NEW 4-HALOGENATED STEROIDS, THEIR PREPARATION PROCESS AND INTERMEDIATES, THEIR USE AS MEDICAMENTS AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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Appl. No.: 09/757,679
Filed: Jan. 10, 2001

Related U.S. Application Data
Division of application No. 09/402,705, filed on Nov. 29, 1999, which is a 371 of international application No. PCT/FR98/00709, filed on Apr. 8, 1998.

Foreign Application Priority Data
Apr. 9, 1997 (FR) 97/04321

ABSTRACT
A subject of the invention is the compounds of formula (I):

\[
\begin{align*}
\text{in which X is a halogen atom, D represents the remainder of an optionally substituted pentagonal or hexagonal ring and optionally carrying an unsaturation, } R_1, R_2, R_3, R_4, Y \text{ and } n \\
\text{are as defined in the description, their preparation process and intermediates, their use as medicaments and the compositions containing them.}
\end{align*}
\]
NEW 4-HALOGENATED STEROIDS, THEIR PREPARATION PROCESS AND INTERMEDIATES, THEIR USE AS MEDICAMENTS AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

[0001] The present invention relates to 4-halogenated steroid compounds, their preparation process, their use as medicaments and the pharmaceutical compositions containing them.

[0002] Osteoporosis is a pathology which is characterized by a quantitative and qualitative reduction in bone matter, sufficient to lead to vertebral or peripheral fractures, in a spontaneous fashion or on occasions due to minimal traumas. Although this illness has many factors at its origin, it is the menopause which in women constitutes the dominating factor in bone loss or osteopenia.

[0003] This osteopenia manifests itself by a rarefaction and modification of the architecture of the spongy bone, the consequence of which is to increase the fragility of the skeleton and the risk of fractures. Bone loss increases strongly after the menopause due to the suppression of ovarian function and reaches 3 to 5% per year before slowing down after 65 years old.

[0004] For a therapeutic purpose, the post-menopause hormonal deficiency can be compensated for by a hormone replacement therapy where oestrogen plays a major role in preserving the bone mass. But long-term oestrogenotherapy is sometimes accompanied by undesirable effects on the genital apparatus (endometrial hyperplasia, breast tumors . . . ), which constitutes a major drawback and limits its use.

[0005] It is therefore convenient to find compounds other than oestradiol having a dissociated oestrogen activity, namely an oestrogen activity at the bone level, while having no or little endometrial hyperplasia activity, nor breast tumor proliferation activity.

[0006] Therefore, a subject of the invention is the compounds of general formula (I):

\[ R_1 \left( \text{CH}_2 \right)_m \text{AR} \left( \text{CO} \right) \text{AR}_1 \left( \text{CH}_2 \right)_n \text{Alk or (CO)} \text{Alk} \]

![Diagram](image)

[0007] in which:

[0008] R_1 represents a hydrogen atom, a (CH_2)_m—\text{Ar, (CO)—Ar, (CH}_2)_n—\text{Alk or (CO)—Alk radical,}

[0009] R_2 represents a radical derived from a linear or branched, saturated or unsaturated hydrocarbon containing 1 to 6 carbon atoms

[0010] D represents the remainder of a pentagonal or hexagonal ring optionally substituted and optionally carrying an unsaturation,

[0011] X represents a halogen atom,

[0012] Y is chosen from O, S, SO, SO_2 and NH,

[0013] m is an integer varying from 2 to 8,

[0014] either R_3 and R_4, identical or different, represent a hydrogen atom, a (CH_2)_m—\text{Ar, (CH}_2)_n—\text{Het or (CH}_2)_n—\text{Alk group},

[0015] or R_3 and R_4 form together with the atom of nitrogen to which they are linked an aromatic or non-aromatic, saturated or unsaturated mono- or poly cyclic heterocycle with 3 to 15 members optionally containing 1 to 3 additional heteroatoms chosen from oxygen, sulphur and nitrogen, non-substituted or substituted,

[0016] \text{Ar representing a carbocyclic aryl group containing 6 to 18 carbon atoms, Het representing a radical derived from a saturated or unsaturated aromatic or non-aromatic heterocycle containing 1 to 9 carbon atoms and 1 to 5 heteroatoms chosen from oxygen, nitrogen or sulphur atoms, Alk representing a radical derived from a saturated or unsaturated, linear, branched or cyclic, non-aromatic hydrocarbon and containing 1 to 12 carbon atoms, the Ar, Het or Alk radicals being able to be substituted or non substituted, m represents 0, 1, 2 or 3, as well as their addition salts with bases or acids.}

[0017] By halogen is meant: iodine, bromine, chlorine or fluorine.

[0018] By (CH_2)_m is meant the following values: single bond in the case where m is equal to 0, CH_2, (CH_2)_2 and (CH_2)_3.

[0019] By the term \text{AR representing the carbocyclic aryl group containing 6 to 18 carbon atoms}, is meant a derivative of an aromatic cyclic hydrocarbon such as the phenyl, naphthyl, phenanthryl radical or a derivative of a condensed, bicyclic or tricyclic hydrocarbon containing a benzene ring such as indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl or fluorenyl. The junction is carried out at the level of the benzene ring. Preferably it is phenyl.

[0020] By the term (Het) representing a radical derived from a saturated or unsaturated, aromatic or non-aromatic heterocycle containing 1 to 9 carbon atoms and 1 to 5 heteroatoms chosen from oxygen, nitrogen and sulphur atoms, the following are designated in particular:

[0021] heterocyclic monomeric radicals, for example thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, furazanyl, pyrrolyl, imidazolinyl, pyrazolinyl, thiazolinyl, triazolinyl, tetrazolyl radicals,

[0022] condensed heterocyclic rings, for example benzothiophenyl, benzo[2,3-b]thiophenyl, thiadiazolyl, isobenzothiuranyl, chromenyl, xanthenyl, phenoxathiinyl, indolizinyi, isooindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, quinolinizyn, isoquinolyl,
By the term (Alk) representing a radical derived from a saturated or unsaturated, linear, branched or cyclic non-aromatic hydrocarbon, is designated in the case of acyclic hydrocarbons the alkyl radicals such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, 2-methyl pentyl, 2,3-dimethyl butyl, n-heptyl, 2-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethyl pentyl, 3-ethylpentyl, n-octyl, 2,2-dimethylhexyl, 3,3-dimethylhe xyl, 3-methyl-3-ethylpentyl, nonyl, 2,4-dimethylheptyl or n-decyl; the alkyl radicals such as vinyl, propenyl, isopropenyl, allyl, 2-methylallyl, butenyl or isobutenyl, or the alkenyl radicals such as ethynyl, propynyl, propargyl, butynyl or isobutynyl, and in the case of cyclic radicals, the cycloalkyl radicals, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

It will preferably be methyl and ethyl radicals. By CO—Alk is preferably meant COCH₃ and COET₃, by CO—Ar is preferably meant the benzyl radical, when m is different from zero, (CH₃)ₙ—Ar will preferably be the benzyl group.

When R₃ and R₄ form together with the nitrogen atom to which they are linked a heterocycle, it is in particular mono- or bicyclic heterocycles optionally containing another heteroatom chosen from oxygen and nitrogen such as the following unsaturated heterocycles: pyrrolyl, imidazolyl, indazolyl, pyrazolyl, pyrazimidinyl, pyridazinyl, thiazolyl, oxazolyl, furazolinyl, pyrazolinyl, thiazolinyl, or, more particularly, the following saturated heterocycles:

When the different Alk, Ar, Het groups, as well as the remainder of a pentagonal or hexagonal ring mentioned above, are substituted, they can in particular be substituted by the following radicals:

- Halogen, namely fluorine, chlorine, bromine or iodine, alkoxy such as methoxy, ethoxy, propoxyloxy, isopropoxyloxy, butyloxy, alkylthio such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, amino, alkylamino such as methylamino or ethylamino, dialkylamino such as dimethylamino, diethylamino, methylisopropylamino, each of these dialkylamino radicals being optionally in oxidized form, aminomethyl such as aminomethyl or aminomethyl, dialkylaminomethyl such as dimethylamino methyl or ethyl, dialkylaminomethyloxys such as dimethylamino ethyloxys, hydroxyl optionally acylated, acyl such as acetyl, propionyl, butyryl, benzoyl, free, esterified carboxy such as alkoxy carboxyl for example methoxy carboxyl or ethoxy carboxyl, cyano, trifluoromethyl, aryl such as phenyl, aralkyl such as benzyl, alkylen or alkynyl these radicals being themselves optionally substituted by the halogen, alkyl, alkoxy, alkylthio, aminomethyl or dialkylamino radicals indicated above.

The invention naturally extends to the salts of the compounds of formula (I), such as for example the salts formed with mineral or organic acids on the amine. It can then be one of the following acids: hydrochloric, hydrobromic, nitric, sulphuric, phosphoric, acetic, formic, propionic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic, alkane sulphonic such as methane or ethane sulphonics, aroylsulphonics, such as benzene or para-toluene sulphonics and aroyl carboxylics. When the compounds of formula (I) contain an acid function, the invention extends to the salts of alkali metals, alkaline earth or ammonium, optionally substituted.

A more particular subject of the invention is the compounds of general formula (I) as defined above in which (II) represents the remainder of a pentagonal ring of formula:

[0033] in which R₂ retains the same meaning as previously,

[0034] either R₇ represents an OH, O—(CH₃)ₙ—Alk, O—(CO)—Alk, O—(CH₃)ₙ—Ar, O—(CO)—Ar, O—(CH₃)ₙ—Het, O—(CO)—Het radical and R₈ represents a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms substituted or non substituted, m, Alk, Ar and Het being as defined previously,

[0035] or R₇ and R₈ form together with the carbon atom which carries them one of the following rings:
[0036] in which Z represents a \((\text{CH}_2)_n\) or \(-\text{CH}=-\text{CH}(\text{CH}_2)_n\) group, 1 being an integer comprised between 1 and 4 and \(\text{I}'\) being an integer equal to 1 or 2;

[0037] or \(R_3\) and \(R_6\) form together an oxo group, as well as their addition salts with acids or bases.

[0038] A quite particular subject of the invention is the compounds of formula (I) as defined previously corresponding to general formula (I') as defined previously in which:

\[
(I')
\]

\[\begin{align*}
R_3' & \quad \text{and} \quad R_6' \quad \text{form together an oxo group, as well as their addition salts with acids or bases.}
\end{align*}\]

[0039] A quite particular subject of the invention is the compounds of formula (I) as defined previously corresponding to general formula (I') as defined previously in which:

\[
(I')
\]

\[\begin{align*}
R_3' & \quad \text{and} \quad R_6' \quad \text{form together an oxo group, as well as their addition salts with acids or bases.}
\end{align*}\]

[0040] \(X'\) represents a chlorine or bromine atom

[0041] \(n'\) is comprised between 2 and 5,

[0042] either \(R_3'\) and \(R_6'\), identical or different, represent an alkyl radical containing 1 to 6 carbon atoms

[0043] or \(R_3'\) and \(R_6'\) form together with the nitrogen atom to which they are linked, a saturated mono- or polyyclic remainder with 3 to 15 members optionally containing an additional heteroatom chosen from oxygen, sulphur and nitrogen,

[0044] \(R_3'\) and \(R_6'\) have the same meaning as \(R_3\) and \(R_6\), as well as their addition salts with acids and bases.

