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Señor

SUPERINTENDENTE DE INDUSTRIA Y C
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-037834- -00003-0000

Fecha: 2010-06-01 16:34:50 Dep. 2020 DIR.NUEVASCR
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Act. 329 CTOINFORMACION Folios: 16

Re: PI.-**CILAG AG.**-Solicitud de Patente de Invención en Fase
Nacional PCT para "**MÉTODO PARA PRODUCIR 2'-DESOXI-5-**
AZACITIDINA (DECITABINA)".-Clase **C07H 19/12.-**
Expediente número **10-037.834.-**

1. Me refiero a mi solicitud de patente de 5 de Abril de 2010.
2. Atentamente me permito presentar a ese Despacho copia debidamente certificada de la solicitud de Patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad**, a saber, la solicitud Europea número **EP 07019826.2** de 10 de Octubre de 2007, junto con su Traducción Oficial, correspondiente a dicho documento.
3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,


ALICIA LLOREDA RICAURTE

T.P. 53.215

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TRADUCCION OFICIAL No. 2010-06-01-356
DE UN DOCUMENTO ESCRITO EN INGLES

Certificado

Los documentos adjuntos son copias exactas
de la solicitud de patente europea descrita en la
siguiente página, como se presentó originalmente.

Solicitud de patente No.
07019826.2 / EP07019826

El código de la organización y el número de su solicitud de prioridad, que se
usarán para presentación en el exterior bajo la Convención de París, es
EP07019826.

Por el Presidente de la Oficina Europea de Patentes
(firma: ilegible)
R.C. van Dijk

Reivindicaciones

1. Método para producir 2'-deoxi-5-azacitidina (Decitabina) que proporciona un compuesto de fórmula (I):



donde

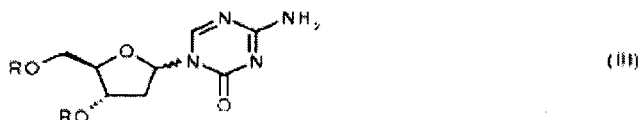
R es un sustituyente removible conocido per se, preferiblemente (C₁-C₈) alquilcarbonilo, u opcionalmente fenilcarbonilo sustituido, u opcionalmente bencilcarbonilo sustituido;

R₁ es un donante glicósido preferiblemente un derivado de 1-halógeno, o un imidato preferiblemente un derivado de triclorometilo, o un derivado de tioalquilo, preferiblemente derivado de tiometilo; además proporciona una base sililada de fórmula (II):



donde R₂ es un grupo protector, preferiblemente un residuo de trimetilsililo (TMS);

que reacciona el compuesto de fórmula (I) y el compuesto de fórmula (II) juntos en un solvente anhidro apropiado y en presencia de un catalizador apropiado, donde el compuesto de fórmula (III):



se obtiene; y remueve los sustituyentes R para obtener el compuesto 2'-deoxi-5-azacitidina (Decitabina), caracterizado en que dicho catalizador es seleccionado del grupo que comprende una sal de un ácido sulfónico alifático y/o la sal de un ácido sulfónico aromático opcionalmente sustituido.

2. Método para producir un compuesto de fórmula (III) de conformidad con la reivindicación 1, que proporciona un compuesto de fórmula (I):



donde

R es un sustituyente removible conocido per se, preferiblemente (C₁-C₈) alquilcarbonilo, u fenilcarbonilo opcionalmente sustituido, o bencilcarbonilo opcionalmente sustituido;

R₁ es un donante glicósido preferiblemente un derivado de 1-halógeno, o un imidato preferiblemente un derivado de triclorometilo, o un derivado de tioalquilo, preferiblemente tiometilo;

además proporciona una base sililada de fórmula (II):



donde R_2 es un grupo protector, preferiblemente un residuo de trimetilsililo (TMS);

que reacciona el compuesto de fórmula (I) y el compuesto de fórmula (II) juntos en un solvente anhidro apropiado y en presencia de un catalizador apropiado, donde el compuesto de fórmula (III) se obtiene, caracterizado en que dicho catalizador es seleccionado del grupo que comprende una sal de un ácido sulfónico alifático y/o la sal de un ácido sulfónico aromático opcionalmente sustituido.

