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(54) Title: 7BETA–METHYL–16BETA–((4–METHYLSULFONYL)–PHENOXY)–4–AZA–5ALPHA–ANDROST–1–EN–3–ONE AS A 5–ALPHA–REDUCTASE ISOZYME 1 INHIBITOR

(57) Abstract

The compound 7$\beta$–methyl–16$\beta$–((4–methylsulfonyl)–phenoxy)–4–aza–5$\alpha$–androst–1–en–3–one is an inhibitor of the 5$\alpha$–redctase 1 isozyme, and is useful alone or in combination with a 5$\alpha$–reductase 2 inhibitor for the treatment of hyperandorgenic disorders such as acne vulgaris, seborrhea, female hirsutism, male pattern baldness, and benign prostatic hyperplasia, and in pharmaceutical compositions.

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# TITLE OF THE INVENTION

7BETA-METHYL-16BETA-((4-METHYLSULFONYL)-PHENOXY)-4-AZA-5ALPHA-ANDROST-1-EN-3-ONE AS A 5-ALPHA-REDUCTASE ISOZYME 1 INHIBITOR

## CROSS REFERENCE TO RELATED APPLICATIONS

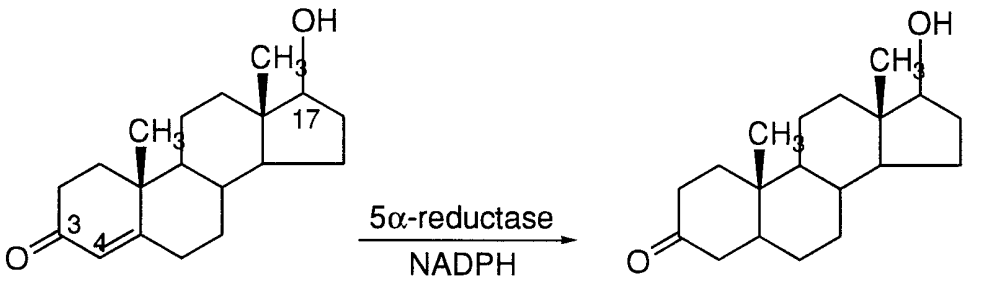
The present application claims priority of U.S. provisional application Serial No. 60/085,450, filed May 14, 1998.

## BACKGROUND OF THE INVENTION

Certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, androgenic alopecia which includes female and male pattern baldness, and benign prostatic hyperplasia, are the result of hyper-androgenic stimulation caused by an excessive accumulation of testosterone ("T") or similar androgenic hormones in the metabolic system. Early attempts to provide a chemotherapeutic agent to counter the undesirable results of hyperandrogenicity resulted in the discovery of several steroidal antiandrogens having undesirable hormonal activities of their own. The estrogens, for example, not only counteract the effect of the androgens but have a feminizing effect as well. Non-steroidal antiandrogens have also been developed, for example, 4'-nitro-3'-trifluoromethyl-isobutyranilide. See Neri, et al., *Endocrinol.* **1972**, *91* (2). However, these products, though devoid of hormonal effects, compete with all natural androgens for receptor sites, and hence have a tendency to feminize a male host or the male fetus of a female host and/or initiate feed-back effects which would cause hyperstimulation of the testes.

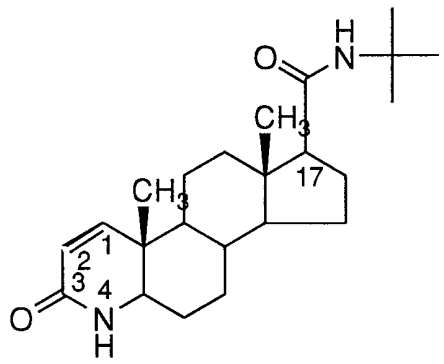
The principal mediator of androgenic activity in some target organs, e.g. the prostate, is 5α-dihydrotestosterone ("DHT"), formed locally in the target organ by the action of testosterone-5α-reductase (or simply 5α-reductase). Inhibitors of 5α-reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation in these organs. See especially United States Patent Nos. 4,377,584, issued March 22, 1983, and 4,760,071, issued July 26, 1988, both assigned to Merck & Co., Inc.

The enzyme 5α-reductase catalyzes the reduction of testosterone to the more potent androgen, dihydrotestosterone, as shown below:




testosterone dihydrotestosterone

Finasteride, (17β-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5α-androst-1-ene-3-one) as shown below, is a potent inhibitor of the human prostate enzyme.




finasteride

Under the trade name PROSCAR®, finasteride is known to be useful in the treatment of hyperandrogenic conditions; see eg. U.S. 4,760,071. Finasteride is currently prescribed for the treatment of benign prostatic hyperplasia (BPH), a condition afflicting to some degree the majority of men over age 55. Finasteride's utility in the treatment of androgenic alopecia and prostatic carcinoma is also disclosed in the following documents: EP 0 285,382, published 5 October 1988; EP 0 285,383,

published 5 October 1988; Canadian Patent no. 1,302,277; and Canadian Patent no. 1,302,276.

There are two isozymes of 5α-reductase in humans. One isozyme (type 1 or 5α-reductase 1) predominates in sebaceous glands of facial and skin tissue and is relatively insensitive to finasteride (see, e.g., G. Harris, et al., *Proc. Natl. Acad. Sci. USA, Vol. 89*, pp. 10787-10791 (Nov. 1992)); the other (type 2 or 5α-reductase 2) predominates in the prostate and is potently inhibited by finasteride. A genus of 16β-substituted-4-azasteroids are described in U.S. Patent 5,719,158.

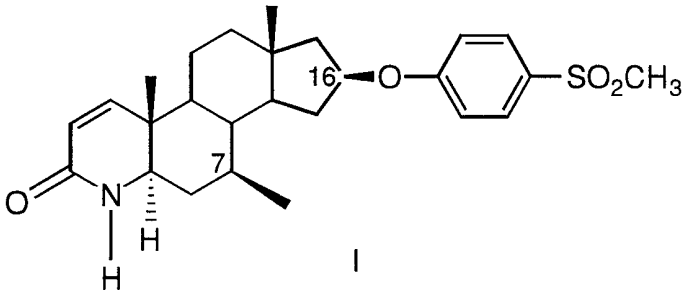
In the treatment of hyperandrogenic disease conditions, e. g. benign prostatic hyperplasia (BPH) and/or the prevention and treatment of prostatic cancer, it would be desirable to have one drug entity which is active against both isozymes in the prostate to significantly inhibit dihydrotestosterone production. It would also be desirable to have another drug entity which is highly selective for inhibiting the isozyme 5α-reductase 1 associated with the scalp, for use in treating conditions of the skin and scalp. Additionally, a selective 5α-reductase 1 inhibitor could be used in combination with a selective 5α-reductase 2 inhibitor such as, e.g., finasteride (PROSCAR®), for therapy in the treatment of hyperandrogenic conditions such as BPH and/or the prevention and treatment of prostatic cancer, and for the treatment of disorders such as acne vulgaris, seborrhea, female hirsutism, and androgenic alopecia. Alternatively, a single drug entity capable of inhibiting both isozymes could be used for treatment of such hyperandrogenic conditions. Therefore it is an object of this invention to provide compounds that have sufficient activity in the inhibition of 5α-reductase isozyme 1.

## SUMMARY OF THE INVENTION

The present invention provides the novel compound 7β-methyl-16β-((4-methylsulfonyl)phenoxy)-4-aza-5α-androst-1-en-3-one, novel compositions containing 7β-methyl-16β-((4-methylsulfonyl)phenoxy)-4-aza-5α-androst-1-en-3-one, methods of its use and methods of its manufacture, where such compound is generally pharmacologically useful as an agent in therapies whose

mechanism of action rely on the selective inhibition of the isozyme 5α-reductase 1.

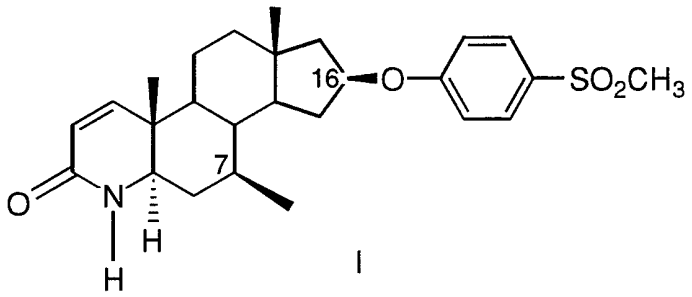
The novel compound of this invention has the structural formula (I):




I

and salts and crystal forms thereof and is a selective inhibitor of 5α-reductase 1. Compared with structurally related type 1 5α-reductase inhibitors, this compound has superior pharmacokinetic properties in primates, including humans. It is an object of this invention to provide a compound that alone or in combination with inhibitors of 5α-reductase 2 is useful in the treatment of benign prostatic hyperplasia, prostatitis, and/or the prevention and treatment of prostatic cancer, as well as in the treatment of prostatitis, the treatment of sweat-related conditions such as apocrine gland sweating, hyperhidrosis, and hydradenitis suppurativa, the treatment of polycystic ovary syndrome, the prevention and treatment of bone loss and related diseases, and the prevention and treatment of premature labor, the treatment of acne vulgaris, the treatment of female hirsutism, and the treatment of androgenic alopecia (also known as androgenetic alopecia and human pattern baldness). The compounds of the present invention may also be useful to raise HDL cholesterol levels. The compound of the invention has utility in one or more of the aforementioned areas.

The novel compound of the present invention has the general structural formula I:




I

or a pharmaceutically acceptable salt, ester or crystal form thereof

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of this invention.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disorder being treated.

Some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention.

Accordingly, the present invention has the objective of providing methods of treating the hyperandrogenic conditions of androgenic alopecia including male pattern baldness, acne vulgaris, seborrhea, and female hirsutism by oral, systemic, parenteral or topical administration of the novel compounds of formula I either alone or in combination with a 5α-reductase 2 inhibitor and/or a potassium channel opener. The term "treating androgenic alopecia" is intended to include the arresting and/or reversing of androgenic alopecia, and the promotion of hair growth. The method of the present invention may also be employed in the treatment of sweat-related conditions such as apocrine gland sweating, hyperhidrosis, and hydradenitis suppurativa, in the treatment of polycystic ovary

syndrome, in the treatment and prevention of premature labor, in the prevention and treatment of bone loss, and to treat cardiovascular disease by raising HDL cholesterol levels. The present invention has the further objective of providing methods of treating benign prostatic hyperplasia, prostatitis, and treating and/or preventing prostatic carcinoma by oral, systemic or parenteral administration of the novel compounds of formula I either alone or in combination with a 5α-reductase 2 inhibitor.

The use of 5α-reductase inhibitors in the treatment of sweat related conditions is described in U.S. 5,512,555. Hyperhidrosis is defined as an increase above normal in sweat production. This is diagnosed when sweating occurs under contions where it would not normally be expected or is excessive in response to emotional or thermal stimuli. Hydradenitis suppurativa (HS) is a chronic inflammatory disorder of apocrine sweat glands in which abscesses and drainage sinuses develop in the axilla and/or perineal area. The pathogenesis of HS is felt to be similar to acne: poral occlusion, bacterial colonization, androgenic stimulations and inflammation all seem to be important.

