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(71) Applicant *(for all designated States except US)*: **UNIVERSITE DE LA MEDITERRANEE** [FR/FR]; 58, boulevard Charles Livon, F-13284 MarseillE Cedex 07 (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BRUNEL, Jean Michel** [FR/FR]; 68, Bd des Alpes, Bât C3 Les Hespérides, F-13012 Marseille (FR). **VIDAL, Nicolas** [FR/FR]; Chez Pierre Stocker, 10 Bd Tempête, F-13820 Ensues la Redonne (FR). **PAGES, Jean-Marie** [FR/FR]; 6, rue Monte Cristo, F-13005 Marseille (FR). **LETOURNEUX, Yves** [FR/FR]; Résidence le Marceau, 110 Bd de Paris, F-13003 Marseille (FR).

(74) Agent: **SANTARELLI**; Bureau de Marseille, 146 Rue Paradis, F-13294 Marseille Cedex 6 (FR).

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(54) Title: NEW PROCESS OF SYNTHESIS OF A SQUALAMINE AND/OR TRODUSQUEMINE PRECURSOR

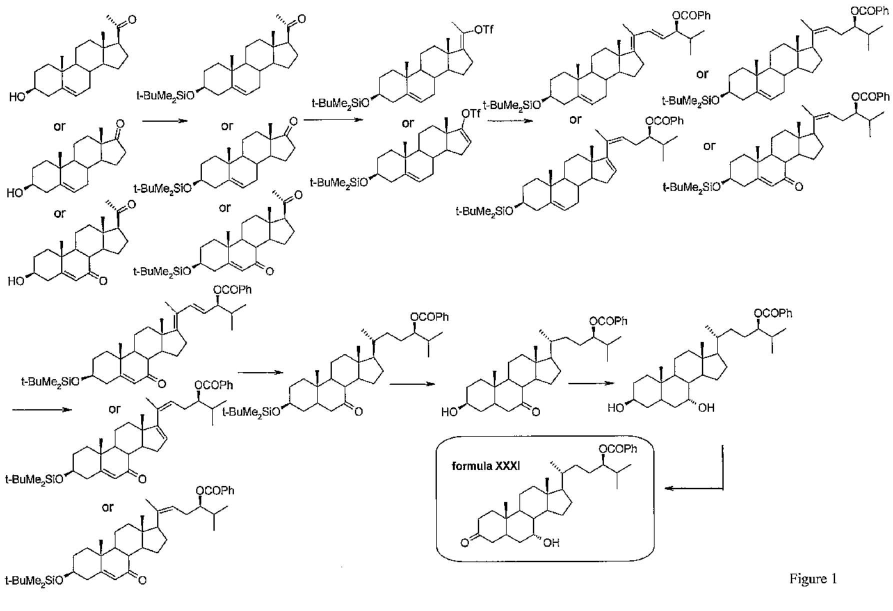


Figure 1

(57) **Abstract:** The invention relates to a new process of synthesis of a squalamine and/or trodusquemine precursor like 24-substituted oxy-7-substitutedoxycholestan-3- one, preferably of 24β-benzoyloxy-7α-hydroxycholestan-3-one.

New process of synthesis of a squalamine and/or trodusquemine precursor

The invention relates to a new process of synthesis of a squalamine and/or trodusquemine precursor.

Issued from the tissues of dogfish shark *Squalus Acanthias*, squalamine and trodusquemine belong to a novel class of water soluble cationic steroids and are the first example of natural products which are adducts of a polyamine and a sterol.

These compounds display potent antifungal and antibacterial activities against various yeasts and both Gram negative and Gram positive bacteria. However the most significant property is their antiangiogenic activity which led to their development for cancer chemotherapy in the treatment of late stage lung cancer and ovarian cancer.

At present the feasibility of obtaining large quantities of steroidal antibiotic from natural sources appears questionable since only trace amounts of squalamine and trodusquemine are present in the liver and gallbladder of the shark.

To date several synthetic routes have been established to prepare these compounds on a large scale to supply them for clinical trials.

Thus, the first synthesis of squalamine has been performed in 1994 by Moriarty *et al.* from 3β-acetoxy-5-cholenic acid in a 17 steps sequence and 0.3% overall yield epimeric in C-24.

In 2000, Kinney *et al.* (Kinney, W. A.; Jones, S.; Zhang, X.; Rao, M. N.; Bulliard, M.; Meckler, H.; Lee, N. In *PCT Int. Appl.*; (Magainin Pharmaceuticals Inc., USA). Wo, 1998, p 116 pp. and Kinney, W. A.; Zhang, X.; Williams, J. I.; Johnston, S.; Michalak, R. S.; Deshpande, M.; Dostal, L.; Rosazza, J. P. N. *Organic Letters* 2000, *2*, 2921-2922.) reported a ten steps preparation of squalamine from 3-keto-23,24-bisnorchol-4-en-22-ol in 9% overall yield and 91% diastereomeric excess (de).

More recently, Zhou *et al. (Zhou, X. D.; Cai, F.; Zhou, W. S. Tetrahedron Letters 2001, 42, 2537-2539* and *Zhou, X.-D.; Cai, F.; Zhou, W.-S. Tetrahedron 2002, 58, 10293-10299)* have described a stereoselective construction of squalamine sidechain by using methyl-3-keto-5α-chenodeoxycholanate as starting material. This short route to squalamine was achieved in eleven steps with an overall yield of 19% and 99% de but the starting material involved in this synthesis remains still expensive.

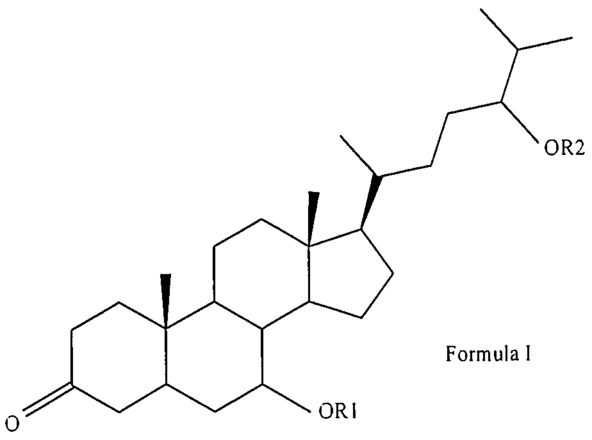
It is one of the aims of the present invention to propose a stereoselective preparation of 24-benzoyloxy-7-hydroxycholestan-3-one, preferentially 24-benzoyloxy-7a-hydroxycholestan-3-one, key intermediate valuable for the total synthesis of squalamine or trodusquemine using of commercially available inexpensive starting material as for example pregnelone.

The stereoselective controlled synthesis of the lateral chain group and its introduction on a sterol moiety constitutes the innovative and new step of the process of the invention.

According to the invention, is meant by :

- an alkyl group, a carbon radical with 1 to 24 carbon atoms, either linear or branched, possibly substituted with a halogen atom, a hydroxyl radical, an amino group, a carboxylic acid group. By an either linear or branched carbon radical having 1 to 6 carbon atoms, is meant a radical selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl radicals. According to the invention, a preferred alkyl group is a methyl radical;
- an aryl group, a radical derived from a monocyclic or polycyclic aromatic group having from 6 to 10 carbon atoms, optionally substituted with one or more substituents. The substituants may be selected from a halogen atom, an alkyl group, either linear or branched, having from 1 to 4 carbon atoms, optionally substituted with one or more halogen atoms, with a hydroxyl group, with an amino group, or with an alkoxy group having from 1 to 3 carbon atoms, a hydroxyl group, a nitro group, a cyano group, a 1,3-dioxolyl group, a carbonyl group, a methylsulfonyl group or an amino group optionally mono-or di-substituted with an alkyl group having from 1 to 3 carbon atoms; preferentially according to the invention, the aryl group is a phenyl group optionally substituted as defined above;

The invention relates to an innovative process of synthesis of 24-substituted oxy-7-substitutedoxycholestan-3-one of formula I

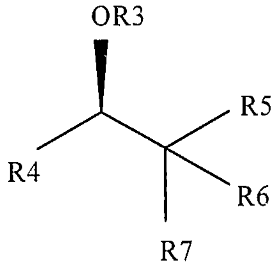


Formula I

wherein R1 and R2 can be, simultaneously or independently, an alkyl, aryl, ester, ether, silyl, substituted silyl, sulfate or phosphate group.

process in which in

- step A, one prepares an oxy disubstituted derivative of formula II

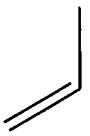


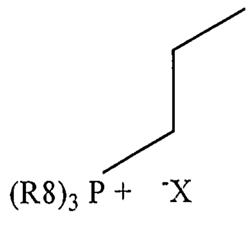
Formula II

wherein

R3 represents an ester or an ether group

R4 represents a vinyl group, methylallyl group or a diethylphosphonium group of formula IIa, IIb or IIC

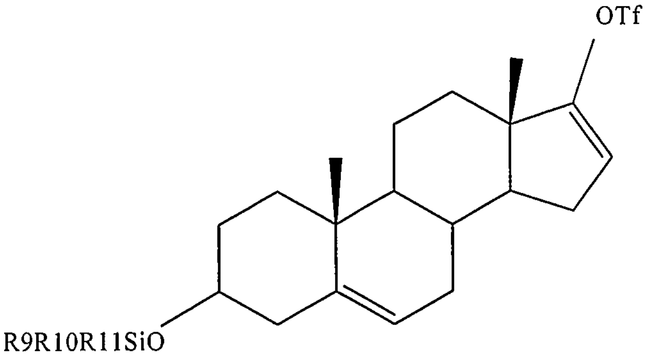




Formula IIa or Formula IIb or Formula IIc and

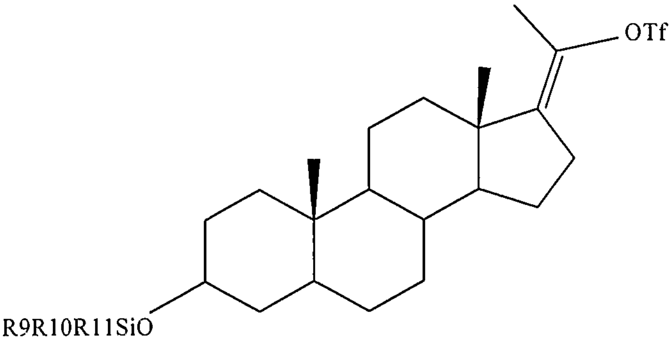
R5, R6, R7 and R8 represent an alkyl, aryl, halide or amine group

- step B, one prepares a 3-siloxy-18-trifluoromethanesulfonyloxy dehydroepiandrosterone derivatives of formula III



Formula III

or a 3-siloxy-20-trifluoromethanesulfonyloxy pregnane derivative of formula IV

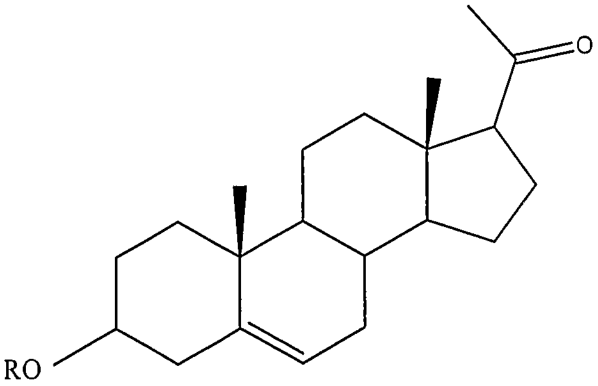


Formula IV

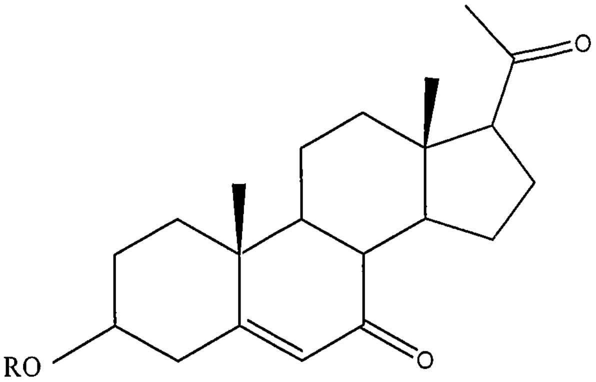
in which R9, R10 and R11, different or identical, represent a linear or branched alkyl or ether radical, with 1 to 24 carbons, preferentially with 1 to 4 carbons, or an aryl radical (phenyl or substituted phenyl group);

or a 3-substituted oxy pregnenolone of formula V,

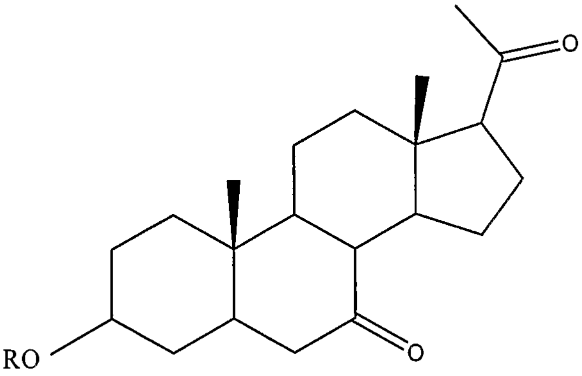
or a 3-substituted oxy-7-oxy pregnane derivatives of formula VI or VII.



Formula V



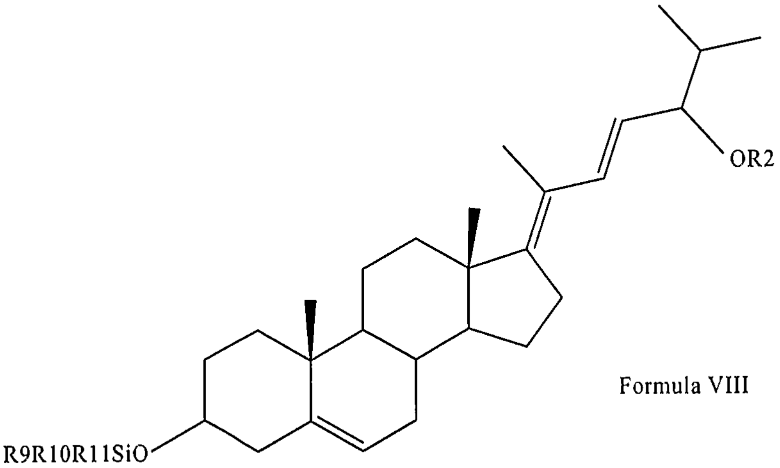
Formula VI



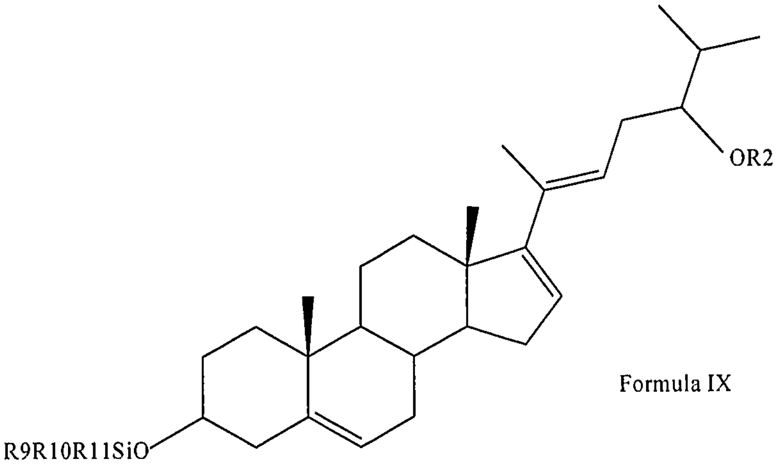
Formula VII

wherein R represents an ether, silyl, substituted silyl or ester group;

