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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/435, 31/47, 31/535, C07D 221/02 — A1

(11) International Publication Number: **WO 94/20104**

(43) International Publication Date: 15 September 1994 (15.09.94)

(21) International Application Number: PCT/US94/02697

(22) International Filing Date: 11 March 1994 (11.03.94)

(30) Priority Data:
030,508 12 March 1993 (12.03.93) US

(60) Parent Application or Grant
(63) Related by Continuation
US 030,508 (CIP)
Filed on 12 March 1993 (12.03.93)

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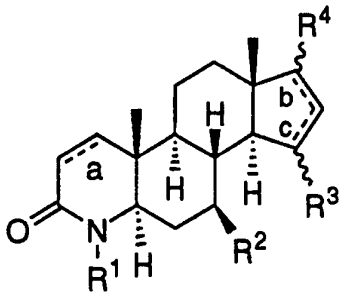
(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 15-SUBSTITUTED 4-AZASTEROIDS

(57) Abstract

Compounds of formula (I) or a pharmaceutically acceptable salt or ester thereof, wherein R^1 is -H or C_{1-10} alkyl; R^2 is -H or C_{1-10} alkyl; R^3 is C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxyl, cyano, or triphenylthio-C_{1-6} alkyl; and R^4 is a mono-substituent or di-substituent are useful as inhibitors of 5α-reductase. These compounds can be used alone or in combination with other active agents to treat acne, androgenic alopecia, female hirsutism, benign prostatic hyperplasia, prostatitis, and treat and prevent prostatic carcinoma.



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TITLE OF THE INVENTION
15-SUBSTITUTED 4-AZASTEROIDS

FIELD OF THE INVENTION

The present invention provides novel compounds, novel compositions, methods of their use and methods of their manufacture, where such compounds are generally pharmacologically useful as agents in therapies whose mechanism of action rely on the inhibition of the isozyme 5α-reductase 1.

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.

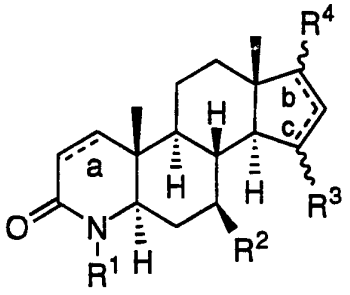
The principal mediator of androgenic activity in some target organs, e.g. the prostate, is 5α-dihydrotestosterone ("DHT"), formed locally in the target organ by the action of testosterone-5α-reductase (or simply 5α-reductase). Inhibitors of 5α-reductase will serve to prevent or lessen symptoms of hyperandrogenic 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. It is now known that a second 5α-reductase isozyme exists, which interacts with skin tissues, especially in scalp tissues. See, e.g., G. Harris, et al., *Proc. Natl. Acad. Sci. USA, Vol. 89*, pp. 10787-10791 (Nov. 1992). The isozyme that principally interacts in skin tissues is conventionally designated as 5α-reductase 1 (or 5α-reductase type 1), while the isozyme that principally interacts within the prostatic tissues is designated as 5α-reductase 2 (or 5α-reductase type 2).

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 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, e.g. acne vulgaris, male pattern baldness and hirsutism in females. Additionally, a selective 5α-reductase 1 inhibitor could be used in combination with a 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 skin and scalp-related 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. Still further the 5α-reductase 1 inhibitors of this invention could be used in combination with a potassium channel opener such as minoxidil for the treatment of androgenic alopecia. Therefore it is an object of this invention to provide compounds that have sufficient activity in the inhibition of 5α-reductase isozyme 1.

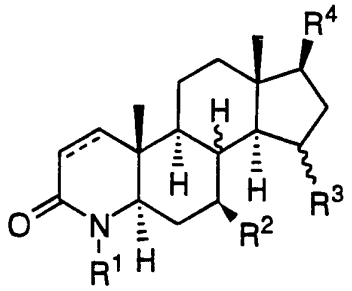
SUMMARY OF THE INVENTION

The compounds of the present invention are inhibitors of 5α-reductase type 1 and have the general structural formula:



or a pharmaceutically acceptable salt or ester thereof,
wherein
the dotted lines a, b and c each independently represent a single or double bond, provided that b and c may not both be double bonds simultaneously;
R^1 is selected from the group consisting of hydrogen and C_{1-10} alkyl;
R^2 is selected from the group consisting of hydrogen and C_{1-10} alkyl;
R^3 is selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxyl, cyano, hydroxyl and triphenylthio-C_{1-6} alkyl;
R^4 is either monosubstituted by a substituent selected from the group consisting of keto, spiro-dioxolane and oximino or is disubstituted by hydrogen and R^5;
R^5 is selected from the group consisting of hydrogen, hydroxyl, Alk-R^6, Alk-X-Alk-R^6, Het, and unsubstituted or mono- or di-substituted phenyl wherein said substituent is selected from halogen (-F, -Cl, -Br, or -I), C_{1-6} alkyl and C_{1-6} alkoxyl;
R^6 is selected from the group consisting of hydrogen, hydroxyl, -CO-R^7, -COO-R^7, -CO-NH-R^7, -NH-CO-R^7 and phenyl;
R^7 is selected from the group consisting of hydrogen, C_{1-6} alkyl, pyridyl and unsubstituted or mono- or di-substituted phenyl wherein said substituent is selected from halogen, C_{1-5} alkoxyl, C_{1-5} alkylcarbonyl, C_{1-5} alkoxycarbonyl, and C_{1-5} alkylaminocarbonyl;
X is O or NH;
Alk is C_{0-10} alkyl or C_{2-10} alkenyl with the proviso that when C is 0 (zero), there is no Alk moiety present; and
Het is selected from the group consisting of pyridyl, thiophene, morpholinyl and thiazole.

In one embodiment of this invention are compounds of the general formula



or a pharmaceutically acceptable salt or ester thereof,
wherein
the dotted line a represents a single or a double bond;
R^1 is selected from the group consisting of hydrogen and C_{1-10} alkyl;
R^2 is selected from the group consisting of hydrogen and C_{1-10} alkyl;
R^3 is selected from the group consisting of C_{1-10} alkoxyl, C_{1-10} alkyl and cyano;
R^4 is selected from the group consisting of C_{2-10} alkenyloxyl, C_{1-10} alkoxyl, C_{1-10} alkyl, C_{1-10} alkylaminocarbonyloxy, C_{1-10} alkylcarbonyloxyl, carbonyl, hydroxyl, and -NHR^5; and
R^5 is selected from the group consisting of hydrogen and C_{1-10} alkylcarbonyl.

Most particularly examples of compounds within the scope of this invention include but are not limited to those of the following group:

4, 15β-dimethyl-17β–propyloxy-4-aza-5α-androstan-3-one;
15β-ethyl-17β-hydroxy-4-aza-5α-androstan-3-one;
4-methyl-15β-methoxy-17β-hydroxy-4-aza-5α-androstan-3-one;
4-methyl-15β-cyano-17β-hydroxy-4-aza-5α-androstan-3-one;
15β-ethyl-17-keto-4-aza-5α-androstane-3-one;

4-methyl-15β-methoxy-17β-allyloxy-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-17β-amino-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-21-isopentyl-4-aza-5α-pregnan-3-one;
4, 15β-dimethyl-17β-(2,2-dimethyl-propanoylamino)-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-17β-(4-methyl-n-pentanoylamino-4-aza-5α-androstane;
4-methyl-15β-methoxy-17β-n-propyloxy-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-17β-hydroxy-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-17β-(tert-butyl-oxycarbonylamino)-4-aza-5α-androstan-3-one;
4-methyl-15β-ethyl-4-aza-5α-androstan-3, 17-dione;
4, 15β- 17β-trimethyl-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-4-aza-5α-androstan-3, 17-dione;
4-methyl-15β-ethyl-17β-hydroxy-4-aza-5α-androstan-3-one;
4-methyl-15α-isopropyl-4-aza-5α- androstan-3, 17-dione;
4-methyl-15β-isopropyl-4-aza-5α-androstan-3, 17-dione;
4-aza-15β-ethyl-17β-n-propyloxy-5α-androstan-3-one,
4-aza-15β-methyl-17β-hydroxy-5α-androst-1-en-3-one;
4, 15β,-dimethyl-4-aza-5α-androstan-3-one;
4-aza-15β-methyl-17β-hydroxy-5α-androstan-3-one;
4-methyl-15β-methoxy-4-aza-5α-androstan-3, 17-dione;
4, 15β-dimethyl-17β-(2, 2-dimethylpropanoyloxy)-4-aza-5α-androstan-3-one;
4-aza-15β-methyl-5α-androstan-3, 17-dione;
4-methyl-15β-cyano-4-aza-5α–androstane-3, 17-dione;
4, 7β, 15-trimethyl-17β-hydroxy-4-aza-5α-androstan-3-one;
4, 7β, 15-trimethyl-17β-allyloxy-4-aza-5α-androstan-3-one;
4, 7β, 15-trimethyl-4-aza-5α-androstan-3, 17-dione;

4-aza-15β-methyl-17β-hydroxy-5α-androstan-3-one; and
4-aza-15β ethyl-5α-androstan 3, 17-dione.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful for inhibiting 5α-reductase, and particularly for inhibiting the 5α-reductase type 1 isozyme. In addition to 5α-reductase type 1 inhibition, some of the instant compounds also inhibit the 5α-reductase type 2 isozyme. Since both 5α-reductase type 1 and 2 convert testosterone to 5α-dihydro-testosterone, the instant compounds are useful in the treatment of hyperandrogenic conditions such as benign prostatic hyperplasia, acne, female hirsutism, male pattern baldness, androgenic alopecia, and the prevention and treatment of prostatic carcinoma, as well as in the treatment of prostatitis.

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following salts:
acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, cihydrochloride, cdetate, cdisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, n-methylglucamine ammonium salt, napsylate, nitrate, oleate, oxalate, palmitate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the bio-logical or medical response of a tissue, system, animal or human that is being

sought by a researcher or clinician which includes alleviation of the symptoms of the disease being treated. The term "mammal" includes, of course, humans.

The term "alkyl" shall mean straight or branched chain alkanes of one to ten total carbon atoms, or any number within this range.

The term "alkenyl" shall mean straight or branched chain alkenes with one or more degrees of unsaturation at any position on the chain, of two to ten total carbon atoms, or any number within this range.

Whenever the terms "alkyl" or "alkenyl" or either of their prefix roots appear in a name of a substituent (e.g. aralkoxyaryloxy) they shall be interpreted as including those limitations given above for "alkyl" and "alkenyl". Designated numbers of carbon atoms (e.g. C1-10) shall refer independently to the number of carbon atoms in an alkyl or alkenyl moiety or to the alkyl or alkenyl portion of a larger substituent in which alkyl or alkenyl appears as its prefix root.

The terms "alkylaminocarbonyloxy" and "alkylcarbamic" are intended to have the same meaning and may be used interchangeably herein.

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 another 5α-reductase inhibitor, and/or a potassium channel opener. Particularly, the 5α-reductase inhibitor can be a 5α-reductase 2 inhibitor such as finasteride, or a dual 5α-reductase type 1 and type 2 inhibitor. 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 and/or in combination with a dual 5α-reductase type 1 and type 2 inhibitor.

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 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 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 or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.05 to 1000mg/day orally. The compositions are preferably provided in the form of tablets containing 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0 and 50.0mg of active ingredient. Effective plasma levels of the compounds of the present invention range from 0.002mg to 50mg per kg of body weight per day. Advantageously, compounds 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. Furthermore, 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 that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

For the treatment of androgenic alopecia including male pattern baldness, acne vulgaris, seborrhea, and female hirsutism, the compounds of the present invention may be administered in a pharmaceutical composition comprising the active compound in combination with a pharmaceutically acceptable carrier adapted for topical administration. 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. These topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.001% to 15% by weight of the active compound in admixture with a pharmaceutically acceptable vehicle.

For the treatment of acne vulgaris, androgenic alopecia including male pattern baldness, seborrhea, female hirsutism, benign prostatic hyperplasia, prostatitis and the prevention and/or treatment of prostatic cancer, the compounds of the instant invention can be combined with a therapeutically effective amount of a 5α-reductase 2 inhibitor, such as finasteride, or a 5α-reductase 1 inhibitor, such as 4,7β-dimethyl-4-aza-5α-cholestan-3-one, 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 5α-reductase 1 or 2 inhibitor are administered in separate oral, systemic, or parenteral dosage formulations. Also, for the skin and scalp related disorders of acne vulgaris, androgenic alopecia including male pattern baldness, seborrhea, and female hirsutism, the compounds

of the instant invention and a 5α-reductase 1 or 2 inhibitor 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.

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. 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. 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 and/or androgenic alopecia, 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.

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.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and 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.

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. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, 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 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, 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.

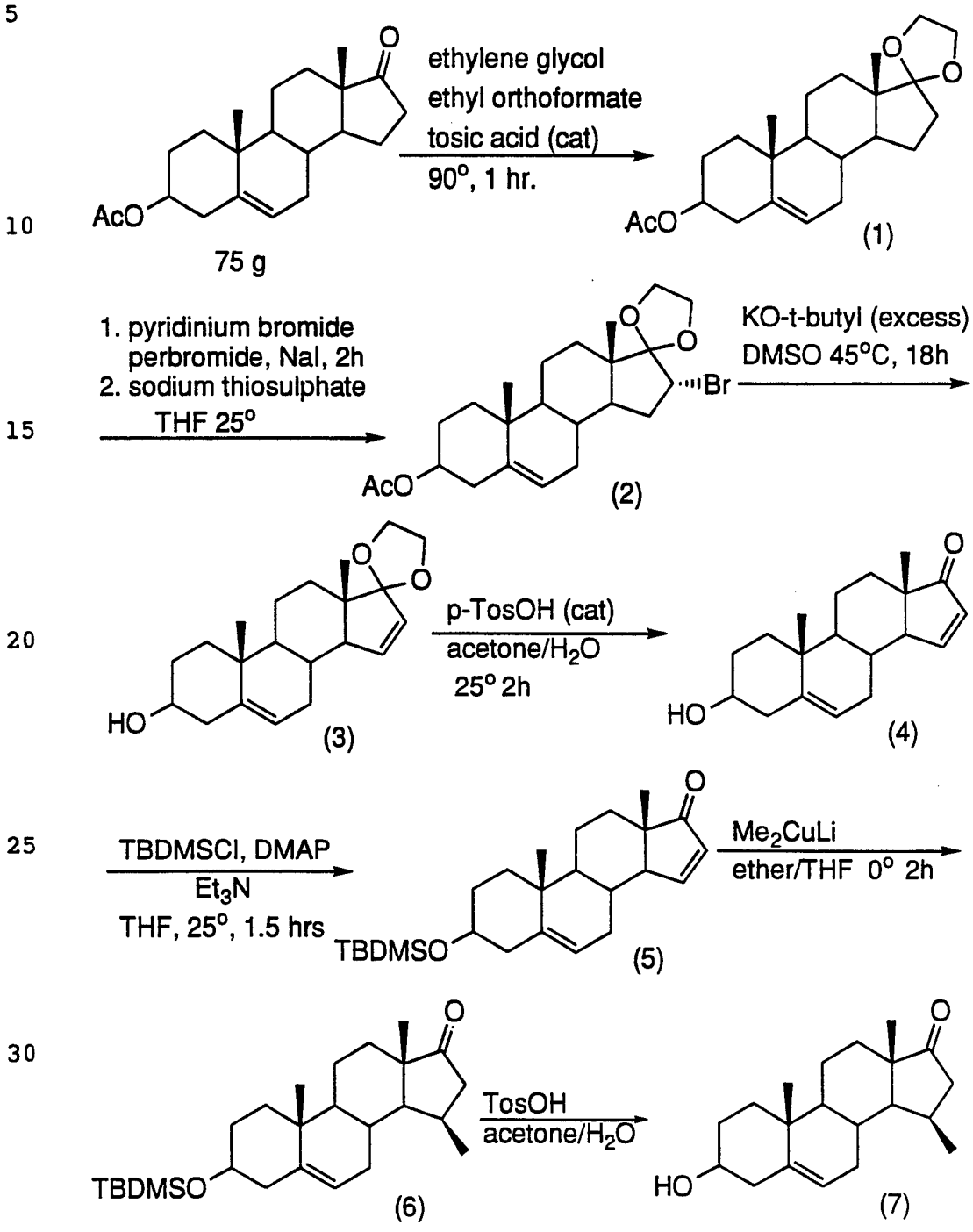
Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropyl-methacrylamide-phenol, polyhydroxy-ethylaspartamidephenol, 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, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The compounds 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.

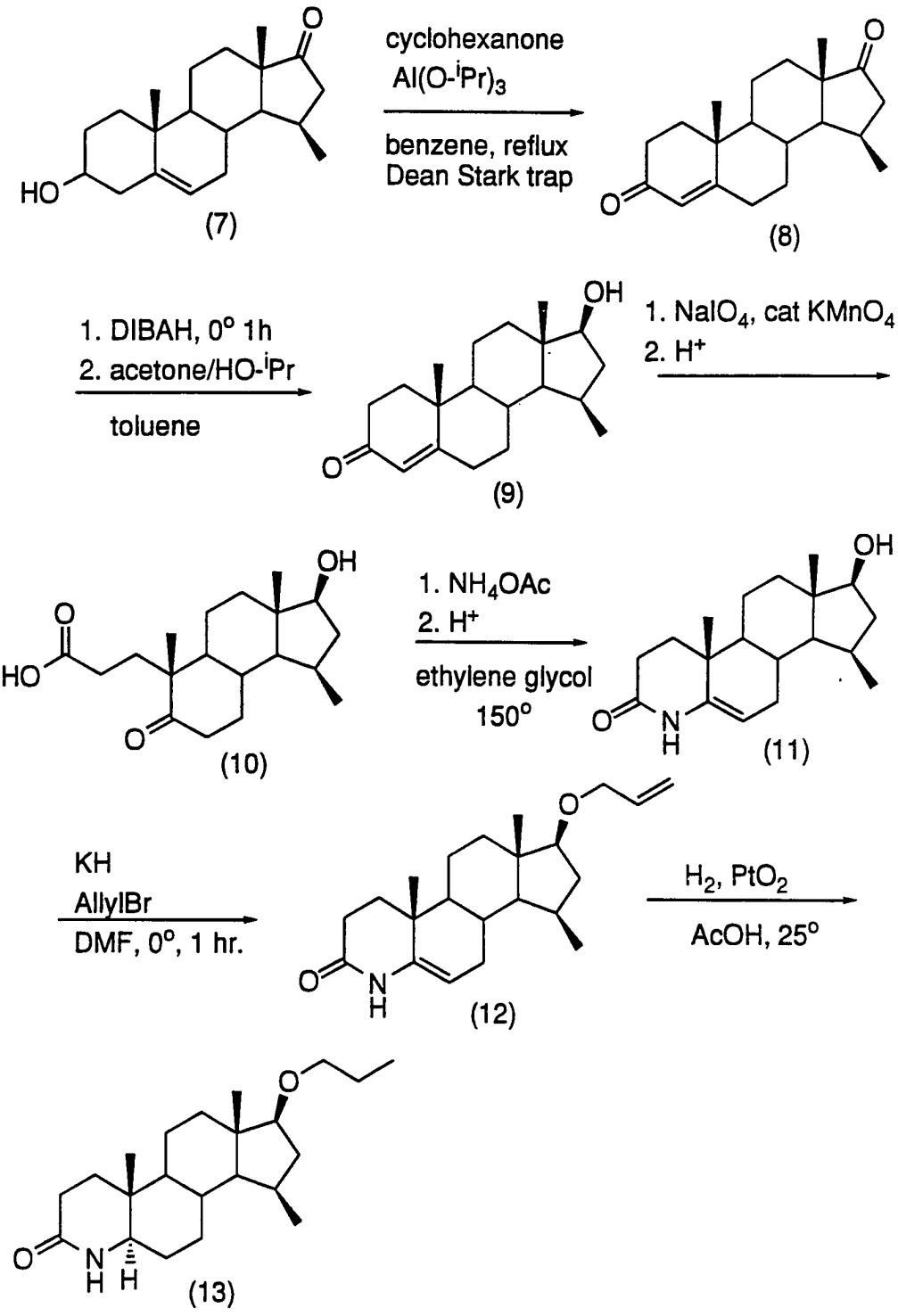
The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. 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 degrees Celsius unless noted otherwise.

