Methods for Making 2-Debenzooyl and 2-Acetyl Taxol Derivatives

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Related U.S. Application Data


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DEUTSCHE PATENTANMELDUNGEN

U.S. PATENT DOCUMENTS

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Abstract

The present invention relates a method of making to 2-debenzooyl-2-acyl taxol derivatives and analogues thereof.
OTHER PUBLICATIONS


6 R₁ = R₂ = H

7 R₁ = COOBut, R₂ = H

8 R₁ = R₂ = COOBut

Figure 1
Figure 3

RC(O)X

99% formic acid
Na(OH) → RCOOH → Figure 6
METHODS FOR MAKING 2-DEBENZOYL AND 2-ACYL TAXOL DERIVATIVES


FIELD OF THE INVENTION

The present invention relates to methods for making 2-debenzoyl-taxol and 2-debenzoyl-2-acyl taxol analogues.

BACKGROUND OF THE INVENTION


Factors that contribute to the paucity of taxol congeners relative to their importance as anti-cancer agents include: the large size and complexity of these compounds, the presence of multiple reactive sites, and the presence of many stereospecific sites, which makes synthesis of even close analogues difficult. The large number of possible reaction mechanisms for even the simplest reactions leads to unpredictability of new reactions.

Although taxol has exhibited promising antineoplastic activity, there is a need for compounds which have even greater antineoplastic activity. It is believed that, by altering certain portions of the taxol structure, compounds with improved antineoplastic activity can be produced. Nevertheless, the aforementioned synthetic difficulties have prevented or at least slowed the development of more than only a few compounds, such as taxotere, which have similar or greater activity than taxol. Since it is believed that the tetracyclic taxane nucleus contributes to the antineoplastic activity of compounds incorporating same, it is desired to alter the ring substituents in order to develop derivatives of taxol and taxol analogues. Based on the previously noted studies, it is anticipated that such derivatives will have antineoplastic activity. Nevertheless, the complexity of taxol and its analogues makes it difficult to selectively alter certain substituents on the molecule. In particular, it has been previously impossible to selectively deacylate the C-2 position of taxol, and to produce taxol analogue modified at the C-2 position. Thus, there is a need for C-2 debenzyolated taxol analogues and congeners modified at the C-2 position, having antineoplastic activity, and intermediates thereof. There is also a need for methods for producing same and for using same to treat cancer. Since taxol and taxol analogues have low water solubility, there is a need to produce taxol analogues modified at the C-2 position having improved water solubility to aid in administration to cancer patients.
OBJECTS OF THE INVENTION

Thus, it is a primary object of this invention to produce taxol analogues which have a modified substituent at the C-2 position.

It is a further object of the present invention to provide taxol analogues having antineoplastic activity.

It is another object of this invention to produce taxol analogues that have improved in vivo activities for use as anti-cancer agents.

It is another object of the present invention to produce taxol analogues that have increased water solubility as compared with taxol.

It is yet another object of the present invention to make intermediates which are useful for producing taxol analogues having a modified substituent at the C-2 position. It is a further object to use taxol analogues which have a modified substituent at the C-2 position to treat cancer.

It is another object of this invention to provide methods for preparing derivatives of taxol and taxol analogues which have a modified substituent at the C-2 position.

SUMMARY OF THE INVENTION

The present application describes 2-debenzoyl taxol analogues, 2-debenzoyl-2-acyl taxol analogues, as well as procedures for preparing these compounds, and intermediates which can be utilized in preparing these compounds.

The compounds of the present invention may be used to treat patients suffering from cancer or as intermediates for making compounds which can be used to treat cancer. In a preferred embodiment, the taxol analogues have improved in vivo activities for use as anti-cancer agents. In another preferred embodiment, the taxol analogues have improved water solubility as compared with taxol.

Compounds of the present invention include compounds having the general formula:

wherein R₁ is an alkyl or substituted alkyl; R₃ is selected from the group consisting of H and C(O)Ra; R₂ is selected from the group consisting of H, OH, oxy protecting groups (i.e. triethylsilyloxy), ORb, and OC(O)Rc; R₃ is selected from the group consisting of H, OH, and OC(O)Rc wherein R₇ is other than phenyl and 3-hydroxyphenyl and R₄ is H or OH.

Alternate embodiments of the above-described compounds include compounds:

wherein R₂ is OH or an oxy protecting group;

wherein R₂ is H or C(O)R₇ and R is an alkyl or a substituted aryl;

wherein R₄ is OH and/or wherein R₁ has the general formula:

wherein Ar is an aryl; Z is selected from the group consisting of alkyls, alkenyls, alkynyls, alkoxyis, and aryls; X is H or a protecting group, and Y is selected from the group consisting of H, protecting groups, alkoyis, substituted alkyloyis, substituted arlyloyis, and arlyloyis.

Other preferred embodiments of the present invention include compounds having the formula:

wherein R is selected from the group consisting of H and C(O)Ra wherein R₇ is selected from the group consisting of alkyls, substituted alkyls, aryls, and substituted aryls; provided that R₇ is other than phenol and 3-hydroxyphenyl.

Yet another preferred embodiment of the present invention includes compounds having the general formula:

wherein Z is C(O)OC(CH₃)₃; R₁ is selected from the group consisting of H and C(O)OC(CH₃)₃; R₃ is selected from the group consisting of H and C(O)Ra wherein R₂ is selected from the group consisting of alkyls, substituted alkyls, aryls, and substituted aryls and is a protecting group (e.g. triethylsilyl, C(O)OC(CH₃)₃), or hydrogen.

Yet another preferred embodiment of the present invention comprises pharmaceutical compositions, which comprise an antineoplastically effective amount of at least one of the compounds described above.

The present invention also contemplates a method for treating cancer comprising the administration of an antineoplastically effective amount of at least one of the compounds described herein.
Another preferred embodiment of the present invention comprises a method of making a first compound having the general formula:

\[
\begin{align*}
\text{R}_1 \text{O} & \quad \text{O} \\
\text{O} & \quad \text{OH} \\
\text{O} & \quad \text{CH}_3
\end{align*}
\]

wherein \( \text{R}_1 \) is an alkyl or substituted alkyl; \( \text{R}_2 \) is selected from the group consisting of \( \text{H} \) and \( \text{C(O)}\text{R}_\text{a} \); \( \text{R}_3 \) is selected from the group consisting of \( \text{H} \), protecting groups, \( \text{R}_\text{b} \), and \( \text{C(O)}\text{R}_\text{b} \); \( \text{R}_4 \) is selected from the group consisting of \( \text{H} \) and \( \text{C(O)}\text{R}_\text{c} \), and wherein \( \text{R}_\text{a} \), \( \text{R}_\text{b} \), and \( \text{R}_\text{c} \) are independently selected from the group consisting of alkyls, substituted alkyls, alkenyls, alkynyls, aryls, and substituted aryls; provided that \( \text{R}_4 \) is other than phenyl and 3-hydroxyphenyl; comprising the step of replacing a moiety situated at the C-2 position of a second compound wherein said second compound is selected from the group consisting of taxol and taxol analogues.

