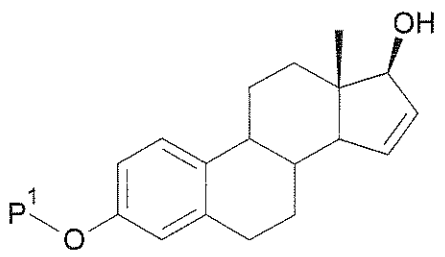
the preparation of 3-Protected-oxy-estra-1,3,5(10),15-tetraene-17-ol which overcome at least one the disadvantages of the prior art.

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.

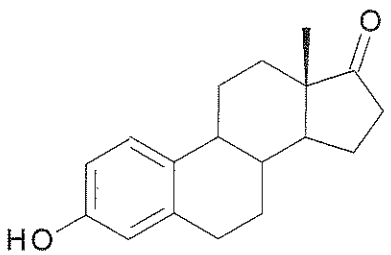
According to a first aspect of the present ~~invention~~disclosure, a process for the preparation of a compound of formula (I) (3-P^1-oxy-estra-1,3,5(10),15-tetraene-17-ol) is provided:



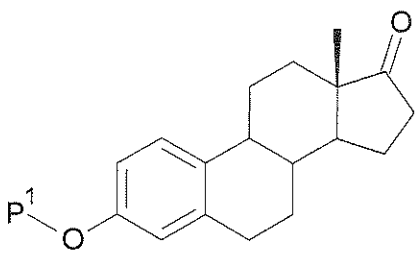
(I)

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;



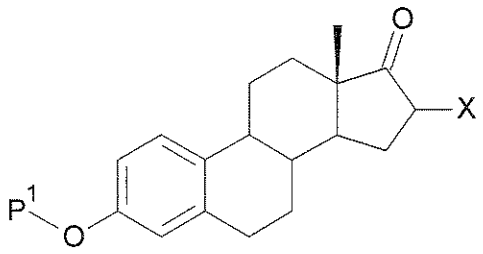
(II)



(III)

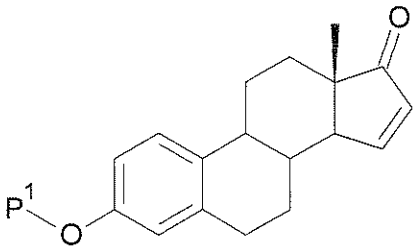
b) halogenation or sulfinylation of the compound of formula (III) to produce a compound of formula (IV) ; wherein X is halo, or -SO-R^5, and R^5 is a group selected from C_{6-10}aryl or

heteroaryl, each group being optionally substituted by one or more substituents independently selected from chloro or C_{1-4}alkyl;



(IV)

c) dehalogenation or desulfinylation of the compound of formula (IV) to produce compound of formula (V); and



(V)

d) reacting the compound of formula (V) with a reducing agent to produce compound of formula (I).

The ~~invention~~present disclosure provides an improved process for producing 3-P^1-oxy-estra-1,3,5(10),15-tetraene-17-ol of formula (I) in significantly higher yield and /or at lower cost than possible by the previous known syntheses.

According to a second aspect, the present ~~invention~~disclosure also encompasses a process for the preparation of estetrol, said process comprising preparing a compound of formula (I) by a process according to the first aspect of the ~~invention~~present disclosure and further reacting the compound of formula (I) to produce estetrol.

~~According to a third aspect, t~~The present ~~invention~~disclosure also encompasses estetrol directly obtained by the process according to the second aspect of the ~~invention~~present disclosure, 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.

The above and other characteristics, features and advantages of the present ~~invention~~disclosure will become apparent from the following detailed description, which illustrate, by way of example, the principles of the invention.

Detailed description of the invention

It is to be understood that the terminology used herein is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

As used herein, the singular forms "a", "an", and "the" include both singular and plural referents unless the context clearly dictates otherwise.

The terms "comprising", "comprises" and "comprised of" as used herein are synonymous with "including", "includes" or "containing", "contains", and are inclusive or open-ended and do not exclude additional, non-recited members, elements or method steps. It will be appreciated that the terms "comprising", "comprises" and "comprised of" as used herein comprise the terms "consisting of", "consists" and "consists of".

The recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within the respective ranges, as well as the recited endpoints.

All references cited in the present specification are hereby incorporated by reference in their entirety. In particular, the teachings of all references herein specifically referred to are incorporated by reference.

Unless otherwise defined, all terms used in disclosing the invention, including technical and scientific terms, have the meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. By means of further guidance, term definitions are included to better appreciate the teaching of the present invention.

In the following passages, different aspects of the invention are defined in more detail. Each aspect so defined may be combined with any other aspect or aspects unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Reference throughout this specification to “one embodiment” or “an embodiment” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus,

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.~~