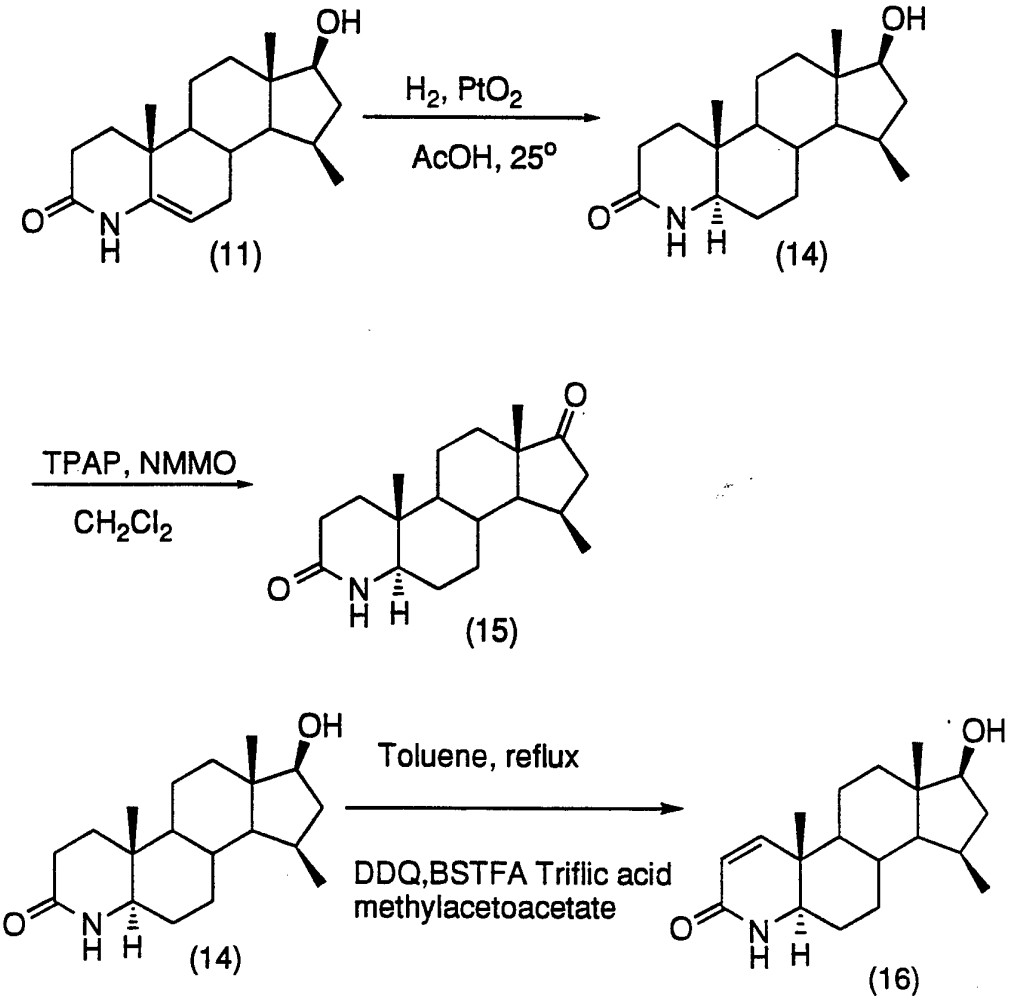
SCHEME 1



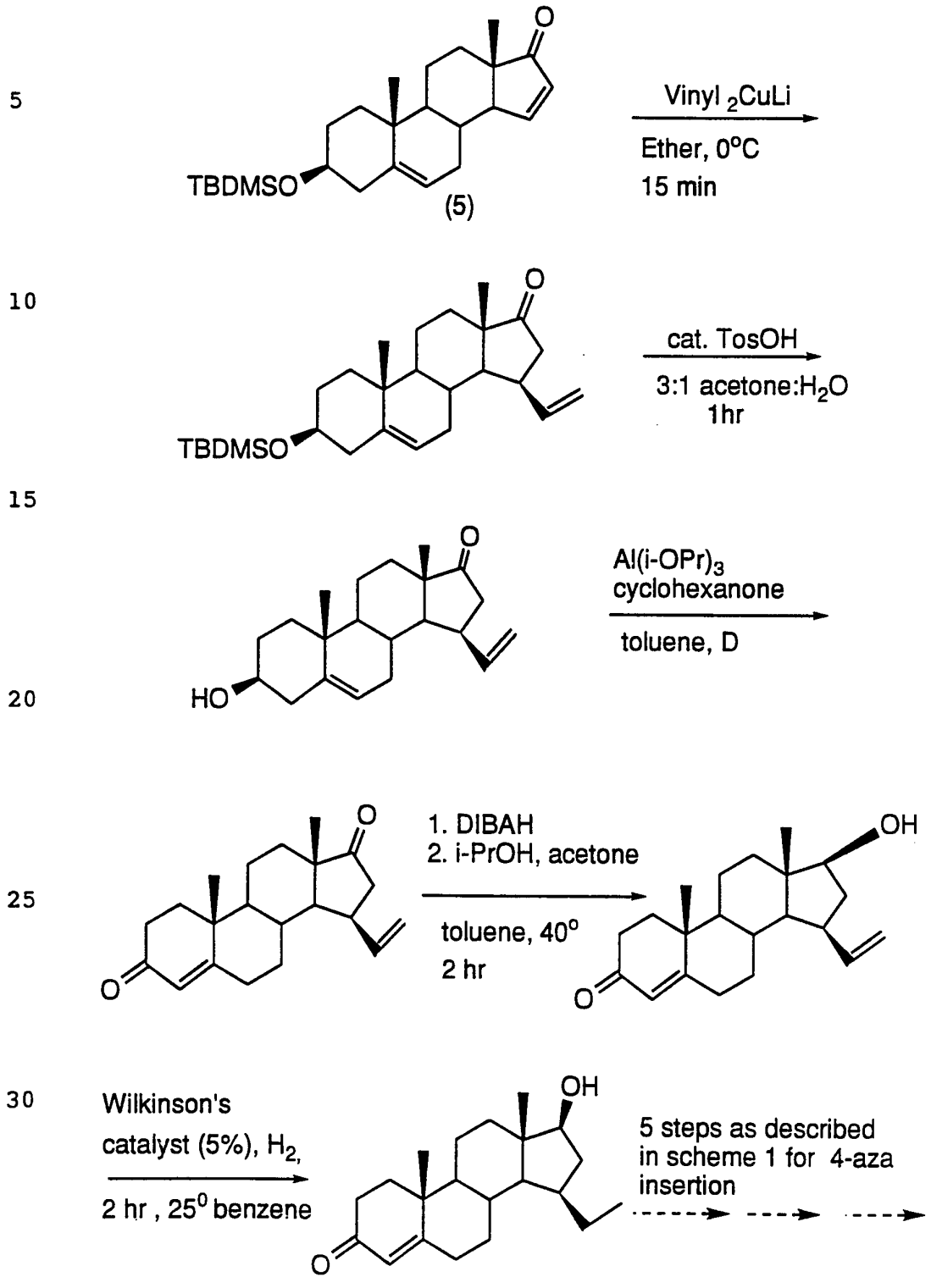
SCHEME 1 CONT'D



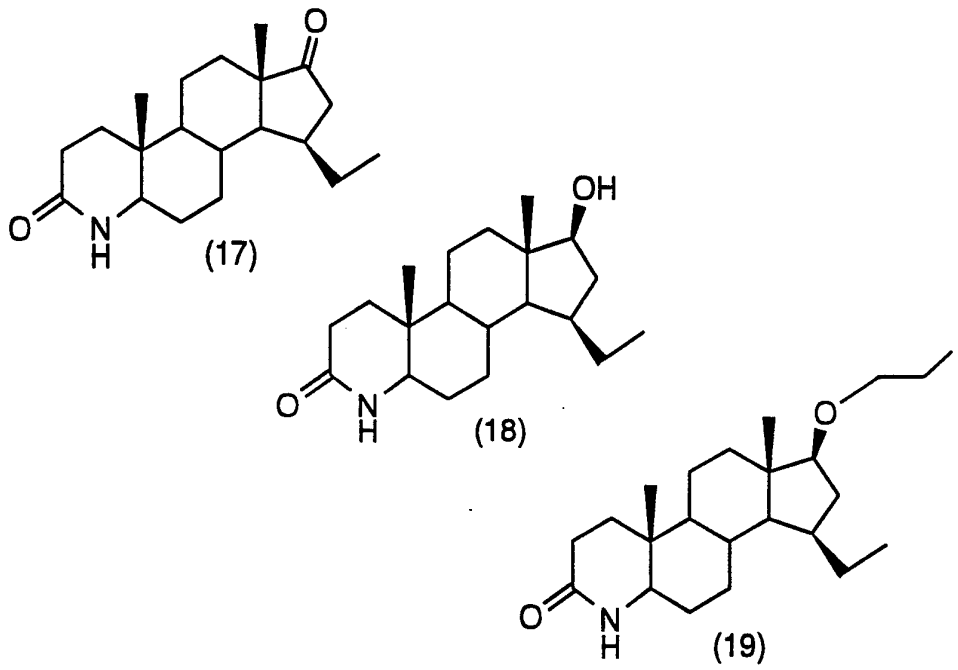
SCHEME 2


OH
H_2, PtO_2
AcOH, 25°
O
N
H
(11)
(14)
TPAP, NMMO
CH_2Cl_2
(15)
Toluene, reflux
DDQ,BSTFA Triflic acid
methylacetoacetate
(16)

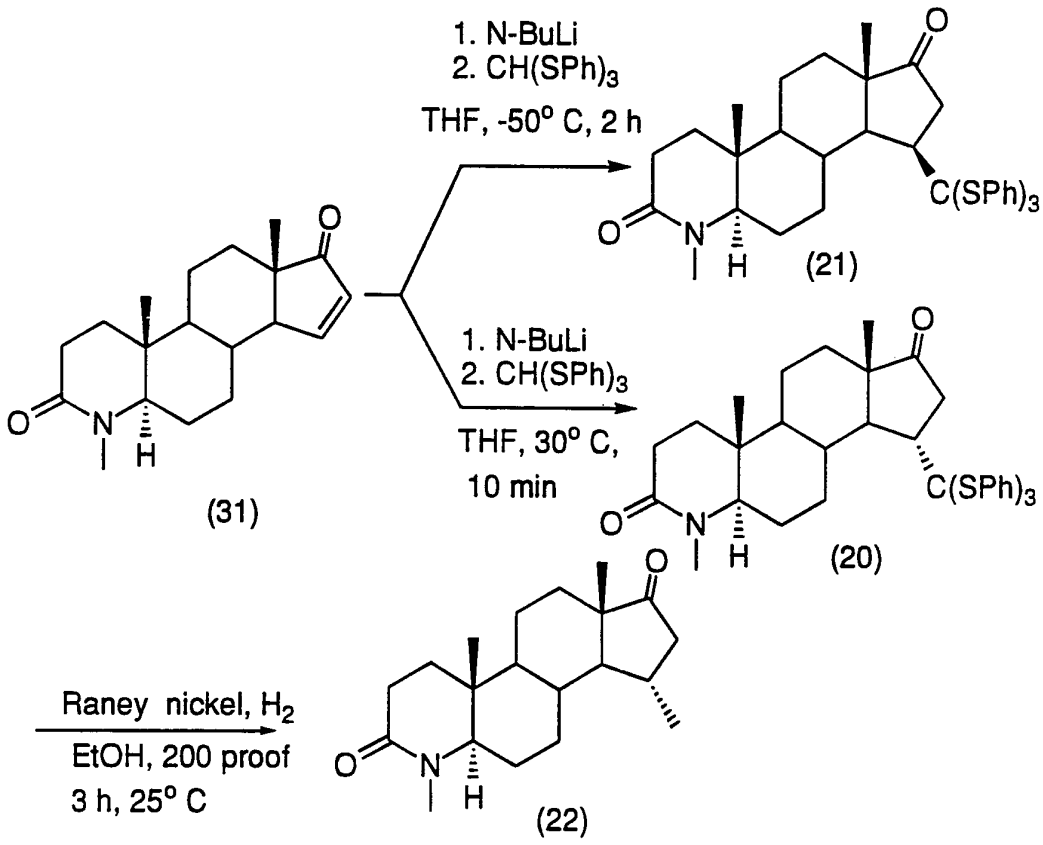
SCHEME 2 CONT'D



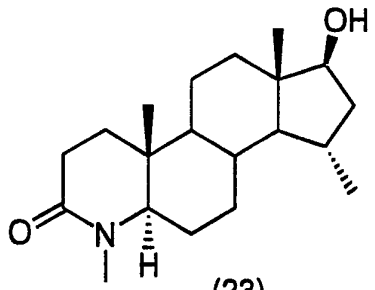
SCHEME 2 CONT'D



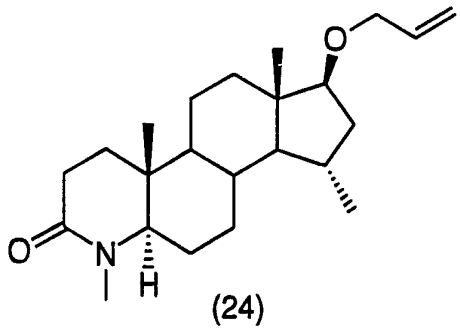
SCHEME 3


1. N-BuLi
2. CH(SPh)3
THF, -50° C, 2 h
C(SPh)3
(21)
1. N-BuLi
2. CH(SPh)3
THF, 30° C,
10 min
C(SPh)3
(20)
(31)
Raney nickel, H2
EtOH, 200 proof
3 h, 25° C
(22)

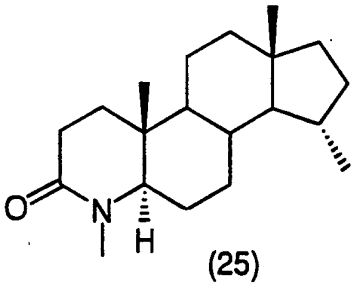
SCHEME 3 CONT'D



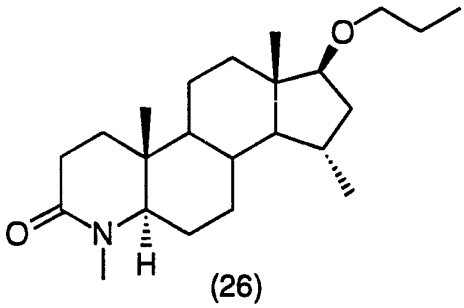
(23)



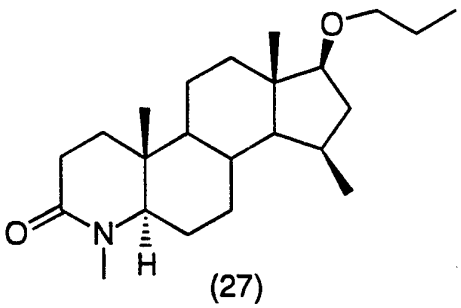
(24)



(25)

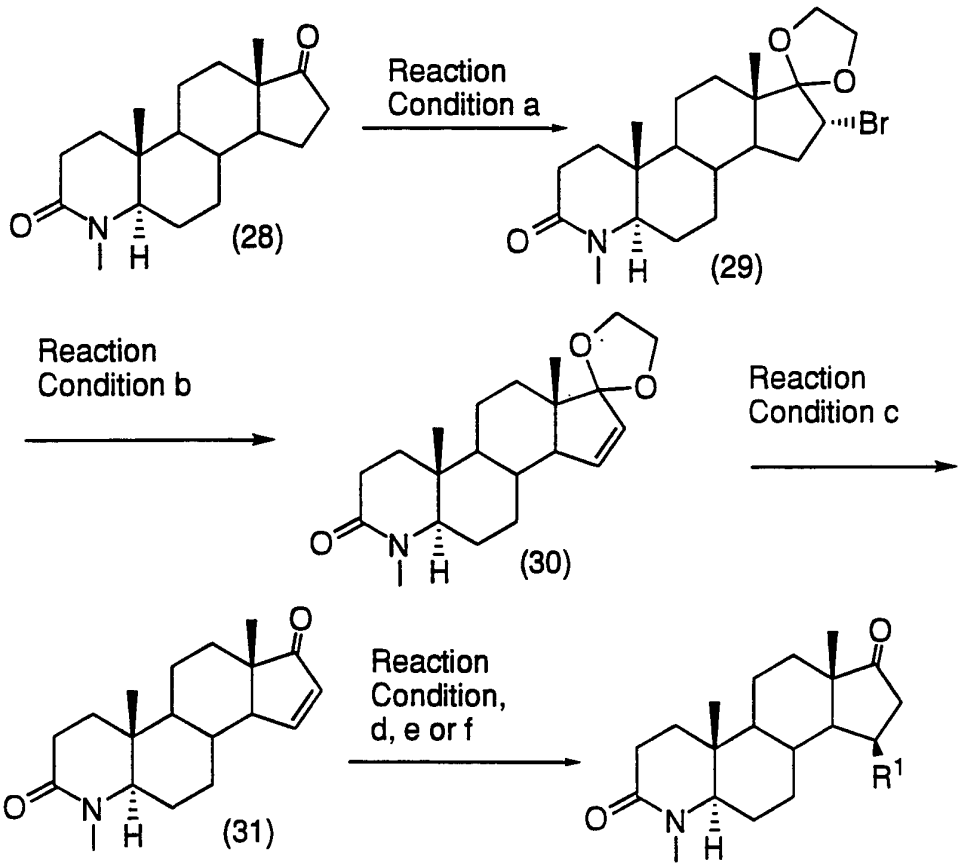


(26)



