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(54) Title: PROCESS FOR THE PREPARATION OF EPROSARTAN

(57) **Abstract:** Disclosed herein is an improved novel synthetic process for the preparation of Eprosartan, which comprises treating 2-n-butyl-4-formylimidazole of formula (II) with N-protecting group selected from the group consisting of C1-C4 alkyl ester derivative of methacrylic acid; C1 -C4 alkyl ester derivative of crotonic acid; or C1 -C4 alkyl ester derivative of acrylic acid in the presence of a base selected from anion exchange resin or DBU and optionally in presence of a solvent, to get N-protected compound(III) in Stage-I. Stage-II comprises reacting N-protected compound (III) with 2-(2-thienyl methyl) propanedioic acid monoethyl ester to get compound (V). Stage-III comprises reacting compound(V) obtained from stage-II with methyl-4-(bromomethyl) benzoate to get compound (VII). Further, simultaneous hydrolysis of ester groups and removal of N-protecting group is accomplished using caustic soda solution, to yield Eprosartan of Formula (I) in Stage-IV. Finally, pharmaceutical acceptable salt of Eprosartan is prepared in Stage-V.



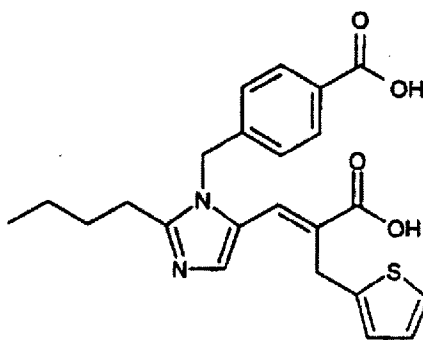
PROCESS FOR THE PREPARATION OF EPROSARTAN

Technical Field:

The present invention relates to a novel cost effective synthetic process for the preparation of Eprosartan and its pharmaceutically acceptable acid addition salts thereof in high yield and purity.

Background and prior art :

Eprosartan is first described in US 5,185,351 as an angiotensin II receptor antagonist, useful in the treatment of hypertension, congestive heart failure and renal failure. Eprosartan acts on the renin-angiotensin system in two ways to decrease total peripheral resistance. First, it blocks the binding of angiotensin II to AT₁ receptors in vascular smooth muscle, causing vascular dilatation. Second, it inhibits sympathetic norepinephrine production, further reducing blood pressure. Eprosartan chemically known as 4-({2-butyl-5-[2-carboxy-2-(thiophen-2-ylmethyl) eth-1-en-1-yl]-1*H*-imidazol-1-yl} methyl) benzoic acid is represented by formula (I).



Eprosartan

(I)

Processes for the preparation of Eprosartan and related compounds are disclosed in US 5185351, EP 0403159 (W092/10189), US 6172237, WO 98/35962 and WO 2008/078330.

According to the U.S. Patent No. 5,185,351, methyl 4-[[2-butyl-5-formyl-1*H*-imidazol-1-yl]methyl]benzoate is reacted with ethyl 2-carboxy-3-(2-thienyl) propionate, in the presence of a base, such as piperidine, in a suitable solvent, such as toluene, at a

temperature of 80°C to 110°C, preferably at 100°C, to give ethyl (αE)- α-[[2-n-Butyl-1-[[4- (methoxycarbonyl)phenyl] methyl] -1 H -imidazol - 5-yl] methylene - 2 - thiophene propionate, which is then hydrolyzed with a base such as sodium hydroxide to give Eprosartan, which is further converted to Eprosartan mesylate.

By following the process as described in US'351, relatively large amounts of impurities were obtained, and hence the yield of the product is very poor (6-7%). If the above reaction is carried out in toluene without refluxing at 80 - 90°C, no reaction will occur. Further, the process described in US'351 patent involves column chromatographic purifications.

Based on the aforementioned drawbacks, this process finds to be unsuitable for preparation of Eprosartan at lab scale and commercial scale operations.

The US'351 patent further described another process for preparation of Eprosartan by using lithium derivatives such as n-butyl lithium. This process also suffers from drawbacks since it would be very difficult to handle lithium derivatives in large-scale scale operations, thereby making the process commercially not viable.

EP 0403159 and the corresponding PCT Patent publication No W0 92/10189 describes the preparation of certain imidazolyl-alkenoic acids useful for regulating hypertension, and for treating congestive heart failure, renal failure and glaucoma. Eprosartan is prepared by a process, which comprises treating methyl-3-acetoxy-3-[2-n-butyl-1-{(4-carbomethoxyphenyl) methyl}-1H-imidazol-5-yl]-2-(2-thienyl) methyl propanoate with 1, 8-diazabicyclo [5.4.0]undec-7-ene, followed by ester hydrolysis. The efficiency of this process and the quality and yield of the imidazole product are particularly important, when preparing said product on a large scale for therapeutic use.

A regioselective synthesis of 1,2,5-trisubstituted-1 H-imidazoles is described (Shilcrat, S.C. et al (1997) J. Org. Chem., Nov 28, 62(24): 8449-8454), which are useful intermediates in the preparation of Eprosartan.

