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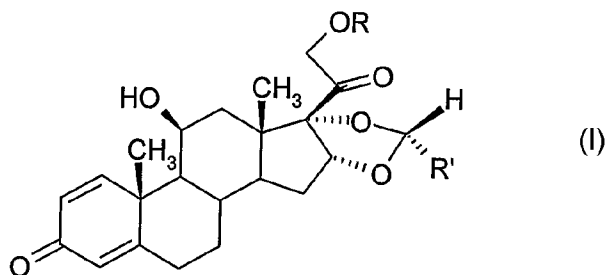
(43) International Publication Date
18 May 2007 (18.05.2007)

PCT

(10) International Publication Number
WO 2007/054974 A2

- (51) International Patent Classification: **Not classified**
- (21) International Application Number:
PCT/IN2006/000399
- (22) International Filing Date:
28 September 2006 (28.09.2006)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
1210/MUM/2005
28 September 2005 (28.09.2005) IN
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Declarations under Rule 4.17:**
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 - as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
 - of inventorship (Rule 4.17(iv))
- Published:**
- without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A GREEN CHEMISTRY PROCESS FOR THE PREPARATION OF PREGNADIENE ESTERS



(57) Abstract: A process for the preparation of Pregna-1, 4-diene - 3,20-dione-16,17-acetal-21 esters of Formula (I) by a green process chemistry using a combination of an ionic liquid, organic solvent optionally in the presence of an inorganic nitrite. Formula I, wherein R and R' represent a) R= H, R'-cyclohexyl or b) R=CO-CH (CH₃)₂, R'=cyclohexyl or c) R=H, R'=CH₂-CH₂-CH₃.

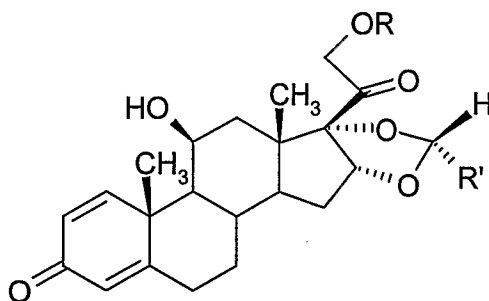
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A Green Chemistry Process For The Preparation Of Pregnadiene Esters

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of Pregna-1,4-diene 3,20-dione-16,17-acetal-21 esters of Formula (I).

5



Formula I

Wherein R and R' represent

- a) R= H, R'-cyclohexyl or
- 10 b) R=CO-CH (CH₃)₂, R'=cyclohexyl or
- c) R=H, R'=CH₂-CH₂-CH₃

in predominantly epimerically pure form over the other form. The present invention particularly relates to the use of non-hazardous green solvent system.

15

BACKGROUND OF THE INVENTION

Pregna-1,4-diene-3,20-dione-16,17-acetal-21 esters of Formula (I) are inhaled corticosteroids which are currently the most effective agents used to treat chronic asthma. They have novel release and distribution properties resulting in lung-targeted anti-inflammatory effects. Inhaled corticosteroids, considered to be the foundation of asthma treatment, work by reducing inflammation in the lungs and airways.

EP Patent 0164636 describes a process for the preparation of 16, 17-acetals of pregnane derivatives involving transketalisation of desonides. Here desonides are converted to acetals in the presence of aldehyde and hydrofluoric

25

acid or hydrochloric acid in aqueous medium. Use of hydrofluoric acid is carried out at the temperature of 0°C to -30°C. But hydrofluoric acid is highly corrosive and known to cause etching of the glass and therefore its use on industrial scale is not safe.

5 16,17-[(cyclohexylmethylene) bis (oxy)]-11,21-dihydroxy pregnadiene-3,20-dione [11 β , 16 α (R)] and processes for the preparation of the same are disclosed in US Patent 5482934. Here 16,17-[(cyclohexylmethylene) bis (oxy)]-11,21-dihydroxy pregnadiene- 3,20-dione [11 β , 16 α (R)] is prepared by the hydrolysis ketalisation with suitable adequate catalyst. The triester derivative
10 undergoes selective hydrolysis at C16 & C17 without affecting ester group at C21.

US patent 4,835,145 describes the reaction of desonide and butyraldehyde using 70% hydrofluoric acid at -5°C. The reaction mixture is stirred at 0°C for 1hr and then poured into demineralized water at 0°C. The precipitate is filtered and
15 washed with water followed by drying under vacuum, which results into budesonide chemically known as [11 β , 16 α] 1-16,17-[(butylidene) bis (oxy)]-11,21-dihydroxy pregnadiene-3, 20-dione.