[0045] A quite particular subject of the invention is the compounds of formula (I) as defined previously corresponding to general formula (I') as in which:

\[
(I')
\]

\[\begin{align*}
R_3' & \quad \text{and} \quad R_6' \quad \text{form together an oxo group, as well as their addition salts with acids or bases.}
\end{align*}\]

[0046] either \(R_3'\) represents an OH radical and \(R_6'\) represents a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms, substituted or non-substituted,

[0047] or \(R_3'\) and \(R_6'\) form together with the carbon atom that carries them one of the following rings:

[0054] and either \(R_3'\) represents an OH radical and \(R_6'\) represents a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms, substituted or non-substituted,

[0055] or \(R_3'\) and \(R_6'\) form together with the carbon atom that carries them one of the following rings:

[0056] or \(R_3'\) and \(R_6'\) form together an oxo group, as well as their addition salts with acids or bases.

[0057] A quite particular subject of the invention is the compounds of formula (I) as well as their addition salts with acids the names of which follow:

\[
(I)
\]

\[\begin{align*}
R_3' & \quad \text{and} \quad R_6' \quad \text{form together an oxo group, as well as their addition salts with acids or bases.}
\end{align*}\]

[0058] 4-chloro-3-hydroxy-11\(\beta\)-[4\{2-(diethylamino)ethoxy\}phenyl] \(\text{estra-1,3,5(10)-trien-17-one,}

[0059] 4-chloro-3-hydroxy-11\(\beta\)-[4\{2-(dimethylamino)ethoxy\}phenyl] \(\text{estra-1,3,5(10)-trien-17-one,}

[0060] 4-chloro-3-hydroxy-11\(\beta\)-[4\{2-(1-piperidinyl)ethoxy\}phenyl] \(\text{estra-1,3,5(10)-trien-17-one,}

[0061] and either \(R_3'\) represents an OH radical and \(R_6'\) represents a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms, substituted or non-substituted,
[0061] 4-chloro-3-hydroxy-11β-[4-{2-(1-pyrrolidinyl)ethoxy}phenyl]-estra-1,3,5(10)-triene-17-one,
[0062] 4-bromo-3-hydroxy-11β-[4-{2-(1-piperidinyl)ethoxy}phenyl]-estra-1,3,5(10)-triene-17-one,
[0063] 4-chloro-11β-[4-{2-(dimethylamino)ethoxy}phenyl]-estra-1,3,5(10)-triene-3,17beta-diol,
[0064] 4-chloro-11β-[4-{2-(diethylamino)ethoxy}phenyl]-estra-1,3,5(10)-triene-3,17beta-diol,
[0065] 4-chloro-11β-[4-{2-(1-piperidinyl)ethoxy}phenyl]-estra-1,3,5(10)-triene-3,17beta-diol,
[0066] 4-bromo-11β-[4-{2-(1-piperidinyl)ethoxy}phenyl]-estra-1,3,5(10)-triene-3,17beta-diol,
[0067] 4-chloro-11β-[4-{2-(1-pyrrolidinyl)ethoxy}phenyl]-estra-1,3,5(10)-triene-3,17beta-diol,
[0068] 4-chloro-11β-[4-{2-(diethylamino)ethoxy}phenyl]-19-nor-17alpha-pregn-1,3,5(10)-triene-20-yn-3-one-3,17beta-diol,
[0069] 4-chloro-11β-[4-{3-(1-piperidinyl)propoxy}phenyl]-estra-1,3,5(10)-triene-3,17beta-diol,
[0070] 4-chloro-11β-[4-{4-(1-piperidinyl)butoxy}phenyl]-estra-1,3,5(10)-triene-3,17beta-diol,
[0071] 4-chloro-11β-[4-{5-(1-piperidinyl)pentoxynyl}phenyl]-estra-1,3,5(10)-triene-3,17beta-diol,
[0072] gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-{2-(diethylamino)ethoxy}phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,
[0073] gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-{2-(1-pyrrolidinyl)ethoxy}phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,
[0074] gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-{2-(1-piperidinyl)ethoxy}phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,
[0075] gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-{3-(1-piperidinyl)propoxy}phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,
[0076] gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-{4-(1-piperidinyl)butoxy}phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,
[0077] gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-{5-(1-piperidinyl)pentoxynyl}phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,
[0078] (17beta)-4-chloro-11β-[4-{2-(diethylamino)ethoxy}phenyl]-spiro[estra-1,3,5(10)-triene-17,2(5H)furan]-3-one,
[0079] (17beta)-4-chloro-11β-[4-{2-(1-piperidinyl)ethoxy}phenyl]-spiro[estra-1,3,5(10)-triene-17,2(5H)furan]-3-one,
[0080] (17beta)-4-chloro-11β-[4-{2-(1-pyrrolidinyl)ethoxy}phenyl]-spiro[estra-1,3,5(10)-triene-17,2(5H)furan]-3-one,
[0081] (17beta)-4-chloro-4,5,6,7-tetrahydro-11β-[4-{2-(1-piperidinyl)ethoxy}phenyl]-spiro[estra-1,3,5(10)-triene-17,2(5H)furan]-3-one,
[0082] (17beta)-4-chloro-11β-[4-{3-(1-piperidinyl)propoxy}phenyl]-spiro[estra-1,3,5(10)-triene-17,2(5H)furan]-3-one,
[0083] (17beta)-4-chloro-4,5,6,7-tetrahydro-11β-[4-{3-(1-piperidinyl)propoxy}phenyl]-spiro[estra-1,3,5(10)-triene-17,2(5H)furan]-3-one,
[0084] (17beta)-4-chloro-11β-[4-{4-(1-piperidinyl)butoxy}phenyl]-spiro[estra-1,3,5(10)-triene-17,2(5H)furan]-3-one,
[0085] (17beta)-4-chloro-4,5,6,7-tetrahydro-11β-[4-{4-(1-piperidinyl)butoxy}phenyl]-spiro[estra-1,3,5(10)-triene-17,2(5H)furan]-3-one,
[0086] 4-chloro-11β-[4-{2-(diethylamino)ethoxy}phenyl]-17alpha-methyl-estra-1,3,5(10)-triene-3,17beta-diol,
[0087] 4-chloro-17alpha-methyl-11β-[4-{2-(1-piperidinyl)ethoxy}phenyl]-estra-1,3,5(10)-triene-3,17beta-diol,
[0088] Quite particularly a subject of the invention is also the compound of formula (I) as defined above, the name of which follows:
[0089] 4-chloro-11β-[4-{2-(diethylamino)ethoxy}phenyl]-estra-1,3,5(10)-triene-3,17beta-diol, as well as its addition salts with acids.
[0090] A subject of the invention is also a preparation process for the compounds of general formula (I) as defined previously, characterized in that a compound of general formula (II):

![Chemical Structure](image)

[0091] in which D and R₃ are as defined previously, R₇ represents one of the following groups:
in which n, Y, R₃ and R₄ are as defined previously, P is a protective group, Hal represents a halogen, is subjected to the action of a halogenation reagent in order to obtain the compound of formula (III):

![Diagram of compound (III)]

which is subjected to the action of an aromatization reagent of ring A, then to the action of a base in order to obtain the compound of formula (IV) corresponding to certain compounds of general formula (I):

![Diagram of compound (IV)]

which compounds of formula (II), (III) or (IV) are subjected, if desired and if necessary, in an appropriate order, to one or more of the following reactions:

- protection of the compounds in which R₇ is a —Ph—YH group,
- deprotection of the compounds in which R₇ is a Ph—YP group,
- the action of a compound of formula Hal₁ —(CH₂)n—Hal₂ on the compounds in which R₇ is a —Ph—YH group, Hal₁ or Hal₂ identical or different representing a halogen in order to obtain compounds in which R₇ is a —Ph—Y—(CH₂)n—Hal₂ group,
- the action of a compound of formula R₂—NH—R₃ on the compounds in which R₇ is a Ph—Y—(CH₂)n—Hal₂ group, in order to obtain compounds in which R₂ is a Ph—Y—(CH₂)n—NR₃R₄ group,
- the action of a halide salt (M—Hal₂) on the compounds in which R₇ is a Ph—Y—(CH₂)n—Hal₂ group in order to obtain the compounds in which R₇ is a —Ph—Y—(CH₂)n—Hal₂ group,
- protection of the OH group in position 3 or 17,
- deprotection of the OH group in position 3 or 17,
- alkylation of the OH group in position 3 or 17,
- acylation of the OH group in position 3 or 17,
- the action of a reducing agent when D represents the remainder of a pentagonal ring as defined previously and R₅ and R₆ together form an oxo group,
- the action of an organometallic on the compounds of formula (IV) with D representing the remainder of a pentagonal ring as defined previously and R₅ and R₆ together forming an oxo group,
- the action of a lactonization agent on the compounds of formula (IV) with D representing the remainder of a pentagonal ring as defined previously and R₅ and R₆ forming together an oxo group,
- the action of a reducing agent of the double bond, when D represents the remainder of a pentagonal ring as defined previously and R₅ and R₆ form together with the carbon that carries them, an O—(CH₂)n—CH—CH— group,
- the action of a reducing agent of the double bond, when D represents the remainder of a pentagonal ring as defined previously, and R₅ is an alkynyl or alkynyl radical containing 2 to 6 carbon atoms,
- halogenation in position 4, then aromatization of ring A, of the compound of general formula (II),
- aromatization of ring A of the compound of formula (III),
- salification.

The action of a halogenation reagent such as N-bromosuccinimide or N-chlorosuccinimide on the compounds of formula (II) is carried out in particular in the presence of a dipolar aprotic solvent such as dimethylformamide.

The aromatization reaction followed by the saponification reaction (action of the base) is carried out according to standard methods as described in the European Patent 0097572. A mixture of acetic anhydride and acetyl bromide is preferably used as the aromatization agent then a base such as soda in methanol as the saponification agent.

The protection and deprotection reactions are standard methods known to a person skilled in the art. A fairly complete review is found in the following work: Protective groups in organic synthesis T.W. Greene, John Wiley & Sons (1981).

The protective group P preferably represents an alkyl radical containing 1 to 4 carbon atoms, a benzyl group, an R₇R₈R₉Si group, in which R₇, R₈ and R₉, identical or different, independently of each other each represent an alkyl radical containing 1 to 4 carbon atoms or a phenyl group. Quite particularly it is the Si(Me)₃CMe₃ or —Si(Ph)₂CMe₃ groups.
[0116] As an example, the deprotection reactions of the compounds of formula (I), (II) or (IV) with R₃=Ph—OP or the compounds of formula (IV) the 3—OH of which is protected (3—OP), when P is a methyl radical, can be carried out by the action of tribromoborane in dichloromethane or hydrochloric acid in pyridine, the deprotection reactions when P is a benzylic group can be carried out by the action of hydrogen in the presence of palladium on carbon in ethyl acetate or by the action of trifluoroacetic acid, the deprotection reactions when P is a tertbutyldiphenylsilyl group can be carried out by the action of tetraethyl amonium fluoride in solution in tetrahydrofuran.

[0117] When P is a tetrahydropyran group, the deprotection is carried out in the presence of an aqueous acid in an alcoholic solvent and preferably by the action of hydrochloric acid in methanol.

[0118] The action of a compound of formula Hal,—(CH₃)₃—I on a compound of formula (II), (III) or (IV) in which R₃=Ph—YH can be carried out, in particular when Y=O, in the presence of a base in a solvent such as acetone.

[0119] The action of a compound of formula R₃—NH—Hal₃ on the compounds in which R₃ is a Ph—Y—(CH₃)₃—Hal₃ group is carried out under standard conditions for the substitution of nucleophiles, in particular in the presence of an aprotic solvent such as tetrahydrofuran.

[0120] The substitution reaction of a halogen by another when in particular R₃ is a Ph—Y—(CH₃)₃—Cl group is preferably carried out by the action of NaI in methyl-ethylketone.

