, H3), 3.53 (1H, d, *J* = 4.5, 2′OH), 2.81 (1H, m, CH_2), 2.64 (1H, m, CH_2), 2.57

(1H, m, H6a), 2.45 (1H, m, H14a), 2.31 (1H, m, H14b), 2.23 (3H, s, 10OAc), 1.88 (3H, s, $CH_3$18), 1.86 (1H, m, H6b), 1.77 (2H, m, CH_2), 1.69 (3H, s, $CH_3$19), 1.32 (2H, m, CH_2), 1.25 (3H, s, $CH_3$17), 1.14 (3H, s, $CH_3$16), 0.85 (3H, t, J = 7.3, CH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.67, 13.87, 14.92, 20.95, 22.09, 22.36, 26.95, 27.71, 35.69, 35.68, 35.77, 43.32, 45.73, 50.64, 58.70, 71.28, 72.28, 72.93, 75.13, 75.64, 76.61, 79.18, 81.06, 84.76, 105.09, 111.21, 121.31, 123.37, 124.84, 127.25, 127.98, 128.80, 128.85, 129.24, 130.37, 132.29, 133.28, 133.30, 133.80, 142.07, 153.07, 155.07, 167.08, 167.13, 171.39, 172.58, 173.33, 203.79. HRMS (FAB+) calcd for $C_{52}H_{58}NO_{15}$ [M+H]$^+$ *m/z* 936.3806, found 936.3851.

Synthesis of 2′-triisopropylsilyl-3′-(benzofuran-3-yl)-7-triethylsilyl-4-pentanoyl paclitaxel (3.31b)

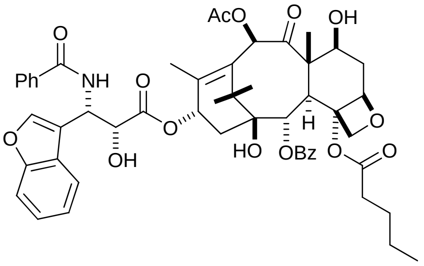


3.31b

The synthesis of compound **3.31b** was followed the same method described for compound **3.31a**. β-Lactam **3.16b** (15 mg, 0.032 mmol) and baccatin **3.26** (16 mg, 0.022 mmol) gave compound **3.31b** (17 mg, yield 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (2H, d, J = 7.8), 7.70 (4H, m), 7.61 (1H, t, J = 7.4), 7.48 (4H, m), 7.36 (3H, m), 7.31 (1H, t, J = 7.5), 6.83 (1H, d, J = 9.4), 6.45 (1H, s), 6.18 (1H, t, J = 9.0), 6.02 (1H, d, J = 9.3), 5.69 (1H, d, J = 7.1), 5.13 (1H, d, J = 1.8), 4.82 (1H, d, J = 8.1), 4.47 (1H, dd, J = 6.7, 10.5), 4.26 (1H, d, J = 8.3), 4.20 (1H, d, J = 8.3), 3.83 (1H, d, J

= 7.1), 2.70 (1H, m), 2.51 (1H, m), 2.37 (2H, m), 2.27 (1H, m), 2.17 (3H, s), 2.04 (3H, s), 1.88 (1H, m), 1.70 (3H, s), 1.53 (1H, m), 1.44 (1H, m), 1.22 (3H, s), 1.18 (3H, s), 1.10 (3H, m), 1.06 (9H, d, *J* = 6.7), 1.02 (9H, d, *J* = 6.9), 0.92 (9H, t, *J* = 8.0), 0.63 (3H, t, *J* = 7.4), 0.58 (6H, m). ^{13}C NMR (500 MHz, $CDCl_3$) *δ* 5.38, 6.83, 10.20, 13.04, 13.58, 14.40, 18.09, 18.10, 20.97, 21.48, 22.02, 26.63, 27.78, 35.89, 37.31, 43.40, 46.86, 49.02, 58.52, 72.06, 72.33, 73.99, 75.07, 75.11, 76.67, 78.97, 81.00, 84.55, 111.94, 119.17, 119.80, 123.15, 125.18, 126.40, 127.00, 128.70, 128.76, 129.51, 130.41, 131.90, 133.56, 133.66, 133.83, 140.36, 142.57, 155.54, 166.82, 166.99, 169.44, 171.63, 172.85, 201.87. HRMS (FAB+) calcd for $C_{67}H_{92}NO_{15}Si_2$ $[M+H]^+$ *m/z* 1206.6006, found 1206.6055.

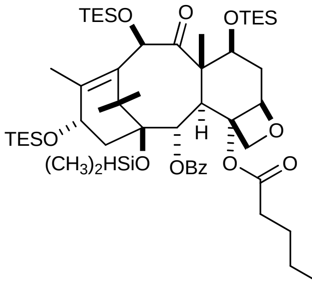
Synthesis of 3′-(benzofuran-3-yl)-4-pentanoyl paclitaxel (3.19b)



3.19b

The synthesis of compound **3.19b** was followed the same method described for compound **3.19a.** Protected paclitaxel **3.31b** (17 mg, 0.014 mmol) yielded **3.19b** (10.5 mg, yield 82%). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.18 (2H, d, *J* = 8.0, ArH), 7.93 (1H, s, ArH), 7.65 (4H, m, ArH), 7.53 (3H, m, ArH), 7.46 (1H, t, *J* = 7.5, ArH), 7.35 (3H, m, ArH), 7.29 (1H, t, *J* = 7.5, ArH), 6.60 (1H, d, *J* = 9.2, CONH), 6.28 (1H, s, H10), 6.25 (1H, t, *J* = 9.0, H13), 6.05 (1H, d, *J* = 9.1, H3′), 5.68 (1H, d, *J* = 7.2, H2), 4.86 (2H, m, H5, H2′), 4.43 (1H, m, H7), 4.29 (1H, d, *J* = 8.4, H20a), 4.21 (1H, d, *J* = 8.4, H20b), 3.83 (1H, d, J = 7.2, H3), 3.63 (1H, d, J = 5.4, 2′OH), 2.59 (1H, m, H6a), 2.49 (3H, m, CH_2, H14a), 2.24 (1H, m, H14b), 2.23 (3H, s, 10OAc), 1.87 (1H, m, H6b), 1.86 (3H, s, $CH_3$18), 1.68 (3H, s, $CH_3$19), 1.51 (1H, m, CH_2), 1.40 (1H, m, CH_2), 1.26 (3H, s, $CH_3$17), 1.15 (3H, s, $CH_3$16), 0.96 (2H, m, CH_2), 0.61(3H, t, J = 7.3, CH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.67, 13.60, 14.99, 20.96, 22.04, 22.07, 26.94, 27.48, 35.52, 35.65, 35.88, 43.29, 45.76, 47.34, 58.69, 72.19, 72.27, 73.10, 75.17, 75.67, 76.59, 79.19, 81.10, 84.72, 111.90, 118.87, 119.86, 123.31, 125.26, 126.46, 127.13, 128.75, 128.77, 129.37, 130.43, 132.10, 133.28, 133.44, 133.81, 142.11, 143.36, 155.37, 167.05, 171.40, 172.99, 173.11, 203.79. HRMS (FAB+) calcd for $C_{52}H_{58}NO_{15}$ $[M+H]^+$ m/z 936.3806, found 936.3836.

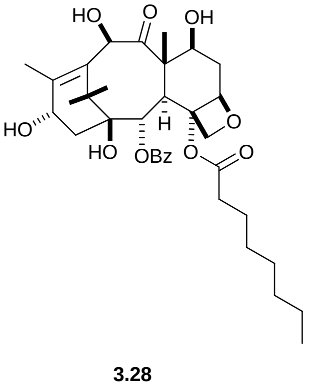
Synthesis of 1-dimethylsilyl-7,10,13-tris(triethylsilyl)-4-octanoyl baccatin III (3.27)



3.27

To a solution of baccatin **3.22** (212 mg, 0.24 mmol) in 4 mL THF at 0 °C, 1M LiHMDS (0.48 mL) was added and the solution was stirred for 10 min. Then octanoyl chloride (59 mg, 0.36 mmol) was added and the solution was stirred for 5 h at 0 °C. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to obtain compound **3.27** (140 mg, yield 57%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.10 (2H, d, J = 8.2), 7.56 (1H, t, J = 7.4), 7.43 (2H, t, J = 7.8), 5.70(1H, d, J = 7.0), 5.14 (1H, s), 4.95 (1H, t, J = 8.5), 4.87 (1H, d, J = 9.5), 4.53 (1H, m), 4.37 (1H, m), 4.21 (2H, m), 3.81 (1H, d, J = 7.0), 2.57 (1H, m), 2.50 (2H, m), 2.27 (2H, m), 1.95 (3H, s), 1.87 (1H, m), 1.77 (2H, m), 1.64 (3H, s), 1.38 (4H, m), 1.31 (4H, m), 1.17 (3H, s), 1.09 (3H, s), 0.99 (27H, m), 0.89 (3H, t, J = 6.9), 0.60 (18H, m), 0.04 (3H, d, J = 2.8), -0.31 (3H, d, J = 2.8). ^{13}C NMR (500 MHz, CDCl$_3$) δ 0.10, 0.42, 4.87, 5.32, 6.08, 6.96, 7.05, 10.48, 14.12, 14.51, 21.58, 22.71, 25.34, 27.44, 29.26, 29.42, 31.77, 35.83, 37.46, 39.42, 44.16, 46.71, 58.31, 68.44, 72.77, 75.75, 76.02, 76.81, 80.98, 82.17, 84.33, 128.40, 130.22, 130.65, 133.17, 135.97, 138.71, 165.42, 172.40, 205.67. HRMS (FAB+) calcd for $C_{55}H_{96}O_{10}Si_4Na$ [M+Na]$^+$ *m/z* 1051.5978, found 1051.5997.

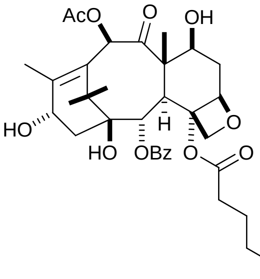
Synthesis of 4-octanoyl-10-deacetyl baccatin III (3.28)



3.28

HF/pyridine (70% wt, 0.6 mL) was added dropwise to a solution of baccatin **3.27** (130 mg, 0.13 mmol) in THF (5 mL) at 0 °C. The solution was allowed to warm up to room temperature and stirred overnight. The reaction was quenched with saturated NaHCO$_3$ solution and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to obtain compound **3.28** (62 mg, yield 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (2H, dd, J = 1.3, 8.5), 7.59 (1H, t, J = 7.4), 7.45 (2H, t, J = 7.7), 5.58 (1H, d, J = 7.0), 5.23(1H, s), 4.92 (1H, dd, J = 1.3, 9.2), 4.81 (1H, t, J = 7.7), 4.28 (3H, m), 4.14 (1H, d, J = 8.3), 3.96 (1H, d, J = 7.0), 2.55 (3H, m), 2.22 (4H, m), 2.03 (3H, s), 1.78 (1H, m), 1.70 (3H, s), 1.34 (8H, m), 1.05 (6H, s), 0.88 (3H, t, J = 6.9). ^{13}C NMR (400 MHz, $CDCl_3$) δ 9.78, 14.09, 15.03, 19.78, 22.62, 24.60, 26.66, 29.09, 29.18, 31.68, 35.35, 36.89, 38.70, 42.59, 46.95, 57.63, 67.72, 71.99, 74.88, 74.94, 76.63, 78.81, 80.59, 84.40, 128.57, 129.34, 130.09, 133.64, 134.57, 142.56, 167.02, 173.48, 211.58. HRMS (FAB+) calcd for $C_{35}H_{49}O_{10}$ $[M+H]^+$ m/z 629.3326, found 629.3335.

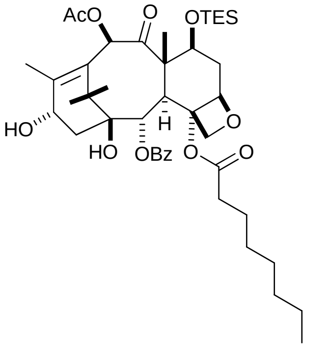
Synthesis of 4-octanoyl baccatin III (3.29)



3.29

To a solution of 4-octanoyl baccatin III **3.28** (40 mg, 0.06 mmol) in THF (2 mL), a catalytic amount of $CeCl_3$ was added at room temperature, followed by acetic anhydride (30 mg, 0.30 mmol). The solution was stirred for 3 h, quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to obtain compound **3.29** (39.7 mg, yield 93%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (2H, d, J = 8.2), 7.59 (1H, t, J = 7.4), 7.45 (2H, t, J = 7.6), 6.29 (1H, s), 5.59 (1H, d, J = 7.0), 4.92 (1H, d, J = 9.4), 4.84 (1H, m), 4.47 (1H, m), 4.27 (1H, d, J = 8.4), 4.13 (1H, d, J = 8.4), 3.85 (1H, d, J = 7.0), 2.55 (3H, m), 2.25 (4H, m), 2.21 (3H, s), 2.02 (3H, s), 1.83 (1H, m), 1.64 (3H, s), 1.30 (8H, m), 1.08(3H, s), 1.07 (3H, s), 0.88 (3H, t, J = 7.0). ^{13}C NMR (500 MHz, CDCl$_3$) δ 9.53, 14.17, 15.61, 20.97, 21.08, 22.71, 24.67, 27.00, 29.19, 29.28, 31.77, 35.40, 35.65, 38.82, 42.78, 46.21, 58.75, 67.92, 72.39, 75.07, 76.33, 76.56, 79.16, 80.70, 84.73, 128.67, 129.44, 130.20, 131.72, 133.74, 146.73, 167.10, 171.47, 173.43, 204.32. HRMS (FAB+) calcd for $C_{37}H_{51}O_{11}$ [M+H]$^+$ m/z 671.3431, found 671.3420.

Synthesis of 4-octanoyl-7-triethylsilyl baccatin III (3.30)

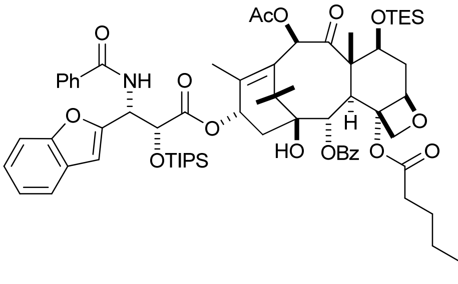


3.30

At room temperature, a solution of baccatin **3.29** (35 mg, 0.05 mmol) in DCM (2 mL) was treated with imidazole (17 mg, 0.25 mmol) and chlorotriethylsilane (24 mg, 0.15 mmol). The solution was stirred for 3 h, quenched with saturated NaHCO$_3$ solution, and extracted with EtOAc. The organic phase was washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash chromatography to obtain compound **3.30** (36.8 mg, yield 90%). ^{1}H NMR (500 MHz,

$CDCl_3$) δ 8.11 (2H, dd, J = 1.2, 8.4), 7.59 (1H, t, J = 7.4), 7.45 (2H, t, J = 7.8), 6.44 (1H, s), 5.61 (1H, d, J = 7.0), 4.92 (1H, d, J = 9.3), 4.81 (1H, m), 4.48 (1H, dd, J = 6.8, 10.4), 4.28 (1H, d, J = 8.3), 4.13 (1H, d, J = 8.3), 3.86 (1H, d, J = 7.0), 2.54 (3H, m), 2.24 (2H, m), 2.16 (6H, s), 1.86 (1H, m), 1.67 (3H, s), 1.34 (8H, m), 1.18 (3H, s), 1.02 (3H, s), 0.92 (9H, t, J = 7.9), 0.90 (3H, t, J = 7.0), 0.57(6H, m). ^{13}C NMR (500 MHz, $CDCl_3$) δ 5.35, 6.83, 10.01, 14.17, 14.98, 20.17, 21.04, 22.70, 24.84, 26.87, 29.17, 29.33, 31.77, 35.78, 37.36, 38.41, 42.88, 47.33, 58.78, 68.04, 72.42, 74.84, 75.89, 76.69, 78.37, 80.78, 84.48, 128.62, 129.49, 130.22, 132.70, 133.70, 144.09, 167.19, 169.47, 173.39, 202.33. HRMS (FAB+) calcd for $C_{43}H_{65}O_{11}Si$ $[M+H]^+$ m/z 785.4296, found 785.4321.

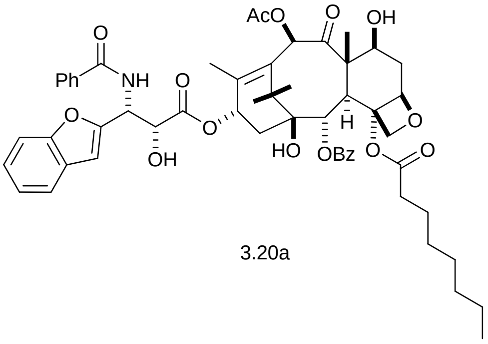
Synthesis of 2′-triisopropylsilyl-3′-(benzofuran-2-yl)-7-triethylsilyl-4-octanoyl paclitaxel (3.32a)



3.32a

To a solution of β-lactam **3.16a** (15 mg, 0.032 mmol) and baccatin **3.30** (16.5 mg, 0.021 mmol) in THF, 1M LiHMDS (0.064 mmol) was added slowly at -45 °C, and the solution was stirred at -45 °C for 6 h with monitoring by TLC. The solution was then quenched with saturated NH_4Cl and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography to obtain compound **3.32a** (19.6 mg, yield 75%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.11 (2H, d, *J* = 7.3), 7.76 (2H, d, *J* = 7.3), 7.58 (2H, d, *J* = 7.3), 7.50 (4H, m), 7.43 (3H, m), 7.25 (3H, m), 7.00 (1H, d, *J* = 9.3), 6.67 (1H, s), 6.47 (1H, s), 6.19 (1H, t, *J* = 9.8), 5.93 (1H, d, *J* = 9.2), 5.70 (1H, d, *J* = 7.0), 5.32 (1H, d, *J* = 1.2), 4.90 (1H, d, *J* = 9.0), 4.50 (1H, dd, *J* = 6.8, 10.5), 4.30 (1H, d, *J* = 8.4), 4.21 (1H, d, *J* = 8.4), 3.86 (1H, d, *J* = 7.0), 2.92 (1H, m), 2.74 (1H, m), 2.55 (1H, m), 2.42 (1H, m), 2.19 (1H, m), 2.17 (3H, s), 2.07 (3H, s), 1.91 (3H, m), 1.71 (3H, s), 1.26 (6H, m), 1.22 (3H, s), 1.16 (3H, s), 1.07 (2H, m), 0.93 (30H, m), 0.79 (3H, t, *J* = 7.2), 0.60 (6H, m). ^{13}C NMR (500 MHz, CDCl$_3$) δ 5.40, 6.85, 10.16, 12.47, 14.10, 14.47, 17.78, 17.79, 20.98, 22.57, 26.02, 26.62, 29.17, 29.20, 31.55, 35.60, 36.51, 37.41, 43.40, 46.87, 52.21, 58.58, 71.77, 72.38, 72.57, 75.02, 75.18, 76.71, 78.79, 81.01, 84.54, 105.08, 110.85, 121.07, 123.24, 124.53, 127.13, 128.17, 128.77, 128.91, 129.36, 130.37, 132.10, 133.68, 133.80, 140.33, 153.99, 154.93, 167.11, 169.39, 171.30, 173.10, 201.90. HRMS (FAB+) calcd for $C_{70}H_{98}NO_{15}Si_2$ $[M+H]^+$ *m/z* 1248.6475, found 1248.6519.

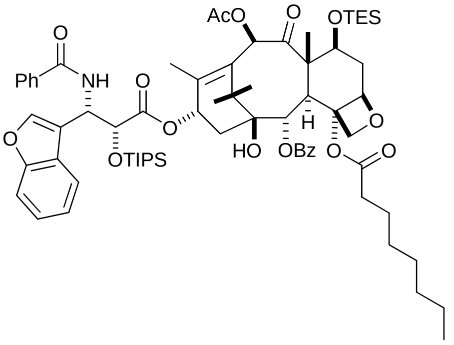
Synthesis of 3′-(benzofuran-2-yl)-4-octanoyl paclitaxel (3.20a)



3.20a

To a solution of **3.32a** (16 mg, 0.013 mmol) in THF (3 mL) at 0 °C, 70% hydrogen fluoride pyridine (0.24 mL) was added. The solution was stirred in a plastic vial overnight. Saturated $NaHCO_3$ was added to quench the reaction and EtOAc was used to do the extraction. The organic phase was washed with brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography (50% EtOAc in hexanes) to obtain a solid compound **3.20a** (10 mg, yield 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (2H, d, J = 8.3, ArH), 7.75 (2H, d, J = 8.3, ArH), 7.60 (1H, t, J = 7.4, ArH), 7.50 (5H, m, ArH), 7.41 (2H, t, J = 7.4, ArH), 7.30 (1H, t, J = 8.0, ArH), 7.27 (2H, m, ArH), 6.88 (1H, d, J = 9.4, CONH), 6.80 (1H, s, ArH), 6.29 (1H, s, H10), 6.26 (1H, t, J = 8.6, H13), 5.68 (1H, d, J = 7.1, H3′), 5.01 (1H, s, H2), 4.89 (1H, d, J = 8.8, H5), 4.45 (1H, m, H2′), 4.30 (1H, d, J = 8.4, H20a), 4.20 (1H, d, J = 8.4, H20b), 3.84 (1H, d, J = 7.1, H3), 3.51 (1H, brs, 2′OH), 2.80 (1H, m, CH_2), 2.66 (1H, m, CH_2), 2.55 (1H, m, H6a), 2.45 (2H, m, H14a), 2.31 (1H, m, H14b), 2.23 (3H, s, 10OAc), 1.89 (3H, s, $CH_3$18), 1.88 (1H, m, H6b), 1.76 (3H, m, CH_2), 1.69 (3H, s, $CH_3$19), 1.24 (3H, s, $CH_3$17), 1.23 (6H, m, CH_2), 1.14 (3H, s, $CH_3$16), 1.05 (2H, q, J = 7.2, CH_2), 0.78 (3H, t, J = 7.2, CH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 14.09, 14.94, 20.96, 22.10, 22.59, 25.70, 26.94, 29.14, 29.20, 31.53, 35.69, 35.77, 36.02, 43.31, 45.77, 50.62, 58.70, 71.24, 72.29, 72.90, 75.13, 75.65, 76.59, 79.18, 81.04, 84.77, 105.08, 111.27, 121.30, 123.39, 124.84, 127.24, 127.98, 128.81, 128.86, 129.25, 130.38, 132.29, 133.27, 133.30, 133.80, 142.07, 153.61, 155.08, 167.06, 167.14, 171.40, 172.59, 173.35, 203.80. HRMS (FAB+) calcd for $C_{55}H_{64}NO_{15}$ $[M+H]^+$ m/z 978.4276, found 978.4320.

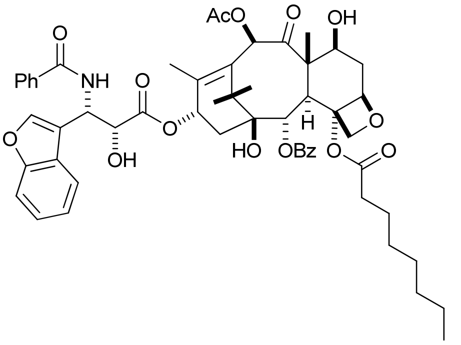
Synthesis of 2′-triisopropylsilyl-3′-(benzofuran-3-yl)-7-triethylsilyl-4-octanoyl paclitaxel (3.32b)



3.32b

The synthesis of compound **3.32b** followed the same method described for compound **3.32a**. Reaction of baccatin **3.30** (17 mg, 0.021 mmol) with β-lactam **3.16b** (15 mg, 0.032 mmol) gave compound **3.32b** (20 mg, yield 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (2H, d, *J* = 8.2), 7.70 (4H, m), 7.61 (1H, t, *J* = 7.4), 7.50 (3H, m), 7.45 (1H, t, *J* = 7.4), 7.36 (3H, m), 7.31 (1H, t, *J* = 7.4), 6.82 (1H, d, *J* = 9.4), 6.45 (1H, s), 6.17 (1H, t, *J* = 9.8), 6.03 (1H, d, *J* = 9.3), 5.69 (1H, d, *J* = 7.2), 5.12 (1H, s), 4.82 (1H, d, *J* = 9.4), 4.47 (1H, dd, *J* = 6.7, 10.5), 4.26 (1H, d, *J* = 8.4), 4.20 (1H, d, *J* = 8.4), 3.83 (1H, d, *J* = 7.2), 2.70 (1H, m), 2.51 (1H, m), 2.42 (1H, m), 2.34 (1H, m), 2.22 (1H, m), 2.16 (3H, s), 2.04 (3H, s), 1.88 (1H, m), 1.70 (3H, s), 1.53 (1H, m), 1.46 (1H, m), 1.24 (2H, m), 1.22 (3H, s), 1.18 (3H, s), 1.09 (6H, m), 1.06 (3H, m), 1.06 (9H, d, *J* = 6.6), 1.05 (9H, d, *J* = 6.6), 0.92 (9H, t, *J* = 7.8), 0.81 (3H, t, *J* = 7.3), 0.58 (6H, m). ^{13}C NMR (500 MHz, $CDCl_3$) δ 5.38, 6.83, 10.20, 13.04, 14.09, 14.41, 18.10, 18.11, 20.97, 21.57, 22.52, 25.74, 26.62, 28.85, 31.41, 35.80, 36.22, 37.28, 43.39, 46.85, 49.01, 58.52, 72.05, 72.32, 73.99, 75.07, 75.12, 76.67, 78.97, 80.98, 84.57, 111.99, 119.18, 119.80, 123.16, 125.17, 126.39, 127.00, 128.71, 128.76, 129.52, 130.42, 131.89, 133.55, 133.64, 133.84, 140.36, 142.57, 155.54, 166.85, 167.00, 169.44, 171.62, 172.89, 201.89. HRMS (FAB+) calcd for $C_{70}H_{98}NO_{15}Si_2$ $[M+H]^+$ *m/z* 1248.6475, found 1248.6524.

Synthesis of 3′-(benzofuran-3-yl)-4-octanoyl paclitaxel (3.20b)



3.20b

The synthesis of compound **3.20b** followed the same method described for compound **3.20a.** Deprotection of **3.32b** (18 mg, 0.014 mmol) with HF/pyridine gave compound **3.20b** (11.5 mg, yield 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 7.2, ArH), 7.93 (1H, s, ArH), 7.67 (4H, m, ArH), 7.52 (3H, m, ArH), 7.46 (1H, t, *J* = 7.4, ArH), 7.35 (3H, m, ArH), 7.29 (1H, t, *J* = 7.4, ArH), 6.59 (1H, d, *J* = 9.2, CONH), 6.28 (1H, s, H10), 6.25 (1H, t, *J* = 8.8, H13), 6.05 (1H, d, *J* = 9.2, H3′), 5.68 (1H, d, *J* = 7.1, H2), 4.86 (2H, m, H5, H2′), 4.43 (1H, m, H7), 4.29 (1H, d, *J* = 8.5, H20a), 4.21 (1H, d, *J* = 8.5, H20b), 3.83 (1H, d, *J* = 7.1, H3), 3.62 (1H, d, *J* = 5.4, 2′OH), 2.60 (1H, m, CH_2), 2.45 (4H, m, CH_2), 2.24 (3H, s, 10OAc), 1.87 (1H, m, H6b), 1.86 (3H, s, $CH_3$18), 1.68 (3H, s, $CH_3$19), 1.51 (1H, m, CH_2), 1.42 (1H, m, CH_2), 1.25 (3H, s, $CH_3$17), 1.15 (3H, s, $CH_3$16), 1.11 (2H, m, CH_2), 0.99 (2H, m, CH_2), 0.90 (4H, m, CH_2), 0.80 (3H, t, *J* = 7.3, CH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.67, 14.08, 14.99, 20.96, 22.01, 22.56, 25.44, 26.93, 28.90, 28.93, 31.33, 35.63, 35.82, 35.89, 43.29, 45.75, 47.32, 58.69, 72.18, 72.26, 73.13, 75.18, 75.67, 76.59, 79.19, 81.09, 84.74, 111.95, 118.69, 119.84, 123.33, 125.26, 126.46, 127.14, 128.77, 129.37, 130.45, 132.09, 133.29, 133.45, 133.80, 142.11, 143.36, 155.37, 167.01, 167.07, 171.40, 173.02, 173.14, 203.80. HRMS (FAB+) calcd for $C_{55}H_{64}NO_{15}$ $[M+H]^+$ *m/z* 978.4276, found 978.4315.

References:

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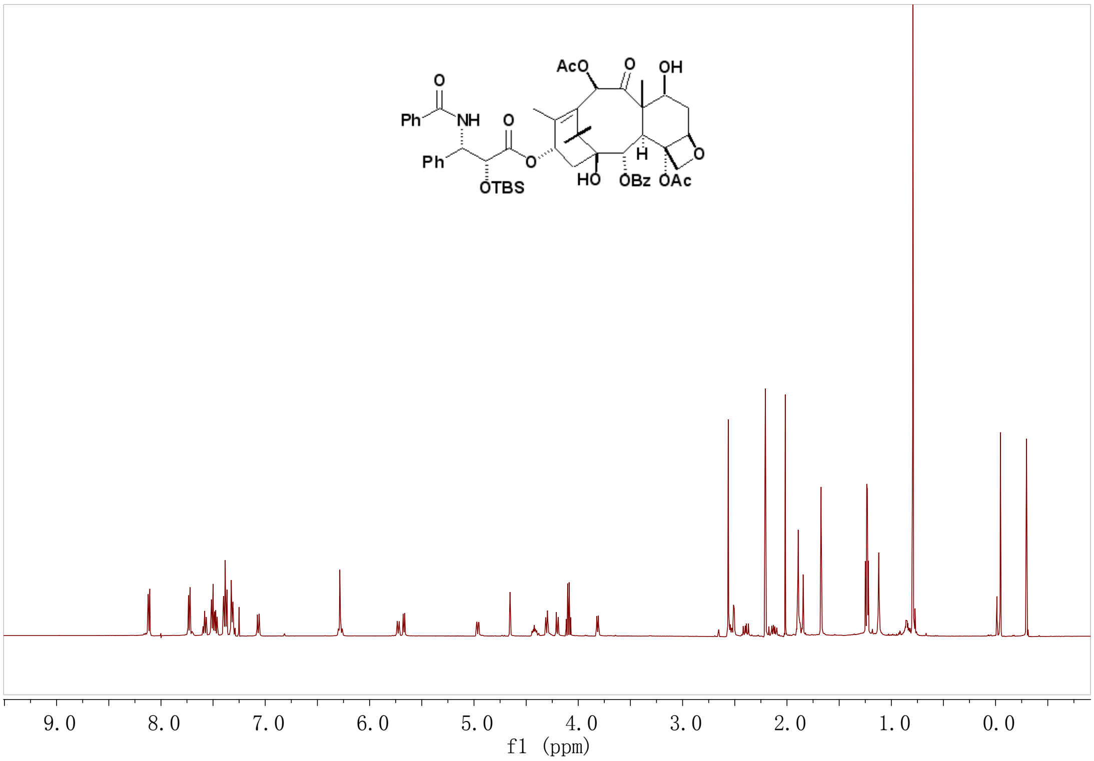
NMR Spectra



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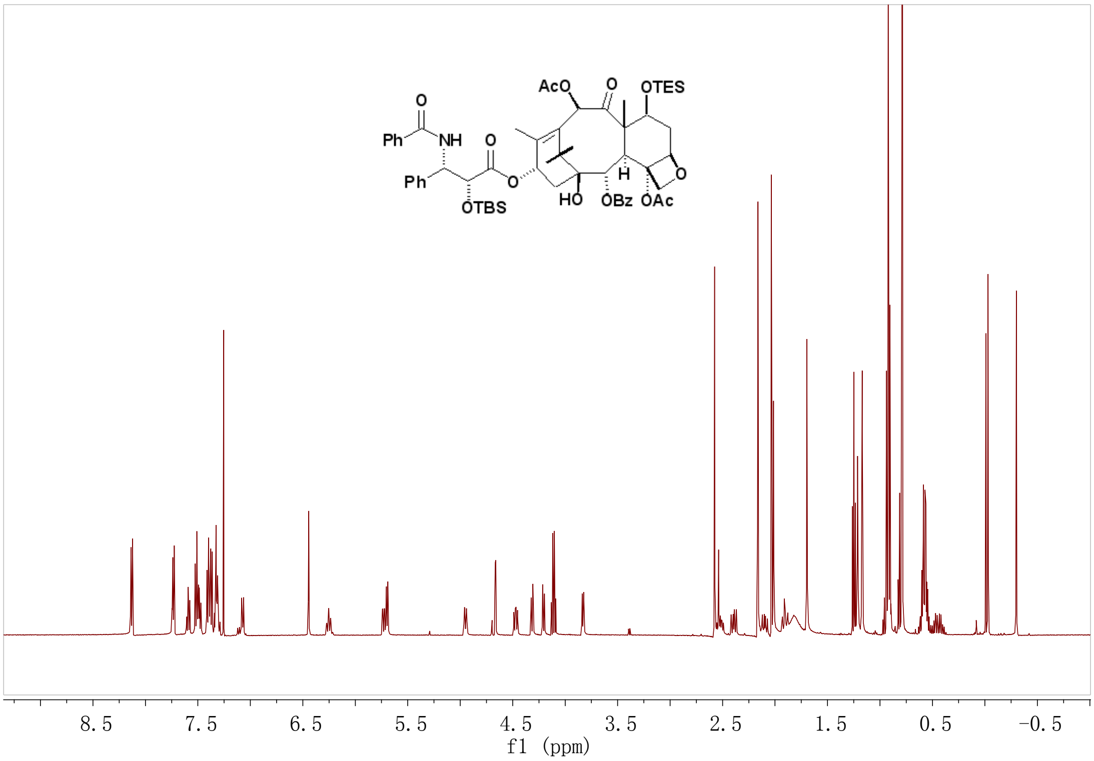

