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(54) Titre : PROCEDE AMELIORE PERMETTANT LA PREPARATION ET LA PURIFICATION DE L'EPLERENONE

(54) Title: IMPROVED PROCESS FOR THE PREPARATION AND PURIFIATION OF EPLERENONE

(57) Abrégé/Abstract:

A process for the preparation and purification of Eplerenone is described wherein hydroxylated impurities are removed using a novel derivatization procedure.



ABSTRACT

- 5 A process for the preparation and purification of Eplerenone is described wherein hydroxylated impurities are removed using a novel derivatization procedure.

TITLE

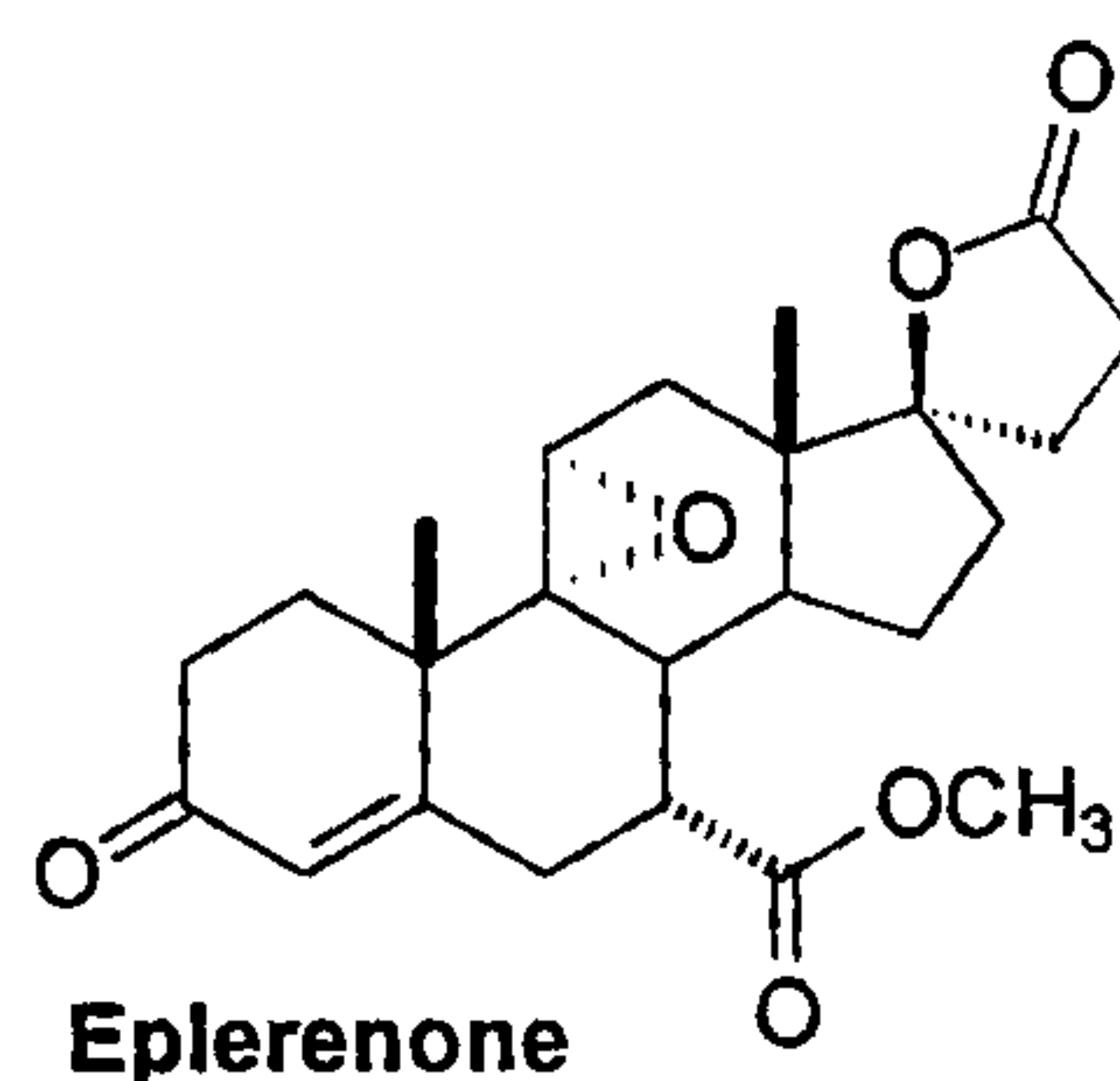
Improved process for the preparation and purification of Eplerenone

5 **FIELD OF THE INVENTION**

The present invention describes a new process for the preparation and purification of Eplerenone.

