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(54) **Title**: PROCESS FOR THE PREPARATION OF ESTETROL

(57) **Abstract**: The present invention relates to a process for the preparation of estra-1,3,5(10)- trien-3, 15α, 16α, 17β-tetraol (estetrol), via a silyl enol ether derivative 17-B-oxy-3-A-oxy-estra-l,3,5(10), 16-tetraene, wherein A is a protecting group and B is -Si(R^2)$_3$. The invention further relates to a process for the synthesis of 3-A-oxy-estra-1,3,5(10), 15-tetraen-17-one, wherein A is a protecting group, via said silyl enol ether derivative.

Process for the preparation of estetrol

Technical field of the invention

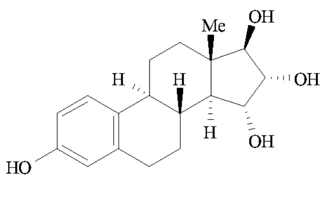
The present invention relates to a process for the preparation of estra-1,3,5(10)-trien-3,15α,16α,17β-tetraol (estetrol), starting from estrone. The invention further relates to a process for the preparation of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one, starting from estrone, via the corresponding silyl enol ether 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene, wherein A is a protecting group and B is $-Si(R^2)_3$.

Background of the invention

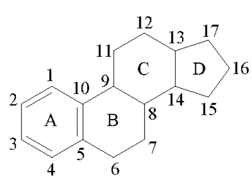
Estrogenic substances are commonly used in methods of Hormone Replacement Therapy (HRT) and in methods of female contraception. These estrogenic substances can be divided in natural estrogens and synthetic estrogens. Examples of natural estrogens that have found pharmaceutical application include estradiol, estrone, estriol and conjugated equine estrogens. Examples of synthetic estrogens, which offer the advantage of high oral bioavailability, include ethinyl estradiol and mestranol.

Estetrol has been found effective as an estrogenic substance for use in HRT, as is disclosed in WO 02/094276. Estetrol is a biogenic estrogen that is endogeneously produced by the fetal liver during human pregnancy. Other important applications of estetrol are in the fields of contraception, therapy of auto-immune diseases, prevention and therapy of breast and colon tumors, enhancement of libido, skin care, and wound healing as described in WO 02/094276, WO 02/094279, WO 02/094278, WO 02/094275, WO 03/041718 and WO 03/018026.

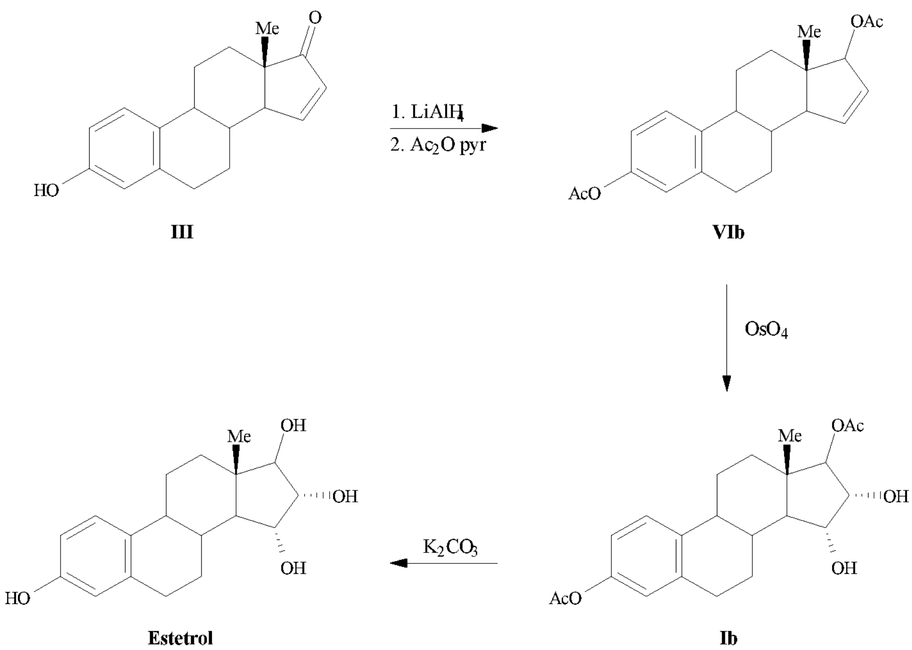
The structural formula of estetrol [estra-1,3,5(10)-trien-3,15α,16α,17β-tetraol] **I** is shown below. In this description the IUPAC-recommended ring lettering and atom numbering for steroids and steroid derivatives, as depicted below, are applied.



I
estetrol



The synthesis of estetrol on a laboratory scale is for example disclosed in Fishman *et al.*, *J. Org. Chem.* **1968**, *33*, 3133 – 3135, wherein estetrol is synthesised from estrone derivative **III** as shown in Scheme 1 (numbering according to Fishman *et al.*).

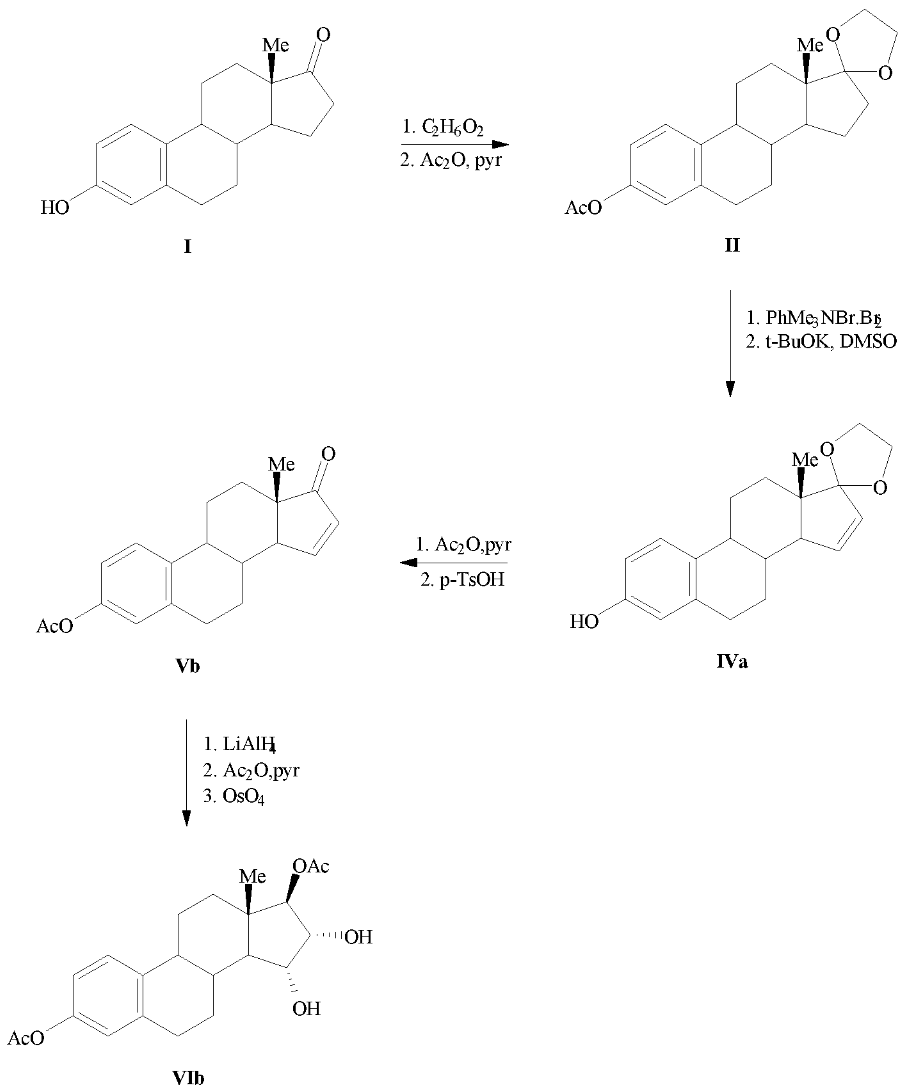


Scheme 1

Fishman *et al.* prepared estrone derivative **III** according to the procedure disclosed by Cantrall *et al.*, *J. Org. Chem.* **1964**, *29*, 214 – 217 and Johnson *et al.*, *J. Am. Chem. Soc.* **1957**, *79*, 2005 – 2009, as described in more detail below. The overall yield of the 3-step process shown in Scheme 1 is, starting from estrone derivative **III**, about 7%.

Another synthesis of estetrol wherein estrone is the starting material is disclosed in Nambara *et al.*, *Steroids* **1976**, *27*, 111 – 121. This synthesis is shown in Scheme 2 (numbering according to Nambara *et al.*). The carbonyl group of estrone **I** is first protected by treatment with ethylene glycol and pyridine hydrochloride followed by acetylation of the hydroxyl group at C_3. The next sequence of steps involved a bromination/base catalyzed dehydrobromination resulting into the formation of 17,17-ethylenedioxyestra-1,3,5(10),15-tetraene-3-ol (compound **IVa**). This compound **IVa** was subsequently acetylated which produced 17,17-ethylenedioxyestra-1,3,5(10),15-

tetraene-3-ol-3-acetate (compound **IVb**). In a next step, the dioxolane group of compound **IVb** was hydrolysed by using p-toluene sulfonic acid to compound **Vb**, followed subsequently by reduction of the carbonyl group at C_{17} (compound **Vc**) and oxidation of the double bond of ring D thereby forming estra-1,3,5(10)-triene-3,15α,16α,17β-tetraol-3,17-diacetate (compound **VIb**).

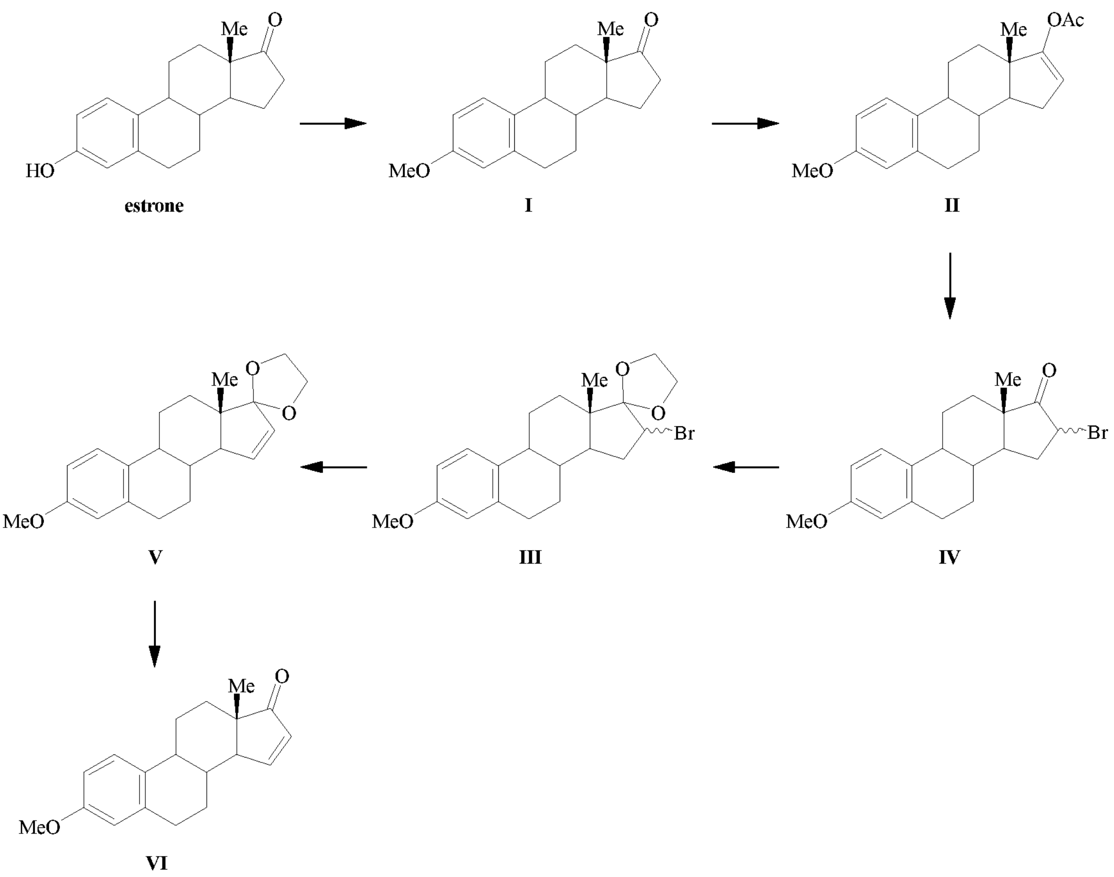


Scheme 2

Suzuki *et al.*, *Steroids* **1995**, *60*, 277 – 284 also discloses the synthesis of estetrol by using compound **Vb** of Nambara *et al.* as starting material. The carbonyl group at C_{17} of this compound was first reduced followed by acetylation yielding estra-1,3,5(10),15-tetraene-3,17-diol-3,17-diacetate (compound **2b**). The latter was subjected to oxidation with OsO_4 which provided estra-1,3,5(10)-triene-3,15α,16α,17β-tetraol-3,17-diacetate (compound **3b**) in 46% yield.

