B-RING ESTRATRIENE DIOL SULPHATES

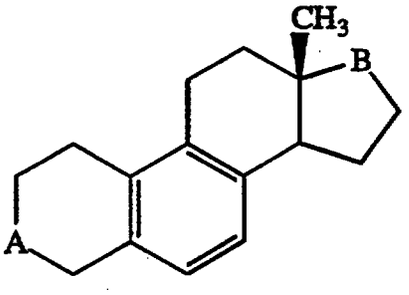
BACKGROUND OF THE INVENTION

The use of naturally occurring estrogenic compositions of substantial purity and low toxicity such as PREMARIN (conjugated equine estrogens) has become a preferred medical treatment for alleviating the symptoms of menopausal syndrome, osteoporosis/osteopenia in estrogen deficient women and in other hormone related disorders. The estrogenic components of the naturally occurring estrogenic compositions have been generally identified as sulfate esters of estrone, equilin, equilenin, 17-β-estradiol, dihydroequilenin and 17-β-dihydroequilenin (U.S. Patent 2,834,712). The estrogenic compositions are usually buffered or stabilized with alkali metal salts of organic or inorganic acids at a substantially neutral pH of about 6.5 to 7.5. Urea has also been used as a stabilizer (U.S. 3,608,077). The incorporation of antioxidants to stabilize synthetic conjugated estrogens and the failure of pH control with tris(hydroxymethyl)aminomethane (TRIS) to prevent hydrolysis is discussed in U.S. 4,154,820.

One of the compounds described herein, 5,7,9-estratriene-3β,17β-diol 3-sulfate ester sodium salt is a minor component of PREMARIN (conjugated equine estrogens).

DESCRIPTION OF THE INVENTION

In accordance with this invention, there are provided estrogenic agents having the formula I



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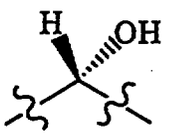
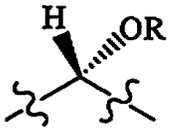
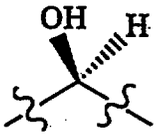
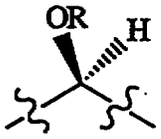
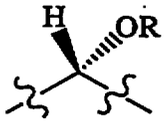
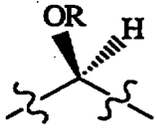
A and B are each, independently,  ,  ,

 , or  :

R is $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium containing 1-6 carbon atoms in each alkyl group;

with the proviso that at least one of A or B is  or  .

Alkali metal salts include sodium and potassium salts, particularly preferred are sodium salts. Alkaline earth metal salts include calcium and magnesium salts. Suitable alkyl groups include methyl, ethyl, propyl, butyl, pentyl and hexyl, preferred alkyl groups being methyl and ethyl. Where more than one alkyl group is present the groups may be the same or different. Preferred trialkylammonium salts are trimethyl-ammonium salts and triethylammonium salts.

The salts of the invention are preferably in greater than 1 percent purity.

As 5,7,9-estratriene-3β,17β-diol 3-sulfate ester sodium salt is a minor component of PREMARIN (conjugated equine estrogens), this invention also provides 5,7,9-estratriene-3β,17β-diol 3-sulfate ester sodium salt in greater than one percent purity; and a compound consisting essentially of 5,7,9-estratriene-3β,17β-diol 3-sulfate ester sodium salt.

This invention further provides a composition of matter consisting essentially of a compound having the formula

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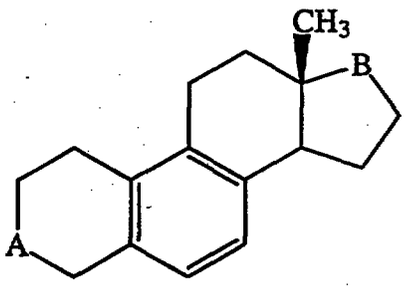

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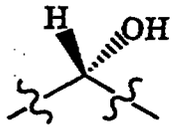
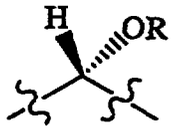
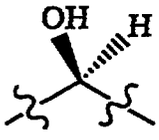
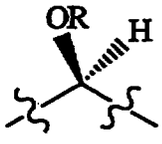
A and B are each, independently,  ,  ,

 , or  :

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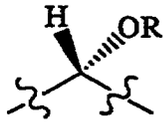
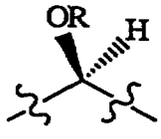
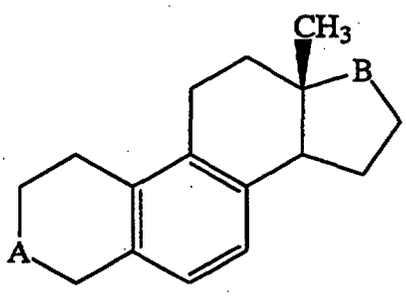
with the proviso that at least one of A or B is  or  .

This invention additionally provides a method of providing estrogen therapy to a mammal in need thereof, which comprises administering an effective amount of a compound having the formula



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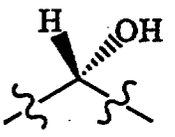
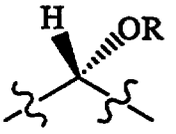
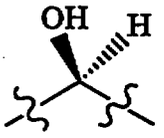
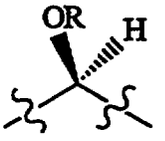
A and B are each, independently,  ,  ,

 , or  :

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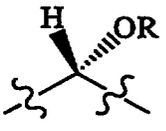
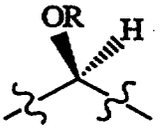
with the proviso that at least one of A or B is  or 

to said mammal.

As used in accordance with this invention, treating covers treatment of an existing condition, ameliorating the condition, or providing palliation of the condition and inhibiting includes inhibiting or preventing the progress or development of the condition.

The present invention further provides compositions comprising a compound of formula I. In particular it provides compositions comprising at least 1% of a compound of formula I. One aspect of the present invention provides compositions wherein the only estrogenic agent is a compound of formula I. Embodiments of the present invention include compositions wherein the only active compound is a compound of formula I. In these embodiments other excipients and carriers may be included but no further active materials are included.