[0121] The alkylation or acylation reactions of the OH group in position 3 or 17 are carried out by standard methods known to a person skilled in the art.

[0122] The reduction of 17-keto into the corresponding alcohol (R₃=OH and R₄=H) is carried out according to standard methods, in particular by the action of an alkaline borohydride such as sodium borohydride in methanol or ethanol or by the action of aluminium and lithium tetrahydride.

[0123] The action of an organometallic on 17-keto allows access to the products of formula (IV) in which D represents the remainder of a pentagonal ring as defined previously, R₃ is a hydroxyl and R₄ represents an optionally substituted alkyl, alkenyl, alkynyl radical.

[0124] The organometallic derivative of an alkyl, alkenyl or alkynyl or the magnesium compounds of formula AlkMgHal and the lithium compounds of formula AlkLi in which Alk represents an alkyl, alkenyl or alkynyl group containing at most 8 carbon atoms, Hal represents a halogen atom. In a preferred method of implementing the process, Hal represents a chlorine, bromine or iodine atom, preferably bromine. The reaction preferably takes place in the presence of cerium chloride. In a preferred method for implementing the process, Hal represents a chlorine, bromine or iodine atom, preferably bromine.

[0125] The lactonization reaction from 17 keto is carried out according to the method of STURTZ (ref. G. STURTZ and J-J. YAOUAN, Synthesis, (1980), 289) in particular in the presence of alkyl bisdimethylaminomethophosphorate in the presence of an alkyllithium compound such as n-butyllithium in tetrahydrofuran.

[0126] The total or partial reduction reaction when R₃ is an alkynyl or alkynyl or when R₃ and R₄ form together with the carbon that carried them an O—(CH₂)₃—CH=CH— group, can be carried out either in a total manner by the action of hydrogen in the presence of a catalyst such as palladium on carbon or a rhodium catalyst such as Wilkinson's reagent or in a partial manner (alkynyl becomes alkynyl) by the action of a poisoned catalyst such as palladium on barium sulphate poisoned with pyridine or triethylamine.

[0127] The esterification and salification reactions are carried out by current methods known to a person skilled in the art.

[0128] A more particular subject of the invention is a preparation process for the compounds of general formula (I) as described previously characterized in that a compound of general formula compound (II):

\[
\text{(II')}
\]

[0129] in which R₅ and R₆ are as-defined previously, R'7 represents:

\[
\text{R'7}
\]

[0130] is subjected to the action of a halogenation reagent in order to obtain the compound of formula (III):

\[
\text{R'7}
\]

[0131] which is subjected to the action of an aromatization reagent of ring A, then to the action of a base in order to
obtain the compound of formula (IV) corresponding to certain compounds of general formula (I):

![Chemical structure of compound IV]

[0132] which compounds of formula (II), (III) or (IV), are subjected, if desired and if necessary, in an appropriate order, to one or more of the following reactions:

[0133] protection of the compounds in which \( R_7 \) is a —Ph—OH group,

[0134] deprotection of the compounds in which \( R_7 \) is a Ph—OP group,

[0135] the action of a compound of formula \( \text{Hal}_1—(\text{CH}_3)_2—\text{Hal}_2 \) on the compounds in which \( R_7 \) is a —Ph—OH group, \( \text{Hal}_1 \) or \( \text{Hal}_2 \), identical or different, representing a halogen in order to obtain the compounds in which \( R_7 \) is a —Ph—O—(CH)_n—Hal group,

[0136] the action of a compound of formula \( \text{R}_1—\text{R}_3 \), on the compounds in which \( R_7 \) is a Ph—O—(CH)_n—Hal group, in order to obtain the compounds in which \( R_7 \) is a Ph—O—(CH)_n—NR_1,R_3 group,

[0137] the action of a halide salt (M—Hal_2) on compounds in which \( R_7 \) is a Ph—O—(CH)_n—Hal group, in order to obtain the compounds in which \( R_7 \) is a —Ph—O—(CH)_n—Hal group,

[0138] protection of the OH group in position 3 or 17,

[0139] deprotection of the OH group in position 3 or 17,

[0140] alkylation of the OH group in position 17,

[0141] acylation of the OH group in position 17,

[0142] the action of a reducing agent when \( R_5 \) and \( R_6 \) together form an oxo group,

[0143] the action of an organometallic on the compounds of formula (IV) with \( R_5 \) and \( R_6 \) together forming an oxo group,

[0144] the action of a lactonization agent on the compounds of formula (IV) with \( R_5 \) and \( R_6 \) together forming an oxo group,

[0145] the action of a reducing agent of the double bond, when \( R_5 \) and \( R_6 \) form together with the carbon which carries them, an \( O—(\text{CH})_3—\text{CH}═\text{CH}—\) group,

[0146] the action of a reducing agent of the double bond, when \( R_5 \) is an alkyl or alkynyl radical containing 2 to 6 carbon atoms,

[0147] halogenation in position 4, then aromatization of ring A, of the compound of formula (II),

[0148] aromatization of the compound of formula (III),

[0149] salification.

[0150] The compounds of general formula (I) as well as their addition salts with pharmaceutically acceptable acids have oestrogen, anti-oestrogen and anti-proliferative activities.

[0151] Therefore the compounds of formula (I) can be used in the treatment of disorders linked to hypofoliculinitia, for example, amenorrhoeas, dysmenorrhoeas, repeated abortions, premenstrual disorders, in the treatment of certain oestrogen-dependent pathologies such as prostatic adenomas or carcinomas, mammary carcinomas and their metastases or in the treatment of benign breast tumors, as an anti-uterotrophic as well as in the replacement treatment for the menopause or the perimenopause.

[0152] Among the symptoms and consequences linked to the menopause are more specifically meant hot flushes, sweats, vaginal atrophy and dryness, urinary symptoms and in the long term a reduction in bone mass and an increased risk of fractures, and the loss of the cardiovascular protection provided by the oestrogens.

[0153] In particular, the compounds of formula (I) and their addition salts with pharmaceutically acceptable acids or bases can be used in the prevention or the treatment of osteoporosis.

[0154] The compounds of formula (I) and their addition salts with pharmaceutically acceptable acids can also be used for the prevention or the treatment of osteoporosis in man.

[0155] They can also be used for the prevention or the treatment of secondary osteoporoses (for example cortisonal, linked with immobilization).

[0156] The compounds of formula (I) and their addition salts with pharmaceutically acceptable acids or bases in particular have a dissociated oestrogenic activity.

[0157] By dissociated oestrogenic activity is meant an oestrogenic activity at bone level while demonstrating only minimal activity at uterine level, thus not entailing an endometrial proliferation (much lower activity than that of oestriadiol).

[0158] Furthermore, the compounds according to the invention have the following advantages:

[0159] They have an anti-oestrogenic activity at the level of the breast. Unlike oestradiol, they do not stimulate the growth of human mammary tumor cells and can even inhibit their growth. The compounds according to the invention are therefore particularly advantageous for the treatment of the menopause in women at risk from breast cancer (family antecedents) who are therefore excluded from a replacement treatment using oestradiol.

[0160] They can also be used in the treatment of breast cancers.
[0161] They lead to a lowering of the seric cholesterol level to a level equivalent to that induced by oestradiol. Therefore, they strengthen cardiovascular protection.

[0162] Finally, as the compounds according to the invention have no oestrogen activity at the uterine level, they do not require to be administered in combination with a progestogenetic compound.

[0163] A subject of the invention is thus compounds of general formula (I) as well as their addition salts with pharmaceutically acceptable acids or bases, as medicaments.

[0164] A more particular subject of the invention is compounds of formula (I) and their addition salts with pharmaceutically acceptable acids or bases as medicaments used for the prevention or the treatment of osteoporosis.

[0165] The invention extends to the pharmaceutical compositions containing at least one of the medicaments defined above as active ingredients.

[0166] The compounds of formula (I) are used by digestive, parenteral or local route, for example by percutaneous route. They may be prescribed in the form of plain or coated tablets, capsules, granules, suppositories, pessaries, injectable preparations, ointments, creams, gels, microspheres, implants, intravaginal rings, patches, which are prepared according to the usual methods.

[0167] The active ingredient or ingredients can be incorporated with excipients usually employed in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents, preservatives.

[0168] The useful dose varies as a function of the illness to be treated and the administration route; it can vary for example from 1 to 1000 mg per day for an adult by oral route. Patent 0057115.

[0169] The compounds of general formula (II) or (II') with

\[ R_1 = \text{[Diagram]} \quad Y = (\text{CH}_2)_n-\text{Hal} \]

5 or \( R_1' = \text{[Diagram]} \quad O - (\text{CH}_2)_n-\text{Hal} \)

[0170] can also be formed from the compounds of formula (IIa):

[0171] or (IIa):

[0172] in which \( D, R_2, R_3 \) and \( R_6 \) are as defined previously and \( K \) represents a protective group of the ketone function, which is subjected to the action of an \( O \)-alkylation reagent of formula \( \text{Hal}-(\text{CH}_2)_n-\text{Hal} \) then to the action of a dehydration reagent which is equally capable of releasing the ketone.

[0173] The compounds of formula (IIa) or (IIa') are also known compounds and described in the following patent: U.S. Pat. No. 5 043 332.

[0174] A subject of the invention is also, as intermediate products, the compounds of formulae (III), (III'), (IV) and (IV).

[0175] The examples below illustrate the invention without however limiting it.

[0176] Solvents described in the examples: AcOEt (ethyl acetate), TEA (triethylamine), \( \text{CH}_2\text{Cl}_2 \) (dichloromethane), CHCl\(_3\) (chloroform), MeOH (methanol), NH\(_2\)OH (ammonium hydroxide), iPrOH (isopropyl alcohol).

**EXAMPLE 1**

[0177] 4-chloro-3-hydroxy-11beta-[4-{[2-(1-piperidinyl) ethoxy]phenyl}]-estra-1,3,5 (10)-iden-17-one

[0178] Stage A: 11beta-[4-{2-bromoethoxy} phenyl]-estra-4,9-diene-3,17-dione

[0179] a) \( O \)-alkylation

[0180] 8.0 g of 5\( \alpha \)-hydroxy-11\( \beta \)-[4-hydroxy-phenyl]-estra-9-en-3,17-dione cyclic 3-(1,2-ethanediyl acet) is dissolved under an inert atmosphere in 80 ml of 99% 1,2-dibro-
momethane, 21 ml of 50% soda, 0.800 g of tetrabutyl ammonium bromide, and agitation is carried out under reflux for 1 hour.

[0181] b) acid hydrolysis

[0182] 93 ml of 6M hydrochloric acid is added at ambient temperature, agitation is carried out for 45 minutes, followed by extraction, washing, drying and evaporating under pressure reduced until the crude product is obtained (m=13.17 g) which is recrystallized from a 50 ml of dichloromethane/50 ml of isopropyl ether mixture. 5.96 g+7.0 g of pure expected product is obtained (RI CHCl₃/ACOET 70/0 = 0.45). M.p. = 208° C. IR (CHCl₃) 1735 cm⁻¹: 17 keton; 1658 and 1609 cm⁻¹; conjugated ketone; 1583 and 1509: aromatic.

[0183] Stage B: 11beta-[4-(2-bromoethoxy) phenyl]-4-chloro-estra-4,3,17-dione (introduction of cl in position 4)

[0184] 1.86 g of N-chlorosuccinimide is added to a solution, under inert atmosphere, at 60° C, of 5.025 g of the product obtained in Stage A, in 67 ml of dimethylformamide and agitation is carried out for 10 minutes. Salt water is added, followed by extraction, drying and evaporating under reduced pressure until the crude product is obtained (m=8.149 g) which is purified by chromatography on silica eluting with a cyclohexane/ethyl acetate mixture (60/40), 5.43 g of pure expected product is obtained (RF essence G/ACOET 60/0 = 0.35). IR (CHCl₃) 1736 cm⁻¹: 17-ketone; 1677 cm⁻¹: conjugated ketone; 1609, 1582, 1550 and 1509 cm⁻¹: C=C and aromatic.