(27)

SCHEME 4



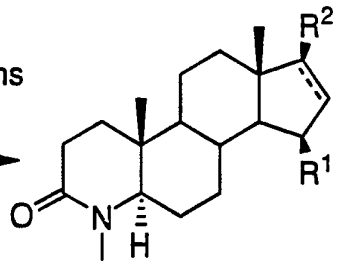
Product 32: $R^1 = \beta\text{-}CH_3$

Product 33: $R^1 = \beta\text{-}CH_3CH_2$

Product 34,35: $R^1 =$ α-,β-$(CH_3)_2CH$

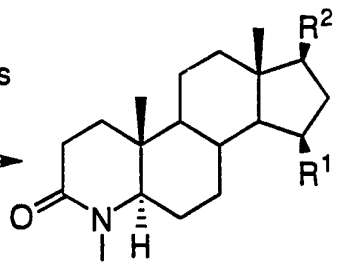
SCHEME 4 CONT'D

Reaction Conditions g or h



Product 36: $R^1 = CH_3$, $R^2 = OH$
Product 37: $R^1 = CH_3CH_2$, $R^2 = OH$
Product 38: $R^1 = CH_3$, $R^2 = OSO_2CF_3$, Δ16

Reaction Conditions i, j or k

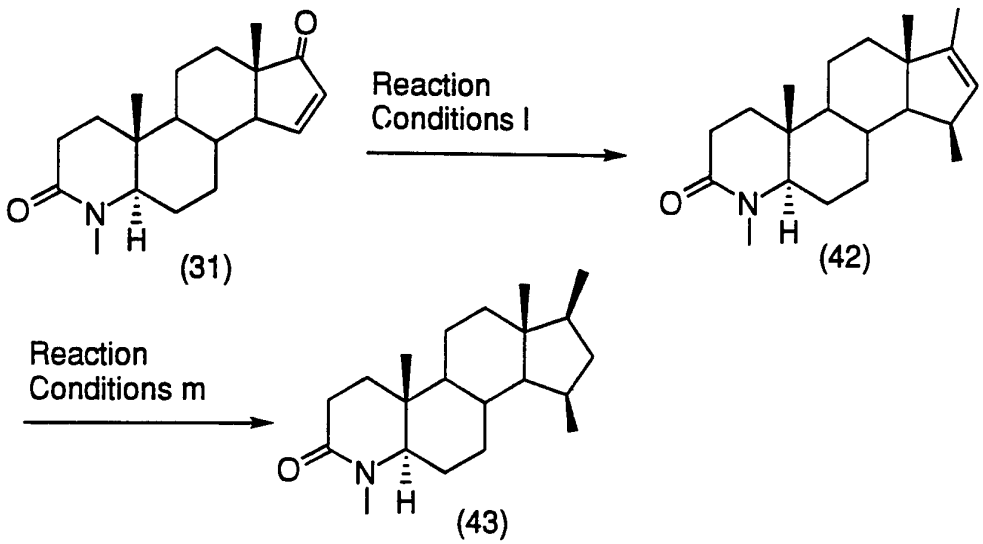


Product 39: $R^2 = (CH_3)_3CNHCOO$, $R^1 = CH_3$
Product 40: $R^2 = (CH_3)_3CCOO$, $R^1 = CH_3$
Product 41: $R^2 = H$, $R^1 = CH_3$

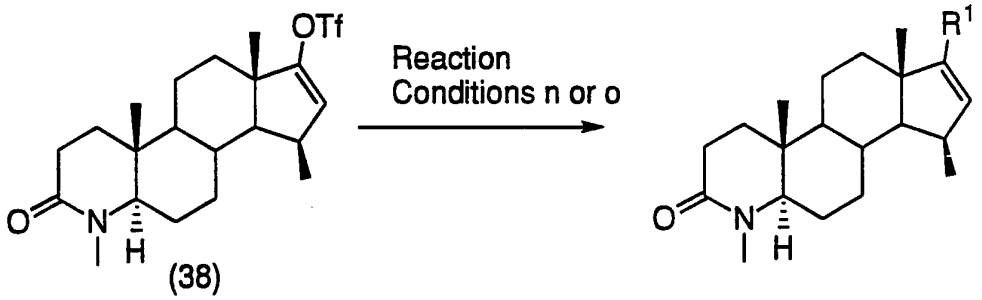
Conditions Defined For Scheme 4

a:$CuBr_2$, ethylene glycol, dioxane, 80o, 3hrs.
b: KO^tBu, DMSO, 50°, 2 hrs.
c: TsOH, Acetone, H_2O, 25°, 4 hrs.
d: CuI, MeLi, ether, THF, 0°, 3hrs.
e: EtBr, Li, CuCN, THF, -40°, 3hrs.
f: CuBr, Me_2S, ^{i}PrMgCl, THF, -78°, 6hrs.
g: $NaBH_4$, EtOH, 0°, 4hrs.
h: Hexamethyldisilizane, BuLi, $PhNTf_2$, THF, 0-25°, 2hrs.
i: ^{t}butylisocyanate, DBU, CH_2Cl_2, 25° 7 days.
j: trimethylacetylchloride, pyridine, DMAP, CH_2Cl_2, 25°, 24hrs.
k: H_2, PtO_2, EtOAc. 25°, 16hrs.

SCHEME 5



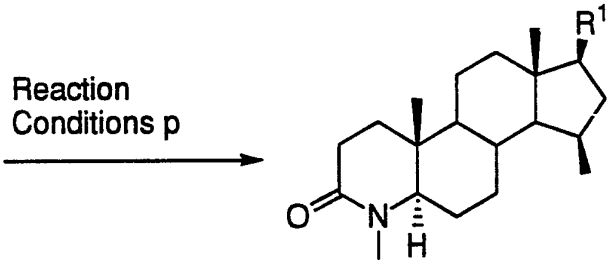
SCHEME 6



(38)

Product 44: $R^1 = (CH_3)_2CH(CH_2)_2C{\equiv}C$

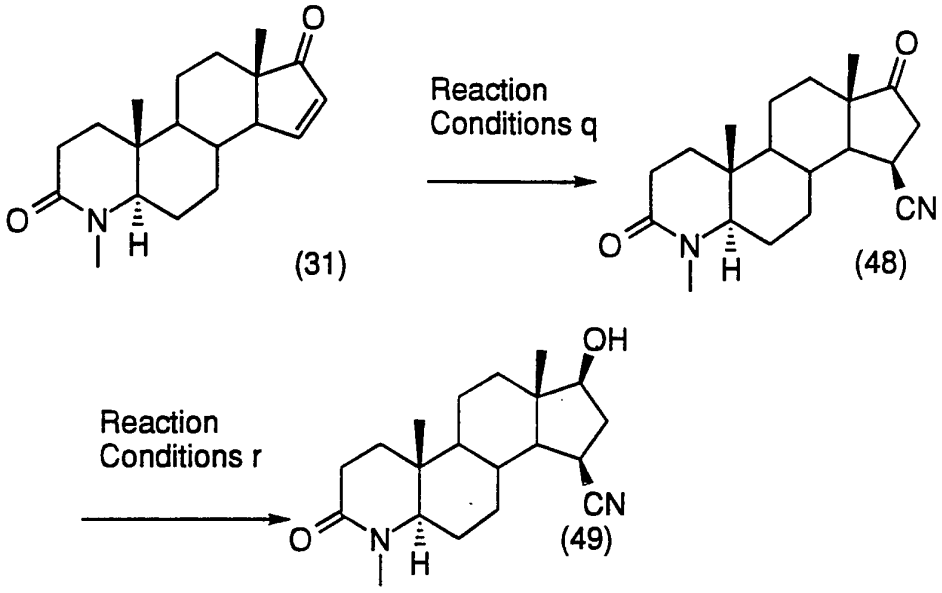
Product 45: $R^1 = CH_3O_2CCH{=}CH$



Product 46: $R^1 = (CH_3)_2CH(CH_2)_4$

Product 47: $R^1 = CH_3O_2CCH_2CH_2$

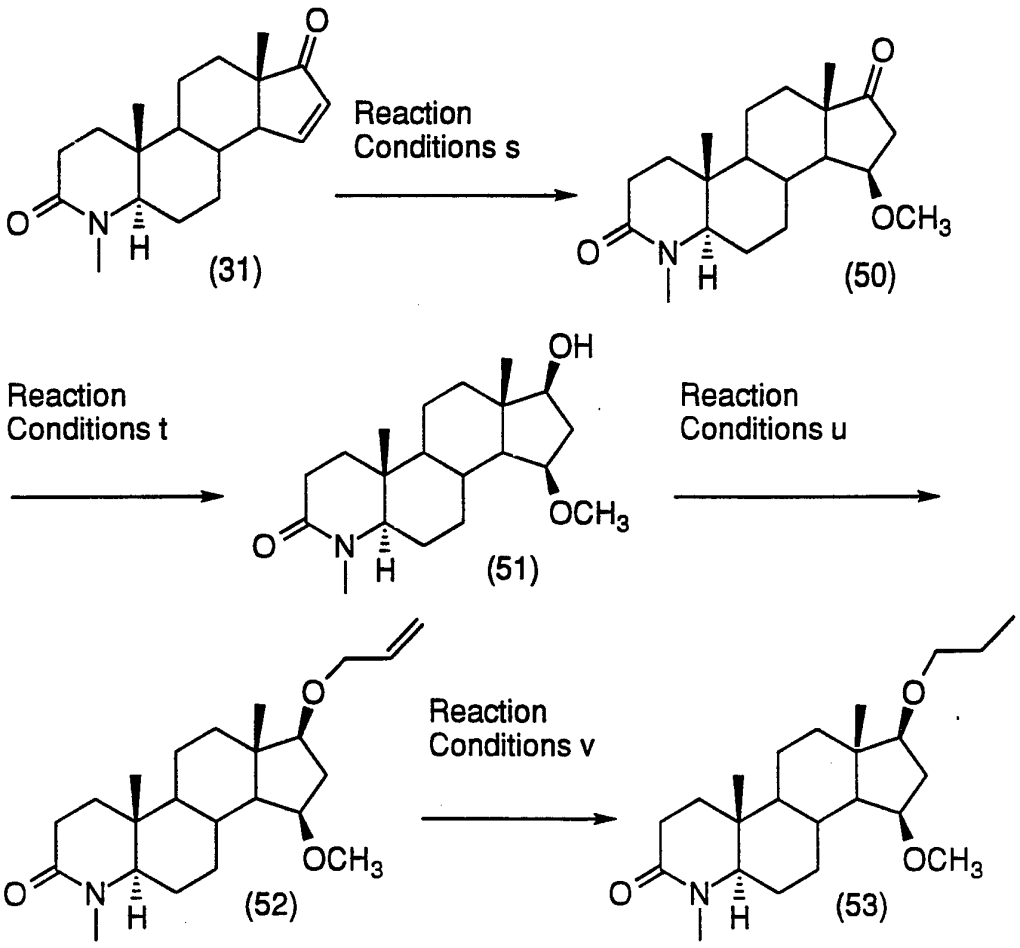
SCHEME 7



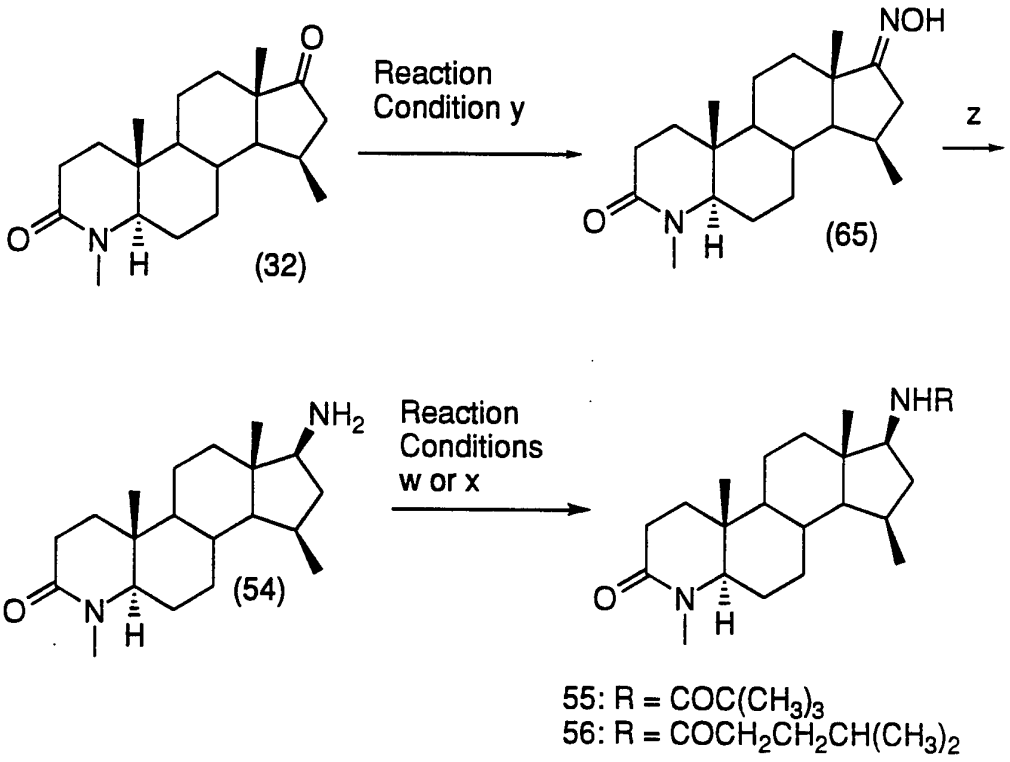
Conditions for Schemes 5, 6 and 7:

l: CuI, MeLi, $PhNTf_2$, THF, 0-25°, 16 hrs.
m: H_2, PtO_2, EtOAc, 25°, 16 hrs.
n: 5-methyl-hexyne, $(Ph_3P)_2Pd(OAc)_2$, CuI, $(^iPr)_2NH$, DMF, 25°, 16hrs.
o: methyl acrylate, $(Ph_3P)_2Pd(OAc)_2$, KOAc, DMF, 60°, 12h.
p: H_2, PtO_2, EtOAc, MeOH, 25°, 16 hrs.
q: KCN, THF, 60°, 3hrs.
r: $NaBH_4$, EtOH, 0°, 4 hrs.

SCHEME 8


Reaction Conditions s
(31)
(50)
Reaction Conditions t
(51)
Reaction Conditions u
(52)
Reaction Conditions v
(53)

SCHEME 9

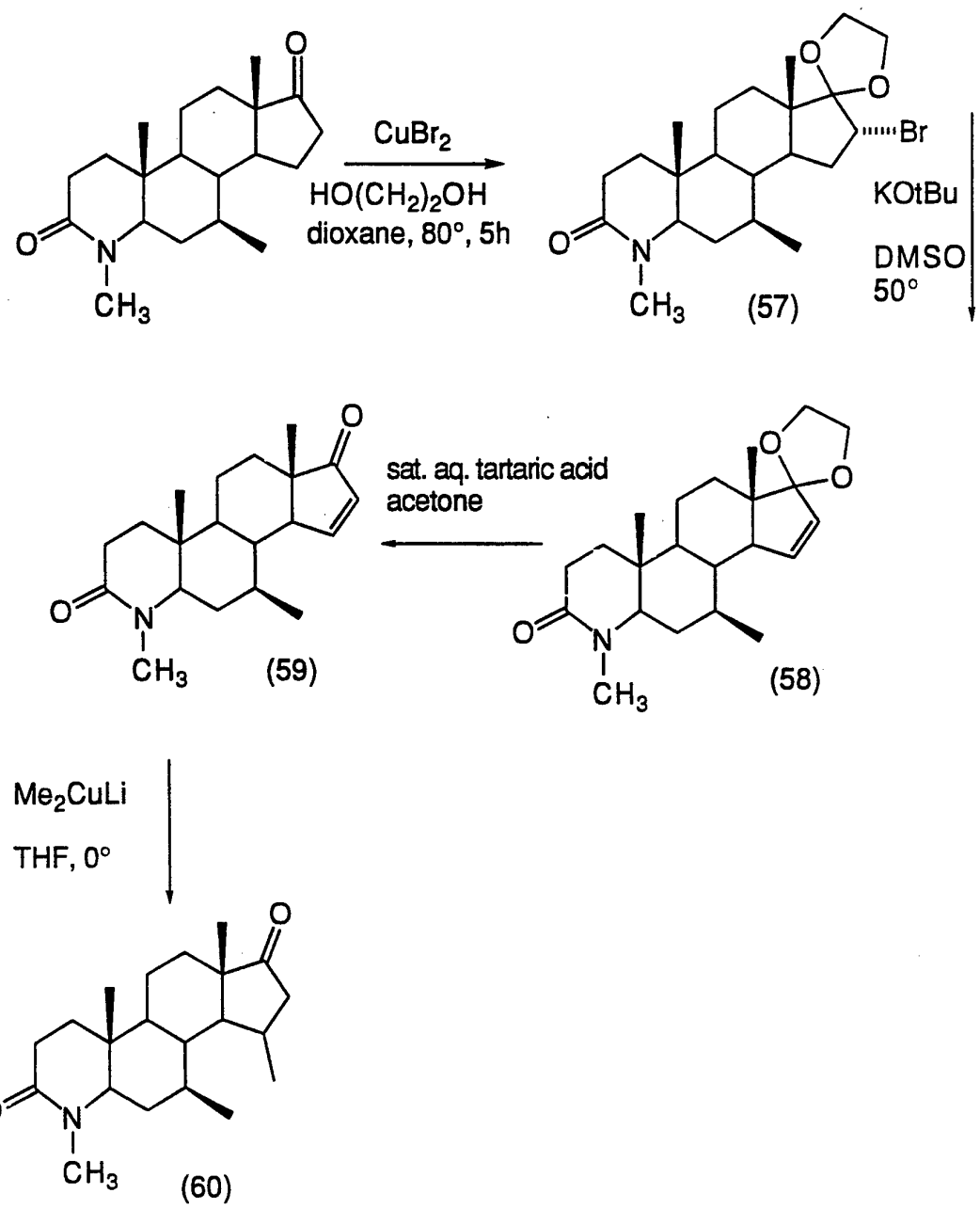


55: R = $COC(CH_3)_3$
56: R = $COCH_2CH_2CH(CH_3)_2$

Reaction Conditions for Schemes 8 and 9:

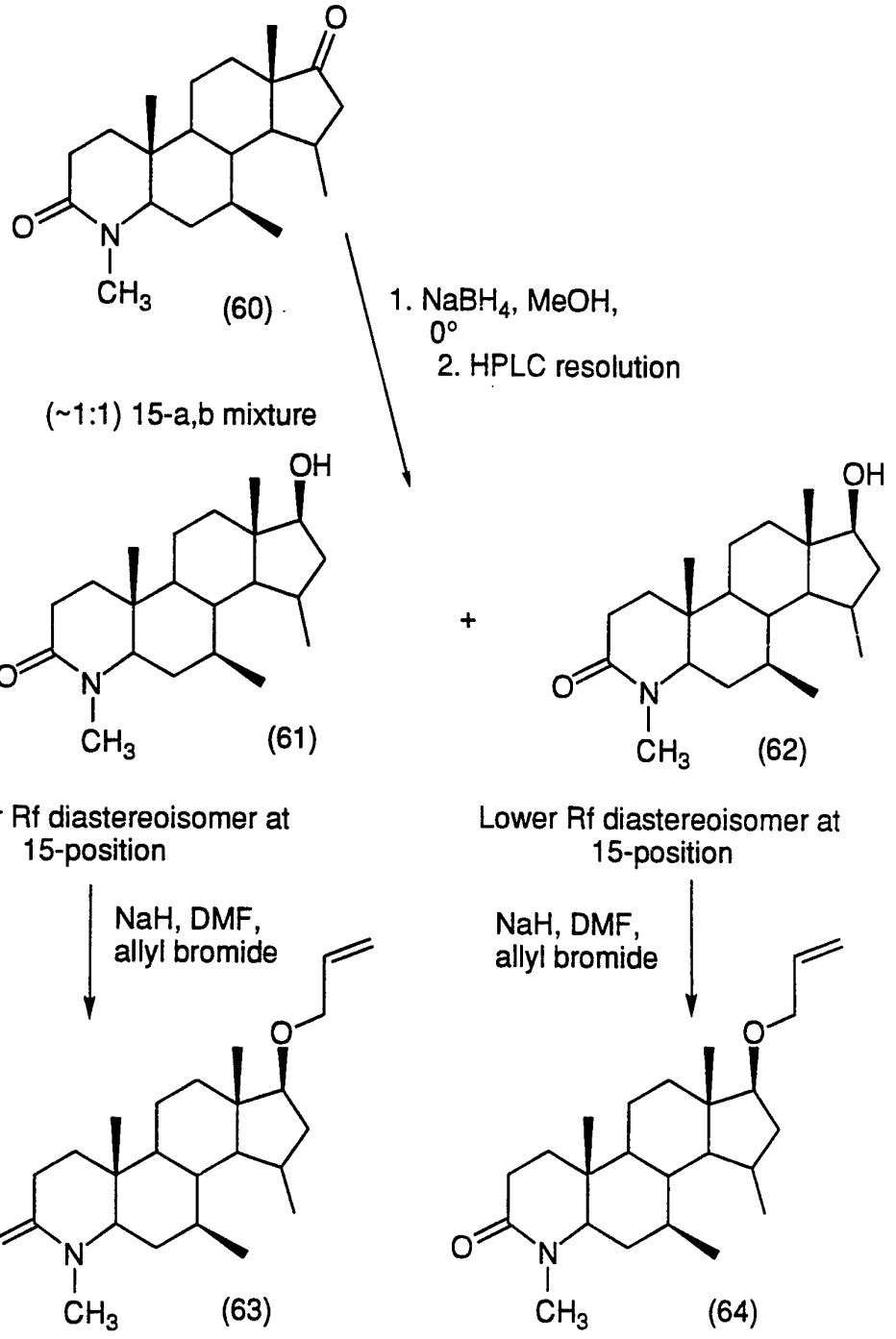
s: NaOMe, MeOH, 25°, 1 hr.
t: $NaBH_4$, EtOH, 0°, 4 hrs.
u: KH, Allylbromide, DMF, 0°, 1 hr.
v: H_2, 10% Pd on Carbon, MeOH, 25°
w: Trimethylacetyl chloride, pyridine, CH_2Cl_2, 25°, 6 hrs.
x: 4-methylvaleric acid, 1-hydrobenzotriazole hydrate, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, THF, 25°, 16hrs.
y: $NH_2OH{\cdot}HCl$, NaOAc, EtOH, 80°, 6 hrs.
z: H_2, PtO_2, EtOH, 25°

SCHEME 10

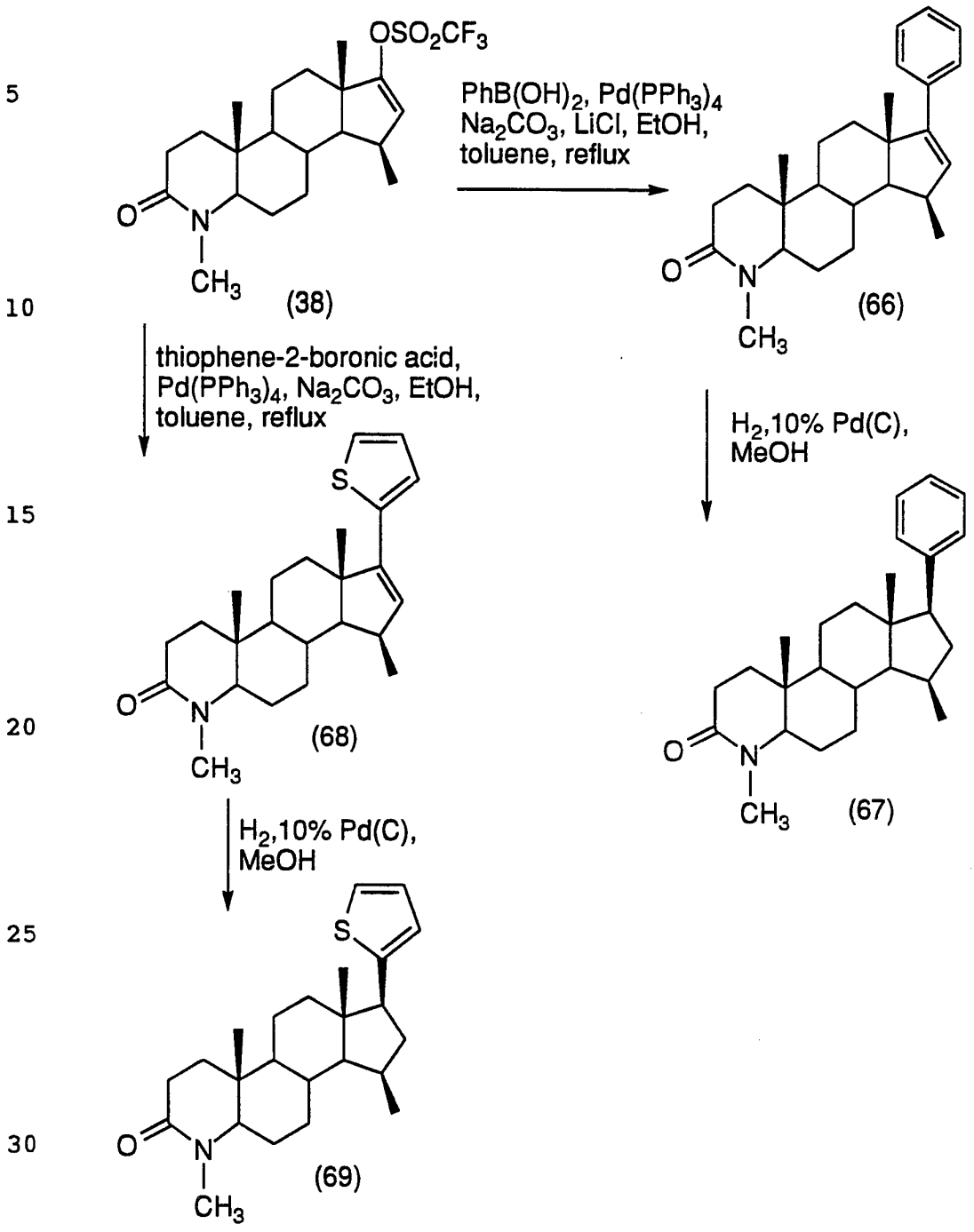


~1:1 15 α,β mixture

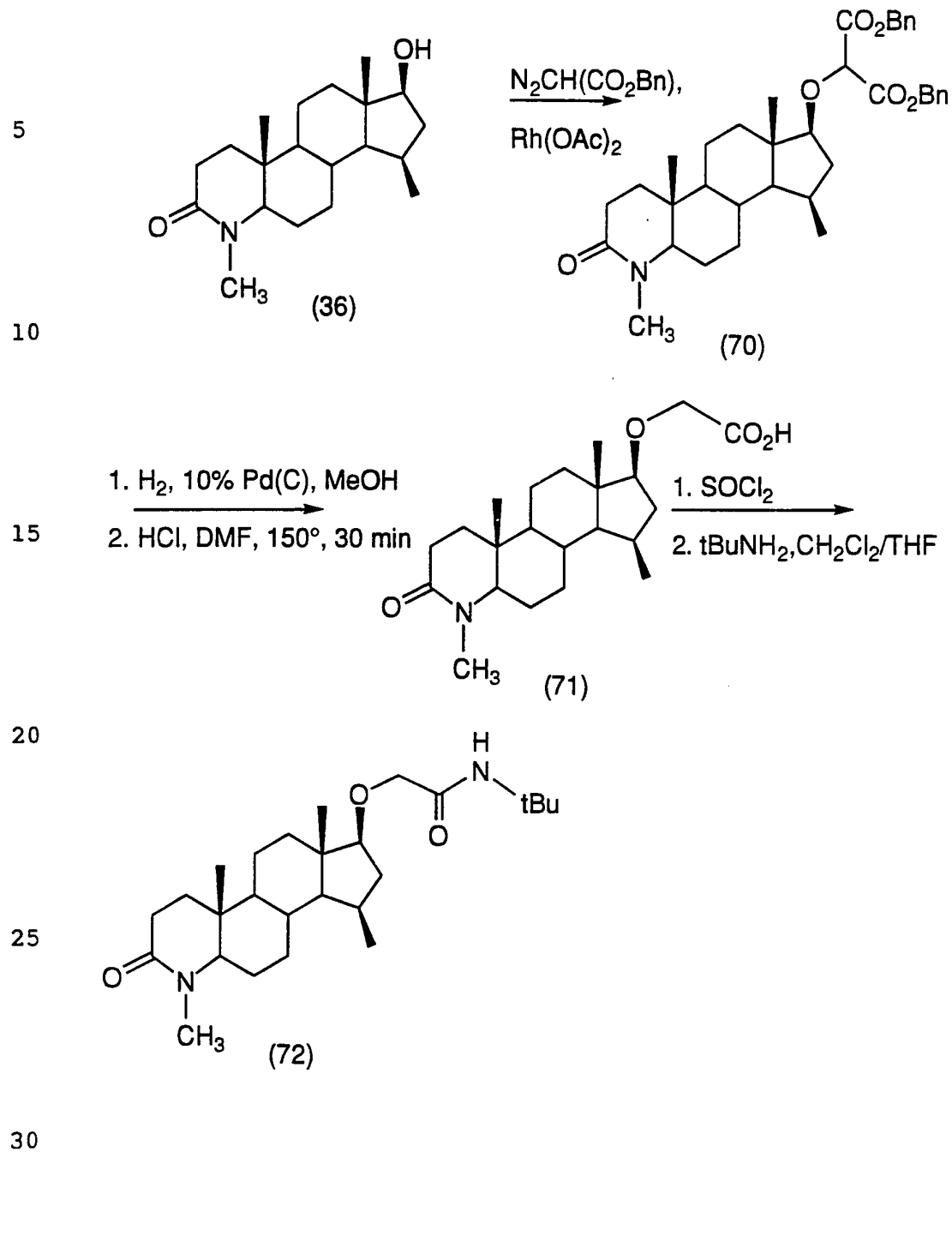
SCHEME 10 cont'd



SCHEME 11


OSO2CF3
PhB(OH)2, Pd(PPh3)4
Na2CO3, LiCl, EtOH,
toluene, reflux
(38)
(66)
thiophene-2-boronic acid,
Pd(PPh3)4, Na2CO3, EtOH,
toluene, reflux
H2,10% Pd(C),
MeOH
(68)
(67)
H2,10% Pd(C),
MeOH
(69)

SCHEME 12


OH
O
N
CH3
(36)
N2CH(CO2Bn),
Rh(OAc)2
CO2Bn
O
CO2Bn
O
N
CH3
(70)
1. H2, 10% Pd(C), MeOH
2. HCl, DMF, 150°, 30 min
O
CO2H
O
N
CH3
(71)
1. SOCl2
2. tBuNH2,CH2Cl2/THF
H
N
tBu
O
O
O
N
CH3
(72)

EXAMPLE 1

3β-Acetoxy-17-Ethylenedioxyandrost-5-Ene (1)

Toluene-p-sulphonic acid (1.0 g, 5.2 mmole), 3β-acetoxyandrost-5-ene-17-one (didehydroepiandrosterone acetate) obtained as described in D. Liu et al., J. Chem. Soc., Perkin Trans. I, p 2161 (1988), the entire disclosure of which is incorporated herein by reference, (50 g, 151.4 mmol), ethylene glycol 18.6 mL, 520 mmol), and triethylorthoformate (72 mL, 428 mmole) were stirred together at 90° and refluxed under anhydrous conditions. After 1h, the solvent was slowly distilled off and the distillation was continued until the temperature of the mixture reached 110°C. The hot mixture was poured cautiously into hot methanol (285 mL) containing pyridine (8 mL). Water (72 mL) was then added and the solution allowed to cool slowly to room temperature. The crystals were filtered off and dried to give the title acetal (52.3 g , 92%), mp=143° δ_H ($CDCl_3$) 0.86 (s, 3H), 1.03 (s, 3H), 2.03 (s, 3H), 3.75-4.05 (m, 4H, 17-acetal), 4.48-4.73 (m, 1H), and 5,38 (brd, 1H, J 4.5 Hz).

EXAMPLE 2

3β-Acetoxy-16α-bromo-17-ethylenedioxyandrost-5-ene (2)

The acetal (1) (40g, 107 mmol) was dissolved in freshly distilled anhydrous THF (120 ml). Pyridinium bromide perbromide (80 g, 250 mmol) in 120 mL THF was added and the resulting mixture stirred for 2 h. Sodium iodide (60g, 403 mmol) was added and stirring continued for 30 min. A solution of sodium thiosulphate (80g) in 120 mL of water and pyridine (24 mL) was added and the resulting solution stirred for 3h. The mixture was diluted with water (250 mL) and the THF evaporated off under reduced pressure. The crystalline material was filtered off, washed well with water, dried and recrystallized from aqueous ethanol to give the 16α-bromo derivative (45g, 99 mmol, 93%) δ_H ($CDCl_3$) 0.90 (s, 3H), 1.02 (s, 3H), 2.03 (s, 3H), 3.85-4.05 (m, 2H), 4.10-4.20 (m,1H), 4.20-4.30 (m, 1H), 4.50-4.70 (m, 1H), 4.50-4.60 (dd, J_1= 10.5, J_2= 4.5 Hz), and 5.36 (br d, 1H).

EXAMPLE 3

3β-Hydroxy-17-ethylenedioxy androst-5,15-diene (3)

Product (2) (17 g, 37.5 mmol) was dissolved in dry dimethyl sulphoxide (DMSO,170 mL) at 40-45°. Dry potassium t-butoxide (13.5 g, 120 mmol) was added under nitrogen and the mixture left at 40-45° C overnight (18 h). The solution was then poured into dry ether (1000 mL) and stirred for 10 minutes to dissolve any solids. Water was added (500 mL) and the ethereal solution was washed with water followed by saturated brine. The solution was dried ($MgSO_4$), filtered and evaporated to dryness. Recrystallization of the residue from aqueous ethanol gave the diene δ_H ($CDCl_3$) 0.94 (s, 3H), 3.46-3.63 (m, 1H), 3.79-4.08 (m, 4H), 5.37 (br d, 1H), 5.71 (dd, J=3.3 Hz, 1H), and 6.13 (br d, J=4.8 Hz, 1H).

EXAMPLE 4

3β-Hydroxy-androstan-5,15-diene -17-one (4)

The diene (3) (5.9 g, 16.8 mmole) was dissolved in 150 mL of acetone. and 15mL of H_2O. p-Toluene sulphonic acid (250 mg, 1.3 mmol) was added and the solution stirred at 4° overnight. Water was added (75 mL) and the solvent removed under reduced pressure at 25°. A precipitate formed and was filtered, washed with cold water and dried under vacuum. The 17-ketone was recovered: (4.4 g, 96%), mp=186-188° δ_H ($CDCl_3$) 1.09 (s, 3H), 1.59 (s, 3H), 3.50-3.60 (m, 1H), 5.41 (m, 1h), 6.05 (dd, J=3 and 6Hz, 1H) and 7.51 (br d, J=6 Hz,1H).

EXAMPLE 5

3β-(Dimethyl-t-butylsilyloxy)-androstan-5,15-diene-17-one (5)

To the dieneone (4), (4.4 g, 15.3 mmol) in dichloromethane (40 mL) was added t-butyldimethylsilyl chloride (5.61g, 37 mmol), dry triethylamine (5.6 mL, 40mmol) and 4-

dimethylaminopyridine (4.52g, 37 mmol). The mixture was stirred at 20° for 5 h, then water was added along with additional methylene chloride (200 mL and 50 mL, respectively). The mixture was extracted with methylene chloride, pooled, washed sequentially with 10% aqueous ammonium chloride, saturated brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was chromatographed with 70/30 dichloromethane/hexane on a flash silica gel column. Recovered 4.4 g (11 mmole, 72%) of product δ_H ($CDCl_3$) 1.05 (s, 3H), 1.06 (s, 3H), 3.20-3.60 (m, 1H), 5.38 (d, 3 Hz, 1H), 6.03 (dd, J=3 and 6 Hz, 1H), and 7.47 (br d, J=6 Hz, 1H).

EXAMPLE 6

3β-(Dimethyl-t-butylsilyloxy)-15β-methyl-androst-5-en-17-one (6)

A 250 mL round bottomed flask fitted with a stirrer bar and rubber septum was flamed dried under nitrogen. Copper (I) iodide (6.21 g, 32.8 mmol) was added and the flask flushed with N_2. A 2:1 mixture (v/v) of dried diethyl ether (120 mL) and tetrahydrofuran (60 mL) was cannulated into the flask and the solution cooled to 0°. Two equivalents of methyl lithium (1.6 N, 41 mL, 66 mmol) was slowly added to the reaction mixture while insuring that the solution temperature remained below 5°. The solution was stirred until all of the copper iodide was consumed (30 min). The enone (5) (3.30 g, 8.2 mmol) was added via syringe in 40 mL of dry THF over 5 min, again keeping the solution temperature below 5°. The mixture was stirred at 0° for 1h , then 10 ml of 10% ammonium choride was carefully added dropwise over 10 min. This mixture was stirred 15 minutes, then 100 mL of dichloromethane was added, the mixture extracted and the organic phase was decanted. The aqueous phase was extracted with 3 x 50 ml dichloromethane. The organic layer was pooled, dried over $MgSO_4$, filtered and the volume reduced under reduced pressure. The product was chromatographed (75/25 dichloromethane/hexane). Product recovered: (3.10 g,7.5 mmol, 70%) δ_H ($CDCl_3$) 1.01 (s, 3H), 1.03 (s, 3H), 1.09 (d, J=7 Hz,), 3.4-3.5 (m, 1H), 5.34 (d, 1H).

