Replacement page 28

Methyl 3α-acetoxy-5β-chol-9(11)-en-12-one-24-oate (**10a**); and

Methyl 3α-acetoxy-5β-cholan-12-one-24-oate (**11a**).

**Pharmaceutical compositions and modes of administration**

The compositions can be comprised of a disclosed compound in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the disclosed compound. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

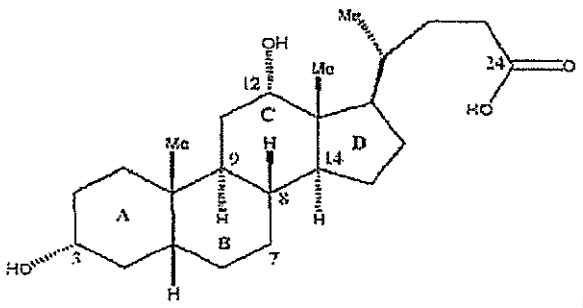
Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

In general, the compounds of preferred embodiments will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the compound of preferred embodiments, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors. The drug can be administered more than once a day, preferably once or twice a day. All of these factors are within the skill of the attending clinician.

The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. The present compositions in various aspects as described herein may be prepared wherein the deoxycholic acid moiety is in the range of about 0.5%-10% on a weight per aqueous volume basis, or, on a w/w basis assuming the density of water (i.e., a 1:1 correspondence between weight and volume). In another aspect, the present embodiments relate to the presently described pharmaceutical compositions in

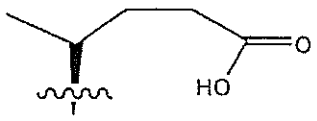
What is claimed is:

1. Synthetic deoxycholic acid (DCA):



(DCA)

or a pharmaceutically acceptable salt thereof, wherein said synthetic deoxycholic acid comprises a synthetic side chain of formula



wherein the side chain is synthetically joined with ring-D of synthetic DCA, and wherein the synthetic DCA is of non-mammalian or non-microbial origin.

2. A composition for use in an adipolytic therapy in a mammal comprising the synthetic DCA of claim 1 and a pharmaceutically acceptable excipient.

3. The composition as claimed in clam 2 wherein said salt is sodium.

4. The composition as claimed in claim 2 or claim 3, wherein the concentration of deoxycholic acid (DCA) or pharmaceutically acceptable salt thereof is between 0.001 and 10% w/w, w/v or v/v such as between 0.001 and 5% w/w, w/v or v/v.

5. The composition as claimed in any of claims 2 to 4, which additionally comprises a lipid, a phospholipid, or a phosphatidylcholine, such as up to 5% w/w, w/v or v/v.

6. The composition as claimed in any of claims 2 to 5, which additionally comprises at least one additional active ingredient selected from the group consisting of: anti-microbial agents, vasoconstrictors, anti-thrombotic agents, anti-coagulation agents, suds-depressants, anti-inflammatory agents, analgesics, dispersion agents, anti-dispersion agents, penetration enhancers, steroids, tranquilizers, muscle relaxants, and anti-diarrhea agents.

7. The composition as claimed in any of claims 2 to 6, which additionally comprises one or more detergents.

8. The composition as claimed in any of claims 2 to 7, which additionally comprises at least one additional active ingredient selected from the group consisting of a neuropeptide Y (NPY) receptor antagonist and a fat selective pro-apoptotic peptide.