- step C, one prepares a pregnane derivative of formula VIII or IX



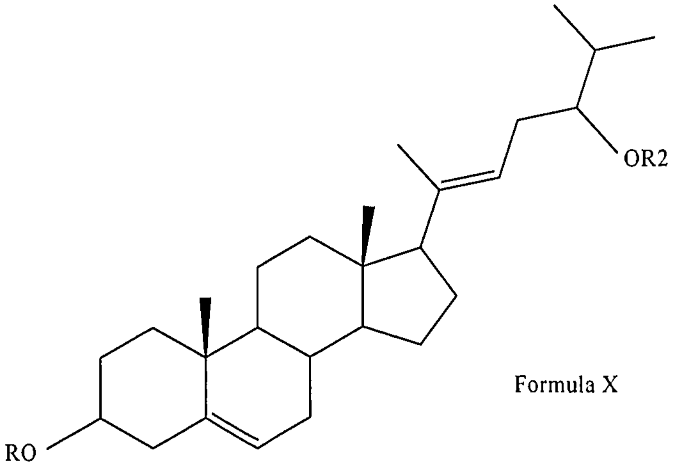
Formula VIII



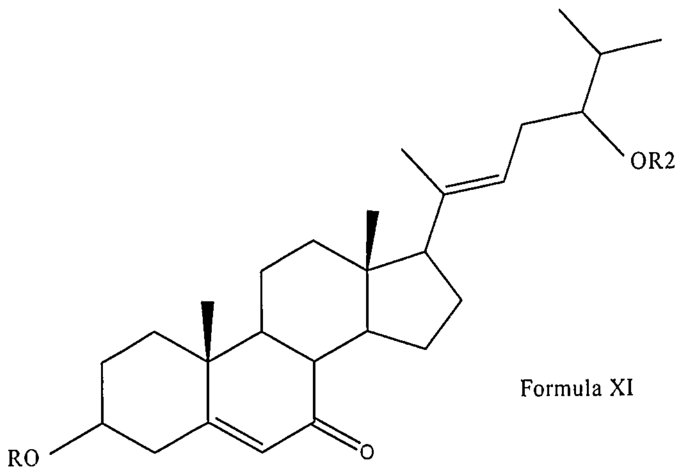
Formula IX

by reacting the substited oxy derivative IIa or IIb obtained in step A with the activated pregnane derivatives (formula III-IV) obtained in step B, in the presence of a first catalyst made of a mixture of Palladium acetate [$Pd(OAc)_2$] or Palladium salt like $Pd(OAc)_2$ and a first ligand like a phosphine, for example triphenylphosphine, tributylphosphine, tri *tert*-butyl phosphine and preferentially tri-*ortho*-tolylphosphine, under inert atmosphere like argon or nitrogen, in a first polar solvent like diméthylformamide (DMF) or dimethylacetamide or hexamethylphosphoramide (HMPA), and in the presence of a first base, which can be an aromatic amine like triethylamine or pyridine at a temperature comprised between 50°C to 70°C, preferentially 60°C, during 1 to 24 hours, preferably 12 hours, the expected compound being eventually purified;

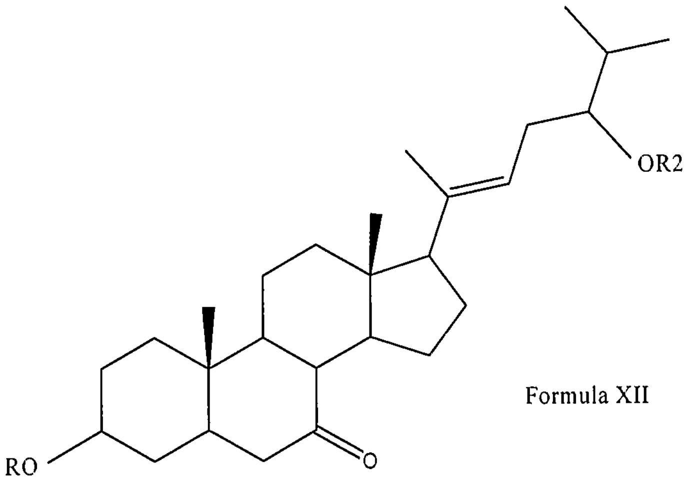
or one prepares a pregnane derivative of Formula X, XI or XII



Formula X



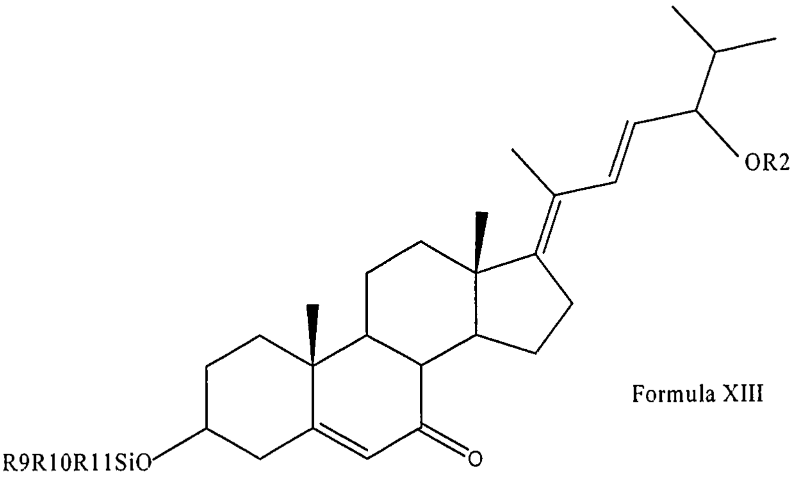
Formula XI



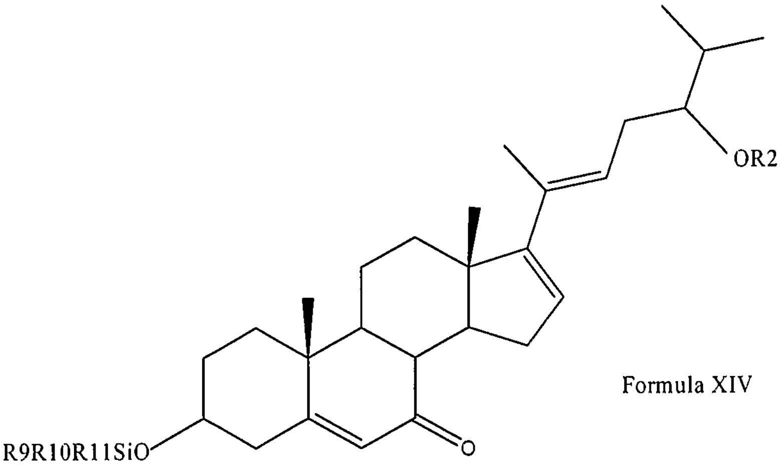
Formula XII

by reacting the substited oxy derivative IIc obtained in step A with the pregnane derivatives (formula V-VII) obtained in step B, in the presence of a second base like sodium hydride, lithium hexamethyldisilazane, butyllithium, sec-butyllithium or tert-butyllithium, preferentially sodium hydride under inert atmosphere like argon or nitrogen, in a second polar solvent like THF at a temperature comprised between 0 to 25°C, preferentially 0°C, during 1 to 24 hours, preferably 12 hours, the expected compound being eventually purified;

- step D, one prepares a 3-siloxy-24-substituted oxy-7 one pregnane derivatives of formula XIII or XIV or a 3-substituted-24-substituted oxy-7 one pregnane derivatives of Formula XI



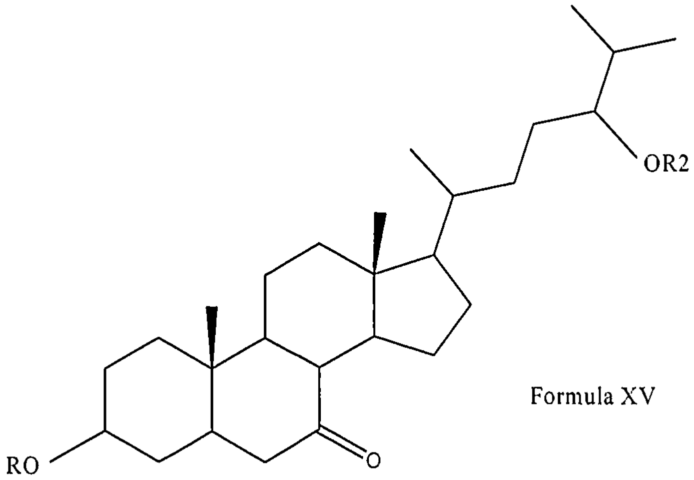
Formula XIII



Formula XIV

by oxidizing derivatives of formula VIII or X obtained in step C, the expected compound being eventually purified;

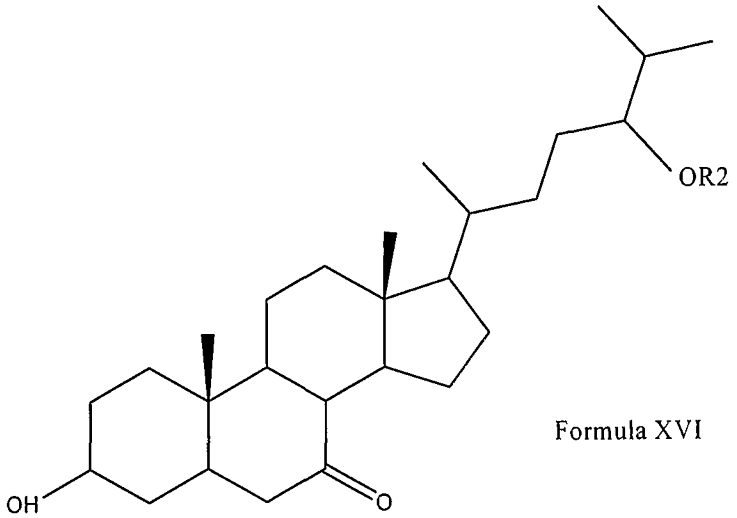
- step E, one prepares a 3-substituted oxy-24-substituted 7-one derivative of formula XV



Formula XV

by hydrogenation of the 3-substituted-24-substituted oxy-7-one derivative of formulas XI, XII, XIII or XIV obtained in step C or D, in the presence of a catalyst, preferentially platinum oxide catalyst, under hydrogen, at a pressure comprised between 1 to 100 bars, preferably 3 bars, during 1 to 30 hours, preferably 24 hours, preferably at 25°C, in a polar solvent like DMF, dimethylacetamide, THF, dioxame or hexamethylphosphoramide (HPMA), the expected compound being eventually purified;

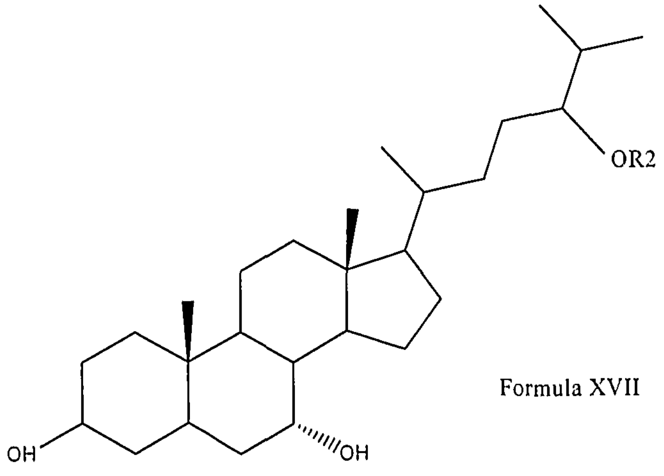
- step F, one prepares a 24-substituted oxy-3-hydroxycholestan-7-one derivative of formula XVI



Formula XVI

by deprotection of the 3-substituted-24-substituted-7-one derivative of formula XV obtained in step E preferentially in presence of a fluorhydric acid-based reagent (HF-based reagent), the expected compound being eventually purified;

- step G, one prepares a 24-substituted oxy-3,7-dihydroxycholestane derivative of formula XVII



Formula XVII

by the reduction of the ketone in position 7 of the 24-substituted-3-

hydroxycholestan-7-one derivative of formula XVI obtained in step F with a stereoselective reducing hydride reagent, preferentially

- in the presence of potassium tri-*sec*-butylborohydride (L-selectride®) to obtain a 7α dihydrocholestane
- or lithium/NH3 to obtain a 7βdihydrocholestane

at a temperature raising from-78°C to room temperature (25°C), the expected compound being eventually purified;

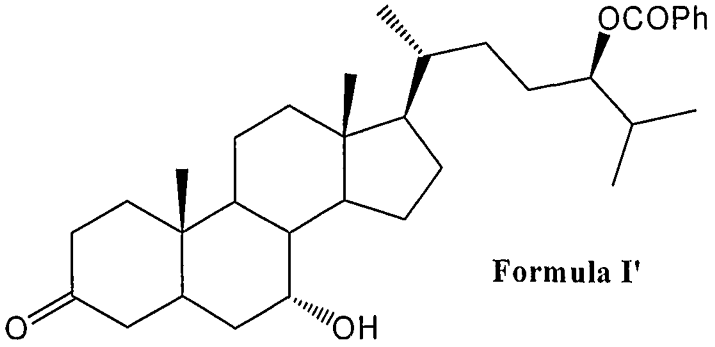
❖ step H, one prepares the 24-substituted oxy-7-hydroxycholestan-3-one of formula I by oxidation of the hydroxyl substituant in position 3 of the 24-substituted-3,7-dihydroxycholestane derivative of formula XVII obtained in step G, in presence of silver carbonate in a solvent preferentially like toluene, benzene, hexane, heptane or cyclohexane, at the reflux temperature of the solvent, the expected compound being eventually purified.

According to the invention, the process renders possible the synthesis of 3, 7 and/or 24 α or β substituted compounds. Preferentially the process of the invention is used to prepare 3β, 24β and 7α substituted compounds.

For example, in one preferred embodiment, one of the aims of the present invention is to propose a stereoselective preparation of 24β-benzoyloxy-7α-hydroxycholestan-3-one key intermediate valuable for the total synthesis of squalamine or trodusquemine implying the use of easily available cheaper starting material as for example pregnelone.

Contrarily to all the other reported methods, the stereoselective controlled synthesis of the lateral chain group and its introduction on a sterol moiety constitutes the key step of the process of the invention.

