AU9341202

(12) PATENT ABRIDGMENT (11) Document No. AU-B-41202/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 666945

(54) Title
NEW PREPARATION PROCESS FOR 16ALPHA-METHYL STEROIDS

International Patent Classification(s)
(51)[5] **C07J 005/00** **C07J 013/00** **C07J 071/00**

(21) Application No. : **41202/93** (22) Application Date : **11.06.93**

(30) Priority Data

(31) Number (32) Date (33) Country
92 07048 **11.06.92** **FR FRANCE**

(43) Publication Date : **23.12.93**

(44) Publication Date of Accepted Application : **29.02.96**

(71) Applicant(s)
ROUSSEL-UCLAF

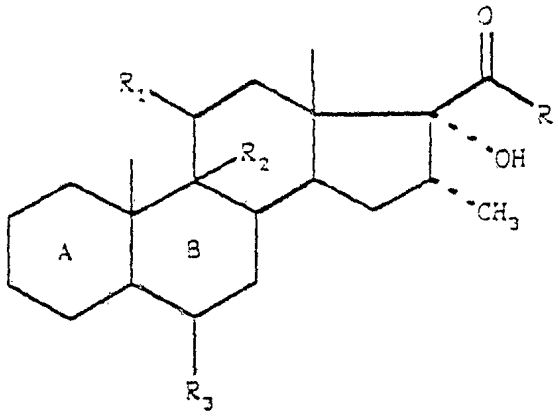
(72) Inventor(s)
JEAN BUENDIA; PATRICK ROUSSEL; MICHEL VIVAT

(74) Attorney or Agent
CALLINAN LAWRIE , Private Bag 7, KEW VIC 3101

(56) Prior Art Documents
AU 18478/92 C07J 31/00, 5/00, 75/00

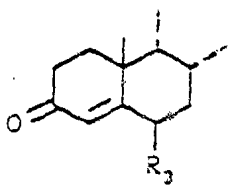
(57) Claim

1) Preparation process for the compounds of formula (I):



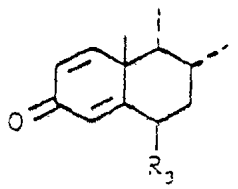
(I)

in which the rings A and B represent a remainder:

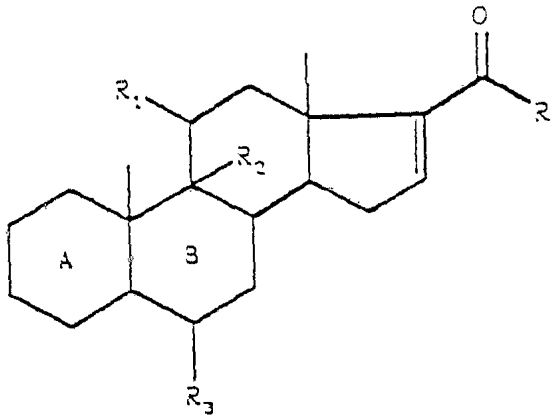


.../2

in which the ketone function in position 3 is optionally protected in the form of a ketal, thioketal, hemithioketal or enol ether, or a remainder:



R represents a methyl radical or a $-CH_2-OR'$ radical, in which R' represents a hydrogen atom or an ether remainder or an ester remainder, R_1 and R_2 form together a second bond, or R_1 and R_2 form together an epoxide in position beta, or R_1 represents a hydrogen atom, a ketone function or a hydroxy function in position alpha or beta, free or protected in the form of an ether or ester and R_2 represents a hydrogen atom, or R_1 represents a hydrogen atom and R_2 represents a hydroxy function in position alpha, or R_1 represents a hydroxy function in position beta, free or protected in the form of an ether or ester and R_2 represents a fluorine or bromine atom in position alpha, and R_3 represents a hydrogen atom or a fluorine atom or a methyl radical, in position alpha or beta, characterized in that a compound of formula (II):



(II)

in which A, B, R, R_1, R_2 and R_3 have the meaning already indicated, is treated with a methylation agent in the presence of a copper-based catalyst, then the methylated enolate intermediate thus obtained is hydrolyzed to obtain the ~~enolate~~ corresponding enol which is oxidized with molecular oxygen in the presence of a reducing and complexing agent of the copper, in order to obtain the expected compound.