For example, the foregoing method may be employed wherein said second compound has the general formula:

\[
\begin{align*}
\text{R}_5 \text{O} & \quad \text{O} \\
\text{O} & \quad \text{OH} \\
\text{O} & \quad \text{CH}_3
\end{align*}
\]

wherein \( \text{R}_5 \) is an alkyl or substituted alkyl; \( \text{R}_6 \) is selected from the group consisting of \( \text{H} \) and \( \text{C(O)}\text{R}_\text{d} \); \( \text{R}_7 \) is selected from the group consisting of \( \text{H} \), protecting groups, \( \text{R}_\text{b} \), and \( \text{C(O)}\text{R}_\text{b} \); \( \text{R}_8 \) is selected from the group consisting of \( \text{H} \) and \( \text{C(O)}\text{R}_\text{c} \), and wherein \( \text{R}_\text{d} \), \( \text{R}_\text{e} \), and \( \text{R}_\text{c} \) are independently selected from the group consisting of alkyls, substituted alkyls, alkenyls, alkynyls, aryls, and substituted aryls;

and further comprising a step wherein said second compound is reacted with lithium hydroxide;

and further comprising a reaction with an acylating agent, followed by the step of deprotection;

wherein the deprotection step comprises a reaction with formic acid; and

wherein said acylating agent comprises a reagent selected from the group consisting of acid halides, \( \beta \)-lactams, anhydrides, and carboxylic acids.

In another embodiment of the method described above said first compound has the formula:

\[
\begin{align*}
\text{R}_9 \text{O} & \quad \text{O} \\
\text{O} & \quad \text{OH} \\
\text{O} & \quad \text{CH}_3
\end{align*}
\]

wherein \( \text{R}_9 \) is a protecting group and \( \text{R} \) is selected from the group consisting of alkyl, substituted alkyl, aryl, and substituted aryl.

The method further comprises the step of deprotection; said deprotection step occurring subsequent to the step of adding an acylating agent; and

wherein said deprotection step comprises the addition of formic acid.

The present invention also discloses a method for making a first compound having the formula:

\[
\begin{align*}
\text{R}_3 & \quad \text{R}
\end{align*}
\]

wherein \( \text{R}_3 \) is a protecting group and \( \text{R} \) is selected from the group consisting of alkyl, substituted alkyl, aryl, and substituted aryl.

The method further comprises the step of deprotection; said deprotection step occurring subsequent to the step of adding an acylating agent; and

wherein said deprotection step comprises the addition of formic acid.

The present invention also comprises analogues of taxol in which the benzoic group has been replaced by an acyl.
C(O)Ra, wherein Ra is selected from the group consisting of alkyl, substituted alkyl, alkenyl, alkynyl, aryl, and substituted aryl;

provided that Ra is not phenyl or 3-hydroxyphenyl.

Another preferred embodiment of the present invention includes a method for making taxol analogues having a hydroxy or acyloxy substituent, other than benzoyloxy and 3-hydroxybenzoyloxy, the C-2 position of the B-ring of the taxane tetracyclic nucleus comprising the step of removing a benzoyl moiety from said C-2 position of a taxol congener having a benzoyloxy group at said C-2 position.

In a variation of the above-described method, said taxol analogues have the general formula:

wherein R1 is an alkyl or substituted alkyl; R5 is selected from the group consisting of H and C(O)Ra; R2 is selected from the group consisting of H, OH, oxy protecting groups, ORb, and C(O)Rb; R3 is selected from the group consisting of H, OH, and OC(O)Rc, and wherein Ra, Rb, and Re are independently selected from the group consisting of alkyls, substituted alkyls, alkenyls, alkynyls, aryls, and substituted aryls provided that R1 is other than phenyl and 3-hydroxyphenyl; and R4 is H or OH.

The subject matter of the present application includes taxol analogues comprising a substituted benzoyloxy substituent at the C-2 position. Non-limiting examples include meta substituted benzoxys, meta- and para-substituted benzoals, and ortho-substituted benzoals. Analogues in which a heterocyclic moiety replaces the phenyl ring of the benzoyl moiety are also disclosed. Certain non-limiting examples of such compounds are shown in Table I, compounds 13a, 13c–13t, and 13y–13ee. Certain, non-limiting preparative methods are also described herein. The present invention also contemplates the use of these compounds in the treatment of cancer.

In a preferred embodiment of the present invention, it has been surprisingly discovered that, by acylating the C-2 hydroxyl of a taxol analogue with 3,5-fluorobenzoic acid, followed by deprotection of the resulting compound, a compound having about 25,000 times taxol's antineoplastic activity as determined by a cell culture assay is formed. The compound prepared is shown below:

The compounds of the present invention may be used to treat patients suffering from cancer or as intermediates for making compounds which can be used to treat cancer. In a preferred embodiment, the taxol analogues have improved in vivo activities for use as anti-cancer agents. In another preferred embodiment, the taxol analogues have improved water solubility as compared with taxol.

In a preferred embodiment, compounds of the present invention are taxol or taxol congeners having a meta-substituted benzoyloxy group at the C-2 position of the B-ring of the tetracyclic nucleus. Preferred meta-substituents include, but are not limited to halogens (e.g., chlorine, bromine, fluorne, iodine), alkoxy (e.g., methoxy, ethoxy, etc.), diatomic species (e.g., CN, NC, etc.), linear triatomic species (e.g., N3, NCO, etc.), and azido containing moieties. The meta-substituted benzoyloxy group may additionally comprise a (non-hydrogen) para-substituent and/or ortho-substituents.

Another preferred embodiment of the present invention involves compounds having the general formula:

wherein R1 is an alkyl or a substituted alkyl, R2 is selected from the group consisting of H, OH, alkyloxy, arkyloxy, oxy protecting groups (e.g. triethylsilyloxy) and OC(O)Ra, R3 is selected from the group consisting of H, OH, and OC(O)Ra, wherein Ra and Rb can be the same or different and are selected from the group consisting of alkyls, substituted alkyloxy, alkenyls, alkyloxy, aryls, and substituted aryls, wherein T, U, W, V, and X are any substituents, provided that T, U, W, V, and X are not all H and when T, U, W, and V are H, X is other than OH and when T, U, V, and X are H, W is other than OH and R4 is H or OH.

Other preferred embodiments of the present invention include the compound having the general formula described above wherein.
R₁ has the general formula:

![Chemical Structure 1](image1)

in which Ar is an aryl; Z is selected from the group consisting of alkyls, alkenyls, alkynyls, alkoxy (e.g. OC(CH₃)₃) and aryls (e.g. C₆H₅); and Y is selected from the group consisting of H, protecting groups, alkyls, aryls.

T, U, W, V, and X are independently selected from the group consisting of hydrogens, halogens, alkoxy, diatoms, and linear triatoms.

Alternatively, X may be selected from the group consisting of alkyls, substituted alkyls, alkenyls, alkynyls, and substituted aryls.

In many preferred embodiments, R₁ is the substituted alkyl appearing at the C-13 side-chain of taxol.

Particularly preferred compounds have the general formula:

![Chemical Structure 2](image2)

wherein T, U, V, W, and X are any substituents provided that T, U, V, W, and X are not all H and when T, U, V, and W are H, X is not OH, and when T, U, V, and X are H, W is not OH.

Alternative preferred embodiments of the present invention include the compounds having the general formula described above wherein X is selected from the group consisting of alkyls, substituted alkyls, alkenyls, alkynyls, aryls, substituted alkyls, amides, amines, nitros, and carboxylates; or wherein T, U, V, W, and X are all fluorine.

The present invention contemplates methods of treating cancer comprising the administration of an antineoplastically effective amount of any of the taxol analogues described herein.