[0185] Stage C: 11beta-[4-(2-bromoethoxy) phenyl]-4-chloro-3-hydroxy-estra-1,3,5(10)triene-17-one

[0186] a) Aromatization

[0187] 4.7 ml of acetic anhydride and 4.7 ml of acetyl bromide is added, under an inert atmosphere, at ambient temperature to 4.7 g of the product obtained in Stage B in 50 ml of dichloromethane/siliporite, while cooling the reaction medium down and agitation is carried out for 5 hours 30 minutes.

[0188] b) Saponification of the phenolic acetate

[0189] After the dichloromethane is evaporated off under reduced pressure and at ambient temperature, 47 ml of tetrahydrofuran is added under an inert atmosphere while cooling down the reaction medium, the 47 ml of methanol then 47 ml of -soda are added, agitation is carried out for 1 hour at ambient temperature. After acidification with hydrochloric acid, extraction is carried out followed by washing, drying and evaporating under pressure reduced until the crude product is obtained (m=4.84 g) which is purified by chromatography on silica eluting with a cyclohexane/ethyl acetate mixture (70/30). 4.37 g of expected product is obtained (RF essence G/ACOET 70/30 = 0.18). IR (CHCl₃) 3537 cm⁻¹: phenolic—OH; 1733 cm⁻¹: 17-ketone; 1609, 1580, 1511 and 1481 cm⁻¹: aromatic.

[0190] Stage D: 4-chloro-3-hydroxy-11beta-[4-(2-idoethoxy) phenyl]-estra-1,3,5(10)triene-17-one (iodization)

[0191] 2.44 g of sodium iodide is added under an inert atmosphere, at ambient temperature, to a solution of 4.11 g of the brominated derivative prepared in Stage C in 80 ml of methylethyl ketone, and agitation is carried out overnight under reflux. Water is added followed by extraction, drying and evaporating under reduced pressure until 4.184 g of expected crude product is obtained (RF = methanol/water (90/10) = 0.30).

[0192] Stage E: 4-chloro-3-hydroxy-11beta-[4-[2-(1-piperidinyl) ethoxy]phenyl]-estra-1,3,5(10)triene-17-one (substitution of the iodine by piperidine)

[0193] 1.248 g of the iodized derivative obtained in Stage D, is dissolved under inert atmosphere, at ambient temperature in 25 ml of tetrahydrofuran/siliporite and 1.35 ml of piperidine is added and the reaction medium is heated under reflux for 1 hour 30 minutes. After evaporation of the tetrahydrofuran under reduced pressure at ambient temperature, water and ethyl acetate are added, followed by washing, drying and evaporation under reduced pressure until 1.185 g of the crude amino derivative is obtained which is purified by chromatography on silica eluting with an ethyl acetate/triethylamine mixture 95/5. 1.039 g of expected pure product is obtained (RF = ethyl acetate/TEA (95/5) = 0.20). NMR (CDCl₃): 0.45 ppm (s): CH₃ in position 18; 2.48 ppm: cyclic—CH₂—N₃; 2.71 ppm (t): CH₂—N of the chain; 3.99 ppm: (t): CH₂—OAr; 3.99 ppm: H₂β; 6.63 ppm: H₂β; 6.81 ppm: H₂β; 6.60 ppm: Ar—O; 6.91 ppm: Ar—C.

EXAMPLE 2

[0194] 4-chloro-3-hydroxy-11beta-[4-[2-(1-pyrrolidinyl) ethoxy]phenyl]-estra-1,3,5(10)triene-17-one

[0195] The operation is carried out as in Example 1 Stage E, but starting with 6 g of the iodized derivative obtained in Stage of Example 1, 60 ml of tetrahydrofuran/siliporite and 4.6 ml of pyrrolidine. 4.2 g 9 of expected pure product is obtained (RF = ACOEt/TEA (80/20) = 0.24). NMR (CDCl₃): 0.45 ppm (s): CH₃ in position 18; 1.78 ppm (m): CH₂ in beta position of N; 2.59 ppm (m): CH₃ in alpha position of N; 2.84 ppm (t): CH₂—N of the chain; 3.98 ppm (t): CH₂—OAr; 3.98 ppm (t): H₂β, CH₂—O of the chain; 6.62 ppm: H₂β; 6.81 ppm: H₂β; 6.62 ppm: Ar—O; 6.91 ppm: Ar—C.

EXAMPLE 3

[0196] 4-chloro-3-hydroxy-11beta-[4-[2-diethylamino] ethoxy]phenyl]-estra-1,3,5(10)triene-17-one

[0197] The operation is carried out as in Example 1 Stage E, but starting with 1.2 g of the iodized derivative obtained in Stage D of Example 1, 25 ml of tetrahydrofuran/siliporite and 1 ml of diethylamine.

[0198] 0.688 g of expected pure product is obtained (RF: ACOET/TEA (95/5) = 0.22). NMR (CDCl₃): 0.45 ppm (s): CH₃ in position 18; 1.03 ppm (t): N—CH₂—CH₃; 2.60 ppm (q): N—CH₂—CH₂; 2.81 ppm (t): CH₂—N of the chain; 3.93 ppm (t): CH₂—OAr; 4.00 ppm (t): H₂β; 6.63 ppm: H₂β; 6.82 ppm: H₂β; 6.63 ppm: Ar—O; 6.91 ppm: Ar—C.

EXAMPLE 4

[0199] 4-bromo-3-hydroxy-11beta-[4-(1-piperidinyl) ethoxy]phenyl]-estra-1,3,5(10)triene-17-one

[0200] Stage A: 11beta-[4-(2-chloroethoxy) phenyl]-estra-4,9-diene-3,17-dione (O-alkylation)

[0201] (7.9 ml x 2) 1-bromo-2-chloroethane followed by 6 ml of 50% soda and 500 mg of tetrabutylammonium bromide are added to a suspension of 5 g of 11beta-[4-(4-hydroxyphenyl)-estra-4,9-diene-3,17-dione in 50 ml of acetone.
The mixture is taken to reflux for 4 hours. Water is added followed by extracting, drying and evaporating under reduced pressure until a crude product is obtained which is purified in ether.

**[0202]** 5.45 g of expected product is obtained (RF CH₂Cl₂/acetone 90/10=0.82). NMR (CDCl₃): 0.58 3H (s): CH₃ in position 18; 3.80 2H (t): CH₂Cl; 4.28 2H (t): CH₂O; 4.49 1H (d): H₃; 5.80 1H (s): H₄; 6.82 2H (d): 2H arom.; 7.08 2H (d): H arom.

**[0203]** Stage B: 4-bromo-11beta-[4-(2-chloroethoxy) phenyl]-estra-4,9-diene-3,17-dione (introduction of Br in position 4)

**[0204]** A solution of 2.43 g of N-bromo succinimide is added under a nitrogen atmosphere to a suspension of 5.35 g of the product of Stage A in 70 ml of dimethylformamide. After agitation for 2 hours at ambient temperature, 200 ml of ethyl acetate and 400 ml of water saturated in NaCl are added followed by extraction, washing, drying and evaporating under reduced pressure until 8 g of crude product is obtained which is purified by chromatography eluting with a dichloromethane/acetone mixture 98/2. 4.66 g of expected pure product is obtained. (RF CH₂Cl₂/acetone 95/5=0.92). NMR (CDCl₃): 0.57 3H (s): CH₃ in position 18; 3.25 1H (dt): H₆; 3.80 2H (t): CH₂Cl; 4.20 2H (t): CH₂O; 4.38 1H (d, wide): H₅; 7.07 and 6.83 4H: AABBBH arom.

**[0205]** Stage C: 4-bromo-11beta-[4-(2-chloro ethoxy) phenyl]-3'-hydroxy-estra-1,3,5(10)-trien-17-one ( aromatization of ring A)

**[0206]** The operation is carried out as in Stage C of Example 1, starting with 4.5 g of the product obtained in the preceding stage. 3.05 g of expected product is obtained. (RF CH₂Cl₂/AcOEt 90/10=0.64). NMR (CDCl₃): 0.45 3H (s): CH₃ in position 18; 3.75 2H (t): CH₂Cl; 4.12 2H (t): CH₂O; 4.00 1H (t): H₃; 5.48 1H (s): OH; 6.93 and 6.64 2H (d): AABBB arom; 6.85 and 6.64 2H (d): H₅H₆.

**[0207]** Stage D: 4-bromo-3-hydroxy-11beta-[4-(2-iodo ethoxy) phenyl]-estra-1,3,5(10)-trien-17-one (iodization)

**[0208]** The operation is carried out as in Stage D of Example 1, starting with 1 g of the product obtained in the preceding stage. 1.14 g of expected product is obtained.

**[0209]** Stage E: 4-bromo-3-hydroxy-11beta-[4-[2-(1-piperidinyl) ethoxy]phenyl]-estra-1,3,5(10)-trien-17-one (substitution of the iodine by piperidine)

**[0210]** The operation is carried out as in Stage E of Example 1 starting with 1.1 g of the product obtained in the preceding stage. 270 mg of expected pure product is obtained (RF AcOEt/TEA 90/10=0.43). NMR (CDCl₃): 0.45 3H (s): CH₃ in position 18; 2.47 4H (m): cyclic CH₂N; 2.70 2H (t): CH₂-N; 3.98 2H (t): CH₂-O; 3.98 1H (t, wide): H₃; 6.88 and 6.62 2H (d): H₅ and H₆; 6.90 and 6.62 4H: AABBB H aromatic.

**EXAMPLE 5**

**[0211]** 4-chloro-11beta-[4-[3-(1-piperidinyl) propoxy]phenyl]-estra-1,3,5(10)-trien-3,17-beta-diol

**[0212]** Stage A: 4-chloro-11beta-[4-(phenylmethoxy) phenyl]-estra-4,9-diene-3,17-dione (chlorination in position 4)

**[0213]** 5.295 g of N-chlorosuccinimide is added at 60°C under an inert atmosphere to a solution of 13.6 g of 11β-[4-(phenylmethoxy) phenyl]-estra-4,9-diene-3,17-dione in 120 ml of dimethylformamide. After 8 hours, the reaction medium is poured into a saturated aqueous solution of NaCl, followed by extraction, washing, drying and evaporating under reduced pressure until the crude product is obtained (m = 19.128 g). A second trial is carried out, the crude products are collected and purified by chromatography eluting with an ethyl acetate-cyclohexane mixture 30/70. 23.28 g of expected pure product is obtained. (RF AcOEt/cyclohexane 30/70=0.19). NMR (CDCl₃): 0.50 3H (s): CH₃ in position 18; 3.25 1H (dt): H₃; 4.39 1H (d): H₅; 5.02 2H: CH₂Ph; 6.89: H in ortho position of Ph—O; 7.00: H in meta position of Ph—O; 7.29 to 7.45: aromatic of CH₃—Ph.

**[0214]** Stage B: 4-chloro-3-[[2,2-dimethylthyl] (diphenyl silyl) oxy] 11-beta-[4-(phenylmethoxy) phenyl]-estra-1,3,5(10)-trien-17-one (aromatisation/saponification/blocking of the phenol)

**[0215]** a) aromatization and saponification

**[0216]** The operation is carried out as in Stage C of Example 1 starting with the product obtained in the preceding stage. 13.5 g of expected pure product is obtained (S—OH).