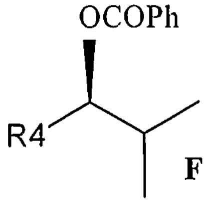
Thus, the invention relates to a new process of synthesis of 24β-benzoyloxy-7α-hydroxycholestan-3-one of formula I'



Formula I'

in which in

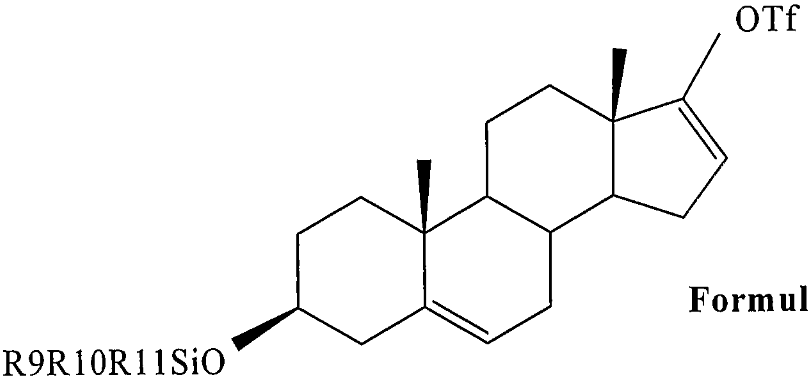
❖ step A, one prepares a benzoate derivative of formula II



Formula II'

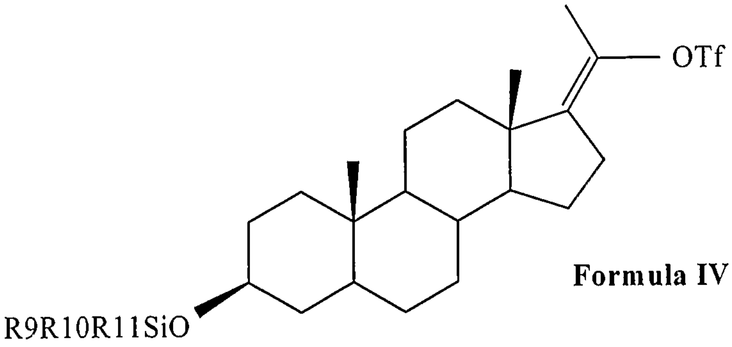
in which R4 represents a vinyl group or a methylallyl group;

❖ step B, one prepares a 3β-siloxy-18-trifluoromethanesulfonyloxydehydroepiandrosterone derivatives of formula III



Formula III

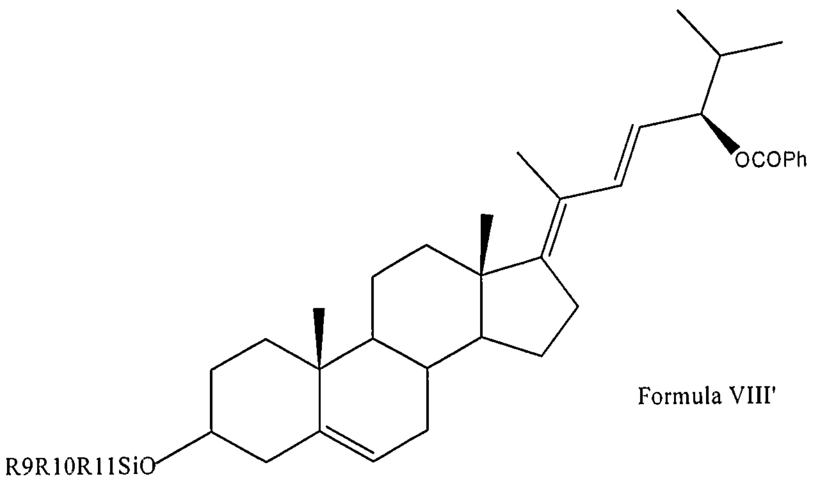
or a 3β-siloxy-20-trifluoromethanesulfonyloxy pregnenane derivative of formula IV



Formula IV

in which R9, R10 and R11, different or identical, represent a linear or branched alkyl radical, with 1 to 24 carbons, preferentially with 1 to 4 carbons, or an aryl radical (phenyl or substituted phenyl group);

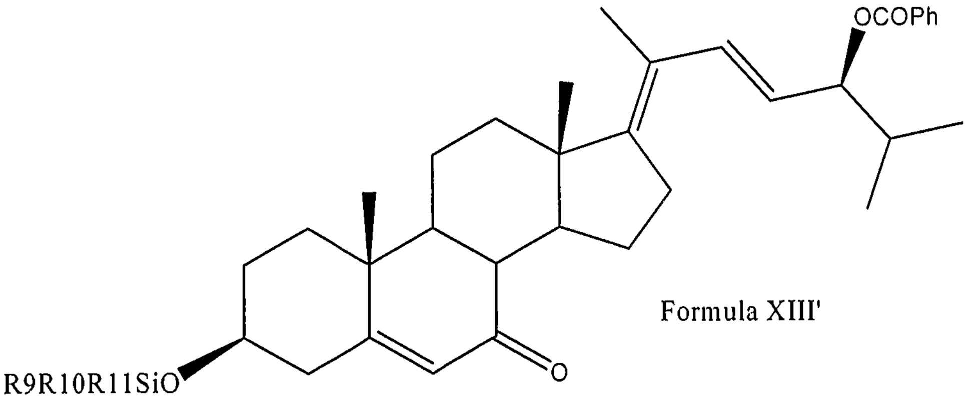
❖ step C, one prepares a 3β-siloxy-24β-benzoyloxy-5,20,22 triene-hydroxycholestane derivative of formula VIII'



Formula VIII'

by reacting the benzoate derivative obtained in step A with the 3β-siloxy-20-trifluoromethanesulfonyloxy pregnenane derivative (formula IV) or a 3β-siloxy-18-trifluoromethanesulfonyloxy dehydroepiandrosterone derivative (formula III) obtained in step B, in the presence of a first catalyst made of a mixture of Palladium acetate [$Pd(OAc)_2$] or Palladium salt like $Pd(OAc)_2$ and a first ligand which can be a phosphine ligand like triphenylphosphine, tributylphosphine, tri *tert*-butyl phosphine and preferentially tri-*ortho*-tolylphosphine in a 1:2 P/Ligand ratio, under inert atmosphere like argon or nitrogen, in a first polar solvent like DMF or dimethylacetamide, and a first base like triethylamine or pyridine at a temperature comprised between 50°C to 70°C, preferentially 60°C, during 10 to 24 hours, preferably 12 hours, the expected compound being eventually purified;

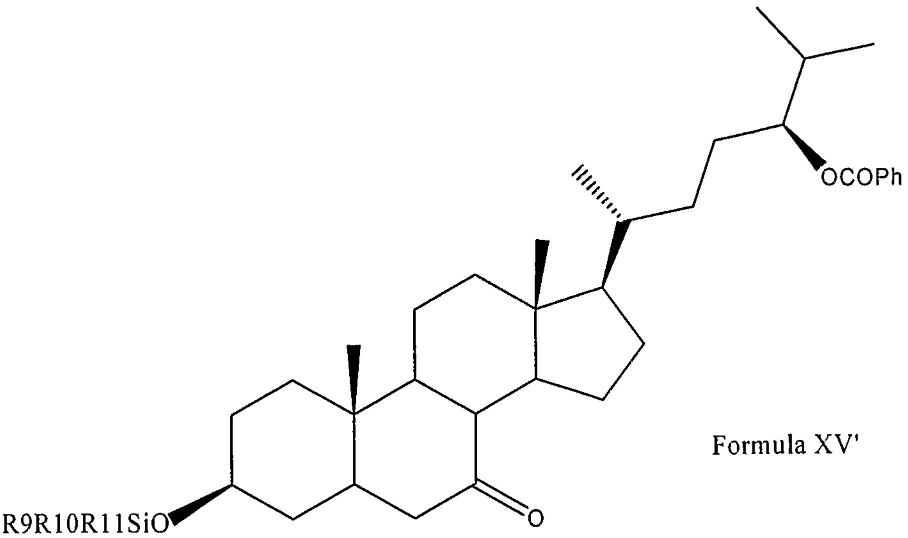
- step D, one prepares a 3β-siloxy-24β-benzoyloxy-5, 20, 22 triene-hydroxycholestane-7-one derivative of formula XIII'



Formula XIII'

by oxidizing a 3β-siloxy-24β-benzoyloxy-5, 20, 22 triene-hydroxycholestane derivative of formula VIII' obtained in step C, the expected compound being eventually purified;

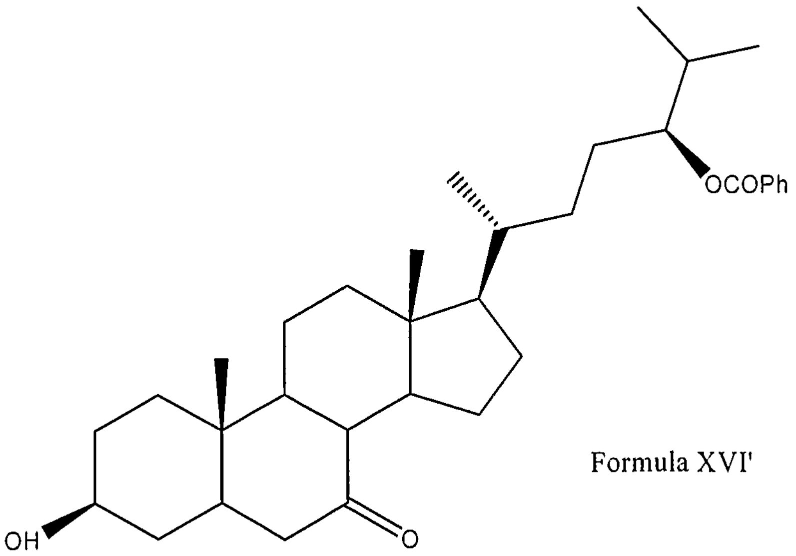
- step E, one prepares a 3β-siloxy-24β-benzoyloxy-7-one derivative of formula XV'



Formula XV'

by hydrogenation of the 3β-siloxy-24β-benzoyloxy-5, 20, 22 triene-hydroxycholestane-7-one derivative of formula VIII' obtained in step D, in the presence of platinum oxide under hydrogen under pressure, during 1 to 30 hours, preferably 24 hours, at a temperature comprised between 20 to 30 °C, preferably 25°C, in a solvent indifferently chosen as ethyl acetate or ethanol, the expected compound being eventually purified;

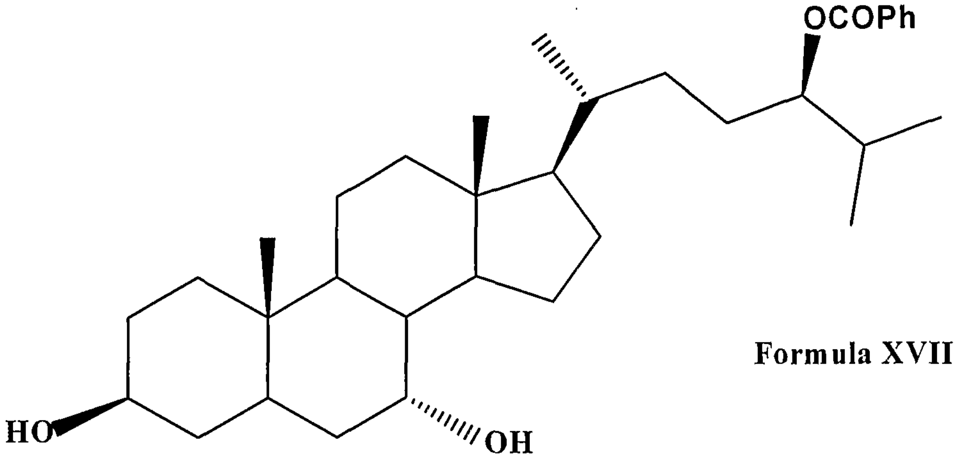
- step F, one prepares a 24β-benzoyloxy-3β-hydroxycholestan-7-one derivative of formula XVI'



Formula XVI'

by deprotection of the 3β-siloxy-24β-benzoyloxy-7-one derivative of formula XV' obtained in step E in presence of a fluorhydric acid-based reagent (HF-based reagent), the expected compound being eventually purified;

- ❖ step G, one prepares a 24β-benzoyloxy-3β,7α-dihydroxycholestane derivative of formula XVIII'



Formula XVIII'

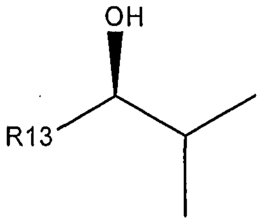
by the reduction of the ketone in position 7 of the 24β-benzoyloxy-3β-hydroxycholestan-7-one derivative of formula XVI' obtained in step F, in the presence of potassium tri-*sec*-butylborohydride (L-selectride®), the expected compound being eventually purified;

- ❖ step H, one prepares the 24-benzoyloxy-7α-hydroxycholestan-3-one of formula I' by oxidation of the hydroxyl substituent in position 3 of the 24β-benzoyloxy-3β,7α-dihydroxycholestane derivative of formula XVIII' obtained in step G, in presence of silver carbonate in an aromatic solvent like toluene, at the reflux temperature of the solvent during 24 hours, the expected compound being eventually purified.

According to the invention, an efficient highly straightforward synthesis of 24-substituted oxy-7-substitutedoxycholestan-3-one of formula I, particularly an efficient highly stereoselective straightforward synthesis of squalamine and trodusquemine precursor of formula I' is described constituting the shorter and chipper synthesis reported to date.

According to step A of the invention, the chiral derivative of formula II may be prepared by any well known processes, as for example according to the method describes by Enders et al. (Enders, D. *Synlett* 1994, 969).

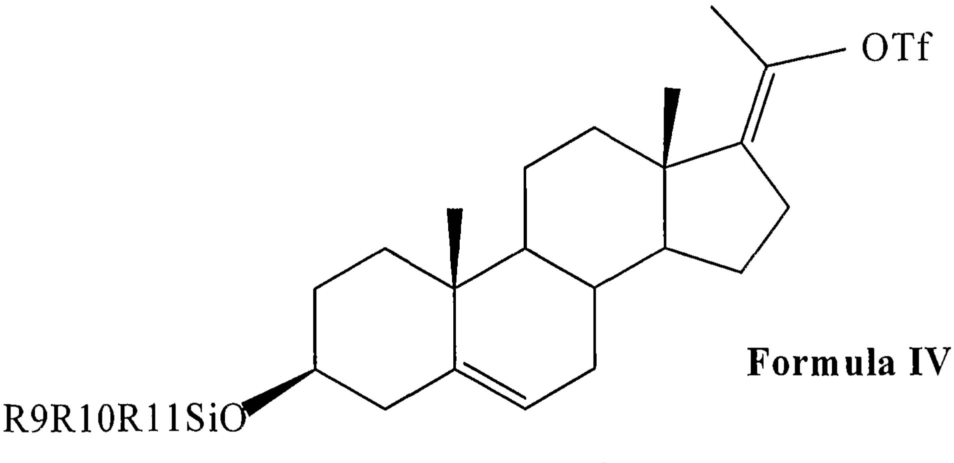
According to one particular embodiment of the invention, the compound of Formula II is a benzoate derivative, obtained by reacting an hydroxyl derivative of formula XVIII.



Formula XVIII

in which R13 represents a vinyl, a methylallyl or an halogeno ethyl group with benzoylchloride in the presence of a base at temperature growing from 0°C to 25°C during a minimum of 24 hours, the expected compound being eventually purified.

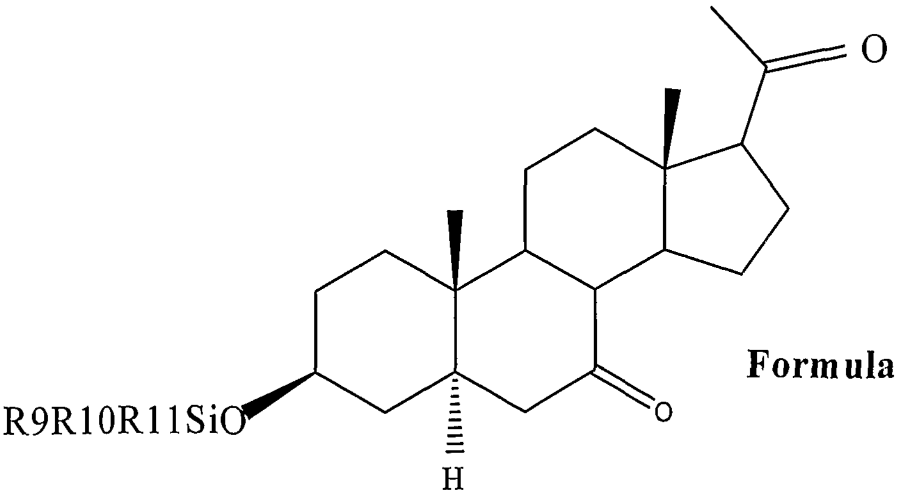
According to a first alternative of step B of the invention, the 3-siloxy-20-trifluoromethanesulfonyloxy pregnane of formula IV



Formula IV

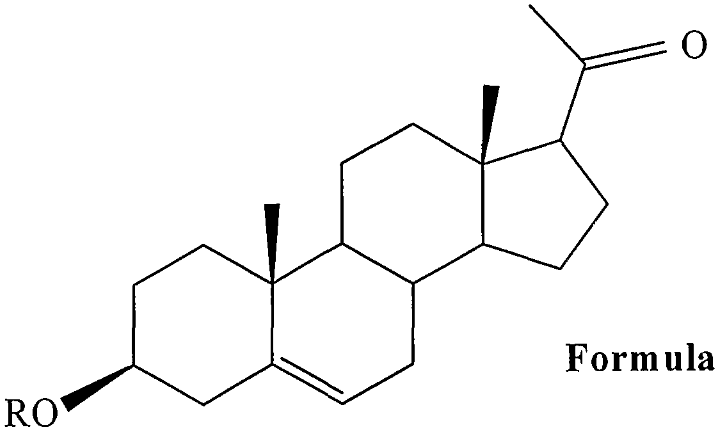
can be prepared according to a process wherein in