The use of 5α-reductase inhibitors to increase HDL cholesterol levels is described in PCT application US95/07215, which published as WO96/08239.

"Preventing and treating bone loss and related diseases" relates to methods of treating and/or preventing osteoporosis and osteopenia and other diseases where inhibiting bone loss may be beneficial, including: Paget's disease, malignant hypercalcemia, periodontal disease, joint loosening and metastatic bone disease, as well as reducing the risk of fractures, both vertebral and nonvertebral.

The present invention has the objective of providing methods of treating hyperandrogenic conditions including androgenic alopecia, male pattern baldness, acne vulgaris, seborrhea, and female hirsutism by oral, systemic, parenteral or topical administration of the novel compounds of formula I either alone or in combination with a 5α-reductase 2 inhibitor, preferably selected from finasteride and epristeride, or a potassium channel opener, or a retinoic acid or derivative thereof. Alternatively,

treatment may encompass administration of a combination of a compound of formula I with a 5α-reductase 2 inhibitor, preferably selected from finasteride and epristeride and another active agent such as a potassium channel opener, or a retinoic acid or derivative therof. The term "treating androgenic alopecia" is intended to include the arresting and/or reversing of androgenic alopecia, and the promotion of hair growth.

The present invention has the further objective of providing methods of treating benign prostatic hyperplasia, prostatitis, and treating and/or preventing prostatic carcinoma by oral, systemic or parenteral administration of the novel compounds of formula I either alone or in combination with a 5α-reductase 2 inhibitor, preferably selected from finasteride and epristeride. Alternatively, treatment may encompass administration of a combination of a compound of formula I with a 5α-reductase 2 inhibitor and/or another active agent such as an α1 or an $\alpha 1_a$ adrenergic receptor antagonist ($\alpha 1_a$ receptor antagonists were formerly called $\alpha 1_c$ receptor antagonists).

The present invention also has a further objective of providing methods of treating acne vulgaris, androgenic alopecia, seborrhea, female hirsutism, benign prostatic hyperplasia, prostatitis and the preventing and/or treating of prostatic cancer, by oral, systemic, parental or topical administration of a combined therapy of a therapeutically effective amount of a compound of formula I with a therapeutically effective amount of an anti-androgen, such as, e.g., flutamide, spironolactone or casodex.

The present invention further has the objective of treating, preventing, and reducing the risk of premature labor and stopping labor preparatory to Cesarean delivery by oral, rectal, intravaginal, topical or parenteral (including subcutaneous, intramuscular and intravenous administration) administration of a compound of structural formula I either alone or in combination with another 5α-reductase inhibitor, either a type 1 inhibitor, a type 2 inhibitor, or a dual inhibitor, other tocolytic agents used in the treatment of preterm labor such as β-adrenergic agonists (e.g., ritodrine, isoproterenol, terbutaline,

albuterol), magnesium sulfate, ethanol, other oxytocin antagonists (e.g., atosiban), calcium transport blockers (e.g., nicardipine, nifedipine), prostaglandin synthesis inhibitors (e.g., indomethacin), nitric oxide donors (e.g., nitroglycerine, S-nitroso-N-acetylpenicillamine), phosphodiesterase inhibitors, and progestins (e.g., progesterone). The compound of structural formula I of the instant invention may also be used in combination with antenatal steroids (e.g., dexamethasone). This particular combination has beneficial effects on the neonate by both decreasing uterine activity to prolong gestation and increasing fetal maturation. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating preterm labor related conditions includes in principle any combination with any pharmaceutical composition useful for treating preterm labor, or stopping labor prior to Cesarean delivery.

The present invention further has the objective of treating apocrine gland sweating and hyperhidrosis, by administration of a compound of structural formula I either alone or in combination with a therapeutically effective amount of a topical antiperspirant such as an aluminum salt, e.g. aluminum hydroxide and/or a topical or oral anti-cholinergic agent and optionally including a deodorant.

Still another objective of the present invention is the treatment of hydradenitis suppurativa by administration of the compounds of structural formula I either alone or in combination with an anticholinergic agent, antibiotics and/or isotretinoin each of which can be administered topically or orally.

For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents can be administered concomitantly, or they each can be administered at separately staggered times.

The present invention also has the objective of providing suitable topical, oral, systemic and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compositions containing the present compounds as the active ingredient for use in the treatment of the above-noted

hyperandrogenic conditions can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration. For example, the compounds can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions, or by injection. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an antiandrogenic agent.

The compounds of structural formula I useful in the present invention are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices may be administered systemically, by oral administration or by intravenous or intramuscular injection or topically.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Capsules containing the product of this invention can be prepared by mixing an active compound of the present invention with lactose and magnesium stearate, calcium stearate, starch, talc, or other carriers, and placing the mixture in gelatin capsules.

Tablets may be prepared by mixing the active ingredient with conventional tableting ingredients such as calcium phosphate, lactose, corn starch or magnesium stearate. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia,

tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The liquid forms in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. Other dispersing agents which may be employed include glycerin and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

Topical pharmaceutical compositions may be, e.g., in the form of a solution, cream, ointment, gel, lotion, shampoo or aerosol formulation adapted for application to the skin. Topical pharmaceutical compositions useful in the method of treatment of the present invention may include about 0.001% to 0.1% of the active compound in admixture with a pharmaceutically acceptable carrier.

Topical preparations containing the active drug component can be admixed with a variety of carrier materials well known in the art, such as, e.g., alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG2 myristyl propionate, and the like, to form, e.g., alcoholic solutions, topical cleansers, cleansing creams, skin gels, skin lotions, and shampoos in cream or gel formulations. See, e.g., EP 0 285 382.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug

carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamide-phenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter, arrest or reverse the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug. Preferably, doses of the compound of structural formula I useful in the method of the present invention range from 0.01 to 1000 mg per adult human

per day. Most preferably, dosages range from 0.1 to 50 mg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01 to 1000 milligrams of the active ingredient, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.0002 mg/kg to about 50 mg/kg of body weight per day. The range is more particularly from about 0.001 mg/kg to 1 mg/kg of body weight per day.

Advantageously, the active agent of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily.

The compounds of the present invention may be used in the preparation of a medicament useful for the treatment of hyperandrogenic disorders including: acne vulgaris, androgenic alopecia, male pattern baldness, seborrhea, female hirsutism, benign prostatic hyperplasia, prostatitis, prostatic cancer, bone-loss related diseases, polycystic ovary syndrome, and preterm labor.

For the treatment of acne vulgaris, androgenic alopecia, male pattern baldness, seborrhea, female hirsutism, benign prostatic hyperplasia, prostatitis and the prevention and/or treatment of prostatic cancer, as well as sweat-related conditions and bone loss, the compounds of the instant invention can be combined with a therapeutically effective amount of another 5α-reductase inhibitor, such as finasteride or epristeride, or other 5α-reductase inhibitor compounds having type 2 activity, type 1 activity or dual activity for both isozymes, in a single oral, systemic, or parenteral pharmaceutical dosage formulation. Alternatively, a combined therapy can be employed wherein the compound of formula I and the other 5α-reductase inhibitor are administered in separate oral, systemic, or parenteral dosage formulations. Also, for the skin and scalp related disorders of acne vulgaris, androgenic alopecia, male pattern baldness, seborrhea, and female hirsutism, the compounds

of the instant invention and another 5α-reductase inhibitor such as finasteride or epristeride can be formulated for topical administration. For example, a compound of formula I and finasteride can be administered in a single oral or topical dosage formulation, or each active agent can be administered in a separate dosage formulation, e.g., in separate oral dosage formulations, or an oral dosage formulation of finasteride in combination with a topical dosage formulation of a compound of formula I. See, e.g., U.S. Patent No.'s 4,377,584 and 4,760,071 which describe dosages and formulations for 5α-reductase inhibitors.

Furthermore, administration of a compound of the present invention in combination with a therapeutically effective amount of a potassium channel opener, such as minoxidil, cromakalin, pinacidil, a compound selected from the classes of S-triazine, thiane-1-oxide, benzopyran, and pyridinopyran derivatives or a pharmaceutically acceptable salt thereof, may be used for the treatment of androgenic alopecia including male pattern baldness. Therapy may further comprise the administration of a 5α-reductase type 2 inhibitor such as finasteride or epristeride, or a 5α-reductase type 1 inhibitor, or a type 1 and type 2 dual inhibitor, in combination with a compound of the present invention and a potassium channel opener such as minoxidil. The active agents can be administered in a single topical dosage formulation, or each active agent can be administered in a separate dosage formulation, e.g., in separate topical dosage formulations, or an oral dosage formulation of a compound of formula I in combination with a topical dosage formulation of, e.g., minoxidil, or a single oral dosage formulation of a compound of formula I and another 5α-reductase inhibitor, in combination with a topical dosage formulation of, e.g., minoxidil. See, e.g., U.S. Patent No.'s 4,596,812, 4,139,619 and WO 92/02225, published 20 February 1992, for dosages and formulations of calcium channel openers.

Furthermore, for the treatment of acne vulgaris, a combined therapy can be used by administering a therapeutically

effective amount of a compound of formula I in combination with a therapeutically effective amount of retinoic acid or a derivative thereof, e.g. an ester or amide derivative thereof, such as e.g., tretinoin or isotretinoin. Optionally, this combined therapy for acne vulgaris may further include a 5α-reductase type 2 inhibitor such as finasteride or epristeride, or a 5α-reductase type 1 inhibitor, or a dual type 1 and type 2 inhibitory compound.

Also, for the treatment of benign prostatic hyperplasia, a combined therapy comprising a administration of a compound of formula I with a 5α-reductase type 2 inhibitor, such as e.g., finasteride, and an alpha-1 adrenergic receptor antagonist, such as e.g., terazosin, doxazosin, prazosin, bunazosin, indoramin or alfuzosin, may be employed. More particularly, the combined therapy can comprise administering a compound of formula I with a 5α-reductase type 2 inhibitor, such as e.g., finasteride, and an alpha-$1_a$ adrenergic receptor antagonist (formerly called an alpha-$1_c$ adrenergic receptor antagonist). Compounds which are useful as alpha-$1_a$ adrenergic receptor antagonists can be identified according to procedures known to those of ordinary skill in the art, for example, as described in PCT/US93/09187 (WO94/08040, published April 14, 1994); PCT/US94/03852 (WO 94/22829, published October 13, 1994); PCT/US94/10162 (WO 95/07075, published March 16, 1995), and U.S. Patent 5,403,847.

Also, for the treatment of acne vulgaris, androgenic alopecia, seborrhea, female hirsutism, benign prostatic hyperplasia, prostatitis and the prevention and/or treatment of prostatic cancer, a combined therapy can be used by administering a therapeutically effective amount of a compound of formula I with a therapeutically effective amount of an anti-androgen, such as, e.g., flutamide, spironolactone or casodex.

