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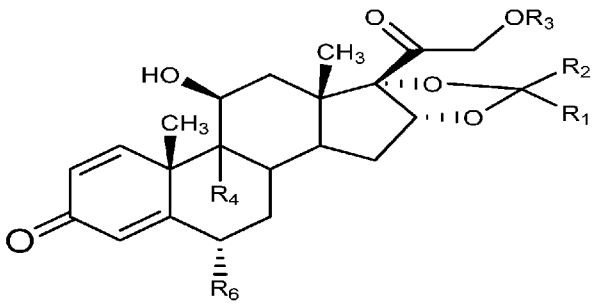
(54) Title: NOVEL PROCESS FOR PREPARATION OF CORTICOSTEROIDS



Formula I

(57) Abstract: The present invention discloses a process for the preparation of pregnadiene derivatives having formula I, their stereoisomer and intermediate thereof. Formula I wherein each substituent is independently, R_1 and R_2 is hydrogen or C_1 – C_8straight, branched alkyl chain, saturated or unsaturated cycloalkyl; R_3 is hydrogen or wherein R_5 represents C_1-C_8 straight, branched alkyl chain or cycloalkyl; R_4 is hydrogen or halogen; R_6 is hydrogen or halogen;

"NOVEL PROCESS FOR PREPARATION OF CORTICOSTEROIDS"

FIELD OF THE INVENTION

The present invention provides a novel process for the preparation of pregnadiene derivatives

BACKGROUND OF THE INVENTION

Corticosteroids also referred as glucocorticosteroids, glucocorticoids or just steroids influence different body tissues and produceeffects on various responsive cells.

Corticosteroids have been found to possess anti-inflammatory and immunosuppressive properties. Several Corticosteroids such as Flunisolide, Fluocinolone acetonide and Fluocinonide are used for treatment of several disorders.

Corticosteroids with significant structural changes and chemical manipulation have been developed. In general, therapeutic corticosteroids have a 21-carbon steroid skeleton; Modifications to this skeleton selectively alter the degree of anti-inflammatory activity and the metabolic consequences and vary the duration of activity and protein-binding affinity of the resultant compound.

Therapeutic corticosteroids are typically classified based on their relative glucocorticoid and mineralocorticoid potency. Such as, acetonides at C-16, C-17 are to improve potency of anti-inflammatory activity of steroids but possess low systematic activity.

Further, halogenations of steroids molecule by 9-halo or 6, 9 dihalo substitutions increase their systematic activity and enhances both glucocorticoid and mineralocorticoid activity of C-16, C-17 substituted acetals, ketals, acetonides, fused ring compounds. For example, Flunisolide is a topical corticosteroid having 6-fluoro and C-16, C-17 acetonide group.

The process for preparation of Corticosteroids having C-16, C-17 substituted acetals, ketals, acetonides, fused ring compounds and halogens at C-6, C-9 or both positions have been disclosed at different instances. However, most of these synthetic procedures involve 6 halo or 6, 9 dihalo, 16α, 17α diols or both as starting materials, which are compounds difficult to prepare handle and purify, the use of toxic solvents or long reaction times are ineffective for large scale synthesis.

For instance, US 3,126,375discloses a process for the preparation of 6 halo corticoids. The known methods for the preparation of pregnadiene 16, 17acetals, ketals involve the starting material as 6 halo or 6, 9 halo having 16α, 17α diols with aldehydes in the presence of catalyst such as copper sulphate or copper sulphate or perchloricacid solvent which are compounds difficult to prepare and purify and unstable and use of these solvents on large scale require specialized equipments.

WO 03/47329 discloses a method for the preparation of 6α-fluorinated corticosteroids. This application is specific to a 21 ester, 17-hydroxy corticosteroids and does not disclose the various chemicals, starting material, products or reactions and modification thereof. Therefore, the process is not repeatable.

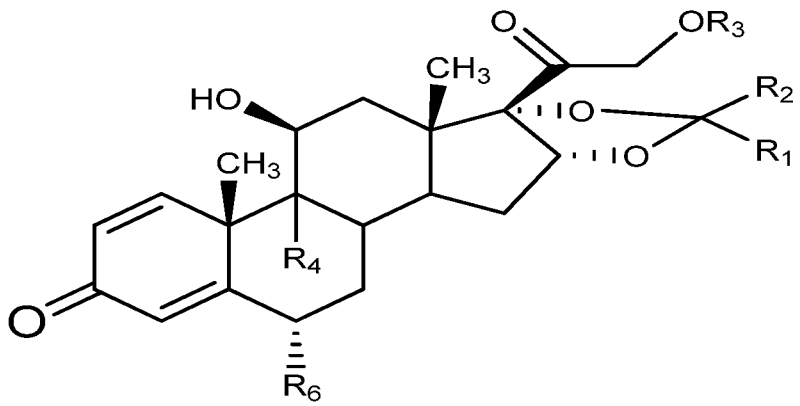
Hence, there is a need to prepare novel Corticosteroidshalogenated at C-6, C-9 or both positions and C-16, C-17 acetals, ketals, acetonides, fused ring compounds using stable, easily available starting materials whichcan be easily purified, convenient, having high yields, industrially scalable and which does not involve the use of harmful solvents.

OBJECT OF THE INVENTION

An object of the present invention is to provide a novel process for the preparation of pregnadiene derivatives, their stereoisomer and intermediate thereof using stable, easily available and purifiable starting materials without the use of toxic and harmful solvents.

BRIEF DESCRIPTION OF THE INVENTION

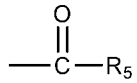
The present invention discloses a process for the preparation of pregnadiene derivatives having formula I, their stereoisomer and intermediate thereof.



Formula I

wherein each substituent is independently,

R_1 and R_2 is hydrogen or C_1 –C_8straight, branched alkyl chain, saturated or unsaturated cycloalkyl;

R_3 is hydrogen or  wherein R_5 represents C_1-C_8 straight, branched alkyl chain or cycloalkyl;

R_4 is hydrogen or halogen;

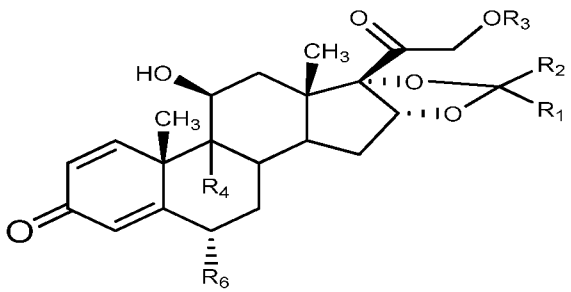
R_6 is hydrogen or halogen;

The present invention discloses, a novel process for preparing the compounds of formula I;

i. epoxidation of compound of formula II to obtain 9,11-oxido derivative of compound of formula III;
ii. dihydroxylation and optional fluorination of compound of formula III to obtain compound of formula IV with a proviso when R_6 is F.
iii. epoxide ring opening of compound of formula IV followed by acetalisation to obtain compound of formula V and optionally, debromination of compound of formula V with a proviso R_4 is Br to obtain compound of formula V when R4 is H
iv. deacetylation of compound of Formula V to obtain compound of formula I

DETAILED DESCRIPTION OF THE INVENTION

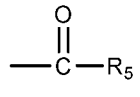
The present invention discloses a novel process for the preparation of pregnadiene derivatives of formula I, their stereoisomer and intermediate thereof.



Formula I

wherein

R_1 and R_2 is independently hydrogen or C1 –C8 straight, branched alkyl chain, saturated or unsaturated cycloalkyl;

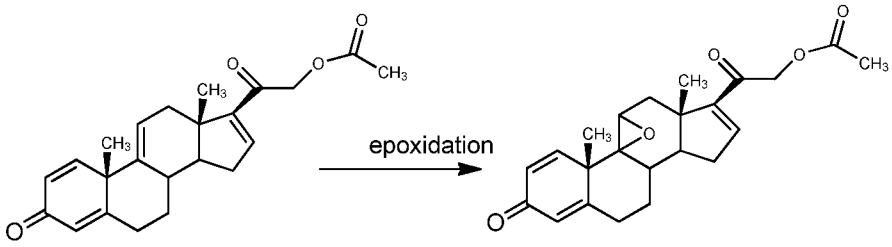
R_3 is hydrogen or  ;

R_5 represents C1-C8 straight, branched alkyl chain or cycloalkyl;

R_4 and R_6 is independently hydrogen or halogen;

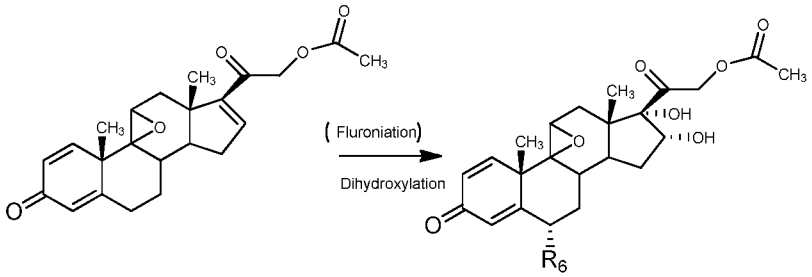
comprising the steps of:

i. epoxidation of compound of formula II to obtain 9,11-oxido derivative of compound of formula III;



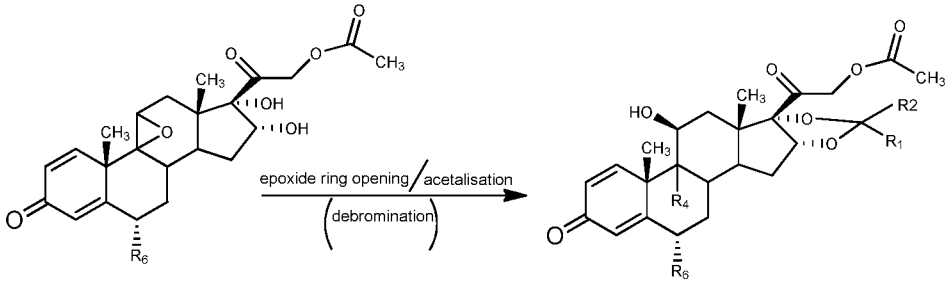
Formula II Formula III

ii. dihydroxylation and optional fluorination of compound of formula III to obtain compound of formula IV with a proviso when R_6 is F.



