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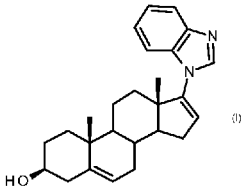

(I)

(57) Abstract: A process for the synthesis of 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene is described, a compound also known as Galeterone and used in the treatment of prostate cancer, having the formula (I) given below.

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PROCESS FOR THE PREPARATION OF GALETERONE

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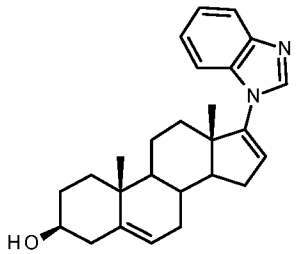
FIELD OF THE INVENTION

The present invention relates to the field of processes for the synthesis of active ingredients for pharmaceutical use, and in particular to a process for the industrial-scale preparation of 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene, also known as Galeterone, an intermediate useful for the treatment of prostate cancer, a compound having the formula given below:

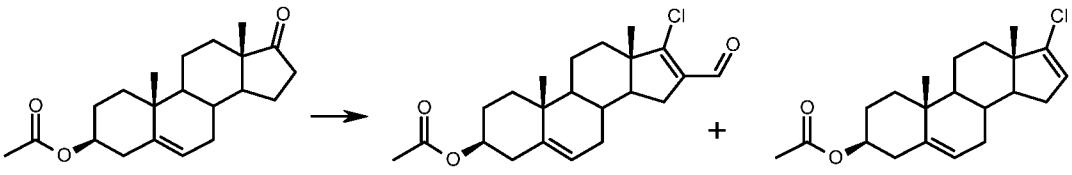


PRIOR ART

Galeterone, 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene was first described in article "Three dimensional pharmacophore modeling of human CYP17 inhibitors. Potential agents for prostate cancer therapy", O. Omoshile *et al*, J. Med. Chem. **2003**, *46* (12), pages 2345-2351, in figure 1 on page 2347, with the code VN/124-1*. The article does not report an experimental description of the preparation of the molecules object of the text, among which Galeterone, but refers to several other publications for the synthesis.

Among the articles cited in Omoshile's article *et al* is significant "Novel 17-azolyl steroids, potent inhibitors of human cytochrome 17α-Hydroxylase-$C_{17,20}$-lyase ($P450_{17\alpha}$): potential agents for the treatment of prostate cancer", V. C. O. Njar *et al, J. Med. Chem.*, **1998**, *41* (6), pages 902-912, which describes the sequence of reactions that, explicitly recalled and described in J. Med. Chem. **2005**, 48, 2972-2984, leads to obtaining Galeterone.

The first synthetic step is described in "Novel C-17-Heteroaryl steroidal CYP17 inhibitors/antiandrogens: synthesis, in vitro biological activity, pharmacokinetics, and antitumor activity in the LAPC4 human prostate cancer xenograft model", V. D. Handratta et al., *J. Med. Chem.*, **2005**, *48* (8), pages 2972-2984. This synthetic step consists of a Vilsmeier-Haack reaction which uses as a starting material 3β-acetoxyandrost-5-en-17-one (1) to yield 3β-acetoxy-17-chloroandrost-5,16-diene (2) and 3β-acetoxy-17-chloro-16-formylandrost-5,16-diene (3), as shown in the following scheme:

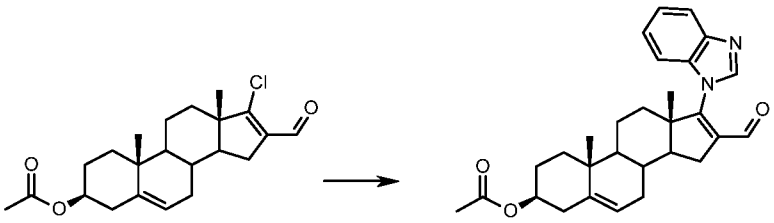


(1) (3) (2)

Only intermediate (3), 77% of the reaction yield, is useful for the subsequent reactions while compound (2), 11.4% of the reaction yield, must be discarded.

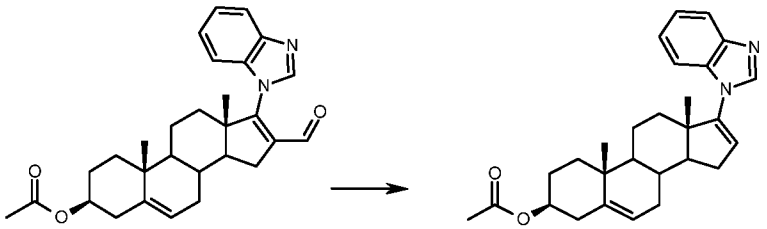
In the above article by Njar *et al.*, the separation of the two reaction products is obtained by flash chromatography (FCC) on silica gel.

The synthesis described in the article by Handratta *et al.* starts from compound (3) prepared as described above; compound (3) is reacted with benzimidazole, thus yielding the intermediate 3β-acetoxy-17-(1H-benzimidazol-1-yl)-16-formylandrosta-5,16-diene (4):



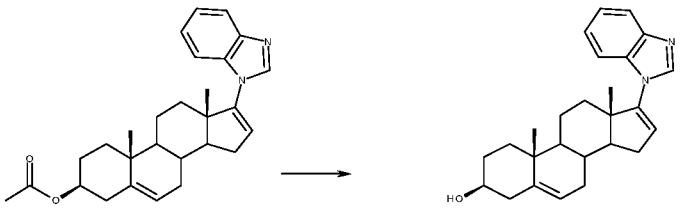
(3) (4)

The purification of intermediate (4) is obtained by flash chromatography (FCC) on silica gel. Intermediate (4) is then thermally deformylated using 10% palladium on carbon (Pd/C) as catalyst in an amount equal to 50% of the weight of intermediate (4):



(4) (5)

The purification of intermediate (5) is obtained by flash chromatography (FCC) on silica gel. Finally, intermediate (5) is deacetylated in bases and the crude Galeterone (6) is crystallized from the ethyl acetate/methanol mixture:



(5) (6)

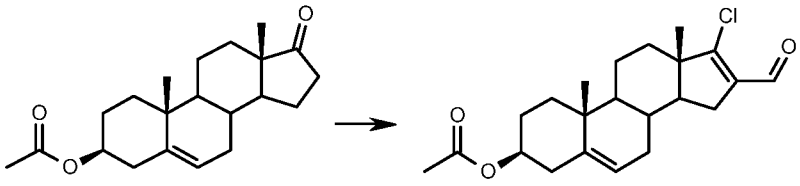
As with the reactions above, no quality data (titre and HPLC purity) is provided in the experimental descriptions.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a synthesis route for the preparation of Galeterone, that is simpler than the prior art processes and industrially applicable.