According to Nambara *et al.* and Suzuki *et al.*, the synthesis of estetrol can be performed with a yield of approximately 8%, starting from estrone.

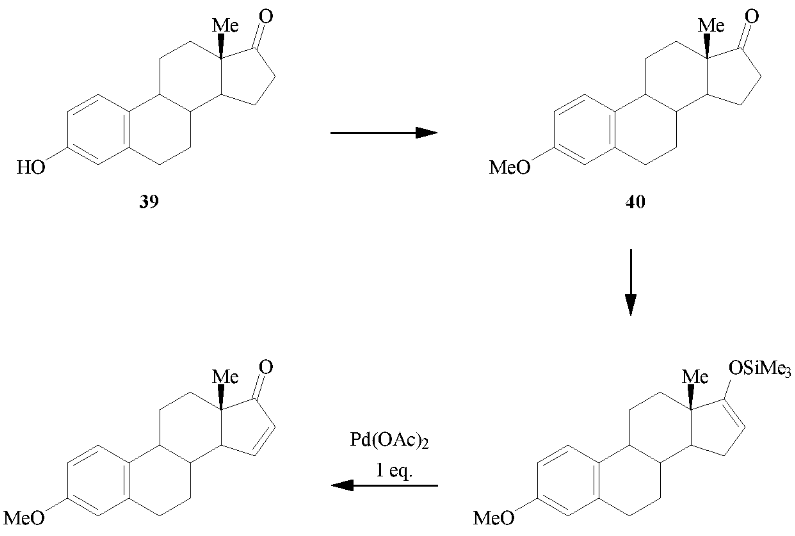
The synthesis of estrone derivative **VI** starting from estrone is disclosed by Cantrall *et al.*, *J. Org. Chem.* **1964**, *29*, 214 – 217 and 64 – 68, and by Johnson *et al.*, *J. Am. Chem. Soc.* **1957**, *79*, 2005 – 2009, and is shown in Scheme 3 (numbering according to Johnson *et al.*).



Scheme 3

The synthetic route depicted in Scheme 3 was also applied by Poirier *et al.*, *Tetrahedron* **1991**, *47*, 7751 – 7766 for the synthesis of an analogue of compound **VI** wherein a benzyl ether is present on the 3-position instead of the methyl ether in **VI**.

Another method to prepare estrone derivative **VI** of Scheme 3, wherein the hydroxyl group on the 3-position of estrone is protected as a methyl ether, is disclosed in Li *et al.*, *Steroids* **2010**, *75*, 859 – 869, and is shown in Scheme 4 (numbering according to Li *et al.*). After protection of the 3-OH group of estrone **39** as the methyl ether to form **40**, the keto function on C_{17} is converted into trimethylsilyl enol ether **41**. Compound **41** is then converted into **42** (corresponding to estrone derivative **VI** of Scheme 3) in the presence of 1 equivalent of palladium(II) acetate, $Pd(OAc)_2$. According to Li *et al.* **42** is obtained in three steps in a yield of about 60%, starting from estrone.



Scheme 4

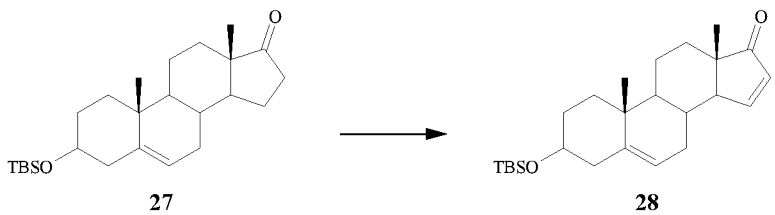
The method shown in Scheme 4 for the preparation of **42** in the presence of 1 equivalent of $Pd(OAc)_2$ is also disclosed in Smith *et al.*, *Org. Lett.* **2006**, *8*, 2167 – 2170, Smith *et al.*, *J. Org. Chem.* **2007**, *72*, 4611 – 4620 and Bull *et al.*, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1003 – 1013.

Said method is not applied in a total synthesis of estetrol **I**.

In order to get a high conversion and an acceptable yield of **42**, one equivalent of $Pd(OAc)_2$, with respect to **41**, needs to be employed. Due to the high cost of palladium, application of this method is therefore not desirable for a process that is executed on an industrial scale.

A method for the preparation of enones using hypervalent iodine(V) species is disclosed by Nicolaou *et al.*, *Angew. Chem.* **2002**, *114*, 1038 – 1042. Various ketones are converted into α,β-unsaturated enones via oxidation of the corresponding trimethylsilyl enol ethers, induced by *o*-iodoxybenzoic acid (IBX) or IBX complexed to an N-oxide ligand such as 4-methoxypyridine-N-oxide (IBX·MPO).

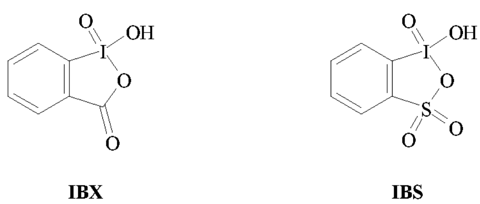
One of the examples with a more complex molecule that is disclosed by Nicolaou *et al.* is the conversion of steroid derivative **27** into α,β-unsaturated **28** in 62% yield (Scheme 5, numbering according to Nicolaou *et al.*).



Scheme 5

The method disclosed by Nicolaou *et al.* is not employed in the preparation of estrone derivatives such as compound **III** of Scheme 1, compound **Vb** of Scheme 2, compound **VI** of Scheme 3 or compound **42** of Scheme 4, nor in the preparation of estetrol **I**.

Another iodine(V) species, 2-iodoxybenzenesulphonic acid (IBS) was disclosed recently in EP 2085373 and in Yamada *et al.*, *Spec. Chem. Mag.* **2011**, *31*, 18 – 20. The structure of both IBX and IBS is shown below.



Yamada *et al.* discloses the use of IBS, in a catalytic amount, for the conversion of several cyclic alcohols with a relatively simple structure such as cyclopentanol and (optionally substituted) cyclohexanol into α,β-unsaturated enones.

The use of IBS for the conversion of complex molecules such as steroids into α,β-unsaturated enone derivatives is not disclosed in Yamada *et al.* or in EP 2085373.

A process for the preparation of estetrol that is suitable for the preparation of estetrol on an industrial scale is disclosed in WO 2004/041839. This process is shown in Scheme 6 (numbering according to WO 2004/041839), and comprises the following steps:

(1) converting estrone (**7**) into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one (**6**), wherein A is a protecting group;

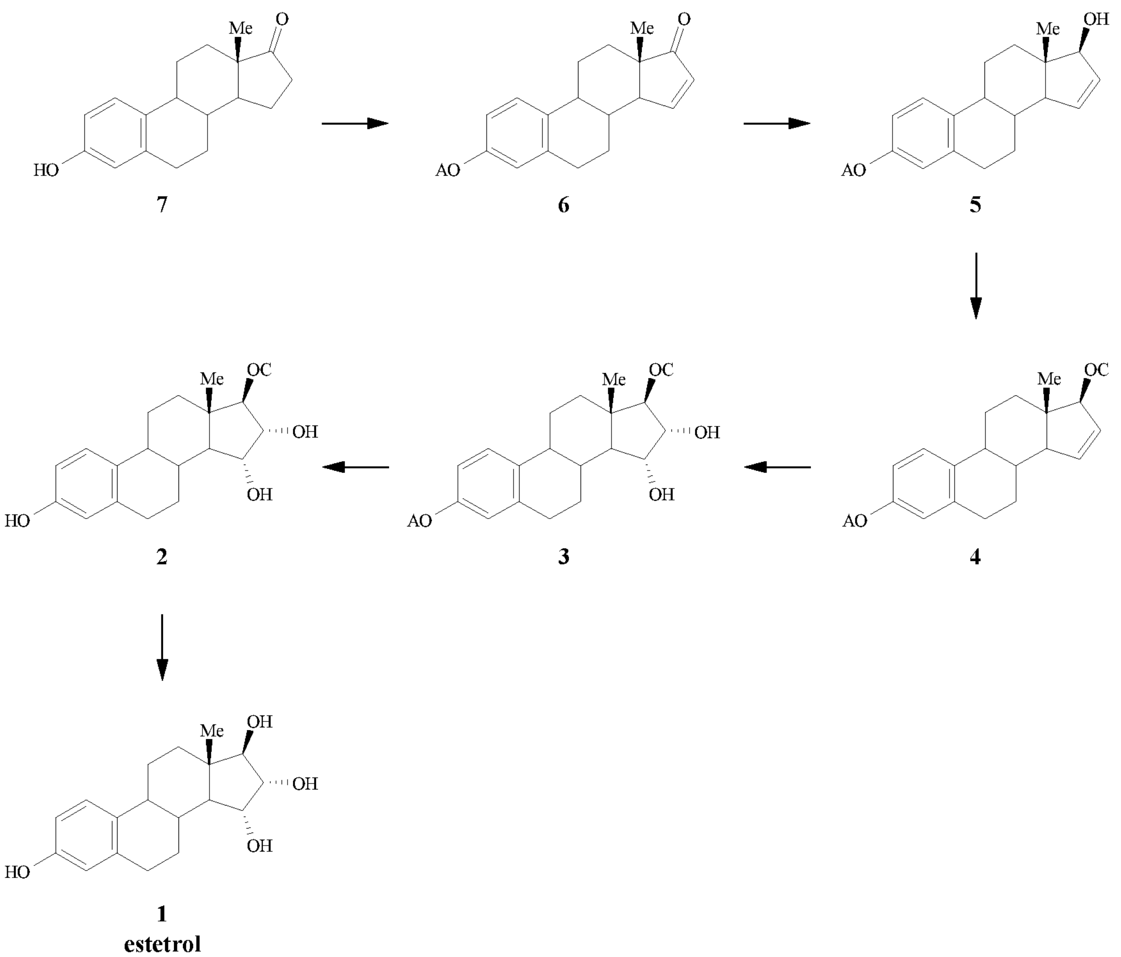
(2) reduction of the 17-keto group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one (**6**) to 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol (**5**);

(3) protection of the 17-OH group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol (**5**) to 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene (**4**), wherein C is a protecting group;

(4) oxidizing the carbon-carbon double bond of ring D of 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene (**4**) to protected estetrol (**3**); and

(5) removing the protecting groups, wherein preferably protecting group A is removed first to form 17-OC protected estetrol (**2**) and subsequently protecting group C is removed to form estetrol (**1**);

wherein the protecting group A is selected from an C_1-C_5 alkyl group or a $C_7 - C_{12}$ benzylic group and the protecting group C is selected from monofunctional aliphatic hydroxyl protecting groups.