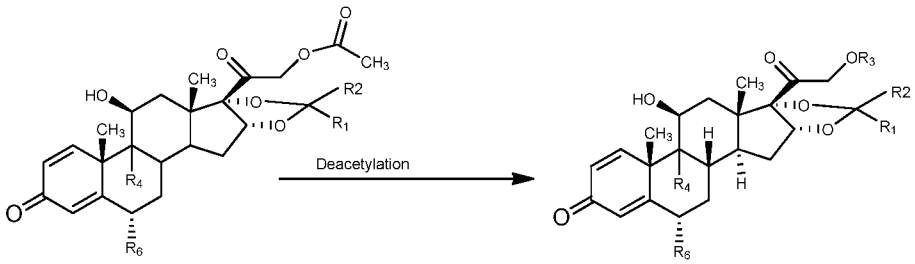
Formula III Formula IV

iii. epoxide ring opening of compound of formula IV followed by acetalisation to obtain compound of formula V and optionally, debromination of compound of formula V with a proviso R_4 is Br to obtain compound of formula V when R4 is H



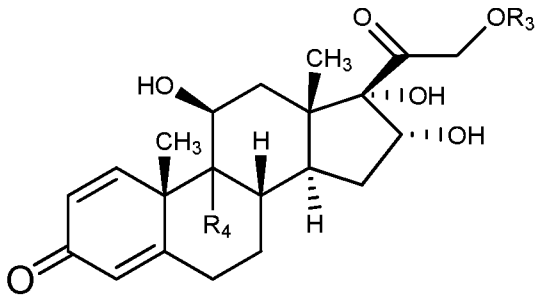
Formula IV Formula V

iv. deacetylation of compound of Formula V to obtain compound of formula I



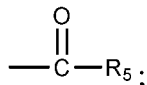
Formula V Formula I

The present invention also provides a process for preparation of pregnadiene derivatives of Formula A



Formula A

wherein

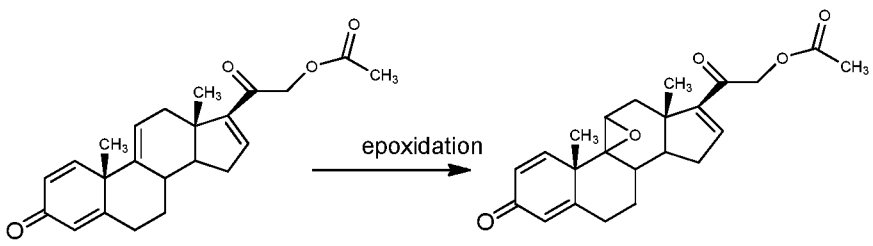
R_3 is hydrogen or  ;

R_5 represents C1-C8 straight, branched alkyl chain or cycloalkyl;

R_4 is halogen;

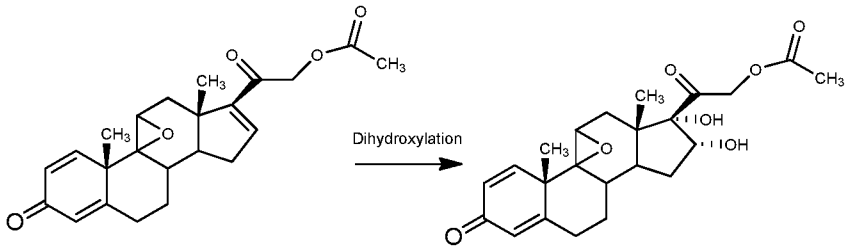
comprising the steps of:

i. epoxidation of compound of formula II to obtain 9,11-oxido derivative of compound of formula III;



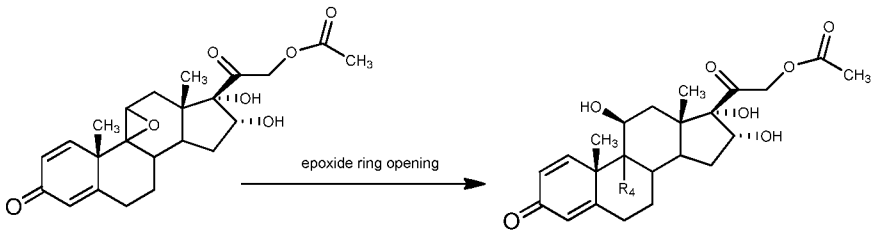
Formula II Formula III

ii. dihydroxylation of compound of formula III to obtain compound of formula IV



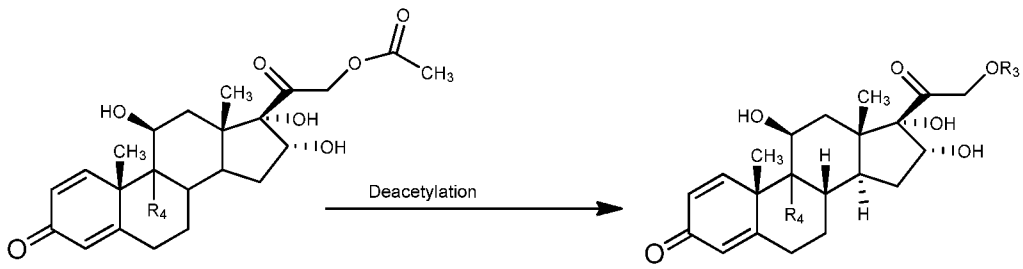
Formula III Formula IV

iii. epoxide ring opening of compound of formula IV followed by acetalisation to obtain compound of formula V



Formula IV Formula V

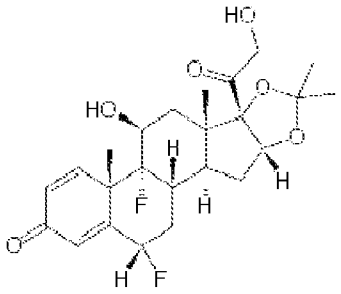
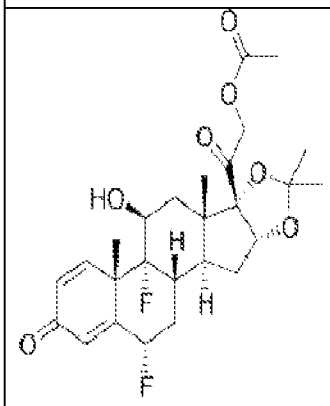
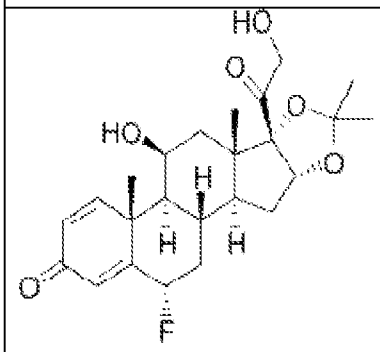
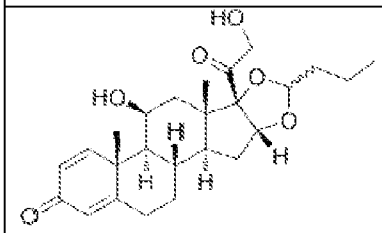
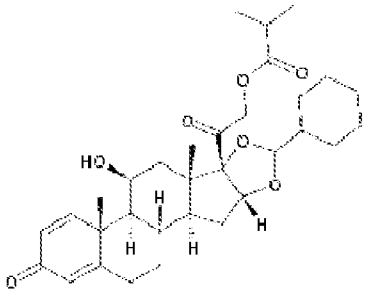
iv. deacetylation of compound of Formula V to obtain compound of formula I

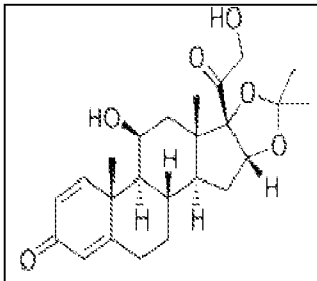
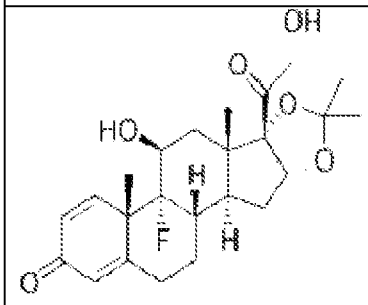
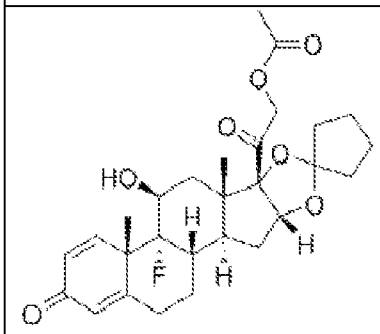
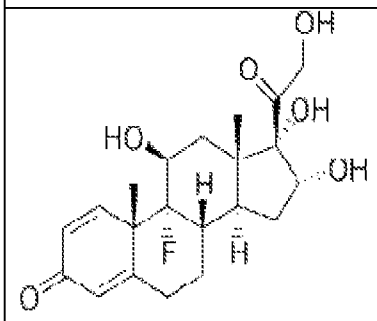
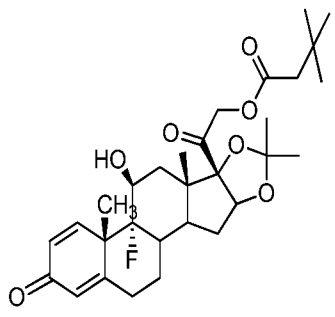


Formula V Formula A

The compounds of formula I, formula V, and formula A may include but are not limited to the following compounds as presented at Table 1:

Table 1: Exemplary compounds of present invention

Structure	Generic name	IUPAC Name
	Fluocinolone acetonide	1*S*,2*S*,4*R*,8*S*,9*S*,11*S*,12*R*,13*S*,19*S*)-12,19-difluoro-11-hydroxy-8-(2-hydroxyacetyl)-6,6,9,13-tetramethyl-5,7-dioxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosa-14,17-dien-16-one
	Fluocinonide	6α,9-difluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione, cyclic 16,17-acetal with acetone,21-acetate
	Flunisolide	1*S*,2*S*,4*R*,8*S*,9*S*,11*S*,12*S*,13*R*,19*S*)-19-fluoro-11-hydroxy-8-(2-hydroxyacetyl)-6,6,9,13-tetramethyl-5,7-dioxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosa-14,17-dien-16-one
	Budesonide	16,17-(butylidenebis(oxy))-11,21-dihydroxy-, (11-β,16-α)-pregna-1,4-diene-3,20-dione
	Ciclesonide	2-[(1*S*,2*S*,4*R*,8*S*,9*S*,11*S*,12*S*,13*R*)-6-cyclohexyl-11-hydroxy-9, 13-dimethyl-16-oxo-5, 7-dioxapentacyclo [10.8.0.02,9.04, 8.013,18] icosa-14, 17-dien-8-yl]-2-oxoethyl 2-methylpropanoate.