For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents can be administered concurrently, or they each can be administered at separately staggered times.

The compound of the present invention can be prepared readily according to the following reaction Schemes and Examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Some abbreviations used herein are as follows: Ph is phenyl; Ac is an acyl group; t-Bu is tert-butyl; Et is ethyl; Me is methyl; i-Am is iso-amyl; and EtOAc is ethyl acetate.

The starting material for the process is produced according to the procedures in Miller et al., Tetrahedron Letters 37(20) 3429-3432 (1996) and those in PCT publication WO 95/32215, and is generally known and available in the art.

Addition of methyl magnesium chloride to the 7-keto-3,16 diacetate starting material (1) cleaves the 3 and 16 acetates with concurrent addition to the 7-ketone to produce (2). Anhydrous cerium trichloride, in the proper needle form, was added to the Grignard before addition to the 7-ketone and improved the yield of the reaction by >15%. The triol (2) can be carried on to the next step without purification, or it may be isolated.

Oxidation of the triol (2) to the dienedione (3) was carried out under Oppenauer conditions with 2-butanone, aluminum isopropoxide, and triethylamine. Concurrent hydrolysis of the aluminum salts and elimination of the 7-OH occurred upon aging with concentrated HCl. Butanone dimers can be removed from the reaction mixture by a water distillation before carrying on to the next step, or the dienedione (3) may be isolated.

A chemo- and stereoselective reduction of the dienone (3) to the 7-β methyl enone (4) was achieved under transfer hydrogenation conditions using 10% Pd/C and cyclohexene as the hydrogen donor. Careful front run of the reaction and frequent monitoring ensured little overreduction and a high yield of enone.

The oxidative cleavage of the enone (4) to the seco acid (5) was carried using sodium periodate and catalytic potassium permangante with sodium carbonate.

Introduction of the nitrogen atom into the A ring occurs in refluxing acetic acid with ammonium acetate. BHT was added as a radical inhibitor to prevent decomposition of enelactam ketone (6).

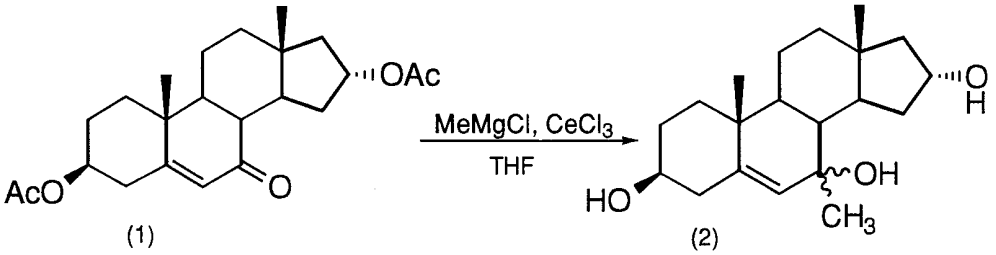
Chemo- and stereoselective reduction of the crude enelactam ketone (6) was carried out with L-Selectride (tri-sec-butyl-borohydride) at -5°C. After an oxidative workup to convert the trialkylboron by-products to boric acid, the enelactam alcohol (7) is crystallized from acetonitrile. Running this reaction under more dilute conditions and reducing the level of toluene improves yield.

Hydrogenation of the enelactam alcohol (7) is critical because enelactam left behind does not crystallize away from the NH lactam β-alcohol (8) and impacts on the purity of the final product.

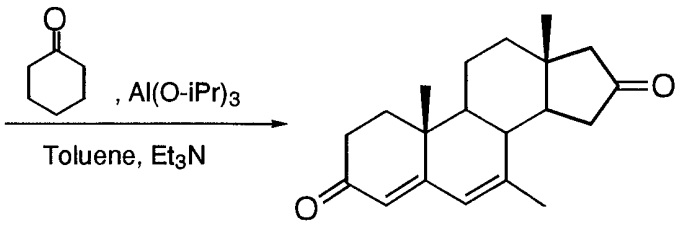
Conversion of the lactam β-alcohol (8) to the lactam α-alcohol (10) proceeds through the 4-nitrophenyl ester (9) which is not purified.

Introduction of the delta-1 double bond to form the 7β-methyl-16α-hydroxy-4-aza-5α-androst-1-en-3-one (11) proceeds through the process described in U.S. 5,084,574 by reacting with a silylating agent in the present of a quinone. Alternatively, other known processes for insertion of the delta-1-double bond may be employed, see e.g., U.S. 5,091,534; U.S. 5,120,847; and U.S. 5,021,575. Formation of the 16α-mesylate (12) is optionally carried out in a non-polar aprotic solvent such as methylene chloride in the presence of an organic base such as pyridine by reaction with methane sulfonylchloride. Optionally, dimethylaminopyridine (DMAP) may be added to the reaction as a catalyst.

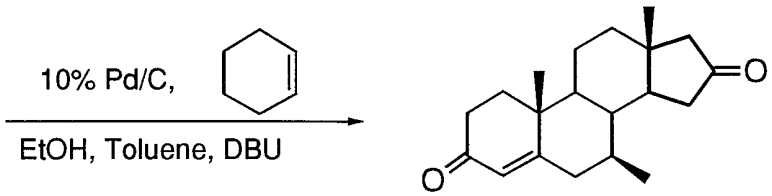
The 16α-mesylate is converted into the desired 16β-(4-(methylsulfonyl)phenoxy) product (13) by reaction with 4-(methylsulfonyl)phenol and cesium carbonate in a polar aprotic solvent such as DMSO.


OAc
AcO
O
MeMgCl, CeCl3
THF
HO
OH
CH3
O
H

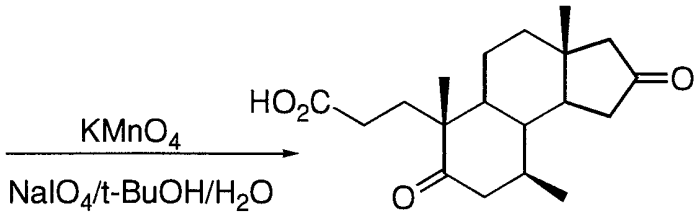
(1) (2)


O
, Al(O-iPr)3
Toluene, Et3N
O
O

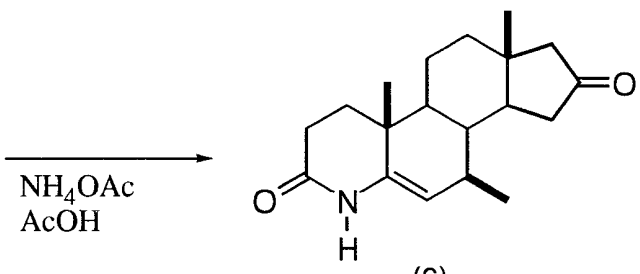
(3)


10% Pd/C,
EtOH, Toluene, DBU
O
O

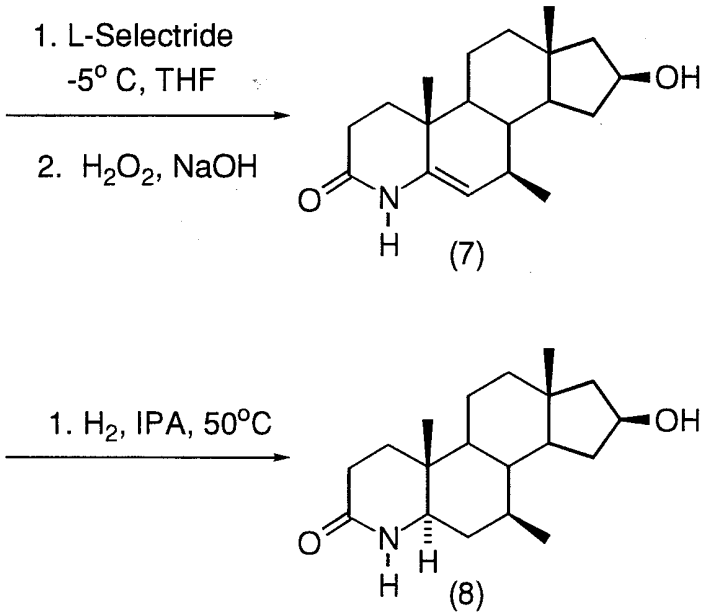
(4)


KMnO4
NaIO4/t-BuOH/H2O
HO2C
O
O

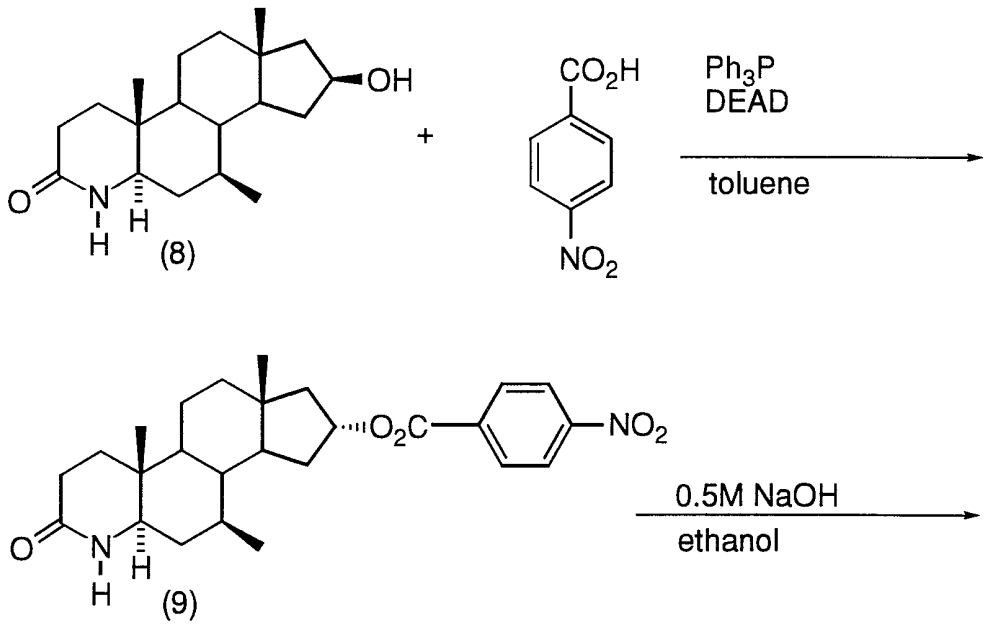
(5)

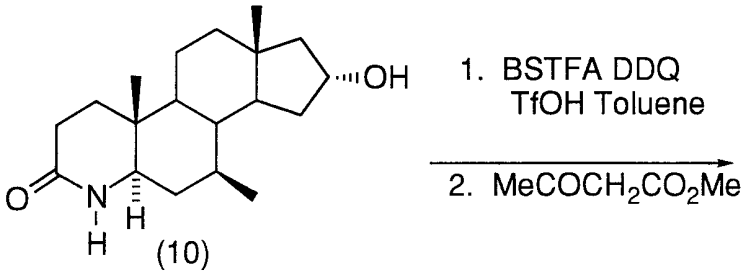

NH4OAc
AcOH
O
O
N
H

(6)

