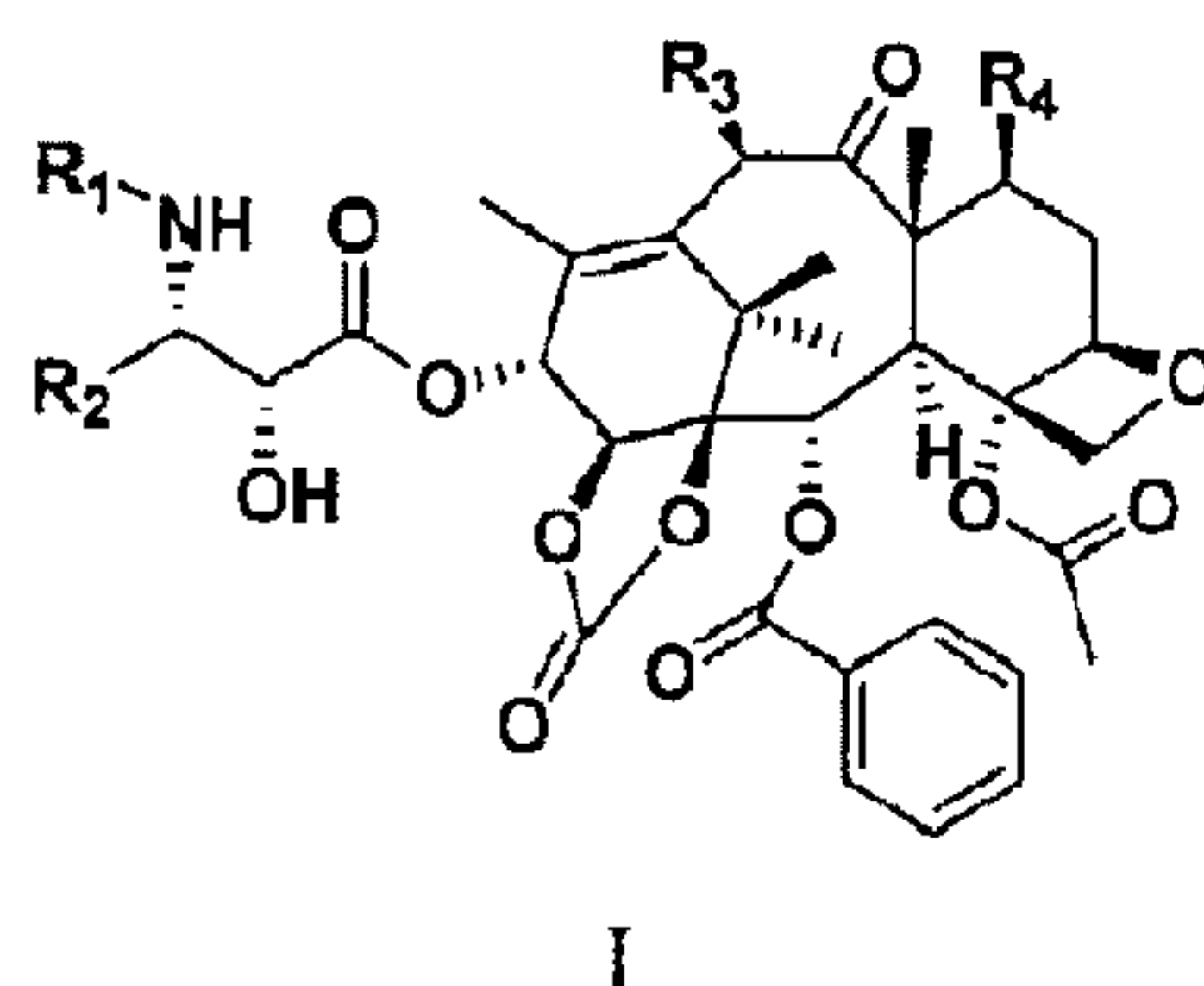
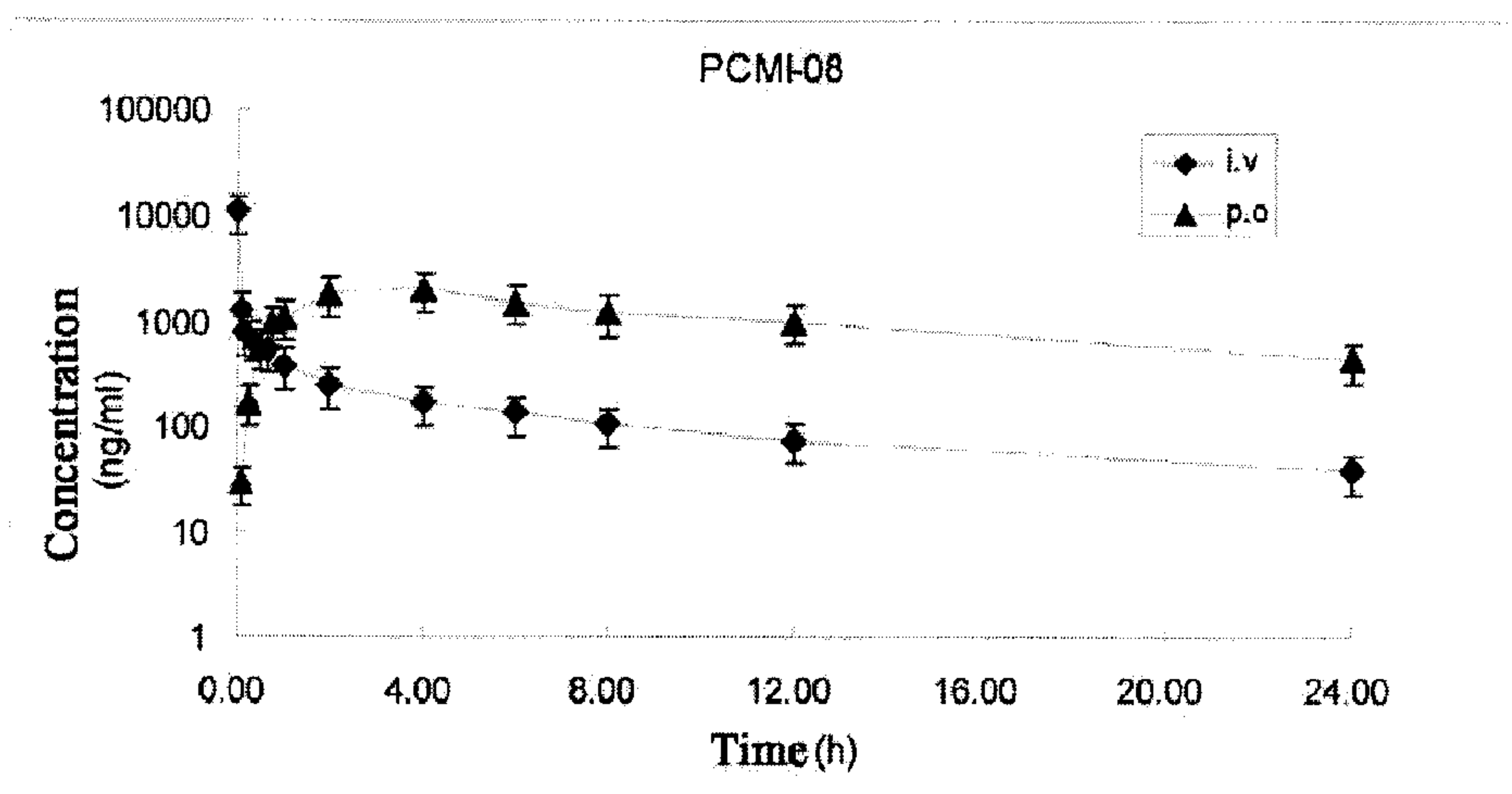




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(54) **Titre : COMPOSE TAXANE, ET SON PROCEDE DE PREPARATION ET SON UTILISATION**
(54) **Title: TAXANE COMPOUND, AND PREPARATION METHOD AND USE THEREOF**



(57) **Abrégé/Abstract:**

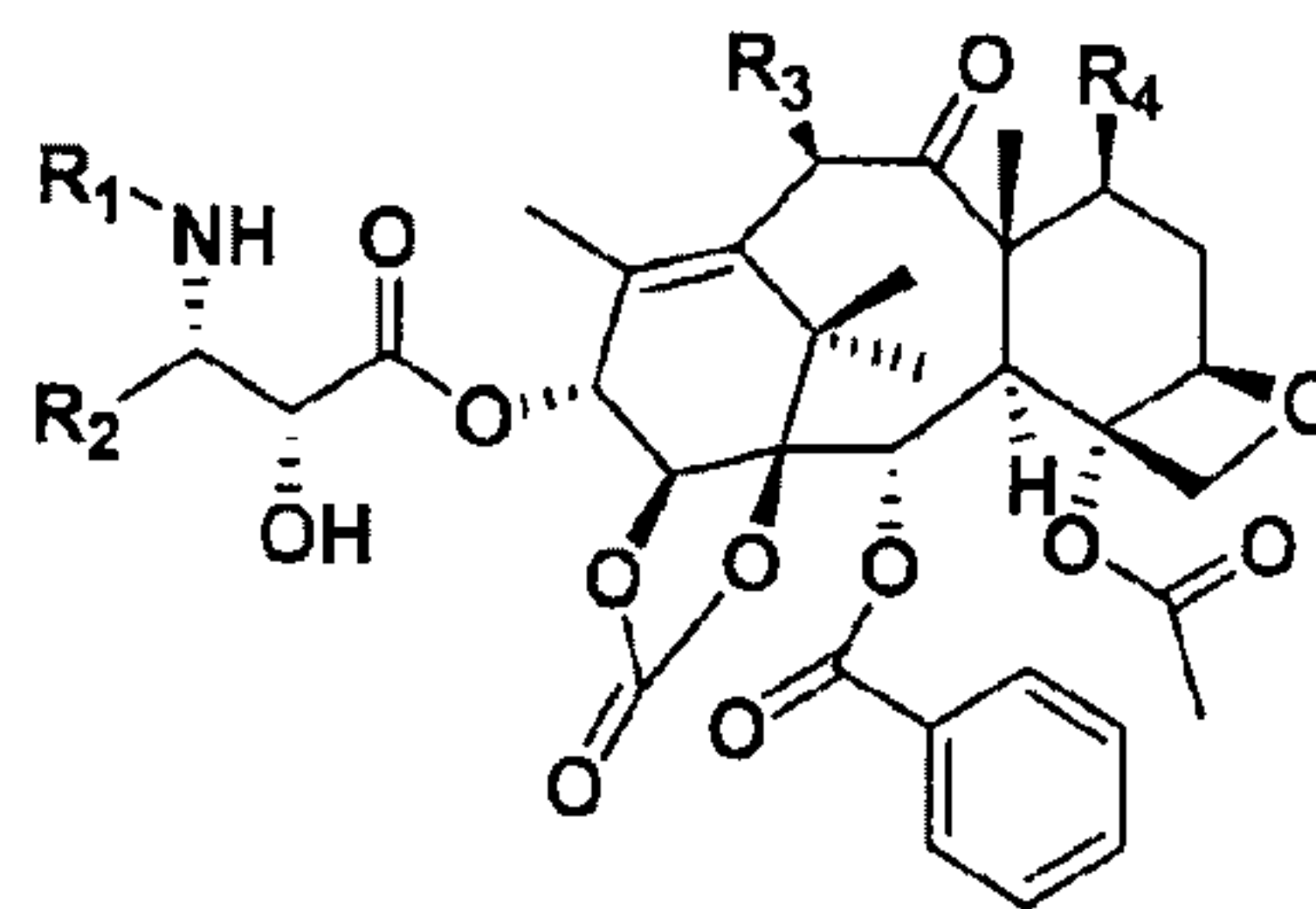
Provided are taxanes compounds having the structure of formula I, preparation method thereof, and uses of compositions having the compound, pharmaceutical salts and solvates thereof as active ingredients in the preparation of oral antitumor drugs. In the

(57) Abrégé(suite)/Abstract(continued):

formula, R_1 is $-\text{COR}_6$, $-\text{COOR}_6$, and $-\text{CONR}_{7a}\text{R}_{7b}$; R_2 is C1-C6 alkyl, C1-C6 alkenyl group, a substituted hydrocarbon group, a heterocyclic group, an aromatic group or a substituted aromatic group; R_3 is $-\text{OR}_6$, $-\text{OCOOR}_6$, $-\text{OCOSR}_6$, and $-\text{OCONR}_{7a}\text{R}_{7b}$; R_4 is $-\text{OR}_6$, $-\text{OCOOR}_6$, $-\text{OCOSR}_6$, $-\text{OCONR}_{7a}\text{R}_{7b}$, H, and OH; R_6 is C1-C6 alkyl, C1-C6 alkenyl, C1-C6 alkynyl group, a substituted hydrocarbon group, an aromatic group or a heterocyclic group; and R_{7a} and R_{7b} are respectively hydrogen, a hydrocarbon group, a substituted hydrocarbon group or a heterocyclic group. (see formula I)

Abstract

Provided are taxanes compounds having the structure of formula I, preparation method thereof, and uses of compositions having the compound, pharmaceutical salts and solvates thereof as active ingredients in the preparation of oral antitumor drugs. In the formula, R_1 is $-\text{COR}_6$, $-\text{COOR}_6$, and $-\text{CONR}_{7a}\text{R}_{7b}$; R_2 is C1-C6 alkyl, C1-C6 alkenyl group, a substituted hydrocarbon group, a heterocyclic group, an aromatic group or a substituted aromatic group; R_3 is $-\text{OR}_6$, $-\text{OCOOR}_6$, $-\text{OCOSR}_6$, and $-\text{OCONR}_{7a}\text{R}_{7b}$; R_4 is $-\text{OR}_6$, $-\text{OCOOR}_6$, $-\text{OCOSR}_6$, $-\text{OCONR}_{7a}\text{R}_{7b}$, H, and OH; R_6 is C1-C6 alkyl, C1-C6 alkenyl, C1-C6 alkynyl group, a substituted hydrocarbon group, an aromatic group or a heterocyclic group; and R_{7a} and R_{7b} are respectively hydrogen, a hydrocarbon group, a substituted hydrocarbon group or a heterocyclic group.



I

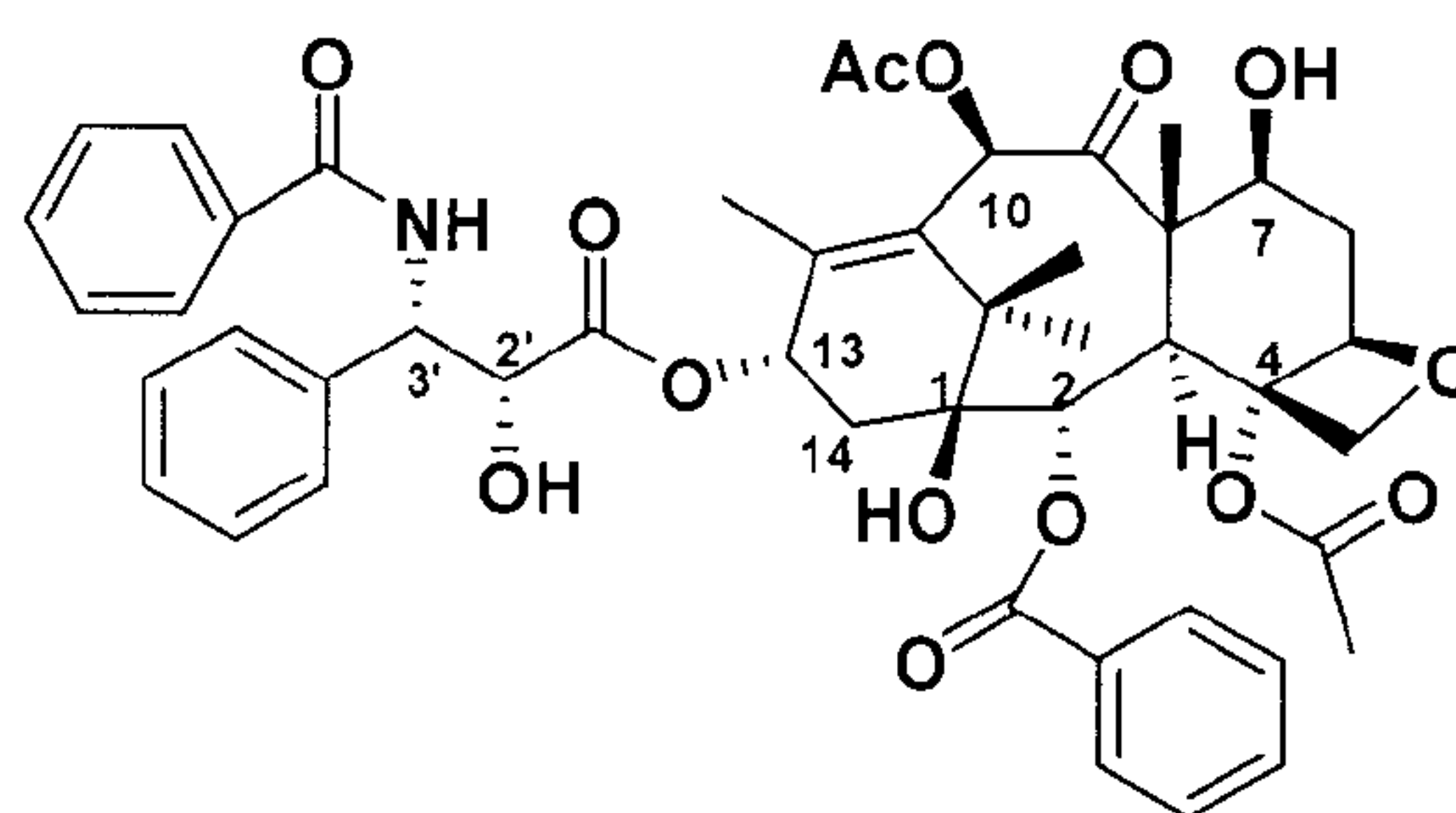
TAXANE COMPOUND, AND PREPARATION METHOD AND USE THEREOF

FIELD OF THE INVENTION

The present invention belongs to the field of pharmaceutical chemistry, and specifically relates to a novel compound, in particular to taxanes compounds. The present invention also relates to the preparation method of the taxanes compounds and use thereof as active ingredients in manufacturing oral antitumor medicaments.

BACKGROUND OF THE INVENTION

Paclitaxel (PTX) has a structure represented by the following formula:



Paclitaxel was extracted from the bark of *Taxus* genus *Taxus brevifolia* in 1971, which is an active antitumor compound with a unique anticancer mechanism and has definite therapeutic effect on a variety of cancers. Currently in clinical practice, paclitaxel is usually administered by intravenous injection. However, due to its poor water solubility, paclitaxel is usually dissolved in a mixed solvent of polyoxyethylated castor oil (Chremophor EL) and ethanol (1:1, v/v), to prepare paclitaxel injections, which is sold under the trade name “Taxol”TM or “Paxene”TM.

Although a great success has been achieved in clinical application, paclitaxel is also restricted by many factors in the meantime: (1) firstly, paclitaxel itself has toxic and side effects, including dose-limiting toxicity and bone marrow suppression (clinically, it is necessary be used in combination with a growth factor for treatment), on normal tissues and cells, and cannot cross the blood-brain barrier, etc; (2) with the use of Chremophor EL, the ensuing problem is serious allergic reactions, primary hyperlipidemia, central nervous system (CNS) toxicity and pharmacokinetics change of paclitaxel [ten Tije AJ, et al, Clin Pharmacokinet 42, 655-685, 2003;

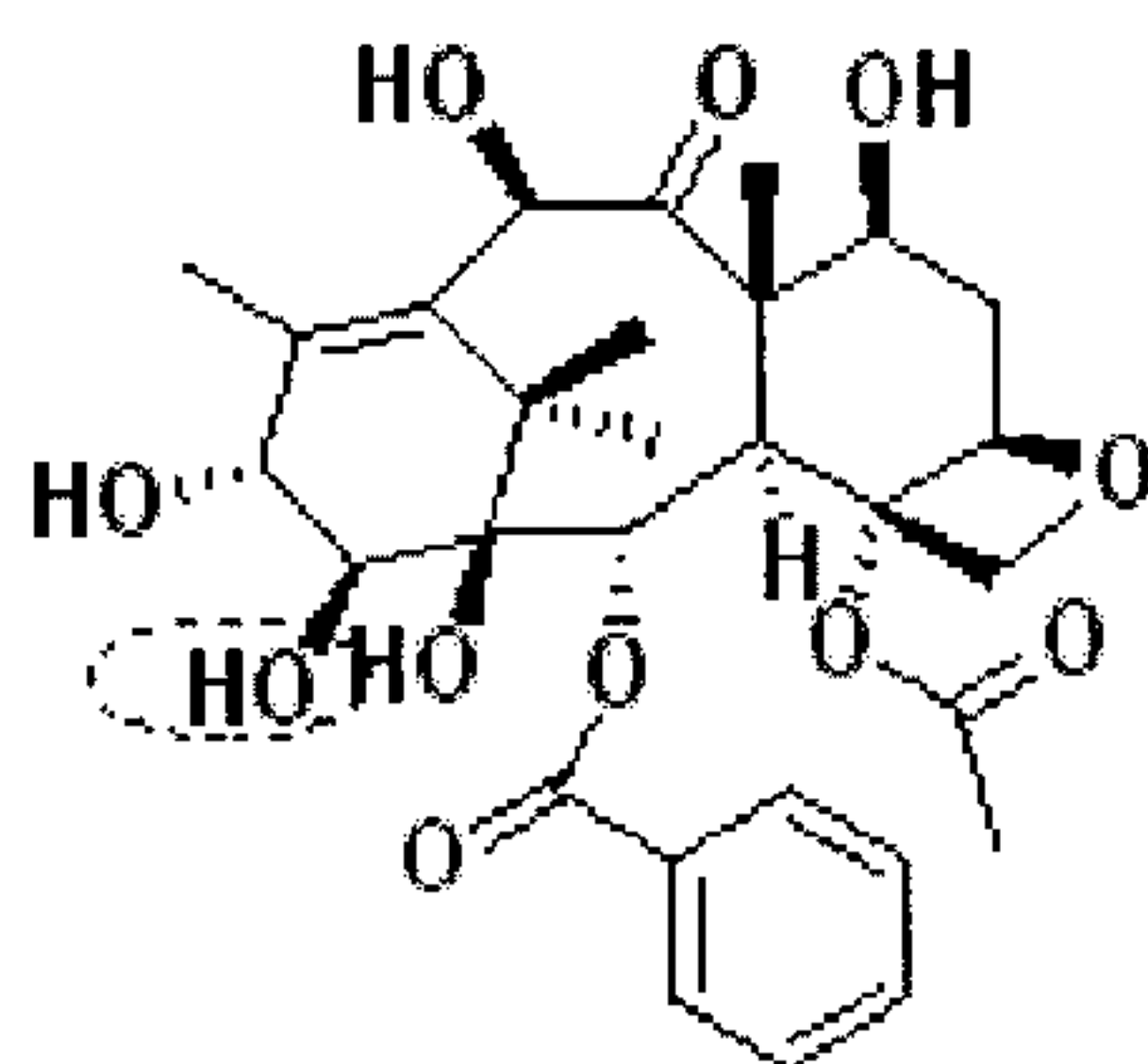
H. Gelderblom, et al, Eur. J. Cancer 37 (13), 1590-1598, 2001; van Zuylen L, et al, Invest New Drugs 19, 125-141, 2001; R. B. Weiss, et al, J. Clin. Oncol. 8 (7), 1263-1268, 1990]; (3) multiple drug resistance happens due to long-term medication.

In order to solve the aforesaid problems, many scholars at home and abroad have carried out in-depth studies on the structure-activity relationships of paclitaxel, including changing pharmaceutical dosage form, developing a prodrug of paclitaxel, synthesizing taxane derivatives, medication in combination with P-gp inhibitor, and the like. New ways are continuously explored to improve its water solubility, enhance therapeutic effect as well as reduce toxic and side effects.

It has enormous practical significance to carry out studies on the oral taxanes derivatives, since changing the nature of taxanes compounds themselves can fundamentally solve the problems thereof such as poor water-solubility, high toxicity and the like, so as to improve the oral bioavailability, reduce toxic and side effects and enhance therapeutic effect thereof. Furthermore, it will be able to avoid adverse reactions brought by co-solvents, and help prolong therapeutic effect and enhance tolerance of patients by converting injection administration to oral administration.

The researchers found that in the structural modification of paclitaxel molecule, the variation of substituents at C7, C9 and C10 positions have little effect on activity thereof, but these positions are binding sites with P-gp protein. The affinity of paclitaxel molecule with P-gp protein is affected by the size, electrical, hydrogen bond forming ability of the substituents on the positions. Thus, modification on these groups could overcome the multiple drug resistance caused by P-gp over-expression and solve the problem of low oral bioavailability and the like.

14 β -hydroxy baccatin III (14 β -OH-DAB) has a structure represented by the following formula:



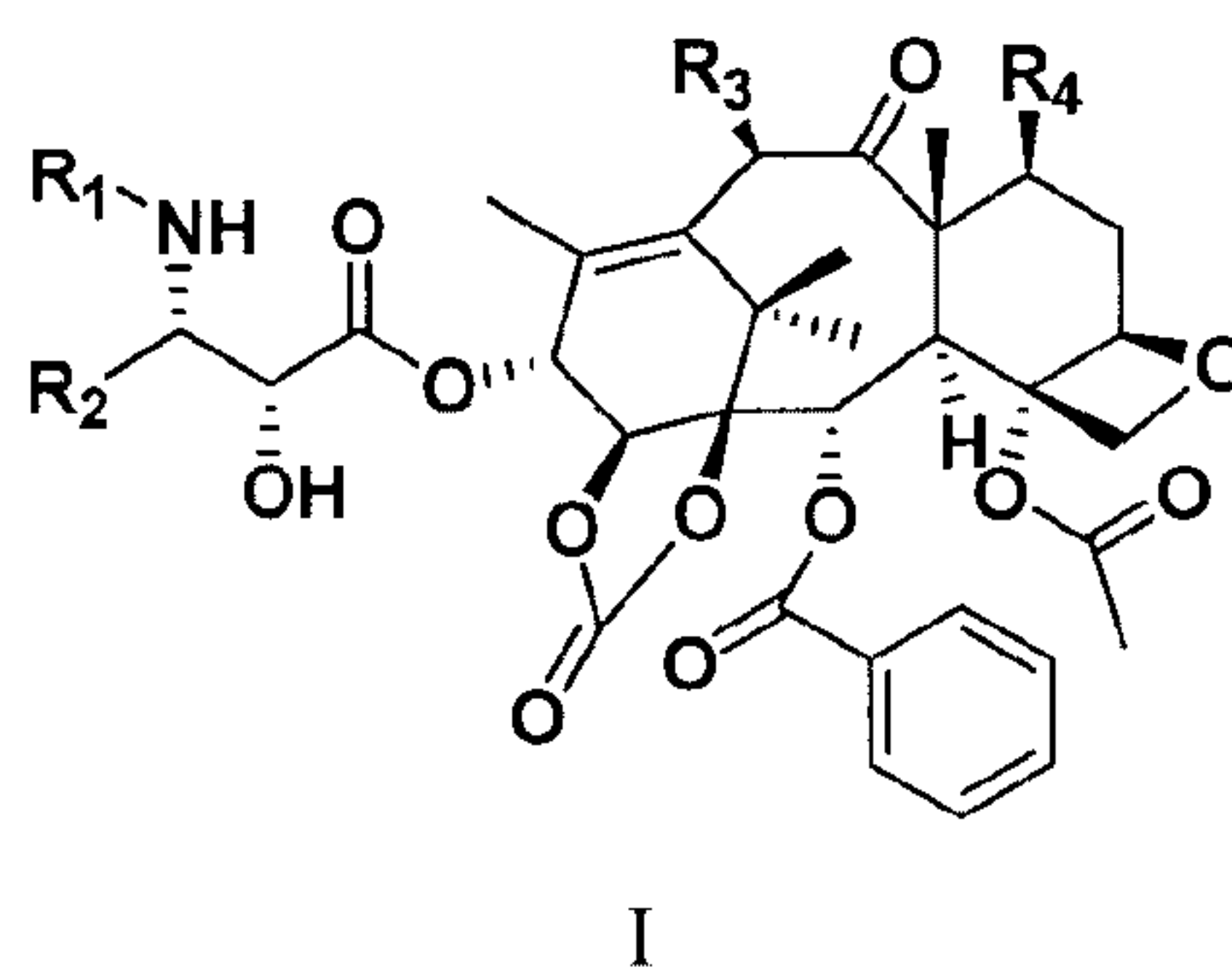
It is a natural taxane derivative extracted from needle leaves of *T. wallichiana* Zucc. It has good

water-solubility, mainly because a hydroxy group is introduced at C14 position thereof. For this purpose, such compound derived from 14 β -OH-DAB is expected to have improved water-solubility and increased oral bioavailability (Appendino, G. et al, J. Chem. Soc., Perkins Trans, 1, 2925-2929, 1992).

5 In view of this, the inventors were engaged in research of 14 β -OH-DAB derivatives, and eventually found out a series of novel compounds with improved oral bioavailability. As shown in pharmacological experiments, compared with the prior art, these taxanes derivatives containing structure of 1,14-carbonate baccatin III synthesized in the present invention have strong cytotoxicity to a variety of human cancer cell lines and broad-spectrum anti-tumor effects. It can
10 be seen from the *in vitro* activity data on MCF-7 breast cancer cell line that the cytotoxicity is maintained, while some derivatives even have better cytotoxicity than that of the prior art. The *in vivo* absorption and transport of taxanes derivatives is predicted by using the human-derived colorectal adenocarcinoma cell line Caco-2 cell monolayer model. It can be seen from the experimental results that, compared with the prior art, most of these derivatives have improved
15 oral bioavailability. Therefore, the cytotoxicity of these taxanes derivatives containing structure of 1,14-carbonate baccatin III are maintained (or even enhanced), furthermore, their oral bioavailability are also enormously improved.

CONTENT OF THE INVENTION

The present invention provides taxanes compounds having the structure represented by the
20 following general formula I:



wherein,

R₁ is -COR₆, -COOR₆, or -CONR_{7a}R_{7b};

R₂ is a C1-C6 alkyl, a C1-C6 alkenyl group, a substituted hydrocarbon group, a heterocyclic group, an aromatic group or a substituted aromatic group;

R₃ is -OR₆, -OCOOR₆, -OCOSR₆, or -OCONR_{7a}R_{7b};

R₄ is -OR₆, -OCOOR₆, -OCOSR₆, -OCONR_{7a}R_{7b}, H or OH;

- 5 wherein, R₆ is a C1-C6 alkyl, a C1-C6 alkenyl, a C1-C6 alkynyl group, a substituted hydrocarbon group, an aromatic group or a heterocyclic group; R_{7a} and R_{7b} are respectively hydrogen, a hydrocarbon group, a substituted hydrocarbon group or a heterocyclic group.

The present invention further provides a preparation method of taxanes compounds of the present invention.

- 10 Said preparation method of taxanes compounds of the present invention comprises the following steps:

Step 1 synthesis of taxanes mother nucleus part: by using 10-deacetyl baccatin III (10-DAB) as raw material, firstly, the hydroxyl groups at C7 and C10 positions of the mother nucleus part are selectively protected with substituents, then the C13 hydroxy group is oxidized
15 into keto-carbonyl group, followed by highly stereoselectively introducing a hydroxyl group with β configuration at C14 by using N-(sulfonyl)oxaziridine, to form 1,14-carbonate structure under the action of N,N'-carbonyldiimidazole (CDI), and finally the C13 keto-carbonyl group is highly stereoselectively reduced into hydroxyl group with α configuration by CBS reduction method to give the taxanes mother nucleus part;

- 20 Step 2 synthesis of a precursor of five-member ring oxazolidine acid side chain: the precursor of five-member ring oxazolidine acid side chain is prepared by a series of reactions including introduction of protective groups, addition condensation, acid hydrolysis, aldol condensation, catalytic hydrogenation and the like;

Step 3 synthesis of taxanes derivatives: the precursor of five-member ring oxazolidine acid
25 side chain is linked with the taxanes mother nucleus part by esterification, and a series of taxanes derivatives are generated after removal of protective group by acid hydrolysis.

More specifically, the preparation method of the taxanes compounds of the present invention comprises the following steps:

Step 1 synthesis of taxanes mother nucleus part: by using 10-deacetyl baccatin III (10-DAB) as raw material, firstly, the hydroxyl groups at C7 and C10 positions of the mother nucleus part are selectively protected with substituents, then the C13 hydroxy group is oxidized into keto-carbonyl group, followed by highly stereoselectively introducing a hydroxyl group with β configuration at C14 by using N-(sulfonyl)oxaziridine, to form 1,14-carbonate structure under the action of CDI, and finally C13 keto-carbonyl group is highly stereoselectively reduced into hydroxyl group with α configuration by CBS reduction method to give the taxanes mother nucleus part;

Step 2 synthesis of a precursor of five-member ring oxazolidine acid side chain: glycolic acid, used as raw material, is protected successively by benzyl group and butyloxycarbonyl group (Boc group) to generate the Boc-protected benzyl glycolate; different substituted aldehydes are condensed with (S_R)-*t*-butyl sulfinamide to form the corresponding enamine compounds; the Boc-protected benzyl glycolate and the enamine compound are reacted via an addition reaction in the presence of lithium salt, and then a chiral intermediate is given after acid hydrolysis, and the obtained intermediate is reacted with 1,1'-(dimethoxymethyl) *p*-methoxybenzene via an aldol condensation reaction, catalyzed by pyridinium *p*-toluenesulfonate (PPTS) to obtain a condensation compound. The amino group of the condensation compound is substituted with different substituents, and the precursor of five-member ring oxazolidine acid side chain is finally given after catalytic hydrogenation;

Step 3 synthesis of taxanes derivatives: the precursor of five-member ring oxazolidine acid side chain is linked with the taxanes mother nucleus part by esterification, and a series of taxanes derivatives are generated after removal of the protective group by acid hydrolysis.

Furthermore, the present invention provides a pharmaceutical composition comprising the compounds of the above defined general formula (I), pharmaceutically acceptable salts or solvates thereof as active ingredients, as well as the use of the same in manufacturing oral antitumor medicaments.

The present invention has the following advantages:

1. In the present invention, the CBS reduction method is selected in stereoselective reduction of C13 keto-carbonyl group. Compared with the traditional reduction method by

using metal borohydride, the CBS reduction method is able to highly stereoselectively reduce to obtain hydroxyl group with α configuration on C13 with an ee value >99.9% and a yield of 90% or higher.

2. A series of taxanes derivatives containing 1,14-carbonate baccatin III were synthesized by simultaneously changing substituents at multiple positions of C7, C10, C14, C3'N and C3' of paclitaxel. In the *in vitro* cytotoxicity assay on a variety of cancer cell lines, they showed good antitumor activities. The *in vitro* oral bioavailability of such taxanes derivatives was predicted by using Caco-2 cell monolayer trans-membrane transport assay, showing from the experimental results that the membrane permeability of most of such derivatives were higher than that of paclitaxel and the oral bioavailability thereof were expected to be improved at different levels. By analyzing the result of efflux ratio in the bidirectional transport assay, it was shown that such derivatives could inhibit the efflux effect of P-gp in different degrees, and further verified that the oral absorption capacity of these compounds was improved. In addition, the compound PCMI-08, which showed the highest membrane permeability in the *in vitro* assay, was selected to carry out *in vivo* oral bioavailability with rats. It was shown from the experimental results that its absolute oral bioavailability was increased to 65.8%, indicating that the *in vivo* oral absorption capability thereof was improved in a significant degree by compared with that of paclitaxel. Accordingly, the taxanes derivatives containing 1,14-carbonate baccatin III of the present invention were potential oral antitumor medicaments.

DESCRIPTION OF THE DRAWINGS

Fig. 1 is the plasma concentration-time curve of PCMI-08.

Fig. 2 is the ^1H NMR spectrum of PCMI-01.

Fig. 3 is the ^{13}C NMR spectrum of PCMI-01.

25 Fig. 4 is the MS spectrum of PCMI-01.

Fig. 5 is the ^1H NMR spectrum of PCMI-02.

Fig. 6 is the ^{13}C NMR spectrum of PCMI-02.

Fig. 7 is the ^1H NMR spectrum of PCMI-03.

Fig. 8 is the ^{13}C NMR spectrum of PCMI-03.

30 Fig. 9 is the ^1H NMR spectrum of PCMI-04.

Fig. 10 is the ^{13}C NMR spectrum of PCMI-04.

Fig. 11 is the MS spectrum of PCMI-04.

Fig. 12 is the IR spectrum of PCMI-04.

Fig. 13 is the ^1H NMR spectrum of PCMI-05.

5 Fig. 14 is the ^{13}C NMR spectrum of PCMI-05.

Fig. 15 is the MS spectrum of PCMI-05.

Fig. 16 is the IR spectrum of PCMI-05.

Fig. 17 is the ^1H NMR spectrum of PCMI-06.

Fig. 18 is the ^{13}C NMR spectrum of PCMI-06.

10 Fig. 19 is the MS spectrum of PCMI-06.

Fig. 20 is the ^1H NMR spectrum of PCMI-07.

Fig. 21 is the ^{13}C NMR spectrum of PCMI-07.

Fig. 22 is the MS spectrum of PCMI-07.

Fig. 23 is the ^1H NMR spectrum of PCMI-08.

15 Fig. 24 is the ^{13}C NMR spectrum of PCMI-08.

Fig. 25 is the MS spectrum of PCMI-08.

Fig. 26 is the ^1H NMR spectrum of PCMI-09.

Fig. 27 is the ^{13}C NMR spectrum of PCMI-09.

Fig. 28 is the MS spectrum of PCMI-09.

20 Fig. 29 is the ^1H NMR spectrum of PCMI-10.

Fig. 30 is the ^{13}C NMR spectrum of PCMI-10.

Fig. 31 is the MS spectrum of PCMI-10.

Fig. 32 is the ^1H NMR spectrum of PCMI-11.

Fig. 33 is the ^{13}C NMR spectrum of PCMI-11.

25 Fig. 34 is the ^1H NMR spectrum of PCMI-12.

Fig. 35 is the ^{13}C NMR spectrum of PCMI-12.

Fig. 36 is the MS spectrum of PCMI-12.

Fig. 37 is the ^1H NMR spectrum of PCMI-13.

Fig. 38 is the ^{13}C NMR spectrum of PCMI-13.

30 Fig. 39 is the ^1H NMR spectrum of PCMI-14.

Fig. 40 is the ^{13}C NMR spectrum of PCMI-14.

Fig. 41 is the MS spectrum of PCMI-14.

Fig. 42 is the ^1H NMR spectrum of PCMI-15.

Fig. 43 is the ^{13}C NMR spectrum of PCMI-15.

Fig. 44 is the MS spectrum of PCMI-15.

5 Fig. 45 is the ^1H NMR spectrum of PCMI-16.

Fig. 46 is the ^{13}C NMR spectrum of PCMI-16.

Fig. 47 is the MS spectrum of PCMI-16.

Fig. 48 is the ^1H NMR spectrum of PCMI-17.

Fig. 49 is the ^{13}C NMR spectrum of PCMI-17.

10 Fig. 50 is the MS spectrum of PCMI-17.

Fig. 51 is the IR spectrum of PCMI-17.

Fig. 52 is the ^1H NMR spectrum of PCMI-18.

Fig. 53 is the ^{13}C NMR spectrum of PCMI-18.

Fig. 54 is the MS spectrum of PCMI-18.

15 Fig. 55 is the ^1H NMR spectrum of PCMI-19.

Fig. 56 is the ^{13}C NMR spectrum of PCMI-19.

Fig. 57 is the MS spectrum of PCMI-19.

Fig. 58 is the ^1H NMR spectrum of PCMI-20.

Fig. 59 is the ^{13}C NMR spectrum of PCMI-20.

20 Fig. 60 is the MS spectrum of PCMI-20.

Fig. 61 is the ^1H NMR spectrum of PCMI-21.

Fig. 62 is the ^{13}C NMR spectrum of PCMI-21.

DETAILED DESCRIPTION OF THE INVENTION

The term "alkyl" used herein refers to the group consisting of carbon and hydrogen atoms
 25 only without any unsaturated degree (such as double bonds, triple bonds or rings), which
 covers all kinds of possible geometric isomers and stereo-isomers thereof. The groups are
 attached to the rest of the molecule by a single bond. The term "C1-C6 alkyl" used herein
 refers to the above defined alkyl with a carbon number of 1-6. As non-limiting examples of
 C1-C6 alkyl, the following groups with straight chain or branched chain may be enumerated:
 30 methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl and

isomers thereof, as well as *n*-hexyl and isomers thereof.

The term "alkenyl" used herein refers to the group which is formed from the above mentioned alkyl group (except methyl) by having one or more double bonds. The term "C1-C6 alkenyl" refers to the above defined alkenyl with a carbon number of 1-6.

- 5 The term "alkynyl" used herein refers to the group which is formed from the above mentioned alkyl group (except methyl) by having one or more triple bonds. The term "C1-C6 alkynyl" refers to the above defined alkynyl with a carbon number of 1-6.

The term "hydrocarbon group" used herein refers to the group consisting of carbon and hydrogen atoms only. The term "substituted hydrocarbon group" refers to the above
 10 defined alkyl, alkenyl or alkynyl group and the like having substituents. The substituent can be a hydroxyl group, an amino group and the like.

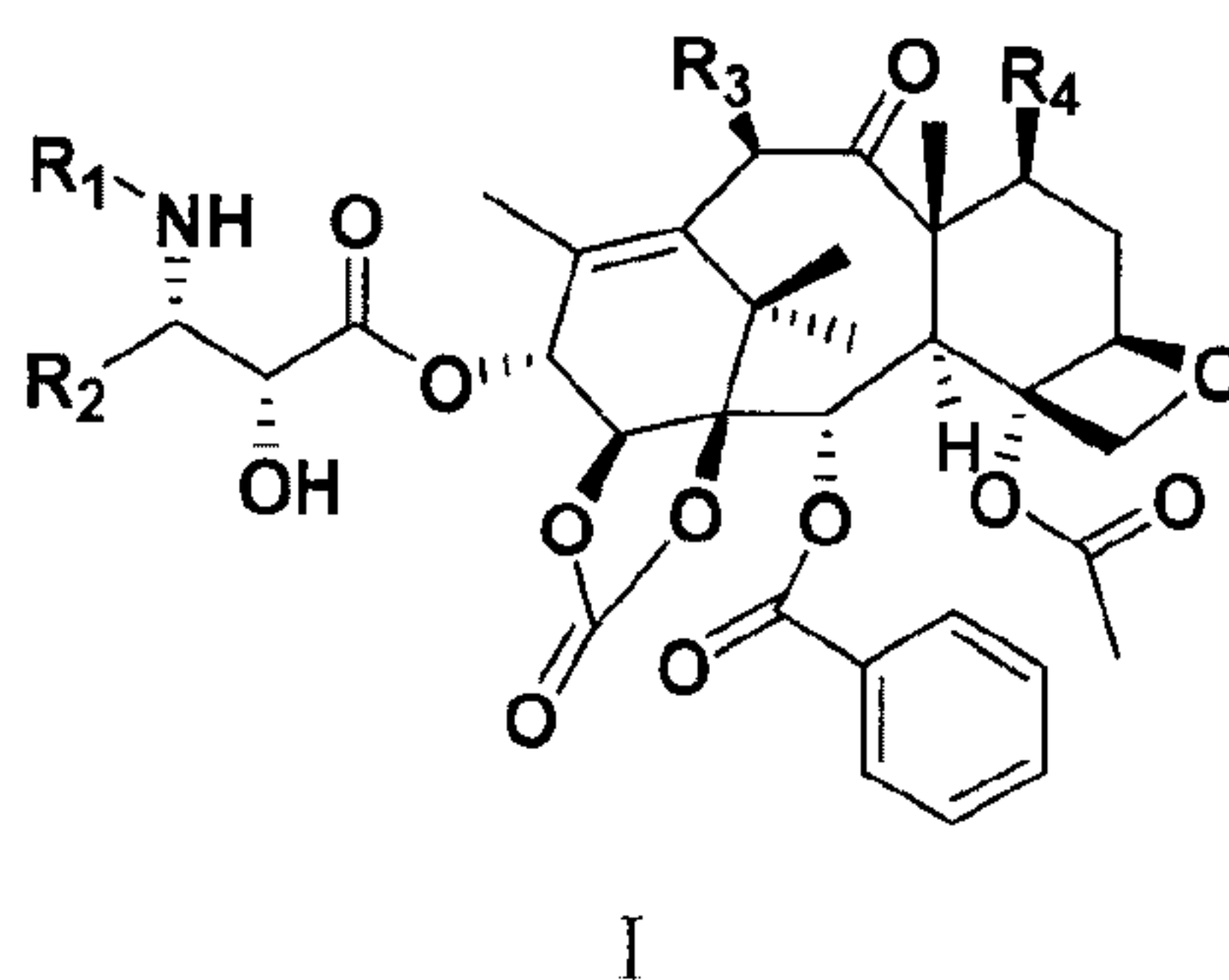
The term "heterocyclic group" used herein refers to an aromatic 5-14 member ring or a non-aromatic 3-15 member ring consisting of carbon atoms and heteroatoms independently selected from N, O or S. The aromatic ring may be monocyclic, bicyclic or polycyclic, in
 15 which the bicyclic and polycyclic groups are formed from monocyclic groups by connected with each other through single bonds or in a fused way. As non-limiting examples of heteroaryl groups, the following groups may be enumerated: oxazolyl, isoxazolyl, imidazolyl, furyl, indolyl, isoindolyl, pyrrolyl, triazolyl, triazinyl, tetrazolyl, thienyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzofuranyl,
 20 benzothiazolyl, benzoxazolyl, benzimidazolyl, benzothieryl, benzopyranyl, carbazolyl, quinolinyl, isoquinolinyl, quinazolinyl, cinnolinyl, naphthyridinyl, pteridinyl, purinyl, quinoxalinyl, thiadiazolyl, indolizinyl, acridinyl, phenazinyl, phthalazinyl, coumarinyl, pyrazolopyridinyl, pyridinopyridazinyl, pyrrolopyridinyl, imidazopyridinyl, pyrazolopyridazinyl; and the groups formed from the above heteroaryl groups by connected
 25 with each other through single bonds or in a fused way. The non-aromatic ring may be monocyclic, bicyclic or polycyclic, and fused ring, bridged ring or spiro ring, which may optionally contain one or more double bonds. As non-limiting examples of the heterocyclic groups, the following groups may be enumerated: azepinyl, acridinyl, benzodioxolyl, benzodioxanyl, chromanyl, dioxolanyl, dioxaphospholanyl, decahydro isoquinolinyl,
 30 indanyl, indolinyl, isoindolinyl, isochromanyl, isothiazolidinyl, isoxazolidinyl, morpholinyl,

oxazoliny, oxazolidiny, oxadiazoly, 2-oxo-piperaziny, 2-oxo-piperidiny, 2-oxopyrrolidiny, 2-oxo-azepiny, octahydroindoly, octahydroisoindoly, perhydroazepiny, piperaziny, 4-piperidony, piperidiny, phenothiaziny, phenoxaziny, quinuclidiny, tetrahydroisoquinoliny, tetrahydrofurany, tetrahydropyrany, tetrahydropyrrolidiny, thiazoliny, thiazolidiny, thiomorpholiny, thiomorpholine sulfoxide and thiomorpholiny sulfone.

The term "aryl" used herein refers to an aromatic ring consisting of at least 6 carbon atoms, which may be monocyclic, bicyclic or polycyclic, in which bicyclic and polycyclic rings may be formed from monocyclic rings by connected with each other through single bonds or in a fused way. As non-limiting examples of the aryl groups, the following groups may be enumerated: phenyl, naphthyl, anthryl, phenanthryl, indenyl, pyrenyl, perylenyl, azulenyl, acenaphthenyl, fluorenyl, benzoacenaphthenyl, triphenylenyl, chrysenyl, biphenyl, binaphthyl and the like.

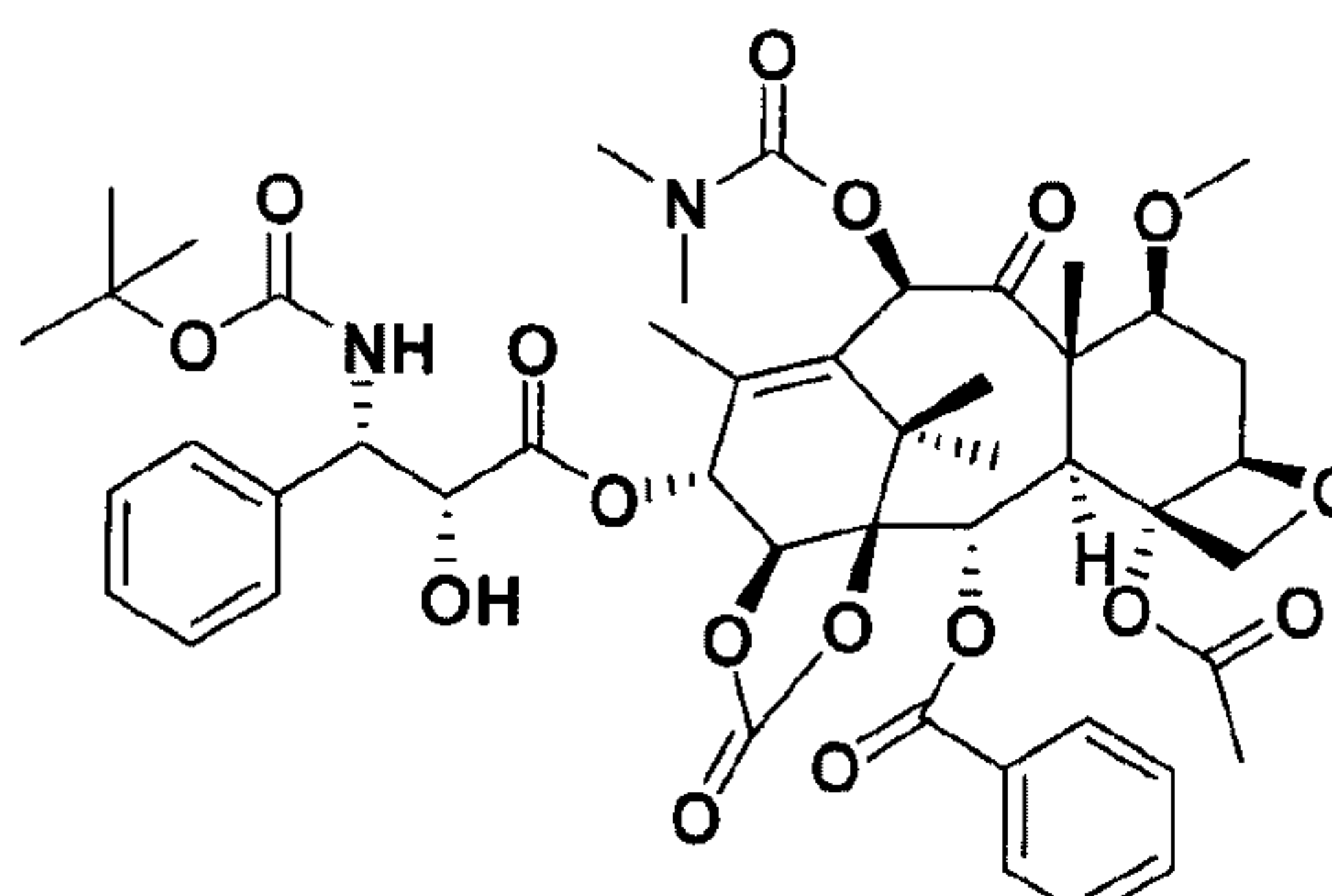
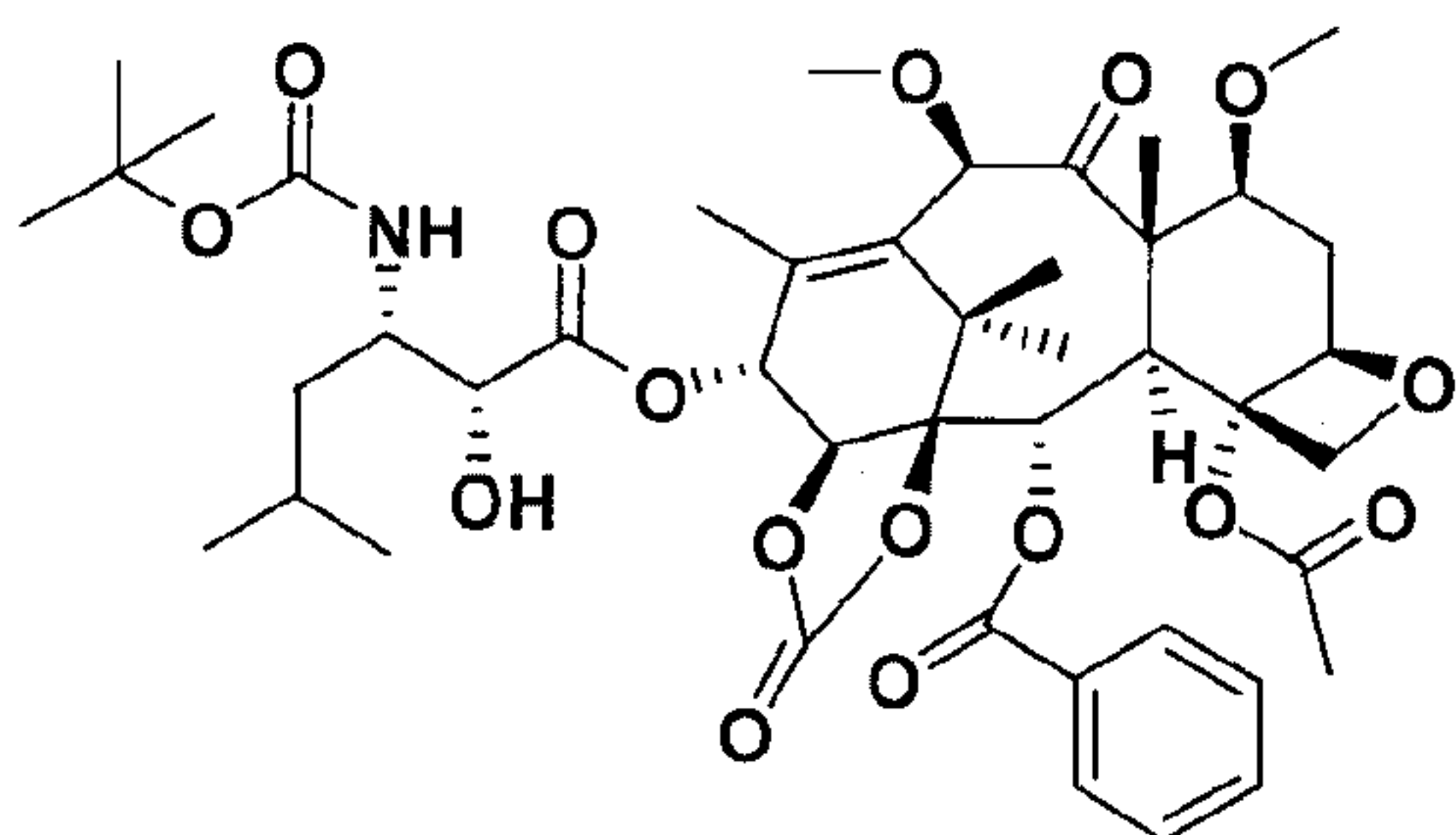
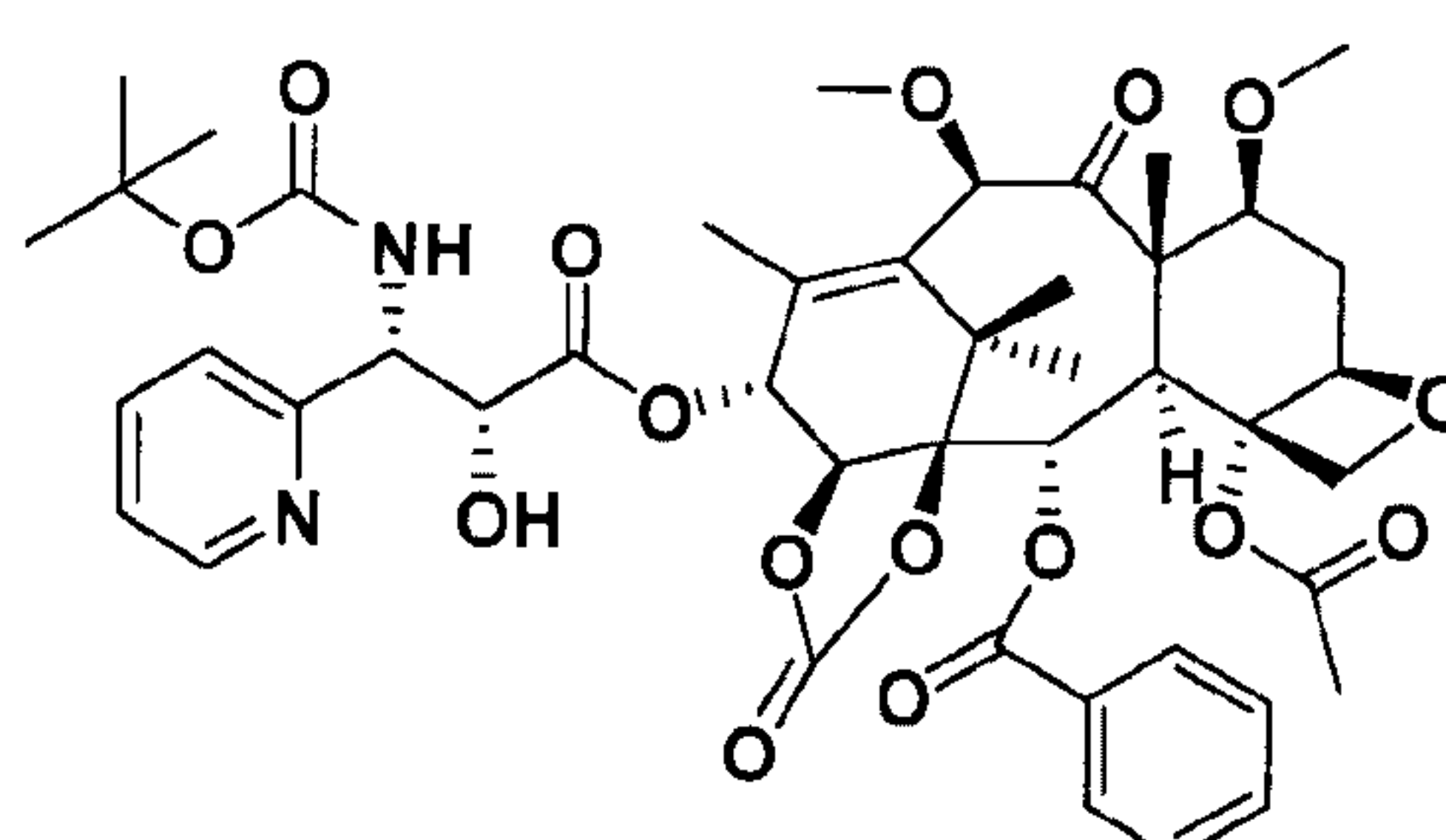
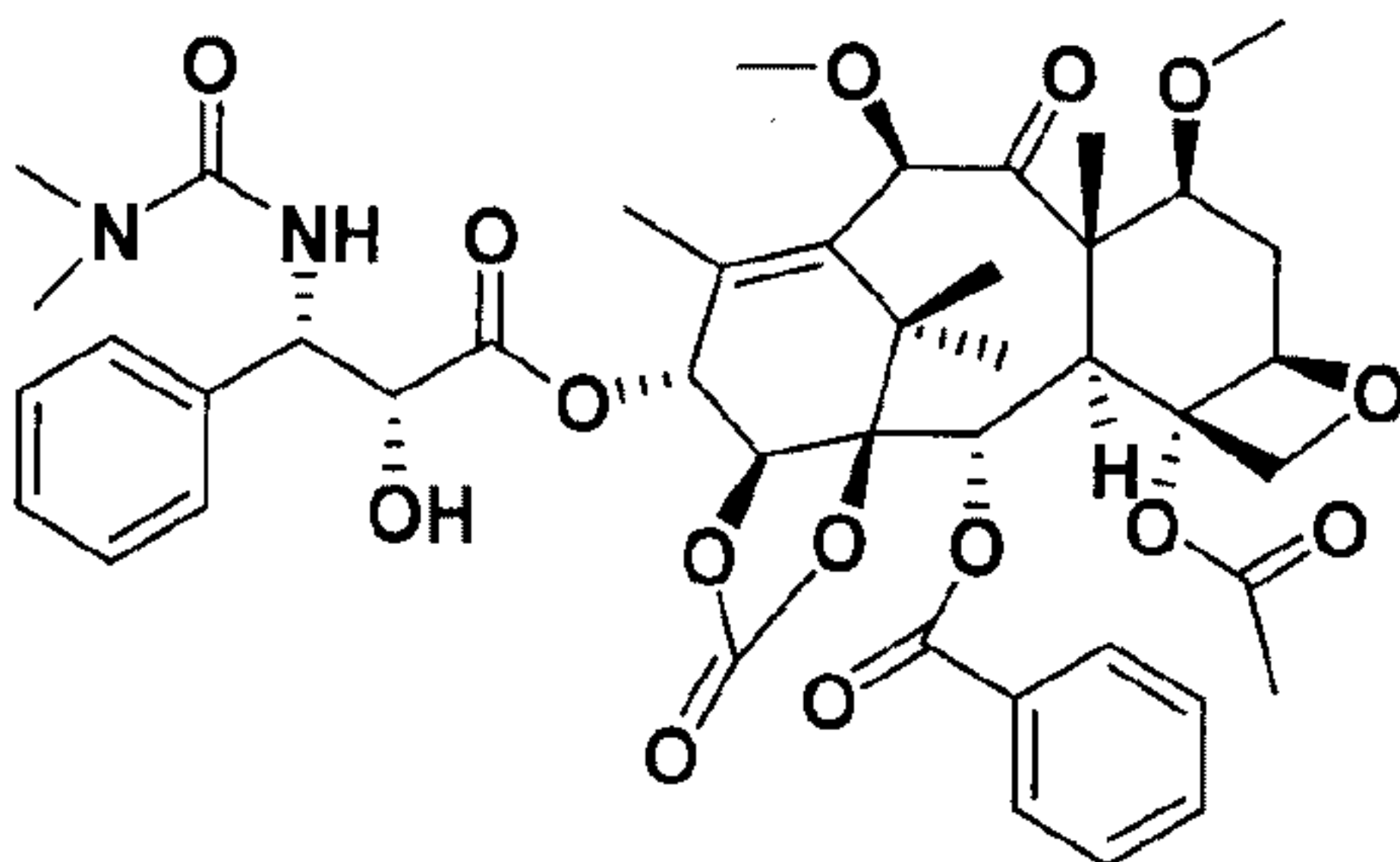
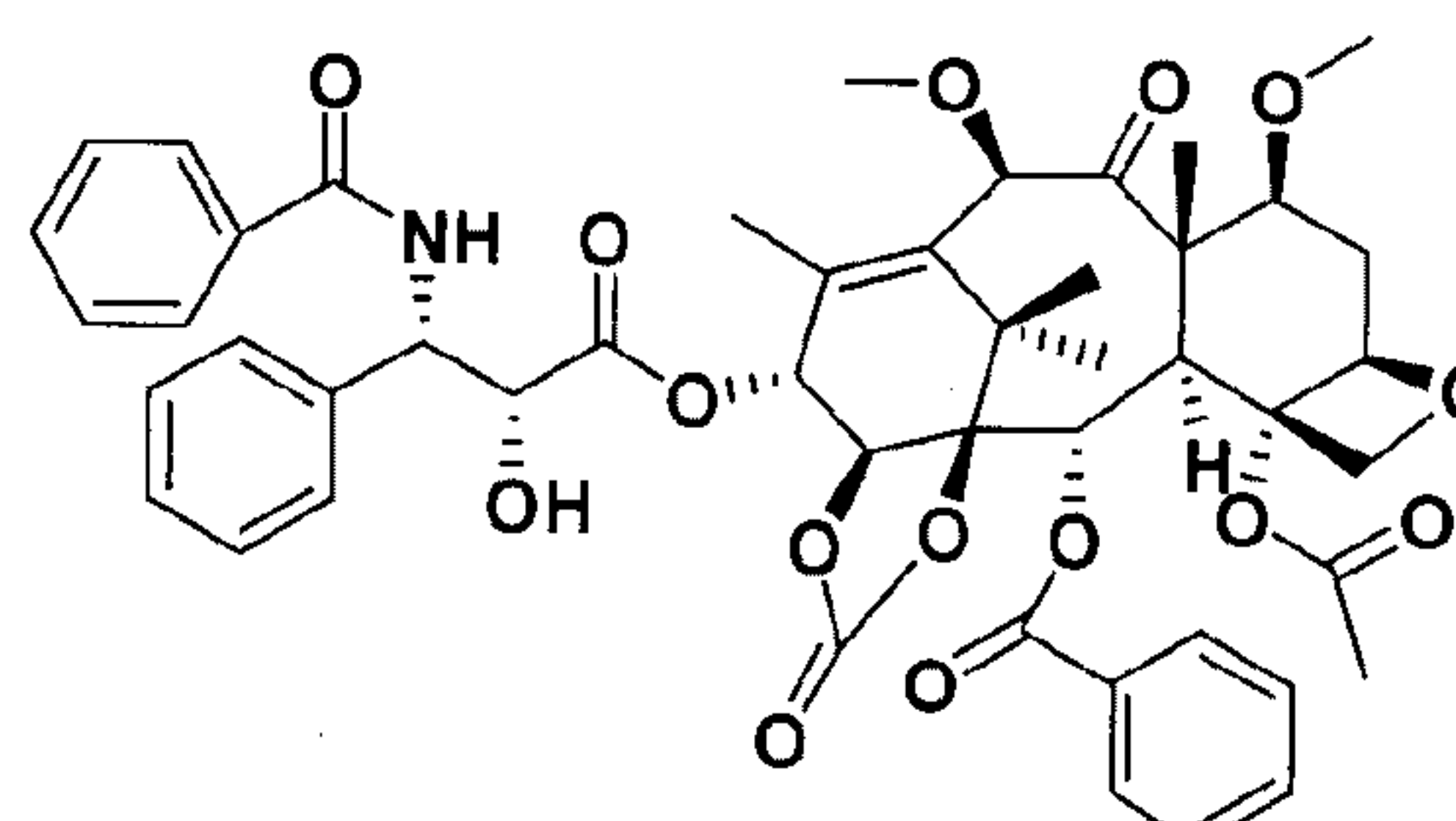
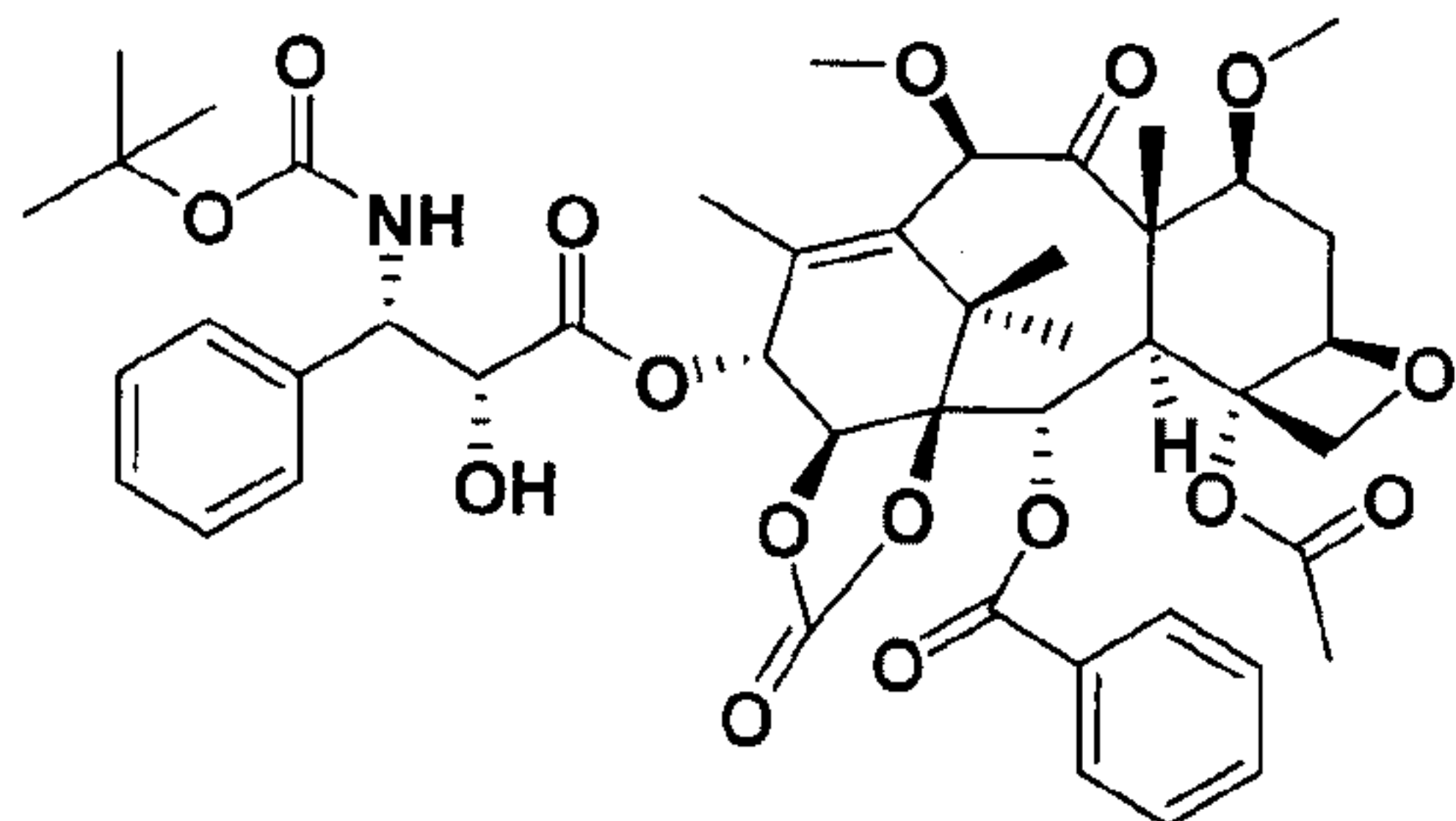
The term "substituted aromatic group" used herein refers to the above defined aromatic group having substituents. The substituent may be an alkyl, an alkenyl, an alkynyl, a hydroxyl, an amino and the like.

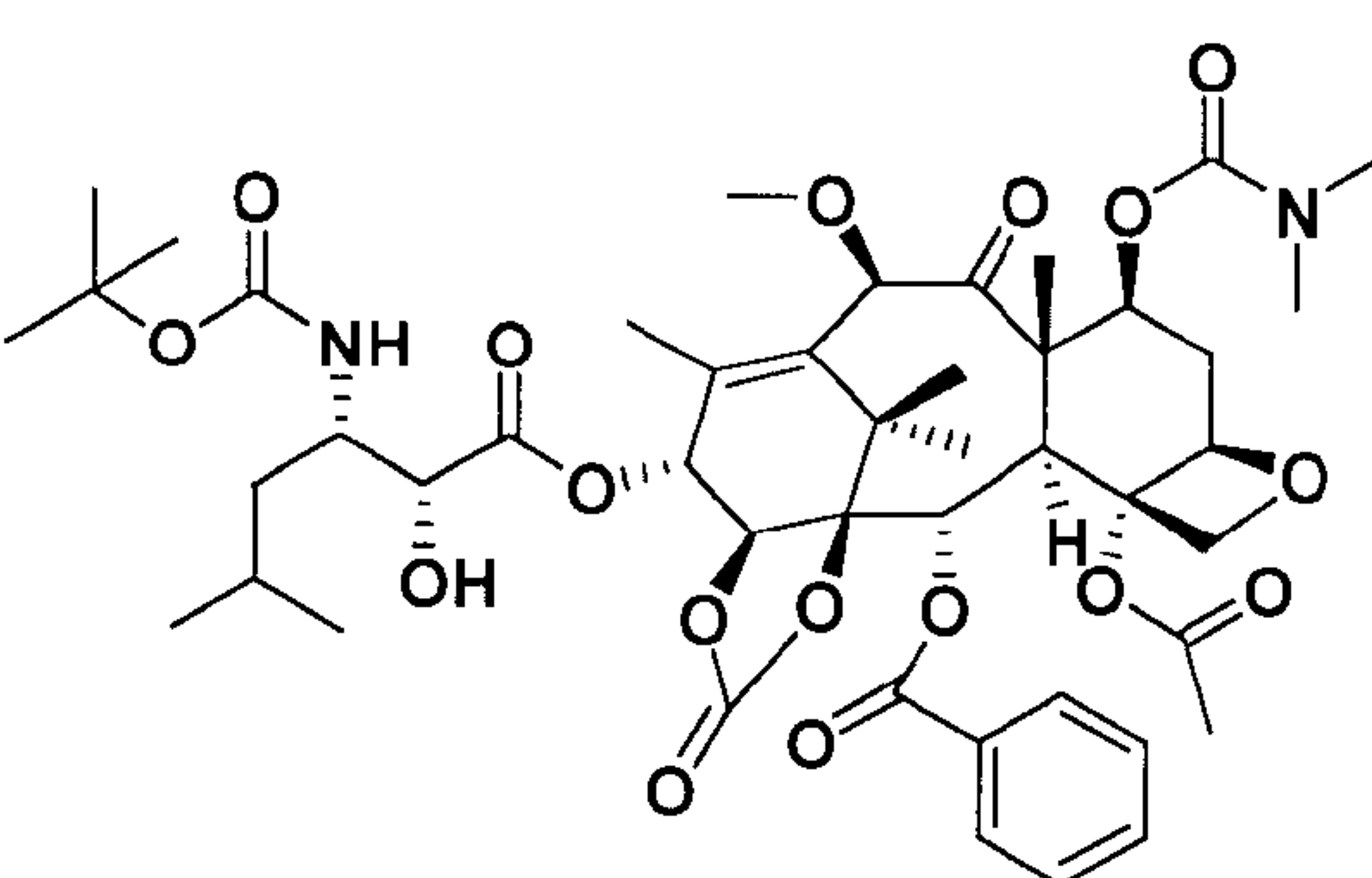
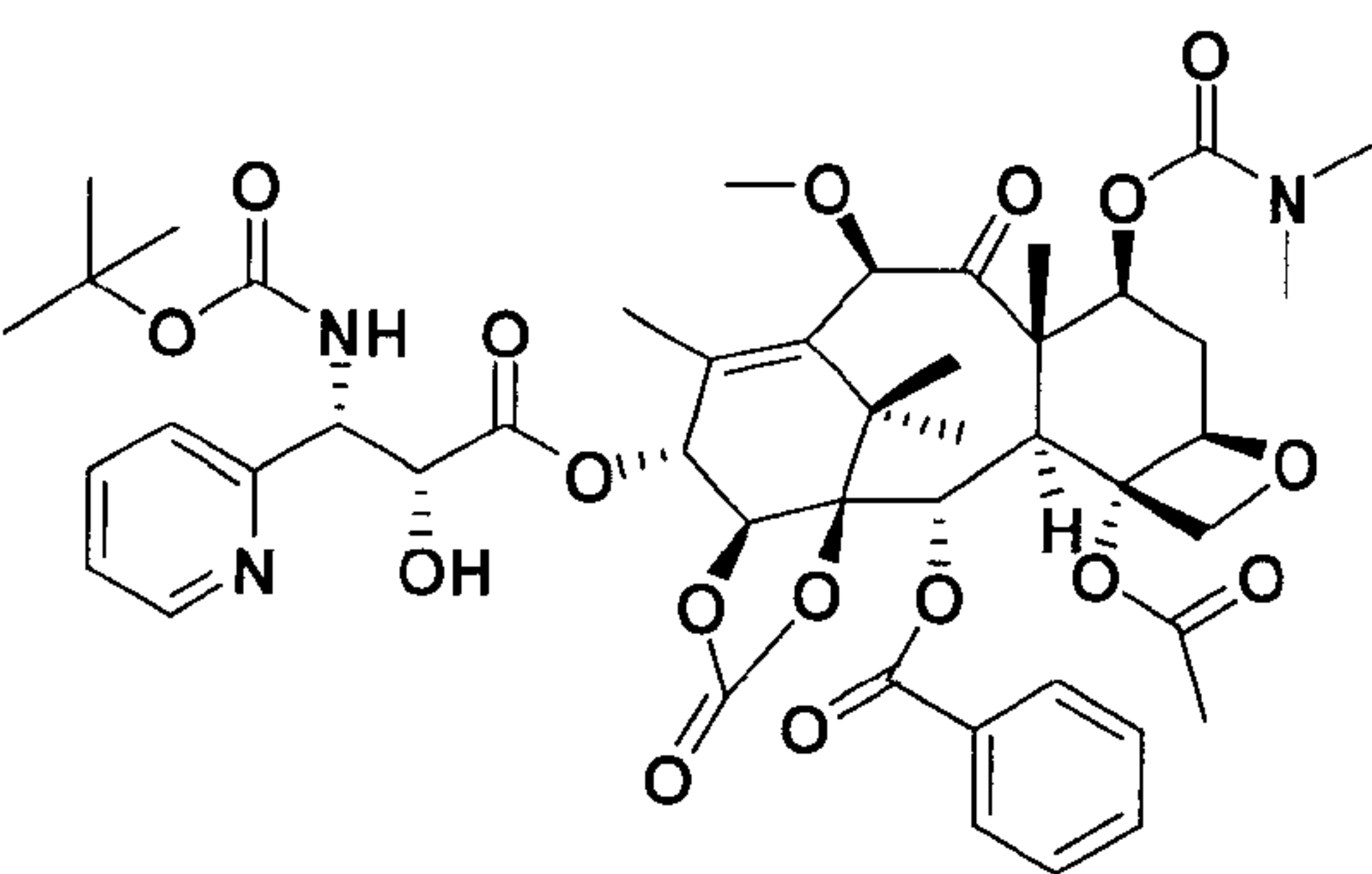
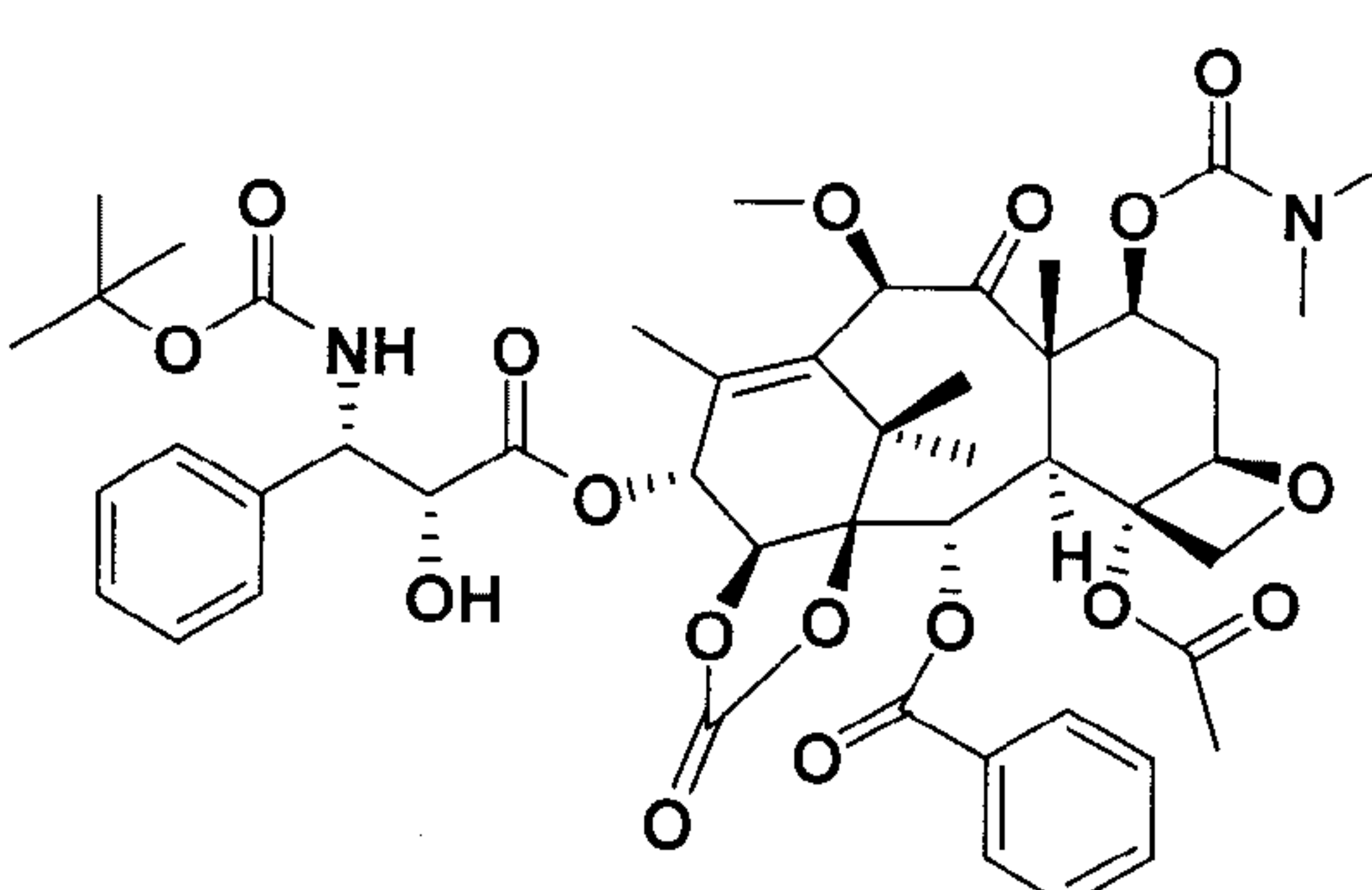
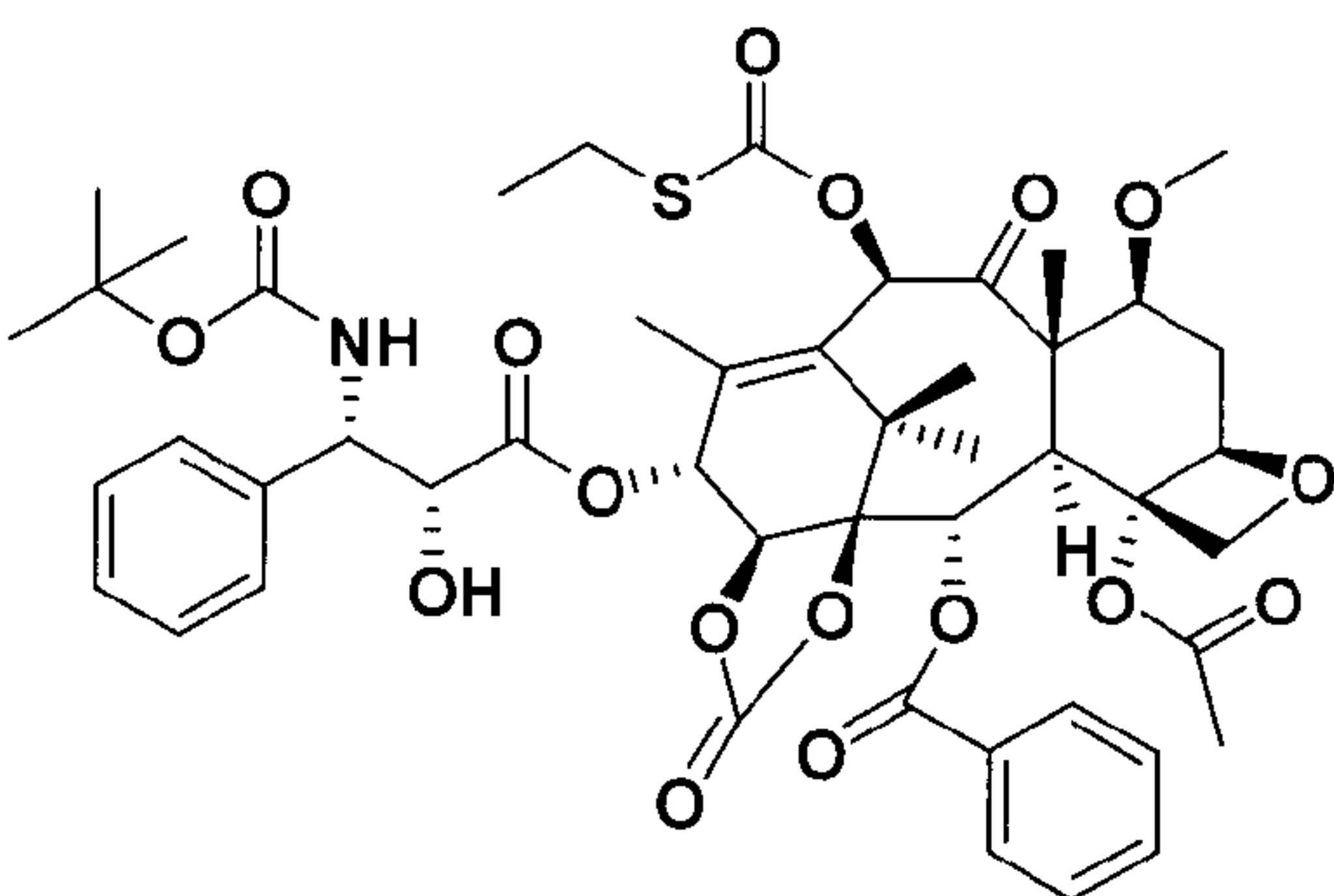
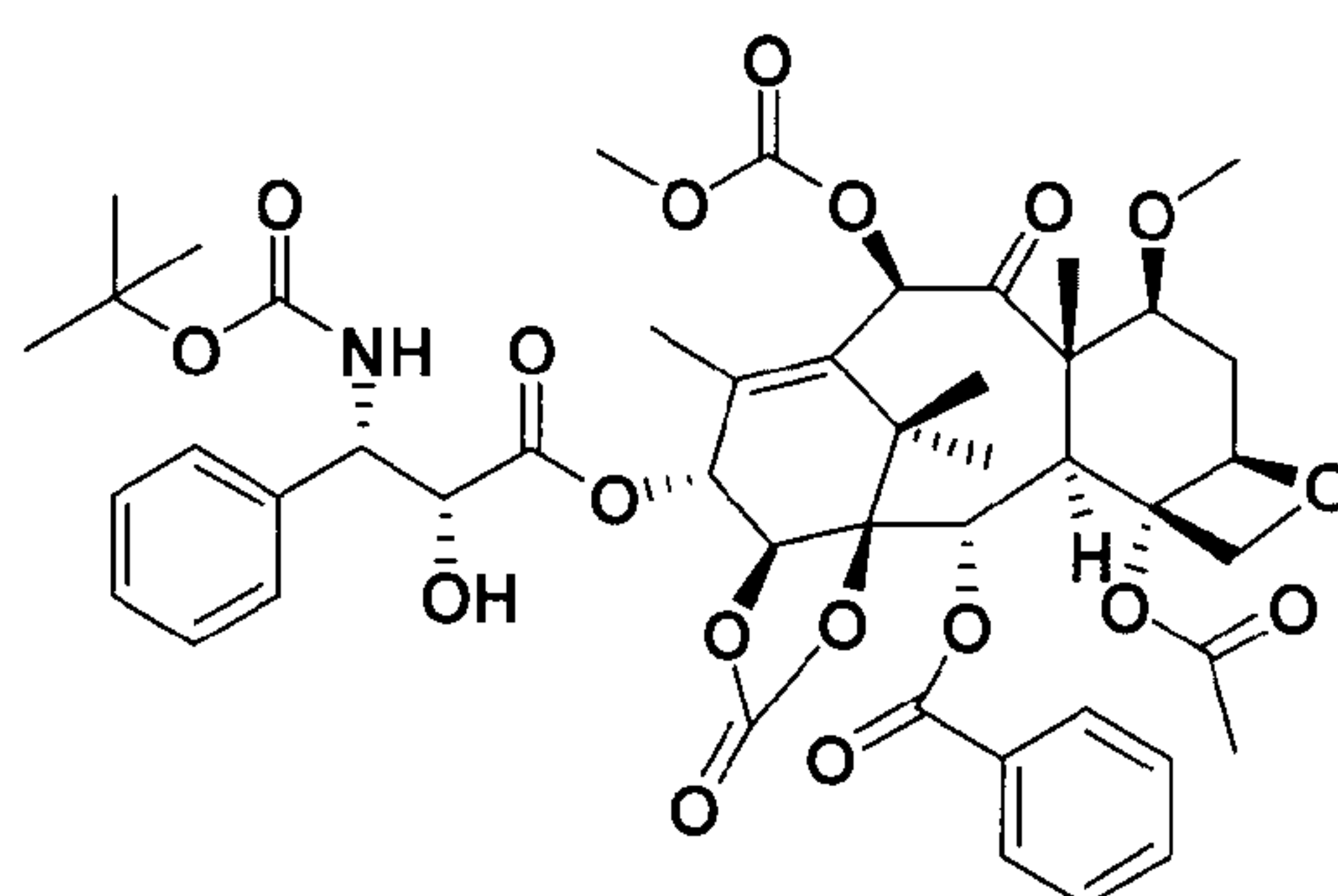
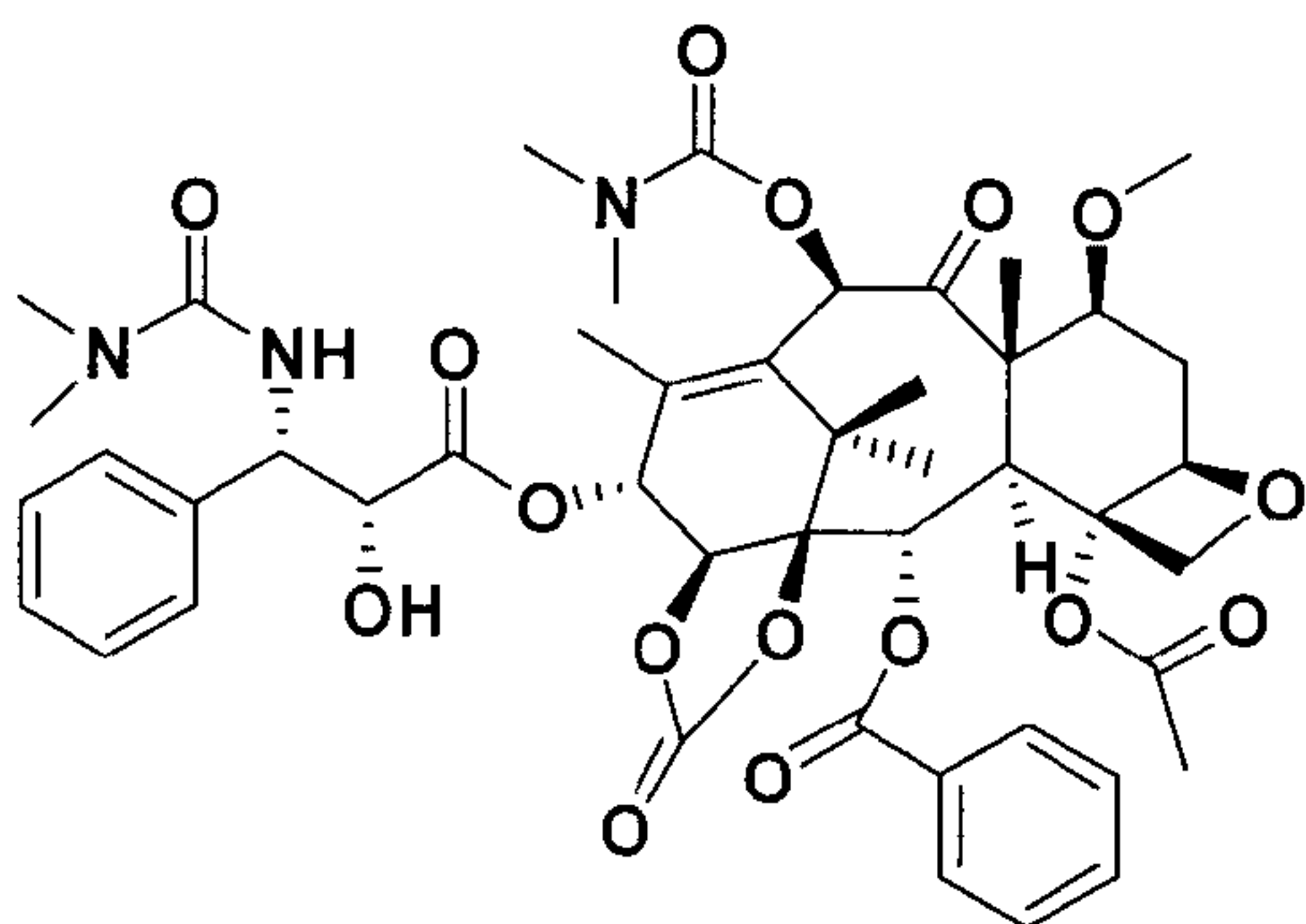
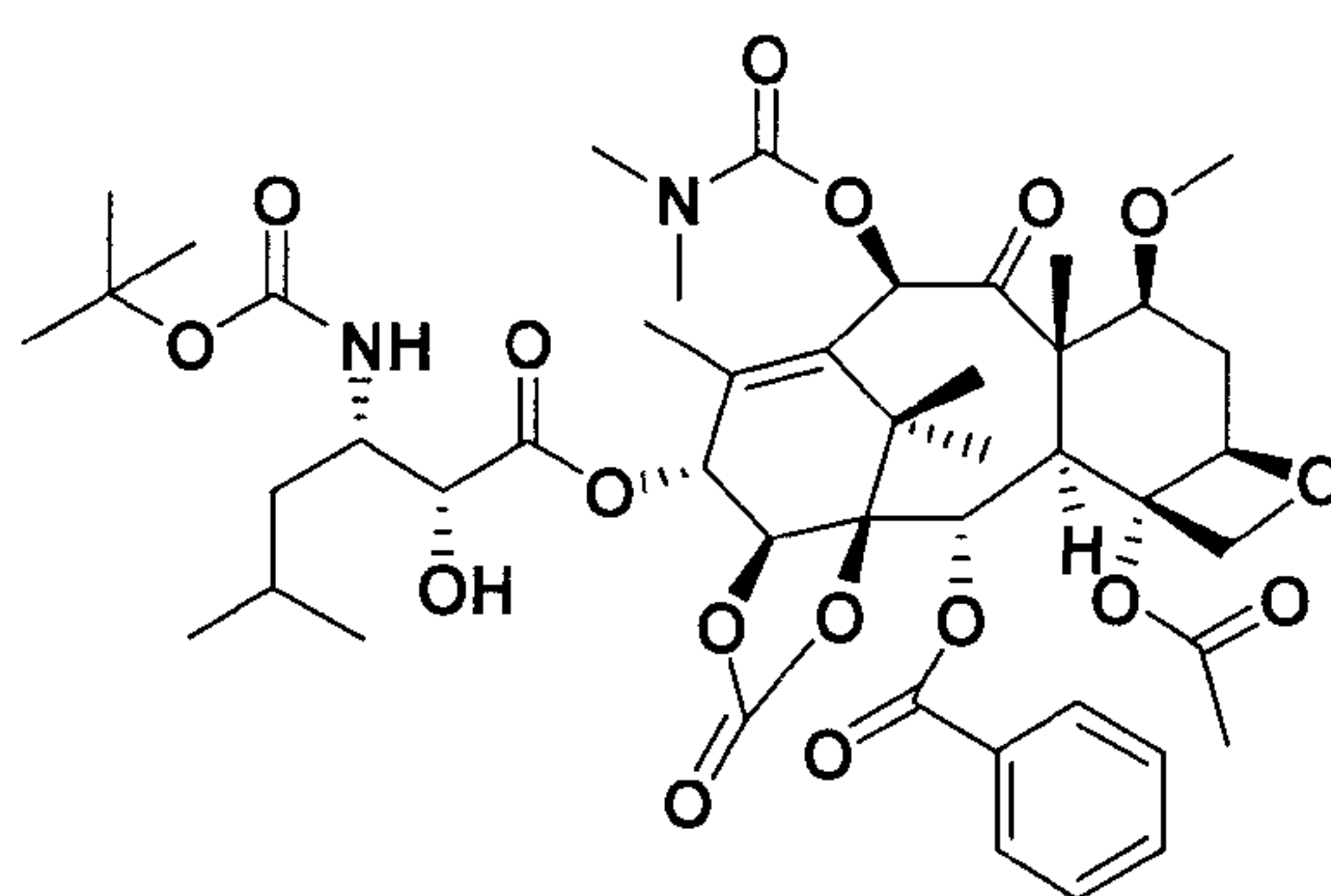
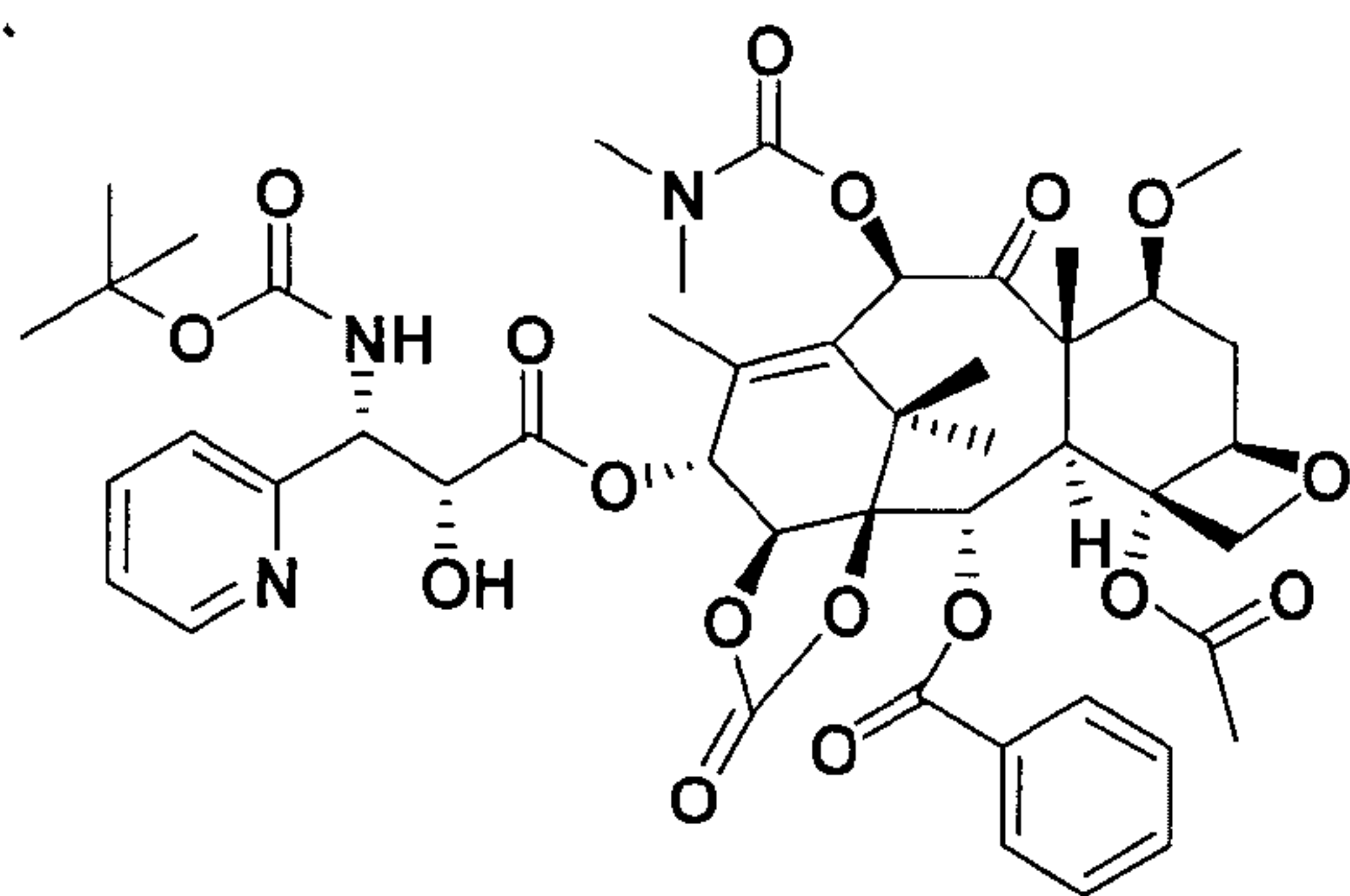
In one aspect, there is provided a taxane compound having the structure represented by the following general formula I:

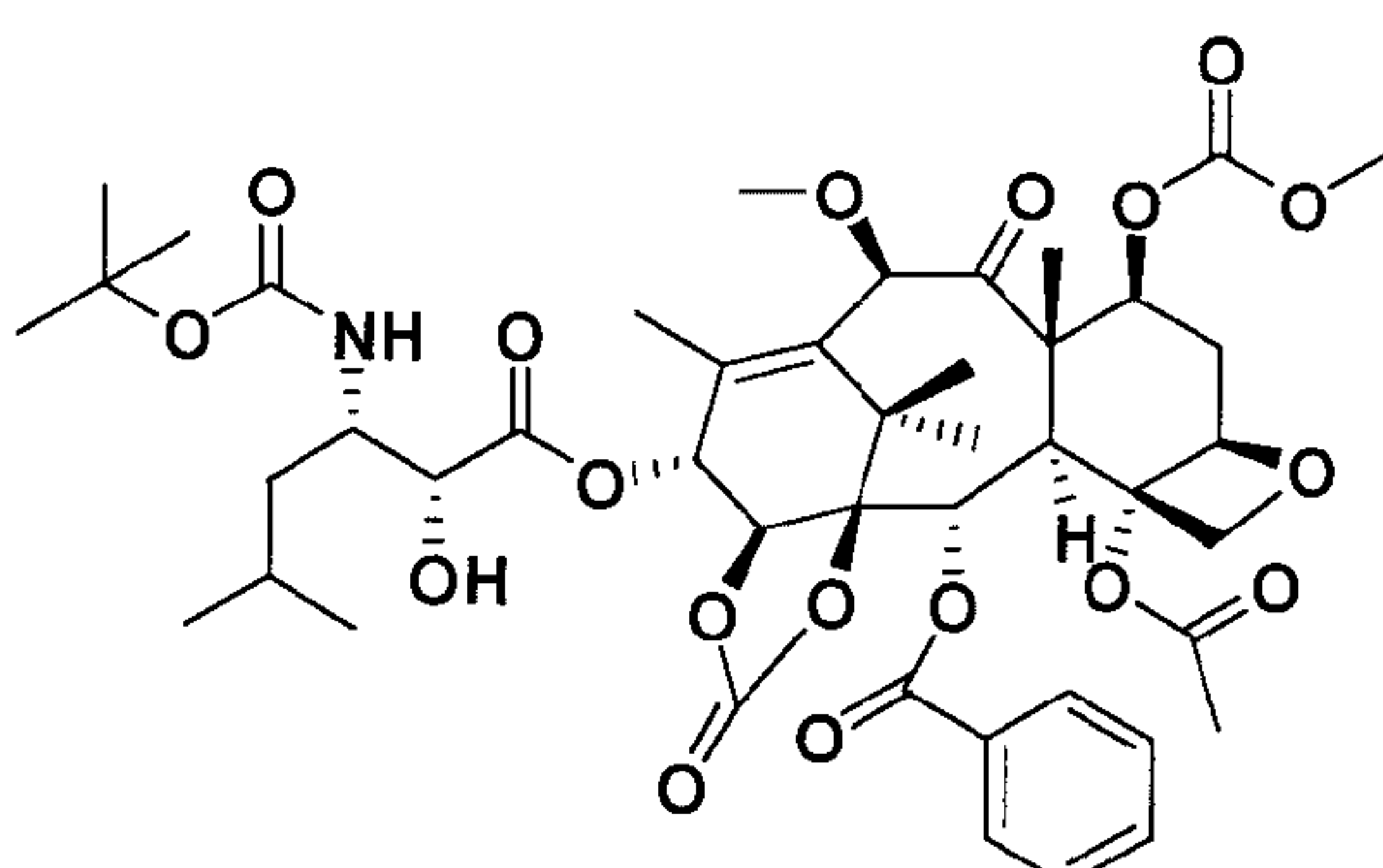
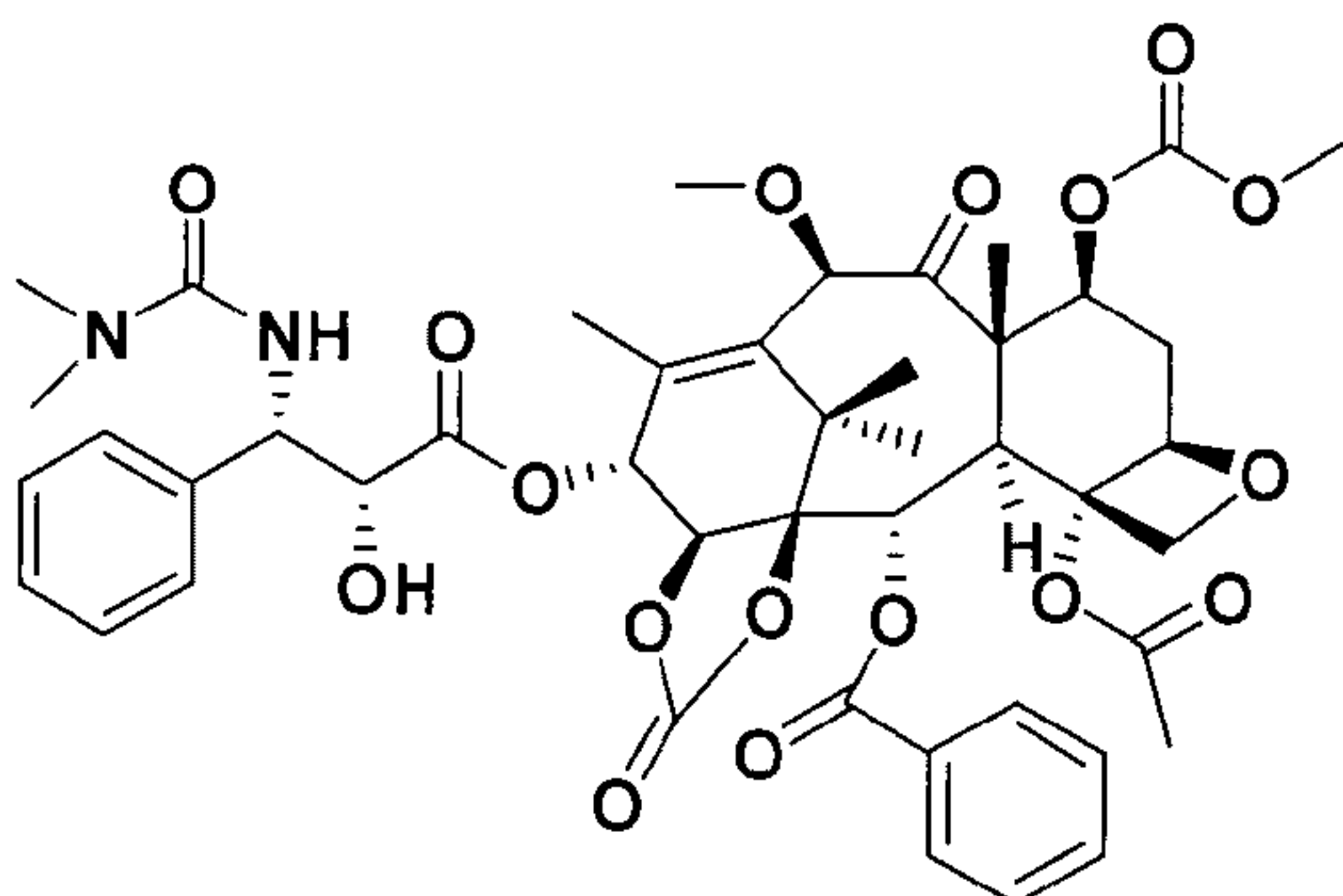
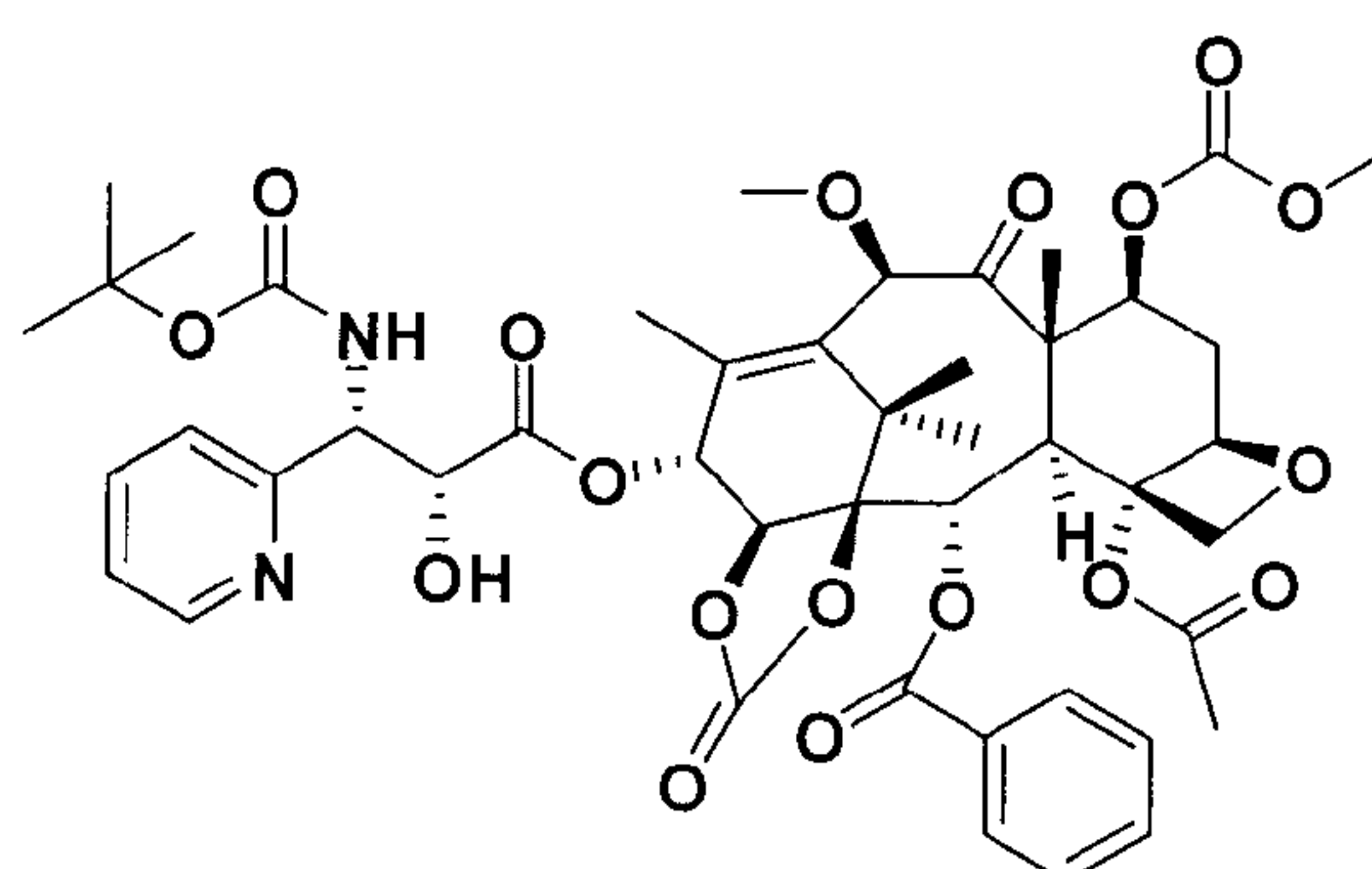
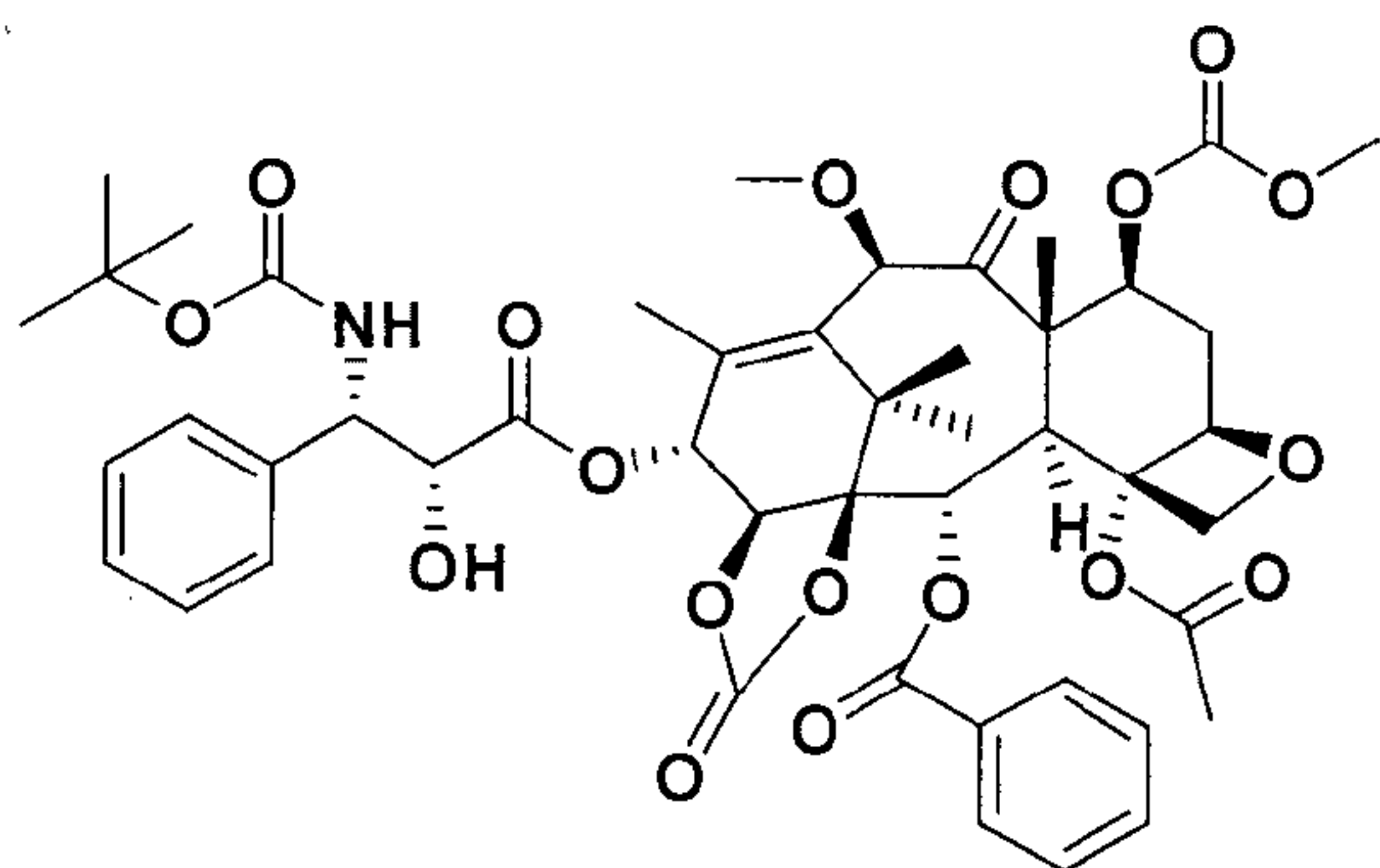


wherein R_1 is benzoyl, *t*-butyloxycarbonyl, or *N,N'*-dimethylcarbamoyl; R_2 is phenyl, (pyridyl-2-yl), or (isobutyl); R_3 is -OMe, -OCOOCH₃, -OCON(CH₃)₂, or -OCOSC₂H₅; R_4 is -OMe, -OCOOCH₃, -OCON(CH₃)₂, or -OCOSC₂H₅.