BACKGROUND OF THE INVENTION

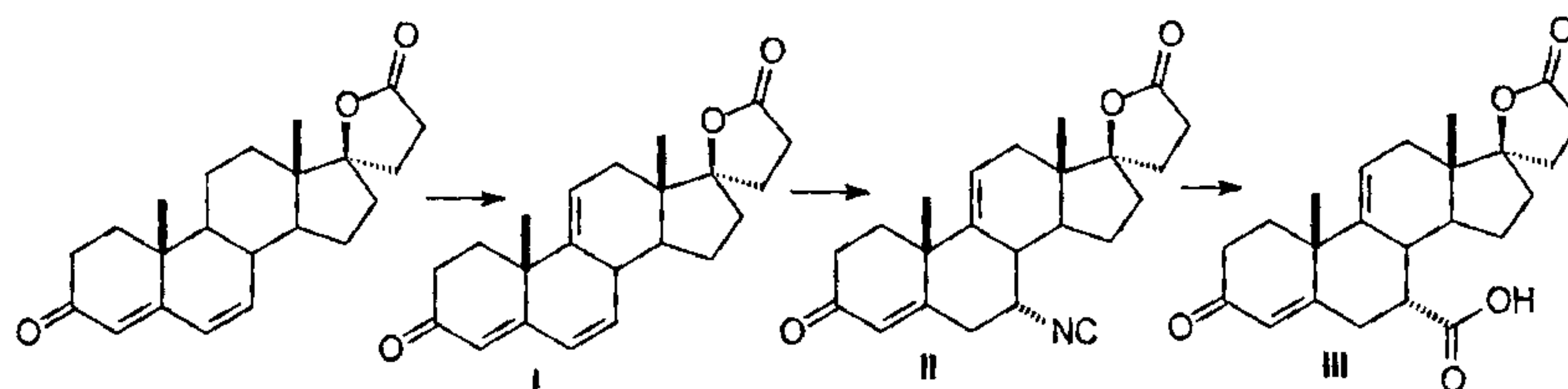
- 10 Eplerenone, (7 α ,11 α ,17 α)-9,11-epoxy-17-hydroxy-3-oxo-pregn-4-ene-7,21-dicarboxylic acid, γ -lactone, 7-methyl ester, is a mineralocorticoid receptor antagonist useful in the treatment of high blood pressure and congestive heart failure. It is marketed under the name of INSPRA™.



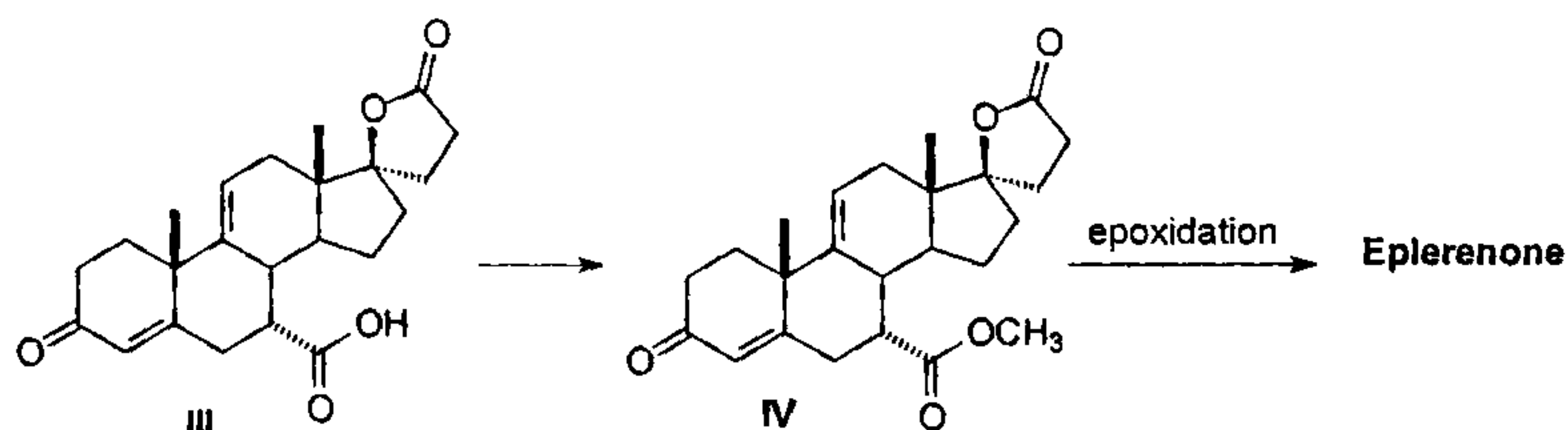
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Most of the patents and literature information dealing with the preparation of Eplerenone are based on the use of the known trienone I as a starting material. In turn, the trienone I is obtained from the natural product Canrenone by 11-bio-hydroxylation followed by mesylation and elimination. The trienone I is then treated with diethylaluminum cyanide to form the 7-cyano derivative II that, after a reduction/oxidation sequence, yields intermediate III.