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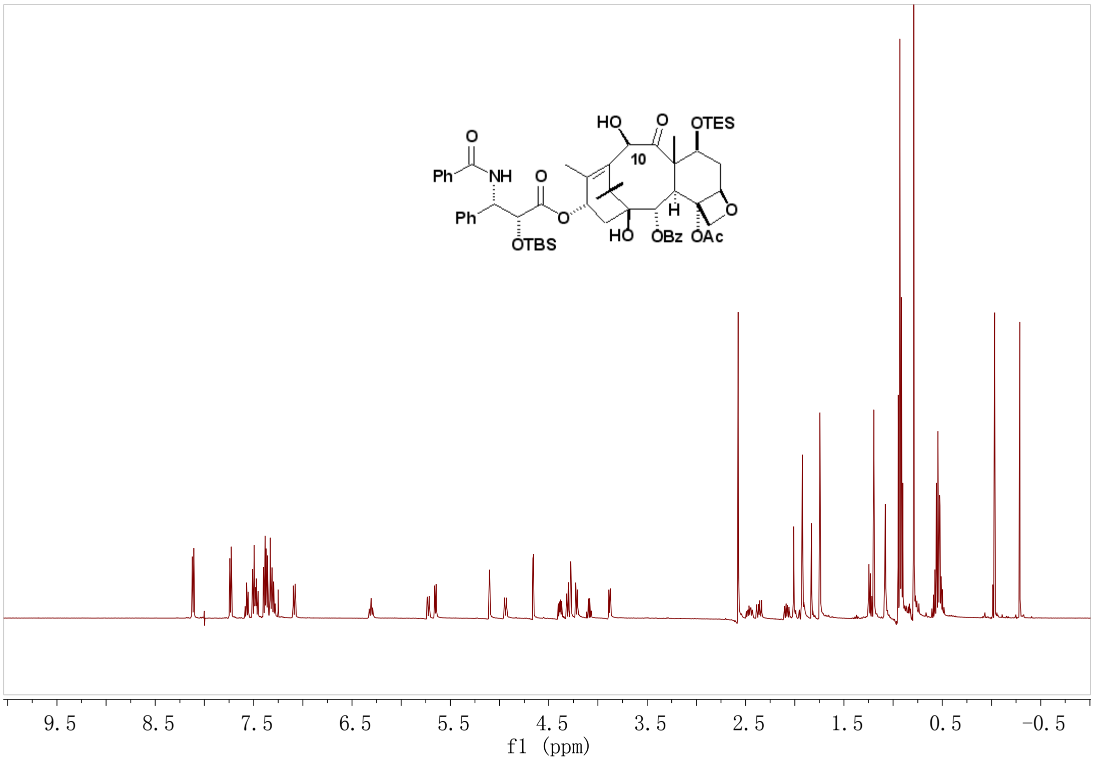
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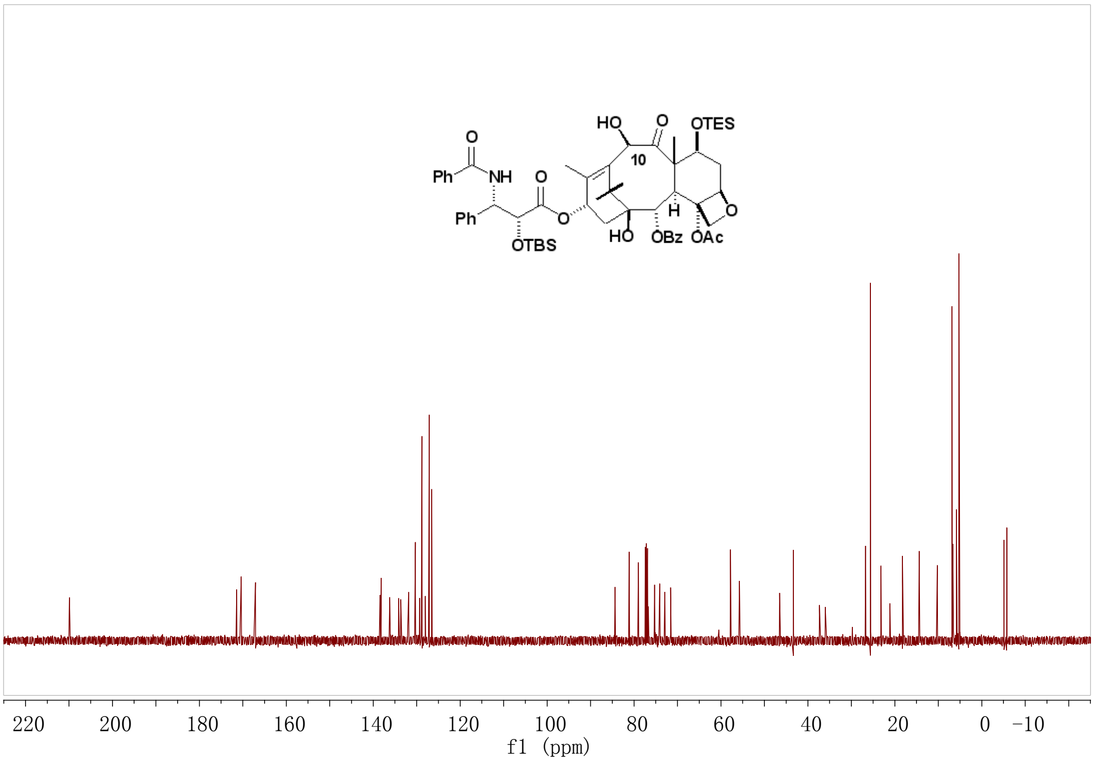
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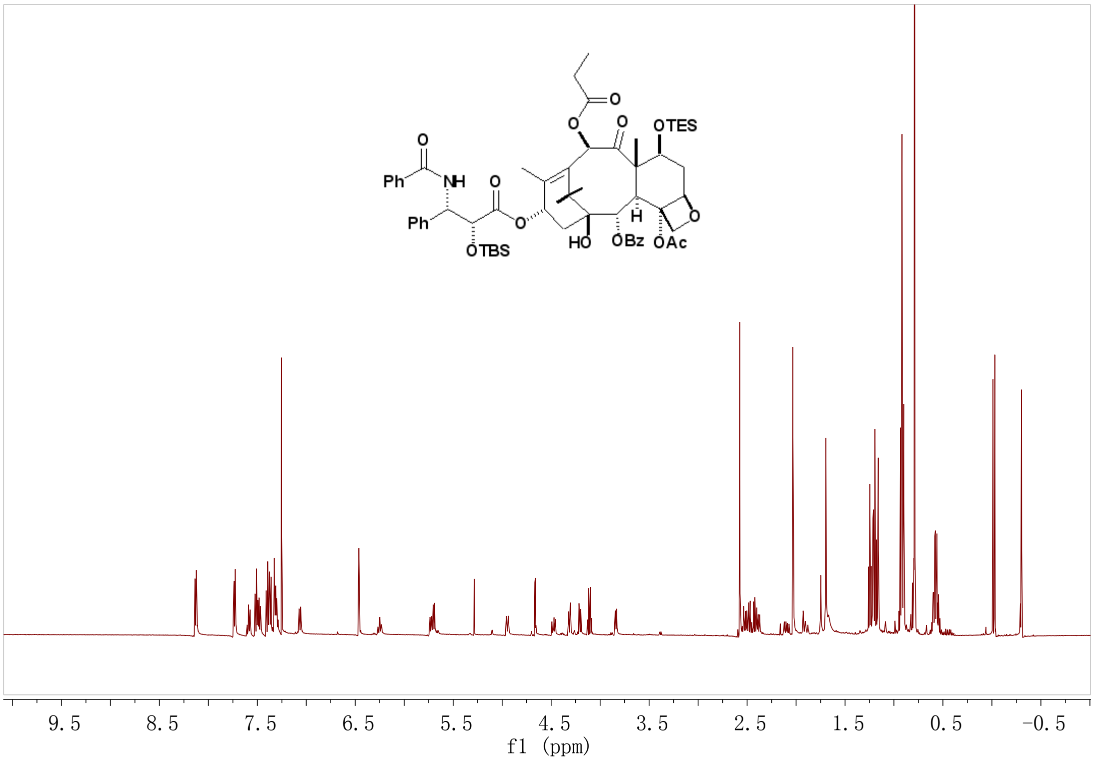
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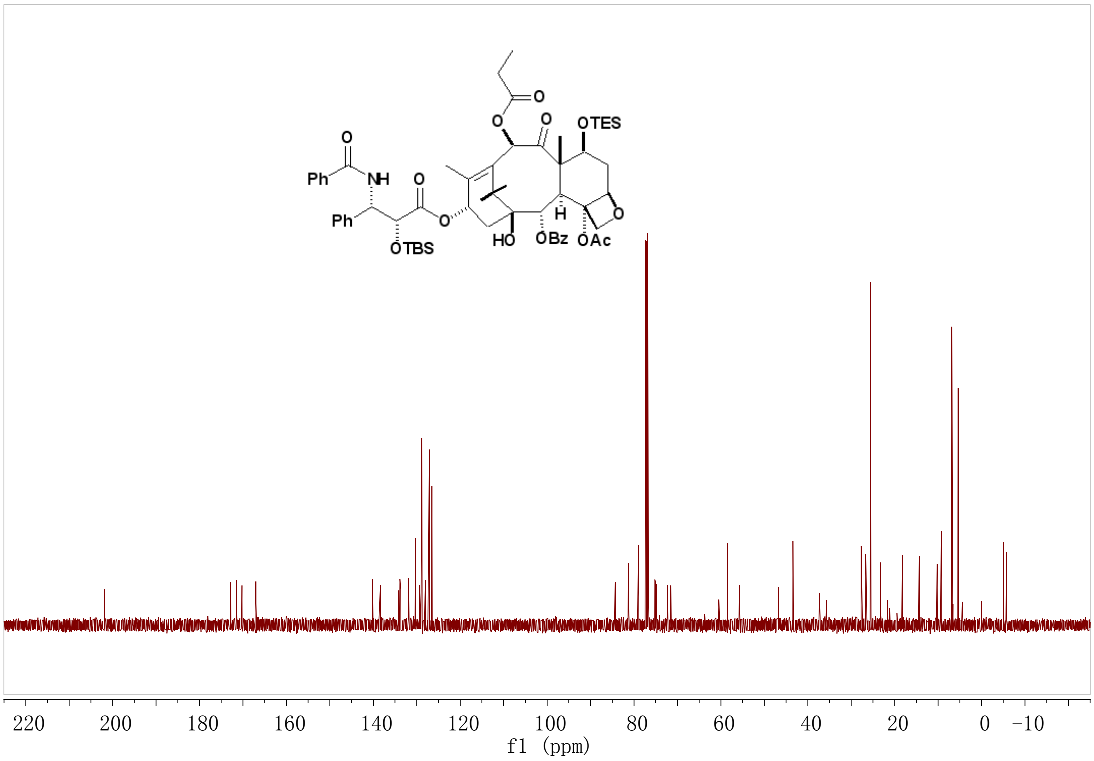
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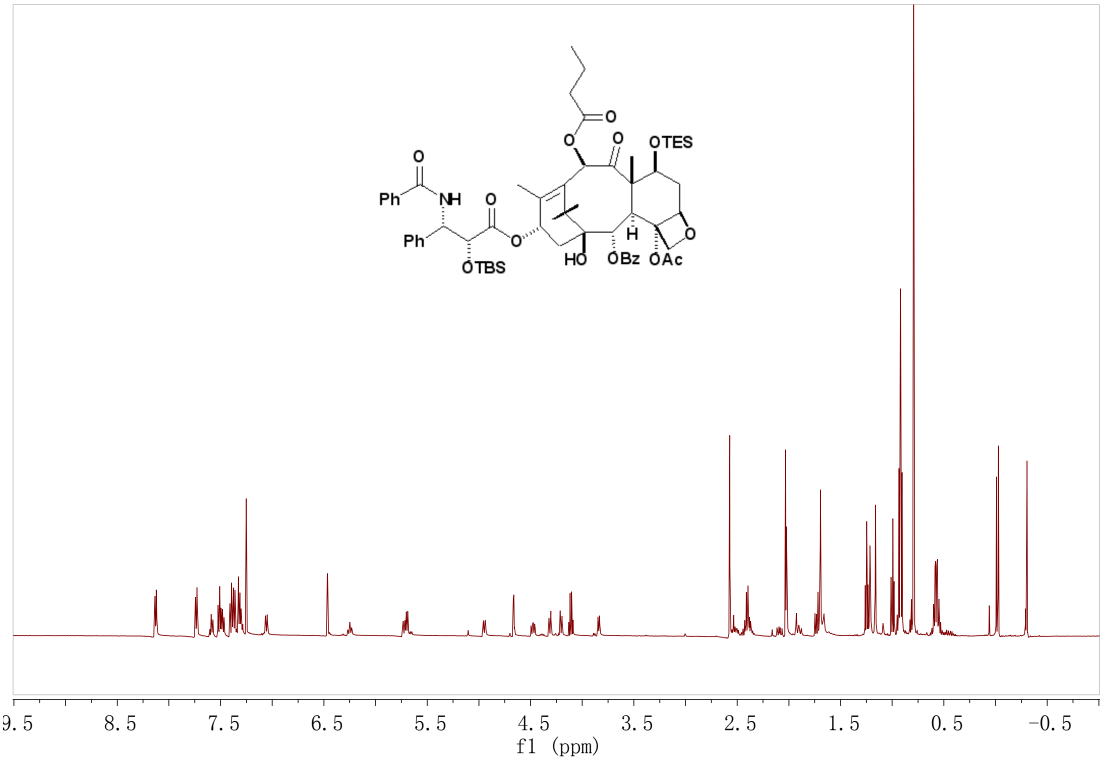
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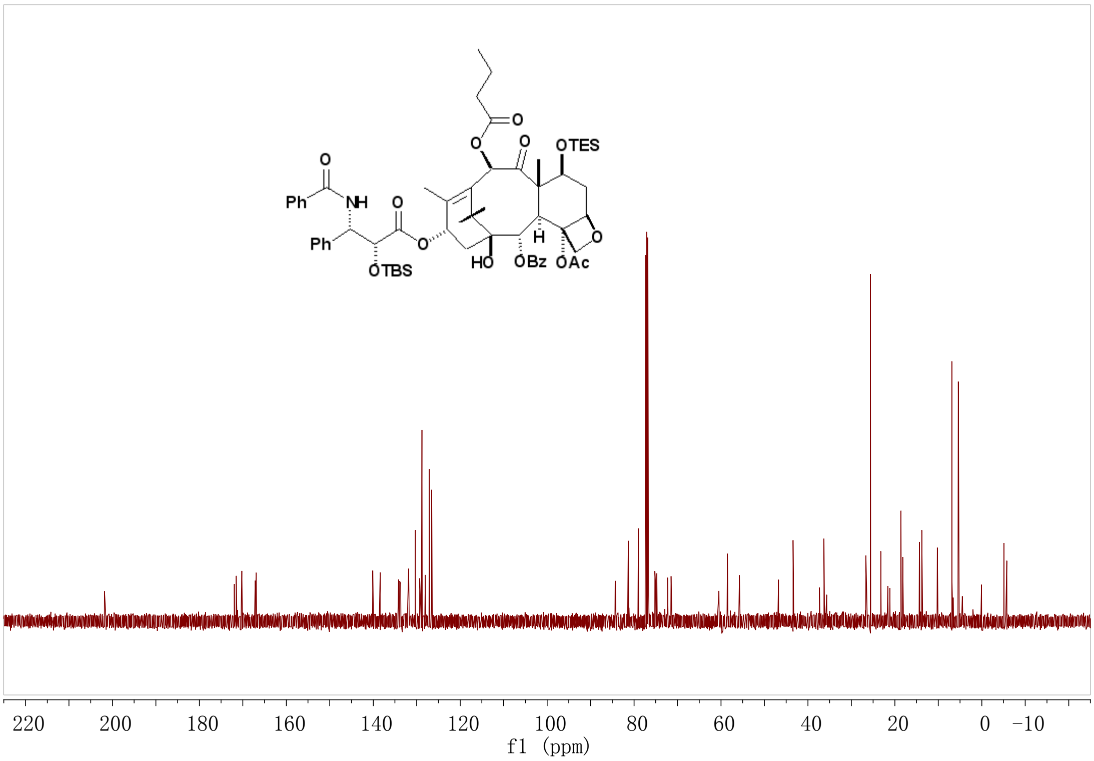
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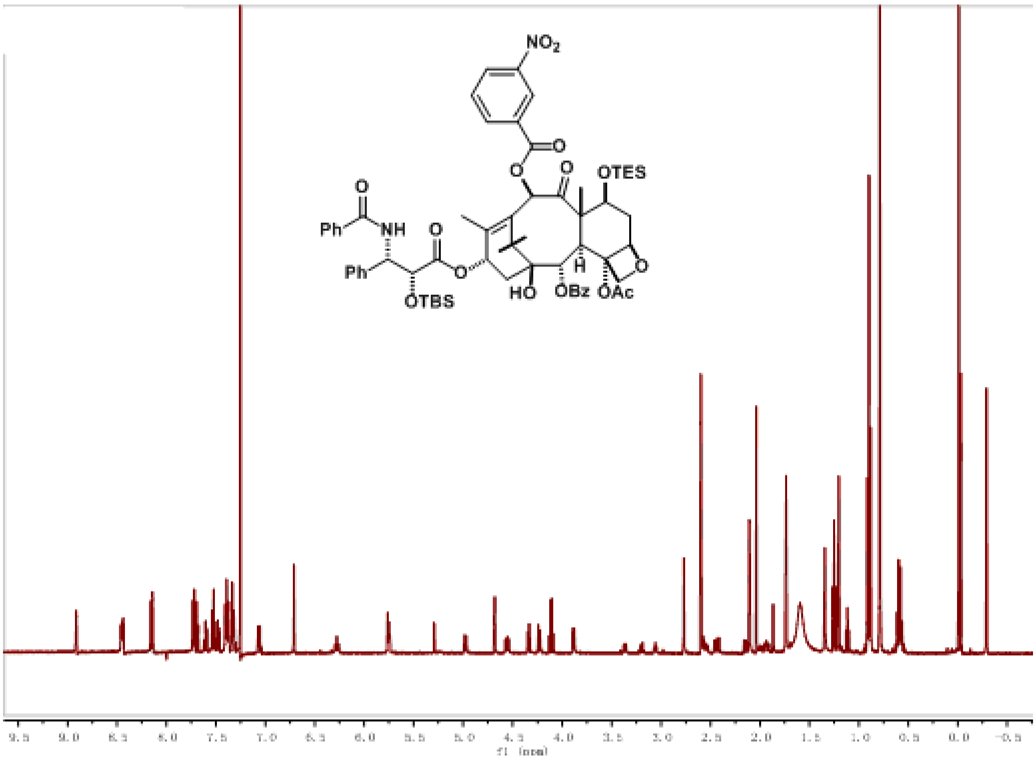
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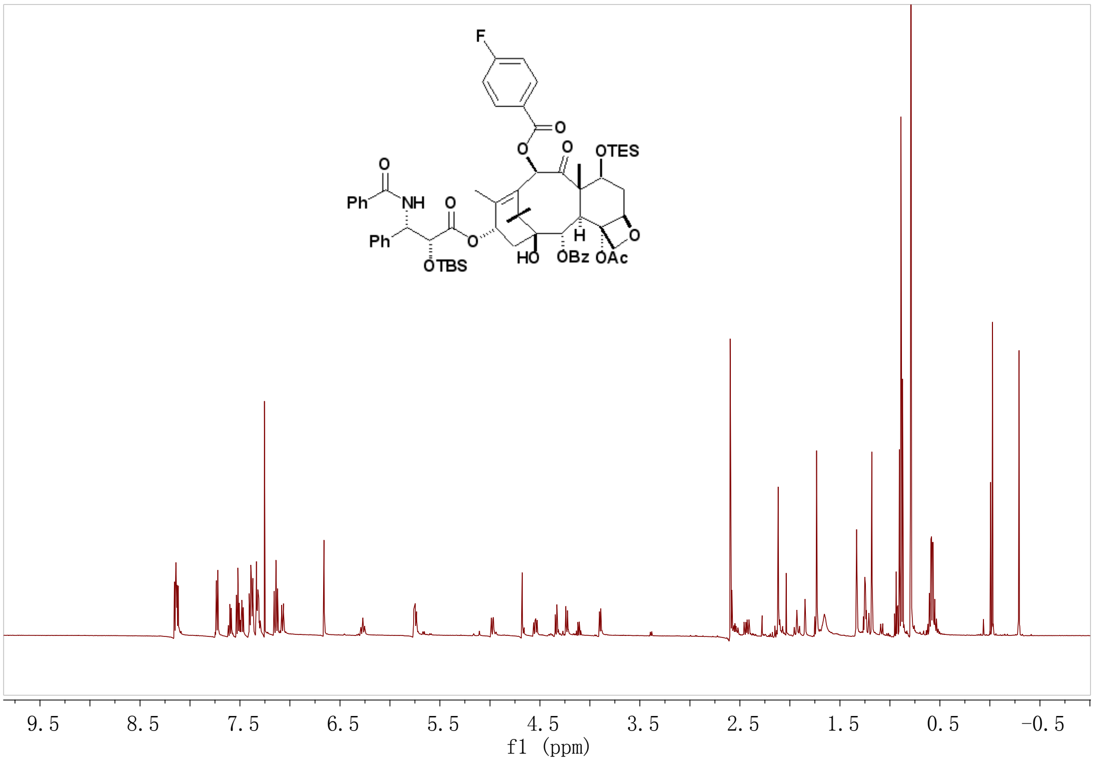
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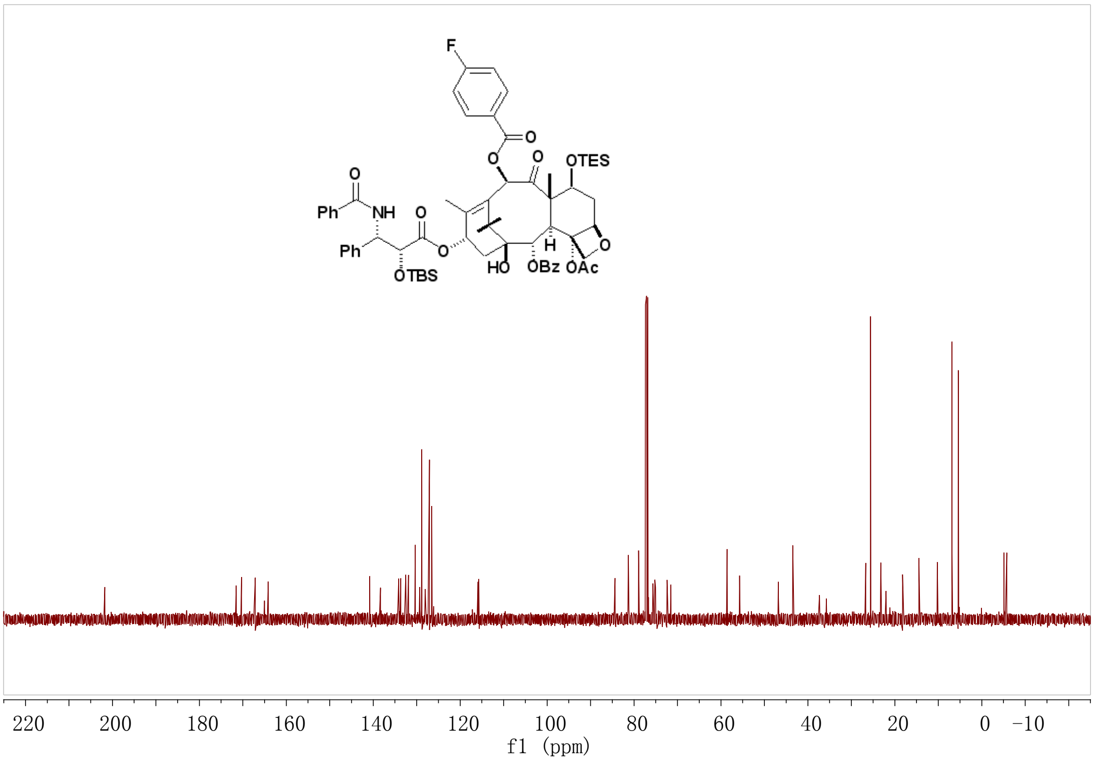
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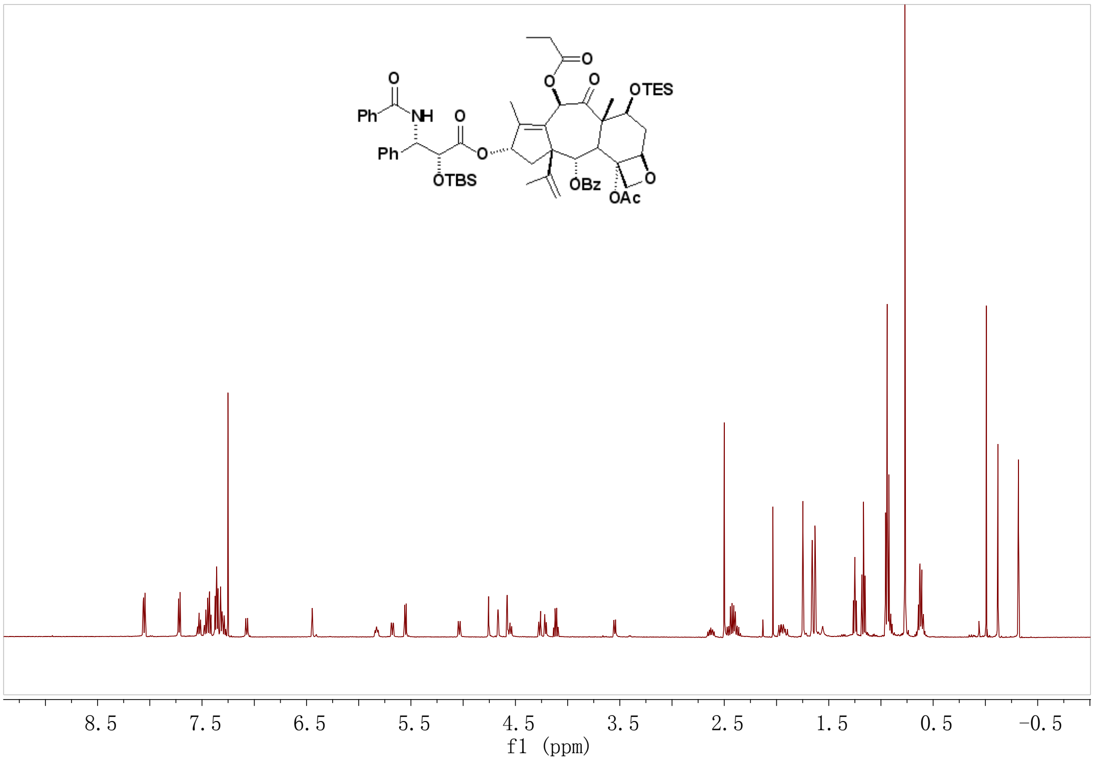
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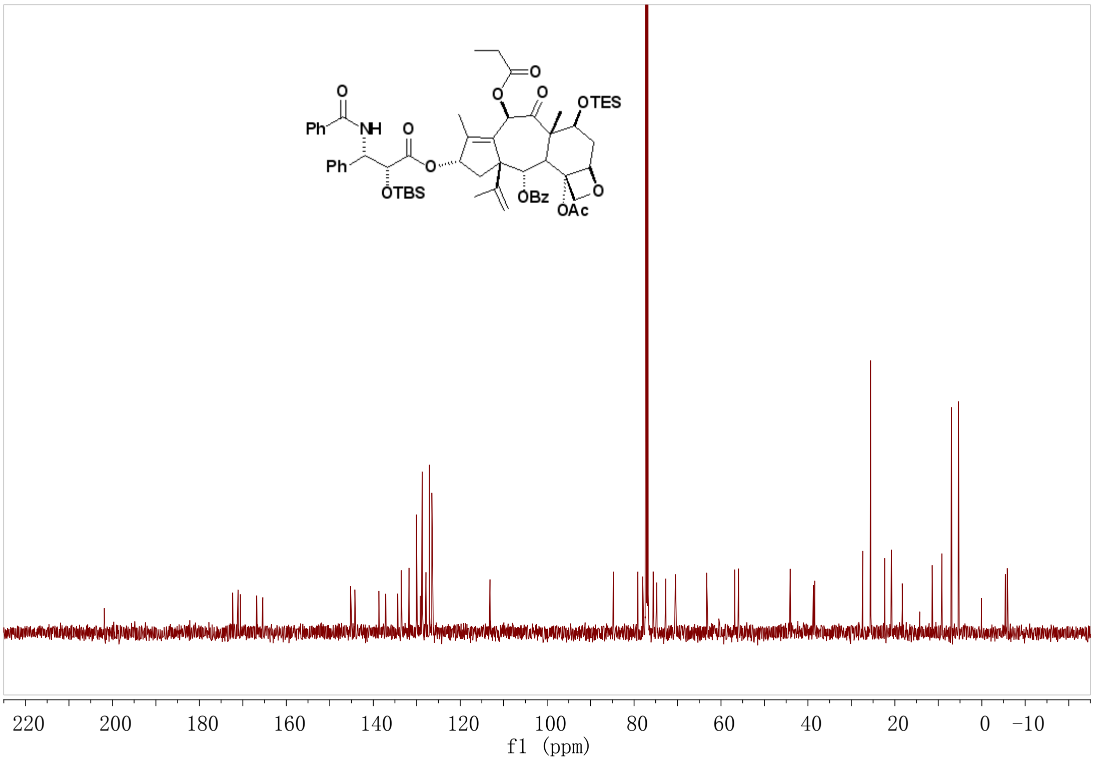
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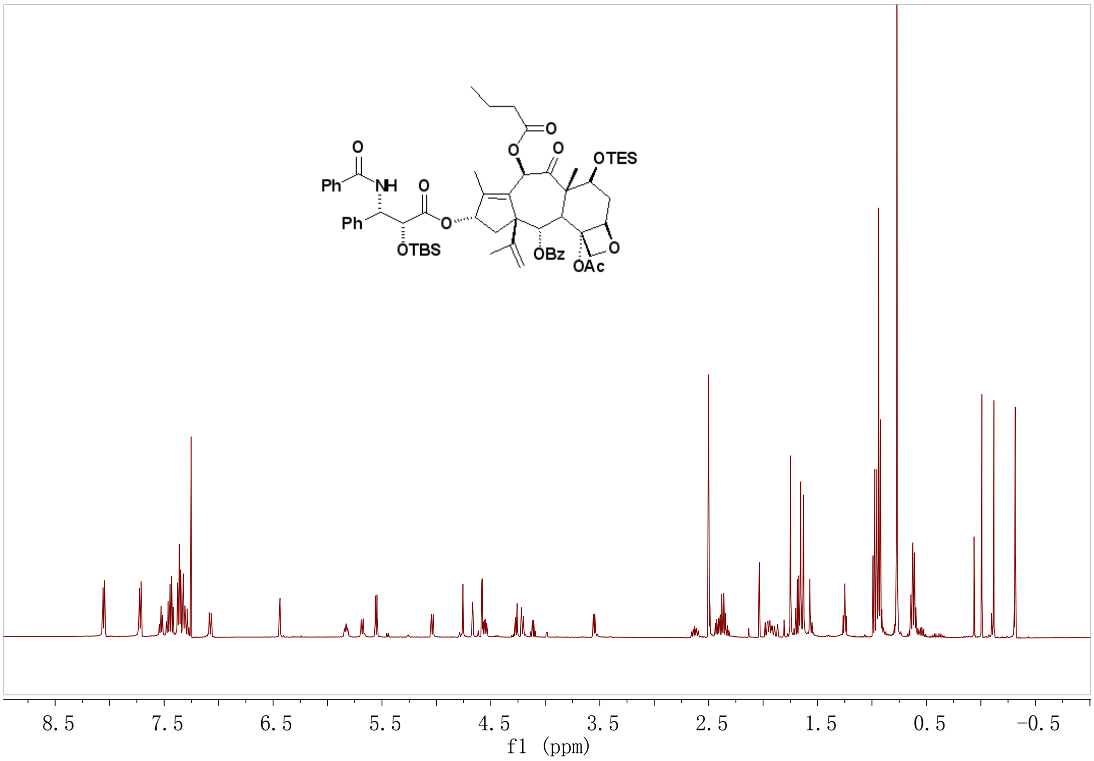
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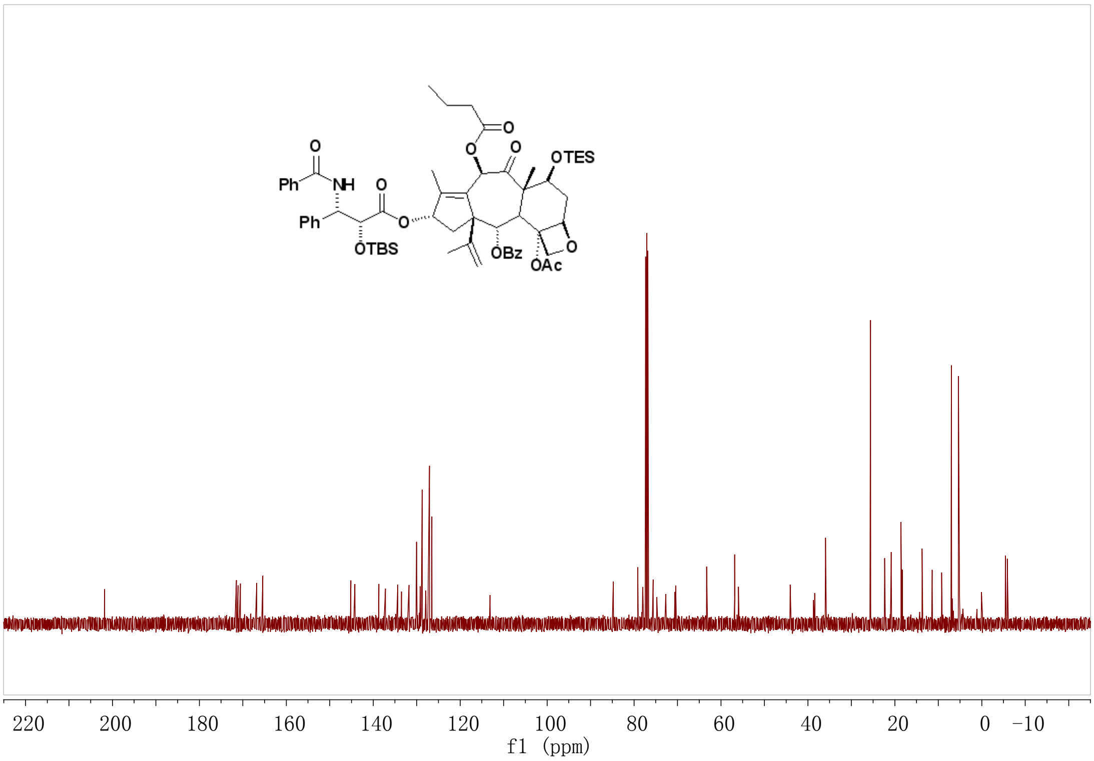
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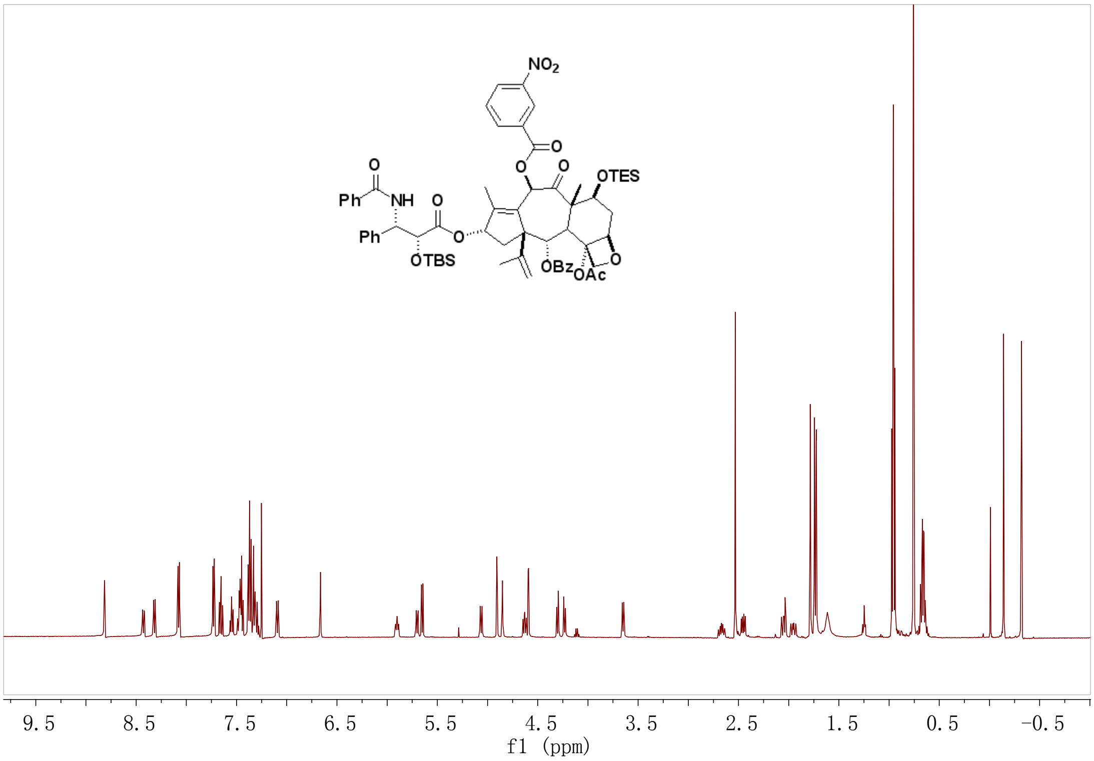
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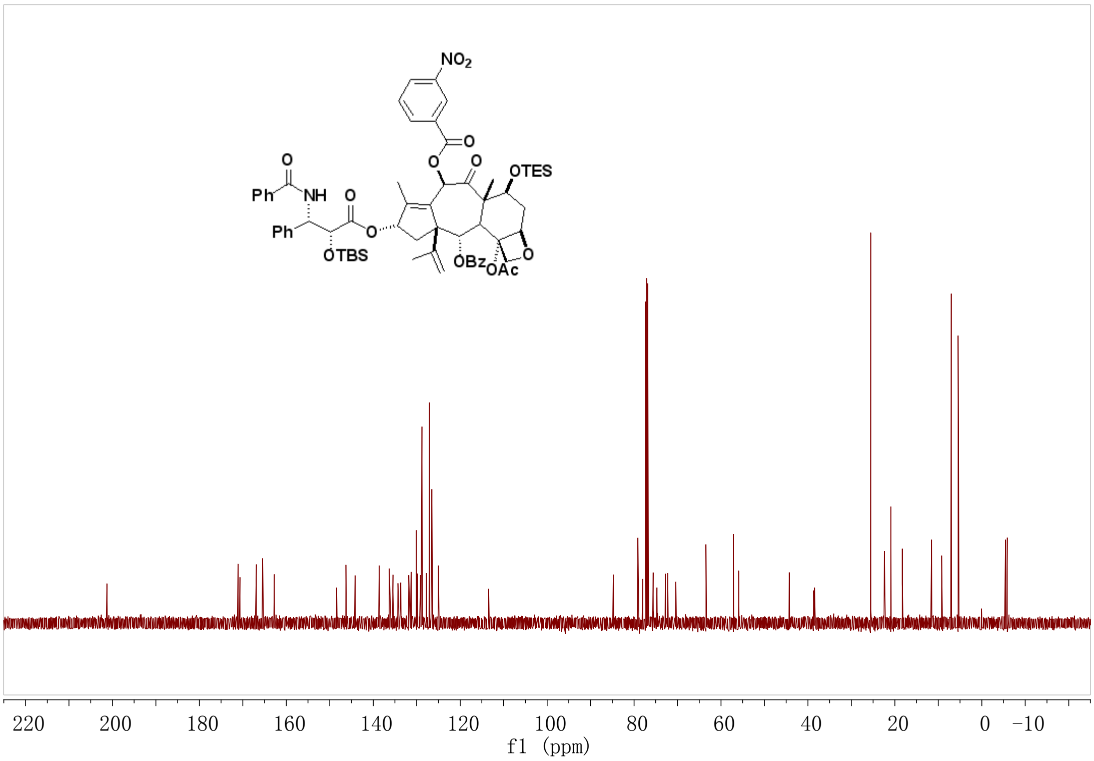
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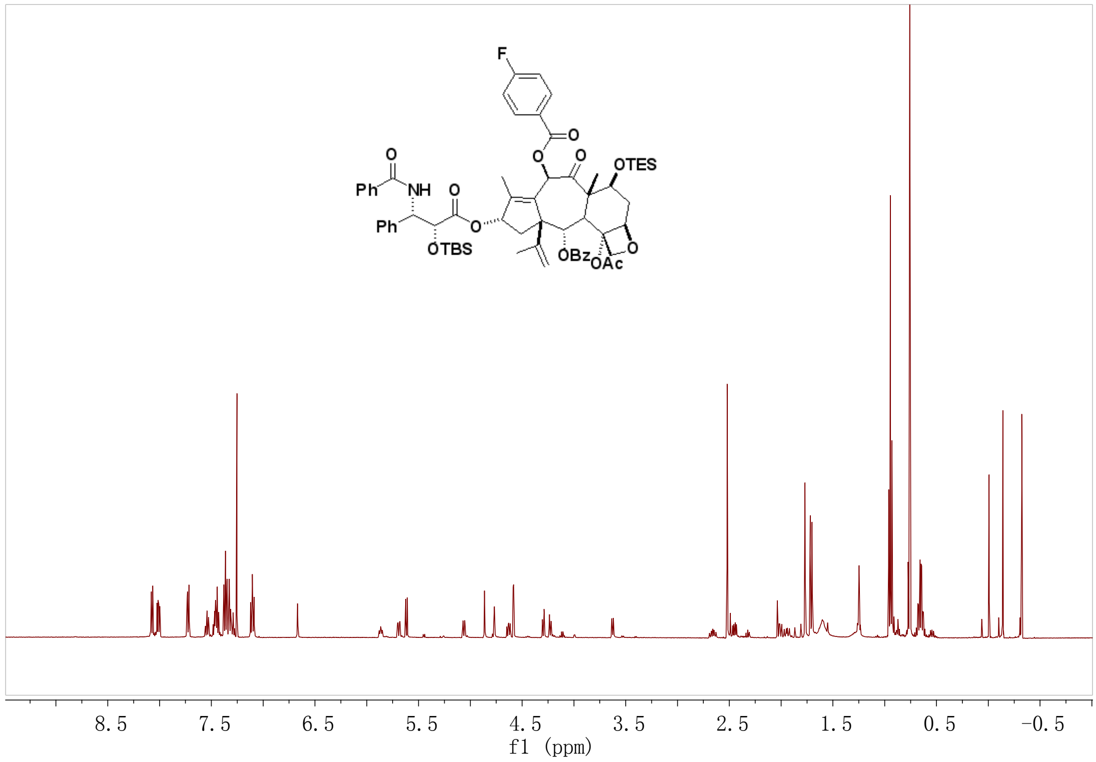
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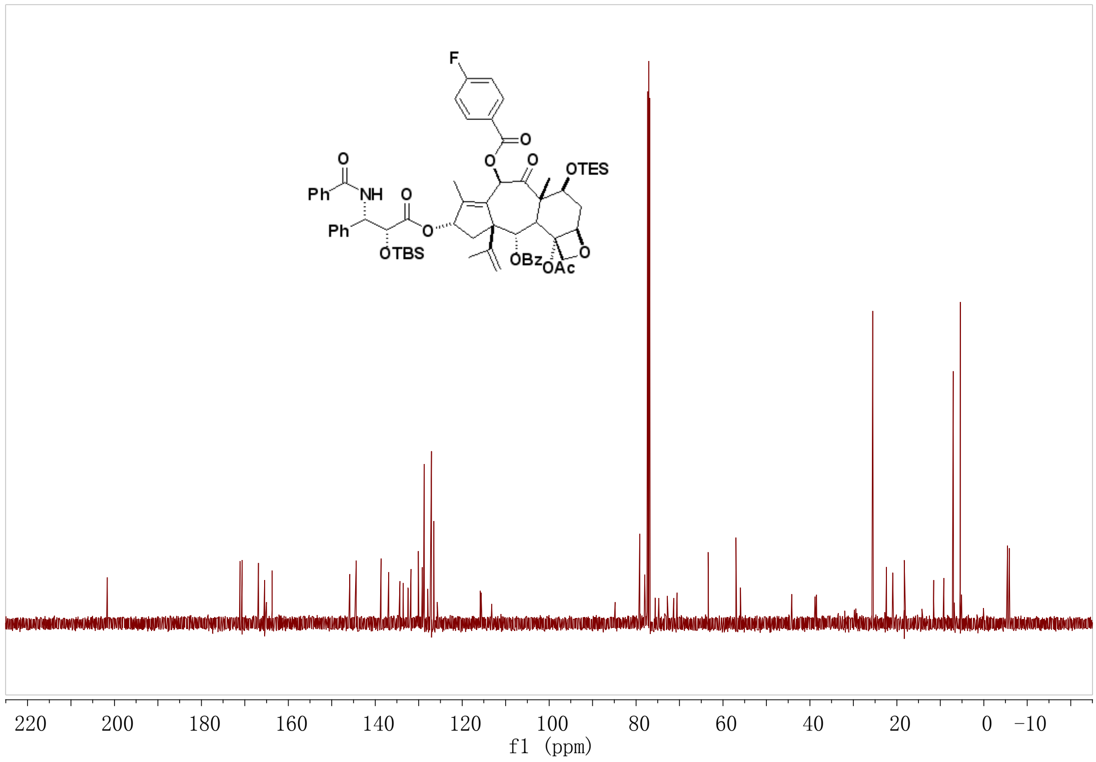
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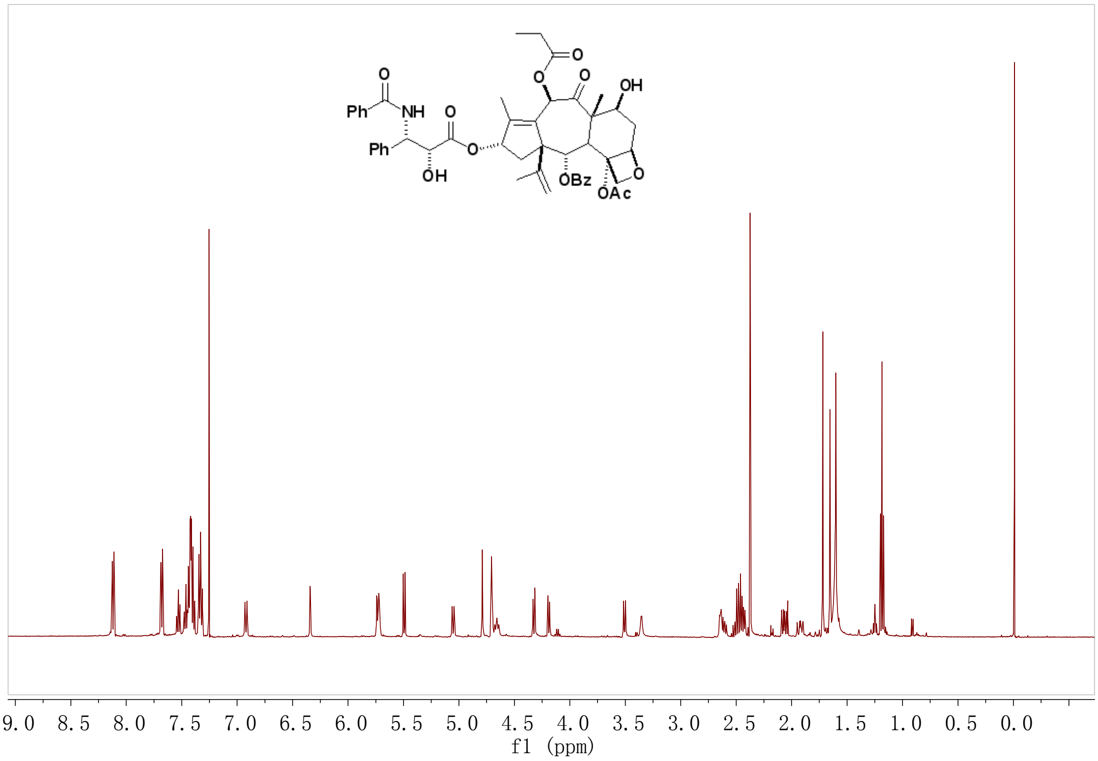
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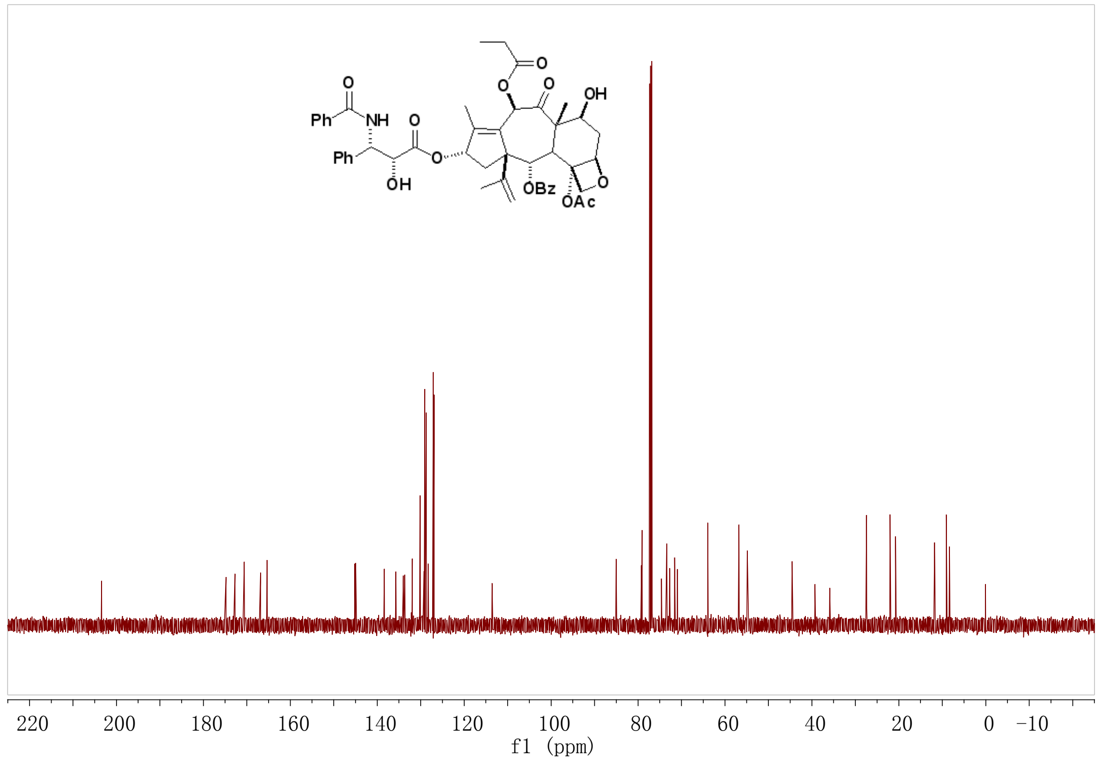
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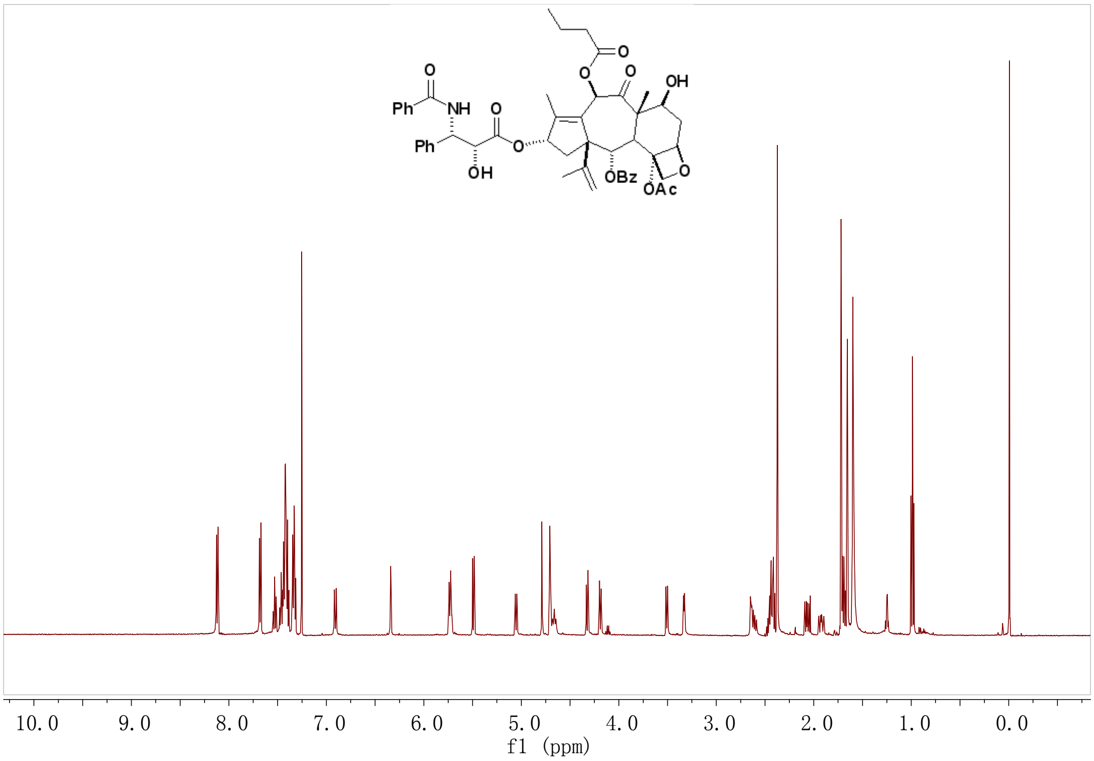
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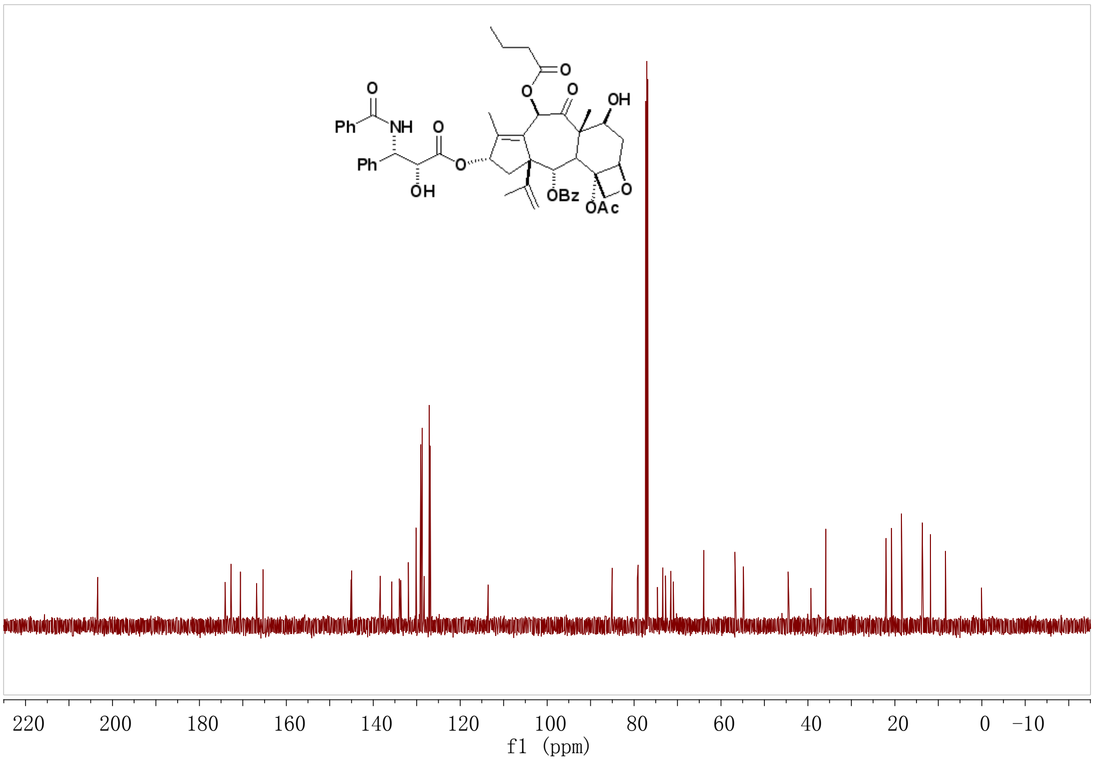
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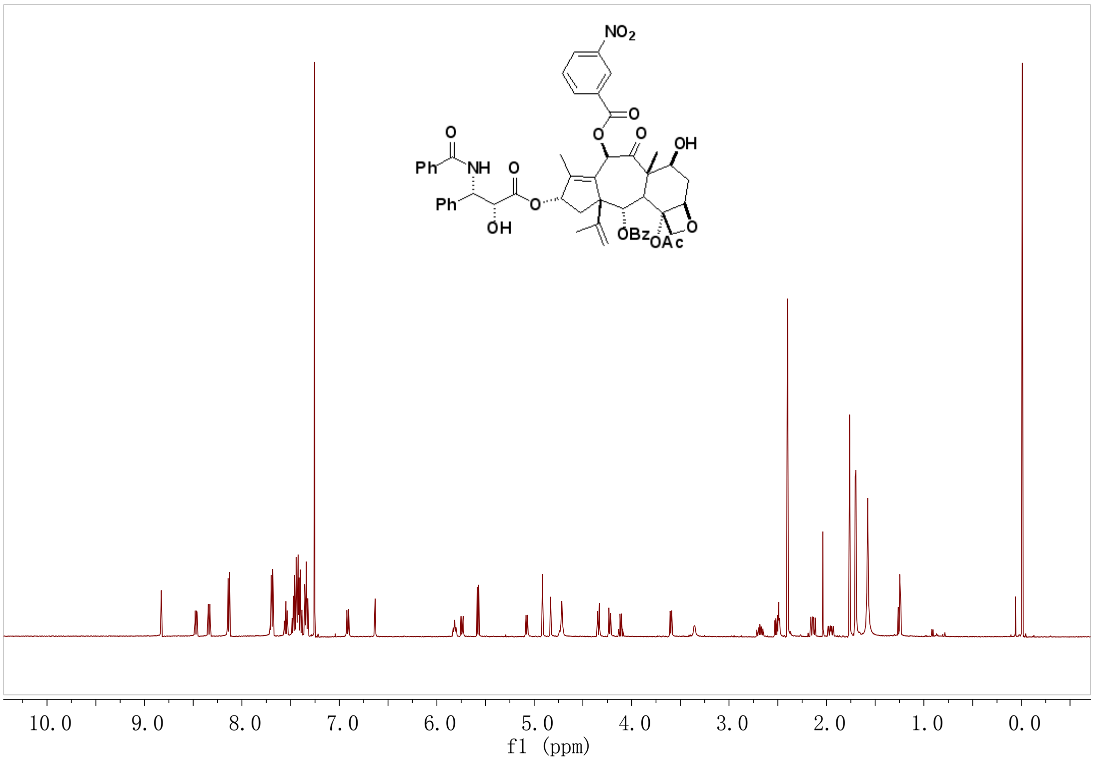
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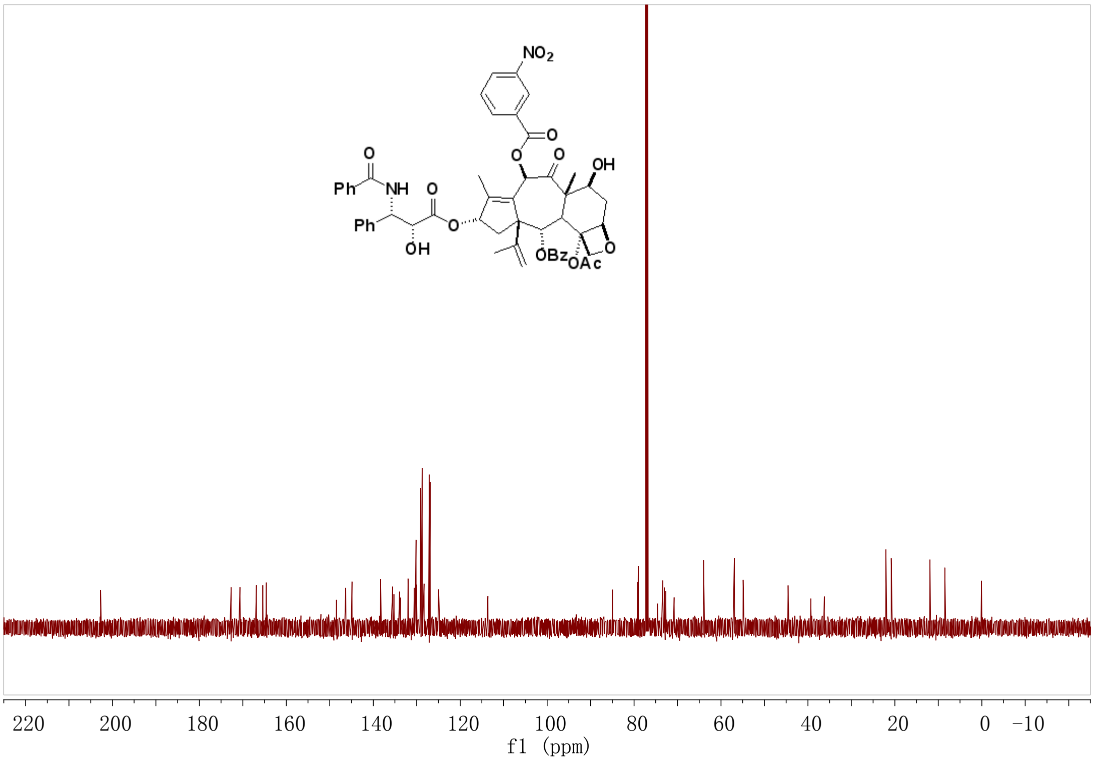
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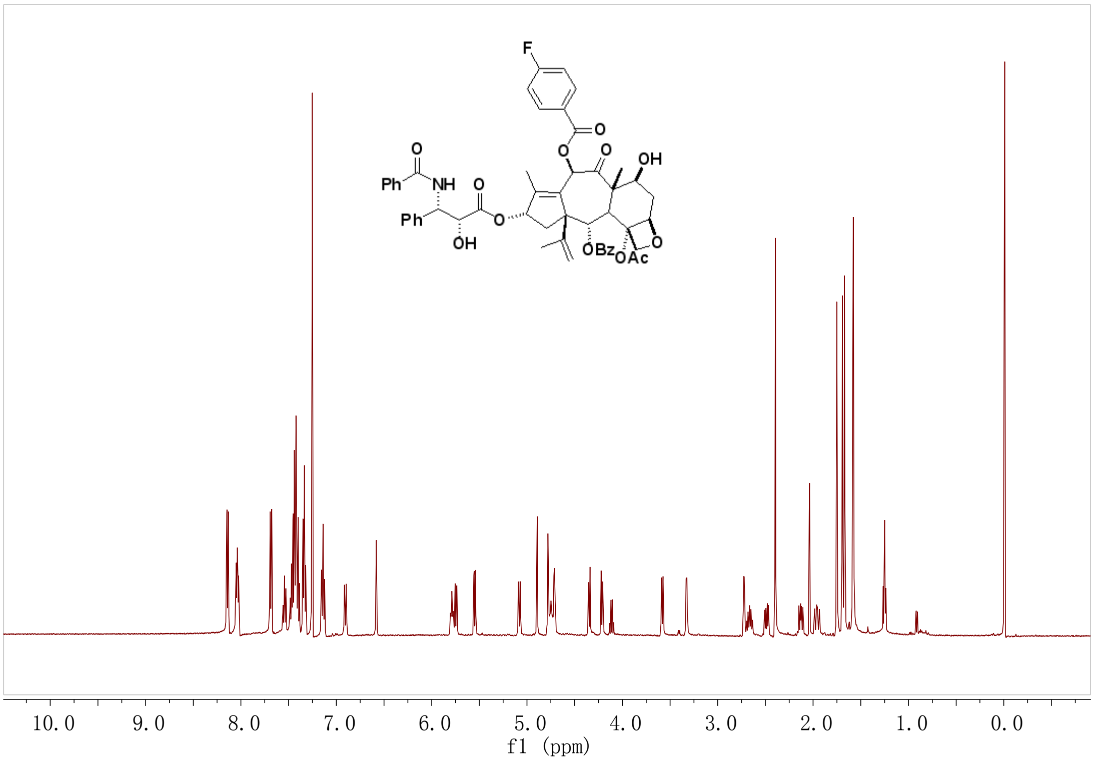
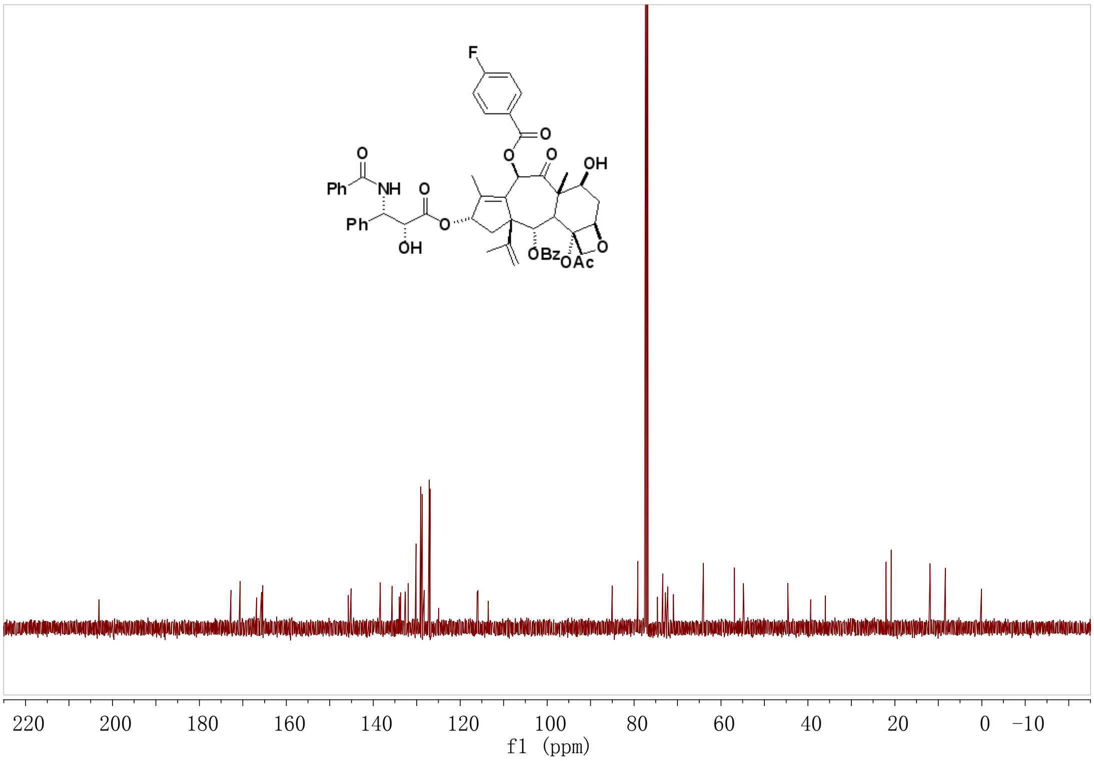
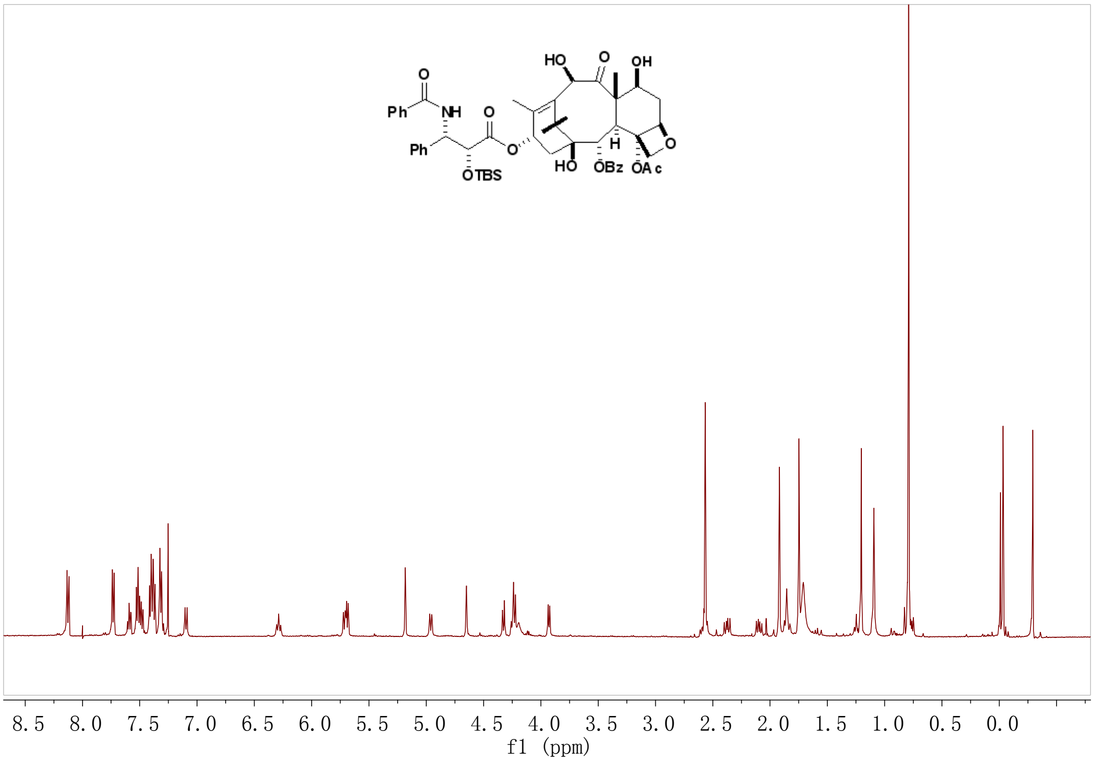
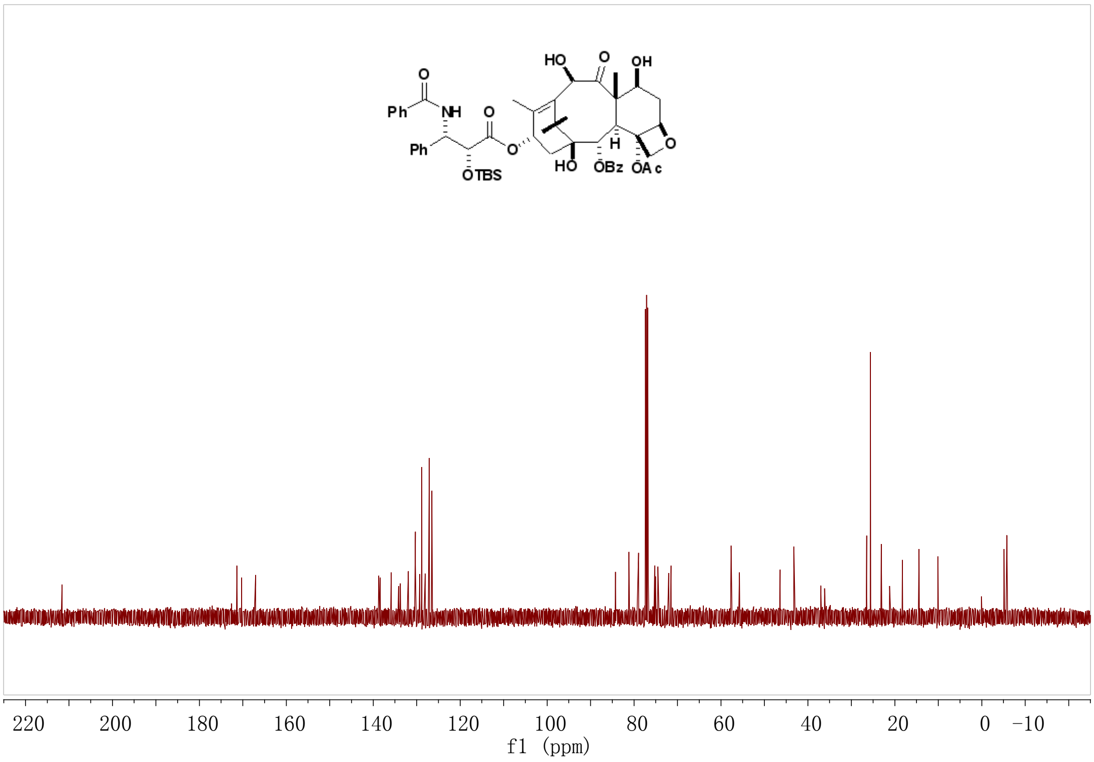
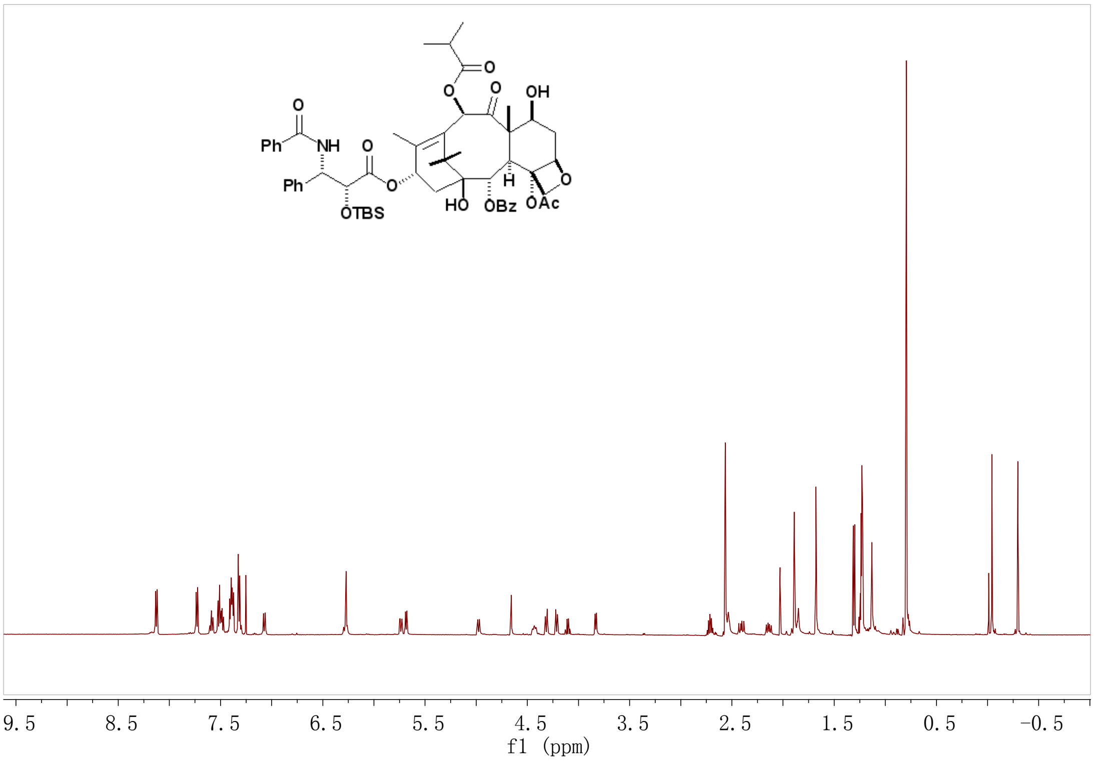
NH
O
Ph
O
OH
OBz
OAc
O
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