According to U.S.Pat. No. 6172237, Eprosartan is prepared by reacting 4-[[2-butyl-5-formyl-1 H-imidazol-1-yl]methyl]benzoic acid or the bisulfite addition compound of 4-[[2-butyl-5-formyl-1H-imidazol-1-yl]methyl]benzoic acid with (2-thienylmethyl)-

propanedioic acid, mono-ethyl ester in a solvent (and/or solvent systems) selected from the group consisting of toluene, cyclohexane, cyclohexane:dichloroethane, cyclohexane:pyridine, and cyclohexane:ethyl acetate:pyridine, in the presence of piperidine as catalyst at reflux temperature at reduced pressure followed by hydrolysis of the intermediate ethyl ester. The yield of Eprosartan obtained is very low. Moreover, it is difficult to maintain the reaction at reflux under vacuum. The vacuum creates loss of solvent from reaction medium. So there is a need to add extra solvent to the reaction medium.

International Publication No WO 98/35962 also discloses process for preparing eprosartan involving the step of treating 2-n-butyl-4-formylimidazole in a solvent (such as ethyl acetate, acetonitrile, toluene, DMF); with a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene, followed by reaction with a specific N-protecting group.

The drawback of the processes described in the prior art involve the use of costly reagent 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) along with reactive solvents such as ethyl acetate.

WO 2008/078330 describes a process for preparing Eprosartan comprising reacting methyl 4-[[2-butyl-5-formyl-1H-imidazol-1-yl] methyl] benzoate with ethyl 2-carboxy-3-(2-thienyl) propionate, in the presence of a base, in a solvent selected from cyclohexane and n-hexane to give diester intermediate, and further hydrolyzing the above compound with sodium or potassium hydroxide to obtain pure Eprosartan and optionally pharmaceutically acceptable acid addition salts thereof.

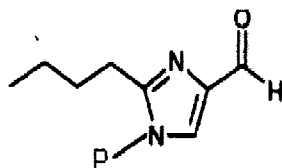
However, there is still a need in the art for an improved and commercially viable process of preparing pure Eprosartan which will be suitable for large-scale preparation of Eprosartan, in terms of economic viability, chemical yield and purity of the product.

Objective of the invention:

The object of the present invention is to provide an improved, cost effective and process for preparing Eprosartan with improved yield and purity by ameliorating the drawbacks of existing prior art processes.

Summary of the invention:

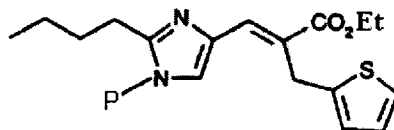
The present invention discloses an improved novel synthetic process for the preparation of Eprosartan, which comprises treating 2-n-butyl-4-formylimidazole with N-protecting group (P) selected from the group of C₁-C₄ alkyl ester derivative of methacrylic acid, preferably ethyl methacrylate C₁-C₄ alkyl ester derivative of crotonic acid, preferably ethyl crotonate; in the presence of anion resin or DBU and optionally in presence of solvent to get N-protected (P) compound of formula III in Stage-I.



(III)

Alternatively treating 2-n-butyl-4-formylimidazole with N-protecting group(P)selected from the group of C₁-C₄ alkyl ester derivative of methacrylic acid, preferably ethyl methacrylate or C₁-C₄ alkyl ester derivative of crotonic acid, preferably ethyl crotonate; in the presence 1,8-Diazabicyclo [5,4.0] undec-7-ene (DBU) to get N-protected compound of formula (III) in stage-I.

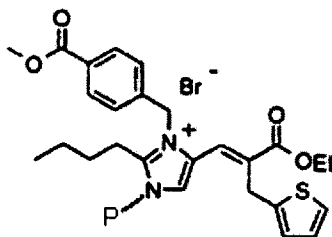
Stage-II comprises reacting N-protected compound of formula (III) with 2-(2-thienyl methyl) propanedioic acid monoethyl ester to get the compound of formula (V),



(V)

wherein P is as defined above.

Stage III comprises bromo condensation of compound of formula (V) with methyl-4-bromo methyl) benzoate of formula to get compound of formula VII,



(VII)

where P is as defined above.

Further, simultaneous hydrolysis of ester groups is accomplished using caustic soda solution and removal of N-protecting group yields Eprosartan of Formula (I) in Stage-IV. Finally, pharmaceutical acceptable salt of Eprosartan is prepared in Stage-V.

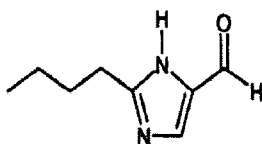
Detailed description of the invention:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

In a preferred embodiment, the present invention provides a synthetic method for the preparation of Eprosartan, comprising the following stages:

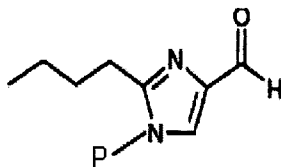
(i) Stage-I-Protection Step

Stage-I comprises reacting 2-n-butyl-4-formylimidazole of formula (II)



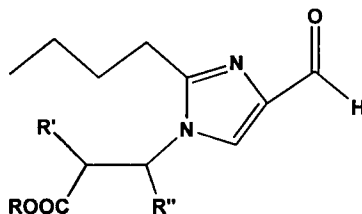
(II)

with a N-protecting reagent "P" selected from the group consisting of C₁-C₄ alkyl ester derivative of methacrylic acid or crotonic acid, preferably ethyl methacrylate, ethyl acrylate or ethyl crotonate, in the presence of anion resin and optionally in presence of solvent to obtain the compound of formula III, i.e., formula (III-A), (III-B) or (III-C) respectively.



(III)

The compound of formula III is same as III' ,



III'

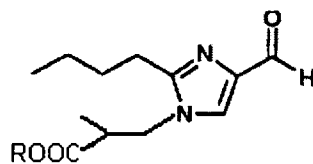
wherein R is a C₁-C₄ alkyl; R' is H or C₁-C₄ alkyl and R'' is H or C₁-C₄ alkyl; preferably when R' is H, R'' is C₁-C₄ alkyl and when R'' is H, R' is C₁-C₄ alkyl.

