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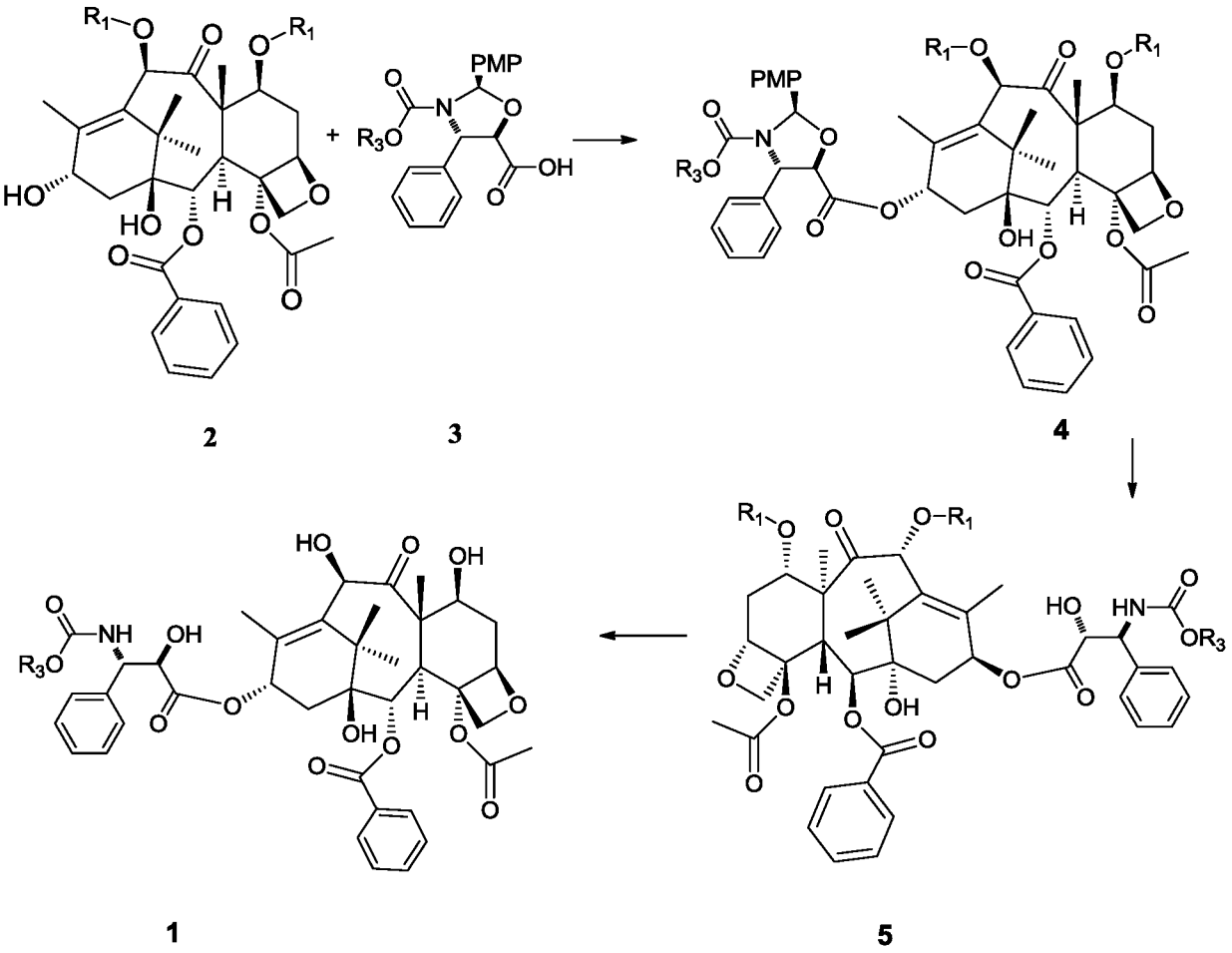
(54) Title: NEW EFFICIENT METHODS FOR THE SYNTHESIS OF TAXANE DERIVATIVES SUCH AS DOCETAXEL AND THEIR STRUCTURAL ANALOGOUS, AND A METHOD FOR THE PREPARATION THEREOF

(57) Abstract: The present invention relates to a novel process for the preparation of taxanes such as Docetaxel, a very important anticancer drug. Docetaxel 1 is a clinically well-established anti -mitotic chemotherapy medication used mainly for the treatment of breast, ovarian and non-small cell lung cancer. In this work we introduce an efficient and simple process for producing Docetaxel 1 (vide infra), including the following steps: a) hydroxyl acylation reaction of 10-DAB-III with chloroacetic acid to obtaine compound 2; b) condensation reaction of compounds 2 and 3 to obtain compound 4; c) deprotection of protecting group parathoxy phenyl (PMP) protecting group to obtain compound 5 d) deprotection of protecting group Rl of compound 5 to prepare Docetaxel 1; wherein, Rl is, among other acetylation reagents, chloroacetyl chloride, R2 is, among other ketones and aldehydes, paramethoxy phenyl (PMP), and R3 is, among other alkanes, tert-butyl e) subjecting the crude Docetaxel to fast filtration over a short silica gel filter to obtain anhydrous Docetaxel of > 95% purity f) crystallizing the anhydrous Docetaxel of step e) to obtain pharmaceutical grade Docetaxel trihydrate. In the methods for preparation of the present invention, the protective groups used are easily removed, the purification of the intermediates is convenient, the cost of production is reduced, the steps of reaction are fewer, the yield and the purity are higher, and the processes can be scaled to commercial scale production. Another important aspect of the present invention is the preparation of pharmaceutical grade Docetaxel without resorting to chromatography.



NEW EFFICIENT METHODS FOR THE SYNTHESIS OF TAXANE DERIVATIVES SUCH AS DOCETAXEL AND THEIR STRUCTURAL ANALOGOUS, AND A METHOD FOR THE PREPARATION THEREOF

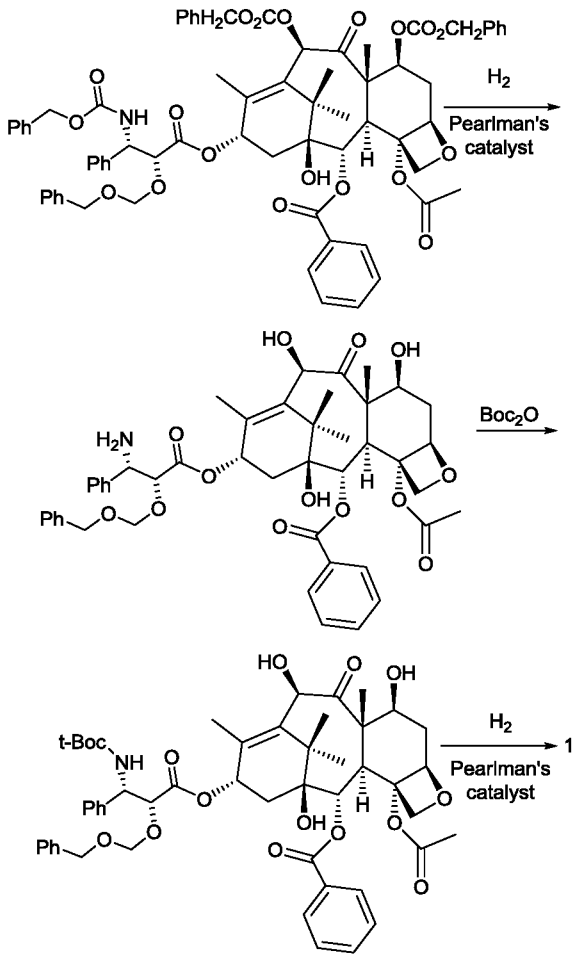
FIELD OF THE INVENTION

A novel process is outlined for the synthesis and preparing an anticancer medicine and it's intermediate. This invention generally relates the synthesis of Docetaxel, its intermediates and methods for preparation thereof with using a suitably protected 10-deacetyl baccatin III (10-DAB), which is esterified with a suitably protected side chain acid to produce an intermediate that may be further deprotected to produce Docetaxel.