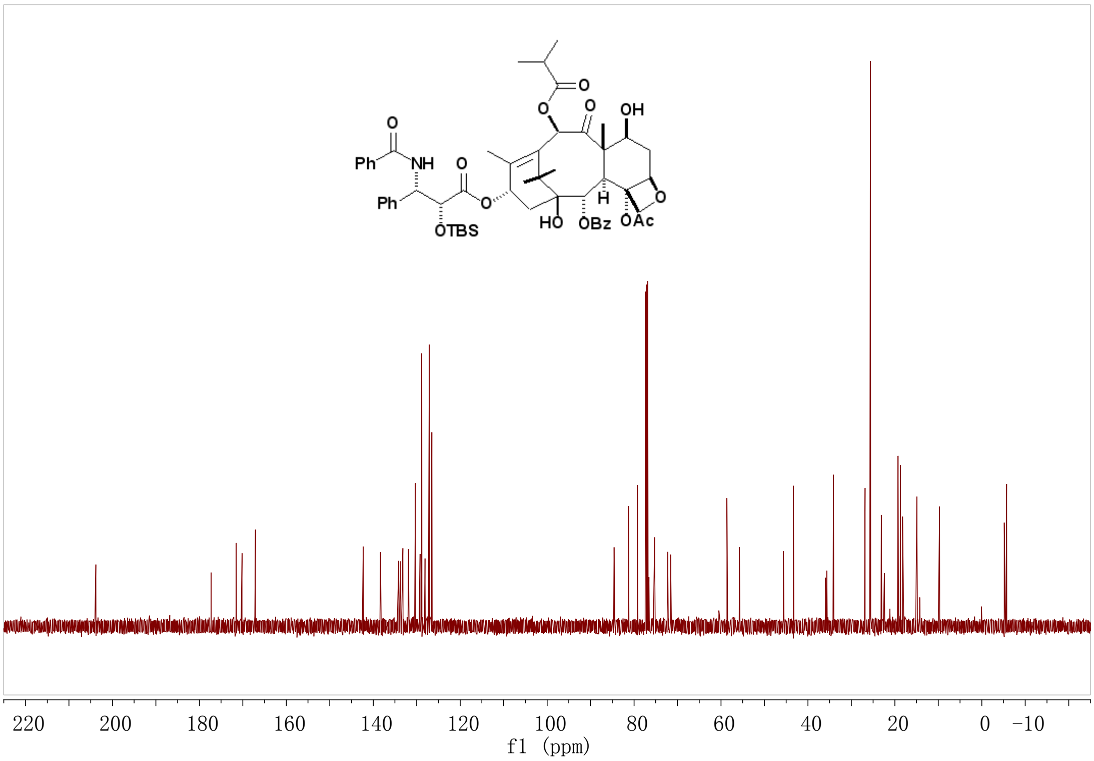

F
O
O
O
OH
O
Ph
NH
O
Ph
O
OH
OBz
OAc
O
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

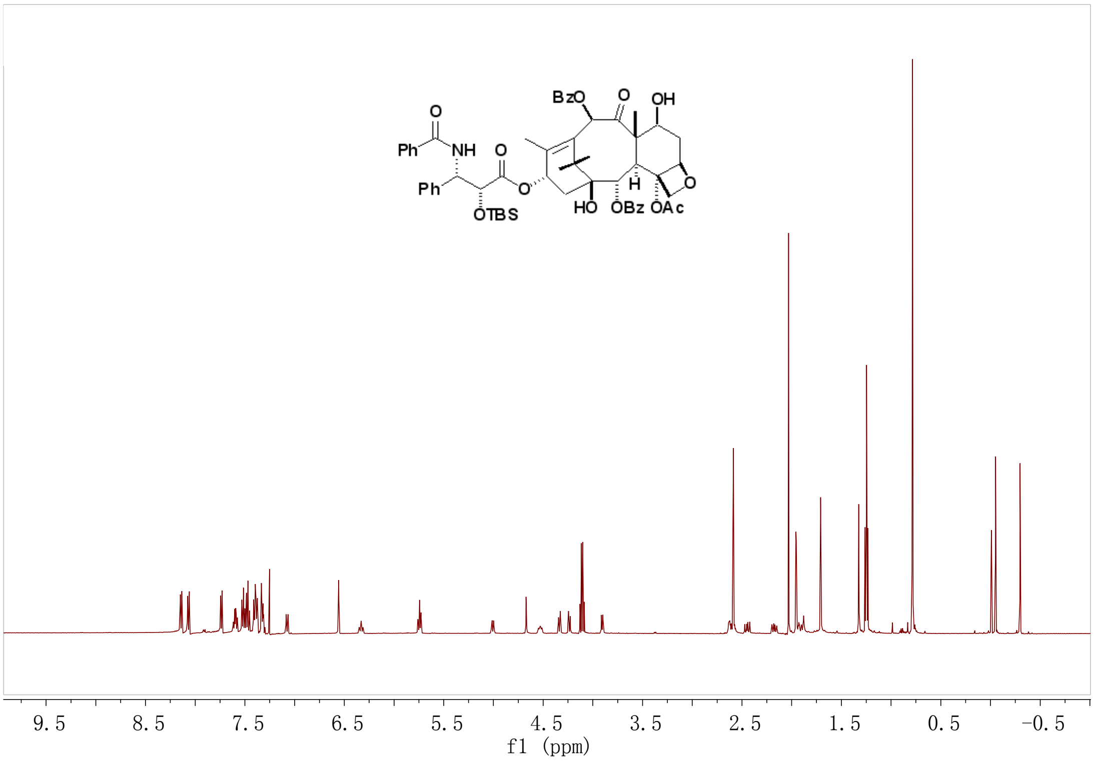

F
O
O
O
OH
O
Ph
NH
O
Ph
O
OH
OBz
OAc
O
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

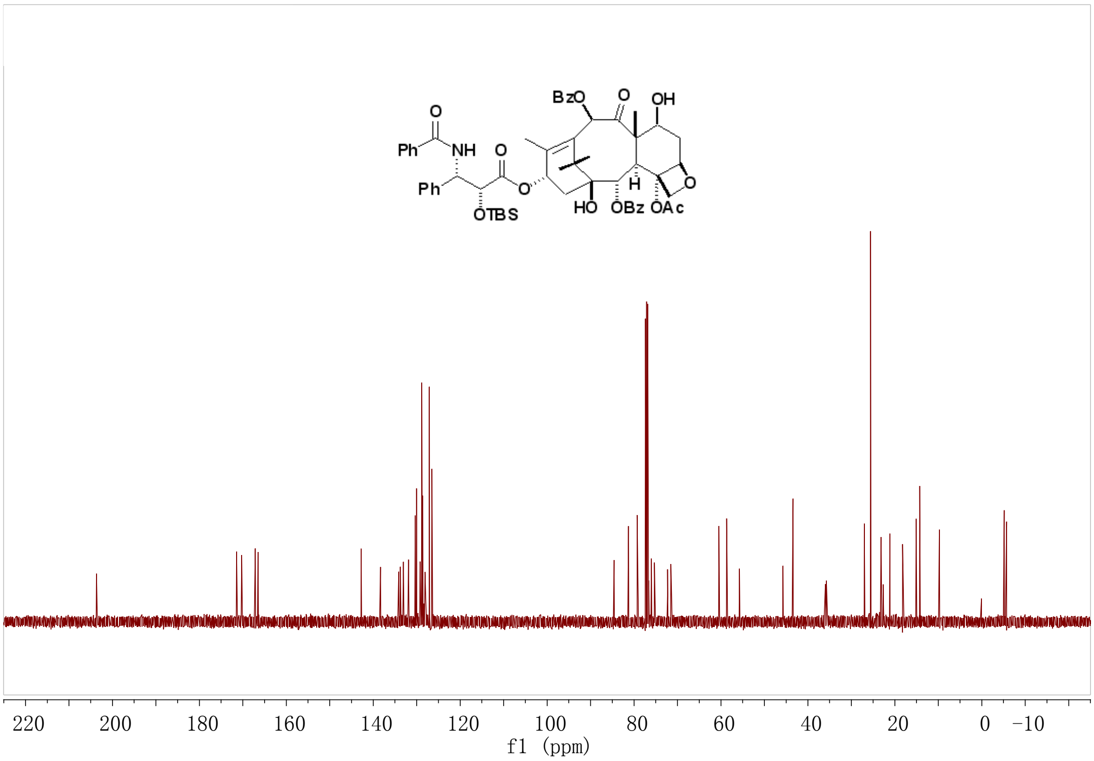

HO
O
OH
O
Ph
NH
O
Ph
O
H
O
OTBS
HO
OBz
OAc
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

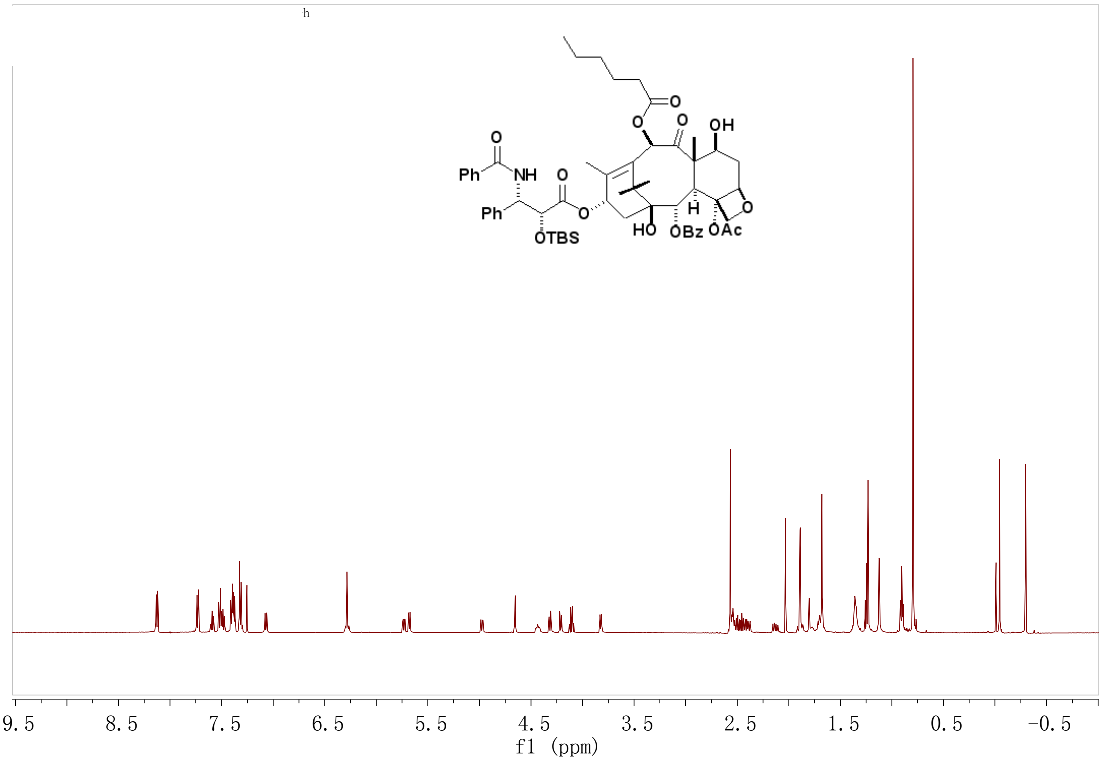

HO
O
OH
O
Ph
NH
O
Ph
O
H
O
OTBS
HO
OBz
OAc
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)


O
OH
O
O
O
Ph
NH
O
Ph
O
H
O
OTBS
HO
OBz
OAc
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
−0.5
f1 (ppm)


O
OH
O
O
O
Ph
NH
O
Ph
O
H
O
OTBS
HO
OBz
OAc
220
200
180
160
140
120
100
80
60
40
20
0
−10
f1 (ppm)


BzO
O
OH
O
Ph
NH
O
Ph
O
H
O
OTBS
HO
OBz
OAc
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
−0.5
f1 (ppm)


BzO
O
OH
O
Ph
NH
O
Ph
O
H
O
OTBS
HO
OBz
OAc
220
200
180
160
140
120
100
80
60
40
20
0
−10
f1 (ppm)


h
O
O
O
OH
O
Ph
NH
O
Ph
O
H
O
OTBS
HO
OBz
OAc
9.5
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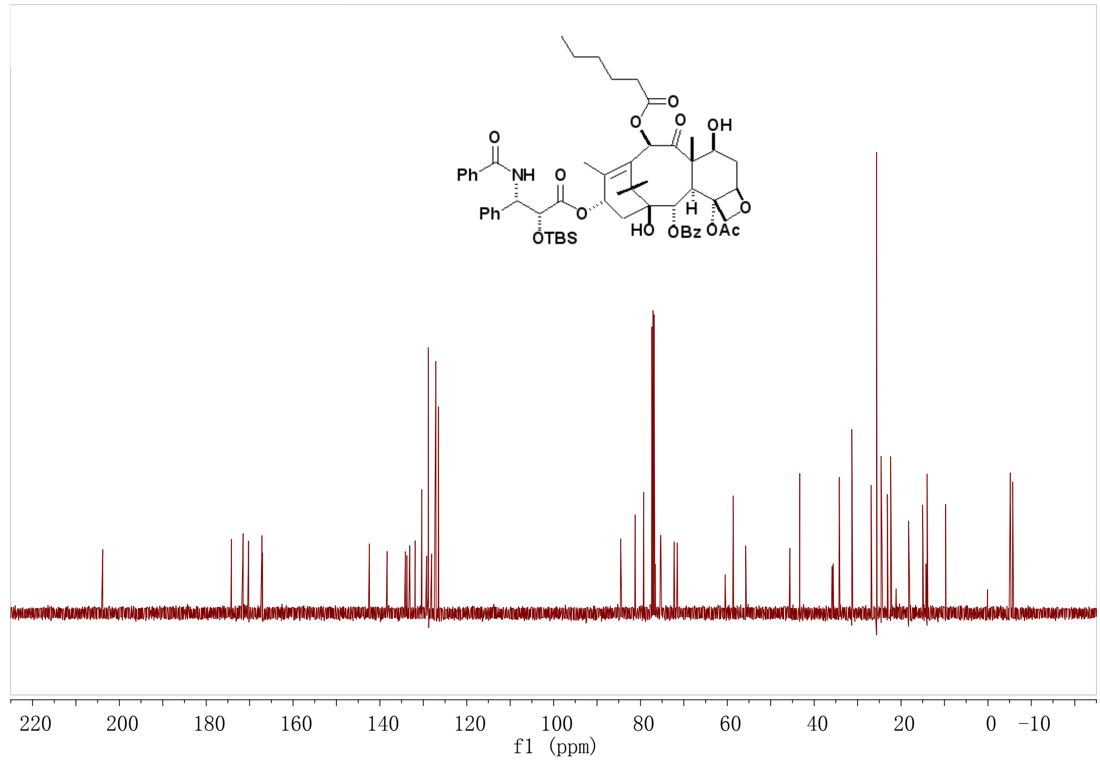
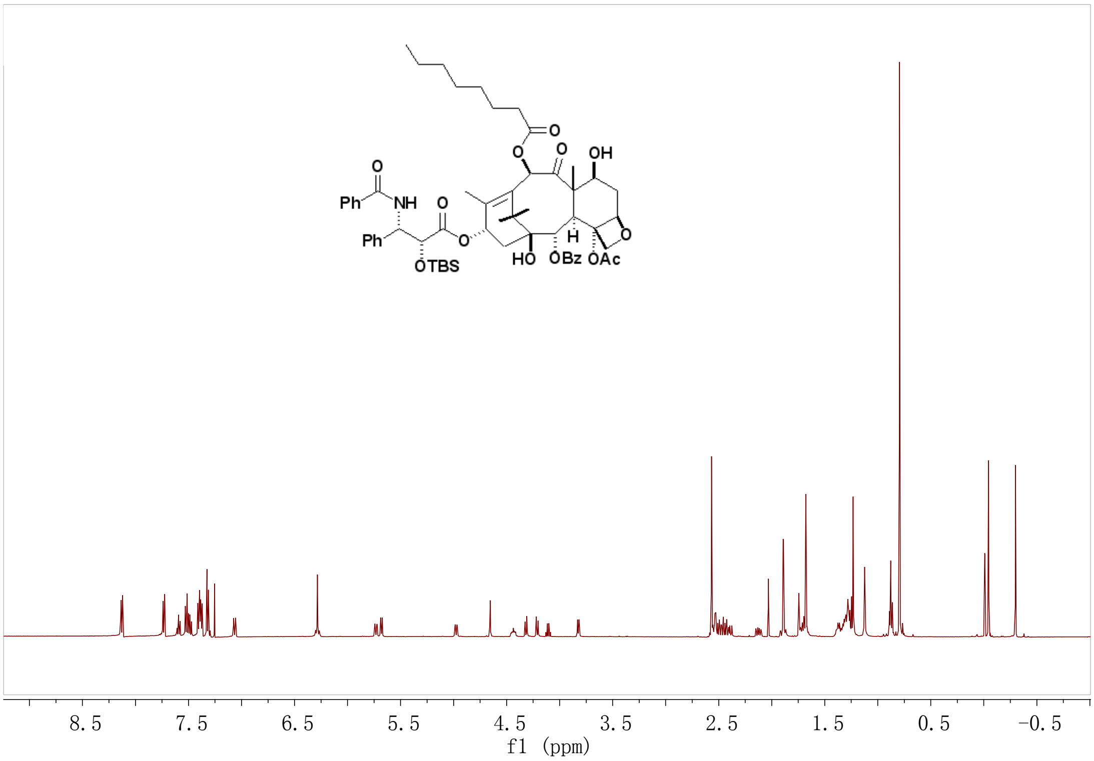
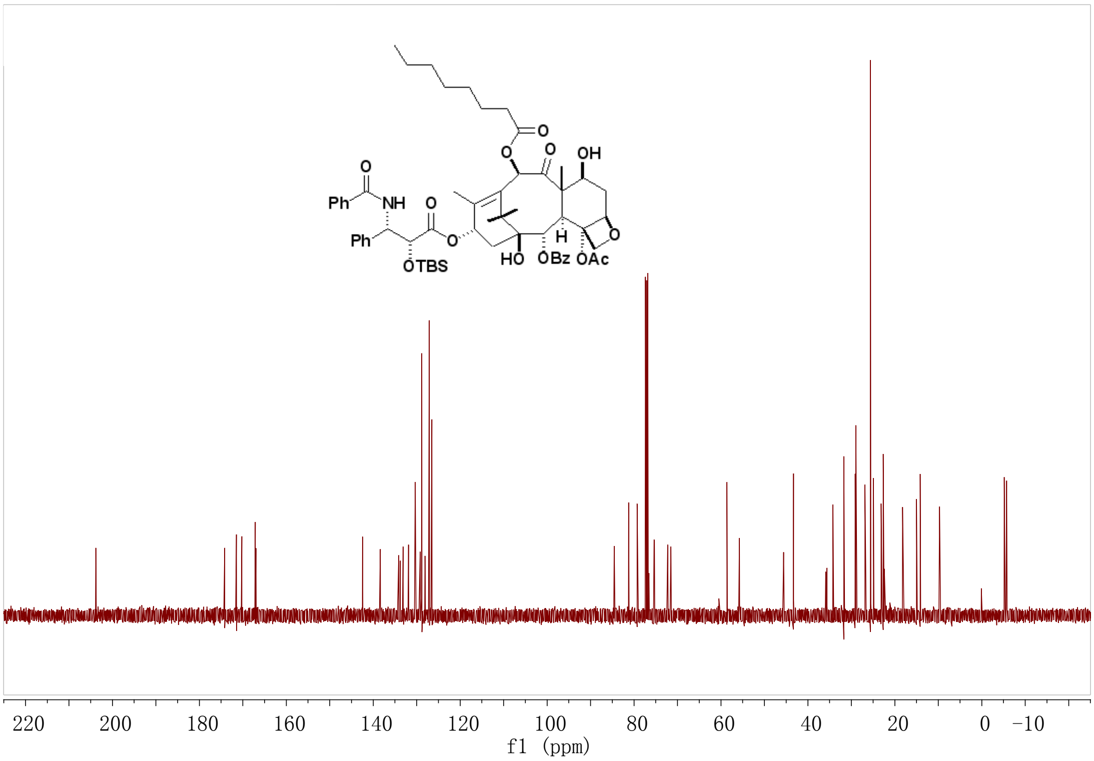
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

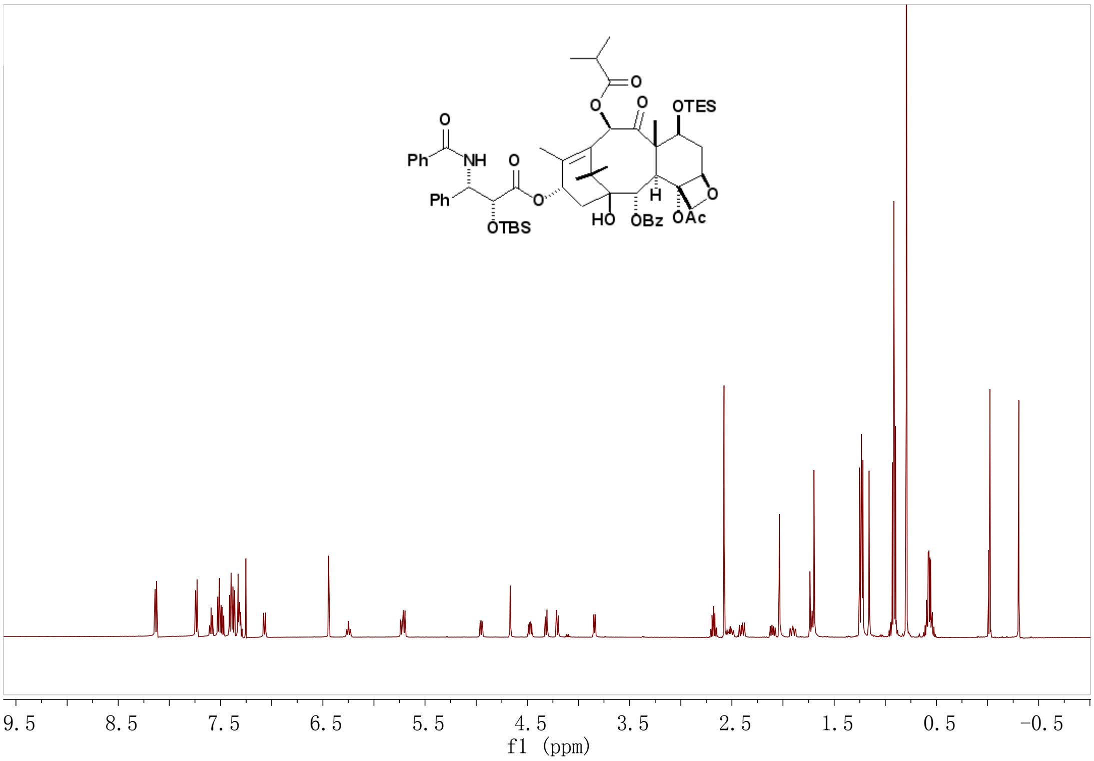

O
O
O
OH
O
Ph
NH
O
Ph
O
H
O
OTBS
HO
OBz
OAc
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

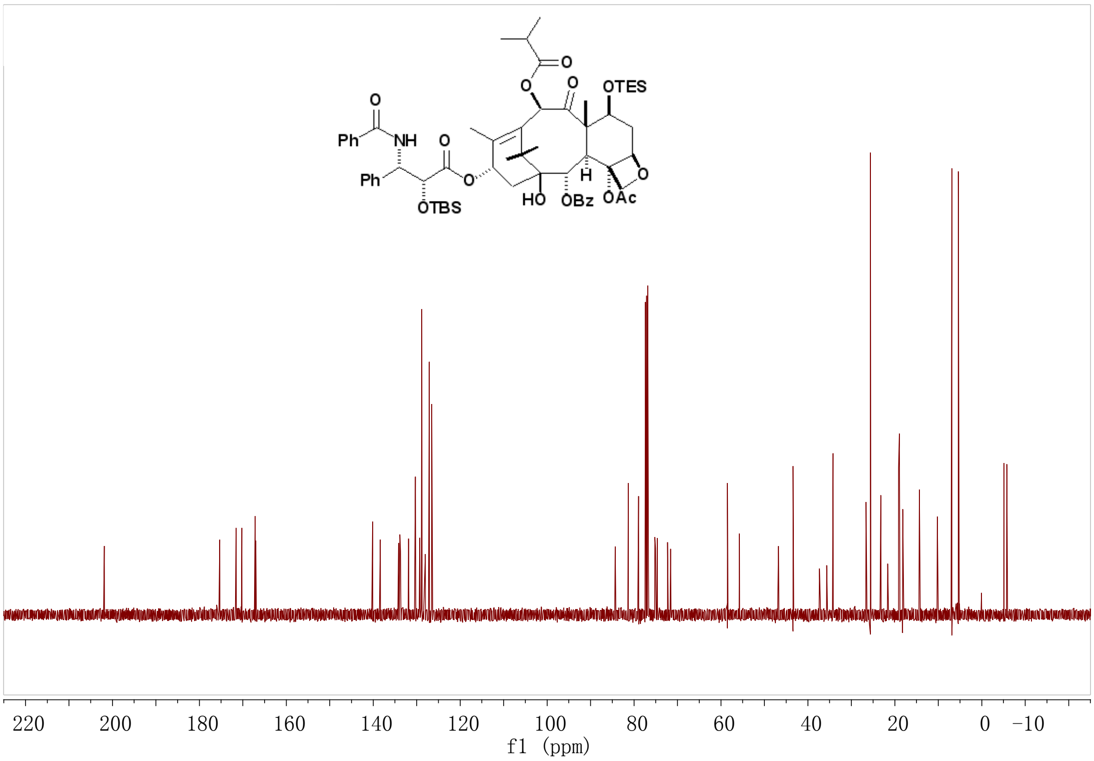


O
OH
O
O
O
Ph
NH
O
Ph
O
OTBS
H
O
HO
OBz
OAc
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
−0.5
f1 (ppm)



O
OH
O
O
O
Ph
NH
O
Ph
O
OTBS
H
O
HO
OBz
OAc
220
200
180
160
140
120
100
80
60
40
20
0
−10
f1 (ppm)


Ph
NH
O
O
Ph
OTBS
O
O
O
O
OTES
H
HO
OBz
OAc
O
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)


Ph
NH
O
O
Ph
OTBS
O
O
O
O
OTES
H
HO
OBz
OAc
O
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200
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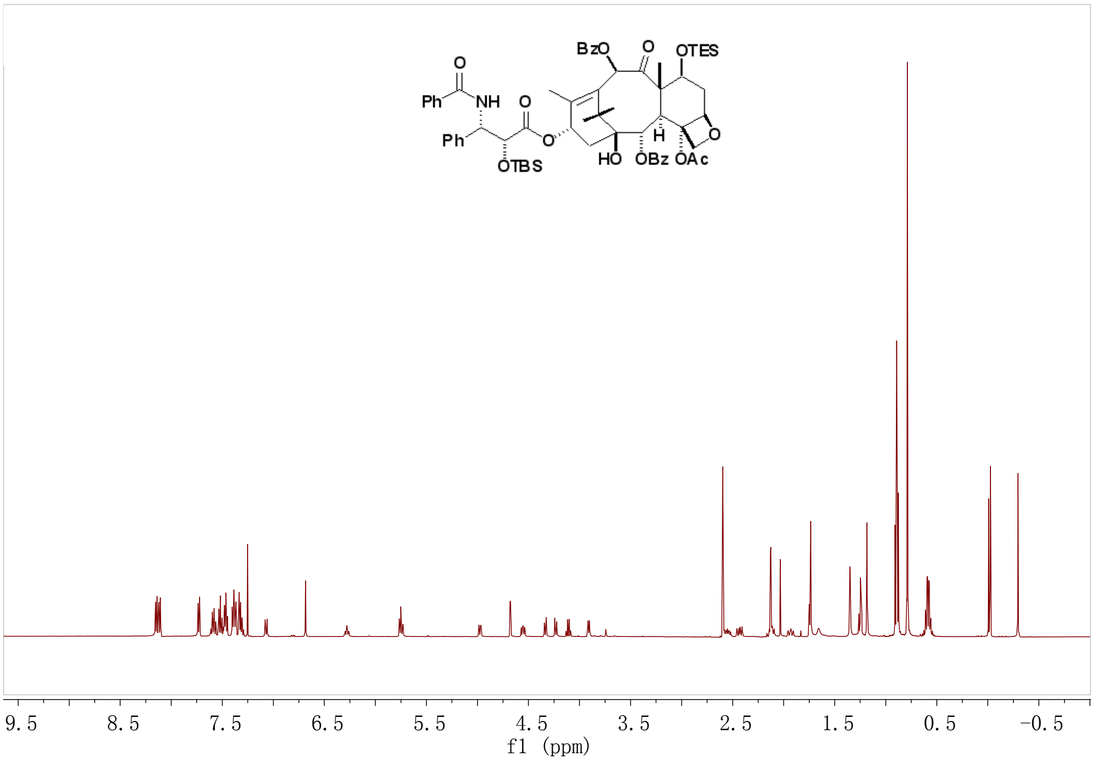
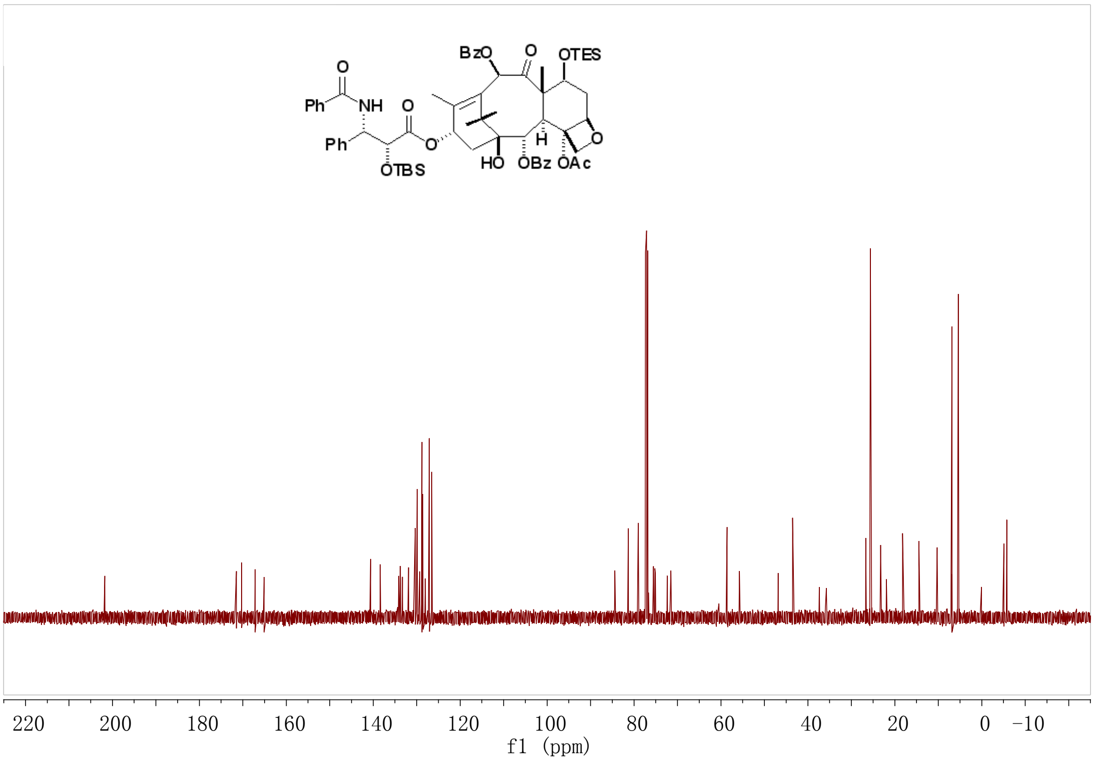
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)


BzO
O
OTES
O
Ph
NH
O
Ph
O
OTBS
HO
H
O
OBz
OAc
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)


BzO
O
OTES
O
Ph
NH
O
Ph
O
OTBS
HO
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O
OBz
OAc
220
200
180
160
140
120
100
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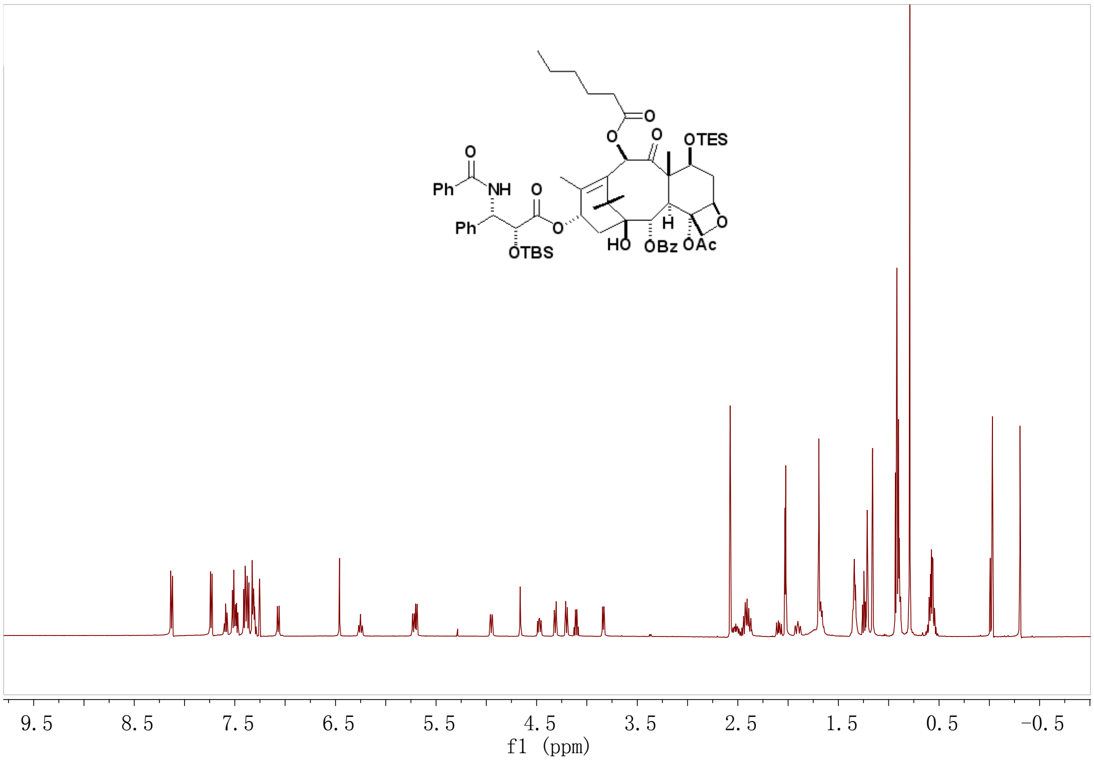
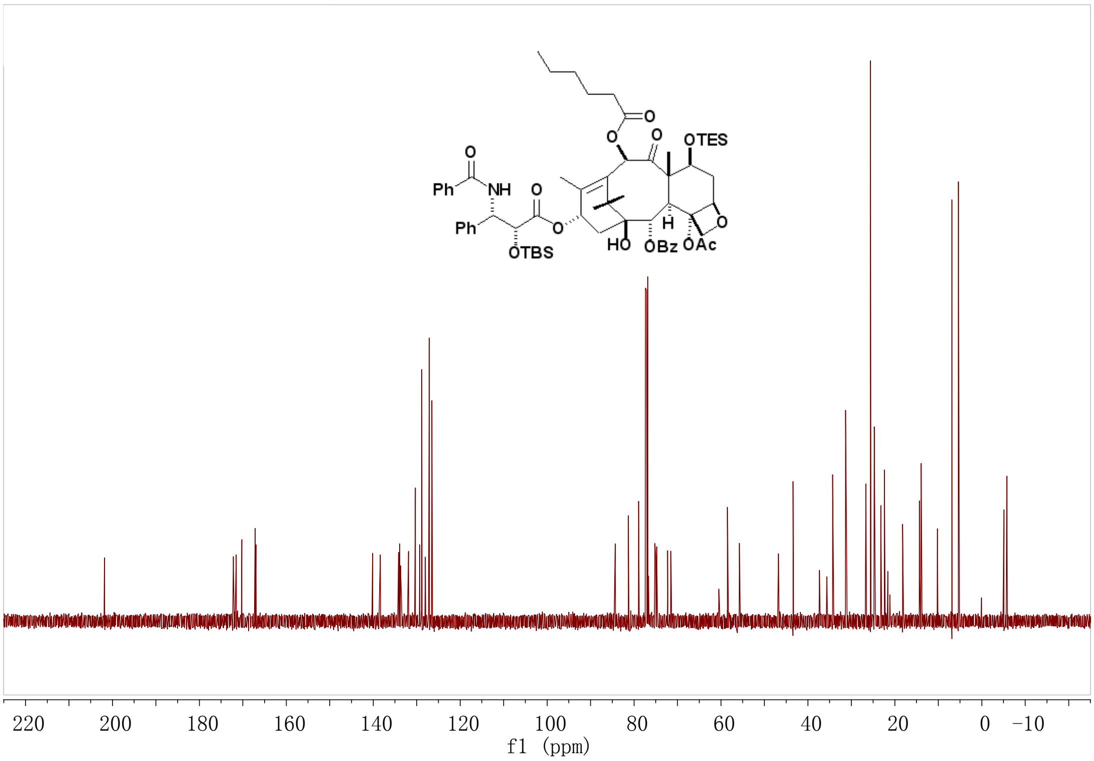
60
40
20
0
-10
f1 (ppm)


O
OTES
O
Ph
NH
O
Ph
O
H
O
OTBS
HO
OBz
OAc
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)