The present invention also provides a method for making a first compound having the formula:

![Chemical Structure 3](image3)

wherein T, U, V, W, and X are any substituents provided that T, U, V, W, and X are not all H and when T, U, V, and W are H, X is not OH, and when T, U, V, and X are H, W is not OH.

Alternative preferred embodiments of the present invention include the compounds having the general formula described above wherein X is selected from the group consisting of alkyls, substituted alkyls, alkenyls, alkynyls, aryls, substituted alkyls, amides, amines, nitros, and carboxylates; or wherein T, U, V, W, and X are all fluorine.

The present invention contemplates methods of treating cancer comprising the administration of an antineoplastically effective amount of any of the taxol analogues described herein.

The present invention also provides a method for making a first compound having the formula:

![Chemical Structure 4](image4)

wherein R₄ is H or OH, R₅ is an alkyl or a substituted alkyl, R₆ is selected from the group consisting of H, OH, alkoxy, aryloxy, and substituted aryls.

Alternative preferred embodiments of the present invention include the compounds having the general formula described above wherein X is selected from the group consisting of alkyls, substituted alkyls, alkenyls, alkynyls, aryls, substituted alkyls, amides, amines, nitros, and carboxylates; or wherein T, U, V, W, and X are all fluorine.

The present invention contemplates methods of treating cancer comprising the administration of an antineoplastically effective amount of any of the taxol analogues described herein.

The present invention also provides a method for making a first compound having the formula:
Alternative preferred embodiments of the method of making said first compound, described above, include:

wherein R₆ has the general formula:

wherein Ar is an aryl; Z is selected from the group consisting of alkyls, alkenyls, alkylnyls, alkoxyis, (e.g., OC(CH₃)₃), and aryls (e.g., C₆H₅) and Y is selected from the group consisting of H, protecting groups, alkoxyis, and arlylos;

wherein T, U, V, and W are H and X is selected from the group consisting of halogens, diatomics and linear triatomics; and

wherein Y in said second compound is triethylsilyl and R₇ is triethylsilyloxoy and further wherein said second compound is debenzyolated via reaction in a mixture comprising aqueous sodium hydroxide, a phase-transfer catalyst, and an organic solvent, to yield a compound having a hydroxyl at the C-2 position, wherein said compound having a hydroxyl at the C-2 position is reacted in a subsequent step with meta-C₆H₅X-COOH.

DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates the reaction of taxol with excess di-tert-butyldicarbonate in the presence of 4-dimethylaminopyridine (DMAP) to yield 2',7-di(t-butoxycarbonyloxy) taxol, 2',7,N-tri(t-butoxycarbonyloxy) taxol, and 1,2',7,N-tetra(t-butoxycarbonyloxy) taxol.

FIG. 2 illustrates the reaction of 2',7,N-tri(t-butoxycarbonyloxy) taxol with LiOH to yield 2',7,N-tri(t-butoxycarbonyloxy)-2-debenzoyl taxol; and prolonged reaction resulting in cleavage of the D-ring of the taxane skeleton.

FIG. 3 illustrates the reaction of 2',7,N-tri(t-butoxycarbonyloxy)-2-debenzoyl taxol with an acylating agent to yield 2',7,N-tri(t-butoxycarbonyloxy)-2-debenzoyl-2-acyl taxol, followed by removal of the oxyprotecting groups with formic acid to yield 2-debenzoyl-2-acyl taxol.

FIG. 4 illustrates the reaction of taxol with one equivalent of di-tert-butyldicarbonate in the presence of 4-dimethylaminopyridine to yield the 2'-t-butoxycarbonyloxy derivative of taxol followed by reaction with triethylsilyl chloride to yield 2-t-butoxycarbonyloxy-7-triethylsilyltaxol, and the subsequent reaction with an excess of di-tert-butyldicarbonate to yield 2',N-di-t-butoxycarbonyloxy-7-triethylsilyl taxol.

FIG. 5 illustrates the reaction of 2N-t-butoxycarbonyloxy-7-(triethylsilyl)taxol with lithium hydroxide to yield 2N-di-t-butoxycarbonyloxy-2-debenzoyl-7-(triethylsilyl) taxol followed by reaction with an acylating agent and subsequent deprotection with formic acid to yield 2-debenzoyl-2-acyl taxol.

FIG. 6 illustrates the reaction of taxol with triethylsilyl chloride in the presence of imidazole to yield 2',7-triethylsilyl taxol, followed by reaction with sodium hydroxide under phase-transfer conditions to yield 2-debenzoyl-2',7-(triethylsilyl) taxol followed by reaction with a carboxylic acid to yield 2-debenzoyl-2',7-triethylsilyl-2-acyl taxol.

DEFINITIONS

Unless clearly indicated by context or statement to the contrary, the terms used herein have the meanings as conventionally used in the chemical arts, and definitions incorporate those used in standard texts, such as but not limited to Grant & Hack's Chemical Dictionary, 5th edition, McGraw-Hill, 1987; Streitwieser et al., Introduction to Organic Chemistry, 2nd edition, Macmillan, 1981; and March, Advanced Organic Chemistry, 3rd edition, Wiley, 1985.

The term alkyl refers to straight-chain or branched-chain hydrocarbons. In some preferable embodiments, alkyl refers to the lower alkyls containing from one to six carbon atoms in the principal chain and up to 10 carbon atoms the lower alkyls may be straight or branched chain and by way of non-limiting example include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, and the like.

The term substituted alkyl refers to groups including, but not limited to, the alkyl groups discussed above which have as substituents halo (e.g., chloro, bromo), nitro, sulfate, sulfonyloxy, carboxy, carboxylate, phosphate (e.g., OP(O)(OH)₂, OP(O)(OH)), carbo-lower-alkoxy (e.g., carboxemethoxy, carboxethoxy), amino, mono- and di-lower-alkylamino (e.g., methylamino, dimethylamino, carboxamido, sulfonamido, diethylamino, methylamino; amide lower-alkoxy (e.g., methoxy, ethoxy), lower-alkanoyloxy (e.g., acetoxy), alkenyl, alkynyl, aryl, aryloxy, and combinations of these (e.g., alkylbenzenesulfonates).

The term aryl has the meaning known in the chemical arts, and aryl also refers to heterocyclic aryls. Substituted aryls have the same substituents discussed above for the substituted alkyls and also include, but are not limited to, aryls having lower alkyl substituents such as methyl, ethyl, butyl, etc.

The use of the term “any substituent” in the present application refers only to those substituents capable of bonding to the C-2 position of the taxane tetracyclic nucleus and which are not incompatible with the remainder of the taxol analogue structure (i.e. not so large as to preclude bonding to the C-2 position, or not so reactive as to lead to rapid decomposition of the structure of the taxol or taxol analogue). The term “analogues of taxol” refers to compounds comprising the taxane tetracyclic nucleus and an acetyl group at the C-4 position.

In the context of the present invention, protecting groups can be used to protect hydroxyls, or the NH group of an amide.

DETAILED DESCRIPTION OF THE INVENTION

The present invention pertains to the removal of the benzyol group at the C-2 position of taxol and taxol analogues, thus resulting in a 2-debenzoyl taxol analogue. The 2-debenzoyl taxol analogues can be reacylated with acylating agents to produce 2-debenzoyl-2-acyl taxol analogues.