Alternatively reacting 2-n-butyl-4-formylimidazole of formula (II) with a N-protecting reagent selected from the group of C₁-C₄ alkyl ester derivative of methacrylic acid or crotonic acid, preferably ethyl methacrylate, or ethyl crotonate, in the presence of 1,8-Diazabicyclo [5,4.0] undec-7-ene (DBU), optionally in presence of solvent to obtain the compound of formula (III-A) or (III-C) respectively.

Alternatively reacting 2-n-butyl-4-formylimidazole of formula (II) with N-protecting reagent selected from the group of C₁-C₄ alkyl ester derivative of methacrylic acid or crotonic acid, preferably ethyl methacrylate, or ethyl crotonate, in the presence of anion resin or DBU, optionally in presence of solvent.

The solvent can be selected from the group consisting of ethyl acetate, 1,4 dioxane and dimethylformamide.

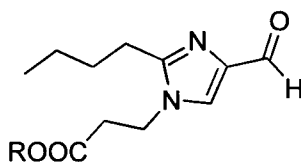
In an embodiment, the compound of formula III wherein the protecting group "P" is ethyl methacrylate;



wherein R = C₁-C₄ alkyl

(III-A)

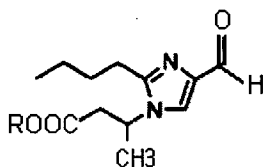
The compound of formula III wherein the protecting group "P" is ethyl acrylate;



wherein R = C₁-C₄ alkyl

(III-B)

The compound of formula III wherein the protecting group "P" is ethyl crotonate;

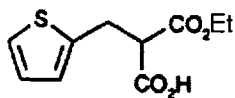


wherein R = C₁-C₄ alkyl

(III-C)

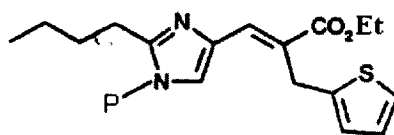
(ii) Stage-II -Knoevenagel Condensation

This stage comprises reacting N-protected compound of formula III with 2-(2-thienyl methyl) propanedioic acid monoethyl ester of formula (IV)



(IV)

in a suitable solvent selected from toluene, xylene, DMF, DCM etc and in presence of a base selected from pyridine, piperidine etc, at a temperature of about 40-75°C to obtain compound of formula (V);

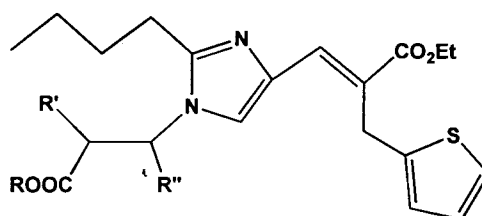


(V)

wherein P is as defined above,

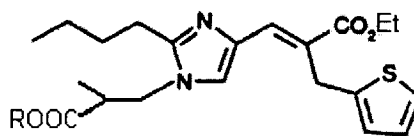
Preferably the reaction is carried out in presence of piperidine and toluene at a temperature of about 40-60°C under vacuum.

The compound of formula V is same as V',



V'

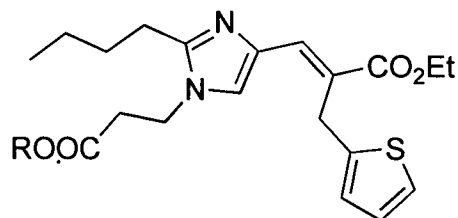
In an embodiment, the compound of formula V wherein the protecting group "P" is ethyl methacrylate;



(V-A)

Where, R is as defined above,

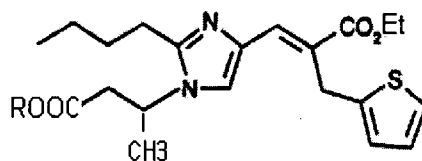
The compound of formula (V) wherein the protecting group "P" is ethyl acrylate;



(V-B)

Where, R is as defined above

The compound of formula (V) wherein the protecting group "P" is ethyl crotonate;

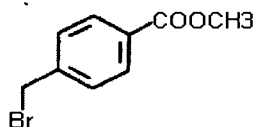


(V-C)

where, R is as defined above.

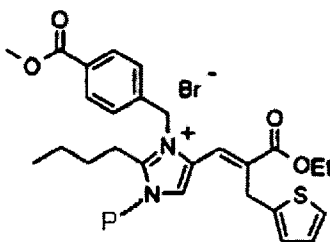
(iii) Stage-III-Bromo Condensation

This stage comprises reaction of compound of formula V with methyl-4-(bromo methyl) benzoate of formula (VI)



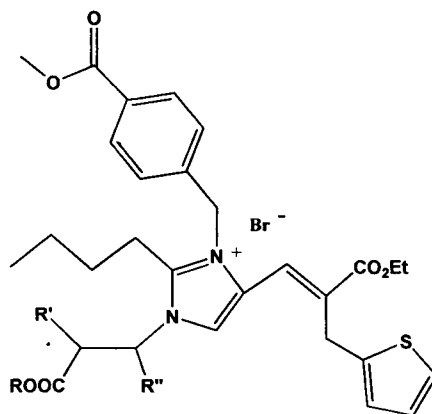
(VI)

in the temperature range of about 100-105° C to get the quaternary salt of formula VII,