**[0217]** b) blocking of the phenol

**[0218]** 13.5 g of the product obtained in the preceding stage, 191 ml of dichloro methane/siliporite, 14.5 ml of terbutyl diphenyl chlorosilane and 258 mg of 4-DMP are dissolved under an inert atmosphere, and agitation is carried out for 24 hours under reflux. The reaction medium is then poured into water, extraction is carried out followed by washing, drying and evaporating under reduced pressure until 41.322 g of crude product is obtained in the form of a white oil which is purified by chromatography eluting with an ethyl acetate/petroleum ether mixture 20/80 then 40/60. 1.275 g of expected pure product is obtained. (RF AcOEt/ petroleum ether 20/80=0.27). NMR (CDCl₃): 0.42 3H (s): CH₃ in position 18; 1.11 2H (s): C(CH₃)₂; 7.25 to 7.40-7.6 to 7.75 Si—Ph; 3.85 1H (t): H₃; 4.94 2H (s): CH₂Ph; 6.65: H in ortho position (Ph—O); 6.84: H in para position (Ph—O); 6.17 1H; 6.47 1H.

**[0219]** Stage C: 4-chloro-3-[[2,2-dimethylthyl] (diphenyl silyl) oxy] 11-beta-[4-(4-hydroxypropoxy) estra-1,3,5(10)-trien-17-one (deprotection (debenzylation))

**[0220]** 15.6 g of palladium hydroxide on magnesia and 40 ml of 1,4-cyclohexadiene are added, under an inert atmosphere, at ambient temperature to a suspension of 20.82 g of the product obtained -in the preceding stage in 420 ml of methanol, then taken to reflux for 8 hours. After filtration and evaporation under reduced pressure, 22 g of crude product is obtained which is purified by chromatography eluting with a cyclohexane/ethyl acetate mixture 7/3. 19.4 g of expected pure product is obtained. (RF cyclohexane/AcOEt 7/3=0.27). NMR (CDCl₃): 0.42 3H (s): CH₃ in position 18; 1.11 2H (s): C(CH₃)₂; 3.83 1H (t): H₃; 4.56 2H (s): OH; 6.17 (d) 6.46 1H (d): H₃; 7.25 to 7.43 (m) 6H and 7.64 1H (4H: SiPh₂).

**[0221]** Stage D: 4-chloro-3-[[2,2-dimethylthyl] (diphenyl silyl) oxy] 11-beta-[4-(3-iodopropoxy) phenyl]-estra-1,3,5(10)-trien-17-one (O-alkylation)

**[0222]** 3.18 g of the product obtained in the preceding stage, 15 ml of 1,3-diodopropane, 800 mg of ground soda
and 300 mg of tetrabutylammonium bromide, acidified with
2N hydrochloric acid are mixed together for 4 hours at
ambient temperature, followed by extraction, washing, drying
and evaporating under reduced pressure until the crude
product is obtained (39.8 g) which is purified by chroma-
tography eluting with a petroleum ether/ACOEt mixture
75/25. 2.43 g of expected pure product 1 is obtained (RF:
petroleum ether/ACOEt 80/20=0.35). NMR (CDCl3): δ 0.41 (s): CH3 in position 18; 1.10 (s): (CH3)2; 3.54 (t): O—CH2—
CH—CH3—H, 3.85 (t): H1, 3.91 (t): O—CH2—CH—H; 6.16
(d): H2, 7.25 to 7.45 6H and 7.66-7.64 4H: SiPh2.

[0223] Stage E: 4-chloro-3-[[2,2-dimethyl(ethyl) (diphe-
nyl)]silyl]oxy] 11-beta-[4-[3-(1-piperidinyl) propoxy] phen-
nyl]-estradiol-1,3,5(10)-trien-17-one (substitution of the iodine
by piperidine)

[0224] The operation is carried out as in Stage E of Example
1, starting with the product obtained in the pre-
ceeding stage. 2.07 g of the expected pure product is obtained
(Rf ACOEt/TEA 98/2=0.23). NMR (CDCl3): δ 0.42 (s): CH3 in
position 18; 1.10 (s): (CH3)2; 2.52: cyclic CH—N; 2.83: CH2—
N of the chain; 3.84 (t): H1; 3.88 (t): CH2—O; 6.16 (d): H2; 6.56-6.80: Ph—O; 7.25-7.40 6H and 7.65 4H: SiPh2.

[0225] Stage F: 4-chloro-11beta-[4-[3-(1-piperidinyl) pro-
proxy] phenyl]-estradiol-1,3,5(10)-trien-3-17-beta-diol (reduction
of 17-keto and deprotection)

[0226] a) Reduction of 17-keto
[0227] 63 mg of 97% sodium borohydride is added under
an inert gas atmosphere and at ambient temperature to
a solution of 600 mg of the product obtained in the preceding
stage in 4 ml of methanol and 2 ml of tetrahydrofuran, while
cooling the reaction medium down in an ice bath and
agitation is carried out for 50 minutes. Ethyl acetate is added
followed by washing with salt water, drying and evaporating
under reduced pressure until 614 mg of the expected crude
product is obtained.

[0228] b) Degradation of the phenol in position 3
[0229] 1.6 ml of a solution of tetrabutyl ammonium fluoro-
de in tetrahydrofuran is added under an inert gas atmos-
phere, at ambient temperature to a solution of 614 mg of the
product obtained previously in 6 ml of tetrahydrofuran and
agitation is carried out for 50 minutes at ambient temperature.
The reaction medium is poured into water followed by
extraction, washing, drying and evaporating under reduced
pressure until 840 mg of crude product is obtained which is
purified by chromatography eluting with dichloromethane/
methanol/ammonium hydroxide mixture 90/10/1. 215 g of
expected pure product is obtained. (RF CH2Cl2/Methanol/
NH4OH 90/10/1=0.3). NMR (CDCl3): 0.38 (s): CH3 in
position 18; 2.45 (m): CH2—N; 3.72 (t): H1; 3.86: H11, 6.61-6.93: Ph—O; 6.61-6.75: H2, H3.

EXAMPLE 6

[0230] 4-chloro-11beta-[4-[3-(1-piperidinyl) butoxy] phen-
nyl]-estradiol-1,3,5(10)-trien-3-17-beta-diol

[0231] The operation is carried out in the same manner as in
Example 5, the O-alkylation being carried out: either with
4-chloro-1-butanol, by Misunobu’s reaction in the presence
of triphenylphosphine, diethylzodicarboxylate in tetrahy-
drofuran and the chlorinated product obtained being con-
verted into the iodized product according to the process
described in Example 1 Stage D, or by direct action with
1,4-diodobutane (cf Ex. 6). 189 mg of expected pure product
is obtained (RF CH2Cl2/Methanol/NH4OH 90/10/1=0.24).

EXAMPLE 7

[0232] 4-chloro-11beta-[4-[5-(1-piperidinyl) pentoxyl phenyl]
estradiol-1,3,5(10)-trien-3-17-beta-diol

[0233] The operation is carried out as in Example 5, the O-
alkylation is carried out with 1,5-diodopentane. 125 mg of
expected pure product is obtained. (RF CH2Cl2/Methanol/
NH4OH 90/10/1=0.30).

EXAMPLE 8

[0234] (17beta)-4-chloro-11beta-[4-[2-(1-piperidinyl) ethyl]
ethoxy]phenyl]-spiro-[estradiol-1,3,5(10)-trien-17,2(5H)
furan] 3-ol

[0235] Stage A: (17beta)-4-chloro-11beta-(4-hydroxyphy-
nyl) spiro-[estradiol-4,9-diene-17,2(5H)-furan]-3-one (chlori-
nation) 4.51 g of N-chlorosuccinimide is added under an
inert atmosphere, at 60° C to a suspension of 10.46 g of
(17beta)-11beta-(4-hydroxy phynyl) spiro-[estradiol-4,9-diene-
17,2(5H)-furan]-3-one (WO 87/059088) in 100 ml of dim-
ethylformamide and the reaction medium is left to react for
10 minutes under agitation. The reaction medium is then
poured onto an iced-cooled solution of sodium chloride
followed by extracting, drying and evaporating under reduced
pressure until 20.85 g of crude product is obtained. 8.93 g of
the product obtained in a related trial carried out in an
identical manner is added and the whole is purified by
chromatography eluting with a CH2Cl2/aceton mixture
95/5, then recrystallization from ethyl ether. 0.98 g of
expected pure product is obtained. (RF CH2Cl2/acetone
95/5=0.2). M.p=258° C.

[0236] Stage B: (17beta)-4-chloro-11beta-[4-[2-bromoeth-
hoxy] phenyl]-spiro-[estradiol-4,9-diene-17,2(5H)
furan]-3-one

[0237] The operation is carried out as in Example 1 Stage
A, but starting with 1,2-dibromoethane. 5.34 g of expected
pure product is obtained. (RF essence of ACOEt 75/25=0.21).

[0238] Stage C: Aromatization and saponification

[0239] Stage D: Iodization

[0240] Stage E: Condensation of the piperidine

[0241] Stages C, D and E are carried out in a similar
manner to Stages C, D and E of Example 1.

[0242] 0.657 g of expected pure product is obtained (RF
ACOEt/TEA 92/8=0.21). NMR (CDCl3): δ 0.48 (s): CH3 in
position 18; 2.47 (m): cyclic CH—N; 2.70 (t): CH2—N
chain; 3.89 (t): H1; 3.99 (t): CH—O chain; 4.56: CH—O
ring; 5.78: OH; 5.87: H3; H4; 6.60-6.80: H5 and H6;
6.60-6.86: Ph—O.

EXAMPLE 9

[0243] (17beta)-4-chloro-11beta-[4-[2(diethylamino) eth-
hoxy] phenyl]-spiro-[estradiol-1,3,5(10)-trien-17,2(5H)
furan]-3-ol

[0244] The operation is carried out as in Example 8 but
with final condensation of diethylamine on the iodine
derivative. 0.512 g of expected pure product is obtained (RF
CH₂Cl₂/MeOH/NH₄OH 93/7/0.2=0.29). NMR (CDCl₃): 0.48 (s): CH₃ in position 18; 1.03 (t): CH₂—CH₃; 2.60 (q): CH₃—CH₂—CH₂; 2.81 (t): CH₂—N; 3.89 (d): H₁; 3.95 (s): CH₂—O chain; 4.56: CH₂—O ring (H₂); 5.87: H₃; H₂; 6.61-6.79: H₁ and H₂; 6.61-6.86: Ph—O.

EXAMPLE 10
[0245] (17beta) 4-chloro-11beta-[4-[2-(1-pyrroldinyl) ethoxy] phenyl]-spiro[estre-1,3,5(10)-triene-17,2(5H) furan]-3-ol

[0246] The operation is carried out as in Example 8 but with final condensation of the pyroline on the iodine derivative. 0.628 g of expected product is obtained. M.p.= 226-227°C. (RF CH₂Cl₂/MeOH/NH₄OH 93/7/0.2=0.25). NMR (CDCl₃): 0.48 (s): CH₃ in position 18; 2.59 (m): cyclic CH₂—N; 2.80 (m): CH₂—N chain; 3.89 (d): H₁; 3.98 (t): CH₂—O of the chain; 4.56 (m): cyclic CH₂—O (H₂); 5.87 (m): H₃; H₂; 6.60-6.78 (d): H₁ and H₂; 6.60-6.86 AA'B'B': Ph—O.