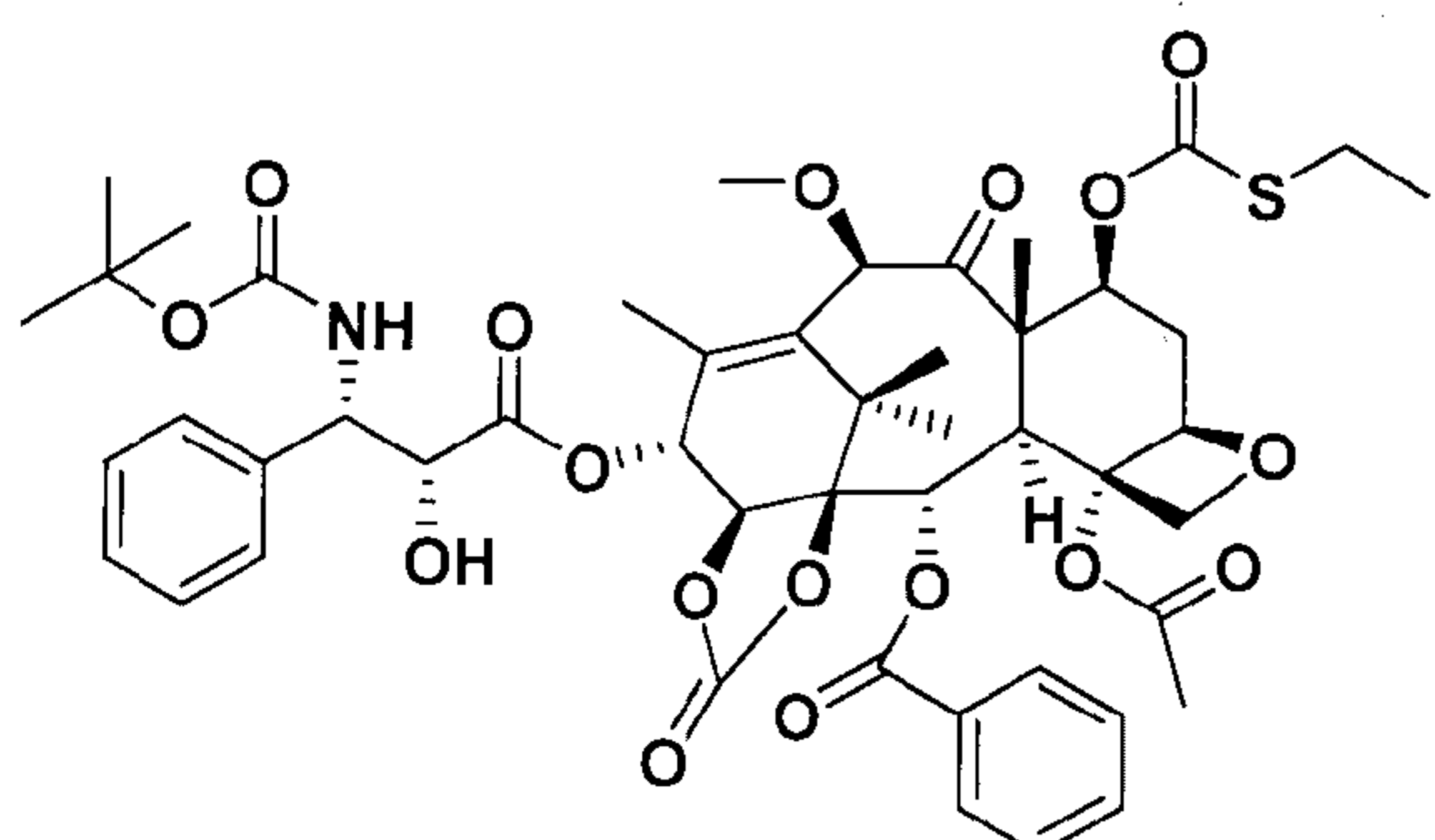
The compound may be selected from compounds having one of the following structures:







and



- 5 In another aspect, there is provided a compound comprising an isomer of a taxane compound disclosed herein.

In a further aspect, there is provided a pharmaceutically acceptable non-toxic salt of a taxane compound disclosed herein.

In a further aspect, there is provided a solvate of a taxane compound disclosed herein.

- 10 In a further aspect, there is provided an antitumor pharmaceutical composition, comprising a compound of formula I as disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, as an active ingredient. A weight ratio of the active ingredient in the composition may be 0.01% to 99.99%, with the balance of a pharmaceutically acceptable carrier.

In a further aspect, there is provided use of a compound as disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition as disclosed herein, in manufacturing an oral antitumor medicament.

In another aspect, there is provided a preparation method of a taxane compound as disclosed herein, wherein the method comprising the following steps:

Step 1 synthesis of taxanes mother nucleus part: by using 10-deacetyl baccatin III (10-DAB) as raw material, firstly, the hydroxyl groups at C7 and C10 positions of the mother nucleus part are selectively protected with substituents, then the C13 hydroxy group is oxidized into keto-carbonyl group, followed by highly stereoselectively introducing a hydroxyl group with β configuration at C14 by using N-(sulfonyl)oxaziridine, to form 1,14-carbonate structure under the action of CDI, and finally the C13 keto-carbonyl group is highly stereoselectively reduced into hydroxyl group with α configuration by CBS reduction method to give the taxanes mother nucleus part;

Step 2 synthesis of a precursor of five-member ring oxazolidine acid side chain: glycolic acid, used as raw material, is protected successively by benzyl group and butyloxycarbonyl group (Boc group) to generate the Boc-protected benzyl glycolate; different substituted aldehydes are condensed with (*S_R*)-*t*-butyl sulfinamide to form the corresponding enamine compounds; the Boc-protected benzyl glycolate and the enamine compound are reacted via an addition reaction in the presence of lithium salt, and then a chiral intermediate is given after acid hydrolysis, and the obtained intermediate is reacted with 1,1'-(dimethoxymethyl) *p*-methoxybenzene via an aldol condensation reaction, catalyzed by pyridinium *p*-toluenesulfonate (PPTS) to obtain a condensation compound; the amino group of the condensation compound is substituted with different substituents, and the precursor of five-member ring oxazolidine acid side chain is finally given after catalytic hydrogenation;

Step 3 synthesis of taxanes derivatives: the precursor of five-member ring oxazolidine acid side chain is linked with the taxanes mother nucleus part by esterification, and a series of taxanes derivatives are generated after removal of the protective group by acid hydrolysis.

In an embodiment of the preparation method:

in Step 1, the C7- and C10-hydroxyl groups may be protected with substituents:

(1) When R_3 and R_4 are -OMe, the reaction involved is: firstly, the hydroxyl group is reacted with *p*-toluenesulfonyl chloride (TsCl) at room temperature to 0°C in tetrahydrofuran or dichloromethane as the solvent and pyridine (Py) as the alkali to give *p*-toluenesulfonate, which is further reacted with a Grignard reagent to give the corresponding ether -OMe;
5

(2) When R_3 and R_4 are $-\text{OCOOCH}_3$ or $-\text{OCON}(\text{CH}_3)_2$, the reaction involved is: under alkaline conditions, the hydroxyl group is reacted with the corresponding acyl chloride in tetrahydrofuran as the solvent at room temperature to -70°C;

(3) When R_3 and R_4 are $-\text{OCOSC}_2\text{H}_5$, the reaction involved is: the hydroxyl group is reacted with N,N'-carbonyldiimidazole (CDI) in tetrahydrofuran as the solvent at room temperature, and the obtained product is further reacted with mercaptan via substitution reaction;
10

In Step 1, the stereoselective reduction on the C13 keto-carbonyl group by CBS reduction method may include the following specific steps: C13-oxo is stereoselectively reduced into C13- α -OH by using anhydrous tetrahydrofuran, dry dichloromethane or alcohols as the solvent, (R)-2-methyl oxazaborodine as the catalyst and boranes as the reducing agent at room temperature to -70°C;
15

In Step 2, the different substituted aldehydes may include C1-C6 hydrocarbyl aldehydes, C1-C6 substituted hydrocarbyl aldehydes, aromatic aldehydes, substituted aromatic aldehydes and heteroaromatic aldehydes; the reaction involved in the substitution of the amino group of the chiral intermediate may be carried out by using tetrahydrofuran, dichloromethane or dioxane as the solvent, to react with the corresponding acyl chlorides under alkaline conditions at room temperature to -70°C; in the catalytic hydrogenation reaction, palladium-charcoal or palladium hydroxide may be used as the catalyst, hydrogen is introduced at normal pressure or pressurized conditions, and the reaction may be carried out in alcohols, tetrahydrofuran or dichloromethane as the solvent.
20
25

In another embodiment of the preparation method:

in Step 1, the C7- and C10-hydroxyl groups may be protected by substituents:

(1) When R_3 and R_4 are -OMe, dichloromethane is used as the solvent, and the temperature is at 0°C ; and

(2) When R_3 and R_4 are $-\text{OCOOCH}_3$ or $-\text{OCON}(\text{CH}_3)_2$, lithium hexamethyldisilazide is used as the alkali and the temperature is at -40°C ;

- 5 In Step 1, the stereoselective reduction on the C13 keto-carbonyl group by CBS reduction method may be carried out at room temperature by using anhydrous tetrahydrofuran as the solvent;

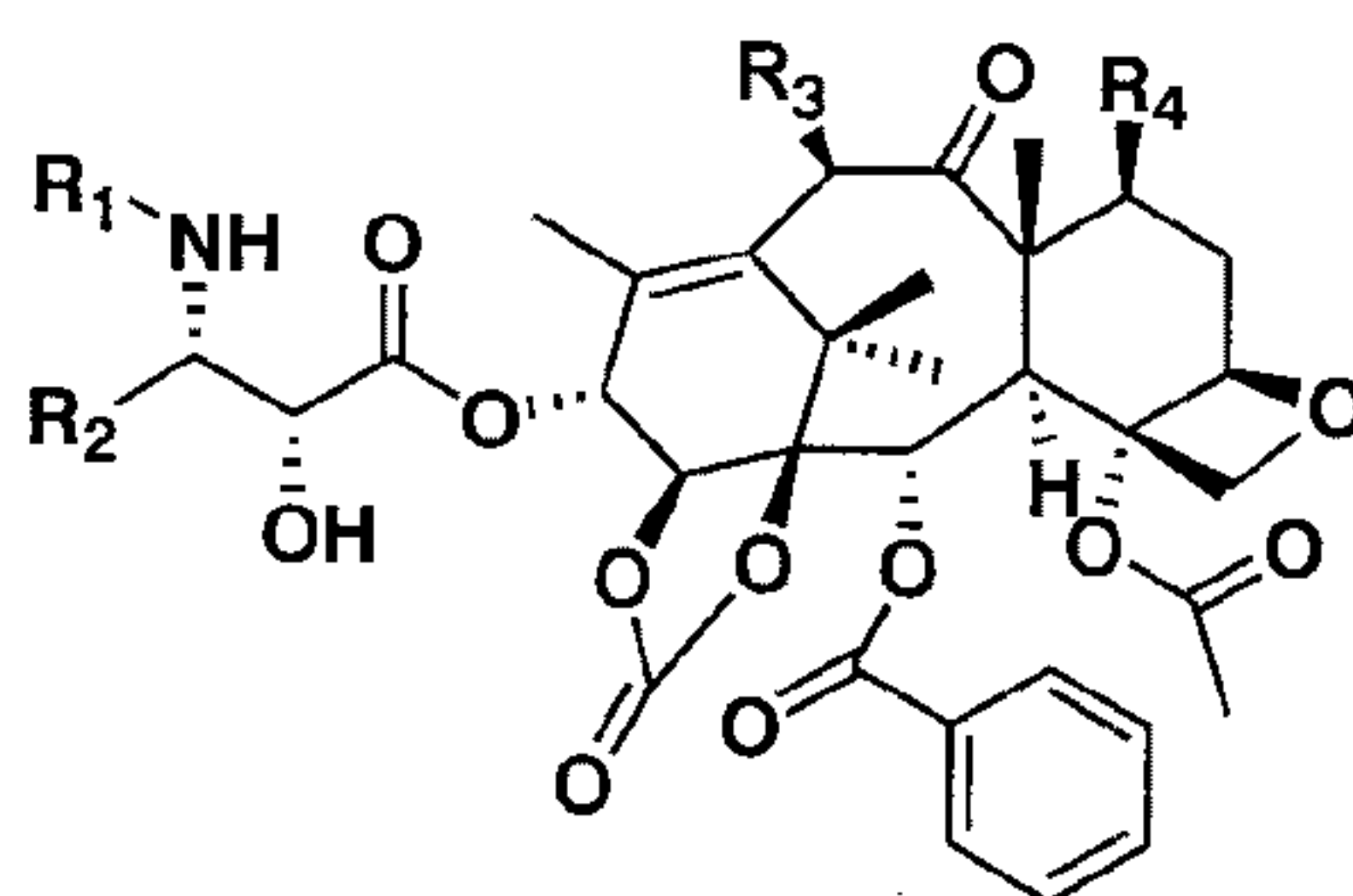
In Step 2, in the reaction involved in the substitution of the amino group on the intermediate, lithium hexamethyldisilazide may be used as the alkali and tetrahydrofuran is used as the
10 solvent; the temperature may be at -40°C , the acyl chloride may comprise PhCOCl , $(\text{CH}_3)_3\text{OCOCl}$ and $(\text{CH}_3)_2\text{NCOCl}$; in the catalytic hydrogenation reaction, palladium hydroxide may be used as the catalyst, hydrogen may be introduced at 20psi and the reaction may be carried out in an alcoholic solution.

In an embodiment of the preparation method the Grignard reagent may comprise CH_3MgBr .

- 15 In another embodiment of the preparation method the acyl chloride may comprise at least one of $(\text{CH}_3)_3\text{OCOCl}$ and $(\text{CH}_3)_2\text{NCOCl}$.

In another embodiment of the preparation method, in step 1, when R_3 and R_4 are $-\text{OCOSC}_2\text{H}_5$, the mercaptan may comprise $\text{C}_2\text{H}_5\text{SH}$.

The present disclosure also discloses taxanes compounds having the structure represented by the
20 following general formula I:



I

wherein,

R_1 is $-\text{COR}_6$, $-\text{COOR}_6$, or $-\text{CONR}_{7a}\text{R}_{7b}$;

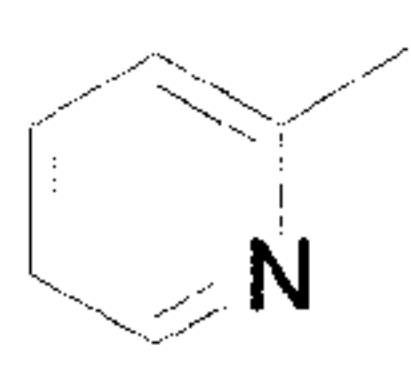
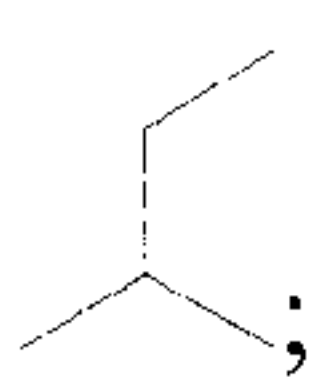
R₂ is a C1-C6 alkyl, a C1-C6 alkenyl group, a substituted hydrocarbon group, a heterocyclic group, an aromatic group or a substituted aromatic group;

R_3 is $-OR_6$, $-OCOOR_6$, $-OCOSR_6$, or $-OCONR_{7a}R_{7b}$;

R_4 is $-OR_6$, $-OCOOR_6$, $-OCOSR_6$, $-OCONR_{7a}R_{7b}$, H or OH;

wherein, R_6 is a C1-C6 alkyl, a C1-C6 alkenyl, a C1-C6 alkynyl, a substituted hydrocarbon group, an aromatic group or a heterocyclic group; R_{7a} and R_{7b} are respectively hydrogen, a
5 hydrocarbon group, a substituted hydrocarbon group or a heterocyclic group.

Preferably, R_1 is benzoyl, *t*-butyloxycarbonyl, or N,N'-dimethylcarbamoyl;

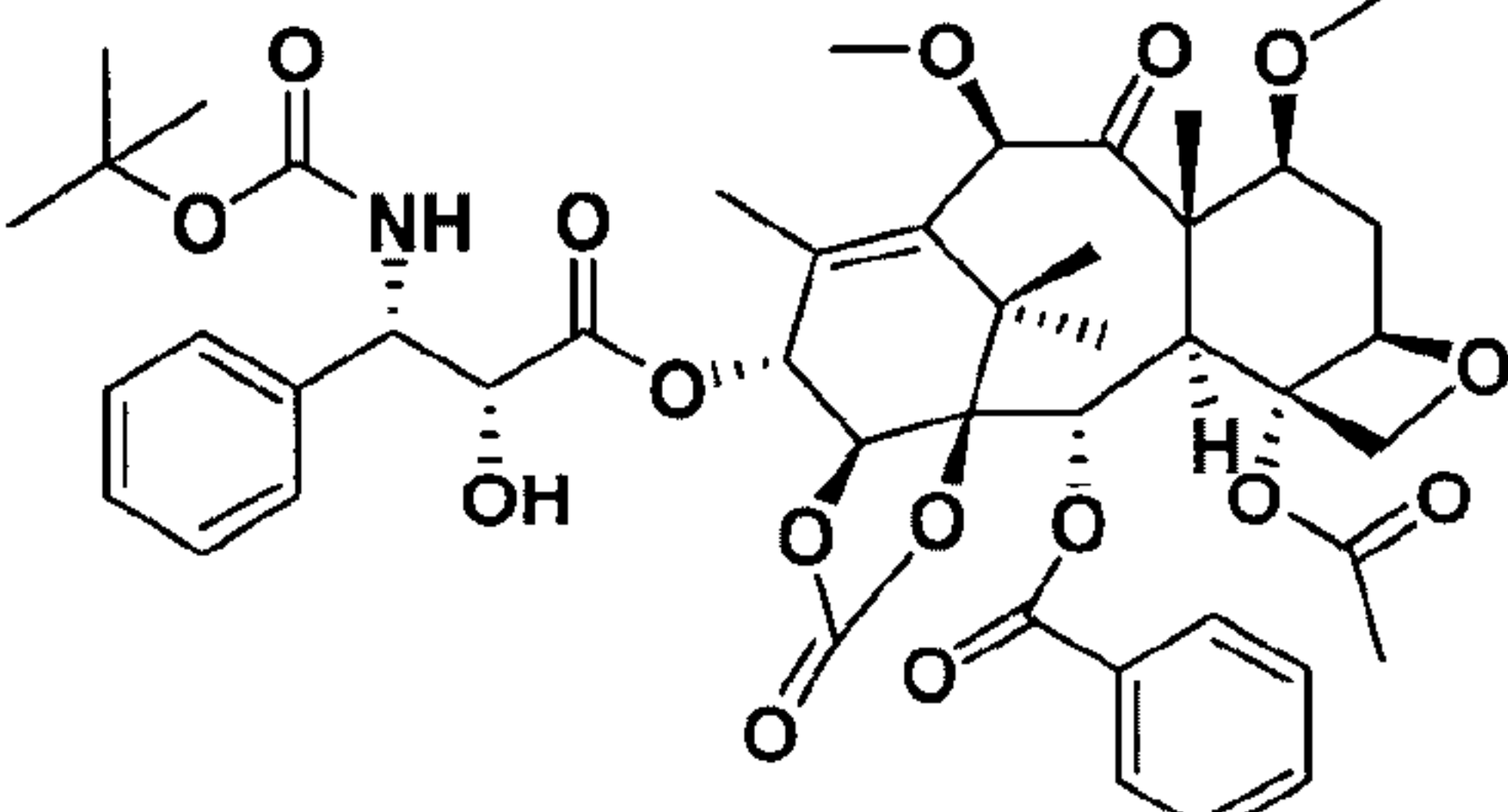
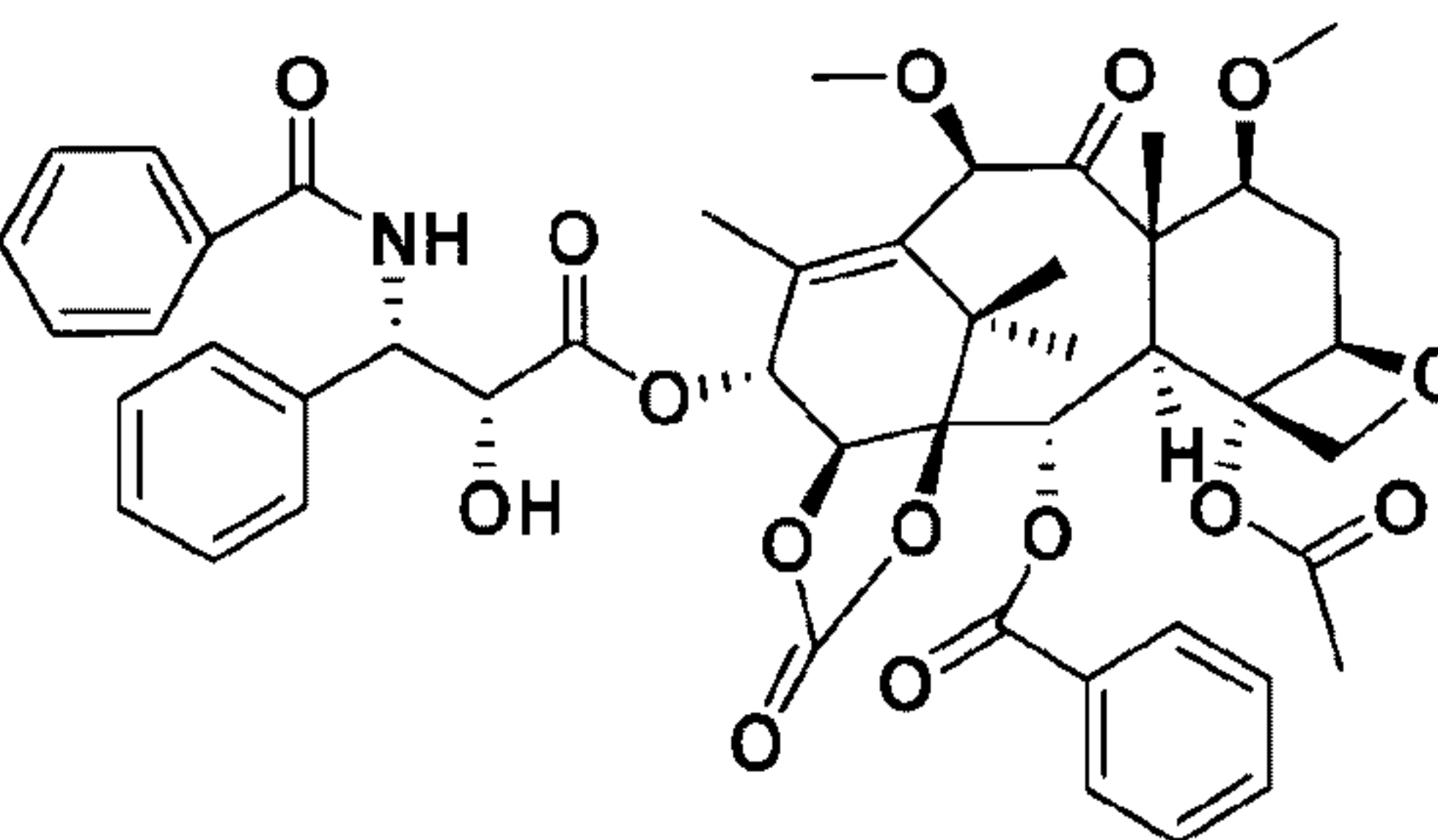
R_2 is phenyl, , or ;

R_3 is $-OMe$, $-OCOCH_3$, $-OCON(CH_3)_2$, or $-OCOSC_2H_5$;

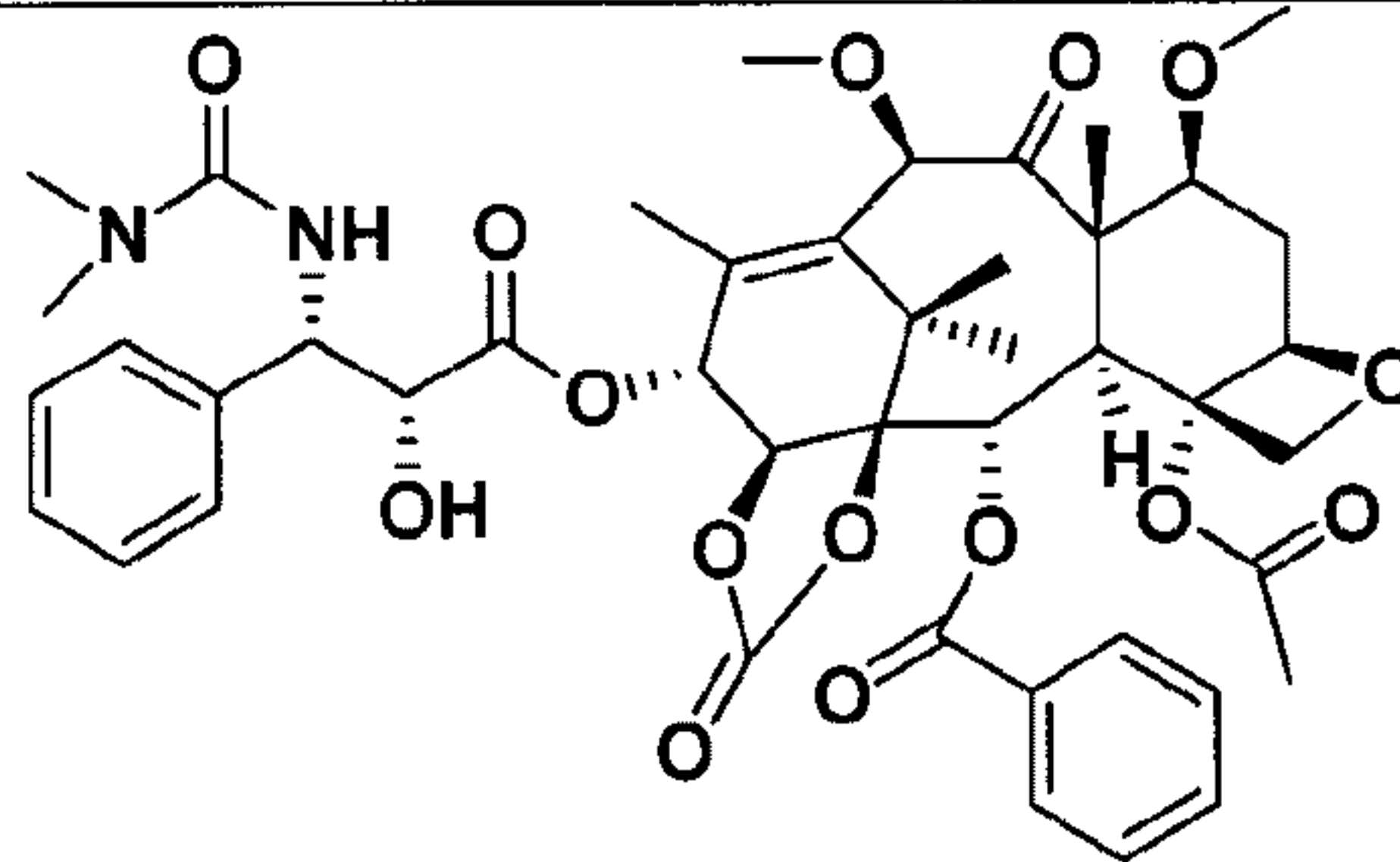
R_4 is $-OMe$, $-OCOCH_3$, $-OCON(CH_3)_2$, $-OCOSC_2H_5$, H or OH.

10

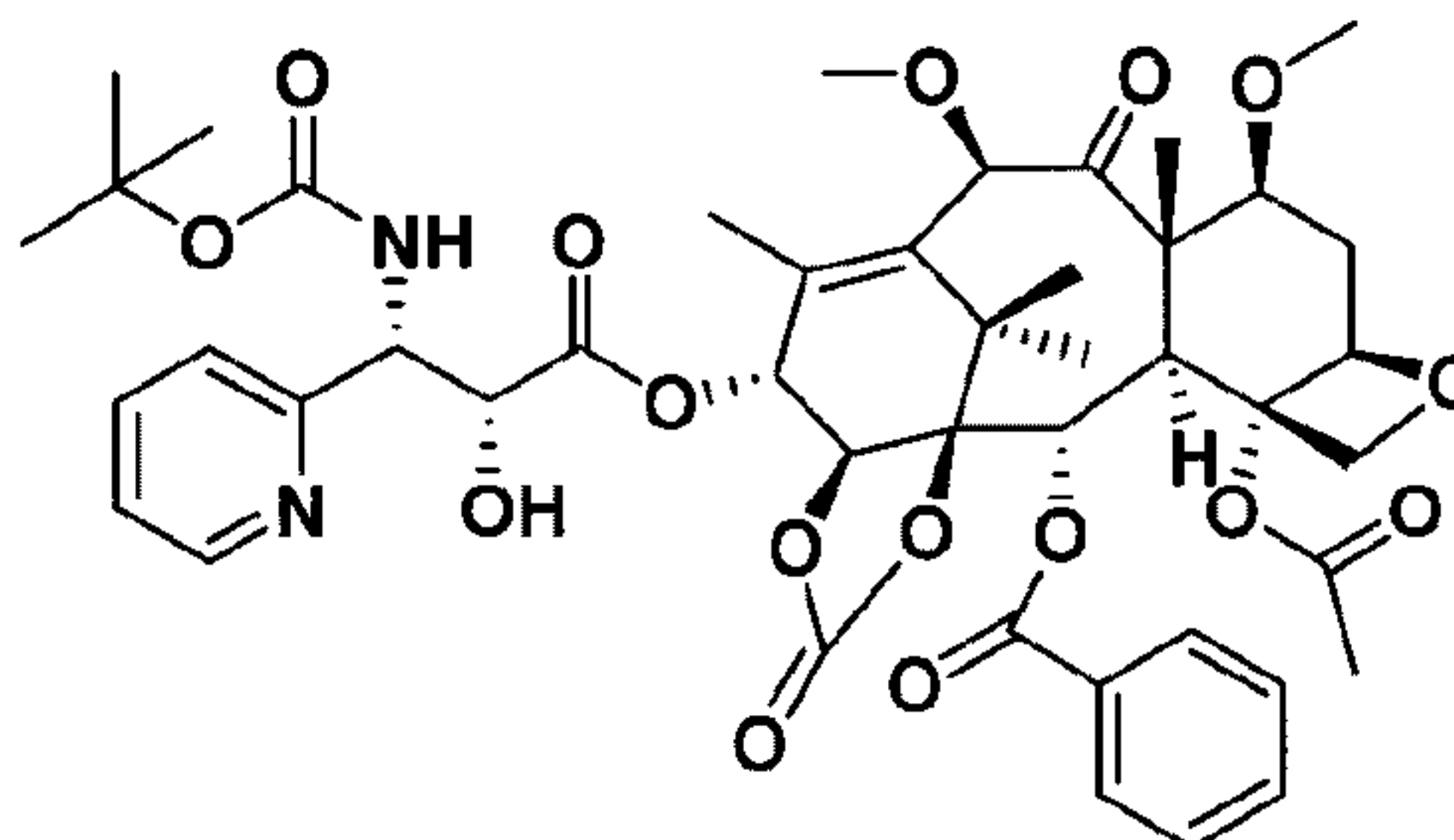
Most preferably, the taxanes compounds of the present invention are selected from the compounds having the following structures:

Code	MW	Formula	Structure
PCMI-01	877	$C_{46}H_{55}NO_{16}$	
PCMI-02	881	$C_{48}H_{51}NO_{15}$	

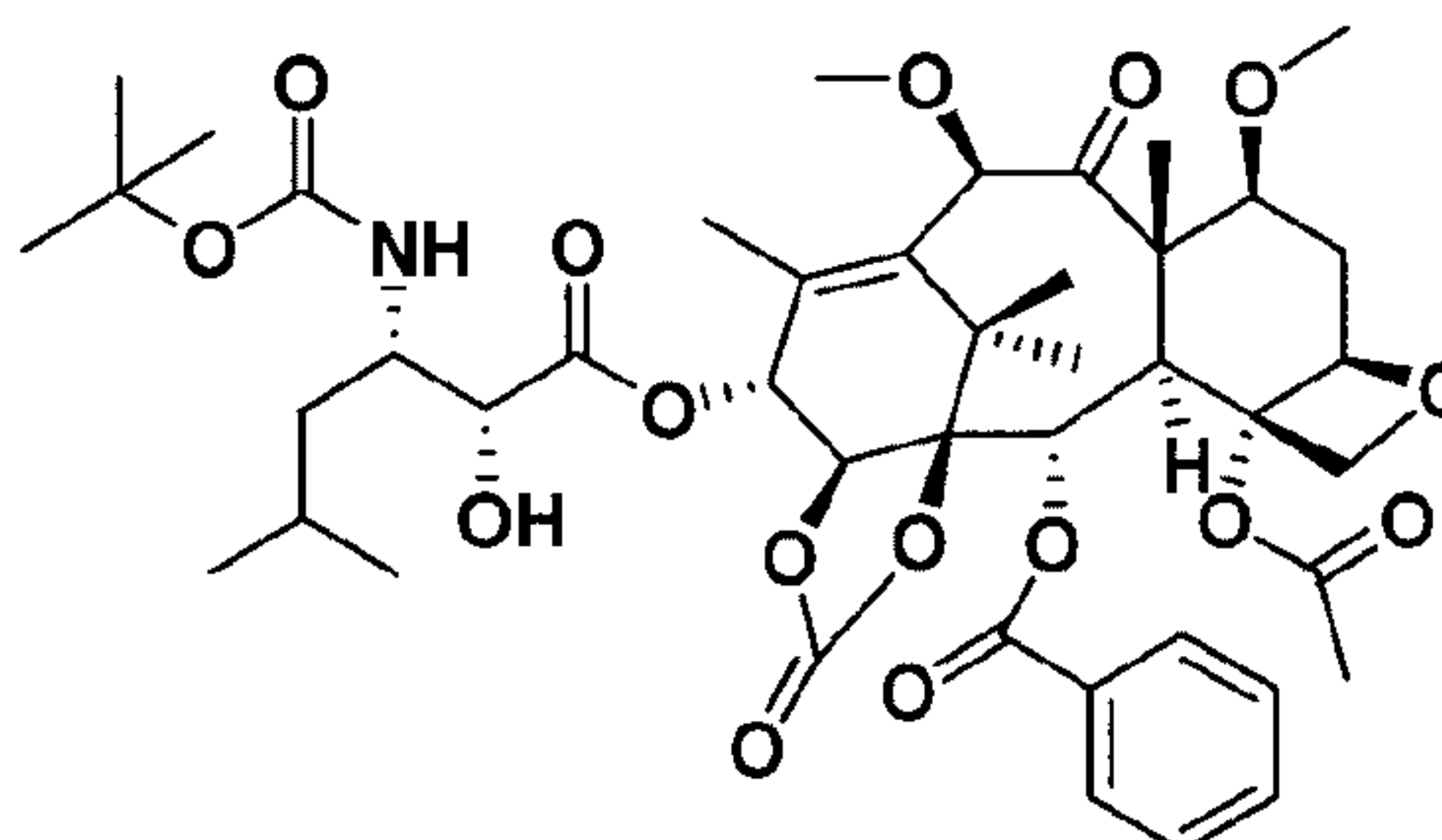
PCMI-03 848 $C_{44}H_{52}N_2O_{15}$



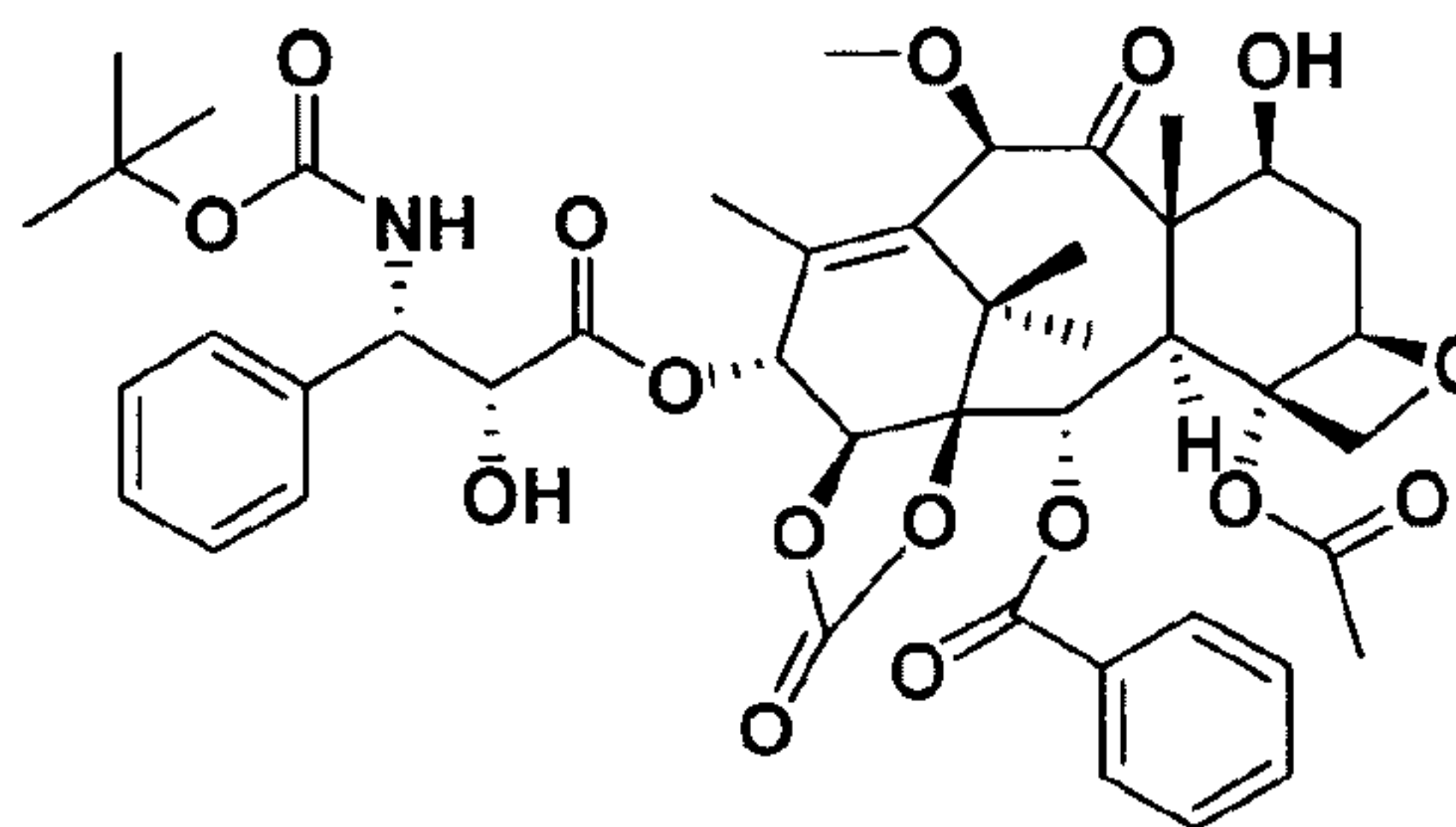
PCMI-04 878 $C_{45}H_{54}N_2O_{16}$



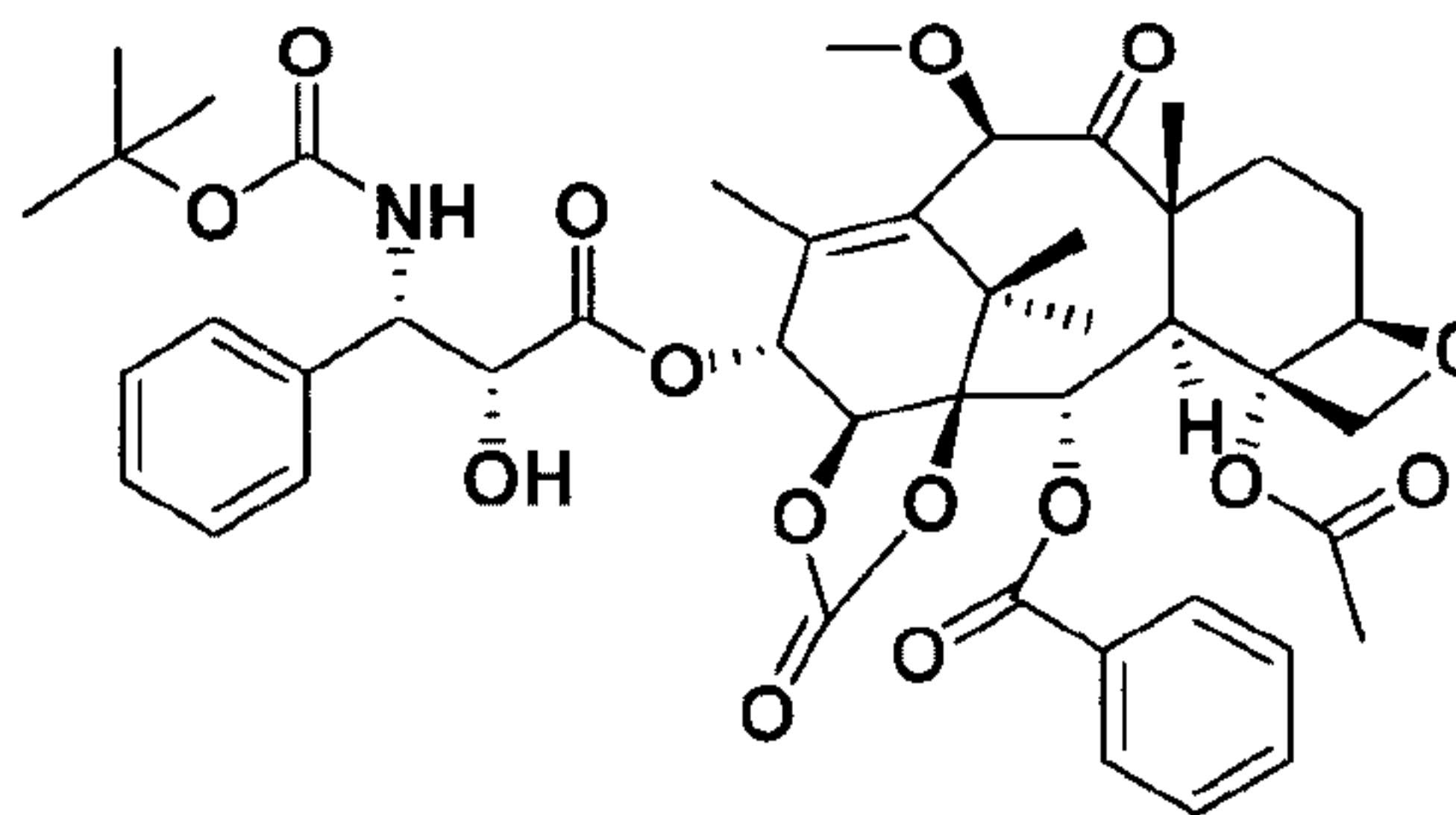
PCMI-05 857 $C_{44}H_{59}NO_{16}$

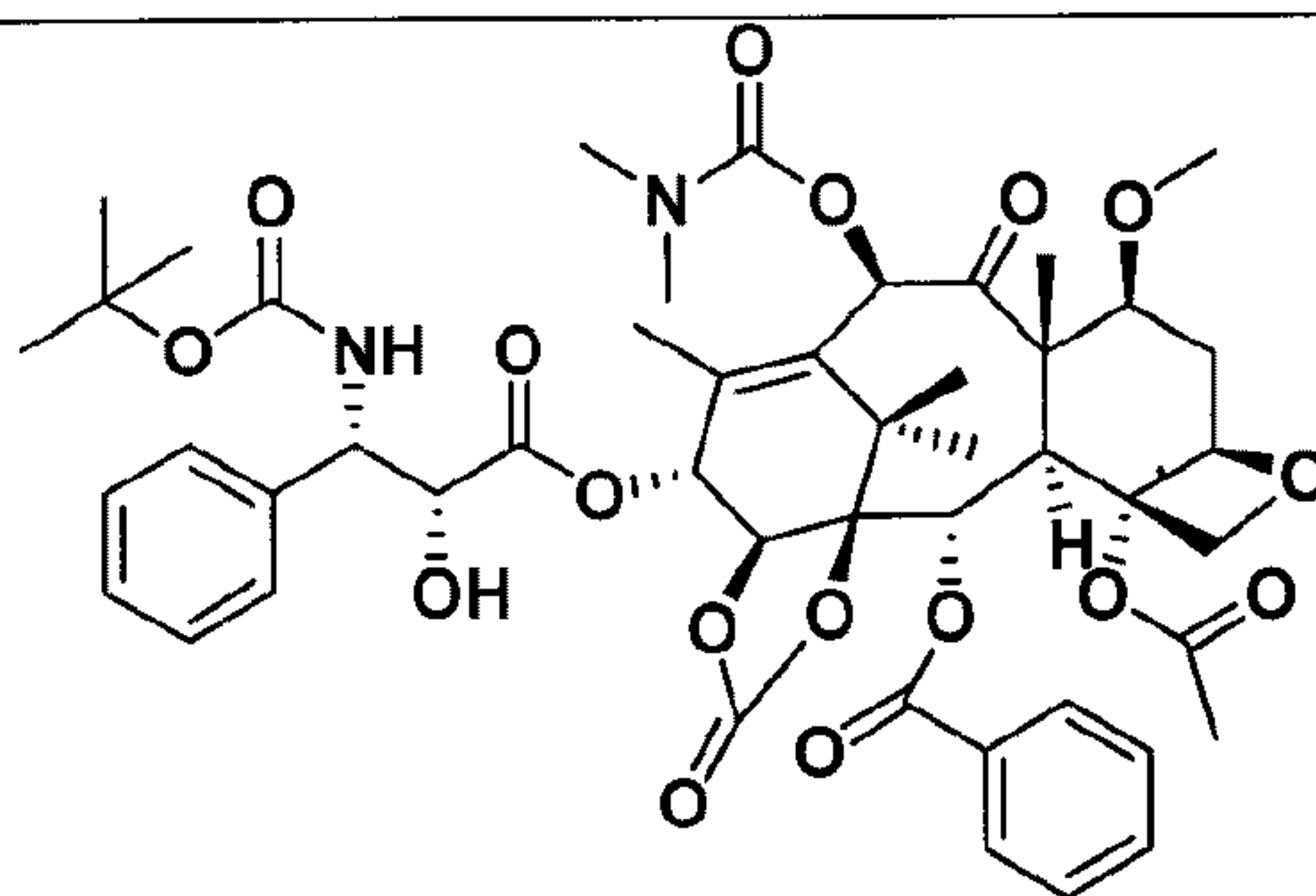
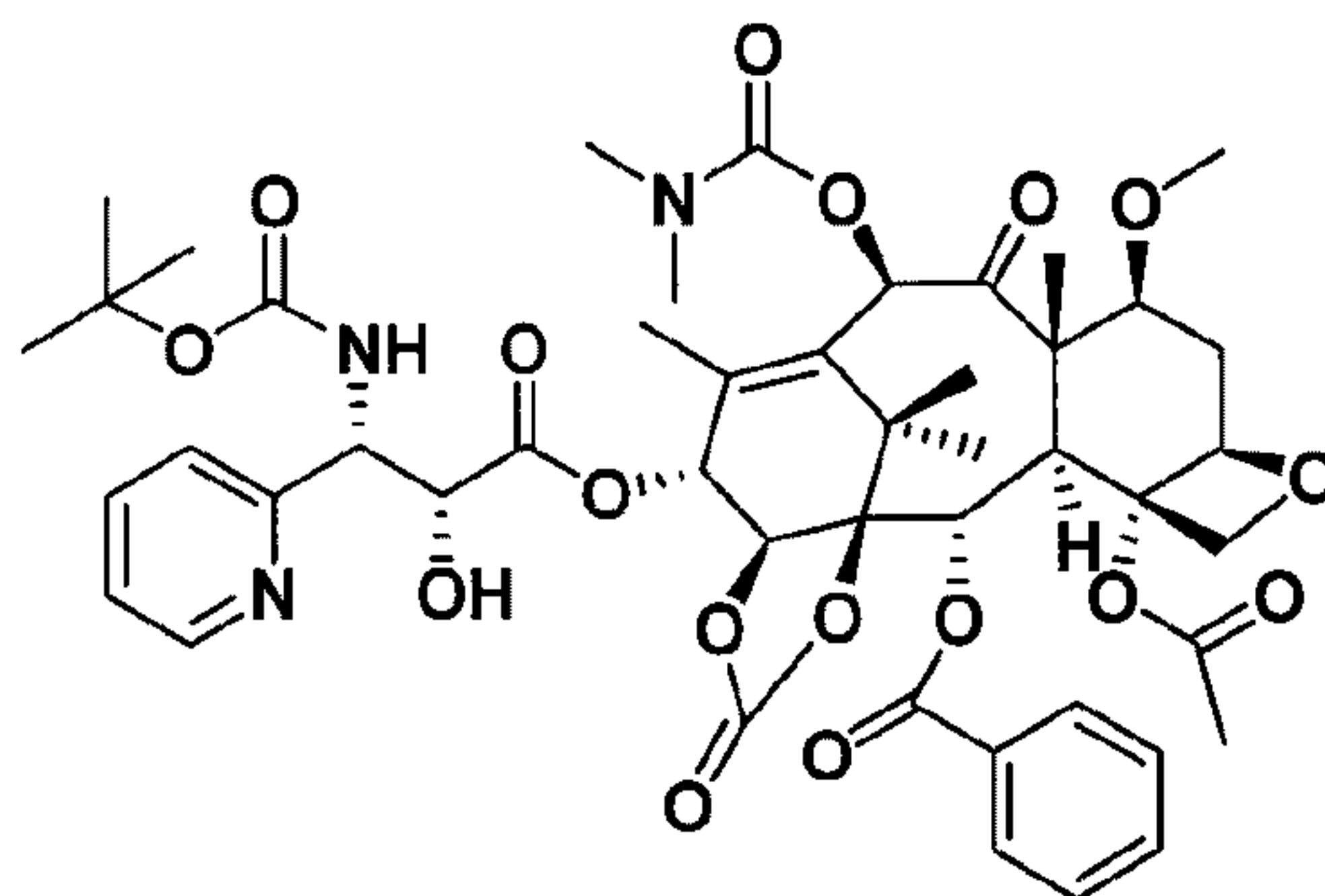
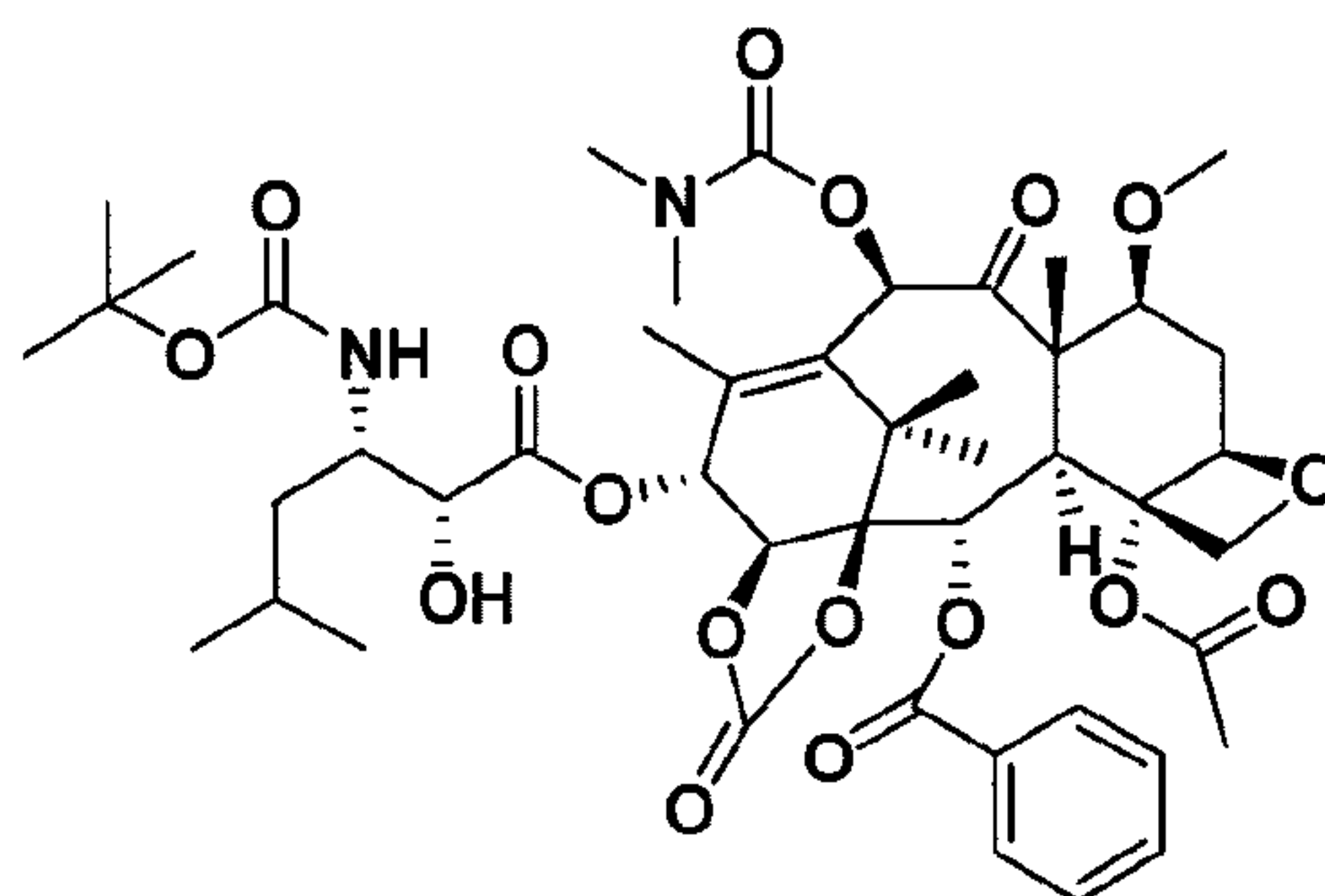
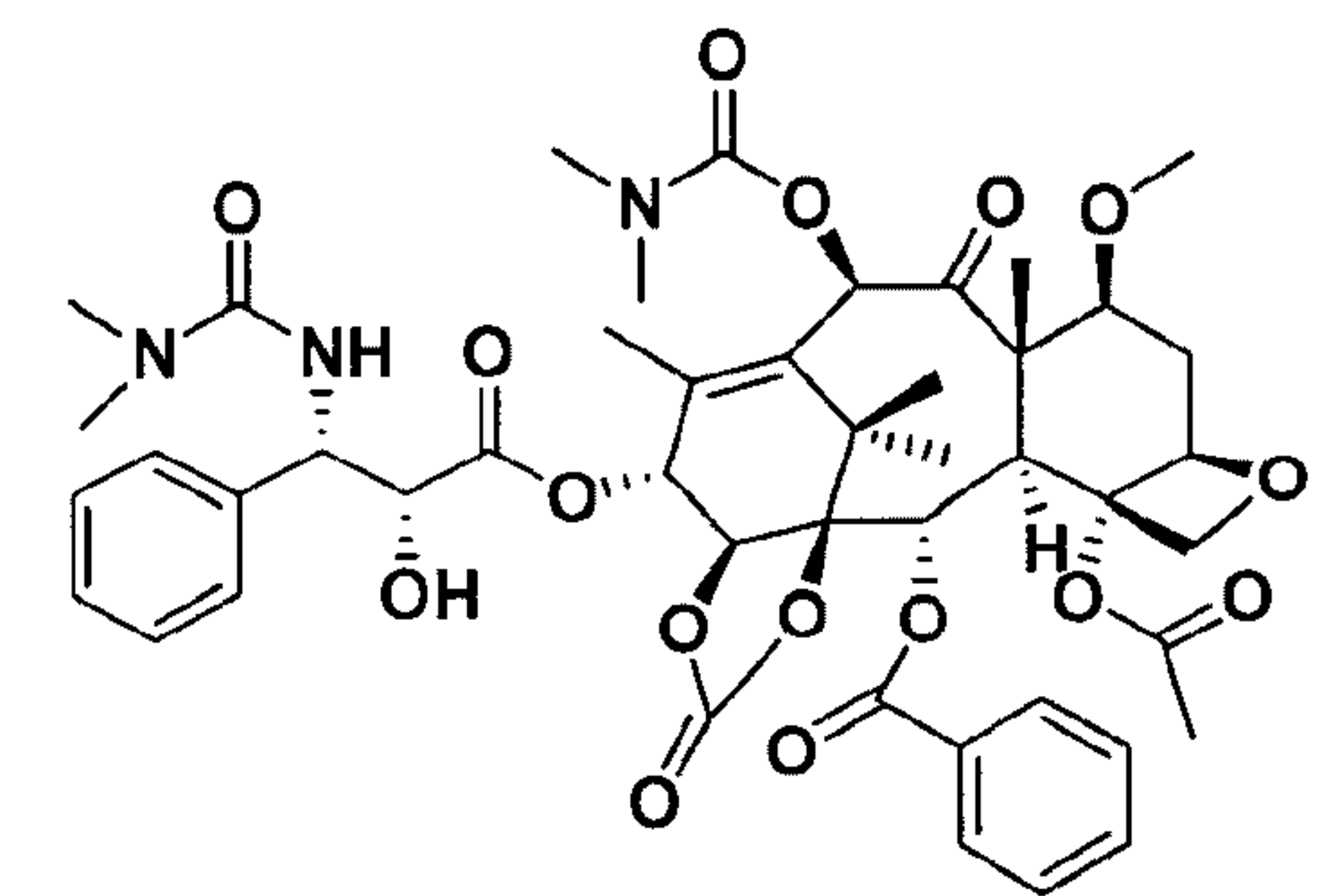


PCMI-06 863 $C_{45}H_{53}NO_{16}$

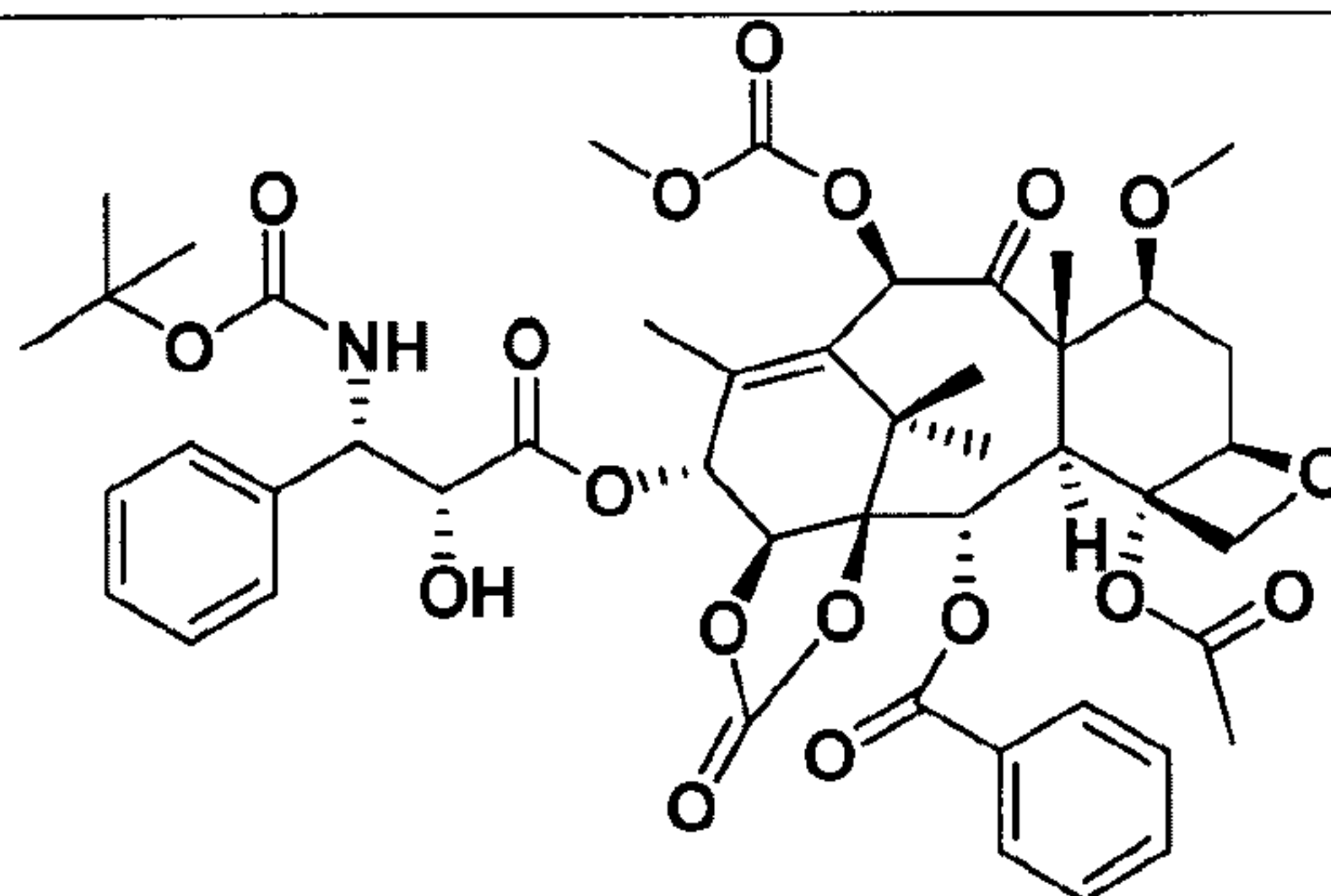


PCMI-07 847 $C_{45}H_{53}NO_{15}$

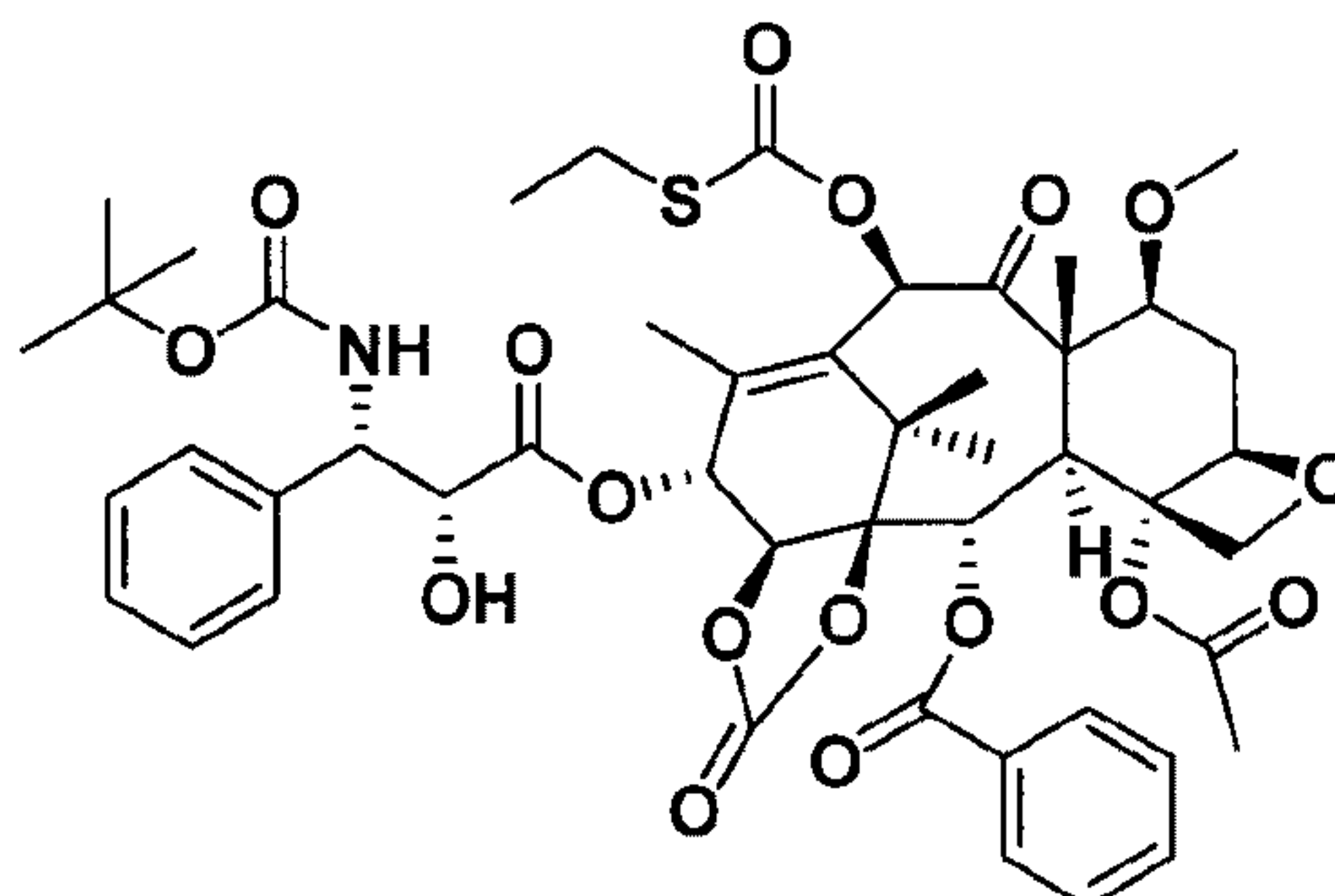


PCMI-08 934 $C_{48}H_{58}N_2O_{17}$ PCMI-09 935 $C_{47}H_{57}N_3O_{17}$ PCMI-10 914 $C_{46}H_{62}N_2O_{17}$ PCMI-11 905 $C_{46}H_{55}N_3O_{16}$ 

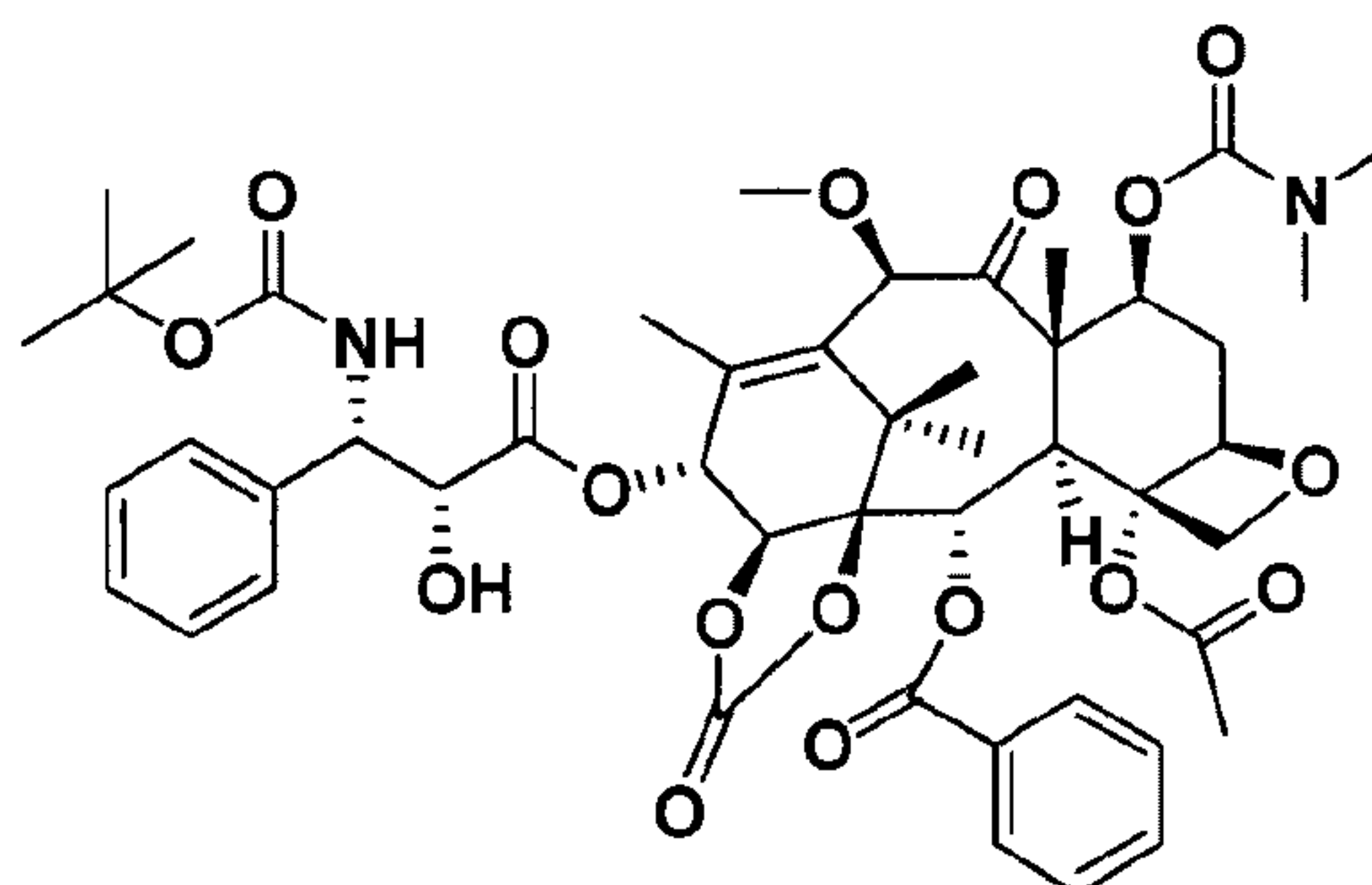
PCMI-12 921 $C_{47}H_{55}NO_{18}$



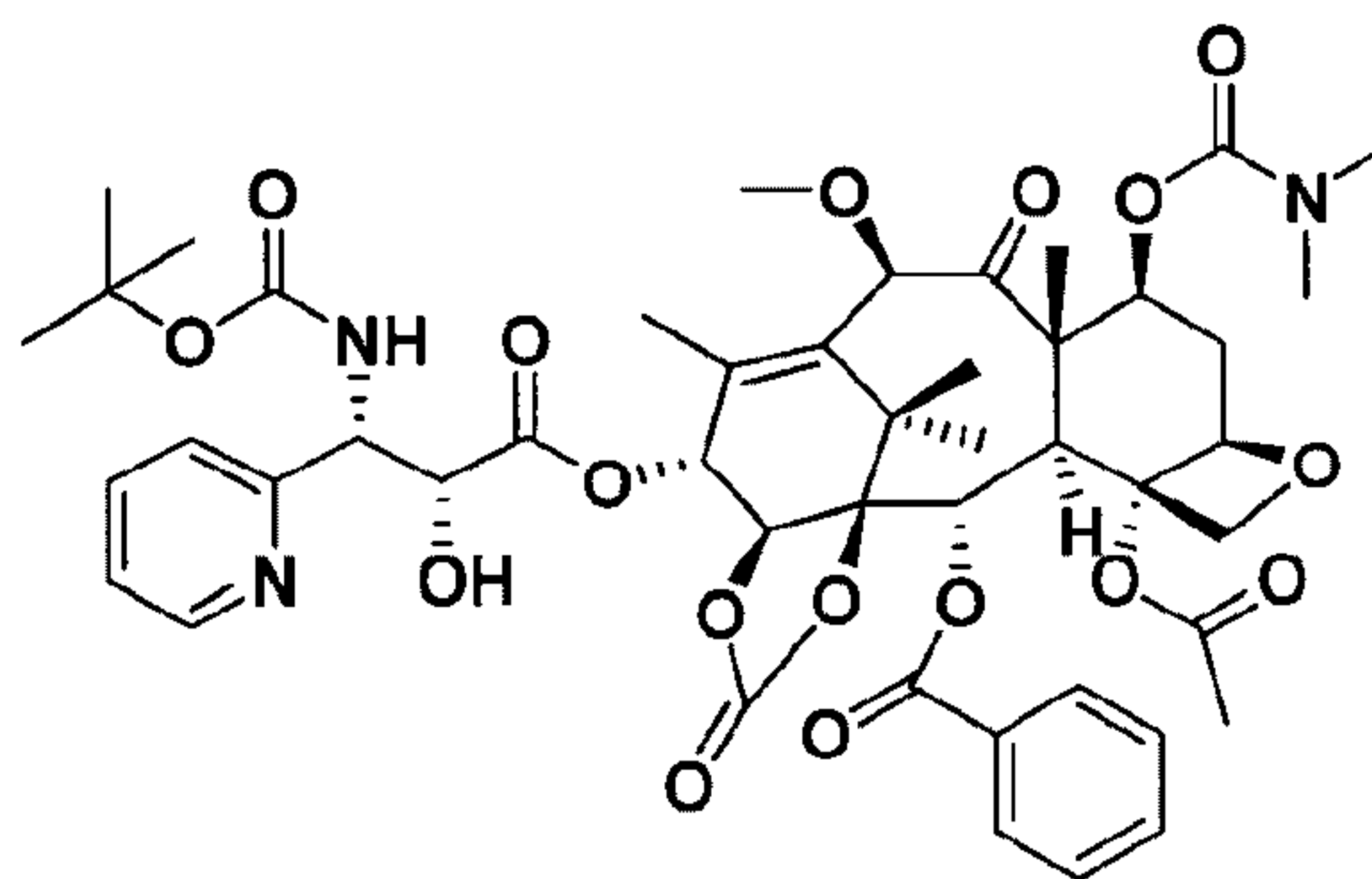
PCMI-13 951 $C_{48}H_{57}NO_{17}S$



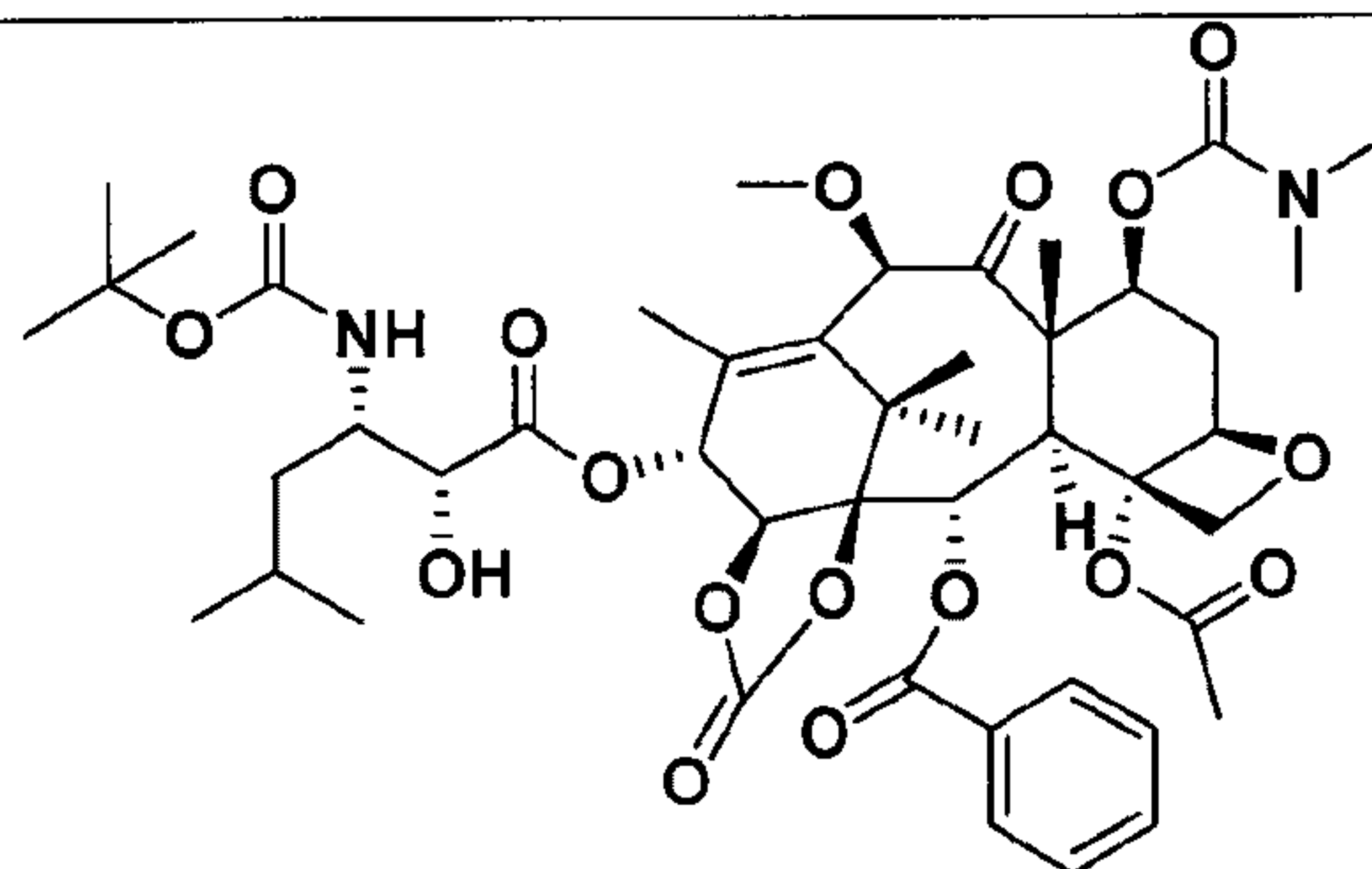
PCMI-14 934 $C_{48}H_{58}N_2O_{17}$



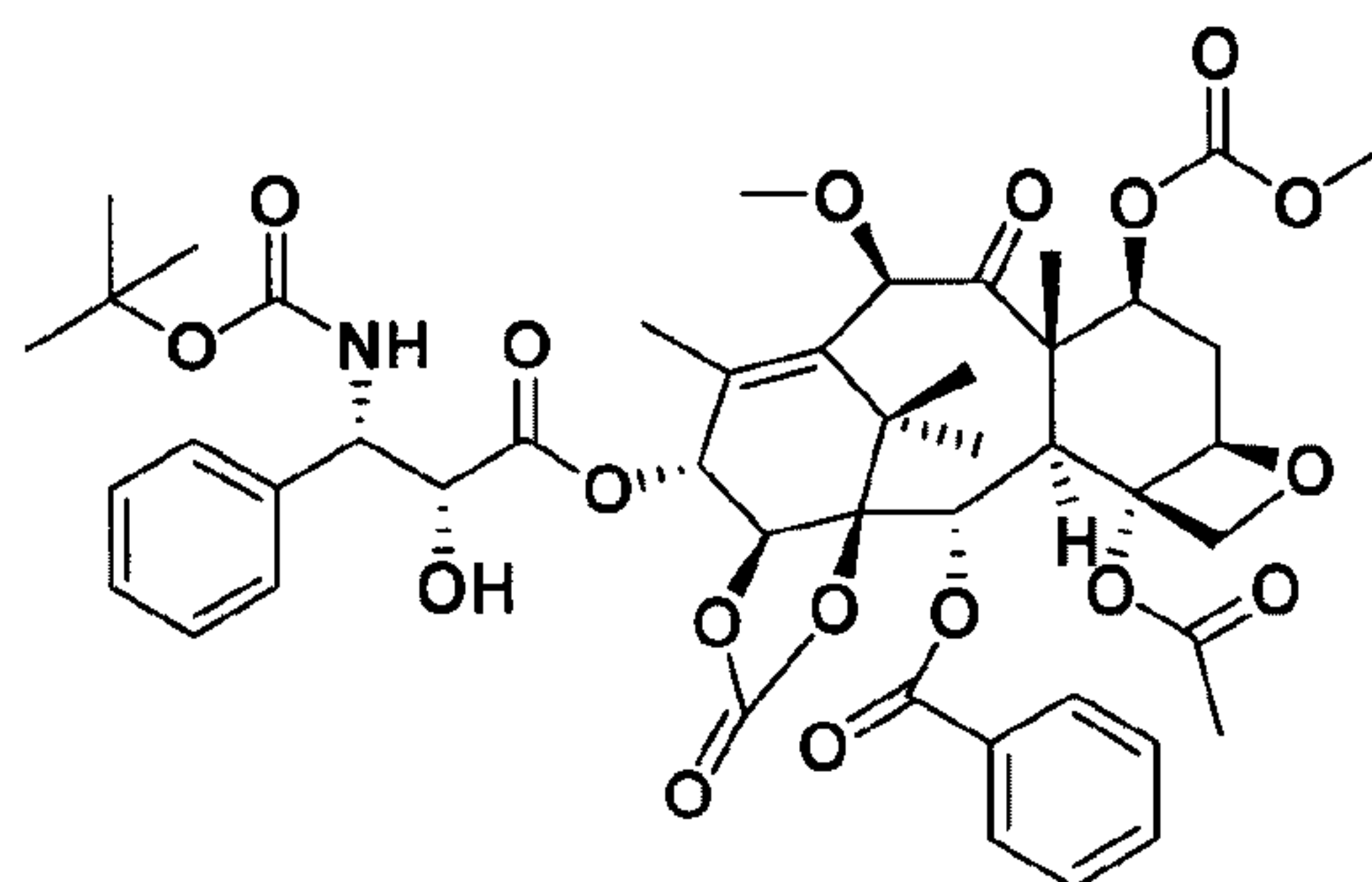
PCMI-15 935 $C_{47}H_{57}N_3O_{17}$



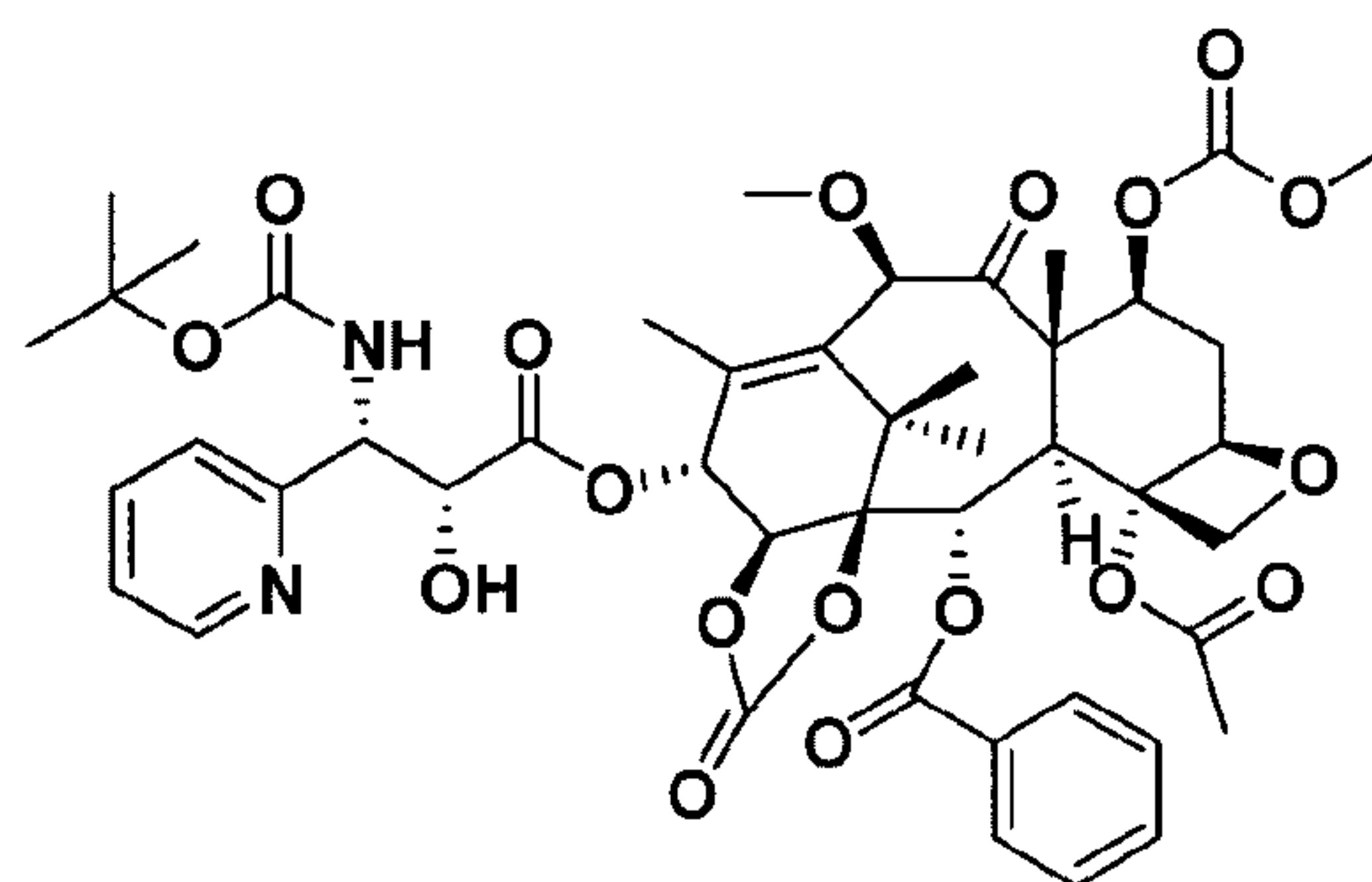
PCMI-16 914 $C_{46}H_{62}N_2O_{17}$



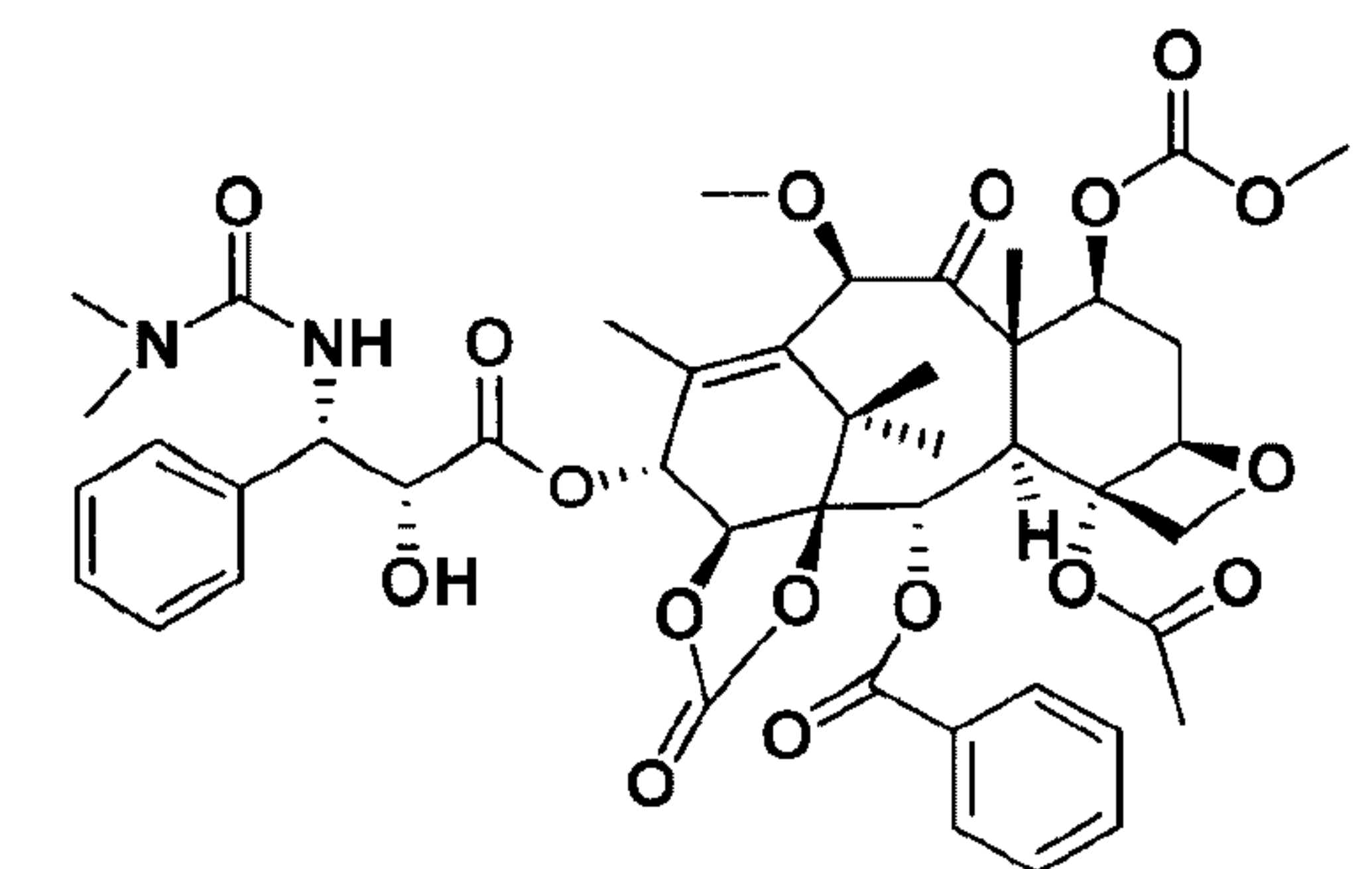
PCMI-17 921 $C_{47}H_{55}NO_{18}$



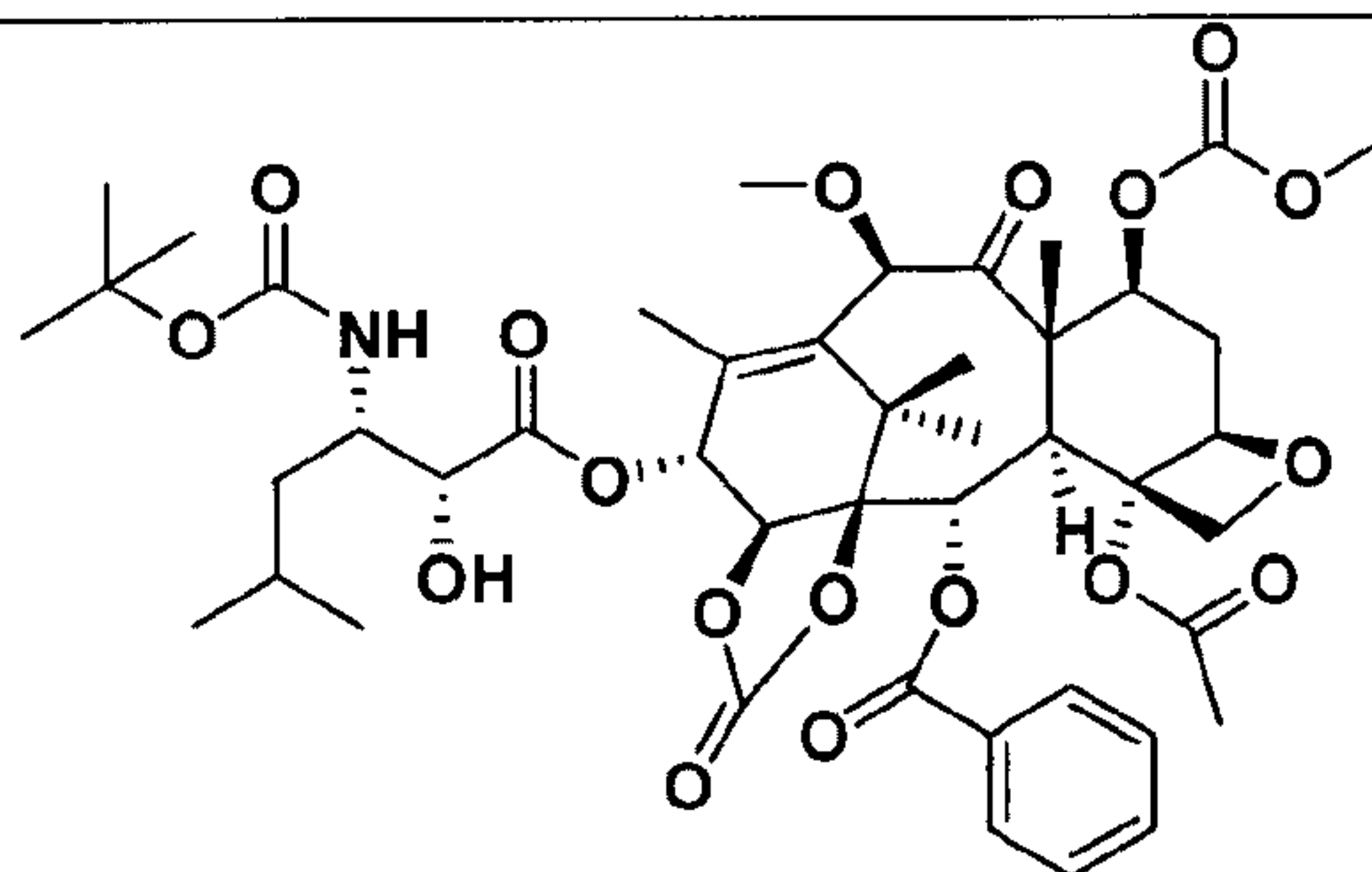
PCMI-18 922 $C_{46}H_{54}N_2O_{18}$



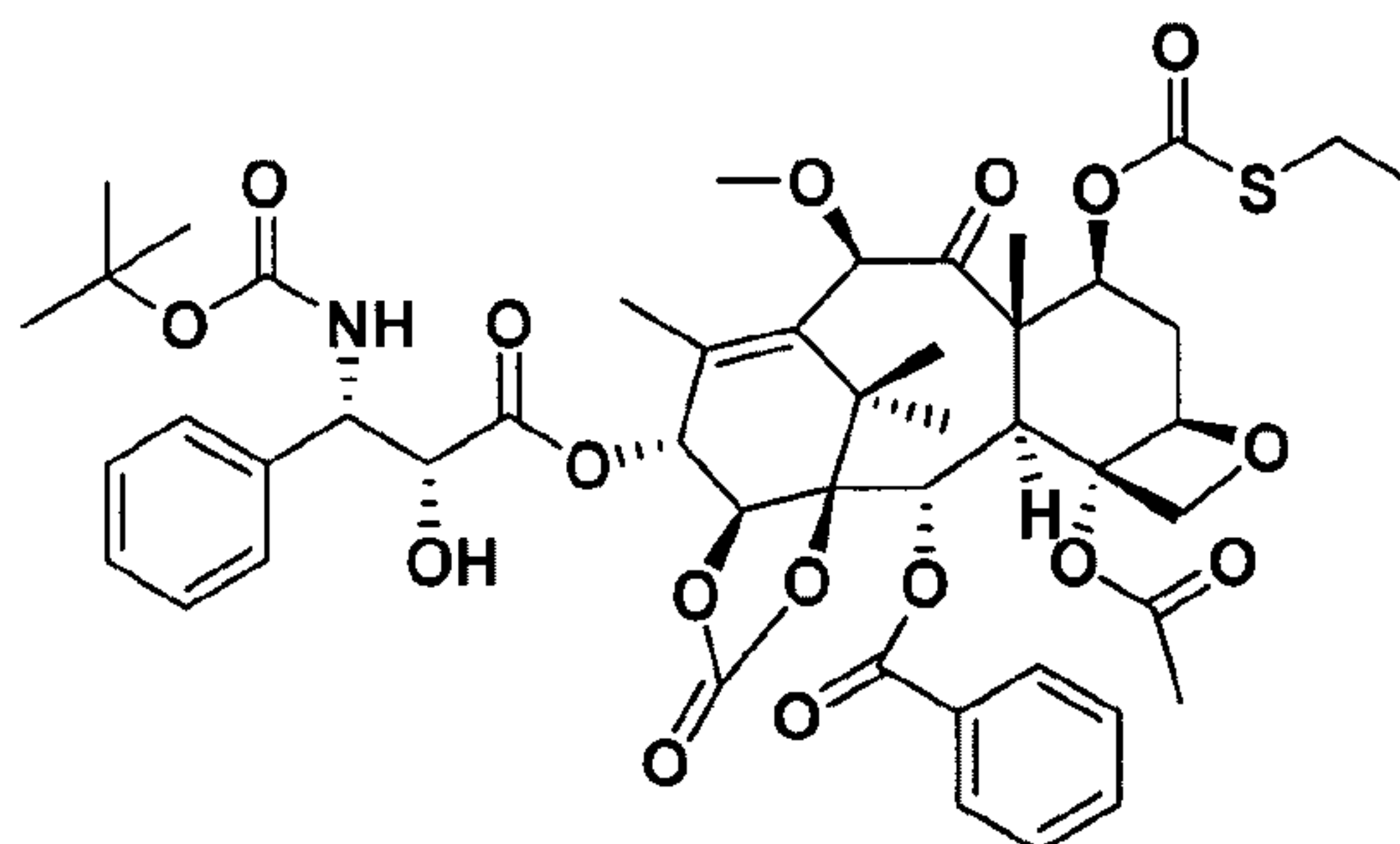
PCMI-19 892 $C_{45}H_{52}N_2O_{17}$



PCMI-20 901 $C_{45}H_{59}NO_{18}$



PCMI-21 951 $C_{48}H_{57}NO_{17}S$



According to the present invention, the compounds having the structures represented by the general formula (I) also include all isomers of these compounds and mixtures of the isomers.

