1. Introduction

1.1 Taxol as an anticancer agent

1.1.1 History of the development of taxol

Taxol\(^1\) (Figure 1.1), first discovered in the bark of the Pacific yew about 37 years ago, is an important drug for the treatment of cancer.

![Figure 1.1 Structure of taxol](image)

During the 1960’s, the National Cancer Institute (NCI) started to search for some plants which could be used for cancer chemotherapy. The process was very time consuming and many plant extracts underwent random screening. In 1971, Wall and Wani reported the structure of a new compound from the Pacific yew tree (Taxus brevifolia Nutt.).\(^2\) This compound showed good activities both in 9KB (human nasopharyngeal carcinoma) assay and \textit{in vivo} leukemia assays (P-388, in mice), and it was named taxol. Problems with low water solubility and the lack of supply of taxol delayed further research to make it a drug. But the National Cancer Institute (NCI) continued testing, and this testing revealed taxol’s activities in various solid human tumors (breast cancer, lung cancer, melanoma) in “nude” mice. Nude mice are mice without a thymus,

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\(^1\) Although the name of taxol was assigned to the compound of Fig. 1 by its discoverers, Drs. Wall and Wani, the name taxol was claimed as a trademark by Bristol-Myers Squibb on the basis of an early trademark for a French laxative drug of the same name. The name paclitaxel is thus used as an alternate name for the chemical substance of Fig. 1. In this Dissertation the name taxol will be used; no infringement of the BMS trademark is intended.

and hence they do not reject human tumors. Preclinical studies on the pharmacology and toxicology of taxol were initiated with support from NCI on the basis of these promising results. This research proceeded smoothly, maybe a little bit slowly, until in 1979 Horwitz and her co-workers discovered the unique mechanism of taxol’s activity as a promoter of microtubule polymerization.\(^3\) The discovery of this mechanism triggered great interest among researchers, and the fortunes of taxol were changed.

The NCI began to sponsor clinical studies of taxol against a number of different types of cancers in the early 1980’s. The major object of the Phase I clinical trial was to test the drug’s efficacy and toxicity on humans.\(^4\)-\(^6\) Unfortunately, this trial was complicated by allergic reactions in some patients. This fact made the NCI suspend some aspects of the research, until the problem was solved by lengthening the time of administration and by premedication. It later turned out that it was the solvent used for the delivery of taxol that caused the allergic reactions and not taxol itself.

Phase II clinical tests were initiated in 1983, and the first report of taxol’s activity against advanced cancer was published in 1989. Rowinsky and his co-workers in Johns Hopkins Oncology Center, Baltimore, Maryland, reported a thirty-percent response rate in patients with advanced ovarian cancer receiving taxol.\(^7\) During the Phase II clinical trials, more and more

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\(^3\) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature*, 1979, 277, 665-657.


\(^7\) McGuire, W. P.; Rowinsky, E. K.; Rosenshein, N. B.; Grumbine, F. C.; Ettinger, D. S.; Armstrong, D. K.;
evidence was presented to support taxol as a potent anticancer drug, especially for advanced ovarian cancer and metastatic breast cancer.\textsuperscript{8-10} But the difficulties in producing the drug still existed, and this prevented the scientists from testing more patients. The NCI thus sought a pharmaceutical company to be involved in the development of taxol, and Bristol-Myers Squibb in New York was chosen by the NCI to be a partner in its development.

Because of its effectiveness and the relatively high response rate shown in the clinical trials, taxol received Food and Drug Administration (FDA) approval in 1992 for the treatment of advanced ovarian cancer, and in 1994 for metastatic breast cancer. A semisynthetic route to taxol from 10-deacetylbaccatin III, a renewable resource of yew needles, made it much faster and easier for Bristol-Myers Squibb to produce and market it for those needy patients.\textsuperscript{11} The FDA approved taxol for the second-line treatment of AIDS related Kaposi's sarcoma in 1997\textsuperscript{12} and in 1998\textsuperscript{13} for use in combination with cisplatin for the first-line treatment of non-small cell lung cancer in patients who are not candidates for surgery or radiation therapy.

\textbf{1.1.2 The mechanism of taxol's activity}

As mentioned earlier, the antimitotic toxicity of taxol comes from its promotion of the polymerization of tubulin into microtubules, and also from the stabilization of the microtubules.\textsuperscript{3}

In the normal cell cycle, it is very important to create the mitotic spindle in the chromosome

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\textsuperscript{11} Markman, M.; \textit{Yale Biol. Med.}, 1991, 64, 583-590.


\textsuperscript{13} http://www.fda.gov/cder/dq/da0897.htm

\textsuperscript{13} http://www.fda.gov/cder/approval/main5.htm
separation step, and it is also required that the spindle be destroyed after that. The mitotic spindle, which has various cellular functions, is composed of microtubules and some structural proteins.\textsuperscript{14} It is not surprising that many anticancer chemotherapeutic drugs interfere with this subcellular target.

To achieve a better understanding of the mechanism of taxol’s activity, it is essential to understand how microtubules are formed and the equilibrium between the polymer (microtubules) and the monomers (α-tubulin and β-tubulin). Microtubules are formed by polymerization of two structurally similar but distinct proteins, α-tubulin and β-tubulin. The molecular weight of these proteins is about 50,000,\textsuperscript{15} and there is about 35-40% of homology between them.\textsuperscript{16} The first step of microtubule polymerization from α-tubulin and β-tubulin is a heterodimer formation step. This heterodimer comes from the dimerization of one molecule of α-tubulin and one molecule of β-tubulin, and its dissociation constant to α-tubulin and β-tubulin monomers is about \(10^{-6}\) mol/L.\textsuperscript{17} To initiate microtubule polymerization, two molecules of guanosine 5'-triphosphate (GTP) and magnesium ions are required. One of the GTP molecule binds to α-tubulin, the other binds to β-tubulin. Then the heterodimers start to form a nucleation center for further polymerization to form protofilaments. Continuous growth occurs both along and perpendicular to the axis of the initial protofilaments in a slightly staggered manner, and the edge filaments meet together to form a microtubule with a left-handed helix.\textsuperscript{18-19} A normal microtubule with a

\textsuperscript{14} Dustin, P. Microtubules (2\textsuperscript{nd} Ed.), Springer-Verlag, New York, 1984, pp. 8-16.
\textsuperscript{17} Bershadsky, A. D.; Vasiliev, J. M. Cytoskeleton, Plenum, New York, 1989, pp.100-107.
diameter of about 24 nm is formed by 13 protofilaments. Finally the filament structure is surrounded by heterogeneous microtubule-associated proteins (MAPs) to give biologically active microtubules.\textsuperscript{20} In a cell system, the formation and decomposition of microtubules are at equilibrium at both ends of the microtubule with constant loss and gain of tubulin subunits. Under formation or decomposition conditions, the relative rates of loss or gain at these two ends are quite different, which gives the microtubules a growing polarity. The fast growing end is marked as the (+) pole and the relatively slower growing end is thus the (-) pole.\textsuperscript{21} (Figure 1.2)

![Figure 1.2 The equilibrium of tubulins and microtubules\textsuperscript{21}](image)

When a cell needs to form microtubules for some biological purpose, like cell division, it may trigger the formation process. Under this condition, the rate of formation of microtubules is greater than the rate of decomposition. Thus the concentration of free tubulin decreases until it achieves the critical concentration (C\textsubscript{r}) of tubulin, and then this process reaches an equilibrium.\textsuperscript{18}

Under normal cell conditions, the formation and decomposition of microtubules are totally reversible processes. What microtubule-targeted chemotherapeutic anticancer drugs do is to block a specific step in this process. In the case of taxol, it is found to be a promoter of microtubule polymerization. It affects the tubulin-microtubule equilibrium and irreversibly converts tubulins into microtubules. Taxol decreases both the critical concentration of tubulin necessary for polymerization and also the induction time for polymerization, and it does this either in the presence or absence of GTP, MAPs, and magnesium ions. Thus it can shift the dynamic equilibrium toward polymerization rather than disassembly. The microtubules formed by taxol induction are quite different from those formed under normal conditions. The taxol-induced microtubules are thinner than normal microtubules. They have a mean diameter of 22 nm rather than 24 nm, and they are composed of 12 protofilaments, not 13 as usual. (Figure 1.3) On the other hand, taxol-induced microtubules are much more stable than normal microtubules at low temperatures and after treatment with calcium, conditions which normally depolymerize microtubules. Attempts to remove taxol from both microtubules and tubulin after depolymerization indicate that taxol binds much more tightly to the microtubule than to the tubulin dimer. The binding site of taxol has been localized to the β-tubulin subunit through direct photoaffinity labeling and analysis of the binding profiles of strains of algae with mutations in tubulin genes.

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Studies have also shown that taxol affects microtubules in all phases of the cell cycle, but the primary effect is disruption of mitotic spindle formation. Microtubules are normally attached to microtubule-organizing centers (MTOC), however, it turns out that taxol-induced microtubules exhibit star-shaped arrays, meaning they are not organized around MTOC. It is also found that taxol induces disarrangement of the centrally located MTOC, and thus affects the interaction between microtubules and MTOC. So the best explanation of taxol’s cytotoxicity is its disruption of the mitotic spindle.

1.1.3 Potential problems with taxol

1.1.3.1 Drug resistance

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The occurrence of drug resistance is a significant problem that develops during the treatment of cancer with chemotherapeutic agents. The problem is not that useful antitumor drugs are not available, but rather that tumor cells can, by a variety of methods, develop resistance and replicate in the presence of cytotoxic agents. Every organism has its own way to overcome a life-threatening situation. Cancer cells also want to survive, so they will try their best to develop resistance to anticancer drugs. That is why there are so many mechanisms by which cells may become resistant to a single drug.

Taxol, a drug that has been in clinical use for about eight years and has shown great promise in treating breast cancer, cannot bypass the drug resistance problem. Multidrug resistance (MDR) is the emergence of cancer cells resistant to both the original anticancer agent and also to structurally and mechanistically unrelated agents.\textsuperscript{28} MDR has been related to overexpression of two transport proteins (P-gp\textsuperscript{29} and MRP\textsuperscript{30}). The function of these two transport proteins is to exclude hydrophobic compounds, like taxol, and results in a relatively low concentration of such compounds inside cancer cells. Since taxol is a substrate of P-gp transport protein, the increasing expression of this protein is the major reason for drug resistance.\textsuperscript{31,32}

The presence of the P-gp and MRP transport proteins could eliminate intracellular taxol, resulting in a taxol-resistant cell line. Alternatively, a mutation in the microtubule binding site for taxol could be another mechanism, resulting in elimination of the intracellular target for

\textsuperscript{29} Endicott, J. A.; Ling, V. *Annu. Rev. Biochem.*, 1989, 58, 137-171.
There is no doubt that there are other mechanisms that could be responsible to taxol-resistance. The better we know the mechanism of drug resistance, the better chance we can really overcome it.

1.1.3.2 Toxicity and side-effects

Like many other chemotherapeutic drugs, taxol also has toxicity and side effects. During Phase I clinical trials, the first obstacle for taxol to become a clinically usable drug was how to administrate it, since it is very hydrophobic. A Cremophor EL® (polyether of castor oil and ethylene oxide) and alcohol mixture is used to administer it, and allergic reactions were observed in some patients. This situation almost killed taxol as a drug. Later on it was discovered that the solvent (Cremophor EL®) used for the delivery of taxol was the ingredient causing the allergic reactions and not taxol itself. Taxol has many of the side effects seen with other cancer therapies, such as hair loss, decrease in white blood cells (which may cause susceptibility to infections) and numbness of the fingers and toes. Bone marrow suppression is the major dose-limiting toxicity of taxol. Neutropenia (loss of neutrophil), the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible.4-6

1.1.3.2 Taxol's supplies

Early research using taxol was limited due to difficulties in obtaining the drug. The amount of taxol in yew bark is low, and extracting it is a complicated and expensive process. In addition, bark collection is restricted because the Pacific yew is a limited resource located in forests that

are home to the endangered spotted owl.

As demand for taxol grew, NCI, in collaboration with other Government agencies and Bristol-Myers Squibb, worked to increase its availability. Bark collection and processing expanded to increase the short-term supply of the drug while NCI encouraged research to find other sources of taxol and related compounds.

One alternative is to synthesize taxol. The total synthesis of taxol has been achieved by six groups, but none of them is a feasible route to commercial production. Currently, taxol is prepared commercially by semisynthesis from commercially available 10-deacetylbaccatin III (Figure 1.4)

\[
\begin{align*}
\text{HO-} & \quad \text{OCOPh} \\
\text{HO} & \quad \text{OH} \\
\text{HO} & \quad \text{OH} \\
\text{AcO} & \quad H \\
\end{align*}
\]

Figure 1.4 Structure of 10-deacetylbaccatin III

1.1.4 Structure activity relationships (SAR) of taxol analogs

The better we understand a drug’s structure-activity relationships (SAR), the better we can

make changes to make it more potent. Any new analogs designed to achieve better drug activity must be based on known SAR. In some of the studies to be described we propose to target taxol, a potent anticancer drug, specifically to the cancer cell. Thus it is definitely important to understand the SAR of taxol. The interactions of drugs with their receptors are very specific, and usually only a portion of a drug structure is really involved in the site of action. SAR studies can provide us with useful information about the action of drug, the particular functional groups necessary for the action, and essential structure requirements for the activity of the drug.

As a relatively new class of anticancer drugs, taxol and its analogs combined novel molecular structure, significant antimitotic activity, unique mechanism of action, and fascinating chemistry. That is why taxol will continue to be a hotspot of anticancer research for a long time. From a chemist's point of view, the studies of the SAR of taxol and its analogs will provide information about which substituents on its side-chain or main skeleton could be modified or removed without loss of its activity. It will make subsequent synthetic work easier and will help to develop more active analogs for new candidate anticancer drugs.

In the past 30 years, extensive studies have been carried out on the SAR of taxol. The results of these studies will be summarized in the following sections. Figure 1.5 is the molecular structure of taxol with the proper numbering and three main regions, which will be discussed in more detail below.
1.1.4.1 The Side chain

In general, the C-13 side chain of taxol is essential to its activity. Most studies of the structure requirement for the C-13 side chain have found that major modification of the C-13 side chain usually results in the decrease or maybe loss of taxol’s bioactivity. The most potent compounds among these analogs are those with the naturally occurring side chain configuration, such as docetaxel— with an N-tert-butoxycarbonyl side chain and a C-10 free hydroxyl group. (Figure 1.6)

The following sections are some details of side chain SAR:

1. Substitution of the 3’- phenyl group by small alkyl groups like a methyl group causes a significant loss in bioactivity, but substituted phenyl compounds were found to have a similar but slightly decreased activity. Some larger alkyl groups such as isobutyl or

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isobutenyl give analogs with improved activity.  

2. Homologation of the side chain by addition of a methylene group between the 1' and 2' carbon also lowers the activity dramatically.  

3. The N-acyl group is required for activity, but structural modifications at this position are allowed without a marked loss of activity, even in some cases with a small increase of activity.  

4. A 2'-free hydroxyl or easily cleaved 2'-hydroxyl ester is required.  

5. The stereochemistry at C-2' and C-3' has a moderate effect on the activity. Analogs with the naturally occurring stereochemistry were more active than those with inverted stereochemistry.  

1.1.4.2 The northern hemisphere  

Structure modifications to the northern hemisphere of taxol do not have a remarkable effect on the activity. This probably means that this part of structure does not play an important role in the binding interaction with microtubules. Some details below:  

1. C-6 hydroxylation of taxol can decrease the activity by 30-fold.
2. Taxol analogs with a C-7 position modification, such as acylation or dehydroxylation, usually have comparable activity to taxol itself.\textsuperscript{42,51-56} Oxidation of the C-7 hydroxyl group to a ketone will decrease the activity dramatically, because the 7-oxotaxol can easily undergo an oxetane-ring opening.\textsuperscript{57}

3. The C-9 keto group can be converted into a hydroxyl group without loss of activity.\textsuperscript{58-59}

4. A C-10 modification will only affect the analog’s activity slightly.\textsuperscript{42,60}

5. Modification of the C-11 and C-12 double bond can moderately decrease the activity.\textsuperscript{61}

6. A C-19 modification of taxol analogs can affect the activity to some extent, but it usually will not cause a significant loss of activity.\textsuperscript{62-63}

1.1.4.3 The southern hemisphere

The southern hemisphere of taxol’s structure turns out to be a very sensitive region for its activities. The modifications of this region can dramatically change the activity of taxol analogs. Some of them improve the activity while others cause complete loss of activity, as shown below:

\textsuperscript{37, 706-709.}


1. Deoxygenation at the C-1 position will cause a slight loss in activity.  

2. The benzoyloxy group at the C-2 position is essential to activity. Modifications at the aromatic ring can affect the activity, and a series of analogs with meta-substituents were highly active. The stereochemistry at the C-2 position is also important for its activity.  

3. There are no reports of modifications at the C-3 position of taxol.  

4. At the C-4 position, the acetyl group is essential to taxol’s activity. Other acylated analogs are generally less active than taxol, but some groups such as a methyl carbonate give improved activities.  

5. The C-13 stereochemistry is essential to taxol’s bioactivity.  

6. C-14 hydroxylated compounds were found to be similar in activity to taxol.  

7. The oxetane ring is a very important structure to maintain the activity of taxol. Ring opened compounds were dramatically less active in both cytotoxicity and microtubule

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assembly assays.\textsuperscript{57,76}

As a summary of what we discussed above, Figure 1.7 provides a visual summary of the SAR of taxol.

\begin{center}
\includegraphics[width=\textwidth]{structure.png}
\end{center}

\textbf{Figure 1.7} Structure-activity relationships of taxol\textsuperscript{44}

\subsection*{1.2 Breast cancer}

According to the database (2002) of the National Alliance of Breast Cancer Organizations, New York,\textsuperscript{77} breast cancer is the most common form of cancer in women in the United States.

* In 2003, 211,300 new cases of female invasive breast cancer will be diagnosed, and 40,800 women will die from the disease. Nearly 55,700 cases of female \textit{in situ} (preinvasive) breast cancer will be diagnosed in 2003. Breast cancer is the second leading cause of cancer death for all women (after lung cancer), and the leading overall cause of death in women between the ages of 20 and 59. Men can develop breast cancer too, although its incidence is low. In 2003, 1,300 male cases are projected to be diagnosed, and 400 men will die from the disease.

\textsuperscript{77} http://www.nabco.org/resources/
* In the United States, one out of nine women will develop breast cancer in her lifetime -- a risk that was one out of 14 in 1960. This year, a woman will die from breast cancer every 13 minutes and over 1 million women in the United States have died of this disease since 1970.

* Every woman is at risk for breast cancer. The risk of developing breast cancer increases as a woman ages, if she has a family history of breast cancer, has never had children or had her first child after age 30, and if she has had prior treatment with radiation therapy for Hodgkin's disease. However, over 70 percent of cases occur in women who have no identifiable risk factors.

* Breast cancer cannot yet be prevented. But it can be detected at an early, treatable stage in women age 40 and older. More widespread use of regular screening mammography has been a major contributor to recent improvements in the breast cancer survival rate. A 1997 survey showed that on average, 58 percent of U.S. women age 50 and older had received a mammogram within the last year. A screening mammogram is a simple, low-dose x-ray procedure that can reveal breast cancer at its earliest stage, up to two years before it is large enough to be felt. In NABCO's view, annual screening mammography should begin at age 40 and continue as long as a woman is healthy and able to undergo the test.

* If detected early, breast cancer can be treated effectively with surgery that preserves the breast, followed by radiation therapy. This local therapy is often accompanied by systemic chemotherapy and/or hormonal therapy. Currently, 62 percent of breast
cancers are discovered at an early, "localized" stage, and five-year survival after
treatment for early-stage breast cancer is 96 percent.

* Breast cancer incidence increases with age, rising sharply after age 40. About 77
percent of invasive breast cancers occur in women over age 50. Average age at
diagnosis is 62.

From these facts it is clear that although significant progress has been made in detection
and treatment of breast cancer, there still remains much to be done.

1.3. Drug targeting

Drug targeting is the selective delivery of a drug to a specific site or sites, which are the
sources of the illness. Targeting a drug to a specific pharmacological site should enhance its
therapeutic effectiveness and bioavailability while reducing any toxic side effects, without loss in
drug potency. Drug targeting can be classified into three different levels of selectivity:

a. organ/tissue targeting - delivery to specific organs or tissues

b. cellular targeting - delivery to specific cells within the target organs

c. subcellular targeting - delivery to specified subcellular compartments in the target cell

Drug targeting can also be classified by targeting vehicles, such as antibodies, hormones,
and liposomes.\textsuperscript{78} Each of these targeting approaches has its own advantages and disadvantages.

Because of the toxicity of most anticancer drugs, drug targeting could in principle provide a
major benefit in cancer chemotherapy, and it is a major field in this area.

\textsuperscript{78} Langer, R. Nature, 1998, 392(S30), 5-10.
1.3.1 Various targeting methods in treating cancers

In the fight against the cancer, scientists have been searching for a long time for the “biological missile”, a drug which can selectively attack the cancer cell without any bad effects on healthy cells. Extensive studies of drug targeting have thus been carried out.\(^79\)\(^-\)\(^81\) Although no targeting approach has achieved complete selectivity against cancer cells, there are still many positive results which have revealed a partial selectivity. With these promising results, several targeting methods have been developed. Some of them have become standard methods to target a drug to a specific site in the human body, such as the antibody approach, the ligand-directed approach, and some other approaches.\(^79\)\(^-\)\(^80\)

1.3.1.1 Antibody approach

The delivery of a monoclonal antibody (Ab) drug complex to tumor-associated antigens has been the most commonly used method to target anticancer drugs. It is known that cancer cells often overexpress many proteins. These proteins can function as surface receptors to monoclonal antibodies.\(^80\) Modern hybridoma technology has provided many monoclonal antibodies from their corresponding tumor-associated antigens.\(^82\)\(^-\)\(^86\) By using the ability of the recognition and binding of a tumor-associated antigen to its antibody, an antibody-drug complex may be

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selectively delivered the to tumor cells. A good antibody-drug complex should have a linkage between the drug and the antibody which is cleavable under cellular conditions, so that the drug can be released to do its own job. The conjugation between a cytotoxic drug and an antibody and the type of linkage used are very important for antibody directed drug delivery. The linkage may determine how many drug molecules can be carried without loss of antibody-antigen binding ability, selectivity and efficiency of drug release. A good site for drug binding should be abundant on the surface of the antibody, and the linkage should be stable but cleavable. There are three types of functional groups usually used to attach cytotoxic drugs to antibodies:

1. **N-Terminal lysines**, which are abundant on the surfaces of the antibodies, can react with the drug-COOH to form an amide;\(^{87-88}\)

2. Aldehydes, formed from metaperiodate oxidation of the carbohydrate portion of the antibody, can react with a drug-NH\(_2\) group to form an imine, which can be reduced to an amine;\(^{89}\)

3. Thiols can be generated from selective reduction of interchain disulfides without significant perturbation of the antibody’s structure and its binding ability.\(^{90-91}\)

Studies also found that using the proper linker is very important to achieve specific drug

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targeting. There are many linkers that have been developed to date. They can be classified as follows:

1. Nonselective linkers, a stable linkage without facile drug release,\textsuperscript{92-94} may present excellent antigen – specific activity.\textsuperscript{95} An example is shown in Figure 1.8.\textsuperscript{80}

\[
\text{Lys}_{(Ab)} \text{NH}_2 + \text{Drug-COOH} \xrightarrow{\text{coupling agent}} \text{Lys}_{(Ab)} \text{NHCO-Drug}
\]

**Direct coupling to Ab lysines**

\[
\text{Lys}_{(Ab)} \text{NH}_2 + \text{Drug-NH}_2 \xrightarrow{\text{Glutaraldehyde crosslinking}} \text{Drug-NRH} + \text{O}
\]

**Glutaraldehyde crosslinking**

\[
\text{Drug-NRH} + \text{coupling agent} \xrightarrow{\text{Succinate crosslinking}} \text{Drug-NH}_2 \text{Lys}_{(Ab)}
\]

**Succinate crosslinking**

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2. Acid – cleavable linkers with different hydrolysis rates at lysosomal pH (ca. 5) and systemic pH (ca. 7.4). An example is shown in Figure 1.9.

![Acid Cleavable Linkers](image)

**Figure 1.9 Acid cleavable linkers**

3. Lysosomally degradable peptide linkers, which are peptide linkers that are only cleavable when the drug-antibody complexes are internalized within the lysosome. An example is shown in Figure 1.10.

![Lysosomally Degradable Peptide Linker](image)

**Figure 1.10 Lysosomally degradable peptide linker**

4. Disulfide linkers, usually used for highly potent cytotoxic anticancer drugs, will be

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cleaved in the cell where glutathione and other thiols are in relatively high concentration.\textsuperscript{99-100} An example is shown in Figure 1.11.\textsuperscript{101}

![Disulfide linker](image)

**Figure 1.11 Disulfide linker**\textsuperscript{101}

Besides the methods discussed above, studies have also used antibodies just for tumor cell recognition. Drug-carrier vehicles, such as synthetic polymers\textsuperscript{102} and liposomes,\textsuperscript{103} can be linked to the antibody to fulfill their specific transportation of drugs.

1.3.1.2 Ligand-directed approach

It is known that hormones are involved in the growth of many cancers,\textsuperscript{104} and the presence of hormonal receptors in cancer cells provides an opportunity to target the anticancer drug specifically to the tumors. Recent studies of peptide-directed approaches have found that the pyrrolino-doxorubicin (DOX) conjugate (AN-207) can retain luteinizing hormone-releasing hormone (LH-RH) receptor binding ability and lead to cell death.\textsuperscript{105} The conjugates turn out to

have higher efficacy and less toxicity than the free drug. Pyrrolino-DOX conjugates have also been coupled to fragments of bombesin (AN-215)\(^{106}\) and somatostatin (AN-238).\(^{107}\) These conjugates also turn out to be 1000 –fold more potent than free DOX in cells with LH-RH receptor.

As for steroid hormone targeting, estradiol analogs have been widely studied for their binding affinity to estrogen receptor (ER).\(^{108-109}\) Many estradiol linked conjugates have been reported. Recently, a conjugate of estradiol linked to mitomycin C (MMC) through glutaric acid has been reported. It showed 81% binding affinity to rat uterine ER compared to estradiol.\(^{110}\) Another report also achieved ER – specific delivery by attaching nitrosoureas to estradiol.\(^{111}\) There are also some other reports which have shown that drugs can be linked to the 11\(\beta\)-position of estradiol\(^{112}\) or to the 16\(\alpha\)-position.\(^{113}\) Besides estradiol, people are also looking for some other steroid hormones for drug targeting, like testosterone. Kuduk and his co-worker have published a paper for targeting geldanamycin to prostate cancer cells through the binding interaction of testosterone to androgen receptors.\(^{114}\)


1.3.2 Targeting to breast cancer

As can be seen from the previous discussions of the status of breast cancer and of drug targeting, there are still many things that could be done to improve breast cancer therapy. In particular, it is desirable to use drug targeting methods to selectively deliver anticancer drugs to tumor cells rather than to healthy cells. To achieve this goal, there must be a reasonable targeting site in the cancer cells. For breast cancer, that will result from the hormone dependence of the cancer.

The hormone dependence of some kinds of human breast cancers was first reported by Beatson in the late 1800’s.\textsuperscript{115} Further studies revealed the interaction between steroid hormones and their receptors in breast cancer cells,\textsuperscript{116} and thus led to a better understanding of the hormone in controlling the growth of breast cancer cells. Hormone-dependent breast cancer is characterized by the presence of steroid hormone (estrogen and progesterone) receptors.\textsuperscript{117} When the cancer is metastatic, the ER-positive types can be effectively treated by various hormonal manipulations. Blockade of estrogen receptor (ER) action by antiestrogen therapy with tamoxifen\textsuperscript{118} or other triphenylethyene derivatives, such as toremifene\textsuperscript{119} or droloxifene,\textsuperscript{120} is currently the best approach to the endocrine treatment of breast cancer.

The hormone-dependence of breast cancer can also be used to facilitate drug delivery by

\textsuperscript{117} McGuire, W. L.; Chamness, G. C.; Costlow, M. E.; Shepherd, R. E. \textit{Metabolism}, \textbf{1974}, 23, 75-100.
targeting the recognition and binding of estrogen to its receptor. As mentioned before, many conjugates of estradiol have been reported. They all showed positive binding affinity to the ER and thus achieved ER specific delivery by this steroid hormone targeting.\(^{110-113}\) Recently, Kuduk and his co-workers reported a series of geldanamycin-estradiol hybrids which can induce the selective degradation of the ER.\(^{113}\) Geldanamycin,\(^ {121-122}\) first isolated from *Streptomyces hygroscopicus*, was identified as a potent inhibitor of src kinase (a member of family of non-receptor tyrosine kinase) by inducing the proteosome dependent degradation of src and other tyrosine kinases.\(^ {123-126}\) The hybrids turn out to be active and more selective than geldanamycin itself to degrade ER and HER2, while there is no selectivity to other geldanamycin targets.

According to the positive results that have been discussed above for targeting estradiol to its receptor in the tumor cell, we elected to target taxol, a potent anticancer drug, to estradiol-responsive breast cancer cells through estradiol-taxol conjugates. Studies of breast cancer have shown that most breast cancer cells are responsive to estrogen and progesterone.\(^ {127}\) One promising approach to the treatment of breast cancer is to use the hormone receptors of ER-positive breast cells as the ways to target anticancer drugs to these specific cells. This approach would reduce the toxicity of anticancer drugs to normal cells, which do not have ER,
and thus enhance their selectivity toward tumor cells.

1.4. Targeted taxol analogs

As a potent anticancer drug, taxol and its analogs have intrigued a lot of scientists. Many studies have been reported on their activities, mechanisms, SAR, and clinical effectiveness.\textsuperscript{128-130} Among them, targeted taxol analogs, although relatively new, have also been studied. Since taxol is a highly hydrophobic molecule, its delivery has been achieved through carriers, like cremophor / alcohol (1:1).\textsuperscript{131} Improvement of its solubility has been extensively studied by linking taxol to water-soluble and biodegradable polymers. The water-soluble taxol prodrugs developed by Greenwald’s group were a series of compounds in which the taxol was attached at its 2'-position to a poly(ethylene glycol) (PEG) unit through different linkers.\textsuperscript{132-134} The prodrug demonstrated enhanced anticancer activity and less toxicity in the P388/0 murine leukemia cell line. The use of this prodrug in the treatment of HT-29, A549, and SKOV3 solid tumor-bearing xenografted mice also turned out to give significant, positive results.\textsuperscript{134} Another biodegradable polymer which has been used as taxol carrier is hyaluronic acid (HA).\textsuperscript{135-136} HA is a linear polysaccharide of alternating $D$-glucuronic acid and $N$-acetyl-$D$-glucosamine units. Since HA

\begin{thebibliography}{99}
\end{thebibliography}
receptors are overexpressed in transformed human breast epithelial cells and other cancers,\textsuperscript{137} the HA-Taxol conjugate showed selective toxicity toward human cancer cell lines which are known to overexpress HA receptors.\textsuperscript{135}

Although many studies have been carried out in the taxol area, ligand-directed targeting of taxol has not been well studied. Recently, Safavy and his co-workers have reported a water-soluble and tumor – recognizing conjugate of taxol.\textsuperscript{138} A synthetic peptide, BBN[7-13], which can bind to the surface bombesin/gastrin-releasing peptide (BBN/GRP) receptor, was coupled to the 2'-position of taxol through a bifunctional PEG linker. The resulting conjugate completely retained the binding ability to BBN/GRP receptor compared to the free BBN[7-13] molecule. The bioassay of this conjugate in NCI-H1229 cell line showed that the cytotoxicity of this conjugate had been enhanced.\textsuperscript{138} This research provides a new method to design and synthesize targeted and water-soluble prodrugs. Another study published recently by Huang\textsuperscript{139} also revealed that ligand-targeted taxol can improve selectivity and thus reduce its toxicity to healthy cells. In this paper, they used the binding ability of somatostatin (SST) to its receptors (SSTRs) to specifically target taxol to tumor cells rather than healthy cells. It is known that many SSTRs are present in most hormone–secreting tumor cells.\textsuperscript{140-142} Octreotide, an analog of SST,


has been used to conjugate taxol through a succinate linker and target it to the breast cancer cell. The bioactivity of this conjugate in the MCF-7 breast cancer cell line was examined. The conjugate retained taxol’s activity as a tubulin-assembly promoter, while the toxicity was exclusive to SSTR-expressing cells.

1.5. Proposed research outline

In our group, the research interests in taxol area include the following two major parts: the drug targeting and the elucidation of the biological active conformation.

As shown above, many breast cancer cells are hormone-dependent, and contain hormone receptors. We thus plan to use this feature of breast cancer in a hormone approach to getting taxol selectively into breast cancer cells. It has been shown previously that drugs can be linked to the 11-position of estradiol or to the 16-position and that the resulting conjugates retain hormonal activity. We thus propose to prepare taxol-estradiol conjugates at both positions of estradiol, and determine the activity of these conjugates in MDA-MB-231 (ER negative) breast cancer cell line against MCF-7 (ER positive) breast cancer cell line.

Taxol has a rigid four-ring baccatin core and a flexible C-13 side chain. In order to lock the conformation of taxol, we try to put a cyclopropane ring at the side chain or a macrocyclic bridge from baccatin core to the side chain. Both of them are capable of reducing the flexibility of the side chain and result in a “locked conformation” which might mimic the bioactive conformation. Recently, 2-phenylspiro(cyclopropane-1’,4-oxazoline)-5-carboxylic acid was disclosed and considered to be a potential precursor to a taxol analog with a cyclopropane-containing side chain. Also there are a lot of macrocyclic taxol analogs were made
to examine the proposed conformations. We thus propose to synthesize the cyclopropane-containing taxol analogs and macrocyclic taxol lactones.

Outline of the proposed research is shown below:

1. Synthesis and biological evaluation of taxol conjugates at the C-11 position of estradiol – to link taxol (2’, 7, or 10 position) to the 11 position of estradiol. A target molecule is shown below. (Figure 1.12)

![Figure 1.12 11-estradiol linked to 2’-taxol through succinic acid](image)

2. Synthesis and biological evaluation of taxol conjugates at the C-16 position of estradiol – to link taxol (2’, 7, or 10 position) at the 16 position of estradiol. An example is shown below. (Figure 1.13)

![Figure 1.13 16-estradiol linked to 10-taxol](image)
3. Synthesis and biological evaluation of cyclopropane-containing taxol analogs at the C-3' position of taxol. A target molecule is shown below. (Figure 1.14)

![Cyclopropane-containing taxol analog](image)

**Figure 1.14** Cyclopropane-containing taxol analog

4. Synthesis and biological evaluation of macrocyclic taxol lactones from the \textit{meta} position of the C-3' phenyl to the C-4 position oxygen. A target molecule is shown below. (Figure 1.15)

![Macrocyclic taxol lactone](image)

**Figure 1.15** Macro cyclic taxol lactone
2. Syntheses and Bioactivities of Steroid-Linked Taxol Analogs

2.1 Introduction

Taxol (1) was first isolated from the bark of the Pacific yew about 35 years ago by Drs. Wall and Wani. Although its development as an anticancer agent was delayed by numerous reasons, including its scarcity and insolubility, the discovery of its tubulin-assembly activity and other factors motivated oncologists to overcome these problems. It has since become one of the most important current drugs for the treatment of several cancers, including breast and ovarian cancers; its importance in the treatment of breast cancer has been reviewed, as has its chemistry.

Like almost all anticancer drugs, taxol does have some toxic side effects, such as bone marrow suppression and neutropenia, and many tumors also show significant resistance to therapy with taxol. One approach to improving its selectivity and efficacy is by targeting it to selected tumors through the use of various conjugates, and several taxol conjugates with

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144 Levin, M. *Drugs Today* 2001, 37, 57-65.
improved selectivity and solubility have been synthesized recently. Thus Safavy reported a water-soluble and tumor-recognizing conjugate of taxol and BBN[7-13], which retained binding ability to the BBN/GRP receptor compared to the free BBN[7-13] molecule. Huang used the binding ability of somatostatin (SST) to its receptors (SSTRs) to target taxol specifically to tumor cells. A report from Luo revealed that a conjugate of hyaluronic acid and taxol was selectively toxic toward the human cancer cell lines which are known to overexpress HA receptors. Fuchs and his co-workers have reported the preparation and evaluation of taxol-folic acid conjugates. Ojima reported a C-10 methyldisulfanylpropanoyl taxoid conjugated to monoclonal antibodies. These conjugates were shown to possess selective antitumor activity in vivo against EGFR-expressing A431 tumor xenografts.

One approach that has not yet been explored is that of targeting taxol to breast cancer by means of selected steroid hormone conjugates. The female hormone estradiol (2) plays an important role in breast cancer, and the hormone dependence of breast cancer was first reported by Beatson in the late 1800’s. Further studies revealed the interaction between steroid hormones and their receptors, and thus led to a better understanding of the hormone in controlling the growth of breast cancer. The hormone-dependence of breast cancer can also be used as a drug delivery target through the recognition and binding of estrogen to its receptor, and several studies have investigated the targeting of drug molecules into breast cancer cells by

linking them to estradiol or other estrogens.\textsuperscript{111-114,147} The potential benefits of this approach include the improvement of a drug’s therapeutic effectiveness and bioavailability, coupled with a reduction in MDR and toxic side-effects.

The goal of the present research was to target taxol to ER positive breast cancer cells through the interaction between estradiol and its corresponding receptor, with the goal of developing new drug candidates against breast cancer, the second leading death causing cancer in women.\textsuperscript{148} From previous studies of the SAR of estradiol, it is known that estradiol can be modified at the 16- and 11-positions without losing its ability to bind to the ER.\textsuperscript{147} As for taxol, SAR studies have shown that the 10- and 7- positions can be acylated with only relatively minor effects on the drug’s activity.\textsuperscript{145a,149} Another position which can be used for targeting is the 2′-position, because ester linkages at this position can be hydrolyzed in vivo,\textsuperscript{47} and hence an estradiol-taxol conjugate at the 2′-position could serve as a “targeted pro-drug” if the targeting occurred before hydrolysis. In this chapter, we describe the synthesis of estradiol-taxol conjugates through ester linkers from the 11- and 16-positions of estradiol to the 2′-, 7-, and 10-positions of taxol.

\subsection*{2.2 Syntheses of steroid-linked taxol analogs}

The synthesis of estradiol linkers 7 and 10 is outlined in Scheme 2.1. The commercially available estrone (2) was converted into compounds 6\textsuperscript{147b} and 9\textsuperscript{150} through reported procedures.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Synthesis} & \textbf{Literature} \\
\hline
Ishiki, N.; Onishi, H.; Machida, Y. \textit{Biol. Pharm. Bull.} \textbf{1997}, 20, 1096-1102. & (a) \textsuperscript{147} \\
Swamy, N.; James, D. A.; Mohr, S. C.; Hanson, R. N.; Ray, R. \textit{Bioorg. Med. Chem.} \textbf{2002}, 10, 3237-3243. & (b) \textsuperscript{148} \\
Tedesco, R.; Fiaschi, R.; Napolitano, E. \textit{J. Org. Chem.} \textbf{1995}, 60, 5316-5318. & (c) \textsuperscript{149} \\
\hline
\end{tabular}
\end{table}
Compound 6 was hydrolyzed to generate compound 7 with a free carboxyl group for coupling. The linker 10 was obtained by reacting 9 with succinic anhydride. The use of pyridine as solvent only gave a 30% yield, but deprotonation of 9 with LHMDS in THF followed by addition of succinic anhydride gave 10 in 70% yield based on unrecovered starting materials.

Scheme 2.1 Synthesis of the two estradiol linkers

With the two estradiol linkers 7 and 10 in hand, the estradiol-taxol conjugates could be assembled. According to SAR studies, the most reactive hydroxyl group in taxol is the 2′-OH, followed by the 7- and 10-OH groups; the 1-OH group is inert to ester formation under normal conditions. Direct acylation of taxol with compounds 7 and 10 thus yielded the 2′-acyl

Reagents and conditions: (a) TBSCI, imidazole, DMF, 90%; (b) LDA, THF, then allyl bromide, 70%; (c) LAH, THF, 93%; (d) TESCl, imidazole, DMF, 92%; (e) OsO₄, NMO, t-BuOH/H₂O, then NaIO₄, acetone, 70%; (f) Ph₃PCHCO₂Et, benzene, 92%; (g) LiOH, THF, H₂O, 36h, 72%; (h) LAH, THF, 91%; (i) TBSCI, imidazole, DMF, 92%; (j) DDQ, CH₂Cl₂/MeOH, 65%; (k) BH₃, THF, then H₂O₂, NaOH, 74%; (l) LHMDS, succinic anhydride, 24h, 70%

derivatives 11 and 13 (Scheme 2.2), respectively. Protection of the 2′-hydroxyl group as its tert-butyldimethylsilyl ether 15, followed by acylation with compounds 7 and 10 gave the 7-acyl analogs 16 and 18. In general, conjugate formation occurred in low yield, with conversion percentages of 25-35%, and with significant amounts of unreacted taxol; the yields based on unrecovered taxol were in the range of 60-70%. Deprotection of the silyl groups with HF-pyridine proceeded in good yields to give the estradiol-taxol complexes 12, 14, 17, and 19.