EXAMPLE 11
[0247] (17beta) 4-chloro-11beta-[4-[3-(1-piperidinyl) propoxy] phenyl]-spiro-Eestra-1,3,5(10)-triene-17,2(5H) furan]-3-ol

[0248] The operation is carried out as in Example 8, the O-alkylation is carried out directly with 1,3-diodopropane (avoids Stage D of Example 8). 0.591 g of expected pure product is obtained (RF AcOEt/TEA 92/8=0.19). NMR (CDCl₃): 0.48 (s): CH₃ in position 18; 2.30 to 2.50: CH₂—N; 3.87 (m): CH₂—O chain; 4.56: CH₂—O ring (H₂); 5.88: H₃; H₂; 6.61-6.79: H₁ and H₂; 6.61-6.86: Ph—O.

EXAMPLE 12
[0249] (17beta) 4-chloro-11beta-[4-[4-(1-piperidinyl) butoxy] phenyl]-spiro-estre-1,3,5(10)-triene-17,2(5H) furan]-3-ol

[0250] The operation is carried out as in Example 8 Stages A, B, C, D, E, the O-alkylation is carried out with 1-bromo-4-chlorobutane. 0.494 g of pure product is obtained. RF AcOEt/TEA 95/5=0.22 M.p.=154°C. NMR (CDCl₃): 0.50 (s): CH₂ in position 18; 2.36 (DH): CH₂—N ring; 3.85 (t): CH₂—O; 3.89 (t): H₁; 4.57 (s): cyclic CH₂—O (H₂); 6.60 (m): 3H)-6.86 (m): 2H); Ph—O and H₂; 6.79 (d): H₁.

EXAMPLE 13
[0251] 4-chloro-3-hydroxy-11beta-[4-[2-(1-dimethylamino) ethoxy] phenyl]-estre-1,3,5(10)-triene-17-one


[0253] 6 ml of sulphuryl chloride at 10% in dichloromethane is added under an inert atmosphere, at ambient temperature to a solution of 1.08 g of 11-[4-(2-(dimeylamino) ethoxy) phenyl]-estre-4,9-diene-3,17-dione in 11 ml of pyridine and agitation is carried out for 30 minutes at approximately ±36°C. The reaction medium is poured into sodium bicarbonate, followed by extraction, washing, drying and evaporating under reduced pressure until 1.84 g of crude product is obtained, which is purified by chromatography, eluting with an ethyl acetate/triethylamine mixture 80/20. 616 mg of expected pure product is obtained. (RF AcOEt/TEA 8/2=0.35).

[0254] Stage B: 4-chloro-11beta-[4-[2-(2-dimethylamino) ethoxy] phenyl]-3-hydroxy-estre-1,3,5(10)-triene-17-one (chromatography and saponification)

[0255] The saponification reaction is then the saponification reaction are carried out as in Example 1, Stage C, starting with 700 mg of the product obtained in the preceding stage. 360 mg of expected pure product is obtained. M.p.=254°C. (RF CH₂Cl₂/iPrOH/NH₄OH 93/7/0.7=0.18). NMR (CDCl₃): 0.44 (s): CH₃ in position 18; 2.30 (s): NMe₂; 2.67 (m): CH₂—N; 3.94 (m): CH₂—O; 4.00 (H₁); 6.62-6.91: Ph—O; 6.62-6.81 (d): H₂; H₂.

[0256] The compound of Example 3 was prepared in the same manner.

EXAMPLE 14
[0257] gamma lactone of 4-chloro-3,17beta-dihydroxy-11beta-[4-(2-(1-pyrroldinyl) ethoxy) phenyl]-19-nor-17alpha-pregna-1,3,5(10)-triene-21-carboxylic acid

[0258] 6 ml of tetrahydrofuran/silicopore is added under an inert atmosphere, at ambient temperature to 5.93 ml of n-butylithium at 15% in hexane, then at −50°C, 0.291 g of allyl bis-dimethylamido phosphate in solution in tetrahydrofuran is added and finally at −30°C 0.580 g of the product obtained in Example 2 is added and the reaction medium is agitated for 1 hour 45 minutes at ambient temperature.

[0259] 8 ml of 2N hydrochloric acid and 50 ml of a saturated solution of sodium bicarbonate are added followed by extraction, washing, drying and evaporating under reduced pressure until 0.590 g of crude product is obtained which is purified by chromatography eluting with an ethyl acetate/triethylamine mixture 60/40, then recrystallization from isobutanol. 0.162 g of expected pure product is obtained. M.p.=231°C. RF AcOEt/TEA 60/40=0.20. NMR (CDCl₃): 0.51 (s): CH₃ in position 18; 1.79 (m): CH₂ in beta position of N ring; 2.58 (m): CH₂ in alpha position of N ring; 2.83 (t): CH₂—N of the chain; 3.99 (t): CH₂—OAr; 3.99 (t): H₁; 6.62: H₂; 6.82: H₂; 6.62: ArO; 6.82: ArC.

EXAMPLE 15

[0261] The operation is carried out as in as in Example 14, but starting with 1.179 g of the product of Example 1, 0.388 g of the expected pure product is obtained. (RF CH₂Cl₂/iPrOH/NH₄OH 95/5/0.5=0.20). NMR (CDCl₃): 0.52 (s): CH₃ in position 18; 2.50 (m): cyclic CH₂ N; 2.71 (t): CH₂—N of the chain; 4.00 (t): CH₂—OAr; 4.00 (t masked): H₁; 6.62: H₂; 6.81: H₂; 6.62: ArO; 6.85: ArC.

EXAMPLE 16

[0263] The operation is carried out as in Example 14, but starting with 0.428 g of the product of Example 3, 0.195
g expected pure product is obtained. (Rf AcOEt/TEA/Essence G (50/30/20=0.25)) NMR (CDCl₃): 0.51 (s); CH₃ in position 18; 1.03 (t); N—CH₃—CH₂; 2.60 (q); N—CH₂—CH₂—CH₂; 2.81 (t); CH₂—N of the chain; 3.94 (t); CH₃—O—Ar; 3.98 (t); H₁; 6.59; H₂; 6.79; H₃; 6.59; ArO; 6.85: ArC.

EXAMPLE 17


[0265] Stage A Lactonization

[0266] The operation is carried out as in Example 14, but starting with 1.44 g of the compound of Example 5 Stage E. 2.36 g of crude product is obtained which is used directly in the deprotection reaction of the phenol in position 3.

[0267] Stage B: Deprotection of the phenol in position 3.

[0268] 3.8 ml of a solution of tetrabutyl ammonium fluoride in tetrahydrofuran is added to a solution of 2.36 g of the product obtained in the preceding stage in 24 ml of tetrahydrofuran and agitation is carried out for 50 minutes at ambient temperature. The reaction medium is poured into water followed by extraction, drying and evaporating under reduced pressure until 695 mg of crude product is obtained which is purified by chromatography eluting with a dichloromethane/methanol mixture 95/3, then by recrystallization. 238 mg of expected pure product is obtained. M.p.=243°C. RF CH₃Cl₂/McOH/NH₄OH 93/7/0.7 0.28. NMR (CDCl₃): 0.51 (s); CH₃ in position 18; 2.30 to 2.60; CH₂—N; 3.88; CH₃—O; 3.98 (t); H₁; 6.61; 6.87: Ar—O, Ar—C; 6.61-6.76: H₂, H₃.

EXAMPLE 18


[0270] The operation is carried out as in Example 17, but starting with 1.2 g of the product of Example 6 Stage E. 310 mg of expected pure product is obtained (RF CH₃Cl₂/McOH/NH₄OH 95/5/0.5 0.17). NMR (CDCl₃): 0.51 (s); CH₃ in position 18; 3.83 (t); CH₃—O chain; 3.99 (t); H₁; 6.61-6.85: Ar—O, Ar—C; 6.61-6.79: H₂, H₃.

EXAMPLE 19


[0272] The operation is carried out as in Example 17, but 25 starting with 1.44 g of the product of Example 7 Stage E. 330 mg of expected pure product is obtained (RF AcOEt/TEA 90/10=0.22). NMR (CDCl₃): 0.52 (s); CH₃; 3.83 (t); CH₃—O; 3.99 (t); H₁; 6.60 (m) H₂, 6.67 (d) H₂, 6.85 (d) 2H: Aromatic H₁, H₂.

EXAMPLE 20

[0273] 4-chloro-11beta-[4-[2-(diethylamino) ethoxy] phenyl]-estro-1,3,5 (10)-triene-3,17beta-diol

[0274] 37 mg of sodium borohydride is added under an inert atmosphere to a solution of 241 mg of the compound of Example 3, in 4 ml of methanol, agitation is carried out for 1 hour in an ice bath, then 2 ml of hydrochloric acid is added then the reaction medium is poured into an aqueous solution of sodium bicarbonate, followed by extraction with ethyl acetate, washing, drying and evaporating under reduced pressure until 245 mg of crude product is obtained which is purified by chromatography eluting with a dichloromethane/methanol/ammonium hydroxide mixture 90/10/1. 195 mg of expected pure product is obtained. RF CH₃Cl₂/McOH/NH₄OH 90/10=0.27. NMR (CDCl₃): 0.32 (s); CH₂; 1.03 (t); CH₃CH₂; 2.60 (q); CH₂CH₂; 2.81 (t); CH₂—N; 3.68; H₁; 3.95 (t); CH₃—O; 6.62: ArO; 6.89: ArC; 6.80 (d); H₁; 6.62 (d): H₂.

[0275] In a similar manner to Example 20, the following products of formula (I) are obtained with R"₂=OH and R"₃=H:

<table>
<thead>
<tr>
<th>Starting product</th>
<th>n&quot;</th>
<th>X&quot;</th>
<th>NR corporations</th>
<th>R&quot;s</th>
<th>Ex.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex. 21</td>
<td>2</td>
<td>Br</td>
<td>Piperidino</td>
<td>0.45: AcOEt/TEA 90/10</td>
<td></td>
</tr>
<tr>
<td>Ex. 22</td>
<td>2</td>
<td>Cl</td>
<td>Piperidino</td>
<td>0.13: AcOEt/TEA 95/5</td>
<td></td>
</tr>
<tr>
<td>Ex. 23</td>
<td>2</td>
<td>Cl</td>
<td>Piperidino</td>
<td>0.13: CH₃Cl₂/McOH NH₄OH 93/7/0.5</td>
<td></td>
</tr>
<tr>
<td>Ex. 24</td>
<td>3</td>
<td>Cl</td>
<td>NMe₂</td>
<td>0.25: CH₃Cl₂/McOH NH₄OH 90/10/1</td>
<td></td>
</tr>
</tbody>
</table>

EXAMPLE 25


[0277] 4.7 ml of a 0.43 M solution of potassium acetylide is added under an inert atmosphere to a solution of 250 mg of the product of Example 3 in 3 ml of tetrahydrofuran/ siliporite, agitation is carried out for 1 hour at ambient temperature, then 4 ml of hydrochloric acid is added. The reaction medium is poured into a saturated aqueous solution of sodium bicarbonate followed by extraction, washing, drying and evaporating under reduced pressure until 200 mg of crude product is obtained which is purified by chromatography eluting with a CH₃Cl₂/McOH/NH₄OH mixture 90/10/0.5: 215 mg of expected pure product is obtained. RF CH₃Cl₂/McOH/NH₄OH 90/10/0.5=0.31. NMR (CDCl₃): 0.43 (s); CH₃ in position 18; 1.04 (t); CH₂CH₂; 2.62 (q); CH₂CH₂; 2.64 (s); C—H₂; 2.83 (t); CH₃—N; 3.95 (t); CH₃—O; 4.00 (t); H₁; 6.62: Ph—O; 6.90: Ph—C; 6.82 (d); H₁; 6.62 (d): H₂.

