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(54) **Title**: PROCESS FOR PREPARATION OF 17-SUBSTITUTED STEROIDS

(57) **Abstract**: The specification relates to a process for preparation of 17-substituted steroid and intermediates useful therein. Embodiments of 17-substituted steroid have been shown as useful for treatment of androgen-dependent disorders, especially prostatic cancer, and also oestrogen-dependent5 disorders such as breast cancer.

PROCESS FOR PREPARATION OF 17-SUBSTITUTED STEROIDS

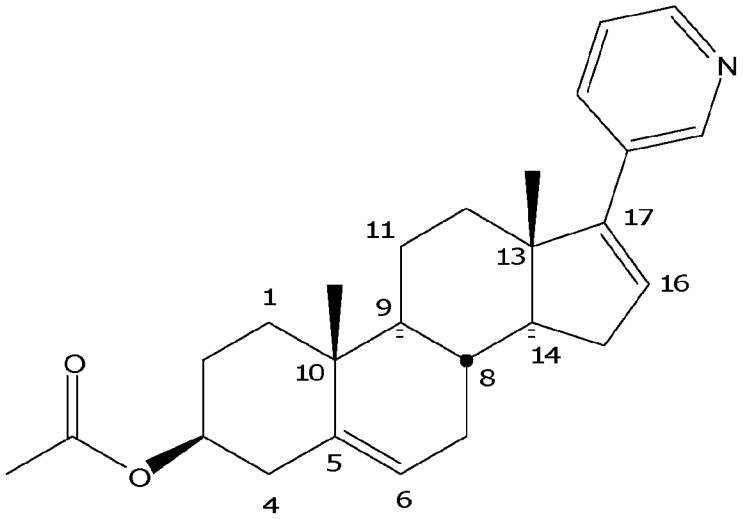
This application claims priority to and the benefit of United States Provisional Patent Application Serial Number 61/637,048 filed April 23, 2012, and Provisional Patent Application No. 61/642,253 filed May 3, 2012, the subject matter of which is incorporated herein by reference.

FIELD

[0001] The specification relates to a process for preparation of 17-substitued steroids, and intermediates useful therein.

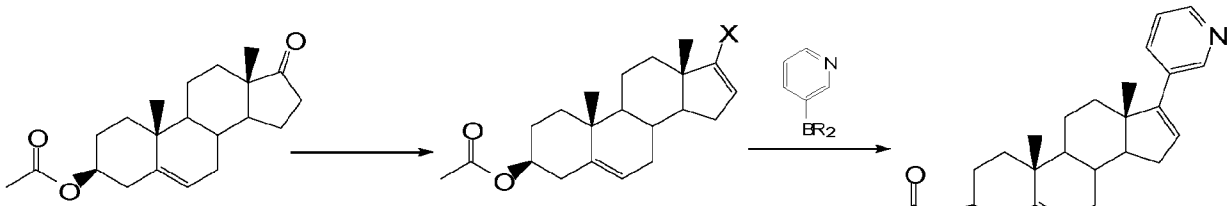
BACKGROUND

[0002] Abiraterone acetate has been disclosed as an androgen biosynthesis inhibitor, and was approved and launched in the U.S. in 2011 in combination with prednisone for the oral treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel (US 5,604,213; FDA News Release 28 Apr, 2011, (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm253055.htm, incorporated herein by reference)). Abiraterone acetate has been commercially marketed as Zytiga™. The structure of abiraterone acetate along with numbering of the carbon atoms is shown below.



Abiraterone acetate

[0003] The published routes (US Patent Nos 5,604,213 and 5,618,807, incorporated herein by reference) toward abiraterone acetate start with dehydroepiandrosterone (DHEA) and involve manipulation of the cyclopentanone moiety to install the pyridyl group. The preferred method appears to be a Suzuki-type cross coupling reaction involving a pyridylborane and an appropriately substituted steroid, as shown below.



X = OTf or I

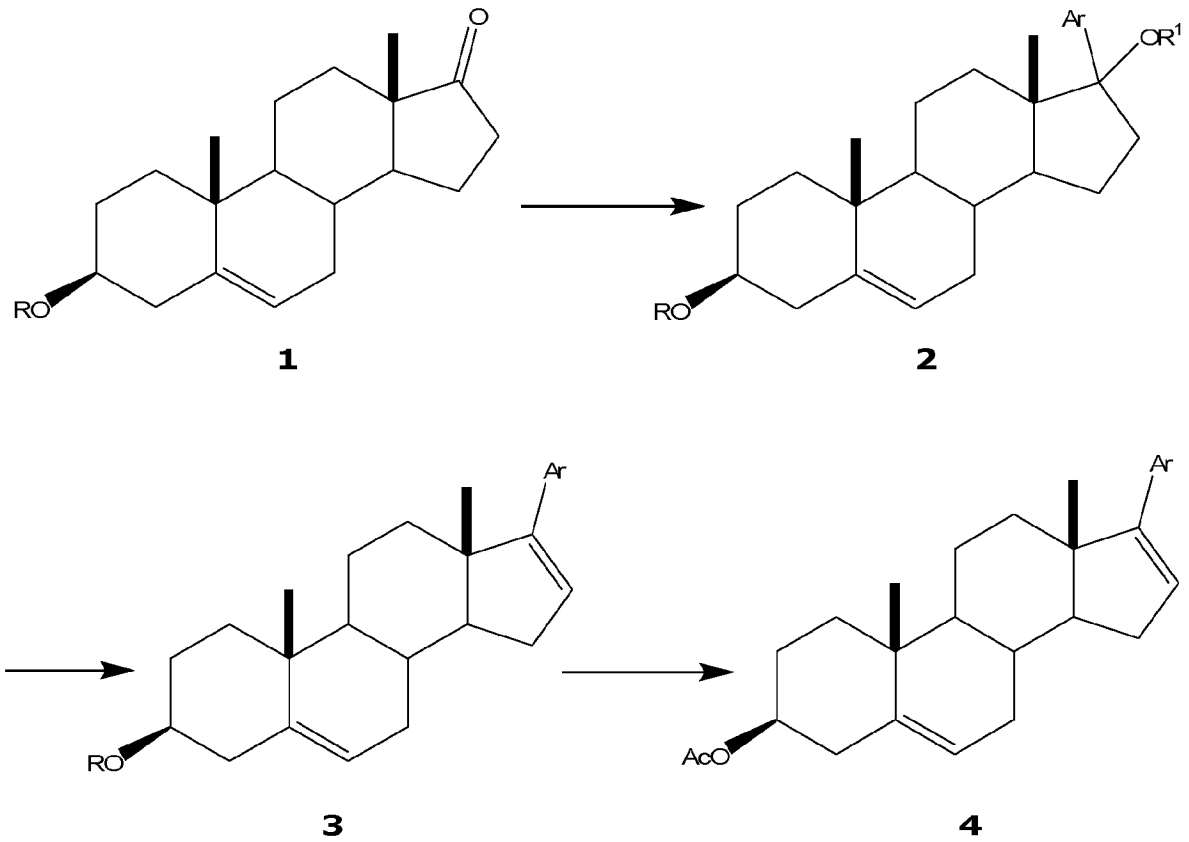
[0004] The known synthetic route can have certain drawbacks, such as the use of expensive reagents (triflate). In addition, the synthetic route can lead to an elimination side product, forming a double bond between the C3 and C4 position. Further, the coupling reaction with pyridylborane utilizes a palladium (Pd) catalyst and boranes at the final synthetic step, which need to be removed from the active

pharmaceutical ingredient (API), and can require column chromatographic purification. Moreover, US Patent No. 5,618,807 discloses in Example 20 that the coupling reaction leads to an impurity (16,17'-bis(steroidal) contaminant) in significant amounts (6.8% w/w), which crystallization was unsuccessful in removing. Further to the above, the compounds prepared in the process for preparation of abiraterone acetate can require column chromatography, which usually is undesirable, especially for manufacturing at industrial scale.

[0005] Hence, there is a need in the art for a process for preparation of abiraterone acetate that can avoid the use of expensive reagents, the elimination reaction, the formation of additional impurities or formation of the bis(steroidal) contaminant. In addition, there is a need in the art for a process for preparation of abiraterone acetate that can avoid or reduce the use of column chromatography. Further, there is a need in the art for a process for preparation of abiraterone acetate, where any one of the intermediates or final product prepared is in high purity and can be purified by crystallization. Moreover, there is a need in the art for an alternate route to synthesis of 17-substituted steroids, which is suitable for large scale production.

SUMMARY OF INVENTION

[0006] In one aspect, the specification discloses a process for preparation of the compound of formula **4**, the process containing the steps of:



- nucleophillic addition reaction of the compound of formula **1** with a compound of formula Ar–M to form the compound of formula **2**;

- dehydrating the compound of formula **2** to form the compound of formula **3** or **4**;

- optionally, deprotecting the compound of formula **3**; and

- optionally, acylating the compound of formula **3** to form the compound of formula **4**,

wherein

R is H or an alcohol protecting group;

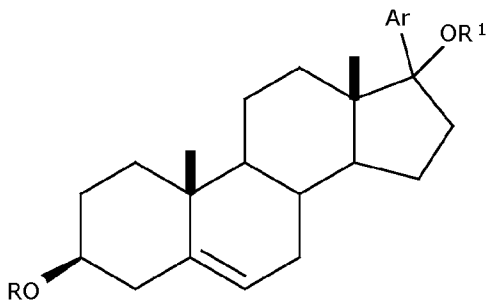
R^1 is H, an alcohol protecting group or R^1 together with the oxygen to which it is attached forms a leaving group;

M is alkali metal, alkali earth metal or a transition metal of group 11 or 12;

Ar is an aryl or heteroaryl group and

Ac is an acyl group.

[0007] In another aspect, the specification relates to the compound of formula **2**,



2

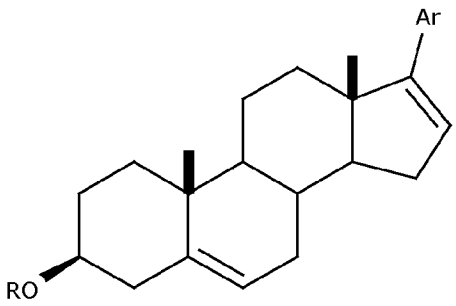
wherein

Ar is an aryl or heteroaryl group;

R is H or an alcohol protecting group; and

R^1 is H, an alcohol protecting group or R^1 together with the oxygen to which it is attached forms a leaving group.

[0008] In a further aspect, the specification relates to the compound of formula **3**,



3

wherein

Ar is an aryl or heteroaryl group; and

R is a silyl-based protecting group.

[0009] In a still further aspect, the specification relates to abiraterone acetate having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC.

[0010] In still another aspect, the specification relates to abiraterone acetate substantially free of the bis(steroidal) contaminant as determined by HPLC analysis.