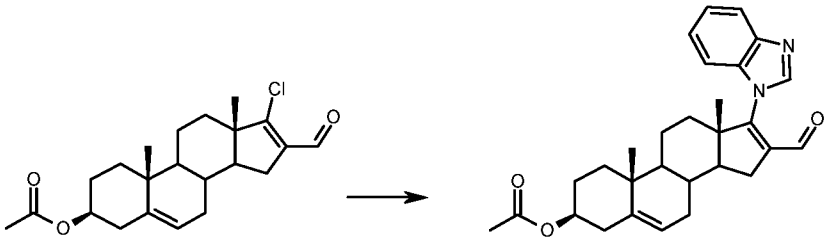
This object is achieved with the present invention, which in a first aspect thereof relates to a process for the synthesis of Galeterone comprising the following steps:

a) reaction between 3β-acetoxyandrost-5-en-17-one (1) and $POCl_3$ to yield 3β-acetoxy-17-chloro-16-formylandrost-5,16-diene (3):



(1) (3)

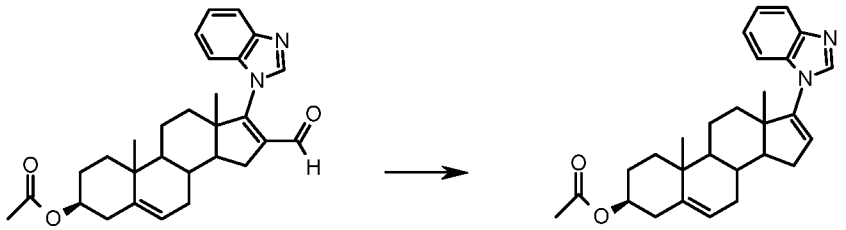
b) reaction of 3β-acetoxy-17-chloro-16-formylandrost-5,16-diene (3) with benzimidazole, to yield the intermediate 3β-acetoxy-17-(1H-benzimidazol-1-yl)-16-formylandrosta-5,16-diene (4):



(3) (4)

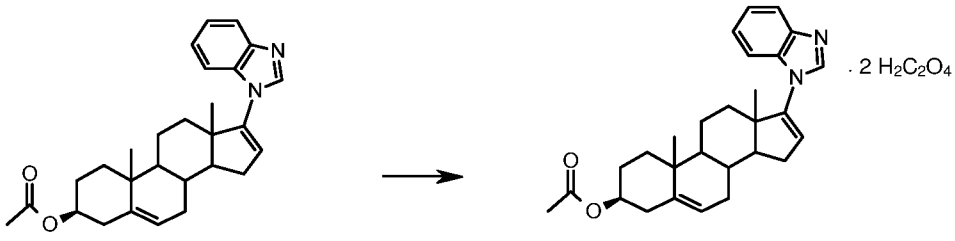
c) reaction, at a temperature above 100 °C, of 3β-acetoxy-17-(1H-benzimidazol-1-yl)-16-formylandrosta-5,16-diene (4) with palladium on carbon as a catalyst in an amount between 5 and 20% by weight compared to intermediate (4), adding the catalyst when the mixture is at a temperature below 100 °C, to yield the intermediate (5), 3β-acetoxy-17-

(1H-benzimidazol-1-yl)androsta-5,16-diene:



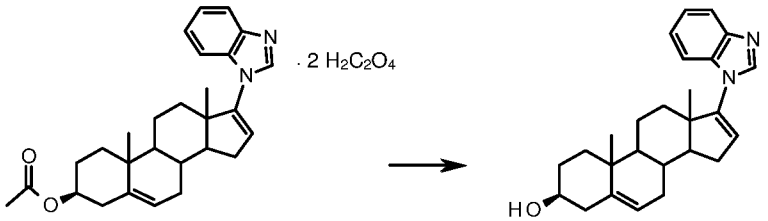
(4) (5)

d) reaction of the intermediate (5) with oxalic acid to yield compound (V), 3β-acetoxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene dioxalate:



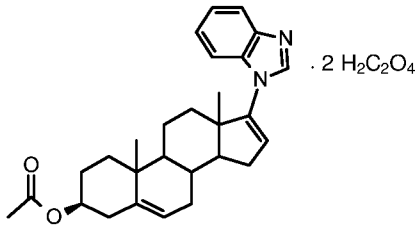
(5) (V)

e) reaction of the intermediate (V) with a base to yield 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene, Galeterone (6):



(V) (6)

A further object of the invention is intermediate (V), 3β-acetoxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene dioxalate:



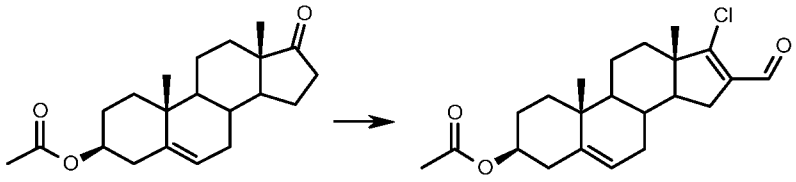
(V)

DETAILED DESCRIPTION OF THE INVENTION

In its first aspect, the invention relates to an industrially applicable process for the synthesis of Galeterone, comprising steps a)-e) described in detail hereinafter.

In the present description and in the claims, in case of a discrepancy between the chemical name of a compound and the formula given for the same, the latter must be regarded as correct.

Step a) consists in the reaction of 3β-acetoxyandrost-5-en-17-one (1) and $POCl_3$, wherein a mixture of 3β-acetoxy-17-chloro-16-formylandrost-5,16-diene (3) and 3β-acetoxy-17-chloroandrost-5,16-diene (2) is obtained:



(1) (3)

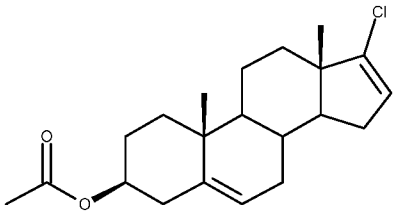
Compound (1), 3β-acetoxyandrost-5-en-17-one is also known by the usage name prasterone acetate, which will be used in the rest of the description.

The reaction is conducted in a single solvent selected from arylalkylamides and dialkylamides, such as N-phenyl-N-methylformamide or, preferably, N,N-dimethylformamide (also referred to simply as dimethylformamide or its abbreviation DMF) in the presence of an inorganic reagent such as phosphorus oxychloride, $POCl_3$. 3 to 6 moles, preferably 4.5 moles of inorganic reagent per mole of prasterone acetate are used for the reaction.

In order to carry out this step, the necessary amount of inorganic reagent is dissolved in the solvent, and the resulting solution is poured dropwise, over a time of between 15 minutes and 1.5 hours, on the suspension obtained by mixing the same solvent and prasterone acetate, keeping the temperature between 15 and 50 °C; preferably, the solution of the inorganic compound in DMF is poured dropwise on the suspension of prasterone acetate in DMF over a time of between 15 minutes and 45 minutes, keeping the temperature between 15 and 40 °C. The total amount of amide solvent is higher than 10 moles per mole of prasterone acetate, preferably at least 16 moles per mole of prasterone acetate. Thereafter, in order to promote the reaction, the mixture temperature is brought to between 60 and 90 °C, preferably between 70 and 80 °C.

The overall reaction time is between 1 and 5 hours, preferably between 2 and 4 hours.