O
OTES
O
Ph
NH
O
Ph
O
H
O
OTBS
HO
OBz
OAc
220
200
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160
140
120
100
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60
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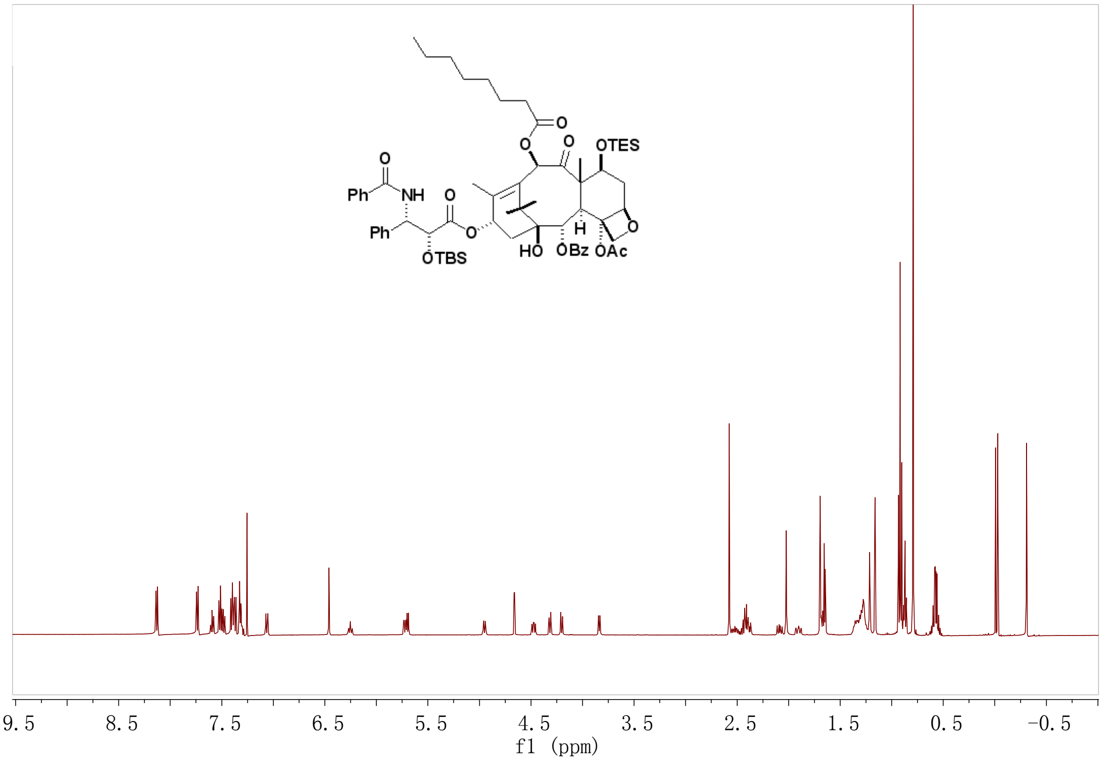
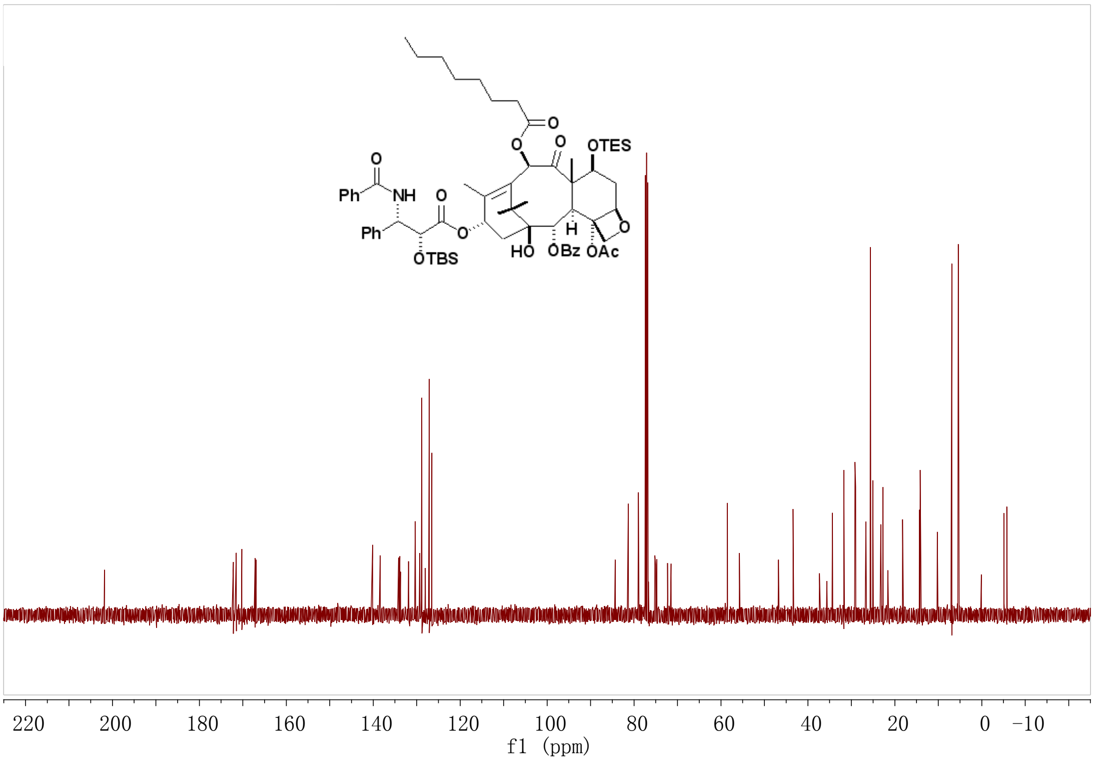
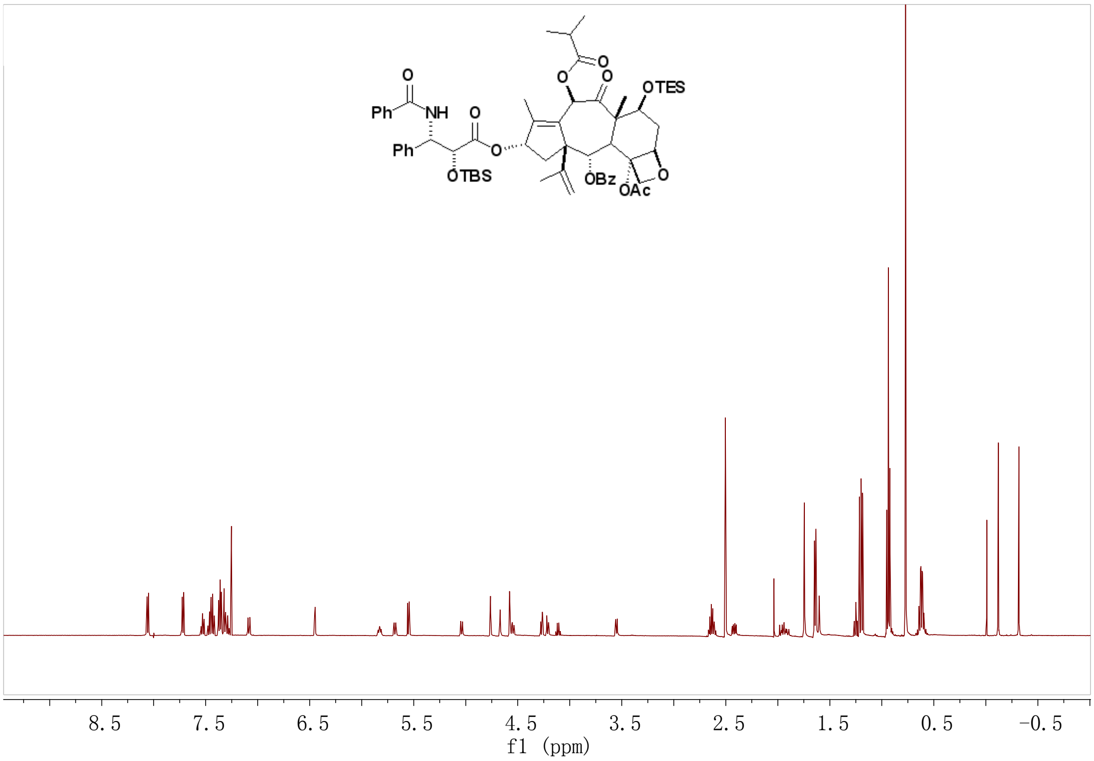
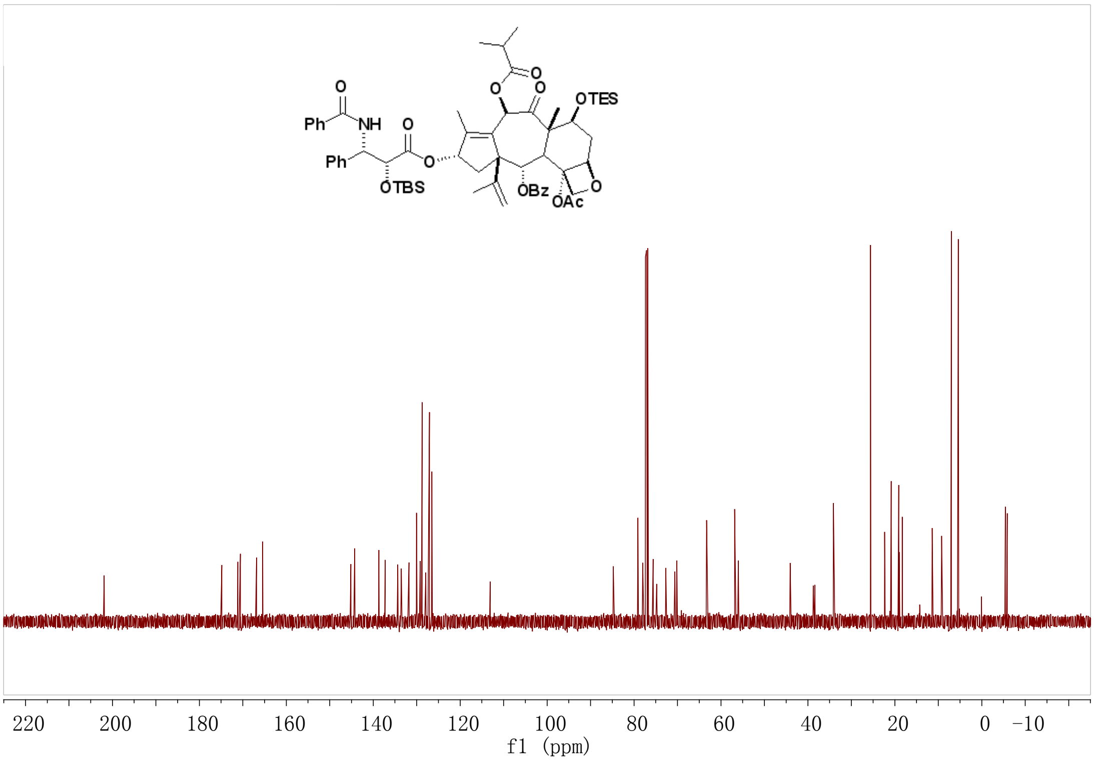
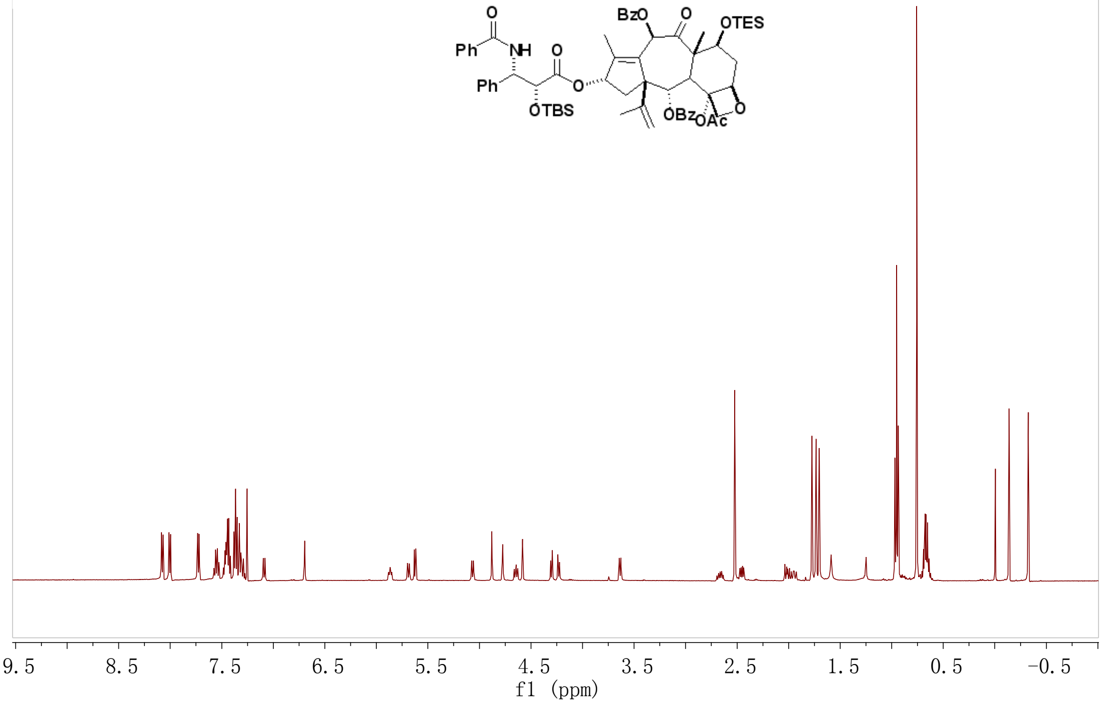
20
0
-10
f1 (ppm)


O
OTES
O
O
Ph
NH
O
O
Ph
H
O
OTBS
HO
OBz
OAc
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

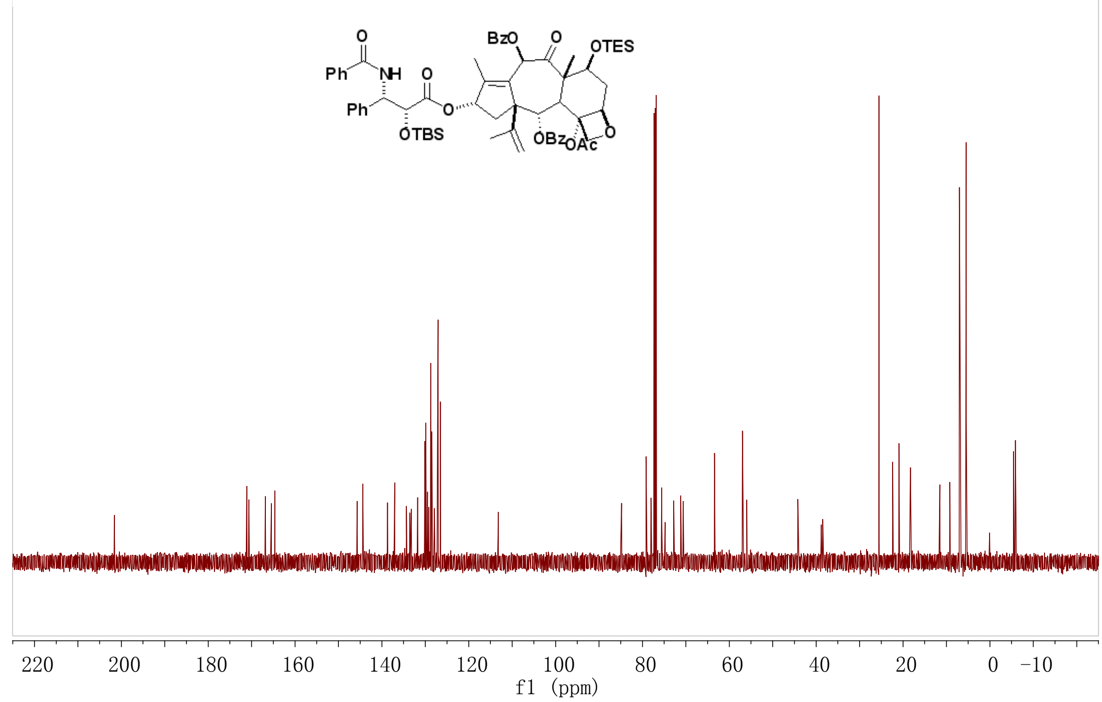

O
OTES
O
O
Ph
NH
O
O
Ph
H
O
OTBS
HO
OBz
OAc
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)


O
Ph
NH
O
Ph
O
OTBS
O
O
O
OTES
OBz
OAc
O
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

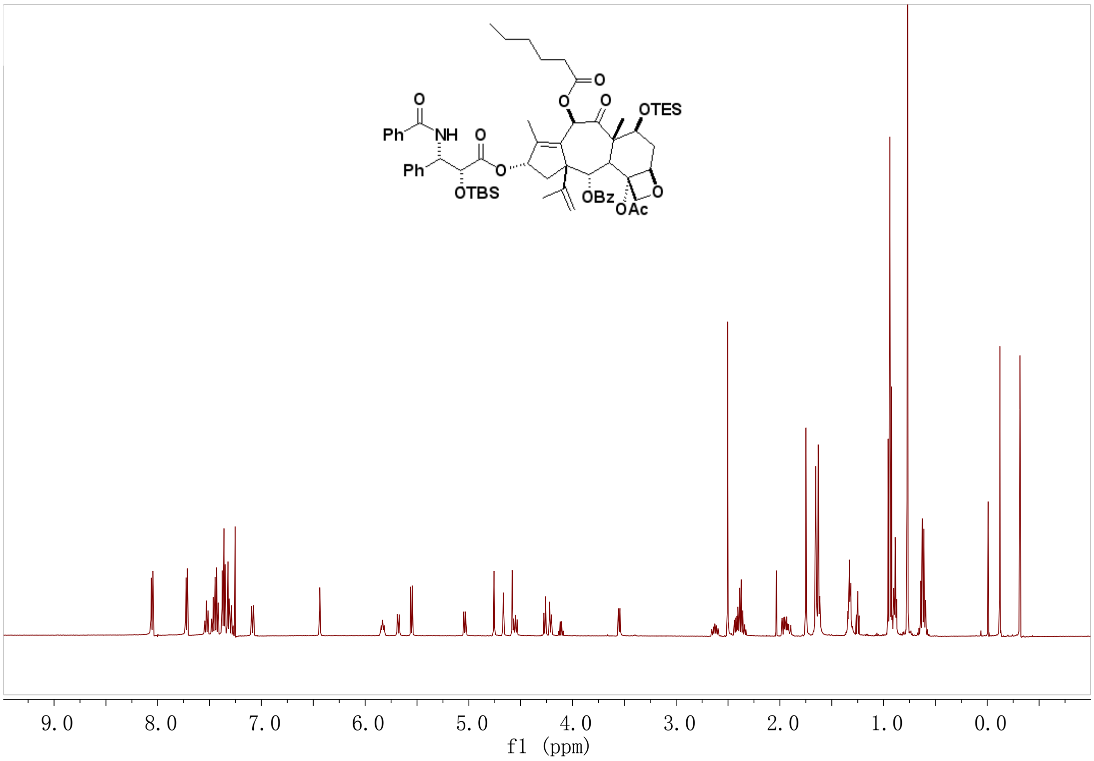

O
Ph
NH
O
Ph
O
OTBS
O
O
O
OTES
OBz
OAc
O
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

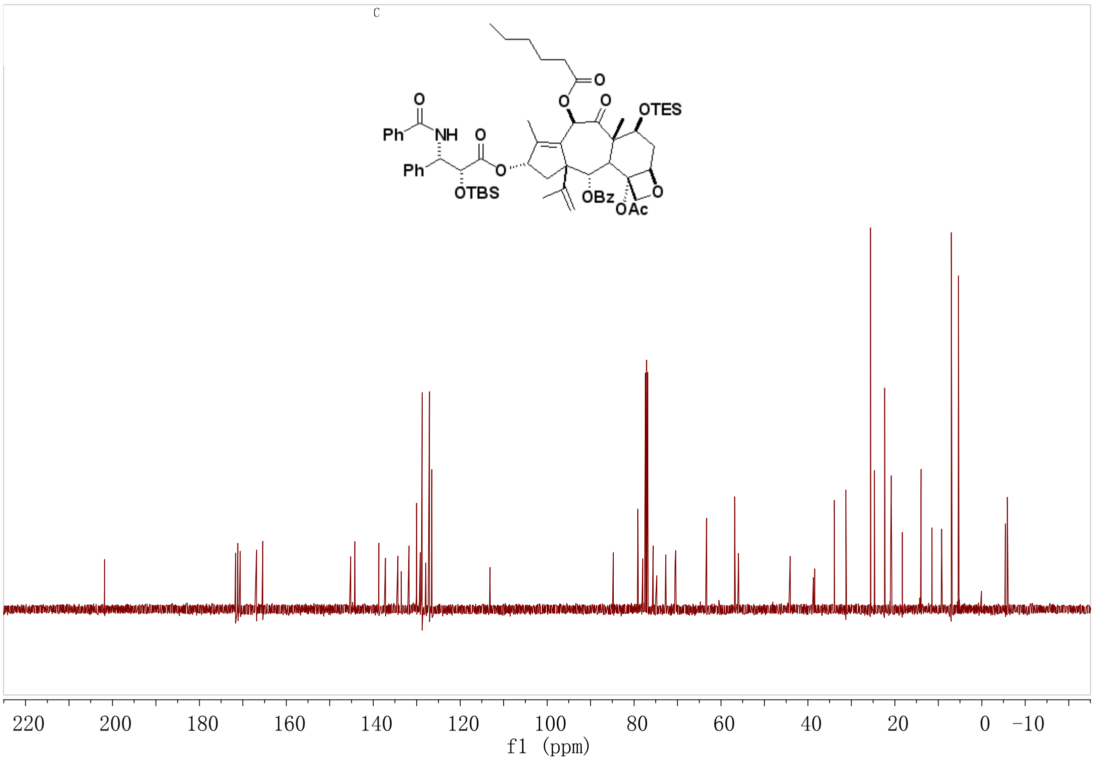


Ph
NH
O
Ph
OTBS
BzO
O
OTES
OBz
OAc
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)



Ph
NH
O
Ph
OTBS
BzO
O
OTES
OBz
OAc
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)


OTES
Ph
NH
Ph
OTBS
OBz
OAc
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


C
OTES
Ph
NH
Ph
OTBS
OBz
OAc
220
200
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160
140
120
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60
40
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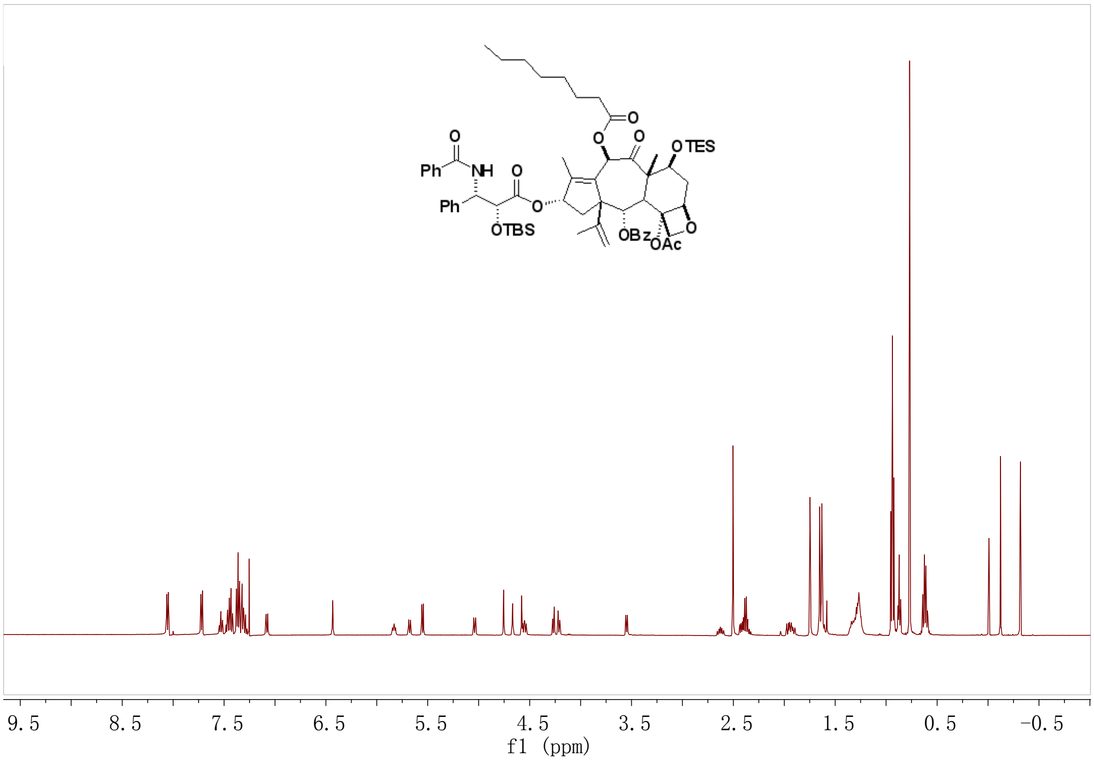
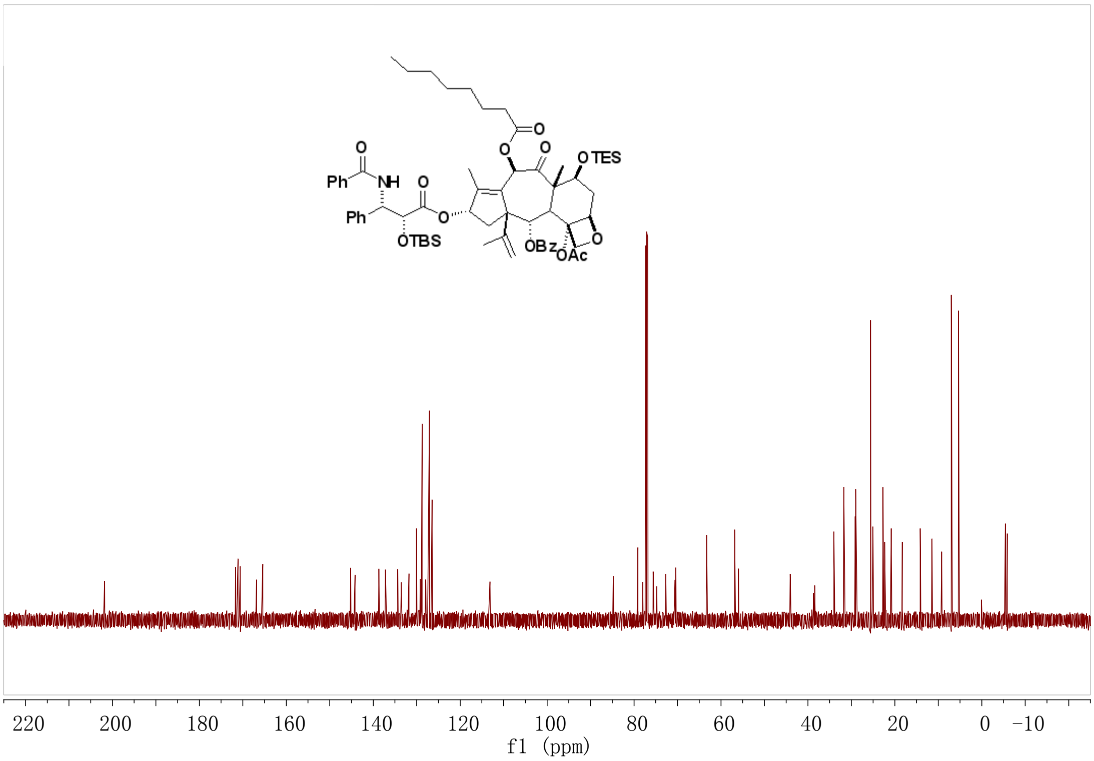
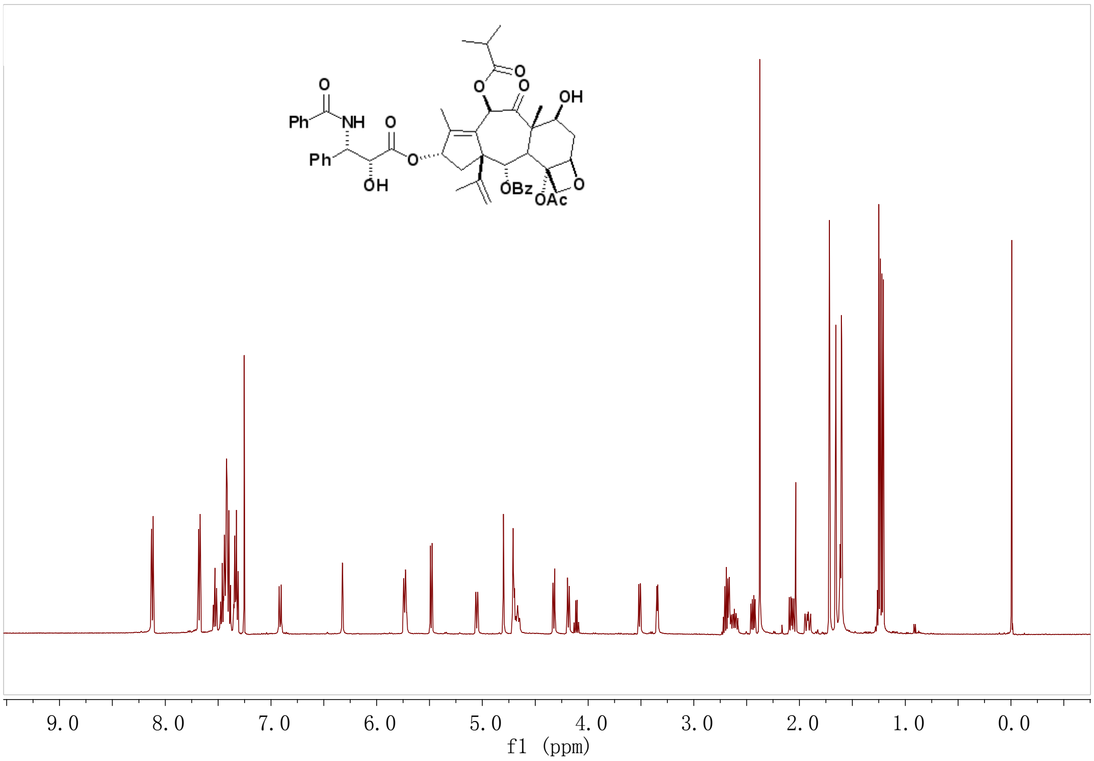
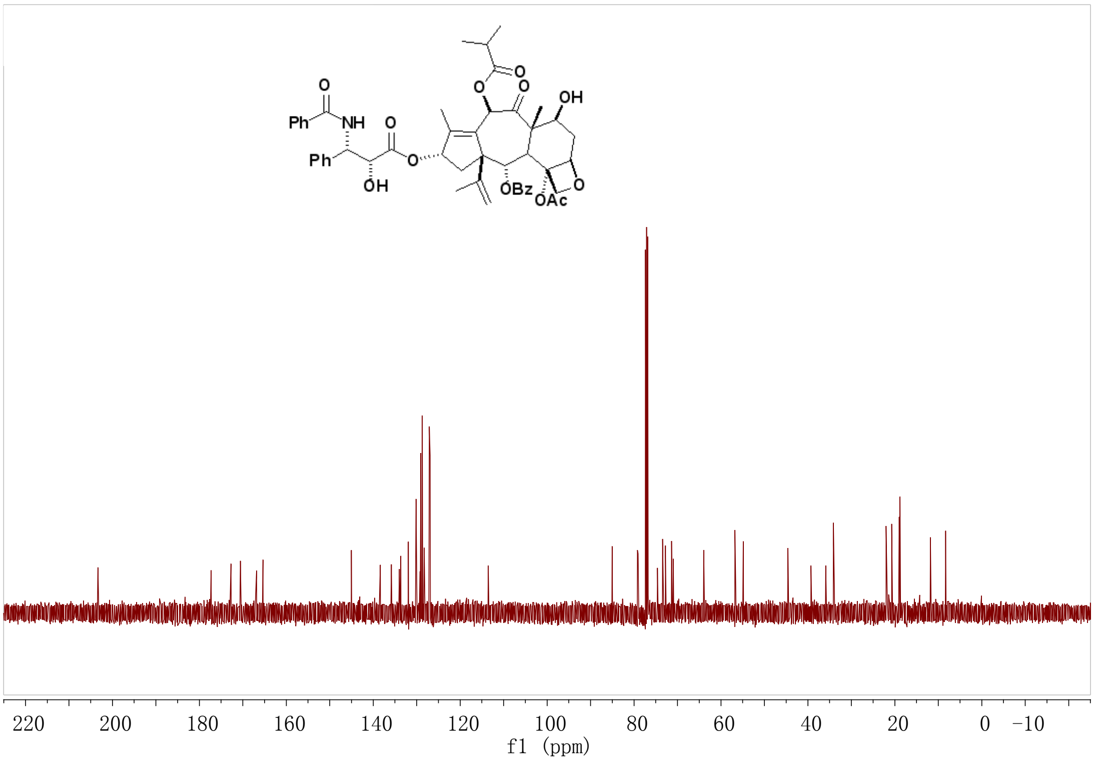
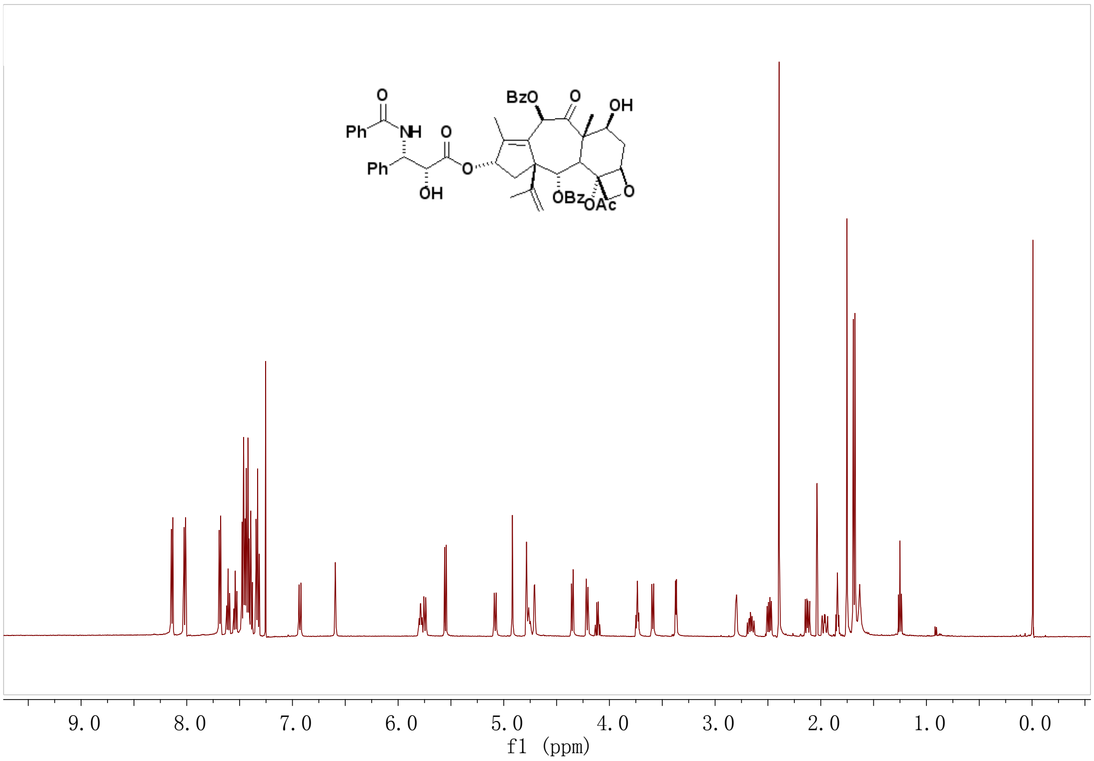
0
-10
f1 (ppm)

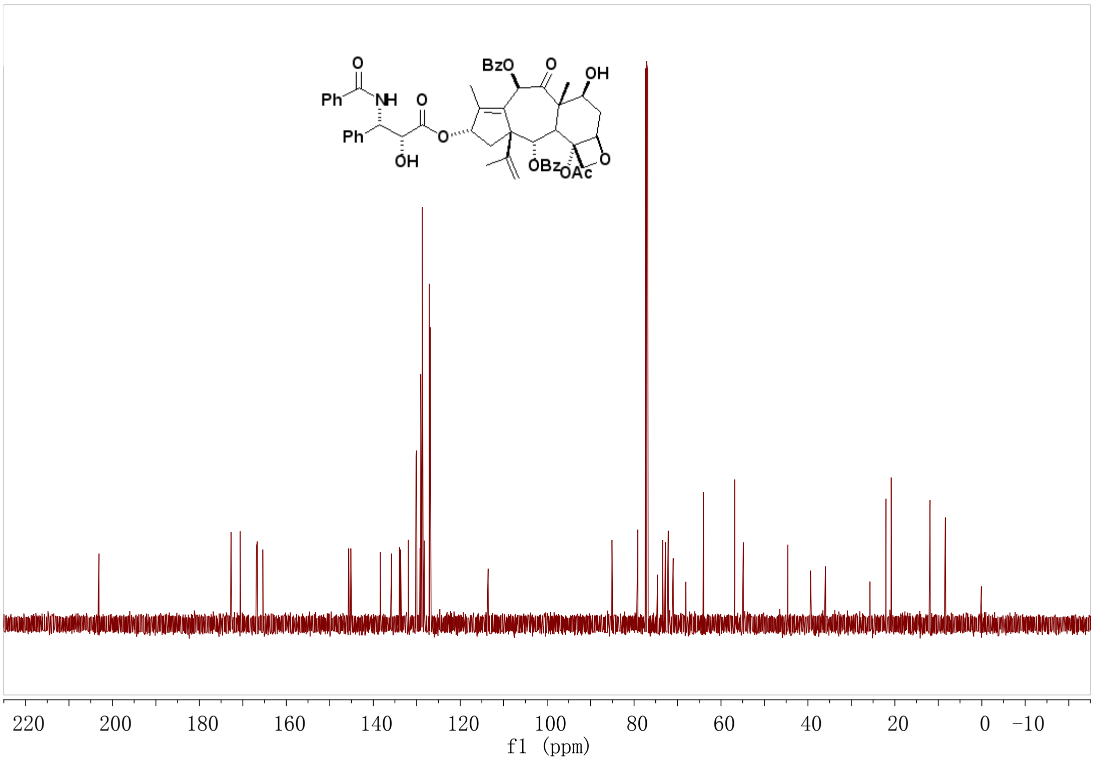

O
Ph
NH
O
Ph
O
OTBS
O
O
O
O
OTES
OBz
OAc
O
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
−0.5
f1 (ppm)

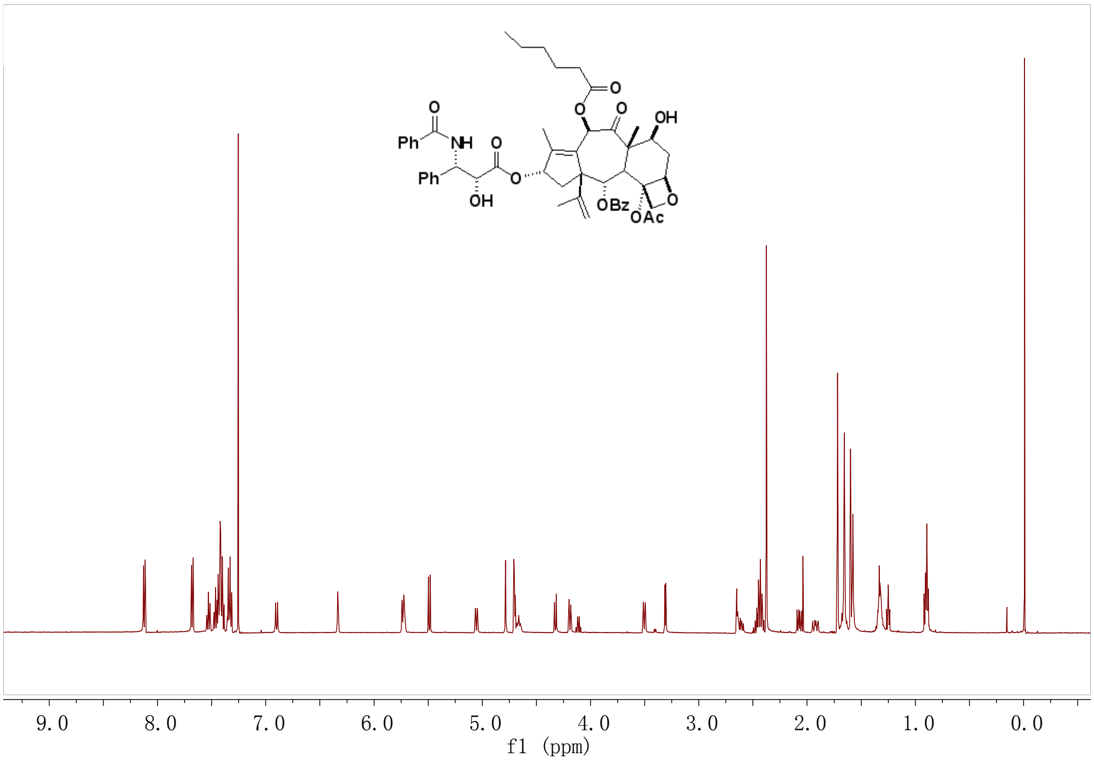

O
Ph
NH
O
Ph
O
OTBS
O
O
O
O
OTES
OBz
OAc
O
220
200
180
160
140
120
100
80
60
40
20
0
−10
f1 (ppm)

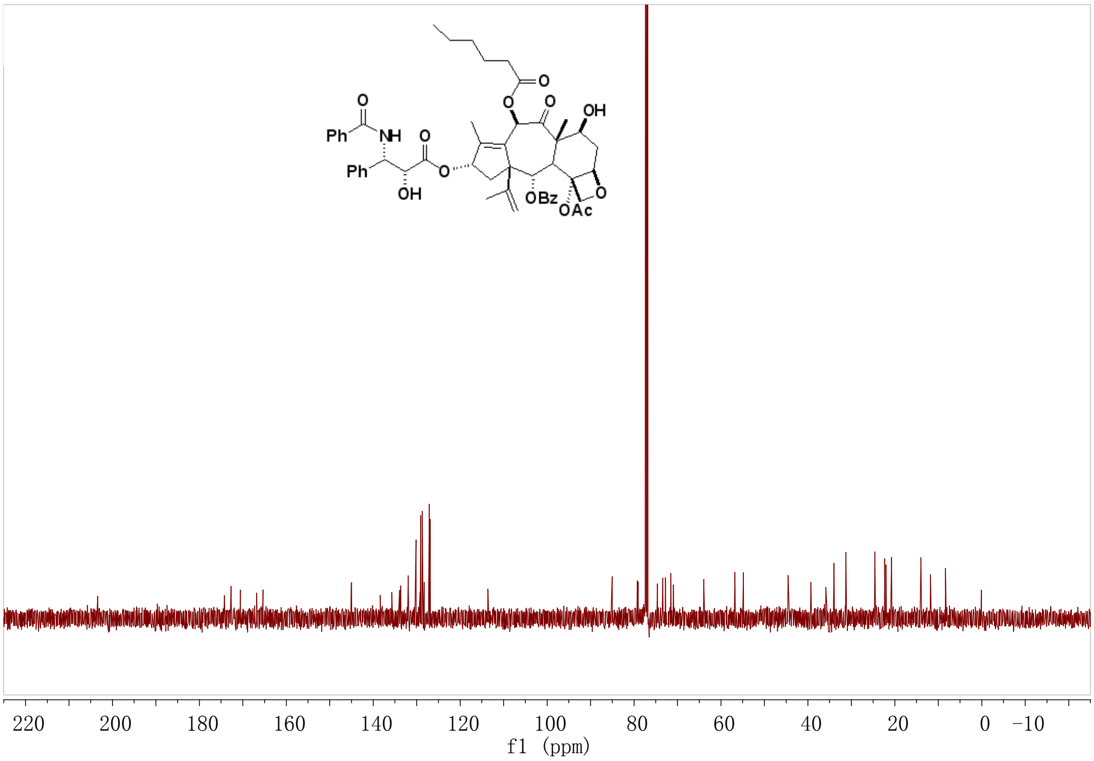

O
Ph
NH
O
Ph
O
OH
O
O
O
OH
OBz
OAc
O
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

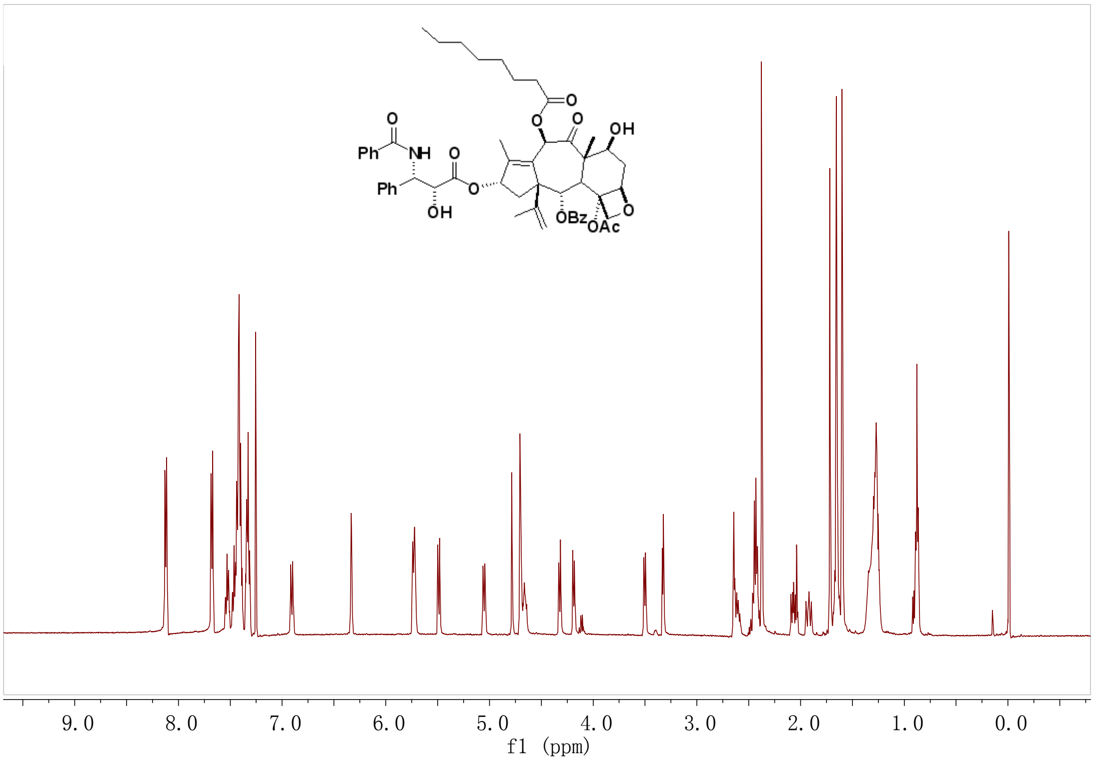

O
Ph
NH
O
Ph
O
OH
O
O
O
OH
OBz
OAc
O
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

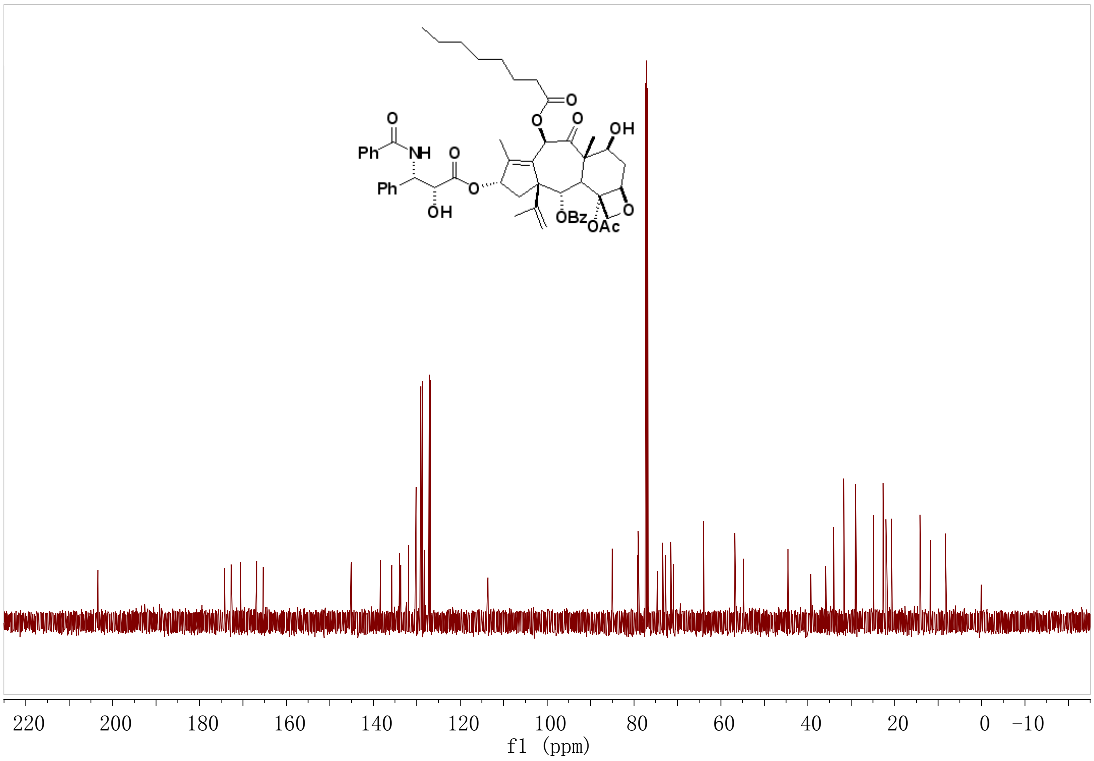

Ph
NH
O
Ph
OH
BzO
OH
OBz
OAc
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

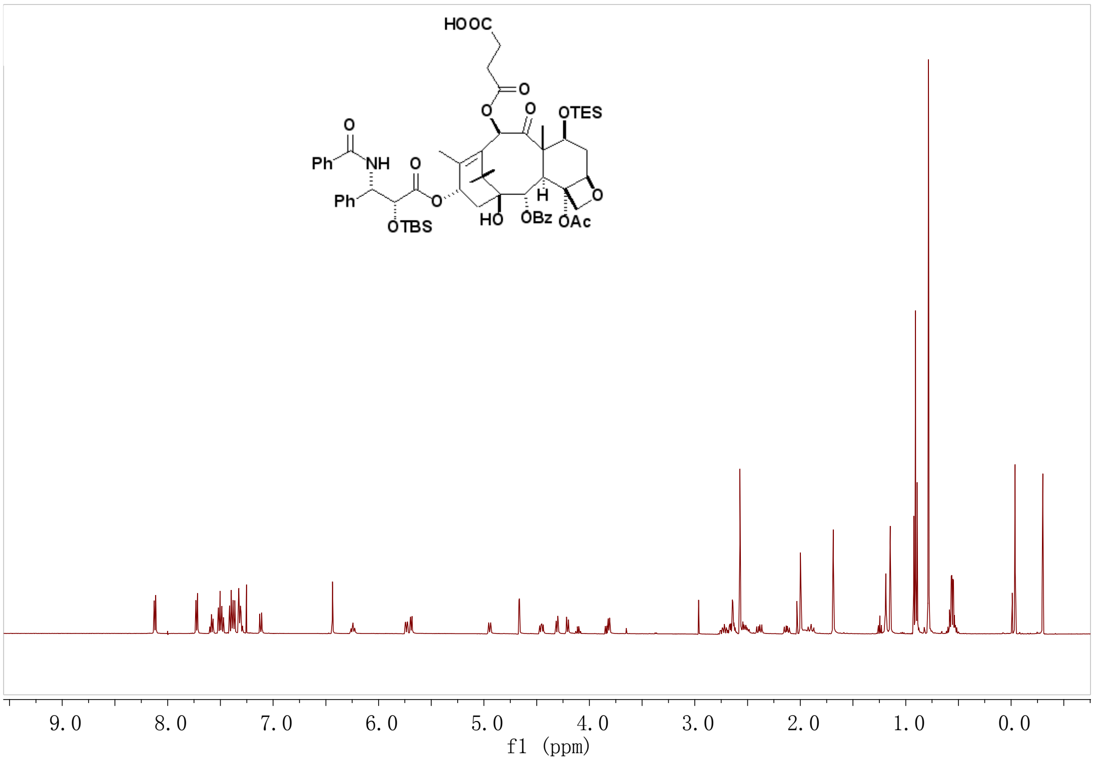

Ph
NH
O
Ph
OH
BzO
OH
OBz
OAc
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

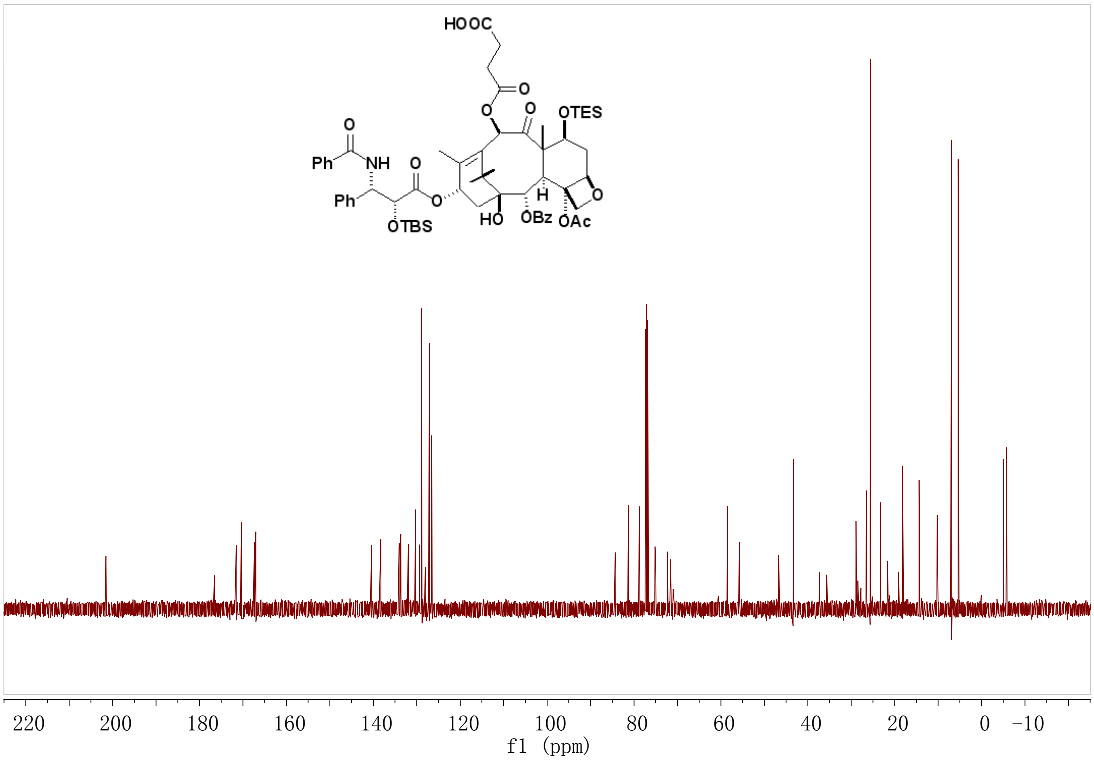

O
Ph
NH
O
Ph
OH
O
O
O
O
OH
OBz
OAc
O
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