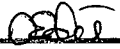
3. Método de conformidad con la reivindicación 1 o 2, caracterizado en que el catalizador usado en dicha reacción es una sal de un ácido sulfónico alifático, preferiblemente de ácido metilsulfónico o de ácido etilsulfónico, o una sal de ácido sulfónico alifático fluorinado, preferiblemente de ácido trifluorometano-sulfónico, ácido pentafluoro-etil-sulfónico, o ácido heptafluoropropil-sulfónico.
4. Método de conformidad con la reivindicación 3, caracterizado en que el catalizador es una sal de ácido metilsulfónico y/o las sales de ácido trifluorometanosulfónico.
5. Método de conformidad con una de las reivindicaciones 1-4, caracterizado en que el catalizador es una sal alcalina o sal alcalinotérrea, preferiblemente una sal de litio, preferiblemente ácido metilsulfónico de litio o litio-trifluorometanosulfonato.
6. Método de conformidad con la reivindicación 1 o 2, caracterizado en que el catalizador es escogido de las sales que comprenden sales de escandio preferiblemente $\text{Sc}(\text{OTf})_3$; o sales de cobre preferiblemente $\text{Cu}(\text{OTf})_2$; o sales de magnesio preferiblemente $\text{Mg}(\text{OTf})_2$.

7. Método de conformidad con la reivindicación 1 o 2, caracterizado en que el catalizador es escogido de las sales que comprenden ácidos sulfónicos aromáticos opcionalmente sustituidos, preferiblemente las sales alcalinas y sales alcalinotérreas de las mismas.
8. Método de conformidad con la reivindicación 7, caracterizado en que el catalizador es escogido de las sales que comprenden sales alcalinas y sales alcalinotérreas de ácido bencenosulfónico, ácido toluenosulfónico, y ácidos conocidos relacionados, preferiblemente la sal de litio de dichos ácidos sulfónicos aromáticos.
9. Método de conformidad con cualquiera de las reivindicaciones 1-8, caracterizado en que el solvente para llevar a cabo la reacción es escogido del grupo que comprende solventes clorinados, preferiblemente diclorometano, dicloroetano, cloroformo, clorobenceno; o tolueno, xilol, acetonitrilo y/o propileno carbonato o solventes relacionados, y preferiblemente es un solvente clorinado.
10. Método de conformidad con cualquiera de las reivindicaciones 1-9, caracterizado en que el catalizador es litio-trifluorometanosulfonato y el solvente es un solvente clorinado, preferiblemente diclorometano, dicloroetano, cloroformo y/o clorobenceno.
11. Método de conformidad con cualquiera de las reivindicaciones 1-10, caracterizado en que el sustituyente removible R es (C₁-C₄) alquil-carbonilo, o fenilcarbonilo opcionalmente sustituido o bencilcarbonilo, preferiblemente fenilcarbonilo, tolilcarbonilo, xililcarbonilo, preferiblemente acetil o p-cloro-fenilcarbonilo.
12. Método de conformidad con cualquiera de las reivindicaciones 1-11, caracterizado en que el sustituyente removible R1 es -O-acil (C₁-C₄), -O-

alquilo (C_1-C_4) o cloro, preferiblemente $-O-(O)CCH_3$ o cloro, preferiblemente cloro.

Traducido según mi mejor saber y entender, este día 1 de junio de 2010, en la ciudad de Bogotá, D.C., por Anita Escobar de Tamayo, Traductora Oficial, Res. 2177 de 1989, Ministerio de Justicia, República de Colombia.

TRADUCTORA OFICIAL
RES. 2177/89 MINJUSTICIA


ANITA ESCOBAR DE TAMAYO



Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr.

Patent application No.

Demande de brevet n°

07019826.2 / EP07019826

The organization code and number of your priority application, to be used for filing abroad under the Paris Convention, is EP07019826

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R.C. van Dijk



Anmeldung Nr.:
Application no.: 07019826.2
Demande no:

Anmeldetag:
Date of filing: 10.10.07
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Cilag AG
Hochstrasse 201
8205 Schaffhausen/CH

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Method of producing 2'-deoxy-5-azacytidine (Decitabine)

In anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen / State/Date/File no. / Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation / International Patent Classification / Classification internationale de brevets:

C07H

Am Anmeldetag benannte Vertragstaaten / Contracting states designated at date of filing / Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR

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Method of producing 2'-deoxy-5-azacytidine (Decitabine)

The present invention refers to a method of producing 2'-deoxy-5-azacytidine (Decitabine) by reacting a glycoside donor preferably a 1-halogen derivative, or an imidate preferably a trichloromethyl derivative, or a thio-alkyl derivative of a blocked monosaccharide with a selected silylated base in the presence of a selected catalyst.