The present invention also provides processes for the preparation of the compounds described above. It provides processes for the preparation of 5,7,9-

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estratriene-3,17-diol-3,17-disulfate ester salts (i.e. compounds wherein A and B are each independently a sulphate ester salt) which comprise:

a) converting the appropriate 5,7,9-estratriene-3,17-diol-3,17-disulfate ester to a pharmaceutically acceptable salt,

b) converting a pharmaceutically acceptable salt of the 5,7,9-estratriene-3,17-diol-3,17-disulfate ester to a different pharmaceutically acceptable salt of the appropriate 5,7,9-estratriene-3,17-diol-3,17-disulfate ester or

c) directly converting the appropriate 5,7,9-estratriene-3,17-diol to the desired pharmaceutically acceptable salt of 5,7,9-estratriene-3,17-disulfate ester.

5,7,9-estratriene-3,17-diol-3,17-disulfate esters may be converted to pharmaceutically acceptable salts by neutralising the acid with an appropriate base, e.g. with an alkali metal carbonate, an alkaline earth metal carbonate or a primary, secondary, tertiary or quaternary amine carbonate. Alkali metal or alkaline earth metal salts may be prepared by using the appropriate alkali metal hydride e.g. sodium hydride, potassium hydride or lithium hydride.

A pharmaceutically acceptable salt of the appropriate 5,7,9-estratriene-3,17-diol-3,17-disulfate ester may be converted to a different pharmaceutically acceptable salt by displacement, by using an ion exchange resin or by double decomposition (metastasis). Displacement of a weak base with a stronger one may be utilised to convert, e.g. an amine salt to an alkali metal salt or an alkaline earth metal salt using an appropriate base, e.g. a hydroxide. For example a trialkylamine salt such as a triethylamine salt may be converted to an alkali metal salt such as a sodium salt by treating it with an alkali metal hydroxide such as aqueous sodium hydroxide. The displacement may be carried out using an ion exchange resin. Alternatively one salt may be converted to another by double decomposition, e.g. an alkaline earth metal salt such as the calcium salt may be replaced with an alkali metal salt. E.g. the calcium salt of the 5,7,9-estratriene-3,17-diol-3,17-disulfate ester may be dissolved in water followed by the addition of e.g. sodium carbonate. Insoluble calcium carbonate would then precipitate out to provide the sodium salt of the desired 5,7,9-estratriene-3,17-diol-3,17-disulfate ester.

A pharmaceutically acceptable salt of the desired 5,7,9-estratriene-3,17-diol-3,17-disulfate ester may be prepared by directly converting the appropriate 5,7,9-estratriene-3,17-diol. This may be performed by reacting it with the appropriate aminesulfurtrioxide complex, e.g. by reacting it with a trialkylaminesulfurtrioxide (such as triethylaminesulfurtrioxide complex) to provide the corresponding trialkylamine salt (such as the triethylamine salt). If desired the salt may then be converted to another salt of the invention as described above.

The invention also provides processes for the preparation of 5,7,9-estratriene-3,17-diol-3-sulfate ester salts or 5,7,9-estratriene-3,17-diol-17-sulfate ester salts (i.e. compounds wherein one of A and B is a sulphate ester salt and the other is hydrogen) which comprise:

a) converting the appropriate 5,7,9-estratriene-3,17-diol-mono sulfate ester to a pharmaceutically acceptable salt,

b) converting a pharmaceutically acceptable salt of the appropriate 5,7,9-estratriene-3,17-diol-mono sulfate ester to a different pharmaceutically acceptable salt of the 5,7,9-estratriene-3,17-diol-mono sulfate ester,

c) converting the corresponding 5,7,9-estratriene-3-ol,17-keto 3 sulfate ester salt or 5,7,9-estratriene-17-ol,3-keto 17 sulfate ester salt to the desired 5,7,9-estratriene-3,17-diol-3-sulfate ester salt or 5,7,9-estratriene-3,17-diol-17-sulfate ester salt

d) converting 5,7,9-estratriene-3,17-diol to the desired pharmaceutically acceptable salt of the desired 5,7,9-estratriene-3,17-diol-monosulfate ester,

e) deprotecting the corresponding 17 protected 5,7,9-estratriene-3,17-diol-3-sulfate ester salt or 3 protected 5,7,9-estratriene-3,17-diol-17-sulfate ester salt or

f) converting one stereo isomer of the pharmaceutically acceptable salt of the appropriate 5,7,9-estratriene-3,17-diol-mono sulfate ester to another by inversion.

The conversion of the appropriate 5,7,9-estratriene-3,17-diol-mono sulfate ester to a pharmaceutically acceptable salt and the conversion of a pharmaceutically acceptable salt of the appropriate 5,7,9-estratriene-3,17-diol-mono sulfate ester to a

different pharmaceutically acceptable salt of the 5,7,9-estratriene-3,17-diol-mono sulfate ester may be performed by analogy to the methods described above.

5,7,9-estratriene-3-ol,17-keto mono sulfate ester salt may be converted to the desired 5,7,9-estratriene-3,17-diol-mono-sulfate ester salt by reduction with a suitable reducing agent, e.g. $LiBH_4$. The steric influence of the nearby methyl will cause some reducing agents to preferentially provide the 17β compounds. These can be converted to the corresponding α compounds by inversion, e.g. by a MITSUNOBU inversion.

5,7,9-estratriene-3,17-diol may be converted directly to the desired pharmaceutically acceptable salt of the desired 5,7,9-estratriene-3,17-diol-monosulfate ester by analogy to the methods described above.

In order to prepare the desired 5,7,9-estratriene-3-ol,17-keto mono sulfate ester salt it may be necessary to protect the second hydroxy group. This may be achieved by conventional means using a suitable protecting group which will finally be removed to provide the product.