	Desonide	(1*S*,2*S*,4*R*,8*S*,9*S*,11*S*,12*S*,13*R*)-11-hydroxy-8-(2-hydroxyacetyl)-6,6,9,13-tetramethyl-5,7-dioxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosa-14,17-dien-16-one
	Triamcinolone acetonide	(4a*S*,4b*R*,5*S*,6a*S*,6b*S*,9a*R*,10a*S*,10b*S*)-4b-fluoro-6b-glycoloyl-5-hydroxy-4a,6a,8,8-tetramethyl-4a,4b,5,6,6a,6b,9a,10,10a,10b,11,12-dodecahydro-2*H*-naphtho[2',1':4,5]indeno[1,2-*d*][1,3]dioxol-2-one
	Amcinonide	2-[(1*S*,2*S*,4*R*,8*S*,9*S*,11*S*,12*R*,13*S*)-12'-fluoro-11'-hydroxy-9',13'-dimethyl-16'-oxo-5',7'-dioxaspiro[cyclopentane-1,6'-pentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane]-14',17'-dien-8'-yl]-2-oxoethyl acetate
	Triamcinolone	(11β,16α)-9-Fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione
	Triamcinolone hexacetonide	(11β,16α)-21-(3,3-Dimethyl-1-oxobutoxy)-9-fluoro-11-hydroxy-16,17-((1-methylethylidene)bis(oxy))pregna-1,4-diene-3,20-dione

The process of the present invention is explained at scheme 1.

Scheme 1: Process of the present invention

The process of the present invention comprises of the following steps:

i. epoxidation of compound of formula II to obtain 9,11-oxido derivative of compound of formula III;
ii. dihydroxylation and optional fluorination of compound of formula III to obtain compound of formula IV with a proviso when R_6 is F.
iii. epoxide ring opening of compound of formula IV followed by acetalisation to obtain compound of formula V and optionally, debromination of compound of formula V with a proviso R_4 is Br to obtain compound of formula V when R4 is H
iv. deacetylation of compound of Formula V to obtain compound of formula I

The process of the present invention may be suitably started from the compound of formula II, known by its IUPAC name 2-((10S,13S,14S)-10,13-dimethyl-3-oxo-6,7,8,10,12,13,14,15-octahydro-3H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl acetate and hereinafter referred to as 3TR (formula II).

3TR is suitably epoxidized by an epoxidizing agent. The epoxidizing agents may be selected from the group comprising dibromantin, N-bromoacetaminde or N-bromosuccinimide with Perchloric acid to get bromohydrin, followed by alkali treatment from the group comprising sodium or potassium hydroxide or their carbonates or acetate to form compound of formula (III). The epoxidation of 3TR results in a compound of formula III.

In the present invention, epoxidation of compound of formula (II) is carried out with an epoxidizing agent, selected from group comprising dibromantin, N-bromoacetaminde or N-bromosuccinimide with Perchloric acid, preferably dibromantin with perchloric acid in aqueous acetone to get bromohydrin and epoxidation by alkali from the group comprising sodium or potassium hydroxide or their carbonates or acetate, preferably potassium carbonate to form compound of formula (III).

The process of the present invention involves the fluorination followed by dihydroxylationof the compound of formula III to yield the dihydroxylated fluorinated compound of formula IV. The fluorination of the compound of Formula III may be conducted by suitably reacting the

compound of Formula III with a fluorinating agent selected from the group comprising N-fluoro-benzene sulfonamide, N-fluoro-N-chloromethyltrimethylene diamine bistetrafluoroborate, Selectfluor®, 1-fluoropyridinium triflate, 1-fluoropyridinium tetrafluoroborate, or 1-fluoropyridinium pyridine heptafluorodiborateetc, preferably Selectfluor® in presence of a solvent and an acid catalyst. The solvent may be selected from the group comprising acetonitrile, isopropenyl acetate, dichloromethane, dimethyl formamide, diethyl ether, and tetrahydrofuran, preferably isopropenylacetate .

Further, dihydroxylation of the 6-fluoro derivative may be conducted by suitably reacting the compound of Formula III with an oxidizing agent selected from the group comprising potassium permanganate, potassium dichromate, chromic acid, peroxyacids or mixtures thereof, preferably potassium permanganate, formic acid to form compound of formula (IV). Under acidic conditions formic acid promotes oxidation reaction in the formulated product.

In the present invention, compound of formula (III) is fluorinated with a fluorinating agent selected from the group comprising N-fluoro-benzene sulfonamide, N-fluoro-N-chloromethyltrimethylene diamine bistetrafluoroborate, Selectfluor®, 1-fluoropyridinium triflate, 1-fluoropyridinium tetrafluoroborate, or 1-fluoropyridinium pyridine heptafluorodiborate etc, preferably Selectfluor® in presence of a solventin presence of a solvent. The solvent may be selected from the group comprising acetonitrile, dichloromethane, dimethyl formamide, diethyl ether, and tetrahydrofuran followed by dihydroxylation with an oxidizing agent selected from the group comprising potassium permanganate, potassium dichromate, chromic acid, peroxyacids or mixtures thereof, preferably potassium permanganate, formic acid to form compound of formula (IV). Under acidic conditions formic acid promotes oxidation reaction in the formulated product

The epoxide ring opening of compound of formula IV may be conducted in the presence of hydrohalic acid followed by acetalisation with aldehyde or ketone to form compound of formula (V). The epoxide ring opening of the compound of Formula IV may be conducted by suitably reacting the compound of Formula IV with a hydrohalic acid selected from the group comprising HF, HCl, HBr etc, preferably HF.

The acetalisation of the compound of Formula IV may be conducted by suitably reacting the compound of Formula III with an aldehyde or ketone selected from the group comprising

formaldehyde, paraldehyde, acetone, benzaldehyde, acetophenone, diethylketone, cyclohexane corboxaldehyde sodium metabisulphite complex, cyclopentanone preferably acetone.

In the present invention, the epoxide ring opening of compound of formula IV may be conducted in the presence of hydrohalic acid selected from the group comprising HF, HCl, HBr etc, preferably HF followed by acetalisation with aldehyde or ketone selected from the group comprising formaldehyde, paraldehyde, acetone, benzaldehyde, acetophenone, diethylketone, cyclohexane corboxaldehyde sodium metabisulphite complex, cyclopentanone preferably acetone to form compound of formula (V).

The compound of formula V may be converted to the compound of formula I by deacetylation by reacting with reagents selected from group comprising sodium hydroxide, potassium hydroxide etc. and solvent as methanol, methylene chloride, water or their combination thereof.

Optionally, the debromination of compound of formula IV may be conducted in presence of a catalyst, a thiol compound and an aprotic solvent to obtain the compound of formula VI when R4 in formula VI is H.

In the present invention, catalyst is selected from the group comprising chromous or chromium sulfate, chromous or chromium chloride or its hydrate, preferably chromium chloride hexahydrate. The chromium (III) can be recycled to chromium (II) as is known to those skilled in the art. The means for recycling chromium (III) to chromium (II) includes zinc, magnesium, zinc amalgam and magnesium amalgam. Preferred is zinc and magnesium; most preferred is zinc. It is preferred that when the means for recycling is zinc it be present as zinc dust.

Thiols include compounds of the formula R_t–SH (Formula VIII). It is preferred that R_t be --CH_2 --COOH or --CH_2CH_2 --COOH; it is more preferred that the thiol be thioglycolic (thiovanic) acid where R_t is --CH_2 --COOH. Improved chemical yields result from the use of greater than 1 equivalent of the thiol, preferably from about 1.5 to about 3.0 equivalents.
In the present invention compound of formula (V) is debrominated to form compound of formula (VI) when R4 in formula VI is H in presence of catalyst, Rt---SH (VIII) with an aprotic solvent at appropriate temperature, wherein

R_t---SH

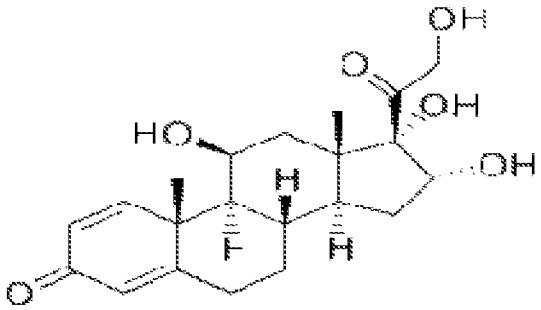
Formula VIII

wherein R_t is $–CH_2COOH$ or $–CH_2CH_2COOH$ preferably R_t is $–CH_2COOH$.

Suitable aprotic solvents include DMF, DMAC, acetone, methylene chloride, THF, acetonitrile, DMSO and mixtures thereof. Alcoholic solvents include methanol, ethanol, isopropanol and butanol. Preferred are DMF and DMSO.

In the present invention, aprotic solvent is selected from the group comprising DMF, DMAC, acetone, methylene chloride, THF, acetonitrile, DMSO and mixtures thereof, preferably DMF and DMSO.

In one embodiment, the compound of formula IV may undergo epoxide ring opening by suitably reacting the compound of Formula IV with a hydrohalic acid selected from the group comprising HF, HCl, HBr etc, preferably HF followed by deacetylation to form the compound of Formula A and optionally purified and utilized for commercial purposes. When on C-16 and C-17 of the compound of formula is "OH", then the compound as (11β, 16α)-9-Fluoro-11, 16, 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione (Formula A), also known as Triamcinolone.



Formula A

In another embodiment of the present invention, the compound of formula (IV) is converted to compound of formula (I) comprising R_1 is $–CH_3$, $R_2$is $-CH_3$, R_3 is $-COCH_3$, R_4 is –F, R_6 is –F by treating with acetone and hydrofluoric acid i.e. Fluocinonide

In yet another embodiment of the present invention, the compound of formula (IV) is converted to compound of formula (I) comprising R_1 is $–CH_3$, R_2 is -CH3, R3 is –H, , R_4 is –F, R_6 is –F by treating with acetone and hydrofluoric acid followed by deacetylation with Methanol and Methylene chloride in the presence of sodium hydroxide i.e. Fluocinolone acetonide

In yet another embodiment of the present invention, the compound of formula (IV) is converted to compound of formula (I) comprising R_1 is $–CH_3$, $R_2$is -CH3, R3 is –H, ,R_4 is –H, R_6 is –F by

treating with acetone and hydrobromic acid followed by sequential step of debromination and deacetylation i.e. Flunisolide.