- ❖ step B1-1, one prepares a 3-siloxypregnenolone derivative of formula XIX



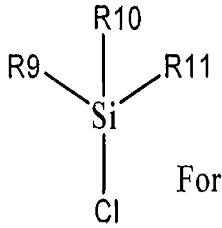
Formula XIX

by reacting a pregnenolone of formula VII



Formula VII

with a chlorosilane derivative of formula XX



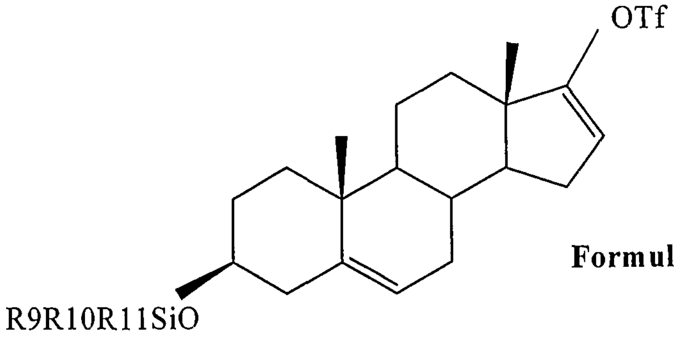
Formula XX

in which R9, R10 and R11, different or identical, represent a linear, branched alkyl or ether radical, with 1 to 24 carbons, preferentially with 1 to 4 carbons, or an aryl radical (phenyl or substituted phenyl group), under inert atmosphere like argon or nitrogen, in the presence of a solvent chosen indifferently from tetrahydrofuran (THF) or other ethers, dichloromethane (CH_2Cl_2) or chloroform ($CHCl_3$) or other chlorinated solvent, or dimethylformamide (DMF) or acetonitrile (CH_3CN) or toluene or benzene in the presence of a base like pyridine or triethylamine , at a temperature between 20 to 50 °C, during 20 to 30 hours, preferentially in presence of DMF at 25°C for 24 hours, the expected compound being eventually purified; and in

- step B1-2, one prepares the 3-siloxy-20-trifluoromethanesulfonyloxy pregnenolone derivatives of formula IV by reacting the 3-siloxypregnenolone derivative of formula XIX obtained in step B1-1 with potassium bis(trimethylsilyl)amide in toluene (5 to 15 %, preferentially 10%) and N-phenyltrifluoromethanesulfonimide in THF, under inert atmosphere like argon, at a temperature comprised between-80°C to-70°C, preferentially-78°C, during 15 to 45 minutes, and then warmed to a temperature around 0°C, the expected compound being eventually purified.

According to a second alternative of step B of the invention, the 3-siloxy-18-

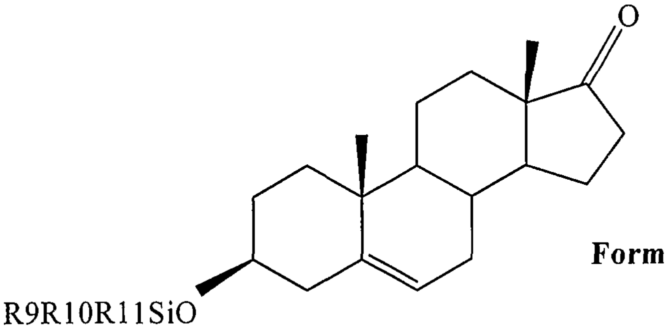
trifluoromethanesulfonyloxy dehydroepiandrosterone derivatives of formula III



Formula III

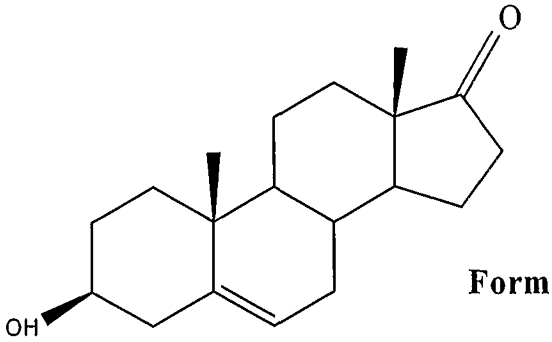
can be prepared according to a process wherein in

- step B2-1, one prepares a 3-siloxydehydroepiandrosterone derivative of formula XXI



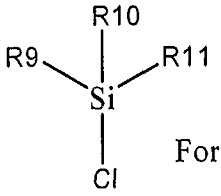
Formula XXI

by reacting a dehydroepiandrosterone XXII



Formula XXII

with a chlorosilane derivative of formula XX

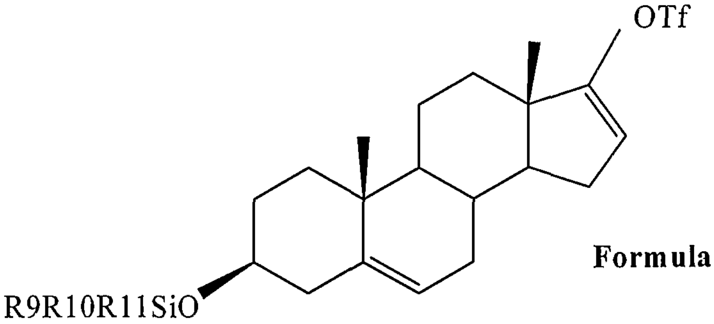


$\mathrm{R9R10R11SiCl}$

Formula XX

in which R9, R10 and R11, different or identical, represent a linear, branched alkyl or ether radical, with 1 to 24 carbons, preferentially with 1 to 4 carbons, or an aryl radical (phenyl or substituted phenyl group), under inert atmosphere like argon or nitrogen, in the presence of a solvent chosen indifferently from tetrahydrofuran (THF) or other ethers, dichloromethane (CH_2Cl_2) or chloroform ($CHCl_3$) or other chlorinated solvent, or dimethylformamide (DMF) or acetonitrile (CH_3CN) or toluene or benzene in the presence of a base like pyridine or triethylamine , at a temperature between 20 to 50 °C, during 20 to 30 hours, preferentially in presence of DMF at 25°C for 24 hours, the expected compound being eventually purified; and in

- step B2-2 one prepares the 3-siloxy-18-trifluoromethanesulfonyloxy dehydroepiandrosterone derivative of formula III



Formula III

by reacting the 3-siloxydehydroepiandrosterone derivative of formula XXI obtained in step B2-1 with potassium bis(trimethylsilyl)amide in toluene (5 to 15 %, preferentially 10%) and N-phenyltrifluoromethanesulfonimide in THF, under inert atmosphere like argon, at a temperature comprised between-80°C to-70°C, preferentially-78°C, during 15 to 45 minutes, and then warmed to a temperature around 0°C, the expected compound being eventually purified.

According to the invention, at each steps, the expected compound is preferentially purified according to well known methods. Preferentially the compounds may be purified by chromatography, for example on a silicagel column or by crystallization.

According to the invention in step D, the oxidation may be performed by well known methods. In one particular embodiment of the invention, the oxidation may be performed for example in the presence of ruthenium trichloride and *tert*-butylhydroperoxide in cyclohexane, during 20 to 30 hours, preferentially 24 hours, at a temperature comprised between 20 to 30°C, preferentially 25 °C.

In another embodiment of the invention, the oxidation of step D may be performed for example in the presence of $Na_2Cr_2O_7$ in acetone, during 45 to 50 hours, preferentially 48 hours, at a temperature comprised between 35 to 45°C, preferentially 40 °C, in the presence of sodium sulfite.

Preferentially according to the invention, the oxidation of step D may be performed in the presence of N-hydroxyphtalamide, under a flux of oxygen or air, in the a 50/50 solvent mixture of ethylacetate and acetone, at 60°C, during 30 to 40 hours, preferentially 36 hours.

According to the invention, in step F of the process of synthesis the deprotection may be performed in the presence of a fluorhydric acid-based reagent (HF-based reagent), in a solvent chosen from tetrahydrofuran (THF) or other ethers, dichloromethane (CH_2Cl_2) or Chloroform ($CHCl_3$) or other chlorinated solvent, or acetonitrile (CH_3CN) or ethyl acetate or diethylether, at temperature raising from-85°C to-65°C, preferentially-78°C, to 25°C during a time comprised between 30 to 60 minutes, preferentially 45 minutes.

According to the invention HF-based reagent may be chosen from tetrabutylammoniumfluoride $(Bu_4)N$, tetraalkylarylammoniumfluoride derivative or polymer-bound ammonium fluoride salt, preferentially the HF-based reagent is tetrabutylammoniumfluoride $(Bu_4)N$.

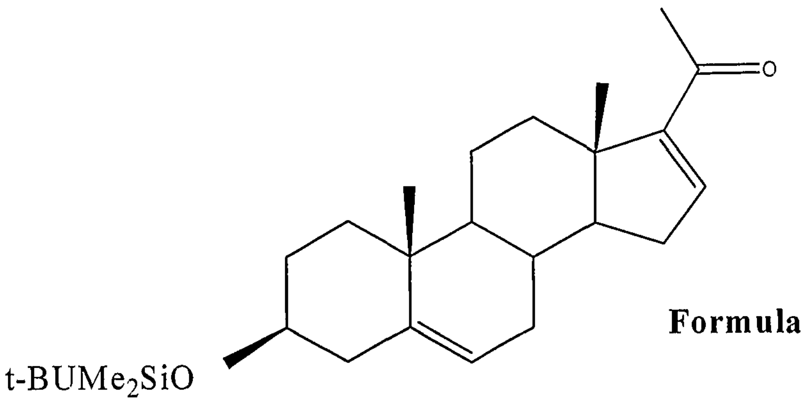
Other characteristics and advantages of the invention will appear in Figure 1 which summarizes the complete way of synthesis of 24β-benzoyloxy-7α-hydroxycholestan-3-one (Formula XXXI) and in the following examples which are illustrations of the invention and which do not limit the invention.

Experimental Section

All solvents were purified according to reported procedures, and reagents were used as commercially available. Ethyl acetate and petroleum ether (35-60°C) were purchased from SDS and used without further purification. Column chromatography was performed on SDS silica gel (70-230 mesh). ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AC 300 spectrometer working at 300.00 MHz and 75 MHz, respectively (the usual abbreviations are used: s: singulet, d: doublet, t: triplet, q: quadruplet, m: multiplet). Tetramethylsilane was used as internal standard. All chemical shifts are given in ppm.

Example 1: Example of step B of the invention

Synthesis of 3β-*tert*-Butyl-dimethylsiloxy-pregnenolone of formula XXIII

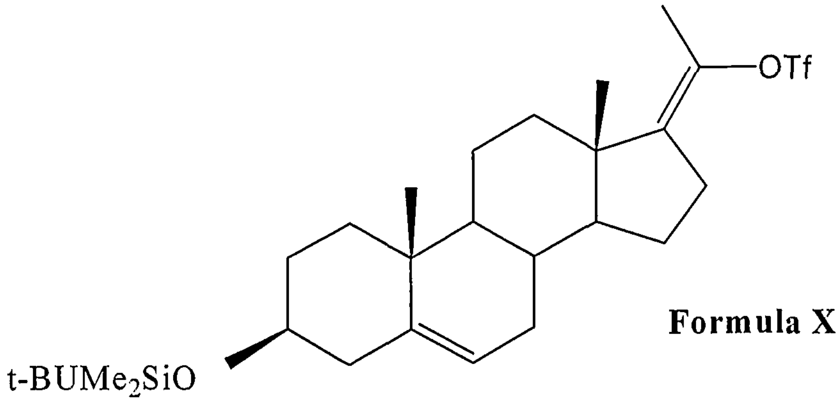


Formula XXIII

A solution of 2g of pregnenolone (6.3 10^{-3} mol) and 474 mg (7 10^{-3} mol) of imidazole in 10 mL of DMF is treated under argon at room temperature with 1 g of *tert*-butyldimethylchlorosilane (7 10^{-3} mol). The reaction mixture is stirred for 48 hours at room temperature, diluted with ethylacetate and washed with water and brine. The organic layer is dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude residue is purified by flash chromatography on silicagel (eluent: petroleum ether/ethylacetate 9/1) affording the expected compound of formula XIV as a white solid in 74% yield (2 g).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6H), 0.60 (s, 3H), 0.86-2.24 (m, 34H), 2.50 (m, 1H), 3.46 (m, 1H), 5.28 (m, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): d =-4.6, 13.15, 18.17, 19.37, 21.03, 22.79, 24.44, 25.88, 31.46, 31.77, 31.83, 32.01, 36.55, 37.35, 38.83, 42.74, 43.94, 50.04, 56.92, 63.66, 72.47, 120.80, 141.47, 209.32.

Example 2: Synthesis of 3β-*tert*-butyl-dimethylsiloxy-20-trifluoromethanesulfonyloxy derivative of formula XXIV

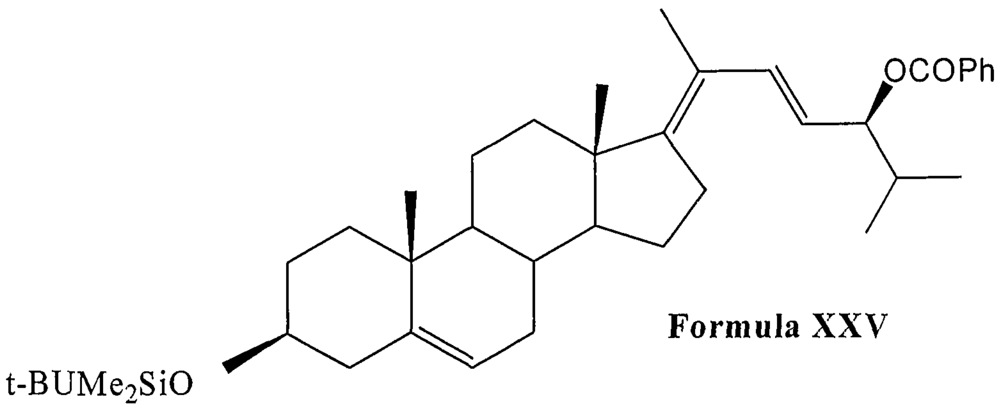


Formula XXIV

A solution of 6.0 mL of potassium bis(trimethylsilyl)amide (10% in toluene) is added under argon at-78°C to a solution of 3β-*tert*-Butyl-dimethylsiloxy-pregnenolone (219 mg, 5.1 10^{-4} mol) dissolved in 25 mL of anhydrous THF. The reaction mixture is warmed to 5°C, stirred for 0.5 hours at this temperature and then cooled to-30°C before the rapid addition of 1.25 g (3.5 10^{-3} mol) of N-phenyltrifluoromethanesulfonimide dissolved in 10 mL of THF. The reaction mixture is warmed to 0°C, stirred at this temperature for additionnal 15 minutes, poured on buffer pH 7 and then extracted three times with Et_2O. The combined ether phases are dried over sodium sulfate, filtered, evaporated to dryness and purified by chromatography on silicagel (eluent: petroleum ether/ethylacetate 97/3) affording the expected compound of formula XXIV as a white solid in 46% yield (133 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.33 (s, 6H), 0.90-95 (m, 3H), 1.17-2.90 (m, 33H), 3.72-3.80 (m, 1H), 5.23-5.59 (m, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): d =-4.61,-0.15, 12.65, 18.21, 19.42, 20.96, 24.09, 25.08, 25.91, 30.30, 32.04, 32.21, 36.59, 37.33, 37.90, 42.80, 43.47, 50.05, 54.61, 55.91, 72.51, 104.01, 120.68, 125.50 (m, CF_3), 129.93, 141.66, 158.34.