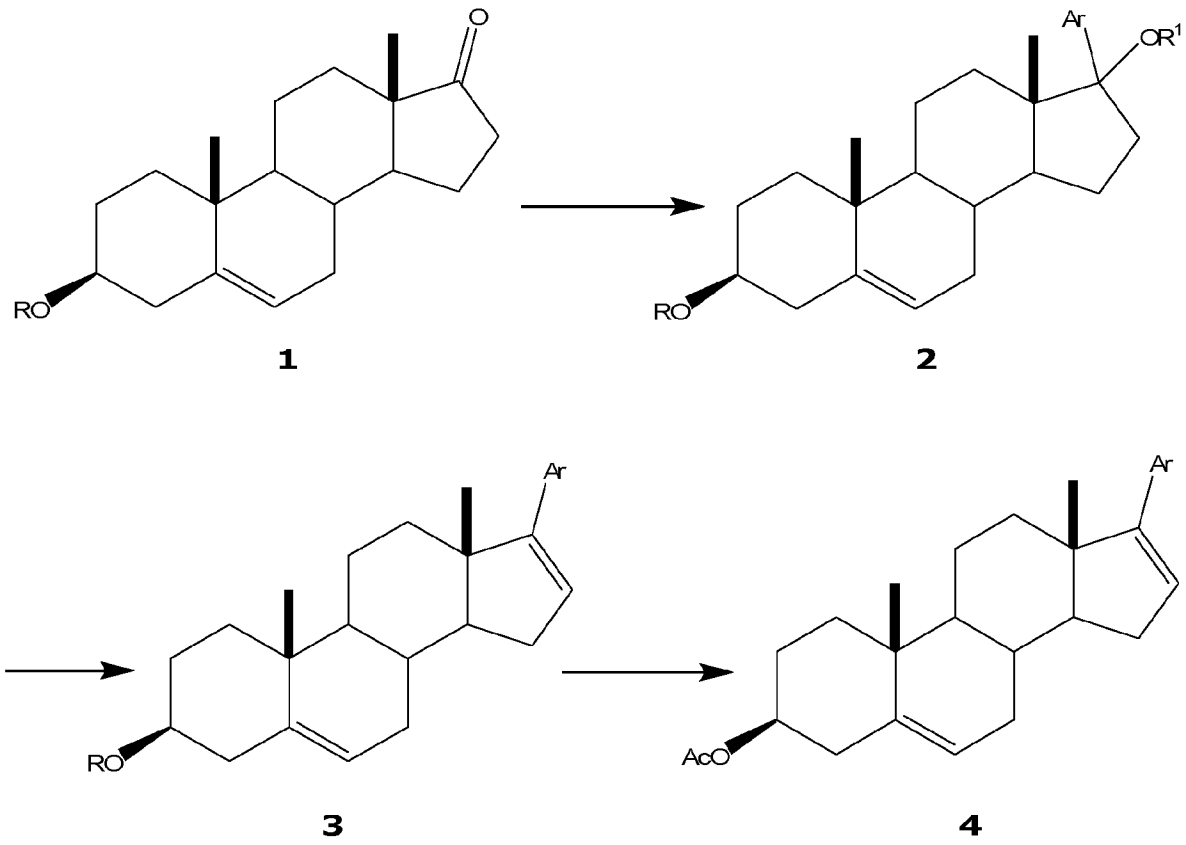
[0011] In still another aspect, the specification relates to the compound of formula **3** having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC.

[0012] In another further aspect, the specification relates to the compound of formula **2** having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC.

[0013] In another still further aspect, the specification relates to a process for purification of the compound of formula **3** or **4**, as disclosed herein, by recrystallization of the compound of formula **3** or **4**.

DESCRIPTION

[0014] A process for preparation of the compound of formula **4**, the process containing the steps of:



- nucleophillic addition reaction of the compound of formula **1** with a compound of formula Ar–M to form the compound of formula **2**;

- dehydrating the compound of formula **2** to form the compound of formula **3** or **4**;

- optionally, deprotecting the compound of formula **3**; and

- optionally, acylating the compound of formula **3** to form the compound of formula **4**,

wherein

R is H or an alcohol protecting group;

R^1 is H, an alcohol protecting group or R^1 together with the oxygen to which it is attached forms a leaving group;

M is alkali metal, alkali earth metal or a transition metal of group 11 or 12;

Ar is an aryl or heteroaryl group and

Ac is an acyl group.

[0015] The term "alcohol protecting group" as used herein is not particularly limited, and should be known to a skilled worker or can be determined. In one embodiment, for example and without limitation, the protecting group forms an ester, ether or is a silyl-based protecting group. In a further, embodiment for example and without limitation, the ester formed is acetyl (Ac), benzoyl (Bz) or pivaloyl (Piv). In another embodiment, for example and without limitation, the ether protecting group formed is benzyl (Bn), β-methoxyethoxymethyl ether (MEM), trityl (Tr), dimethoxy trityl (DMT), methoxymethyl ether (MOM), or the like. In a still further embodiment, for example and without limitation, the silyl-based protecting group formed is tert-butyldimethylsilyl (TBDMS or TBS), tri-iso-propylsilyloxymethyl (TOM), or triisopropylsilyl (TIPS).

[0016] A "leaving group" as disclosed herein is a molecular fragment or stable species that can be detached from a molecule in a bond-breaking step. The

process can also involve, for example and without limitation, a bond-breaking step between the leaving group and molecule, along with formation of a double bond in the molecule. The leaving group, in accordance with the specification, is not particularly limited and should be known to a person of skill in the art or can be determined. The ability of a leaving group to depart is correlated with the pK_a of the conjugate acid, with lower pK_a being associated with better leaving group ability. Examples of a leaving group include, without limitation, an acyl ester or a sulfonate. Examples of sulfonates can include, without limitation, nonaflate, triflate, fluorosulfonate, tosylate, mesylate or besylate. In one embodiment, for example and without limitation, the leaving group is mesylate or tosylate.

[0017] The term "alkali metal" as used herein is not particularly limited, and should be known to a person of skill in the art. Alkali metals contain the group 1 elements of the periodic table, excluding hydrogen, and include lithium (Li), sodium (Na), potassium (K), rubidium (Rb) and caesium (Cs). In one embodiment, for example and without limitation, the alkali metals used in accordance with the specification include lithium (Li), sodium (Na) or potassium (K). In a further embodiment, for example and without limitation, the alkali metal used in accordance with the specification includes lithium (Li).

[0018] The term "alkali earth metal" as used herein is not particularly limited, and should be known to a person of skill in the art. Alkali earth metals contain group 2 elements of the periodic table, and can include, for example, beryllium (Be), magnesium (Mg), calcium (Ca), Strontium (Sr), Barium (Ba). In one embodiment, for example and without limitation, the alkali earth metal used in accordance with the specification is magnesium (Mg).

[0019] The term "transition metals of group 11 or 12" should be understood by a skilled worker, and includes transition metals of group 11 or 12 of the periodic table. The transition metals of group 11 can include copper (Cu) and silver (Ag),

while the transition metals of group 12 can include zinc (Zn), cadmium (Cd) and mercury (Hg).

[0020] The term "aryl" as used herein is not particularly limited, and should be known to a person of skill in the art. The term "aryl" as used herein refers to any functional group or substituent derived from an aromatic carbocyclic ring. In one embodiment, for example and without limitation, the aryl group is a C_{6-14} aryl. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Examples of aryl include, for example and without limitation, phenyl, naphthyl, anthracenyl, and phenanthrenyl.

[0021] The term "heteroaryl" as used herein is not particularly limited, and should be known to a person of skill in the art. The term "heteroaryl" as used herein refers to any functional group or substituent derived from an aromatic ring where one or more of the atoms in the aromatic ring is of an element other than carbon. In another embodiment, for example and without limitation, heteroaryl includes 5-, 6-, and 7-membered substituted or unsubstituted single-ring aromatic groups that can have one or more heteroatoms as part of the ring system. Examples of heteroaryls include, for example and without limitation, pyridinyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, or thiophenyl. In a further embodiment in accordance with the specification, the heteroaryl group is a pyridinyl.

[0022] The term "acyl group" as used herein is not particularly limited and should be known to a skilled worker. In one embodiment, for example and without limitation, the acyl group refers to the general formula "RC(=O)−" , where R is a hydrocarbon; and can also include the acyl protecting groups noted herein. In a further embodiment in accordance with the specification, the acyl group is, for example and without limitation, acetyl (Ac), benzoyl (Bz) or pivaloyl (Piv). In a still

further embodiment in accordance with the specification, the acyl group is, for example and without limitation, acetyl (Ac).

[0023] The term "hydrocarbon", as used herein, refers to a group that contains hydrogen and carbon, linked generally via a carbon backbone, but can optionally include heteroatoms. Hydrocarbyl groups include, but are not limited to alkyl, aryl, heteroaryl, carbocycle, heterocycle, alkyl, alkenyl, alkynyl, and combinations thereof. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this specification.

[0024] The term "heteroatom", is not particularly limited and should be understood by a skilled worker. As used herein, the term means an atom of any element other than carbon or hydrogen. In one embodiment, for the example and without limitation, heteroatoms include nitrogen, oxygen, and sulfur.

[0025] The term "alkyl" as used herein is not particularly limited and should be known to a person of skill in the art; and refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. In one embodiment, for example and without limitation, the alkyl group is a C_{1-6} alkyl.

[0026] The term "C_{1-6} alkyl" in accordance with the specification is not particularly limited and should be known to a person of skill in the art. The C_{1-6} alkyl may be, for example, and without limitation, any straight or branched alkyl, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, i-pentyl, sec-pentyl, t-pentyl, n-hexyl, i-hexyl, 1,2-dimethylpropyl, 2-methylbutyl, 1,2-dimethylbutyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 2-ethylbutyl, 1,3-dimethylbutyl, 2-methylpentyl or 3-methylpentyl.

[0027] The term "nucleophilic addition reaction" as used herein is not particularly limited and should be known to a skilled worker. Nucleophilic addition reaction can be considered an addition reaction where in a chemical compound a π-bond is removed by creation of two new σ-bonds by the addition of a nucleophile. The term "nucleophile" as used herein is not particularly limited and should be known to a skilled worker. Nucleophile can be considered as a species that donate an electron-pair to an electrophile to form a chemical bond in a reaction. All molecules or ions with a free pair of electrons or at least one pi bond can act as nucleophiles. The term "electrophile" is also not particularly limited and should be known to a skilled worker. An electrophile (literally electron-lover) can be considered as a reagent attracted to electrons that participates in a chemical reaction by accepting an electron pair in order to bond to a nucleophile.

[0028] In the process as disclosed herein, "Ar" in the compound Ar–M can act as the nucleophile, while carbonyl carbon can act as the electrophile. Without being particularly limited, various embodiments of the compound Ar–M can be used so long as the nucleophilic addition of Ar to the carbonyl carbon can take place. In one embodiment, the term Ar–M can include, for example and without limitation, 3-pyridinyl lithium, phenyl magnesium bromide or 3-pyridinyl magnesium bromide. In a further embodiment, for example and without limitation, the term Ar–M can include 3-pyridinyl lithium.