EXAMPLE 7

3β-Hydroxy-5-ene-15β-methyl-androst-5-ene-17-one (7)

A 100 mL round bottomed flask was fitted with a stir bar and filled with 60 mL of a 5:1 solution of acetone: water and 3.1 g of 6. The solution was warmed to 50° and p-toluenesulfonic acid (800mg, 4.2 mmol) was added. This was stirred until the silyl protecting group was removed (2 h). The solution volume was reduced under reduced pressure and 100 mL of water was added. The product precipitated out of solution and was isolated by filtration on a fritted glass funnel and washed with 3 x 30 mL of ice water. The product was dried overnight under reduced pressure. Recovered product: (2.28 g, 7.5 mmol, 95%) δ_H ($CDCl_3$) 1.01 (s, 3H), 1.04 (s, 3H), 1.09 (d, J=7 Hz,), 3.45-3.55 (m, 1H), 4.82 (bs, 1H), 5.39 (d, 1H).

EXAMPLE 8

15β-Methyl-androst-4-ene 3,17-dione (8)

A 50 mL round bottomed flask is fitted with a stir bar, 26 mL of dry benzene, 2.28 g of (7) and 7 mL of cyclohexanone. The flask is fitted with a Dean Stark trap attached to a condenser. The solution is refluxed and 3 mL of solvent is removed (water azeotrope). Then 10 mL more of toluene with 1.44g (7.1 mmol) of aluminum isopropoxide is added to the flask and 10 mL of distillate is removed by reflux over 2 h. Cool to 65° and add 600 mg each of Darco activated charcoal and Celite filter aid with 1 mL of water. Stir for 1 h and filter through a sintered glass funnel and wash the precipitate with 6 x 15 mL of hot ethyl acetate. Reduce the filtrate volume under reduced pressure and chromatograph the product by flash chromatography with a 4/1 mixture of hexane/ethyl acetate. Recovered product (1.5 g, 5 mmol, 63%) δ_H ($CDCl_3$) 1.05 (s, 3H), 1.13 (d, J=7 Hz,), 1.22 (s, 3H), 5.73 (d, 1H).

EXAMPLE 9

15β-Methyl-17-β-hydroxy-androst-4-ene 3-one (9)

A 250 mL round bottomed flask was fitted with a stirrer bar and was flame dried under nitrogen. Then enone (8) (1.5g, 5 mmol) and 75 mL of toluene was added and the flask sealed with a rubber septum. The solution was cooled to -78° and diisobutyl-aluminum hydride (7.5 mL, 25% solution in toluene) was added dropwise, keeping the temperature under -60°. This was stirred for 1 h at -78°. 3 mL of acetone was slowly added dropwise, then 3 mL of isopropanol, keeping the temperature under -30°. The solution was slowly warmed up to room temperature and stirred for 1 h. Another 1 mL of acetone was added and the solution was warmed to 35° for 2 h. By TLC, we saw a single, slightly lower strongly UV active spot, indicating that the 3-enone has been reformed. Workup was performed by pouring the solution into 5% sodium hydrogen sulphate. The solution was then acidified with 2 N H_2SO_4 to pH =3, extracted with 1:1 ether: ethyl acetate and chromatographed on silica gel with 3:2 hexane: ethyl acetate. Recovered product: (1.33g , 89%) δ_H ($CDCl_3$) 0.89 (s, 3H), 1.00 (d, J=7 Hz,), 1.18 (s, 3H), 3.58 (m, 1H), 5.70 (d, 1H).

EXAMPLE 10

15β-Methyl-androstan-17β-ol seco acid (10)

Periodate cleavage of (9) was effected by dissolving sodium periodate (6.52 g, 30.5 mmol), potassium permanganate (48mg, 0.3 mmole) and sodium carbonate (680 mg, 6.4 mmole in 25 mL of hot water) and adding this solution dropwise over 20 minutes to a refluxing solution of 9 (1.33 g, 4.4 mmol) in 30 mL of tert-butanol. The suspension was refluxed for 1h after the addition is complete, cooled to 30° and filtered with washing (3 x 10 mL of hot H_2O). The filtrate was concentrated under reduced pressure to remove the tert-butanol and then acidified to pH=3 with 5 N hydrochloric acid. The product was

extracted with 4 x 20 mL of dichloromethane, the extracts pooled and dried over $MgSO_4$. The solvent was removed under reduced pressure. Recovered product: 1.24 g (3.7 mmol, 84%). The product was used without further purification δ_H ($CDCl_3$) 0.92 (s, 3H), 1.02 (d, J=7 Hz), 1.13 (s, 3H), 3.58 (m, 1H).

EXAMPLE 11

15β-Methyl-17β-hydroxy-4-aza androst-5-en-3-one (11)

The secoacid (10) (1.24 g, 3.7 mmol) was mixed with ammonium acetate (1.7 g, 22.2 mmol) and ethylene glycol (23 mL) in a 50 mL round bottomed flask fitted with a stirrer bar and a rubber septum. The flask was heated under nitrogen to 180° slowly over 40 minutes at kept there for 2 h. The mixture was cooled to 70° and the solution poured into 200 mL of ice water. The product precipitated out, was filtered and washed with water. The precipitate was dried under reduced pressure. Recovered product: (0.72 g, 2.2 mmol, 61%) δ_H ($CDCl_3$) 0.90 (s, 3H), 0.99 (d, J=7 Hz,), 1.11 (s, 3H), 3.60 (t, J=7 Hz, 1H), 4.81(m, 1H), 7.37(bs, 1H).

EXAMPLE 12

15β-Methyl-17β-allyloxy-4-aza-androst-5-en-3-one (12)

Potassium hydride (40% oil dispersion, 114 mg, 2 mmol) was added to a 5 mL round bottomed flask fitted with a stirrer bar and a rubber septum. The potassium hydride dispersion was washed with dry hexane (2 x 5 ml) to remove the mineral oil and 3 mL of dry dimethylform-amide was added to the flask. Azasteroid (11) (158 mg, 0.5 mmol) was added to the dispersion and the solution stirred at 0° under nitrogen for 1h. Then allyl bromide (183 mg, 1.5 mmol) was syringed into the solution and the mixture stirred for 2 h at room temperature. The entire solution was poured into 5 mL of 1N HCl and the mixture extracted with 5 x 2 mL of dichloromethane. The pooled organic layer was washed with 3 x 5 mL of saturated brine. The

product was flash chromatographed with 3/1 dichloromethane/ethyl acetate. Recovered product (78 mg, 0.2 mmol, 44%) δ_H ($CDCl_3$) 0.89 (s, 3H), 0.99 (d, J=7 Hz,), 1.06 (s, 3H), 3.60 (m, J=7 Hz, 1H), 3.95 (dd, J=12 Hz, J=5 Hz), 4.64 (dd, J=12 Hz, J=5 Hz), 5.1(m, 2H), 5.79 (m, 1H).

EXAMPLE 13

15β-Methyl-17β-propyloxy-4-aza-5α-androstan-3-one (13)

Azasteroid (12) (78 mg, 0.2 mmol) was hydrogenated in 1 mL of ethanol with stirring over 20 mg of platinum oxide under a hydrogen atmosphere. The reaction was complete after 2 h at 40°. The solution was filtered to remove the platinum catalyst. The solution was added to 10 mL of water. The product crystallized out of solution and was dried under reduced pressure. Recovered product: 48 mg (61%). δ_H ($CDCl_3$) 0.85 (t, J=7 Hz, 3H), 0.87 (s, 3H), 0.89 (s, 3H), 0.99 (d, J=7 Hz,), 2.65 (m, 2H), 3.3 (m, 2H), 3.82 (t, J=7 Hz, 1H), 3.95 (m, 1H), Mass spectrum (M+= 347).

EXAMPLE 14

17β-Hydroxy-15β-methyl-4-aza-5α-androstan-3-one (14)

Intermediate (11) (0.2 g, 0.65 mmole) was dissolved in 3 mL of glacial acetic acid. Platinum oxide (25 mg) was added, the flask sealed with a rubber septum and hydrogen gas was introduced via syringe with stirring at 25°. No starting material was seen by TLC after 2 h.. The reaction mixture was filtered and the solvent removed under reduced pressure. The product was recrystallized from ethyl acetate. Recovered product: (0.15 g, 75%) δ_H ($CDCl_3$) 0.87 (s, 3H), 0.92 (s, 3H), 0.98 (d, J=7 Hz,), 2.40 (m, 2H), 3.08 (dd, =12 Hz, J=5 Hz), 3.58(t, J=9 Hz, 1H), 5.72 (bs, 1H) Mass spectrum (M+= 305).

EXAMPLE 15

15-Methyl-4-aza-5α-androstan-3,17-dione (15)

Compound 14 (40 mg, 0.126 mmole) was dissolved in 3 mL of dichloromethane in a 10 mL round bottomed flask fitted with a stirrer bar and rubber septum. The solution was cooled to 0° and 100 mg of 4 angstrom powdered molecular sieve, 210 mg of N-methyl morpholine N-oxide (1.7 mmole) and tetrapropylammonium perruthenate (3 mg, 0.01 mmol) were added and stirred for 2 h. Analysis by TLC (95/5 dichloromethane/methanol) indicated that starting material was gone. The product was purified by flash chromatography (97/3 dichloromethane/methanol). Recovered product: 35 mg, 0.110 mmole) δ_H ($CDCl_3$) 0.94 (s, 3H), 1.02 (s, 3H), 1.10 (d, J=7 Hz,), 2.42 (m, 2H), 3.1 (dd, =12 Hz, J=4 Hz), 5.78 (bs, 1H) Mass spectrum (M^+= 303).

EXAMPLE 16

17β-Hydroxy-15β-methyl-4-aza-5α-androst-1-en-3-one (16)

Compound (14) (55 mg, 0.17 mmole), dichloro-dicyano benzoquinone (DDQ) (47 mg, 0.21 mmole), bis(trimethylsilyl)-trifluoroacetamide (BSTFA) (175 mg, 0.68 mmole) and trifluoro-methanesulfonic acid (2 mg, 0.0013 mmol) were stirred overnight in 2 mL of toluene in a 5 mL round bottomed flask fitted with a stirrer bar and condenser. The next day 40 microliters of methyl acetoacetate was added to quench the red colored DDQ complex which was then refluxed overnight. The solution was then diluted with 5 mL dichloromethane and the solution extracted sequentially with 25 mL of water, 10 mL of water with 400 mg of sodium carbonate, and 150 mg of sodium sulfite in 5 mL of water. The layers were separated and the organic phase washed with 5% sodium bicarbonate, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification was by flash chromatography (9/1 dichoromethane/acetone). Recovered product: (26 mg, 47%) δ_H ($CDCl_3$) 0.92 (s, 3H), 0.99 (s, 3H), 1.01 (d, J=7 Hz,),

2.53 (m, 1H), 3.35 (dd, J=12 Hz, J=4 Hz), 5.5 (bs, 1H), 5.80 (d, J=10 Hz, 1H), 6.81 (d, J=10 Hz, 1H) Mass spectrum (M+= 303).

Refer to Schemes 1 and 2 for the procedural workup for Examples 17, 18 and 19.

EXAMPLE 17

15β-Ethyl-4-aza-5α-androstane-3,17-dione (17)

δ_H ($CDCl_3$) 0.89(t, J=7 Hz, 3H), 0.92 (s, 3H), 0.97 (s, 3H), 2.45 (m, 2H), 3.07 (dd, J=12 Hz, J=3Hz, 1H), 5.67 (bs, 1H): Mass spectrum (M+= 317).

EXAMPLE 18

17β-Hydroxy-15β-ethyl-4-aza-5α-androstan-3-one (18)

δ_H ($CDCl_3$) 0.81 (t, J=7 Hz), 0.83 (s, 3H), 0.89 (s, 3H), 2.32 (m, 1H), 2.43 (m, 1H), 3.08 (dd, J=12 Hz, J=4 Hz), 3.60 (t, J=7 Hz, 1H) Mass spectrum (M+= 319).

EXAMPLE 19

15β-Ethyl-17β-propyloxy-4-aza-5α-androstan-3-one (19)

δ_H ($CDCl_3$) 0.85 (t, J=7 Hz, 3H), 0.87 (s, 3H), 0.89 (s, 3H), 0.99 (d, J=7 Hz,), 2.65 (m, 2H), 3.3 (m, 2H), 3.82 (t, J=7 Hz, 1H), 3.95 (m, 1H), Mass spectrum (M+= 361).

EXAMPLE 20

4-Methyl-15α-(tris(phenylthio)methane)-4-aza-5α-androstan-3,17-dione (20)

To a 50 mL round bottomed flask flamed under nitrogen, fitted with a stirrer bar and sealed with a rubber septum was added tris(phenylthio)methane (850 mg, 2.5 mmol) and 30 mL of dry

tetrahydrofuran. The solution was cooled to -78° with a dry ice/acetone bath and 1.05 equivalents of 1.6 N n-butyllithium (1.56 mL, 2.1 mmole) is added slowly to the solution. The temperature was allowed to come to 25°. Then 31, as prepared in Scheme 4, (0.60 g, 2.0 mmole) in 5 mL of dry tetrahydrofuran was cannulated dropwise over 5 min into the reaction mixture. The solution was stirred for 1 h and then quenched with 2 mL of 30% ammonium chloride. The solution was poured into 50 mL of water and extracted with 3 x 25 mL of dichloromethane. The organic layer was pooled, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. By NMR (400 MHz), we saw a 9/1 ratio of 15α/15β methyl product. Purification by flash chromatography (80/20 hexane/isopropanol) gave the higher R_f 15α derivative (823 mg, 74%) δ_H ($CDCl_3$) 0.73 (s, 3H), 0.91 (s, 3H), 2.32 (m, 1H), 2.05 (t, J=8 Hz 1H), 2.2 (m, 1H), 2.45 (q, J=5 Hz), 2.55 (dd, J=20, J=10 Hz), 2.70 (dd, J=14, J=7 Hz), 2.97 (s, 3H), 3.17 (dd, J=16 Hz, J=5 Hz), 3.83 (bd, 2H), 7.23-7.40 (m, 13H), 7.53-7.55 (m, 2H).

EXAMPLE 21

4-Methyl-15β-(tris(phenylthio)methane)-4-aza-5α-androstane-3,17-dione (21)

To a 10 mL round bottomed flask flamed under nitrogen, fitted with a stirrer bar and sealed with a rubber septum was added tris(phenylthio)methane (134 mg, 0.4 mmol) and 3 mL of dry tetrahydrofuran. The solution was cooled to -78° with a dry ice/acetone bath and 1.05 equivalents of 1.6 N n-butyllithium (0.25 mL, 0.4 mmole) was added slowly to the solution. The temperature was allowed to come to -40°. Then 4-aza-methyl-androstan-15-ene-3,17-dione 31, (0.10 g, 0.33 mmole) in 1 mL of dry tetrahydrofuran was cannulated dropwise into the reaction mixture. The solution was stirred for 1 h at -40° and then quenched with 1 mL of 30% ammonium chloride. The solution was poured into 5 mL of water and extracted with 3 x 5 mL of dichloromethane. The organic layer was pooled, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. By NMR

(400 MHz), we saw a 18/1 ratio of 15β/15α methyl product. Purification by flash chromatography (80/20 hexane/isopropanol) gave the lower R_f 15β derivative (175 mg, 90%) δ_H ($CDCl_3$) 0.90 (s, 3H), 1.55 (s, 3H), 2.43(m, 2H), 2.88 (s, 3H), 3.21 (dd, J=16 Hz, J=5 Hz), 7.23-7.40 (m, 13H), 7.53-7.55 (m, 2H).

EXAMPLE 22

4,15α-Dimethyl-4-aza-5α-androstan-3,17-dione (22)

4-Aza-methyl-15α-(tris(phenylthio)methane)-androstane-3,17-dione (18) (650 mg, 1.12 mmol) was dissolved in 25 mL of absolute ethanol. Then 4 g of W2 Raney Nickel (Aldrich) was thoroughly washed with absolute ethanol (10 x 10 mL), added to the reaction mixture and the product agitated under hydrogen (STP) for 18 h at 25°. The reaction mixture was filtered and the Raney Nickel washed with ethanol to give about 150 mL of filtrate. The solvent was removed under reduced pressure and the solid chromatographed on silica gel (80/20 dichloromethane/acetone) to give the desired product 22 (300 mg, 84%): δ_H ($CDCl_3$) 0.89 (s, 3H), 0.91 (s, 3H), 1.15 (d, J=6 Hz), 1.70 (dd J=20 Hz, J=8 Hz), 2.43 (m, 2H), 2.70 (dd J=20 Hz, J=8 Hz), 2.90 (s, 3H), 3.03 (dd, J=12 Hz, J=3 Hz) Mass spectrum (M+= 317).

EXAMPLE 23

4,15α-Dimethyl-17β-hydroxy-4-aza-5α-androstan-3-one (23)

δ_H ($CDCl_3$) 0.65 (t, J=9 Hz, 1H), 0. 76 (s, 3H), 0.88 (s, 3H), 1.02 (d, J=6 Hz), 2.40 (q, J=5 Hz, 2H), 2.90 (s, 3H), 2.98 (dd, J=12 Hz, J=3 Hz), 3.65 (bt, 1H): Mass spectrum (M+= 319).

EXAMPLE 24

4,15α-Dimethyl-17β-allyloxy-4-aza-5α-androstan-3-one (24)

δ_H ($CDCl_3$) 0.65 (t, J=9 Hz, 1H), 0.80 (s, 3H), 0.87 (s, 3H), 1.00 (d, J=7 Hz), 2.40 (q, J=5 Hz, 2H), 2.90 (s, 3H), 2.98 (dd, J=12 Hz, J=3 Hz), 3.35 (t, J=8 Hz, 1H), 3.97 (d, J=7 Hz, 2H), 5.12 (dd, J=12 Hz, J=3 Hz, 1H), 5.25 (dd, J=18 Hz, J=3 Hz, 1H), 5.8-5.9 (m, 1H): Mass spectrum (M+= 359).

EXAMPLE 25

4,15α-Dimethyl-4-aza-5α-androstan-3-one (25)

δ_H ($CDCl_3$) 0.57 (t, J=10 Hz, 1H), 0.72 (s, 3H), 0.86 (s, 3H), 1.02 (d, J=7 Hz), 2.40 (q, J=5 Hz, 2H), 2.89 (s, 3H), 2.98 (dd, J=12 Hz, J=3 Hz): Mass spectrum (M+= 303).