If necessary, the compounds having the structures represented by the general formula (I) may be formed into a pharmaceutically acceptable non-toxic salts.

- 5 According to the present invention, the compounds having the structures represented by the general formula (I) may optionally exist in the form of solvates (such as hydrates). Therefore, these solvates (such as hydrates) are also included within the compounds of the present invention.

Furthermore, the present invention provides a pharmaceutical composition comprising the
 10 compounds having the structures represented by the above defined general formula (I), the pharmaceutically acceptable salts or solvates thereof as active ingredients, as well as and the use thereof in manufacturing oral antitumor medicaments.

In the pharmaceutical composition of the present invention, the weight ratio of the compounds of the present invention is 0.01%-99.99% with the balance of pharmaceutically
 15 acceptable carriers. The pharmaceutical composition is in the form of suitable preparations. The preparations include: tablets, capsules, granules, pills, powders, slurries, suspensions, injections, powder-injections, suppositories, creams, drops or patches. Wherein, the tablets

are sugar-coated tablets, film-coated tablets, enteric coated tablets or sustained release tablets; the capsules are hard capsules, soft capsules or sustained release capsules; the powder-injections are lyophilized powder-injections.

5 In the dosage form of the pharmaceutical composition of the present invention, each dosage form contains an effective amount of 0.1mg-1000mg of the compounds of the present invention. Wherein, each dosage form refers to each unit thereof, e.g. each tablet in tablets, each capsule in capsules. Alternatively, it can also refer to the dose administrated at each time (e.g. a dose of 100mg at each time).

10 The solid carriers may be used, when the pharmaceutical composition of the present invention is prepared into solid or semi-solid preparations such as powders, tablets, dispersible powders, capsules, cachets, suppositories and ointments. The usable solid carrier is preferably selected from one or more substances of diluents, flavors, solubilizers, lubricants, suspending agents, binders, bulking agents and the like, or may be encapsulating materials. In powder preparations, it contains 5-70wt% of the micronized active ingredient
15 in the carriers. Suitable solid carriers include magnesium carbonate, magnesium stearate, talc powder, sucrose, lactose, pectin, dextrin, starch, gelatin, methyl cellulose, sodium carboxymethyl cellulose, low boiling point wax, cocoa butter and the like. Since tablets, powders, cachets and capsules are easily to be administrated, they represent the most advantageous oral solid preparations.

20 The liquid preparations of the present invention include solutions, suspensions and emulsions. For example, the injection preparations for parenteral administration can be in the form of water solution or water-propylene glycol solution, which is used to adjust isotonicity, pH, etc., making it adapted to the physiological conditions of the living body. Alternatively, liquid preparations can be prepared in the form of polyethylene glycol or
25 water solution. The oral water solution can be prepared by dissolving the active ingredients in water and adding appropriate amounts of colorants, flavors, stabilizing agents and thickening agents therein. In addition, the oral water suspensions can be prepared by dispersing the micronized active ingredients into viscous materials, such as natural and synthetic gums, methylcellulose, sodium carboxymethyl cellulose and other known
30 suspending agents.

For convenience of administration and dose uniformity, it is particularly advantageous to prepare the aforementioned pharmaceutical preparations in the form of a preparation unit. The preparation unit refers to a physically separable unit containing a single dose. Each unit contains a well-calculated predetermined amount of active ingredients, which can
 5 produce desired therapeutic effects. This preparation unit may be in the packaged form, for example tablets, capsules, powders in small tubes or bottles, or ointments, gels or creams in tubes or bottles.

Although the amount of active ingredient in the preparation unit can be varied, it is generally in a range of 1mg-1000mg based on the efficacy of the selected active ingredient.

10 When the compounds of the present invention represented by the formula (I) are used as antitumor agents, their dose may be varied depending on the needs of patients, conditions of the disease, the selected compounds and the like.

According to the present invention, the taxanes compounds are prepared by a method comprising the following steps:

15 Step 1 synthesis of taxanes mother nucleus part: by using 10-deacetyl baccatin III (10-DAB) as raw material, firstly, the hydroxyl groups at C7 and C10 positions of the mother nucleus part are selectively protected with substitutents, then the C13 hydroxy group is oxidized into keto-carbonyl group, followed by highly stereoselectively introducing a hydroxyl group with β configuration at C14 by using N-(sulfonyl)oxaziridine, to form 1,14-carbonate
 20 structure under the action of CDI, and finally C13 keto-carbonyl group is highly stereoselectively reduced into hydroxyl group with α configuration by CBS reduction method to give the taxanes mother nucleus part;

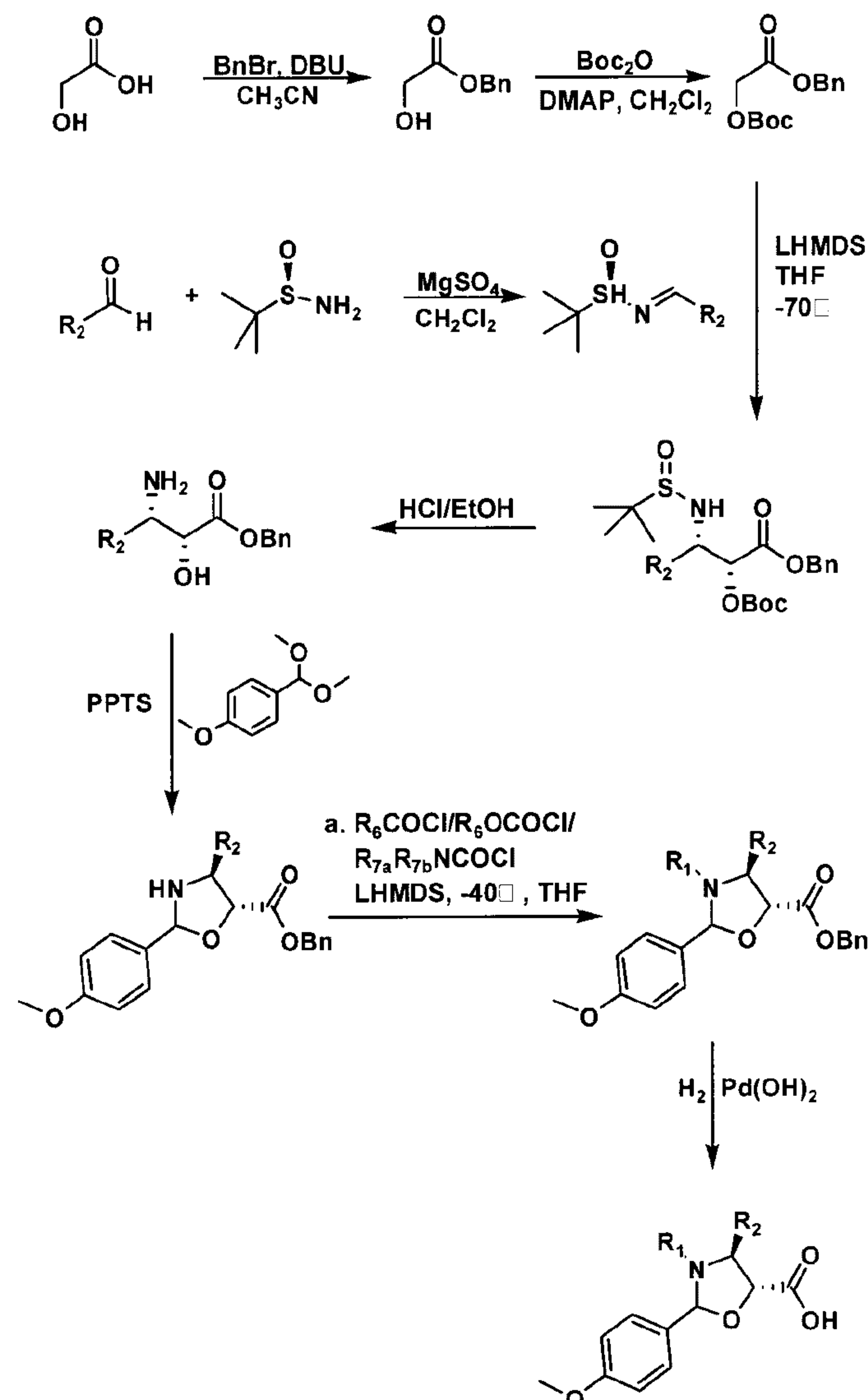
Step 2 synthesis of a precursor of five-member ring oxazolidine acid side chain: the precursor of five-member ring oxazolidine acid side chain is prepared by a series of
 25 reactions including introduction of protective groups, addition condensation, acid hydrolysis, aldol condensation, catalytic hydrogenation and the like;

Step 3 synthesis of taxanes derivatives: the precursor of five-member ring oxazolidine acid side chain is linked with the taxanes mother nucleus part by esterification, and a series of taxanes derivatives are generated after removal of the protective group by acid hydrolysis.

Preferably, the preparation method of the taxanes compounds of the present invention comprises the following steps:

Step 1 synthesis of taxanes mother nucleus part: by using 10-deacetyl baccatin III (10-DAB) as raw material, firstly, the hydroxyl groups at C7 and C10 positions of the mother nucleus
 5 part are selectively protected with substituents, then the C13 hydroxy group is oxidized into keto-carbonyl group, followed by highly stereoselectively introducing a hydroxyl group with β configuration at C14 by using N-(sulfonyl)oxaziridine, to form 1,14-carbonate structure under the action of CDI, and finally C13 keto-carbonyl group is highly
 10 stereoselectively reduced into hydroxyl group with α configuration by CBS reduction method to give the taxanes mother nucleus part.

Step 2 synthesis of a precursor of five-member ring oxazolidine acid side chain: glycolic acid, used as raw material, is protected successively by benzyl group and *t*-butyloxycarbonyl group (Boc group) to generate the Boc-protected benzyl glycolate; different substituted aldehydes are condensed with (S_R)-*t*-butyl sulfinamide to form the corresponding enamine compounds;
 15 the Boc-protected benzyl glycolate and the enamine compound are reacted via an addition reaction in the presence of lithium salt, and then a chiral intermediate is given after acid hydrolysis, and the obtained intermediate is reacted with 1,1'-(dimethoxymethyl) *p*-methoxybenzene via an aldol condensation reaction, catalyzed by pyridinium *p*-toluenesulfonate (PPTS) to obtain a condensation compound. The amino group of the
 20 condensation compound is substituted with different substituents, and the precursor of five-member ring oxazolidine acid side chain is finally given after catalytic hydrogenation. The reaction route is as follows:



Step 3 synthesis of taxanes derivatives: the precursor of five-member ring oxazolidine acid side chain is linked with the taxanes mother nucleus part by esterification, and a series of taxanes derivatives are generated after removal of the protective group by acid hydrolysis.

5 wherein, in Step 1, the hydroxyl groups at C7 and C10 positions are protected with substituents:

(1) When R_3 and R_4 are $-\text{OR}_6$, the reaction involved is: firstly, the hydroxyl group is reacted with *p*-toluenesulfonyl chloride (TsCl) at room temperature to 0°C in tetrahydrofuran or dichloromethane as the solvent and pyridine (Py) as the alkali to give *p*-toluenesulfonate,

10 which is further reacted with a Grignard reagent to give the corresponding ether $-\text{OR}_6$;

(2) When R_3 and R_4 are $-\text{OCOOR}_6$ or $-\text{CONR}_{7a}\text{R}_{7b}$, the reaction involved is: under alkaline conditions, the hydroxyl group is reacted with the corresponding acyl chloride in tetrahydrofuran as the solvent at room temperature to -70°C ;

(3) When R_3 and R_4 are $-\text{OCOSR}_6$, the reaction involved is: the hydroxyl group is reacted
 5 with N,N'-carbonyldiimidazole (CDI) in tetrahydrofuran as the solvent at room temperature, and the obtained product is further reacted with mercaptan via substitution reaction.

In Step 1, the stereoselective reduction on the C13 keto-carbonyl group by CBS reduction method includes the following specific steps: C13-oxo is stereoselectively reduced into C13- α -OH by using anhydrous tetrahydrofuran, dry dichloromethane or alcohols as the
 10 solvent, (R)-2-methyl oxazaborodine as the catalyst and boranes as the reducing agent at room temperature to -70°C .

In Step 2, said different substituted aldehydes include C1-C6 hydrocarbyl aldehydes, C1-C6 substituted hydrocarbyl aldehydes, aromatic aldehydes, substituted aromatic aldehydes and heteroaromatic aldehydes and the like; The reaction involved in the substitution of the
 15 amino group on the chiral intermediates is carried out by using tetrahydrofuran, dichloromethane or dioxane as the solvent, to react with the corresponding acyl chlorides under alkaline conditions at room temperature to -70°C ; In the catalytic hydrogenation reaction, palladium-charcoal or palladium hydroxide is used as the catalyst, hydrogen is introduced at normal pressure or pressurized conditions, and the reaction is preferably
 20 carried out in alcohols, tetrahydrofuran or dichloromethane and the like as the solvent.

Preferably,

In Step 1, the hydroxyl groups C7 and C10 positions are protected by substituents:

(1) When R_3 and R_4 are $-\text{OR}_6$, dichloromethane is preferably used as the solvent, the temperature is at 0°C and the Grignard reagent includes R_6MgBr ;

25 (2) When R_3 and R_4 are $-\text{OCOOR}_6$ or $-\text{CONR}_{7a}\text{R}_{7b}$, lithium hexamethyldisilazide is preferably used as the alkali and the temperature is preferably at -40°C ; the acyl chloride includes R_6OCOCl and $\text{R}_{7a}\text{R}_{7b}\text{NCOCl}$;

(3) When R_3 and R_4 are $-\text{OCOSR}_6$, the mercaptan includes R_6SH .

In Step 1, the stereoselective reduction on the C13 keto-carbonyl group by CBS reduction method is preferably carried out at room temperature by using anhydrous tetrahydrofuran as the solvent;

In Step 2, in the reaction involved in the substitution of the amino group on the intermediate, lithium hexamethyldisilazide (LHMDS) is preferably used as the alkali and tetrahydrofuran is used as the solvent; the temperature is preferably at -40°C, the acyl chloride includes $R_6\text{COCl}$, $R_6\text{OCOCl}$ and $R_{7a}R_{7b}\text{NCOCl}$; in the catalytic hydrogenation reaction, palladium hydroxide is preferably used as the catalyst, hydrogen is introduced at 20psi and the reaction is preferably carried out in an alcoholic solution.

The taxanes compounds of the present invention have oral antitumor activity and the beneficial effects of the present invention are illustrated below by experimental data.

1. cytotoxicity assay using human tumor cell lines

Paclitaxel was used as the positive drug. MTT assay was used to investigate the proliferation inhibition rate of taxanes derivatives containing 1,14-carbonate baccatin III of the present invention on 16 cancer cell lines (including MCF-7, MDA-MB-436 breast cancer cells; A549, NCI-H460 non-small cell lung cancer; A2780 ovarian cancer; A375, B16 melanoma; HCT 116, HT-29 colon cancer; Hela cervical cancer; HL-60, K562 leukemia; LNCaP, Du145 prostate cancer; LN-18, BGC-823 gastric cancer) at a concentration of 1μM and the experimental results are shown in Table 1.

20

Table 1 Proliferation inhibition rate of the taxanes compounds of the present invention on 16 cancer cell lines

Compounds	Proliferation inhibition rate at a concentration of 1μM							
	A2780	HeLa	MCF-7	NCI-H460	A375	HT29	HL60	DU145
	Ovarian cancer	Uterin cancer	Breast cancer	Non-small cell lung cancer	Melanoma	Colon cancer	Leukemia	Prostate cancer
Paclitaxel	96.68	101.04	94.20	87.48	96.22	88.36	96.80	90.62
PCMI-01	96.72	100.54	96.00	87.94	90.80	89.41	96.57	87.76
PCMI-02	94.69	98.20	93.54	82.25	89.84	88.98	95.90	84.71

PCMI-03	95.13	99.36	95.27	85.31	88.56	88.47	95.69	84.96
PCMI-04	94.65	98.28	100.73	81.84	82.17	88.28	95.81	83.87
PCMI-05	94.59	99.45	84.86	81.98	87.90	87.93	97.17	83.88
PCMI-06	96.00	99.89	86.26	84.68	94.40	87.33	97.66	89.14
PCMI-07	95.02	100.10	87.12	82.65	92.54	86.58	97.46	86.78
PCMI-08	92.50	97.27	81.28	85.19	92.85	81.67	96.85	86.73
PCMI-09	95.63	101.39	89.77	85.82	96.93	87.84	98.52	90.26
PCMI-10	94.98	99.86	85.90	81.01	94.18	86.21	97.49	87.98
PCMI-11	94.58	99.59	82.38	82.16	92.37	85.91	97.89	87.16
PCMI-12	94.33	100.43	81.75	82.32	91.97	85.44	97.19	86.65
PCMI-13	95.86	100.48	84.68	86.23	93.14	87.38	97.53	90.66
PCMI-14	94.23	99.88	88.45	86.94	95.31	87.26	97.45	89.78
PCMI-15	95.73	101.19	95.53	86.03	97.86	88.67	97.83	90.76
PCMI-16	96.12	101.60	97.22	87.23	96.29	89.19	97.81	91.41
PCMI-17	96.60	100.94	93.12	89.16	94.89	88.49	97.34	90.68
PCMI-18	95.69	98.75	96.23	88.59	95.06	85.23	97.85	89.68
PCMI-19	94.24	99.56	89.65	87.35	95.16	87.23	96.89	89.97
PCMI-20	95.51	100.57	85.40	86.79	93.38	87.25	96.92	88.62
PCMI-21	96.40	99.54	88.69	85.51	96.65	87.65	96.52	90.58

Compound	Proliferation inhibition rate at a concentration of 1μM							
	MDA-	LN-18	BGC-823	A549	B16	HCT 116	K562	LNCaP
	MB-436 Breast cancer	Gastric cancer	Gastric cancer	Non-small cell lung cancer	Melanoma	Colon cancer	Leukemia	Prostate cancer
Paclitaxel	83.09	94.49	92.52	81.59	84.05	70.36	96.62	87.10
PCMI-01	81.46	92.82	93.10	66.90	78.06	59.69	92.85	80.67
PCMI-02	82.62	96.58	94.22	79.59	84.07	66.36	94.67	83.65
PCMI-03	80.12	95.35	92.32	68.57	78.23	58.31	93.56	82.64
PCMI-04	79.43	91.80	89.83	66.26	73.24	55.04	91.52	79.19
PCMI-05	74.46	93.26	90.89	67.81	71.49	58.72	91.36	81.59
PCMI-06	77.82	94.58	93.63	75.52	80.65	67.08	93.35	83.63
PCMI-07	80.47	96.12	94.14	74.89	78.60	68.85	94.01	84.87
PCMI-08	65.68	87.69	80.81	68.13	70.64	58.70	90.79	84.32
PCMI-09	81.34	94.98	94.88	75.80	81.71	65.46	92.60	86.16
PCMI-10	77.27	93.66	91.21	70.51	71.43	65.57	90.63	85.87
PCMI-11	78.96	92.88	90.64	72.34	72.56	64.32	92.13	86.45
PCMI-12	81.41	93.44	93.01	73.59	75.91	66.56	91.22	86.32
PCMI-13	81.03	93.83	94.04	77.11	81.23	68.45	94.25	86.33
PCMI-14	80.24	93.45	95.78	76.18	80.33	65.45	92.69	85.32
PCMI-15	81.99	95.71	94.98	74.60	80.75	68.33	93.24	86.66

PCMI-16	81.23	95.24	95.28	74.65	83.06	67.09	94.95	86.77
PCMI-17	85.08	95.94	95.12	80.34	82.31	69.56	96.53	86.69
PCMI-18	82.34	94.65	94.32	78.68	81.25	68.32	94.52	84.56
PCMI-19	83.58	93.87	93.27	80.24	83.65	67.28	92.68	87.25
PCMI-20	81.08	94.30	94.95	80.39	81.60	68.59	93.78	85.96
PCMI-21	83.09	94.74	93.26	74.88	75.81	70.09	94.95	87.38

Preliminary activity evaluation indicates that such taxanes derivatives show similar or stronger cytotoxicity on most cancer cell lines than that of the positive control drug. Only in both cancer cell lines of A549 and B16, the cytotoxicity of the taxanes derivatives is slightly lower than that of the positive control drug. Experimental results show that such taxanes derivatives of the present invention have excellent tumor inhibiting activity.

From the activity evaluation data of the above-mentioned preliminary screen, it can be seen that the series of taxanes derivatives synthesized in the present invention have activity. Afterward, the compounds are investigated to examine their IC₅₀ values on breast cancer cell line MCF-7. Paclitaxel was used as the positive control drug. Experiments for each compound were independently repeated for three times and multiple holes were used in each experiment. The exposure time of drugs was 72 hours. The median lethal dose (IC₅₀) is expressed as mean $\pm$ SD and the experimental data are shown in Table 2.

Table 2 IC₅₀ values of the taxanes compounds of the present invention on breast cancer cell line MCF-7

Compounds	MCF-7 (IC ₅₀ , nM)	Compounds	MCF-7 (IC ₅₀ , nM)
Paclitaxel	7.05 $\pm$ 0.12	PCMI-11	4.25 $\pm$ 0.06
PCMI-01	2.10 $\pm$ 0.08	PCMI-12	3.24 $\pm$ 0.04
PCMI-02	6.93 $\pm$ 0.12	PCMI-13	3.89 $\pm$ 0.12
PCMI-03	2.89 $\pm$ 0.10	PCMI-14	15.40 $\pm$ 0.16
PCMI-04	3.40 $\pm$ 0.14	PCMI-15	18.21 $\pm$ 0.24
PCMI-05	4.04 $\pm$ 0.18	PCMI-16	21.17 $\pm$ 0.21
PCMI-06	16.24 $\pm$ 0.08	PCMI-17	3.84 $\pm$ 0.08
PCMI-07	4.49 $\pm$ 0.02	PCMI-18	4.12 $\pm$ 0.16
PCMI-08	7.93 $\pm$ 0.14	PCMI-19	6.58 $\pm$ 0.02
PCMI-09	14.31 $\pm$ 0.12	PCMI-20	2.94 $\pm$ 0.04
PCMI-10	6.44 $\pm$ 0.18	PCMI-21	3.46 $\pm$ 0.16

As shown from the data of Table 2, the IC₅₀ value of the positive control drug paclitaxel is 7.05nM. The IC₅₀ values of taxanes derivatives containing the structure of 1,14-carbonate baccatin III of the present invention thereof are quite equal to that of paclitaxel, maintaining at the same order of magnitude. While IC₅₀ values of some derivatives are better than that of paclitaxel. Thus, it can be seen that *in vitro* activity of the derivatives of the present invention remain unchanged or even be improved as compared with paclitaxel.

2. Caco-2 cell monolayer membrane transport assay

Human-derived colorectal adenocarcinoma cell line Caco-2 cell monolayer model was used to study the bidirectional transport of the target compounds from the apical (AP) side to the basolateral (BL) side and from BL side to AP side. HPLC was used for quantitative analysis to calculate transport parameters, apparent permeability coefficient (Papp) and the efflux ratio. Paclitaxel was used as the positive control drug and the P-gp substrates erythromycin was used as a reference to predict the oral bioavailability *in vivo* of these taxanes derivatives and affinity thereof with P-gp.

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Table 3 A-to-B Papp of the taxanes derivatives of the present invention in Caco-2 cell model

Compounds [Ⓢ]		Papp×10 ⁻⁶ cm/sec [Ⓢ]			
		Sample-01 [Ⓢ]	Sample-02 [Ⓢ]	Mean [Ⓢ]	SD [Ⓢ]
Erythromycin [Ⓢ]	A-B [Ⓢ]	0.80 [Ⓢ]	0.63 [Ⓢ]	0.71 [Ⓢ]	0.16 [Ⓢ]
	B-A [Ⓢ]	7.15 [Ⓢ]	7.04 [Ⓢ]	7.09 [Ⓢ]	0.01 [Ⓢ]
<u>Metoprolol</u> [Ⓢ]	A-B [Ⓢ]	28.09 [Ⓢ]	26.25 [Ⓢ]	27.17 [Ⓢ]	0.05 [Ⓢ]
	B-A [Ⓢ]	22.44 [Ⓢ]	22.96 [Ⓢ]	22.70 [Ⓢ]	0.02 [Ⓢ]
<u>Atenolol</u> [Ⓢ]	A-B [Ⓢ]	1.07 [Ⓢ]	0.67 [Ⓢ]	0.87 [Ⓢ]	0.32 [Ⓢ]
	B-A [Ⓢ]	0.50 [Ⓢ]	0.55 [Ⓢ]	0.53 [Ⓢ]	0.06 [Ⓢ]
<u>Paclitaxel</u> [Ⓢ]	A-B [Ⓢ]	1.02 [Ⓢ]	0.93 [Ⓢ]	0.97 [Ⓢ]	0.07 [Ⓢ]
PCMI-01 [Ⓢ]	A-B [Ⓢ]	4.47 [Ⓢ]	3.87 [Ⓢ]	4.17 [Ⓢ]	0.10 [Ⓢ]
PCMI-02 [Ⓢ]	A-B [Ⓢ]	1.50 [Ⓢ]	1.47 [Ⓢ]	1.48 [Ⓢ]	0.02 [Ⓢ]
PCMI-03 [Ⓢ]	A-B [Ⓢ]	3.45 [Ⓢ]	3.89 [Ⓢ]	3.67 [Ⓢ]	0.31 [Ⓢ]
PCMI-04 [Ⓢ]	A-B [Ⓢ]	4.46 [Ⓢ]	2.86 [Ⓢ]	3.66 [Ⓢ]	0.31 [Ⓢ]
PCMI-05 [Ⓢ]	A-B [Ⓢ]	2.59 [Ⓢ]	2.56 [Ⓢ]	2.57 [Ⓢ]	0.01 [Ⓢ]
PCMI-06 [Ⓢ]	A-B [Ⓢ]	1.31 [Ⓢ]	1.13 [Ⓢ]	1.22 [Ⓢ]	0.11 [Ⓢ]
PCMI-07 [Ⓢ]	A-B [Ⓢ]	3.24 [Ⓢ]	2.05 [Ⓢ]	2.64 [Ⓢ]	0.32 [Ⓢ]
PCMI-08 [Ⓢ]	A-B [Ⓢ]	19.53 [Ⓢ]	17.33 [Ⓢ]	18.43 [Ⓢ]	0.08 [Ⓢ]
PCMI-09 [Ⓢ]	A-B [Ⓢ]	5.78 [Ⓢ]	3.59 [Ⓢ]	4.68 [Ⓢ]	0.33 [Ⓢ]
PCMI-10 [Ⓢ]	A-B [Ⓢ]	1.25 [Ⓢ]	0.89 [Ⓢ]	1.07 [Ⓢ]	0.24 [Ⓢ]
PCMI-11 [Ⓢ]	A-B [Ⓢ]	1.24 [Ⓢ]	1.02 [Ⓢ]	1.13 [Ⓢ]	0.16 [Ⓢ]
PCMI-12 [Ⓢ]	A-B [Ⓢ]	<1.36* [Ⓢ]	<1.43* [Ⓢ]	<1.43 [Ⓢ]	N/A [Ⓢ]
PCMI-13 [Ⓢ]	A-B [Ⓢ]	<1.30* [Ⓢ]	<1.67* [Ⓢ]	<1.67 [Ⓢ]	N/A [Ⓢ]
PCMI-14 [Ⓢ]	A-B [Ⓢ]	3.21 [Ⓢ]	2.87 [Ⓢ]	3.04 [Ⓢ]	0.24 [Ⓢ]
PCMI-15 [Ⓢ]	A-B [Ⓢ]	2.14 [Ⓢ]	2.78 [Ⓢ]	2.46 [Ⓢ]	0.18 [Ⓢ]
PCMI-16 [Ⓢ]	A-B [Ⓢ]	1.41 [Ⓢ]	1.87 [Ⓢ]	1.64 [Ⓢ]	0.20 [Ⓢ]
PCMI-17 [Ⓢ]	A-B [Ⓢ]	4.70 [Ⓢ]	3.16 [Ⓢ]	3.93 [Ⓢ]	0.28 [Ⓢ]
PCMI-18 [Ⓢ]	A-B [Ⓢ]	2.65 [Ⓢ]	2.33 [Ⓢ]	2.49 [Ⓢ]	0.23 [Ⓢ]
PCMI-19 [Ⓢ]	A-B [Ⓢ]	3.78 [Ⓢ]	4.05 [Ⓢ]	3.92 [Ⓢ]	0.19 [Ⓢ]
PCMI-20 [Ⓢ]	A-B [Ⓢ]	1.08 [Ⓢ]	0.75 [Ⓢ]	0.92 [Ⓢ]	0.25 [Ⓢ]
PCMI-21 [Ⓢ]	A-B [Ⓢ]	2.32 [Ⓢ]	2.58 [Ⓢ]	2.45 [Ⓢ]	0.08 [Ⓢ]

*: The measured value was lower than the minimum limit; N/A: Undetectable by known methods

Table 4 Trans-membrane recovery rate in mass of the taxanes derivatives of the present invention in Caco-2 cell model

Compounds		Recovery rate in mass (%)			
		Sample-01	Sample-02	Mean	SD
Erythromycin	A-B	99.58	98.51	99.04	0.01
Metoprolol	A-B	102.51	95.49	99.00	0.05
Atenolol	A-B	93.89	96.29	95.09	0.02
Paclitaxel	A-B	94.61	107.07	100.84	0.09
PCMI-01	A-B	48.17	61.18	54.67	0.17
PCMI-02	A-B	44.14	57.37	50.75	0.18
PCMI-03	A-B	65.12	58.23	61.68	0.08
PCMI-04	A-B	85.19	66.54	75.87	0.17
PCMI-05	A-B	58.11	51.29	54.70	0.09
PCMI-06	A-B	128.21	96.59	112.40	0.20
PCMI-07	A-B	54.25	46.29	50.27	0.11
PCMI-08	A-B	101.83	97.05	99.44	0.03
PCMI-09	A-B	70.43	82.62	76.53	0.11
PCMI-10	A-B	33.99	40.55	37.27	0.12
PCMI-11	A-B	79.65	80.23	79.94	0.01
PCMI-12	A-B	27.8-29.1*	38.2-39.5*	27.8-39.5	N/A
PCMI-13	A-B	40.8-42.0*	41.5-43.1*	40.8-43.1	N/A
PCMI-14	A-B	95.04	87.58	91.31	0.06
PCMI-15	A-B	83.68	74.85	79.27	0.08
PCMI-16	A-B	32.69	33.52	33.10	0.02
PCMI-17	A-B	103.50	73.90	88.70	0.24
PCMI-18	A-B	85.64	90.87	88.26	0.04
PCMI-19	A-B	78.23	70.69	74.46	0.07
PCMI-20	A-B	89.75	83.30	86.52	0.05
PCMI-21	A-B	76.56	67.49	72.03	0.09

*: The measured value was lower than the minimum limit; N/A: Undetectable by known methods

- 5 Table 5 Efflux ratio of the representative taxanes derivatives of the present invention in Caco-2 cell model

Compounds	Caco-2 cell line (21 days)				Efflux ratio ^a
	Papp (10 ⁻⁶ cm/s)				
	A-B	SD	B-A	SD	
Erythromycin	0.58	0.08	9.89	0.04	16.92
Paclitaxel	0.97	0.07	33.39	0.01	34.38
PCMI-08	16.40	0.04	33.48	0.07	2.04
PCMI-09	3.56	0.05	28.97	0.08	8.14
PCMI-01	2.83	0.19	18.20	0.18	6.42
PCMI-17	2.40	0.21	5.74	0.24	2.39
PCMI-19	2.79	0.12	21.34	0.08	7.65
PCMI-03	2.97	0.07	28.56	0.04	9.62
PCMI-04	3.21	0.14	26.45	0.07	8.24
PCMI-14	1.98	0.06	18.96	0.15	9.58
PCMI-07	2.64	0.32	25.26	0.20	9.56
PCMI-20	0.92	0.25	7.16	0.10	7.81

a. efflux ratio = Papp B-A/Papp A-B

The experimental results are shown in Table 3. It can be seen that the A-to-B Papp values of the most of taxanes derivatives of the present invention are higher than that of paclitaxel (Papp A-to-B=0.97), particularly for PCMI-08, the Papp A-to-B value thereof > 10×10⁻⁶ cm/s, which belongs to highly permeable substrate. These data indicate that these taxanes derivatives containing the structure of 1,14-carbonate baccatin III have good trans-membrane capacity, thus they are predicted to be better absorbed *in vivo* than paclitaxel.

The trans-membrane recovery rates of these taxanes derivatives are shown in Table 4. Bidirectional transports of 10 compounds selected from the 21 taxanes derivatives are evaluated and the results are shown in Table 5. It can be seen from the efflux ratios that, as compared with paclitaxel, efflux ratios of these derivatives of the present invention are reduced at different levels. Accordingly, the oral absorption *in vivo* is predicted to be improved.

3. *In vivo* oral bioavailability assay

Materials

The compound PCMI-08 was synthesized and detected according to the methods provided

in the present invention. The internal standard, paclitaxel, was purchased from China's National Institute for the Control of Pharmaceutical and Biological Products (NICPBP). Chromatography-grade acetonitrile was purchased from Sigma-Aldrich Inc. Tween™ 80 and ethyl acetate were purchased from Aladdin reagent Inc. Male S.D. rats were purchased
5 from Beijing Weitonglihua Inc. and raised in animal house for two weeks.

Apparatus

Agilent™ 1100 series HPLC, Agilent G1313A Autosampler, Thermo Finnigan™ TSQ quadrupole mass spectrometer (San Jose, CA, USA), Xcalibur® (version 1.3) software (Thermo Finnigan) data analysis software.

10 Experimental procedure:

200mg of PCMI-08 was dissolved in 4ml of a mixed solution of Tween 80 and anhydrous ethanol (1:1) to prepare a stock solution at 50mg/ml and normal saline was added to adjust to a suitable concentration. 12 male S.D. rats (300g of body weight) were taken and divided into two groups after overnight fasting. One group was treated with intravenous
15 injection (5mg/kg) and the other group was treated orally (60mg/kg). Blood was sampled in the intravenous group at 0th min, 5th min, 10th min, 20th min, 40th min, 1st h, 2nd h, 4th h, 6th h, 8th h, 12th h, 24th h, while the oral group at 5th min, 15th min, 30th min, 45th min, 1st h, 2nd h, 4th h, 6th h, 8th h, 12th h, 24th h. After 10min centrifugation of plasma at 4500rpm, the upper serum was taken and transferred to the corresponding EP tube, placed in a -40℃
20 freezer for assay.

Construction of standard curve of PCMI-08

Agilent 1100 series configuration: Agilent G1313A HPLC autosampler device, 150mm × 2.1mm C18 Thermo column (particle size 3μm) reversed-phase column, detection wavelength at 230nm, column temperature at 30℃, mobile phase of acetonitrile / water
25 (7:3), a flow rate at 0.2ml/min, injection volume of 20μl. The mass spectrometry (MS) combined was Thermo Finnigan TSQ Quantum triple quadrupole configured with electrospray ionization (ESI) in the positive ion mode. The parameters of MS analysis were as follows: spray chamber voltage, 4.0kv; heated capillary temperature, 350℃; protective gas (nitrogen); 20psi; auxiliary gas (nitrogen): 5psi; collision gas (argon); pressure:

1.5mmTorr.; Collision energy: CA 17eV; FA and IFA were 19eV; IS was 15eV.

Paclitaxel was selected as an internal standard with a retention time of 3.07min. Retention time of PCMI-08 was 5.13min. MS detection condition to PCMI-08 was set as follows: 957→901m/z; paclitaxel as an internal standard. Detection conditions: 876→308m/z. The
5 concentration range of the standard curve of PCMI-08 was 5-10,000ng/ml ($\gamma^2>0.99$) and the minimum detection limit was 5ng/ml.

Extraction and analysis of plasma samples

100μL of plasma samples were taken, into which 100μL of the internal standard (paclitaxel, 500ng/ml acetonitrile solution) was added, followed by addition of 3ml of ethyl acetate
10 after well homogenized via vortex, after 5min shaking, centrifuging for 8min at a rotating speed of 4500rpm. The supernatant was transferred to a clean EP tube with nitrogen to blow to dry under heating condition. After reconstitution with 120μl mobile phase (CH₃CN / H₂O=7:3), the solution was centrifuged at 12,000rpm for 3min, 100μl of supernatant was taken and transferred to an autosampler vial. After LC-MS/MS detection, statistical data
15 and pharmacokinetic parameters were processed by Xcalibur® (version 1.3) software (Thermo Finnigan).

Results

Drug concentration-time curve of the compound PCMI-08 by oral or intravenous administration is shown in Fig. 1. Related pharmacokinetic parameters of PCMI-08 are
20 shown in the following Table. The half-life of PCMI-08 is relatively long, generally 10h, and the mean retention time thereof is also extended relatively up to 10h or longer. The absolute oral bioavailability (F%) is up to 65.8%. As compared with the reported absolute oral bioavailability of paclitaxel of less than 6%, the oral bioavailability of PCMI-08 in animals has been improved to a significant extent.

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Table 6 Relevant pharmacokinetic parameters of PCMI-08 by intravenous and oral administration

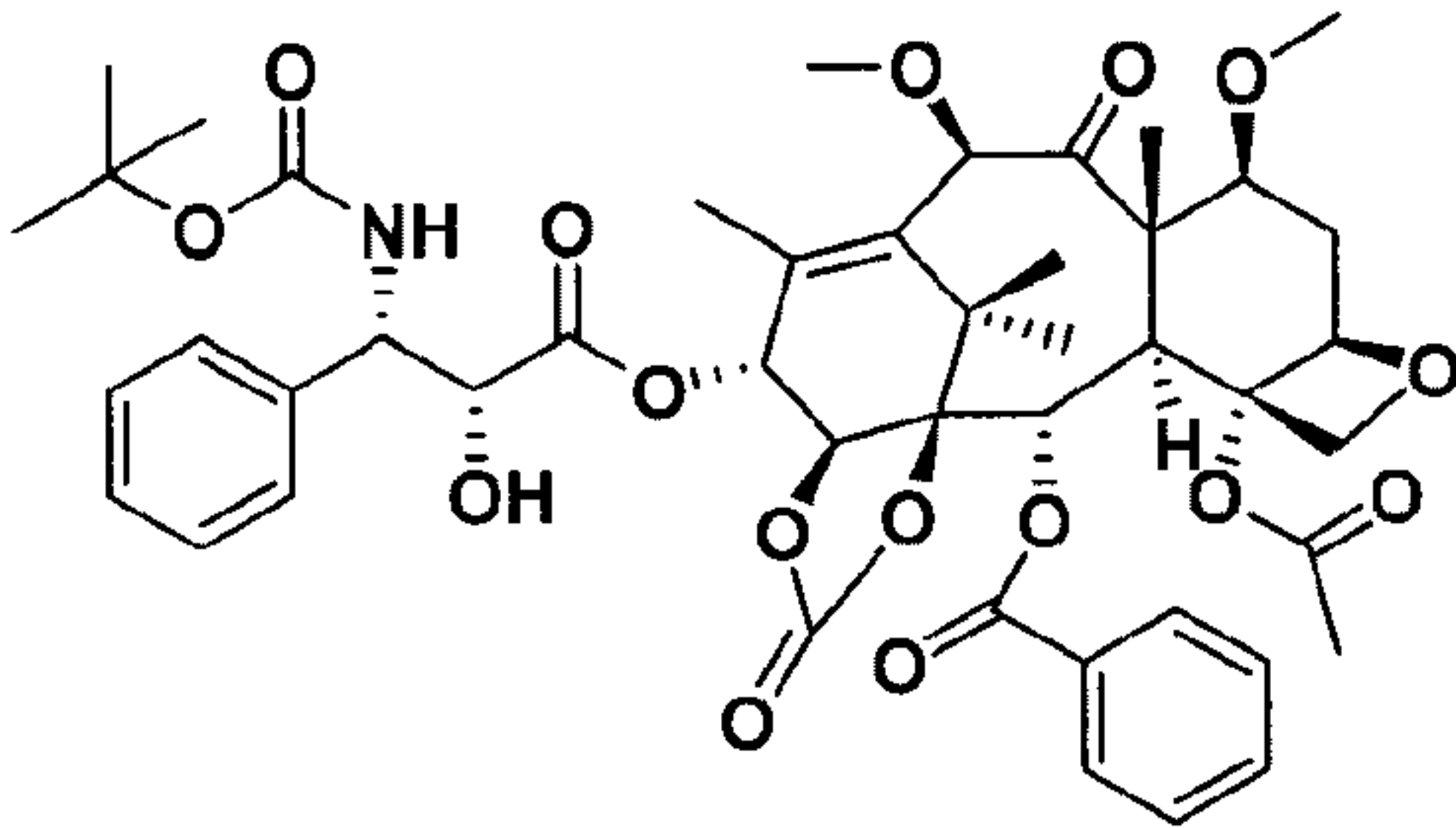
Parameters	Unit	PCMI-08	
		Intravenous administration	Oral administration
		(5 mg/kg)	(60 mg/kg)
t _{1/2}	h	10.21±1.72	10.44±1.14
C _{max}	ng/ml	11017.79±2679.59	2121.12±454.09
t _{max}	h	0	3.0±1.1
AUC _{0-t}	ng·h/ml	3439.76±1479.88	25306.31±6148.79
AUC _{0-∞}	ng·h/ml	4054.33±1860.39	32010.17±8537.60
MRT _{0-∞}	h	10.08±2.60	15.19±1.71
F	(%)	65.79	

AUC_{0-t}: 0-24 hours area under the curve; AUC_{0-∞}: area under the curve; C_{max}: peak concentration; t_{max}: peak time; MRT: mean residence time; t_{1/2}: half-life time; F: Absolute oral bioavailability, F = 5 (AUC_{p.o}×dose_{i.v})/(AUC_{i.v}×dose_{p.o})×100%

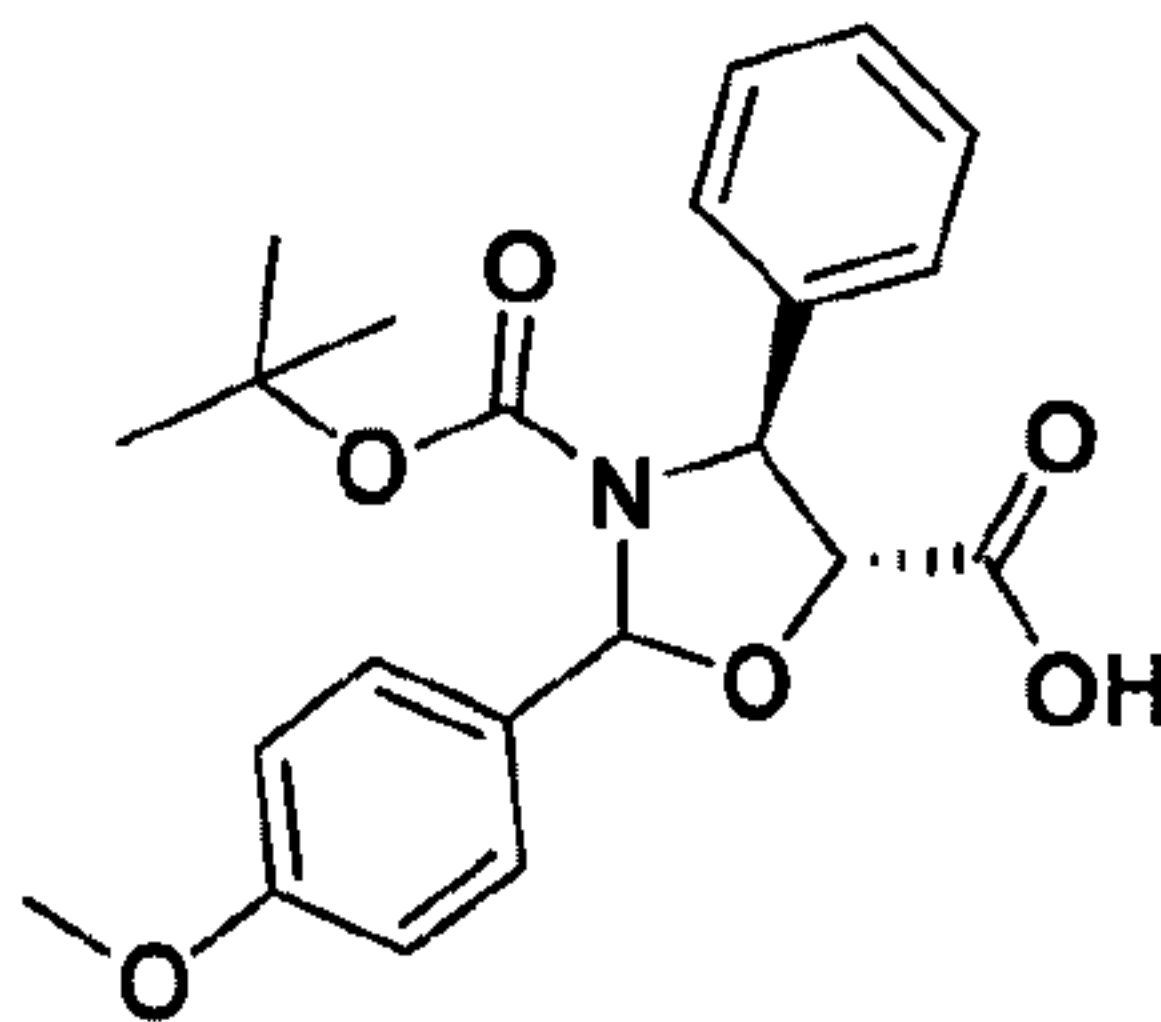
EXAMPLES

The following examples are provided to further illustrate the present invention and not intended to limit the present invention in any way.

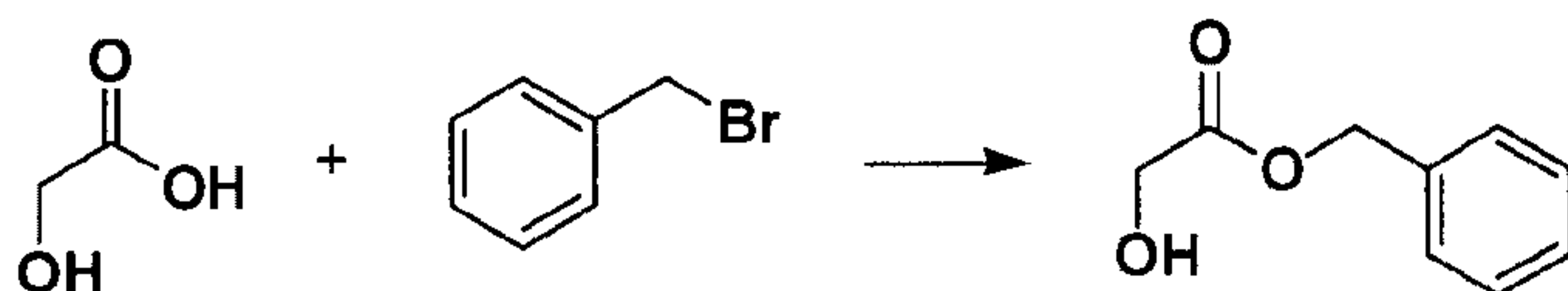
10 Example 1 Preparation of PCMI-01



1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

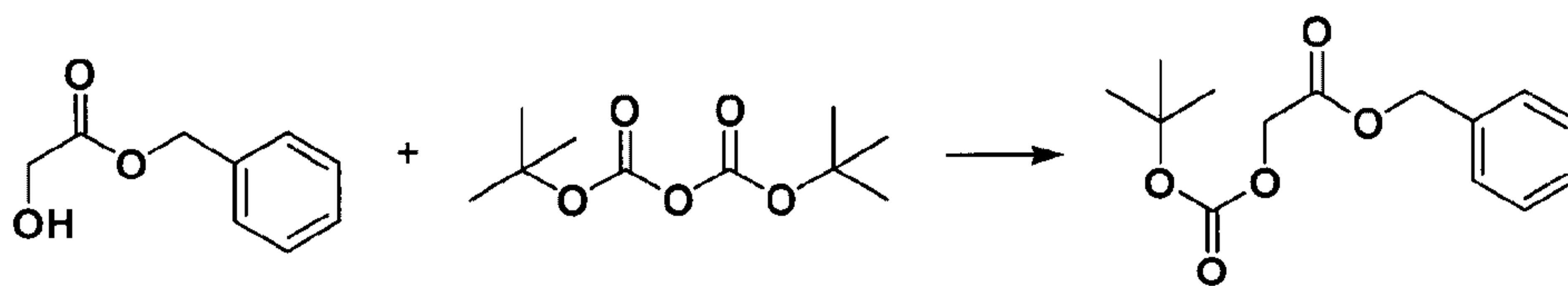


a. Preparation of benzyl glycolate

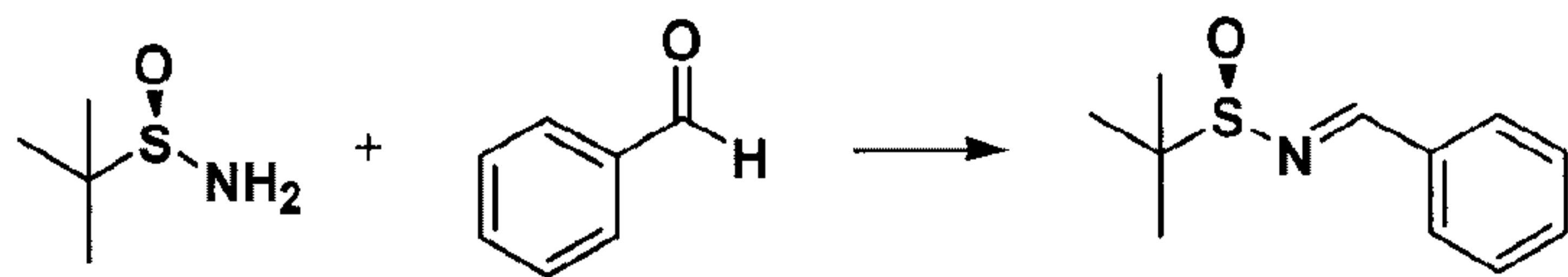


Glycolic acid (7.60g, 0.10mol) was dissolved in 10ml of acetonitrile, into which benzyl
 5 bromide (13.60g, 0.08mol) was added and uniformly stirred. DBU (12.16g, 0.08mol) was
 slowly added dropwise into the reaction liquid at 0°C. After that, the reaction liquid was
 stirred overnight at room temperature. The reaction liquid was poured into ice water,
 extracted with ethyl acetate, the combined resultant organic phase was washed with 1M
 hydrochloric acid solution and saturated salt water successively, dried with anhydrous
 10 sodium sulfate and concentrated by rotary evaporation to give the compound as a yellow oil
 (12.50g, 94%).

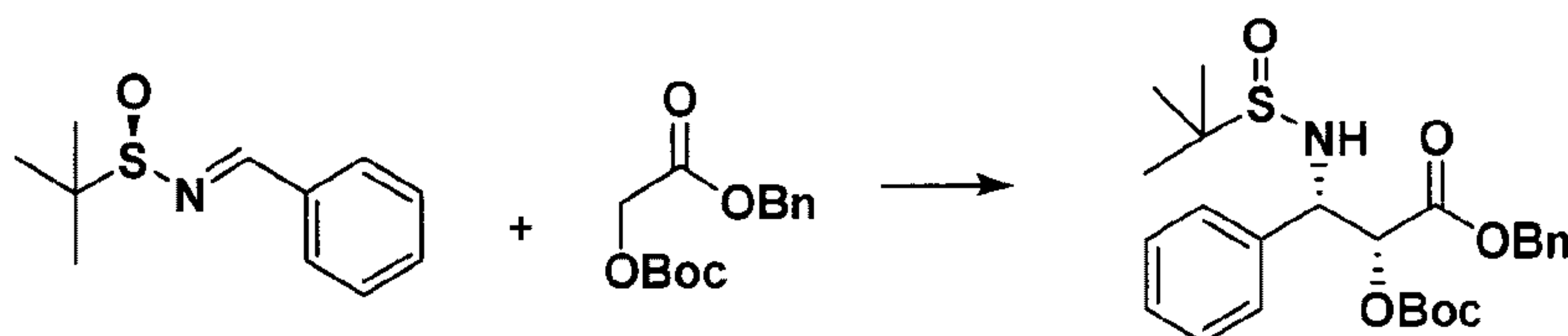
b. Preparation of Boc-protected benzyl glycolate



Benzyl glycolate (30g, 0.25mol) and Boc anhydride (39.1g, 0.19mol) were dissolved in
 15 30ml of dichloromethane. 5ml of DMAP (4.62g, 0.038 mol) in dichloromethane solution
 was added dropwise into the resultant reaction liquid at 80°C. After that, the reaction liquid
 was reacted at 15°C for 0.5h. After completion of the reaction, the reaction liquid was
 poured into ice water, extracted with ethyl acetate, the combined resultant organic phase
 was washed with water and saturated salt water successively. The organic phase was
 20 concentrated and recrystallized with petroleum ether/ethyl acetate in a ratio of 10: 1 to give
 a white solid (32.5g, 66%).

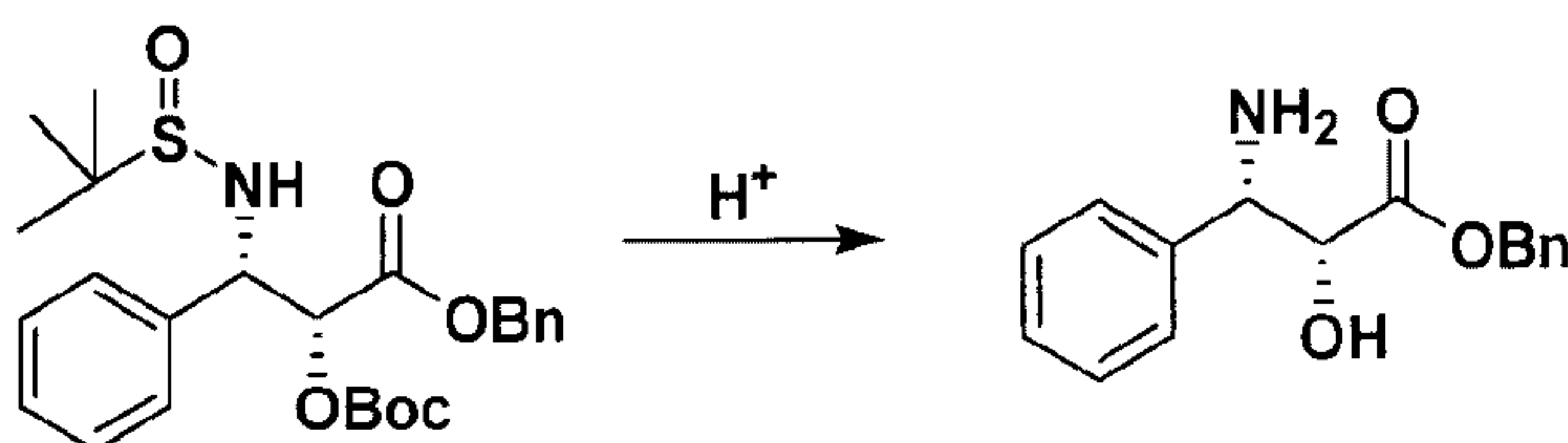
c. Preparation of N-*t*-butyl sulfinyl benzylenamine

(S_R)-*t*-butyl sulfonamide (5.22g, 0.043mol) and benzaldehyde (5.51g, 0.052mol) were dissolved in 20ml of dichloromethane and the solution was added with magnesium sulfate (25.90g, 0.22mol) and PPTS (0.54g, 2.20mmol). The reaction liquid was stirred at room temperature for 24h, filtered and the obtained filter cake was rinsed with dichloromethane for 3 times (20ml×3) to give the crude product after concentration. The crude product was purified by column chromatography (petroleum ether/ethyl acetate=15:1) to give a colorless oil (7.71g, 85.8%).

10 d. Preparation of benzyl 2R-*t*-butyloxycarbonyl-3S-*t*-butyl sulfinamide-phenyl propionate

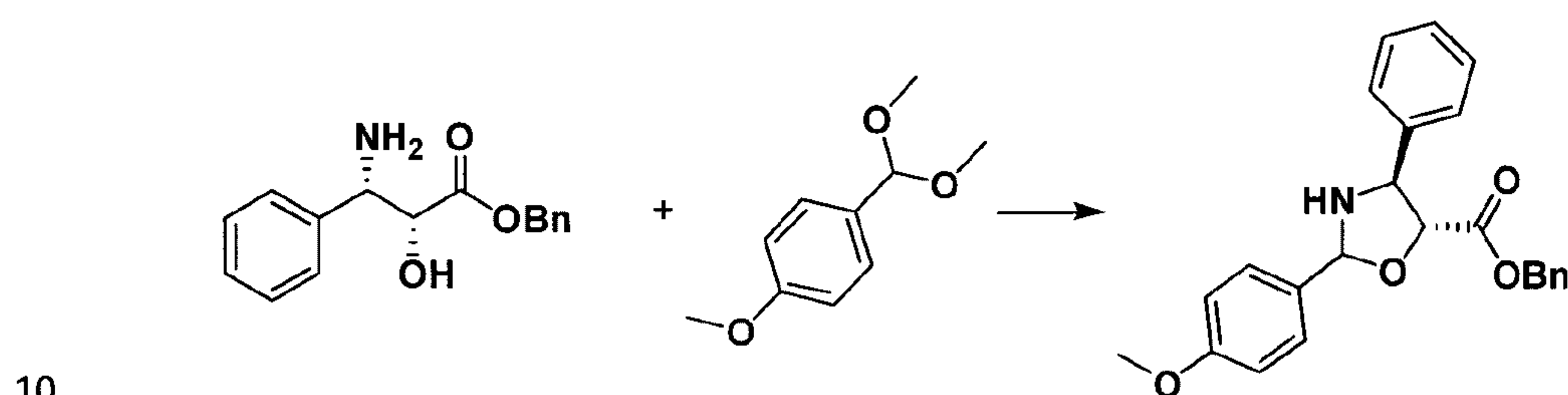
Boc-protected benzyl glycolate (32.5g, 0.12mol) was dissolved in 15ml of tetrahydrofuran and LHMDs (120ml, 0.12mol) was slowly added dropwise into the reaction liquid at -70°C. After that, the reaction liquid was stirred for 0.5h, followed by slowly adding N-*t*-butyl sulfinyl benzylenamine in THF solution (5.02g, a solution of 0.024mol in 8ml of THF) dropwise and 4 hours later, the reaction was finished. The reaction liquid was poured into 50ml of saturated ammonium chloride solution and extracted with ethyl acetate for 3 times (30ml×3). The combined organic phases were dried, concentrated by rotary evaporation and purified by column chromatography (petroleum ether / ethyl acetate =10:1) to obtain a white solid (5.25g, 46%).

e. Preparation of benzyl 2R-hydroxy-3S-aminophenyl propionate



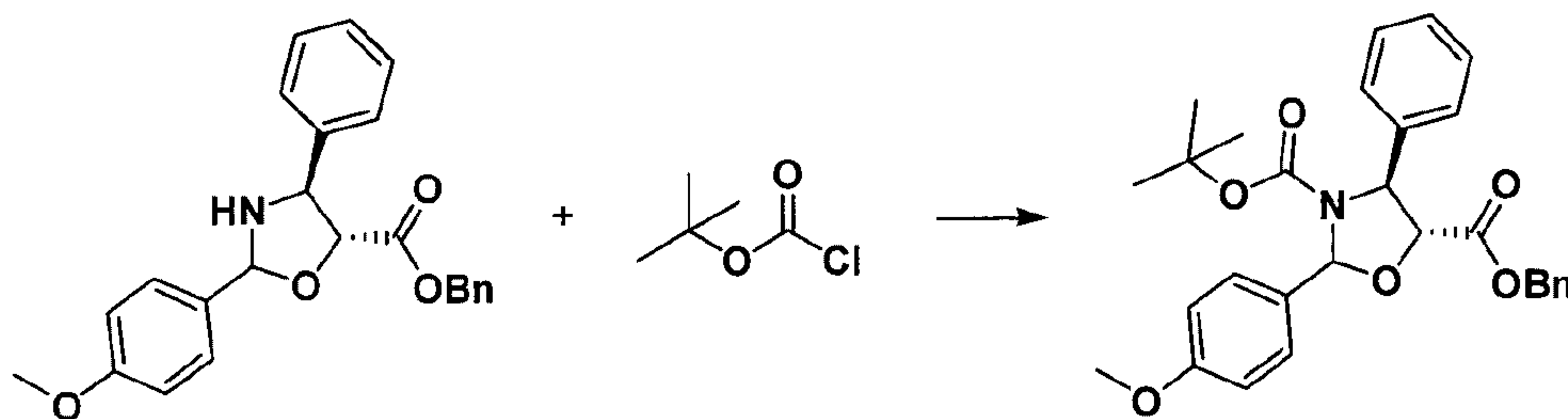
The product obtained in the previous step (5.25g, 0.011mol) was dissolved in 20ml of 2N HCl/EtOAc solution and reacted at room temperature for 10 hours. After the completion of the reaction, the reaction liquid was concentrated and the obtained concentrate was extracted with dichloromethane/water (50ml/100ml). The aqueous phase was collected,
 5 extracted with dichloromethane and the pH value thereof was adjusted with 28% aqueous ammonia to 9-10. Finally, the aqueous phase was extracted with dichloromethane for 3 times (20ml×3). The combined organic phase was dried, filtered and concentrated to give a white solid (2.85g, 95.7%).

f. Preparation of benzyl (4S,5R)-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylate



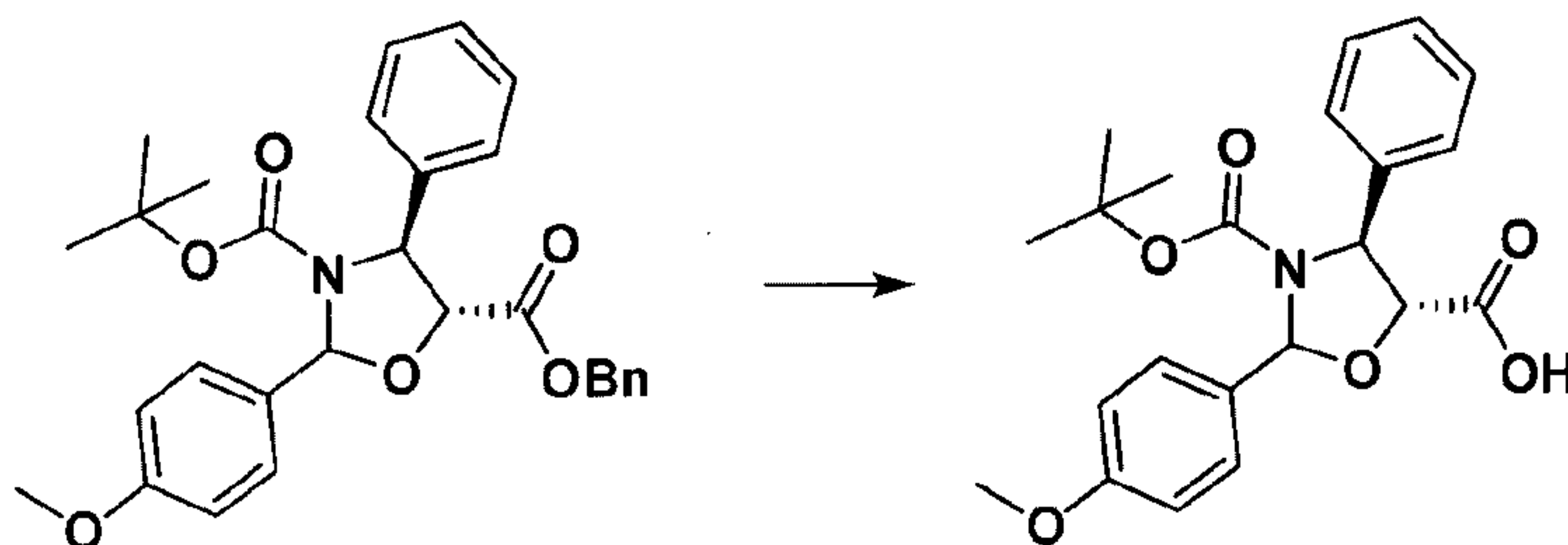
Benzyl 2R-hydroxy-3S-amino-phenyl propionate (2.66g, 9.84mmol) and the catalyst PPTS (0.24g, 0.93mmol) were dissolved in 10ml of toluene and 1,1-dimethoxymethyl-4-methoxybenzene (2.15g, 11.79mmol) was slowly added dropwise into the reaction liquid at 100°C. After that, the reaction was maintained at a temperature of 90-100°C for 2 hours,
 15 which was continued to be supplemented with 2.4g of 1-dimethoxymethyl-4-methoxybenzene and then reacted for about 2 hours before finishing the reaction. The obtained reaction liquid was concentrated, separated and purified by column chromatography (petroleum ether/ethyl acetate=10:1), yielding a yellow oil (3.52g, 92%). The yellow oil contained a small amount of *p*-methoxybenzaldehyde.

20 g. Preparation of benzyl (4S,5R)-3-*t*-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylate



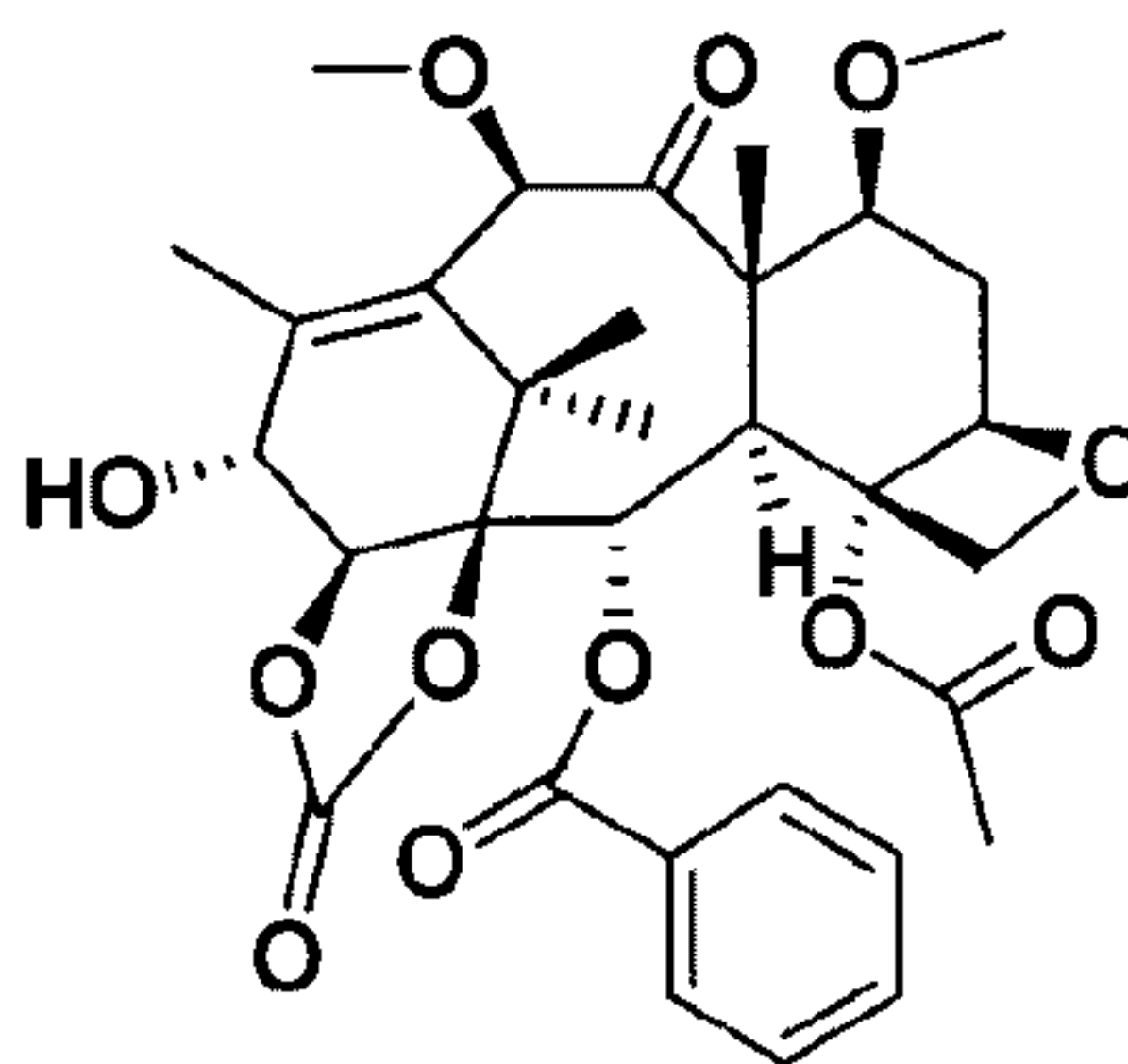
The oil obtained in the previous step (4.07g, 10.47mmol), *t*-butoxy formyl chloride (1.56g, 12.57mmol) and triethylamine (2.64g, 26.17mmol) were dissolved in 10ml of dichloromethane and stirred overnight at room temperature. The reaction liquid was concentrated, separated and purified by column chromatography (petroleum ether/ethyl acetate=10:1) to give a yellow oil (4.83g, 94.4%).

h. Preparation of (4S,5R)-3-*t*-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid



The product obtained in the previous step (4.83g, 9.88mmol) was dissolved in 10ml of methanol, into which 1.0g of palladium hydroxide was added. Hydrogen was introduced (20psi) at room temperature and reacted for about 1h, the completion of the reaction was monitored by TLC. The reaction liquid was filtered, concentrated, separated and purified by column chromatography (petroleum ether/ethyl acetate=5:1), to give the final product as a white solid (2.68g, 67.9%).

2) Preparation of 7,10-dimethoxyl-1,14-carbonate baccatin III



10-DAB (1 eq.) was used as raw material, dissolved in dichloromethane which was used as the solvent and added with 3 equivalents of pyridine at 0°C. Then the obtained reaction liquid was added dropwise with 3 equivalents of *p*-toluenesulfonyl chloride to react for 4 hours. By post-treatment of purification by column chromatography, the compound **1** was
5 given in a yield of 85-90%.

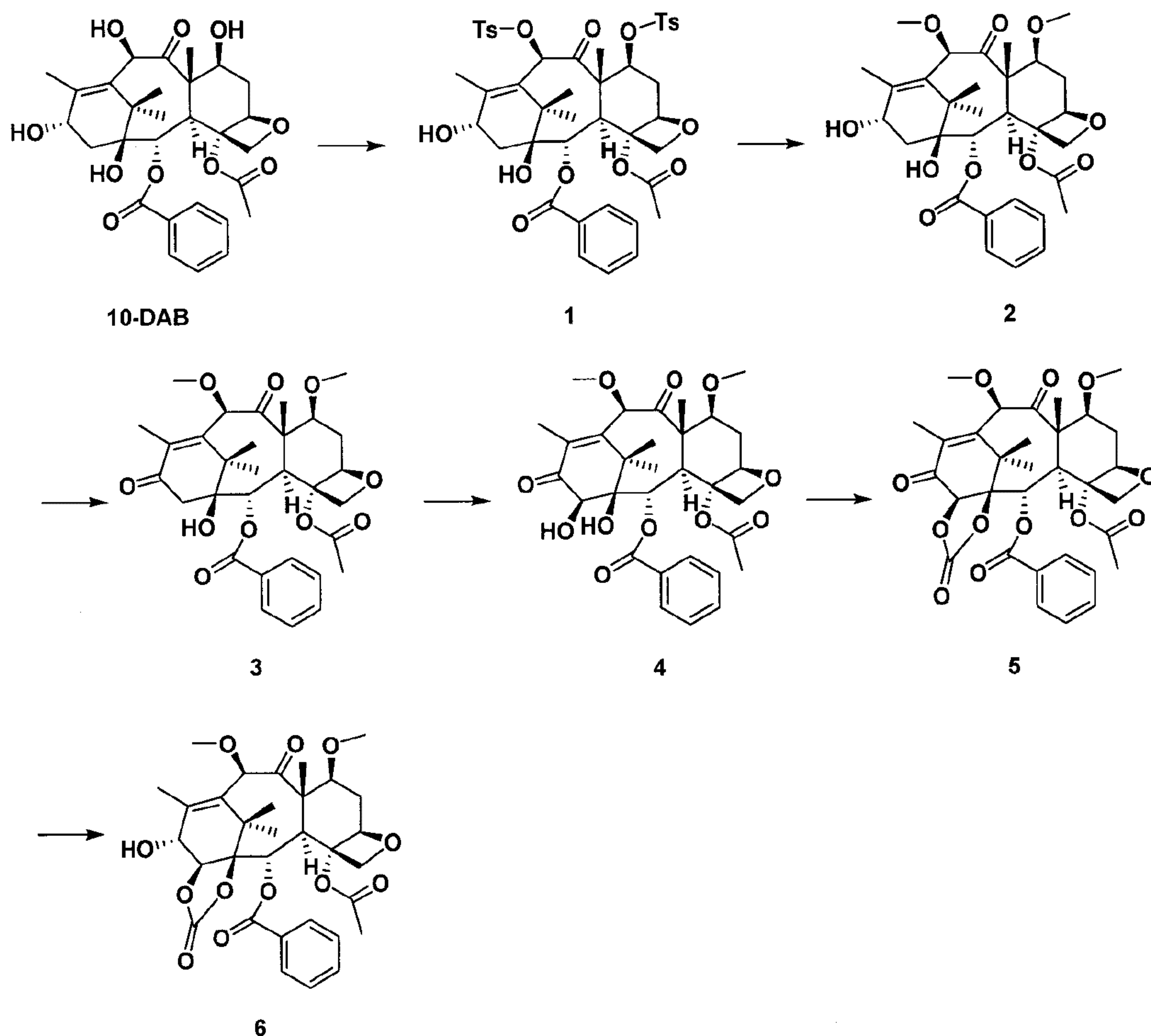
The compound **1** (1 eq.) was dissolved in anhydrous tetrahydrofuran to react with methyl magnesium bromide (2.5 eq.) for 3 hours at room temperature under the protection of nitrogen. After post-treatment, the crude compound **2** was obtained after dried.

The compound **2** (1 eq.) was dissolved in acetone solution, into which 10 equivalents of
10 manganese dioxide was added at room temperature to react for 4 hours. By post-treatment of purification by column chromatography, the compound **3** was given in a yield of 85%.

The compound **3** (1 eq.) was dissolved in dry THF/DMPU (4:1) solution, into which 1.2 equivalents of potassium *t*-butoxide was added at -70°C to react for 20min. The obtained reaction liquid was slowly added dropwise with 2 equivalents of N-(sulfonyl) oxaziridine to
15 react for 2 hours. By post-treatment of purification by column chromatography, the compound **4** was given in a yield of 75%.

The compound **4** (1 eq.) was reacted with 2 equivalents of N,N'-carbonyldiimidazole(CDI) in dry tetrahydrofuran, to give the compound **5** in a yield of 95%.

The compound **5** (1 eq.) was dissolved in dry tetrahydrofuran, into which 0.2 equivalents of
20 (R)-2-methyl oxazaborodine was added as the catalyst, followed by adding 5 equivalents of borane/THF solution to react for 8 hours at room temperature. After completion of reaction, by post-treatment of purification by column chromatography, the compound **6** of 7,10-dimethoxyl-1,14-carbonate baccatin III was obtained as the final product in a yield of 86%.



3) Preparation of PCMI-01

7,10-Dimethoxyl-1,14-carbonate baccatin III (1 eq.) and (4S,5R)-3-*t*-butoxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid (4 eq.) were dissolved in dichloromethane which was used as the solvent, into which 0.5 equivalents of DMAP and 2.0 equivalents of DCC were added successively to react overnight at room temperature. The obtained product was reacted in 2 equivalents of acetyl chloride/methanol solution to give the taxane derivative PCMI-01 as the final product. The overall yield of two steps was 71% and the purity of the final product was 95% or higher.

10 PCMI-01: mp: 242-243 °C;

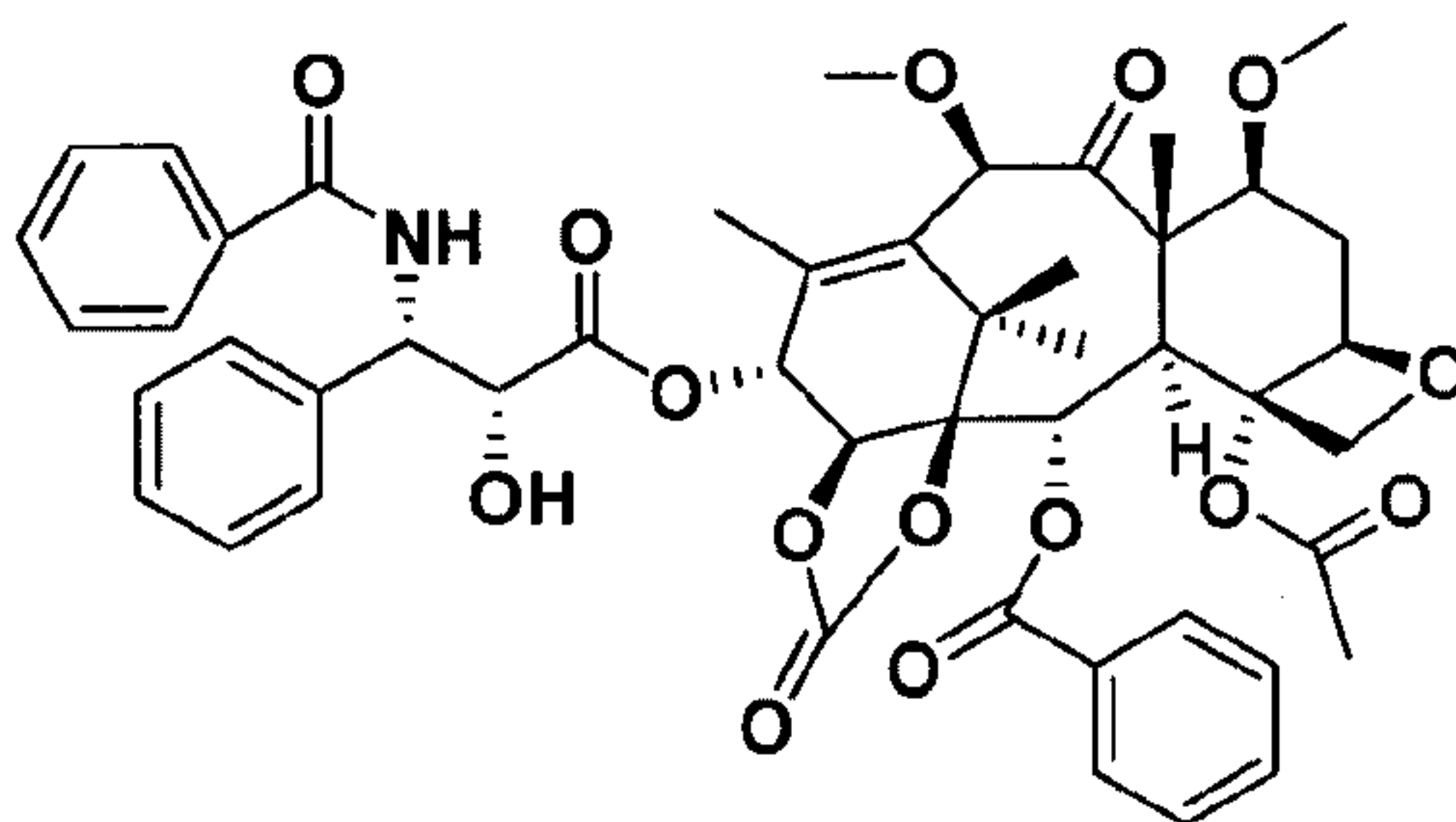
MS (m/z) ESI: 900.4 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 7.3 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.47 – 7.33 (m, 5H), 6.47 (d, *J* = 5.7 Hz, 1H), 6.09 (d, *J* = 7.5 Hz, 1H),

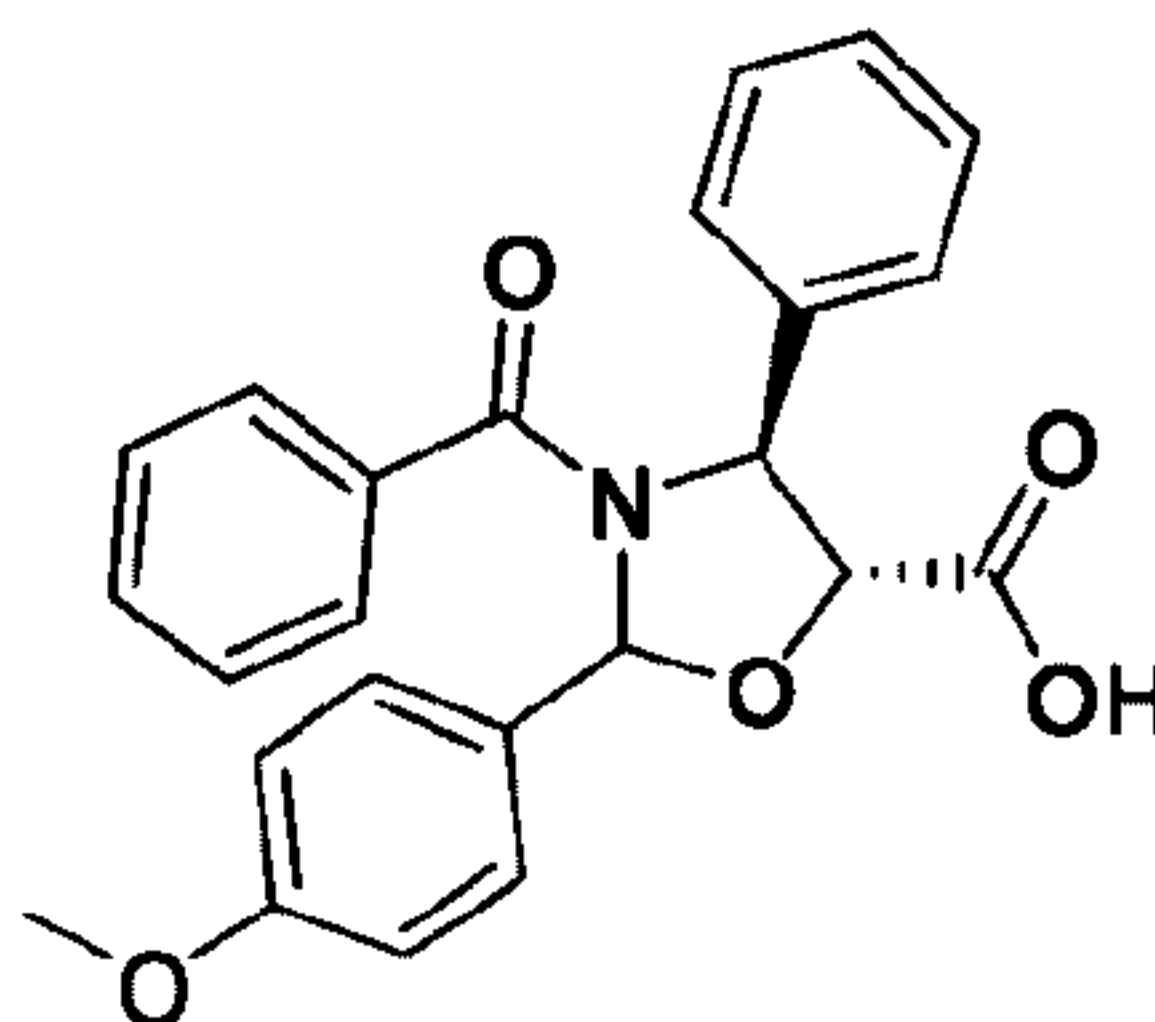
5.50 (d, $J = 9.0$ Hz, 1H), 5.34 (s, 1H), 4.96 (d, $J = 8.0$ Hz, 1H), 4.78 (d, $J = 6.8$ Hz, 1H), 4.74 (s, 1H), 4.72 (s, 1H), 4.30 (d, $J = 8.5$ Hz, 1H), 4.25 (d, $J = 8.5$ Hz, 1H), 3.86 (dd, $J = 10.8, 6.3$ Hz, 1H), 3.71 (d, $J = 7.5$ Hz, 1H), 3.49 (s, 3H), 3.32 (s, 3H), 2.75-2.67 (m, 1H), 2.45 (s, 3H), 1.93 (s, 3H), 1.87 – 1.78 (m, 1H), 1.77 (s, 3H), 1.41 (s, 9H), 1.33 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 203.51, 171.19, 164.63, 151.96, 135.97, 134.09, 129.92, 128.95, 128.12, 126.67, 88.08, 83.97, 82.17, 81.17, 80.51, 79.69, 75.99, 74.94, 74.42, 69.18, 57.88, 57.08, 46.76, 41.90, 31.83, 29.69, 28.25, 26.06, 22.61, 22.14, 14.56, 10.39.

Example 2 Preparation of PCMI-02

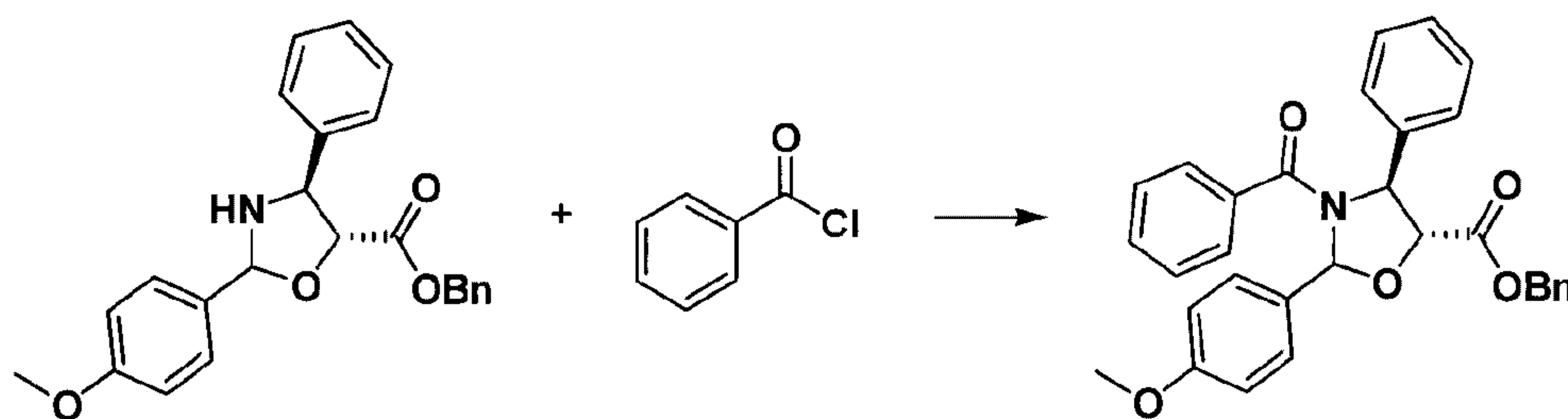


i) Preparation of (4S,5R)-3-benzoyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid



(4S,5R)-3-benzoyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid was prepared with the substantially same method as shown in **Example 1**, except for Step g. Other steps could be seen in the reactions of **Example 1**.

g. Preparation of benzyl (4S,5R)-3-benzoyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylate



Benzyl (4S,5R)-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylate (1 eq.) was dissolved in dry tetrahydrofuran, into which 1.5 equivalents of LHMDs was added at -40°C. After 1 hour of reaction, the reaction liquid was added dropwise with 2 equivalents of benzoyl chloride, reacted for 3 hours and finished the reaction. After post-treatment of purification by column chromatography, the product was obtained in a yield of 85%.

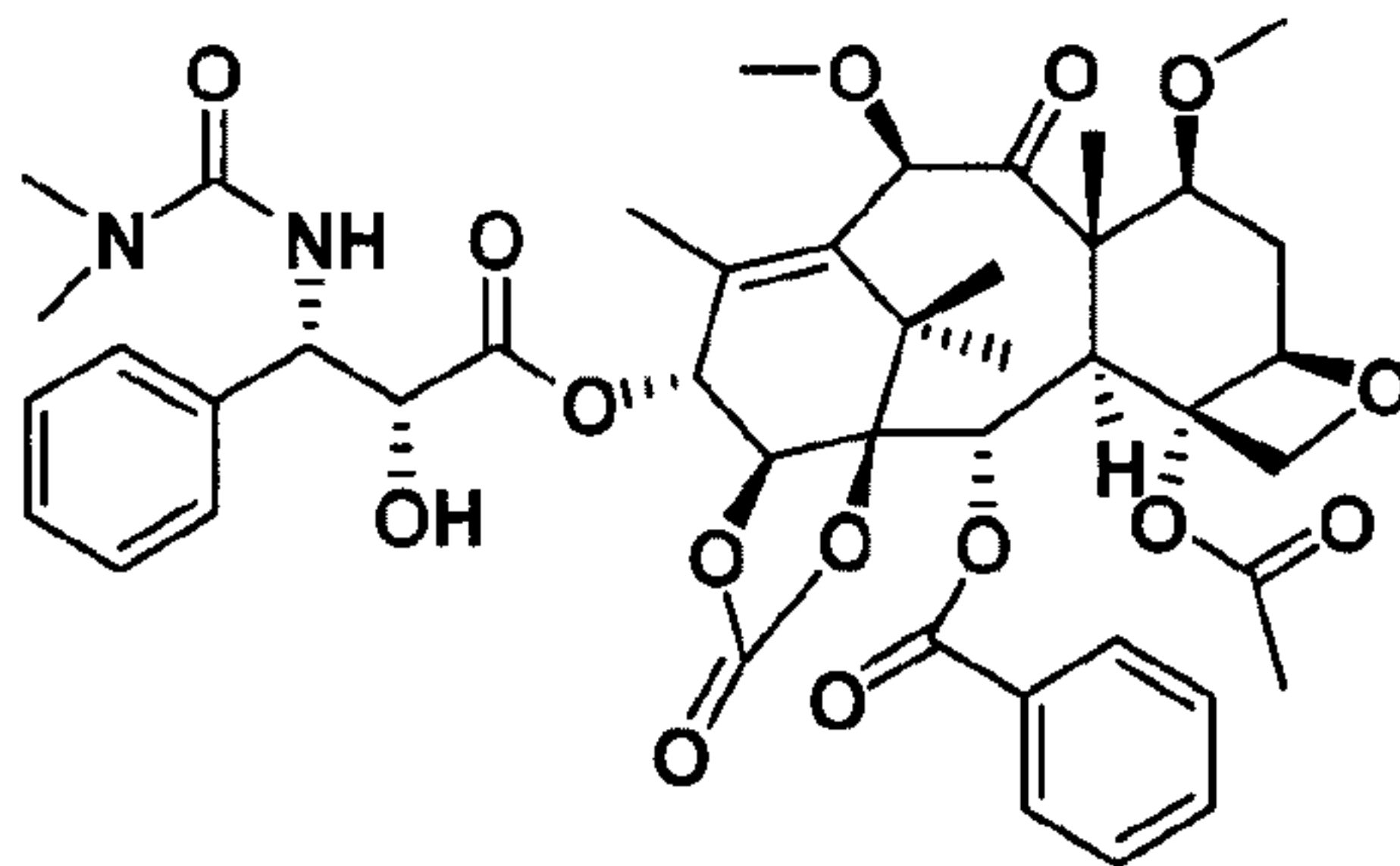
The preparation of 7,10-dimethoxyl-1,14-carbonate baccatin III in Step 2) and PCMI-02 in Step 3) had the same procedures as those in Step 2) and Step 3) in Example 1. The procedures could be seen particularly in Step 2) and Step 3) in **Example 1** and the purity of the final product was 95% or higher.