The compound of formula I may be optionally purified to obtain a pure compound. Such purification may be done by means of crystallization or column chromatography.

ADVANTAGES OF THE PRESENT INVENTION:

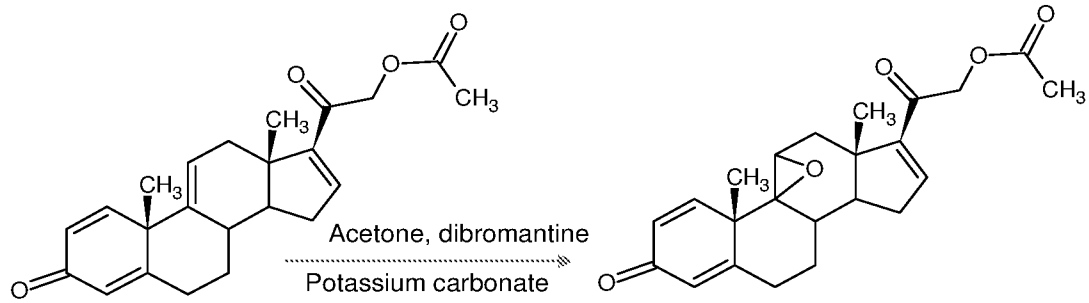
1. The process of the present invention uses commonly available and inexpensive materials.
2. The process is simple and does not involve any toxic materials.
3. The process yields several intermediates that have biological activity and commercial utility.

The invention will now be further illustrated by non limiting examples.

Working Examples:

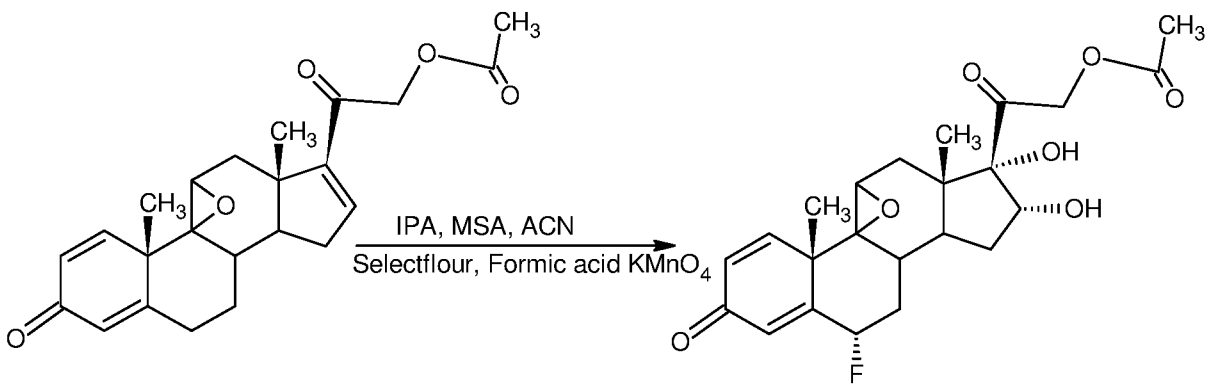
Example-1: Process for preparation of Flunisolide of Formula I from 3TR

Stage-I



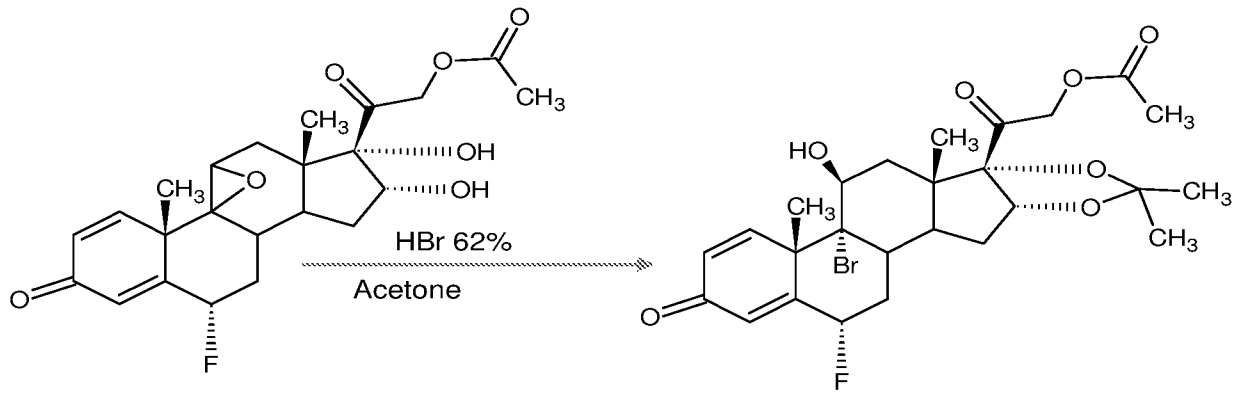
3TR, $C_{23}H_{26}O_4$,366.45 Stage-I, $C_{23}H_{26}O_5$, 382.45

Stage-II



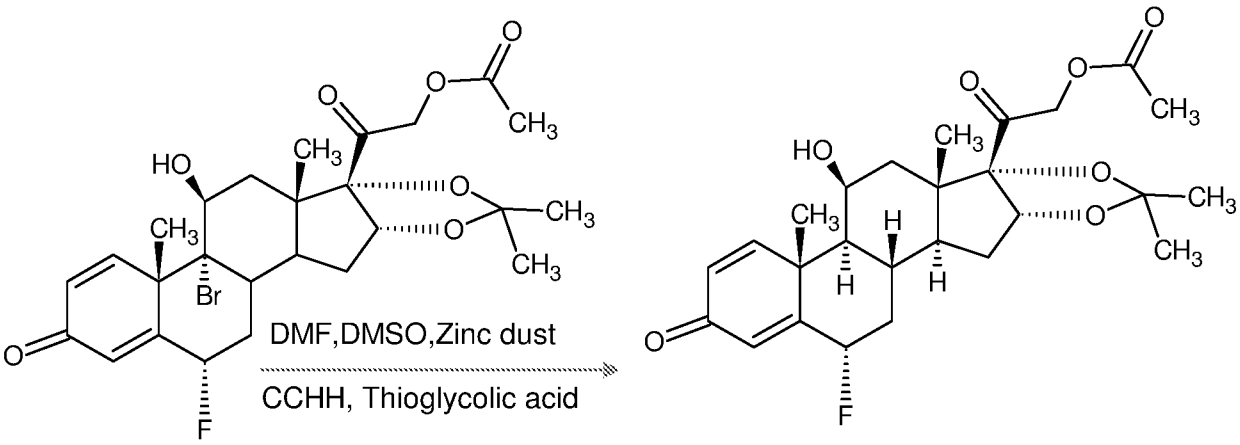
Stage-I , $C_{23}H_{26}O_5$, 382.45 Stage-II, $C_{23}H_{27}FO_7$, 434.45

Stage-III



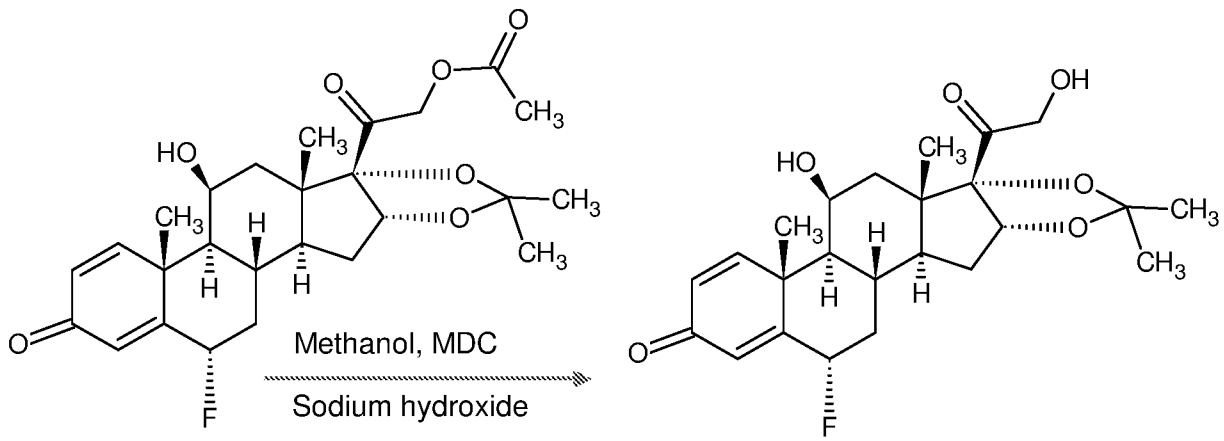
Stage-II, $C_{23}H_{27}FO_7$,434.45 Stage-III, $C_{26}H_{32}BrFO_7$, 555.43

Stage-IV



Stage-III, $C_{26}H_{32}BrFO_7$, 555.43 Stage-IV, $C_{26}H_{33}FO_7$,476.53

Stage-V



Stage-IV, $C_{26}H_{33}FO_7$,476.53 Flunisolide, $C_{24}H_{31}FO_6$,434.498

Scheme 1: Synthesis of Flunisolide from 3TR

Stage-I: (Epoxidation)

Charge 1.30L of acetone (13.0volume), 100gm 0f 3TR (0.27mol) in a glass flask, stir till clear solution, cool to -5°C to -10°C, added 4.0ml of perchloric acid solution (0.044mol) in 650ml purified water (6.5volume) at -5°C to -10°Cand added 50gm of dibromantine (0.18mol) at same temperature. Stir at -5°C to -10°C for 02hours. In-process check by TLC against 3TR, should be absent. Added 100gm of potassium carbonate solution (0.72mol) in 400ml purified water (4.0volume) at -5°C to 0°C, temperature gradually raised up to 35°c±2°C, stir at same temperature for 12hours. In-process check by TLC against inter-step, should be absent. Cool to 0°C to 5°C, added 36ml of acetic acid (0.63mol) to neutralized the pH of reaction mass, distill the solvent till thick mass under reduced pressure further added 3.0L of purified water (30volume) at 0°C to 5°C, maintaining the temperature 10°C±5°C for 02 hours. Filter and washed with purified water. Dry the wet material at 45°C±2°C until the moisture contents less than 0.50%

Output= 100 gm

Yield= 96%

HPLC Purity=97.1%

Stage-II: (Sequential steps of Dihydroxylation and Fluorination)

