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(54) **Therapeutic treatment of androgen receptor driven conditions**

Therapeutische Behandlung androgenrezeptorbedingter Leiden

Traitement thérapeutique des maladies liées au récepteur androgène

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(56) References cited:
WO-A-00/32201 **WO-A-97/37662**
US-A- 4 898 694 **US-A- 5 387 583**

- **HONG-CHIANG CHANG ET AL: "Suppression of Delta5-androstenediol-induced androgen receptor transactivation by selective steroids in human prostate cancer cells" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC.; US, vol. 96, 28 September 1999 (1999-09-28), pages 11173-11177, XP002190178 ISSN: 0027-8424**
- **HIROSHI MIYAMOTO ET AL: "Delta5-Androstenediol is a natural hormone with androgenic activity in human prostate cancer cellsw" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC.; US, vol. 95, 1 September 1998 (1998-09-01), pages 11083-11088, XP002190179 ISSN: 0027-8424**

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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

BACKGROUND OF THE INVENTION

[0001] The Invention provides methods and compositions comprising steroids or analogs, such as analogs of androst-5-ene-3β,17β-diol ("AED") or 1,3,5(10)-estratriene-17α-ethynyl-3β,17β-diol ("EED") for use as agents to modulate the biological activity of the androgen receptor ("AR") or to treat androgen responsive or related conditions such as prostate cancer and benign prostatic hypertrophy ("BPH").

[0002] Prostate cancer represents the most commonly diagnosed non-cutaneous malignancy in aging males and is the second leading cause of cancer-related death In North American men. Androgen ablation has been the cornerstone of treatment for advanced forms of this disease, typically by a combination of surgical or medical antiandrogen therapy. Antiandrogens that are commonly used include hydroxyflutamide (HF), cyproterone acetate and bicalutamide (casodex). Androgen ablation treatments are used to reduce the level of endogenous androgens. However, most androgen-dependent prostate cancer cases appear to progress to androgen-independent malignancies. Limiting the availability of androgens to regional or metastatic prostate cancers usually induces remission, but after some time the cancer often becomes refractory to androgen ablation treatments. It has been suggested that genetic changes of the AR gene may contribute to a short response to anti-androgen therapy. However, the mechanisms responsible for conversion of prostate cancer cells to an androgen Independent condition are not fully characterized.

[0003] BPH Is a disease that affects approximately 60% of males older than about 60 years of age. An elevated accumulation of male hormones such as dihydrotestosterone ("DHT") in prostate tissue may contribute to prostate enlargement The accumulation of DHT appears to result from elevated intracellular DHT receptor levels. The increase is associated with an elevation of estrogen levels relative to androgen levels, which decrease with age. The urological symptoms consist In an elevated frequency of miction due to elevated residual urine. This is typically accompanied by a weak flow of urine, a time-delayed start of miction, and repeated infections of the bladder and kidneys. BPH treatment includes surgery to remove the obstruction, but this is not always effective or has unwanted side-efects, e.g., incontinence or decreased libido. Other treatments such as androgen ablation by bilateral orchiectomy or androgen ablation chemotherapy are too invasive or have unwanted side-effects. Less invasive methods exist, e.g. balloon dilatation treatment with hyperthermia or microwaves, but they can have limited efficacy.

[0004] Chemotherapy for conditions such as prostate cancer and BPH, or their smptoms, include administering androgen synthesis inhibitors such as 5α reductase inhibitors to inhibit production of sex hormones such as testosterone or dihydrotestosterone, or administering Naftopidil for dysuria. Treatment with 5α reductase inhibitors has been combined with other treatments such as antiestrogens, aromatase (estrogen synthetase) inhibitors, inhibitors of 17β-hydroxysteroid dehydrogenase or lutenizing hormone releasing hormone agonists or antagonists. Other proposed treatments include administering aromatase inhibitors such as 4-hydroxyandrostene-3,17-dione. Chemotherapy typically has drawbacks. It can have unwanted side effects, particularly in older patients or it can become ineffective over time. Various treatments and their limitations have been described, see, e.g., U.S. patents 4,059,630, 4,310,523, 4,659,695, 4,970,204, 5,137,882, 5,372,996, 5,494,914, 5,561,124, 5,593,981, 5,994,334, 5,994,335, 5,998,377, 6,015,808, 6,093,722, 8,110,906 and European publication EP 0 401 653.

[0005] Biological properties of AED and related steroid compounds have been disclosed, see, e.g., U.S. patent numbers 2833793, 2911418, 3148198, 3471480, 3710795, 3711606 3976691, 4268441, 4427649, 4542129, 4666898, 4898694, 4956355, 4978532, 5001119, 5043165, 5077284, 5028631, 5110810, 5157031, 5162198, 5175154, 5206008, 5277907, 5292730, 5296481, 5372996, 5387583, 5407684, 5424463, 5461042, 5478566, 5506223, 5518725, 5527788, 5527789, 5532230, 5559107, 5562910, 5583126, 5585371, 5587369, 5591736, 5593981, 5610150, 5635496, 5641768, 5641768, 5656621, 5660835, 5677366, 5686438, 5696106, 5700793, 5707983, 5709878, 5710143, 5714481, 5728688, 5736537, 5744462, 5753237, 5756482, 5776921, 5776923, 5780460, 5795880, 5798347, 5798348, 5804576, 5807848, 5807849, 5811418, 5824313, 5824668, 5824671, 5827841, 5837269, 5837700, 5843932, 5846963, 5856340, 5859000, 5869090, 5863910, 5872114, 5872147 and 5910407; German patent numbers 2035738 and 2705917; PCT publication numbers WO 95/21617, WO 97/48367, WO 98/05338, WO 98/50040, WO 98/50041, WO 98/58650; European publication number 0020029.

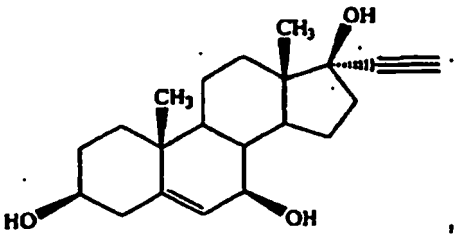
[0006] The androgen receptor and co-activators such as ARA_{70}, ARA_{24}, ARA_{54}, ARA_{55} and Rb, and methods to use them have been described, e.g., U.S. patent 5789170, 5614620; international publication number WO 00/04152.

[0007] The invention methods and compositions accomplish one or more of several objets. Invention objects include providing methods and compositions to inhibit proliferation of prostate cancer cella a subject. Other objects are to provide methods to make and use compositions and formulations comprising EED analogs or othercompounds disclosed herein. Additional objects will be apparent from the disclosure.

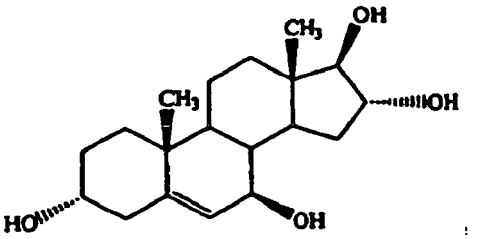
SUMMARY OF THE INVENTION

[0008] In accordance with the object, the invention provides the use as a medicament of a compound, wherein

(a) the compound is 17α-ethynylandrost-5-ene-3β,7β, 17β-triol (compound 1.2.1.3) which has the structure

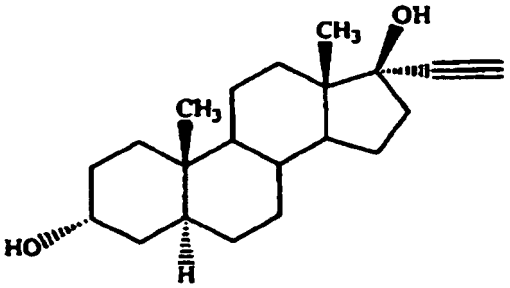


(b) the compound is androst-5-ene-3α, 7β, 16α, 17β-tetrol (compound 2.2.6.1) which has the structure



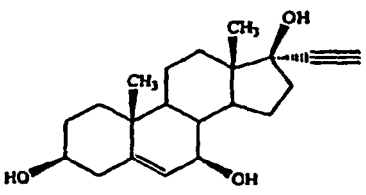
or

(c) the compound is 17α-ethynylandrostane-3α, 17β-diol (compound 2.1.1.3) which has the structure



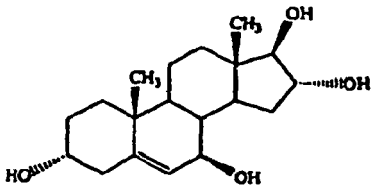
[0009] The invention further provides the use of a compound for the preparation of a medicament for the treatment of benign prostatic hyperplasia, prostate cancer or breast cancer, wherein

(a) the compound has the structure



(compound 1.2.1.3),

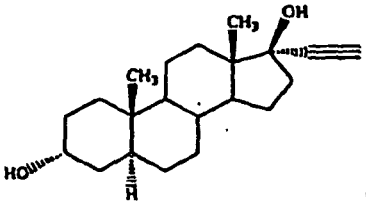
(b) the compound has the structure



(compound 2.2.6.1),

or

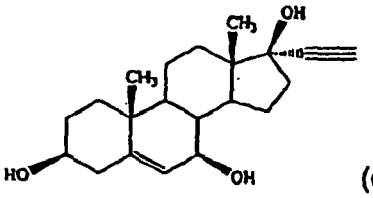
(c) the compound has the structure



(compound 2.1.1.3).

[0010] The invention further provides a compound having the structure

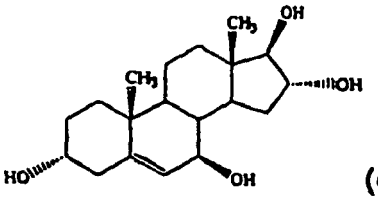
(a



(compound 1.2.1.3),

or

(b

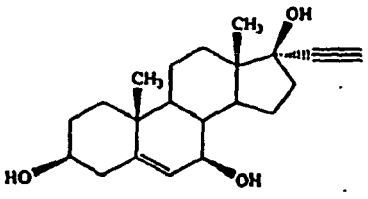


(compound 2.2.6.1).

[0011] The inventive compound can be a powder or granules.

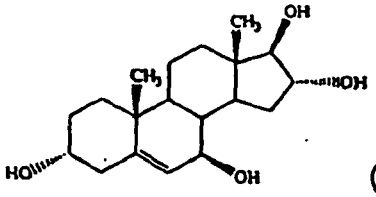
[0012] The invention further provides a formulation comprising one or more excipients and a compound wherein the compound has the structure

(a)



(compound 1.2.1.3),

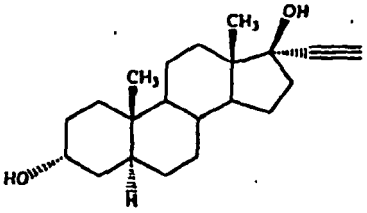
(b)



(compound 2.2.6.1),

or

(c)



(compound 2.1.1.3).

DETAILED DESCRIPTION OF THE INVENTION

[0013] As used herein and unless otherwise stated or implied by context, the following terms have the meanings defined here.

[0014] Stereoisomers. The compounds according to the invention include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions. Both racemic and diasteromeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners.

[0015] One or more of the following methods are used to prepare the enantiomerically enriched or pure isomers herein. The methods are listed In approximately their order of preference, i.e., one ordinarily should employ stereospecific synthesis from chiral precursors before chromatographic resolution or before before spontaneous crystallization.

[0016] Stereospecific synthesis is conveniently used when the appropriate chiral starting material is available and reaction steps are chosen that do not result in undesired racemization at chiral sites. One advantage of stereospecifc synthesis is that it does not produce undesired enantiomers that must be removed from the final product, thereby lowering overall syntheticyield. In general, those skilled in the art would understand what starting materials and reaction conditions should be used to obtain the desired enantiomerically enriched or pure isomers by stereospecific synthesis.

[0017] Another synthesis method of general utility is chromatographic resolution of enantiomers on chiral chromatography resins. These resins are packed In columns, commonly called Pirkle columns, and are commercially available. The columns contain a chiral stationary phase. The racemate is placed in solution and loaded onto the column, and thereafter separated by HPLC. See for example, Proceedings Chromatographic Society - international Symposium on Chiral Separations, Sept. 3-4,1987. Examples of chiral columns that could be used to screen for the optimal separation technique would include Diacel Chriacel OD, Regis Pirkle Covalent D-phenylglycine, Regis Pirkle Type 1A, Astec Cyclobond II, Astec Cyclobond III, Serva Chiral D-DL=Daltosil 100, Bakerbond DNBLeu, Sumipax OA-1000. Merck Cellulose Triacetate column, Astec Cyclobond I-Beta, or Regis Pirkle Covalent D-Naphthylalanine. Not all of these columns are

likely to be effective with every racemic mixture. However, those skilled in the art understand that a certain amount of routine screening may be required to identify the most effective stationary phase. When using such columns it is desirable to employ embodiments of the compounds of this invention in which the charges are not neutralized, e.g., where acidic functionalities such as carboxyl are not esterifled or amidated.