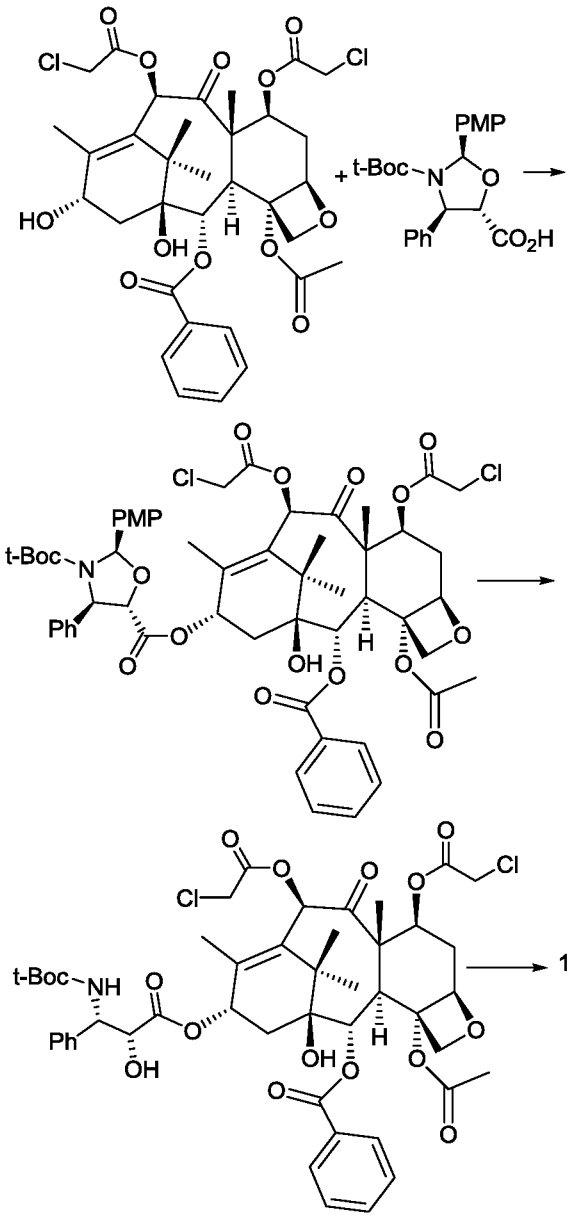
BACKGROUND OF THE INVENTION

Docetaxel is a diterpene taxane found in very low concentration in the bark of Pacific yew tree *Taxus brevifolia.* A number of semi-synthetic strategies have been developed for its synthesis from more readily available 10-DAB. However, the taxane nucleus is highly prone to degradation and semi-synthetic crude materials are often contaminated with structurally similar impurities. As a result, elaborate purification procedure using HPLC are required to produce pharmaceutical grade material. Thus, it becomes highly desirable to develop alternative routes, which involves minimal degradation.

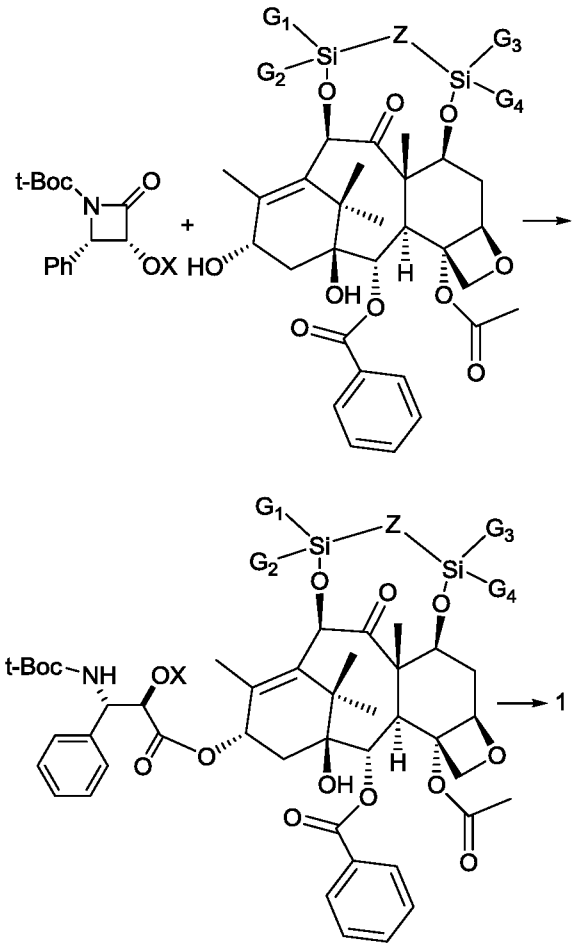
US patent 5,688,977 teaches a process for preparing of Docetaxel by reaction of a protecting acid and a suitably protected 10-deacetyl baccatin III and selective removal of protecting groups. Furthermore, the procedure described by US patent 5,688,977 requires three steps for removal of protecting groups to convert to Docetaxel. The described method requires Pearlman's catalyst which is very expensive. Also, esterification preferably employs an excess of the hydroxyl function protecting group, such as six equivalents of the side chain for each equivalent of protected 10-deacetyl baccatin III.