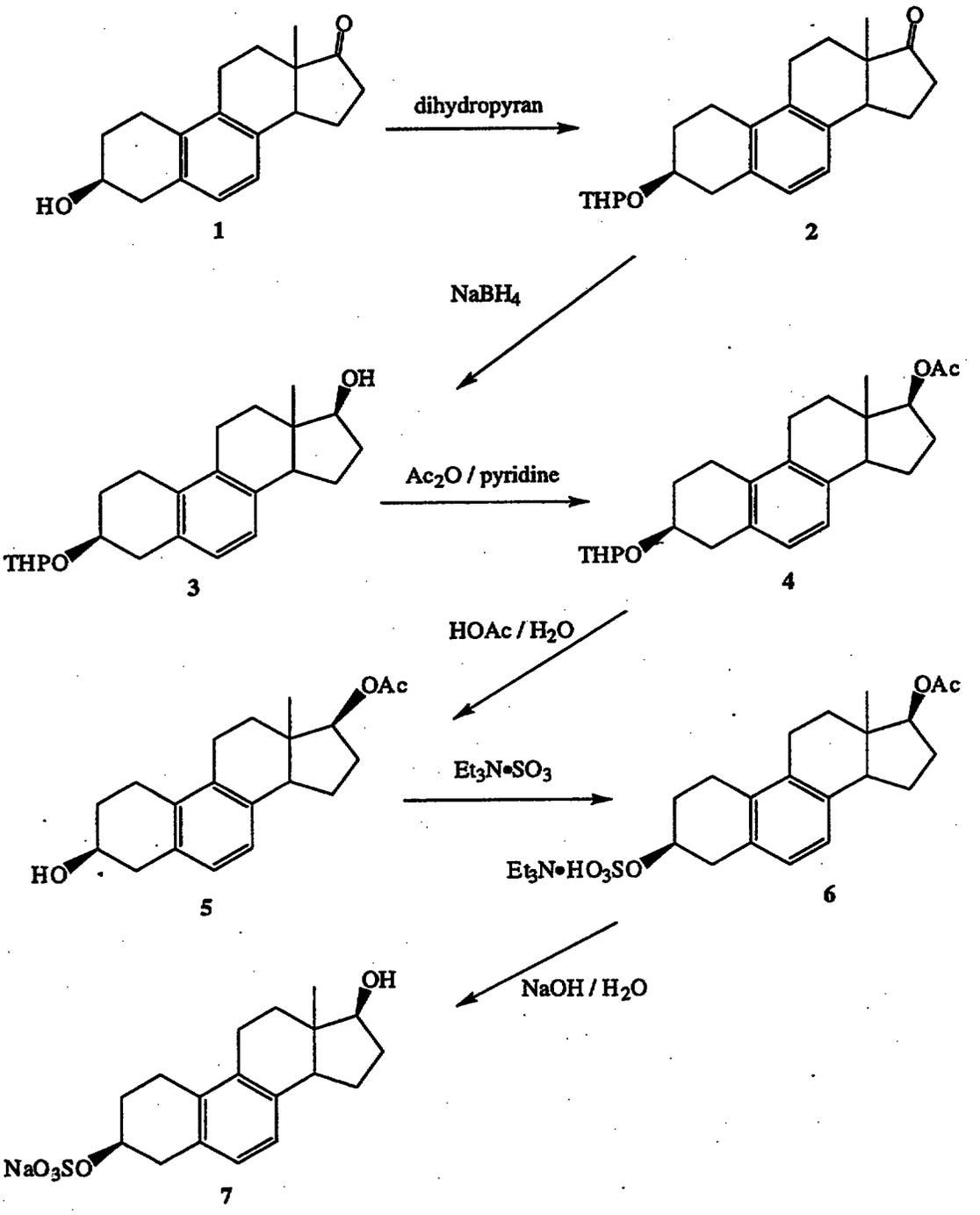
In order to protect the less reactive 17 hydroxy group it may be necessary to first protect the 3 hydroxy group. For example the 3 hydroxy group may be protected with a first protecting group and then the 17 hydroxy with a second protecting group. The 3 hydroxy group may then be converted to the desired sulphate salt. The first protecting group may be removed before this conversion or at the same time by utilising a reagent which will replace the first protecting group with the sulphate group. The second protecting group may then be removed to provide the desired product. Alternatively the second protecting group may be removed at the same time the 3 hydroxy is converted to the sulphate salt.

The present invention also provides compounds of formula I prepared by a chemical process, particularly those prepared according to the processes described above. The invention also provides compounds of formula I obtainable by such processes.

The compounds of this invention can be prepared from readily available starting materials. The following schemes show the preparation of representative compounds of this invention. For example, 5,7,9-estratriene-3β,17β-diol 3-sulfate ester sodium

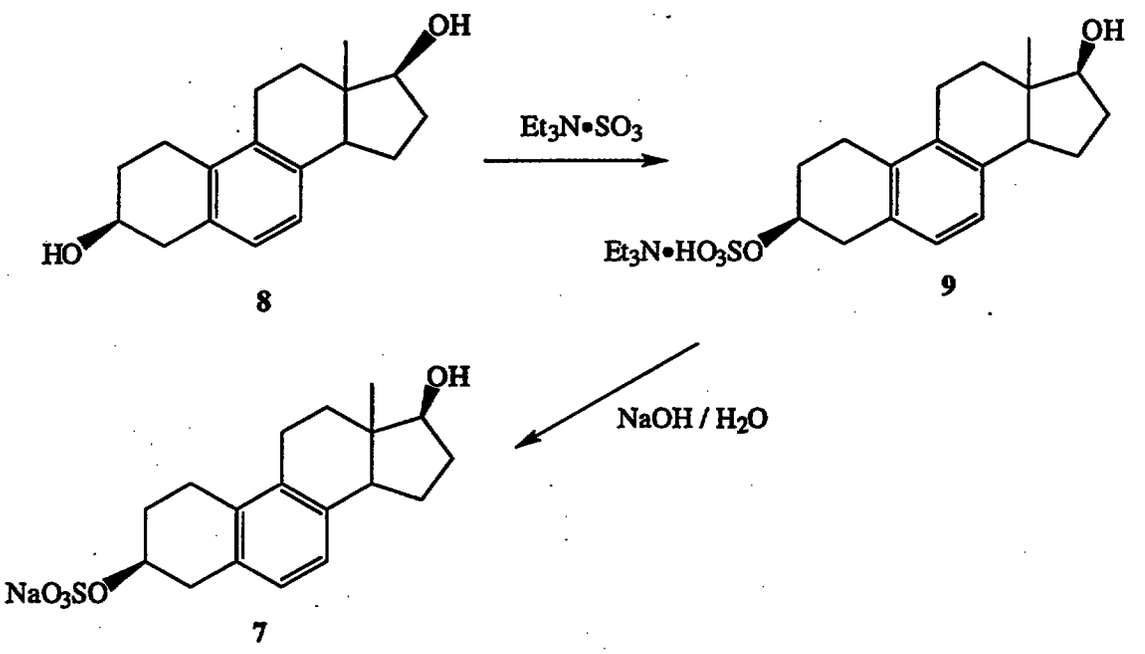
salt (7) can be prepared from 3β-hydroxy-5,7,9-estratriene-17-one according to Scheme I. 3β-Hydroxy-5,7,9-estratriene-17-one can be prepared according to D. Banerjee in Ind. Chim. Belge. Suppl. 2: 435 (1959).