EXAMPLE 26

4,15α-Dimethyl-17β-propyloxy-4-aza-5α-androstan-3-one (26)

δ_H ($CDCl_3$) 0.65 (t, J=9 Hz, 1H), 0. 78 (s, 3H), 0.87 (s, 3H), 1.01(d, J= 7 Hz), 2.40 (q, J=5 Hz, 2H), 2.90 (s, 3H), 2.98 (dd, J=12 Hz, J=3 Hz), 3.35 (m, 2H), 4.3 (m, 1H): Mass spectrum (M+= 361).

EXAMPLE 27

4,15B-Dimethyl-17B-propyloxy-4-aza-5α-androstan-3-one (27)

δ_H ($CDCl_3$) 0.889 (s, 3H), 0.893 (s, 3H), 0.98(d, J= 7 Hz), 2.43 (q, J=5 Hz, 2H), 2.91 (s, 3H), 3.25 (m 1H), 3.35 (m, 2H): Mass spectrum (M+= 361).

EXAMPLE 28

4-Methyl-4-aza-5α-androstan-3,17-dione (28)

δH ($CDCl_3$) 0.85(s, 3H), 0.89 (s, 3H), 2.92 (s, 3H) 3.85-4.0 (m, 2H), 4.05-4.15 (m, 1H), 4.20-4.25 (m, 1H), 4.50-4.60 (dd, J_1=10.5, J_2=4.5 Hz).

EXAMPLE 29

4-Methyl-16α-bromo-17-(3-dioxolane)-4-aza-5α-androstan-3-one (29)

δH ($CDCl_3$) (0.85 (s, 3H), 0.86 (s, 3H), 2.89 (s, 3H).

EXAMPLE 30

4-Methyl-17-(1,3-dioxolane)-4-aza-5α-androstan-15-en-3-one (30)

(See also *J. Chem. Soc. Perkin Trans. 1* 1988, 2161, the entire disclosure of which is incorporated herein by reference) 16.76 g (39.3 mmol) of (29), 9.26 g (82.5 mmol) of potassium tert-butoxide and 200 mL of DMSO were combined together and stirred at 50° in a flask fitted with a condenser for 2 hours. The mixture was diluted with CH_2Cl_2 and sat. NaCl, and the aqueous layer extracted with CH_2Cl_2. The organic layer was washed with sat. NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was crystallized from CH_2Cl_2 with ethyl ether to obtain 9.18 g of white solid. The mother liquor was purified by MPLC on a 40 x 350 mm silica column by eluding with 15% acetone/CH_2Cl_2. 2.29 g of a white solid was recovered from the column. Yield = 84%.

EXAMPLE 31

4-Methyl-4-aza-5α-androst-15 ene-3,17 dione (31)

(See also *J. Chem. Soc. Perkin Trans. 1* 1988, 2161, the entire disclosure of which is incorporated herein by reference). To a solution of 11.07 g (32.0 mmol) of (30) in 500 ml of acetone at 25° was

added 1.22 g (6.4 mmol) of *p*-toluenesulfonic acid monohydrate followed by 50 ml H_2O. This mixture was stirred at 25° for 4 hours, then the acetone was evaporated *in vacuo*. The resulting solution was diluted with sat. $NaHCO_3$ and CH_2Cl_2, and the aqueous layer extracted with CH_2Cl_2. The organic layer was dried over KCO_3, filtered, and concentrated *in vacuo*. Crystallization of this solid from CH_2Cl_2 with ethyl ether yielded the product contaminated with a lower R_f impurity, so it was dissolved in CH_2Cl_2 and repurified by MPLC on a 40 x 700 mm silica column by eluting with 8.0 L of 15% acetone/CH_2Cl_2. 8.63 g of a white solid was recovered from the column. Yield = 89%.

EXAMPLE 32

4,15β-Dimethyl-4-aza-5α-androstan-3,17-dione (32)

(See also *J. Chem. Soc. Perkin Trans.* 1 1981, 1994, the entire disclo-sure of which is incorporated herein by reference). To a solution of 628 mg (3.3 mmol) of copper(I) iodide in 5 ml THF at 0° under N_2 was added 4.7 ml (6.6 mmol) of methyllithium (1.4 M in ether) dropwise with stirring. This solution was stirred for 15 min., then a solution of 200 mg (0.66 mmol) of (31) in 2 ml THF was added dropwise. Stirring was continued at 0° for 2 hours, then at 25° overnight. The reaction mixture was poured into sat. NH_4Cl with stirring, then diluted with EtOAc, and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2, then the organic layers were combined and washed with sat. NH_4Cl and sat. NaCl, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting solid was purified by MPLC on a 21 x 300 mm silica column by eluding with 1.0 L of 15% acetone/CH_2Cl_2. 150 mg of white solid was recovered from the column. Yield = 72%.

EXAMPLE 33

4-Methyl-15β-ethyl-4-aza-5α-androstan-3,17-dione (33)

(See also *Tet. Lett.* 1982, 23(37), 3755 and *J. Med. Chem.* 1971, 14(3), 194, the entire disclosure of which is incorporated herein by reference). 220 mg (7.91 mmol) of lithium dispersion (25% in mineral oil) was washed with hexane and kept under N_2 atmosphere. To this was added 10 ml of THF and the slurry was cooled to -20°. To this was added 0.295 ml (3.95 mmol) of ethylbromide dropwise with stirring. In a separate flask, 177 mg (1.98 mmol) of copper(I) cyanide was azeotropically dried with toluene, then kept under N_2. 2 ml of THF was added to the CuCN and this slurry was cooled to -40°. To this was added the ethyllithium solution at -40° via canula and the reaction was stirred for 3 hours. To this was added a solution of 100 mg (0.33 mmol) (31) in 3 ml THF at -40° and stirring continued for 3 hours. The reaction was quenched with slow addition of sat. NH_4Cl, then diluted with EtOAc, and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined and washed with sat. NH_4Cl, H_2O, and sat. NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant oil was purified by MPLC on a 21 x 300 mm silica column by eluting with 1.0 L of 15% acetone/CH_2Cl_2. 27mg of white solid was recovered from the column. Yield = 25%.

EXAMPLES 34 AND 35

4-Methyl-15(α and β)-isopropyl-4-aza-5α-androstane-3,17-dione (34 and 35)

(See also *J. Org. Chem.* 1990, *55(12)*, 3954, the entire disclosure of which is incorporated herein by reference). To a solution of 135 mg (0.66 mmol) copper(I) bromide dimethylsulfide complex in 1 ml THF at -78° under N_2 was added 0.660 ml (1.32 mmol) isopropyl-magnesium chloride (2.0 M in THF). This slurry was stirred for 30 min., then a solution of 100 mg (0.33 mmol) (31) in 1 ml THF was

added to it, and stirring was continued at -78° for 6 hours. The reaction was quenched with 5 ml of sat. NH_4Cl, diluted with EtOAc, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by MPLC on a 21 x 300 mm silica column by eluting 1.0 L of 15% acetone/CH_2Cl_2. 30 mg of a sticky white solid was recovered from the column. NMR and mass spec. of this material indicated it was a mixture of isomers at C_{15}. This material was further purified by HPLC with two passes through a 7.8 x 300 mm Waters Porosil column eluting with 15% isopropanol/hexane at 2.9 ml/min., but injecting with CH_2Cl_2. About 10mg of each isomer was recovered from the column. Yield = 18%.

EXAMPLE 36

4-Methyl-15β-methyl-17β-hydroxy-4-aza-5α-androstan-3-one (36)

To a stirred solution of 150 mg (0.47 mmol) of (32) in 2 ml ethanol at 0° is added 36 mg (0.94 mmol) sodium borohydride. Stirring was continued at 0° for 4 hours, then the reaction mixture was poured into 100 ml H_2O and stirred. A precipitate formed and was collected by filtration, washed with H_2O, and dried under high vacuum. 89 mg of white solid was recovered. Yield = 59%.

EXAMPLE 37

4-Methyl-15β-ethyl-17β-hydroxy-4-aza-5α-androstane-3-one (37)

To a stirred solution of 24 mg (0.07 mmol) of (33) in 1 ml ethanol at 0° is added 6 mg (0.14 mmol) sodiumborohydride. Stirring was continued at 0° for 6 hours, then the reaction mixture was poured into 1 ml H_2O and stirred. The ethanol was evaporated *in vacuo*, then the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under high vacuum. 15 mg of white solid was recovered. Yield = 64%.

EXAMPLE 38

4,15β-Dimethyl-17-trifluoromethanesulfonyloxy ester-4-aza-5α-androstan-16-ene-3-one (38)

(See also *Tet. Lett.* 1983, *24(10)*, 979, the entire disclosure of which is incorporated herein by reference.) 1.69 ml (8.03 mmol) hexamethyldisilizane was dissolved in 10 ml THF and cooled to 0°. Under a N_2 atmosphere, 2.78 ml (6.96 mmol) butylithium (2.5 M in hexane) was added, followed by another 30 ml THF to dilute the precipitate that formed. This slurry was stirred for 15 min., then a solution of 1.70 g (5.35 mmol) (32) in 10 ml THF was added to it. This was stirred for 30 min. at 0°, then 2.87 g (8.03 mmol) N-phenyltrifluoromethanesulfonimide was added in one portion. The cooling bath was removed and the mixture was stirred. After 2 hours the reaction was diluted with EtOAc and sat. NH_4Cl. The aqueous layer was extracted with EtOAc. The organic layers were combined and washed with sat. $NaHCO_3$, H_2O, and sat. NaCl, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting oil was purified by MPLC on a 40 x 350 mm silica column by eluting with 10% acetone/CH_2Cl_2. 1.54 g of white solid was recovered from the column. Yield = 64%.

EXAMPLE 39

4,15β-Dimethyl-17β-tert-oxycarbonylamino-4-aza-5a-androstane (39)

40 mg (0.13 mmol) of (36), 1 ml CH_2Cl_2, 0.057 ml (0.50 mmol) tert-butylisocyanate, and 75 µl (0.50 mmol) 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) were combined and stirred at 25° for 7 days. The crude reaction mixture was then directly applied to a 21 x 300 mm silica column and purified by MPLC by eluding with 15% acetone/-CH_2Cl_2. NMR and mass spec. of a white solid recovered from column indicated desired product.

EXAMPLE 40

4,15β-Dimethyl-17β-(tertbutyl-carbonyloxy)-4-aza-5α-androstan-3-one (40)

40 mg (0.13 mmol) of (36), 1 ml CH_2Cl_2, 0.062 ml (0.50 mmol) trimethylacetylchloride, 40 µl (0.50 mmol) pyridine, and a few crystals of N,N-dimethylaminopyridine were combined and stirred at 25° for 1 day. The crude reaction mixture was then directly applied to a 21 x 300 mm silica column and purified by MPLC by eluting with 1.0 L of 5% acetone/CH_2Cl_2, then 0.5 L of 15% acetone/CH_2Cl_2. NMR and mass spec. of white solid recovered from column indicated desired product.

EXAMPLE 41

4,15β-Dimethyl-4-aza-5α-androstan-3-one (41)

45 mg of (38) was dissolved in 1 ml EtOAc. To this was added 5 mg platinum oxide and hydrogen gas by balloon reservoir. This mixture was stirred at 25° overnight, then the catalyst was removed by filtration and the solvent removed *in vacuo*. The resulting oil was purified by MPLC on a 21 x 300 mm silica column by eluting with 10% acetone/CH_2Cl_2. NMR and mass spec. of a white solid recovered from column indicated desired product.

EXAMPLE 42

4,15β-17-Trimethyl-4-aza-5α-androst-16-ene-3-one (42)

(See also *J. Org. Chem.* 1990, *55(3)*, 964, the entire disclosure of which is incorporated herein by reference.) To a solution of 2.20 g (11.5 mmol) of copper(I) iodide in 15 ml THF at 0° under N_2 was added 16.5 ml (23.1 mmol) of methyllithium (1.4 M in ether) dropwise with stirring. This was stirred for 15 min., then a solution of 700 mg (2.31 mmol) of (31) in 6 ml THF was added dropwise. Stirring was continued at 0° for 2 hours, then at 25° overnight. The reaction

was recooled to 0°, then a solution of 907 mg (2.54 mmol) N-phenyl-trifluoromethanesulfonimide in 5 ml THF was added in one portion. The cooling bath was removed and the reaction stirred at 25° for 1 hour. The reaction was quenched by adding 50 ml sat. NH_4Cl slowly, then diluted with EtOAc, and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed with sat. NH_4Cl, H_2O, and sat. NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by MPLC on a 40 x 350 mm silica column by eluding with 3.5 L of 15% acetone/CH_2Cl_2. 510 mg of a white solid was recovered from column. Yield = 70%.

EXAMPLE 43

4-15β-17β-Trimethyl-4-aza-5-androstan-3-one (43)

50 mg of (42) was dissolved in 1 ml EtOAc. To this was added 5 mg platinum oxide and hydrogen gas by balloon. The mixture was stirred at 25° overnight, then the catalyst was removed by filtration and the solvent evaporated *in vacuo*. The resulting oil was purified by MPLC on a 21 x 300 mm silica column by eluting 10% acetone/CH_2Cl_2. NMR and mass spec. of white solid recovered from column indicated desired product.

EXAMPLE 44

4,15β-Dimethyl-20-yne-21-isopentyl-4-aza-5α-pregn-16-ene-3-one (44)

(See also *Synlett.* 1991, 409, the entire disclosure of which is incorporated by reference) 110 mg (0.24 mmol) of (38), 1 ml disopropylamine, 2 mg copper(I) iodide, 10mg bis(triphenylphosphine)-palladium(II) acetate, 39 µl (0.29 mmol) 5-methyl-1-hexyne, and 2 ml DMF were combined at 25° in a flame-dried flask and stirred at 25° for 16 hours under nitrogen. The reaction was diluted with EtOAc and filtered to remove catalyst. The filtrate was washed with sat. $NaHCO_3$,

H_2O, and sat. NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by MPLC on a 21 x 300 mm silica column by eluting 10% acetone/CH_2Cl_2. 69 mg of yellowish oil was recovered from column. Yield = 73%.

EXAMPLE 45

4-15β-Dimethyl-16, 20-diene-21-(methyl carboxylate)-4-aza-5α-pregnan-3-one (45)

(See also *Synthesis* 1986, 320, the entire disclosure of which is incorporated by reference) 750 mg (1.67 mmol) (38), 250 mg (0.33 mmol) bis(triphenylphosphine)palladium(II) acetate, 522 mg (6.67 mmol) potassium acetate, 601 µl (6.67 mmol) methyl acrylate, and 5 ml DMF were combined in a flask fitted with a condenser and stirred at 60° for 12 hours. The reaction was diluted with EtOAc and filtered to remove catalyst. The filtrate was washed with sat. $NaHCO_3$, H_2O, and sat. NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by MPLC on a 40 x 350 mm silica column by eluting 15% acetone/CH_2Cl_2. 665 mg of reddish solid was recovered from the column. NMR indicated product had a significant amount of degraded catalyst contaminating it, but it was used as is, and repurified again after reduction of the diene.

EXAMPLE 46

4, 15β-Dimethyl-21-isopentyl-4-aza-5α-pregnan-3-one (46)

69 mg of (44) was dissolved in 2 ml EtOAc and 0.5 ml MeOH. To this was added 10 mg platinum oxide and hydrogen gas by balloon. The mixture was stirred at 25° overnight, then the catalyst was removed by filtration and the solvent evaporated *in vacuo*. NMR and mass spec. of the waxy solid recovered from filtration indicated desired product.

EXAMPLE 47

15β-Dimethyl-21-(methyl carboxylate)-4-aza-5α-pregnan-3-one (47)

665 mg of (45) was dissolved in 10 ml EtOAc. To this was added 60 mg platinum oxide and hydrogen gas by balloon. The mixture was stirred at 25° overnight, then the catalyst was removed by filtration and the solvent evaporated *in vacuo*. The resulting oil was purified by MPLC on a 40 x 350 mm silica column by eluting 15% acetone/-CH_2Cl_2. 360 mg of a white solid was recovered from the column.

EXAMPLE 48

4-Methyl-15β-cyano-4-aza-5α-androstan-3,17-dione (48)

(See also *J. Org. Chem.* 1964, *29*, 64, the entire disclosure of which is incorporated herein by reference.) To a solution of 125 mg (0.41 mmol) of (31) in 4 ml THF was added 268mg potassium cyanide, followed by 3 drops of H_2O to help solubilize the KCN. This mixture was stirred at 25° for 2 hours, then at 60° for 3 hours. Then the reaction was diluted with EtOAc and H_2O, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2, and the organic layers combined and concentrated *in vacuo*. The resulting oil was purified by MPLC on a 21 x 300 mm silica column by eluting with 20% acetone/CH_2Cl_2. 20mg of white solid was recovered from the column. Yield = 15%.

EXAMPLE 49

4-Methyl-15β-cyano-17β-hydroxy-4-aza-5α-androstan-3-one (49)

18 mg (0.05 mmol) of (48) was stirred in 1 ml EtOH at 0°, then 4 mg (0.11 mmol) sodium borohydride was added and this mixture was stirred at 0° for 4 hours, then diluted with H_2O and EtOH evaporated *in vacuo*. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by MPLC on a 21

x 100 mm silica column by eluting a gradient from 20 to 50% with acetone/CH_2Cl_2. 10 mg of a white solid was recovered from the column. Yield = 61%.

EXAMPLE 50

4-Methyl-15β-methoxy-4-aza-5α-androstane-3,17-dione (50)

(See also *J. Org. Chem.* 1964, *29*, 64, the entire disclosure of which is incorporated herein by reference.) 100 mg (0.33 mmol) of (31) was dissolved in 1 ml MeOH. To this was added 21 mg (0.40 mmol) sodium methoxide and the mixture was stirred at 25° for 1 hour. The reaction was dilute with sat. NaCl and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by MPLC on a 21 x 300 mm silica column by eluting 15% with acetone/CH_2Cl_2. 65 mg of a white solid was recovered from the column. Yield = 59%.

EXAMPLE 51

4-Methyl-15β-methoxy-17β-hydroxy-4-aza-5α-androstan-3-one(51)

60 mg (0.18 mmol) of (50) was stirred in 1 ml EtOH at 0°, then 14 mg (0.36 mmol) sodiumborohydride was added and this mixture stirred at 0° for 4 hours. The reaction was diluted with H_2O and the EtOH evaporated *in vacuo*. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by MPLC on a 21 x 300 mm silica column by eluting with a gradient from 15 to 50% acetone/CH_2Cl_2. 35 mg of a white solid was recovered from the column. Yield = 58%.

EXAMPLE 52

4-Methyl-15β-methoxy-17β-allyloxy-4-aza-5α-androstan-3-one (52).

30 mg (0.09 mmol) of (51) was dissolved in 0.5 ml DMF and cooled to 0°. This solution was added to a solution of 15 mg (0.13 mmol) potassium hydride (35% in oil) in 0.5 ml DMF that was washed with hexane and kept under N_2. This was stirred at 0° for 30 min., then 12 µl (0.13 mmol) allyl bromide was added. The reaction was stirred for 1 hour, then quenched by adding sat. NH_4Cl. This solution was diluted with EtOAc, and organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by MPLC on a 20 x 100 mm silica column by eluting with 10% acetone/CH_2Cl_2, then dried under high vacuum. 15 mg of a white solid was recovered from the column. Yield = 44%.

