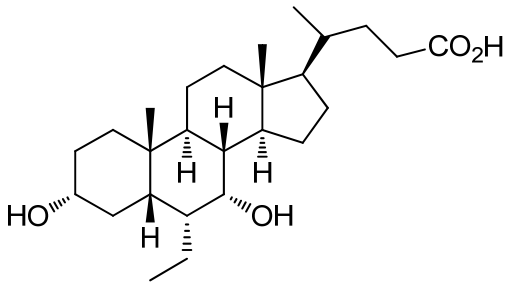
# PREPARATION, USES AND SOLID FORMS OF PBETICHOLIC ACID

## SUMMARY

The present disclosure relates to obeticholic acid, an agonist for FXR, processes of preparation for obeticholic acid, pharmaceutical formulations comprising obeticholic acid, and the therapeutic use of the same.




**obeticholic acid**
**(also known as INT-747)**

In one aspect of the present disclosure, there is provided a process of preparing non-crystalline obeticholic acid comprising the steps of

purifying 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid by crystallization and

precipitating non-crystalline obeticholic acid from a solution comprising crystalline obeticholic acid,

wherein crystalline obeticholic acid is prepared from purified 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid.

In another aspect of the present disclosure, there is provided a process of preparing crystalline obeticholic acid comprising precipitating said crystalline obeticholic acid from a solution comprising obeticholic acid.

In a further aspect of the present disclosure, there is provided a process of preparing obeticholic acid, comprising the steps of

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with $CH_3OH$ and $H_2SO_4$ to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester in which the reaction is heated for about 3 hours and the pH of the reaction mixture is adjusted with an aqueous basic solution;

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester in which the carried out in a polar aprotic solvent at a temperature at about −10 °C to about −30 °C;

reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with $CH_3CHO$ to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester is which the carried out in a polar aprotic solvent at a temperature at about −50 °C to about −70 °C in the presence of boron trifluoride ($BF_3$) solvated complex;

reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid in which the reaction is carried out at a temperature at about 20°C to about 60 °C;

purifying 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid by crystallization;

reacting purified 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid is which the reaction is carried out at a temperature at about 90 °C to about 110 °C;

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid is carried out at a temperature at about 85 °C to about 110 °C in a basic aqueous solution; and

converting crystalline obeticholic acid to non-crystalline obeticholic acid by dissolving crystalline obeticholic acid in aqueous NaOH solution and hydrochloric acid quench.

In another aspect of the present disclosure, there is provided non-crystalline obeticholic acid prepared by process comprising the steps of

purifying 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid by crystallization and

precipitating non-crystalline obeticholic acid from a solution comprising crystalline obeticholic acid,

wherein crystalline obeticholic acid is prepared from purified 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid,

and wherein non-crystalline obeticholic acid comprises less than 1% of chenodeoxycholic acid.

In a further aspect of the present disclosure, there is provided non-crystalline obeticholic acid prepared by process comprising the steps of

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with $CH_3OH$ and $H_2SO_4$ to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester in which the reaction is heated for about 3 hours and the pH of the reaction mixture is adjusted with an aqueous basic solution;

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester in which the carried out in a polar aprotic solvent at a temperature at about −10 °C to about −30 °C;

reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with $CH_3CHO$ to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester is which the carried out in a polar aprotic solvent at a temperature at about −50 °C to about −70 °C in the presence of boron trifluoride ($BF_3$) solvated complex;

reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid in which the reaction is carried out at a temperature at about 20°C to about 60 °C;

purifying 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid by crystallization;

reacting purified 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid is which the reaction is carried out at a temperature at about 90 °C to about 110 °C;

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid is carried out at a temperature at about 85 °C to about 110 °C in a basic aqueous solution; and

converting crystalline obeticholic acid to non-crystalline obeticholic acid by dissolving crystalline obeticholic acid in aqueous NaOH solution and hydrochloric acid quench,

and wherein non-crystalline obeticholic acid comprises less than 1% of chenodeoxycholic acid.