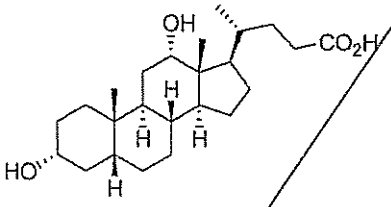
9. The composition of claim 8, wherein said neuropeptide Y (NPY) receptor antagonist is selected from the group consisting of BIBP-3226, neuropeptide Y5 antagonist (the Amgen NPY receptor antagonists), BIBO-3304 (the Boehringer Ingleheim NPY receptor antagonist), BMS-192548 (the Bristol-Myers Squibb NPY receptor antagonist), AR-H040922 (the Bristol-Myers Squibb NPY receptor antagonist), LY-357897 (the Eli Lilly NPY receptor antagonist), the Esteve NPY-Y5 receptor antagonist, 1229U91 (the GlaxoSmithKline NPY receptor antagonists), GW438014S (the GlaxoSmithKline NPY receptor antagonists), JNJ-5207787 (the Johnson & Johnson NPY receptor antagonist), Lu-AA-44608 (the Lundbeck NPY receptor antagonist), MK-0557 (the Merck NPY receptor antagonist), NGD-95-1 (the Neurgogen NPY receptor antagonist), NLX-E201 (the Neurologix NPY receptor antagonist), CGP-71683 (the Novartis NPY receptor antagonist), PD-160170 (the Pfizer NPY receptor antagonists), SR-120819A (the Sanofi Aventis NPY receptor antagonists), BIIE0246 (the Sanofi Aventis NPY receptor antagonists), S.A.0204 (the Sanofi Aventis NPY receptor antagonists), S-2367 (the Shiongli NPY receptor antagonist), dihydropyridine NPY receptor antagonists, dihydropyridine derivative NPY receptor antagonists, bicyclic compound NPY receptor antagonists, carbazole NPY receptor antagonist, and tricyclic compounds NPY receptor antagonists.

10. The composition as claimed in claim 9, which additionally comprises CKGGRAKDC peptide that homes to white fat vasculature as a fat selective proapoptotic peptide.

11. The composition as claimed in any of claims 2 to 10, wherein said adipolytic therapy is for treating a pathological localized fat deposit.

12. The composition as claimed in claim 11, wherein the fat deposit is associated with a condition selected from the group consisting of: obesity, fat redistribution syndrome, eyelid fat herniation, lipomas, Dercum's disease, lipodystrophy, buffalo hump lipodystrophy, dorsocervical fat, visceral adiposity, breast enlargement, hyperadiposity, diffused body fat around trunk and arms, and cellulite.

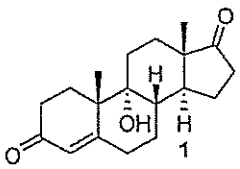
13. The synthetic DCA or a pharmaceutically acceptable salt thereof as claimed in claim 1:

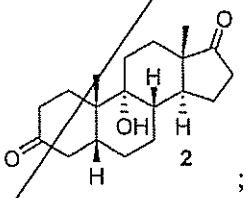



(DCA)

which is obtainable by a method comprising

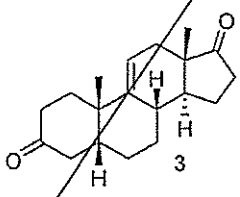
(a) reacting 9α-hydroxyandrost-4-en-3,17-dione **1** with $H_2$ under hydrogenation conditions to form compound **2**



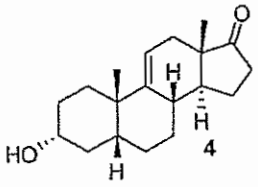

;

(b) reacting compound **2** with acid to form compound **3**

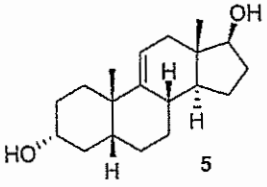



;

(c) reacting compound **3** with a reducing agent to form compound **4** as a mixture of **4** and **5**

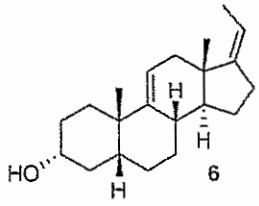


**4**



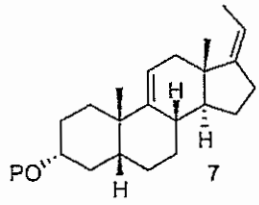
**5** ;

(d) reacting compound **4** with a two carbon olefination reagent under olefin forming conditions to form compound **6**



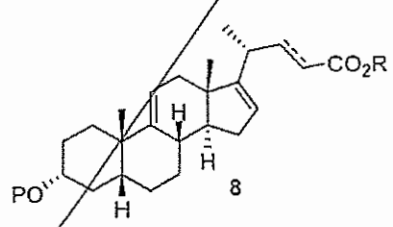
**6** ;

(e) converting compound **6** to a compound of formula **7** wherein P is a protecting group



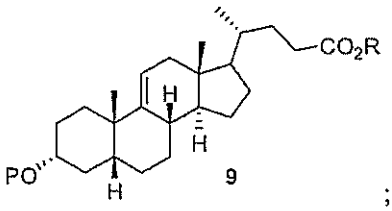
**7** ;

