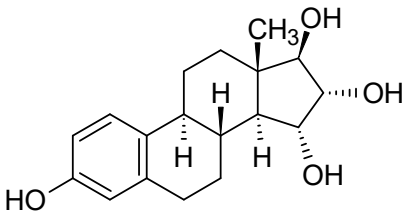
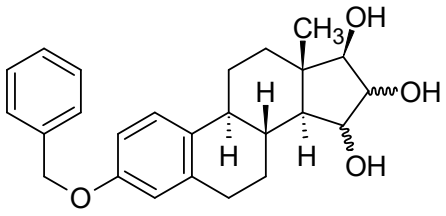
Claims

1. ~~Process~~ A process for the preparation of estetrol of formula (I),



I

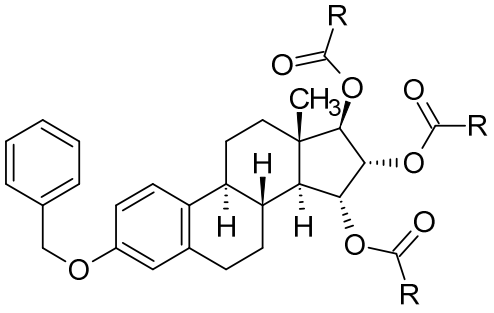
starting from the compound of formula (II)



II

characterized in that

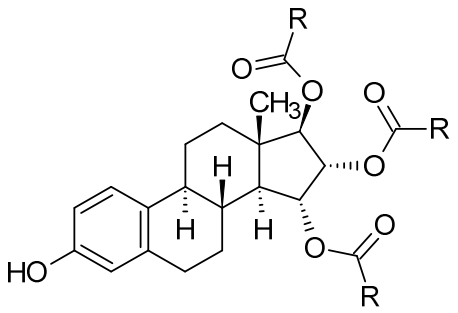
(a) a compound of formula (II) is acylated in a suitable solvent using a suitable reactant to give a compound of general formula (III)



III

wherein R = methyl group or hydrogen

(b) removal of the benzyl protecting group in position 3 by transfer or catalytic hydrogenation to give a compound of general formula (IV)



IV

wherein R = methyl group or hydrogen

(c) deprotection in an alkaline medium with an alkali metal carbonate, alkali metal hydrogen carbonate or alkali metal hydroxides in a suitable solvent.

2. The process according to claim 1, wherein the solvent used in step (a) is selected from the group consisting of aliphatic and aromatic hydrocarbons, halogenated hydrocarbons, esters, and ethers.

3. The process according to any one of claims 1 to 2, wherein the reactant used in step (a) is acetic anhydride, acetyl chloride or bromide.

4. The process according to any one of claims 1 to 3, wherein the reactant used in step (a) is acetic acid-formic acid mixed anhydride.

5. The process according to any one of claims 1 to 4, wherein step (a) is carried out in the presence of a tertiary amine base.

6. The process according to any one of claims 1 to 5, wherein the step (a) further comprises crystallizing the resulting compound of general formula (III) from C_{1-3}alcohols.

7. The process according to any one of claims 1 to 5, wherein the step (a) is carried out without the purification and/or isolation of the compounds of formula (II).

8. The process according to any one of claims 1 to 7, wherein the step (b) is carried out by catalytic hydrogenation, with hydrogen gas, wherein the catalyst is selected from the group consisting of palladium or palladium on a support.

9. The process according to claims 8, wherein the solvent used for the catalytic hydrogenation is selected from the group consisting of alcohols, esters and ketones.

10. The process according to any one of claims 1 to 7, wherein the step (b) is carried out by transfer hydrogenation using a cyclohexene reagent.

11. The process according to claim 10, wherein the solvent used for the transfer hydrogenation is an alcohol.

12. The process according to any one of claims 1 to 11, wherein the step (b) further comprises crystallizing the resulting compound of general formula (IV) from esters, hydrocarbons, alcohols, or mixtures thereof.

13. The process according to any one of claims 1 to 12, wherein the solvent used in the step (c) is selected from the group consisting of water, an alcoholic solvent, or a mixture thereof.

14. The process according to any one of claims 1 to 13, wherein the step (c) is carried out in the presence of an alkali metal carbonate or an alkali metal hydrogen carbonate.

15. The process according to any one of claims 1 to 13, wherein the step (c) is carried out in the presence of an alkali metal alcoholate or an alkali metal hydroxide.

16. The process according to any one of claims 1 to 15, wherein R is methyl group.

17. The process according to any one of claims 1 to 15, wherein R is hydrogen.

~~18. Use of a product of formula (I) obtained by the process according to any one of claims 1 to 17 for the manufacture of a medicament.~~

~~19. Use of a product of formula (I) obtained by the process according to any one of claims 1 to 17 for the manufacture of a medicament for use in hormone replacement therapy, treating vaginal dryness, treating perimenopausal symptoms, contraception, enhancing libido, treating skin and promoting wound healing.~~

~~20. The product according to claim 19 for use in contraception.~~

~~21. The product according to claim 20 for use in contraception in combination with drospirenon.~~

~~22. Use of a product of formula (I) obtained by the process according to any one of claims 1 to 17 for the manufacture of a medicament for use in treating or preventing a disease selected from the group consisting of an autoimmun disorder, breast tumors, prostate cancer and colorectal tumors, or for use in neuroprotection.~~

~~23~~18. A compound of general formula (III), wherein the compound is selected from the group consisting of (15α,16α,17β)-3-(benzyloxy)estra-1,3,5(10)-triene-15,16,17-triyl triacetate and (15α,16α,17β)-3-(benzyloxy)estra-1,3,5(10)-triene-15,16,17-triyl triformiate.

~~24~~19. A compound of general formula (IV), wherein the compound is (15α,16α,17β)-3-hydroxyestra-1,3,5(10)-triene-15,16,17-triyl triformiate.