As illustrated in FIG. 1, treatment of taxol [1] with excess di-tert-butyldicarbonate (BOC₂O) in the presence of 4-dimethylaminopyridine (DMAP) converts it over a period of five days to a mixture of 2,7-di(t-BOC)taxol [6], 2',7,N-tri(t-BOC)taxol [7], and 1,2',7,N-tetra(t-BOC)taxol [8] (t-BOC is tert buty oxy carbonate).

Compound 8 could be isolated after careful work-up that avoids acidic conditions, but it was most conveniently converted into the tri(t-BOC)taxol [7] by a mild acid treatment during work up. Using this procedure the tri(t-BOC) taxol [7] could be obtained in 41% yield and the di(t-BOC)taxol [6] in 32% yield, for a combined yield of 73%.
It has been surprisingly discovered that treatment of taxol analogues, in which the C-2' and C-7 positions have been protected with t-BOC groups with lithium hydroxide results in selective hydrolysis at the C-2 position. For example, with reference to FIG. 2, treatment of 2',7,N-tri(t-BOC)taxol with lithium hydroxide converted it into 2',7,N-tri(t-BOC)-2-debenzoyltaxol [9].

In this process the 2-benzoyl group is cleaved, but the t-BOC groups are not cleaved and neither are any of the other ester functions. If reaction with lithium hydroxide is prolonged, conversion of 9 into the rearranged product 10 occurs, and it has not so far been possible to obtain 9 without some formation of 10.

Conversion of 2',7,N-tri-(t-BOC)-2-debenzoyltaxol [9] into 2-debenzoyl taxol was not possible with conventional t-BOC cleavage agents, because rearrangement occurs simultaneously with deprotection to yield the isotaxol 11.

FIG. 3 illustrates, by way of a non-limiting example, preparation of 2-debenzoyl-2-acyl taxols by reacylation of the debenzoyl derivative 9 with a desired acyl group to yield the protected derivative 12. Deprotection of 12 a with 99% formic acid then yields the taxol analogue 13.

A second process for the preparation of 2-debenzoyl-2-acyl taxol analogues involves the selective protection of the C-7 position with a protecting group such as a triethylsilyl. A preferred embodiment of a second process for the synthesis of C-2 analogues of taxol is illustrated in FIGS. 4 and 5. Taxol is first converted to its 2'-t-BOC derivative 14, and this is treated with triethylsilyl chloride to give the 2-t-BOC, 7-triethylsilyl derivative 15. Finally 15 is treated again with di-t-butyl dicarbonate to give the N-t-BOC, 2'-t-BOC, 7-triethylsilyl derivative 16.

The taxol derivative 16 can be debenzyolated as described earlier to give the 2-debenzoyl analogue 17. Reacylation of 17 with a desired acyl group then yields the acyl derivative 18, where CO(R) is any desired acyl group. Deprotection of 18 with 99% formic acid then gives a 2-debenzoyl-2-acyltaxol derivative 13. One example of this chemistry is the conversion of 17 back to taxol by benzylation to the benzoyl derivative 16 and deprotection to yield taxol. Reaction of 17 with 3-(3-(3-trifluoromethyl)-3H-diazirin-3-yl)phenoxyacetic acid yields 2,N-di(t-BOC)-7-(triethylsilyl)-2-debenzoyl-2(3-(3-trifluoromethyl)-3H-diazirin-3-yl)phenoxyacetyltaxol, which can be subsequently deprotected to yield the compound shown below.

In a particularly advantageous process for the preparation of 2-debenzyolated-2-acyl taxol analogues, the substituent at the C-2 position is converted from an acyl to a hydroxy by base catalyzed hydrolysis under phase transfer conditions. An embodiment of this preferred process for the preparation of 2-debenzyolated-2-acyl taxol analogues is illustrated in FIG. 6. Conversion of taxol 1 to its 2,7-di(triethylsilyl) derivative 21 proceeds smoothly and in good yield on treatment of taxol with triethylsilyl chloride and imidazole in DMF. The key reaction is thus the hydrolysis of 21 under phase-transfer conditions with aqueous sodium hydroxide. This converts 21 to 2,7-di(triethylsilyl)-2-debenzyolated taxol 22. Acylation of 22 with an appropriate benzoic, or substituted benzoic, or other carboxylic acid then gave the protected 2-debenzyolated-2-acyltaxol analogue 23, which could be deprotected readily to the 2-debenzyolated-2-acyltaxol 13.

Acylation of 22 with various aromatic carboxylic acids in the presence of dicyclohexylcarbodiimide and 4-pyrrolidinopyridine has led to the preparation of various 2-debenzyolated-2-acyl taxols 13. As shown in Table 1, the activities of several 2-debenzyolated-2-acyltaxol analogues were determined in a cell culture assay using P-388 lymphocytic leukemia cells, and compared with that of taxol; compounds with an ED_{50}(taxol) value of less than 1 are more active than taxol in this assay. For details of the cell culture assay, see Abbott, B. J., "Protocol 14 of Instruction 275," National Cancer Institute, National Institutes of Health, Jan. 24, 1978.

It was found that compounds lacking the benzoyl group, such as [13b], were less active or about as active as taxol. Of particular significance compounds with an ortho-substituted benzoyl group, such as 13e, were found to have increased bioactivity as compared with taxol. Of particular significance is the discovery that compounds with a meta-substi-
tuted benzoyl group have much greater biological activity than taxol [13c, 13d, 13f]. For example, 2-debenzoyl-2-(m-
azidobenzoyl)taxol [13f] shows activity against P-388 leu-
kenia in vitro that is 500 times higher than that of taxol. The co-
pending application also discloses that compounds with
fluoro substituted benzoyls have especially high biological
activity; for example 2-debenzoyl-2-(5,5-difluorobenzoyl)
taxol [13f] shows activity against P-388 leukemia in vitro
that is 25,000 times higher than that of taxol. The com-
pounds disclosed in the co-pending U.S. application are thus
highly promising candidates for use as anticancer drugs
when administered in an antineoplastically effective amount
to patients suffering from cancer.

Having shown the preparation of 2-debenzoyl taxols and
2-debenzoyl-2-(acyl) taxols, additional non-limiting pre-
ferred embodiments of this invention include congeners of
2-debenzoyl taxols and 2-debenzoyl-2-(acyl)taxols in which
various modifications are made to the taxol structure, such
as, but not limited to, varying substituents at the C-1
position, C-7 position and/or the C-13 side
chain.

Particularly desired modifications include, but are not
limited to, modifications which increase water solubility or
stability of the 2-debenzoyl-2-(meta-substituted benzoyl)
taxols and taxol congeners. Non-limiting examples of such
water soluble derivatives can be produced by the methods
disclosed in U.S. Pat. Nos. 5,059,699 and 4,942,184, the
solubilizing groups described therein can likewise be
attached to compounds of the present invention to increase
their water solubility.

It is known that the C-7 hydroxyl group on taxol and
Baccatin III can be readily epimerized, and that epimeriza-
tion has little effect on bioactivity. See “The Chemistry of
Taxol,” Pharmac. Ther., 52, 1–34 (1991). It is therefore to be
understood that this invention contemplates either or both
C-7 enantiomers in the compounds of the present invention.
Nonetheless, it is often preferred to prevent epimerization of
the C-7 hydroxy and in the Examples of the present
invention epimerization is avoided by protecting the C-7
hydroxyl prior to exposing taxol or its analogues to condi-
tions which catalyze epimerization.