The process for the preparation of compounds of Formula (I) disclosed in US Patent 5482934 comprises following steps:

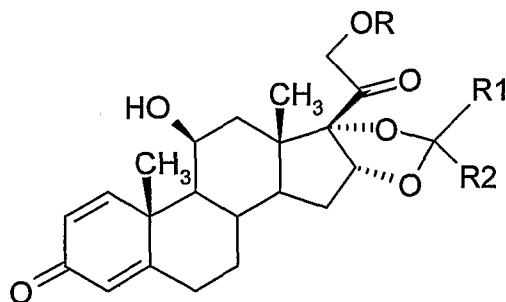
- 20 (i) Anhydrous dioxane is placed in a reactor provided with mechanical agitation and an addition funnel, and pregna-1, 4-diene-3,20-dione, 16,17,21-tris- (2-methyl-1-oxo-propoxy)-11-hydroxy (11 β , 16 α .) and of cyclohexanecarboxaldehyde (4.3g , 0.038 mol) are dissolved in it; subsequently the mixture is stirred for 30 minutes.
- 25 (ii) To the mixture of Step (i), dioxane HCl (45 ml) containing 13% HCl gas are added slowly, and finally, 70% perchloric acid in glacial acetic acid (taking on a reddish color) is added drop wise and then reaction mixture is kept under agitation for 190 hours and then heated to 40°C for 12 hours.
- 30 (iii) To the mixture of Step (ii), methylene chloride is added; the mixture is treated with 5% K₂CO₃ in aqueous solution, with vigorous agitation in a

separatory funnel, and the organic mixture is washed three times with water (80 ml, each time).

- (iv) Once decanted, the organic phase is kept over anhydrous MgSO_4 for drying, and is concentrated to dryness on a rotary evaporator; an oil remains, which upon treatment with methylene chloride and petroleum ether (40/60 fraction) yields the crude product.
- (v) Crude is purified either by recrystallization in ether/petroleum ether or by passing through a column with Sephadex LH-20 as the stationary phase and ethanol-free chloroform as the mobile phase.
- (vi) The final product obtained has a purity of 98.5-99% with an epimer proportion of 45/55% to 50/50%.

US Patent 5482934 also exemplified the use of para toluenesulfonic acid as catalyst in place of 70% perchloric acid.

- US Patent Application 20050080063A1 (WO 02/38584/ DE 41 29535) discloses a process for the preparation of compound of Formula (I) in which 16-hydroxyprednisolone ketal of Formula (II) is suspended in 1-nitropropane and treated slowly under ice-cooling with 70% strength perchloric acid and cyclohexanecarboxaldehyde. The reaction mixture is stirred overnight at room temperature and filtered. The filtered cake is dissolved in DMF (90 ml) and the solution is added drop wise with stirring to sodium hydrogen carbonate solution. The precipitate is filtered off with suction, washed with water and dried. 19 g of the title compound having an R-/S-epimer ratio of 97.8/2.2 are obtained.



Formula II

Wherein R, R1 and R2 represent

- a) (R = H, R1 = CH₃, R2 = CH₃) or
- b) (R = CO-CH (CH₃)₂, R1 = CH₃, R2 = CH₃)

US patent 5733901 (WO 94/22899) describes the process for the preparation
5 of compound of Formula (I), which comprises following steps:

- (i) 16-hydroxyprednisolone is suspended in nitromethane (5 ml) and treated with 70% perchloric acid and cyclohexanecarboxaldehyde.
- (ii) After stirring at room temperature for 4.5 hours (epimer ratio in the reaction mixture R/S=55:45, HPLC content 95%), the reaction mixture
10 is treated with sodium hydrogen carbonate solution, and the precipitate is filtered off using suction, washed with water and dried at 50°C under high vacuum. Yield: 440 mg (70%), epimer ratio R: S=57:43 (determined by means of HPLC, stationary phase ODS Hypersil, mobile phase water/ethanol=60:40).

15 US patent 5733901 (WO 94/22899) discloses the process for the preparation of R isomer, which comprises following steps:

- (i) 16-hydroxyprednisolone is suspended in nitromethane at room temperature and treated with methanesulfonic acid and cyclohexanecarboxaldehyde.
- (ii) The solution is stirred at 40°C for 3 hours and diluted with methylene chloride after cooling.
- (iii) The reaction mixture is extracted with sodium hydrogen carbonate solution and water, and the organic phase is dried using sodium sulfate and concentrated in vacuum. The residue is chromatographed. Yield:
20 1.7 g (68%), epimer ratio R: S=85:15.

