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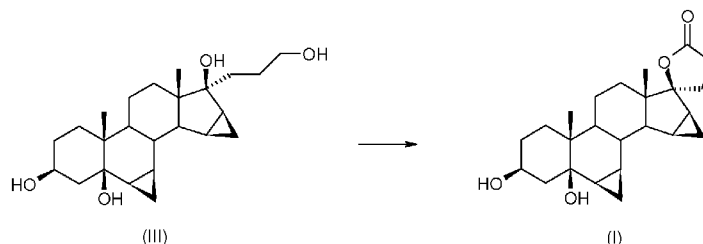
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ML, MR, NE, SN, TD, TG).**Declarations under Rule 4.17:**

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(54) Title: PROCESS FOR PREPARING AN INTERMEDIATE USEFUL IN THE PRODUCTION OF DROSPIRENONE

(57) Abstract: A process is described wherein, using 17 α -(3-hydroxypropyl)-6 β ,7 β ,15 β ,16 β - dimethylene-5 β -androstane-3 β ,5,17 β -triol (III) as starting product, there is obtained 3 β ,5-dihydroxy-6 β ,7 β ,15 β ,16 β -dimethylene-5 β -17 α -pregna-21, 17-carbolactone (I), a useful intermediate in the synthesis of the compound drospirenone, having contraceptive action: (Formula III & I) (III) (I)

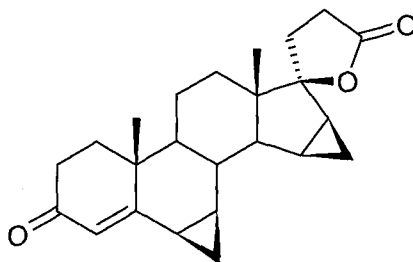
PROCESS FOR PREPARING AN INTERMEDIATE USEFUL IN THE PRODUCTION OF DROSPIRENONE

Field of the invention

The present invention relates to the field of processes for the synthesis of steroids, and in particular to a process for the preparation of an intermediate useful in the production of drospirenone on an industrial scale.

Background of the invention

The below-reported compound of formula (II), the chemical name of which is 6 β ,7 β ;15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone, is commonly indicated by the name drospirenone:

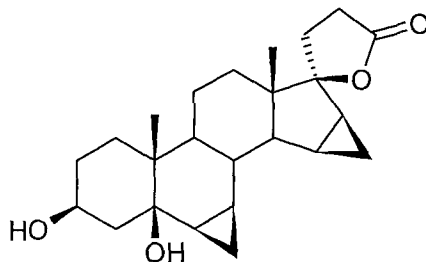


(II)

Drospirenone is a synthetic steroid with progestogenic, antimineralocorticoid and antiandrogenic action; thanks to these characteristics, it has been used for some time in the preparation of pharmaceutical compositions with contraceptive action for oral administration.

Various processes for the preparation of drospirenone are known in literature.

One of these processes is described in patent US 4,416,985 and passes through the intermediate 3 β ,5-dihydroxy-6 β ,7 β ;15 β ,16 β -dimethylene-5 β ,17 α -pregna-21,17-carbolactone, having the below-reported formula (I):



(I)

This intermediate is obtainable according to the procedure reported in example

5(b) of said patent, and can then be transformed into drospirenone, as described in example 5(c) of the said patent, by treatment with chromium trioxide and pyridine in water at 50 °C; alternatively, the conversion to drospirenone can be carried out with gaseous oxygen in the presence of a catalytic system consisting of a palladium salt in oxidation state (+2) and an organic base in the presence of molecular sieves, according to the procedure described in international patent application PCT/IB2013/052918 assigned to the present Applicant.

Example 5(b) of US 4,416,985 describes a procedure suitable for the preparation of compound (I) on a laboratory scale, but not at an industrial level. Even after chromatographic purification, the product obtained in this example is still significantly impure, presenting itself in the form of an oil, while the pure product is a solid with a melting point higher than 126 °C. The yield that can be calculated from this example, equal to about 85%, is thus only fictitious, since it is not possible to determine the actual content of the desired product in the oil.

There is thus a need in the sector for an improved process for the synthesis of the cited intermediate (I).