In addition to the acylations and acylxooxy hydroxy
conversions at the C-7 and C-10 positions, of which certain
embodiments are exemplified in the literature; this invention
also contemplates the removal of the oxygen group(s) from the
C-1, C-7, and/or C-10 positions. Certain, preferred embodi-
ments of these removals are described below.

10-deacetoxytaxol can be prepared by treatment of 7-(tri-
ethylsilyl)-10-deacetyl baccatin III with carbon disulfide,
methyl iodide, and sodium hydride to yield the 10-(methyl-
xyanxyl) derivative. Treatment of this with triethylamine
hydroxide (TBTH) and azobisisobutyronitrile (AIBN) yields
7-(triethylsilyl)-10-deacetoxy baccatin III, which can be
esterified with the taxol side-chain as previously disclosed.
(Highly efficient, practical approach to natural taxol, J. Am.
Chem. Soc., 1988, 110, 5917–5919). Treatment of this 10-deacetoxytaxol as described for taxol itself then converts it to the 10-deacetoxy-2-debenzoyl-2-acetyl taxol analogues
described.

7-deoxytaxol can be made by treatment of 2',3-triethylsilyl-
taxol with sodium hydride, carbon disulfide, and methyl
iodide to give the 7-(methylxanxyl) derivative, which is
then deoxygenated with TBTH, and AIBN to yield 2',3-
triethylsilyl-7-deoxytaxol. This is then converted to its 2-de-
benzoyl-2-acetyl derivative as previously described for taxol.

It is contemplated that 1-deoxytaxol can be made by
treating 2',7-di(triethylsilyl)taxol with 2N NaOH in the
presence of carbon disulfide, methyl iodide, benzene, and a
phase-transfer catalyst, to give the 1-(methylxanxyl)-2-
debenzyxyl derivative. Acylation with a suitable 25 sub-
stituted benoic acid then yields the corresponding 2-aryl
derivative, which can be reduced to the 1-deoxy derivative
with TBTH and AIBN. Deprotection of the 2'-and the
7-positions then gives a 1-deoxy-2-debenzyxyl-2-aryl taxol
derivative.

In addition to the described alterations to the C-2 position,
the C-2 position can also be converted to a methylene. For
example, 1-benzoyl-2-deoxytaxol can be prepared by treat-
ing 2',7-di(triethylsilyl)taxol with sodium hydride, carbon
disulfide, and methyl iodide, to yield 1-benzoyl-2-(methyl-
xyanxyl)2',7-di(triethylsilyl)taxol; the benzoyl group is trans-
ferred from the C-2 to the C-1 position during this reaction.
Deoxygenation with AIBN and TBTH followed by removal of
the 2',7-TES groups then yields 1-benzoyl-2-deoxytaxol.

METHODS AND MATERIALS

Specific reaction methods are described in more detail in
the following non-limiting examples. Certain methods used
herein are generally described in the “Journal of Organic
Chemistry,” 51, pp. 797–802 (1986). Low resolution mass
spectrometry data were obtained on a VG 7070 E-HF mass
spectrometer. All technical and scientific terms used herein
have the same meaning as commonly understood by one of
ordinary skill in the art. Other methods and materials similar
or equivalent to those described herein can be used in the
practice or testing of the present invention.

EXAMPLES

Preparation of 2',7,N-tri(t-BOC)taxol (7).

Taxol (25 mg, 0.0293 mole) and acetonitrile (1.5 ml,
freshly dried and distilled over calcium hydride) were added
to a flame dried 25 ml round bottom flask, under argon
atmosphere. To this solution was added 84.9 mg (0.389
mmole) of di-t-tert-butyl dicarbonate in 1.00 ml of dry aceto-
nitrile under argon. After stirring for 5 min., DMAP (4.8 mg)
was added. The reaction mixture, which became pale yellow
to orange in color, was then stirred for five days; on the
second and fourth days after initiating the reaction, 85 mg of
di-t-tert-butyl dicarbonate in 0.5 ml of dry acetonitrile was
added, followed by addition of 4.8 mg of DMAP. The
reaction mixture was quenched by diluting it with ethyl
acetate, followed by removal of the solvent on a rotary
evaporator. The orange residue was then dissolved in ethyl
acetate and washed with dilute HCl followed by a rapid
wash with cold 0.05N NaHCO3 solution. The solution was
washed with brine, dried with sodium sulfate, and the
solvent was removed by use of a rotary evaporator. Purifi-
cation by preparative thin layer chromatography (PTLC)
(Araltech, 500m SiO2) gave two major bands with Rf 0.27
and 0.23. The band with Rf 0.27 was scraped off and eluted
with acetone to give the title compound on evaporation (11.1
mg, 33%) mp 188°–192°C. Elution of the band at Rf 0.23
was added, followed by addition of 4.8 mg of DMAP. The
reaction mixture was quenched by diluting it with ethyl
acetate, followed by removal of the solvent on a rotary
evaporator. The orange residue was then dissolved in ethyl
acetate and washed with dilute HCl followed by a rapid
wash with cold 0.05N NaHCO3 solution. The solution was
washed with brine, dried with sodium sulfate, and the
solvent was removed by use of a rotary evaporator. Purifi-
cation by preparative thin layer chromatography (PTLC)
(Araltech, 500m SiO2) gave two major bands with Rf 0.27
and 0.23. The band with Rf 0.27 was scraped off and eluted
with acetone to give the title compound on evaporation (11.1
mg, 33%) mp 188°–192°C. Elution of the band at Rf 0.23
gave 2',7-di(BOC) taxol (10.1 mg, 33%). For 1H-NMR, see
Table 2; Mass Spectrometer, MS, gave m/z of 1053 (MH+).
Conversion of 2',7,N-tri(t-BOC)-2-debenzoyl taxol (9) to
2',7-N-tri(t-BOC)-2-debenzoyl taxol 9 (7 mg, 0.007
mmol), benzoic acid (24 mg, 0.198 mmol) and dicyclohexy-
larbodiimide, DCC, (41 mg, 0.198 mmol) in 50 ml dry
toluene were mixed under an argon atmosphere, and 4-pyr-
rolidinopropiridaine was added as a catalyst. The reaction mix-
ture was stirred at room temperature (24°C) overnight and
then diluted with ethyl acetate. The residue was filtered and
the filtrate was then purified by PTLC (Analtech 500 μm; hexane: ethyl acetate 1:1) to give 2',7,N-tri(t-BOC)-taxol 7 (4.5 mg, 58%).

Preparation of 2',7,N-tri(t-BOC)-2-debenzoyl yltaool 9.

To a stirred solution of 2',7,N-tri(t-BOC)taxol (34.5 mg, 0.034 mmole) in 2.5 ml of tetrahydrofuran (THF), 0.4 ml 0.1N lithium hydroxide solution at 0° C. was slowly added. After complete addition (about 5 minutes) the ice bath was removed and the reaction mixture was stirred for 1.5 hour at room temperature. TLC showed conversion of the starting material to two new products (Rf 0.28 and 0.19 in hexane:ethyl acetate, 1:1), together with unreacted starting material. The reaction mixture was then diluted with 10 ml diethyl ether, washed with brine, and dried over sodium sulfate. The solvent was evaporated on a rotary evaporator to obtain crude product, which was purified by preparative TLC (Analtech, 500 μm, SiO2, hexane:ethyl acetate, 1:1) to yield 2',7,N-tri(t-BOC)-2-debenzoyl taxol (Rf 0.19) (8.7 mg, 8.7%).