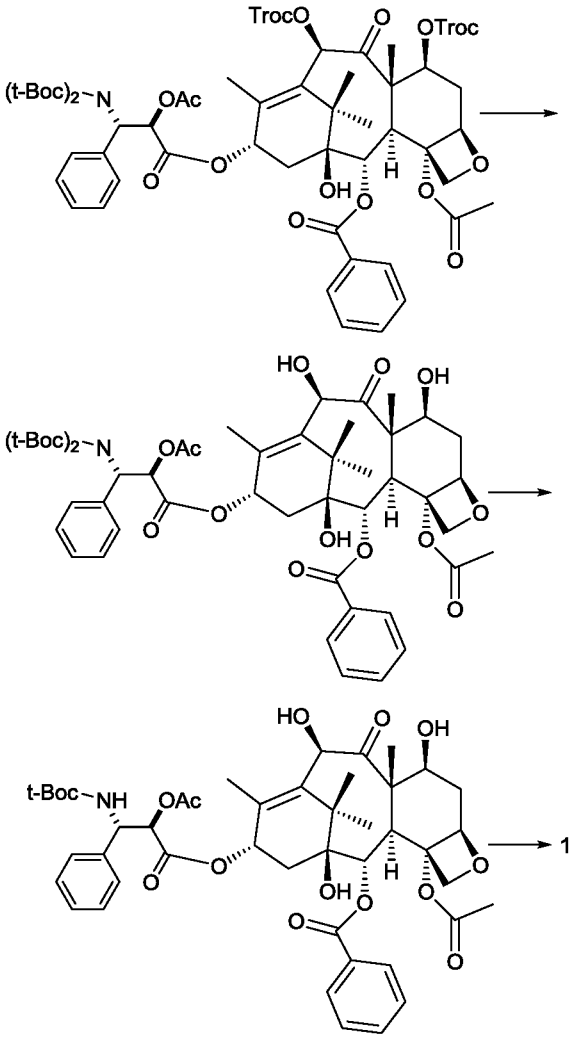
US patent 6,900,342, disclose a process for preparing Docetaxel, wherein a protected 10-deacetylbaccatin III and five-membered oxazolidine side chain is de-protected through hydrolysis to yield Docetaxel. Furthermore, the procedure described by US patent 6,900,342 requires a large excess of condensation reagent DCC (N,N'-dicyclohexyl carbodiimide), which causes considerable difficulty in the following purification step.



US patent 7,550,608 disclosed a method for the preparation Docetaxel with esterification of β-lactam under very low temperature in the presence of strong base. However, the use of strong base will cause decomposition of the protected 10-deacetylbaccatin III, waste of the expensive raw material and considerable problems in the following purification steps. Our method, on the other hand, is devoid of these problems.



In US patent application 2010/0311991 Al, the reaction of an acid and a suitably protected 10-deacetyl baccatin III and selective removal of protecting groups trichloroethoxycarbonyl (Troc) or triethylsilyl (TES) at 7 and 10 hydroxyl functions in the presence of an acetyl group used for the protection of hydroxyl function of the acid has been reported under different condition. However, in this method the tert-butoxycarbonyl (Boc) group is also removed followed by deacetylation of hydroxyl group in organic solvent. Furthermore, the procedure described by US patent application 2010/0311991 Al requires three steps to convert the coupling product to Docetaxel, whereas in our process we describe a one-step procedure.



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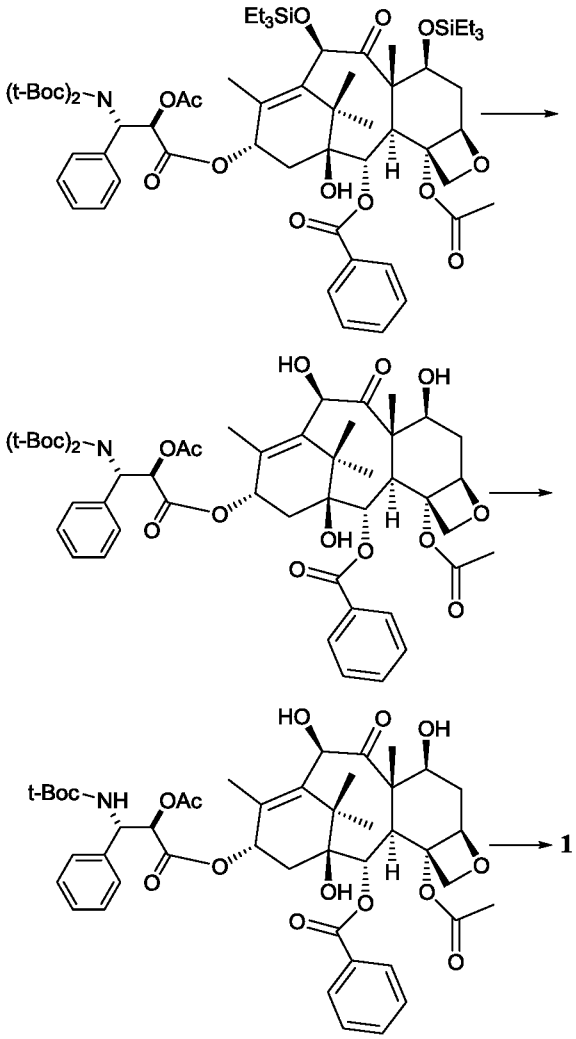
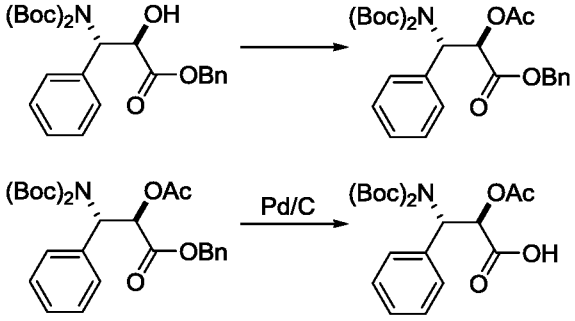


In US patent application 2010/0311991 Al, the reaction of a (2R,3S)-butyl 2-acetoxy-3-(tert-butoxycarbonylamino)-3-phenylpropanoate with acetic anhydride and selective removal of benzyl protection group is reported to afford (2R,3S)-2-acetoxy-3-(tert-butoxycarbonylamino)-3-phenylpropanoic acid in 81.7% yield. However, this process requires palladium catalyst which is very expensive. Our process, on the other hand, affords a higher yield of 89.3% using inexpensive reagents.



US patent 5,476,954 discloses a process for preparing Docetaxel that involves reacting protected 10-deacetylbaccatin III and with (4S,5R)-3-tert-butoxycarbonyl-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid in the presence of DCC, DMAP, and toluene and in continuation deprotection of the hydroxyl protecting group, 2,2,2-trichloroethoxycarbonyl, using zinc in the presence of acetic acid and methanol to obtained Docetaxel. In this process excess molar equivalents of di-tert-butyl dicarbonate (about 16 equivalents), a very expensive reagent, is used. The reported yield is lower than the yield obtained in our process using 1.2 equivalents of di-tert-butyl dicarbonate.

Nearly all patents in this domain resort to various forms of chromatography for the purification of process intermediates, the product or both. Our process, on the other hand, affords pharmaceutical grade Docetaxel without utilizing chromatography.

OBJECTS OF THE INVENTION

The object of this invention is a novel process for the preparation of Docetaxel and its intermediates which minimize degradation during the process and thereby increase yield and purity of the target product. Our process also circumvents the use of expensive reagents as well as large molar excess of the same. Furthermore, our process does not resort to chromatography of the process intermediates or the product. Accordingly, the process described herein is eco-friendly, cost-effective, and well suited for an industrial scale production of Docetaxel and its intermediates.