EXAMPLE 26

[0278] (17beta)-4-chloro-4',5'-dihydroxy-11beta-[4-[2-(1-piperidinyl) ethoxy]phenyl]-spiro[estra-1,3,5(10)-triene-17,2'-(3H-furan)]-3-ol

[0279] 0.041 g of 9.5% Pd/C catalyst is added to a solution of 0.411 g of the product of Example 8 in 15 ml of ethanol and 5 ml of tetrahydrofuran and hydrogenation is carried out for 2 hours 30 minutes (vol. of H₂ absorbed=17.5 cm³). After filtration of the catalyst, evaporation is carried out under reduced pressure until 0.42 g of crude product is obtained which is purified by chromatography eluting with an ethyl...
acetate/triethylamine mixture 92/8. 0.33 g of expected pure product is obtained. M.p.=170°C. RF AcOEt/TEA 92/8=0.21.

[0280] In a similar manner to Example 26, the following products of formula (I) are obtained, in which R, and R' form together with the carbon that carries them the saturated

<table>
<thead>
<tr>
<th>Starting product</th>
<th>n'</th>
<th>X</th>
<th>NR'₃R₄</th>
<th>RF s.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex. 27</td>
<td>3</td>
<td>Cl</td>
<td>Piperidino</td>
<td>0.19 AcOEt/TEA 92/8</td>
</tr>
<tr>
<td>Ex. 28</td>
<td>4</td>
<td>Cl</td>
<td>Piperidino</td>
<td>0.22 AcOEt/TEA 95/5</td>
</tr>
</tbody>
</table>

EXAMPLE 29

[0281] 4-chloro-11β-[4-[2-(diethy lamino) ethoxy]-phenyl]-17α-methyl-1,3,5(10)-trien-3,17β-diol

[0282] a) Preparation of “cerium compound”

[0283] 24 ml of anhydrous THF is added to 2.42 g of CeCl₃·7H₂O, dried beforehand under reduced pressure at 140°C for 2 hours, then put under an inert atmosphere, the suspension is agitated for 2 hours, cooled down to -78°C and 4.35 ml of CH₃Li in ether is added and agitation is carried out for 30 minutes at -78°C.

[0284] b) Condensation

[0285] 0.644 g of the compound prepared in Example 3 in solution in 8.5 ml of anhydrous THF is added at -78°C and the reaction medium is maintained at this temperature for one hour. The reaction medium is poured into 25 ml of a saturated solution of NH₄Cl followed by extraction, washing, drying and evaporating under reduced pressure until 0.599 g of crude product is obtained which is purified by chromatography (after having added 0.192 g of crude product obtained during a related trial carried out in an identical manner) eluting with a CH₂Cl₂/CH₃OH/NH₄OH mixture (92/8/0.2), then with an AcOEt/TEA mixture (97/3). 0.402 g of expected pure product is obtained. RF CH₂Cl₂/MeOH/NH₄OH (92/8/0.2)=0.18 M.p.=161-163°C. NMR (CDCl₃): 0.44 (s): CH₃ in position 18; 1.28 (s): CH₃ in position 17; 1.03 (t): CH₃CH₂; 2.61 (q): CH₃CH₂; 2.81 (t): CH₂—N; 3.94 (t): CH₂—O; 3.96: H₁₁; 6.61-6.80: H₁ and H₂; 6.61-6.83: Ph—O.

EXAMPLE 30

[0286] 4-chloro-17α-methyl-11β-[4-[2-(1-piperidiny1) ethoxy]phenyl]-1,3,5(10)-trien-3,17β-diol.

[0287] The operation is carried out as in Example 28, but starting with 2.79 g of the product obtained in Example 1.

[0288] 2.12 g of expected pure product is obtained. RF CH₂Cl₂/CH₃OH/NH₄OH (95/7/0.2) =0.19 M.p.=163°C. NMR (CDCl₃): 0.44 (s): CH₃ in position 18; 1.28 (s): CH₃ in position 17; 2.48 (t): H₁: CH₂N ring; 2.71 (t): CH₂—N chain; 3.99 (t): CH₂—O; 4.00 masked: H₁₁; 6.80 (d): H₁; 6.98 (d): H₂; 6.60-6.88: Ph—O.

[0289] PHARMACOLOGICAL TESTS Effect on the proliferation of mammary cells

[0290] The proliferative activity of the molecules is studied in comparison to that of oestradiol on MCF-7 human mammary cells in culture.

[0291] In order to reveal an agonistic effect of the oestradiol and/or the tested molecules, the cell maintenance culture (rich in growth factors and steroids) is replaced by an impoverished medium, amongst others free of steroids (DMEM supplemented with 5% of steroid-free serum and without phenol red). Cells undergo this severance two days before the start of the test.

[0292] After 7 days culture in the presence of the products to be studied, the cell proliferation is evaluated by determination of the DNA. In each test, the effect of the oestradiol at 10-10M (cell growth in the presence of oestradiol less cell growth in the presence of the solvent) determines the 100% agonist activity. The activity of the molecules is evaluated in comparison to this internal control. The molecules inducing an identical cell growth to that observed with the solvent alone are classified as “inactive”, those inducing a lower cell growth to that observed with the solvent are classified as “inhibitor”.

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>Oestradiol</th>
<th>Example 20</th>
<th>Example 22</th>
<th>Example 23</th>
<th>Example 1</th>
<th>Example 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Agonist</td>
<td>Mixed*</td>
<td>Inactive</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Mixed</td>
</tr>
</tbody>
</table>

[0293] Bone impact study of a product in the ovarectomized female rat at the age of 3 months Compounds A, B, C, D, E are tested in order to determine their effect on the bone mass and on the formation and resorption activity in the model of the ovariectomized rat at the age of 3 months. The animals are treated in a preventive fashion.

[0294] Animals: Species rat Strain Sprague-Dawley Sex female Weight 250 g to 280 g No. of animals/group 8

[0295] Products:

[0296] 1 - Product to be tested: Products of Examples 20, 22, 23, 30 and 1.

[0297] * vehicle(s): corn oil, 0.5% methylcellulose

[0298] * dose(s): one dose per tested product (0.3 mg/kg/d)

[0299] * number of administrations: once/day; 5 days/week for 4 weeks

[0300] * administration route: oral route for the products

[0301] * volumes: 5 ml/kg (p.o.)

[0302] * period between the last injection and sacrifice: 24 hours

[0303] * number of administrations: 20.
[0304] Reference product: 17β oestradiol is administered by subcutaneous route at a dose of 0.1 mg/kg/d in solution in a 30% mixture of cort oil-benzyl alcohol (99:1, v/v) under a volume of 0.2 ml/kg.

[0305] Experimental protocol

[0306] Animals

[0307] The study is carried out with female rats ovariectomized at the age of 3 months. The animals are kept in an air conditioned room (temperature 20° C ± 2° C) and grouped by 4 into boxes. The animals receive, ad libitum, demineralized water and compressed foods (pelleis: AO4CR-10 UAR).

[0308] Surgery

[0309] The 3 month old female rats weighing approximately 250 g are ovariectomized under anaesthesia with Imalgene 1000, at a dose of 100 mg/kg by intraperitoneal route (i.p.) and under a volume of 1 ml/kg. They also receive Nembutal (3 mg/kg i.p. under a volume of 0.3 ml/kg).

[0310] After lateral incision, cutaneous and muscular planes are sectioned. The evisceration of each ovary is carried out after ligature of the oviduct.

[0311] The "SHAM" control rats are anaesthetized under the same conditions. After incision of the cutaneous and muscular planes, each ovary is exposed then replaced in situ.

[0312] Treatment

[0313] The effects of the products are determined in a preventive treatment. They are administered immediately after the ovariectomy. Animals distributed into groups of 8.

[0314] Group 1: "SHAM" control rats receiving the vehicle or vehicles

[0315] Group 2: "OVX" control rats receiving the vehicle or vehicles.

[0316] Groups X: "OVX" rats receiving respectively defined doses of the product or products to be tested.

[0317] Blood samples

[0318] At the end of 4 weeks (duration of the study) the animals are decapitated by guillotine. The sera collected after centrifugation are preserved at -20° C.

[0319] A lipicid balance will be established from the serum determinations of total cholesterol, of triglycerides and of phospholipids on a 500 µl aliquot of serum. The lowering of the serum cholesterol level is expressed in % relative to the level shown by the ovariectomized animals receiving only the solvent.

[0320] Organ samples

[0321] After sacrificing the animals, the following organs are removed:

[0322] tractus genitais

[0323] The uteri are removed. The latter are weighed. The increase in weight is expressed in % of the weight of the uterus of ovariectomized animals receiving only the solvent.

[0324] at the bone level:

[0325] The bone mass (BMD or Bone mineral density) is measured by biphotonic dual energy X-ray absorptiometry (DEXA). The measurements are carried out on bone excized and cleaned of all soft tissue. The BMD (Bone mineral density) is measured on the whole bone as well as on the metaphyscal part at the level of the proximal extremity for the left tibia. This zone is defined as being the region which is richest in trabecular bone; and consequently, is the most sensitive to variations in bone volume and bone mineral density.

[0326] The results are expressed in % according to the formula:

Tested product BMD - OVX BMD x 100/ SHAM BMD - OVX BMD

[0327] | Dose Route | Tibia Bone BMD % | Uterus Weight % | Cholesterol % |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OVX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHAM</td>
<td></td>
<td></td>
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<tr>
<td>Oestriol</td>
<td>0.1 s.c.</td>
<td>315</td>
<td>35</td>
</tr>
<tr>
<td>Ex. 20</td>
<td>0.2 po</td>
<td>69</td>
<td>60</td>
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<td>55</td>
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<td>55</td>
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<td>68</td>
</tr>
<tr>
<td>Ex. 30</td>
<td>1.0 po</td>
<td>71</td>
<td>55</td>
</tr>
</tbody>
</table>

1. Compounds of general formula (I):

\[
\begin{align*}
\text{R}_1 & \text{ represents a hydrogen atom, a (CH}_2\text{)}_n- \text{Ar, (CO)—Ar, (CH}_2\text{)}_n- \text{Alk or (CO)—Alk radical,} \\
\text{R}_2 & \text{ represents a radical derived from a linear or branched,} \\
& \text{saturated or unsaturated hydrocarbon containing 1 to 6 carbon atoms} \\
\text{D} & \text{represents the remainder of a pentagonal or hexagonal} \\
& \text{ring optionally substituted and optionally carrying an} \\
& \text{unsaturation,} \\
\text{X} & \text{represents a halogen atom,} \\
\text{Y} & \text{is chosen from O, S, SO, SO}_2 \text{ and NH,}
\end{align*}
\]
n is an integer varying from 2 to 8,
either R₁ and R₅, identical or different, represent a hydrogen atom, a (CH₂)ₙ—Ar, (CH₂)ₙ—Het or (CH₂)ₙ—Alk group,
or R₃ and R₆ form together with the atom of nitrogen to which they are linked an aromatic or non-aromatic, saturated or unsaturated mono- or polycyclic heterocycle with 3 to 15 members optionally containing 1 to 3 additional heteroatoms chosen from oxygen, sulphur and nitrogen, non-substituted or substituted,
Ar representing a carbocyclic aryl group containing 6 to 18 carbon atoms, Het representing a radical derived from a saturated or unsaturated aromatic or non-aromatic heterocycle containing 1 to 9 carbon atoms and 1 to 5 heteroatoms chosen from oxygen, nitrogen or sulphur atoms, Alk representing a radical derived from a saturated or unsaturated, linear, branched or cyclic, non-aromatic hydrocarbon and containing 1 to 12 carbon atoms, the Ar, Het or Alk radicals being able to be substituted or non-substituted, m represents 0, 1, 2 or 3, as well as their addition salts with bases or acids.
2. Compounds of general formula (I) as defined in claim 1, in which D represents the remainder of a pentagonal ring of formula:

![Diagram of molecular structure](image)
in which R₅ retains the same meaning as in claim 1,
either R₅ represents an OH, O—(CH₂)ₙ—Alk, O—(CO)—Alk, O—(CH₂)ₙ—Ar, O—(CO)—Ar, O—(CH₂)ₙ—Het, O—(CO)—Het and R₆ represents a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms substituted or non substituted, m, Alk, Ar and Het being as defined in claim 1,
or R₃ and R₆ form together with the carbon atom which carries them one of the following rings:

![Rings](image)
in which Z represents a —(CH₂)ₙ — or —CH=CH—(CH₂)ₙ group, l being an integer comprised between 1 and 4 and l' being an integer equal to 1 or 2,
or R₃ and R₆ form together an oxo group, as well as their addition salts with acids or bases.