Conversion of 2',7,N-tri(t-BOC) taxol 7 to Taxol.

A solution of 50% formic acid in dry methylene chloride (200 μl 99% formic acid+200 μl dry CH2Cl2), 2',7,N-tri(t-BOC)taxol (10 mg) was added and stirred for 5 hours at room temperature. The excess formic acid was removed by evaporation on a vacuum pump, and then washed with 5% NaHCO3, water and brine, and evaporated. Purification of the crude material by PTLC (Analtech 500 mm; hexane:ethyl acetate 1:1) yielded taxol (3 mg, 38.5%), identical with an authentic sample.

Preparation of 2',7,N-tri(t-BOC)-2-debenzoyl isoxatol 10.

If the preparation of compound 9 described above is allowed to proceed for a longer time, the spot with Rf 0.28 becomes the major product. After a 3 hour reaction, 4.2 mg of this material could be isolated from 10.5 mg of starting material (56.7%). Characterization gave a melting point, Mp, of 158°—160° C.; for proton NMR data, see Table 2.

Preparation of 2-Debenzoylisoxatol 11.

A mixture of 2',7,N-tri(t-BOC)-2-debenzoyl isoxatol 10 (14 mg, 0.0133 mol), and 0.5 ml of 99% formic acid was stirred at room temperature in a 5 ml round bottom flask for 90 minutes under argon. The excess formic acid was removed under reduced pressure. The residue was diluted with ethyl acetate (10 ml), washed quickly with 0.05N aqueous NaHCO3, water and brine, and evaporated. The crude product was purified by PTLC (hexanecetyl acetate, 1:1). The lower band of Rf 0.1 was scraped and eluted several times with acetone. Removal of the solvent gave 2-debenzoylisoxatol 11, 3.8 mg (34%). For 1H-NMR data, see Table 2. MS gave m/z 772 (MNa+, MH+).

Preparation of 2-(t-BOC)taxol 14.

Taxol (85.3 mg, 0.1 mmol) and acetonitrile (2 ml, freshly dried and distilled over calcium hydride) were added to a flame dried 25 ml round bottom flask under argon. To this solution at 0° C. was added 21.8 mg (0.1 mmol) of di-tert-butyl dicarbonate in 2.00 ml of dry acetonitrile under argon. Flame dried 25 ml round bottom flask under argon. To this solution of 2',7,N-di(t-BOC)-7-(triethylsilyl)taxol (34.5 mg, 0.034 mmol) at 0° C. under argon. The reaction mixture was stirred for 3 hours at room temperature, and then quenched by diluting with ethyl acetate and washing the organic layer several times with water and brine, followed by drying with sodium sulfate. The reaction mixture was then evaporated to obtain the pure compound 15, (94.9 mg, 89%), Rf (hexanecetyl acetate, 1:1) 0.66. For 1H-NMR, see Table 3.

Preparation of 2',N-di(t-BOC)-7-(triethylsilyl)taxol 16.

To a stirred solution of 2-(t-BOC)taxol (92.4 mg, 0.09 mmol) in 0.5 ml dry acetonitrile under argon atmosphere di-t-butyl dicarbonate (377.6 mg, 20 mmol) in 0.5 ml of CH3CN was added. After stirring for 5 minutes at room temperature, DMAP (5 mg) was added. The reaction mixture was then stirred for 3 hours at room temperature, and then worked up by diluting with ethyl acetate, followed by removal of the solvent on a rotary evaporator. The residue was then diluted with ethyl acetate and washed with cold dilute HCl, cold 0.05N NaHCO3, water, and brine, and dried over sodium sulfate. The solvent was then evaporated to yield crude product, which was purified by passing through a small silica gel column to yield the pure compound 16 (89 mg, 88%). Rf (hexanecetyl acetate, 1:1) 0.55. For 1H-NMR data, see Table 3.

Preparation of 2',N-di(t-BOC)-7-(triethylsilyl)-2-debenzoyl taxol 17.

To a stirred solution of 2',N-di(t-BOC)-7-(triethylsilyl) taxol (45 mg, 0.038 mmol) in 4.5 ml of THF, 0.45 ml of 0.1N LiOH solution was added. The mixture was held at 0° C. with an ice bath during combination of the ingredients. After complete addition, the ice bath was removed and the solution was stirred for 2 hours at room temperature. TLC showed the presence of two new spots at lower Rf, along with starting material. The reaction was then worked up by diluting with ether and washing with brine. The brine layer was washed with fresh ether and the combined organic layer was dried over sodium sulfate and evaporated. The crude product was then purified on PTLC (Analtech, 500 μm, Hexane:EtOAc, 1:1). The slower moving band of Rf 0.66 was scraped and eluted several times with ethyl acetate. Removal of the solvent gave 2-debenzoyl taxol 17 (95.3 mg, 99.6%), Rf (hexanecetyl acetate, 1:1) 0.36. For 1H-NMR data, see Table 3.

Preparation of 2-(t-BOC)-7-(triethylsilyl) taxol 15.

To a stirred solution of 2-(t-BOC)taxol (95.3 mg, 0.1 mmol) in 2 ml dry DMF, imidazole (34 mg, 0.5 mmol) was slowly added, followed by addition of triethylsilyl chloride (83.9 ml, 0.5 mmol) at 0° C. under argon. The reaction mixture was stirred for 3 hours at room temperature, and then quenched by diluting with ethyl acetate and washing the organic layer several times with water and brine, followed by drying with sodium sulfate. The solvent was then evaporated to yield the pure compound 15, (94.9 mg, 89%), Rf (hexanecetyl acetate, 1:1) 0.66. For 1H-NMR, see Table 3.
and evaporated. Purification of the residue by PTLC (EtOAc:hexanes, 1:1) yielded taxol (2 mg, 28%), identical with an authentic sample. Preparation of 2',N-di(t-BOC)-7-(triethylsilyl)-2-debenzoyl-2-(3-(trifluoromethyl)-3H-diazirin-3-yl)phenoxyacetyl-taxol.

A mixture of 2',7-di(triethylsilyl)-2-debenzoyltaxol 22 (10.0 mg, 0.01 mmol), DCC (42.0 mg, 0.20 mmol), 4-pyrolidinopyridine (catalytic quantity), m-nitrobenzoic acid (0.20 mmol), and toluene (0.1 mL) was stirred at room temperature for 12 hours and then diluted with (10 mL) of ethyl acetate, EtOAc. The organic layer was separated and washed with water (2×5 mL), brine (2×5 mL), dried over MgSO4, and evaporated. The crude product was purified on PTLC (Analytech, 500 μm, hexane:EtOAc, 1:1). The slower moving band (Rf 0.32 and 0.75) on short silica gel column using 20% ethyl acetate/80% hexane, evaporated. The required product along with some inseparable impurities co-eluted, and hence the crude product (25 mg) was carried through the next reaction. For 1H-NMR data, see Table 4. Preparation of 2',7-Di(triethylsilyl)-2-debenzoyl taxol 21.