666945

P/00/011
Regulation 3.2

AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

TO BE COMPLETED BY APPLICANT

Name of Applicant: ROUSSEL-UCLAF

Actual Inventor(s): Jean BUENDIA; Patrick ROUSSEL; and Michel VIVAT

Address for Service: CALLINAN LAWRIE, 278 High Street, Kew, 3101, Victoria, Australia

Invention Title: "NEW PREPARATION PROCESS FOR 16ALPHA-METHYL STEROIDS"

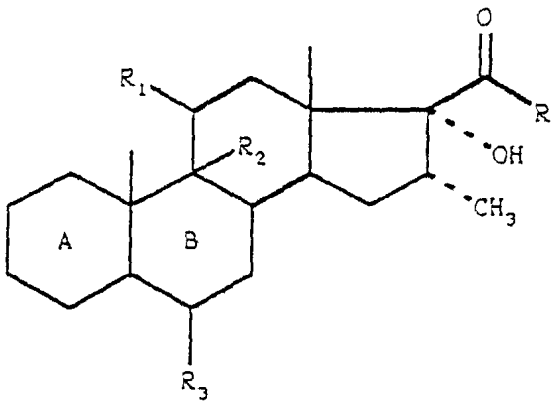
The following statement is a full description of this invention, including the best method of performing it known to me:-

---

New preparation process for 16alpha methyl steroids.

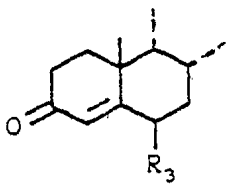
The present invention relates to a new preparation process for 16alpha-methyl steroids.

Therefore a subject of the invention is a preparation process for the compounds of formula (I):

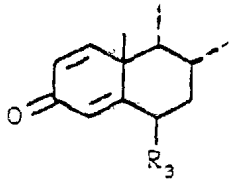


(I)

in which the rings A and B represent a remainder:

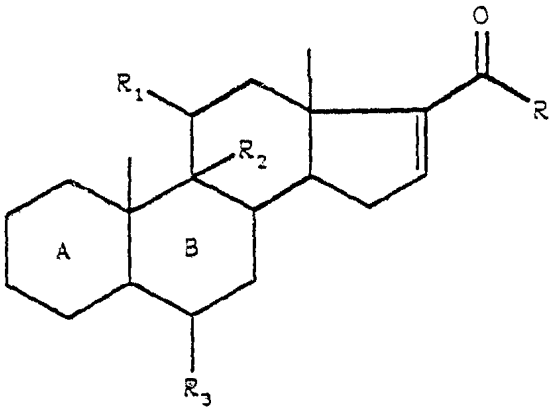


in which the ketone function in position 3 is optionally protected in the form of a ketal, thioketal, hemithioketal or enol ether, or a remainder:



R represents a methyl radical or a $-CH_2-OR'$ radical, in which R' represents a hydrogen atom or an ether remainder or an ester remainder, R_1 and R_2 form together a second bond, or R_1 and R_2 form together an epoxide in position beta, or R_1 represents a hydrogen atom, a ketone function or a hydroxy function in position alpha or beta, free or protected in the

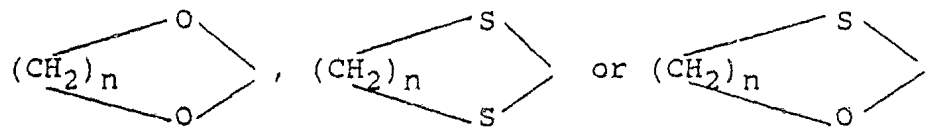
form of an ether or ester and R_2 represents a hydrogen atom, or R_1 represents a hydrogen atom and R_2 represents a hydroxy function in position alpha, or R_1 represents a hydroxy function in position beta, free or protected in the form of an ether or ester and R_2 represents a fluorine or bromine atom in position alpha, and R_3 represents a hydrogen atom or a fluorine atom or a methyl radical, in position alpha or beta, characterized in that a compound of formula (II):



(II)

in which A, B, R, R_1, R_2 and R_3 have the meaning already indicated, is treated with a methylation agent in the presence of a copper-based catalyst, then the methylated enolate intermediate thus obtained is hydrolyzed to obtain the corresponding enol which is oxidized with molecular oxygen in the presence of a reducing and complexing agent of the copper, in order to obtain the expected compound.

When the ketone function in position 3 is protected in the form of a ketal, thioketal or hemithioketal, it is preferably a group of formula:



in which n is equal to 2 or 3 and quite particularly an ethylenedioxy or ethylenedithio group.

When the ketone function in position 3 is protected in

the form of an enol ether, it is preferably an alkoxy or alkoxyalkoxy group containing 1 to 8 carbon atoms and more particularly a methoxy, ethoxy, ethoxyethoxy or 1-ethoxy-ethoxy group, rings A and B in that case comprising a system of 3,5 double bonds.

When R′ represents an ether remainder, it can be any remainder known to a man skilled in the art and notably an alkyl radical containing 1 to 6 carbon atoms, for example methyl, ethyl or propyl, a tetrahydropyranyl radical, or a remainder of a silylated ether, for example trialkylsilyl such as trimethyl- or dimethylterbutylsilyl, triarylsilyl such as triphenylsilyl or diarylalkylsilyl such as diphenyl-terbutylsilyl.