PCMI-02: mp: 234-235°C;

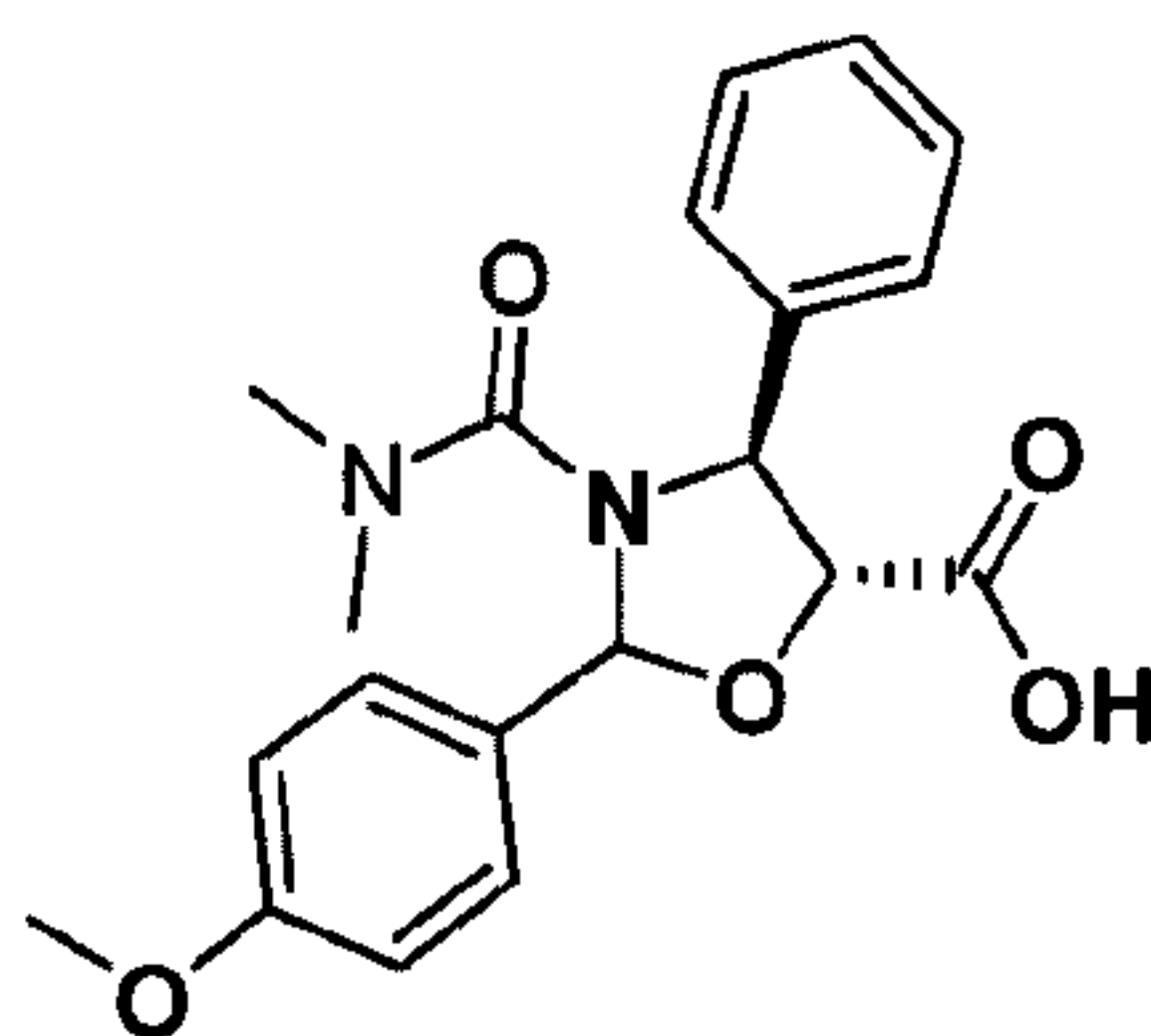
MS (m/z) ESI: 904.3 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 7.9 Hz, 2H), 7.62 (t, *J* = 7.1 Hz, 1H), 7.53-7.44 (m, 7H), 7.38 (t, *J* = 7.4 Hz, 3H), 7.20 (d, *J* = 8.9 Hz, 1H), 6.49 (d, *J* = 6.6 Hz, 1H), 6.08 (d, *J* = 7.6 Hz, 1H), 5.95 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.97 (d, *J* = 8.8 Hz, 1H), 4.92-4.88 (m, 2H, H-2'), 4.71 (s, 1H), 4.29 (q, *J* = 8.5 Hz, 2H), 3.98 (d, *J* = 5.1 Hz, 1H), 3.86 (m, 1H), 3.73 (d, *J* = 7.5 Hz, 1H), 3.48 (s, 3H), 3.31 (s, 3H), 2.78 – 2.65 (m, 1H), 2.56 (s, 3H), 1.88 (s, 3H), 1.85 – 1.74 (m, 4H), 1.31 (s, 3H), 1.28 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 203.54, 172.05, 171.20, 167.55, 164.79, 151.88, 137.66, 136.28, 135.77, 134.10, 133.55, 131.98, 130.12, 129.03, 128.61, 128.30, 128.05, 127.33, 126.86, 88.25, 84.07, 82.08, 81.10, 80.39, 79.82, 76.07, 74.88, 73.97, 69.25, 57.92, 57.08, 55.02, 46.81, 41.86, 31.79, 29.70, 25.98, 24.89, 22.70, 22.28, 14.49, 10.46.

Example 3 Preparation of PCMI-03

- 1) Preparation of (4S,5R)-3-dimethylcarbamoyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

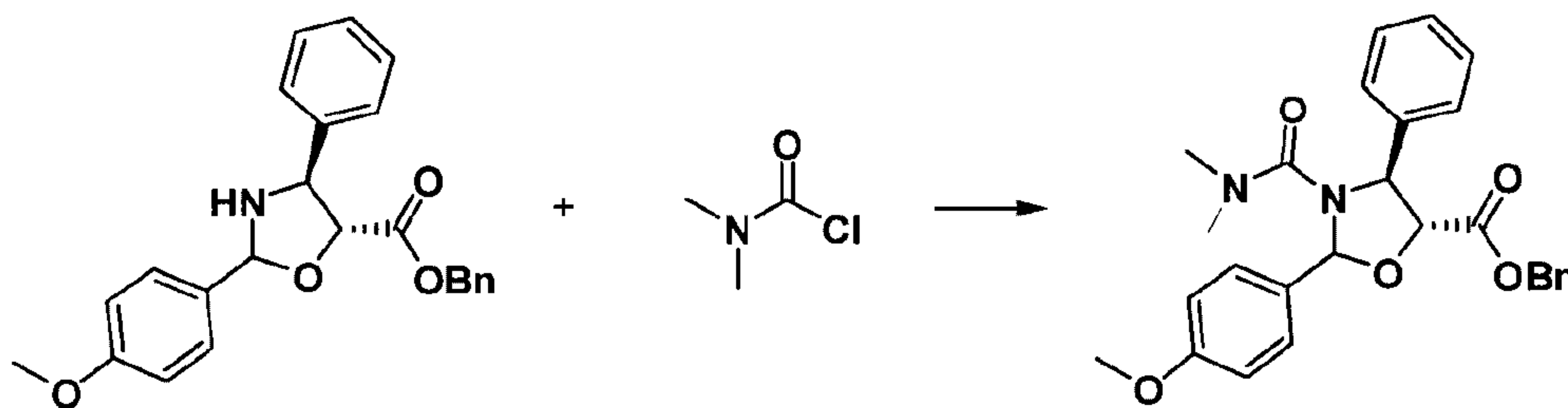


5

(4S,5R)-3-dimethylcarbamoyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid was prepared with the substantially same method as shown in **Example 1**, except for Step g. Other steps could be seen in the reactions of **Example 1**.

- g. Preparation of benzyl (4S,5R)-3-dimethylcarbamoyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylate

10



Benzyl (4S,5R)-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylate (1 eq.) was dissolved in dry tetrahydrofuran, into which 1.5 equivalents of LHMDs was added at -40°C.

- 15 After 1 hour of reaction, the reaction liquid was added dropwise with 2 equivalents of dimethylcarbamoyl chloride, reacted for 3 hours and finished the reaction. After post-

treatment of purification by column chromatography, the product was obtained in a yield of 80%.

The preparation of 7,10-dimethoxyl-1,14-carbonate baccatin III in Step 2) and PCMI-03 in Step 3) had the same procedures as those in Step 2) and Step 3) in Example 1. The procedures could be seen particularly in Step 2) and Step 3) in **Example 1** and the purity of the final product was 95% or higher.

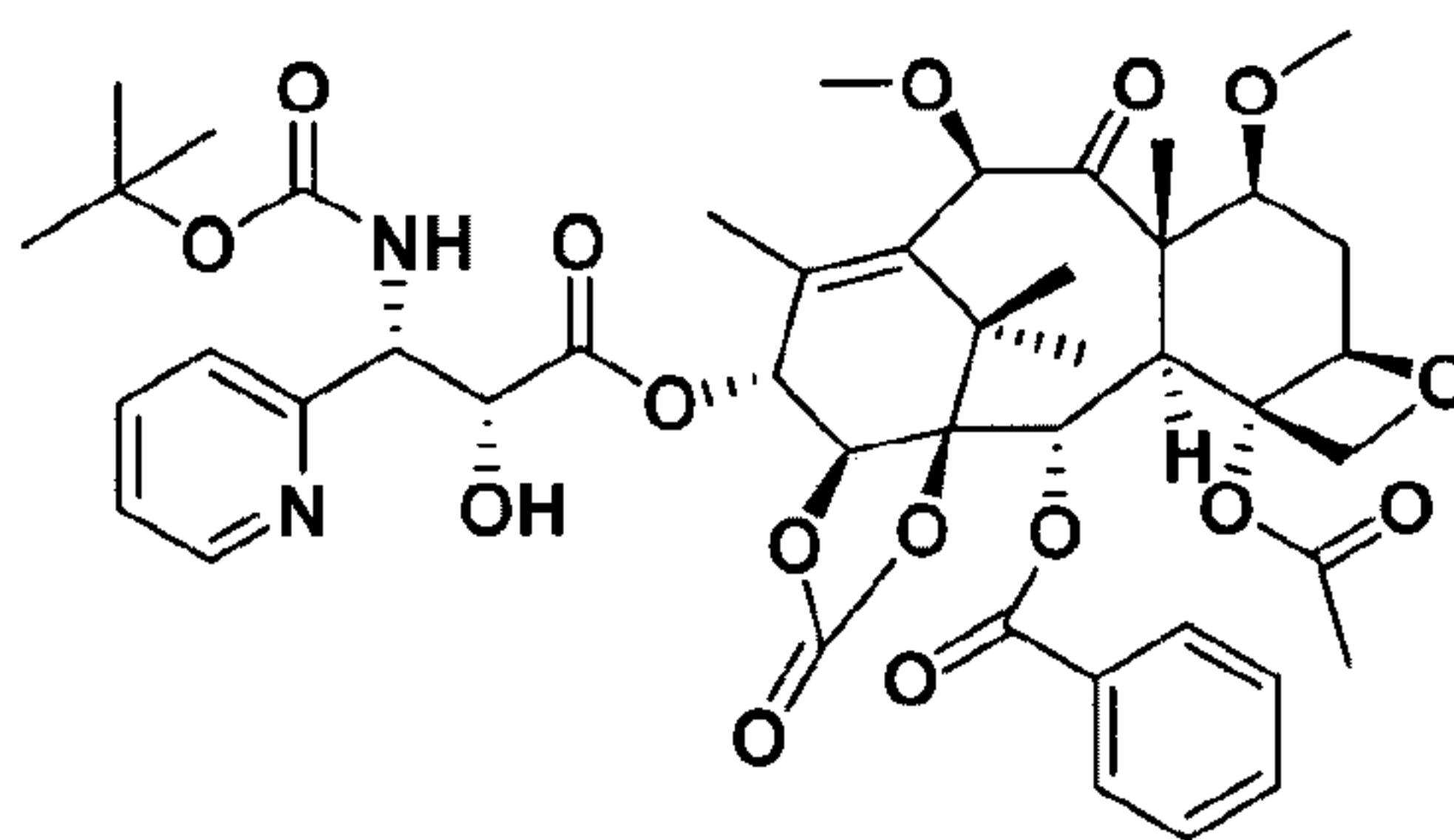
PCMI-03: mp: 205-206°C;

MS (m/z) ESI: 871.5 (M+Na)⁺;

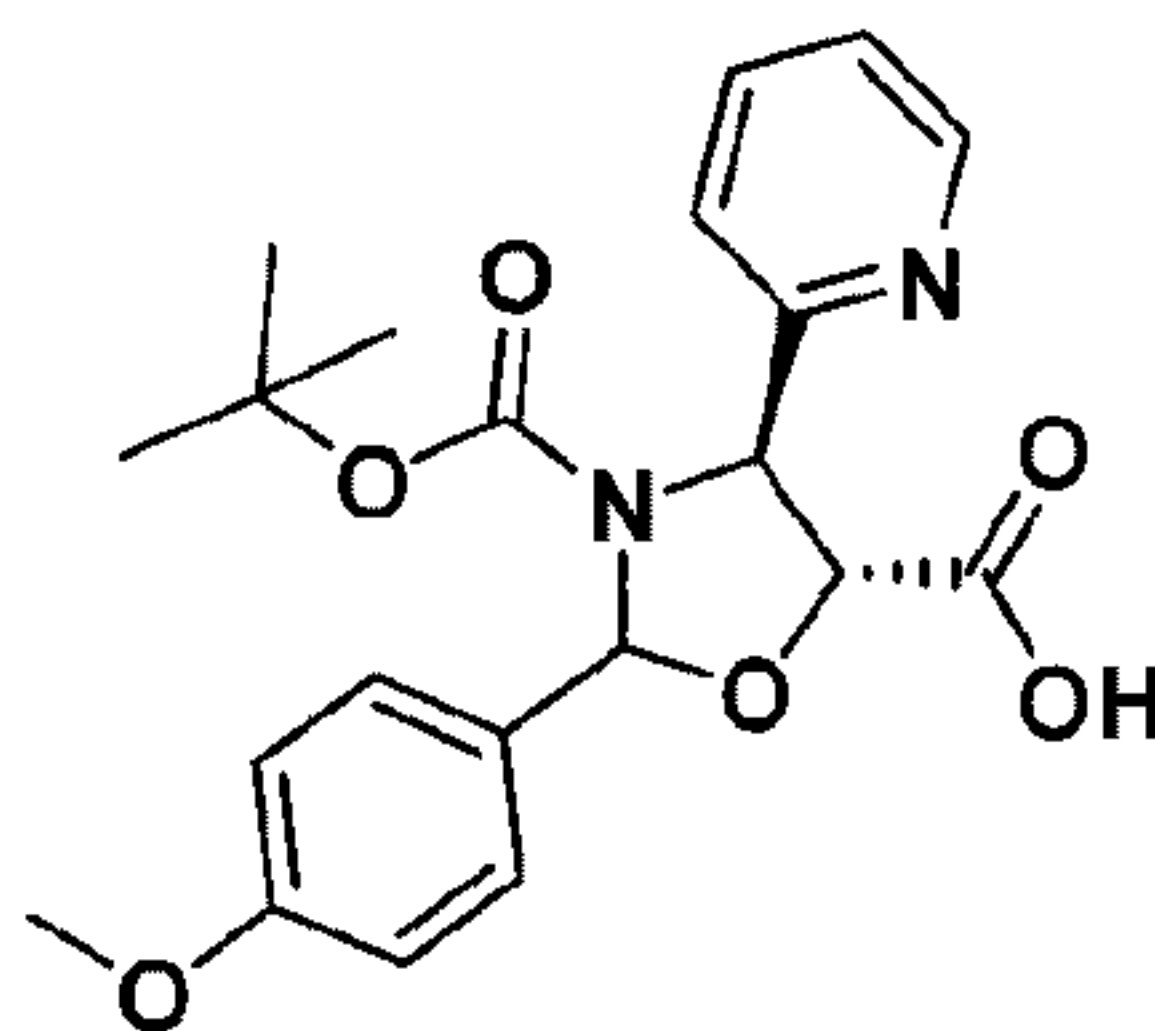
¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 7.2 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.35 – 7.29 (m, 1H), 6.11 (t, *J* = 8.1 Hz, 1H), 5.97 – 5.88 (m, 1H), 5.80 (d, *J* = 6.1 Hz, 1H), 5.67 (d, *J* = 9.7 Hz, 1H), 5.30 (d, *J* = 9.3 Hz, 1H), 4.93 (d, *J* = 8.7 Hz, 1H), 4.63 (s, 1H), 4.29 (d, *J* = 8.3 Hz, 1H), 4.17 (d, *J* = 8.3 Hz, 1H), 3.97 (t, *J* = 11.1 Hz, 1H), 3.01 (d, *J* = 6.0 Hz, 1H), 2.64 – 2.52 (m, 1H), 2.38 (dd, *J* = 15.3, 10.0 Hz, 1H), 2.28 (d, *J* = 11.0 Hz, 5H), 2.16-2.10 (m, 1H), 2.11 (s, 3H), 1.88-1.82 (m, 1H) 1.73 (s, 6H), 1.42 (s, 12H), 1.25 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 171.64, 171.21, 170.78, 170.62, 167.10, 155.18, 138.80, 137.60, 136.85, 133.72, 130.09, 129.20, 128.65, 128.58, 127.82, 127.04, 84.73, 82.82, 79.96, 78.61, 76.58, 73.96, 72.18, 70.96, 69.23, 60.42, 55.89, 44.99, 42.98, 42.33, 37.36, 36.66, 35.66, 29.70, 28.30, 22.60, 21.81, 21.40, 16.71, 14.94.

20 **Example 4 Preparation of PCMI-04**

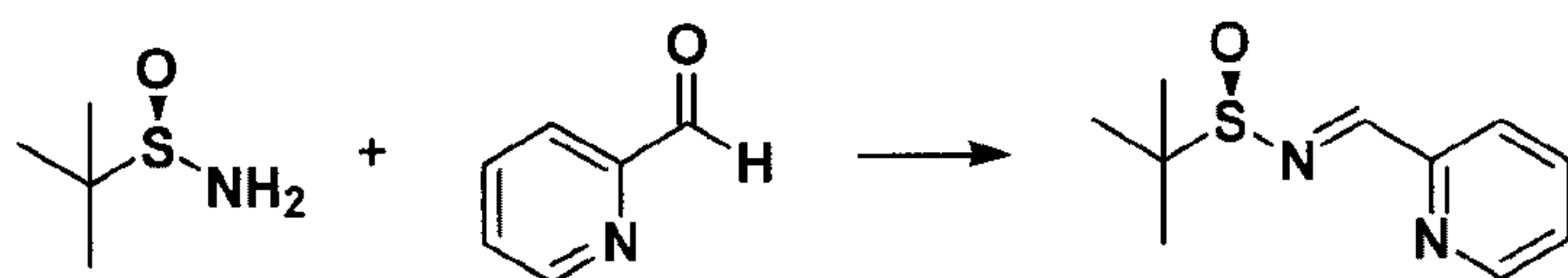


i) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-(2-pyridyl)-5-oxazolidine carboxylic acid



(4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-(2-pyridyl)-5-oxazolidine-carboxylic acid was prepared with the substantially same method as shown in **Example 1**, except for Step c. Other steps could be seen in the reaction of **Example 1**.

5 c. Preparation of N-*t*-butyl sulfinyl-2-pyridinyl carboxaenamine



(S_R)-*t*-butyl sulfinamide (5.22g, 0.043mol) and 2-pyridine carboxaldehyde (4.47g, 0.052mol) were dissolved in 20ml of dichloromethane, into which magnesium sulfate (25.90g, 0.22mol) and PPTS (0.54g, 2.20mmol) were added. The reaction liquid was stirred at room temperature for 24 hours, filtered and the filter cake was rinsed with dichloromethane for 3 times (20ml×3) and concentrated to give the crude product. The crude product was purified by column chromatography (petroleum ether/ethyl acetate=15:1) to give a colorless oil (7.13g, 80.2%).

The preparation of 7,10-dimethoxyl-1,14-carbonate baccatin III in Step 2) and PCMI-04 in Step 3) had the same procedures as those in Step 2) and Step 3) in **Example 1**. The procedures could be seen particularly in Step 2) and Step 3) in **Example 1** and the purity of the final product was 95% or higher.

PCMI-04: mp: 244-245°C;

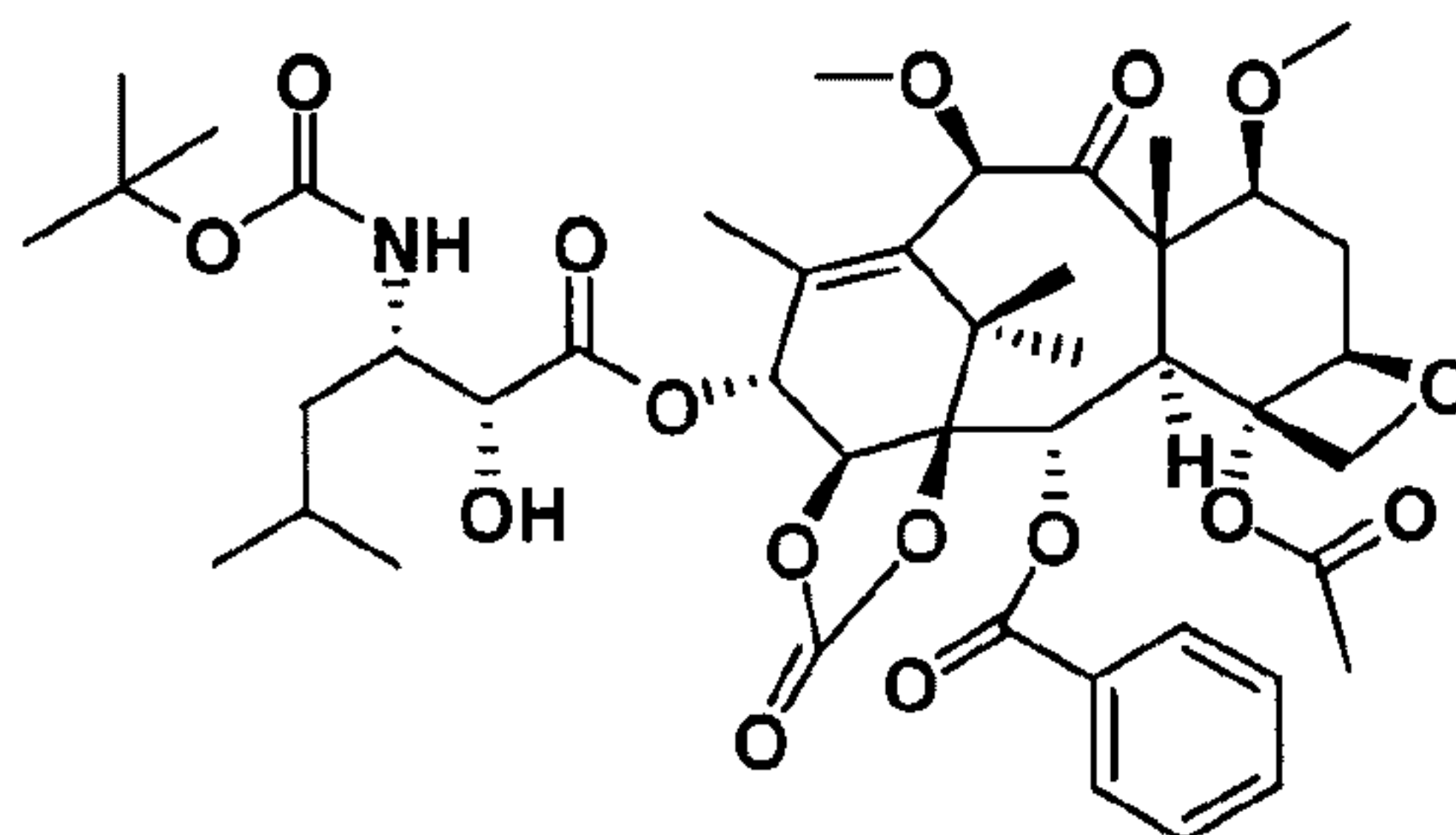
MS (m/z) ESI: 901.3 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.46 (d, *J* = 4.5 Hz, 1H), 8.06 – 7.99 (m, 2H), 7.83 – 7.75 (m, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 3H), 7.29 (m, 1H), 6.39 (dd, *J* = 6.7, 1.4 Hz, 1H), 6.08 (d, *J* = 7.4 Hz, 1H), 5.81 (d, *J* = 10.0 Hz, 1H), 5.49 – 5.39 (m, 1H), 4.99 (d, *J* = 8.2 Hz, 1H), 4.82 (d, *J* = 6.7 Hz, 1H), 4.78 (s, 1H), 4.73 (s, 1H), 4.30 (d, *J* = 8.3 Hz, 1H), 4.22 (d, *J* = 8.2 Hz, 1H), 3.89 (dd, *J* = 10.8, 6.3 Hz, 1H), 3.72 (d, *J* = 3.7 Hz, 1H),

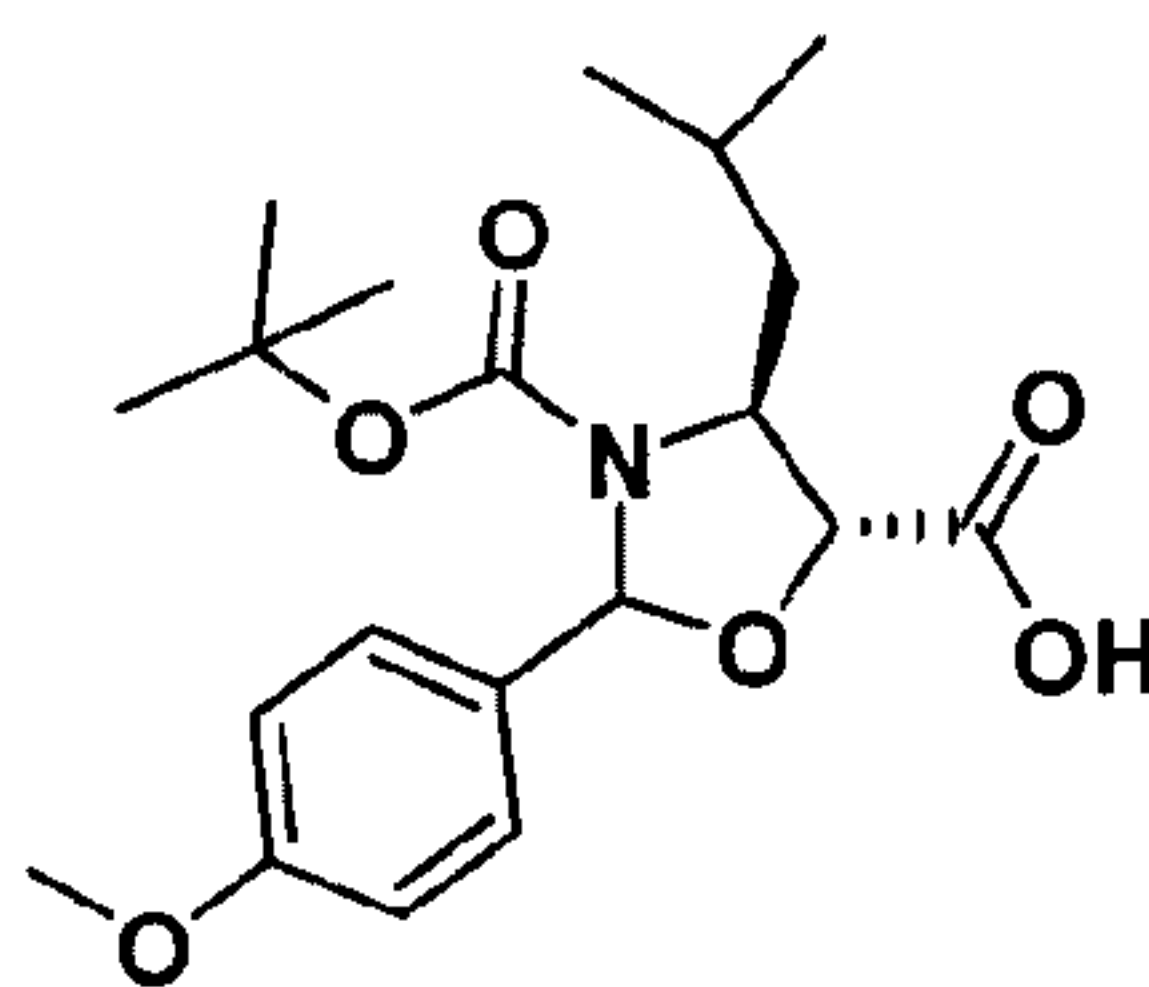
3.45 (s, 3H), 3.31 (s, 3H), 2.77 – 2.67 (m, 1H, H-6), 2.52 (s, 3H), 1.92 (d, $J = 1.0$ Hz, 3H), 1.82-1.77 (dd, $J = 19.3, 7.9$ Hz, 1H), 1.76 (s, 3H), 1.48 (s, 9H), 1.30 (s, 3H), 1.24 (s, $J = 8.0$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 203.62, 171.02, 164.65, 159.41, 152.08, 148.04, 137.91, 136.46, 136.21, 134.12, 129.86, 128.90, 123.04, 122.28, 88.26, 83.97, 82.23, 80.91, 80.40, 80.05, 75.93, 73.92, 69.37, 57.87, 57.10, 57.03, 46.82, 41.85, 31.82, 29.68, 28.34, 26.00, 22.07, 14.55, 10.37.

Example 5 Preparation of PCMI-05

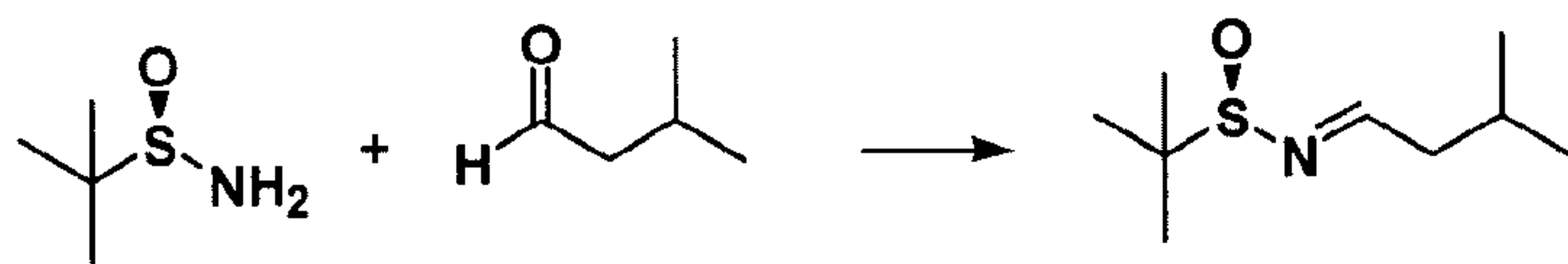


- 1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-isobutyl-5-oxazolidine carboxylic acid



- (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-isobutyl-5-oxazolidine carboxylic acid was prepared with the substantially same method as shown in **Example 1**, except for Step c. Other steps could be seen in the reaction of **Example 1**.

c. Preparation of N-*t*-butyl sulfinyl isobutyl carboxaenamine



(*S_R*)-*t*-butyl sulfinamide (5.22g, 0.043mol) and isovaleraldehyde (5.51g, 0.052mol) were dissolved in 20ml of dichloromethane, into which magnesium sulfate (25.90g, 0.22mol) and

PPTS (0.54g, 2.20mmol) were added. The reaction liquid was stirred for 24 hours at room temperature, filtered and the filter cake was rinsed with dichloromethane for 3 times (20ml×3) and concentrated to give the crude product. The crude product was purified by column chromatography (petroleum ether/ethyl acetate=15:1) to give a colorless oil (7.26g, 89.3%).

The preparation of 7,10-dimethoxyl-1,14-carbonate baccatin III in Step 2) and PCMI-05 in Step 3) had the same procedures as those in Step 2) and Step 3) in Example 1. The procedures could be seen particularly in Step 2) and Step 3) in **Example 1** and the purity of the final product was 95% or higher.

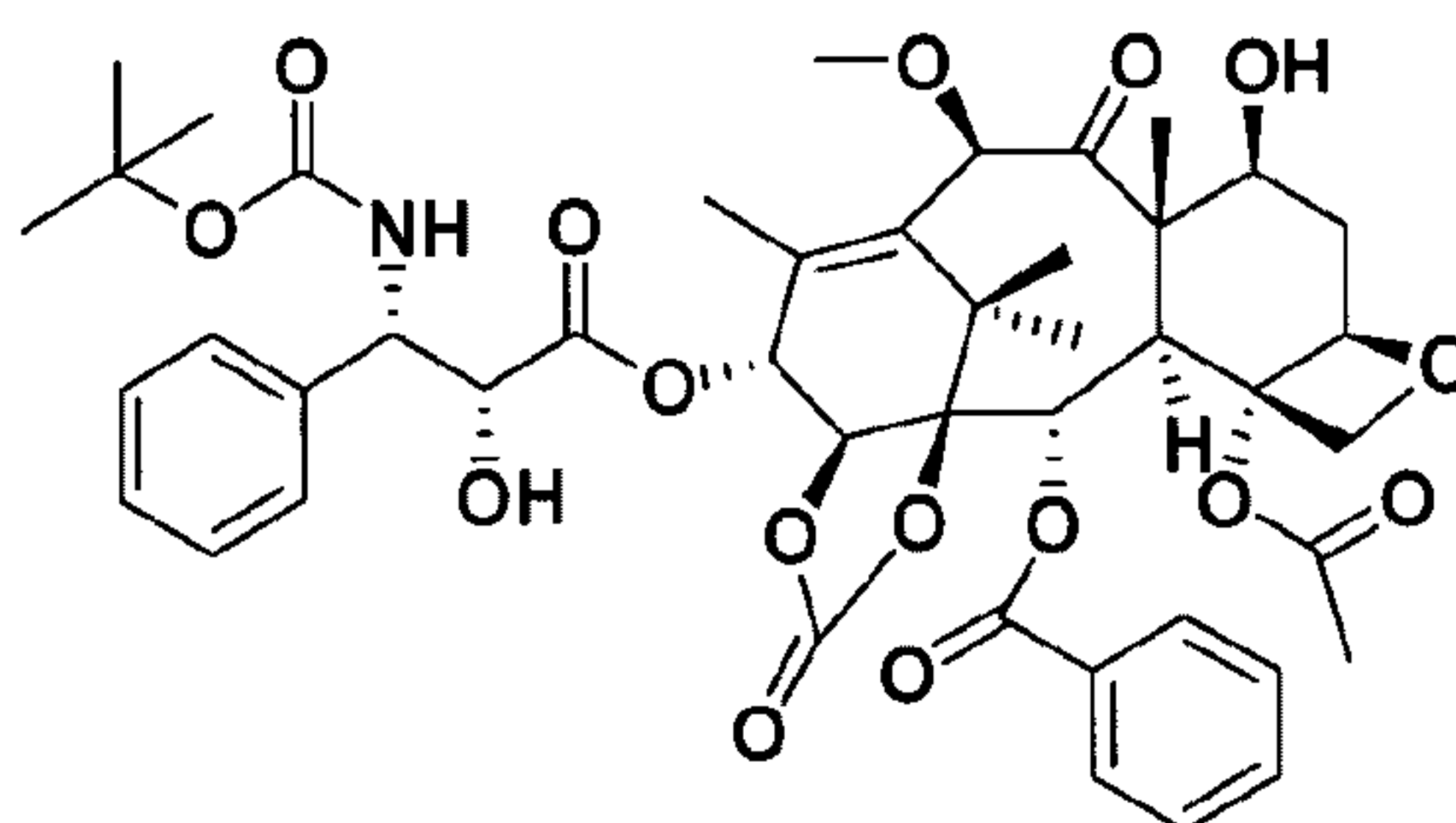
PCMI-05: mp: 237-238°C;

MS (m/z) ESI: 880.4 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 6.46 (d, *J* = 6.2 Hz, 1H), 6.08 (d, *J* = 7.5 Hz, 1H), 4.97 (d, *J* = 7.9 Hz, 1H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.80 (d, *J* = 9.1 Hz, 1H), 4.74 (s, 1H), 4.33 (dd, *J* = 6.2, 3.2 Hz, 1H), 4.29 (d, *J* = 8.4 Hz, 1H), 4.23 (d, *J* = 8.4 Hz, 1H), 4.17 – 4.07 (m, 1H), 4.03 (d, *J* = 6.2 Hz, 1H), 3.86 (dd, *J* = 10.7, 6.4 Hz, 1H), 3.71 (d, *J* = 7.4 Hz, 1H), 3.47 (s, 3H), 3.30 (s, 3H), 2.70 (ddd, *J* = 14.3, 9.8, 6.3 Hz, 1H), 2.49 (s, 3H), 1.96 (d, *J* = 1.2 Hz, 3H), 1.86 – 1.77 (m, 1H), 1.76 (s, 3H), 1.73-1.67 (m, 2H), 1.52-1.42 (m, 1H), 1.39 (s, 9H), 1.31 (d, *J* = 5.9 Hz, 6H), 0.99 (t, *J* = 6.5 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 203.58, 172.84, 170.75, 164.68, 156.23, 152.06, 136.25, 134.08, 129.92, 128.93, 128.06, 88.16, 83.98, 82.17, 81.03, 80.36, 79.73, 75.95, 74.73, 73.81, 69.22, 57.85, 57.09, 57.07, 46.74, 41.92, 31.80, 29.69, 28.24, 26.04, 24.86, 23.25, 22.55, 22.16, 14.66, 10.41.

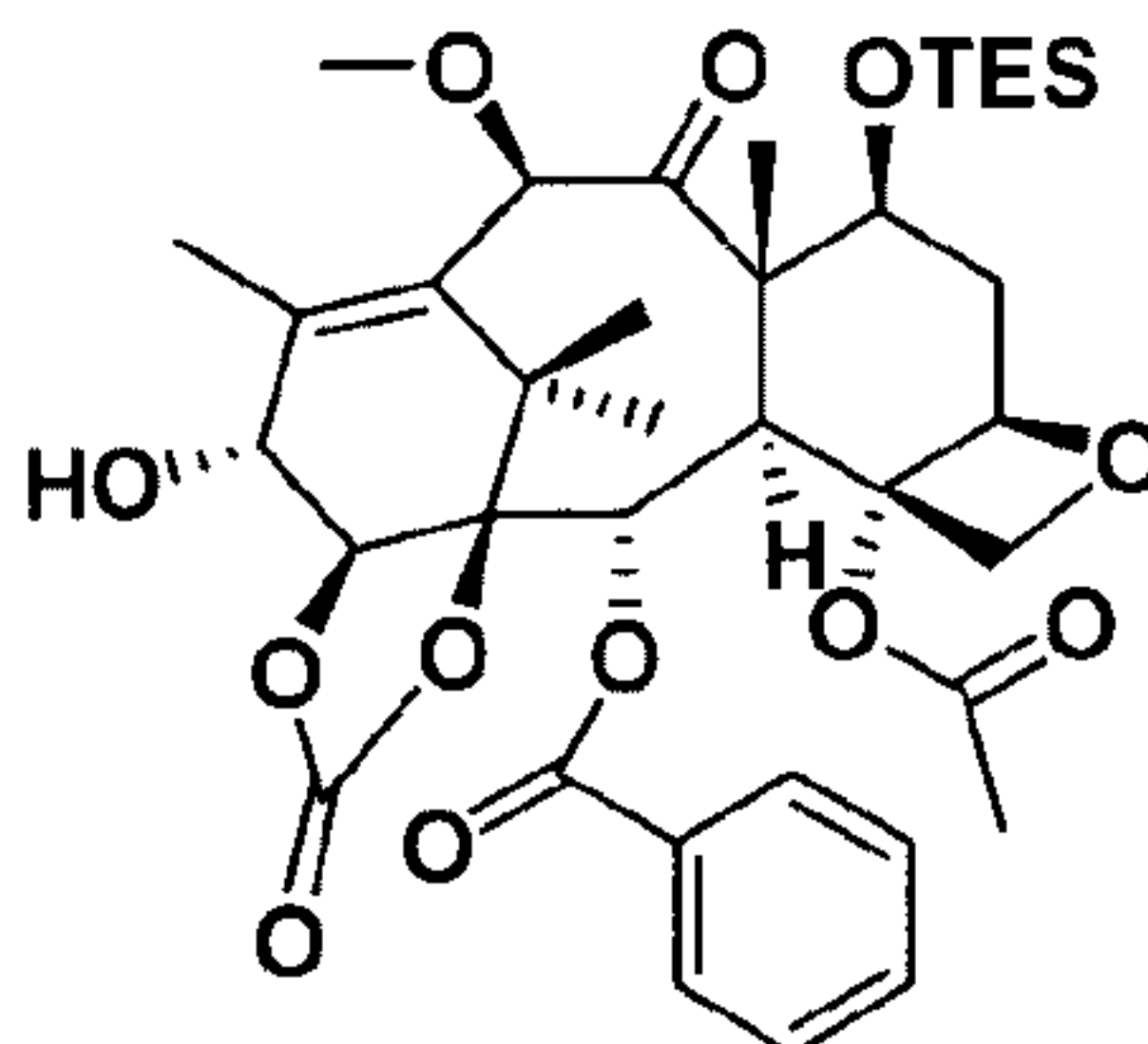
Example 6 Preparation of PCMI-06



- 1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

The specific method was seen in **Example 1**.

- 2) Preparation of 10-methoxyl-7-triethylsilicane-1,14-carbonate baccatin III



5

10-DAB (1 eq.) was used as raw material, dissolved in DMF and added successively with 2.5 equivalents of imidazole and 2.5 equivalents of triethyl chlorosilane. By post-treatment, the crude compound **7** was given.

The compound **7** was dissolved in dichloromethane which was used as the solvent, into which 2 equivalents of pyridine was added at 0°C. Successively, the reaction liquid was added dropwise with 2 equivalents of *p*-toluenesulfonyl chloride to react for 4 hours. By post-treatment of purification by column chromatography, the compound **8** was given in a yield of 85-90%.

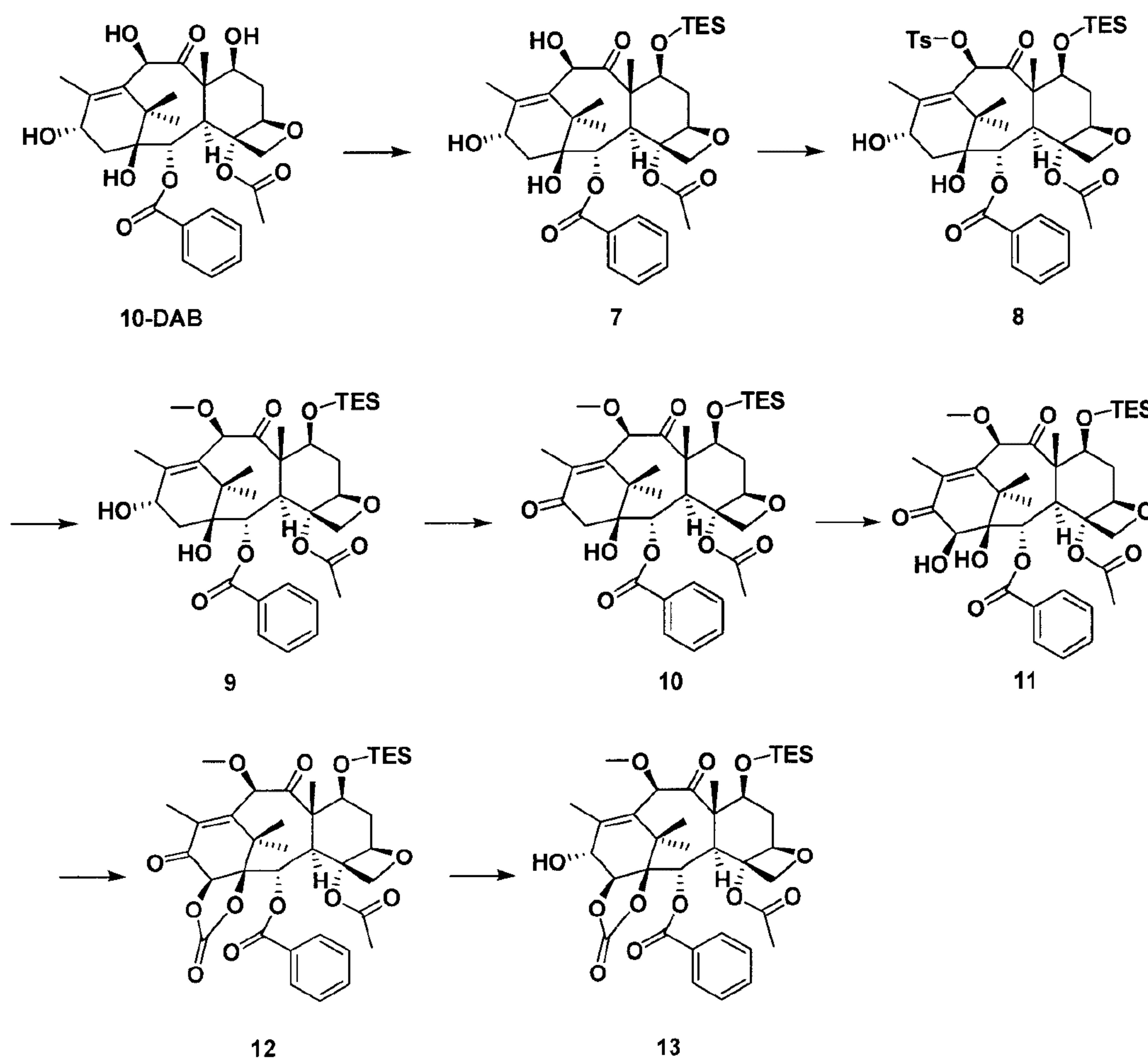
The compound **8** (1 eq.) was dissolved in anhydrous tetrahydrofuran to react with methyl magnesium bromide (2 eq.) at room temperature for 3 hours under the protection of nitrogen. After post-treatment, the crude compound **9** was obtained after dried.

The compound **9** (1 eq.) was dissolved in acetone solution, into which 10 equivalents of manganese dioxide was added to react for 4 hours at room temperature. By post-treatment of purification by column chromatography, the compound **10** was given in a yield of 75%.

The compound **10** (1 eq.) was dissolved in dry THF/DMPU (4:1) solution, into which 1.2 equivalents of potassium *t*-butoxide was added at -70°C to react for 20min. The obtained reaction liquid was slowly added dropwise with 2 equivalents of N-(sulfonyl)oxaziridine to react for 2 hours. By post-treatment of purification by column chromatography, the compound **11** was given in a yield of 75%.

The compound **11** (1 eq.) was reacted with 2 equivalents of N,N'-carbonyldiimidazole (CDI) in dry tetrahydrofuran to give the compound **12** in a yield of 95%.

The compound **12** (1 eq.) was dissolved in dry tetrahydrofuran, into which 0.2 equivalents of (R)-2-methyl oxazaborodine was added at room temperature as a catalyst, followed by addition of 5 equivalents of borane/THF solution to react for 8 hours. After completion of reaction, by post-treatment of purification by column chromatography, the compound **13** of 10-methoxyl-1,14-carbonate baccatin III was obtained as the final product in a yield of 80%.



3) Preparation of PCMI-06

The specific method was seen in Step 3) in **Example 1** and the purity of the final product was 95% or higher.

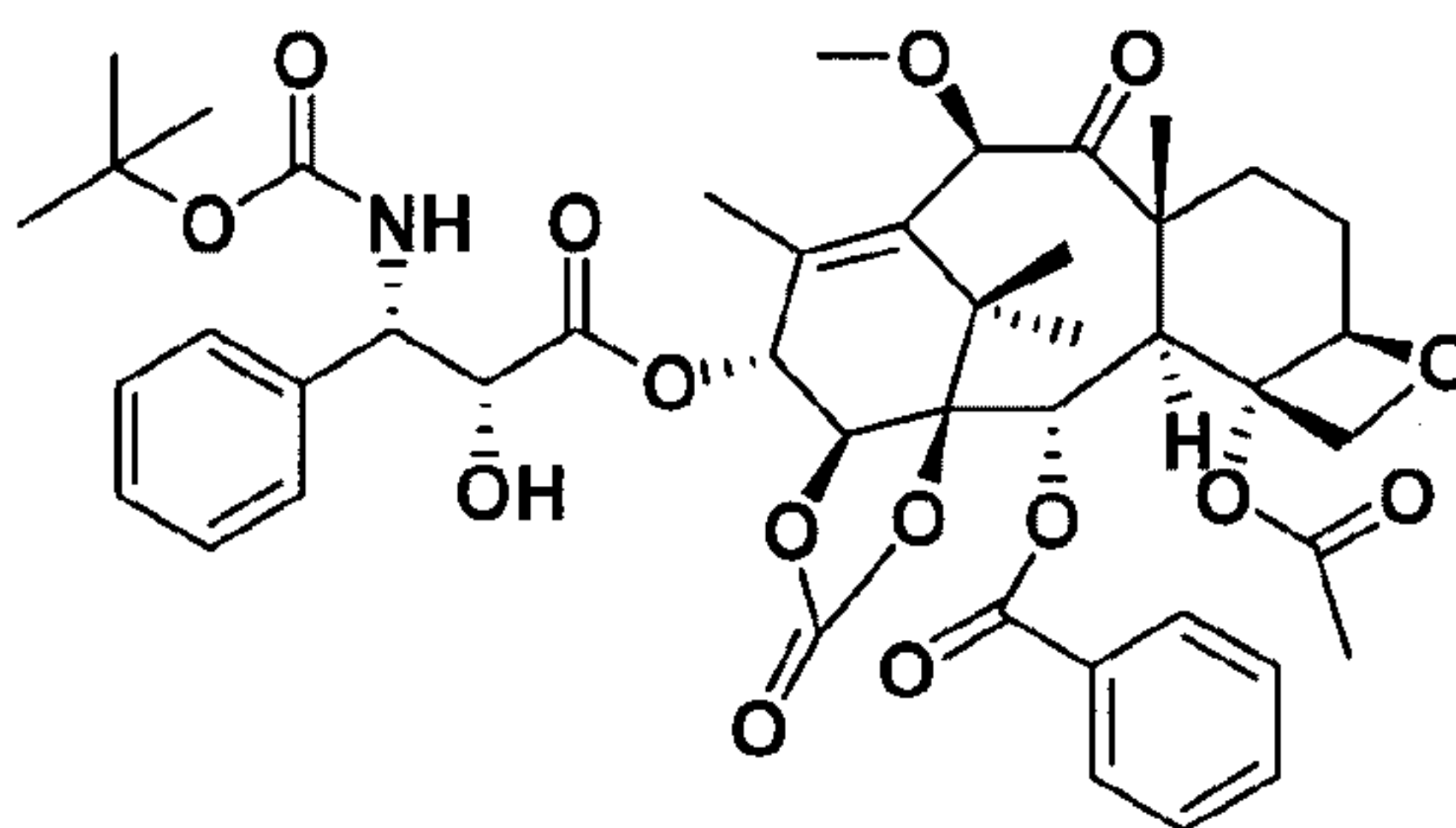
PCMI-06: mp: 233-235°C;

MS (m/z) ESI: 886.3 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.46 – 7.37 (m, 4H), 7.37 – 7.30 (m, 1H), 6.46 (d, *J* = 6.2 Hz, 1H), 6.10 (d, *J* = 7.6 Hz, 1H), 5.51 (d, *J* = 7.4 Hz, 1H), 5.33 (s, 1H), 4.92 (d, *J* = 7.9 Hz, 1H), 4.87 (s, 1H), 4.78 (d, *J* = 6.8 Hz, 1H), 4.71 (s, 1H), 4.28 (d, *J* = 8.5 Hz, 1H), 4.22 (t, *J* = 6.8 Hz, 2H), 3.73 (d, *J* = 7.4 Hz, 1H), 3.44 (s, 3H), 2.55 (ddd, *J* = 15.8, 9.6, 6.5 Hz, 1H), 2.43 (s, 3H), 1.91 – 1.79 (m, 4H), 1.73 (s, 3H), 1.38 (s, 9H), 1.30 (d, *J* = 2.5 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 205.25, 170.66, 164.75, 151.96, 136.44, 135.77, 134.17, 129.95, 128.98, 128.17, 127.99, 126.66, 88.11, 84.13, 82.19, 80.74, 79.63, 76.07, 74.41, 71.66, 69.34, 60.46, 58.02, 57.36, 46.23, 41.77, 36.79, 28.25, 25.73, 22.54, 22.22, 14.51, 9.83.

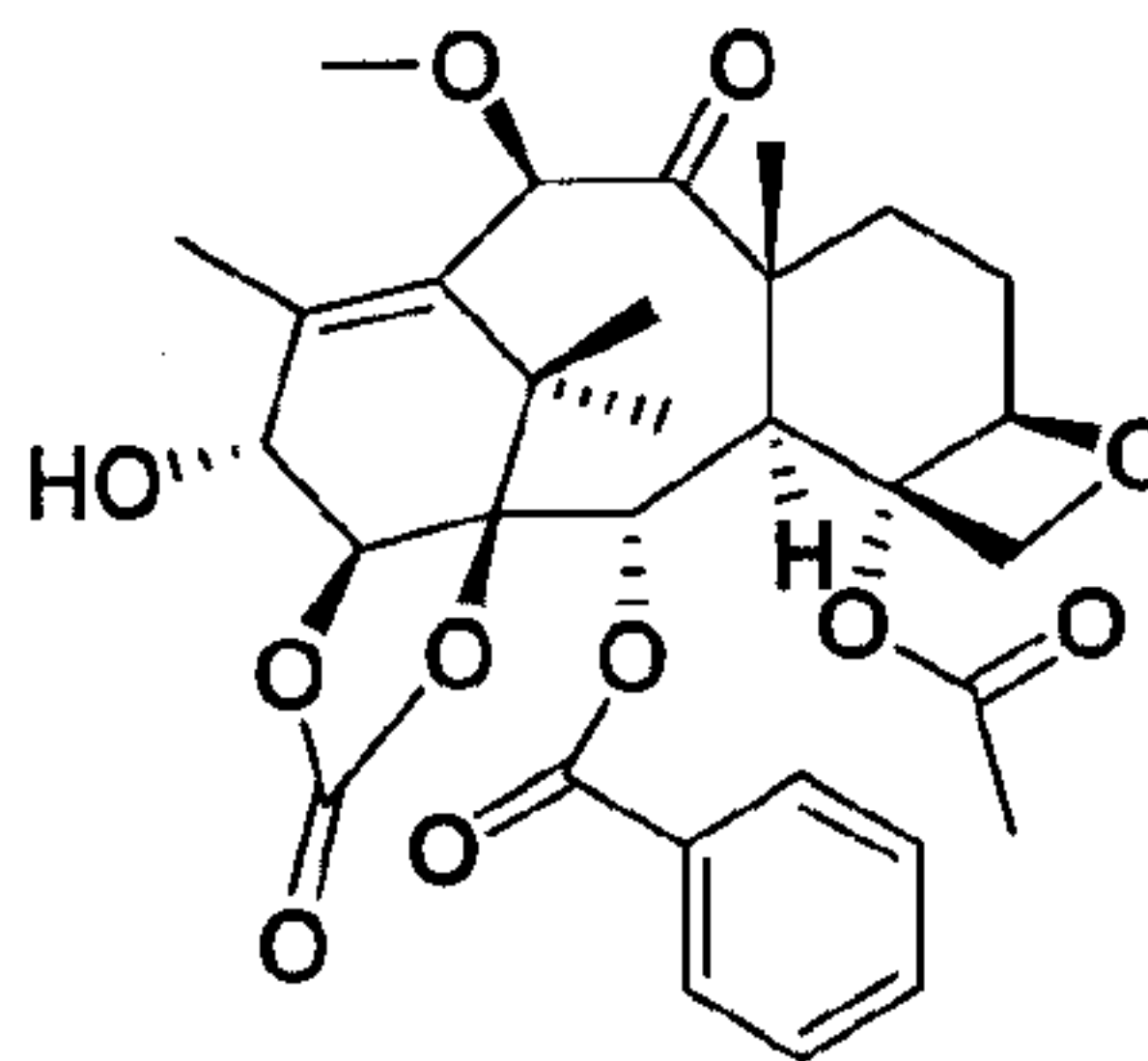
Example 7 Preparation of PCMI-07



1) Preparation of (4*S*,5*R*)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

The specific method was seen in **Example 1**.

2) Preparation of 10-methoxyl-7-dihydro-1,14-carbonate baccatin III



10-DAB (1 eq.) was used as raw material, dissolved in DMF and added successively with 2.5 equivalents of imidazole and 2.5 equivalents of triethyl chlorosilane. By post-treatment,

the crude compound **7** was given.

The compound **7** was dissolved in dichloromethane which was used as the solvent, into which 2 equivalents of pyridine was added at 0°C. Successively, the reaction liquid was added dropwise with 2 equivalents of *p*-toluenesulfonyl chloride to react for 4 hours. By
 5 post-treatment of purification by column chromatography, the compound **8** was given in a yield of 85-90%.

The compound **8** (1 eq.) was dissolved in anhydrous tetrahydrofuran to react with methyl magnesium bromide (2 eq.) at room temperature for 3 hours under the protection of nitrogen. After post-treatment, the crude compound **9** was obtained after dried.

10 The compound **9** (1 eq.) was dissolved in dry THF, into which 1.5 equivalents of tetrabutylammonium fluoride (which is in the form of a solution in THF) was added at room temperature. After 1 hour of reaction, the reaction was completed. By post-treatment of purification by column chromatography, the compound **14** was given in a yield of 92%.

The compound **14** (1 eq.) was dissolved in dry THF, into which 8 equivalents of N,N'-
 15 carbonyldiimidazole (CDI) was added at room temperature. After 2 hour of reaction, the reaction was completed. By post-treatment of purification by column chromatography, the compound **15** was obtained in a yield of 78%.

The compound **15** (1 eq.) was dissolved in the solution of dioxane/tetrahydrofuran (10:1). 0.2 Equivalents of azobisisobutyronitrile was added at 100°C as a catalyst to induce free
 20 radicals reaction. Afterward, the reaction liquid was added with 4 equivalents of *n*-butyl tin hydride (Bu₃SnH) to react for 1 hour, cooled at room temperature overnight. By purification by column chromatography, the compound **16** was given in a yield of 52%.

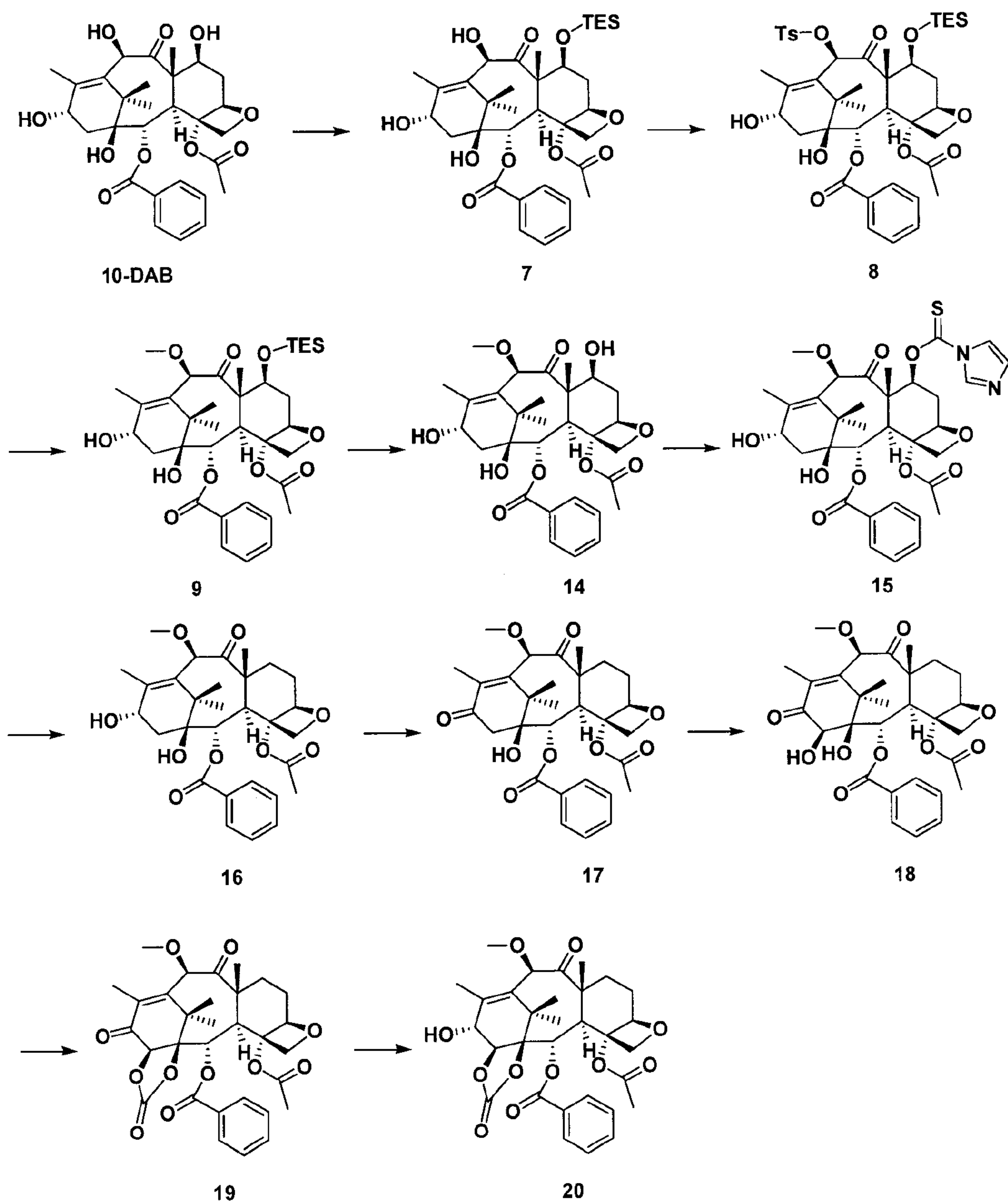
The compound **16** (1 eq.) was dissolved in acetone solution, into which 10 equivalents of manganese dioxide was added at room temperature to react for 4 hours. By post-treatment
 25 of purification by column chromatography, the compound **17** was given in a yield of 75%.

The compound **17** (1 eq.) was dissolved in dry THF/DMPU (4:1) solution, into which 1.2 equivalents of potassium *t*-butoxide was added at -70°C to react for 20min. The obtained reaction liquid was slowly added dropwise with 2 equivalents of N-(sulfonyl)oxaziridine to

react for 2 hours. By post-treatment of purification by column chromatography, the compound **18** was given in a yield of 75%.

The compound **18** (1 eq.) was reacted with 2 equivalents of N,N'-carbonyldiimidazole(CDI) in dry tetrahydrofuran to give the compound **19** in a yield of 95%.

- 5 The compound **19** (1 eq.) was dissolved in dry tetrahydrofuran, into which 0.2 equivalents of (R)-2-methyl oxazaborodine was added at room temperature as a catalyst, followed by addition of 5 equivalents of borane/THF solution to react for 8 hours. After completion of reaction, by post-treatment of purification by column chromatography, the compound **20** of 10-methoxyl-7-dihydro-1,14-carbonate baccatin III was obtained as the final product in a yield
10 of 80%.



3) Preparation of PCMI-07

The specific method was seen in Step 3) in **Example 1** and the purity of the final product was 95% or higher.

5 PCMI-07: mp: 226-227°C;

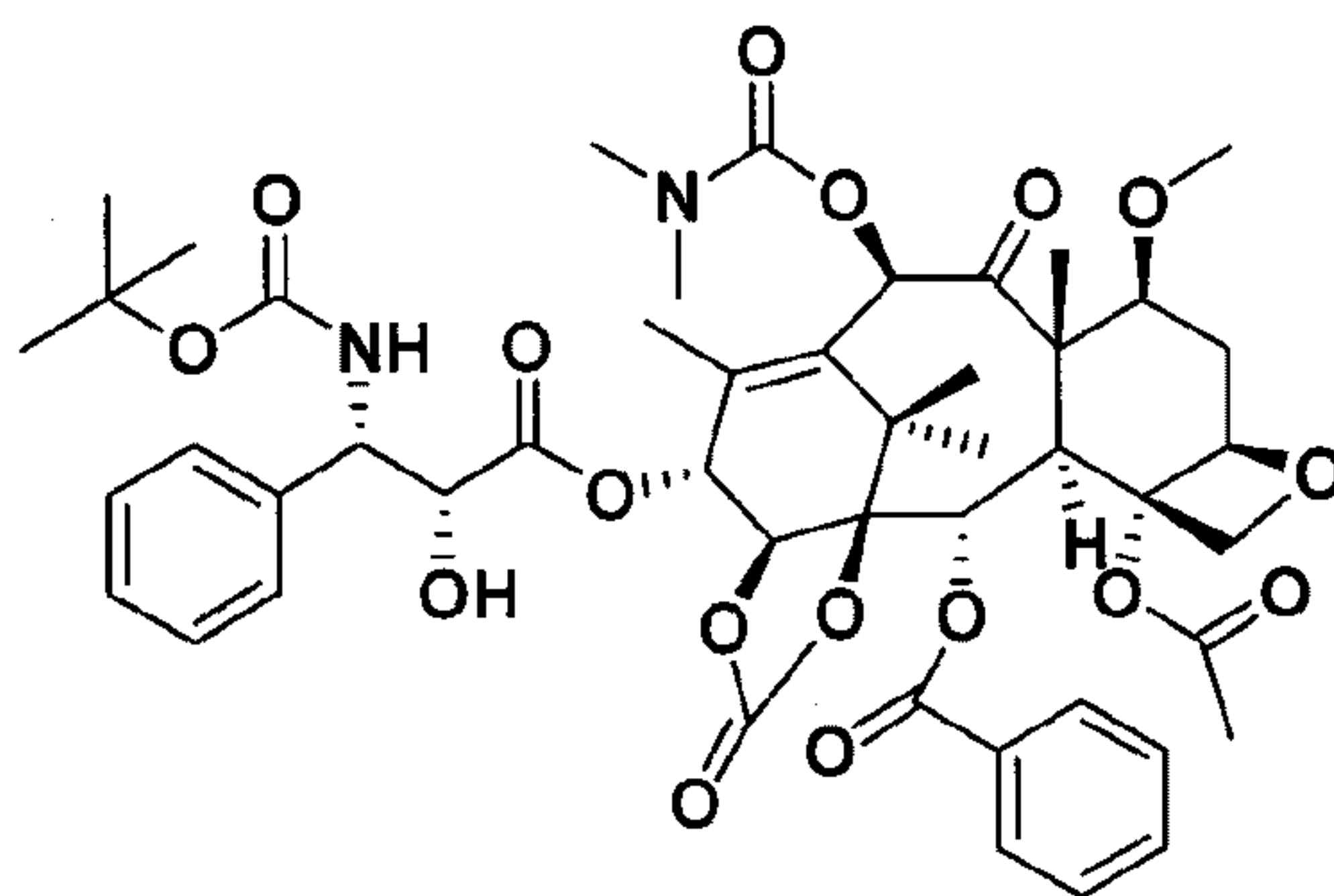
MS (m/z) ESI: 870.3 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 7.4 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.50 (t,

$J = 7.7$ Hz, 3H), 7.47 – 7.31 (m, 5H), 6.46 (d, $J = 6.3$ Hz, 1H), 6.09 (d, $J = 7.8$ Hz, 1H), 5.43 (d, $J = 9.0$ Hz, 1H), 5.35 (s, 1H), 4.90 (d, $J = 8.0$ Hz, 1H), 4.86 (s, 1H), 4.82 (d, $J = 7.0$ Hz, 1H), 4.70 (s, 1H), 4.28 (s, 2H), 3.66 (d, $J = 7.7$ Hz, 1H), 3.58 (s, 1H), 3.46 (s, 3H), 2.43 (s, 3H), 2.23 (dd, $J = 15.0, 6.1$ Hz, 1H), 2.04 – 1.93 (m, 2H), 1.89 (d, $J = 1.1$ Hz, 3H),
 5 1.80 (s, 3H), 1.59 (dd, $J = 11.9, 5.7$ Hz, 1H), 1.38 (s, 9H), 1.30 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 207.81, 171.18, 164.83, 151.95, 136.00, 134.05, 129.97, 129.01, 128.94, 128.19, 128.16, 126.59, 88.25, 84.31, 81.75, 81.02, 80.67, 79.59, 76.20, 74.43, 70.08, 57.20, 53.30, 41.52, 35.53, 31.93, 29.70, 28.23, 27.02, 25.35, 22.70, 22.10, 14.93, 14.31.

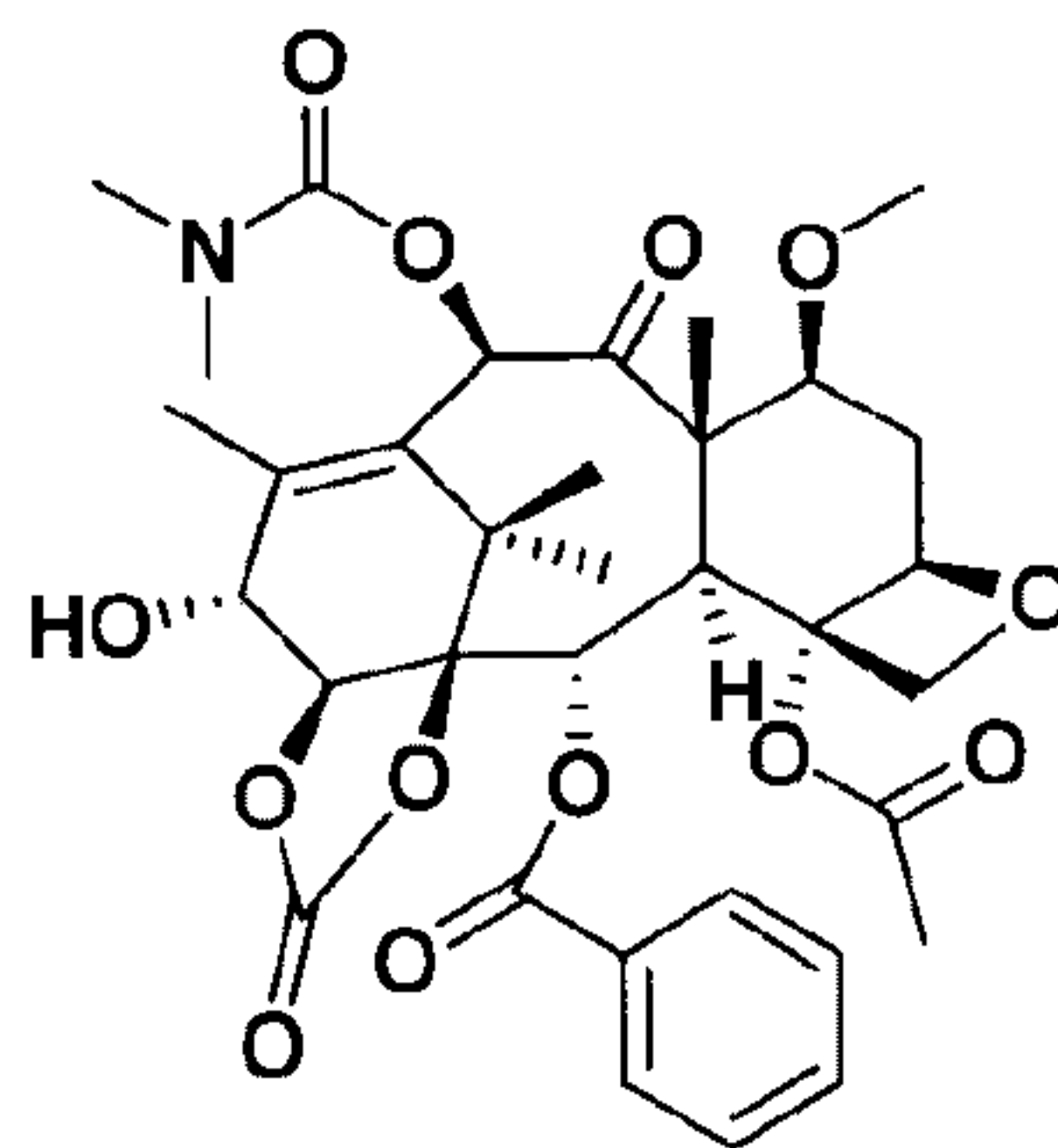
10 Example 8 Preparation of PCMI-08



1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 1**.

15 2) Preparation of 10-dimethylcarbamoyl-7-methoxyl-1,14-carbonate baccatin III



10-DAB (1 eq.) was used as raw material, dissolved in DMF and added successively with 2.5 equivalents of imidazole and 2.5 equivalents of triethyl chlorosilane. By post-treatment,

the crude compound **7** was given.

The compound **7** (1 eq.) was dissolved in dry THF which was used as the solvent, into which 1.5 equivalents LHMDs was added at 0°C. After 1 hour of reaction, 2 equivalents of dimethylcarbamoyl chloride was slowly added dropwise to the reaction liquid and reacted
 5 for 2 hours. By post-treatment of purification by column chromatography, the compound **21** was given in a yield of 87%.

The compound **21** (1 eq.) was dissolved in acetone solution, into which 10 equivalents of manganese dioxide was added at room temperature to react for 4 hours. By post-treatment of purification by column chromatography, the compound **22** was given in a yield of 75%.

10 The compound **22** (1 eq.) was dissolved in dry THF, into which 1.5 equivalents of tetrabutylammonium fluoride (which is in the form of a solution in THF) was added at room temperature. After 1 hour of reaction, the reaction was completed. By post-treatment of purification by column chromatography, the compound **23** was given in a yield of 90%.

The compound **23** was reacted with *p*-toluenesulfonyl chloride to give the compound **24**.

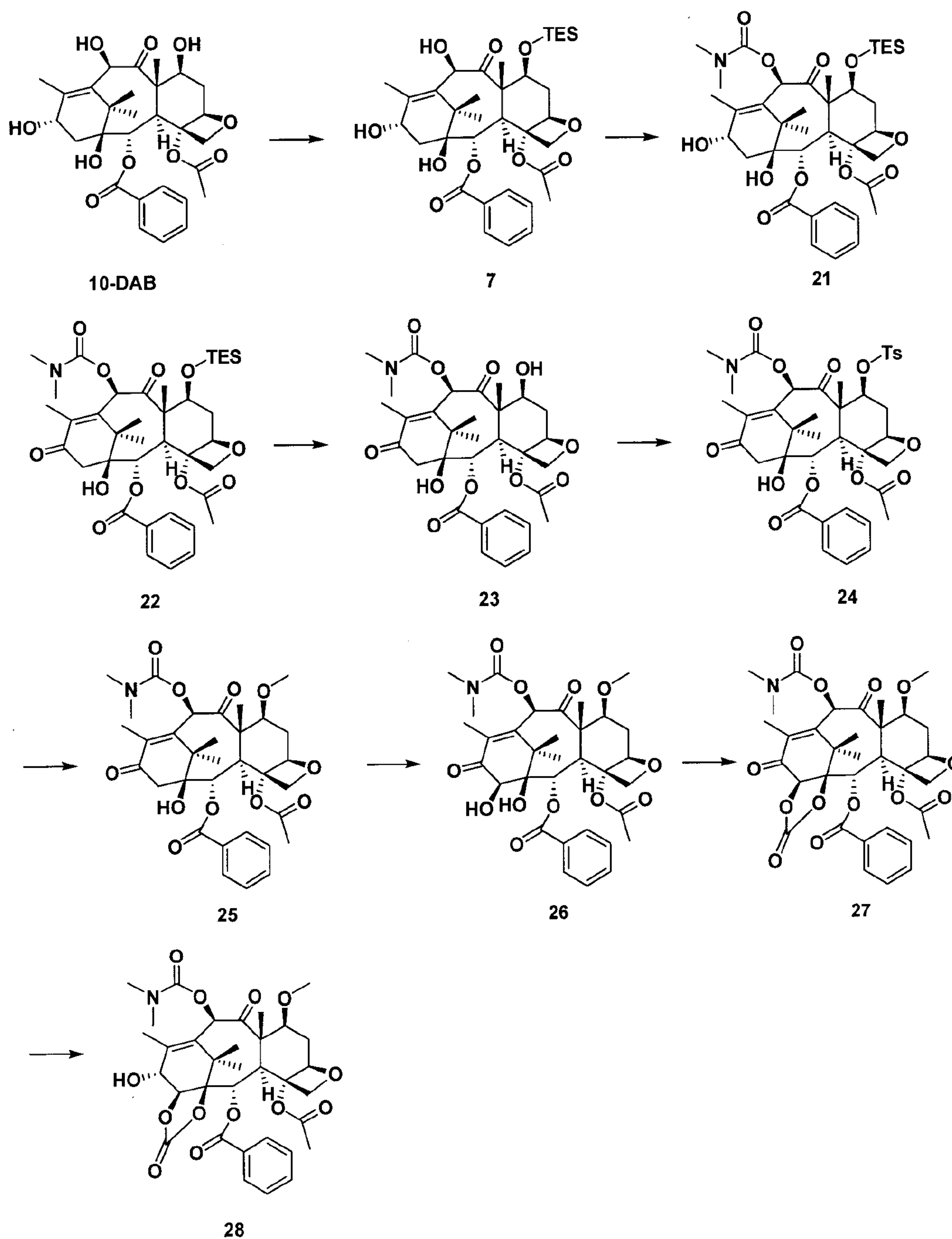
15 The compound **24** (1 eq.) was dissolved in anhydrous tetrahydrofuran to react with methyl magnesium bromide (2 eq.) at room temperature for 3 hours under the protection of nitrogen. After post-treatment, the crude compound **25** was obtained after dried.

The compound **25** (1 eq.) was dissolved in dry THF/DMPU (4:1) solution, into which 1.2 equivalents of potassium *t*-butoxide was added at -70°C to react for 20min. The obtained
 20 reaction liquid was slowly added dropwise with 2 equivalents of N-(sulfonyl)oxaziridine to react for 2 hours. By post-treatment of purification by column chromatography, the compound **26** was given in a yield of 75%.

The compound **26** (1 eq.) was reacted with 2 equivalents of N,N'-carbonyldiimidazole (CDI) in dry tetrahydrofuran to give the compound **27** in a yield of 95%.

25 The compound **27** (1 eq.) was dissolved in dry tetrahydrofuran, into which 0.2 equivalents of (R)-2-methyl oxazaborodine was added at room temperature as a catalyst, followed by addition of 5 equivalents of borane/THF solution to react for 8 hours. After completion of reaction, by post-treatment of purification by column chromatography, the compound **28** of

10-dimethylcarbamoyl-7-methoxy-1,14-carbonate baccatin III was obtained as the final product in a yield of 80%.



3) Preparation of PCMI-08

5 The specific method was seen in Step 3) in **Example 1** and the purity of the final product

was 95% or higher.

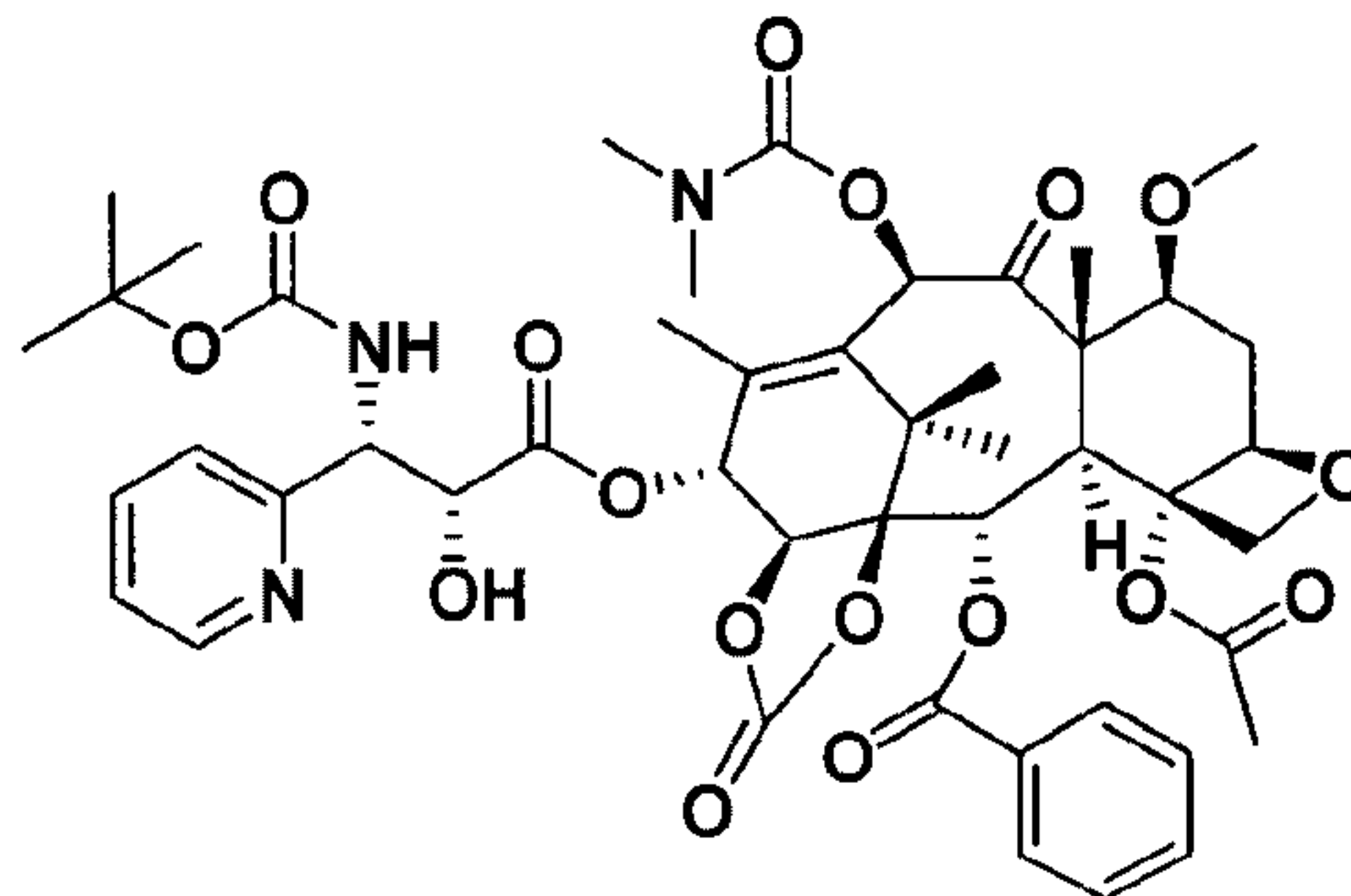
PCMI-08: mp: 246-247°C;

MS (m/z) ESI: 957.5 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.45 – 7.31 (m, 5H), 6.45 (d, *J* = 6.0 Hz, 1H), 6.39 (s, 1H), 6.11 (d, *J* = 7.4 Hz, 1H), 5.55 (d, *J* = 8.7 Hz, 1H), 5.35 (s, 1H), 4.96 (d, *J* = 8.2 Hz, 1H), 4.82 (d, *J* = 6.6 Hz, 1H), 4.71 (s, 1H), 4.29 (d, *J* = 8.5 Hz, 1H), 4.22 (d, *J* = 8.4 Hz, 1H), 3.86 (dd, *J* = 10.6, 6.5 Hz, 1H), 3.78 (d, *J* = 7.8 Hz, 1H), 3.35 (s, 3H), 3.07 (s, 3H), 2.98 (s, 3H), 2.72 (ddd, *J* = 14.6, 9.7, 6.5 Hz, 1H), 2.46 (s, 3H), 1.98 (d, *J* = 0.9 Hz, 3H), 1.85 – 1.74 (m, 4H), 1.40 (s, 9H), 1.36 (s, 3H), 1.32 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 202.12, 171.91, 171.24, 170.81, 164.68, 155.71, 154.81, 151.92, 138.16, 137.39, 134.64, 134.15, 129.93, 128.95, 128.12, 128.01, 126.63, 88.01, 84.02, 81.04, 80.60, 80.16, 79.68, 75.91, 75.00, 74.74, 74.34, 69.12, 57.81, 57.36, 46.68, 41.83, 36.81, 36.21, 32.12, 28.26, 25.87, 22.75, 22.62, 14.55, 10.39.

15 Example 9 Preparation of PCMI-09



1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-(2-pyridyl)-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 4**.

20 2) Preparation of 10-dimethylcarbamoyl-7-methoxyl-1,14-carbonate baccatin III

The specific method was seen in Step 2) in **Example 8**.

3) Preparation of PCMI-09

The specific method was seen in Step 3) in **Example 1** and the purity of the final product

was 95% or higher.

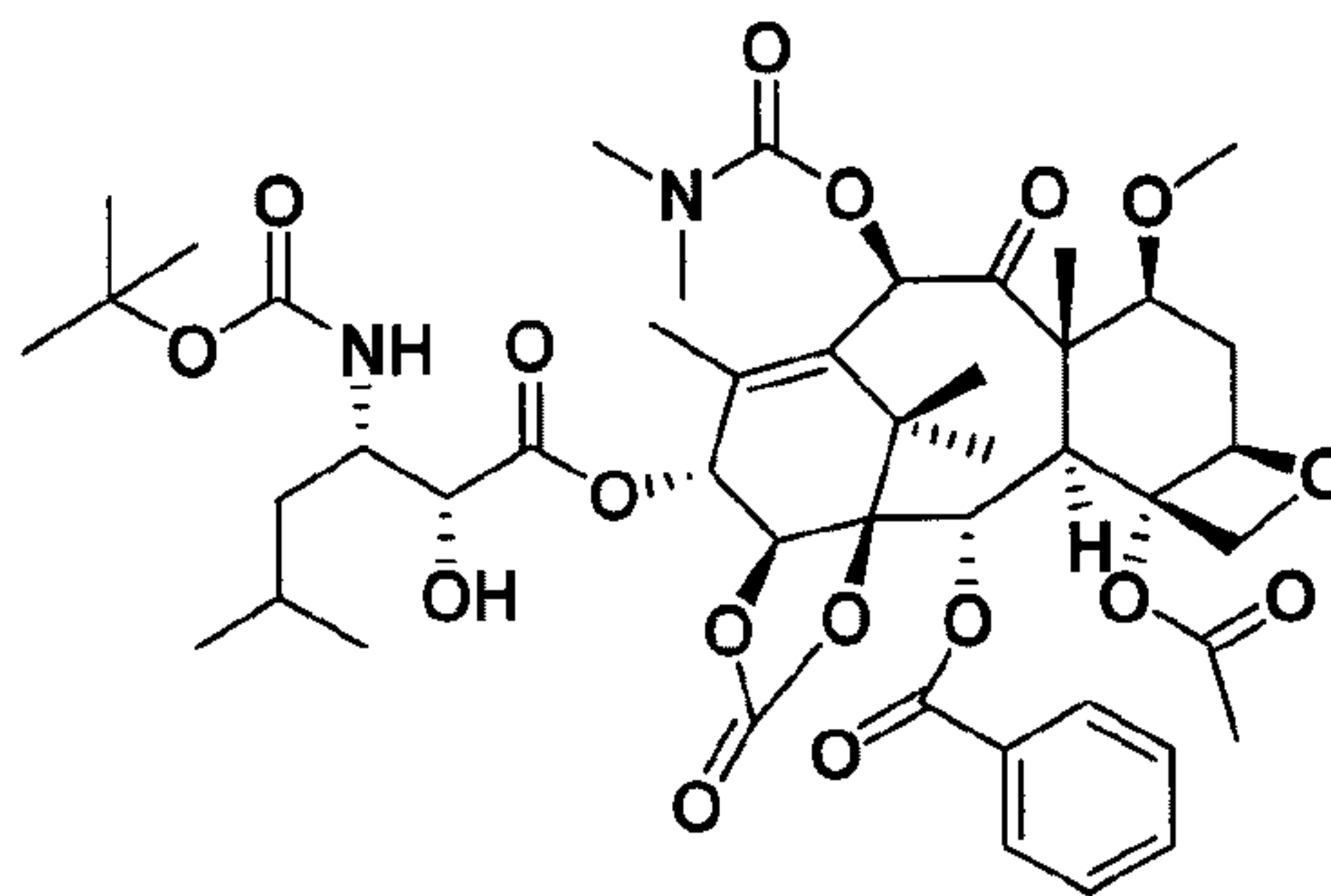
PCMI-09: mp: 241-242 °C;

MS (m/z) ESI: 958.3 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 6.48 (d, *J* = 6.3 Hz, 1H), 6.42 (s, 1H), 6.14 (d, *J* = 7.4 Hz, 1H), 4.95 (d, *J* = 8.3 Hz, 1H), 4.89 (d, *J* = 6.9 Hz, 1H), 4.77 (d, *J* = 9.0 Hz, 1H), 4.33 (dd, *J* = 8.9, 5.8 Hz, 2H), 4.27 (d, *J* = 8.4 Hz, 1H), 4.22 – 4.09 (m, 1H), 3.93 – 3.83 (m, 2H, H-7), 3.77 (d, *J* = 7.3 Hz, 1H), 3.41 (s, 3H), 2.88 (s, 6H), 2.60 – 2.41 (m, 4H), 2.02 (s, 3H), 1.96 (dd, *J* = 19.7, 7.7 Hz, 1H), 1.85 (s, 3H), 1.75 – 1.69 (m, 1H), 1.52 – 1.37 (m, 11H), 1.30 (s, 3H), 1.27 (s, 3H), 1.01 (t, *J* = 6.3 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 205.08, 172.96, 170.35, 164.81, 154.97, 152.01, 136.39, 134.05, 129.95, 128.94, 128.11, 88.09, 84.03, 80.96, 80.39, 80.16, 79.69, 75.89, 75.02, 74.64, 73.84, 69.17, 57.29, 57.07, 51.49, 45.88, 41.76, 40.57, 36.54, 35.86, 33.76, 29.67, 28.24, 25.57, 24.85, 23.24, 22.46, 22.08, 14.42, 10.90.

15 Example 10 Preparation of PCMI-10



- 1) Preparation of (4S,5R)-3-*t*-butoxycarbonyl-2-(4-methoxyphenyl)-4-isobutyl-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 5**.

- 20 2) Preparation of 10-dimethylcarbamoyl-7-methoxyl-1,14-carbonate baccatin III

The specific method was seen in Step 2) in **Example 8**.

- 3) Preparation of PCMI-10

The specific method was seen in Step 3) in **Example 1** and the purity of the final product

was 95% or higher.

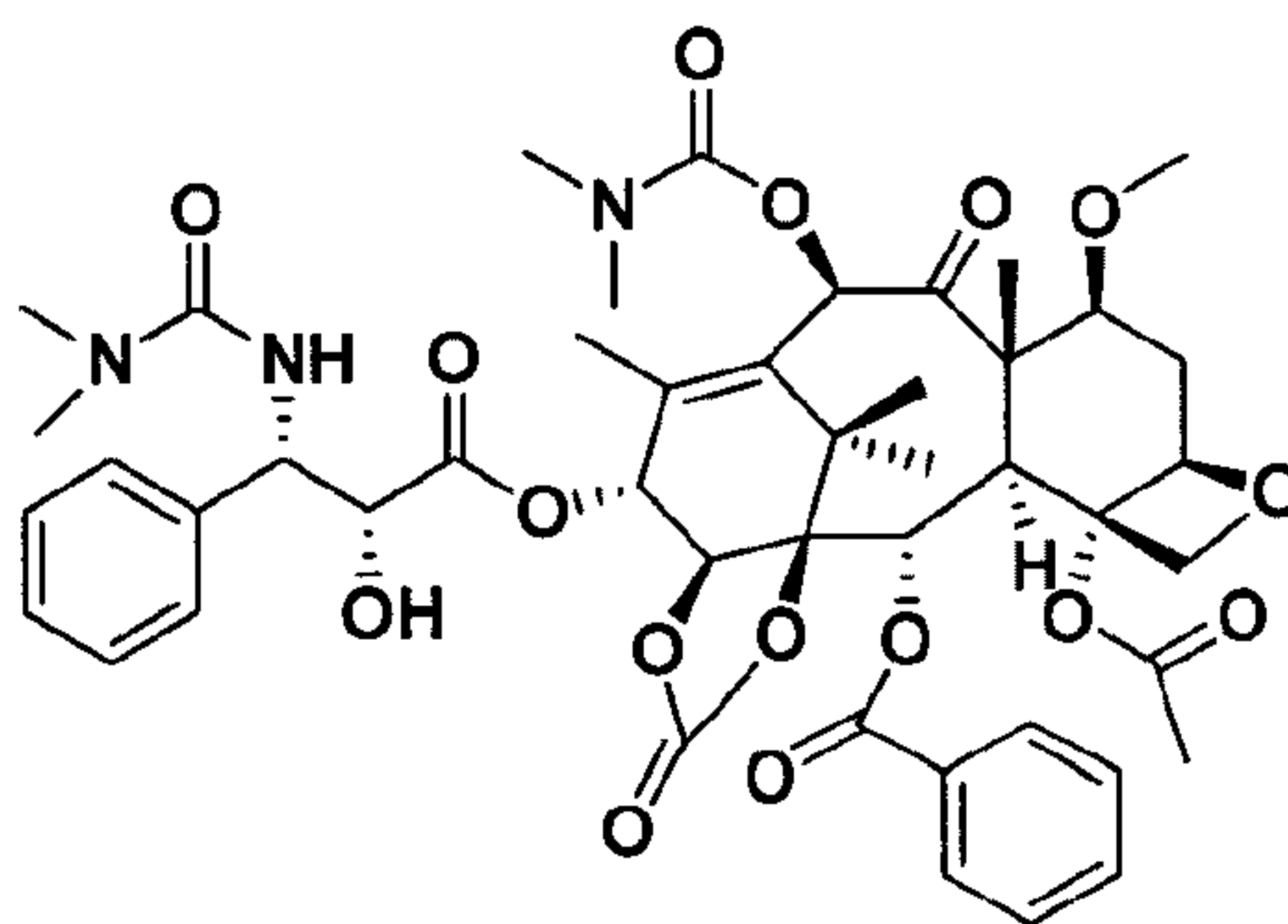
PCMI-10: mp: 236-237°C;

MS (m/z) ESI: 937.4 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 6.47 (d, *J* = 6.3 Hz, 1H), 6.41 (s, 1H), 6.13 (d, *J* = 7.4 Hz, 1H), 4.98 (d, *J* = 8.0 Hz, 1H), 4.89 (d, *J* = 6.8 Hz, 1H), 4.77 (d, *J* = 9.0 Hz, 1H), 4.37 – 4.32 (m, 1H), 4.30 (d, *J* = 8.5 Hz, 1H), 4.24 (d, *J* = 8.5 Hz, 1H), 4.17 – 4.06 (m, 1H), 4.04 (d, *J* = 6.2 Hz, 1H), 3.88 (dd, *J* = 10.6, 6.5 Hz, 1H), 3.77 (d, *J* = 7.3 Hz, 1H), 3.36 (s, 3H), 3.08 (s, 3H), 2.99 (s, 3H), 2.74 (ddd, *J* = 14.5, 9.7, 6.4 Hz, 1H), 2.52 (s, 3H), 2.04 (d, *J* = 1.2 Hz, 3H), 1.88 – 1.77 (m, 5H), 1.77 – 1.66 (m, 3H), 1.41 (s, 11H), 1.37 (s, 3H), 1.34 (s, 3H), 1.01 (t, *J* = 6.7 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 202.17, 172.86, 170.75, 164.73, 156.27, 154.81, 151.99, 137.55, 134.58, 134.12, 129.94, 128.96, 128.03, 88.09, 84.03, 80.96, 80.39, 80.16, 79.69, 75.89, 75.02, 74.64, 73.84, 69.17, 57.83, 57.35, 51.68, 46.68, 41.86, 40.30, 36.81, 36.21, 32.10, 29.70, 28.24, 25.87, 24.87, 23.23, 22.56, 22.20, 14.65, 10.41.

Example 11 Preparation of PCMI-11



1) Preparation of (4S,5R)-3-dimethylcarbamoyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

20 The specific method was seen in Step 1) in **Example 3**.

2) Preparation of 10-dimethylcarbamoyl-7-methoxyl-1,14-carbonate baccatin III

The specific method was seen in Step 2) in **Example 8**.

3) Preparation of PCMI-11

The specific method was seen in Step 3) in **Example 1** and the purity of the final product was 95% or higher.

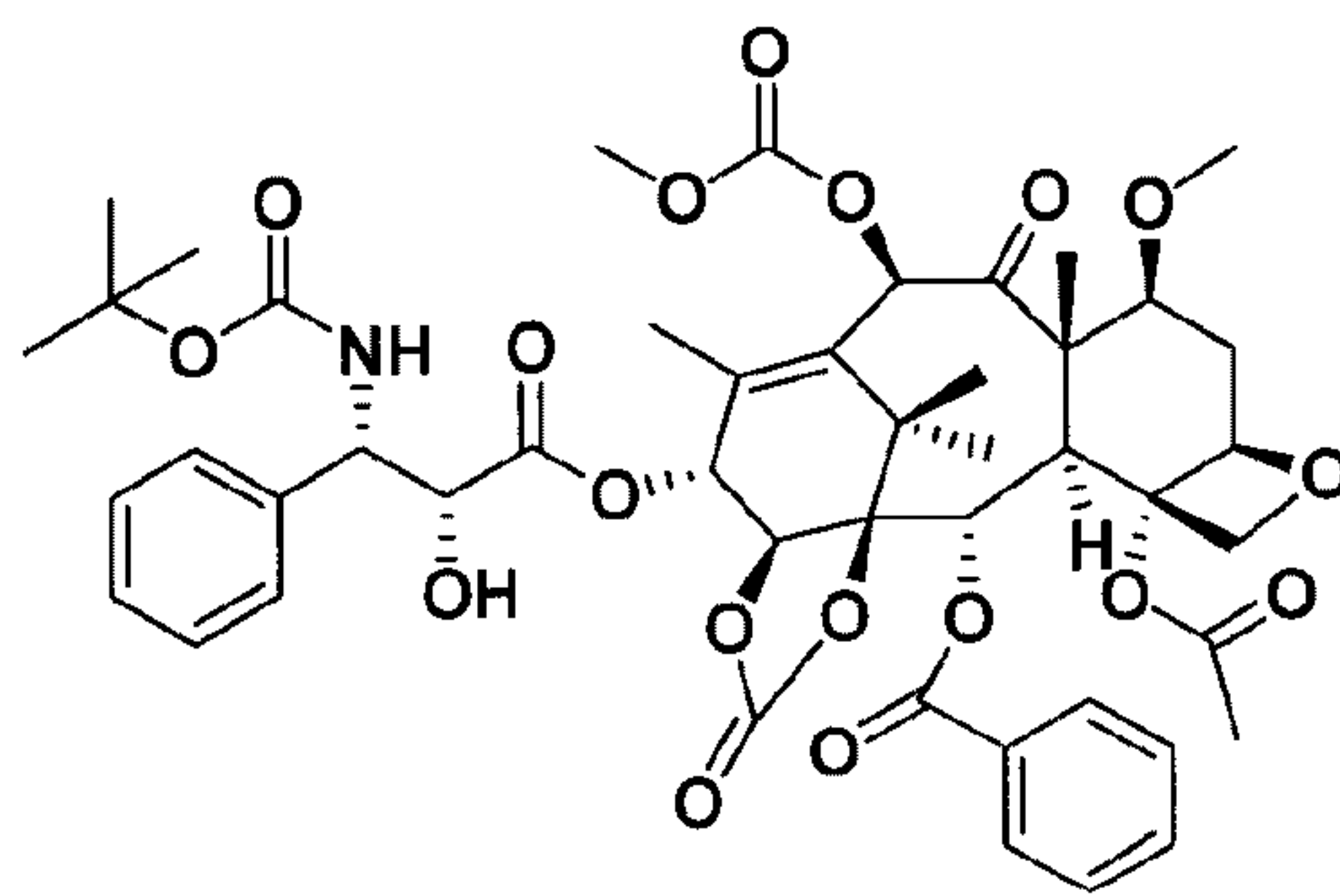
PCMI-11: mp: 241-242°C;

MS (m/z) ESI: 928.5 (M+Na)⁺;

5 ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 7.3 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 6.08 (d, *J* = 7.2 Hz, 1H), 5.49 (dd, *J* = 10.7, 7.2 Hz, 1H), 5.23 (s, 1H), 5.04 (t, 1H), 4.97 (d, *J* = 8.3 Hz, 1H), 4.80 (d, *J* = 5.8 Hz, 1H), 4.32 (d, *J* = 8.4 Hz, 1H), 4.22 (d, *J* = 8.4 Hz, 1H), 3.87 (d, *J* = 7.2 Hz, 1H), 3.67 (d, *J* = 5.3 Hz, 1H), 3.40 (s, 3H), 2.87 (s, 6H), 2.54 (m, *J* = 14.5, 9.5, 7.3 Hz, 1H), 2.31 (s, 3H), 2.17 (s, 3H), 1.92 (ddd, *J* = 14.2, 8.1, 2.6 Hz, 1H), 1.81 (s, 3H), 1.24 (s, 3H), 1.14 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 205.73 , 171.28, 170.21, 164.84, 155.01 , 152.98 , 141.50 , 134.17, 133.99 , 129.83 , 128.91, 128.14 , 88.54 , 84.21, 83.86, 82.88, 80.06, 75.99, 72.28, 71.79 , 69.45, 57.11, 57.00, 46.25, 41.32 , 36.53, 35.89 , 33.73 , 25.62, 22.21, 21.33, 14.91, 10.85.