US patent 5733901 (WO 94/22899) further discloses the process for the preparation of S-isomer in which 16-hydroxyprednisolone is suspended in

dioxane and treated with cyclohexanecarboxaldehyde while cooling in an ice bath, and 15 ml of 14.8% strength hydrogen chloride gas/dioxane solution are added drop wise in the course of 20 minutes. After stirring at 0°C and at room temperature for 2 hours, the mixture is added to sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic phase is washed with water, dried using sodium sulfate and concentrated in vacuum. The residue is chromatographed. Yield: 620 mg (25%), epimer ratio R: S=25:75.

US patent 5733901 (WO 94/22899) employs the use of solvents such as Dioxane, Diisopropyl ether, Ethyl acetate, Dichloromethane, chloroform, nitroalkanes for e.g. Nitromethane.

DE Patent 10055820 describes the process for the preparation of compound of Formula (I) which comprises reaction of compound of formula (II) (where R = H or isobutyryl [CO-CH-(CH₃)₂]), with cyclohexanecarboxaldehyde in nitropropane containing 70% perchloric acid to yield the compound of Formula (I) where R = H.

The processes disclosed in the prior art have the following disadvantages:

1. Nitroalkanes especially nitromethane has a flash point of 44°C which some times is observed as ambient temperature in some regions. Due to lower flash point there is always a risk of explosion and fire during the reaction and therefore nitromethane is unsafe to use at industrial scale.
2. Nitropropane has less solubility in water and does not hydrolyze appreciably in water even at elevated temperature, which makes the effluent treatment problematic. It can undergo hydrolysis with aqueous mineral acid solution, which again creates the problems towards the effluent treatment.
3. As per the ICH guidelines permissible limit for nitroalkanes in product particularly nitromethane is only 50ppm.
4. Process requires longer time to complete reaction.
5. Dimethylformamide used for the purification remains as residual solvent, which becomes difficult to remove.

6. Purification becomes a must to make the product free from nitroalkanes but it increases a unit operation.

None of the processes in the prior art have made the use of ionic liquids alone
5 or in combination with other constituents for the preparation of pregnadiene esters.

The present invention is advantageous as the solvents used are non-hazardous green solvents and compounds of Formula (I) are obtained in high yield with high epimeric purity.

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OBJECT OF THE INVENTION

It is an object of the present invention to provide a process for the preparation of compound of Formula (I) using a combination of ionic liquid, inorganic nitrite and organic solvent.

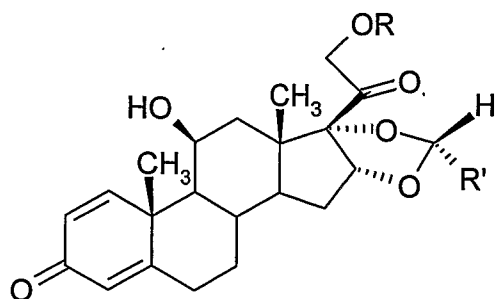
15 It is yet another object of the present invention to provide a process for the preparation of compound of Formula (I) using a combination of an ionic liquid and an organic solvent which induce good chiral selectivity.

It is a further object of the present invention to provide a process for the preparation of compound of Formula (I) which gives high yield and high epimeric
20 purity of compound of Formula (I).

It is yet another object of the present invention to provide a process for the preparation of compound of Formula (I), which employs the use of non-hazardous green solvents.

25 SUMMARY OF INVENTION

According to an aspect of the present invention there is provided a process for the preparation of compounds of Formula (I)



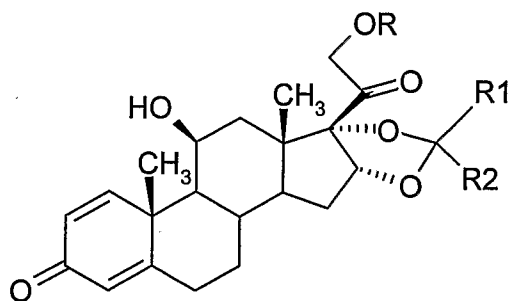
Formula I

Wherein R and R' represent

- a) R= H, R'-cyclohexyl or
- b) R=CO-CH(CH₃)₂, R'=cyclohexyl or
- 5 c) R=H, R'=CH₂-CH₂-CH₃

in predominantly epimerically pure form comprising the step of:

i. reaction of the compound of Formula (II)



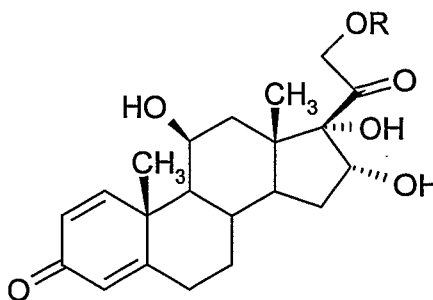
Formula II

10

Wherein R, R1 and R2 represent

- a) (R = H, R1 = CH₃, R2= CH₃) or
- b) (R= CO-CH (CH₃)₂, R1 = CH₃, R2= CH₃)

15 or reaction of the compound of Formula (III)



Formula III

Wherein R represents

- a) H or
- b) $\text{CO-CH}(\text{CH}_3)_2$

- 5 with an alicyclic aldehyde or an aliphatic aldehyde at room temperature using ionic liquids in presence of organic solvents optionally in the presence of inorganic nitrite.