Scheme 6

Step (1) of this process, the preparation of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one (**6**) starting from estrone (**7**), is shown in Scheme 7 and comprises the following steps:

(1a) conversion of the 3-OH group of estrone (**7**) into a 3-AO group to form 3-A-oxy-estra-1,3,5(10)-trien-17-one (**8**);

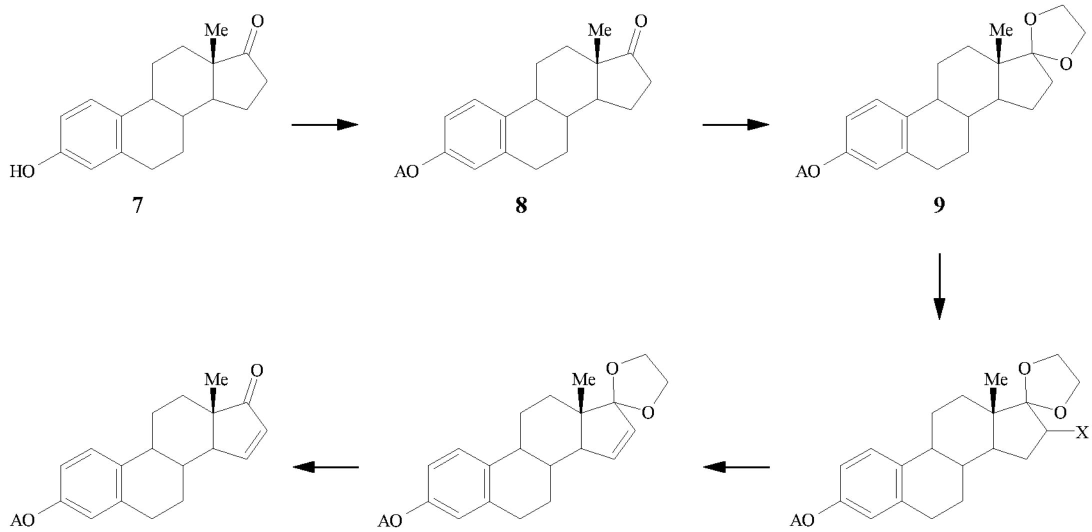
(1b) conversion of the 17-keto group of 3-A-oxy-estra-1,3,5(10)-trien-17-one (**8**) into a protected keto group to form 3-A-oxy-17-D-estra-1,3,5(10)-triene (**9**);

(1c) halogenation of C_{16} of 3-A-oxy-17-D-estra-1,3,5(10)-triene (**9**) to form 3-A-oxy-16-X-17-D-estra-1,3,5(10)-triene (**10**) wherein X is a halogen atom selected from the group chloride, bromide and iodide and wherein X is preferably bromide;

(1d) dehalogenation of 3-A-oxy-16-X-17-D-estra-1,3,5(10)-triene (**10**) to 3-A-oxy-17-D-estra-1,3,5(10),15-tetraene (**11**); and

(1e) deprotection of the protected keto group of 3-A-oxy-17-D-estra-1,3,5(10),15-tetraene (**11**) to form 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one (**6**),

wherein A is selected from an C_1-C_5 alkyl group, preferably a methyl group, or a C_7 – C_{12} benzylic group, preferably a benzyl group, and wherein D is ethylene dioxy.



Scheme 7

With the method as disclosed in WO 2004/041839 and shown in Schemes 6 and 7 above, estetrol is obtained in an overall yield of 10.8%, starting from estrone.

Although the process disclosed in WO 2004/041839 is suitable for an industrial scale preparation of estetrol **1**, and although estetrol is obtained with a reasonable overall yield, the process still suffers from several disadvantages. For example, the conversion of 7 into **6** is performed in a total of 5 steps. Isolation and purification of each intermediate product inevitably results in a loss of yield, thereby reducing the overall yield of estetrol. Furthermore, the conversion of 7 into **6** involves a halogenation (step 1c) and a dehalogenation step (step 1d), typically a bromination and a debromination step. In particular during said halogenation and dehalogenation reactions, various side products are produced. Since these side products need to be removed from the intermediate products, an extensive amount of purification of the intermediate products is required, resulting in a substantial loss of yield of the intermediate products, and therefore, ultimately, in a substantial loss in the overall yield of estetrol.

It is an object of the present invention to provide a process for the preparation of estetrol that is suitable for the production of estetrol on an industrial scale, wherein estetrol is preferably obtained in a high purity and in a good yield. Also, there is a need for a process for the preparation of estetrol wherein the formation of side products is minimal, *i.e.* as low as possible. Particularly, there is a need for a process for the preparation of estetrol wherein the halogenation and subsequent dehalogenation reactions of the process as disclosed in WO 2004/041839 are omitted.

Summary of the invention

The present invention relates to a process for the preparation of estra-1,3,5(10)-trien-3,15α,16α,17β-tetraol **I** which comprises the steps of:

(1) conversion of estrone **II** into 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III**, wherein A is a protecting group and B is $–Si(R^2)_3$;

(2) conversion of 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III** into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV**, wherein A is a protecting group;

(3) reduction of the 17-keto group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV** to form 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol **V**, wherein A is a protecting group;

(4) protection of the 17-OH group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol **V** to form 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene (**VI**), wherein A and C are protecting groups;

(5) oxidation of the carbon-carbon double bond of ring D of 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene (**VI**) to form protected estetrol **VII**, wherein A and C are protecting groups; and

(6) removal of protecting groups A and C to form estetrol **I**;

wherein:

A is a protecting group selected from the group consisting of a C_1-C_5 alkyl group, a $C_7 – C_{12}$ benzylic group and a $–Si(R^1)_3$ group, wherein R^1 is independently selected from the group consisting of a $C_1 – C_6$ alkyl group and a $C_6 – C_{12}$ aryl group;

B is $-Si(R^2)_3$, wherein R^2 is independently selected from the group consisting of a $C_1 - C_6$ alkyl group and a $C_6 - C_{12}$ aryl group; and

C is a protecting group selected from the group consisting of monofunctional aliphatic hydroxyl protecting groups.

This process is shown below in Scheme 8.

The invention further relates to a process for the synthesis of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV**, wherein A is a protecting group, which comprises the steps of:

(1) conversion of estrone **II** into 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III**, wherein A is a protecting group and B is $-Si(R^2)_3$; and

(2) conversion of 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III** into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV**, wherein A is a protecting group, wherein said conversion of **III** into **IV** is performed in the presence of an iodine(V) species, and wherein the iodine(V) species is present in an amount of about 0.1 mol% or more with respect to compound **III**;

wherein:

A is a protecting group selected from the group consisting of a C_1-C_5 alkyl group, a $C_7 - C_{12}$ benzylic group and a $-Si(R^1)_3$ group, wherein R^1 is independently selected from the group consisting of a $C_1 - C_6$ alkyl group and a $C_6 - C_{12}$ aryl group; and

B is $-Si(R^2)_3$, wherein R^2 is independently selected from the group consisting of a $C_1 - C_6$ alkyl group and a $C_6 - C_{12}$ aryl group.

This process is shown in Scheme 11 below.

Detailed description of the invention

The verb “to comprise” and its conjugations as used in this description and in the claims are used in their non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded.

In addition, reference to an element by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present, unless the context clearly requires that there is one and only one of the elements. The indefinite article "a" or "an" thus usually means "at least one".

In this patent application the term “alkyl” includes linear, branched and cyclic alkyl groups such as for example methyl, ethyl, *n*-propyl, *i*-propyl, cyclopropyl, *n*-butyl, *s*-butyl, *t*-butyl, cyclobutyl, *n*-pentyl, *s*-pentyl, *t*-pentyl, cyclopentyl, methylcyclobutyl and cyclohexyl.

A benzyl group is defined as a $-CH_2(C_6H_5)$ group.

A $C_7 - C_{12}$ benzylic group is defined as a benzyl group, *i.e.* a $-CH_2(C_6H_5)$ group as defined above, or a benzyl group that is substituted with one or more substituents at the *ortho*, *meta* and/or *para* position of the aromatic nucleus, wherein the substituents are aliphatic groups, optionally substituted by one or more heteroatoms and/or halogen atoms that do not adversely interfere with the synthetic process. Examples of a substituted benzyl group include $–CH_2(C_6H_4Me)$ or $-CH_2(C_6H_3Me_2)$, wherein Me is defined as a methyl group ($-CH_3$).

A $C_6 - C_{12}$ aryl group is defined as a monocyclic, bicyclic or polycyclic structure comprising 6 to 12 carbon atoms. Optionally, the aryl groups may be substituted by one or more substituents at the *ortho*, *meta* and/or *para* position of the aromatic nucleus, wherein the substituents are aliphatic groups, optionally substituted by one or more heteroatoms and/or halogen atoms that do not adversely interfere with the synthetic process. Examples of an aryl group include phenyl, *p*-tolyl, mesityl and naphthyl.

As is obvious to a person skilled in the art, the alkyl and benzylic groups and the $-Si(R^1)_3$ groups are intended as a protecting group and these groups must therefore be relatively easy to add and relatively easy to remove under conditions that have substantially no adverse effect on the molecular structure of the estrone derived steroid molecules.

The present invention relates to a process for the preparation of estra-1,3,5(10)-trien-3,15α,16α,17β-tetraol **I** (estetrol) which comprises the steps of:

(1) conversion of estrone **II** into 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III**, wherein A is a protecting group and B is $–Si(R^2)_3$;

(2) conversion of 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III** into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV**, wherein A is a protecting group;

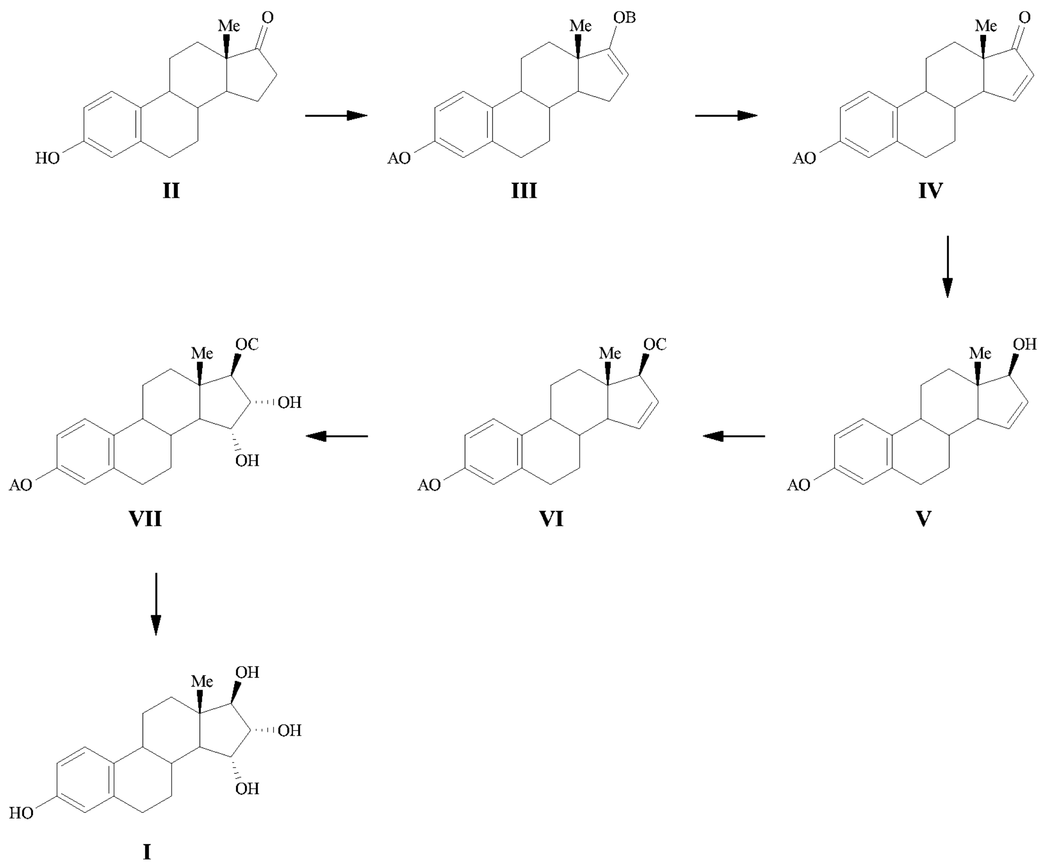
(3) reduction of the 17-keto group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV** to form 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol **V**, wherein A is a protecting group;

(4) protection of the 17-OH group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol **V** to form 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene **VI**, wherein A and C are protecting groups;

(5) oxidation of the carbon-carbon double bond of ring D of 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene **VI** to form protected estetrol **VII**, wherein A and C are protecting groups; and

(6) removal of protecting groups A and C to form estetrol **I**;

wherein A is a protecting group selected from the group consisting of a C_1-C_5 alkyl group, a $C_7 - C_{12}$ benzylic group and a $-Si(R^1)_3$ group, wherein R^1 is independently selected from the group consisting of a $C_1 - C_6$ alkyl group and a $C_6 - C_{12}$ aryl group; B is $-Si(R^2)_3$, wherein R^2 is independently selected from the group consisting of a $C_1 - C_6$ alkyl group and a $C_6 - C_{12}$ aryl group; and C is a protecting group selected from the group consisting of monofunctional aliphatic hydroxyl protecting groups, *i.e.* a monofunctional protecting group that is suitable for the protection of an aliphatic hydroxyl group. The process according to the invention is depicted in Scheme 8.