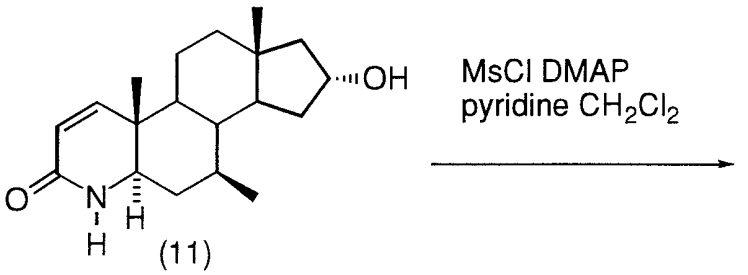

1. L-Selectride
-5° C, THF
2. $H_2O_2$, NaOH
OH
O
N
H
(7)
1. $H_2$, IPA, 50°C
OH
O
N
H
H
(8)

Scheme 2:

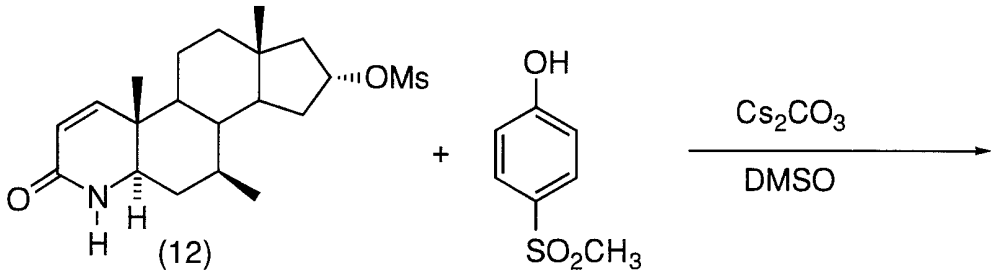

OH
O
N
H
H
(8)
+
$CO_2H$
$NO_2$
$Ph_3P$
DEAD
toluene
$O_2C$
$NO_2$
O
N
H
H
(9)
0.5M NaOH
ethanol


OH
O
N
H
H
1. BSTFA DDQ
TfOH Toluene
2. MeCOCH2CO2Me

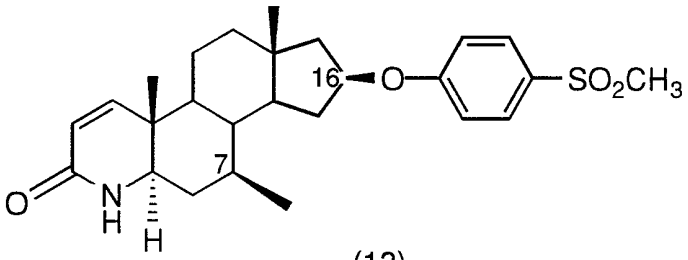
(10)


OH
O
N
H
H
MsCl DMAP
pyridine CH2Cl2

(11)


OMs
O
N
H
H
+
OH
SO2CH3
Cs2CO3
DMSO

(12)


16
O
SO2CH3
7
O
N
H
H

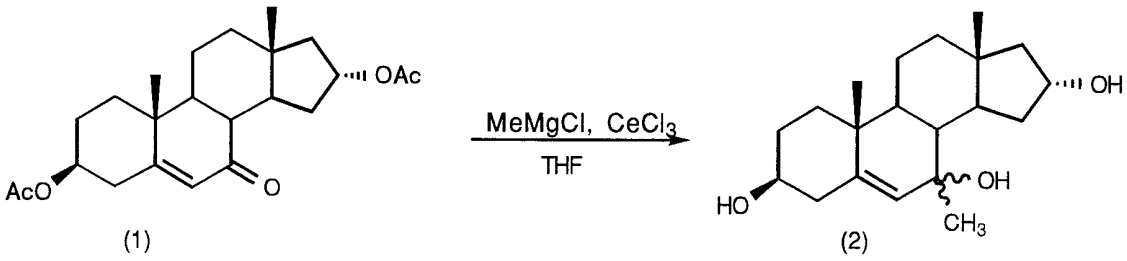
(13)

The following examples are provided to further illustrate details for the preparation of the compound of the present invention. The examples are not intended to be limitations on the scope of the instant invention in any way, and they should not be so construed. Furthermore, the compounds described in the following examples are not to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are in degrees Celsius unless noted otherwise.

Abbreviations: ACN is acetonitrile; BHT is 2,6-t-butyl-4-methylphenol; ca is *circa*; DBU is (1,8-diazabicyclo[5.4.0]undec-7-ene; IPA is isopropyl alcohol; L-Selectride® is lithium tri-sec-butylborohydride; MEK is methyl ethyl ketone; NMP is 1-methyl-2-pyrrolidinone; PDA is photodiode array; THF is tetrahydrofuran; TMEDA is N,N,N',N'-Tetramethylethylenediamine; TMSCl is chlorotrimethylsilane.

## EXAMPLE 1

Preparation of 3,6,16-Triol (2)




(1) (2)

Cerium chloride (3.96 kg) was charged as a solid to the reaction vessel. THF (35 kg) was charged using vacuum, then water (20 mL) was added via the charge port and the mixture aged at 35°C for 1 hr.

A sample was taken and examined by microscopy to ensure that conversion to the required crystal form had occurred.

(Amorphous cerium chloride stirred in THF converts to a fine rod-like crystalline form. This crystalline form is necessary to obtain the stereo-selectivity in the Grignard reaction. Previous experience had shown that the water content of the THF/cerium chloride should be less than 1000ppm in order to get the required crystal form. Wetter slurries were found to irreversibly form another crystal form that did not exhibit the same specificity in the Grignard reaction. However, the THF used in this instance was extremely dry (<50ppm) and stirring the amorphous cerium chloride in it did not produce the required conversion and the solid remained amorphous. It was demonstrated that a small amount of water is necessary for the conversion to take place, and water was added to the batch to give a total water content of ca 500ppm.)

After cooling the batch to 25°C, 3M methyl magnesium chloride in THF (80.46 kg) was added to the vessel. The mixture was cooled to 0-5°C and aged for 30 minutes. The 7-ketone starting material (1) (9.2 kg) was slurried in THF (50L) and added to the Grignard reagent slurry over 75 minutes, maintaining a temperature of <20°C.

The batch was sampled and reaction completion confirmed by HPLC: <0.1A% (1) detected. The Grignard reaction mixture was slowly added to a quenching solution formed by the addition of toluene (70 kg) to a solution of water (146L) and solid citric acid (43.9 kg). Care was made to maintain the temperature at <20°C. The reaction vessel and transfer lines were rinsed with THF (10 kg).

The mixture was stirred for 15 minutes then settled for 30 minutes. Both phases were cut to drums and the aqueous layer returned to was back extracted with 39 kg of ethyl acetate (agitated for 10 mins, settled for 30 mins). The aqueous layer was cut to waste drums and the THF batch layer was combined with the ethyl acetate layer. 20% sodium carbonate solution (49.2 kg) was added to the stirred solution over 15 minutes then the mixture settled for 30 minutes and the aqueous phase cut to waste.

The batch layer was washed with 51.5 kg of 20% sodium chloride solution (agitated for 10 mins, settled for 30 minutes) and the aqueous phase cut to waste. Triethylamine (4.8 kg) was added and the solution concentrated *in vacuo* to ca 100L. Toluene was added and distillation continued, until the level of THF/ethyl acetate had dropped to <0.5vol% by GC. The final volume was made up to 275L, with toluene and the slurry held was used in Example 2.

HPLC Conditions:

| | |
|---|---|
| Column | YMC J-Sphere ODS H80 250 x 4.6 mm I.D. |
| Eluent A | ACN |
| Eluent B | Unbuffered water |
| Gradient | 30% A to 80% A in 25 min; hold for 5 min |
| Inj vol | 20 µl |
| Detection | UV at 200nm |
| Flow | 1.5 ml/min |
| Column temp | 35° C |
| Sample preparation | 100x dilution with acetonitrile; waste aq layers diluted 50x |

| Compound | Retention Times | Response Factor(area counts/wt) |
|---|---|---|
| Triols | 4.6, 6.4 | 0.71 |
| 7-ketone | 14.6 | 1 |
| Toluene | 16.4 | |
| BHT | 29.5 | |

GC conditions

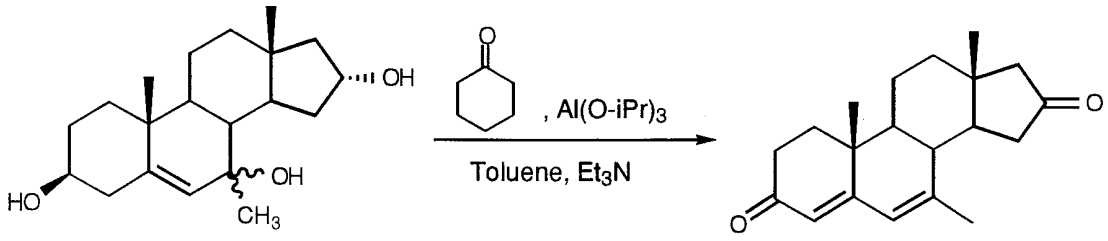
| | |
|---|---|
| Column coating | Chrompack plot fused silica 25mx0.53mm poraplot Q |
| Oven temperature | 250C Isothermal |
| Inj temp | 275C |
| Det temp | 275C |
| Sample preparation | 40x dilution with MeOH |

| Compound | Retention | Relative Response Factor |
|---|---|---|

| | | |
|---|---|---|
| MeOH | 2.0 min | |
| THF/EtOAc | 2.8,3.2 min | 1 |
| Toluene | 4.5 min | 1.5 |

EXAMPLE 2

Preparation of Diene-Dione (3)




(2) (3)

To a slurry of triol in toluene (7.59 kg in 275L) was added triethylamine (3.8 kg) and aluminium isopropoxide (10 kg) followed by 2-butanone (100 kg). The mixture was heated at reflux for 6 hrs, cooled slightly, a sample was taken, and reaction completion confirmed by HPLC(<5A% 16-OH's dienone relative to 16-keto-diene-dione). The batch was cooled to 20°C, then allowed to stand overnight.

A mixture of water (62.5L) and 12N hydrochloric acid (73.7 kg) was transferred to the reaction mixture. The reaction mixture was heated to 58-60°C and aged for 4 hrs. A sample was taken and the disappearance of 7-OH enone intermediate confirmed by HPLC. The batch was cooled to 20°C, allowed to settle for 15 mins and the aqueous phase cut to waste.

2.5% sodium bicarbonate solution (100L) was added to the toluene layer, stirred for 15 mins, settled for 30 mins and the aqueous phase cut to waste. This procedure was repeated with 100L of water.