The aim of the present invention is to provide a synthesis route that allows the preparation of high quality 3 β ,5-dihydroxy-6 β ,7 β ;15 β ,16 β -dimethylene-5 β ,17 α -pregna-21,17-carbolactone (I) with a process transferable to an industrial plant.

Summary of the invention

This aim is achieved with the present invention, which relates to a process for the production of 3 β ,5-dihydroxy-6 β ,7 β ;15 β ,16 β -dimethylene-5 β ,17 α -pregna-21,17-carbolactone which consists in the oxidation of 17 α -(3-hydroxypropyl)-6 β ,7 β ;15 β ,16 β -dimethylene-5 β -androstane-3 β ,5,17 β -triol with an oxidant system comprising gaseous oxygen in the presence of a copper compound wherein the metal has oxidation state +1 and of the 2,2,6,6-tetramethylpiperidine-1-oxyl radical or a derivative thereof, in an organic solvent at a temperature of between 20 and 80 °C.

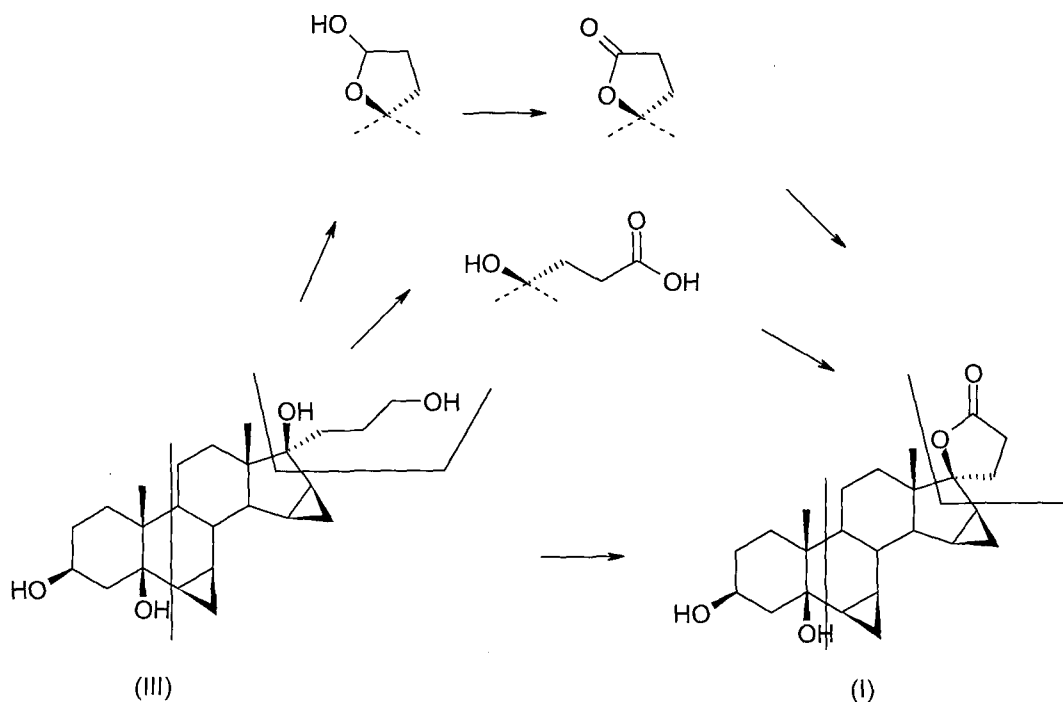
Detailed description of the invention

The Applicant has developed a new, extremely simple, process, for the obtainment of 3 β ,5-dihydroxy-6 β ,7 β ;15 β ,16 β -dimethylene-5 β ,17 α -pregna-21,17-carbolactone, compound (I), which uses gaseous oxygen as an oxidant in the presence of a cuprous compound (i.e. wherein the copper is present in oxidation state +1) and of

the 2,2,6,6-tetramethylpiperidine-1-oxyl radical, better known in the sector by the abbreviation TEMPO, or a derivative thereof.