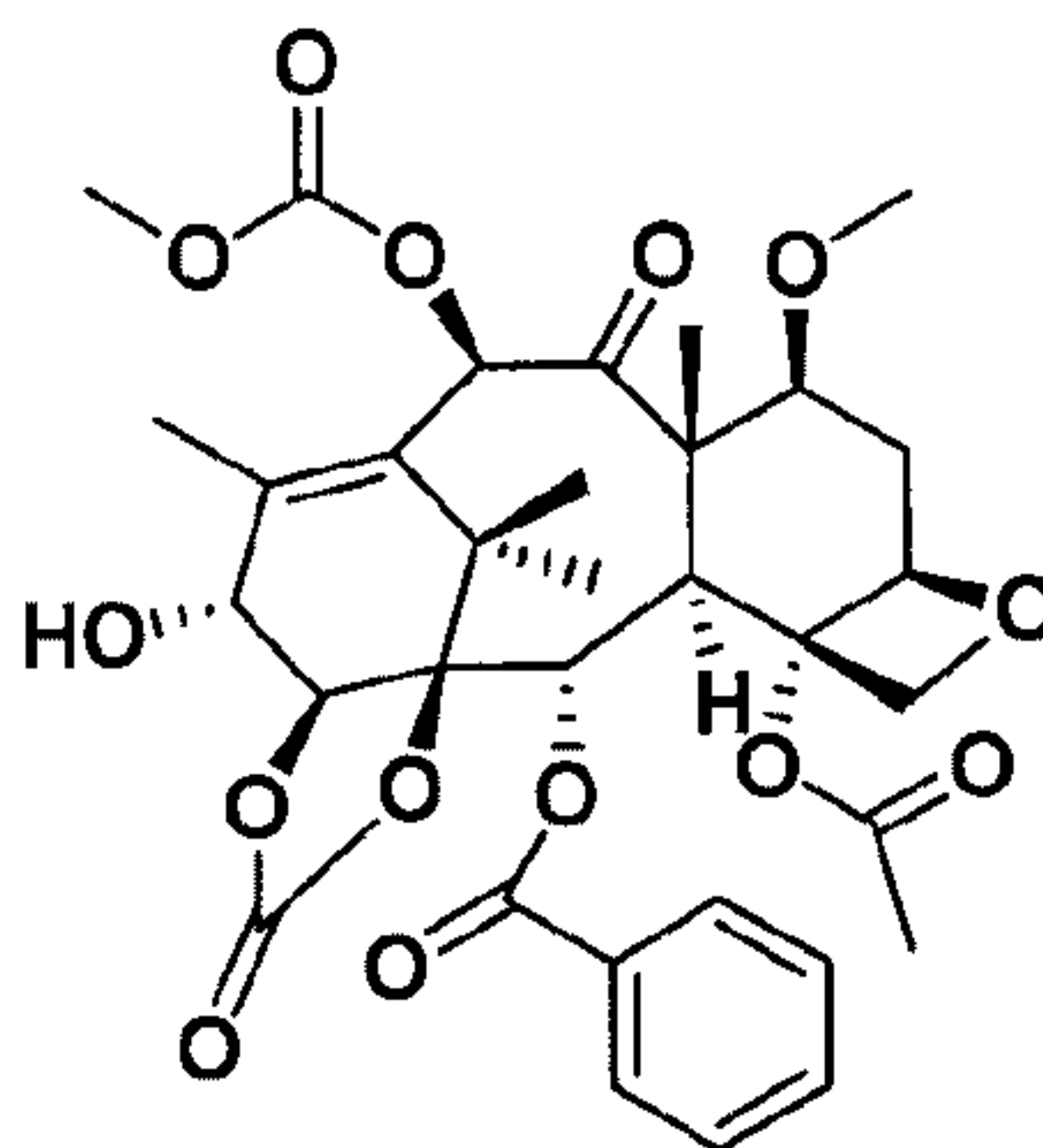
15 **Example 12 Preparation of PCMI-12**



1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 1**.

20 2) Preparation of 10-methoxyl formyl-7-methoxyl-1,14-carbonate baccatin III



10-DAB (1 eq.) was used as raw material, dissolved in DMF and added successively with 2.5 equivalents of imidazole and 2.5 equivalents of triethyl chlorosilane. By post-treatment, the crude compound **7** was given.

- 5 The compound **7** (1 eq.) was dissolved in dry THF which was used as the solvent, into which 1.5 equivalents LHMDs was added at 0°C. After 1 hour of reaction, 2 equivalents of methoxyl formyl chloride was slowly added dropwise to the reaction liquid and reacted for 2 hours. By post-treatment of purification by column chromatography, the compound **29** was given in a yield of 62%.
- 10 The compound **29** (1 eq.) was dissolved in acetone solution, into which 10 equivalents of manganese dioxide was added at room temperature to react for 4 hours. By post-treatment of purification by column chromatography, the compound **30** was given in a yield of 75%.

The compound **30** (1 eq.) was dissolved in dry THF, into which 1.5 equivalents of tetrabutylammonium fluoride (which is in the form of a solution in THF) was added at room temperature. After 1 hour of reaction, the reaction was completed. By post-treatment of purification by column chromatography, the compound **31** was given in a yield of 90%.

The compound **31** was reacted with *p*-toluenesulfonyl chloride to give the compound **32**.

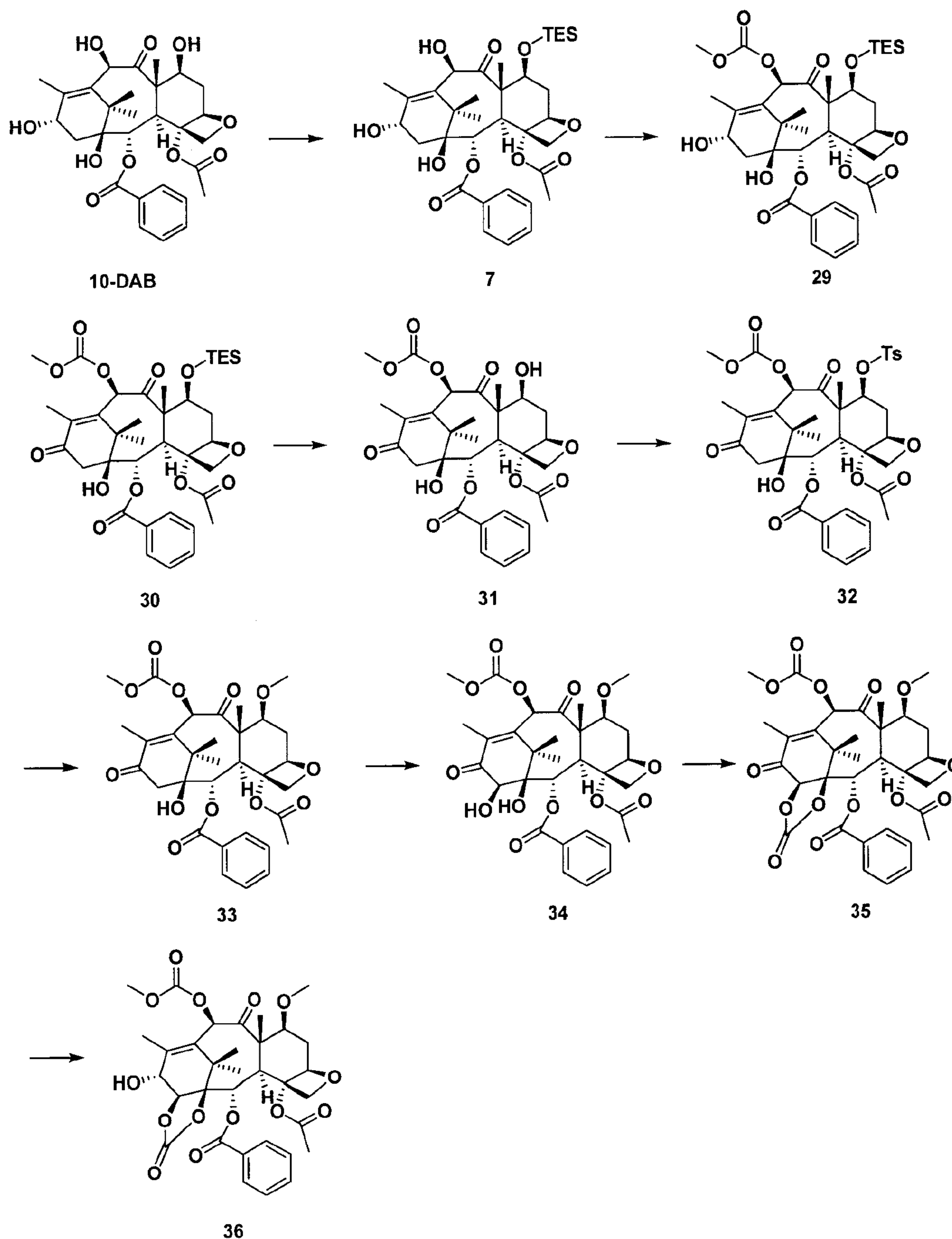
The compound **32** (1 eq.) was dissolved in anhydrous tetrahydrofuran to react with methyl magnesium bromide (2 eq.) at room temperature for 3 hours under the protection of nitrogen. After post-treatment, the crude compound **33** was obtained after dried.

The compound **33** (1 eq.) was dissolved in dry THF/DMPU (4:1) solution, into which 1.2 equivalents of potassium *t*-butoxide was added at -70°C to react for 20min. The obtained reaction liquid was slowly added dropwise with 2 equivalents of N-(sulfonyl)oxaziridine to

react for 2 hours. By post-treatment of purification by column chromatography, the compound **34** was given in a yield of 75%.

The compound **34** (1 eq.) was reacted with 2 equivalents of N,N'-carbonyldiimidazole (CDI) in dry tetrahydrofuran to give the compound **35** in a yield of 95%.

- 5 The compound **35** (1 eq.) was dissolved in dry tetrahydrofuran, into which 0.2 equivalents of (R)-2-methyl oxazaborodine was added at room temperature as a catalyst, followed by addition of 5 equivalents of borane/THF solution to react for 8 hours. After completion of reaction, by post-treatment of purification by column chromatography, the compound **36** of 10-methoxyl formyl-7-methoxy-1,14-carbonate baccatin III was obtained as the final product in
10 a yield of 80%.



3) Preparation of PCMI-12

The specific method was seen in Step 3) in **Example 1** and the purity of the final product was 95% or higher.

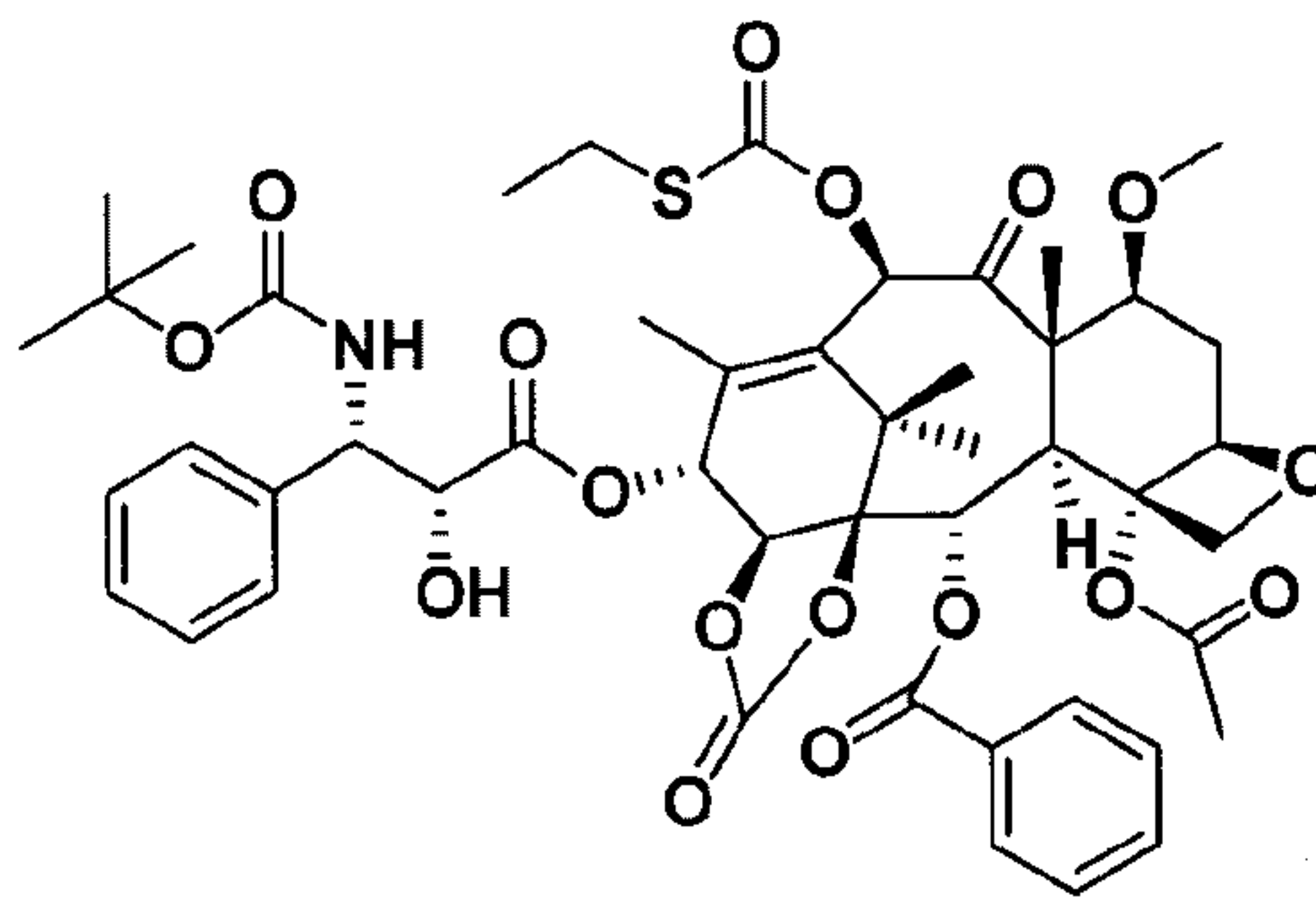
5 PCMI-12: mp: 231-232°C;

MS (m/z) ESI: 944.4 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.45 – 7.30 (m, 5H), 6.44 (d, *J* = 6.1 Hz, 1H, H-13), 6.15 (s, 1H, H-10), 6.09 (d, *J* = 7.5 Hz, 1H, H-2), 5.47 (d, *J* = 9.0 Hz, 1H, NH-3'), 5.33 (s, 1H, H-3'), 4.94 (d, *J* = 7.9 Hz, 1H, H-5), 4.78 (d, *J* = 6.7 Hz, 1H, H-14), 4.71 (s, 1H, H-2'), 4.28 (d, *J* = 8.4 Hz, 1H, H-20), 4.21 (d, *J* = 8.3 Hz, 1H, H-20), 3.92 – 3.80 (m, 4H, OH-2'), 3.70 (d, *J* = 7.4 Hz, 1H, H-3), 3.35 (s, 3H), 2.72 (ddd, *J* = 14.5, 9.8, 6.4 Hz, 1H, H-6), 2.44 (s, 3H), 1.94 (d, *J* = 1.1 Hz, 3H), 1.86 – 1.73 (m, 4H, H-6), 1.40 (s, 9H), 1.32 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 200.44, 171.89, 170.88, 164.62, 154.60, 151.81, 138.29, 134.17, 133.84, 129.94, 129.03, 128.95, 128.23, 127.97, 126.65, 87.92, 83.94, 81.04, 80.72, 80.10, 79.56, 75.91, 74.74, 74.40, 69.00, 57.67, 57.38, 55.41, 46.62, 41.79, 32.06, 29.70, 28.25, 25.74, 22.62, 22.35, 14.71, 10.40.

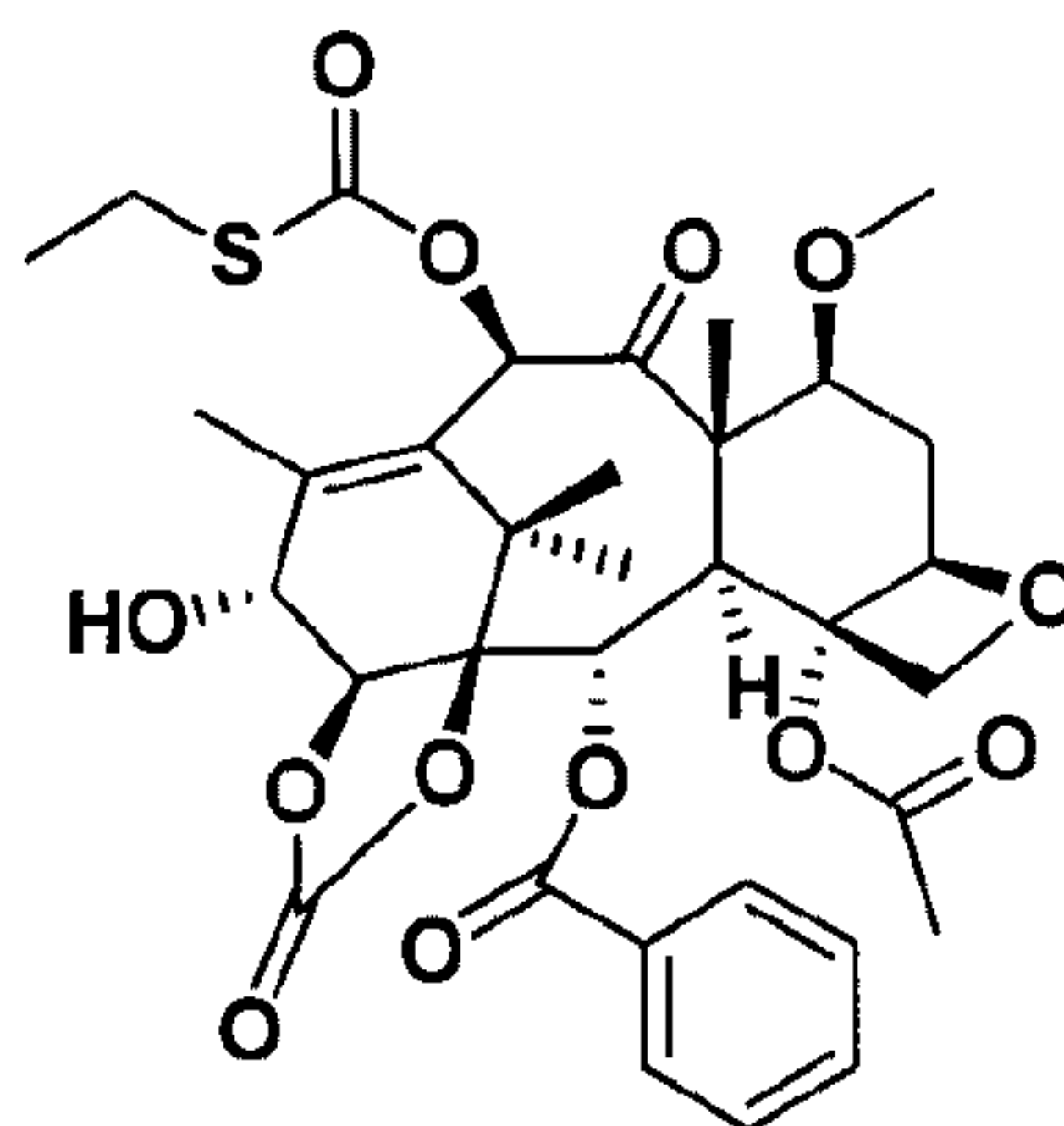
Example 13 Preparation of PCMI-13



- 1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 1**.

- 2) Preparation of 10-ethylthioformyl-7-methoxyl-1,14-carbonate baccatin III



10-DAB (1 eq.) was used as raw material, dissolved in DMF and added successively with 2.5 equivalents of imidazole and 2.5 equivalents of triethyl chlorosilane. By post-treatment, the crude compound **7** was given.

5 The compound **7** (1 eq.) was dissolved in dry THF which was used as the solvent and firstly reacted with 2 equivalents of N,N'-carbonyldiimidazole at room temperature for 2 hours. Then the reaction liquid was added with 2 equivalents of ethanethiol. After 4 hours of reaction, by post-treatment of purification by column chromatography, the compound **37** was given in a yield of 72%.

10 The compound **37** (1 eq.) was dissolved in acetone solution, into which 10 equivalents of manganese dioxide was added at room temperature to react for 4 hours. By post-treatment of purification by column chromatography, the compound **38** was given in a yield of 86%.

The compound **38** (1 eq.) was dissolved in dry THF, into which 1.5 equivalents of tetrabutylammonium fluoride (which is in the form of a solution in THF) was added at room
15 temperature. After 1 hour of reaction, the reaction was completed. By post-treatment of purification by column chromatography, the compound **39** was given in a yield of 90%.

The compound **39** was reacted with *p*-toluenesulfonyl chloride to give the compound **40**.

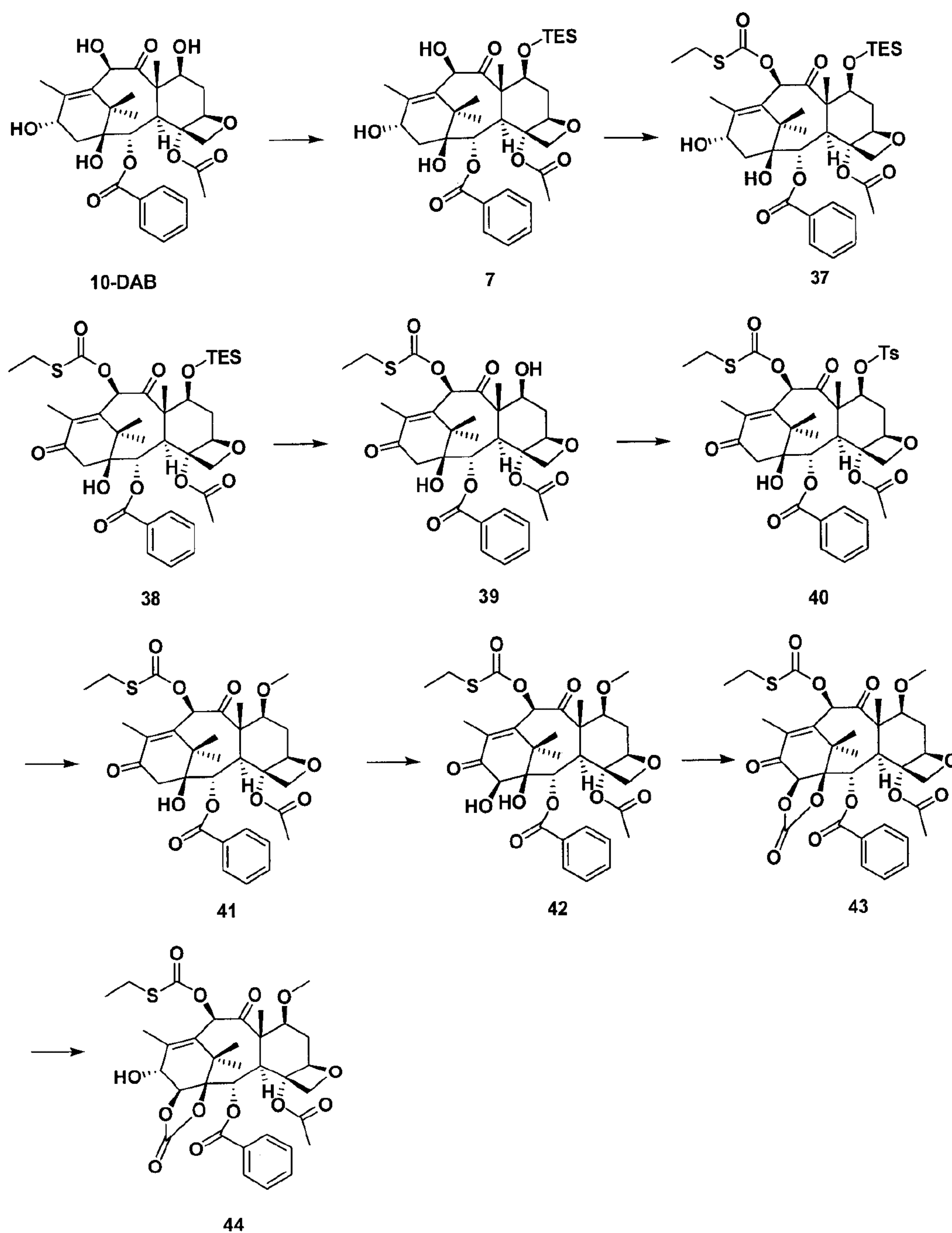
The compound **40** (1 eq.) was dissolved in anhydrous tetrahydrofuran to react with methyl magnesium bromide (2 eq.) at room temperature for 3 hours under the protection of
20 nitrogen. After post-treatment, the crude compound **41** was obtained after dried.

The compound **41** (1 eq.) was dissolved in dry THF/DMPU (4:1) solution, into which 1.2 equivalents of potassium *t*-butoxide was added at -70°C to react for 20min. The obtained reaction liquid was slowly added dropwise with 2 equivalents of N-(sulfonyl)oxaziridine to

react for 2 hours. By post-treatment of purification by column chromatography, the compound **42** was given in a yield of 75%.

The compound **42** (1 eq.) was reacted with 2 equivalents of N,N'-carbonyldiimidazole (CDI) in dry tetrahydrofuran to give the compound **43** in a yield of 95%.

- 5 The compound **43** (1 eq.) was dissolved in dry tetrahydrofuran, into which 0.2 equivalents of (R)-2-methyl oxazaborodine was added at room temperature as a catalyst, followed by addition of 5 equivalents of borane/THF solution to react for 8 hours. After completion of reaction, by post-treatment of purification by column chromatography, the compound **44** of 10-ethylthioformyl-7-methoxy-1,14-carbonate baccatin III was obtained as the final product in
10 a yield of 80%.



3) Preparation of PCMI-13

The specific method was seen in Step 3) in **Example 1** and the purity of the final product was 95% or higher.

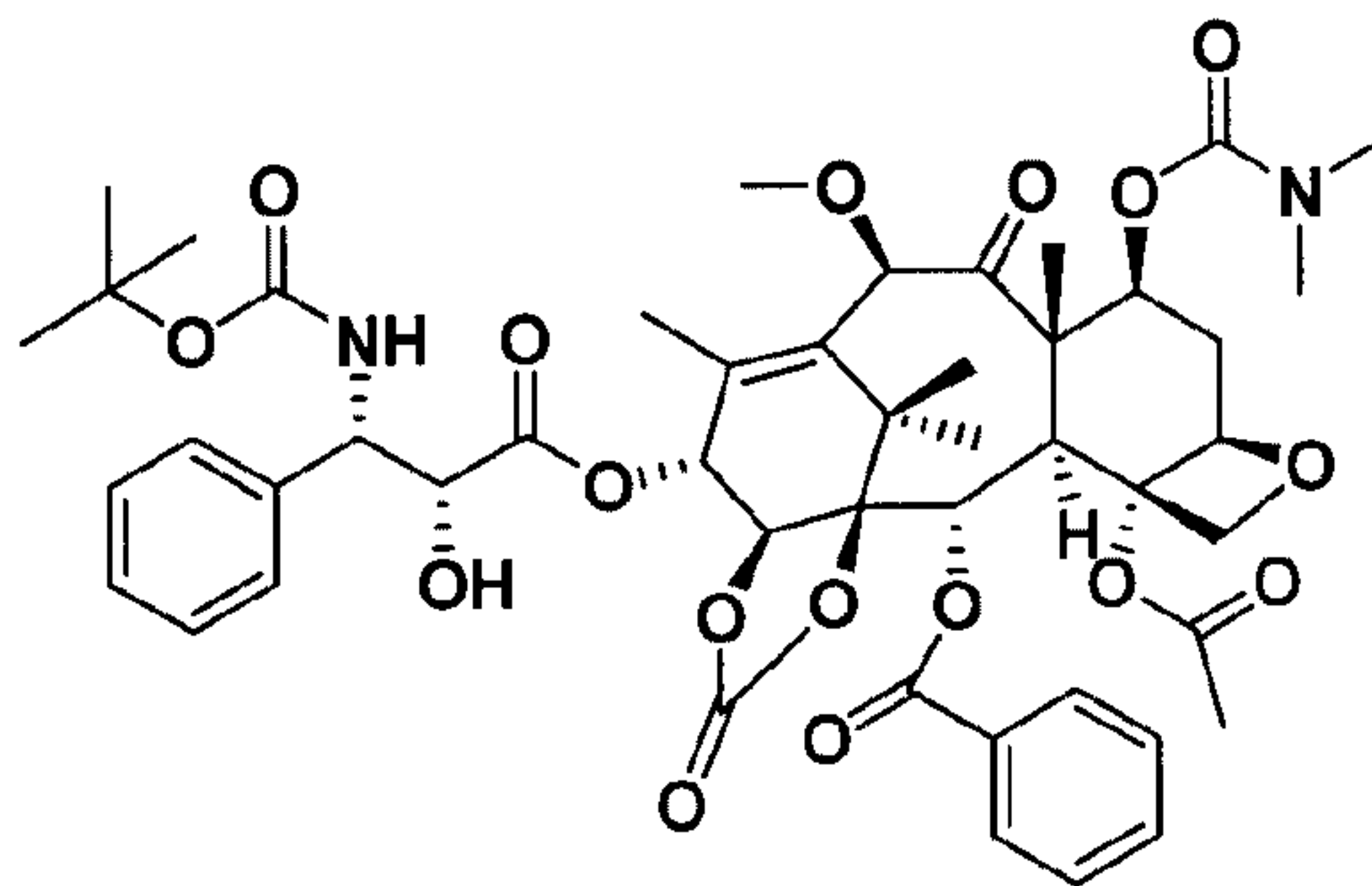
5 PCMI-13: mp: 215-216°C;

MS (m/z) ESI: 974.4 (M+Na)⁺;

¹H NMR (400 MHz, MeOD) δ 8.14 (d, J = 7.6 Hz, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.58 (t, J = 7.7 Hz, 2H), 7.44 – 7.36 (m, 4H), 7.34 – 7.27 (m, 1H), 6.39 (d, J = 10.7 Hz, 1H), 6.15 (t, J = 8.9 Hz, 1H), 5.87 (d, J = 6.3 Hz, 1H), 5.23 (d, J = 10.7 Hz, 1H), 5.15 (s, 1H),
 5 4.99 (d, J = 9.0 Hz, 1H), 4.89 (m, 1H), 4.56 (d, J = 2.3 Hz, 1H), 4.25 (d, J = 8.3 Hz, 1H), 4.19 (d, J = 8.3 Hz, 1H), 3.33 (s, 1H), 3.24 (d, J = 6.1 Hz, 1H), 2.77 – 2.62 (m, 1H), 2.34 (s, 3H), 2.22 (t, J = 9.2 Hz, 2H), 2.14 (s, 3H), 1.99 – 1.88 (m, 4H), 1.78 (s, 3H), 1.66 (s, 3H), 1.39 (s, 9H), 1.27 (s, 3H).

¹³C NMR (101 MHz, MeOD) δ 173.20, 171.57, 170.61, 170.09, 166.07, 156.40, 146.86,
 10 141.17, 139.00, 133.34, 129.90, 129.68, 128.29, 127.40, 126.90, 84.25, 83.21, 80.84, 79.21, 79.01, 77.19, 75.68, 73.67, 73.54, 71.10, 70.96, 60.15, 56.99, 45.14, 42.88, 38.23, 34.89, 33.87, 33.37, 27.33, 26.98, 25.37, 24.68, 22.31, 21.85, 19.53, 13.59, 13.12, 12.31.

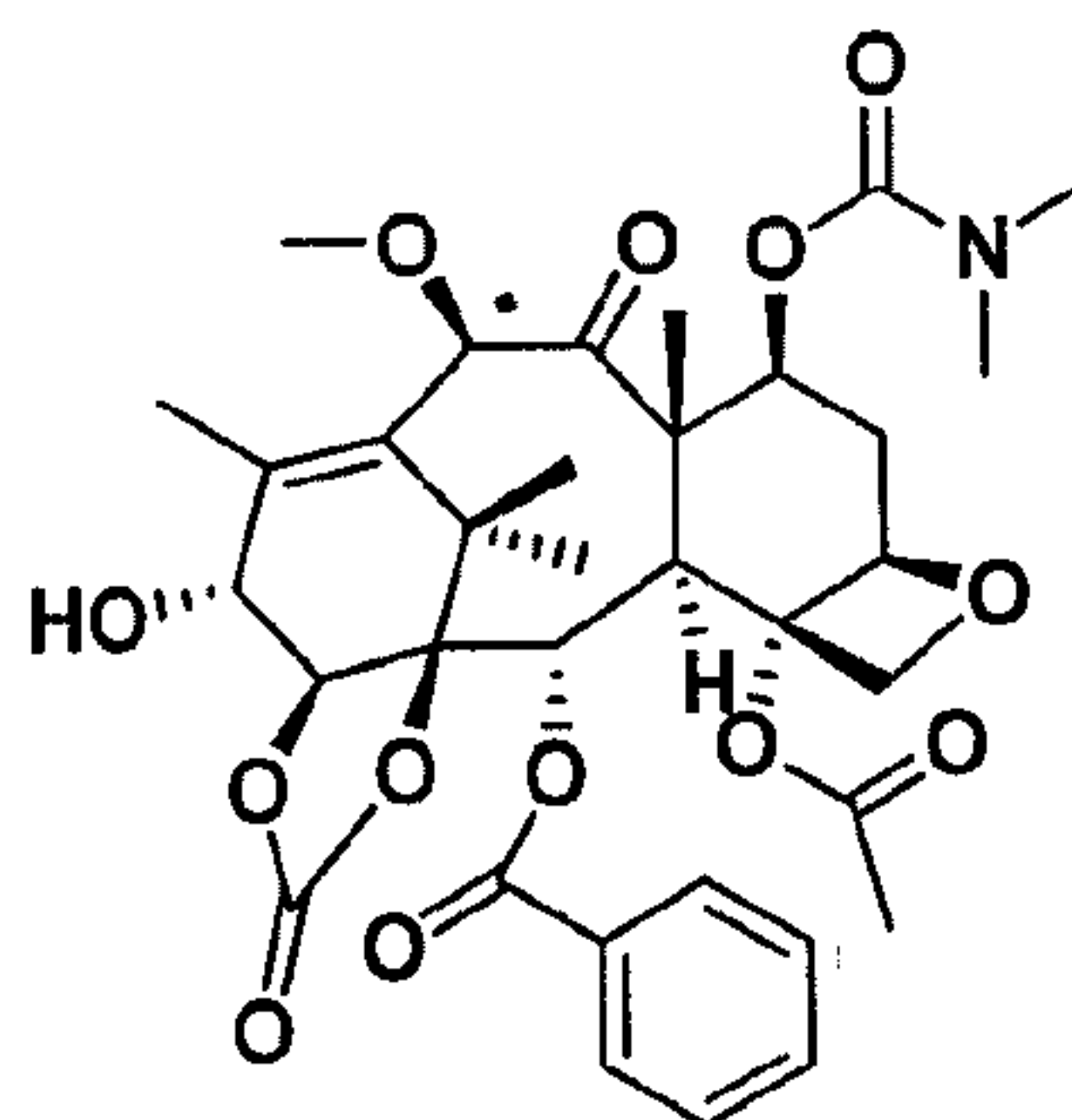
Example 14 Preparation of PCMI-14



- 15 1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 1**.

- 2) Preparation of 7-dimethylcarbamoyl-10-methoxyl-1,14-carbonate baccatin III



10-DAB (1 eq.) was used as raw material, dissolved in DMF and added successively with 2.5 equivalents of imidazole and 2.5 equivalents of triethyl chlorosilane. By post-treatment, the crude compound 7 was given.

- 5 The compound 7 was dissolved in dichloromethane which was used as the solvent, into which 2 equivalents of pyridine was added at 0°C. Successively, the reaction liquid was added dropwise with 2 equivalents of *p*-toluenesulfonyl chloride. After 4 hours of reaction, by post-treatment of purification by column chromatography, the compound 8 was given in a yield of 85-90%.
- 10 The compound 8 (1 eq.) was dissolved in anhydrous tetrahydrofuran to react with methyl magnesium bromide (2 eq.) at room temperature for 3 hours under the protection of nitrogen. After post-treatment, the crude compound 9 was obtained after dried.

The compound 9 (1 eq.) was dissolved in acetone solution, into which 10 equivalents of manganese dioxide was added at room temperature to react for 4 hours. By post-treatment of purification by column chromatography, the compound 10 was given in a yield of 75%.

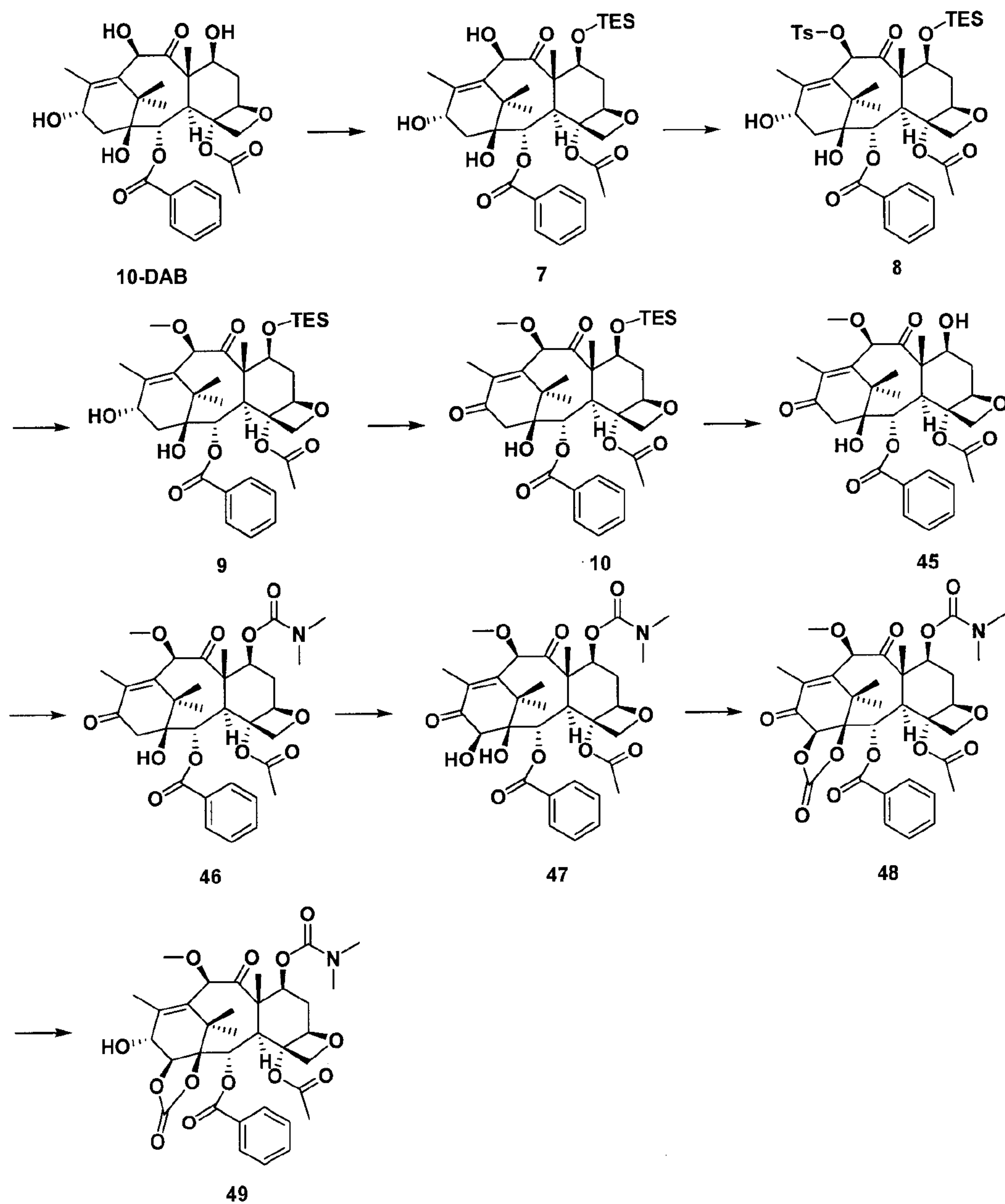
The compound 10 (1 eq.) was dissolved in dry THF, into which 1.5 equivalents of tetrabutylammonium fluoride (which is in the form of a solution in THF) was added at room temperature. After 1 hour of reaction, the reaction was completed. By post-treatment of purification by column chromatography, the compound 45 was given in a yield of 90%.

- 20 The compound 45 (1 eq.) was dissolved in dry THF which was used as the solvent, into which 1.5 equivalents LHMDS was added at 0°C. After 1 hour of reaction, 2 equivalents of dimethylcarbamoyl chloride was slowly added dropwise to the reaction liquid and reacted for 2 hours. By post-treatment of purification by column chromatography, the compound 46 was given in a yield of 87%.

The compound **46** (1 eq.) was dissolved in dry THF/DMPU (4:1) solution, into which 1.2 equivalents of potassium *t*-butoxide was added at -70°C to react for 20min. The obtained reaction liquid was slowly added dropwise with 2 equivalents of N-(sulfonyl)oxaziridine to react for 2 hours. By post-treatment of purification by column chromatography, the
5 compound **47** was given in a yield of 75%.

The compound **47** (1 eq.) was reacted with 2 equivalents of N,N'-carbonyldiimidazole (CDI) in dry tetrahydrofuran to give the compound **48** in a yield of 95%.

The compound **48** (1 eq.) was dissolved in dry tetrahydrofuran, into which 0.2 equivalents of (R)-2-methyl oxazaborodine was added at room temperature as a catalyst, followed by
10 addition of 5 equivalents of borane/THF solution to react for 8 hours. After completion of reaction, by post-treatment of purification by column chromatography, the compound **49** of 7-dimethylcarbamoyl-10-methoxyl-1,14-carbonate baccatin III was obtained as the final product in a yield of 80%.



3) Preparation of PCMI-14

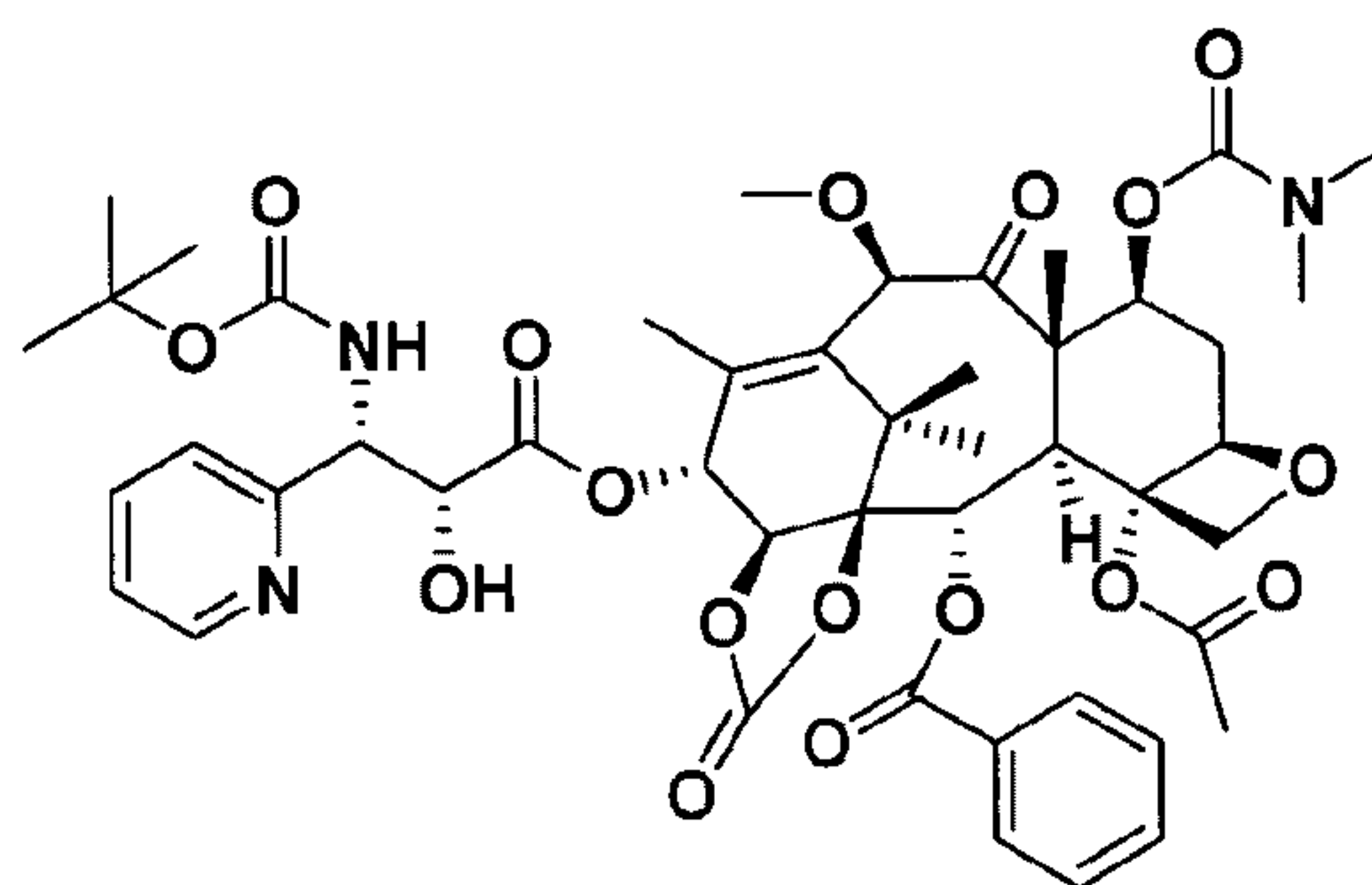
The specific method was seen in Step 3) in **Example 1** and the purity of the final product was 95% or higher.

- 5 PCMI-14: mp: 236-237°C;
 MS (m/z) ESI: 957.3 (M+Na)⁺;
 ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 7.3 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t,

$J = 7.7$ Hz, 2H), 7.47 – 7.31 (m, 5H), 6.48 (d, $J = 6.1$ Hz, 1H, H-13), 6.12 (d, $J = 7.4$ Hz, 1H, H-2), 5.54 (d, $J = 9.1$ Hz, 1H, NH-3'), 5.46 (dd, $J = 10.7, 7.2$ Hz, 1H, H-7), 5.38 (s, 1H, H-3'), 5.23 (s, 1H, H-10), 4.93 (d, $J = 8.0$ Hz, 1H, H-5), 4.82 (d, $J = 6.8$ Hz, 1H, H-14), 4.73 (d, $J = 4.1$ Hz, 1H, H-2'), 4.31 (d, $J = 8.4$ Hz, 1H, H-20), 4.26 (d, $J = 8.5$ Hz, 1H, H-20), 3.85 (d, $J = 7.4$ Hz, 1H, H-3), 3.68 (s, 1H, OH-2'), 3.40 (s, 3H), 2.88 (s, 6H), 2.59 – 2.49 (m, 1H, H-6), 2.00 – 1.94 (m, 4H, H-6), 1.84 (s, 3H), 1.40 (s, 9H), 1.30 (d, $J = 3.2$ Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ 205.07, 172.08, 170.45, 164.78, 154.96, 151.98, 136.29, 135.82, 134.15, 129.96, 128.97, 128.12, 128.02, 126.64, 88.12, 83.89, 82.34, 80.59, 80.41, 79.67, 76.06, 74.87, 74.27, 71.99, 69.33, 57.30, 57.07, 45.85, 41.72, 36.57, 35.89, 33.90, 33.76, 29.70, 28.25, 25.60, 25.55, 24.94, 22.56, 22.04, 14.38, 10.91.

Example 15 Preparation of PCMI-15



- 1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-(2-pyridyl)-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 4**.

- 2) Preparation of 7-dimethylcarbamoyl-10-methoxyl-1,14-carbonate baccatin III

The specific method was seen in Step 2) in **Example 14**.

- 3) Preparation of PCMI-15

- The specific method was seen in Step 3) in **Example 1** and the purity of the final product was 95% or higher.

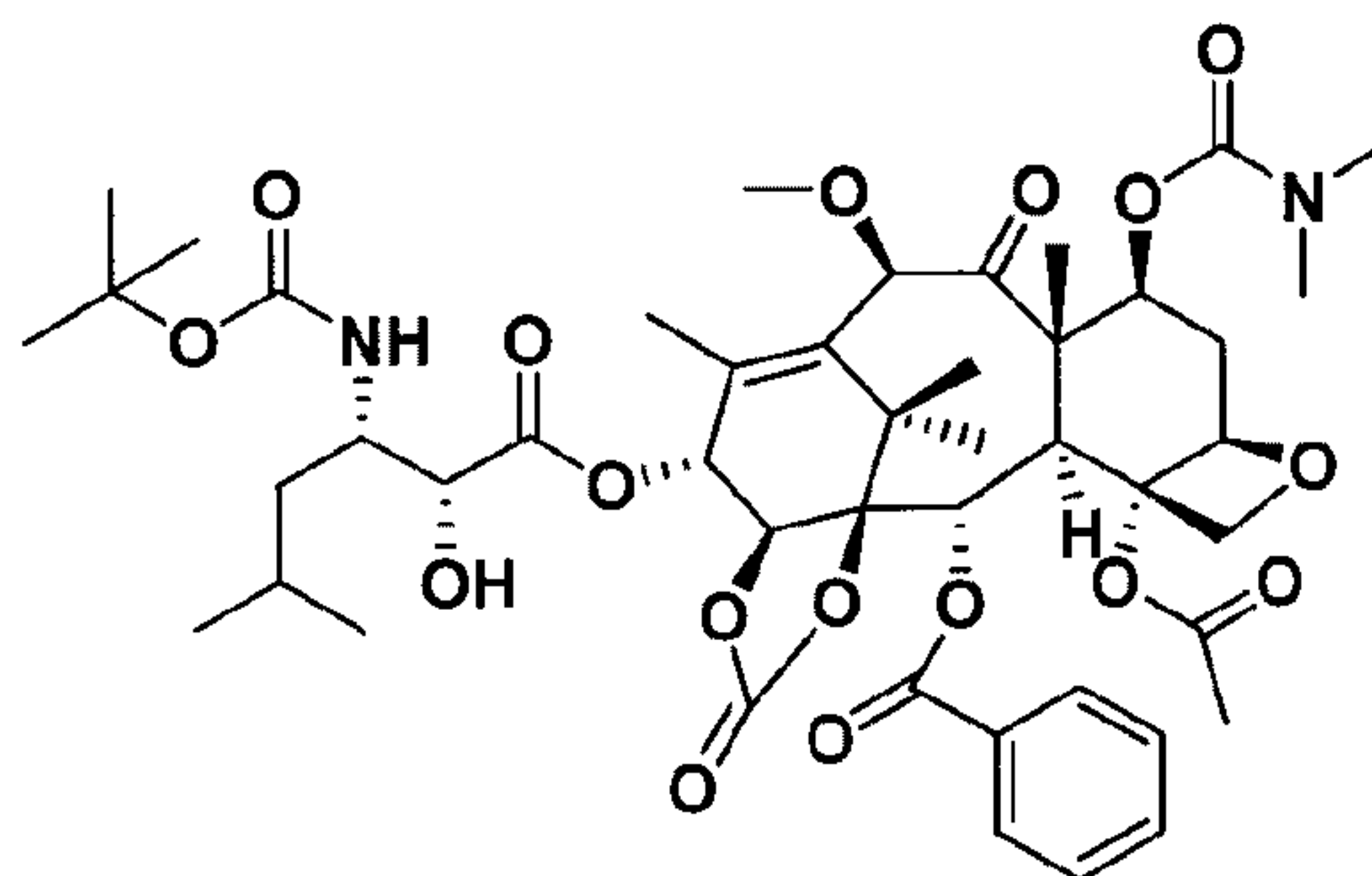
PCMI-15: mp: 231-232°C;

MS (m/z) ESI: 958.3 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.50 (d, *J* = 4.6 Hz, 1H), 8.10 – 8.01 (m, 2H), 7.80 (td, *J* = 7.8, 1.6 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.51 (dd, *J* = 16.2, 8.2 Hz, 3H), 7.30 (d, *J* = 9.9 Hz, 1H), 6.40 (d, *J* = 6.2 Hz, 1H), 6.13 (d, *J* = 7.4 Hz, 1H), 5.85 (d, *J* = 10.0 Hz, 1H), 5.55 – 5.42 (m, 2H, H-7), 5.24 (s, 1H), 4.98 (d, *J* = 8.2 Hz, 1H), 4.88 (d, *J* = 6.9 Hz, 1H), 4.80 (s, 1H), 4.34 (d, *J* = 8.3 Hz, 1H), 4.26 (d, *J* = 8.4 Hz, 1H), 3.87 (d, *J* = 7.5 Hz, 1H), 3.38 (s, 3H), 2.88 (t, *J* = 3.5 Hz, 6H), 2.61 – 2.51 (m, 4H), 2.01 – 1.91 (m, 4H), 1.85 (s, 3H), 1.51 (s, 9H), 1.27 (s, 3H), 1.25 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 205.25, 172.80, 170.69, 164.80, 159.45, 154.99, 152.14, 148.17, 137.90, 136.87, 135.58, 134.23, 129.89, 128.97, 128.02, 123.07, 122.09, 88.33, 83.89, 82.38, 80.49, 80.10, 80.00, 76.01, 74.20, 72.05, 69.52, 57.24, 57.09, 55.40, 45.87, 41.64, 36.57, 35.92, 33.79, 31.93, 29.70, 28.34, 25.47, 22.70, 22.00, 21.93, 14.36, 14.13, 10.89.

Example 16 Preparation of PCMI-16



- 1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-isobutyl-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 5**.

- 2) Preparation of 7-dimethylcarbamoyl-10-methoxyl-1,14-carbonate baccatin III

The specific method was seen in Step 2) in **Example 14**.

- 3) Preparation of PCMI-16

The specific method was seen in Step 3) in **Example 1** and the purity of the final product was 95% or higher.

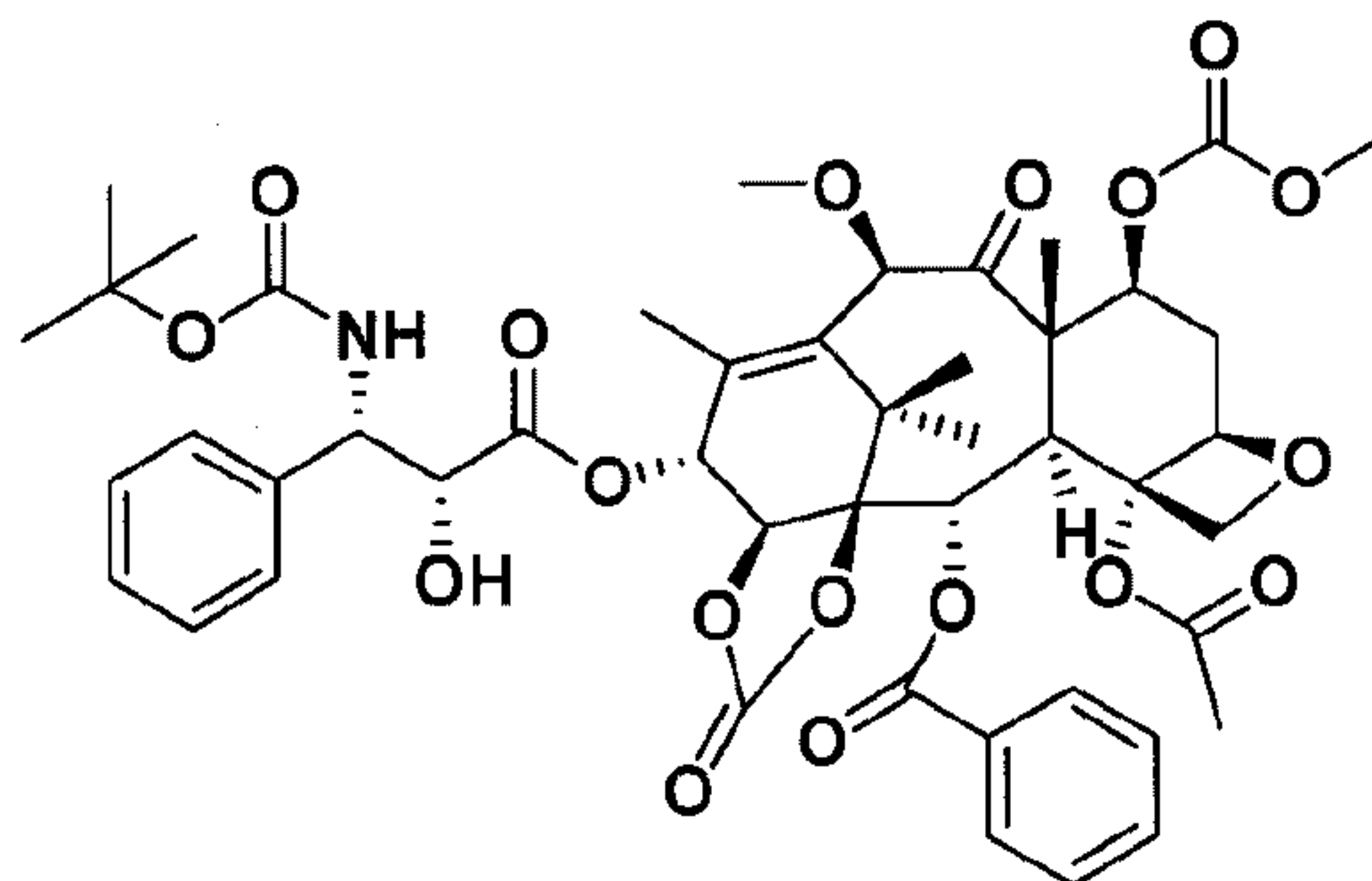
PCMI-16: mp: 227-228°C;

MS (m/z) ESI: 937.2 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 6.48 (d, *J* = 6.3 Hz, 1H), 6.13 (d, *J* = 7.4 Hz, 1H), 5.48 (dd, *J* = 10.6, 7.2 Hz, 1H), 5.25 (s, 1H), 4.95 (d, *J* = 8.3 Hz, 1H), 4.89 (d, *J* = 6.9 Hz, 1H), 4.77 (d, *J* = 9.0 Hz, 1H), 4.33 (dd, *J* = 8.9, 5.8 Hz, 2H), 4.27 (d, *J* = 8.4 Hz, 1H), 4.22 – 4.09 (m, 1H), 3.93 – 3.83 (m, 2H, H-3), 3.41 (s, 3H), 2.88 (s, 6H), 2.60 – 2.41 (m, 4H), 2.02 (s, 3H), 1.96 (dd, *J* = 19.7, 7.7 Hz, 1H), 1.85 (s, 3H), 1.75 – 1.69 (m, 1H), 1.52 – 1.37 (m, 11H), 1.30 (s, 3H), 1.27 (s, 3H), 1.01 (t, *J* = 6.3 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 205.08, 172.96, 170.35, 164.81, 154.97, 152.01, 136.39, 134.05, 129.95, 128.94, 128.11, 88.19, 83.90, 82.39, 80.25, 79.67, 76.04, 74.74, 73.71, 71.99, 69.44, 57.29, 57.07, 54.34, 51.49, 45.88, 41.76, 40.57, 36.54, 35.86, 33.76, 29.67, 28.24, 25.57, 24.85, 23.24, 22.46, 22.08, 14.42, 10.90.

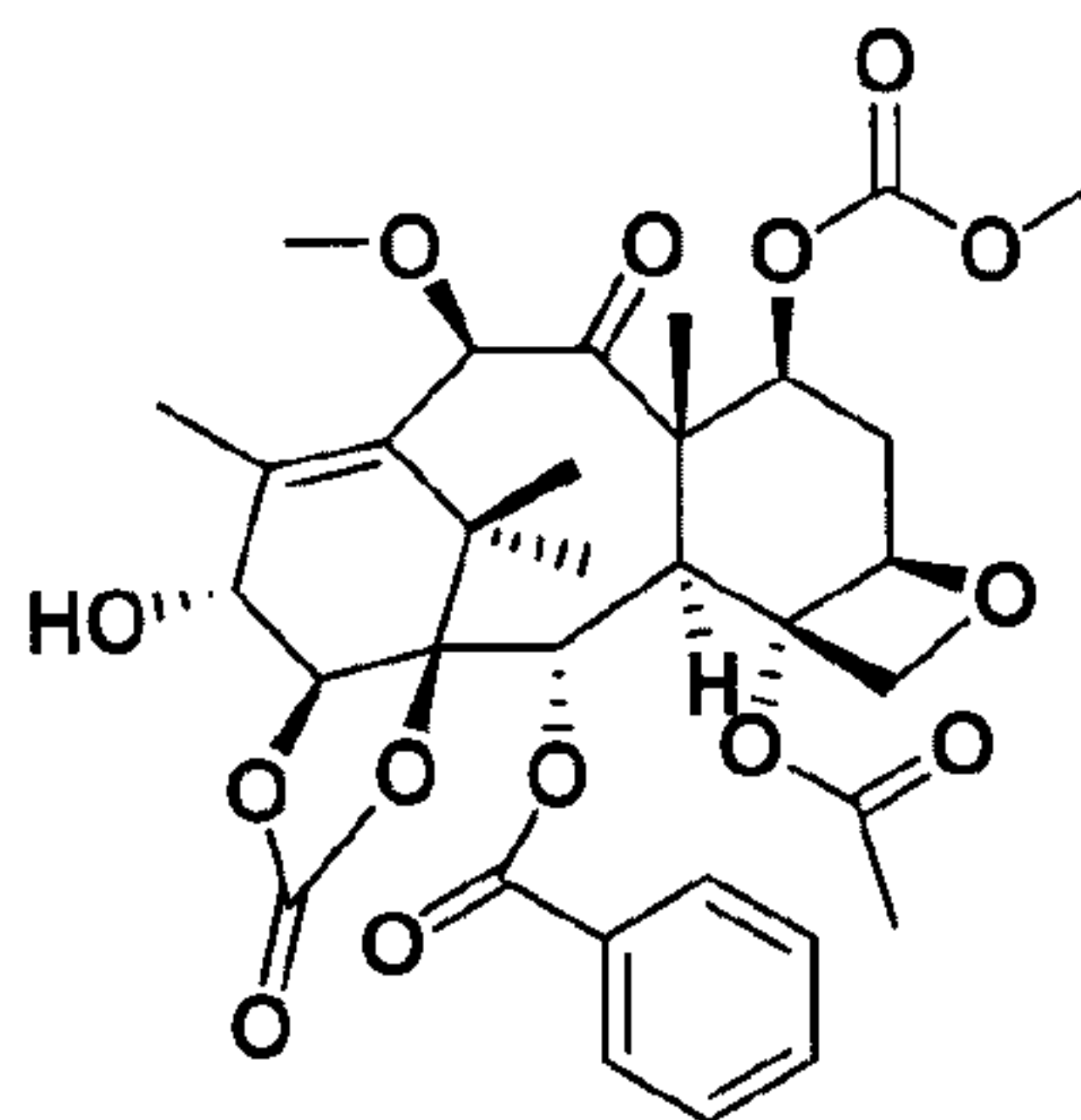
Example 17 Preparation of PCMI-17



- i) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 1**.

- 2) Preparation of 7-methoxyformyl-10-methoxyl-1,14-carbonate baccatin III



10-DAB (1 eq.) was used as raw material, dissolved in DMF and added successively with 2.5 equivalents of imidazole and 2.5 equivalents of triethyl chlorosilane. By post-treatment, the crude compound **7** was given.

5 The compound **7** was dissolved in dichloromethane which was used as the solvent, into which 2 equivalents of pyridine was added at 0°C. Successively, the reaction liquid was added dropwise with 2 equivalents of *p*-toluenesulfonyl chloride. After 4 hours of reaction, by post-treatment of purification by column chromatography, the compound **8** was given in a yield of 85-90%.

10 The compound **8** (1 eq.) was dissolved in anhydrous tetrahydrofuran to react with methyl magnesium bromide (2 eq.) at room temperature for 3 hours under the protection of nitrogen. After post-treatment, the crude compound **9** was obtained after dried.

The compound **9** (1 eq.) was dissolved in acetone solution, into which 10 equivalents of manganese dioxide was added at room temperature to react for 4 hours. By post-treatment of purification by column chromatography, the compound **10** was given in a yield of 75%.

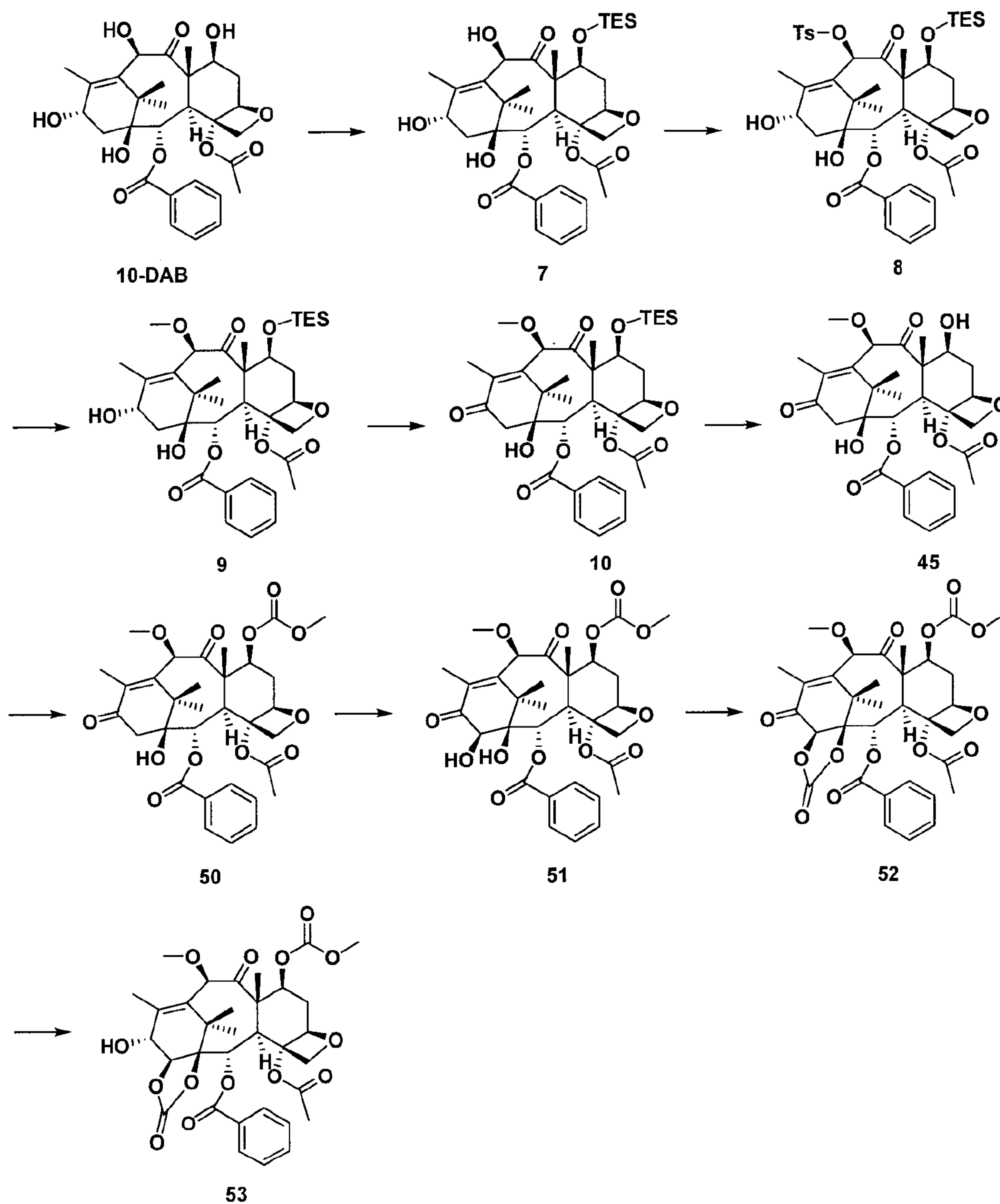
The compound **10** (1 eq.) was dissolved in dry THF, into which 1.5 equivalents of tetrabutylammonium fluoride (which is in the form of a solution in THF) was added at room temperature. After 1 hour of reaction, the reaction was completed. By post-treatment of purification by column chromatography, the compound **45** was given in a yield of 90%.

20 The compound **45** (1 eq.) was dissolved in dry THF which was used as the solvent, into which 1.5 equivalents LHMDs was added at 0°C. After 1 hour of reaction, 2 equivalents of methoxyformyl chloride was slowly added dropwise to the reaction liquid and reacted for 2 hours. By post-treatment of purification by column chromatography, the compound **50** was given in a yield of 71%.

The compound **50** (1 eq.) was dissolved in dry THF/DMPU (4:1) solution, into which 1.2 equivalents of potassium *t*-butoxide was added at -70°C to react for 20min. The obtained reaction liquid was slowly added dropwise with 2 equivalents of N-(sulfonyl)oxaziridine to react for 2 hours. By post-treatment of purification by column chromatography, the
5 compound **51** was given in a yield of 75%.

The compound **51** (1 eq.) was reacted with 2 equivalents of N,N'-carbonyldiimidazole (CDI) in dry tetrahydrofuran to give the compound **52** in a yield of 95%.

The compound **52** (1 eq.) was dissolved in dry tetrahydrofuran, into which 0.2 equivalents of (R)-2-methyl oxazaborodine was added at room temperature as a catalyst, followed by
10 addition of 5 equivalents of borane/THF solution to react for 8 hours. After completion of reaction, by post-treatment of purification by column chromatography, the compound **53** of 7-methoxyformyl-10-methoxyl-1,14-carbonate baccatin III was obtained as the final product in a yield of 80%.



3) Preparation of PCMI-17

The specific method was seen in Step 3) in **Example 1** and the purity of the final product was 95% or higher.

5 PCMI-17: mp: 233-234°C;

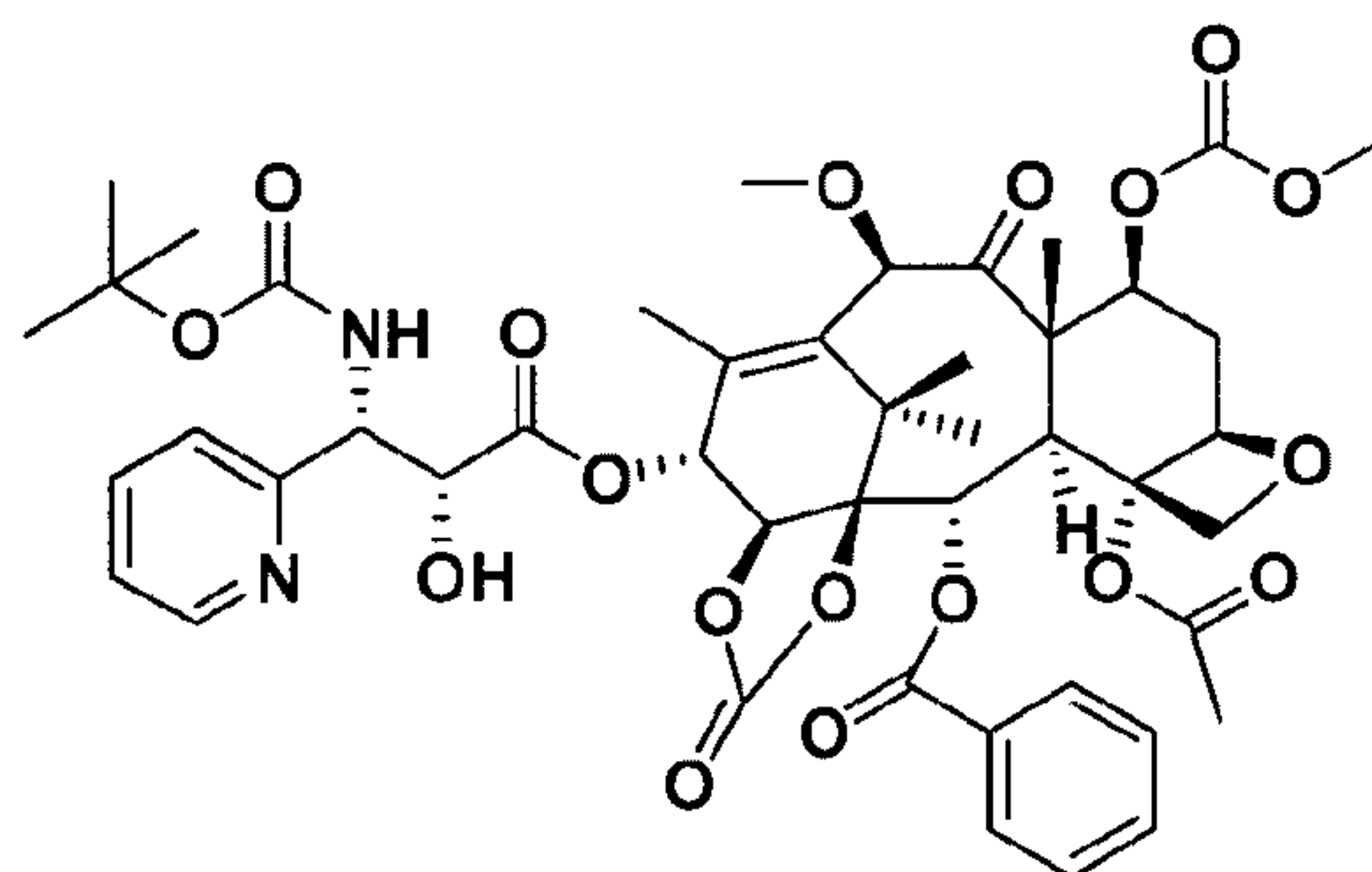
MS (m/z) ESI: 944.4 (M+Na)⁺;

IR: 3411, 2979, 2933, 1820, 1731, 1712, 1490, 1367, 1259, 1163, 1085, 713.

^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, $J = 7.4$ Hz, 2H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.49 (t, $J = 7.7$ Hz, 2H), 7.45 – 7.37 (m, 4H), 7.37 – 7.30 (m, 1H), 6.46 (d, $J = 6.1$ Hz, 1H), 6.12 (d, $J = 7.4$ Hz, 1H), 5.58 (d, $J = 8.6$ Hz, 1H), 5.35 (dd, $J = 10.6, 7.2$ Hz, 2H), 5.14 (s, 1H), 4.95 – 4.86 (m, 1H), 4.80 (d, $J = 6.8$ Hz, 1H), 4.71 (s, 1H), 4.30 (d, $J = 8.4$ Hz, 1H), 4.23 (d, $J = 8.5$ Hz, 1H), 3.89 – 3.78 (m, 2H), 3.75 (s, 3H), 3.41 (s, 3H), 2.56 (ddd, $J = 14.6, 9.5, 7.3$ Hz, 1H), 2.46 (s, 3H), 2.08 – 1.98 (m, 1H), 1.95 (d, $J = 1.1$ Hz, 3H), 1.83 (s, 3H), 1.39 (s, 9H), 1.29 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 204.25, 172.06, 171.24, 170.73, 164.70, 155.73, 155.00, 151.92, 136.31, 135.79, 134.19, 129.95, 128.98, 128.94, 128.10, 127.93, 126.63, 88.09, 83.49, 82.19, 80.58, 80.25, 79.61, 76.01, 75.28, 74.71, 74.36, 69.24, 57.45, 56.89, 55.31, 49.22, 45.77, 41.63, 33.83, 33.25, 29.68, 28.24, 25.57, 25.51, 24.90, 22.48, 22.10, 14.33, 10.78.

Example 18 Preparation of PCMI-18



- 1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-(2-pyridyl)-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 4**.

- 2) Preparation of 7-methoxyformyl-10-methoxyl-1,14-carbonate baccatin III

The specific method was seen in Step 2) in **Example 17**.

- 3) Preparation of PCMI-18

The specific method was seen in Step 3) in **Example 1** and the purity of the final product was 95% or higher.

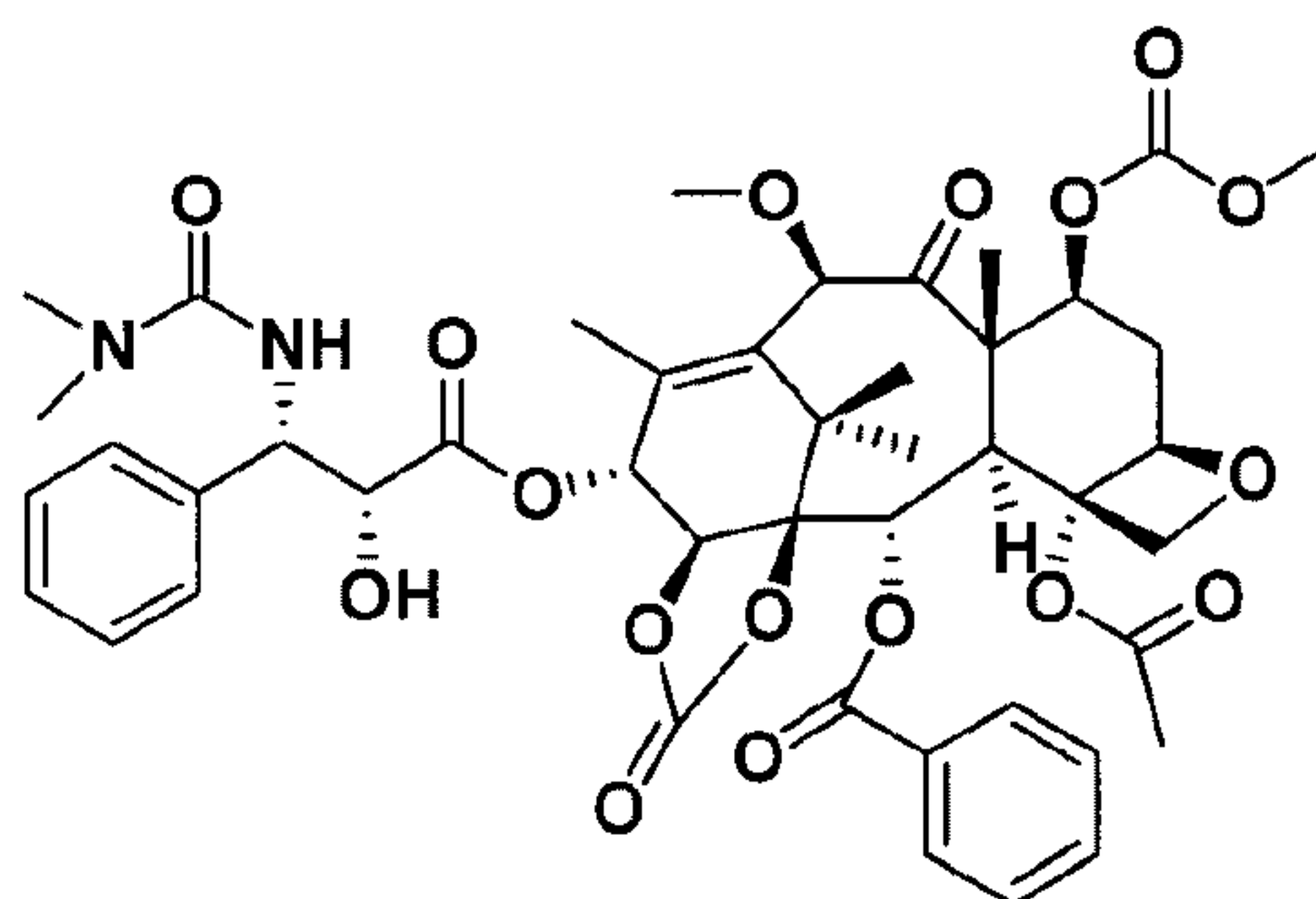
PCMI-18: mp: 235-236°C;

MS (m/z) ESI: 923.4 (M+H)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.50 (d, *J* = 4.6 Hz, 1H), 8.10 – 8.01 (m, 2H), 7.80 (td, *J* = 7.8, 1.6 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.51 (dd, *J* = 16.2, 8.2 Hz, 3H), 7.30 (d, *J* = 9.9 Hz, 1H), 6.46 (d, *J* = 6.1 Hz, 1H), 6.12 (d, *J* = 7.4 Hz, 1H), 5.58 (d, *J* = 8.6 Hz, 1H), 5.35 (dd, *J* = 10.6, 7.2 Hz, 2H), 5.14 (s, 1H), 4.95 – 4.86 (m, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.71 (s, 1H), 4.30 (d, *J* = 8.4 Hz, 1H), 4.23 (d, *J* = 8.5 Hz, 1H), 3.89 – 3.78 (m, 2H, H-3), 3.75 (s, 3H), 3.41 (s, 3H), 2.56 (ddd, *J* = 14.6, 9.5, 7.3 Hz, 1H), 2.46 (s, 3H), 2.08 – 1.98 (m, 1H), 1.95 (d, *J* = 1.1 Hz, 3H), 1.83 (s, 3H), 1.39 (s, 9H), 1.29 (s, 3H), 1.28 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 205.25, 172.80, 170.69, 164.80, 159.45, 154.99, 152.14, 148.17, 137.90, 136.87, 135.58, 134.23, 129.89, 128.97, 128.02, 123.07, 122.09, 88.09, 83.49, 82.19, 80.58, 80.25, 79.61, 76.01, 75.28, 74.71, 74.36, 69.24, 57.45, 56.89, 55.31, 49.22, 45.77, 41.63, 33.83, 33.25, 29.68, 28.24, 25.57, 25.51, 24.90, 22.48, 22.10, 14.33, 10.78.

15 Example 19 Preparation of PCMI-19



- 1) Preparation of (4S,5R)-3-dimethylcarbamoyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 3**.

- 20 2) Preparation of 7-methoxyformyl-10-methoxyl-1,14-carbonate baccatin III

The specific method was seen in Step 2) in **Example 17**.

- 3) Preparation of PCMI-19

The specific method was seen in Step 3) in **Example 1** and the purity of the final product

was 95% or higher.

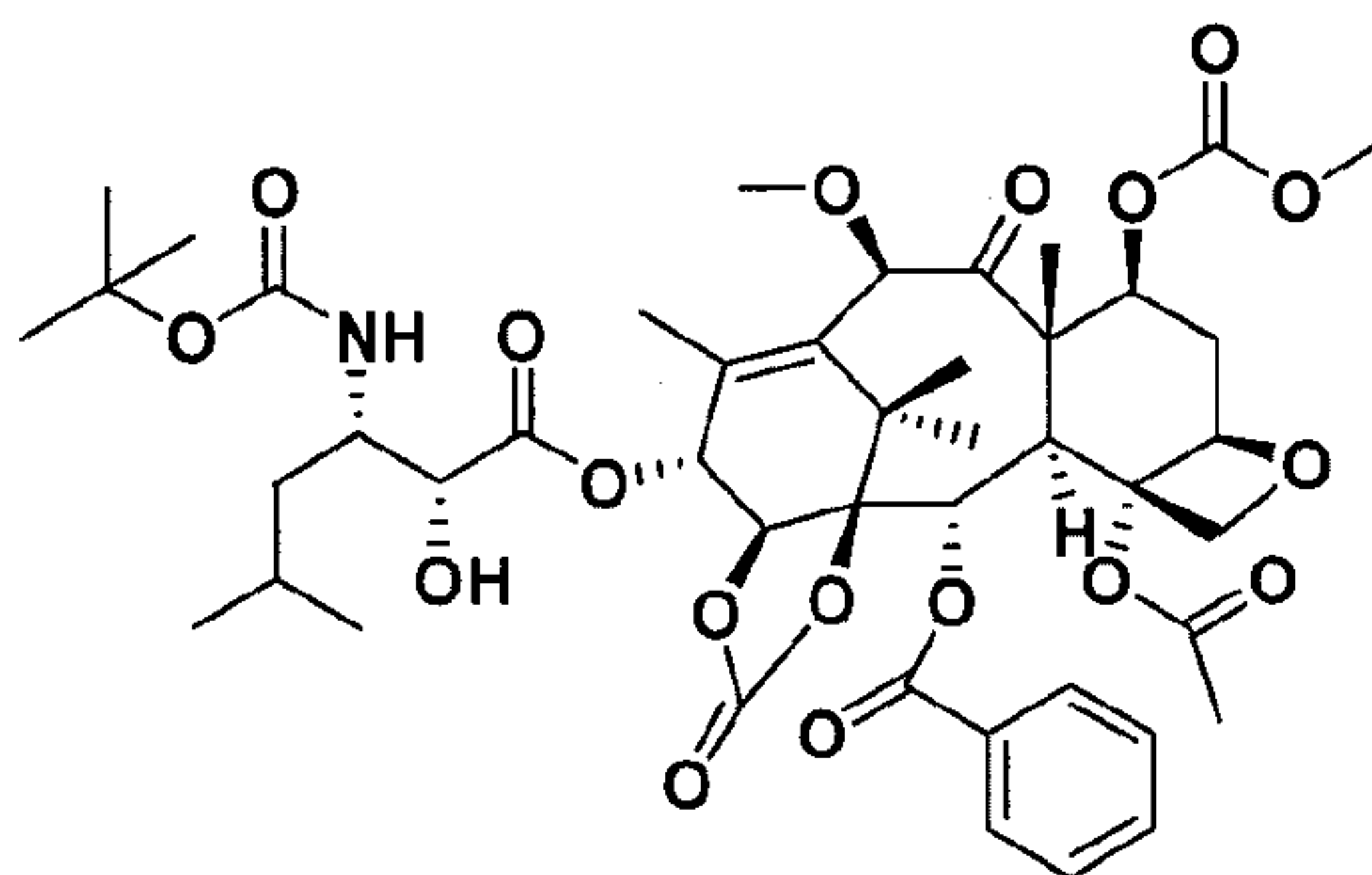
PCMI-19: mp: 213-214°C;

MS (m/z) ESI: 894.3 (M+H)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 6.47 (d, *J* = 6.1 Hz, 1H), 6.27 (s, 1H), 6.11 (d, *J* = 7.5 Hz, 1H), 4.94 (d, *J* = 7.9 Hz, 1H), 4.87 (d, *J* = 6.9 Hz, 1H), 4.75 (d, *J* = 8.9 Hz, 1H), 4.39 (dd, *J* = 10.0, 5.2 Hz, 1H), 4.36 – 4.31 (m, 1H), 4.30 (d, *J* = 8.6 Hz, 1H), 4.24 (d, *J* = 8.4 Hz, 1H), 4.14 – 4.06 (m, 1H), 4.00 (d, *J* = 6.0 Hz, 1H), 3.71 (d, *J* = 7.4 Hz, 1H), 2.61 – 2.43 (m, 4H), 2.38 (d, *J* = 3.7 Hz, 1H), 2.26 (s, 3H), 1.95 – 1.84 (m, 4H), 1.71 (d, *J* = 12.4 Hz, 4H), 1.52 – 1.37 (m, 11H), 1.34 (s, 3H), 1.28 (s, 3H), 0.99 (t, *J* = 6.8 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 202.19, 172.97, 170.93, 170.65, 164.76, 156.27, 151.87, 139.79, 134.15, 133.52, 129.97, 129.00, 127.95, 88.19, 84.23, 80.46, 79.63, 75.94, 74.79, 74.59, 73.87, 71.73, 69.45, 58.71, 51.67, 45.05, 41.78, 40.42, 35.46, 29.70, 28.24, 25.98, 24.85, 23.23, 22.50, 22.15, 20.76, 15.01, 9.70.

15 Example 20 Preparation of PCMI-20



1) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-isobutyl-5-oxazolidine carboxylic acid

The specific method was seen in Step 1) in **Example 5**.

20 2) Preparation of 7-methoxyformyl-10-methoxyl-1,14-carbonate baccatin III

The specific method was seen in Step 2) in **Example 17**.

3) Preparation of PCMI-20

The specific method was seen in Step 3) in **Example 1** and the purity of the final product

was 95% or higher.

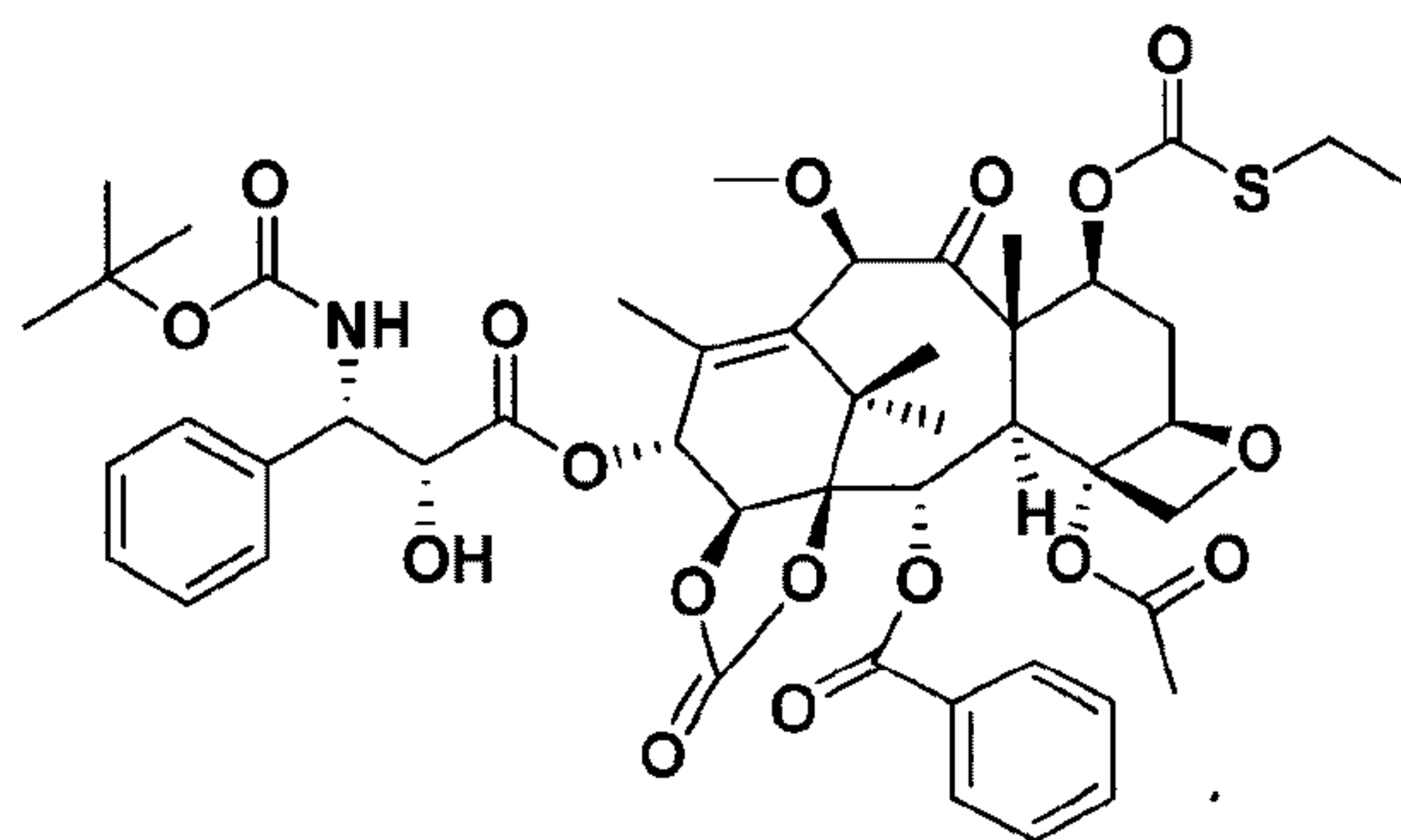
PCMI-20: mp: 229-230 °C;

MS (m/z) ESI: 924.4 (M+Na)⁺;

¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 6.47 (d, *J* = 6.3 Hz, 1H), 6.13 (d, *J* = 7.4 Hz, 1H), 5.36 (dd, *J* = 10.6, 7.2 Hz, 1H), 5.15 (s, 1H), 4.93 (d, *J* = 7.8 Hz, 1H), 4.88 (d, *J* = 6.9 Hz, 1H), 4.80 (d, *J* = 9.3 Hz, 1H), 4.39 – 4.28 (m, 2H), 4.25 (d, *J* = 8.5 Hz, 1H), 4.13 (m, 1H), 4.01 (d, *J* = 5.4 Hz, 1H), 3.84 (d, *J* = 7.3 Hz, 1H), 3.75 (s, 3H), 3.41 (s, 3H), 2.62 – 2.47 (m, 4H), 2.10 – 2.03 (m, 1H), 1.99 (d, *J* = 1.1 Hz, 3H), 1.83 (s, 3H), 1.71 (dd, *J* = 11.2, 4.6 Hz, 1H), 1.44 (dd, *J* = 10.1, 3.6 Hz, 2H), 1.41 (d, *J* = 14.4 Hz, 9H), 1.30 (s, 3H), 1.29 (s, 3H), 0.99 (t, *J* = 6.4 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 204.27, 172.97, 171.21, 170.71, 164.75, 156.21, 155.00, 151.99, 136.46, 134.15, 129.96, 128.99, 127.95, 88.18, 83.51, 82.20, 80.34, 80.19, 79.63, 76.73, 76.01, 75.27, 74.61, 73.82, 69.29, 57.43, 56.89, 55.30, 51.61, 45.76, 41.66, 40.44, 33.25, 29.69, 28.24, 25.51, 24.85, 23.25, 22.44, 22.16, 14.41, 10.81.

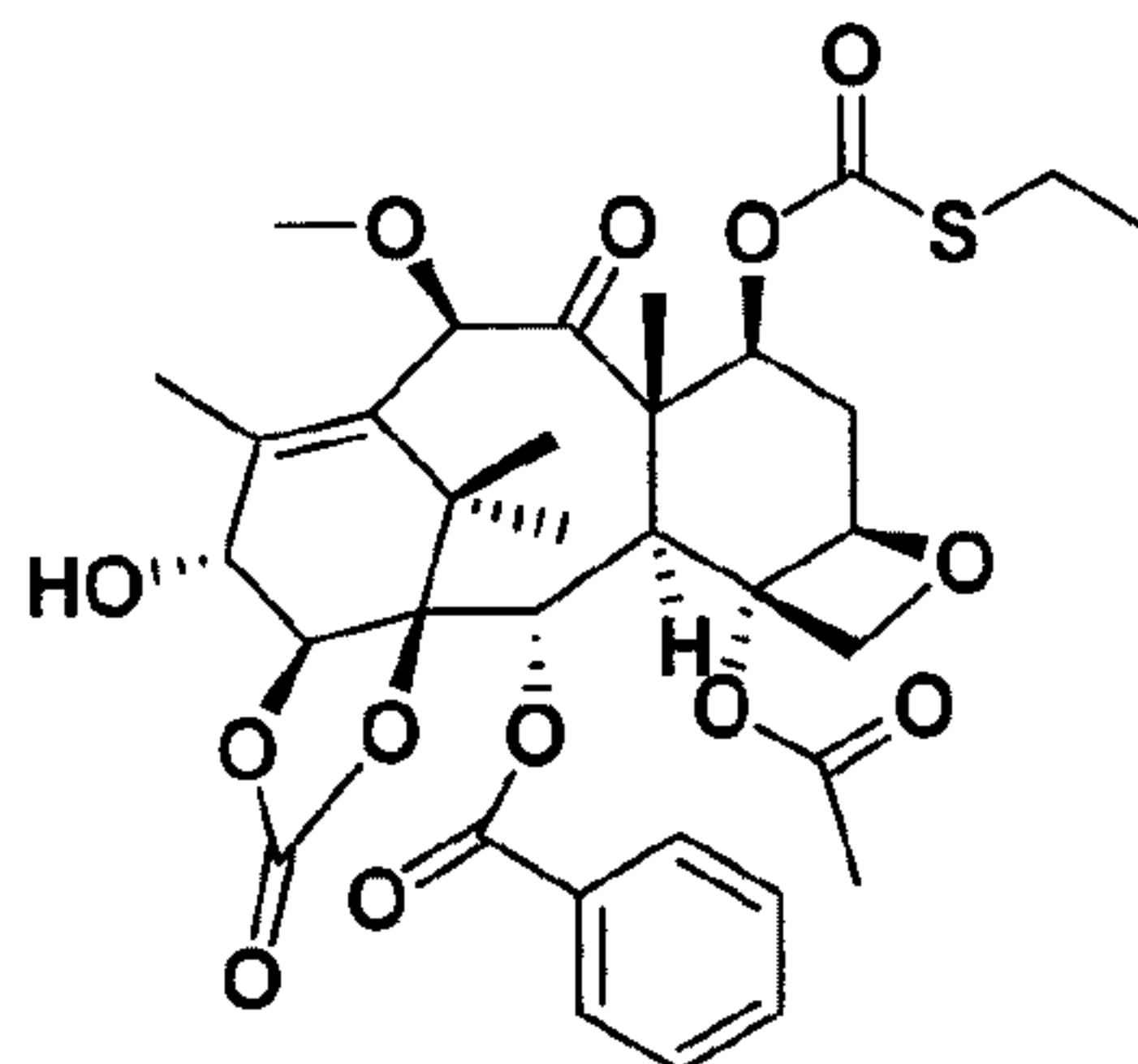
Example 21 Preparation of PCMI-21



i) Preparation of (4S,5R)-3-*t*-butyloxycarbonyl-2-(4-methoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid

20 The specific method was seen in Step 1) in **Example 1**.

2) Preparation of 7-ethylthioformyl-10-methoxy-1,14-carbonate baccatin III



10-DAB (1 eq.) was used as raw material, dissolved in DMF and added successively with 2.5 equivalents of imidazole and 2.5 equivalents of triethyl chlorosilane. By post-treatment, the crude compound **7** was given.

5 The compound **7** was dissolved in dichloromethane which was used as the solvent, into which 2 equivalents of pyridine was added at 0°C. Successively, the reaction liquid was added dropwise with 2 equivalents of *p*-toluenesulfonyl chloride. After 4 hours of reaction, by post-treatment of purification by column chromatography, the compound **8** was given in a yield of 90%.

10 The compound **8** (1 eq.) was dissolved in anhydrous tetrahydrofuran to react with methyl magnesium bromide (2 eq.) at room temperature for 3 hours under the protection of nitrogen. After post-treatment, the crude compound **9** was obtained after dried.

The compound **9** (1 eq.) was dissolved in acetone solution, into which 10 equivalents of manganese dioxide was added at room temperature to react for 4 hours. By post-treatment
15 of purification by column chromatography, the compound **10** was given in a yield of 75%.