Charge 801ml of Isopropenyl acetate (9.0volume), 2.67ml of methane sulphonic acid (0.04mol) in a glass flask. Heated to 85°C±5°C, added 89.0gm of stage-I (0.23mol), stir for 03hours at same temperature. In-process check by TLC against stage-I, should be absent. Cool to 25°C±5°C and adjust pH neutral using 4.0ml of tri ethyl amine (0.03mol). Recovery of isopropenyl acetate under vacuum at below 60°C and degassed with 178ml of acetonitrile (02volume). Charge 979ml of acetonitrile (11volume), cool to -5°C to -10°C, added 89.0ml of purified water (1.0volume) at same temperature, added 89gm of select fluor (0.25mol) at -5°C to -10°C, stir for 12hours at same temperature. In-process check by TLC against inter step, should be absent. Added 1.1L of purified water (12.4volume) at same temperature, Adjust pH neutral using liq. Ammonia at 15°C±5°C. Charge 445ml of methylene dichloride (5volume) at same temperature, stir, settle, separate methylene chloride layer, distill till last drop and degassed with acetone. Charge 5.0L of acetone (56.18volume), still till clear solution, cool to -5°C to -10°C, added 40ml of formic acid (1.06mol) and 60gm of potassium permanganate (0.38mol) at same temperature, stir for one hour. In-process check by TLC against interstep,

should be absent, added 10gm of sodium meta bisulphite solution (0.053mol) in 100ml of water (1.0volume) at same temperature, temperature raised up to 15°c and added 30gm of hyflow super cell, further raised the temperature up to 28°C, stir for one hour, filter the reaction mass and washed with 1.0L of acetone (11.2volume). Collect the filtrate in a glass flask and added 10gm of charcoal activated, stir and filter through hyflow bed and washed with 500ml of acetone (5.6volume), collect the total filtrate in a clean glass flask and recover the acetone under vacuum at below 45°C±5°C till reaction volume app. 400ml. Cool to ambient temperature, added 600ml of purified water (6.7volume), cool to 0°C to 5°C, stir for one hour, filter and washed with purified water, wet material dried at 45°C±5°C till moisture contents less than 1.0%

Output=100gm

Yield=98.9%

HPLC Purity=81.35%

Stage-III: (Sequential steps of opening of epoxide ring with hydrohalic acid and acetalisation with aldehyde or ketone)

Charge 25ml of Hydro bromic acid 62% (0.33mol) in a glass flask and cool to -5°C to -10°C, added 5.0gm of stage-II (0.012mol) at same temperature, stir for one hour. In-process check by TLC against stage-II, should be absent. Added 5.0ml of acetone (1.0volume) at -10°C±2°C, stir for one hour. In-process check by TLC against inter step, should be absent. Quenched the reaction mass in 100ml of chilled purified water (20volume) at 0°C to 5°C, stir for 03hours, filter and washed with purified water till neutral pH, wet material dried at 40°C±5°C till moisture content less than 3.0%

Output=5.0gm

Yield =78.3%

HPLC Purity=88.74%

Stage-IV: (Debromination)

Charge 4.1ml of N, N-dimethyl form amide (0.82volume) in a glass flask under argon gas bubbling, added 3.0ml of N, N-dimethyl sulphoxide (0.60volume), 0.5gm of chromium chloride hexahydrate (0.002mol), 0.58gm of zinc dust (0.009mol) at ambient temperature. Cool to -7°C to-10°C, added 1.91ml of thioglycolic acid (0.027mol) at same temperature and added 5gm of stage-III (0.009mol) solution in 25ml of N, N-dimethyl form amide (5volume) at same

temperature, stir for 02hours. In-process check by TLC against stage-III, should be absent. Reaction mass quenched in 200ml of purified water (40volume), stir for one hour at 10°C±2°C, filtered and washed with purified water, wet material dried at 40°C±5°C till moisture content less than 3.0%

Output=3.6gm

Yield=83.9%

HPLC Purity= 80.5%

Stage-V: (Deacetylation)

Charge 30ml of methanol (10volume), 30ml of methylene chloride (10volume) in a glass flask under argon gas bubbling, added 3.0gm of stage-IV (0.0063mol), cool to -5°C±2°C, added 0.06gm of sodium hydroxide (0.0015mol) solution in 3.0ml of methanol (1.0volume) at -5°C±2°C, stir for 02hours at same temperature. In-process check by TLC against stage-III, should be absent. Adjust pH neutral using 0.09ml of acetic acid (0.0016mol), distilled the methanol and methylene chloride mixture under vacuum at below 40°C till thick mass, cool to ambient temperature and added 9.0ml of purified water (03volume), cool to 0°C to 5°C and stir for one hour, filter and washed with purified water, wet material dried at 45°C±5°C till loss on drying less than 1.0%

Output=2.40gm

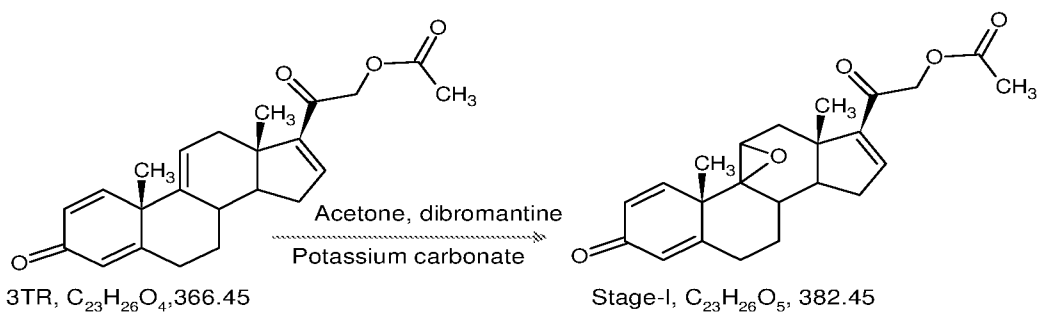
Yield=87.60%

HPLC Purity= 98.4

Specific rotation: +104.78°

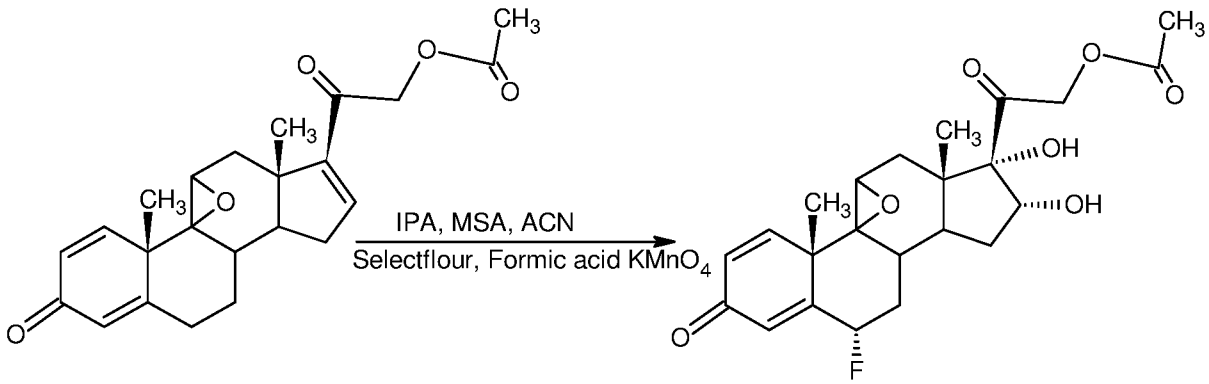
Example - 2: Process for preparation of Fluocinolone acetonide of Formula I from 3TR

Stage-I



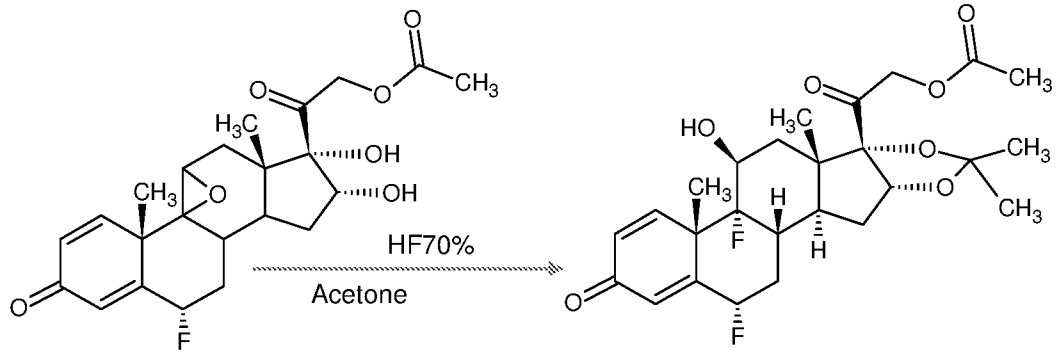
3TR, $C_{23}H_{26}O_4$,366.45 Stage-I, $C_{23}H_{26}O_5$, 382.45

Stage-II



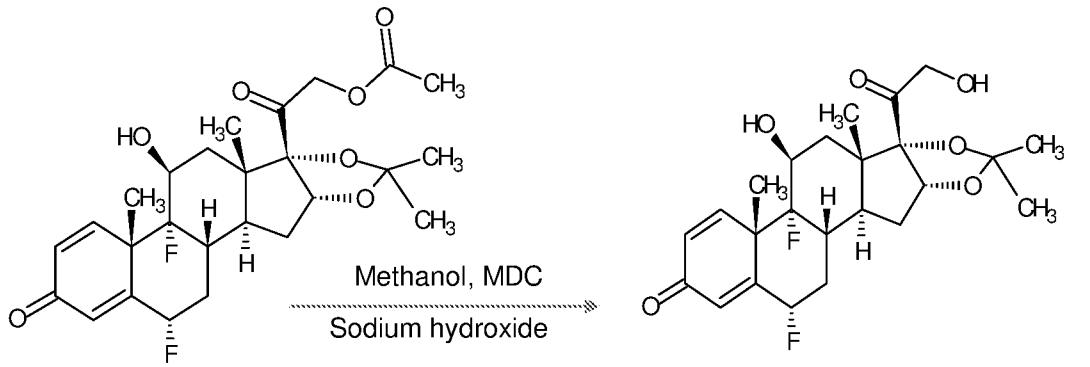
Stage-I , $C_{23}H_{26}O_5$, 382.45 Stage-II, $C_{23}H_{27}FO_7$, 434.45