Scheme 2.2 Synthesis of estradiol-taxol conjugates at the taxol C-2′ and C-7 position

Reagent and conditions: (a) 7, EDC/DMAP, toluene, 60 °C, 24h, 73%; (b) HF-pyridine, THF, RT, overnight, 97%; (c) 10, EDC/DMAP, toluene, 60 °C, 24h, 78%; (d) HF-pyridine, THF, RT, overnight, 92%; (e) TBSCl, imidazole, DMF, 65 °C, 3h, 95%; (f) 7, EDC/DMAP, toluene, 60 °C, 48h, 65%; (g) HF-pyridine, THF, RT, overnight, 82%; (h) 10, EDC/DMAP, toluene, 60 °C, 48h, 65%; (i) HF-pyridine, THF, RT, overnight, 91%.
Scheme 2.3 Synthesis of estradiol-taxol conjugate at the taxol C-10 position

The synthesis of estradiol-taxol conjugates at the 10-position was achieved by converting 2′-(tert-butyldimethylsilyl)-taxol (15) into 2′-(tert-butyldimethylsilyl)-10-deacetyl-taxol (20) and hence to 2′-(tert-butyldimethylsilyl)-10-deacetyl-7-(triethylsilyl)-taxol (22) through a known procedure.\(^\text{152}\) During the deacetylation of 15 using hydrazine monohydrate in ethanol, a

\(^{152}\) Taxol derivative 19 was prepared by protecting the known 2′-TBS-10-deacetyltaxol as its triethylsilyl ether at the
by-product of 30% of 2′-(tert-butyldimethylsilyl)-7-epi-taxol (21) was observed (Scheme 2.3). Unfortunately, compound 22 did not undergo ester formation using standard EDC/DMAP conditions. One possibility is that the 10-position was too sterically hindered to accept the relatively short linkage to estradiol because the bulky 7-TES group might somehow block this position. To test this hypothesis, 2′-(tert-butyldimethylsilyl)-7-epi-taxol was used as a substrate, since this not only lacked the bulky 7-TES group but also had an unreactive 7-epi-hydroxyl group.\(^{55}\) Compound 21 reacted with estradiol 10 smoothly under EDC/DMAP conditions in CH\(_2\)Cl\(_2\) to give product 23 in 79% yield. Deprotection of 23 by HF-pyridine gave 24 in good yield. Coupling of linker 7 with 21 was also attempted under the same conditions, but two inseparable products were obtained as determined by NMR spectroscopy.

It is well known that taxol has very low solubility in water, and the estradiol-taxol conjugates would be expected to be even less soluble, since estradiol is hydrophobic. We thus synthesized two estradiol-taxol conjugates with improved water solubility. It is been reported that a hemisuccinate at the 2′-position of taxol can improve the drug’s solubility when the free carboxyl group is neutralized as its sodium or (triethanol)ammonium salts. Scheme 2.4 shows the synthesis of two estradiol-taxol conjugates with either a 2′-hemisuccinate or a 7-hemisuccinate ester group. Compound 25 was prepared by reaction of taxol with monobenzyl succinate using EDC/DMAP conditions to protect the 2′-position. This was followed by introduction of the estradiol linker 10 at the 7-position using the conditions described previously.

Scheme 2.4 Synthesis of estradiol-taxol conjugates with improved water solubility

Reagents and conditions: (a) BnOCOCH$_2$CH$_2$COOH, EDC/DMAP, CH$_2$Cl$_2$, RT, 24 h, 40%; (b) 7, EDC/DMAP, CH$_2$Cl$_2$, RT, 48 h, 70%; (c) HF-pyridine, THF, RT, overnight, 98%; (d) H$_2$, Pd-C, EtOAc, 30 psi, 24 h, 80%; (e) BnOCOCH$_2$CH$_2$COOH, EDC/DMAP, CH$_2$Cl$_2$, RT, 48 h, 90%; (f) HF-pyridine, THF, RT, overnight, 99%; (g) H$_2$, Pd-C, EtOAc, 50 psi, 24 h, 50%.
The desired compound 28 was obtained after desilylation and hydrogenolysis; its sodium and triethanolamine salts (29 and 30) were also prepared. The 7-hemisuccinate 33 was obtained using the reverse order of steps, with initial acylation of taxol with estradiol 10 followed by acylation with monobenzyl succinate at C-7 and deprotection; its sodium and triethanolamine salts (34 and 35) were also prepared by a previously reported procedure.\textsuperscript{151a}

2.3 Biological results for estradiol-linked taxol analogs.

The biological activities of taxol and of the estrogen conjugates 12, 14, 17, 19, and 24 were compared in a tubulin-assembly assay, for cytotoxicity to estrogen receptor (ER) negative A2780 ovarian cancer cells, ER (beta) positive PC-3 prostate cancer cells, and two lines of human breast tumor cells (Table 2.1).

### Table 2.1 Bioassay results for estradiol-taxol conjugates

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>% assembly 0.2 µM\textsuperscript{a}</th>
<th>% assembly 1.0 µM\textsuperscript{a}</th>
<th>A2780 IC\textsubscript{50} (nM)</th>
<th>PC-3 IC\textsubscript{50} (nM)</th>
<th>MDA-MB-231 IC\textsubscript{50} (nM)</th>
<th>MCF-7 IC\textsubscript{50} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>taxol (1)</td>
<td>100</td>
<td>100</td>
<td>25</td>
<td>77</td>
<td>4.5</td>
<td>4.9</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>55</td>
<td>180</td>
<td>73</td>
<td>22</td>
<td>39</td>
</tr>
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<td>60</td>
<td>60</td>
<td>680</td>
<td>40</td>
<td>51</td>
<td>62</td>
</tr>
<tr>
<td>17</td>
<td>100</td>
<td>100</td>
<td>8300</td>
<td>120</td>
<td>2200</td>
<td>1600</td>
</tr>
<tr>
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<td>100</td>
<td>100</td>
<td>2900</td>
<td>320</td>
<td>780</td>
<td>557</td>
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<td>100</td>
<td>100</td>
<td>1900</td>
<td>68</td>
<td>304</td>
<td>103</td>
</tr>
<tr>
<td>28</td>
<td>NT</td>
<td>NT</td>
<td>15000</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
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<tr>
<td>29</td>
<td>NT</td>
<td>NT</td>
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<td>30</td>
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<td>NT</td>
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<td>33</td>
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<td>NT</td>
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<td>NT</td>
<td>10000</td>
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<td>NT</td>
<td>NT</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The extent of tubulin assembly induced by 0.2 and 1.0 µM taxol and by each compound with 10 µM tubulin was determined. The extent of tubulin assembly in the presence of taxol is defined as 100%, and the extent of tubulin assembly with each ligand was compared with this value.\textsuperscript{b} n=3 experiments in quadruplicate, p<0.001.

\textsuperscript{b} The MCF-7 and MDA-MB-231 assays were performed by Rayhana Rahim-Bata and Meredith McCracken in Dr. Strobl’s group in West Virginia Univ.; The tubulin assembly and PC-3 assays were performed by Sabarni K. Chatterjee in Dr. Bane’s group in New York State Univ., and A2780 assay was done by Jennifer K. Schilling in Virginia Tech. Their work is greatly appreciated.
The taxol IC$_{50}$ value estimated by non-linear regression analysis was similar in the ER-alpha positive MCF-7 and ER-alpha negative MDA-231 lines, 4.9 nM and 4.5 nM, respectively, and both these values were lower by over an order of magnitude than the IC$_{50}$ value in the PC-3 prostate cancer cell line. The 2'-substituted taxol conjugates 12 and 14 were both about as active as taxol in the PC-3 cell line, but were less active than taxol in the breast cancer lines. They were also less active than taxol in the tubulin assembly assay. These results are explicable by postulating that the 2'-derivatives undergo slow conversion into taxol under the conditions of the cell culture, with the conversion being more rapid in the PC-3 assay than in the two breast cancer cell lines; the lower activity of both compounds in the tubulin assembly assay is consistent with this hypothesis. Similar results were obtained for the activity of 2'-acetyl taxol. Neither compound 12 nor 14 showed any significant selectivity for the ER-alpha positive cell line MCF-7 as compared with the ER-alpha negative line MDA-MB-231; this result is also consistent with hydrolysis under cell culture conditions. Interestingly, the MDA-MB-231 breast tumor cell line which expresses ER-beta receptors was more sensitive to compounds 12 and 14 than the ER-alpha positive MCF-7 breast tumor line. In addition, the steroid conjugate 14 may show improved activity compared with taxol against the PC-3 line. Recently, clinical samples of prostate cancer as well as certain prostate cell lines (PC-3) have been found to express ER-beta receptors, and expression is correlated with tumor aggressiveness on the Gleason scale. These data raise the possibility that these derivatives target the beta form of the estrogen receptor.

154. (a) Linja M. J.; Savinainen, K. J.; Rammela, T. L.; Isola, J. J.; Visakorpi, T. *Prostate* 2003, 55, 180-186. (b)
The two C-7 substituted derivatives 17 and 19 were both significantly less potent cytotoxic agents than taxol in the two breast cancer cell lines, although both compounds were comparable to taxol in their tubulin-assembly activity and were only less active in the PC-3 cell line by factors of 1.6 and 4.2, respectively. Although both compounds showed modest selectivities towards the ER-alpha positive cell line MCF-7, the observed differences were not statistically significant.

The dose-response curves for taxol and compound 19 are shown in Figure 2.3. The maximal antiproliferative response to either taxol or 19 was 85-90% inhibition of cell survival by 48 h; thus the efficacy of both compounds was equivalent. In MCF-7 cells, the maximal reduction in cell survival elicited by either taxol or 19 in a 48 h incubation was 20-30%. When MCF-7 cells were incubated with taxol or 19 for 7 days, the maximal decrease in cell survival was approximately 70%. The difference in the efficacy of taxol and the steroid conjugated derivative between MDA-MB-231 cells and MCF-7 cells is most likely the differences in the cell doubling time. For MDA-MB-231 cells with a cell doubling time of approximately 22 h, nearly all cells are exposed to taxol or 19 during a sensitive stage of the cell cycle during the 48 h incubation period. However, MCF-7 cells, with a doubling time of nearly 60 h, require a much longer period of drug exposure before a similar fraction of the cells enter or transit the taxol-sensitive phase of the cell cycle.

Figure 2.3 Inhibition of breast tumor cell survival in vitro by taxol and compound 19. Human breast tumor cell lines were incubated for 48 h with the indicated drug concentrations. The cell survival response in estrogen-receptor negative MDA-MB-231 cells and estrogen-receptor positive MCF-7 cells was determined using the MTS assay. Response (A_{490} nm) is plotted as a fraction of control cells, which was set to 100%. A nonlinear regression fit to a sigmoidal dose-response equation is shown. Data are representative of n = 2 independent experiments performed in quintuplicate.

The 10-substituted derivative 24 gave the most interesting results. It had comparable activity to taxol in both the tubulin-assembly and PC-3 assays, and it also showed a threefold greater activity towards the ER-alpha positive MCF-7 cell line than the ER-alpha negative MDA-MB-231 cell line. It was, however, significantly less potent than taxol to both these cell lines. Our results do, however, suggest that future efforts at targeting taxol to ER-alpha positive breast cancer cells would be most fruitful if centered around modifications at the C-10 position.

The hemisuccinates 28 - 30 and 33 - 35 were only tested in the A2780 ovarian cancer cell line; they were all found to be significantly less active that taxol, and so were not subjected to further testing.

* The MCF-7 and MDA-MB-231 assays were performed by Rayhana Rahim-Bata and Meredith McCracken in Dr. Strobl’s group in West Virginia Univ. Their work is greatly appreciated.
2.4 Conclusions and proposed future work.

A series of estradiol-taxol conjugates (ETCs) were synthesized. All conjugates were active in cytotoxicity assays and tubulin polymerization assay, although they were less active than taxol. Compound 24 showed the selectivity for MCF-7 (ER positive) against MDA-MB-231 (ER negative) cells, and it was three times more cytotoxic in MCF-7 cell lines than in MDA-MB-231 cell lines, while the rest of the ETCs showed no significant selectivity. Two ETC hemisuccinates were also synthesized to achieve better water solubility. Their corresponding Na and triethanolammonium salts were slightly more cytotoxic than the acid form, but were much less cytotoxic than the corresponding ETCs.

As the results of this drug targeting research, we synthesized a series of estradiol linked taxol analogs. The one with the desired selectivity against ER positive cancer cell lines was the estradiol linked at the C-10 position of taxol. But in general, the ETCs lack biological activities.
In order to improve the selectivity and bioactivity, we synthesized “self-immolating” taxol analog\textsuperscript{155} to target taxol itself to cancer cells through ligand-receptor interactions as shown in Figure 2.4. Disulfide linkers can be cleaved in the cell where glutathione and other thiols are in relatively high concentration.\textsuperscript{99-100} The resulting sulfur anion will attack the ester carbonyl group at taxol C-2’ to form cyclic 3,3-dimethyl-dihydrothiophen-2(3H)-one, which lead to the release of free taxol.\textsuperscript{155}

3. Syntheses of Thio-containing Taxol Analogs for Drug Targeting through Colloidal Gold

3.1 Introduction

Taxol, a compound isolated from the bark of Pacific yew, is effective in treating a variety of cancers. However its systemic administration is hampered by its poor solubility and a low therapeutic index. Efforts to address these issues have focused on packaging the drug in liposomes and biodegradable micropheres. Colloidal gold nanoparticles (cAu) as a vector for tumor targeted drug delivery have been used by our collaborator (CytImmune Sciences, Inc.). They have developed cAu vectors that deliver Tumor Necrosis Factor (TNF) to solid tumors. It was observed that TNF acts both as a tumor targeting ligand and as a therapeutic agent. Theoretically, we can use TNF bound to cAu to selectively deliver taxol, which binds to the same nanoparticles, to solid tumor cells. (Figure 3.1)

![Figure 3.1 Schematic of the TNF-targeted colloidal gold taxol vector.](image)

In order to have taxol bound to cAu, we need to introduce a functional group into taxol
which has a strong binding interaction. Since the thiol group is well known for its excellent
gold-binding ability, we decided to synthesize thio-containing taxol analogs to achieve this goal.
The modification was set to the C-7 and C-10 positions of taxol because SAR studies showed
these parts of the molecule have relatively less impact on taxol’s bioactivity. A series of taxol
analogs were prepared with different chain lengths from taxol (7-O or 10-O) to \(-\text{SH}\) and their
bioactivities were determined.

3.2 Syntheses of thio-containing taxol analogs

There are two reports on thio-containing taxol analogs; one has a C2'-SH group\(^{156}\) and the
other one has a C7-SH group,\(^{157}\) but they are unlikely to have a strong binding to the cAu
because the linkage is too short. We decided to investigate how to put a thiol group into the taxol
structure. The first thing we tried was to do acylation at the taxol 7-OH position. We chose
iodoacetic acid as the acylation agent using EDC/4-PP coupling conditions. Then we proposed to
convert the –I group into the –SH group by using an SN2 substitution. If this procedure worked,
we could generate a series of thio-containing taxol analogs by changing the terminal halide
carboxylic acid. The acylation between iodoacetic acid and 15 proceeded smoothly to give
compound 36 in 90% yield. Compound 36 was then treated with NaSH in anhydrous DMF to
convert the iodo group into a thiol. Unfortunately, this reaction gave complex mixtures, and
NMR analysis indicated that the TBS group was partially deprotected. Thus, we tested the
deprotection first. The deprotection of TBS was performed using 5% HCl in methanol at room


temperture for 3 h. The reason for not using HF-pyridine as deprotecting agent is the fluoride ion could conceivably attack the terminal –I group, which could make the following step more difficult. The desired deprotection product 37 was obtained in 85% yield. The conversion of –I into –SH was then performed in anhydrous DMF, and one highly polar product 38 was generated in 78% yield. After NMR and HRFABMS analysis, we confirmed that we had the desired product. (Scheme 3.1)

With the standard procedures worked out, we started to prepare more analogs by changing the acid we used at the taxol 7-OH. 3-Bromopropanoic acid was coupled under several coupling conditions, but no desired product was produced. Coupling of 5-bromopentanoic acid, 6-bromohexanoic acid, 11-bromoundecanoic acid, and 12-bromododecanoic acid all proceeded well with the standard procedures. Four more thio-containing taxol analogs (47-50) were produced as shown in Scheme 3.2.

Scheme 3.1 Synthesis of thio-containing taxol analog at C-7
Besides the modification at C-7, we also attempted to put –SH groups at the C-10 position. The acylation of 22 by iodoacetic acid did not proceed very well. The use of EDC/4-PP conditions in toluene gave a very low yield. DCC gave a 35% yield of the desired product (51) with about 10% unreacted 22, but we could not separate the product from the starting material. A change of solvent to DCM and the use of EDC/4-PP coupling conditions gave 52 in 85% yield, but the terminal –I had been converted into –Cl. This presumably occurred from chloride ions from the EDC reagent in the reaction mixture, since we used about 20 equivalents to push the reaction to go. As noted earlier, the products from DCC coupling were inseparable at this stage, but after deprotection of the two silyl groups, they could be separated and the desired 53 was obtained. The conversion of –I into –SH then proceeded well in DMF to give the desired product 55. Compound 52 was also subjected to deprotection of silyl groups and gave 54 in 60% yield. Compound 54, however, under the same NaSH/DMF conditions only gave mixtures instead of
the desired 55 (Scheme 3.3).

Scheme 3.3 Synthesis of thio-containing taxol analog at C-10

For the synthesis of thio-containing taxol analogs at the C-10 position with longer chains, we decided to use the EDC/4-PP coupling method in DCM. The products were still inseparable from the starting material, but prolongation of the reaction time to 7 days gave 100% conversion of the starting materials into products. However, as discussed above, substitution of halogen by chlorine occurred again. In the case of 5-bromopentanoic acid, NMR analysis showed that 70% of the bromine atoms were replaced by chlorine (56). For 6-bromohexanoic acid and 11-undecanoic acid, the replacement percentages were even higher, 90% (57) and 95% (58).
respectively. The HRFABMS results confirmed the NMR results, showing molecular ions containing both Cl and Br with appropriate intensity ratios. Deprotection of the silyl groups was carried out with 5% HCl/MeOH to give compounds 59, 60, and 61 in good yield, each with a mixture of terminal halides. Compounds 61 were then treated with NaSH in DMF to give the desired thio-containing product 62 from the bromine-containing component together with most of the starting material with a terminal chloride. This result suggested that the chlorides must be converted back into bromides or iodides to have a successful substitution for this series of reactions. The iodide option was chosen and the reaction was performed in acetone at room temperature using an excess amount of NaI. Since TLC did not show any differences between the product and starting material, we quenched the reaction after 3 days and used NMR to tell how far this reaction had gone. It turned out that 3 days at room temperature only gave low conversion (<30%). We then raised the temperature to 40 °C for another 3 days, which resulted in complete conversion of the terminal halides (both chloride and bromide) into iodide. Reaction of resulting iodides 64 and 65 with NaSH then gave the desired products 66 and 67 in good yield.
3.3 Biological results for thio-containing taxol analogs

The biological activities of taxol and of the thio-containing taxol analogs \textsuperscript{38, 47-50, 62, 66}, and \textsuperscript{67} were compared in the A2780 ovarian cancer cell line (Table 3.1). Compound \textsuperscript{55} turned out to be a very unstable compound; thus no bioassay was performed for this molecule. From the bioassay results we got, acyl groups with a terminal \textendash SH acylated at either 7-O or 10-O decrease taxol’s bioactivity to a certain extent. Compound \textsuperscript{38} has the smallest IC\textsubscript{50} in that table, which means it has the best activity among this series of compounds. Thus, the following studies done
by our collaborators used 38 as their primary material, while the rest of the compounds were also used for the best fit.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Cytotoxicity A2780 IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>0.16</td>
</tr>
<tr>
<td>47</td>
<td>6.4</td>
</tr>
<tr>
<td>48</td>
<td>5.4</td>
</tr>
<tr>
<td>49</td>
<td>15.2</td>
</tr>
<tr>
<td>50</td>
<td>15.0</td>
</tr>
<tr>
<td>55</td>
<td>NT</td>
</tr>
<tr>
<td>62</td>
<td>4.6</td>
</tr>
<tr>
<td>66</td>
<td>10.1</td>
</tr>
<tr>
<td>67</td>
<td>6.7</td>
</tr>
</tbody>
</table>

With the thio-containing taxol analogs made, our collaborator (CytImmune Sciences, Inc.) worked on development of the vector formulation. The first thing was to make sure that the thio-containing taxol analogs (Taxol-SH) bound to the colloidal Au nanoparticles. It was found that Taxol-SH bound optimally to cAu particles at pH 4.5, and this binding was saturable with 100-300 µg of drug per mL of cAu (Figure 3.2). With the TNF and Taxol-SH binding chemistries defined, a TNF/cAu/Taxol-SH vector was developed by titrating the amounts of TNF and Taxol-SH added to a fixed volume of cAu. Control vector consisted of cAu particles coated with only TNF or Taxol-SH. After binding, the particles were isolated by centrifugation and the cAu pellets analyzed for TNF and taxol concentration by quantitative EIAs. To confirm the presence of both TNF and Taxol-SH on the same particle of gold the TNF/cAu/Taxol-SH vector was

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*The A2780 assay was performed by Jennifer K. Schilling in Virginia Tech. Her work is greatly appreciated.
added to EIA plates coated with a TNF monoclonal antibody, which captured the vector through the TNF moiety. After washing, a rabbit anti-taxol antibody was added to the wells. The bound rabbit anti-taxol was detected with an enzyme labeled secondary antibody followed by the addition of substrate to initiate color development. Results from these studies showed that TNF and Taxol-SH control vectors generated an OD of 0.3 and 0.4, respectively, while the chimeric vector generated an OD of 1.5. From a series of comparative ratio experiments the lead vector formulation contained 33 ng of TNF and 500 ng of Taxol-SH per mL of cAu. This vector is currently being evaluated for its therapeutic potential.

**Figure 3.2** Saturation binding of cAu nanoparticles with the taxol-SH

### 3.4 Conclusions

A series of thio-containing taxol analogs were synthesized at taxol C-7 and C-10 positions. They were all active in A2780 cytotoxicity assays, and the activity decreased as the chain length increased. Compound 38 was the most active one and was tested for the binding ability to gold nanoparticles (cAu).
4. Syntheses and Bioactivities of Cyclopropyl-Containing Taxol Analogs

4.1 Introduction

Cyclopropyl groups have proved to be highly effective in improving the activity of many biologically active compounds,\textsuperscript{158,159} and several cyclopropane-bearing analogs of taxol\textsuperscript{160} and epothilone\textsuperscript{161} have previously been synthesized and shown to have improved or retained anticancer activity. (Figure 4.1) Recently, a new simple access to the spirocyclopropanated oxazoline-5-carboxylic acid 72 was disclosed, and 72 was considered to be a potential precursor to a taxol analog with a cyclopropane-containing side chain.\textsuperscript{162}

![Figure 4.1](image_url)

\textbf{Figure 4.1} previously reported cyclopropane-bearing analogs of taxol and epothilone\textsuperscript{160-161}


4.2 Syntheses of cyclopropyl-containing taxol analogs

![Chemical structures](image)

**Figure 4.2** Structure of taxol (1), 7-TES-baccatin III (68), synthetic targets (69-71), and substituted (±)-2-phenylspiro(cyclopropane-1',4-oxazoline)-5-carboxylic acids (72-74)

The synthesis of a taxol analog with a cyclopropane-containing side chain was of interest, since the 1,1-disubstituted cyclopropyl group in the side-chain would constrain the conformational mobility of the side chain and might potentially bring it closer to the biologically active binding conformation of taxol. The synthetic strategy, the principle of which has been successfully executed before,\(^\text{163}\) would be to couple the oxazolinecarboxylic acid 72, 73, or 74 to 7-TES-baccatin III (68), and then hydrolytically open the oxazoline moiety to the desired side chain. The acids 72-74 were obtained through the courtesy of Professor Armin de Meijere.

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Reagents and conditions: a. DCC, 4-PP, toluene, RT, 24h, 85%; b. HF-pyridine, THF, 0°C to RT, 24h, 90%; c. 0.1 N HCl/1,4-dioxane (1:1), 50°C, 1h, 85%; d. 0.1 N NaHCO₃/1,4-dioxane (1:1), RT, 6h, 80%.

**Scheme 4.1 Synthesis of cyclopropyl-containing taxol analogs**

The coupling of 68 with (±)-2-phenylspiro(cyclopropane-1',4-oxazoline)-5-carboxylic acid (72) using DCC/4-PP proceeded in good yield (85%). The two diastereomers 75 and 76 were obtained in a ratio of 2:3 and were separated by preparative thin layer chromatography. Unfortunately, the products 75 and 76 proved resistant to hydrolysis under the conditions previously used [0.1 N HCl/dioxane (1:1)]. Only starting material and various decomposition products could be detected under the literature conditions, while prolonged reaction times led to cleavage of the side chain. Surprisingly, however, when the triethylsilyl groups in 75 and 76 were first removed by treatment with HF-pyridine, and the product subsequently hydrolyzed with 0.1 N HCl/dioxane (1:1) at 50 °C, the 2'-O-benzoyl taxol derivatives with free C-3’ amino groups were obtained. These intermediates somehow were less prone to rearrange by benzoyl
migration from the 2'-oxy group to the 3'-amino group than other taxol analogs. Thus under neutral aqueous conditions and basic non-aqueous conditions, migration of the benzoyl group did not take place, but treatment with 0.1 N NaHCO₃/dioxane (1:1) led to clean rearrangement, and the four cyclopropane-containing taxol analogs 79, 80, 81, and 69 were obtained. High-resolution FAB mass spectra (HRFABMS) showed that all four of them had the same mass and elemental composition. The chemical shift differences between the 7-H and 10-H protons in the ¹H-NMR spectra of compounds 79 and 80 (or 81 and 69) were quite large. By comparison with literature values, it could be concluded that 79 and 81 had the 7-(R) (7-epi) configuration rather than the normal 7-(S) configuration.

\[ \Delta \delta_{RS} = \delta^R(82) - \delta^S(83) \]

Scheme 4.2 Absolute configuration assignment using Mosher ester analysis

In order to determine the absolute configuration at the 2'-position, compound 79 was converted into two esters with (R)- or (S)-methoxyphenylacetic acid (MPA), using the EDC/DMAP coupling conditions. Since the 7-hydroxy group in this compound is highly hindered,\textsuperscript{166} reaction occurred only at the 2'-OH position to yield the Mosher esters 82 and 83. This observation also supported the assigned configuration being (R) at C-7 for 79 and 81, since 7-epitaxol is much less reactive at this position than taxol itself. The resulting 2'-MPA esters 82 and 83 were subjected to NMR analysis.\textsuperscript{167} Fortunately, the chemical shift differences $\Delta \delta^{RS}$ were significant (Scheme 4.2). From these data it was concluded that the taxoid 79 must have the (S)-configuration at C-2', which is the configuration of 2'-epi-taxol. Thus the diastereomers 81 and 69 must be 2'-(R), and 80 must be 2'-(S).

The cytotoxic activities of these four taxoids were evaluated \textit{in vitro} using the A2780 ovarian cancer cell line. This assay showed that compounds 79 and 80, with the unnatural configuration at 2', are essentially inactive, while the isomers 81 and 69 with the natural configuration at 2' are active, but much less so than taxol itself. After discussing the results with our collaborators, we decided to put substituent groups on the cyclopropane ring to examine how this affected the activity of the derivatives. Another two spirocyclopropanated oxazoline-5-carboxylic acids (73 and 74) were made by our collaborators, and with them we prepared several more cyclopropyl-containing taxol analogs using the same procedures we developed above.

Reagents and conditions: a. EDC, DMAP, toluene, RT, 48h, 84-90%; b. HF-pyridine, THF, 0°C to RT, 24h, 71-99%; c. 0.1N HCl/1,4-dioxane (1:1), 55°C, 3h, then 0.1N NaHCO₃/1,4-dioxane (1:1), RT, 24h, 75-80%.

Scheme 4.3 Synthesis of substituted cyclopropyl-containing taxol analogs

The syntheses of substituted cyclopropyl-containing taxol analogs were basically the same as previously described, except the DCC/4-PP coupling conditions were replaced with EDC/DMAP conditions for easier work-up. With a methyl or isopropyl group on the cyclopropane ring, compounds 88-91 turned out to be more resistant to the acid hydrolysis. We thus were obliged to raise the temperature and prolong the reaction time to achieve the completion of these reactions. The migration of benzoyl from 2'-oxy to the 3'-amino group was also slower and a longer time was needed. For compounds 88 and 89, the final products (92-95) underwent epimerization at the taxol C-7 OH under slightly basic aqueous condition, just like 77 and 78. But compounds 90 and 91, on the other hand, gave only 70 and 71 with the normal taxol C-7 configuration.

The absolute configuration at C-2' for 70-71 and 92-95 was also checked using the Mosher
ester analysis. Two compounds 93 and 95 were converted into four esters with (R)- or (S)-methoxyphenylacetic acid (MPA), using EDC/DMAP coupling conditions. Again, reactions occurred only at the 2'-OH position to yield the Mosher esters 96, 97, 98, and 99. The resulting 2'-MPA esters 96 and 97 (or 98 and 99) were subjected to NMR analysis. The chemical shift differences $\Delta \delta^{RS}$ were quite large (Scheme 4.4). From these data it was concluded that the taxoids 93 and 95 must have the (S)-configuration at C-2', thus the diastereomers 70 and 71 must be 2'-(R), while 92 and 94 must be 2'-(S).

![Scheme 4.4 Absolute configuration assignment using Mosher ester analysis](image)

4.3 Biological results for cyclopropyl-containing taxol analogs

The biological activities of taxol and of the cyclopropyl-containing taxol analogs 69-71, 79-81, and 92-95 were tested in a tubulin-assembly assay and two cytotoxicity assays—A2780
ovarian cancer cells and PC-3 prostate cancer cells (Table 4.1).

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Tubulin Assembly IC₅₀ (µM)</th>
<th>A2780 IC₅₀ (µM)</th>
<th>PC-3 IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxol (1)</td>
<td>0.25</td>
<td>0.024</td>
<td>0.52</td>
</tr>
<tr>
<td>69</td>
<td>6.7</td>
<td>8.2</td>
<td>&gt;6.6</td>
</tr>
<tr>
<td>70</td>
<td>1.3</td>
<td>2.9</td>
<td>0.69</td>
</tr>
<tr>
<td>71</td>
<td>0.92</td>
<td>1.2</td>
<td>0.69</td>
</tr>
<tr>
<td>79</td>
<td>&gt;30</td>
<td>22</td>
<td>&gt;6.6</td>
</tr>
<tr>
<td>80</td>
<td>&gt;30</td>
<td>&gt;25</td>
<td>&gt;6.6</td>
</tr>
<tr>
<td>81</td>
<td>12</td>
<td>9.5</td>
<td>&gt;6.6</td>
</tr>
<tr>
<td>92</td>
<td>9.53</td>
<td>19</td>
<td>6.45</td>
</tr>
<tr>
<td>93</td>
<td>8.42</td>
<td>21</td>
<td>10.0</td>
</tr>
<tr>
<td>94</td>
<td>1.76</td>
<td>3.4</td>
<td>0.88</td>
</tr>
<tr>
<td>90</td>
<td>1.68</td>
<td>5.4</td>
<td>0.95</td>
</tr>
</tbody>
</table>

In general, these cyclopropyl-containing taxol analogs were less active than taxol itself. Among them, the most active compounds are those with the natural configuration at C-2' and C-7. The C-2' configuration was even more important than the C-7 was, since 79 and 80 were less active than the corresponding 76. The activities were also related to the substituents on the cyclopropane ring. As the proton was changed to methyl, we saw a more than 10 times increase in activity in the PC-3 prostate cancer cell line, 5 times in the tubulin assembly assay, and 3 times in the A2780 ovarian cancer cell line. The same trend was observed if we change the methyl to isopropyl, although its activity did not increase dramatically in those three assays.

4.4 Conclusions and proposed future work

Ten cyclopropyl-containing taxol analogs were synthesized with different substituents on the

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The tubulin assembly and PC-3 assays were performed by Natasha Shanker and Rudravajhala Ravindra in Dr. Bane’s group in New York State Univ., and A2780 assays was done by Jennifer K. Schilling in Virginia Tech. Their work is greatly appreciated.
cyclopropane ring and different stereo centers at the C-2' and the C-7 positions. They were active in A2780, PC-3 cytotoxicity assays and tubulin assembly assay, and the best activity came from the one with natural chiral centers at the C-2' and C-7 positions and an isopropyl group on the cyclopropane ring.

These results suggest that the substitution on the cyclopropane ring could affect the taxol’s activity and a larger group might even be better, since an isopropyl group was better than a methyl group. This finding also suggests that these novel taxol analogs are conformationally restricted in such a way that they do not bind well to the receptor. If further work is planned, it would be interesting to put a phenyl on the cyclopropane ring to examine how much it would affect the activity, because a C-3’ phenyl group is important for the activity of taxol (Figure 4.3).

![Figure 4.3 Cyclopropyl-containing taxol analog with phenyl group on the cyclopropane ring](image-url)
5. Syntheses and Bioactivities of Macrocyclic Taxol Analogs

5.1 Introduction

As we know, taxol is currently one of the most successful anticancer drugs, and its anticancer activity comes mainly from its binding to microtubules, thus preventing them from depolymerization. Recently, several studies have attempted to elucidate the bioactive binding conformation of taxol on microtubules. Three models have been proposed for this conformation, based on the electron crystallographic coordinates of polymerized αβ-tubulin. A study based on REDOR NMR and fluorescence spectroscopy led to a hydrophobically-collapsed conformation, while the same result came from modeling studies based on photoaffinity labeling. The single-crystal X-ray structure of taxotere turned out to be very useful in epothilone binding models derived from docking it into β-tubulin. More recently, Snyder deduced a T-shaped (Figure 5.1) taxol conformation from the binding of taxol to tubulin using the crystallographic density together with an analysis of several taxol’s existing conformations.

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In order to test these hypotheses, many conformationally restricted taxol analogs have been made, like analogs with conformationally restricted side chains\(^\text{174}\) and analogs with bridged linkages from the C-3' phenyl to the C-2 phenyl with both shorter\(^\text{175}\) and longer\(^\text{176}\) linkers. More recently, a series of macrocyclic docetaxel analogs were prepared with the bridge from the C-3' nitrogen to C-2 oxygen.\(^\text{177}\) Our group also prepared two macrocyclic taxol analogs tethered from the C-4 position to the side chain C-3' through ring closing metathesis (RCM) to test the T-taxol hypothesis.\(^\text{178}\) Among all these conformationally restricted taxol analogs, none of them had comparable tubulin assembly activity to taxol, and the cytotoxicity of the best analogs was less than that of taxol.

---


In the proposed T-taxol conformation, the distances between the two C-13 side chain terminal phenyl rings and the C-2 phenyl group are approximately 9-10 Å. Thus, a short conformationally directing tether between these centers is quite impossible. However, the C-4 acetate methyl holds a position very close to one edge of the C-3’ phenyl moiety in this conformer, indicating a possible conformational control. A variety of positional isomers and C3’-C4 linkers were modeled as T-Taxol mimics. From them, we designed and synthesized a series of analogs (Figure 5.2) linked between the C-3’-phenyl group and the C-4 position through macrocyclic lactonization.

![Figure 5.2 Structures of proposed macrocyclic taxol lactones](image)

5.2 Synthesis of macrocyclic taxol lactones

The retrosynthetic analysis of 100-104 is shown in Scheme 5.1. In order to prepare the macrocyclic taxol lactones, we had to make two key fragments—the fully functionalized baccatin part (105-109) and a general β-lactam (110), which served as a side chain precursor. Compounds 105-109 can be synthesized through known C-4 deacetylation and reacylation procedures from commercially available 10-deacetylbaccatin III (111, 10-DAB), while 110 could be synthesized through standard β-lactam synthesis from 3-hydroxybenzaldehyde (112).

---

We started the synthesis of 105-109 from 10-DAB (111) as shown in Scheme 5.2. The 4-decetyl 10-DAB analog 113 was made through reported procedures.\textsuperscript{70} The reacylation at the C-4 position was first tried using 3-benzyloxy carbonylpropanoyl chloride.\textsuperscript{180} Unfortunately, this reaction gave very low yield and we thus used 4-pentenoyl chloride to make compound 114 as shown in the literature.\textsuperscript{178} We planned to use an oxidative cleavage reaction to convert the terminal double bond into a carboxyl group, which is necessary for macrolactonization. Compound 115 was prepared in the same way as 114. As we tried to prolong the chain length, we found that the carboxylic acid with a terminal double bond was not commercially available, while the terminal dicarboxylic acids were available. Acylation using 7-benzyloxy carbonyl heptanoyl chloride worked well, but the product 118 and the starting

\textsuperscript{180} These series of $\omega$-benzyloxy carbonyl acid chlorides were made two steps from commercial available terminal dicarboxylic acid.
material could not be separated. From previous experience, these two should be separable after desilylation. The HF-pyridine conditions were used to deprotect 118 and the desired product (123) was isolated in good yield. Compounds 121 and 122 were made using the same procedures as 123. After selective acetylation at the C-10 position and selective silylation at the C-7 position, the fully protected baccatin analogs (105-109) were ready for the coupling with the β-lactam.

Scheme 5.2 Synthesis of baccatin III core (105-109)

The synthesis of β-lactam (110) was achieved as shown in Scheme 5.3. The commercially available aldehyde 112 was first protected as its benzyl ether. The resulting aldehyde was reacted with p-anisidine to form the imine, which subsequently reacted with a ketene generated from acetoxyacetyl chloride to give the racemic β-lactam (131). This lactam was then subjected to an enzymatic resolution using lipase to generate (+)-131 in 48% yield. A basic deacetylation followed by silyl re-protection afforded TIPS protected 133 in good yield. Oxidative deprotection
of the PMP group using cerium(IV) ammonium nitrate (CAN) gave 134, which was then treated with benzoyl chloride to generate the desired β-lactam 110.

Scheme 5.3 Synthesis of (+)-β-lactam 110

The coupling between C-4 modified baccatin derivatives (105-109) and (+)-β-lactam (110) was performed using standard coupling conditions. In Scheme 5.4, baccatin derivatives 105 or 106 were first treated with NaH in anhydrous THF at 0 °C for 5 mins, then the β-lactam 110 was added. The reaction generally gave 50-60% yields of the desired products 135 and 136.
oxidative cleavages of terminal alkenes were carried out using Sharpless conditions\textsuperscript{181} to produce two carboxylic acids (137 and 138). After hydrogenolysis, the desired hydroxy acids (139 and 140) were obtained in 75-80% yield.

As for the other three C-4 modified baccatin derivatives, the coupling reaction was performed using LHMDS as base, since the NaH condition did not work for them. The resulting three taxol analogs (141-143) were then converted into hydroxy acids (144-146) under hydrogenolysis conditions.

With five hydroxy acids in hand, we started to investigate the best conditions for macrocyclic lactonization. The Yamaguchi lactonization strategy was chosen to achieve this goal. In general, the macro lactonization proceeded well and gave the desired products in 18-65% yields. As the ring size changes, the yield started at 25% for 147, then 18% for 148, and 47% to 65% for 149-151. These results indicated that 147 and 148 might have larger ring strain than 149-151. Surprisingly, desilylation of 147-151 under HF-pyridine or HF-TEA conditions gave two series of products (100-104 and 157-161) with the same HRFABMS results. The NMR analysis of these two series of products showed that 100-104 were the desired products, while 157-161 were rearranged products with a bridge from C-4 to C-2', because their chemical shift of C-2' proton was shifted down field dramatically and the ortho proton at the C-3' phenyl ring was shifted up field. The ratio between these two series of products varied with the ring size. In the formation of 100 and 101, the major products were actually 157 and 158, which suggests that the
ring strain for these two macrocycles was quite large. On the other hand, 103 and 104 were the
dominant products, while only trace amounts of 160 and 161 could be found in TLC. Compound
102 was somewhere in between, with 102 and 159 formed in comparable yields. This is
consistent with the results that 139 and 140 gave lower yields when the macrocycles were
generated. In order to have a better understanding of the bioactivities for these macrocyclic taxol
analogs, we also prepared a series of open chain analogs 152-156 from desilylation of 139-140
and 144-146.

Scheme 5.6 Syntheses of macrocyclic taxol lactones

5.3 Biological results for macrocyclic taxol lactones

The biological activities of taxol and of the macrocyclic taxol analogs 100-104, 157-159,
and open chain 152-156 were in the A2780 ovarian cancer cell line (Table 5.1).
Table 5.1 Cytotoxicities of macrocyclic taxol analogs

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>A2780 IC50 (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxol (1)</td>
<td>0.024</td>
</tr>
<tr>
<td>100</td>
<td>18</td>
</tr>
<tr>
<td>101</td>
<td>5.2</td>
</tr>
<tr>
<td>102</td>
<td>&gt;21</td>
</tr>
<tr>
<td>103</td>
<td>10</td>
</tr>
<tr>
<td>104</td>
<td>4.2</td>
</tr>
<tr>
<td>157</td>
<td>&gt;21</td>
</tr>
<tr>
<td>158</td>
<td>20</td>
</tr>
<tr>
<td>159</td>
<td>21</td>
</tr>
<tr>
<td>152</td>
<td>&gt;21</td>
</tr>
<tr>
<td>153</td>
<td>&gt;21</td>
</tr>
<tr>
<td>154</td>
<td>18</td>
</tr>
<tr>
<td>155</td>
<td>&gt;21</td>
</tr>
<tr>
<td>156</td>
<td>&gt;21</td>
</tr>
</tbody>
</table>

From the A2780 ovarian cancer cell line results, all these taxol analogs were much less active than taxol itself. Among them, the five proposed macrocyclic taxol analogs were the most active, with 104 being the best. The three undesired macrocyclic taxol analogs and all five open chain taxol analogs were essentially inactive.