When R′ represents an ester remainder, it can be any remainder known to a man skilled in the art and notably an acyl radical containing 1 to 8 carbon atoms, for example formyl, acetyl, propionyl, butyryl, valeryl or benzoyl.

When R_1 represents a protected hydroxy function in the form of an ether or ester, it is one of the ether or ester remainders mentioned above for R′, it being understood that these remainders are not necessarily identical.

Notably a subject of the invention is a process as defined previously, characterized in that at the start a compound of formula (II) is used in which rings A and B represent a remainder:



in which R_3 is defined as previously and the ketone function in position 3 is free.

Notably a subject of the invention is also a process as defined previously, characterized in that at the start a compound of formula (II) is used in which R_1 and R_2 form together a second bond, or R_1 and R_2 form together an epoxide in position beta, or R_1 represents a hydroxy function in

position beta, free or protected in the form of an ether or ester and R_2 represents a fluorine atom in position alpha, and R_3 represents a hydrogen atom, a fluorine atom or a methyl radical and, preferably, a hydrogen atom.

The methylation agent used can be a methylated copper derivative, for example CH_3Cu, $(CH_3)_2$ CuMg, $(CH_3)_2$ CuLi or, preferably, a methylmagnesium chloride, bromide or iodide, used in the presence of a copper-based catalyst. The catalyst can be a salt such as cupric acetate, propionate or chloride, cuprous chloride, bromide, iodide or cyanide, or also a complex, for example copper acetylacetonate, cuprous dimethylsulphide bromide or also cuprous tri-nbutylphosphine chloride or any other complex of the same type known to a man skilled in the art. Cupric acetate and proprionate are quite particularly preferred.

The operation takes place in a solvent which is preferably an ether such as tetrahydrofuran, dioxane, ter-butylmethylether, dimethoxyethane. Tetrahydrofuran is more particularly preferred.

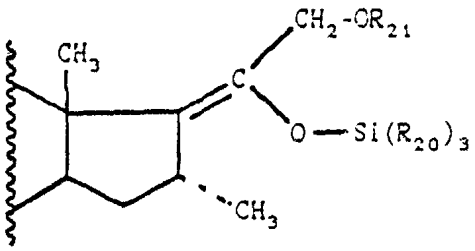
The operation advantageously takes place at a temperature of 0 to -30°C and, preferably, at -20°C.

The hydrolysis of the methylated intermediate is preferably carried out by pouring the reaction solution into an aqueous solution of a monoalkaline phosphate, for example of sodium or potassium, or in a buffer of weakly acidic pH, notably a phosphate buffer, in an aqueous solution of ammonium chloride or, more generally, in a weak acidic agent such as acetic, propionic or butyric acid.

The oxidation of the enol is carried out by bubbling oxygen through or, preferably, by bubbling air through the hydrolysis medium and the operation takes place in the presence of a reducing and complexing agent of the copper and compatible with the oxidizing agent, which is notably a dialkylsulphide, tetrahydrothiophene, a trialkyl or triphenylphosphite or triphenylphosphine. Dimethyl sulphide and tetrahydrothiophene are quite particularly preferred. The operation preferably takes place at ambient temperature.

Preparation processes for the compounds of formula (I)

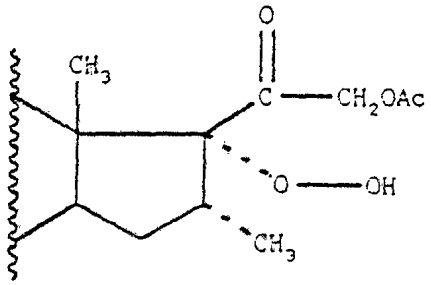
have already been described, for example in the Application WO 87/07612. The process of this Application consists of methylating an unsaturated 16 derivative with a methylation agent in the presence of a copper-based catalyst and a silylation agent, with the purpose of intermediatelyisolating a derivative of type:



which is then treated with a peracid in order to form the 17alpha-20 epoxide which is finally hydrolyzed with an acid or a base.

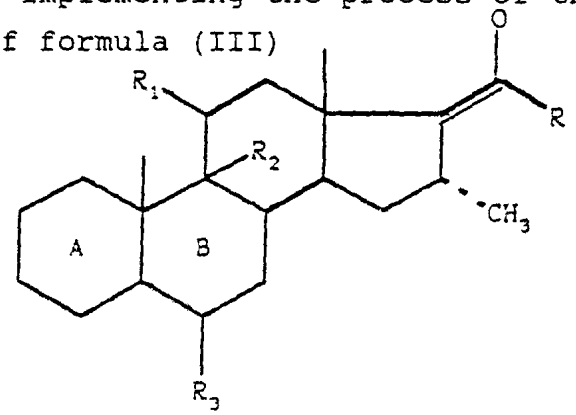
The process of the present invention does not require the isolation of any intermediate, the product resulting from the methylation reaction being directly hydrolyzed then oxidized under conditions which have never been envisaged to date and particularly useful from an industrial point of view. Its implementation is far more straightforward than that of known processes and in particular than that of the Application mentioned above.