[0018] Another method entalis converting the enantiomers In the mixture to diasteriomers with chiral auxillaries and then separating the conjugates by ordinary column chromatography. This is a very suitable method, particularty when the embodiment contains free carboxyl, amino or hydroxyl that will form a salt or covalent bond to a chiral auxiliary. Chirally pure amino acids, organic acids or organosulfonic acids are all worthwhile exploring as chiral auxiliaries, all of which are well known In the art Salts with such auxiliaries can be formed, or they can be covalently (but reversibly) bonded to the functional group. For example, pure D or L amino acids can be used to amidate the carboxyl group of invention embodiments that comprise a carboxyl group and then separated by chromatography.

[0019] Enzymatic resolution Is another method of potential value. In such methods one prepares covalent derivatives of the enantiomers in the racemic mixture, generally lower alkyl esters (for example of carboxyl), and then exposes the derivative to enzymatic cleavage, generally hydrolysis. For this method to be successful an enzyme must be chosen that is capable of stereospecific cleavage, so it is frequently necessary to routinely screen several enzymes. If esters are to be cleaved, then one selects a group of esterases, phosphatases, and lipases and determines their activity on the derivative. Typical esterases are from liver, pancreas or other animal organs, and include porcine liver esterase.

[0020] If the enantiomeric mixtures separates from solution or a melt as a conglomerate, i.e., a mixture of enantiomerically-pure crystals, then the crystals can be mechanically separated, thereby producing the enantiomerically enriched preparation. This method, however, is not practical for large scale preparations and is of limited value for true racemic compounds.

[0021] Asymmetric synthesis is another technique for achieving enantiomeric enrichment. For example, a chiral protecting group is reacted with the group to be protected and the reaction mixture allowed to equilibrate. If the reaction is enantiomerically specific then the product will be enriched in that enantiomer.

[0022] Further guidance in the separation of enantiomeric mixtures can be found, by way of example and not limitation, in "Enantiomers, Racemates, and resolutions", Jean Jacques, Andre Collet, and Samuel H. Wilen (Krieger Publishing Company, Malabar, FL, 1991, ISBN 0-89464-618-4): Part 2, Resolution of Enantiomer Mixture, pages 217-435; more particularly, section 4, Resolution by Direct Crystallization, pages 217-251, section 5, Formation and Separation of Diastereomers, pages 251-369, section 6, Crystallization-induced Asymmetric Transformations, pages 369-378, and section 7, Experimental Aspects and Art of Resolutions, pages 378-435; still more particularly, section 5.1.4, Resolution of Alcohols, Transformation of Alcohols into Salt-Forming Derivatives, pages 263-266, section 5.2.3, Covalent Derivatives of Alcohols, Thiols, and Phenols, pages 332-335, section 5.1.1, Resolution of Acids, pages 257-259, section 5.1.2, Resolution of Bases, pages 259-260, section 5.1.3, Resolution of Amino Acids, page 261-263, section 5.2.1, Covalent Derivatives of Acids, page 329, section 5.2.2, Covalent derivatives of Amines, pages 330-331, section 5.2.4, Covalent Derivatives of Aldehydes, Ketones, and Sulfoxides, pages 335-339, and section 5.2.7, Chromatographic Behavior of Covalent Diastereomers, pages 348-354.

[0023] The compounds according to the invention are useful to treat conditions that are associated with or that respond to modulation of AR activity, including prostate cancer, acne, male pattern baldness, hirsutism, hypogonadism and breast cancer. These compounds may be optionally be used in combination therapies to treat any of these diseases or conditions. The combinations include compound(s) according to the invention combined with surgery, radiation therapy, cytotoxic agents, cytostatic agents or hormone therapies, including any of the therapies or treatments disclosed herein or in any of the references cited herein.

[0024] The compounds according to the invention are also useful to determine if the AR or another steroid receptor, e.g., an orphan receptor, are present in a cell population or cell extract. In these applications, the compounds will typically be labeled, e.g., radiolabels (^{14}C, ^{3}H, ^{32}P, ^{35}S or a radioactive iodine isotope) or labeled with a crosslinking molety. In related applications, the compounds are useful as reference standards to compare their capacity to modulate AR activity with the capacity of known AR modulators, such as AED. In these applications, a compound according to the invention is used in a suitable assay system, e.g., one that comprises cells (*in vitro* or *in vivo*) that contain functional AR, an AR-responsive gene, e.g., ornithine carboxylase, that can be conveniently assayed, a compound according to the invention and a test compound. In such methods, the effect of the compound according to the invention on the capacity of the test compound to modulate the AR is examined, usually using a suitably controlled system, e.g., with varying concentrations of the compound according to the invention or varying concentrations of the test compound. Assay systems, or components thereof that comprise the Ar have been described, see, e.g., U.S. patents 4981784 and 5071773, Evans, et al., Science 240:889-895 1988, T. Berger et al., J. Steriod Biochem. Molec. Biol. 41:773-778 1992, J. Simenthal, et al., J. Biol. Chem. 266:510-514 1991, G. Scalabrino et al., Mol. Cell. Endocrinol. 77:1-35 1991, O. Janne, et al., Ann. N. Y. Acad. Sd. 438:72-841984, and R. Djurtluus, Anal. Biochem. 113:352-355 1981.

[0025] An effective dose of a compound according to the invention or the "active ingredient", for use in therapeutic applications, e.g., prostate cancer treatment, will depend to a certain extent at least on factors such as the status of the

condition being treated, whether the compound(s) is being used prophylactically (lower doses) or the severity of the malignancy, the method of delivery, and the pharmaceutical formulation. These factors will be determined by the clinician using conventional dose escalation studies. Typically the dose administered to the subject will be from about 0.03 to about 30 mg/kg body weight per day, generally about 0.1 to about 10 mg/kg body weight per day. For example, for topical delivery the daily candidate dose for an adult human of approximately 70 kg body weight will range from about 1 mg to about 750 mg, generally between about 5 mg and about 300 mg, usually between about 30 mg and about 250 mg. A dally dose may take the form of single or multiple doses or administration sites. For a formula 1 or 2 compound that is delivered parenterally, e.g., i.v., s.c. or i.m., the dose will generally be lower (e.g., about 0.02 to about 6 mg/kg) than a dose administered orally.

[0026] Pharmaceutical formulations that comprise a compound according to the invention will typically comprise one or more carriers or excipients and optionally other therapeutic ingredients. The carrier(s) will generally be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically Innocuous to the recipient thereof. Such carriers or excipients are known, e.g., fillers, lubricants, binders and various liquid excipients for liquid formulations. Suitable carriers include those disclosed In the references cited herein.

[0027] Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for parenteral delivery of the active ingredient include aqueous and non-aqueous compositions where the active ingredient is dissolved or suspended in solution. Such formulations will typically comprise about 25-300 mg/mL of the active ingredient, usually about 40-200 mg/mL Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats or solutes that render the formulation isotonic with the blood of the intended recipient. Other parenteral formulations may comprise aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

[0028] Formulations suitable for topical administration Include creams or ointments wherein the formula 1 or 2 compound is dissolved orsuspended in a suitable carrier, especially anon-aqueous solvent or carrier for the active ingredient. The active ingredient is typically present in such formulations in a concentration of 0.5 to 20% w/w, often 0.5 to 10% w/w. Such formulations are suitable for use in applications such as treating male pattern baldness or acne.

[0029] Formulations suitable for buccal or sublingual administration include lozenges comprising the active ingredient, which is optionally present in a flavored basis such as sucrose and acacia or tregacanth. Pastilles may comprise the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia, and mouthwashes may comprise the active ingredient In a suitable liquid carrier.

[0030] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0031] Formulations suitable for intrapulmonary or nasal administration will have a particle size for example in the range of 0.01 to 200 microns (including particle sizes in a range between 0.01 and 500 microns in increments of 0.1 microns such as 0.1, 0.2, 0.3, 0.4, 0.5, 1, 2, 5, 30 microns, 35 microns, etc.), which is administered by inhalation through the nasal passage or by inhalation through the mouth so as to reach the various bronchi or alveolar sacs. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of prostate cancer.

[0032] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing In addition to the active ingredient such carriers as are known in the art to be appropriate.

[0033] Formulations comprising an active ingredient are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored In a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as described herein, or an appropriate fraction thereof, of the active ingredient

[0034] It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation In question, for example those suitable for oral administration may include flavoring or coloring agents.

[0035] The Invention further provides veterinary compositions comprising at least one active ingredient together with a veterinary carrier therefor.

[0036] Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

[0037] The active ingredeints may be used to provide controlled release pharmaceutical formulations containing an active ingredient (controlled release formulations') in which the release of the active ingredient is controlled and regulated to allow less frequency dosing or to improve the phamacokineticor toxicity profile of a given active ingredient

[0038] The formulations include those suitable for any of the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients or excipients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0039] Formulations of the invention suitable for oral administration are prepared as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oilliquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0040] A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

[0041] If desired, the aqueous phase of a cream base may include, for example, polyhydric alcohol, i.e. an alcohol having two ormore hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

[0042] The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifler with a fat or an oil or with both a fat and an oli**.** Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifler which acts as a stabilizer. It is also preferred to include both an oil and a fat Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and tat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

[0043] Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween.RTM. 60, Span.RTM. 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

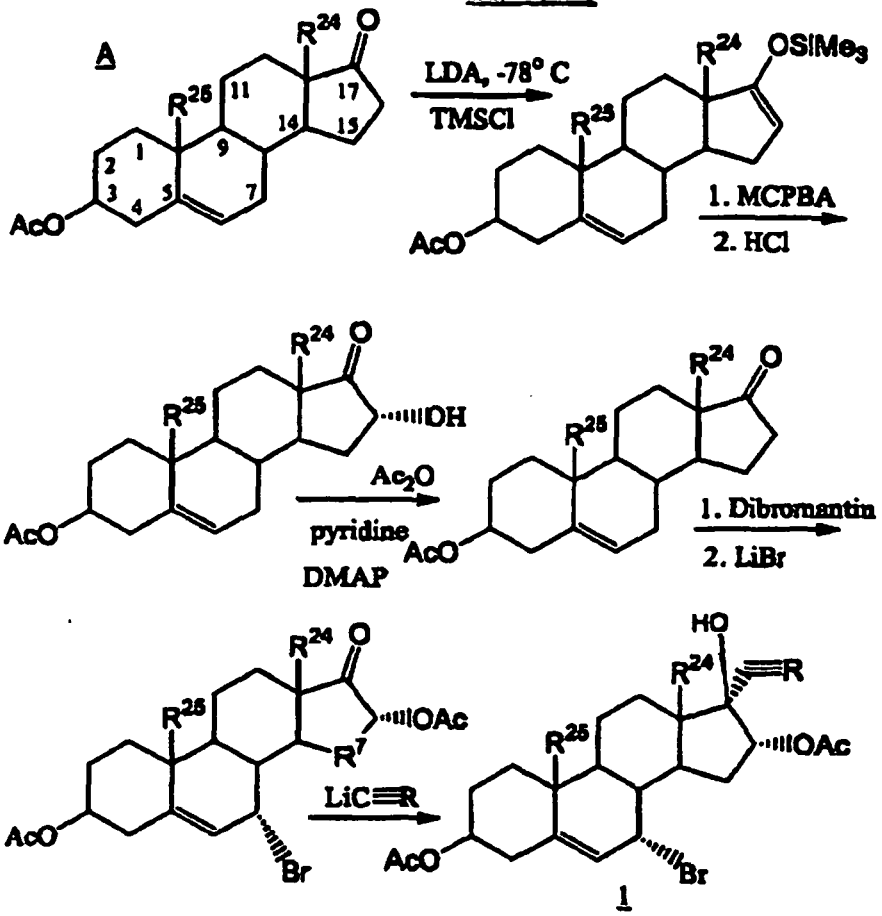
[0044] The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate. butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

[0045] Exemplary synthesis methods. By way of exemplification and not limitation,the following methods are used to prepare the one or more of the compounds disclosed herein. Starting materials or straightforward variations of the schemes are found, e.g., in the following citations US patents 4602008, 4989694, 5001119, 5175154, 5571795, 5627270, 5681984, 5714481, 5744453, 5939545, 5939570, 5962442, 5962443. 5994568; international publication numbers WO 9408588, WO 9508558, WO 9508559, WO 9638466, WO 9809450: and European patent applications EP 232788, EP 430078.

[0046] Scheme 1. Principles for synthesis of compounds according to the invention are shown in the schemes below. When R^{24} and R^{25} are both $-CH_3$ in the β-configuration, H at the 9 and 14 positions are in the α-configuration, acetate at the 3-position is in the β-configuration. and H at the 8 position is in the β-configuration, the first compound in scheme 1 is DHEA acetate. The acetate groups at the 3, 7, 16, 17 or other positions in this scheme and in other schemes disclosed herein may independently be other ester moieties as described herein, e.g., $C_{2\text{-}50}$ esters including $-C(OKCH_2)_{0\text{-}4}\text{-}(CF_2)_{0\text{-}4}\text{-}CF_3$, including $-C(O)\text{-}CF_3$,-C (O)-$C_{2\text{-}29}$ optionally substituted alkyt, $-C(O)\text{-}CH_2\text{-}C_{2\text{-}28}$ optionally substituted alkenyl, $-C(O)CH_2\text{-}C_{2\text{-}28}$ optionally substituted alkynyl, $-C(OKCH_2)_{0\text{-}6}$ substituted phenyl, or $-C(O)\text{-}(CH_2)_{0\text{-}6}$-optionnaly substituted heterocycle or other organic moieties as disclosed herein or in the cited references.