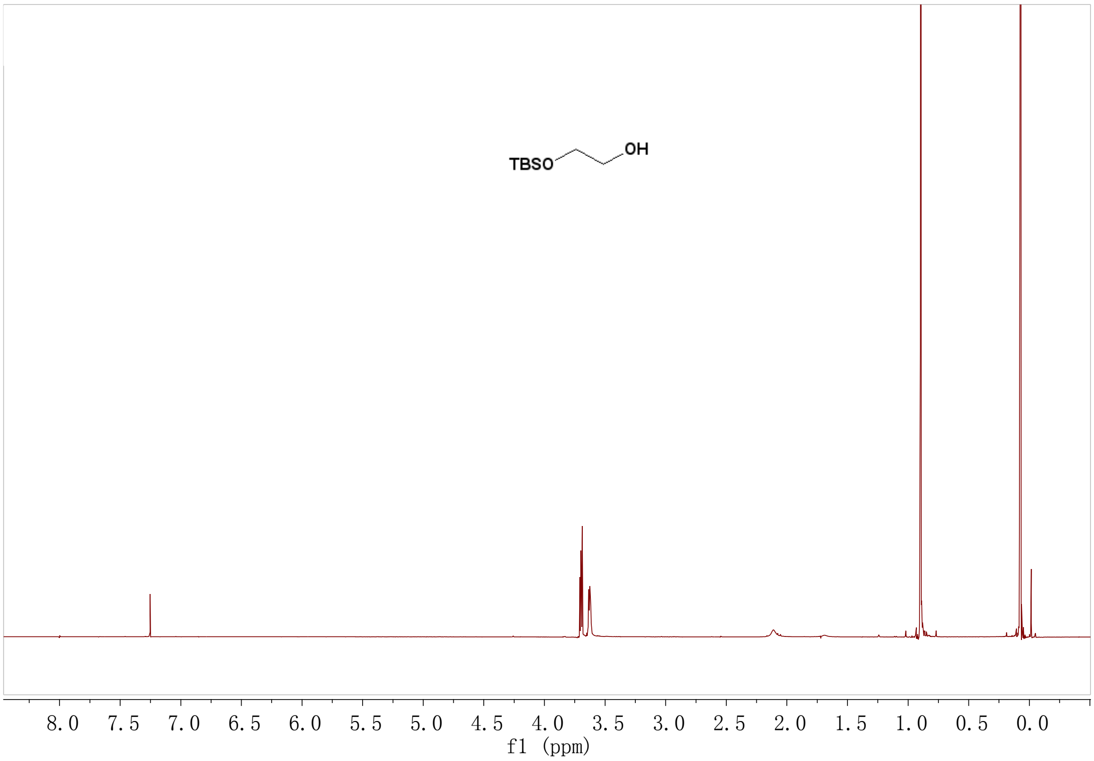

O
Ph
NH
O
Ph
OH
O
O
O
O
OH
OBz
OAc
O
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

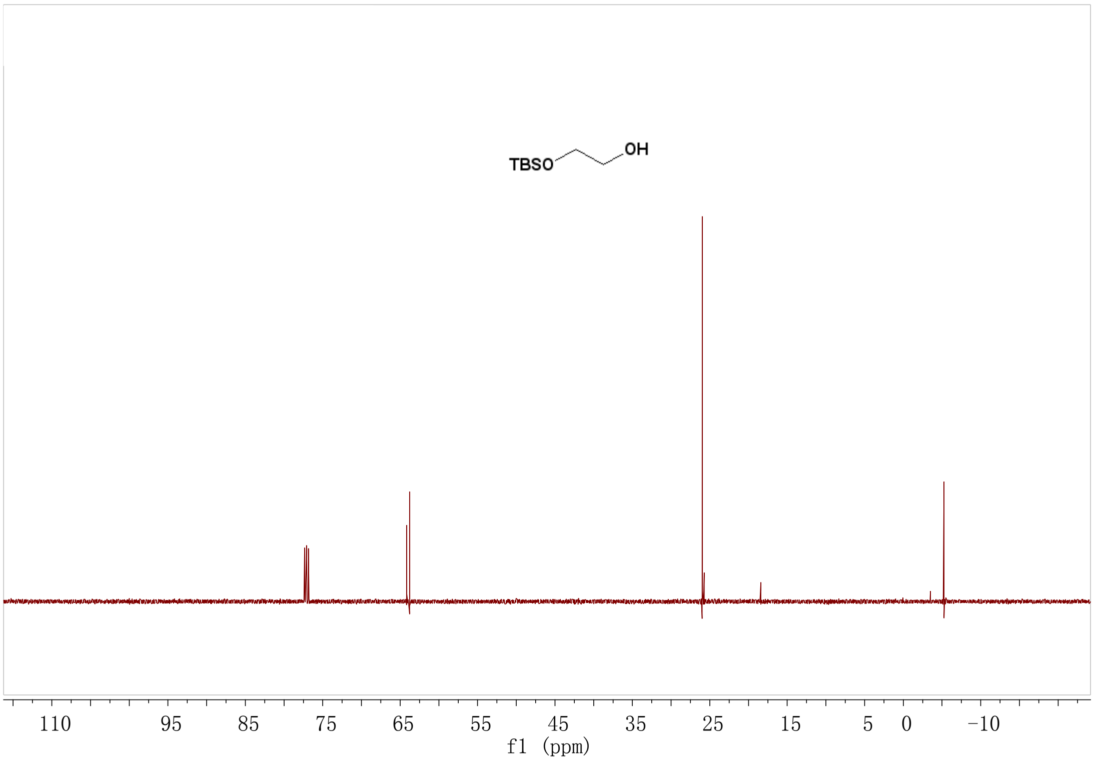

O
Ph
NH
O
Ph
O
OH
O
O
O
OH
O
OBz
OAc
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

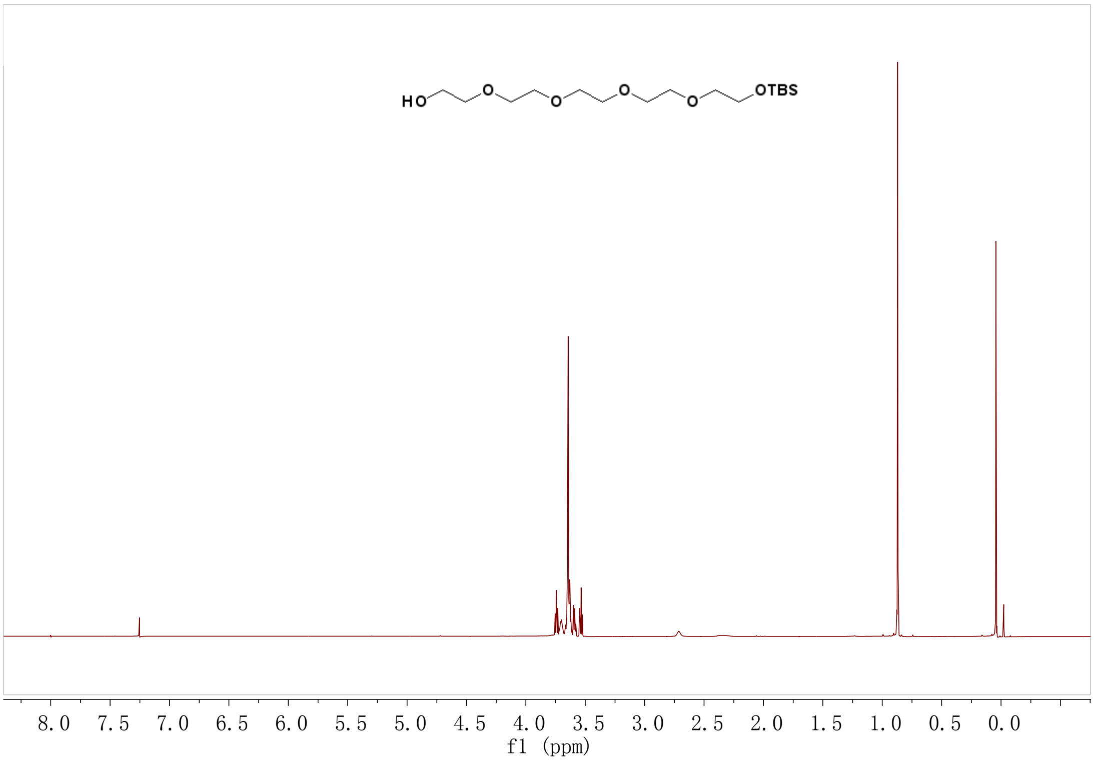

O
Ph
NH
O
Ph
O
OH
O
O
O
OH
O
OBz
OAc
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

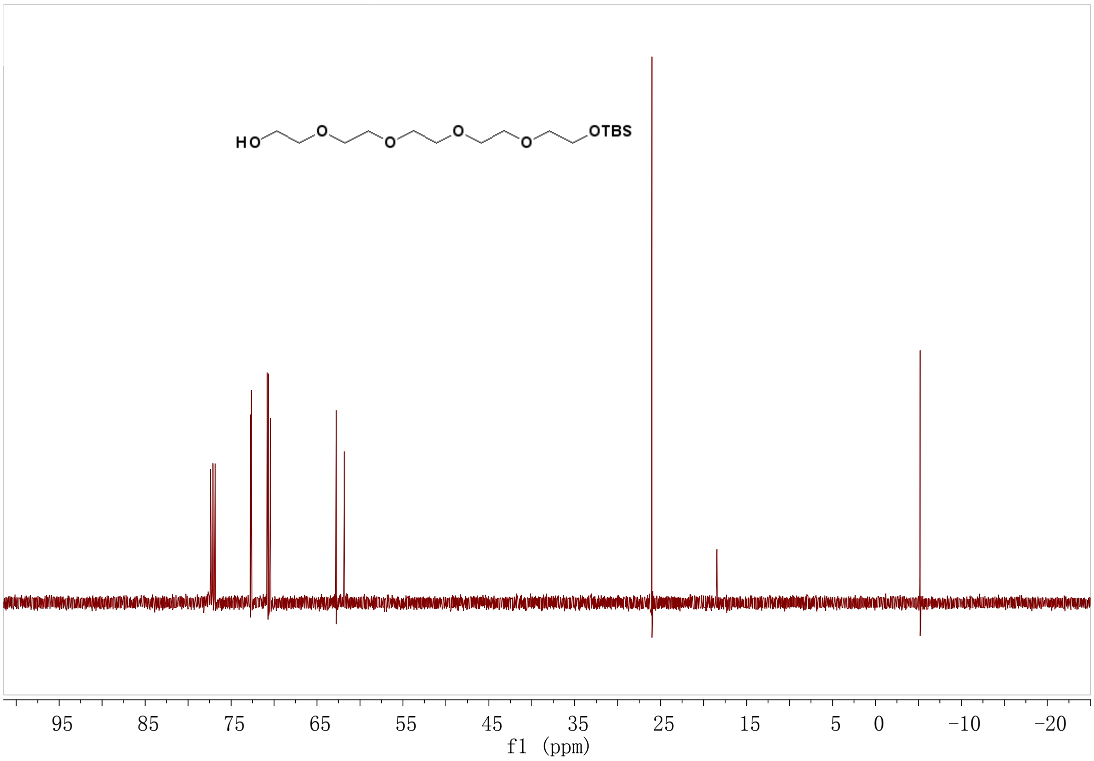

HOOC
O
O
OTES
O
Ph
NH
O
Ph
O
OTBS
HO
OBz
OAc
H
O
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

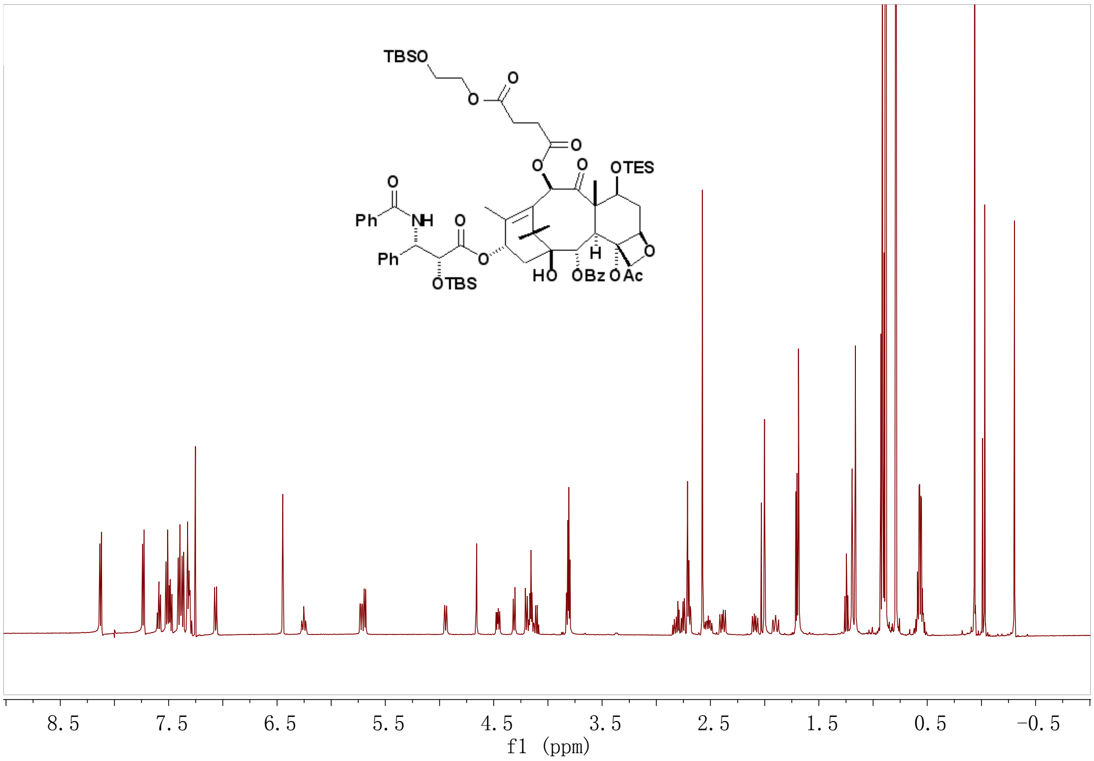

HOOC
O
O
OTES
O
Ph
NH
O
Ph
O
OTBS
HO
OBz
OAc
H
O
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

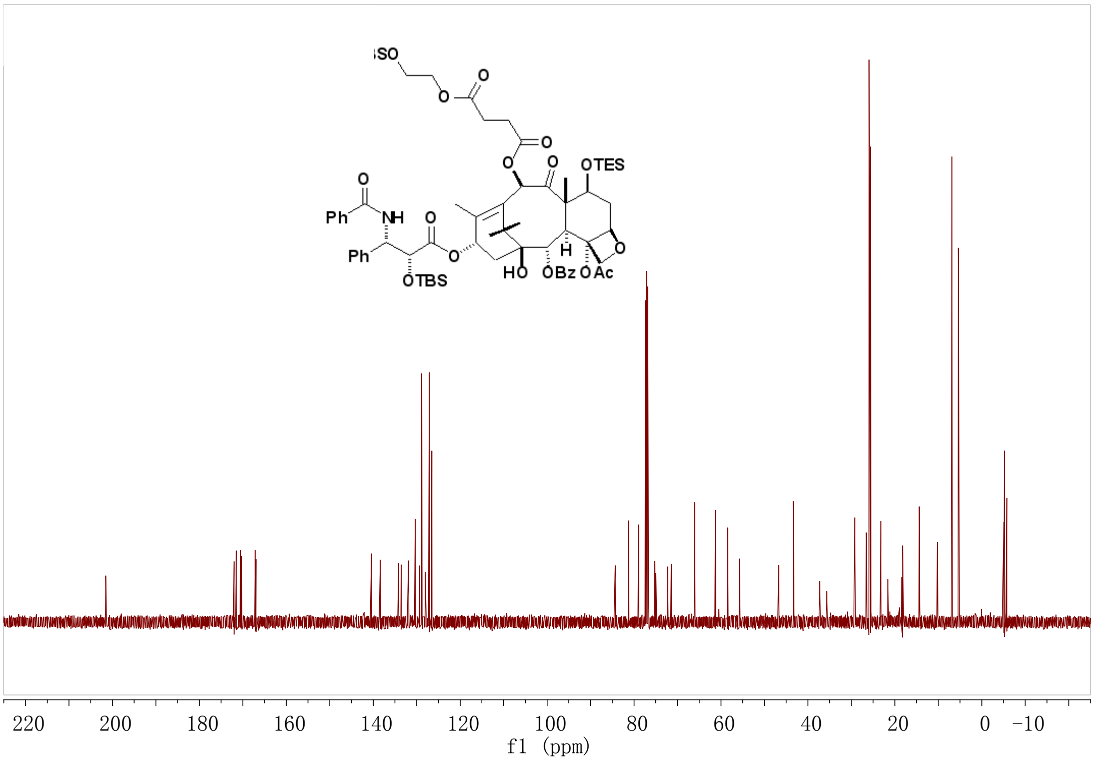

TBSO
OH
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

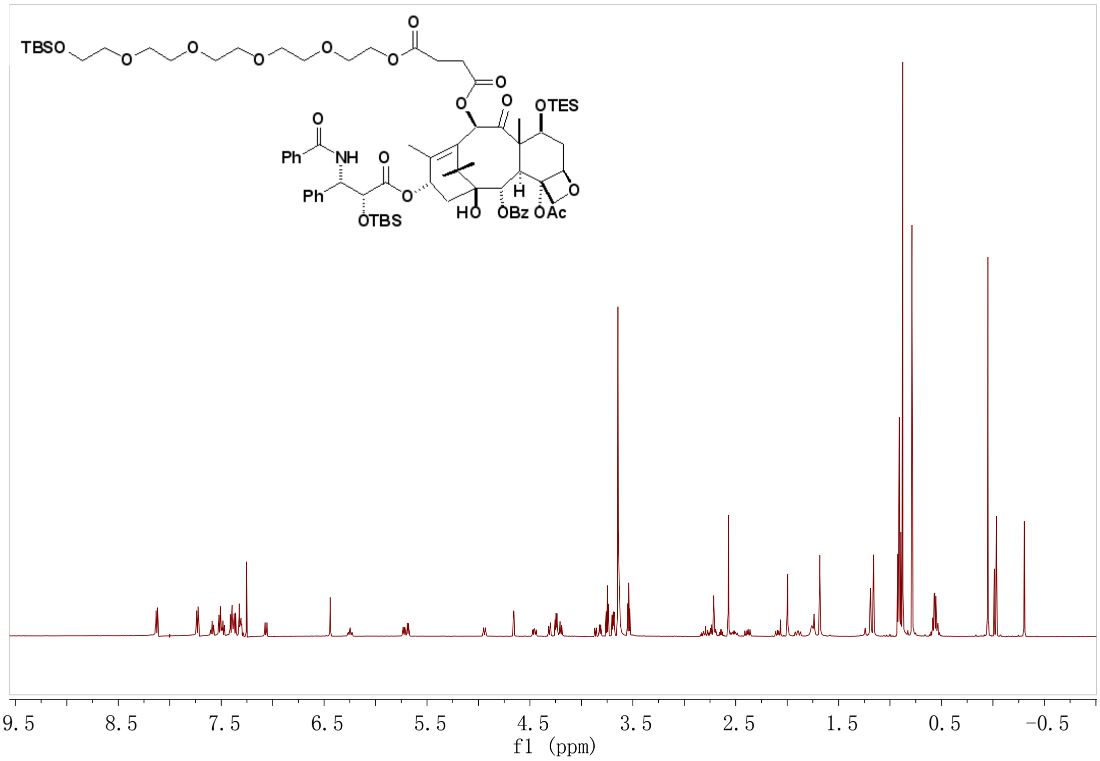

TBSO
OH
110
95
85
75
65
55
45
35
25
15
5
0
-10
f1 (ppm)

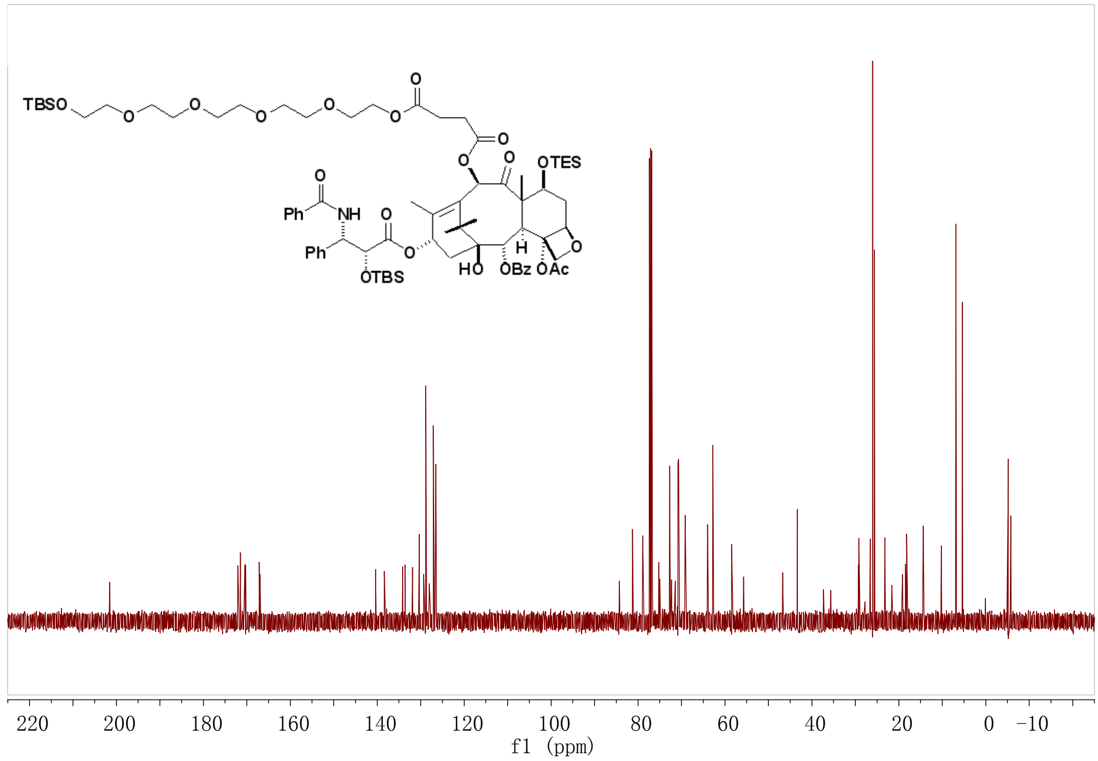

HO
O
O
O
O
OTBS
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

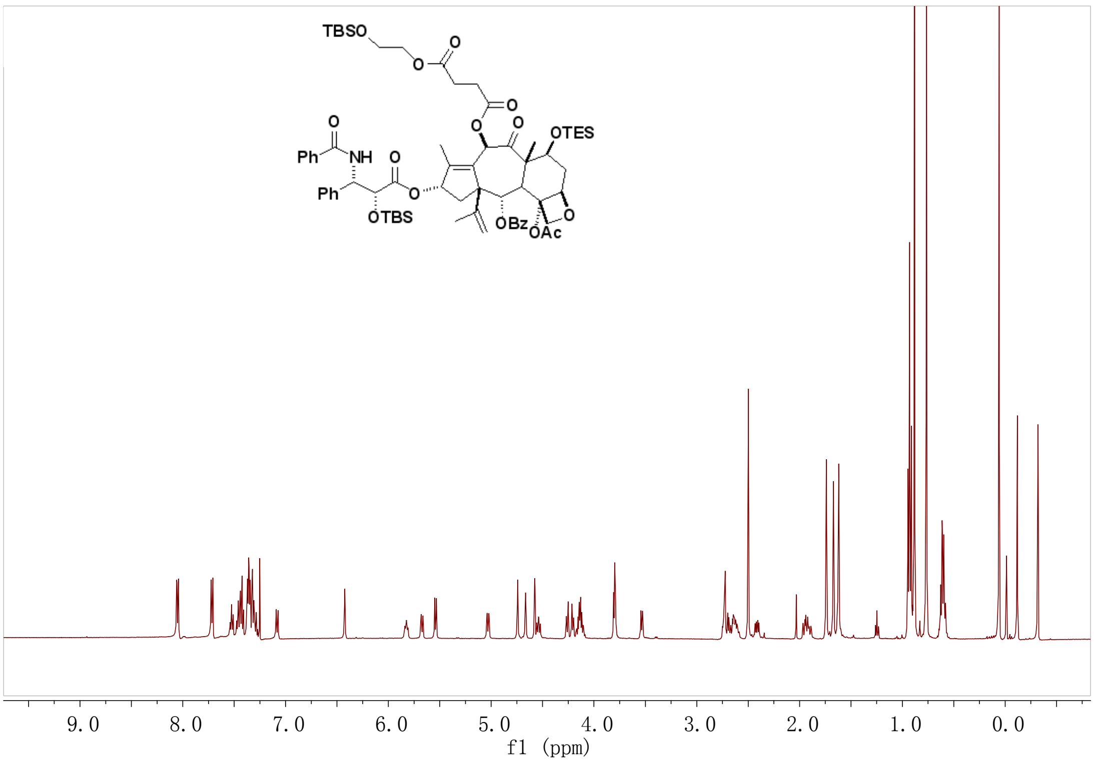

HO
O
O
O
O
OTBS
95
85
75
65
55
45
35
25
15
5
0
−10
−20
f1 (ppm)

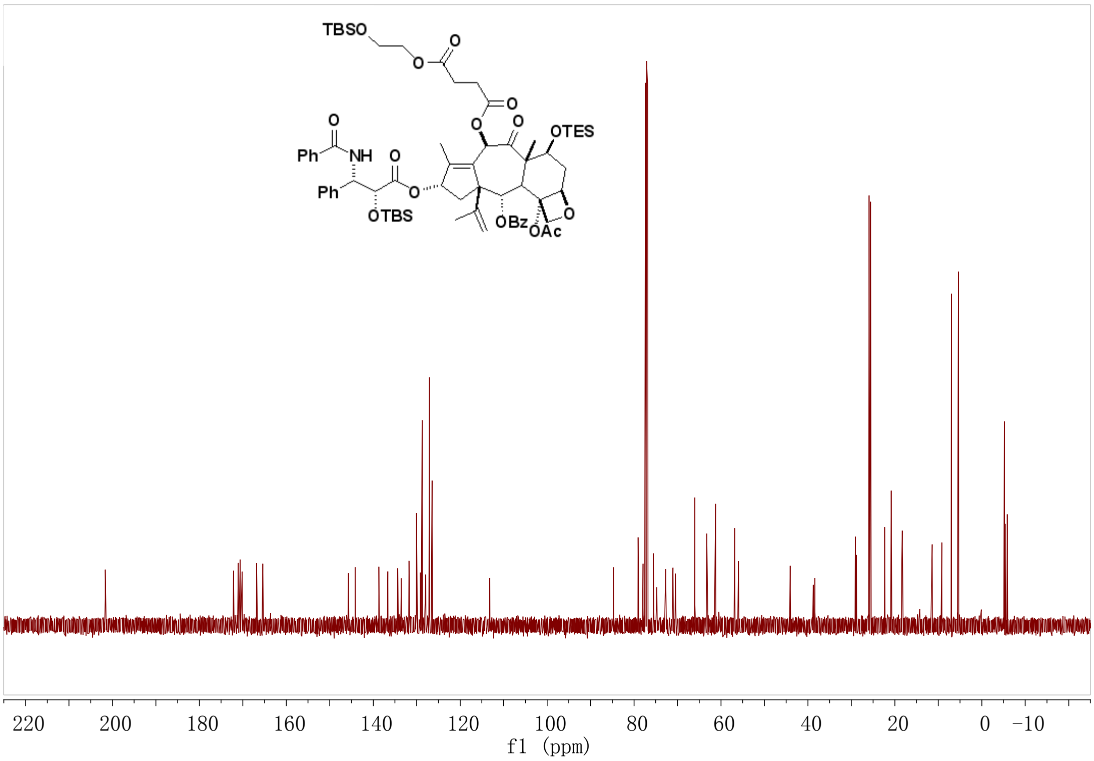

TBSO
O
O
O
O
O
OTES
O
Ph
NH
O
Ph
O
OTBS
H
HO
OBz
OAc
O
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

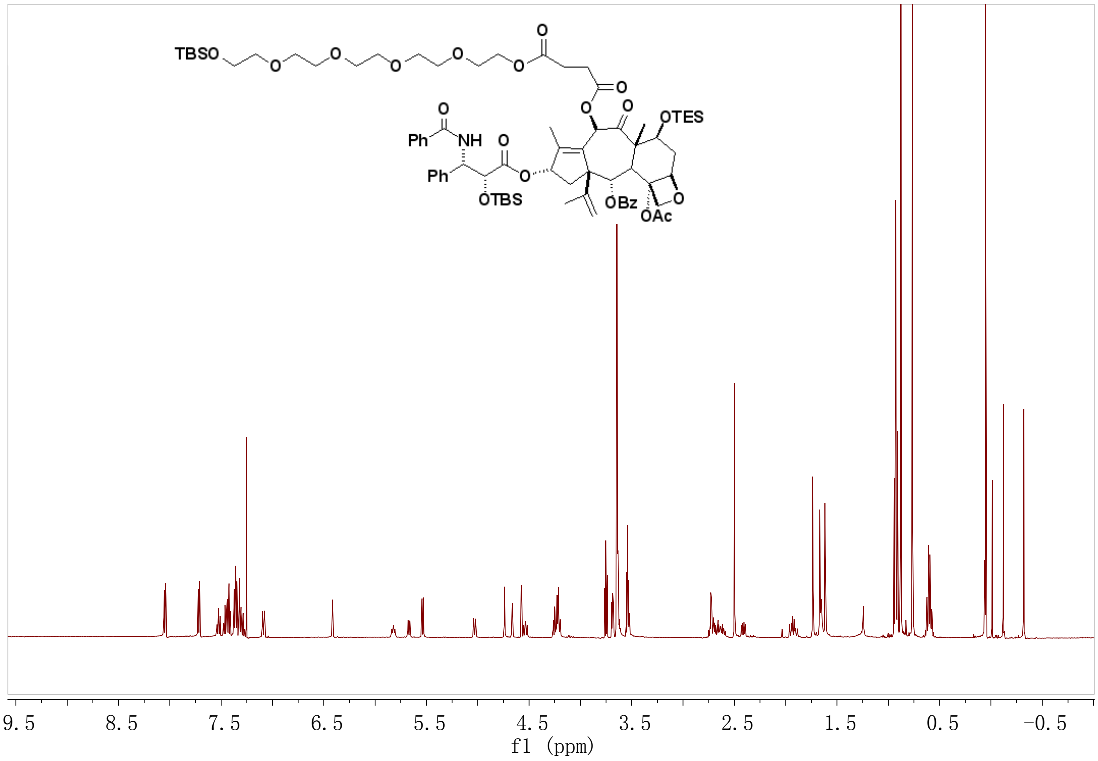

SO
O
O
O
O
O
OTES
O
Ph
NH
O
Ph
O
OTBS
H
HO
OBz
OAc
O
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)


TBSO
O
O
O
O
O
O
O
O
OTES
Ph
NH
O
Ph
OTBS
HO
OBz
OAc
H
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

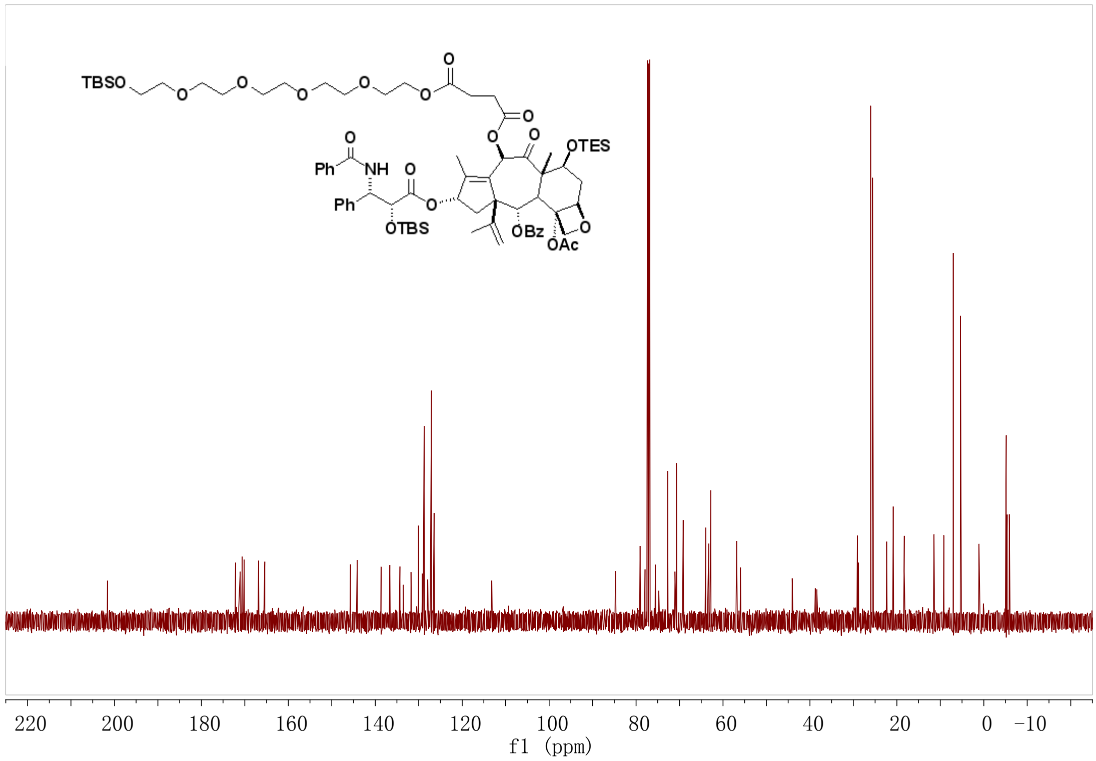

TBSO
O
O
O
O
O
O
O
O
OTES
Ph
NH
O
Ph
OTBS
HO
OBz
OAc
H
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)


TBSO
O
O
O
O
O
OTES
Ph
NH
O
Ph
O
OTBS
OBz
OAc
O
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

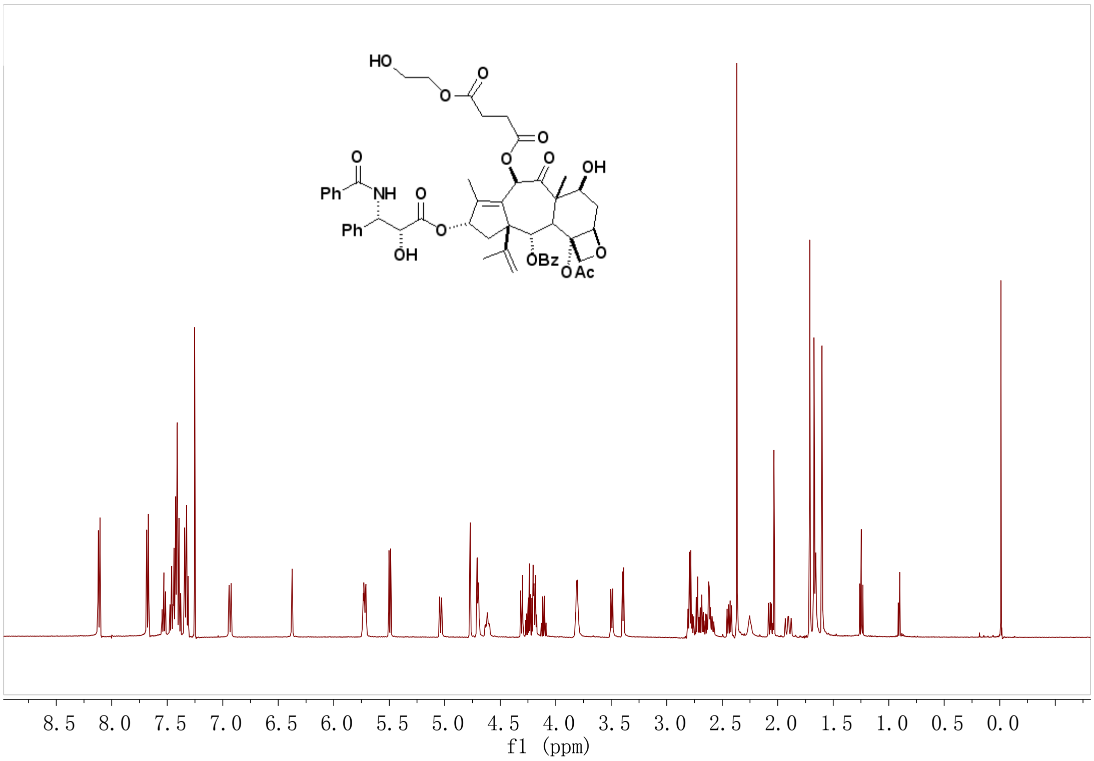

TBSO
O
O
O
O
O
OTES
Ph
NH
O
Ph
O
OTBS
OBz
OAc
O
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

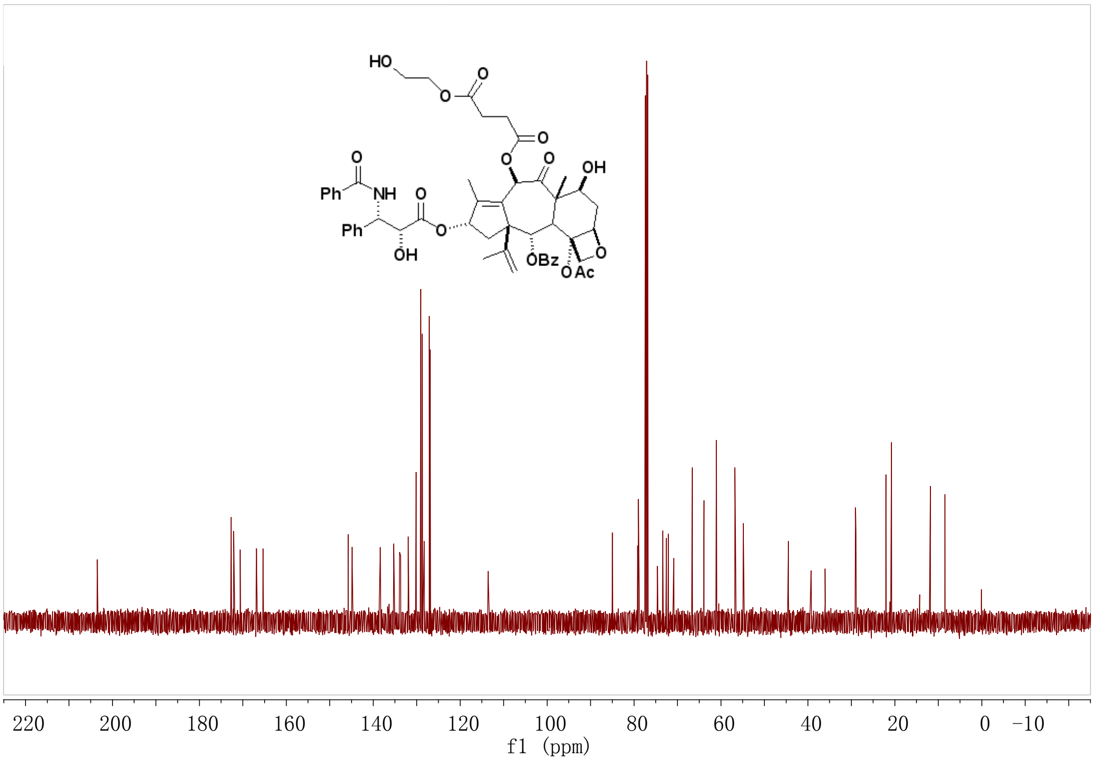


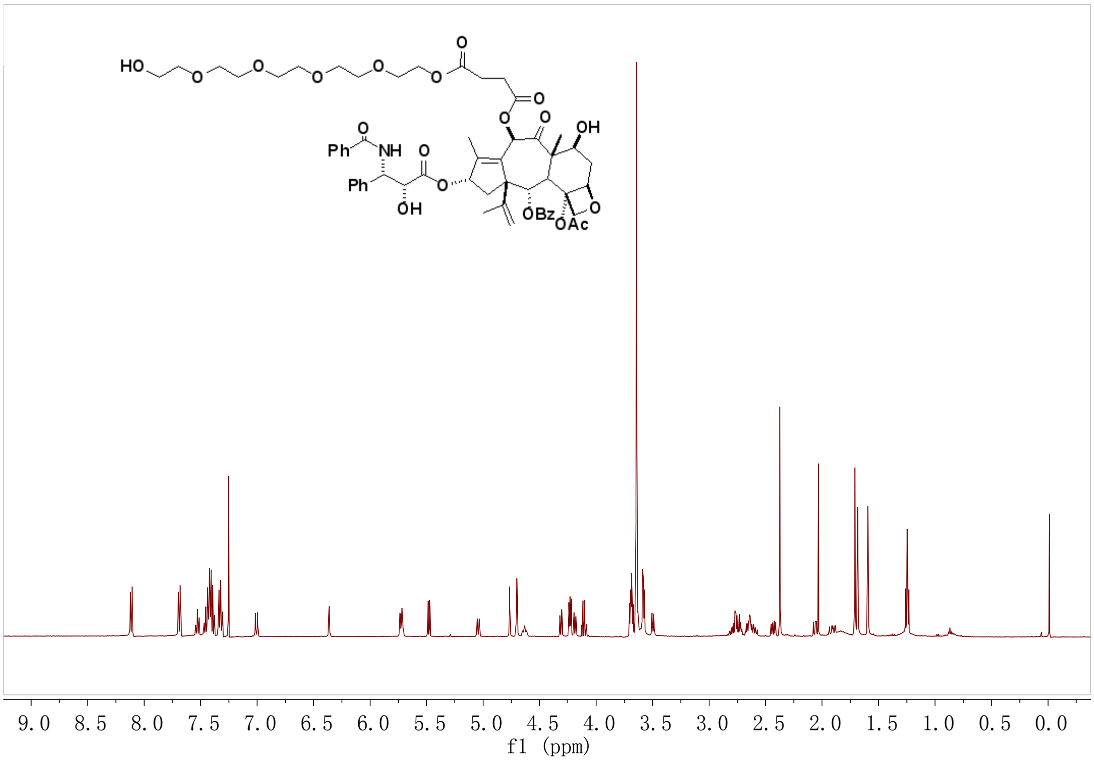
TBSO
O
O
O
O
O
O
O
O
O
O
OTES
Ph
NH
O
Ph
O
OTBS
OBz
OAc
O
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

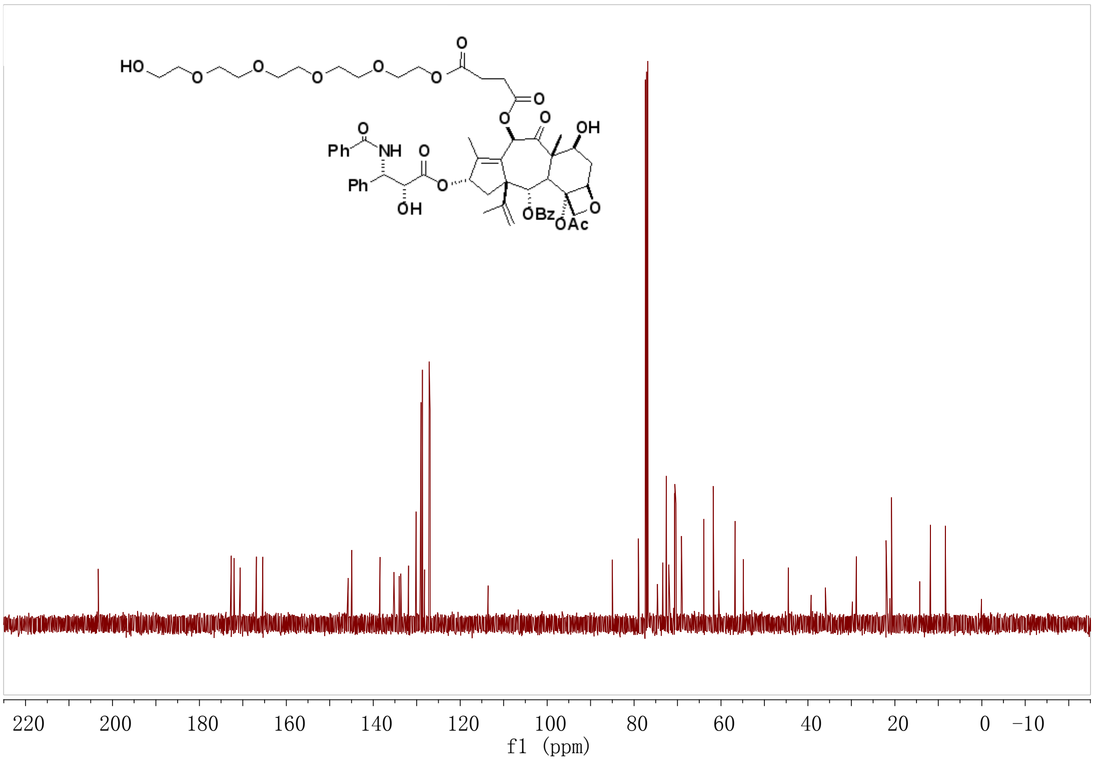


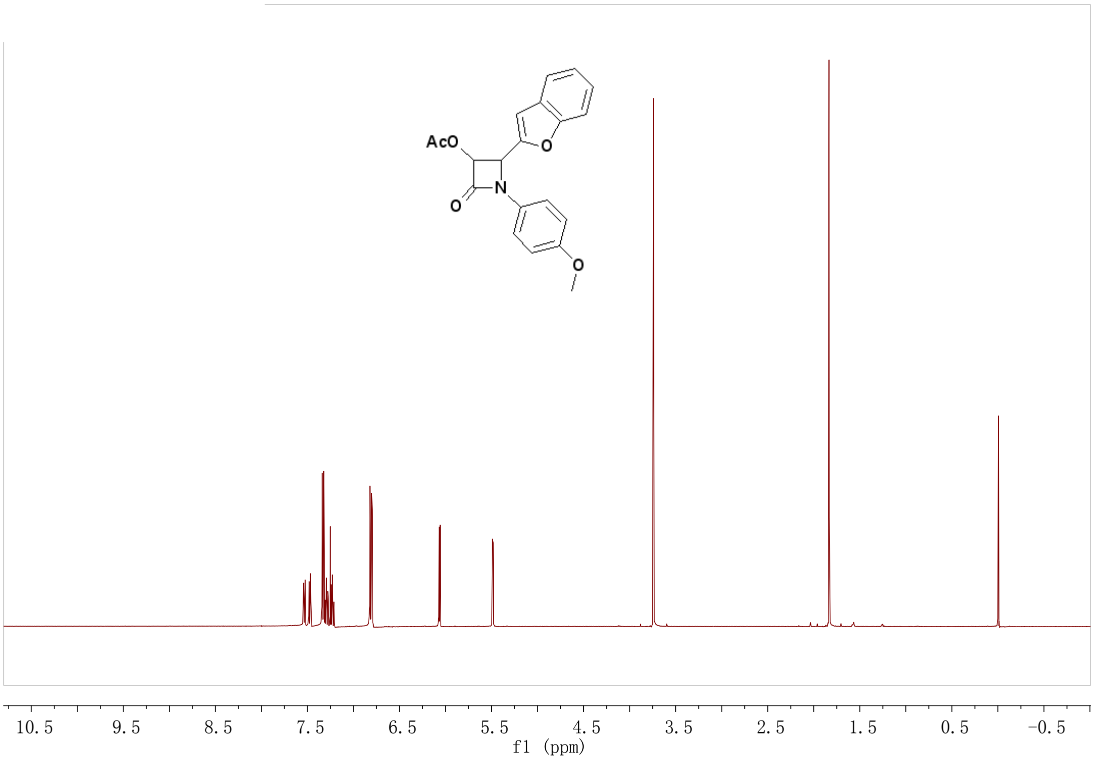
TBSO
O
O
O
O
O
O
O
O
O
O
OTES
Ph
NH
O
Ph
O
OTBS
OBz
OAc
O
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

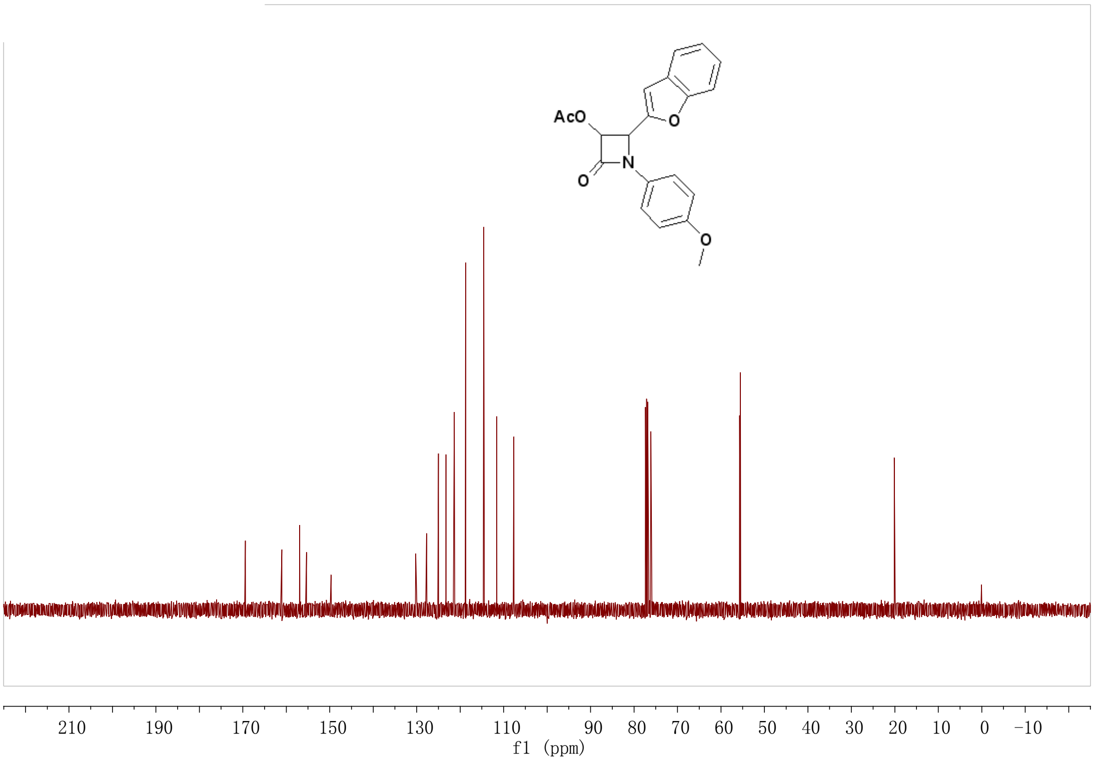

HO
O
O
O
O
O
OH
Ph
NH
O
Ph
O
OH
OBz
O
OAc
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

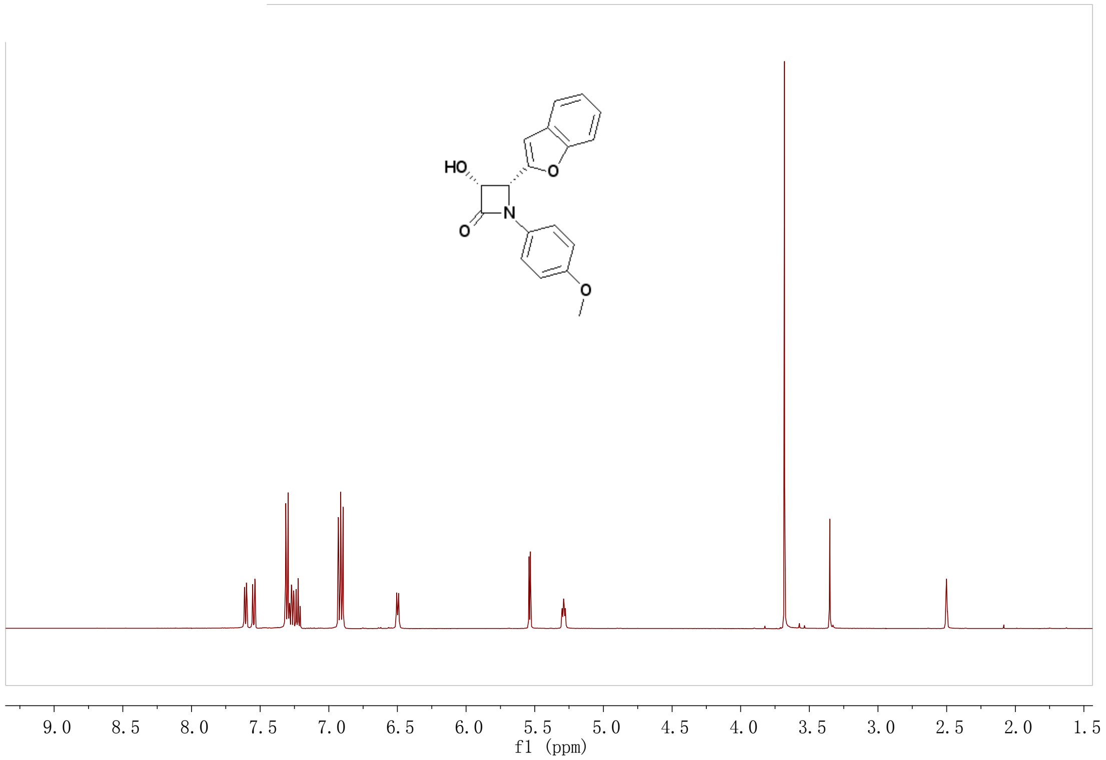

HO
O
O
O
O
O
OH
Ph
NH
O
Ph
O
OH
OBz
O
OAc
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