5.4 Conclusions and proposed future work

Five desired macrocyclic taxol lactones (100-104) and their corresponding open chain taxoids (152-156) were synthesized. Macrocyclic taxol lactones with 19- to 21-membered rings are prone to isomerization to form smaller rings (157-159). The bioassay showed the desired macrocyclic taxol lactones were active against A2780 cell line, but less active than taxol. The open chain taxoids and rearranged macrocyclic taxol lactones were inactive or much less active.

*The A2780 assays was done by Jennifer K. Schilling in Virginia Tech. Her work is greatly appreciated.
than taxol.

The desired macrocyclic taxol lactones were not as active as taxol. One reason may be that the macrocyclic taxol lactones are not stable, and are prone to rearrange to inactive macrocyclics (157-159). However, it is also likely that these macrocyclic taxol analogs have a close contact between the ester moiety on the C-3’ phenyl ring and Phe272 of the β-tubulin protein when they adopt T-taxol conformation. This type of contact will push the macrocyclics out the binding pocket and lead to the loss of bioactivities just like the other series of macrocyclic taxoids made in our group.178 To overcome this problem, we chose to move the bridge from the meta position to the ortho position at the C-3’ phenyl group as shown in Figure 5.3. Several bridged taxoids tethered from the ortho position of C-3’ phenyl to C4-O were made in our group. Some turned out to be very active in several assays and were found to adopt T-conformation.182 A macrocyclic taxol lactone with the same bridge tether could presumably also support the T-taxol conformation.

![Proposed macrocyclic taxol lactones](image)

![Highly active bridage taxoids](image)

Figure 5.3 Highly active bridged taxol analogs and proposed macrocyclic taxol lactone

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6. Conclusion

A series of estradiol-taxol conjugates (ETCs) were synthesized. They were active in four cytotoxicity assays and tubulin polymerization assay, although they were less active than taxol. Compound 24 showed the selectivity for MCF-7 (ER positive) against MDA-MB-231 (ER negative) cells, and it was three times more cytotoxic in MCF-7 cell lines than in MDA-MB-231 cell lines, while the rest of the ETCs showed no significant selectivity. Two ETC hemisuccinates were also synthesized to achieve better water solubility. Their corresponding Na and triethanolammonium salts were slightly more cytotoxic than the acid form, but were much less cytotoxic than the corresponding ETCs. In order to improve the selectivity and bioactivity, we proposed a “self-immolating” taxol analog to target taxol to cancer cells through ligand-receptor interactions, while free taxol would be released in the cell.

Ten cyclopropyl-containing taxol analogs were synthesized with different substituents on the cyclopropane ring and different stereo centers at the C-2’ and the C-7 positions. They were active in A2780, PC-3 cytotoxicity assays and tubulin assembly assay, and the best activity came from the one with natural chiral centers at the C-2’ and C-7 positions and an isopropyl group on the cyclopropane ring. These results also suggest that the substitution on the cyclopropane ring could affect the taxol’s activity and a larger group, like phenyl, might even be better, since an isopropyl group was better than a methyl group.

Five desired macrocyclic taxol lactones (100-104) and their corresponding open chain taxoids (152-156) were synthesized. The macrocyclic taxol lactones with a 19- to 21-member ring are prone to undergo isomerization to form smaller rings (157-159). The bioassay showed
the desired macrocyclic taxol lactones were active against A2780 cell line, but less active than taxol. The open chain taxoids and rearranged macrocyclic taxol lactones were inactive or much less active than taxol. The desired macrocyclic taxol lactones were not quite as active as taxol. One reason may be that the macrocyclic taxol lactones are not stable, and are prone to rearrange to inactive macrocyclics (157-159). However, it is also likely that these macrocyclic taxol analogs have a close contact between the ester moiety on the C-3’ phenyl ring and Phe272 of the β-tubulin protein when they adopt T-taxol conformation. This type of contact will push the macrocyclics out of the binding pocket and lead to the lost of bioactivities just like the other series of macrocyclic taxoids made in our group. Several bridged taxoids tethered from the ortho position of C-3’ phenyl to C4-O were made in our group. Some turned out to be very active in several assays and were found to adopt T-conformation. A macrocyclic taxol lactone with the same bridge tether could presumably also support the T-taxol conformation.
7. Experimental

**General Experiment Methods.** Chemicals were obtained from Aldrich Chemical Co. and were used without further purification. All anhydrous reactions were performed in oven-dried glassware under nitrogen or argon. All solvents were of reagent grade or HPLC grade. Tetrahydrofuran (THF) was distilled over sodium/benzophenone, and dichloromethane (DCM) was distilled over calcium hydride. All reaction were monitored by the E. Merck analytical thin layer chromatography (TLC) plates (silica gel 60 GF, aluminum back) and analyzed with 254 nm UV light and/or vanillin/sulfuric acid spray. Preparative thin layer chromatography (PTLC) plates (silica gel 60 GF) were purchased from Analtech. All $^1$H NMR spectral data were obtained in CDCl$_3$ or CD$_3$OD on Varian Unity 400 or Inova 400 spectrometer (operating at 399.951 MHz for $^1$H and 100.578 MHz for $^{13}$C). Chemical shifts reported as $\delta$-values relative to known solvent residue peaks, and coupling constants reported in Hertz. Mass spectra were obtained in Analytical Services in the Department of Chemistry (HRFABMS) or the Department of Biochemistry (MALDI-TOFMS) at Virginia Tech. The phrase “worked-up in the usual way” refers to diluting the reaction mixture with an excess amount of organic solvent, washing with water and brine, drying with anhydrous sodium sulfate and evaporating the solvent under vacuum unless otherwise noted. The known intermediates were prepared through the reported procedures in the literature, and NMR data of these compounds were identical to literature values. All compounds were $>95\%$ pure as judged by the TLC and $^1$H NMR.
**16α-(3-carboxy-2-E-propenyl)-3-tert-butyldimethylsilyl-17β-triethylsilylestradiol (7).** To a solution of 6\(^{147b}\) (836 mg, 1.36 mmol) in THF (8 mL) was added LiOH (131 mg, 5.44 mmol) in water (8 mL). After stirring at room temperature for 36 h, the reaction mixture was quenched with saturated ammonium chloride, and extracted three times with ethyl acetate (50 mL). The combined organic phase was washed through water, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was purified by column chromatography (10% EtOAc/hexane) to give 7 as white solid (560 mg, 72%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.21 (6H, s), 0.64 (6H, q, \(J = 7.9 \) Hz), 0.82 (3H, s), 1.00 (9H, s), 1.01 (9H, t, \(J = 7.9 \) Hz), 1.20-2.90 (16H, steroid skeleton), 3.33 (1H, d, \(J = 7.3 \) Hz), 5.88 (1H, d, \(J = 15.6 \) Hz), 6.56 (1H, d, \(J = 2.7 \) Hz, Ar), 6.63 (1H, dd, \(J = 8.5, 2.7 \) Hz, Ar), 7.07-7.16 (2H, overlapped); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) -4.1, 5.7, 7.3, 12.4, 18.4, 26.0, 26.5, 27.5, 29.4, 29.8, 37.5, 37.8, 38.8, 43.1, 44.2, 44.6, 48.6, 87.8, 117.4, 120.2, 121.7, 126.3, 133.2, 138.1, 151.7, 153.5, 172.3; HRFABMS \(m/z\) 584.3707 [M+H\(^+\)]; calcd for C\(_{34}\)H\(_{56}\)O\(_4\)Si\(_2\), 584.3717.

**11α-(3-carboxypropanoxy)-3,17β-diter-butyldimethylsilylestradiol (10).** To a solution of 9\(^{150}\) (275 mg, 0.532 mmol) in 20 mL dry THF was added LHMDS (1M, 0.80 mL, 0.80 mmol) at 0 °C. After stirring for 1 h, succinic anhydride (1.06 g, 10.6 mmol) was added in one portion. The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was then poured into 200 mL water, and EtOAc (150 mL) was used to extract the product. The extract was washed through water, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was purified by column chromatography (25% EtOAc/Hexane) to give 10 as white
solid (164 mg, 50%), and recovered 9 (55 mg, 20%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.02 (3H, s), 0.03 (3H, s), 0.19 (6H, s), 0.79 (3H, s), 0.89 (9H, s), 0.98 (9H, s), 1.10-2.85 (17H, steroid skeleton), 3.67 (1H, t, $J = 8.5$ Hz), 5.45 (1H, td, $J = 10.6$, 5.2 Hz), 6.58-6.63 (2H, m, Ar), 6.93 (1H, d, 8.1 Hz, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ -4.5, -4.3, -4.17, -4.15, 12.2, 18.3, 18.4, 23.4, 26.0, 26.1, 27.1, 28.4, 29.2, 29.6, 31.3, 37.7, 42.6, 44.5, 46.6, 49.7, 74.8, 81.2, 117.3, 120.0, 125.5, 132.4, 139.3, 153.9, 171.9, 179.0; HRFABMS $m/z$ 616.3619 [M+H$^+$]; calcd for C$_{34}$H$_{56}$O$_6$Si$_2$, 616.3615.

**General Procedure for Preparation of Estradiol-taxol Conjugates.** To a solution of estradiol derivative 7 (13.7 mg, 0.0234 mmol) in 2 mL toluene, was added EDC (4.5 mg, 0.0234 mmol). After 15 min stirring, DMAP (2 mg, cat.) was added and keep stirred for 5 min before taxol 1 (20 mg, 0.0234 mmol) was added. The reaction mixture was allowed to stir at 60 °C for 24 h to 48 h. Then, 50 mL EtOAc were added to the reaction mixture, and the organic phase was washed with sodium bicarbonate, water, and brine, dried over sodium sulfate, and concentrated in vacuum. The residue was applied to preparative TLC (50% EtOAc/hexane) to give silyl protected estradiol-taxol conjugate 11 as colorless gum (15.1 mg, 73%). A similar procedure was applied to estradiol derivative 10 to give 13, and to the reaction of 2'-t-butyldimethylsilyltaxol (15) with estradiols 7 and 10 to give the 7-acyl analogs 16 and 18, respectively.

2'-(4-[3-tert-butyldimethylsilyl-17β-triethylsilylestradiol-16α]-2-E-butenoyl)taxol  (11).

Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.19 (6H, s), 0.61 (6H, q, $J = 7.9$ Hz), 0.79 (3H, s),
0.97 (9H, t, J = 7.9 Hz), 0.98 (9H, s), 1.13 (3H, s), 1.24 (3H, s), 1.68 (3H, s), 1.95 (3H, brs), 2.23 (3H, s), 2.44 (3H, s), 1.20-2.90 (20H, taxol and steroid skeletons), 3.29 (1H, d, J = 7.4 Hz), 3.82 (1H, d, J = 7.4 Hz), 4.20 (1H, d, J = 8.4 Hz), 4.32 (1H, d, J = 8.4 Hz), 4.46 (1H, m), 4.98 (1H, dd, J = 9.6, 2.0 Hz), 5.56 (1H, d, J = 3.6 Hz), 5.58 (1H, d, J = 7.2 Hz), 5.93 (1H, d, J = 15.6 Hz), 5.96 (1H, dd, J = 9.3, 3.6 Hz), 6.26 (1H, t, J = 9.1 Hz), 6.30 (1H, s), 6.55 (1H, d, J = 2.6 Hz, Ar), 6.61 (1H, dd, J = 8.5, 2.6 Hz, Ar), 6.93 (1H, d, J = 9.3 Hz), 7.10 (1H, d, J = 8.5 Hz, Ar), 7.30-7.70 (11H, m, Ar), 7.75 (2H, m, Ar), 8.13 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ -4.2, 5.6, 7.3, 9.8, 12.3, 15.1, 18.4, 21.1, 22.9, 25.9, 26.4, 26.5, 27.1, 29.3, 29.8, 35.7, 35.8, 37.4, 37.9, 38.8, 43.1, 43.4, 44.2, 44.5, 45.8, 48.4, 53.2, 58.7, 72.0, 72.4, 74.0, 75.3, 75.8, 76.6, 79.5, 81.2, 84.7, 87.8, 117.4, 120.1, 126.3, 126.9, 127.3, 128.7, 128.9, 129.0, 129.3, 129.4, 130.4, 132.2, 132.9, 133.1, 133.92, 133.95, 137.3, 138.0, 143.2, 152.3, 153.5, 165.6, 167.25, 167.29, 168.5, 170.0, 171.5, 204.1; HRFABMS m/z 1442.6644 [M+Na$^+$]; calcd for C$_{81}$H$_{105}$NO$_{17}$Si$_2$Na, 1442.6819.

2’-[[3,17β-di-tert-butyldimethylsilylestradiol-11α]-4-carboxyloxypropanoyl]taxol (13).

Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.02 (6H, brs), 0.17 (6H, s), 0.77 (3H, s), 0.88 (9H, s), 0.96 (9H, s), 1.13 (3H, s), 1.23 (3H, s), 1.68 (3H, s), 1.94 (3H, brs), 2.22 (3H, s), 2.45 (3H, s), 1.15-2.90 (21H, taxol and steroid skeletons), 3.66 (1H, t, J = 8.4 Hz), 3.82 (1H, d, J = 7.2 Hz), 4.20 (1H, d, J = 8.6 Hz), 4.32 (1H, d, J = 8.6 Hz), 4.45 (1H, dd, J = 9.7, 7.2 Hz), 4.97 (1H, dd, J = 9.6, 1.7 Hz), 5.41 (1H, td, J = 10.5, 5.2 Hz), 5.54 (1H, d, J = 3.0 Hz), 5.68 (1H, d, J = 7.0 Hz), 6.00 (1H, dd, J = 9.2, 3.0 Hz), 6.24-6.31 (2H, overlapped), 6.54-6.61 (2H, overlapped,
Ar), 6.85 (1H, d, J = 8.3 Hz, Ar), 6.99 (1H, d, J = 9.2 Hz), 7.30-7.65 (11H, Ar), 7.76 (2H, m, Ar), 8.15 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ -4.5, -4.3, -4.1, 9.8, 12.2, 15.1, 18.3, 18.4, 21.1, 22.4, 22.9, 23.4, 25.9, 26.1, 27.0, 27.1, 28.4, 29.1, 29.7, 31.2, 35.7, 35.8, 37.7, 42.6, 43.4, 44.6, 45.7, 46.6, 49.7, 53.0, 59.7, 72.0, 72.4, 74.3, 75.0, 75.3, 75.5, 75.8, 76.6, 79.4, 81.2, 81.3, 84.7, 117.4, 120.2, 125.2, 126.8, 127.4, 128.7, 128.9, 129.0, 129.3, 129.4, 130.5, 132.2, 132.4, 132.9, 133.8, 133.9, 137.2, 139.4, 143.1, 153.9, 167.28, 167.30, 168.1, 170.0, 171.47, 171.54, 204.1; HRFABMS m/z 1452.6803 [M+H\(^+\)]; calcd for C\(_{81}\)H\(_{106}\)NO\(_{19}\)Si\(_2\), 1452.6898.

2'-\textit{tert}-butyldimethylsilyl-7-[4-\textit{[3}-\textit{tert}-butyldimethylsilyl-17β-triethylsilylestradiol-16α]-2-E-butenoyl\textit{]}taxol (16). Colorless gum; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ -0.30 (3H, s), -0.02 (3H, s), 0.18 (6H, s), 0.61 (6H, q, J = 7.9 Hz), 0.79 (3H, s), 0.80 (9H, s), 0.98 (9H, t, J = 7.9 Hz), 1.18 (3H, s), 1.21 (3H, s), 1.86 (3H, s), 2.01 (3H, brs), 2.11 (3H, s), 2.59 (3H, s), 1.10-2.85 (20H, taxol and steroid skeletons), 3.29 (1H, d, J = 7.1 Hz), 4.00 (1H, d, J = 7.1 Hz), 4.23 (1H, d, J = 8.1 Hz), 4.36 (1H, d, J = 8.1 Hz), 4.68 (1H, d, J = 2.0 Hz), 5.00 (1H, d, J = 9.4 Hz), 5.64 (1H, dd, J = 10.5, 7.2 Hz), 5.68-5.82 (3H, overlapped), 6.26 (1H, t, J = 9.2 Hz), 6.35 (1H, s), 6.54 (1H, d, J = 2.5 Hz, Ar), 6.61 (1H, dd, J = 8.5, 2.5 Hz, Ar), 6.89 (1H, m), 7.09 (1H, d, J = 8.8 Hz), 7.11 (1H, d, J = 8.5 Hz, Ar), 7.28-7.66 (11H, Ar), 7.76 (2H, m, Ar), 8.14 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ -5.6, -4.9, -4.2, 5.7, 7.3, 11.2, 12.4, 14.9, 18.35, 18.40, 20.8, 21.6, 23.3, 25.8, 25.9, 26.6, 27.5, 29.3, 29.8, 33.6, 35.8, 37.5, 37.6, 38.8, 43.0, 43.6, 44.2, 44.5, 47.0, 48.4, 55.9, 56.4, 71.52, 71.55, 74.8, 75.2, 75.3, 76.7, 78.9, 81.2, 84.3, 87.8, 117.3, 120.2, 122.0, 126.3, 126.6, 127.2, 128.2, 128.97, 129.02, 129.3, 130.4, 132.0, 133.0, 133.4, 134.0, 134.3, 138.1, 138.5, 141.1, 149.1,
153.5, 165.6, 167.20, 168.6, 170.0, 171.7, 202.3; HRFABMS \( m/z \) 1534.7910 [M+H\(^+\)]; calcd for \( C_{87}H_{120}NO_{17}Si_3 \), 1534.7864.

2'-tert-butylidimethylsilyl-7-\([3,17\beta\)-di-tert-butylidimethylsilylestradiol-11\(\alpha\)]-4-carboxyloxypr opanoyl]taxol (18). Colorless gum; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) -0.31 (3H, s), -0.03 (3H, s), 0.01 (3H, s), 0.02 (3H, s), 0.19 (6H, s), 0.77 (3H, s), 0.80 (9H, s), 0.88 (9H, s), 0.97 (9H, s), 1.15 (3H, s), 1.21 (3H, s), 1.81 (3H, s), 1.97 (3H, brs), 2.11 (3H, s), 2.58 (3H, s), 1.10-2.80 (21H, taxol and steroid skeletons), 3.65 (1H, t, \( J = 8.4 \) Hz), 3.97 (1H, d, \( J = 6.8 \) Hz), 4.21 (1H, d, \( J = 8.5 \) Hz), 4.34 (1H, d, \( J = 8.5 \) Hz), 4.67 (1H, d, \( J = 2.1 \) Hz), 4.97 (1H, d, \( J = 9.3 \) Hz), 5.40 (1H, td, \( J = 10.4, 5.2 \) Hz), 5.61 (1H, dd, \( J = 10.6, 7.1 \) Hz), 5.70 (1H, d, \( J = 7.0 \) Hz), 5.73 (1H, dd, \( J = 8.9, 1.7 \) Hz), 6.25 (1H, s), 6.27 (1H, t, \( J = 9.4 \) Hz), 6.57 (1H, d, \( J = 2.5 \) Hz, Ar), 6.61 (1H, dd, \( J = 8.5, 2.5 \) Hz, Ar), 6.91 (1H, d, \( J = 8.5 \) Hz, Ar), 7.08 (1H, d, \( J = 8.9 \) Hz), 7.30-7.65 (11H, m, Ar), 7.75 (2H, m, Ar), 8.13 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) -5.6, -4.9, -4.5, -4.2, -4.15, -4.13, 11.1, 12.2, 14.8, 18.28, 18.34, 18.39, 20.9, 21.7, 23.2, 23.4, 25.7, 25.9, 26.1, 26.6, 27.0, 28.5, 29.5, 29.9, 31.1, 33.5, 35.8, 37.7, 42.7, 43.6, 44.6, 46.7, 47.0, 49.7, 55.9, 56.2, 71.5, 71.8, 74.5, 74.7, 75.3, 75.4, 76.6, 77.6, 78.9, 81.2, 84.2, 117.4, 119.9, 125.6, 126.6, 127.2, 128.2, 128.96, 129.01, 129.3, 130.4, 132.0, 132.5, 132.8, 134.0, 134.3, 138.5, 139.2, 141.2, 153.9, 167.15, 167.17, 169.2, 170.0, 171.6, 171.7, 172.2, 202.2; HRFABMS \( m/z \) 1566.7789 [M+H\(^+\)]; calcd for \( C_{97}H_{120}NO_{19}Si_3 \), 1566.7762.

2'-tert-butylidimethylsilyl-10-deacetyl-10-\([3,17\beta\)-di-tert-butylidimethylsilylestradiol-11\(\alpha\)]-4-c arboxyloxypropanoyl]-7-epi-taxol (23). Colorless gum; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) -0.30
(3H, s), -0.04 (3H, s), 0.02 (3H, s), 0.03 (3H, s), 0.19 (6H, s), 0.77 (3H, s), 0.78 (9H, s), 0.88 (9H, s), 0.98 (9H, s), 1.13 (3H, s), 1.19 (3H, s), 1.67 (3H, s), 1.88 (3H, brs), 2.67 (3H, s), 1.10-2.96 (21H, taxol and steroid skeletons), 3.67 (1H, t, \( J = 8.3 \) Hz), 3.71 (1H, m), 3.92 (1H, d, \( J = 7.5 \) Hz), 4.40 (2H, brs), 4.66 (1H, d, \( J = 2.2 \) Hz), 4.71 (1H, d, \( J = 11.7 \) Hz), 4.94 (1H, dd, \( J = 8.9, 3.5 \) Hz), 5.44 (1H, td, \( J = 10.3, 5.2 \) Hz), 5.75 (1H, d, \( J = 7.5 \) Hz), 5.78 (1H, dd, \( J = 9.0, 1.8 \) Hz), 6.30 (1H, t, \( J = 8.9 \) Hz), 6.58 (1H, d, \( J = 2.6 \) Hz, Ar), 6.61 (1H, dd, \( J = 8.4, 2.6 \) Hz, Ar), 6.86 (1H, s), 6.91 (1H, d, \( J = 8.4 \) Hz, Ar), 7.07 (1H, d, \( J = 9.0 \) Hz), 7.30-7.63 (11H, Ar), 7.72 (2H, m, Ar), 8.17 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) -5.7, -5.0, -4.5, -4.3, -4.1, 12.2, 15.2, 16.5, 18.3, 18.38, 18.39, 21.9, 23.1, 23.4, 25.7, 25.9, 26.12, 26.14, 27.1, 28.4, 29.3, 30.1, 31.3, 35.6, 36.5, 37.7, 40.5, 42.6, 42.9, 44.5, 46.6, 49.6, 55.8, 57.7, 71.1, 74.7, 75.52, 75.56, 76.0, 77.9, 78.5, 79.5, 81.2, 82.3, 83.0, 117.4, 119.9, 125.4, 126.6, 127.2, 128.2, 128.9, 129.0, 129.1, 129.5, 130.5, 132.0, 132.6, 133.1, 133.9, 134.3, 135.8, 139.3, 140.6, 153.9, 167.1, 167.4, 170.9, 171.2, 171.9, 172.5, 207.3; HRFABMS \textit{m/z} 1524.7583 [M+H\(^+\)]; calcd for C\(_{85}\)H\(_{118}\)NO\(_{18}\)Si\(_3\), 1524.7657.

2'-\((3\text{-benzyloxy}carbonylpropanoyl)taxol\) (25). Colorless gum; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.14 (3H, s), 1.23 (3H, s), 1.68 (3H, s), 1.88 (1H, m), 1.93 (3H, brs), 2.16 (1H, m), 2.22 (3H, s), 2.38 (1H, m), 2.45 (3H, s), 2.55 (1H, m), 2.66 (2H, m), 2.77 (2H, m), 3.81 (1H, d, \( J = 7.0 \) Hz), 4.20 (1H, d, \( J = 8.4 \) Hz), 4.31 (1H, d, \( J = 8.4 \) Hz), 4.44 (1H, dd, \( J = 10.9, 6.6 \) Hz), 4.97 (1H, dd, \( J \) = 9.6, 2.0 Hz), 5.15 (1H, d, \( J = 3.1 \) Hz), 5.69 (1H, d, \( J = 7.0 \) Hz), 5.99 (1H, dd, \( J = 9.2, 3.1 \) Hz), 6.25 (1H, t, \( J = 9.0 \) Hz), 6.30 (1H, s), 7.11 (1H, d, \( J = 9.2 \) Hz), 7.25-7.65 (16H, Ar), 7.80 (2H, m, Ar), 8.14 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 9.8, 15.0, 21.1, 22.4, 22.9, 27.0, 29.4, 29.5,
2′-(3-benzyloxycarbonylpropanoyl)-7-[[3,17β-di-tert-butyldimethylsilylestradiol-11α]-4-carboxyloxypropanoyl]taxol (26). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.00 (3H, s), 0.01 (3H, s), 0.17 (6H, s), 0.76 (3H, s), 0.86 (9H, s), 0.95 (9H, s), 1.14 (3H, s), 1.19 (3H, s), 1.79 (3H, s), 1.97 (3H, brs), 2.10 (3H, s), 2.44 (3H, s), 1.10-2.80 (25H, taxol and steroid skeletons), 3.64 (1H, t, $J = 8.5$ Hz), 3.94 (1H, d, $J = 6.9$ Hz), 4.18 (1H, d, $J = 8.5$ Hz), 4.31 (1H, d, $J = 8.5$ Hz), 4.94 (1H, d, $J = 9.3$ Hz), 4.99 (2H, s), 5.39 (1H, td, $J = 10.4$, 5.2 Hz), 5.52 (1H, d, $J = 3.0$ Hz), 5.58 (1H, dd, $J = 10.5$, 7.2 Hz), 5.68 (1H, d, $J = 7.0$ Hz), 5.99 (1H, dd, $J = 9.2$, 3.0 Hz), 6.22 (1H, t, $J = 9.4$ Hz), 6.23 (1H, s), 6.56 (1H, d, $J = 2.6$ Hz, Ar), 6.60 (1H, dd, $J = 8.5$, 2.6 Hz, Ar), 6.91 (1H, d, $J = 8.5$ Hz, Ar), 7.11 (1H, d, $J = 9.2$ Hz), 7.25-7.65 (16H, Ar), 7.80 (2H, m, Ar), 8.13 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ -4.6, -4.3, -4.2, 11.0, 12.1, 14.6, 18.2, 18.3, 20.8, 21.5, 22.8, 23.3, 25.9, 26.0, 26.6, 27.0, 28.4, 29.2, 29.4, 29.5, 29.8, 31.2, 33.4, 35.6, 37.6, 42.6, 43.4, 44.5, 46.6, 46.9, 49.6, 52.9, 56.1, 66.9, 71.7, 74.3, 74.4, 74.7, 75.3, 76.4, 78.8, 81.0, 81.1, 84.1, 117.3, 119.8, 125.5, 126.7, 127.4, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.2, 129.3, 130.4, 132.1, 132.4, 132.6, 133.7, 133.8, 135.6, 137.1, 139.1, 141.4, 153.8, 167.1, 167.4, 168.1, 169.1, 169.7, 171.0, 171.3, 172.2, 202.2; MALDI-TOF MS $m/z$ 1665 [M+Na$^+$]; calcd for C$_{92}$H$_{115}$NO$_{22}$Si$_2$Na, 1664.8.
7-(3-benzyloxycarbonylpropanoyl)-2'-(3,17β-di-tert-butylmethylsilylestradiol-11α)-4-carboxyloxypropanoyl]taxol (31). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.02 (3H, s), 0.03 (3H, s), 0.17 (6H, s), 0.77(3H, s), 0.88 (9H, s), 0.96 (9H, s), 1.15(3H, s), 1.20 (3H, s), 1.79 (3H, s), 1.98 (3H, brs), 2.13 (3H, s), 2.45 (3H, s), 1.10-2.83 (25H, taxol and steroid skeletons), 3.67 (1H, t, $J$ = 8.5 Hz), 3.95 (1H, d, $J$ = 6.9 Hz), 4.19 (1H, d, $J$ = 8.5 Hz), 4.32 (1H, d, $J$ = 8.5 Hz), 4.93 (1H, d, $J$ = 9.4 Hz), 5.12 (2H, AB, $J$ = 12.4 Hz), 5.41 (1H, td, $J$ = 10.4, 5.3 Hz), 5.58 (1H, d, $J$ = 3.1 Hz), 5.60 (1H, dd, $J$ = 10.5, 7.1 Hz), 5.68 (1H, d, $J$ = 7.0 Hz), 6.01 (1H, dd, $J$ = 9.3, 3.1 Hz), 6.22 (1H, s), 6.24 (1H, t, $J$ = 9.1 Hz), 6.55-6.59 (2H, overlapped, Ar), 6.85 (1H, d, $J$ = 8.0 Hz, Ar), 7.03 (1H, d, $J$ = 9.3 Hz), 7.27-7.65 (16H, Ar), 7.77 (2H, m, Ar), 8.14 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ -4.5, -4.3, -4.2, 11.0, 12.1, 14.6, 18.2, 18.3, 20.9, 21.5, 22.8, 23.3, 25.9, 26.0, 26.6, 26.9, 28.1, 28.3, 29.2, 29.3, 29.7, 31.2, 33.3, 37.2, 37.6, 42.5, 43.3, 44.5, 46.5, 47.0, 49.6, 52.9, 56.1, 66.5, 71.7, 71.9, 74.1, 74.7, 74.9, 75.4, 76.5, 78.8, 81.00, 81.04, 84.2, 117.3, 119.9, 125.1, 126.7, 127.3, 128.31, 128.35, 128.37, 128.67, 128.71, 128.8, 129.25, 129.30, 130.4, 132.1, 132.4, 132.5, 133.7, 133.8, 136.1, 137.1, 139.3, 141.3, 153.9, 167.1, 167.4, 168.2, 169.0, 169.7, 171.2, 171.3, 171.6, 172.6, 202.2; HRFABMS $m/z$ 1642.8468 [M+H$^+$]; calcd for C$_{92}$H$_{116}$NO$_{22}$Si$_2$ 1642.7528.

**General Procedure for Deprotection of Silyl Group.** To a solution of silyl protected estradiol-taxol conjugate 11 (15.1 mg, 0.0106 mmol), in 0.6 mL dried THF, was added 0.1 mL anhydrous pyridine, then the solution was cooled to 0 °C, and 0.1 mL HF-pyridine was added.
The reaction mixture was allowed to warm to room temperature, and stirred for overnight. The reaction mixture was then diluted with EtOAc, the organic phase was washed with sodium bicarbonate, water, and brine, dried over sodium sulfate, and concentrated in vacuum. The residue was applied to preparative TLC (50% EtOAc/hexane) to give 12 as colorless gum (12.3 mg, 97%). Compounds 14, 17, 19, 24, 27, and 32 were prepared similarly.

2’-{4-[3,17β-estradiol-16α]-2-E-butenoyl}taxol (12). Colorless gum; 1H NMR (400 MHz, CD3OD) δ 0.78 (3H, s), 1.11 (3H, s), 1.13 (3H, s), 1.65 (3H, s), 1.93 (3H, brs), 2.16 (3H, s), 2.40 (3H, s), 2.15-2.80 (20H, taxol and steroid skeletons), 3.23 (1H, d, J = 8.0 Hz), 3.81 (1H, d, J = 7.2 Hz), 4.18 (2H, brs), 4.34 (1H, dd, J = 11.0, 6.7 Hz), 4.99 (1H, dd, J = 9.6, 1.9 Hz), 5.50 (1H, d, J = 6.8 Hz), 5.63 (1H, d, J = 7.1 Hz), 5.85 (1H, d, J = 6.8 Hz), 5.99 (1H, d, J = 15.6 Hz), 6.06 (1H, t, J = 9.1 Hz), 6.45 (1H, s), 6.47 (1H, d, J = 2.6 Hz, Ar), 6.53 (1H, dd, J = 8.5, 2.6 Hz, Ar), 7.05 (1H, d, J = 8.5 Hz, Ar), 7.16 (1H, td, J = 15.6, 7.1 Hz), 7.23-7.70 (11H, Ar), 8.11 (2H, m, Ar); 13C NMR (100 MHz, CD3OD) δ 9.3, 11.3, 13.8, 19.6, 21.2, 22.1, 25.7, 26.2, 27.3, 29.1, 29.5, 35.2, 36.3, 36.8, 37.6, 39.0, 42.0, 43.4, 43.9, 44.1, 46.7, 48.3, 54.2, 58.0, 71.1, 71.7, 74.7, 75.1, 75.6, 76.3, 77.8, 81.0, 84.7, 86.7, 112.5, 114.9, 120.3, 126.0, 127.4, 127.5, 128.4, 128.5, 128.9, 130.0, 130.2, 131.3, 131.7, 133.4, 133.7, 134.4, 137.2, 137.6, 141.3, 151.6, 154.7, 165.8, 166.4, 169.3, 169.4, 170.1, 170.4, 204.0; HRFABMS m/z 1192.5267 [M+H]+; calcd for C69H78NO17, 1192.5270.
2'-[[3,17β-estradiol-11α]-4-carboxyloxypropanoyl]taxol (14). Colorless gum; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 0.74 (3H, s), 1.15 (3H, s), 1.16 (3H, s), 1.65 (3H, s), 1.97 (3H, brs), 2.17 (3H, s), 2.42 (3H, s), 1.24-2.86 (21H, taxol and steroid skeletons), 3.59 (1H, t, \(J = 8.7\) Hz), 3.84 (1H, d, \(J = 7.2\) Hz), 4.20 (2H, brs), 4.36 (1H, dd, \(J = 11.1, 6.7\) Hz), 5.02 (1H, dd, \(J = 9.6, 2.0\) Hz), 5.29 (1H, td, \(J = 10.4, 5.3\) Hz), 5.48 (1H, d, \(J = 5.2\) Hz), 5.65 (1H, d, \(J = 7.1\) Hz), 5.89 (1H, d, \(J = 5.2\) Hz), 6.17 (1H, t, \(J = 9.1\) Hz), 6.43 (1H, s), 6.52 (1H, d, \(J = 2.7\) Hz, Ar), 6.54 (1H, dd, \(J = 8.4, 2.7\) Hz, Ar), 6.83 (1H, d, \(J = 8.4\) Hz, Ar), 7.25-7.69 (11H, Ar), 7.77 (2H, m, Ar), 8.13 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD) \(\delta\) 9.3, 11.0, 14.1, 19.8, 21.2, 22.7, 25.9, 26.8, 28.1, 28.2, 29.2, 29.5, 35.3, 36.3, 37.9, 41.6, 43.5, 43.9, 45.7, 46.6, 49.5, 53.7, 58.0, 71.2, 71.6, 74.6, 75.09, 75.11, 75.7, 76.3, 77.8, 80.4, 81.1, 84.7, 112.5, 114.8, 125.0, 127.3, 127.4, 128.3, 128.54, 128.56, 128.9, 130.0, 130.2, 130.9, 131.6, 133.4, 133.8, 134.4, 137.1, 139.0, 141.3, 155.2, 166.5, 168.9, 169.6, 170.2, 170.4, 171.9, 172.3, 204.0; HRFABMS \(m/z\) 1224.5200 [M+H\(^+\)]; calcd for C\(_{69}\)H\(_{78}\)NO\(_{19}\), 1224.5168.

7-{4-[3,17β-estradiol-16α]-2-E-butenoyl}taxol (17). Colorless gum; \(^1\)H NMR (400 MHz, CD\(_3\)OD) \(\delta\) 0.82 (3H, s), 1.11 (3H, s), 1.15 (3H, s), 1.81 (3H, s), 1.90 (3H, brs), 2.13 (3H, s), 2.37 (3H, s), 1.20-2.80 (20H, taxol and steroid skeletons), 3.27 (1H, d, \(J = 7.7\) Hz), 3.92 (1H, d, \(J = 7.1\) Hz), 4.20 (2H, brs), 4.75 (1H, d, \(J = 5.2\) Hz), 5.00 (1H, d, \(J = 9.3\)), 5.60 (1H, dd, \(J = 10.6, 7.4\) Hz), 5.63-5.68 (2H, overlapped), 5.75 (1H, d, \(J = 15.6\) Hz), 6.15 (1H, t, \(J = 9.1\) Hz), 6.31 (1H, s), 6.37 (1H, d, \(J = 2.5\) Hz, Ar), 6.53 (1H, dd, \(J = 8.5, 2.5\) Hz, Ar), 6.92 (1H, td, \(J = 15.6, 7.3\) Hz), 7.26-7.69 (11H, Ar), 7.85 (2H, m, Ar), 8.11 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CD\(_3\)OD) \(\delta\) 10.3,
11.3, 13.5, 19.5, 20.9, 22.0, 25.55, 25.58, 26.3, 27.3, 29.50, 29.55, 35.3, 36.9, 39.1, 42.2, 43.4, 44.0, 44.1, 46.8, 48.3, 56.2, 56.5, 71.0, 71.7, 73.6, 74.7, 75.4, 76.1, 77.7, 80.8, 84.0, 86.5, 112.5, 114.9, 121.6, 126.0, 127.3, 127.8, 128.4, 128.55, 128.57, 130.0, 130.1, 131.4, 131.7, 133.3, 133.5, 134.4, 137.6, 138.8, 140.9, 149.1, 154.7, 165.6, 166.4, 169.1, 169.7, 170.8, 173.3, 202.5; HRFABMS m/z 1192.5237 [M+H⁺]; calcd for C₆₉H₇₈NO₁₁ 1192.5270.

7-[[3,17β-estradiol-11α]-4-carboxyloxypropanoyl]taxol (19). Colorless gum; ¹H NMR (400 MHz, CD₃OD) δ 0.76 (3H, s), 1.11 (3H, s), 1.15 (3H, s), 1.78 (3H, s), 1.89 (3H, brs), 2.11 (3H, s), 2.38 (3H, s), 1.17-2.81 (21H, taxol and steroid skeletons), 3.67 (1H, t, J = 8.7 Hz), 4.77 (1H, d, J = 5.3 Hz), 5.00 (1H, d, J = 9.1 Hz), 5.32 (1H, td, J = 10.6, 5.2 Hz), 5.68-5.78 (3H, overlapped), 6.16 (1H, t, J = 9.1 Hz), 6.21 (1H, s), 6.53 (1H, d, J = 2.7 Hz, Ar), 6.58 (1H, dd, J = 8.6, 2.7 Hz, Ar), 6.91 (1H, d, J = 8.6 Hz), 7.26-7.69 (11H, Ar), 7.85 (2H, m, Ar), 8.11 (2H, m, Ar); ¹³C NMR (100 MHz, CD₃OD) δ 10.3, 11.0, 13.7, 19.5, 20.9, 22.0, 22.7, 25.6, 26.8, 28.1, 29.0, 29.3, 29.4, 33.0, 35.3, 37.9, 42.3, 43.4, 43.9, 46.3, 46.9, 49.7, 56.0, 56.5, 71.0, 72.0, 73.6, 74.59, 74.63, 75.5, 76.1, 77.7, 80.4, 80.8, 84.1, 112.6, 114.8, 125.4, 127.3, 127.8, 128.4, 128.56, 128.59, 130.0, 130.1, 130.6, 131.7, 133.1, 133.5, 134.4, 138.8, 139.0, 141.0, 155.2, 166.4, 169.1, 169.7, 170.9, 171.8, 172.8, 173.3, 202.4; HRFABMS m/z 1224.5176 [M+H⁺]; calcd for C₆₉H₇₈NO₁₉ 1224.5168.

10-deacetyl-10-[[3,17β-estradiol-11α]-4-carboxyloxypropanoyl]-7-epi-taxol (24). Colorless gum; ¹H NMR (400 MHz, CDCl₃) δ 0.74 (3H, s), 1.12 (3H, s), 1.14 (3H, s), 1.63 (3H, s), 1.77
(3H, brs), 2.47 (3H, s), 1.20-2.94 (21H, taxol and steroid skeletons), 3.6-3.74 (2H, overlapped), 3.87 (1H, d, $J = 7.2$ Hz), 4.22 (1H, brs), 4.37 (2H, brs), 4.78 (1H, d, $J = 1.8$ Hz), 4.84-4.92 (2H, overlapped), 5.38 (1H, td, $J = 10.3$, 5.5 Hz), 5.73 (1H, d, $J = 7.2$ Hz), 5.77 (1H, dd, $J = 9.0$, 2.0 Hz), 6.19 (1H, t, $J = 8.7$ Hz), 6.46-6.55 (2H, Ar), 6.76 (1H, s), 6.88 (1H, d, $J = 8.1$ Hz, Ar), 7.28 (1H, d, $J = 8.9$ Hz, Ar), 7.29-7.63 (12H, Ar & -NH), 7.72 (2H, d, $J = 7.9$ Hz, Ar), 8.14 (2H, d, $J = 7.9$ Hz, Ar); $^{13}C$ NMR (100 MHz, CDCl$_3$) $\delta$ 11.8, 15.0, 16.7, 21.6, 22.8, 23.2, 26.1, 27.0, 28.4, 29.4, 30.0, 30.3, 35.4, 36.3, 37.7, 40.5, 42.2, 42.8, 44.2, 46.3, 49.8, 55.4, 57.7, 72.3, 73.4, 74.6, 75.5, 76.1, 77.9, 78.7, 79.1, 81.1, 82.3, 82.9, 112.9, 115.3, 125.9, 127.1, 127.4, 128.1, 128.9, 129.0, 129.2, 129.5, 130.4, 131.3, 132.2, 133.4, 133.8, 133.9, 138.3, 139.4, 140.3, 154.4, 167.2, 167.9, 171.2, 172.1, 172.6, 173.1, 207.2; MALDI-TOF MS $m/z$ 1204.5 [M+Na$^+$]; calcd for C$_{67}$H$_{75}$NO$_{18}$Na, 1204.5.