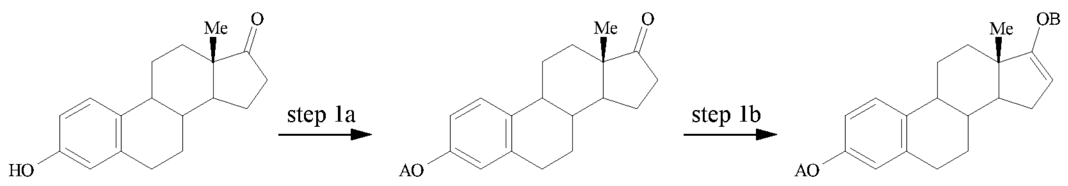


Scheme 8

Step (1): Conversion of estrone II into 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene III, wherein A is a protecting group and B is $–Si(R^2)_3$

Step 1 of the process comprises the steps of (1a) the protection of the hydroxyl group on the 3-position of estrone **II** with a protecting group A, and (1b) the conversion of the keto functionality on the 17-position into the corresponding silyl enol ether.

In a preferred embodiment, step (1a) is executed first, followed by step (1b), in other words, the 3-hydroxyl group of estrone **II** is first protected with a protecting group A, followed by the conversion of the thus obtained 3-protected estrone into the corresponding 3-protected silyl enol ether **III**, as is shown in Scheme 9. Alternatively, and more preferably, step (1a) and (1b) may be executed simultaneously, or in a "two-reactions-one-pot" procedure.



II **III**

Scheme 9

Step (1a): Protection of the 3-OH-group

Step (1a) relates to the protection of the 3-hydroxyl group of estrone **II** with a protecting group A. Protecting group A is selected from the group consisting of a C_1-C_5 alkyl group, a C_7 – C_{12} benzylic group and a $–Si(R^1)_3$ group, wherein R^1 is independently selected from the group consisting of a C_1 – C_6 alkyl group and a C_6 – C_{12} aryl group.

When protecting group A is a C_1 – C_5 alkyl group, A may for example be methyl, ethyl, propyl, iso-propyl (*i*-propyl), butyl, iso-butyl (*i*-butyl) or tertiair butyl (*t*-butyl). Preferably, if A is a C_1 – C_5 alkyl group, A is methyl.

When A is a C_7 – C_{12} benzylic group, it is preferred that A is a benzyl group, $-CH_2(C_6H_5)$. However, the C_7 – C_{12} benzylic group may also be a substituted benzyl group, such as for example $–CH_2(C_6H_3Me_2)$. Most preferably, A is a benzyl group.

When A is a $–Si(R^1)_3$ group each R_1 group is independently selected, in other words, each of the three R^1 groups within one $–Si(R^1)_3$ group may be different from the others. Preferably, R^1 is selected from the group consisting of methyl, ethyl, propyl, *i*-propyl, butyl, *i*-butyl, *t*-butyl, phenyl, *p*-tolyl and mesityl. Examples of suitable -$Si(R^1)_3$ groups include trimethylsilyl (TMS), triethylsilyl (TES), diethylisopropylsilyl (DEIPS), isopropyldimethylsilyl (IPDMS), triisopropylsilyl (TIPS), *t*-butyldimethylsilyl (TBDMS) and *t*-butyldiphenylsilyl (TBDPS). Preferably, when A is a –$Si(R^1)_3$ group, the –$Si(R^1)_3$ group is a sterically hindered ("bulky") –$Si(R^1)_3$ group such as for example a DEIPS, IPDMS, TIPS, TBDMS or TBDPS group.

The protection of the hydroxyl group on C_3 by alkylation is typically carried out by reacting estrone with a component selected from an alkylating reagent, preferably a $C_1 - C_5$ alkyl halogenide, preferably a methyl halogenide, or a $C_7 - C_{12}$ benzylic halogenide, preferably benzyl halogenide. Preferably, the halogen atom of the alkylating agent is bromide, chloride or iodide, most preferably bromide or iodide. According to the present invention, the most preferred alkylating agent is benzyl bromide or methyl iodide, wherein benzyl bromide is more preferred than methyl iodide. However, it is also possible to use a dialkyl sulphate instead of a $C_1 - C_5$ alkyl halogenide, wherein the alkyl groups contain 1 – 5 carbon atoms and wherein the alkyl groups are preferably methyl (*i.e.* the preferred dialkyl sulphate is then dimethyl sulphate).

The protection of the 3-OH group by silylation is typically carried out by reacting estrone with a silylation reagent, such as for example a silyl chloride, a silyl iodide or a silyl triflate, in the presence of a base, for example an amine base.

The protection of the 3-OH group is typically executed in the presence of a base. Suitable bases are known to a person skilled in the art, and include for example potassium bases such as potassium carbonate (K_2CO_3), potassium *t*-butoxide (KO*t*Bu), potassium hexamethyldisilazide (KHMDS) or potassium hydride (KH), sodium bases such as sodium methoxide (NaOMe), sodium *t*-butoxide (NaO*t*Bu), sodium hexamethyldisilazide (NaHMDS) or sodium hydride (NaH), lithium bases such as lithium diisopropylamide (LDA), lithium tetramethylpiperidide (LiTMP) or lithium hexamethyldisilazide (LiHMDS), amine bases such as triethyl amine (Et_3N), tetramethylethylene diamine (TMEDA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), imidazole and 2,6-lutidine, and the like.

As will be clear to a person skilled in the art, the type of base that is preferred in a specific reaction depends strongly on the type of alkylating or silylation reagent used in said reaction. When for example the 3-OH group is protected via an alkylation reaction, *e.g.* with benzyl bromide as alkylating reagent, then the use of an amine base in that reaction is less preferred. When the 3-OH group is protected via a silylation reaction, then the use of a small alkoxide, such as for example NaOMe, as a base is less preferred.

Suitable solvents for the protection reaction are known to the person skilled in the art, and include for example dimethylformamide (DMF), dichloromethane (DCM), ethyl acetate (EtOAc), toluene, acetonitrile (MeCN), dimethyl sulfoxide (DMSO), dimethylacetamide, dimethyl carbonate (DMC), tetrahydrofuran (THF) and other ethers such as for example 1,4-dioxane, 2-methyltetrahydrofuran (2-MeTHF), methyl *t*-butyl ether (MTBE), 1,2-dimethoxyethane (DME) and cyclopentyl methylether, mixtures of two or more of these solvents, and mixtures of these solvents with different solvents such as for example methanol (MeOH).

The reaction may be executed at ambient temperature, at an elevated temperature (*e.g.* reflux), or at low temperature.

As will be clear to a person skilled in the art, the preferred reaction conditions such as solvent and reaction temperature strongly depend on the nature of the specific reaction, in particular on the alkylating or silylation reagent and/or the type of base used in said reaction. When for example benzyl bromide is used as an alkylating reagent, K_2CO_3 may be used as a base and the reaction may be executed in a mixture of DCM and MeOH (*e.g.* a 1:1 mixture) at elevated temperature (reflux). Alternatively, also with benzyl bromide as alkylating reagent, NaOMe may be used as a base and the reaction may be performed in a mixture of 2-methyltetrahydrofuran and methanol at an elevated temperature of around 60°C. When methyl iodide is used as an alkylating reagent, for example K_2CO_3 may be used as a base and the reaction may be performed in DMF while keeping the temperature around 20°C.

Extensive purification of the product of step (1a), the obtained 3-protected estrone derivative, is not necessary before the conversion step (1b). In a preferred embodiment, crude 3-protected estrone derivative, *i.e.* 3-protected estrone derivative that has not undergone extensive purification, is used as starting material for the conversion into 3-protected silyl enol ether **III**.

As was described above, in a preferred embodiment, step (1a) and (1b) may be executed simultaneously or in a “two-reactions-one-pot” procedure, *e.g.* by reaction of estrone **II** with at least two equivalents of a base followed by reaction with at least two equivalents of silylation reagent (such as for example trimethylsilyl chloride or triethylsilyl chloride) in order to introduce A and B, or, alternatively, by reaction of estrone **II** with at least two equivalents of a base (such as for example LDA), followed by reaction with one equivalent of a silylation agent (such as for example trimethylsilyl chloride) in order to introduce B, followed by reaction with one equivalent of alkylating agent (such as for example benzyl bromide) in order to introduce A.

Step (1b): Conversion of the 17-keto-group

Step (1b) relates to the conversion of the keto functionality on C_{17} into the corresponding silyl enol ether to form the 3-protected 17-silyl enol ether 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III**.

B is a $-Si(R^2)_3$ group, wherein each R^2 is independently selected from the group consisting of a $C_1 - C_6$ alkyl group and a $C_6 - C_{12}$ aryl group. As was explained above for $-Si(R^1)_3$, each R^2 group in $-Si(R^2)_3$ is independently selected, in other words each of the three R^2 groups within one $-Si(R^2)_3$ group may be different from the others. Preferably, R^2 is selected from the group consisting of methyl, ethyl, propyl, *i*-propyl, butyl, *i*-butyl, *t*-butyl, phenyl, *p*-tolyl and mesityl. More preferably, B is a trimethylsilyl (TMS) or a triethylsilyl (TES) group. Most preferably, B is a TMS group.

The formation of silyl enol ether **III** is typically carried out by reacting the 3-protected estrone with a silylation reagent, such as for example a silyl chloride or a silyl triflate, in the presence of a base. Preferably, the silylation reagent is trimethylsilylchloride (TMSCl), trimethylsilyliodide (TMSI) or trimethylsilyltriflate (TMSOTf).

Suitable bases are known to a person skilled in the art, and include for example potassium bases such as K_2CO_3 or KH, sodium bases such as NaH or NaOMe, lithium bases such as $LiAlH_4$, LDA, LiTMP or LiHMDS, amine bases such as Et_3N, imidazole and 2,6-lutidine, TMEDA, DBU and the like. In a preferred embodiment, the base is LDA or Et_3N.

Suitable solvents for the silyl enol ether conversion are known to the person skilled in the art, and include for example dimethylformamide (DMF), dichloromethane (DCM), toluene, tetrahydrofuran (THF) and other ethers such as for example 1,4-

dioxane, 2-methyltetrahydrofuran (2-MeTHF), methyl *t*-butyl ether (MTBE), 1,2-dimethoxyethane (DME) and cyclopentyl methylether, or mixtures thereof.

As will be clear to a person skilled in the art, the preferred reaction conditions such as solvent and reaction temperature strongly depend on the nature of the specific reaction, in particular on the silylation reagent and/or the type of base used in said reaction. For example, when A is benzyl and B is trimethylsilyl (TMS), the reaction may be executed at ambient temperature with TMSOTf as silylation reagent, Et_3N as a base and in toluene or DCM as a solvent.

Extensive purification of silyl enol ether **III** before subjecting it to the next step of the process is not necessary. In a preferred embodiment, crude **III**, *i.e.* **III** that has not undergone extensive purification, is used as the starting material for step (2).

Step (2): Conversion of 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene III into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one IV, wherein A is a protecting group

Step (2) relates to the conversion of silyl enol ether **III** into α,β-unsaturated enone **IV**. There are several methods to execute this oxidation.