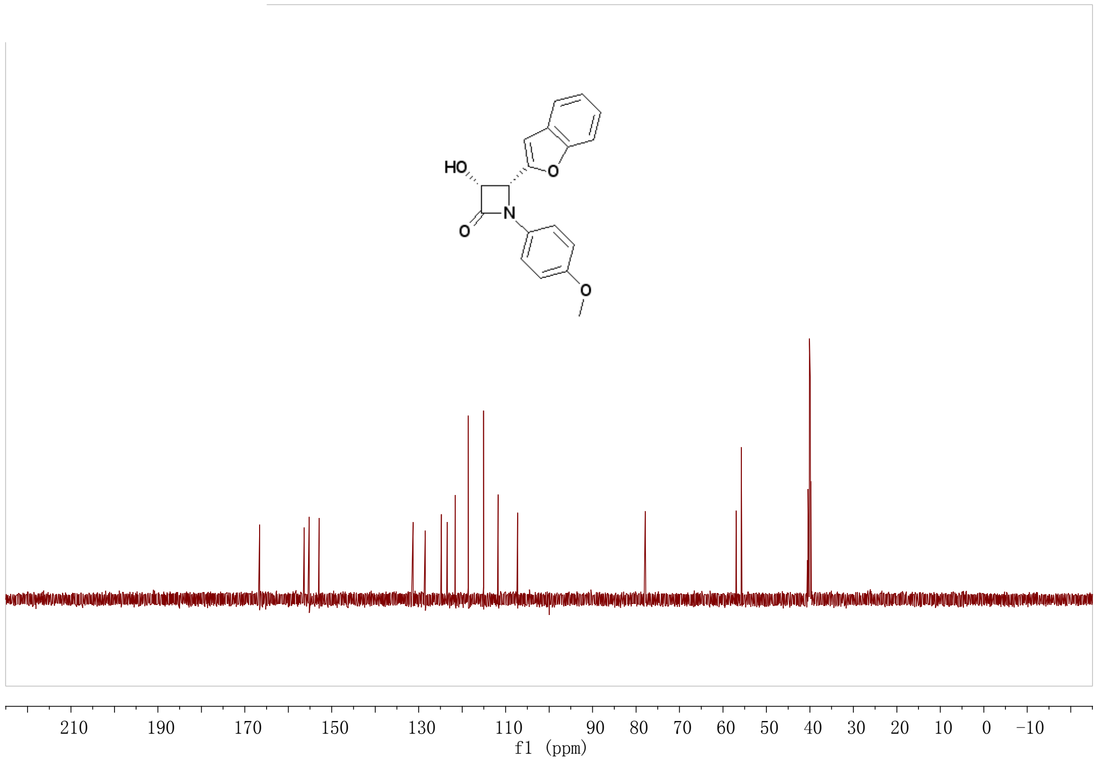

HO
O
O
O
O
O
O
O
O
O
OH
Ph
NH
O
Ph
O
OH
OBz
OAc
O
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

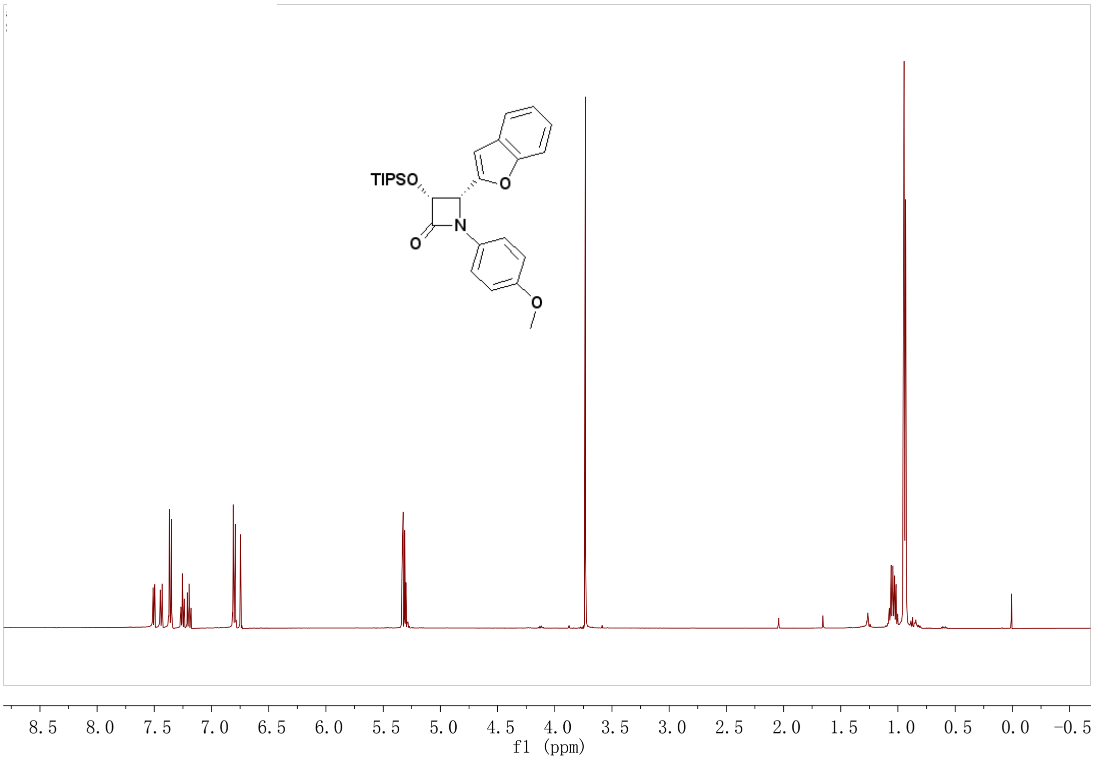

HO
O
O
O
O
O
O
O
O
O
OH
Ph
NH
O
Ph
O
OH
OBz
OAc
O
220
200
180
160
140
120
100
80
60
40
20
0
-10
f1 (ppm)

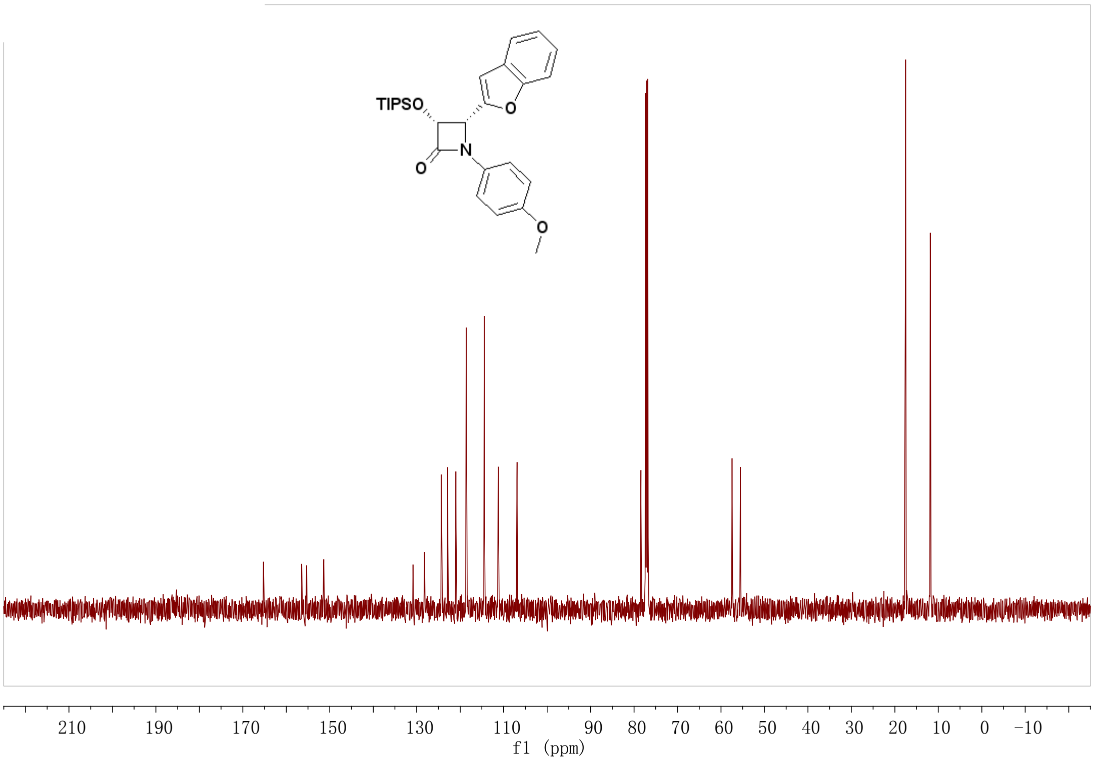

AcO
O
N
O
O
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

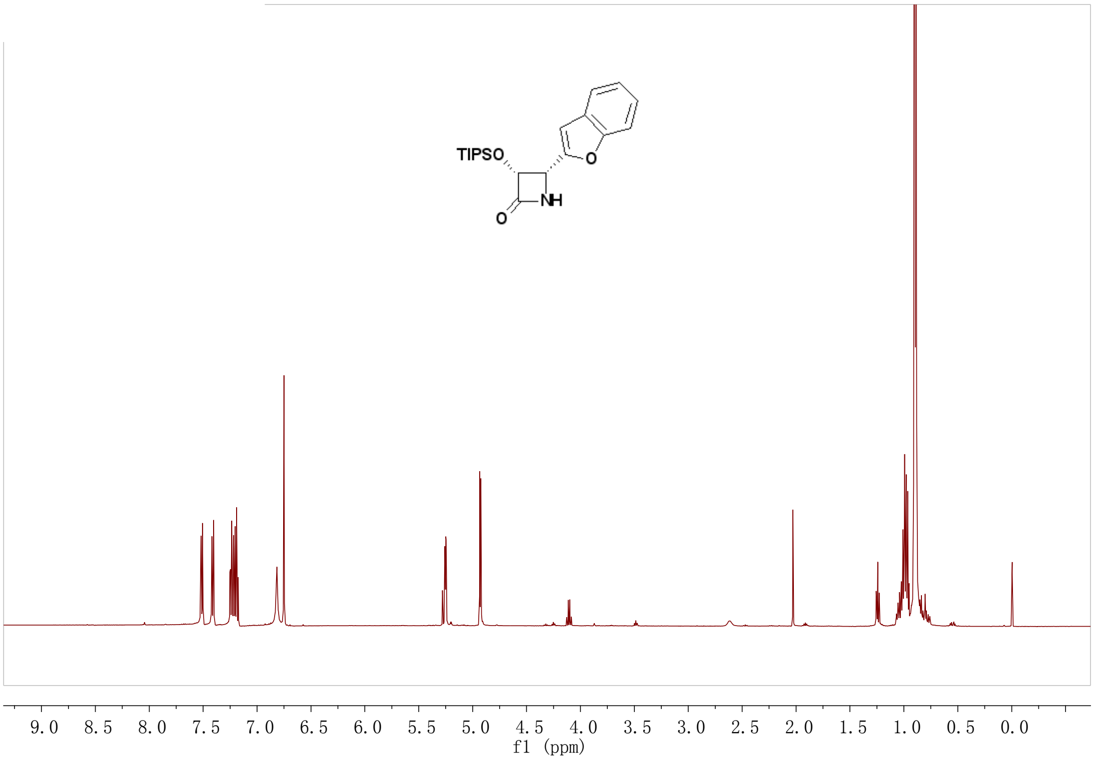

AcO
O
N
O
O
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

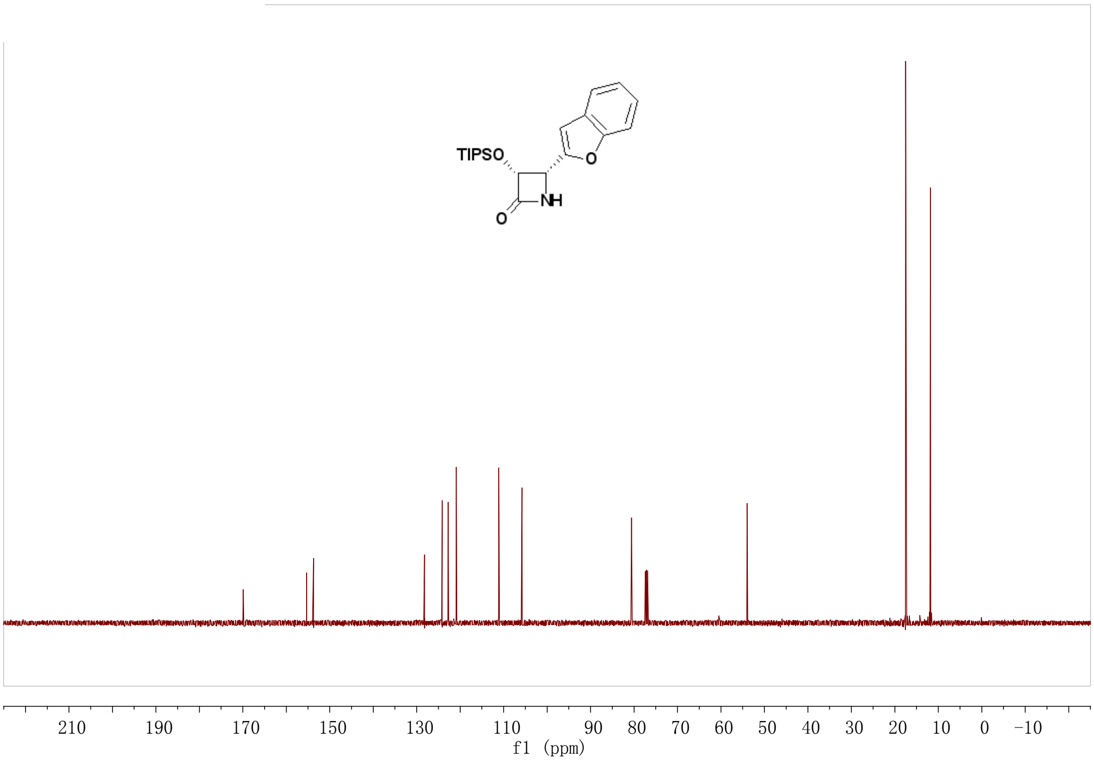

HO
N
O
O
O
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

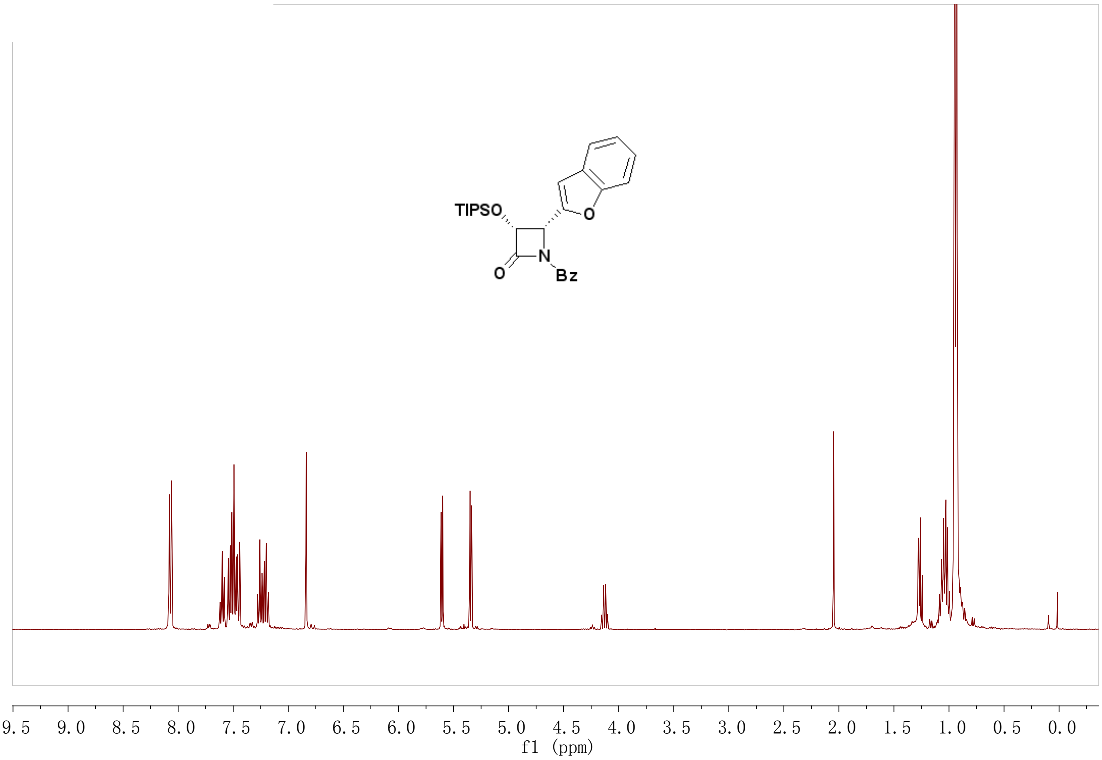

HO
N
O
O
O
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

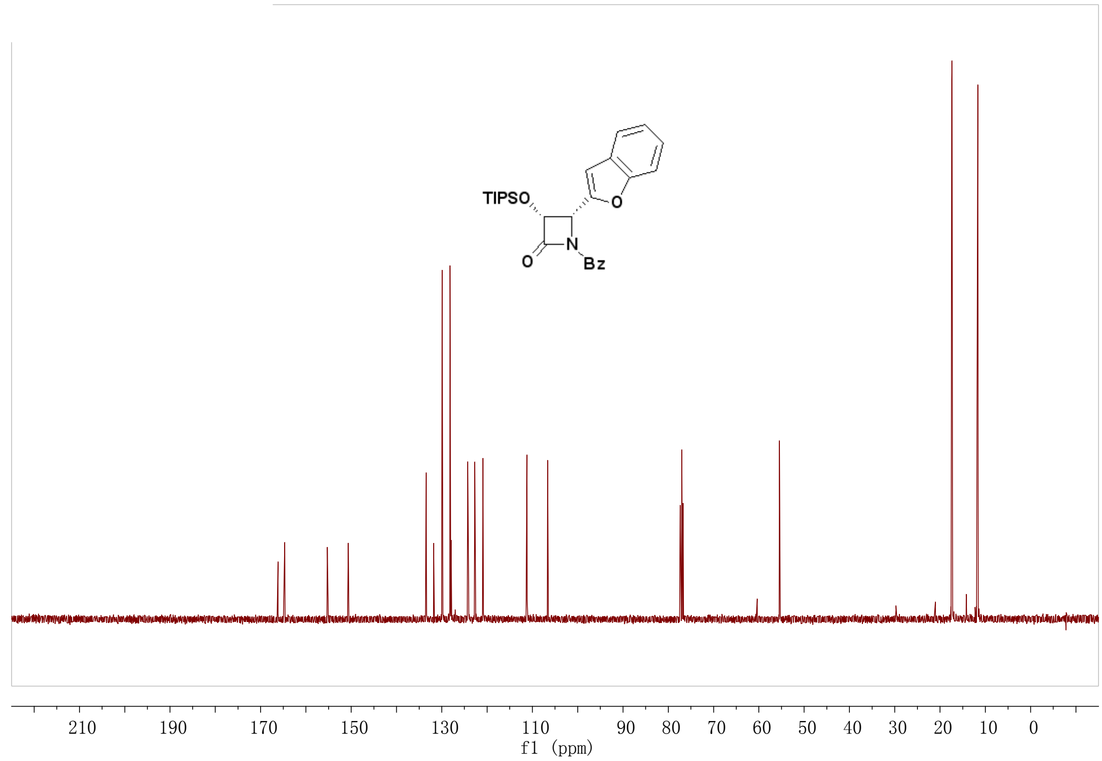

TIPSO
O
N
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

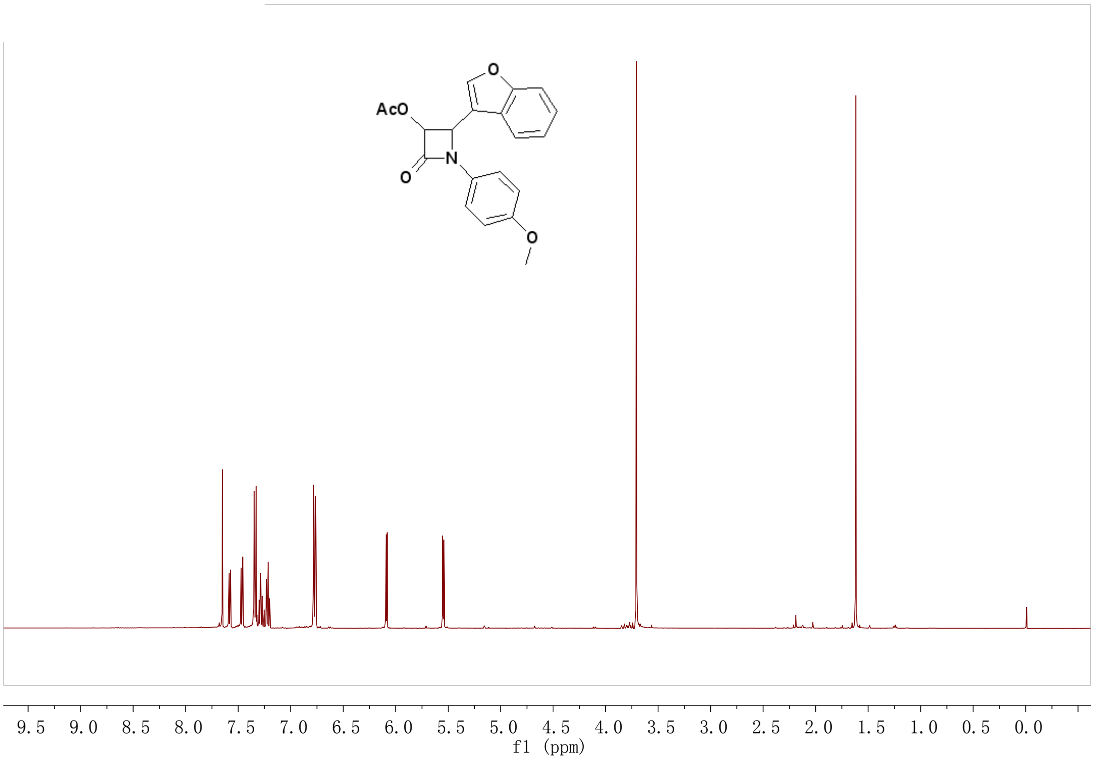

TIPSO
O
N
O
O
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

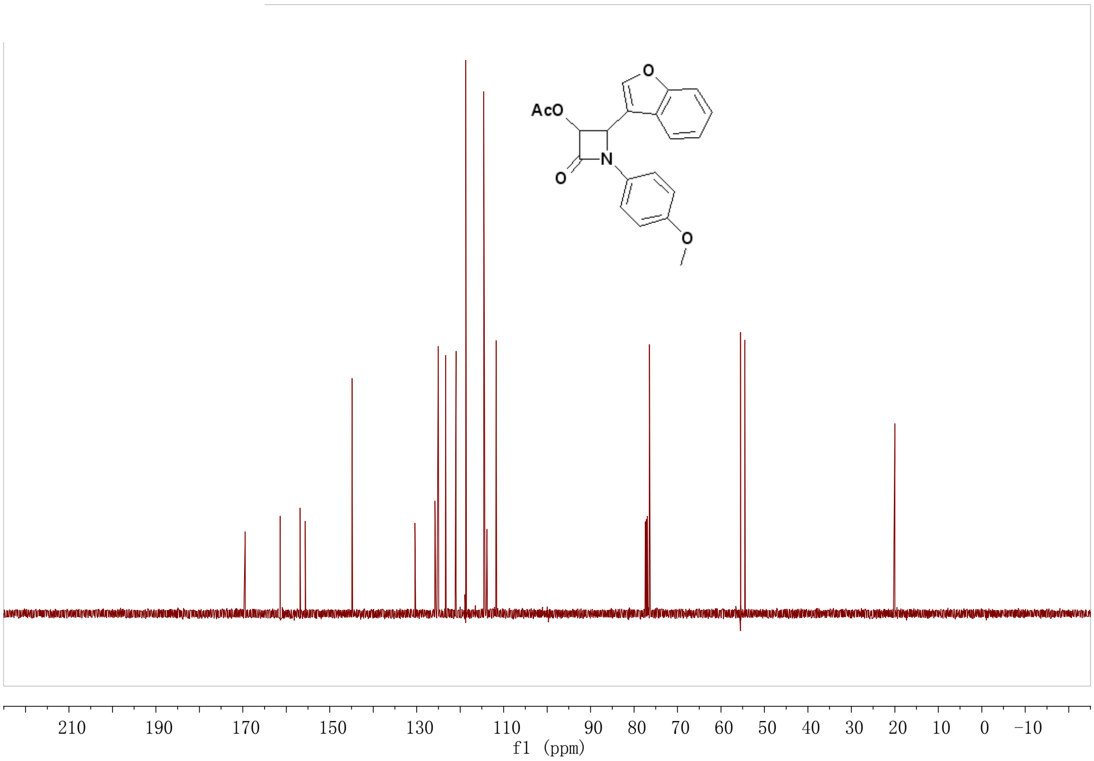

TIPSO
O
NH
O
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

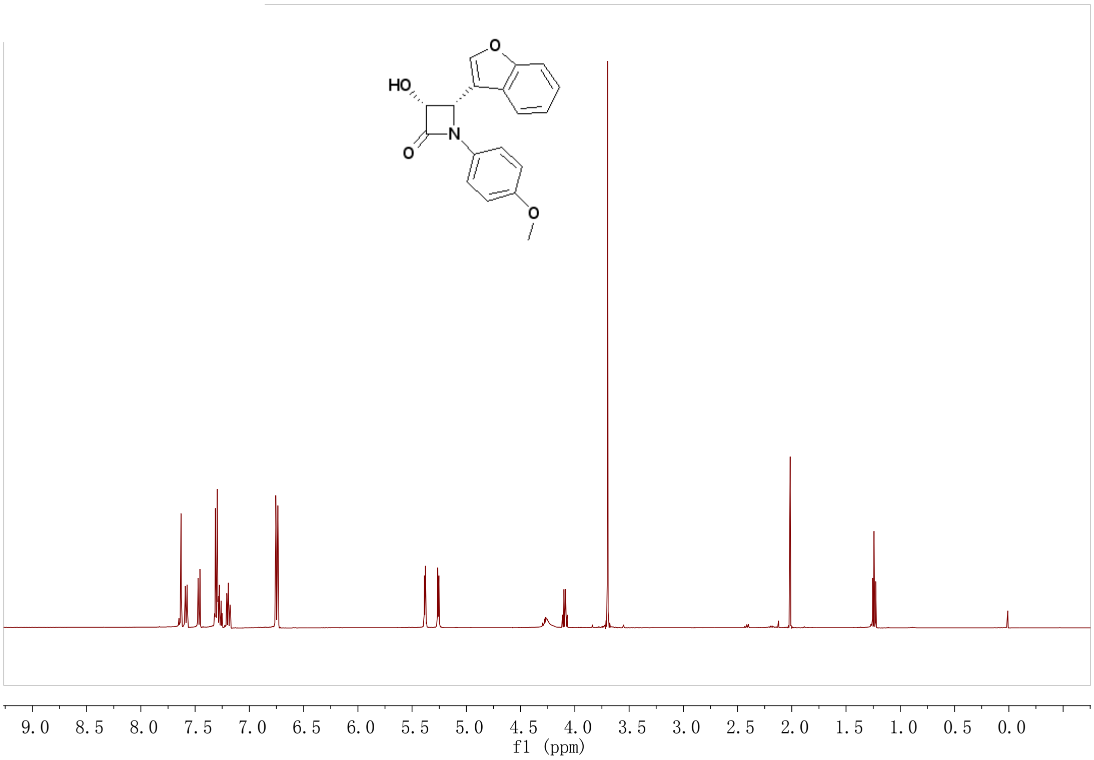

TIPSO
O
NH
O
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

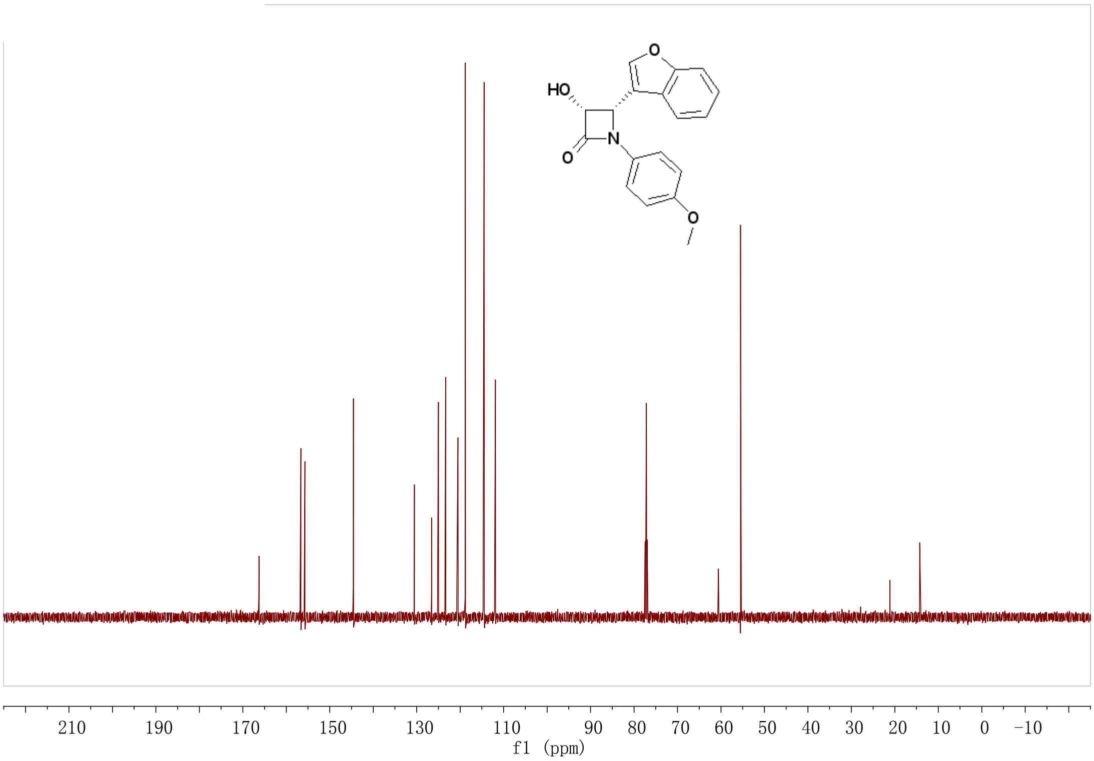

TIPSO
O
N
Bz
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

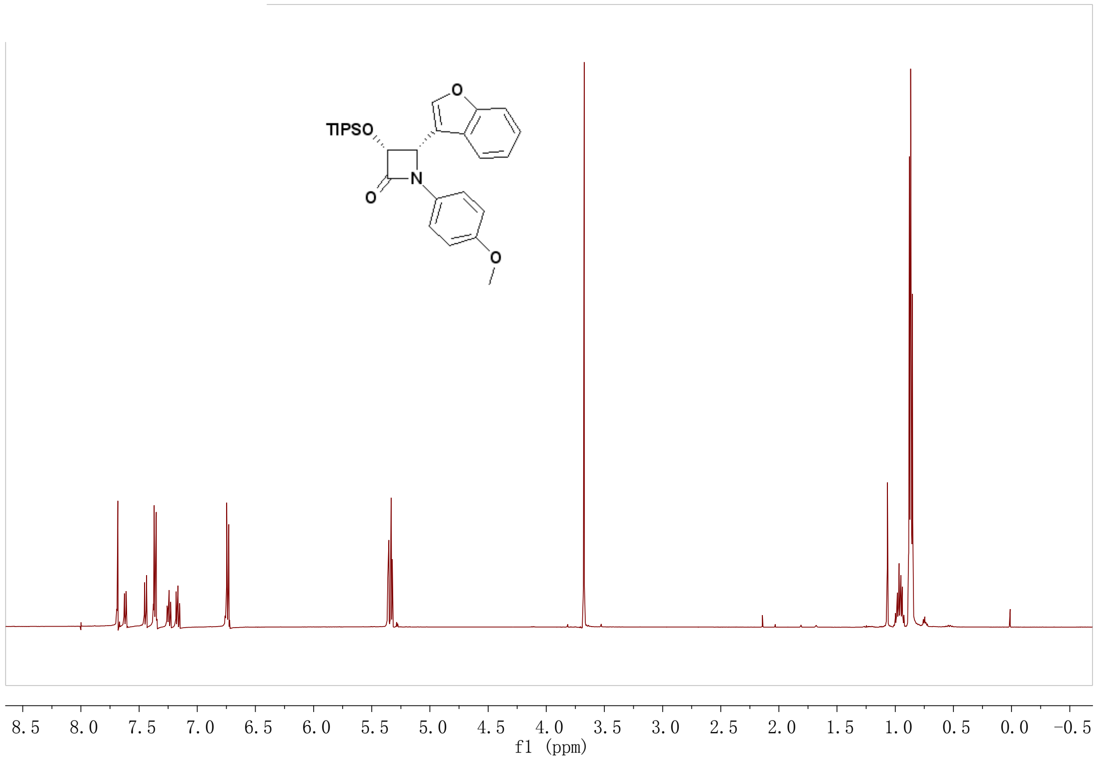

TIPSO
O
N
Bz
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

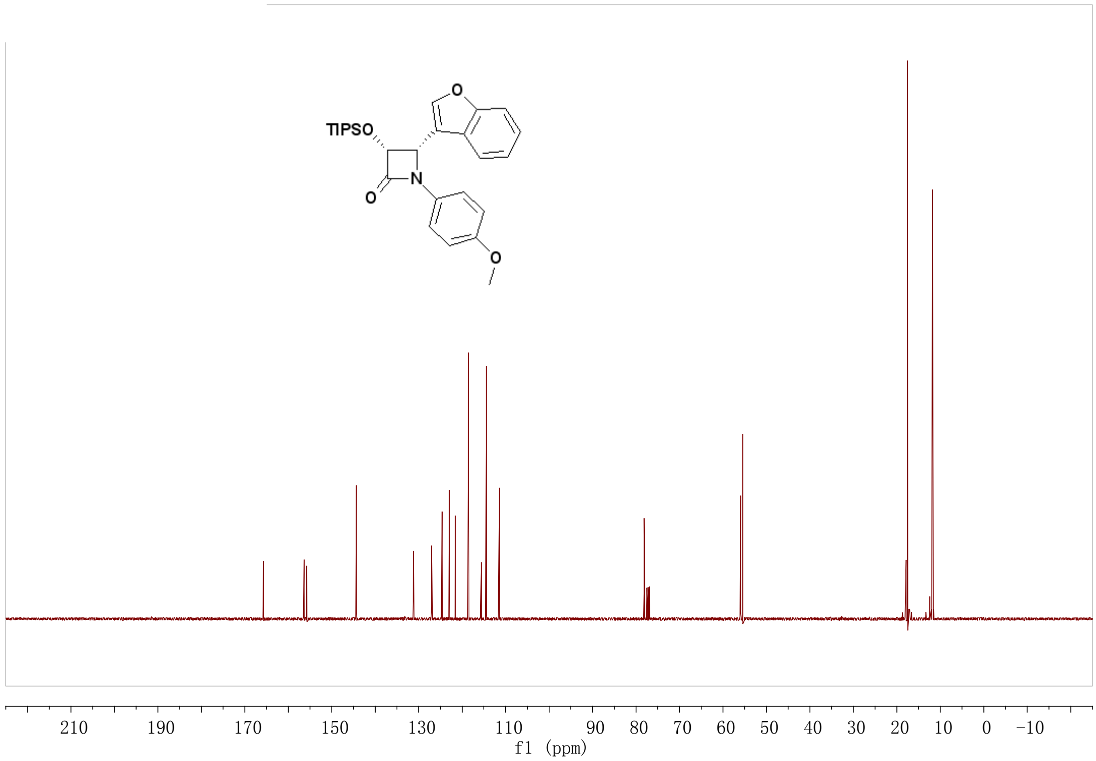

AcO
O
N
O
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

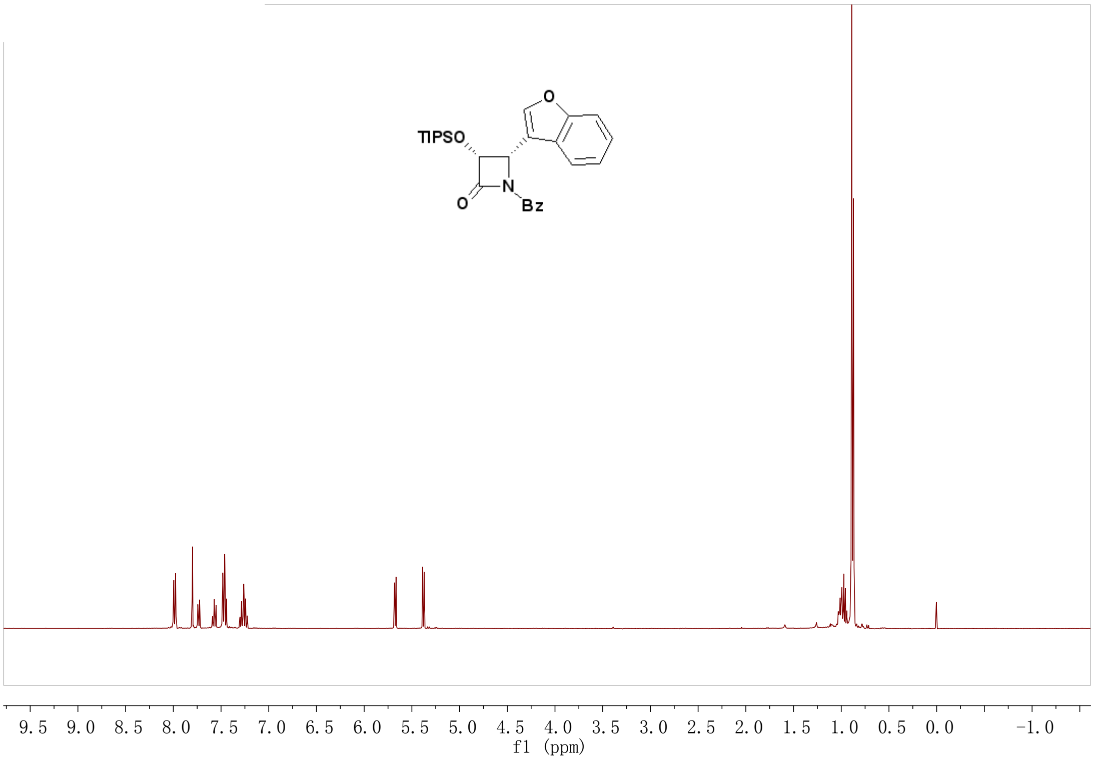

AcO
O
N
O
O
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

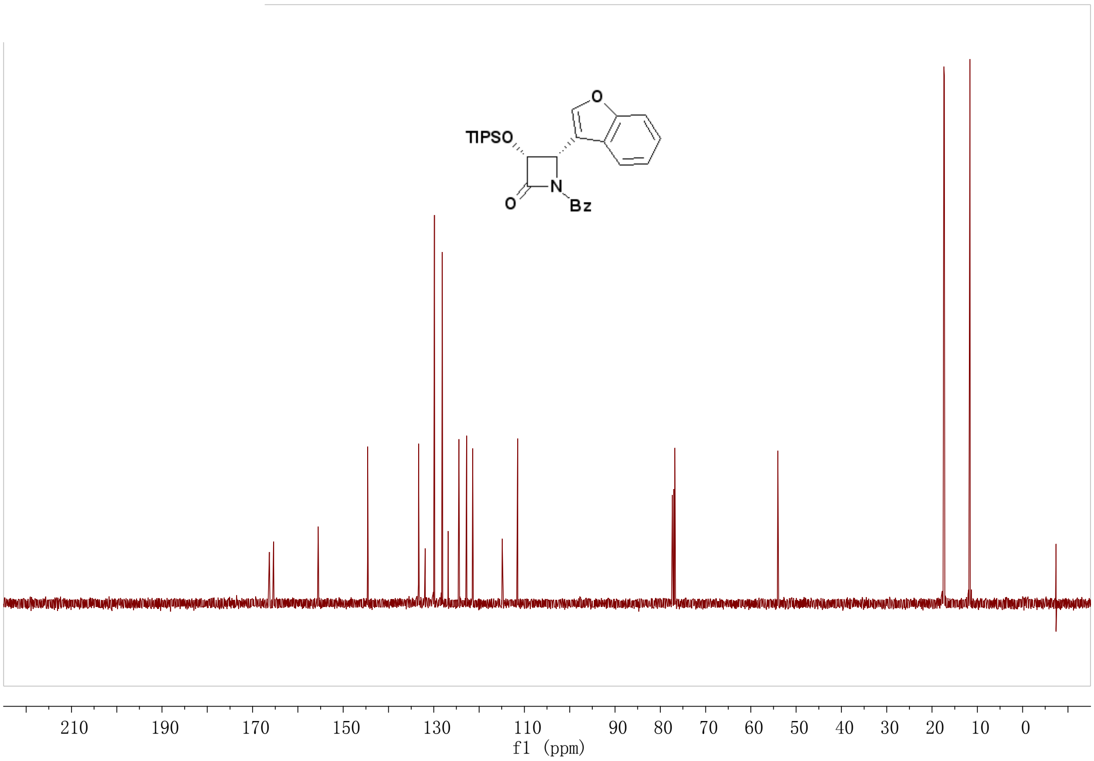

HO
O
N
O
O
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

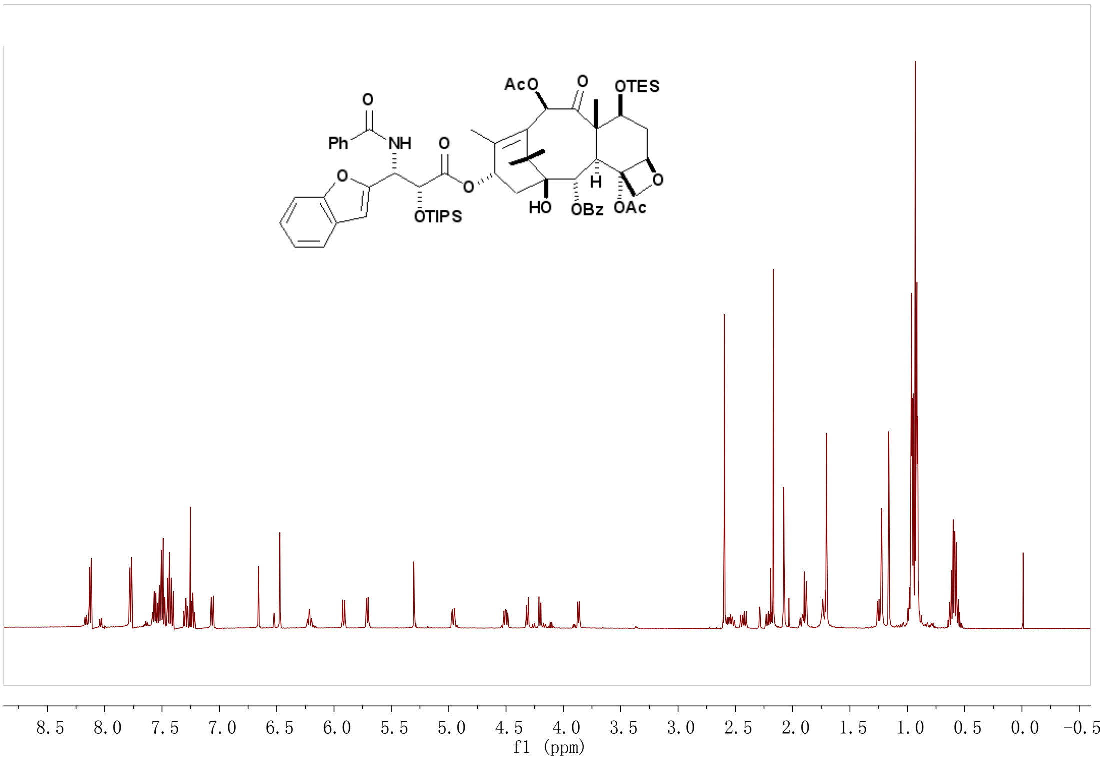

HO
O
N
O
O
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

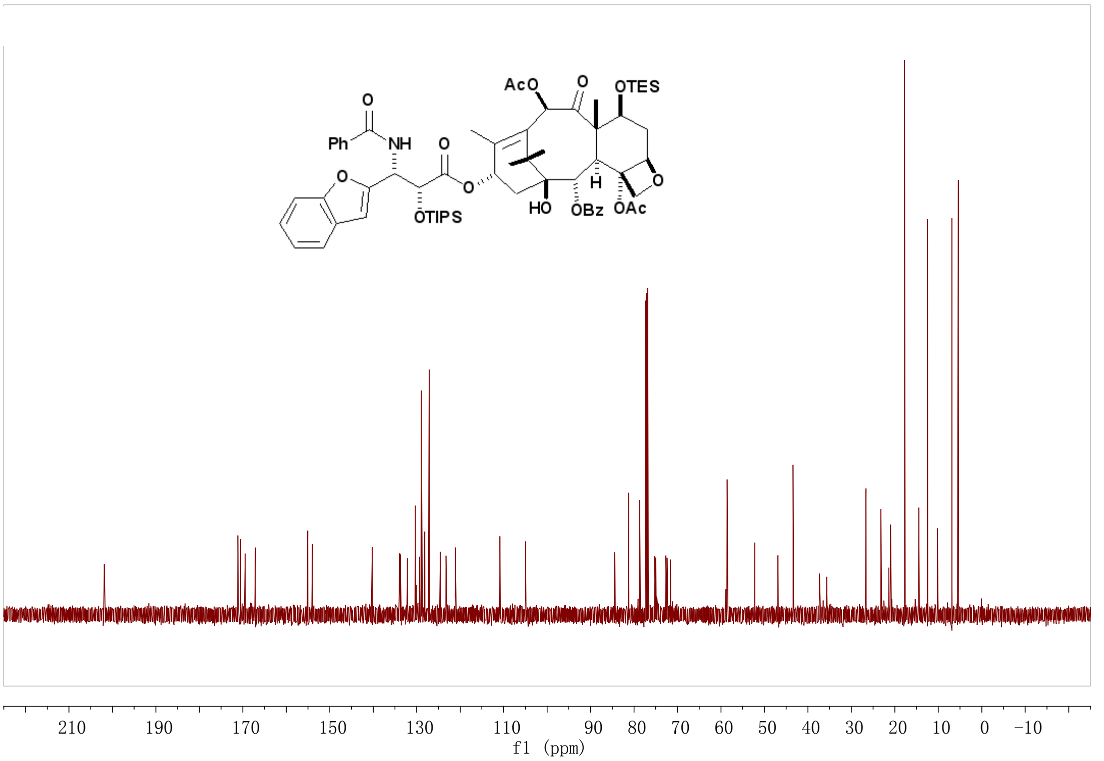

TIPSO
O
N
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

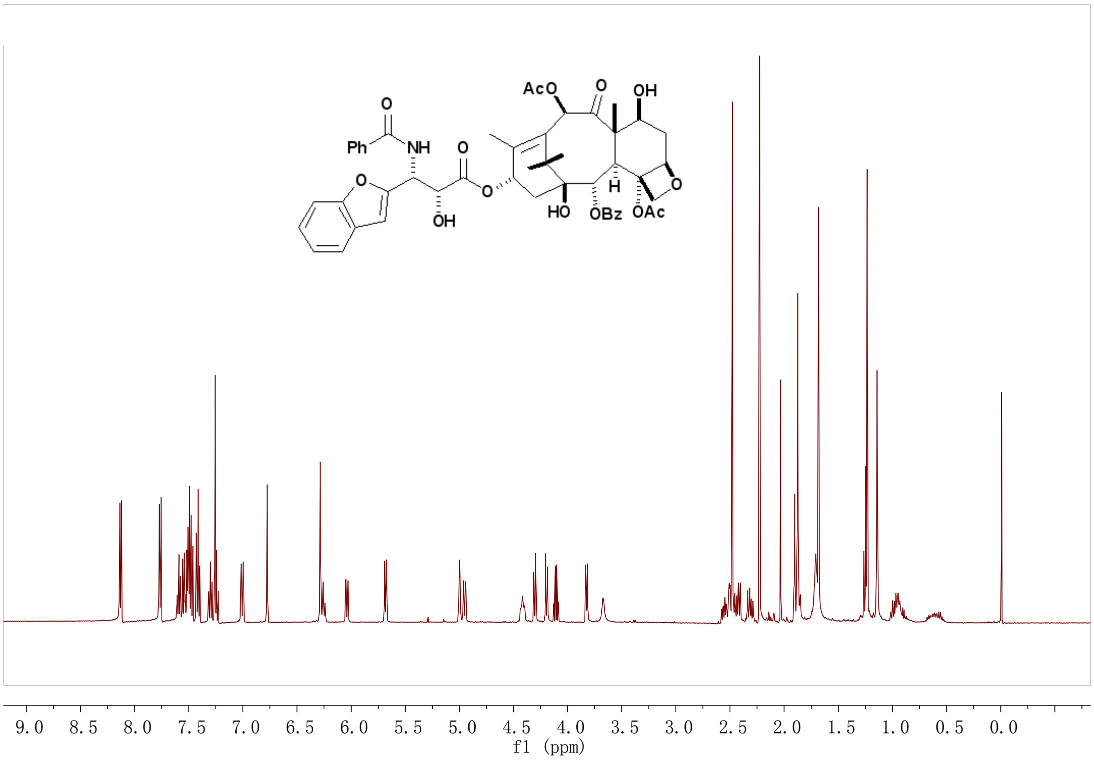

TIPSO
O
N
O
O
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

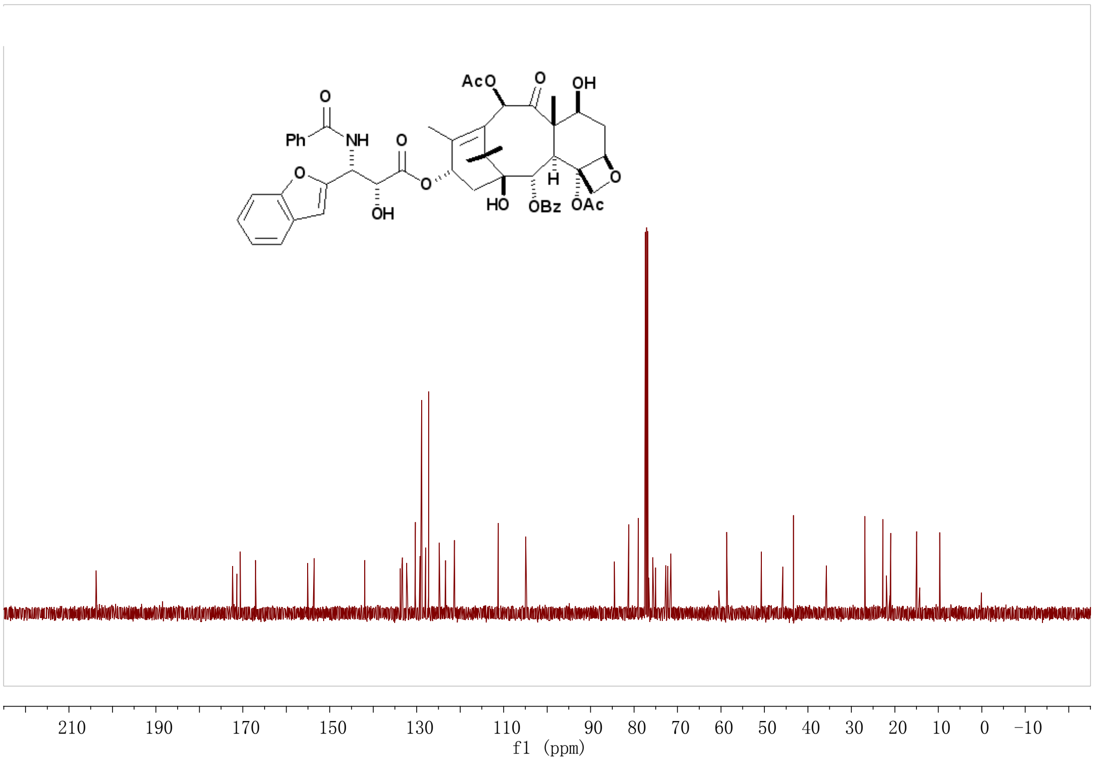

TIPSO
O
N
Bz
O
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-1.0
f1 (ppm)