(f) reacting a compound of formula **7** with an alkylpropiolate $CH_2CH_2C(O)OR$ or an alkyl acrylate $CH_2$=CHC(O)OR wherein R is alkyl in the presence of a Lewis acid to form a compound of formula **8** wherein P is a protecting group, R is alkyl, and the dashed line ---- is a single or double bond;



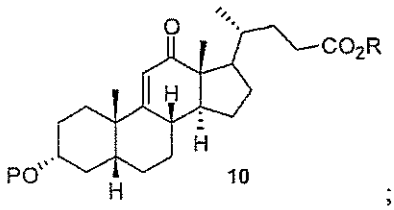
**8**

(g) reacting a compound of formula **8** with $H_2$ under hydrogenation conditions to form a compound of formula **9** wherein P is a protecting group and R is alkyl



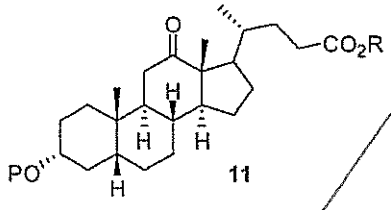

**9** ;

(h) reacting compound of formula **9** with an oxidizing agent to form a compound of formula **10** wherein P is a protecting group and R is alkyl



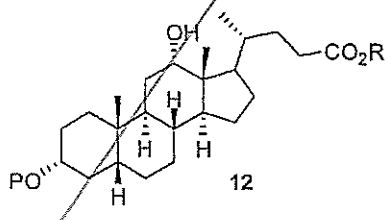

**10** ;

(i) reacting a compound of formula **10** with $H_2$ under hydrogenation conditions to form compound of formula **11** wherein P is a protecting group and R is alkyl




**11** ;

(j) reacting compound of formula **11** with a reducing agent to form a compound of formula **12** wherein P is a protecting group and R is alkyl




**12** ; and

(k) exposing compound of formula **12** to deprotection conditions to form an ester thereof and optionally to suitable hydrolysis conditions to form deoxycholic acid or the pharmaceutically acceptable salt thereof.

14. The method of claim 13 wherein

i. the hydrogenation conditions of part (a) comprises a Pd/C catalyst;

ii. the acid of part (b) is a mineral acid optionally wherein the mineral acid is $H_2SO_4$;

iii. the reducing agent of part (c) is $LiAl(OtBu)_3H$;

iv. the two carbon olefination reagent of part (d) is $Ph_3PCH_2CH_3^+Br^-$;

v. the protecting group P of compound **7-12** is $-C(O)CH_3$;

vi. the Lewis acid of part (f) is $EtAlCl_2$;

vii. the alkylpropiolate or alkylacrylate is methylpropriolate or methylacrylate;

viii. the hydrogenation conditions of part (g) comprises a $PtO_2$ catalyst;

ix. the oxidizing agent of part (h) is $CrO_3$;

x. the hydrogenation conditions of part (i) comprises a Pd/C catalyst; or

xi. the reducing agent of part (j) is $LiAl(OtBu)_3H$.

15. The method of claim 12 wherein the deprotection and hydrolysis conditions of part (k) when P is $-C(O)CH_3$ comprises reacting compound 12 with an alkali earth hydroxide, alkali metal hydroxide, or a mixture of both, optionally wherein the alkali metal hydroxide is LiOH.

16. A non-surgical cosmetic method for reducing localized fat deposit in a skin region of a human subject comprising administering to said skin region a therapeutically effective amount of the compound or composition as defined in any of claims 1 to 15.

17. The method as claimed in claim 16, wherein said administering is subcutaneous, subdermal or transdermal.

18. The method as claimed in claim 16 or 17, which additionally comprises simultaneously administering a local anesthetic to said skin region.

19. The method as claimed in any of claims 16 to 18, wherein said skin region is selected from the group consisting of: under eye, under chin, under arm, buttock, cheek, brow, calf, back, thigh, ankle, or stomach.

Methyl 3α-acetoxy-5β-chol-9(11), 16-dien-24-oate (8b);

Methyl 3α-acetoxy-5β-chol-9(11)-en-12-one-24-oate (10a); and

Methyl 3α-acetoxy-5β-cholan-12-one-24-oate (11a).