[0029] The term "dehydrating a compound", as used herein is not particularly limited and should be known to a skilled worker. A dehydration reaction can be considered as an elimination reaction that involves the loss of water, or analogue, from the reacting molecule, and which can lead to formation of an additional bond. The method of performing the dehydration reaction is not particularly limited. In one embodiment, for example and without limitation, the dehydration reaction is carried out using an acid or a base.

[0030] The term "acid" as used herein is not particularly limited and should be known to a skilled worker. An acid can be considered as a substance that can act as a proton donor (Brønsted-Lowry acid) or an electron pair acceptor (Lewis acid). In one embodiment, the acid used in the process disclosed herein is, for example and without limitation, hydrochloric acid (HCl), hydrobromic acid (HBr), acetic acid (CH_3CO_2H), sulfuric acid (H_2SO_4) or *p*-toluenesulfonic acid (*p*-TSA).

[0031] The term "base" as used herein is not particularly limited and should be known to a skilled worker. A base can be considered as a substance that can accept hydrogen ions (protons) or donate an electron pair. In one embodiment, the base used in the process disclosed herein is, for example and without limitation, triethylamine (TEA), N,N-diisopropylethylamine, (DIPEA), 1,8-diazabicycloundec-7-ene (DBU), sodium *tert*-butoxide (*t*-BuONa), potassium *tert*-butoxide (*t*-BuOK), lithium diisopropylamide (LDA), sodium bis(trimethylsilyl)amide (NaHMDS), potassium bis(trimethylsilyl)amide (KHMDS) or lithium tetramethylpiperidide (LiTMP). In a further embodiment, for example and without limitation, the base used in the process disclosed herein is triethylamine (TEA).

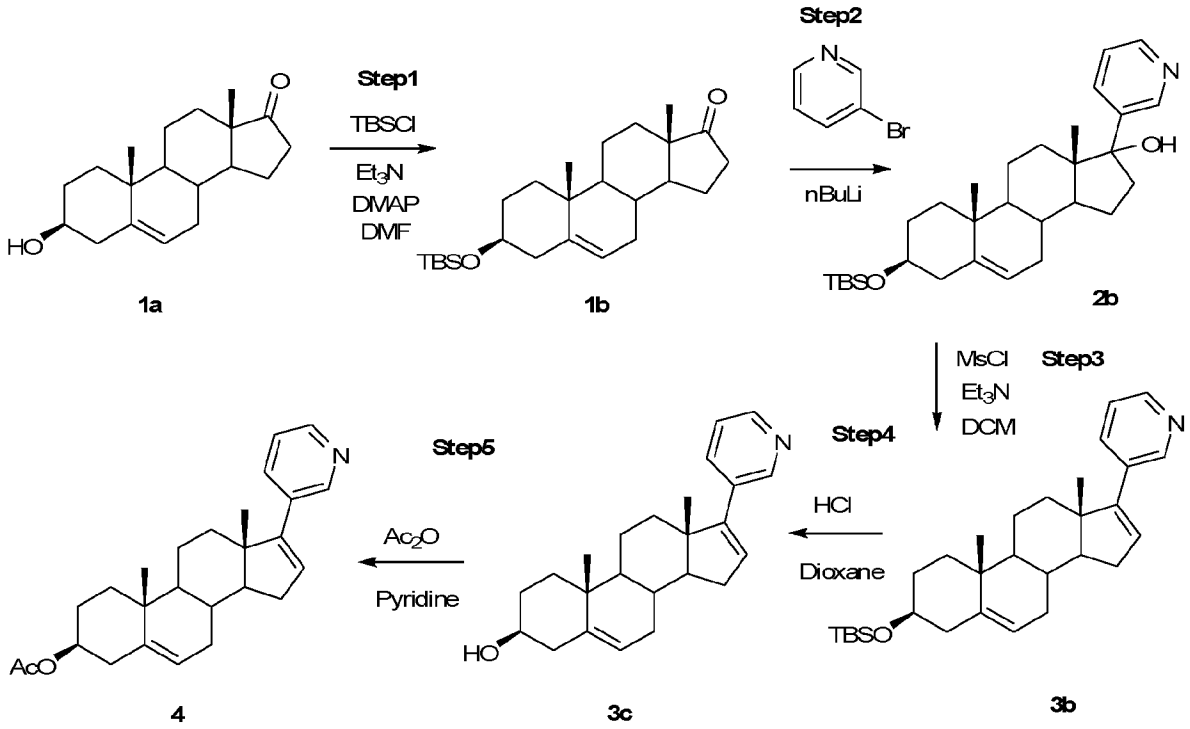
[0032] The step of deprotecting the compound of formula **3** as disclosed herein can be optional depending upon the substituents present. Further, the step of deprotection is not particularly limited and should be known to a skilled worker or can be determined. The method of carrying out the deprotection step can depend upon the substituent. In one embodiment, for example and without limitation, deprotection is carried out using an acid. The acid used for deprotection is not particularly limited and should be known to a skilled worker or can be determined. Examples of an acid include acids as are described herein.

[0033] In another embodiment, the step of deprotection is carried out, for example and without limitation, using a fluoride source. The fluoride source is not particularly limited and should be known to a skilled worker or can be determined. In one embodiment, for example and without limitation, the fluoride source is

sodium fluoride (NaF), tetra-butyl ammonium fluoride or pyridine hydrofluoride (HF-Py). The step of deprotection using a fluoride source can be carried out, for example, when the protecting group is a silyl-based protecting group, as described herein.

[0034] The step of acylating the compound of formula **3** as disclosed herein can be optional depending upon the substituent present. As used herein, acylation can be considered as the process of adding an acyl group to a compound. Further, the step of acylation is not particularly limited and should be known to a skilled worker or can be determined. In one embodiment, for example and without limitation, the step of acylation involves acetylating the compound of formula **3**, where R is H. The process of acetylation is not particularly limited and should be known to a skilled worker or can be determined. In one embodiment, for example and without limitation, the step of acetylation is carried out using acetic anhydride (Ac_2O) or acetyl chloride (AcCl), in the presence of base. The base used is not particularly limited and can include one of the bases as noted herein.

[0035] Referring to Scheme 1 shown below, an embodiment of the process as disclosed herein is further described.



Scheme 1

[0036] Step 1 involves protecting the hydroxyl group of compound of formula **1a** to form the compound of formula **1b**. The protecting group used is a silyl-based protecting group, and is tert-butyldimethylsilyl (TBS), although other protecting groups, including other silyl-based protecting groups can be used. The use of the silyl-based protecting group, such as the tert-butyldimethylsilyl (TBS), can avoid generation of or reduce the amount of the impurity having a double bond at the C3–C4 position. As noted above, the impurity having a double bond between the C3–C4 position can be formed in an elimination reaction, for example in the presence of a base, where, for example, an acetate (leaving group) at the C3 position is removed and a double bond formed. Upon completion of the reaction, the reaction mixture can be quenched using water, which can allow precipitation of the solid product that can be separated by filtration.

[0037] Nucleophilic addition reaction of the compound of formula **1b** with pyridinyl lithium in step 2, leads to formation of the compound of formula **2b**. Other pyridinyl-metal complexes can be used for nucleophilic addition. These include, for example and without limitation, pyridinyl-magnesium, pyridinyl-cuprate or pyridinyl-zinc reagent. The use of pyridinyl lithium can help avoid use of more toxic metals and can provide cleaner and safer reaction conditions.

[0038] The reaction conditions, such as, for example and without limitation, solvent, temperature and ratio of reagents, for the nucleophilic reaction can vary. The solvent used in the nucleophilic reaction in Step 2 of Scheme 1, can include, for example, toluene, tetrahydrofuran (THF), dimethyl ether (DME) or diethyl ether. In one embodiment, the solvent used in Step 2, as shown in Scheme 1, is toluene.

[0039] The temperature for carrying out the nucleophilic coupling reaction can also vary. Temperatures for the nucleophilic coupling reaction can range from low temperatures, such as, for example and without limitation, -80°C to higher temperatures, such as, for example and without limitation, 50°C. In one embodiment, the temperature for carrying out the nucleophilic addition reaction, as shown in Step 2 of Scheme 1, is from -80°C to 25°C, and values in between. In another embodiment, the temperature can range from -80°C to 0°C, -75°C to -10°C, -70°C to -20°C, -70°C to -40°C or -70°C to -60°C.

[0040] Upon completion, the reaction can be quenched using an aqueous solution, which can include, for example and without limitation, brine. Extraction and evaporation of the organic layer can provide crude compound **2b**. Crude compound **2b** can be triturated with an organic solvent to provide compound **2b** that can be used in subsequent process steps without further purification. The solvent used for trituration can vary. In one embodiment, in the process step 2 as shown in Scheme 1 above, trituration was performed using acetonitrile.

[0041] The hydroxyl group formed in step 2 can be converted into a leaving group in step 3, by reaction with mesyl chloride to form a mesylate, which can then undergo a dehydration reaction in the presence of a base to form compound **3b**. The leaving group formed can vary and different leaving groups can be used for the elimination reaction to form the double bond. In one embodiment, the hydroxyl group is converted into a sulfonate-based leaving group, which can include, for example and without limitation, nonaflate, triflate, fluorosulfonate, tosylate, mesylate or besylate, as noted above. In another embodiment, as shown in Scheme 2 below, dehydration of the alcohol is performed in the presence of an acid, where H_2O forms the leaving group. The sulfonate-based leaving groups can form good leaving groups and can help in improving the overall elimination reaction to form the double bond. In a further embodiment, the sulfonate-based leaving group is a mesylate.

[0042] The reaction conditions, such as, for example and without limitation, solvent, temperature and ratio of reagents, for the dehydration reaction can vary. The solvent used in the nucleophilic reaction in Step 3 of Scheme 1, can include, for example, dichloromethane (DCM), toluene, tetrahydrofuran (THF), dimethyl ether (DME) or diethyl ether. In one embodiment, the solvent used in Step 3, as shown in Scheme 1, is dichloromethane (DCM).

[0043] The temperature for carrying out the dehydration reaction can also vary. Temperatures for the dehydration reaction can range from temperatures as low as, for example and without limitation, -40°C to higher temperatures, such as, for example and without limitation, 200°C, and can depend upon the leaving group. In one embodiment, the temperature for carrying out the dehydration reaction, as shown in Step 3 of Scheme 1, is from -40°C to 50°C, and values in between. In another embodiment, the temperature can range from -20°C to 40°C, -15°C to 30°C, -10°C to 25°C, 0°C to 25°C or 5°C to 25°C. In the embodiment shown in step 3 of Scheme 1, the reaction is initially performed at about 5°C and then allowed to continue at about 25°C.

[0044] Deprotection of compound **3b** using an acid leads to compound **3c** (Step 4). Step 5 involves acylation of the compound **3c** using acetic anhydride to form compound **4**. The reaction mixture can be quenched with an aqueous solution, for example water, to precipitate compound **4**, which can be separated by filtration. Following the process as outlined in Scheme 1, compound **4** having purities of about 95% or greater can be achieved. Moreover, the process can avoid formation of the bis(steroidal) impurity that can be difficult to separate by purification.