The oxidation of alcohols with oxygen and the TEMPO/cuprous compound catalytic system is described in the article "Oxidation of alcohols to aldehydes with oxygen and cupric ion, mediated by nitrosonium ion" by M. F. Semmelhack *et al.*, *J. Am. Chem. Soc.*, 1984, 106 (11), pages 3374–3376. From the reading of the article, however, a chemist with the objective of synthesizing compound (I) would not have had a helpful suggestion for embodying the present invention.

Indeed, the transformation involved in obtaining 3 β ,5-dihydroxy-6 β ,7 β ;15 β ,16 β -dimethylene-5 β ,17 α -pregna-21,17-carbolactone (I) from 17 α -(3-hydroxypropyl)-6 β ,7 β ;15 β ,16 β -dimethylene-5 β -androstande-3 β ,5,17 β -triol (hereinafter also indicated as compound (III)) is synthesized in the following scheme:



The cited article clearly indicates that with the oxidizing system that uses cuprous compounds only the transformation from an alcohol to the corresponding aldehyde is obtained, without further oxidation of the latter to acid (p. 3374). In addition, the article does not provide any example or indication of a possible oxidation by lactol to lactone (transformation represented in the top row of above-reported reaction scheme). Finally, according to the article, acceptable reaction yields are only obtained with allyl or benzyl alcohols, while primary aliphatic alcohols, such as the

terminal -OH group of the propyl chain in position 17 of compound (III), do not lead to a complete reaction (p. 3375).

As a consequence of these teachings, and in particular of the fact that the aldehyde formed by oxidation of a primary alcohol does not further proceed to carboxylic acid in the described reaction conditions, would have convinced a person skilled in the art on the impossibility of obtaining the lactone ring 21,17 with the oxygen/TEMPO/cuprous compound oxidant system.

The present inventors have on the other hand discovered, that, surprisingly, the reaction in these conditions proceeds in a quantitative manner up to lactone.

The first component of the oxidizing system is gaseous oxygen. Gaseous oxygen can be supplied into the reaction vessel as pure oxygen, air, or a synthetic mixture of oxygen with an inert gas (for example, the so-called synthetic air, widely used in the medical field); oxygen, in any one of these forms, can be used in static conditions, i.e. in a closed vessel containing a gaseous atmosphere either of oxygen or containing it, or in conditions of slight flow of the gaseous atmosphere itself. The operating pressure is between ambient pressure (approximately 1 bar) and 10 bar.

The second component of the oxidizing system is a cuprous compound such as CuCl, CuBr, CuI, or the (1,4-Diazabicyclo[2.2.2]octane)copper(I)chloride complex; CuCl is preferably used for the purposes of the invention. The cuprous compound is used in amounts by weight of between 1% and 100% with respect to the substrate to be oxidized.

The third component of the oxidizing system is the compound known as TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl radical) or a derivative thereof. The TEMPO derivatives of possible use are 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl radical, 4-methoxy-2,2,6,6-tetramethylpiperidine-1-oxyl radical, 4-(benzoyloxy)-2,2,6,6-tetramethylpiperidine-1-oxyl radical, 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxyl radical and 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl radical. This component is used in an amount of between 5 and 50% by weight, preferably between 5% and 25% by weight, with respect to the substrate to be oxidized.

TEMPO or its derivatives can be used as such or supported on inert materials such as such for example silica gel or polymer matrices.

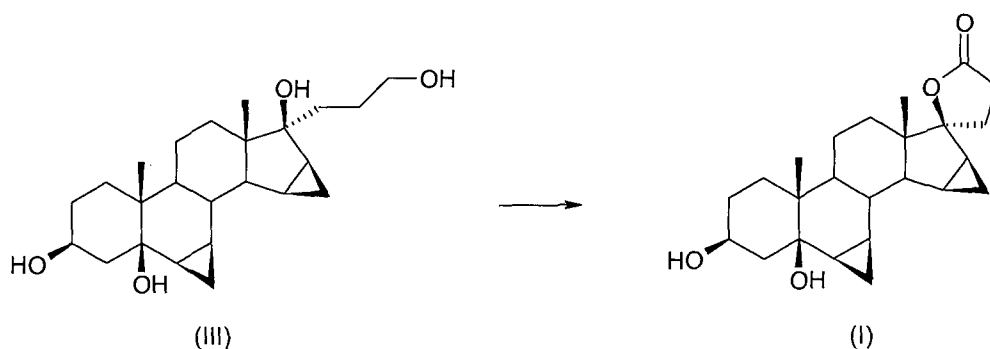
The solvent used must obviously be inert in the reaction conditions; it is possible to use a solvent selected from ethyl ether, diisopropyl ether, methyl t-butyl ether, tetrahydrofuran, methyltetrahydrofuran, ethyl acetate, isopropyl acetate, butyl acetate, heptane, hexane, cyclohexane, toluene, xylene, methylene chloride, 1,1-dichloroethane, 1,1,2-trichloroethane, acetone, methyl ethyl ketone, methyl isobutyl ketone, acetonitrile, dimethylformamide, dimethylacetamide, dimethylsulphoxide, chlorobenzene, N-methyl-pyrrolidone or mixtures thereof; dimethyl sulfoxide (DMSO) is preferred.