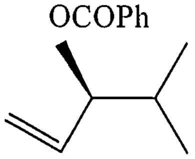
Example 3: Synthesis of 3β-tert-butyldimethylsiloxy-24β-benzoyloxy-5,20,22 triene-cholestane derivative of formula XXV



Formula XXV

In a typical procedure, 7 mg of $Pd(OAc)_2$ (3.0 10^{-5} mol) and 18 mg of tri-*ortho*-tolylphosphine (6.0 10^{-5} mol) were mixed under argon in 2 mL of DMF and warmed at 60°C for 30 minutes. A mixture of 3b-*tert*-butyl-dimethylsiloxy-20-

trifluoromethanesulfonyloxy derivative of formula XXIV (133 mg, 2.4 10^{-4} mol), benzoate derivative of formula XXVI (145 mg, 7.0 10^{-4} mol)

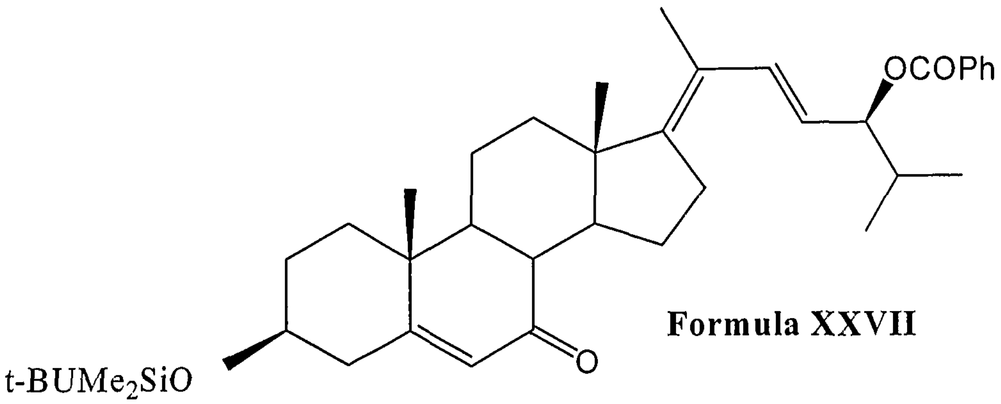


Formula XXVI

and triethylamine (56 µL, 4.0 10^{-4} mol) dissolved in 4 mL of DMF was then added under argon and stirring was maintained at 60°C for 12 hours. After cooling to room temperature, the raction mixture was then diluted with brine and extracted Et_2O and ethylacetate. The organic phase was washed twice with brine, dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silicagel (eluent: petroleum ether/ethylacetate 9/1) affording the expected compound of formula XXVI as a white solid in 28% yield (40 mg).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.05-0.14 (s, 6H), 0.61-3.46 (m, 44H), 4.83-4.99 (m, 2H), 5.42 (m, 2H), 7.42-8.17 (m, 6H). – ^{13}C NMR (75 MHz, $CDCl_3$): d =-3.81, 0.45, 14.13, 14.89, 20.18, 21.90, 23.61, 25.69, 26.32, 28.64, 29.87, 30.47, 32.67, 32.92, 37.88, 38.97, 42.68, 44.46, 50.87, 55.69, 70.63, 75.25, 86.70, 123.23, 129.04, 129.32, 130.31, 131.35, 133.50, 135.31, 140.55, 166.78.

Example 4: Synthesis of 3β-tert-butyldimethylsiloxy-24β-benzoyloxy-5, 20, 22 triene-hydroxycholestane-7-one of formula XXVII

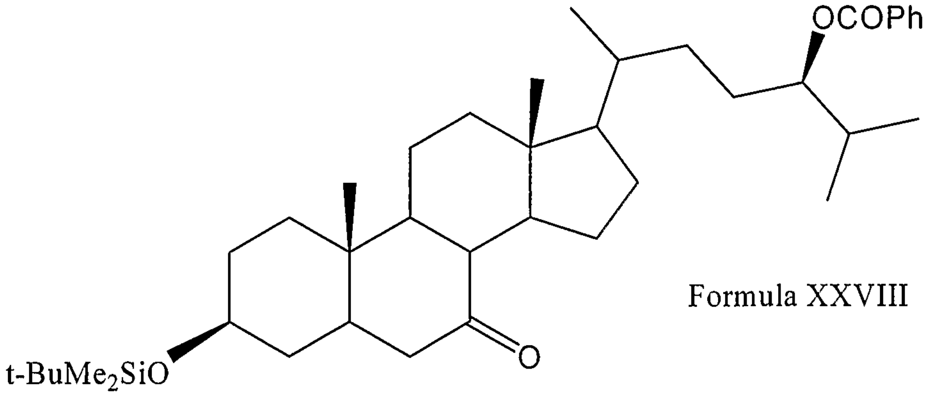


Formula XXVII

Compound of formula XVI obtained at the example 3 (40 mg, 6.5 10^{-5} mol) and N-hydroxyphtalimide (11 mg, 7.1 10^{-5} mol) were dissolved in ethylacetate-acetone (6 mL, 1:1 v/v) and benzoyl peroxide (5 mg) was added to the reaction solution at 60°C. Air was bubbled into the reaction mixture with stirring for 48 hours at 60°C, and then the reaction mixture was concentrated *in vacuo*. Dichloromethane (10 mL) was added to the residual oil. The suspension was stirred for 10 minutes and the insoluble material eliminated by filtration over a pad of Celite. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography on silicagel (eluent: petroleum ether/ethylacetate 95/5 to 9/1) affording the expected compound of formula XXVIII as a white solid in 92% yield (38 mg).

^{13}C NMR (75 MHz, $CDCl_3$): δ =-4.59,-1.00, 13.34, 18.24, 19.41, 20.87, 23.41, 25.93, 26.02, 26.38, 29.08, 29.68, 31.76, 31.92, 32.03, 37.14, 37.28, 37.44, 41.90, 42.24, 44.19, 50.17, 54.98, 56.99, 69.85, 71.73, 85.92, 117.15, 121.38, 125.02, 126.87, 129.57, 135.20, 140.85, 166.99, 168.40, 199.21.

Example 5: Synthesis of 3β-tert-butyldimethylsiloxy-24β-benzoyloxy-7-one of formula XXVIII

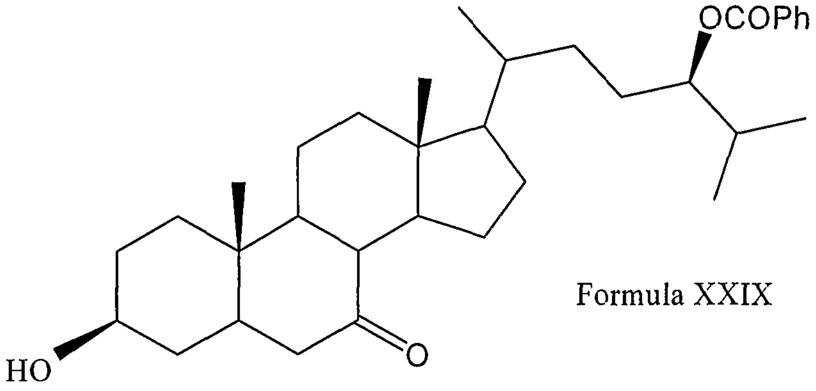


Formula XXVIII

A solution of 7-oxo compound of formula XXVIII obtained at the example 4 (38 mg, 6.0 10^{-5} mol) in ethylacetate (10 mL) was stirred at room temperature in the presence of platinum oxide (10 mg) under an atmospher of H2 (3 bars) for 24 hours. The reaction mixture was filtered over Celite, the solvents removed under reduced pressure and the crude residue purified by chromatography on a silicagel column (eluent petroleum ether/ethylacetate 9/1 to 8/2) affording the expected compound of formula XXIX as a white powder in 95% yield (36 mg).

^{13}C NMR (75 MHz, $CDCl_3$): δ =-5.56, 11.78, 12.81, 18.19, 21.31, 24.22, 27.41, 31.52, 36.09, 36.60, 37.42, 37.75, 43.40, 43.88, 49.83, 55.23, 68.63, 73.06, 76.81, 128.39, 129.53, 129.56, 130.20, 132.84, 165.98, 209.53.

Example 6: Synthesis of 24β-benzoyloxy-3β-hydroxycholestan-7-one of formula XXIX

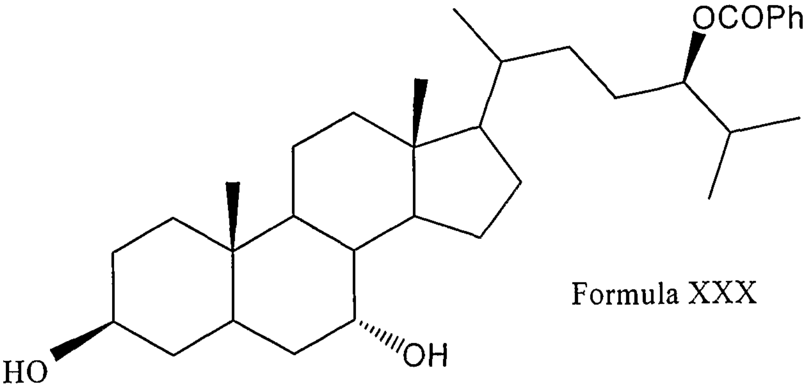


Formula XXIX

To a solution of 36 mg (5.7 10^{-5} mol) of compound of formula XXVIII obtained at the example 5 in 3 mL of anhydrous THF at-78°C was added dropwise 70 µL (6.8 10^{-5} mol) of a 1.0M TBAF solution in THF for 20 min. The reaction mixture was warmed to room temperarture and monitored by TLC analysis. After 40 min, the reaction mixture was quenched by the addition of distilled water (3 mL). The reaction mixture was extracted with ethylacetate, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using petroleum ether/ethylacetate 6/4 to obtain 27 mg (91% yield) of the expected compound of formula XXIX as a colorless oily material.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.21, 11.80, 18.62, 20.97, 21.75, 21.93, 23.72, 27.96, 31.35, 35.53, 35.74, 35.94, 36.12, 36.24, 39.47, 42.62, 45.84, 48.85, 50.53, 56.10, 71.12, 79.24, 128.01, 128.25, 129.21, 129.52, 130.89, 132.58, 166.43, 212.59.

Example 7: Synthesis of 3β, 7α-dihydroxy-24β-benzoyloxycholestane of formula XXX

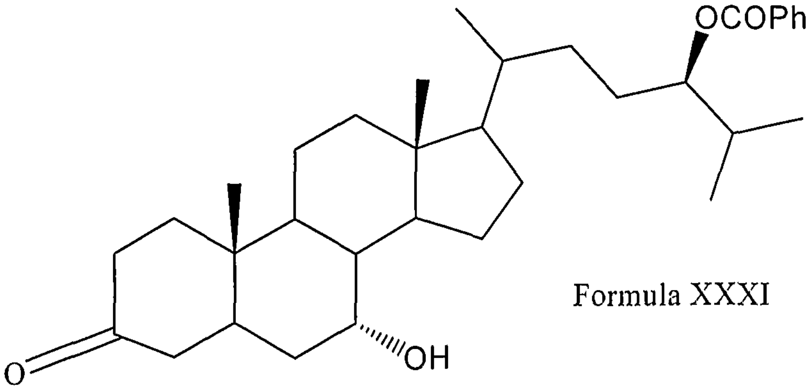


Formula XXX

In a 25 mL two necked round flask were placed under argon at-78°C, compound of formula XXIX obtained at the example 6 (27 mg, 5.2 10^{-5} mol) dissolved in anhydrous THF (10 mL). L-Selectride (2 equivalents) were slowly added at-78°C and stirred for 5 hours before being quenched by the addition of H_2O_2 and a solution of $NaHCO_3$ (3 mL). The residue was dissolved in 10 mL of ethylacetate, washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvents, the crude residue was purified by chromatography on a silicagel column using petroleum ether/ethylacetate (5/5 to 4/6)) as eluent affording the expected compound of formula XXX in 41% yield.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.21, 11.80, 17.61, 18.62, 20.97, 21.83, 21.95, 23.72, 27.96, 31.35, 34.90, 35.74, 36.11, 37.91, 39.47, 42.62, 45.84, 50.53, 56.10, 71.12, 75.12, 78.93, 128.25, 129.67, 130.89, 132.58, 166.20.

Example 8: Synthesis of 24β-benzoyloxy-7α-hydroxycholestan-3-one of formula XXXI

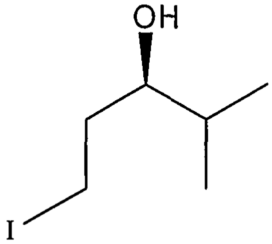


Formula XXXI

A suspension of compound of formula XXX obtained at the example 7 (11 mg, 2.1 10^{-5} mol) and silver carbonate on Celite (25 mg) in toluene (10 mL) was stirred under argon at reflux overnight. The reaction mixture was filtered through a column of Florisil and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on a silicagel column using petroleum ether/ethylacetate (6/4) as eluent affording the expected compound of formula XXXII (9 mg) as a white powder in 82% yield.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.72, 11.88, 17.17, 18.79, 22.72, 27.27, 27.91, 30.89, 35.81, 36.10, 36.33, 37.52, 38.15, 38.23, 38.79, 39.40, 43.52, 45.33, 49.74, 54.71, 67.52, 79.23, 128.33, 129.22, 130.03, 133.35, 163.83, 210.95.

Example 9: 1-iodo-4-methylpentan-3(S)-ol of formula XXXII

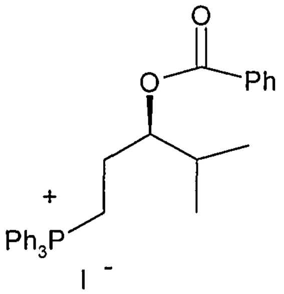


Formula XXXII

A 100 mL three necked flask equipped with an argon inlet, a magnetic stirring bar, an internal thermometer and a septum cap was charged with Ni(acac)2 (258 mg, 1.01 mmole) and cyclooctadiene (242 µL, 2.02 mmole) followed by the chiral isopropyl vinyl alcohol (2 g, 2.02 mmole). The mixture was cooled to-78°C and Et_2Zn (6.5 mL, 6.06 mmole) was added dropwise. After completion of the addition, the cooling bath was removed and the reaction mixture was warmed gradually to 40°C. It was stirred at this temperature for 5 hours and the excess of Et_2Zn was distilled off *in vacuo*. THF (5 mL) was added to the reaction mixture and was distilled off again. This procedure was repeated twice. The black residue was dissolved in THF (10 mL) and cooled to 78°C. At this temperature, a solution of CuCN.2LiCl prepared from CuCN (1.8 g, 2 10^{-2} mole) and LiCl (1.68 g, 4 10^{-2} mole) dissolved in 20 mL of THF was added. The mixture was stirred for 10 minutes at 0°C and was cooled back to-78°C. Iodine (15.24 g, 6 10-2 mole) dissolved in THF (20 mL) was added and the reaction mixture was warmed to room temperature and stirred for 12 hours. It was diluted with diethylether (50 mL) and quenched by addition of a saturated aqueous NH_4Cl (50 mL). The aqueous layer was separated and extracted with diethylether (3x50 mL). The combined organic layer was dried ($MgSO_4$) and filtered and the solvent was evaporated. The residual oil was purified by flash chromatography (petroleum ether/ethylacetate: 19/1) to afford the expected Ioldoalcohol XXXII as a pale yellow oil in 54% yield.

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.9, 16.1, 32.6, 38.9, 79.6$.

Example 10: 4-methylpentan-3(S)-benzoate triphenylphosphonium iodide of formula XXXIII



Formula XXXIII

To a solution of 1 g (3 10^{-3} mole) of the benzoate iodide derivative issued from compound XXXII in 10 mL of acetonitrile was added 3.93 g (1.5 10^{-2} mole) of PPh3. The mixture was heated to 80°C under pressure for 48 hours. After the mixture was cooled to ambient temperature, the solvents were removed *in vacuo*. The residue was purified by flash chromatography (gradient of 100% Ethylacetate to 100% acetonitrile then methanol).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.3, 17.0, 30.1, 36.2, 85.3, 129.1\text{-}132.8, 167{,}0$.