The present disclosure relates to a crystalline obeticholic acid Form C characterized by an X-ray diffraction pattern including characteristic peaks at about 4.2, 6.4, 9.5, 12.5, and 16.7 degrees 2-Theta. The crystalline obeticholic acid Form C is characterized by an X-ray diffraction pattern substantially similar to that set forth in Figure 5 and further characterized by a Differential Scanning Calorimetry (DSC) thermogram having an endotherm value at about 98±2 ºC.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the step of converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid; and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid, and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with $CH_3CHO$ to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid, and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester; reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with $CH_3CHO$ to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid, and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, comprising the steps of reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with $CH_3OH$ and $H_2SO_4$ to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester; reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester; reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with $CH_3CHO$ to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid; reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid; reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid, and converting crystalline obeticholic acid to obeticholic acid Form 1.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein converting crystalline obeticholic acid Form C to obeticholic acid Form 1 comprises the step of dissolving crystalline obeticholic acid Form C in aqueous NaOH solution and adding HCl.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein in reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid is carried out at a temperature at about 85 ºC to about 110 ºC in a basic aqueous solution.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid is carried out at a temperature at about 100 ºC to about 105 ºC and at a pressure at about 4 to about 5 bars.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid is carried out at a temperature at about 20 ºC to about 60 ºC.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with

$CH_3CHO$ to form E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester is carried out in a polar aprotic solvent at a temperature at about -50 ºC to about -70 ºC in the presence of $BF_3$.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester is carried out in a polar aprotic solvent at a temperature at about -10 ºC to about -30 ºC.

The present disclosure relates to a process for preparing obeticholic acid Form 1, wherein reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with $CH_3OH$ and $H_2SO_4$ to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester is heated for about 3 hours and the pH of the reaction mixture is adjusted with an aqueous basic solution to a pH-value of about 6.5 to about 8.0.

The present disclosure relates to a obeticholic acid, or a pharmaceutically acceptable salt, solvate or amino acid conjugate thereof, having a potency of greater than about 98%, greater than about 98.5%, greater than about 99.0%, or greater than about 99.5%. The present invention relates to a pharmaceutical composition comprising obeticholic acid Form 1 produced by a process of the invention and a pharmaceutically acceptable carrier.

The present disclosure relates to a method of treating or preventing an FXR mediated disease or condition in a subject comprise of administering an effective amount of obeticholic acid Form 1. The disease or condition is selected from biliary atresia, cholestatic liver disease, chronic liver disease, nonalcoholic steatohepatitis (NASH), hepatitis C infection, alcoholic liver disease, primary biliary cirrhosis (PBC), liver damage due to progressive fibrosis, liver fibrosis, and cardiovascular diseases including atherosclerosis, arteriosclerosis, hypercholesteremia, and hyperlipidemia. The present disclosure relates to a method for lowering triglycerides in a subject comprise of administering an effective amount of obeticholic acid Form 1.

## BRIEF DESCRIPTION OF THE DRAWINGS

WE CLAIM:

1. A process of preparing non-crystalline obeticholic acid comprising the steps of

purifying 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid by crystallization and

precipitating non-crystalline obeticholic acid from a solution comprising crystalline obeticholic acid,

wherein crystalline obeticholic acid is prepared from purified 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid.

2. The process of claim 1, further comprising the steps of

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid.

3. The process of claim 1, further comprising the steps of

reacting E- or E/Z-3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid, and

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid.

4. The process of claim 1, further comprising the steps of

reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid,

reacting hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid, and

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid.

5. The process of claim 1, further comprising the steps of

reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with $CH_3CHO$ to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester,

reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid,

reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid, and

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid.

6. The process of claim 1, further comprising the steps of:

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester,

reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with $CH_3CHO$ to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester,

reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid,

reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid, and

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid.

7. The process of claim 1, further comprising the steps of:

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with $CH_3OH$ and $H_2SO_4$ to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester,

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester,

reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with $CH_3CHO$ to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester,

reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid,

reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid, and

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form obeticholic acid.

8. The process of claim 7, further comprising a step of adding n-butyl acetate to obeticholic acid to form crystalline obeticholic acid.

9. The process of claim 8, wherein precipitating non-crystalline obeticholic acid from a solution comprising crystalline obeticholic acid comprises a step of dissolving crystalline obeticholic acid in aqueous NaOH solution and hydrochloric acid quench.

10. The process of claim 9, wherein reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form obeticholic acid is carried out at a temperature at about 85 °C to about 110 °C in a basic aqueous solution.

11. The process of claim 9, wherein reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid is carried out at a temperature at about 90 °C to about 110 °C.

12. The process of claim 9, wherein reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid is carried out at a temperature at about 20°C to about 60 °C.