SUMMARY OF THE INVENTION

The present invention consists of a process for the preparation of Docetaxel, its intermediates comprising of subjecting 7,10-di-O-chloroacetyl-10-deacetylbaccatin III **(2)** to coupling with (4S,5R)-3-(tert-butoxycarbonyl)-2-(4-methoxyphenyl)-4-phenyloxazolidine-5-carboxylic acid **(3)** in the presence of a condensation agent and an activating agent at a temperature between 50 and 80° C to obtain coupled product **4,** that

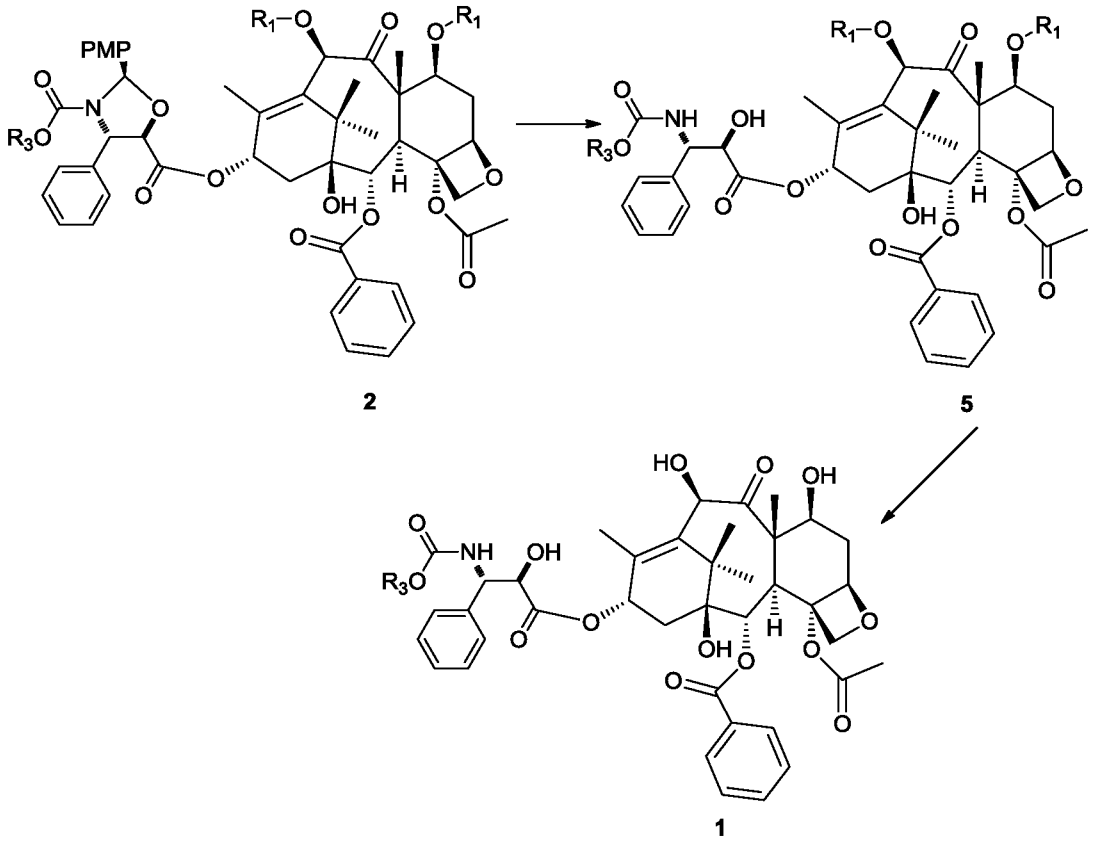
may thereafter be deprotected. The de-protection of haloacyl and paramethoxy phenyl (PMP) groups affords Docetaxel.

This route solves the technical problems of purification, waste of raw material, low yield, use of high temperature, use of chromatography, and reduces the high cost of manufacturing Docetaxel encountered in previously reported methods.

In this method, protective groups used are easily removed, the purification of the intermediates is convenient, and the cost of production of Docetaxel and its intermediates is reduced. These advantages and the higher yields obtained afford an efficient process that can be scaled to commercial production of Docetaxel and its intermediates.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for the preparation of Docetaxel 1, which is prepared by removing two protecting groups R1 and one protecting group R2 from compound **4,**

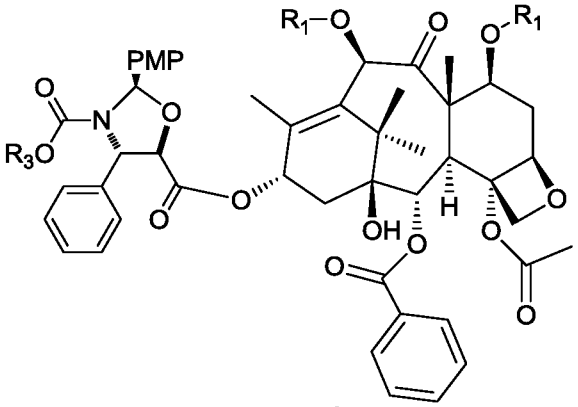


Wherein, R1 is chloroacetyl chloride, R2 is paramethoxy phenyl (PMP), and R3 is tert-butoxycarbonyl.

Deprotection of haloacyl groups can be carried out in the intermediate **4** under mild alkaline condition in two steps, first in the presence of an aliphatic acid or perhalo aliphatic acids such as triflouroacetic acid for deprotecting paramethoxy phenyl (PMP) group and secondly in the presence of ammonia or aliphatic or aromatic amines or a combination thereof, preferably ammonia and pyridine (1:5) for deprotecting haloacyl groups. The reactionin both steps are carried out at 0-5° C , preferably at 2° C. The reaction time is decided by detection of the completion of the reaction, usually 6-24 hours, preferably 12 h, to obtain Docetaxel.

The removal of protecting haloacyl groups and paramethoxy phenyl (PMP) group at 7-, 10-baccatin III and hydroxyl and amine functions of the side chain carboxylic acid groups are