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Decitabine is a nucleoside and a known pharmaceutically active compound. From US 3,817,980 it is known to synthesize nucleosides by silylating the corresponding nucleoside base and reacting the silylated base with a glycosyl donor preferably a 1-halogen derivative of a blocked monosaccharide or oligosaccharide in the presence of a selected catalyst by silylating the base and reacting the sugar derivative in a single step in the presence of trimethylhalosilane and/or hexamethyldisilazane. The catalysts used are e.g. selected from SnCl_4 , TiCl_4 , ZnCl_2 , BF_3 -etherate, AlCl_3 and SbCl_5 , or a trialkylester of a perfluoroalkanesulfonic acid. The major disadvantage is that all catalysts mentioned in the patent (tin tetrachloride, titanium tetrachloride, zinc chloride or boron trifluoride etherate) are prone to hydrolysis giving irritant hydrolysis products like HCl or are forming insoluble oxides (TiO_2 , SnO_2), which are difficult to remove from the reaction product and difficult to handle, especially on large scale production.

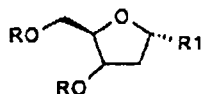
It has now been found that a 1-halo sugar derivative can be reacted with a silylated or alkylated 5-azacytosine in the presence of a selected catalysts, i.e. an inorganic salt like lithium trifluoromethane sulfonate, to give excellent product yields. This type of catalyst is stable under aqueous conditions, easy to handle, does not produce irritant hydrolysis products, and can be easily removed. Instead of the highly toxic and

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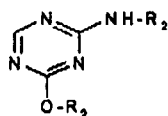
- cancerogenous solvent dichloroethane as exemplified in US 3,817,980, much less toxic solvents such as dichloromethane can be used. Additionally, the selectivity of the reaction for obtaining the desired anomer, i.e. ratio of the alpha/beta anomers, and the final yields are considerably improved. Using the reaction conditions of the present invention a selectivity of at least 1:2 in favor of the beta-isomer (β -isomer), in the average about three quarter of the reaction yield is the beta isomer and, depending on the particular reaction condition, a ratio of the alpha to the beta isomer of 18:82 was obtained. Further, according to the present invention a reaction yield that is higher than 95% (reaction yield >95%), and regularly is within the range of 97-98% is obtained.
- 15 The present invention is defined in the claims. The present invention refers to a method of producing 2'-deoxy-5-azacytidine (Decitabine) by providing a compound (a blocked monosaccharide derivative) of formula (I):



(I)

wherein

- R is a removable substituent (protecting group) known per se, preferably (C₁-C₈)alkylcarbonyl, or optionally substituted phenylcarbonyl, or optionally substituted benzylcarbonyl;
- 25 R1 a glycoside donor preferably a 1-halogen derivative, or an imidate preferably a trichloromethyl derivative, or a thio-alkyl derivative;
- further providing a silylated base of formula (II):

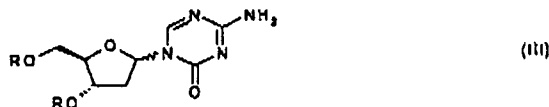


(II)

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wherein R_2 is a protecting group, preferably a trimethylsilyl (TMS)-residue;
reacting the compound of formula (I) and the compound of formula (II) together in a suitable anhydrous solvent and in the presence
5 of a suitable catalyst, whereby the compound of formula (III):



is obtained; and removing the substituent R in order to obtain
10 the compound 2'-deoxy-5-azacytidine (Decitabine), characterized in that said catalyst is selected from the group comprising a salt of an aliphatic sulphonic acid and/or the salt of a optionally substituted aromatic sulphonic acid.

15 The present invention refers also to the production of the compound of formula (III). Preferred is the beta-glycoside, as indicated in formula (III).