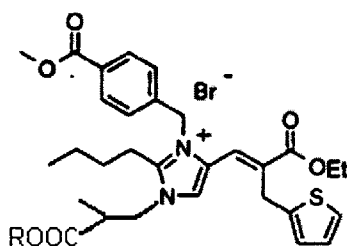
(VII)

The compound of formula VII is same as VII',



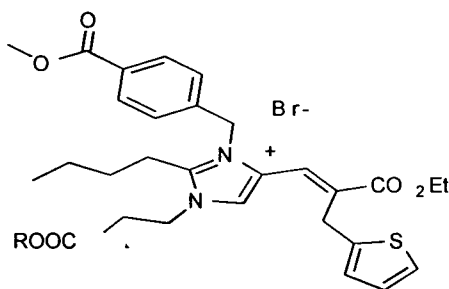
VII'

In an embodiment, the quaternary salt of formula VII wherein the protecting group "P" is ethyl methacrylate,



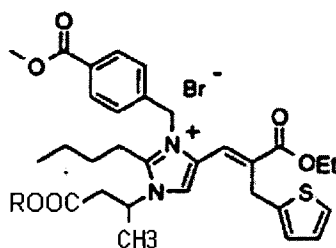
(VII-A)

The quaternary salt of formula VII wherein the protecting group "P" is ethyl acrylate;



(VII-B)

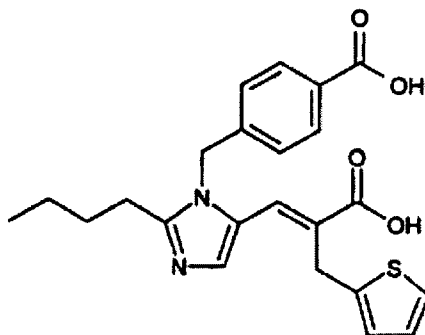
The quaternary salt of formula VII wherein the protecting group "P" is ethyl crotonate;



(VII-C)

(iv) Stage-IV- Hydrolysis and deprotection

Stage-IV comprises simultaneous hydrolysis of ester groups and removal of N-protecting group of the quaternary salt of Formula VII to get Eprosartan of Formula (I).

**Eprosartan****(I)**

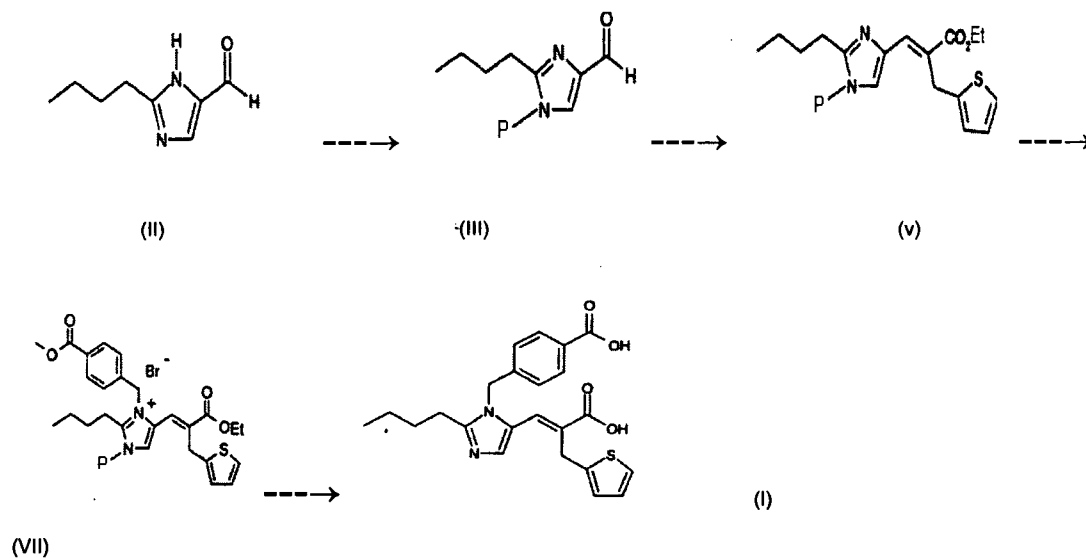
The ester groups are hydrolysed and the N-protecting group is removed using a base such as sodium hydroxide or potassium hydroxide.

(v) Stage-V-Formation of Eprosartan Mesylate

Stage-V comprises formation of mesylate salt of Eprosartan by reacting Eprosartan with methane sulphonic acid.

The synthetic route of the present invention is as depicted in scheme -1

Scheme 1



Wherein P= Nitrogen protecting group selected from; C₁-C₄ alkyl ester derivative of acrylic acid, C₁-C₄ alkyl ester derivative of methacrylic acid or C₁-C₄ alkyl ester derivative of crotonic acid. One preferred compound of ester derivative of methacrylic acid is ethyl methacrylate or ester derivative of acrylic acid which is ethyl acrylate and one preferred compound of ester derivative of crotonic acid is ethyl crotonate. .

The following examples, which include preferred embodiments, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purpose of illustrative discussion of preferred embodiments of the invention.

