Beside the poor selectivity for osmium–catalyzed dihydroxylation of these 17β-acetyloxy derivatives, exhaustive purifications are needed.

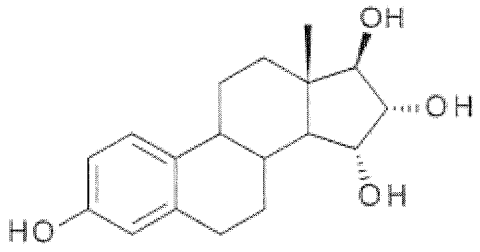
There remain a need for an improved synthesis of estra-1,3,5 (10),15α,16α,17β-tetrol (estetrol).

It is therefore an object of the present invention to provide a process for the preparation of estra-1,3,5(10),-triene 15α,16α,17β-tetrol 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.

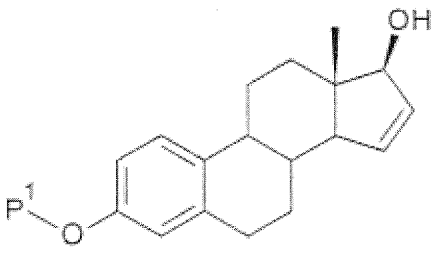
According to ~~the present invention~~a first aspect, there is provided a process for the preparation of a compound of formula (I) (estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol) ~~is provided:~~, hydrates or solvates thereof;



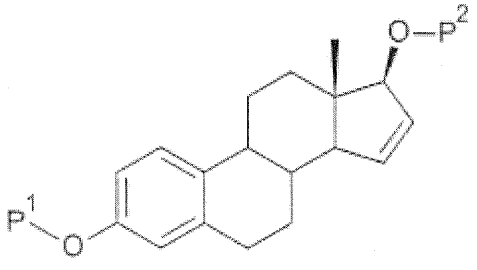
(I)

said process ~~comprises~~ comprising the steps of :

a) reacting a compound of formula (II), with an acylating or a silylating agent to produce a compound of formula (III),



(II)

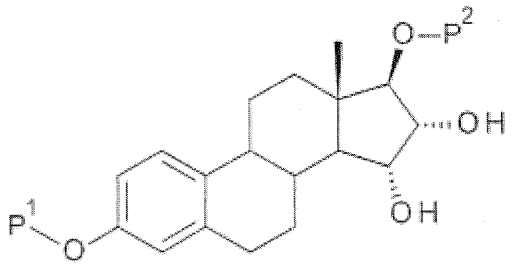


(III)

wherein P^1 is a protecting group selected from R^1CO-, or $R^2Si(R^3)(R^4)$-, P^2 is a protecting group selected from $(R^6R^5R^7)C$-CO-, or $(R^2)Si(R^3)(R^4)$-, wherein 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; R^5 is 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; R^6 and R^7 are each independently hydrogen or 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;

b) reacting the compound of formula (III) in the presence of at least one oxidizing agent selected from permanganate salt, osmium oxide, hydrogen peroxide, or iodine and silver acetate to produce compound of formula (IV); and



(IV)

c) deprotecting the compound of formula (IV) to produce compound of formula (I).

The ~~invention~~ present disclosure provides an improved process for producing a compound of formula (I) in significantly higher yield and /or at lower cost than possible by the previous known syntheses. In particular, the present process allows the preparation of estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol as the major product with little or no estra-1,3,5(10)-triene-3,15β,16β,17β-tetrol isomer.

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

Detailed description of the invention

It is also 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, appearances of the phrases “in one embodiment” or “in an embodiment” in various places throughout this specification are not necessarily all referring to the same embodiment, but may. Furthermore, the particular features, structures or characteristics may be combined