As in the prior art method described above, a non-formylated by-product of the compound of interest (3) is formed in the reaction, i.e. the compound having the following formula (2):

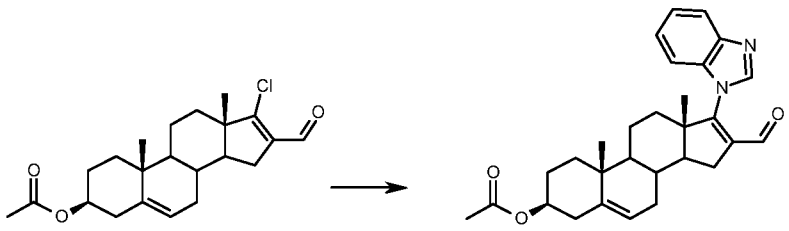


(2)

Unlike said known method, however, in the process of the invention compound (3) is obtained to a largely predominant extent, with minimal amounts of by-product (2), so that chromatographic separation is not required.

Intermediate (3) is then purified by crystallization from an organic solvent selected from methanol, ethanol, isopropanol, chloroform and dichloromethane, either pure or mixed with each other; preferred solvents for this purification are the methanol/dichloromethane mixture or pure methanol.

In step b), intermediate (3) obtained as described above is reacted with benzimidazole in the presence of an alkali metal carbonate or alkaline earth metal carbonate to yield intermediate (4), 3β-acetoxy-17-(1H-benzimidazol-1-yl)-16-formylandrosta-5,16-diene:



(3) (4)

The amount in moles of benzimidazole used for the reaction is of between 1.0 and 1.75 moles, preferably between 1.05 and 1.25 moles, with respect to the moles of intermediate (3).

The solvent for the reaction is selected from dimethylacetamide, dimethylsulfoxide and, preferably, dimethylformamide.

The volume amount of organic solvent used, measured in millilitres, is between 4 and 6 times with respect to the amount by weight, measured in grams, of intermediate (3) reacted; preferably, the amount by volume of organic solvent used is of between 4.5 and 5.5 times

the amount by weight of intermediate (3) reacted.

The volume of water used to quench the reaction is between 3 and 5 times, preferably between 3.5 and 4.5 times the volume of the organic solvent used in reaction.

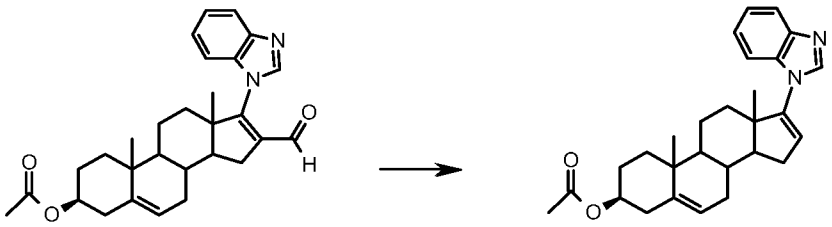
The carbonate is selected from sodium, calcium and, preferably, potassium carbonate.

The reaction temperature is between 65 and 90 °C, preferably between 75 and 85 °C.

The reaction time is between 1 and 3 hours, preferably between 1 and 2 hours.

These reaction conditions make possible obtaining an intermediate (4) having such a quality that it can be used for the subsequent reactions without the need for additional purification, in particular chromatographic purifications.

Step c) of the process of the invention consists in the reaction of intermediate (4) to yield intermediate (5), 3β-acetoxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene, referred to hereinafter as Galeterone acetate:



(4) (5)

This step is conducted by reacting intermediate (4) with palladium on carbon (Pd/C) as a catalyst at temperatures above 100 °C. Laboratory tests with catalysts different from Pd/C, such as platinum on carbon (Pt/C), ruthenium on carbon (Ru/C), rhodium on carbon (Rh/C) and palladium on alumina (Pd/Al_2O_3), did not provide useful results.

The amount by weight of catalyst is of between 5% and 20%, with respect to the weight of intermediate (4) reacted, and the percentage of palladium in the catalyst can range between 5 and 10%.

The reaction solvent is selected from: Dowtherm® A (an eutectic mixture of diphenyl and diphenyl oxide; Dowtherm® is a registered trademark of Dow Corning Corporation); phthalic esters of alcohols selected from linear or branched aliphatic C_1-C_{10} alcohols, aromatic alcohols and cyclic alcohols, symmetrical or asymmetrical, such as dimethylphtalate, diethylphtalate, dibutyl phthalate, dicyclohexyl phthalate, butyl benzyl phthalate, diisobutyl phthalate; benzonitrile, dimethylformamide and dimethylacetamide; said solvents can be pure or mixed with one another. The preferred solvent for this reaction

is Dowtherm® A.

The reaction temperature depends on the boiling point of the solvent and the reaction time is reduced significantly for reaction temperatures higher than 200 °C.

Preferably, the reaction temperature is higher than 200 °C and the reaction time ranges between 1 and 12 hours, preferably between 1 and 6 hours.

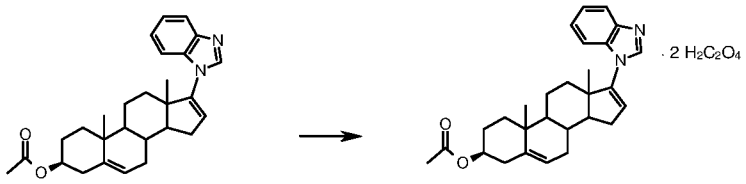
Laboratory tests with solvents having a boiling temperature lower than those mentioned above, such as xylene, did not provide useful results.

Although the reaction temperature in this step is higher than 100 °C, and preferably higher than 200 °C, the catalyst must be added to the other components of the reaction mixture at a temperature lower than 100 °C, preferably lower than 50 °C; the inventors have observed that the addition of the catalyst when the temperature of the mixture is higher than 100 °C leads to an increase of impurities in the final product.

In preparation for the next step in the process of the invention, Galeterone acetate (5) can be separated from the crude reaction mixture using standard techniques known to the man skilled in the art; alternatively, after the elimination of the metal catalyst alone by filtration, the next step can be carried out by adding oxalic acid directly to the organic solution obtained in step c), which contains Galeterone acetate (5).

If the oxalic acid is added to the solution where Galeterone acetate (5) has formed, after eliminating most of the metal catalyst by filtration, the solution can be treated with a metal scavenging agent to eliminate any residual amounts of metal possibly present; suitable for the purpose are the products of the QuadraSil® family sold by Sigma-Aldrich, in particular the QuadraSil® MP product, consisting of spherical particles of macroporous silica functionalized to remove residual metals from products containing them (QuadraSil® is a registered trademark of the company Johnson Matthey).

The formation of dioxalate (V) takes place, in step d) of the process, by reaction of Galeterone acetate (5) with oxalic acid in an organic solvent solution, from which dioxalate separates as filterable solid:

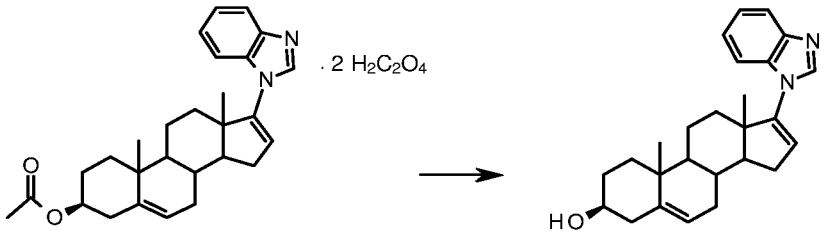


(5) (V)

The amount of oxalic acid used is at least two moles per mole of intermediate (4) used in the previous step. The oxalic acid used is anhydrous or, preferably, dihydrate.