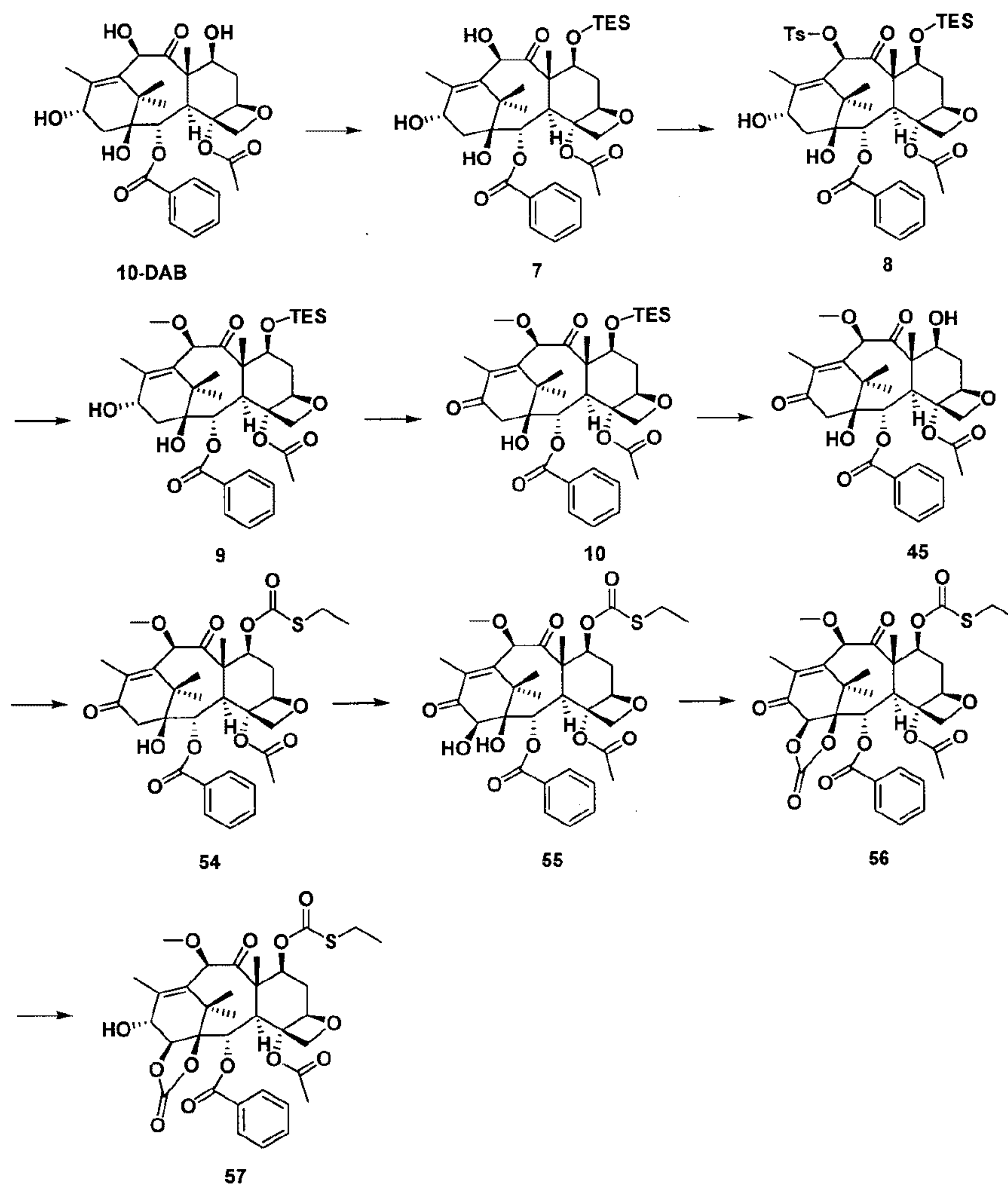
The compound **10** (1 eq.) was dissolved in dry THF, into which 1.5 equivalents of tetrabutylammonium fluoride (which is in the form of a solution in THF) was added at room temperature. After 1 hour of reaction, the reaction was completed. By post-treatment of purification by column chromatography, the compound **45** was given in a yield of 90%.

20 The compound **45** (1 eq.) was dissolved in dry THF which was used as the solvent and firstly reacted with 2 equivalents of *N,N'*-carbonyldiimidazole at room temperature for 2 hours. Then the reaction liquid was added with 2 equivalents of ethanethiol. After 4 hours of reaction, by post-treatment of purification by column chromatography, the compound **54** was given in a yield of 78%.

The compound **54** (1 eq.) was dissolved in dry THF/DMPU (4:1) solution, into which 1.2 equivalents of potassium *t*-butoxide was added at -70°C to react for 20min. The obtained reaction liquid was slowly added dropwise with 2 equivalents of N-(sulfonyl)oxaziridine to react for 2 hours. By post-treatment of purification by column chromatography, the
5 compound **55** was given in a yield of 75%.

The compound **55** (1 eq.) was reacted with 2 equivalents of N,N'-carbonyldiimidazole (CDI) in dry tetrahydrofuran to give the compound **56** in a yield of 95%.

The compound **56** (1 eq.) was dissolved in dry tetrahydrofuran, into which 0.2 equivalents of (R)-2-methyl oxazaborodine was added at room temperature as a catalyst, followed by
10 addition of 5 equivalents of borane/THF solution to react for 8 hours. After completion of reaction, by post-treatment of purification by column chromatography, the compound **57** of 7-ethylthioformyl-10-methoxy-1,14-carbonate baccatin III was obtained as the final product in a yield of 80%.



3) Preparation of PCMI-21

The specific method was seen in Step 3) in **Example 1** and the purity of the final product was 95% or higher.

5 PCMI-21: mp: 238-239°C;

MS (m/z) ESI: 974.4 (M+Na)⁺;

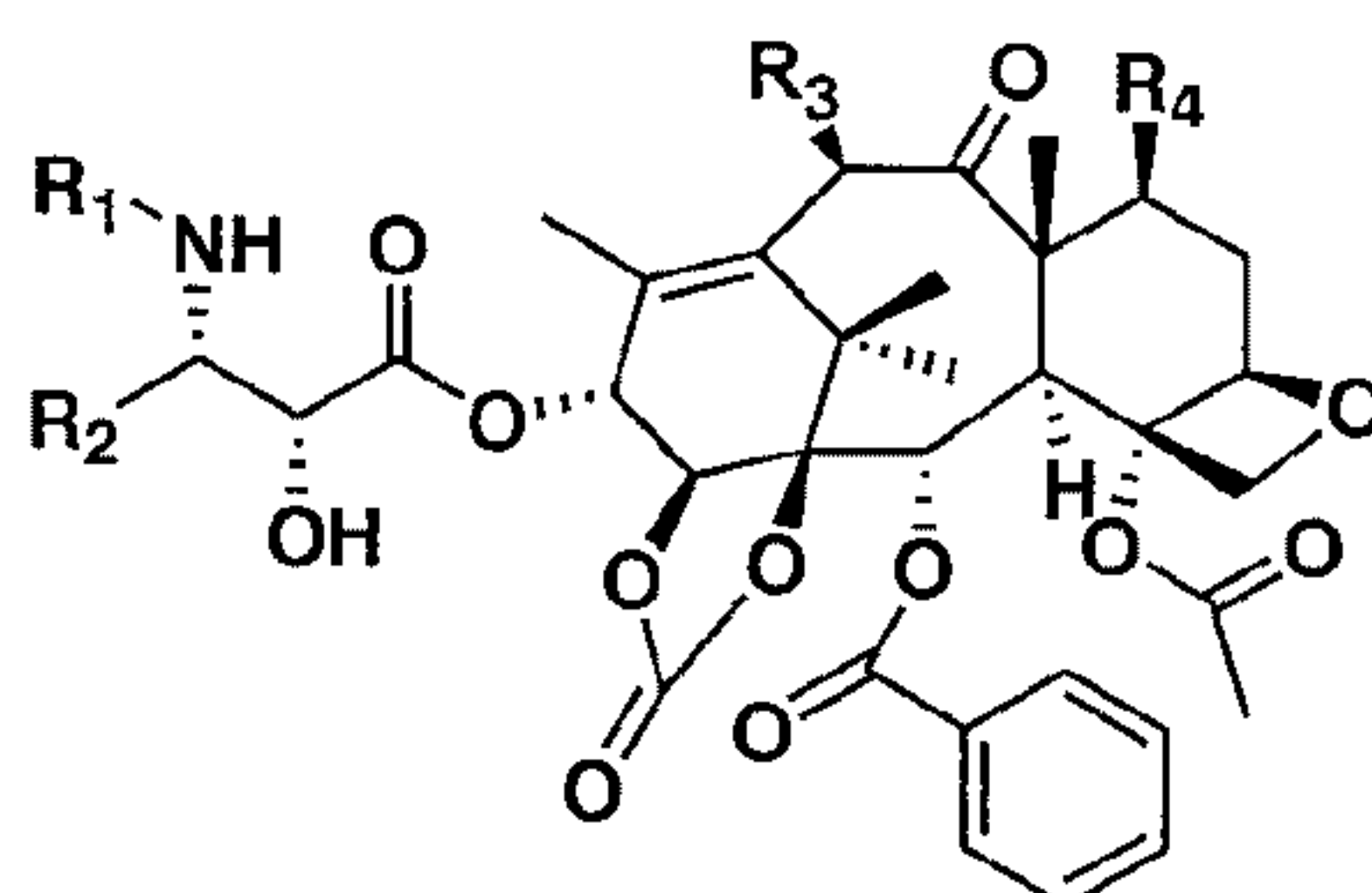
¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 7.4 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.45 – 7.37 (m, 4H), 7.37 – 7.30 (m, 1H), 6.46 (d, *J* = 6.1 Hz, 1H), 6.12 (d, *J* = 7.4 Hz, 1H), 5.58 (d, *J* = 8.6 Hz, 1H), 5.35 (dd, *J* = 10.6, 7.2 Hz, 2H), 5.14 (s, 1H), 4.95 – 4.86 (m, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.71 (s, 1H), 4.30 (d, *J* = 8.4 Hz, 1H), 4.23 (d, *J* = 8.5 Hz, 1H), 3.89 – 3.78 (m, 2H), 3.75 (s, 3H), 3.41 (s, 3H), 2.56 (ddd, *J* = 14.6, 9.5, 7.3 Hz, 1H), 2.46 (s, 3H), 2.08 – 1.98 (m, 1H), 1.95 (d, *J* = 1.1 Hz, 3H), 1.83 (s, 3H), 1.39 (s, 9H),

1.29 (s, 3H), 1.28 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 204.25, 172.06, 171.24, 170.73, 164.70, 155.73, 155.00, 151.92, 136.31, 135.79, 134.19, 129.95, 128.98, 128.94, 128.10, 127.93, 126.63, 88.09, 83.49, 82.19, 80.58, 80.25, 79.61, 76.01, 75.28, 74.71, 74.36, 69.24, 57.45, 56.89, 55.31, 5 49.22, 45.77, 41.63, 33.83, 33.25 , 29.68, 28.24, 25.57, 25.51, 24.90, 22.48, 22.10, 14.33, 10.78.

What is claimed is:

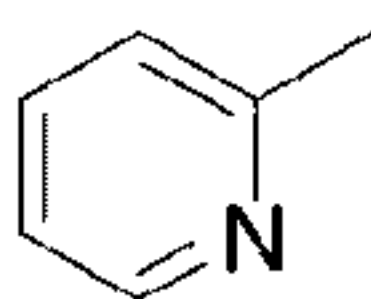
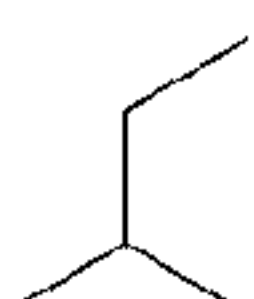
1. A taxane compound having the structure represented by the following general formula I:



I

5 wherein,

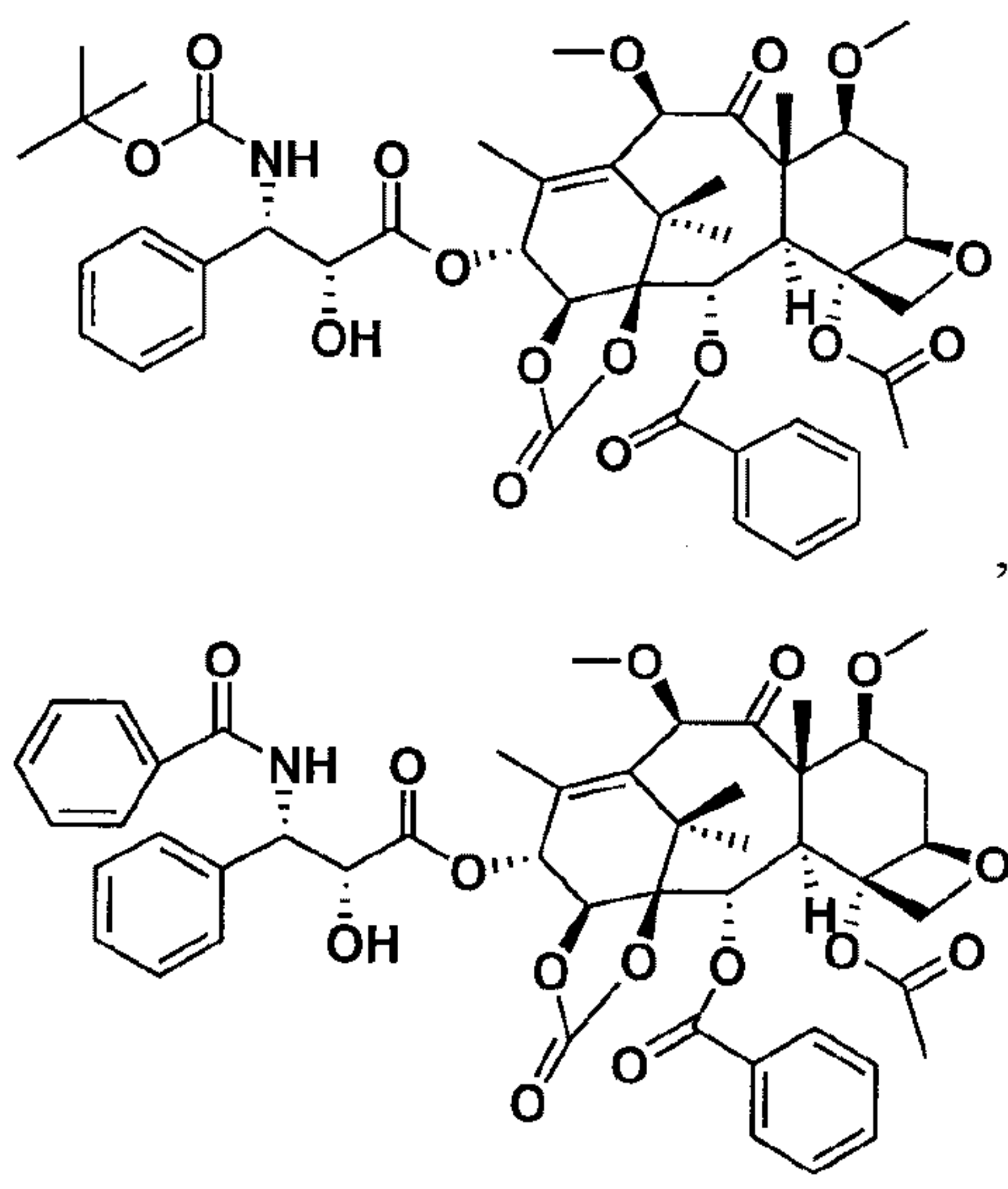
R₁ is benzoyl, *t*-butoxycarbonyl, or N,N'-dimethylcarbamoyl;

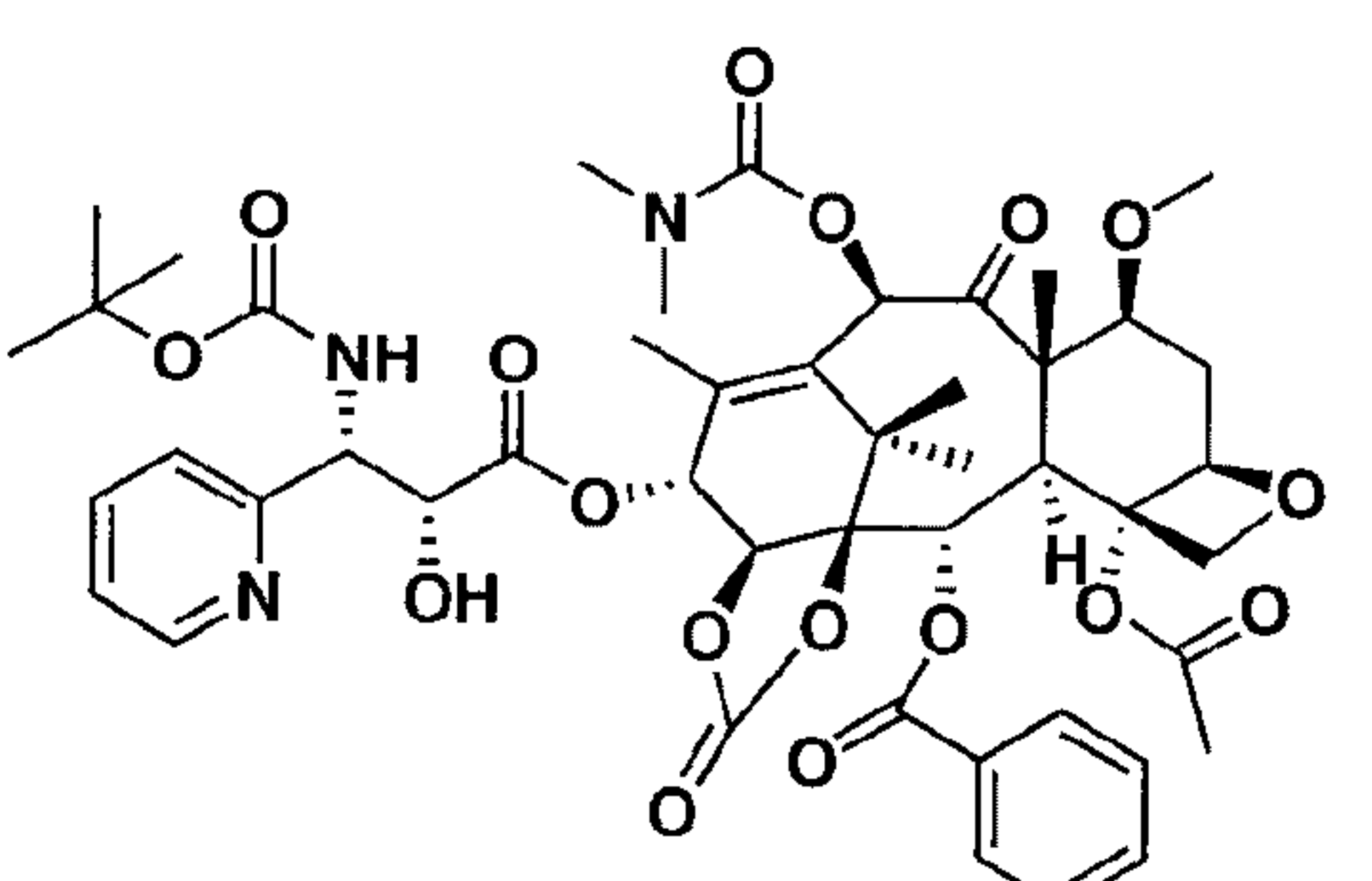
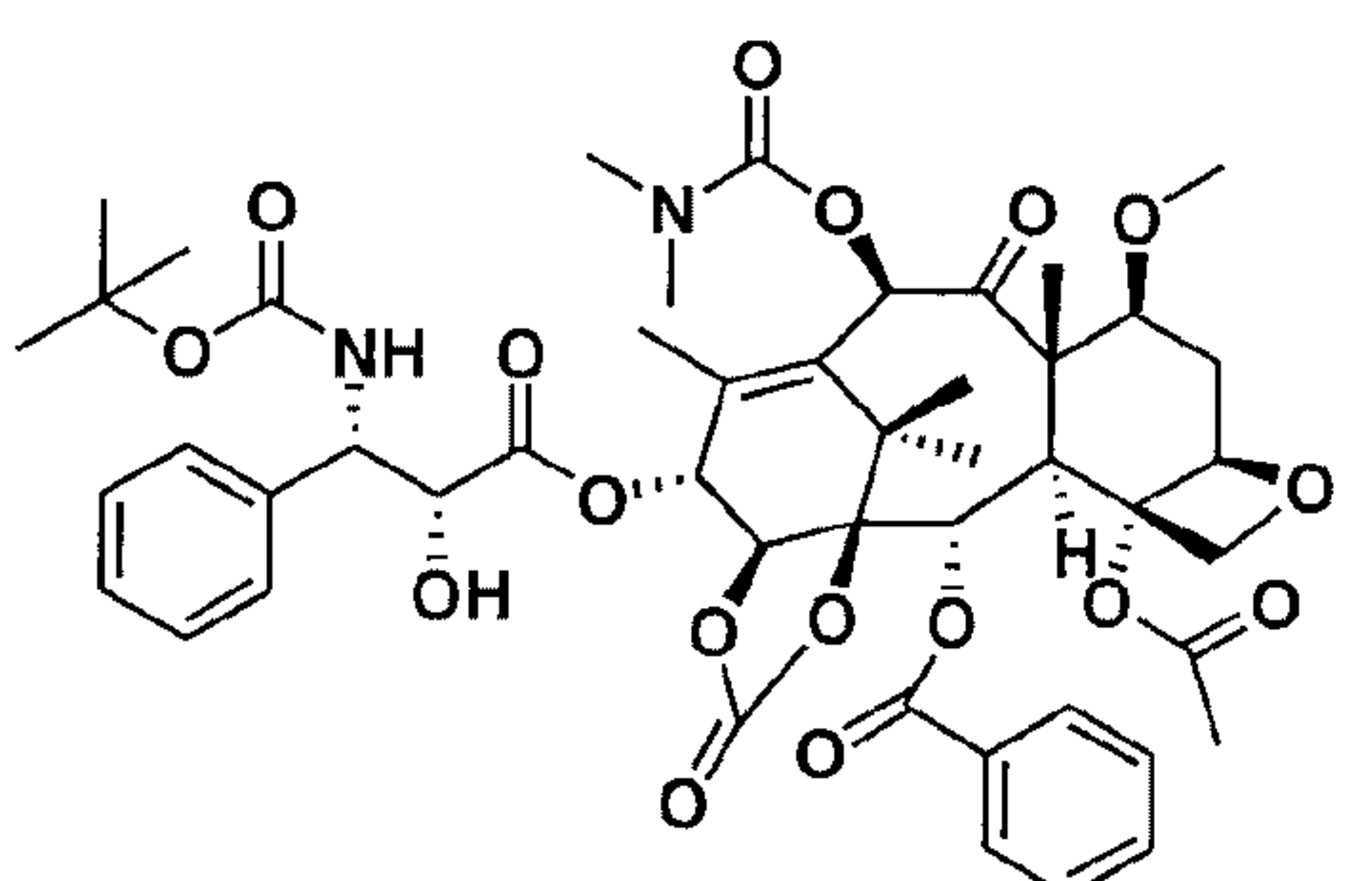
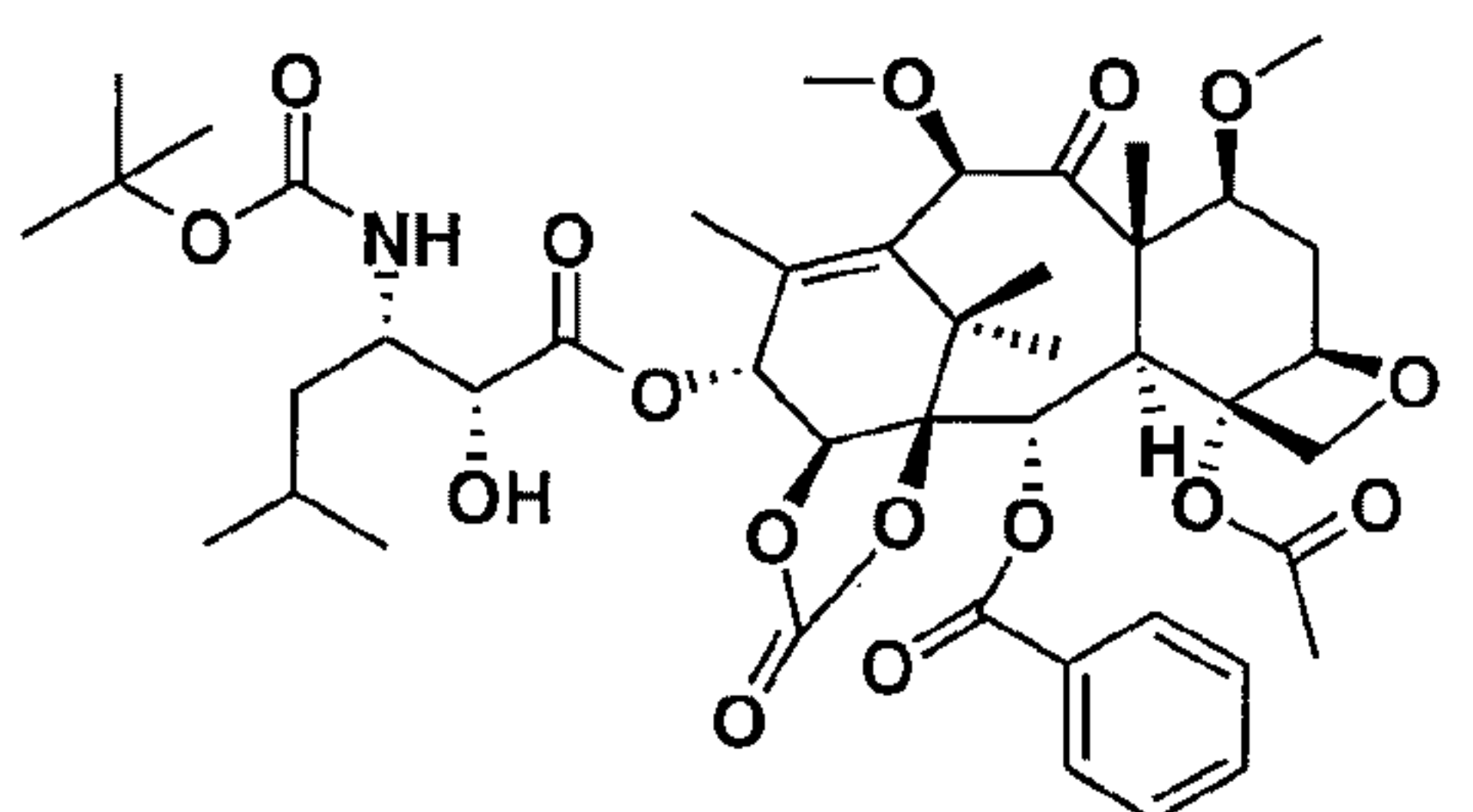
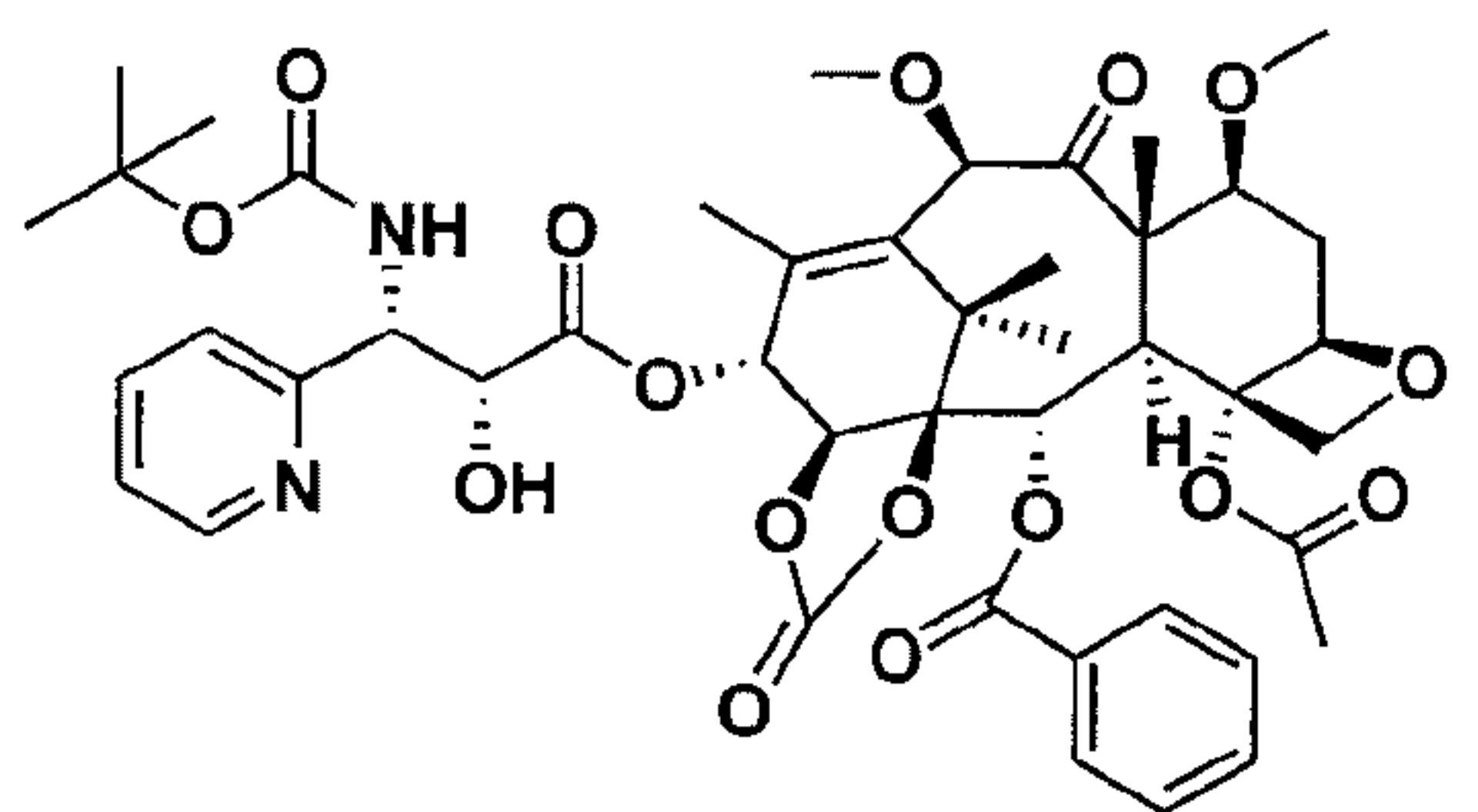
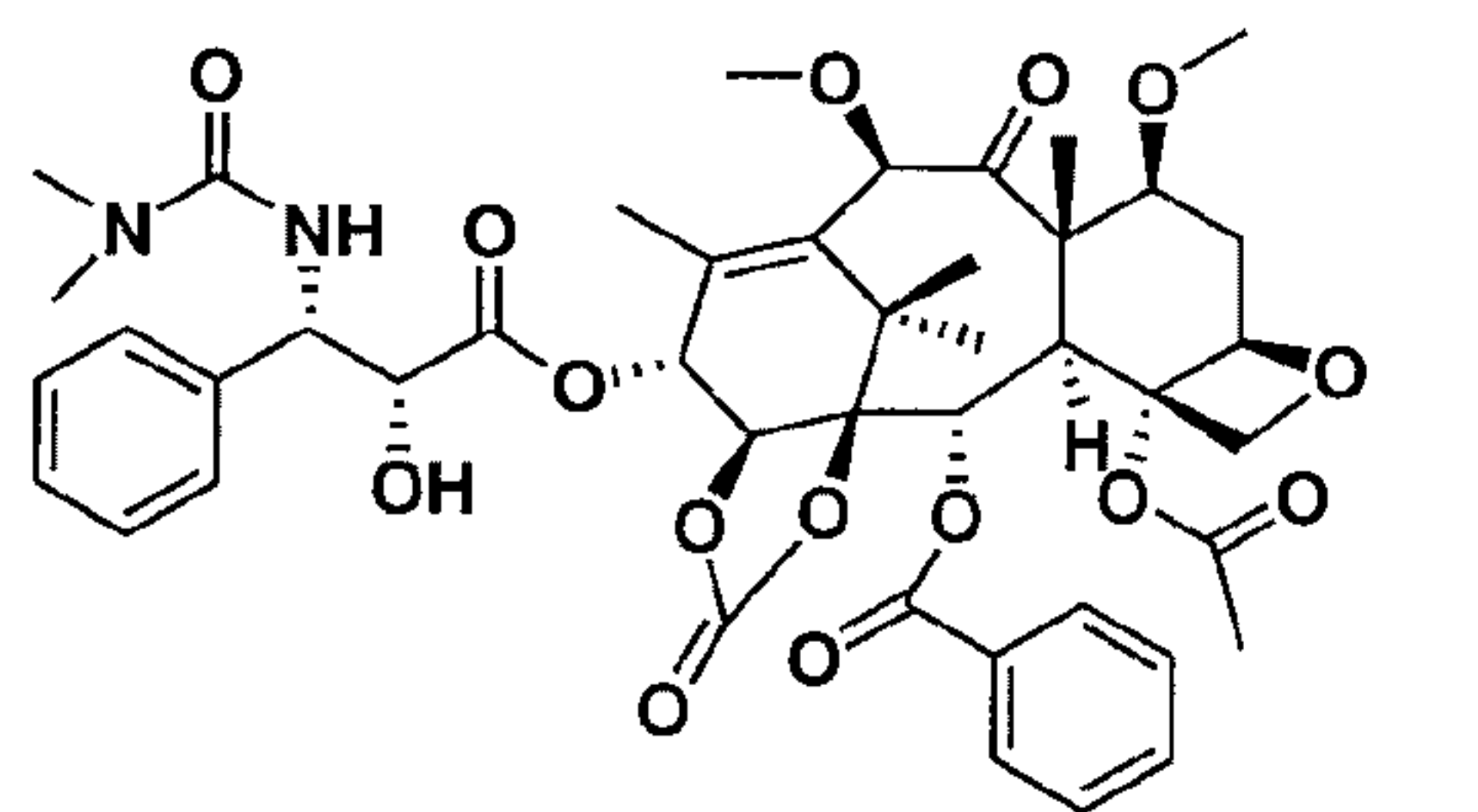
R₂ is phenyl,  (pyridyl-2-yl), or  (isobutyl);

R₃ is -OMe, -OCOOCH₃, -OCON(CH₃)₂, or -OCOSC₂H₅; and

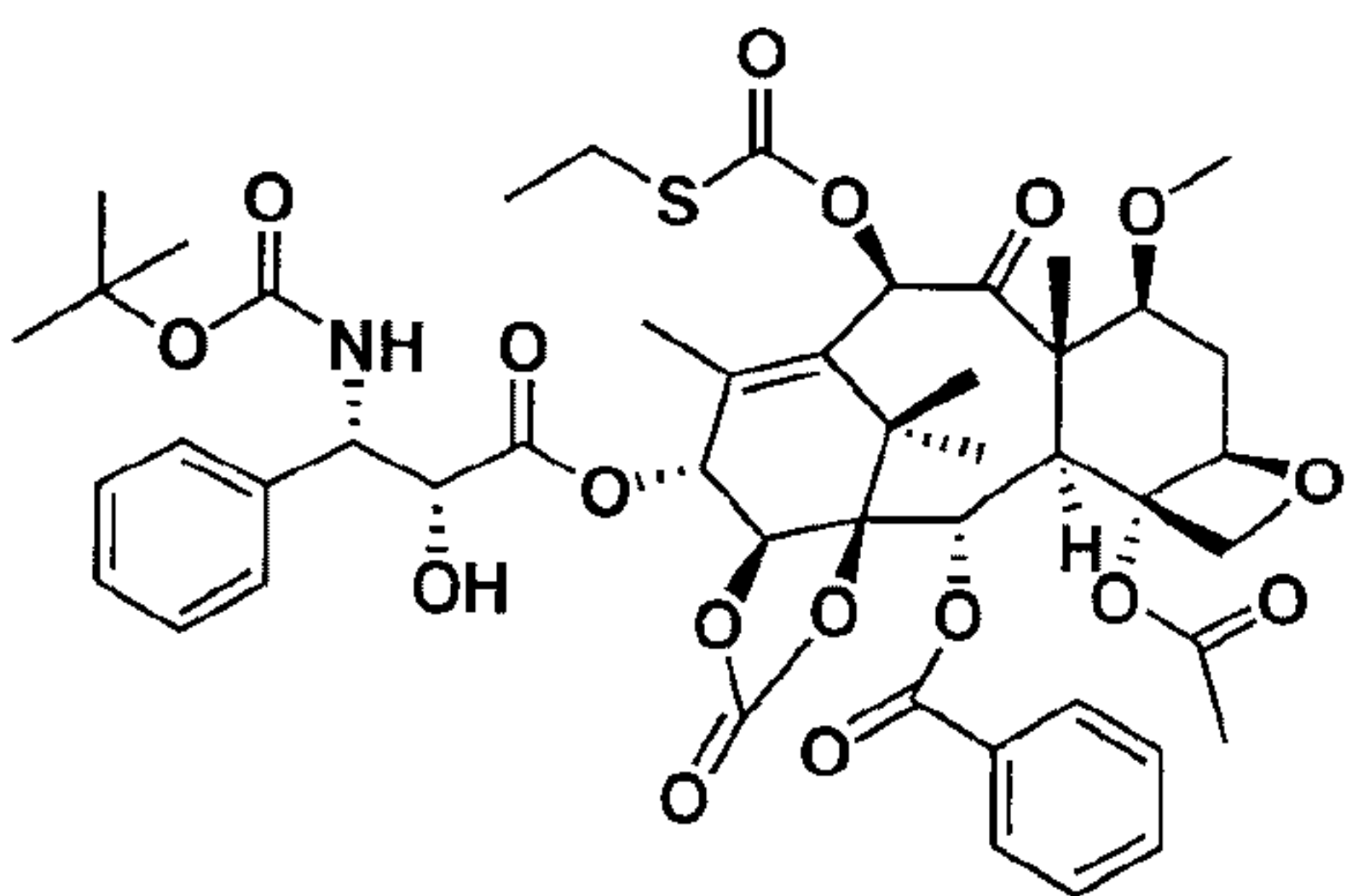
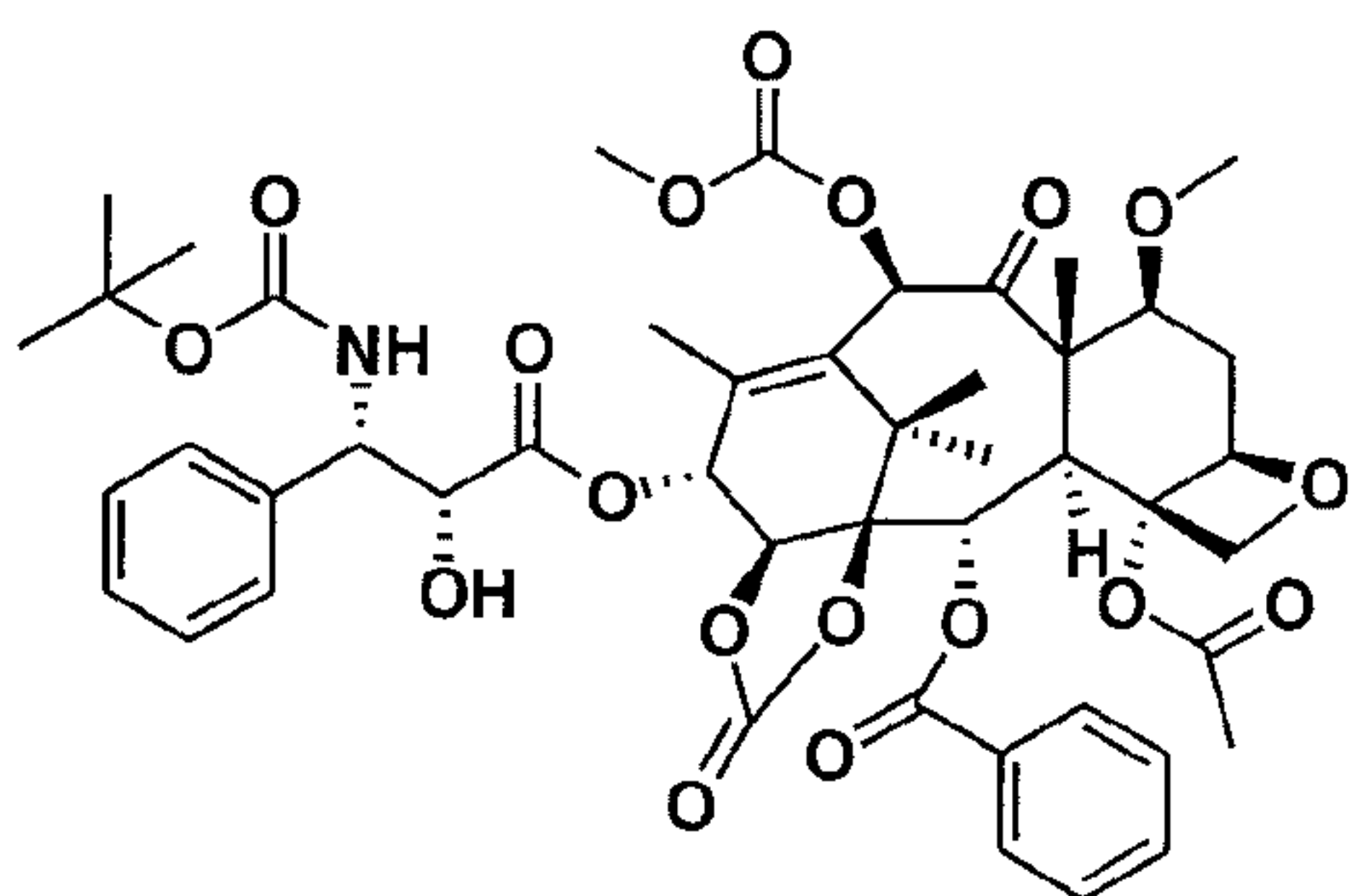
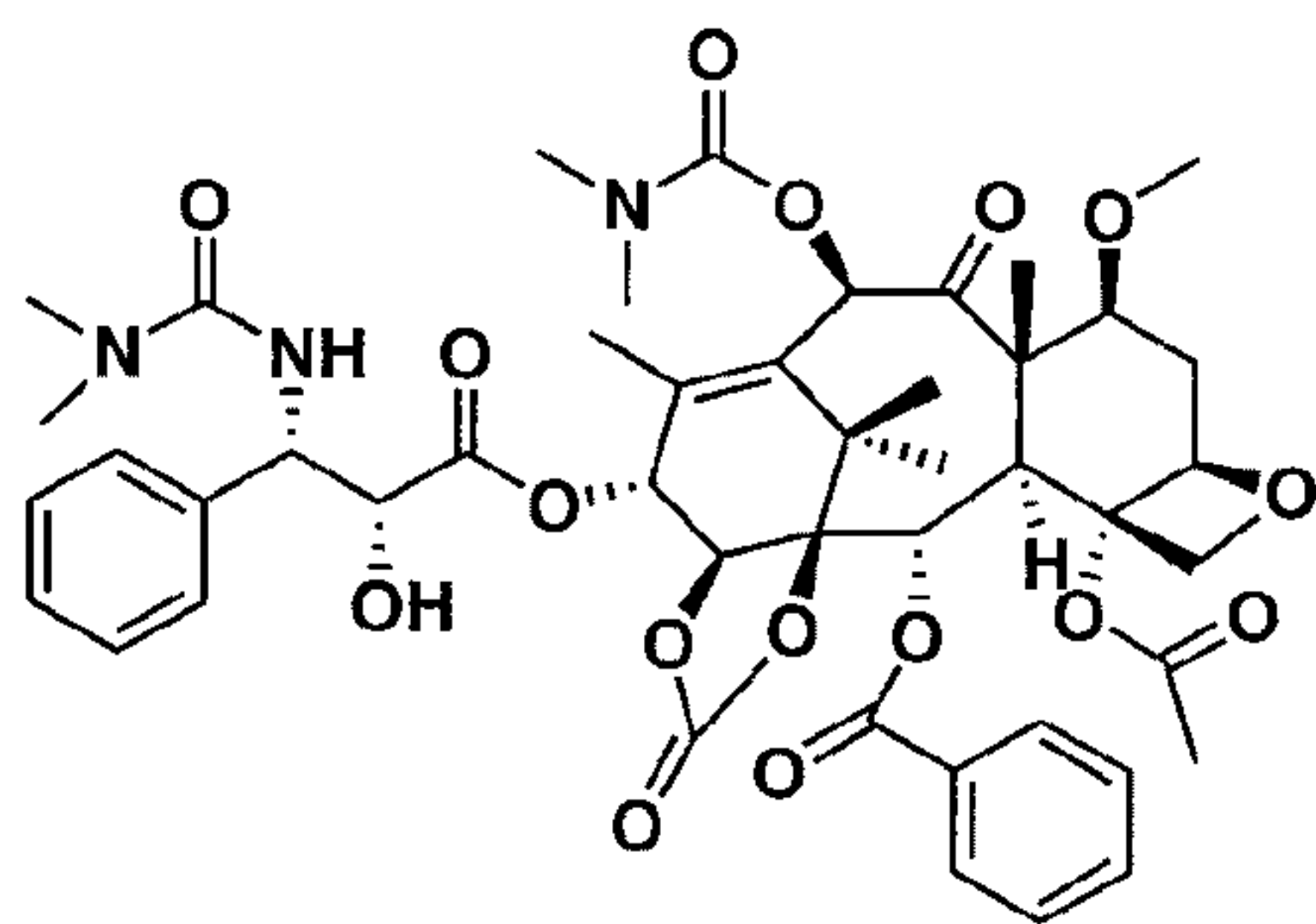
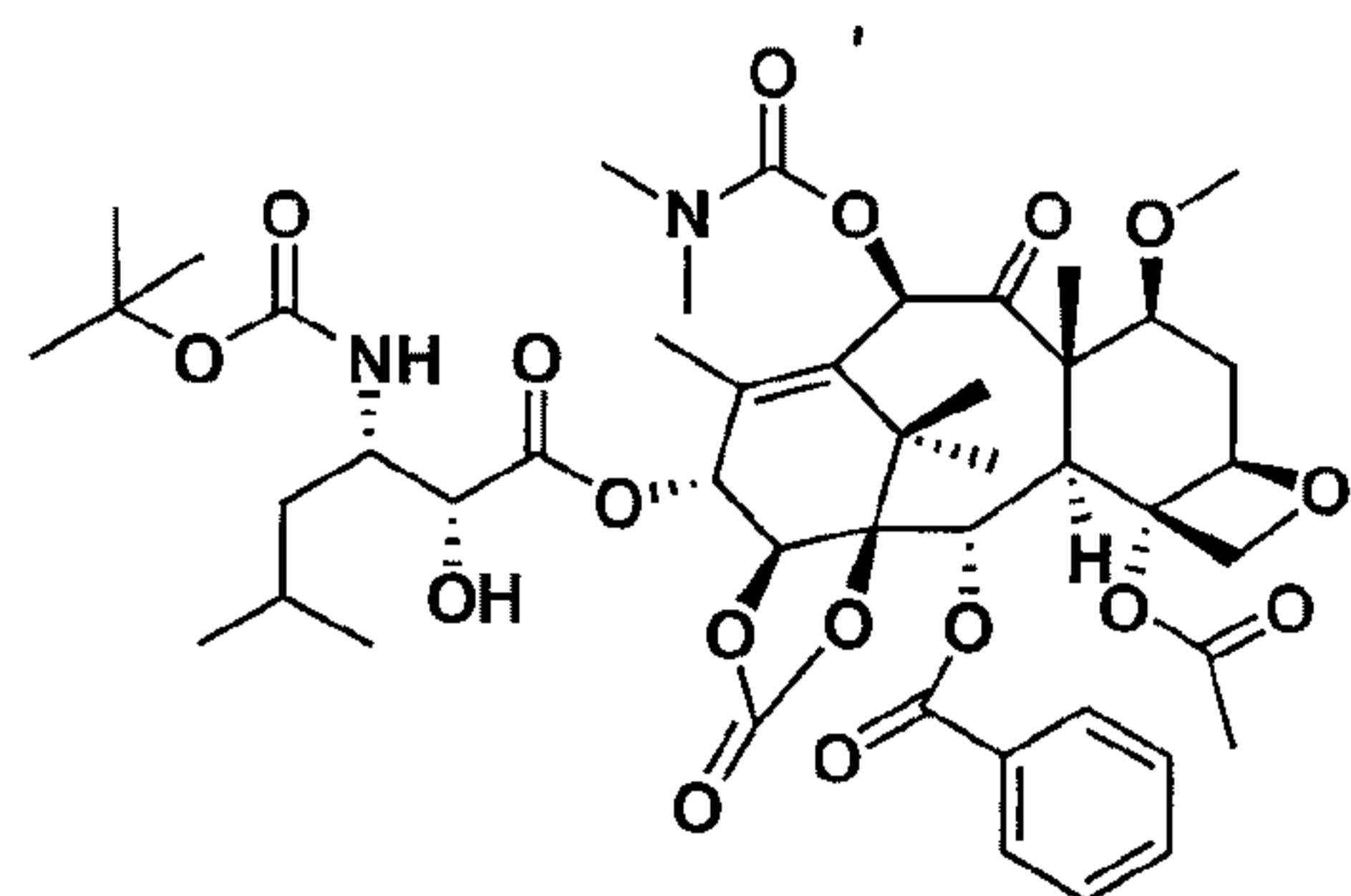
R₄ is -OMe, -OCOOCH₃, -OCON(CH₃)₂, or -OCOSC₂H₅.

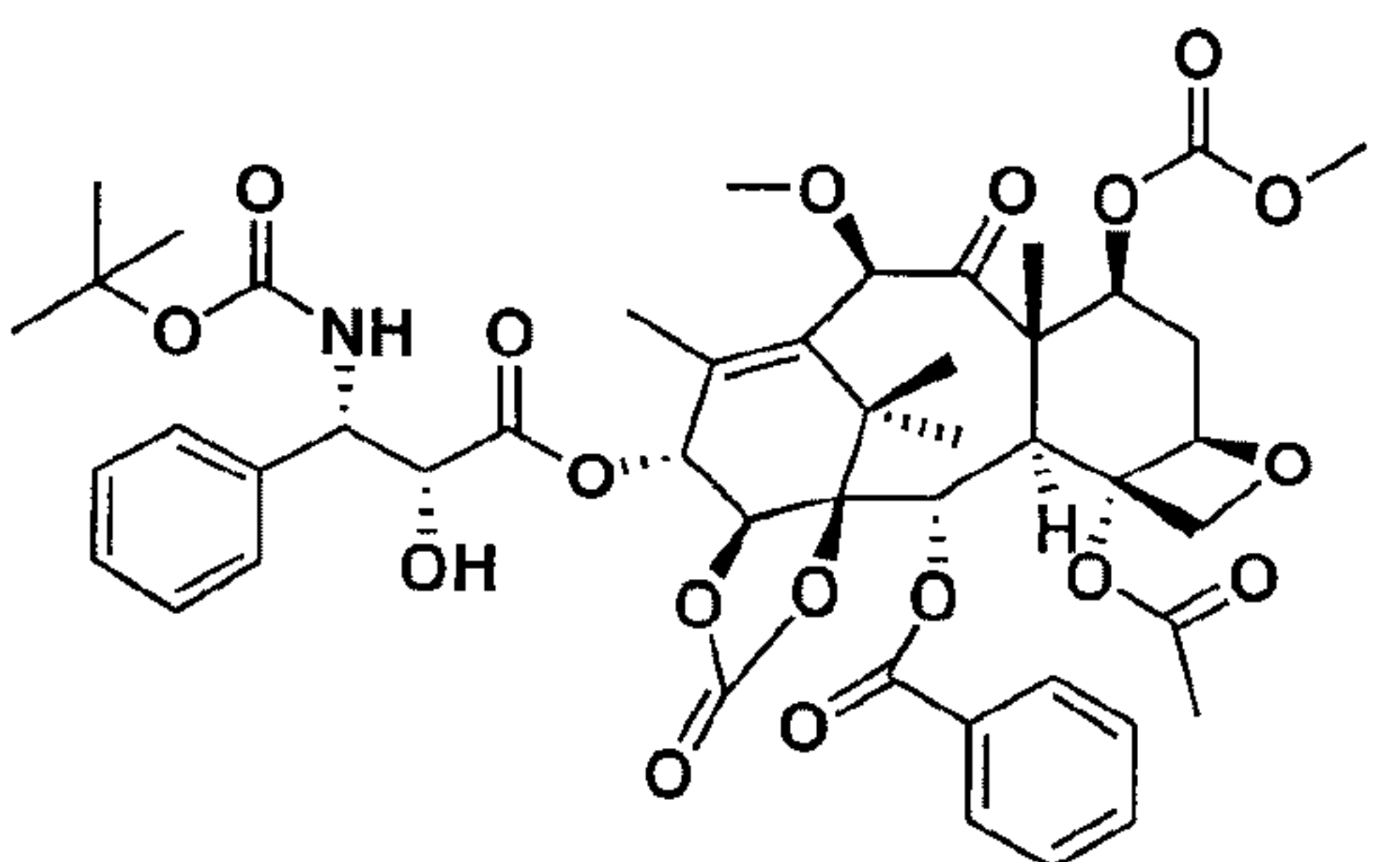
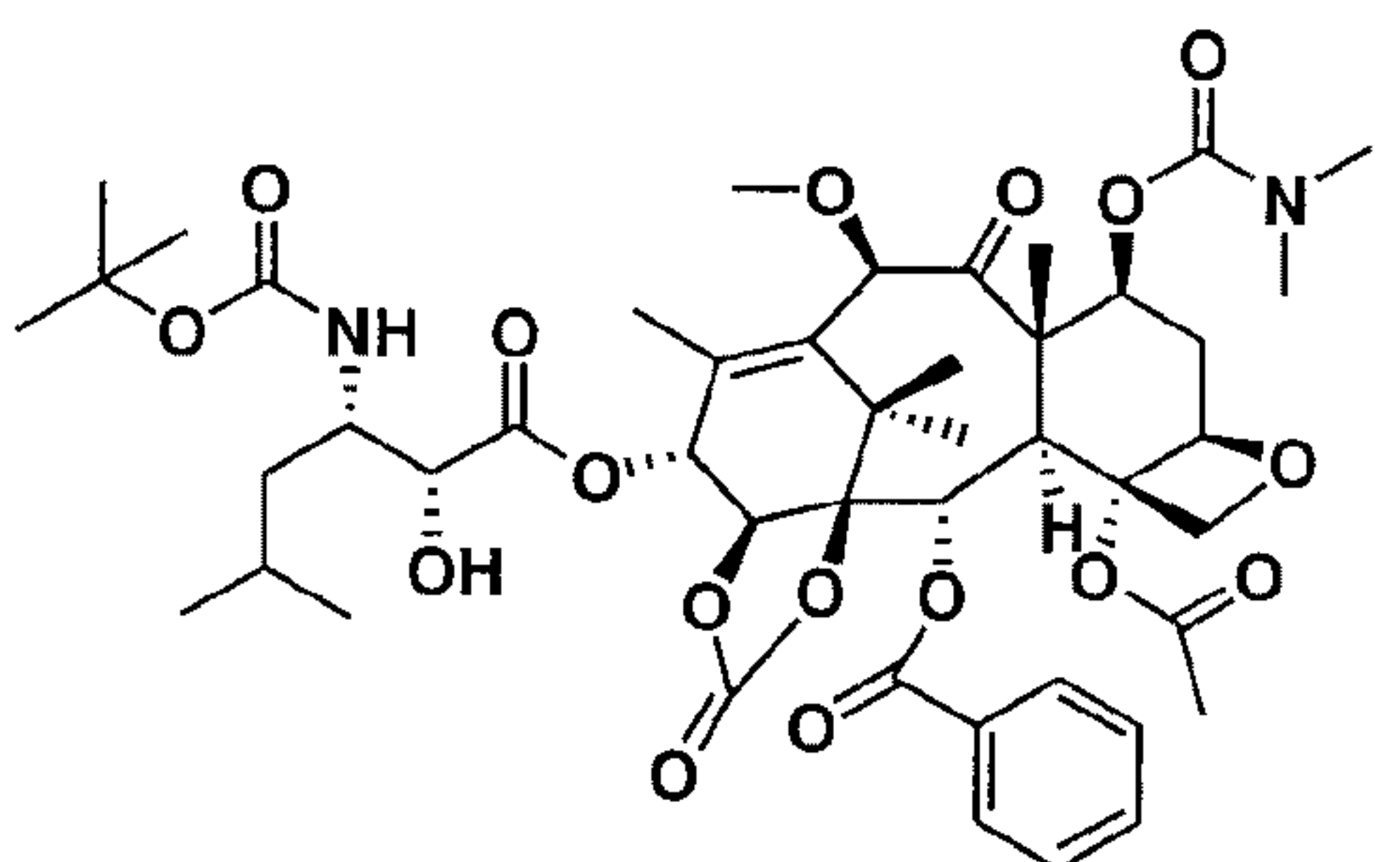
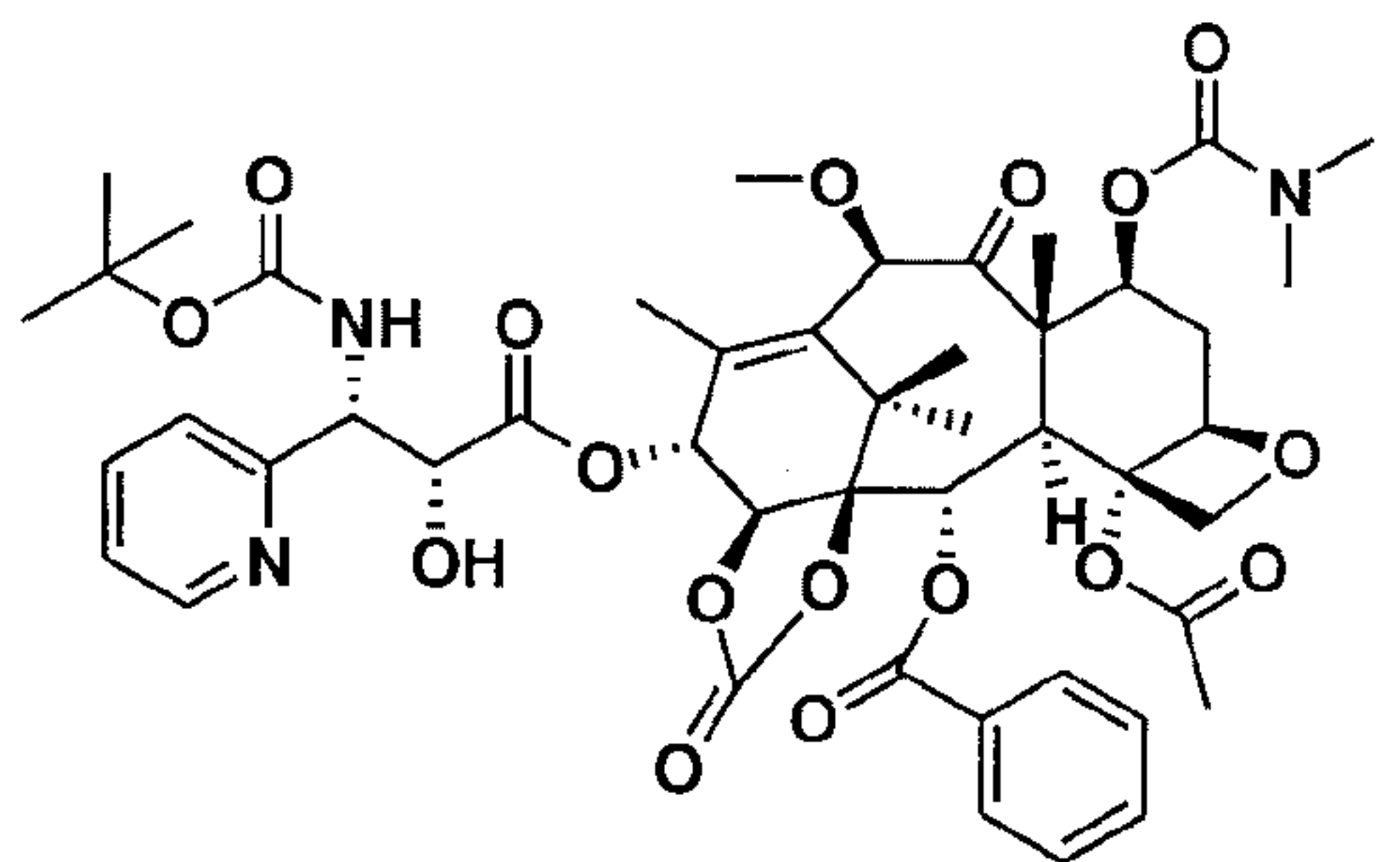
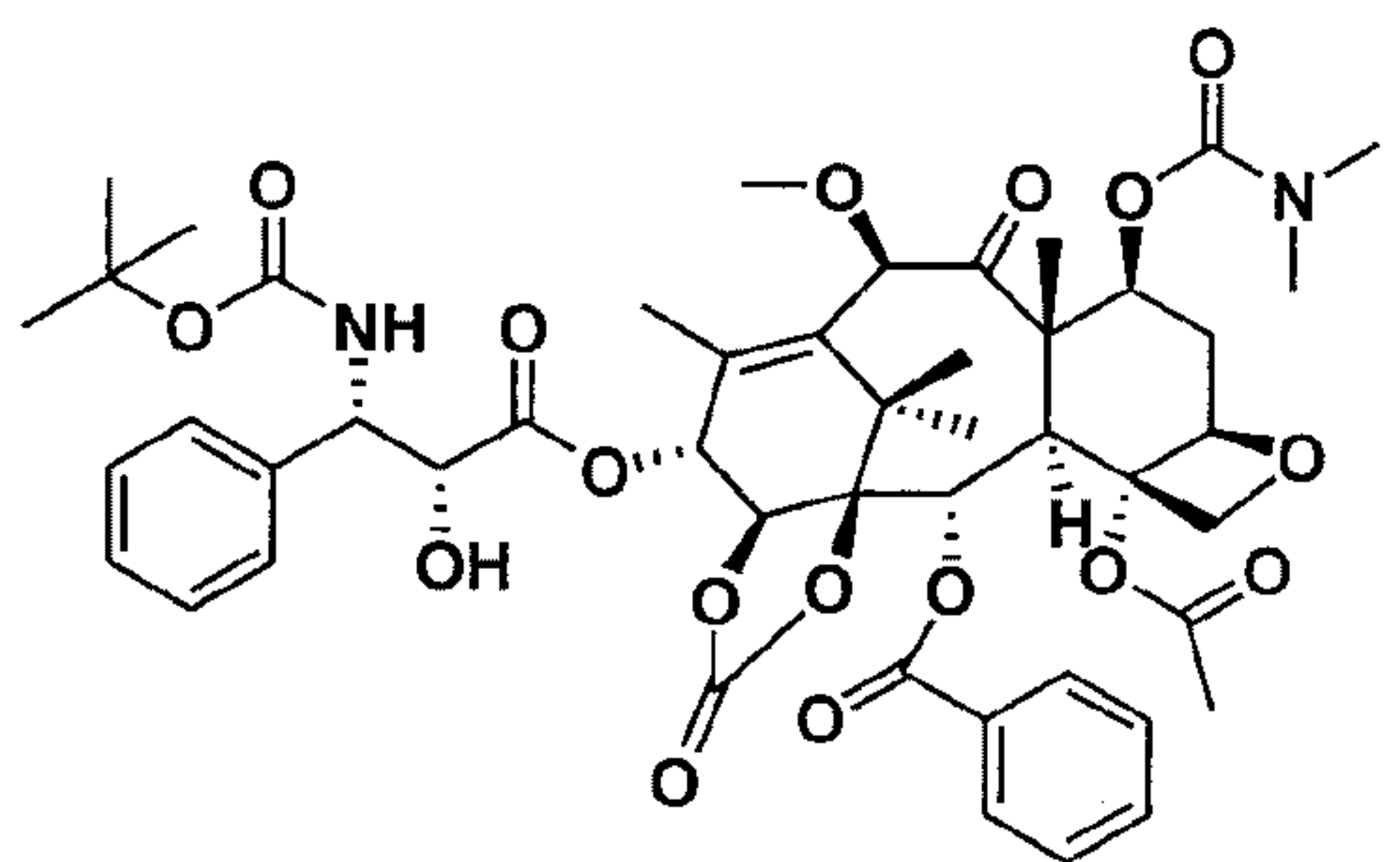
10 2. The taxane compound according to claim 1, wherein the compound has a structure represented by:

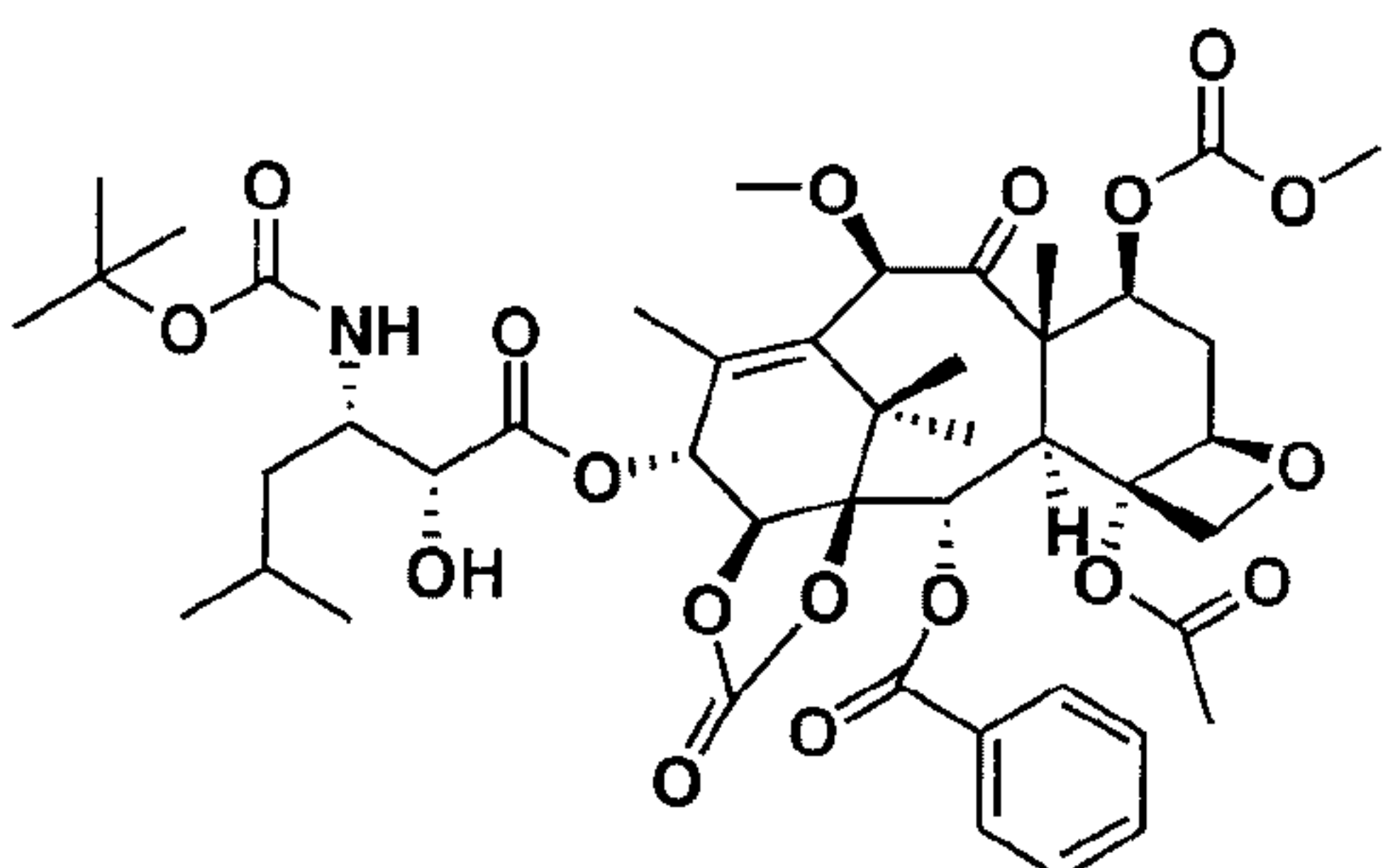
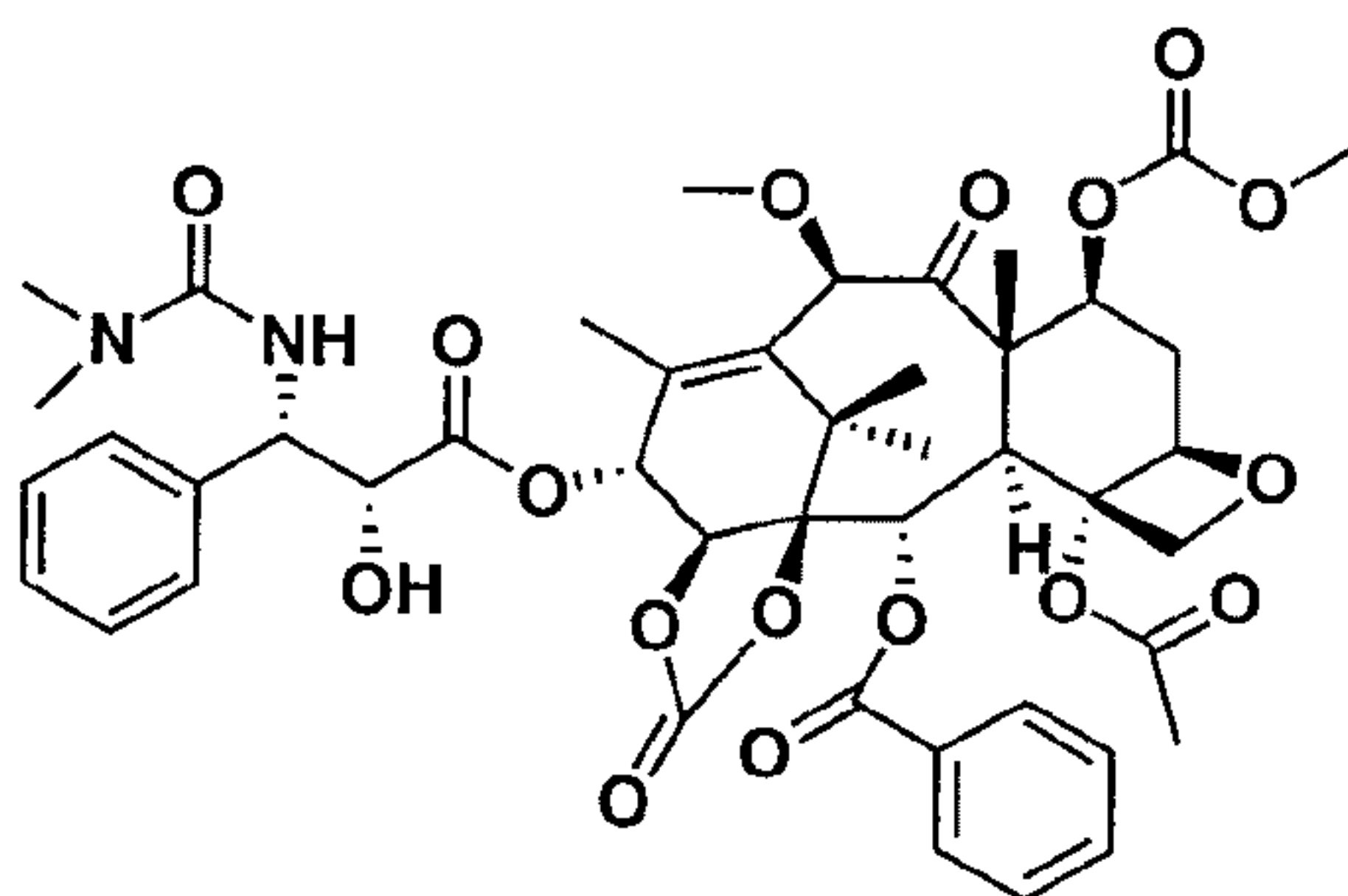
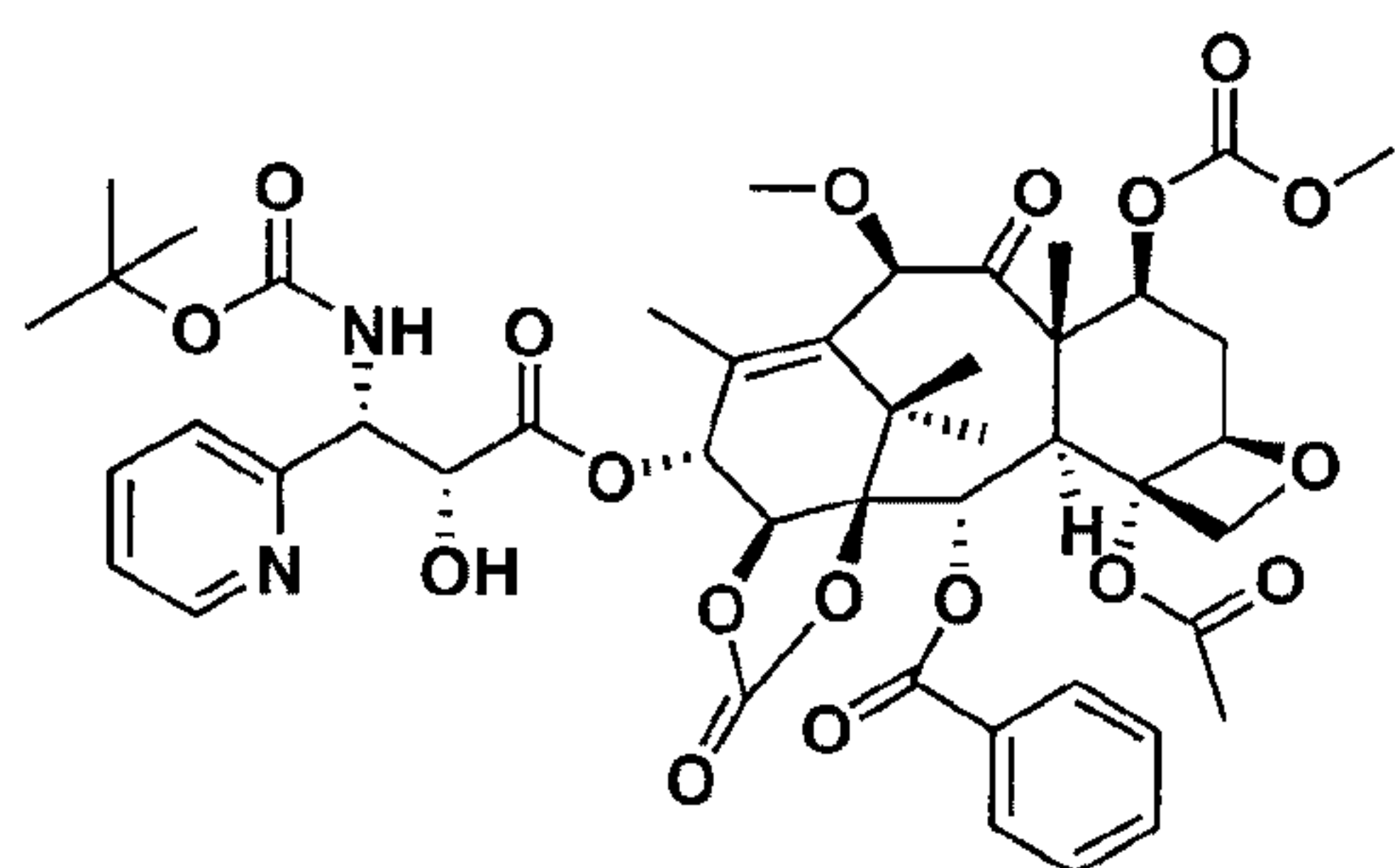




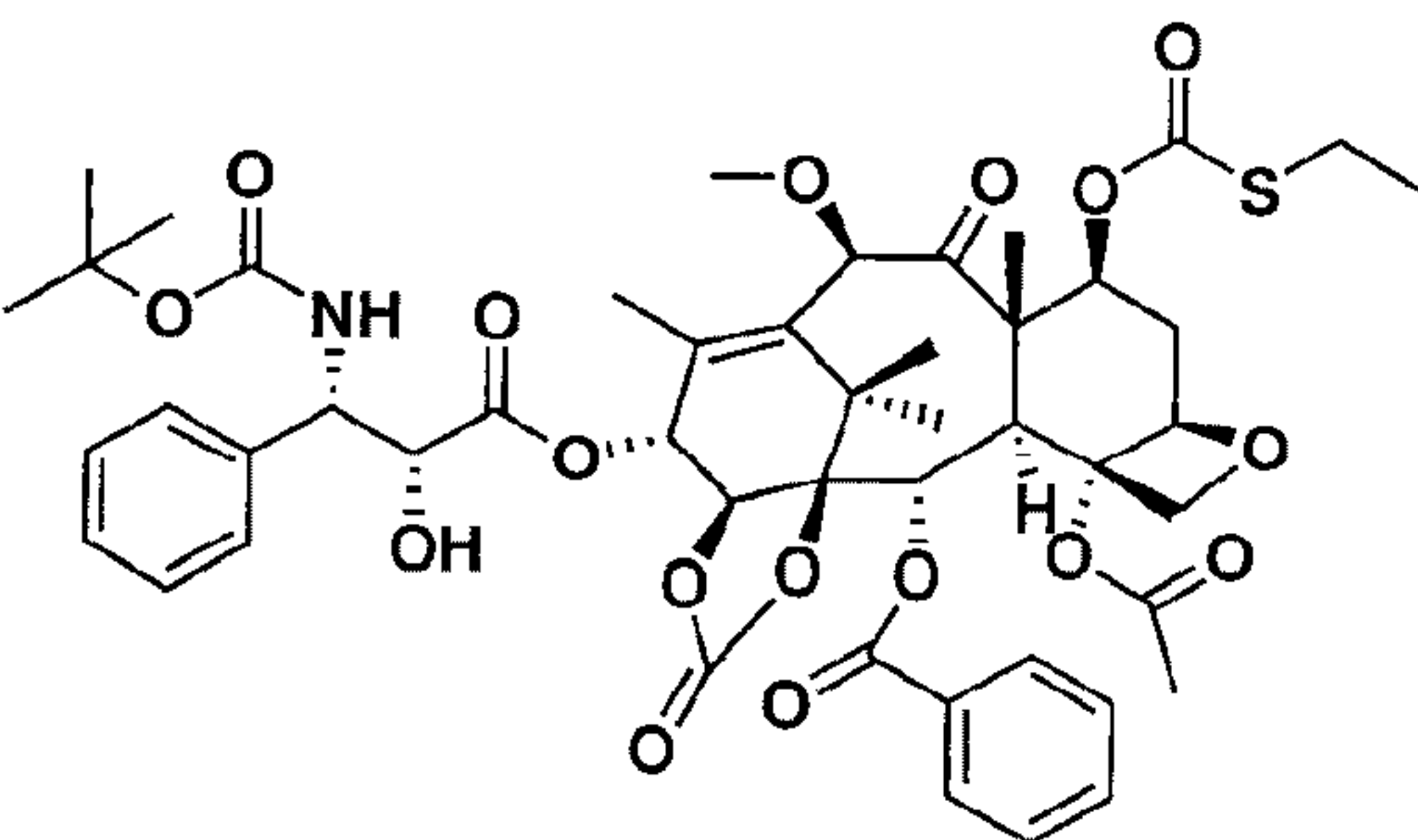
5







, or



- 5 3. A pharmaceutically acceptable non-toxic salt of the taxane compound of claim 1 or 2.
4. A solvate of the taxane compound of claim 1 or 2.
5. An antitumor pharmaceutical composition, comprising a compound of formula I as defined in claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, as the active ingredient, and a pharmaceutically acceptable carrier.

6. The antitumor pharmaceutical composition according to claim 5, wherein a weight ratio of the active ingredient in the composition is 0.01% to 99.99%, with the balance being the pharmaceutically acceptable carrier.

7. Use of a compound as defined in claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 5 or claim 6, in manufacturing an oral antitumor medicament.

8. A preparation method of the taxane compound as defined in claim 1 or 2, wherein the method comprising the following steps:

Step 1 synthesis of taxanes mother nucleus part: by using 10-deacetyl baccatin III (10-DAB) as raw material, firstly, the hydroxyl groups at C7 and C10 positions of the mother nucleus part are selectively protected with substituents, then the C13 hydroxy group is oxidized into keto-carbonyl group, followed by highly stereoselectively introducing a hydroxyl group with β configuration at C14 by using N-(sulfonyl)oxaziridine, to form 1,14-carbonate structure under the action of CDI, and finally the C13 keto-carbonyl group is highly stereoselectively reduced into hydroxyl group with α configuration by CBS reduction method to give the taxanes mother nucleus part;

Step 2 synthesis of a precursor of five-member ring oxazolidine acid side chain: glycolic acid, used as raw material, is protected successively by benzyl group and butyloxycarbonyl group (Boc group) to generate the Boc-protected benzyl glycolate; different substituted aldehydes are condensed with (*S_R*)-*t*-butyl sulfinamide to form the corresponding enamine compounds; the Boc-protected benzyl glycolate and the enamine compound are reacted via an addition reaction in the presence of lithium salt, and then a chiral intermediate is given after acid hydrolysis, and the obtained intermediate is reacted with 1,1'-(dimethoxymethyl) *p*-methoxybenzene via an aldol condensation reaction, catalyzed by pyridinium *p*-toluenesulfonate (PPTS) to obtain a condensation compound; the amino group of the condensation compound is substituted with different substituents, and the precursor of five-member ring oxazolidine acid side chain is finally given after catalytic hydrogenation;

Step 3 synthesis of taxanes derivatives: the precursor of five-member ring oxazolidine acid side chain is linked with the taxanes mother nucleus part by esterification, and a series of taxanes derivatives are generated after removal of the protective group by acid hydrolysis.

9. The preparation method of claim 8, wherein,

In Step 1, the C7- and C10-hydroxyl groups are protected with substituents:

(1) When R_3 and R_4 are -OMe, the reaction involved is: firstly, the hydroxyl group is reacted with *p*-toluenesulfonyl chloride (TsCl) at room temperature to 0°C in
5 tetrahydrofuran or dichloromethane as the solvent and pyridine (Py) as the alkali to give *p*-toluenesulfonate, which is further reacted with a Grignard reagent to give the corresponding ether -OMe;

(2) When R_3 and R_4 are -OCOOCH₃ or -OCON(CH₃)₂, the reaction involved is: under alkaline conditions, the hydroxyl group is reacted with the corresponding acyl chloride in
10 tetrahydrofuran as the solvent at room temperature to -70°C;

(3) When R_3 and R_4 are -OCOSC₂H₅, the reaction involved is: the hydroxyl group is reacted with N,N'-carbonyldiimidazole (CDI) in tetrahydrofuran as the solvent at room temperature, and the obtained product is further reacted with mercaptan via substitution reaction;

In Step 1, the stereoselective reduction on the C13 keto-carbonyl group by CBS reduction
15 method includes the following specific steps: C13-oxo is stereoselectively reduced into C13-α-OH by using anhydrous tetrahydrofuran, dry dichloromethane or alcohols as the solvent, (R)-2-methyl oxazaborodine as the catalyst and boranes as the reducing agent at room temperature to -70°C;

In Step 2, said different substituted aldehydes include C1-C6 hydrocarbyl aldehydes, C1-C6
20 substituted hydrocarbyl aldehydes, aromatic aldehydes, substituted aromatic aldehydes and heteroaromatic aldehydes; the reaction involved in the substitution of the amino group of the chiral intermediate is carried out by using tetrahydrofuran, dichloromethane or dioxane as the solvent, to react with the corresponding acyl chlorides under alkaline conditions at room temperature to -70°C; in the catalytic hydrogenation reaction, palladium-charcoal or
25 palladium hydroxide is used as the catalyst, hydrogen is introduced at normal pressure or pressurized conditions, and the reaction is carried out in alcohols, tetrahydrofuran or dichloromethane as the solvent.

10. The preparation method of claim 9, wherein,

In Step 1, the C7- and C10-hydroxyl groups are protected by substituents:

(1) When R_3 and R_4 are -OMe, dichloromethane is used as the solvent, and the temperature is at 0°C; and

(2) When R_3 and R_4 are -OCOOCH₃ or -OCON(CH₃)₂, lithium hexamethyldisilazide is used
5 as the alkali and the temperature is at -40°C;

In Step 1, the stereoselective reduction on the C13 keto-carbonyl group by CBS reduction method is carried out at room temperature by using anhydrous tetrahydrofuran as the solvent;

In Step 2, in the reaction involved in the substitution of the amino group on the intermediate,
10 lithium hexamethyldisilazide is used as the alkali and tetrahydrofuran is used as the solvent; the temperature is at -40 °C, the acyl chloride comprises PhCOCl, (CH₃)₃OCOCl and (CH₃)₂NCOCl; in the catalytic hydrogenation reaction, palladium hydroxide is used as the catalyst, hydrogen is introduced at 20psi and the reaction is carried out in an alcoholic solution.

15 11. The preparation method of claim 10, wherein the Grignard reagent comprises CH₃MgBr.

12. The preparation method of claim 10, wherein the acyl chloride comprises at least one of (CH₃)₃OCOCl and (CH₃)₂NCOCl.

13. The preparation method of claim 9, wherein in step 1, when R_3 and R_4 are -OCOSC₂H₅, the mercaptan comprises C₂H₅SH.

20

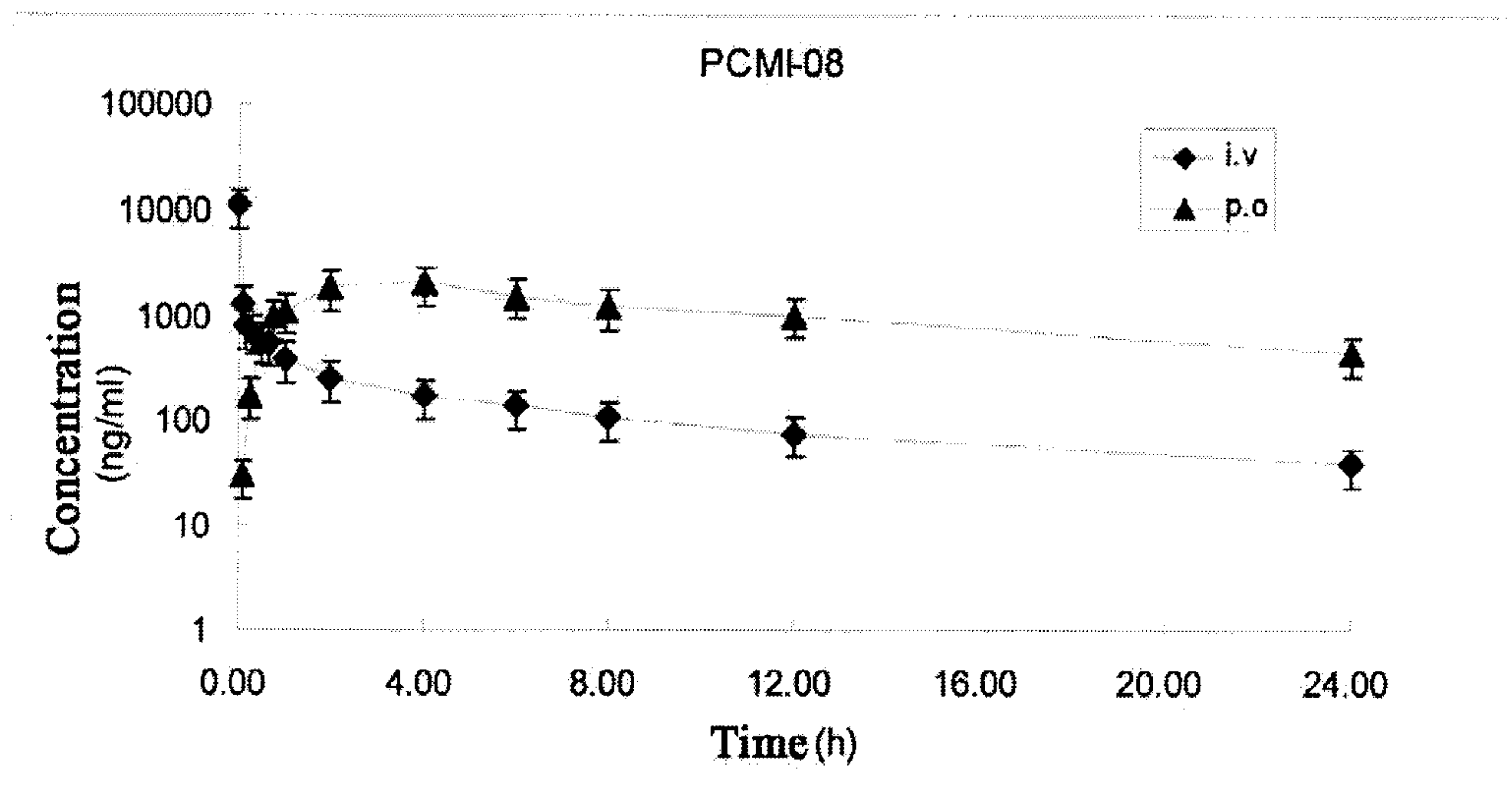


Fig.1

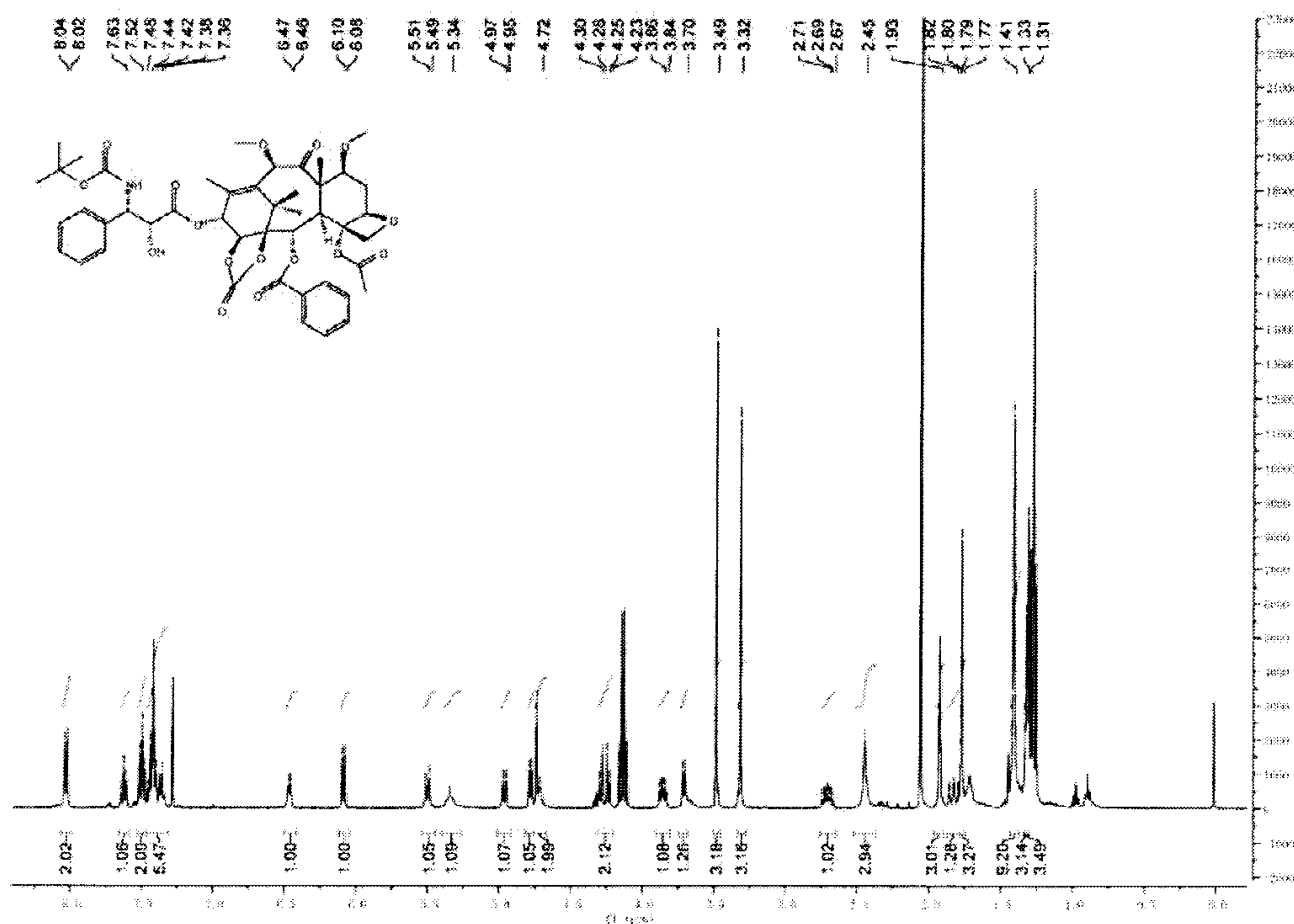


Fig.2

*Patent Agents
Smart & Biggar*

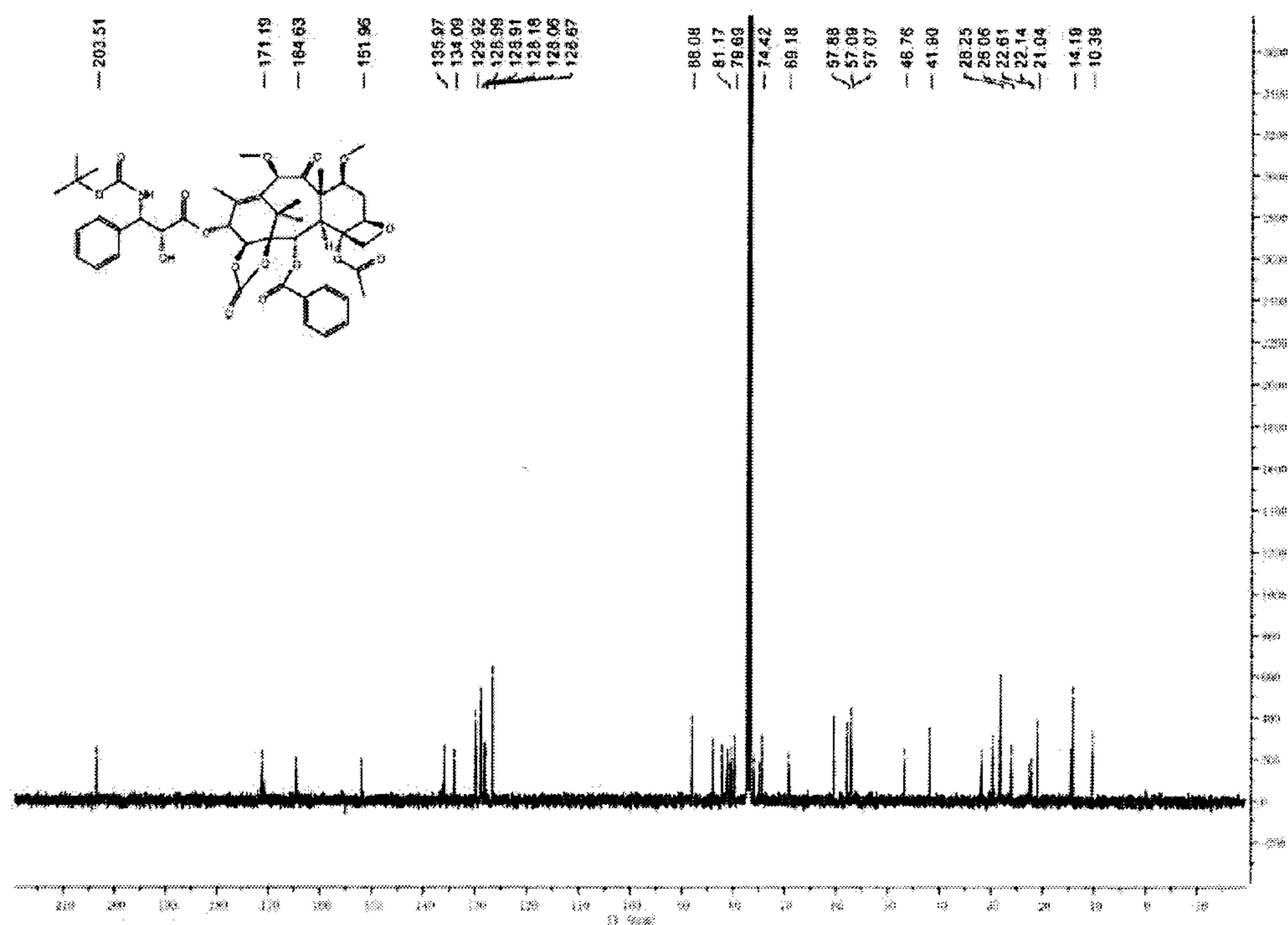


Fig.3

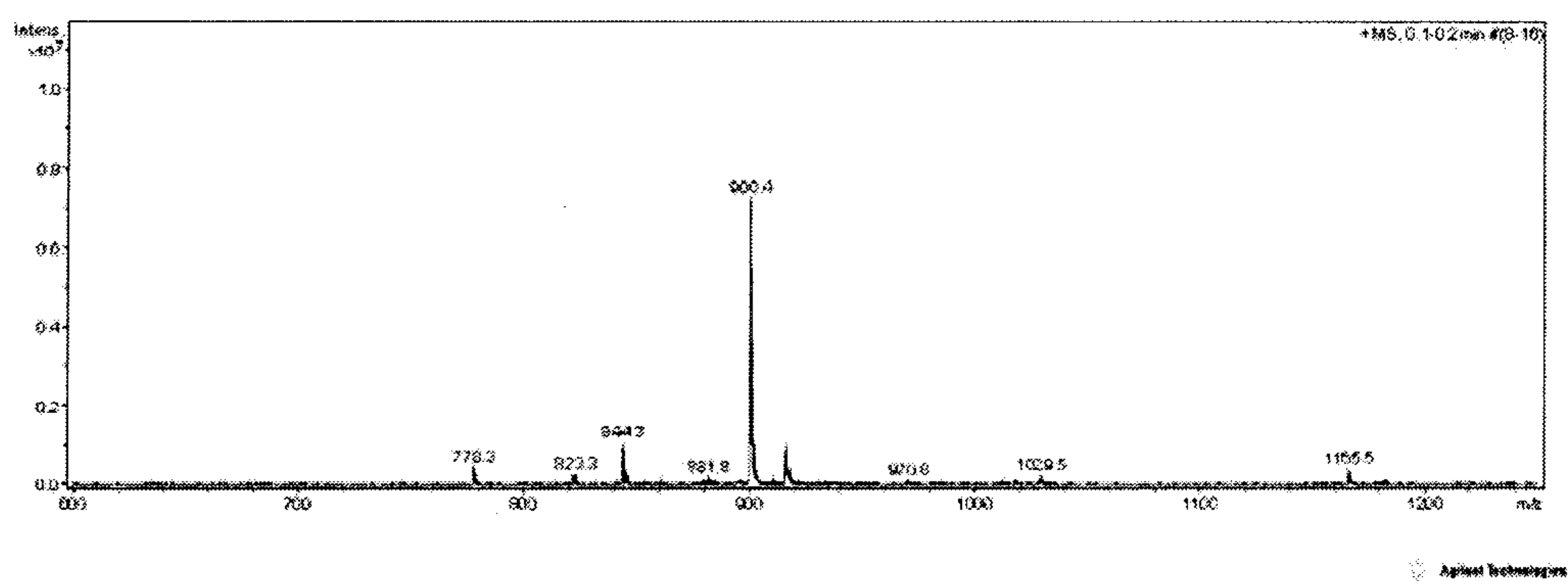


Fig.4

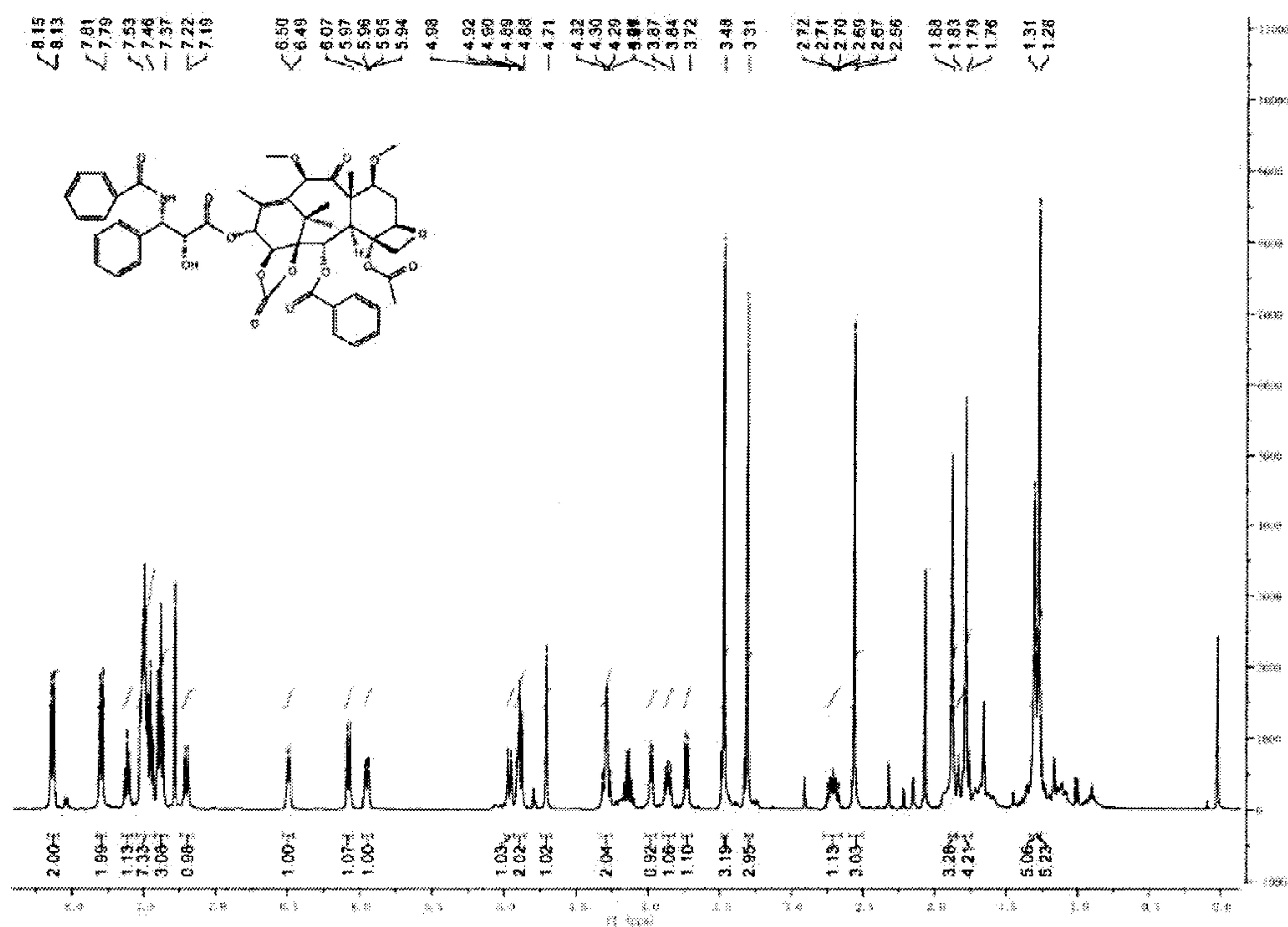


Fig.5

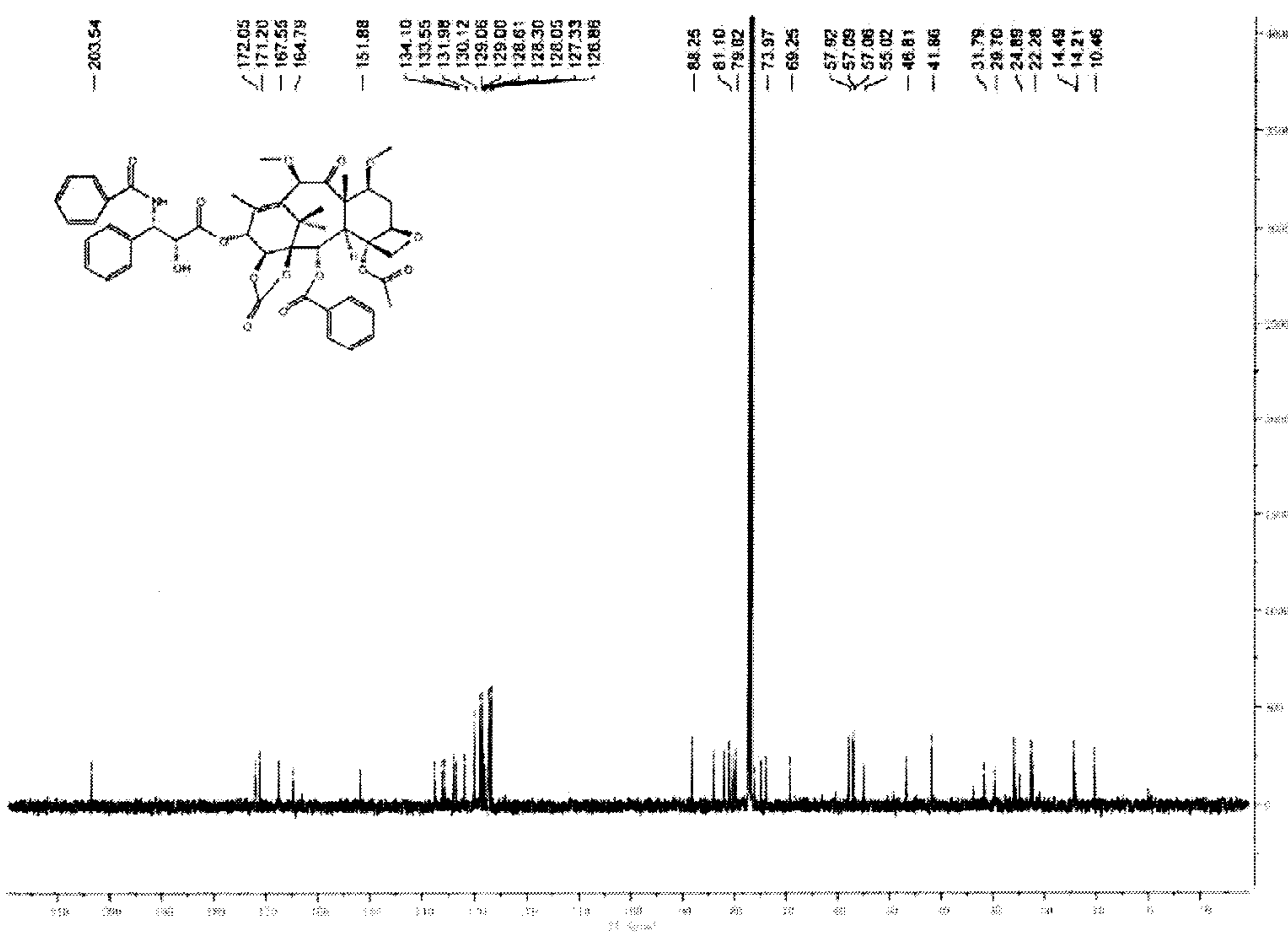


Fig.6

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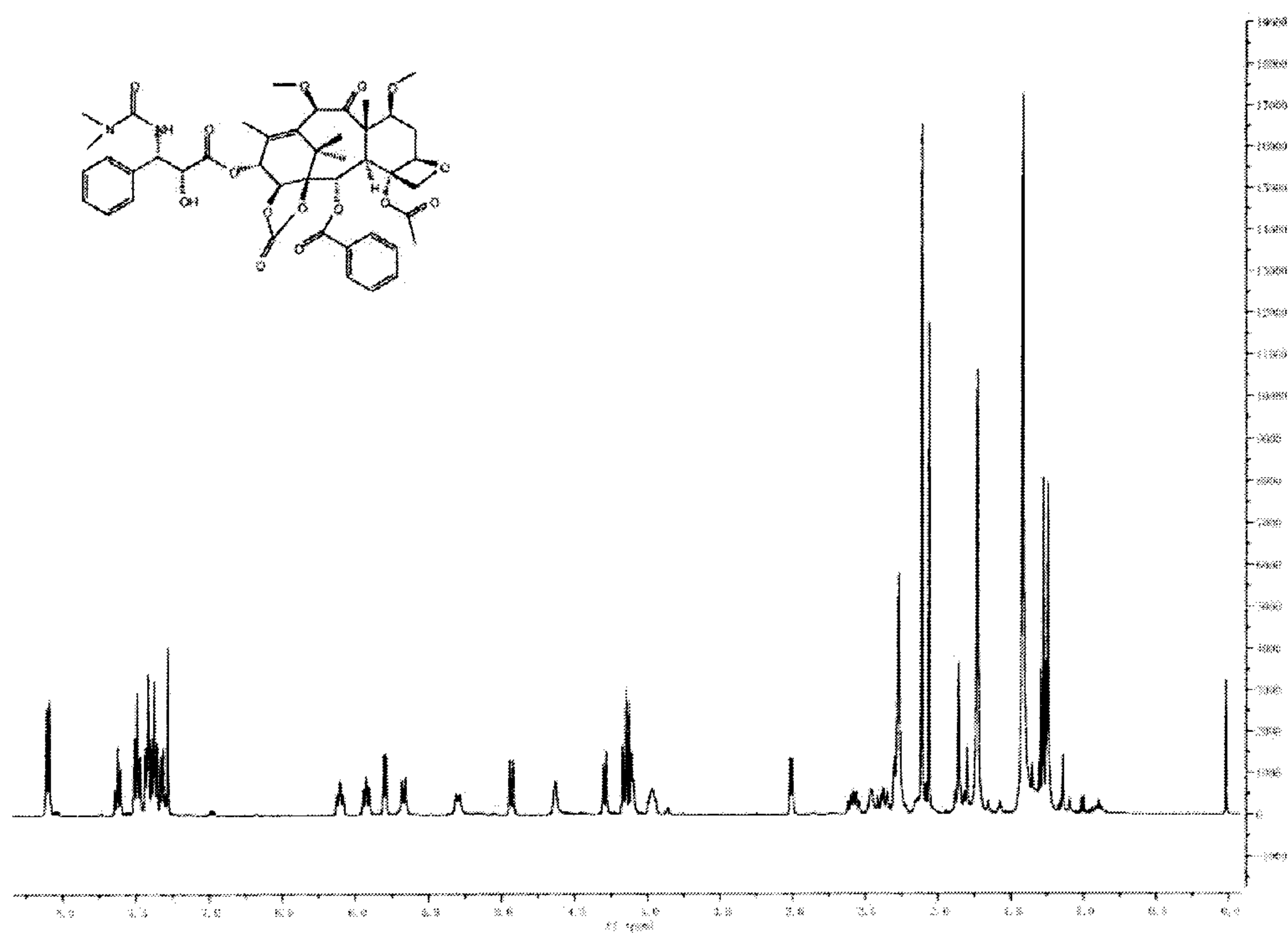