2'-{(3-benzyloxycarbonylpropanoyl)-7-[[3,17$\beta$-estradiol-11$\alpha$]-4-carboxyloxypropanoyl]taxol (27). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.76 (3H, s), 1.16 (3H, s), 1.20 (3H, s), 1.83 (3H, s), 1.99 (3H, brs), 2.12 (3H, s), 2.47 (3H, s), 3.66 (1H, t, $J = 8.6$ Hz), 3.95 (1H, d, $J = 6.8$ Hz), 4.19 (1H, d, $J = 8.4$ Hz), 4.35 (1H, d, $J = 8.4$ Hz), 4.96 (2H, s), 5.00 (1H, d, $J = 9.4$ Hz), 5.37 (1H, td, $J = 10.6$, 5.3 Hz), 5.59 (1H, d, $J = 3.1$ Hz), 5.67-5.75 (2H, overlapped), 6.01 (1H, dd, $J = 9.1$, 3.1 Hz), 6.17-6.25 (2H, overlapped), 6.54 (1H, d, $J = 2.5$ Hz, Ar), 6.68 (1H, dd, $J = 8.5$, 2.5 Hz, Ar), 7.05 (1H, d, $J = 8.5$ Hz, Ar), 7.19 (1H, d, $J = 9.1$ Hz), 7.23-7.65 (16H, Ar), 7.83 (2H, m, Ar), 8.12 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.2, 11.9, 14.8, 20.9, 21.3, 23.0, 23.1, 26.6, 27.1, 28.5, 29.3, 29.5, 29.6, 29.7, 30.2, 33.5, 35.5, 37.8, 42.7, 43.5, 44.1, 46.5, 47.4,
7-(3-benzyloxycarbonylpropanoyl)-2’-[[3,17β-estradiol-11α]-4-carboxyloxypropanoyl]taxol (32). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.77 (3H, s), 1.15 (3H, s), 1.19 (3H, s), 1.78 (3H, s), 2.01 (3H, brs), 2.12 (3H, s), 2.42 (3H, s), 1.10-2.95 (25H, taxol and steroid skeletons), 3.71 (1H, t, J = 8.5 Hz), 3.93 (1H, d, J = 6.8 Hz), 4.17 (1H, d, J = 8.5 Hz), 4.32 (1H, d, J = 8.5 Hz), 4.95 (1H, d, J = 9.3 Hz), 5.11 (2H, AB, J = 12.3 Hz), 5.39 (1H, td, J = 10.4, 5.2 Hz), 5.44 (1H, d, J = 3.1 Hz), 5.63 (1H, dd, J = 10.6, 7.0 Hz), 5.69 (1H, d, J = 6.8 Hz), 5.92 (1H, dd, J = 9.0, 2.9 Hz), 6.22 (1H, t, J = 9.0 Hz), 6.24 (1H, s), 6.55-6.60 (2H, overlapped, Ar), 6.86 (1H, d, J = 8.2 Hz, Ar), 7.10 (1H, d, J = 9.0 Hz), 7.26-7.64 (16H, Ar), 7.77 (2H, m, Ar), 8.11 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 11.0, 11.9, 14.7, 21.0, 21.4, 22.9, 23.2, 26.6, 26.9, 28.3, 28.6, 29.2, 29.51, 29.54, 30.6, 33.3, 35.6, 37.7, 42.1, 43.5, 44.1, 46.2, 47.2, 49.9, 53.0, 56.2, 66.7, 71.8, 72.0, 74.2, 74.6, 74.7, 75.6, 76.5, 78.8, 81.0, 81.2, 84.1, 112.8, 115.5, 125.6, 126.9, 127.4, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 129.2, 129.3, 130.4, 131.2, 132.2, 132.6, 133.8, 134.0, 136.1, 137.1, 139.4, 141.7, 154.7, 167.1, 167.6, 168.3, 169.4, 170.2, 171.6, 171.7, 172.3, 172.6, 202.2; HRFABMS m/z 1436.5613 [M+Na$^+$]; calcd for C$_{80}$H$_{87}$NO$_{22}$Na, 1436.5617.
**General Procedure for Deprotection of Benzyl Group.** To a solution of benzyl protected estradiol-taxol conjugate 27 (38.3 mg, 0.0266 mmol), in 10 mL EtOAc, was added 10 mg Pd-C (10%), and the mixture was hydrogenated at 30 psi at room temperature for 24 h. The reaction mixture was filtered, and the organic phase was concentrated in vacuum. The residue was purified by preparative TLC (70% EtOAc/hexane) to give 28 as colorless gum (27.0 mg, 74%).

2’-(3-carboxypropanoyl)-7-[[3,17β-estradiol-11α]-4-carboxyloxypropanoyl]taxol (28).

Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.75 (3H, s), 1.14 (3H, s), 1.17 (3H, s), 1.81 (3H, s), 1.96 (3H, brs), 2.11 (3H, s), 2.43 (3H, s), 1.20-2.80 (25H, taxol and steroid skeletons), 3.67 (1H, t, $J = 8.7$ Hz), 3.91 (1H, d, $J = 6.8$ Hz), 4.17 (1H, d, $J = 8.7$ Hz), 4.32 (1H, d, $J = 8.7$ Hz), 4.97 (1H, d, $J = 9.5$ Hz), 5.36 (1H, td, $J = 10.4, 7.8$ Hz), 5.68 (1H, d, $J = 6.7$ Hz), 5.96 (1H, dd, $J = 9.1, 3.9$ Hz), 6.17 (1H, t, $J = 8.7$ Hz), 6.20 (1H, s), 6.55 (1H, d, $J = 2.7$, Ar), 6.67 (1H, dd, $J = 8.5, 2.7$ Hz, Ar), 7.02 (1H, d, $J = 8.5$ Hz, Ar), 7.24 (1H, d, $J = 9.2$ Hz), 7.28-7.65 (11H, Ar), 7.77 (2H, m, Ar), 8.10 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.2, 11.8, 14.8, 21.0, 21.3, 22.9, 23.1, 26.6, 27.1, 28.5, 28.77, 28.80, 29.13, 29.15, 29.2, 33.5, 35.4, 37.8, 42.6, 43.5, 44.1, 46.5, 47.4, 49.8, 53.3, 56.2, 71.7, 72.0, 74.4, 74.54, 74.56, 75.7, 76.6, 78.7, 81.2, 81.3, 84.4, 113.1, 115.1, 126.9, 127.4, 128.8, 129.0, 129.25, 129.34, 130.4, 131.3, 132.3, 132.6, 133.7, 134.0, 136.9, 139.3, 141.4, 154.3, 167.0, 167.7, 168.3, 169.2, 170.7, 171.8, 172.0, 172.9, 175.0, 202.2; HRFABMS $m/z$ 1346.5162 [M+Na$^+$]; calcd for C$_{73}$H$_{81}$NO$_{22}$Na, 1346.5148.

7-(3-carboxypropanoyl)-2’-[[3,17β-estradiol-11α]-4-carboxyloxypropanoyl]taxol (33).
(Hydrogenation was carried out at 50 psi); colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.77 (3H, s), 1.15 (3H, s), 1.19 (3H, s), 1.80 (3H, s), 2.01 (3H, brs), 2.13 (3H, s), 2.41 (3H, s), 1.23-2.93 (25H, taxol and steroid skeletons), 3.73 (1H, t, $J = 8.6$ Hz), 3.92 (1H, d, $J = 6.9$ Hz), 4.17 (1H, d, $J = 8.4$ Hz), 4.32 (1H, d, $J = 8.4$ Hz), 4.97 (1H, d, $J = 9.3$ Hz), 5.40 (1H, dt, $J = 10.7$, 5.2 Hz), 5.44 (1H, d, $J = 3.2$ Hz), 5.63 (1H, dd, $J = 10.4$, 7.2 Hz), 5.69 (1H, d, $J = 6.9$ Hz), 5.91 (1H, dd, $J = 9.1$, 3.0 Hz), 6.21 (1H, t, $J = 9.3$ Hz), 6.23 (1H, s), 6.55-6.62 (2H, overlapped, Ar), 6.86 (1H, d, $J = 8.2$ Hz, Ar), 7.15 (1H, d, $J = 9.1$ Hz), 7.31-7.65 (11H, Ar), 7.77 (2H, m, Ar), 8.11 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 11.0, 11.9, 14.7, 21.0, 21.3, 22.9, 23.2, 26.6, 26.9, 28.3, 28.5, 28.7, 29.4, 29.5, 30.5, 33.3, 35.6, 37.7, 42.1, 43.4, 44.1, 46.2, 47.2, 49.9, 53.0, 56.3, 71.8, 72.1, 74.3, 74.6, 74.7, 75.7, 76.5, 78.8, 81.1, 81.2, 84.1, 112.8, 115.5, 125.5, 126.9, 127.4, 128.7, 128.95, 128.98, 129.24, 129.27, 130.4, 131.3, 132.3, 132.6, 133.8, 134.0, 137.1, 139.5, 141.7, 154.6, 167.1, 167.7, 168.4, 169.7, 170.2, 171.67, 171.71, 172.3, 176.1, 202.1; HRFABMS $m/z$ 1346.5078 [M+Na$^+$]; calcd for C$_{73}$H$_{81}$NO$_{22}$Na, 1346.5148.

**General procedure for esterification at taxol C-7 OH.** To a solution of iodoacetic acid (100 mg, 0.54 mmol) in toluene (3 mL) was added EDC (206 mg, 1.07 mmol). After stirring at room temperature for 15 min, 4-PP (7.6 mg, cat.) was added and kept stirring for 5 min before 2'-TBS-taxol (15) (52.2 mg, 0.054 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24h. It was then diluted with ethyl acetate (40mL). The organic phase was washed with sodium bicarbonate (3-5 times), water, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was purified by column chromatography (30%
EtOAc/hexane) to give 36 as colorless gum (56.3 mg, 90%). Compounds 39, 40, 41, and 42 were prepared similarly.

**7-Iodoacetyl-2'-TBS-taxol (36).** $^1$H NMR (400 MHz, CDCl$_3$) δ: -0.30 (3H, s), -0.03 (3H, s), 0.80 (9H, s), 1.15 (3H, s), 1.21 (3H, s), 1.83 (3H, s), 1.84-1.94 (1H, m), 1.96 (3H, d, $J = 1.2$ Hz), 2.12-2.20 (4H, overlapped), 2.36-2.45 (1H, m), 2.54-2.65 (4H, overlapped), 3.68 (1H, d, $J = 10.7$ Hz), 3.76 (1H, d, $J = 10.7$ Hz), 3.96 (1H, d, $J = 7.0$ Hz), 4.20 (1H, d, $J = 8.5$ Hz), 4.34 (1H, d, $J = 8.5$ Hz), 4.68 (1H, d, $J = 2.1$ Hz), 4.99 (1H, dd, $J = 9.6$, 1.7 Hz), 5.60-5.76 (3H, overlapped), 6.19 (1H, s), 6.26 (1H, dt, $J = 9.3$, 1.2 Hz), 7.08 (1H, d, $J = 9.0$ Hz), 7.28-7.64 (11H, m, Ar, overlapped), 7.72-7.77 (2H, m, Ar), 8.10-8.15 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: -5.6, -5.0, -3.8, 11.0, 14.9, 18.3, 21.0, 21.6, 23.2, 25.8, 26.7, 32.5, 35.8, 43.6, 47.2, 55.9, 56.1, 71.5, 73.1, 74.6, 75.3, 75.6, 76.6, 78.8, 81.2, 84.0, 126.6, 127.2, 128.2, 128.9, 129.0, 129.3, 130.4, 132.0, 132.7, 134.3, 138.5, 141.5, 167.1, 167.2, 168.4, 169.4, 170.2, 171.7, 201.9; HRFABMS m/z 1158.3156 [M+Na$^+$]; calcd for C$_{55}$H$_{66}$INO$_{15}$SiNa, 1158.3144.

**7-(5-bromopentanoyl)-2'-TBS-taxol (39).** Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: -0.27 (3H, s), 0.00 (3H, s), 0.83 (9H, s), 1.19 (3H, s), 1.23 (3H, s), 1.70-1.81 (2H, m), 1.84 (3H, s), 1.86-1.98 (3H, overlapped), 2.00 (3H, d, $J = 1.2$ Hz), 2.15-2.23 (4H, overlapped), 2.26-2.35 (1H, m), 2.38-2.49 (2H, overlapped), 2.57-2.67 (4H, overlapped), 3.43 (2H, t, $J = 6.7$ Hz), 3.99 (1H, d, $J = 7.0$ Hz), 4.23 (1H, d, $J = 8.4$ Hz), 4.37 (1H, d, $J = 8.4$ Hz), 4.70 (1H, d, $J = 2.1$ Hz), 5.00 (1H,
dd, $J = 9.5$, 1.6 Hz), 5.64 (1H, dd, $J = 10.6$, 7.1 Hz), 5.73 (1H, d, $J = 7.0$ Hz), 5.76 (1H, dd, $J = 8.9$, 1.9 Hz), 6.24-6.32 (2H, overlapped), 7.12 (1H, d, $J = 8.9$ Hz), 7.31-7.66 (11H, m, Ar, overlapped), 7.75-7.80 (2H, m, Ar), 8.12-8.17 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: -5.8, -5.2, 10.9, 14.6, 18.1, 20.7, 21.4, 23.0, 25.5, 26.4, 32.0, 33.0, 33.2, 33.4, 35.6, 43.3, 46.9, 55.7, 56.1, 71.3, 71.4, 74.6, 75.1, 75.2, 76.4, 78.6, 81.0, 84.0, 126.4, 127.0, 128.0, 128.7, 128.8, 129.1, 130.2, 131.8, 132.7, 133.7, 134.1, 138.3, 140.9, 166.9, 167.0, 168.9, 169.9, 171.5, 172.3, 202.0; HRFABMS $m/z$ 1154.3730 [M+Na$^+$]; calcd for C$_{58}$H$_{72}$BrNO$_{15}$SiNa, 1154.3749.

7-(6-bromohexanonyl)-2'-TBS-taxol (40). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: -0.27 (3H, s), 0.00 (3H, s), 0.83 (9H, s), 1.19 (3H, s), 1.24 (3H, s), 1.42-1.53 (2H, m), 1.56-1.73 (2H, m), 1.82-1.95 (6H, overlapped), 2.01 (3H, d, $J = 1.0$ Hz), 2.14-2.33 (5H, overlapped), 2.36-2.49 (2H, overlapped), 2.56-2.67 (4H, overlapped), 3.43 (2H, t, $J = 6.7$ Hz), 3.99 (1H, d, $J = 7.0$ Hz), 4.24 (1H, d, $J = 8.5$ Hz), 4.37 (1H, d, $J = 8.5$ Hz), 4.70 (1H, d, $J = 2.1$ Hz), 5.01 (1H, dd, $J = 9.7$, 1.5 Hz), 5.64 (1H, dd, $J = 10.6$, 7.1 Hz), 5.73 (1H, d, $J = 7.0$ Hz), 5.76 (1H, dd, $J = 8.9$, 1.9 Hz), 6.24-6.32 (2H, overlapped), 7.12 (1H, d, $J = 8.9$ Hz), 7.30-7.67 (11H, m, Ar, overlapped), 7.75-7.80 (2H, m, Ar), 8.12-8.18 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: -5.8, -5.2, 10.9, 14.6, 18.1, 20.7, 21.4, 23.0, 23.4, 25.5, 26.4, 27.5, 29.7, 32.4, 33.4, 33.5, 33.8, 35.6, 43.3, 46.9, 55.7, 56.1, 71.2, 71.3, 74.5, 75.1, 75.2, 76.4, 78.6, 81.0, 84.0, 126.4, 127.0, 127.9, 128.7, 128.8, 129.1, 130.2, 131.8, 132.7, 133.7, 134.1, 138.3, 140.9, 166.9, 167.0, 168.9, 169.9, 171.5, 172.6, 202.0; HRFABMS $m/z$ 1168.4011 [M+Na$^+$]; calcd for C$_{59}$H$_{72}$BrNO$_{15}$SiNa, 1168.3906.
7-(11-bromoundecanonyl)-2’-TBS-taxol (41). Colorless gum; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): -0.31 (3H, s), -0.03 (3H, s), 0.79 (9H, s), 1.16 (3H, s), 1.20 (3H, s), 1.27 (10H, brs), 1.35-1.45 (2H, m), 1.51-1.63 (2H, m), 1.78-1.90 (6H, overlapped), 1.98 (3H, d, \(J = 1.2\) Hz), 2.14 (3H, s), 2.14-2.46 (4H, overlapped), 2.52-2.64 (4H, overlapped), 3.39 (2H, t, \(J = 7.0\) Hz), 4.20 (1H, d, \(J = 8.5\) Hz), 4.33 (1H, d, \(J = 8.5\) Hz), 4.67 (1H, d, \(J = 2.1\) Hz), 4.98 (1H, dd, \(J = 9.5, 1.5\) Hz), 5.61 (1H, dd, \(J = 10.6, 7.0\) Hz), 5.67-5.76 (2H, overlapped), 6.21-6.30 (2H, overlapped), 7.09 (1H, d, \(J = 8.9\) Hz), 7.28-7.63 (11H, m, Ar, overlapped), 7.72-7.77 (2H, m, Ar), 8.09-8.14 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): -5.6, -5.0, 11.1, 14.9, 18.3, 21.0, 21.6, 23.3, 24.7, 25.7, 26.6, 28.4, 29.0, 29.2, 29.4, 29.5, 29.6, 33.0, 33.6, 34.3, 34.4, 35.8, 43.6, 47.1, 55.9, 56.3, 71.2, 71.6, 74.8, 75.3, 75.4, 76.6, 78.8, 81.2, 84.2, 126.6, 127.2, 128.2, 129.0, 129.3, 130.4, 132.0, 132.9, 133.9, 134.3, 138.5, 141.1, 167.1, 167.3, 169.0, 170.0, 171.7, 173.3, 202.3; HRFABMS \(m/z\) 1216.4830 [M+H\(^+\)]; calcd for C\(_{64}\)H\(_{85}\)BrNO\(_{15}\)Si, 1216.4871.

7-(12-bromododecanonyl)-2’-TBS-taxol (42). Colorless gum; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): -0.31 (3H, s), -0.03 (3H, s), 0.79 (9H, s), 1.16 (3H, s), 1.20 (3H, s), 1.26 (12H, brs), 1.36-1.46 (2H, m), 1.52-1.62 (2H, m), 1.79-1.89 (6H, overlapped), 1.98 (3H, d, \(J = 1.2\) Hz), 2.14 (3H, s), 2.14-2.46 (4H, overlapped), 2.54-2.64 (4H, overlapped), 3.40 (2H, t, \(J = 6.9\) Hz), 3.97 (1H, d, \(J = 7.0\) Hz), 4.21 (1H, d, \(J = 8.5\) Hz), 4.34 (1H, d, \(J = 8.5\) Hz), 4.67 (1H, d, \(J = 2.1\) Hz), 4.98 (1H, dd,
\[ J = 9.4, 1.5 \text{ Hz}, \, 5.61 \, (1\text{H}, \, dd, \, J = 10.6, \, 7.0 \text{ Hz}), \, 5.67-5.75 \, (2\text{H}, \, overlapped), \, 6.21-6.30 \, (2\text{H}, \, overlapped), \, 7.09 \, (1\text{H}, \, d, \, J = 9.0 \text{ Hz}), \, 7.28-7.63 \, (11\text{H}, \, m, \, Ar, \, overlapped), \, 7.72-7.77 \, (2\text{H}, \, m, \, Ar), \, 8.09-8.14 \, (2\text{H}, \, m, \, Ar); \, ^{13}\text{C} \text{ NMR} \, (100 \text{ MHz, CDCl}_3) \, \delta: \, -5.6, \, -5.0, \, 11.1, \, 14.9, \, 18.3, \, 21.0, \, 21.6, \, 23.3, \, 24.7, \, 25.7, \, 26.6, \, 28.4, \, 29.0, \, 29.2, \, 29.4, \, 29.6, \, 29.7, \, 33.1, \, 33.6, \, 34.3, \, 34.4, \, 35.8, \, 43.6, \, 47.1, \, 55.9, \, 56.3, \, 71.2, \, 71.6, \, 74.8, \, 75.3, \, 75.4, \, 76.6, \, 78.8, \, 81.2, \, 84.2, \, 126.6, \, 127.2, \, 128.2, \, 129.0, \, 129.3, \, 130.4, \, 132.0, \, 132.9, \, 133.9, \, 134.3, \, 138.4, \, 141.1, \, 167.1, \, 167.3, \, 169.0, \, 170.0, \, 171.7, \, 173.3, \, 202.3; \, \text{HRFABMS} \, m/z \, 1230.4989 \, [\text{M+H}^+] \; \text{calcd for C}_{65}\text{H}_{87}\text{BrNO}_{15}\text{Si}, \, 1230.5028.

**General procedure for esterification at taxol C-10 OH.** To a solution of 6-bromohexanoic acid (149 mg, 0.76 mmol) in DCM (4 mL) was added EDCI (291 mg, 1.52 mmol). After stirring at room temperature for 15 min, 4-PP (8 mg, cat.) was added and kept stirring for 5 min before 2'-TBS-10-deacetyl-7-TES-taxol (22) (80 mg, 0.076 mmol) was added. The reaction mixture was allowed to stir at room temperature for 7 days. It was then diluted with ethyl acetate (40mL). The organic phase was washed with sodium bicarbonate (3-5 times), water, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was purified by preparative thin-layer chromatography (20% EtOAc/hexane) to give 57 as colorless gum (70 mg, 80%). Compounds 52, 56, and 58 were prepared similarly.
2'-TBS-10-deacetyl-10-chloroacetyl-7-TES-taxol (52). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: -0.26 (3H, s), 0.01 (3H, s), 0.56-0.67 (6H, m), 0.83 (9H, s), 0.96 (9H, t, $J = 7.9$ Hz), 1.21 (3H, s), 1.24 (3H, s), 1.71 (1H, s), 1.74 (3H, s), 1.90-1.99 (1H, m), 2.06 (3H, brs), 2.09-2.18 (1H, m), 2.39-2.48 (1H, m), 2.52-2.64 (4H, overlapped), 3.85 (1H, d, $J = 7.2$ Hz), 4.18-4.27 (3H, overlapped), 4.35 (1H, d, $J = 8.4$ Hz), 4.51 (1H, dd, $J = 10.6$, 6.7 Hz), 4.70 (1H, d, $J = 2.3$ Hz), 4.98 (1H, dd, $J = 9.6$, 1.6 Hz), 5.73 (1H, d, $J = 7.2$ Hz), 5.77 (1H, dd, $J = 8.9$, 2.0 Hz), 6.30 (1H, t, $J = 9.2$ Hz), 6.52 (1H, s), 7.09 (1H, d, $J = 8.9$ Hz), 7.31-7.66 (11H, m, Ar, overlapped), 7.74-7.80 (2H, m, Ar), 8.14-8.20 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: -5.7, -5.0, 5.5, 6.9, 10.3, 14.5, 18.3, 21.7, 23.3, 25.7, 26.3, 26.7, 37.4, 40.9, 43.5, 46.8, 55.8, 58.7, 71.4, 72.4, 75.0, 75.3, 76.7, 79.0, 81.3, 84.4, 126.6, 127.2, 128.1, 128.90, 128.91, 128.94, 129.3, 130.4, 132.0, 133.8, 134.2, 138.5, 139.7, 141.5, 166.1, 167.0, 167.2, 169.0, 170.4, 171.6, 201.0; HRFABMS $m/z$ 1116.4729 [M+H$^+$]; calcd for C$_{59}$H$_{79}$ClNO$_{14}$Si$_2$, 1116.4728.

2'-TBS-10-deacetyl-10-(5-halopentanoyl)-7-TES-taxol (56). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: -0.27 (3H, s), 0.00 (3H, s), 0.55-0.67 (6H, m), 0.83 (9H, s), 0.96 (9H, t, $J = 7.9$ Hz), 1.20 (3H, s), 1.24 (3H, s), 1.72 (3H, s), 1.74 (1H, s), 1.82-1.17 (9H, overlapped), 2.39-2.60 (4H, overlapped), 2.61 (3H, s), 3.47 (2H, t, $J = 6.6$ Hz for Br), 3.61 (2H, t, $J = 6.6$ Hz for Cl), 3.87 (1H, d, $J = 7.1$ Hz), 4.23 (1H, d, $J = 8.4$ Hz), 4.35 (1H, d, $J = 8.4$ Hz), 4.51 (1H, dd, $J = 10.5$, 6.6 Hz), 4.70 (1H, d, $J = 2.3$ Hz), 4.98 (1H, dd, $J = 9.6$, 1.6 Hz), 5.73 (1H, d, $J = 7.1$ Hz), 5.77 (1H, d, $J = 8.8$, 2.0 Hz), 6.29 (1H, t, $J = 9.0$ Hz), 6.50 (1H, s), 7.09 (1H, d, $J = 8.8$ Hz), 97
7.31-7.65 (11H, m, Ar, overlapped), 7.75-7.80 (2H, m, Ar), 8.13-8.19 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: -5.8, -5.2, 5.3, 6.8, 10.2, 14.3, 18.1, 21.6, 22.3, 23.2, 23.5, 25.5, 26.6, 31.6, 31.7, 31.8, 33.1, 33.2, 33.3, 35.6, 37.3, 43.3, 44.5, 46.7, 55.7, 58.5, 71.4, 72.2, 74.8, 74.9, 75.1, 76.6, 78.9, 81.2, 84.2, 126.4, 127.0, 128.0, 128.71, 128.73, 128.75, 129.2, 130.2, 131.8, 133.6, 133.7, 134.1, 138.3, 140.2, 166.9, 167.1, 170.2, 171.3, 171.4, 201.7; HRFABMS $m/z$ 1180.4974 [M+Na$^+$/]; calcd for C$_{62}$H$_{84}$ClNO$_{14}$Si$_2$Na, 1180.5017.

2'-TBS-10-deacetyl-10-(6-halohexanoyl)-7-TES-taxol (57). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: -0.27 (3H, s), 0.00 (3H, s), 0.56-0.68 (6H, m), 0.83 (9H, s), 0.96 (9H, t, $J = 7.9$ Hz), 1.20 (3H, s), 1.23 (3H, s), 1.52-1.62 (2H, m), 1.70-2.18 (12H, overlapped), 2.39-2.60 (4H, overlapped), 2.61 (3H, s), 3.44 (2H, t, $J = 6.7$ Hz for Br), 3.57 (2H, t, $J = 6.5$ Hz for Cl), 3.86 (1H, d, $J = 7.0$ Hz), 4.23 (1H, d, $J = 8.4$ Hz), 4.35 (1H, d, $J = 8.4$ Hz), 4.52 (1H, dd, $J = 10.5, 6.6$ Hz), 4.70 (1H, d, $J = 2.2$ Hz), 4.98 (1H, dd, $J = 9.6, 1.6$ Hz), 5.73 (1H, d, $J = 7.0$ Hz), 5.77 (1H, dd, $J = 8.9, 2.0$ Hz), 6.27 (1H, t, $J = 9.0$ Hz), 6.50 (1H, s), 7.09 (1H, d, $J = 8.9$ Hz), 7.32-7.66 (11H, m, Ar, overlapped), 7.73-7.78 (2H, m, Ar), 8.12-8.18 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: -5.8, -5.2, 5.3, 6.8, 10.1, 14.3, 18.1, 21.6, 23.1, 24.3, 25.5, 26.4, 26.6, 32.3, 34.1, 35.6, 37.3, 43.3, 44.7, 46.7, 55.7, 58.4, 71.4, 72.2, 74.8, 75.0, 75.1, 76.6, 78.9, 81.2, 84.3, 126.4, 127.0, 127.9, 128.7, 128.8, 129.2, 130.2, 131.8, 133.6, 133.7, 134.1, 138.3, 140.2, 166.8, 167.1, 170.2, 171.4, 171.6, 201.7; HRFABMS m/z 1194.5208 [M+Na$^+$]; calcd for C$_{63}$H$_{86}$ClNO$_{14}$Si$_2$Na, 1194.5173.
2′-TBS-10-deacetyl-10-(11-haloundecanoyl)-7-TES-taxol (58). Colorless gum; 1H NMR (400 MHz, CDCl$_3$) $\delta$: -0.27 (3H, s), 0.01 (3H, s), 0.55-0.66 (6H, m), 0.83 (9H, s), 0.95 (9H, t, $J = 7.9$ Hz), 1.19 (3H, s), 1.25 (3H, s), 1.32 (10H, brs), 1.33-1.48 (2H, m), 1.64-1.83 (7H, overlapped), 1.85-1.99 (1H, m), 2.06 (3H, s), 2.08-2.18 (1H, m), 2.37-2.60 (4H, overlapped), 2.61 (3H, s), 3.42 (2H, t, $J = 6.9$ Hz for Br), 3.55 (2H, t, $J = 6.9$ Hz for Cl), 3.87 (1H, d, $J = 7.1$ Hz), 4.23 (1H, d, $J = 8.4$ Hz), 4.35 (1H, d, $J = 8.4$ Hz), 4.51 (1H, dd, $J = 10.6$, 6.7 Hz), 4.70 (1H, d, $J = 2.2$ Hz), 4.98 (1H, dd, $J = 9.6$, 1.6 Hz), 5.73 (1H, d, $J = 7.1$ Hz), 5.76 (1H, dd, $J = 8.9$, 2.0 Hz), 6.28 (1H, t, $J = 9.2$ Hz), 6.49 (1H, s), 7.10 (1H, d, $J = 8.9$ Hz), 7.30-7.65 (11H, m, Ar, overlapped), 7.74-7.80 (2H, m, Ar); 13C NMR (100 MHz, CDCl$_3$) $\delta$: -5.8, -5.2, 5.3, 6.8, 10.1, 14.3, 18.1, 21.5, 23.1, 25.0, 25.5, 26.6, 26.9, 28.9, 29.1, 29.2, 29.3, 29.4, 32.6, 34.3, 35.6, 37.3, 43.3, 45.2, 46.7, 55.7, 58.4, 71.4, 72.2, 74.7, 75.0, 75.1, 76.6, 78.9, 81.2, 84.3, 126.4, 127.0, 127.9, 128.70, 128.72, 128.74, 129.2, 130.2, 131.8, 133.6, 133.8, 134.1, 138.3, 140.1, 166.8, 167.1, 170.1, 171.4, 172.0, 201.7; HRFABMS m/z 1264.5979 [M+Na$^+$]; calcd for C$_{68}$H$_{98}$ClNO$_{14}$Si$_2$Na, 1264.5956.

General Procedure for silyl deprotection. To the compound 2′-TBS-7-iodoacetyl-taxol (36) (86 mg, 0.074 mmol) in a 50 mL round bottom flask was added 10 mL 5% HCl in methanol. After stirring at room temperature for 2.5 h, TLC showed that most of starting materials was
converted to a more polar product. The reaction mixture was diluted with ethyl acetate (50mL). The organic phase was washed with water, sodium bicarbonate, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was purified by preparative thin-layer chromatography (50% EtOAc/hexane) to give 37 as colorless gum (66.4 mg, 85%). Compounds 43, 44, 45, 46, 53, 59, 60, and 61 were prepared similarly.

7-Iodoacetyltaxol (37). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.13 (3H, s), 1.18 (3H, s), 1.78 (3H, s), 1.81 (3H, s), 1.82-1.92 (1H, m), 2.15 (3H, s), 2.23-2.34 (2H, overlapped), 2.36 (3H, s), 2.51-2.63 (1H, m), 3.67 (1H, d, $J = 10.5$ Hz), 3.73 (1H, d, $J = 10.5$ Hz), 3.88 (1H, d, $J = 7.0$ Hz), 4.16 (1H, d, $J = 8.5$ Hz), 4.29 (1H, d, $J = 8.5$ Hz), 4.78 (1H, d, $J = 2.2$ Hz), 4.93 (1H, d, $J = 9.4$ Hz), 5.17 (1H, dd, $J = 10.6, 7.2$ Hz), 5.64 (1H, d, $J = 7.0$ Hz), 5.77 (1H, dd, $J = 8.9, 2.4$ Hz), 6.10-6.18 (2H, overlapped), 7.14-7.63 (12H, overlapped), 7.70-7.76 (2H, m, Ar), 8.06-8.12 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: -4.2, 10.8, 14.7, 20.9, 21.0, 22.6, 26.7, 32.4, 35.7, 43.3, 47.2, 55.1, 56.1, 72.1, 73.0, 73.4, 74.3, 75.5, 76.5, 78.6, 81.1, 83.8, 127.2, 128.4, 128.8, 128.9, 129.1, 129.2, 130.3, 132.0, 132.8, 133.8, 133.9, 138.1, 140.9, 166.9, 167.2, 168.3, 169.3, 170.5, 172.5, 201.7; HRFABMS m/z 1044.2277 [M+Na$^+$]; calcd for C$_{49}$H$_{52}$INO$_{15}$Na 1044.2279.

7-(5-Bromopentanoyl)taxol (43). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.18 (3H, s), 1.21 (3H, s), 1.70-1.95 (11H, overlapped), 2.18 (3H, s), 2.25-2.48 (7H, overlapped), 2.55-2.66
(1H, m), 3.43 (2H, t, J = 6.9 Hz), 3.82 (1H, d, J = 4.5 Hz), 3.93 (1H, d, J = 6.9 Hz), 4.21 (1H, d, J = 8.5 Hz), 4.33 (1H, d, J = 8.5 Hz), 4.82 (1H, dd, J = 4.5, 2.7 Hz), 4.96 (1H, d, J = 9.2 Hz), 5.57 (1H, dd, J = 10.4, 7.3 Hz), 5.69 (1H, d, J = 6.9 Hz), 5.82 (1H, dd, J = 8.9, 2.4 Hz), 6.18 (1H, t, J = 8.7 Hz), 6.24 (1H, s), 7.17 (1H, d, J = 8.9 Hz), 7.33-7.68 (11H, m, Ar, overlapped), 7.75-7.80 (2H, m, Ar), 8.10-8.16 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 10.8, 14.6, 20.7, 20.8, 22.5, 23.0, 26.5, 32.0, 33.0, 33.5, 35.6, 43.2, 47.0, 54.9, 56.2, 71.4, 72.1, 73.2, 74.4, 75.3, 76.4, 78.5, 81.0, 83.9, 127.0, 127.1, 128.3, 128.7, 128.8, 129.0, 129.1, 130.2, 131.9, 133.0, 133.7, 133.8, 138.1, 140.4, 166.9, 167.0, 168.9, 170.4, 172.3, 172.4, 201.9; HRFABMS m/z 1040.2830 [M+Na$^+$]; calcd for C$_{52}$H$_{58}$NO$_{15}$Na, 1040.2882.

7-(6-Bromohexanoyl)taxol (44). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.18 (3H, s), 1.21 (3H, s), 1.60-1.95 (13H, overlapped), 2.18 (3H, s), 2.25-2.47 (7H, overlapped), 2.56-2.66 (1H, m), 3.43 (2H, t, J = 6.8 Hz), 3.82 (1H, d, J = 4.7 Hz), 3.93 (1H, d, J = 6.9 Hz), 4.21 (1H, d, J = 8.5 Hz), 4.33 (1H, d, J = 8.5 Hz), 4.82 (1H, dd, J = 4.1, 2.7 Hz), 4.96 (1H, d, J = 9.1 Hz), 5.57 (1H, dd, J = 10.6, 7.3 Hz), 5.69 (1H, d, J = 6.9 Hz), 5.82 (1H, dd, J = 9.1, 2.4 Hz), 6.18 (1H, t, J = 8.8 Hz), 6.24 (1H, s), 7.17 (1H, d, J = 9.1 Hz), 7.33-7.68 (11H, m, Ar, overlapped), 7.75-7.80 (2H, m, Ar), 8.10-8.16 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 10.8, 14.6, 20.7, 20.8, 22.5, 23.4, 26.5, 27.5, 32.4, 33.5, 33.6, 35.6, 43.2, 47.0, 54.9, 56.2, 71.2, 72.1, 73.2, 74.4, 75.3, 76.4, 78.5, 81.1, 83.9, 127.0, 127.1, 128.3, 128.7, 128.8, 129.0, 129.1, 130.2, 131.9, 133.0, 133.7, 133.8, 138.1, 140.4, 166.9, 167.0, 168.9, 170.4, 172.3, 172.4, 201.9; HRFABMS m/z 1040.2830 [M+Na$^+$]; calcd for C$_{52}$H$_{58}$NO$_{15}$Na, 1040.2882.
1032.3165 [M+H⁺]; calcd for C₅₃H₆₃BrNO₁₅, 1032.3219.

7-(11-Bromoundecanoyl)taxol (45). Colorless gum; ¹H NMR (400 MHz, CDCl₃) δ: 1.19 (3H, s), 1.21 (3H, s), 1.29 (10H, brs), 1.39-1.48 (2H, m), 1.52-1.63 (2H, m), 1.79-1.91 (9H, overlapped), 2.18 (3H, s), 2.20-2.42 (7H, overlapped), 2.56-2.65 (1H, m), 3.43 (2H, t, J = 6.9 Hz), 3.93 (1H, d, J = 6.9 Hz), 4.20 (1H, d, J = 8.4 Hz), 4.33 (1H, d, J = 8.4 Hz), 4.81 (1H, dd, J = 2.7 Hz), 4.96 (1H, dd, J = 9.4, 1.4 Hz), 5.57 (1H, dd, J = 10.4, 7.0 Hz), 5.69 (1H, d, J = 6.9 Hz), 5.82 (1H, dd, J = 9.0, 2.5 Hz), 6.18 (1H, dt, J = 9.0, 1.3 Hz), 6.26 (1H, s), 7.17 (1H, d, J = 9.0 Hz), 7.33-7.67 (11H, m, Ar, overlapped), 7.76-7.81 (2H, m, Ar), 8.11-8.16 (2H, m, Ar); ¹³C NMR (100 MHz, CDCl₃) δ: 10.8, 14.6, 20.7, 20.8, 22.5, 24.5, 26.6, 28.2, 28.7, 29.0, 29.2, 29.3, 29.4, 32.8, 33.5, 34.0, 34.1, 35.6, 43.2, 47.0, 54.9, 56.2, 71.1, 72.1, 73.3, 74.4, 75.3, 76.4, 78.5, 81.1, 83.9, 127.0, 127.1, 128.3, 128.6, 128.7, 128.9, 129.1, 130.2, 131.9, 133.0, 133.7, 138.1, 140.3, 166.9, 167.0, 168.8, 170.3, 172.3, 172.9, 201.9; HRFABMS m/z 1102.3979 [M+H⁺]; calcd for C₅₈H₇₁BrNO₁₅, 1102.4004.