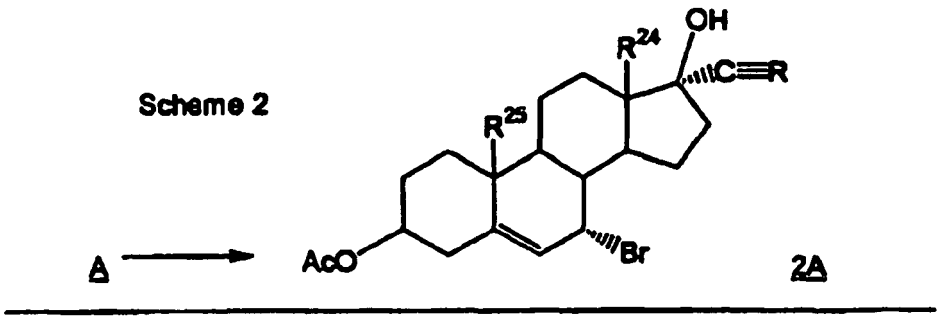
[0047] Typical substituents for these organic moieties are as described herein, e.g., one, two, three or more independently selected -O-, =O, optionally protected hydroxyl, -S-, optionally protected thiol, -NH-, optionally protected $-NH_2$, optionally protected -C(O)OH, -C(O)-NH-, $-C(O)\text{-}NH_2$, $-NH_2\text{-}C(O)\text{-}H$,$-NH_2\text{-}C(O)C_{0\text{-}4}H_{1.9}$,$-NH_2\text{-}C(O)O\text{-}C_{0\text{-}4}H_{1.9,}$-CN, $-NO_2$, $-N_3$ or halogen. Reactive groups are protected as needed, e.g., =O would usually be protected in the LiCR reaction that is used to generate compound 1 in scheme 1 below.

Scheme 1

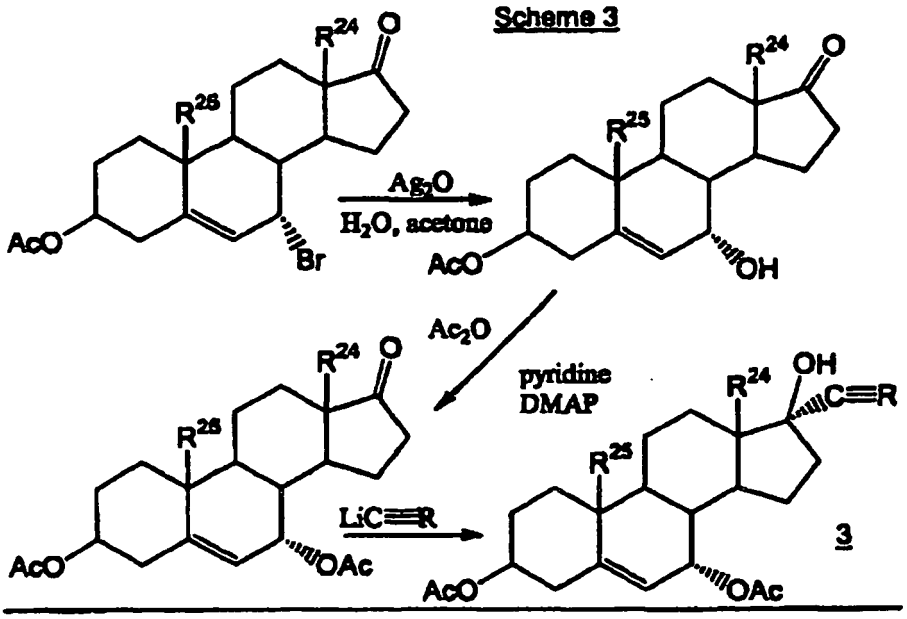


Abbreviations:
LDA = lithium diisopropyl amide; MCPBA = m-chloroperbenzoic acid; TMSCl = trimethychlorosilane; DMAP = 4-dimethylaminopyridine; Dibromantin = 1,3-dibromo-4,4-dimethylhydantoin.
R = CR^A; R^A = -H or a C1-C50 organic moiety as described herein, e.g., -H, -C_{1-20} optionally substituted alkyl, -C_{1-20} optionally substituted alkenyl, -C_{1-20} optionally substituted alkynyl, -$(CH_2)_{0-6}$-optionally substituted phenyl or -$(CH_2)_{0-6}$-optionally substituted heterocycle.

Scheme 2. Compounds of formula 2A are prepared from structure A compounds shown In scheme 1 using the last two steps of Scheme 1: (1) dibromantin, (2) UBr, (3) LI-C-R,where R is CR^A and R^A is -H or -C_{1-12} optionally substituted alkyl. When H at the 9 and 14 positions are In the α-configuration and H at the 8 position Is In the β-configuration the first compound In scheme 1 is DHEA acetate. Typical substituents for the R^A alkyl moiety includes one, two or more independently selected -O-, optionally protected =O, optionally protected hydroxyl,- S-, optionally protected thiol, -NH-, optionally protected -NH_2, optionally protected . C(O)OH, -C(O)-NH-, -C(O)-NH_2, -NH_2-C (O)-H, -NH_2-C (O)-$C_{0-4}H_{1-8}$,-NH_2-C(O)O-$C_{0-4}H_{1.9}$ -CN, -NO_2, -N_3 or halogen.

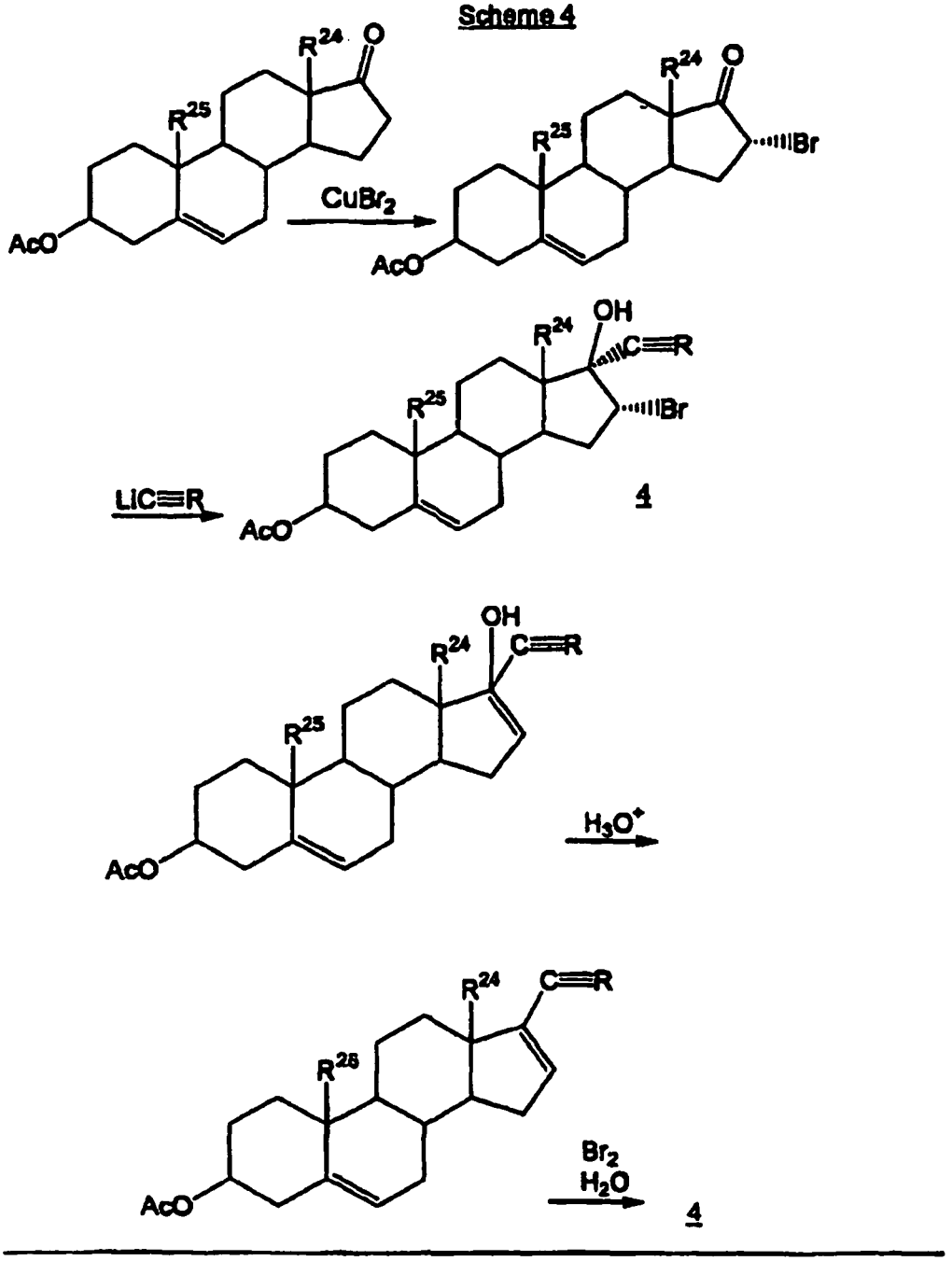


Scheme 3. The allylic bromination at C-7 is accomplished essentially as shown in Scheme 1. R and R^A are as defined in Schemes 1 and 2.



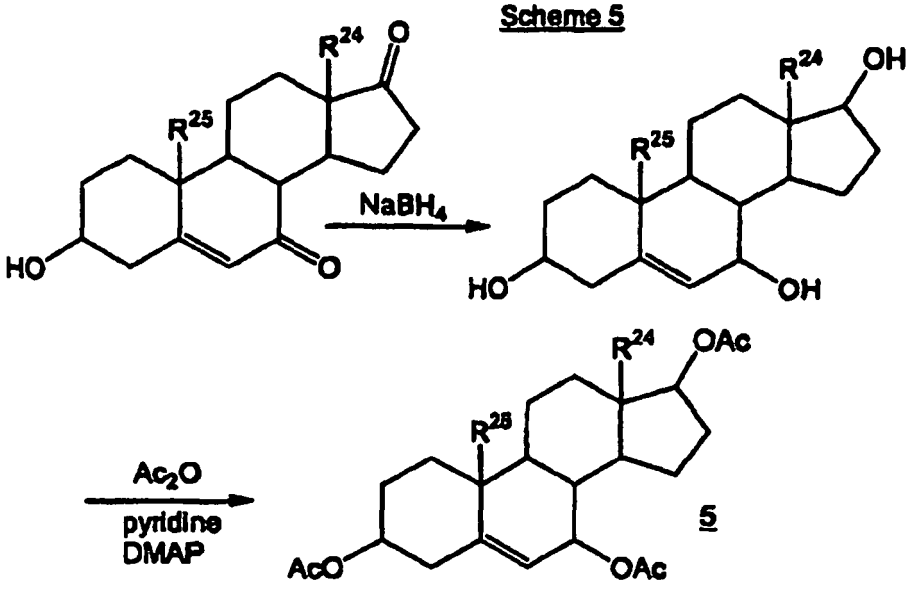
Scheme 4. The addition of lithium reagent (lithium acetylide when R is-CH) to the 17-position >C=O **in** the presence of the bromide at C-16 results in epoxide formation or in a pinacol rearrangement Alternatively, compounds without of structure 3 can be dehydrated by mild acid catalysis to form compounds of formula 4 by treatment of the alkene with Br_2, H_2O. R and R^A are as defined in Schemes 1 and 2.

Scheme 4

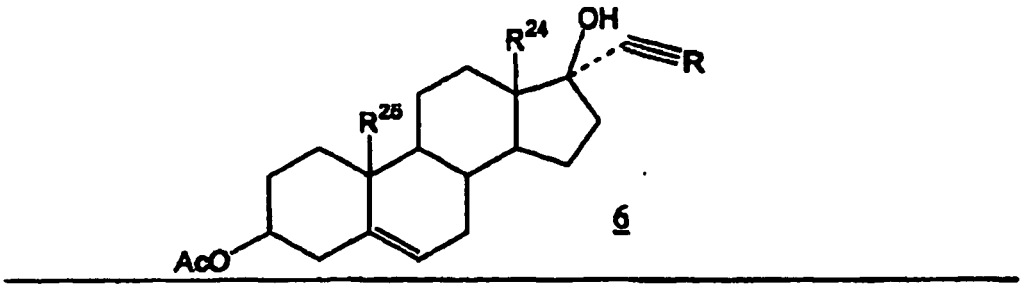


Scheme 5. Sodium borohydride gives a mixture of epimers at C-7, which may be separated by standard methods, e.g., HPLC, TLC or column chromatography. To obtain the pure 7α-OH compound, allylic bromination followed by hydrolysis is accomplished, e.g., essentially as described in Schemes 1 and 3.