Intermediate (V) is separated from the reaction mixture by filtration, washed with a suitable solvent, e.g. toluene, and dried (conveniently under reduced pressure) before the next step.

The last step in the process of the invention, e), is the reaction from intermediate (V) to Galeterone (6):



(V) (6)

This reaction is conducted by adding a base to intermediate (V) suspended in an organic solvent inert in the reaction conditions; the base can be added either pure or dissolved in a solvent.

The organic solvent in which intermediate (V) is suspended is selected from xylene, toluene, cyclohexane, heptane, hexane and methylene chloride, either pure or mixed with each other; the preferred solvent for this operation is pure methylene chloride.

The base is selected from sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, cesium carbonate or potassium carbonate dissolved in water or in an alcohol such as methanol, ethanol, isopropanol, preferably sodium hydroxide dissolved in methanol.

The invention will be further described by the following examples.

Abbreviations R_f and RRT adopted in the examples indicate the delay factor in thin layer chromatography (TLC) and the relative retention time of a compound in high pressure liquid chromatography (HPLC), respectively.

METHODS AND TEST CONDITIONS

NMR

Spectrometer NMR JEOL 400 YH (400 MHz); Tubes NMR Aldrich® ColorSpec®;

JEOL Delta Software v5.1.1;

Spectra recorded in deuterated chloroform Sigma-Aldrich: Chloroform-d, D 99.8% atomic, containing 0.1% (v/v) tetramethylsilane (TMS) as internal standard; and Chloroform-d,

"100%", D 99.96% atomic, containing 0.03% (v/v) TMS.

MS

HPLC-mass system AB Sciex API 2000 LC/MS/MS;

Samples injected directly and chemically ionized (CI) with formic acid.

DSC

Instrument Perkin Elmer mod. Diamond;

Perkin Elmer Standard aluminium capsules and lids, code 02190041;

Scanning rate: 10 °C/min;

Temperature range: 20 °C to 200 °C.

IR

Thermo Scientific Nicolet 6700 spectrometer;

FT-IR spectra recorded in KBr (solid) and smart-iTR-diffuse reflectance (ATR);

Potassium bromide Sigma-Aldrich Code 221864 (for IR analysis).

HPLC

Chromatographic system Agilent model 1200 and 1260;

Detector UV MODEL 1260 DAD VL and laser detector 1290 Infinity ELSD;

HPLC method used to analyse Galeterone samples;

Mobile phase A: methanol, Mobile phase B: water;

Gradient method:

time (minutes)	Mobile phase A	Mobile phase B
0.00	75%	25%
15.00	75%	25%
20.00	90%	10%
30.00	90%	10%
31.00	75%	25%
35.00	75%	25%

Chromatographic conditions:

Column:	Ascentis Express C18; 150 mm x 4.6 mm; 2.7µm
Flow:	1.0 mL/minute
Detector (UV):	254 nm and 280 nm
Temperature:	40 °C
Injection volume:	5.0 µL
Sample:	1.0 g/L in methanol

LC/Ms/Ms system

Chromatographic system Agilent model 1100 with UV DAD detector connected to an API 2000 mass by Applied Biosystem.

TLC

MERCK: TLC silica gel 60 F_{254} Aluminium sheets 20 x 20 cm, code 1.0554.0001.

HPTLC

MERCK: HPTLC silica gel 60 F_{254} with concentration zone 10 x 2.5 cm, code 1.13727.0001.

TLC detectors

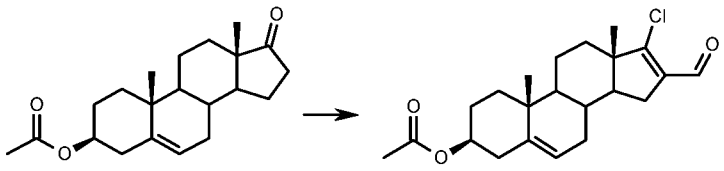
Acid solution of cerium phosphomolybdate.

Preparation: 25 g of phosphomolybdic acid hydrate (Aldrich P7390), 10 g of cerium (IV) sulfate hydrate (Aldrich 31606) and 600 mL of water are stirred to dissolution with 60 mL of 95-98% sulfuric acid (Aldrich 258105); this is brought to a final volume of 1000 mL with water; the sheet is then impregnated with the solution, then heated to blue staining.

UV light at 254 and 366 nm.

EXAMPLE 1

This example relates to step a) of the process of the invention:



(1) (3)

To a flask under nitrogen are added 423 mL of dimethylformamide (DMF) at 20 < T < 25 °C, then it is cooled to 0 < T < 2 °C. 208.8 g of $POCl_3$ are added slowly under stirring keeping T < 20 °C. The resulting yellow solution is stirred for 20 minutes at T = 10 °C.

To a second flask under nitrogen are added 100 mL DMF and 100 g prasterone acetate (1), obtaining a dense suspension.

Under stirring, the solution with $POCl_3$ is transferred into the prasterone suspension over 15 minutes, keeping 20 < T < 30 °C.

Once the addition is completed, it is stirred at 20 < T < 30 °C for 40 minutes, then heated to 75 °C for 2 hours obtaining a dark red solution.

The TLC control (isopropyl acetate/heptane 8/2 eluent) shows the largely predominant formation of intermediate (3) with R_f 0.65, the formation of intermediate (2) in traces (R_f

0.68) and the permanence of a starting product residue (R_f 0.51).

The solution is poured onto a mixture of cold water (1.5 L) and ice (1 kg) under stirring for 1 hour at 0 < T < 5 °C; then, it is brought to 20 < T < 25 °C over 45 minutes.

The precipitated solid is filtered by washing with water at 20 °C. The wet solid is dissolved in 1 L dichloromethane (DCM) and the spontaneously formed aqueous phase is separated.

The organic phase is washed first with water which results to have pH = 1, then with a basic aqueous solution ($NaHCO_3$), obtaining a pH = 8, finally with an aqueous solution saturated with NaCl.

The organic solution is concentrated under reduced pressure, the residue is dissolved with 345 mL methanol, which is partially distilled under reduced pressure to eliminate virtually all DCM and half of the methanol added.

173 mL of methanol are added, cooled to 0 < T < 2 °C for 1 hour. The precipitated solid is filtered by washing with methanol, then dried at 45 °C under reduced pressure for 16 hours. 96.7 g of solid are obtained, essentially consisting of intermediate (3) only, with 99.94% HPLC purity.

The identification is confirmed by NMR spectroscopy and comparison with the literature data.

In the filtration waters combined with wash water, a precipitate is observed which is filtered and washed with water. The wet solid is dissolved in 250 mL DCM and the spontaneously formed aqueous phase is separated. The organic phase is washed first with water which turns out to have pH = 1, then with a basic aqueous solution ($NaHCO_3$), obtaining a pH = 8, finally with an aqueous solution saturated with NaCl.