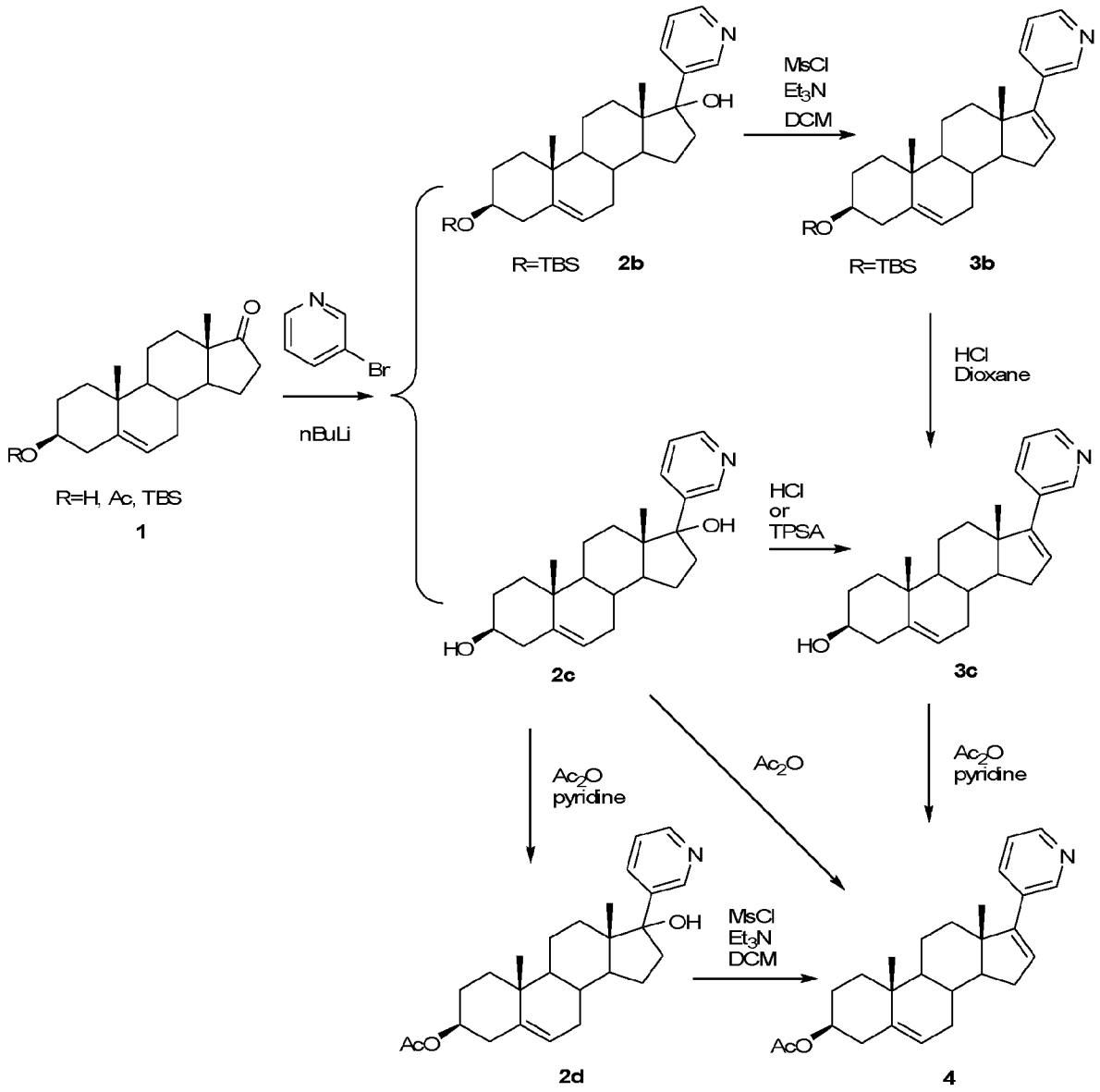
[0045] Further to the above, methods of crystallization of compound **4** have been determined that can assist with purification and avoid use of column chromatography. Different solvent and solvent mixtures have been tested. In one embodiment, for example, the solvent system used for recrystallization is methanol, ethanol, isopropanol, isopropanol/water, toluene/heptanes or acetonitrile/water. In a further embodiment, different ratios of the solvent system have been determined for recrstallization. For example, methanol or ethanol was used for recrystallization from about 3 to 10 parts v/w and values in between like about 4 to 6 parts v/w or about 5 parts v/w. For solvent mixture systems, the ratio of the solvents can vary. For example, toluene/heptanes mixtures of about 0.5/3 v/v or about 1/2 v/v parts can be used; and for acetonitrile/water, mixtures of about 8/1 v/v, about 7/1, about 6/1 or about 5/1 parts can be used. In a further embodiment, the compound of formula **4** can be recrystallized using ethanol (5 v/w part) to provide a product having 98% purity or more, as disclosed herein, and lacking any bis(steroidal) contaminant. Further optimization using solvent and scale can improve purity.

[0046] The term "recrystallization" as used herein is not particularly limited and should be known to a skilled worker. The term "recrystallization" as used herein refers to a technique used to purify chemical compounds. The process can be carried out by dissolving both impurities and a compound in an appropriate solvent, either the desired compound or impurities can be coaxed out of solution,

leaving the other behind. In the process disclosed herein, the compound of formula **3** or **4**, along with impurities, is dissolved in the relevant solvent. Dissolution can take place at elevated temperatures, including at the boiling point of the solvent used. This solvent is allowed to cool and crystallization of the compound of formula **3** or **4** to take place, followed by collection of the crystals.

[0047] Scheme 2, shown below, discloses alternate embodiments of carrying out the process for preparation of the compound of formula **4** in accordance with the specification, and where different R groups can be present and the reaction can be carried out in the presence or absence of a protecting group.

[0048] Scheme 2 also discloses alternative methods for carrying out the elimination reaction. For example, compound of formula **2c** can be converted to the compound of formula **3c** by use of an acid. The acid used in not particularly limited, and can include, for example and without limitation, hydrochloric acid, *para*-toluenesulfonic acid (PTSA) or acetic acid (AcOH). In a further embodiment, the acetylation and elimination reaction can be carried out concurrently by reaction of the compound of formula **2c** with acetic anhydride to form compound of formula **4**.

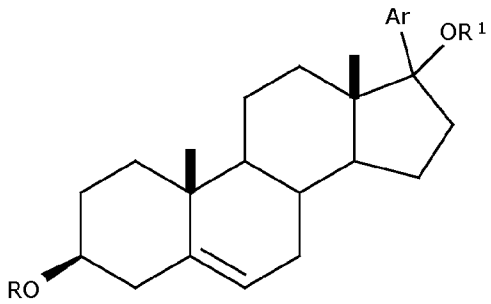


Scheme 2

[0049] The organic solvent used in the reactions described herein is not particularly limited and should be known to a person of skill in the art or can be determined. The particular solvent used would depend upon the reactants and the reaction being carried out, to allow the reaction to proceed. Similarly, the reaction temperature used in the process steps disclosed herein is not particularly limited

and should be known to a skilled worker or can be determined. The reaction temperature can depend upon a number of factors including reagents, solvent and presence of catalyst.

[0050] The process as disclosed herein can lead to different intermediates that can be useful for the preparation of the compound of formula **4**. Therefore, in another aspect the specification discloses compounds of formula **2**, where Ar is an aryl group, R is H or an alcohol protecting group and R^1 is H, an alcohol protecting group or R^1 together with the oxygen to which it is attached forms a leaving group.



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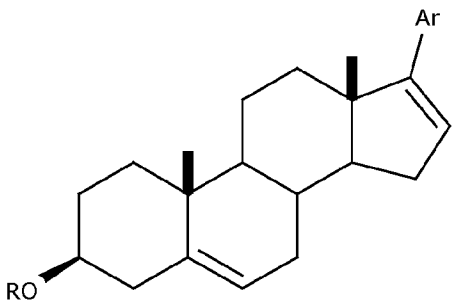
[0051] In a further aspect, the specification relates to the compound of formula **3**, where Ar is an aryl group; and R is a silyl-based protecting group.



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[0052] In a still further aspect, the specification relates to abiraterone acetate having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC. Further, the specification discloses abiraterone acetate being substantially free of the bis(steroidal) contaminant.

[0053] In still another aspect, the specification relates to the compound of formula **3** having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC.

[0054] In another further aspect, the specification relates to compound of formula **2** having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC.

EXAMPLE EMBODIMENTS

[0055] Disclosed herein below are example embodiments of the specification, which are not intended to be limiting of the invention as described and claimed herein.

[0056] **EXAMPLE 1: Compound 1b**

[0057] A 250 ml three necks round bottom flask equipped with a magnetic stirrer, thermometer and nitrogen inlet was charged with compound **1a** (60g 208mmole), dimethylformamide (DMF) (600ml), tert-butyldimethylsilyl chloride (TBSCl) (38g 250mmol), N,N-dimethylamino pyridine (DMAP) (5g 42mmole) and triethylamine (Et_3N) (32g, 312mmol). The suspension is stirred 24 hr. TLC analysis indicated the depletion of compound **1a** (Hep: EtOAc 1:1 AMCS). The reaction mixture is poured in water (3L) and agitated for 1.5hr. The solid product is collected by filtration and washed with water (2L) and dried at high vacuum at 45°C for 24 hour to give 83g of compound **1b** off white solid (Quantitative yield). NMR confirmed structure.

[0058] **EXAMPLE 2: Compound 2b**

[0059] A 500 ml three neck round bottom flask equipped with a magnetic stirrer, thermometer and nitrogen inlet was charged with 3-bromopyridine (19.6g 124mmol) and toluene (100 ml). The solution was cooled to -65°C. With agitation, 2.5M n-butyl lithium (nBuLi) in hexanes (5oml, 124mmol) was charged while maintaining a temperature of reaction less than -60°C. The mixture was then agitated at same temperature for 1.5 hours. Charged with a solution of compound **1b** (5g, 12.4mmol) in toluene (100 ml). The brown reaction mixture was agitated at for -65°C 1 hour. TLC analysis indicated formation of compound **2b** (Hep:EtOAc 1:1 UV, AMCS) The mixture was quenched with the mixture of 12% of NaCl solution (200ml). The reaction mixture was warm to10°C. The mixture was extracted with 200ml of methy tert-butyl ether (MTBE). Organic layer was separated and concentrated to dryness. The crude was triturated with acetonitrile (100ml). Solid product was collected by filtration and washed with acetonitrile (40ml) and dried at high vacuum oven at 45°C for 16 hours to give compound **2b** as an off white solid 4.7g (79% yield). NMR and MS confirmed structure.