Scheme 5

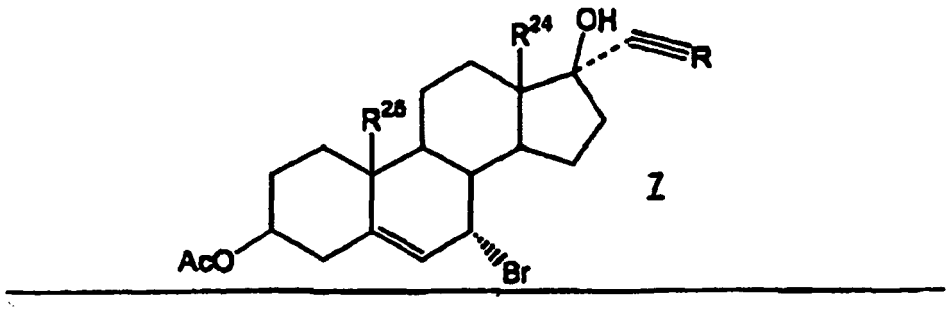


Scheme 6

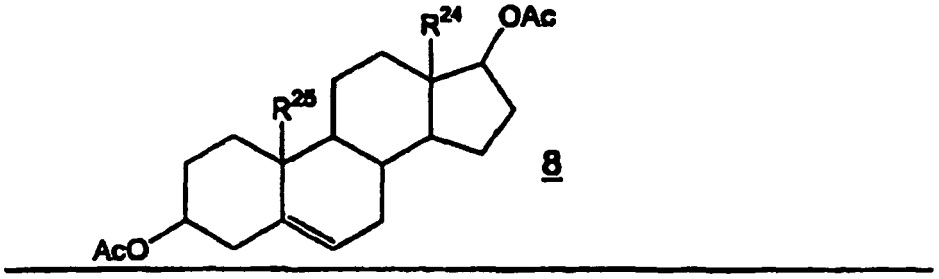


Scheme 6. Formula 6 compounds are prepared by treatment of the acetate with lithium acetylide as in Schemes 1, 2, 3 or 4. R and R^A are as defined in Schemes 1 and 2.

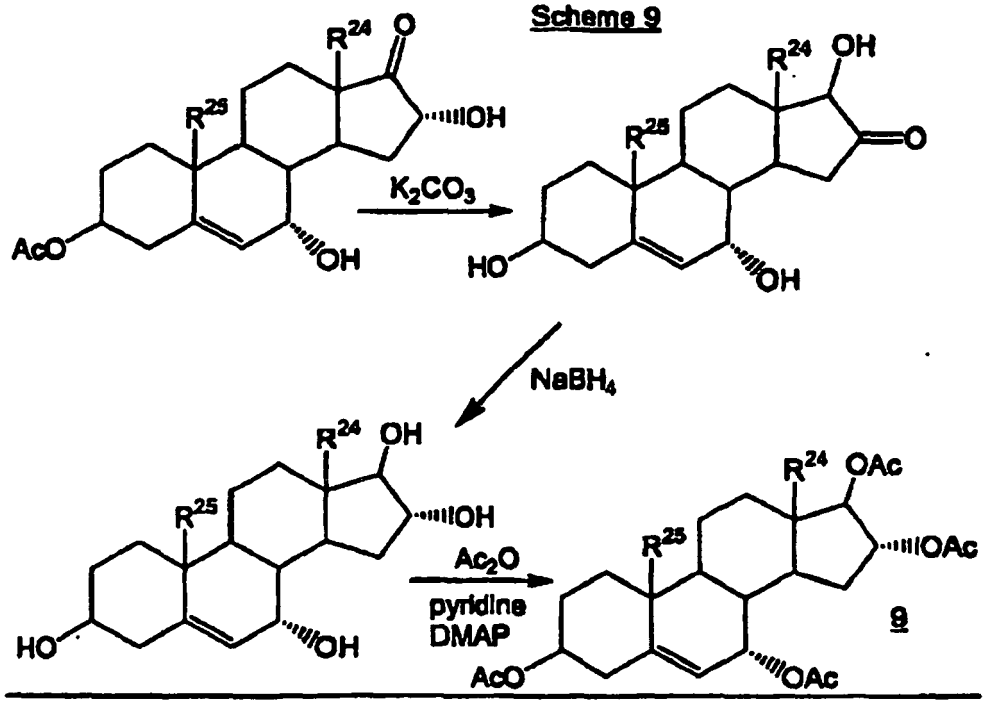
Scheme 7. Formula 7 compounds are prepared from the 3-acetate with reagents described In Schemes 1 and 4. R and R^A are as defined in Schemes 1 and 2.



Scheme 8. Formula 8 compounds are prepared from the formula A compounds by sodium borohydride reduction at C-17 followed by acetylation.

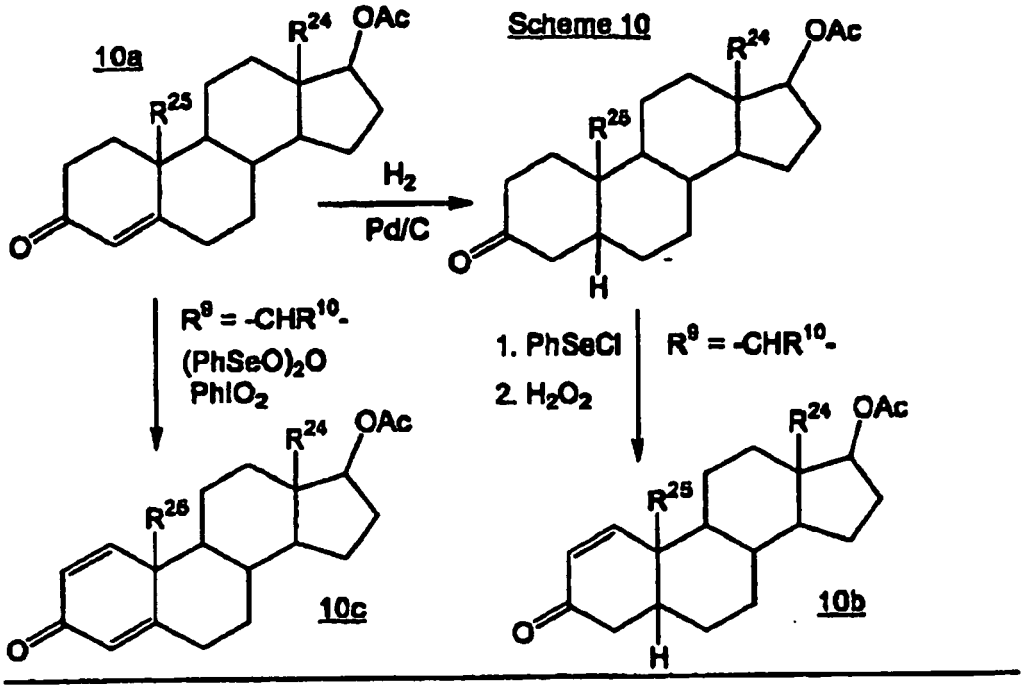


Scheme 9. The starting material is made using reactions described in Schemes 1 and 3.



Scheme 10. Reduction and acetylation at C-3 and hydrolysis and oxidation at C-17 will allow formula 10a and 10b compounds to undergo functionalization as shown in Schemes 1-9 at C-3. C-16 and C-17. The 7-oxo acetate can be substituted for the formula A compound 3-acetate and functionalization at C-3, C-18 and C-17 is achieved similarly for 7-oxo compounds using the reactions shown in schemes 1-9.

Treatment of 10a with LDA, followed by alkylation of the enolate allows introduction of side chains, which may be, e.g., C1-C20 alkyl (methyl, ethyl), C1-C20 alkenyl (CH_2=CH-(CH_2)$_{0-6}$-), benzyl, -(CH_2)$_{1-4}$-O(CH_2)$_{0-4}$$CH_3$.



Schemes 1-9 show the introduction of the hydroxyl function at the positions shown. Methods to convert hydroxyl to other functional groups are accomplished essentially as described, e.g., in the references cited herein. For example, esters, of formula 1 -10c compounds, such as -O-C(O)R^8 where R^8 is a C_{1-50} organic moiety, are prepared from the steroid alcohol by treatment with the appropriate acid anhydride or acid chloride (R^8-C(O)-Cl) to form any desired ester. Ethers, such as -O-R^8, are prepared from alcohols by formation of the alkaline metal alkoxide (Na^+ or K^+) followed by treatment with a primary or secondary iodide (R^8-I). Thionoesters, R^8-C(S)-O-, are prepared by treating the R^8-C(O)-O- ester with Lawesson's reagent.

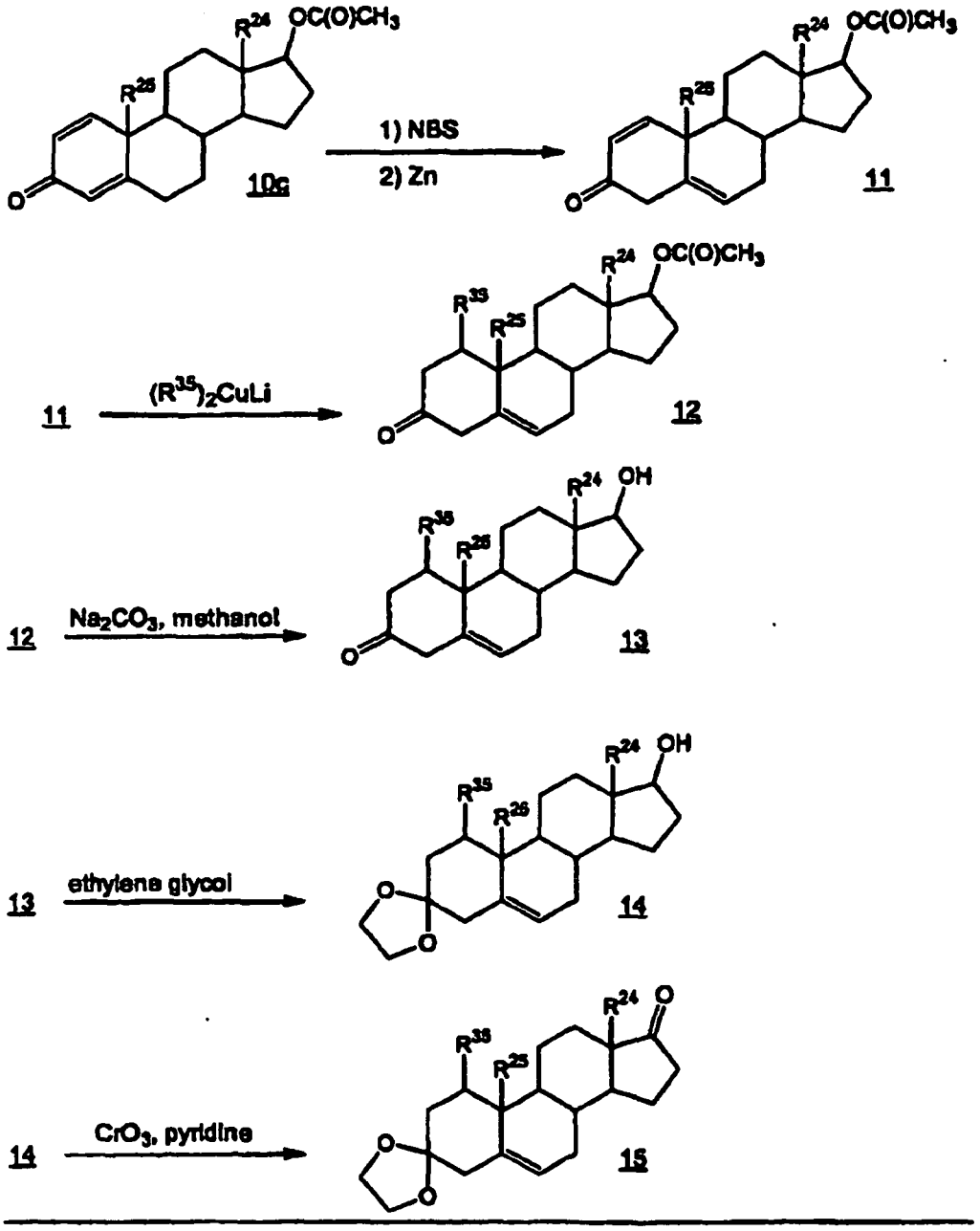
Sulfates, NaO-S(O)(O)-O-, R^8-O-S(O)(O)-O-, e.g., $CH_3(CH_2)_{0\cdot18}$-S(O)(O)-O-. are prepared by treatment of alcohols with chlorosulfonic acid followed by NaOH or alternatively by oxidation of sulfites using $KMnO_4$. If the alkyl (e.g., methyl) ester is desired alkylchloro-sulfonate (methylchloro-sulfonate) can be used. Sulfites HO-S(O)-O- and ammonium salts NH_4 O-S(O)-O, or R^8 O-S(O)-O- esters (e.g., CH_3 O-S(O)-O-) are prepared by standard methods. The ammonium salts are prepared by treatment of alcohols with ammonia and sulfur dioxide. The esters such as alkyl, alkenyl and alkynyl esters (e.g., methyl ester) are obtained when alcohols are treated with alkylchlorosulfite (e.g., methycholorosulfite), alkanylchlorosulfite or alkynylchlorosulfite in the presence of a suitable base such as triethylamine. Phosphoesters, R^8O-P(OR^{PR}O)-O-are prepared by treating the alcohol with diethylchlorophosphate In the presence of Na_2CO_3. Alternatively, if the alcohol is treated with phosphoric acid diesters in the presence of triphenylphospine (PPh_3) and diethylazodicaboxylate (DEAD) the corresponding triesters are formed with inversion (Mitsunobu reaction).