Examples:

Example 1

a) Preparation of compound of Formula (III) with ethyl methacrylate as protecting group (in presence of anion resin and in absence of solvent):

2-n-butyl-4-formylimidazole (25.0 gm) and ethyl methacrylate (42.4 gm) were charged in a 500 ml round bottom flask equipped with over head stirrer, reflux condenser and thermometer; followed by the addition of Activated anion resin (31.2 gm) at room temperature. The reaction mixture was then heated slowly to 90-95⁰C. The temperature

was maintained for about 5-10 hours. The reaction was monitored by HPLC. Brown colored viscous mass was observed. Reaction mass was cooled to room temperature, and Ethyl Acetate (75.0 ml) was added. Filtered the Reaction mass and washed with Ethyl Acetate (62.0 ml) to separate the resin for reuse. The ethyl acetate layer was washed with water (2 × 50.0 ml), dried over Sodium Sulfate and distilled out completely under reduced pressure at below 60°C temperature. Reaction mass was cooled to room temperature and toluene (100.0 ml) was added. Toluene layer containing desired compound of formula III was used for stage-II.

Yield : 40.3 gm

Purity by HPLC : 87 %

¹H NMR δ (ppm): BRUKER - 400 MHz, CDCl₃: 9.8 (s, 1 H), 7.5 (s, 1 H), 4.2 m, 2H), 4.1 (q, 2 H), 2.9 (m, 1 H), 2.7 (t, 2 H), 1.8 (p, 2 H), 1.4 (q, 2 H), 1.2 (m, 6 H), 0.9 (t, 3 H).

b) Preparation of compound of Formula (III) with ethyl acrylate as protecting group (in presence of anion resin and in absence of solvent):

2-n-butyl-4-formylimidazole (25.0 gm) and ethyl acrylate (25.4 gm) were charged in a 500 ml round bottom flask equipped with over head stirrer, reflux condenser and thermometer; followed by the addition of Activated anion resin (31.2gm) at room temperature. The reaction mixture was then heated slowly to 90-95⁰C. The temperature was maintained for about 3-4 hours. The reaction was monitored by HPLC. Brown colored viscous mass was observed. Reaction mass was cooled to room temperature, and Ethyl Acetate (75.0 ml) was added. Filtered the Reaction mass and washed with Ethyl Acetate (62.0 ml) to separate the resin for reuse. The ethyl acetate layer was washed with water (2 × 50.0 ml), dried over Sodium Sulfate and distilled out completely under reduced pressure at below 60°C temperature. Reaction mass was cooled to room temperature and toluene (100.0 ml) was added. Toluene layer containing N-Protected compound was used for stage-II.

Yield: 38.6 gm

Purity by HPLC : 87.56%

¹H NMR δ (ppm): BRUKER - 400 MHz, CDCl₃ 9.8 (s, 1 H), 7.6 (s, 1 H), 4.2 (t, 2 H), 4.1 (q, 2 H), 2.8 (t, 2 H), 2.7 (t, 2 H), 1.8 (p, 2 H), 1.4 (m, 2 H), 1.2 (t, 3 H),

0.9 (t, 3 H).

c) Preparation of compound of Formula (III) with Ethyl crotonate as protecting group (in presence of anion resin and in absence of solvent):

2-n-butyl-4-formylimidazole (25.0 gm) and ethyl crotonate (42.2 gm) were charged in a 500 ml round bottom flask equipped with over head stirrer, reflux condenser and thermometer; followed by the addition of Activated anion resin (31.2 gm) at room temperature. The reaction mixture was then heated slowly to 90-95°C. The temperature was maintained for about 5-10 hours. The reaction was monitored by HPLC. Brown colored viscous mass was observed. Reaction mass was cooled to room temperature, and Ethyl Acetate (75.0 ml) was added. Filtered the Reaction mass and washed with Ethyl Acetate (62.0 ml) to separate the resin for reuse. The ethyl acetate layer was washed with water (2 × 50.0 ml), dried over Sodium Sulfate and distilled out completely under reduced pressure at below 60°C temperature. Reaction mass was cooled to room temperature and toluene (100.0 ml) was added. Toluene layer containing N-Protected compound was used for stage-II.

Yield: 40.0 gm

Purity by HPLC : 91.73%

¹H NMR δ (ppm): BRUKER - 400 MHz, CDCl₃ 9.8 (s, 1 H), 7.6 (s, 1 H), 4.7(m,1H), 4.1 (q, 2 H), 2.7 (m, 4 H), 1.7 (m, 2 H), 1.5 (d, 3 H), 1.4 (m, 2 H), 1.2(t,3 H), 0.9 (t, 3 H).

d) Preparation of compound of Formula (III) with ethyl methacrylate as protecting group (in presence of DBU in absence of solvent):

2-n-butyl-4-formylimidazole (25.0 gm) and ethyl methacrylate (42.4gm) were charged in a 500 ml round bottom flask equipped with over head stirrer, reflux condenser and thermometer; followed by the addition of 1,8-Diazabicyclo [5,4.0] undec-7-ene (DBU) (1.37gm) at room temperature. The reaction mixture was then heated slowly to 90-95°C. The temperature was maintained for about 5-8 hours. The reaction was monitored by HPLC. Reaction mass was cooled to room temperature, ethyl acetate (75.0ml) was added. The ethyl acetate layer was washed with water (2 × 50.0 ml), dried over Sodium Sulfate

and distilled out completely under reduced pressure at below 60°C temperature. Reaction mass was cooled to room temperature and toluene (100.0ml) was added. Toluene layer containing desired compound of formula III was used for stage-II.