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Crude intermediate **III** is reacted with diazomethane to provide the methyl ester intermediate **IV** which is then epoxidized using hydrogen peroxide in the presence of an initiator to yield Eplerenone.



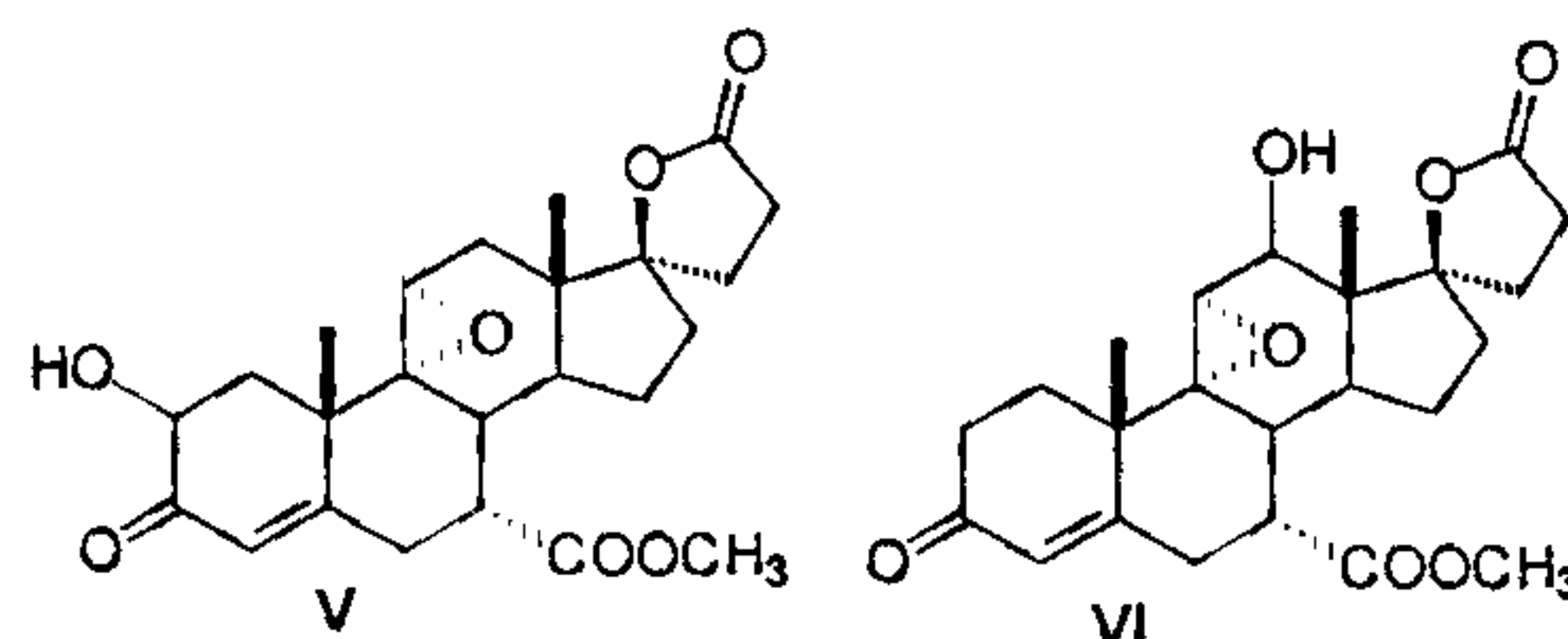
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The original patent, US 4,559,332, for the preparation of Eplerenone describes the epoxidation reaction of **IV** using hydrogen peroxide in the presence of trichloroacetonitrile as initiator. This patent does not disclose any information with respect to the purity of the material obtained, its purification, or the removal of impurities.

