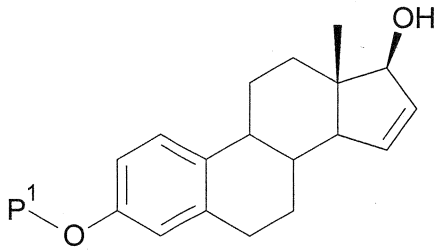
the preparation of 3-Protected-oxy-estra-1,3,5(10),15-tetraene-17-ol which overcome at least one the disadvantages of the prior art.

Summary of the invention

The present inventors have now found that this object can be obtained by using a process as defined in the appended claims.

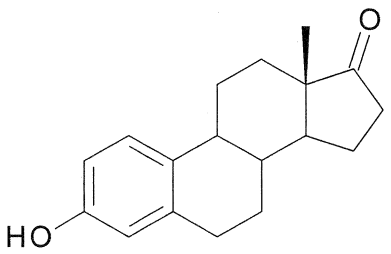
According to a first aspect of the present invention, a process for the preparation of a compound of formula (I) (3-P^1-oxy-estra-1,3,5(10),15-tetraene-17-ol) is provided:



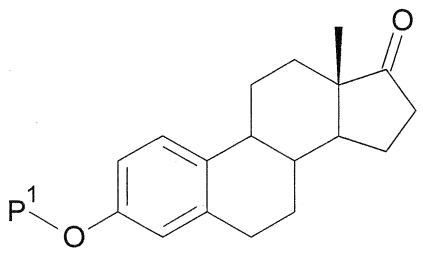
(I)

said process comprises the steps of

a) reacting a compound of formula (II) with a silylating or an acylating agent to produce compound of formula (III), wherein P^1 is a protecting group selected from R^2-Si-R^3R^4 or R^1CO-, R^1 is a group selected from C_{1-6}alkyl or C_{3-6}cycloalkyl, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl; R^2, R^3 and R^4 are each independently a group selected from C_{1-6}alkyl or phenyl, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl;



(II)

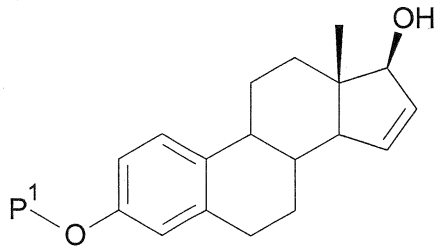


(III)

b) halogenation or sulfinylation of the compound of formula (III) to produce a compound of formula (IV) ; wherein X is halo, or -O-SO-R^5, and R^5 is a group selected from C_{6-10}aryl or

C_{1-4}alkyl; more preferably R^1 is methyl, ethyl, propyl, isopropyl, cyclopentyl, or cyclohexyl, yet more preferably R^1 is methyl, or ethyl;

R^2, R^3 and R^4 are each independently a group selected from C_{1-6}alkyl or phenyl, said C_{1-6}alkyl or phenyl, being optionally substituted with 1, 2 or 3 substituents independently selected from fluoro or C_{1-6}alkyl; preferably R^2, R^3 and R^4 are each independently selected from the group comprising methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, and phenyl, each group being optionally substituted with 1, 2 or 3 substituents each independently selected from fluoro or C_{1-4}alkyl; preferably R^2, R^3 and R^4 are each independently selected from the group comprising methyl, ethyl, propyl, isopropyl, or *tert*-butyl, and phenyl, each group being optionally substituted with 1, 2 or 3 substituents each independently selected from fluoro or C_{1-2}alkyl,

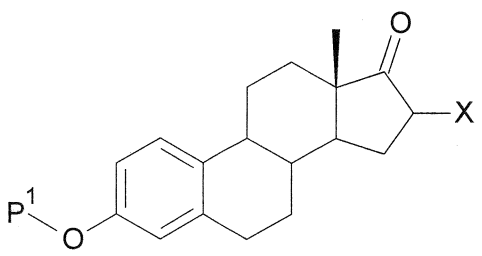


(I)

said process comprising the steps of :

a) protecting the hydroxyl of estrone of formula (II) to produce compound of formula (III), wherein P^1 is as defined above,

b) halogenation or sulfinylation of the compound of formula (III) to produce a compound of formula (IV) ; wherein X is halo, or -O-SO-R^5, and R^5 is a group selected from C_{6-10}aryl or heteroaryl, each group being optionally substituted by one or more substituents independently selected from chloro or C_{1-4}alkyl;



(IV)

lutidine, collidine, triethylamine, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction can be performed at room temperature or under reflux. The reaction can be performed in the presence of a suitable solvent such as dichloromethane, toluene, or dimethylformamide or a mixture thereof.

In another embodiment, estrone of formula (II) is reacted with an acylating agent. In an embodiment, said acylating agent can be selected from the group comprising C_{2-6}alkenylC_{1-6}alkanoate, C_{2-6}alkenylC_{3-6}cycloalkanoate, acyl chloride, and anhydrides. Preferably, the acylating agent is selected from the group comprising C_{2-6}alkenylpropanoate, C_{2-6}alkenylbutanoate, C_{2-6}alkenylpentanoate, C_{2-6}alkenylhexanoate, C_{2-6}alkenylcyclopropanoate, C_{2-6}alkenylcyclobutanoate, C_{2-6}alkenylcyclopentanoate, and C_{2-6}alkenylcyclohexanoate, acyl chloride and anhydrides. More preferably, the acylating agent is selected from the group comprising isopropenyl acetate, isopropenyl propionate, isopropenyl butyrate, isopropenyl isobutyrate, vinyl acetate, vinyl propionate, prop-2-enyl cyclohexanecarboxylate, ethenyl cyclopentanecarboxylate, vinyl cyclohexanoate, acetyl chloride, propionylchloride, butyrylchloride, acetic anhydride and the like. More preferably, the acylating agent is selected from the group comprising isopropenyl acetate, isopropenyl propionate, isopropenyl butyrate, isopropenyl isobutyrate, vinyl acetate, vinyl propionate, acetyl chloride, propionylchloride, butyrylchloride, acetic anhydride and the like.