DETAILED DESCRIPTION

- 10 Pregna-1,4-diene-3,20-dione-16,17-acetal-21 esters of formula (I) are inhaled corticosteroids with novel release and distribution properties resulting in lung-targeted anti-inflammatory effects. Inhaled corticosteroids, considered to be the foundation of asthma treatment, work by reducing inflammation in the lungs and airways.

- 15 The present inventors have addressed the need of a process for the preparation of Pregna-1, 4-diene- 3,20-dione-16,17-acetal-21 esters of formula (I) in predominantly epimerically pure form by employing non-hazardous green solvents.

- 20 The advantages of the ionic liquids of the present invention which make them ecofriendly and solvents of choice are set out as under:

- they give good dissolution properties for most of organic and inorganic compounds,
- they have high thermal stability,
- they have no measurable vapor pressure and are non-flammable,
- 25 • they are soluble in water and are biodegradable,

- They can be tailored according to the process requirement.

The present inventors have conducted rigorous experiments to select the best combination of ionic liquids, organic solvents optionally in the presence of inorganic nitrites, which work in combination to induce selective chirality.

5 After several experimentations the present inventors have observed that best results are obtained by using a combination of 1-butyl-3-methyl-1H-imidazolium tetrafluoroborate, sodium nitrite and acetonitrile. The present inventors have carried out various experiments with 1-butyl-3-methyl-1H-imidazolium tetrafluoroborate, 1-butyl-3-methyl-1H-imidazolium trifluoroacetic acid, 1-butyl-3-
10 methyl-1H-imidazolium chloride, 1-butyl- 3-methyl-1H-imidazolium phosphorous hexafluoride but the most satisfactory results are obtained with 1-butyl-3-methyl-1H-imidazolium tetrafluoroborate and 1-butyl- 3-methyl-1H-imidazolium phosphorous hexafluoride.

Thus, the present invention explains a surprising effect in the mixture of 1-
15 butyl-3-methyl-1H-imidazolium tetrafluoroborate or 1-butyl- 3-methyl-1H-imidazolium phosphorous hexafluoride with sodium nitrite and acetonitrile for preparing pregnadiene esters in predominantly epimerically pure form over the other form.

According to yet another embodiment of the present invention, a combination
20 of 1-butyl-3-methyl-1H-imidazolium tetrafluoroborate and acetonitrile also gives the best results. Thus, the present invention also explains a surprising effect in the mixture of 1-butyl-3-methyl-1H-imidazolium tetrafluoroborate and acetonitrile for preparing pregnadiene esters in predominantly epimerically pure form over the other form.

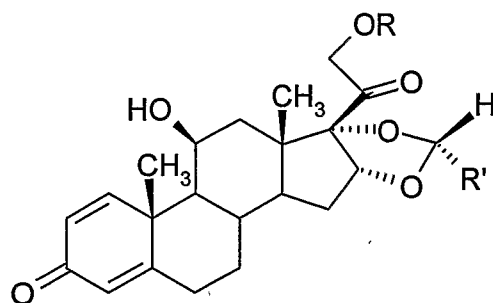
25 Non-hazardous green solvents used in the present invention are ionic liquids such as 1-butyl-3-methyl-1H-imidazolium tetrafluoroborate (bmimBF₄) 1-butyl- 3-methyl-1H-imidazolium phosphorous hexafluoride, 1-butyl-3-methyl-1H-imidazoliumtrifluoroacetic acid, 1-butyl-3-methyl-1H-imidazolium chloride optionally in the presence of inorganic nitrites where the inorganic nitrites include
30 alkali metal nitrites preferably sodium nitrite or potassium nitrite.

Ionic liquids have a high viscosity and therefore diluent is required to reduce the viscosity of the ionic liquids. For the purpose of the invention the organic

solvents used are acetonitrile or methylene dichloride which act as co-diluents. As per ICH guidelines permissible limit of the residuals for acetonitrile is 410 ppm whereas for nitromethane it is 50 ppm. Further acetonitrile gets easily removed with water or other aqueous media. This makes the use of the acetonitrile
 5 advantageous. Methylene dichloride is low boiling and more volatile solvent.