10

When the present inventors repeated the preparation taught in US 4,559,332, it was observed that the purity of the resulting Eplerenone was low (70%) and attempts to purify the resulting product to a level meeting the requisite specifications for use as a pharmaceutical active were unsuccessful [typically, known impurities cannot be >0.2% (w/w)]. In particular, dihydroxylated compounds **V** and **VI**, which were isolated and identified, were very difficult to remove. Noteworthy is that similar compounds were mentioned elsewhere in the literature (US 6,887,991), although methods for their removal were not disclosed.

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Other patent literature on processes for the synthesis of Eplerenone, for instance WO2001/042272, discloses examples for the purification of Eplerenone by recrystallization; however, the main objective of these patents was the preparation of various polymorphic and solvated forms. Again, even after numerous attempts to

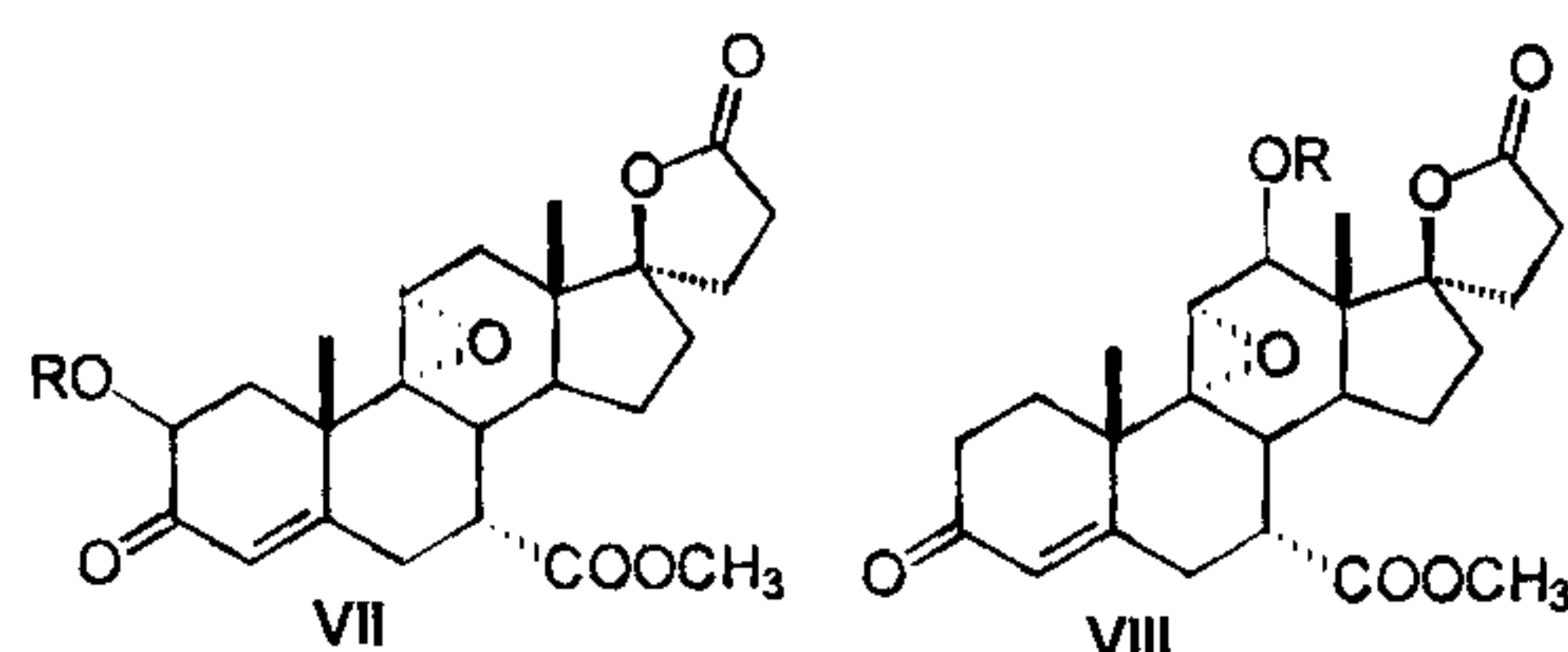
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remove the dihydroxylated impurities V and VI from crude Eplerenone by recrystallization using these solvents and solvent mixtures, we were unable to obtain satisfactory purities of finished pharmaceutical active.