Scheme I



5,7,9-Estratriene-3β,17β-diol 3-sulfate ester sodium salt (**7**) can also be prepared by the selective sulfation of diol (**8**) as shown in Scheme II. Diol (**8**) can be prepared from (**1**) by the reduction of the 17-ketone with a reducing agent such as sodium borohydride.

Scheme II



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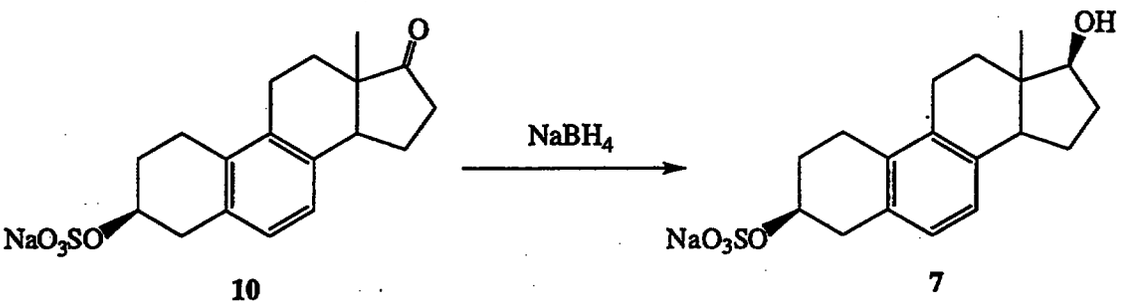
5,7,9-Estratriene-3β,17β-diol 3-sulfate ester sodium salt (**7**) can also be prepared according to Scheme III by the reduction of 3β-hydroxy-5,7,9-estratriene-17-one 3-sulfate ester sodium salt (**10**) with a reducing agent such as sodium borohydride.