The oxidation reaction can be carried out at a temperature of between 10 and 80 °C, and preferably between 25 and 45 °C, for a time of between 18 and 48 hours, preferably between 20 and 40 hours.

The crude compound (I) obtained with the present process is purifiable with techniques known to persons skilled in the art; for example, the purification can be obtained by crystallization.

The invention will be further illustrated by the following examples, which are provided by way of an illustrative and non-limiting example of the present invention. The reagents used in the examples are commonly available commercially and are used without the need for preventive purifications. In the examples, the percentages are to be understood as by weight unless otherwise indicated.

EXAMPLE 1



Into a 3-litre flask are loaded 50 g of 93% 17 α -(3-hydroxypropyl)-6 β ,7 β ;15 β ,16 β -dimethylene-5 β -androstane-3 β ,5,17 β triol (II) into 500 ml of dimethyl sulfoxide (DMSO) at room temperature.

TEMPO (4 g) and cuprous chloride (2.53 g) are added and the system is brought to 40 °C in an oxygen atmosphere. The system is kept under stirring in these

conditions for 16 h.

The solution is cooled to 20-25 °C and a solution obtained by dissolving 70 g of ammonium chloride in 500 ml of water is added, and stirred for 30 minutes.

500 ml of methylene chloride are added and, under agitation, air is blown for 30 minutes until the formation of a blue solution is observed.

The phases are separated by washing the organic phase, in sequence, with a 2M solution of ammonium chloride, with water, with a 2% aqueous solution of sodium bisulphate and finally with a 4% aqueous solution of sodium chloride.

The organic phase is dry concentrated (rotavapor distillation) thus obtaining 55 g of crude product.

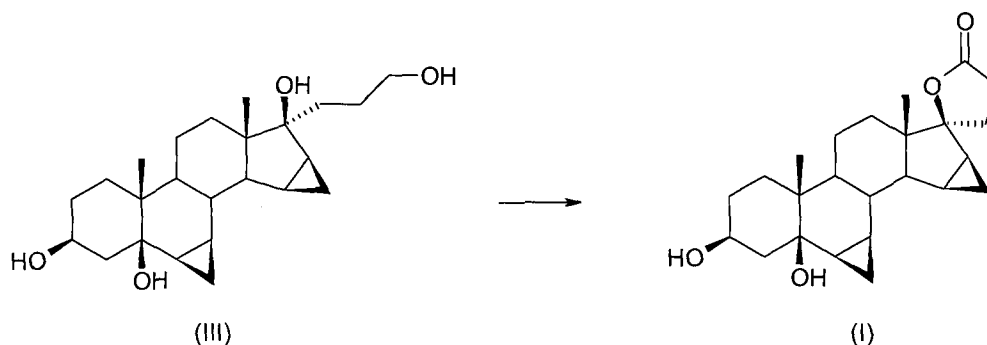
The product obtained is crystallised by isopropyl acetate thus obtaining, after drying at constant weight, 37.2 g of the desired compound (I).