7-(12-Bromododecanoyl)taxol (46). Colorless gum; ¹H NMR (400 MHz, CDCl₃) δ: 1.19 (3H, s), 1.21 (3H, s), 1.29 (12H, brs), 1.39-1.48 (2H, m), 1.53-1.63 (2H, m), 1.78-1.91 (9H, overlapped), 2.18 (3H, s), 2.21-2.42 (7H, overlapped), 2.56-2.65 (1H, m), 3.43 (2H, t, J = 6.9 Hz), 3.93 (1H, d,
\( J = 6.9 \text{ Hz}, \ 4.21 (1H, d, J = 8.4 \text{ Hz}), \ 4.33 (1H, d, J = 8.4 \text{ Hz}), \ 4.81 (1H, \text{ brd}, J = 2.3 \text{ Hz}), \ 4.96 (1H, dd, J = 9.4, 1.4 \text{ Hz}), \ 5.57 (1H, dd, J = 10.3, 7.2 \text{ Hz}), \ 5.69 (1H, d, J = 6.9 \text{ Hz}), \ 5.82 (1H, dd, J = 9.0, 2.5 \text{ Hz}), \ 6.18 (1H, dt, J = 8.9, 1.3 \text{ Hz}), \ 6.26 (1H, s), \ 7.17 (1H, d, J = 9.0 \text{ Hz}), \ 7.33-7.67 (11H, m, Ar, overlapped), \ 7.76-7.81 (2H, m, Ar); \ ^{13}\text{C NMR (100 MHz, CDCl}_3) \delta: 11.0, 14.8, 20.8, 20.9, 22.7, 24.6, 26.7, 28.3, 28.9, 29.2, 29.4, 29.5, 29.6, 33.0, 33.6, 34.2, 34.3, 35.7, 43.4, 47.2, 55.1, 56.4, 71.2, 72.2, 73.4, 74.5, 75.4, 76.6, 78.7, 81.3, 84.1, 127.2, 127.3, 128.4, 128.8, 129.1, 129.3, 130.3, 132.0, 133.2, 133.9, 138.2, 140.5, 167.0, 167.1, 168.9, 170.5, 172.5, 173.1, 202.0; \text{ HRFABMS } m/z 1116.4153 \text{ [M+H]}; \text{ calcd for C}_{59}\text{H}_{73}\text{BrNO}_{15}, \text{ 1116.4161.}

**10-Deacetyl-10-iodoacetyltaxol (53).** Colorless gum; \(^1\text{H NMR (400 MHz, CDCl}_3) \delta: 1.19 (3H, s), \ 1.28 (3H, s), \ 1.70 (1H, s), \ 1.72 (3H, s), \ 1.84 (3H, s), \ 1.85-1.94 (1H, m), \ 2.26-2.44 (6H, overlapped), \ 2.52-2.62 (1H, m), \ 3.64 (1H, d, J = 5.2 \text{ Hz}), \ 3.81 (1H, d, J = 7.1 \text{ Hz}), \ 3.89 (2H, s), \ 4.22 (1H, d, J = 8.4 \text{ Hz}), \ 4.33 (1H, d, J = 8.4 \text{ Hz}), \ 4.39 (1H, m), \ 4.82 (1H, dd, J = 5.2, 2.7 \text{ Hz}), \ 4.96 (1H, dd, J = 9.5, 1.9 \text{ Hz}), \ 5.71 (1H, d, J = 7.1 \text{ Hz}), \ 5.81 (1H, dd, J = 8.8, 2.6 \text{ Hz}), \ 6.22-6.30 (2H, overlapped), \ 7.03 (1H, d, J = 8.8 \text{ Hz}), \ 7.35-7.68 (11H, m, Ar, overlapped), \ 7.74-7.79 (2H, m, Ar), \ 8.13-8.19 (2H, m, Ar); \ ^{13}\text{C NMR (100 MHz, CDCl}_3) \delta: -6.5, 9.6, 14.9, 21.7, 22.6, 35.7, 35.8, 43.1, 45.8, 55.1, 58.7, 72.0, 72.3, 73.2, 74.9, 76.5, 76.7, 79.0, 81.1, 84.3, 127.0, 128.4, 128.7, 128.8, 129.0, 129.1, 130.2, 132.0, 132.8, 133.6, 133.7, 138.0, 142.5, 167.0, 167.1, 168.7, 170.4, 172.7, 203.0; \text{ HRFABMS } m/z 980.2354 \text{ [M+H]}; \text{ calcd for C}_{47}\text{H}_{51}\text{INO}_{14}, \text{ 980.2354.}
10-Deacetyl-10-(5-halopentanoyl)taxol (59). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.15 (3H, s), 1.25 (3H, s), 1.70 (3H, s), 1.81 (3H, d, $J = 1.1$ Hz), 1.84-1.97 (6H, overlapped), 2.26-2.39 (2H, overlapped), 2.40 (3H, s), 2.48-2.65 (4H, overlapped), 3.47 (2H, t, $J = 6.6$ Hz for Br), 3.61 (2H, t, $J = 6.1$ Hz for Cl), 3.74 (1H, d, $J = 5.4$ Hz), 3.81 (1H, d, $J = 7.1$ Hz), 4.21 (1H, d, $J = 8.4$ Hz), 4.31 (1H, d, $J = 8.4$ Hz), 4.42 (1H, m), 4.81 (1H, dd, $J = 5.3$, 2.8 Hz), 4.96 (1H, dd, $J = 9.4$, 1.8 Hz), 5.69 (1H, d, $J = 7.1$ Hz), 5.80 (1H, dd, $J = 8.9$, 2.7 Hz), 6.24 (1H, dt, $J = 9.2$, 1.1 Hz), 6.31 (1H, s), 7.08 (1H, d, $J = 8.9$ Hz), 7.34-7.67 (11H, m, Ar, overlapped), 7.73-7.79 (2H, m, Ar), 8.13-8.18 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 9.6, 14.9, 21.9, 22.1, 22.6, 23.4, 26.9, 31.6, 31.7, 33.1, 33.2, 33.3, 35.6, 35.7, 43.2, 44.5, 45.7, 55.1, 58.6, 72.2, 72.3, 73.2, 75.0, 75.5, 76.5, 79.0, 81.1, 84.4, 127.0, 127.1, 128.3, 128.7, 128.8, 129.0, 129.2, 130.2, 131.9, 133.1, 133.6, 133.7, 138.0, 142.0, 167.0, 167.1, 170.4, 172.7, 173.3, 203.6; HRFABMS $m/z$ 930.3428 [M+H$^+$]; calcd for C$_{50}$H$_{57}$ClNO$_{14}$, 930.3468.

10-Deacetyl-10-(5-halohexanoyl)taxol (60). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.15 (3H, s), 1.25 (3H, s), 1.53-1.62 (2H, m), 1.70 (3H, s), 1.72-1.97 (9H, overlapped), 2.25-2.39 (2H, overlapped), 2.40 (3H, s), 2.45-2.62 (4H, overlapped), 3.22 (2H, t, $J = 7.1$ Hz for I), 3.44 (2H, t, $J = 6.6$ Hz for Br), 3.57 (2H, t, $J = 6.6$ Hz for Cl), 3.75 (1H, d, $J = 5.4$ Hz), 3.82 (1H, d, $J = 7.0$ Hz), 4.21 (1H, d, $J = 8.5$ Hz), 4.31 (1H, d, $J = 8.5$ Hz), 4.42 (1H, m), 4.81 (1H, dd, $J = 5.3$, 2.8 Hz).
10-Deacetyl-10-(11-haloundecanoyl) taxol (61). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.16 (3H, s), 1.25 (3H, s), 1.33 (10H, brs), 1.38-1.48 (2H, m), 1.68-1.90 (11H, overlapped), 2.25-2.60 (8H, overlapped), 3.21 (2H, t, $J = 7.1$ Hz for I), 3.43 (2H, t, $J = 6.7$ Hz for Br), 3.56 (2H, t, $J = 6.7$ Hz for Cl), 3.70 (1H, d, $J = 5.4$ Hz), 3.82 (1H, d, $J = 7.0$ Hz), 4.21 (1H, d, $J = 8.5$ Hz), 4.32 (1H, d, $J = 8.5$ Hz), 4.43 (1H, m), 4.81 (1H, dd, $J = 5.2$, 2.8 Hz), 4.96 (1H, dd, $J = 9.6$, 1.9 Hz), 5.69 (1H, d, $J = 7.0$ Hz), 5.81 (1H, dd, $J = 9.0$, 2.7 Hz), 6.25 (1H, t, $J = 9.1$ Hz), 6.29 (1H, s), 7.06 (1H, d, $J = 9.0$ Hz), 7.34-7.67 (11H, m, Ar, overlapped), 7.74-7.79 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.6, 14.8, 21.9, 22.6, 24.8, 26.9, 28.9, 29.0, 29.2, 29.3, 29.4, 32.6, 34.2, 35.6, 35.7, 43.2, 45.2, 45.7, 55.1, 58.6, 72.2, 72.3, 73.2, 75.0, 75.3, 76.5, 79.1, 81.2, 84.4, 127.0, 127.1, 128.3, 128.7, 128.8, 129.0, 129.2, 130.2, 132.0, 133.3, 133.6, 133.7, 138.0, 141.9, 167.0, 167.1, 170.4, 172.7, 174.0, 203.6; HRFABMS $m/z$ 1014.4440 [M+Na$^+$]; calcd for C$_{56}$H$_{69}$ClNO$_{14}$, 1014.4407.
General Procedure to convert terminal halide to thio group. To a solution of compound 7-(5-bromopentanoyl)taxol (43) (42 mg, 0.040 mmol) in 2 mL dry DMF was added NaSH (20 mg, 0.36 mmol) and 15-crown-5 (0.1 mL, cat.). After stirring at room temperature for about 2.5 h. TLC showed that all the starting material was consumed, and a much more polar compound was formed. The reaction mixture was diluted with EtOAc (20 mL), and then washed with water, brine, and dried with sodium sulfate. The organic phase was concentrated in vacuum, and the residue was applied to preparative thin-layer chromatography (10% MeOH/DCM) to give 47 (36 mg, 86%). Compounds 38, 48, 49, 50, 55 and 62 were prepared in similar procedure. For those compounds with a terminal chloride, the chloride was first converted to iodide using NaI in acetone at 40 °C for 3 days. The resulting iodide product was then treated with the same procedure described above to get thio compound 66 and 67.

7-(2-Mercaptoacetyl)taxol (38). Colorless gum; \( ^1H \hspace{0.5mm} \text{NMR} \ (400 \hspace{0.5mm} \text{MHz}, \ \text{CD}_3\hspace{0.5mm} \text{OD}) \ \delta: \ 1.10 \ (3\text{H, s}), \ 1.15 \ (3\text{H, s}), \ 1.79 \ (3\text{H, s}), \ 1.82-1.91 \ (4\text{H, overlapped}), \ 1.94-2.02 \ (1\text{H, m}), \ 2.15 \ (3\text{H, s}), \ 2.18-2.26 \ (1\text{H, m}), \ 2.35 \ (3\text{H, s}), \ 2.55-2.65 \ (1\text{H, m}), \ 3.74 \ (1\text{H, d, }J = 15.9 \ \text{Hz}), \ 3.82 \ (1\text{H, d, }J = 15.9 \ \text{Hz}), \ 3.90 \ (1\text{H, d, }J = 7.0 \ \text{Hz}), \ 4.18 \ (2\text{H, ABq, }J = 10.3, \ 8.6 \ \text{Hz}), \ 4.74 \ (1\text{H, dd, }J = 5.6 \ \text{Hz}), \ 4.98 \ (1\text{H, d, }J = 9.5 \ \text{Hz}), \ 5.58-5.67 \ (3\text{H, overlapped}), \ 6.15 \ (1\text{H, t, }J = 9.0 \ \text{Hz}), \ 6.21 \ (1\text{H, s}), \ 7.25-7.70 \ (11\text{H, m, Ar, overlapped}), \ 7.83-7.89 \ (2\text{H, m, Ar}), \ 8.08-8.13 \ (2\text{H, m, Ar}); \ ^{13}C \hspace{0.5mm} \text{NMR} \ (100 \hspace{0.5mm} \text{MHz, } \text{CD}_3\hspace{0.5mm} \text{OD}) \ \delta:
10.2, 13.6, 19.5, 20.9, 22.0, 25.7, 32.7, 35.3, 36.4, 43.5, 46.9, 55.9, 56.6, 70.9, 73.0, 73.7, 74.6, 75.5, 76.0, 77.7, 80.8, 84.1, 127.3, 127.4, 127.9, 128.4, 128.5, 128.6, 130.0, 130.1, 131.7, 133.1, 133.5, 134.4, 138.8, 141.0, 166.4, 169.2, 169.5, 169.7, 170.8, 173.3, 202.2; HRFABMS m/z 950.3036 [M+Na$^+$]; calcd for C$_{49}$H$_{53}$NO$_{15}$SNa, 950.3034.

7-(5-Mercaptopentanoyl)taxol (47). Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) δ: 1.11 (3H, s), 1.15 (3H, s), 1.61-1.82 (8H, overlapped), 1.89 (3H, d, J = 1.2 Hz), 1.95-2.03 (1H, m), 2.14 (3H, s), 2.18-2.34 (3H, overlapped), 2.36 (3H, s), 2.48-2.58 (1H, m), 3.07 (2H, t, J = 7.3 Hz), 3.90 (1H, d, J = 7.1 Hz), 4.19 (2H, ABq, J = 10.2, 8.8 Hz), 4.75 (1H, dd, J = 5.5 Hz), 4.98 (1H, dd, J = 9.5, 1.5 Hz), 5.57 (1H, dd, J = 10.6, 7.2 Hz), 5.62-5.66 (2H, overlapped), 6.15 (1H, dt, J = 9.2, 1.2 Hz), 6.25 (1H, s), 7.25-7.70 (11H, m, Ar, overlapped), 7.82-7.88 (2H, m, Ar), 8.07-8.13 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) δ: 10.2, 13.6, 19.5, 20.9, 22.1, 23.4, 25.6, 28.7, 33.1, 33.2, 34.4, 35.3, 43.4, 46.9, 56.1, 56.6, 70.9, 71.7, 73.7, 74.7, 75.4, 76.1, 77.7, 80.8, 84.0, 127.3, 127.4, 127.9, 128.4, 128.5, 128.6, 130.0, 130.1, 131.7, 133.2, 133.5, 134.4, 138.8, 140.9, 166.4, 169.1, 169.5, 170.8, 172.9, 173.3, 202.4; HRFABMS m/z 992.3508 [M+Na$^+$]; calcd for C$_{52}$H$_{59}$NO$_{15}$SNa, 992.3503.

7-(6-Mercaptopentanoyl)taxol (48). Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) δ: 1.10 (3H, s), 1.15 (3H, s), 1.37-1.46 (2H, m), 1.52-1.65 (2H, m), 1.71-1.82 (6H, overlapped), 1.89 (3H, d, J
= 1.2 Hz), 1.94-2.02 (1H, m), 2.14 (3H, s), 2.17-2.35 (3H, overlapped), 2.36 (3H, s), 2.49-2.58 (1H, m), 3.07 (2H, t, J = 7.4 Hz), 3.90 (1H, d, J = 7.3 Hz), 4.19 (2H, ABq, J = 9.2 Hz), 4.75 (1H, d, J = 5.3 Hz), 4.99 (1H, dd, J = 9.6, 1.5 Hz), 5.57 (1H, dd, J = 10.6, 7.1 Hz), 5.62-5.66 (2H, overlapped), 6.15 (1H, dt, J = 9.3, 1.2 Hz), 6.25 (1H, s), 7.25-7.70 (11H, m, Ar, overlapped), 7.83-7.88 (2H, m, Ar), 8.08-8.13 (2H, m, Ar); 13C NMR (100 MHz, CD3OD) δ: 10.2, 13.5, 19.5, 23.7, 25.6, 28.0, 29.1, 33.1, 33.6, 34.6, 43.4, 46.9, 56.1, 56.6, 70.9, 71.6, 73.6, 74.7, 75.4, 76.1, 77.7, 80.7, 84.0, 127.3, 127.4, 127.8, 128.4, 128.5, 128.6, 130.0, 130.1, 131.7, 133.2, 133.4, 134.4, 138.8, 140.8, 166.4, 166.6, 169.4, 170.8, 173.1, 173.3, 202.4; HRFABMS m/z [M+Na+]; calcd for C53H61NO15SNa, 1006.3660.

7-(11-Mercaptoundecanoyl)taxol (49). Colorless gum; 1H NMR (400 MHz, CD3OD) δ: 1.15 (3H, s), 1.18 (3H, s), 1.33 (10H, brs), 1.38-1.48 (2H, m), 1.50-1.64 (2H, m), 1.73-1.83 (6H, overlapped), 1.92 (3H, d, J = 1.2 Hz), 1.98-2.06 (1H, m), 2.16 (3H, s), 2.18-2.36 (3H, overlapped), 2.39 (3H, s), 2.51-2.60 (1H, m), 3.09 (2H, t, J = 7.5 Hz), 3.93 (1H, d, J = 7.1 Hz), 4.22 (2H, ABq, J = 10.9, 8.5 Hz), 4.78 (1H, d, J = 5.5 Hz), 5.02 (1H, dd, J = 9.5, 1.4 Hz), 5.60 (1H, dd, J = 10.6, 7.1 Hz), 5.65-5.69 (2H, overlapped), 6.18 (1H, dt, J = 9.3, 1.2 Hz), 6.28 (1H, s), 7.29-7.73 (11H, m, Ar, overlapped), 7.86-7.91 (2H, m, Ar), 8.11-8.16 (2H, m, Ar); 13C NMR (100 MHz, CD3OD) δ: 10.0, 13.3, 19.3, 20.7, 21.8, 24.0, 25.4, 28.5, 28.6, 28.8, 28.9, 29.0, 29.1, 29.2, 32.9, 33.6, 34.6, 35.2, 43.2, 46.7, 55.9, 56.3, 70.8, 71.4, 73.4, 74.5, 75.2, 75.9, 77.5, 80.6, 83.8, 127.0, 127.1, 127.6, 128.2, 128.3, 128.4, 129.8, 129.9, 131.4, 133.1, 133.2, 134.2, 138.6, 108
7-(12-Mercaptododecanoyl)taxol (50). Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) δ: 1.14 (3H, s), 1.18 (3H, s), 1.32 (12H, brs), 1.38-1.47 (2H, m), 1.50-1.63 (2H, m), 1.72-1.82 (6H, overlapped), 1.92 (3H, d, $J = 1.3$ Hz), 1.97-2.05 (1H, m), 2.16 (3H, s), 2.18-2.36 (3H, overlapped), 2.39 (3H, s), 2.50-2.60 (1H, m), 3.09 (2H, t, $J = 7.5$ Hz), 3.93 (1H, d, $J = 7.1$ Hz), 4.22 (2H, ABq, $J = 11.7, 8.4$ Hz), 4.78 (1H, d, $J = 5.6$ Hz), 5.01 (1H, dd, $J = 9.5, 1.4$ Hz), 5.60 (1H, dd, $J = 10.6, 7.1$ Hz), 5.65-5.69 (2H, overlapped), 6.18 (1H, dt, $J = 9.2, 1.3$ Hz), 6.28 (1H, s), 7.28-7.73 (11H, m, Ar, overlapped), 7.86-7.91 (2H, m, Ar), 8.11-8.16 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) δ: 10.1, 13.4, 19.3, 20.7, 21.8, 24.0, 25.4, 28.5, 28.7, 28.8, 28.9, 29.1, 29.2, 32.9, 33.6, 34.6, 35.2, 43.2, 46.7, 55.9, 56.3, 70.8, 71.4, 73.4, 74.5, 75.2, 75.9, 77.5, 80.6, 83.8, 127.1, 127.2, 127.6, 128.2, 128.3, 128.4, 129.8, 129.9, 131.5, 133.1, 133.2, 134.2, 138.6, 140.7, 166.2, 168.9, 169.2, 170.6, 173.0, 173.1, 202.3; HRFABMS $m/z$ 1090.4598 [M+Na$^+$]; calcd for C$_{59}$H$_{73}$NO$_{15}$SNa, 1090.4599.

10-Deacetyl-10-(2-mercaptoacetyl)taxol (55). Colorless gum; $^1$H NMR (400 MHz, (CD$_3$)$_2$CO) δ: 1.20 (3H, s), 1.23 (3H, s), 1.68 (3H, s), 1.76-1.84 (1H, m), 1.94 (3H, d, $J = 1.3$ Hz), 2.13-2.24 (1H, m), 2.33-2.57 (5H, overlapped), 3.86 (1H, d, $J = 7.1$ Hz), 4.01 (2H, s), 4.15 (1H, d, $J = 8.2$
Hz), 4.19 (1H, d, J = 8.2 Hz), 4.43 (1H, m), 4.86 (1H, brt, J = 5.2 Hz), 4.96 (1H, dd, J = 9.4, 1.7 Hz), 5.21 (1H, d, J = 7.0 Hz), 5.69 (1H, d, J = 7.1 Hz), 5.76 (1H, dd, J = 8.7, 4.9 Hz), 6.21 (1H, t, J = 9.0 Hz), 6.45 (1H, s), 7.26-7.71 (11H, m, Ar, overlapped), 7.90-7.95 (2H, m, Ar), 8.11-8.17 (2H, m, Ar); HRFABMS m/z 886.3088 [M+H⁺]; calcd for C₄₇H₅₂NO₁₄S, 886.3109. This compound was not stable in methanol solution at room temperature, decomposing to 10-deacetyl-taxol.

10-Deacetyl-10-(5-mercaptopentanoyl)taxol (62). Colorless gum; ¹H NMR (400 MHz, CD₃OD) δ: 1.16-1.20 (6H, overlapped), 1.68 (3H, s), 1.77-2.04 (9H, overlapped), 2.21-2.30 (1H, m), 2.38 (3H, s), 2.44-2.61 (3H, m), 3.13 (2H, t, J = 7.0 Hz), 3.85 (1H, d, J = 7.2 Hz), 4.21 (2H, brs), 4.35 (1H, dd, J = 11.0, 6.6 Hz), 4.76 (1H, d, J = 5.6 Hz), 5.02 (1H, dd, J = 9.6, 1.8 Hz), 5.64-5.70 (2H, overlapped), 6.19 (1H, dt, J = 9.3 Hz), 6.48 (1H, s), 7.28-7.72 (11H, m, Ar, overlapped), 7.86-7.91 (2H, m, Ar), 8.11-8.16 (2H, m, Ar); ¹³C NMR (100 MHz, CD₃OD) δ: 9.3, 13.6, 21.2, 22.0, 24.0, 25.8, 28.7, 33.3, 34.3, 35.4, 36.3, 43.4, 46.7, 56.6, 58.0, 71.0, 71.1, 73.7, 75.1, 75.5, 76.3, 77.9, 81.1, 84.7, 127.3, 127.8, 128.4, 128.5, 128.6, 130.0, 130.2, 131.7, 133.4, 133.8, 134.4, 138.8, 140.8, 166.4, 169.1, 170.6, 172.3, 173.2, 203.7; HRFABMS m/z 950.3370 [M+Na⁺]; calcd for C₅₀H₅₇NO₁₄SNa, 950.3397.
10-Deacetyl-10-(6-mercaptophexanoyl)taxol (66). Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) δ: 1.14-1.16 (6H, overlapped), 1.48-1.55 (2H, m), 1.62-1.85 (9H, overlapped), 1.89-2.00 (4H, overlapped), 2.18-2.26 (1H, m), 2.36 (3H, s), 2.41-2.54 (4H, overlapped), 3.08 (2H, t, $J = 7.4$ Hz), 3.82 (1H, d, $J = 7.2$ Hz), 4.18 (2H, brs), 4.32 (1H, dd, $J = 10.9$, 6.5 Hz), 4.73 (1H, d, $J = 5.5$ Hz), 4.99 (1H, dd, $J = 9.6$, 1.9 Hz), 5.61-5.66 (2H, overlapped), 6.16 (1H, dt, $J = 9.1$ Hz), 6.45 (1H, s), 7.25-7.70 (11H, m, Ar, overlapped), 7.83-7.88 (2H, m, Ar), 8.08-8.13 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) δ: 9.3, 13.6, 21.3, 22.1, 24.4, 25.8, 28.1, 29.1, 33.7, 34.6, 35.4, 36.3, 43.4, 46.7, 56.6, 58.1, 71.1, 71.2, 73.7, 75.1, 75.4, 76.3, 77.9, 81.1, 84.7, 127.3, 127.4, 127.8, 128.4, 128.5, 128.6, 130.0, 130.2, 131.7, 133.4, 133.8, 134.4, 138.8, 140.8, 166.4, 169.1, 170.7, 172.5, 173.3, 203.8; HRFABMS m/z 964.3512 [M+Na$^+$]; calcd for C$_{51}$H$_{59}$NO$_{14}$SNa, 964.3554.

10-Deacetyl-10-(11-mercaptoundecanoyl)taxol (67). Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) δ: 1.12-1.16 (6H, overlapped), 1.68 (3H, s), 1.27-1.44 (12H, overlapped), 1.60-1.84 (8H, overlapped), 1.91 (3H, d, $J = 1.3$ Hz), 1.92-2.00 (1H, m), 2.19-2.27 (1H, m), 2.36 (3H, s), 2.41-2.50 (3H, overlapped), 3.07 (2H, t, $J = 7.4$ Hz), 3.82 (1H, d, $J = 7.2$ Hz), 4.18 (2H, brs), 4.32 (1H, dd, $J = 11.0$, 6.6 Hz), 4.74 (1H, d, $J = 5.6$ Hz), 4.99 (1H, dd, $J = 9.6$, 1.9 Hz), 5.62-5.66 (2H, overlapped), 6.15 (1H, dt, $J = 9.4$, 1.3 Hz), 6.45 (1H, s), 7.24-7.70 (11H, m, Ar, overlapped), 7.83-7.88 (2H, m, Ar), 8.08-8.13 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) δ: 9.3, 13.6, 21.3, 22.1, 25.0, 25.9, 28.8, 28.9, 29.1, 29.2, 29.3, 29.4, 33.9, 34.8, 35.4, 36.3, 43.4, 46.7, 56.6, 58.1, 71.0, 71.1, 73.8, 75.0, 75.4, 76.3, 77.9, 81.1, 84.7, 127.4, 127.8, 128.4, 128.5, 128.6, 130.0, 130.2,
112.7, 133.4, 133.9, 134.4, 138.8, 140.8, 166.4, 169.1, 170.7, 172.7, 173.2, 203.8; HRFABMS m/z 1034.4294 [M+Na]; calcd for C₅₆H₆₉NO₁₄SNa, 1034.4336.

**General Procedure for acylation at C-13 of 7-TES-Baccatin III.** To a solution of (+)-2-phenylspiro(cyclopropane-1',4-oxazoline)-5-carboxylic acid (72) (70 mg, 0.32 mmol) in toluene (4 mL) was added DCC (68 mg, 0.32 mmol). After stirring at room temperature for 15 min, 4-PP (3 mg, cat.) was added and kept stirring for 5 min before 7-TES-baccatin III (68) (75 mg, 0.11 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24h. It was then diluted with ethyl acetate (50 mL). The organic phase was washed with aqueous sodium bicarbonate, water, and brine, dried over sodium sulfate, and concentrated in vacuum. The residue was purified by preparative thin layer chromatography (30% EtOAc/Hexane) to give 75 (35 mg, 36%) and 76 (48mg, 49%) both as colorless gum.; Compound 84, 85, 86, and 87 were prepared similarly using EDC instead of DCC.

(7-TES-baccatin III)-13-yl 2-phenylspiro(cyclopropane-1',4-oxazoline)-5S-carboxylate (75).

¹H NMR (400 MHz, CDCl₃) δ: 0.64 (6H, dq, J = 7.9, 2.3 Hz), 0.95 (9H, t, J = 7.9 Hz), 1.05 (1H, m), 1.18-1.36 (2H, m, overlapped), 1.23 (3H, s), 1.26 (3H, s), 1.71 (3H, s), 1.90 (1H, m), 2.13 (3H, d, J = 1.1 Hz), 2.20 (3H, s), 2.21 (3H, s), 2.17-2.25 (1H, m), 2.40-2.58 (2H, m, overlapped), 3.81 (1H, d, J = 7.1 Hz), 4.17 (1H, d, J = 8.3 Hz), 4.31 (1H, d, J = 8.3 Hz), 4.48 (1H, dd, J = 10.7, 6.6 Hz), 4.91 (1H, dd, J = 9.4, 1.6 Hz), 5.07 (1H, s), 5.71 (1H, d, J = 7.1 Hz), 6.17 (1H, dt, J = 8.9, 1.3 Hz), 6.48 (1H, s), 7.44-7.58 (5H, m, Ar, overlapped), 7.64 (1H, m, Ar), 7.99 (2H, m, Ar),
8.09 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 5.5, 6.9, 10.2, 11.5, 14.3, 14.8, 21.0, 21.4, 22.5, 26.8, 36.3, 37.4, 43.5, 46.9, 53.5, 58.7, 72.1, 72.4, 75.0, 75.1, 76.6, 79.4, 80.2, 81.2, 84.3, 126.9, 128.2, 128.7, 128.8, 129.4, 130.2, 131.9, 133.9, 134.2, 139.6, 163.6, 167.2, 168.9, 169.5, 169.8, 201.8; HRFABMS m/z 900.3983 [M+H$^+$]; calcd for C$_{49}$H$_{62}$NO$_{13}$Si, 900.3990.

(7-TES-baccatin III)-13-yl 2-phenylspiro(cyclopropane-1',4-oxazoline)-5R-carboxylate (76).

$^1$H NMR (400 MHz, CDCl$_3$) δ: 0.57 (6H, m), 0.92 (9H, t, $J = 7.9$ Hz), 1.21 (3H, s), 1.25 (3H, s), 1.19-1.44 (4H, m, overlapped), 1.71 (3H, s), 1.91 (1H, m), 1.99 (3H, d, $J = 1.2$ Hz), 2.18 (3H, s), 2.19-2.29 (1H, m), 2.35 (3H, s), 2.43-2.59 (2H, m, overlapped), 3.80 (1H, d, $J = 7.0$ Hz), 4.17 (1H, d, $J = 8.3$ Hz), 4.34 (1H, d, $J = 8.3$ Hz), 4.47 (1H, dd, $J = 10.5, 6.6$ Hz), 4.98-5.00 (2H, overlapped), 5.71 (1H, d, $J = 7.0$ Hz), 6.00 (1H, dt, $J = 8.9, 1.3$ Hz), 6.42 (1H, s), 7.45-7.57 (5H, m, Ar, overlapped), 7.64 (1H, m, Ar), 8.09 (2H, m, Ar), 8.11 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 5.4, 6.9, 10.2, 10.3, 14.7, 15.3, 21.0, 21.2, 22.2, 26.9, 36.2, 37.4, 43.4, 47.1, 53.9, 58.6, 72.5, 72.7, 75.0, 75.2, 76.6, 79.3, 79.5, 81.1, 84.3, 126.9, 128.4, 128.6, 128.8, 129.4, 130.2, 131.8, 133.9, 134.0, 140.2, 163.7, 167.2, 169.32, 169.33, 169.7, 201.9; HRFABMS m/z 900.3999 [M+H$^+$]; calcd for C$_{49}$H$_{62}$NO$_{13}$Si, 900.3990.

(7-TES-baccatin III)-13-yl 2-phenylspiro(2'R-methylcyclopropane-1'R,4-oxazoline)-5S-carboxylate (84). $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.53-0.67 (6H, m), 0.95 (9H, t, $J = 8.0$ Hz), 1.20-1.30 (10H, overlapped), 1.43-1.50 (1H, m), 1.60-1.68 (1H, m), 1.71 (3H, s), 1.80 (1H, s), 1.82-1.97 (1H, m), 2.17 (3H, d, $J = 1.1$ Hz), 2.20 (3H, s), 2.22 (3H, s), 2.18-2.24 (1H, m, ...
overlapped), 2.40-2.56 (2H, overlapped), 3.82 (1H, d, J = 7.1 Hz), 4.17 (1H, d, J = 8.4 Hz), 4.31 (1H, d, J = 8.4 Hz), 4.47 (1H, dd, J = 10.5, 6.7 Hz), 4.90 (1H, dd, J = 9.4, 1.6 Hz), 5.03 (1H, s), 5.71 (1H, d, J = 7.1 Hz), 6.20 (1H, dt, J = 8.9, 1.1 Hz), 6.48 (1H, s), 7.44-7.57 (5H, m, Ar, overlapped), 7.65 (1H, m, Ar), 7.98 (2H, m, Ar), 8.10 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 5.3, 6.7, 10.1, 13.0, 15.0, 17.4, 18.4, 20.9, 21.3, 22.3, 26.6, 36.2, 37.2, 43.4, 46.7, 57.9, 58.5, 71.9, 72.3, 74.8, 75.0, 76.5, 76.7, 79.3, 81.0, 84.2, 126.8, 128.0, 128.5, 128.6, 129.2, 130.1, 131.6, 133.7, 134.0, 139.6, 162.4, 167.0, 169.3, 169.4, 201.6; HRFABMS m/z 914.4114 [M+H$^+$]; calcd for C$_{50}$H$_{64}$NO$_{13}$Si, 914.4147.

(7-TES-baccatin III)-13-yl 2-phenylspiro(2'R-isopropylcyclopropane-1'R,4-oxazoline)-5S-carboxylate (85). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.57 (6H, m), 0.92 (9H, t, J = 7.9 Hz), 0.84-0.94 (1H, m, overlapped), 1.10 (3H, d, J = 6.2 Hz), 1.12 (3H, d, J = 6.2 Hz), 1.20 (3H, s), 1.23 (3H, s), 1.18-1.26 (1H, m), 1.27-1.42 (2H, m, overlapped), 1.68 (3H, s), 1.72 (1H, s), 1.87 (1H, m), 2.11 (3H, d, J = 1.1 Hz), 2.14-2.18 (1H, m), 2.17 (3H, s), 2.18 (3H, s), 2.38-2.54 (2H, m, overlapped), 3.78 (1H, d, J = 7.1 Hz), 4.14 (1H, d, J = 8.4 Hz), 4.28 (1H, d, J = 8.4 Hz), 4.45 (1H, dd, J = 10.5, 6.7 Hz), 4.88 (1H, dd, J = 9.4, 1.5 Hz), 4.97 (1H, brs), 5.68 (1H, d, J = 7.1 Hz), 6.17 (1H, dt, J = 8.8, 1.1 Hz), 6.45 (1H, s), 7.40-7.54 (5H, m, Ar, overlapped), 7.62 (1H, m, Ar), 7.95 (2H, m, Ar), 8.07 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 5.8, 7.3, 10.3, 14.6, 16.2, 21.2, 21.3, 22.1, 22.3, 22.4, 26.8, 28.4, 32.3, 36.4, 37.5, 43.8, 47.2, 58.5, 58.7, 72.1, 72.3, 75.1, 75.3, 76.6, 79.6, 81.2, 84.4, 126.9, 128.5, 128.7, 128.9, 129.4, 130.3,
115.7, 134.0, 139.8, 162.2, 167.3, 169.6, 169.7, 169.8, 201.9; HRFABMS m/z 942.4451 [M+H⁺]; calcd for C₅₂H₆₈NO₁₃Si, 942.4460.

(7-TES-baccatin III)-13-yl 2-phenylspiro(2'S-methylcyclopropane-1'S,4-oxazoline)-5R-carboxylate (86). Colorless gum; ¹H NMR (400 MHz, CDCl₃) δ: 0.45-0.62 (6H, m), 0.80 (1H, t, J = 6.2 Hz), 0.89 (9H, t, J = 7.9 Hz), 1.15-1.25 (9H, overlapped), 1.34-1.40 (1H, m), 1.48-1.58 (1H, m), 1.68 (3H, s), 1.73 (1H, s), 1.83-1.92 (1H, m), 1.94 (3H, d, J = 1.0 Hz), 2.14 (3H, s), 2.18-2.26 (1H, m), 2.34 (3H, s), 2.46-2.56 (2H, overlapped), 2.76 (1H, d, J = 7.0 Hz), 4.14 (1H, d, J = 8.3 Hz), 4.30 (1H, d, J = 8.3 Hz), 4.43 (1H, dd, J = 10.6, 1.0 Hz), 4.94-4.98 (2H, overlapped), 5.67 (1H, d, J = 7.0 Hz), 5.85 (1H, dt, J = 8.9, 1.0 Hz), 6.37 (1H, s), 7.41-7.54 (5H, m, Ar, overlapped), 7.61 (1H, m, Ar), 8.04-8.11 (4H, m, Ar, overlapped); ¹³C NMR (100 MHz, CDCl₃) δ: 5.5, 7.0, 10.3, 13.4, 14.8, 16.9, 18.9, 21.1, 21.2, 22.1, 26.9, 36.5, 37.4, 43.4, 47.2, 58.6, 58.7, 72.5, 73.1, 75.0, 75.3, 76.0, 76.6, 79.4, 81.0, 84.4, 127.0, 128.4, 128.6, 128.8, 129.4, 130.3, 131.6, 133.9, 134.0, 140.4, 162.5, 167.2, 169.4, 169.8, 169.9, 202.0; HRFABMS m/z 914.4147 [M+H⁺]; calcd for C₅₀H₆₄NO₁₃Si, 914.4147.

(7-TES-baccatin III)-13-yl 2-phenylspiro(2'S-isopropylcyclopropane-1'S,4-oxazoline)-5R-carboxylate (87). Colorless gum; ¹H NMR (400 MHz, CDCl₃) δ: 0.53 (6H, m), 0.87 (9H, t, J = 8.0 Hz), 0.82-0.91 (1H, m, overlapped), 1.05 (3H, d, J = 6.1 Hz), 1.09 (3H, d, J = 6.1 Hz), 1.17 (3H, s), 1.21 (3H, s), 1.19-1.30 (2H, m, overlapped), 1.35 (1H, m), 1.68 (3H, s), 1.70 (1H, s), 1.87 (1H, m), 1.92 (3H, d, J = 1.1 Hz), 2.14 (3H, s), 2.17-2.25 (1H, m), 2.35 (3H, s), 2.46-2.56
(2H, m, overlapped), 3.75 (1H, d, $J = 7.1$ Hz), 4.14 (1H, d, $J = 8.4$ Hz), 4.30 (1H, d, $J = 8.4$ Hz), 4.42 (1H, dd, $J = 10.6, 6.7$ Hz), 4.92 (1H, brs), 4.96 (1H, dd, $J = 9.5, 1.6$ Hz), 5.67 (1H, d, $J = 7.1$ Hz), 5.85 (1H, dt, $J = 8.8, 1.1$ Hz), 6.37 (1H, s), 7.42-7.54 (5H, m, Ar, overlapped), 7.61 (1H, m, Ar), 8.04-8.12 (4H, m, Ar, overlapped); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 5.5, 7.0, 10.3, 14.8, 15.6, 21.1, 21.2, 22.2, 22.3, 26.9, 28.5, 32.6, 36.4, 37.4, 43.4, 47.1, 58.6, 58.8, 72.5, 73.2, 75.0, 75.2, 76.2, 76.6, 79.5, 81.0, 84.4, 127.0, 128.4, 128.6, 128.8, 129.5, 130.3, 131.7, 133.92, 133.94, 140.4, 162.4, 167.2, 169.4, 169.8, 169.9, 202.0; HRFABMS $m/z$ 942.4463 [M+H$^+$]; calcd for C$_{52}$H$_{68}$NO$_{13}$Si, 942.4460.

**General Procedure for silyl deprotection.** To a solution of (7-TES-baccatin III)-13-yl 2-phenylspiro(cyclopropane-1',4-oxazoline)-5S-carboxylate (75) (15.1 mg, 0.0106 mmol), in 0.6 mL dried THF, was added 0.1 mL anhydrous pyridine, then the solution was cooled to 0 °C, and 0.1 mL HF-pyridine was added. The reaction mixture was allowed to warm to room temperature, and stirred for overnight. The reaction mixture was then diluted with EtOAc, the organic phase was washed with sodium bicarbonate, water, and brine, dried over sodium sulfate, and concentrated in vacuum. The residue was applied to preparative TLC (50% EtOAc/hexane) to give 77 as colorless gum (12.3 mg, 97%). Compounds 78, 91, 89, 90, and 88 were prepared similarly.

(Baccatin III)-13-yl 2-phenylspiro(cyclopropane-1',4-oxazoline)-5S-carboxylate (77). $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.03 (2H, m, overlapped), 1.17 (3H, s), 1.26-1.30 (1H, m), 1.30 (3H,
s), 1.47-1.52 (1H, m), 1.69 (3H, s), 1.88 (1H, m), 2.01 (3H, d, \( J = 1.3 \) Hz), 2.12 (3H, s), 2.18-2.25 (1H, m), 2.27 (3H, s), 2.37-2.58 (2H, m, overlapped), 3.79 (1H, d, \( J = 7.1 \) Hz), 4.17 (1H, d, \( J = 8.4 \) Hz), 4.30 (1H, d, \( J = 8.4 \) Hz), 4.44 (1H, m), 4.92 (1H, dd, \( J = 7.6, 2.1 \) Hz), 5.09 (1H, s), 5.68 (1H, d, \( J = 7.1 \) Hz), 6.26 (1H, td, \( J = 8.9, 1.3 \) Hz), 6.32 (1H, s), 7.46-7.59 (5H, m, Ar, overlapped), 7.64 (1H, m, Ar), 7.99 (2H, m, Ar), 8.08 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 9.6, 11.2, 14.0, 15.1, 20.9, 22.16, 22.20, 26.9, 35.5, 36.3, 43.2, 45.5, 53.2, 58.5, 71.8, 72.1, 75.1, 75.4, 76.3, 79.6, 80.1, 80.9, 84.4, 126.7, 128.0, 128.6, 128.7, 129.1, 130.0, 131.9, 133.2, 133.8, 141.9, 163.5, 166.9, 168.7, 169.8, 171.3, 203.6; HRFABMS \( m/z \) 786.3108 [M+H\(^+\)]; calcd for C\(_{43}\)H\(_{48}\)NO\(_{13}\), 786.3126.

(Baccatin III)-13-yl 2-phenylspiro(cyclopropane-1',4-oxazoline)-5\(R\)-carboxylate (78).

Colorless gum; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 0.96 (1H, m), 1.16 (3H, s), 1.17-1.24 (1H, m), 1.28 (3H, s), 1.25-1.34 (1H, m), 1.38-1.45 (1H, m), 1.69 (3H, s), 1.88 (3H, d, \( J = 1.3 \) Hz), 1.85-1.93 (1H, m, overlapped), 2.20-2.30 (1H, m, overlapped), 2.24 (3H, s), 2.31 (3H, s), 2.40-2.60 (2H, m, overlapped), 3.79 (1H, d, \( J = 7.1 \) Hz), 4.18 (1H, d, \( J = 8.3 \) Hz), 4.32 (1H, d, \( J = 8.3 \) Hz), 4.42 (1H, m), 4.99 (1H, dd, \( J = 7.6, 2.0 \) Hz), 5.02 (1H, s), 5.69 (1H, d, \( J = 7.1 \) Hz), 6.08 (1H, dt, \( J = 8.9, 1.3 \) Hz), 6.27 (1H, s), 7.46-7.60 (5H, m, Ar, overlapped), 7.64 (1H, m, Ar), 8.04 (2H, m, Ar), 8.08 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 9.6, 10.3, 15.00, 15.04, 20.8, 21.9, 22.0, 26.9, 35.5, 36.2, 43.2, 45.6, 53.7, 58.5, 72.1, 72.4, 75.0, 75.5, 76.4, 79.5, 80.9, 84.4, 126.7, 128.1, 128.6, 128.7, 129.1, 130.1, 131.8, 133.1, 133.8, 142.3, 163.5, 167.0, 169.0, 169.6, 171.2, 203.7; HRFABMS \( m/z \) 786.3115 [M+H\(^+\)]; calcd for C\(_{43}\)H\(_{48}\)NO\(_{13}\), 786.3126.