Phosphothloesters, R^8O-P(SR^{PR})(O)-O- are generated by treatment of alcohols with the monothio analog of diethylchlorophosphate as described for phosphoesters yielding the phosphothioesters. Carbonates, R^8O-C(O)-O-are generated from the corresponding steroid alcohol using the chloroformate (R^8-C(O)-Cl), e.g., C_{1-20} alkyl, alkenyl or alkynyl chloroformates (e.g. $CH_3(CH_2)_{0-5}$-C(O)Cl). Carbamates, R^8-NH-C(O)-O- are made from steroid alcohols by treatment with isocyanates (R^8N-C=O) or NaOCN in the presence of trifluroroacetic acid. Aminoacid esters, ZNX-CHY-C(O)-O- are generated by coupling the steroid alcohol with the acid chloride of the N-protected amino acid. Oxidation of hydroxyl groups that are linked to the steroid nucleus is used to obtain ketones and related functionalities. For example, conversion of alcohols to ketones can be achieved using a variety of oxidizing agents such as CrO_3 in AcOH, or pyridinium cholorchromate, pyridinium dichromate or oxalyl chloride with triethylamine (Swem oxidation). Thioketones (=S) are prepared by treating ketones with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithladiphosphetane-2,4-disulfide; commercially available from Aldrich). Thioacetals, -C(SR^8)(SR^8)-, are prepared from ketones (-C(O)-) by treatment with R^8-SH thiols under acid catalysis conditions (e.g., HCl). Phosphonoesters, RO-P(OR^{PR})(O)-, are generated by addition of the phosphorus acid diester to ketones in the presence of KF to yield hydroxy phosphonoesters. One may optionally remove the hydroxy group using a dehydration and hydrogenation sequence.

Substitution of hydroxyl groups is used to generate a number of functionalities. For example, thiols, -SH, are prepared from alcohols by conversion of the alcohol with inversion to the bromide using PBr_3. Treatment of the bromide with

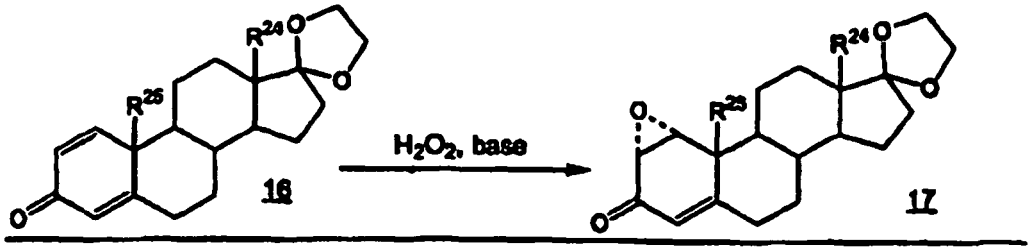
thiourea followed by NaOH gives the thiol. Thioethers, R^8-S-,
are prepared from thiols by treatment with NaOH and the required halide, e.g., alkyl halide. Alternatively, alcohol derivatives like tosylates or mesylates can be displaced by thiolate anions, R^8-S^-, to yield the thloether. Thioesters, R-C(O)-S-, are prepared by treating the tosylate (mesylate) of the alcohol with the sodium salt of the thioacid.
Substitution of hydroxy groups can be used to generate both esters, R^8O-C(O)-, and amides. NHR^8-C(O)-, linked to the steroid at carbon atoms. For amides and amines, R^8 is -H, a protecting group or a C_{1-50} organic moiety. These are synthesized from the steroid bromide with inversion by displacement with NaCN. The cyanide group can be hydrolyzed to the amide or the acid. The acid is esterified or treated by standard peptide coupling reactions with an O-protected amino acid in the presence of a suitable carboxyl activating agents such as dicyclohexylcarbodiimide (DCC) to form steroid -C(O)-NH-CHY-C(O)-OR, where Y is the side chain of an amino acid or a C1-C10 organic moiety and R is a protecting group (or hydrogen when deprotected).
Amines and derivatives of amines, e.g., R^8NH-, R^8-C(O)NH-, R^8OC(O)-NH- or R^8O-C(O)-CHR^8-NH- linked to steroid carbon atoms, are typically prepared by standard methods. For example, amines (NH_2-steroid) are generally prepared using the Hoffmann rearrangement (Br_2, NaOH) from the amide (NH_2-C(O)-steroid) or the Curtius rearrangement (NaN_3) from the acid chloride of the steroid. The R^8 substituent can subsequently be introduced by alkylation. Steroid alcohols can be used as starting materials under standard Mitsunobu conditions (PPh_3, DEAD) to yield N-Boc sulfonamides using N-(t-butoxycarbonyl)-p-toluenesulfonamide. One can selectively remove either protecting group. Treatment with trifluoroacetic acid affords the sulfonamide (R^8-S(O)(O)-NH-steroid). Alternatively, sodium napthalenide deprotects to give the N-Boc compound. Amines (NH_2-steroid) can be converted to amides (R^8NH-C(O)-steroid) using acyl chlorides (R^8-C(O)-Cl). Treatment with ethyl chloroformate gives the N-carbamate (R^8O-C(O)-NH-steroid). The amine (NH_2-steroid) can be alkylated with an α-bromoester (R^8-C(O)-CHY-NH_2) to yield the amio acid substituted steroid (R^8-O-C(O)-CHY-NH-steroid).
Where reactions such as substitutions give a product mixture, the desired intermediate is optionally separated from other products or at least partially enriched (e.g., enriched at least about 10-fold, usually at least about 50-1 00-fold) from other products before subsequent reactions are conducted. Substitution at steroid carbon atoms will generally proceed with greatest efficiency at the 3-position, which is relatively sterically unhindered and C-17 is generally somewhat less accessible than the C-3 position. The relative reactivities of the C-3, C-7, C-17 and C-16 positions allows one to use their reactivities to control the sequential introduction of different functional groups into the same steroid molecule. Also, groups, such as hydroxyl at more reactive positions, C-3 or C-17, may be sequentially protected or deprotected to allow introduction of functional groups at other positions, such as C-7 or C-16. Polymers such as PEG are linked to the compounds essentially as described above. For example, PEG 200 or PEG 300 is linked to the steroid at the 3, 7, 16, 17 or other positions by an ether linkage (PEG-O-steroid) using a PEG alkoxide (PEG-ONa), to displace the steroid bromide. Alternatively, PEG-Br can be treated with the steroid alkoxide. Polyethylene glycol esters such as those described in U.S. patent 5681 964 can also be prepared using a suitable formula 1 compound and the methods described therein. Monosaccharides or polysaccharides and oligonucleotides are linked to steroid hydroxyl groups using known methods, see e.g., U.S. patent 5627270.
Scheme 11. Formula 1 or 2 compounds that contain an an organic moiety that is linked to the 1 position are prepared essentially as follows. The allylic bromination reaction to generate 11 may utilize any suitable reagent, e.g., N-bromosuccinimide ('NBS') to yield the 1-bromo derivative. This intermediate is treated with zinc to yield the alkylated derivative 12. Organic moieties are introduced into the 1 position using a corresponding reagent, e.g., $(R^{35})_2$CuLi, where R^{35} is a C1-C25 organic moiety that may comprise 1, 2, 3, 4 or more substituents, e.g., -O-. -S-, -NH-, -OR^{PR}. protected ketone (e.g., ethylene ketal),
-SR^{PR} or -$N(R^{PR})_2$- In other embodiments, R^{35} is R^1. Thus, when R^{35} is methyl, a methyl group is introduced into the 1 position, or when R^{35} is -CH2-OR^{PR}, the -CH_2-OR^{PR} group is introduced into the 1 position. Compound 12 is converted to the 17 hydroxyl derivative 13 by hydrolysis using standard methods, e.g., treatment with sodium carbonate in ethanol The compound 15 is converted to the 17-hydroxy derivative by reduction of the ketone, e.g., using UBH_4 or $NaBH_4$, in ethanol or by catalytic hydrogenation with H_2/Ni, H_2/Pt or H_2/Pd. Catalytic hydrogenation will also result in reduction of the double bond in 12, 13, 14 or 15. Alternatively, a hydroxyl at both the 3 and 17 positions is obtained by reducing the ketone in compound 12 and removing the acetate group or by directly reducing the 3 ketone in compound 13.

Scheme 11



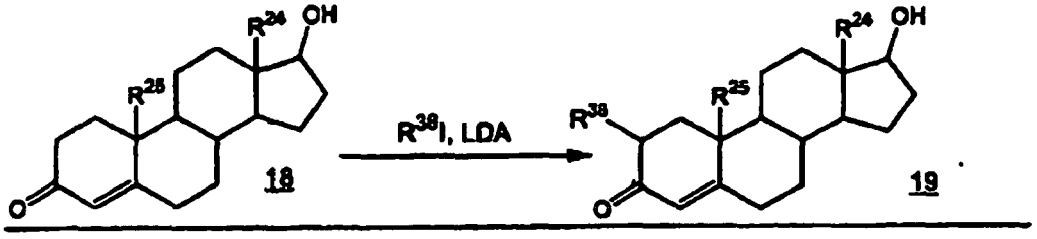
Scheme 12. Formula 1 or 2 compounds that contain a hydroxyl or ether that Is linked to the 1 position are prepared essentially as follows. A hydroxyl is introduced into the 1 position by oxidation of a suitable starting material using alkaline hydrogen peroxide to obtain the epoxide 16. The compound 16 is converted to the 1-hydroxyl derivative by treatment, e.g., with excess lithium metal and excess ammonium chloride in NH_4-THF (1:1) at reflux to give 17. The ketal group is hydrolyzed to give the 17 ketone. The hydroxyl group at 1 is optionally further converted to other moleties essentially as described above.

Scheme 12



Scheme 13. Formula 1 or 2 compounds that contain an an organic moiety that is linked to the 2 position are prepared essentially as follows. Organic moieties are introduced Into the 2 position using a corresponding reagent, e.g., $(R^{35})_2CuLi$, where R^{38} is a C1-C25 organic moiety that may comprise 1, 2, 3, 4 or more substituents, e.g., -O-, -S-, -NH-, $-OR^{PR}$, protected ketone (e.g., ethylene ketal), $-SR^{PR}$ or $-N(R^{PR})_2$. In other embodiments, R^{38} is R^3. Thus, when R^{38} is methyl, a methyl group is introduced into the 2 position, or when R^{38} is $-CH_2-OR^{PR}$, the $-CH_2-OR^{PR}$ group is Introduced Into the 2 position. The starting material 18 is testosterone when R^{24} and R^{25} are both methyl. The compound 18 is alkyleted using an alkylating agent such as the iodide $R^{36}I$ in the presence of a strong base such as lithium diisopropylamide ("LDA"), n-butyllithium sodium *t*-pentoxide or $(C_2H_5)_2Ni$ to give R^{38} bonded to the steroid in the a and β configurations. The 2β-R^{36} group is epimerized to the 2a configuration using a strong base, e.g., a sodium alkoxide such as sodium methoxide in an alcohol such as methanol Alternatively the two epimers are at least substantially separated by routine methods.

Scheme 13

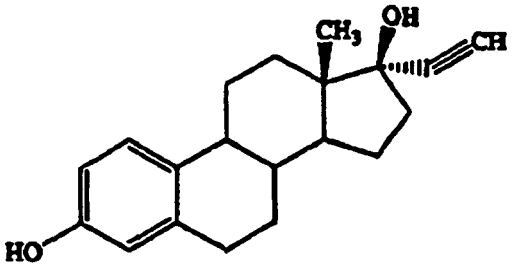


[0048] Other formula 1 and 2 compounds are prepared using methods similar to e.g., those described herein or in the cited references.

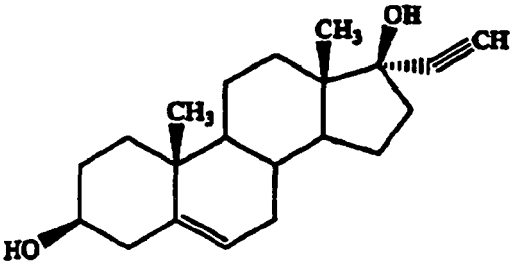
[0049] The following reference examples further illustrate the invention

[0050] Reference example 1. AR activity assay. One biological function of the AR Is to act as a transcription factor, which can modulate transcription of target genes. AED, 5α-dihydrotestosterone (DHT), 17β-estradiol (E2), and progesterone were purchased from Sigma. Ethynyl derivatized steroids were purchased from Steraloids. The plasmid pSG5-wild-type AR (pSG5) and mouse mammalian tumor virus (MMTV) -chloramphenicol acetyltransterase (CAT) were constructed as described (6). The numbers in parentheses, e.g., (8) in the preceding sentence, refer to the references listed in the reference section below. Other steroid compounds, were synthesized using routine protocols and others have been described (19, 20). The human prostate cancer cell line, PC-3, and human breast cancer cell line, MCF-7, were maintained in Dulbecco's modified eagles medium (DMEM) containing 10% fetal calf serum. DNA transfection and CAT assays were performed essentially as described (4, 6, 7). Briefly, 4 x 10^5 cells were plated on 60 mm dishes 24 h before transfection, and the medium was changed to DMEM (without phenol red) with 10% charcoal-stripped fetal calf serum 1 hour before transfection. The cells were transfected using the calcium phosphate precipitation method. The total amount of DNA was adjusted to 8.5 μg with pSG5 in each transfection assay. After transfecting the cells for 24 hours, the transfection medium was removed, fresh DMEM was added and steroids were added. The cells were then Incubated in DMEM with steroids for 24 hours. After incubation, the cells were harvested and whole cell extracts were used for CAT assay. Transfection efficiency was normalized by cotransfection with a β-galactosidase vector, which acted as an Internal control. The CAT enzyme activity was quantitated by phosphor Imager according to the manufacturer's instructions (Molecular Dynamics).