EXAMPLE 53

4-Methyl-15β-methoxy-17β-propyloxy-4-aza-5α-androstan-3-one 53)

12 mg of (52) was dissolved in 1 ml MeOH. To this was added 2 mg 10% palladium on carbon and hydrogen gas by balloon. The mixture was stirred at 25° overnight, then the catalyst was removed by filtration and the solvent evaporated *in vacuo*. The resulting oil was purified by HPLC on a 7.8 x 300 mm Waters µPorisil column by eluting with 5% isopropanol/hexane at 2.9 ml/min. 7 mg of a colorless oil was recovered from the column. Yield = 58%.

EXAMPLE 54

4,15β-Dimethyl-17β-amino-4-aza-5α-androstan-3-one (54)

150 mg (0.47 mmol) of (32), 5 ml EtOH, 116 mg (1.42 mmol) sodium acetate and 98 mg (1.452 mmol) hydroxylamine hydrochloride were combined and stirred at 80° for 6 h. The mixture was allowed to cool to room temperature then diluted with water. The

precipitate that formed was collected by filtration, washed with water, then air dried. 120 mg of beige solid 4-methyl-15β-methyl-17-oxime-4-aza-5α-androstan-3-one (65) was recovered Yield = 77%.

120 mg of 4-methyl-15β-methyl-17-oxime-4-aza-5α-androstan-3-one was dissolved in 2 ml EtOH. To this was added 10 mg platinum oxide, 0.5 ml acetic acid and hydrogen gas by balloon. The mixture was stirred at 25° overnight, then the catalyst was removed by filtration and the solvent evaporated *in vacuo*. The resulting oil was purified by MPLC on a 21 x 300 mm silica column by eluting with a gradient from 0% to 10% (10% ammoniumhydroxide/MeOH) in CH_2Cl_2. 115 mg of a white solid was recovered from the column. Yield = 99%.

EXAMPLE 55

4-15β-Dimethyl-17β-(2,2-dimethylpropanoylamino)4-aza-5α-androstan-3-one (55)

50 mg (0.16 mmol) of (54), 1 ml CH_2Cl_2, 39 µl (0.31 mmol) trimethyl-acetyl chloride, and 25 µl (0.31 mmol) pyridine were combined and stirred at 25° for 6 hrs. At this time, a few drops of MeOH was added to the crude reaction mixture to dissolve the precipitate, and the mixture was directly applied to a 21 x 300 mm silica column and purified by MPLC by eluting with a gradient from 15 to 50% acetone/CH_2Cl_2. 51 mg of a white solid was recovered from the column. Yield = 79%.

EXAMPLE 56

4-15β-Dimethyl-17β-iso-pentylamide-4-aza-5α-androstane (56)

50 mg (0.16 mmol) of (54), 42 mg (0.31 mmol) 1-hydroxybenzotriazole hydrate, 39 µl 4-methylvaleric acid, and 1 ml THF were combined and stirred for 30 min. at 25°. To this was added 60 mg (0.31 mmol) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and the mixture was stirred at 25° overnight. The

reaction was diluted with EtOAc and sat. $NaHCO_3$, and the aqueous layer extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by MPLC on a 21 x 300 mm silica column by eluting with 25% acetone/CH_2Cl_2. 50 mg of a white solid was recovered from the column. Yield = 75%.

EXAMPLE 57

4-Aza-16α-Bromo-4,7β-dimethyl-17-(ethylenedioxy)-5α-androstan-3-one (57)

Preparation of Starting Material

The following teaching is for the preparation of starting material 4-aza-4,7β-dimethyl-5α-androstan-3,17-dione. Additional background information can be found in US patent application 07/886,537, filed May 20, 1992, pending, the entire disclosure of which is incorporated herein by reference.

Synthesis of 3-acetoxy-androst-5-en-17-ol

To a solution of 100 mg. (0.303 mmol) of 3-acetoxy-androst-5-en-17-one, 1, in 3 ml EtOH at -10°C, was added 22.9 mg (0.606 mmol) of sodium borohydride with stirring. After the reaction mixture was stirred for one and 1/2 hours, the mixture was diluted with 10 ml water, the ethanol solvent removed under vacuum, and the residue extracted with ethyl acetate. The organic layer was washed with aqueous Na_2CO_3, brine, dried over sodium sulfate and concentrated to leave a residue of crude title compound. Proton NMR confirmed the assigned structure.

Synthesis of 3-acetoxy-androst-5-en-17-ol, 17-t-butyl-dimethyl-silyl ether

To a solution of the androstan-17-ol, from the previous synthesis, being 4.5 g (13.55 mmol) in 50 ml dimethylformamide at

23°C was added 2.76 g (40-65 mmol) imidazole followed by 3.063 g (20.32 mmol) of t-butyldimethylsilyl chloride. The reaction mixture was stirred and a solid began to precipitate. Twenty additional ml of DMF were added and the mixture further stirred overnight. The mixture was poured into 1 liter water, the solid filtered and washed with water. The solid was dissolved in ethylacetate, the organic layer washed with brine and dried over sodium sulfate, concentrated to yield the silyl protected 17-ol title compound. The proton NMR confirmed the assigned structure.

Synthesis of 3-acetoxy-androst-5-ene-7-one-17β-ol, 17-t-butyl-dimethylsilyl ether

To a solution of the TBMS protected 17-ol from the previous synthesis, being 5.6 g (12.55 mmol) in 100 ml acetonitrile at 23°C was added 90% t-butyl hydrogen peroxide, 3.958 g (43.92 mol), and 138 mg chromium hexacarbonyl. After refluxing the mixture under nitrogen for 24 hours, the reaction mixture was poured into one liter water, solid was filtered, the residue washed with 500 ml water and the residue dissolved in 350 ml methylene chloride. The organic layer was washed with brine, dried over sodium sulfate and concentrated to yield crude material. Thin layer chromatography (3:1 hexane/ethyl acetate on silica gel) showed the presence of starting material. The solid was purified by column chromatography over silica gel by elution with 7% ethyl acetate/-hexane to yield the title compound. Proton NMR confirmed the assigned structure.

Synthesis of 3,7-dihydroxy-7-methyl-androst-5-en-17β-ol, 17-TBMS ether

To a solution of the product from the previous synthesis, being 440 mg. (0.956 mmol) in dry tetrahydrofuran at 0°C was added dropwise methyl magnesium chloride over 5-10 minutes. The reaction mixture was then allowed to stir at room temperature for 24 hours, then poured into saturated aqueous ammonium chloride. The THF solvent was removed under vacuum and the aqueous phase extracted with ethyl

acetate. The organic layer was washed with brine, dried, concentrated to yield crude product. Proton NMR confirmed the assigned structure of the title compound which was used in the next step without further purification.

Synthesis of 7-methyl-androst-4,6-dien-3-one-17β-ol, 17-t-butyl-dimethylsilyl ether

The above Grignard product, 3.5 g. (7.142 mmol) was dissolved in 50 ml toluene/50 ml cyclohexanone and 20 ml of solvent distilled off under vacuum. To this was added 4.54 g. aluminum isopropoxide and the reaction mixture refluxed overnight for 15 hours. The mixture was cooled, diluted with ethyl acetate, washed with sodium potassium tartarate, brine, and the organic layer was concentrated under vacuum and the residue steam distilled. The residue was extracted with ethyl acetate, washed with brine, dried and purified by column chromatography on silica gel, eluting with 5% EtOAc/hexane to yield the title compound.

Synthesis of 7β-methyl-androst-5-en-3-one-17β-ol, t-butyl-dimethylsilyl ether

To a solution of 370 mg of the product of the previous synthesis, in 5.5 ml ammonia, 1 ml THF, 1 ml toluene, was added 50 mg. of metallic lithium in small pieces. After stirring the blue solution for 2 hours, a solution of 1,2-dibromethane in 2 ml THF was added. After stirring the solution at -78°C for 10 minutes, 250 mg of ammonium chloride was added and the mixture stirred for 10 minutes. The excess ammonia was removed by evaporation under a nitrogen steam. The reaction mixture was diluted with brine, extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to yield crude material which was used as such in the next synthesis.

Synthesis of 7β-methyl-androst-4-en-3-on-17β-ol, t-butyl-dimethylsilyl ether

To a solution of the product of the previous synthesis, being 432 mg in 4 ml THF was added 150 microliters DBU (1,8-diaza-bicyclo[5.4,0] undec-7-ene under nitrogen with stirring. The mixture was refluxed for 1.5 hours, then cooled, diluted with NH_4Cl solution. The solvent THF was removed under vacuum and the residue extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated under reduced pressure to yield crude material. The titled product was purified by chromatography on silica gel using 10% EtOAc/ hexane as eluant.

Synthesis of 17β-(t-butyldimethylsilyloxy)-7β-methyl-5-oxo-a-nor-3,5-secoandrostan-3-oic acid

To a solution of 884 mg of the product of the previous synthesis in 15 ml. t-butyl alcohol at 80°C was added 248 mg sodium carbonate in 1.5 ml water followed by a dropwise addition over 15-20 minutes of a mixture of 2.273 g sodium periodate with 16.8 mg potassium permanganate in 8 ml. water. The reaction mixture was heated at 80°C for 2 hours, cooled, filtered, the residue washed with water, and then the extract L- concentrated under vaccum. The extract was acidified with aqueous HCl, extracted with ethyl acetate and the organic layer washed with aqueous $NaHSO_3$, brine, dried and concentrated to yield crude 9. The proton NMR confirmed the assigned structure.

Synthesis of 4,7β-dimethyl-4-aza-androst-5-en-3-one-17β-ol, t-butyldimethylsilyl ether

To a solution of the product of the previous synthesis, 840 mg in 5 ml ethylene glycol, was added 1.5 g sodium acetate and 737 mg. methylamine hydrochloride. After stirring the reaction mixture 4 hours at 180°C, the mixture was cooled, diluted with water, extracted with ethyl acetate, dried and concentrated to afford crude title compound. Proton NMR confirmed the assigned structure.

Synthesis of 4,7β-dimethyl-4-aza-androst-5-en-3-one-17β-ol

To a solution of 700 mg of the product of the previous example, in 20 ml of acetonitrile at 0°C, was added 500 microliters. aqueous HF. After stirring the reaction mixture for one hour, the HF was neutralized with aqueous sodium carbonate, diluted with water, acetonitrile removed under vacuum, and the residue extracted with ethyl acetate. The organic layer was dried, concentrated to give crude title compound which was further purified by preparative chromatography on silica gel using 3:1 chloroform/acetone.

Synthesis of 4,7β-dimethyl-4-aza-androstan-3-one-17β-ol

To a solution of the product of the previous synthesis, being 350 mg in 10 ml acetic acid was added 100 mg platinum dioxide and the resulting mixture was evacuated and flushed with hydrogen. The reaction was shaken overnight at room temperature under 40 Psig hydrogen pressure. The solution was filtered concentrated. The residue was worked up with ethyl acetate, the organic layer was then concentrated under vacuum, diluted with ethyl acetate, washed with aqueous $NaHCO_3$, brine, dried, concentrated to yield the title compound. Mass Spec: 320 (M+1).

Synthesis of 4-aza-4,7β-dimethyl-5α-androstan-3,17-dione

The product of the previous synthesis, 1.013 g (3.176 mmol) was placed with 6 ml methylene chloride into a dry flask. Powdered molecular 4Å sieves, 1.6 g, and 0.558 g (4.76 mmol) of N-methylmorpholine-N-oxide (NMO) and then tetrapropyl-ammonium perruthanate (TPAP), 55 mg (0.159 mmol) were added. The reaction was stirred for 2 hours, diluted with 150 ml ethyl acetate and filtered. The filtrate was evaporated to dryness to yield crude product which was recrystallized from EtOAc to yield pure product, mp 135-138°C.

Calc'd for $C_{20}H_{31}NO_2$, mw=317.48
Calcd: C, 75.67; H, 9.84; N, 4.41
Found: C, 75.16; H, 10.22; N, 4.13
Mass Spec. 318 (M+1).

To a solution of the 4-aza-4,7β-dimethyl-5α-androstan-3,17-dione product of the previous synthesis (1.0 g, 3.15 mmol) in 1:1 ethylene glycol-1,4-dioxane (10 mL) was added copper (II) bromide (3.5 g, 15.7 mmol). The dark red reaction mixture was stirred for 5 hours at 80°C under a nitrogen atmosphere. The mixture was allowed to cool to room temperature, diluted with a large volume of methylene chloride, washed with water (2X), washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, evaporated, and dried under high vacuum to afford the desired product in essentially quantitative yield. The material was used without further purification in the subsequent transformation.

EXAMPLE 58

4,7β-Dimethyl-17-(ethylenedioxy)-4-aza-5α-androstan-15-ene-3-one (58)

To a solution of 16α-bromo-4,7β-dimethyl-17-(ethylenedioxy)-4-aza-5α-androstan-3-one (1.20 g, 2.72 mmol) in methyl sulfoxide (25 mL) was added potassium tert-butoxide (0.79 g, 7.04 mmol). The reaction, which immediately turned dark red, was stirred for 2 hours at 50°C under a nitrogen atmosphere. The mixture was allowed to cool to room temperature, diluted with methylene chloride, washed with water, washed with saturated sodium chloride solution, dried (sodium sulfate), and evaporated. The crude product was purified by flash silica gel chromatography using 15% acetone/methylene chloride as an eluant. Yield = 400 mg (41%).

EXAMPLE 59

4,7β-Dimethyl-4-aza-5α-androstan-15-ene-3,17-dione (59)

A solution of 4,7β-dimethyl-17-(ethylenedioxy)-4-aza-5α-androstan-15-ene-3-one (0.35 g, 0.97 mmol) in acetone (35 mL) was stirred with saturated aqueous tartaric acid (7 mL) overnight at room temperature. The reaction mixture was concentrated, partitioned between methylene chloride and water, the organic layer washed with saturated aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, filtered, and evaporated. The crude product was purified by means of flash silica gel chromatography using 35% acetone/methylene chloride as the eluant. Yield = 133mg (43%).

EXAMPLE 60

4,7β,15-Trimethyl-4-aza-5α-androstan-3,17-dione (60)

To a mixture of copper (I) iodide (325 mg, 1.71 mmol) in diethyl ether (2.7 mL) cooled to 0°C was added methyllithium (1.4 M solution in diethyl ether) (2.5 mL, 3.5 mmol) with stirring under a nitrogen atmosphere. After stirring for 30 min at 0°C, a solution of 4,7β-dimethyl-4-aza-5α-androstan-15-ene-3,17-dione, (131 mg, 0.42 mmol) in tetrahydrofuran (1.1 mL) was added dropwise via syringe. The reaction mixture was then stirred for 3 hours at 0°C and quenched into a saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (2X), and the combined organic extracts were washed with saturated brine solution, dried over sodium sulfate, filtered and evaporated. The crude product was purified by means of flash silica gel chromatography using 2% methanol/methylene chloride as an eluant. The yield was 56.3mg (41%). The 400 MHz NMR spectrum of the product indicated an approximately 1:1 diastereo-isomeric mixture at the 15-position. The mixture was treated with sodium borohydride as described in the subsequent step.

EXAMPLES 61 AND 62

4,7β,15-Trimethyl-17β-hydroxy-4-aza-5α-androstan-3-one (61, 62)

The mixture obtained from the previous transformation (56mg, 0.17 mmol) was dissolved in methanol (3 mL), cooled in an ice-bath, and treated with sodium borohydride (20 mg, 0.53 mmol) for 2 hours at ice temperature. The mixture was concentrated, partitioned between methylene chloride and water. The aqueous layer was extracted with methylene chloride, and the combined organic extracts were washed with saturated sodium chloride solution, dried over sodium sulfate, filtered, and evaporated. The diastereoisomeric mixture at the 15-position was resolved by HPLC on a 7.8 x 300 mm Waters μPorisil column eluting with an isopropanol/hexane gradient (5-10% over 60 min) as the mobile phase. The yield of: (1) more mobile isomer A - 16.2 mg (29%); (2) less mobile isomer B - 22 mg (39%).

EXAMPLE 63

4,7β,15-Trimethyl-17β-allyloxy-4-aza-5α-androstan-3-one (isomer a) (63)

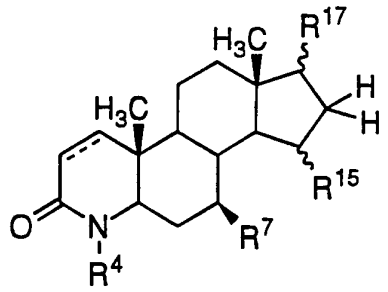
To a solution of 4,7β,15-trimethyl-17β-hydroxy-4-aza-5α-androstan-3-one (isomer A from previous transformation (13 mg, 0.039 mmol) in N,N-dimethylformamide (0.5 mL) was added sodium hydride (80% dispersion in mineral oil) (8 mg, 0.27 mmol). The mixture was stirred for 15 min at room temperature, at which time allyl bromide (50 μL, 0.58 mmol). The reaction mixture was stirred overnight at room temperature, diluted with diethyl ether, washed with water, dried over sodium sulfate, filtered, and evaporated. The product was purified by means of flash silica gel chromatography using 1-2% methanol/-methylene chloride as an eluant. Yield = 10 mg (47%).

EXAMPLE 64

4,7β,15-Trimethyl-17β-allyloxy-4-aza-5α-androstan-3-one (isomer β) (64)

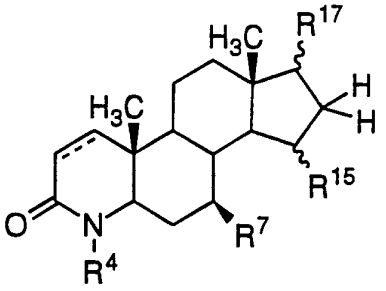
To a solution of 4,7β,15-trimethyl-17β-hydroxy-4-aza-5α-androstan-3-one (isomer B from previous transformation) (19 mg, 0.057 mmol) in N,N-dimethylformamide (0.5 mL) was added sodium hydride (80% dispersion in mineral oil) (8 mg, 0.27 mmol). The mixture was stirred for 15 min at room temperature, at which time allyl bromide (50 mL, 0.58 mmol). The reaction mixture was stirred overnight at room temperature, diluted with diethyl ether, washed with water, dried (sodium sulfate), and evaporated. The product was purified by means of flash silica gel chromatography using 1-2% methanol/ methylene chloride as eluant; yield 11 mg (52%).