[0060] **EXAMPLE 3: Compound 3b**

[0061] A 250 ml three neck round bottom flask with a magnetic stirrer and nitrogen inlet was charged with compound **2b** (4.5g, 9.3 mmol) and dichloromethane (DCM) (90 ml). The solution was cooled to 5°C. With agitation, triethylamine (Et_3N) (9.5g 93mmol) and mesyl chloride (MsCl) (5.4g 47mmol) was charged. The mixture was then agitated at same temperature for 1 hour and ambient temperature for 1 hour. TLC analysis indicated the depletion of compound **2b** (EtOAc UV and AMCS). The reaction solution was quenched with sat $NaHCO_3$. Separated organic is dried with $MgSO_4$ and separated and concentrated to dryness. The crude was purified with silica gel (100g) with Biotage. Eluted with ethyl acetate (EtOAc) and Heptane 10% to 50%. Pure fraction was collected and concentrated to

dryness to give compound **3b** as a white solid 3g (69% yield). NMR and MS confirmed structure.

[0062] **EXAMPLE 4: Compound 3c**

[0063] A 100 ml one neck round bottom flask with a magnetic stirrer was charged with compound **3b** (2.5g, 5.4 mmol), 1,4-dioxane (25 ml), methanol (MeOH) (12.5ml) and HCl 4M in 1,4-dioxane (5.4 ml 22mmol). The suspension was agitated for 0.5 hour at ambient temperature. The reaction mixture was turn to solution. Continue agitating for 1 hour the solution was turn to suspension. The mixture was then agitated for another 3 hours. TLC analysis indicated the depletion of compound **3b** (Hep:EtOAc 1:1 UV and AMCS). The solution concentrated to dryness. The crude was triturated with 1,4-dioxane(25ml) for 1hour. The solid product was collected by filtration and washed with 1,4-dioxane (10ml) and dried at high vacuum oven at 45°C for 16 hours to give compound **3c** as a white solid 2.1g (quantitative yield). NMR and MS confirmed structure.

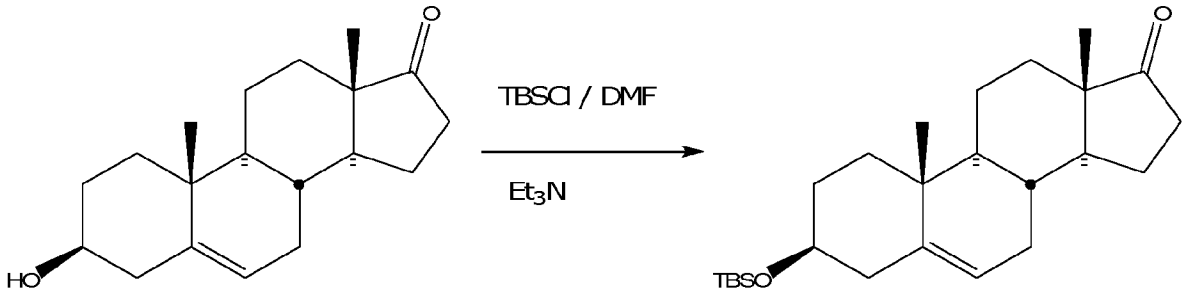
[0064] **EXAMPLE 5: Compound 4**

[0065] A 100 ml one neck round bottom flask with a magnetic stirrer was charged with compound **3c** (2.0g, 5.7 mmol), pyridine (20ml) and acetyl anhydride (2.7 ml 29mmol). The suspension was agitated for 0.5 hour at ambient temperature. The reaction mixture was turn to solution. The reaction solution was then agitated for another 1.5 hours. TLC analysis indicated the depletion of compound **3c** (EtOAc UV and AMCS). The reaction solution was quenched with water (40ml) at ice bath. The temperature was remained under 15°C. After quench, the white solid product was precipitated out. The mixture was agitated at ice bath for 2 hours. The solid product was collected by filtration and washed with water (20ml) and dried at high vacuum oven at 45°C for 72 hours to give compound **4** a white solid 1.9g (85% yield, 95% purity by HPLC). NMR and MS confirmed structure.

[0066] **EXAMPLE 6: Purification of Compound 4 by crystallization**

[0067] Charge a round bottom flask with 1.0 g of compound **4** and 5 to 10 mL of ethanol. With agitation, heat the mixture to reflux until clear solution is attained. Cool the solution gradually to 0°–25°C. Collect crystallized product by filtration, dry under nitrogen flow until constant weight is achieved. HPLC analysis indicates purity of 98%.

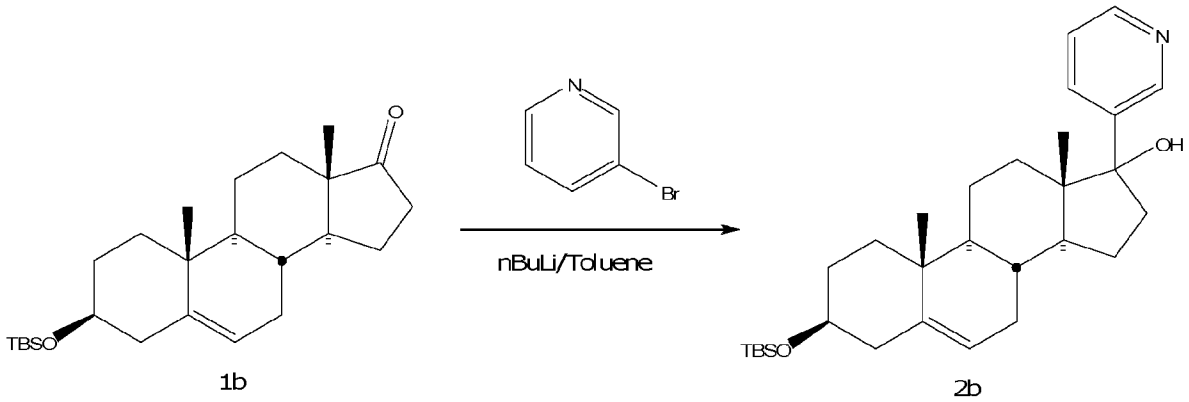
[0068] **EXAMPLE 7: Preparation of compound 1b**



1a 1b

[0069] A 1L three necks round bottom flask equipped with a over head stirrer, thermometer and nitrogen inlet was charged with compound **1a** (50g, 173mmole), *tert*-butyl dimethyl silyl chloride (TBSCl) (31.4g 208mmol), dimethylformamide (DMF) (375ml) and triethylamine (Et_3N) (26g, 260mmol). The suspension is heated up to 50°C, stirred 3 hr. HPLC analysis indicated the depletion of compound **1a**. The reaction mixture was cooled to 5°C and quenched the reaction mixture with water (375 ml). The temperature of the mixture was raised to 15°C and then agitated at ambient temperature for 2hr. The solid product is collected by filtration and washed with water (750ml) and dried at high vacuum at 45°C for 24 hour to give 69g of compound **1b** off white solid (99% yield). NMR confirmed structure.

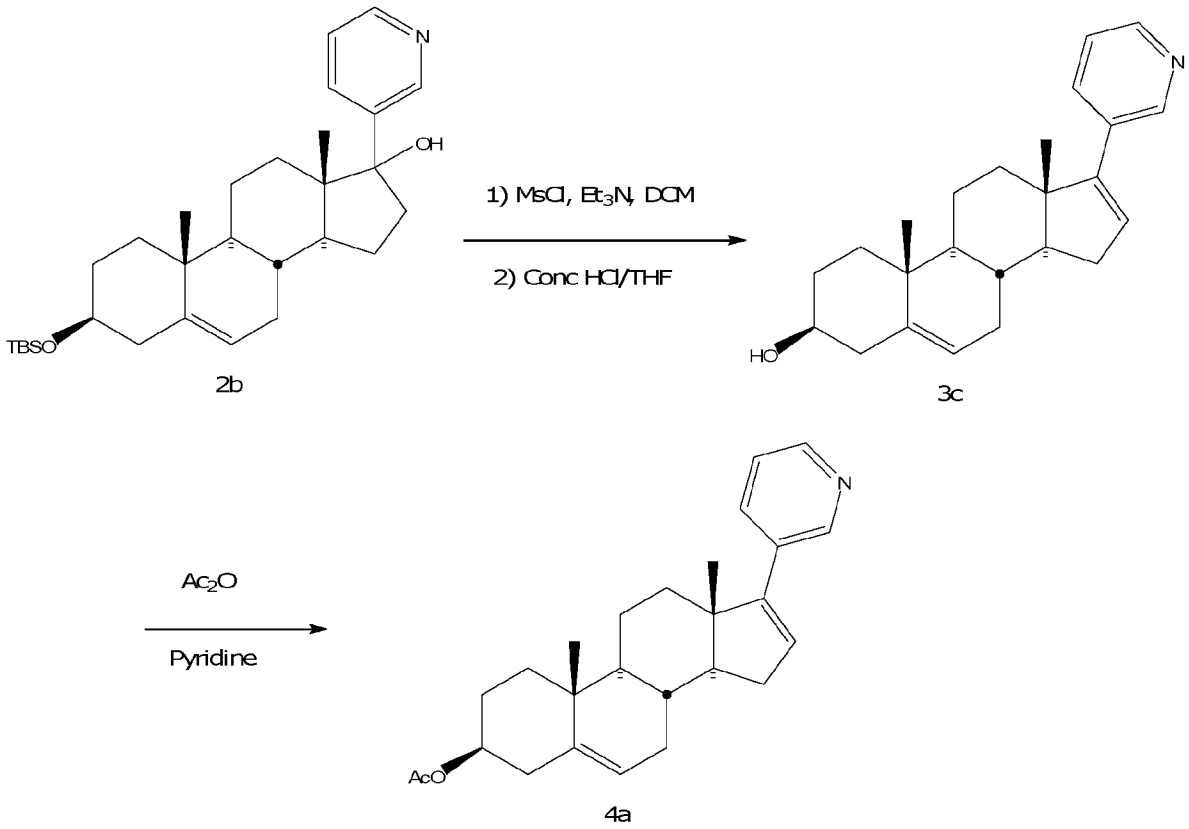
[0070] **EXAMPLE 8: Preparation of compound 2b**



1b 2b

[0071] A 2L three neck round bottom flask equipped with a overhead stirrer, thermometer, dropping funnel and nitrogen inlet was charged with toluene (500 ml) and cooled to -65°C. With agitation, 2.5M n-butyl lithium (nBuLi) in hexanes (225ml, 550mmol) was charged while maintaining a temperature of reaction less than -60°C. Addition took 50 min. Then 3-bromopyridine (59g 373mmol) in toluene (100 ml) was charged over 2 hr. The solution was agitated at -65°C for 0.5 hr. Prepared a solution of compound 1b (50g, 124mmol) in toluene (400 ml) and charged to the reaction solution over 2 hr. The light brown reaction mixture was agitated at for -65°C 0.5 hour. TLC analysis indicated formation of compound **2b** (Hep:EtOAc 1:1 UV, AMCS) The mixture was warmed up to -35°C and quenched with the water (500ml). The reaction mixture was then warm to10°C. Organic layer was separated and the aqueous is extracted with toluene (500ml). Combined organic was washed with water (500ml). Separated organic layer was concentrated to 250 ml. Charged with heptane (750ml). The mixture was concentrated to 250 ml and then charged with heptane (750ml). Repeated this procedure for another time. At the last, to the 250 ml mixture, charged with heptane (250ml). The mixture was agitated at ambient temperature for 1 hr. Solid product was collected by filtration and washed with heptane (150ml) and dried at high vacuum oven at 45°C for 16 hours to give compound **2b** a off white solid 46g (77% yield). NMR and MS confirmed structure.