Stage-III



Stage-II,$C_{23}H_{27}FO_7$,434.45 Stage-III,$C_{26}H_{32}F_2O_7$,494.53

Stage-IV



Stage-III,$C_{26}H_{32}F_2O_7$,494.53 Fluocinolone acetonide, $C_{24}H_{30}F_2O_6$, 452.49

Scheme 2: Synthesis of Fluocinolone acetonide from 3TR

Stage-I: (Epoxidation)

Charge 130ml of acetone (13.0volume), 10gm 0f 3TR (0.027mol) in a glass flask, stir till clear solution, cool to -5°C to -10°C, added 0.4ml of perchloric acid (0.0044mol) solution in 65ml of

purified water (6.5volume) at -5°C to -10°Cand added 5.0gm of dibromantine (0.018mol) at same temperature. Stir at -5°C to -10°C for 02hours. In-process check by TLC against 3TR, should be absent. Added 10gm of potassium carbonate (0.072mol) solution in 40ml of purified water (4.0vlume) at -5°C to 0°C, temperature gradually raised up to 35°C±2°C, stir at same temperature for 12hours. In-process check by TLC against inter-step, should be absent. Cool to 0°C to 5°C, added 3.6ml of acetic acid (0.063mol) to neutralized the pH of reaction mass, distill the solvent till thick mass under reduced pressure further added 0.30L of purified water(30volume) at 0°C to 5°C, maintaining the temperature 10°C±5°C for 02hours. Filter and washed with purified water. Dry the wet material at 45°C±2°C until the moisture contents less than o.50%

Output=10 gm

Yield= 96 %

HPLC Purity=97.0%

Stage-II: (Sequential steps of Fluorination and Dihydroxylation)

Charge 81ml of Isopropenyl acetate (9.0volume), 0.27ml of methane sulphonic acid (0.004mol) in a glass flask. Heated to 85°C±5°C, added 9.0gm of stage-I (0.024mol), stir for 03hours at same temperature. In-process check by TLC against stage-I, should be absent. Cool to 25°C±5°C and adjust pH neutral using 0.40ml of triethyl amine (0.0029mol). Recovery of isopropenyl acetate under vacuum at below 60°C and degassed with 18ml of acetonitrile (02volume). Charge 100ml of acetonitrile (11.1volume), cool to -5°C to -10°C, added 9.0ml of purified water (1.0volume) at same temperature, added 9gm of selectfluor (0.025mol) at -5°C to -10°C, stir for 12 hours at same temperature. In-process check by TLC against inter step, should be absent. Added 110ml of purified water (12.2volume) at same temperature, Adjust pH neutral using liq. Ammonia at 15°C±5°C. Charge 45ml of methylene dichloride (5volume) at same temperature, stir, settle, separate methylene chloride layer, distill till last drop and degassed with acetone. Charge 500ml of acetone (56.18volume), still till clear solution, cool to -5°C to -10°C, added 4.0ml of formic acid (1.06mol) and 6.0gm of potassium permanganate (0.38mol) at same temperature, stir for one hour. In-process check by TLC against inter step, should be absent, added 1.0gm of sodium metabisulphite (0.0053mol) solution in 10ml of water at same temperature, temperature raised up to 15°C and added 3.0gm of hyflow super cell, further raised the temperature up to 28°C, stir for one hour, filter the reaction mass and washed with 100ml of acetone (11.1volume). Collect the filtrate in a glass flask and added

1.0gm of charcoal activated, stir and filter through hyflow bed and washed with 50ml of acetone (5.6volume), collect the total filtrate in a clean glass flask and recover the acetone under vacuum at below 45°C±5°C till reaction volume app. 40ml. Cool to ambient temperature, added 60ml of purified water (6.7volume), cool to 0°C to 5°C, stir for one hour, filter and washed with purified water, wet material dried at 45°C±5°C till moisture contents less than 1.0%

Output=9.2gm

Yield=80.96%

HPLC Purity=81.0%

Stage-III: (Sequential steps of opening of epoxide ring with hydrohalic acid and acetalisation with aldehyde or ketone)

Charge 36.8ml of Hydrofluoric acid 70% (1.52mol) in a HDPE reactor and cool to -25°C to -30°C, added 9.2gm of stage-II (0.021mol) at -25°C to -30°C, stir for 04hours. In-process check by TLC against stage-II, should be absent. Cool to -45°C to -50°C and added 5.52ml of acetone (0.076mol) at same temperature, stir for 02hours. In-process check by TLC against inter step, should be absent. Added 18.4ml of purified water (02volume) up to 0°C adjust pH neutral using 147.2ml of liq. Ammonia (16.0volume) at 0°C to 5°C stir and filter and washed with purified water, wet material dried at 45°C to 50°C till moisture content less than 1.0%

Output=8.20gm

Yield=78.32%

HPLC Purity=80.0%

Purification:

Charge 80ml of methylene chloride (9.8volume), 80ml of methanol (9.8volume) in a glass flask, added 8.0gm of stage-III (0.016mol) and stir till clear solution, added 0.8gm of charcoal activated, stir for 30min.,filter through hyflow bed and washed with 8.0ml of methanol and 8.0ml of methylene chloride mixture, collect the filtrate in a glass flask and distilled to attained the temperature up to 60°C, apply vacuum and distilled till thick mass, cool to 0°C to 5°C, stir for 0ne hour, filter and washed with 8.0ml of chilled methanol, wet material dried at 45°C±5°C till moisture content less than 1.0%

Output=7.20gm

HPLC Purity=87.0%

Stage-IV: (Deacetylation)

Charge 70ml of methanol (10volume), 70ml of methylene chloride (10volume) in a glass flask under argon gas bubbling, added 7.0gm of stage-III (0.014mol), cool to -5°C±2°C, added 0.14gm of sodium hydroxide (0.0035mol) solution in 7.0ml of methanol at -5°C±2°C, stir for 02hours at same temperature. In-process check by TLC against stage-III, should be absent. Adjust pH neutral using 0.21ml of acetic acid (0.0037mol), distilled the methanol and methylene chloride mixture under vacuum at below 40°C till thick mass, cool to ambient temperature and added 10.5ml of purified water (1.5volume), cool to 0°C to 5°C and stir for one hour, filter and washed with purified water, wet material dried at 45°C±5°C till moisture content less than 1.0%

Output=3.25gm

Yield=50.78%

HPLC Purity=90.0%

Stage-V: (purification)

Charge 30ml of methylene chloride (10volume), 30ml of methanol (10volume) in a glass flask, added 3.0gm of stage-IV (0.0066mol) and stir till clear solution, added 0.3gm of charcoal activated, stir for 30min.,filter through hyflow bed and washed with 3.0ml of methanol and 3.0ml of methylene chloride mixture, collect the filtrate in a glass flask and distilled to attained the temperature up to 60°C, apply vacuum and distilled till thick mass, cool to 0°C to 5°C, stir for one hour, filter and washed with 3.0ml of chilled methanol, wet material dried at 45°C±5°C till loss on drying less than 1.0%

Output=1.20gm

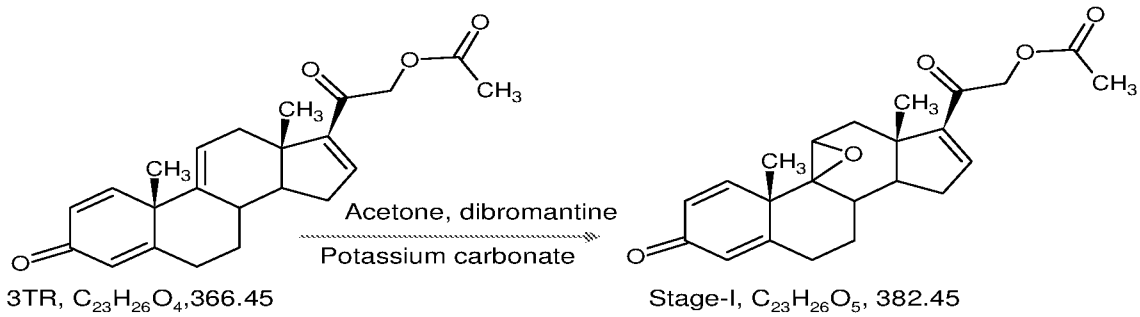
HPLC Purity=88.7 %

Specific rotation: +108.51°

Further purification required to achieve purity of >98% with desired solvent.

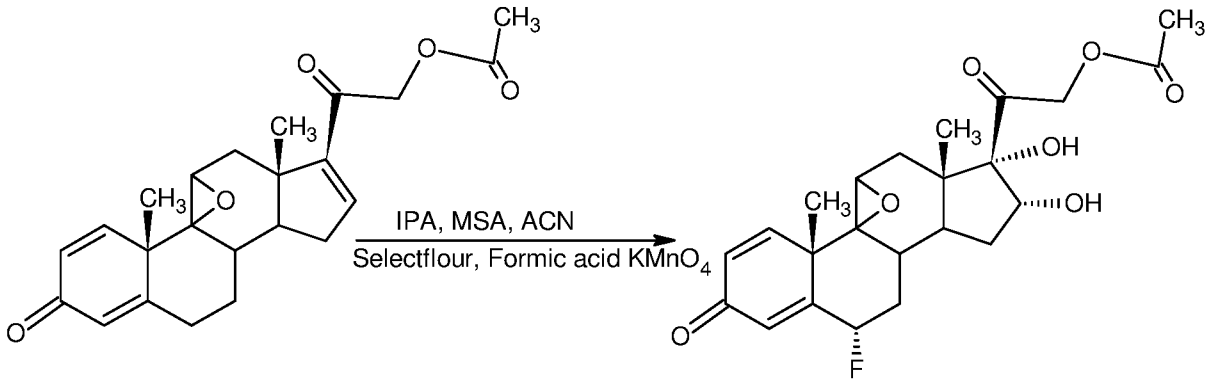
Example-3: Process for preparation of Fluocinonide of Formula A from 3TR