**Pharmaceutical compositions and modes of administration**

The compositions can be comprised of a disclosed compound in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the disclosed compound. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

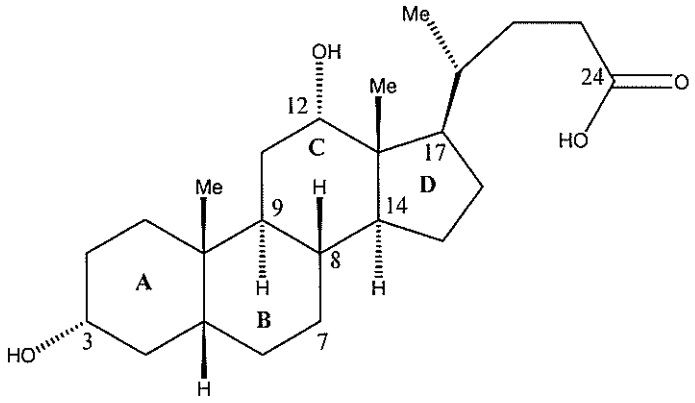
Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

In general, the compounds of preferred embodiments will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the compound of preferred embodiments, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors. The drug can be administered more than once a day, preferably once or twice a day. All of these factors are within the skill of the attending clinician.

The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. The present compositions in various aspects as described herein may be prepared wherein the deoxycholic acid moiety is in the range of about 0.5%-10% on a weight per aqueous volume basis, or, on a w/w basis assuming the density of water (i.e., a 1:1 correspondence between weight and volume). In another aspect, the present embodiments relate to the presently described pharmaceutical compositions in

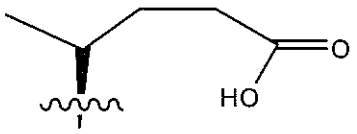
**What is Claimed is:**

1. A compound that is synthetic deoxycholic acid (DCA) or a prodrug thereof or a pharmaceutically acceptable salt of the compound or the prodrug:




(DCA),

wherein said synthetic DCA is not of animal or microbial origin, and comprises a synthetic side chain:




that is synthetically introduced at the 17 position.

2. A composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient.

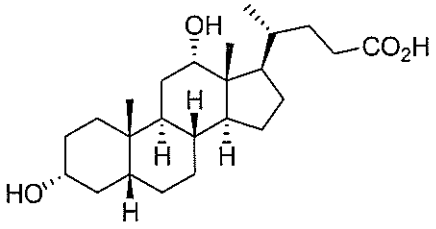
3. The composition of claim 2 further comprising at least one additional active ingredient selected from the group consisting of a neuropeptide Y (NPY) receptor antagonist and a fat selective pro-apoptotic peptide.

4. The composition of claim 3, wherein said neuropeptide Y (NPY) receptor antagonist is selected from the group consisting of BIBP-3226, neuropeptide Y5 antagonist (the Amgen NPY receptor antagonists), BIBO-3304 (the Boehringer Ingleheim NPY receptor antagonist), BMS-192548 (the Bristol-Myers Squibb NPY receptor antagonist), AR-H040922 (the Bristol-Myers Squibb NPY receptor antagonist), LY-357897 (the Eli Lilly NPY receptor antagonist), the Esteve

NPY-Y5 receptor antagonist, 1229U91 (the GlaxoSmithKline NPY receptor antagonists), GW438014S (the GlaxoSmithKline NPY receptor antagonists), JNJ-5207787 (the Johnson & Johnson NPY receptor antagonist), Lu-AA-44608 (the Lundbeck NPY receptor antagonist), MK-0557 (the Merck NPY receptor antagonist), NGD-95-1 (the Neurgogen NPY receptor antagonist), NLX-E201 (the Neurologix NPY receptor antagonist), CGP-71683 (the Novartis NPY receptor antagonist), PD-160170 (the Pfizer NPY receptor antagonists), SR-120819A (the Sanofi Aventis NPY receptor antagonists), BIIE0246 (the Sanofi Aventis NPY receptor antagonists), S.A.0204 (the Sanofi Aventis NPY receptor antagonists), S-2367 (the Shiongli NPY receptor antagonist), dihydropyridine NPY receptor antagonists, dihydropyridine derivative NPY receptor antagonists, bicyclic compound NPY receptor antagonists, carbazole NPY receptor antagonist, and tricyclic compounds NPY receptor antagonists.