The British Patent 2,001,990 also describes a preparation process for the compounds of formula (I) which consists, as above, of methylating an unsaturated 16 derivative, then preparing and isolating the hydroperoxide of formula:



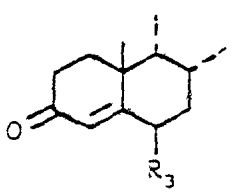
which is then reduced with zinc in acetic acid or with an alkaline iodide in an aliphatic ketone. It should be noted 1) that such a process which firstly isolates a hydroperoxide and then treats it with a reducing agent is not industrially viable due to the dangers inherent in these operations; 2) that contrary to the process of our Application which allows the oxidation and the reduction to take place in a single stage by using a compatible reducing agent, the above process does not allow this, due to incompatibility between the reagents used. In others words, the principle on which the process of our Application is based is different and this essentially relates to the reducing (or oxidizable) ligand that it uses and whose presence is indispensable.

Further more a subject of the invention as new industrial compounds and notably as new necessary intermediates for implementing the process of the invention is the compound of formula (III)

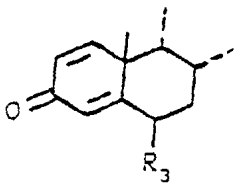


(III)

in which A, B, R, R_1, R_2 and R_3 have the meanings defined previously and notably the compounds of formula (III) as defined above in which the A and B rings represent a rest



or



in which R_3 is defined as previously and the ketone function in position 3 is free and those in which R_1 and R_2 form together a second bond, or R_1 and R_2 form together an epoxyde in beta position or R_1 represents a hydroxyl function in beta position free or protected under an ether or ester form and R_2 represents a fluorine atom in alpha position and R_3 a

AUSTRALIA PATENT OFFICE

hydrogen atom, a fluorine atom or a methyl radical.

The compounds of formula (II) are known and described, for example, in US Patents 2,345,711, 2,883,400, 2,963,496, 2,966 504, 2,975,197, 3,029,233, 3,210,341, 3,377,343, 3,839,369, 3,976,638, 4,031,080, 4,277,409, 4,929,395, the German Patent 2,207,420, the Dutch Patent 69 02 507 or Belgian Patents 539,498, 540,478, 711,016, or can be easily prepared starting from compounds described in these Patents, by processes known to a man skilled in the art.

The 16alpha-methyl compounds of formula (I) are known to possess an anti-inflammatory activity and this formula includes notably dexamethasone, its derivatives (6alpha-fluoro) flumethasone, (6alpha-fluoro 9H) paramethasone and possible precursors (Δ 9,11,9alpha-OH or 9,11-epoxy).

The following examples illustrate the invention without however limiting it.

EXAMPLE 1: 9beta, 11beta-epoxy 16alpha-methyl 17alpha-hydroxy 21-acetyloxy pregna 1,4-diene 3,20-dione

0.1 g of monohydric cupric acetate, 3.83 g of 9beta, 11beta-epoxy 21-acetyloxy pregna 1,4,16(17)-triene 3,20-dione and 50 cm^3 of tetrahydrofuran are mixed together at 20°C under an inert gas atmosphere for 15 minutes, then the solution is cooled down to -20°C and 3.75 cm^3 of a 3M solution of methylmagnesium bromide in ethyl ether is slowly introduced. Agitation takes place for one hour at -20°C. Also, 40 cm^3 of a 13.6% aqueous solution of monopotassium phosphate is cooled down to approximately 0°C, and the mixture obtained above is added to it, under agitation over about 5 minutes. The temperature of the enol solution is allowed to rise, under agitation then 4 cm^3 of dimethyl-sulphide is added at +15°C, in the presence of air.

Air is bubbled through the mixture, under agitation, while allowing the temperature to rise and condensing the entrained dimethylsulphide. After 3 hours, another 2 cm^3 of dimethylsulphide is added and the bubbling through of air is continued for 2 hours. After decanting and extracting with ethyl acetate, the organic phase is washed with water, dried and the solvent is evaporated off. The residue is

chromatographed on silica eluting with a methylene chloride - ether mixture (7-3). 3.124 g of expected crystallized product is obtained.