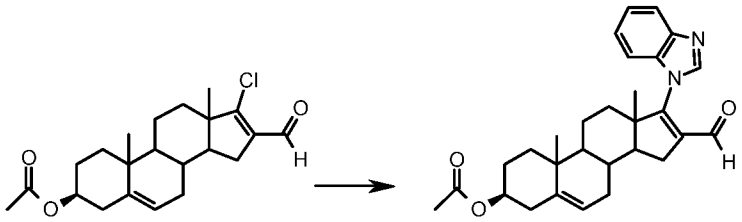
The organic solution is concentrated under reduced pressure, the residue is dissolved with 40 mL methanol, which is partially distilled under reduced pressure to eliminate virtually all DCM and half of the methanol added.

20 mL of methanol are added, cooled to 0 < T < 2 °C for 1 hour. The precipitated solid is filtered by washing with methanol, then dried at 45 °C under reduced pressure for 16 hours. 6.3 g of solid are obtained, essentially consisting of intermediate (3) only, with 99.08% HPLC purity.

The first and second step mixture is used for the next reaction without needing additional purifications.

EXAMPLE 2

This example relates to step b) of the process of the invention, formation of 3β-acetoxy-17-(1H-benzimidazol-1-yl)-16-formylandrosta-5,16-diene (4):



(3) (4)

To a flask under nitrogen are loaded 102.5 g of intermediate (3) obtained in the previous example, 500 mL DMF, 56.4 g K_2CO_3, 35.3 g of benzimidazole and it is stirred for 1.5 hours at T = 80 °C.

The TLC control (isopropyl acetate/heptane 8/2 eluent) shows the formation of product (4) with R_f 0.27, and a trace of a less polar impurity with R_f 0.35.

The reaction mixture is brought to 20 < T < 25 °C, 2 L of water are added and the system is cooled to 0 < T < 2 °C for 1 hour.

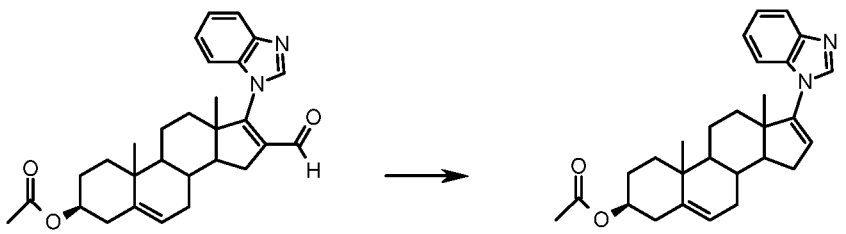
The precipitated solid is filtered by washing with water, then dried at 60 °C under reduced pressure for 20 hours.

120.1 g of solid are obtained which the NMR analysis shows to be compound (4) with 99.25% HPLC purity.

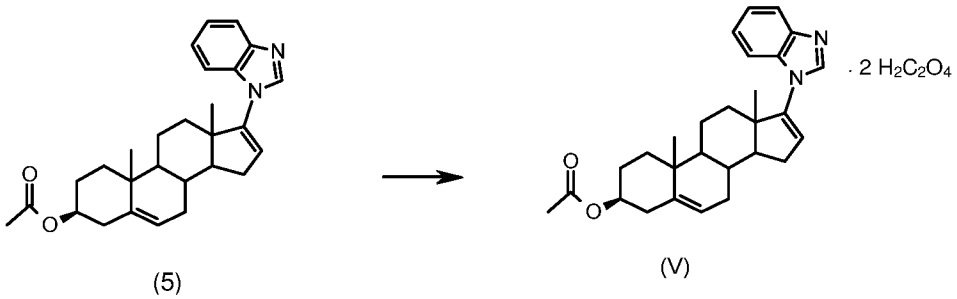
The identification is confirmed by NMR spectroscopy and comparison with the literature data.

EXAMPLE 3

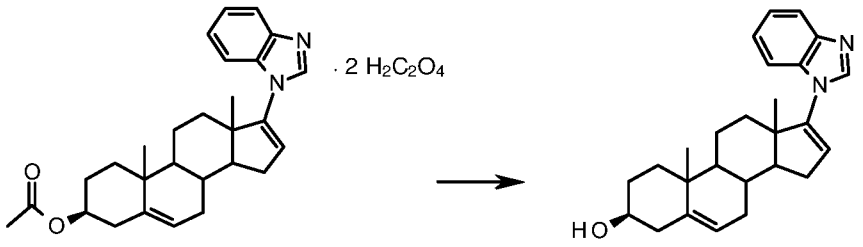
This example relates to the sequence of steps c), d) and e) of the process of the invention, which lead to the formation of 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene, Galeterone (6):



(4) (5)



(5) (V)



(V) (6)

To a flask under nitrogen are loaded 119.5 g of compound (4) obtained in example 2, 600 mL of benzonitrile, 12 g of 10% Pd/C (Strem Chemicals escat™ 1921) and under stirring it is brought to reflux, about T = 190 °C over 5 hours, observing the distillation of some mL of solvent in Dean Stark.

It is kept under reflux for 40 hours.

The TLC control (isopropyl acetate/heptane 8/2 eluent) shows the disappearance of the start (4) (R_f 0.24), the formation of the product (5) (R_f 0.31) and the formation of some impurities (R_f 0.55 ~ 0.79).

The reaction mixture is brought to 20 < T < 25 °C and 360 mL of toluene are added.

It is filtered on a dicalite panel washed with additional 360 mL of toluene.

5 g of QuadraSil® MP are added and it is stirred for 16 hours.

It is filtered on a MILLIPORE filtering membrane and washed with 50 mL toluene.

72.3 g of dihydrate oxalic acid are added and the mixture is stirred for 1 hour, observing the formation of a precipitate (pH is about 2, measured by sampling of a liquid sample and TRITEST check).

The suspension is stirred for 1 hour at 20 < T < 25 °C and 1 hour at 0 < T < 5 °C, the solid is filtered by washing with 120 mL of toluene. The wet solid is dissolved with 600 mL of toluene.

The suspension is stirred for 15 minutes at 20 < T < 25 °C and 15 minutes at 0 < T < 5 °C, the solid is filtered by washing with 120 mL of toluene.

After drying under reduced pressure and T = 65 °C to constant weight, 114 g of intermediate

(V) are obtained which, as shown by elemental analysis, consists of carbon 62.63%, hydrogen 6.27%, nitrogen 4.92%, oxygen 26.06%, corresponding to the molecular formula $C_{28}H_{34}N_2O_2 \cdot 2\ C_2H_2O_4$ of intermediate (V).

104 g of compound (V) are loaded to a flask under nitrogen and stirred with 1.1 L DCM at 20 < T < 25 °C (a suspension is formed).

To the suspension is added a solution obtained by mixing 350 mL methanol and 40.9 g NaOH and it is stirred for 4 hours (pH is about 12: measured by sampling a liquid sample and TRITEST check).

The TLC control (DCM/methanol 9/1 eluent) shows the formation of compound (6) with R_f 0.44 (start R_f 0.68).

It is diluted with 1.1 L DCM, 2.2 L water are charged and stirred for 15 minutes.

It is filtered on a dicalite panel and the organic phase is separated and concentrated to about one tenth of the initial volume under reduced pressure after washing with saturated saline water solution (NaCl).

400 mL of ethyl acetate are added and 200 mL solvent distilled.

Additional 200 mL of ethyl acetate are added and 200 mL solvent distilled.

It is cooled to 0 < T < 5 °C for 1 hour (the formation of a precipitate is observed).