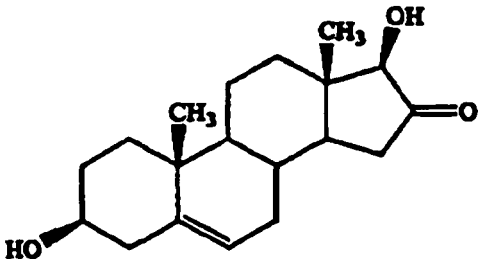
reference compound number	reference compound name
0	7-oxo-dehydroepiendrosterone
1	17α-ethynyl-17β-hydroxy-4-estrene-3-one
2	17α-ethynyl-17β-hydroxy-4-estrene-3-one
3	17α-ethynyl-17β-hydroxy-5(10)-estrene-3-one
4	1, 3, 5(10)-estratriene-17α-ethynyl-3β,17β-diol
5	androst-5-one-3β,11β,17β-triol
6	17α-ethynyl-androst-5-ene-3β,17β-diol
7	17α-ethynyl-17β-hydroxy-4-androsten-3-one
8	3β,17β-dihydroxy-androst-5-en-16-one
9	3β,17β-dihydroxy-androst-4-en
10	3β,-methylcarbonate-androst-5-en-7,17-dione
11	3β,17β-dihydroxy-androst-5-en-11-one
13	3β,17β-diacetoxy-androst-5-ene-7α, 17β-diol
14	3β,17β-diacetoxy-androst-5-ene-7-one
15	3β-methoxy-17β-hydroxy-androst-5-ene-7-one
16	3β-methoxy-androst-5-ene-?, 17β-diol
17	17β-mothoxy-androst-3,5-diene-7-one
18	17-methyl-marrienolic acid
19	17β-hydroxy-androst-3,5-diene-7-one
21	5α-androstane-3α, 17β-diol
22	7-oxo-androstene-3β, 17β-diol



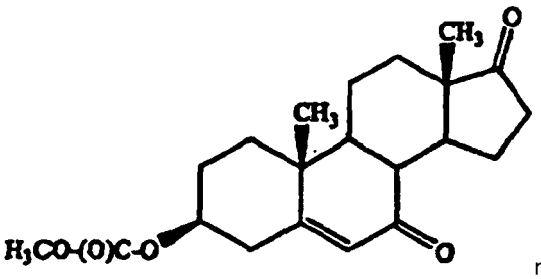
reference compound 4



reference compound 6



reference compound 8



reference compound 10

[0051] Example 2. Induction of AR-mediated transcriptional activity. Steroid compounds were screened for their ability to induce AR transcriptional activity in the AR-negative PC-3 cell line. The results of the CAT assay were obtained by transient co-transfection of AR plasmid and a reporter plasmid (MMTVCAT) containing the CAT gene linked to the androgen response element (ARE). After transfection, the cells were treated with various DHEA derivatives at 1000, 10, and 0. 1 nM. As shown in figure 1 reference compounds 0, 4, 5, 6, 8, 10, 13, 15, 16, 18, and 22 had little androgenic activity but they did induce a low level of AR-mediated CAT gene transactivation. AED (reference compound 21) had about the same capacity as DHT to stimulate AR-mediated CAT gene transcription.

[0052] Example 3. Identification of anti-adiol activity of steroids with low androgenic effects. Several compounds were screened for their capacity to modulate AED's effects on AR-mediated activation of gene transcription in PC-3 cells. The chemical structures of reference compounds 4, 6, 8 and 10 are shown in figure 2A. The PC-3 cells were co-transfected with pSG5 and the MMTV-CAT reporter vector in the presence of 50 nM AED and each reference compound at a concentration of 10, 100, or 1000 nM. As shown in figure 2B, reference compounds 4, 6, 8 and 10 antagonized AED-mediated AB transcriptional activity. At concentrations of 0.1 μM and 1 μM, reference compounds 4 and 6 suppressed the AED-induced AR transactivation to less than 30%. Reference compounds 0, 5, 13, 15, 18 an 22 show either activation of AED-mediated AR transcriptional activity or they have no effect.

[0053] Example 4. Identification of anti-DHT effects of steroids. Reference compounds 4, 6, 8 and 10 were examined to determine whether these AED antagonists had the ability to repress DHT-induced AR transactivation. PC-3 cells were co-transfected with pSG5 and the MMTV-CAT reporter plasmid in the presence of 1 nM DHT and each reference compound at 10, 100, or 1000 nM. Reference compound 4 repressed the DHT-induced AR transactivation to less than 40% at 1 μM (figure 3).

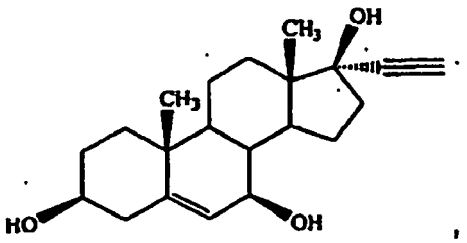
[0054] Example 5. Suppression of the AED-induced AR transcriptional activity in the presence of HF. To mimic the in vivo condition of total androgen blockage in prostate cancer patients, compounds 4, 6, 8 and 10 were examined for their capacity to antagonize AED-induced AR transactivation in the presence of HF. In the presence of 1 μM HF, 50 nM AED, and each compound at 0.01, 0.1 or 1 μM, PC-3 cells were transiently transfected with pSG5 and the MMTV-CAT reporter plasmid. As shown in figure 4, HF suppressed AED-mediated AR transcription activity by about 40%. The compounds tested decreased AED-mediated AR transcription activity by about 75%.

[0055] Example 6. Steroid Hormone Specificity of DHEA Metabolites (No. 4, 6, 8, & 10). The estrogen receptor (ER)-positive MCF-7 cell line was transfected with a CAT reporter plasmid containing an estrogen response element linked to the CAT gene. PC-3 cells were transfected with MMTV-CAT reporter and progesterone receptor (PR) or glucocorticoid receptor (GR) to test the steroid hormone specificity of reference compounds 4, 6, 8 and 10. All 4 reference compounds have some estrogenic activity and only reference compound 4, which has a 17α-ethynyl group, shows some weak PR activity. None of these four reference compounds showed any GR activity.

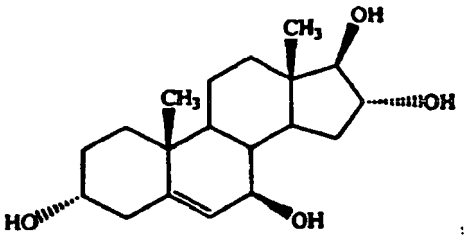
Claims

1. Use as a medicament of a compound, wherein

(a) the compound is 17α-ethynylandrost-5-ene-3β, 7β, 17β-triol (compound 1.2.1.3), which has the structure

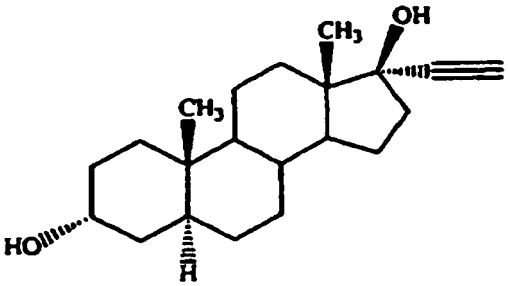


(b) the compound is androst-5-ene-3α, 7β, 16α, 17β-tetrol (compound 2.2.6.1), which has the structure

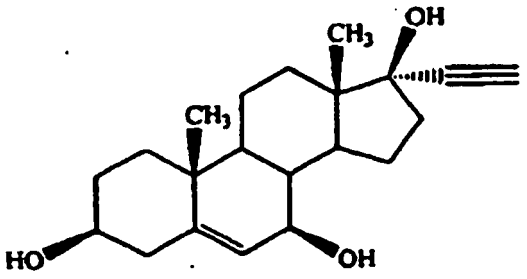


or

(c) the compound is 17α-ethynylandrostane-3α, 17β-diol (compound 2.1.1.3), which has the structure

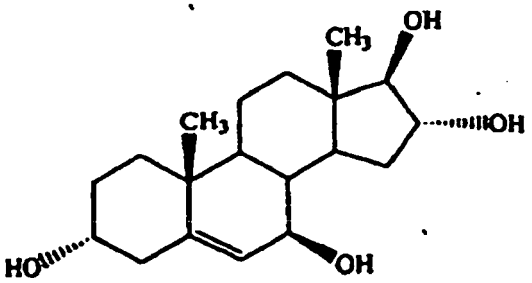


2. Use according to claim 1 wherein the compound has the structure



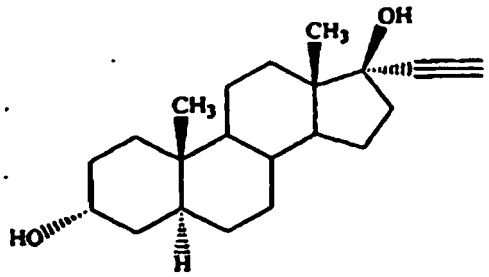
(compound 1.2.1.3).

3. Use according to claim 1 wherein the compound has the structure



(compound 2.2.6.1).

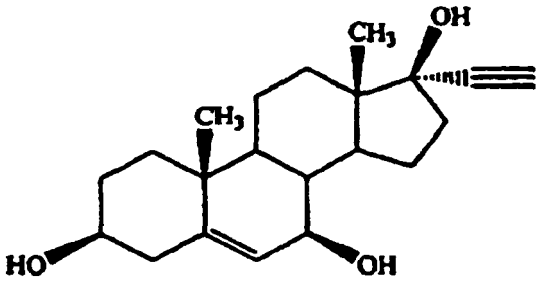
4. Use according to claim 1 wherein the compound has the structure



(compound 2.1.1.3).

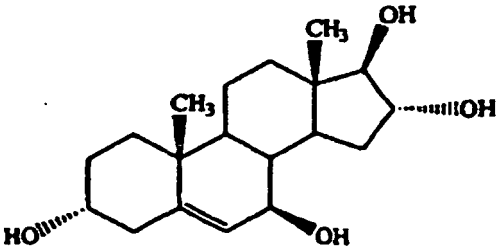
5. Use of a compound for the preparation of a medicament for the treatment of benign prostatic hyperplasia, prostate cancer or breast cancer, wherein

(a) the compound has the structure



(compound 1.2.1.3),

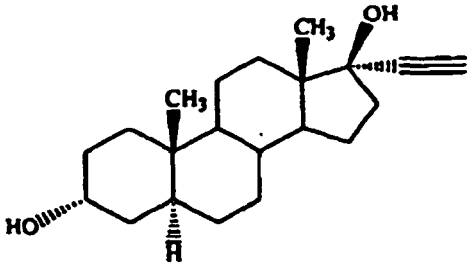
(b) the compound has the structure



(compound 2.2.6.1),

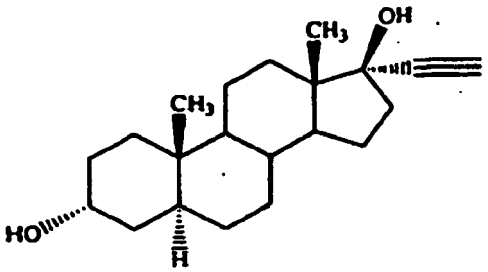
or

(c) the compound has the structure



(compound 2.1.1.3).

6. Use according to claim 5 wherein the compound has the structure



(compound 2.1.1.3).

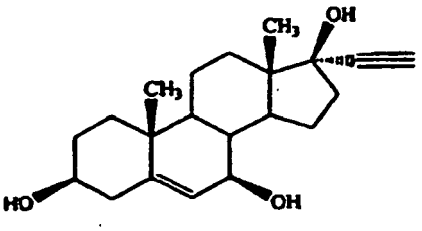
7. Use according to claim 6 wherein the medicament is for the treatment of benign prostatic hyperplasia.

8. Use according to claim 6 wherein the medicament is for the treatment of prostate cancer.

9. Use according to claim 6 wherein the medicament is for the treatment of breast cancer.

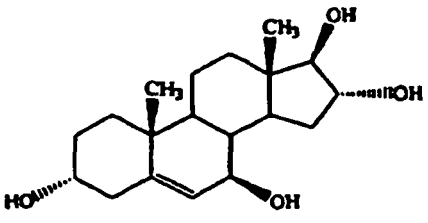
10. A compound having the structure

(a



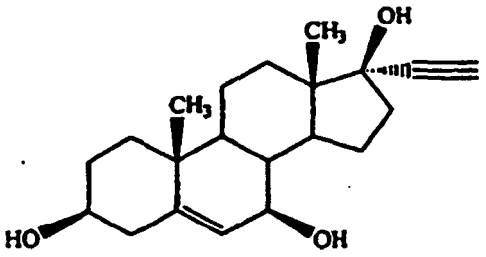
(compound 1.2.1.3),

or
(b



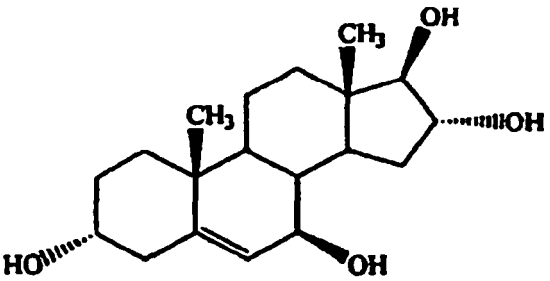
(compound 2.2.6.1).