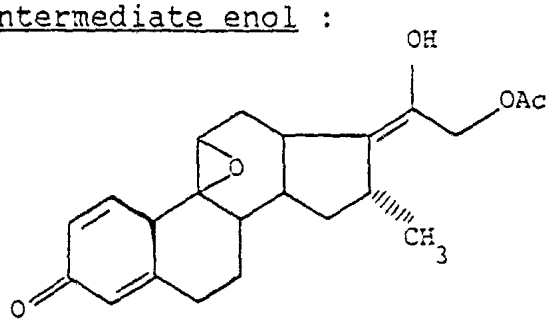
IR Spectrum ($CHCl_3$)

Absorptions at 3616 cm^{-1} (OH), 1747-1728 cm^{-1} (C=O), 1663-1624-1607 cm^{-1} (1,4 3-one).

NMR Spectrum ($CDCl_3$, 300 MHz, ppm)

0.88: 16-CH_3; 0.93: H of 18-CH_3; 1.44: H of 19-CH_3; 2.16: CH_3 of OAc; 2.94: H of 17-OH; 3.21: H in position 11; 4.69-5.04: 2H in position 21; 6.14: H in position 4; 6.20: H in position 2; 6.62: H in position 1.

Analysis of the intermediate enol :



IR Spectrum ($CHCl_3$) (under inert atmosphere)

3588 + associated 3430 cm^{-1} (F) : OH ; 1738 cm^{-1} (shoulder), 1718 cm^{-1} (max) : >=O ; 1663 cm^{-1} >=O, 1625 cm-1 C=C, 1607 cm^{-1} conjugated : Δ_{1-4} 3-one.

RMN Spectrum ($CDCl_3$, 400 MHz , ppm)

5,17 and 5,20 (s) isomers E + Z : OH ; 1,01 (d) and 1,08 (d): CH_3-CH ; 1,08 (s) and 1,10 (s) : 18-Me ; 1,45 : 19-Me ; 2,11 (s) - 2,12 (s) : OAc ; 3,15 and 3,19 : H_{11} ; 4,49 (d) and 4,67 (d) : C-CH_2O ; 6,16 : H_4 ; 6,20 (dd) : H_2 ; 6,61 (d), 6,63 (d) : H_1.

Analysys of the metals :

Mg 0,1 to 0,2% of the theorical stoechiometric quantity necessary to the enolate formation.

Alcaline 1 to 2% of the theroical stoechiometric quantity necessary to the enolate formation.

EXAMPLE 2: 9beta, 11beta-epoxy 16alpha-methyl 17alpha-hydroxy pregna 1,4-diene 3,20-dione

The operation takes place as indicated in Example 1, using at the start 0.02 g of monohydric cupric acetate and 0.649 g of 9beta, 11beta-epoxy pregna 1,4,16(17)-triene 3,20-

dione in 10 cm^3 of tetrahydrofuran, then 0.8 cm^3 of methylmagnesium bromide (3M in ether), 8 cm^3 of a 13.6% solution of monopotassium phosphate and 1.5 cm^3 of dimethyl sulphide. Agitation and bubbling through of air are maintained for 16 hours in total. After extraction with ethyl acetate, the crude product is purified by chromatography on silica eluting with a methylene chloride - ether mixture (75-25) and 0.326 g of expected crystallized product is obtained.

IR Spectrum ($CHCl_3$)

Absorption at 3610 cm^{-1} (OH), 1706-1688 cm^{-1} (C=O), 1663-1625-1607 cm^{-1} (1,4 3-one).

NMR Spectrum ($CDCl_3$, 300 MHz, ppm)

0.88: 16-CH_3; 1.01 (s): 18-CH_3; 1.44 (s): 19-CH_3; 2.24 (s): -CO-CH_3; 3.05 (s) -O-H; 3.21 (s): H_{11}; 6.15: H_4; 6.18 (dd): H_2; 6.6 (d): H_1.

EXAMPLE 3: 16alpha-methyl 17alpha-hydroxy 21-acetyloxy pregna 1,4,9(11)-triene 3,20-dione

The operation is carried out as indicated in Example 1, using at the start 0.02 g of monohydric cupric acetate, 0.733 g of 21-acetyloxy pregna 1,4,9(11), 16(17)-tetraene 3,20-dione in 10 cm^3 of tetrahydrofuran, then 0.77 cm^3 of methylmagnesium bromide (3M in ether), 7 cm^3 of a 13.6% solution of monopotassium phosphate and 2.25 cm^3 of dimethylsulphide. The reaction medium is maintained under agitation and bubbling through of air for 18 hours in total then extraction takes place with ethyl acetate. The product is purified by chromatography on silica eluting with a methylene chloride - ether mixture (7-3). 0.16 g of expected crystallized product is obtained.

IR Spectrum ($CHCl_3$)

Absorption at 3610 cm^{-1} (OH), 1747-1728 cm^{-1} (C=O), 1663-1623-1606 cm^{-1} (1,4 3-one).