The organic phases from the two batches prepared as described above were combined and concentrated *in vacuo* to a volume of 100L. Water was fed in under vacuum then distillation continued at

atmospheric pressure until the level of 2-butanone dimers in the batch had dropped to <3A% relative to diene-dione; a total of 70L of water was distilled. Toluene (100L) was added to the residue, the mixture agitated for 5 mins then settled for 15 mins. The organic layer was saved. The aqueous phase returned was extracted with toluene (40L). The organic layers were combined and concentrated *in vacuo* to a final volume of ca 60L. The solution was held for Example 3.

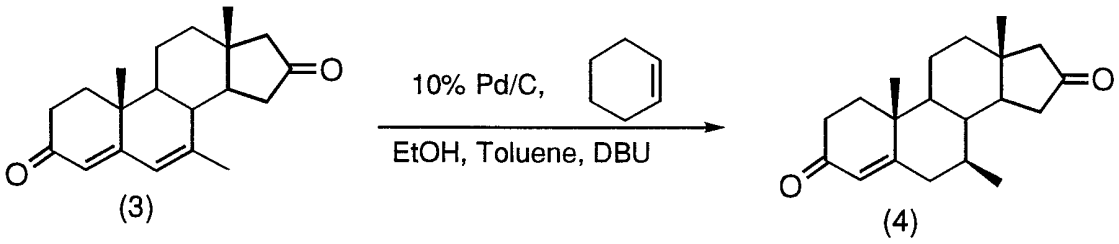
HPLC Conditions

| | |
|---|---|
| Column | YMC J-Sphere ODS H80 250 x 4.6 mm I.D. |
| Eluent A | ACN |
| Eluent B | Unbuffered water |
| Gradient | 30% A to 80% A in 25 min; hold for 5 min |
| Flow | 1.5 ml/min |
| Inj vol | 20 µl |
| Detection | UV at 200nm for triols, 240nm for 7-OH enone and |
| MEK by-product | removal, 290 nm for dienone assays |
| Column temp | 35° C |
| Sample preparation | 100x dilution with acetonitrile; waste aq layers diluted 25-50x |

| Compound | Retention Times | λ |
|---|---|---|
| Triols | 4.6, 6.4 | 200nm |
| 7-OH enone | 6.6 | 240nm |
| Dienedione | 13.1 | 290nm |
| Toluene | 16.4 | 200nm |
| BHT | 29.5 | 200nm |

## EXAMPLE 3

Preparation of Enone (4)




(3) (4)

Diene-dione (3) (12.9 kg) was converted to enone (4) (11.69 assay kg, 90.0% yield) in one batch. The enone was not isolated but carried through for use in Example 4 as a solution in t-butanol.

To the reaction vessel was added 10% Pd/C (5.32kg, 51.5% water wet), followed by the toluene solution of diene-dione obtained as a product of Example 2, (12.9 kg in 70L), ethanol (38.1L), and cyclohexene (64.9L). The mixture was agitated and DBU (1.28 kg) was added.

A sample was taken and the mixture warmed to reflux. The reaction was sampled periodically and heating continued (6 hrs) until the diene-dione level, measured by HPLC fell below 1.0 mg/ml.

(As benzene is produced as a by-product of the reaction, care was taken to use local extraction when sampling.)

After cooling to 25°C, the batch was filtered through a 45cm plate filter set with a polypropylene cloth, card, and Solka Floc diatomaceous earth (1.5 kg).

The filter became blocked after about 50% of the slurry had passed through and had to be dismantled and reset.

The vessel, lines and filter pad were rinsed with toluene (20L) and the combined filtrates allowed to stand overnight. 1N hydrochloric acid (44L) was added to the filtrate. The mixture was agitated for 5 mins, settled for 15 mins and the lower aqueous phase cut to waste. This wash procedure was repeated with 5% sodium chloride solution (42L).

The organic phase was concentrated *in vacuo* to *ca* 50L then transferred to a reaction vessel via a 0.5m cotton cartridge filter and distillation continued to ca 22L. The solvent was switched to t-butanol. t-Butanol (total of 144 kg) was charged and distilled in vacuo (30L distilled) until the required removal of the previous solvents was achieved (toluene

<15mg/ml, cyclohexene, 0.05 mg/ml). The batch (11.69 kg of enone in 136.2 kg of solution) was held for further reaction in Example 4.

(Because t-Butanol freezes at 26°C, all drums of pure solvent and batch solutions were stored on a heating pad to maintain a temperature of ca 40°C.)

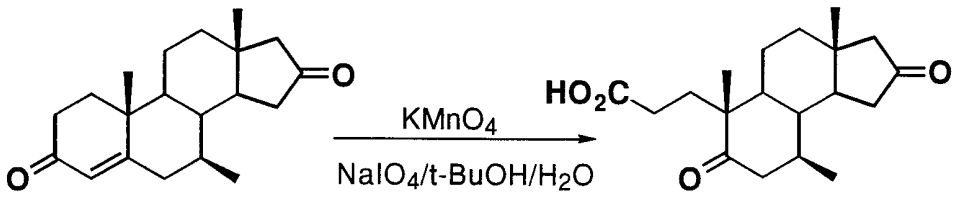
HPLC Conditions

| | |
|---|---|
| Column | Zorbax SB Phenyl 250 x 4.6 mm I.D. |
| Eluent A | ACN |
| Eluent B | Aqueous 0.1v/v% $H_3PO_4$ |
| Gradient | 30% A to 80% A in 25 min; hold for 5 min |
| Flow | 1.5 ml/min |
| Inj vol | 20 µl |
| Detection | UV at 192nm (benzene, cyclohexene), 245nm(enone), 295nm(dienone) |
| Column temp | 35° C |
| Sample preparation layers | 100x - 1000x dilution with acetonitrile; waste aq diluted 10x-25x (non-linearity for dienedione, enone) |

| Compound | Retention Times |
|---|---|
| Benzene | 7.7 |
| Toluene | 10.0 |
| Cyclohexene | 10.9 |
| Dienedione | 13.9 |
| Enone | 14.9 |

EXAMPLE 4

Preparation of Seco acid (5)




(4) (5)

Enone (4) (11.69 assay kg) was converted to seco acid (10.3 assay kg) in 83% yield in two batches. The product was not isolated but held as a solution in ethyl acetate for Example 5.

The oxidizing solution was made up first. Water (150L), sodium periodate (25.54 kg) and potassium permanganate (0.47 kg) were added to the reaction vessel and the mixture warmed to 65°C until all the solids had dissolved (ca 30 minutes).

A solution of enone (4) (5.9 kg) in t-butanol (70 kg) was added to a second reaction vessel and rinsed in with t-butanol (16 kg). A solution of sodium carbonate (2.10 kg) in water (80 L) was added to the enone solution and stirred at 55°C. The oxidant was added over 1 hr, maintaining the temperature at 60°C.

The batch was aged at 60°C for 30 mins then sampled and assayed for starting material (0.07 mg/ml, 99% complete), and then heated at 80°C for 30 mins to decompose excess oxidant. The resulting brown slurry was cooled to 12-15°C, aged for 15 mins then filtered through a 65 cm filter fitted with a polypropylene cloth. The vessel and filter pad were rinsed with aqueous t-butanol (water 70L, t-butanol 35L). The filter removed the bulk of the inorganic solids but some fine brown material passed through.

The liquors were returned to the reaction vessel via a 0.5μ cotton cartridge filter, then the pH of the solution was measured at 9. The cartridge filter became blocked with the fine brown inorganic solid and required changing several times during the transfer. If the pH had been <9, it would have been adjusted by addition of sodium carbonate solution.

Hexane (30 kg) was added. The mixture was agitated for 15 minutes, settled for 15 mins then the aqueous layer cut to drums and the hexane layer cut to waste. The aqueous phase was returned to the reaction vessel together with ethyl acetate (41 kg), then the pH of the batch adjusted to 1-2 by addition of 12N hydrochloric acid solution, maintaining the temperature at 15-20°C. The mixture was stirred for 15 mins, settled for 30 mins and both phases cut to plastic lined drums. The aqueous phase was returned to the vessel and extracted with ethyl

acetate (26 kg). This extraction was repeated, and then all the organic phases combined in the reaction vessel, and washed with 10% brine solution (27L). The aqueous phase was cut to waste and the organic phase drummed and assayed.

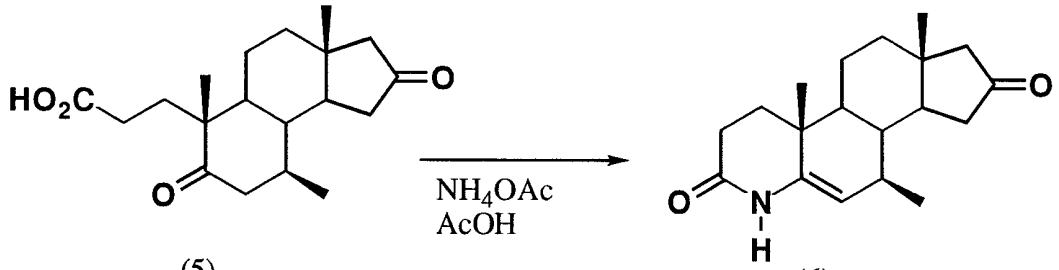
HPLC Conditions

| | |
|---|---|
| Column | Zorbax SB Phenyl 250 x 4.6 mm I.D. |
| Eluent A | ACN |
| Eluent B | Aqueous 0.1v/v% $H_3PO_4$ |
| Gradient | 30% A to 80% A in 25 min; hold for 7 min |
| Flow | 1.5 ml/min |
| Inj vol | 20 µl |
| Detection | UV at 192nm (seco acid), 245nm (enone) |
| Column temp | 35° C |
| Sample preparation | 100x dilution with acetonitrile; waste aq, |
| hexane | layers diluted 10x-25x |

| Compound | Retention Times |
|---|---|
| Acetic acid | 2.1 |
| Ethyl acetate | 3.6 |
| Seco acid | 8.1 |
| Toluene | 10.0 |
| Enone | 14.9 |

EXAMPLE 5

Preparation of Enelactam Ketone (6)




(5) (6)

Seco-acid (9.8 kg) was converted to ene lactam ketone (9.07 kg) in a single batch. The product was not isolated, but instead carried through to Example 6 as a toluene solution.

A solution of seco-acid (10.3 kg) in ethyl acetate (282 kg) was added to a reaction vessel and concentrated in vacuo to a minimum stirred volume of ca 35L. The solvent was then switched to acetic acid *in vacuo*. A total of 80kg of acetic acid was added, and 60L distilled to achieve an ethyl acetate concentration of <1mg/ml in a final volume of 76L (seco-acid concentration: 124.9 g/L). A portion of this solution (4L, containing 500g of seco-acid) was removed for other studies.