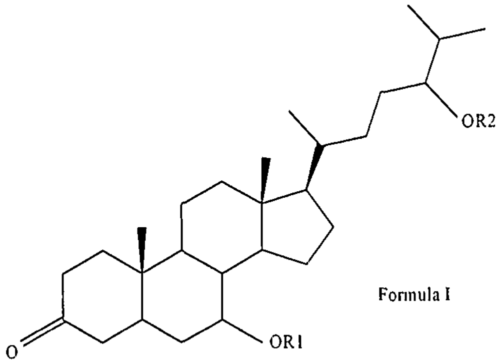
Example 11: synthesis of 3β-tert-butyldimethylsiloxy-24β-benzoyloxy-5,20 diene-cholestane of formula XXXIV

Sodium hydride (2.01 mmole) and phosphonium salt XXXIII were added to 25 mL of dry THF. The 3β-tertbutyldimethylsiloxy-pregnenolone of formula XXIII was added and the mixture was refluxed for 12 hours. The reaction mixture was partioned between ether and water, extracted with ether and dried over magnesium sulfate. The crude residue is purified by flash chromatography on silicagel (eluent: ethylacete/petroleum ether) to afford the expected derivative in 69% yield.

Synthesis of derivative of formula XXI from derivative XXXIV was realized according to the methodology described in example 4 to example 8.

CLAIMS

1) Process of synthesis of 24-substituted oxy-7-substitutedoxycholestan-3-one of formula I

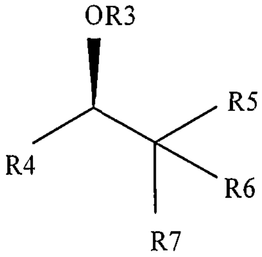


Formula I

wherein R1 and R2 can be, simultaneously or independently, an alkyl, aryl, ester, ether, silyl, substituted silyl, sulfate or phosphate group.

in which in

- step A, one prepares an oxy disubstituted derivative of formula II

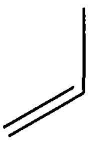


Formula II

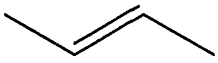
wherein

R3 represents an ester or an ether group

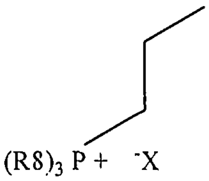
R4 represents a vinyl group, methylallyl group or a diethylphosphonium group of formula IIa, IIb or IIc



Formula IIa or



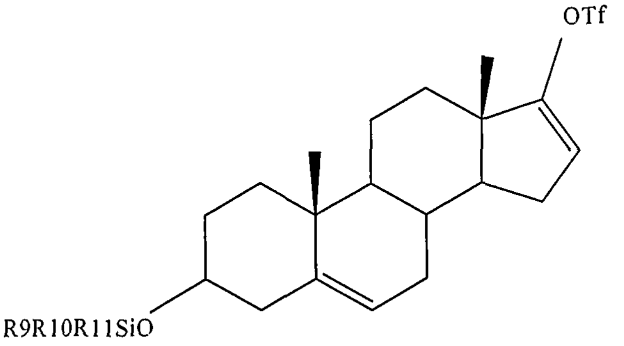
Formula IIb or



Formula IIc and

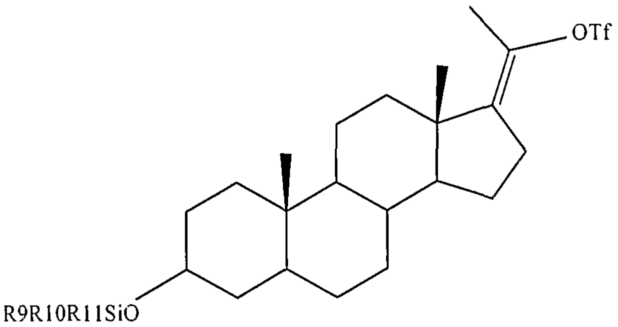
R5, R6, R7 and R8 represent an alkyl, aryl, halide or amine group

- step B, one prepares a 3-siloxy-18-trifluoromethanesulfonyloxy dehydroepiandrosterone derivatives of formula III



Formula III

or a 3-siloxy-20-trifluoromethanesulfonyloxy pregnane derivative of formula IV

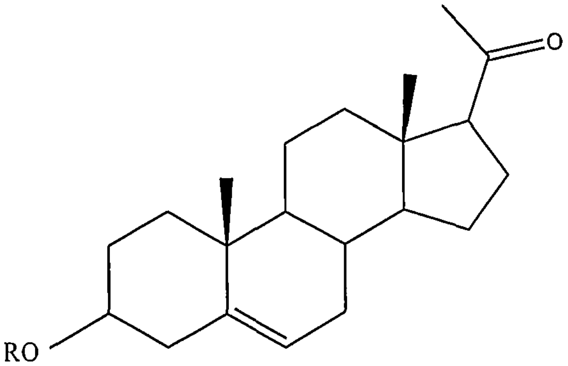


Formula IV

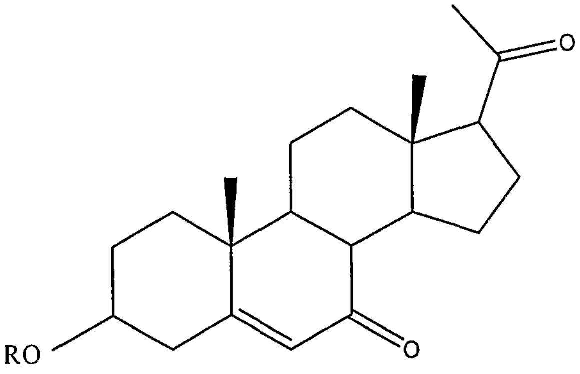
in which R9, R10 and R11, different or identical, represent a linear or branched alkyl or ether radical, with 1 to 24 carbons, preferentially with 1 to 4 carbons, or an aryl radical (phenyl or substituted phenyl group);

or a 3-substituted oxy pregnenolone of formula V,

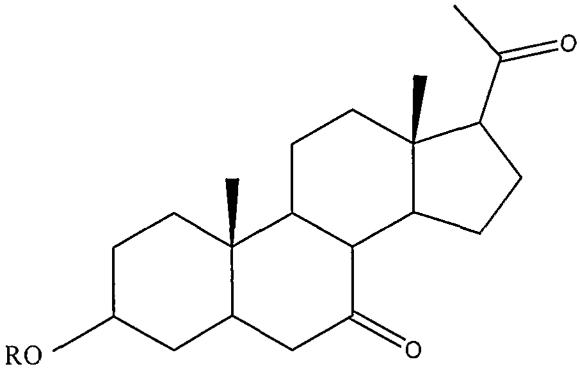
or a 3-substituted oxy-7-oxy pregnane derivatives of formula VI or VII.



Formula V



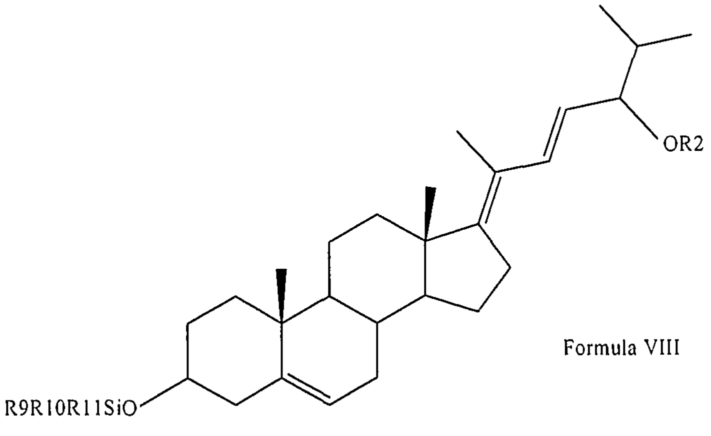
Formula VI



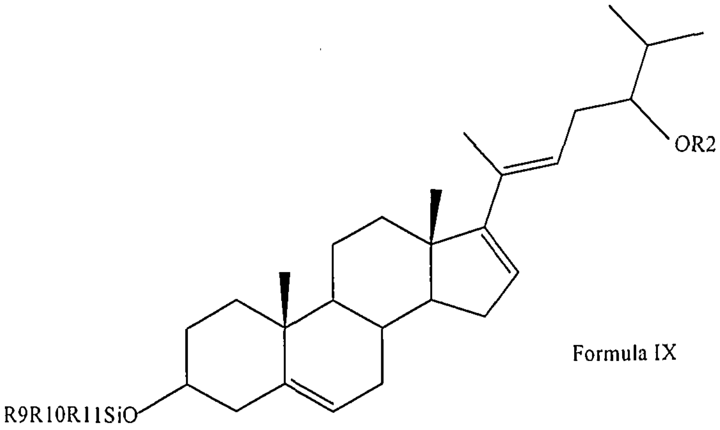
Formula VII

wherein R represents an ether, silyl, substituted silyl or ester group;

- step C, one prepares a pregnane derivative of formula VIII or IX
-



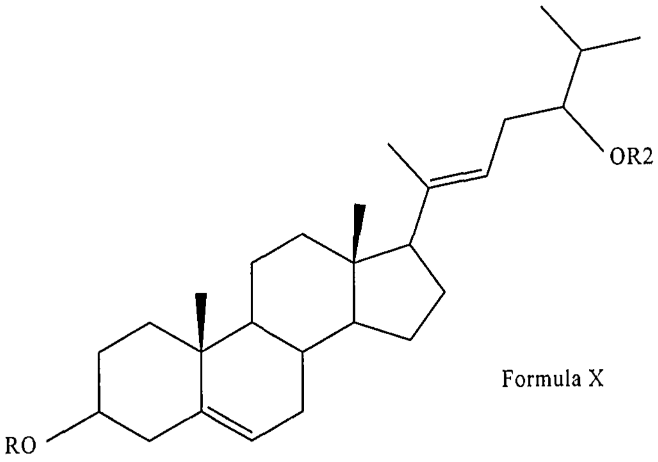
Formula VIII



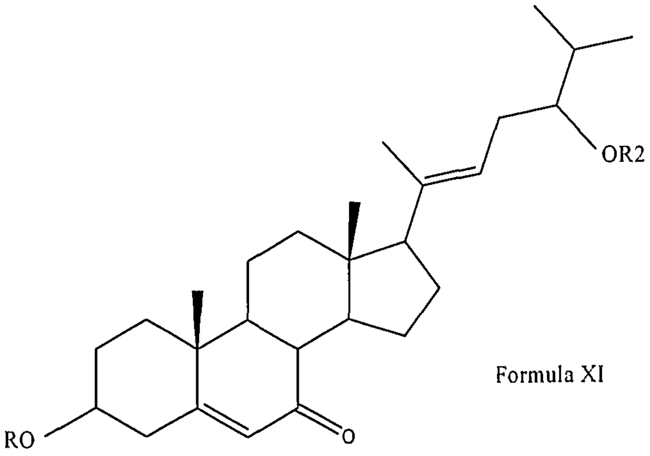
Formula IX

by reacting the substited oxy derivative IIa or IIb obtained in step A with the activated pregnane derivatives (formula III-IV) obtained in step B, in the presence of a first catalyst and a first ligand, under inert atmosphere, in a first polar solvent and in the presence of a first base, at a temperature comprised between 25°C to 95°C[1], preferentially between 50°C to 70°C, most preferentially 60°C, the expected compound being eventually purified;

or one prepares a pregnane derivative of Formula X, XI or XII



Formula X



Formula XI

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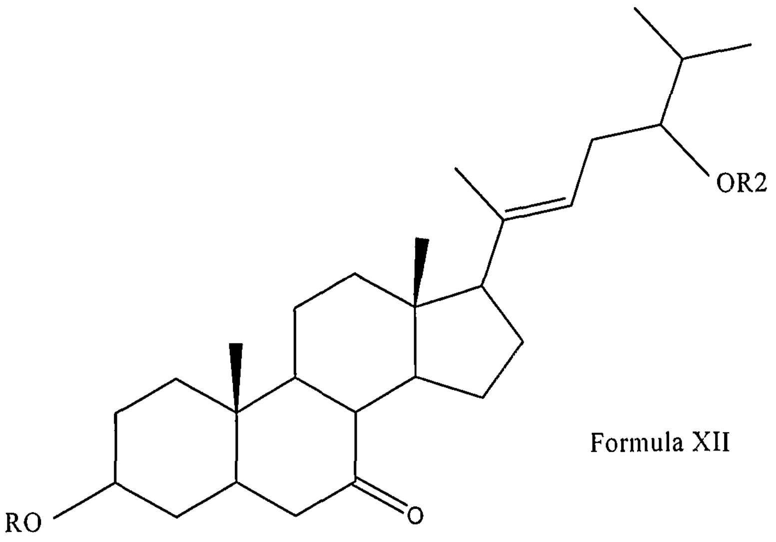
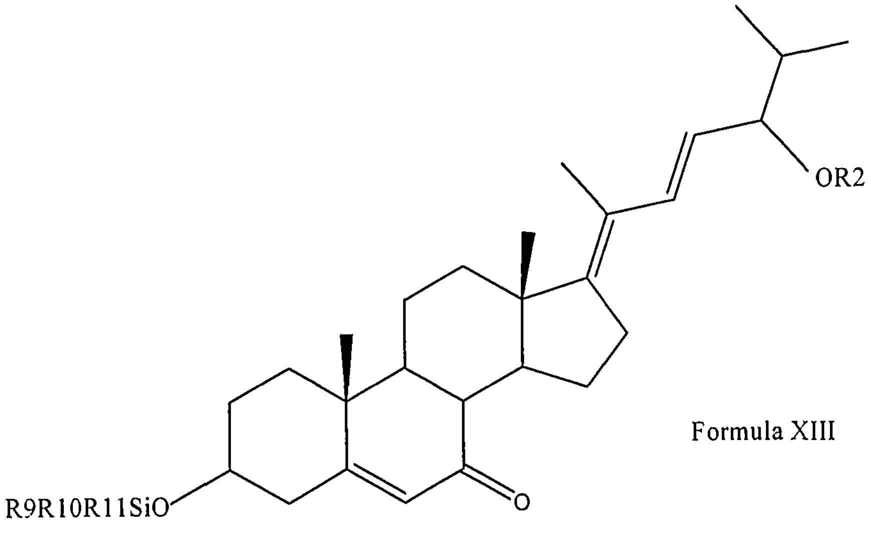
[1] Est envisageable



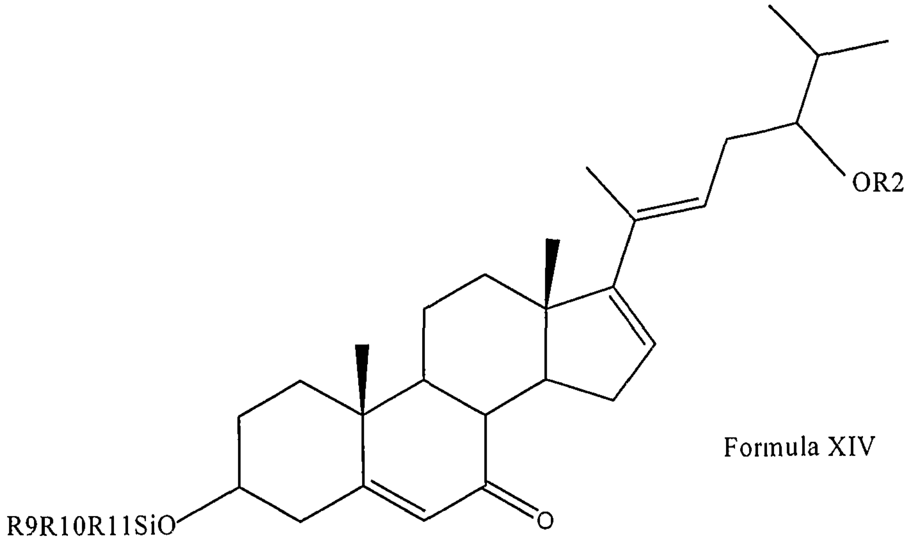
Formula XII

pregnane derivatives (formula V-VII) obtained in step B, in the presence of a second base, under inert atmosphere, in a second polar solvent at a temperature comprised between 0 to 25°C, preferentially 0°C, the expected compound being eventually purified;