[0072] **EXAMPLE 9: Preparation of compound 4a**



2b 3c 4a

[0073] A solution of compound **2b** (200 g, 415mmol, 1 equiv) in CH_2Cl_2 (DCM) (1600 mL, 8 parts) in a 5L 3-neck round-bottom flask equipped with a dropping funnel was flushed with nitrogen (N_2) for 5 min. The solution was cooled to 5°C and triethyl amine (578.5 mL, 4151mmol, 10 equiv) was added slowly over 30 min and was stirred at 5°C for 15 minutes. Then mesyl chloride (MsCl) (161.3 mL, 2075 mmol, 5 equiv) was added drop wise over 45 min by controlling the temperature below12°C. The reaction mixture was then stirred at 5°C for 1.5 – 2 h. The ice-bath was removed and the reaction mixture was stirred to room temperature for 12 h. DI water (600 mL 3 parts) was added to the reaction mixture and stirred for 30 minutes, separated out the DCM layer. The DCM layer is then washed with DI water (600 mL, 3 parts) and was concentrated on a rotovap (bath @35°C) down to 1000 mL (5 parts). Then solvent exchanged to tetrahydrofuran (THF) by charging THF (2×2000 mL, 10 parts each) and concentrated to 1000 mL (5 parts).The concentrated reaction mixture was transferred into a 5L 3-neck

round-bottom flask equipped with a dropping funnel. Charged THF (2000 mL, 10 parts) at room temperature and slowly added concentrated hydrochloric acid (76 mL, 2.2 equiv) from the dropping funnel over 1hour. Agitated the reaction mixture (light-brown suspension) at room temperature for 2 hours and was filtered. Washed with THF (2×1000 mL, 5 parts each). Dried the solids at room temperature under suction with nitrogen atmosphere to afford compound **3c** (170.3 g).

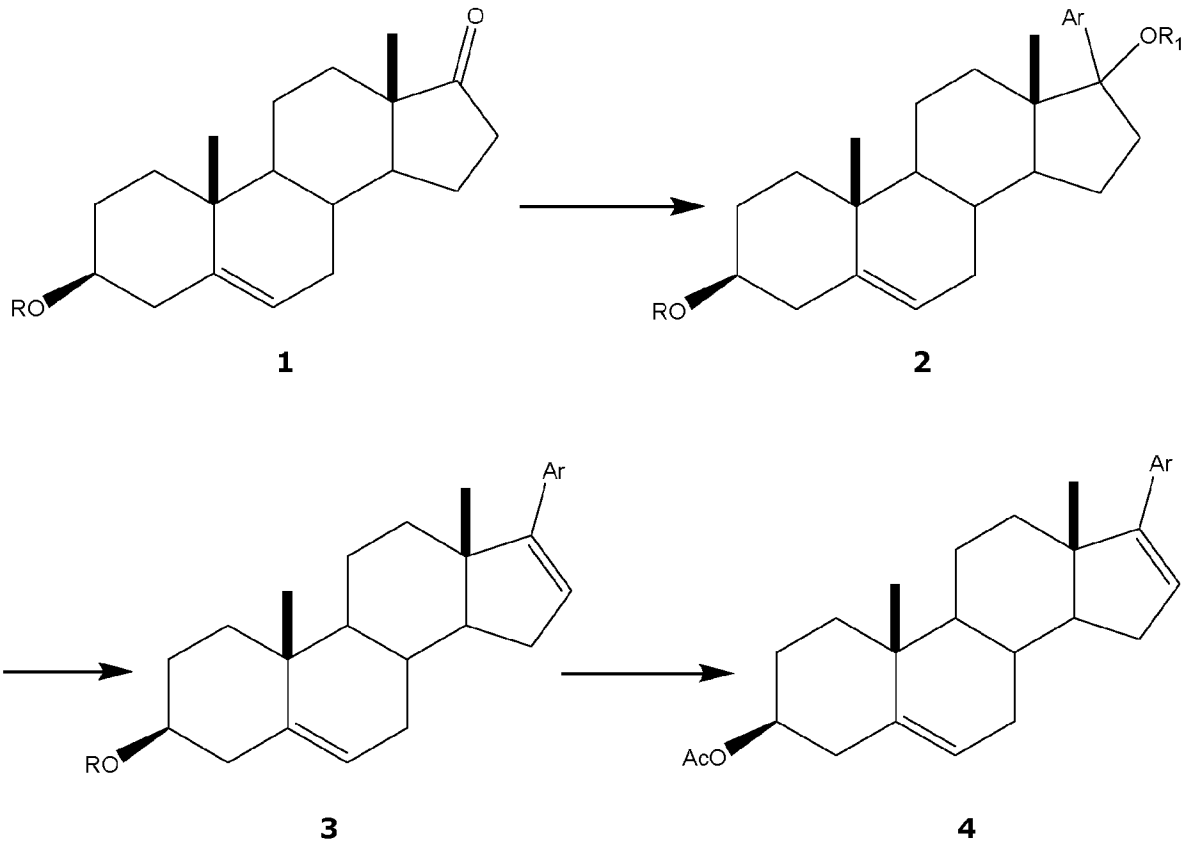
[0074] To a suspension of compound **3c** (170 g, 440.8 mmol) in pyridine (680 mL, 4 parts) in a 5L 3-neck round-bottom flask equipped with a dropping funnel was added acetic anhydride solution (208.5 mL, 2204 mmol,5 equiv) at room temperature slowly from an addition funnel over 30 minutes. The mixture was stirred at room temperature for 4 h. Cooled the reaction mixture to 5°C and D.I. water (1700 mL, 10 parts) was added slowly by controlling the temperature below 15°C. Agitated the reaction mixture at 5°C for 3 h and the solids were filtered, washed with DI water (2× 850 mL, 5 parts each) and dried at room temperature under suction for 18 h and then in a vacuum oven at 45°C under vacuum for 24 h to afford crude compound **4a** (140.2 g).

[0075] **EXAMPLE 10: Recrystallization of compound 4a**

[0076] 5g of the crude compound **4** (where Ar is 3-pyridinyl) was dissolved in isopropanol (IPA) (100 mL, 20 parts) and was filtered through a celite pad, washed the celite pad with IPA (15 mL, 3parts). The filtered IPA solution of compound **4** is then passed through a carbon cartridge filter (SUPRACAP AKS-1 60D, PALL FILTER). Washed the carbon filter with IPA (75mL, 15 parts). Combined all the IPA filtrates and washes and was concentrated to 30 mL (6 parts) on a rotovap (bath@40°C). Charged DI water 30mL (6 parts) and heated the reaction mixture to 80°C to dissolve all the solids and maintained for 1 h at 80°C. Then cooled to room temperature and maintained for 12 h and then cooled to 5°C and maintained for 4 h. The white solids were filtered, washed with 1:1 IPA/water mixture (10 mL, 2 parts) and dried in a vacuum oven at 45°C under vacuum for 24 h to afford pure compound **4a** (3.34 g). HPLC analysis indicates purity of 99.7%.

EMBODIMENTS

[0077] 1. A process for preparation of the compound of formula **4**, the process comprising:



[0078] nucleophillic addition reaction of the compound of formula **1** with a compound of formula Ar–M to form the compound of formula **2**;

[0079] dehydrating the compound of formula **2** to form the compound of formula **3** or **4**;

[0080] optionally, deprotecting the compound of formula **3**; and

[0081] optionally, acylating the compound of formula **3** to form the compound of formula **4**,

[0082] wherein

[0083] R is H or an alcohol protecting group;

[0084] R^1 is H, an alcohol protecting group or R^1 together with the oxygen to which it is attached forms a leaving group;

[0085] M is alkali metal, alkali earth metal or a transition metal of group 11 or 12;

[0086] Ar is an aryl group and

[0087] Ac is an acyl group.

[0088] 2. The process according to embodiment 1, wherein Ar is a heteroaryl group.

[0089] 3. The process according to embodiment 1, wherein Ar is pyridinyl.

[0090] 4. The process according to embodiment 1, wherein Ar is 3-substituted pyridinyl.

[0091] 5. The process according to any one of embodiments 1 to 4, wherein R is an alcohol protecting group.

[0092] 6. The process according to any one of embodiments 1 to 4, wherein R is an alcohol protecting group and the alcohol protecting group is acetyl.

[0093] 7. The process according to any one of embodiments 1 to 4, wherein R is an alcohol protecting group and the alcohol protecting group is a silyl-based protecting group.

[0094] 8. The process according to embodiment 7, wherein the silyl-based protecting group is tert-butyldimethylsilyl (TBDMS or TBS).

[0095] 9. The process according to any one of embodiments 1 to 8, wherein M is alkali metal.

[0096] 10. The process according to embodiment 9, wherein the alkali metal is Li.

[0097] 11. The process according to any one of embodiments 1 to 10, wherein R^1 is H.

[0098] 12. The process according to any one of embodiments 1 to 10, wherein R^1 together with the oxygen to which it is attached forms a leaving group.

[0099] 13. The process according to any one of embodiments 1 to 10, wherein R^1 together with the oxygen to which it is attached forms a leaving group and the leaving group is mesylate or tosylate.

[00100] 14. The process according to any one of embodiments 1 to 13, wherein the step of dehydrating the compound of formula **2** is carried out in the presence of an acid.

[00101] 15. The process according to embodiment 14, wherein the acid is hydrochloric acid (HCl) or *p*-toluene sulfonic acid (*p*TSA).

[00102] 16. The process according to any one of embodiments 1 to 13, wherein the step of dehydrating the compound of formula **2** is carried out in the presence of a base.

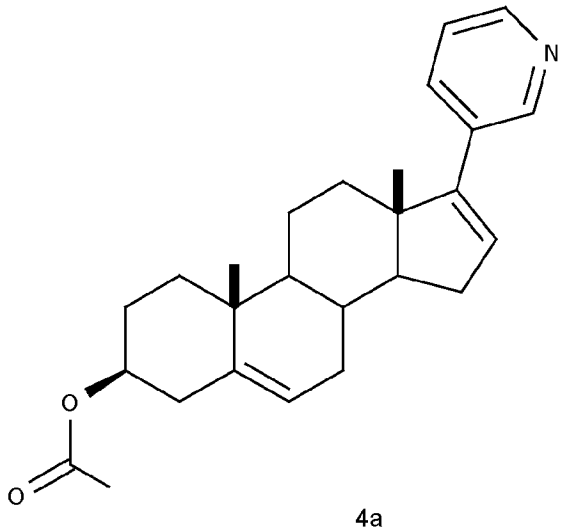
[00103] 17. The process according to embodiment 16, wherein the base is triethylamine (TEA).