5. The composition of claim 3, wherein the fat selective pro-apoptotic peptide is CKGGRAKDC peptide that homes to white fat vasculature.

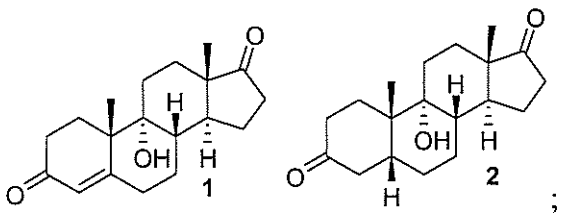
6. A method for preparing deoxycholic acid (DCA) or an ester thereof or a pharmaceutically acceptable salt thereof:




(DCA)

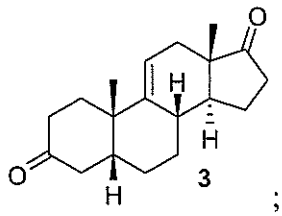
said method comprising

(a) reacting 9α-hydroxyandrost-4-en-3,17-dione **1** with $H_2$ under hydrogenation conditions to form compound **2**



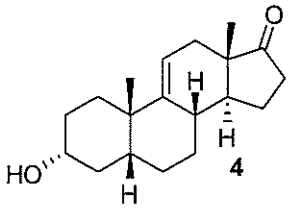

;

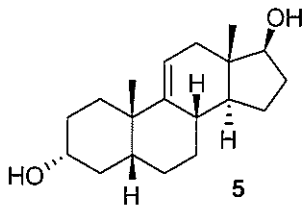
(b) reacting compound **2** with acid to form compound **3**



;

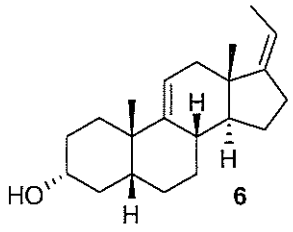
(c) reacting compound **3** with a reducing agent to form compound **4** as a mixture of **4** and **5**



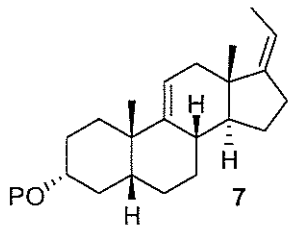
;

(d) reacting compound **4** with a two carbon olefination reagent under olefin forming conditions to form compound **6**



;

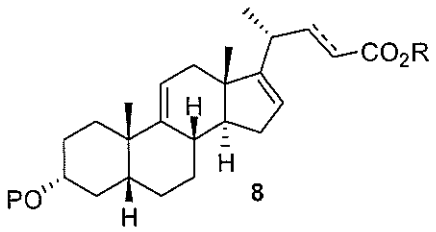
(e) converting compound **6** to a compound of formula **7** wherein P is a protecting group



;

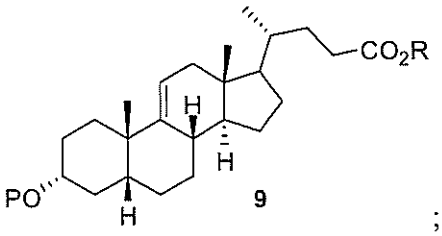
(f) reacting a compound of formula **7** with an alkylpropiolate CHCC(O)OR or an alkyl acrylate $CH_2$=CHC(O)OR wherein R is alkyl in the presence of a Lewis acid to form a

compound of formula **8** wherein P is a protecting group, R is alkyl, and the dashed line ---- is a single or double bond;




**8**

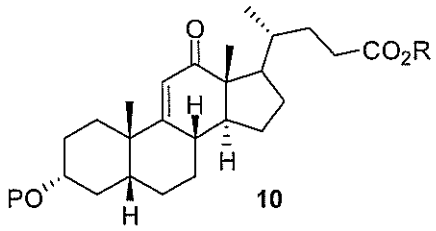
(g) reacting a compound of formula **8** with $H_2$ under hydrogenation conditions to form a compound of formula **9** wherein P is a protecting group and R is alkyl




**9**

;