NMR Spectrum ($CDCl_3$, 300 MHz, ppm)

0.75: 13-CH_3; 0.94: 16-CH_3; 1.40: 10-CH_3; 2.17: CH_3 of OAC; 4.82 and 4.99: 2H in position 21; 5.54: H in position 11; 6.05: H in position 4; 6.28: H in position 2; 7.19: H in position 1.

EXAMPLE 4: 9alpha-fluoro 11beta-hydroxy 16alpha-methyl

17alpha-hydroxy 21-acetyloxy pregna 1,4-diene 3,20-dione

The operation is carried out as indicated in Example 1, using at the start 0.02 g of monohydric cupric acetate and 0.805 g of 9alpha-fluoro 11beta-hydroxy 21-acetyloxy pregna 1,4,16 (17) triene-3,20-dione in 10 cm^3 of tetrahydrofuran, then 1.5 cm^3 of methylmagnesium bromide (3M in ether), 8 cm^3 of a 13.6% solution of monopotassium phosphate and 1.6 cm^3 of dimethylsulphide. The reaction medium is maintained under agitation and bubbling through of air for 17 hours in total then extraction takes place with ethyl acetate. The product is purified by chromatography on silica eluting with a methylene chloride - ethyl acetate mixture (7-3). 0.276 g of expected crystallized product is obtained.

IR Spectrum ($CHCl_3$)

Absorptions at 3450-3360 cm^{-1} (OH), 1740 cm^{-1} (C=O/acetate), 1720 cm^{-1} (non conjugated C=O), 1660 cm^{-1} (conjugated C=O).

NMR Spectrum ($CDCl_3$, 300 MHz, ppm)

0.93 (d): 16-CH_3; 1.07: 13-CH_3; 1.57: 10-CH_3; 2.17: CH_3 of OAC; 3.39: 17alpha OH and 11beta-OH; 4.38: 11alpha-H; 4.92: 2H in position 21; 6.11: H in position 4; 6.33: H in position 2; 7.25: H in position 1.

EXAMPLE 5: 9alpha-fluoro 11beta,21-diacetyloxy 16alpha-methyl 17alpha-hydroxy pregna 1,4-diene 3,20-dione

The operation is carried out as indicated in Example 1, using at the start 0.02 g of monohydric cupric acetate and 0.889 g of 9alpha-fluoro 11beta,21-diacetyloxy pregna 1,4,16(17) triene-3,20-dione in 10 cm^3 of tetrahydrofuran, then 0.78 cm^3 of methylmagnesium bromide (3M in ether), 8 cm^3 of a 13.6% solution of monopotassium phosphate and 1.6 cm^3 of dimethylsulphide. The reaction medium is maintained under agitation and bubbling through of air for 18 hours then extraction takes place with ethyl acetate. The product is purified by chromatography on silica eluting with a methylene chloride - ethyl ether mixture (75-25) and 0.634 g of expected crystallized product is obtained.

IR Spectrum ($CHCl_3$)

Absorptions at 3615 cm^{-1} (OH), 1746 cm^{-1} (-OAC), 1730 cm^{-1} (non conjugated C=O), 1668-1631 and 1610 cm^{-1}: 1,4 3-one.

NMR Spectrum ($CDCl_3$, 300 MHz, ppm)
0.93 (d): CH_3 in position 16 and 0.93 (s): CH_3 in position 13; 1.58: CH_3 in position 10; 2.13-2.15: CH_3 of Ac; 2.74: 17alpha-OH; 4.71-4.99: 2H in position 21; 5.42: H in position 11alpha; 6.11: H in position 4; 6.33: H in position 2; 6.82: H in position 1.

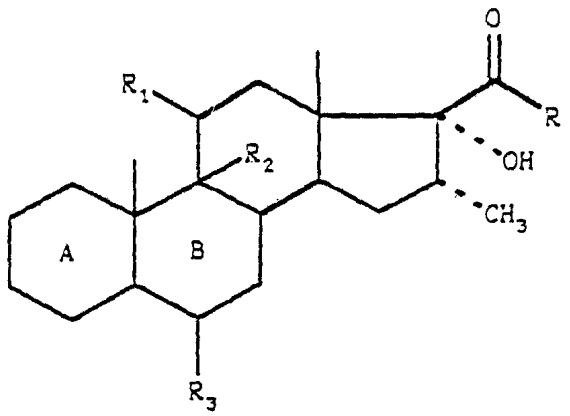
EXAMPLE 6: 9beta, 11beta-epoxy 16alpha-methyl 17alpha-hydroxy 21-acetyloxy pregna 1,4-diene 3,20-dione

The operation is carried out as indicated in Example 1, using at the start 0.766 g of the 9,11-epoxy derivative and 0.02 g of monohydric cupric acetate in 10 cm^3 of tetrahydrofuran, 0.8 cm^3 of a 3M solution of methyl magnesium bromide in ether and 8 cm^3 of a phosphate buffer solution (1 mol of H_3PO_4 for 1.2 mol of soda).