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(Baccatin III)-13-yl 2-phenylspiro(2'R-methylcyclopropane-1'R,4-oxazoline)-5S-carboxylate (88). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.57 (1H, t, $J = 6.3$ Hz), 1.18 (3H, s), 1.26 (3H, d, $J = 6.3$ Hz), 1.32 (3H, s), 1.42-1.47 (1H, m), 1.60-1.69 (1H, m), 1.69 (3H, s), 1.83-1.92 (2H, overlapped), 2.04 (3H, d, $J = 1.3$ Hz), 2.13 (3H, s), 2.16-2.24 (1H, m), 2.28 (3H, s), 2.39-2.47 (1H, m), 2.49-2.58 (2H, overlapped), 3.79 (1H, d, $J = 7.1$ Hz), 4.18 (1H, d, $J = 8.4$ Hz), 4.30 (1H, d, $J = 8.4$ Hz), 4.44 (1H, m), 4.91 (1H, dd, $J = 9.5, 1.9$ Hz), 5.05 (1H, s), 5.69 (1H, $J = 7.1$ Hz), 6.29 (1H, dt, $J = 8.8, 1.3$ Hz), 6.32 (1H, s), 7.47-7.59 (5H, m, Ar, overlapped), 7.66 (1H, m, Ar), 7.98 (2H, m, Ar), 8.08 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.6, 12.8, 15.4, 17.3, 18.4, 20.9, 22.2, 22.3, 26.9, 35.5, 36.4, 43.3, 45.5, 57.8, 58.5, 71.7, 72.1, 75.1, 75.4, 76.3, 76.8, 79.8, 80.9, 84.4, 126.7, 127.9, 128.6, 128.7, 129.1, 130.0, 131.8, 133.1, 133.8, 142.0, 162.4, 166.9, 169.3, 169.8, 171.3, 203.6; HRFABMS m/z 800.3292 [M+H$^+$]; calcd for C$_{44}$H$_{50}$NO$_{13}$, 800.3282.

(Baccatin III)-13-yl 2-phenylspiro(2'R-isopropylcyclopropane-1'R,4-oxazoline)-5S-carboxylate (89). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.57 (1H, m), 1.09 (3H, d, $J = 6.2$ Hz), 1.10 (3H, d, $J = 6.2$ Hz), 1.14 (3H, s), 1.21-1.29 (1H, m, overlapped), 1.28 (3H, s), 1.30-1.41 (2H, m, overlapped), 1.66 (3H, s), 1.79 (1H, s), 1.80-1.89 (1H, m), 1.98 (3H, d, $J = 1.2$ Hz), 2.10 (3H, s0, 2.11-2.21 (1H, m), 2.24 (3H, s), 2.37-2.55 (3H, overlapped), 3.76 (1H, d, $J = 7.1$ Hz), 4.14 (1H, d, $J = 8.5$ Hz), 4.27 (1H, d, $J = 8.5$ Hz), 4.40 (1H, m), 4.89 (1H, dd, $J = 9.6, 2.1$ Hz), 4.99 (1H, brs), 5.66 (1H, d, $J = 7.1$ Hz), 6.23 (1H, dt, $J = 8.9, 1.2$ Hz), 6.29 (1H, s), 7.43-7.55 (5H, m,
Ar, overlapped), 7.62 (1H, m, Ar), 7.95 (2H, m, Ar), 8.05 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 9.8, 15.6, 16.3, 21.1, 22.2, 22.36, 22.44, 22.45, 27.1, 28.3, 32.1, 35.7, 36.6, 43.5, 45.7, 58.3, 58.7, 72.0, 72.3, 75.3, 75.6, 76.6, 77.1, 79.9, 81.1, 84.6, 126.9, 128.2, 128.8, 128.9, 129.3, 130.3, 133.3, 134.0, 142.1, 162.4, 167.2, 169.5, 169.9, 171.5, 203.8; HRFABMS $m/z$ 828.3604 [M+H$^+$]; calcd for $\text{C}_{46}\text{H}_{54}\text{NO}_{13}$, 828.3595.

(Baccatin III)-13-yl 2-phenylspiro(2'S-methylcyclopropane-1'S,4-oxazoline)-5$R$-carboxylate (90). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 0.78 (1H, t, $J = 6.2$ Hz), 1.17 (3H, s), 1.23 (3H, d, $J = 6.2$ Hz), 1.29 (3H, s), 1.40-1.45 (1H, m), 1.54-1.62 (1H, m), 1.70 (3H, s), 1.79 (1H, s), 1.87 (3H, d, $J = 1.2$ Hz), 1.82-1.97 (1H, m, overlapped), 2.21-2.29 (1H, m), 2.35 (3H, s), 2.33 (3H, s), 2.48-2.62 (3H, overlapped), 3.79 (1H, d, $J = 7.1$ Hz), 4.19 (1H, d, $J = 8.3$ Hz), 4.33 (1H, d, $J = 8.3$ Hz), 4.43 (1H, m), 4.97-5.03 (2H, overlapped), 5.70 (1H, d, $J = 7.1$ Hz), 6.00 (1H, dt, $J = 8.8$, 1.2 Hz), 6.27 (1H, s), 7.48-7.55 (4H, m, Ar, overlapped), 7.56-7.68 (2H, m, Ar, overlapped), 8.04-8.12 (4H, m, Ar, overlapped); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 9.6, 13.1, 15.0, 16.9, 18.7, 20.8, 21.9, 22.0, 27.0, 35.5, 36.4, 43.1, 45.6, 58.3, 58.5, 72.1, 72.8, 75.1, 75.5, 76.1, 76.4, 79.6, 80.8, 84.4, 126.8, 128.0, 128.6, 128.7, 129.2, 130.1, 131.7, 133.0, 133.8, 142.5, 162.3, 167.0, 169.6, 169.8, 171.2, 203.8; HRFABMS $m/z$ 800.3292 [M+H$^+$]; calcd for $\text{C}_{44}\text{H}_{56}\text{NO}_{13}$, 800.3282.

(Baccatin III)-13-yl 2-phenylspiro(2'S-isopropylcyclopropane-1'S,4-oxazoline)-5$R$-carboxylate (91). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 0.77 (1H, t, $J = 5.9$ Hz), 1.06 (3H, d, $J =
6.2 Hz), 1.09 (3H, d, J = 6.2 Hz), 1.13 (3H, s), 1.25 (3H, s), 1.19-1.32 (2H, m, overlapped), 1.33-1.38 (1H, m), 1.66 (3H, s), 1.75 (1H, s), 1.82 (3H, d, J = 1.2 Hz), 1.82-1.90 (1H, m), 2.17-2.25 (1H, m), 2.21 (3H, s), 2.30 (3H, s), 2.44-2.58 (3H, overlapped), 3.74 (1H, d, J = 7.1 Hz), 4.15 (1H, d, J = 8.4 Hz), 4.29 (1H, d, J = 8.4 Hz), 4.39 (1H, m), 4.94-4.98 (2H, overlapped), 5.66 (1H, d, J = 7.1 Hz), 5.96 (1H, dt, J = 8.8, 1.2 Hz), 6.22 (1H, s), 7.44-7.51 (4H, m, Ar, overlapped), 7.55 (1H, m, Ar), 7.62 (1H, m, Ar), 8.00-8.08 (4H, m, Ar, overlapped); \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \(\delta\): 9.8, 15.2, 15.8, 21.0, 21.13, 21.19, 22.19, 22.27, 22.29, 27.2, 28.5, 32.5, 35.7, 36.6, 43.3, 45.8, 58.7, 58.8, 72.3, 73.6, 75.2, 75.7, 76.4, 76.6, 79.9, 81.0, 84.6, 126.9, 128.3, 128.8, 128.9, 129.4, 130.3, 131.9, 133.2, 134.0, 142.7, 162.4, 167.2, 169.87, 169.90, 171.4, 204.0; HRFABMS \(m/z\) 828.3571 [M+H\(^+\)]; calcd for C\(_{46}\)H\(_{54}\)NO\(_{13}\), 828.3595.

**General Procedure for Hydrolysis of the Oxazoline Ring.** To a solution of compound (Baccatin III)-13-yl 2-phenylspiro(cyclopropane-1’,4-oxazoline)-5S-carboxylate (77) (25 mg, 0.032 mmol) in 5 mL 1,4-dioxane was added HCl (0.1N, 5 ml) and stirring was continued at 50°C for 1 h. TLC showed that all the starting material was consumed, and a much more polar compound was formed. Then, 84 mg of NaHCO\(_3\) powder was added at room temperature. The reaction was allowed to stir overnight until TLC showed the highly polar intermediate was converted to two less polar compounds. The reaction mixture was diluted with EtOAc (20 mL), and then washed with water, brine, and dried with sodium sulfate. The organic phase was concentrated in vacuum, and the residue was applied to PTLC (50% EtOAc/hexane) to give 80 (7.7 mg, 48%) and 79 (5.1 mg, 32%) both as colorless gum. Compounds 69, 81, 71, 95, 94, 70,
93 and 92 were prepared in similar procedure. All the optical rotation data were measured in chloroform.

3'-Desphenyl-3',3'-ethylene-2'-epi-taxol (80). Colorless gum; $[\alpha]_{D}^{20}=-60^\circ$ (c 0.23); $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.14 (3H, s), 1.24 (3H, s), 1.05–1.40 (4H, m), 1.68 (3H, s), 1.88 (1H, m), 2.12 (3H, d, $J = 1.1$ Hz), 2.15–2.35 (2H, m), 2.24 (3H, s), 2.28 (3H, s), 2.51–2.61 (1H, m), 3.68 (1H, s), 3.84 (1H, d, $J = 7.1$ Hz), 4.16 (1H, d, $J = 8.3$ Hz), 4.29 (1H, d, $J = 8.3$ Hz), 4.45 (1H, dd, $J = 10.7$, 6.6 Hz), 4.96 (1H, dd, $J = 7.7$, 1.8 Hz), 5.66 (1H, d, $J = 7.1$ Hz), 6.15 (1H, td, $J = 8.9$, 1.3 Hz), 6.34 (1H, s), 6.66 (1H, s), 7.33–7.52 (5H, m), 7.61 (1H, m), 7.67 (2H, m), 8.05 (2H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.7, 13.7, 14.7, 15.9, 21.1, 21.9, 22.8, 26.9, 35.8, 36.3, 36.8, 43.3, 46.0, 58.8, 72.0, 72.5, 75.1, 75.9, 76.6, 77.3, 79.6, 81.2, 84.6, 127.2, 128.93, 128.94, 129.3, 130.3, 132.5, 132.8, 133.4, 143.0, 143.0, 167.2, 170.3, 170.4, 171.5, 172.3, 204.0; HRFABMS m/z 804.3197 [M+H$^+$]; calcd for C$_{43}$H$_{50}$NO$_{14}$, 804.3231.

3'-Desphenyl-3',3'-ethylene-2',7-epi-taxol (79). Colorless gum; $[\alpha]_{D}^{20}=-56^\circ$ (c 0.41); $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.14 (3H, s), 1.17 (3H, s), 1.07–1.31 (4H, m), 1.65 (3H, s), 1.65–1.75 (1H, m), 2.00 (3H, d, $J = 1.3$ Hz), 2.19 (3H, s), 2.20–2.39 (3H, m), 2.39 (3H, s), 3.66–3.73 (1H, m), 3.72 (1H, s), 3.94 (1H, d, $J = 7.4$ Hz), 4.33 (1H, d, $J = 8.6$ Hz), 4.38 (1H, d, $J = 8.6$ Hz), 4.70 (1H, d, $J = 10.3$ Hz), 4.92 (1H, dd, $J = 5.7$, 3.3 Hz), 5.73 (1H, d, $J = 7.4$ Hz), 6.11 (1H, td, $J = 8.9$, 1.5 Hz), 6.71 (1H, s), 6.83 (1H, s), 7.32–7.52 (5H, m), 7.62 (1H, m), 7.68 (2H, m), 8.06 (2H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 14.0, 14.6, 15.9, 16.4, 21.1, 21.3, 22.7, 26.2, 35.6, 36.6, 37.0,
3’-Desphenyl-3’,3’-ethylenetaxol (69). Colorless gum; [α]$_D^{20}$ = -68° (c 0.30); $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.15 (3H, s), 1.27 (3H, s), 1.07–1.35 (4H, m), 1.69 (3H, s), 1.79 (3H, d, J = 1.3 Hz), 1.88 (1H, m), 2.23 (3H, s), 2.25–2.38 (2H, m), 2.46 (3H, s), 2.57 (1H, m), 3.82 (1H, d, J = 7.1 Hz), 3.91 (1H, s), 4.18 (1H, d, J = 8.5 Hz) 4.33 (1H, d, J = 8.5 Hz), 4.44 (1H, dd, J = 10.8, 6.7 Hz), 4.99 (1H, dd, J = 7.5, 2.1 Hz), 5.68 (1H, d, J = 7.1 Hz), 6.24 (1H, td, J = 9.2, 1.5 Hz), 6.25 (1H, s 6.83), 1H (s), 7.44–7.60 (5H, m), 7.64 (1H, m), 7.74 (2H, m), 8.10 (2H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.6, 13.6, 14.3, 14.8, 20.9, 22.01, 22.04, 26.7, 35.5, 35.9, 37.2, 43.2, 45.6, 58.5, 71.0, 72.1, 75.1, 75.6, 76.4, 77.9, 79.5, 80.7, 84.5, 127.2, 128.7, 128.9, 129.2, 129.3, 130.1, 132.59, 132.60, 132.7, 132.8, 133.8, 142.8, 167.0, 170.6, 170.8, 171.2, 172.3, 203.8, 207.4; HRFABMS m/z 804.3239 [M+H$^+$]; calcd for C$_{43}$H$_{50}$NO$_{14}$, 804.3231.

3’-Desphenyl-3’,3’-ethylene-7-epi-taxol (81). Colorless gum; [α]$_D^{20}$ = -70° (c 0.24); $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.16 (3H, s), 1.22 (3H, s), 1.08–1.37 (4H, m) 1.66 (3H, s), 1.71 (3H, d, J = 1.4 Hz), 2.18 (3H, s), 2.23–2.41 (3H, m), 2.57 (3H, s), 3.69 (1H, m), 3.89 (1H, s), 3.92 (1H, d, J = 7.5 Hz), 4.35 (1H, d, J = 8.5 Hz), 4.41 (1H, d, J = 8.5 Hz), 4.78 (1H, d, J = 11.7 Hz), 4.96 (1H, dd, J = 5.7, 3.4 Hz), 5.76 (1H, d, J = 7.5 Hz), 6.21 (1H, td, J = 9.0, 1.4 Hz), 6.74 (1H, s) 6.80 (1H, s) 7.44–7.60 (5H, m) 7.65 (1H, m), 7.73 (2H, m), 8.12 (2H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) δ:
3’-Desphenyl-3’,3’-(1S-isopropylethylene)-3’S-taxol (71). Colorless gum; [$\alpha$]$_D$ 20° = -66° (c 0.66); $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.89 (1H, m), 1.07 (3H, d, $J = 6.2$ Hz), 1.10 (3H, s), 1.04-1.12 (1H, m, overlapped), 1.15-1.20 (1H, m), 1.23 (3H, s), 1.32-1.42 (4H, overlapped), 1.65 (3H, s), 1.70 (1H, s), 1.71 (3H, d, $J = 1.1$ Hz), 1.80-1.88 (1H, m), 2.19 (3H, s), 2.20-2.38 (2H, m, overlapped), 2.43 (3H, s), 2.27-2.57 (1H, m), 3.77 (1H, d, $J = 7.1$ Hz), 4.06 (1H, s), 4.15 (1H, d, $J = 8.3$ Hz), 4.29 (1H, d, $J = 8.3$ Hz), 4.39 (1H, dd, $J = 10.9, 6.6$ Hz), 4.95 (1H, d, $J = 9.6, 1.9$ Hz), 5.64 (1H, d, $J = 7.1$ Hz), 6.18 (1H, s), 6.20 (1H, dt, $J = 9.0, 1.1$ Hz), 6.79 (1H, s), 7.40-7.64 (6H, m, Ar, overlapped), 7.71 (2H, m, Ar), 8.07 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.6, 14.7, 19.3, 20.9, 22.0, 22.2, 22.6, 23.1, 26.7, 29.6, 35.5, 35.9, 36.5, 41.5, 43.2, 45.6, 58.5, 71.0, 72.0, 75.2, 75.6, 76.1, 76.4, 79.6, 80.6, 84.5, 127.2, 128.7, 128.9, 129.2, 130.1, 132.5, 133.7, 142.9, 167.0, 170.5, 171.18, 171.24, 172.9, 203.9; HRFABMS m/z 846.3708 [M+H$^+$]; calcd for C$_{46}$H$_{56}$NO$_{14}$, 846.3701.

3’-Desphenyl-3’,3’-(1R-isopropylethylene)-3’R-2’,7-epi-taxol (95). Colorless gum; [$\alpha$]$_D$ 20° = -58° (c 0.17); $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.94 (1H, m), 1.11 (3H, d, $J = 6.1$ Hz), 1.13 (3H, s), 1.08-1.14 (1H, m, overlapped), 1.16 (3H, s), 1.20-1.26 (1H, m), 1.32-1.42 (4H, overlapped), 1.62
(1H, s), 1.65 (3H, s), 1.98 (3H, d, J = 1.0 Hz), 2.10-2.45 (4H, overlapped), 2.19 (3H, s), 2.40 (3H, s), 3.69 (1H, m), 3.94 (1H, d, J = 7.6 Hz), 3.98 (1H, s), 4.33 (1H, d, J = 8.7 Hz), 4.38 (1H, d, J = 8.7 Hz), 4.93 (1H, dd, J = 9.1, 3.4 Hz), 5.72 (1H, d, J = 7.6 Hz), 6.13 (1H, dt, J = 8.8, 1.0 Hz), 6.67 (1H, s), 6.82 (1H, s), 7.36 (2H, m, Ar), 7.44-7.51 (3H, m, Ar, overlapped), 7.62 (1H, m, Ar), 7.68 (2H, m, Ar), 8.05 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 15.9, 16.3, 19.1, 21.1, 21.3, 22.77, 22.82, 23.1, 26.1, 29.8, 35.6, 36.6, 36.8, 40.6, 41.0, 42.8, 57.8, 71.2, 75.1, 75.4, 75.9, 77.8, 78.4, 79.5, 82.3, 82.9, 127.3, 128.95, 128.98, 129.4, 130.2, 132.6, 133.2, 134.0, 140.4, 167.2, 169.6, 171.1, 172.3, 172.5, 207.5; HRFABMS m/z 846.3725 [M+H$^+$]; calcd for C$_{46}$H$_{56}$NO$_{14}$, 846.3701.

3'-Desphenyl-3',3'-(1R-isopropylethylene)-3'R-2'-epi-taxol (94). Colorless gum; [α]$_D^{20}=-74^\circ$
(c 0.54); $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.98-1.16 (8H, overlapped), 1.23 (3H, s), 1.27-1.39 (5H, overlapped), 1.88 (1H, m), 2.10 (3H, d, J = 1.1 Hz), 2.15-2.33 (2H, m, overlapped), 2.23 (3H, s), 2.30 (3H, s), 2.56 (1H, m), 3.84 (1H, d, J = 7.1 Hz), 3.95 (1H, d, J = 5.5 Hz), 4.16 (1H, d, J = 8.3 Hz), 4.28 (1H, d, J = 8.3 Hz), 4.45 (1H, d, J = 10.8, 6.8 Hz), 4.96 (1H, d, J = 9.5, 1.9 Hz), 5.17 (1H, d, J = 6.1 Hz), 5.65 (1H, d, J = 7.1 Hz), 6.16 (1H, dt, J = 8.9, 1.1 Hz), 6.33 (1H, s), 6.60 (1H, s), 7.36 (2H, m, Ar), 7.42-7.52 (3H, m, Ar, overlapped), 7.60 (1H, m, Ar), 7.67 (2H, m, Ar), 8.04 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.7, 15.9, 18.8, 21.1, 22.0, 22.8, 22.9, 23.0, 26.9, 29.8, 35.8, 36.3, 36.5, 40.8, 43.3, 46.0, 58.8, 71.8, 72.5, 74.3, 75.1, 75.9, 76.6, 79.6, 81.3, 84.6, 127.3, 128.91, 128.92, 129.3, 130.2, 132.5, 132.7, 133.5, 134.0, 143.0, 167.1, 170.3, 170.5, 171.5, 172.9, 204.0; HRFABMS m/z 846.3725 [M+H$^+$]; calcd for C$_{46}$H$_{56}$NO$_{14}$, 846.3701.
3'-Desphenyl-3',3'-(1S-methylethylene)-3'S-taxol (70). Colorless gum; \([\alpha]_D^{20}=-57^\circ (c\ 0.43);\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 0.93 (1H, t, \(J = 6.1\) Hz), 1.11 (3H, s), 1.20-1.26 (4H, overlapped), 1.33-1.41 (1H, m), 1.43 (3H, d, \(J = 6.1\) Hz), 1.65 (3H, s), 1.71 (3H, d, \(J = 1.3\) Hz), 1.79 (1H, s), 1.80-1.89 (1H, m), 2.19 (3H, s), 2.21-2.36 (2H, m, overlapped), 2.43 (1H, d, \(J = 4.2\) Hz), 2.45 (3H, s), 2.48-2.58 (1H, m), 3.78 (1H, d, \(J = 7.1\) Hz), 4.08 (1H, d, \(J = 7.1\) Hz), 4.15 (1H, d, \(J = 8.5\) Hz), 4.30 (1H, d, \(J = 8.5\) Hz), 4.40 (1H, m), 4.96 (1H, dd, \(J = 9.6, 2.0\) Hz), 5.65 (1H, d, \(J = 7.1\) Hz), 5.94 (1H, d, \(J = 7.1\) Hz), 6.19 (1H, s), 6.22 (1H, dt, \(J = 8.9, 1.3\) Hz), 6.75 (1H, s), 7.42-7.64 (6H, m, Ar, overlapped), 7.71 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 9.8, 14.9, 15.0, 21.1, 22.0, 22.2, 22.3, 22.4, 27.0, 35.7, 36.1, 40.9, 43.4, 45.8, 58.6, 71.2, 72.3, 75.4, 75.8, 76.4, 76.6, 79.8, 80.8, 84.7, 127.4, 128.9, 127.1, 129.4, 130.3, 132.7, 132.8, 132.9, 134.0, 143.1, 167.2, 170.8, 171.4, 171.5, 173.0, 204.1; HRFABMS \(m/z\) 818.3392 [M+H\(^+\)]; calcd for C\(_{44}\)H\(_{52}\)NO\(_{14}\), 818.3388.

3'-Desphenyl-3',3'-(1R-methylethylene)-3'R-2',7-epi-taxol (93). Colorless gum; \([\alpha]_D^{20}=-58^\circ (c\ 0.29);\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.02 (1H, t, \(J = 6.1\) Hz), 1.17 (3H, s), 1.20 (3H, s), 1.28-1.33 (1H, m), 1.39-1.47 (1H, m), 1.47 (3H, d, \(J = 5.7\) Hz), 1.68 (3H, s), 1.74 (1H, s), 2.02 (3H, d, \(J = 1.3\) Hz), 2.22 (3H, s), 2.24-2.42 (4H, overlapped), 2.45 (3H, s), 3.73 (1H, m), 3.98 (1H, d, \(J = 7.4\) Hz), 4.03 (1H, d, \(J = 6.7\) Hz), 4.34 (1H, d, \(J = 8.7\) Hz), 4.41 (1H, d, \(J = 8.7\) Hz), 4.74 (1H, d, \(J = 11.6\) Hz), 4.96 (1H, dd, \(J = 8.9, 3.3\) Hz), 5.68 (1H, d, \(J = 6.7\) Hz), 5.76 (1H, d, \(J = 7.4\) Hz), 6.16 (1H, dt, \(J = 8.7, 1.3\) Hz), 6.69 (1H, s), 6.87 (1H, s), 7.39 (2H, m, Ar), 7.48-7.54
(3H, m, Ar, overlapped), 7.66 (1H, m, Ar), 7.71 (2H, m, Ar), 8.09 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 14.5, 15.7, 16.1, 20.9, 21.1, 21.3, 22.2, 22.6, 26.0, 35.4, 36.5, 40.1, 40.4, 42.6, 57.6, 71.0, 75.0, 75.2, 75.7, 77.6, 78.2, 79.3, 82.1, 82.7, 127.1, 128.76, 128.78, 129.2, 130.0, 132.4, 132.9, 133.1, 133.8, 140.2, 167.0, 169.4, 171.0, 172.1, 172.2, 207.3; HRFABMS m/z 818.3405 [M+H$^+$]; calcd for C$_{44}$H$_{52}$NO$_{14}$, 818.3388.

3'-Desphenyl-3',3'-(1R-methylethylene)-3'R-2'-epi-taxol (92). Colorless gum; $[\alpha]_D^{20}$ = -76° (c 0.61); $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.07 (1H, m), 1.16 (3H, s), 1.26 (3H, s), 1.34-1.47 (5H, overlapped), 1.71 (3H, s), 1.78 (1H, s), 1.87-1.96 (1H, m), 2.14 (3H, d, $J$ = 1.2 Hz), 2.19-2.26 (1H, m), 2.27 (3H, s), 2.29-2.36 (1H, m, overlapped)), 2.35 (3H, s), 2.54-2.64 (2H, overlapped), 3.87 (1H, d, $J$ = 7.1 Hz), 4.00 (1H, brs), 4.19 (1H, d, $J$ = 8.4 Hz), 4.32 (1H, d, $J$ = 8.4 Hz), 4.48 (1H, m), 4.99 (1H, dd, $J$ = 9.4, 1.8 Hz), 5.17 (1H, brs), 5.68 (1H, d, $J$ = 7.1 Hz), 6.18 (1H, dt, $J$ = 8.9, 1.2 Hz), 6.37 (1H, s), 6.68 (1H, s), 7.39 (2H, m, Ar), 7.46-7.54 (3H, m, Ar), 7.64 (1H, m, Ar), 7.69 (2H, m, Ar), 8.07 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.5, 14.4, 15.7, 20.9, 21.0, 21.8, 22.6, 26.7, 35.6, 36.2, 39.9, 43.1, 45.8, 58.6, 71.6, 72.3, 74.2, 74.9, 75.7, 76.4, 79.4, 81.0, 84.4, 127.0, 128.71, 128.73, 129.1, 130.0, 132.3, 132.6, 133.2, 133.8, 142.8, 166.9, 170.0, 170.4, 171.3, 172.6, 203.8; HRFABMS m/z 818.3392 [M+H$^+$]; calcd for C$_{44}$H$_{52}$NO$_{14}$, 818.3388.

General procedure for acylation of 4-deacetylbbacattins at C-4. To a solution of 1-DMS-7,10,13-triTES-4-deacetyl-10-deacetylbbacatin III 113$^{70}$ (610 mg, 0.676 mmol) in dried THF (5.5 mL) at 0 °C was added 1M LHMDS (0.81 mL, 0.81 mmol), then the solution was
stirred for 0.5 h before 5-hexenoyl chloride (0.879 mmol in 0.5 mL THF) was added. The reaction mixture was allowed to stir at 0 °C for 2.5 h, and then quenched with saturated NH₄Cl. After diluted with EtOAc, the organic phase was washed with water, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was applied to preparative TLC (30% EtOAc/hexane) to give 115 as colorless gum (350 mg, 67%) and recover 113 (140 mg, 23%). Compounds 114, 116, 117, and 118 were prepared similarly.

1-DMS-7,10,13-triTES-4-deacetyl-4-(5-hexenoyl)-10-deacetylbaccatin III (115). ¹H NMR (400 MHz, CDCl₃) δ: -0.28 (3H, d, J = 2.8 Hz), 0.08 (3H, d, J = 2.8 Hz), 0.57-0.78 (18H, overlapped), 0.96-1.09 (27H, overlapped), 1.13 (3H, s), 1.21 (3H, s), 1.60 (1H, s), 1.68 (3H, s), 1.86-1.98 (3H, overlapped), 1.99 (3H, d, J = 1.2 Hz), 2.19-2.40 (4H, overlapped), 2.49-2.70 (3H, overlapped), 3.85 (1H, d, J = 6.9 Hz), 4.24 (1H, d, J = 8.3 Hz), 4.27 (1H, d, J = 8.3 Hz), 4.41 (1H, J = 10.6, 6.6 Hz), 4.91 (1H, dd, J = 9.6, 2.0 Hz), 4.99 (1H, t, J = 8.4 Hz), 5.08-5.17 (2H, overlapped), 5.18 (1H, s), 5.74 (1H, d, J = 6.9 Hz), 5.84-5.95 (1H, m), 7.44-7.50 (2H, m, Ar), 7.56-7.62 (1H, m, Ar), 8.11-8.16 (2H, m, Ar); ¹³C NMR (100 MHz, CDCl₃) δ: 0.2, 0.6, 5.0, 5.4, 6.2, 7.1, 7.2, 10.6, 14.6, 21.7, 24.7, 27.6, 33.5, 35.2, 37.6, 39.5, 44.3, 46.8, 58.4, 68.6, 72.9, 75.9, 76.1, 76.9, 81.2, 82.3, 84.4, 115.9, 128.5, 130.3, 130.7, 133.3, 136.2, 137.6, 138.8, 165.5, 172.3, 205.7; HRFABMS m/z 1021.5504 [M+H⁺]; calcd for C₅₃H₉₀O₁₀Si₄Na, 1021.5509.

General procedures for deprotection of silyl groups. To a solution of 1-DMS-7,10,13-triTES-4-deacetyl-4-(5-hexenoyl)-10-deacetylbaccatin III 115 (350 mg, 0.34
mmol) in dried THF (10 mL) was added anhydrous pyridine (2.0 mL), then the solution was cooled to 0 °C, and HF-pyridine (2.0 mL) was added. The reaction mixture was allowed to warm to room temperature, and stirred for overnight. The reaction mixture was diluted with EtOAc (100 mL), and the organic phase was washed with sodium bicarbonate, water, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was applied to preparative TLC (60% EtOAc/hexane) to give 120 as colorless gum (184 mg, 88%). Compounds 119, 121, 122, and 123 were prepared similarly.

4-Deacetyl-4-(5-hexenoyl)-10-deacetylbaccatin III (120). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.08 (6H, s), 1.73 (3H, s), 1.78-1.90 (3H, m, overlapped), 2.05 (3H, s), 2.15-2.43 (6H, overlapped), 2.53-2.70 (3H, overlapped), 3.98 (1H, d, \(J = 7.1\) Hz), 4.18 (1H, d, \(J = 8.3\) Hz), 4.25-4.36 (3H, overlapped), 4.70-4.87 (1H, m), 4.94 (1H, dd, \(J = 9.3, 1.5\) Hz), 5.05-5.15 (2H, overlapped), 5.26 (1H, s), 5.61 (1H, d, \(J = 7.1\) Hz), 5.81-5.92 (1H, m), 7.45-7.52 (2H, m, Ar), 7.58-7.64 (1H, m, Ar), 8.08-8.14 (2H, m, Ar); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 9.9, 15.2, 19.9, 23.8, 26.8, 33.2, 34.7, 37.0, 38.9, 42.8, 47.2, 57.8, 67.8, 72.1, 75.0, 75.1, 76.8, 79.0, 80.8, 84.5, 115.7, 128.7, 129.5, 130.2, 133.8, 134.7, 137.8, 167.2, 173.3, 211.7; HRFABMS \(m/z\) 599.2886 [M+H\(^+\)]; calcd for C\(_{33}\)H\(_{43}\)O\(_10\), 599.2856.

4-Deacetyl-4-(5-benzyloxycarbonylpentanoyl)-10-deacetylbaccatin III (121). Colorless gum; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.09 (6H, s), 1.69 -1.90 (9H, overlapped), 2.04 (3H, d, \(J = 1.0\) Hz), 2.17-2.33 (3H, overlapped), 2.41-2.64 (4H, overlapped), 2.68-2.88 (2H, overlapped), 3.99
(1H, d, \(J = 7.1\) Hz), 4.19 (1H, d, \(J = 8.5\) Hz), 4.27-4.36 (3H, overlapped), 4.81 (1H, dd, \(J = 9.3, 1.6\) Hz), 5.16 (2H, s), 5.27 (1H, d, \(J = 1.7\) Hz), 5.64 (1H, d, \(J = 7.1\) Hz), 7.32-7.42 (5H, m, Ar, overlapped), 7.46-7.53 (2H, m, Ar), 7.58-7.65 (1H, m, Ar), 8.10-8.15 (2H, m, Ar);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 9.8, 15.1, 19.8, 23.5, 24.2, 26.7, 33.8, 34.4, 36.9, 38.8, 42.6, 47.1, 57.7, 66.5, 67.6, 72.0, 74.9, 75.0, 76.6, 78.9, 80.7, 84.4, 128.2, 128.4, 128.6, 128.7, 129.4, 130.1, 133.6, 134.5, 135.8, 142.8, 167.1, 172.8, 173.7, 211.7; HRFABMS \(m/z\) 721.3218 [M+H\(^+\)]; calcd for C\(_{40}\)H\(_{49}\)O\(_2\), 721.3224.

4-Deacetyl-4-(6-benzyloxycarbonylhexanoyl)-10-deacetylbaccatin III (122). Colorless gum;

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.05 (6H, s), 1.34-1.51 (2H, m), 1.63-1.76 (7H, overlapped), 1.77-1.87 (2H, overlapped), 2.01 (3H, d, \(J = 1.0\) Hz), 2.12-2.30 (2H, overlapped), 2.37-2.45 (3H, overlapped), 2.46-2.59 (2H, overlapped), 2.61-2.70 (1H, m), 2.77 (1H, d, \(J = 4.8\) Hz), 3.94 (1H, d, \(J = 7.1\) Hz), 4.15 (1H, d, \(J = 8.3\) Hz), 4.23-4.33 (3H, overlapped), 4.76 (1H, m), 4.91 (1H, dd, \(J = 9.3, 1.5\) Hz), 5.11 (2H, s), 5.23 (1H, d, \(J = 1.5\) Hz), 5.59 (1H, d, \(J = 7.1\) Hz), 7.28-7.40 (5H, m, Ar, overlapped), 7.42-7.49 (2H, m, Ar), 7.54-7.60 (1H, m, Ar), 8.06-8.11 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 10.1, 15.3, 20.1, 23.9, 24.7, 26.9, 28.5, 34.2, 34.8, 37.0, 39.0, 42.8, 47.2, 57.9, 66.6, 67.7, 72.2, 75.2, 76.8, 79.1, 80.8, 84.6, 128.4, 128.5, 128.8, 129.6, 130.3, 133.9, 134.6, 136.0, 143.2, 167.2, 173.3, 174.2, 211.9; HRFABMS \(m/z\) 735.3356 [M+H\(^+\)]; calcd for C\(_{41}\)H\(_{51}\)O\(_2\), 735.3381.

4-Deacetyl-4-(7-benzyloxycarbonylheptanoyl)-10-deacetylbaccatin III (123). Colorless gum;
$^1$H NMR (400 MHz, CDCl$_3$) δ: 1.08 (6H, s), 1.36-1.50 (4H, overlapped), 1.65-1.78 (7H, overlapped), 1.79-1.85 (1H, m), 1.91 (1H, s), 2.05 (3H, s), 2.17-2.32 (2H, overlapped), 2.41 (2H, t, $J = 7.3$ Hz), 2.49-2.71 (4H, overlapped), 2.88 (1H, m), 3.98 (1H, d, $J = 7.1$ Hz), 4.18 (1H, d, $J = 8.3$ Hz), 4.26-4.38 (3H, overlapped), 4.82 (1H, m), 4.94 (1H, dd, $J = 9.4$, 1.5 Hz), 5.13 (2H, s), 5.27 (1H, s), 5.62 (1H, d, $J = 7.1$ Hz), 7.30-7.41 (5H, m, Ar, overlapped), 7.45-7.51 (2H, m, Ar), 7.57-7.63 (1H, m, Ar), 8.09-8.14 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.8, 15.0, 19.9, 23.9, 24.5, 26.7, 28.5, 28.6, 34.1, 34.9, 36.8, 38.9, 42.6, 47.0, 57.7, 66.3, 67.5, 72.0, 74.9, 75.0, 76.6, 78.9, 80.6, 84.5, 128.2, 128.3, 128.6, 129.5, 130.1, 133.6, 134.4, 135.9, 143.0, 167.0, 173.2, 174.1, 211.7; HRFABMS m/z 749.3574 [M+H$^+$]; calcd for C$_{42}$H$_{53}$O$_{12}$, 749.3537.

General Procedure for selective acetylation of 10-DAB derivatives at C-10. To a solution of 4-Deacetyl-4-(5-hexenoyl)-10-deacetylbaccatin III 120 (226 mg, 0.38 mmol) in dried THF (3.5 mL) was added CeCl$_3$ (10 mg, cat.), and then acetic anhydride (0.55 mL, 5.7 mmol) was added. After stirring at room temperature for 3 h, the reaction mixture was diluted with EtOAc (50 ml), and then washed with saturated NaHCO$_3$, brine, and dried with sodium sulfate. The organic phase was concentrated in vacuum, and the residue was applied to PTLC (50% EtOAc/hexane) to give 125 as colorless gum (230 mg, 95%). Compounds 124$^{178}$, 126, 127, and 128 were prepared in similar procedure.

4-Deacetyl-4-(5-hexenoyl)baccatin III (125). $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.03 (3H, s), 1.05 (3H, s), 1.74-1.84 (3H, overlapped), 1.94-2.00 (4H, overlapped), 2.09-2.29 (7H, overlapped),
2.45-2.82 (5H, overlapped), 3.82 (1H, d, J = 7.0 Hz), 4.11 (1H, d, J = 8.3 Hz), 4.24 (1H, d, J = 8.3 Hz), 4.44 (1H, dd, J = 10.2, 7.3 Hz), 4.75-4.84 (1H, m), 4.89 (1H, dd, J = 9.4, 1.2 Hz), 4.98-5.09 (2H, overlapped), 5.56 (1H, d, J = 7.0 Hz), 5.75-5.87 (1H, m), 6.27 (1H, s), 7.38-7.46 (2H, m, Ar), 7.52-7.60 (1H, m, Ar), 8.01-8.08 (2H, m, Ar); 

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.5, 15.6, 20.0, 21.0, 23.6, 26.9, 33.1, 34.5, 35.6, 39.0, 42.7, 46.2, 58.6, 67.6, 72.3, 75.0, 76.4, 76.5, 79.0, 80.6, 84.7, 115.5, 128.7, 129.4, 130.1, 131.3, 133.7, 137.8, 147.1, 166.9, 171.5, 173.0, 204.4; 

HRFABMS m/z 641.2967 [M+H$^+$]; calcd for C$_{35}$H$_{45}$O$_{11}$, 641.2962.

4-Deacetyl-4-(5-benzyloxycarbonylpentanoyl)baccatin III (126). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.12 (6H, s), 1.69 (3H, s), 1.72 -1.92 (6H, overlapped), 2.03 (3H, brs), 2.20-2.36 (5H, overlapped), 2.40-2.77 (6H, overlapped), 2.90 (1H, brs), 3.88 (1H, d, J = 7.1 Hz), 4.17 (1H, d, J = 8.4 Hz), 4.31 (1H, d, J = 8.4 Hz), 4.51 (1H, m), 4.84 (1H, m), 4.96 (1H, d, J = 9.2 Hz), 5.15 (2H, s), 5.64 (1H, d, J = 7.1 Hz), 6.33 (1H, s), 7.32-7.42 (5H, m, Ar, overlapped), 7.46-7.54 (2H, m, Ar), 7.58-7.65 (1H, m, Ar), 8.09-8.14 (2H, m, Ar); 

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.5, 15.6, 20.9, 21.0, 23.5, 24.2, 27.0, 33.8, 34.4, 35.6, 38.7, 42.7, 46.3, 58.7, 66.5, 67.7, 72.3, 75.0, 76.3, 76.4, 79.1, 80.7, 84.6, 128.2, 128.4, 128.6, 128.7, 129.4, 130.1, 131.5, 133.7, 135.8, 146.9, 167.1, 171.4, 172.7, 173.7, 204.3; 

HRFABMS m/z 763.3360 [M+H$^+$]; calcd for C$_{42}$H$_{51}$O$_{13}$, 763.3330.

4-Deacetyl-4-(6-benzyloxycarbonylhexanoyl)baccatin III (127). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.10 (3H, s), 1.11 (3H, s), 1.38-1.52 (2H, m), 1.68 (3H, s), 1.69-1.81 (4H,
overlapped), 1.82-1.90 (1H, m), 1.93 (1H, s), 2.03 (3H, d, \( J = 1.0 \) Hz), 2.20-2.35 (5H, overlapped), 2.43 (2H, t, \( J = 7.5 \) Hz), 2.50-2.61 (2H, overlapped), 2.63-2.74 (2H, overlapped), 3.00 (1H, d, \( J = 5.0 \) Hz), 3.87 (1H, d, \( J = 7.1 \) Hz), 4.17 (1H, d, \( J = 8.4 \) Hz), 4.30 (1H, d, \( J = 8.4 \) Hz), 4.50 (1H, m), 4.83 (1H, m), 4.95 (1H, dd, \( J = 9.5, 1.6 \) Hz), 5.14 (2H, s), 5.63 (1H, d, \( J = 7.1 \) Hz), 6.33 (1H, s), 7.32-7.42 (5H, m, Ar, overlapped), 7.45-7.51 (2H, m, Ar), 7.57-7.63 (1H, m, Ar), 8.08-8.14 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 9.5, 15.5, 20.9, 21.1, 23.6, 24.5, 26.9, 28.2, 34.0, 34.5, 35.6, 38.9, 42.7, 46.2, 58.6, 66.3, 67.6, 72.3, 75.1, 76.3, 76.4, 79.1, 80.6, 84.6, 128.2, 128.3, 128.6, 129.4, 130.1, 131.4, 133.6, 135.9, 147.0, 167.0, 171.4, 173.0, 173.9, 204.3; HRFABMS \( m/z \) 777.2447 [M+H\(^+\)]; calcd for C\(_{43}\)H\(_{53}\)O\(_{13}\), 777.3486.