[00104] 18. The process according to any one of embodiments 1 to 17, wherein the step of deprotecting the compound of formula **3** is carried out in the presence of an acid.

[00105] 19. The process according to any one of embodiments 1 to 17, wherein the step of deprotecting the compound of formula **3** is carried out in using a fluoride source.

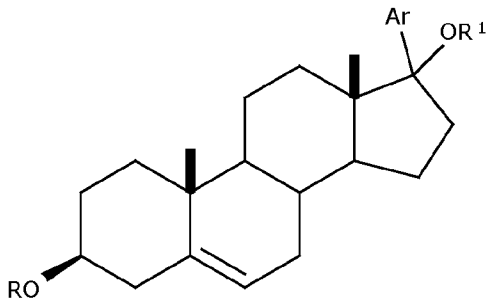
[00106] 20. The process according to any one of embodiments 1 to 19, wherein the step of acylating comprises acetylating the compound of formula **3**.

[00107] 21. The process according to any one of embodiments 1 to 20, wherein the process comprises forming the compound of formula **4a**



4a

[00108] 22. The compound of formula **2**,



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[00109] wherein

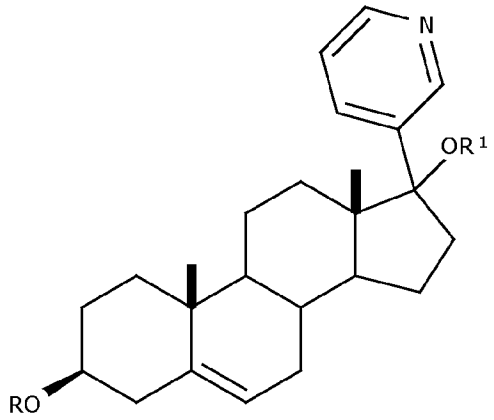
[00110] Ar is an aryl group;

[00111] R is H or an alcohol protecting group; and

[00112] R^1 is H, an alcohol protecting group or R^1 together with the oxygen to which it is attached forms a leaving group.

[00113] 23. The compound of embodiment 22, wherein Ar is pyridinyl.

[00114] 24. The compound of embodiment 23, wherein the compound of formula **2** is a compound of formula **2a**



2a

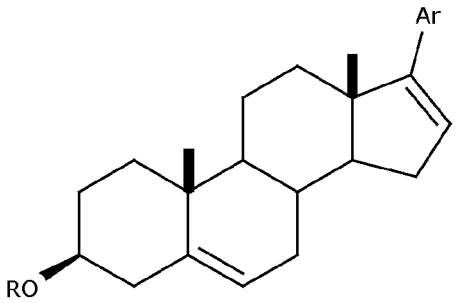
[00115] 25. The compound of any one of embodiments 22 to 24, wherein R^1 is H.

[00116] 26. The compound of any one of embodiments 22 to 24, wherein R^1 together with the oxygen to which it is attached forms a leaving group.

[00117] 27. The compound of any one of embodiments 22 to 26, wherein R is acetyl.

[00118] 28. The compound of any one of embodiments 22 to 26, wherein R is a silyl-based protecting group.

[00119] 29. The compound of formula **3**,



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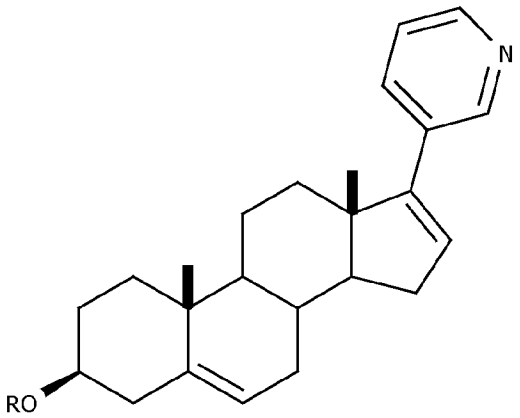
[00120] wherein

[00121] Ar is an aryl group; and

[00122] R is a silyl-based protecting group.

[00123] 30. The compound of embodiment 29, wherein Ar is pyridinyl.

[00124] 31. The compound of embodiment 29 or 30, wherein the compound is the compound of formula **3a**



3a

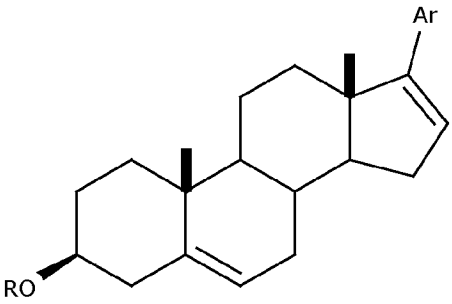
[00125] 32. The compound of any one of embodiments 29 to 31, wherein the silyl-based protecting group is tert-butyldimethylsilyl (TBDMS or TBS).

[00126] 33. Abiraterone acetate having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC.

[00127] 34. The compound of formula **3** having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC.

[00128] 35. The compound of formula **2** having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC.

[00129] 36. A process for purification of the compound of formula **3** or **4**,



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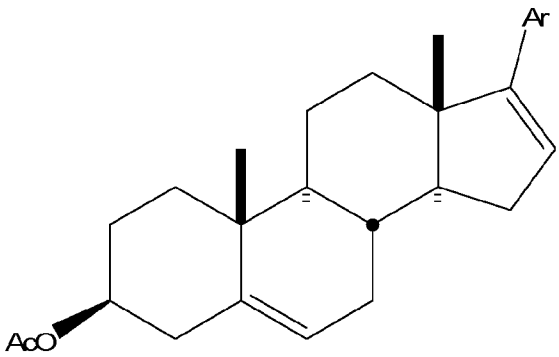


4

[00130] wherein R is H or an alcohol protecting group; Ar is an aryl or heteroaryl group and Ac is an acyl group;

[00131] the process containing the step of recrstallizing the compound of formula **3** or **4** with a solvent selected from the group consisting of methanol, ethanol, isopropanol, isopropanol/water, toluene/heptanes and acetonitrile/water.

[00132] 37. The process of embodiment 36, wherein the solvent is methanol, ethanol or isopropanol.

[00133] 38. The process of embodiment 37, wherein the solvent used is 3 to 10 parts v/w of the compound of formula **3** or **4**.

[00134] 39. The process of embodiment 36, wherein the solvent is isopropanol/water, toluene/heptanes and acetonitrile/water.

[00135] 40. The process of embodiment 39, wherein the solvent is toluene/heptanes and the solvent used is 0.5/3 to 1/2 parts v/w of the compound of formula **3** or **4**.

[00136] 41. The process of embodiment 39, wherein the solvent is acetonitrile/water and the solvent used is 8/1 to 5/1 parts v/w of the compound of formula **3** or **4**.

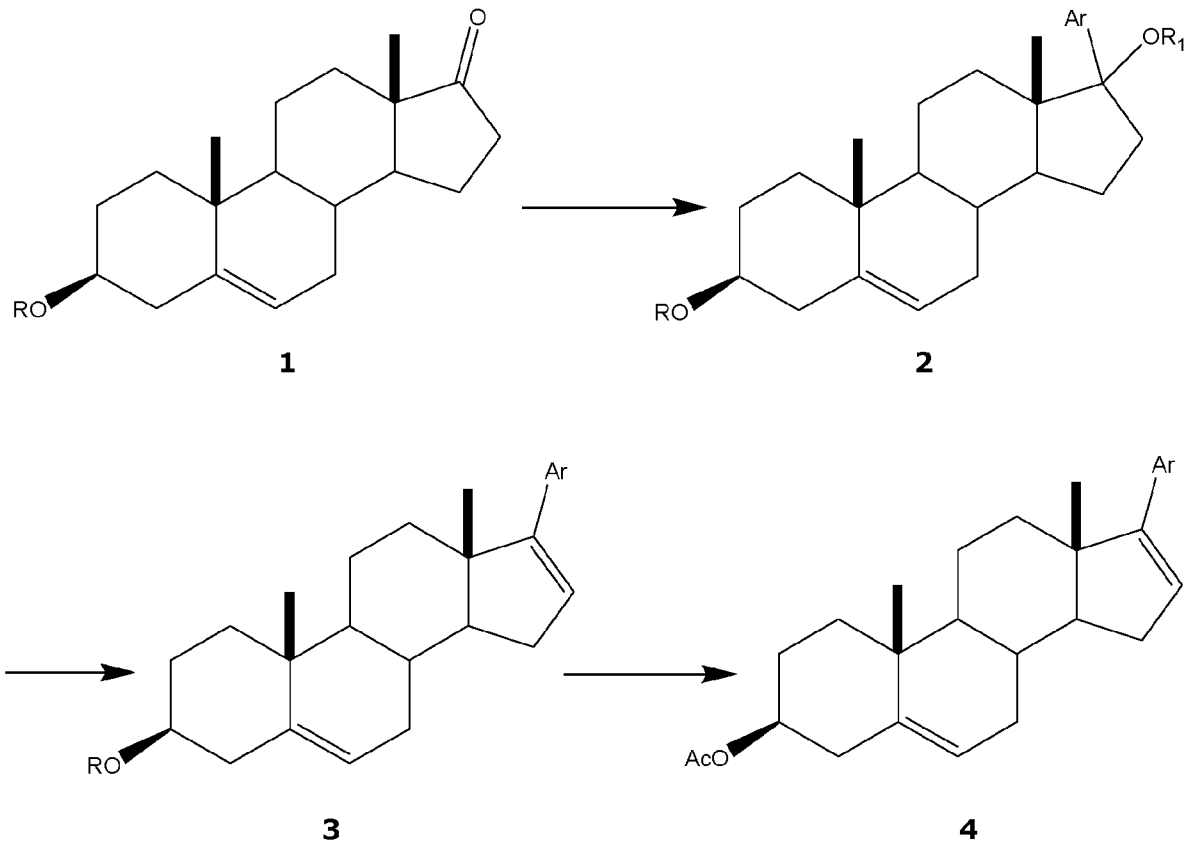
[00137] 42. The process of embodiment 39, wherein the solvent is isopropanol/water and the solvent used is 0.5/3 to 2/1 parts v/w of the compound of formula **3** or **4**.

[00138] 43. The process of any one of embodiments 36 to 42, wherein the compound of formula **3** or **4** has a purity of ≥98%, as determined by HPLC.

[00139] Certain adaptations and modifications of the described embodiments can be made. Therefore, the above discussed embodiments are considered to be illustrative and not restrictive.

WHAT IS CLAIMED IS:

1. A process for preparation of the compound of formula **4**, the process comprising:



- nucleophillic addition reaction of the compound of formula **1** with a compound of formula Ar–M to form the compound of formula **2**;
- dehydrating the compound of formula **2** to form the compound of formula **3** or **4**;
- optionally, deprotecting the compound of formula **3**; and
- optionally, acylating the compound of formula **3** to form the compound of formula **4**,

wherein

R is H or an alcohol protecting group;

R^1 is H, an alcohol protecting group or R^1 together with the oxygen to which it is attached forms a leaving group;

M is alkali metal, alkali earth metal or a transition metal of group 11 or 12;

Ar is an aryl or heteroaryl group and

Ac is an acyl group.