Stage-I



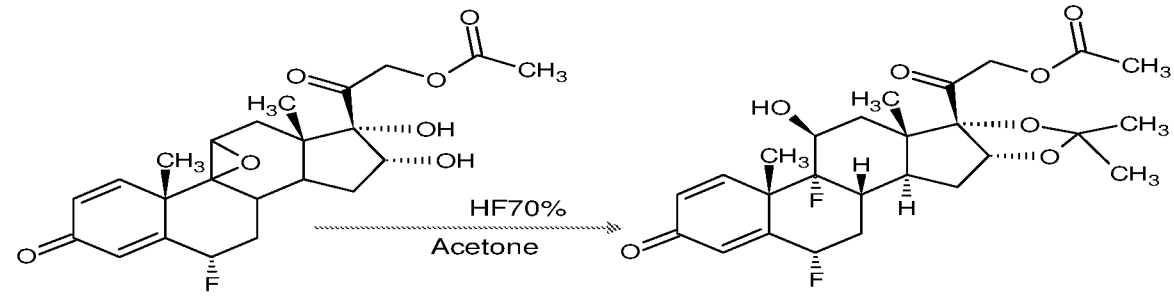
3TR, $C_{23}H_{26}O_4$,366.45 Stage-I, $C_{23}H_{26}O_5$, 382.45

Stage-II



Stage-I , $C_{23}H_{26}O_5$, 382.45 Stage-II, $C_{23}H_{27}FO_7$, 434.45

Stage-III



Stage-II,$C_{23}H_{27}FO_7$,434.45 Fluocinonide,$C_{26}H_{32}F_2O_7$,494.53

Scheme 3: Synthesis of Fluocinonide from 3TR

Stage-I: (Epoxidation)

Charge 130ml of acetone (13.0volume), 10gm 0f 3TR (0.027mol) in a glass flask, stir till clear solution, cool to -5°C to -10°C, added 0.4ml of perchloric acid (0.0044mol)solution in 65ml purified water (6.5volume) at -5°C to -10°C and added 5.0gm of dibromantine (0.018mol) at same temperature. Stir at -5°C to -10°C for 02 hours. In-process check by TLC against 3TR,

should be absent. Added 10gm of potassium carbonate (0.072mol) solution in 40ml purified water (4.0volume) at -5°C to 0°C, temperature gradually raised up to 35°C±2°C, stir at same temperature for 12hours. In-process check by TLC against inter-step, should be absent. Cool to 0°C to 5°C, added 3.6ml of acetic acid (0.063mol) to neutralized the pH of reaction mass, distill the solvent till thick mass under reduced pressure further added 0.30L of purified water (30volume) at 0°C to 5°C, maintaining the temperature 10°C±5°C for 02hours. Filter and washed with purified water. Dry the wet material at 45°C±2°C until the moisture contents less than 0.50%

Output=10 gm

Yield=96 %

HPLC Purity=97.0%

Stage-II: ((Sequential steps of Fluorination and Dihydroxylation)

Charge 81ml of Isopropenyl acetate (9.0volume), 0.27ml of methane sulphonic acid (0.004mol) in a glass flask. Heated to 85°C±5°C, added 9.0gm of stage-I (0.024mol), stir for 03hours at same temperature. In-process check by TLC against stage-I, should be absent. Cool to 25°C±5°C and adjust pH neutral using 0.40ml of tri ethyl amine (0.003mol). Recovery of isopropenyl acetate under vacuum at below 60°C and degassed with 18ml of acetonitrile (02volume). Charge 100ml of acetonitrile (11.0volume), cool to -5°C to -10°C, added 9.0ml of purified water (1.0volume)at same temperature, added 9gm of selectfluor (0.025mol) at -5°C to -10°C, stir for 12hours at same temperature. In-process check by TLC against inter step, should be absent. Added 110ml of purified water (12.2volume) at same temperature, Adjust pH neutral using liq. Ammonia at 15°C±5°C. Charge 45ml of methylene dichloride (5volume) at same temperature, stir, settle, separate methylene chloride layer, distill till last drop and degassed with acetone. Charge 500ml of acetone (56.18volume), still till clear solution, cool to -5°C to -10°C, added 4.0ml of formic acid (1.06mol) and 6.0gm of potassium permanganate (0.38mol) at same temperature, stir for one hour. In-process check by TLC against inter step, should be absent, added 1.0gm of sodium meta bisulphite (0.0053mol) solution in 10ml of water(1.1volume) at same temperature, temperature raised up to 15°C and added 3.0gm of hyflow super cell, further raised the temperature up to 28°C, stir for one hour, filter the reaction mass and washed with 100ml of acetone (11.1volume). Collect the filtrate in a glass flask and added 1.0gm of charcoal activated, stir and filter through hyflow bed and washed with 50ml of acetone (5.6volume), collect the total filtrate in a clean glass flask and recover the acetone

under vacuum at below 45°C±5°C till reaction volume app. 40ml. Cool to ambient temperature, added 60ml of purified water (6.7volume), cool to 0°C to 5°C, stir for one hour, filter and washed with purified water, wet material dried at 45°C±5°C till moisture contents less than 1.0%

Output=8.2gm

Yield=80.24%

HPLC Purity=81%

Stage-III (Sequential steps of opening of epoxide ring with hydrohalic acid and acetalisation with aldehyde or ketone)

Charge 32.0ml of Hydrofluoric acid 70% (1.32mol) in a HDPE reactor and cool to -25°C to -30°C, added 8.0gm of stage-II (0.018mol) at -25°C to -30°C, stir for 04hours. In-process check by TLC against stage-II should be absent. Cool to -45°C to -50°C and added 4.8ml of acetone (0.066mol) at same temperature, stir for 02hours. In-process check by TLC against inter step, should be absent. Added 12.0ml of purified water (1.5volume) up to 0°C adjust pH neutral using 128.0ml of liq. Ammonia (16volume) at 0°C to 5°C stir and filter and washed with purified water, wet material dried at 45°C to 50°C till moisture content less than 1.0%

Output=3.52gm

Yield=38.68%

HPLC Purity=80%

Purification:

Charge 30ml of methylene chloride (10volume), 30ml of methanol (10volume)in a glass flask, added 3.0gm of stage-III (0.006mol) and stir till clear solution, added 0.3gm of charcoal activated, stir for 30min.,filter through hyflow bed and washed with 3.0ml of methanol and 3.0ml of methylene chloride mixture, collect the filtrate in a glass flask and distilled to attained the temperature up to 60°C, apply vacuum and distilled till thick mass, cool to 0°C to 5°C, stir for 0ne hour, filter and washed with 3.0ml of chilled methanol, wet material dried at 45°C±5°C till loss on drying less than 1.0%

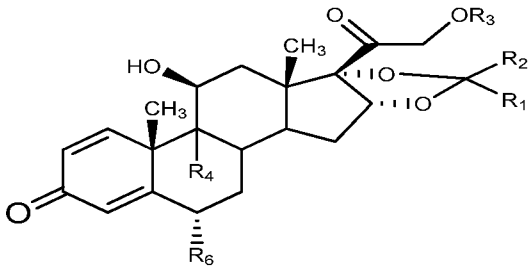
Output=1.50gm

HPLC Purity=96%

Specific rotation: +86.96°

We claim

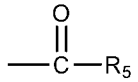
1. A novel process for the preparation of pregnadiene derivatives of formula I, their stereoisomer and intermediate thereof.



Formula I

wherein

R_1 and R_2 is independently hydrogen or C1 –C8 straight, branched alkyl chain, saturated or unsaturated cycloalkyl;

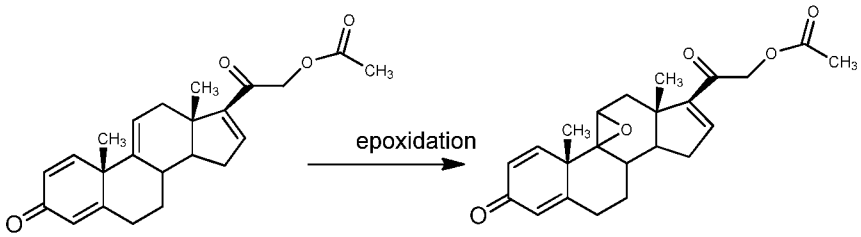
R_3 is hydrogen or  ;

R_5 represents C1-C8 straight, branched alkyl chain or cycloalkyl;

R_4 and R_6 is independently hydrogen or halogen;

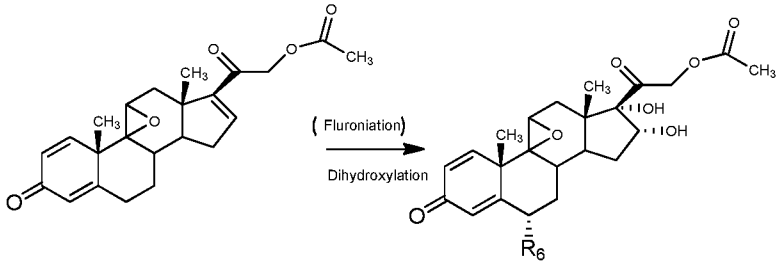
comprising the steps of:

i. epoxidation of compound of formula II to obtain 9,11-oxido derivative of compound of formula III;



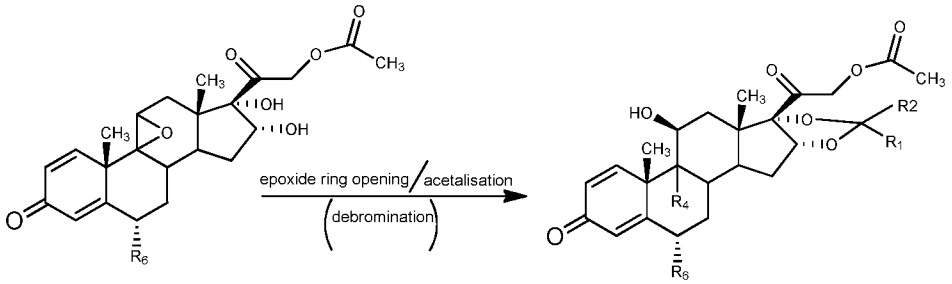
Formula II Formula III

ii. dihydroxylation and optional fluorination of compound of formula III to obtain compound of formula IV with a proviso when R_6 is F.