Method (a):in the presence of an iodine(V) species

In one embodiment of the present invention, step (2) of the process, *i.e.* the conversion of **III** into **IV**, is performed in the presence of an iodine(V) species. Preferably, said iodine(V) species is present in an amount of about 0.001 mol% or more, for example in an amount of about 0.1 mol% or more, or in an amount of about 0.5 mol% or more, with respect to compound **III**.

In one embodiment, the iodine(V) species is present in an amount of about 100 to about 500 mol% (about 1 to 5 equivalents), preferably in an amount of about 100 to about 300 mol% (about 1 to 3 equivalents), more preferably in an amount of about 100 to about 150 mol% (about 1 to 1.5 equivalents), even more preferably in an amount of about 100 to about 130 mol% (about 1 to 1.3 equivalents), and most preferably in an amount of about 100 mol% (about 1 equivalent), with respect to compound **III**.

In another, more preferred embodiment, the iodine(V) species is present in an amount of about 100 mol% or less, preferably in an amount of about 75 mol% or less, more preferably in an amount of about 50 mol% or less, even more preferably in an amount of about 30 mol% or less, and even more preferably in an amount of about 20 mol% or less, all with respect to the amount of **III**. Most preferably, the iodine(V) species is present in an amount of about 15 mol% or less, preferably about 10 mol% or less, more preferably about 5 mol% or less, with respect to the amount of **III**.

In a preferred embodiment, the iodine(V) species comprises 2-iodoxybenzoic acid (IBX), 2-iodoxybenzenesulphonic acid (IBS), and/or a derivative thereof. The iodine(V) species may be generated *in situ*. As is known to a person skilled in the art, IBX may for example be generated *in situ* from 2-iodobenzoic acid and Oxone ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$), and IBS may for example be generated *in situ* from 2-iodobenzenesulphonic acid and Oxone.

An example of a derivative of IBX is "stabilised IBX" (SIBX), a formulation comprising IBX, isophthalic acid and benzoic acid disclosed by Ozanne *et al.*, *Org. Lett.* **2003**, *5*, 2903 – 2906, incorporated by reference. In a preferred embodiment, the iodine(V) species comprises stabilised IBX.

Other examples of IBX derivatives are, amongst others, 2,3,4,5-tetrafluoro-6-iodoxybenzoic acid (FIBX), disclosed by Richardson *et al.*, *Angew. Chem. Int. Ed.* **2007**, *46*, 6529 – 6532, incorporated by reference, and 5-methoxy-3-methyl-2-iodoxybenzoic acid, disclosed by Moorthy *et al.*, *Tetrahedron Lett.* **2008**, *49*, 80 – 84, incorporated by reference. An example of an IBS derivative is 5-methyl-2-iodoxybenzenesulphonic acid (5-Me-IBS), disclosed by Yamada, *Spec. Chem. Mag.* **2011**, *31*, 18 – 20, incorporated by reference. 5-Me-IBS may for example be generated *in situ* from 5-methyl-2-iodobenzenesulphonic acid potassium salt and Oxone.

In a preferred embodiment, the iodine(V) species comprises a derivative formed by complexation of IBX, IBS and/or a derivative thereof with a ligand, in particular with dimethyl sulfoxide (DMSO) or with an N-oxide. Examples of suitable N-oxides are N-methylmorpholine-N-oxide (NMO), 4-methoxypyridine-N-oxide (MPO), trimethylamine-N-oxide, 2-picoline-N-oxide and 4-phenylpyridine-N-oxide. Preferably, the ligand is selected from DMSO, NMO, MPO, or a combination of two or more of these ligands.

Said derivatives may be formed for example by stirring a solution of said IBX, IBS and/or derivative thereof with said ligand, optionally at an elevated temperature.

In an alternative embodiment, the iodine(V) species comprises a species formed by activation of I_2O_5 and/or HIO_3 in DMSO. In another alternative embodiment, the iodine(V) species comprises a species formed by complexation of I_2O_5 and/or HIO_3 with a ligand, in particular with an N-oxide as described above.

In another specific embodiment, the iodine(V) species comprises 2-iodoxybenzenesulphonic acid (IBS) and/or a derivative thereof, as described above. The IBS and/or derivative thereof is then preferably present in an amount of less than 100 mol% (1 equivalent), for example in an amount of about 0.001 to about 50 mol%, preferably about 0.01 to about 40 mol%, more preferably about 0.1 to about 30 mol% even more preferably about 0.5 to about 20 mol% and most preferably about 1 to about 10 mol%, all with respect to compound **III**.

Suitable solvents for the conversion of **III** into **IV** in the presence of an iodine(V) species are known to the person skilled in the art, and include for example dimethyl sulfoxide (DMSO), dimethylformamide (DMF), dimethylacetamide (DMA), N-methylpyrrolidone (NMP), acetonitrile, ethyl acetate, acetone, or a mixture thereof. Alternatively, a mixture of said solvents with other organic solvents such as for example dichloromethane (DCM), chloroform or fluorobenzene may be used. In a preferred embodiment, the solvent is selected from the group consisting of DMSO, DMF, DMA, NMP, a combination thereof, and a combination of DMSO, DMF, DMA and/or NMP with one or more organic solvents, such as for example DCM, chloroform or fluorobenzene. In another preferred embodiment, the reaction is executed in DMSO, or in a mixture of DMSO with one or more organic solvents, such as for example DCM, chloroform or fluorobenzene. In yet another preferred embodiment, the reaction is executed in DMF, or in a mixture of DMF with one or more organic solvents, such as for example DCM, chloroform or fluorobenzene.

The reaction may be executed at ambient temperature or at elevated temperature.

As will be clear to a person skilled in the art, the preferred reaction conditions such as solvent and reaction temperature strongly depend on the nature of the specific reaction, in particular on the type of iodine(V) species that is employed in the reaction.

The conversion of **III** into **IV** in the presence of an iodine(V) species, in particular in the presence of IBX, IBS and/or a derivative thereof, proceeds in a very clean way with minimal, if at all, side-product formation. Compound **IV** is obtained in a good yield and purity.

Method (b): in the presence of a transition metal

In another embodiment of the present invention, step (2) of the process, *i.e.* the conversion of **III** into **IV**, is performed in the presence of a transition metal compound. Preferably, said transition metal compound is present in an amount of about 0.001 mol% or more, for example in an amount of about 0.01 mol% or more, or in an amount of about 0.1 mol% or more, with respect to compound **III**.

Preferably, the transition metal compound comprises a palladium (Pd) compound, and more preferably, the transition metal is a palladium compound. Examples of palladium compounds are palladium black, $Pd(OH)_2$ on carbon ($Pd(OH)_2/C$, also known as Pearlman's catalyst), $Pd(dba)_2$ or $Pd(OAc)_2$. The palladium compound may also be a ligand-stabilised palladium compound, wherein the palladium is stabilised with for example a bidentate nitrogen or carbene ligand, such as for example palladium stabilised with 1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline (neocuproine), 2,2'-bipyridine, *etc*. The palladium compound may be a palladium(0) or a palladium(II) compound. In a preferred embodiment, the palladium compound comprises a palladium(II) compound, such as for example palladium(II) acetate, $Pd(OAc)_2$. Most preferably, the transition metal compound is palladium(II) acetate.

The transition metal compound may be present in an amount of about 100 mol% (1 equivalent) with respect to compound **III**, or more. However, it is preferred that the transition metal compound is present in a substoichiometric amount, in other words in an amount of less than about 100 mol% with respect to **III**. The transition metal compound may for example be present in an amount of 0.01 to about 50 mol%, or in an amount of about 0.1 to about 30 mol%, about 0.5 to about 20 mol%, about 1 to about 15 mol%, or about 3 to about 10 mol%, relative to compound **III**. Most preferably, the transition metal compound is present in an amount of about 1 to about 5 mol% relative to **III**.

The reaction may also be performed in the presence of an oxidizing agent (an oxidant) in order to facilitate the reoxidation of the transition metal. The presence of an oxidant is particularly preferred when the transition metal compound is a palladium(0) compound, or when a palladium(II) compound is present in a substoichiometric amount, *i.e.* in an amount of less than 1 equivalent, with respect to the compound **III**.

When the reaction is performed in the presence of an oxidant, the oxidant is preferably present in an amount of about 1 equivalent (about 100 mol%) or more, relative to compound **III**. The amount of oxidant present may range for example from about 1 to about 3 equivalents, preferably from about 1 to about 2 equivalents and more preferably from about 1 to about 1.5 equivalents, relative to the amount of **III**.

Suitable oxidants are known to a person skilled in the art, and include for example molecular oxygen (O_2), copper(II) acetate ($Cu(OAc)_2$), allyl methyl carbonate, *t*-butylhydroperoxide (TBHP), N-methylmorpholine N-oxide (NMO) and similar N-oxides, benzoquinone, and the like. In a preferred embodiment, the oxidant is copper(II) acetate. In another preferred embodiment, the oxidant is allyl methyl carbonate. In another preferred embodiment, the oxidant is O_2.

For example, the reaction may be performed in an O_2-atmosphere. It is then preferred that the reaction is executed at atmospheric pressure (about 1 bar). However, execution of the reaction in an O_2-atmosphere at elevated pressure is also possible. Alternatively, the reaction may be performed by using the O_2 in air as an oxidant. The reaction is then executed in an air atmosphere, either at atmospheric pressure or at an elevated pressure. In addition, the reaction may be performed in "diluted air", such as for example 8% O_2 in nitrogen (N_2) at elevated pressure, for example at a pressure of about 10 bar or more. In a specific embodiment, the reaction is executed in an O_2-atmosphere or an air atmosphere, optionally at an elevated pressure. In another specific embodiment, the reaction is executed in an atmosphere of "diluted air" (*e.g. ca.* 8% O_2 in N_2) at an elevated pressure (*e.g.* about 10 bar or more).

Suitable solvents for the conversion of **III** into **IV** in the presence of a transition metal compound, in particular a palladium compound, are known to the person skilled in the art, and include for example dimethyl sulfoxide (DMSO), sulfolane, *etc.* Additionally, a mixture of said solvents with for example DCM or chloroform may also be used. In a preferred embodiment, the reaction is executed in DMSO, or in a mixture of DMSO with one or more organic solvents, such as for example DCM or chloroform.

The reaction may be executed at ambient temperature or at elevated temperature.

The conversion of **III** into **IV** in the presence of transition metal, in particular in the presence of a palladium compound, particularly $Pd(OAc)_2$, proceeds in a very clean way with minimal, if at all, side-product formation. Compound **IV** is obtained in a good yield and purity.

Step (3): Reduction of the 17-keto group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one IV to form 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol V, wherein A is a protecting group

Step (3) relates to the reduction of the 17-keto functionality to form **V**, and said reduction of the 17-keto group may be performed as disclosed in WO 2004/041839. Said reduction is preferably performed by reacting 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV** with a reducing agent selected from the group of metal hydride compounds, said group of metal hydride compounds preferably comprising $LiAlH_4$, AlH_3, $NaBH_4$, $NaBH(OAc)_3$, $ZnBH_4$, and $NaBH_4/CeCl_3$. Most preferably the metal hydride compound is $NaBH_4/CeCl_3$. More preferred reducing agents for use herein are those that will provide a chemo- and stereo-selective reduction of the 17-keto group in favour of the β position. For that reason, the most preferred chemo- and stereo-selective reducing agent for use herein is $NaBH_4$ in combination with $CeCl_3$ hydrate, preferably the heptahydrate.

In particular, it is preferred to suspend 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV** and $CeCl_3$ heptahydrate in a mixture of a protic solvent, preferably MeOH and THF, and to stir the mixture at room temperature, preferably for about 1 h. A preferred volume ratio of MeOH to THF is 2:1 to 4:1. Then the mixture is cooled, preferably to 0° – 5°C, and $NaBH_4$ is added in small portions maintaining the temperature below 8°C. After a period of time, preferably 2 hours, 1 N NaOH and DCM are added. After 30 minutes of stirring, the layers are separated and the aqueous layer is extracted with DCM. The combined organic extracts are dried with sodium sulphate and concentrated to give the product as a white solid.