Yield: 38.8 gm

Purity by HPLC: 94%

¹H NMR δ (ppm): BRUKER - 400 MHz, CDCl₃ 9.7 (s, 1 H), 7.5 (s, 1 H), 4.0 (m, 4 H), 2.8 (m, 1 H), 2.6 (t, 2 H), 1.7 (p, 2 H), 1.4 (m, 2 H), 1.2 (m, 6 H), 0.9 (t, 3 H).

e) Preparation of compound of Formula (III) with ethyl crotonate as protecting group (in presence of DBU in absence of solvent):

2-n-butyl-4-formylimidazole (25.0gm) and ethyl crotonate (42.4gm) were charged in a 500 ml round bottom flask equipped with over head stirrer, reflux condenser and thermometer; followed by the addition of 1,8-Diazabicyclo [5,4.0] undec-7-ene (DBU) (1.37gm) at room temperature. The reaction mixture was then heated slowly to 90-95°C. The temperature was maintained for about 4-6 hours. The reaction was monitored by HPLC. Reaction mass was cooled to room temperature, toluene (100.0 ml) was added at room temperature. The toluene layer was washed with water (2 × 50.0 ml), dried over Sodium Sulfate and distilled out completely under reduced pressure at below 60°C temperature. Reaction mass was cooled to room temperature and toluene (100.0ml) was added. Toluene layer containing desired compound of formula III was used for stage-II.

Yield: 42.5 gm.

f) Preparation of compound of Formula (III) with ethyl methacrylate as protecting group (in presence of anion resin and in presence of solvent):

2-n-butyl-4-formylimidazole (25.0 gm) and ethyl methacrylate (42.4 gm) in presence of ethyl acetate followed by the addition of anion resin and further prepared the title compound as described in Example 1(a).

g) Preparation of compound of Formula (III) with ethyl crotonate as protecting group (in presence of anion resin and in presence of solvent):

2-n-butyl-4-formylimidazole (25.0 gm) and ethyl crotonate (42.2 gm) in presence of ethyl acetate followed by the addition of anion resin and further and prepared the title

compound as described in Example 1(c).

h) Preparation of compound of Formula (III) with ethyl methacrylate as protecting group (in presence of DBU and in presence of solvent):

2-n-butyl-4-formylimidazole (25.0 gm) and ethyl methacrylate (42.4 gm) followed by the addition of DBU and further prepared the title compound as described in Example 1(d).

i) Preparation of compound of Formula (III) with ethyl crotonate as protecting group (in presence of DBU and in presence of solvent):

2-n-butyl-4-formylimidazole (25.0 gm) and ethyl crotonate (42.2 gm) followed by the addition of DBU and further and prepared the title compound as described in Example 1(e).

j) Preparation of compound of Formula (III) with ethyl acrylate as protecting group (in presence of anion resin and in solvent):

2-n-butyl-4-formylimidazole (25.0 gm) and ethyl acrylate (25.4 gm) followed by the addition of anion resin and further prepared the title compound as described in Example 1(b)

Example 2: Preparation of compound of formula V

A solution of N-protected compound of formula III obtained from stage-I in toluene was treated with 2-(2-thienyl methyl) propanedioic acid monoethyl ester (53.0 gm) and piperidine (5.0 gm) in a 1.0 lit. 3-necked round bottom flask equipped with Dean Stark apparatus, at 25-35⁰C. Mixture was slowly heated to 45-50⁰C. Low vacuum was applied slowly at 50⁰C. Temperature was raised and maintained between 65-70⁰C under vacuum for 5 hours.. The reaction was monitored by HPLC. If HPLC complied, the reaction mixture was cooled to 55⁰C and washed with 20% sodium chloride solution (3 × 50.0 ml). Toluene layer was separated and distilled out under vacuum at below 60⁰C, and fresh toluene was added. The toluene layer containing stage –II was used for stage-III.

NMR of Formula V wherein the protecting group is ethyl methacrylate

^1H NMR δ (ppm): BRUKER - 400 MHz, CDCl_3 7.6 (s, 1 H), 7.0 (t, 2 H), 6.9 (d, 1 H), 6.8 (m, 1 H), 4.4 (s, 2 H), 4.1 (m, 4 H), 3.0 (q, 2 H), 2.8 (m, 1 H), 2.6 (t, 2 H), 1.8 (p, 2 H), 1.5 (m, 2 H), 1.3 (t, 3 H), 1.2 (t, 6 H), 0.9 (t, 3 H).

NMR of Formula V wherein the protecting group is ethyl crotonate

^1H NMR δ (ppm): BRUKER - 400 MHz, CDCl_3 7.6 (s, 1 H), 7.1 (m, 2 H), 6.9 (d, 1 H), 6.8 (m, 1 H), 4.6 (m, 1 H), 4.4 (m, 2 H), 4.2 (q, 2 H), 4.0 (q, 2 H), 2.7 (m, 4 H), 1.8 (p, 2 H), 1.4 (m, 5 H), 1.2 (t, 3 H), 1.1 (t, 3 H), 0.9 (t, 3 H).

Example 3: Preparation of compound of formula (VII)

A solution of compound of formula V obtained from Stage-II in toluene was reacted at 25-35 $^{\circ}\text{C}$ with methyl-4-(bromo methyl) benzoate (48.0 gm) in a 500 ml three-neck round bottom flask equipped with condenser. The reaction mixture was slowly heated to 50-55 $^{\circ}\text{C}$ for dissolution and toluene was distilled out completely under vacuum. Vacuum was released with nitrogen and temperature of 103-107 $^{\circ}\text{C}$ was maintained for 5 hours under nitrogen atmosphere. Reaction mass was monitored by HPLC. On completion of reaction, mass was cooled to 80-85 $^{\circ}\text{C}$, isopropyl alcohol (200.0 ml) was added with stirring at 80 $^{\circ}\text{C}$ and finally cooled to 25-35 $^{\circ}\text{C}$ to obtain stage- III product .