The solid is filtered and dried under reduced pressure for 16 hours at T = 45 °C, yielding 40.7 g of product which the HPLC analysis shows to have an impurity at RTT = 0.87 equal to 0.04%.

The solid is loaded, suspended in tert-butanol (61 mL), brought to reflux. PPI water is added dropwise (61 mL) and it is again brought to reflux.

It is cooled to 0 < T < 5 °C for 1 hour.

The solid is filtered, washed with 40 mL of a 1/1 mixture of PPI precooled water/tert-butanol and is dried under reduced pressure and T = 50 °C to constant weight; this yields to 37.4 g of product.

The solid thus obtained is suspended in methanol (187 mL) and it is brought to reflux (complete solution).

It is cooled to 20 < T < 25 °C until the start of precipitation of the product.

It is cooled to 0 < T < 5 °C for 1 hour.

The solid is filtered and washed with 37 mL of precooled methanol.

42.5 g wet are obtained which after drying to constant weight (reduced P and T = 50 °C) yield 26.4 g of pure Galeterone (6).

HPLC titre 101.1% (RRT impurity 0.87 = 0.017%); DSC: 195.05 °C (onset); residual

methanol 1323 ppm; residual palladium 0.3 ppm.

The identification is confirmed by NMR spectroscopy:

^{1}H-NMR($CDCl_3$) δ: 1.02 (s, 3H, 18-CH_3), 1.06 (s, 3H, 19-CH_3), 1.06-1.17 (m, 2H, H aliphatic), 1.47-1.89 (∑m, 11H, H aliphatic), 2.08-2.45 (∑m, 5H, H aliphatic), 3.53-3.58 (m, 1H, 3αH), 5.41 (m, 1H, 6-H), 5.98 (dd, 1H, 16-H), 7.26-7.31 (m, 2H, H aromatic), 7.47-7.51 (m, 1H, H aromatic), 7.79-7.83 (m, 1H, H aromatic), 7.96 (s, 1H, H aromatic).

EXAMPLE 4 (COMPARATIVE)

The preparation of Example 3 is repeated, using however in the first step (conversion from intermediate (4) to intermediate (5)) an amount of Pd/C catalyst greater than the amounts allowed by the invention.

To a flask under nitrogen are loaded 51 g of compound (4) obtained according to the above procedure, 250 mL of benzonitrile, 12.5 g (24.5% by weight with respect to intermediate (4)) of 10% Pd/C (Strem Chemicals escat™ 1921) and under stirring it is brought to reflux, about T = 190 °C over 5 hours, observing the distillation of some mL of solvent in Dean Stark.

It is kept under reflux for 24 hours.

The TLC control (isopropyl acetate/heptane 8/2 eluent) shows the disappearance of the start (4) (R_f 0.24), the formation of the product (5) (R_f 0.31) and the formation of some impurities (R_f 0.55 ~ 0.79).

The reaction mixture is brought to 20 < T < 25 °C and 150 mL of toluene are added.

It is filtered on a dicalite panel washed with additional 150 mL of toluene.

2 g of QuadraSil® MP are added and stirred for 16 hours.

It is filtered on a MILLIPORE filtering membrane and washed with 10 mL toluene.

30.8 g of dihydrate oxalic acid are added and the mixture is stirred for 1 hour, observing the formation of a precipitate (pH is about 2, measured by sampling of a liquid sample and TRITEST check).

The suspension is stirred for 1 hour at 20 < T < 25 °C and 1 hour at 0 < T < 5 °C, the solid is filtered by washing with toluene.

The wet solid is recovered with 250 mL of toluene.

The suspension is stirred for 15 minutes at 20 < T < 25 °C and 15 minutes at 0 < T < 5 °C, the solid is filtered by washing with toluene.

After drying under reduced pressure and T = 65 °C to constant weight, 56 g of intermediate (V) are obtained.

55 g of compound (V) are loaded to a flask under nitrogen and stirred with 600 mL DCM at

20 < T < 25 °C (a suspension is formed).

To the suspension is added a solution obtained by mixing 150 mL methanol and 16 g NaOH and it is stirred for 4 hours (pH is about 12: measured by sampling a liquid sample and TRITEST check).

The TLC control (DCM/methanol 9/1 eluent) shows the formation of compound (6) with R_f 0.44 (start R_f 0.68).

It is diluted with 500 mL DCM, 1 L water is charged and stirred for 15 minutes.

It is filtered on a dicalite panel and the organic phase is separated and concentrated to about one tenth of the initial volume under reduced pressure after washing with saturated saline water solution (NaCl).

200 mL of ethyl acetate are loaded, distilled to a residue of 100 mL of solvent in the reaction flask.

Additional 200 mL of ethyl acetate are loaded, distilled to a residue of 100 mL of solvent in the reaction flask.

It is cooled to 0 < T < 5 °C for 1 hour (precipitate).

The solid is filtered and dried under reduced pressure for 16 hours at T = 45 °C, obtaining 28.5 g of crude Galeterone which the HPLC analysis shows to have an impurity at RTT = 0.87 equal to 0.5 %.

The solid is loaded to a flask, suspended in tert-butanol (44 mL), and brought to reflux.

PPI water is added dropwise (44 mL) and it is again brought to reflux.

It is cooled to 0 < T < 5 °C for 1 hour.

The solid is filtered, washed with 40 mL of a 1/1 mixture of PPI precooled water/tert-butanol and is dried under reduced pressure and T = 50 °C to constant weight.

The solid is suspended in methanol and it is brought to reflux (complete solution with 142.5 mL).

It is cooled to 20 < T < 25 °C until the start of precipitation of the product.

It is cooled to 0 < T < 5 °C for 1 hour.

The solid is filtered and washed with precooled methanol; it is dried at reduced pressure and T = 50 °C until constant weight; 22.5 g of Galeterone (6) are obtained and the HPLC analysis shows that the impurity at RRT = 0.87 is 0.41%.

The solid is loaded to a flask, suspended in methanol (123.8 mL), and brought to reflux (complete solution).

It is cooled to 20 < T < 25 °C until the start of precipitation of the product.

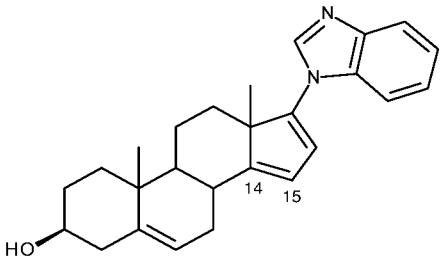
It is cooled to 0 < T < 5 °C for 1 hour.

The solid is filtered and washed with precooled methanol; it is dried at reduced pressure and T = 50 °C until constant weight; 18.5 g of Galeterone (6) are obtained and the HPLC analysis shows that the impurity at RRT = 0.87 is 0.35 %.

A Galeterone sample (6) is analysed in Lc/Ms/Ms (chemical ionization).

At peak at RRT = 0.87 corresponds a mass [M^++1] = 387, that is, a molecular weight of two units less than the molecular weight of Galeterone.

The UV spectrum of the impurity, obtained from the HPLC chromatogram, in accordance with the result obtained from the Lc/Ms/Ms analysis, is compatible with the following structure of 14,15-dehydrogaleterone:



A part of the Galeterone (6) sample thus obtained is crystallized from isopropanol, yielding only a modest drop in the impurity content at RRT = 0.87 (from 0.35% to 0.30%).