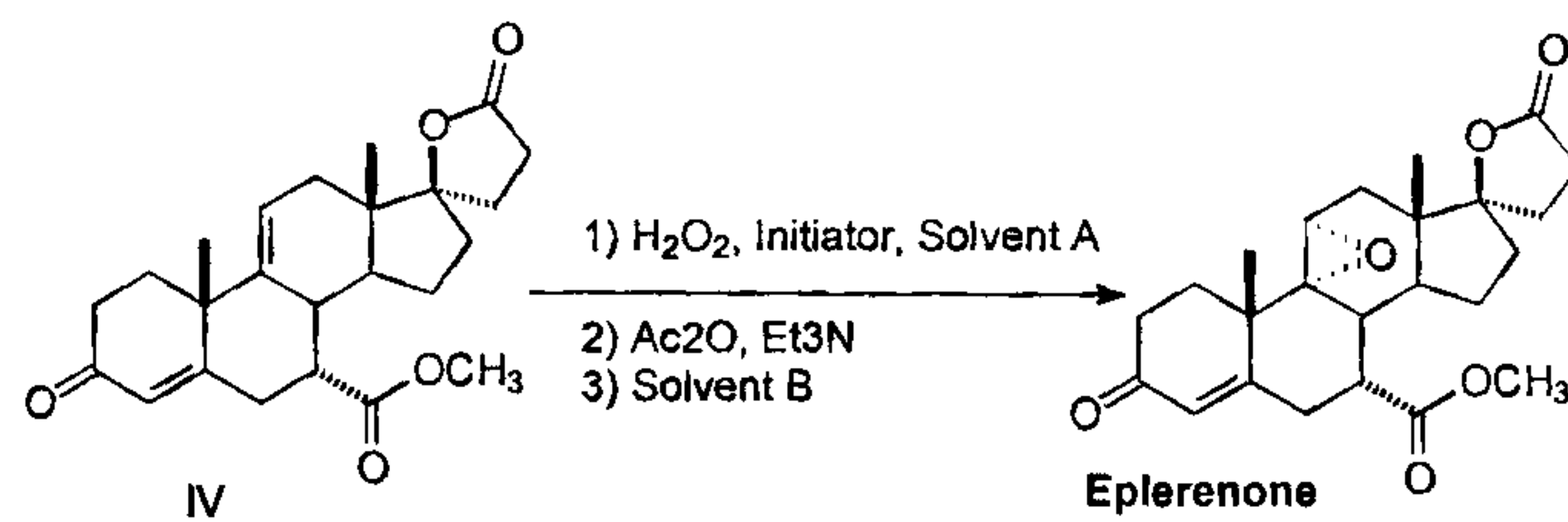
- 5 Therefore, an industrially acceptable method to prepare and purify Eplerenone was required.

SUMMARY OF THE INVENTION

- 10 Surprisingly, we have discovered a novel process for the preparation of Eplerenone which is based on the reaction of trienone IV with hydrogen peroxide in the presence of an initiator followed by the purification of the crude material by converting the compounds V and VI into their corresponding protected alcohols (VII and VIII wherein R = C(O)R' or S(O)₂R'', more preferably R = C(O)CH₃ or S(O)₂CH₃,) and precipitation of Eplerenone from the reaction mixture. It could optionally be further purified by
15 subsequent recrystallization.



- 20 This new method of purification by derivatization was extensively studied using various reagents, bases and solvents. The most preferred results were obtained by treatment of the reaction mixture with acetic anhydride and triethylamine, followed by recrystallization. This novel method of derivatization of the impurities present in crude Eplerenone allowed removal of the corresponding acetylated derivatives VII and VIII (wherein R = C(O)CH₃) by recrystallization in a single solvent.



According to one embodiment of the present invention there is provided a new and improved three step, one-pot process for the preparation and purification of Eplerenone.

5 This process is robust and amenable to scale-up to industrial levels.

Other advantages of the present invention include the improved cost efficiency and simplicity of the process. As well, the Eplerenone produced meets purity specifications of >99% with all known impurities being <0.2% (w/w).

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Further and other advantages of this invention will be appreciated by those skilled in the art.

This method of purification has not been reported previously for the preparation of Eplerenone, to our understanding.

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DESCRIPTION OF A PREFERRED EMBODIMENT

The hydrogen peroxide-mediated epoxidation of IV to crude Eplerenone was achieved by dissolution in an organic solvent, most preferably a C1-C3 chlorinated organic solvent, for instance dichloromethane followed by the addition of an initiator and a base. Examples of the initiator include trichloroacetonitrile and examples of the base include potassium hydrogenphosphate dibasic. Aqueous hydrogen peroxide is then added and the reaction is performed between 10 and 40°C and further processed using standard aqueous extractive techniques.