According to present invention, the compounds of the Formula (I) are prepared by using a starting material as desonide and 16-hydroxy prednisolone.

According to a preferred embodiment of the present invention; compounds of formula (I)

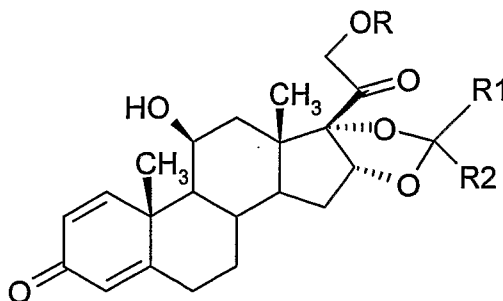


Formula I

Wherein R and R' represent

- a) R= H, R'-cyclohexyl or
- b) R=CO-CH(CH₃)₂, R'=cyclohexyl or
- c) R=H, R'=CH₂-CH₂-CH₃

in predominantly epimerically pure form are prepared by reacting the compound
 of Formula (II)



Formula II

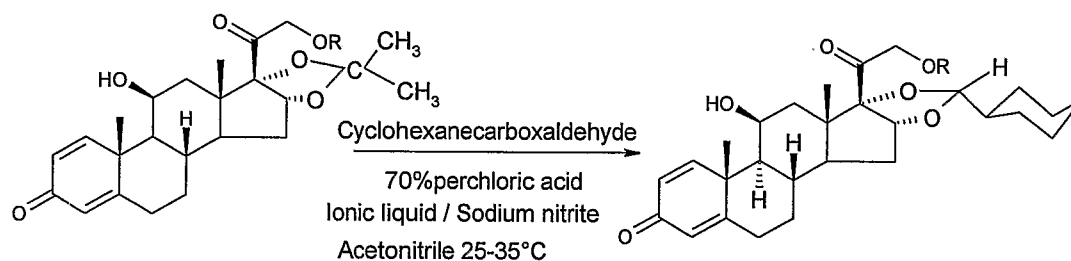
Wherein R, R1 and R2 represent

- a) ($R = H$, $R1 = CH_3$, $R2 = CH_3$) or
- b) ($R = CO-CH(CH_3)_2$, $R1 = CH_3$, $R2 = CH_3$)

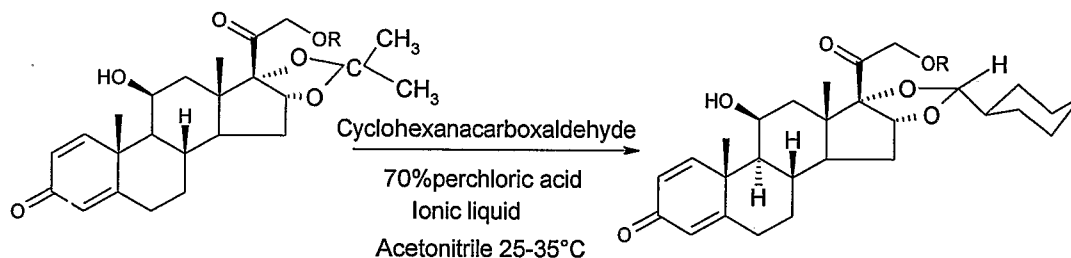
- 5 with an alicyclic aldehyde or an aliphatic aldehyde at room temperature using ionic liquids in presence of organic solvents and perchloric acid optionally in the presence of an inorganic nitrite.

Reaction scheme for Process 1:

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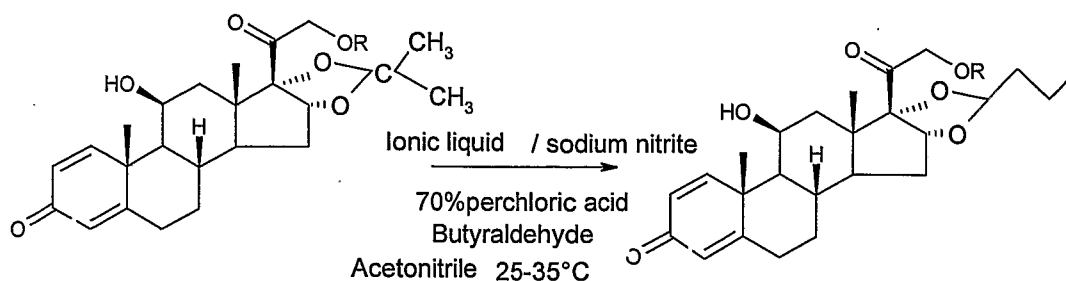