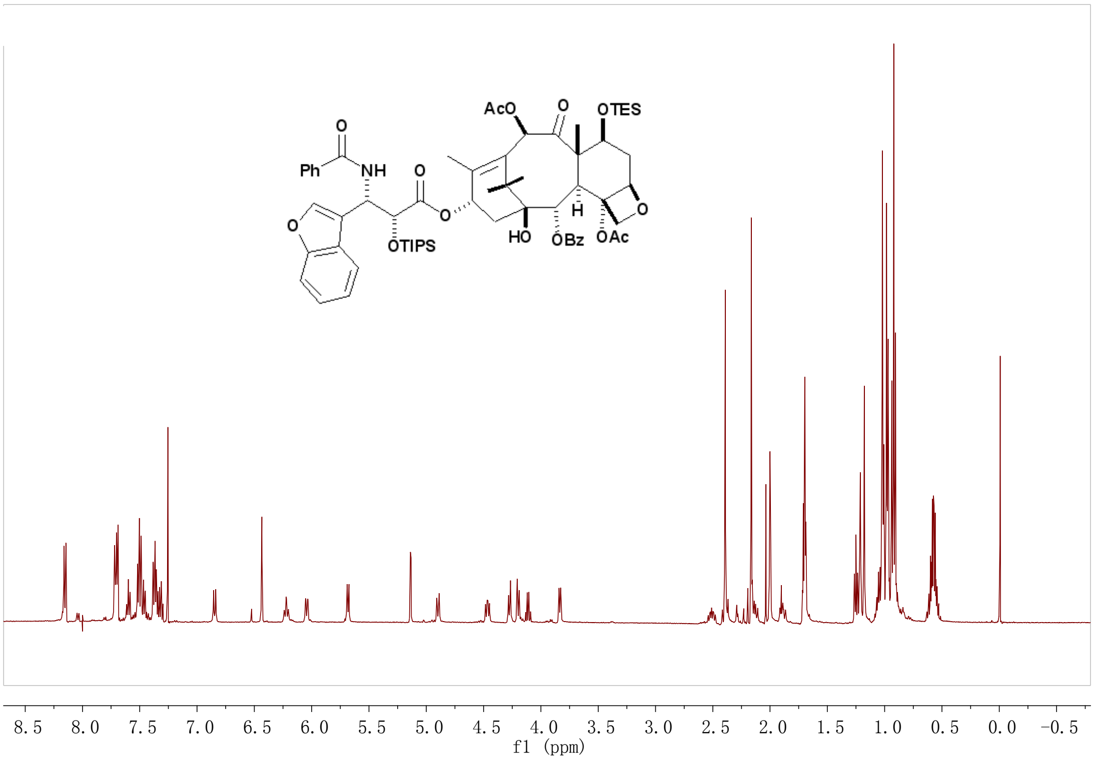

TIPSO
O
N
Bz
O
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

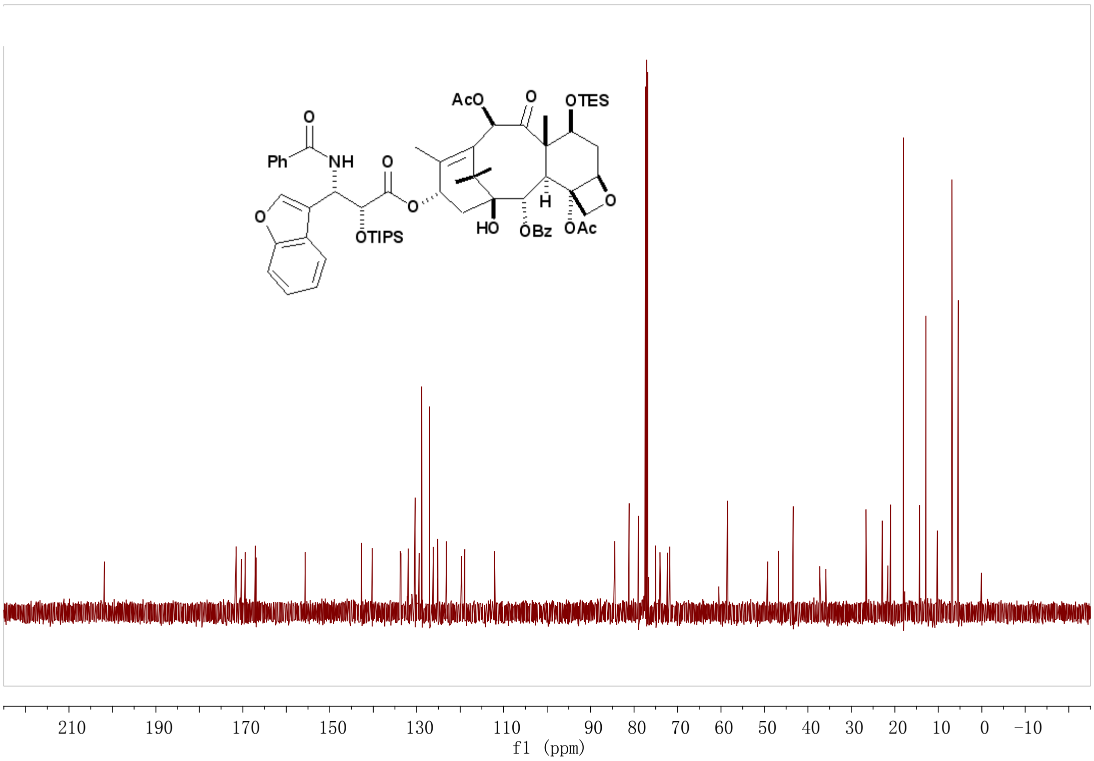

AcO
O
OTES
O
Ph
NH
O
O
O
OTIPS
HO
OBz
H
OAc
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


AcO
O
OTES
O
Ph
NH
O
O
O
OTIPS
HO
OBz
H
OAc
O
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


AcO
O
OH
O
Ph
NH
O
O
O
O
OH
HO
H
OBz
OAc
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


AcO
O
OH
O
Ph
NH
O
O
O
O
OH
HO
H
OBz
OAc
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


AcO
O
OTES
O
Ph
NH
O
O
O
OTIPS
HO
H
OBz
OAc
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


AcO
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O
Ph
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O
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OTIPS
HO
H
OBz
OAc
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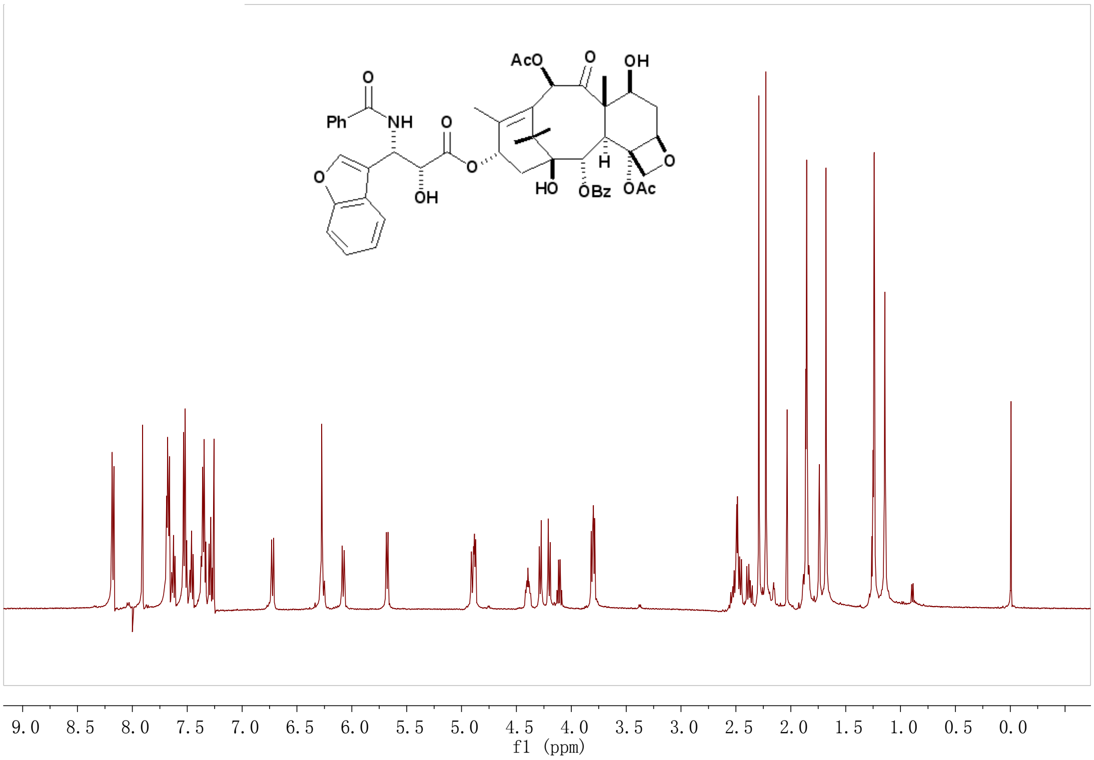
-10
f1 (ppm)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OBz
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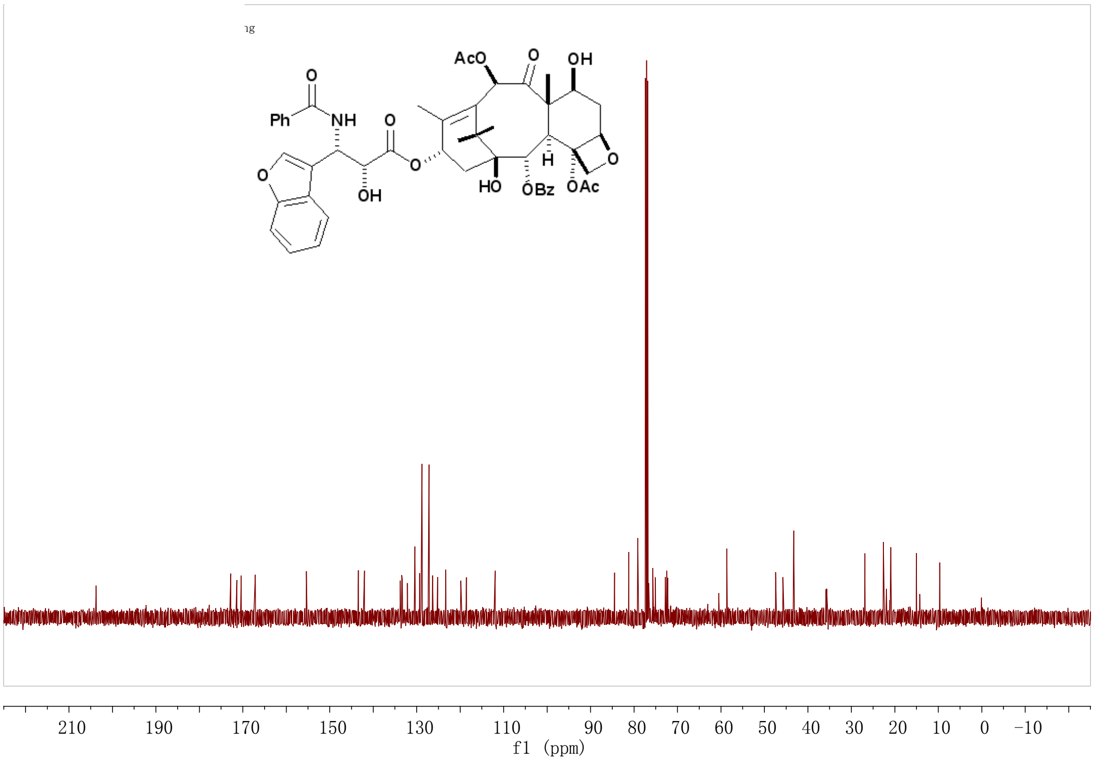
f1 (ppm)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OH
HO
OBz
OAc
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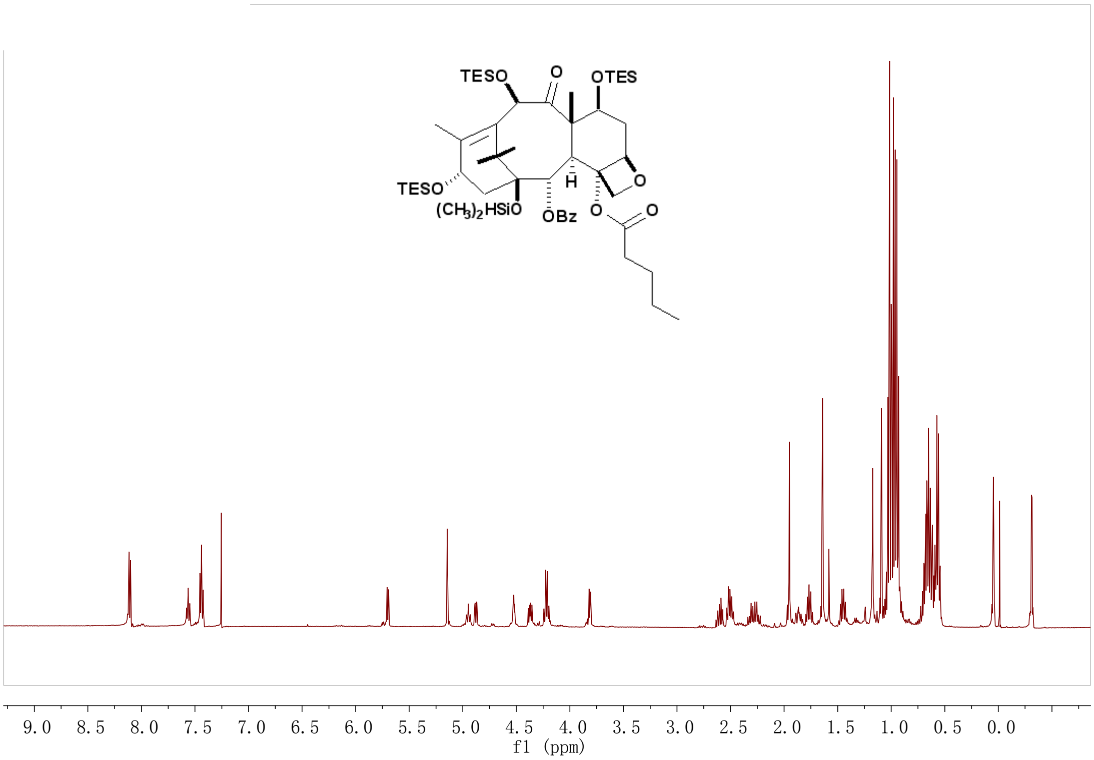
f1 (ppm)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OTES
H
O
TESO
(CH3)2HSiO
OBz
O
O
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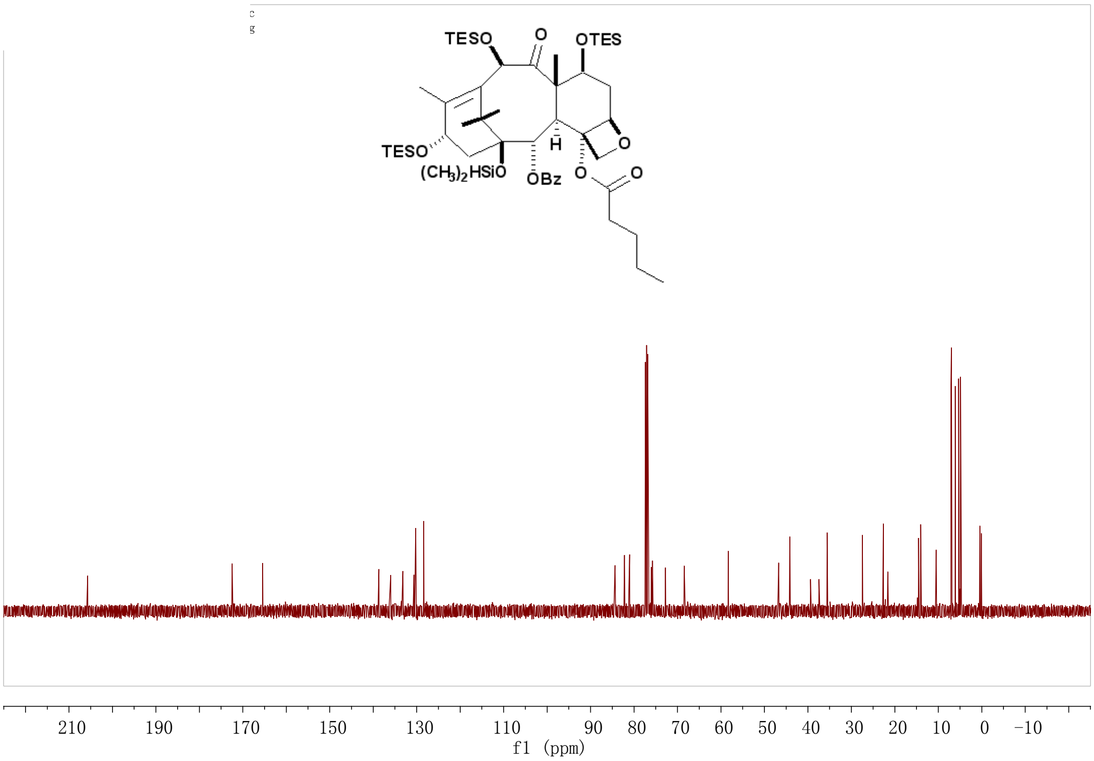
f1 (ppm)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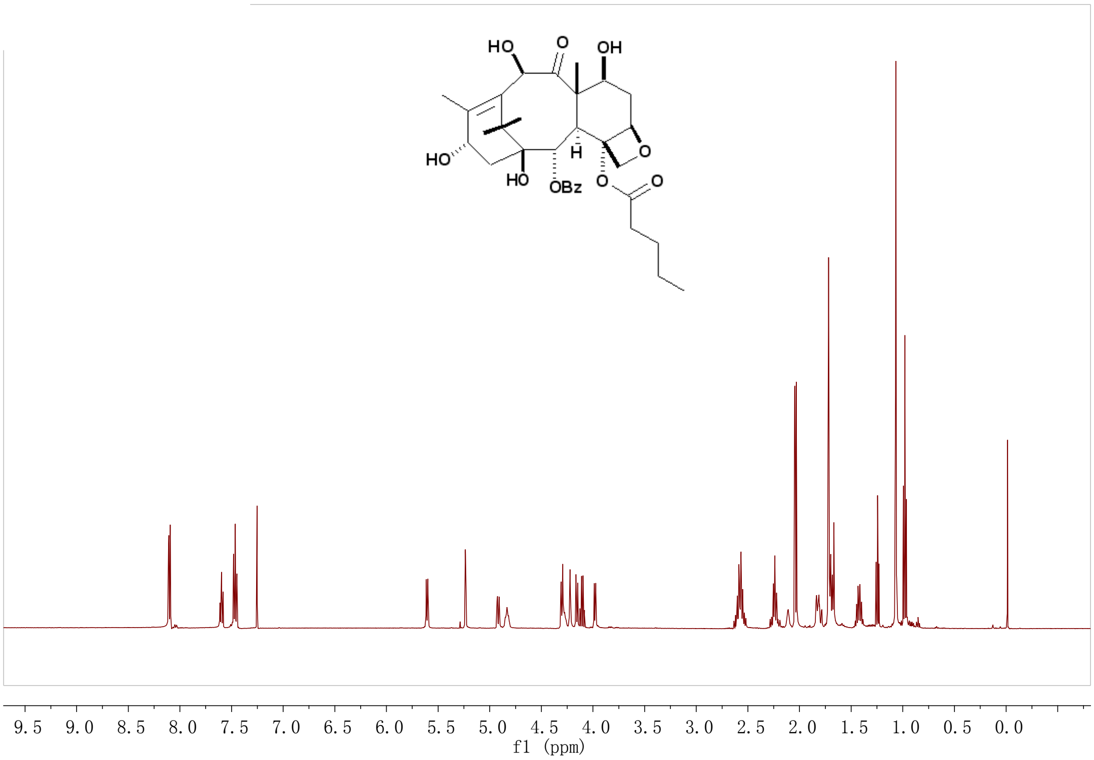
TESO
(CH3)2HSiO
OBz
O
O
210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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OH
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HO
HO
OBz
O
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6.0
5.5
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1.0
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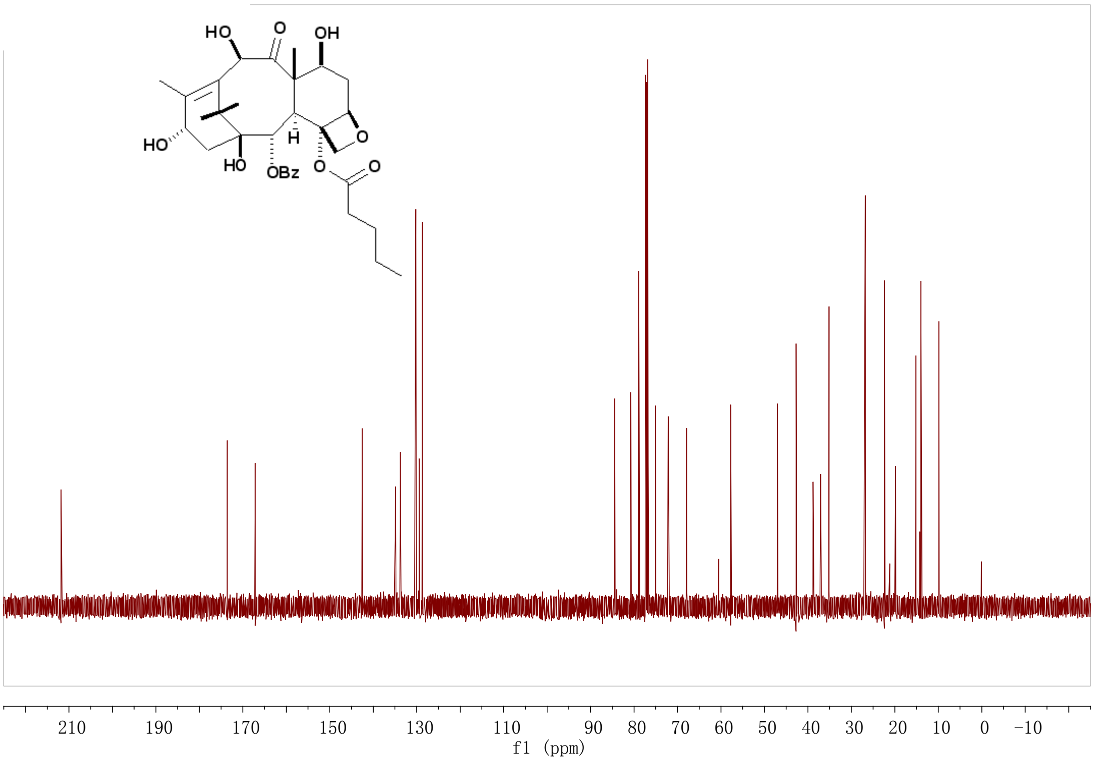
0.0
f1 (ppm)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OH
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HO
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OBz
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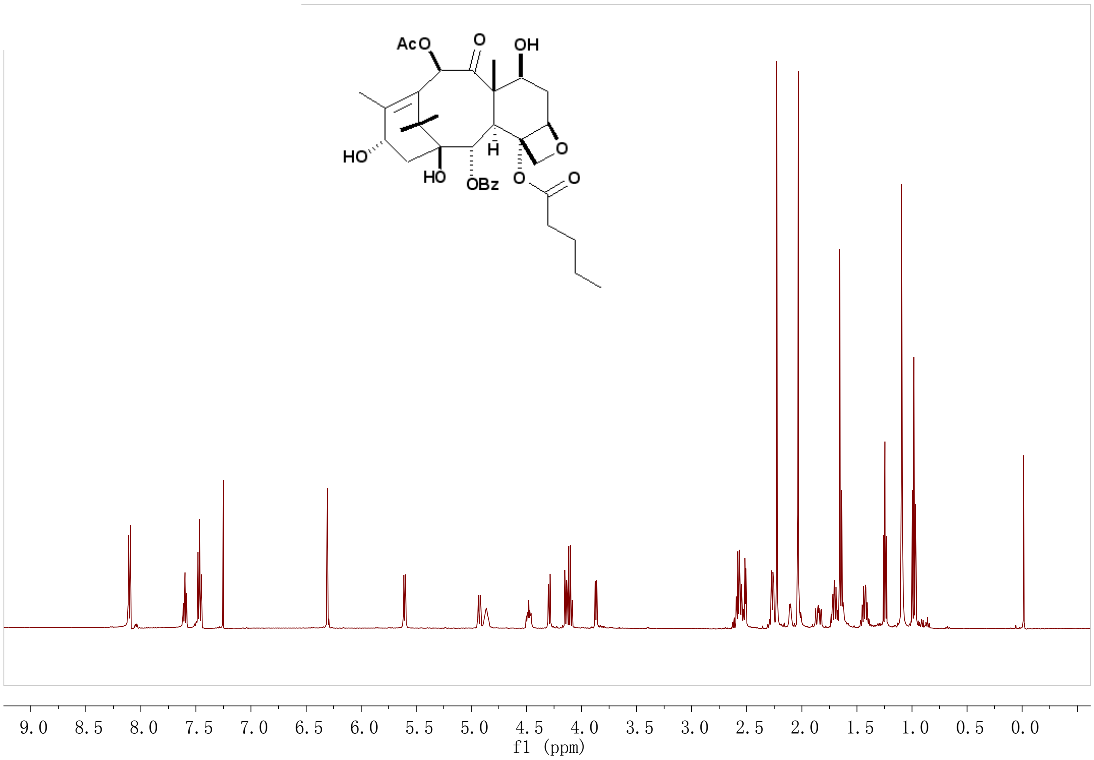
f1 (ppm)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OH
HO
HO
H
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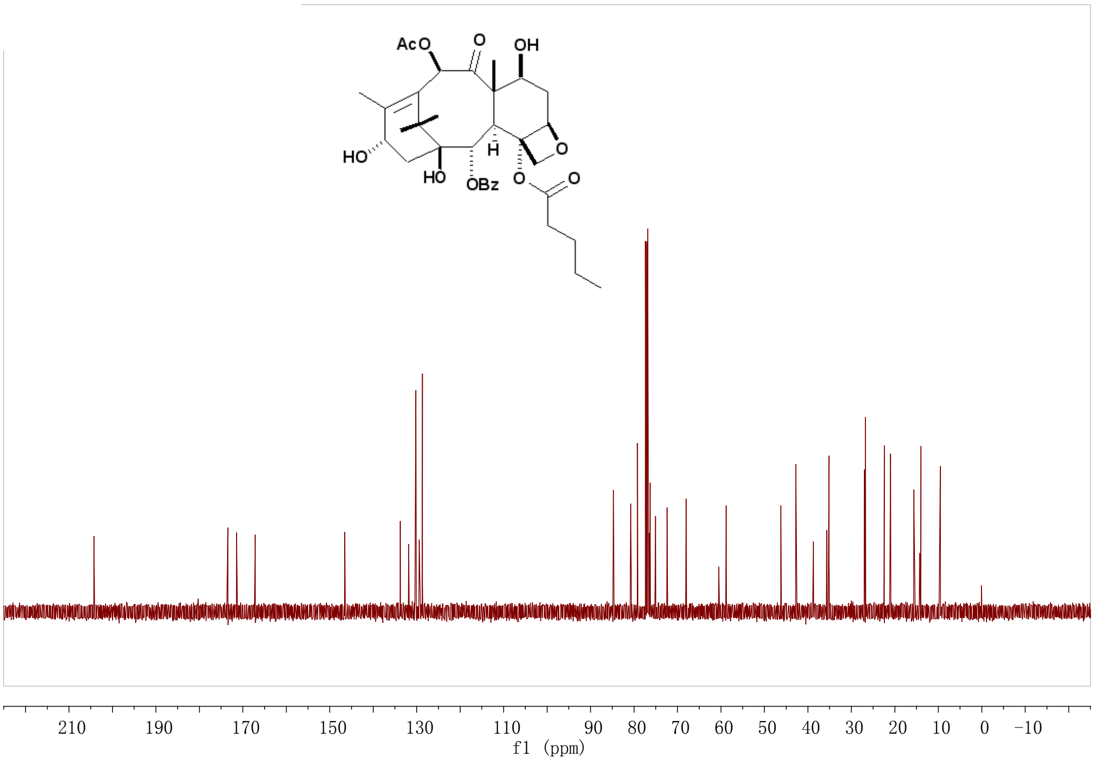
f1 (ppm)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HO
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OBz
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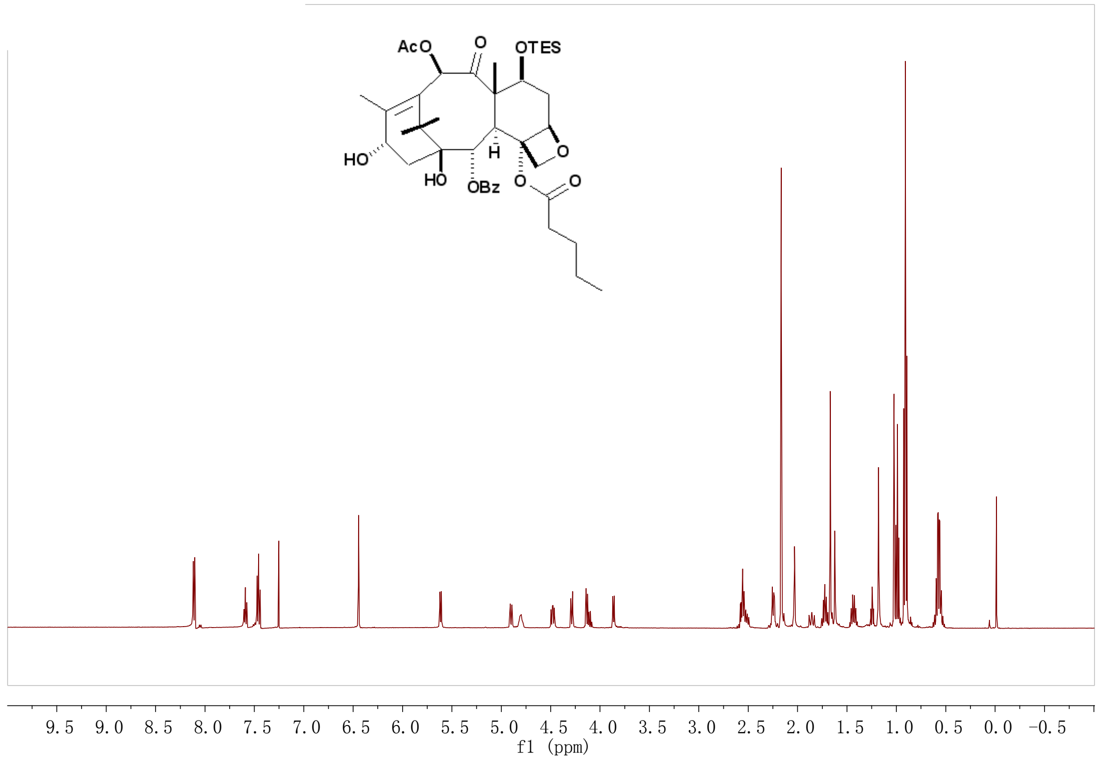
f1 (ppm)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HO
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ŌBz
O
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8.0
7.5
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6.5
6.0
5.5
5.0
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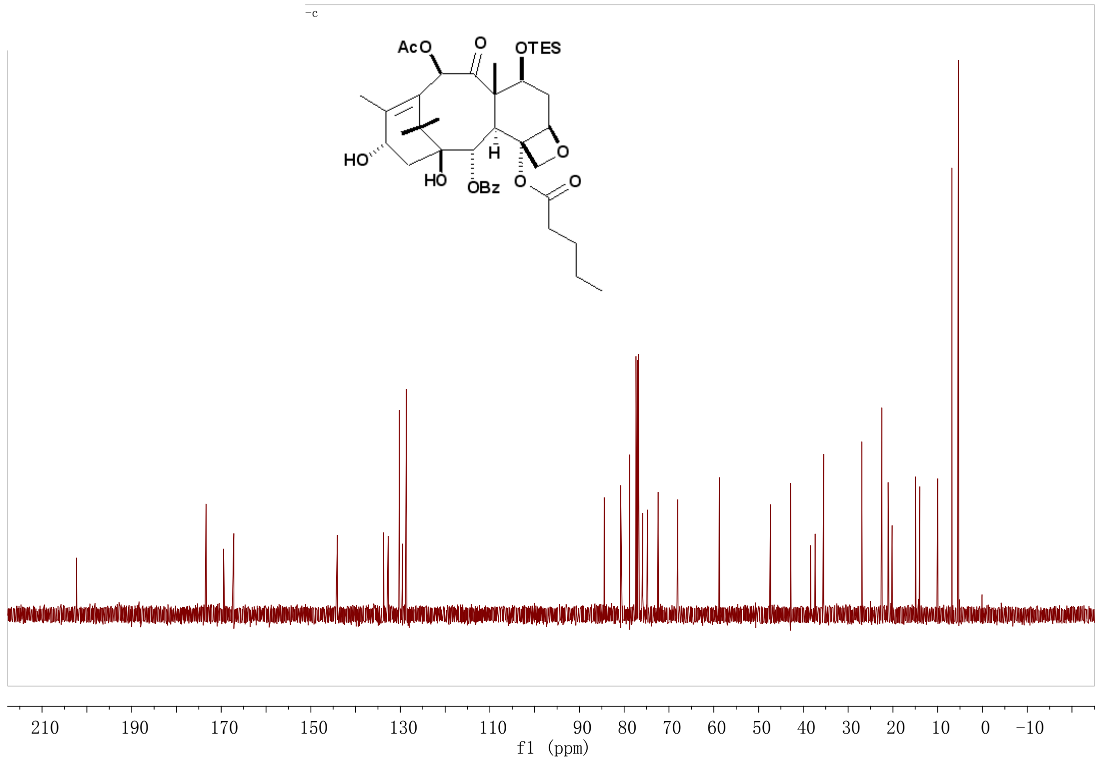
f1 (ppm)