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The reaction mixture is then derivatized using a derivatizing agent in combination with an organic amine base such as triethylamine. Examples of the derivatizing agent

include anhydrides of formula $[R'OC(O)]_2$ or $[R'C(O)]_2$ and activated carboxylates of formula $R'C(O)X$ wherein X is a leaving group such as a halogen, most preferably X is chlorine. R' can be C1 to C6 alkyl, aryl or aralkyl, most preferably, R' is methyl. In another embodiment, the derivatizing agent can be sulfonate-ester forming agents of formula $R''S(O)_2X$ wherein R'' is C1 to C6 alkyl or aryl, most preferably R'' is methyl and X is as defined above.

The most preferred derivatizing agents for this invention are acetylating and sulfonating agents, such as acetic anhydride and acetyl chloride or sulfonates such as methanesulfonyl chloride. This reaction is preferably carried out at about 5°C to about 50°C, most preferably at reflux temperature. The amount of organic base and derivatizing reagent should be sufficient to effect conversion of V and VI to their respective acetates or sulfonates, for instance about 0.1 to about 1.0 equivalents based on the original amount of III. Eplerenone is then optionally further purified by recrystallization from suitable organic solvents, for instance C3-C6 ketones, most preferably methyl ethyl ketone.

The following examples are representative of embodiments of the present invention and are not intended to be limiting.

Example 1: Preparation of Crude Eplerenone

A mixture of 7- α -(methoxycarbonyl)-3-oxo-17- α -pregna-4,9(11)-diene-21,17-carbolactone (100 g, 0.25 mol), (48.8 g, 0.29 mol), trichloroacetonitrile (91.0 g, 0.63 mol) in dichloromethane (1000 mL) was stirred at reflux for 1 hour. Hydrogen peroxide 30% (398.4 g, 3.51 mol) was added over 3 to 5 hours. The reaction mixture was stirred at reflux for 24 hours. After cooling to room temperature, the organic phase was washed twice with sodium sulfite 10% aqueous solution (2 X 400 g) followed by water (500 g). The solution was tested for peroxides and, when the test was negative, it was evaporated to 200 mL. If the test was positive, the aqueous sodium sulfite and water washes were repeated and the solution was retested.

Example 2: Preparation of Pure Eplerenone

The above organic phase was treated with triethylamine (12.7 g, 0.13 mol) and acetic anhydride (12.8 g, 0.13 mol). The reaction mixture was heated to reflux for 12 hours. Acetone (200 mL) was added and the solvent was evaporated. Another 600 mL of acetone were charged to the reaction mixture and it was heated to reflux for 4 to 6 hours. After cooling at 0-5°C, the suspension was filtered and the cake was rinsed twice with acetone (80 mL) to give 49.1g of Eplerenone. The purity of the Eplerenone obtained at this stage was 99.1%. This material was suspended in 500 ml of methyl ethyl ketone and heated to reflux to give a turbid to clear solution. The solution was filtered hot through cartridge filter. The clear solution was heated to reflux and 175 ml of methyl ethyl ketone were distilled off. The remaining solution (325 mL) was cooled gradually to 0-4° C and stirred at that temperature for 1 hour. The precipitation was filtered and washed twice with methyl ethyl ketone (50 mL) to provide pharmaceutical grade Eplerenone (recovery = 41 g). The product is characterized as follows:

LRMS (APCI+): 415.35 (100.00, [M+H⁺])

HRMS (EI⁺): Calculated for: C₂₄H₃₀O₆ [M]⁺ 414.2042

Found: 414.2050.

¹H NMR (DMSO-d₆): δ (ppm) 5.98 (1H, s, H₄); 3.65 (3H, s, H₂₄); 3.13 (1H, d, J = 5.3 Hz, H₁₁); 2.87-2.90 (1H, m, H₇); 2.72 (2H, d, J = 2.9 Hz, H₆); 2.57-2.66 (1H, m, H_{21b}); 2.45-2.54 (4H, m, H_{2,8,21a}); 2.27-2.38 (1H, m, H_{20b}); 2.17-2.24 (2H, m, H_{1b,16b}); 1.83-2.07 (5H, m, H_{16a,15b,14,12b,20a}); 1.67-1.73 (1H, dd, J = 5.3, 14.6 Hz, H_{12a}); 1.47-1.55 (1H, m, H_{15a}); 1.49 (3H, s, H₁₉); 1.38-1.46 (1H, m, H_{1a}); 1.01 (3H, s, H₁₈).