Similar results are obtained by refluxing part of the Galeterone (6) sample thus obtained in 12 volumes (partial dissolution) of isopropyl ether, methyl ethyl ketone and methyl tertbutyl ether.

RRT 0.87 impurity remains at values of between 0.32 and 0.34%.

EXAMPLE 5 (COMPARATIVE)

The preparation of Example 3 is repeated, using however a catalyst other than Pd/C in the first step (conversion from intermediate (4) to intermediate (5)).

To a flask under nitrogen are loaded 4 g of compound (4) obtained according to the above procedure, 20 mL of benzonitrile, 400 mg (10% by weight) of 5% Pd/Al_2O_3 (Johnson Matthey code A302099-5) and stirring, it is brought to reflux, about T = 190 °C over 1 hour. It is kept under reflux for 16 hours.

The TLC control (isopropyl acetate/heptane 8/2 eluent) shows the disappearance of the start (4) (R_f 0.24), the formation of the product (5) (R_f 0.31), and the formation of an impurity (R_f 0.36).

The reaction mixture is brought to 20 < T < 25 °C and is processed as described in the example above.

2.61 g of crude Galeterone are obtained, which the HPLC analysis shows to have a purity of 97.7% but an impurity content at RRT = 0.87 equal to 0.25%, which was not possible to reduce to a satisfactory level for pharmaceutical use using the known techniques that can be used normally in industrial production processes, similar to the example above.

EXAMPLE 6

This example relates to the sequence of steps c), d) and e) of the process of the invention, which lead to the formation of 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene, Galeterone (6):

To a flask under nitrogen are loaded 5 g of compound (4) obtained in example 2, 25 mL of Dowtherm® A, 0.5 g of 10% Pd/C (Strem Chemicals escat™ 1921) and under stirring it is brought to reflux, about T = 250 °C over 20 minutes.

The system is kept under reflux for 1 hour.

The TLC control (isopropyl acetate/heptane 8/2 eluent) shows the disappearance of the start (4) (R_f 0.24), the formation of the product (5) (R_f 0.31), and the formation of some impurities (R_f 0.55 ~ 0.79).

The reaction mixture is brought to 20 < T < 25 °C and 15 mL of toluene are added.

It is filtered on a dicalite panel washed with additional 15 mL of toluene.

3 g of dihydrate oxalic acid are added and the mixture is stirred for 1 hour, observing the formation of a precipitate (pH is about 2, measured by sampling of a liquid sample and TRITEST check).

The suspension is stirred for 1 hour at 20 < T < 25 °C and 1 hour at 0 < T < 5 °C, the solid is filtered by washing with 5 mL of toluene. The wet solid is dissolved with 30 mL of toluene.

The suspension is stirred for 15 minutes at 20 < T < 25 °C and 15 minutes at 0 < T < 5 °C, the solid is filtered by washing with 5 mL of toluene.

After drying under reduced pressure and T = 65 °C to constant weight, 4.6 g of intermediate (V) are obtained which are loaded to a flask under nitrogen and stirred with 50 mL of DCM at 20 < T < 25 °C (a suspension is formed).

To the suspension is added a solution obtained by mixing 17 mL methanol and 1.8 g NaOH and it is stirred for 7 hours (pH is about 12: measured by sampling a liquid sample and TRITEST check).

The TLC control (DCM/methanol 9/1 eluent) shows the formation of compound (6) with R_f 0.44 (start R_f 0.68).

It is diluted with 50 mL DCM, 100 mL water are charged and stirred for 15 minutes.

It is filtered on a dicalite panel and the organic phase is separated and concentrated to dryness.

The HPLC analysis carried out on the raw galeterone (3.2 g) thus obtained shows an amount of impurity at RRT = 0.87 equal to 0.043%.

EXAMPLE 7 (COMPARATIVE)

This example relates to the sequence of steps c), d) and e) of the process of the invention, which lead to the formation of 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene, Galeterone (6):

In this Example, the procedure of Example 6 is essentially repeated with the only difference that in step c) (conversion of intermediate (4) to intermediate (5)), the Pd/C catalyst is added when the reagent system is already at the final reaction temperature.

To a flask under nitrogen are loaded 5 g of compound (4) obtained in example 2, 25 mL of Dowtherm® A, and under stirring it is brought to T = 200 °C over 20 minutes.

0.5 g 10% Pd/C are added (Strem Chemicals escat™ 1921) then it is brought to reflux and maintained at about 250 °C for 1 hour.

The TLC control (isopropyl acetate/heptane 8/2 eluent) shows the disappearance of the start (4) (R_f 0.24), the formation of the product (5) (R_f 0.31), and the formation of some impurities (R_f 0.55 ~ 0.79).

The reaction mixture is brought to 20 < T < 25 °C and 15 mL of toluene are added.

It is filtered on a dicalite panel washed with additional 15 mL of toluene.

3 g of dihydrate oxalic acid are added and the mixture is stirred for 1 hour, observing the formation of a precipitate (pH is about 2, measured by sampling of a liquid sample and TRITEST check).

The suspension is stirred for 1 hour at 20 < T < 25 °C and 1 hour at 0 < T < 5 °C, the solid is filtered by washing with 5 mL of toluene. The wet solid is recovered with 30 mL of toluene.

The suspension is stirred for 15 minutes at 20 < T < 25 °C and 15 minutes at 0 < T < 5 °C, the solid is filtered by washing with 5 mL of toluene.

After drying under reduced pressure and T = 65 °C to constant weight, 4.8 g of intermediate (V) are obtained which are loaded to a flask under nitrogen and stirred with 50 mL of DCM at 20 < T < 25 °C (a suspension is formed).

To the suspension is added a solution obtained by mixing 17 mL methanol and 1.9 g NaOH and it is stirred for 7 hours (pH is about 12: measured by sampling a liquid sample and TRITEST check).

The TLC control (DCM/methanol 9/1 eluent) shows the formation of compound (6) with R_f 0.44 (start R_f 0.68).

It is diluted with 50 mL DCM, 100 mL water are charged and stirred for 15 minutes.

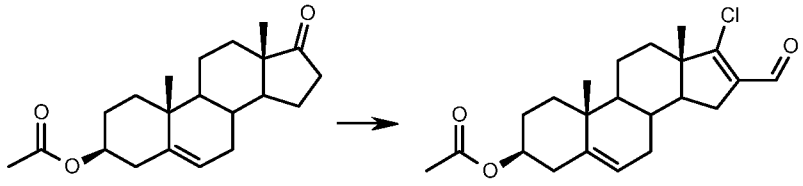
It is filtered on a dicalite panel and the organic phase is separate and concentrated to dryness.

The HPLC analysis carried out on the raw galeterone (2.7 g) thus obtained shows an amount of impurity at RRT = 0.87 equal to 0.16%, almost four times greater than that obtained with the procedure of Example 6.