However, it is even more preferred to quench the reaction mixture with an acid, preferably 2 N HCl, to remove the solvents by distillation under vacuum at about 30°C to about 40°C and to add toluene. Preferably, the temperature is then raised to about 70°C to induce phase separation. The organic phase is then separated, washed with an aqueous solution of Na_2CO_3 and water. The final organic phase is dried by azeotropic distillation, cooled to about 50°C and used for the next step.

Step (4): Protection of the 17-OH group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol V to form 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene VI, wherein A and C are protecting groups

Step (4) of the process relates to the protection of the hydroxyl group on the 17-position of **V** with a protecting group C, wherein C is a protecting group selected from the group consisting of monofunctional aliphatic hydroxyl protecting groups, *i.e.* monofunctional protecting groups that are suitable for the protection of an aliphatic hydroxyl group. These protecting groups are known to a person skilled in the art, and described in for example P.J. Kocienski, *"Protecting Groups"*, 3rd ed., Georg Thieme Verlag, New York **2005**, and T.W. Greene *et al.*, *"Protective Groups in Organic Synthesis"*, 3rd ed., John Wiley & Sons, New York, **1991**.

Step (4) may for example be executed as disclosed in WO 2004/041839.

In a preferred embodiment, C is an acetyl protecting group. The 17-OH group is preferably protected by acetylation using a reagent selected from acetic anhydride or acetyl chloride. Preferably, acetic anhydride is used.

In particular, it is preferred to treat a solution of the compound in pyridine with acetic anhydride and 4-dimethylaminopyridine. The mixture is stirred for a period of time. Preferably after 2 hours at room temperature the volatiles are removed. The residue is dissolved in ethyl acetate (EtOAc) and the resulting solution is washed with water and brine. The solution is dried using sodium sulphate and concentrated to give the crude product. Recrystallization from a mixture of organic solvents, preferably ethyl acetate, heptane and ethanol gives the product as a white solid.

Alternatively, the reaction may be performed with a trialkylamine, preferably triethylamine, and an acetyl halide (about two equivalents), preferably acetyl chloride (about 1.5 equivalent) in toluene at about 25°C to about 60°C, preferably about 40°C to about 50°C. The work up is then performed by washing with water, aqueous acid and aqueous base. Purification of the product is then achieved by crystallisation, *i.e.* by removing the toluene by distillation, dissolving the crude product in ethyl acetate and heating this solution to about 70°C to about 80°. To this heated solution, small portions of ethanol are added to induce crystallisation (preferred ratio of ethyl acetate to ethanol is about 1 to about 8).

Step (5): Oxidation of the carbon-carbon double bond of ring D of 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene VI to form protected estetrol VII, wherein A and C are protecting groups

Step (5) relates to the oxidation of the carbon-carbon double bond of ring D to form protected estetrol **VII**, and is preferably executed as is disclosed in WO 2004/041839.

The oxidation of the carbon-carbon double bond in ring D is carried out with an oxidising agent providing selective *cis*-hydroxylation of the carbon-carbon double bond. Preferably, the oxidising agent is osmium tetroxide (OsO_4) and more preferably the oxidising agent is osmium tetroxide immobilized on PVP (OsO_4-PVP) that is used in a catalytic amount (*cf.* G. Cainelli *et al.*, *Synthesis* **1989**, 45 – 47) in combination with a co-oxidant selected from trimethylamine-N-oxide, N-methyl morpholine-N-oxide or hydrogen peroxide, preferably trimethylamine-N-oxide. More preferably, OsO_4-PVP and trimethylamine-N-oxide are used with THF as the solvent.

In particular, it is preferred to add OsO_4-PVP to a heated solution of the compound prepared in the previous step in THF. Preferably, the addition is performed at 50°C followed by the addition of trimethylamine-N-oxide. Preferably, the addition of trimethylamine-N-oxide is performed portion wise during 1 hour. The mixture is stirred at this temperature for a period of time. Preferably, after 12 hours the mixture is cooled to room temperature and filtered. The volatiles are removed and the residue is dissolved in ethyl acetate and water is added. The aqueous layer is acidified and the layers are separated. The aqueous layer is extracted with ethyl acetate. The combined extracts are dried with sodium sulphate and concentrated. The resulting residue is triturated with heptanes and ethyl acetate to give the product as a white precipitate that is filtered off. The product is purified by recrystallization from a mixture of organic solvents, preferably ethyl acetate, heptane and ethanol to give the product as a white solid.

Step 6: Removal of protecting groups A and C to form estetrol I

Step (6) of the process relates to the removal of the protecting groups A and C to form estetrol **I**, and is preferably performed as disclosed in WO 2004/041839. WO 2004/041839 discloses that not all protective groups can be removed without adverse effects on the obtained product.

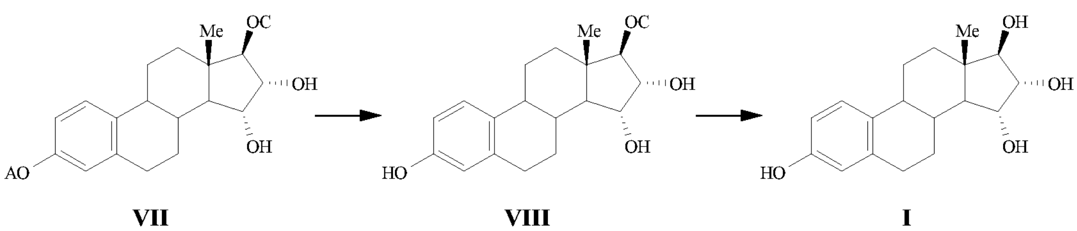
When A is a C_1-C_5 alkyl group, removal of the protecting group is preferably performed using BBr_3. When A is a $C_7 – C_{12}$ benzylic group, removal of the protecting group is preferably performed using catalytic hydrogenation conditions, for example Pd/H_2, as is well known to the person skilled in the art.

In particular, it is preferred to dissolve the protected estetrol **VII** in a protic solvent, preferably methanol. The conversion is then executed at ambient temperature in the presence of a catalytic amount of Pd/C (*e.g.* 10%) on carbon (*e.g.* as a preformed suspension in methanol) in a hydrogen atmosphere, preferably of 1 atmosphere.

Removal of protecting group C is effective using a protic solvent such as methanol and a base, preferably K_2CO_3, to yield estetrol.

Alternatively, the order of the two deprotection steps above can be reversed. Thus, the complete deprotection can be accomplished by first removing protecting group C, followed by catalytic hydrogenation to remove protecting group A where A is a protective $C_7 – C_{12}$ benzylic group. The procedures are identical to the ones described above. However, it is preferred to first remove protecting group A and subsequently protective group C.

Therefore, in a preferred embodiment of step (6), protecting group A is removed first to form 17-OC protected estetrol **VIII**, and subsequently protecting group C is removed to form estetrol **I**, as is depicted in Scheme 10.



Scheme 10

According to a most preferred embodiment of step (6), the deprotection reactions, *i.e.* the removal of A and C, are performed in a single step if A is a protective $C_7 – C_{12}$ benzylic group. Preferably, compound **VII** is dissolved in a $C_1 – C_3$ alkyl alcohol, preferably methanol, and subjected to hydrogenation at room temperature. Thereafter, the solution of compound **VIII** is preferably used in the subsequent step, *i.e.* the removal of C as described above.

Process for the synthesis of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one IV

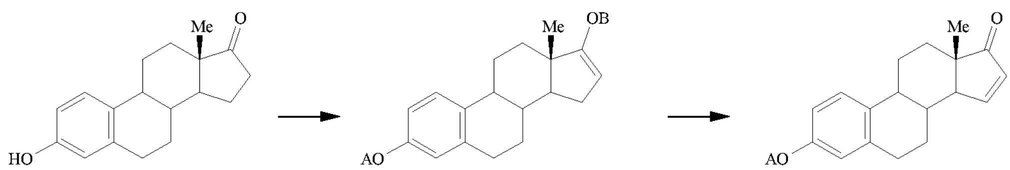
In a second aspect of the invention, the invention relates to a process for the synthesis of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV**, wherein A is a protecting group, which comprises the steps of:

(1) conversion of estrone **II** into 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III**, wherein A is a protecting group and B is $–Si(R^2)_3$; and

(2) conversion of 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III** into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV**, wherein A is a protecting group, wherein said conversion of **III** into **IV** is performed in the presence of an iodine(V) species, and wherein the iodine(V) species is present in an amount of about 0.1 mol% or more with respect to compound **III**;

wherein A is a protecting group selected from the group consisting of a C_1-C_5 alkyl group, a $C_7 – C_{12}$ benzylic group and a $–Si(R^1)_3$ group, wherein R^1 is independently selected from the group consisting of a $C_1 – C_6$ alkyl group and a $C_6 – C_{12}$ aryl group; and B is $–Si(R^2)_3$, wherein R^2 is independently selected from the group consisting of a $C_1 – C_6$ alkyl group and a $C_6 – C_{12}$ aryl group.

Said process is shown in Scheme 11.



II **III** **IV**

Scheme 11

In a preferred embodiment, the iodine(V) species comprises 2-iodoxybenzoic acid (IBX), stabilised 2-iodoxybenzoic acid (SIBX) 2-iodoxybenzenesulphonic acid (IBS), and/or a derivative thereof. A detailed disclosure of this process according to the invention is described above, in step (1) and step (2) of the process for the synthesis of estetrol.

Examples

General

The following methods and materials for determination were used. ^{1}H-NMR spectra were recorded on a Varian 200 MHz apparatus in CD_3OD or $CDCl_3$. DSC was measured using a Mettler Toledo DSC822 apparatus.

HPLC-MS was performed using a Hewlett Packard 1100 series (column: Discovery C18 (150 x 4.6 mm) Supelco; mobile phase: Solution A/Solution B = 70/30 (5 min) → (10 min) → 10/90 (5 min); flow 1 ml/min; UV: 280 nm; T = 22°C; MS: API-ES negative; Solution A: 9.65 g NH_4OAc, 2250 ml H_2O, 150 ml MeOH, 100 ml CH_3CN; Solution B: 9.65 g NH_4OAc, 250 ml H_2O, 1350 ml MeOH, 900 ml CH_3CN).

Reversed phase HPLC was performed using UV detection at 230 nm, using three different isocratic methods, all at a flow of 1 ml/min and at ambient temperature. Method A used a 250 x 4.6 mm Supelcosil LC-ABZ column (medium polarity) and methanol /20 mM aqueous phosphate buffer pH 3.8 in a 80/20 ratio. Method B used a 250 x 4 mm Nucleosil C-18 column and H_2O/MeOH/acetonitrile in a 15/50/35 ratio, containing 50 mM ammonium acetate. Method C used a 250 x 4 mm Nucleosil C-18 column and methanol/20 mM aqueous phosphate buffer pH 3.8 in a 80/20 ratio.

Example 1: 3-Benzyloxy-estra-1,3,5(10)-trien-17-one (3-protected estrone, A is benzyl)

To a suspension of estrone (**II**; 100 g, 0.370 mol) and K_2CO_3 (160 g, 1.16 mol) in DCM/MeOH (800 ml, 1:1 v/v ratio) at room temperature (RT) was added benzyl bromide (132 ml, 1.10 mol) in one portion. The resulting mixture was refluxed for 16 h (50% conversion after 4 h according to TLC). The reaction mixture was cooled to RT and solids were filtered off. The filter-cake was washed with MeOH. The solution was concentrated (to a total volume of ca. 300 ml). The precipitate that had formed was collected by filtration and washed with heptanes to give a white solid. The filtrate was concentrated further (to a total volume of 100 ml) and triturated with heptane. The resulting precipitate was filtered off and combined with the first batch of product. The product (153 g, max 0.370 mol) still contained traces off benzyl bromide but was used without further purification. The product can be purified by recrystallization from DCM/MeOH (1/2).