Scheme III



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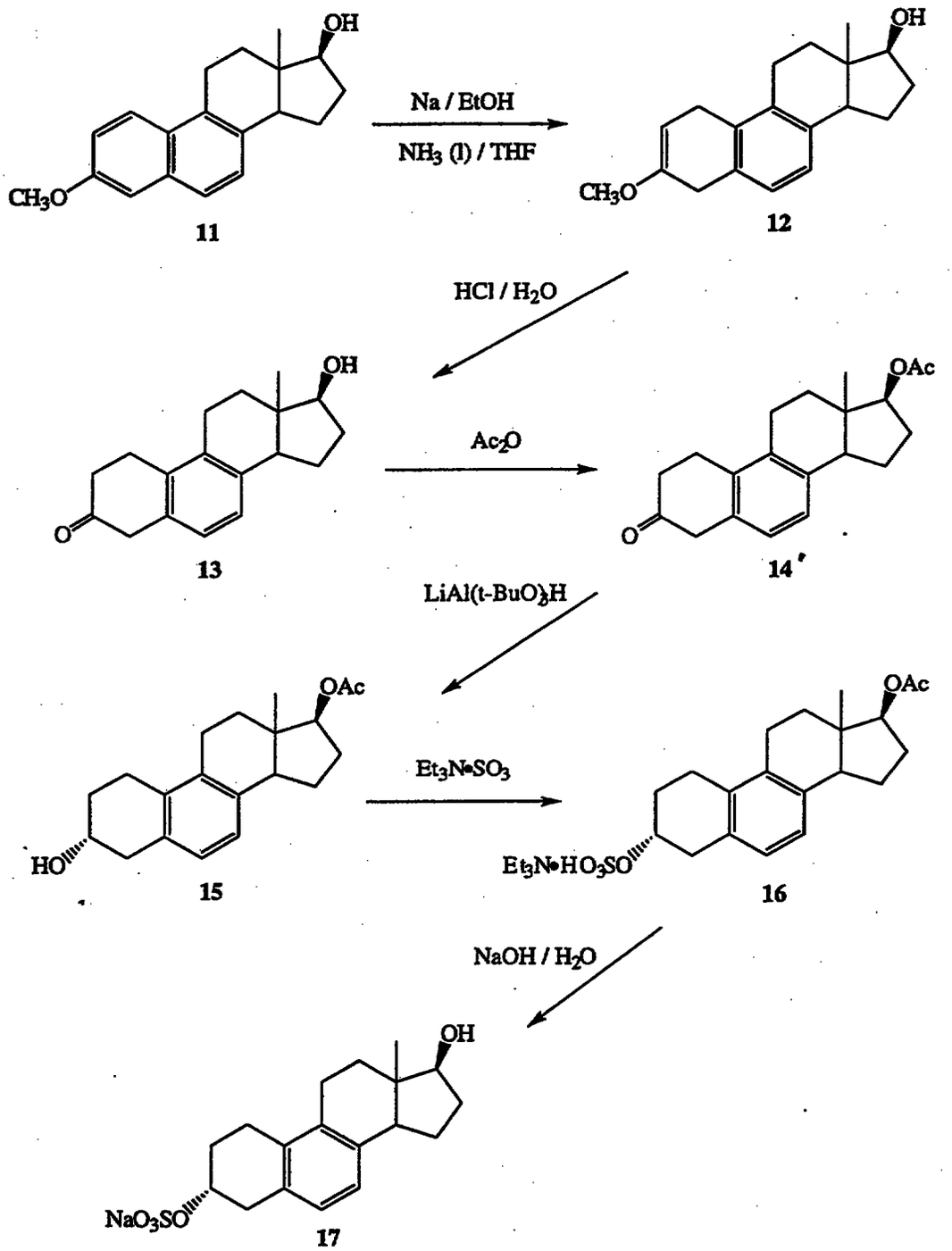
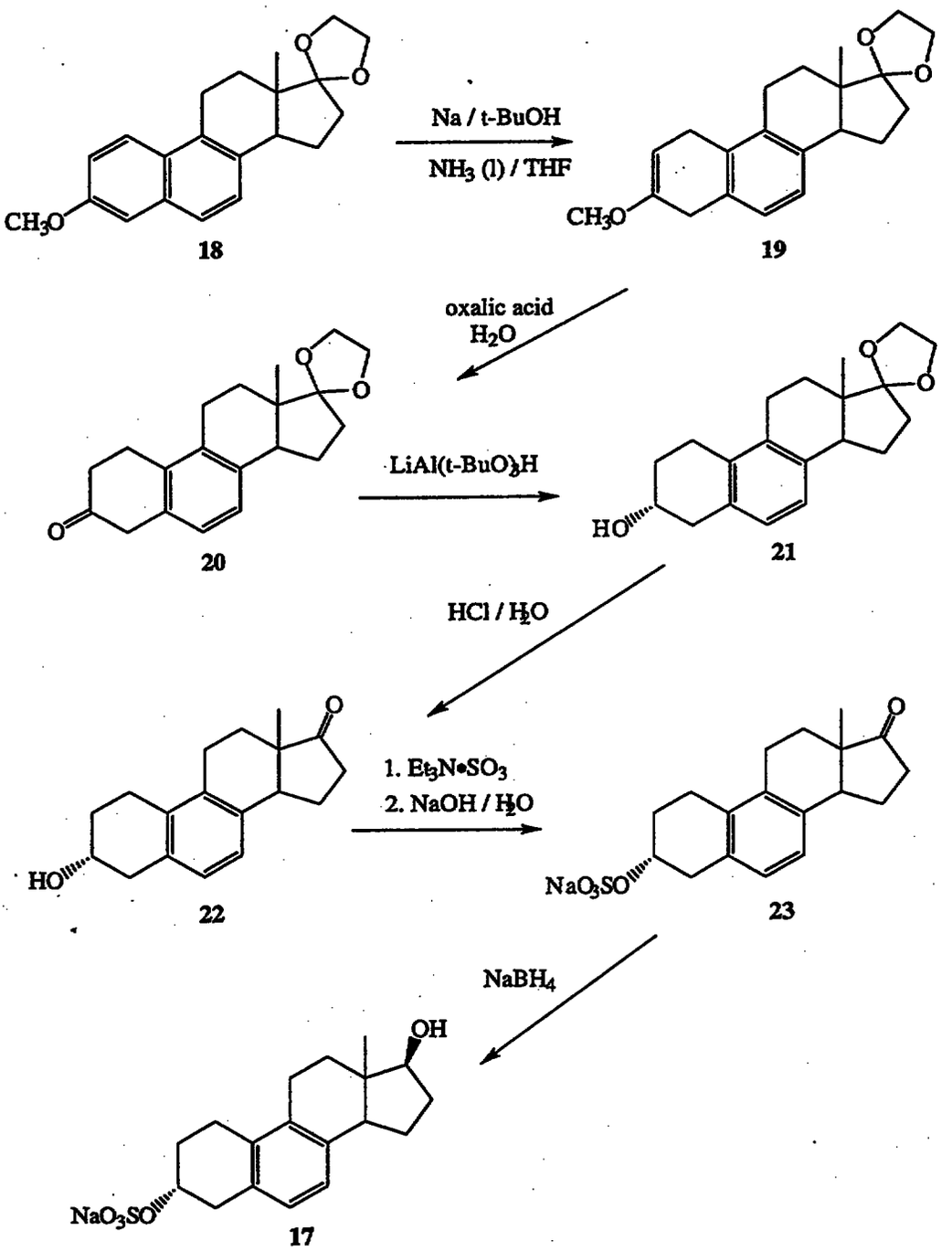
5,7,9-Estratriene-3α,17β-diol 3-sulfate ester sodium salt (**17**) can be prepared according to Scheme IV according to standard literature procedures. The introduction of the 3α-hdyroxyl group can be accomplished by the reduction of the 3-ketone (**14**) with a bulky reducing agent such as lithium tri-t-butoxy aluminumhydride.