¹³C NMR (DMSO-d₆): δ (ppm) 198.1, C₃; 176.3, C₂₂; 172.7, C₂₃; 165.2, C₅; 127.2, C₄; 94.7, C₁₇; 65.4, C₉; 51.7, C₂₄; 51.6, C₁₁; 44.0, C₁₃; 41.4, C₇; 39.8, C₁₀; 38.8, C₈; 37.4, C₁₄; 35.1, C₁₆; 34.9, C₆; 33.2, C₂; 31.0, C₁₂; 31.0, C₂₀; 29.1, C₂₁; 27.1, C₁; 22.4, C₁₉; 22.2, C₁₅; 16.3, C₁₈

Example 3: Production of Crude Eplerenone using Methanesulfonyl chloride and Triethylamine

A mixture of crude Eplerenone (2.00 g, 4.83 mmol), prepared in a similar manner as the procedure in Example 1, in 10 mL of dichloromethane was treated with triethylamine (48.3 mg, 0.48 mmol) and methanesulfonyl chloride (55.3 mg, 0.48 mmol). The reaction mixture was heated to reflux for 12 hours. The solvent was evaporated and to the residue was added acetone (6 mL) whereupon it was heated to reflux for 4 to 6 hours. After cooling at 0-5°C, the suspension was filtered and the cake was rinsed twice with acetone (3 mL) to give 1.10 g of Eplerenone. The purity of the Eplerenone obtained at this stage was 99.2%. This material was further purified by recrystallization from methyl ethyl ketone to provide pharmaceutical grade Eplerenone.

Example 4: Production of Eplerenone using Acetyl chloride and Triethylamine

A mixture of crude Eplerenone (20.00 g, 48.25 mmol)), prepared in a similar manner as the procedure in Example 1, in 40 mL of dichloromethane was treated with triethylamine (482.6 mg, 48.25 mmol) and acetyl chloride (3.79 g, 48.25 mmol). The reaction mixture was heated to reflux for 12 hours. The solvent was evaporated and to the residue was added acetone (40 mL) and it was heated to reflux for 4 to 6 hours. After cooling at 0-5°C, the suspension was filtered and the cake was rinsed twice with acetone (2 X 16 mL) to furnish 9.30 g of Eplerenone. The purity of the Eplerenone obtained at this stage was 99.0%. This material was further purified by recrystallization from methyl ethyl ketone to provide pharmaceutical grade Eplerenone.

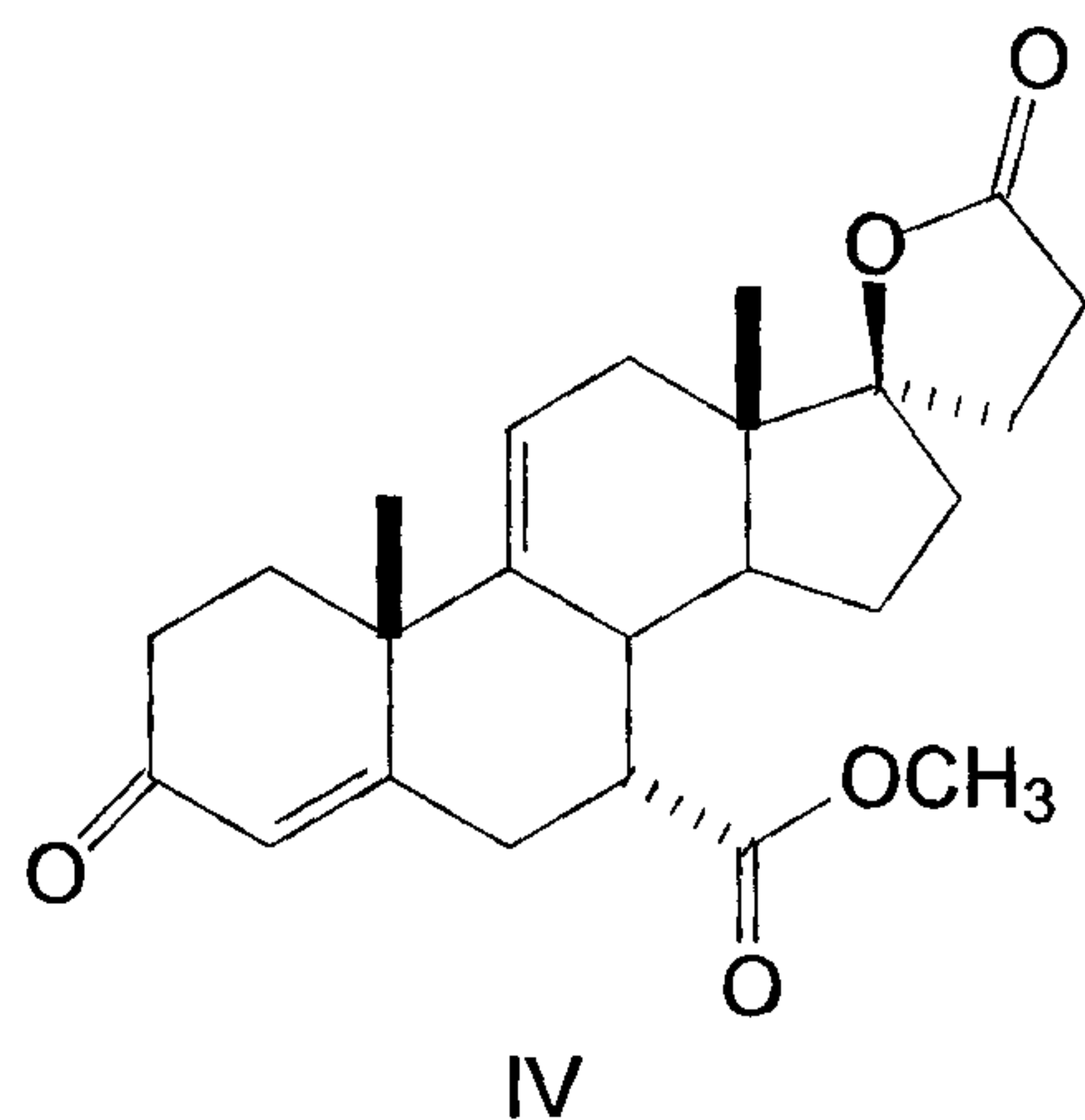
As many changes can be made to the examples which exemplify the invention without departing from the scope of the invention, it is intended that all matter contained herein be considered illustrative of the invention and not in a limiting sense.