11. The compound according to claim 10 wherein the compound has the structure



(compound 1.2.1.3).

12. The compound according to claim 10 wherein the compound has the structure

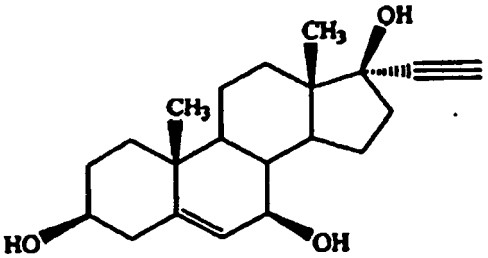


(compound 2.2.6.1).

13. The compound according to claim 11 or 12 wherein the compound is a powder or granules.

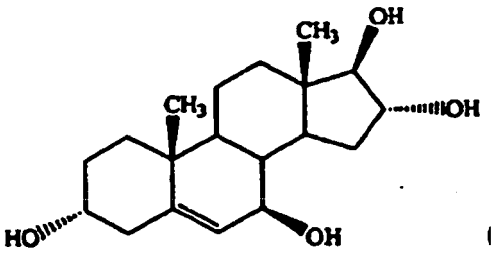
14. A formulation comprising one or more excipients and a compound wherein the compound has the structure

(a)



(compound 1.2.1.3),

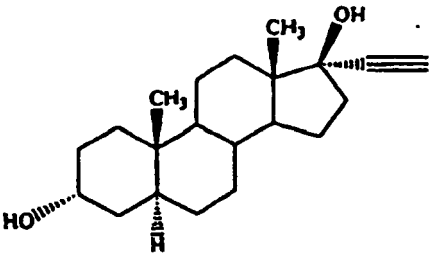
(b)



(compound 2.2.6.1),

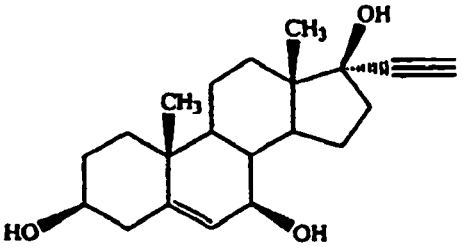
or

(c)



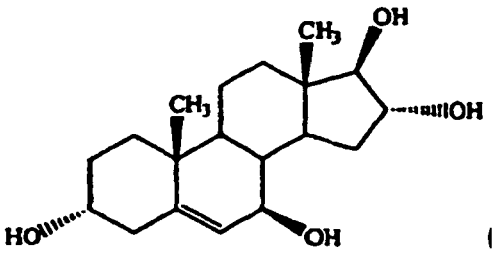
(compound 2.1.1.3).

15. The formulation according to claim 14 wherein the compound has the structure



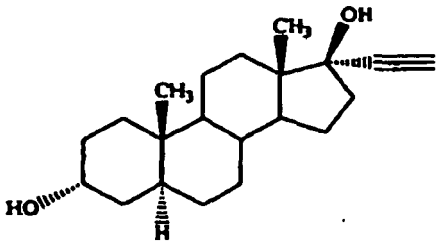
(compound 1.2.1.3).

16. The formulation according to claim 14 wherein the compound has the structure



(compound 2.2.6.1).

17. The formulation according to claim 14 wherein the compound has the structure

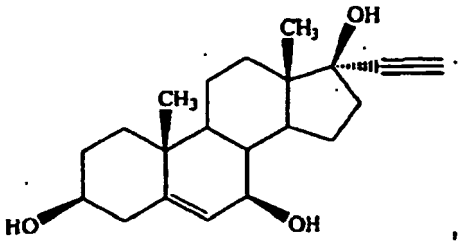


(compound 2.1.1.3).

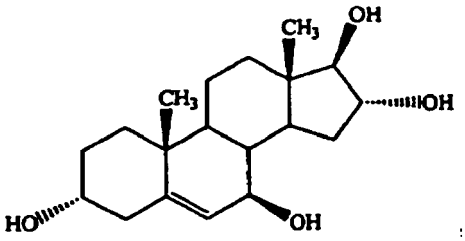
Patentansprüche

1. Verwendung einer Verbindung als Medikament, wobei

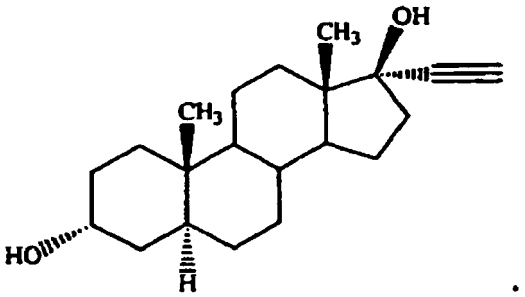
(a) die Verbindung 17α-Ethinylandrost-5-en-3β, 7β, 17β-triol (Verbindung 1.2.1.3) ist, welches die Struktur



hat;
(b) die Verbindung Androst-5-en-3α, 7β, 16α, 17β-tetrol (Verbindung 2.2.6.1) ist, welches die Struktur

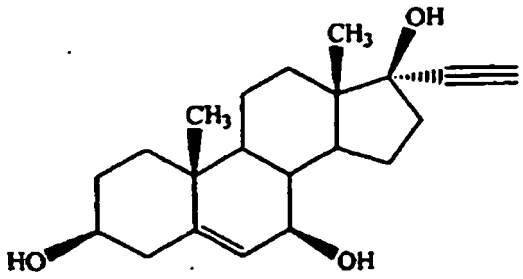


hat; oder
(c) die Verbindung 17α-Ethinylandrostan-3α, 17β-diol (Verbindung 2.1.1.3) ist, welches die Struktur



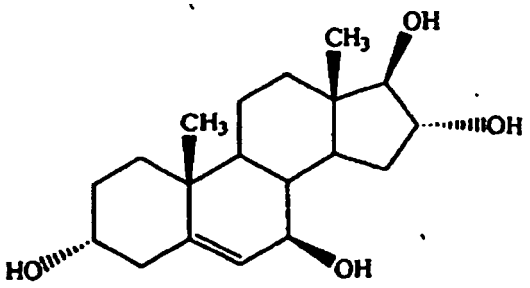
hat.

2. Verwendung nach Anspruch 1, wobei die Verbindung die Struktur



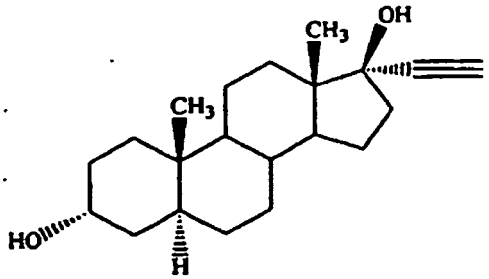
(Verbindung 1.2.1.3) hat.

3. Verwendung nach Anspruch 1, wobei die Verbindung die Struktur



(Verbindung 2.2.6.1) hat.

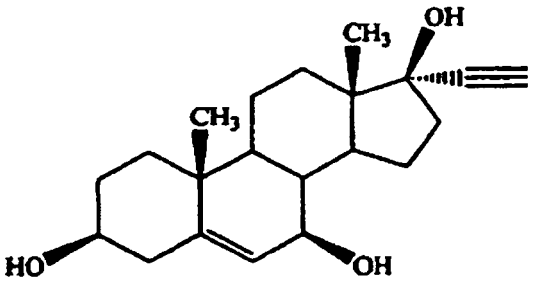
4. Verwendung nach Anspruch 1, wobei die Verbindung die Struktur



(Verbindung 2.1.1.3) hat.

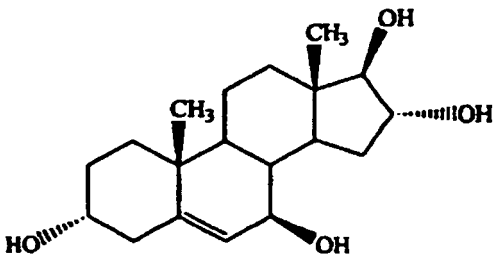
5. Verwendung einer Verbindung zur Herstellung eines Medikaments zur Behandlung von benigner Prostatahyperplasie, Prostatakrebs oder Brustkrebs, wobei

(a) die Verbindung die Struktur



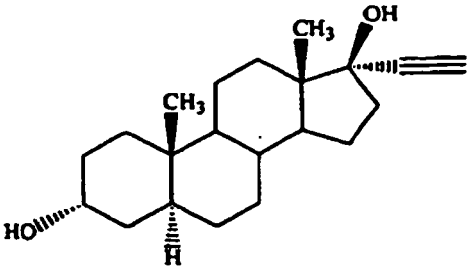
(Verbindung 1.2.1.3) hat,

(b) die Verbindung die Struktur



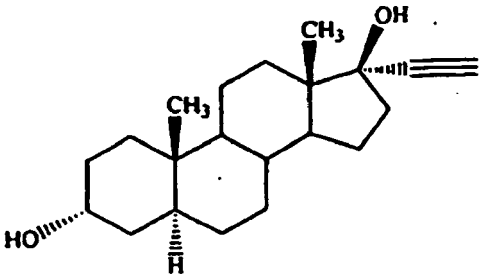
(Verbindung 2.2.6.1) hat, oder

(c) die Verbindung die Struktur



(Verbindung 2.1.1.3) hat.

6. Verwendung nach Anspruch 5, wobei die Verbindung die Struktur



(Verbindung 2.1.1.3) hat.

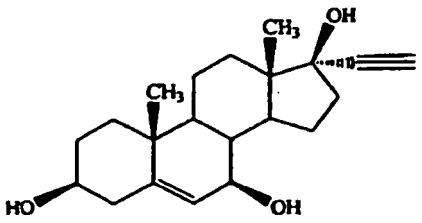
7. Verwendung nach Anspruch 6, wobei das Medikament zur Behandlung von benigner Prostatahyperplasie ist.

8. Verwendung nach Anspruch 6, wobei das Medikament zur Behandlung von Prostatakrebs ist.

9. Verwendung nach Anspruch 6, wobei das Medikament zur Behandlung von Brustkrebs ist.

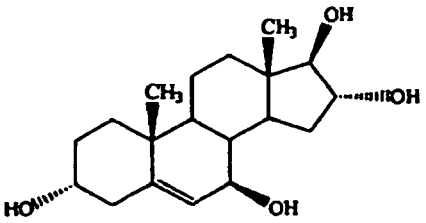
10. Verbindung mit der Struktur

(a



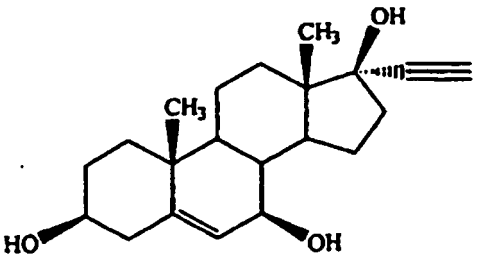
(Verbindung 1.2.1.3), oder

(b



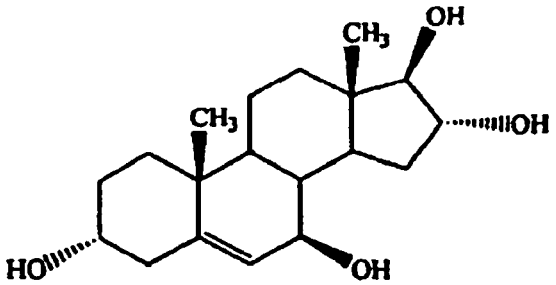
(Verbindung 2.2.6.1).

11. Verbindung nach Anspruch 10, wobei die Verbindung die Struktur



(Verbindung 1.2.1.3) hat.

12. Verbindung nach Anspruch 10, wobei die Verbindung die Struktur

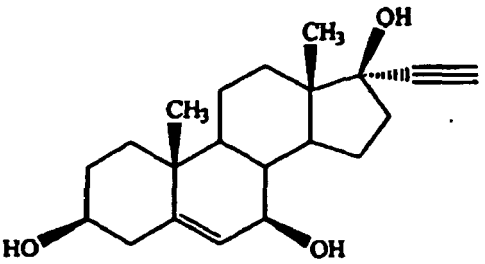


(Verbindung 2.2.6.1) hat.