-c
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OTES
HO
HO
H
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ŌBz
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0
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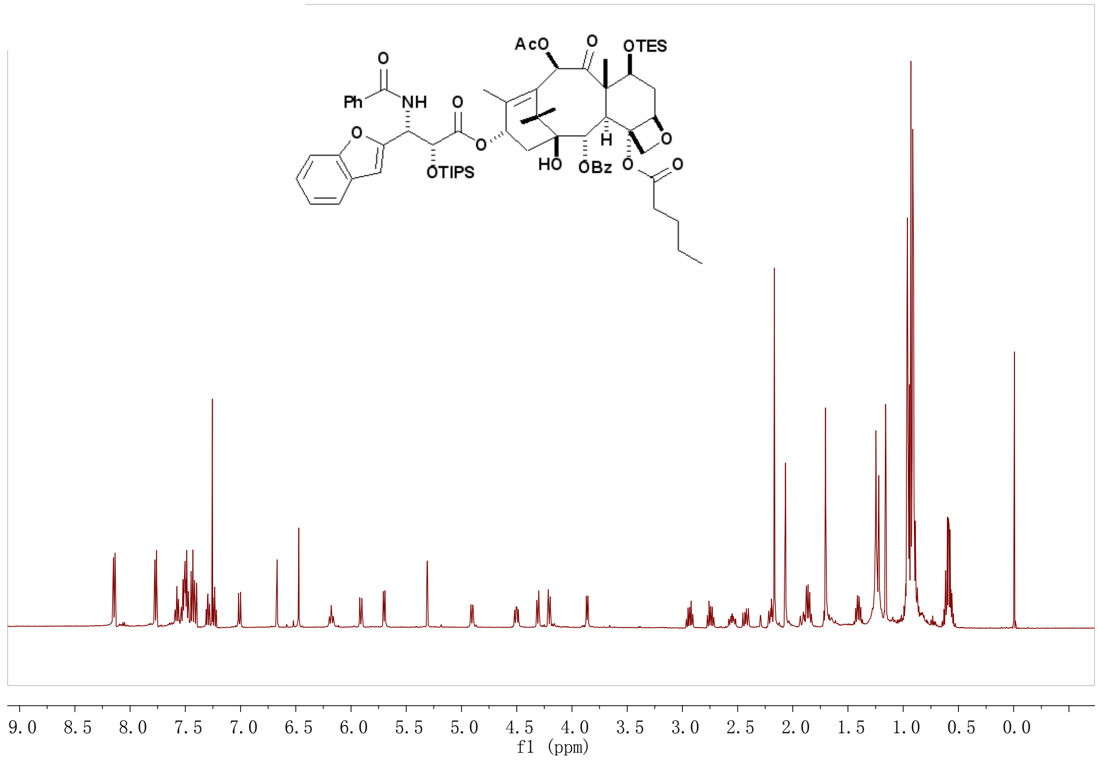
f1 (ppm)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OTIPS
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8.0
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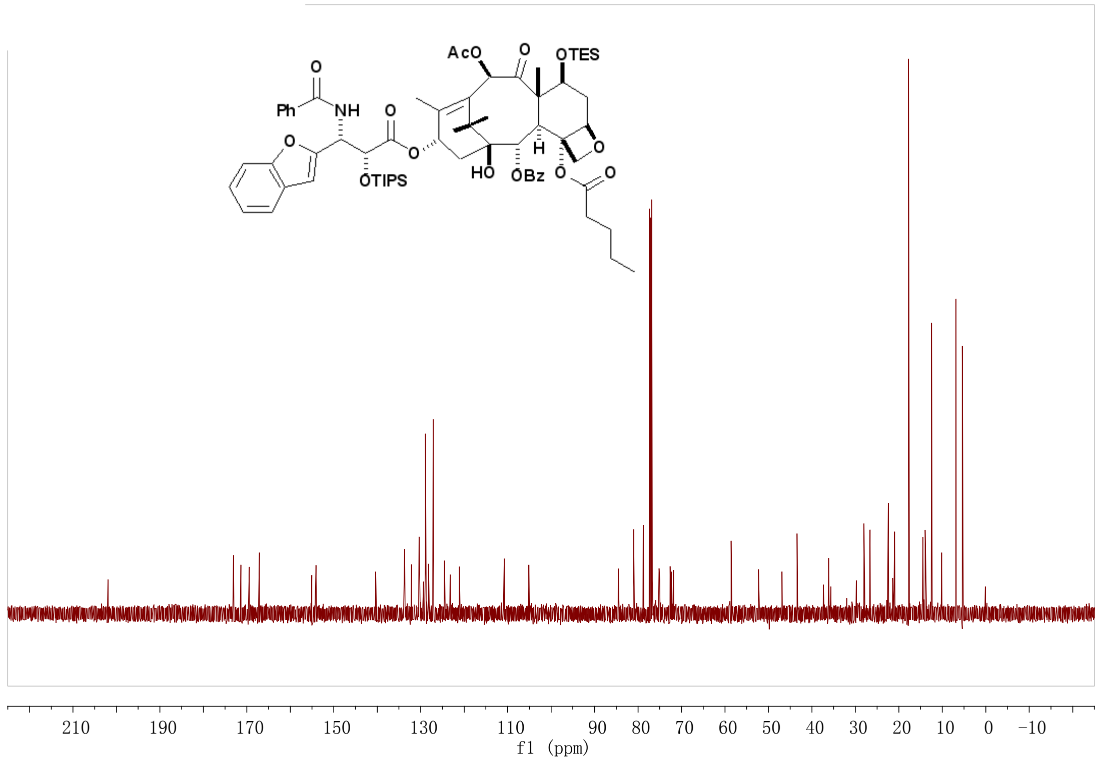
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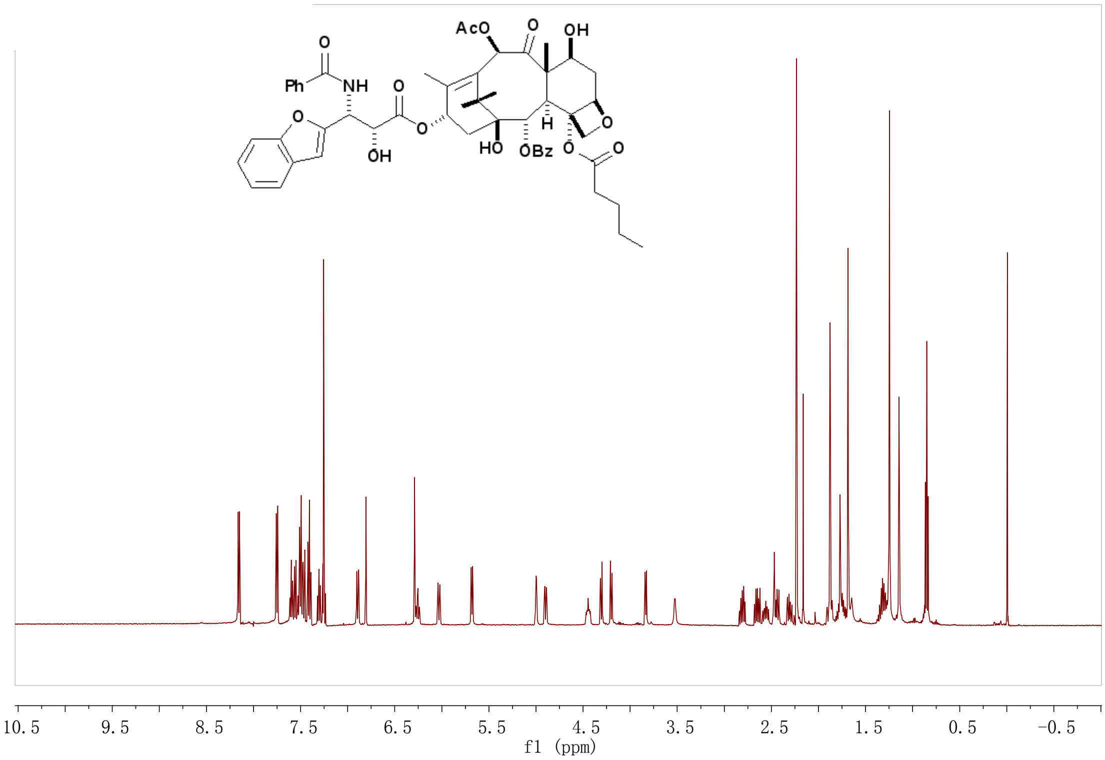
f1 (ppm)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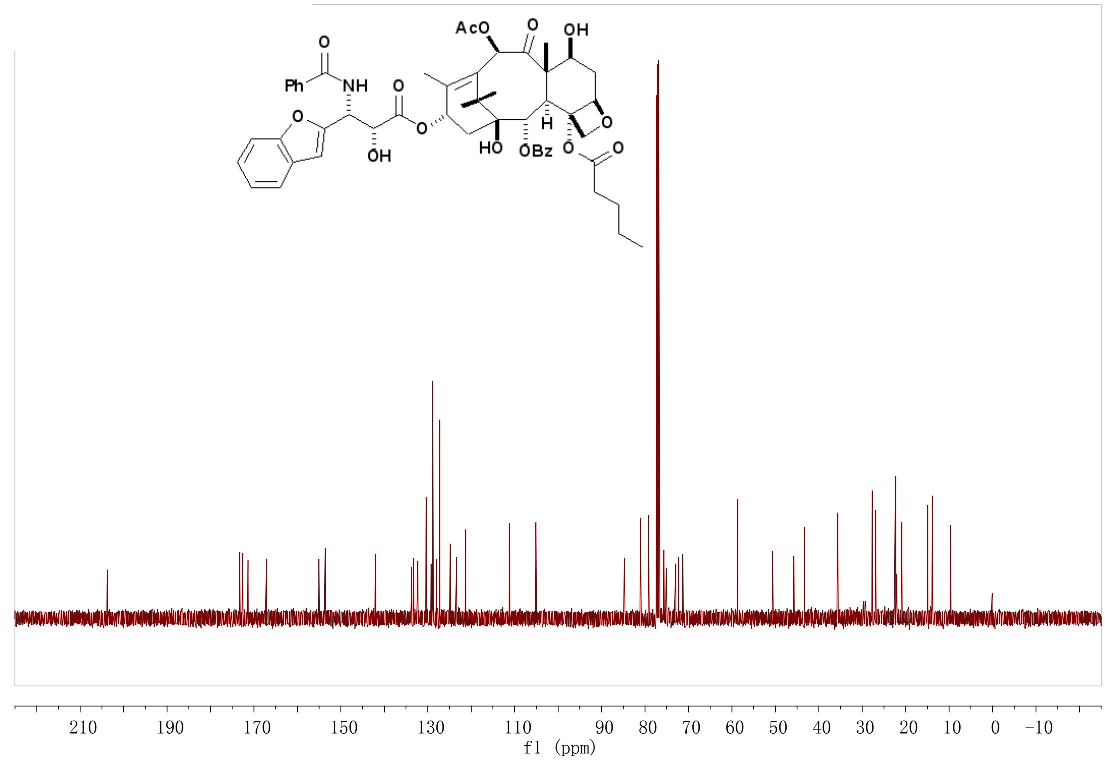
f1 (ppm)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OBz
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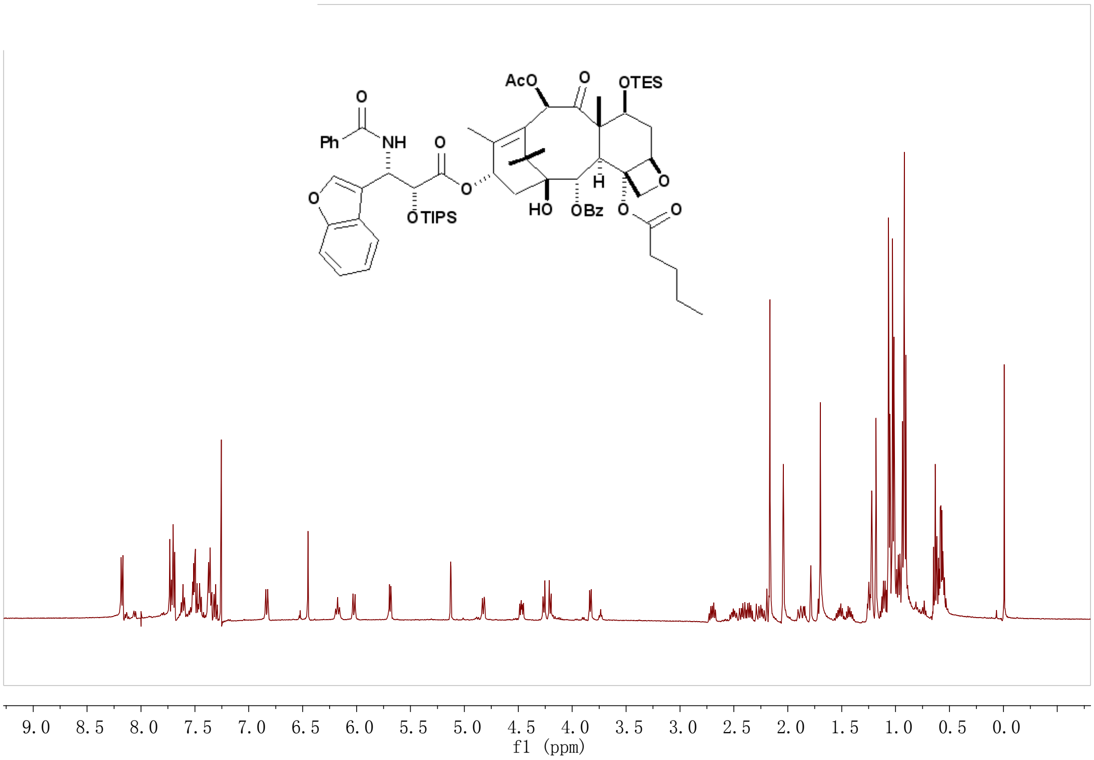
f1 (ppm)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Ph
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OTIPS
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OBz
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6.0
5.5
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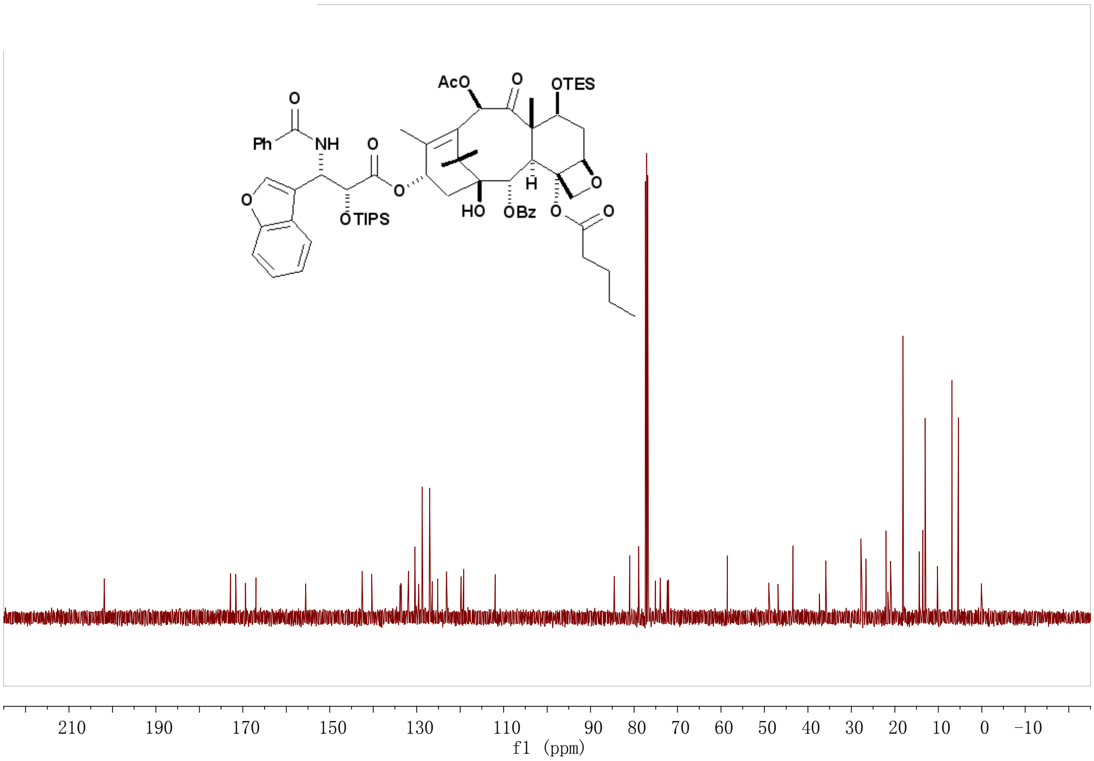
f1 (ppm)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Ph
NH
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OTIPS
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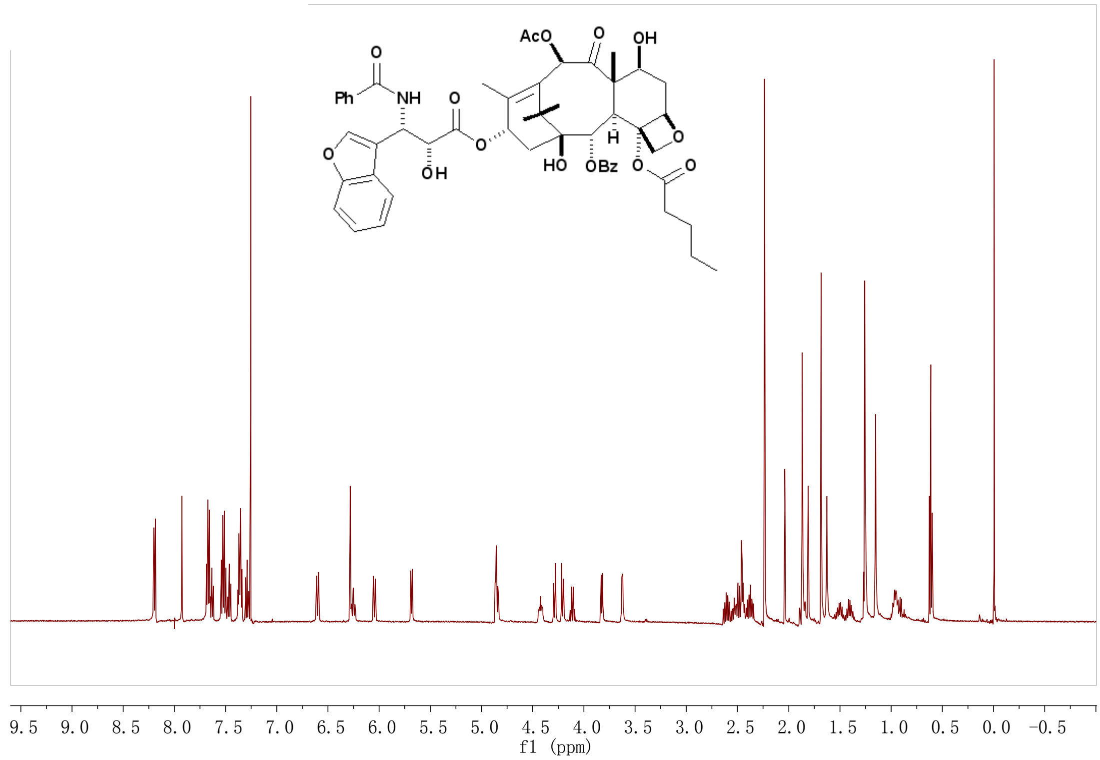
f1 (ppm)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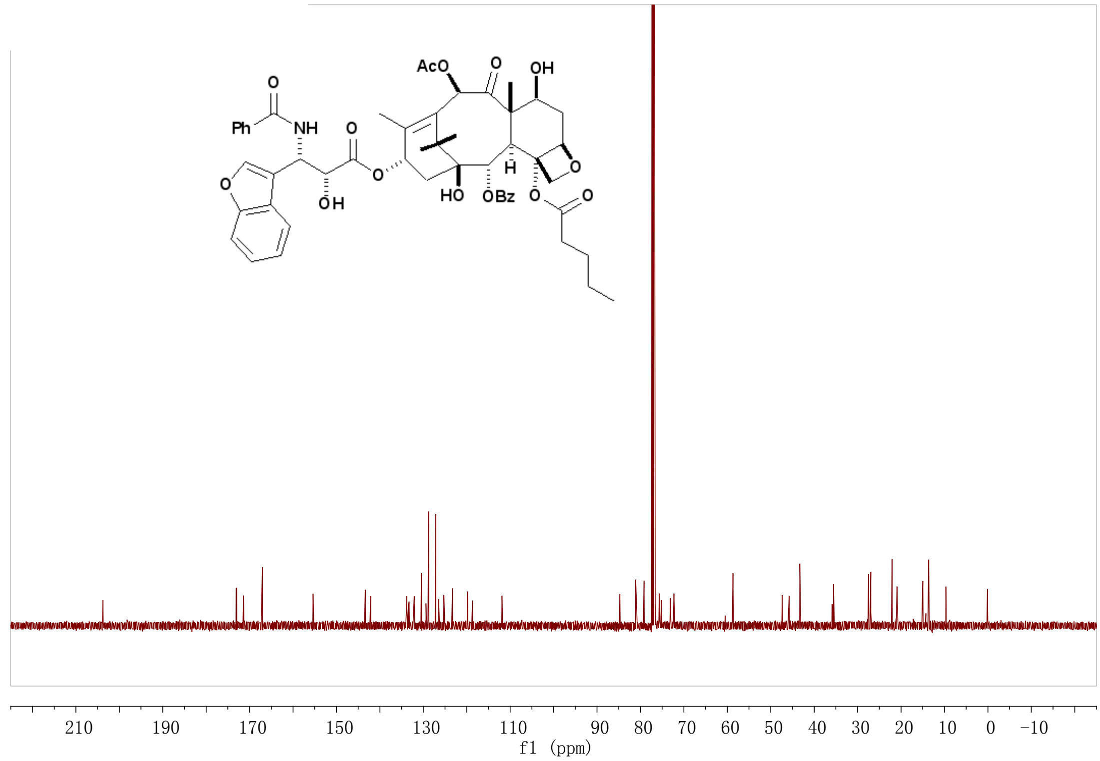
f1 (ppm)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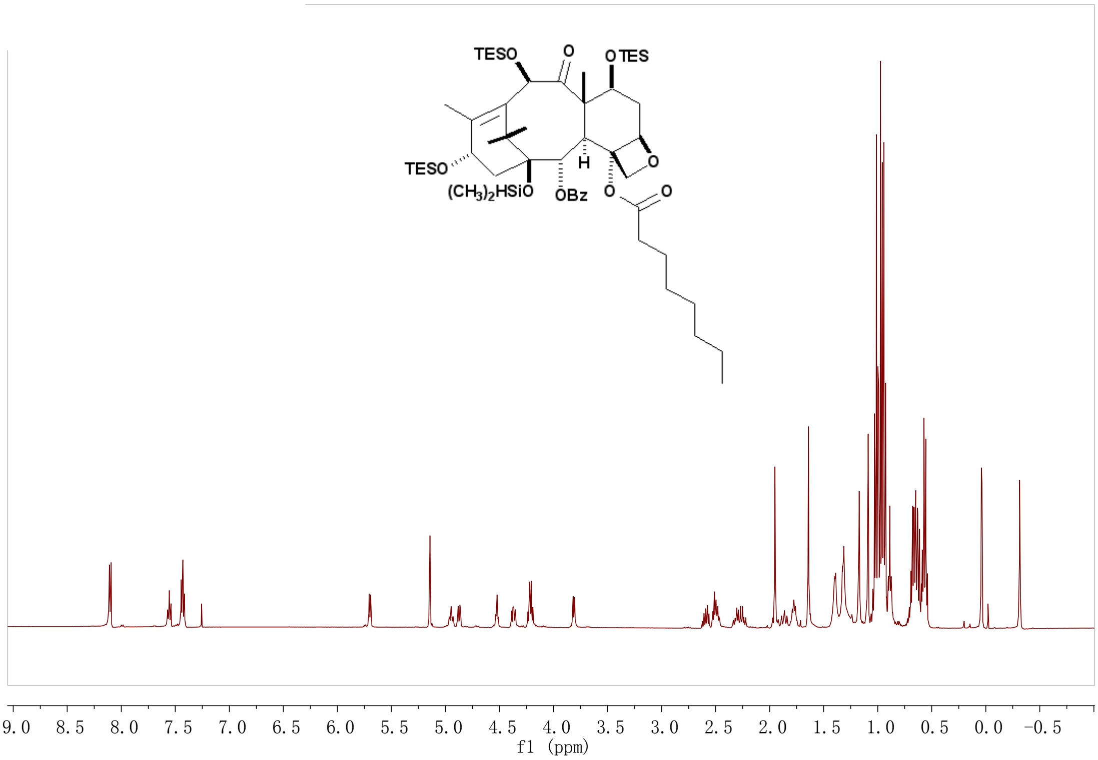
f1 (ppm)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TESO
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OBz
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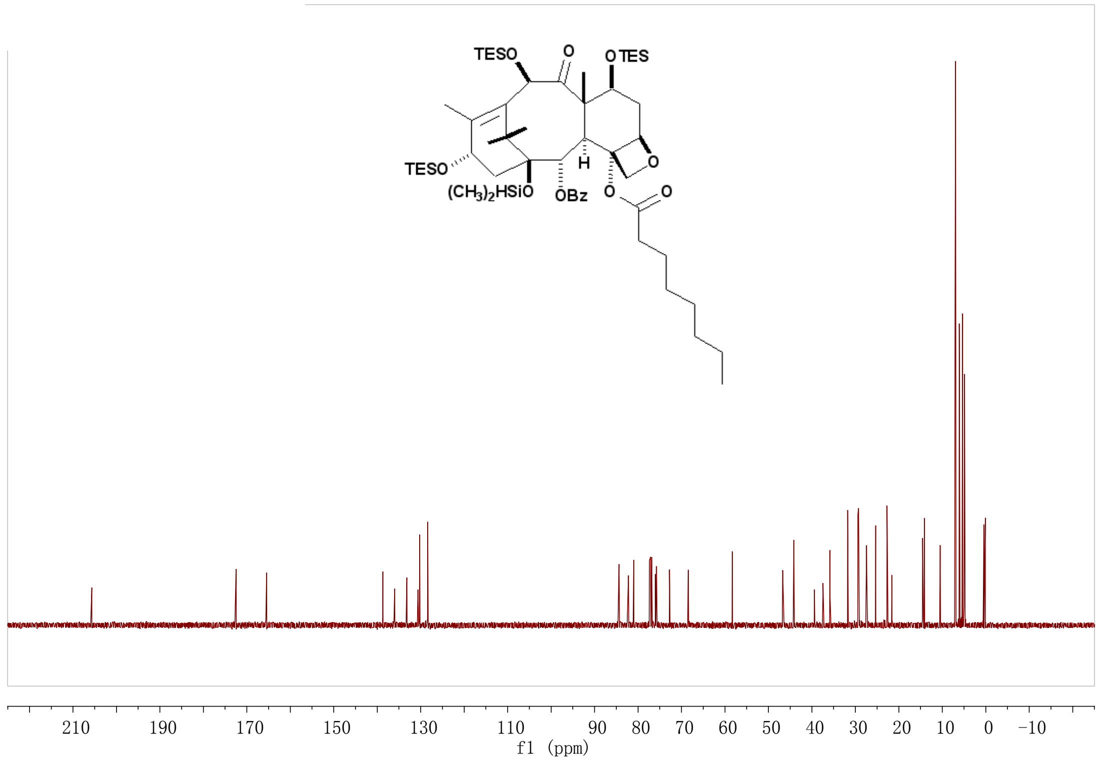
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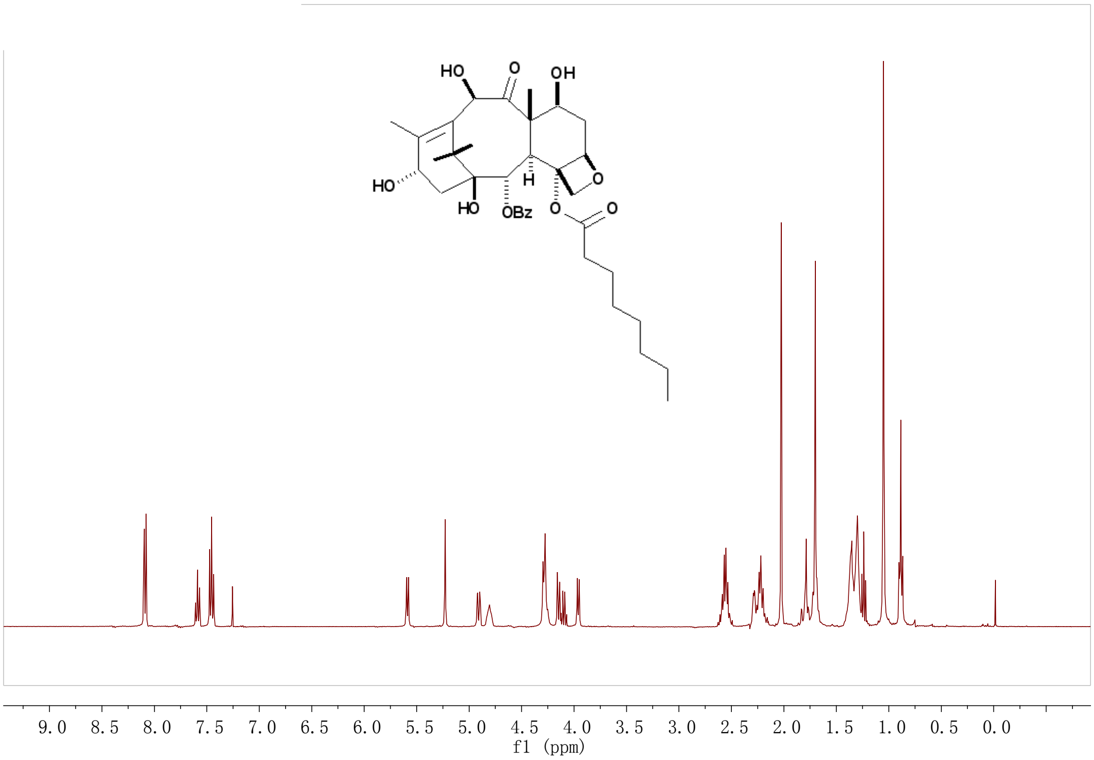
f1 (ppm)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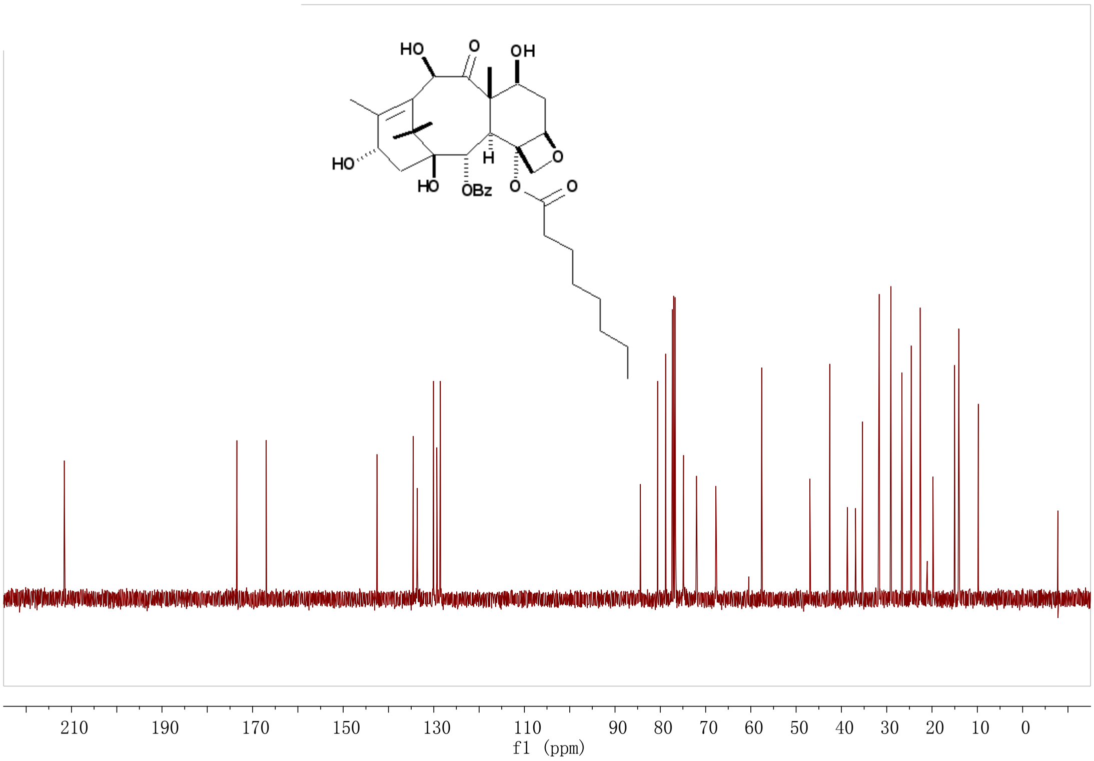
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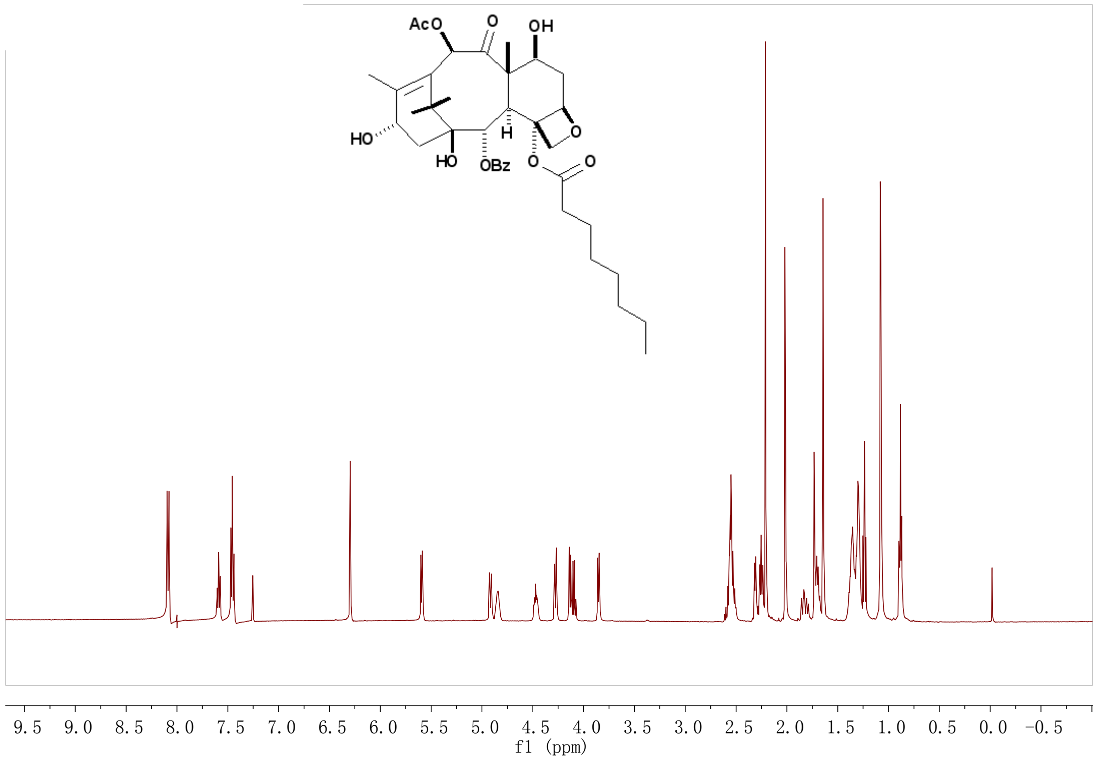
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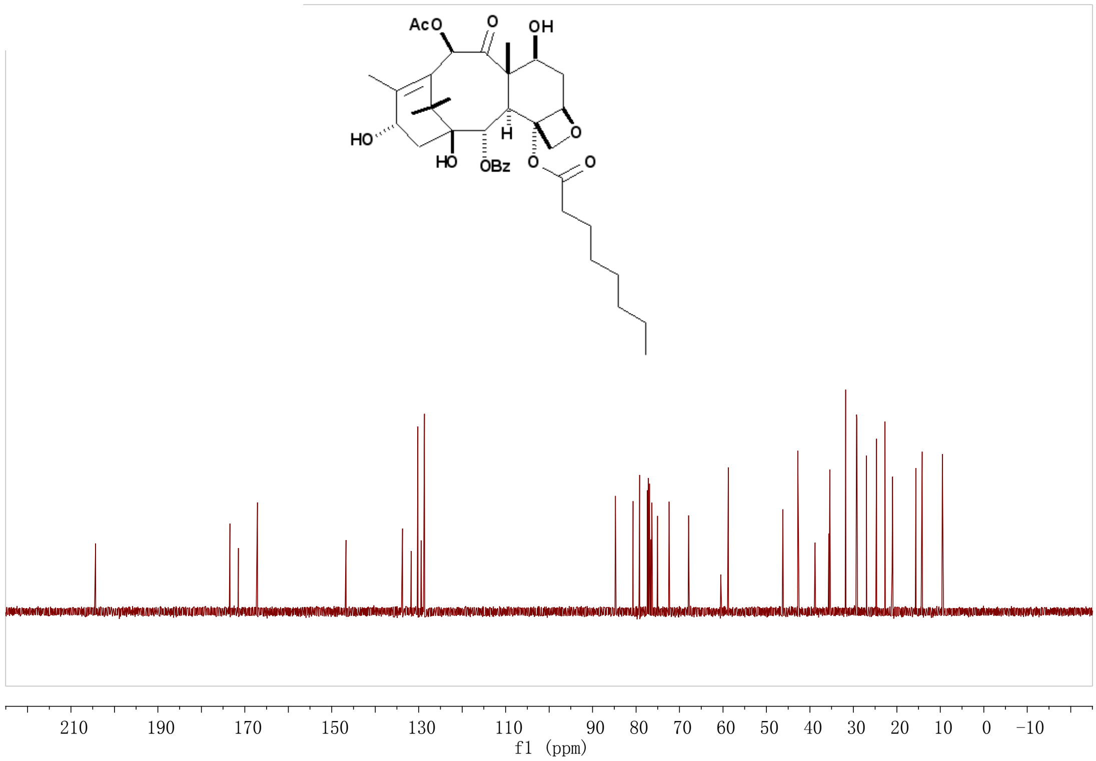
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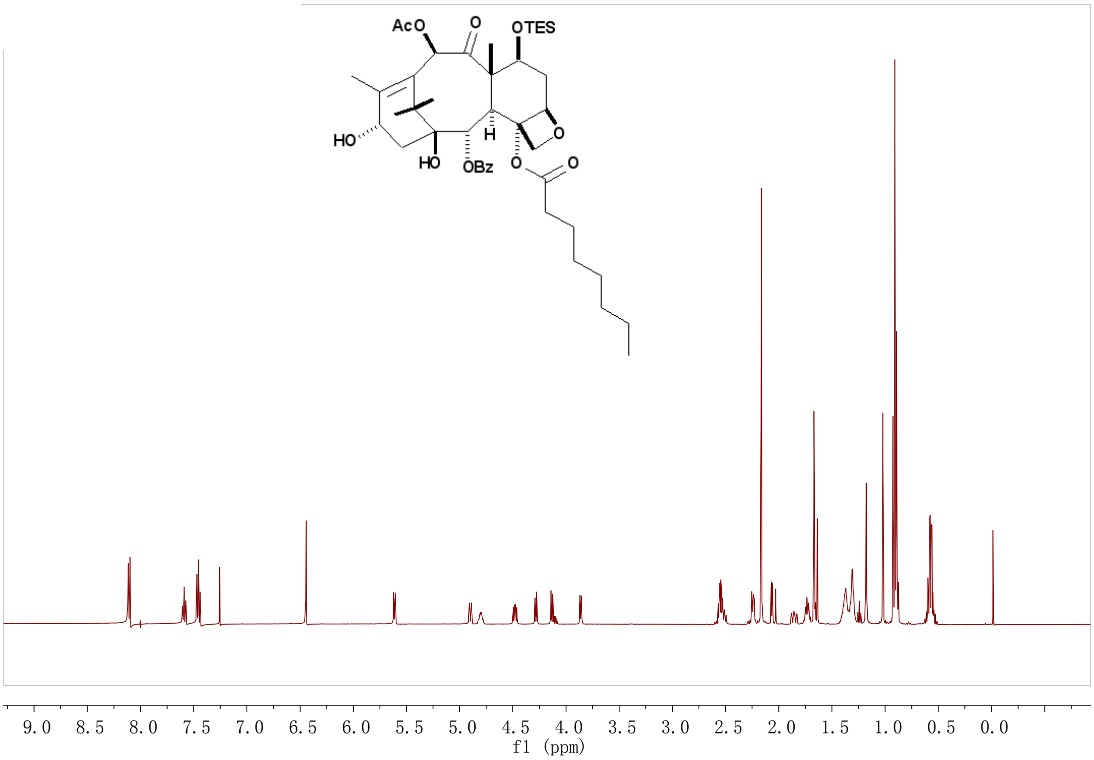
f1 (ppm)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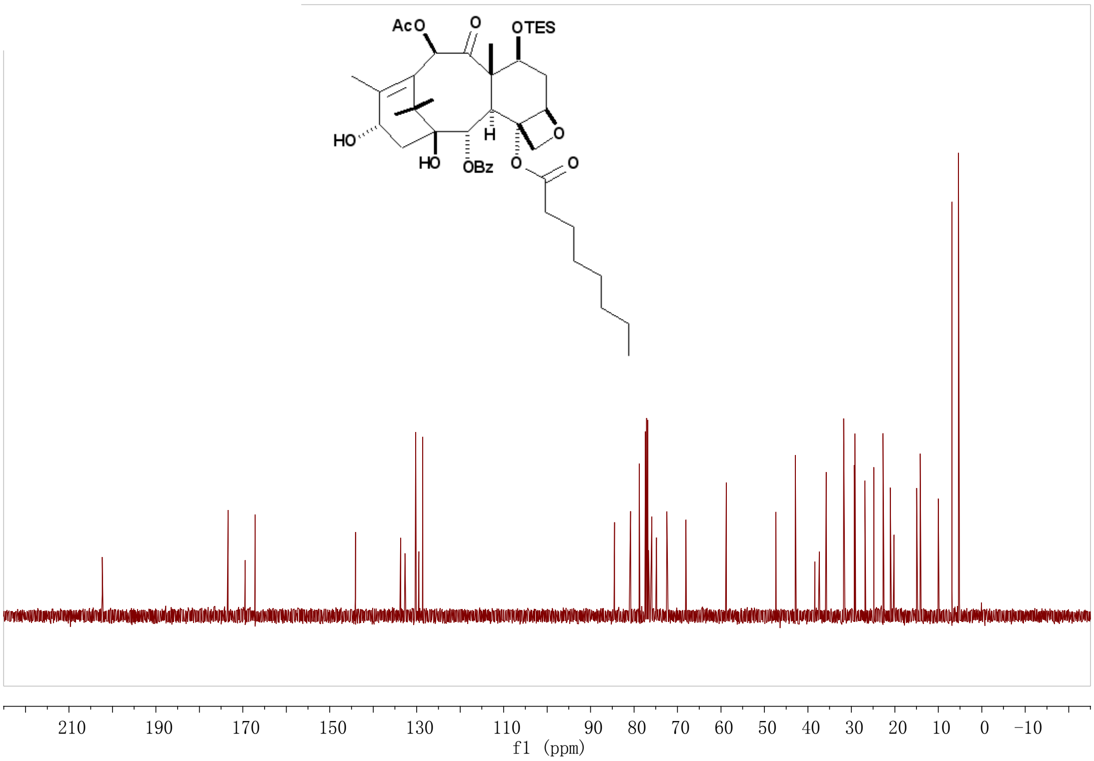
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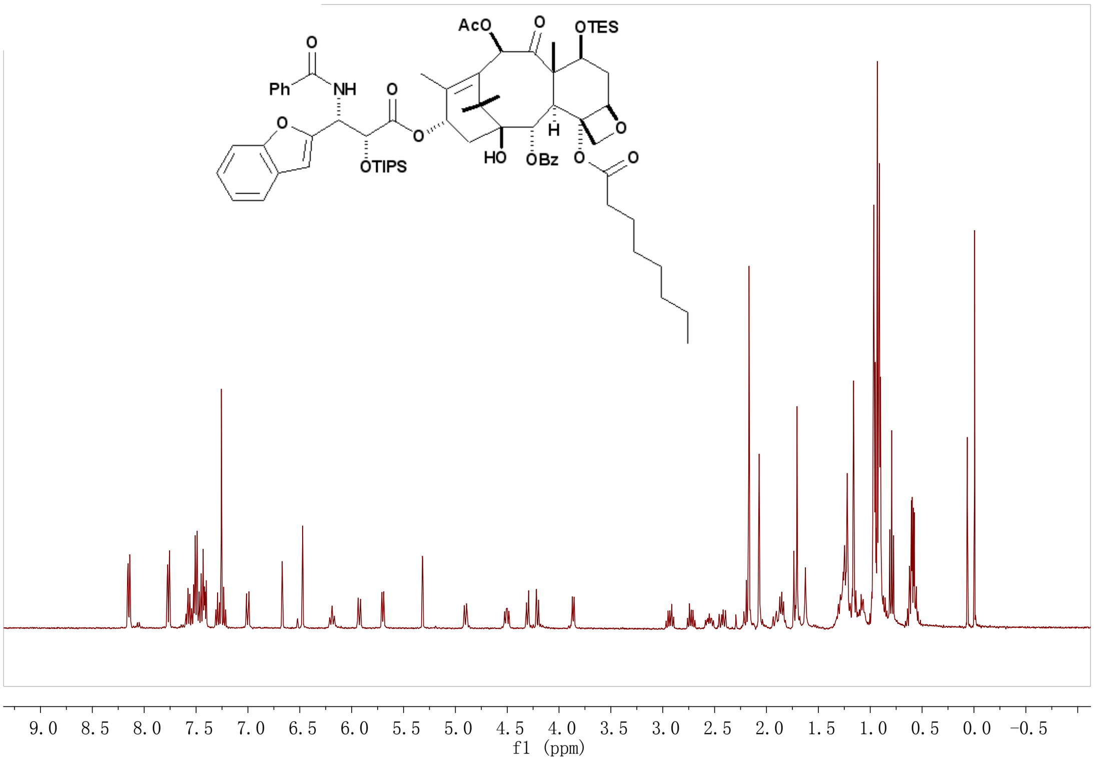
f1 (ppm)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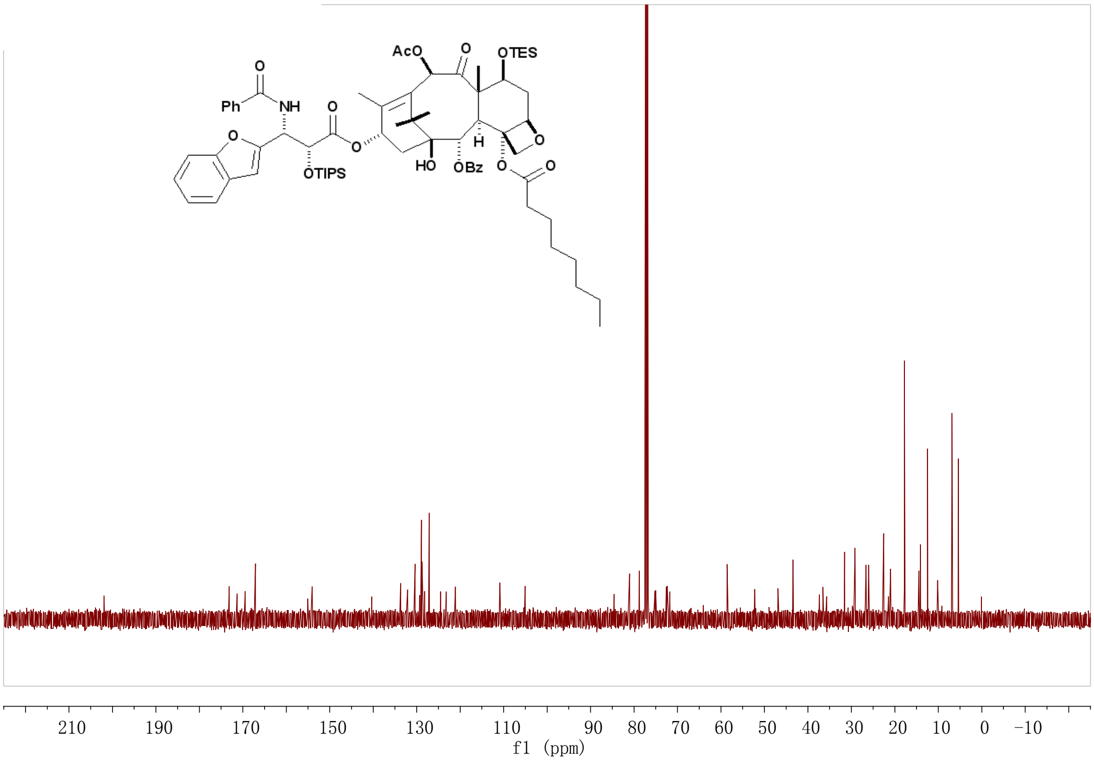
f1 (ppm)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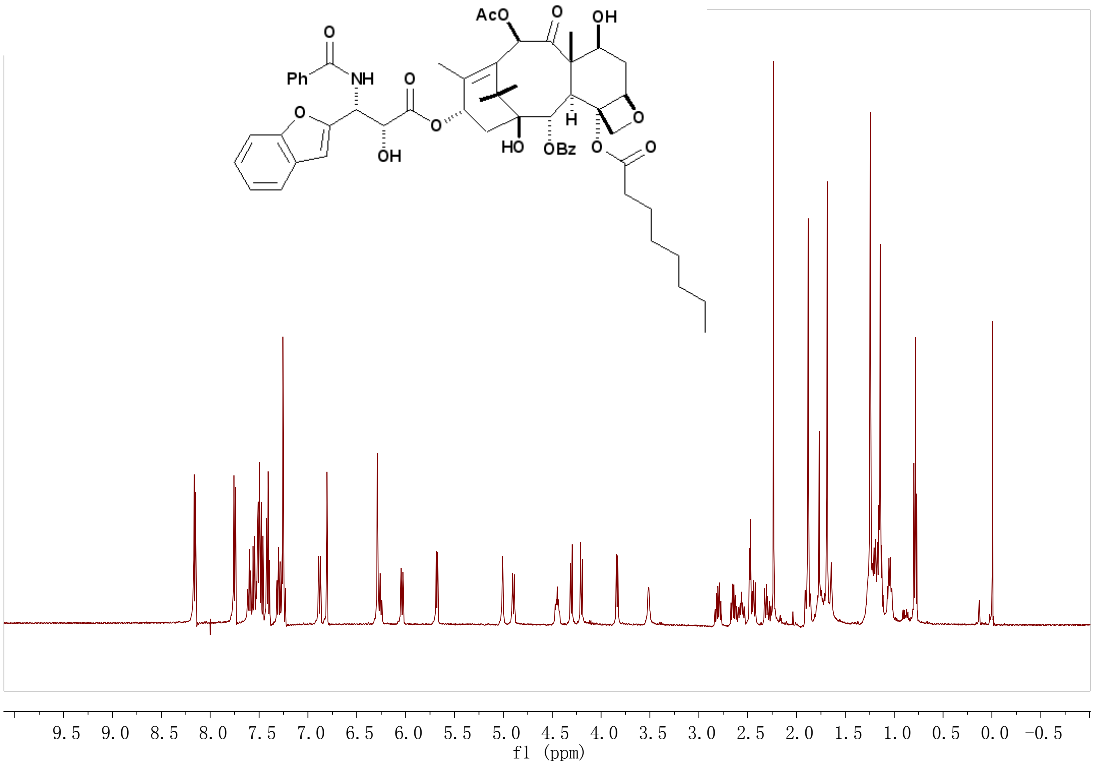
f1 (ppm)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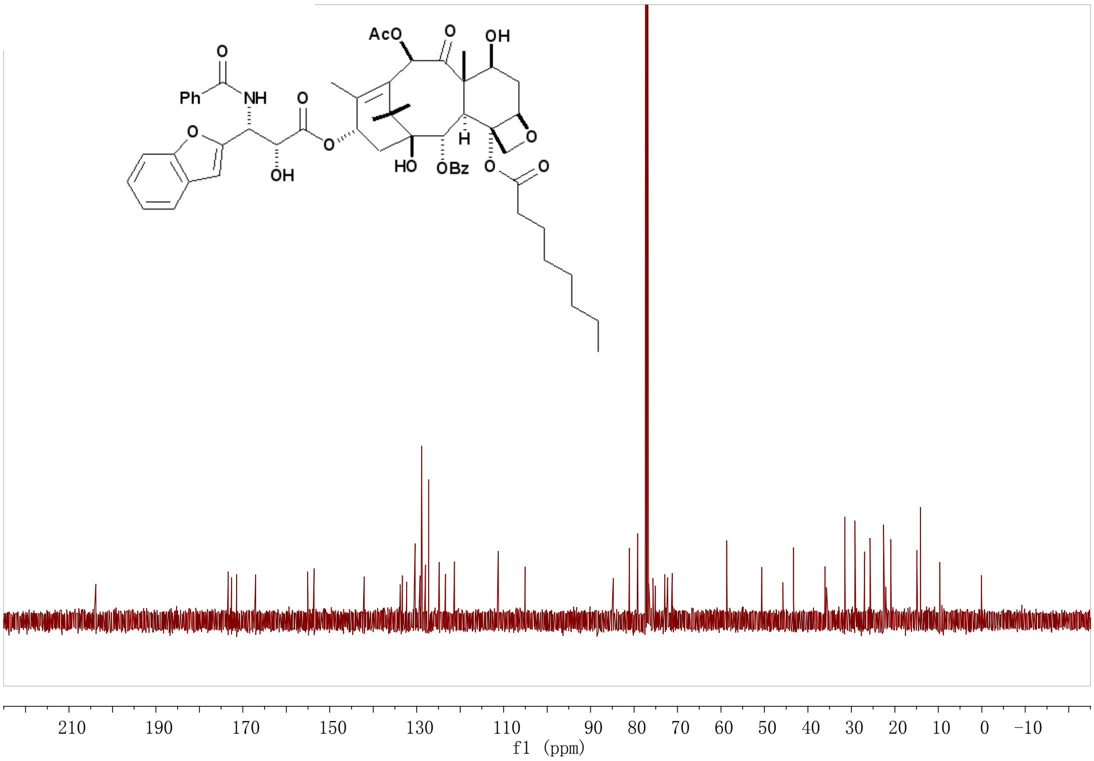
f1 (ppm)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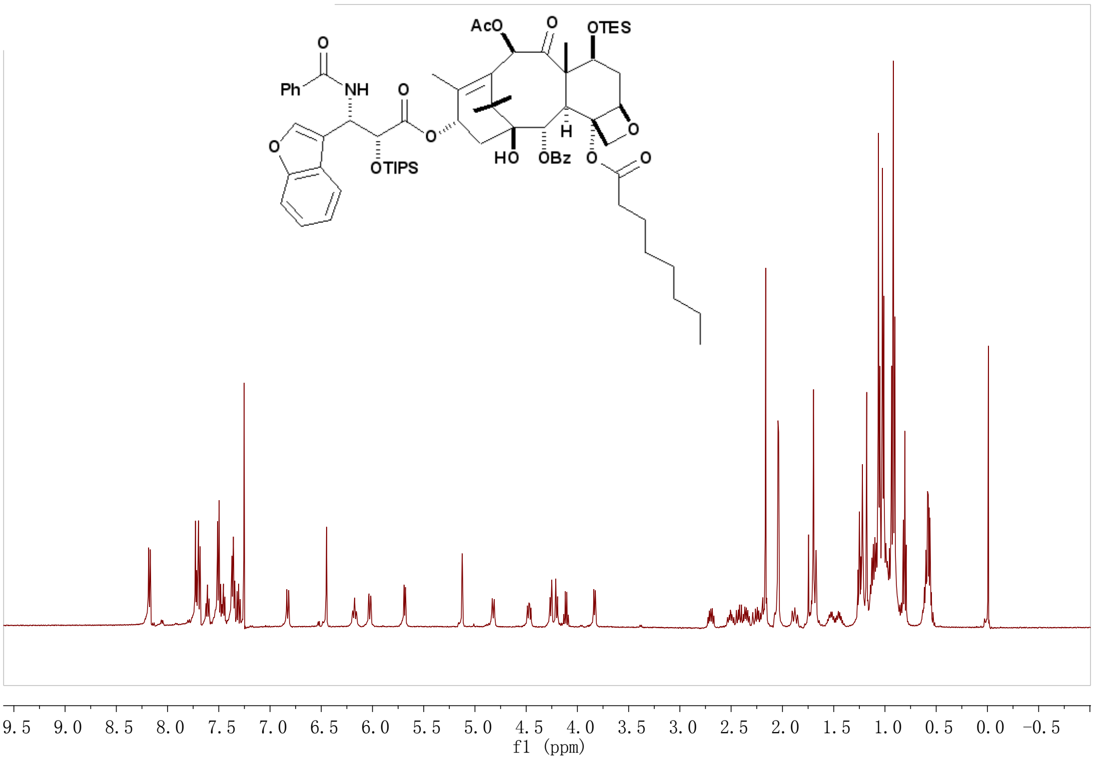
f1 (ppm)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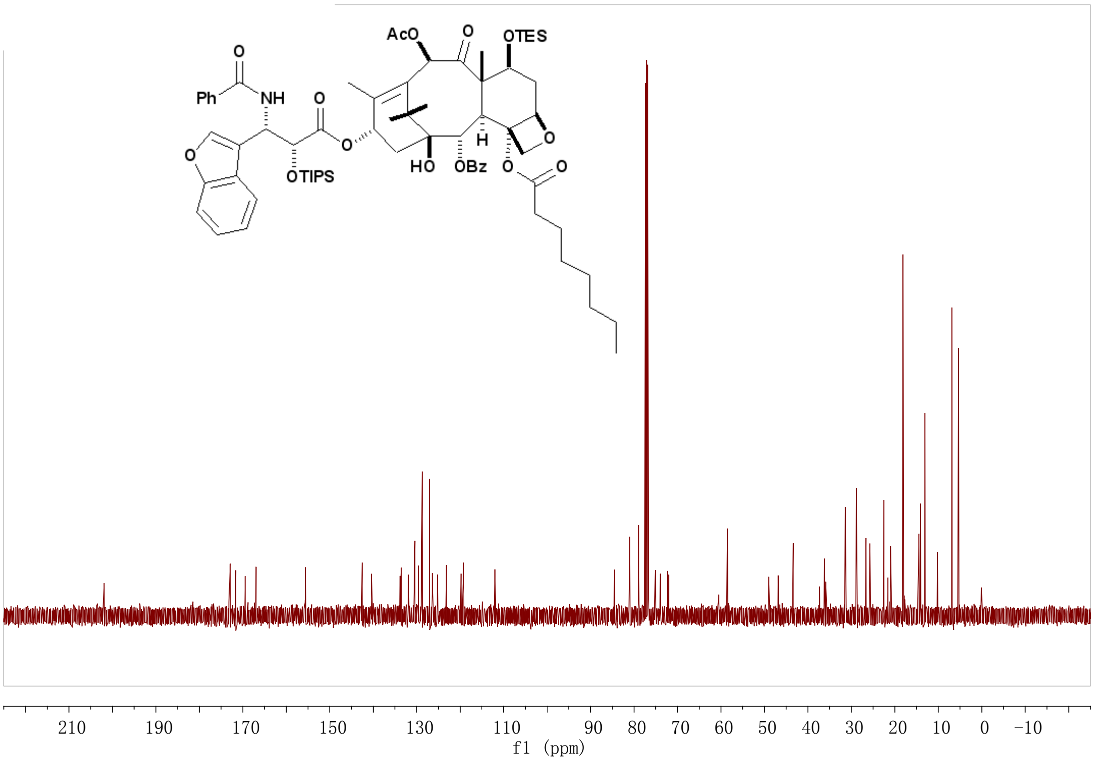
f1 (ppm)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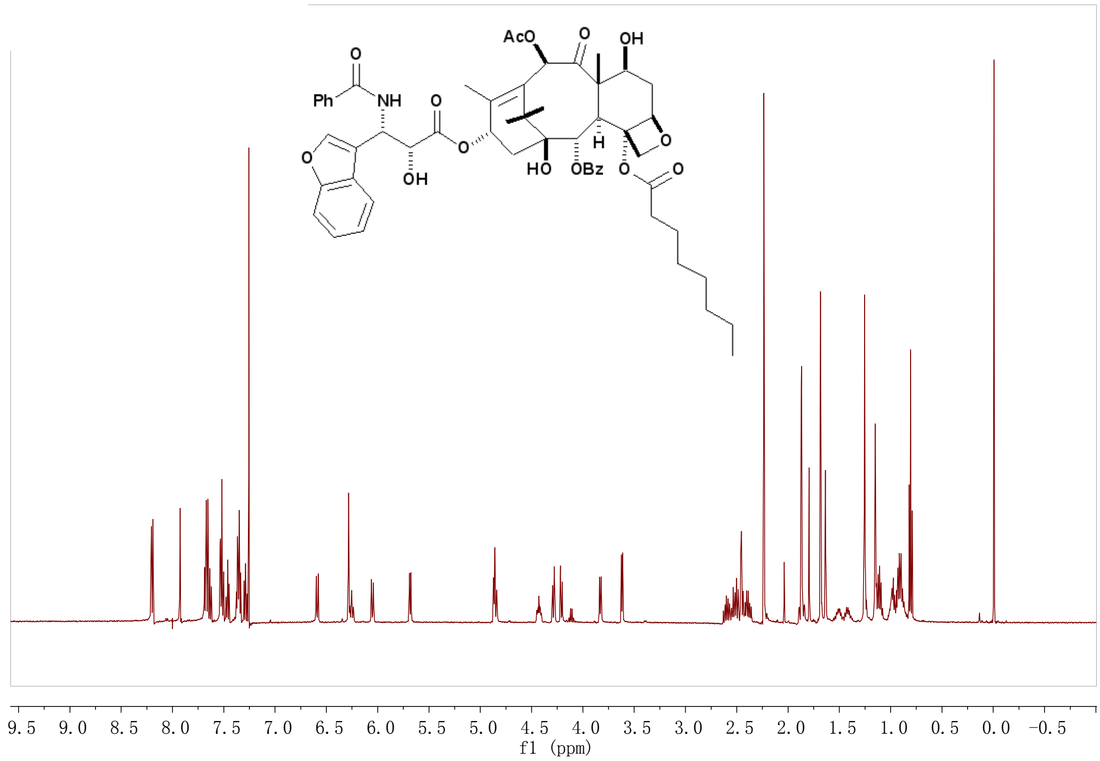
f1 (ppm)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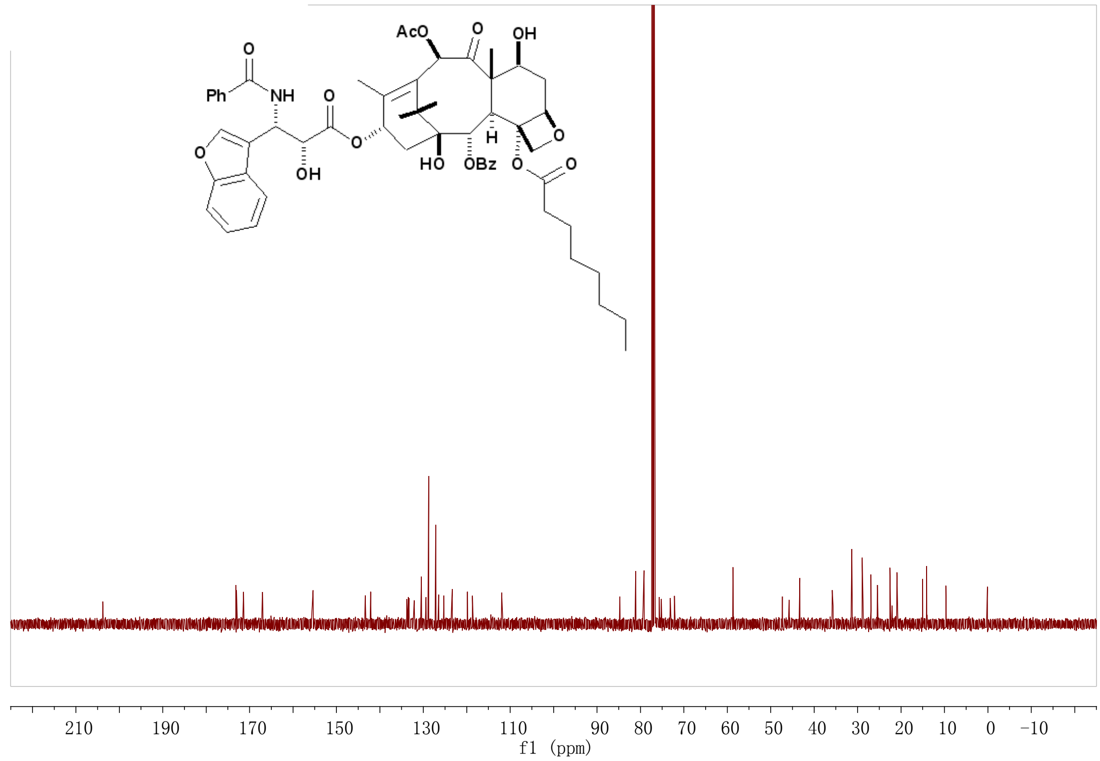
f1 (ppm)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Ph
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210 190 170 150 130 110 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)