To a stirred solution of 2',7-di(triethylsilyl) taxol 21, (65.0 mg, 0.060 mmol) prepared according to the procedure described in "Modified Taxol. 5. Reaction of Taxol With Electrophilic Reagents and Preparation of a Rearranged Taxol Derivative with Tubulin Assembly Activity," J. Org. Chem., 56, 5114–5119 (1991). Benzene:methylene chloride (8 mL, 1:1.2 ml) and tetrabutyl-ammonium hydrogen sulfate (500 mg) at room temperature 8 ml of aqueous 2N sodium hydroxide solution was added. The reaction mixture was stirred for 1.5–2 hours, and then diluted with 15 ml of benzene. The organic layer was separated, washed with water (3×10 mL), brine (10 mL), dried over MgSO4 and evaporated. The residue was filtered and the filtrate was purified by PTLC (Analytech, 500 μm:hexane:EtOAc, 1:1) to give 11 mg of the title compound (38.3%). 1H-NMR, see Table 4.

Preparation of 2',N—di(t-BOC)—7—triethylsilyl-2-debenzoyl—2',7-di(triethylsilyl)taxol 23c (yield 60 to 75%). Deprotection of 2',7-di(triethylsilyl)-2-debenzoyl taxol With m-nitro-benzoic Acid

A mixture of 2',7-di(triethylsilyl)-2-debenzoyl taxol 22 (10.0 mg, 0.01 mmol), DCC (42.0 mg, 0.20 mmol), 4-pyrolidinopyridine (catalytic quantity), m-nitrobenzoic acid (0.20 mmol), and toluene (0.1 mL) was stirred at room temperature for 12 hours and then diluted with (10 mL) of ethyl acetate, EtOAc. The organic layer was separated and washed with water (2×5 mL), brine (2×5 mL), dried over MgSO4 and evaporated. The crude product was purified on PTLC (Analytech, 500 μm, hexane:EtOAc, 1:1). The band (Rf 0.72) was extracted to furnish 2-debenzoyl-2-(m-nitro benzoyl)-2',7-di (triethylsilyl) taxol 23c (yield 60 to 75%).

Preparation of 2',2-di(t-triethylsilyl)Taxol 23f.

A mixture of 2-debenzoyl-2-(m-nitrobenzoyl)-2',7-di(t-triethylsilyl) taxol 23s (10.0 mg) and (0.10 mL) of 5% HCl:MeOH was stirred at room temperature for 0.5 hours and then diluted with (10 mL) of EtOAc. The organic layer was separated and washed with water (2×5 mL), brine (5 mL), dried over MgSO4, and evaporated. The crude product was purified on PTLC (Analytech, 500 μm, hexane:EtOAc, 1:1). The band (Rf 0.2) was extracted to give 2-debenzoyl-2-(m-nitrobenzoyl) taxol derivative (yield 80 to 90%). For 1H-NMR, see Table 2. Preparation of 2-(m-Azidobenzoyl)-2-debenzoyl -2',7-di(t-triethylsilyl) Taxol 23f.

To a solution of 2-debenzoyl-2',7di (triethylsilyl) taxol 22, (21 mg, 0.002 mmol) in dry toluene (200 μL), 1,3-dicyclohexylcarbodiimide (88 mg, 0.43 mmol), m-azidobenzoic acid (70 mg, 0.043 mmol), and a catalytic amount of 4-pyrolidinopyridine were added, and stirred at 50° C. for 3 hours. The crude reaction mixture was filtered through a short silica gel column using 20% ethyl acetate/80% hexane. The required product along with some inseparable impurities co-eluted, and hence the crude product (25 mg) was carried through the next reaction. For 1H-NMR data, see Table 5.

Preparation of 2-(m-Azidobenzoyl)-2-debenzoyl Taxol 13f.

To crude 2-(m-azidobenzoyl)-2-debenzoyl-2',7di(triethylsilyl) taxol (22.1 mg), 200 μL of freshly prepared 5% HCl in methanol was added. The reaction mixture was stirred at room temperature for 30 minutes, and then diluted with 20 ml of ethyl acetate. The organic layer was washed with water (10 mLx3) and brine and dried over sodium sulfate. The crude product was purified by PTLC (500 μM layer, hexane:ethyl acetate, 1:1) to yield 2-(m-azidobenzoyl)-2-debenzoyl taxol 13f (16 mg, 83%). For 1H-NMR data, see Table 5.

In a preferred embodiment, compounds of the present invention having antineoplastic properties are administered in antineoplastic amounts to patients suffering from cancer. For example, 2-debenzoyl-2-meta-azido-benzoyl taxol can be administered in a pharmaceutically acceptable carrier in an antineoplastically effective amount to a patient suffering from cancer. Likewise, water soluble derivatives may be made of the antineoplastically effective compounds of the present invention and administered in an effective amount to cancer patients. Thus, the present invention discloses methods for selective decylation and reacylation of the C-2 position on taxol and taxol analogues, as well as new antineoplastically effective compounds which result therefrom.

The compounds and methods of the present invention are not limited to the specific examples discussed in the section entitled Detailed Description of the Invention. The methods of the present invention are broadly applicable and can be used to prepare a large variety of taxol and baccatin III analogues in which the tetracyclic taxane nucleus is acylated at the C-2 position. A wide array of taxol and baccatin III analogues may be used as starting materials in the methods of the present invention. This invention further contemplates reactions, such as acylations, prior to and subsequent to acylation of the C-2 position which can produce a wide variety of compounds. Various synthetic steps such as protecting steps (for example at the C-2' and C-7 positions), and acylating and deacylating steps (for example at the C-10 and C-13 positions) may be those described herein or those otherwise known in the prior art. The products of the present invention may be prepared as desired final products, or as intermediates in the synthesis of desired taxol analogues.

It is contemplated that substituents on the tetracyclic taxane nucleus be selected based upon the medicinal or synthetic characteristics that various substituents will impart to the taxol analogue. Workers of ordinary skill in the chemical and pharmaceutical arts will appreciate that the widely applicable methods of the present invention enable the strategic selection of substituents (from a very large number of possible substituents which could be placed on the tetracyclic taxane nucleus) at certain locations on the taxane tetracyclic nucleus.

Although preferred embodiments have been described herein, it is to be understood that the invention can be practiced otherwise than as specifically described.
### TABLE 1
Cytotoxicity of Selected 2-Debenzoyl-2-Acyltaxols Against P-388 Leukemia

<table>
<thead>
<tr>
<th>Compound (Taxol)</th>
<th>R</th>
<th>ED50/ED90 (taxol)</th>
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<tr>
<td>1 (Taxol)</td>
<td>benzoyl</td>
<td>1.0</td>
</tr>
<tr>
<td>13a</td>
<td>m-amino-benzoyl</td>
<td>1500</td>
</tr>
<tr>
<td>13b</td>
<td>cinnamoyl</td>
<td>10</td>
</tr>
<tr>
<td>13c</td>
<td>m-nitro-benzoyl</td>
<td>0.3</td>
</tr>
<tr>
<td>13d</td>
<td>m-chloro-benzoyl</td>
<td>0.1</td>
</tr>
<tr>
<td>13e</td>
<td>m-dinitro-benzoyl</td>
<td>2.0</td>
</tr>
<tr>
<td>13f</td>
<td>m-azido-benzoyl</td>
<td>0.002</td>
</tr>
<tr>
<td>13g</td>
<td>trimethoxy</td>
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<td>13h</td>
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<td>methylbenzoyl</td>
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<td>13j</td>
<td>m-fluoro-benzoyl</td>
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<td>13k</td>
<td>2-thiophene-carboxyl</td>
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</tr>
<tr>
<td>13l</td>
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<td>13ag</td>
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### TABLE 2
1H-NMR Spectra of Compounds 6, 7, 10, 11