1 g of compound (I), chromatographed on silica gel for analytical purposes only, provides the following analytical data:

- NMR(D₂O): 4.82 ppm, broadened singlet, 1H on OH, disappears by deuteration; 4.35 ppm, broadened singlet, 1H on OH, disappears by deuteration; 3.85 ppm, broadened singlet, 1H, H(3).
- IR(KBr): 1770 cm⁻¹; 3419 cm⁻¹
- Ms(EI): [M⁺]+1 = 387; [M⁺]+1-H₂O = 369; [M⁺]+1-2H₂O = 351
- Melting point: 126-129 °C
- HLC purity (195 nm): 96%.

CLAIMS

1. Process for preparing 3 β ,5-dihydroxy-6 β ,7 β ;15 β ,16 β -dimethylene-5 β ,17 α -pregna-21,17-carbolactone (I) by oxidation of 17 α -(3-hydroxypropyl)-6 β ,7 β ,15 β ,16 β -dimethylene-5 β -androstane-3 β ,5,17 β -triol (II):



with an oxidizing system comprising gaseous oxygen in the presence of a copper compound wherein the metal has oxidation state +1 and of the 2,2,6,6-tetramethylpiperidine-1-oxyl radical or a derivative thereof, in an organic solvent at a temperature between 20 and 80 °C.

2. Process according to claim 1, wherein oxygen is used in the form of pure oxygen, air, or a synthetic mixture of oxygen with an inert gas, under static conditions or under light flow conditions, at a pressure of between 1 and 10 bar.
3. Process according to any one of claims 1 or 2, wherein said copper compound is selected from CuCl, CuBr, CuI and the (1,4-Diazabicyclo[2.2.2]octane)copper(I)chloride complex.
4. Process according to any one of the preceding claims, wherein the cuprous compound is used in amounts between 1% and 100% by weight with respect to 17 α -(3-hydroxypropyl)-6 β ,7 β ,15 β ,16 β -dimethylene-5 β -androstane-3 β ,5,17 β -triol.
5. Process according to any one of the preceding claims, wherein said derivative of the 2,2,6,6-tetramethylpiperidine-1-oxyl radical is selected from 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl radical, 4-methoxy-2,2,6,6-tetramethylpiperidine-1-oxyl radical, 4-(benzoyloxy)-2,2,6,6-tetramethylpiperidine-1-oxyl radical, 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxyl radical and 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl radical.

6. Process according to any one of the preceding claims, wherein the 2,2,6,6-tetramethylpiperidine-1-oxyl radical or a derivative thereof are used in amounts between 5% and 50% by weight with respect to 17 α -(3-hydroxypropyl)-6 β ,7 β ,15 β ,16 β -dimethylene-5 β -androstane-3 β ,5,17 β -triol.
- 5 7. Process according to claim 6, wherein the 2,2,6,6-tetramethylpiperidine-1-oxyl radical or a derivative thereof are used in amounts between 5% and 25% by weight with respect to 17 α -(3-hydroxypropyl)-6 β ,7 β ,15 β ,16 β -dimethylene-5 β -androstane-3 β ,5,17 β -triol.
- 10 8. Process according to any one of the preceding claims, wherein the solvent is selected from ethyl ether, diisopropyl ether, methyl t-butyl ether, tetrahydrofuran, methyltetrahydrofuran, ethyl acetate, isopropyl acetate, butyl acetate, heptane, hexane, cyclohexane, toluene, xylene, methylene chloride, 1,1-dichloroethane, 1,1,2-trichloroethane, acetone, methyl ethyl ketone, methyl isobutyl ketone, acetonitrile, dimethylformamide, dimethylacetamide, 15 dimethylsulphoxide, chlorobenzene, N-methyl-pyrrolidone or mixtures thereof.
9. Process according to any one of the preceding claims, wherein the oxidation reaction is carried out at a temperature between 10 and 80 °C for a time between 18 and 48 hours.
- 20 10. Process according to claim 9, wherein said reaction is carried out at a temperature between 25 and 45 °C for a time between 20 and 40 hours.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/053158A. CLASSIFICATION OF SUBJECT MATTER
INV. C07J75/00
ADD.

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)
C07J

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)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/061309 A1 (IND CHIMICA SRL [IT]; COSTANTINO FRANCESCA [IT]; LENNA ROBERTO [IT]; P) 15 June 2006 (2006-06-15) claim 1 page 6 -----	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2013/053158

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