achieved under much milder condition. Furthermore, the procedure described by US patent application. 2010/0311991 Al, requires three steps to convert the coupling product to Docetaxel, whereas this invention describes a two-step process wherein, R1 are hydroxy-protecting group refers to any derivative known in the art which can be used to mask the hydroxy function during a chemical transformation and later removed under conditions resulting in the hydroxy group being recovered without other undesired effects on the remainder of the molecule. Many esters, acetals, ketals and silyl ethers are suitable protecting groups. Examples of hydroxy-protecting groups include, without limitation, formyl, acetyl (Ac), benzyl (PhCH2), 1-ethoxyethyl (EE), methoxymethyl (MOM), (methoxyethoxy)methyl (MEM), (p-methoxyphenyl)methoxymethyl (MPM), tert-butyldimethylsilyl (TBS), tert-butyldiphenylsilyl (TBPS), tert-butoxycarbonyl (t-Boc, t-Boc, t-BOC, t-BOC), tetrahydropyranyl (THP), triphenylmethyl (Trityl, Tr), 2- methoxy-2-methylpropyl, benzyloxycarbonyl (Cbz), chloroacetyl, dichloroacetyl, trichloroacetyl (OCCHyClX), 2,2,2-trichloroethoxycarbonyl (Troc), benzyloxymethyl (BOM), tert-butyl (t-Bu), triethylsilyl (TES), trimethylsilyl (TMS), triisopropylsilyl (TIPS), propionyl, isopropionyl, pivalyl, dimethylisopropylsilyl, diethylisopropylsilyl, methyldiphenylsilyl, dimethylphenylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triphenylsilyl, trichloroethoxycarbonyl, benzyl, para-nitrobenzyl, para- methoxybenzyl, benzoyl, methoxyethyl, para-methoxyphenyl, tetrahydrofuranyl, alkylsulfonyl and arylsulfonyl. The related term "protected hydroxy group" or "protected -OH" refers to a hydroxy group that is bonded to a hydroxy-protecting group. General examples of protected hydroxy groups include, without limitation, - O-alkyl, -O-acyl, acetal, and -O-ethoxyethyl, where some specific protected hydroxy groups include, formyloxy, acetoxy, propionyloxy, chloroacetoxy, bromoacetoxy, dichloroacetoxy, trichloroacetoxy, trifluoroacetoxy, methoxyacetoxy, phenoxyacetoxy, benzoyloxy, benzoylformoxy, p-nitro benzoyloxy, ethoxycarbonyloxy, methoxycarbonyloxy, propoxycarbonyloxy, 2,2,2-trichloroethoxycarbonyloxy, benzyloxycarbonyloxy, tert-butoxycarbonyloxy, 1-cyclopropylethoxycarbonyloxy, phthaloyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, oxalyoxy, succinyloxy and pivaloyloxy, phenylacetoxy, phenylpropionyloxy, mesyloxy, chlorobenzoyloxy, para-nitrobenzoyloxy, para-tert- butyl benzoyloxy, capryloyloxy, acryloyloxy, methylcarbamoyloxy, phenylcarbamoyloxy, naphthylcarbamoyloxy, and the like.



4

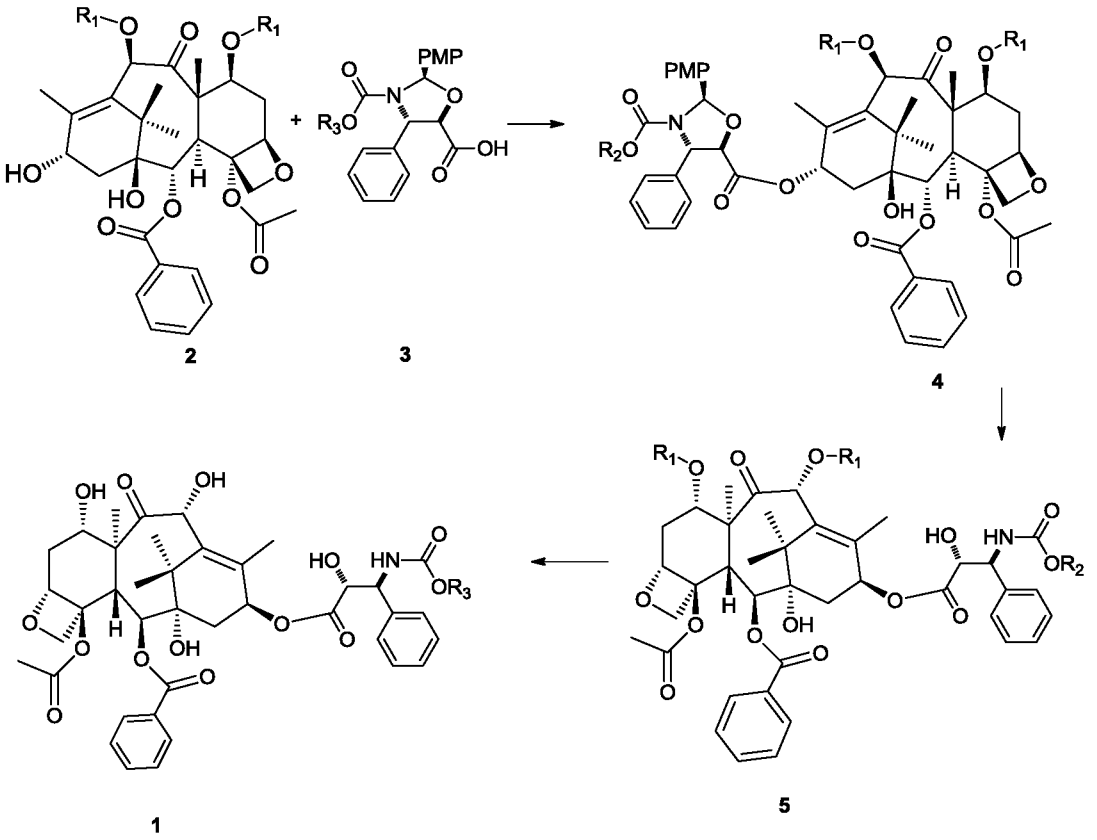
The methods and conditions of removing protection group of the hydroxyl group described can be the common methods and conditions of deprotection group of the hydroxyl group known to men of art in the field.

In formula (4) R1 is a hydrogen atom of a suitable hydroxyl-protecting group, R2 is paramethoxy phenyl (PMP), and R3 is a hydrogen atom, a linear C1-C20 alkyl, a branched C3-C50 alkyl group, a C1-C50 acyl group, a C1-C50 halogenated acyl group, a C3-C50 cycloalkyl, a C1-C50 heterocyclyl, a C2-C50 alkenyl, a C2-C50 alkynyl, a C6-C20 aryl, a C6-C50 aralkyl, a C1-C50 alkyloxy C6-C50 alkylaryl, a C1-C50 heteroaryl, a C2-C50 alkylheterocyclyl or a C2-C50 alkylheteroaryl, said alkyl, cycloalkyl, heterocyclyl, alkenyl, alkynyl, aryl, aralkyl, alkylaryl, heteroaryl, alkylheterocyclyl, alkylheteroaryl, formyl, acetyl (Ac), benzyl (PhCH2), 1-ethoxyethyl (EE), methoxymethyl (MOM), (methoxyethoxy)methyl (MEM), (p-methoxyphenyl)methoxymethyl (MPM), tert-butyldimethylsilyl (TBS), tert-butyldiphenylsilyl (TBPS), tert-butoxycarbonyl (tBoc, t-Boc, tBOC, t-BOC), tetrahydropyranyl (THP), triphenylmethyl (Trityl, Tr), 2-methoxy-2-methylpropyl, benzyloxycarbonyl (Cbz), chloroacetyl, dichloroacetyl, trichloroacetyl (OCCHyClx), 2,2,2-trichloroethoxycarbonyl (Troc), benzyloxymethyl (BOM), tert-butyl (t-Bu), triethylsilyl (TES), trimethylsilyl (TMS), triisopropylsilyl (TIPS), propionyl, isopropionyl, pivalyl, dimethylisopropylsilyl, diethylisopropylsilyl, methyldiphenylsilyl, dimethylphenylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triphenylsilyl, trichloroethoxycarbonyl, benzyl, para-nitrobenzyl, para-methoxybenzyl, benzoyl, methoxyethyl, para-methoxyphenyl, tetrahydrofuranyl, alkylsulfonyl and arylsulfonyl. The