$R = H$ or $-CO-CH(CH_3)_2$

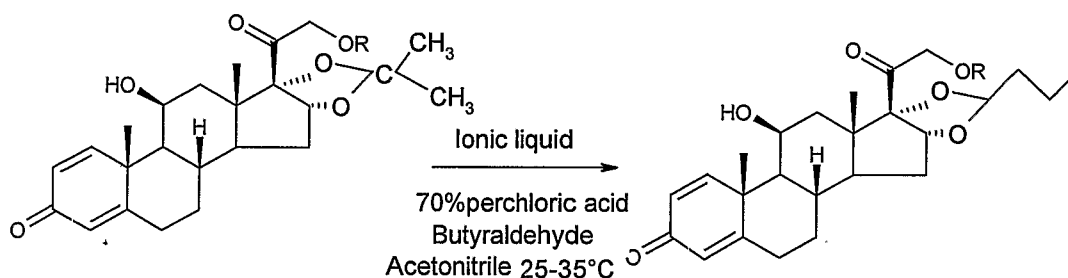


$R = H$ or $-CO-CH(CH_3)_2$

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R= H or isobutyryl



R= H or isobutyryl

Ionic liquid stands for Bmim BF₄/Bmim PF₆

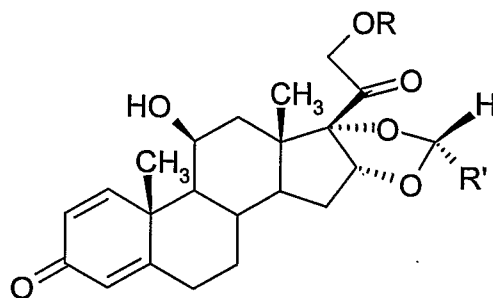
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The reaction of desonide of Formula IIa with cyclohexanecarboxaldehyde normally yields an epimer mixture. However in the present invention, the reaction is controlled by means of suitable reaction conditions. In the presence of sodium nitrite, acetonitrile as co-solvent, 70% perchloric acid as catalyst and specified ionic liquid at 25-35°C, the reaction stereo selectively yields the R-isomer rich compound of Formula (I) than the S- isomer.

According to the present invention the reaction is also controlled by means of suitable reaction conditions viz acetonitrile as co-solvent, 70% perchloric acid as catalyst and specified ionic liquid at 25-35°C. These conditions stereo selectively yields the R-isomer rich compound of Formula (I) than the S- isomer.

According to yet another preferred embodiment of the present invention; compounds of formula (I)

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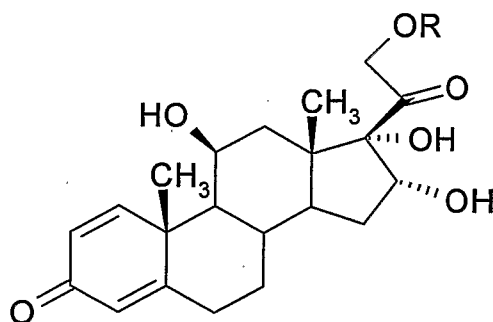


Formula I

Wherein R and R' represent

- a) R= H, R'-cyclohexyl or
- b) R=CO-CH (CH₃)₂, R'=cyclohexyl or
- 5 c) R=H, R'=CH₂-CH₂-CH₃

in predominantly epimerically pure form can be prepared by reacting the compound of Formula (III)

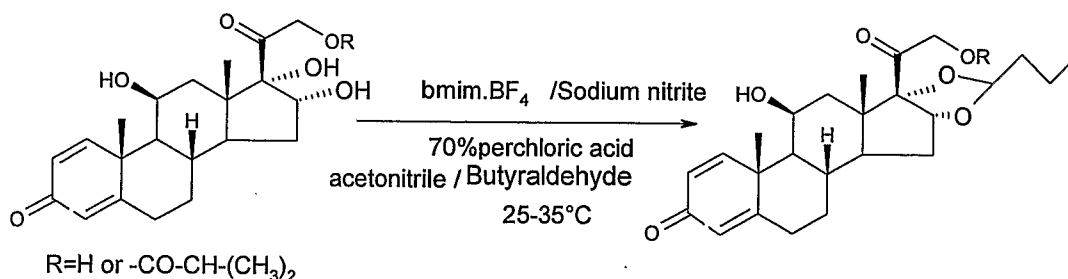


Formula III

- 10 Wherein R = H, or
 R=CO-CH(CH₃)₂

with an alicyclic aldehyde or an aliphatic aldehyde at room temperature using ionic liquids in the presence of organic solvents and perchloric acid optionally in the presence of inorganic nitrite.

15

Reaction scheme for Process 2:

5

For the purpose of the present invention; the catalyst used is 70% perchloric acid.