Example 4: Preparation of Eprosartan (formula 1)

Solution of the compound of formula VII obtained from stage-III in isopropyl alcohol was charged in a 1.0 lit three-neck round bottom flask equipped with condenser at 25-35 $^{\circ}\text{C}$. Water (77.0 ml) was charged at 35 $^{\circ}\text{C}$, followed by slow heating to 45-55 $^{\circ}\text{C}$. Caustic soda solution (36.5 gm caustic soda flakes in DM water 36.5 ml) was added at below 60 $^{\circ}\text{C}$ in about 2.0 hours, followed by slowly heating to 75- 78 $^{\circ}\text{C}$. This condition was maintained for 3-5 hours. Reaction was monitored by HPLC. On completion of reaction, mass was cooled to 50-60 $^{\circ}\text{C}$. pH was adjusted to 5.1 to 5.3 with 20% hydrochloric acid at 50-60 $^{\circ}\text{C}$, followed by stirring for 30 minutes. Reaction mass was slowly cooled to 25-35 $^{\circ}\text{C}$ and further cooled to 0-5 $^{\circ}\text{C}$ and maintained for 2.0 hours. Product was filtered and washed with 1:1 chilled aqueous isopropyl alcohol (100.0 ml), followed by washing with chilled

water. Product was dried at 65-75⁰C for 8-10 hours to obtain a pale yellow colour powder of formula (I). (Eprosartan).

Yield :- 50.0 gm

Purity: - 98.5 %

Example 5: Preparation of Eprosartan Mesylate

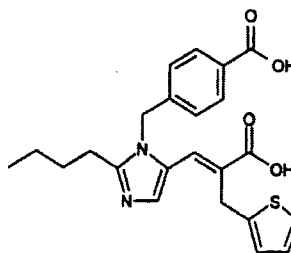
Eprosartan (50.0 gm) obtained from Stage-IV was charged in a 500 ml three-neck round bottom flask at 25-35⁰C, followed by addition of isopropyl alcohol (200.0 ml) and water (25.0ml). Reaction mass was heated to 35-40⁰C, followed by slow addition of methanesulphonic acid (30.0 ml) for 30 minutes. Temperature was maintained between 35-45⁰C for 30 minutes. Reaction mass was cooled to 10-15⁰C and maintained for 2.0 hours. The precipitated product was filtered and washed with isopropyl alcohol. Product was dried at 55-60⁰C

Yield: - 53.0 gm.

Purity: - 99.5 %

We claim,

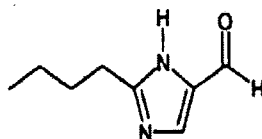
1. A process for the preparation of Eprosartan (formula I),



I

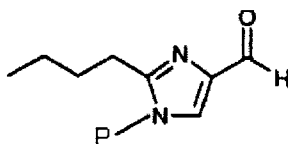
or pharmaceutically acceptable salt thereof, comprising the steps of :

a) reacting 2-n-butyl-4-formylimidazole of formula (II)



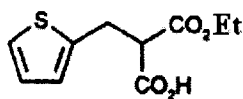
II

with a N-protecting reagent (P) selected from the group consisting C₁-C₄ alkyl ester derivative of methacrylic acid or C₁-C₄ alkyl ester derivative of crotonic acid in presence of a base, to obtain the compound of formula (III);



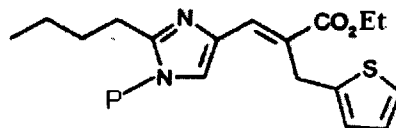
III

b) reacting N-protected compound of formula (III) with 2-(2-thienyl methyl) propanedioic acid monoethyl ester of formula (IV)



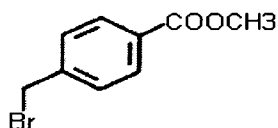
IV

to obtain the compound of formula (V);



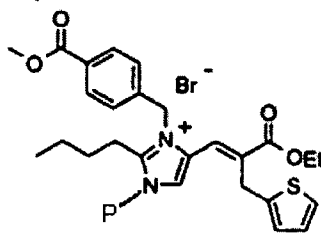
V

- c) condensing compound of formula (V) with methyl-4-(bromo methyl) benzoate of formula (VI)



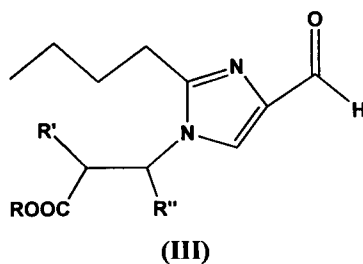
VI

to obtain compound of formula (VII) in isopropyl alcohol;



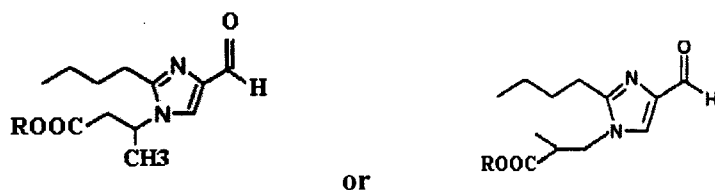
VII

- d) simultaneously hydrolyzing the ester groups and removing the N- protecting group (P) of compound VII in presence of base to yield eprosartan; and
 - e) converting eprosartan to its mesylate salt.
2. The process as claimed in claim 1, wherein step (a) may optionally be conducted in the presence of solvent.
 3. The process as claimed in claim 2, wherein the solvent is selected from the group consisting of ethyl acetate, 1,4 dioxane and dimethylformamide.
 4. The process as claimed in claim 1, wherein the base is selected from anion resin or DBU.
 5. The compound of formula III,