The remaining solution (9.8 kg in 72L) was diluted with acetic acid to a total volume of 150L, then BHT (0.1 kg) and ammonium acetate (23.7 kg) were added via the charge port and the mixture warmed to reflux. Acetic acid (60L) was distilled and then reflux continued for a total of 5 hrs. The progress of the reaction was monitored by HPLC and the reaction was considered complete when the concentration of seco-acid fell to <0.5mg/ml.

The batch was cooled to 20°C, then toluene (100L) and water (100L) added, the solution stirred for 20 mins, settled for 20 mins and both phases cut to plastic lined drums. The aqueous phase was returned to the reaction vessel and extracted with toluene (50L). The organic phases were combined, washed with 5% aqueous sodium chloride solution (50L) and assayed (total volume 160L, 56.7 g/L for 98.5% yield). The solution was concentrated *in vacuo* to give a thick slurry (37L) of ene-lactam ketone.

HPLC Conditions

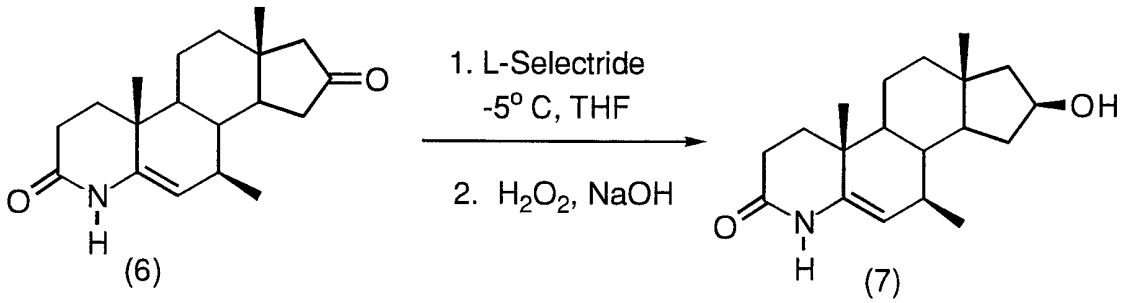
| | |
|---|---|
| Column | Zorbax SB Phenyl 250 x 4.6 mm I.D. |
| Eluent A | ACN |
| Eluent B | Aqueous 0.1v/v% $H_3PO_4$ |
| Gradient | 30% A to 80% A in 20 min; hold for 15 min |
| Flow | 1.5 ml/min |
| Inj vol | 20 µl |
| Detection | UV at 192nm (seco acid), 240nm (enelactam) |
| Column temp | 35° C |

| | |
|---|---|
| Sample preparation | 100x dilution with acetonitrile; waste aq layers diluted 25x |

| Compound | Retention Times |
|---|---|
| Acetic acid | 2.1 |
| Ethyl acetate | 3.5 |
| Seco acid | 8.5 |
| Toluene | 9.4 |
| Enelactam ketone | 9.9 |
| BHT | 17.1 |

EXAMPLE 6

Preparation of Enelactam Alcohol (7)




(6) (7)

The slurry of ene-lactam ketone (9.07 kg) in toluene (35L) in the reaction vessel was diluted with THF (89 kg) and cooled to -5°C. L-Selectride (34.5 kg of 1M solution) was added to the slurry over 1 hr, maintaining the temperature between -5°C and 0°C. The batch was aged at 0°C for 20 mins then sampled. HPLC analysis showed that 11.7 mol% still remained. Further L-Selectride (3.4 kg) was added then aged for 40 minutes at 0°C and sampled. HPLC analysis showed that 9.9 mol% still remained.

The reaction was quenched by addition of 20% aqueous sodium hydroxide solution (37.4 kg), maintaining the temperature at <20°C, followed by 27% hydrogen peroxide (19.8 kg) at <30°C. The mixture was stirred at 15-20°C for 1 hr then excess peroxide confirmed using a Merckoquant test strip (E. Merck).

The nitrogen purge rate was increased to 15L/min during the hydrogen peroxide addition.

10% aqueous sodium sulfite solution (129 kg) was added, and the batch aged for 15 mins. The absence of peroxide was confirmed, and then the batch was settled for 15 mins and the aqueous phase cut to waste. 10% aqueous sodium chloride solution (58 kg) was added, the mixture agitated for 5 mins, settled for 15 mins and the aqueous phase cut to waste. The brine wash was repeated.

The organic phase (128.3 kg) was transferred to another reaction vessel via a 0.5m cotton cartridge filter. The batch was concentrated to ca 40L at atmospheric pressure then the solvent was switched to acetonitrile. A total of 200 kg of acetonitrile was charged and the mixture distilled to a final volume of 65L. A sample was taken and toluene level (spec-200 mg/ml, measured-0.7 mg/ml) and KF(spec-400 mg/L, measured-73 mg/L) measured.

The batch was allowed to cool to room temperature slowly overnight with gentle agitation, and then cooled to 5°C over 1 hr and aged for 30 minutes. The solid was collected on a 33cm stainless steel filter, washed with acetonitrile, then dried at ambient temperature in vacuo overnight. The dry solid was bagged.

HPLC Conditions:

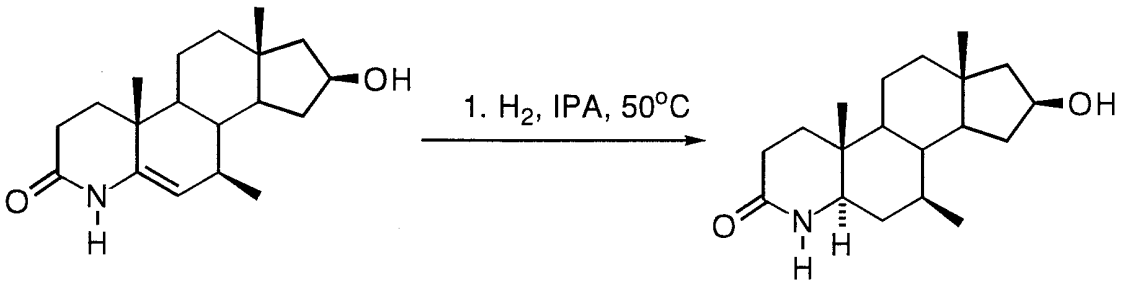
| | |
|---|---|
| Column | Zorbax SB Phenyl 250 x 4.6 mm I.D. |
| Eluent A | ACN |
| Eluent B | Aqueous 0.1v/v% $H_3PO_4$ |
| Gradient | 30% A to 80% A in 20 min; hold for 15 min |
| Flow | 1.5 ml/min |
| Inj vol | 20 µl |
| Detection | UV at 240nm (enelactam ketone, enelactam alcohol) |
| and | 200nm (BHT, toluene) |
| Column temp | 35° C |
| Sample preparation | 100x dilution with acetonitrile; waste aq layers, |
| filtrate | and washes diluted 25x |

| Compound | Retention Times |
|---|---|
| Enelactam 16-β alcohol | 8.7 |

| | |
|---|---|
| Toluene | 9.5 |
| Enelactam ketone | 9.9 |
| BHT | 17.1 |

EXAMPLE 7

Preparation of Lactam Alcohol (8)




(7) (8)

Ene-lactam alcohol (750 g) was dissolved in a mixture of IPA (10L) and water (1.6L) by warming to 30-40°C in a 20L flask. BHT (3 g) and 50% wet 10%Pd/C (375 g) was added and the mixture charged using vacuum via the dip-leg to a 20L autoclave, and then rinsed in with IPA (1L). The slurry was stirred under an atmosphere of hydrogen (60psig) at 50°C for 6 hours then at 68°C for 16 hrs. The batch was sampled via the dip-leg and checked for completion by HPLC (spec<0.05A% starting material). If the end point had not been reached, stirring under hydrogen was continued.

The hydrogenation was carried out at 50°C for the first few half-lives and then warmed to 68°C. Meeting the end of reaction specification is important as ene-lactam alcohol is carried through to the final product.

The batch was cooled to 30-40°C, flushed with nitrogen several times, then transferred from the autoclave and filtered through Solka Floc (1 kg). The autoclave and filter pad were washed with 1:10 water/IPA (2L), and the combined filtrates stored.

The procedure above was repeated 10 times and the 10 batches of filtrate were combined and concentrated at atmospheric pressure to a volume of ca 25L. After cooling to room temperature, water (42L) was added over 45 minutes and the batch cooled to 5°C and aged for 1 hr. The solid was collected on a 33cm filter fitted with a polypropylene cloth and then washed with 4:1 water/IPA (10L). The damp solid was transferred to trays and dried in vacuo at 35°C overnight to give the lactam alcohol (8).

EXAMPLE 8

Preparation of 7β-Methyl-16α-hydroxy-4-aza-5α-androstan-3-one (10)

To a suspension of 7β-methyl-16β-hydroxy-4-aza-5α-androstan-3-one (9) (98.0 g, 0.321 moles) in toluene (2.5 L) was added triphenylphosphine (168.4 g, 0.642 moles), 4-nitrobenzoic acid (107.3 g, 0.642 moles), diethyl azodicarboxylate (107.3 ml, 0.642 moles). The mixture was heated at 80° for 1.5 hr with mechanical stirring in a N atmosphere. The toluene was removed *in vacuo*; the residue dissolved in $CH_2Cl_2$ and washed once with 1 N HCl and saturated brine. The aqueous washes were extracted once with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were dried (MgSO) and concentrated *in vacuo*. The residue was partially purified by column chromatography on 4 Kg of silica gel eluting with 5-25% acetone-$CH_2Cl_2$ to give a mixture of the desired 16β-(4-nitrophenyl) ester and triphenylphosphine oxide.

The impure 4-nitrophenyl ester was suspended in EtOH (6.8 L) and 0.5 N NaOH (1.3 L, 0.65 moles) was added. The mixture was stirred mechanically at room temperature for 1.5 hr in a N atmosphere. Most of the EtOH was removed *in vacuo*. The residue was diluted with HO and extracted three times with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were washed once with 1N HCl and saturated brine. The aqueous washes were extracted twice with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were dried (MgSO) and concentrated *in vacuo*. The residue as stirred with 20% acetone-$CH_2Cl_2$ (500 ml) for 18 hr, filtered, and dried to give the title compound. Additional product was obtained from column chromatography (silica gel, elution with 20-40% acetone-

$CH_2Cl_2$ and 5-10 MeOH-$CH_2Cl_2$) of the residue from the 20% acetone-$CH_2Cl_2$ extracts.