CLAIMS

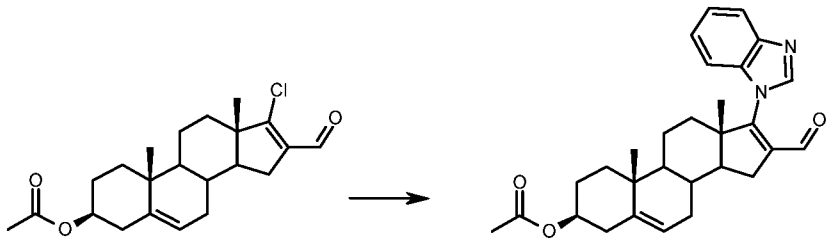
1. Process for the preparation of 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene (Galeterone) comprising the following steps:

a) reaction between 3β-acetoxyandrost-5-en-17-one (1) and $POCl_3$ to yield 3β-acetoxy-17-chloro-16-formylandrost-5,16-diene (3):



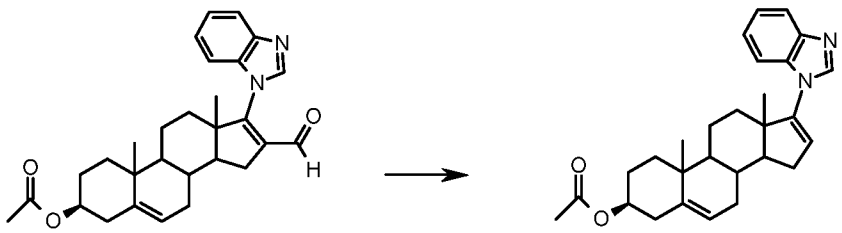
(1) (3)

b) reaction of 3β-acetoxy-17-chloro-16-formylandrost-5,16-diene (3) with benzimidazole, to yield the intermediate 3β-acetoxy-17-(1H-benzimidazol-1-yl)-16-formylandrosta-5,16-diene (4):



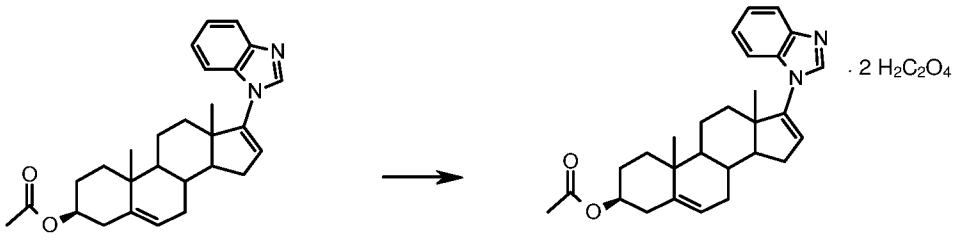
(3) (4)

c) reaction of 3β-acetoxy-17-(1H-benzimidazol-1-yl)-16-formylandrosta-5,16-diene (4) at a temperature above 100 °C with palladium on carbon as a catalyst in an amount between 5 and 20% by weight compared to intermediate (4), adding the catalyst when the mixture is at a temperature below 100 °C, to yield the intermediate (5), 3β-acetoxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene:



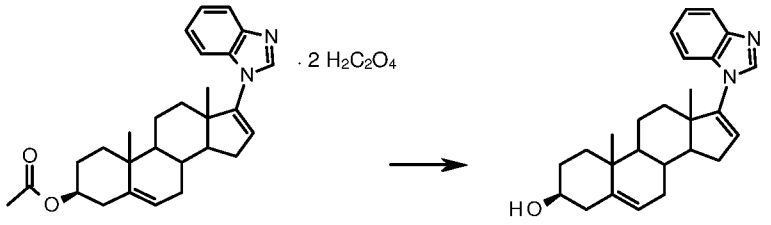
(4) (5)

d) reaction of the intermediate (5) with oxalic acid to yield compound (V), 3β-acetoxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene dioxalate:



(5) (V)

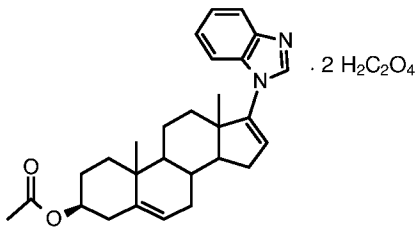
e) reaction of the intermediate (V) with a base to yield Galeterone (6):



(V) (6)

2. Process according to claim 1, wherein step c) is carried out at a temperature above 200 °C, using as solvent Dowtherm® A, an eutectic blend of diphenyl and diphenyl oxide.

3. Compound (V), 3β-acetoxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene dioxalate:



(V)

4. 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene (Galeterone) obtained according to the process of claim 1, having a content of the impurity at RRT = 0,87 lower than 0.10%.

5. 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene (Galeterone) obtained by treatment with a base of compound (V).

6. 3β-hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-diene (Galeterone), obtained by treatment with a base of compound (V), having a content of the impurity at RRT = 0,87 lower than 0.10%.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053147

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07J43/00 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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/091306 A1 (TOKAI PHARMACEUTICALS [US]; CASEBIER DAVID [US]) 12 August 2010 (2010-08-12) page 13, paragraph 51 - page 14 -----	1-6
X	US 2011/034428 A1 (MORRISON JODIE POPE [US] ET AL) 10 February 2011 (2011-02-10) page 13, paragraph 136 - page 14, paragraph 140 page 15; example 1 ----- -/--	1-6

[X] 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 September 2017	14/09/2017

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HANDRATTA VENKATESH D ET AL: "Novel C-17-Heteroaryl Steroidal CYP17 Inhibitors/Antiandrogens: Synthesis, in Vitro Biological Activity, Pharmacokinetics, and Antitumor Activity in the LAPC4 Human Prostate Cancer Xenograft Model", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 48, no. 8, 25 March 2005 (2005-03-25) , pages 2972-2984, XP002535274, ISSN: 0022-2623, DOI: 10.1021/JM040202W Scheme 1, page 2974	1-6

A	ANDERSON ET AL: "TOOLS FOR PURIFYING THE PRODUCT: COLUMN CHROMATOGRAPHY, CRYSTALLIZATION AND RESLURRYING", PRACTICAL PROCESS RESEARCH AND DEVELOPMENT, ACADEMIC PRESS, SAN DIEGO, US, 1 January 2000 (2000-01-01), pages 223-247, XP002382432, Section III.C "Salt selection", pages 238-240	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/053147

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010091306 A1	12-08-2010	AU 2010210422 A1	18-08-2011
		CA 2761389 A1	12-08-2010
		CN 102686600 A	19-09-2012
		EP 2393827 A1	14-12-2011
		EP 3023433 A1	25-05-2016
		ES 2552087 T3	25-11-2015
		JP 2012516900 A	26-07-2012
		JP 2016034946 A	17-03-2016
		US 2011312916 A1	22-12-2011
		US 2014371181 A1	18-12-2014
		WO 2010091306 A1	12-08-2010
US 2011034428 A1	10-02-2011	AU 2010279398 A1	08-03-2012
		CA 2770092 A1	10-02-2011
		EP 2461814 A2	13-06-2012
		JP 2013501722 A	17-01-2013
		JP 2016074687 A	12-05-2016
		KR 20120056267 A	01-06-2012
		US 2011034428 A1	10-02-2011
		US 2014343024 A1	20-11-2014
		US 2015166599 A1	18-06-2015
		US 2015203528 A1	23-07-2015
		US 2017157148 A1	08-06-2017
		WO 2011017534 A2	10-02-2011