The acylation when performed with C_{2-6}alkenylC_{1-6}alkanoate or C_{2-6}alkenylC_{3-6}cycloalkanoate, can be performed in the presence of an acid, such as in the presence of sulfuric acid, or in the presence of a C_{6-10}arylsulfonic acid, optionally substituted by one or more chloro substituents. Non-limiting examples of a suitable acid include para-toluene sulfonic acid, and sulfuric acid.

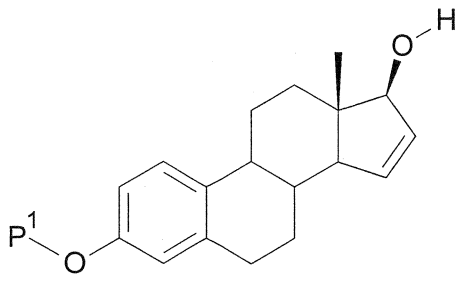
The acylation when performed with an acyl chloride or an anhydride, can be performed in the presence of an organic base, such as imidazole, triethylamine and the like.

Step (b) of the process comprises halogenation or sulfinylation of the compound of formula (III) to produce a compound of formula (IV) ; wherein X is halo, or -O-SO-R^5, and R^5 is a group selected from C_{6-10}aryl or heteroaryl, each group being optionally substituted by one or more substituents independently selected from chloro or C_{1-4}alkyl; preferably R^5 is phenyl or pyridinyl.

In an embodiment, step (b) is a halogenation and the halogenation is performed by reacting the compound of formula (III) with a halogenating reagent.

CLAIMS

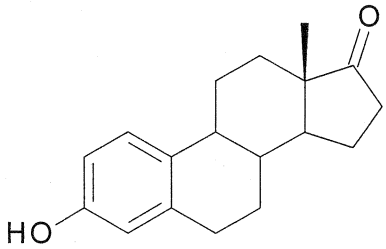
1. A process for the preparation of a compound of formula (I)



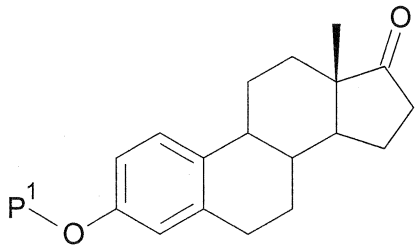
(I)

comprising the steps of

a) reacting a compound of formula (II) with a silylating or an acylating agent to produce compound of formula (III), wherein P^1 is a protecting group selected from R^2-Si-R^3R^4 or R^1CO-, R^1 is a group selected from C_{1-6}alkyl or C_{3-6}cycloalkyl, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl; R^2, R^3 and R^4 are each independently a group selected from C_{1-6}alkyl or phenyl, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl;



(II)



(III)

b) halogenation or sulfinylation of the compound of formula (III) to produce a compound of formula (IV) ; wherein X is halo, or -O-SO-R^5, and R^5 is a group selected from C_{6-10}aryl or heteroaryl, each group being optionally substituted by one or more substituents independently selected from chloro or C_{1-4}alkyl;

6. The process according to claim 1 or 5 wherein step (b) is a bromination and the brominating reagent is selected from the group comprising copper(II) bromide, bromine, and pyridine bromine perbromine.

7. The process according to any of claims 1 to 4, wherein the desulfinylation step is carried out with heat, optionally in the presence of cupric sulfate.

8. The process according to any of claims 1, 5-6, wherein the dehalogenation step is performed in the presence of a base.

9. The process according to claim 8, wherein the base is selected from the group comprising imidazole, collidine, 2,6-lutidine, triethylamine, or 1,8-diazabicyclo[5.4.0]undec-7-ene.

10. The process according to any of claims 1 to 9, wherein step (c) is performed using a reducing agent selected from the group of metal hydride compounds.

11. The process according to any of claims 1 to 10, wherein step (c) is performed using a reducing agent selected from the group comprising $NaBH_4/CeCl_3$, $LiAlH_4$, $NaBH_4$, $NaBH(OAc)_3$, and $ZnBH_4$.

12. Process according to any of claims 1 to 11, wherein the silylating agent is selected from the group comprising C_{1-6}alkylsilylchloride, C_{1-6}alkylsilyltriflate, phenylsilylchloride, phenylsilyltriflate, C_{1-6}alkylphenylsilylchloride, C_{1-6}alkylphenylsilyltriflate, each group being optionally substituted by one or more substituents independently selected from fluoro or C_{1-4}alkyl.

13. Process according to any of claims 1 to 11, wherein the acylating agent is selected from the group comprising C_{2-6}alkenylC_{1-6}alkanoates, C_{2-6}alkenylC_{3-6}cycloalkanoate, acyl chlorides and anhydrides.

14. Process for the preparation of estetrol, said process comprising preparing a compound of formula (I) by a process according to any of claims 1 to 13 and further reacting compound of formula (I) to produce estetrol.

15. ~~Estetrol directly obtained by the process of claim 14 for use in a method selected from a method of hormone replacement therapy, a method of treating vaginal dryness, a method of contraception, a method of enhancing libido, of method of treating skin, a method of promoting wound healing, and a method of treating or preventing a disorder selected from the group consisting of autoimmune diseases, breast tumors and colorectal tumors.~~