Scheme IV



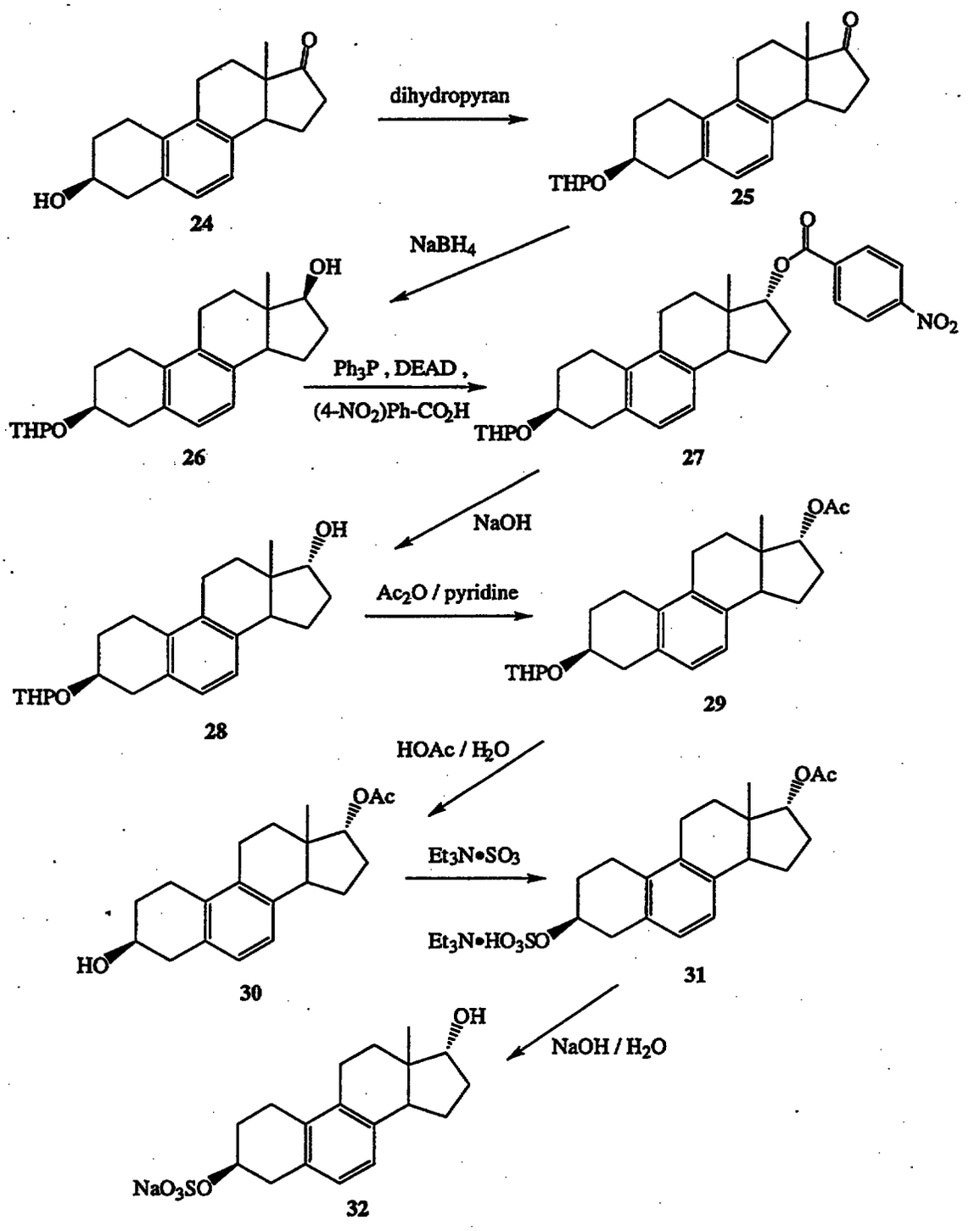
5,7,9-Estratriene-3α,17β-diol 3-sulfate ester sodium salt (**17**) can also be prepared according to Scheme V according to standard literature procedures.

Scheme V



The preparation of 5,7,9-Estratriene-3β,17α-diol 3-sulfate ester sodium salt (32) can be prepared by standard methodology as shown in Scheme VI.

Scheme VI



Compounds of this invention having the 3α,17α-configuration can be prepared by stereochemical inversion of the 3β-alcohol. For example, the 3β-hydroxyl group of compound (**30**) can be treated under the conditions used to effect the transformation from (**26**) to (**27**) to provide 3α,17α-stereochemistry. Sulfation hydroxyl groups at the 17-position for compounds of this invention can be accomplished via a protected 3-hydroxyl group or 3-ketone.

The compounds of this invention are estrogenic, as shown in the in vitro and in vivo standard pharmacological test procedures described below in which 5,7,9-estratriene-3β,17β-diol was evaluated as a representative compound of this invention.

Estrogen Receptor Binding

An initial evaluation examined the competitive binding properties of 5,7,9-estratriene-3β,17β-diol to the human estrogen receptor (hER-α) prepared as a soluble cell extract (cytosol). In this standard pharmacological test procedure, 5,7,9-estratriene-3β,17β-diol demonstrated no specific binding activity. However, when estrogen receptor binding was analyzed using a whole cell test procedure, specific binding was clearly demonstrated. This test procedure indicated an IC_{50} of 2.3×10^{-8} M for 5,7,9-estratriene-3β,17β-diol. This would be compared with a K_i for estrone, equilin and equilinen of 51, 67 and 375nM, respectively.

In Vitro Cotransfection Test Procedure

In this standard pharmacological test procedure, hER-α over-expressed in Chinese hamster ovary (CHO) cells infected with adeno-2x-ERE-tk-luciferase, an estrogen responsive reporter gene construct, cells were exposed to varying concentrations (10^{-12}-10^{-5}M) of 5,7,9-estratriene-3β,17β-diol for 24 hours. Cells were also exposed to 17β-estradiol at 10^{-9} M. Following the 24-hour treatment, cells were lysed and cell extracts assayed for luciferase activity. The results provided that 5,7,9-estratriene-3β,17β-diol had an EC_{50} of approximately 30 nM. Using a similar test procedure, previous data indicate a 5.6nM EC_{50} for estrone.

In Vivo Uterotropic Activity

Immature rats were treated with doses of 0.2 and 2 mg/kg 5,7,9-estratriene-3β,17β-diol for three days (S.C.) as well as additional groups (n=6) of rats treated with 0.5 μg ethinyl estradiol and vehicle as positive and negative controls, respectively.

Rats treated with 5,7,9-estratriene-3β,17β-diol had uterine weight gains at both concentrations demonstrating that 3β-hydroxy-5,7,9-estratriene-17-one was estrogenic..

The results of these standard pharmacological test procedures demonstrate that the compounds of this invention are estrogenic.

Based on the results obtained in the standard pharmacological test procedures, the compounds of this invention are useful in providing estrogen replacement therapy following ovariectomy or menopause, and in relieving symptoms related to estrogen deficiency, including vasomotor symptoms, such as hot flushes, and other menopausal related conditions, such as vaginal atrophy, vaginitis, and atrophic changes of the lower urinary tract which may cause increased urinary frequency, incontinence, and dysuria. The compounds of this invention are useful in preventing bone loss and in the inhibition or treatment of osteoporosis. The compounds of this invention are cardioprotective and they are useful in the treatment of atherosclerosis, ischemic disease, and hypertension. These cardiovascular protective properties are of great importance when treating postmenopausal patients with estrogens to prevent osteoporosis and in the male when estrogen therapy is indicated. Additionally, the compounds of this invention are useful in the suppression of lactation, and in the prophylaxis and treatment of mumps orchitis.

The compounds of this invention can be used alone as a sole therapeutic agent or can be used in combination with other agents, such as other estrogens, progestins, or and androgens.