- step D, one prepares a 3-siloxy-24-substituted oxy-7 one pregnane derivatives of formula XIII-XIV or a 3-substituted-24-substituted oxy-7 one pregnane derivatives of Formula XI



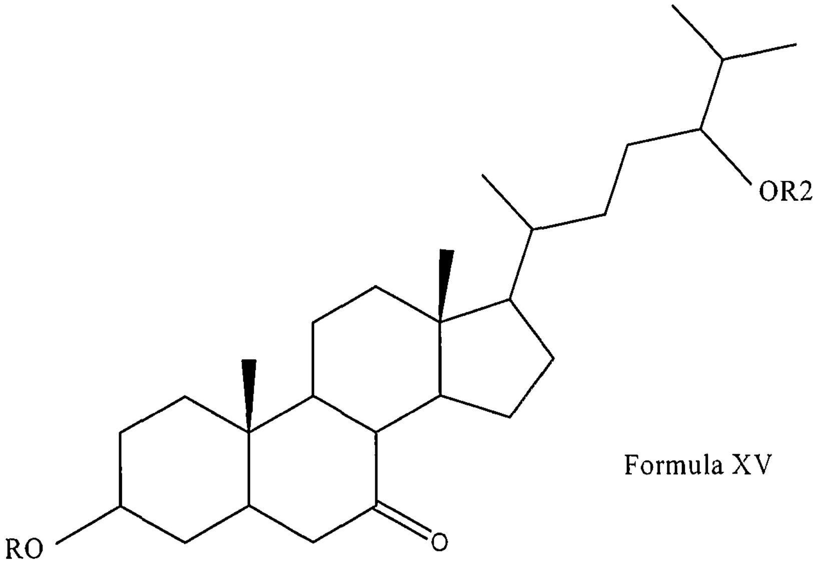
Formula XIII



Formula XIV

by oxidizing derivatives of formula VIII orX obtained in step C, the expected compound being eventually purified;

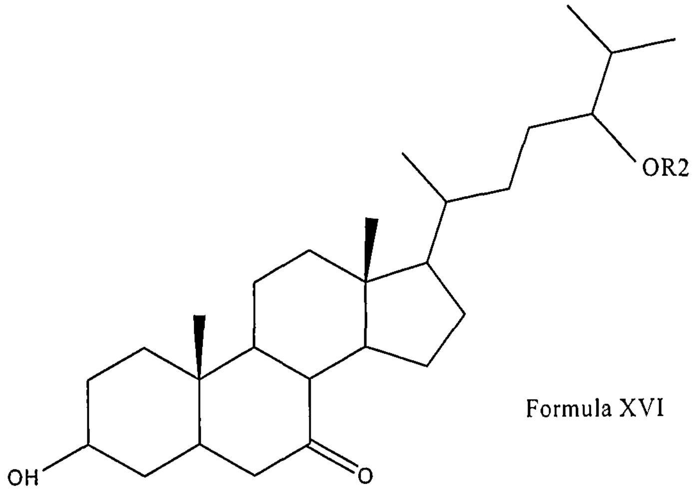
- ❖ step E, one prepares a 3-substituted oxy-24-substituted-7-one derivative of formula XV



Formula XV

by hydrogenation of the 3-substituted-24-substituted oxy-7-one derivative of formulas XI, XII, XIII or XIV obtained in step C or D, in the presence of a catalyst under hydrogen, in a polar solvent, the expected compound being eventually purified, at a temperature comprised between 0°C to 50°C, preferably at 25°C;

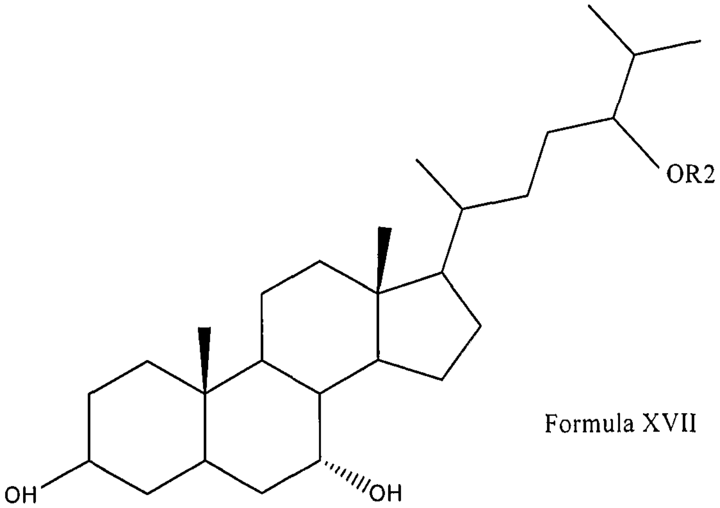
- ❖ step F, one prepares a 24-substituted oxy-3-hydroxycholestan-7-one derivative of formula XVI



Formula XVI

by deprotection of the 3-substituted-24-substituted-7-one derivative of formula XV obtained in step E preferentially in presence of fluoride ions, the expected compound being eventually purified;

- ❖ step G, one prepares a 24-substituted oxy-3,7-dihydroxycholestane derivative of formula XVII



Formula XVII

by the reduction of the ketone in position 7 of the 24-substituted-3-hydroxycholestan-7-one derivative of formula XVI obtained in step F with a stereoselective reducing hydride reagent.

at a temperature raising from -78°C to room temperature (25°C), the expected compound being eventually purified;

- ❖ step H, one prepares the 24-substituted oxy-7-hydroxycholestan-3-one of formula I by oxidation of the hydroxyl substituant in position 3 of the 24-substituted-3,7-dihydroxycholestane derivative of formula XVII obtained in step G, in presence of silver carbonate in a solvent, at the reflux temperature of the solvent, the expected compound being eventually purified.

2.) Process of synthesis according to claim 1, wherein in step C the first catalyst is Palladium acetate [$Pd(OAc)_2$] or Palladium salt like $Pd(OAc)_2$.3.) Process of synthesis according to anyone of claims 1 or 2, wherein in step C the first ligand is a phosphine, for example triphenylphosphine, tributylphosphine, tri *tert*-butyl phosphine and preferentially tri-*ortho*-tolylphosphine.

4.) Process of synthesis according to anyone of claims 1 to 3, wherein in step C the first polar solvent is diméthylformamide (DMF), dimethylacetamide or hexamethylphosphoramide (HMPA).

5.) Process of synthesis according to anyone of claims 1 to 4, wherein in step C the first base is an aliphatic tertiary amine like triethylamine or pyridine, preferentially pyridine.

6.) Process of synthesis according to anyone of claims 1 to 5, wherein in step C the inert atmosphere is argon or nitrogen.

7.) Process of synthesis according to anyone of claims 1 to 6, wherein in step C the second polar solvent is tétrahydrofurane, dioxane or diethylether.

8.) Process of synthesis according to anyone of claims 1 to 7, wherein in step C the second base is sodium hydride, potassium hydride, potassium tert butylate, preferentially sodium hydride, lithium hexamethyldisilazane, butyllithium, sec-butyllithium or tert-butyllithium.

9.) Process of synthesis according to anyone of claims 1 to 8, wherein step C is performed during 1 to 24 hours, preferably 12 hours.

10.) Process of synthesis according to anyone of claims 1 to 9, wherein in step E the catalyst is a platinum oxide catalyst.

11.) Process of synthesis according to anyone of claims 1 to 10, wherein in step E the polar solvent is DMF, dimethylacetamide, THF, dioxame or HMPA.

12.) Process of synthesis according to anyone of claims 1 to 11, wherein step E is performed at a pressure comprised between 1 to 100 bars, preferably 3 bars.

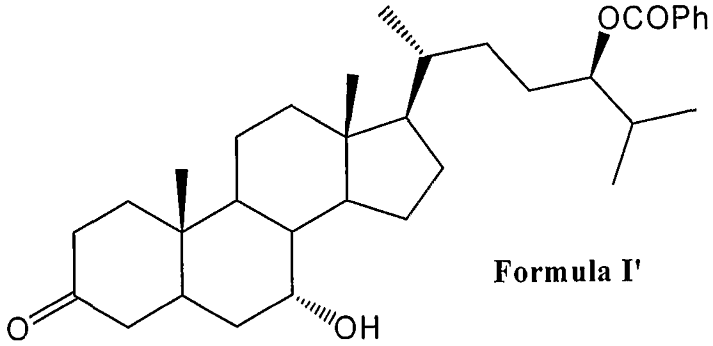
13.) Process of synthesis according to anyone of claims 1 to 12, wherein step E is performed during 1 to 30 hours, preferably 24 hours.

14.) Process of synthesis according to anyone of claims 1 to 13, wherein step G the stereoselective reducing hydride reagent is

- either potassium tri-*sec*-butylborohydride (L-selectride®) to obtain a 7α dihydrocholestane;
- or lithium/NH3 to obtain a 7β dihydrocholestane.

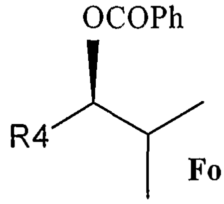
15.) Process of synthesis according to anyone of claims 1 to 14, wherein step H the solvent is toluene, benzene, hexane, heptane or cyclohexane.

16.) Process of synthesis according to anyone of claims 1 to 15, to prepare 24β-benzoyloxy-7α-hydroxycholestan-3-one of formula I'



Formula I'

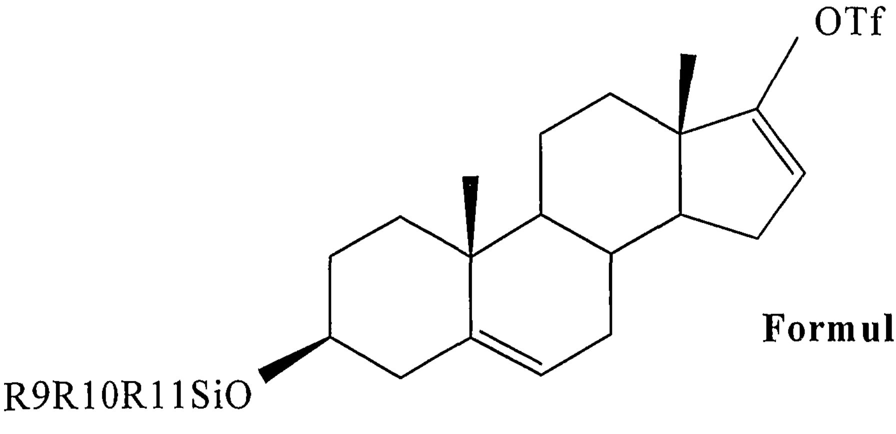
17.) Process of synthesis according to claim 16, wherein in step A, one prepares a benzoate derivative of formula II



Formula II'

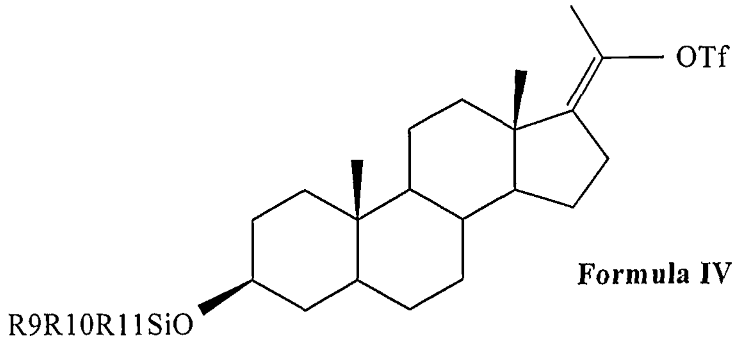
in which R4 represents a vinyl group or a methylallyl group;

18.) Process of synthesis according to anyone claims 16 or 17, wherein in step B one prepares a 3β-siloxy-18-trifluoromethanesulfonyloxydehydroepiandrosterone derivatives of formula III



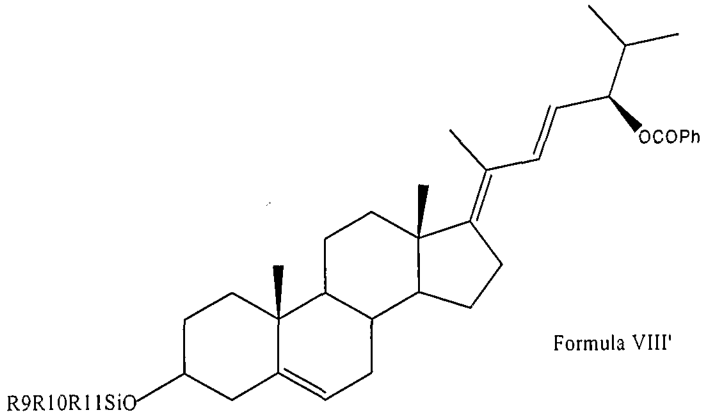
Formula III

or a 3β-siloxy-20-trifluoromethanesulfonyloxy pregnenane derivative of formula IV


Formula IV

in which R9, R10 and R11, different or identical, represent a linear or branched alkyl radical, with 1 to 24 carbons, preferentially with 1 to 4 carbons, or an aryl radical (phenyl or substituted phenyl group);

19.) Process of synthesis according to anyone claims 16 to 18, wherein in step C one prepares a 3β-siloxy-24b-benzoyloxy-5,20,22 triene-hydroxycholestane derivative of formula VIII'


Formula VIII'

by reacting the benzoate derivative obtained in step A with the 3β-siloxy-20-trifluoromethanesulfonyloxy pregnenane derivative (formula IV) or a 3β-siloxy-18-trifluoromethanesulfonyloxy dehydroepiandrosterone derivative (formula III) obtained in step B, in the presence of a catalyst made of a mixture of palladium acetate [Pd(OAc)2] and a phosphine ligand, under inert atmosphere, in a polar solvent and a base, the expected compound being eventually purified;

20.) Process of synthesis according to claim 19, wherein the phosphine ligand is triphenylphosphine, tributylphosphine, tri *tert*-butyl phosphine and preferentially tri-*ortho*-tolylphosphine.

21.) Process of synthesis according to anyone claims 19 or 20, wherein the ratio Pd/Ligand is 1:2.

22.) Process of synthesis according to anyone claims 19 to 21, wherein the inert atmosphere is argon or nitrogen.

23.) Process of synthesis according to anyone claims 19 to 22, wherein the polar solvent is DMF or dimethylacetamide.

24.) Process of synthesis according to anyone claims 19 to 23, wherein the base is triethylamine or pyridine.

25.) Process of synthesis according to anyone claims 19 to 24, wherein step C is performed at a temperature comprised between 50°C to 70°C, preferentially 60°C

26.) Process of synthesis according to anyone claims 19 to 25, wherein step C is performed during 10 to 24 hours, preferably 12 hours.

27.) Process of synthesis according to anyone claims 16 to 26, wherein in step E the pressure is comprised between 2 to 10 bars, preferably 3 bars.

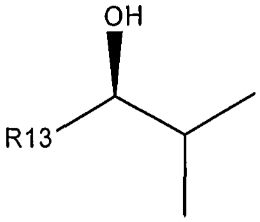
28.) Process of synthesis according to anyone claims 16 to 27, wherein in step E the hydrogenation is performed during 20 to 30 hours, preferably 24 hours.

29.) Process of synthesis according to anyone claims 16 to 28, wherein in step E the hydrogenation is performed at a temperature comprised between 20 to 30 °C, preferably 25°C.

30.) Process of synthesis according to anyone claims 16 to 29, wherein in step E, the reduction is performed at a temperature raising from-78°C to room temperature (25°C).

31.) Process of synthesis according to anyone claims 16 to 30, wherein in step E, the reduction is performed during a minimum of 5 hours.