13. Verbindung nach Anspruch 11 oder 12, wobei die Verbindung ein Pulver oder ein Granulat ist.

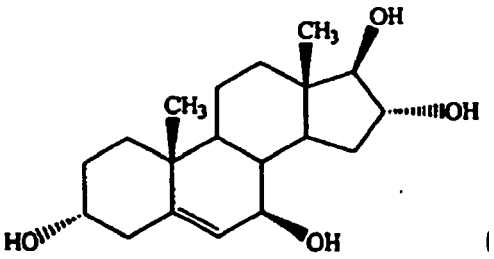
14. Formulierung umfassend einen oder mehrere Hilfsstoffe und eine Verbindung, wobei die Verbindung die Struktur

(a)



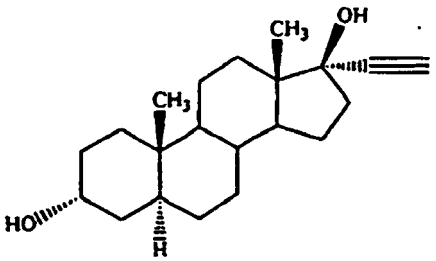
(Verbindung 1.2.1.3),

(b)



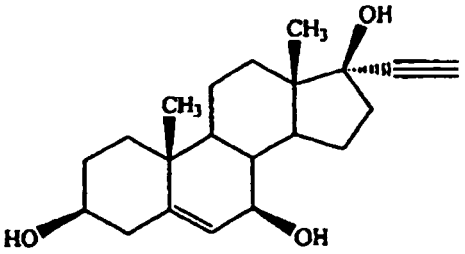
(Verbindung 2.2.6.1), oder

(c)



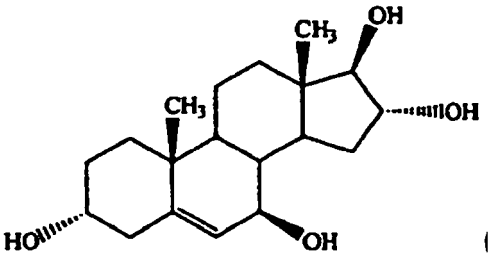
(Verbindung 2.1.1.3) hat.

15. Formulierung nach Anspruch 14, wobei die Verbindung die Struktur



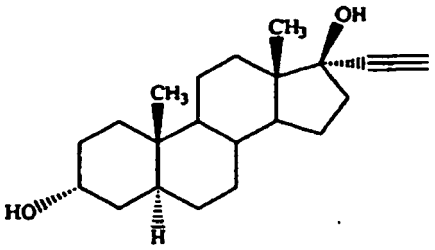
(Verbindung 1.2.1.3) hat.

16. Formulierung nach Anspruch 14, wobei die Verbindung die Struktur



(Verbindung 2.2.6.1) hat.

17. Formulierung nach Anspruch 14, wobei die Verbindung die Struktur

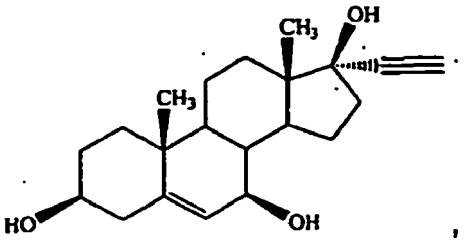


(Verbindung 2.1.1.3) hat.

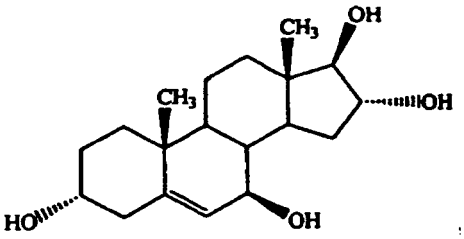
Revendications

1. Utilisation d'un composé comme médicament, où

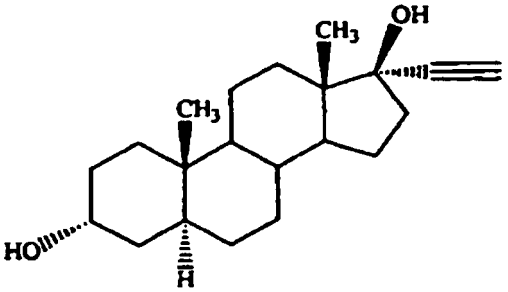
(a) le composé est 17α-éthynylandrost-5-ene-3β, 7β, 17β-trio (composé 1.2.1.3), qui présente la structure



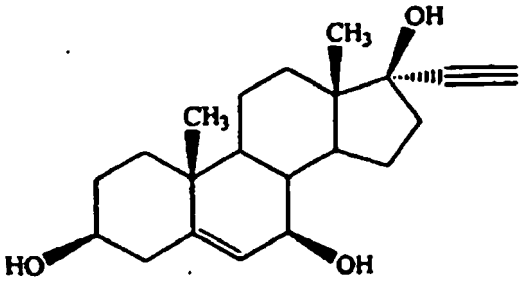
(b) le composé est androst-5-ene-3α, 7β, 16α, 17β-tétrol (composé 2.2.6.1), qui présente la structure



(c) le composé est 17α-éthynylandrostane-3α, 17β-diol (composé 2.1.1.3), qui présente la structure

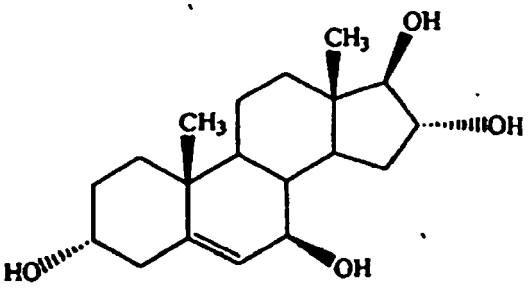


2. Utilisation selon la revendication 1, où le composé présente la structure



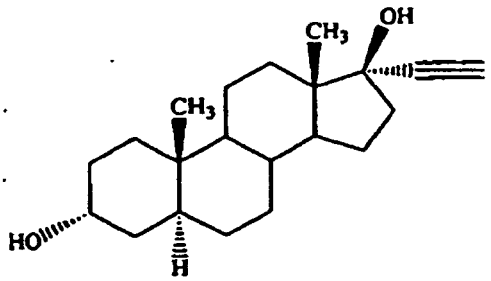
(composé 1.2.1.3).

3. Utilisation selon la revendication 1, où le composé présente la structure



(composé 2.2.6.1).

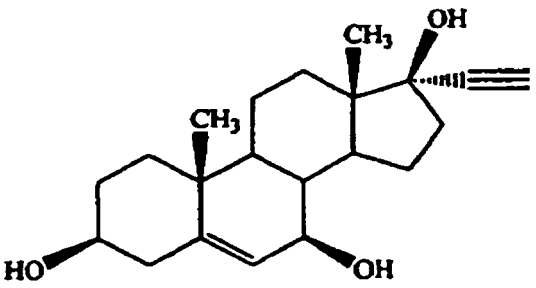
4. Utilisation selon la revendication 1, où le composé présente la structure



(composé 2.1.1.3).

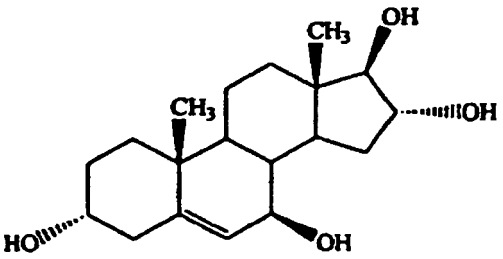
5. Utilisation d'un composé pour la préparation d'un médicament pour le traitement de l'hyperplasie prostatique bénine, le cancer de la prostate ou le cancer du sein, où

(a) le composé présente la structure



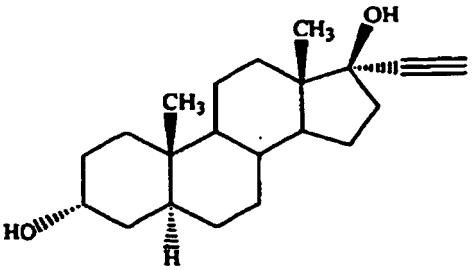
(composé 1.2.1.3),

(b) le composé présente la structure



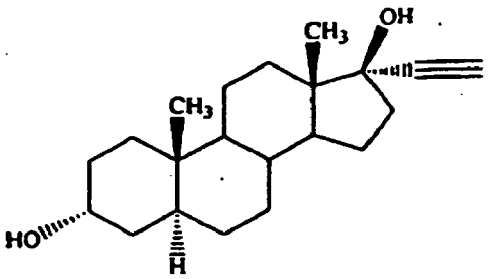
(composé 2.2.6.1), ou

(c) le composé présente la structure



(composé 2.1.1.3).

6. Utilisation selon la revendication 5, où le composé présente la structure



(composé 2.1.1.3).

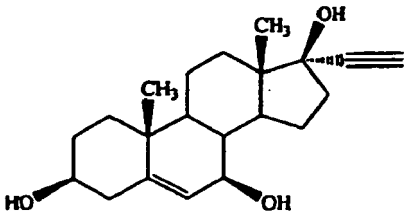
7. Utilisation selon la revendication 6, où le médicament est destiné au traitement de l'hyperplasie prostatique bénine.

8. Utilisation selon la revendication 6, où le médicament est destiné au traitement du cancer de la prostate.

9. Utilisation selon la revendication 6, où le médicament est destiné au traitement du cancer du sein.

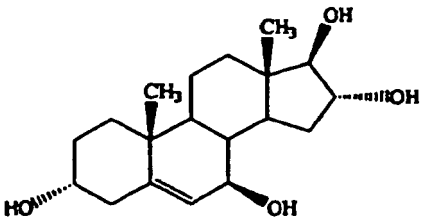
10. Un composé présentant la structure

(a



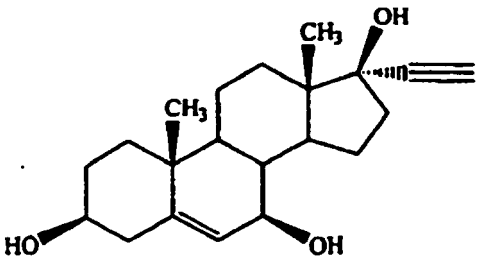
(composé 1.2.1.3), ou

(b



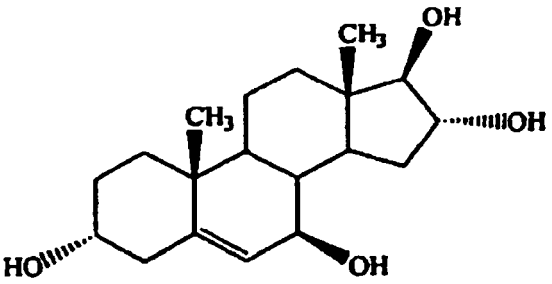
(composé 2.2.6.1).

11. Le composé selon la revendication 10, où le composé présente la structure



(composé 1.2.1.3).

12. Le composé selon la revendication 10, où le composé présente la structure

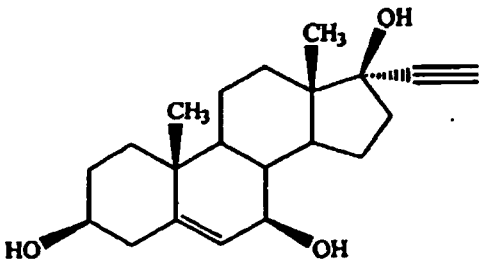


(composé 2.2.6.1).

13. Le composé selon la revendication 11 ou 12, où le composé est une poudre ou des granules.

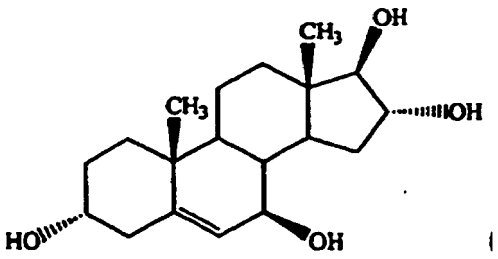
14. Une formule comportant un ou plusieurs excipients et un composé, le composé présentant la structure

(a)



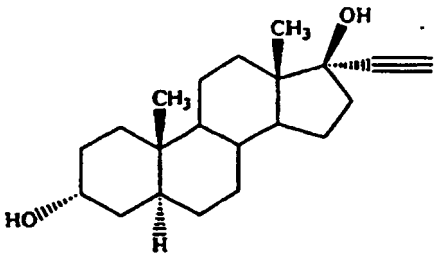
(composé 1.2.1.3),

(b)



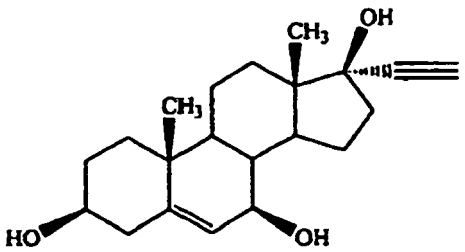
(composé 2.2.6.1), ou

(c)



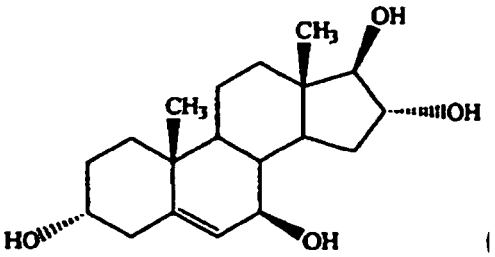
(composé 2.1.1.3).

15. La formule selon la revendication 14, où le composé présente la structure



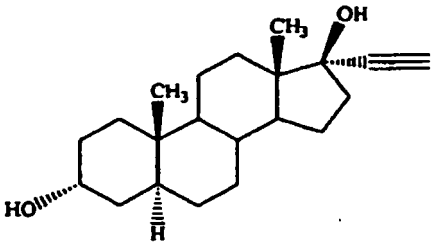
(composé 1.2.1.3).

16. La formule selon la revendication 14, où le composé présente la structure



(composé 2.2.6.1).

17. La formule selon la revendication 14, où le composé présente la structure



(composé 2.1.1.3).

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