The catalyst used in said reaction preferably is a salt of an
20 aliphatic sulphonic acid, preferably of methylsulphonic acid (mesylate) or of ethylsulphonic acid, or of a fluorinated aliphatic sulfonic acid, such as a salt of trifluoromethane-sulfonic acid, pentafluoroethyl-sulfonic acid, or heptafluoropropyl-sulfonic acid. Preferred of these salts are the salts of methyl-
25 sulphonic acid (mesylate) and the salts of trifluoromethane-sulfonic acid. Preferred are the alkali salts, and earth alkali salts. Preferred further are the lithium salts, preferably lithium methylsulphonic acid (lithium mesylate) or lithium-trifluoromethanesulfonate (LiOTf, lithiumtriflate). Generally also
30 other salts, for example the salts of scandium, such as $\text{Sc}(\text{OTf})_3$, or of copper such as $\text{Cu}(\text{OTf})_2$ or of magnesium such as $\text{Mg}(\text{OTf})_2$ can be used. However, the lithium salt and especially LiOTf is preferred. Further salts of known, optionally substituted, aromatic sulphonic acids may also be used; preferably the alkali

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salts and earth alkali salts thereof. Preferred are the alkali salts and earth alkali salts of benzenesulphonic acid (besylate), toluenesulphonic acid (tosylate), and known related acids. Preferred are the lithium salts of said aromatic sulphonic acids.

5

Preferred solvents to carry out the reaction according to the present invention are chlorinated solvents, such as dichloromethane, dichloroethane, chloroform, chlorobenzene, or toluene, xylol, acetonitril and/or propylene carbonate or related

10 solvents. Preferred are chlorinated solvents. Preferred is the use of lithium-trifluoromethanesulfonate (LiOTf) in a chlorinated solvent, preferably in dichloromethane, dichloroethane, chloroform and/or chlorobenzene.

15 The compound of formula (I) and its preparation are known per se. The removable substituent R is preferably (C₁-C₄)alkylcarbonyl, or optionally substituted phenylcarbonyl, like phenylcarbonyl, tolylcarbonyl, xylylcarbonyl or benzylcarbonyl; preferably acetyl or p-chloro-phenylcarbonyl. The removable substituent R₁ is
20 preferably halogen, preferably chlorine, bromine, fluorine, preferably chlorine, or an imidate, preferably trichloromethyl imidate, or a thio-alkyl derivative, preferably -S-methyl.

The preparation of compound of formula (II) and its preparation
25 are known. The compound is preferably prepared by reaction of the free base with trimethylchlorosilane or with hexamethyldisilazane.

When reacting the compounds of formulae (I) and (II) together,
30 the reaction temperature generally is within the range of 0°C to about 90°C, preferably at about room temperature, whereby the components are reacted in about equimolar amounts and preferably with a slight excess of compound of formula (II). The catalyst is used preferably in a concentration of about 10 mol-% - 90 mol-%,
35 calculated to the total molar presence of the two reacting

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components. For the expert in the art it is no problem to optimize the molar ratios of the components.

For removing the substituents R from the compound of formula
5 (III) in order to obtain the compound 2'-deoxy-5-azacytidine (Decitabine), containing free hydroxyl groups, known methods are used. The substituents R may be preferably removed, for example, by treatment in an alcoholic solution of ammonia or alcoholates; but other known methods may be applied. The following example
10 illustrates the invention.

Example 1

(A) A mixture of 5-Azacytosine (20 g, 178.4 mmol), ammonium sulfate (2.4 g, 18.16 mmol), and hexamethyldisilazane (160 g,
15 991.3 mmol) was heated to reflux until a clear solution was obtained. The excess of hexamethyldisilazane was removed in the vacuum at 60°C.

(B) A mixture of 264 g of dichloromethane, lithium trifluoromethane sulfonate (12.53 g, 80.3 mmol) and the "chloro sugar" C-
20 137 [69.0 g, 160.6 mmol, corresponding to compound of formula (I)] were prepared and added to the residue obtained in step (A).

(C) The mixture was stirred for 4 hours at ambient temperature (20-25°C). Then the solvent was removed at 40°C in the vacuum and the obtained residue was dissolved in 60 g ethyl acetate. The
25 solution was added drop wise to a mixture of 220 g of aqueous sodium hydrogen carbonate (2.5% w-solution), 174 g ethyl acetate, 36 g cyclohexane and 70 g acetonitrile at 30°C and the obtained reaction mixture is cooled to 0°C and stirred for 3 h. The precipitate of the blocked (protected) aminotriazine was filtered
30 off, washed with water and finally with a mixture of acetonitrile and ethyl acetate (1:1).