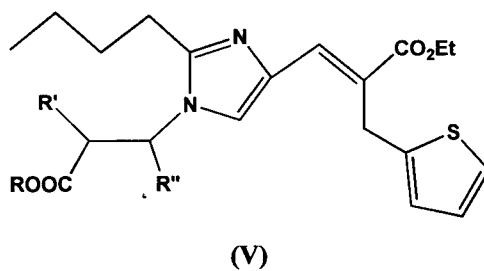
wherein R is a C1-C4 alkyl; when R' is H, R'' is C1-C4 alkyl and when R'' is H, R' is C1-C4 alkyl.

6. The compound of formula III as claimed in claim 5, is



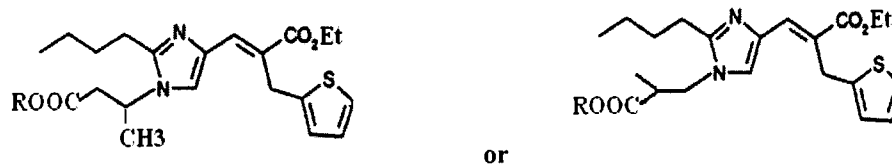
wherein R is C1-C4 alkyl.

7. The compound of formula V,



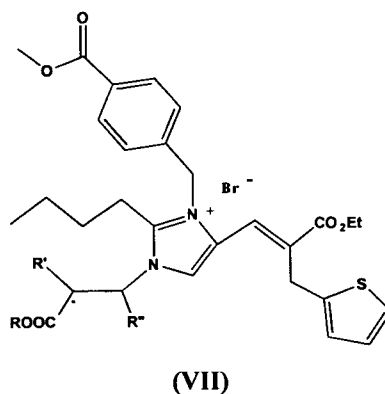
wherein R, R' & R'' are as defined above.

8. The compound of formula V as claimed in claim 7, is



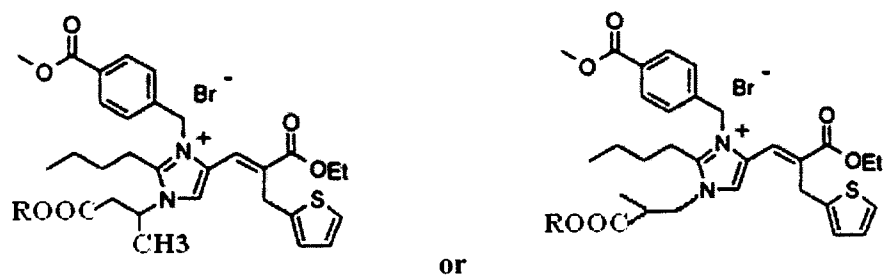
wherein R is C1-C4 alkyl.

9. The compound of formula VII,



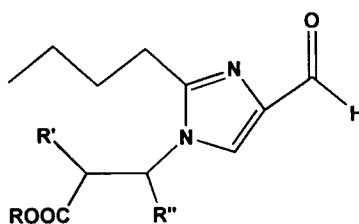
wherein R, R' & R'' are as defined above.

10. The compound of formula VII as claimed in claim 9, is



wherein R is C1-C4 alkyl.

11. The process for the preparation of compound of formula III,

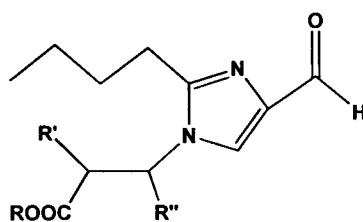


(III)

wherein R, R' & R'' are as defined above.

comprising reacting 2-n-butyl-4-formylimidazole of formula (II) with a N-protecting reagent selected from the group consisting of C1-C4 alkyl ester derivative of methacrylic acid or C1-C4 alkyl ester derivative of crotonic acid preferably ethylmethacrylate, or ethyl crotonate, in presence of anion resin.

12. The process for the preparation of compound of formula III,



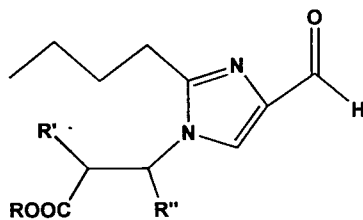
(III)

wherein R, R' & R'' are as defined above.

comprising reaction of 2-n-butyl-4-formylimidazole of formula (II) with a N-protecting reagent selected from the group consisting of C1-C4 alkyl ester derivative of methacrylic acid or C1-C4 alkyl ester derivative of crotonic acid preferably ethyl methacrylate, or ethyl crotonate, in presence of DBU.

13. The process for the preparation of compound of formula III, as claimed in claim 11 and 12, wherein the process may optionally be conducted in presence of solvent.

14. The process for the preparation of compound of formula III,



(III)

wherein R is C1-C4 alkyl; R' and R'' is hydrogen

comprising reaction of 2-n-butyl-4-formylimidazole of formula (II) with a N-protecting reagent selected from the group consisting of C1-C4 alkyl ester derivative

of acrylic acid, preferably ethyl acrylate in presence of anion resin and optionally in presence of solvent.

15. The process for the preparation of compound of formula III, as claimed in claim 13 and 14, wherein the solvent is selected from the group consisting of ethyl acetate, 1,4 dioxane and dimethylformamide.