500 MHz H NMR (CDCl): δ 0.76 (s, 3H); 0.88 (s, 3H); 1.03 (d, 3H); 3.12 (dd, 1H); 4.46 (m, 1H); 5.73 (bs, 1H).

EXAMPLE 9

Preparation of 7β-Methyl-16α-hydroxy-4-aza-5α-androst-1-en-3-one (11)

7β-Methyl-16β-hydroxy-4-aza-5α-androstan-3-one (10) (83.8 g, 0.274 moles) was suspended in toluene (2 L), and about 300 ml was distilled at atmospheric pressure. To the cooled suspension was added bis(trimethylsilyl)trifluoroacetamide (340 g, 1.32 moles), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (71.5 g, 1.15 moles) and trifluoromethylsulfonic acid (1.9 ml, 0.021 moles). The dark mixture was stirred at room temperature for 18 hrs. Methyl acetoacetate (3.5 ml, 0.032 moles) was added, and the mixture was heated under reflux for 19 hrs. TLC (1:1 acetone-$CH_2Cl_2$ indicated that (10) was still present. Bis(trimethylsilyl)trifluoroacetamide (95.9 g, 0.373 moles), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (12.5 g, 0.55 moles) and trifluoromethylsulfonic acid (1.0 ml) were added, and the mixture heated at reflux for 19 hrs. The cooled reaction was extracted with a mixture of saturatedNaHCO (1 L), water (1 L), and sodium sulfite (50 g). The organic phase was washed once with saturatedNaHCO andsaturated NaCl solutions. The combined aqueous phases were extracted twice with$CH_2Cl_2$. The combined organic phases were evaporated *in vacuo* without drying. The residue was dissolved in $CH_2Cl_2$ (1 L) and stirred at room temperature for 1.25 hr with 2N HCl (1 L). The acid phase was extracted three times with $CH_2Cl_2$. The combined $CH_2Cl_2$ phases were evaporated *in vacuo* to give crude (11). The material was purified by column chromatography on silica gel (1.6 Kg). The steroid was dissolved in a small amount of MeOH-$CH_2Cl_2$ for loading on the column; then elution with 5-40% acetone-$CH_2Cl_2$ and 5-10% MeOH-$CH_2Cl_2$ gave after evaporation *in vacuo* and flushing with hexane the title compound as a brown solid.

500 MHz H NMR (CDCl): δ 0.75 (s, 3H); 0.92 (s, 3H); 1.02 (d, 3H); 3.36 (dd, 1H); 4.44 (m, 1H); 5.30 (bs, 1H), 5.81 (dd, 1H); 6.81 (d, 1H).

EXAMPLE 10

Preparation of 7β-Methyl-16α-methanesulfonyloxy-4-aza-5α-androst-1-en-3-one (12)

A magnetically stirred suspension of 7β-methyl-16α-hydroxy-4-aza-5α-androst-1-en-3-one (11) (73.8 g, 0.244 moles), pyridine (52 ml, 0.641 moles), and 4-dimethylaminopyridine (2.98 g, 0.0244 moles) in $CH_2Cl_2$ (1 L) was cooled to 0-5° while methanesulfonyl chloride (47.2 ml, 0.61 mole) was added dropwise over 15 min. After 20 min the ice bath was removed, and the mixture was stirred at room temperature for 18 hrs. TLC (30% acetone-$CH_2Cl_2$) indicated a little 11 was still present; small quantities (10% of initial amounts) of pyridine, DMAP, and MsCl were added. After 2.5 hr at room temperature no 11 was detectable by TLC. The reaction mixture was washed with water (2 L), and the aqueous wash back extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ phases were washed with 1N HCl (1 L), and the acid wash was back extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ phases were washed once with water, saturated NaHCO, and saturated NaCl and dried (MgSO). Evaporation *in vacuo* gave crude 12. The material was purified by column chromatography on silica gel (1.6 Kg). Elution with 10-30% acetone-$CH_2Cl_2$ and evaporation *in vacuo* gave the pure material which was recrystallized from $CH_2Cl_2$-hexane to give the title compound as a tan solid.

500 MHz H NMR (CDCl): δ 0.77 (s, 3H); 0.93 (s, 3H); 1.02 (d, 3H); 2.99 (s, 3H); 3.38 (dd, 1H); 5.20 (m, 1H); 5.30 (bs, 1H), 5.82 (dd, 1H); 6.80 (d, 1H).

EXAMPLE 11

Preparation of 7β-Methyl-16β-(4-(methylsulfonyl)phenoxy)-4-aza-5α-androst-1-en-3-one (13)

A magnetically stirred suspension of 7β-methyl-16α-methanesulfonyloxy-4-aza-5α-androst-1-en-3-one (12) (1.14 g, 3 mmoles), 4-(methylsulfonyl)phenol (Acros) (0.542 g, 3.15 mmoles), and cesium

carbonate (1.47 g, 4.5 mmoles) in DMSO (6 ml) was heated at 65° for 6 hours in a $N_2$ atmosphere. The cooled suspension was diluted with water (60 ml), and the suspension stirred at room temperature for 30 min. The cream colored solid was filtered, slurry-washed three times with water, and dried (house vacuum, 45°, 16 hrs) to give crude 13. HPLC purity: 87.8% (YMC J'sphere ODS-H80 column, 250 x 4.6 mm, 70/30 MeCN/0.1% TFA (10 min), then to 90/10 over 5 min, 1.0 ml/min, PDA detection at 200 nm, 13 retention time = 6.68 min). Recrystallization from MeCN (35 ml) gave 13, mp 245-247°. HPLC purity 98.7% (one impurity, 1.05%, 6.18 min).

500 Mhz H NMR (CDCl): δ 0.96 (s, 3H); 0.99 (s, 3H); 1.06 (d, 3H); 3.04 (s, 3H); 3.38 (m, 1H); 4.82 (m, 1H); 5.19 (bs, 1H), 5.84 (dd, 1H); 6.81 (d, 1H); 6.95 (d, 2H); 7.85 (d, 2H).

A larger batch of 13 was prepared using less pure 12. On a 20 mmoles scale 12 was reacted as above to give crude 13. Chromatography on silica gel with EtOAc, followed by recrystallization from MeOH afforded pure 13 (HPLC purity: 99.3%). Recrystallization from MeOH (charcoal) gave 13 in two crops (Crop 1 purity: 99.5%) and (Crop 2 purity: 99.6%), mp 245-247°.

## EXAMPLE 12

## ORAL COMPOSITION

As a specific embodiment of an oral composition of a compound of this invention, 5 mg of 7β-methyl-16β-(4-methylsulfonyl)phenoxy)-4-aza-5α-androst-1-en-3-one is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

## Biological Assays

Preparation of Human prostatic and scalp 5α-reductases.

Samples of human tissue were pulverized using a freezer mill and homogenized in 40 mM potassium phosphate, pH 6.5, 5 mM magnesium sulfate, 25 mM potassium chloride, 1 mM phenylmethyl-

sulfonyl fluoride, 1 mM dithiothreitol (DTT) containing 0.25 M sucrose using a Potter-Elvehjem homogenizer. A crude nuclear pellet was prepared by centrifugation of the homogenate at 1,500xg for 15 min. The crude nuclear pellet was washed two times and resuspended in two volumes of buffer. Glycerol was added to the resuspended pellet to a final concentration of 20%. The enzyme suspension was frozen in aliquots at -80°C. The prostatic and scalp reductases were stable for at least 4 months when stored under these conditions.

5α-Reductase Assay

The reaction mixture for the type 1 5α-reductase contained 40 mM potassium phosphate, pH 6.5, 5 μM [7-$^3$H]-testosterone, 1 mM dithiothreitol and 500 μM NADPH in a final volume of 100 μl. The reaction mixture for the type 2 5α-reductase contained 40 mM sodium citrate, pH 5.5, 0.3 μM [7-$^3$H]-testosterone, 1 mM dithiothreitol and 500 μM NADPH in a final volume of 100 μl. Typically, the assay was initiated by the addition of 50-100 μg prostatic homogenate or 75-200 μg scalp homogenate and incubated at 37°C. After 10-50 min the reaction was quenched by extraction with 250 μl of a mixture of 70% cyclohexane: 30% ethyl acetate containing 10 μg each DHT and T. The aqueous and organic layers were separated by centrifugation at 14,000 rpm in an Eppendorf microfuge. The organic layer was subjected to normal phase HPLC (10 cm Whatman partisil 5 silica column equilibrated in 1 ml/min 70% cyclohexane: 30% ethyl acetate; retention times: DHT, 6.8-7.2 min; androstanediol, 7.6-8.0 min; T, 9.1-9.7 min). The HPLC system consisted of a Waters Model 680 Gradient System equipped with a Hitachi Model 655A autosampler, Applied Biosystems Model 757 variable UV detector, and a Radiomatic Model A120 radioactivity analyzer. The conversion of T to DHT was monitored using the radioactivity flow detector by mixing the HPLC effluent with one volume of Flo Scint 1 (Radiomatic). Under the conditions described, the production of DHT was linear for at least 25 min. The only steroids observed with the human prostate and scalp preparations were T, DHT and androstanediol.

Inhibition Studies

Compounds were dissolved in 100% ethanol. $IC_{50}$ values represent the concentration of inhibitor required to decrease enzyme activity to 50% of the control. $IC_{50}$ values were determined using a 6 point titration where the concentration of the inhibitor was varied from 0.1 to 1000 nM.

Representative compounds of this invention were tested in the above desribed assay for 5α-reductase type 1 and type 2 inhibition. For the inhibition of 5α-reductase type 1, the compounds have $IC_{50}$ values lower than 600 nM, with the majority of compounds having $IC_{50}$ values ranging from about 0.3 nM to about 200 nM. For the inhibition of 5α-reductase type 2, the same compounds have $IC_{50}$ values greater than about 155 nM, with the majority of compounds having $IC_{50}$ values greater than 1000 nM. Each compound has at least a 2-fold greater selectivity for inhibition of 5α-reductase type 1 over type 2, with the majority of the compounds having a 10-fold or greater selectivity for inhibition of 5α-reductase type 1 over type 2. These results demonstrate the utility of the compounds of the instant invention for the treatment of hyperandrogenic conditions.

A compound referrred to herein as a 5α-reductase 2 inhibitor is a compound that shows inhibition of the 5α-reductase 2 isozyme in the above-described assay.

Human Dermal Papilla Cell Assay

The dermal papilla is a small group of cells at the base of each hair follicle, and it is presently thought that these cells are stem cells that form the basis for hair growth. These cells have been shown to have 5 alpha reductase activity, and it is therefore possible to test inhibitors of 5 alpha reductase in these cell culture systems.

Isolated and cultured dermal papilla cells are prepared according to the methods of Messenger, A.G., *The Culture of Dermal Papilla Cells From Human Hair Follicles*, Br. J. Dermatol. 110:685-689, 1984 and Itami, S. et. al., *5α-Reductase Activity In Cultured Human Dermal Papilla Cells From Beard Compared With Reticular*

*Dermal Fibroblasts*, J. Invest. Dermatol. 94:150-152, 1990. Beard dermal papilla cells and occipital scalp hair of two different individuals are used throughout the study. All experiments are performed at confluency after the fourth to sixth subculture. Confluent monolayers are rinsed twice with phosphate-buffered saline, scraped from dishes by rubber policemen, and collected into a centrifuge tube. The cell suspensions are centrifuged at 1,500 rpm for 10 min at 4°C. The pellets are resuspended in 20 mM Tris-HCl buffer, pH 7.5, at 4°C, containing 250 mM sucrose, 1mM $MgCl_2$, and 2mM $CaCl_2$, by vortexing and 10 passes through a 25-gauge needle. The crude homogenate is further homogenized by a teflon-glass homogenizer, and is used as the cell homogenate. For the study of subcellular localization of 5α-reductase, the cell homogenate is centrifuged at 800 x g for 10 min to yield a crude nuclear pellet. The resultant supernatant is centrifuged at 10,000 x g for 15 min to produce a crude mitochondrial pellet. The supernatant is centrifuged at 100,000 x g for 60 min to yield a microsomal pellet and cytosol. Each particulate fraction is washed twice and resuspended in the buffer.