Fig.7

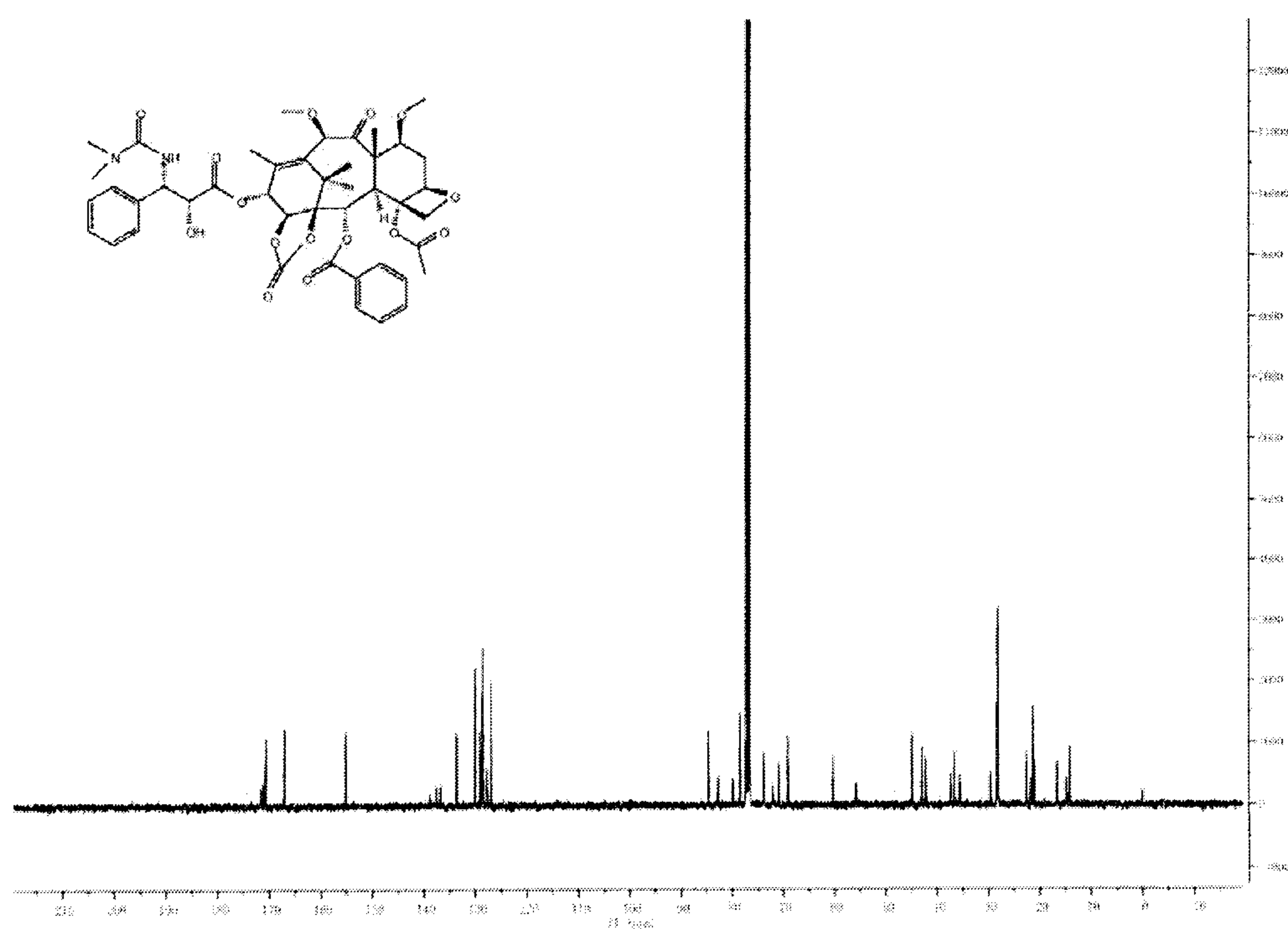


Fig.8

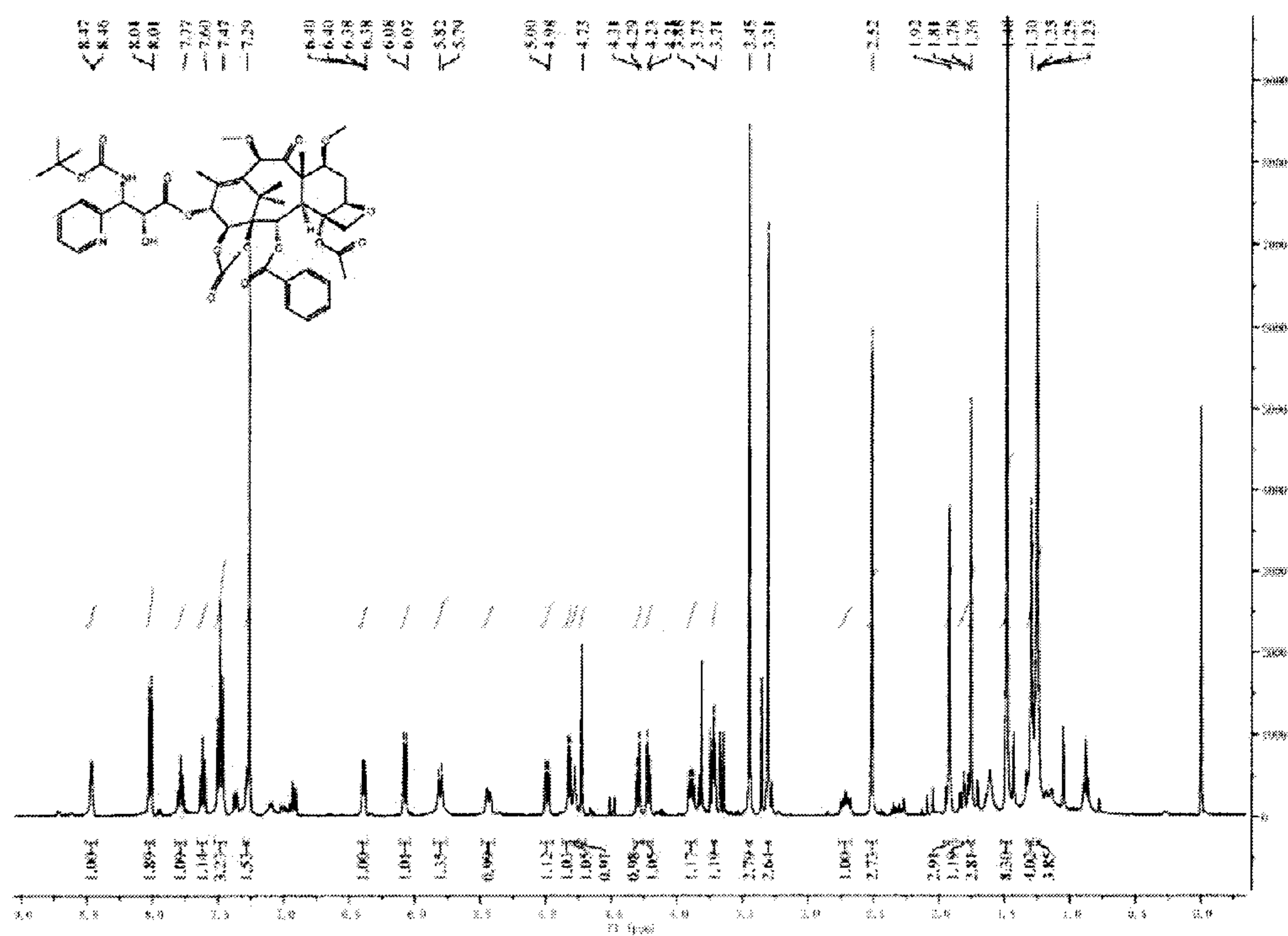


Fig.9

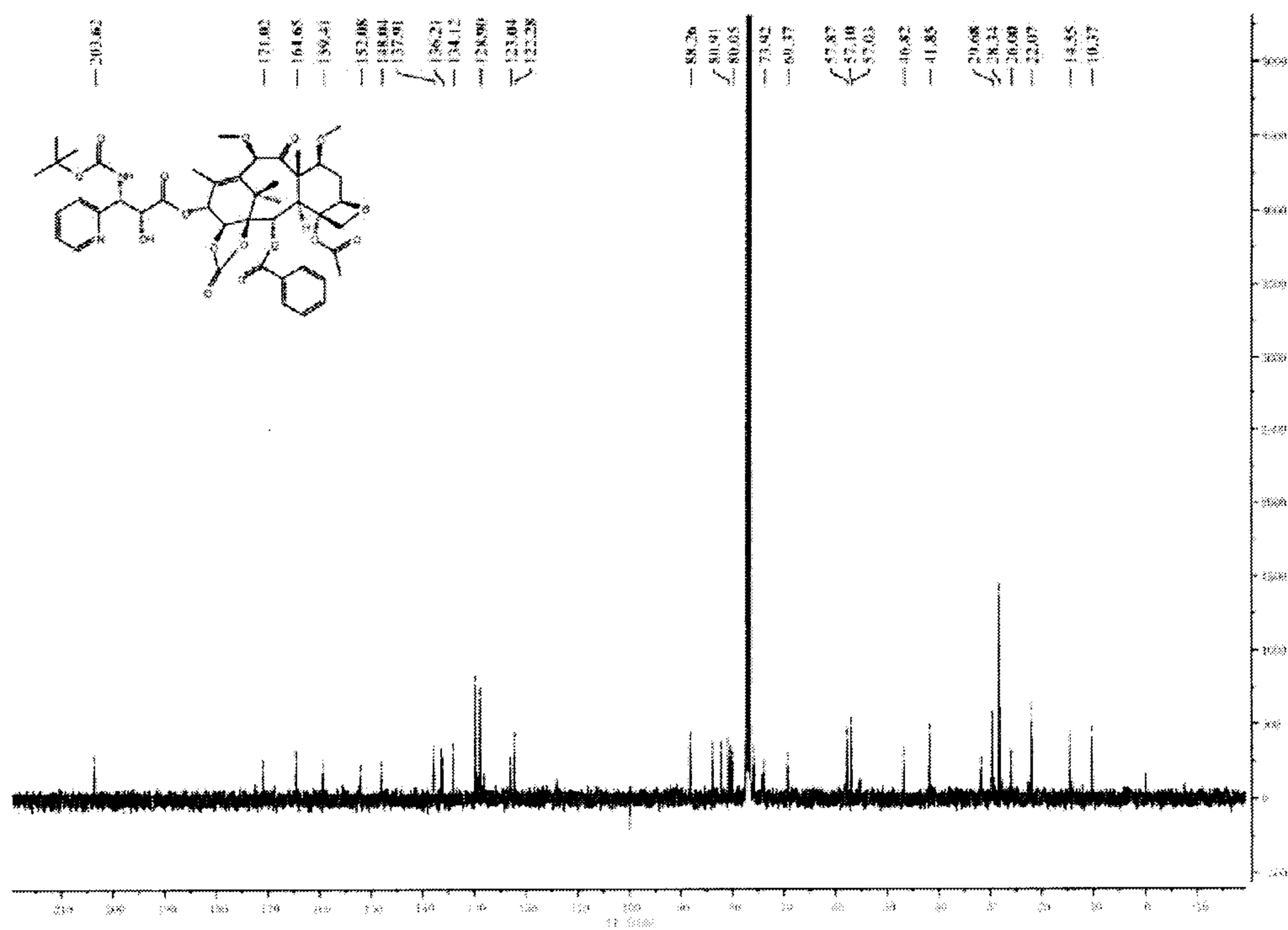


Fig.10

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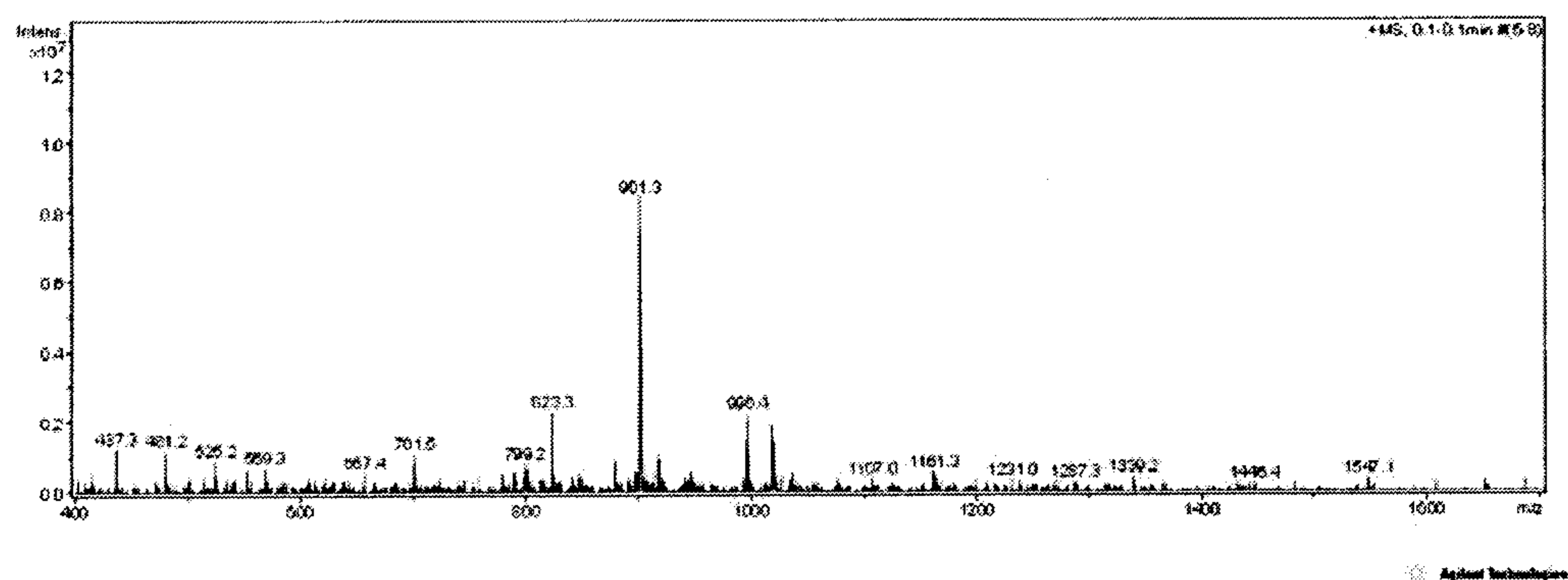


Fig.11

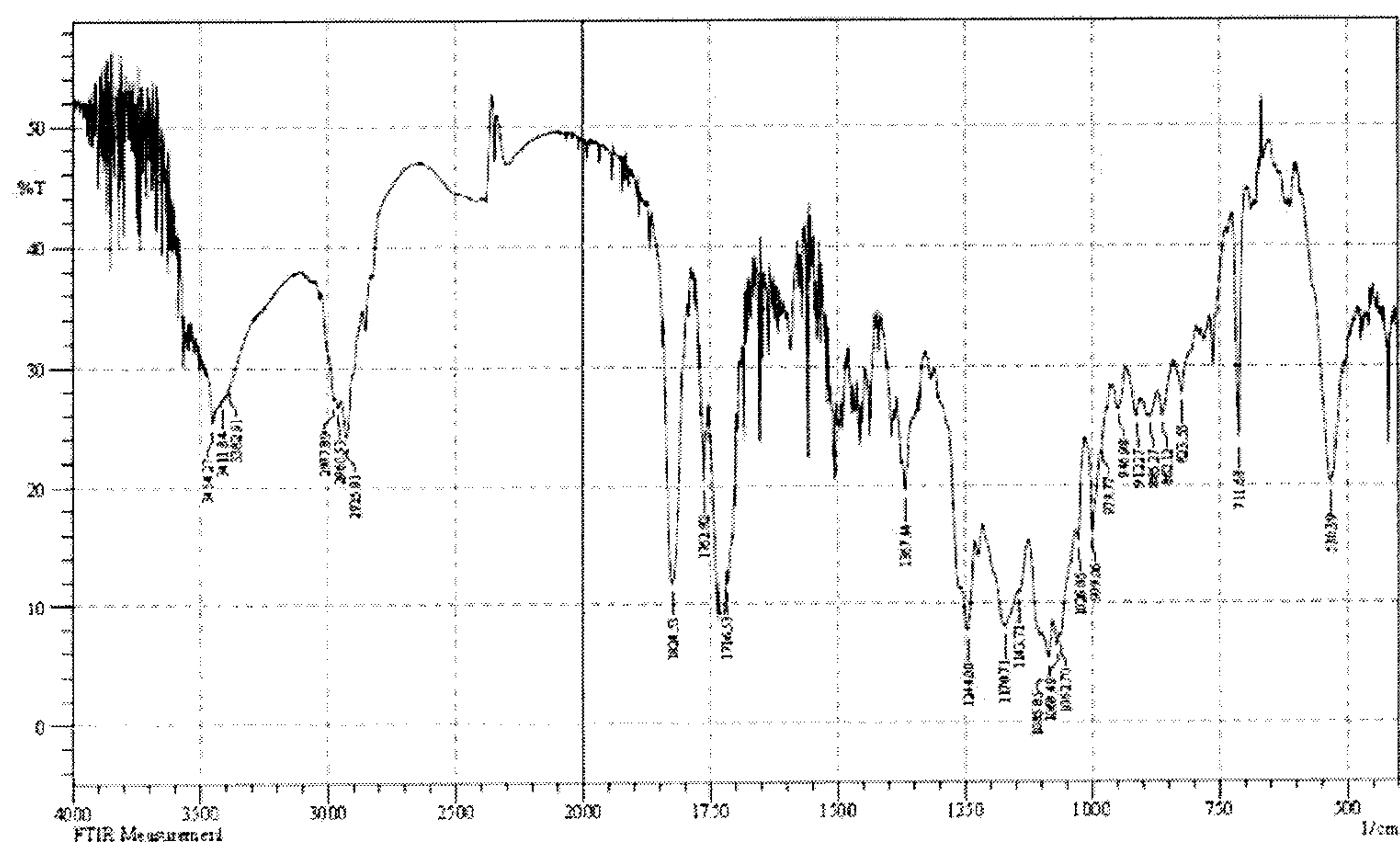


Fig.12

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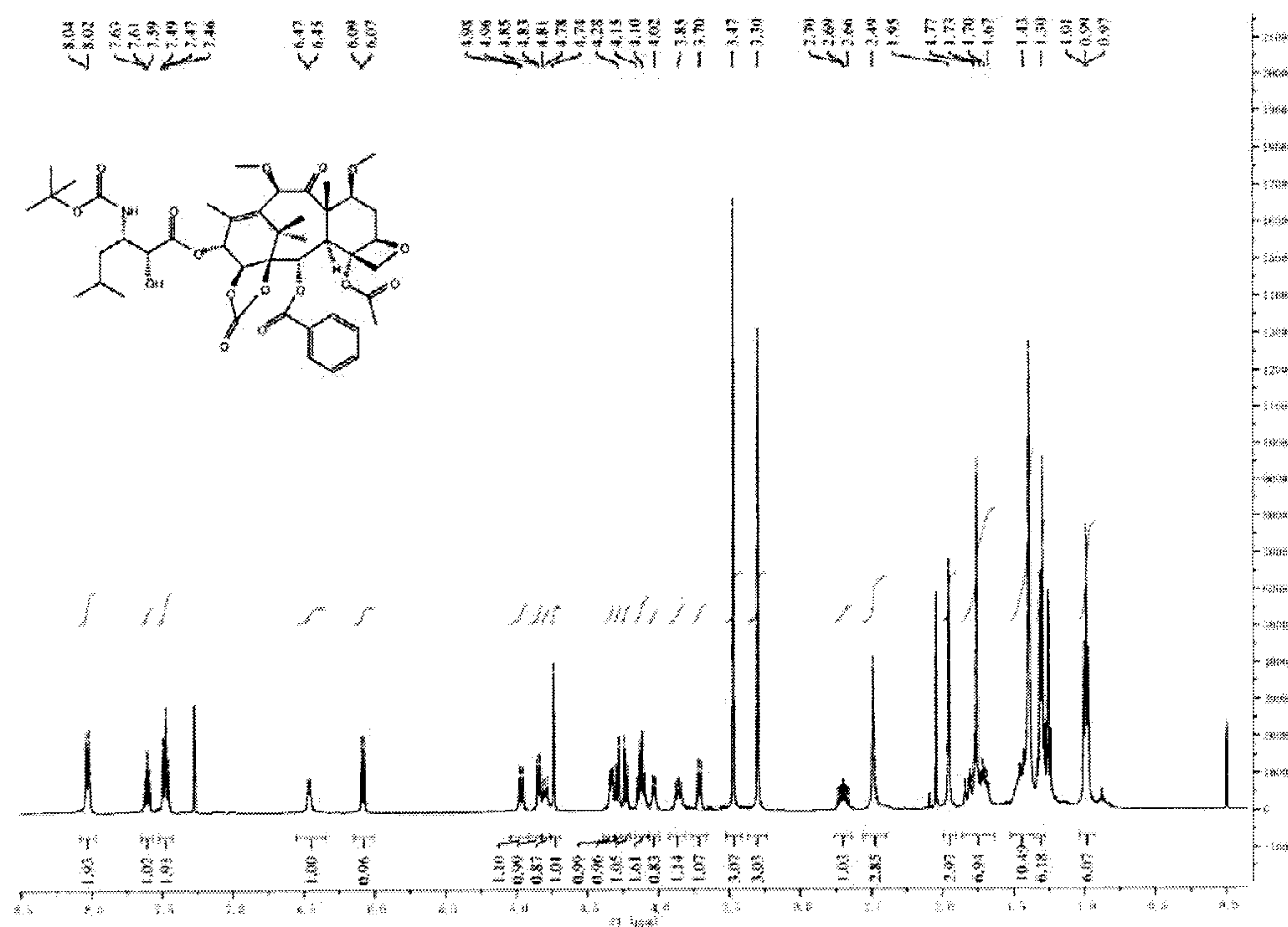


Fig. 13

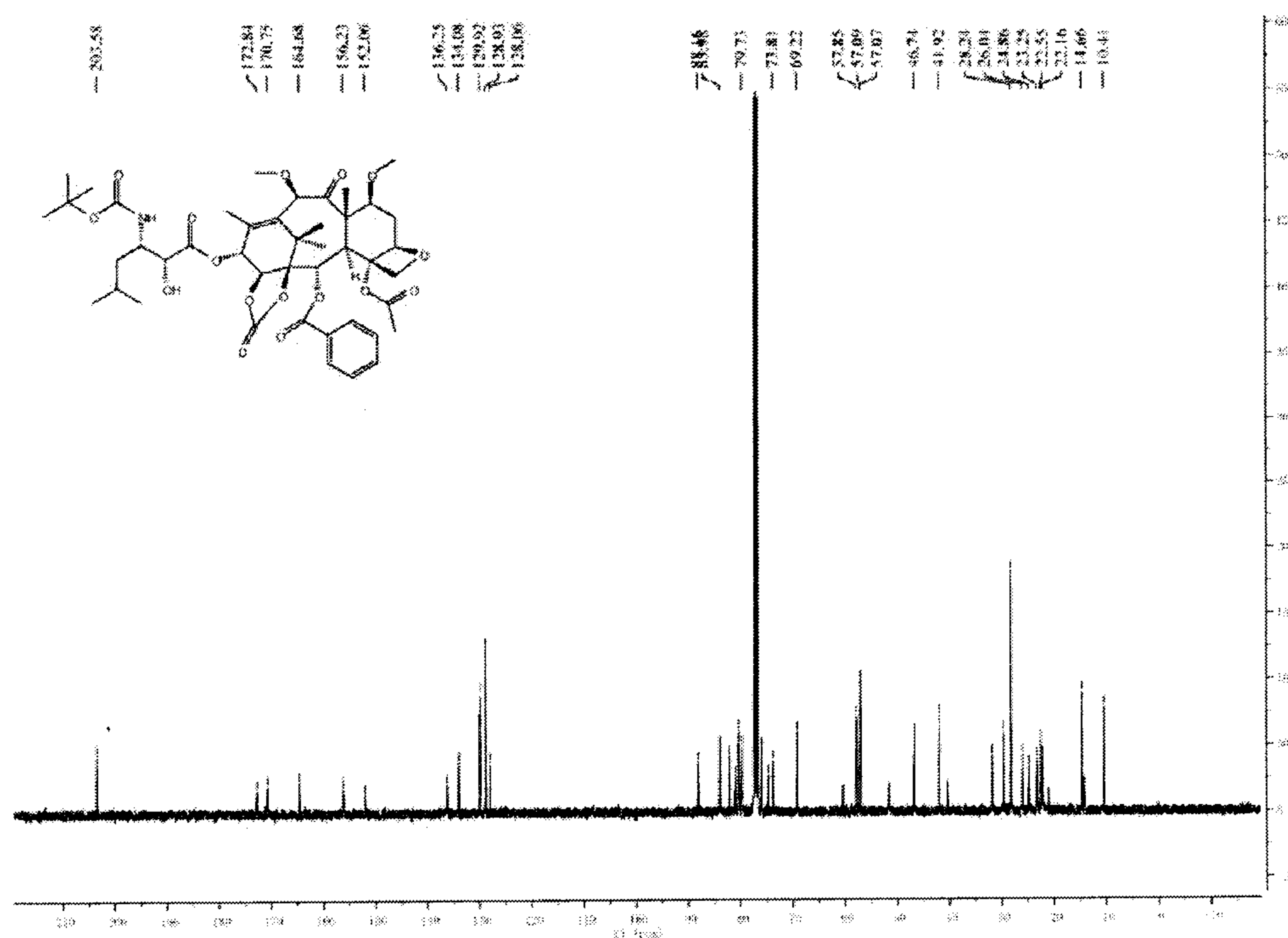


Fig.14

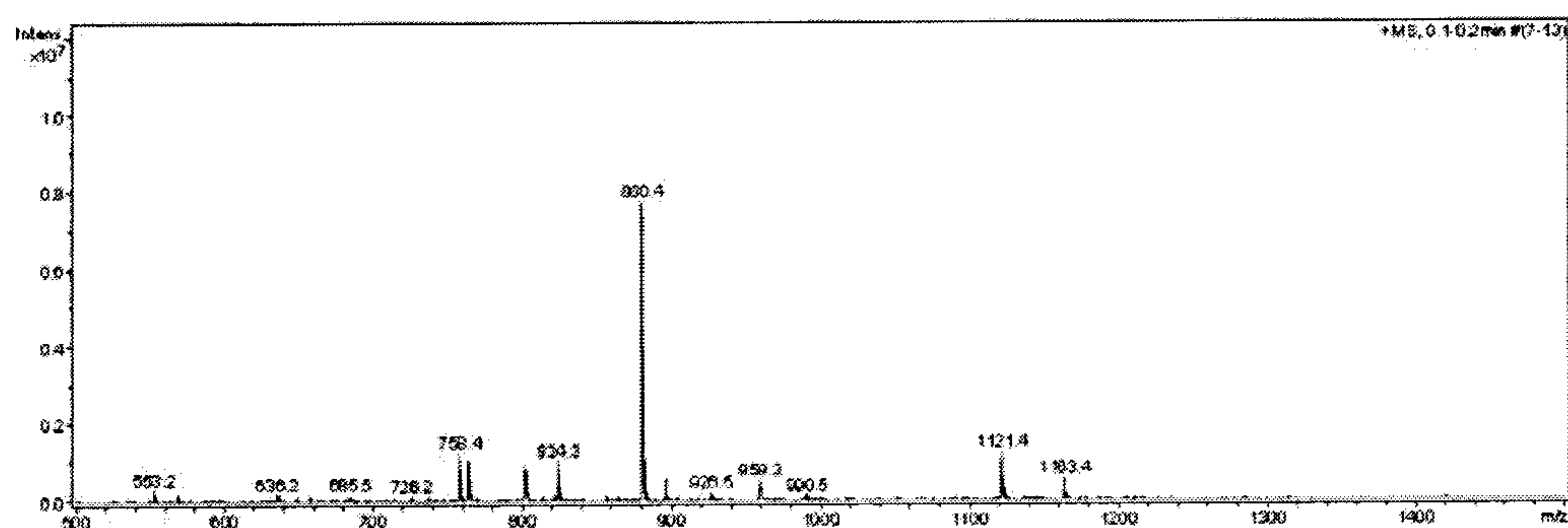


Fig.15

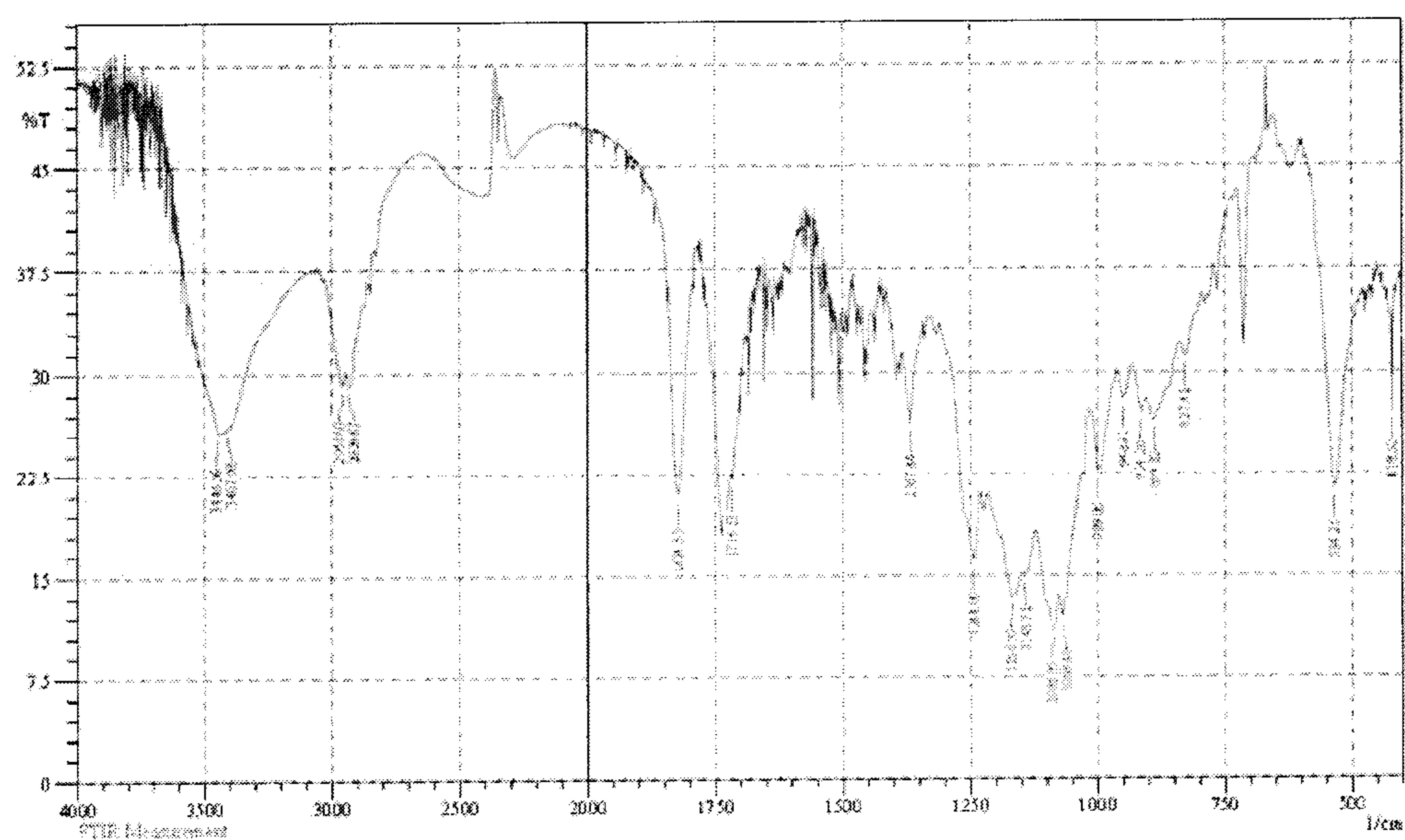


Fig.16

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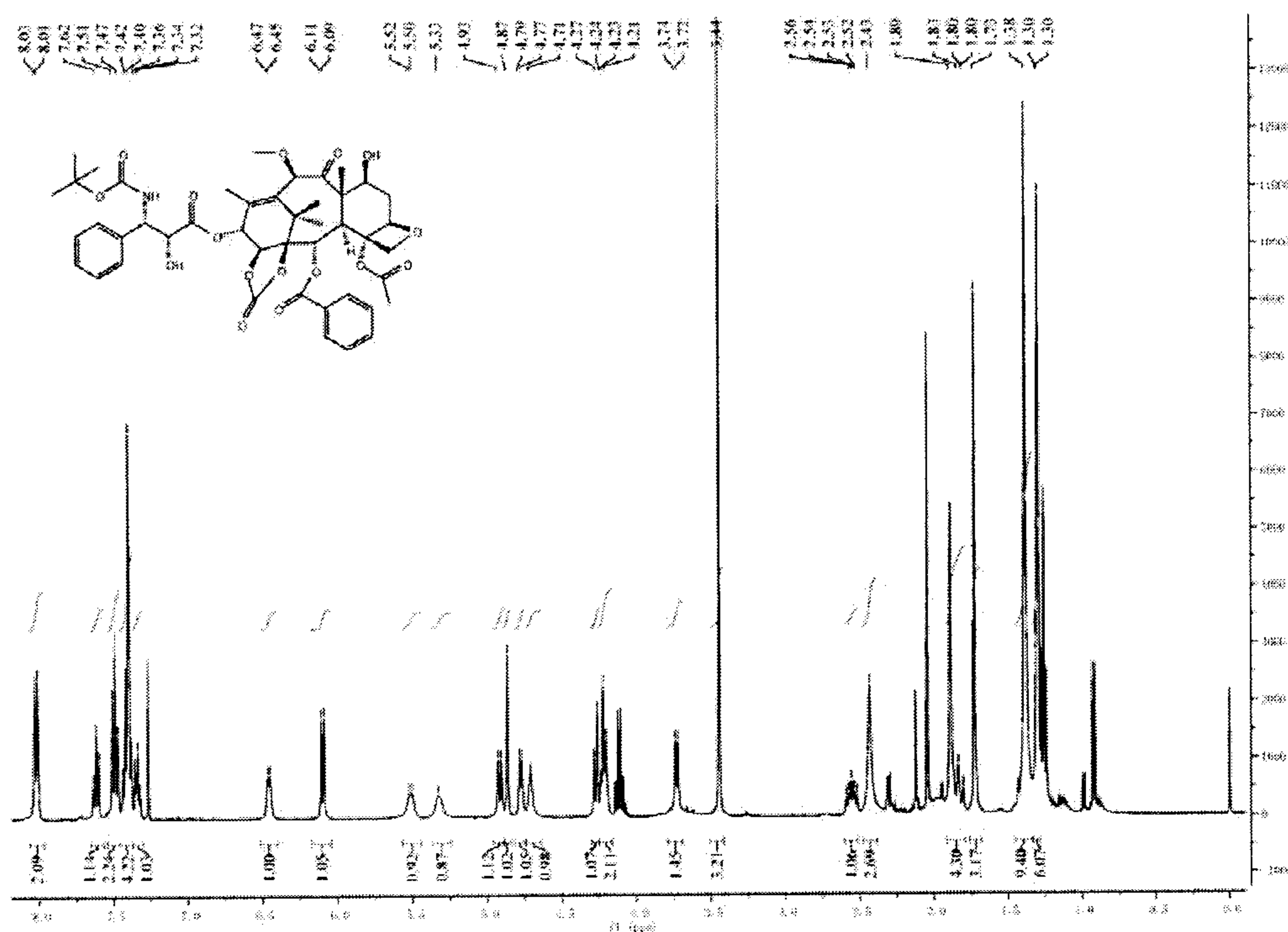


Fig.17

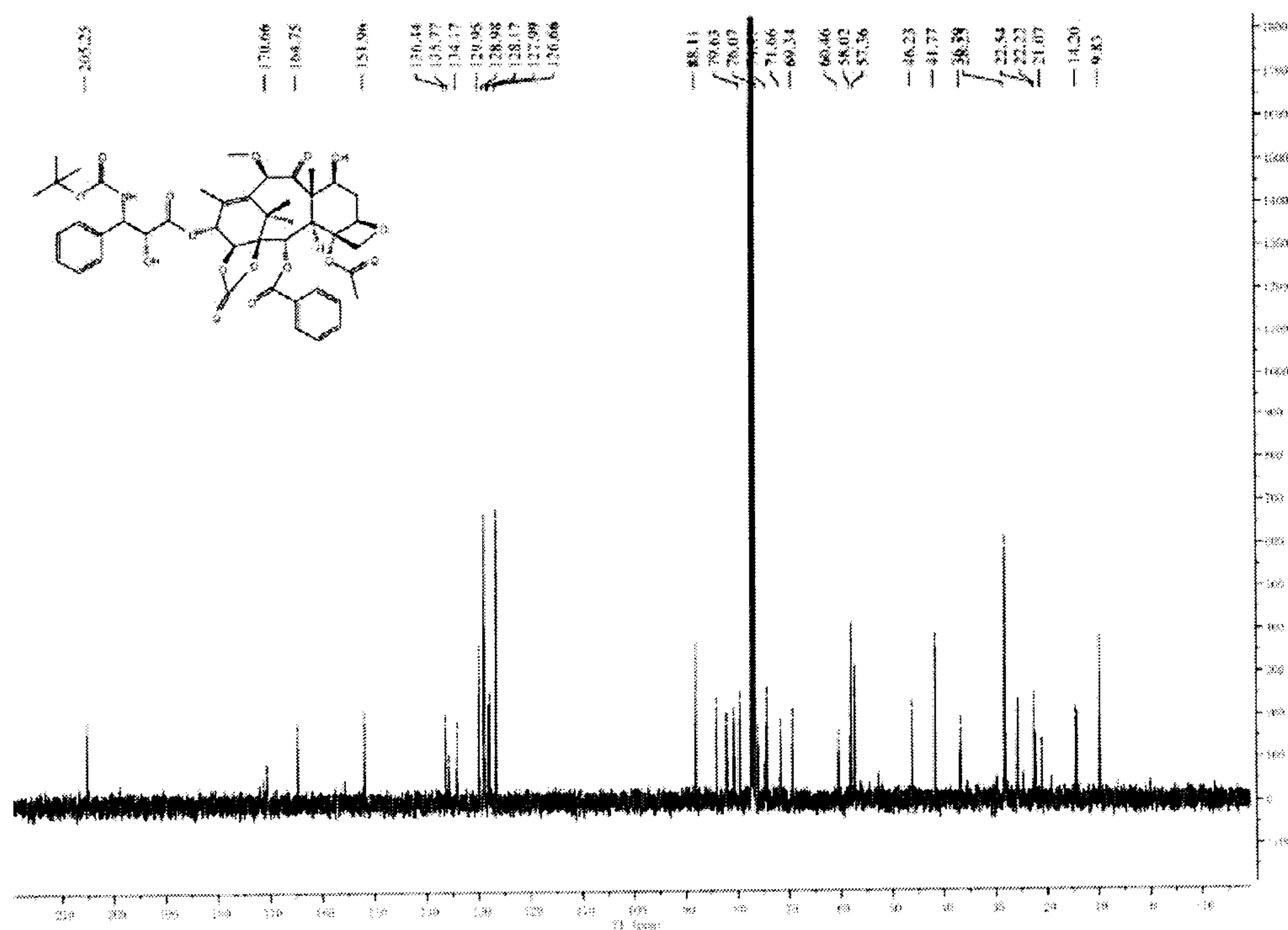


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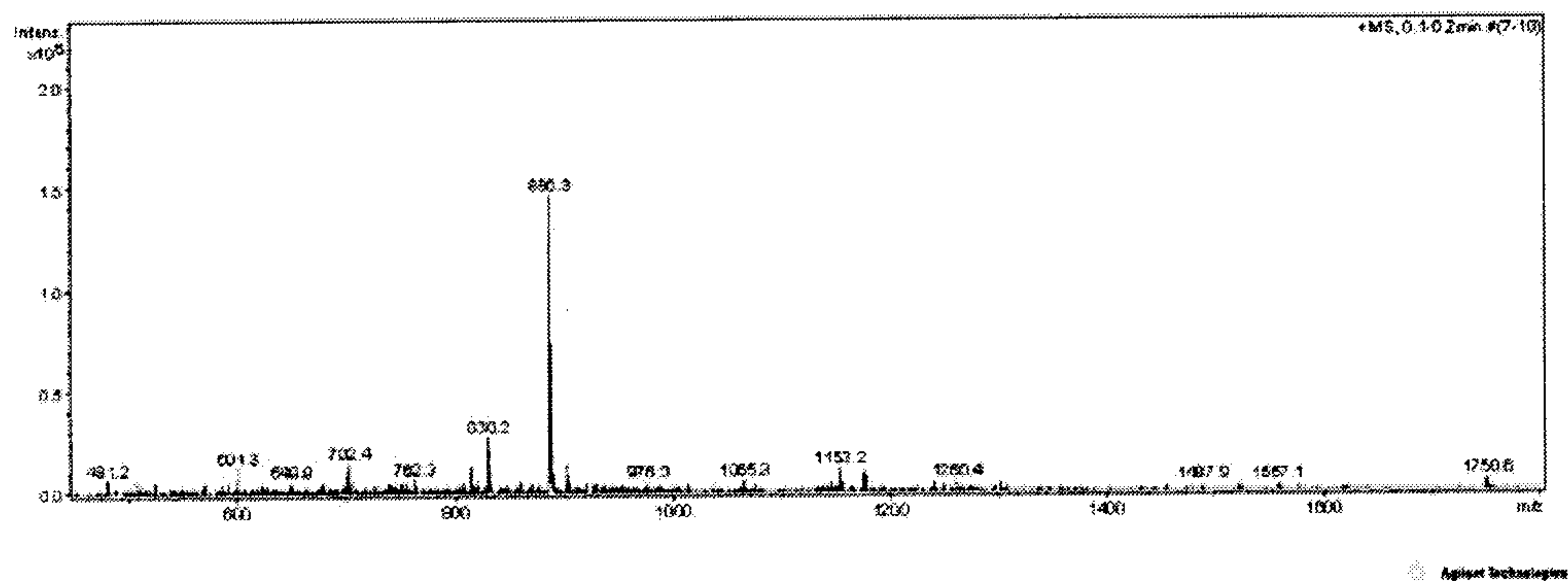


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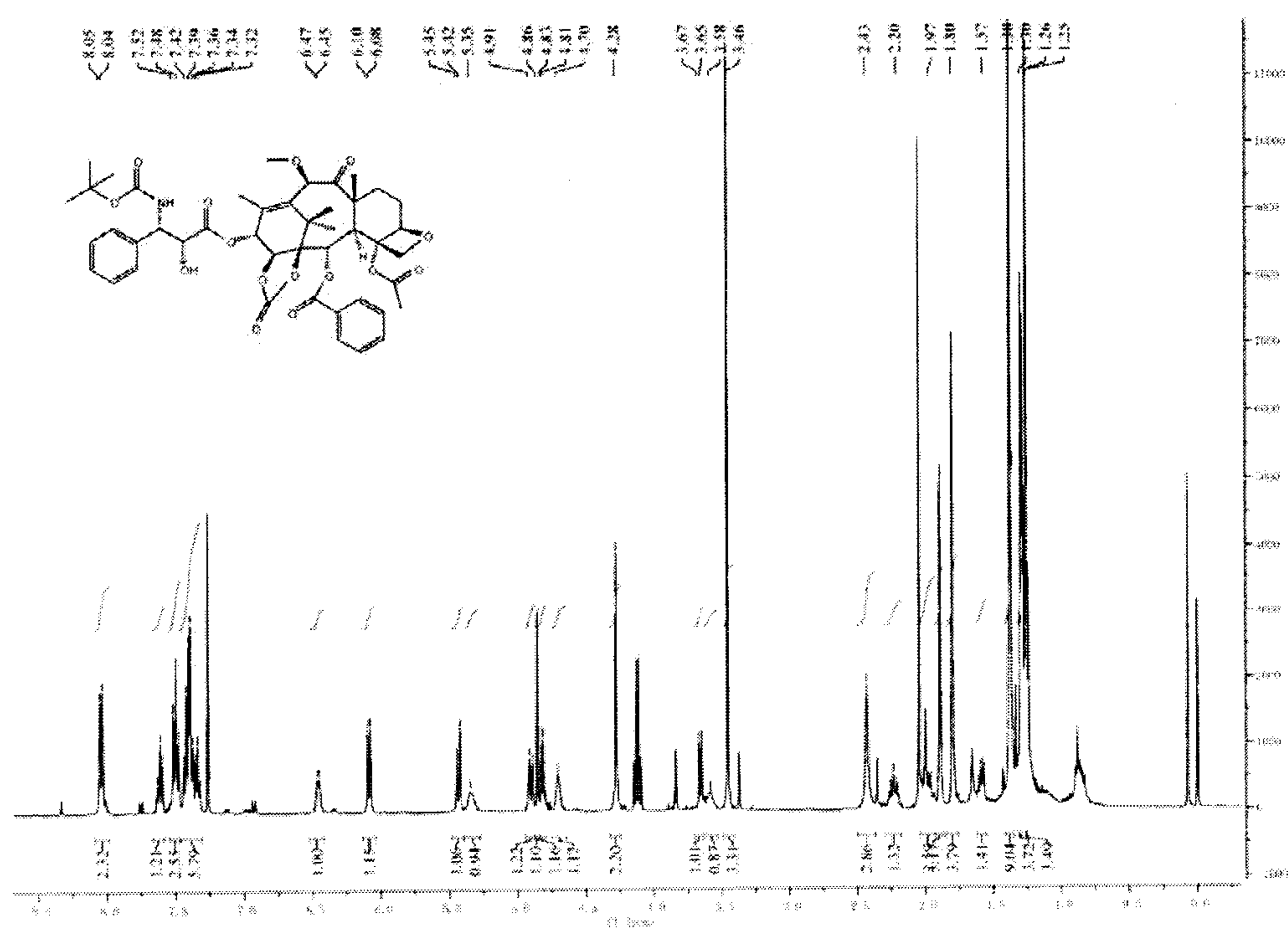


Fig.20

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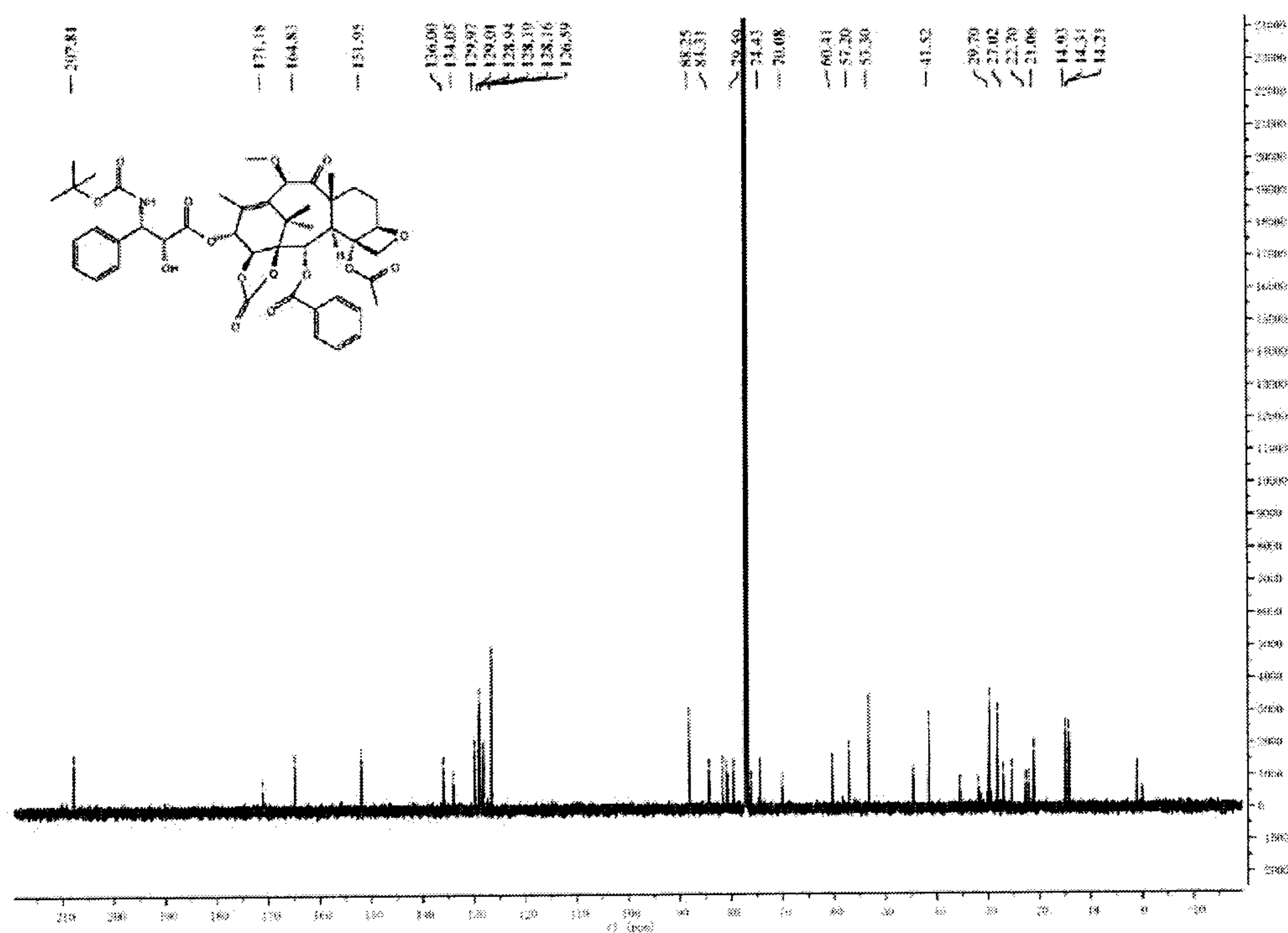


Fig.21

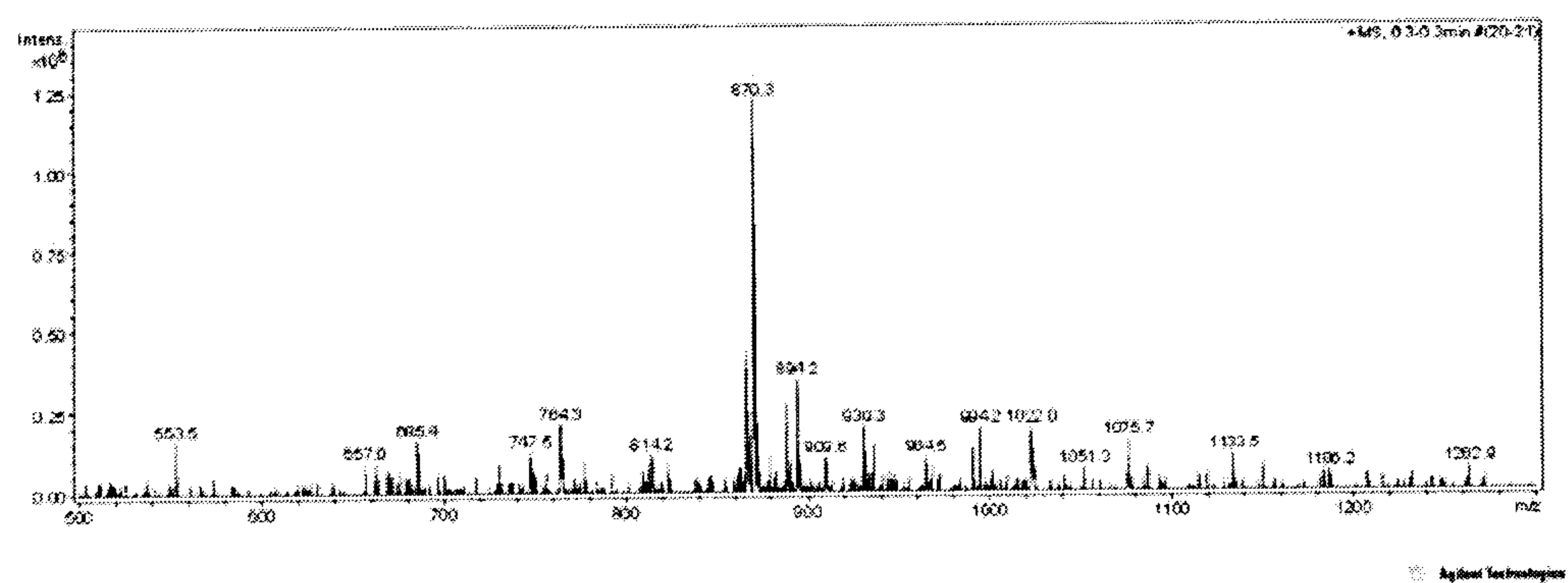


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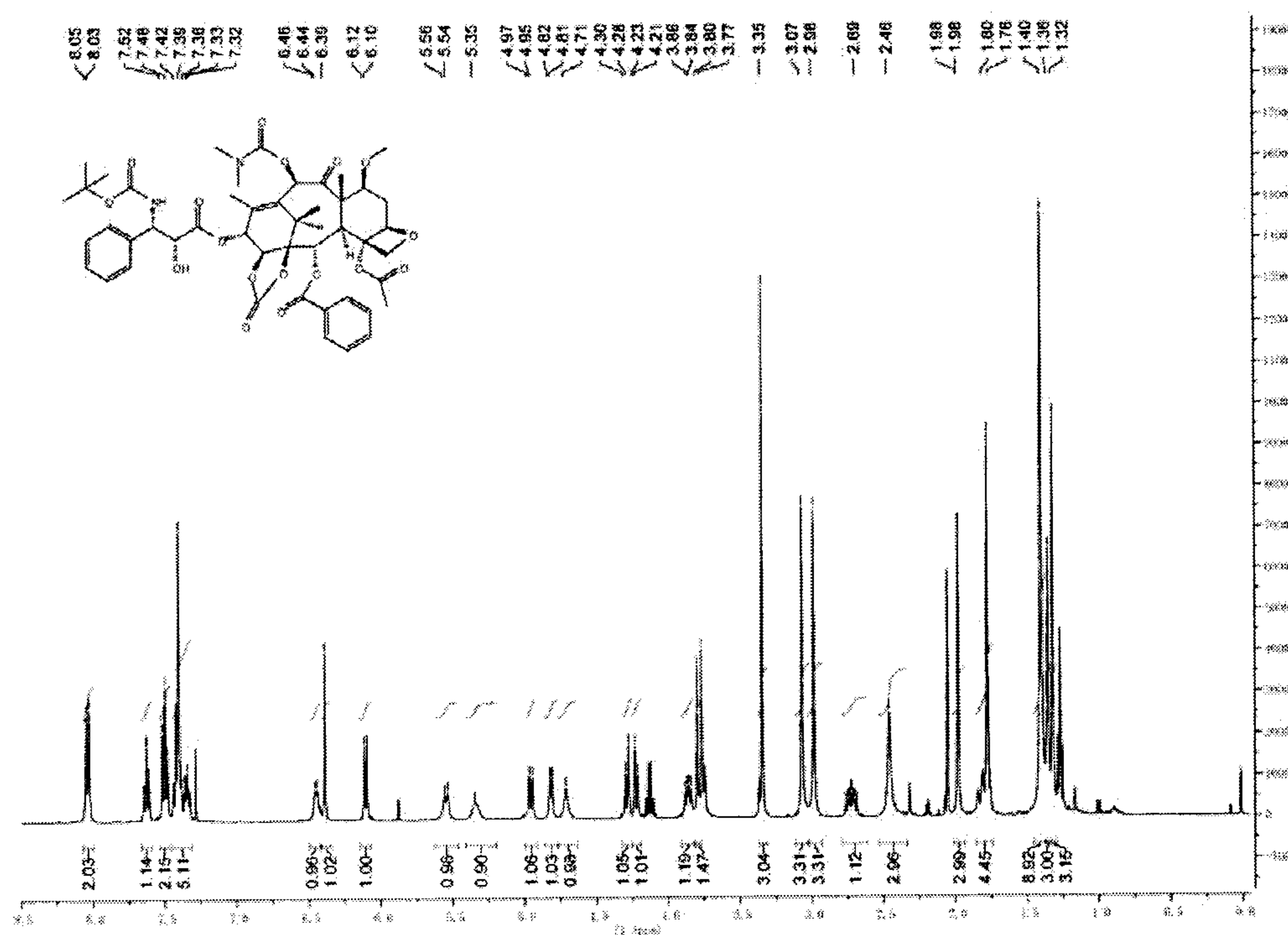


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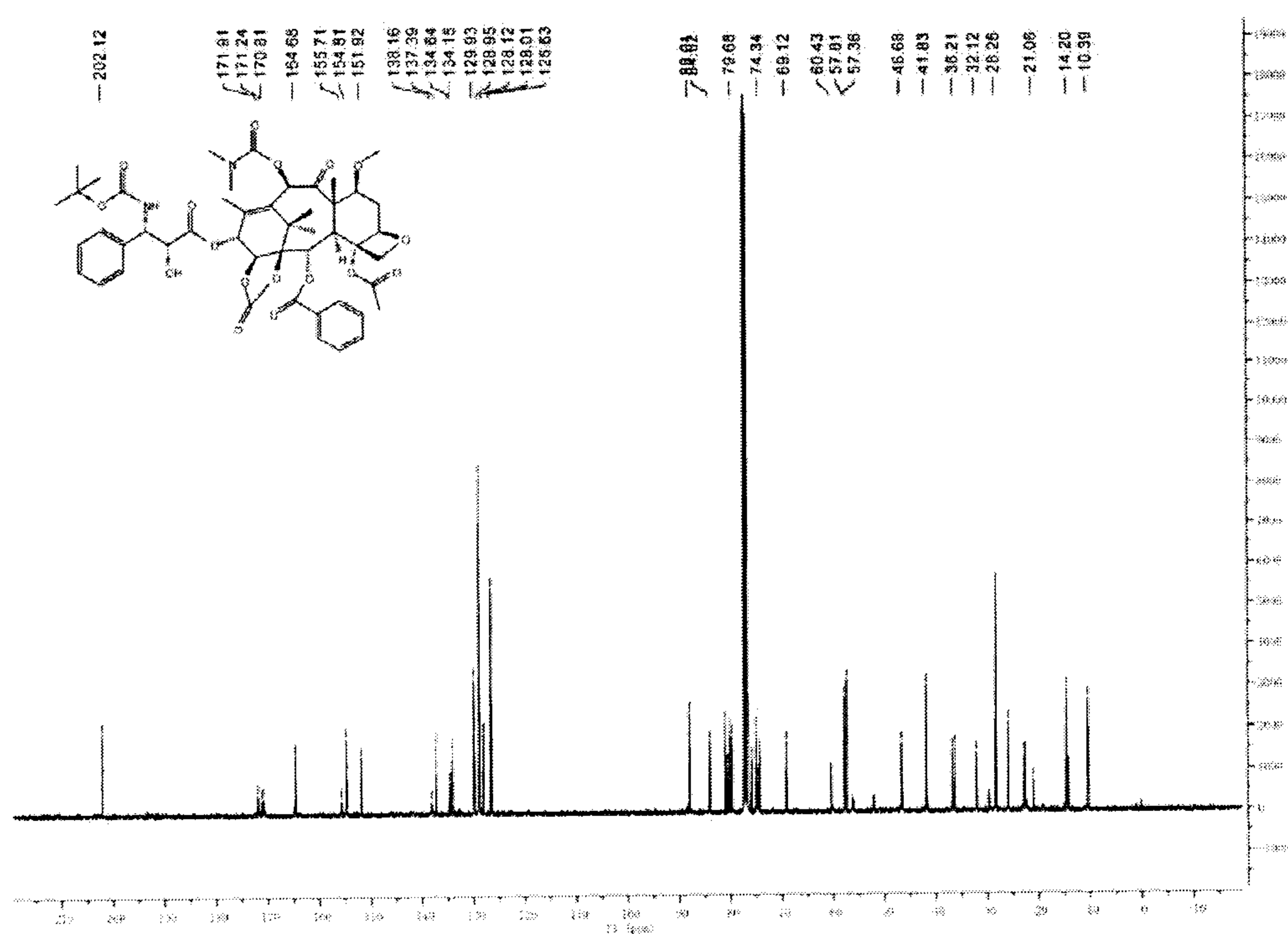


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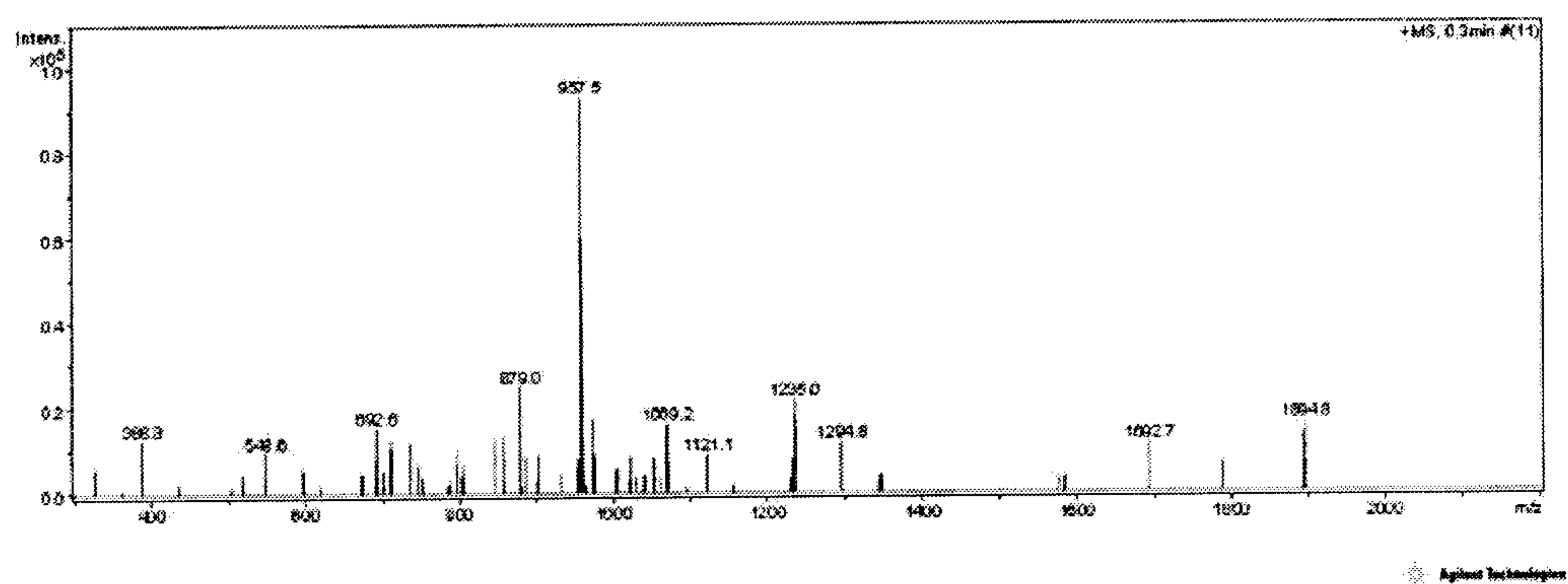


Fig.25

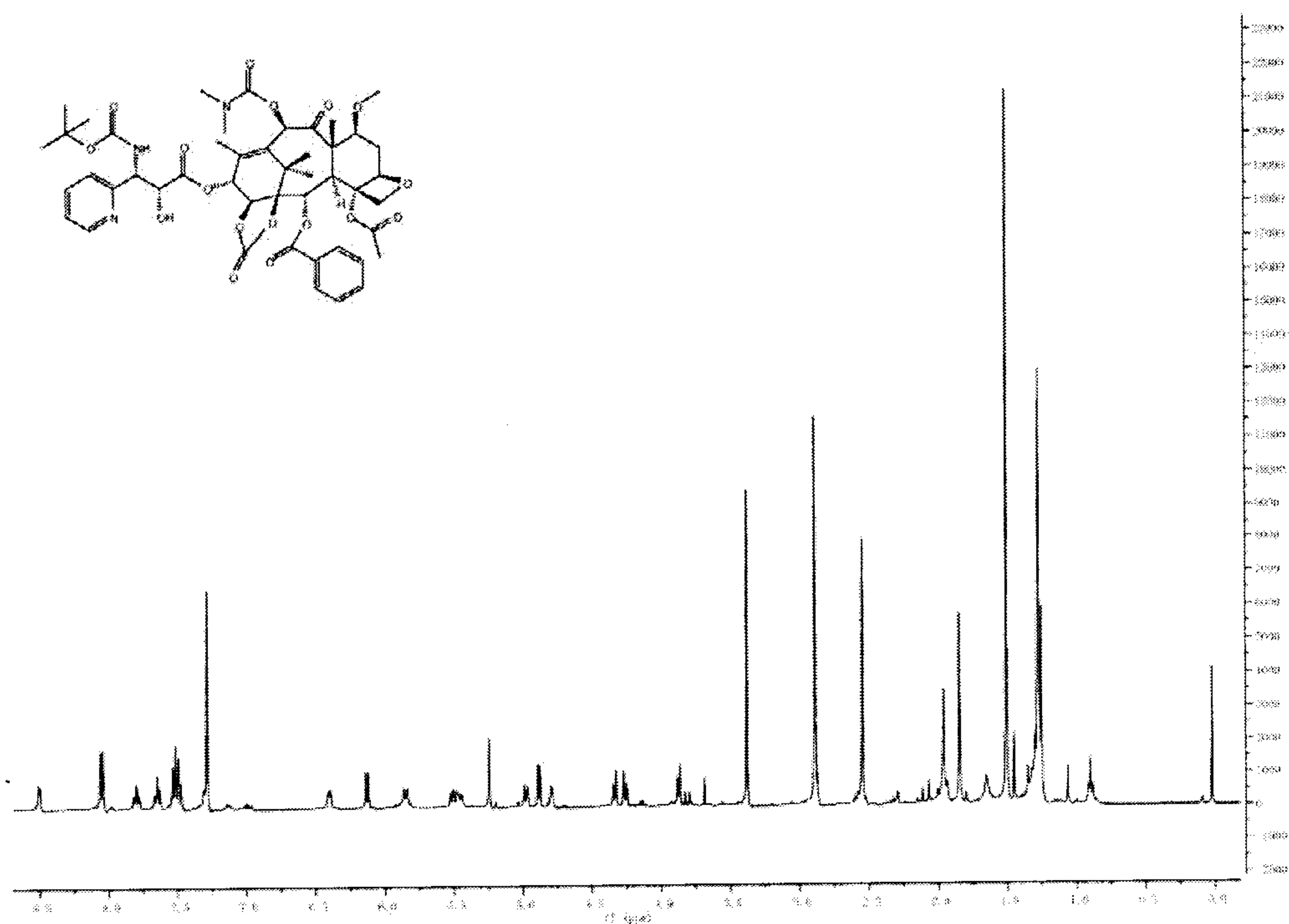


Fig.26

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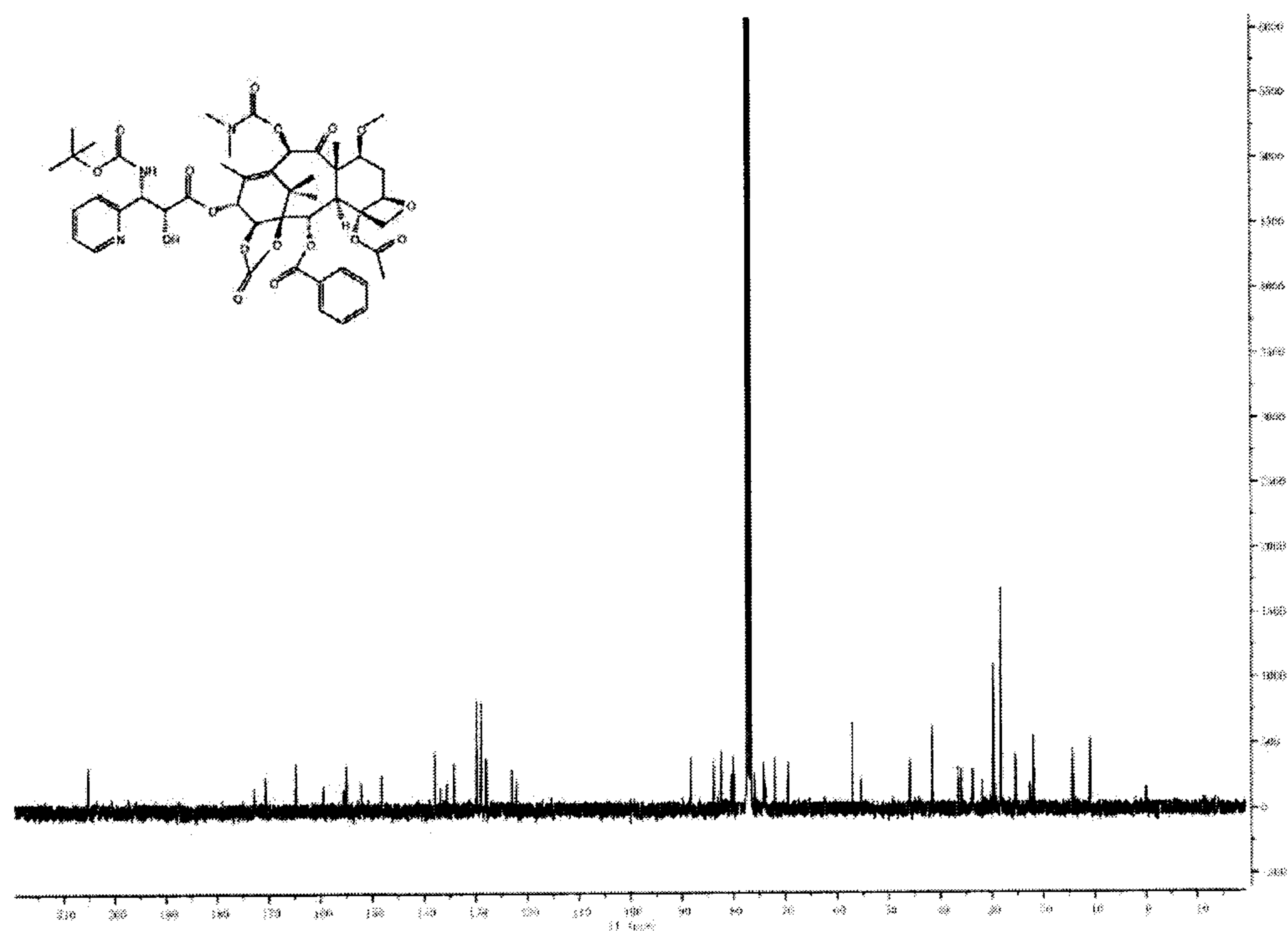


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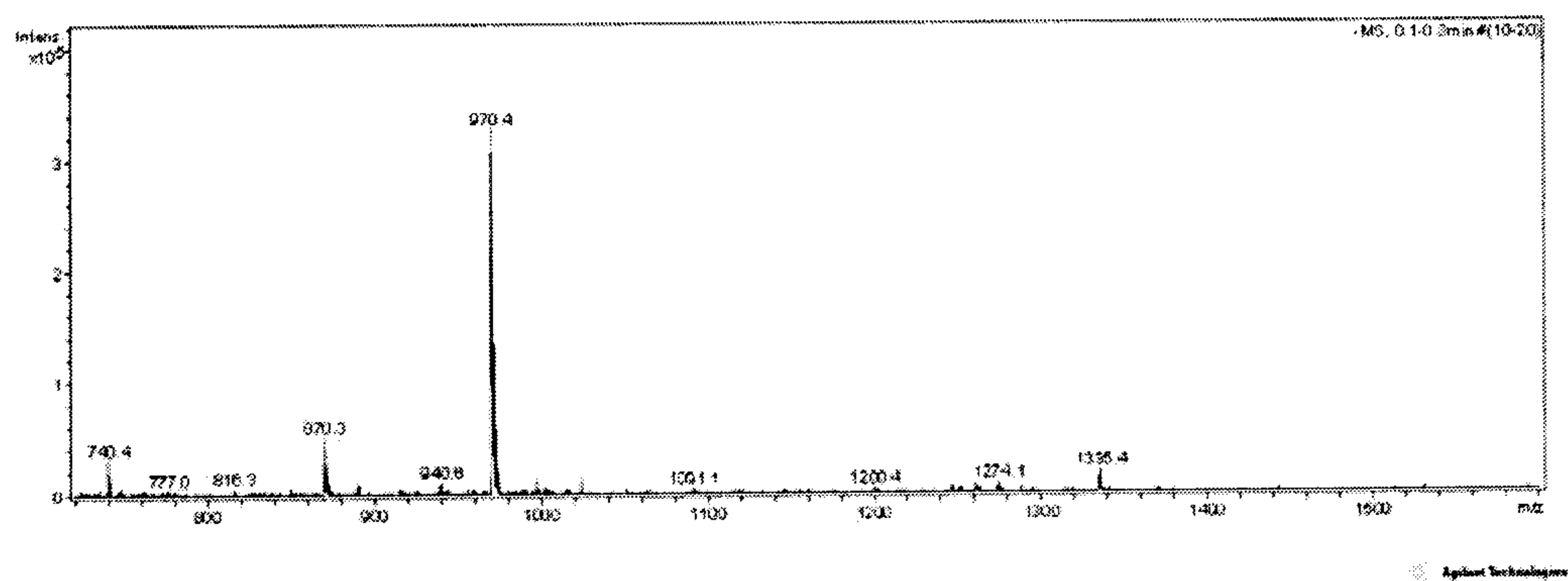


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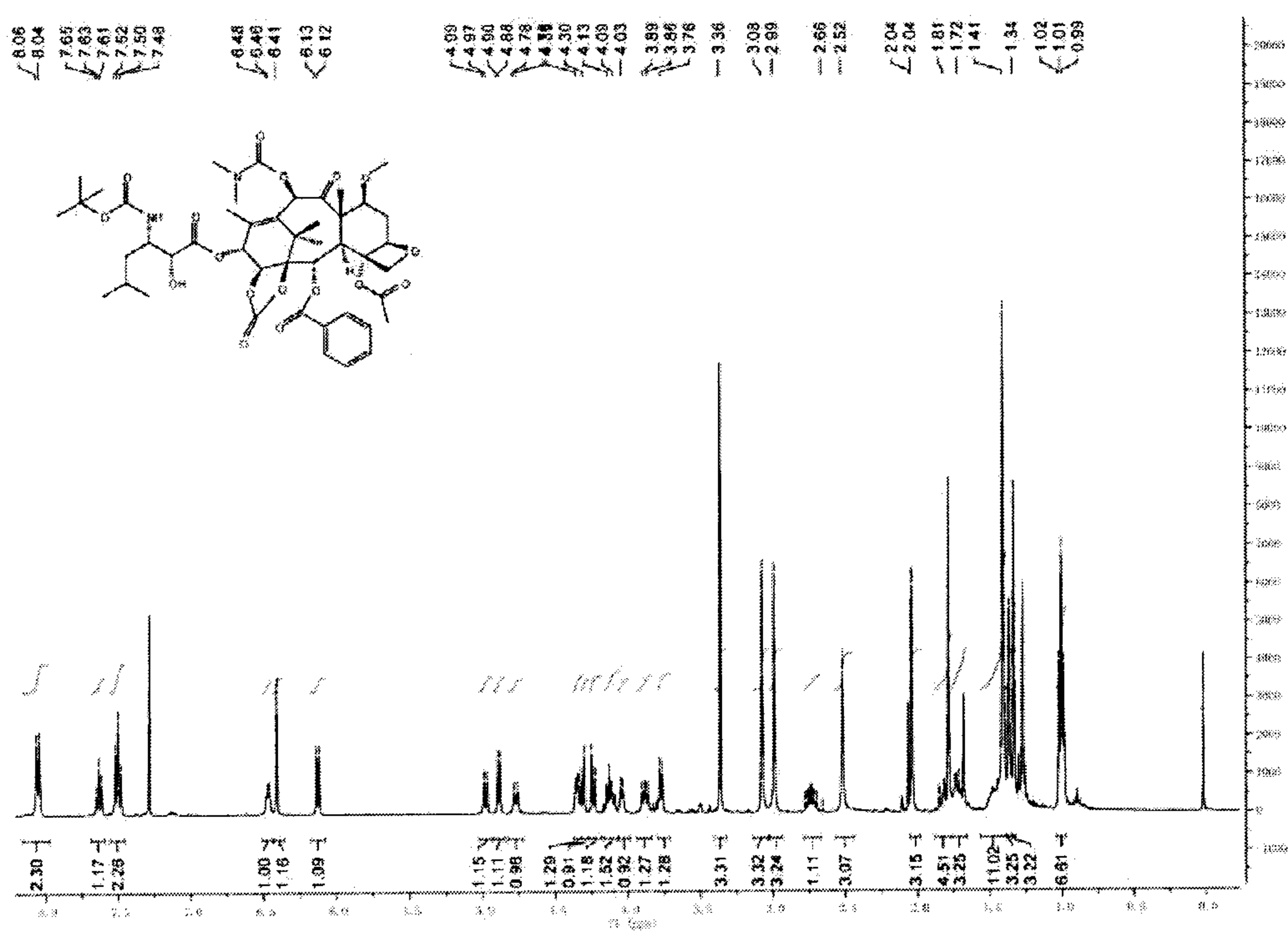


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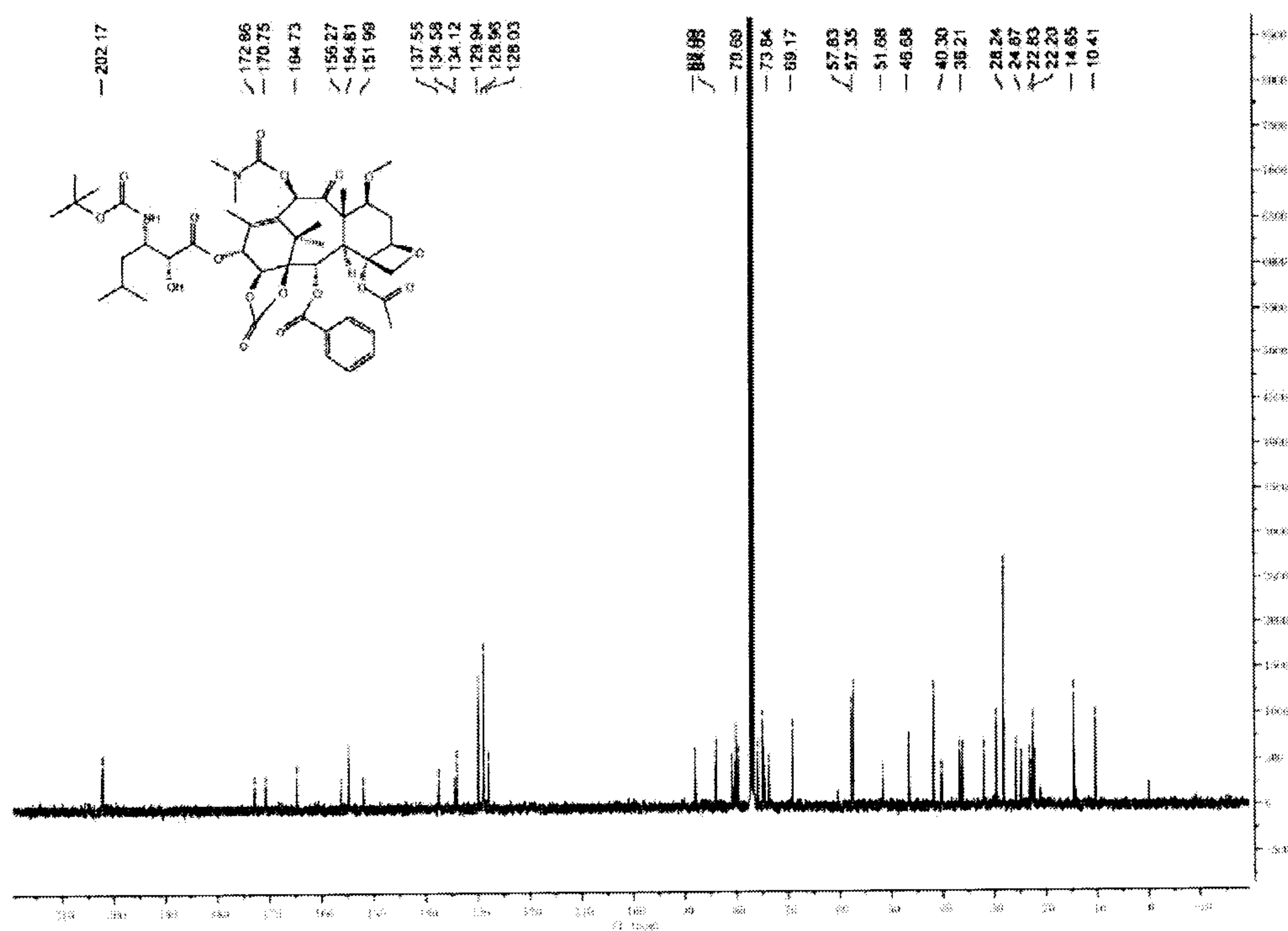


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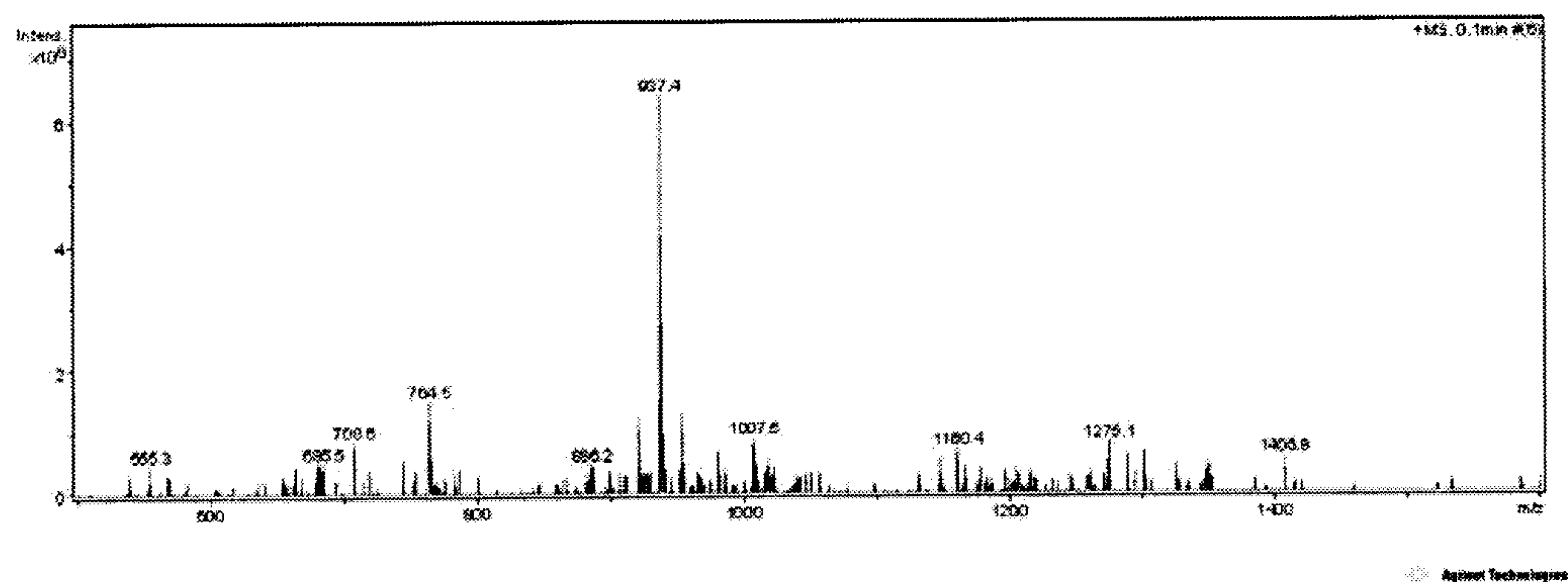


Fig.31

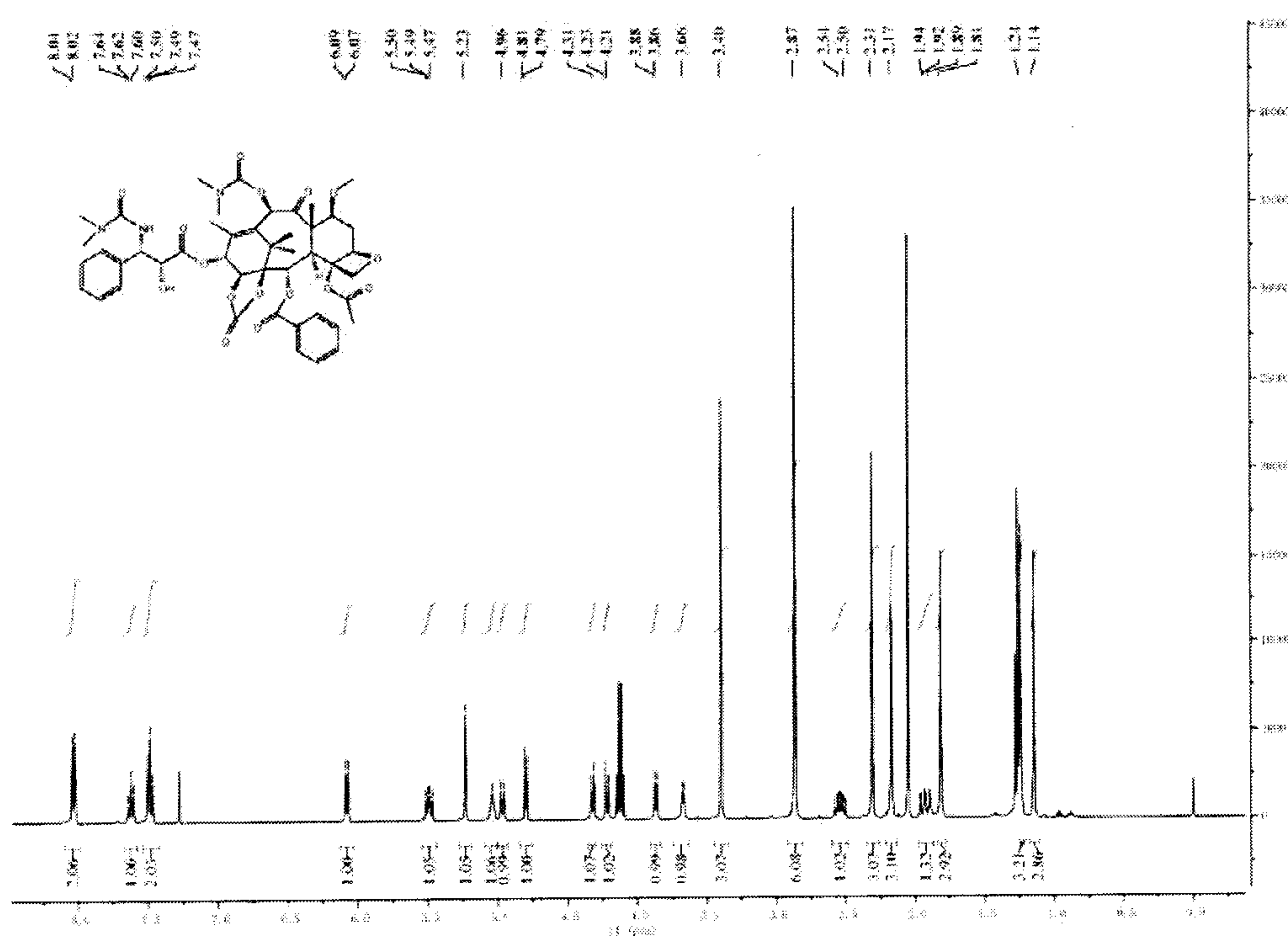


Fig.32

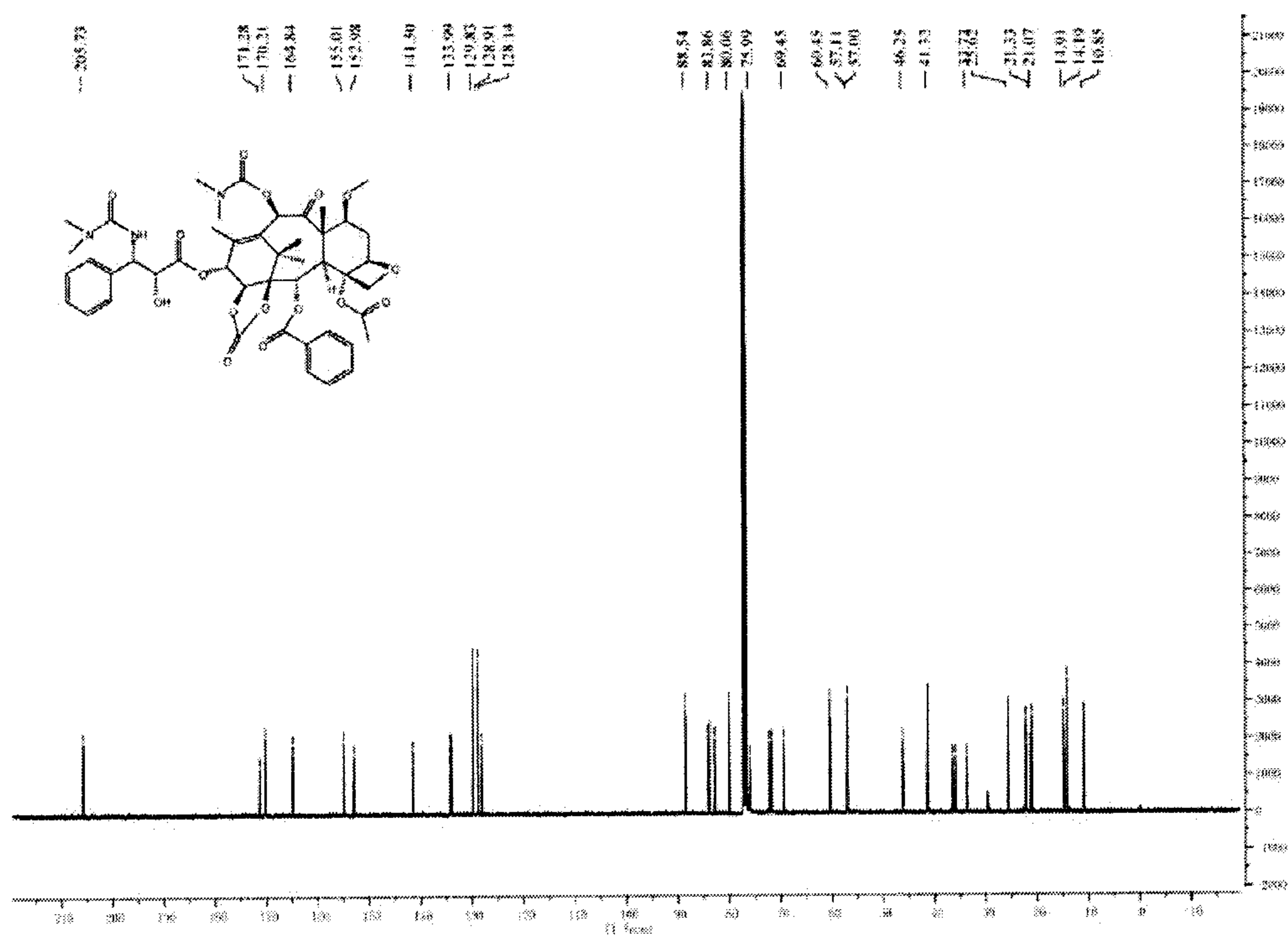


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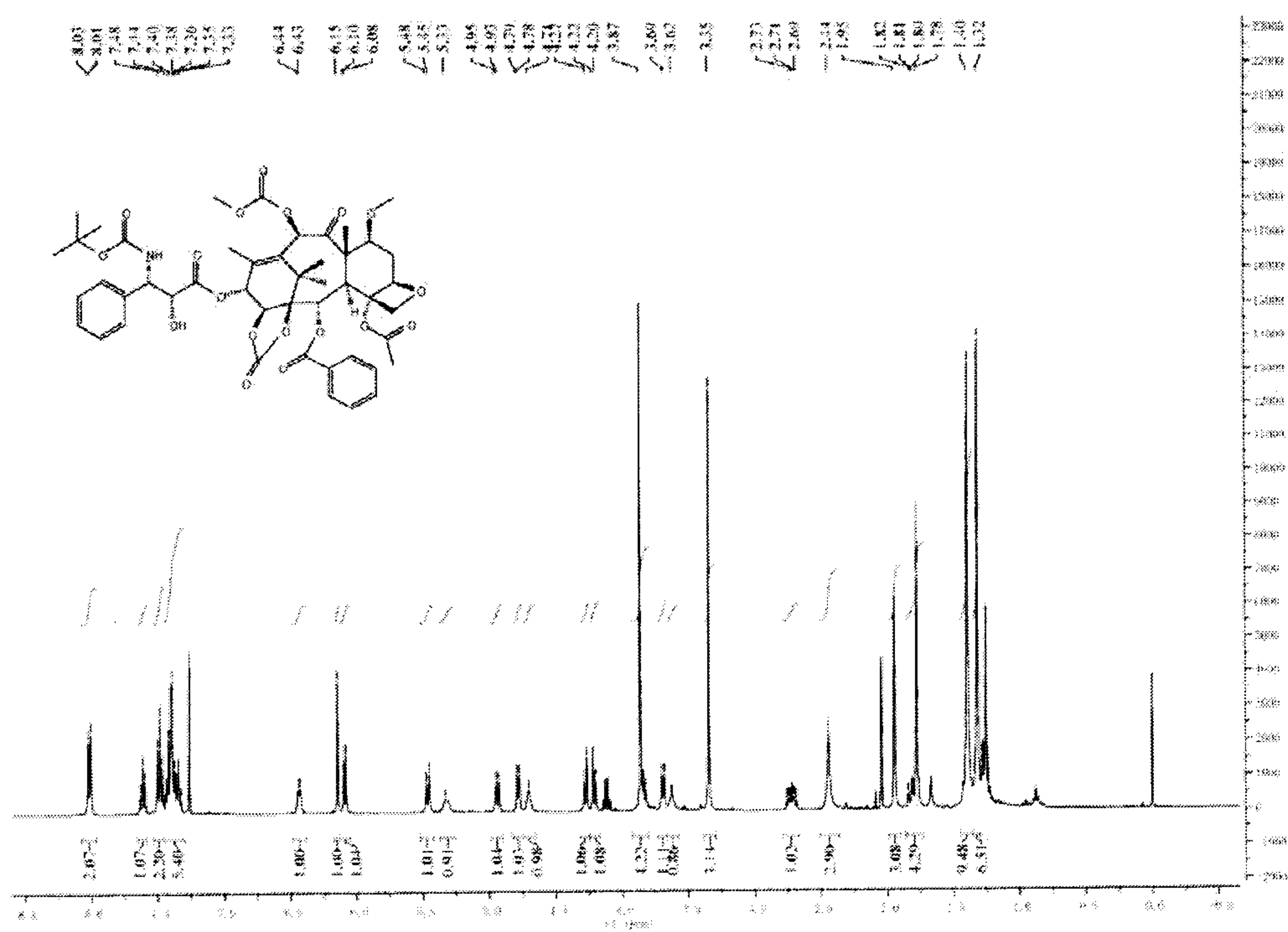