related term "protected hydroxy group" or "protected -OH" refers to a hydroxy group that is bonded to a hydroxy-protecting group. General examples of protected hydroxy groups include, without limitation, - O-alkyl, -O-acyl, acetal, and -O-ethoxyethyl, where some specific protected hydroxy groups include, formyloxy, acetoxy, propionyloxy, chloroacetoxy, bromoacetoxy, dichloroacetoxy, trichloroacetoxy, trifluoroacetoxy, methoxyacetoxy, phenoxyacetoxy, benzoyloxy, benzoylformoxy, p-nitro benzoyloxy, ethoxycarbonyloxy, methoxycarbonyloxy, propoxycarbonyloxy, 2,2,2-trichloroethoxycarbonyloxy, benzyloxycarbonyloxy, tert-butoxycarbonyloxy, 1-cyclopropylethoxycarbonyloxy, phthaloyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, oxalyoxy, succinyloxy and pivaloyloxy, phenylacetoxy, phenylpropionyloxy, mesyloxy, chlorobenzoyloxy, para-nitrobenzoyloxy, para-tert- butyl benzoyloxy, capryloyloxy, acryloyloxy, methylcarbamoyloxy, phenylcarbamoyloxy, naphthylcarbamoyloxy, and the like.

In this invention R1 is chloroacetyl chloride and R2 is paramethoxy phenyl (PMP), the deprotection of compound **4** is performed under mild alkaline condition to remove haloacyl groups , for example in the presence of ammonia or aliphatic amines or aromatic amines or their combinations, preferably ammonia and pyridine (1:5). The reaction is performed at temperature between 0-5° C , preferably at temperature between -3° to 0° C. The reaction time is decided by detection of the completion of the reaction, 6-24 hours, preferably 12 h. The deprotection of compound **4** is performed under acidic condition to remove paramethoxy phenyl (PMP) group, for example in the presence of halo-acetic acid and preferably trifluoroacetic acid.

The present invention further relates to a process for preparing compound **4,** including the following steps: compound **4** was prepared from condensation reaction between compounds **3** and **2** in the presence of a condensation agent and an activating agent, wherein, compound **4** is obtained from reaction of 7, 10-di-O-protected-lO-deacetylbaccatin III **2** with protected side chain acid **3** in the presence of a condensation agent and an activating agent in organic solvent to obtain compound **4.**



The organic solvent is preferably one or several chosen from dichloromethane, ethyl acetate, toluene, diethyl ether, isopropyl ether, acetone, acetonitrile, tetrahydrofuran, methanol and ethanol or a mixture thereof, preferably toluene. The reaction is performed by dissolving the two compounds in the above-said organic solvent(s), preferably toluene, followed by the addition of the condensation agents. The sequence of addition of the compounds and reagents may be changed as is known to the men of art.

The condensation agents used is, among other agents known in the art, dimethylamine pyridine (DMAP) and dialkylcarbodiimide. The dialkylcarbodiimide is preferably in equal proportion to the amount of the side chain compound. This dialkylcarboiimide is selected from a group consisting of a diisopropylcarbondiimide and dicyclohexylcarbodiimide or other analogues thereof.

The reaction is carried out at temperature between 0-100° C , preferably at 25-70° C , and most preferably at 60° C. Among aromatic hydrocarbons, toluene is found to be the most

suitable. The reaction time is determined by detection of the completion of the reaction, usually 12-36 hours.

In the present invention, R1 in formula **(4)** is a hydrogen atom of a suitable hydroxyl-protecting group, in formula **(5)** R2 and R3 can be hydrogen atoms, a linear C1-C20 alkyl, a branched C3-C50 alkyl group, a C1-C50 acyl group, a C1-C50 halogenated acyl group, a C3- C50 cycloalkyl, a C1-C50 heterocyclyl, a C2-C50 alkenyl, a C2-C50 alkynyl, a C6 -C20 aryl, a C6-C50 aralkyl, a C1-C50 alkyloxy C6-C50 alkylaryl, a C1-C50 heteroaryl, a C2-C50 alkylheterocyclyl or a C2-C50 alkylheteroaryl, said alkyl, cycloalkyl, heterocyclyl, alkenyl, alkynyl, aryl, aralkyl, alkylaryl, heteroaryl, alkylheterocyclyl, alkylheteroaryl, tert-butoxycarbonyl (tBoc, t-Boc, tBOC, t-BOC), formyl, acetyl (Ac), benzyl (PhCH2), and the like.

Synthesis of 7,10-di-O-chloroacetyl-lO-deacetylbaccatin III (2)

A mixture of 10-deacetylbaccatin III (250 g, 0.46 mol), pyridine (483.5 g, 6.25 mol) and 4-DMAP (26.3 g, 206 mmol) is dissolved in 3.75 L of dichloromethane. The reaction mixture is stirred for 10 minutes. 266.5 g (2.36 mol) of chloroacetyl chloride dissolved in 3.75 L dichloromethane is slowly added to the reaction mixture at 5-10° C. Then, the whole mixture is stirred for 2 hours. 6.25 L ice water is added to decompose the excess reagent, and then the reaction mixture is acidified with 5% hydrochloric acid. The organic layer thus obtained is successively washed with aqueous sodium-bicarbonate, sodium chloride solution, dried over anhydrous sodium sulfate, and then distilled under reduced pressure. The residue is added into 2.5 L n-heptane and then mixed for another 2 hours. The resulting fine solid is filtered and then washed with 1 L of heptane to obtain of compound **2** (272.7 g, 0.391 mol, yield 85%), which is used in the next step without any purification.

7,10-Di-O-[2-(Chloroacetyl)]-13-[(4S, 5R)-2(-p-methoxyphenyl)-3-tert-butoxycarbonyl-4-phenyl-l,3-oxazolidinyl -5-carbonyl]-10-deacetylbaccatin III (4)

Compound **4** is obtained from 7, 10-di-O-(2-chloroacetyl)- 10-deacetylbaccatin III **(2,** 100 g, 0.143 mol), (4S,5R)-3-(tert-butoxycarbonyl)-2-(4-methoxyphenyl)-4-phenyloxaz-

olidine-5-carboxylic acid **(5,** 71.53 g, 179 mmol), DCC (36.9 g, 179 mmol) and 4-dimethyl- aminopyridine (4.80 g, 31.54 mmol) in toluene (1.0 L) and stirred for 5-8 h at 60° C , followed by the separation of the resulting dicyclohexylurea by filtration. The resulting cake was washed with 200 ml of toluene, and the combined organic layer was sequentially washed with 3L ml of 3N hydrochloric acid and 3L of saturated sodium bicarbonate and dried over anhydrous Na_2S0_4, filtered and the organic solvent was removed from the filtrate under a reduced pressure. The residue is added into 1.2 L n-heptane and then mixed for another 2 hours. The resulting fine solid is filtered and then washed with 100 ml of heptane to afford pure compound **4** (Yield: 146.6 g, 0.136 mol, 90%) which is used in the next step without any purification.