^{1}H NMR data and mass spectral is given in the following tables for the compounds exemplified above. NMR's were run at 400MHz in $CDCl_3$. Positions given in the table are with reference to the following generic structural formula:



Ex. No.	R4	R7	R15	R17	
14	H	H	β-CH_3	β-OH	
15	H	H	β-CH_3	=O	
16	H	H	β-CH_3	β-OH	(Δ^1 double bond)
17	H	H	β-C_2H_5	=O	
18	H	H	β-C_2H_5	β-OH	
19	H	H	β-C_2H_5	β-O-n-C_3H_7	
22	CH_3	H	α-CH_3	=O	
23	CH_3	H	α-CH_3	β-OH	
24	CH_3	H	α-CH_3	β-$OCH_2CH{=}CH_2$	
25	CH_3	H	α-CH_3	H	
26	CH_3	H	α-CH_3	β-O-n-C_3H_7	
27	CH_3	H	β-CH_3	β-O-n-C_3H_7	
32	CH_3	H	β-CH_3	=O	
33	CH_3	H	β-C_2H_5	=O	
34	CH_3	H	i-C_3H_7	=O	(C_{15} stereoisomer A)
35	CH_3	H	i-C_3H_7	=O	(C_{15} stereoisomer B)
36	CH_3	H	β-CH_3	β-OH	
37	CH_3	H	β-C_2H_5	β-OH	
39	CH_3	H	β-CH_3	β-OCONH-t-C_4H_9	
40	CH_3	H	β-CH_3	β-OCO-t-C_4H_9	
41	CH_3	H	β-CH_3	H	
43	CH_3	H	β-CH_3	β-CH_3	

Ex. No.	R^4	R^7	R^{15}	R^{17}
46	CH_3	H	β-CH_3	β-$(CH_2)_4CH(CH_3)_2$
48	CH_3	H	β-CN	=O
49	CH_3	H	β-CN	β-OH
50	CH_3	H	β-OCH_3	=O
51	CH_3	H	β-OCH_3	β-OH
52	CH_3	H	β-OCH_3	β-$OCH_2CH=CH_2$
53	CH_3	H	β-OCH_3	β-O-n-C_3H_7
54	CH_3	H	β-CH_3	β-NH_2
55	CH_3	H	β-CH_3	β-NHCO-t-C_4H_9
56	CH_3	H	β-CH_3	β-$NHCO(CH_2)_2CH(CH_3)_2$
61	CH_3	β-CH_3	CH_3	β-OH (C_{15} stereoisomer A)
62	CH_3	β-CH_3	CH_3	β-OH (C_{15} stereoisomer B)
63	CH_3	β-CH_3	CH_3	β-$OCH_2CH=CH_2$ (C_{15} stereoisomer A)
64	CH_3	β-CH_3	CH_3	β-$OCH_2CH=CH_2$ (C_{15} stereoisomer B)



Example Number	H1 NMR (δ) C18	C19	other	Mass spec m/e
14	0.87	0.92	d, 0.98	M+ = 305
15	0.94	1.02	d, 1.10	M+ = 303
16	0.92	0.99	d, 1.01	M+ = 303
17	0.92	0.97		M+ = 317
18	0.83	0.89		M+ = 319
19	0.87	0.89	d, 0.99	M+ = 361
22	0.89	0.91	d, 1.15	M+ = 317
23	0.76	0.88	d, 1.15	M+ = 319
24	0.80	0.87	d, 1.00	M+ = 359
25	0.72	0.86	d, 1.02	M+ = 303
26	0.78	0.87	d, 1.01	M+ = 361
27	0.889	0.893	d, 0.98	M+ = 361
32	0.93	1.02	d, 1.12	M++1 = 318
33	0.91	0.97	t, 0.90	M+ = 331
34	0.91	1.04	d, 1.08	M+ = 345
35	0.89	0.93	d, 0.87	M+ = 345
36	0.87	0.90	t, 3.58	M++1 = 320
37	0.83	0.89	t, 3.60	M+ = 333
39	0.88	0.88	t, 4.42	M+ = 418
40	0.90	0.93	t, 4.51	M+ = 403

Example Number	H^1 NMR (δ)			Mass spec m/e
	C_{18}	C_{19}	other	
41	0.84	0.89	d, 0.94	M++1 = 304
43	0.67	0.89	d, 0.91	M+ = 317
46	0.69	0.89	d, 0.91	M++1 = 402
48	0.96	1.18	td, 3.23	M++1 = 329
49	0.93	1.01	t, 3.64	M+ = 330
50	0.92	1.09	s, 3.26	M+ = 333
51	0.89	0.93	t, 3.58	M+ = 335
52	0.89	0.97	t, 3.30	M+ = 375
53	0.89	0.95	s, 3.16	M+ = 378
54	0.82	0.90	t, 2.67	M+ = 318
55	0.81	0.89	s, 1.17	M+ = 402
56	0.82	0.89	q, 3.85	M+ = 416
61	0.78	0.82	s, 2.91	ND
62	0.87	0.89	s, 2.91	ND
63	0.80	0.81	s, 2.90	M+ = 373
64	0.87	0.90	s, 2.90	M+ = 373

EXAMPLE 65

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.

A compound referred to herein as a 5α-reductase type 1 or 2 inhibitor is a compound that shows inhibition of the 5α-reductase type 1 or 2 isozyme, respectively, in the above-described assay, i.e., having an IC_{50} of about 1000nM or less.

Representative compounds of this invention were tested in the above described assay for 5α-reductase type 1 and type 2 inhibition. For the inhibition of 5α-reductase type 1, the tested compounds have IC_{50} values at or below about 500 nM. These results demonstrate the utility of the compounds of the instant invention for the treatment of hyperandrogenic conditions.

EXAMPLE 66

15β–Methyl-17β-phenyl-4-aza-5α-androstan-3-one (67)

Intermediate **38** is reacted under standard Suzuki coupling conditions with phenylboronic acid in the presence of tetrakis(triphenylphosphine)palladium, sodium carbonate, lithium chloride, ethanol, in refluxing toluene. The desired 15β–methyl-17β-phenyl-4-aza-5α-androstan-3-one-16-ene **66** is obtained by flash silica gel chromatography and subsequently subjected to hydrogenation in methanol in the presence of 10% palladium-on-charcoal to afford the title compound. Suzuki coupling conditions are described in, for example, N. Miyaura et al., Synth. Commun., (1981) vol. 11, page 513.

EXAMPLE 67

15β–Methyl-17β-(2-thienyl)-4-aza-5α-androstan-3-one (69)

This compound is prepared in an analogous fashion as Example 66, using thiophene-2-boronic acid in place of phenylboronic acid in the Suzuki coupling reaction. The title compound is obtained after saturation of the intermediate 16-ene derivative **68**.

EXAMPLE 68

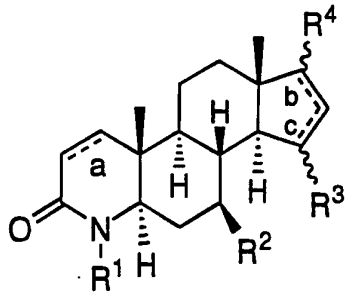
15β–Methyl-17β-(t-butylaminocarbonylmethyleneoxy)-4-aza-4-methyl-5α-androstan-3-one (72)

The product of Example 36 is reacted with dibenzyl diazamalonate in the presence of rhodium acetate to afford intermediate **70** in Scheme 12. Hydrogenolysis in methanol in the presence of 10% palladium-on-charcoal followed by decarboxylation in hot dimethylformamide (DMF) in the presence of hydrochloric acid gives the 17β-(carboxymethylene-oxy) derivative **71. 71** is converted into its acid chloride with thionyl chloride which is then treated with t-butylamine in methylene chloride/tetrahydrofuran to afford the pure title compound after silica gel chromatographic purification.

While the invention has been described and illustrated with reference to certain preferred 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 preferred 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 limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

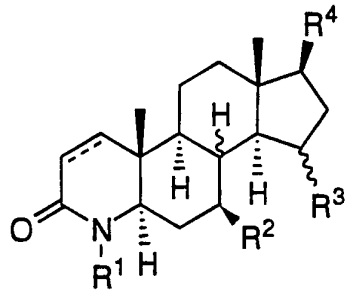
1. A compound of the formula



or a pharmaceutically acceptable salt or ester thereof,
wherein
the dotted lines a, b and c each independently represent a single or double bond, provided that b and c may not both be double bonds simultaneously;
R^1 is selected from the group consisting of hydrogen and C_{1-10} alkyl;
R^2 is selected from the group consisting of hydrogen and C_{1-10} alkyl;
R^3 is selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxyl, cyano, hydroxyl and triphenylthio-C_{1-6} alkyl;
R^4 is either monosubstituted by a substituent selected from the group consisting of keto, spiro-dioxolane and oximino or is disubstituted by hydrogen and R^5;
R^5 is selected from the group consisting of hydrogen, hydroxyl, Alk-R^6, Alk-X-Alk-R^6, Het, and unsubstituted or mono- or di-substituted phenyl wherein said substituent is selected from, halogen, C_{1-6} alkyl and C_{1-6} alkoxyl;
R^6 is selected from the group consisting of hydrogen, hydroxyl, -CO-R^7, -COO-R^7, -CO-NH-R^7, -NH-CO-R^7 and phenyl;
R^7 is selected from the group consisting of hydrogen, C_{1-6} alkyl, pyridyl and unsubstituted or mono- or di-substituted phenyl wherein said substituent is selected from halogen, C_{1-5} alkoxyl, C_{1-5} alkylcarbonyl, C_{1-5} alkoxycarbonyl, and C_{1-5} alkylaminocarbonyl;
X is O or NH;

Alk is C_{0-10} alkyl or C_{2-10} alkenyl with the proviso that when C is 0 (zero), there is no Alk moiety present; and
Het is selected from the group consisting of pyridyl, thiophene, morpholinyl and thiazole.

2. The compound of Claim 1 having the structural formula



or a pharmaceutically acceptable salt or ester thereof, wherein
the dotted line a represents a single or a double bond;
R^1 is selected from the group consisting of hydrogen and C_{1-10} alkyl;
R^2 is selected from the group consisting of hydrogen and C_{1-10} alkyl;
R^3 is selected from the group consisting of C_{1-10} alkoxyl, C_{1-10} alkyl and cyano;
R^4 is selected from the group consisting of C_{2-10} alkenyloxyl, C_{1-10} alkoxyl, C_{1-10} alkyl, C_{1-10} alkylaminocarbonyloxy, C_{1-10} alkylcarbonyloxyl, carbonyl, hydroxyl, and $-NHR^5$; and
R^5 is selected from the group consisting of hydrogen and C_{1-10} alkylcarbonyl.

3. The compound of Claim 2 wherein:
R^1 is selected from hydrogen and methyl;
R^2 is selected from hydrogen and methyl;
R^3 is selected from C_{1-3}alkyl, C_{1-3}alkoxyl and cyano.

4. A compound selected from the group consisting of:
4, 15β-dimethyl-17β–propyloxy-4-aza-5α-androstan-3-one;
15β-ethyl-17β-hydroxy-4-aza-5α-androstan-3-one;

4-methyl-15β-methoxy-17β-hydroxy-4-aza-5α-androstan-3-one;
4-methyl-15β-cyano-17β-hydroxy-4-aza-5α-androstan-3-one;
15β-ethyl-17-keto-4-aza-5α-androstane-3-one;
4-methyl-15β-methoxy-17β-allyloxy-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-17β-amino-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-21-isopentyl-4-aza-5α-pregnan-3-one;
4, 15β-dimethyl-17β-(2,2-dimethyl-propanoylamino)-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-17β-(4-methyl-n-pentanoylamino)-4-aza-5α-androstane;
4-methyl-15β-methoxy-17β-n-propyloxy-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-17β-hydroxy-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-17β-(tert-butyl-oxycarbonylamino)-4-aza-5α-androstan-3-one;
4-methyl-15β-ethyl-4-aza-5α-androstan-3, 17-dione;
4, 15β- 17β-trimethyl-4-aza-5α-androstan-3-one;
4, 15β-dimethyl-4-aza-5α-androstan-3, 17-dione;
4-methyl-15β-ethyl-17β-hydroxy-4-aza-5α-androstan-3-one;
4-methyl-15α-isopropyl-4-aza-5α- androstan-3, 17-dione;
4-methyl-15β-isopropyl-4-aza-5α-androstan-3, 17-dione;
4-aza-15β-ethyl-17β-n-propyloxy-5α-androstan-3-one;
4-aza-15β-methyl-17β-hydroxy-5α-androst-1-en-3-one;
4, 15β,-dimethyl-4-aza-5α-androstan-3-one;
4-aza-15β-methyl-17β-hydroxy-5α-androstan-3-one;
4-methyl-15β-methoxy-4-aza-5α-androstan-3, 17-dione;
4, 15β-dimethyl-17β-(2, 2-dimethylpropanoyloxy)-4-aza-5α-androstan-3-one;
4-aza-15β-methyl-5α-androstan-3, 17-dione;
4-methyl-15β-cyano-4-aza-5α–androstane-3, 17-dione;
4, 7β, 15-trimethyl-17β-hydroxy-4-aza-5α-androstan-3-one;
4, 7β, 15-trimethyl-17β-allyloxy-4-aza-5α-androstan-3-one;
4, 7β, 15-trimethyl-4-aza-5α-androstan-3, 17-dione;
4-aza-15β-methyl-17β-hydroxy-5α-androstan-3-one;
4-aza-15β ethyl-5α-androstan 3, 17-dione;

4-methyl-15α-isopropyl-4-aza-5α-androstane-3, 17-dione; and
4-methyl-15β-isopropyl-4-aza-5α-androstane-3, 17-dione.

5. A method for treating the hyperandrogenic conditions of acne, androgenic alopecia, male pattern baldness, and female hirsutism comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

6. The method of Claim 5 wherein the compound is administered orally.

7. The method of Claim 5 wherein the compound is administered topically.

8. The method of Claim 5 further comprising the administration of a therapeutically effective amount of a 5α-reductase type 2 inhibitor.

9. The method of Claim 8 wherein the 5α-reductase type 2 inhibitor is finasteride or a pharmaceutically acceptable salt thereof.

10. A method of treating benign prostatic hyperplasia, prostatitis, and treating or preventing prostatic carcinoma comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

11. The method of Claim 10 further comprising the administration of a therapeutically effective amount of a 5α-reductase type 2 inhibitor.

12. The method of Claim 11 wherein the 5α-reductase type 2 inhibitor is finasteride or a pharmaceutically acceptable salt thereof.

13. A method of treating androgenic alopecia comprising administering to a person in need of such treatment a therapeutically effective amount of each of a compound of Claim 1 and a potassium channel opener.

14. The method of Claim 13 wherein the potassium channel opener is minoxidil or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as claimed in Claim 1.

16. The composition of Claim 15 further comprising a therapeutically effective amount of a 5α-reductase type 2 inhibitor.

17. The composition of Claim 16 wherein the 5α-reductase type 2 inhibitor is finasteride or a pharmaceutically acceptable salt thereof.

18. The pharmaceutical composition of Claim 15 wherein the composition is adapted for topical administration and further comprising a therapeutically effective amount of a potassium channel opener.

19. The pharmaceutical composition of Claim 18 wherein the potassium channel opener is minoxidil or a pharmaceutically acceptable salt therof.

INTERNATIONAL SEARCH REPORT

Int[illegible]ional application No.
PCT/US94/02697

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/435, 31/47 ; 31/535; C07D 221/02
US CL :514/232.8, 284; 544/125; 546/77, 78

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)

U.S. : A61K 31/435, 31/470, 31/535
514/232.8, 284; 544/125; 546/77, 78

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

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

CAS online structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Jour. Pharm. Sci, Vol. 62, issued 1973, Doorenbos et al. "Synthesis and Antimicrobial Properties of 17 B Isopentyloxy-4Aza5 androstan and the 4 methyl derivative," pages 638-40. See page 639 Formula VII.	1, 15
X	Jour. Org. Chem., Vol. 54, issued 1989, Back et al. "N chloroazasteroids: A Novel Class of Reactive steroid Analogues," pages 1904-10, see page 1906, Structure 4.	1, 15
X	US, A, 4,377,584 (RASMUSSON et al) 22 March 1983. See column 15, particularly compounds 12, 16, 17, 21, 19. See claims 1-3 and 14-19.	1, 4-19

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

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

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"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

21 APRIL 1994

Date of mailing of the international search report

JUL 05 1994

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INTERNATIONAL SEARCH REPORT

Int. tional application No.
PCT/US94/02697

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,760,071 (RASMUSSON et al.) 26 July 1988. See claims 1-4.	1, 4-19
X	EP, A, 0,314,199 (RASMUSSON et al.) 03 June 1989. See claims 1, 2, 6-7.	1, 4-19
X	EP, A, 0,004,949 (JOHNSTON et al) 31 October 1979. See Table, page 21, Ex. 5 to 8 and claim 2.	1, 4-19
X	US, A, 4,859,681 (RASMUSSON et al.) 22 August 1989. See Example 1 and claims 1-11.	1, 4-19
X	US, A, 4,845,104 (CARLIN et al) 04 July 1989. See claims 1 and 7-9.	1, 4-19
X	US, A, 5,049,562 (RASMUSSON et al) 17 September 1991. See claims 1-9, especially 2.	1, 4-19
X	US, A, 5,098,908 (STEINBERG et al) 24 March 1992. See claims 1-9.	1, 4, 15
X	Jour. Med. Chem., Vol. 27, issued 1984, Rasmusson et al., "Azasteroids as Inhibitors of Rat Prostatic 5 Reductase," pages 1670-71. See p. 1691, e.g. compounds 4a-d, 4f, 4l, 4m, 4w, 4y.	1, 4, 10-12, 15-19
X	Jour. of Med. Chem., Vol. 29, issued 1986, Rasmusson et al, "Azasteroids: Structure-Activity Relationships for Inhibition of 5 Reductase and of Androgen acceptor binding," pages 2298-2315. See Table IV. p. 2304 Nos. 13a, 14a, 13h, 14h, 13, 14r, 14k, 14o, 13m, 14m, 5g, 5j, 5ae. See Table II, p. 2300 Nos. 9a, 10a, 10az etc.	1, 4, 10-12, 15-19
X	US, A, 5,138,063 (RASMUSSON et al) 11 August 1992. See claims 1-4.	1, 4-19
X	US, A, 5,151,429 (RASMUSSON et al.) 29 September 1992. See claims 1-6.	1, 4-19
X	EP, A, 0,200,859 (CARNELLI et al) 12 November 1986. See page 2.	1-4, 15
Y	Jour. Clin. Endo. & Metab., Vol. 74, No. 2, issued 1992, Diani et al, "Hair Growth Effects of Oral Administration of Finasteride a Steroid 5 Reductase Inhibitor alone and in combination with Topical Minoxidil in the Balding Stumptail Macaque", see entire article.	5-9, 13-19

INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/US94/02697

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	The Prostate, Vol. 9., issued 1986, Brooks, "Prostatic Effects Induced in Dogs by Chronic or Acute Oral Administration of 5 Reductase Inhibitors," pages 65-75. See Tables I, II.	10-12, 15
X	EP, A, 0,155,096 (RASMUSSON et al.) 18 September 1985. See claims 1, 11-12.	1, 4-19