2. The process according to claim 1, wherein Ar is a heteroaryl group.

3. The process according to claim 1, wherein Ar is pyridinyl.

4. The process according to claim 1, wherein Ar is 3-substituted pyridinyl.

5. The process according to any one of claims 1 to 4, wherein R is an alcohol protecting group.

6. The process according to any one of claims 1 to 4, wherein R is an alcohol protecting group and the alcohol protecting group is acetyl.

7. The process according to any one of claims 1 to 4, wherein R is an alcohol protecting group and the alcohol protecting group is a silyl-based protecting group.

8. The process according to claim 7, wherein the silyl-based protecting group is tert-butyldimethylsilyl (TBDMS or TBS).

9. The process according to any one of claims 1 to 8, wherein M is alkali metal.

10. The process according to claim 9, wherein the alkali metal is Li.

11. The process according to any one of claims 1 to 10, wherein R^1 is H.

12. The process according to any one of claims 1 to 10, wherein R^1 together with the oxygen to which it is attached forms a leaving group.

13. The process according to any one of claims 1 to 10, wherein R^1 together with the oxygen to which it is attached forms a leaving group and the leaving group is mesylate or tosylate.

14. The process according to any one of claims 1 to 13, wherein the step of dehydrating the compound of formula **2** is carried out in the presence of an acid.

15. The process according to claim 14, wherein the acid is hydrochloric acid (HCl) or *p*-toluene sulfonic acid (*p*TSA).

16. The process according to any one of claims 1 to 13, wherein the step of dehydrating the compound of formula **2** is carried out in the presence of a base.

17. The process according to claim 16, wherein the base is triethylamine (TEA).

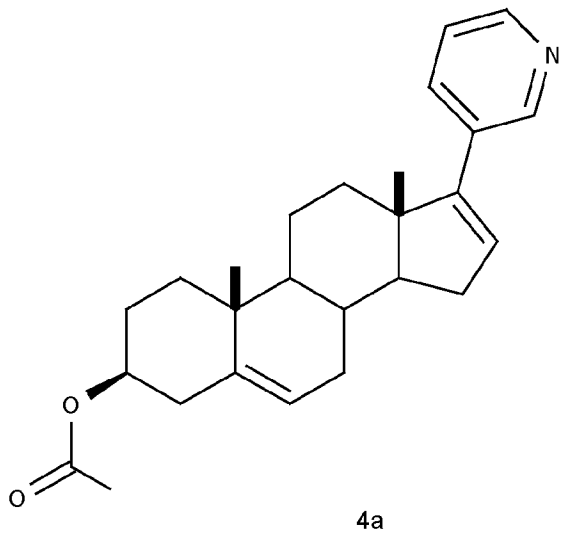
18. The process according to any one of claims 1 to 17, wherein the step of

deprotecting the compound of formula **3** is carried out in the presence of an acid.

19. The process according to any one of claims 1 to 17, wherein the step of deprotecting the compound of formula **3** is carried out in using a fluoride source.

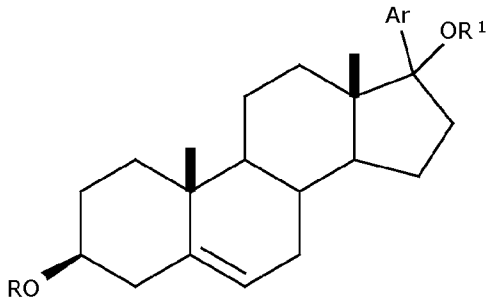
20. The process according to any one of claims 1 to 19, wherein the step of acylating comprises acetylating the compound of formula **3**.

21. The process according to any one of claims 1 to 20, wherein the process comprises forming the compound of formula **4a**



4a .

22. The compound of formula **2**,



2

wherein

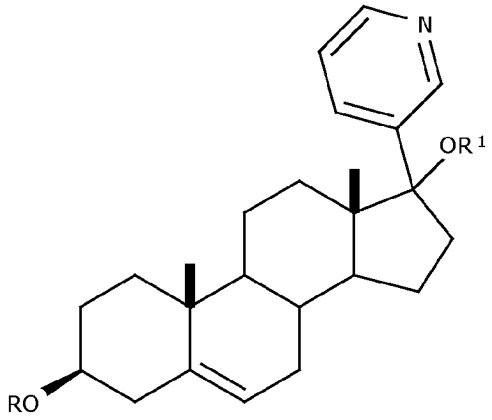
Ar is an aryl group;

R is H or an alcohol protecting group; and

R^1 is H, an alcohol protecting group or R^1 together with the oxygen to which it is attached forms a leaving group.

23. The compound of claim 22, wherein Ar is pyridinyl.

24. The compound of claim 23, wherein the compound of formula **2** is a compound of formula **2a**



2a

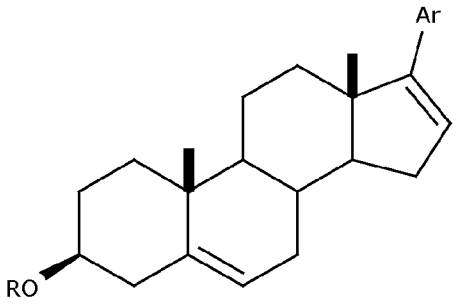
25. The compound of any one of claims 22 to 24, wherein R^1 is H.

26. The compound of any one of claims 22 to 24, wherein R^1 together with the oxygen to which it is attached forms a leaving group.

27. The compound of any one of claims 22 to 26, wherein R is acetyl.

28. The compound of any one of claims 22 to 26, wherein R is a silyl-based protecting group.

29. The compound of formula **3**,



3

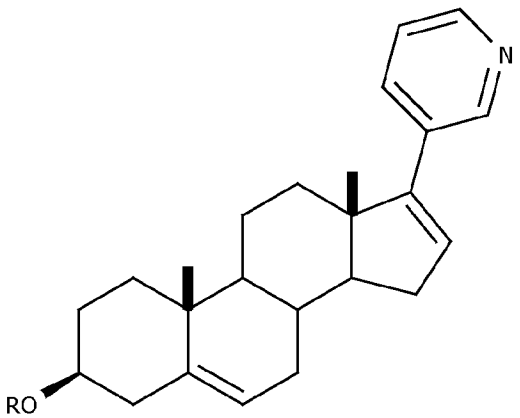
wherein

Ar is an aryl group; and

R is a silyl-based protecting group.

30. The compound of claim 29, wherein Ar is pyridinyl.

31. The compound of claim 29 or 30, wherein the compound is the compound of formula **3a**



3a

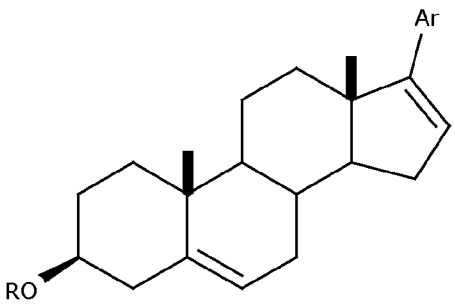
32. The compound of any one of claims 29 to 31, wherein the silyl-based protecting group is tert-butyldimethylsilyl (TBDMS or TBS).

33. Abiraterone acetate having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC.

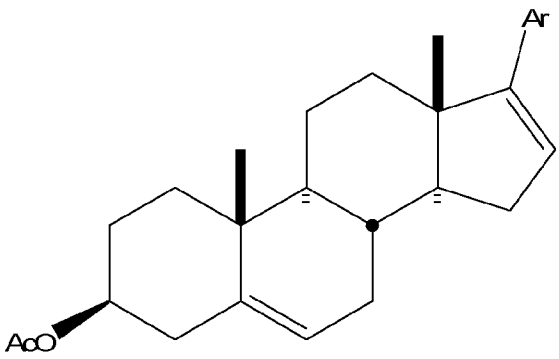
34. The compound of formula **3** or **3a** having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC.

35. The compound of formula **2** or **2a** having a purity of ≥95%, ≥96%, ≥97%, ≥98%, ≥99%, ≥99.5% or ≥99.9%, as determined by HPLC.

36. A process for purification of the compound of formula 3 or 4,



3



4

wherein R is H or an alcohol protecting group; Ar is an aryl or heteroaryl group and Ac is an acyl group;

the process comprising the step of recrstallizing the compound of formula 3 or 4 with a solvent selected from the group consisting of methanol, ethanol, isopropanol, isopropanol/water, toluene/heptanes and acetonitrile/water.

37. The process of claim 36, wherein the solvent is methanol, ethanol or isopropanol.

38. The process of claim 37, wherein the solvent used is 3 to 10 parts v/w of the compound of formula 3 or 4.

39. The process of claim 36, wherein the solvent is isopropanol/water, toluene/heptanes and acetonitrile/water.

40. The process of claim 39, wherein the solvent is toluene/heptanes and the solvent used is 0.5/3 to 1/2 parts v/w of the compound of formula 3 or 4.

41. The process of claim 39, wherein the solvent is acetonitrile/water and the solvent used is 8/1 to 5/1 parts v/w of the compound of formula 3 or 4.

42. The process of claim 39, wherein the solvent is isopropanol/water and the solvent used is 0.5/3 to 2/1 parts v/w of the compound of formula 3 or 4.

43. The process of any one of claims 36 to 42, wherein the compound of formula 3 or 4 has a purity of ≥98%, as determined by HPLC.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2013/050311

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07J 43/00*** (2006.01) , ***A61K 31/58*** (2006.01) , ***C07J 75/00*** (2006.01) , ***C07J 9/00*** (2006.01)

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)

IPC: ***C07J 43/00*** (2006.01) , ***A61K 31/58*** (2006.01) , ***C07J 75/00*** (2006.01) , ***C07J 9/00*** (2006.01)

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

C07J

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

Canadian Patent Database, STN, Google Scholar: abiraterone, lithium, acetate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	CN 102898495 A (Li, *et al.*) 30 January 2013 (30.01.2013) see page 1 of abstract and page 3 of description.	1-43
X	Mendieta, *et al.*, "Synthesis, Biological Evaluation, and Molecular Modeling of Abiraterone Analogues: Novel CYP17 Inhibitors for the Treatment of Prostate Cancer", *J. Med. Chem.*, **2008**, *51*(16), p5009-5018. see scheme 1 on page 5011, left column.	1-43
X	Potter, *et al.*, "A convenient, large-scale synthesis of abiraterone acetate [3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene], a potential nwe drug for the treatment of prostate cancer", *Org. Prep. Proc. Int.*, **1997**, *29*(1), p123-128. See whole document, especially experimental procedure on page 127.	33, 34, 36-43

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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
29 April 2013 (26-04-2013)	08 May 2013 (08-05-2013)

Name and mailing address of the ISA/CA	Authorized officer
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2013/050311

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CN102898495A	30 January 2013 (30-01-2013)	None	