TLC: R_f = 0.5 (heptanes/ethyl acetate = 4/1); HPLC-MS: 91%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.60-7.24 (m, 5H), 7.49 (d, 1H, J = 8.4 Hz), 6.87 (dd, 1H, J_1 = 2.6 Hz, J_2 = 8.4 Hz), 6.82 (d, 1H, J = 2.4 Hz), 5.12 (s, 2H), 3.05-2.90 (m, 2H), 2.66 – 2.01 (m, 5H), 1.77 – 1.47 (m, 8H), 0.99 (s, 3H) ppm.

Example 2: 3-Benzyloxy-17-trimethylsilyloxy-estra-1,3,5(10),16-tetraene(compound ***III****, A is benzyl, B is trimethylsilyl)*

3-Benzyloxy-estra-1,3,5(10)-trien-17-one (3-protected estrone, A is benzyl; 238 mg, 0.660 mmol) was dissolved in DCM (10 ml). Et_3N (0.166 ml, 1.188 mmol) and TMS-OTf (0.143 ml, 0.792 mmol) were added and the solution was stirred at ambient temperature for 1 h. According to TLC (alumina, heptane/ethyl acetate 4/1 plus Et_3N). The entire content of the flask was transferred onto a small column of basic alumina (type II) and eluted with heptane/ethyl acetate 4/1 plus Et_3N. The product was obtained as a white solid (248 mg, 87%).

Example 3: 3-Benzyloxy-estra-1,3,5(10),15-tetraen-17-one (compound ***IV****, A is benzyl)*

Unstabilised IBX (1.0 g; 3.6 mmol), a catalytic amount of trimethylamine-*N*-oxide (40 mg, 10 mol%) and 3A molecular sieves (100 mg) were added to 10 ml dry DMSO.

A fluorobenzene solution containing about 2.8 mmol crude (94 % GC) benzylestrone-trimethylsilyl enol ether **III** (4.5 ml; corresponding to 1.0 g ketone) was added, giving a sudden solidification of the reaction mixture due to precipitated substrate. Mild heating to 40-45°C was needed for dissolution. After 1h HPLC showed a clean conversion of the enol ether to the enone with some ketone present due to advantageous hydrolysis.

Example 4: 3-Benzyloxy-estra-1,3,5(10),15-tetraen-17-one (compound ***IV****, A is benzyl)*

Stabilised 2-iodoxybenzoic acid (SIBX, 0.5 g; 0.8 mmol oxidant) was dissolved in 4 ml anhydrous DMSO containing 0.8 mmol of amine-*N*-oxide cocatalyst. These mixtures were pre-incubated for 30 minutes at ambient temperature. To this solution was added a solution of benzylestrone-trimethylsilyl enol ether **III** (0.215 g; 0.5 mmol) in 1 ml anhydrous fluorobenzene. The solidified mixtures were heated slightly to 30 – 35°C to enable mixing. After 20-30 minutes the reaction mixtures became homogeneous. HPLC analysis by showed a clean conversion of the enol ether to the enone, with in some cases some ketone present due to hydrolysis. Results are summarized in Table 1.

Table 1: SIBX mediated dehydrogenation of TMS enol ether, in the presence of co-catalyst.

Entry	Co-catalyst	Time (h)	Conversion (%)	Enone selectivity (%)
1	4-Methoxypyridine-*N*-oxide	1	94	75
2	4-Methoxypyridine-*N*-oxide	3	> 99 [1]	80
3	Trimethylamine-N oxide [2]	1	100	68
4	Trimethylamine-N oxide [3]	1	100	63
5	4-Methoxypyridine-*N*-oxide [4]	1	> 99	72

[1] 19% ketone present due to hydrolysis.
[2] Anhydrous 4-methoxypyridine-*N*-oxide.
[3] 4-Methoxypyridine-*N*-oxide dihydrate.
[4] Anhydrous 4-Methoxypyridine-*N*-oxide.

*Example 5: 3-Benzyloxy-estra-1,3,5(10),15-tetraen-17-one (compound **IV**, A is benzyl)*

Stabilised 2-iodoxybenzoic acid (SIBX, 0.5 g; 0.8 mmol oxidant) was dissolved in 4 ml anhydrous dimethylformamide (DMF) containing 0.8 mmol of *N*-methylmorpholine-*N*-oxide cocatalyst. These mixtures were pre-incubated for 30 minutes at ambient temperature. To this solution was added solid benzylestrone-trimethylsilyl enol ether **III** (0.215 g; 0.5 mmol). The reaction mixture was agitated for 1 hour at ambient temperature and then further heated to 40°C. The total reaction time was 2 hours. Results are summarized in Table 2.

Table 2: SIBX mediated dehydrogenation of TMS enol ether in DMF.

Entry	Solvent	Time (h)	Conversion (%)	Enone selectivity (%)
1	dimethylformamide (DMF)	0.5	83	86
2	dimethylformamide (DMF)	1	99	86
3	dimethylformamide (DMF)	2	> 99 [1]	85

[1] 14% hydrolysis.

*Example 6: 3-Benzyloxy-estra-1,3,5(10),15-tetraen-17-one (compound **IV**, A is benzyl)*

An 8 ml vial equipped with a stirring bar was charged under air with compound **III** (A is benzyl, B is trimethylsilyl; 50 mg, 0.116 mmol), palladium acetate (2.6 mg, 0.116 mmol) and DMSO (dry, 0.9 ml), chloroform (0.1 ml). The vial was purged with pure oxygen gas and kept under an oxygen atmosphere with a balloon. The mixture was stirred at 35°C overnight. Complete conversion was obtained according to TLC (Si, *n*-heptane/ethyl acetate 4/1). Clean conversion into the desired product was obtained according to HPLC.

An 8 ml vial equipped with a stirring bar was charged under air with compound **III** (A is benzyl, B is trimethylsilyl; 100 mg, 0.231 mmol), palladium acetate (5.19 mg, 0.023 mmol) and DMSO (dry, 0.9 ml), DCM (0.1 ml). The vial was purged with pure oxygen gas and kept under an oxygen atmosphere with a balloon. The mixture was stirred at 35°C overnight. Complete conversion was obtained according to TLC (Si, *n*-heptane/ethyl acetate 4/1). Clean conversion into the desired product **IV** was obtained according to HPLC.

*Example 7: 3-Benzyloxy-estra-1,3,5(10),15-tetraen-17-one (compound **IV**, A is benzyl)*

Benzylestrone-trimethylsilyl enol ether **III** (0.20/0.215 g; 0.5 mmol) and allyl methyl carbonate (0.115 ml; 1.0 mmol) were mixed with 4.5 ml anhydrous acetonitrile. Palladium acetate stock solution (0.25 ml; 5 µmol; 1 mol%) in acetonitrile was added and the mixture was stirred in an argon atmosphere at 75°C. HPLC analysis after 67 hours showed a complete conversion of the enol ether with a 51% selectivity for the enone **IV**.

Example 8: 3-Benzyloxy-estra-1,3,5(10),15-tetraen-17-ol (compound V, A is benzyl)

To a solution of 3-benzyl-dehydroestrone (compound **IV**; A = benzyl; 58 g, 162 mmol) in a mixture of MeOH (900 ml) and THF (200 ml) at room temperature was added $CeCl_3$ heptahydrate (66.4 g, 178 mmol). After stirring for 1 h the mixture was cooled to 0 – 5°C using an ice/water bath. Then $NaBH_4$ (12.2 g, 324 mmol) was added in small portions maintaining a temperature below 8°C. After stirring for 2 h at 0 – 5°C (TLC showed the reaction to be complete) 1 N NaOH (300 ml) and DCM (1 l) were added and the mixture was stirred for ½ h at room temperature. The layers were separated and the aqueous layer was extracted with DCM (200 ml). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo* to give an off-white solid (55.0 g, 152.8 mmol, 94%).

TLC: R_f = 0.25 (heptanes/ethyl acetate = 4:1); HPLC-MS: 93% β-isomer, 2% α-isomer; DSC: Mp. 149.7°C, purity 96.6%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.48 (m, 5H), 7.27 (d, 1H, J = 8.4 Hz), 6.85 (dd, 1H, J_1 = 2.8 Hz, J_2 = 8.6 Hz), 6.81 (d, 1H, J = 2.4 Hz), 6.10 (d, 1H, J = 5.8 Hz), 5.79 (dd, 1H, J_1 = 1.8 Hz, J_2 = 3.4 Hz), 5.11 (s, 2H), 4.48 (d, 1H, J = 7.6), 2.96 (m, 2H), 2.46 – 1.64 (m, 9H), 0.93 (s, 3H) ppm.

Example 9: 17-Acetyloxy-3-benzyloxy-estra-1,3,5(10),15-tetraene (compound VI, A is benzyl, C is acetyl)

A solution of 3-benzyloxy-estra-1,3,5(10),15-tetraen-17-ol (compound V; A = benzyl; 55.0 g, max. 153 mmol) in pyridine (400 ml) was treated with Ac_2O (50 ml, 0.53 mol) and 4-dimethylaminopyridine (1.5 g, 12.3 mmol). The mixture was stirred for 2 h at room temperature (TLC showed the reaction to be complete). It was concentrated *in vacuo*. The residue was dissolved in EtOAc (400 ml), washed with water (200 ml) and brine (150 ml), dried (Na_2SO_4) and concentrated *in vacuo* to yield a yellow solid (54.0 g, 49.8 mmol, 88%). The product was purified by recrystallization from heptanes/EtOAc/EtOH (1:0.5:1) to afford a white solid (45.0 g, 112 mmol, 73%).

TLC: R_f = 0.6 (heptanes/ethyl acetate = 4/1); HPLC-MS: 98% β-isomer, 1% α-isomer, 1.3% ß-estradiol; DSC: Mp. 122.8°C, purity 99.8%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.44 (m, 5H), 7.27 (d, 1H, J = 8.4 Hz), 6.86 (dd, 1H, J_1 = 2.6 Hz, J_2 = 8.4 Hz), 6.80 (d, 1H, J = 2.6 Hz), 6.17 (d, 1H, J = 5.8 Hz), 5.78 (dd, 1H, J_1 = 1.4 Hz, J_2 =

3.2 Hz), 5.45 (m, 1H), 5.11 (s, 2H), 2.96 (m, 2H), 2.40 – 1.54 (m, 10H), 2.18 (s, 3H), 0.93 (s, 3H) ppm.

Example 10: 17-Acetyl-3-benzyl estetrol (compound VII, A is benzyl, C is acetyl)

OsO_4 on PVP (9 g, ~5% w/w OsO_4 on PVP, prepared according to Cainelli *et al.* *Synthesis* 1989, 45 - 47 was added to a solution of 17-acetyloxy-3-benzyloxy-estra-1,3,5(10),15-tetraene (compound VI; A = benzyl, C = acetyl; 45 g, 112 mmol) in THF (450 mL) and the mixture was heated to 50°C. Trimethylamine-N-oxide dihydrate (24.9 g, 224 mmol) was added portion-wise over 2 h. After stirring for 36 h at 50°C (TLC showed the reaction to be complete) the reaction mixture was cooled to room temperature. The solids were filtered off, washed with THF (100 ml) and the filtrate was concentrated. The residue was taken up in EtOAc (250 ml) and water (250 ml) was added. The aqueous layer was acidified with 1 N HCl (ca. 10 ml). The layers were separated and the aqueous layer was extracted with EtOAc (150 ml). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was triturated with heptanes/EtOAc (1:1, 100 ml), stirred for 2 h and the resulting white precipitate was filtered off to give the product as a white solid (41 g, 94 mmol, 84%). The product was purified by recrystallization from heptanes/ ethyl acetate/ EtOH (2:1:1) three times to afford a white solid (21 g, 48.2 mmol, 43%).

HPLC-MS: 99.5% βαα-isomer; DSC: Mp. 159.3°C, purity 98.7%; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.49 (m, 5H), 7.27 (d, 1H, J = 8.4 Hz), 6.84 (dd, 1H, J_1 = 2.6 Hz, J_2 = 8.4 Hz), 6.81 (d, 1H, J = 2.4 Hz), 5.11 (s, 2H), 4.45 (d, 1H, J = 4.4), 4.11 (m, 3H), 3.12 (m, 1H) 2.95 (m, 2H), 2.46 – 1.64 (m, 10H), 2.24 (s, 3H), 0.93 (s, 3H) ppm.