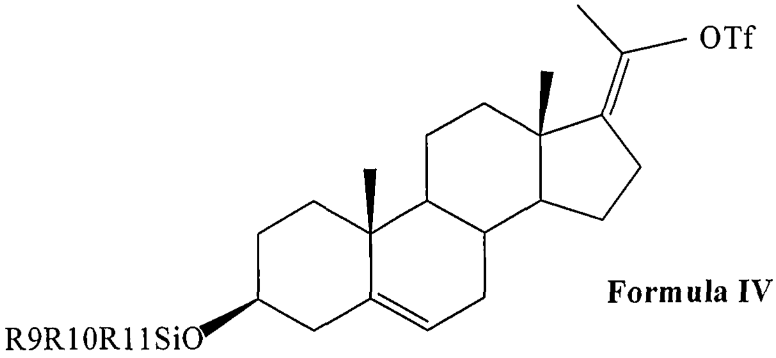
32.) Process of synthesis according to anyone claims 1 to 31, wherein in step A, the compound of Formula II is a benzoate derivative, obtained by reacting an hydroxyl derivative of formula XVIII



Formula XVIII

in which R13 represents a vinyl, a methylallyl or an halogeno ethyl group with benzoylchloride in the presence of a base at temperature growing from 0°C to 25°C during a minimum of 24 hours, the expected compound being eventually purified.

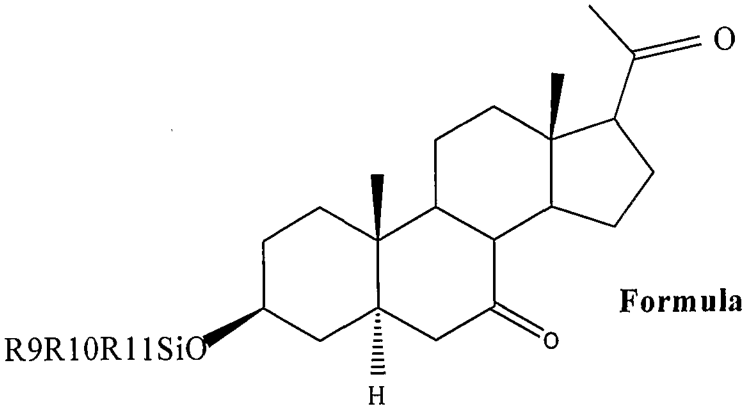
33.) Process of synthesis according to anyone claims 1 to 32, wherein In step B, the 3-siloxy-20-trifluoromethanesulfonyloxy pregnane of formula IV



Formula IV

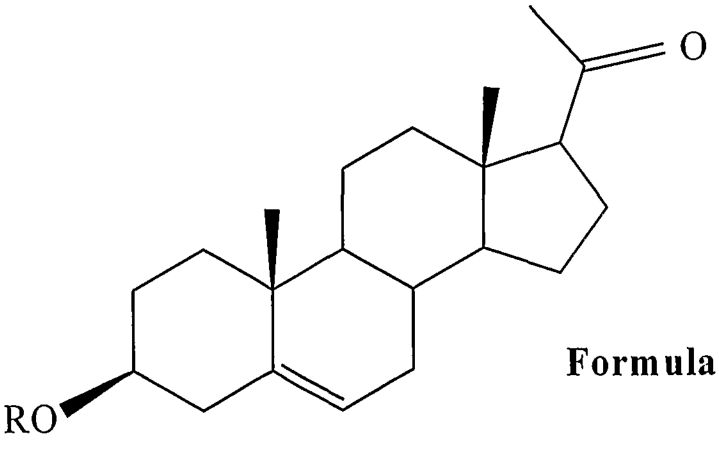
can be prepared according to a process wherein in

+ step B1-1, one prepares a 3-siloxypregnenolone derivative of formula XIX



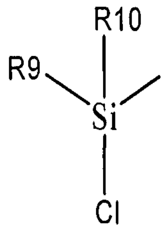
Formula XIX

by reacting a pregnenolone of formula VII



Formula VII

with a chlorosilane derivative of formula XX

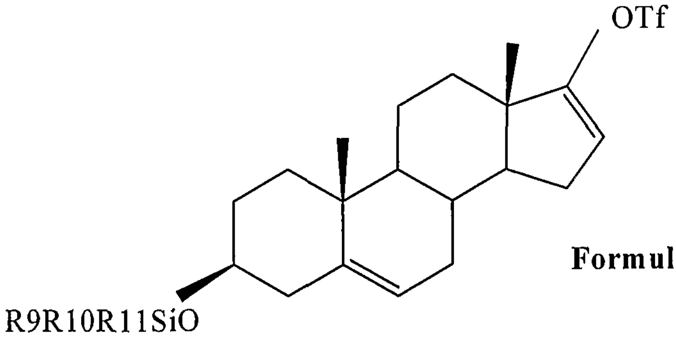


Formula XX

in which R9, R10 and R11, different or identical, represent a linear, branched alkyl or ether radical, with 1 to 24 carbons, preferentially with 1 to 4 carbons, or an aryl radical (phenyl or substituted phenyl group), under inert atmosphere in the presence of a solvent, in the presence of a base, the expected compound being eventually purified; and in

+ step B1-2, one prepares the 3-siloxy-20-trifluoromethanesulfonyloxy pregnenolone derivatives of formula IV by reacting the 3-siloxypregnenolone derivative of formula XIX obtained in step B1-1 with potassium bis(trimethylsilyl)amide in toluene (5 to 15 %, preferentially 10%) and N-phenyltrifluoromethanesulfonimide in THF, under inert atmosphere like argon, at a temperature comprised between-80°C to-70°C, preferentially-78°C, during 15 to 45 minutes, and then warmed to a temperature around 0°C, the expected compound being eventually purified.

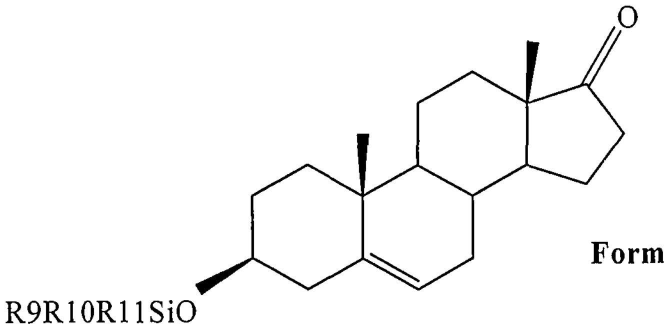
33.) Process of synthesis according to anyone claims 1 to 32, wherein In step B, the 3-siloxy-18-trifluoromethanesulfonyloxy dehydroepiandrosterone derivatives of formula III



Formula III

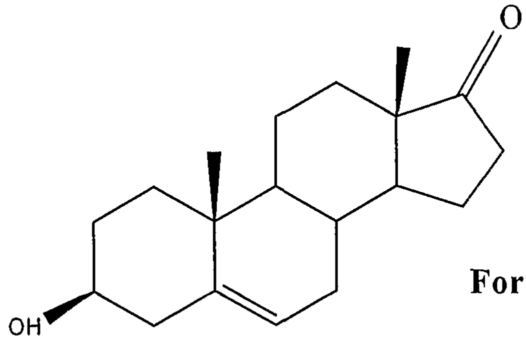
can be prepared according to a process wherein in

+ step B2-1, one prepares a 3-siloxydehydroepiandrosterone derivative of formula XXI



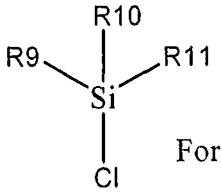
Formula XXI

by reacting a dehydroepiandrosterone XXII



Formula XXII

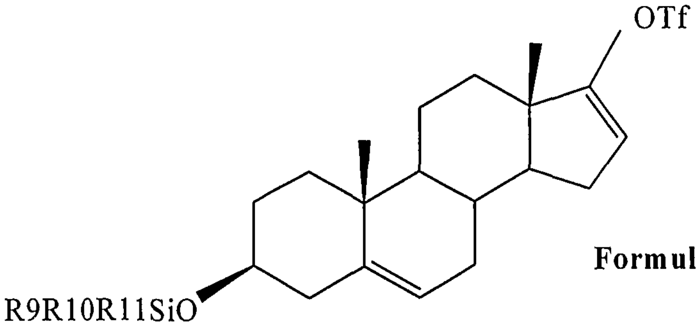
with a chlorosilane derivative of formula XX



Formula XX

in which R9, R10 and R11, different or identical, represent a linear, branched alkyl or ether radical, with 1 to 24 carbons, preferentially with 1 to 4 carbons, or an aryl radical (phenyl or substituted phenyl group), under inert atmosphere, in the presence of a solvent, in the presence of a base, at a temperature between 20 to 50 °C, during 20 to 30 hours, preferentially in presence of DMF at 25°C for 24 hours, the expected compound being eventually purified; and in

+ step B2-2 one prepares the 3-siloxy-18-trifluoromethanesulfonyloxy dehydroepiandrosterone derivative of formula III



Formula III

by reacting the 3-siloxydehydroepiandrosterone derivative of formula XXI obtained in step B2-1 with potassium bis(trimethylsilyl)amide in toluene (5 to 15 %, preferentially 10%) and N-phenyltrifluoromethanesulfonimide in THF, under inert atmosphere like argon, at a temperature comprised between-80°C to-70°C, preferentially-78°C, during 15 to 45 minutes, and then warmed to a temperature around 0°C, the expected compound being eventually purified.

34.) Process of synthesis according to anyone claims 32 or 33, wherein in step B1-1 or B2-1 the inert atmosphere is argon or nitrogen.

35.) Process of synthesis according to anyone claims 32 to 35, wherein in step B1-1 or B2-1, the solvent is chosen indifferently from tetrahydrofuran (THF) or other ethers, dichloromethane (CH_2Cl_2) or chloroform ($CHCl_3$) or other chlorinated solvent, or dimethylformamide (DMF) or acetonitrile (CH_3CN) or toluene or benzene.

36.) Process of synthesis according to anyone claims 32 to 35, wherein in step B1-1 or B2-1, the base is pyridine or triethylamine

37.) Process of synthesis according to anyone claims 32 to 36, wherein step B1-1 or B2-1 is performed at a temperature between 20 to 50 °C.

38.) Process of synthesis according to anyone claims 32 to 37, wherein step B1-1 or B2-1 is performed during 20 to 30 hours.

39.) Process of synthesis according to anyone claims 32 to 38, wherein step B1-1 or B2-1 is performed in presence of DMF at 25°C for 24 hours.

40.) Process of synthesis according to anyone claims 1 to 39, wherein in step D, the oxidation is performed in the presence of ruthenium trichloride and *tert*-butylhydroperoxide in cyclohexane, during 20 to 30 hours, preferentially 24 hours, at a temperature comprised between 20 to 30°C, preferentially 25 °C.

41.) Process of synthesis according to anyone claims 1 to 39, wherein in step D, the oxidation is performed in the presence of $Na_2Cr_2O_7$ in acetone, during 45 to 50 hours, preferentially 48 hours, at a temperature comprised between 35 to 45°C, preferentially 40 °C, in the presence of sodium sulfite.

42.) Process of synthesis according to anyone claims 1 to 39, wherein in step D, the oxidation is performed in the presence of N-hydroxyphtalamide, under a flux of oxygen or air, in the a 50/50 solvent mixture of ethylacetate and acetone, at 60°C, during 30 to 40 hours, preferentially 36 hours.

43.) Process of synthesis according to anyone claims 1 to 42, wherein in step F, the deprotection is performed in the presence of a fluorhydric acid-based reagent (HF-based reagent) or polymer-bound ammonium fluoride salt, in a solvent.

44.) Process of synthesis according to claim 43, wherein fluorhydric acid-based reagent (HF-based reagent) is chosen from tetrabutylammoniumfluoride $(Bu_4)N$, tetraalkylarylammoniumfluoride derivative; preferentially the HF-based reagent is tetrabutylammoniumfluoride $(Bu_4)N$.

45.) Process of synthesis according to anyone claims 43 to 45, wherein the solvent is chosen from tetrahydrofuran (THF) or other ethers, dichloromethane (CH_2Cl_2) or Chloroform ($CHCl_3$) or other chlorinated solvent, or acetonitrile (CH_3CN) or ethyl acetate or diethylether.

46.) Process of synthesis according to anyone claims 43 to 45, wherein step F is performed at temperature raising from-85°C to-65°C, preferentially-78°C, to 25°C.

47.) Process of synthesis according to anyone claims 43 to 46, wherein step F is performed during a time comprised between 30 to 60 minutes, preferentially 45 minutes.

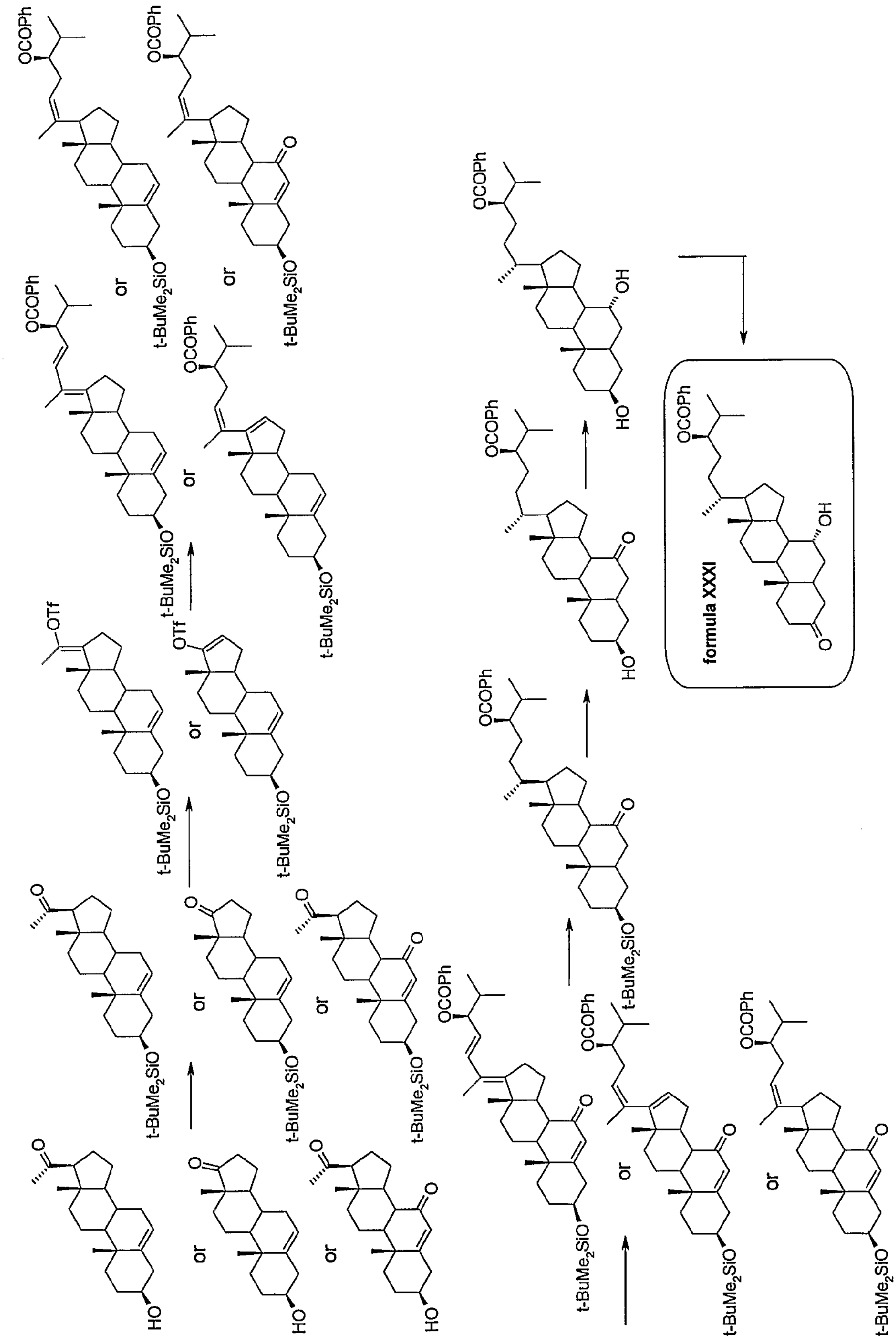


Figure 1