13. The process of claim 9, wherein reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with $CH_3CHO$ to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester is carried out in a polar aprotic solvent at a temperature at about −50 °C to about −70 °C in the presence of boron trifluoride ($BF_3$) solvated complex.

14. The process of claim 9, wherein reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester is carried out in a polar aprotic solvent at a temperature at about −10 °C to about −30 °C.

15. The process of claim 9, wherein reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with $CH_3OH$ and $H_2SO_4$ to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester is heated for about 3 hours and the pH of the reaction mixture is adjusted with an aqueous basic solution.

16. A process of preparing crystalline obeticholic acid comprising precipitating said crystalline obeticholic acid from a solution comprising obeticholic acid.

17. The process of claim 16, wherein the solution comprising obeticholic acid further comprises n-butyl acetate.

18. A process of preparing obeticholic acid, comprising the steps of

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with $CH_3OH$ and $H_2SO_4$ to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester in which the reaction is heated for about 3 hours and the pH of the reaction mixture is adjusted with an aqueous basic solution;

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester in which the carried out in a polar aprotic solvent at a temperature at about −10 °C to about −30 °C;

reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with $CH_3CHO$ to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester is which the carried out in a polar aprotic solvent at a temperature at about −50 °C to about −70 °C in the presence of boron trifluoride ($BF_3$) solvated complex;

reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid in which the reaction is carried out at a temperature at about 20°C to about 60 °C;

purifying 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid by crystallization;

reacting purified 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid is which the reaction is carried out at a temperature at about 90 °C to about 110 °C;

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid is carried out at a temperature at about 85 °C to about 110 °C in a basic aqueous solution; and

converting crystalline obeticholic acid to non-crystalline obeticholic acid by dissolving crystalline obeticholic acid in aqueous NaOH solution and hydrochloric acid quench.

19. The process of claim 1, wherein non-crystalline obeticholic acid comprises less than 1% of chenodeoxycholic acid.

20. The process of claim 1, wherein non-crystalline obeticholic acid characterized by a Differential Scanning Calorimetry (DSC) thermogram having an endotherm with an onset at about 89 to 94 °C.

21. The process of claim 18, wherein non-crystalline obeticholic acid comprises less than 1% of chenodeoxycholic acid.

22. Non-crystalline obeticholic acid prepared by process comprising the steps of

purifying 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid by crystallization and

precipitating non-crystalline obeticholic acid from a solution comprising crystalline obeticholic acid,

wherein crystalline obeticholic acid is prepared from purified 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid,

and wherein non-crystalline obeticholic acid comprises less than 1% of chenodeoxycholic acid.

23. Non-crystalline obeticholic acid prepared by process comprising the steps of

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid with $CH_3OH$ and $H_2SO_4$ to form 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester in which the reaction is heated for about 3 hours and the pH of the reaction mixture is adjusted with an aqueous basic solution;

reacting 3α-hydroxy-7-keto-5β-cholan-24-oic acid methyl ester with $Li[N(CH(CH_3)_2)_2]$ and $Si(CH_3)_3Cl$ to form 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester in which the carried out in a polar aprotic solvent at a temperature at about −10 °C to about −30 °C;

reacting 3α,7-ditrimethylsilyloxy-5β-chol-6-en-24-oic acid methyl ester with $CH_3CHO$ to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester is which the carried out in a polar aprotic solvent at a temperature at about −50 °C to about −70 °C in the presence of boron trifluoride ($BF_3$) solvated complex;

reacting 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid methyl ester with NaOH to form 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid in which the reaction is carried out at a temperature at about 20°C to about 60 °C;

purifying 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid by crystallization;

reacting purified 3α-hydroxy-6-ethylidene-7-keto-5β-cholan-24-oic acid with Pd/C and hydrogen gas in the presence of a basic solution to form 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid is which the reaction is carried out at a temperature at about 90 °C to about 110 °C;

reacting 3α-hydroxy-6α-ethyl-7-keto-5β-cholan-24-oic acid with $NaBH_4$ to form crystalline obeticholic acid is carried out at a temperature at about 85 °C to about 110 °C in a basic aqueous solution; and

converting crystalline obeticholic acid to non-crystalline obeticholic acid by dissolving crystalline obeticholic acid in aqueous NaOH solution and hydrochloric acid quench,

and wherein non-crystalline obeticholic acid comprises less than 1% of chenodeoxycholic acid.