According to present invention the aldehyde is selected from alicyclic aldehyde e.g. cyclohexanecarboxaldehyde or an aliphatic aldehyde like butyraldehyde.

According to the present invention the isomeric purity of compounds of Formula (I) for R: S is in the ratio of (78-92): (22-8).

The details of the invention, its objects and advantages are explained hereunder in greater details in relation to non-limiting exemplary illustrations. The examples are merely illustrative and do not limit the teaching of this invention and it would be obvious that various modifications or changes in the procedural steps by those skilled in the art without departing from the scope of the invention and shall be consequently encompassed within the ambit and spirit of this approach and scope thereof.

20

EXAMPLE 1:

16, 17-[cyclohexylmethylene]-bis (oxy)-11, 21-dihydroxypregna-1, 4-diene-3, 20-Dione [11 β , 16 α (R)]:

5 ml of ionic liquid bmim-BF₄ is taken in a suitable flask to which 0.4 gm of sodium nitrite is added. The contents are thoroughly mixed followed by the addition of 2 gm desonide. To this mixture is added 1 ml of cyclohexanecarboxaldehyde, diluted in 5 ml acetonitrile and 2 ml of 70%

perchloric acid which is also diluted in 5 ml acetonitrile at temperature of 25-35°C. The reaction is monitored by TLC. The reaction gets completed within 10-30 minutes. After the completion of reaction, 50 ml of sodium bicarbonate solution is added which results in the precipitation of solid 3.1g. Product formed is rich in the stereo selective R isomer. The R: S ratio is found to be 92:8 as indicated by HPLC. (Determined by means of HPLC, stationary phase C18.250mm,4.6mm id.5µm, mobile phase water: ethanol(40:60v/v).

EXAMPLE 2:

10 **16, 17-[cyclohexylmethylene)-bis (oxy)-11, 21-dihydroxypregna-1, 4-diene-3, 20-Dione [11β, 16α (R)]:**

2 ml of ionic liquid bmim-PF6 is taken in suitable flask to which 0.2 gm of sodium nitrite is added. The contents are thoroughly mixed followed by the addition of 1 gm desonide. To this mixture is added 0.4 ml of cyclohexanecarboxaldehyde, 15 diluted in 1ml acetonitrile and 0.6 ml of 70% perchloric acid which is also diluted in 1 ml acetonitrile at temperature of 25-35°C. The reaction is monitored by TLC. The reaction gets completed within 10-30 minutes. After the completion of reaction, 50 ml of sodium bicarbonate solution is added which results in the precipitation of 1.8 gm solid. Product formed is rich in the stereo selective R isomer. The R: S ratio is found to be 89:11 as indicated by HPLC.

EXAMPLE 3:

16, 17-[cyclohexylmethylene)-bis (oxy)-11, 21-dihydroxypregna-1, 4-diene-3, 20-Dione [11β, 16α (R)]:

25 2 ml of ionic liquid bmim-PF6 is taken in a suitable flask followed by the addition of 1gm desonide. To this mixture is added 0.4 ml of cyclohexanecarboxaldehyde, diluted in 1 ml methylene dichloride and 0.6 ml of 70% perchloric acid which is also diluted in 1 ml methylene dichloride at temperature of 25-35°C. The reaction is monitored by TLC. The reaction gets 30 completed within 10-30 minutes. After the completion of reaction, 50 ml of sodium bicarbonate solution is added which results in the precipitation of 2.4 gm

solid. Product formed is the stereo selective R isomer. The R: S ratio is found to be 88:12 as indicated by HPLC.

EXAMPLE 4:

5 **16, 17-[cyclohexylmethylene)-bis (oxy)-11, 21-dihydroxypregna-1, 4-diene-3, 20-Dione [11 β , 16 α (R)]:**

2 ml of ionic liquid bmim-BF₄ is taken in a suitable flask followed by the addition of 1gm desonide. To this mixture is added 0.4 ml of cyclohexanecarboxaldehyde, diluted in 1 ml methylene dichloride and 0.6 ml of
10 70% perchloric acid which is also diluted in 1 ml methylene dichloride at temperature of 25-35°C. The reaction is monitored by TLC. The reaction gets completed within 10-30 minutes. After the completion of reaction, 50 ml of sodium bicarbonate solution is added which results in the precipitation of 1.7 gm solid. Product formed is rich in the stereo selective R isomer. The R: S ratio is
15 found to be 78:22 as indicated by HPLC.