The compounds of this invention can be formulated neat or with a pharmaceutical carrier for administration, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmacological practice. The pharmaceutical carrier may be solid or liquid.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in

the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, lethicins, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds of this invention can also be administered orally either in liquid or solid composition form.

The compounds of this invention may be administered rectally or vaginally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of

absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermiable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Based on the results obtained in the standard pharmacological test procedures, projected daily dosages of active compound would be 0.02 μg/kg - 750 μg/kg. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated. Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

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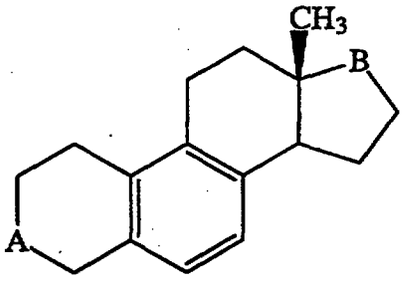
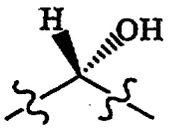
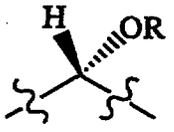
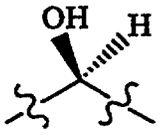
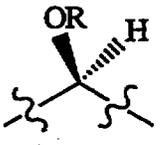
WHAT IS CLAIMED IS:

1. A compound having the formula



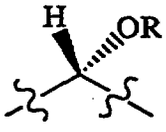
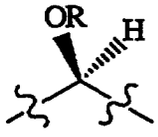
wherein

A and B are each, independently,  ,  ,

 , or  :

R is $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium containing 1-6 carbon atoms in each alkyl group;

with the proviso that at least one of A or B is  or  .

2. 5,7,9-Estratriene-3β,17β-diol 3-sulfate ester sodium salt in greater than one percent.

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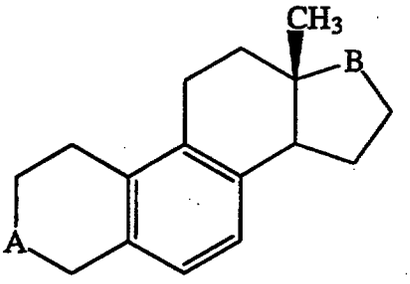
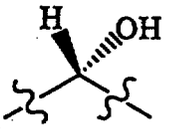
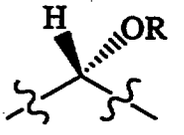
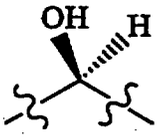
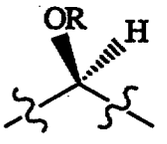
3. A composition of matter consisting essentially of a compound having the formula



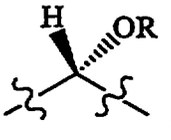
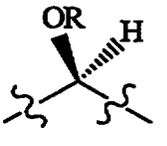
wherein

A and B are each, independently,  ,  ,

 , or  :

R is $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium containing 1-6 carbon atoms in each alkyl group;

with the proviso that at least one of A or B is  or  .

4. The compound according to claim 3 which is 5,7,9-estratriene-3β,17β-diol 3-sulfate ester sodium salt.

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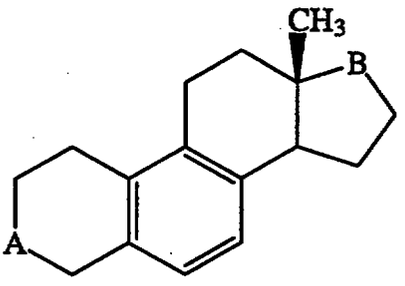
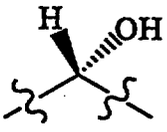
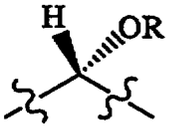
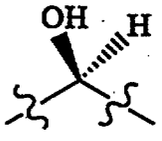
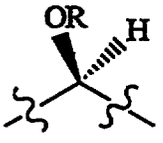
5. A method of providing estrogen replacement therapy or treating estrogen deficiency in a mammal in need thereof, which comprises administering an estrogenic amount of a compound having the formula



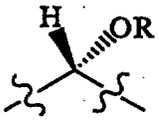
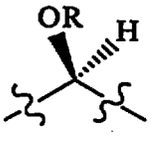
wherein

A and B are each, independently,  ,  ,

 , or  :

R is $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium containing 1-6 carbon atoms in each alkyl group;

with the proviso that at least one of A or B is  or  ,

to said mammal.

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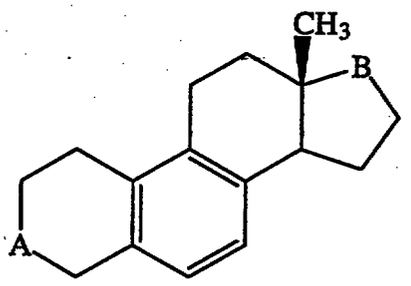
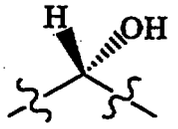
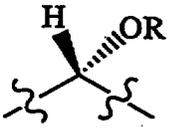
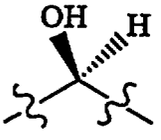
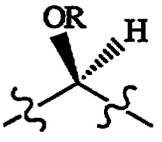
6. A method of treating vasomotor symptoms related to estrogen deficiency in a mammal in need thereof, which comprises administering an effective amount of a compound having the formula



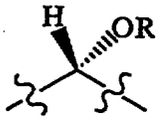
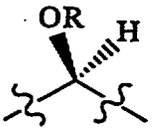
wherein

A and B are each, independently,  ,  ,

 , or  :

R is $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium containing 1-6 carbon atoms in each alkyl group;

with the proviso that at least one of A or B is  or  ,

to said mammal.