7, 10-Di-O-(2-chlroacetyl) Docetaxel (5)

7,10-Di-O-[2-(Chloroacetyl)]-13(2R,3S)-2-acetoxy-3-(tert-butoxycarbonylamino)-3-phenylpropanoic-5-carbonyl]-10-deacetylbaccatin III **(4,** 108 g, 0.1 mol) is added to a mixture of trifluoroacetic acid (65.23 ml), acetic acid (1080 ml) and water (108 ml). The mixture is stirred at the same temperature for 8 h and then poured into a solution of disodium hydrogen phosphate (3.38 kg in 6.08 L water) at 5-10° C. followed by ethyl acetate (2.0 L). After extraction the organic layer is successively washed with saturated sodium bicarbonate, brine and then dried over anhydrous sodium sulfate and the organic solvent was removed under a reduced pressure. The residue is added into 6.0 L n-heptane. The resulting fine solid is filtered and then washed with 1000 ml of heptane to afford pure compound **5** (86.56 g, 0.09 mol, 90%) which is used in the next step without any purification.

Preparation of Anhydrous Docetaxel

Anhydrous Docetaxel is obtained from 7, 10-Di-O-(2-chlroacetyl) Docetaxel **(5,** 80 g, 0.08 mol) using 25% ammonia (510 ml) in pyridine (2.5 L) and stirred at 0-5 °C for 2 h. 1.6 L ethyl acetate and 0.8 L water is used for extraction of the product. After extraction the organic layer is successively washed with 3 M HC1, saturated sodium bicarbonate, brine and then dried over anhydrous sodium sulfate. The organic layer is treated by activated charcoal and the organic solvent was removed under a reduced pressure. The residue is added into 1.2 L n-heptane. The resulting fine solid is filtered and then washed with 200 ml

of heptane to afford Docetaxel **1** (51.7 g, 0.06 mol, 80%) which is used in the next step without any purification.

Purification of Docetaxel

A. Preparation of 95% Pure Anhydrous Docetaxel By Fast Filtration

50 g of anhydrous Docetaxel obtained from the previous experiment was dissolved in 150 ml acetone and mixed with silica gel (100 g) and then the solvent was removed under reduced pressure to afford a cream-colored powder. Thereafter, the powder was placed on a silica gel 60 (0.063 - 0.200 mm) filter bed and the product washed down with Ethyl acetate (2 L). The filtrate is concentrated under reduced pressure to 700 ml and then added into the 6 L of n-heptane and stirred at room temperature for 3 hrs. The precipitate was filtered and washed with 150 ml of n-heptane and dried in an oven at 50°C to the constant weight to yield 40 g (80%) the anhydrous Docetaxle as a white powder with HPLC purity of> 95%.

B. Preparation of Docetaxel Trihydrate (Docetaxel.3$H_2$0)

40 g purified anhydrous Docetaxel was dissolved in 400 ml acetone and heated to 40°C. The resulting clear solution is treated with 5% activated charcoal (2 g) and stirred for half an hour and then filtered. Thereafter, water (1.2 L) was added to the filtrate and cooled to room temperature and stirred for 5 hrs and then filtered and washed with water (100 ml) and dried on a vacuum for 18 hrs to the constant weight to yield 40.54 g (95%) of the titled compound as a white powder with HPLC purity of > 99.5%.

CLAIMS

We claim:

1. A process for preparing Docetaxel 1, wherein R1 is haloacetyl chlorides comprising, and R2 is parамethoxy phenyl (PMP) or alkyl or aryl analogues thereof, R3 is tert-butoxycarbonyl or alkyl or aryl analogues thereof by:

a) Protecting the C-7 and C-10 hydroxyl group of 10-deacetylbaccatin III with haloacetyl chlorides to obtain **(2);**

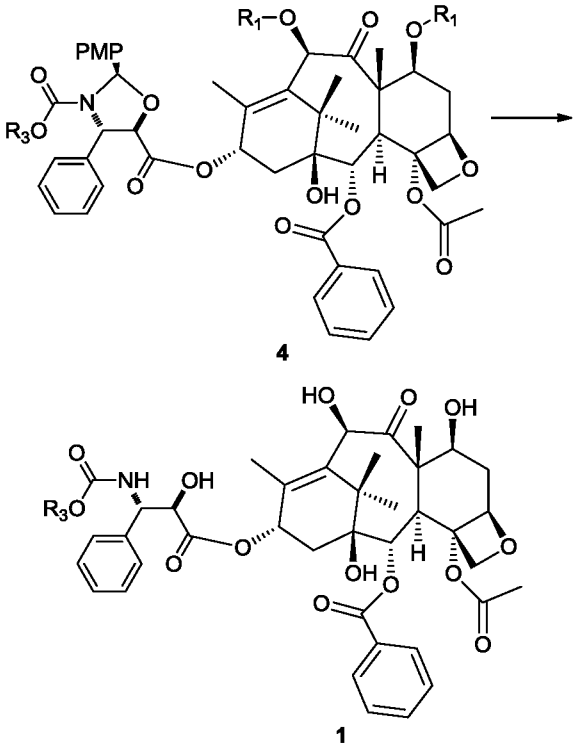
b) subjecting the protected 10-deacetylbaccatin III **(2)** to coupling with (4S,5R)-3-(tert-butoxycarbonyl)-2-(4-methoxyphenyl)-4-phenyloxazolidine-5-carboxylic acid **(3)** to obtain **(4)** ; wherein R1 is haloacetyl group or aryl analogues thereof; and R2 is paramethoxy phenyl (PMP), R3 is tert-butoxycarbonyl or aryl analogues thereof;

c) subjecting the intermediates of compound **4** to deprotection of haloacyl group in the presence of polyhaloacetic acid to obtain**(5);**

d) subjecting the intermediates of compound **5** and deprotection of paramethoxy phenyl (PMP) group in the presence of ammonia or aliphatic amine or aromatic amines or their combination both at -20 to +40° C for 6-12 h to obtain crude Docetaxel **1.**

e) Subjecting the crude Docetaxel to fast filtration over a short silica gel filter to obtain anhydrous Docetaxel of > 95% purity

f) crystallizing the anhydrous Docetaxel of step e) to pharmaceutical grade Docetaxel trihydrate by dissolving anhydrous Docetaxel in an organic solvent such as a ketone, a nitrile a halogenated solvent an ester, an alcohol an amide, a sulfoxide or a sulfone followed by the addition of water to obtain pharmaceutical grade Docetaxel trihydrate.



2. The process of claim 1, wherein the solvent used in step a) is a halogenated hydrocarbon and preferably dichloromethane or chloroform and most preferably dichloromethane.

3. The process of claim 1, wherein the reaction in step a) is carried out at temperature between 0-40° C and preferably at 0-25° C , most preferably at 25° C.

4. The process of claim 1, wherein in step a) the process is carried out in 1-10 hrs, preferably in 2- 8 hrs and most preferably in 2 hrs.

5. The process of claim 1, wherein in step a) the reaction mixture is cooled to 5-40° C, and preferably to 10-25° C , most preferably to 25° C.

6. The process of claim 1, wherein step a) the said aromatic hydrocarbon used in step a) is benzene or arylalkanes and most preferably toluene.