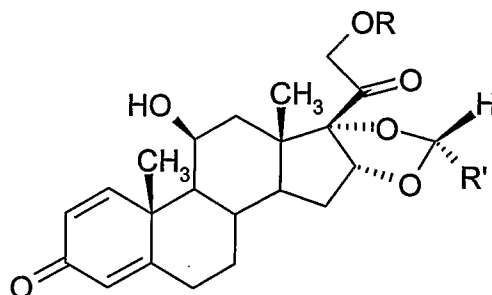
EXAMPLE 5: (PROCESS 2)

16, 17-[butylidenebis (oxy)]-11, 21-dihydroxypregna-1, 4-diene-3, 20-Dione [11 β , 16 α (R)]:

20 2 ml of ionic liquid bmim-PF₆ is taken in a suitable flask followed by the addition of 1gm desonide. To this mixture is added 0.4 ml of butyraldehyde, diluted in 1 ml acetonitrile and 0.6 ml of 70% perchloric acid which is also diluted in 1 ml acetonitrile at temperature of 25-35°C. The reaction is monitored by TLC. The reaction gets completed within 10-30 minutes. After the completion of reaction,
25 50 ml of sodium bicarbonate solution is added which results in the precipitation of 2.2 gm solid. Product formed is rich in the stereo selective R isomer. The R: S ratio is found to be 84:16 as indicated by HPLC.

CLAIMS

1. A process for the preparation of compounds of Formula (I)



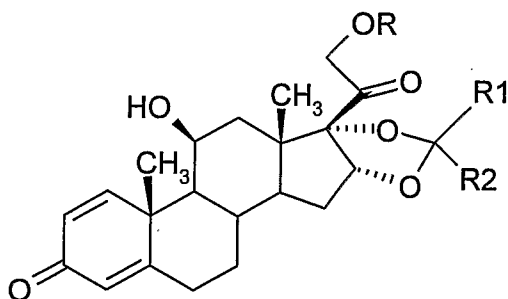
Formula I

Wherein R and R' represent

- 5 a) R= H, R'-cyclohexyl or
 b) R=CO-CH(CH₃)₂, R'=cyclohexyl or
 c) R=H, R'=CH₂-CH₂-CH₃

in predominantly epimerically pure form comprising the step of:

- 10 i. reaction of the compound of Formula (II)



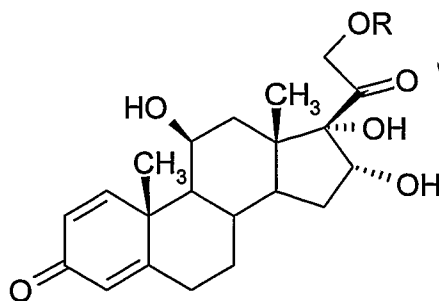
Formula II

Wherein R, R1 and R2 represent

- a) (R = H, R1 = CH₃, R2= CH₃) or
 15 b) (R= CO-CH (CH₃)₂, R1 = CH₃, R2= CH₃)

or reaction of the compound of Formula (III)

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Formula III

Wherein R represents

a) H or

b) $\text{CO-CH}(\text{CH}_3)_2$

5 with an alicyclic aldehyde or an aliphatic aldehyde at 27-35°C using ionic liquid in presence of organic solvents optionally in the presence of inorganic nitrite.

2. The process according to claim 1 wherein the aldehyde is an alicyclic aldehyde.

10 3. The process according to claim 2 wherein the alicyclic aldehyde is cyclohexanecarboxaldehyde.

4. The process according to claim 1 wherein the aldehyde is an aliphatic aldehyde.

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5. The process according to claim 4 wherein the aliphatic aldehyde is butyraldehyde.

6. The process according to claim 1 wherein the ionic liquid is selected from the group consisting of 1-butyl-3-methyl-1H-imidazolium tetrafluoroborate, 1-butyl-3-methyl-1H-imidazoliumtrifluoroacetic acid, 1-butyl-3-methyl-1H-imidazolium chloride, 1-butyl- 3-methyl-1H-imidazolium phosphorous hexafluoride.

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7. The process according to claim 6 wherein the ionic liquid is 1-butyl-3-methyl-1H-imidazolium tetrafluoroborate or 1-butyl-3-methyl-1H-imidazolium phosphorous hexafluoride.
- 5 8. The process according to claim 1 wherein the inorganic nitrite is an alkali metal nitrite.
9. The process according to claim 8 wherein the alkali metal nitrite is selected from sodium nitrite or potassium nitrite.
- 10 10. The process according to claim 1 wherein the organic solvent is selected from acetonitrile or methylene dichloride.
11. The process according to claim 10 wherein the organic solvent is acetonitrile.
- 15 12. The process according to claim 1 wherein the isomeric purity of compounds of Formula (I) for R: S is in the ratio of (78-92): (22-8).