7. The method of claim 6, wherein the vasomotor symptom is hot flushes.

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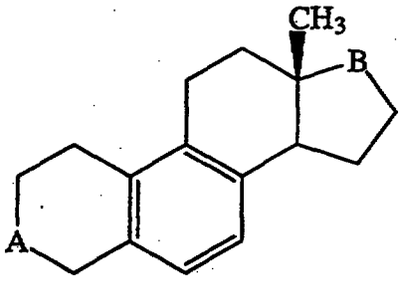
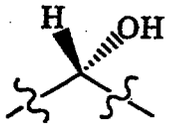
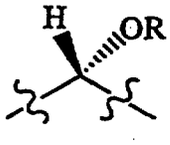
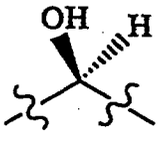
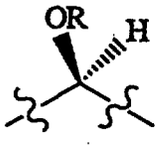
8. A method of treating or inhibiting osteoporosis in a mammal in need thereof which comprises administering an anti-osteoporosis effective amount of a compound having the formula



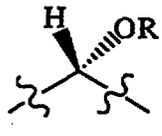
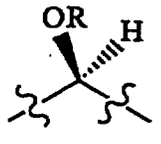
wherein

A and B are each, independently,  ,  ,

 , or  :

R is $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium containing 1-6 carbon atoms in each alkyl group;

with the proviso that at least one of A or B is  or  ,

to said mammal.

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9. A method of treating or inhibiting atherosclerosis in a mammal in need thereof which comprises administering an anti-atherosclerosis effective amount of a compound having the formula

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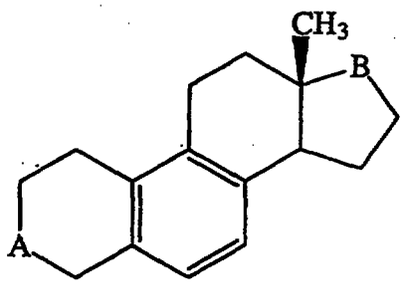
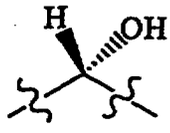


wherein

A and B are each, independently,



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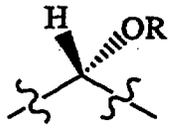

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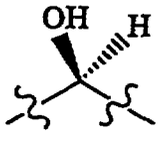

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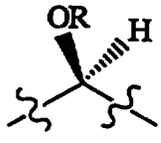
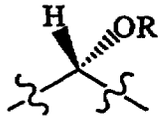


:

R is $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium containing 1-6 carbon atoms in each alkyl group;

with the proviso that at least one of A or B is



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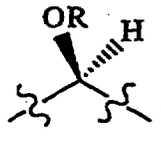

,

to said mammal.

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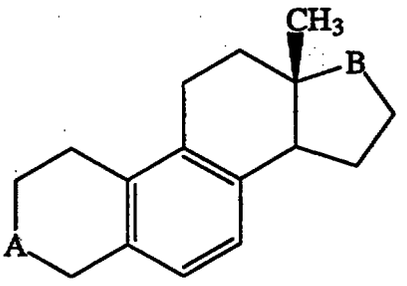
10. A pharmaceutical composition which comprises a compound having the formula



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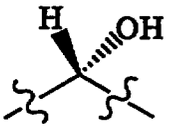
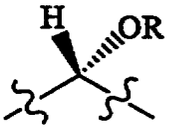
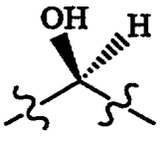
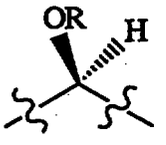
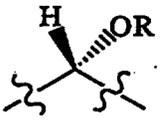
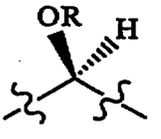
wherein

A and B are each, independently,  ,  ,

 , or  :

R is $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium containing 1-6 carbon atoms in each alkyl group;

with the proviso that at least one of A or B is  or  ,

and a phatmaceutical carrier.

11. A pharmaceutical composition which comprises at least 1% of a compound as defined in any one of claims 1 to 4.

12. Use of a compound as defined in any one of claims 1 to 4 as a medicament.

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13. Use of a compound as defined in any one of claims 1 to 4 in the preparation of a medicament for:

a) providing estrogen replacement ~~therapy~~ or treating estrogen deficiency,

b) treating vasomotor symptoms related to estrogen deficiency,

c) treating or inhibiting osteoporosis or

d) treating or inhibiting atherosclerosis

in a mammal in need thereof.

14. A process for the preparation of 5,7,9-estratriene-3,17-diol-3,17-disulfate ester salts which comprise:

a) converting the appropriate 5,7,9-estratriene-3,17-diol-3,17-disulfate ester to a pharmaceutically acceptable salt,

b) converting a pharmaceutically acceptable salt of the 5,7,9-estratriene-3,17-diol-3,17-disulfate ester to a different pharmaceutically acceptable salt of the 5,7,9-estratriene-3,17-diol-3,17-disulfate ester or

c) directly converting the appropriate 5,7,9-estratriene-3,17-diol to the desired pharmaceutically acceptable salt of 5,7,9-estratriene-3,17-disulfate ester.

15. A process for the preparation of 5,7,9-estratriene-3,17-diol-3-sulfate ester salts or 5,7,9-estratriene-3,17-diol-17-sulfate ester salts which comprises:

a) converting the appropriate 5,7,9-estratriene-3,17-diol-mono sulfate ester to a pharmaceutically acceptable salt,

b) converting a pharmaceutically acceptable salt of the appropriate 5,7,9-estratriene-3,17-diol-mono sulfate ester to a different pharmaceutically acceptable salt of the appropriate the appropriate 5,7,9-estratriene-3,17-diol-mono sulfate ester,

c) converting the corresponding 5,7,9-estratriene-3-ol,17-keto 3 sulfate ester salt or 5,7,9-estratriene-17-ol,3-keto 17 sulfate ester salt to the desired 5,7,9-estratriene-3,17-diol-3-sulfate ester salt or 5,7,9-estratriene-3,17-diol-17-sulfate ester salt,

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d) converting 5,7,9-estratriene-3,17-diol to the desired pharmaceutically acceptable salt of the desired 5,7,9-estratriene-3,17-diol-monosulfate ester directly,

e) deprotecting the corresponding 17 protected 5,7,9-estratriene-3,17-diol-3-sulfate ester salt or 3 protected 5,7,9-estratriene-3,17-diol-17-sulfate ester salt or

f) converting one stereo isomer of the pharmaceutically acceptable salt of the appropriate 5,7,9-estratriene-3,17-diol-mono sulfate ester to another by inversion.

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