4-Deacetyl-4-(7-benzyloxy carbonyl heptanoyl)baccatin III (128). Colorless gum; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 1.07 (3H, s), 1.09 (3H, s), 1.33-1.45 (4H, overlapped), 1.62-1.75 (7H, overlapped), 1.78-1.88 (2H, overlapped), 2.01 (3H, s), 2.16-2.33 (5H, overlapped), 2.35-2.41 (2H, m), 2.45-2.68 (4H, overlapped), 2.88 (1H, m), 2.96 (1H, brs), 3.84 (1H, d, \( J = 7.0 \) Hz), 4.13 (1H, d, \( J = 8.3 \) Hz), 4.27 (1H, d, \( J = 8.3 \) Hz), 4.48 (1H, m), 4.82 (1H, m), 4.92 (1H, dd, \( J = 9.5, 1.6 \) Hz), 5.10 (2H, s), 5.60 (1H, d, \( J = 7.0 \) Hz), 6.30 (1H, s), 7.27-7.37 (5H, m, Ar, overlapped), 7.41-7.48 (2H, m, Ar), 7.54-7.60 (1H, m, Ar), 8.05-8.11 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 9.7, 15.7, 21.1, 21.3, 23.9, 24.7, 27.1, 28.6, 28.7, 34.3, 34.9, 35.8, 39.1, 42.9, 46.4, 58.8, 66.5, 67.8, 72.5, 75.3, 76.5, 76.6, 79.3, 80.8, 84.9, 128.4, 128.5, 128.8, 129.6, 130.3, 131.5, 133.8, 136.1, 147.3, 167.2, 171.6, 173.3, 174.3, 204.5; HRFABMS \( m/z \) 791.3688 [M+H\(^+\)]; calcd for C\(_{44}\)H\(_{55}\)O\(_{13}\), 791.3643.
General procedure for selective silylation of baccatin III derivatives at C-7. To a solution of 4-Deacetyl-4-(5-hexenoyl)baccatin III 125 (230 mg, 0.36 mmol) in anhydrous DMF (2 mL) was added imidazole (144 mg, 2.2 mmol) and TESCl (180 µL, 1.1 mmol). The reaction mixture was stirring for 10 min, and then diluted with EtOAc (50 mL). The organic phase was washed with water, brine, and dried with sodium sulfate. After concentrated in vacuum, the residue was applied to PTLC (30% EtOAc/hexane) to give 106 as colorless gum (241 mg, 89%). Compounds 105, 107, 108, and 109 were prepared in similar procedures.

4-Deacetyl-4-(5-hexenoyl)-7-TESO-baccatin III (106). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.52 (6H, m), 0.93 (9H, t, $J = 7.9$ Hz), 1.03 (3H, s), 1.19 (3H, s), 1.68 (3H, s), 1.74 (1H, s), 1.82-1.91 (3H, overlapped), 2.15-2.33 (8H, overlapped), 2.50-2.62 (3H, overlapped), 3.88 (1H, d, $J = 7.0$ Hz), 4.15 (1H, d, $J = 8.3$ Hz), 4.30 (1H, d, $J = 8.3$ Hz), 4.50 (1H, dd, $J = 10.5$, 6.7 Hz), 4.77-4.85 (1H, m), 4.92 (1H, dd, $J = 9.4$, 1.4 Hz), 5.04-5.14 (2H, overlapped), 5.63 (1H, d, $J = 7.0$ Hz), 5.80-5.92 (1H, m), 6.46 (1H, s), 7.44-7.50 (2H, m, Ar), 7.58-7.64 (1H, m, Ar), 8.09-8.14 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 5.4, 6.8, 10.0, 15.0, 20.2, 21.1, 23.9, 26.9, 33.3, 34.9, 37.4, 38.5, 42.9, 47.4, 58.8, 68.0, 72.4, 74.9, 75.9, 76.7, 78.8, 80.8, 84.5, 115.7, 128.7, 129.5, 130.2, 132.6, 133.7, 137.8, 144.3, 167.1, 169.5, 173.0, 202.5; HRFABMS $m/z$ 755.3873 [M+H$^+$]; calcd for C$_{41}$H$_{59}$O$_{11}$Si, 755.3827.

4-Deacetyl-4-(5-benzyloxycarbonylpentanoyl)-7-TESO-baccatin III (107). Colorless gum;
1H NMR (400 MHz, CDCl₃) δ: 0.56-0.66 (6H, m), 0.95 (9H, t, J = 7.8 Hz), 1.06 (3H, s), 1.21 (3H, s), 1.70 (3H, s), 1.72 (1H, s), 1.74-1.93 (6H, overlapped), 2.17 (3H, d, J = 1.1 Hz), 2.20 (3H, s), 2.21-2.34 (2H, overlapped), 2.42-2.73 (6H, overlapped), 3.88 (1H, d, J = 7.0 Hz), 4.16 (1H, d, J = 8.4 Hz), 4.31 (1H, d, J = 8.4 Hz), 4.52 (1H, dd, J = 10.4, 6.7 Hz), 4.80 (1H, m), 4.94 (1H, dd, J = 9.5, 1.6 Hz), 5.16 (2H, s), 5.65 (1H, d, J = 7.0 Hz), 6.48 (1H, s), 7.32-7.48 (5H, m, Ar, overlapped), 7.46-7.52 (2H, m, Ar), 7.57-7.64 (1H, m, Ar), 8.10-8.16 (2H, m, Ar); 13C NMR (100 MHz, CDCl₃) δ: 5.3, 6.7, 10.0, 14.9, 20.2, 21.0, 23.6, 24.3, 26.8, 33.8, 34.7, 37.2, 38.4, 42.8, 47.4, 58.7, 66.4, 67.7, 72.3, 74.8, 75.8, 76.5, 78.8, 80.7, 84.3, 128.2, 128.3, 128.5, 128.6, 129.5, 130.1, 132.4, 133.6, 135.8, 144.4, 167.1, 169.4, 172.5, 173.6, 202.3; HRFABMS m/z 877.4147 [M+H⁺]; calcd for C₄₈H₆₅O₁₃Si, 877.4194.

4-Deacetyl-4-(6-benzyloxycarbonylhexanoyl)-7-TESO-baccatin III (108). Colorless gum; 1H NMR (400 MHz, CDCl₃) δ: 0.53-0.68 (6H, m), 0.95 (9H, t, J = 7.7 Hz), 1.05 (3H, s), 1.20 (3H, s), 1.39-1.55 (2H, m), 1.70 (3H, s), 1.71-1.93 (6H, overlapped), 2.18 (3H, s), 2.19 (3H, s), 2.20-2.34 (2H, overlapped), 2.44 (2H, t, J = 7.2 Hz), 2.50-2.70 (3H, overlapped), 2.73 (1H, d, J = 5.0 Hz), 3.88 (1H, d, J = 7.0 Hz), 4.16 (1H, d, J = 8.3 Hz), 4.30 (1H, d, J = 8.3 Hz), 4.52 (1H, d, J = 10.3, 6.7 Hz), 4.79 (1H, m), 4.93 (1H, d, J = 9.2 Hz), 5.14 (2H, s), 5.64 (1H, d, J = 7.0 Hz), 6.48 (1H, s), 7.31-7.42 (5H, m, Ar, overlapped), 7.44-7.51 (2H, m, Ar), 7.56-7.63 (1H, m, Ar), 8.10-8.16 (2H, m, Ar); 13C NMR (100 MHz, CDCl₃) δ: 5.3, 6.8, 10.0, 14.9, 20.2, 21.0, 23.8, 24.5, 26.8, 28.4, 34.0, 34.9, 37.3, 38.5, 42.8, 47.3, 58.6, 66.3, 67.7, 72.3, 74.9, 75.9, 76.6, 78.8, 80.7, 84.4, 128.2, 128.3, 128.5, 128.6, 129.5, 130.1, 132.3, 133.6, 135.9, 144.5, 167.0, 169.4, 172.8,
173.8, 202.4; HRFABMS m/z 891.4338 [M+H+]; calcd for C_{49}H_{67}O_{13}Si, 891.4351.

4-Deacetyl-4-(7-benzyloxycarbonylheptanoyl)-7-TESO-baccatin III (109). Colorless gum; ¹H NMR (400 MHz, CDCl₃) δ: 0.56-0.66 (6H, m), 0.95 (9H, t, J = 7.8 Hz), 1.06 (3H, s), 1.21 (3H, s), 1.38-1.50 (4H, overlapped), 1.67-1.82 (8H, overlapped), 1.84-1.93 (2H, overlapped), 2.20 (6H, s), 2.21-2.36 (2H, overlapped), 2.42 (2H, t, J = 7.3 Hz), 2.51-2.71 (4H, overlapped), 3.89 (1H, d, J = 7.0 Hz), 4.16 (1H, d, J = 8.3 Hz), 4.31 (1H, d, J = 8.3 Hz), 4.53 (1H, dd, J = 10.4, 6.8 Hz), 4.82 (1H, m), 4.94 (1H, dd, J = 9.6, 1.3 Hz), 5.14 (2H, s), 5.65 (1H, d, J = 7.0 Hz), 6.49 (1H, s), 7.31-7.42 (5H, m, Ar, overlapped), 7.45-7.51 (2H, m, Ar), 7.58-7.64 (1H, m, Ar), 8.11-8.17 (2H, m, Ar); ¹³C NMR (100 MHz, CDCl₃) δ: 5.3, 6.8, 10.0, 14.9, 20.2, 21.0, 24.0, 24.5, 26.8, 28.5, 34.1, 35.2, 37.3, 38.5, 42.8, 47.3, 58.7, 66.3, 67.7, 72.3, 74.9, 75.9, 76.6, 78.8, 80.6, 84.4, 128.2, 128.3, 128.5, 128.6, 129.5, 130.1, 132.4, 133.6, 135.9, 144.5, 167.1, 169.4, 173.0, 173.9, 202.4; HRFABMS m/z 905.4471 [M+H+]; calcd for C_{50}H_{69}O_{13}Si, 905.4507.

Preparation of racemic β-lactam (131). To a solution of m-benzyloxylbenzaldehyde (129) (21.2 g, 0.10 mol) in anhydrous DCM (250 mL) was added p-anisidine (14.8 g, 0.12 mol) and anhydrous MgSO₄ (12.0 g, 0.1 mol). After stirring at room temperature for overnight, the imine (130) solution was filtrated and used directly. The filtrate was cooled to –78 °C, and then triethylamine (40.47 g, 0.4 mol) and acetyloxyacetyl chloride (17.75 g, 0.13 mol) were added. The reaction mixture was then allowed to warm up slowly to room temperature. After stirring for overnight, the reaction mixture was concentrated under vacuum. The residue was purified by
column chromatography (30% EtOAc/hexane) to give 131 as slightly yellow solid (25.1 g, 60%).

Cis-2-(3-(benzyloxy)phenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl acetate (131). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.69 (3H, s), 3.76 (3H, s), 5.02 (2H, ABq, $J = 12.0$ Hz), 5.29 (1H, d, $J = 4.8$ Hz), 5.94 (1H, d, $J = 4.8$ Hz), 6.78-6.83 (2H, m, Ar), 6.87-6.97 (3H, m, Ar, overlapped), 7.23-7.41 (8H, m, Ar, overlapped); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 20.1, 55.6, 61.6, 70.2, 76.5, 114.4, 114.6, 115.6, 119.0, 120.8, 127.7, 128.2, 128.8, 129.9, 130.5, 134.2, 136.8, 156.8, 159.0, 161.5, 169.5; HRFABMS m/z 418.1644 [M+H$^+$]; calcd for C$_{25}$H$_{24}$NO$_5$, 418.1654.

Resolution of $\beta$-lactam 131. To a solution of racemic $\beta$-lactam (131) (1.0 g, 2.4 mmol) in CH$_3$CN (5mL) and phosphate buffer (45mL) was added Lipase PS 30 (1.0 g). The reaction mixture was allowed to stir for 7 days, and then extracted with EtOAc (3×100mL). The combined organic phase was washed with brine, dried with anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (30-50% EtOAc/hexane) to give (+)-lactam acetate 131 (476 mg, 48%) and (-)-lactam 132 (465 mg, 47%) both as white solid.

Preparation of (+)-$\beta$-lactam 132. To a solution of (+)-lactam acetate 131 (1.05 g, 2.5 mmol) in THF (100mL) was added 1M KOH (100 mL) at 0 °C. The reaction mixture was allowed to stir for 45 min, and then extracted with EtOAc (3×100mL). The combined organic phase was washed with saturated NH$_4$Cl, water, brine, dried with anhydrous sodium sulfate, and
concentrated under vacuum. The residue was purified by column chromatography (50% EtOAc/hexane) to give (+)-β-lactam 132 as white solid (900 mg, 92%).

\[(3R,4S)-4-(3-(benzyloxy)phenyl)-3-hydroxy-1-(4-methoxyphenyl)azetidin-2-one \ (132)\]

\[\text{\textsuperscript{1}H NMR (400 MHz, (CD\textsubscript{3})\textsubscript{2}CO) \delta: 3.74 (3H, s), 5.03 (1H, d, } J = 7.7 \text{ Hz), 5.09 (2H, ABq, } J = 11.8 \text{ Hz), 5.26 (1H, dd, } J = 7.7, 5.2 \text{ Hz), 5.30 (1H, d, } J = 5.2 \text{ Hz), 6.83-6.88 (2H, m, Ar), 6.95-7.00 (2H, m, Ar), 7.03-7.05 (1H, m, Ar), 7.27-7.39 (6H, m, Ar, overlapped), 7.42-7.47 (2H, m, Ar);}\]

\[\text{\textsuperscript{13}C NMR (100 MHz, (CD\textsubscript{3})\textsubscript{2}CO) \delta: 54.9, 62.5, 69.7, 78.1, 114.2, 114.4, 114.9, 118.5, 120.7, 127.8, 127.9, 128.6, 129.6, 131.6, 137.0, 137.6, 156.4, 159.2, 165.9; HRFABMS m/z 376.1539 [M+H\textsuperscript{+}]; calcld for C\textsubscript{23}H\textsubscript{22}NO\textsubscript{4}, 376.1549.}\]

**Preparation of (+)-O-TIPS-β-lactam 133.** To a solution of (+)-β-lactam 132 (900 mg, 2.4 mmol) in DMF (5 mL) was added imidazole (653 mg, 9.6 mmol) and TIPSCl (924 mg, 4.8 mmol). The reaction mixture was allowed to stir for 3 h, and then quenched with water. The resulting mixture was added EtOAc (150 mL). The combined organic phase was washed with water, brine, dried with anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (30% EtOAc/hexane) to give (+)-O-TIPS-β-lactam 133 as white solid (1.21 g, 95%).

\[(3R,4S)-4-(3-(benzyloxy)phenyl)-1-(4-methoxyphenyl)-3-TIPSO-azetidin-2-one \ (133)\]

\[\text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta: 0.98-1.14 (21H, overlapped), 3.78 (3H, s), 5.00-5.08 (3H,}...}
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overlapped), 5.09 (1H, d, J = 4.9 Hz), 6.78-6.84 (2H, m, Ar, overlapped), 6.95-7.06 (3H, m, Ar, overlapped), 7.27-7.45 (8H, m, Ar, overlapped); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 11.8, 17.6, 17.7, 56.3, 63.2, 70.0, 77.9, 114.3, 114.8, 114.9, 118.7, 121.1, 127.5, 127.9, 128.6, 129.3, 131.0, 135.9, 137.0, 156.2, 165.6; HRFABMS m/z 532.2887 [M+H$^+$]; calcd for C$_{32}$H$_{42}$NO$_4$Si, 532.2883.

Preparation of (+)-β-lactam 134. To a solution of (+)-β-lactam 133 (1.21 g, 2.3 mmol) in CH$_3$CN (50mL) was added CAN reagent (3.53g in 30 mL H$_2$O) at 0 °C dropwise in 15 min. The reaction mixture was allowed to stir for another 30 min, and then extracted with EtOAc (3×50mL). The combined organic phase was washed with saturated Na$_2$S$_2$O$_4$, water, brine, dried with anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (30% EtOAc/hexane) to give (+)-β-lactam 134 yellowish solid (922 mg, 96%).

(3R,4S)-4-(3-(benzyloxy)phenyl)-3-TIPSO-azetidin-2-one (134). $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.89-1.05 (21H, overlapped), 4.80 (1H, d, J = 4.7 Hz), 5.08 (2H, ABq, J = 12.4 Hz), 5.18 (1H, dd, J = 4.7, 2.7 Hz), 6.37 (1H, brs), 6.91-6.98 (2H, m, Ar), 7.00-7.03 (1H, m, Ar), 7.24-7.30 (2H, m, Ar), 7.32-7.48 (4H, m, Ar, overlapped); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 11.6, 17.5, 17.6, 59.5, 70.0, 80.0, 114.6, 114.8, 120.9, 127.4, 127.9, 128.6, 129.0, 137.0, 138.0, 158.7, 169.9; HRFABMS m/z 426.2467 [M+H$^+$]; calcd for C$_{25}$H$_{36}$NO$_3$Si, 426.2464.

Preparation of (+)-β-lactam 110. To a solution of (+)-β-lactam 134 (922 mg, 2.2 mmol) in
anhydrous DCM (5 mL) was added TEA (658 mg, 6.5 mmol), benzoyl chloride (365 mg, 2.6 mmol) and DAMP (50 mg, cat.). The reaction mixture was allowed to stir for 2 h, and then diluted with EtOAc (150 mL). The combined organic phase was washed with saturated NaHCO₃, water, brine, dried with anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (20% EtOAc/hexane) to give (+)-β-lactam 110 as white solid (900 mg, 90%).

**(3R,4S)-1-benzoyl-4-(3-(benzyloxy)phenyl)-3-TIPSO-azetidin-2-one (110).** ¹H NMR (400 MHz, CDCl₃) δ: 0.96-1.10 (21H, overlapped), 5.10 (2H, ABq, J = 11.9 Hz), 5.28 (1H, d, J = 6.1 Hz), 5.45 (1H, d, J = 6.1 Hz), 6.95-7.00 (1H, m, Ar), 7.04-7.10 (2H, m, Ar), 7.28-7.70 (9H, m, Ar, overlapped), 8.07-8.12 (2H, m, Ar); ¹³C NMR (100 MHz, CDCl₃) δ: 11.7, 17.5, 17.6, 61.1, 70.1, 76.7, 114.7, 114.9, 121.0, 127.4, 128.0, 128.2, 128.6, 129.3, 129.9, 132.1, 133.4, 135.5, 137.1, 158.8, 165.4, 166.3; HRFABMS m/z 529.2638 [M+H⁺]; calcd for C₃₂H₃₉NO₄Si, 529.2648.

**General procedure for coupling of baccatin and the β-lactam.** To a solution of compound 4-Deacetyl-4-(4-pentenoyl)-7-TESO-baccatin III 105 (55 mg, 0.074 mmol) in dried THF (3.6 mL) at 0 °C was added NaH (40 mg, 1.67 mmol) and stirred for 5 min, then (+)-β-lactam 110 (75 mg, 0.15 mmol in 0.8 mL THF) was added and reaction was allowed to stir at room temperature for 24 h. The reaction mixture was quenched with saturated NH₄Cl and diluted with EtOAc (30 ml), and then washed with water, brine, and dried with sodium sulfate. The organic phase was concentrated in vacuum, and the residue was applied to PTLC (20% EtOAc/hexane).
to give taxol derivative 135 (50 mg, 57%). Compounds 136, 141, 142, and 143 were prepared in similar procedures, but the last three used LHMDS (1.2 eq) as base and only ran for 3-4 h.

4-Deacetyl-4-(4-pentenoyl)-3’-desphenyl-3’-(m-benzyloxyphenyl)-7-TESO-2’-TIPSO-taxol (135). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 0.57-0.70 (6H, m), 0.94-1.07 (30H, overlapped), 1.21 (3H, s), 1.26 (3H, s), 1.73 (3H, s), 1.87-1.97 (1H, m), 2.07 (3H, d, $J$ = 1.3 Hz), 2.11-2.25 (2H, overlapped), 2.20 (3H, s), 2.38-2.75 (5H, overlapped), 3.03-3.12 (1H, m), 3.87 (1H, d, $J$ = 7.0 Hz), 4.24 (1H, d, $J$ = 8.4 Hz), 4.34 (1H, d, $J$ = 8.4 Hz), 4.51 (1H, dd, $J$ = 10.6, 6.7 Hz), 4.89-4.94 (2H, overlapped), 5.03-5.07 (1H, m), 5.10 (2H, s), 5.11-5.17 (1H, m), 5.69 (1H, d, $J$ = 8.9 Hz), 5.73 (1H, d, $J$ = 7.0 Hz), 5.81-5.92 (1H, m), 6.20 (1H, dt, $J$ = 9.1, 1.3 Hz), 6.47 (1H, s), 6.90-7.03 (3H, m, Ar, overlapped), 7.11 (1H, d, $J$ = 8.9 Hz), 7.30-7.65 (12H, m, Ar, overlapped), 7.74-7.78 (2H, m, Ar), 8.17-8.21 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 5.5, 6.9, 10.3, 12.7, 14.4, 18.0, 18.1, 21.0, 21.7, 26.7, 29.9, 35.7, 36.0, 37.4, 43.5, 46.9, 56.1, 58.6, 70.2, 72.1, 72.4, 75.1, 75.2, 75.7, 76.7, 79.0, 81.4, 84.6, 113.3, 114.6, 117.0, 119.1, 127.1, 127.5, 128.2, 128.8, 128.9, 129.0, 129.5, 129.9, 130.4, 131.9, 133.7, 133.8, 134.1, 135.9, 137.0, 140.2, 140.4, 159.4, 167.1, 169.5, 172.0, 172.1, 201.9; HRFABMS $m/z$ 1292.6179 [M+Na$^+$]; calcd for C$_{72}$H$_{95}$NO$_{15}$Si$_2$Na, 1292.6138.

4-Deacetyl-4-(5-hexenoyl)-3’-desphenyl-3’-(m-benzyloxyphenyl)-7-TESO-2’-TIPSO-taxol (136). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 0.51-0.72 (6H, m), 0.93-1.03 (30H, overlapped), 1.20 (3H, s), 1.25 (3H, s), 1.74 (3H, s), 1.77 (1H, s), 1.84-2.04 (3H, overlapped),
2.08 (3H, d, J = 1.0 Hz), 2.10-2.22 (6H, overlapped), 2.38-2.47 (1H, m), 2.52-2.69 (2H, overlapped), 2.95-3.04 (1H, m), 3.87 (1H, d, J = 7.0 Hz), 4.25 (1H, d, J = 8.3 Hz), 4.34 (1H, d, J = 8.3 Hz), 4.53 (1H, dd, J = 10.6, 6.6 Hz), 4.90-4.96 (2H, overlapped), 4.99-5.05 (2H, overlapped), 5.10 (2H, s), 5.67-5.83 (3H, overlapped), 6.21 (1H, t, J = 9.1Hz), 6.50 (1H, s), 6.90-7.12 (4H, overlapped), 7.30-7.65 (12H, m, Ar, overlapped), 7.73-7.79 (2H, m, Ar), 8.16-8.21 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 5.3, 6.8, 10.1, 12.6, 14.3, 17.8, 17.9, 20.9, 21.6, 25.0, 26.6, 32.8, 35.4, 35.8, 37.3, 43.4, 46.8, 55.9, 58.4, 70.1, 71.9, 72.2, 74.9, 75.0, 75.5, 76.6, 78.9, 81.1, 84.5, 113.1, 114.5, 115.8, 118.9, 127.0, 127.4, 128.0, 128.5, 128.6, 128.7, 129.3, 129.7, 130.3, 131.7, 133.5, 133.6, 134.0, 136.8, 137.1, 140.1, 140.3, 159.3, 166.8, 167.0, 169.3, 171.9, 172.5, 201.8; HRFABMS m/z 1306.6212 [M+Na$^+$]; calcd for C$_{73}$H$_{97}$NO$_{15}$Si$_2$Na, 1306.6294.

4-Deacetyl-4-(5-benzoxylcarbonylpentanoyl)-3'-desphenyl-3'-(m-benzoxyphenyl)-7-TESO-2'-TIPSO-taxol (141). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.52-0.67 (6H, m), 0.90-1.01 (30H, overlapped), 1.18 (3H, s), 1.22 (3H, s), 1.60-1.74 (5H, overlapped), 1.75-1.95 (4H, overlapped), 2.05 (3H, d, J = 1.1 Hz), 2.09-2.20 (4H, overlapped), 2.48-2.64 (2H, overlapped), 2.95-3.04 (1H, m), 3.83 (1H, d, J = 7.2 Hz), 4.21 (1H, d, J = 8.4 Hz), 4.29 (1H, d, J = 8.4 Hz), 4.49 (1H, dd, J = 10.5, 6.5 Hz), 4.87 (1H, dd, J = 9.5, 1.6 Hz), 4.91 (1H, d, J = 1.6 Hz), 5.05 (2H, s), 5.06 (2H, s), 5.65-5.72 (2H, overlapped), 6.20 (1H, t, J = 9.3 Hz), 6.46 (1H, s), 6.87 (1H, dd, J = 8.2, 2.4 Hz), 6.94-7.01 (2H, overlapped), 7.06 (1H, d, J = 8.9 Hz), 7.26-7.42 (13H, m, Ar, overlapped), 7.44-7.59 (4H, overlapped), 7.70-7.75 (2H, m, Ar), 8.13-8.18 (2H, m, Ar);
13C NMR (100 MHz, CDCl3) δ: 5.5, 7.0, 10.4, 12.8, 14.4, 18.0, 18.1, 21.1, 21.9, 24.4, 25.5, 26.8, 33.8, 36.0, 36.1, 37.5, 43.6, 47.0, 56.1, 58.6, 66.4, 70.3, 71.9, 72.5, 75.1, 75.2, 75.7, 76.7, 79.1, 81.4, 84.7, 113.3, 114.6, 119.0, 127.2, 127.6, 128.3, 128.4, 128.5, 128.7, 128.8, 128.9, 129.5, 130.1, 130.5, 132.0, 133.7, 133.8, 134.2, 136.1, 137.0, 140.2, 140.4, 159.5, 167.1, 167.2, 169.6, 172.0, 172.6, 172.9, 202.0; HRFABMS m/z 1428.6735 [M+Na]+; calcd for C80H103NO17Si2Na, 1428.6662.

4-Deacetyl-4-(6-benzyloxycarbonylhexanoyl)-3’-desphenyl-3’-(m-benzyloxyphenyl)-7-TESO-2’-TIPSO-taxol (142). Colorless gum; 1H NMR (400 MHz, CDCl3) δ: 0.57-0.71 (6H, m), 0.96-1.06 (30H, overlapped), 1.22 (3H, s), 1.27 (3H, s), 1.30-1.44 (2H, m), 1.57-1.71 (2H, m), 1.76 (3H, s), 1.77-2.00 (4H, overlapped), 2.10 (3H, d, J = 1.1 Hz), 2.15-2.24 (4H, overlapped), 2.27 (2H, t, J = 7.6 Hz), 2.39-2.48 (1H, m), 2.53-2.68 (2H, overlapped), 2.98-3.07 (1H, m), 3.89 (1H, d, J = 7.1 Hz), 4.27 (1H, d, J = 8.4 Hz), 4.34 (1H, d, J = 8.4 Hz), 4.55 (1H, dd, J = 10.4, 6.6 Hz), 4.91 (1H, dd, J = 9.5, 1.6 Hz), 4.97 (1H, d, J = 1.6 Hz), 5.10 (2H, s), 5.12 (2H, s), 5.72-5.77 (2H, overlapped), 6.25 (1H, t, J = 9.1 Hz), 6.52 (1H, s), 6.92 (1H, dd, J = 8.3, 2.4 Hz), 7.00-7.07 (2H, overlapped), 7.11 (1H, d, J = 8.9 Hz), 7.30-7.46 (13H, m, Ar, overlapped), 7.49-7.63 (4H, overlapped), 7.75-7.80 (2H, m, Ar), 8.17-8.23 (2H, m, Ar); 13C NMR (100 MHz, CDCl3) δ: 5.4, 6.8, 10.2, 12.6, 14.2, 17.8, 17.9, 20.9, 21.7, 24.5, 25.5, 26.6, 28.6, 33.9, 35.9, 36.1, 37.3, 43.4, 46.8, 55.9, 58.5, 66.1, 70.1, 71.8, 72.3, 75.0, 75.5, 76.6, 78.9, 81.1, 84.5, 113.1, 114.5, 118.9, 127.0, 127.4, 128.0, 128.1, 128.2, 128.5, 128.6, 128.7, 129.4, 129.8, 130.3, 131.8, 133.6, 134.0, 136.1, 136.9, 140.1, 140.2, 159.3, 166.8, 167.0, 169.3, 171.8, 172.6, 173.1, 201.7; HRFABMS
$m/z$ 1419.6912 [M$^+$]; calcd for C$_{81}$H$_{105}$NO$_{17}$Si$_2$, 1419.6921.

4-Deacetyl-4-(7-benzyloxycarbonylheptanoyl)-3'-desphenyl-3'-(m-benzyloxyphenyl)-7-TESO-2'-TIPSO-taxol (143). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 0.56-0.71 (6H, m), 0.95-1.05 (30H, overlapped), 1.21 (3H, s), 1.26 (3H, s), 1.28-1.38 (4H, overlapped), 1.52-1.62 (2H, m), 1.75 (3H, s), 1.76-2.00 (4H, overlapped), 2.09 (3H, d, $J = 1.1$ Hz), 2.14-2.24 (4H, overlapped), 2.29 (2H, t, $J = 7.6$ Hz), 2.39-2.48 (1H, m), 2.53-2.65 (2H, overlapped), 2.96-3.06 (1H, m), 3.88 (1H, d, $J = 7.2$ Hz), 4.26 (1H, d, $J = 8.4$ Hz), 4.33 (1H, d, $J = 8.4$ Hz), 4.54 (1H, dd, $J = 10.5$, 6.7 Hz), 4.91 (1H, dd, $J = 9.5$, 1.6 Hz), 4.96 (1H, d, $J = 1.6$ Hz), 5.09 (2H, s), 5.13 (2H, s), 5.70-5.76 (2H, overlapped), 6.24 (1H, t, $J = 9.1$ Hz), 6.51 (1H, s), 6.91 (1H, dd, $J = 8.3$, 2.4 Hz), 6.99-7.06 (2H, overlapped), 7.10 (1H, d, $J = 8.9$ Hz), 7.31-7.48 (13H, m, Ar, overlapped), 7.49-7.65 (4H, overlapped), 7.74-7.79 (2H, m, Ar), 8.18-8.23 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 5.4, 6.8, 10.2, 12.6, 14.2, 17.8, 17.9, 20.9, 21.7, 24.7, 25.8, 26.6, 28.7, 28.8, 34.1, 35.9, 36.3, 37.3, 43.4, 46.8, 55.9, 58.5, 66.1, 70.1, 71.8, 72.3, 75.0, 75.5, 76.6, 78.9, 81.1, 84.5, 113.1, 114.5, 118.9, 127.0, 127.3, 128.0, 128.1, 128.2, 128.5, 128.6, 128.7, 129.4, 129.7, 130.3, 131.7, 133.5, 133.6, 134.0, 136.1, 136.9, 140.1, 140.2, 159.3, 166.8, 167.0, 169.3, 171.8, 172.7, 173.3, 201.7; HRFABMS $m/z$ 1434.7103 [M+H$^+$]; calcd for C$_{81}$H$_{105}$NO$_{17}$Si$_2$, 1434.7156.

**General procedure for oxidative cleavage of double bond to carboxylic acid.** To a solution of 4-Deacetyl-4-(4-pentenoyl)-3'-desphenyl-3'-(m-benzyloxyphenyl)-7-TESO-2'-TIPSO-taxol 135 (44 mg, 0.035 mmol) in H$_2$O/CH$_3$CN/CCl$_4$ (0.9 mL/0.6 mL/0.6 mL) was added RuCl$_3$ (1 mg, cat.)
and NaIO₄ (75 mg, 0.35 mmol). After stirring for 24h, the reaction was quenched with saturated NH₄Cl. The aqueous phase was extracted with EtOAc (2×20mL). The combined organic phase was washed with water, brine, and dried with sodium sulfate. After concentrated in vacuum, the residue was applied to PTLC (35% EtOAc/hexane) to give 137 as colorless gum (25.9 mg, 58%). Compound 138 was prepared in similar procedures.

**4-Deacetyl-4-(3-carboxypropanoyl)-3'-desphenyl-3'-(m-benzylxyphenyl)-7-TESO-2'-TIPSOTaxol (137).** ¹H NMR (400 MHz, CDCl₃) δ: 0.55-0.65 (6H, m), 0.90-1.03 (30H, overlapped), 1.20 (3H, s), 1.24 (3H, s), 1.72 (3H, s), 1.85-1.94 (1H, m), 2.05 (3H, d, J = 1.2 Hz), 2.09-2.22 (5H, overlapped), 2.33-2.41 (1H, m), 2.48-2.58 (1H, m), 2.82-2.96 (3H, overlapped), 3.09-3.18 (1H, m), 3.85 (1H, d, J = 7.1 Hz), 4.21 (1H, d, J = 8.4 Hz), 4.30 (1H, d, J = 8.4 Hz), 4.50 (1H, dd, J = 10.6, 6.6 Hz), 4.91 (1H, d, J = 1.9 Hz), 4.97 (1H, dd, J = 9.5, 1.7 Hz), 5.07 (2H, s), 5.69 (1H, d, J = 8.8 Hz), 5.73 (1H, d, J = 7.1 Hz), 6.23 (1H, t, J = 9.1 Hz), 6.47 (1H, s), 6.89-7.01 (3H, m, Ar, overlapped), 7.14 (1H, d, J = 8.9 Hz), 7.29-7.61 (12H, m, Ar, overlapped), 7.73-7.77 (2H, m, Ar), 8.11-8.16 (2H, m, Ar); ¹³C NMR (100 MHz, CDCl₃) δ: 5.3, 6.8, 10.2, 12.5, 14.1, 17.8, 17.9, 20.9, 21.8, 26.6, 29.0, 30.9, 35.9, 37.2, 43.4, 46.7, 56.0, 58.5, 70.1, 71.9, 72.2, 74.9, 75.0, 75.5, 76.5, 78.9, 81.7, 84.1, 113.4, 114.3, 118.7, 120.1, 127.0, 127.4, 128.1, 128.6, 128.8, 129.2, 129.9, 130.2, 131.9, 133.6, 133.7, 136.7, 139.9, 140.2, 155.1, 159.2, 167.0, 167.2, 169.3, 171.0, 171.7, 174.5, 201.7; HRFABMS m/z 1310.5851 [M+Na⁺]; calcd for C₇₁H₸₃NO₁₇Si₂Na, 1310.5880.
4-Deacetyl-4-(4-carboxybutanoyl)-3'-desphenyl-3'-(m-benzyloxyphenyl)-7-TESO-2'-TIPSO-taxol (138). Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$: 0.52-0.66 (6H, m), 0.94 (9H, t, $J$ = 7.9 Hz), 0.97-1.07 (21H, overlapped), 1.13 (3H, s), 1.19 (3H, s), 1.68 (3H, s), 1.77-1.86 (1H, m), 1.96 (3H, brs), 2.06-2.23 (6H, overlapped), 2.29-2.48 (3H, overlapped), 2.51-2.61 (1H, m), 2.70-2.80 (1H, m), 2.94-3.04 (1H, m), 3.84 (1H, d, $J$ = 7.1 Hz), 4.20 (1H, d, $J$ = 8.3 Hz), 4.23 (1H, d, $J$ = 8.3 Hz), 4.53 (1H, dd, $J$ = 10.4, 6.7 Hz), 4.94-5.00 (2H, overlapped), 5.11 (2H, ABq, $J$ = 12.3 Hz), 5.65-5.72 (2H, overlapped), 6.11 (1H, t, $J$ = 9.2 Hz), 6.47 (1H, s), 6.92-6.98 (1H, m, Ar), 7.08-7.15 (2H, m, overlapped), 7.24-7.63 (12H, m, Ar, overlapped), 7.73-7.79 (2H, m, Ar), 8.12-8.18 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$: 6.3, 7.2, 10.7, 13.8, 15.0, 18.5, 18.6, 20.8, 22.0, 22.4, 27.0, 34.0, 36.5, 36.8, 38.3, 44.7, 48.0, 57.9, 59.7, 71.1, 73.3, 73.8, 76.1, 76.4, 77.0, 77.5, 78.9, 82.4, 85.6, 115.2, 115.8, 120.8, 128.3, 128.5, 128.9, 129.5, 129.7, 129.8, 131.1, 131.2, 131.3, 133.0, 134.5, 135.2, 135.5, 138.6, 140.8, 141.4, 160.6, 167.6, 170.1, 170.8, 173.5, 173.6, 176.3, 204.2; HRFABMS m/z 1324.6067 [M+Na$^+$]; calcd for C$_{72}$H$_{95}$NO$_{17}$Si$_2$Na, 1324.6036.

**General procedure for deprotection of benzyl group using hydrogenolysis.** To a solution of 4-Deacetyl-4-(3-carboxypropanoyl)-3'-desphenyl-3'-(m-benzyloxyphenyl)-7-TESO-2'-TIPSO-taxol 137 (33 mg, 0.026 mmol) in EtOAc (10 mL) was added 10% Pd-C (10mg, cat.). The mixture was hydrogenated at 30 psi at room temperature for 48 h. The reaction mixture was filtered, and the organic phase was concentrated in vacuum. The residue was purified by preparative TLC (70% EtOAc/hexane) to give 139 as colorless gum (22.5 mg, 73%). Compounds 140, 144, 145,
and 146 were prepared in similar procedures.

4-Deacetyl-4-(3-carboxypropanoyl)-3'-desphenyl-3'-(m-hydroxyphenyl)-7-TESO-2'-TIPSO-taxol (139). $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.50-0.65 (6H, m), 0.90-0.98 (30H, overlapped), 1.16 (3H, s), 1.22 (3H, s), 1.70 (3H, s), 1.86-1.96 (1H, m), 2.02 (3H, d, $J$ = 1.0 Hz), 2.07-2.20 (4H, overlapped), 2.31-2.41 (1H, m), 2.46-2.57 (1H, m), 2.75-3.00 (3H, overlapped), 3.11-3.20 (1H, m), 3.85 (1H, d, $J$ = 6.9 Hz), 4.24 (1H, d, $J$ = 8.5 Hz), 4.34 (1H, d, $J$ = 8.5 Hz), 4.47 (1H, dd, $J$ = 10.6, 6.6 Hz), 4.88 (1H, dd, $J$ = 9.5, 1.5 Hz) 4.94 (1H, d, $J$ = 1.7 Hz), 5.62 (1H, dd, $J$ = 9.1 Hz), 5.74 (1H, d, $J$ = 6.9 Hz), 6.14 (1H, t, $J$ = 9.2 Hz), 6.45 (1H, s), 6.69-6.86 (3H, m, Ar, overlapped), 7.08-7.19 (2H, overlapped), 7.32-7.39 (2H, m, Ar), 7.45-7.60 (4H, m, Ar, overlapped), 7.65-7.71 (2H, m, Ar), 8.10-8.16 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 5.5, 7.0, 10.4, 12.7, 14.4, 18.0, 21.1, 21.9, 26.6, 29.9, 31.3, 35.9, 37.4, 43.6, 46.8, 56.6, 58.7, 72.3, 72.4, 75.2, 75.6, 78.8, 82.0, 84.7, 113.5, 115.4, 117.8, 127.2, 129.0, 129.1, 129.4, 130.1, 130.4, 132.3, 133.6, 133.8, 133.9, 139.2, 140.5, 157.2, 167.3, 168.1, 169.6, 171.5, 172.3, 175.5, 201.9; HRFABMS m/z 1220.5438 [M+Na$^+$]; calcd for C$_{64}$H$_{87}$NO$_{17}$Si$_2$Na, 1220.5410

4-Deacetyl-4-(4-carboxybutanoyl)-3'-desphenyl-3'-(m-hydroxyphenyl)-7-TESO-2'-TIPSO-taxol (140). Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) δ: 0.53-0.67 (6H, m), 0.91-1.06 (30H, overlapped), 1.13 (3H, s), 1.18 (3H, s), 1.67 (3H, s), 1.78-1.87 (1H, m), 1.98 (3H, brs), 2.00-2.20 (6H, overlapped), 2.25-2.50 (3H, overlapped), 2.52-2.63 (1H, m), 2.68-2.79 (1H, m), 2.92-3.04 (1H, m), 3.84 (1H, d, $J$ = 7.0 Hz), 4.17-4.26 (2H, overlapped), 4.54 (1H, dd, $J$ = 10.4,
6.7 Hz), 4.95-5.01 (2H, overlapped), 5.62 (1H, d, $J = 3.4$ Hz), 5.67 (1H, d, $J = 7.0$ Hz), 6.08 (1H, t, $J = 9.3$ Hz), 6.47 (1H, s), 6.71-6.77 (1H, m, Ar), 6.93-7.00 (2H, m, Ar), 7.21-7.27 (1H, m, Ar), 7.41-7.68 (6H, m, Ar, overlapped), 7.77-7.83 (2H, m, Ar), 8.12-8.18 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$: 5.1, 6.1, 9.6, 12.7, 13.9, 17.3, 17.4, 19.6, 21.2, 21.7, 25.8, 35.0, 35.5, 35.6, 37.2, 43.6, 46.8, 57.0, 58.5, 72.1, 72.7, 75.0, 75.3, 75.9, 76.4, 77.7, 81.1, 84.6, 114.1, 115.1, 118.1, 127.1, 128.5, 128.7, 129.8, 130.0, 130.1, 131.8, 133.4, 134.0, 134.5, 139.4, 140.3, 158.0, 165.7, 166.5, 168.9, 169.7, 172.6, 172.7, 203.2; HRFABMS m/z 1212.5789 [M+H$^+$]; calcd for C$_{65}$H$_{90}$NO$_{17}$Si$_2$, 1212.5747.