Yield: 70.0 g; 60.6% [assay (beta-isomer): 70.3 %; purity (beta-isomer): 64.7%].

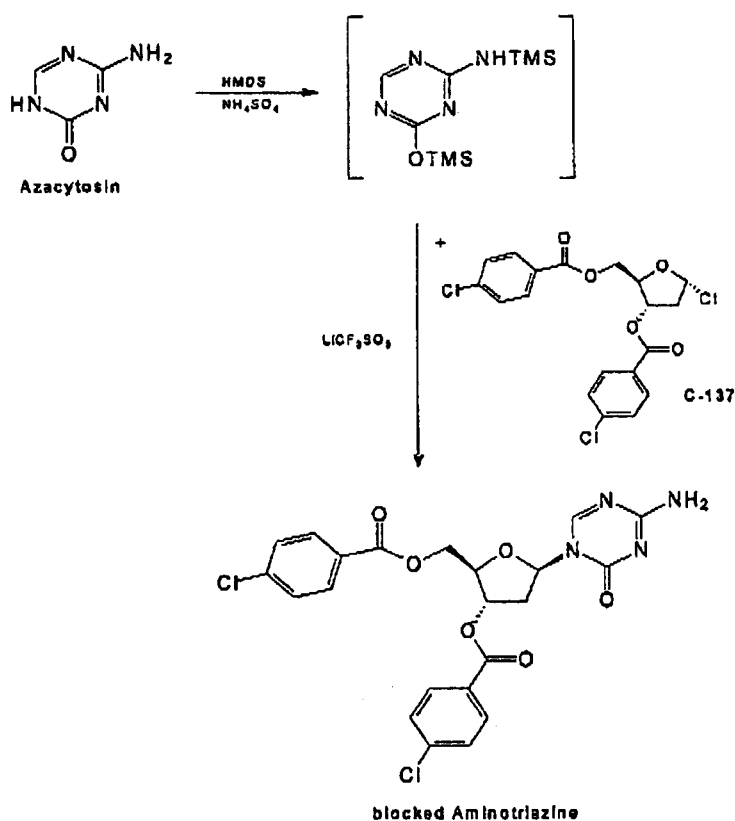
Scheme 1 shows the chemical reaction.

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Example 2

The compound corresponding to formula (III) as obtained in Example 1 is further treated with in an alcoholic solution of ammonia in a known manner so that 2'-deoxy-5-azacytidine (Decitabine) is obtained in practically quantitative yield.

Scheme 1

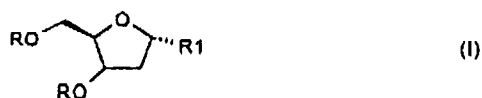
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Claims

1. Method of producing 2'-deoxy-5-azacytidine (Decitabine) by providing a compound of formula (I):

5



wherein

R is a removable substituent known per se, preferably (C₁-C₈)alkylcarbonyl, or optionally substituted phenylcarbonyl, or optionally substituted benzylcarbonyl;

R₁ is a glycoside donor preferably a 1-halogen derivative, or an imidate preferably a trichloromethyl derivative, or a thioalkyl derivative, preferably thiomethyl derivative;

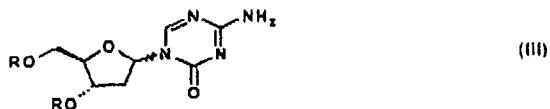
further providing a silylated base of formula (II):

15



wherein R₂ is a protecting group, preferably a trimethylsilyl (TMS)-residue;

20 reacting the compound of formula (I) and the compound of formula (II) together in a suitable anhydrous solvent and in the presence of a suitable catalyst, whereby the compound of formula (III):



25

is obtained; and removing the substituents R in order to obtain the compound 2'-deoxy-5-azacytidine (Decitabine), characterized in that said catalyst is selected from the group comprising a salt of an aliphatic sulphonic acid and/or the salt of a

30 optionally substituted aromatic sulphonic acid.