CLAIMS

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A process for the preparation and purification of Eplerenone comprising the steps of:

(a) epoxidation of trienone **IV**:



with hydrogen peroxide in the presence of an initiator in a solvent,

(b) treatment of the reaction mixture with a derivatizing agent in the presence of a base,

(c) precipitation of the Eplerenone and,

(d) optionally recrystallization of Eplerenone.

2. The process of Claim 1 wherein the epoxidation of the trienone **IV** with hydrogen peroxide is carried out in dichloromethane.
3. The process of Claim 1 wherein the epoxidation of the trienone **IV** with hydrogen peroxide is performed using trichloroacetonitrile as initiator.

4. The process of Claim 1 wherein the treatment of the reaction mixture with acetic anhydride is performed in the presence of pyridine or collidine.
5. The process of Claim 1 wherein the treatment of the reaction mixture with acetic anhydride and base is performed in methyl ethyl ketone.
6. The process of Claim 1 where step (b) is performed at about 5°C to about 50°C.
7. The process of Claim 1 where step (b) is performed using about 0.1 equivalents to about 1.0 equivalents of derivatizing agent.
8. The process of Claim 1 wherein the recrystallization of Eplerenone wherein is performed in methyl ethyl ketone.
9. The process of Claim 1 wherein the derivatization agent has a formula $[R'OC(O)]_2$ or $[R'C(O)]_2$ and R' is C1 to C6 alkyl, aryl or aralkyl.
10. The process of Claim 1 wherein the derivatization agent has a formula of $R'C(O)X$ wherein X is a halogen leaving group.
11. The process of Claims 9 and 10 wherein R" is methyl.
12. The process of Claim 10 wherein X is chloro.
13. The process of Claim 1 wherein the derivatization agent has a formula of $R''S(O)_2X$ wherein X is a leaving group and R" is C1 to C6 alkyl or aryl.
14. The process of Claim 12 wherein R" is methyl and X is chloro.

15. A process for the preparation and purification of Eplerenone comprising the steps of:
 - (a) epoxidation of the trienone **IV** with hydrogen peroxide carried out in the presence of trichloroacetonitrile in dichloromethane,
 - (b) treatment of the reaction mixture with acetic anhydride carried out in the presence of triethylamine,
 - (c) precipitation of the Eplerenone and,
 - (d) optionally recrystallization of Eplerenone.
16. The process of Claim 15 wherein the solvent used in step (d) is methyl ethyl ketone.
17. The process of Claim 15 where step (b) is performed at about 5°C to about 50°C.
18. The process of Claim 15 where step (b) is performed using about 0.1 equivalents to about 1.0 equivalents of acetic anhydride.