<table>
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<tr>
<th>Protons of 2,7-N-tri-(t-BOC) taxol (6)</th>
<th>2,7-N-tri-(t-BOC) iso-taxol (10)</th>
<th>2-Debenzoyl iso-taxol (7)</th>
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<tbody>
<tr>
<td>C-2</td>
<td>5.75 d</td>
<td>4.06 bd</td>
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<td>4.78 dd</td>
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<td>C-6</td>
<td>5.35 m</td>
<td>4.33 m</td>
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### TABLE 3
1H-NMR Spectra of Compounds 14, 15, 16, 17

<table>
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<tr>
<th>Protons of 2-(t-BOC)-7-TES-2-debenzoyl taxol (14)</th>
<th>2-(t-BOC)-7-TES-2-debenzoyl taxol (15)</th>
<th>2-N-dit-(t-BOC)-7-TES-2-debenzoyl taxol (17)</th>
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<tbody>
<tr>
<td>C-2</td>
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<tr>
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<td>C-6</td>
<td>5.35 d</td>
<td>5.35 d</td>
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TABLE 3—continued

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<tr>
<th>1H-NMR Spectra of Compounds 14, 15, 16, 17</th>
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<td>Protons</td>
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<td>SiCH2CH3</td>
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a Aromatic protons of diazirine ring.
b ArOCH2COOR.

TABLE 4—continued

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</tbody>
</table>

2'-hydroxy
2'- and 4'—positions of the m-nitrobenzoyl ring.

We claim:
1. A method for making a taxol analogue having a hydroxy substituent at the C-2 position from a taxol analogue having a benzyloxy substituent at the C-2 position, comprising: a step of base catalyzed hydrolysis under phase transfer conditions of a compound having the formula...
wherein said benzoyloxy substituent at the C-2 position is replaced by a hydroxyl to make a compound having the formula:

wherein R₅ is H, R₂ is selected from the group consisting of H, OH, oxy protecting group and acyloxy, and R₃ is selected from the group consisting of H, OH, and acyloxy, and

wherein R₆ is selected from the group consisting of H, OH, oxy protecting group and acyloxy, wherein said acyloxy can be the same or different, and R₄ is H or OH; and R₁ and R₇ are the same or different and have the general formula:

wherein Ar is phenyl or substituted phenyl; Z is selected from the group consisting of alkoxy, phenyl, and substituted phenyl; and Y is selected from the group consisting of H, acyl, and protecting group.

2. The method of claim 1, wherein R₄ is OH and R₂ is selected from the group consisting of OH, oxy protecting group and acyloxy.

3. A method for making a taxol analogue having a hydroxy substituent at the C-2 position from a taxol analogue having a benzoyloxy substituent at the C-2 position, comprising: a step of base catalyzed hydrolysis under phase transfer conditions of a compound having the formula:

wherein said benzoyloxy substituent at the C-2 position is replaced by a hydroxyl and further comprising a reaction with an acylating agent comprising an acid halide, β-lactam, anhydride, or carboxylic acid occurring subsequently to the replacement of said benzoyl moiety by H, to make a compound having the formula:

wherein R₅ is acyl, R₂ is selected from the group consisting of H, OH, oxy protecting group and acyloxy, and R₃ is selected from the group consisting of H, OH, and acyloxy,

and wherein R₆ is selected from the group consisting of H, OH, oxy protecting group and acyloxy, and wherein said acyloxy can be the same or different, and R₄ is H or OH; and R₁ and R₇ are the same or different and have the general formula:

wherein Ar is phenyl or substituted phenyl; Z is selected from the group consisting of alkoxy, phenyl, and substituted phenyl; and Y is H, acyl, or a protecting, group.

4. The method of claim 3, wherein R₁ and R₇ are the same, Y is H, R₃ is OC(O)CH₃, R₄ is OH and R₆ is OH, and further comprising a step of protecting the hydroxyl groups at the C-2' and C-7 positions prior to said step of base catalyzed hydrolysis; and further comprising a step of deprotecting said C-2' and C-7 positions by acid catalyzed hydrolysis following said reaction with an acylating agent.

5. The method of claim 4, wherein Ar is C₆H₅, Z is selected from the group consisting of C₆H₅ and O(CH₃)₃, and further wherein said step of protecting the hydroxyl groups comprises reacting with a trialkylsilylhalide, and wherein said base catalyzed hydrolysis consists of reacting a 2',7-trialkylsilyl-protected derivative of said second com-
6. The method of claim 5, wherein said reaction with an acylating agent comprises reaction with a carboxylic acid conducted in the presence of dicyclohexylcarbodiimide and a catalytic amount of 4-pyrrolidinopyridine.

7. The method of claim 6, wherein R₂ is QC(O) and Q is thiophene.

8. The method of claim 2, wherein said base catalyzed hydrolysis comprises reaction in a mixture comprising aqueous sodium hydroxide, an organic solvent and a phase transfer catalyst.

9. The method of claim 3, wherein R₅ has the formula:

wherein T, U, W, V, and X are independently selected from the group consisting of hydrogen, halogen, cyano, alkoxy, and azido.

10. The method of claim 9, wherein R₅ is C(O)CH₃, Ar is C₆H₆, Z is selected from the group consisting of C₆H₅ and OC(CH₃)₃, and Y is selected from the group consisting of H and triethylsilyl.

11. The method of claim 10, wherein Y is triethylsilyl and R₆ is triethylsilyloxy and further wherein said second compound is debenzoylated via reaction in a mixture comprising aqueous sodium hydroxide, a phase transfer catalyst, and an organic solvent, to yield a compound having a hydroxyl at the C-2 position.

12. The method of claim 11, wherein T, U, W and V are H, and further comprising a step wherein said compound having a hydroxyl at the C-2 position is reacted with meta-C₆H₄X—COOH.

13. The method of claim 12 where X is N₃.

14. A method for debenzoylating and reacylating the C-2' position of a taxol analogue comprising: mixing, in the presence of a phase transfer catalyst, a taxol analogue having a benzoyloxy substituent at the C-2 position in organic solvent and aqueous sodium hydroxide to produce a C-2 debenzoylated taxol analogue dissolved in said organic phase; and reacting said C-2 debenzoylated taxol analogue with a carboxylic acid to reacylate the C-2' position.

15. The method of claim 14 herein said reaction with a carboxylic acid is conducted in the presence of dicyclohexylcarbodiimide and a catalytic amount of 4-pyrrolidinopyridine.

16. The method of claim 15 wherein said phase transfer catalyst is a quaternary ammonium salt.

17. The method of claim 15 wherein said phase catalyst is tetrabutylammonium hydrogen sulfate.

18. The method of claim 14 wherein said taxol analogue having a benzoxacyloxy substituent at the C-2 position is a 2',7-triethylsilyl taxol.

19. The method of claim 18 further comprising a process of making said 2',7-triethylsilyl taxol is prepared by reacting taxol with triethylsilyl chloride.

20. The method of claim 18 wherein said phase transfer catalyst is a quaternary ammonium salt.
and further wherein said step of protecting the hydroxyl groups comprises reacting with a trialkylsilylhalide, and wherein said base catalyzed hydrolysis consists of reacting a 2',7-trialkylsilyl-protected derivative of said second compound in a mixture comprising aqueous sodium hydroxide, an organic solvent and a phase transfer catalyst.

37. The method of claim 36 wherein said phase transfer catalyst is a quaternary ammonium salt.

38. The method of claim 8 wherein said phase transfer catalyst is a quaternary ammonium salt.