A standard incubation mixture will consist of 50 nM [$^3$H]-testosterone, 1 mM NADPH, 100 mM sodium citrate, pH 5.5 or 100 mM Tris-HCl, pH 7.5, and 50 µl of the cell homogenate, in a final volume of 100 µl. Each tube contains 50-100 µg of cellular protein. Incubation is carried out at 37°C for 30 min. During this incubation, the reaction is proportional to the time. For the study of optimum pH, citrate buffer is used at pH 4.5-6.5, and the Tris HCl buffer at pH 7.0-9.0. The protein content is determined by the method of Lowry, et. al., *Protein Measurement With The Folin Phenol Reagent.* J. Biol. Chem. 193:265-275, 1951.

After incubation, the reaction is stopped by adding 4 times volume of chloroform-methanol (2/1:V/V) containing 110 µg each of carrier steroids. The extracted steroids are analyzed by thin-layer chromatography as previously described by Gomez, et. al., *In Vitro Metabolism Of Testosterone-4-$^{14}$C and Δ-androstene-3, 17-dione-4-$^{14}$C In Human Skin.* Biochem. 7:24-32, 1968, and the purity of

each steroid is determined by the recrystallization method. The activity of 5α-reductase is expressed by the sum of dihydrotestosterone, androstanediol and androstanedione formed. [1,2-$^3$H]-testosterone (55.2 Ci/mmol) is obtainable from New England Nuclear Corporation (Boston, MA) and unlabeled steroids can be purchased from Sigma Chemical Company (St. Louis, MO). Fetal calf serum is obtainable from Hazleton (Lenaxa, Kansas). All other chemicals are of reagent grade.

Fuzzy Rat Acne Model

Adult fuzzy rats are a variety of rat that has stunted hair growth, brown colored seborrhea covering their entire back skin and abnormally increased sebum production after puberty that has been demonstrataed to be due to circulating androgens. 0.1, 0.05 and 0.025% solutions of a selected 5α-reductase inhibitor of interest are prepared in a vehicle of propylene glycol, isopropanol, isopropyl myristate and water (50/30/2/18%), and is topically applied onto the backs of adult male fuzzy rats, 0.2 ml per animal daily for 4 weeks. Controls receive the vehicle alone and 5 of them are castrated. After 2 weeks seborrhea will be dose-dependently depleted and after 4 weeks bromodeoxyuridine (BrdU, 200 mg/kg) is intraperitoneally injected 2 hours before sacrifice. The skin tissues are incubated with EDTA (20 mM) in phosphate buffer, 1.5 hours at 37°C. The pilo-sebaceous unit attached to the epidermis is striped from the dermis and fixed with formalin for immuno-staining of BrdU. DNA synthesis cells showing a BrdU-positive nucleus are located in the outer glandular border. The number of S-phase cells per lobe is determined with a micro-image apparatus. Using formalin fixed skin, frozen serial sections are stained with 1% osmium and the size of the lobes is measured. A positive inhibitor of skin 5α-reductrase will induce suppression of sebum production by inhibiting the rate of glandular cell turnover, and showing reduced lobular size.

The following describes an example methodology that can be used for detection of hair growth.

MACROPHOTOGRAPHY AND GLOBAL PHOTOGRAPHY
PROCEDURE FOR DETECTION OF HAIR GROWTH

A. Macrophotographic Procedure

Location: ID card
Haircount target area
Equipment: Film: Kodak-T-max 24 exposure each of same emulsion lot number
Camera: Nikon N-6000
Lens: Nikkor 60 mm f2.8
Flashes: Nikon SB-21B Macroflash
Device: registration device

Photographic Procedure:

In these clinical photographs, the only variable allowed is the haircount. Film emulsion, lighting, framing, exposure, and reproduction ratios are held constant.

1. The haircount area on the patient is prepared as follows: A small (~1mm) dot tattoo is placed at the beginning of the study at the leading edge of the bald area directly interior to the center of the vertex bald spot, using a commercial tattooing machine or manually (needle and ink). An area approximately one square inch in size, centered at the tattoo at the leading edge of the balding area, is clipped short (~2mm). Cut hairs are removed from the area to be photographed, using tape. Compressed air and/or ethanol wipes may also be used to facilitate removal of cut hairs.
2. Magnification: Each lens supplied has a fixed reproduction ratio of 1:1.2.
   Aperture: Every photograph is taken at f/22.
   Film: T-Max 100 (24 exposure) is used.
3. Patient's haircount target area. Three exposures (-2/3, 0, and +2/3 f-stop).

B. Global Photographic Procedure

Locations: Color card/patient Id
Global photograph
Equipment: Film: Kodachrome KR-64 24 exposure each of same emulsion lot number
Camera: Nikon N-6000
Lens: Nikkor 60 mm f2.8
Flashes: Nikon SB-23
Color card/patient Id

Photographic Procedure

In these clinical photographs, the only variable allowed is the global area's appearance. Anything extraneous to the area (clothing, furniture, walls, etc.) is eliminated from the fields to be photographed.

1. Patients will have global photographs taken prior to hair clipping with the head in a fixed position (determined by the supplied stereotactic device). Hair on the patient's head is positioned consistently so as to not obscure the bald area.
2. Magnification: Each lens supplied has a fixed reproduction ratio of 1:6.
   Aperture: Every photograph will be taken at f/11.
   Film: Kodachrome (24 exposure) is used.
3. Patient's global photographs. Three exposures at zero compensation.

A trained technician places a transparency over the photograph and, using a felt tip pen, places a black dot over each visible hair. The dot map transparency is then counted using image analysis with computer assistance.

Photographs are coded with a random number corresponding to study site, visit number and patient allocation number to insure blinding to time. At Month 6, baseline and Month 6 photographs are counted and data analyzed for interim analysis. At Month 12, baseline, Month 6 and Month 12 photographs are counted and data analyzed for the primary endpoint.

Methodology for detection of hair growth is also described in Olsen, E.A. and Delong, E., J. American Academy of Dermatology, Vol. 23, p. 470 (1990).

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. The compound 7β-methyl-16β-((4-methylsulfonyl)-phenoxy)-4-aza-5α-androst-1-en-3-one or a pharmaceutically acceptable salt thereof.

2. A method of inhibiting 5α-reductase or the isozymes thereof, comprising the step of administering to a mammal in need of such inhibition a therapeutically effective amount of a compound of Claim 1.

3. A method of inhibiting 5α-reductase or the isozymes thereof, comprising the step of administering to a mammal in need of such inhibition a therapeutically effective amount of a compound of Claim 1 in combination with an inhibitor of 5α-reductase 2.

4. The method of Claim 3 wherein the inhibitor of 5α-reductase 2 is finasteride.

5. A method for treating the hyperandrogenic conditions of acne vulgaris, androgenic alopecia, female hirsutism, benign prostatic hyperplasia, prostatitis, and the treatment and/or prevention of prostatic cancer comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

6. A method for treating the hyperandrogenic condition of acne vulgaris, comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

7. A method for treating the hyperandrogenic conditions of acne vulgaris, androgenic alopecia, female hirsutism, benign prostatic hyperplasia, prostatitis, and the treatment and/or

prevention of prostatic cancer comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 in combination with an inhibitor of 5α-reductase 2.

8. The method of Claim 7 wherein the inhibitor of 5α-reductase 2 is finasteride.

9. A method for treating the hyperandrogenic condition of acne vulgaris, comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 in combination with an inhibitor of 5α-reductase 2.

10. The method of Claim 9 wherein the inhibitor of 5α-reductase 2 is finasteride.

11. A method for treating the hyperandrogenic condition of benign prostatic hyperplasia, comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 in combination with an inhibitor of 5α-reductase 2.

12. The method of Claim 11 wherein the inhibitor of 5α-reductase 2 is finasteride.

13. A method for treating the hyperandrogenic condition of prostatic cancer, comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 in combination with an inhibitor of 5α-reductase 2.

14. The method of Claim 13 wherein the inhibitor of 5α-reductase 2 is finasteride.

15. A method of arresting and reversing androgenic alopecia and promoting hair growth in a mammal in need of such treatment comprising the step of administering to said mammal a therapeutically effective amount of a compound of Claim 1.

16. A method of arresting and reversing androgenic alopecia and promoting hair growth in a mammal in need of such treatment comprising the step of administering to said mammal a therapeutically effective amount of a compound of Claim 1 in combination with an inhibitor of 5α-reductase 2.

17. The method of Claim 16 wherein the inhibitor of 5α-reductase 2 is finasteride.

18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1.

19. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1 and finasteride or a pharmaceutically acceptable salt thereof.

20. The use of a compound according to Claim 1 for the preparation of a medicament useful for inhibiting 5α-reductase or the isozymes thereof.

21. The use of a compound according to Claim 1 for the preparation of a medicament useful for treating the hyperandrogenic conditions of acne vulgaris, androgenic alopecia, female hirsutism, benign prostatic hyperplasia, prostatitis, and prostate cancer.

22. The use of a compound according to Claim 1 for the preparation of a medicament useful for preventing prostate cancer.

23. The use of a compound according to Claim 1 for the preparation of a medicament useful for treating acne vulgaris.

# INTERNATIONAL SEARCH REPORT

Inter. ..ional Application No
PCT/US 99/10159

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07J73/00 A61K31/58

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07J A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 95 11254 A (MERCK & CO INC ;DURETTE PHILIPPE L (US); HAGMANN WILLIAM K (US); L) 27 April 1995 (1995-04-27) cited in the application | 1-23 |
| Y | page 1, paragraph 1; examples 37,59,60,66 | 1-23 |
| | -/-- | |

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 3 August 1999 | 23/08/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Watchorn, P |

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Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Inter. ..onal Application No
PCT/US 99/10159

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | LI X ET AL: "SYNTHESIS AND IN VITRO ACTIVITY OF 17BETA-(N-ALKYL/ARYLFORMAMIDO)- AND 17BETA-(N-ALKYL/ARYL)ALKYL/ARYLAMIDO-4-METHYL-AZA-3-OXO -5ALPHA- ANDROSTAN-3-ONES AS INHIBITORS OF HUMAN 5ALPHA-REDUCTASES AND ANTAGONISTS OF THE ANDROGEN RECEPTOR" JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 7, 31 March 1995 (1995-03-31), pages 1158-1173, XP002030536 ISSN: 0022-2623 page 1160, column 2, paragraph 2 ----- | 1-23 |

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 10159

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 2-18
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 2-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ..onal Application No
PCT/US 99/10159

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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