4-Deacetyl-4-(5-carboxypentanoyl)-3'-desphenyl-3'-(m-hydroxyphenyl)-7-TESO-2'-TIPSO-taxol (144). Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$: 0.57-0.72 (6H, m), 0.99 (9H, t, $J = 7.9$ Hz), 1.02-1.10 (21H, overlapped), 1.17 (3H, s), 1.23 (3H, s), 1.72 (3H, s), 1.73-1.99 (5H, overlapped), 2.01 (3H, brs), 2.14-2.26 (4H, overlapped), 2.33-2.50 (3H, overlapped), 2.56-2.66 (1H, m), 2.69-2.79 (1H, m), 2.96-3.06 (1H, m), 3.90 (1H, d, $J = 7.1$ Hz), 4.26 (2H, ABq, $J = 8.3$ Hz), 4.58 (1H, dd, $J = 10.5, 6.8$ Hz), 4.98 (1H, d, $J = 9.2$ Hz), 5.02 (1H, d, $J = 3.0$ Hz), 5.68-5.76 (2H, overlapped), 6.17 (1H, t, $J = 9.1$ Hz), 6.51 (1H, s), 6.80 (1H, dd, $J = 8.1, 2.3$Hz), 6.94-6.97 (1H, m, Ar), 7.00 (1H, d, $J = 7.8$ Hz), 7.30 (1H, t, $J = 8.1$ Hz), 7.45-7.73 (6H, m, Ar, overlapped), 7.79-7.84 (2H, m, Ar), 8.17-8.23 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$: 4.9, 5.8, 9.4, 12.5, 13.7, 17.1, 17.2, 19.4, 21.0, 24.1, 24.9, 25.6, 33.1, 35.5, 35.7, 37.0, 43.4, 46.6, 56.3, 58.3, 71.9, 72.5, 74.8, 75.1, 75.5, 76.1, 77.6, 80.9, 84.4, 114.0, 114.7, 117.8, 126.9, 128.3, 128.4, 129.6, 129.9, 130.0, 131.6, 133.2, 133.9, 134.2, 139.3, 140.1, 157.7, 166.3, 168.6, 169.5, 172.2, 172.6,
4-Deacetyl-4-(6-carboxyhexanoyl)-3’-desphenyl-3’-(m-hydroxyphenyl)-7-TESO-2’-TIPSO-taxol (145). Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$: 0.57-0.72 (6H, m), 0.99 (9H, t, $J$ = 8.1 Hz), 1.01-1.10 (21H, overlapped), 1.18 (3H, s), 1.23 (3H, s), 1.42-1.53 (2H, m), 1.61-1.75 (5H, overlapped), 1.80-1.98 (3H, overlapped), 2.03 (3H, d, $J$ = 1.0 Hz), 2.18 (3H, s), 2.21-2.31 (3H, overlapped), 2.43-2.51 (1H, m), 2.57-2.77 (2H, overlapped), 2.94-3.03 (1H, m), 3.90 (1H, d, $J$ = 7.2 Hz), 4.25 (2H, brs), 4.58 (1H, dd, $J$ = 10.5, 6.7 Hz), 4.96 (1H, dd, $J$ = 9.7, 1.6 Hz), 5.03 (1H, d, $J$ = 2.7 Hz), 5.69-5.74 (2H, overlapped), 6.18 (1H, t, $J$ = 9.1 Hz), 6.51 (1H, s), 6.82 (1H, dd, $J$ = 8.1, 2.1Hz), 6.94-6.97 (1H, m, Ar), 7.01 (1H, d, $J$ = 7.8 Hz), 7.29 (1H, t, $J$ = 8.1 Hz), 7.45-7.70 (6H, m, Ar, overlapped), 7.78-7.83 (2H, m, Ar), 8.17-8.22 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$: 4.9, 5.8, 9.4, 12.5, 13.7, 17.1, 17.2, 19.4, 21.0, 24.4, 25.1, 25.6, 28.3, 33.2, 35.5, 35.7, 37.0, 43.4, 46.6, 56.2, 58.3, 71.9, 72.5, 74.8, 75.1, 75.5, 76.2, 77.6, 80.9, 84.4, 114.0, 114.6, 117.7, 126.8, 128.3, 128.4, 129.6, 129.9, 130.0, 131.6, 133.2, 133.9, 134.2, 139.4, 140.0, 157.8, 166.3, 168.6, 169.5, 172.2, 172.7, 175.9, 202.9; HRFABMS m/z 1262.5826 [M+Na$^+$]; calcd for C$_{67}$H$_{93}$NO$_{17}$Si$_2$Na, 1262.5880.

4-Deacetyl-4-(7-carboxyheptanoyl)-3’-desphenyl-3’-(m-hydroxyphenyl)-7-TESO-2’-TIPSO-taxol (146). Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$: 0.57-0.72 (6H, m), 0.99 (9H, t, $J$ = 8.1 Hz), 1.02-1.10 (21H, overlapped), 1.18 (3H, s), 1.22 (3H, s), 1.34-1.51 (4H, overlapped), 1.52-1.65 (2H, m), 1.72 (3H, s), 1.79-1.95 (3H, overlapped), 2.03 (3H, d, $J$ = 1.0 Hz), 2.18 (3H,
s), 2.19-2.30 (3H, overlapped), 2.44-2.53 (1H, m), 2.56-2.76 (2H, overlapped), 2.94-3.04 (1H, m), 3.91 (1H, d, $J = 7.2$ Hz), 4.25 (2H, ABq, $J = 8.6$ Hz), 4.59 (1H, dd, $J = 10.4, 6.6$ Hz), 4.95 (1H, dd, $J = 9.5, 1.7$ Hz), 5.04 (1H, d, $J = 2.5$ Hz), 5.69-5.75 (2H, overlapped), 6.19 (1H, t, $J = 9.1$ Hz), 6.52 (1H, s), 7.78-6.85 (1H, m, Ar), 6.93-6.98 (1H, m, Ar), 7.00 (1H, d, $J = 7.6$ Hz), 7.28 (1H, t, $J = 8.2$ Hz), 7.45-7.62 (5H, m, Ar, overlapped), 7.65-7.71 (1H, m, Ar), 7.78-7.83 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$: 4.9, 5.8, 9.4, 12.5, 13.7, 17.1, 17.2, 19.4, 21.0, 24.4, 25.3, 25.6, 28.5, 33.4, 35.5, 35.9, 37.0, 43.4, 46.6, 56.1, 56.2, 58.4, 71.9, 72.4, 74.9, 75.1, 75.5, 76.2, 77.7, 80.9, 84.5, 114.0, 114.6, 117.7, 126.8, 128.4, 129.5, 129.9, 130.0, 131.6, 133.2, 133.9, 134.3, 139.4, 139.5, 140.0, 157.8, 166.3, 168.6, 169.5, 172.2, 172.9, 176.1, 202.9; HRFABMS m/z 1276.5984 [M+Na$^+$]; calcd for C$_{68}$H$_{95}$NO$_{17}$Si$_2$Na, 1276.6037.

**General procedures for macroclactonization.** To a solution of compound 4-Deacetyl-4-(3-carboxypropanoyl)-3'-desphenyl-3'-(m-hydroxyphenyl)-7-TESO-2'-TIPSO-taxol 139 (20.4 mg, 0.017 mmol) in anhydrous DCM (1.5 mL) was added 2,4,6-trichlorobenzoyl chloride (7.9 µL, 0.051 mmol). After stirring for 30 min, the reaction mixture was transferred into a syringe. Very slow addition of this mixture through syringe pump to a flask with DMAP (6.4 mg, 0.051 mmol) in DCM (8.5 mL) under stirring. The addition rate was set to be 0.5 mL/h. After addition was over, kept stirring for another hour. The reaction mixture was diluted with DCM (20 ml), and then washed with 0.1 N HCl (3×20 mL), saturated NaHCO$_3$, brine, and dried with sodium sulfate. The organic phase was concentrated in vacuum, and the residue was applied to PTLC (30% EtOAc/hexane) to give 147 as colorless gum (5.1 mg, 25%). Compounds 148,
149, 150, and 151 were prepared in similar procedures.

**Macrocyclic taxoid (147).** $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.50-0.60 (6H, m), 0.92 (9H, t, $J$ = 7.8 Hz), 1.13-1.27 (27H, overlapped), 1.29 (3H, s), 1.62-1.71 (5H, overlapped), 1.81-1.90 (1H, m), 2.16 (3H, s), 2.39-2.48 (1H, m), 2.75-3.15 (4H, overlapped), 3.39 (1H, d, $J$ = 7.8 Hz), 4.15 (1H, d, $J$ = 8.5 Hz), 4.23 (1H, d, $J$ = 8.5 Hz), 4.39 (1H, dd, $J$ = 10.6, 6.5 Hz), 4.77-4.82 (2H, overlapped), 5.63 (1H, d, $J$ = 7.8 Hz), 5.72 (1H, brs), 5.94 (1H, brt, $J$ = 8.7 Hz), 6.24 (1H, s), 7.13-7.20 (2H, overlapped), 7.32-7.37 (1H, m, Ar), 7.46-7.80 (8H, m, Ar, overlapped), 7.89-7.95 (2H, m, Ar), 8.02-8.07 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 5.5, 6.9, 11.0, 12.5, 18.2, 21.1, 28.1, 29.2, 30.5, 36.4, 36.7, 36.98, 36.99, 37.01, 43.5, 47.2, 58.1, 72.1, 73.8, 74.5, 75.9, 76.4, 77.3, 82.0, 84.7, 120.5, 127.4, 128.8, 129.0, 129.5, 130.2, 130.5, 132.3, 132.9, 133.7, 134.09, 134.12, 141.0, 146.3, 152.0, 162.7, 166.6, 167.4, 169.4, 170.6, 201.4; HRFABMS m/z 1202.5312 [M+Na$^+$]; calcd for C$_{64}$H$_{85}$NO$_{16}$Si$_2$Na, 1202.5305.

**Macrocyclic taxoid (148).** Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 0.54-0.68 (6H, m), 0.93-1.12 (30H, overlapped), 1.26 (3H, s), 1.28 (3H, s), 1.65 (3H, s), 1.75 (3H, s), 1.81 (1H, s), 1.81-2.11 (3H, overlapped), 2.21 (3H, s), 2.23-2.90 (7H, overlapped), 3.79 (1H, brs), 4.27 (1H, d, $J$ = 8.3 Hz), 4.39 (1H, d, $J$ = 8.3 Hz), 4.51 (1H, dd, $J$ = 10.6, 6.5 Hz), 4.78 (1H, brs), 4.87 (1H, d, $J$ = 9.2 Hz), 5.45 (1H, brs), 5.76 (1H, d, $J$ = 7.4 Hz), 6.16 (1H, d, $J$ = 9.2 Hz), 6.46 (1H, s), 7.13 (1H, d, $J$ = 8.0 Hz), 7.22 (1H, d, $J$ = 7.8 Hz), 7.38-7.71 (8H, m, Ar, overlapped), 7.88 (2H, d, $J$ = 7.8 Hz), 8.15 (2H, d, $J$ = 7.6 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 5.3, 6.7, 10.4, 12.4, 17.8, 17.9,
20.8, 22.8, 25.1, 26.9, 29.7, 32.6, 36.2, 37.1, 43.4, 47.0, 56.3, 58.3, 68.2, 69.6, 72.2, 74.8, 75.1, 76.5, 81.9, 84.7, 120.1, 120.3, 122.2, 127.1, 128.7, 128.8, 129.2, 130.1, 130.4, 131.9, 133.6, 133.9, 140.1, 140.3, 149.4, 153.0, 166.3, 167.0, 169.3, 171.7, 172.2, 175.2, 201.9; HRFABMS m/z 1216.5433 [M+Na⁺]; calcd for C₆₅H₈₇NO₁₆Si₂Na, 1216.5461.

**Macrocyclic taxoid (149).** Colorless gum; ¹H NMR (400 MHz, CDCl₃) δ: 0.56-0.67 (6H, m), 0.93-1.05 (30H, overlapped), 1.25 (3H, s), 1.26 (3H, s), 1.68-1.80 (5H, overlapped), 1.84-2.13 (6H, overlapped), 2.15-2.31 (7H, overlapped), 2.41-2.87 (6H, overlapped), 3.90 (1H, d, J = 7.3 Hz), 4.28 (1H, d, J = 8.3 Hz), 4.34 (1H, d, J = 8.4 Hz), 4.50 (1H, dd, J = 10.6, 6.5 Hz), 4.76-4.83 (2H, overlapped), 5.53 (1H, d, J = 8.0 Hz), 5.76 (1H, d, J = 7.3 Hz), 6.13 (1H, t, J = 9.1 Hz), 6.50 (1H, s), 7.03-7.12 (2H, m, overlapped), 7.17-7.22 (1H, m, Ar), 7.40 (2H, t, J = 7.8 Hz), 7.47-7.69 (6H, m, Ar, overlapped), 7.85-7.91 (2H, m, Ar), 8.14-8.20 (2H, m, Ar); ¹³C NMR (100 MHz, CDCl₃) δ: 5.3, 6.7, 10.2, 12.4, 14.0, 17.7, 17.8, 20.9, 21.9, 25.3, 26.7, 27.0, 35.1, 36.1, 36.3, 37.3, 43.4, 47.1, 56.4, 58.5, 71.8, 72.2, 74.9, 75.0, 76.8, 79.0, 81.9, 84.9, 120.1, 120.3, 122.3, 127.1, 128.7, 128.8, 129.3, 130.1, 130.2, 131.9, 133.4, 133.8, 134.0, 140.3, 141.4, 151.7, 166.9, 167.3, 169.3, 171.7, 172.5, 173.1, 201.5; HRFABMS m/z 1230.5566 [M+Na⁺]; calcd for C₆₆H₈₉NO₁₆Si₂Na, 1230.5618.

**Macrocyclic taxoid (150).** Colorless gum; ¹H NMR (400 MHz, CDCl₃) δ: 0.56-0.67 (6H, m), 0.92-1.02 (30H, overlapped), 1.23 (3H, s), 1.26 (3H, s), 1.66-1.80 (5H, overlapped), 1.89-2.11 (9H, overlapped), 2.20 (3H, s), 2.25-2.34 (1H, m), 2.41-2.49 (1H, m), 2.51-2.79 (4H,
overlapped), 2.81-2.91 (1H, m), 3.86 (1H, d, J = 7.1 Hz), 4.26 (1H, d, J = 8.5 Hz), 4.37 (1H, d, J = 8.5 Hz), 4.52 (1H, dd, J = 10.5, 6.6 Hz), 4.85 (1H, d, J = 1.0 Hz), 4.89 (1H, dd, J = 9.6, 1.8 Hz), 5.61 (1H, d, J = 8.4 Hz), 5.77 (1H, d, J = 7.1 Hz), 6.10 (1H, t, J = 9.3 Hz), 6.49 (1H, s), 6.98-7.03 (1H, m, Ar), 7.17 (1H, dd, J = 8.0, 1.8 Hz), 7.21-7.25 (1H, m, Ar), 7.29 (1H, d, J = 8.4 Hz), 7.42 (1H, t, J = 8.0 Hz), 7.47-7.69 (6H, m, Ar, overlapped), 7.83-7.88 (2H, m, Ar), 8.14-8.19 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 5.3, 6.7, 10.2, 12.5, 14.0, 17.7, 17.9, 20.8, 21.8, 24.8, 24.9, 26.7, 28.2, 34.5, 35.8, 35.9, 37.2, 43.4, 46.7, 56.3, 58.4, 72.2, 72.6, 74.9, 75.0, 76.2, 76.5, 78.8, 81.4, 84.6, 119.6, 121.8, 123.2, 127.0, 128.7, 128.8, 129.3, 129.9, 130.1, 131.9, 133.6, 133.7, 134.0, 140.2, 140.6, 151.3, 166.9, 167.4, 169.3, 171.9, 172.3, 201.6; HRFABMS \(m/z\) 1244.5759 [M+Na\(^+\)]; calcd for C\(_{67}\)H\(_{91}\)NO\(_{16}\)Si\(_2\)Na, 1244.5774.

**Macroyclic taxoid (151).** Colorless gum; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 0.51-0.64 (6H, m), 0.88-0.98 (30H, overlapped), 1.16 (3H, s), 1.22 (3H, s), 1.60-2.10 (16H, overlapped), 2.16 (3H, s), 2.21-2.30 (1H, m), 2.34-2.74 (5H, overlapped), 2.78-2.88 (1H, m), 3.87 (1H, d, J = 7.0 Hz), 4.22 (1H, d, J = 8.5 Hz), 4.33 (1H, d, J = 8.5 Hz), 4.48 (1H, dd, J = 10.5, 6.6 Hz), 4.80-4.87 (2H, overlapped), 5.59 (1H, d, J = 8.7 Hz), 5.72 (1H, d, J = 7.0 Hz), 6.03 (1H, t, J = 9.0 Hz), 6.47 (1H, s), 7.00-7.08 (2H, m, Ar, overlapped), 7.16-7.24 (2H, m, Ar, overlapped), 7.35-7.67 (7H, m, Ar, overlapped), 7.77-7.83 (2H, m, Ar), 8.10-8.16 (2H, m, Ar); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 5.5, 6.9, 10.3, 12.7, 14.4, 18.0, 18.1, 21.1, 21.6, 25.0, 26.7, 27.0, 28.8, 29.5, 34.6, 35.8, 37.2, 37.4, 43.6, 46.8, 56.6, 58.7, 72.4, 73.1, 75.0, 75.3, 75.9, 76.8, 78.7, 81.4, 84.8, 119.7, 122.0, 124.0, 127.2, 128.9, 129.0, 129.5, 130.1, 130.4, 132.1, 133.9, 134.2, 140.3, 140.5, 151.2, 167.1, 167.4,
General procedures for desilylation. To a solution of macrocyclic taxoid 147 (6.0 mg, 0.005 mmol) in dried THF (1.0 mL) was added anhydrous pyridine (0.2 mL), then the solution was cooled to 0 ºC, and HF-pyridine (0.2 mL) was added. The reaction mixture was allowed to warm to room temperature, and stirred for overnight. The reaction mixture was diluted with EtOAc (20 mL), and the organic phase was washed with sodium bicarbonate, water, brine, dried over sodium sulfate, and concentrated in vacuum. The residue was applied to preparative TLC (50% EtOAc/hexane) to give 100 (1.2 mg, 26%) and 157 (2.3 mg, 49%) both as colorless gum. Compounds 152, 158, 101, 153, 159, 102, 154, 103, 155, 104 and 156 were prepared similarly, while 150, 96, 151, 97, 98, and 99 were using HF-TEA instead of HF-pyridine and also pyridine was changed to TEA.

Macrocyclic taxoid (100). $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.12 (3H, s), 1.29 (3H, s), 1.35 (3H, brs), 1.62-1.69 (1H, m), 1.69 (3H, s), 1.84-1.92 (1H, m), 2.25 (3H, s), 2.47-2.69 (3H, overlapped), 2.83-3.05 (4H, overlapped), 3.48 (1H, d, $J = 7.4$ Hz), 3.79 (1H, brs), 4.18 (1H, d, $J = 8.3$ Hz), 4.25 (1H, d, $J = 8.3$ Hz), 4.35 (1H, m), 4.53 (1H, brs), 4.83 (1H, dd, $J = 9.3$, 1.8 Hz), 5.47 (1H, m), 5.65 (1H, d, $J = 7.4$ Hz), 6.12 (1H, s), 6.15 (1H, t, $J = 9.3$ Hz), 7.15-7.32 (3H, overlapped), 7.39-7.62 (7H, m, Ar, overlapped), 7.68-7.75 (1H, m, Ar), 7.87-7.91 (2H, m, Ar), 8.00-8.04 (2H, m, Ar); HRFABMS $m/z$ 910.3317 [M+H$^+$]; calcd for C$_{49}$H$_{52}$NO$_{16}$Si$_2$, 910.3286.
Macrocyclic taxoid (157). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.08 (3H, s), 1.20 (3H, s), 1.39 (3H, d, $J = 1.0$ Hz), 1.69 (1H, s), 1.71 (3H, s), 1.88-1.96 (1H, m), 2.01-2.08 (1H, m), 2.13-2.21 (1H, m), 2.25 (3H, s), 2.46-2.56 (2H, overlapped), 2.70-2.79 (2H, overlapped), 3.07-3.24 (2H, overlapped), 3.85 (1H, d, $J = 7.6$ Hz), 4.24 (1H, d, $J = 8.6$ Hz), 4.28 (1H, d, $J = 8.6$ Hz), 4.34 (1H, m), 4.78 (1H, dd, $J = 9.7$, 1.8 Hz), 5.52 (1H, d, $J = 3.0$ Hz), 5.61 (1H, d, $J = 7.6$ Hz), 5.94 (1H, dd, $J = 9.3$, 3.0 Hz), 6.14 (1H, s), 6.21 (1H, d, $J = 8.9$ Hz), 6.79-6.84 (1H, m, Ar), 6.98-7.03 (2H, overlapped), 7.24-7.28 (1H, m, Ar), 7.49-7.68 (7H, m, Ar, overlapped), 7.88-7.94 (2H, m, Ar), 8.11-8.16 (2H, m, Ar); HRFABMS $m/z$ 910.3295 [M+H$^+$]; calcd for C$_{49}$H$_{52}$NO$_{16}$, 910.3286.

4-Deacetyl-4-(3-carboxypropanoyl)-3'-desphenyl-3'-($m$-hydroxyphenyl)-taxol (152).

Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$: 1.16 (3H, s), 1.18 (3H, s), 1.67 (3H, s), 1.73-1.85 (2H, overlapped), 1.90 (3H, s), 2.06-2.15 (1H, m), 2.16-2.24 (4H, overlapped), 2.42-2.53 (1H, m), 2.60-2.84 (2H, overlapped), 2.86-2.97 (1H, m), 3.81 (1H, d, $J = 7.3$ Hz), 4.20 (2H, ABq, $J = 8.6$ Hz), 4.35 (1H, dd, $J = 10.9$, 6.6 Hz), 4.68 (1H, d, $J = 7.3$ Hz), 5.06 (1H, d, $J = 9.1$ Hz), 5.43 (1H, d, $J = 7.3$ Hz), 5.65 (1H, d, $J = 7.3$ Hz), 6.08 (1H, t, $J = 9.1$ Hz), 6.45 (1H, s), 6.69 (1H, dd, $J = 8.2$, 2.5 Hz), 6.93 (1H, d, $J = 7.7$ Hz), 7.02 (1H, m, Ar), 7.22 (1H, t, $J = 7.9$ Hz), 7.47-7.73 (6H, m, Ar, overlapped), 7.95-8.00 (2H, m, Ar), 8.10-8.15 (2H, m, Ar); HRFABMS $m/z$ 928.3373 [M+H$^+$]; calcd for C$_{49}$H$_{52}$NO$_{17}$, 928.3392.

Macrocyclic taxoid (158). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.09 (3H, s), 1.29 (3H,
s), 1.40 (3H, d, J = 1.3 Hz), 1.68 (1H, s), 1.82 (3H, s), 1.85-2.16 (4H, overlapped), 2.26 (3H, s), 2.27-2.40 (1H, m), 2.48-2.81 (5H, overlapped), 2.91-3.00 (1H, m), 3.58 (1H, d, J = 7.1 Hz), 4.16 (1H, d, J = 8.5 Hz), 4.31 (1H, d, J = 8.5 Hz), 4.39 (1H, m), 4.98 (1H, dd, J = 9.6, 1.7 Hz), 5.66 (1H, d, J = 7.1 Hz), 5.87 (1H, dd, J = 9.4, 3.5 Hz), 6.01 (1H, d, J = 3.5 Hz), 6.10 (1H, brs), 6.14 (1H, s), 6.42 (1H, dt, J = 9.1, 1.3 Hz), 6.77-6.81 (1H, m, Ar), 6.90-6.94 (1H, m, Ar), 6.96-6.99 (1H, m, Ar), 7.23 (1H, t, J = 7.9 Hz), 7.50-7.69 (7H, m, Ar, overlapped), 7.87-7.92 (2H, m, Ar), 8.05-8.09 (2H, m, Ar); HRFABMS m/z 924.3410 [M+H]+; calcd for C_{50}H_{54}NO_{16}, 924.3443.

**Macrocyclic taxoid (101).** Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.16 (3H, s), 1.35 (3H, s), 1.73 (3H, s), 1.79 (3H, s), 1.80 (3H, s), 1.85-1.98 (2H, overlapped), 2.11-2.26 (2H, overlapped), 2.27 (3H, s), 2.42-2.82 (6H, overlapped), 2.85-2.94 (1H, m), 3.68 (1H, d, J = 7.4 Hz), 3.89 (1H, d, J = 7.0 Hz), 4.25 (1H, d, J = 8.5 Hz), 4.34 (1H, d, J = 8.5 Hz), 4.42 (1H, m), 4.64 (1H, brt, J = 6.5 Hz), 4.89 (1H, dd, J = 9.5, 1.8 Hz), 5.64 (1H, dd, J = 7.8, 6.1 Hz), 5.72 (1H, d, J = 7.4 Hz), 6.22 (1H, t, J = 9.0 Hz), 6.24 (1H, s), 7.02-7.08 (1H, m, Ar), 7.14-7.21 (2H, overlapped), 7.28-7.34 (1H, m, Ar), 7.42-7.73 (7H, m, Ar, overlapped), 7.82-7.87 (2H, m, Ar), 8.12-8.17 (2H, m, Ar); HRFABMS m/z 924.3463 [M+H]+; calcd for C_{50}H_{54}NO_{16}, 924.3443.

**4-Deacetyl-4-(4-carboxybutanoyl)-3'-desphenyl-3'-(m-hydroxyphenyl)-taxol (153).** Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) δ: 1.17 (3H, s), 1.18 (3H, s), 1.68 (3H, s), 1.69-1.87 (2H, overlapped), 1.91 (3H, brs), 2.05-2.18 (3H, overlapped), 2.20 (3H, s), 2.30-2.55 (3H, overlapped), 2.65 (2H, brt, J = 7.8 Hz), 3.83 (1H, d, J = 7.2 Hz), 4.20 (2H, brs), 4.37 (1H, dd, J = 10.9, 6.5
Hz), 4.69 (1H, d, J = 7.8 Hz), 4.96 (1H, d, J = 9.4 Hz), 5.43 (1H, d, J = 7.8 Hz), 5.65 (1H, d, J = 7.2 Hz), 6.05 (1H, t, J = 9.2 Hz), 6.46 (1H, s), 6.68 (1H, dd, J = 8.1, 2.3 Hz), 6.97 (1H, d, J = 7.6 Hz), 7.04-7.06 (1H, m, Ar), 7.24 (1H, t, J = 7.9 Hz), 7.48-7.74 (6H, m, Ar, overlapped), 7.99-8.04 (2H, m, Ar), 8.09-8.14 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) δ: 9.1, 13.2, 19.4, 21.1, 22.2, 25.5, 25.7, 34.8, 35.1, 36.1, 43.2, 46.5, 57.5, 57.8, 70.5, 70.9, 73.8, 74.9, 75.4, 76.1, 77.7, 80.8, 84.8, 114.0, 114.9, 118.5, 127.4, 128.1, 128.5, 129.4, 129.8, 129.9, 131.3, 133.2, 133.4, 134.2, 139.9, 140.9, 157.5, 166.3, 169.3, 169.9, 173.0, 173.2, 203.9; HRFABMS m/z 942.3602 [M+H$^+$]; calcd for C$_{50}$H$_{56}$NO$_{17}$, 942.3548.

**Macrocyclic taxoid (159).** Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.08 (3H, s), 1.30 (3H, s), 1.43 (3H, d, J = 1.1 Hz), 1.68 (3H, s), 1.81 (1H, s), 1.86-2.32 (9H, overlapped), 2.50-2.77 (6H, overlapped), 3.65 (1H, d, J = 7.2 Hz), 4.21 (1H, d, J = 8.6 Hz), 4.33 (1H, d, J = 8.6 Hz), 4.39 (1H, m), 4.93 (1H, dd, J = 9.5, 1.9 Hz), 5.66 (1H, d, J = 7.2 Hz), 5.84 (1H, d, J = 3.5 Hz), 5.94 (1H, dd, J = 9.5, 3.5 Hz), 6.14 (1H, s), 6.36 (1H, t, J = 9.1 Hz), 6.42 (1H, brs), 6.81-6.85 (1H, m, Ar), 6.94-6.98 (1H, m, Ar), 7.07-7.10 (1H, m, Ar), 7.24 (1H, t, J = 8.4 Hz), 7.48-7.68 (7H, m, Ar, overlapped), 7.88-7.93 (2H, m, Ar), 8.06-8.11 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.8, 13.9, 20.8, 22.6, 22.9, 23.0, 27.1, 32.6, 33.7, 35.4, 36.0, 43.2, 45.4, 53.5, 58.3, 71.8, 73.0, 74.2, 75.3, 75.4, 76.3, 79.6, 81.5, 84.5, 114.2, 115.8, 118.4, 127.1, 128.6, 128.9, 129.2, 130.0, 130.2, 132.3, 132.7, 133.3, 133.8, 138.4, 142.1, 156.5, 166.5, 167.0, 169.7, 171.3, 171.4, 172.4, 203.5; HRFABMS m/z 938.3608 [M+H$^+$]; calcd for C$_{51}$H$_{56}$NO$_{16}$, 938.3599.
Macrocyclic taxoid (102). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.17 (3H, s), 1.31 (3H, s), 1.72 (3H, s), 1.82 (1H, s), 1.86 (3H, d, $J = 1.0$ Hz), 1.87-2.25 (6H, overlapped), 2.27 (3H, s), 2.42-2.78 (6H, overlapped), 3.77 (1H, d, $J = 7.1$ Hz), 3.93 (1H, d, $J = 6.8$ Hz), 4.25 (1H, d, $J = 8.4$ Hz), 4.31 (1H, d, $J = 8.4$ Hz), 4.40 (1H, m), 4.58 (1H, brt, $J = 6.1$ Hz), 4.82 (1H, dd, $J = 9.6$, 1.9 Hz), 5.64 (1H, dd, $J = 7.9$, 5.5 Hz), 5.71 (1H, d, $J = 7.1$ Hz), 6.20 (1H, t, $J = 9.2$ Hz), 6.29 (1H, s), 7.00 (1H, d, $J = 7.9$ Hz), 7.14-7.21 (2H, m, Ar, overlapped), 7.30-7.34 (1H, m, Ar), 7.41-7.72 (7H, m, Ar, overlapped), 7.80-7.87 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 9.7, 14.4, 20.8, 22.5, 25.1, 26.2, 27.1, 35.0, 35.6, 43.3, 45.8, 56.1, 58.6, 71.6, 72.2, 75.1, 75.5, 76.7, 79.2, 81.6, 84.9, 119.6, 121.2, 124.4, 127.2, 128.7, 128.8, 129.2, 130.2, 130.7, 132.1, 132.7, 133.5, 133.8, 139.8, 142.6, 151.6, 167.0, 168.2, 171.3, 172.4, 172.7, 203.5; HRFABMS $m/z$ 938.3671 [M+H$^+$]; calcd for C$_{51}$H$_{56}$NO$_{16}$, 938.3599.

4-Deacetyl-4-(5-carboxypentanoyl)-3’-desphenyl-3’-(m-hydroxyphenyl)-taxol (154).

Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$: 1.18 (3H, s), 1.20 (3H, s), 1.69 (3H, s), 1.70-2.04 (9H, overlapped), 2.20 (3H, s), 2.21-2.74 (6H, overlapped), 3.86 (1H, d, $J = 7.2$ Hz), 4.22 (2H, brs), 4.37 (1H, dd, $J = 10.8$, 6.6 Hz), 4.72 (1H, d, $J = 5.8$ Hz), 4.97 (1H, brd, $J = 9.0$ Hz), 5.54 (1H, d, $J = 5.8$ Hz), 5.68 (1H, d, $J = 7.2$ Hz), 6.17 (1H, t, $J = 9.2$ Hz), 6.48 (1H, s), 6.71-6.77 (1H, m, Ar), 6.96-7.02 (2H, m, Ar, overlapped), 7.27 (1H, t, $J = 8.0$ Hz), 7.46-7.74 (6H, m, Ar, overlapped), 7.89-7.95 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$: 9.1, 13.2, 19.4, 21.1, 24.8, 24.9, 25.6, 35.1, 35.3, 36.1, 36.2, 43.2, 46.5, 56.5, 57.8, 70.8, 70.9, 73.3, 74.9, 75.4, 76.2, 77.7, 80.9, 84.8, 114.2, 114.7, 118.2, 127.2, 128.1, 128.4, 129.4, 157
129.8, 130.0, 131.4, 133.2, 133.5, 134.3, 140.1, 140.8, 157.5, 166.3, 168.9, 169.9, 172.9, 173.2, 203.8; HRFABMS m/z 956.3688 [M+H⁺]; calcd for C₅₁H₅₈NO₁₇, 956.3705.

**Macrocyclic taxoid (103).** Colorless gum; ^1^H NMR (400 MHz, CDCl₃) δ: 1.18 (3H, s), 1.31 (3H, s), 1.68-1.75 (5H, overlapped), 1.85 (3H, s), 1.86-2.10 (6H, overlapped), 2.21-2.39 (5H, overlapped), 2.52-2.81 (6H, overlapped), 3.80 (1H, d, J = 7.2 Hz), 3.85 (1H, brs), 4.26 (1H, d, J = 8.5 Hz), 4.35 (1H, d, J = 8.5 Hz), 4.45 (1H, m), 4.64 (1H, d, J = 2.6 Hz), 4.90 (1H, dd, J = 9.4, 1.7 Hz), 5.70-5.77 (2H, overlapped), 6.20 (1H, t, J = 9.1 Hz), 6.30 (1H, s), 7.10-7.20 (3H, m, Ar, overlapped), 7.33 (1H, d, J = 8.1 Hz), 7.43-7.50 (3H, m, Ar, overlapped), 7.52-7.60 (3H, m, Ar, overlapped), 7.63-7.70 (1H, m, Ar), 7.78-7.83 (2H, m, Ar), 8.12-8.18 (2H, m, Ar); ^1^C NMR (100 MHz, CDCl₃) δ: 9.7, 14.4, 20.9, 22.5, 24.9, 25.2, 27.0, 28.3, 34.5, 35.6, 35.7, 35.9, 43.4, 45.6, 55.1, 58.5, 72.1, 72.5, 74.1, 75.1, 75.5, 76.5, 79.2, 81.5, 84.8, 120.1, 121.7, 123.7, 127.1, 128.7, 128.8, 129.2, 130.1, 130.4, 132.1, 133.0, 133.6, 133.8, 140.1, 142.3, 151.4, 166.9, 167.7, 171.3, 172.4, 172.5, 172.9, 203.6; HRFABMS m/z 952.3754 [M+H⁺]; calcd for C₅₂H₅₈NO₁₆, 952.3756.

**4-Deacetyl-4-(6-carboxyhexanoyl)-3’-desphenyl-3’-(m-hydroxyphenyl)-taxol (155).** Colorless gum; ^1^H NMR (400 MHz, CD₃OD) δ: 1.19 (3H, s), 1.21 (3H, s), 1.37-1.51 (2H, m), 1.62-1.75 (5H, overlapped), 1.76-1.90 (3H, overlapped), 1.95 (3H, d, J = 1.0 Hz), 2.02-2.11 (1H, m), 2.16-2.32 (6H, overlapped), 2.45-2.59 (2H, overlapped), 2.62-2.72 (1H, m), 3.86 (1H, d, J = 7.2 Hz), 4.22 (2H, brs), 4.37 (1H, dd, J = 10.8, 6.6 Hz), 4.74 (1H, d, J = 5.4 Hz), 4.95 (1H, d, J = 9.3 Hz).
159 Hz), 5.58 (1H, d, J = 5.4 Hz), 5.68 (1H, d, J = 7.2 Hz), 6.20 (1H, t, J = 9.3 Hz), 6.48 (1H, s), 6.75-6.79 (1H, m, Ar), 6.97-7.02 (2H, m, Ar, overlapped), 7.27 (1H, t, J = 8.3 Hz), 7.46-7.52 (2H, m, Ar, overlapped), 7.54-7.59 (1H, m, Ar), 7.59-7.66 (2H, m, Ar), 7.67-7.74 (1H, m, Ar), 7.89-7.94 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) δ: 9.1, 13.3, 19.4, 21.1, 24.8, 25.3, 25.6, 28.5, 34.9, 35.2, 36.1, 36.2, 43.2, 46.6, 56.2, 57.9, 70.9, 73.0, 74.9, 75.4, 76.2, 77.7, 80.9, 84.8, 114.0, 114.6, 118.2, 127.2, 128.1, 128.4, 129.4, 129.8, 130.0, 131.4, 133.2, 133.4, 134.3, 140.2, 140.9, 157.6, 166.3, 169.5, 169.9, 173.0, 173.3, 174.1, 203.8; HRFABMS m/z 970.3882 [M+H$^+$]; calcd for C$_{52}$H$_{60}$NO$_{17}$, 970.3861.

Macrocyclic taxoid (104). Colorless gum; $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.18 (3H, s), 1.28 (3H, s), 1.60-2.10 (16H, overlapped), 2.26 (3H, s), 2.30-2.64 (5H, overlapped), 2.70-2.87 (2H, overlapped), 3.79 (1H, d, J = 3.8 Hz), 3.88 (1H, J = 7.0 Hz), 4.26 (1H, d, J = 8.5 Hz), 4.35 (1H, d, J = 8.5 Hz), 4.45 (1H, m), 4.67 (1H, brs), 4.87 (1H, dd, J = 9.4, 1.8 Hz), 5.70-5.77 (2H, overlapped), 6.21 (1H, t, J = 8.9 Hz), 6.32 (1H, s), 7.05-7.15 (3H, m, Ar, overlapped), 7.37-7.69 (8H, m, Ar, overlapped), 7.74-7.80 (2H, m, Ar), 8.13-8.19 (2H, m, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 9.6, 14.7, 20.9, 22.1, 24.9, 26.6, 26.9, 28.5, 29.2, 34.6, 35.6, 35.7, 36.3, 43.3, 45.6, 54.8, 58.6, 72.1, 72.8, 73.4, 75.0, 75.6, 76.5, 78.9, 81.3, 84.8, 120.2, 121.7, 124.1, 127.1, 127.7, 128.8, 129.2, 130.2, 130.3, 132.0, 133.1, 133.7, 133.8, 140.1, 142.1, 151.1, 166.9, 167.3, 171.3, 172.6, 172.9, 173.2; HRFABMS m/z 966.3860 [M+H$^+$]; calcd for C$_{53}$H$_{60}$NO$_{16}$, 966.3912.

4-Deacetyl-4-(7-carboxyheptanoyl)-3'-desphenyl-3'-(m-hydroxyphenyl)-taxol (156).
Colorless gum; $^1$H NMR (400 MHz, CD$_3$OD) $\delta$: 1.19 (3H, s), 1.21 (3H, s), 1.31-1.42 (4H, overlapped), 1.52-1.64 (2H, m), 1.70 (3H, s), 1.72-1.92 (3H, overlapped), 1.96 (3H, d, $J = 1.1$ Hz), 2.12-2.29 (6H, overlapped), 2.32-2.40 (1H, m), 2.46-2.60 (2H, overlapped), 2.68-2.77 (1H, m), 3.88 (1H, d, $J = 7.1$ Hz), 4.21 (1H, d, $J = 8.3$ Hz), 4.25 (1H, d, $J = 8.3$ Hz), 4.37 (1H, dd, $J = 10.9$, 6.5 Hz), 4.80 (1H, d, $J = 4.4$ Hz), 4.94 (1H, d, $J = 9.6$ Hz), 5.65 (1H, d, $J = 4.4$ Hz), 5.69 (1H, d, $J = 7.1$ Hz), 6.22 (1H, t, $J = 9.1$ Hz), 6.50 (1H, s), 6.76-6.81 (1H, m, Ar), 6.98-7.05 (2H, m, Ar, overlapped), 7.28 (1H, t, $J = 8.0$ Hz), 7.45-7.73 (6H, m, Ar, overlapped), 7.86-7.91 (2H, m, Ar), 8.14-8.20 (2H, m, Ar); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$: 9.1, 13.3, 19.4, 21.0, 25.0, 25.1, 25.6, 28.4, 28.7, 35.3, 35.4, 35.5, 36.2, 43.3, 46.6, 55.7, 57.9, 70.9, 71.1, 72.8, 74.9, 75.4, 76.2, 77.7, 80.9, 84.8, 114.1, 114.5, 118.1, 127.1, 128.2, 128.4, 129.4, 129.8, 130.0, 131.4, 133.2, 133.5, 134.3, 140.1, 140.8, 157.5, 166.3, 168.9, 169.9, 173.0, 173.3, 203.8; HRFABMS $m/z$ 984.3974 [M+H$^+$]; calcd for C$_{53}$H$_{62}$NO$_{17}$, 984.4018.