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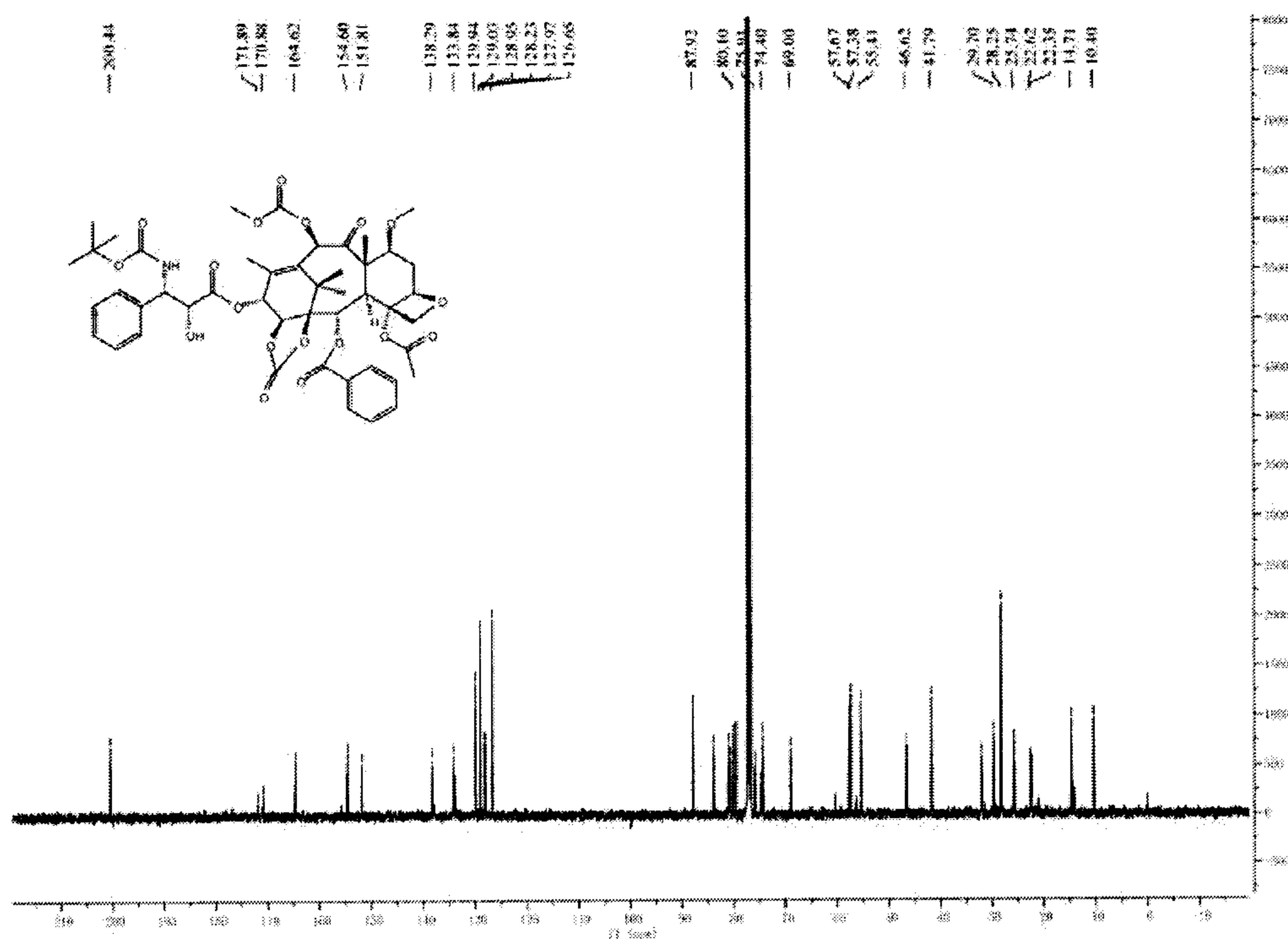


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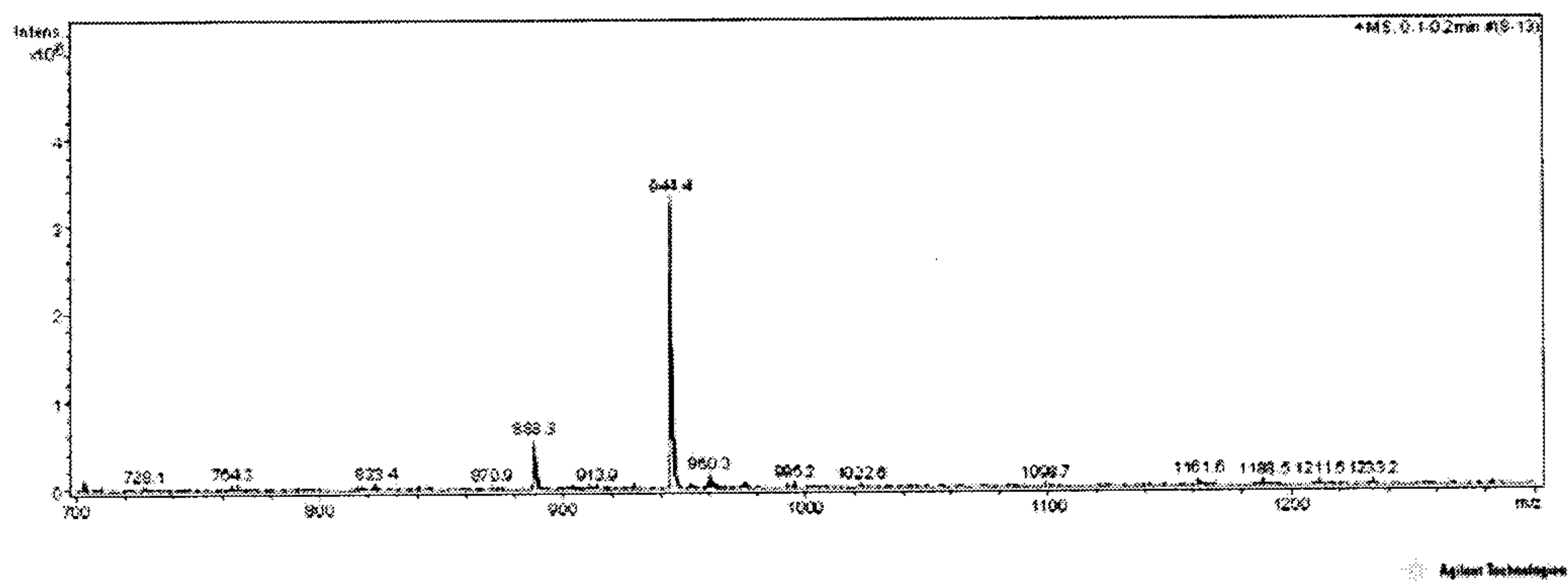


Fig.36

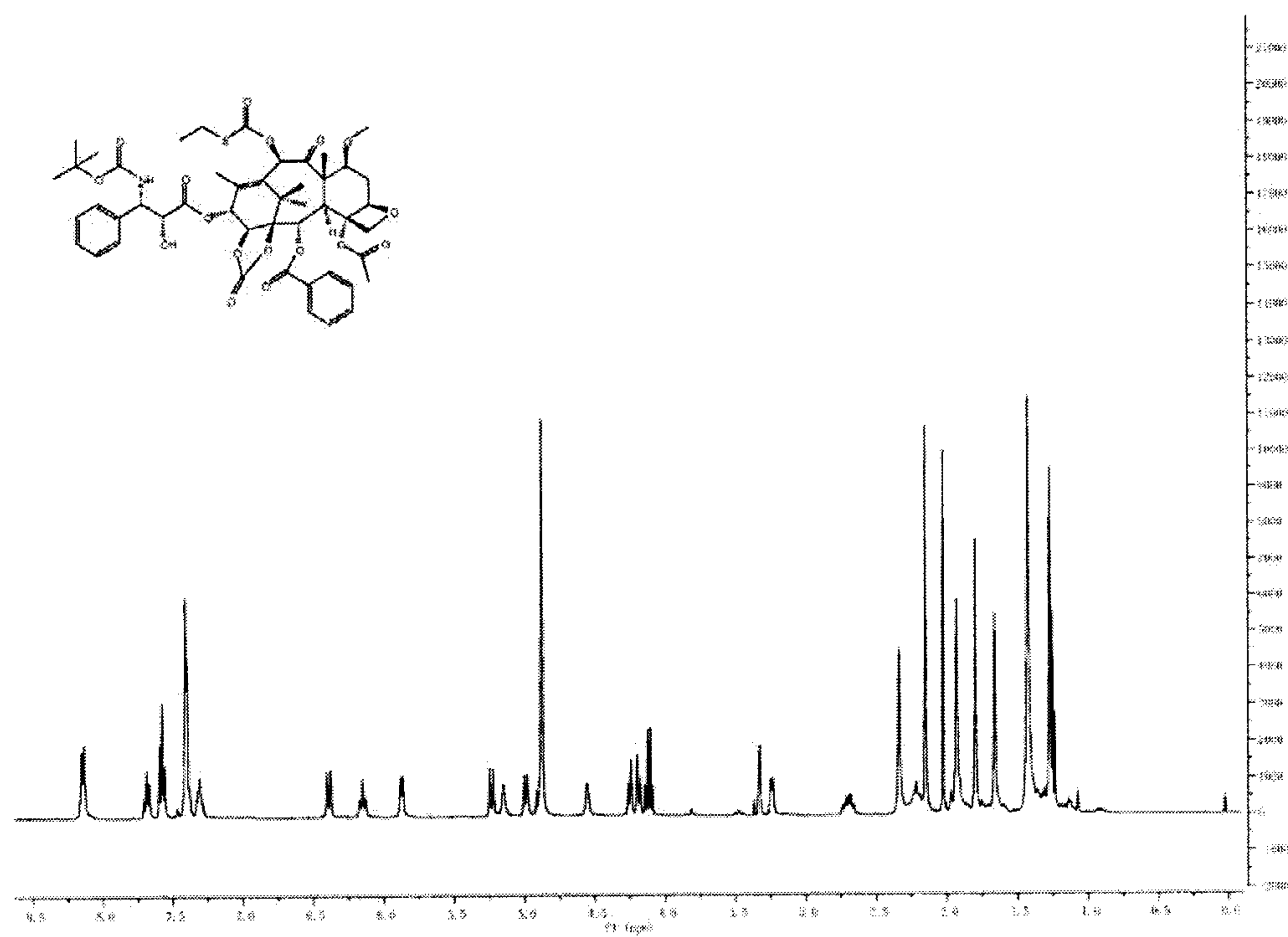


Fig.37

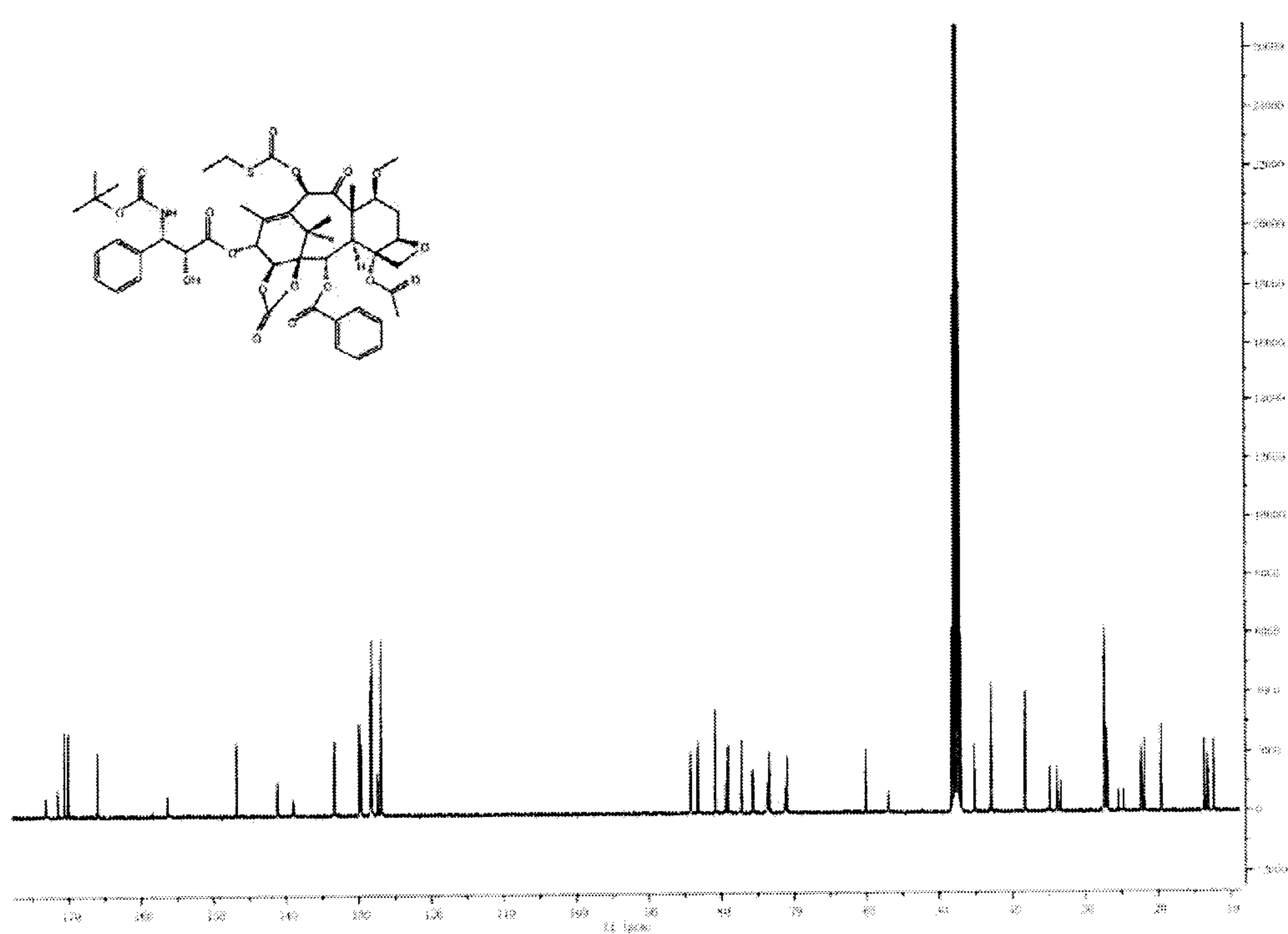


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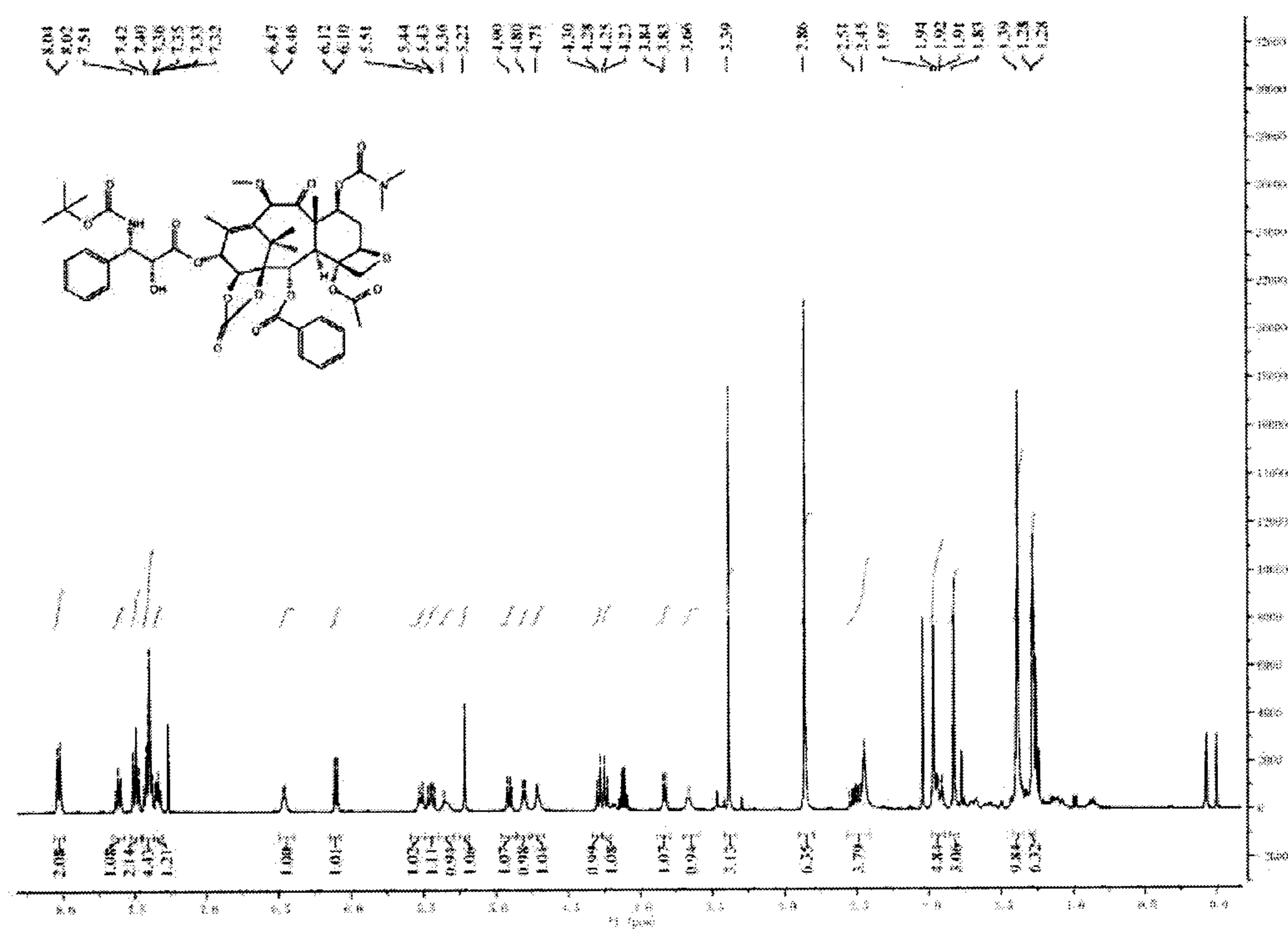


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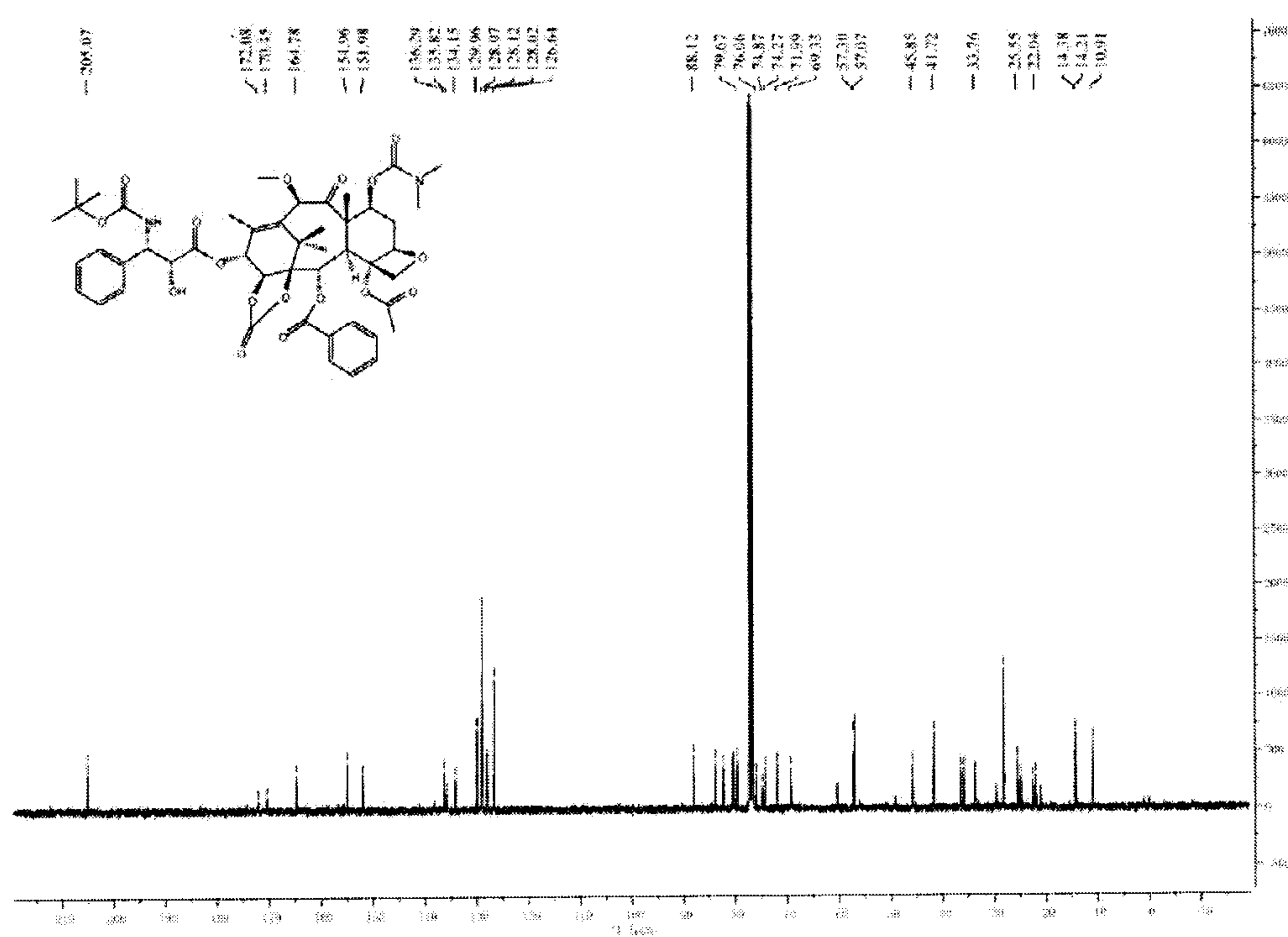


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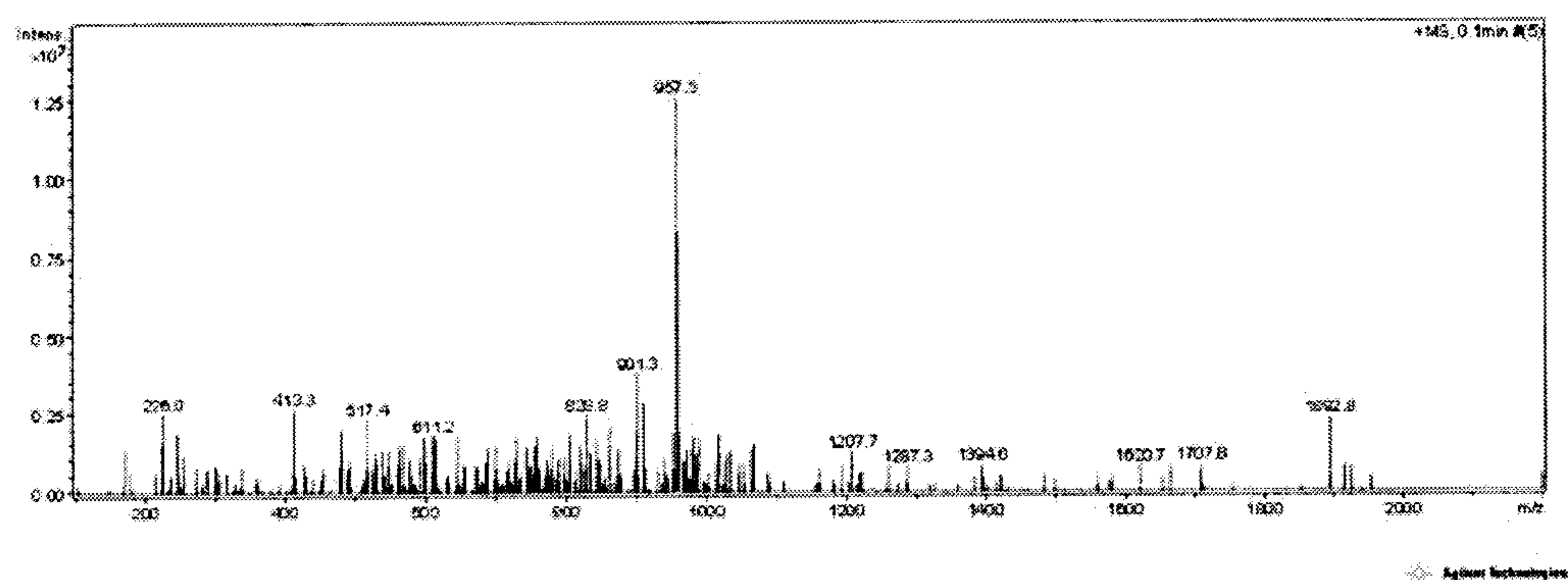


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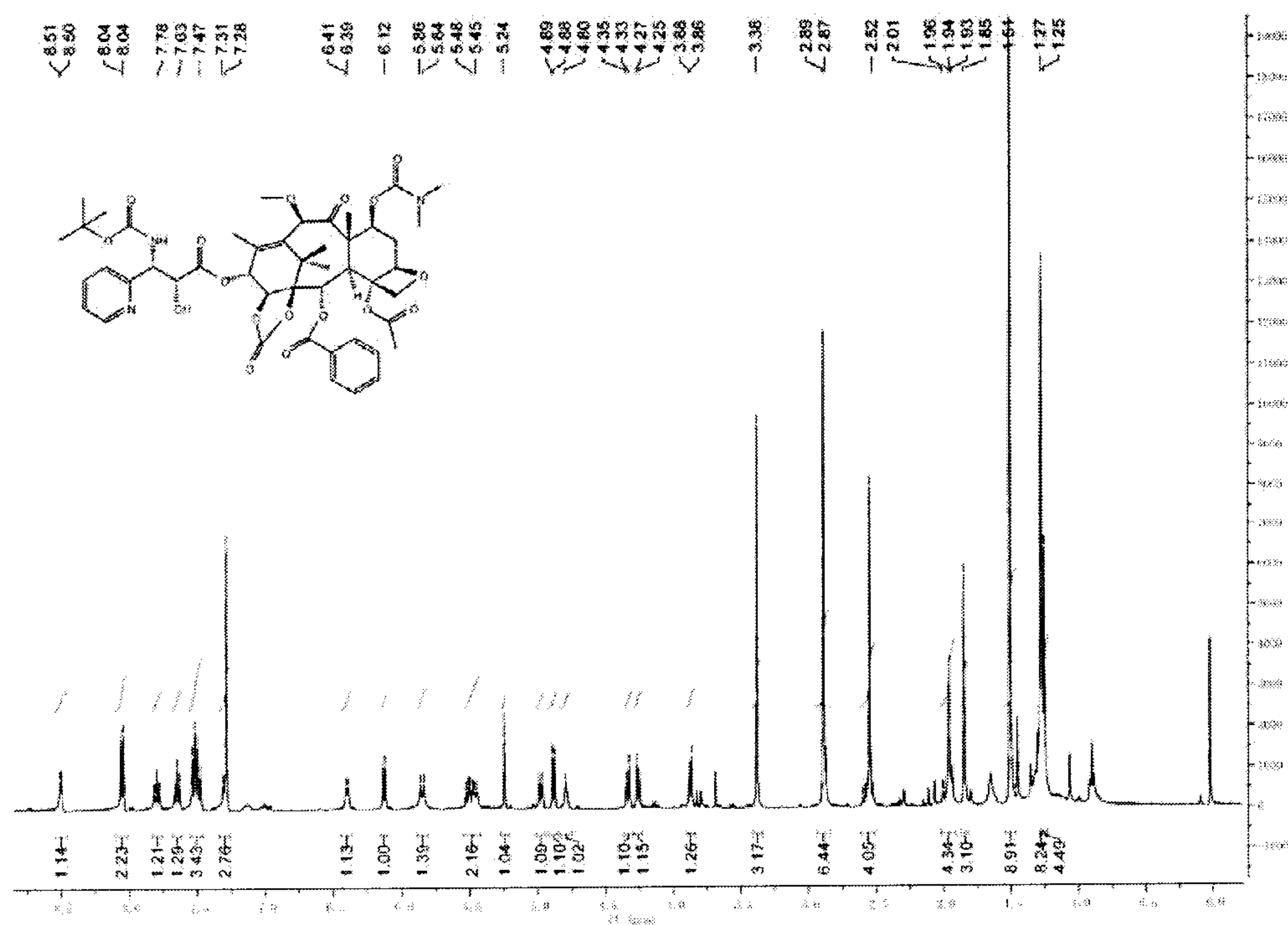


Fig.42

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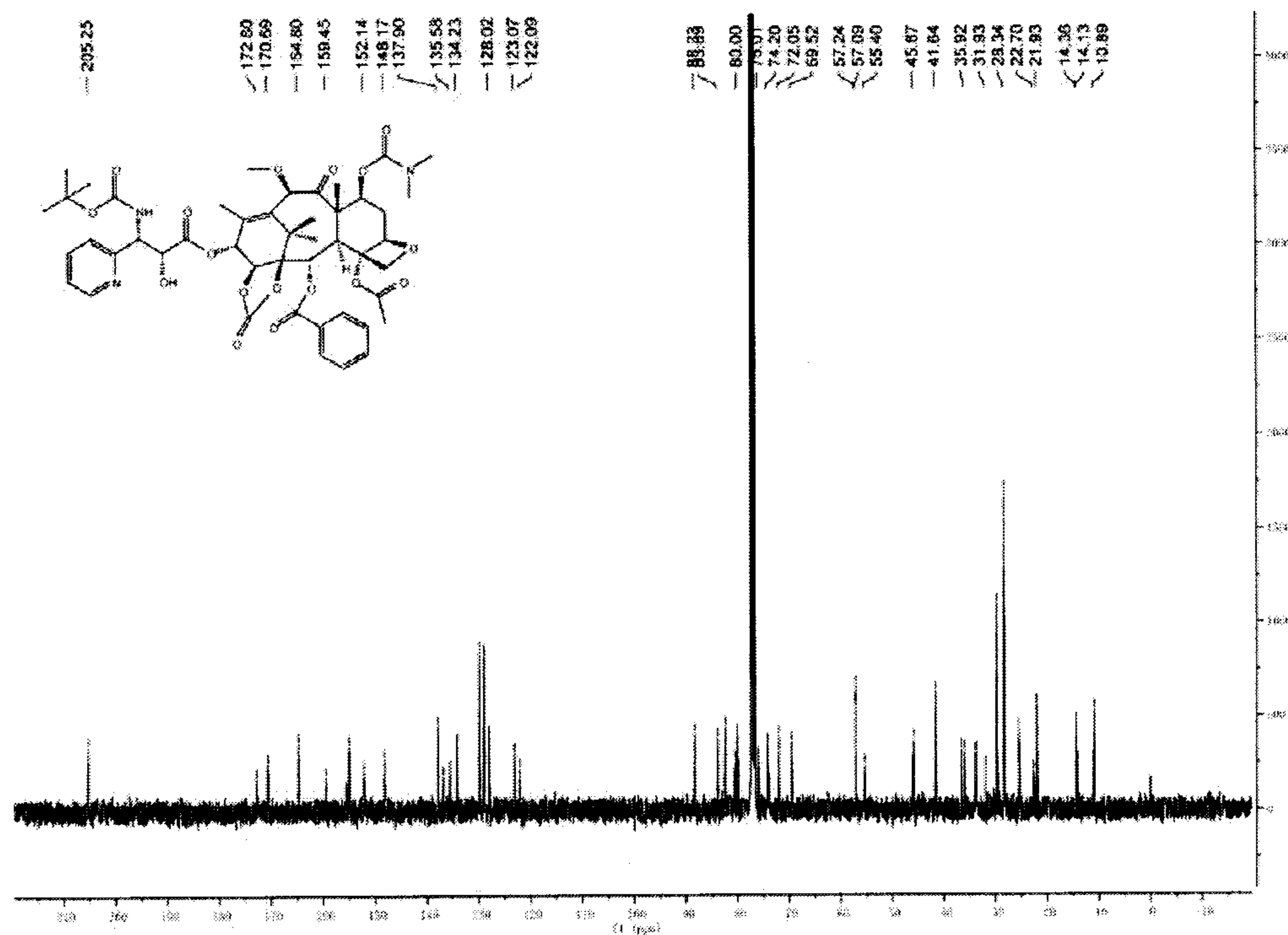


Fig.43

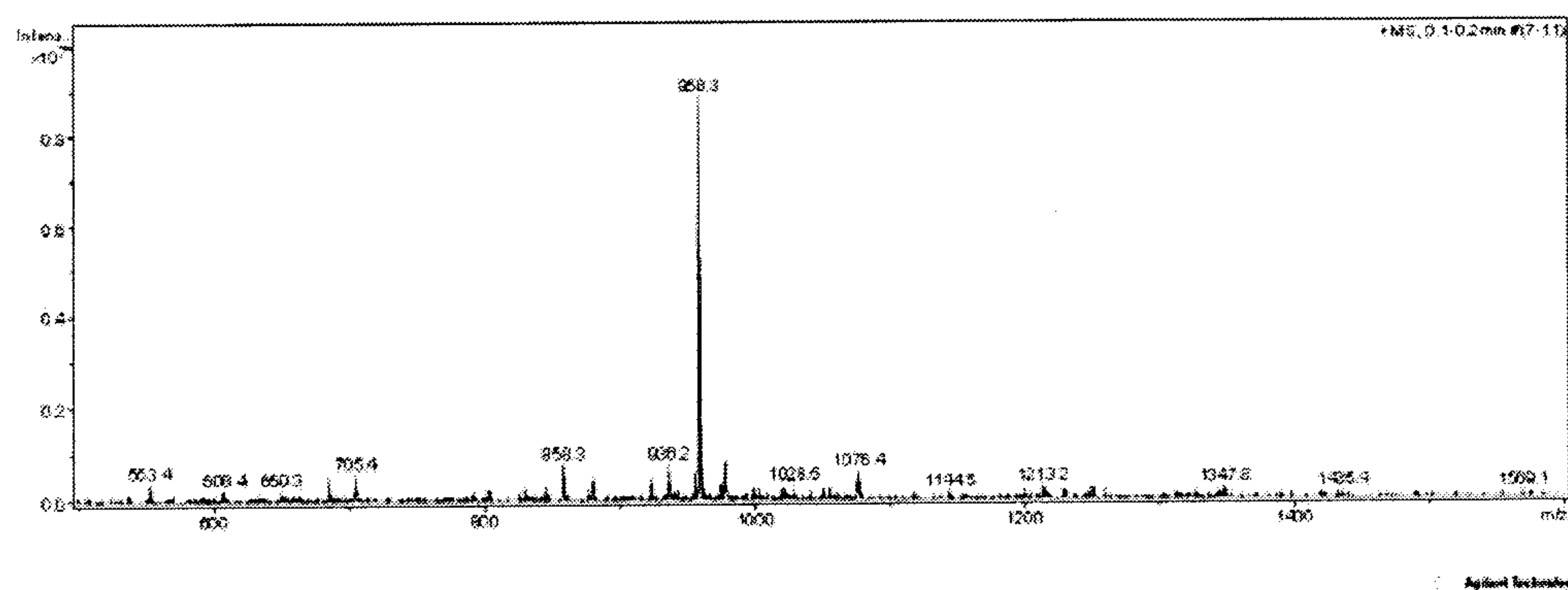


Fig.44

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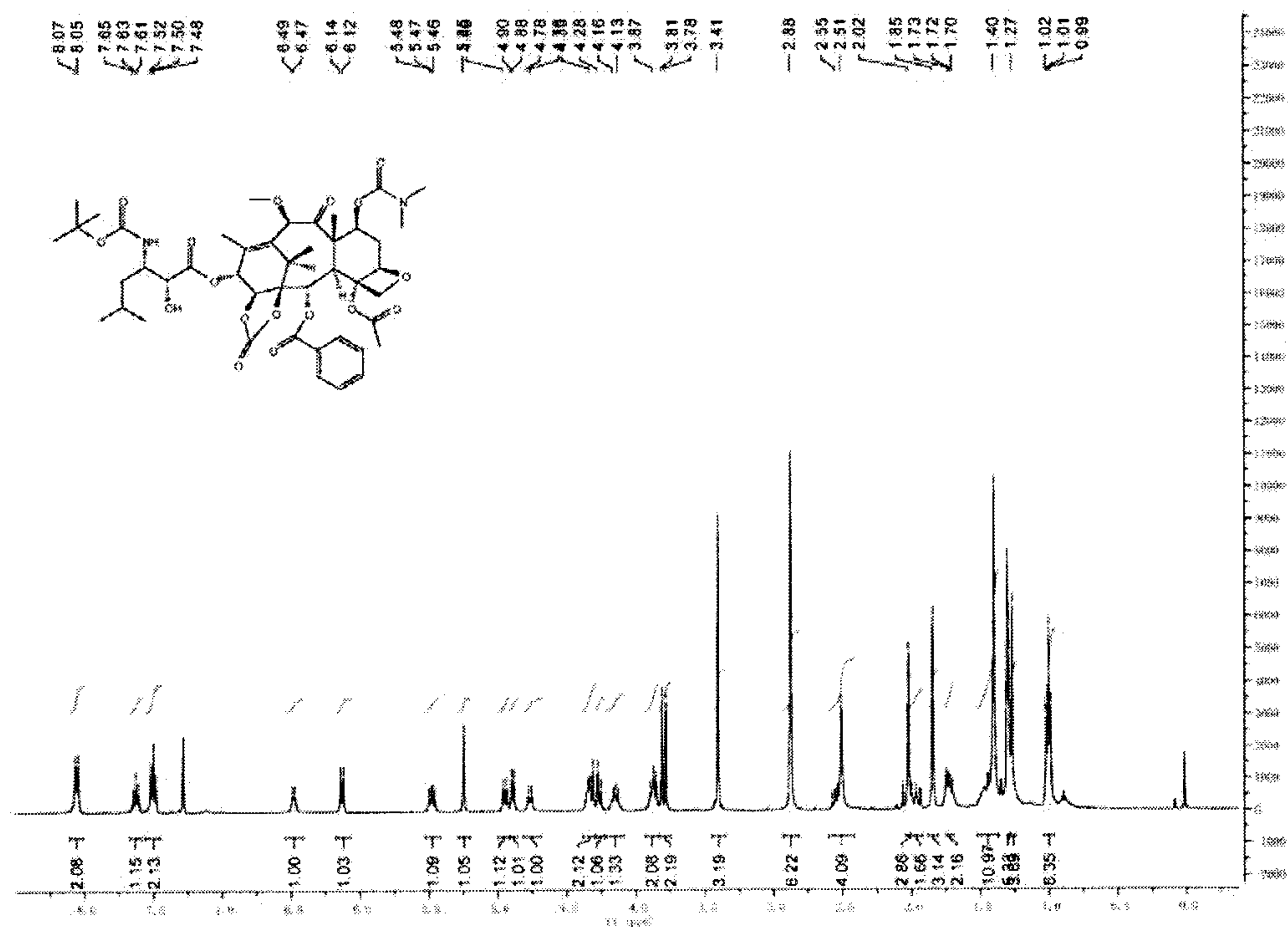


Fig.45

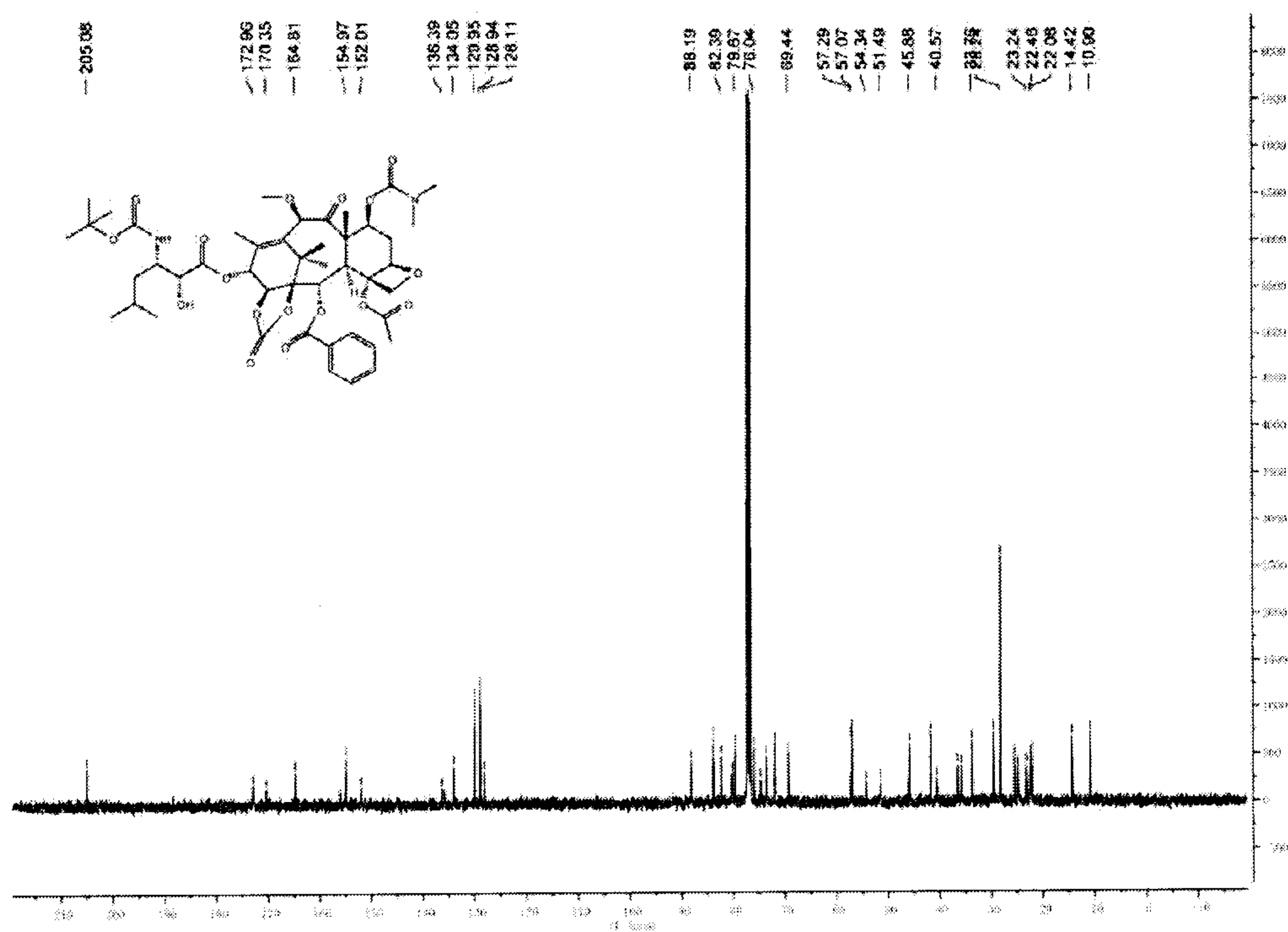


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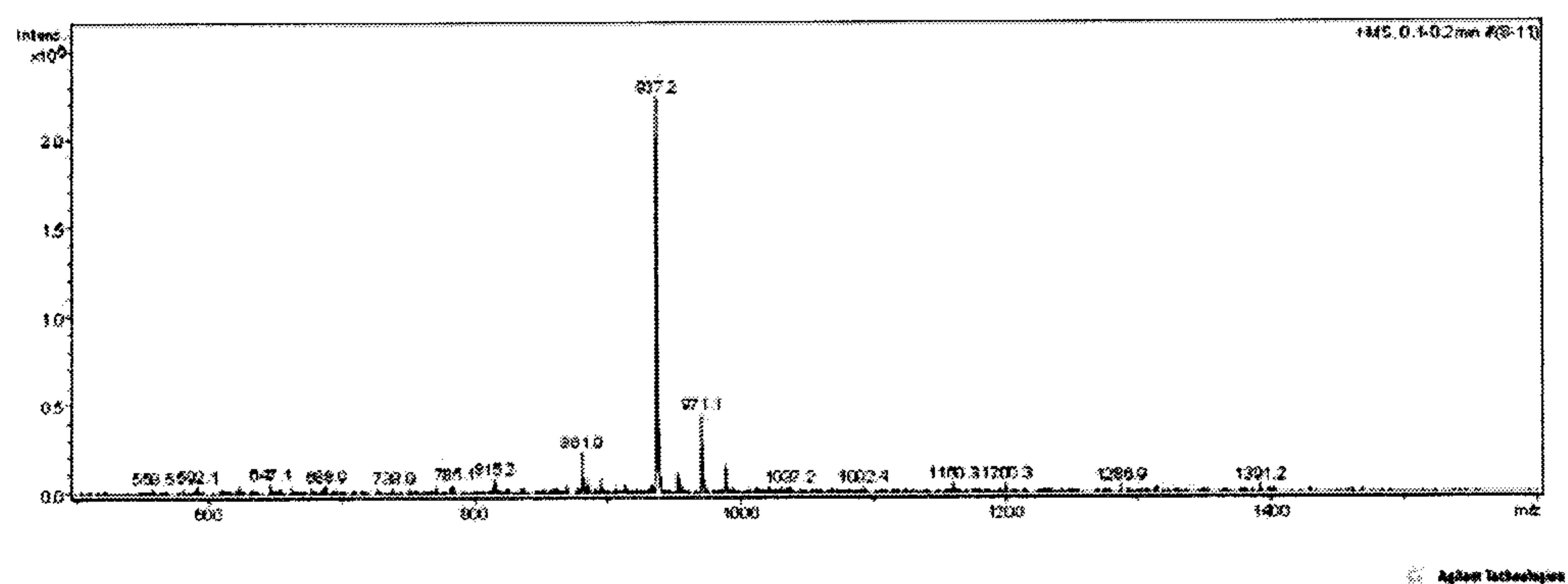


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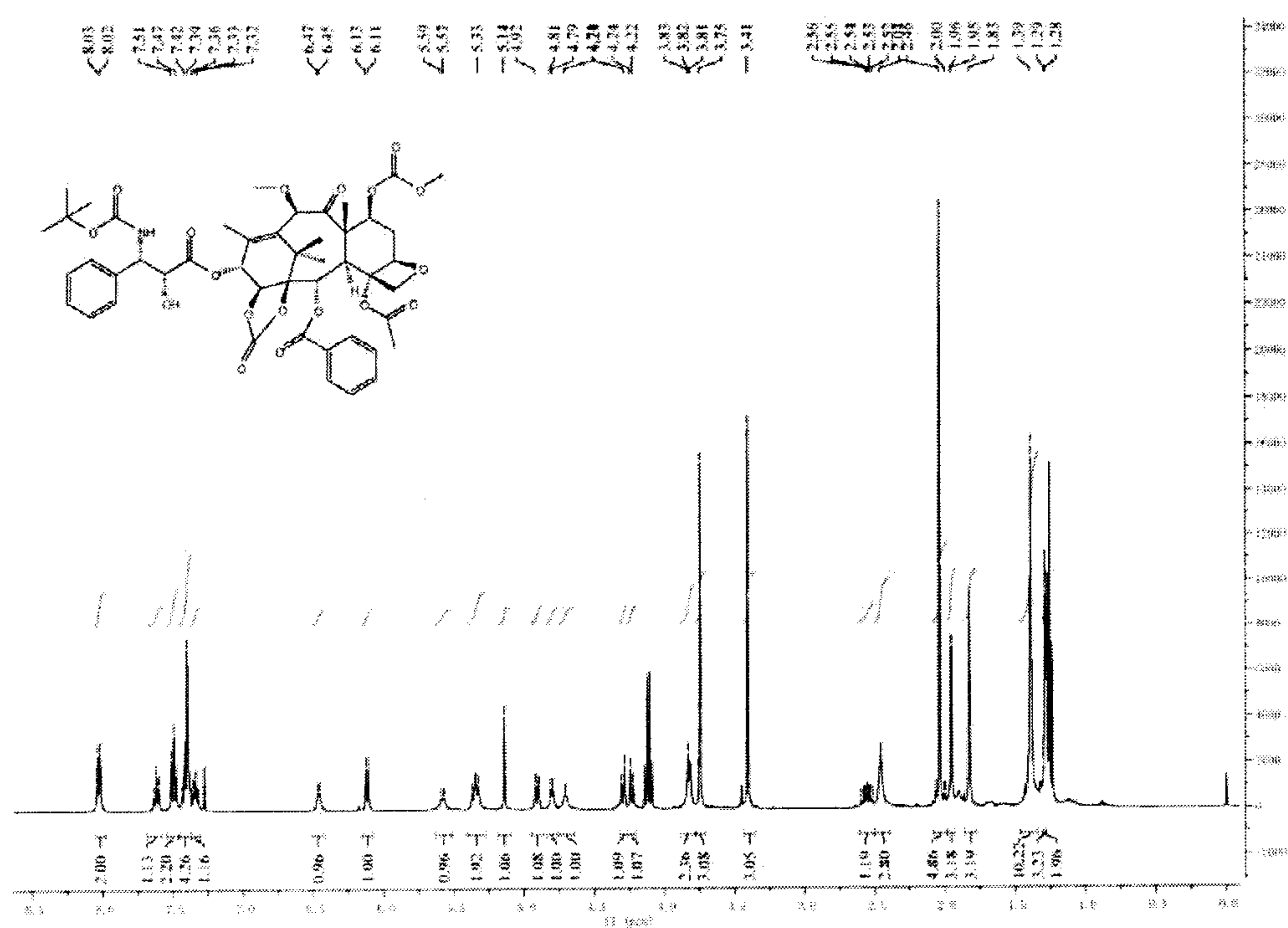


Fig.48

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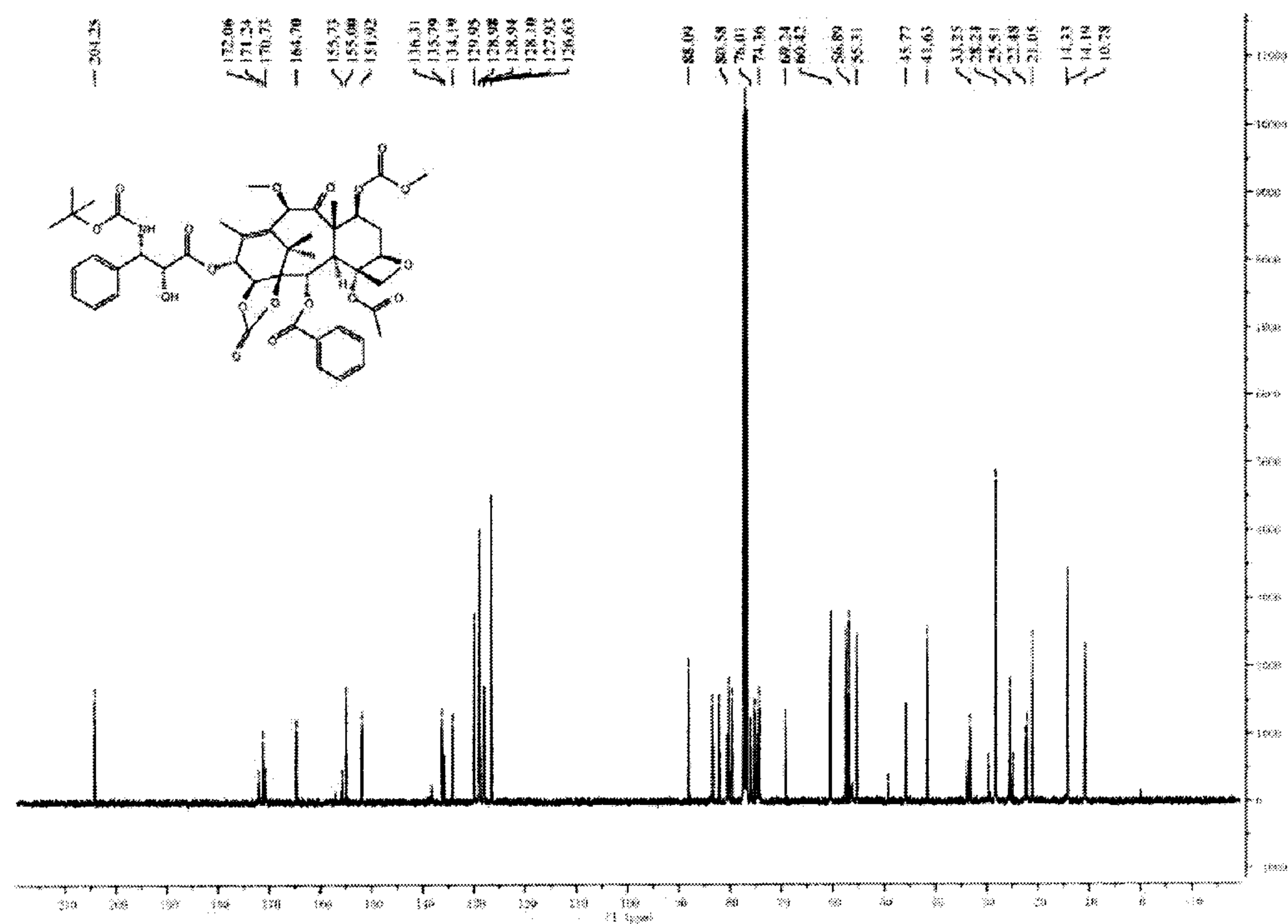


Fig.49

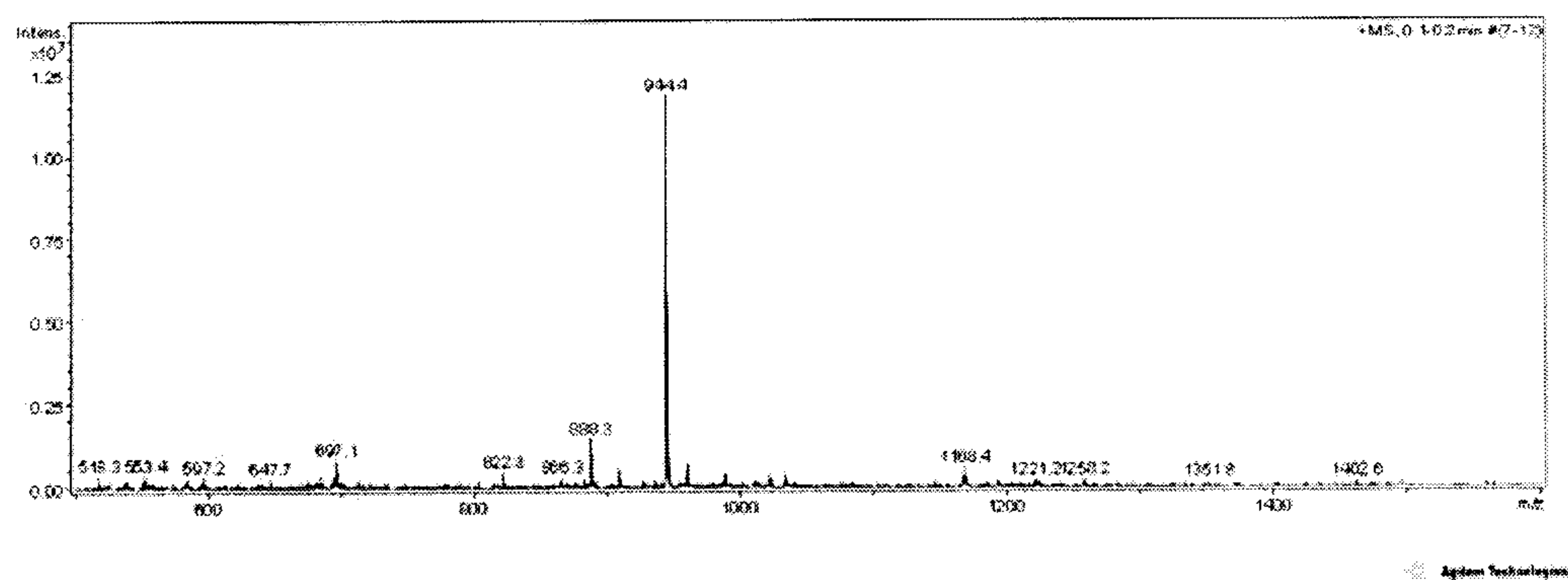


Fig.50

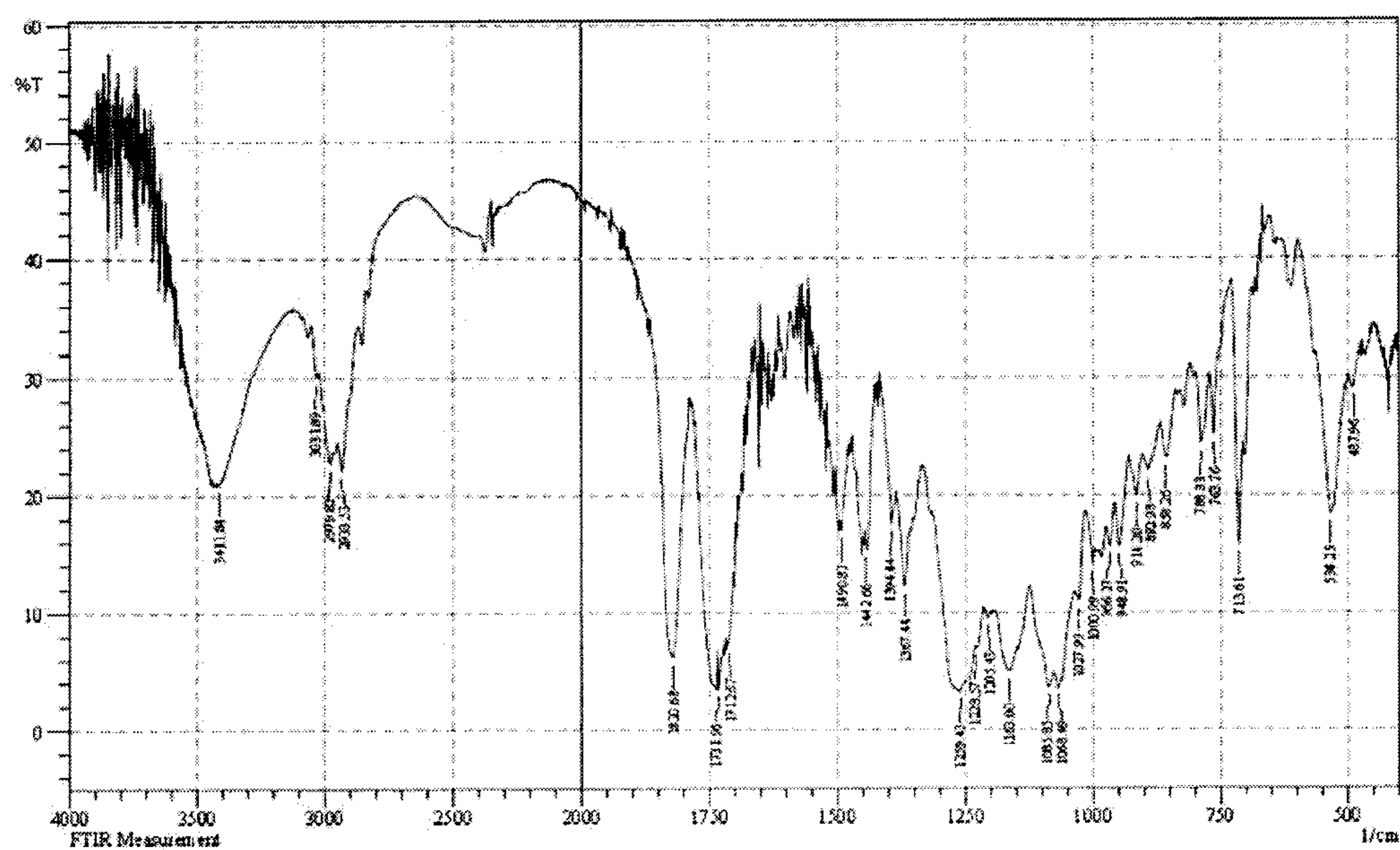


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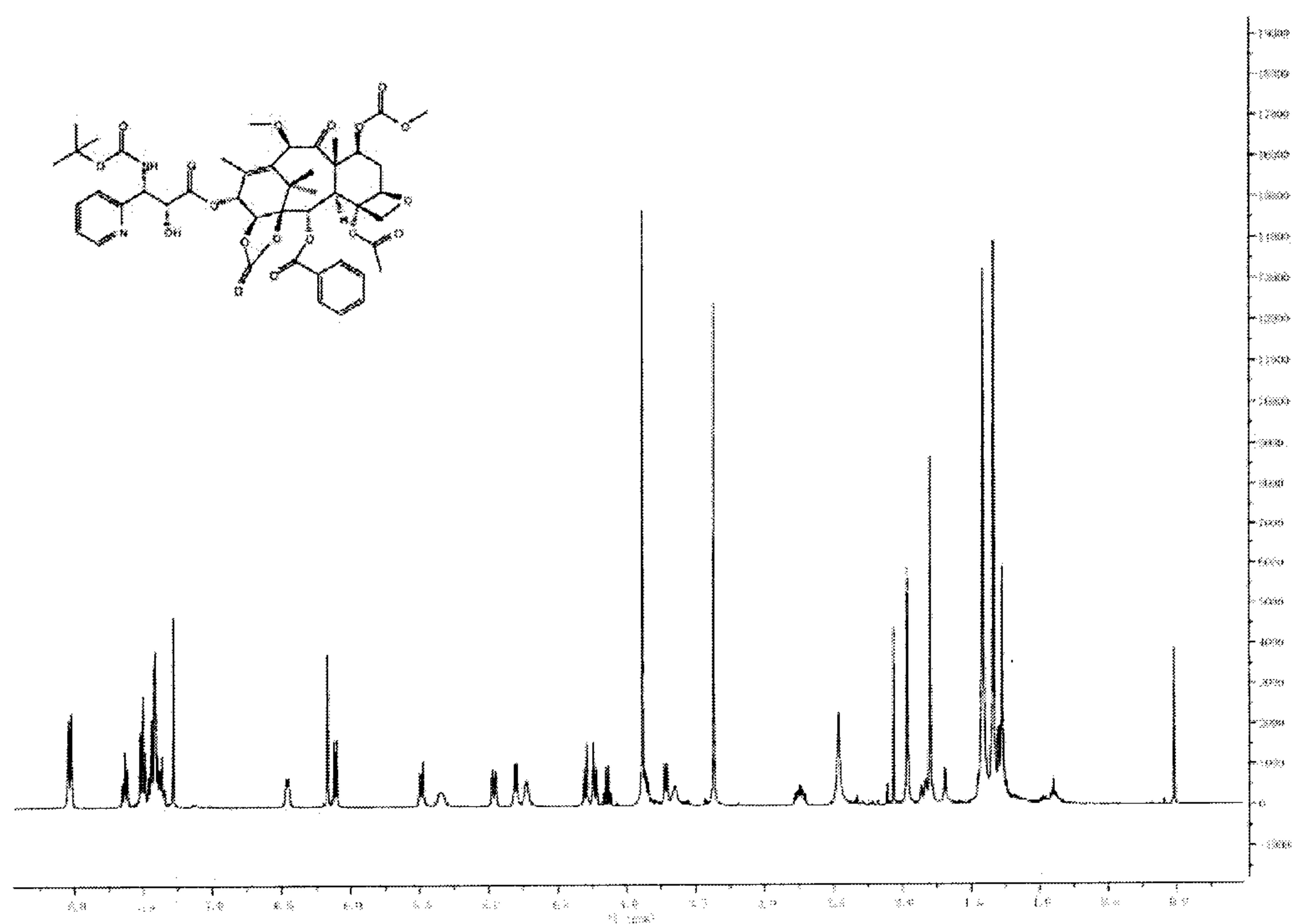


Fig.52

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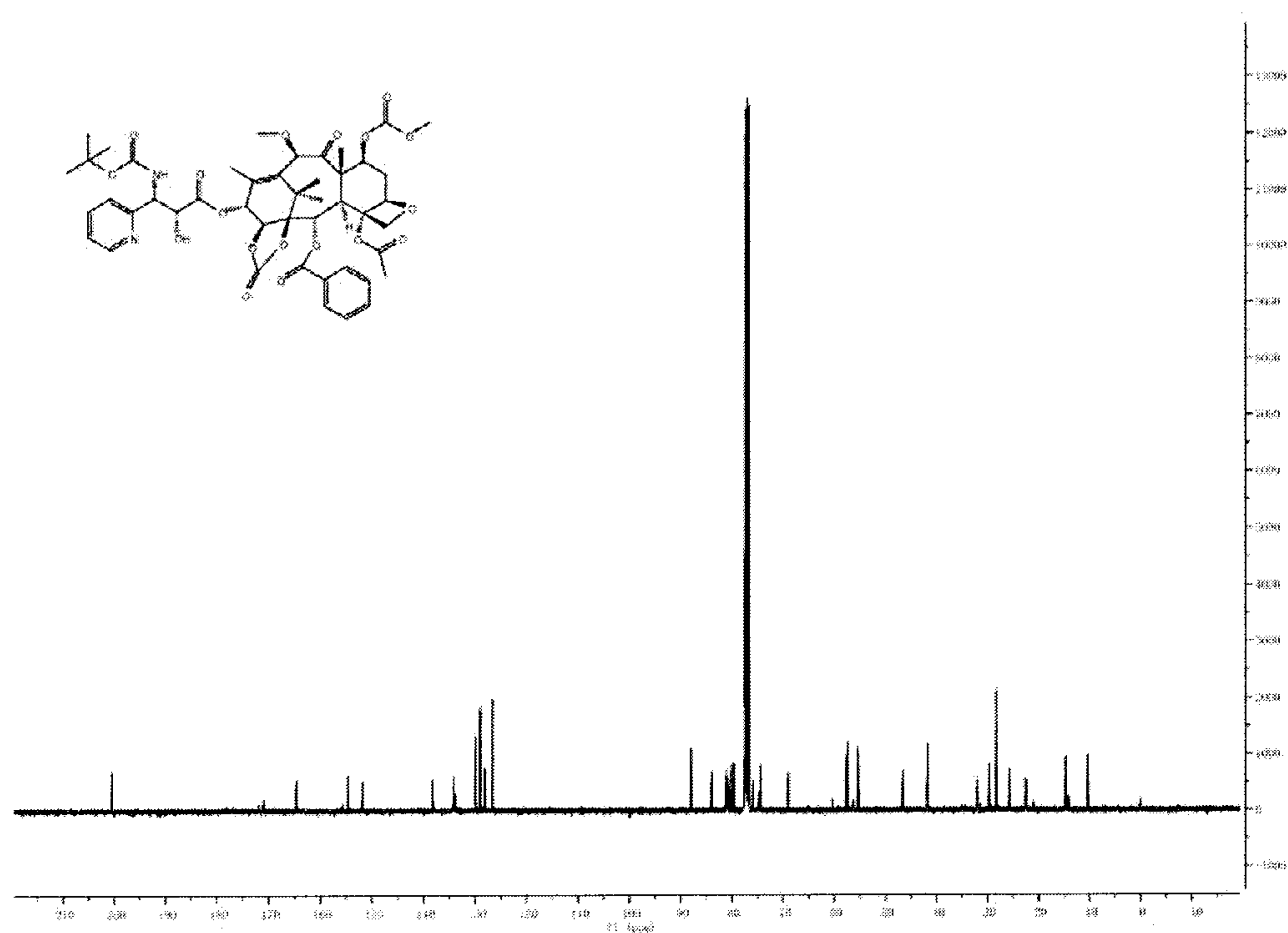


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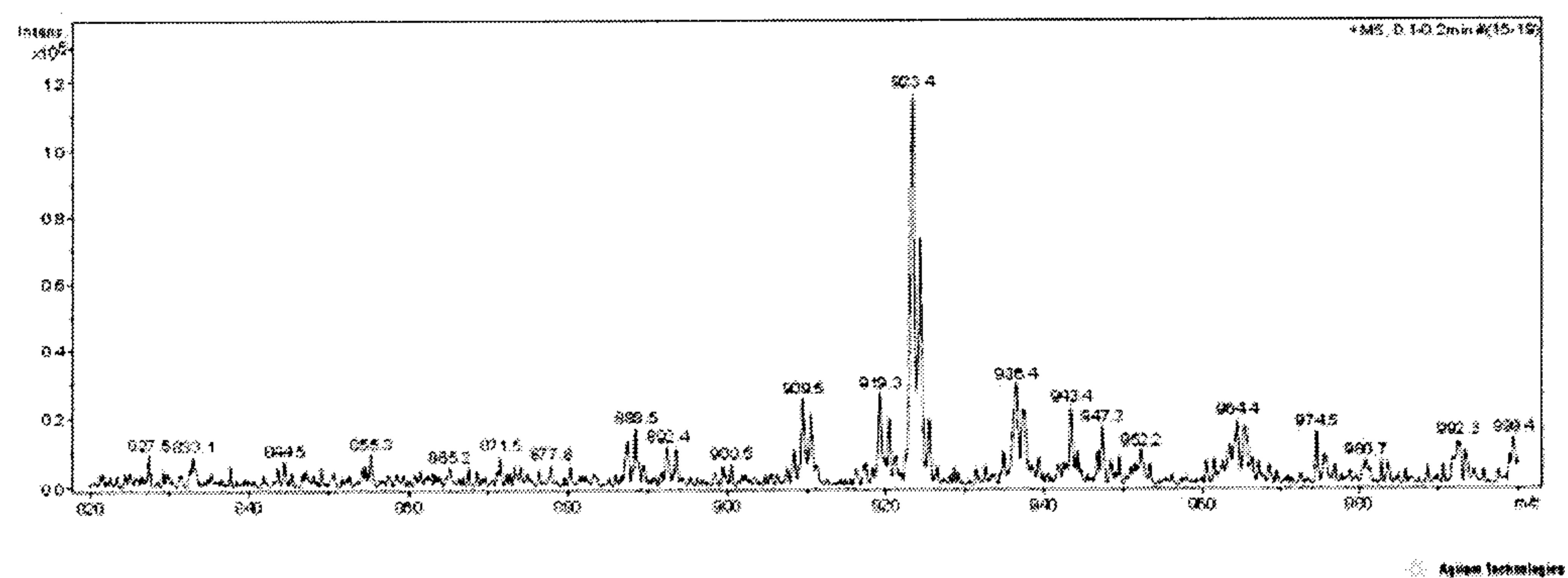


Fig.54

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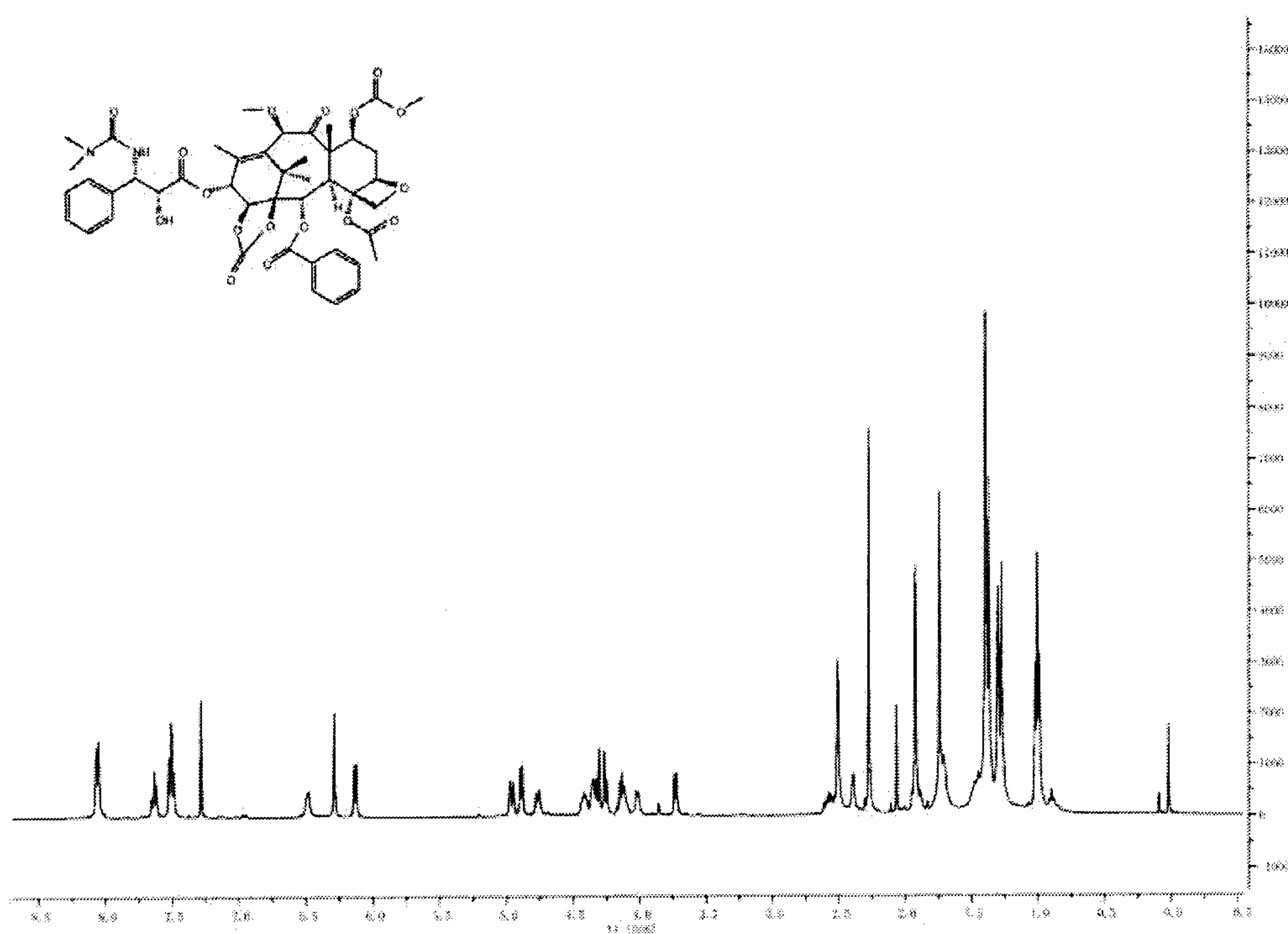


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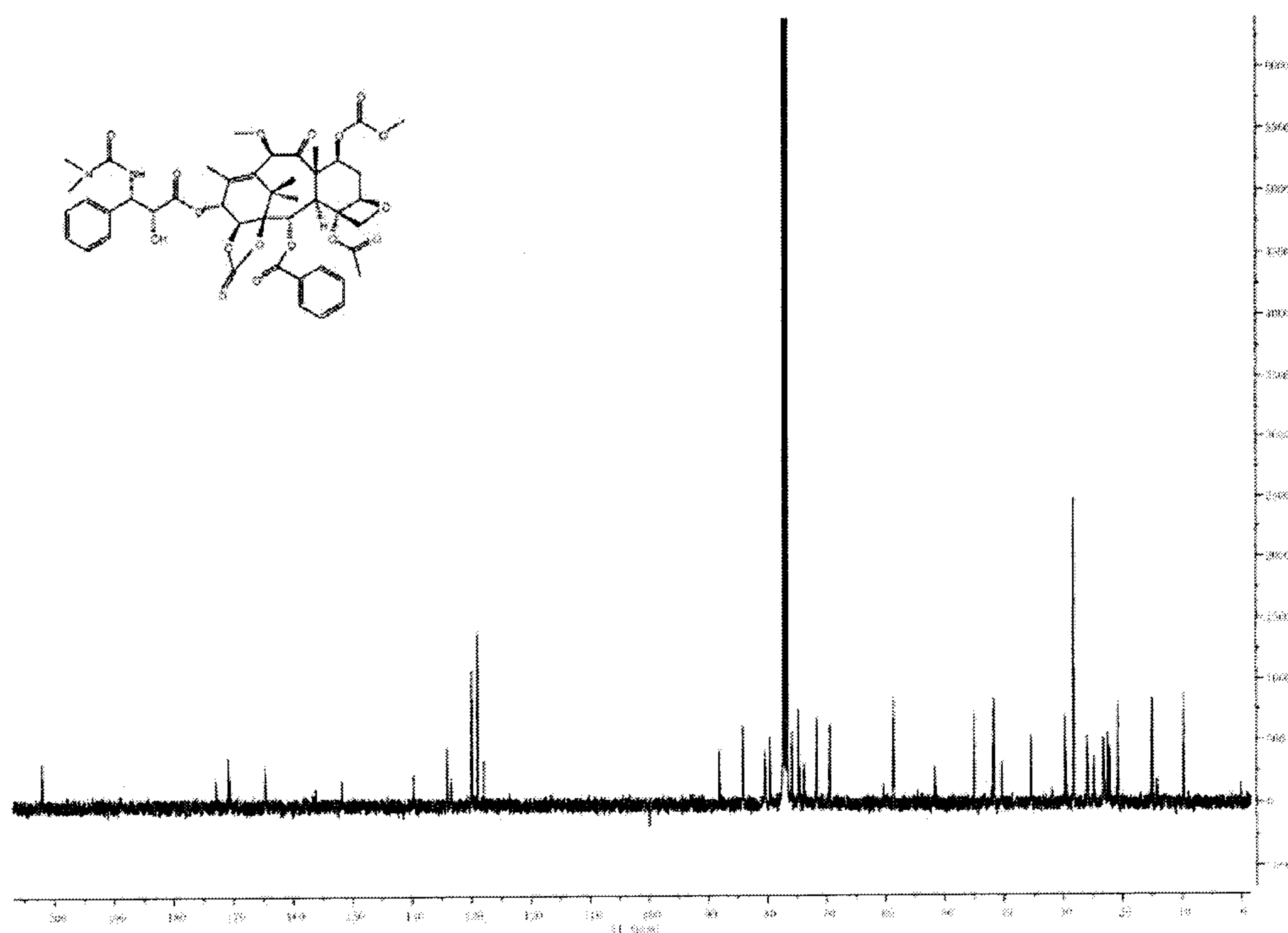


Fig.56

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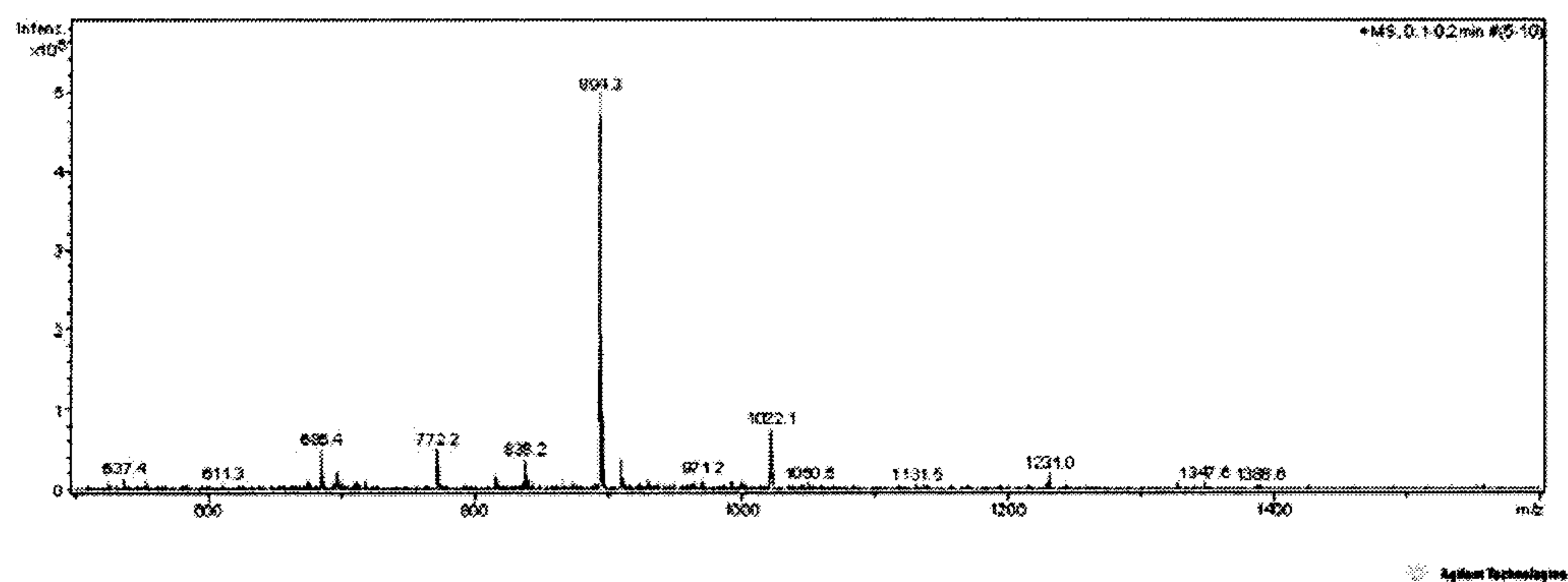


Fig.57

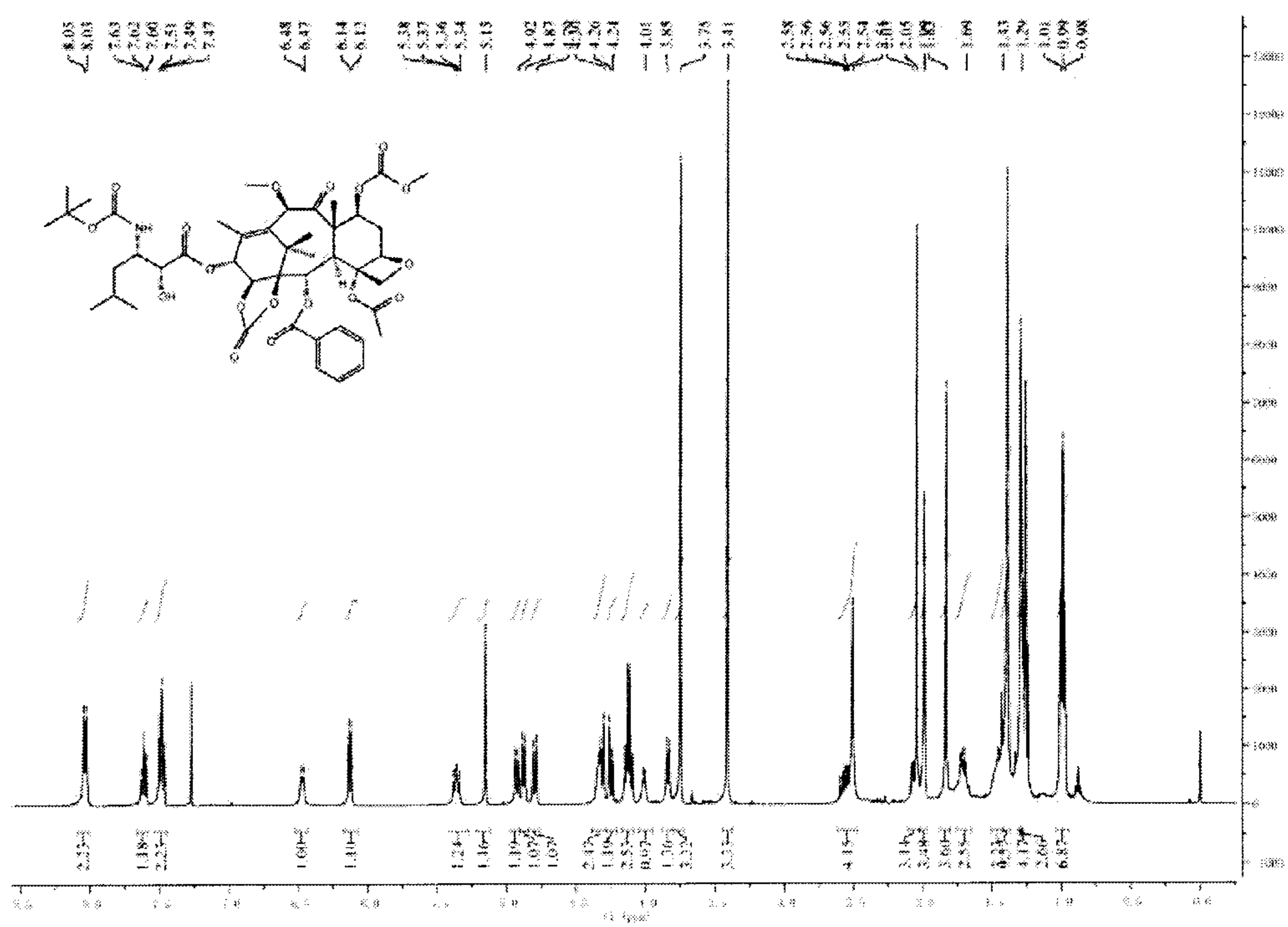


Fig.58

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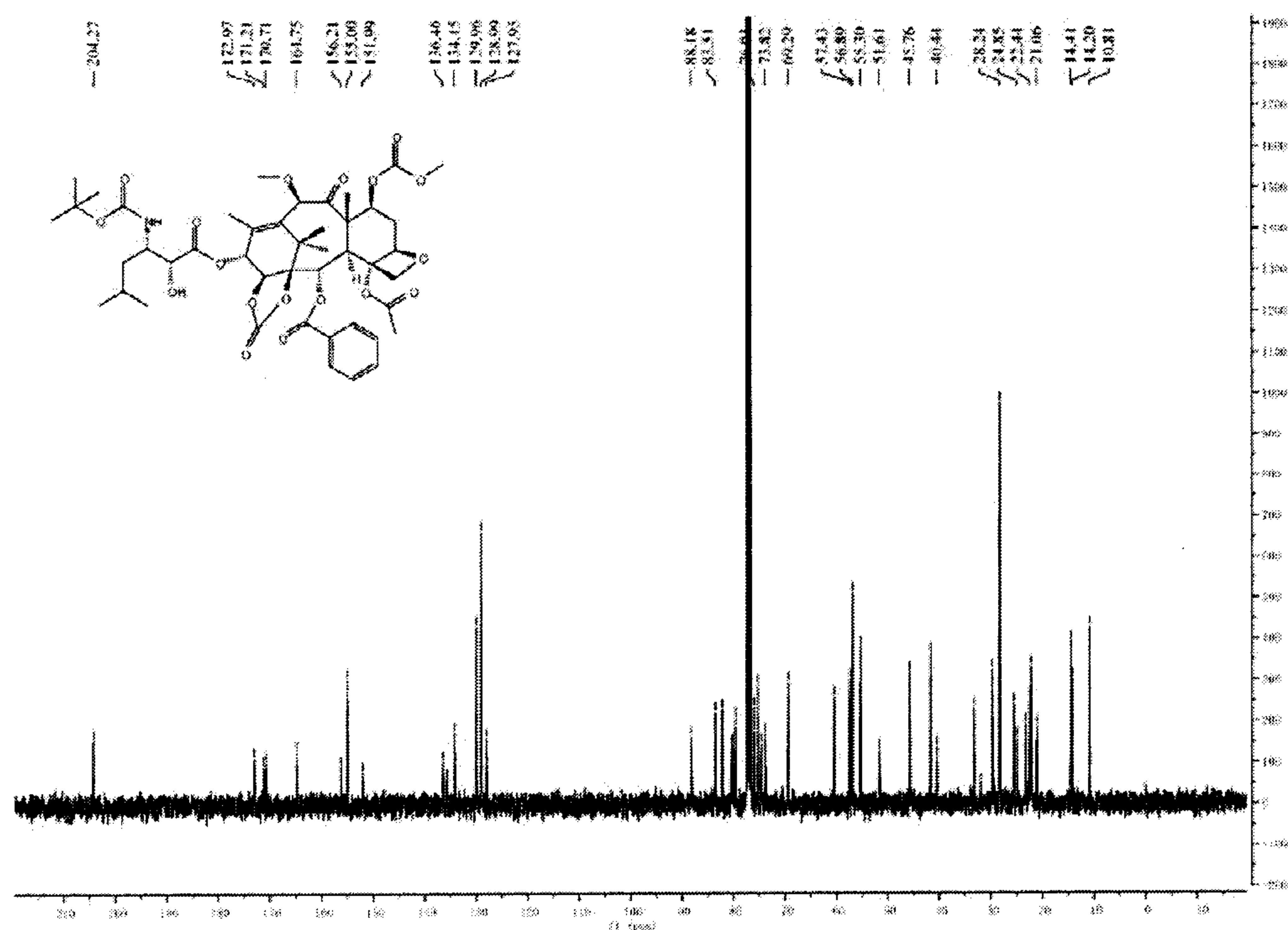


Fig.59

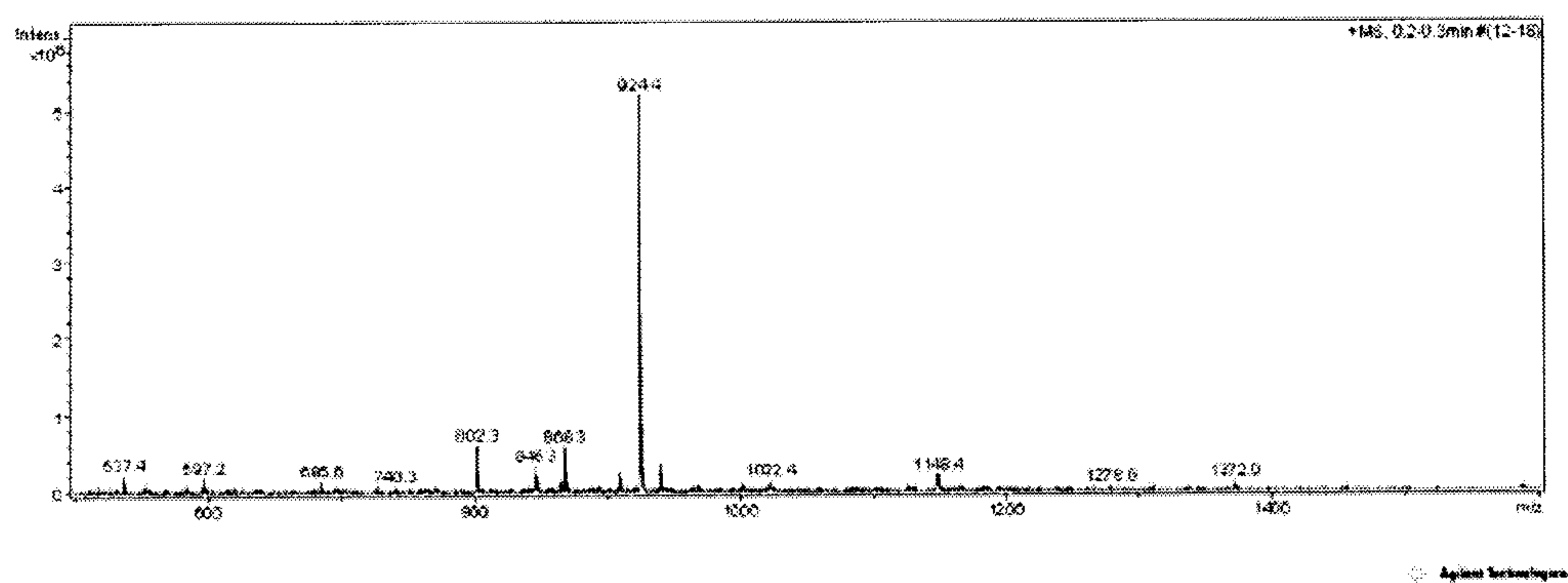


Fig.60

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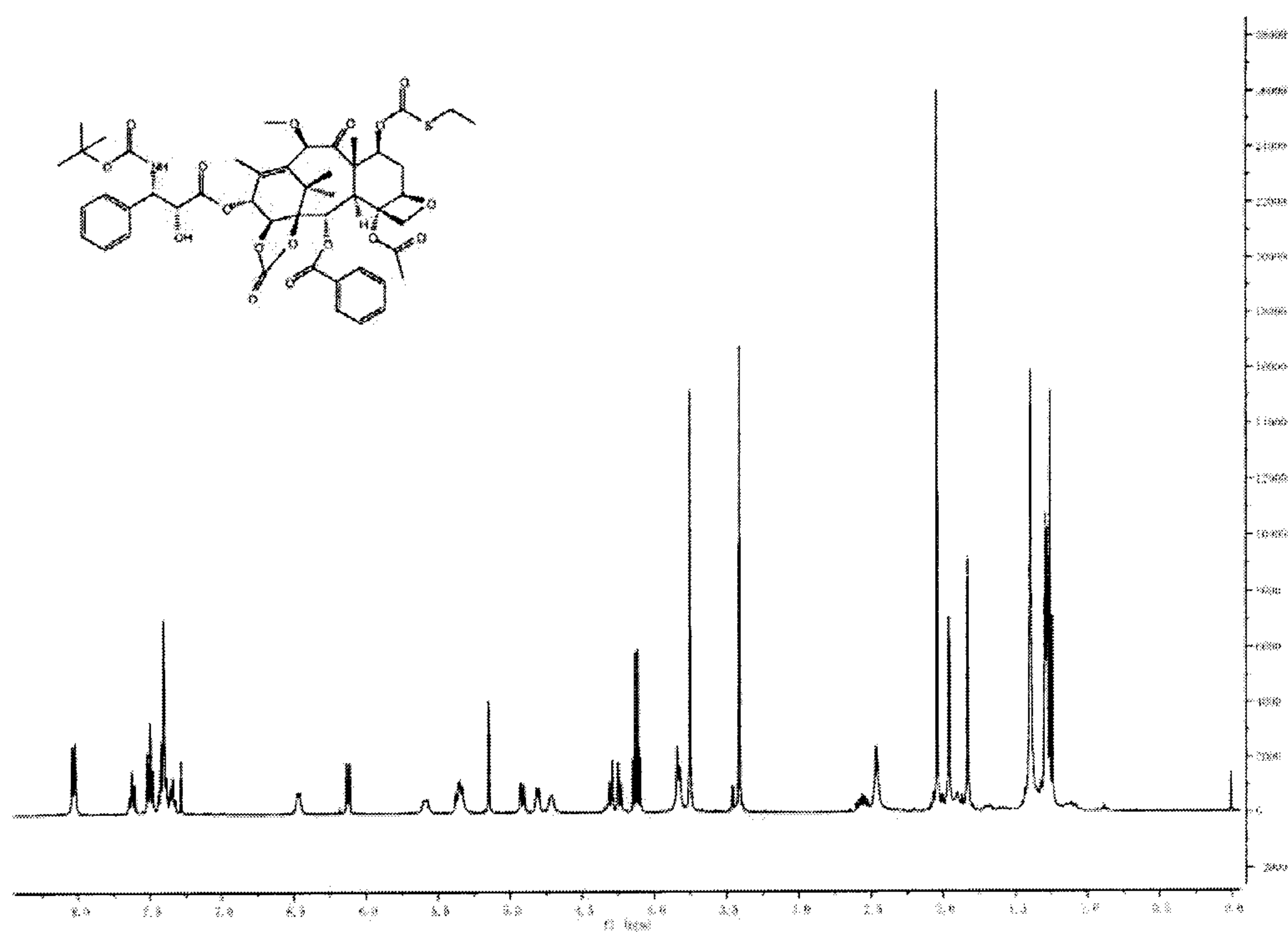


Fig.61

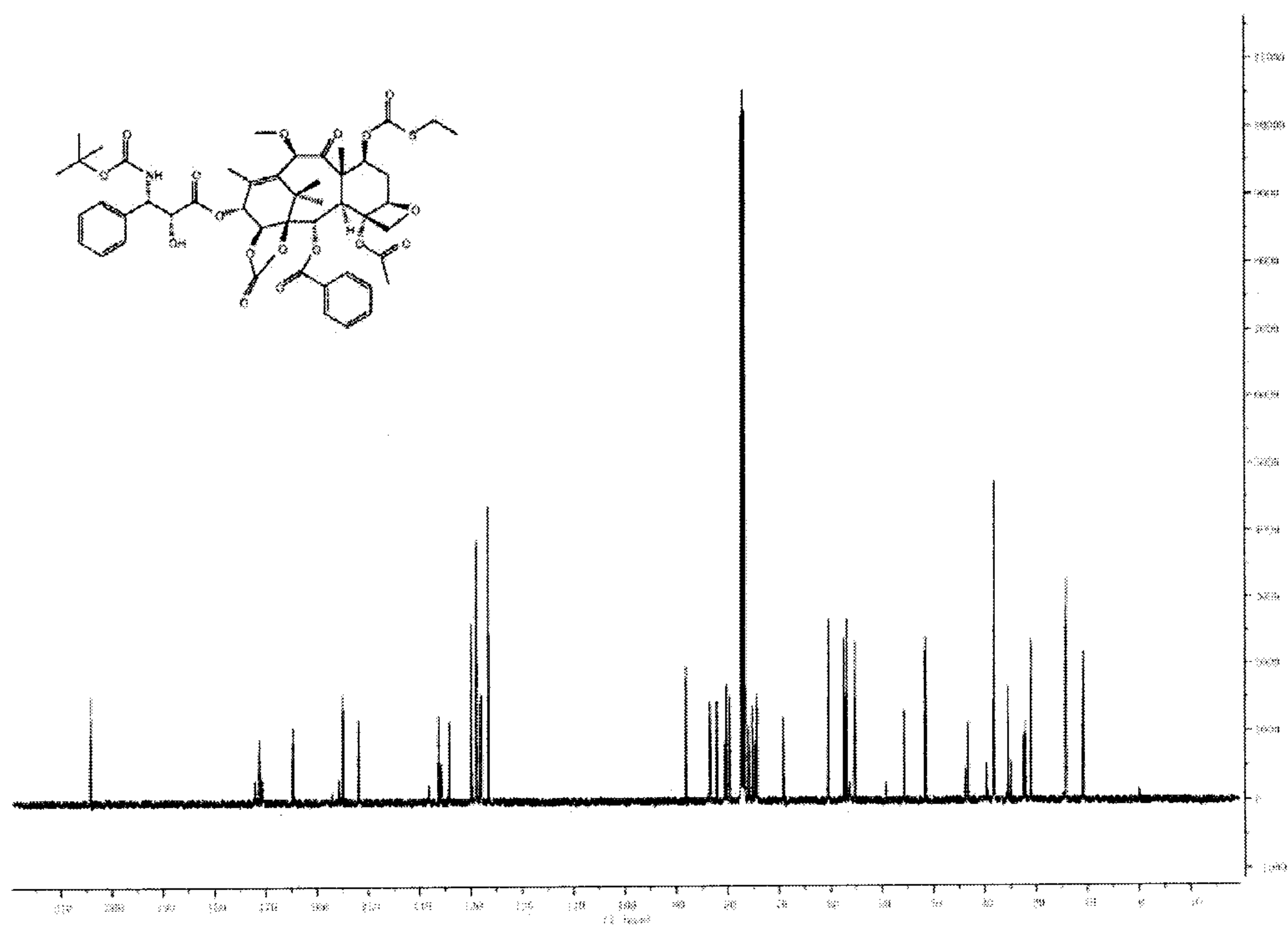


Fig.62

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