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2. Method of producing a compound of formula (III) according

to claim 1, by providing a compound of formula (I):



wherein

R is a removable substituent known per se, preferably (C₁-C₈)alkylcarbonyl, or optionally substituted phenylcarbonyl, or optionally substituted benzylcarbonyl;

R₁ is a glycoside donor preferably a 1-halogen derivative, or an imidate preferably a trichloromethyl derivative, or a thioalkyl derivative preferably thiomethyl;

further providing a silylated base of formula (II):



wherein R₂ is a protecting group, preferably a trimethylsilyl (TMS)-residue;

reacting the compound of formula (I) and the compound of formula (II) together in a suitable anhydrous solvent and in the presence of a suitable catalyst, whereby the compound of formula (III) is obtained, characterized in that said catalyst is selected from the group comprising a salt of an aliphatic sulphonic acid and/or the salt of a optionally substituted aromatic sulphonic acid.

3. Method according to claim 1 or 2, characterized in that the catalyst used in said reaction is a salt of an aliphatic sulphonic acid, preferably of methylsulphonic acid or of ethylsulphonic acid, or a salt of a fluorinated aliphatic sulfonic acid, preferably of trifluoromethane-sulfonic acid, pentafluoroethyl-sulfonic acid, or heptafluoropropyl-sulfonic acid.

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4. Method according to claim 3, characterized in that the catalyst is a salt of methylsulphonic acid and/or the salts of trifluoromethanesulfonic acid.

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5. Method according to any one of the claims 1-4, characterized in that the catalyst is an alkali salt or earth alkali salt, preferably a lithium salt, preferably lithium methylsulphonic acid or lithium-trifluoromethanesulfonate.

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6. Method according to claim 1 or 2, characterized in that the catalyst is chosen from the salts comprising salts of scandium preferably $\text{Sc}(\text{OTf})_3$; or salts of copper preferably $\text{Cu}(\text{OTf})_2$; or salts of magnesium preferably $\text{Mg}(\text{OTf})_2$.

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7. Method according to claim 1 or 2, characterized in that the catalyst is chosen from the salts comprising optionally substituted, aromatic sulphonic acids, preferably the alkali salts and earth alkali salts thereof.

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8. Method according to claim 7, characterized in that the catalyst is chosen from the salts comprising alkali salts and earth alkali salts of benzenesulphonic acid, toluenesulphonic acid, and known related acids, preferably the lithium salt of said aromatic sulphonic acids.

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9. Method according to any one of the claims 1-8, characterized in that the solvent to carry out the reaction is chosen from the group comprising chlorinated solvents, preferably dichloromethane, dichloroethane, chloroform, chlorobenzene; or toluene, xylol, acetonitril and/or propylene carbonate or related solvents, and preferably is a chlorinated solvent.

30

10. Method according to any one of the claims 1-9, characterized in that the catalyst is lithium-trifluoromethanesulfonate

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and the solvent is a chlorinated solvent, preferably dichloromethane, dichloroethane, chloroform and/or chlorobenzene.

11. Method according to any one of the claims 1-10, characterized in that the removable substituent R is (C₁-C₄)alkylcarbonyl, or optionally substituted phenylcarbonyl or benzylcarbonyl, preferably phenylcarbonyl, tolylcarbonyl, xylylcarbonyl; preferably acetyl or p-chloro-phenylcarbonyl.
- 10 12. Method according to any one of the claims 1-11, characterized in that the removable substituent R1 is -O-acyl (C₁-C₄), -O-alkyl (C₁-C₄) or chlorine, preferably -O-(O)CCH₃ or chlorine, preferably chlorine.

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Summary

Method of producing 2'-deoxy-5-azacytidine (Decitabine) by providing a compound of formula (I):

5



wherein

R is a removable substituent known per se; and R₁ is a glycoside donor preferably a 1-halogen derivative, an imidate preferably the trichloromethyl derivative, or a thio-alkyl derivative; further providing a silylated base of formula (II):

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15

wherein R₂ is a protecting group, preferably a trimethylsilyl TMS)-residue; reacting the compound of formula (I) and the compound of formula (II) together in a suitable anhydrous solvent and in the presence of a suitable catalyst; and removing the substituents R from the compound obtained in order to obtain the compound 2'-deoxy-5-azacytidine (Decitabine), characterized in that said catalyst is selected from the group comprising a salt of an aliphatic sulphonic acid and/or the salt of a optionally substituted aromatic sulphonic acid.

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