Example 11: 17-Acetyl estetrol (compound VIII; C is acetyl)

To a solution of 17-acetyl-3-benzyl estetrol (compound **VII**; A = benzyl, C = acetyl; 21 g, 48.2 mmol) in MeOH (600 ml, HPLC-grade) was added a preformed suspension of 10% Palladium on activated carbon (2 g) in methanol (50 ml). The mixture was placed under an atmosphere of H_2 at 1 atm and stirred for 24 h (TLC showed the reaction to be completed) at room temperature. It was filtered over Celite® and the filter cake was washed with MeOH (200 ml). The filtrate was concentrated *in vacuo* to give 17-acetyl estetrol as a white solid (15 g, 43.4 mmol, 90%).

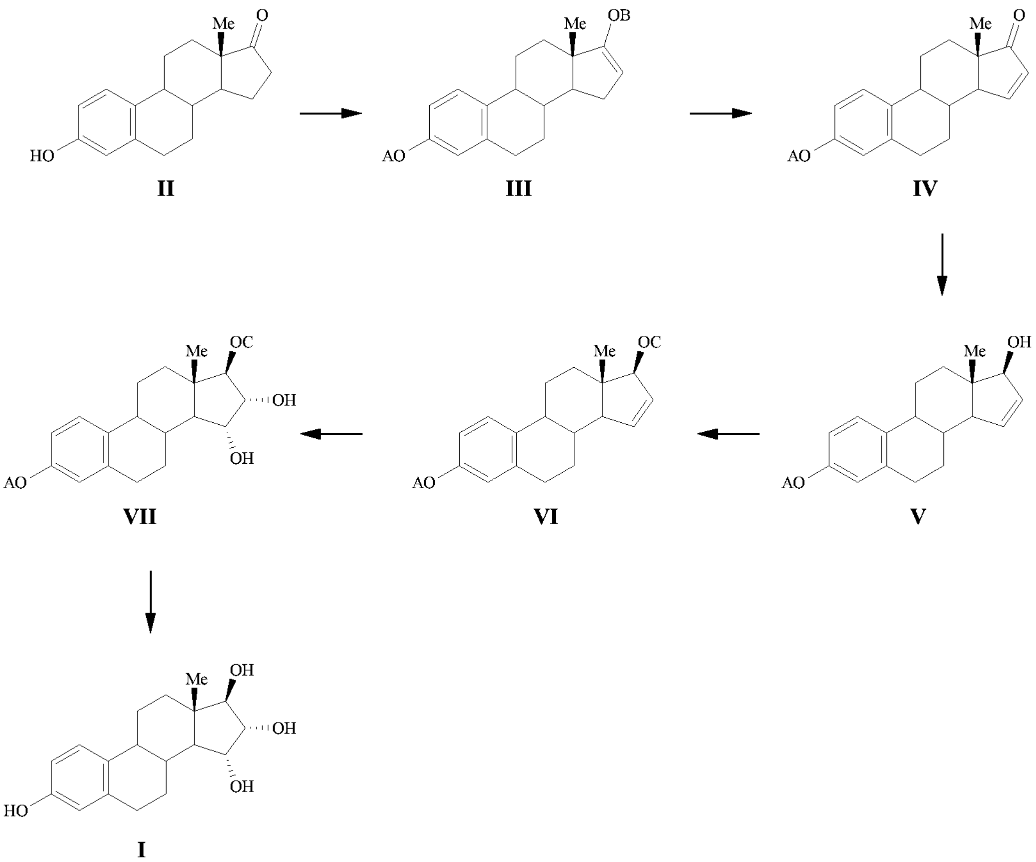
TLC: R_f = 0.2 (heptanes/ethyl acetate = 1/1); HPLC-MS: 99.2%, DSC: Mp. 212.2°C, purity 98.9%; ^{1}H-NMR (200 MHz, CD_3OD) δ 7.14 (d, 1H, J = 8.0 Hz), 6.60 (dd, 1H, J_1 = 2.6 Hz, J_2 = 8.8 Hz), 6.56 (d, 1H, J = 2.4 Hz), 4.81 (dd, 1H, J_1 = 3.4 Hz, J_2 = 6.4 Hz), 4.07 (m, 3H), 3.12 (m, 1H), 2.85 (m, 2H), 2.37 – 1.37 (m, 10H), 2.18 (s, 3H), 0.91 (s, 3H) ppm.

Example 12: Estetrol

17-Acetyl-estetrol (compound **VIII**; C = acetyl; 15 g, 43.4 mmol) and K_2CO_3 (6 g, 43.4 mmol) were suspended in MeOH (500 ml, HPLC-grade) and stirred for 4 h at room temperature (TLC showed the reaction to be complete). The solvents were evaporated *in vacuo*. Water (200 ml) and $CHCl_3$ (70 ml) were added and the mixture was stirred and neutralized with 0.1 N HCl (50 ml). The product was collected by filtration, washed with water (100 ml) and $CHCl_3$ (100 ml) to give estetrol as a white solid (12.2 g, 40.1 mmol, 92.5%) after drying at 40°C in an air-ventilated oven. TLC: R_f = 0.05 (heptanes/ethyl acetate = 1/1); HPLC-MS: 99.1%, DSC: Mp. 243.7°C, purity 99.5%; ^{1}H-NMR (200 MHz, CD_3OD) δ 7.14 (d, 1H, J = 8.6 Hz), 6.61 (dd, 1H, J_1 = 2.6 Hz, J_2 = 8.4 Hz), 6.56 (d, 1H, J = 2.4 Hz), 4.83 (m, 1H), 3.93 (m, 3H), 3.50 (d, 1H, J = 5.2), 3.38 (m, 2H), 2.84 (m, 2H), 2.32 (m, 3H), 1.97 (m, 1H), 1.68 – 1.24 (m, 5H), 0.86 (s, 3H) ppm.

Claims

1. A process for the preparation of estra-1,3,5(10)-trien-3,15α,16α,17β-tetraol **I** which comprises the steps of:



(1) conversion of estrone **II** into 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III**, wherein A is a protecting group and B is $-Si(R^2)_3$;

(2) conversion of 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III** into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV**, wherein A is a protecting group;

(3) reduction of the 17-keto group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV** to form 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol **V**, wherein A is a protecting group;

(4) protection of the 17-OH group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol **V** to form 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene **VI**, wherein A and C are protecting groups;

(5) oxidation of the carbon-carbon double bond of ring D of 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene **VI** to form protected estetrol **VII**, wherein A and C are protecting groups; and

(6) removal of protecting groups A and C to form estetrol **I**;

wherein:

A is a protecting group selected from the group consisting of a C_1-C_5 alkyl group, a $C_7 – C_{12}$ benzylic group and a $–Si(R^1)_3$ group, wherein R^1 is independently selected from the group consisting of a $C_1 – C_6$ alkyl group and a $C_6 – C_{12}$ aryl group ;

B is $–Si(R^2)_3$, wherein R^2 is independently selected from the group consisting of a $C_1 – C_6$ alkyl group and a $C_6 – C_{12}$ aryl group; and

C is a protecting group selected from the group consisting of monofunctional protecting groups that are suitable for the protection of an aliphatic hydroxyl group.

2. The process according to claim 1, wherein step (2) of the process is performed in the presence of an iodine(V) species, and wherein the iodine(V) species is present in an amount of 0.1 mol% or more with respect to compound **III**.

3. The process according to claim 2, wherein the iodine(V) species comprises 2-iodoxybenzoic acid (IBX), stabilised 2-iodoxybenzoic acid (SIBX), 2-iodoxybenzenesulphonic acid (IBS), and/or a derivative thereof.

4. The process according to claim 2 or claim 3, wherein the iodine(V) species comprises a species formed by complexation of IBX, IBS and/or a derivative thereof with a ligand, in particular with DMSO or with an N-oxide.

5. The process according to any one of claims 2 – 4, wherein the iodine(V) species comprises 2-iodoxybenzenesulphonic acid (IBS) and/or a derivative thereof, and wherein the IBS and/or derivative thereof is present in an amount of 0.1 mol% to 50 mol% with respect to compound **III**.

6. The process according to any one of claims 2 – 5, wherein the solvent in step (2) is selected from the group consisting of DMSO, DMF, DMA, NMP, a combination

thereof, and a combination of DMSO, DMF, DMA and/or NMP with one or more organic solvents.

7. The process according to claim 1, wherein step (2) of the process is performed in the presence of a transition metal compound, and wherein the transition metal compound is present in an amount of 0.1 mol% or more with respect to compound **III**.

8. The process according to claim 7, wherein the transition metal compound is a palladium compound.

9. The process according to claim 7 or claim 8, wherein the transition metal compound comprises palladium(II) acetate ($Pd(OAc)_2$).

10. The process according to any one of claims 7 – 9, wherein the transition metal compound is present in an amount of 0.1 mol% to 50 mol% with respect to compound **III**.

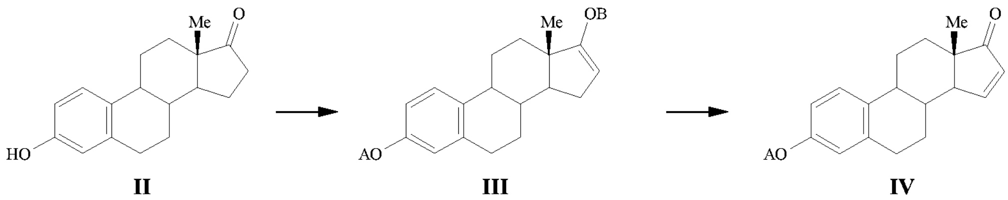
11. The process according to any one of claims 7 – 10, wherein an oxidant is further present.

12. The process according to claim 11, wherein the oxidant is molecular oxygen (O_2), allyl methyl carbonate and/or copper(II) acetate.

13. The process according to any one of the preceding claims, wherein the solvent in step (2) is selected from the group consisting of DMSO, or a combination of DMSO with one or more organic solvents.

14. The process according to any one of the preceding claims, wherein B is a trimethylsilyl or a triethylsilyl group.

15. Process for the synthesis of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV**, wherein A is a protecting group, which comprises the steps of:



(1) conversion of estrone **II** into 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III**, wherein A is a protecting group and B is $-Si(R^2)_3$; and

(2) conversion of 17-B-oxy-3-A-oxy-estra-1,3,5(10),16-tetraene **III** into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one **IV**, wherein A is a protecting group, wherein said conversion of **III** into **IV** is performed in the presence of an iodine(V) species, and wherein the iodine(V) species is present in an amount of 0.1 mol% or more with respect to compound **III**;

wherein:

A is a protecting group selected from the group consisting of a C_1-C_5 alkyl group, a $C_7 - C_{12}$ benzylic group and a $-Si(R^1)_3$ group, wherein R^1 is independently selected from the group consisting of a $C_1 - C_6$ alkyl group and a $C_6 - C_{12}$ aryl group; and

B is $-Si(R^2)_3$, wherein R^2 is independently selected from the group consisting of a $C_1 - C_6$ alkyl group and a $C_6 - C_{12}$ aryl group.

16. The process according to claim 15, wherein the iodine(V) species comprises 2-iodoxybenzoic acid (IBX), 2-iodoxybenzenesulphonic acid (IBS), stabilised 2-iodoxybenzoic acid (SIBX), and/or a derivative thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2012/050514

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07J75/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LI ET AL.: STEROIDS, vol. 75, 2010, pages 859-869, XP002659962, cited in the application Scheme 8; page 865 -----	1-16
Y	WO 2004/041839 A2 (PANTARHEI BIOSCIENCE BV [NL]; VERHAAR MARK THEODOOR [NL]; KOCH THOMAS) 21 May 2004 (2004-05-21) cited in the application the whole document -----	1-14

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 October 2012	10/10/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Tabanella, Stefania

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INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2012/050514

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NICOLAOU, K.C. ET AL.: ANGEWANDTE CHEMIE, vol. 114, no. 6, 2002, pages 1038-1042, XP002659963, cited in the application Entry 9; table 1	15,16

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/NL2012/050514

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