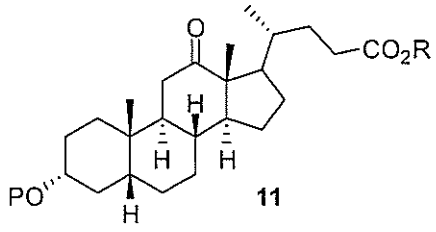
(h) reacting compound of formula **9** with an oxidizing agent to form a compound of formula **10** wherein P is a protecting group and R is alkyl




**10**

;

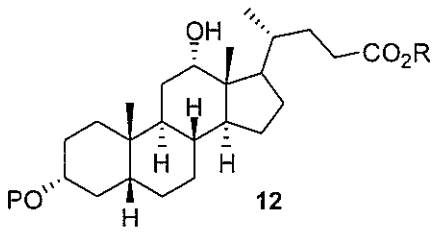
(i) reacting a compound of formula **10** with $H_2$ under hydrogenation conditions to form compound of formula **11** wherein P is a protecting group and R is alkyl




**11**

;

(j) reacting compound of formula **11** with a reducing agent to form a compound of formula **12** wherein P is a protecting group and R is alkyl




**12** ; and

(k) exposing compound of formula **12** to deprotection conditions to form an ester thereof and optionally to suitable hydrolysis conditions to form deoxycholic acid or the pharmaceutically acceptable salt thereof.

7. The method of claim 6 wherein the hydrogenation conditions of part (a) comprises a Pd/C catalyst, or wherein the acid of part (b) is a mineral acid, wherein the mineral acid is $H_2SO_4$, or wherein the reducing agent of part (c) is $LiAl(OtBu)_3H$, or wherein the two carbon olefination reagent of part (d) is $Ph_3PCH_2CH_3^+Br^-$, or wherein the protecting group P of compound **7-12** is $-C(O)CH_3$, or wherein the Lewis acid of part (f) is $EtAlCl_2$, or wherein the alkylpropiolate or alkylacrylate is methylpropriolate or methylacrylate, or wherein the hydrogenation conditions of part (g) comprises a $PtO_2$ catalyst, or wherein the oxidizing agent of part (h) is $CrO_3$, or wherein the hydrogenation conditions of part (i) comprises a Pd/C catalyst, or wherein the reducing agent of part (j) is $LiAl(OtBu)_3H$, or wherein the deprotection and hydrolysis conditions of part (k) when P is $-C(O)CH_3$ comprises reacting compound **12** with an alkali earth hydroxide, alkali earth alkoxide, or a mixture of both.

8. The method of claim 7 wherein the alkali earth alkoxide is LiOH.

9. A compound selected from the group consisting of

9$\alpha$-Hydroxy-5$\beta$-androstan-3,17-dione (**2**);

5$\beta$-Androst-9(11)-en-3,17-dione (**3**);

(Z)-3$\alpha$-Hydroxy-5$\beta$-pregna-9(11),17(20)-diene (**6**);

(Z)-3$\alpha$-Acetoxy-5$\beta$-pregna-9(11),17(20)-diene (**7a**);

(E)-Methyl 3$\alpha$-acetoxy-5$\beta$-chol-9(11), 16, 22-trien-24-oate (**8a**); and

Methyl 3$\alpha$-acetoxy-5$\beta$-chol-9(11), 16-dien-24-oate (**8b**).

10. The composition as claimed in claim 2, wherein the concentration of DCA or an ester or amide prodrug thereof or pharmaceutically acceptable salt of each thereof is between 0.001 and 10% w/w, w/v or v/v, such as between 0.01 and 5 % w/w, w/v or v/v.

11. The composition as claimed in claim 2, which additionally comprises a lipid, a phospholipid, or a phosphatidylcholine, such as up to 5% w/w, w/v or v/v of a lipid, a phospholipid or a phosphatidylcholine.

12. The composition as claimed in claim 2, which additionally comprises at least one additional active ingredient selected from the group consisting of: anti-microbial agents, vasoconstrictors, anti-thrombotic agents, anti-coagulation agents, suds-depressants, anti-inflammatory agents, analgesics, dispersion agents, anti-dispersion agents, penetration enhancers, steroids, tranquilizers, muscle relaxants, and anti-diarrhea agents.

13. The composition as claimed in claim 2, which additionally comprises one or more detergents.