After 5 minutes under agitation and an inert gas atmosphere at 0°C, the temperature is left to rise to +18°C, agitation and the bubbling through of air is continued for 30 minutes and 1.2 cm^3 of tetrahydrothiophene is added. The reaction medium is kept under agitation and bubbling through of air for 4 hours, another 0.4 cm^3 of tetrahydrothiophene is added and agitation and bubbling through is continued. After decanting and extracting with ethyl acetate, the organic phase is washed with water, dried and the solvent is evaporated off. The crude product is purified by chromatography on silica eluting with a methylene chloride - ether mixture (7-3). 0.6075 g of expected product is obtained which is identical to that obtained in Example 1.

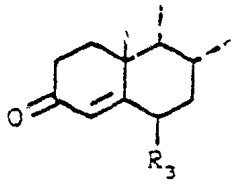
The claims defining the invention are as follows:

1) Preparation process for the compounds of formula (I):

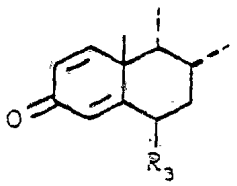


(I)

in which the rings A and B represent a remainder:

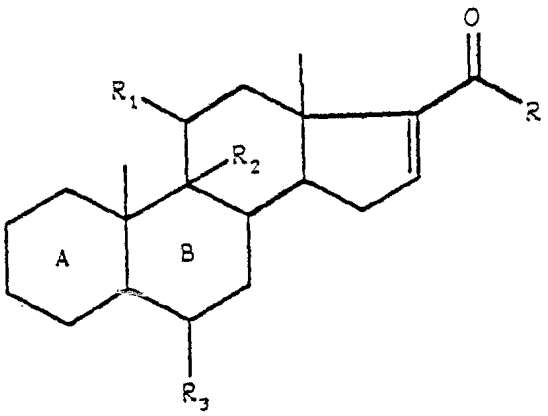


in which the ketone function in position 3 is optionally protected in the form of a ketal, thioketal, hemithioketal or enol ether, or a remainder:



R represents a methyl radical or a $-CH_2-OR'$ radical, in which R' represents a hydrogen atom or an ether remainder or an ester remainder, R_1 and R_2 form together a second bond, or R_1 and R_2 form together an epoxide in position beta, or R_1 represents a hydrogen atom, a ketone function or a hydroxy function in position alpha or beta, free or protected in the form of an ether or ester and R_2 represents a hydrogen atom, or R_1 represents a hydrogen atom and R_2 represents a hydroxy function in position alpha, or R_1 represents a hydroxy function in position beta, free or protected in the form of

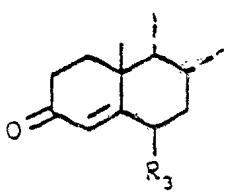
an ether or ester and R_2 represents a fluorine or bromine atom in position alpha, and R_3 represents a hydrogen atom or a fluorine atom or a methyl radical, in position alpha or beta, characterized in that a compound of formula (II):



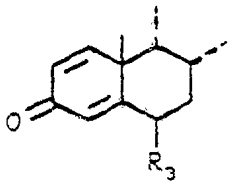
(II)

in which A, B, R, R_1, R_2 and R_3 have the meaning already indicated, is treated with a methylation agent in the presence of a copper-based catalyst, then the methylated enolate intermediate thus obtained is hydrolyzed to obtain the ~~enolate~~ corresponding enol which is oxidized with molecular oxygen in the presence of a reducing and complexing agent of the copper, in order to obtain the expected compound.

2) Process according to claim 1, characterized in that at the start a compound of formula (II) is used in which rings A and B represent a remainder:



or



in which R_3 is defined as in claim 1 and the ketone function in position 3 is free.

3) Process according to claim 1 or 2, characterized in that at the start a compound of formula (II) is used in which R_1 and R_2 form together a second bond, or R_1 and R_2 form together an epoxide in position beta, or R_1 represents a

AUSTRALIA PATENT OFFICE

hydroxy function in position beta, free or protected in the form of an ether or ester and R_2 represents a fluorine atom in position alpha, and R_3 represents a hydrogen atom, a fluorine atom or a methyl radical.

4) Process according to any one of claims 1 to 3, characterized in that at the start a compound of formula (II) is used in which R_3 represents a hydrogen atom.

5) Process according to any one of claims 1 to 4, characterized in that the methylation agent is a methylated copper derivative or a methyl magnesium chloride, bromide or iodide used in the presence of a copper-based catalyst.