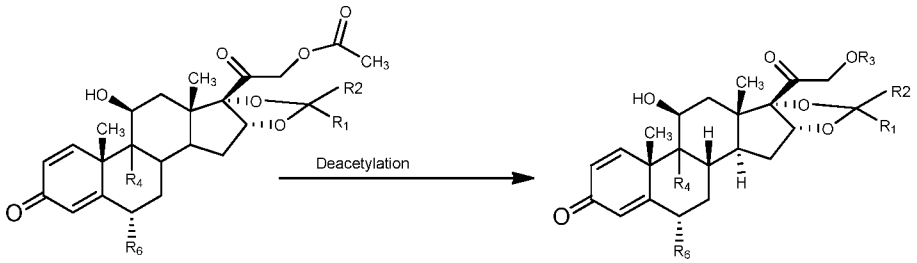
Formula III Formula IV

iii. epoxide ring opening of compound of formula IV followed by acetalisation to obtain compound of formula V and optionally, debromination of compound of formula V with a proviso R_4 is Br to obtain compound of formula V when R4 is H



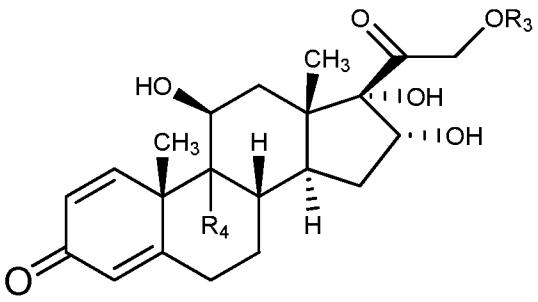
Formula IV Formula V

iv. deacetylation of compound of Formula V to obtain compound of formula I



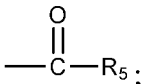
Formula V Formula I

2. A process for preparation of pregnadiene derivatives of Formula A



Formula A

wherein

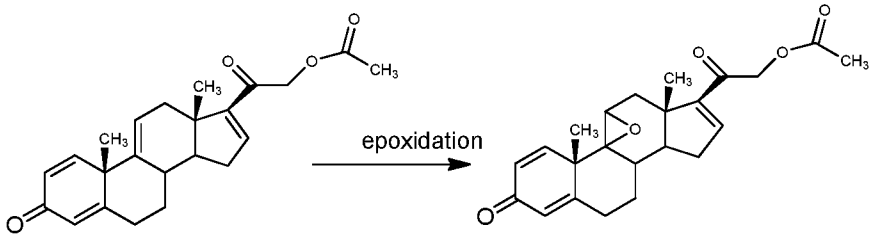
R_3 is hydrogen or  ;

R_5 represents C1-C8 straight, branched alkyl chain or cycloalkyl;

R_4 is halogen;

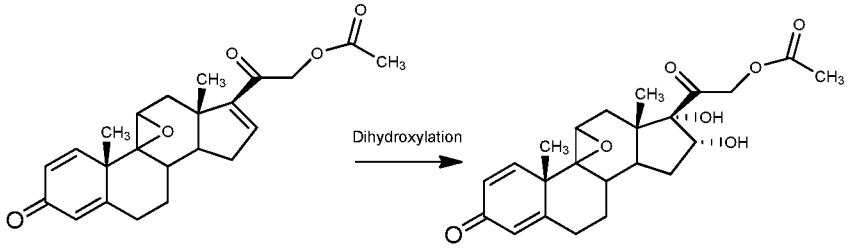
comprising the steps of:

i. epoxidation of compound of formula II to obtain 9,11-oxido derivative of compound of formula III;



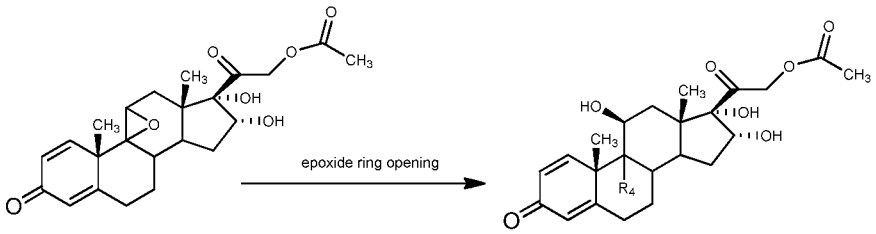
Formula II Formula III

ii. dihydroxylation of compound of formula III to obtain compound of formula IV



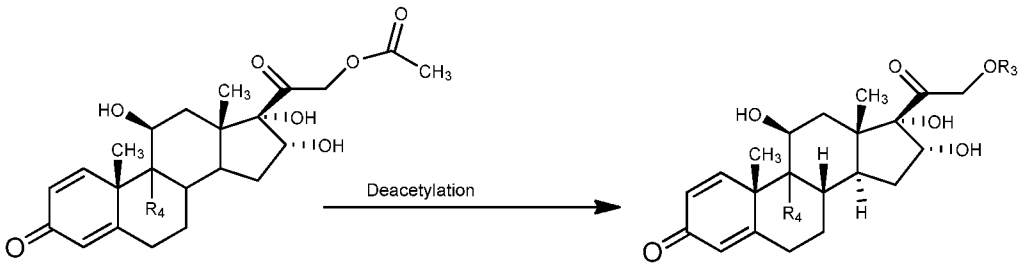
Formula III Formula IV

iii. epoxide ring opening of compound of formula IV followed by acetalisation to obtain compound of formula V



Formula IV Formula VII

iv. deacetylation of compound of Formula V to obtain compound of formula I



Formula VII Formula VII

3. The process as claimed in claim 1, wherein the compound of Formula (1) is
    i. (1S,2S,4R,8S,9S,11S,12R,13S,19S)-12,19-difluoro-11-hydroxy-8-(2-hydroxyacetyl)-6,6,9,13-tetramethyl-5,7-dioxapentacyclo[10.8.0.02,9.04,8.013,18]icosa-14,17-dien-16-one;
    ii. 6α,9-difluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione, cyclic 16,17-acetal with acetone,21-acetate;
    iii. 1S,2S,4R,8S,9S,11S,12S,13R,19S)-19-fluoro-11-hydroxy-8-(2-hydroxyacetyl)-6,6,9,13-tetramethyl-5,7-dioxapentacyclo[10.8.0.02,9.04,8.013,18]icosa-14,17-dien-16- one;
    iv. ((16,17-(butylidenebis(oxy))-11,21-dihydroxy-, (11-β,16-α)-pregna-1,4-diene-3,20-dione
    v. 2-[(1S,2S,4R,8S,9S,11S,12S,13R)-6-cyclohexyl-11-hydroxy-9, 13-dimethyl-16-oxo-5, 7-dioxapentacyclo [10.8.0.02,9.04, 8.013,18] icosa-14, 17-dien-8-yl]- 2-oxoethyl 2-methylpropanoate.
    vi. (1S,2S,4R,8S,9S,11S,12S,13R)-11-hydroxy-8-(2-hydroxyacetyl)-6,6,9,13-tetramethyl-5,7-dioxapentacyclo[10.8.0.02,9.04,8.013,18]icosa-14,17-dien-16-one
    vii. (4aS,4bR,5S,6aS,6bS,9aR,10aS,10bS)-4b-fluoro-6b-glycoloyl-5-hydroxy-4a,6a,8,8-tetramethyl-4a,4b,5,6,6a,6b,9a,10,10a,10b,11,12-dodecahydro-2H-naphtho[2',1':4,5]indeno[1,2-d][1,3]dioxol-2-one
    viii. 2-[(1S,2S,4R,8S,9S,11S,12R,13S)-12'-fluoro-11'-hydroxy-9',13'-dimethyl-16'-oxo-5',7'-dioxaspiro[cyclopentane-1,6' pentacyclo[10.8.0.02,9.04,8.013,18]icosane]-14',17'-dien-8'-yl]-2-oxoethyl acetate;
    ix. (11β,16α)-9-Fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione;
    x. (11β,16α)-21-(3,3-Dimethyl-1-oxobutoxy)-9-fluoro-11-hydroxy-16,17-((1-methylethylidene)bis(oxy))pregna-1,4-diene-3,20-dione

4. The process as claimed in claim 1, wherein the epoxidation is carried out with epoxidizing agents selected from the group comprising dibromantin, N-bromoacetaminde or N-bromosuccinimide with Perchloric acid and an alkali selected from the group comprising sodium or potassium hydroxide or their carbonates or acetate, preferably potassium carbonate.

5. The process as claimed in claim 1, wherein the fluorination is carried out with fluorinating agent selected from the group comprising N-fluoro-benzene sulfonamide, N-fluoro-N chloromethyltrimethylene diamine bistetrafluoroborate, Selectfluor®, 1-fluoropyridinium triflate, 1-fluoropyridinium tetrafluoroborate, or 1-fluoropyridinium pyridine heptafluorodiborateetc, preferably Selectfluor® and the solvent selected from the group comprising acetonitrile, isopropenyl acetate, dichloromethane, dimethyl formamide, diethyl ether, and tetrahydrofuran, preferably isopropenylacetate.

6. The process as claimed in claim 1, wherein the dihydroxylation is carried out with an oxidizing agent selected from the group comprising potassium permanganate, potassium dichromate, chromic acid, peroxyacids or mixtures thereof, preferably potassium permanganate, formic acid.

7. The process as claimed in claim 1, wherein the epoxide ring opening is carried out in the presence of a hydrohalic acid selected from the group comprising HF, HCl, HBr etc, preferably HF and acetalisation is carried out with aldehyde or ketone selected from the group comprising formaldehyde, paraldehyde, acetone, benzaldehyde, acetophenone, diethylketone, cyclohexane corboxaldehyde sodium metabisulphite complex, cyclopentanone preferably acetone.

8. The process as claimed in claim 1, wherein the deacetylation is carried out with reagents selected from group comprising sodium hydroxide, potassium hydroxide etc. and solvent selected from methanol, methylene chloride, water or their combination thereof.

9. The process as claimed in claim 1, wherein the debromination is carried out presence in of a catalyst selected from the group comprising chromous or chromium sulfate, chromous or chromium chloride or its hydrate, preferably chromium chloride hexahydrate, a thiol compound of the formula Rt–SH (Formula VIII) wherein Rt is –CH2COOH or –CH2CH2COOH, preferably thioglycolic (thiovanic) acid wherein Rt is -CH2COOH and an aprotic solvent selected from the group comprising DMF, DMAC, acetone, methylene chloride, THF, acetonitrile, DMSO and mixtures thereof and alcoholic solvents selected from the group selected from methanol, ethanol, isopropanol and butanol, preferably DMF and DMSO.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/050347

A. CLASSIFICATION OF SUBJECT MATTER
C07J5/00,C07J75/00 Version=2017.01

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)

C07J

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)

STN, Patseer, IPO internal database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2016120891, CORAL DRUGS PVT. LTD.; 04-08-2016 (04 AUG 2016). Whole document	1,2,3(part) and 4-9.

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09-11-2017	09-11-2017
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Arun Kumar Yelshetty Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/050347

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 3 (part)
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of process of preparation of compounds which are claimed in claim 3 (part-compound iv to compound x) is not described in the complete specification. Hence the International Searching Authority is not required to search the aforesaid subject matter under Article 17(2)(a)(i) and [Rule 39.1(v)].

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.