3. Compounds of general formula (I) as defined in claim 1, corresponding to general formula (I'):

![Molecular structure](image)
in which:
X' represents a chlorine or bromine atom
n is comprised between 2 and 5,
either R₅ and R₅', identical or different, represent an alkyl radical containing 1 to 6 carbon atoms or R₅ and R₅', form together with the nitrogen atom to which they are linked, a saturated mono- or polycyclic remainder with 3 to 15 members optionally containing an additional heteroatom chosen from oxygen, sulphur and nitrogen, R₅' and R₅ have the same meaning as R₅ and R₅', according to claim 2 as well as their addition salts with acids and bases.
4. Compounds of general formula (I) as defined in claim 3, in which:
either R₅ represents an OH radical and R₅' represents a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms, substituted or non-substituted,
or R₃ and R₆ form together with the carbon atom that carries them one of the following rings:

![Rings](image)
or R₅ and R₅' form together an oxo group, as well as their addition salts with acids or bases.
5. Compounds of general formula (I) as defined in claim 3 or 4, in which:
X' represents a chlorine atom
n' is equal to 2,
either R₅ and R₅', identical or different, represent an alkyl radical containing 1 to 6 carbon atoms
or R₅ and R₅' form together with the nitrogen atom the following saturated heterocycles:
and either R' represents an OH radical and R' represents a hydrogen atom, an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms, substituted or non substituted,

or R' and R' form together with the carbon atom which carries them one of the following rings:

or R' and R' form together an oxo group, as well as their addition salts with acids or bases.

6. Compounds of formula (I) or (I)' as defined in any one of the claims 1 to 5, the names of which follow:

4-chloro-3-hydroxy-11β-[4-[2-(diethylamino)ethoxy]phenyl]-ester-1,3,5(10)-triene-17-one,

4-chloro-3-hydroxy-11β-[4-[2-(dimethylamino)ethoxy]phenyl]-ester-1,3,5(10)-triene-17-one,

4-chloro-3-hydroxy-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-ester-1,3,5(10)-triene-17-one,

4-chloro-3-hydroxy-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-ester-1,3,5(10)-triene-17-one,

4-chloro-3-hydroxy-11β-[4-[2-(2-pyrrolidinyl)ethoxy]phenyl]-ester-1,3,5(10)-triene-17-one,

4-chloro-3-hydroxy-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-ester-1,3,5(10)-triene-17-one,

4-chloro-3-hydroxy-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-ester-1,3,5(10)-triene-17-one,

4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-ester-1,3,5(10)-triene-20-yne-3,17beta-diol,

4-chloro-11β-[4-[3-(1-piperidinyl)propoxy]phenyl]-ester-1,3,5(10)-triene-3,17beta-diol,

4-chloro-11β-[4-[4-(1-piperidinyl)butoxy]phenyl]-ester-1,3,5(10)-triene-3,17beta-diol,

4-chloro-11β-[4-[5-(1-piperidinyl)pentoxyl]phenyl]-ester-1,3,5(10)-triene-3,17beta-diol,

gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-ester-1,3,5(10)-triene-21-carboxylic acid,

gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-ester-1,3,5(10)-triene-21-carboxylic acid,

gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-ester-1,3,5(10)-triene-21-carboxylic acid,

gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[3-(1-piperidinyl)propoxy]phenyl]-ester-1,3,5(10)-triene-21-carboxylic acid,

gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[4-(1-piperidinyl)butoxy]phenyl]-ester-1,3,5(10)-triene-21-carboxylic acid,

gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[5-(1-piperidinyl)pentoxyl]phenyl]-ester-1,3,5(10)-triene-21-carboxylic acid,

gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-ester-1,3,5(10)-triene-21-carboxylic acid,

(17beta)-4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-spiro[ester-1,3,5(10)-triene-17,2(5'H)furan]-3-ol,

(17beta)-4-chloro-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-spiro[ester-1,3,5(10)-triene-17,2(5'H)furan]-3-ol,

(17beta)-4-chloro-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-spiro[ester-1,3,5(10)-triene-17,2(5'H)furan]-3-ol,

(17beta)-4-chloro-4',5'-dihydroxy-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-spiro[ester-1,3,5(10)-triene-17,2(3'H)furan]-3-ol,

(17beta)-4-chloro-11β-[4-[3-(1-piperidinyl)propoxy]phenyl]-spiro[ester-1,3,5(10)-triene-17,2(5'H)furan]-3-ol,

(17beta)-4-chloro-4',5'-dihydroxy-11β-[4-[3-(1-piperidinyl)propoxy]phenyl]-spiro[ester-1,3,5(10)-triene-17,2(3'H)furan]-3-ol,

(17beta)-4-chloro-11β-[4-[4-(1-piperidinyl)butoxy]phenyl]-spiro[ester-1,3,5(10)-triene-17,2(5'H)furan]-3-ol,

(17beta)-4-chloro-4',5'-dihydroxy-11β-[4-[4-(1-piperidinyl)butoxy]phenyl]-spiro[ester-1,3,5(10)-triene-17,2(3'H)furan]-3-ol,

4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-17alpha-methyl-ester-1,3,5(10)-triene-3,17beta-diol,

4-chloro-17alpha-methyl-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-ester-1,3,5(10)-triene-3,17beta-diol,
7. Compound of formula (I) or (II) as defined in any one of claims 1 to 5, the name of which follows:

4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-1,3,5 (10)-triene-3,17beta-diol, as well as its addition salts with acids.

8. Preparation process for the compounds of general formula (I) as defined in claim 1 or 2, characterized in that a compound of general formula (II):

(II)

\[
\begin{align*}
    &R_1 &R_2 &D \\
    &\text{O} &\text{D} &\text{R}_2 \\
\end{align*}
\]

in which D and \( R_2 \) are as defined in claim 1, \( R_2 \) represents one of the following groups:

- \( \text{YH} \)
- \( \text{YP} \)
- \( \text{Hal} \)
- \( \text{Hal} \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- \( \text{Hal} \) on the compounds identical or different representing a halogen in order to obtain compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,

which compounds of formula (II), (III) or (IV) are subjected, if desired and if necessary, in an appropriate order, to one or more of the following reactions:

- protection of the compounds, in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- deprotection of the compounds, in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,
- the action of a compound of formula \( \text{Hal}_n—(\text{CH}_2)_m—\text{Hal}_n \) on the compounds in which \( R_2 \) is a \( \text{Ph—Y—} \) group,

is subjected to the action of a halogenation reagent in order to obtain the compound of formula (III):

(III)

\[
\begin{align*}
    &R_1 &R_2 &D \\
    &\text{O} &\text{D} &\text{R}_2 \\
\end{align*}
\]

which is subjected to the action of an aromatization reagent of ring A, then to the action of a base in order to obtain the compound of formula (IV) corresponding to certain compounds of general formula (I):

(IV)

\[
\begin{align*}
    &R_1 &R_2 &D \\
    &\text{O} &\text{D} &\text{R}_2 \\
\end{align*}
\]
the action of a reducing agent of the double bond, when
D represents the remainder of a pentagonal ring as
defined in claim 2, and R₆ is an alkenyl or alkynyl radical containing 2 to 6 carbon atoms,
halogenation in position 4, then aromatization of ring A,
of the compound of general formula (II),
aromatization of ring A of the compound of formula (III),
salification.

9. Preparation process according to claim 8, for com-
pounds of general formula (I') as defined in claim 3, char-
acterized in that a compound of general formula (I '):

$$\text{(I')}$$

in which $R'_5$ and $R'_6$ are as defined in claim 3, $R'_7$ represents:

$$\text{O}$$

is subjected to the action of a halogenation reagent in
order to obtain the compound of formula (III'):

$$\text{(III')}$$

which is subjected to the action of an aromatization
reagent of ring A, then to the action of a base in order to
obtain the compound of formula (IV) corresponding to
certain compounds of general formula (I):

$$\text{(IV)}$$

which compounds of formula (II'), (III') or (IV) are sub-
ject to, if desired and if necessary, in an appropriate order, to one or more of the following reactions:

- protection of the compounds in which $R'_7$ is a $\text{Ph-OH}$
group,
- deprotection of the compounds in which $R'_7$ is a $\text{Ph-OP}$
group,
- the action of a compound of formula $\text{Hal}_1-(\text{CH}_2)_n-$
  $\text{Hal}_2$ on the compounds in which $R'_7$ is a $\text{Ph-OH}$
group, Hal₁ or Hal₂, identical or different, representing
  a halogen in order to obtain the compounds in which $R'_7$
is a $\text{Ph-O-(CH}_2)_n-$Hal₂ group,
- the action of a compound of formula $R'_x-NH-R'_y$ on
  the compounds in which $R'_7$ is a $\text{Ph-O-(CH}_2)_n-$
  Hal₂ group, in order to obtain the compounds in which
  $R'_7$ is a $\text{Ph-O-(CH}_2)_n-NR'_3 R'_4$ group,
- the action of a halide salt (M-Hal₂) on compounds in
  which $R'_7$ is a $\text{Ph-O-(CH}_2)_n-$Hal₂ group in order to
  obtain the compounds in which $R'_7$ is a $\text{Ph-O-(CH}_2)_n-$Hal₃ group,
- protection of the OH group in position 3 or 17,
- deprotection of the OH group in position 3 or 17,
- acylation of the OH group in position 17,
- acylation of the OH group in position 17,
- the action of a reducing agent when $R'_5$ and $R'_6$ together
  form an oxo group,
- the action of an organometallic on the compounds of
  formula (IV) with $R'_5$ and $R'_6$ together forming an oxo
  group,
- the action of a lactonization agent on the compounds of
  formula (IV) with $R'_5$ and $R'_6$ together forming an oxo
  group,
- the action of a reducing agent of the double bond, when
  $R'_5$ and $R'_6$ form together with the carbon which carries
  them, an $O-(\text{CH}_2)_n-\text{CH=CH-}$ group,
- the action of a reducing agent of the double bond, when
  $R'_6$ is an alkenyl or alkynyl radical containing 2 to 6
  carbon atoms,
- halogenation in position 4, then aromatization of ring A,
  of the compound of formula (II),
- aromatization of the compound of formula (III),
salification.
10. As medicaments the compounds of formula (I) as defined in claim 1, as well as their addition salts with pharmaceutically acceptable acids.

11. As medicaments the compounds of formula (I) or (I') as defined in any one of claims 2 to 5, as well as their addition salts with pharmaceutically acceptable acids.

12. As medicaments the compounds as defined in claim 6 or 7, as well as their addition salts with pharmaceutically acceptable acids.

13. The pharmaceutical compositions containing one or more of the medicaments as defined in any one of claims 10, 11 or 12.

14. As new intermediate products, the compounds of general formula (III), (III'), (IV) or (IV') as defined in claim 8 or 9.