6) Process according to any one of claims 1 to 5, characterized in that the methylation agent is methyl magnesium chloride, bromide or iodide used in the presence of cupric acetate or propionate.

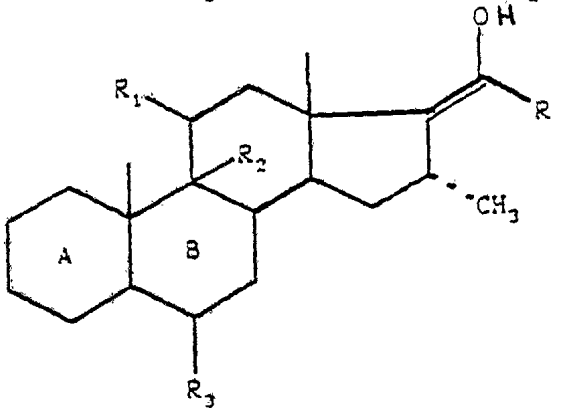
7) Process according to any one of claims 1 to 6, characterized in that the hydrolysis agent is chosen from the group constituted by a monoalkaline phosphate, ammonium chloride, a weak acid and a buffer of weakly acidic pH.

8) Process according to any one of claims 1 to 7, characterized in that the enol oxidation is carried out using oxygen or air.

9) Process according to any one of claims 1 to 8, characterized in that the reducing and complexing agent of the copper is chosen from the group constituted by dialkylsulphides, tetrahydrothiophene, trialkylphosphites, triphenylphosphite and triphenylphosphine.

10) Process according to any one of claims 1 to 9, characterized in that the reducing and complexing agent of the copper is chosen from the group constituted by dimethylsulphide and tetrahydrothiophene.

11) As new industrial products, the compounds of formula (III)

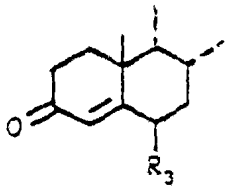


(III)

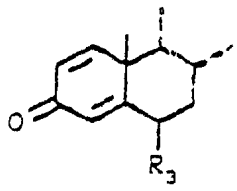
AUSTRALIA PATENT OFFICE

in which A, B, R, R_1, R_2 and R_3 are defined as in claim 1.

12) As new industrial products the compounds of formula (III) defined as in claim 11 in which rings A and B represent a remainder:



or



in which R_3 is defined as in claim 1 and the ketone function in position 3 is free and R_1 and R_2 form together a second bond, or R_1 and R_2 form together an epoxide in position beta, or R_1 represents a hydroxy function in position beta, free or protected in the form of an ether or ester and R_2 represents a fluorine atom in position alpha, and R_3 represents a hydrogen atom, a fluorine atom or a methyl radical.

D A T E D this 11th day of June 1993

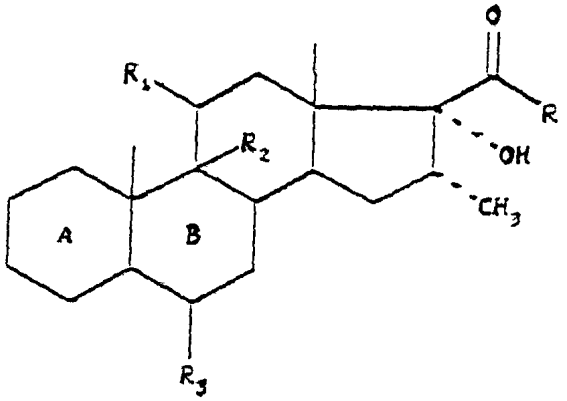
ROUSSEL-UCLAF

By their Patent Attorneys:

CALLINAN LAWRIE

ABSTRACT

The invention relates to a new process for preparing compounds of formula (I):



(I)

in which rings A and B represent a 3-keto 4 6-R_3 remainder, optionally in the protected form in position 3, or 3-keto 1,4 6-R_3 remainder, R is methyl or $-CH_2OR'$ where R' is hydrogen or an ether or ester remainder, R_1 and R_2 form an epoxide in position beta, a second bond, or R_1 is hydrogen, ketone, or hydroxy in position alpha or beta, optionally in etherified or esterified form, and R_2 is hydrogen, or R_1 is hydrogen and R_2 is alpha-hydroxy, or R_1 is beta-hydroxy optionally etherified or esterified and R_2 is a fluorine or a bromine in position alpha, R_3 is hydrogen, fluorine or methyl in position alpha or beta, according to which a 16(17) derivative is treated with a methylation agent, then the intermediate is hydrolyzed and the enol so obtained is oxidized with molecular oxygen in the presence of an appropriate reducing agent.

The compounds (I) are known anti-inflammatory agents or possible precursors.