7. The process of claim 1, wherein step a) the reaction mixture is mixed for 5 to 25 hrs, preferably to 10-15 hrs., most preferably to 5 hrs.

8. The process of claim 1, wherein step a) the reaction precipitate is dried for 4-24 hrs preferably to 10-15 hrs., most preferably to 12 hrs.

9. The process of claim 1, wherein step a) the reaction precipitate is dried for at 30 to 60° C preferably at 40 to 50° C and most preferably at 45° C.

10. The process of claim 1, wherein the solvent used in step b) is an aromatic hydrocarbon and preferably toluene or xylenes and most preferably toluene.

11. The process of claim 1, wherein the reaction in step b) is carried out at temperature between 20-100° C and preferably at 40-80° C , most preferably at 60° C.

12. The process of claim 1, wherein in step b) the process is carried out in 2-10 hrs, preferably in 2- 8 hrs and most preferably in 5 hrs.

13. The process of claim 1, wherein in step b) the reaction mixture is cooled to 5-40° C, and preferably to 10-25° C , most preferably to 25° C.

14. The process of claim 1, wherein step b) the antisolvent used in step b) is C5-C8 alkanes and preferably is n-hexane or n-heptane and most preferably is n-heptane.

15. The process of claim 1, wherein step b) the reaction mixture is mixed for 5 to 25 hrs, preferably to 10-15 hrs., most preferably to 5 hrs.

16. The process of claim 1, wherein step b) the reaction precipitate is dried for 4-24 hrs preferably to 10-15 hrs., most preferably to 12 hrs.

17. The process of claim 1, wherein step b) the reaction precipitate is dried for at 30 to 60° C preferably at 40 to 50° C and most preferably at 45° C.

18. The process of claim 1, wherein the solvent used in step c) is an aliphatic acids such as formic acid or acetic acid and preferably acetic acid and the deprotecting group is a polyhalo acid such polyflouro or polychloro halo acids and preferably triflouroacetic acid.
19. The process of claim 1, wherein the reaction in step c) is carried out at temperature between -20-25° C and preferably at -10-20° C , most preferably at 10° C.
20. The process of claim 1, wherein step c) the process is carried out in 2-15 hrs, preferably in 5- 10 hrs and most preferably in 8 hrs.
21. The process of claim 1, wherein the solvent used for extraction in step c) is an ester or ketone and preferably is ethyl acetate.

22. The process of claim 1, wherein step c) the reaction mixture is cooled to 5-40° C, and preferably to 10-25° C , most preferably to 25° C.

23. The process of claim 1, wherein step c) the antisolvent used in step c) is C5-C8 alkanes and preferably is n-hexane or n-heptane and most preferably is n-heptane.

24. The process of claim 1, wherein step c) the reaction mixture is mixed for 5 to 25 hrs, preferably to 10-15 hrs., most preferably to 5 hrs.

25. The process of claim 1, wherein step c) the reaction precipitate is dried for 4-24 hrs preferably to 10-15 hrs., most preferably to 12 hrs.
26. The process of claim 1, wherein step c) the reaction precipitate is dried for at 30 to 60° C preferably at 40 to 50° C and most preferably at 45° C.

27. The process of claim 1, wherein the solvent used in step d) is an aliphatic or aromatic amine such as pyridine triethylamine and preferably pyridine acid and the deprotecting group is an aliphatic or aromatic amine such as ammonia, dimethylamine or trimethylamine tand preferably ammonia.
28. The process of claim 1, wherein the reaction in step d) is carried out at temperature between -20-25° C and preferably at -10-20° C , most preferably at 10° C.
29. The process of claim 1, wherein step d) the process is carried out in 2-15 hrs, preferably in 5- 10 hrs and most preferably in 8 hrs.

30. The process of claim 1, wherein the solvent used for extraction in step d) is an ester or ketone and preferably is ethyl acetate.

31. The process of claim 1, wherein step d) the reaction mixture is cooled to 5-40° C, and preferably to 10-25° C , most preferably to 25° C.

32. The process of claim 1, wherein step d) the antisolvent used in step c) is C5-C8 alkanes and preferably is n-hexane or n-heptane and most preferably is n-heptane.

33. The process of claim 1, wherein step d) the reaction mixture is mixed for 5 to 25 hrs, preferably to 10-15 hrs., most preferably to 5 hrs.

34. The process of claim 1, wherein step d) the reaction precipitate is dried for 4-24 hrs preferably to 10-15 hrs., most preferably to 12 hrs.

35. The process of claim 1, wherein step d) the reaction precipitate is dried for at 30 to 60° C preferably at 40 to 50° C and most preferably at 45° C.

36) The process of claim 1, wherein step e) wherein the solvent used for washing the column is esters, ketones or halocarbons and preferably is ethyl acetate.

37. The process of claim 1, wherein step e) the antisolvent used is C5-C8 alkanes and preferably is n-hexane or n-heptane and most preferably is n-heptane.

38. The process of claim 1, wherein step e) the reaction mixture is mixed for 5 to 25 hrs, preferably to 10-15 hrs., most preferably to 5 hrs.

39. The process of claim 1, wherein step e) the reaction precipitate is dried for 4-24 hrs preferably to 10-15 hrs., most preferably to 12 hrs.

40. The process of claim 1, wherein step e) the reaction precipitate is dried for at 30 to 60° C preferably at 40 to 50° C and most preferably at 45° C.

41. The process of claim 1, wherein step f) the solvent used is ketones, esters,nitriles or dimethylsolfoxide or dimethylamine and preferably is acetone.

42. The process of claim 1, wherein step f) the antisolvent used is water.

43. The process of claim 1, wherein step f) the solvent to antisolvent ratio is from 2:5 to 20:60 and preferably is 15: 40.

44. The process of claim 1, wherein step f) the reaction mixture is mixed for 5 to 25 hrs, preferably to 10-15 hrs., most preferably to 5 hrs.

45. The process of claim 1, wherein step f) the reaction precipitate is dried for 4-24 hrs preferably to 10-15 hrs., most preferably to 12 hrs.

46. The process of claim 1, wherein step f) the reaction precipitate is dried for at 30 to 60° C preferably at 40 to 50° C and most preferably at 45° C.

47. The process of claim 1, wherein step f) the precipitate is dried to having 5-8 percent water in it.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/059675

A. CLASSIFICATION OF SUBJECT MATTER
C07D305/00,A61K31/222 Version=2016.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US6900342 B2 (DABUR INDIA LTD [IN]) 31 MAY 2005 (31-05-2005) Abstract & Claims	1-47
Y	US6500966 B1 (COUNCIL SCIENT IND RES [IN]) 31 DECEMBER 2002 (31-12-2002) . Claims & Examples	1-47
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A	US7759494 B2 (DABUR INDIA LTD [IN]) 20 JULY 2010 (20-07-2010) . The whole document	1-47

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22-03-2016	22-03-2016
Name and mailing address of the ISA/ Indian Patent Office Plot No. 32, Sector 14,Dwarka, New Delhi-110075 Facsimile No.	Authorized officer K Janardana Telephone No. +91-1125300200

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